10.01
Bicyclic 5-5 Systems: Two Heteroatoms 1:1

A. Krutošíková
University of St. Cyril and Methodius, Trnava, Slovakia
T. Gracza
Slovak University of Technology, Bratislava, Slovakia
© 2008 Elsevier Ltd. All rights reserved.

10.01.1 Introduction 2
10.01.2 Theoretical Methods 5
10.01.3 Experimental Structural Methods 5
10.01.3.1 X-Ray Diffraction Studies 5
10.01.3.2 Proton NMR Spectroscopy 6
10.01.3.3 Carbon-13 NMR Spectroscopy 6
10.01.3.4 Nitrogen-15 NMR Spectroscopy 7
10.01.3.5 Polarography 8
10.01.3.6 UV Spectroscopy 9
10.01.3.7 Photoelectron Spectrometry 9
10.01.4 Thermodynamic Aspects 9
10.01.4.1 Aromaticity 9
10.01.5 Reactivity of Fully Conjugated Rings 11
10.01.5.1 1,4-Diheteropentalene Systems (1) 11
10.01.5.1.1 Electrophilic attack at carbon 11
10.01.5.1.2 Electrophilic attack at nitrogen 13
10.01.5.1.3 Electrophilic attack at sulfur 14
10.01.5.1.4 Ring-opening reactions 15
10.01.5.1.5 Cycloaddition reactions 15
10.01.5.2 1,5-Diheteropentalene Systems (2) 16
10.01.5.2.1 Addition and cycloaddition reactions 16
10.01.5.2.2 Radical reactions 19
10.01.5.3 1,6-Diheteropentalene Systems (3) 20
10.01.5.3.1 Electrophilic attack at carbon 20
10.01.5.3.2 Enzyme catalyzed attack at carbon 20
10.01.5.3.3 Electrophilic attack at nitrogen 20
10.01.5.3.4 Electrophilic attack at sulfur 21
10.01.5.3.5 Addition and cycloaddition reactions 21
10.01.5.4 2,5-Diheteropentalene Systems (4) 21
10.01.5.4.1 Cycloaddition reactions 22
10.01.5.4.2 Other Reactions 23
10.01.6 Reactivity of Nonconjugated Rings 23
10.01.6.1 1,4-Diheteropentalene Systems 23
10.01.6.2 1,5-Diheteropentalene Systems 24
10.01.6.3 1,6-Diheteropentalene Systems 25
10.01.6.4 2,5-Diheteropentalene Systems 25
10.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms 25
10.01.7.1 1,4-Diheteropentalene Systems 25

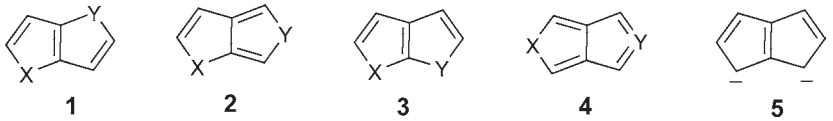
10.01.7.1.1 Carboxylic acids and derivatives 25
10.01.7.1.2 Aldehydes 30
10.01.7.2 1,6-Diheteropentalene Systems 32
10.01.7.2.1 Carboxylic acids and derivatives 32
10.01.7.2.2 Aldehydes 33
10.01.7.2.3 Halogen substituents 36
10.01.8 Reactivity of Substituents Attached to Ring Heteroatoms 37
10.01.8.1 1,4-Diheteropentalene Systems 37
10.01.9 Ring Syntheses 39
10.01.9.1 Syntheses of 1,4-Diheteropentalene Systems (1) 39
10.01.9.1.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle 39
10.01.9.2 Syntheses of 1,5-Diheteropentalene Systems (2) 42
10.01.9.2.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle 42
10.01.9.3 Syntheses of 1,6-Diheteropentalene Systems (3) 50
10.01.9.3.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle 50
10.01.9.4 Syntheses of 2,5-Diheteropentalene Systems (4) 52
10.01.9.4.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle 52
10.01.9.4.2 Other systems 55
10.01.10 Ring Syntheses by Transformation of Another Ring 56
10.01.11 Synthesis of Particular Classes of Compounds 57
10.01.12 Important Compounds and Applications 59
References 60

10.01.1 Introduction

This chapter begins where the earlier chapter in CHEC-II(1996) <1996CHEC-II(7)1> finished and extends the literature coverage to the end of 2006. Some earlier references have been included to cover material absent from the second edition.

As was introduced in CHEC-II(1996) <1996CHEC-II(7)1>, the 5:5 fused heterocyclic systems containing one heteroatom in each ring are represented by the general structures **I–4**, wherein X and Y may be the same or different heteroatoms and represent O, NH, S, Se, Te.

There are four possible modes of 5:5 fusion of the simple five-membered heterocycles leading to structures **I–4**. The fully conjugated title compounds have a central C–C bond and are isoelectronic with the 10-π-electron pentalene dianion **5**. A survey of the nomenclature and numbering of the possible parent 1,4-, 1,5-, 1,6-, and 2,5-ring systems of the title compounds is shown in **Figures 1–4**. New parent compounds since the second edition are represented by structures **15**, **28**, and **38**. The synthesis of them was described <1997H(45)1891>; however, their characterization is still absent in the literature to the best of our knowledge. The remainder of the parent compounds have not been synthesized, probably owing to the lack of mild synthetic methods for the preparation of these highly labile rings. These four general classes of heterocycle **I–4** are referred to herein as 1,4-diheteropentalenes **1**, 1,5-diheteropentalenes **2**, 1,6-diheteropentalenes **3**, and 2,5-diheteropentalenes **4**, or generally as A,B-diheteropentalenes. However the nomenclature as A,B-diheteropentalenes is not used in the literature.



1 **2** **3** **4** **5**

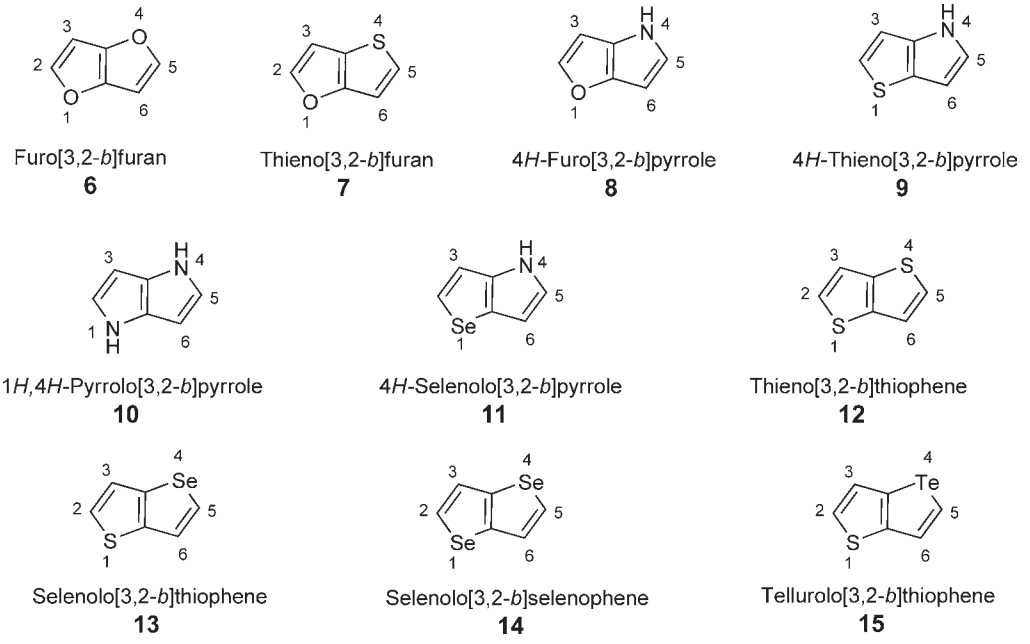


Figure 1 1,4-Diheteropentalene structures.

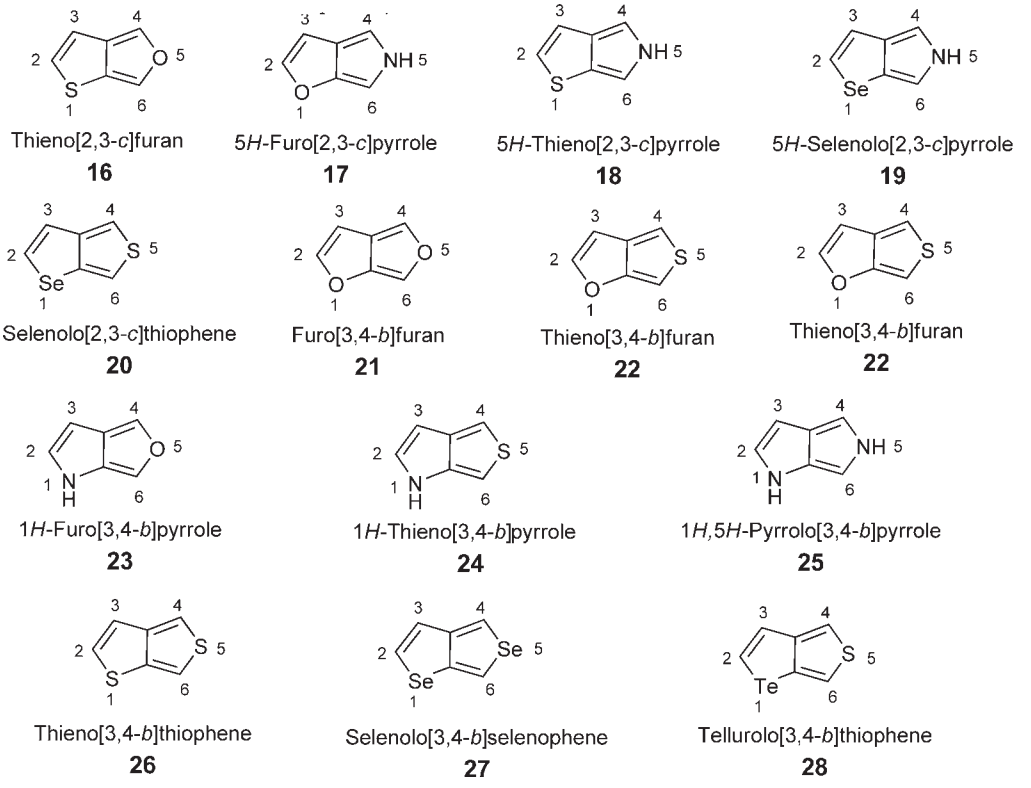


Figure 2 1,5-Diheteropentalene structures.

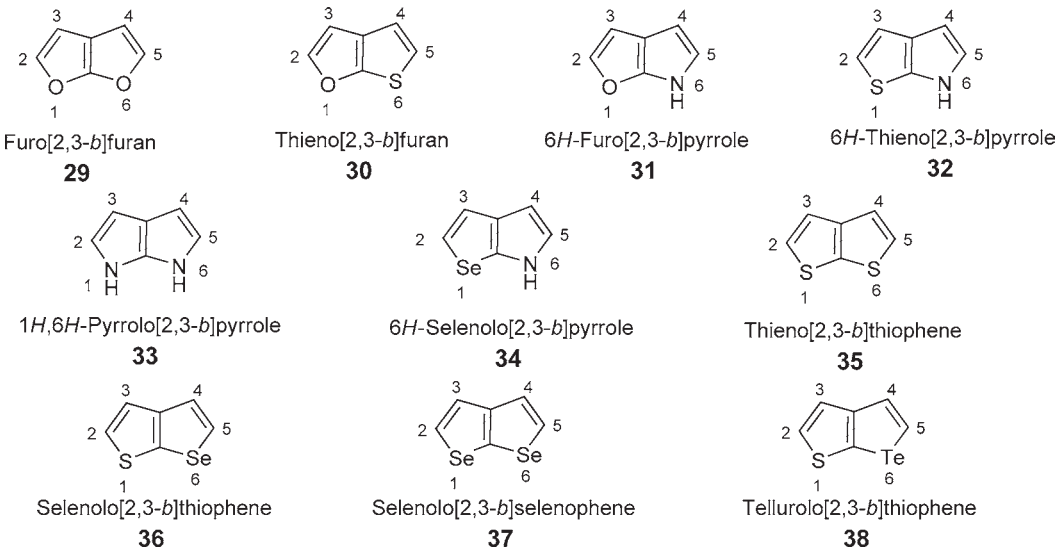


Figure 3 1,6-Diheteropentalene structures.

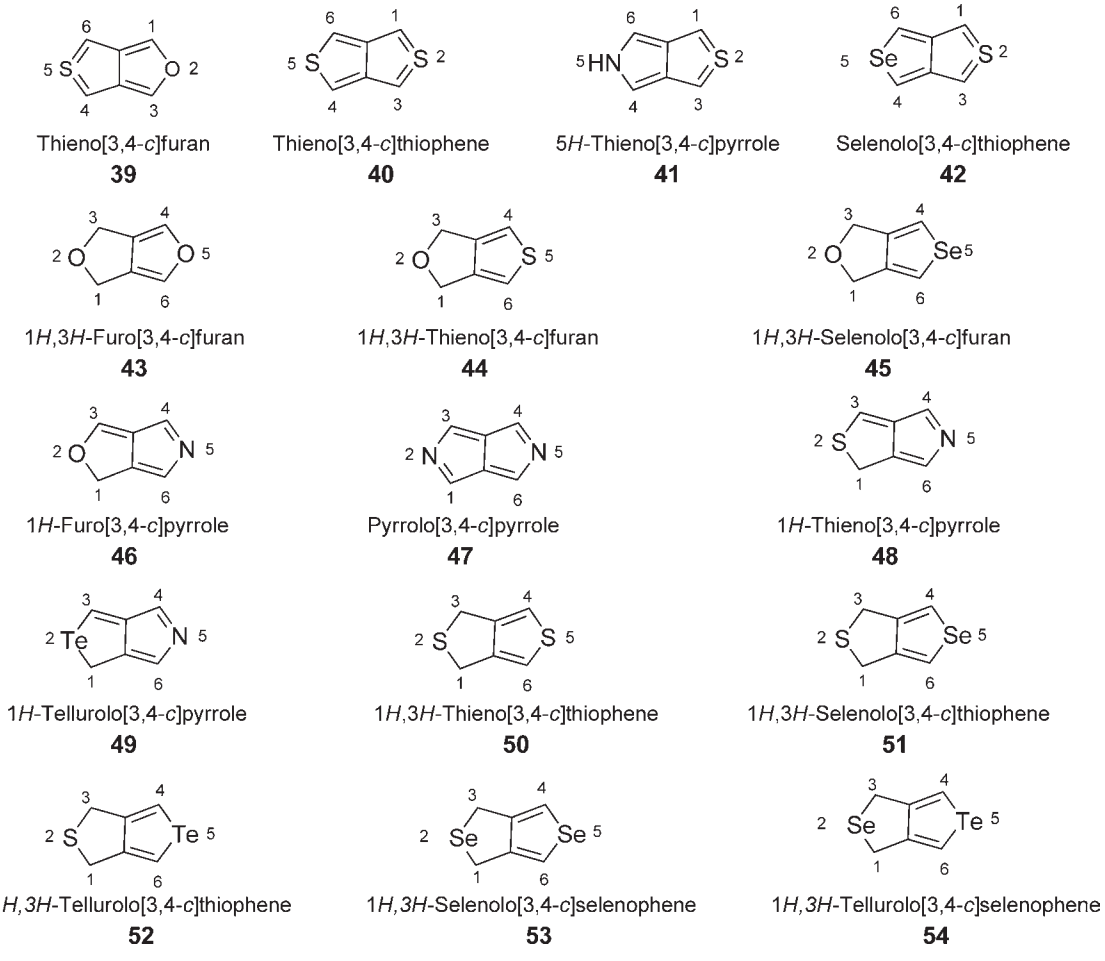
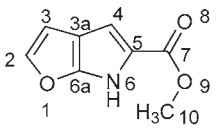


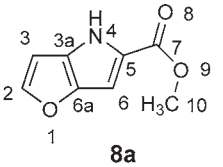
Figure 4 2,5-Diheteropentalene structures.

10.01.2 Theoretical Methods

AM1 semi-empirical molecular orbital (MO) calculations were carried out <1997MOL69> for the parent furopyrroles and the ester derivatives **31a** and **8a**. **Figure 5** shows the calculated properties for the methyl esters **31a** and **8a** including their heats of formation (ΔH_f). The 1,4-system **8a** is calculated to be thermodynamically more stable than the 1,6-isomer **31a**. The 1,4-system **8a** is also calculated to have a significantly larger dipole moment (μ) (**Figure 5**), which may result in greater solvent stabilization. Comparable results were obtained for the unsubstituted heterocycles (**Figure 6**). The calculated ionization potentials (using Koopmaan's theorem) are consistent with the classification of these heterocycles as electron-rich. Calculated net atomic charges and molecular geometries have been reported <1997MOL69>.



31a



8a

	HOMO	*LUMO*		*HOMO*	*LUMO*
e (eV)	–8.88	–0.14	*e* (eV)	–8.79	–0.41
O-1	0.058	0.013	O-1	–0.015	0.180
C-2	0.462	0.251	C-2	0.444	–0.419
C-3	0.181	–0.258	C-3	0.235	0.228
C-3a	–0.484	–0.030	C-3a	–0.453	0.317
C-4	0.000	0.520	N-4	–0.046	–0.349
C-5	0.469	–0.390	C-5	0.539	0.397
N-6	0.166	0.295	C-6	0.205	–0.374
C-6a	–0.485	–0.260	C-6a	–0.407	–0.122
C-7	0.038	–0.406	C-7	0.043	0.333
O-8	–0.158	0.317	O-8	–0.183	–0.275
O-9	–0.068	0.154	O-9	–0.073	–0.129
C-10	0.018	0.007	C-10	0.019	–0.005
	μ = 1.45 D			μ = 3.71 D	
	IP = 8.88 eV			IP = 8.79 eV	
	ΔH_f = –31.27 kcal mol^{-1}			ΔH_f = –33.54 kcal mol^{-1}	

Figure 5 Calculated (AM1) heats of formation (ΔH_f), dipole moments (μ), and frontier orbital coefficient and energies (*e*) for methyl esters **31a** and **8a**.

10.01.3 Experimental Structural Methods

10.01.3.1 X-Ray Diffraction Studies

The crystal structure of ethyl 4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **55** indicates an ethoxycarbonyl group attached to a planar thieno[3,2-*b*]pyrrole ring system <2004AXE2493>.



31

μ = 1.28 D

IP = 8.42 eV

ΔH_f = –53.58 kcal mol^{-1}

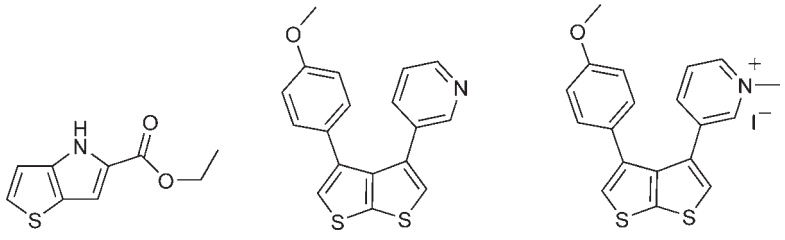
8

μ = 2.57 D

IP = 8.31 eV

ΔH_f = –50.97 kcal mol^{-1}

Figure 6 Calculated (AM1) heats of formation (ΔH_f) and dipole moments (μ) for parent furopyrroles **8** and **31**.



55 **56** **57**

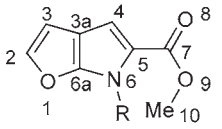
The synthesis of a new class of cofacially oriented neutral donor–acceptor thienothiophenes, namely 3-anisyl-4-pyridylthieno[2,3-*b*]thiophene **56** and its ionic analogue **57**, has been described to probe the presence of through-space charge transfer interaction. The single crystal X-ray analysis of the ionic donor–acceptor thieno[2,3-*b*]thiophene **57** reveals many interesting features, which can be summarized: (1) the donor and acceptor rings are not parallel to each other; (2) the interchromophoric distance is much larger (4.08 Å) than the van der Waals distance; and (3) the torsional angle between the pyridinium ring and the thieno[2,3-*b*]thiophene is unusually small, being only 38°. These structural features preclude effective through-space charge transfer interaction in **57**. Conformational analysis of a model system, 3,4-diphenylthieno[2,3-*b*]thiophene, indicated that conformations with reduced torsion between the phenyl rings and the thieno[2,3-*b*]thiophene, plane are possible to maintain a balance between conjugation and steric congestion and the calculated low-energy barrier between the high- and low-energy conformations of the model system suggests the possibility of aryl ring rotations in peri-disubstituted thieno[2,3-*b*]thiophenes <2004JST107>.

10.01.3.2 Proton NMR Spectroscopy

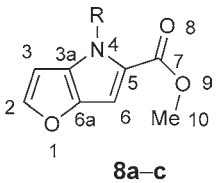
Proton nuclear magnetic resonance (NMR) data of parent A,B-diheteropentalenes have been reviewed <1984CHEC(4)1037, 1984CHEC(6)1027, 1996CHEC-II(7)1>.

10.01.3.3 Carbon-13 NMR Spectroscopy

^{13}C NMR spectra of **8a–c** and **31a–c** have been published (**Table 1**) <1997MOL69>. The different ^{13}C chemical shift values of the corresponding carbon positions for compounds **31a** and **8a** relative to the carbons of furan <1975CS211> and methyl pyrrole-2-carboxylate <1974J(P2)1004> (**Table 2**) show that in the 1,4-isomer **8a** the differences are greater than in **31a**. In **8a**, carbon C-2 shows a downfield shift $\Delta\delta$ = 5.09 ppm, while C-3 shows an upfield shift $\Delta\delta$ = −11.51 ppm as does C-6 $\Delta\delta$ = −18.17 ppm. This demonstrates that the electron density of both systems changes due to the annelated ring interaction, but the effect of the annelated ring is greater in the case of the 1,4-system. An analogous upfield shift was observed in 1*H*,4*H*-pyrrolo[3,2-*b*]pyrrole <1984TL5669>.



31a–c



8a–c

R = H, Me, Bn

Table 1 ^{13}C chemical shifts (δ, ppm) of compounds **31a–c** and **8a–c** in $CDCl_3$

Carbon	*31a*	*31b*	*31c*	*8a*	*8b*	*8c*
C-2	143.65	143.48	143.72	148.69	148.29	148.30
C-3	105.62	105.71	105.67	98.89	97.83	98.64
C-3a	110.56	107.57	108.05	128.86	133.34	132.99
C-4	106.36	106.86	107.76			
C-5	120.70	120.76	120.16	123.77	123.40	123.19
C-6				96.93	97.83	98.80
C-6a	151.60	153.56	153.52	147.93	145.34	145.80
CO	162.75	162.33	162.12	162.61	162.40	162.28
OCH_3	51.60	50.37	50.90	51.58	50.89	51.04
R–		32.00[a]	48.10[b]		−34.59[a]	50.62[c]

[a]Me.
[b]N–CH_2; Ph: 137.33 (C-1′), 128.44 (C-3′, C-5′), 127.16 (C-2′, C-6′), 127.43 (C-4′).
[c]N–CH_2; Ph: 137.60 (C-1′), 128.50 (C-3′, C-5′), 127.46 (C-2′, C-6′), 127.22 (C-4′).

Table 2 Difference of ^{13}C chemical shifts ($\Delta\delta$, ppm) a of **31a** and **8a** carbons relative to carbons of furan and methyl pyrrole-2-carboxylate

Compound	$\Delta\delta$ (*C-2*)	$\Delta\delta$ (*C-3*)	$\Delta\delta$ (*C-4*)	$\Delta\delta$ (*C-5*)	$\Delta\delta$ (*C-6*)
31a	0.05	−4.78	−7.74	−1.30	
8a	5.09	−11.51		1.77	−18.17

[a]Positive sign denotes a downfield shift from furan and methyl pyrrole-2-carboxylate, respectively. Chemical shifts for furan are 143.6 (C-2), 110.4 (C-3) <1975CS211>, and for methyl pyrrole-2-carboxylate 122.0 (C-2), 115.1 (C-3) <1974JP21004>.

10.01.3.4 Nitrogen-15 NMR Spectroscopy

The ^{15}N NMR spectra of **31a–c** and **8a–c** have been measured in order to compare both types (**Table 3**) <1997MOL69>. It was assumed, taking the data for compounds **31a** and **8a** into account, that the greater coupling constants were due to interaction with the proton on the pyrrole ring. The slightly larger negative values of the ^{15}N chemical shifts in **31a–c** compared to **8a–c** agree with the relative values of the calculated (AM1) negative charges on nitrogen.

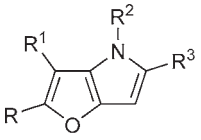
Table 3 ^{15}N chemical shifts (δ, ppm) and $^{n}J(^{15}N,H)$ coupling constants (Hz) of compounds **31a–c** and **8a–c** in $CDCl_3$

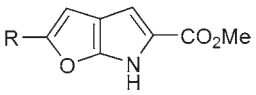
Compound	δ (^{15}N)	$^{1}J(^{15}N,H)$	$^{3}J(^{15}N,H)$[a]	$^{2}J(^{15}N,H)$
31a	−262.1	100.8	3.4	
31b	−260.4		3.3	1.6
31c	−248.3		3.3	1.7
8a	−259.2	100.9	3.8	
8b	−259.0		3.6	1.7
8c	−247.6		3.5	1.7

[a]^{3}J(N,H-4) for **31a–c**, ^{3}J(N,H) for **8a–c**.

10.01.3.5 Polarography

The potential carcinogenicity of furo[3,2-*b*]pyrroles **8** and furo[2,3-*b*]pyrroles **31** was tested by DC polarographic assay in the presence of α-lipoic acid (**Figure 7**; **Table 4**). The method for determination of potential carcinogenic activity has been described in detail earlier <1996CCC657>. The carcinogenic activity is expressed as a parameter of potential carcinogenic activity tg α. Compounds with tg α lower than 0.100 are considered to be noncarcinogenic, while values of tg α in the range from 0.101 to 0.200 are indicative of a marginal carcinogenicity. Compounds with values above 0.201 are considered to be potentially carcinogenic <1997MI389>. Only the compound **31a** showed a marginal carcinogenic activity, the others exhibiting only a negligible carcinogenic potential under the conditions studied <2001CCC1615>.





8	*R*	R^1	R^2	R^3	**31**	*R*
a	H	H	H	CO_2Me	**a**	H
b	Me	H	H	CO_2Me	**d**	CHO
d	Me	Me	H	CO_2Me		
e	Ph	H	H	CO_2Me		
f	4-ClC_6H_4	H	Me	CO_2Me		
g	CHO	H	H	CO_2Me		
h	H	H	H	CO_2H		
i	Me	H	H	CO_2H		
j	Me	Me	H	CO_2H		

Figure 7 Compounds evaluated for their potential carcinogenicity and pK_a values.

Table 4 Experimental polarographic data of the selected derivatives of **8** and **31**

Compound	$E_{1/2,I}$ (*V*)	$E_{1/2,II}$ (*V*)	$E_{1/2,III}$ (*V*)	$E_{1/2,compl.}$[a] (*V*)	*tg* α
8a	−2.320			−1.320	0.0134
8b	−2.400			−1.275	0.0275
8d	−2.460			−1.310	0.0110
8e	−2.120	−2.510		−1.320	0.0253
8f	−1.850	−2.110	−2.300	−1.275	0.0272
8g	−1.340	−1.910			
8h	−2.260			−1.220	0.0244
8i	−2.390			−1.250	0.0254
8j	−2.415			−1.230	0.1040
31a	−2.410			−1.260	0.0439
31d	−1.540	−1.980		−1.250	0.1160

[a]$E_{1/2,compl.}$ is the value of the half-wave potential of complex of selected derivatives of **8** and **31** with α-lipoic acid.

10.01.3.6 UV Spectroscopy

Ultraviolet (UV) spectra of some selected furo[3,2-*b*]- and furo[2,3-*b*]pyrroles were published and their apparent ionization constants determined by spectrometric titration (**Table 5**), and correlated with their structures <2001CCC1615>.

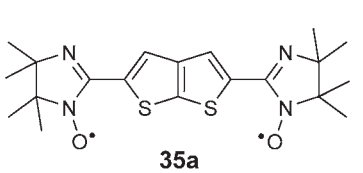
Table 5 UV spectra and pK_a values of the selected derivatives **8** and **31**

Compound	λ_{max}	*log* ε	pK_a[a]	*Compound*	λ_{max}	*log* ε	pK_a[a]
8a	297	4.16	9.58 ± 0.07	**8i**	292	3.98	4.40 ± 0.02
8b	304	4.04	10.08 ± 0.04				10.10 ± 0.07
8d	308	3.98	10.46 ± 0.02	**8j**	294	3.81	4.81 ± 0.03
8e	334	3.97	10.01 ± 0.03				10.36 ± 0.05
	350sh	3.38		**31a**	292	4.16	10.37 ± 0.06
8g	340	3.99	9.80 ± 0.04	**31d**	334	3.95	9.47 ± 0.02
8h	282	3.79	4.01 ± 0.04				
			9.78 ± 0.07				

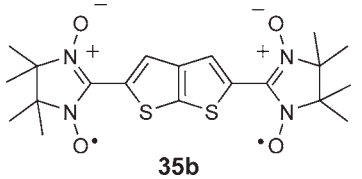
[a]Each of the pK_a values is a mean of three measured values.

10.01.3.7 Photoelectron Spectrometry

Diradical species **35a** and **35b**, in which two imino nitroxide **35a** or nitronyl nitroxide **35b** radical centers are attached to thieno[2,3-*b*]thiophene, were prepared and their intramolecular exchange interactions were investigated in frozen solutions by means of electron spin resonance (ESR) spectroscopy and magnetic susceptibility measurements at cryogenic temperature <1996T6893>.



35a



35b

10.01.4 Thermodynamic Aspects

10.01.4.1 Aromaticity

Schleyer and co-workers <1996AGE2638> have studied the aromatic character of furofurans and thienothiophenes, and concluded that there need not be any direct relationship between the thermodynamic stability of the heterobicyclic isomers and their aromaticity. The analyses were then studied further by Novak <1997JST315>. Both these theoretical studies have importantly revealed, that [1,4] *endo*-substituted thienothiophenes and furofurans are slightly more aromatic than their [1,6] analogues, in line with the Gimarc topological charge stabilization rule <1983JA1979, 1986JA4303>.

Recently, the crystal and molecular structures of eight methyl furo[3,2-*b*]pyrrole-5-carboxylate derivatives **8a,d,g,k–o** and five methyl furo[2,3-*b*]pyrrole-5-carboxylate derivatives **31d–h** (**Figure 8**) have been solved by X-ray diffraction and supplemented by *ab initio* RHF/6-311+G** and B3LYP/6-311+G** calculations <2001T8867>. The molecular geometries of the furo[3,2-*b*]pyrrole and furo[2,3-*b*]pyrrole fragment were used to study the aromatic character of these systems leading to the conclusion that the aromaticity of the rings is practically independent of the nature of the atom in a neighboring ring if a similar topological pattern is concerned. In line with



Compound	R	R^1	R^2	Compound	R	R^1
8a	H	H	H	**31a**	H	H
8d	Me	Me	H	**31d**	CHO	H
8g	CHO	H	H	**31e**	CHO	Me
8k	4-Cl-2-MeC_6H_3O	H	Me	**31f**	CHO	Bn
8l	Me	H	Bn	**31g**	CN	Me
8m	Me	Me	Bn	**31h**	CN	Bn
8n	CHO	H	Bn			
8o	4-Cl-2-MeC_6H_3O	H	Bn			

Figure 8 The studied systems **8** and **31** with bonds labeled.

observed stability of the systems, the aromaticity of furo[2,3-*b*]pyrrole derivatives is definitely less in comparison with the structural isomer furo[3,2-*b*]pyrrole, implying that the most important factor which determines the aromatic character of a compound is topological nature. The stability and aromaticity of the compounds reveal a strong dependence on the substituent effect, much stronger than in the case of benzene derivatives.

The differences in aromaticity follow the results of theoretical analyses on the acidity of the NH proton of the pyrrole fragment of furo[*b*]pyrroles <2000PJC207> and are nicely reflected in the observed stability of both systems. The total energy difference between methyl 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **8a** and methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **31a** is rather small (-7.2 kJ mol^{-1}) indicating the higher stability of the former system. However, if the increase of energy of the appropriate anions is compared (relative to the parent molecules), then it indicates that formation of 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate anion is much easier (by -22.5 kJ mol^{-1}) than formation of 4*H*-furo[3,2-*b*]pyrrole-5-carboxylate anion.

The reason for the lower aromatic character of the furo[2,3-*b*]pyrrole isomer is the close structural proximity of the nitrogen and oxygen atoms. This causes a stronger interaction between the heteroatoms leading to much higher alternation of both CO and CN bond lengths. This effect may be explained by the differences between bond lengths: Δ_{CO} for CO and Δ_{CN} for CN bonds. For [2,3-*b*]pyrroles, both Δ_{CO} and Δ_{CN} are *ca.* 3 times greater than for the furo[3,2-*b*lpyrrole case (**Table 6**). Additionally, a strong shortening of bond lengths in the O–C–N fragment (of *ca.* 0.03 Å) as compared with the furo[3,2-*b*]pyrroles system is observed.

Table 6 Selected experimental bond lengths (Å), the computed bond lengths at B3LYP/6-311+G** (in bold), at HF/6-311 +G** (in italics) for **8g**,**n** and **31d**,**f**. Labeling of bonds according to **Figure 8**

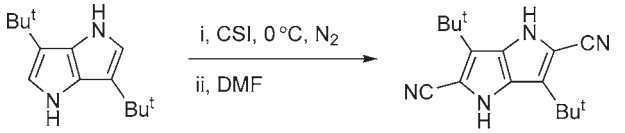
	8*g*	8*g*	8*g*	8*n*	31*d*	31*d*	31*d*	31*f*
a	1.385	**1.379**	*1.350*	1.387	1.405	**1.404**	*1.379*	1.405
b	1.368	**1.383**	*1.356*	1.369	1.355	**1.377**	*1.352*	1.367
c	1.405	**1.414**	*1.427*	1.405	1.419	**1.427**	*1.434*	1.417
d	1.356	**1.365**	*1.356*	1.361	1.422	**1.425**	*1.427*	1.410
e	1.374	**1.386**	*1.371*	1.389	1.368	**1.384**	*1.362*	1.375
f	1.392	**1.396**	*1.372*	1.390	1.402	**1.405**	*1.395*	1.414
g	1.387	**1.402**	*1.408*	1.381	1.333	**1.342**	*1.330*	1.337
h	1.367	**1.353**	*1.337*	1.360	1.339	**1.331**	*1.311*	1.339
i	1.385	**1.395**	*1.363*	1.384	1.372	**1.392**	*1.367*	1.375

10.01.5 Reactivity of Fully Conjugated Rings

10.01.5.1 1,4-Diheteropentalene Systems (1)

10.01.5.1.1 Electrophilic attack at carbon

The reaction of 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole **58** with chlorosulfonyl isocyanate (CSI) giving **59** was investigated (**Scheme 1**) <1996H(43)2361>. The higher reactivity for electrophilic reaction demonstrated the remarkably electron excessive nature of the system when compared with indole and pyrrole derivatives.



58 **59** 30%

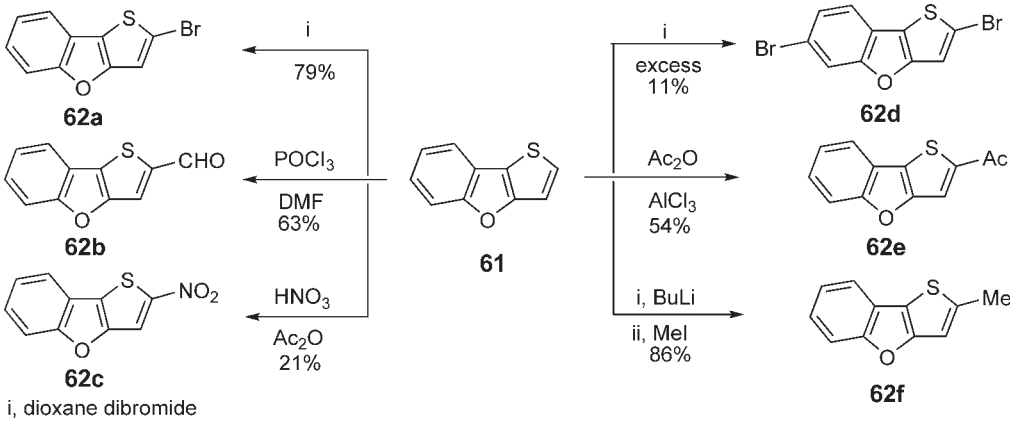
Scheme 1

Svoboda and co-workers studied substitution reactivity of thieno[3,2-*b*][1]benzofuran **61** <1997CCC1468> in comparison with the isomeric [1]benzothieno[3,2-*b*]furan **60**, which was already described <1993CCC2983>. They discovered that under electrophilic substitution conditions, the system **61** is more stable than **60**.



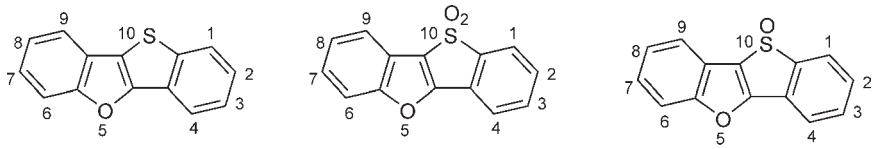
60 **61**

Electrophilic substitution reactions of **61** such as bromination, formylation, and acetylation or nitration take place at C-2, and compounds **62a–e** were formed. An electron–donating group in position 2 directs further electrophilic substitution into positions 3 and 6, whereas compounds with an electron acceptor in position 2 are substituted exclusively at position 6. Metallation with butyllithium took place at position 2 of **61** (**Scheme 2**) <1997CCC1468>.



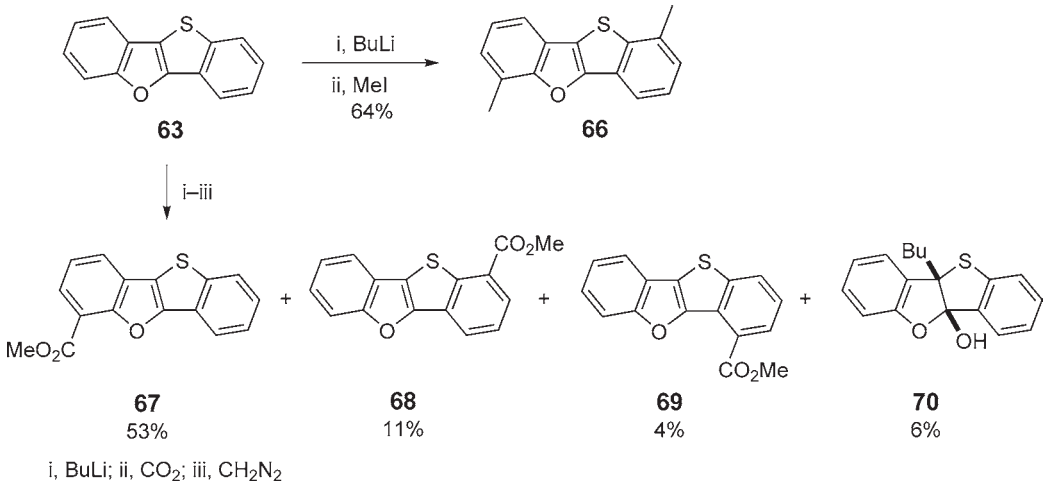
Scheme 2

Electrophilic substitution and metallation reactions of [1]benzothieno[3,2-*b*][1]benzofuran **63** were studied <2000CCC58>. Bromination, acetylation, benzoylation, formylation, and nitration usually afforded inseparable mixtures of 2- and 7-substituted derivatives as the main products. Disubstitution reactions preferably led to 2,7-disubstituted derivatives. [1]Benzothieno[3,2-*b*][1]benzofuran-10,10-dioxide **64** and [1]benzothieno[3,2-*b*][1]benzofuran-10-oxide **65** can be selectively obtained by oxidation of **63**. Mononitration of **64** and **65** led selectively to corresponding 7-nitro derivatives, respectively. Only sulfoxide **65** was successfully reduced.



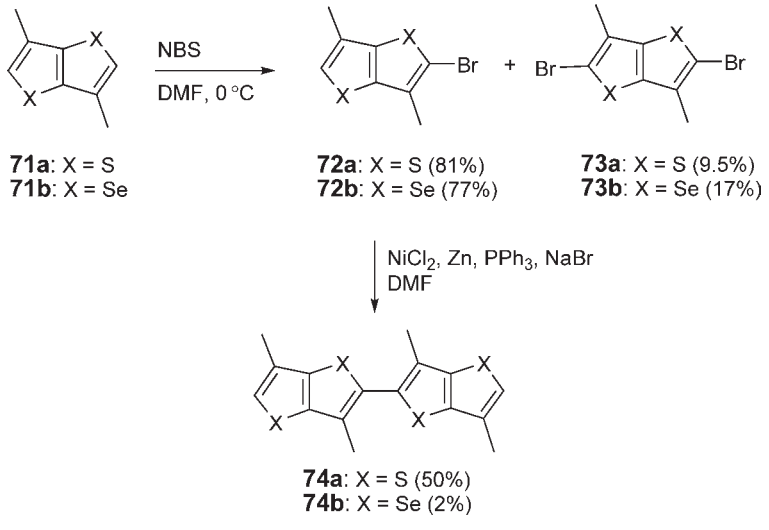
63 **64** **65**

Metallation of **63** with butyllithium preferably proceeds in positions 1 and 6; subsequent reaction with iodomethane or carbon dioxide led to the corresponding dimethyl derivative **66** or esters **67–69**. An unusual addition of butyllithium to the central double bond of **63** was also observed to a small extent producing **70** (**Scheme 3**) <2000CCC58>.



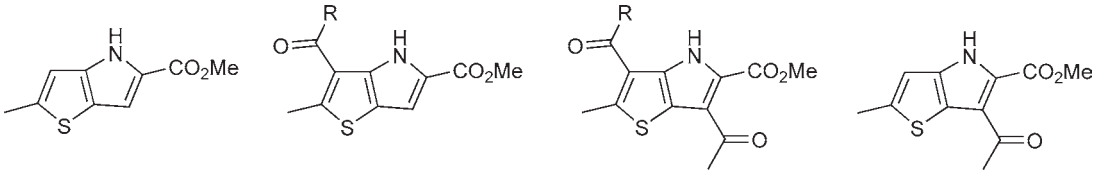
Scheme 3

Starting from 3,6-dimethylthieno[3,2-*b*]thiophene **71a** and 3,6-dimethylselenolo[3,2-*b*]selenophene **71b** <1994H(38)143>, their dimers, trimers, and tetramers, in which each thieno[3,2-*b*]thiophene unit and selenoloselenophene unit was regularly connected at their α-positions, were satisfactorily synthesized (**Scheme 4**) <1996T471>.



Scheme 4

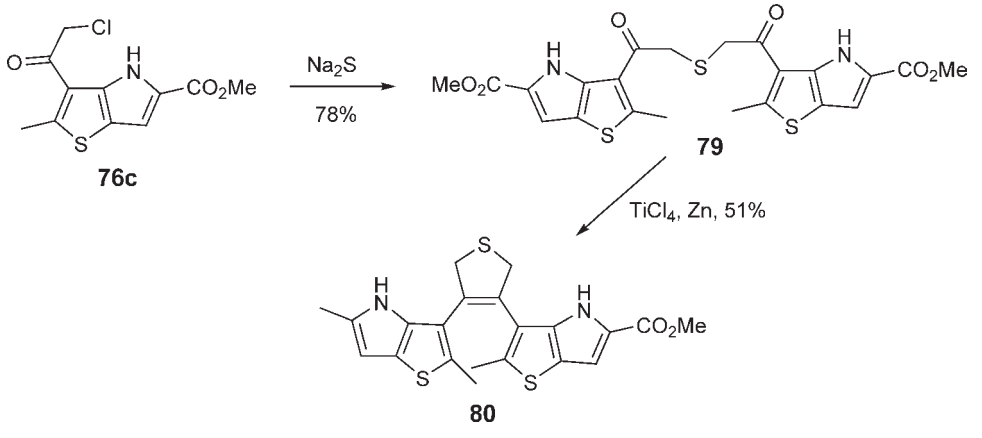
The influence of catalysts ($AlCl_3$ and $SnCl_4$), acid chlorides, and solvents (dichloroethane, nitromethane) in the acylation of methyl 2-methyl-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate **75** was studied. Conditions for the regioselective acylation processes were found and four types of compounds **76a–f, 77a–e**, and **78** were obtained.



75 | **76a–f** 63–77% | **77a–e** 62–78% | **78** 93%

	R		*R*		*R*		*R*
76a	Me	**76d**	$CHCl_2$	**77a**	Me	**77d**	$CHCl_2$
76b	Et	**76e**	CCl_3	**77b**	Et	**77e**	CCl_3
76c	$ClCH_2$	**76f**	Pr^i	**77c**	$ClCH_2$		

Thienopyrrole-based photochromic compound **80** was synthesized for the first time from **76c** via the intermediate **79** (**Scheme 5**) <2002OL387>.

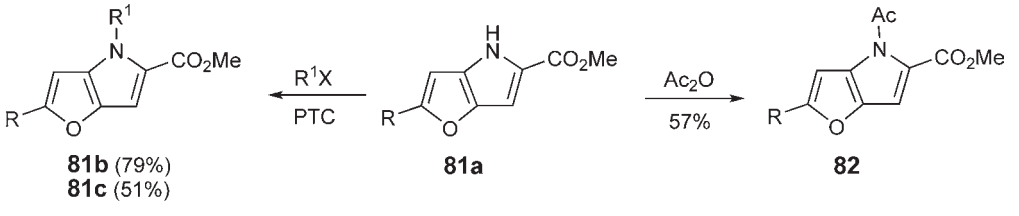


76c | **79** | **80**

Scheme 5

10.01.5.1.2 Electrophilic attack at nitrogen

Phase-transfer catalysis was found <1996CHEC-II(7)1> to be successful for N-substitution of the furo[3,2-*b*]pyrrole system. The reaction of **81a** with methyl iodide or benzyl chloride gave **81b** and **81c** derivatives. Methyl 4-acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole-5-carboxylate **82** was obtained by reacting **81a** in boiling acetic anhydride (**Scheme 6**) <2005CEC311>.



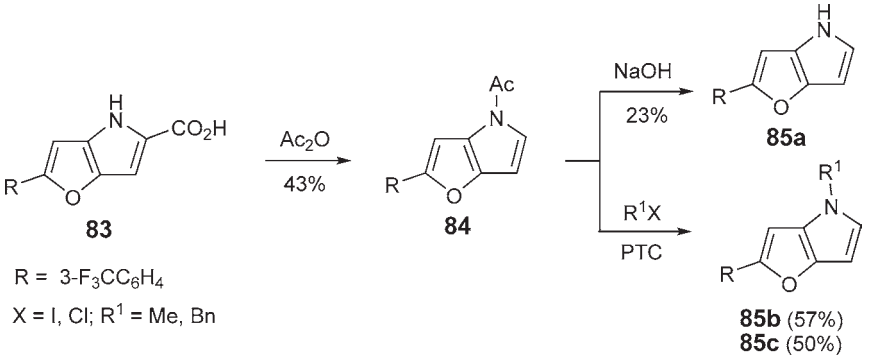
81b (79%)
81c (51%)

R = 3-$F_3CC_6H_4$
X = I, Cl; R^1 = Me, Bn

81a | **82**

Scheme 6

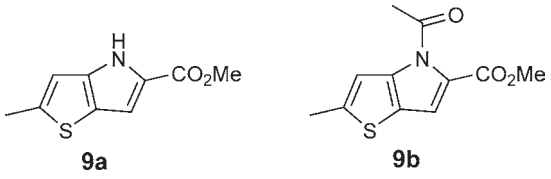
4-Acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole **84** was obtained during heating in boiling acetic anhydride of 2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid **83**, and it was used for preparing parent compound **85a** and the N-substituted compounds **85b** and **85c** (**Scheme 7**) <2005CEC311>.



83 **84**

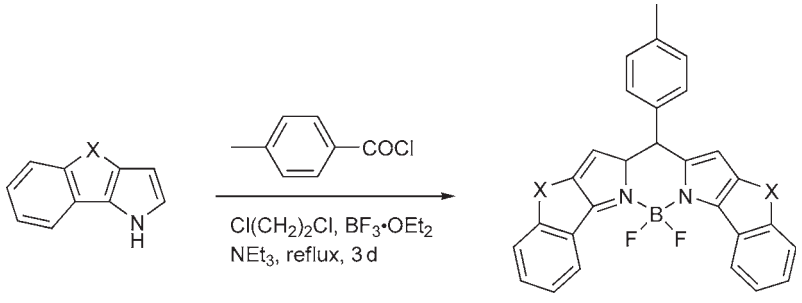
Scheme 7

The possibility of acetylating the pyrrole nitrogen atom of **9a** was investigated. The reaction was performed in the presence of different bases, and the highest yield of the corresponding compound **9b** was achieved for potassium *tert*-butoxide. As should be expected, even trace amounts of this compound are absent from the acylation products of thienopyrrole **9a** under Friedel–Crafts conditions <2002OL387>.



9a **9b**

Benzo[4,5]furo[3,2-*b*]pyrrole **86** and benzo[4,5]thieno[3,2-*b*]pyrrole **87** were used for the synthesis of new constrained aryl-substituted 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (BODIPY) dyes **86** and **89** <2000JOC2900>. Their fluorescence characteristics were investigated and compared with the unconstrained systems published by Burghart and co-workers (**Scheme 8**) <1998S1276, 1999JOC7813>.



86: X = O
87: X = S

88: X = O (22%)
89: X = S (3%)

Scheme 8

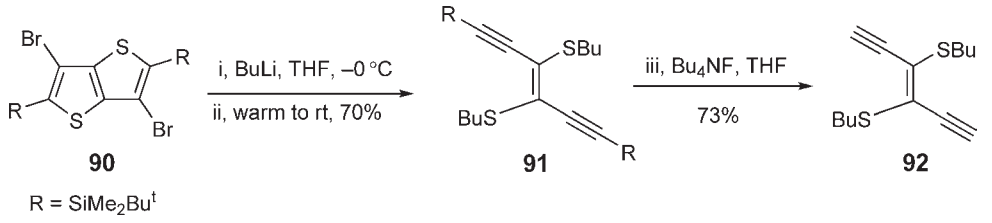
10.01.5.1.3 Electrophilic attack at sulfur

For the preparation of [1]benzothieno[3,2-*b*][l]benzofuran-10,10-dioxide **64**, hydrogen peroxide in acetic acid, 3-chloroperoxybenzoic acid, and also the urea–hydrogen peroxide adduct with phthalic anhydride were employed. All three methods provided **64** in excellent yields (88–94%). Monitoring the course of the reaction showed the

presence of the oxidation intermediate [l]benzothieno[3,2-*b*][l]benzofuran-10-oxide **65**, which can be selectively obtained from **63** with hydrogen peroxide in acetic acid at 40 °C <2000CCC58>.

10.01.5.1.4 Ring-opening reactions

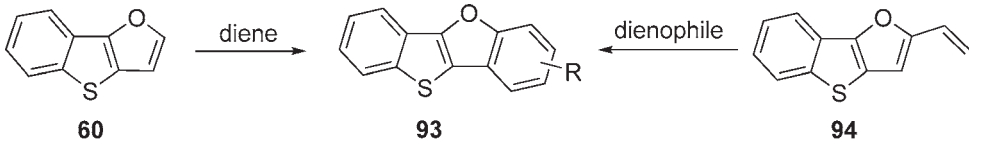
2,5-Disubstituted-3,6-dibromothieno[3,2-*b*]thiophenes **90** on treatment with 1.0 or 2.0 equiv of BuLi (THF, −78 °C) gave lithiated intermediates *via* Br–Li exchange, which on being allowed to warm up to ambient temperature were transformed (by a novel tandem ring-opening process) into polyfunctionated enediynes **91** or **92** (THF = tetrahydrofuran; **Scheme 9**) <1997CC2355>.



Scheme 9

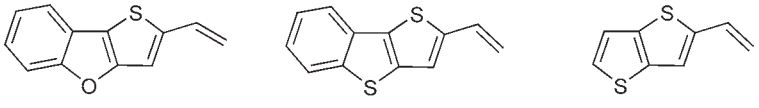
10.01.5.1.5 Cycloaddition reactions

It was shown <1998CCC681> that [1]benzothieno[3,2-*b*]furan **60**, due to its low furan aromaticity, possesses dienophilic behavior and reacts with electron-rich dienes with the formation of a new heterocyclic system [1]benzothieno[3,2-*b*][1]benzofuran **93**. Furthermore, it was reported <1999CCC389> that introduction of a vinyl moiety at C-2 of **57** created a reactive diene **94**, which reacted with various dienophiles. Thus, both cycloaddition reactions led to new derivatives of heterocycle **93** substituted in the benzofuran part of the heterocyclic system (**Scheme 10**).



Scheme 10

A reactivity study of the isomeric 2-vinylthieno[3,2-*b*][1]benzofuran **95** as well as of the structurally related 2-vinyl[1]thieno[3,2-*b*][1]benzothiophene **96** and 2-vinylthieno[3,2-*b*]thiophene **97** with dienophiles was performed by Svoboda and co-workers <2004TL2189>. Cycloaddition reactions were performed by heating **95–97** with dimethyl acetylenedicarboxylate (DMAD) to reflux in toluene under a nitrogen atmosphere.



The yields of the isolated products are summarized in **Table 7** and their structures are shown in **Figure 9**. The mechanism of formation of the fused system **98**, which involves a thiophene–thiopyran ring enlargement, is discussed <2004TL2189>.

The reactions of the furo[3,2-*b*]pyrroles and their benzo derivatives with DMAD have been described earlier <1996CHEC-II(7)1> and it was stated that the reaction course is influenced by the ring substituents. Recently, it was found that the 4-acetyl-2-[3-(trifluoromethyl)phenyl]furo[3,2-*b*]pyrrole **84** reacts with DMAD in acetonitrile at the α- and α'-positions of the pyrrole ring giving a [4+2] cycloadduct, which by subsequent 1,5-sigmatropic rearrangement gives the substituted benzo[*b*]furan **105** in 20% yield <2005CEC311>.

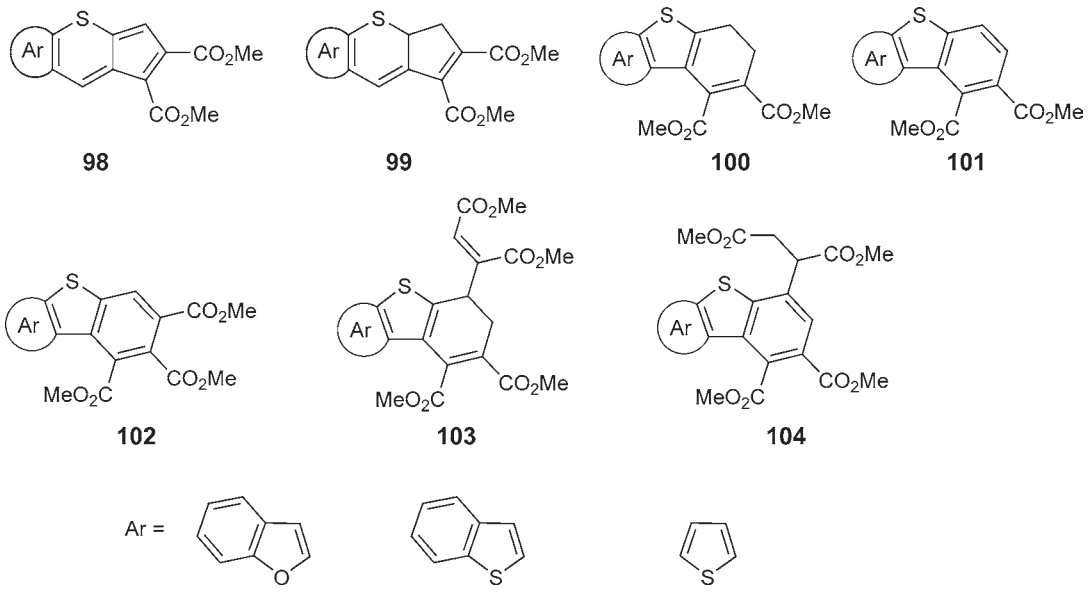
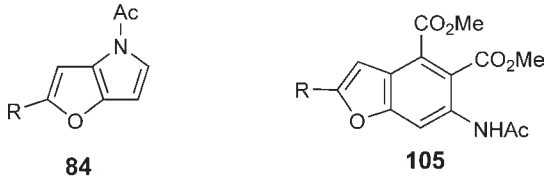


Figure 9 Structures of the isolated products **98–104**.

Table 7 Products distribution and yields (%)

98a	19	**99a**	16	**100a**	20	**101a**	20	**102a**	17	**103a + 104a**	3
98b	10	**99b**	11	**100b**	25	**101b**	21	**102b**	23	**103b + 104b**	2
98c	10	**99c**	4	**100c**	9	**101c**	11	**102c**	9	**103c + 104c**	6



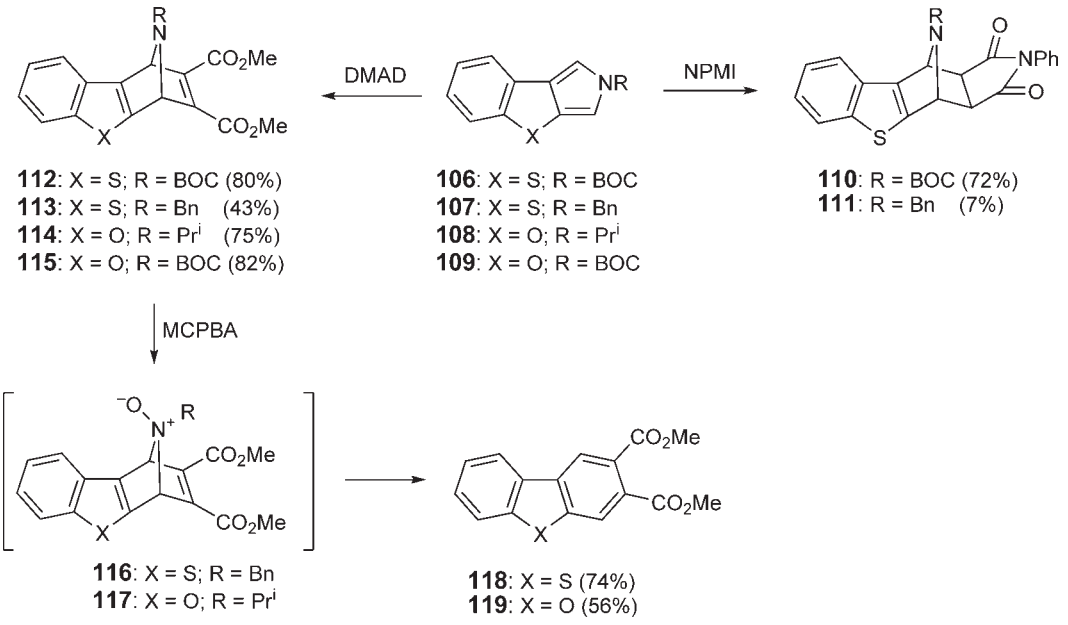
10.01.5.2 1,5-Diheteropentalene Systems (2)

10.01.5.2.1 Addition and cycloaddition reactions

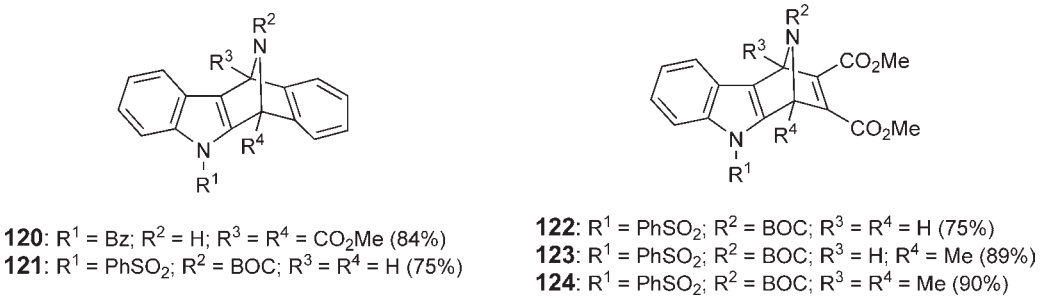
1,5-Diheteropentalene systems are very popular substrates for the investigation of cycloaddition reactions due to their diene character.

Diels–Alder reactions of *N*-substituted benzo[4,5]thieno[2,3-*c*]pyrroles **106**, **107** <2003T1477> and benzo[4,5]-furo[2,3-*c*]pyrroles **108**, **109** <1995T193> with *N*-phenylmaleimide (NPMI) and DMAD gave the corresponding *exo* cycloadducts **110–115** (**Scheme 11**). Oxidative extrusion of the nitrogen bridge in cycloadducts **113** and **114** *via* intermediates **116** and **117** afforded dibenzothiophene **118** <2003T1477> and dibenzofuran **119** <1995T193>.

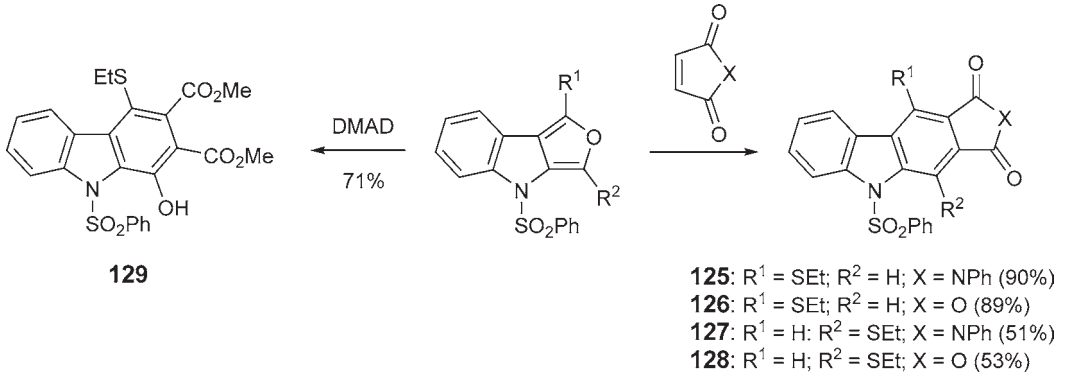
Good to excellent yields of cycloadducts **120–124** have been reported in the reactions of N^2,N^4-diprotected pyrrolo[3,4-*b*]indoles with benzyne and DMAD <1996TL3487, 1997TL8611>.



Scheme 11

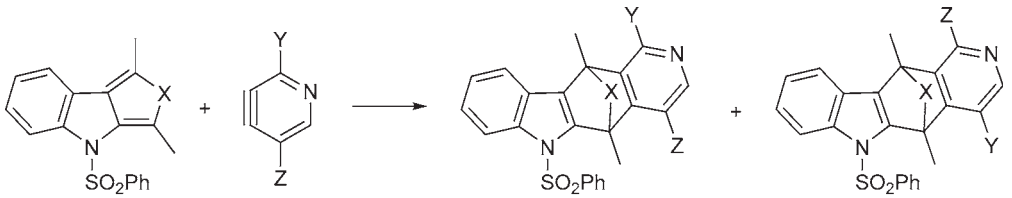


The furo[3,4-*b*]indoles undergo cycloaddition reactions with NPMI, maleic anhydride, and DMAD in the presence of *p*-TsOH to give the fused carbazoles **125–129**, products of the subsequent *in situ* ring-opening of the oxobridge of the intermediary cycloadducts (**Scheme 12**) <1996JOC6166>.



Scheme 12

The regioselectivity of 2,4-cycloaddition of furo- and pyrrolo[3,4-*b*]indoles with 3,4-didehydropyridines was studied <2001EJO4543>. The results of this key reaction step in the synthesis of ellipticines are summarized in Equation (1).

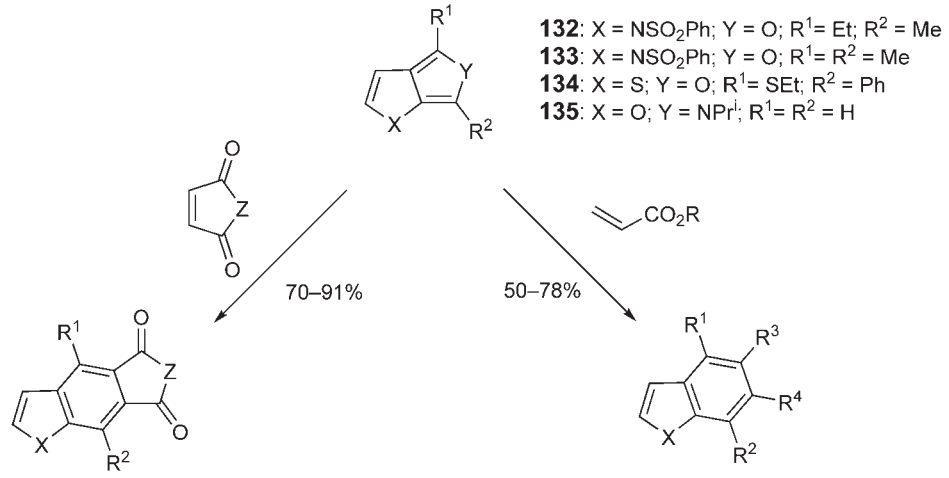


130 **131**

(1)

X	*Y*	*Z*	*Yield* (%)	*Ratio* **130**:**131**
O	Cl	H	88	2.4:1
O	Br	H	40	1:1
O	F	H	38	1.1:1
O	H	F	64	1:1
NH	Cl	H	44	1.7:1
NH	Br	H	28	1:1
N-BOC	Cl	H	52	1:1

The furo[3,4-*b*]pyrroles **132**, **133** <2002TL6983>, thieno[2,3-*c*]furan **134**, <1996JOC6166>, and furo[2,3-*c*]pyrrole **135** <1995T193>, which are mostly less stable than the benzo-fused analogues, were trapped by Diels–Alder reactions with dienophiles followed by elimination of water to give the corresponding indoles **136–139**, **140**, **141**, and benzothiephenes **142**, **143**, and **144** with good to excellent yields (**Scheme 13**).



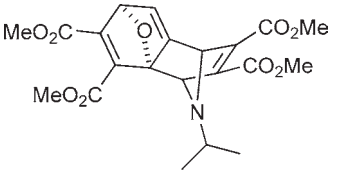
132: X = NSO_2Ph; Y = O; R^1= Et; R^2 = Me
133: X = NSO_2Ph; Y = O; R^1= R^2 = Me
134: X = S; Y = O; R^1= SEt; R^2 = Ph
135: X = O; Y = NPr^i; R^1= R^2 = H

136: X = NSO_2Ph; R^1= Et; R^2 = Me; Z = NPh
137: X = NSO_2Ph; R^1= Et; R^2 = Me; Z = NMe
138: X = NSO_2Ph; R^1= Et; R^2 = Me; Z = O
139: X = NSO_2Ph; R^1= R^2 = Me; Z = O
140: X = S; R^1= SEt; R^2 = Ph; Z = NPh
141: X = S; R^1= SEt; R^2 = Ph; Z = O

142: X = NSO_2Ph; R^1= Et; R^2 = Me; R^3= CO_2Et; R^4= H
143: X = NSO_2Ph; R^1= Et; R^2 = Me; R^3= H; R^4= CO_2Et
144: X = S; R^1= SEt; R^2 = Ph; R^3 = H; R^4= CO_2Me

Scheme 13

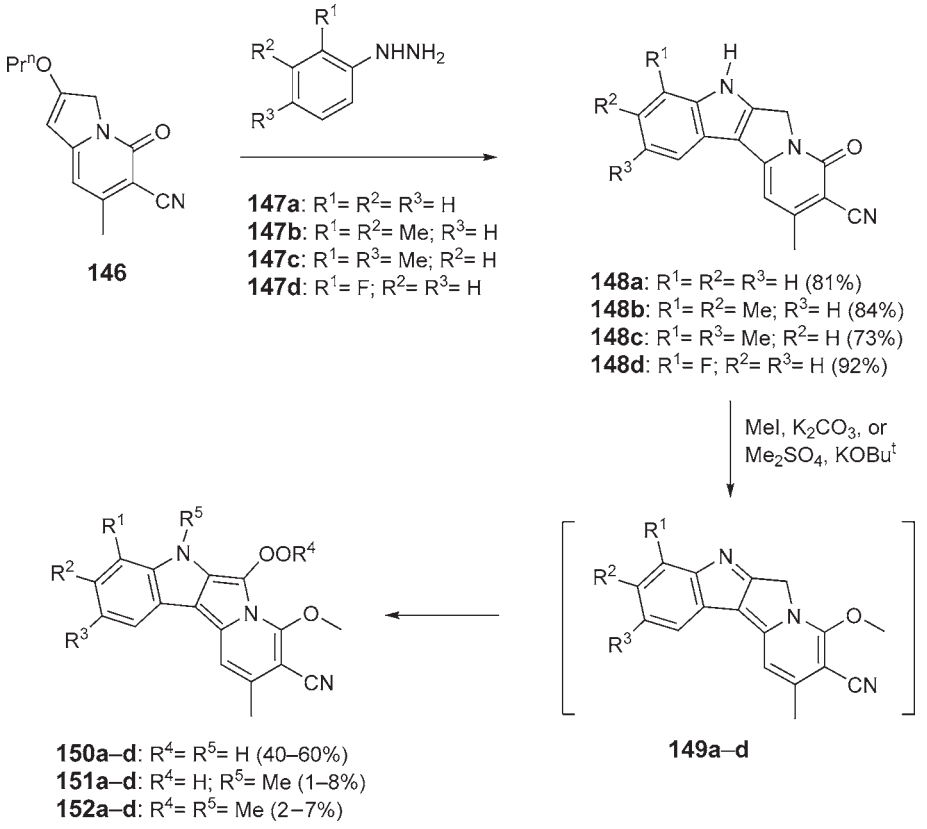
The Diels–Alder reaction of furo[2,3-*c*]pyrrole **135** with either 1 or 2 equiv of DMAD in benzene gave a stable 1:2 cycloadduct **145** in 88% yield <1995T193>.



145

10.01.5.2.2 Radical reactions

The new tetracyclic 9*H*,10*H*-indolizino[1,2-*b*]indole-1-one derivatives **148a–d** have been synthesized by modified Fischer indole synthesis from the enol ether **146** of 2,5-dihydroxy-7-methyl-6-cyano-indolizine and arylhydrazines **147a–d** (**Scheme 14**) <2001JOC426>. Attempted *N*-methylation of **148a–d** produced a series of autoxidized products including 10-hydroperoxy-1-methoxyindolizino[1,2-*b*]indole **150a–d** as the major product accompanied with methyl peroxides **151a–d** and **152a–d** and 2-formyl-3-(pyridine-2-yl)indole **152a** and **152c** derivatives as the minor products.



Scheme 14

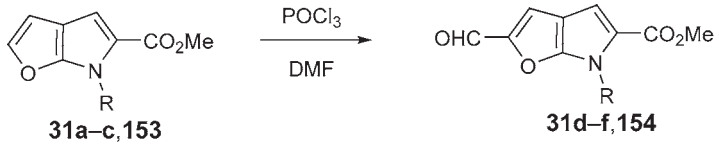
A plausible mechanism for the autoxidation is postulated based on the isolation of some intermediates. The reaction is thought to proceed through intermediates **149a–d** followed by a novel type of autoxidation. The first

step involves abstraction of the indole NH proton in **148** and subsequent *O*-methylation to form azaenolate derivatives **149**, which tautomerize to the enamines. The second step (autooxidation) is thought to be a free-radical process.

10.01.5.3 1,6-Diheteropentalene Systems (3)

10.01.5.3.1 Electrophilic attack at carbon

The formylation of methyl furo[2,3-*b*]pyrrole-5-carboxylate **31a** and its variously *N*-substituted derivatives **31b, 31c**, and **153** has been studied and **31d–f**, and **154** were obtained (Equation 2) <1997MOL69, 1999CCC1135>.

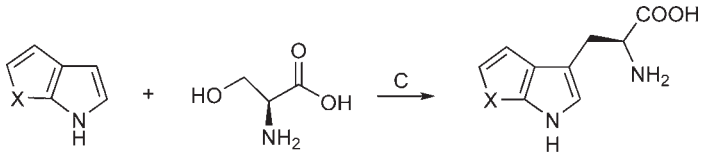


	R	*Yield* (%)
31d	H	70
31e	Me	80
31f	Bn	90
154	MOM	84

(2)

10.01.5.3.2 Enzyme catalyzed attack at carbon

4-(6*H*-Thieno[2,3-*b*]pyrrolyl)-L-alanine **155** and 4-(6*H*-selenolo[2,3-*b*]pyrrolyl)-L-alanine **156**, have been synthesized *via* reactions of thieno[2,3-*b*]pyrrole **32** and selenolo[2,3-*b*]pyrrole **34**, respectively, with L-serine (Equation 3). The reactions are catalyzed by *Salmonella typhimurium* tryptophan synthase <1995BML1133, 1999BML637, 1999HCO305>.



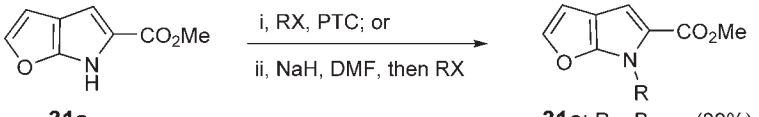
32: X = S
34: X = Se
C = tryptophan synthase

155: X = S (47%)
156: X = Se (35%)

(3)

10.01.5.3.3 Electrophilic attack at nitrogen

Compounds **31c** and **153** were obtained by direct substitution of the *in situ*-prepared sodium salt of **31a** in dimethylformamide (DMF; **Scheme 15**). This method was more efficient <1999CCC321> than the preparation of **31b** and **31c** from **31a** under phase-transfer catalysis conditions <1997MOL69>.

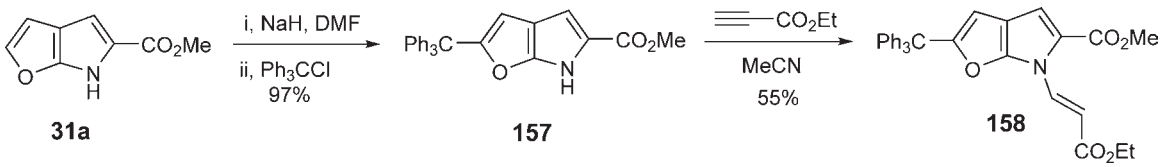


31a

31c: R = Bn (38%)
153: R = MOM (72%)

Scheme 15

An attempt to introduce a bulky triphenylmethyl substituent at *N*-6 of methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **31a** led to C-2 triphenylmethyl substitution giving the product **157**, which with ethyl propynoate in acetonitrile gave the Michael addition product **158** <2000PJC207> (**Scheme 16**).



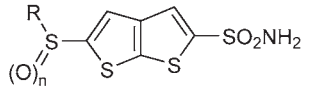
31a **157** **158**

Scheme 16

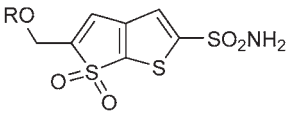
10.01.5.3.4 Electrophilic attack at sulfur

A series of 5-substituted thieno[2,3-*b*]thiophene-2-sulfonamides **159–162** and 6,6-dioxidothieno[2,3-*b*]thiophene-2-sulfonamides **163–166** were prepared for evaluation as inhibitors of carbonic anhydrase II. Oxidation of 5-substituted thieno[2,3-*b*]thiophene-2-sulfonamides provided the first examples of 6,6-dioxidothieno[2,3-*b*]thiophene-2-sulfonamides. It was found that compounds with the more acidic SO_2NH_2 group showed higher activity for human carbonic anhydrase II.

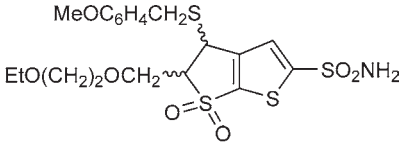
The structure of the benzoate derivative **166** was established by X-ray analysis, confirming the selective oxidation of the sulfur atom at the 6-position of thieno[2,3-*b*]thiophene-2-sulfonamides. The activated double bond of the cyclic vinyl sulfone moiety readily underwent nucleophilic addition, which was exemplified by reaction of **165** with 4-methoxybenzylthiol in the presence of base to provide a mixture of **167** and **168** <1999JHC249>.



159: R = $(CH_2)_4Me$; *n* = 2 (84%)
160: R = $(CH_2)_3OH$; *n* = 2 (85%)
161: R = $(CH_2)_3$(morpholin-4-yl); *n* = 1 (35%)
162: R = $(CH_2)_3$(morpholin-4-yl); *n* = 2 (10%)



163: R = H (81%)
164: R = $(CH_2)_2OMe$ (70%)
165: R = $(CH_2)_2OEt$ (60%)
166: R = COC_6H_5 (39%)



167: 4,5-*cis* (59%)
168: 4,5-*trans* (25%)

10.01.5.3.5 Addition and cycloaddition reactions

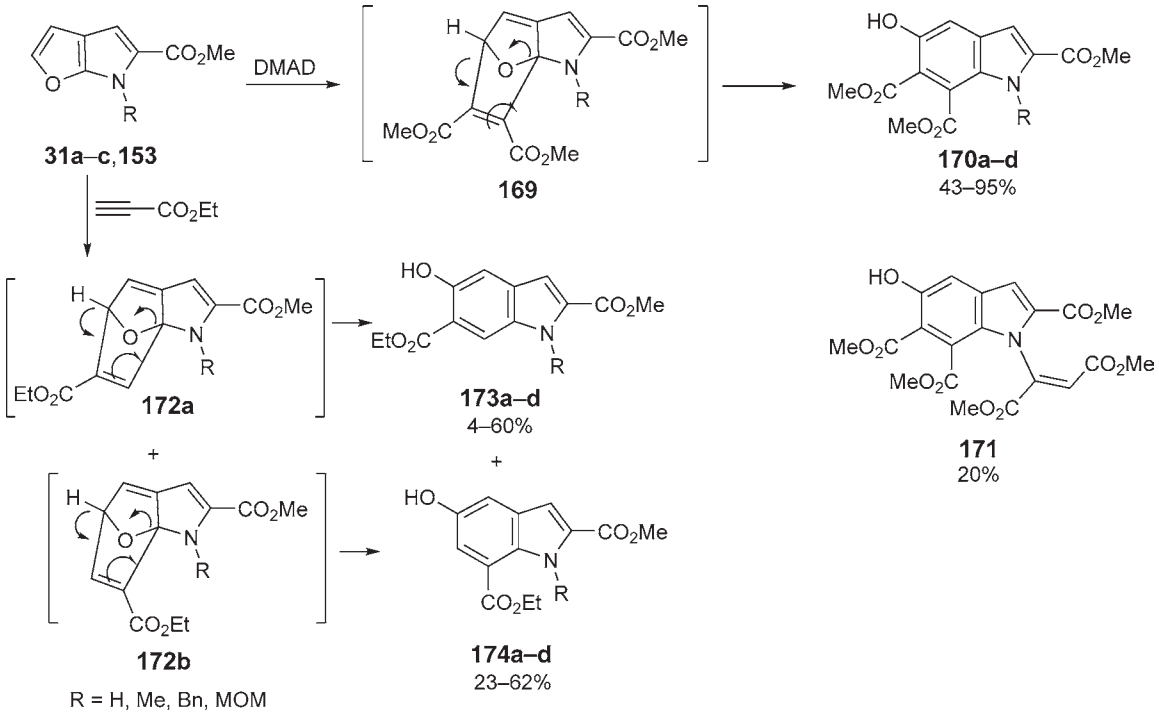
The reaction of the methyl furo[2,3-*b*]pyrrole-5-carboxylate **31a** and its 6-methyl derivative **31b** with DMAD was partly described in <1996CHEC-II(7)1>. This reaction was later studied in more detail <1999CCC321>, and it was found that methyl furo[2,3-*b*]pyrrole-5-carboxylates **31a–c** and **153** with DMAD or ethyl propynoate gave substituted indoles which are not accessible by other routes (**Scheme 17**). The reactions of **31b–c** and **153** with DMAD in acetonitrile gave only cycloaddition products **170b–d** in good yields. The intermediate (undetected) cycloadducts **169** are obviously labile, and are transformed by opening of the furan ring into the corresponding indole derivatives **170b–d**. The reaction of methyl 6*H*-furo[2,3-*b*]pyrrole-5-carboxylate **31a** under the same conditions gave **170a** along with a minor Michael-type addition product **171**. The reactions with ethyl propynoate afforded two regioisomeric adducts **172a** and **172b** which rearranged into minor methyl 6-ethoxycarbonyl-5-hydroxyindole-2-carboxylates **173** and major methyl 7-ethoxycarbonyl-5-hydroxyindole-2-carboxylates **174**. The ratio of the products **173**/**174** is not dependent on the substituent attached in position 6 of the furo[2,3-*b*]pyrrole system. Comparing the course of the Diels–Alder reactions of furo[2,3-*b*]pyrroles with their [3,2-*b*] isomers, it was concluded that the [2,3-*b*] system is a more active diene than its [3,2-*b*] isomer.

10.01.5.4 2,5-Diheteropentalene Systems (4)

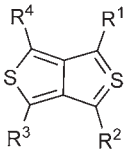
Thieno[3,4-*c*]thiophenes have been the subject of chemical investigations since the early 1970s <1996CHEC-II(7)1>. Despite this interest, only a few isolable compounds of this class have been prepared.

Thieno[3,4-*c*]thiophene **40** <1988CC959> and its 4,6-dimethyl- **175** <1967JA3639, 1973JA2558>, 4,6-bis-(methoxycarbonyl)- **176** <1973JA2558>, and 4,6-di-*tert*-butyl- **177** as well as 4,6-di-*tert*-butyl-1,3-dimethyl **178** derivatives <1990BCJ1026, 1992BCJ2821> have been generated *in situ* and characterized by trapping with *N*-phenylmaleimide (NPMI) On the other hand, 1,3,4,6-tetraphenyl- **179** <1969JA3952, 1973JA2561>, l,3,4,6-tetrakis(alkylthio)- **180** <1985JA5801, 1988JA1793, 1988JHC559, 1989CC223, 1991CC520>, l,3,4,6-tetra-2-thienyl- **181** <1991JOC78>, l,3-dicyano-4,6-dibromo- **182**, 4,6-dibromo-1,3-bis(methoxycarbonyl)- **183**, l,3,4,6-tetrabromo- **184**

<1994JOC2223>, as well as 1,4-bis(*tert*-butylthio)-3,6-diphenyl- **185** and 1,4-bis(*tert*-butylthio)-3,6-di-2-thienylthieno[3,4-*c*]thienophenes **186** <1998JOC163> were successfully synthesized as isolable compounds. These isolable thieno [3,4-*c*]thiophenes owe their stability to steric hindrance together with resonance and the electron-withdrawing effects of the substituents.



Scheme 17

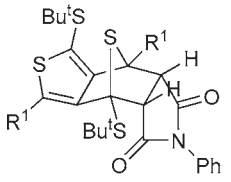


Compound	R^1	R^2	R^3	R^4
40	H	H	H	H
175	H	H	Me	Me
176	H	H	CO_2Me	CO_2Me
177	H	H	Bu^t	Bu^t
178	Me	Me	Bu^t	Bu^t
179	Ph	Ph	Ph	Ph
180	SR	SR	SR	SR
181	2-Thienyl	2-Thienyl	2-Thienyl	2-Thienyl
182	Br	Br	CN	CN
183	Br	Br	CO_2Me	CO_2Me
184	Br	Br	Br	Br
185	SBu^t	Ph	SBu^t	Ph
186	SBu^t	2-Thienyl	SBu^t	2-Thienyl

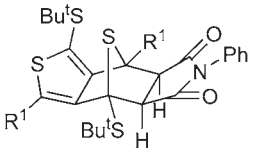
10.01.5.4.1 Cycloaddition reactions

The 1,4-bis(*tert*-butylthio)-3,6-diphenyl- **185** and 1,4-bis(*tert*-butylthio)-3,6-di-2-thienylthieno[3,4-*c*]thienophenes **186** were reacted with NPMI or DMAD in refluxing benzene <1998JOC163>. The reaction of **185** with NPMI for 3 days gave the *endo*- and *exo*-cycloadducts (**187a** and **188a**) in 46% and 35% yields, respectively, while that with **186** gave the *endo*- and *exo*-cycloadducts (**187b** and **188b**) in 69% and 13% yields, respectively.

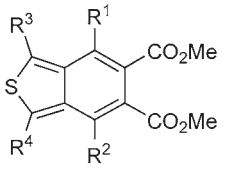
Thus, the reactions of **185** and **186** with NPMI gave predominantly the *endo*-cycloadducts and the *endo*-selectivity was higher in the reaction with **184**, being different from that in the reaction with 1,3,4,6-tetrakis(alkylthio)thieno[3,4-*c*]thiophenes which gave selectively the *exo*-cycloadducts <1988JHC559>. These results indicate that the *endo*/*exo*-selectivity is governed by the steric effect of the substituents in the 4- and 6-positions on the cycloaddition in the 1- and 3-positions. The reaction of **185** with DMAD for 4 days gave 1,4-bis(*tert*-butylthio)-5,6-bis(methoxycarbonyl)-3,7-diphenylbenzo[*c*]thiophene **189** in 29% yield by loss of a sulfur atom from the cycloadduct.



187a: R^1 = Ph
187b: R^1 = 2-Thienyl



188a: R^1 = Ph
188b: R^1 = 2-Thienyl

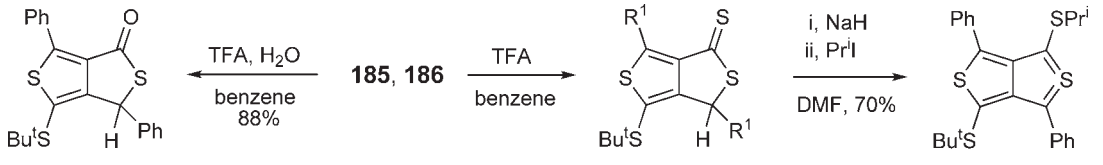


189: $R^1 = R^4$ = Ph; $R^2 = R^3$ = SBu^t
192: $R^1 = R^2$ = H; $R^3 = R^4$ = CO_2Me

The unstable 1,3-bis(methoxycarbonyl)selenolo- **190** and 1,3-bis(methoxycarbonyl)tellurolo[3,4-*c*]thiophene **191** underwent Diels–Alder reaction with DMAD to produce cycloadducts, which lost selenium or tellurium and collapsed to tertracarbomethoxybenzo[*c*]thiophene **192** in low yields <2002OL1193>.

10.01.5.4.2 Other Reactions

The protonation of **185** and **186** with trifluoroacetic acid (TFA) gave 4-(*tert*-butylthio)-3,6-diphenyl- **193** and 4-(*tert*-butylthio)-3,6-di(2-thienyl)thieno[3,4-*c*]thiophene-1(3*H*)-thione **194** (**Scheme 18**). The treatment of **193** with sodium hydride and then isopropyl iodide led to 4-(*tert*-butylthio)-3,6-diphenyl-1-(isopropylthio)thieno[3,4-*c*]thiophene **195** by the regeneration of the thieno[3,4-*c*]thiophene ring system, thus making possible the synthesis of other alkylthio-substituted thieno[3,4-*c*]thiophene derivatives. When the reaction of **185** with TFA was carried out in the presence of water, 4-(*tert*-butylthio)-3,6-diphenylthieno[3,4-*c*]thiophene-1(3*H*)-one **196** was produced <1998JOC163>.



196

193: R^1 = Ph (97%)
194: R^1 = 2-Thienyl (98%)

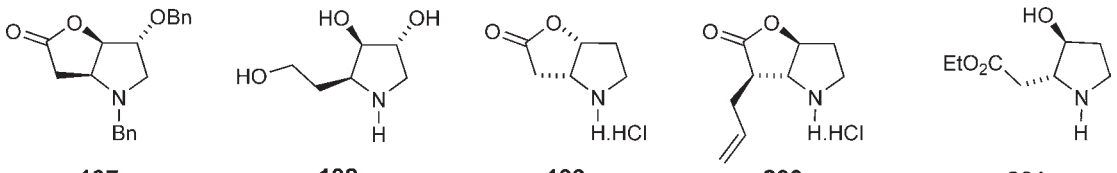
195

Scheme 18

10.01.6 Reactivity of Nonconjugated Rings

10.01.6.1 1,4-Diheteropentalene Systems

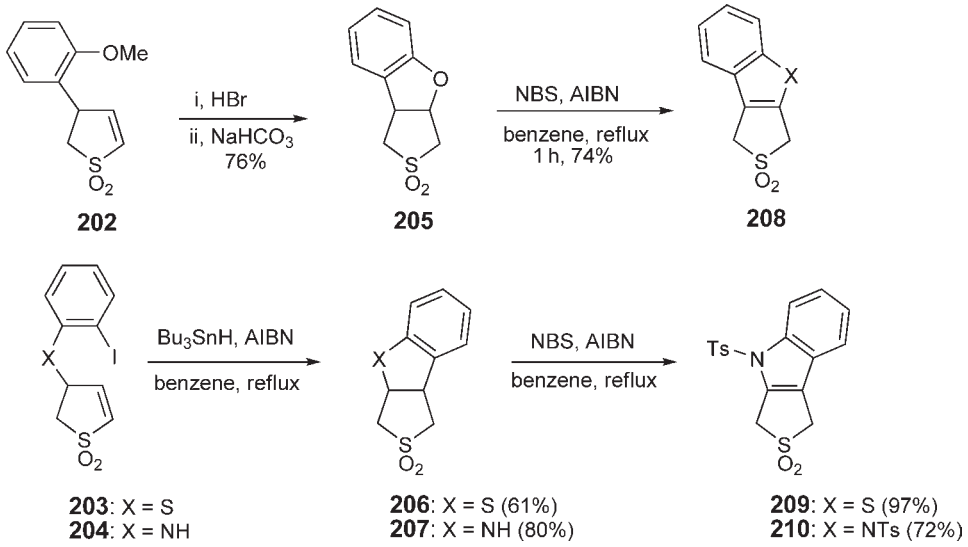
The reduction of the 4-benzyl-6-benzyloxyhexahydrofuro[3,2-*b*]pyrrol-2-one **197** <2004TL8363> with lithium aluminium hydride (LAH) in dry THF afforded the primary alcohol, which, on removal of the *O*- and *N*-benzyl groups by hydrogenolysis (10% Pd/C in MeOH), afforded 1,4,5-trideoxy-1,4-imino-L-*xylo*-hexitol **198**. Hexahydrofuro[3,2-*b*]pyrrol-2-one **199** (latterly known as the Geissman–Waiss lactone) and structurally related pyrrolidine *trans*-lactone **200** prepared from **201** have recently been introduced as scaffolds for designing inhibitors of serine proteases with the aim, among others, of developing therapies for respiratory and cardiovascular diseases <2004TA3461>.



197 198 199 200 201

10.01.6.2 1,5-Diheteropentalene Systems

The 1,3,3,3a,8a-tetrahydro-8-oxa-2-thia- **205**, 1,3,3,3a,8a-tetrahydro-2,8-dioxa- **206**, and 3,3a,8,8a-tetrahydro-1*H*-2-thia-8-aza-cyclopenta[*a*]indene-2,2-dioxide **207** were prepared by Michael addition or radical cyclization from the corresponding sulfones **202–204** and brominated-dehydrobrominated (in the case of **207**, after tosylation) to produce 1,5-diheteropentalene systems **208–210**, respectively <1997TL5315>.



202 **205** **208**

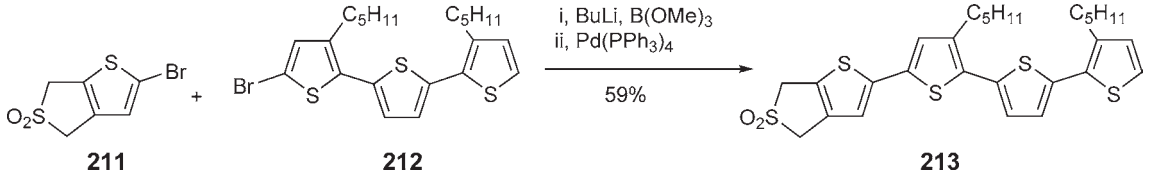
203: X = S
204: X = NH

206: X = S (61%)
207: X = NH (80%)

209: X = S (97%)
210: X = NTs (72%)

Scheme 19

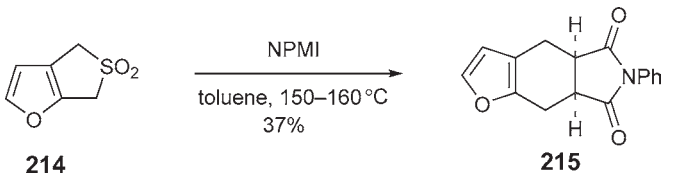
The 2-bromo-4,6-dihydrothieno[3,4-*b*]thiophene-5,5-dioxide **211** was used in the synthesis of 5-(5,5-dioxo-5,6-dihydro-4*H*-5λ^6-thieno[3,4-*b*]thiophen-2-yl)-3,3″-dipentyl[2,2′;5′,2″]terthiophene **213** by Suzuki cross-coupling reaction with 5-bromo-3,3″-dipentyl-[2,2′;5′,2″]terthiophene **212** (**Scheme 20**) <1998S1372>.



211 **212** **213**

Scheme 20

The cycloaddition of the 4,6-dihydrothieno[3,4-*b*]furan-5,5-dioxide **214** with NPMI in toluene at 150–160 °C gave product **215** (**Scheme 21**) <1997MI299>.

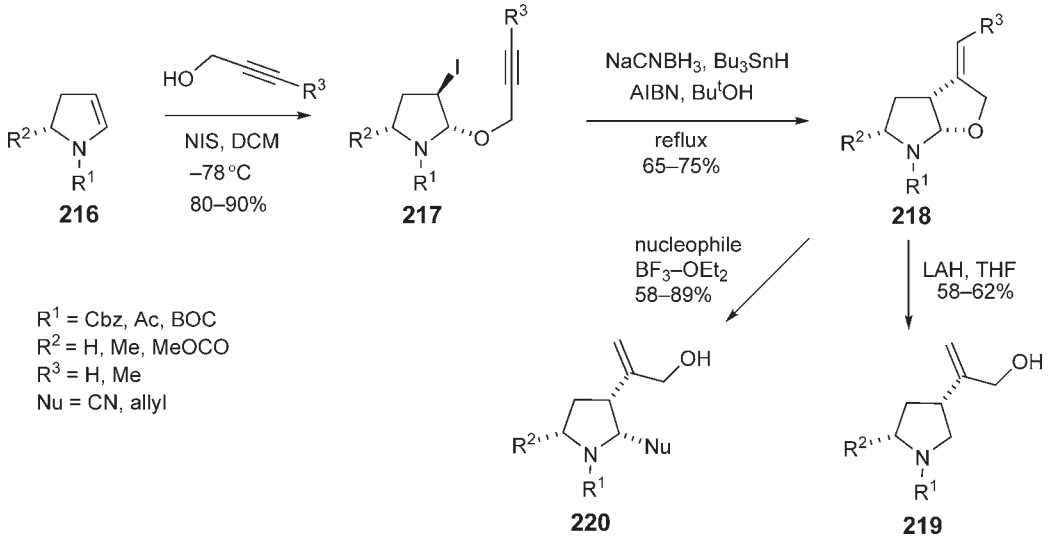


214 215

Scheme 21

10.01.6.3 1,6-Diheteropentalene Systems

An interesting strategy for pyrrolidine α,β-functionalization has been developed <2005T1221>, starting from readily available endocyclic enamine derivatives. A two-step heteroannulation procedure involving iodoetherification of *N*-acyl-2-pyrrolines **216** giving **217** followed by radical cyclization gave access to the bicyclic compounds **218** which can be used in further transformations to form substituted pyrrolidines **219** and **220** (**Scheme 22**).



216 217 218 220 219

Scheme 22

10.01.6.4 2,5-Diheteropentalene Systems

Pyrrole-fused 3-sulfolenes **221** undergo thermal extrusion of sulfur dioxide to produce highly reactive *o*-quinodimethanes which can be trapped in Diels–Alder reactions (**Scheme 23**) <1997H(46)199, 1997TL3639>. The resulting cycloadducts **222–227** are important starting compounds in porphyrin synthesis.

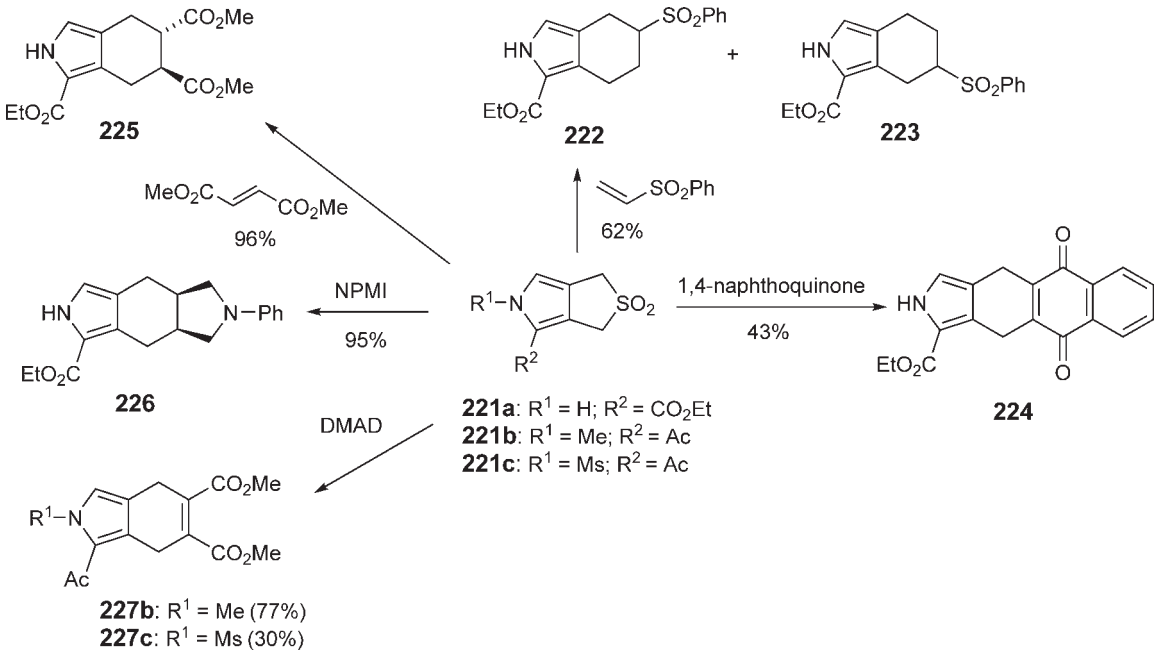
10.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.01.7.1 1,4-Diheteropentalene Systems

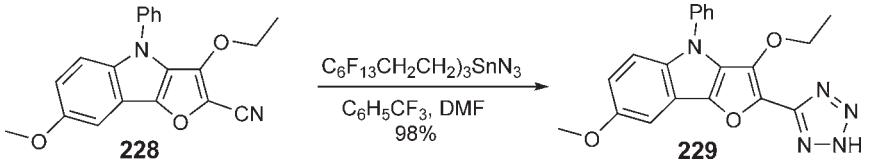
10.01.7.1.1 Carboxylic acids and derivatives

By the hydrolysis of esters **81a–c**, the corresponding acids **83a–c** were formed. The 2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxylic acid **83a** was decarboxylated in acetic anhydride to 4-acetyl-2-[3-(trifluoromethyl)-phenyl]furo[3,2-*b*]pyrrole **84** (see 10.01.05.1.2, **Scheme 7**).

The substituted furo[3,2-*b*]indole-2-carbonitrile **228** with a fluorous tin azide ($(C_6F_{13}CH_2CH_2)_3SnN_3$) gave the corresponding tetrazole derivative **229** (Equation 4) <1999T8997>.



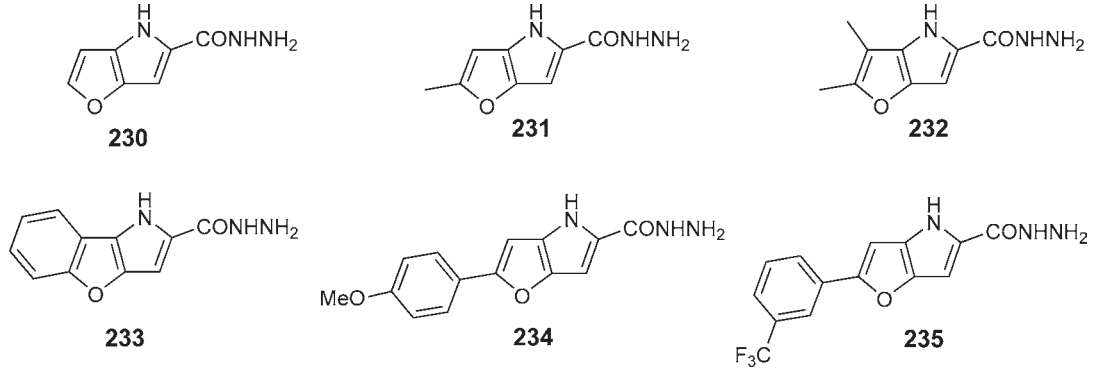
Scheme 23

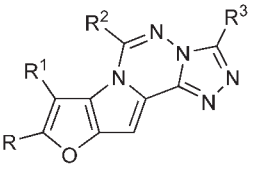


(4)

.

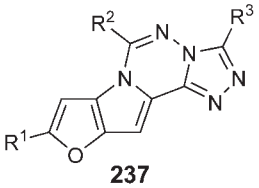
The synthetic utilization of 4*H*-furo[3,2-*b*]pyrrole-5-carbohydrazide **230**, 2-aryl-substituted and 1*H*-benzo[4,5]-furo[3,2-*b*]pyrrole-5-carbohydrazide **233** was described earlier <1996CHEC-II(7)1>. According to procedures described in <1996CHEC-II(7)1> from the corresponding hydrazides **230–235**, the new derivatives **236a–m** <1995CCC709, 1999CPA125>, **237a–j** <1997CCC1613>, **238a** and **238b** <1997CPA398>, pentacyclic polyaza systems **239a–e** <1997CPA412> and **240a–c** <2005CEC311> were prepared.





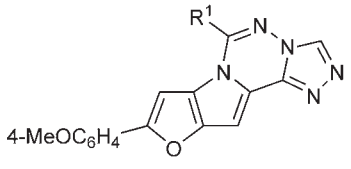
236

236	*R*	R^1	R^2	R^3	236	*R*	R^1	R^2	R^3
a	Me	H	H	H	**h**	Me	Me	Me	Me
b	Me	H	H	Me	**i**	Me	Me	Et	H
c	Me	H	Me	H	**j**	Me	Me	H	Et
d	Me	H	Me	Me	**k**	Me	Me	Me	Et
e	Me	Me	H	H	**l**	Me	Me	Et	Me
f	Me	Me	H	Me	**m**	Me	Me	Et	Et
g	Me	Me	Me						

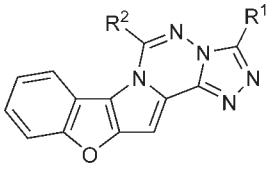


237

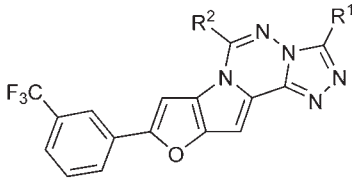
237	R^1	R^2	R^3	237	R^1	R^2	R^3
a	H	H	Et	**f**	Me	H	Et
b	H	Me	Et	**g**	Me	Me	Et
c	H	Et	H	**h**	Me	Et	H
d	H	Et	Me	**i**	Me	Et	Me
e	H	Et	Et	**j**	Me	Et	Et



238a: R^1 = Me
238b: R^1 = Et



239	R^1	R^2
a	H	Et
b	Me	Et
c	Et	Et
d	Et	H
e	Et	Me

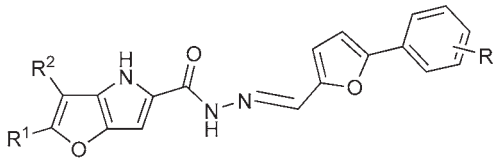


240	R^1	R^2
a	H	H
b	H	Me
c	H	Et

The reactions of substituted furo[3,2-*b*]pyrrole-5-carbohydrazides with 5-arylfuran-2-carbaldehydes, 4,5-disubstituted furan-2-carbaldehydes, and thiophene-2-carbaldehyde have been studied <2005CEC622>. The advantage of microwave (MW) irradiation on some of these reactions was reflected in the reduced reaction time and increased yields (**Table 8**). The series of substituted hydrazones **241–246** was obtained from these reactions.

Table 8 Comparisons between 'classical' and MW reaction

	Classical conditions		*MW reaction*	
Compound	*Reaction time (min)*	*Yield (%)*	*Reaction time (min)*	*Yield (%)*
241a	10	48	3	73
241e	15	32	5	55
241g	30	53	4.5	65
242a	30	66	3	85
242c	50	65	2	90
242e	20	26	5	55



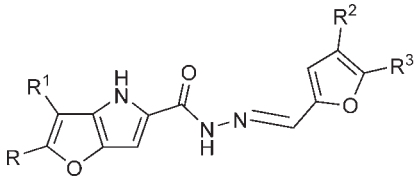
241	*R*	R^1	R^2
a	4-NO_2	H	H
b	3-NO_2	H	H
c	4-Cl	H	H
d	4-Br	H	H
e	3-CF_3	H	H
f	H	H	H
g	4-Me	H	H

242	*R*	R^1	R^2
a	4-NO_2	Me	H
b	3-NO_2	Me	H
c	4-Cl	Me	H
d	4-Br	Me	H
e	3-CF_3	Me	H
f	H	Me	H
g	4-Me	Me	H

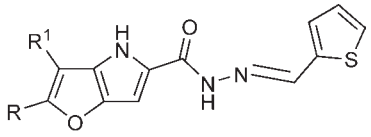
243	*R*	R^1	R^2
a	4-NO_2	Me	Me
b	3-NO_2	Me	Me
c	4-Cl	Me	Me
d	4-Br	Me	Me
e	3-CF_3	Me	Me
f	H	Me	Me
g	4-Me	Me	Me

244	*R*	R^1	R^2
a	4-NO_2	Ph	H
b	3-NO_2	Ph	H
c	4-Cl	Ph	H
d	4-Br	Ph	H
e	3-CF_3	Ph	H
f	H	Ph	H
g	4-Me	Ph	H

Yields of **241a–g** = 25–75%; **242a–g** = 21–66%; **243a–g** = 33–76%; **244a–g** = 34–97%

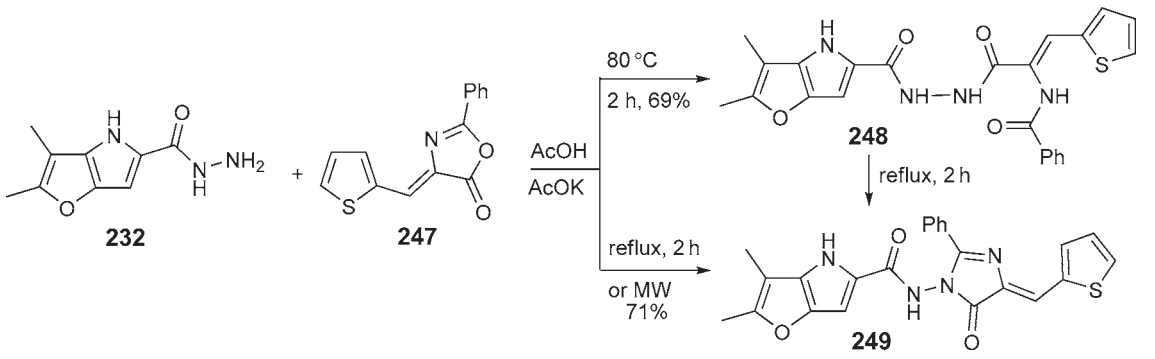


245	*R*	R^1	R^2	R^3	*Yield (%)*
a	H	H	H	H	74
b	Me	H	H	H	56
c	Me	Me	H	H	55
d	Ph	H	H	H	75
e	H	H	Me	Me	42
f	Me	H	Me	Me	45
g	Me	Me	Me	Me	56
h	Ph	Me	Me	Me	78

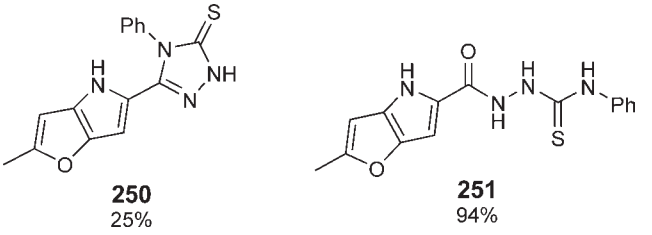


246	*R*	R^1	*Yield (%)*
a	H	H	65
b	Me	H	59
c	Me	Me	66
d	Ph	H	66

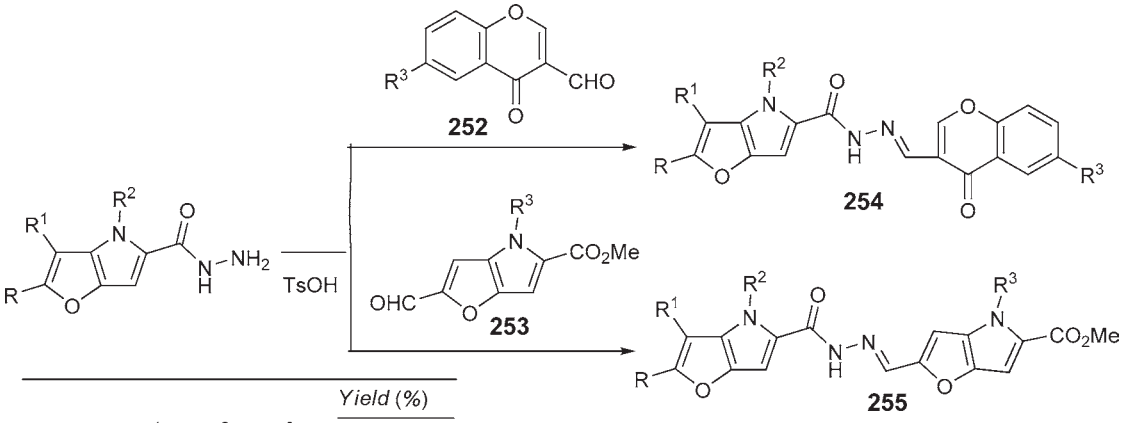
Reaction of **232** with 4-substituted 1,3-oxazol-5(4*H*)-one **247** led to diacylhydrazines **248** or to imidazole derivatives **249** depending on the reaction temperature (**Scheme 24**). 1,2,4-Triazole-3-thione **250** was obtained by a two-step sequence from **232** with phenyl isothiocyanate and subsequent base-catalyzed cyclization of thiosemicarbazide **251**. The effects of hydrazones **241–246** on inhibition of photosynthetic electron transport in spinach chloroplasts and chlorophyll content in the antialgal suspensions of *Chlorella vulgaris* were investigated <2005CEC622>.



Scheme 24



Substituted hydrazones **254** and **255** were synthesized by the reaction of the corresponding furo[3,2-*b*]pyrrole-5-carbohydrazides with 6-substituted 4-oxochromene-3-carbaldehydes **252** and methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylates **253** under MW irradiation as well as by the classical method(C). The beneficial effect of the MW irradiation on these reactions was a shortening of the reaction time and an increase in the yields <2005CCC2101> (**Scheme 25**).



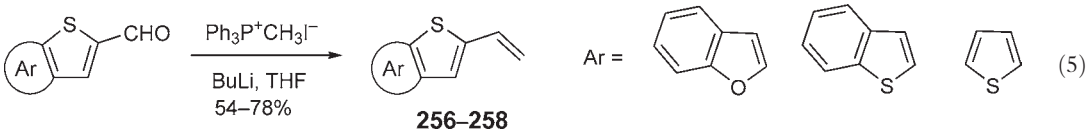
					Yield (%)	
254	*R*	R^1	R^2	R^3	*MW*	*C*
a	Ph	H	H	H	86	80
b	Ph	H	H	Cl	83	80
c	H	H	Bn	NO_2	80	72
d	Me	H	H	Cl	86	83
e	Me	H	Bn	H	85	74
f	Me	Me	Bn	NO_2	79	73
g	H	H	H	H	77	76
h	H	H	H	NO_2	81	72
i	H	H	H	Me	79	75
j	Me	Me	Me	Cl	77	73
k	$CH=(CH)_2=CH$		H	H	83	81

					Yield (%)	
255	*R*	R^1	R^2	R^3	*MW*	*C*
a	Me	Me	H	H	94	81
b	$CH=(CH)_2=CH$		H	Me	79	77

Scheme 25

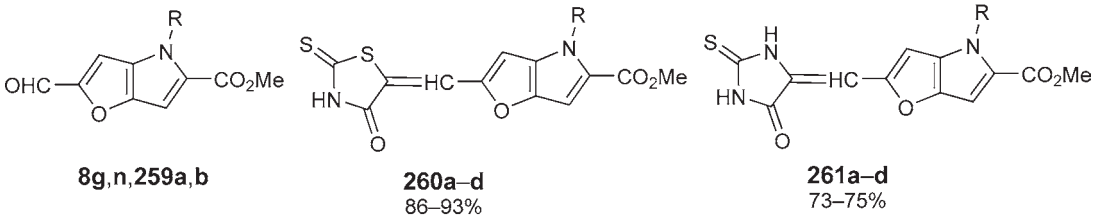
10.01.7.1.2 Aldehydes

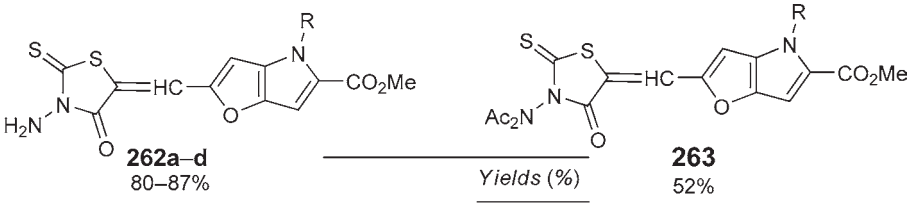
The 2-vinyl derivatives **256–258** were obtained by standard Wittig methylenation of the corresponding aldehydes <1996CCC888, 1997CCC1468> (Equation 5) with methylene(triphenyl)phosphorane in 54–78% yield after chromatographic purification.



(5)

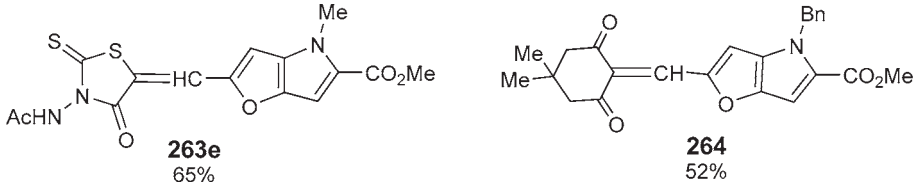
A large series of condensation products **260–264** were obtained from methyl 2-formylfuro[3,2-*b*]pyrrole-5-carboxylates **8g**, **8n**, **259a**, and **259b** by reaction with various heterocyclic active methylene compounds and the effect of MW irradiation on the reactions was studied. This resulted in a shortening of the reaction times to achieve comparable yields <2000ARK409>. The compound **264** was prepared only under MW irradiation <1999CCC1135>.





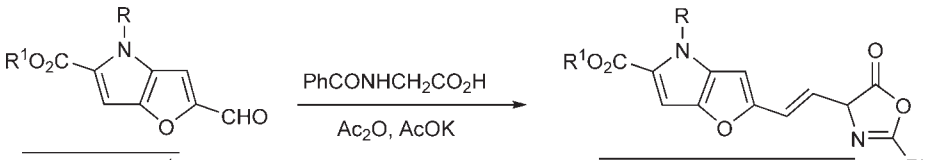
R = H, Me, Bn, MOM

	Yields (%)	
Compound	*MW*	*C*
260a	88	87
260c	89	90
261b	75	75



The condensation of furo[3,2-*b*]pyrrole-type aldehydes **8g** and **265–267** with hippuric acid was carried out in dry acetic anhydride catalyzed by potassium acetate as is shown in **Scheme 26**. The product methyl and ethyl 2-[(*E*)-(5-oxo-2-phenyl-1,3-oxazol-5(4*H*)-ylidene)methyl]furo[3,2-*b*]pyrrol-5-carboxylates **268a–d** were obtained. The course of the reaction was compared with the reaction of 5-arylated furan-2-carbaldehydes with hippuric acid. It was found that the carbonyl group attached at C-2 of the fused system **8** is less reactive than the carbonyl group in 5-arylated furan-2-carbaldehydes in this reaction <2004MOL11>. The configuration of the carbon–carbon double bond was determined using two-dimensional (2-D) NMR spectroscopic measurements and confirmed the (*E*) configuration of the products.

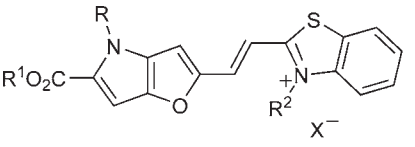
The condensation reaction of some selected furo[3,2-b]pyrrole aldehydes (**8g**, **266**, **267**) with benzothiazolium salts was carried out in refluxing methanol with pyridine as catalyst giving **269a–d** <2004MOL241>.



	R	R^1
89	H	Me
265	H	Et
266	Me	Et
267	Bn	Et

268	R	R^1	Yield (%)
a	H	Me	53
b	H	Et	74
c	Me	Et	90
d	Bn	Et	81

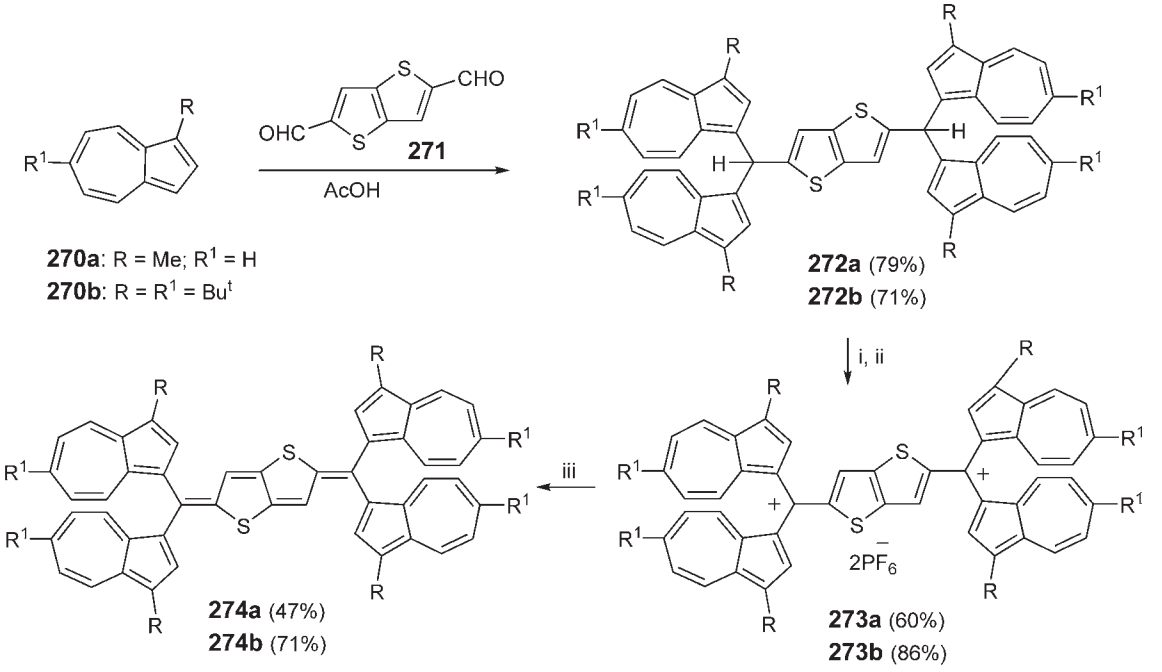
Scheme 26



269

269	R	R^1	R^2	X	Yield (%)
a	H	Me	Me	I	61
b	H	Me	Bn	Br	70
c	Me	Et	Bn	Br	48
d	Bn	Et	Bn	Br	67

The stable di(1-azulenyl)thieno[3,2-*b*]thiophene-2,5-diyl spacers **273a** and **273b** were prepared by hydride abstraction of the corresponding 2,5-bis[bis(methyl and 3,6-di-*tert*-butyl-1-azulenyl)methyl]thieno[3,2-*b*]thiophenes **272a** and **272b**, the synthesis of which was established by the reaction of 1-methyl- and 1,6-di-*tert*-butylazulenes **270a** and **270b** with thieno[3,2-*b*]thiophene-2,5-dicarbaldehyde **271** (**Scheme 27**). The dications **273** showed high stability with large pK_R+ values. The electrochemical behavior of **273** was examined by cyclic voltammetry (CV). Formation of the thienoquinoid products **274** from **273** was characterized by UV–Vis spectroscopy under electrochemical reduction conditions. Chemical reduction of **273** with Zn powder in acetonitrile afforded **274** as deep-colored crystals, which exhibited rather high electron-donating ability <2001JOC2470>.



270a: R = Me; R^1 = H
270b: R = R^1 = Bu^t

272a (79%)
272b (71%)

274a (47%)
274b (71%)

273a (60%)
273b (86%)

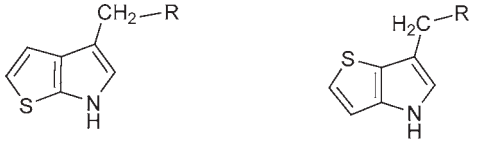
i, DDQ; ii, HPF_6; iii, electrochemical reduction, or Zn powder in MeCN

Scheme 27

10.01.7.2 1,6-Diheteropentalene Systems

10.01.7.2.1 Carboxylic acids and derivatives

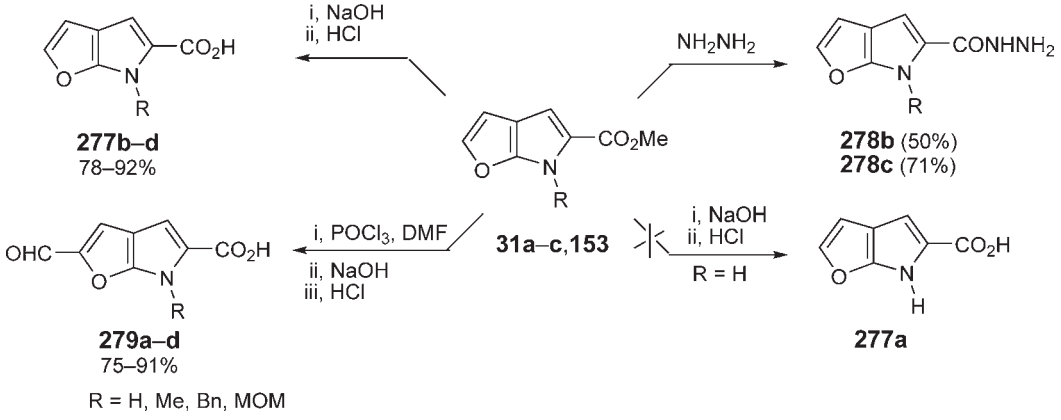
The potassium salts **275a**, **276a** of thieno analogues of indole-3-acetic acid were made by saponification of esters **275b**, **276b** with potassium hydroxide. This salt was stable neat or in water solution for several weeks at room temperature if protected from light. All efforts to obtain the corresponding acid, by mild acidic treatment of the salt and extractive workup, resulted in resinous product <1995T10323>.



275a,**b** **276a**,**b**

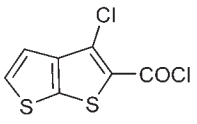
a: R = CO_2K
b: R = CO_2Et

6-Substituted furo[2,3-*b*]pyrrole-5-carboxylic acids **277b–d** were prepared by alkaline hydrolysis of the corresponding esters **31b**,**c** or **153**. By refluxing the compounds **31b**,**c** or **153** with hydrazine in ethanol, the corresponding hydrazides **278b–d** were formed. Attempts to synthesize 6*H*-analogue **277a** under the same conditions were unsuccessful. Methyl 2-formylfuro[2,3-*b*]pyrrole-5-carboxylates **31d–f** or **154**, obtained from **31b**, **31c**, or **153**, on hydrolysis gave acids **279a–d** (**Scheme 28**). The failure to prepare 6*H*-furo[2,3-*b*]pyrrole-5-carboxylic acid **277a** by this route was rationalized by *ab initio* calculations <2000PJC207>.

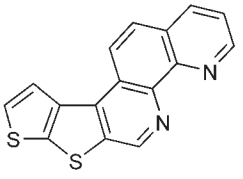


Scheme 28

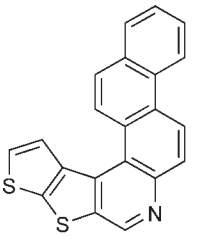
Castle and co-workers <1996JHC119, 1996JHC185, 1997JHC1597, 1998JHC1441> used 3-chlorothieno[2,3-*b*]thiophene-2-carbonyl chloride **280** in the synthesis of the appropriate amides, which by oxidative photocyclization gave novel polycyclic heterocyclic ring systems: thieno[3′,2′:4,5]thieno[2,3-*c*][l,10]phenanthroline **281**, thieno[3′,2′:4,5]thieno[2,3-*c*]naphtho[2,1-*f*]quinoline **282** and thieno[3′,2′:4,5]thieno[2,3-*c*]naphtho[1,2-*g*]quinoline **283**, thieno[3′,2′:4,5]thieno[2,3-*c*]naphtho[1,2-*f*]quinoline **284**, thieno[3′,2′:4,5]thieno[2,3-*c*]naphtho[1,2-*f*]-[1,2,4]triazolo[3,4-*a*]quinoline **286**, thieno[3′,2′:4,5]thieno[2,3-*c*]naphtho[1,2-*f*]tetrazolo[1,5-*a*]quinoline **288**, benzo[*h*]thieno[3′,2′:4,5]thieno[2,3-*c*]quinoline **285**, benzo[*f*]thieno[3′,2′:4,5]thieno[2,3-*c*]quinoline **287**, benzo[*f*]thieno[3′,2′:4,5]thieno[2,3-*c*]tetrazolo[l,5-*a*]quinoline **289**, and benzo[*f*]thieno[3′,2′:4,5]thieno[2.3-*c*][1,2,4]triazolo[4,3-*a*]-quinoline **290**.



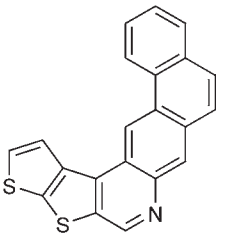
280



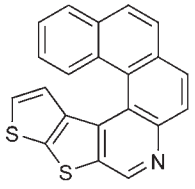
281
75%



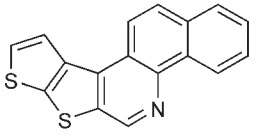
282
60%



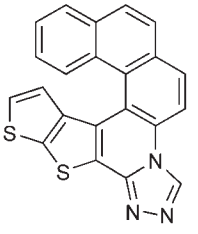
283
63%



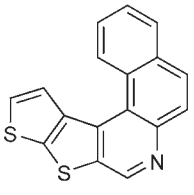
284
63%



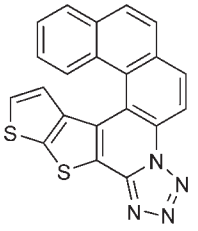
285
67%



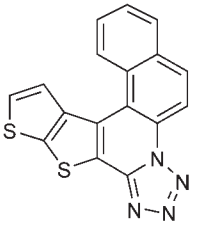
286
59%



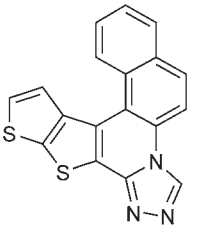
287
49%



288
58%

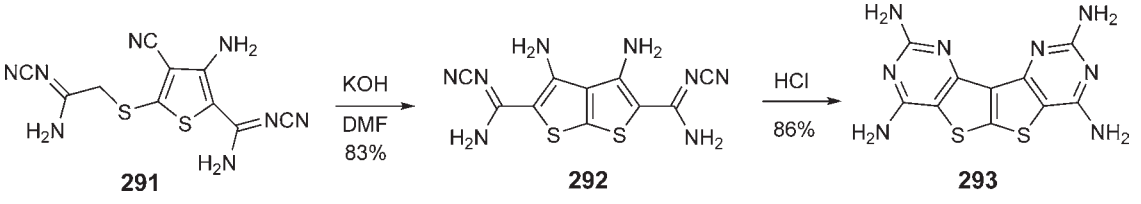


289
51%



290
88%

A tetrasubstituted thiophene **291** with a catalytic amount of base gave 3,4-diamino-N'^{2},N'^{5}-dicyanothieno[2,3-*b*]thiophene-2,5-dicarboximidamide **292**, from which, by heating in methanol in the presence of HCl, 1,3,6,8-tetraaminopyrimido[4″,5″:4′,5′]thieno[3′,2′:4,5]thieno-[2,3-*d*]pyrimidine **293** was prepared (**Scheme 29**) <1996T1011>.



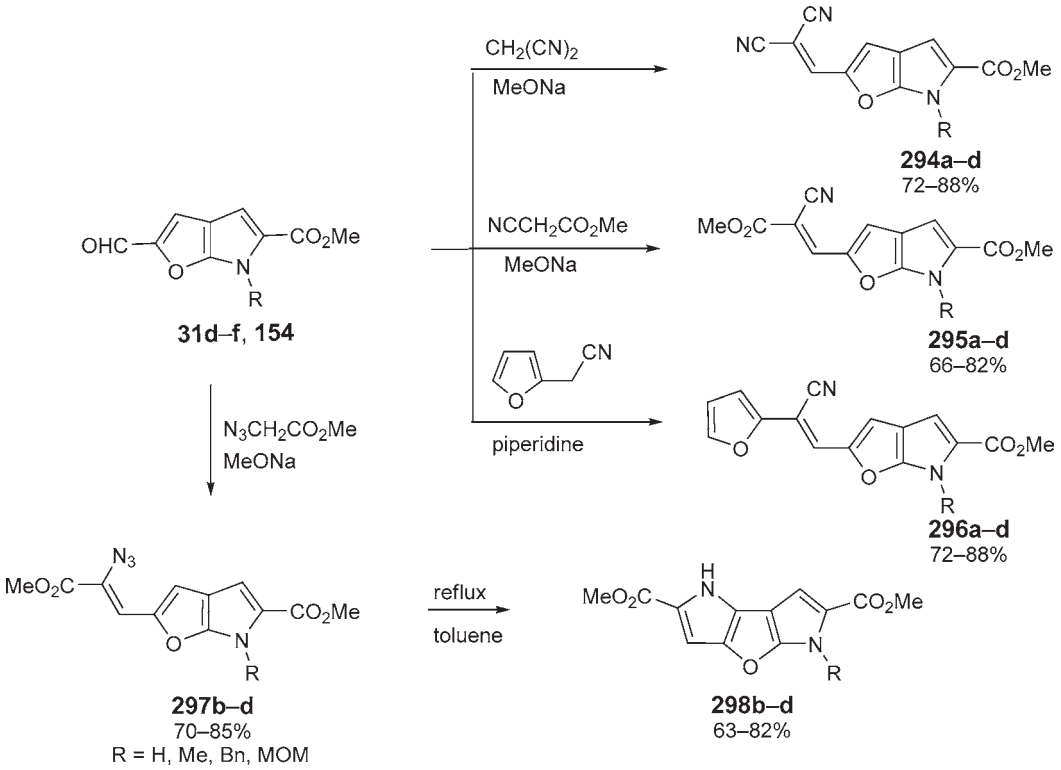
291 **292** **293**

Scheme 29

10.01.7.2.2 Aldehydes

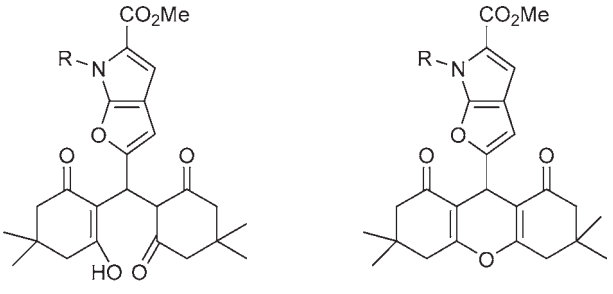
The reactions of methyl 2-formyl-6*H* or 6-substituted furo[2,3-*b*]pyrrole-5-carboxylates **31d–f** or **154** <1997MOL69, 1999CCC1135> with malononitrile, methyl cyanoacetate, and 2-furylacetonitrile, respectively, afforded the corresponding methyl 2-(2,2-dicyanovinyl)-6*H*- or 6-substituted furo[2,3-*b*]pyrrole-5-carboxylates **294a–d**, methyl 2-[2-cyano-2-(methoxycarbonyl)vinyl]-6*H*- or 6-substituted furo[2,3-*b*]pyrrole 5-carboxylates **295a–d**, and methyl

2-[2-cyano-2-(2-furyl)vinyl]- 6*H*- or 6-sustituted furo[2,3-*b*]pyrrole-5-carboxylates **296a–d**. Reaction of **31e**, **31f**, or **154** with methyl azidoacetate in the presence of sodium methoxide was found to proceed smoothly to give **297b–d**, the thermolysis of which was carried out in boiling toluene leading to substituted furo[2,3-*b*:4,5-*b*′]dipyrroles **298b–d** (**Scheme 30**) <1999CCC1135>.



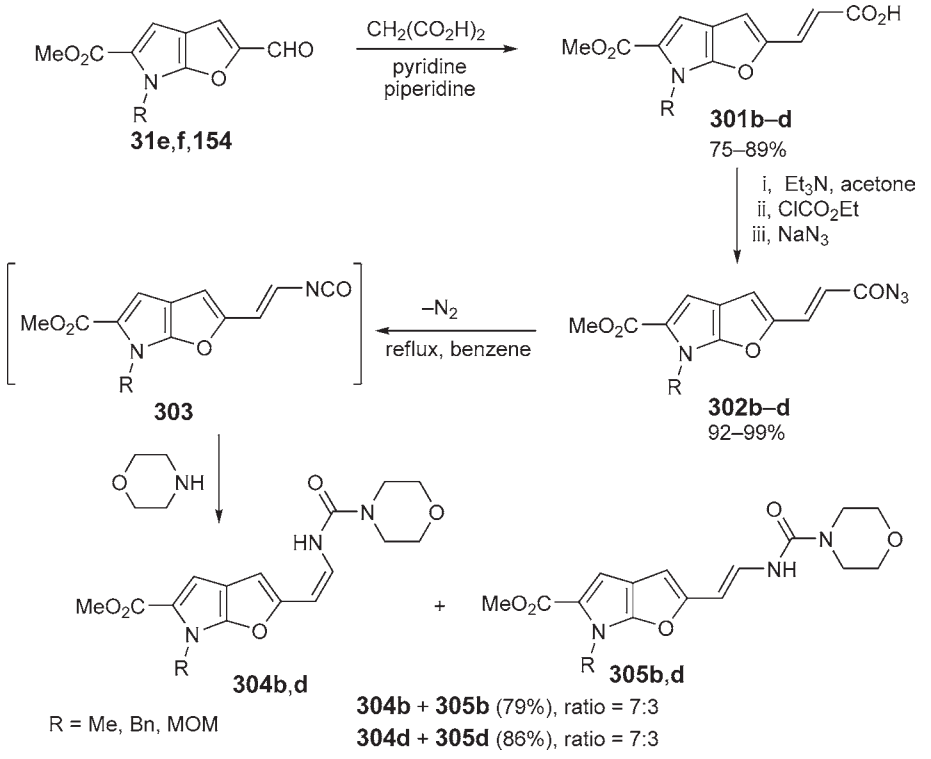
Scheme 30

Reaction of **31d–f** or **154** with a cyclic active methylene compound such as 5,5-dimethylcyclohexane-1,3-dione (dimedone) gave **299a–d** (47–85%), which by subsequent cyclization led to the substituted 1,2,3,4,5,6,7,8-octahydroxanthenes **300a–d** (72–90%) <1999CCC1135>.



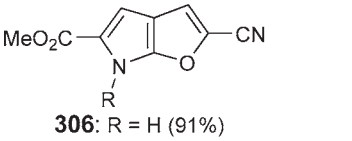
Starting from **31e**, **31f**, or **l54** *via* the Doebner condensation, the corresponding propenoic acids **301b–d** were synthesized, then reacted with ethyl chloroformate and triethylamine in acetone to give mixed acid anhydrides, which were converted into acid azides **302b–d** with (*E*)-configuration at the double bond. The azides **302b–d** were heated in Dowtherm at 240 °C, which facilitated the Curtius rearrangement to give the corresponding nonisolated

isocyanates **303**. The isocyanates were trapped in an addition reaction with morpholine in boiling benzene. As expected, disubstituted ureas **304** and **305** as a mixture of (*Z*)- and (*E*)-isomers in ratio 7:3 were obtained. An attempt to prepare or separate only the (*E*)-isomer was unsuccessful. If the reaction was carried out in boiling toluene, only (*Z*)-isomers of the disubstituted ureas **304b** and **304d** were isolated (**Scheme 31**) <2000PJC207>.

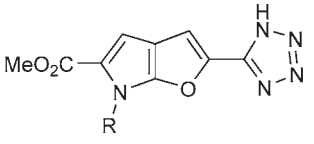


Scheme 31

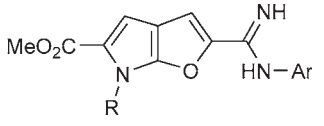
The reaction of **31d–f** and **154** with hydroxyammonium chloride in acetic anhydride in the presence of pyridine at 90 °C gave the corresponding 2-cyano compound **31g**, **31h**, **306**, and **307**, which by reaction with sodium azide and ammonium chloride in DMF led to **308a–d**. The selected cyano derivatives **31g** and **31h** were transformed into the corresponding amidines **309–313** by reaction with aniline or *p*-toluidine in the presence of aluminium chloride in dichloromethane at room temperature. The amidine–aluminium chloride complex was decomposed with warm water and alkali. Treatment of amidines **309** and **312** with (diacetoxyiodo)benzene at 60 °C in toluene gave disubstituted ureas **314a** and **314b** after purification by column chromatography <1997MOL69, 2000PJC207>.



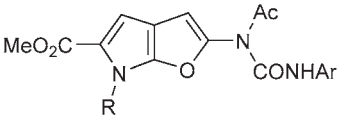
306: R = H (91%)
31g: R = Me (98%)
31h: R = Bn (91%)
307: R = MOM (92%)



308a: R = H (73%)
308b: R = Me (70%)
308c: R = Bn (67%)
308d: R = MOM (90%)

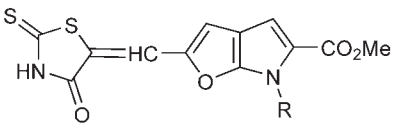


309: R = Me, Ar = Ph (75%)
310: R = Bn, Ar = Ph (96%)
311: R = MOM, Ar = *p*-Tol (92%)
312: R = Me, Ar = *p*-Tol (95%)
313: R = Bn, Ar = *p*-Tol (92%)

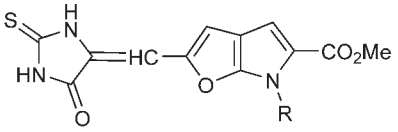


314a: R = Me; Ar = Ph (23%)
314b: R = Me; Ar = *p*-Tol (29%)

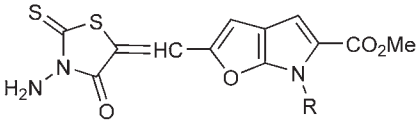
The condensation reactions of 2-formylfuro[2,3-*b*]pyrrole-5-carboxylates **31d–f** and **154** with a series of active methylene compounds provided **315–321** using 'classical' conditions and under MW irradiation <2000ARK409, 2004MOL11, 2004MOL241>.



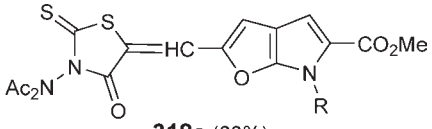
315a–d
68–86%



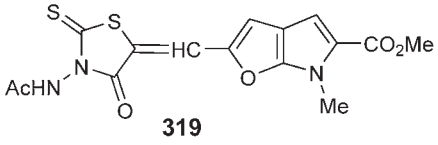
316a–d
70–75%



317a–c
78–88%

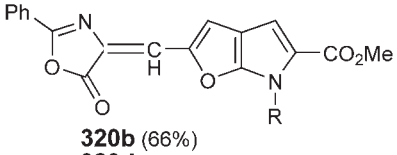


318c (63%)
318d (64%)



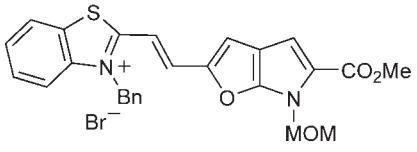
319

R = H, Me, Bn, MOM



320b (66%)
320d (70%)

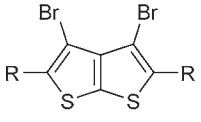
	Yields (%)	
	MW	*C*
316b	80	74
316d	85	73
318c	65	63



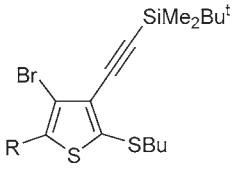
321
45%

10.01.7.2.3 Halogen substituents

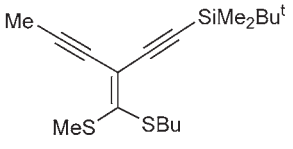
When 2,3,4,5-tetrabromothieno[2,3-*b*]thiophene **322** was treated successively with 3.4 equiv of BuLi (THF, −65 °C) and 4.8 equiv of Me_3SiCl, it gave **323**. A similar attempt (2.6 equiv BuLi, THF at 0 °C; 2.4 equiv of t-BuMe_2SiCl) gave **324–326**. The compound **325**, when treated with 2.0 equiv of BuLi (THF, 0 °C) and excess of MeI, was converted into **327** <1997CC2355>.



322: R = Br
323: R = $SiMe_3$ (59%)
324: R = $SiMe_2Bu^t$ (23%)



325: R = $SiMe_2Bu^t$ (33%)
326: R = H (18%)



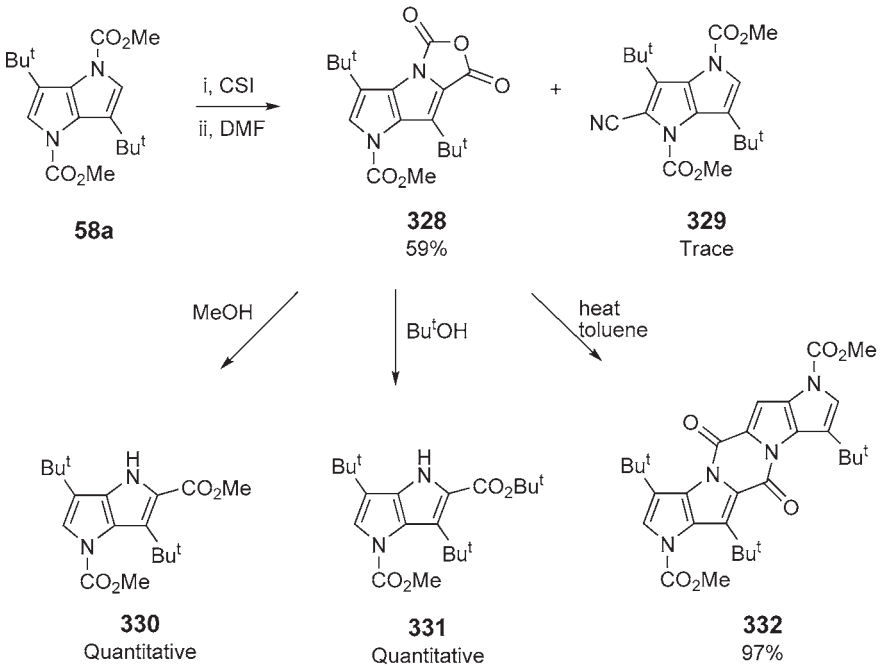
327
87%

10.01.8 Reactivity of Substituents Attached to Ring Heteroatoms

10.01.8.1 1,4-Diheteropentalene Systems

Some reactions of the substituents attached to ring heteroatoms have been partly described in CHEC-II(1996) <1996CHEC-II(7)1>.

The reaction of dimethyl 3,6-di-*tert*-butyl-1,4-dihydropyrrolo[3,2-*b*]pyrrole-1,4-dicarboxylate **58a** with CSI gave anhydride **328** with a trace of the expected **329**. The structure of **328** was confirmed by solvolysis giving **330** or **331**. On heating **328** in toluene for 1 h, evolution of CO_2 occurred to give a bimolecular condensation product **332** (**Scheme 32**) <1996H(43)2361>.

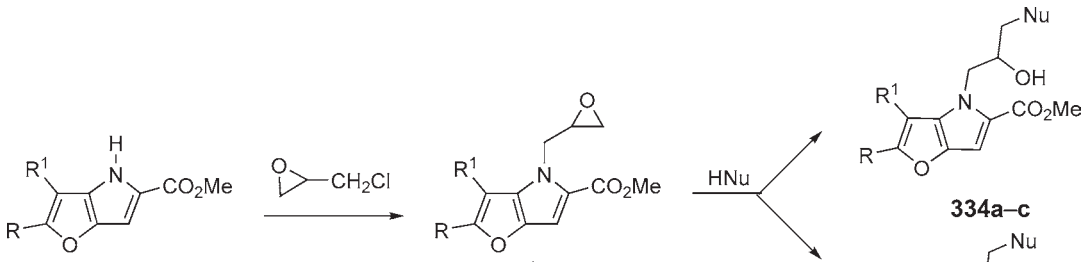


Scheme 32

Methyl 4-oxiranylmethylfuro[3,2-*b*]pyrrole-5-carboxylates **333** were prepared by reaction of the appropriate starting derivatives of **8** with an excess of 2-chloromethyloxirane. The compounds **333** on reaction with heterocyclic amines (morpholine, pyrrolidine, piperidine, or 4-methylpiperazine) undergo oxirane ring opening giving *N*-2-hydroxy-3-heteroaminopropyl substituted compounds **334** or substituted 4,5-dihydrofuro[2′,3′:4,5]pyrrolo[2,1-*c*]-[1,4]oxazin-8-ones **335** (**Scheme 33**). The formation of the compounds **335** is a result of intramolecular reaction of the newly formed OH group with the CO_2Me group present at C-5 of the furo[3,2-*b*]pyrrole unit with loss of MeOH <2001KGS1664>.

Milkiewicz *et al.* <2003TL4257> prepared a series of novel tetrasubstituted furo[3,2-*b*]pyrroles from the methyl or ethyl 3-bromo-2-phenylfuro[3,2-*b*]pyrrole-5-carboxylate **336**. The compounds **336** were subjected to a Suzuki coupling with 4-chlorophenylboronic acid to form **337**, which was treated with a variety of alkylating agents to afford the corresponding esters **338**. The esters were then saponified to acids **339** (**Scheme 34**).

It was found that the order of reactions could be reversed, with the nitrogen alkylation performed prior to the Suzuki reaction. In that way, compounds **340a** and **340b** were synthesized in 79% and 78% yields, respectively. The synthesis of compounds **341–343** was also described <2003TL4257>.



8a,**c**,**d**

R = H, CH_3, C_6H_5
R^1 = H, CH_3

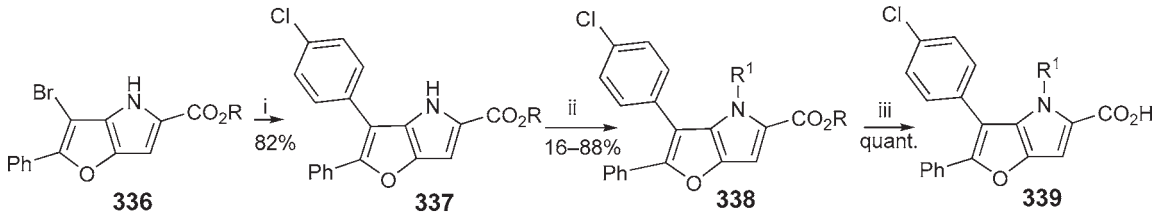
333a: R = R^1 = H (52%)
333b: R = R^1 = Me (69%)
333c: R = Ph, R^1= H (79%)

334a–c

335a–e

334a: R = R^1 = H; Nu = morpholin-4-yl (79%)
334b: R = R^1 = Me; Nu = morpholin-4-yl (60%)
334c: R = Ph; R^1= H; Nu = piperidin-1-yl (58%)
335a: R = R^1 = H; Nu = pyrrolidin-1-yl (45%)
335b: R = R^1 = H; Nu = 4-methylpiperazin-1-yl (62%)
335c: R = Ph; R^1= H; Nu = morpholin-4-yl (64%)
335d: R = Ph; R^1= H; Nu = pyrrolidin-1-yl (54%)
335e: R = Ph; R^1 = H; Nu = 4-methylpiperazin-1-yl (42%)

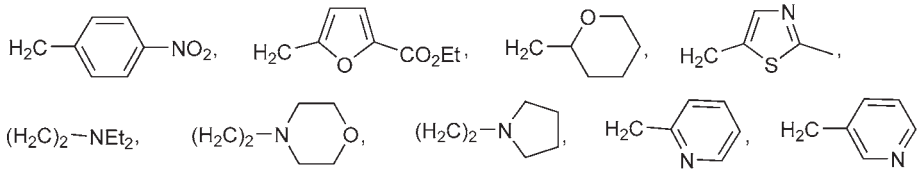
Scheme 33



336 **337** **338** **339**

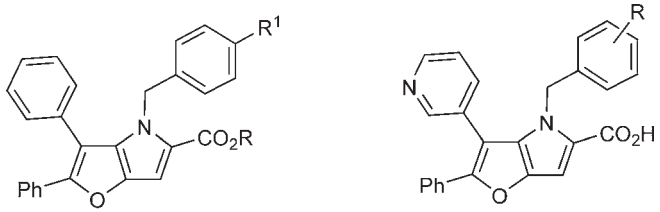
R = Me, Et

R^1 =



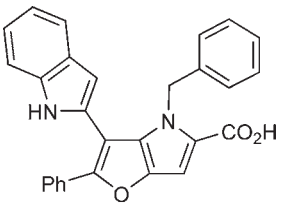
i, 4-chlorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH;
ii, R^1-bromide or chloride, NaH, NaI, 60 °C, 16 h;
iii, NaOH, EtOH, 50 °C, 4 h.

Scheme 34

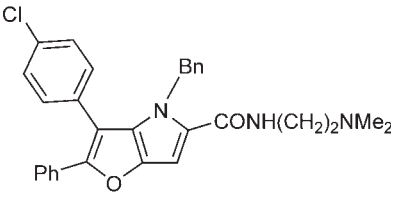


340a,**b**: R^1 = H, Cl

341a: R = 4-Cl
341b: R = 3-CF_3



342



343
21%

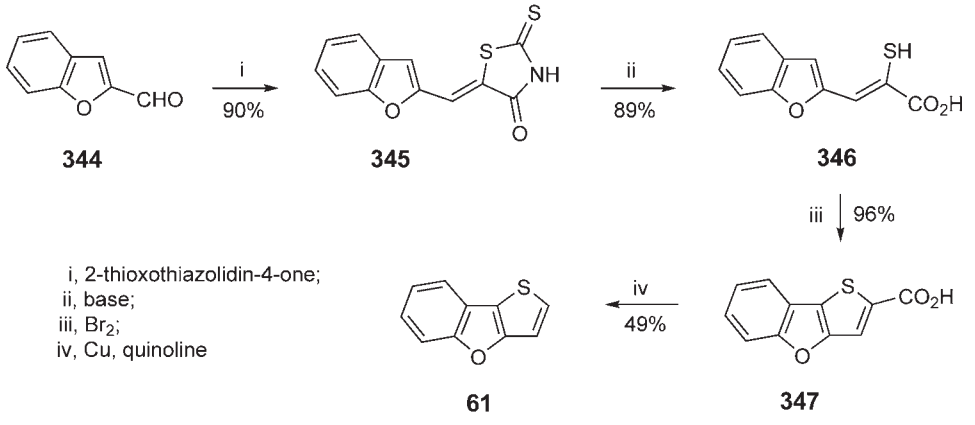
10.01.9 Ring Syntheses

10.01.9.1 Syntheses of 1,4-Diheteropentalene Systems (1)

10.01.9.1.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle

10.01.9.1.1(i) Benzoderivatives

Thieno[3,2-*b*][1]benzofuran **61** was synthesized on a preparative scale starting with benzo[*b*]furan-2-carbaldehyde **344**. Condensation of aldehyde **344** with 2-thioxothiazolidin-4-one in the presence of sodium acetate in acetic acid afforded **345**, which by base-catalyzed hydrolysis gave **346** in good yield. Upon treatment with bromine, acid **346** was cyclized to give acid **347**, which on standard decarboxylation by treatment with copper in quinoline afforded **61** in high yield (**Scheme 35**) <1997CCC1468>.

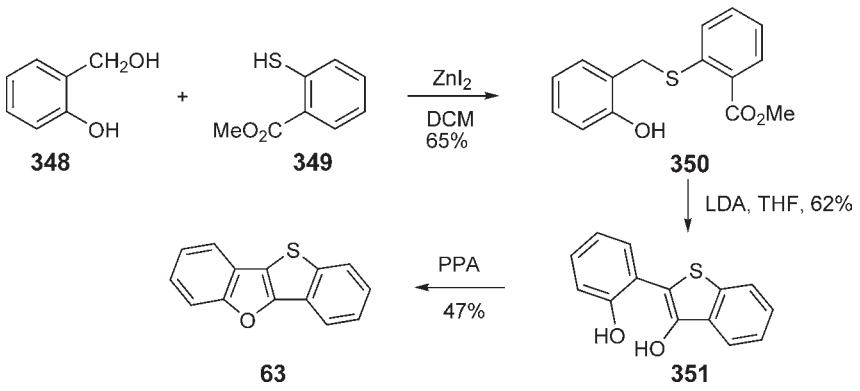


344 345 346

61 347

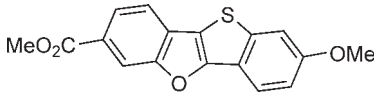
Scheme 35

A synthesis of the [1]benzothieno[3,2-*b*][1]benzofuran **63** based on the formation of the furan ring in the key step was elaborated. Alkylation of methyl 2-sulfanylbenzoate **349** with 2-hydroxybenzylalcohol **348** was effected with freshly prepared ZnI_2 in CH_2Cl_2 and **350** was obtained. Cyclization with lithium diisopropylamide (LDA) in THF afforded **351**, which on subsequent cyclodehydration with polyphosphoric acid (PPA) gave **63** in moderate yield (**Scheme 36**) <2000CCC1939>.

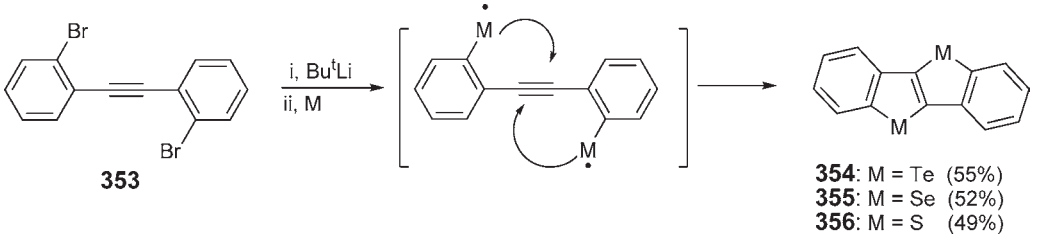


Scheme 36

The compound **352** was prepared as a new type of a core for ferroelectric liquid crystals <2000CCC1939>.

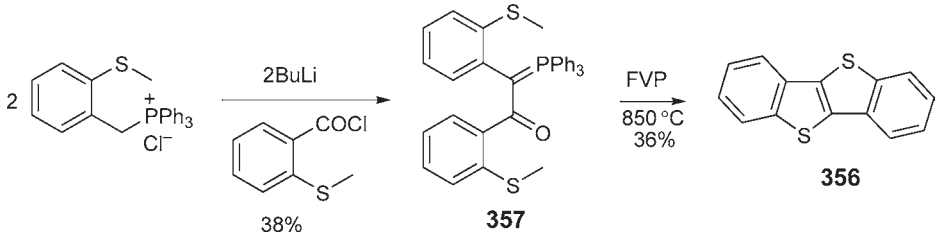


Treatment of 2,2′-dibromodiphenylacetylene **353** with *tert*-butyllithium followed by tellurium insertion resulted in ring closure to afford [l]benzotelluro[3,2-*b*][l]benzotellurophene **354** (Equation 6). Similarly, [l]benzoseleno[3,2-*b*]-[l]benzoselenophene **355** and [l]benzothieno[3,2-*b*][l]benzothiophene **356** were also obtained <1998JHC725>.



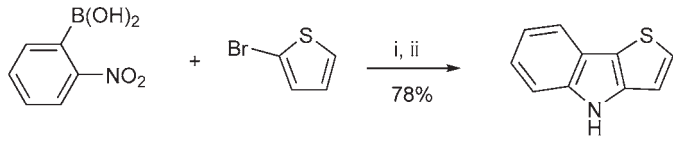
(6)

A new stabilized phosphorus ylide **357** designed to undergo thermal tandem cyclization has been prepared. Upon flash vacuum pyrolysis at 850 °C, loss of Ph_3PO and Me radical results in tandem cyclization to give [l]benzothieno[3,2-*b*][l]benzothiophene **356** (Equation 7) <1998J(P1)3937>.



(7)

Microwave-enhanced Suzuki–Miyaura <2002SL207> cross-coupling reaction in combination with an MW-assisted Cadogan reductive cyclization <B-1979MI279> was presented as an easy access to thieno[2,3-*b*]indole. MW irradiation was found very useful in minimizing the proto-deboronation issues in the cross-coupling reaction, and enhances the rate of reductive cyclization in a dramatic manner. 2-Bromothiophene and 2-nitrophenylboronic acid were successfully cross-coupled in 15 min under MW irradiation to give 2-(2-nitrophenyl)thiophene in good yield, which by reductive cyclization gave 4*H*-thieno[3,2-*b*]indole **358** (**Scheme 37**) <2005SL127>.



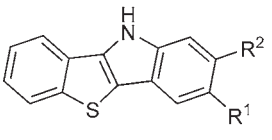
i, $Pd(Ph_3P)_4$, $NaHCO_3$, DMF–H_2O (1:1), MW, 15 min;
ii, $(EtO)_3P$, MW, 15 min

358

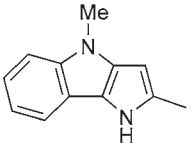
Scheme 37

General procedures for the synthesis of 10*H*-[1]benzothieno[3,2-*b*]indoles **359a–c** <2003T3737> and 2,4-dimethylpyrrolo[3,2-*b*]indole **360** <1997J(P1)2843> using palladium-catalyzed intramolecular cyclization of the appropriate *o*-bromodiarylamines and palladium-catalyzed arylation of a cyano group, respectively, were described.

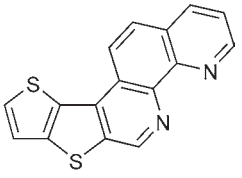
The synthesis of thieno[2′,3′:4,5]thieno[2,3-*c*][l,10]phenanthroline **361** has been described <1996JHC119>. The compound was obtained in four steps from known starting materials. The basic skeleton of the molecule of the phenanthroline ring was formed *via* photocyclization.



359a: R^1 = OMe; R^2 = H (60%)
359b: R^1 = OMe; R^2 = OMe (60%)
359c: R^1 = H; R^2 = H (quantitative)



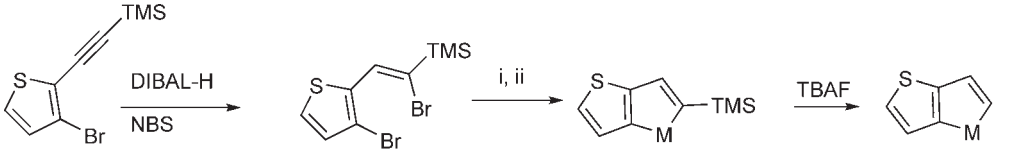
360
52%



361
24%

10.01.9.1.1(ii) From thiophene derivatives

The hetero[3,2-*b*]thiophenes were prepared from the corresponding 1,4-dilithium intermediates, derived from 3-bromo-2-(trimethylsilyl)ethynylthiophene **362**. Treatment of **363** with *tert*-butyllithium and the appropriate reagents resulted in the formation of **364**, which afforded targets **12**, **13**, **15**, and **365–367** by treatment with tetrabutylammonium fluoride (TBAF) (**Scheme 38**) <1997H(45)1891>.



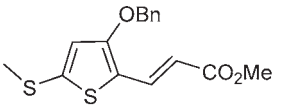
362 **363** **364**

12: M = S
13: M = Se
15: M = Te
365: M = PPh
366: M = AsPh
367: M = SbPh

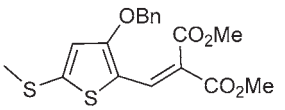
i, Bu^tLi; ii, reagent: $(PhSO_2)_2S$, $(PhSO_2)_2Se$, $TeCl_4$, $PhAsCl_2$ or $PhSbCl_2$

Scheme 38

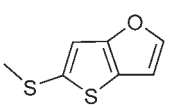
Annelation of a furan ring onto a thiophene is also possible by flash vacuum pyrolysis at 650 °C of the acrylate **368** and malonate **369**, which gave 2-(methylthio)thieno[3,2-*b*]furan **370** and methyl-5-(methylthio)thieno[3,2-*b*]furan-2-carboxylate **371**, respectively, in yields of 21% and 22% <1997J(P1)2483>.



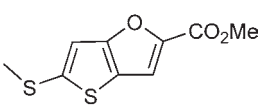
368



369

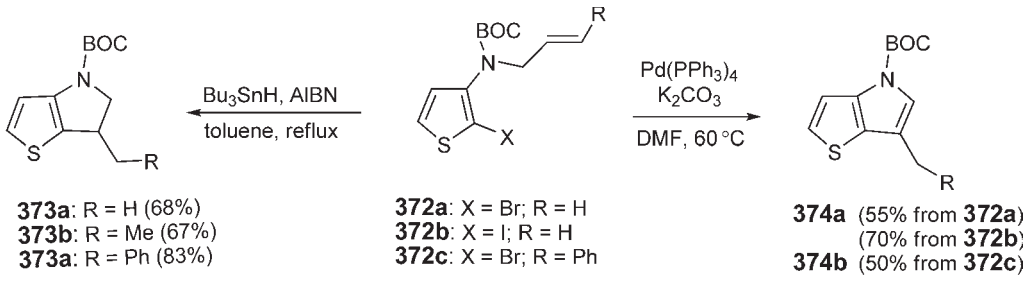


370



371

tert-Butyl-2-allyl- and *N*-allyl-3-thienylcarbamates were used as substrates for the preparation of thieno[3,2-*b*]pyrroles **374** and 5,6-dihydrothieno[3,2-*b*]pyrroles **373**. Pd-Catalyzed cyclization of **372a–c** has allowed access to thieno[3,2-*b*]pyrroles **374** (**Scheme 39**). The radical route has led to the formation of 5,6-dihydrothieno[3,2-*b*]-pyrroles **373a–c** <2001J(P1)37>.



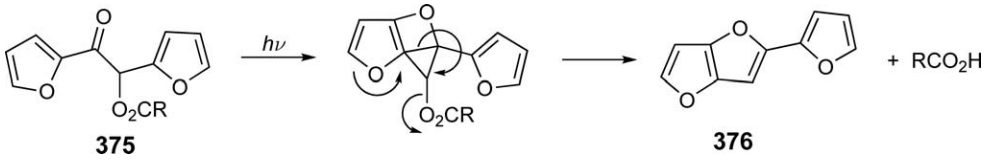
373a: R = H (68%)
373b: R = Me (67%)
373a: R = Ph (83%)

372a: X = Br; R = H
372b: X = I; R = H
372c: X = Br; R = Ph

374a (55% from **372a**)
(70% from **372b**)
374b (50% from **372c**)

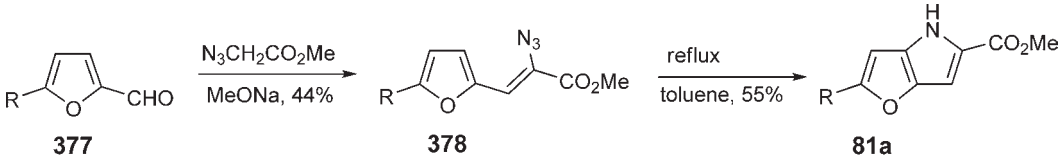
Scheme 39

Peach *et al.* <1995T10013> investigated the potential of furoin esters **375** as protecting groups for the C-terminus of peptides. Furoin esters were perceived as an alternative means of introducing alkoxy groups at appropriate sites of the protecting group, thereby enhancing photolability. During the course of the photolysis of **375**, formation of 2-(2-furyl)furo[3,2-*b*]furan **376** (λ_{max} ca. 325 nm) was proposed, although this did not accumulate in concentrations sufficient to allow for isolation (Equation 8).



375 **376** (8)

Methyl 2-[3-(trifluoromethyl)phenyl]-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate **81a** was made by thermolysis of the corresponding methyl 2-azido-3-{5-[3-(trifluoromethyl)phenyl]-2-furyl}propenoate **378**, which was formed by condensation of 5-[3-(trifluoromethyl)phenyl]furan-2-carbaldehyde **377** with methyl azidoacetate under sodium methoxide catalysis (**Scheme 40**) <2006KGS825>.



377
R = 3-$F_3CC_6H_4$

378

81a

Scheme 40

10.01.9.2 Syntheses of 1,5-Diheteropentalene Systems (2)

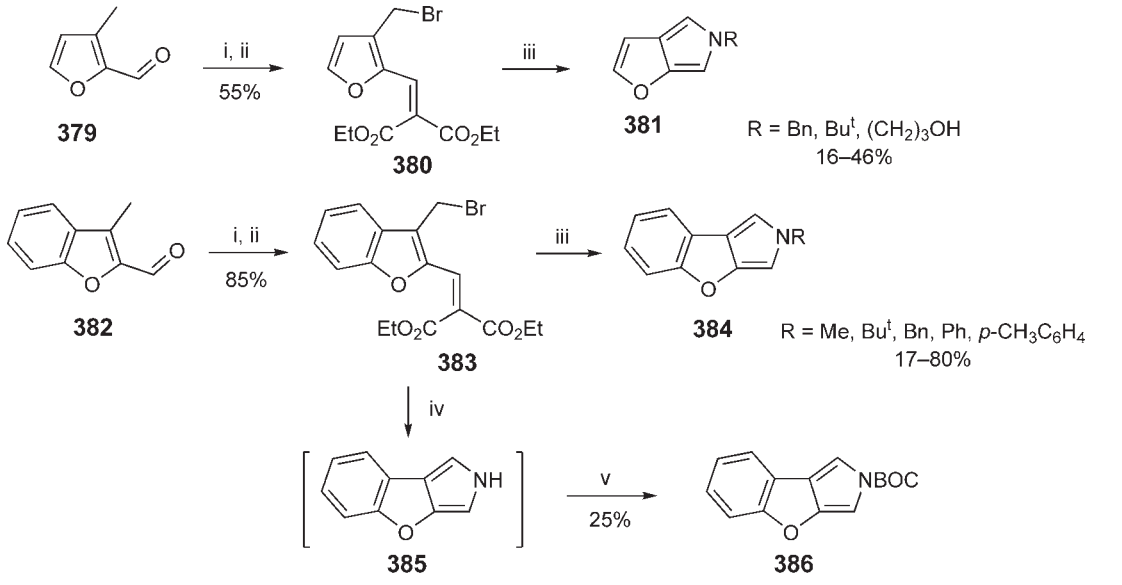
10.01.9.2.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle

10.01.9.2.1(i) Intramolecular cyclization of carbonyl and carboxylic acid intermediates

Three new syntheses of *iso*-condensed heteroaromatic pyrroles and their derivatives were described <1995T193, 2003T1477> using retro-malonate addition and/or 1,3-dipolar cycloaddition–cycloreversion methods.

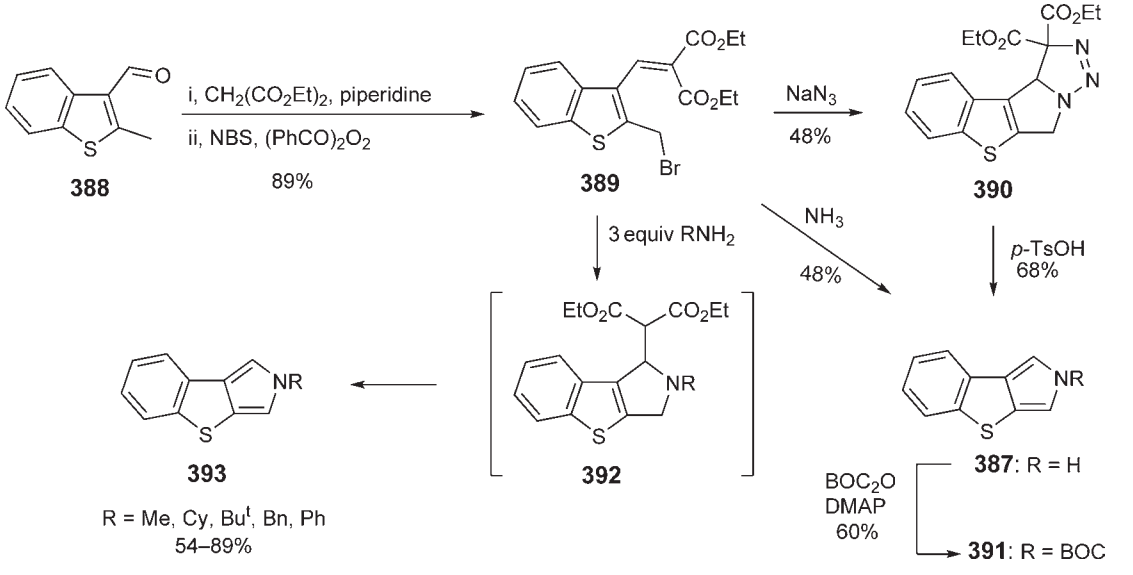
Knoevenagel condensation of the corresponding 3-methylfuran-2-carbaldehyde **379** and 3-methybenzo[*b*]furan-2-carbaldehyde **382** with diethyl malonate followed by bromination with *N*-bromosuccinimide (NBS) in the presence of dibenzoyl peroxide afforded bromides **380** and **383**, respectively. Treatment of **380** and **383** with benzylamine, isopropylamine, *t*-butylamine 3-hydroxypropylamine, aniline and *p*-toluidine in ethanol yielded furo[2,3-*c*]pyrroles **381** and benzo[4,5]furo[2,3-*c*]pyrroles **384**, respectively (**Scheme 41**). The yields of furopyrroles **381** are only moderate (16–46%), because these compounds are highly sensitive to acid, and partially polymerized upon silica

gel chromatography. In addition, treatment of **383** with ammonia in ethanol gave parent compound **385**, which was not isolable, but was treated immediately with di-*t*-butyl dicarbonate to give the stable derivative **386** <1995T193>.



Scheme 41

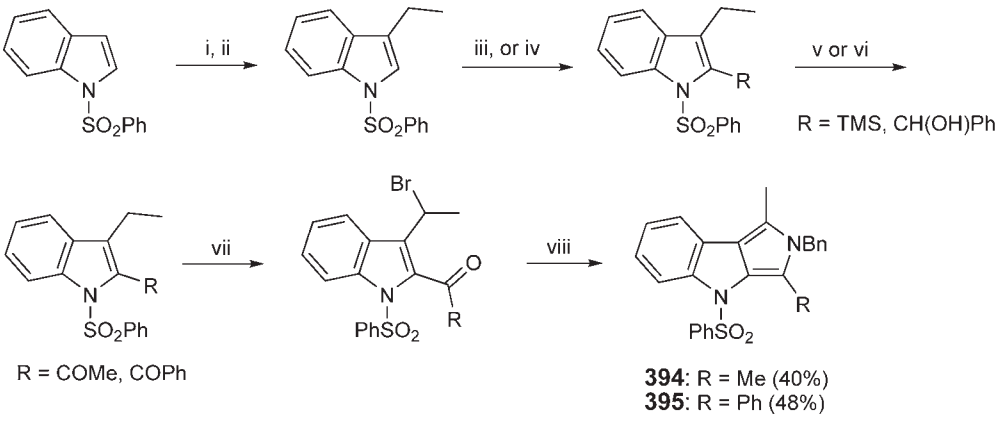
The first synthesis of the parent compound of the benzo[4,5]thieno[2,3-*c*]pyrrole ring system **387** <2003T1477> and its derivatives was accomplished using the same synthetic sequence (**Scheme 42**). Starting with 2-methylbenzo[*b*]thiophene-3-carbaldehyde **388**, an intermediate **389** was obtained. Treatment of bromo compound **389** with sodium azide in ethanol led to the stable triazoline **390**. 1,3-Dipolar cycloreversion of **390** was induced by a catalytic amount of *p*-TsOH to give the parent 2*H*-benzo[4,5]thieno[2,3-*c*]pyrrole **387**. Alternatively, direct treatment of bromo compound **389** with excess ammonia furnished **387** in one step. Compound **387** was treated with di-*t*-butyl dicarbonate and 4-dimethylaminopyridine (DMAP) to give *N*-BOC derivative **391**. Reaction of **389** with



Scheme 42

alkyl- and arylamines, respectively, afforded the *N*-substituted benzo[4,5]thieno[2,3-*c*]pyrroles **393** *via* a retro-malonate addition from intermediate **392**.

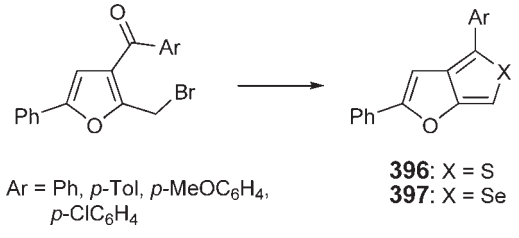
Similarly, pyrrolo[3,4-*b*]indoles **394** and **395** were synthesized according to the method of Srinivasan <1995J(P1)2663, 1998SL1061, 2000T10133>. The pyrrolo[3,4-*b*]indole skeleton was obtained by cyclization of suitable precursors with bromo and carbonyl functions with benzylamine. The syntheses starting with an *N*-phenyl-sulfonyl-protected indole are depicted in **Scheme 43**.



i, Ac_2O, $AlCl_3$; ii, NaBH4, TFA, 94% over 2 steps; iii, *s*-BuLi, THF, –78 °C, TMSCl, 56%; iv, PhCHO, 63%; v, Ac_2O, $AlCl_3$, 66%; vi, MnO_2, DCM, reflux, 75%; vii, NBS, AIBN, CCl_4, 66% (R = COMe), 61% (R = COPh); viii, $BnNH_2$, K_2CO_3, $CHCl_3$

Scheme 43

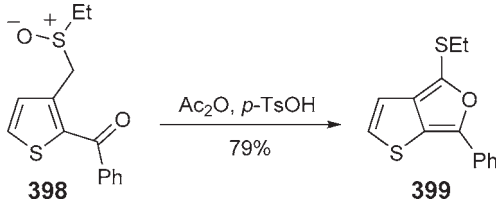
The series of new 4-aryl-2-phenylthieno[3,4-*b*]furans **396** and the selenium analogue **397** were prepared from the readily available aryl 2-bromomethyl-5-phenyl-3-furyl ketones by cyclization with thioacetamide and *N*,*N*-diethyl-selenopropanamide, respectively (Equation 9) <1998JHC71>.



Ar	*X*	*Yield (%)*
Ph	S	75
p-Tol	S	45
p-$MeOC_6H_4$	S	60
p-ClC_6H_4	S	73
p-$MeOC_6H_4$	Se	30

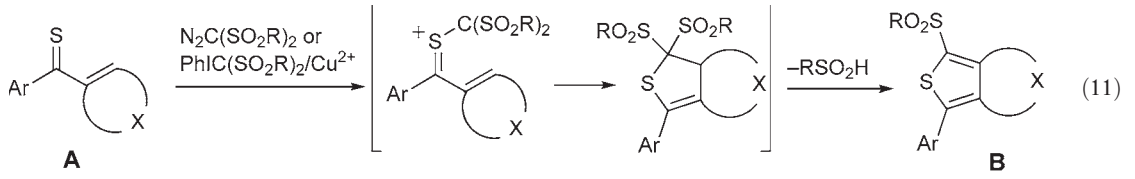
(9)

Cyclization of a suitably substituted sulfoxide thiophene **398** in acidic conditions is the key reaction in the synthesis of 4-(ethylthio)-6-phenylthieno[2,3-*c*]furan **399** from 3-methylthiophene-2-carboxylic acid (Equation 10) <1996JOC6166>.



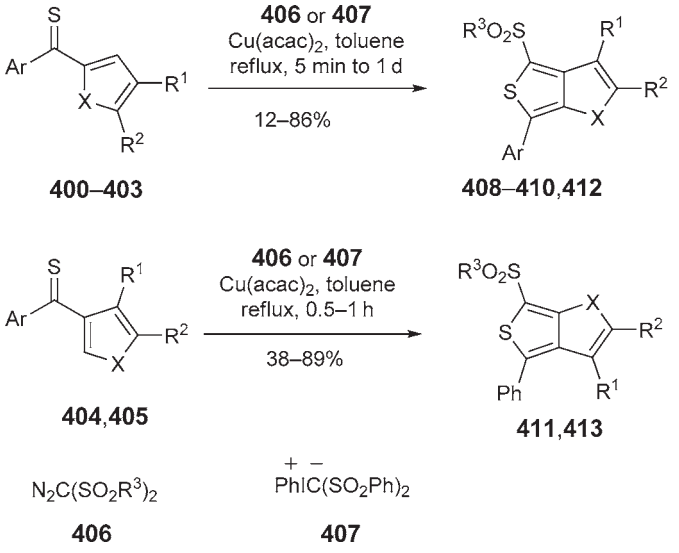
(10)

Saito *et al.* <1995S87> described a new method for the synthesis of heterocycle-fused[*c*]thiophenes *via* reaction of aryl heteroaryl thioketones with the carbene precursors. Heteroaromatic thioketones **A** react with carbenoids generated from bis(arylsulfonyl)diazomethanes or phenyliodonium bis(phenylsulfonyl)methylides to give heterocycle-fused[*c*]thiophenes **B**. The reaction involves the ring closure of the intermediary thiocarbonyl ylides, followed by restorative aromatization *via* the elimination of a sulfenic acid (Equation 11).



(11)

The present method provides simple and facile access to the variety of furo- **408**, benzofuro- **409**, thieno- **410**, benzothieno- **411**, pyrrolo- **412**, and indolo- **413** fused [*c*]thiophenes (**Scheme 44**).



Compound	*X*	*Ar*	R^1	R^2
400a	O	Ph	H	H
400b	O	Mesityl	H	H
401	O	Ph	CH=CH-CH=CH	
402	S	Ph	H	H
403	NMe	Ph	H	H
404	S	Ph	CH=CH-CH=CH	
405	NMe	Ph	CH=CH-CH=CH	
406a	R^3 = Ph			
406b	R^3 = *p*-Tol			

Scheme 44

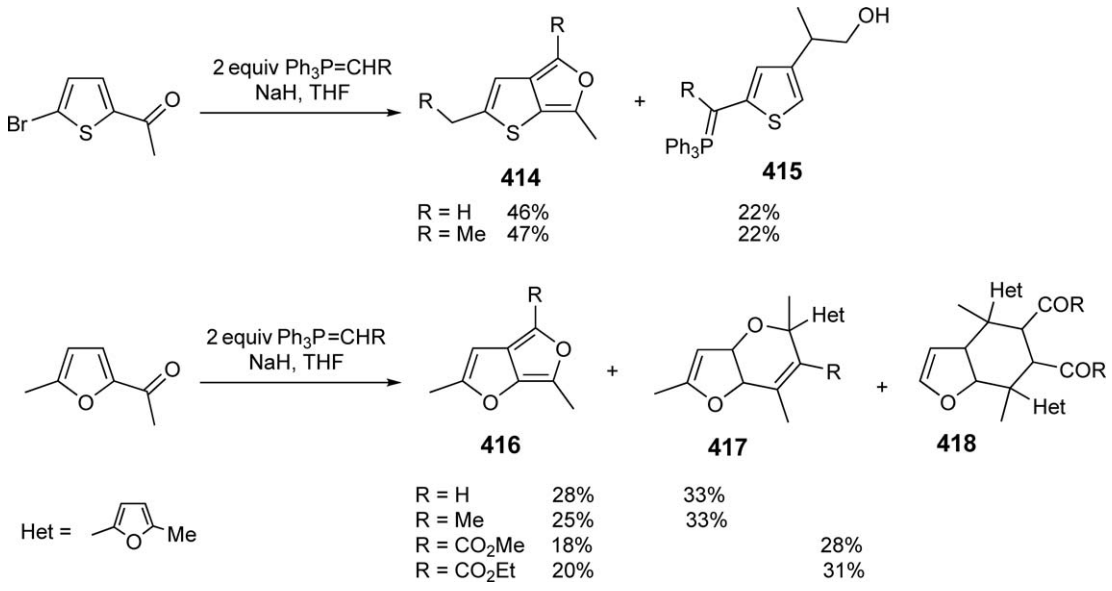
4-Alkylthieno[2,3-*c*]furans **414** and 4-alkylfuro[3,4-*b*]furans **416** were obtained as unexpected side products from the reaction of 2-acetyl-5-bromothiophene and 2-acetyl-5-methylfuran with stabilized and nonstabilized ylides, along with the corresponding phosphoranes **415**, pyrans **417**, and dimeric products **418**, respectively (**Scheme 45**) <2000T7573>.

The fused heterocycle 4-(phenylsulfonyl)-4*H*-furo[3,4-*b*]indole **421**, which is an indole-2,3-quinodimethane synthetic analogue, was prepared in five steps from indole in 48% overall yield <2002JOC1001>. Indole-3-carbaldehyde was protected using a phase-transfer method to give the *N*-phenylsulfonyl derivative **419** (**Scheme 46**). This method is higher yielding than the original method <1983TL5345> of *N*-protection (LDA/$PhSO_2Cl$). Acetalization under typical conditions gave the acetal in excellent yield. Lithiation of the acetal at C-2 with *sec*-BuLi followed by treatment with gaseous formaldehyde gave hydroxy acetal **420**, which was without isolation treated with $BF_3{\cdot}Et_2O$ and hydroquinone to afford furoindole **421** in 52% yield from the acetal. This route to **421** represents a significant improvement over the original synthesis (48% vs. 28%).

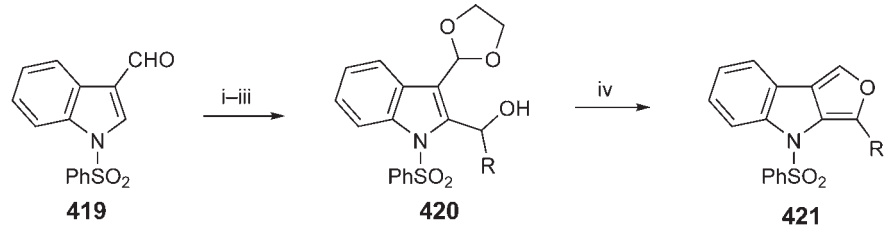
A similar sequence was used to synthesize C-3 alkyl derivatives using the corresponding aldehydes for hydroxyalkylation (**Scheme 46**). Exposure of the hydroxy acetals **420** to TFA and hydroquinone in dichloromethane at room temperature afforded 3-methyl, 3-phenyl, and 3-heptyl furoindoles **421**. The overall yields of the 3-alkyl furoindoles **421** from indole were 46–63% <2002JOC1001>.

10.01.9.2.1(ii) Cyclization of nitro intermediates

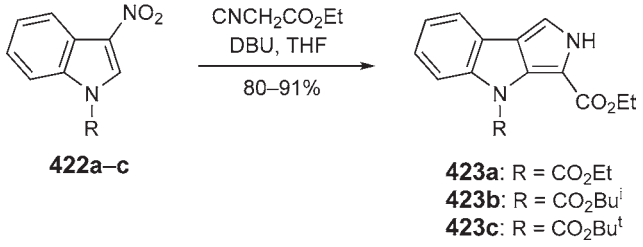
The Barton–Zard pyrrole synthesis <1990T7587> was applied in the syntheses of pyrrolo[3,4-*b*]indoles **423** from 3-nitroindoles **422**. Treatment of appropriate alkyl 3-nitroindole-1-carboxylates **422a–c** with ethyl isocyanoacetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the corresponding pyrrolo[3,4-*b*]indole **423a–c** (Equation 12) <1997CC1873, 1999S1117>.



Scheme 45



Scheme 46

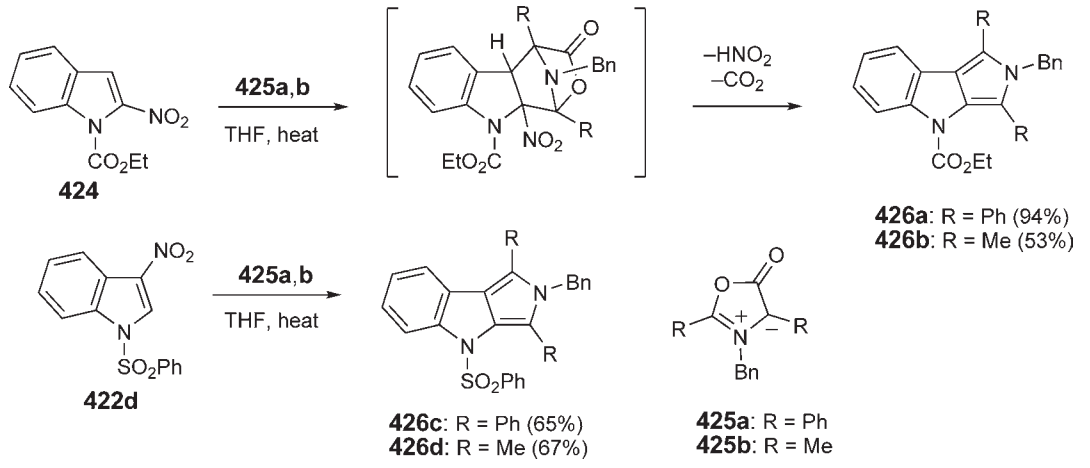


(12)

10.01.9.2.1(iii) Cycloadditions

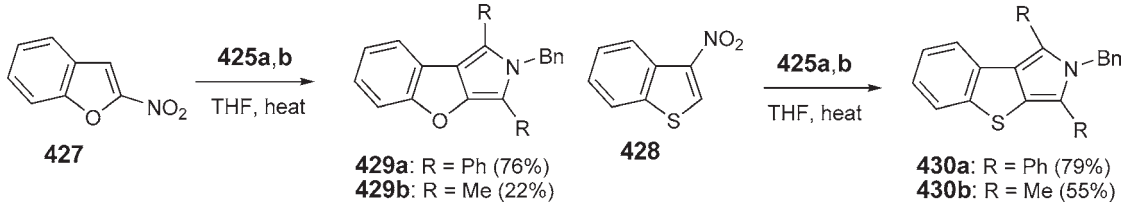
Generally, cycloadditions represent powerful reactions for construction of heterocycles. Tandem intramolecular Diels–Alder/retro-Diels–Alder reaction sequences were applied in the syntheses of many A,B-diheteropentalenes <1996CHEC-II(7)1>. Gribble and co-workers <1998SL1061> reported new syntheses of pyrrolo[3,4-*b*]indoles **426**, benzo[4,5]furo[2,3-*c*]pyrroles **429**, and benzo[4,5]thieno[2,3-*c*]pyrroles **430** using the 1,3-dipolar cycloaddition

reaction of symmetrical münchnones (1,3-oxazolium-5-olates) <1996JOC4319, 1997CC993> with nitroheterocycles. Both 2- and 3-nitroindoles react with mesoionic münchnones **425a** and **425b** to give in one operation the corresponding pyrrolo[3,4-*b*]indoles **426a–d**. This reaction is presumed to involve formation of a cycloadduct that loses the elements of nitrous acid and carbon dioxide to afford the pyrrolo[3,4-*b*]indole **426** in good to excellent yield (**Scheme 47**).



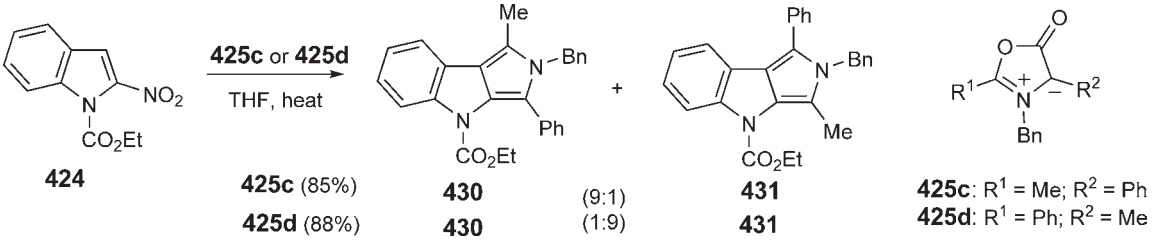
Scheme 47

Likewise, both 2-nitrobenzo[*b*]furan **427** and 3-nitrobenzo[*b*]thiophene **428** give rise to the novel fused heterocycles **429** and **430**, respectively (**Scheme 48**).



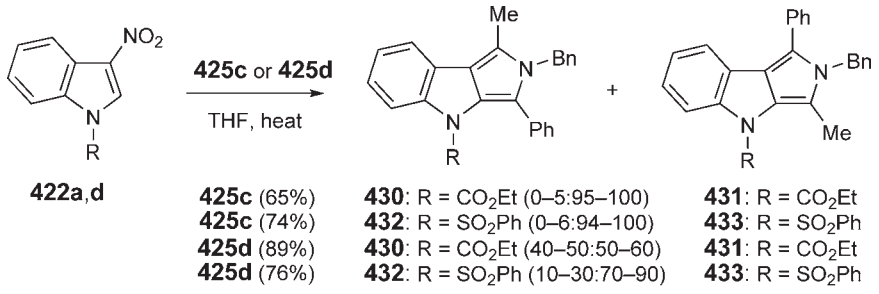
Scheme 48

The regioselectivity of 1,3-dipolar cycloaddition reactions of 2- and 3-nitroindoles with the unsymmetrical münchnones 3-benzyl-2-methyl-4-phenyl-1,3-oxazolium-5-olate **425c** and 3-benzyl-4-methyl-2-phenyl-1,3-oxazolium-5-olate **425d**, which were generated *in situ* from the corresponding *N*-acylamino acids, was studied <2000T10133>. The reactions of 2-nitroindole **424** with münchnones **425c** and **425d** are highly regioselective and afford pyrroloindoles **430** and **431** as reasonably stable crystalline solids in excellent yields (**Scheme 49**).



Scheme 49

Similarly, reaction of 1-ethoxycarbonyl-3-nitroindole **422a** with münchnone **425c** also affords nearly exclusively the '*anti*-FMO' product **431** (FMO = frontier molecular orbital), whereas münchnone **425d** with the same substrate gives **430** and **431** in nearly equal amounts (**Scheme 50**). Reactions of 3-nitro-1-(phenylsulfonyl)indole **422d** with münchnones **425c** and **425d** have also been investigated. The former cycloaddition reaction proceeds to give exclusively the *anti*-FMO pyrroloindole **433** in good yield. However, reaction of the phenylsulfonyl derivative with münchnone **425d** yields pyrroloindoles **432** and **433**, with the FMO product **433** somewhat favored.



Scheme 50

An electron-withdrawing group (EWG) on the indole nitrogen appears to be required for these cycloadditions to occur, since, for example, 1-methyl-3-nitroindole fails to react with münchnone **425d** after 24 h at reflux in THF or diglyme; at most, <1% of products are formed.

AM1 calculations were performed using SPARTAN software, and these FMO predictions are consistent with the fact that the observed cycloaddition regiochemistry is generally '*anti*-FMO'. The HOMO/LUMO energies are listed in **Table 9**, and **Figure 10** depicts the coefficients for the favored HOMO(münchnone) + LUMO(nitroindole) interaction (HOMO = highest, occupied molecular orbital; LUMO = lowest unoccupied molecular orbital).

Table 9 AM1 calculation results for **424**, **422a**, **422d**, **425c**, and **425d** performed using SPARTAN

	Energies (eV)	
Compound	*HOMO*	*LUMO*
1-Ethoxycarbonyl-2-nitroindole **424**	−9.512	−1.247
3-Nitro-1-(phenylsulfonyl)indole **422d**	−9.536	−1.562
1-Ethoxycarbonyl-3-nitroindole **422a**	−9.514	−1.141
425c	−7.674	−0.423
425d	−7.743	−0.683

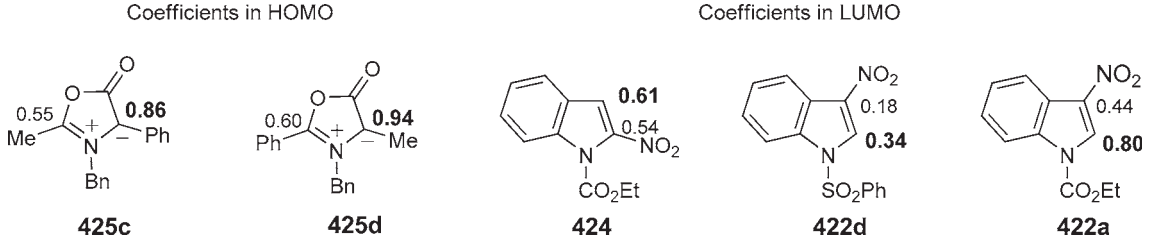


Figure 10 FMO of **422a**, **422d**, **424**, **425c**, and **425d**.

Thus, a comparison of the HOMO–LUMO energies (**Table 10**) predicts that the 1,3-dipolar cycloaddition should involve the HOMO of the münchnone (1,3-dipole) interacting with the LUMO of the nitroindole (dipolarophile). These energy differences are lower by 1.7–3.0 eV than the reverse situation involving the LUMO of the münchnone

and the HOMO of the nitroindole. However, in only one case is the FMO-predicted regiochemistry realized to any extent. The reaction of 3-nitro-1-(phenylsulfonyl)indole **422d** with münchnone **425d** gives a preponderance of pyrroloindole **433** over the isomeric **432** (**Scheme 50**). The reaction of 1-ethoxycarbonyl-3-nitroindole with münchnone **425d** gives perhaps a slight excess of the FMO product **431**.

Table 10 Comparison of LUMO–HOMO energy differences, (eV; energy values are taken from **Table 9**) for interactions of **424**, **422a**, and **422d** with **425c** and **425d**

Reaction	$E_{LUMO(n)}{}^{a} - E_{HOMO(m)}{}^{b}$ (*eV*)	$E_{LUMO(m)}{}^{b} - E_{HOMO\ (n)}{}^{a}$ (*eV*)	ΔeV
424 + **425c**	6.428	8.089	1.661
424 + **425d**	6.497	8.829	2.332
422d + **425c**	6.112	9.113	3.001
422d + **425d**	6.181	8.853	2.672
422a + **425c**	6.533	9.091	2.558
422a + **425c**	6.602	8.831	2.229

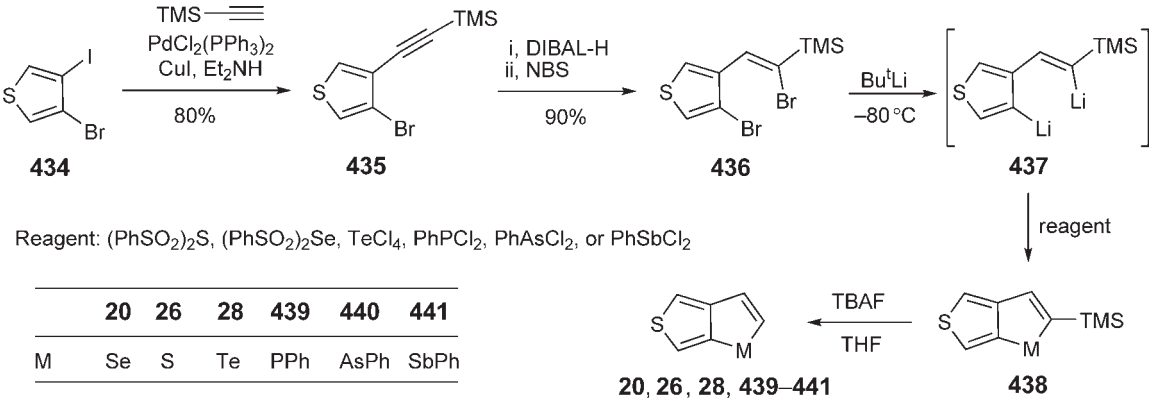
[a](n), nitroindole.
[b](m), münchnone.

One feature of the regiochemistry is that in every case but one the major or exclusive product is the one where the phenyl group of the münchnone is *syn* to the nitro group in the indole (**Schemes 49** and **50**). This may suggest a favorable π-interaction between the phenyl ring of the münchnone and the nitro group in the transition state, leading to the observed regiochemistry that is *anti*-FMO, or it may simply be a consequence of a highly nonsynchronous transition state where bond making between the methyl ring carbon of the münchnone and the electron-deficient carbon of the nitroindole double bond precedes, for steric reasons, bond making involving the phenyl ring carbon of the münchnone.

10.01.9.2.1(iv) Other methods

Syntheses of novel group 15 (P, As, Sb) and 16 (S, Se, Te) hetero[2,3-*c*]thiophenes **20**, **26**, **38**, and **439–441** from common starting material were developed <1997H(45)1891>.

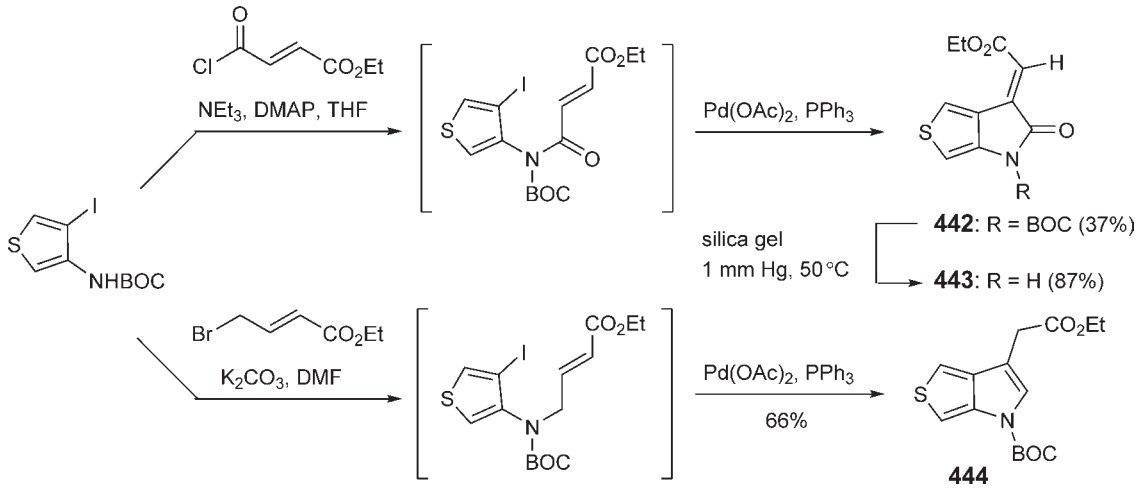
This versatile synthetic route to diheteropentalenes **20**, **26**, **38**, and **439–441** from dihalothiophenes involves Sonogashira cross-coupling reaction of 3-bromo-4-iodothiophene **434** with trimethylsilylethyne giving **435** (**Scheme 51**). The ethynyl compound **435** was hydroaluminated with DIBAL-H followed by bromination with NBS to give dibromo derivate **436**. Treatment of **436** with *t*-BuLi in dry ether at −80 °C, then with a suitable reagent $(PhSO_2)_2S$, $(PhSO_2)_2Se$, $TeCl_4$, $PhPCl_2$, $PhAsCl_2$, or $PhSbCl_2$), resulted in ring closure forming the 2-trimethylsilylhetero[2,3-*c*]thiophenes **438**, presumably via key 1,4-dilithium intermediate **437**. The trimethylsilyl group was removed by treatment TBAF in THF to give new parent compounds **20**, **26**, **38**, and **439–441**.



	20	26	28	439	440	441
M	Se	S	Te	PPh	AsPh	SbPh

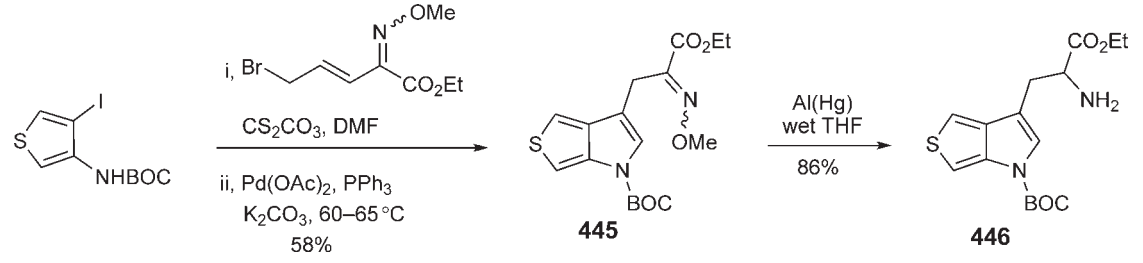
Scheme 51

1-BOC-(*E*)-3-(Ethoxycarbonylmethylene)-2-oxo-2,3-dihydrothieno[3,4-*b*]pyrrole **442** and ethyl 1-BOC-thieno[3,4-*b*]pyrrol-2-ylacetate **444** were prepared starting from *N*-BOC-protected 3-amino-4-iodothiophene. Acylation with ethyl 4-bromocrotonate and ethyl fumaroyl chloride, respectively, followed by palladium-catalyzed ring closure in a one-pot reaction, yielded the *N*-BOC-protected thieno[3,4-*b*]pyrroles **442** and **444**, respectively <1995T10323>. The BOC group of **442** was readily removed after adsorption on silica to yield **443** (**Scheme 52**).



Scheme 52

This synthetic route was applied in the synthesis of thia-tryptophans, which are of interest as potentially bioactive molecules <1995BML1133>. 5,6-Thia-(D,L)-tryptophan ethyl ester **446**, with an additional BOC protecting group attached to nitrogen due to the instability of the parent ring system, was prepared from the corresponding 3-BOC-amino-4-iodothiophene using a one-pot synthesis including Heck cyclization <1996T14975>. Initial allylation of the 3-amino-4-iodothiophene derivative with ethyl (*E*)-2-[(*E*,*Z*)-methyloximino]-5-bromo-3-pentenoate (92:8), and subsequent intramolecular Heck-type cyclization in the presence of palladium acetate, afforded the desired thieno[3,4-*b*]pyrrole **445**. Reduction of the oxime ether function in **445** using Al(Hg) in wet THF provided target *N*-BOC-protected thia-tryptophan **446** (**Scheme 53**).



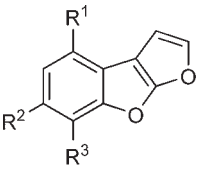
Scheme 53

10.01.9.3 Syntheses of 1,6-Diheteropentalene Systems (3)

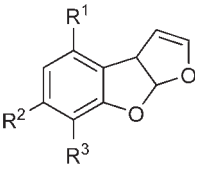
10.01.9.3.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle

10.01.9.3.1(i) Benzoderivatives

A Wittig olefination–Claisen rearrangement approach has been successfully applied in a novel protocol for the synthesis of the furo[2,3-*b*]benzofuran **447** and dihydrofuro[2,3-*b*]benzofuran **448** ring systems <1997J(P1)3127, 1997S1420, 1997T3167, 1997TL1459, 1998J(P1)2479>.

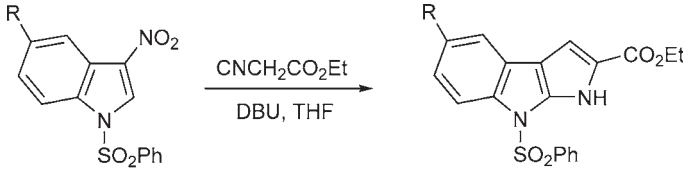


447



448

Pelkey and Gribble <1996CC117> discovered that 3-nitro-1-(phenylsulfonyl)indole **422d**, when treated with ethyl isocyanoacetate and base, undergoes a remarkable transformation leading to the unusual pyrrolo[2,3-*b*]indole ring system **449a** rather than the anticipated pyrrolo[3,4-*b*]indole ring system. Similar treatment of 5-chloro-3-nitro-1-(phenylsulfonyl)indole **422e** with ethyl isocyanoacetate and base affords the rearranged ethyl 5-chloro-1,8-dihydro-8-(phenylsulfonyl)pyrrolo[2,3-*b*]indole-2-carboxylate **449b** (Equation 13) <1999S1117>.

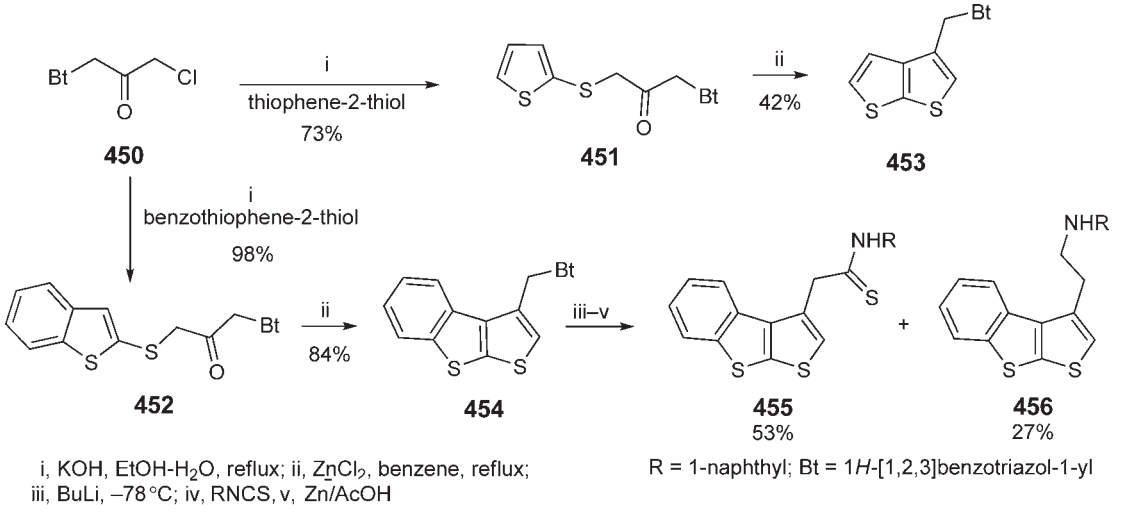


422d,e

449a: R = H (85%)
449b: R = Cl (79%)

(13)

1-(Thieno[2,3-*b*]thiophen-3-ylmethyl)-1*H*-[1,2,3]benzotriazole **453** and (benzo[4,5]thieno[2,3-*b*]thiophen-3-ylmethyl)-1*H*-[1,2,3]benzotriazole **454** were readily available from the condensation of 1-(1*H*-[1,2,3]benzotriazol-3-yl)-3-chloroacetone **450** with the corresponding thiols. Reaction of **454** with BuLi and 1-naphthyl isothiocyanate followed by reduction with Zn–AcOH led to the formation of both thioamide **455** and amine **456** (**Scheme 54**) <2001J(P1)2583>.



450 **451** **453**

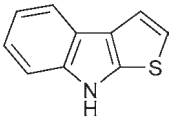
452 **454** **455** 53% **456** 27%

i, KOH, EtOH-H_2O, reflux; ii, $ZnCl_2$, benzene, reflux;
iii, BuLi, –78 °C; iv, RNCS, v, Zn/AcOH

R = 1-naphthyl; Bt = 1*H*-[1,2,3]benzotriazol-1-yl

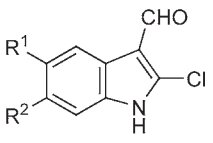
Scheme 54

The 8*H*-thieno[2,3-*b*]indole **457** was prepared by tandem cross-coupling and cyclization reactions analogously to 4*H*-thieno[3,2-*b*]indole **358** (**Scheme 37**) from 3-bromothiophene <2002SL207, 2004OL533>.

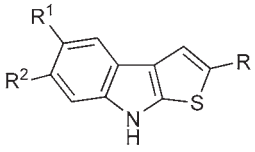


457

Olesen *et al.* presented a synthetic pathway to methyl thieno[2,3-*b*]indole-2-carboxylate **457a** and amides **457b–d** starting from 2-chloroindole-3-carbaldehydes **458** <1995JHC1641, 1995WO9525110, 1998USP5536721>. Bergman and co-workers published a total synthesis of the alkaloid thienodolin **457b** as well as its 5-chloro isomer **457c** and its unsubstituted analogue **457d** starting from the appropriate 2-chloroindole-3-carbaldehydes **458a** and **458b** in total yields of 42%, 35%, and 37%, respectively <2004EJO2589>. The alkaloid **457b** was isolated from the culture broth of *Streptomyces albogriseolus* MJ286—76F7 and the structure elucidated by Nakamura and co-workers <1993MI636>. It has been shown to exhibit both growth-promoting and -inhibiting activities in rice seedlings.



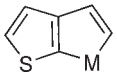
458a,**b**: R^1, R^2 = H, Cl



Compound	*R*	R^1	R^2
457a	CO_2Me	H	H
457b	$CONH_2$	H	Cl
457c	$CONH_2$	Cl	H
457d	$CONH_2$	H	H

10.01.9.3.1(ii) Synthesis from thiophene derivatives

The synthesis of fused systems containing P, As, Sb, S, Se and Te, as are hetero[3,2-*b*]thiophenes **12**, **13**, **15**, **365–367** (Chapter 10.01.9, **Scheme 38**), hetero[2,3-*c*]thiophenes **20**, **26**, **439–441** (Chapter 10.01.9.2.1, **Scheme 51**), also isomeric hetero[2,3-*b*]thiophenes **35**, **36**, **38**, **459–461** was published <1997H(45)1891>.



35, **36**, **38**, **459–461**

	35	**36**	**38**	**459**	**460**	**461**
M	S	Se	Te	PPh	AsPh	SbPh

10.01.9.3.1(iii) Synthesis from acyclic precursors

Thieno[2,3-*b*]pyrrole derivatives **462** were easily synthesized in two different ways using phenyl isothiocyanate and activated methylene compounds (**Scheme 55**) <2001SL1731>. The relative order of thiophene or pyrrole ring formation was investigated <2003T1557>.

The synthesis of substituted selenolo[2,3-*b*]thiophenes *via* ketene dithioacetals was published by the same research group <2004S451>.

A simple one-pot synthesis was described for tetrasubstituted thieno[2,3-*b*]thiophenes **463** by condensation of 1,3-diketones with CS_2, and alkylating agents carrying an EWG such as CO_2Et, COR, and CN in the presence of anhydrous KF or K_2CO_3 as condensation promoter in anhydrous DMF (**Scheme 56**) <1999S2030, 2001JHC1167>.

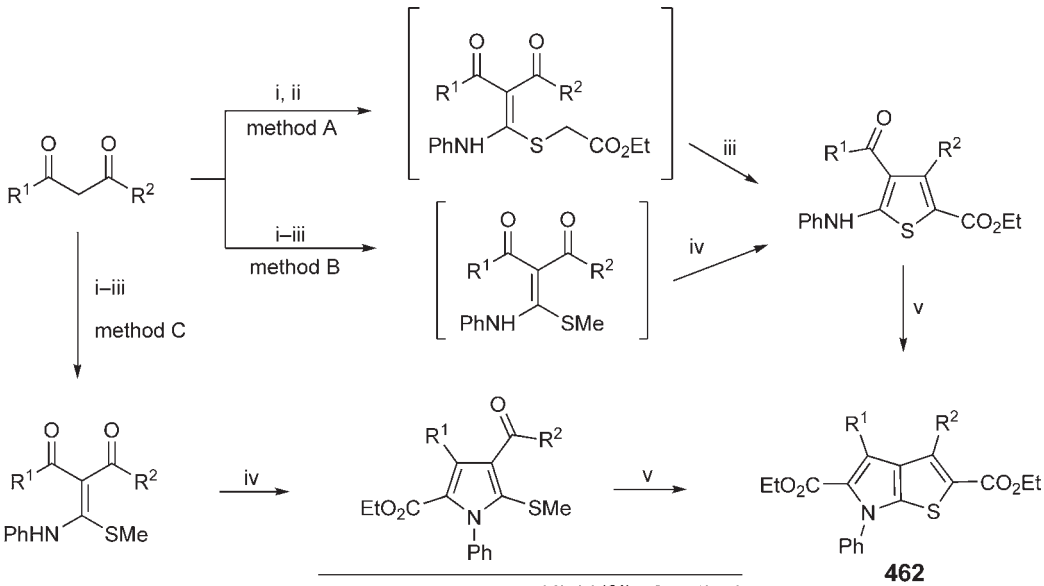
10.01.9.4 Syntheses of 2,5-Diheteropentalene Systems (4)

10.01.9.4.1 Synthesis by construction of the second heterocyclic ring onto an existing heterocycle

10.01.9.4.1(i) Synthesis from thiophene derivatives

The unstable parent thieno[3,4-*c*]thiophene **40** and its unstable derivatives have been synthesized and characterized *in situ* by trapping experiments. The presence of four bulky groups on the rings appeared to confer stability, and it was generally assumed that bulky substituents were necessary for isolable derivatives <1996CHEC-II(7)1>. A general strategy has been to prepare 3,4-dibromomethylthiophenes bearing substituents at the 2,5-positions. Treatment with sodium sulfide led to the 1,3-dihydrothieno[3,4-*c*]thiophene derivatives, which were oxidized to the corresponding sulfoxides. The latter were subjected to a Pummerer dehydration with either acetic anhydride or base to give the target thieno[3,4-*c*]thiophene skeleton. This strategy was extended to the generation of selenium and tellurium analogues of **40**.

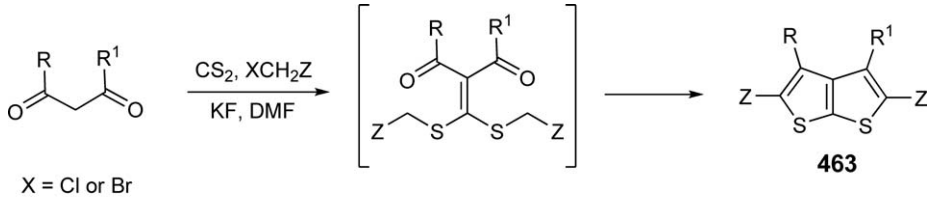
The known dibromide **464** was converted in good yield to the dinitrile **465** by reaction with buffered potassium or sodium cyanide. Reaction of 2,5-dimethoxycarbonyl-3,4-dicyanomethylthiophene **465** with thionyl chloride and selenium oxychloride gave thieno[3,4-*c*]thiophene **466** and selenolo[3,4-*c*]thiophene **467**, respectively (**Scheme 57**) <2002JOC2453>. In the case of thionyl chloride as the sulfur transfer reagent, an intermediate sulfoxide **468** must be involved, which then suffers a spontaneous base-catalyzed Pummerer reaction to give **466** in high yield.



			Yield (%) of method		
	R^1	R^2	A	B	C
462a	Me	Me	42		58
462b	Ph	Ph	22	11	
462c	OH	OH	54		42
462d	OH	Me	20		

Method A: i, K_2CO_3, DMF; ii, PhNCS; iii, $BrCH_2CO_2Et$, K_2CO_3, DMF; v, $BrCH_2CO_2Et$, K_2CO_3, acetone
Method B: i, K_2CO_3, DMF; ii, PhNCS; iii, CH_3I; iv, $HSCH_2CO_2Et$, K_2CO_3, EtOH; v, $BrCH_2CO_2Et$, K_2CO_3, acetone
Method C: i, K_2CO_3, DMF; ii, PhNCS; iii, CH_3I; iv, $BrCH_2CO_2Et$, K_2CO_3, acetone;
v, $HSCH_2CO_2Et$, K_2CO_3, EtOH

Scheme 55

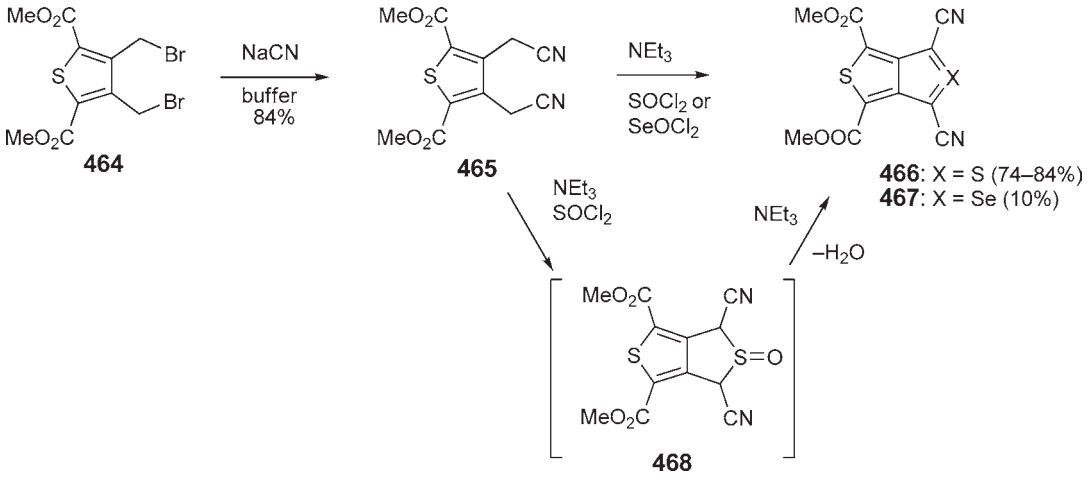


X = Cl or Br

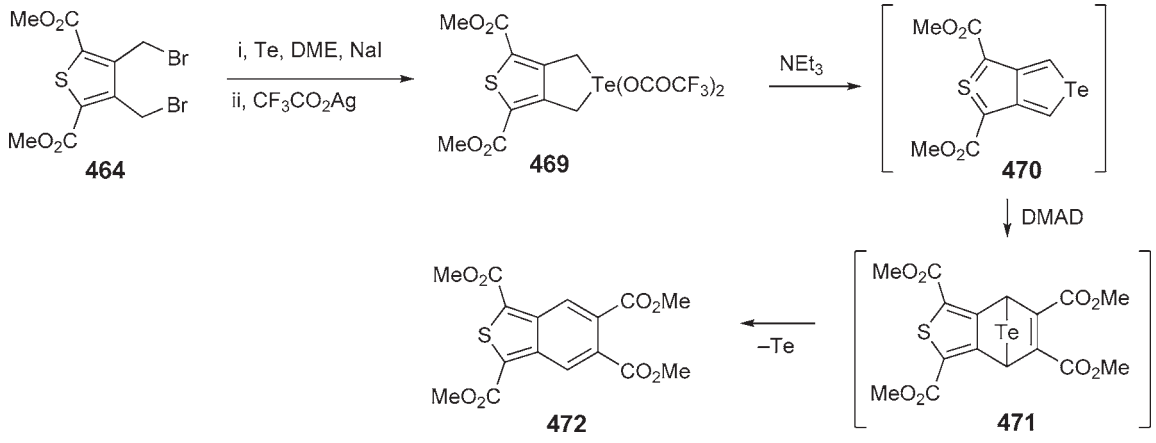
463a: R = R^1 = Me; Z = CO_2Et (50%)
463b: R = R^1 = Me; Z = COMe (46%)
463c: R = R^1 = Me; Z = COPh (40%)
463d: R = R^1 = Ph; Z = CN (67%)
463e: R = R^1 = Ph; Z = COMe (67%)
463f: R = R^1 = 4-MeC_6H_4; Z = CO_2Et (61%)
463g: R = R^1 = 4-MeC_6H_4; Z = COMe (36%)

Scheme 56

The first diheteropentalene bearing the tellurolo[3,4-*c*]thiophene framework, for example, **470**, has been generated from **464** using tellurium metal in the presence of sodium iodide in 1,2-dimethoxyethane (DME). It appears to be stable in solution and adds to DMAD across the 4,6-positions in the tellurophene part. The intermediate **471** loses tellurium and collapses to a 1,3,5,6-tetramethoxycarbonylbenzo[*c*]thiophene derivate **472** (**Scheme 58**) <2002OL1193>.



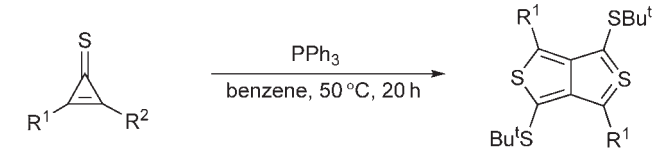
Scheme 57



Scheme 58

10.01.9.4.1(ii) Other methods

1,4-Bis(*tert*-butylthio)-3,6-diphenyl- and 3,6-di(2-thienyl)thieno[3,4-*c*]thiophenes **474a** and **474b** were synthesized from 2-(*tert*-butylthio)-3-phenyl- and 3-(2-thienyl)cyclopropenethiones **473a** and **473b** and triphenylphosphine in dry benzene at 50 °C, although similar treatment of a number of other cyclopropenethiones **473c–h** did not result in the production of the corresponding thieno[3,4-*c*]thiophene derivatives (Equation 14) <1998JOC163>.



473a: R^1 = Ph; R^2 = SBu^t
473b: R^1 = 2-thienyl; R^2 = SBu^t
473c: R^1 = 2,4,6-Tri-Pr^iPh; R^2 = SBu^t
473d: R^1 = 1-pyrrolidino; R^2 = SBu^t
473e: R^1 = NEt_2; R^2 = SBu^t
473f : R^1 = 1-pyrrolidino; R^2 = Ph
473g: R^1 = NEt_2; R^2 = Ph
473h: R^1 = R^2 = Ph

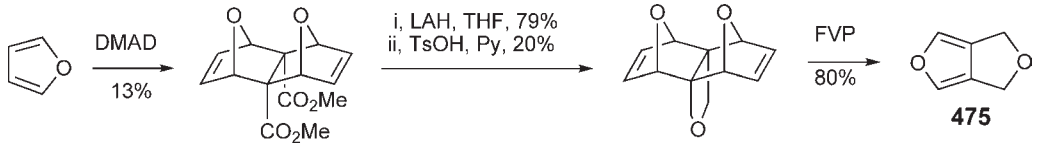
474a: R^1 = Ph
474b: R^1 = 2-thienyl

(14)

10.01.9.4.2 Other systems

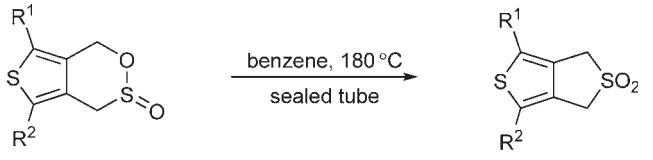
10.01.9.4.2(i) Synthesis from heteroles

1,3-Dihydrofuro[3,4-*c*]furan **475** was prepared in small scale from furan using a flash vacuum pyrolytic route incorporating a reverse Diels–Alder reaction (**Scheme 59**) <1998AJC409>.



Scheme 59

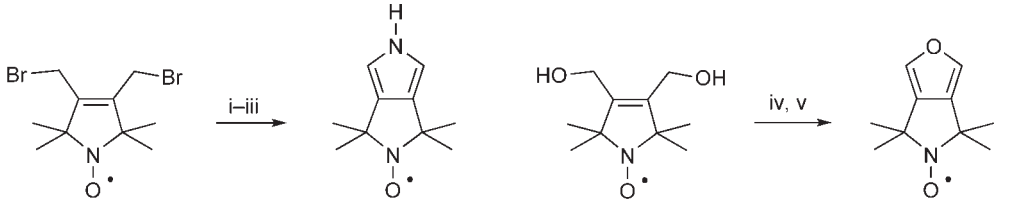
A series of 4,6-disubstituted-1,3-dihydrothieno[3,4-*c*]thiophene-2,2-dioxides (sulfolenes) **477–480** was obtained <2002JOC9267> from 5,7-disubstituted 1,4-dihydrothieno[3,4-*d*][2,3]oxathiin-3-oxides (thienosultines) **476a–d** by heating in benzene in sealed tube (Equation 15).



476a: $R^1 = R^2 = Me$ — **477** (90%)
476b: $R^1 = R^2 = Cl$ — **478** (83%)
476c: $R^1 = Me$, $R^2 = Ph$ — **479** (98%)
476d: $R^1 = R^2 = Ph$ — **480** (94%)

(15)

An interesting class of stable nitroxide radicals **482** and **484** (paramagnetic biomolecules) has been prepared from 1,4-dibromomethyl **481** <1999S973> and 1,4-dihydroxymethyl derivative **483** (**Scheme 60**) <2000S831>.

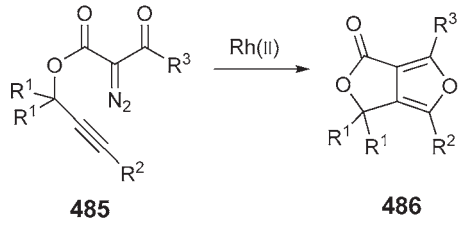


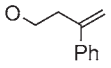
i, $TsNH_2$, K_2CO_3, KOH, 18-crown-6, dioxane, 101 °C, 6 h, 53%; ii, DDQ, toluene, 110 °C, 4 h, 14%; iii, NaOH, MeOH, 65 °C, 1 h, 78%; iv, MnO_2, DCM, 3 h, 40 °C, then rt, 2 h, 28%; v, $BF_3{\cdot}OEt_2$, THF, 0→40 °C, 10 min, 55%

Scheme 60

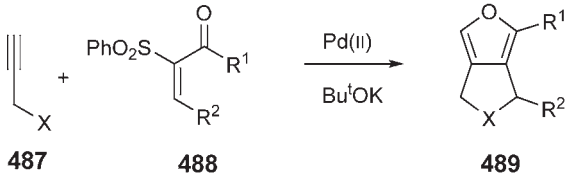
10.01.9.4.2(ii) Synthesis from acyclic precursors

A series of 2-alkynyl 2-diazo-3-oxobutanoates **485**, when treated with a catalytic quantity of rhodium(ii) acetate, afforded furo[3,4-*c*]furans **486** in good yield <2000OL2093, 2003JOC227, 2003OL3337>. The reaction proceeds by addition of a rhodium-stabilized carbenoid onto the acetylenic π-bond to give a vinyl carbenoid that subsequently cyclizes onto the neighboring carbonyl group to produce the furan ring. Similarly, pyrrolidinyl and dimethylamido systems provided the corresponding amino derivatives in these reaction conditions.



R^1	R^2	R^3	Yield (%)	Reference
H	TMS	OMe	95	2003JOC227
H	H	OMe	82	2003JOC227
H	CO_2Me	OMe	73	2003JOC227
Me	Br	OMe	90	2003JOC227
H	TMS	1-Pyrrolidino	90	2003JOC227
H	TMS	NEt_2	98	2003JOC227
Me	Br		36	2003OL3337

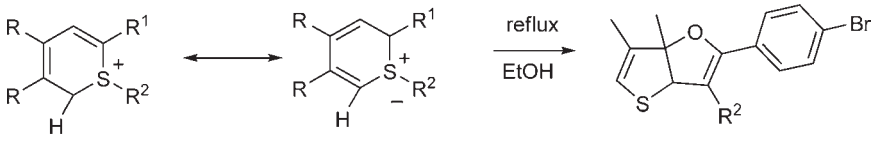
A palladium-mediated Wacker-type cyclization process was applied in an efficient single-step synthesis of furofurans and furopyrroles **489** from propargyl alcohols (or amines) **487** and arylidene (or alkylidene) *β*-ketosulfones **488** <2000JOC3223>.



X	R^1	R^2	Yield (%)
OH	Ph	Ph	57
OH	Ph	3,4-$CH_2O_2C_6H_3$	52
OH	Ph	*p*-F-C_6H_4	58
OH	Ph	Cy	42
OH	Pr^i	Ph	60
OH	*p*-NO_2-C_6H_4	Ph	47
OH	*p*-CH_3O-C_6H_4	Ph	45
OH	Ph	Ph	50
NHMe	Ph	Ph	54
NHBn	Ph	Ph	52

10.01.10 Ring Syntheses by Transformation of Another Ring

Thermal decomposition of the benzoyl-substituted λ^4-thiabenzenes **490a** and **490b** affords alkyl-rearranged 2-(4-bromophenyl)-3a,6a-dihydro-3,6,6a-trimethylthieno[3,2-*b*]furan **491a** and 2-(4-bromophenyl)-3-ethyl-3a,6a-dihydro-6,6a-dimethylthieno[3,2-*b*]furan **491b** (**Scheme 61**). A plausible mechanism for the formation of these products is also discussed <2001J(P1)2269>.



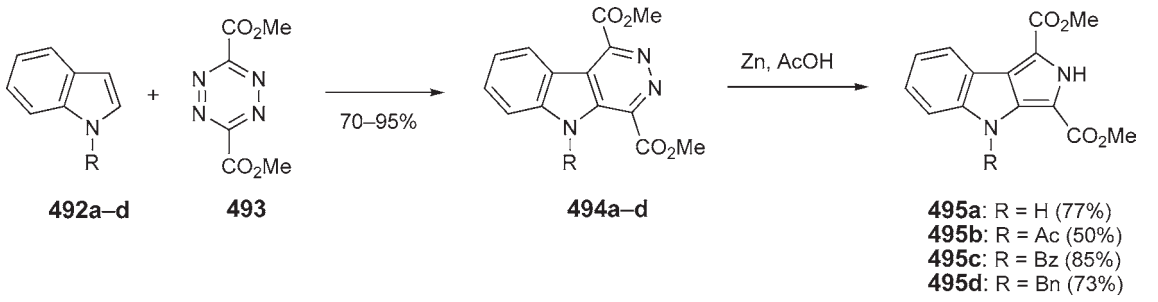
490a: R = R^2 = Me; R^1 = 4-BrC_6H_4CO
490b: R = Me; R^1 = 4-BrC_6H_4CO; R^2 = Et

491a: R^2 = Me (11%)
491b: R^2 = Et (22%)

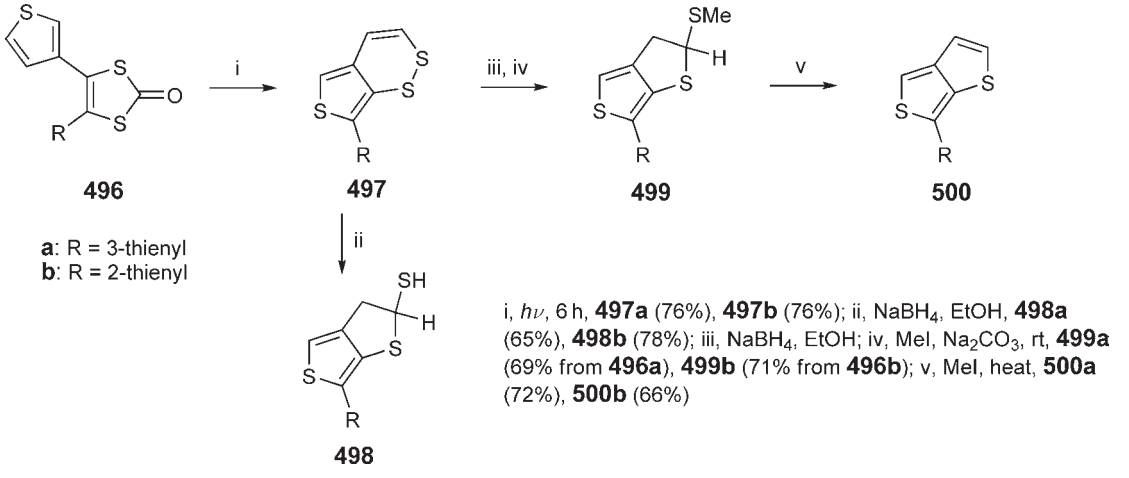
Scheme 61

A preparation of pyrrolo[3,4-*b*]indoles **495** from pyridazino[4,5-*b*]indoles **494** using a Zn/AcOH reductive ring contraction has been described <1997TL8611>. Since **494** are easily prepared from the inverse electron demand cycloaddition of indoles **492** with tetrazine **493**, this represents a simple, two-step sequence to prepare the pyrroloindoles **495** (**Scheme 62**).

Thieno[3,4-*b*]thiophenes **500** were prepared from thiophen-3-yl-substituted [1,3]dithiol-2-ones **496** in good yields <2003JOC7115>. The photochemical irradiation of **496** leads to thieno[3,4-*c*]dithiines **497** via a unique ring cleavage reaction and subsequent reductive treatment of dithiines **497** proceeds to give 2,3-dihydrothieno[3,4-*b*]thiophenes **498** and **499**. Heating of **499** in the presence of further iodomethane leads to the formation of the thieno[3,4-*b*]-thiophenes **500** (**Scheme 63**).



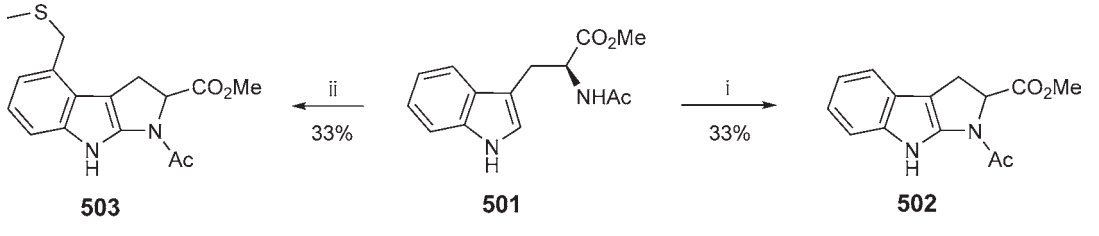
Scheme 62



Scheme 63

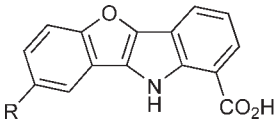
10.01.11 Synthesis of Particular Classes of Compounds

Bailey *et al.* <1999TL4593> studied the Swern oxidation <1981S165> of various indolic substrates. They found that when the Swern oxidation of *N*-acetyl tryptophan methyl ester **501** was carried out at low temperature (−78 °C), **502** was formed, but when the reaction was allowed to warm up to room temperature, before recooling and adding NEt_3, the desired cyclization was always accompanied by the introduction of the CH_2SMe group at C-4, that is, **503** was formed (**Scheme 64**). The introduction of the CH_2SMe group at C-4 indole position *via* an unprecedented rearrangement of the Swern intermediate was discussed <1999TL4593>.



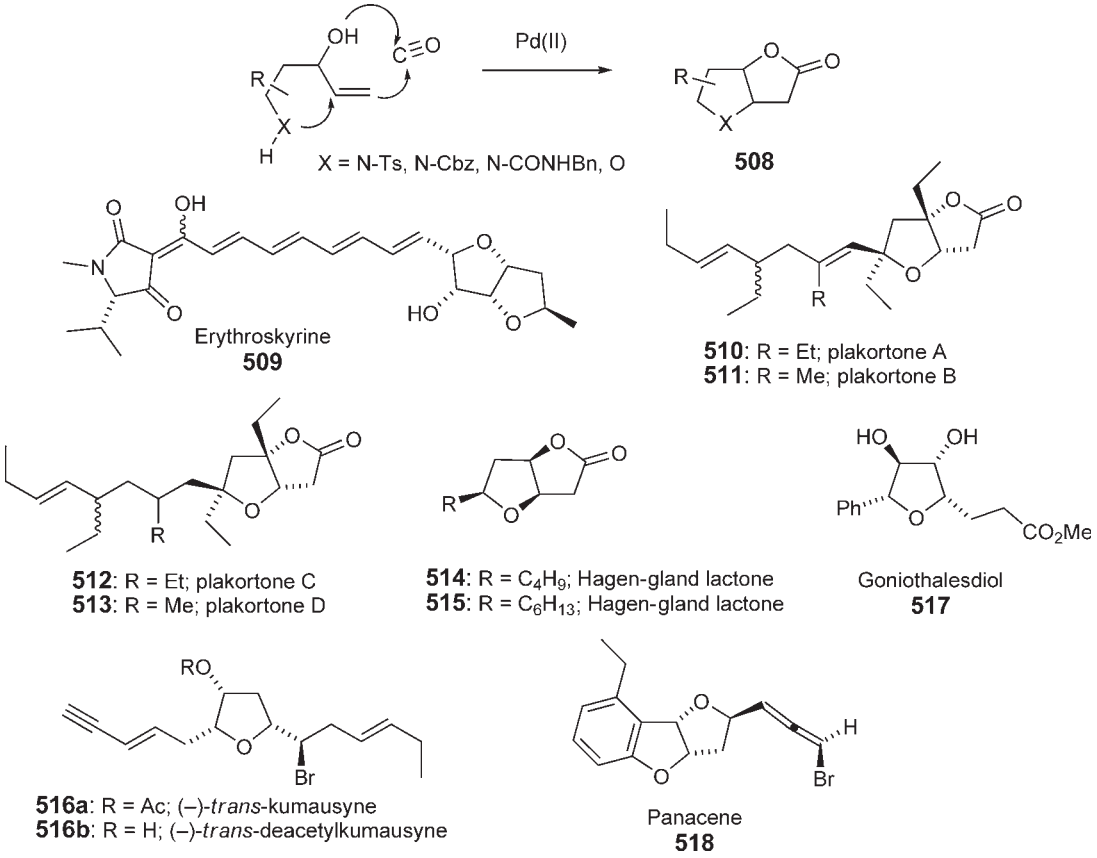
Scheme 64

A structurally novel series of substituted 10*H*-benzo[4,5]furo[3,2-*b*]indole-1-carboxylic acids **504–507** was prepared and shown to possess potent, bladder-selective smooth muscle relaxant properties and thus is potentially useful for the treatment of urge urinary incontinence. Electrophysiological studies using rat detrusor myocytes have demonstrated that prototype compound **8** produces a significant increase in hyperpolarizing current, which is iberiotoxin (IbTx)-reversed, thus consistent with activation of the large-conductance Ca^{2+}-activated potassium channel (BK_{Ca}) <2001BML2093>.



504: R = Br
505: R = I
506: R = Cl
507: R = NO_2

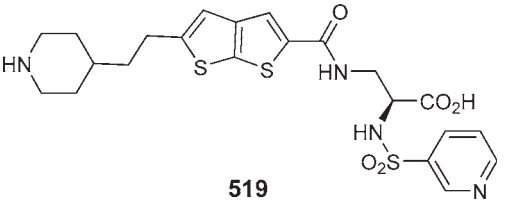
The fully saturated 5:5 fused heterocyclic systems appear in a number of interesting natural products and are versatile precursors for synthesis. A very powerful process for the construction of stereochemically defined bicycles is palladium(II)-promoted bicyclization of unsaturated polyols and amino alcohols <1991S1108, 1997S634>. Alkene polyols and amino alcohols undergo Wacker-type intramolecular oxygen-cyclization, and CO-insertion to form corresponding bicyclic skeletons with high regioselectivity and excellent *cis*-stereoselectivity (**Scheme 65**). The saturated furo[3,2-*b*]furans **508** (X = O) were used as chirons for synthesis of (+)-erythroskyrine **509** <1999J(P1)839>, plakortones A–D **510–513** <1999OL1905, 2000TL3567>, Hagen-Gland lactones **514** and **515** <1997TL3479>, (−)-*trans*-kumausyne **516** <1998JOC916>, (+)-goniothalesdiol **517** <2002TL6983, 2005T2471>, and (−)-panacene <2006OL3597)>.



Scheme 65

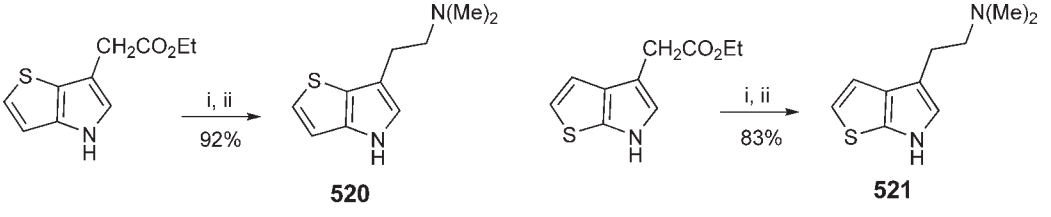
10.01.12 Important Compounds and Applications

The synthesis and pharmacology of the potent thieno[2,3-*b*]thiophene **519** nonpeptide fibrinogen receptor antagonist was reported <1997BML865, 1999JME2409>. Compound **519** inhibited the aggregation of human gel-filtered platelets with IC50 of 8 nM and demonstrated an eightfold improvement in affinity for isolated GPIIb/IIIa receptors over analogues possessing an indolinone backbone. Thus, the combination of the (*R*)-arylsulfonamides and the thieno[2,3-*b*]thiophene backbone acts in a synergistic manner to give compounds with approximately 10-fold improvement in potency over the isoindolinone series <1994BML1835>.



519

The syntheses and biological activity of 6-[2-(*N*,*N*-dimethylamino)ethyl]-4*H*-thieno[3,2-*b*]pyrrole **520** and 4-[2-(*N*,*N*-dimethylamino)ethyl]-6*H*-thieno[2,3-*b*]pyrrole **521** are reported (**Scheme 66**) <1999JME1106>. Hallucinogen-like activity of these compounds as potential bioisosteres of *N*,*N*-dimethyltryptamine was evaluated in the two-lever drug discrimination paradigm using LSD- and DOI-trained rats (LSD = lysergic acid diethylamide; DOI = 2,5-dimethoxy-4-iodoamphetamine).

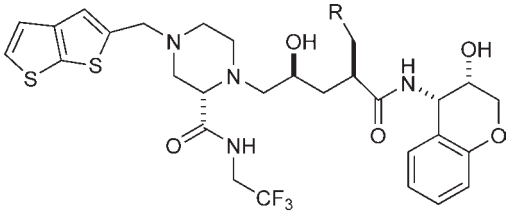


520 **521**

i, $MeAl(Cl)NMe_2$, reflux 2 h, benzene, toluene; ii, LAH, reflux 2 h, THF

Scheme 66

Duffy *et al.* <2003BML3323> synthesized HIV-1 protease inhibitors **522** with picomolar potency against protease inhibitor (PI)-resistant HIV-1 by modification of the P_1' substituent with a thieno[2,3-*b*]thiophene residue.

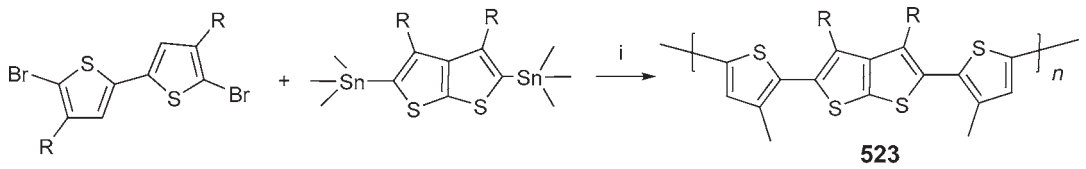


522

R = 3-pyridyl or 4-pyridyl

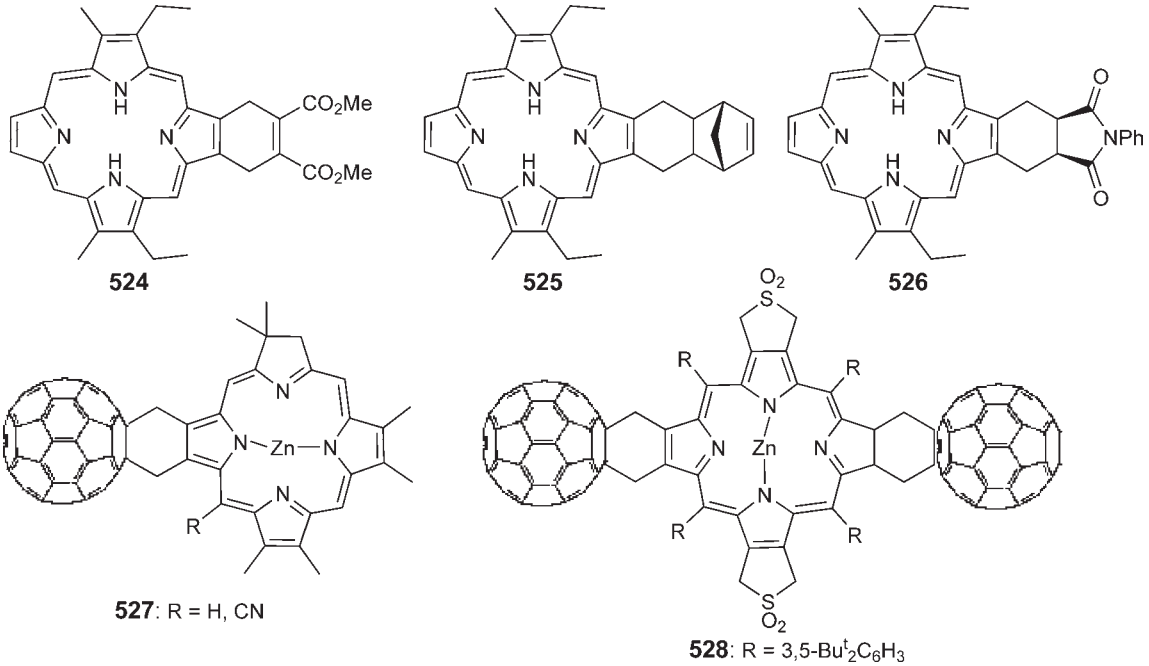
Stable polythiophene semiconductors **523** incorporating thieno[2,3-*b*]thiophene ring system were synthesized (**Scheme 67**) <2005JA1078>.

Porphyrins with *β*-fused 3-sulfolenes on the pyrroles act as porphodimethylidene precursors which can be used for a variety of Diels–Alder cycloaddition reactions <2001SL296>. Sulfolene units are prone to cleavage by thermally induced extrusion of sulfur dioxide and serve as variable building blocks for synthesis of porphyrins <2000TL3583, 2000T4085> **524–526** <1999CC803>, **527** <2000AGE599, 2000HCA2231>, and **528** <2000HCA583>.



i, $Pd_2(dba)_3$/4 P(*o*-tolyl)$_3$, MW
R = C_8H_{17}, $C_{10}H_{21}$, $C_{12}H_{28}$

Scheme 67



References

1967JA3639	M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.*, 1967, **89**, 3639.
1969JA3952	M. P. Cava and G. E. M. Husbands, *J. Am. Chem. Soc.*, 1969, **91**, 3952.
1973JA2558	M. P. Cava, N. M. Pollack, and G. A. Dieterle, *J. Am. Chem. Soc.*, 1973, **95**, 2558.
1973JA2561	M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Am. Chem. Soc.*, 1973, **95**, 2561.
1974J(P2)1004	R. J. Abraham, R. D. Lapper, K. M. Smith, and J. F. Unsworth, *J. Chem., Soc., Perkin Trans. 2*, 1974, 1004.
1975CS211	S. Gronowitz, I. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.*, 1975, **7**, 211.
B-1979MI279	J. I. G. Cadogan; 'Organophosphorus Reagents in Organic Synthesis', Academic Press, London, 1979, p. 279.
1981S165	A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
1983JA1979	B. M. Gimarc, *J. Am. Chem. Soc.*, 1983, **105**, 1979.
1983TL5345	M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, 1983, **24**, 5435.
1984CHEC(4)1037	M. P. Cava and M. V. Lakshmikantham; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katrizky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol.4, p. 1037.
1984CHEC(6)1027	C. A. Ramsden; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katrizky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 1027.
1984TL5669	T. Kumagai, S. Tanaka, and T. Mukai, *Tetrahedron Lett.*, 1984, **25**, 5669.
1985JA5801	S. Yoneda, K. Ozaki, T. Inoue, A. Sugimoto, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, 1985, **107**, 5801.
1986JA4303	B. M. Gimarc, *J. Am. Chem. Soc.*, 1986, **108**, 4303.
1988CC959	J. Nakayama, A. Ishii, Y. Kobayashi, and M. Hoshino, *J. Chem. Soc., Chem. Commun.*, 1988, 959.
1988JA1793	T. Kobayashi, K. Ozaki, and S. Yoneda, *J. Am. Chem. Soc.*, 1988, **110**, 1793.
1988JHC559	S. Yoneda, K. Ozaki, A. Tsubouchi, H. Kojima, and K. Yanagi, *J. Heterocycl. Chem.*, 1988, **25**, 559.
1989CC223	A. Tsubouchi, N. Matsumura, H. Inoue, N. Hamasaki, S. Yoneda, and K. Yanagi, *J. Chem. Soc., Chem. Commun.*, 1989, 223.
1990BCJ1026	J. Nakayama, K. S. Choi, A. Ishii, and M. Hoshino, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 1026.

1990T7587 D. H. R. Barton, J. Kervagoret, and S. Z. Zard, *Tetrahedron*, 1990, **46**, 7587.
1991CC520 A. Tsubouchi, N. Matsumura, and H. Inoue, *J. Chem. Soc., Chem. Commun.*, 1991, 520.
1991JOC78 A. Ishii, J. Nakayama, J. Kazami, Y. Ida, T. Nakamura, and M. Hoshino, *J. Org. Chem.*, 1991, **56**, 78.
1991S1108 T. Gracza, T. Hasenöhrl, U. Stahl, and V. Jäger, *Synthesis*, 1991, 1108.
1992BCJ2821 A. Ishii, Y. Ida, J. Nakayama, and M. Hoshino, *Bull. Chem. Soc Jpn.*, 1992, **65**, 2821.
1993CCC2983 J. Svoboda, M. Nič, and J. Paleček, *Collect. Czech. Chem. Commun.*, 1993, **58**, 2983.
1993MI636 K. Kanbe, H. Naganawa, T. Nakamura, Y. Okami, and T. Takeuchi, *Biosci. Biotech. Biochem.*, 1993, **57**, 636.
1994BML1835 M. S. Egbertson, A. M. Naylor, G. D. Hartman, J. J. Cook, R. J. Gould, M. A. Holahan, J. J. Lynch, Jr., R. J. Lynch, M. T. Stranieri, and L. M. Vassallo, *Bioorg. Med. Chem. Lett.*, 1994, **4**, 1835.
1994H(38)143 K. S. Choi, K. Sawada, H. Dong, M. Hoshino, and J. Nakayama, *Heterocycles*, 1994, **38**, 143.
1994JOC2223 N. Beye and M. P. Cava, *J. Org. Chem.*, 1994, **59**, 2223.
1995BML1133 R. S. Phillips, L. A. Cohen, U. Annby, D. Wensbo, and S. Gronowitz, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1133.
1995CCC709 V. Bobošík, A. Krutošíková, and M. Dandárová, *Collect. Czech. Chem. Commun.*, 1995, **60**, 709.
1995J(P1)2663 A. Jeevanandam and P. C. Srinivasan, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2663.
1995JHC1641 P. Olesen, J. Hansen, and M. Engelstoft, *J. Heterocycl. Chem.*, 1995, **32**, 1641.
1995S87 T. Saito, H. Kikuchi, and A. Kondo, *Synthesis*, 1995, 87.
1995T193 Ch.-K. Sha and R.-S. Lee, *Tetrahedron*, 1995, **51**, 193.
1995T10013 J. M. Peach, A. J. Pratt, and J. S. Snaith, *Tetrahedron*, 1995, **51**, 10013.
1995T10323 D. Wensbo, U. Annby, and S. Gronowitz, *Tetrahedron*, 1995, **51**, 10323.
1995WO9525110 P. Jakobsen, A. Kanstrup, P. Faarup and P. Olesen (Novo Nordisk A/S, Denmark.), *WO Pat.* 9525110 (1995) (*Chem. Abstr.*, 1995, **124**, 117290).
1996AGE2638 G. Subramanian, P. v. R. Schleyer, and H. Jiao, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2638.
1996CC117 E. T. Pelkey, G. W. Gribble, and L. Chang, *J. Chem. Soc., Chem. Commun.*, 1996, 1909.
1996CCC657 L. Novotný, A. Vachálková, and A. Piskala, *Collect. Czech. Chem. Commun.*, 1996, **61**, 657.
1996CCC888 J. Svoboda, P. Pihera, P. Sedmera, and J. Paleček, *Collect. Czech. Chem. Commun.*, 1996, **61**, 888.
1996CHEC-II(7)1 A. Krutošíková; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol.7, p. 1.
1996H(43)2361 K. Satake, K. Yano, M. Fujiwara, and M. Kimura, *Heterocycles*, 1996, **43**, 2361.
1996JHC119 A. P. Halverson, L. W. Castle, and R. N. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 119.
1996JHC185 J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1996, **33**, 185.
1996JOC4319 G. W. Gribble, F. L. Switzer, J. H. Bushweller, J. G. Jewett, J. H. Brown, J. L. Dion, C. H. Bushweller, M. P. Byrn, and C. E. Strouse, *J. Org. Chem.*, 1996, **61**, 4319.
1996JOC6166 C. O. Kappe and A. Padwa, *J. Org. Chem.*, 1996, **61**, 6166.
1996T471 J. Nakayama, H. Dong, K. Sawada, A. Ishii, and S. Kumakura, *Tetrahedron*, 1996, **52**, 471.
1996T1011 V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1996, **52**, 1011.
1996T6893 T. Akita and K. Kobayashi, *Tetrahedron*, 1996, **52**, 6893.
1996TL3487 Ch.-K. Sha, J.-F. Yang, and Ch.-J. Chang, *Tetrahedron Lett.*, 1996, **37**, 3487.
1996T14975 D. Wensbo and S. Gronowitz, *Tetrahedron*, 1996, **52**, 14975.
1997BML865 J. D. Prugh, R. J. Gould, R. J. Lynch, G. Zhang, J. J. Cook, M. A. Holahan, M. T. Stranieri, G. R. Sitko, S. L. Gaul, R. A. Bednar, *et al.*, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 865.
1997CC993 G. W. Gribble, W. R. Sponholtz, III, F. L. Switzer, F. J. Amato, and M. P. Byrn, *J. Chem. Soc., Chem. Commun.*, 1997, 993.
1997CC1873 E. T. Pelkey and G. W. Gribble, *J. Chem. Soc., Chem. Commun.*, 1997, 1873.
1997CC2355 L. S. Fuller, B. Iddon, and K. A. Smith, *J. Chem. Soc., Chem. Commun.*, 1997, 2355.
1997CCC1468 P. Váchal, P. Pihera, and J. Svoboda, *Collect. Czech. Chem. Commun.*, 1997, **62**, 1468.
1997CCC1613 A. Krutošíková, S. Mastik, M. Dandárová, and A. Lyčka, *Collect. Czech. Chem. Commun.*, 1997, **62**, 1613.
1997CPA398 M. Bencková, A. Krutošíková, and M. Dandárová, *Chem. Pap.*, 1997, **51**, 398.
1997CPA412 R. Sleziak and A. Krutošíková, *Chem. Pap.*, 1997, **51**, 412.
1997J(P1)2483 M. Black, J. I. G. Cadogan, H. McNab, A. D. MacPherson, V. P. Roddam, C. Smith, and H. R. Swenson, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2483.
1997J(P1)2843 C.-C. Yang, H.-M. Tai, and P.-J. Sun, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2843.
1997J(P1)3127 M. G. Kulkarni and D. S. Pendharkar, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3127.
1997H(46)199 T. Suzuki, H. Ohyabu, and H. Takayama, *Heterocycles*, 1997, **46**, 199.
1997H(45)1891 S. Yasuike, J. Kurita, and T. Tsuchiya, *Heterocycles*, 1997, **45**, 1891.
1997JHC1597 J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1997, **34**, 1597.
1997MI299 T.-sh. Chou, Ch.-Y. Tsai, and Sh.-J. Lee, *J. Chin. Chem. Soc.*, 1997, **44**, 299.
1997JST315 I. Novak, *J. Mol. Struct.*, 1997, **398**, 315.
1997MOL69 A. Krutošíková, C. A. Ramsden, M. Dandárová, and A. Lyčka, *Molecules*, 1997, **2**, 69.
1997MI389 A. Vachálková and L. Novotný, *Neoplasma*, 1997, **44**, 389.
1997S634 W. Hümmer, E. Dubois, T. Gracza, and V. Jäger, *Synthesis*, 1997, 634.
1997S1420 M. G. Kulkarni and R. M. Rasne, *Synthesis*, 1997, 1420.
1997T3167 M. G. Kulkarni and D. S. Pendharkar, *Tetrahedron*, 1997, **53**, 3167.
1997TL1459 M. G. Kulkarni, D. S. Pendharkar, and R. M. Rasne, *Tetrahedron Lett.*, 1997, **38**, 1459.
1997TL3479 G. C. Paddon-Jones, Ch. J. Moore, D. J. Brecknell, W. A. König, and W. Kitching, *Tetrahedron Lett.*, 1997, **38**, 3479.
1997TL3639 M. G. H. Vicente, A. C. Tome, A. Walter, and J. A. S. Cavaleiro, *Tetrahedron Lett.*, 1997, **38**, 3639.
1997TL5315 Ch.-W. Ko and T.-sh. Chou, *Tetrahedron Lett.*, 1997, **38**, 5315.
1997TL8611 K. Daly, R. Nomak, and J. K. Snyder, *Tetrahedron Lett.*, 1997, **50**, 8611.
1998AJC409 J. H. Buttery and D. Wege, *Aust. J. Chem.*, 1998, **51**, 409.
1998CCC681 P. Pihera, J. Paleček, and J. Svoboda, *Collect. Czech. Chem. Commun.*, 1998, **63**, 681.
1998J(P1)2479 M. G. Kulkarni and R. M. Rasne, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2479.

1998J(P1)3937 R. A. Aitken, G. Burns, and J. J. Morrison, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3937.
1998JHC71 A. Shafiee, M. A. Ebrahimzadeh, J. Shabazi, and S. Hamedpanah, *J. Heterocycl. Chem.*, 1998, **35**, 71.
1998JHC725 H. Sashida and S. Yasuike, *J. Heterocycl. Chem.*, 1998, **35**, 725.
1998JHC1441 J.-K. Luo, R. F. Federspiel, and R. N. Castle, *J. Heterocycl. Chem.*, 1998, **35**, 1441.
1998JOC163 N. Matsamura, H. Tanaka, Y. Yagyu, K. Mizuno, H. Inoue, K. Takada, M. Yasui, and F. Iwasaki, *J. Org. Chem.*, 1998, **63**, 163.
1998JOC916 J. Boukouvalas, G. Fortier, and I.-I. Radu, *J. Org. Chem.*, 1998, **63**, 916.
1998SL1276 L. H. Thoresen, H. Kim, M. B. Welch, A. Burghart, and K. Burgess, *Synlett*, 1998, 1276.
1998S1372 F. Effenberger and G. Grube, *Synthesis*, 1998, 1372.
1998SL1061 G. W. Gribble, E. T. Pelkey, and F. L. Switzer, *Synlett*, 1998, 1061.
1998USP5536721 P. Jakobsen, A. Kanstrup, P. Faarup, P. Olesen, and J. Lundbech, (Novo Nordisk A/S, Denmark), *US Pat.* 5536721 (1998) (*Chem. Abstr.*, 1998, **129**, 148909).
1999BML637 M. Welch and R. S. Phillips, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 637.
1999CC803 M. J. Gunter, H. Tang, and R. N. Warrener, *J. Chem. Soc., Chem. Commun.*, 1999, 803.
1999CCC321 R. Sleziak and A. Krutošíková, *Collect. Czech. Chem. Commun.*, 1999, **64**, 321.
1999CCC389 P. Pihera, H. Dvořáková, and J. Svoboda, *Collect. Czech. Chem. Commun.*, 1999, **64**, 389.
1999CCC1135 R. Sleziak, S. Balážiová, and A. Krutošíková, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1135.
1999CPA125 A. Krutošíková and M. Dandárová, *Chem. Pap.*, 1999, **53**, 125.
1999HCO305 M. Welch and R. S. Phillips, *Heterocycl. Commun.*, 1999, **5**, 305.
1999J(P1)839 D. J. Dixon, S. V. Ley, T. Gracza, and P. Szolcsanyi, *J. Chem. Soc., Perkin Trans. 1*, 1999, 839.
1999JHC249 H.-H. Chen, J. A. May, and V. M. Lynch, *J. Heterocyclic. Chem.*, 1999, **36**, 249.
1999JME1106 J. B. Blair, D. Marona-Lewicka, A. Kanthasamy, V. L. Lucaites, D. L. Nelson, and D. E. Nichols, *J. Med. Chem.*, 1999, **42**, 1116.
1999JME2409 M. S. Egbertson, J. J. Cook, B. Bednar, J. D. Prugh, R. A. Bednar, S. L. Gaul, R. J. Gould, G. D. Hartman, C. F. Homnick, M. A. Holahan, *et al.*, *J. Med. Chem.*, 1999, **42**, 2409.
1999JOC7813 A. Burghart, A. H. Kim, M. B. Welch, L. H. Thoresen, J. Reibenspies, K. Burgess, F. Bergström, and L. B.-A. Johansson, *J. Org. Chem.*, 1999, **64**, 7813.
1999OL1905 C. Paddon-Jones, N. L. Hungerford, P. Hayes, and W. Kitching, *Org. Lett.*, 1999, **1**, 1905.
1999S973 T. Kálai, M. Balog, J. Jekö, and K. Hideg, *Synthesis*, 1999, 973.
1999S1117 E. T. Pelkey and G. W. Gribble, *Synthesis*, 1999, 1117.
1999S2030 S. H. Mashraqui, H. Hariharasubrahmanian, and S. Kumar, *Synthesis*, 1999, 2030.
1999T8997 D. P. Curran, S. Hadida, and S.-Y. Kim, *Tetrahedron*, 1999, **55**, 8997.
1999TL4593 P. D. Bailey, P. J. Cochrane, F. Irvine, K. M. Morgan, D. P. J. Pearson, and K. T. Veal, *Tetrahedron Lett.*, 1999, **40**, 4593.
2000AGE599 F. P. Montforts and O. Kutzki, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 599.
2000ARK409 A. Krutošíková, M. Lácová, M. Dandárová, and J. Chovancová, *ARKIVOC*, 2000, **1**, Part (iii), 409.
2000CCC58 P. Pihera and J. Svoboda, *Collect. Czech. Chem. Commun.*, 2000, **65**, 58.
2000CCC1939 K. Černovská, M. Nič, P. Pihera, and J. Svoboda, *Collect. Czech. Chem.*, 2000, **65**, 1939.
2000HCA583 B. Kräutler, C. S. Sheehan, and A. Rieder, *Helv. Chim. Acta*, 2000, **83**, 583.
2000HCA2231 O. Kutzki, A. Walter, and F. P. Montforts, *Helv. Chim. Acta*, 2000, **83**, 2231.
2000JOC2900 J. Chen, A. Burghart, A. Derecskei-Kovacs, and K. Burgess, *J. Org. Chem.*, 2000, **65**, 2900.
2000JOC3223 N. Monteiro and G. Balme, *J. Org. Chem.*, 2000, **65**, 3223.
2000OL2093 A. Padwa and C. S. Straub, *Org. Lett.*, 2000, **2**, 2093.
2000PJC207 R. Sleziak, A. Krutošíková, M. K. Cyrański, and T. M. Krygovski, *Pol. J. Chem.*, 2000, **74**, 207.
2000S831 T. Kálai, J. Jekö, and K. Hideg, *Synthesis*, 2000, 831.
2000T4085 M. J. Cook and A. Jafari-Fini, *Tetrahedron*, 2000, **56**, 4085.
2000T7573 W. M. Abdou and A. A. Kamel, *Tetrahedron*, 2000, **56**, 7573.
2000T10133 G. W. Gribble, E. T. Pelkey, W. M. Simon, and H. A. Trujillo, *Tetrahedron*, 2000, **56**, 10133.
2000TL3567 M. F. Semmelhack and P. Shanmugam, *Tetrahedron Lett.*, 2000, **41**, 3567.
2000TL3583 O. Siri, L. Jaquinod, and K. M. Smith, *Tetrahedron Lett.*, 2000, **41**, 3583.
2001BML2093 J. A. Butera, S. A. Antane, B. Hirth, J. R. Lennox, J. H. Sheldon, N. W. Norton, D. Warga, and T. M. Argentieri, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2093.
2001CCC1615 D. Romanová, A. Vachálková, K. Horváthová, and A. Krutošíková, *Collect. Czech. Chem. Commun.*, 2001, **65**, 1615.
2001EJO4543 M. Diaz, A. Cobas, E. Guitian, and L. Castedo, *Eur. J. Org. Chem.*, 2001, 4543.
2001J(P1)37 D. Brugier, F. Outurquin, and C. Paulmier, *J. Chem. Soc., Perkin Trans. 1*, 2001, 37.
2001J(P1)2269 H. Shimizu, N. Kudo, T. Kataoka, and M. Hori, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2269.
2001J(P1)2583 A. R. Katritzky, V. Y. Vvedensky, and D. O. Tymoshenko, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2486.
2001JHC1167 A. Comel and G. Kirsch, *J. Heterocycl. Chem.*, 2001, **30**, 1167.
2001JOC426 G. Bhattacharya, T.-L. Su, Ch.-M. Chia, and K.-T. Chen, *J. Org. Chem.*, 2001, **66**, 426.
2001JOC2470 S. Ito, S. Kikuchi, T. Okujima, N. Morita, and T. Asao, *J. Org. Chem.*, 2001, **66**, 2470.
2001KGS1664 A. Krutošíková, L. Kryštofová-Labudová, and M. Dandárová, *Khim. Geterotsikl. Soedin.*, 2001, 1664.
2001SL296 H. Ishida, K. Itoh, S. Ito, N. Ono, and M. Ohno, *Synlett*, 2001, 296.
2001SL1731 G. Sommen, A. Comel, and G. Kirsch, *Synlett*, 2001, 1731.
2001T8867 M. K. Cyrański, T. M. Krygovski, A. Krutošíková, and R. Sleziak, *Tetrahedron*, 2001, **57**, 8867.
2002JOC1001 G. W. Gribble, J. Jiang, and Y. Liu, *J. Org. Chem.*, 2002, **67**, 1001.
2002JOC2453 R. R. Amaresh, M. V. Lakshmikantham, J. W. Baldwin, M. P. Cava, R. M. Metzger, and R. D. Rogers, *J. Org. Chem.*, 2002, **67**, 2453.
2002JOC9267 W.-D. Liu, Ch.-Ch. Chi, I.-F. Pai, A.-T. Wu, and W.-Sh. Chung, *J. Org. Chem.*, 2002, **67**, 9267.
2002OL387 M. M. Krayushkin, V. N. Yarovenko, S. L. Semenov, I. V. Zavarzin, A. V. Ignatenko, A. Yu. Martynkin, and B. M. Uzhinov, *Org. Lett.*, 2002, **4**, 387.
2002OL1193 D. Rajagopal, M. V. Lakshmikantham, E. Morkved, and M. P. Cava, *Org. Lett.*, 2002, **4**, 1193.

2002SL207 T. Watanabe, N. Miyaura, and A. Suzuki, *Synlett*, 2002, 207.
2002TL6983 M. Babjak, P. Kapitan, and T. Gracza, *Tetrahedron Lett.*, 2002, **43**, 6983.
2003BML3323 J. L. Duffy, B. A. Kirk, N. J. Kevin, K. T. Chapman, W. A. Schleif, D. B. Olsen, M. Stahlhut, C. A. Rutkowski, L. C. Kuo, L. Jin, *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3323.
2003JOC227 A. Padwa and C. S. Straub, *J. Org. Chem.*, 2003, **68**, 227.
2003JOC7115 S. J. Roberts-Bleming, G. J. Davies, M. Kalaji, and P. J. Murphy, *J. Org. Chem.*, 2003, **68**, 7115.
2003OL3337 K. R. Crawford, S. K. Bur, C. S. Straub, and A. Padwa, *Org. Lett.*, 2003, **5**, 3337.
2003T1477 Ch.-K. Sha, H.-Y. Hsu, S.-Y. Cheng, and Y.-L. Kuo, *Tetrahedron*, 2003, **59**, 1477.
2003T1557 G. Sommen, A. Comel, and G. Kirsch, *Tetrahedron*, 2003, **59**, 1557.
2003T3737 I. C. F. R. Ferreira, M.-J. R. P. Queiroz, and G. Kirsch, *Tetrahedron*, 2003, **59**, 3737.
2003TL4257 K. L. Milkiewicz, D. J. Parks, and T. Lu, *Tetrahedron Lett.*, 2003, **44**, 4257.
2004AXE2493 W. Clegg and D. G. Watson, *Acta Crystallogr., Sect. E*, 2004, **60**, 2493.
2004EJO2589 R. Engqvist, A. Javaid, and J. Bergman, *Eur. J. Org. Chem.*, 2004, 2589.
2004JST107 S. H. Mashraqui, M. Ashraf, H. Hariharasubrahmanian, R. M. Kellogg, and A. Meetsma, *J. Mol. Struct.*, 2004, **689**, 107.
2004MOL11 Z. Puterová, H. Sterk, and A. Krutošíková, *Molecules*, 2004, **9**, 11.
2004MOL241 Z. Puterová, A. Krutošíková, A. Lyčka, and T. Ďurčeková, *Molecules*, 2004, **9**, 241.
2004OL533 J. H. Smitrovich and I. W. Davies, *Org. Lett.*, 2004, **6**, 533.
2004TA3461 J.-X. Du, H.-Y. Huang, and P.-Q. Huang, *Tetrahedron Asymmetry*, 2004, **15**, 3461.
2004TL2189 A. Machara, M. Kurfürst, V. Kozmík, H. Petříčková, H. Dvořáková, and J. Svoboda, *Tetrahedron Lett.*, 2004, **45**, 2189.
2004TL8363 V. D. Chaudhari, K. S. A. Kumar, and D. D. Dhavale, *Tetrahedron Lett.*, 2004, **45**, 8363.
2004S451 G. Sommen, A. Comel, and G. Kirsch, *Synthesis*, 2004, 451.
2005CCC2101 R. Gašparová, M. Lácová, and A. Krutošíková, *Collect. Czech. Chem. Commun.*, 2005, **70**, 2101.
2005JA1078 M. Heeney, C. Bailey, K. Genevicius, M. Shkunov, D. Sparrowe, S. Tierney, and I. McCulloch, *J. Am. Chem. Soc.*, 2005, **127**, 1078.
2005CEC311 P. Gajdoš, S. Pavlíková, F. Bureš, and A. Krutošíková, *Cent. Eur. J. Chem.*, 2005, **3**, 311.
2005CEC622 R. Gašparová, D. Zbojek, M. Lácová, K. Král'ová, A. Gatial, B. Horváth, and A. Krutošíková, *Cent. Eur. J. Chem.*, 2005, **3**, 622.
2005SL127 P. Appukkuttan, E. Van der Eycken, and W. Dehaen, *Synlett*, 2005, 127.
2005T1221 M. N. Matos, C. A. M. Afonsoc, and R. A. Batey, *Tetrahedron*, 2005, **61**, 1221.
2005T2471 M. Babjak, P. Kapitán, and T. Gracza, *Tetrahedron*, 2005, **61**, 2471.
2006KGS825 P. Gajdoš, J. Miklovič, and A. Krutošíková, *Khim. Geterotsikl. Soed.*, 2006, 825.
2006OL3597 J. Boukovalas, M. Pouliot, J. Robichaud, S. MacNeil, and V. Snieckus, *Org. Lett.*, 2006, **8**, 3597.

Biographical Sketch



Alžbeta Krutošíková started her scientific carrier at Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, in Bratislava. She completed her Ph.D. degree on the synthesis and reaction studies of arylfuran derivatives. During a postdoctoral stay in 1974–75 at University of East Anglia, she joined the group of Prof. A. R. Katritzky. She finished her habilitation in 1978 and D.Sc. at Comenius University Bratislava in 1988. Since 1991, she has been professor of organic chemistry at the Slovak Technical University in Bratislava. In 1999, she moved from STU to UCM in Trnava as Chair of the Department of Chemistry to organize a research group. Her scientific achievements are focused on the synthesis of new heterocyclic compounds, their characterization, and description of their reactivity in the context of the synthesis of the complex compounds. To date, she has synthesized with her research group more than 500 new organic substances, mainly with heterocyclic structure, and participated on the quantitative studies of aromaticity of π-electron-rich newly synthesized furo[*b*]pyrroles.



Tibor Gracza was born on 11 July 1956 in Slovakia. He completed his Ph.D. in furan chemistry under the supervision of J. Kováč at the Slovak University of Technology in Bratislava, Slovakia, in 1986. After working as a Humboldt fellow with V. Jäger on cycloaddition reactions and carbonylations at the University of Würzburg, Germany (1988–89, 1991), he joined the group of A. Vasella in Zürich, Switzerland (1992). In 1992, he returned to Bratislava and started his own research projects. He finished his habilitation in 1996 and D.Sc. at Comenius University Bratislava in 2000. Since 2001, he has been professor of organic chemistry at the Slovak University of Technology in Bratislava. His current research interests in addition to transition metal catalysis include the development of new synthetic methods toward the synthesis of natural products.

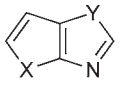
10.02
Bicyclic 5-5 Systems: Three Heteroatoms 1:2

A. J. Moore
University of Sunderland, Sunderland, UK
© 2008 Elsevier Ltd. All rights reserved.

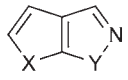
10.02.1 Introduction **66**
10.02.2 Theoretical Methods **67**
10.02.3 Experimental Structural Methods **67**
10.02.4 Thermodynamic Aspects **67**
10.02.5 Reactivity of Fully Conjugated Rings **68**
10.02.5.1 Electrophilic Attack on Carbon and Nitrogen **68**
10.02.5.2 Photochemistry and Thermolysis **68**
10.02.5.3 Metallation **69**
10.02.5.4 Cycloadditions and Dipole-Mediated Transformations **70**
10.02.6 Reactivity of Substituents Attached to Ring Carbon Atoms **70**
10.02.6.1 Metal–Halogen Exchange **70**
10.02.6.2 Direct Substitution **71**
10.02.7 Ring Synthesis of Fully Conjugated Systems **74**
10.02.7.1 Annelations onto π-Excessive Heterocycles **84**
10.02.7.1.1 Oxidative [5+0] and [4+1] cycloamination 84
10.02.7.1.2 [5+0] Electrophilic cyclizations 86
10.02.7.1.3 Nitrene-mediated [5+0] cyclizations 88
10.02.7.1.4 Direct [4+1] thiation 88
10.02.7.1.5 [5+0] and [4+1] Carbon closures 88
10.02.7.1.6 [2+3] Annelations using bisnucleophiles 90
10.02.7.1.7 Miscellaneous cyclizations 92
10.02.7.2 Annelations onto π-Deficient Heterocycles **93**
10.02.7.2.1 Claisen, Thorpe, or aldol cyclizations 93
10.02.7.2.2 Amination, thiation, and selenization 98
10.02.7.2.3 Electrophilic cyclizations 98
10.02.7.2.4 Nitrene-based cyclizations 99
10.02.7.2.5 Miscellaneous cyclizations 99
10.02.8 Ring Syntheses by Transformation of Other Heterocyclic Systems **101**
10.02.8.1 Oxidative Methods **101**
10.02.8.2 Miscellaneous Methods **102**
10.02.9 Syntheses and Reactivity of Nonconjugated Systems **102**
10.02.9.1 1,3-Dipolar Cycloaddition Methodology **102**
10.02.9.2 Miscellaneous Methodology **111**
10.02.10 Important Compounds and Applications **117**
10.02.11 Further Developments **119**
References **122**

10.02.1 Introduction

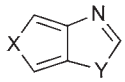
The bicyclic 5-5 heterocycles with 1:2-heteroatom orientation cover a range of known topological types; the parent aromatic heterocycles for which derivatives are currently known are shown in **Figure 1**. The chemistry of the heterocycles covered in this chapter is exceptionally diverse and various aspects were discussed in CHEC(1984)



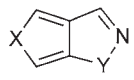
X = NH, Y = NH *1H,4H*-pyrrolo[2,3-*d*]imidazole
X = NH, Y = S pyrrolo[2,3-*d*]thiazole
X = NH, Y = Se pyrrolo[2,3-*d*]selenazole
X = O, Y = S furo[2,3-*d*]thiazole
X = S, Y = NH 1*H*-thieno[2,3-*d*]imidazole (*)
X = S, Y = O thieno[2,3-*d*]oxazole
X = S, Y = S thieno[2,3-*d*]thiazole (*)
X = S, Y = Se thieno[2,3-*d*]selenazole
X = Se, Y = S selenolo[2,3-*d*]thiazole



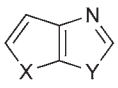
X = NH, Y = O pyrrolo[3,2-*d*]isoxazole
X = NH, Y = NH *1H*-pyrrolo[2,3-*c*]pyrazole
X = NH, Y = S pyrrolo[3,2-*d*]isothiazole
X = NH, Y = Se pyrrolo[3,2-*d*]isoselenazole
X = O, Y = NH *1H*-furo[2,3-*c*]pyrazole
X = O, Y = S furo[3,2-*d*]isothiazole
X = O, Y = Se furo[3,2-*d*]isoselenazole
X = S, Y = NH *1H*-thieno[2,3-*c*]pyrazole
X = S, Y = S thieno[3,2-*d*]isothiazole (*)
X = S, Y = Se thieno[3,2-*d*]isoselenazole (*)
X = Se, Y = S selenolo[3,2-*d*]isothiazole (*)
X = Se, Y = Se selenolo[3,2-*d*]isoselenazole (*)



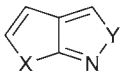
X = NH, Y = NH *3H*-pyrrolo[3,4-*d*]imidazole
X = NH, Y = S pyrrolo[3,4-*d*]thiazole
X = O, Y = O furo[3,4-*d*]oxazole
X = O, Y = S furo[3,4-*d*]thiazole
X = S, Y = NH *3H*-thieno[3,4-*d*]imidazole
X = S, Y = S thieno[3,4-*d*]thiazole
X = Se, Y = S selenolo[3,4-*d*]thiazole



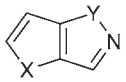
X = NH, Y = O pyrrolo[3,4-*d*]isoxazole
X = S, Y = Se thieno[3,4-*d*]isoselenazole (*)



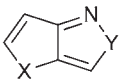
X = NH, Y = NH *3H,4H*-pyrrolo[2,3-*d*]imidazole
X = NH, Y = S pyrrolo[3,2-*d*]thiazole
X = S, Y = NH *3H*-thieno[2,3-*d*]imidazole
X = S, Y = S thieno[3,2-*d*]thiazole (*)



X = NH, Y = NH *2H*-pyrrolo[2,3-*c*]pyrazole
X = NH, Y = O pyrrolo[2,3-*c*]isoxazole
X = NH, Y = S pyrrolo[2,3-*c*]isothiazole
X = O, Y = NH furo[2,3-*c*]pyrazole
X = S, Y = NH *2H*-thieno[2,3-*c*]pyrazole
X = S, Y = S thieno[2,3-*c*]isothiazole (*)



X = NH, Y = NH *1H*-pyrrolo[2,3-*d*]isopyrazole
X = O, Y = NH *1H*-furo[2,3-*d*]isopyrazole
X = S, Y = NH *1H*-thieno[2,3-*d*]isopyrazole
X = S, Y = S thieno[2,3-*d*]isothiazole (*)
X = S, Y = Se thieno[2,3-*d*]isoselenazole (*)
X = Se, Y = O selenolo[2,3-*d*]isoxazole
X = Se, Y = S selenolo[2,3-*d*]isothiazole (*)
X = Se, Y = Se selenolo[2,3-*d*]isoselenazole (*)



X = O, Y = NH *2H*-furo[3,2-*c*]pyrazole
X = O, Y = O furo[3,2-*c*]isoxazole (*)
X = O, Y = S furo[3,2-*c*]isothiazole (*)
X = S, Y = NH *2H*-thieno[3,2-*c*]pyrazole
X = S, Y = O thieno[2,3-*d*]isoxazole (*)
X = S, Y = S thieno[2,3-*d*]isothiazole (*)
X = Se, Y = NH *2H*-selenolo[3,2-*c*]pyrazole
X = Se, Y = O selenolo[3,2-*c*]isoxazole (*)

Figure 1 Known bicyclic 5-5 heterocycles with 1:2-heteroatom orientation ((*) represents heterocycles for which the unsubstituted parent is known).

<1984CHEC(4)741, 1984CHEC(5)32, 1984CHEC(6)333, 1984CHEC(6)973, 1984CHEC(6)1027>, and expanded upon in CHEC-II(1996) <1996CHEC-II(7)49>. This review will build upon these articles, highlighting advances in the period 1995–2006. The format of this chapter follows that established in CHEC-II(1996) <1996CHEC-II(7)49>; the sections on the synthesis and reactivity of the nonconjugated heterocycles are again combined to offer an overview of the more interesting aspects of their synthesis and chemistry rather than a comprehensive review. Not included in this chapter are bicyclic 5-5 heterocycles with 1:2-heteroatom orientation derived from carbohydrates.

10.02.2 Theoretical Methods

Although there is a large body of literature associated with the 5-5 heterocycles with 1:2-heteroatom orientation, very little of it is related to fundamental properties or to structural considerations of the rings themselves. Much of the literature describes synthetic methods designed to create new functionality on existing ring systems. There are no extensive reports on the relative aromaticity of the heterocycles covered in this chapter. *Ab initio* calculations on the furothiazoles and thienothiazoles predicted that electrophilic substitution should occur exclusively on the furan or thiophene subunit with product regioselectivity being a function of the resonance-stabilization of the intermediates <1976KGS1202>. Examples of electrophilic bromination, nitration, and formylation have been described <1996CHEC-II(7)49> (see Section 10.02.5.1) and substitution at C-5 is typical for thieno[3,2-*d*]isothiazoles, thieno[3,2-*d*]thiazoles, thieno[3,2-*d*]oxazoles, and thieno[2,3-*d*]thiazoles. Density functional theoretical studies (B3LYP/6-31G*) on furo[3,4-*d*]thiazoles <1998H853> and furo[3,4-*d*]oxazoles <1998JOC7680> suggest both are planar and indicate that, in their Diels–Alder reactions with model dienophiles (ethane, ethyne), they are less reactive than benzo[*c*]furans; the calculations are in qualitative agreement with observed experimental data (see Section 10.02.5.4).

10.02.3 Experimental Structural Methods

Much of the structural information relating to the title heterocycles has been obtained by standard methods and is included in the references to their synthesis and there is nothing to merit special discussion. No single reference exists discussing the comparative spectroscopic properties of the bicyclic 5-5 heterocycles with 1:2-heteroatom orientation covered in this chapter. As would be expected, ^{1}H NMR data exist for most reported compounds (typically obtained in either $CDCl_3$ or d_6-DMSO, and occasionally d_6-acetone) and limited ^{13}C NMR, infrared (IR), ultraviolet (UV), and mass spectral (MS) data are also reported. ^{1}H and ^{13}C NMR data exist for thieno[2,3-*c*]pyrazoles <1995JPR472, 1998PHA227, 2004TL4143>, pyrrolo[2,3-*c*]isothiazoles <2002T135>, pyrrolo[2,3-*c*]isoxazoles <2002T135>, furo[2,3-*d*]thiazoles <1996CHEC-II(7)49>, pyrrolo[2,3-*d*]thiazoles <1996CHEC-II(7)49, 1996KFZ37, 1996MI643, 1997T9657, 1998J(P1)685>, thieno[2,3-*d*]imidazoles <2000JMC4877, 2002JOC3365>, thieno[2,3-*d*]thiazoles <1996CHEC-II(7)49, 1998J(P1)685>, furo[3,2-*c*]pyrazoles <2004TL4143>, thieno[3,2-*c*]pyrazoles <2005JOC596>, pyrrolo[3,2-*d*]pyrazoles <1995H(40)661, 2004NN805>, thieno[3,2-*d*]thiazoles <1996CHEC-II(7)49>, pyrrolo[3,2-*d*]pyrazoles <1995H(40)661>, pyrrolo[3,2-*d*]isoxazoles <1999TL7615>, pyrrolo[3,2-*d*]isothiazoles <1997P833, 2005JOC1828>, furo[3,4-*d*]thiazoles <1998H(48)853>, furo[3,4-*d*]oxazoles <1998JOC7680>, and furo[3,4-*d*]isoxazoles <1996CHEC-II(7)49>. In addition, ^{1}H, ^{13}C, and ^{77}Se NMR spectral data are reported for pyrrolo[3,2-*d*]selenazoles, thieno[3,2-*d*]isoselenazoles, selenolo[3,2-*d*]isothiazoles, selenolo[3,2-*d*]isoselenazoles, thieno[3,2-*d*]isothiazoles, and thieno[2,3-*d*]isothiazoles <1980BSB773, 1987BSB407, 1996CHEC-II(7)49>. Fluorescence spectroscopy is reported for a benzo[4,5]thieno[2,3-*d*]thiazolium iodide salt <2004SAA129>. A wide variety of structural variants of the nonconjugated heterocycles have reported X-ray crystallographic data; however, perhaps surprisingly, only very limited X-ray structural information has been reported for the fully conjugated heterocycles.

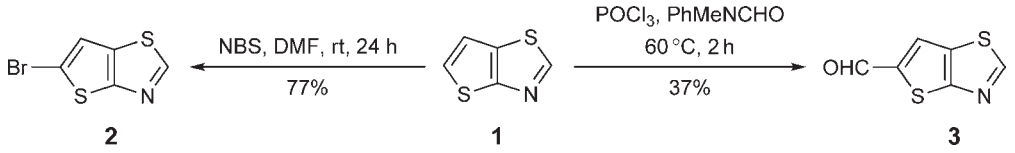
10.02.4 Thermodynamic Aspects

Nothing has been reported about the relationship between the thermodynamic aspects of the bicyclic 5-5 heterocycles with 1:2-heteroatom orientation and their physicochemical properties (bp, mp, volatility, chromatographic behavior).

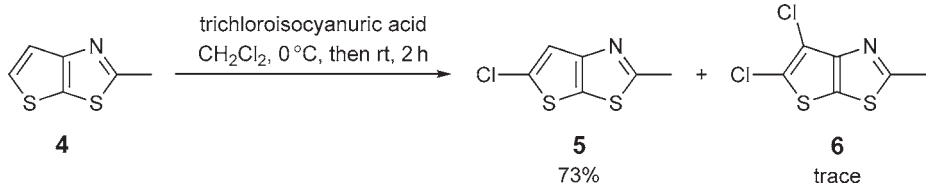
10.02.5 Reactivity of Fully Conjugated Rings

10.02.5.1 Electrophilic Attack on Carbon and Nitrogen

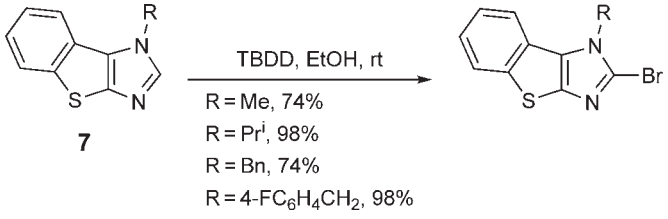
The heterocycles that form the subject of this chapter are, in general, obtained from appropriately substituted monocyclic heterocyclic precursors, and methods for direct functionalization are not commonly investigated. Electrophilic substitution reactions are known for some of the isomeric systems with the product distribution varying with electronic effects associated with the 10π-reactant and its substitution pattern. Examples of bromination, nitration, formylation (acylation), and chloromethylation have been described <1996CHEC-II(7)49>. Typically, substitution at C-5 is common for thieno[3,2-*d*]isothiazoles, thieno[3,2-*d*]thiazoles, thieno[3,2-*d*]oxazoles, and thieno[2,3-*d*]thiazoles. For example, electrophilic substitutions of the parent thieno[2,3-*d*]thiazole **1**, such as bromination with *N*-bromosuccinimide (NBS) to give **2**, or formylation, under Vilsmeier–Haack conditions, to give **3** proceeded at the 5-position of the thiophene ring in good yield <1998J(P1)685> (**Scheme 1**). Efficient chlorination of 2-methylthieno[3,2-*d*]thiazole **4** has been reported using trichloroisocyanuric acid as the electrophilic chlorinating agent (Equation 1) <1998SL407>. A small amount of the dichlorinated product **6** was also obtained. Bromination of 2-methylthieno[3,2-*d*]thiazole using bromine has been similarly reported <1987KGS410, 1996CHEC-II(7)49)>. Bromination of 1-substituted-1*H*-benzothieno[2,3-*d*]imidazoles **7** (Equation 2) <1995JHC591> has also been shown to be efficient using 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBDD) as a selective monobrominating agent <1972J(P1)2567>.



Scheme 1

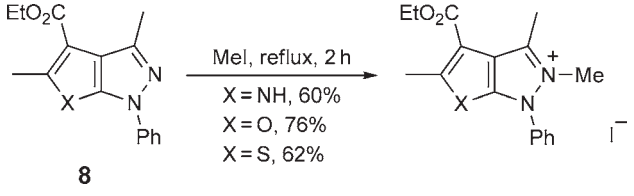


(1)



(2)

Direct *N*-alkylation has been reported for thieno[3,2-*d*]isoxazoles <1976CS165, 1996CHEC-II(7)49> and 5-phenylpyrrolo(furo or thieno)[3,2-*d*]isothiazoles <85KGS223, 1996CHEC-II(7)49>. Similarly, substituted-pyrrolo(furo or thieno)[2,3-*c*]pyrazoles **8** were readily quaternized using an excess of iodomethane (Equation 3) <2002CCS1061>.



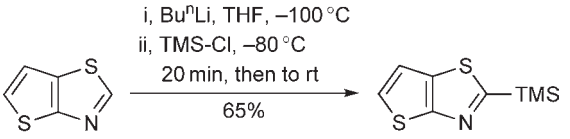
(3)

10.02.5.2 Photochemistry and Thermolysis

Few examples of photochemical transformations of the 10π-heterocycles in this series have been reported. No additional reports have been made subsequent to those described in CHEC-II(1996) <1996CHEC-II(7)49>.

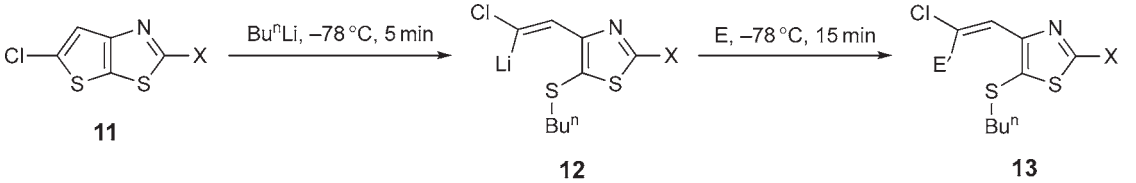
10.02.5.3 Metallation

Relatively few examples of metallation of the subject heterocycles have been reported. Metallation of thieno[2,3-*d*]thiazole **9** with Bu^{n}Li occurred at the 2-position of the thiazole ring; the lithium salt could be reacted with electrophiles, for example, trimethylsilyl chloride to give **10**, in good yield (Equation 4) <1998J(P1)685>.



9 **10** (4)

2-Substituted-chlorothieno[3,2-*d*]thiazoles **11** reacted with Bu^{n}Li by addition to the sulfur of the thiophene ring; the intermediates **12** were readily trapped with reactive electrophiles to yield (*E*)-chloroalkenes **13** with retention of configuration (**Scheme 2**) <1998SL407>. The intermediates **12** were, however, not nucleophilic enough to react with either EtI or BnBr. The more basic Bu^{s}Li yielded, preferentially, products arising from hydrogen abstraction. All other organometallic species investigated, including Grignard, cuprate and organozinc reagents, cyanide, lithium enolates, lithium triethylborohydride, and diisobutylaluminium hydride (DIBAL-H), gave no reaction. When there was a leaving group in position 3 (e.g., chlorine in **14**), products arising from an elimination pathway were observed. Addition of Bu^{n}Li to the sulfur afforded an intermediate chloroalkyne; rapid chlorine–lithium exchange gave the corresponding alkynyllithium **15**, which could be trapped with an electrophile (e.g., benzaldehyde to give the product **16**) (**Scheme 3**) <1998SL407>.

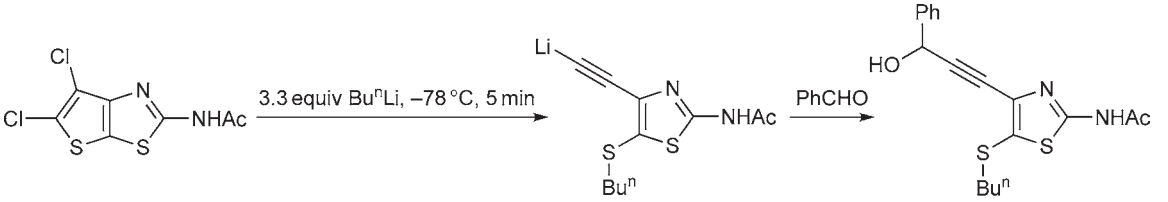


11 **12** **13**

X	*E*	*E'*	*Yield* **13** (%)
Me[a]	NH_4Cl	H	75
Me[a]	NCS	Cl	84
Me[a]	PhCOCl	PhCO	62
Me[a]	PhCHO	PhCH(OH)	77
AcNH[b]	NCS	Cl	56
AcNH[b]	MeI	Me	70
AcNH[b]	CH_2=$CHCH_2Br$	CH_2=$CHCH_2$	10
AcNH[b]	PhCHO	PhCH(OH)	81

[a]1.2 equiv Bu^{n}Li.
[b]2.2 equiv Bu^{n}Li.

Scheme 2

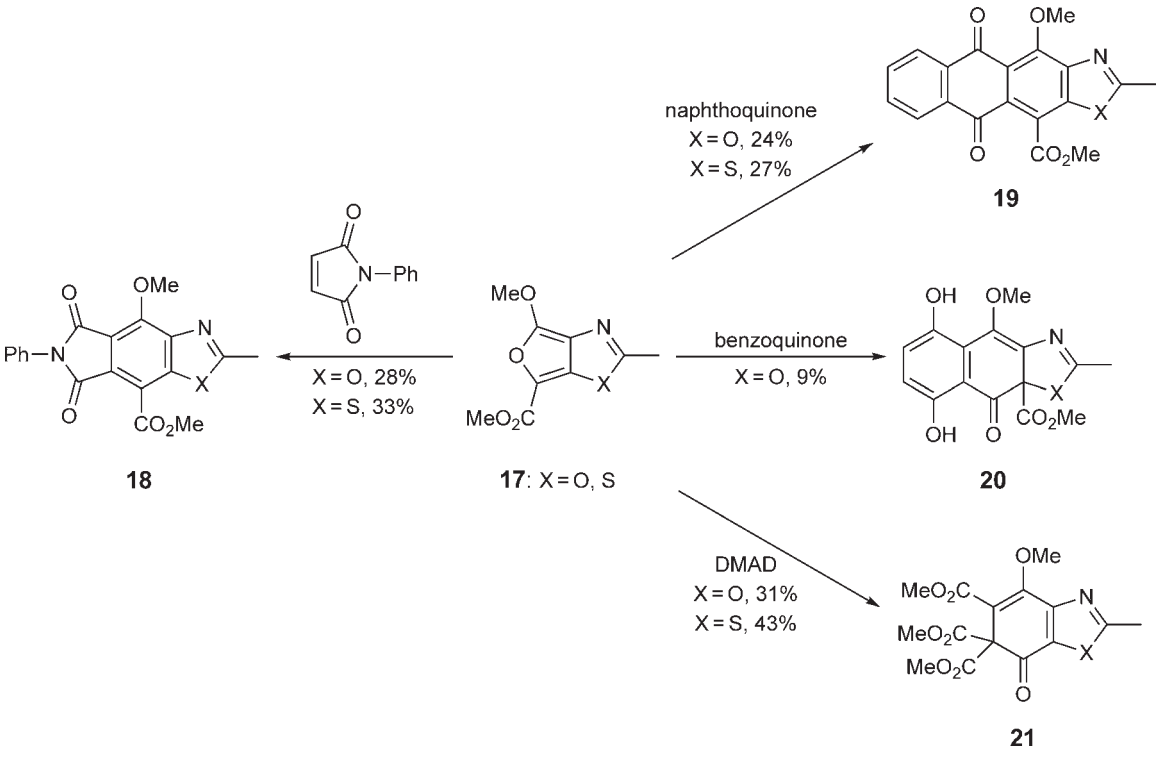


14 **15** **16**

Scheme 3

10.02.5.4 Cycloadditions and Dipole-Mediated Transformations

Several of the 10π-heterocycles cannot be represented by a classical, noncharge separated structure and have an appreciable dipolar character due to contribution of a hypervalent heteroatom. These heterocycles (e.g., thieno[3,4-*c*]isothiazole and thieno[3,4-*c*]pyrazole) react as thiocarbonyl ylides in [3+2] cycloadditions with dipolarophiles to afford 7-heterabicyclo[2.2.1]heptanes or heptenes, which can undergo subsequent aromatization <1996CHEC-II(7)49>. No additional examples have been reported in this period. Thieno[3,4-*d*]thiazoles and seleno[3,4-*d*]thiazoles have diene character and were shown to participate in Diels–Alder reactions with dimethyl acetylenedicarboxylate (DMAD) <1978JHC1455, 1996CHEC-II(7)49>. Similarly, a furo[3,4-*d*]thiazole **17** (X = S) <1998H(48)853> and a furo[3,4-*d*]oxazole **17** (X = O) <1998JOC7680> have been shown to react with electron-poor dienophiles to give the expected adducts **18** and **19**, after aromatization, with both *N*-phenylmaleimide and naphthoquinone, respectively (**Scheme 4**). Reaction with DMAD and benzoquinone afforded products **20** and **21**, respectively, postulated to arise from initial cycloaddition followed by ring-opening and ester group migration (**Scheme 4**) <1998H(48)853>. Similar cycloaddition and subsequent rearrangement reactions have been reported previously for other annulated furans <1963CB329>.



Scheme 4

10.02.6 Reactivity of Substituents Attached to Ring Carbon Atoms

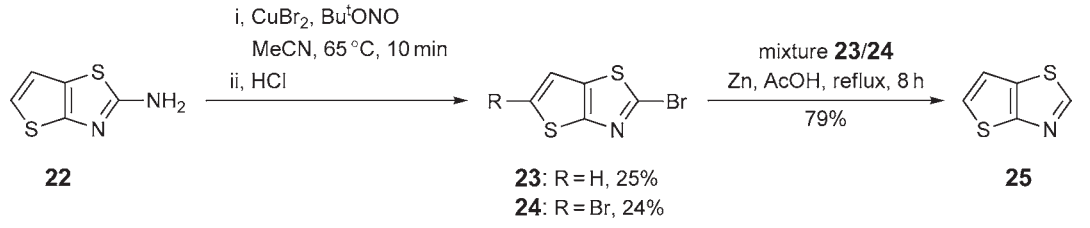
Many of the bicyclic 5-5 heterocycles with 1:2-heteroatom orientation are robust and traditional functional group manipulation of many of the substituted heterocycles is possible and relevant examples are discussed at appropriate points in this chapter.

10.02.6.1 Metal–Halogen Exchange

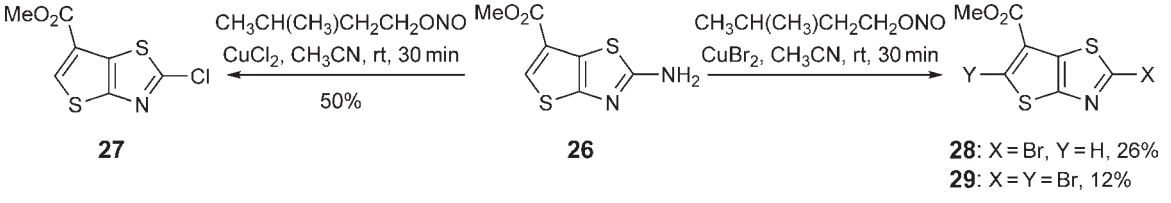
Metal–halogen exchange has been reported <1996CHEC-II(7)49> although no additional reports have been made in this period.

10.02.6.2 Direct Substitution

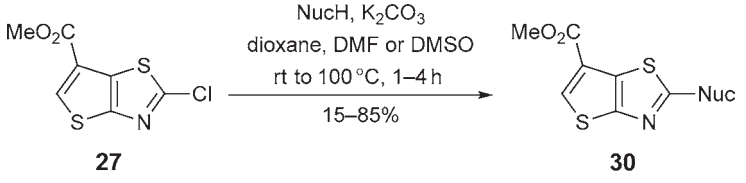
Few examples of substitution reactions on intact heterocycles have been reported. Notably, the parent thieno[2,3-*d*]thiazole **25** was prepared from 2-aminothieno[2,3-*d*]thiazole **22** <1983JHC113> using a Sandmeyer reaction followed by reduction of the resultant mixture of 2-bromo- and 2,5-dibromothieno[2,3-*d*]thiazole, **23** and **24**, respectively, with Zn/AcOH (**Scheme 5**) <1998J(P1)685>. Previous reports on the preparation of the parent thieno[2,3-*d*]thiazole suggested that the product could not be sufficiently purified for full characterization due to its high volatility and instability under standard conditions <1983JHC113, 1992J(P1)973>. However, in this case, **25** was successfully distilled to high purity and found to be stable for several days when stored under air at room temperature. Additionally, it was possible to isolate and separate the two intermediate brominated derivatives **23** and **24** by sublimation. 2-Amino-4-carbomethoxythieno[2,3-*d*]thiazole **26** also reacted under Sandmeyer conditions to give halogenated compounds **27–29** (**Scheme 6**) <2001ARK34>. A series of 2-substituted thieno[2,3-*d*]thiazoles **30** were subsequently prepared from 2-chloro-4-carbomethoxythieno[2,3-*d*]thiazole **27** by nucleophilic substitution reactions using a range of nitrogen, oxygen, and sulfur electrophiles (Equation 5) <2001ARK34>; sulfur electrophiles, in particular, gave excellent conversions to the products, whereas nitrogen and oxygen nucleophiles required elevated reaction temperatures.



Scheme 5



Scheme 6

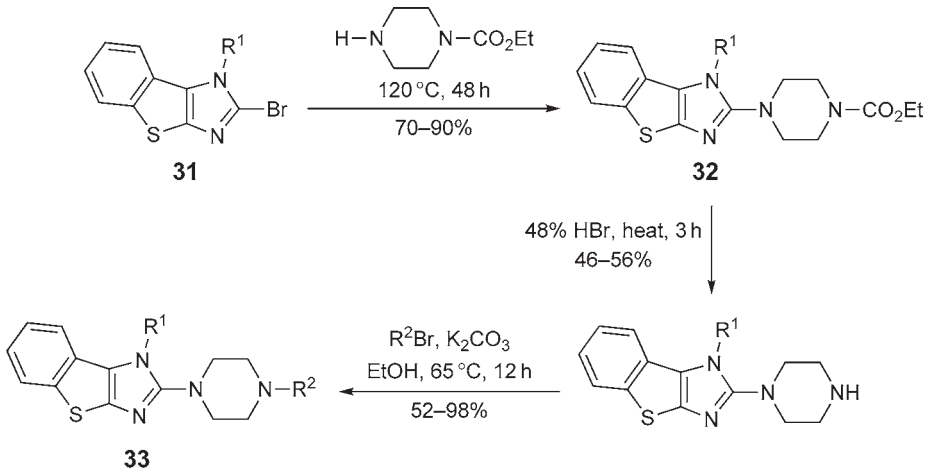


(5)

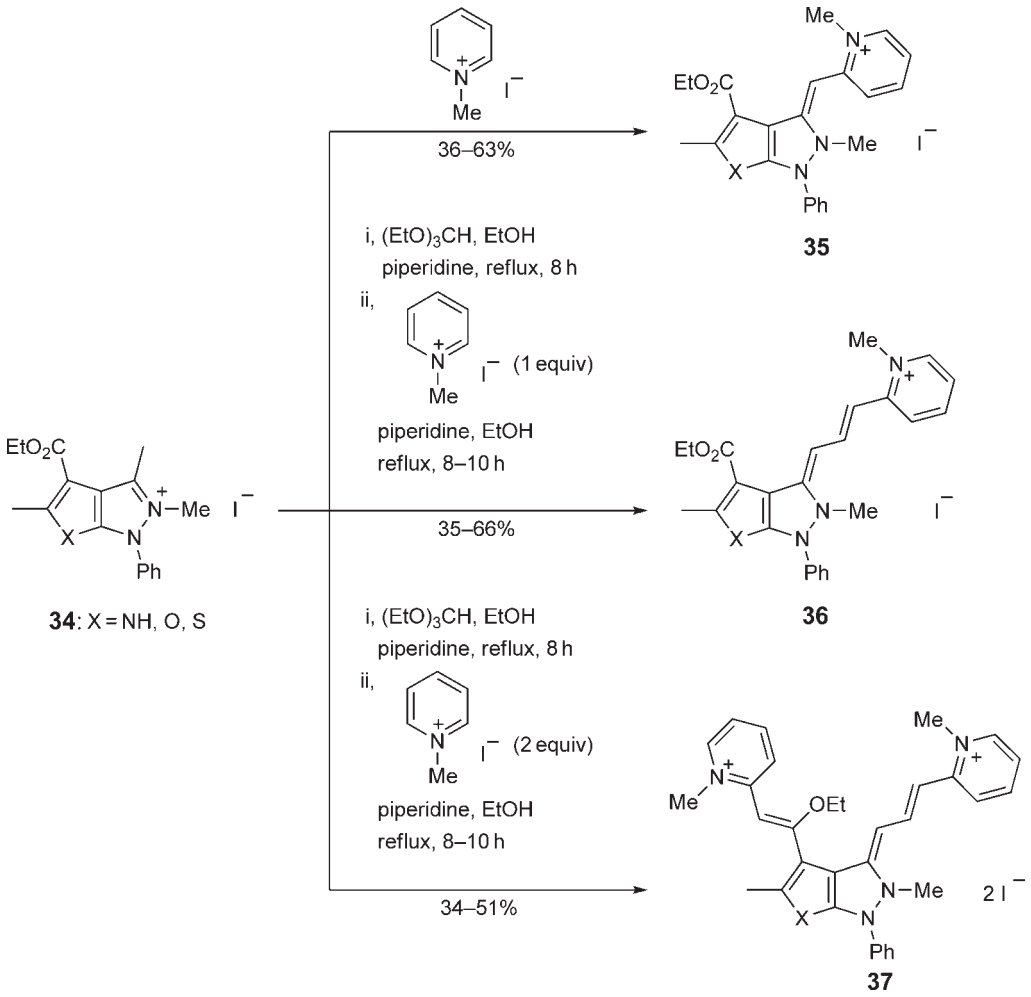
Nuc = $HO(CH_2)_3NH$, $Me_2N(CH_2)_3NH$, $(HOCH_2CH_2)_2N$
pyrrolidino, MeO, Pr^nS, MeO_2CCH_2S, PhS, BnS

Benzothieno[2,3-*d*]imidazoles **32** were simply prepared by heating 2-bromobenzothieno[2,3-*d*]imidazoles **31** with 1-carboxyethylpiperazine (**Scheme 7**) <1995JHC591>. Subsequent functional group manipulation was possible to prepare a series of derivatives **33** tested as H_1-antihistaminic agents; *N*-deprotection was readily effected with 48% hydrobromic acid and the free amine was subsequently alkylated with a range of alkyl halides in ethanol using potassium carbonate as base.

Reaction of the quaternized salts of 4-ethoxycarbonyl-3,5-dimethyl-1-phenylpyrrolo(furo or thieno)[2,3-*c*]pyrazole **34** with the iodomethane quaternary salts of pyridine, quinoline, and isoquinoline in ethanol with catalytic piperidine gave 3-[4(1)]-monomethine cyanine dyes (e.g., **35**). Additionally, 3-[2(4)]-trimethine cyanine dyes and 4-[2(4)]-di-3[2(4)]-tri-mixed methine cyanine dyes (e.g., **36** and **37**, respectively) were similarly prepared from the intermediates derived by reaction of **34** with triethyl orthoformate in the presence of piperidine (**Scheme 8**) <2002CCS1061>.

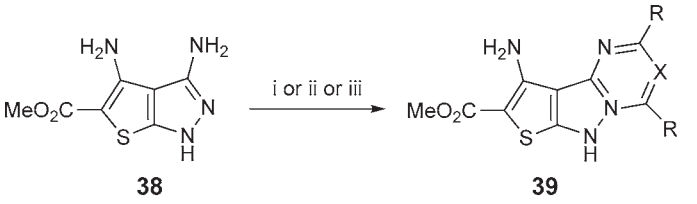


Scheme 7



Scheme 8

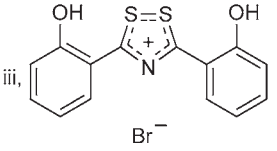
Thieno[2′,3′:3,4]pyrazolo[1,5-*a*]pyrimidines **39** were conveniently prepared by the reaction of thieno[2,3-*c*]pyrazoles **38** with 1,3-dielectrophiles, for example, acetylacetone, dibenzoylmethane, and a 1,2,4-dithiazolium derivative (Equation 6) <1995PHA675>. Similarly, reaction of isothiazolo[5,4-*b*]thiophene **40** with either diethyl malonate or ethyl acetoacetate gave the corresponding pyrimidineoisothiazolo[5,4-*b*]thiophenes **41** and **42**, respectively (**Scheme 9**) <2000PS65>. Both products were screened for antimicrobial activity and showed moderate activity against *Staphylococcus aureus*. Reaction of thienoimidazole **43** with triethyl orthoformate in acetic anhydride gave 1-benzyl-2-(methylsulfanyl)imidazo[4′,5′;4,5]-thieno[3,2-*d*]pyrimidin-5(6H)-one **44**, a thieno-extended purine ring system (Equation 7) <1995T12807>. Thieno[2,3-*c*]pyrazole **45** underwent Curtius rearrangement followed by intramolecular ring closure on heating in benzene to give pyrazolo[4′,3′:4,5]thieno[2,3-*e*]pyrrolo[1,2-*a*]pyrazine-4-one **46** (Equation 8) <2005JCR761>.

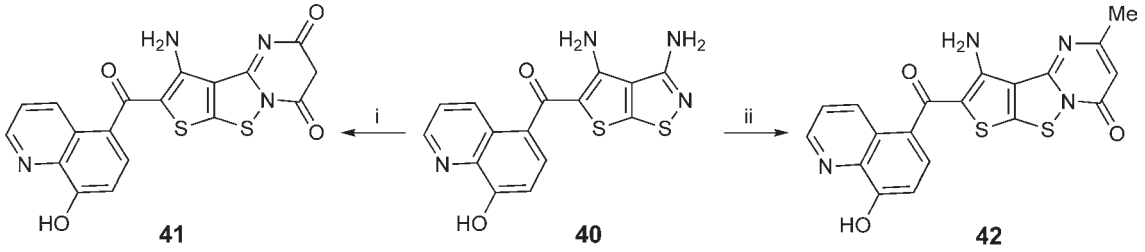


(6)

i, $MeCOCH_2COMe$, AcOH, MeOH, reflux, 10 min, X = CH, R = Me, 77%

ii, $PhCOCH_2COPh$, AcOH, $MeOCH_2CH_2OH$, reflux, 1 h, X = CH, R = Ph, 61%

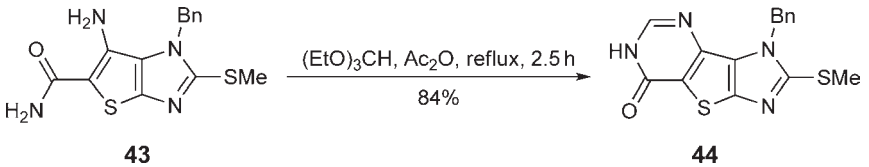
iii,  , Et_3N, MeOH, reflux, 15 min, X = N, R = 2-HOC_6H_4, 89%



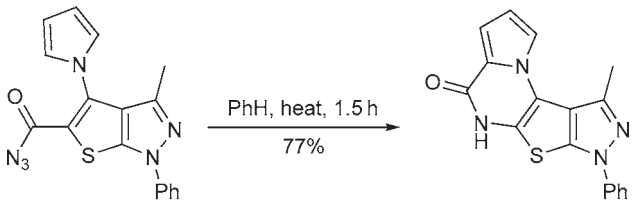
i, $(EtO_2C)_2CH_2$, 1,2-dichlorobenzene, reflux, 3 h, 68%

ii, $CH_3COCH_2CO_2Et$, EtOH, reflux, 3 h, 71%

Scheme 9



(7)

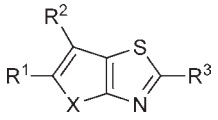


45 46 (8)

10.02.7 Ring Synthesis of Fully Conjugated Systems

The synthetic approaches to these heterocyclic systems are discussed and exemplified in the following sections and a compilation of the new derivatives reported in the period 1995–2006 is given in **Tables 1–15**. Derivatives prepared prior to 1995 are tabulated in CHEC-II(1996) <1996CHEC-II(7)49>.

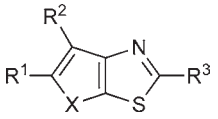
Table 1 1*H*-Pyrrolo[2,3-*d*]thiazoles (X = NH) and thieno[2,3-*d*]thiazoles (X = S)



R^1	R^2	R^3	X	*mp* (°C)	*Reference*
CH=CH-CH=CH		Ph	N	255–256	1997T9657
H	H	H	S	bp 80 (2 torr)[a]	1998J(P1)685
H	H	Br	S	44	1998J(P1)685
H	H	NH_2	S	bp 103–104	1998J(P1)685
H	H	TMS	S	b	1998J(P1)685
H	CO_2Me	Cl	S	155–157	2001ARK34
H	CO_2Me	Br	S	161–164	2001ARK34
H	CO_2Me	NH_2	S	214–216	2001ARK34
H	CO_2Me	MeO	S	78–80	2001ARK34
H	CO_2Me	Pr^nS	S	37–39	2001ARK34
H	CO_2Me	MeO_2CCH_2 S	S	80–82	2001ARK34
H	CO_2Me	PhS	S	93–95	2001ARK34
H	CO_2Me	BnS	S	71–74	2001ARK34
H	CO_2Me	Me_2N	S	96–98	2001ARK34
H	CO_2Me	$HO(CH_2)_3NH$	S	118–120	2001ARK34
H	CO_2Me	$Me_2N(CH_2)_3NH$	S	91–94	2001ARK34
H	CO_2Me	$(HOCH_2CH_2)_2N$	S	121–124	2001ARK34
H	CO_2Me	C_4H_8N	S	130–132	2001ARK34
Br	H	H	S	b	1998J(P1)685
Br	H	Br	S	110	1998J(P1)685
Br	CO_2Me	Br	S	165–167	2001ARK34
Me	H	4-FC_6H_4NHCO	S	190–192	2004RJO137
Me	H	4-ClC_6H_4NHCO	S	156–158	2004RJO137
CHO	H	H	S	143	1998J(P1)685
CO_2H	H	NH_2	S	b	1998AQ186
PhCO	H	4-$Et_2NC_6H_4N{=}N$	S	161.5–162.8	1998AQ186
CO_2H	H	4-$Et_2NC_6H_4N{=}N$	S	242.0–243.5	1998AQ186
CO_2Et	H	NH_2	S	160–162	1998AQ186
CO_2Et	H	4-$Et_2NC_6H_4N{=}N$	S	183.5–184.9	1998AQ186
CN	H	4-$Et_2NC_6H_4N{=}N$	S	221.8–222.2	1998AQ186
MeCO	H	4-$Et_2NC_6H_4N{=}N$	S	232.4–233.8	1998AQ186

[a]bp 110–115 (25 torr) <1979CHE387, 1979KGS477>.
[b]no mp/bp given.

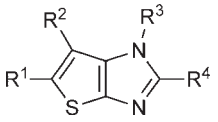
Table 2 Pyrrolo[3,2- *d*]thiazoles (X = NH) and thieno[3,2-*d*]thiazoles (X = S)



R^1	R^2	R^3	X	*mp* (°C)	*Reference*
CH=CH-CH=CH		NH_2	NH	248–250[a]	2001JHC569
CH=CH-CH=CH		MeCONH	NH	>250	2001JHC569
Ph	PhCO	PhNH	PhN	108	1999PS(148)215
Ph	PhCO	4-ClC_6H_4	PhN	178	1999PS(148)215
4-$MeOC_6H_4$	CN	4-$MeOC_6H_4$	4-ClC_6H_4N	300	2005PS(180)573
4-FC_6H_4	CN	4-FC_6H_4	4-MeC_6H_4N	220	2005PS(180)573
CH=CH-CH=CH		Me	MeCON	224–225[b]	1996MI643
CH=CH-CH=CH		$NCCH_2$	MeCON	170–172	1996MI643
CH=CH-CH=CH		Bn	MeCON	195–197[a]	1996MI643
CH=CH-CH=CH		$PhCH_2CH_2$	MeCON	164–166[a]	1996MI643
CH=CH-CH=CH		NH_2	MeCON	>250	2001JHC569
H	H	Me	S	c	1998SL407
H	H	MeCONH	S	d	1998SL407
Cl	H	Me	S	e	1998SL407
Cl	H	MeCONH	S	e	1998SL407
Cl	Cl	MeCONH	S	e	1998SL407
Cl	PhCH(OH)	Me	S	e	1998SL407
Me	H	$PhCH_2NHCO$	S	149–151	2003RJO1161
Me	H	4-$MeC_6H_4CH_2NHCO$	S	183–184	2003RJO1161
Me	H	4-$FC_6H_4CH_2NHCO$	S	185–187	2003RJO1161

[a]As HBr salt.
[b]As HCl salt.
[c]bp 78 °C/13 mmHg <1983JHC113>.
[d]272 °C <1983JHC113>.
[e]no mp/bp given.

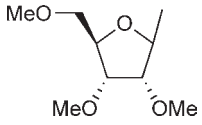
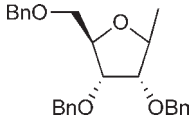
Table 3 1*H*-Thieno[2,3-*d*]imidazoles



R^1	R^2	R^3	R^4	*mp* (°C)	*Reference*
H	H	H	H	a	1997TL4647
H	H	H	CH_2=CH	a	1997TL4647
H	H	H	4-$ClC_6H_4COCH(CH_2CO_2H)S$	164–166	1998JHC923
H	H	H	4-$ClC_6H_4COCH(CH_2CO_2Me)S$	170–172	1998JHC923
CO_2H	H	H	H	a	1997TL4647
CO_2H	H	H	CH_2=CH	a	1997TL4647
CO_2Et	H	H	CH_2=CH	a	1997TL4647
NH_2CO	NH_2	CH_2=CH	H	179–181	2000JMC4877
NH_2CO	NH_2	CH_2=$CHCH_2$	H	179	2000JMC4877

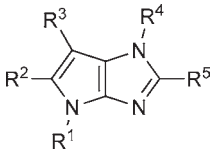
(*Continued*)

Table 3 (Continued)

R^1	R^2	R^3	R^4	*mp* (°*C*)	*Reference*
NH_2CO	NH_2		H	57	2002JOC3365
NH_2CO	NH_2		H	oil, a	2002JOC3365
NH_2CO	NH_2	Bn	SMe	214–215	1995T12807

[a]No mp/bp given.

Table 4 1*H*,4*H*-Pyrrolo[2,3-*d*]imidazoles



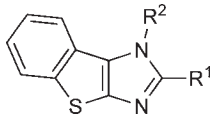
R^1	R^2	R^3	R^4	R^5	*mp* (°*C*)	*Reference*
H	CO_2Et	H	H	Me	163–165	2003MI251
H	CO_2Et	H	4-ClC_6H_4	Me	211–213	1997MI461
H	CO_2Et	H	4-MeC_6H_4	Me	214–217	1997MI461
H	CO_2Et	H	4-MeC_6H_4	Me	209–212	1997MI461
H	CO_2Et	H	PhCO	Me	203–205	1997MI461
H	CO_2Et	H	MeS	Me	144–145	1997JHC549
H	CO_2Et	H	EtS	Me	80–82	1997JHC549
H	CO_2Et	H	Pr^nS	Me	85–87	1997JHC549
H	CO_2Et	H	BnS	Me	155–158	1997JHC549
H	CO_2Et	H	$MeSO_2$	Me	181–182	1997JHC549
H	CO_2Et	H	$EtSO_2$	Me	164–165	1997JHC549
H	CO_2Et	H	Pr^nSO_2	Me	167–168	1997JHC549
H	CO_2Et	H	$BnSO_2$	Me	180–183	1997JHC549
H	CO_2Et	H	MeS	Bn	110–111	1998MI99
H	CO_2Et	H	EtS	Bn	105–107	1998MI99
H	CO_2Et	H	PrS	Bn	88–89	1998MI99
H	CO_2Et	H	BnS	Bn	139–140	1998MI99
H	CO_2Et	H	Pr^n	4-$EtO_2CC_6H_4CH_2$	155	1997IJB813
H	CO_2Et	H	Bu^n	4-$EtO_2CC_6H_4CH_2$	105–108	1997IJB813
H	CO_2Et	H	MeS	4-$MeOC_6H_4CH_2$	132–134	2002JHC367
H	CO_2Et	H	EtS	4-$MeOC_6H_4CH_2$	136–138	2002JHC367
H	CO_2Et	H	Pr^nS	4-$MeOC_6H_4CH_2$	110–112	2002JHC367
H	CO_2Et	H	MeS	4-$EtO_2CC_6H_4CH_2$	109–111	2002JHC367
H	CO_2Et	H	EtS	4-$EtO_2CC_6H_4CH_2$	111–113	2002JHC367
H	CO_2Et	H	Pr^nS	4-$EtO_2CC_6H_4CH_2$	81–83	2002JHC367
H	CO_2Me	H	Pr^n	4-(2-$MeO_2CC_6H_4$)$C_6H_4CH_2$	188–190	2002JHC367

(*Continued*)

Table 4 (Continued)

R^1	R^2	R^3	R^4	R^5	*mp* (°*C*)	*Reference*
H	CO_2Me	H	Bu^n	4-(2-$MeO_2CC_6H_4$)$C_6H_4CH_2$	174–175	2002JHC367
H	CH═CH-CH═CH		4-ClC_6H_4	H	104	1994IJB1093
H	CH═CH-CH═CH		2-Furyl	H	68	1994IJB1093
H	CMe═CH-CH═CH		Ph	H	117	1994IJB1093
H	CMe═CH-CH═CH		4-ClC_6H_4	H	36	1994IJB1093
H	CMe═CH-CH═CH		2-Furyl	H	97	1994IJB1093
H	CF═CH-CH═CH		Ph	H	142	1994IJB1093
H	CF═CH-CH═CH		4-ClC_6H_4	H	116	1994IJB1093
H	CF═CH-CH═CH		2-Furyl	H	72	1994IJB1093
H	CCl═CH-CH═CH		Ph	H	106	1994IJB1093
H	CCl═CH-CH═CH		2-Furyl	H	88	1994IJB1093
CF_3	CH═CH-CH═CH		Ph	H	154	1994IJB1093
4-MeC_6H_4	CO_2Me	CO_2Me	CO_2Me	4-MeC_6H_4	238–240	2001JHC205
$PhSO_2$	CO_2Et	H	H	Me	164–166	2003MI251
4-$BrC_6H_4SO_2$	CO_2Et	H	H	Me	177–178	2003MI251
4-$MeC_6H_4SO_2$	CO_2Et	H	H	Me	156	2003MI251
4-$MeOC_6H_4SO_2$	CO_2Et	H	H	Me	188–190	2003MI251

Table 5 1*H*-Benzo[4,5]thieno[2,3-*d*]imidazoles



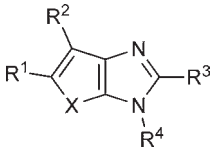
R^1	R^2	*mp* (°*C*)	*Reference*
H	Me	96–97	1995JHC591
H	Pr^i	76–77	1995JHC591
H	Bn	96–97	1995JHC591
H	4-$FC_6H_4CH_2$	76–77	1995JHC591
Br	Me	160–162	1995JHC591
Br	Pr^i	119–120	1995JHC591
Br	Bn	160–162	1995JHC591
Br	4-$FC_6H_4CH_2$	119–120	1995JHC591
$HN(CH_2CH_2)_2N$	Me	152–154	1995JHC591
$HN(CH_2CH_2)_2N$	Pr^i	165–167	1995JHC591
$HN(CH_2CH_2)_2N$	Bn	152–154	1995JHC591
$HN(CH_2CH_2)_2N$	4-$FC_6H_4CH_2$	165–167	1995JHC591
$MeN(CH_2CH_2)_2N$	Me	135–137	1995JHC591
$MeN(CH_2CH_2)_2N$	Pr^i	150–151	1995JHC591
$MeN(CH_2CH_2)_2N$	Bn	135–137	1995JHC591
$MeN(CH_2CH_2)_2N$	4-$FC_6H_4CH_2$	150–151	1995JHC591
$EtO_2CN(CH_2CH_2)_2N$	Me	186–187	1995JHC591
$EtO_2CN(CH_2CH_2)_2N$	Pr^i	173–175	1995JHC591
$EtO_2CN(CH_2CH_2)_2N$	Bn	186–187	1995JHC591
$EtO_2CN(CH_2CH_2)_2N$	4-$FC_6H_4CH_2$	173–175	1995JHC591
$HO(CH_2)_2N(CH_2CH_2)_2N$	Me	158–159	1995JHC591
$HO(CH_2)_2N(CH_2CH_2)_2N$	Pr^i	178–179	1995JHC591
$HO(CH_2)_2N(CH_2CH_2)_2N$	Bn	140–142	1995JHC591
$HO(CH_2)_2N(CH_2CH_2)_2N$	4-$FC_6H_4CH_2$	178–179	1995JHC591
$Me(CH_2)_2N(CH_2CH_2)_2N$	Me	158–159	1995JHC591
$Me(CH_2)_2N(CH_2CH_2)_2N$	Pr^i	181–183	1995JHC591
$Me(CH_2)_2N(CH_2CH_2)_2N$	Bn	158–159	1995JHC591
$Me(CH_2)_2N(CH_2CH_2)_2N$	4-$FC_6H_4CH_2$	181–183	1995JHC591

(*Continued*)

Table 5 (Continued)

R^1	R^2	*mp* (°*C*)	*Reference*
$MeCH(OH)CH_2N(CH_2CH_2)_2N$	Me	125–127	1995JHC591
$MeCH(OH)CH_2N(CH_2CH_2)_2N$	Pr^i	182–184	1995JHC591
$MeCH(OH)CH_2N(CH_2CH_2)_2N$	Bn	125–127	1995JHC591
$MeCH(OH)CH_2N(CH_2CH_2)_2N$	$4\text{-}FC_6H_4CH_2$	182–184	1995JHC591
$Ph(CH_2)_2N(CH_2CH_2)_2N$	Me	132–134	1995JHC591
$Ph(CH_2)_2N(CH_2CH_2)_2N$	Pr^i	160–162	1995JHC591
$Ph(CH_2)_2N(CH_2CH_2)_2N$	Bn	132–134	1995JHC591
$Ph(CH_2)_2N(CH_2CH_2)_2N$	$4\text{-}FC_6H_4CH_2$	160–161	1995JHC591

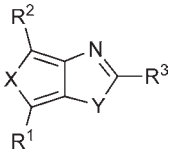
Table 6 3*H*,4*H*-pyrrolo[3,2-*d*]imidazoles (X = NH) and 3*H*-thieno[2,3-*d*]imidazoles (X = S)



R^1	R^2	R^3	R^4	X	*mp* (°*C*)	*Reference*
CO_2Et	H	Pr^n	$4\text{-}EtO_2CC_6H_4CH_2$	NH	160	1997IJB813
CO_2Me	H	Pr^n	$4\text{-}(2\text{-}HO_2CC_6H_4)C_6H_4CH_2$	NH	274–275	2003FA1193
CO_2Me	H	Pr^n	$4\text{-}(2\text{-}MeO_2CC_6H_4)C_6H_4CH_2$	NH	196–198	2002JHC367
CO_2Et	H	Bu^n	$4\text{-}EtO_2CC_6H_4CH_2$	NH	159–161	1997IJB813
CO_2Me	H	Bu^n	$4\text{-}(2\text{-}HO_2CC_6H_4)C_6H_4CH_2$	NH	272–274	2003FA1193
CO_2Me	H	Bu^n	$4\text{-}(2\text{-}EtO_2CC_6H_4)C_6H_4CH_2$	NH	187–188	2002JHC367
OH	HONH	$CH_2CH_2CH_2CH_2$		NH	210	1999SC3227
CH=CH-CH=CH		MeS	H	NH	237	1998RJO570
CH=CH-CH=CH		EtS	H	NH	174	1998RJO570
CH=CH-CH=CH		CH_2=$CHCH_2S$	H	NH	176	1998RJO570
CH=CH-CH=CH		MeS	H	AcN	204	1998RJO570
CH=CH-CH=CH		EtS	H	AcN	182	1998RJO570
CH=CH-CH=CH		MeS	Me	AcN	170	1998RJO570
CH=CH-CH=CH		$Et_2N(CH_2)_2S$	Me	AcN	260[a]	1998RJO570
CH=CH-CH=CH		MeS	Bn	AcN	172	1998RJO570
CH=CH-CH=CH		$Et_2N(CH_2)_2S$	Bn	AcN	169[a]	1998RJO570
CH=CH-CH=CH		Me	Me	S	127–130	1997SC473
CH=CH-CH=CH		CO_2Et	Me	S	118–120	1997SC473

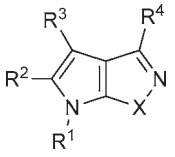
[a]As HCl salt.

Table 7 Furo[3,4-*d*]oxazoles (X = Y = O), furo[3,4-*d*]thiazoles (X = O, Y = S), pyrrolo[3,4-*d*]thiazoles (X = NH, Y = S), and 3*H*-thieno[3,4-*d*]imidazoles (X = S, Y = NH)



R^1	R^2	R^3	X	Y	*mp* (°*C*)	*Reference*
CO_2Me	MeO	Me	O	O	133–134	1998JOC7680
CO_2Me	MeO	Me	O	S	143	1998H(48)853
H	H	Ph	BnN	S	140–142	1998JHC71
H	H	$4\text{-}ClC_6H_4COCH(CH_2CO_2Me)S$	S	NH	185–187	1998JHC923

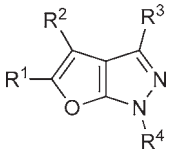
Table 8 Pyrrolo[3,2-*d*]isoxazoles (X = O), pyrrolo[3,2-*d*]isothiazoles (X = S), *1H*-Pyrrolo[3,2-*d*]pyrazoles (X = NH)

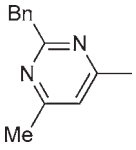


R^1	R^2	R^3	R^4	X	*mp* (°C)	*Reference*
H	Me	CO_2Me	Me	PhN	160	2002CCS1061
H	CO_2Me	H	4-FC_6H_4	PhN	167–169	1999RJOC1812
H	CO_2Me	H	2-(5-Me-furyl)	PhN	152–154	1999RJOC1812
H	CO_2Me	H	2-Thienyl	PhN	172–173	1999RJOC1812
H	CO_2Et	H	Ph	PhN	208–209	2004IJC1355
H	CO_2Et	H	4-MeC_6H_4	PhN	198–199	2004IJC1355
H	CH=CH-CH=CH		H	S	140–142[a]	2005JOC1828
H	CH=C(F)-CH=CH		H	S	168–170	2005JOC1828
H	CH=C(Cl)-CH=CH		H	S	184–186	2005JOC1828
H	CH=C(Br)-CH=CH		H	S	182–185	2005JOC1828
H	CH=C(OMe)-CH=CH		H	S	174–176	2005JOC1828
H	CH=CH-C(F)=CH		H	S	198–200	2005JOC1828
H	CH=CH-C(Cl)=CH		H	S	226–227	2005JOC1828
H	CH=CH-C(Br)=CH		H	S	222–223	2005JOC1828
H	CH=CH-C(Me)=CH		H	S	171–174	2005JOC1828
H	CH=CH-C(OMe)=CH		H	S	169–172	2005JOC1828
H	Ph	Ph	H	NH	b	1999SC311
Me	H	H	CF_3	MeN	150–152	1995H(40)661
Me	CH=CH-CH=CH		H	S	67–69	2005JOC1828
MeCO	4-PhC_6H_4CO	H	Me	EtN	194–195	1999J(P1)3713
Bn	CN	H	4-$O_2NC_6H_4CONH$	NH	245–250	2004H(63)2475
MeO	CH=CH-CH=CH		H	S	36–37	2005JOC1828
$PhSO_2$	CH=CH-CH=CH		NO_2	O	168–170	1999TL7615

[a]164–167 °C <1988TL6447>.
[b]no mp given.

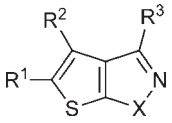
Table 9 *1H*-Furo[2,3-*c*]pyrazoles



R^1	R^2	R^3	R^4	*mp* (°C)	*Reference*
Ph	H	NH_2	H	265	1997G791
Ph	H	NH_2	$NCCH_2CH_2$	279	1997G791
NH_2	NH_2CO	Me	Ph	170–172[a]	2002CCS1061
Me	CO_2Et	Me	Ph	144[b]	2002CCS1061
CH=CH-CH=CH		Ph	Ph	c	1995TL4065
Me	H	Me		162–165	1997CHE698

[a]200 °C <1987AP1010>.
[b]no mp given.
[c]180 °C <1987AP1010>.

Table 10 Thieno[3,2-*d*]isothiazoles (X = S) and 1*H*-thieno[2,3-*c*]pyrazoles (X = NH)



R^1	R^2	R^3	X	*mp* (°C)	*Reference*
CO_2Me	NH_2	NH_2	NH	206[a]	1995PHA675
CO_2Me	MeCONH	NH_2	NH	250[a]	1998PHA227
PhCO	NH_2	NH_2	NH	167–171[a]	1995PHA675
–C(Me$_2$)CH$_2$C(CH=CHC$_6$H$_5$)=CH–		NH_2	NH	289	1997IJB668
–C(Me$_2$)CH$_2$C[CH=CH(2-ClC$_6$H$_4$)]=CH–		NH_2	NH	158	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(4-ClC$_6$H$_4$)]=CH–		NH_2	NH	263	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(3,4Cl$_2$C$_6$H$_3$)]=C–		NH_2	NH	163	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(2-MeOC$_6$H$_4$)]=CH–		NH_2	NH	219	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(4-MeOC$_6$H$_4$)]=CH–		NH_2	NH	173	1997IJCB668
–C(Me$_2$)CH$_2$C{CH=CH[3,4-(MeO)$_2$C$_6$H$_3$]}=CH–		NH_2	NH	264	1997IJCB668
–C(Me$_2$)CH$_2$C{CH=CH[3,4,5-(MeO)$_3$C$_6$H$_2$]}=CH–		NH_2	NH	162	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(3-MeO-4HOC$_6$H$_3$)]=CH–		NH_2	NH	162	1997IJCB668
–C(Me$_2$)CH$_2$C[CH=CH(4-NO$_2$C$_6$H$_4$)]=CH–		NH_2	NH	189	1997IJCB668
$PhSO_2$	Ph	NH_2	NH	>320	1997M687
CO_2Me	MeCONH	NH_2	MeN	210–218	1998PHA227
PhCO	NH_2	NH_2	MeN	270–272	1995JPR472
PhNHCO	NH_2	H	MeN	140	2004RCB580
Me	CO_2Et	Me	PhN	162	2002MI1061
CO_2H	H	Me	PhN	230–231[b]	1996IJB715
CO_2H	H	Pr^n	PhN	195–196	1996IJB715
CO_2H	H	Ph	PhN	259–260[c]	1996IJB715
CO_2H	Cl	Ph	PhN	272–273	2003RJO893
CO_2H	Cl	4-FC$_6$H$_4$	PhN	284–285	2003RJO893
CO_2H	Cl	4-ClC$_6$H$_4$	PhN	324–325	2003RJO893
CO_2H	Cl	4-BrC$_6$H$_4$	PhN	294–295	2003RJO893
CO_2H	Cl	4-MeC$_6$H$_4$	PhN	267–268	2003RJO893
COCl	Cl	Ph	PhN	209–210	2003RJO893
COCl	Cl	4-FC$_6$H$_4$	PhN	240–242	2003RJO893
COCl	Cl	4-ClC$_6$H$_4$	PhN	231–232	2003RJO893
COCl	Cl	4-BrC$_6$H$_4$	PhN	243–244	2003RJO893
COCl	Cl	4-MeC$_6$H$_4$	PhN	215–216	2003RJO893
CO_2Me	H	Me	PhN	120–121	1996IJB715
CO_2Me	H	Pr^n	PhN	176–177	1996IJB715
CO_2Me	H	Ph	PhN	130–131	1996IJB715
CO_2Me	Cl	Ph	PhN	160–161	2003RJO893
CO_2Me	NH_2	Me	PhN	176–177	2005JCR761
CO_2Me	*N*-Pyrrolo	Me	PhN	130–133	2005JCR761
NH_2NHCO	*N*-Pyrrolo	Me	PhN	157–160	2005JCR761
BnNHNHCO	*N*-Pyrrolo	Me	PhN	235–238	2005JCR761
4-ClC$_6$H$_4$CH$_2$NHNHCO	*N*-Pyrrolo	Me	PhN	295–298	2005JCR761
4-O$_2$NC$_6$H$_4$CH$_2$NHNHCO	*N*-Pyrrolo	Me	PhN	271–274	2005JCR761
N_3CO	*N*-Pyrrolo	Me	PhN	114–116	2005JCR761
MeCOCH=C(Me)NHNHCO	*N*-Pyrrolo	Me	PhN	182–184	2005JCR761
PhNHCSNHNHCO	*N*-Pyrrolo	Me	PhN	186–189	2005JCR761
PhNHCONH	*N*-Pyrrolo	Me	PhN	>300	2005JCR761
O(CH$_2$CH$_2$)$_2$NCONH	*N*-Pyrrolo	Me	PhN	176–177	2005JCR761
EtO_2CNH	*N*-Pyrrolo	Me	PhN	156–157	2005JCR761
BnO_2CNH	*N*-Pyrrolo	Me	PhN	>330	2005JCR761
Bu^{t}O$_2$CNH	*N*-Pyrrolo	Me	PhN	>300	2005JCR761
Pr^{i}O$_2$CNH	*N*-Pyrrolo	Me	PhN	174–175	2005JCR761
$C_5H_{10}NCO$	Cl	4-BrC$_6$H$_4$	PhN	171–172	2003RJO893
4-Me-piperidylCO	Cl	4-MeC$_6$H$_4$	PhN	175–176	2003RJO893

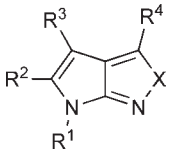
(*Continued*)

Table 10 (Continued)

R^1	R^2	R^3	X	*mp* (°C)	*Reference*
4-OHC-2-$MeOC_6H_3O_2C$	Cl	4-ClC_6H_4	PhN	209–210	2003RJO893
PhNHCO	Cl	4-BrC_6H_4	PhN	194–195	2003RJO893
4-$MeOC_6H_4NHCO$	Cl	4-MeC_6H_4	PhN	174–175	2003RJO893
(2-furyl)CH_2NHCO	Cl	4-FC_6H_4	PhN	146–147	2003RJO893
(3-pyridyl)CH_2NHCO	Cl	4-ClC_6H_4	PhN	186–188	2003RJO893
MeS	CO_2Me	Me	PhN	d	1999SC2355
MeS	CO_2Et	Me	PhN	115–117	1999SC2355
MeO_2CCH_2S	CO_2Et	Me	PhN	126–128	1999SC2355
CH═CH-CH═CH		Ph	PhN	210–212	2004TL4143
5(8-MeO_2C-quinolino)	NH_2	NH_2	S	256	2000PS65

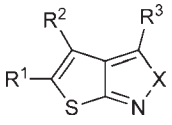
[a]As HCl salt.
[b]235–236 °C <1969CHE567, 1969KGS760, 1971JOU1292, 1971ZOR1253>.
[c]282–283 °C <1969CHE567>.
[d]mp/bp not given.

Table 11 Pyrrolo[2,3-*c*]isoxazoles (X = O), pyrrolo[2,3-*c*]isothiazoles (X = S), *2H*-pyrrolo[2,3-*c*]pyrazoles (X = NH)



R^1	R^2	R^3	R^4	X	*mp* (°C)	*Reference*
H	NH_2	PhCS	NH_2	PhN	265	1999EJC491
H	NH_2	PhCS	NH_2	NH	305	1999EJC491
Ph	MeO	H	MeS	O	198–199	2002T135
Ph	MeO	H	MeS	S	256–257	2002T135
4-MeC_6H_4	MeO	H	MeS	O	212–213	2002T135
4-MeC_6H_4	MeO	H	MeS	S	225–226	2002T135
4-$MeOC_6H_4$	MeO	H	MeS	O	237–238	2002T135
4-$MeOC_6H_4$	MeO	H	MeS	S	247–248	2002T135

Table 12 *2H*-Thieno[2,3-*c*]pyrazoles (X = NH) and thieno[2,3-*c*]isothiazoles (X = S)



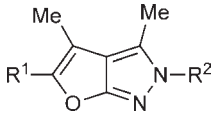
R^1	R^2	R^3	X	*mp* (°C)	*Reference*
PhCO	NH_2	MeO	NH	146	1995CCC1578
PhC(═NNH_2)	MeO	MeO	NH	117	1995CCC1578
PhCO	NH_2	MeO	PhN	146	1995CCC1578
PhC(═NNHPh)	MeO	MeO	PhN	188	1995CCC1578
H	Ph	NH_2	S	113	2005JSC799
H	Ph	4-$Me_2NC_6H_4N$═N	S	213	2005JSC799
H	Ph	4-$Et_2NC_6H_4N$═N	S	227	2005JSC799
H	Ph	4-$HO(CH_2)_2NC_6H_4N$═N	S	194	2005JSC799
H	Ph	2-Cl-4-$HO(CH_2)_2NC_6H_4N$═N	S	209	2005JSC799

(*Continued*)

Table 12 (Continued)

R^1	R^2	R^3	X	*mp* (°*C*)	*Reference*
H	Ph	2-Me-4-HO$(CH_2)_2NC_6H_4N$=N	S	239	2005JSC799
H	Ph	2-MeCONH-4-HO$(CH_2)_2NC_6H_4N$=N	S	241	2005JSC799
CO_2Et	Ph	NH_2	S	117–119	2005JSC799
CO_2Et	Ph	4-$Me_2NC_6H_4N$=N	S	180	2005JSC799
CO_2Et	Ph	4-$Et_2NC_6H_4N$=N	S	217	2005JSC799
CO_2Et	Ph	4-HO$(CH_2)_2NC_6H_4N$=N	S	197	2005JSC799
CO_2Et	Ph	2-Cl-4-HO$(CH_2)_2NC_6H_4N$=N	S	217	2005JSC799
CO_2Et	Ph	2-Me-4-HO$(CH_2)_2NC_6H_4N$=N	S	271	2005JSC799
CO_2Et	Ph	2-MeCONH-4-HO$(CH_2)_2NC_6H_4N$=N	S	183	2005JSC799

Table 13 2*H*-Furo[2,3-*c*]pyrazoles



R^1	R^2	*mp* (°*C*)	*Reference*
H	Me	68–71	1994CPB2036
CHO	Me	122–124	1994CPB2036
CO_2H	Me	a	1994CPB2036
COCl	Me	a	1994CPB2036
$CONH_2$	Me	148–150	1994CPB2036
MeNHCO	Me	186–188	1994CPB2036
Me_2NCO	Me	116–118	1994CPB2036
Pr^nNHCO	Me	168–170	1994CPB2036
Pr^iNHCO	Me	146–148	1994CPB2036
Bu^nNHCO	Me	138–140	1994CPB2036
$Pr^i(CH_2)_2NHCO$	Me	235–238	1994CPB2036
n-$C_5H_{11}NHCO$	Me	213–215	1994CPB2036
c-$C_5H_{10}NCO$	Me	152–154	1994CPB2036
$MeN(CH_2CH_2)_2NCO$	Me	156–158	1994CPB2036
$O(CH_2CH_2)_2NCO$	Me	183–185	1994CPB2036
HO_2CCH=CH	Me	254–256	1994CPB2036
$EtO_2CNHNHCO$	Me	128–130	1994CPB2036
H	Et	32–34	1994CPB2036
CHO	Et	93–94	1994CPB2036
CO_2H	Et	a	1994CPB2036
COCl	Et	a	1994CPB2036
$CONH_2$	Et	145–147	1994CPB2036
MeNHCO	Et	113–115	1994CPB2036
EtNHCO	Et	109–110	1994CPB2036
Pr^nNHCO	Et	106–107	1994CPB2036
Pr^iNHCO	Et	171–172	1994CPB2036
Bu^nNHCO	Et	265–267	1994CPB2036
Et_2NCO	Et	129–131	1994CPB2036
$Me_2N(CH_2)_2NHCO$	Et	79–80	1994CPB2036
$PhN(CH_2CH_2)_2NHCO$	Et	133–135	1994CPB2036
$Ph_2CH(CH_2)_2NHCO$	Et	110–113	1994CPB2036
2-PyridylN$(CH_2CH_2)_2NHCO$	Et	56	1994CPB2036
HO_2CCH=CH	Et	215–217	1994CPB2036
BnNHCO	Et	113–115	1994CPB2036
$EtO_2CNHNHCO$	Et	63–65	1994CPB2036

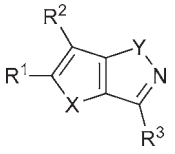
(*Continued*)

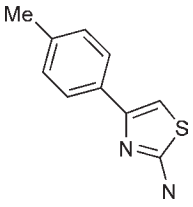
Table 13 (Continued)

R^1	R^2	*mp* (°*C*)	*Reference*
CO_2H	Pr^n	134–135	1994CPB2036
CO_2H	Pr^i	a	1994CPB2036
COCl	Pr^i	a	1994CPB2036
$CONH_2$	Pr^i	134–135	1994CPB2036
CONHMe	Pr^i	128–130	1994CPB2036
EtNHCO	Pr^i	129–131	1994CPB2036
CO_2H	Bn	a	1994CPB2036
COCl	Bn	a	1994CPB2036
$CONH_2$	Bn	225–226	1994CPB2036
MeNHCO	Bn	176–177	1994CPB2036
EtNHCO	Bn	148–150	1994CPB2036
CO_2H	$HO(CH_2)_2$	134–135	1994CPB2036

[a]no mp/bp given.

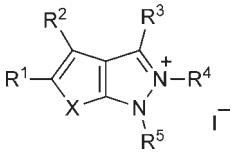
Table 14 1*H*-Furo[2,3-*d*]pyrazoles (X = O, Y = NH), 1*H*-pyrrolo[2,3-*d*]pyrazoles (X = Y = N), selenolo[2,3-*d*]isoxazole (X = Se, Y = O), 1*H*-thieno[2,3-*d*]isopyrazoles (X = S, Y = NH)



R^1	R^2	R^3	*X*	*Y*	*mp* (°*C*)	*Reference*
H	H	Me	NH	(2-Pyridyl)N	159–162	2006TL433
CH-CH=CH-CH		Ph	MeN	PhN	a	1995TL4065
CH-CH=CH-CH		Ph	O	PhN	218–220[b]	2004TL4143
CH-CH=CH-CH		CO_2Et	O	PhN	193–194	2004FA849
CH-CH=CH-CH		CO_2Et	O	4-ClC_6H_4N	203–206	2004FA849
CH-CH=CH-CH		CO_2Et	O	3-ClC_6H_4N	153–154	2004FA849
H	H	H	S	PhN	33–35	2005JOC596
H	H	H	S	4-$CF_3C_6H_4N$	27–29	2005JOC596
H	H	H	S	4-$MeOC_6H_4N$	oil, a	2005JOC596
H	H	H	S	(2-Naphthaleno)N	29–31	2005JOC596
H	H	3-Isoquinolino	S	4-BrC_6H_4N	251–252	1999JOC5499
NH_2	CN	Me	S		200	1997JIC206-8
NH_2NH	MeCO	Ph	S	NH	87	1995CCC1578
PhNHN	MeCO	Ph	S	PhN	92	1995CCC1578
H CH-CH=CH-CH		OH	Se	O	216–218	1996RJC1798

[a]no mp/bp given.
[b]155–157 °C <1972JOC2402>, 151 °C <1981IJB930>.

Table 15 Furo[2,3-*c*]pyrazolium and thieno[2,3-*c*]pyrazolium salts

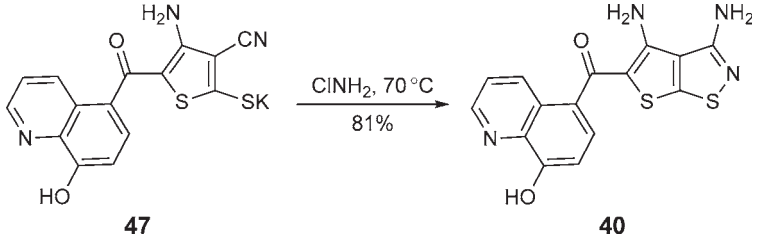


R^1	R^2	R^3	R^4	R^5	X	*mp* (°C)	*Reference*
Me	CO_2Et	Me	Me	Ph	O	158	2002CCS1061
Me	CO_2Et	$(EtO)_2CHCH_2$	Me	Ph	O	173	2002CCS1061
Me	CO_2Et	Me	Me	Ph	S	155	2002CCS1061
Me	CO_2Et	$(EtO)_2CHCH_2$	Me	Ph	S	169	2002CCS1061

10.02.7.1 Annelations onto π-Excessive Heterocycles

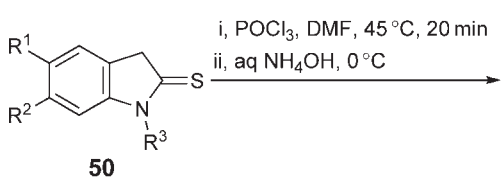
10.02.7.1.1 Oxidative [5+0] and [4+1] cycloamination

This approach is used exclusively for the synthesis of the isomeric annelated isothiazoles and isoselenazoles to form the nitrogen–sulfur(selenium) bond and has been discussed in CHEC-II(1996) <1996CHEC-II(7)49>. A wide variety of oxidative cyclizations have been reported, some of which incorporate an amination. For example, reaction of **47** with chloramine gives the corresponding isothiazolo[5,4-*b*]thiophene **40** (Equation 9) <2000P65>.

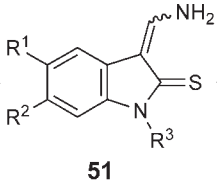


47 **40** (9)

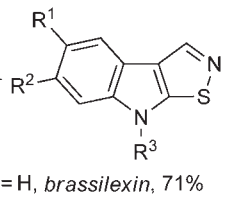
Brassilexin **48** and sinalexin **49** are among the most potent phytoalexins produced by economically important cruciferous plants. The most efficient preparation of brassilexin **48**, sinalexin **49**, and analogues **52** reported uses a Vilsmeier formylation–amination of readily available indoline-2-thiones **50** followed by an aqueous ammonia work-up procedure with subsequent oxidation of the 3-(amino)methyleneindoline-2-thione intermediates **51** using iodine in pyridine (**Scheme 10**) <2001OL1213, 2005JOC1828>. The reaction yields are dictated by the efficiency of the



50



51

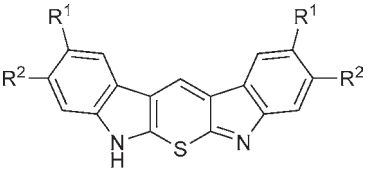


R^1	R^2	R^3	*Yield* **52** (%)
F	H	H	64
Cl	H	H	54
Br	H	H	40
Me	H	H	52
MeO	H	H	67
H	F	H	68
H	Cl	H	58
H	Br	H	45
H	MeO	H	47
H	H	Me	65

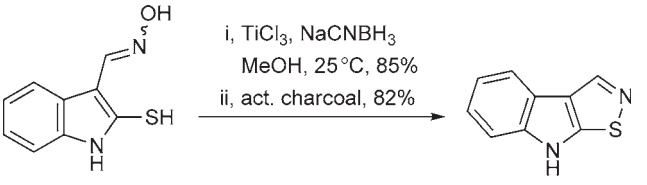
48: $R^1 = R^2 = R^3 = H$, *brassilexin*, 71%
49: $R^1 = R^2 = H$, $R^3 = MeO$, *sinalexin*, 67%
52: see table

Scheme 10

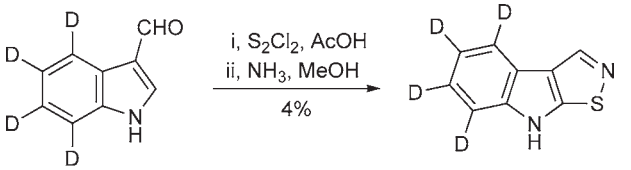
Vilsmeier formylation; optimization of the synthetic protocol (for the synthesis of brassilexin) significantly reduced formation of the concurrently formed pentacyclic by-products **53** and allowed extension to the preparation of a range of analogues **52** (**Scheme 10**) <2005JOC1828>, which were subsequently tested for their antifungal activities. Alternative approaches to brassilexin from **54** (Equation 10) <1998CC1565> and the deuterated form **56** (from **55** in very poor yield) (Equation 11) <1998BML3037> have also been described in work investigating the brassilexin biosynthetic pathway.



53

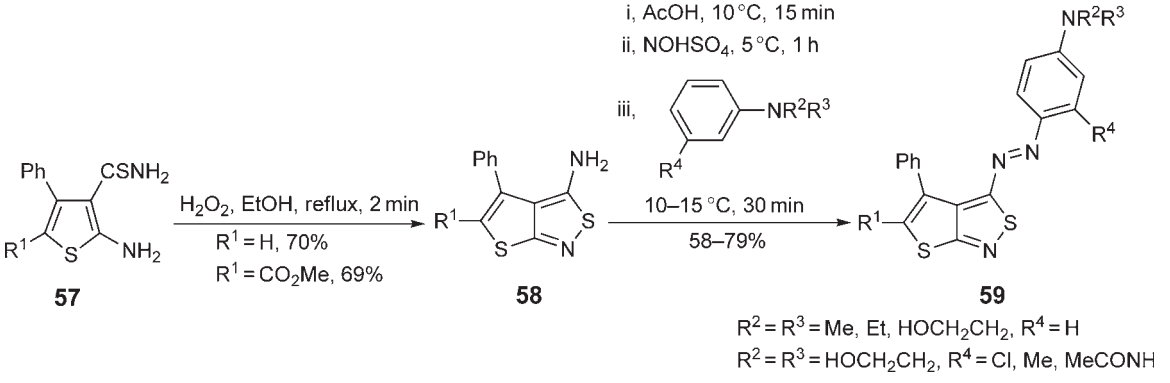


54 brassilexin **48** (10)



55 **56** (11)

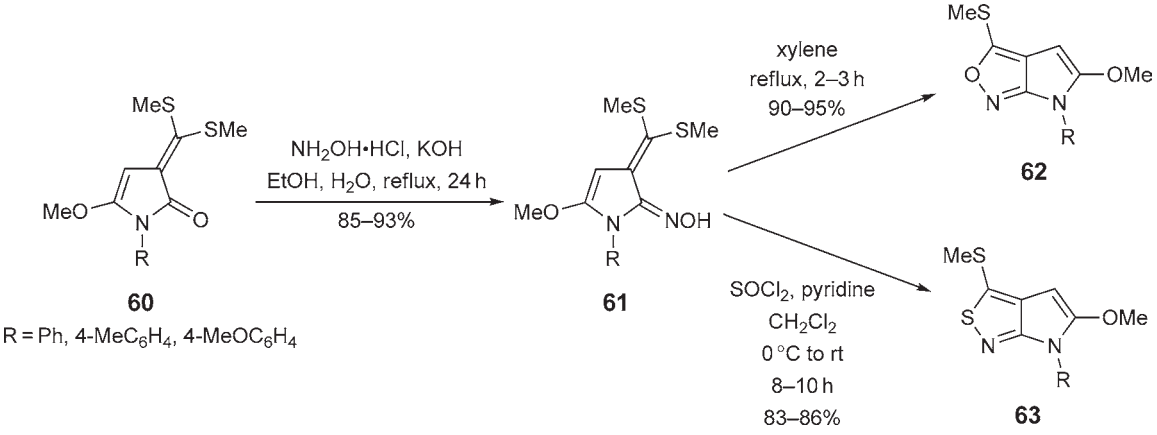
Formation of the nitrogen–sulfur bond in thieno[2,3-*c*]isothiazoles **58** was achieved by oxidative cyclization of **57** using hydrogen peroxide (**Scheme 11**) <2005JSC799>. Subsequent diazotization and reaction with substituted anilines afforded azo dyes **59**, in good yields, for application to polyester fabrics. Novel pyrrolo[2,3-*c*]isoxazoles **62** and pyrrolo-[2,3-*c*]isothiazoles **63** have been prepared in a convenient, high-yielding two-step methodology from a range of *N*-aryl-3-di(methylsulfonyl)methylenepyrrol-2-ones **60**. Reaction of **60** with hydroxylamine gave the corresponding oximes **61**, which were readily converted into either **62** or **63** by heating in xylene or on reaction with thionyl chloride and pyridine, respectively (**Scheme 12**) <2002T135>. Reaction of 2-amino-4-phenyl-5-phenylsulfonylthiophene-3-carbonitrile **64** at room temperature with hydroxylamine hydrochloride and ammonium hydroxide gave the corresponding amidoxime **65**, which readily underwent dehydrative intramolecular cyclization to afford the corresponding thieno[2,3-*c*]pyrazole **66** on



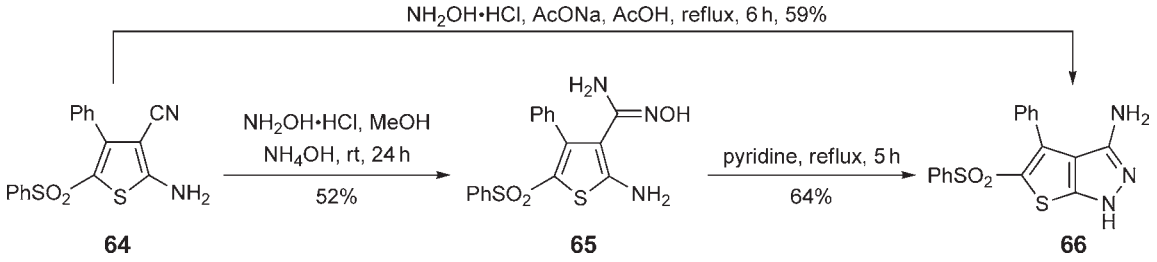
57 **58** **59**

Scheme 11

prolonged heating in pyridine (**Scheme 13**) <1997M687>. Alternatively, the thieno[2,3-*c*]pyrazole **66** was isolated in one step by annealing **64** with hydroxylamine hydrochloride in glacial acetic acid in the presence of sodium acetate.



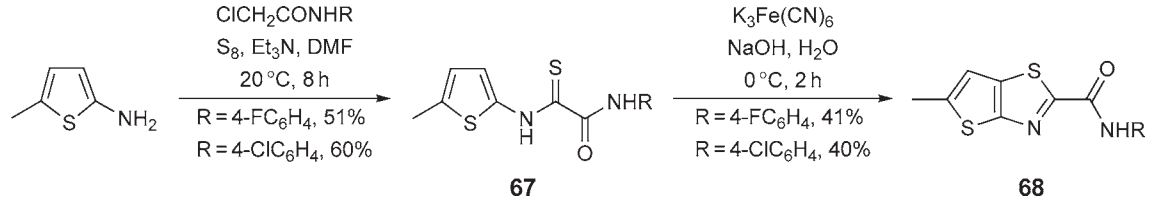
Scheme 12



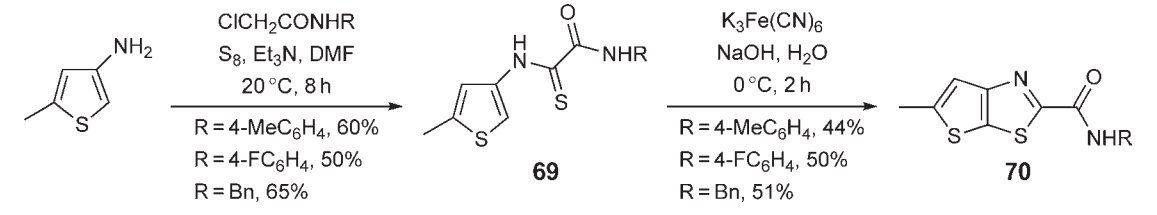
Scheme 13

10.02.7.1.2 [5+0] Electrophilic cyclizations

The cyclization of 2- and 3-(thioacetamido)thiophene mediated by potassium ferricyanide was first reported by Zhirayakov and Levkoev <1958DOK(120)1035, 1996CHEC-II(7)49>. This methodology has now been extended to include the preparation of 2-carbamoylthieno[2,3-*d*]thiazoles **68** and 2-carbamoylthieno[3,2-*d*]thiazoles **70** by potassium ferricyanide-mediated cyclizations of monothiooxamides **67** (**Scheme 14**) <2004RJO137, 2004ZOK146> and **69** (**Scheme 15**) <2003RJO1161, 2003ZOK1232>, respectively.

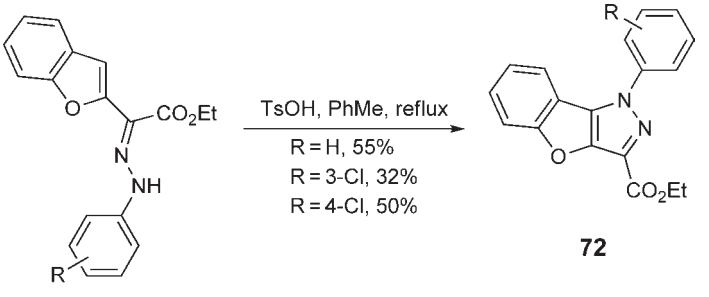


Scheme 14

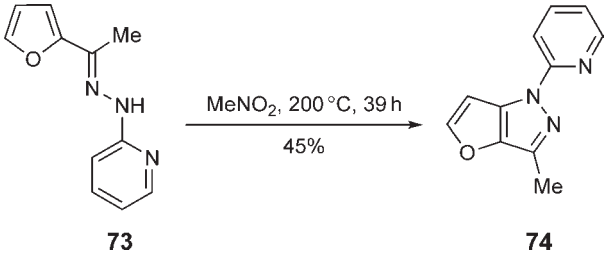


Scheme 15

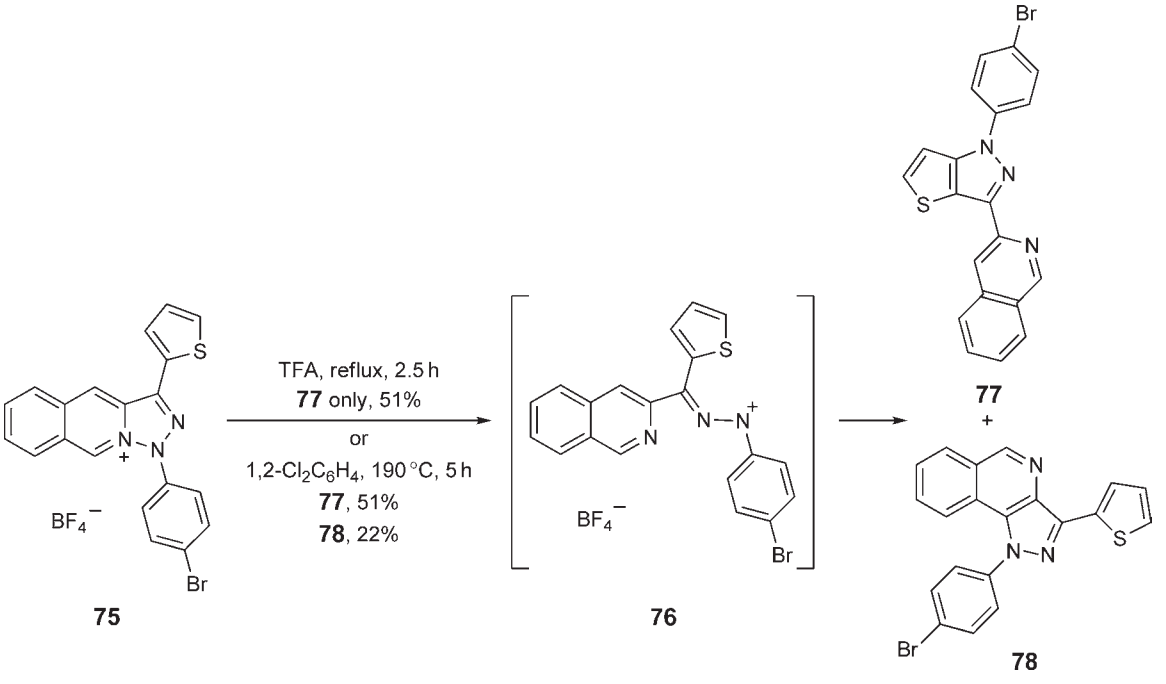
Another electrophilic cyclization strategy is reported in which acid-mediated cyclization of benzofuro-2-hydrazones **71** afforded benzofuro[3,2-*c*]pyrazoles **72** (Equation 12) <2004FA849>. The benzofuro[3,2-*c*]pyrazoles **72** were investigated for their binding at both central and peripheral benzodiazepine receptors. An analogous cyclization of thienyl-2-hydrazones to thieno[2,3-*c*]pyrazoles with polyphosphoric acid has also been reported <1996CHEC-II(7)49>. A thermal cyclization, in the absence of an acid catalyst, of pyrrolo-2-hydrazone **73** is reported to afford a pyrrolo[3,2-*c*]pyrazole **74** (Equation 13) <2006TL433>. A 1-aryl-3-(2-thienyl)[1,2,3]triazolo[1,5-*b*]isoquinolinium salt **75** underwent an interesting electrophilic thermal rearrangement in trifluoroacetic acid (TFA), via a ring-opened nitrenium cation **76** that reacted exclusively to afford thieno[3,2-*c*]pyrazole **77** (**Scheme 16**) <1999JOC5499>. In contrast, repeating the experiment in the absence of TFA gave a mixture of two products **77** and **78**. The absence of **78** in the former reaction is suggested to arise from deactivation of the isoquinoline moiety to electrophilic substitution through protonation.



(12)



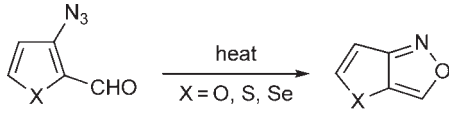
(13)



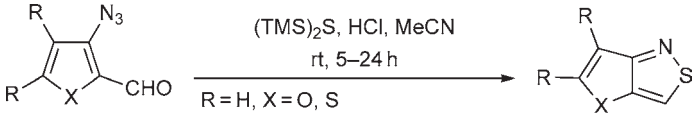
Scheme 16

10.02.7.1.3 Nitrene-mediated [5+0] cyclizations

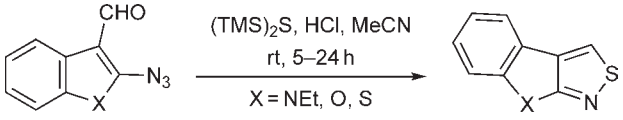
Thermolytic or photolytic nitrene-based cyclizations are used predominantly for the synthesis of annelated imidazoles, isoxazoles, and pyrazoles. A number of examples are highlighted in CHEC-II(1996) <1996CHEC-II(7)49>, including the thermolysis of *o*-azidocarbaldehydes **79** to afford furo[3,2-*c*]-, thieno[3,2-*c*]- and selenolo[3,2-*c*]isoxazoles **80** (X = O, S, Se) (Equation 14) <1976CS165>. An interesting extension of this reaction is the reported formation of fused isothiazoles **82** and **84** by reaction of *o*-azidocarbaldehydes **81** and **83**, respectively, in the presence of an acidic solution of thionating agent bis(trimethylsilyl)sulfide (Equations 15 and 16) <1994CL1873>. It is suggested that a transient heteroaromatic thioaldehyde is formed, which is rapidly intercepted by the adjacent azido function.



79 **80** (14)



81 **82** (15)



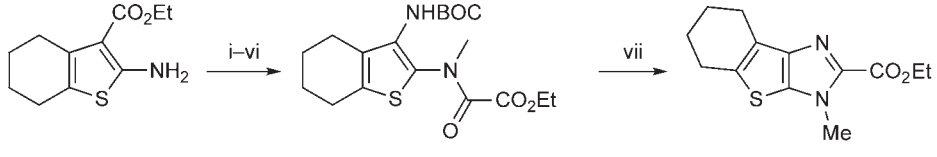
83 **84** (16)

10.02.7.1.4 Direct [4+1] thiation

Direct thiation is used predominantly for the synthesis of annelated thiazoles, most often from heterocyclic acylamides. Examples are highlighted in CHEC-II(1996) <1996CHEC-II(7)49>; no further examples have been reported in this period.

10.02.7.1.5 [5+0] and [4+1] Carbon closures

This approach is used for the syntheses of fused heterocycles which have a [1,3]-heteroatom juxtaposition in one of the rings <1996CHEC-II(7)49>. The unambiguous synthesis of tetrahydro-3*H*-benzothieno[2,3-*d*]imidazole **87**, as a target for the potential treatment of anxiety disorders, was accomplished starting from commercially available ethyl 2-amino-4,5,6,7-tetrahydro-benzothiophene-3-carboxylate **85**; the key formation of the bicyclic heterocycle occurred through a final acid-mediated cyclization of **86** (**Scheme 17**) <1997SC473>.

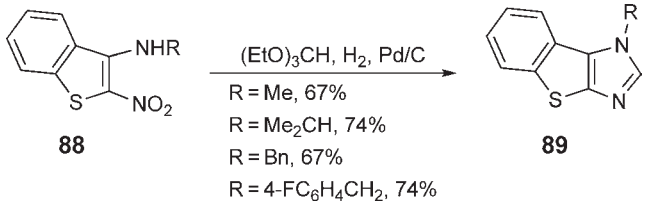


85 **86** **87**

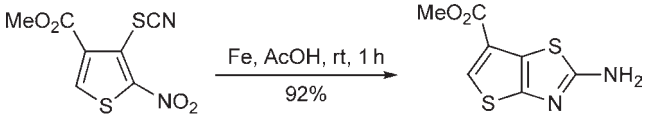
i, NaOH, MeOH, H_2O, reflux, 78%; ii, K_2CO_3, $PhCH_2Br$, DMF, rt, 20 h, 76%
iii, Et_3N, $ClCOCO_2Et$, CH_2Cl_2, rt, 20 h, 100%; iv, K_2CO_3, MeI, DMF, 80 °C, 20 h, 94%
v, H_2, Pd, EtOAc, rt, 80%; vi, $(PhO)_2PON_3$, Et_3N, Bu^tOH, reflux, 24 h, 56%; vii, PPA, 110 °C, 75 min, 47%

Scheme 17

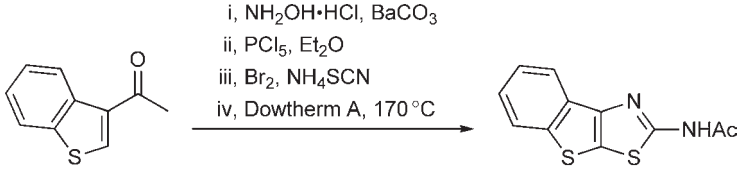
Approaches to cyclizations via an *ortho*-ester have been reported <1996CHEC-II(7)49>. An example of this methodology incorporating a reduction is in the preparation of 1-substituted-1*H*-benzothieno[2,3-*d*]imidazoles **89** (Equation 17) <1995JHC591> from 2-nitro-3-bromobenzo[*b*]thiophene **88** (prepared following published methodology <1986JHC951>). A thieno[2,3-*d*]thiazole **26** was isolated on reduction of the nitro group of nitrothiocyanothiophene **90** with Fe/AcOH; the initially formed thiophenamine spontaneously cyclized under the reaction conditions via intramolecular nucleophilic attack at the carbon of the thiocyanate group to yield **26** (Equation 18) <2001ARK34>. Thieno[3,2-*d*]thiazole **92** was assembled from **91** in four steps, incorporating a Beckmann rearrangement and intramolecular nucleophilic attack at the carbon of a thiocyanate group as key steps (Equation 19) <1998SL407>. A recent synthesis of brassilexin **48** from **93** utilizes a cyclization onto the sulfur of a thiocyanate group (Equation 20) <2006BMC714>.



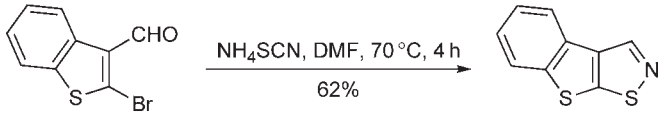
88 **89** (17)



90 **26** (18)

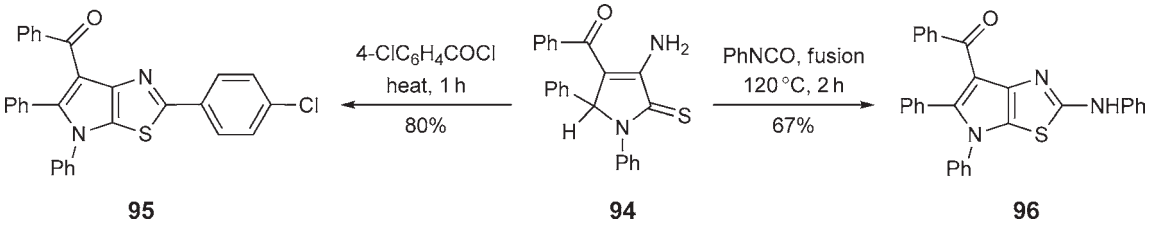


91 **92** (19)



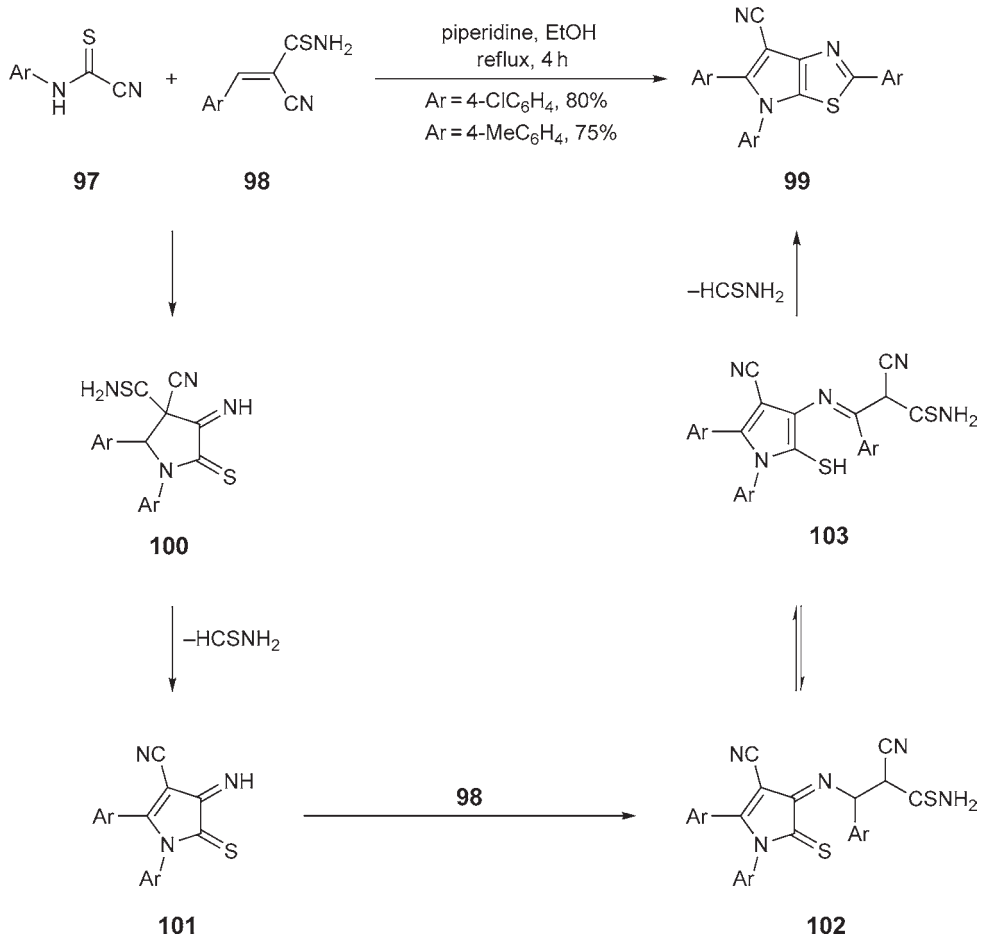
93 **48** (20)

An interesting one-carbon ring closure is found in the reaction of **94** (prepared from phenylcyanothioformamide and 1,3-diphenylpropenone) with either *p*-chlorobenzoyl chloride or phenyl isocyanate to give pyrrolo[3,2-*d*]thiazoles **95** and **96**, respectively (**Scheme 18**) <1999PSS(148)117>. However, attempted extension of this reaction sequence to include acetic anhydride did not afford a pyrrolo[3,2-*d*]thiazole product. In a novel approach, the same workers obtained additional examples of pyrrolo[3,2-*d*]thiazoles **99** in excellent yield as the only isolable product by reaction of *N*-(4-chloro and 4-methylphenyl)cyanothioformamide **97** with arylidene **98**; the formation of the product was rationalized via **100–103** as detailed in **Scheme 19** <2005PS(180)573>.



95 **94** **96**

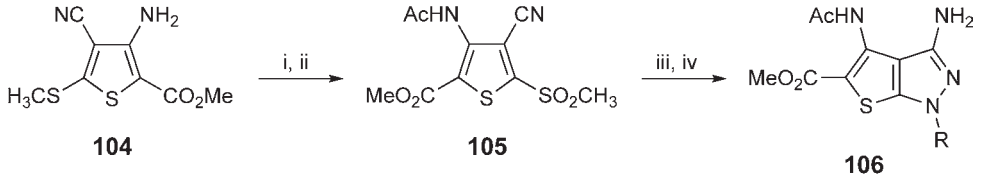
Scheme 18



Scheme 19

10.02.7.1.6 [2+3] Annelations using bisnucleophiles

5-Methylthiothiophen-4-carbonitriles have been shown to be useful building blocks for the synthesis of bicyclic and tricyclic heterocycles <1998PHA227>. An interesting example is found in the investigation of thieno[2,3-*c*]pyrazoles **106** for their antiulcer activity. Reaction of **104** with acetic anhydride followed by *S*-oxidation with hydrogen peroxide gave **105**. Subsequent treatment with either hydrazine hydrate or methylhydrazine occurred as a two-step process with initial S_NAr substitution of the methanesulfonyl group to afford a highly functionalized 5-hydrazinothiophene that readily cyclized under acidic conditions to the target thieno[2,3-*c*]pyrazoles **106** (**Scheme 20**) <1998PHA227>. Analogously, a pre-assembled 2-hydrazinothiophene **107** was easily converted, under mild acidic conditions, into the corresponding thieno[2,3-*c*]pyrazole **108** (Equation 21) <1995PHA675>. Similarly, dihydrobenzothieno[2,3-*d*]pyrazoles **110** were prepared for antimicrobial activity screening against *Bacillus mega*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens* and *Aspergillus awamori* by cyclocondensation of hydrazine hydrate with a series of dihydrobenzo[*b*]thiophenes **109** (Equation 22) <1997IJB668>. Interestingly, reaction of highly functionalized thiophene **111** with 2 equiv of hydrazine hydrate or phenylhydrazine gave thieno[3,2-*c*]pyrazoles **112** (Equation 23) <1995CCC1578>, whereas reaction of **113** under similar conditions gave thieno[2,3-*c*]pyrazoles **114** (Equation 24) <1995CCC1578>. Novel pyrazolo[3,4-*b*]indole nucleosides **116** for antiviral evaluation were readily accessed from the corresponding 3-formyl-2-chloroindole and 3-cyano-2-chloroindole nucleosides, **115** R^1 = CHO and R^1 = CN, respectively, by treatment with either methylhydrazine or hydrazine (Equation 25) <2004NN805>.

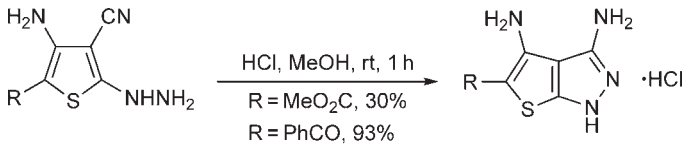


104 105 106

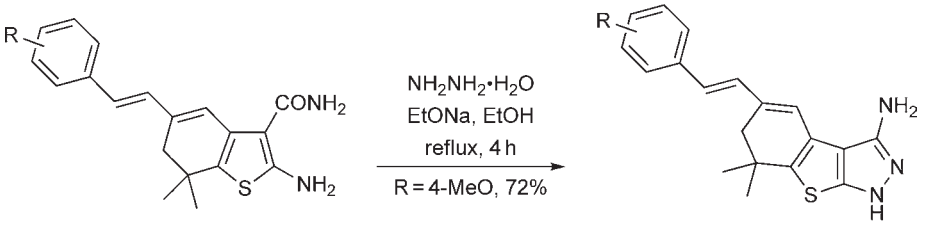
i, Ac_2O, DMAP, reflux, 8 h; ii, H_2O_2, AcOH, 100 °C, 1.5 h 65% (two steps)

iii, $RNHNH_2 \cdot H_2O$, MeOH, reflux, 10 min; iv, HCl, MeOH, rt, 1 h, R = H, 23%, R = Me, 64% (two steps)

Scheme 20

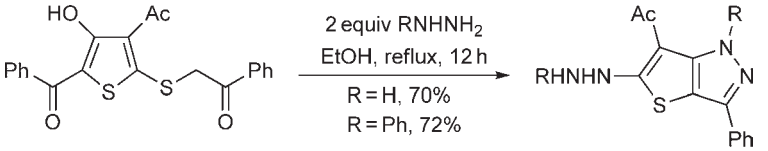


107 108 (21)

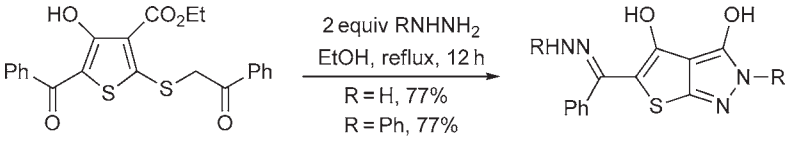


109 110 (22)

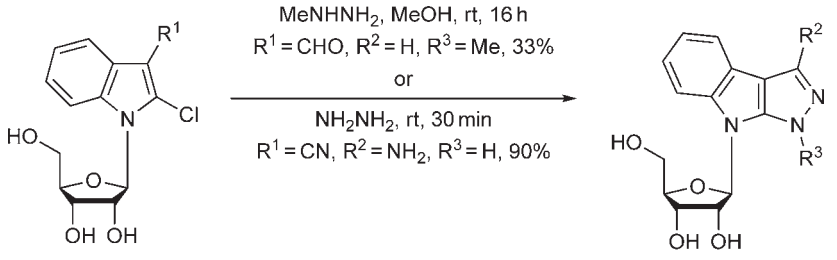
R = H, 2-Cl, 4-Cl, 3,4-Cl_2, 2-MeO, 3,4-$(MeO)_2$, 3,4,5-$(MeO)_3$, 3-MeO-4-OH, 4-NO_2



111 112 (23)



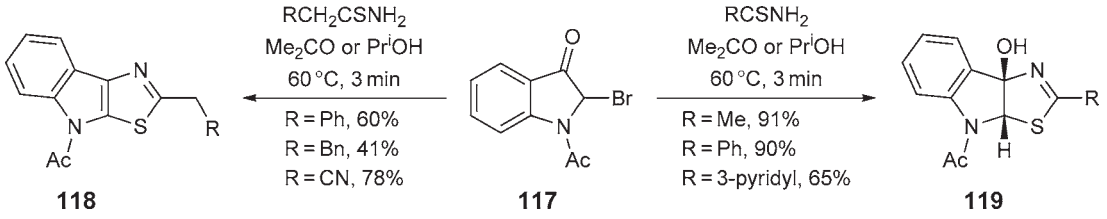
113 114 (24)



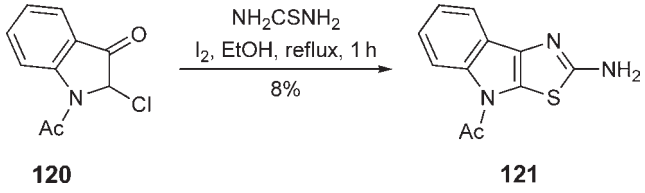
115 116 (25)

Fused 2-substituted thiazoles are most conveniently synthesized by condensing an α-haloketone with a thionoamide. Thiazolo[5,4-*b*]indoles **118** were prepared via the Gunch reaction using bromindoxyl **117** and primary thionoamides of phenylacetic acid, phenylpropionic acid, and cyanoacetic acid affording the products as either

their free base or hydrobromide salts, depending on substituents (**Scheme 21**) <1996MI643>. Interestingly, reaction under the same conditions with thionoamides of acetic, benzoic, nicotinic, and 2-propylisonicotinic acids led to the formation of dihydrothiazolohydroxyindoles **119** (**Scheme 21**). It was shown that thermal dehydration of **119** (R = Me) gave 2-methylthiazoloindole **118** (R = H), although in low yield (12%); further optimization and extension to other derivatives was not investigated. Analogously, the first example of a 2-amino-4*H*-thiazolo[5,4-*b*]indole **121** was reported by Breinholt *et al.*, for use in their investigations of protein tyrosine phosphate inhibitors, through reaction of 1-acetyl-2-chloro-1,2-dihydroindol-3-one **120** <1994S411> with thiourea, although in very poor yield (Equation 26) <2001JHC569>.



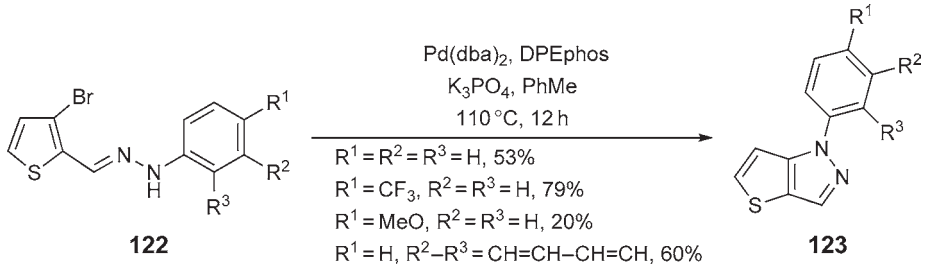
Scheme 21



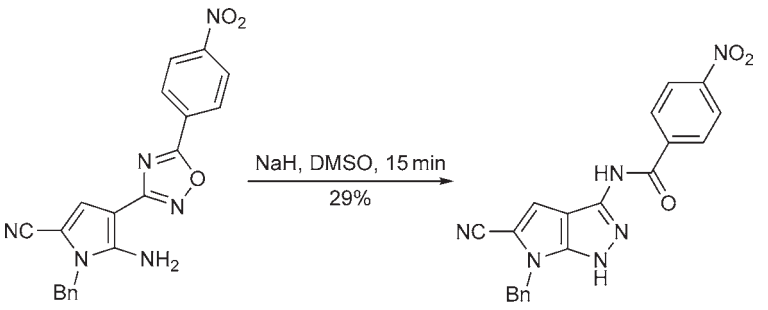
(26)

10.02.7.1.7 Miscellaneous cyclizations

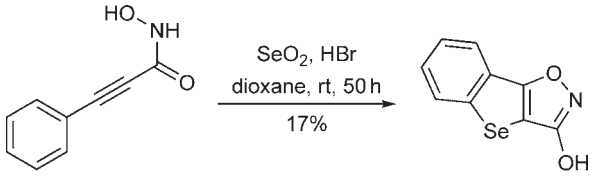
Specialized cyclization sequences should not be overlooked. Examples of intramolecular Pd-catalyzed C–N bond formation leading to heteroaromatic fragments are rare (e.g., <1995JA4708, 1997JA9641, 2000OL519, 2001TL2937>) as stable metallacycles often form leading to catalyst inactivation. However, the cyclization of arylhydrazones **122** (derived from 3-bromo-2-thiophenecarboxaldehyde) using $Pd(dba)_2$ and a chelating phosphine, bis[2-(diphenylphosphino)phenyl] ether (DPEphos), in the presence of a base was shown, in unoptimized reactions, to give novel thieno[3,2-*c*]pyrazoles **123** (Equation 27) <2005JOC596>. A 3-aminopyrrolo[2,3-*c*]pyrazole **125** was prepared by mononuclear heterocyclic rearrangement through ring transformation of a 3-(2-amino-5-cyanopyrrolo)-1,2,4-oxadiazole **124** (Equation 28) <2004H(63)2475>. It is notable that ring transformations of the 5-unsubstituted pyrrole gave no identifiable products with decomposition of the highly electronegative reaction products being suggested. It is proposed that the cyano group reduces the electron density and stabilizes the 5-5 bicyclic ring. Further functional group modification of the reaction product was not possible. A novel 3-hydroxybenzo[*f*]selenopheno[2,3-*d*]isoxazole **127** was isolated in low yield from the reaction of phenylpropynohydroxamic acid **126** <1987JME574> with selenium tetrabromide (Equation 29) <1996RJC1798, 1996ZOB1847>. The reaction is postulated to follow an electrophilic addition of Br_3Se^+ to the triple bond followed by subsequent tandem intramolecular cyclizations. Further examples of this reaction have yet to be reported.



(27)



124 **125** (28)

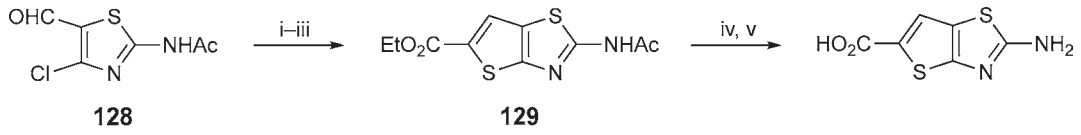


126 **127** (29)

10.02.7.2 Annelations onto π-Deficient Heterocycles

10.02.7.2.1 Claisen, Thorpe, or aldol cyclizations

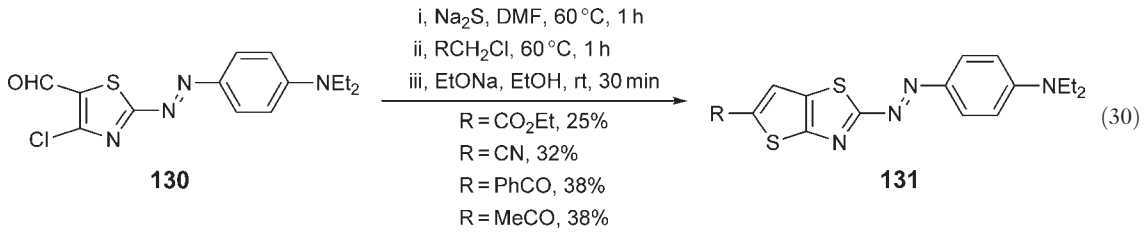
Claisen-type cyclizations have been realized to afford a number of heterocycles in the bicyclic[5,5]heterocycles with 2:1-heteroatom orientation class <1996CHEC-II(7)49>. Successive condensation of **128** with sodium sulfide followed by reaction with ethyl bromoacetate and subsequent cyclization with sodium ethoxide led to a thieno[2,3-*d*]thiazole **129** (**Scheme 22**) <1998AQ186>. An analogous sequence of reactions from **130** led to thieno[2,3-*d*]-thiazoles **131**, investigated for nonlinear optical purposes (Equation 30) <1998AQ186>. A simple, high-yielding, one-step synthesis of thieno[2,3-*c*]pyrazoles **133** was reported via the condensation of methyl mercaptoacetate with 5-chloro-4-formyl-3-substituted-1-phenyl-1*H*-pyrazole **132** (**Scheme 23**) <1996IJB715>. It was suggested that the reaction proceeds via the intermediate formation of methyl *S*-(4-formyl-3-substituted-1-phenyl-1*H*-pyrazol-5-yl-2-mercaptoacetate **134**. This intermediate was isolated on reaction of **132** with methyl mercaptoacetate under similar conditions in the absence of sodium methoxide and subsequently cyclized in an independent step. Saponification of the methyl ester **133** gave the corresponding acid **135** in good yield. Similarly, protected pyrazoles **136** cyclized with methyl mercaptoacetate under basic conditions to afford thieno[2,3-*c*]pyrazoles **137** <2006BML96> (**Scheme 24**). Deprotection of the *p*-methoxybenzyl group was easily achieved by heating in TFA under microwave conditions and the bulkier bis(4-methoxyphenyl)methyl protecting group was readily removed at room temperature under acidic conditions to afford **138**. Functional group manipulation was straightforward: BOC protection followed by NBS bromination gave **139**, and subsequent reaction with secondary amines and deprotection afforded thieno[2,3-*c*]pyr-azoles **140** for evaluation as kinase inhibitors. The bromine atoms in *N*-protected-2,4,5-tribromoimidazole can be sequentially replaced through selective Br–Li (or Br–Mg) exchange strategies in the order 2,5,4 <1994H(38)2487, 1995JP11475>. Application of this strategy to convert various *N*-protected-tribromo-2,4,5-imidazoles to thieno[2,3-*d*]imidazole were originally hindered due to the lack of a suitable *N*-protecting group that could be removed under mild conditions <1985CC1428, 1987J(P1)1457, 1995T12807>. Hartley and Iddon introduced the *N*-vinyl protecting group to synthesize the parent thieno[2,3-*d*]imidazole ⇌ [3,2-*d*]imidazole **142** in a seven-step strategy from 2,4,5-tribromoimidazole **141** incorporating a Thorpe cyclization as a key step (**Scheme 25**) <1997TL4647>. Similar elaboration of 2,4,5-tribromoimidazole, in a seven-step procedure incorporating a final Thorpe cyclization of **143**, afforded vinylthieno[2,3-*d*]-imidazole **144** (Equation 31) <2000JMC4877> and was adapted to prepare the analogous allylthieno[2,3-*d*]imidazole <2000JMC4877>.



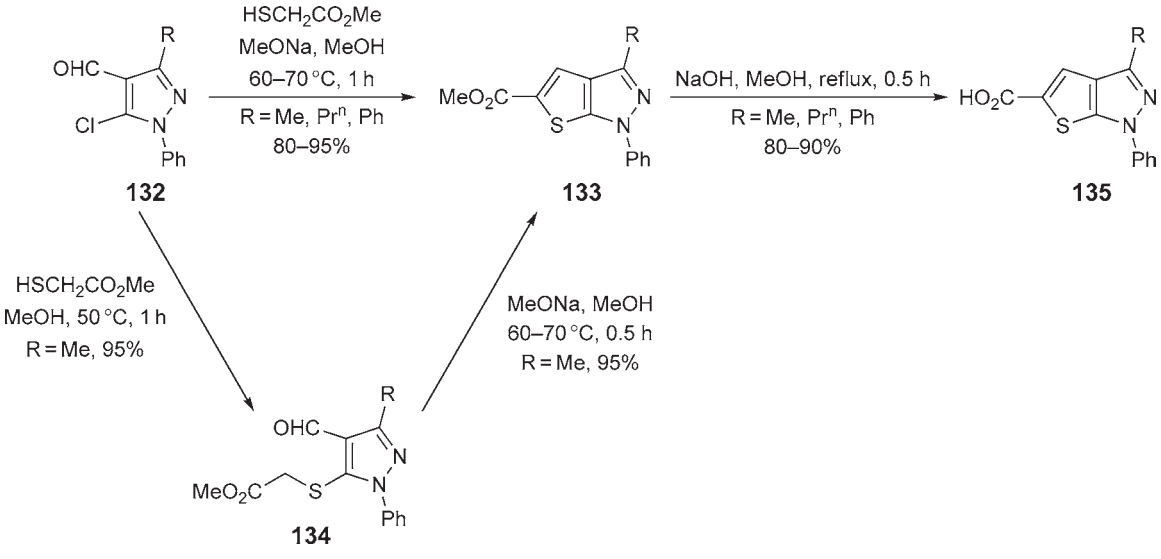
128 129

i, Na_2S, DMF, 60 °C, 1 h; ii, EtO_2CCH_2Br, 60 °C, 30 min; iii, EtONa, EtOH, rt, 30 min, 34% (3 steps)
iv, 40% NaOH, EtOH, reflux, 3 h; v, H_2SO_4, 30% (two steps)

Scheme 22



130 131 (30)

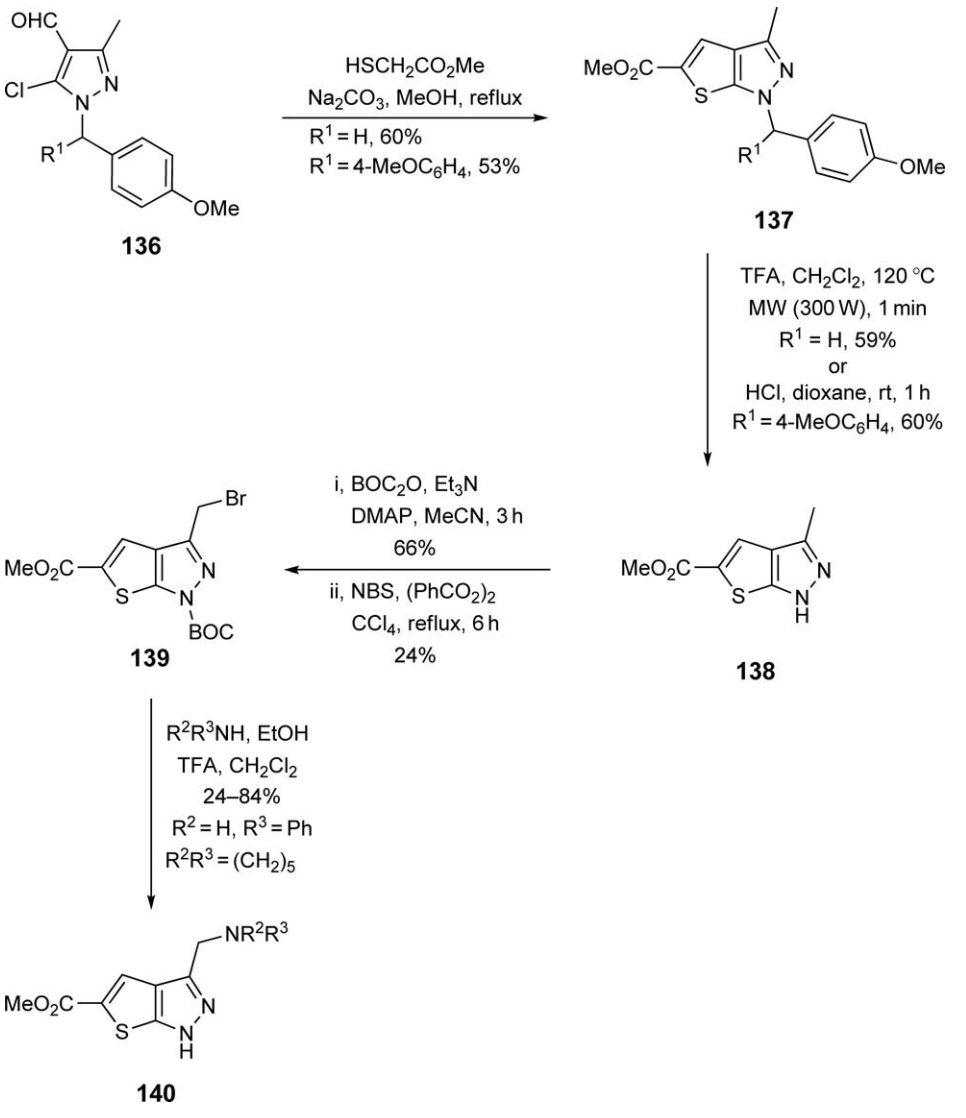


132 133 135

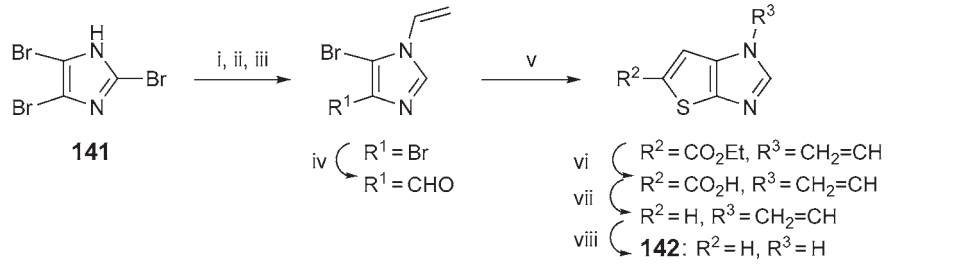
134

Scheme 23

Thorpe-type cyclizations have proved highly useful in accessing examples of the bicyclic 5-5 heterocycles with 2:1-heteroatom orientation <1996CHEC-II(7)49>. Thieno[2,3-*d*]imidazole **43** was obtained by cyclization of **145** with sodium ethoxide (Equation 32) <1995T12807> and heating 1-methyl-5-*N*-phenylthioglcolamide-pyrazole-4-carbonitrile **146** with potassium carbonate induced cyclization to the corresponding thieno[2,3-*c*]pyrazole **147** (Equation 33) <2004RCB580, 2004IZV553>. Thieno[2,3-*c*]pyrazoles **149** and **152** have been obtained in a one-pot reaction of **148** (**Scheme 26**) <2005JCR761> and **151** (**Scheme 27**) <2006BMCL96>, respectively, using mercaptoacetamide in the presence of potassium carbonate. Thieno[2,3-*c*]pyrazole **149** was subsequently converted into carbohydrazide **150**, which was used in the synthesis of a range of substituted thieno[2,3-*c*]pyrazoles derivatives; some interesting examples are highlighted in **Scheme 26** <2005JCR761>. The 4-amino group of **152** reacted with acyl chlorides to afford, after removal of the bis(4-methoxyphenyl)methyl protecting group, acylated thieno[2,3-*c*]pyrazoles **153** (**Scheme 27**) <2006BML96>. Spontaneous Thorpe cyclization of **154** to thieno[2,3-*c*]pyrazole **155** was realized on attempted *N*-methylation with dimethyl sulfate (Equation 34) <1995JPR472>. Fleximers (purine ring systems split into their individual imidazole and pyrimidine components connected by a single carbon–carbon bond) with potential use as bioprobes for investigating enzyme–coenzyme binding sites and nucleic acid and protein interactions were developed by Seley *et al.* <2001OL3209, 2002JOC3365>. A key intermediate in the synthesis of fleximer **158** based on adenosine was thieno[2,3-*d*]imidazole **157** assembled via Thorpe cyclization of **156** (**Scheme 28**).

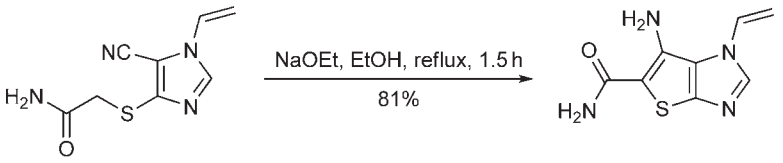


Scheme 24

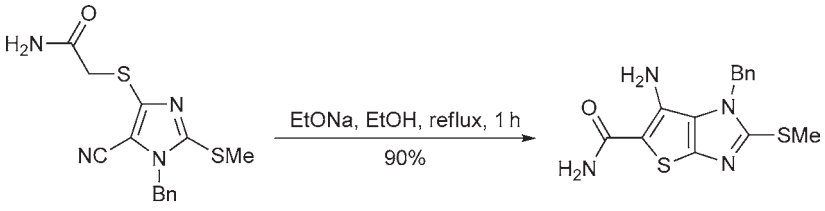


i, $BrCH_2CH_2Br$, Et_3N, reflux; ii, 10% NaOH, reflux, 80% (2 steps); iii, EtMgBr, Et_2O, 0 °C, then H_2O, 81%
iv, EtMgBr, Et_2O, 0 °C then *N*-formylpiperidine, 65%; v, $HSCH_2CO_2Et$, K_2CO_3, DMF, rt, 61%
vi, LiOH, THF, heat, 90%; vii, Ph_2O-Cu_2O, 250 °C, 75%; viii, $KMnO_4$, Me_2CO, reflux, 99%

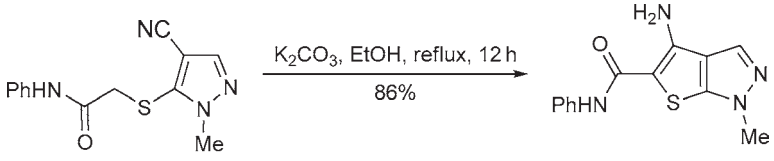
Scheme 25



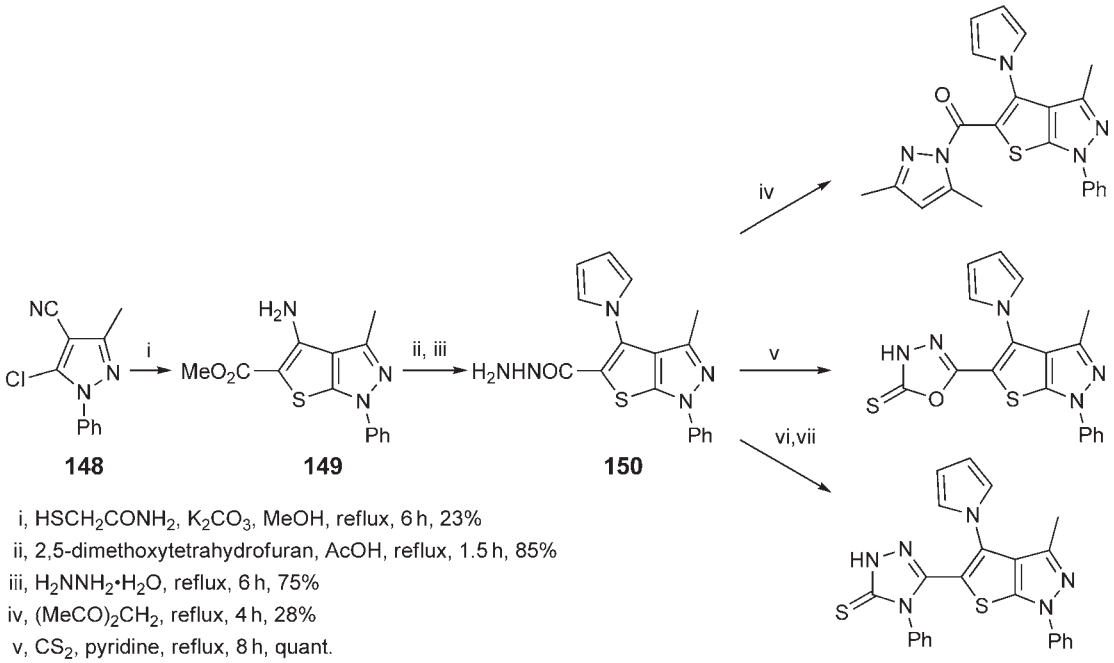
143 144 (31)



145 43 (32)



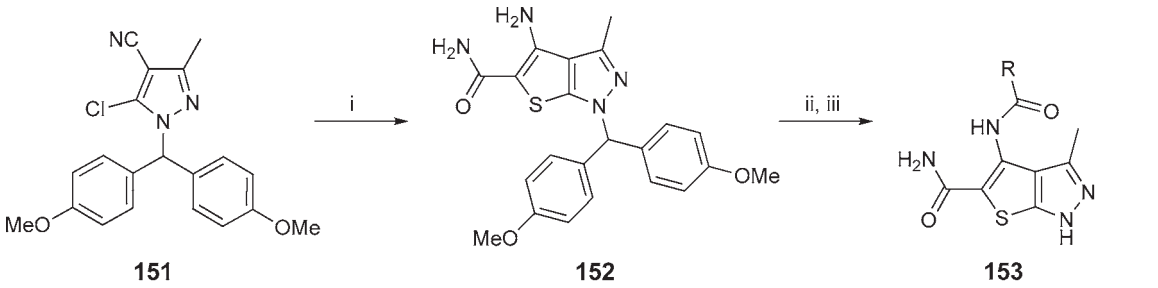
146 147 (33)



148 149 150

i, $HSCH_2CONH_2$, K_2CO_3, MeOH, reflux, 6 h, 23%
ii, 2,5-dimethoxytetrahydrofuran, AcOH, reflux, 1.5 h, 85%
iii, $H_2NNH_2 \cdot H_2O$, reflux, 6 h, 75%
iv, $(MeCO)_2CH_2$, reflux, 4 h, 28%
v, CS_2, pyridine, reflux, 8 h, quant.
vi, PhNCS, EtOH, reflux, 4 h, 93%
vii, NaOH, reflux, 2 h, 95%

Scheme 26



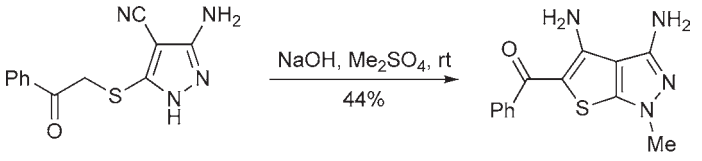
151 **152** **153**

i, $HSCH_2CONH_2$, K_2CO_3, EtOH, reflux, 17 h, 77%

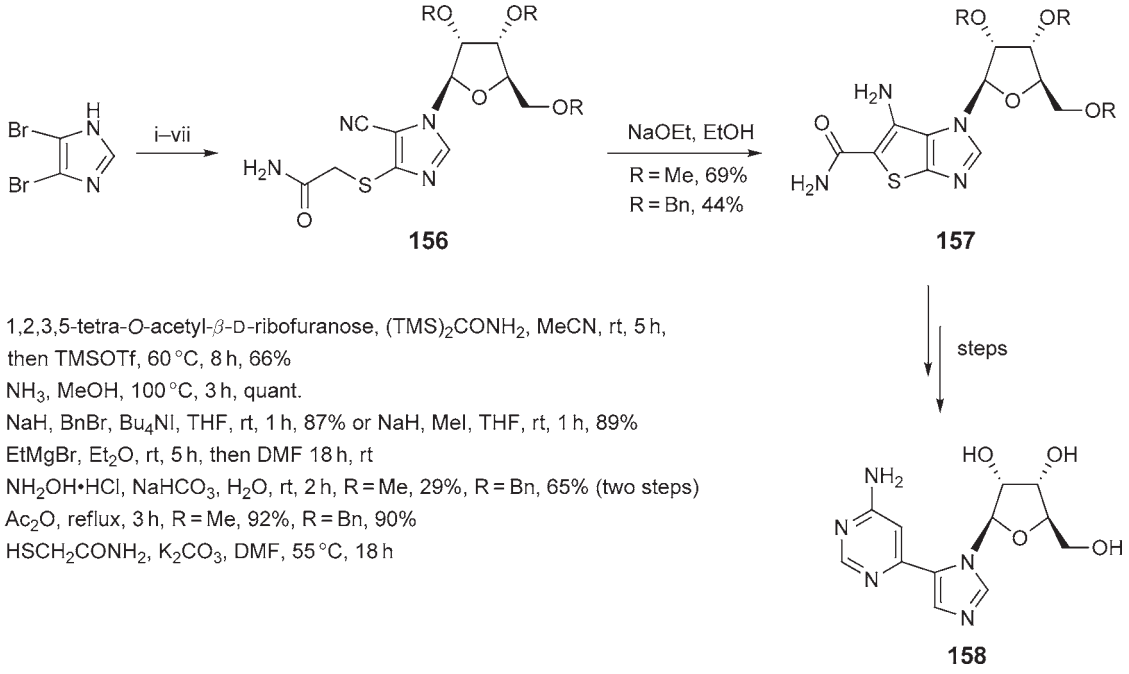
ii, RCOCl, pyridine, rt, 24 h; iii, 4 M HCl, dioxane, 6 h, 4–20% (two steps)

R = Me, CO_2Me, $PhOCH_2$, 2-thienyl, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, PhNH

Scheme 27



154 **155** (34)



156 **157** **158**

i, 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose, $(TMS)_2CONH_2$, MeCN, rt, 5 h, then TMSOTf, 60 °C, 8 h, 66%

ii, NH_3, MeOH, 100 °C, 3 h, quant.

iii, NaH, BnBr, Bu_4NI, THF, rt, 1 h, 87% or NaH, MeI, THF, rt, 1 h, 89%

iv, EtMgBr, Et_2O, rt, 5 h, then DMF 18 h, rt

v, NH_2OH•HCl, $NaHCO_3$, H_2O, rt, 2 h, R = Me, 29%, R = Bn, 65% (two steps)

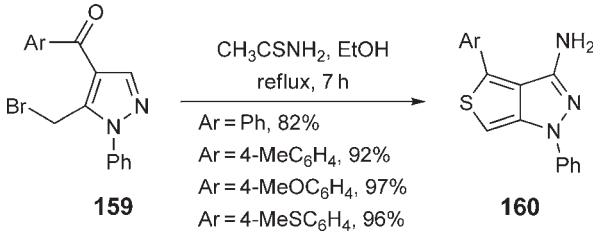
vi, Ac_2O, reflux, 3 h, R = Me, 92%, R = Bn, 90%

vii, $HSCH_2CONH_2$, K_2CO_3, DMF, 55 °C, 18 h

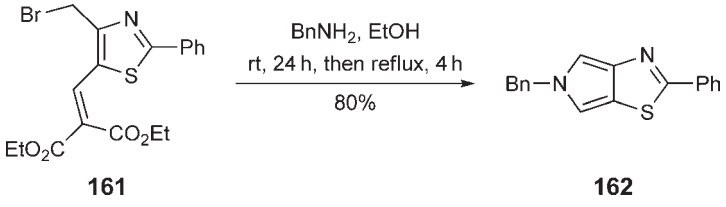
Scheme 28

10.02.7.2.2 Amination, thiation, and selenization

These methods are limited in scope. Direct thiation has been reported for the transformation of vicinal diketones to [3,4]-annelated thiophenes <1996CHEC-II(7)49>. Thionations and selenations of vicinal halomethyl ketones with thioacetamide or *N,N*-diethylselenopropionamide as sulfur and selenium donors, respectively, have also been reported <1996CHEC-II(7)49>. In a recent example, thieno[3,4-*c*]pyrazoles **160** were readily prepared from aryl 5-bromomethyl-1*H*-1-phenylpyrazole-4-yl ketones **159** by reaction with thioacetamide (Equation 35) <1998JHC71>. Additionally, an example of an amination cyclization by reaction of **161** with benzylamine to afford pyrrolo[3,4-*d*]thiazole **162** has been described (Equation 36) <1998JHC71>.



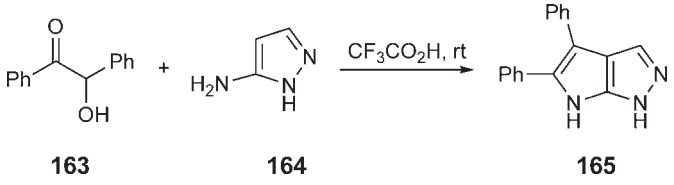
(35)



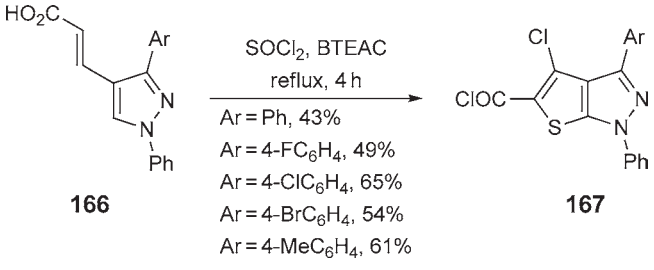
(36)

10.02.7.2.3 Electrophilic cyclizations

Electrophilic additions to π-deficient heterocycles are less common than those to π-excessive heterocycles. However, intramolecular electrophilic cyclizations have been used to access the heterocycles of interest in this chapter <1996CHEC-II(7)49>. Recent examples include the preparation of a pyrrolo[2,3-*c*]pyrazole **165** by acid-catalyzed condensation of **163** and **164** (Equation 37) <1999SC311> and the reaction of 3-(4-pyrazolyl)acrylic acids **166** with excess thionyl chloride in the presence of benzyltriethylammonium chloride (BTEAC) to afford 4-chlorothieno[2,3-*c*]pyrazole-5-carbonyl chlorides **167** (Equation 38) <2003RJO893, 2003ZOK942>. In the latter case, the reaction products were readily manipulated to prepare corresponding carboxylic acids, esters, and amides using standard procedures.



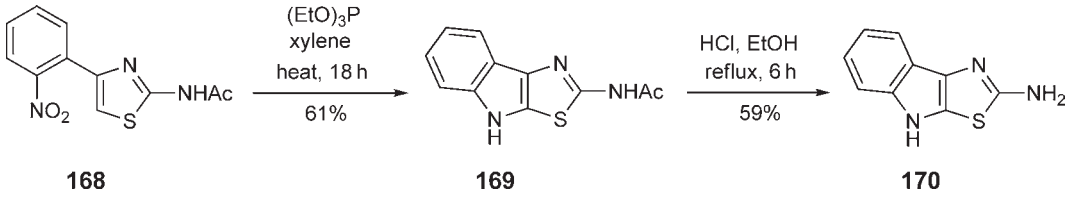
(37)



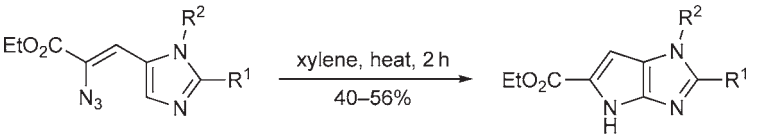
(38)

10.02.7.2.4 Nitrene-based cyclizations

Insertion of nitrenes, normally obtained through photolysis or thermolysis of the corresponding azide, into a π-deficient heterocycle or insertion from a nitrene appended to a π-deficient nucleus into a proximal carbon–hydrogen bond was described in CHEC-II(1996) <1996CHEC-II(7)49>. In a variant to these methods, deoxygenation of the thiazole **168** mediated by triethyl phosphite <1972TL4059> afforded the corresponding *N*-(4*H*-thiazolo[5,4-*b*]indol-2-yl)acetamide **169** via attack of the intermediate nitrene on the unsubstituted 5-thiazole position (**Scheme 29**) <2001JHC569>. Deacetylation was readily achieved using HCl in ethanol to afford 2-amino-4*H*-thiazolo[5,4-*b*]indole **170**. Shafiee *et al.* have used the intermediacy of the nitrene generated by refluxing ethyl α-azido-β-(substituted imidazol-5-yl)acrylates **171** in xylene to synthesise a series of pyrrolo[2,3-*d*]imidazoles **172** (Equation 39) <1998MI99, 2002JHC367> for investigation as potential antihypertensives, anti-inflammatory agents and angiotensin II receptor antagonists <1997JHC549, 1997IJB813, 1997MI461, 1998MI99, 2002JHC367, 2003MI251>. Similarly, pyrrolo[3,2-*d*]imidazoles and pyrrolo[2,3-*c*]pyrazoles could be prepared by reaction of ethyl α-azido-β-(substituted imidazol-4-yl)acrylates <1997IJB813> and ethyl α-azido-β-(substituted pyrazolo-4-yl)acrylates <2004IJC1355>, respectively.



Scheme 29

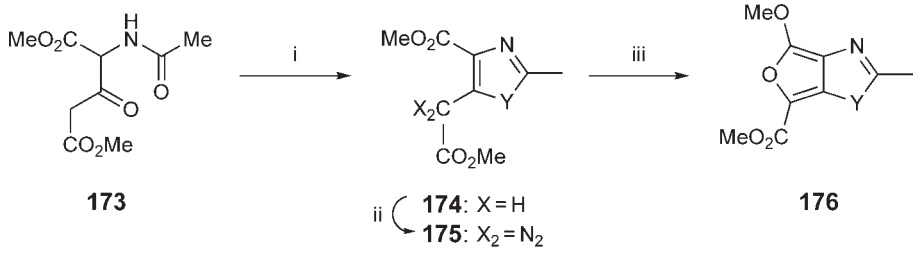


(39)

10.02.7.2.5 Miscellaneous cyclizations

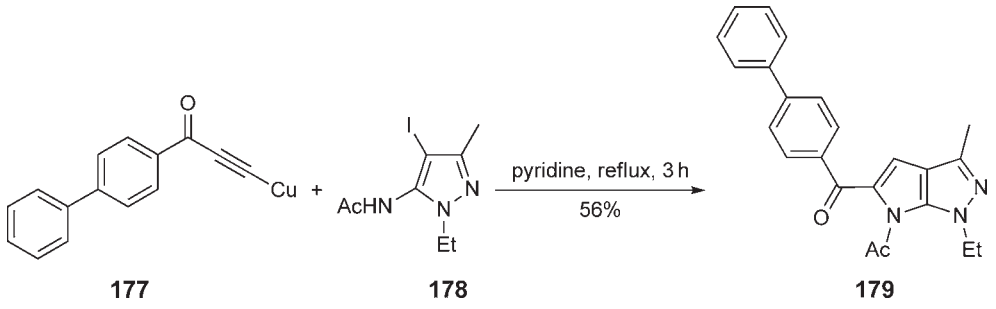
Several specialized cyclizations have also been described. In 1998, Reck *et al.* reported the first synthesis of a furo[3,4-*d*]thiazole **176** (Y = S) <1998H(48)853> and a furo[3,4-*d*]oxazole **176** (Y = O) <1998JOC7680> using a rhodium acetate-mediated cyclization (**Scheme 30**). Reaction of the key starting material **173** with either phosphorus pentasulfide or thionyl chloride gave an intermediate thiazole **174** (Y = S) and oxazole **174** (Y = O), respectively. The furo[3,4-*d*]thiazole and furo[3,4-*d*]oxazole were prepared in two further steps via **175** using a Regitz diazo-group transfer <1965CB1210> followed by a Hamaguchi–Ibata reaction <1976CL287>. A similar cyclization has been discussed for the formation of a furo[3,4-*d*]isoxazole, and is suggested to proceed via a reactive carbenoid intermediate <1991CB2481, 1996CHEC-II(7)49>. Cross-coupling of copper phenylbenzoylacetylide **177** <1963JOC3313> with iodopyrazole **178** gave a pyrrolo[2,3-*c*]pyrazole **179** (Equation 40) <1999J(P1)3713>. It is suggested that the cyclization reaction is favored by the presence of the ketone moiety, but the generality of this cyclization has not been explored. The reported cyclization reaction of trichloroacetonitrile with aminopyrazole ketones to yield pyrrolo[2,3-*c*]pyrazoles <1996CHEC-II(7)49> has been extended to include cyclizations with thionoketones **180** to give **181** (Equation 41) <1999EJC491>. Another reported strategy utilizes the reactivity of 4-halopyrazol-5-ones with stabilized anions <1996CHEC-II(7)49>. Recent examples include reactions of 4-bromo-3-methyl-1-phenylpyrazol-5-one **182** with ethyl acetoacetate, ethyl thioacetoacetate, and ethyl iminoacetoacetate to afford the respective 4-ethoxycarbonyl-3,5-dimethyl-1-phenyl-furo-, thieno-, and

pyrrolo[2,3-*c*]pyrazoles **183** <2002CCS1061> and with cyanoacetamide to form a furo[2,3-*c*]pyrazole **184** (**Scheme 31**) <2004CCS785>. In a variant, a furo[2,3-*c*]pyrazole **187** was isolated on refluxing 3,5-diamino-4-phenacylpyrazole **185** with acrylonitrile in pyridine (**Scheme 32**) <1997G791>; **185** could also be cyclized to furo[2,3-*c*]pyrazole **186** by fusion with subsequent *N*-cyanoethylation yielding furo[2,3-*c*]pyrazole **187**. In an alternative approach, furo[2,3-*c*]pyrazole **190** was prepared in two steps by bromination of allylpyrazole **188** to give **189** followed by sodium ethoxide induced cyclization (**Scheme 33**) <1997CHE698>. The intermediate dibromo-derivative **189** also cyclized slowly to furo[3,2-*d*]pyrazole **190** on standing.

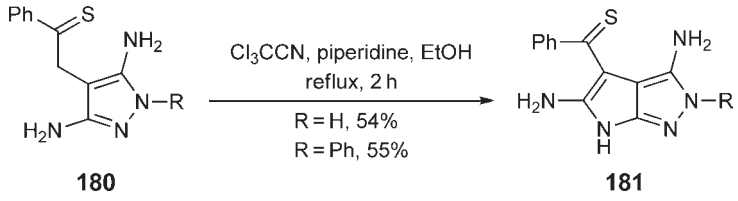


i, Y = S, P_4S_{10}, 29% or Y = O, $SOCl_2$, $CHCl_3$, reflux, 27%
ii, 4-azidosulfonylbenzoic acid, DBU, MeCN, rt, 1 h
iii, $Rh_2(OAc)_4$, 1,2-dichloroethane, reflux, 30 min, Y = S, 59%, Y = O, 39% (two steps)

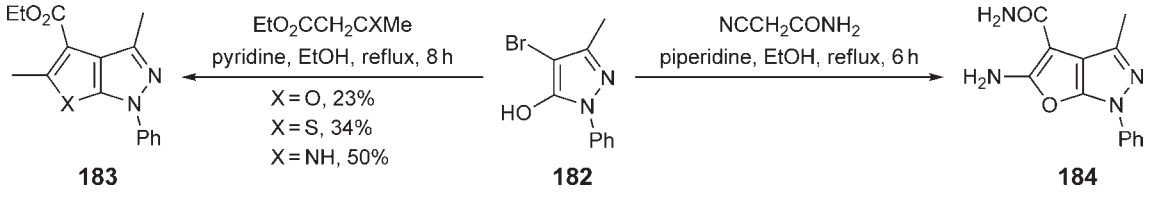
Scheme 30



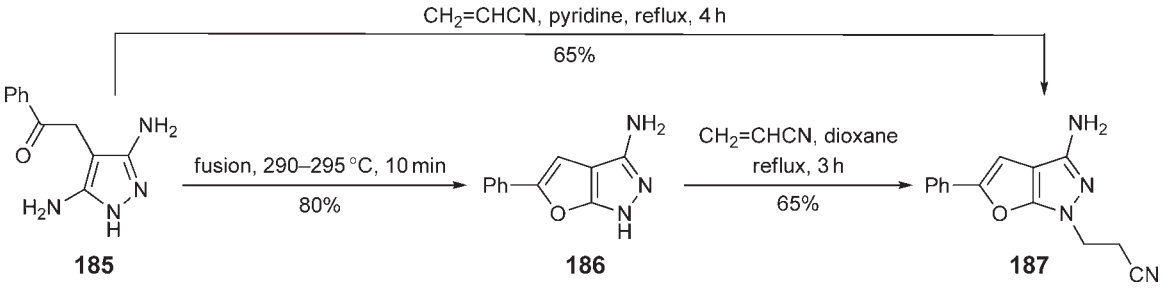
(40)



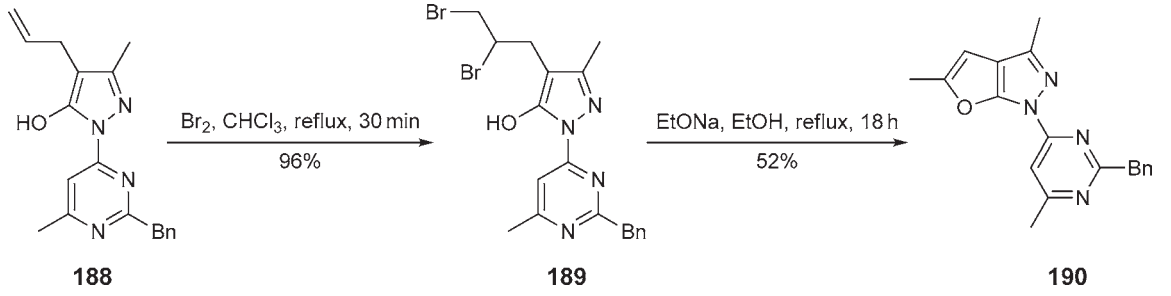
(41)



Scheme 31



Scheme 32

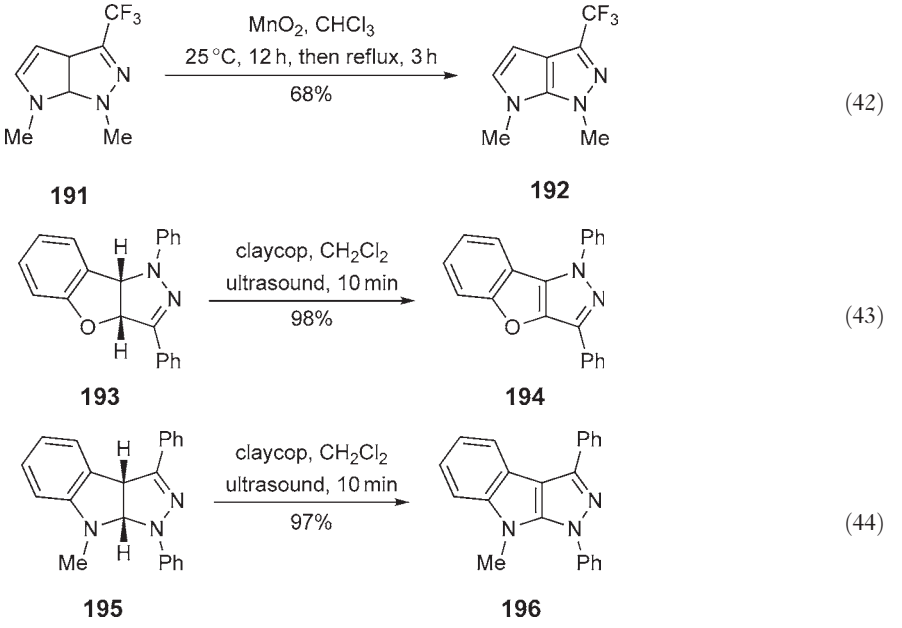


Scheme 33

10.02.8 Ring Syntheses by Transformation of Other Heterocyclic Systems

10.02.8.1 Oxidative Methods

Pyrrolo[3,4-*b*]pyrazole **192** was readily prepared by aromatization of **191** using manganese dioxide (Equation 42) <1995H(40)661>. A simple, efficient, and eco-friendly aromatization of pyrazolines in heterogeneous media using clay-supported copper(II) nitrate (claycop) under ultrasound activation has also been reported, exemplified by the synthesis of benzofuro[3,2-*c*]pyrazole **194** and pyrazolo[3,4-*b*]indole **196** from **193** and **195**, respectively (Equations 43 and 44) <2004TL4143>. The analogous reaction using both clay-supported copper(III) nitrate (clayfen) and claycop at ambient temperature has also been reported to proceed in high yields <1995TL4065>.



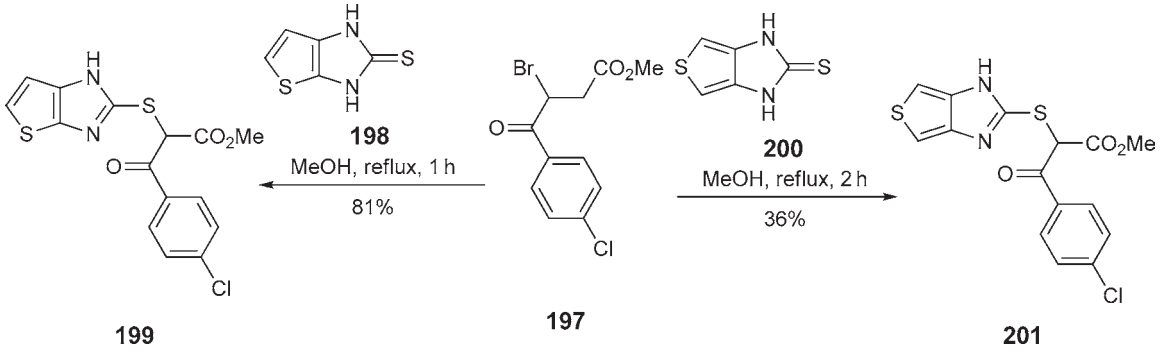
(42)

(43)

(44)

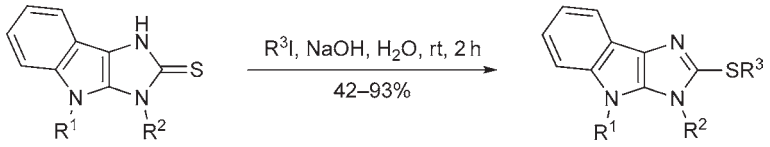
10.02.8.2 Miscellaneous Methods

Thieno[2,3-*d*]imidazole **199** and thieno[3,4-*d*]imidazole **201** were prepared as intermediates in the synthesis of thiophene analogues of the immune modulator TILOMISOL by simply refluxing equimolar mixtures of either 1,3-dihydrothieno[2,3-*d*]imidazole-2-thione **198** or 1,3-dihydrothieno[3,4-*d*]imidazole-2-thione **200** with **197** in methanol (**Scheme 34**) <1998JHC923>. It is notable that the thieno[2,3-*d*]imidazole derivative was prepared in a significantly higher yield than the thieno[3,4-*d*]imidazole derivative and, based on ^{1}H NMR spectroscopy, there was no evidence for the formation of the isomeric thieno[3,2-*d*]imidazole. In a similar manner, imidazo[4,5-*b*]indoles **203** were prepared by alkylation of the corresponding thiones **202** (Equation 45) <1998RJO570, 1998ZOR1849>.



199 **198** **197** **200** **201**

Scheme 34



202 **203** (45)

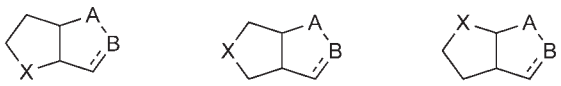
$R^1 = R^2 = H$, R^3 = Me, Et, CH_2=$CHCH_2$
R^1 = MeCO, R^2 = H, R^3 =Me, Et
R^1 = MeCO, $R^2 = R^3$ =Me
R^1 = MeCO, R^2 = Me, $R^3 = Et_2N(CH_2)_2$
R^1 = MeCO, R^2 = Bn, R^3 = Me, $Et_2N(CH_2)_2$

10.02.9 Syntheses and Reactivity of Nonconjugated Systems

There are many structural variations of the nonconjugated heterocycles that form the subject of this chapter and a full review of their synthesis and reactivity is beyond the scope of this chapter. Indeed, despite the topological similarity of many of the heterocycles covered in this chapter, the chemistry of the nonconjugated systems is diverse. The sections on the synthesis and reactivity of the nonconjugated heterocycles are, therefore, combined to offer an overview of the more interesting aspects of their synthesis and chemistry rather than a comprehensive review.

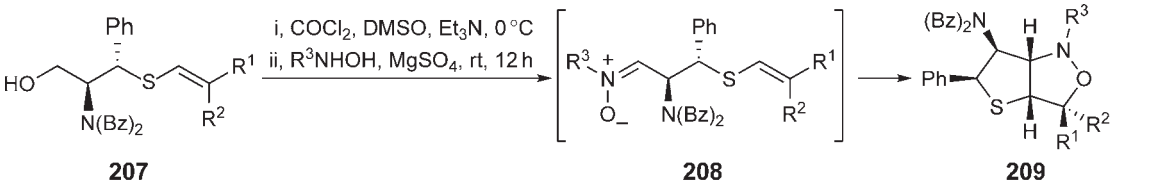
10.02.9.1 1,3-Dipolar Cycloaddition Methodology

Since their introduction by Huisgen (see <1995H(40)1> and references therein), the 1,3-dipolar cycloaddition remains the single most powerful method for the construction of five-membered heterocycles. Literature examples of this approach in an inter- and intramolecular fashion for the assembly of nonconjugated examples of bicyclic 5-5 heterocycles with 1:2-heteroatom orientation are common. Heterocycles with either [1,2,4], [1,2,5], or [1,2,6] heteroatom locants (**204**, **205**, and **206**, respectively) can be assembled utilizing this approach. The stereoelectronic aspects of the various cycloaddition strategies are not discussed here.



[1,2,4]-Juxtaposition **204** [1,2,5]-Juxtaposition **205** [1,2,6]-Juxtaposition **206**

Many examples of intramolecular dipolar cycloadditions have been reported, namely (1) the intramolecular nitrone–olefin cycloaddition; (2) the intramolecular oxime–olefin cycloaddition (IOOC) (or oxime–alkene cycloaddition, IOAC); (3) the intramolecular nitrile oxide–olefin cycloaddition (INOC); (4) the intramolecular nitrile oxide–heterocycle cycloaddition (INHC); and (5) the intramolecular silyl nitronate olefin cycloaddition (ISOC). All offer a versatile synthetic approach to various members of the nonconjugated heterocycles that are the subject of this chapter. Chiral centers in the 1,3-dipolar precursors often give rise to asymmetric induction and the formation of new chiral centers with definite configuration in the cycloadduct <1996CHEC-II(7)49>. The majority of the literature reports access to various [1,2,5]-isomers utilizing these strategies, whereas there are only few reported examples of an intramolecular dipolar cycloaddition giving rise to [1,2,4]-bicyclic systems. As an example of the latter, compounds **207** were subjected to Swern oxidation and treated with a substituted hydroxylamine to form thiaalkenylnitrone **208** that underwent spontaneous intramolecular cyclization to give enantiomerically pure **209** with five contiguous chiral centers (**Scheme 35**) <1994T3929>.

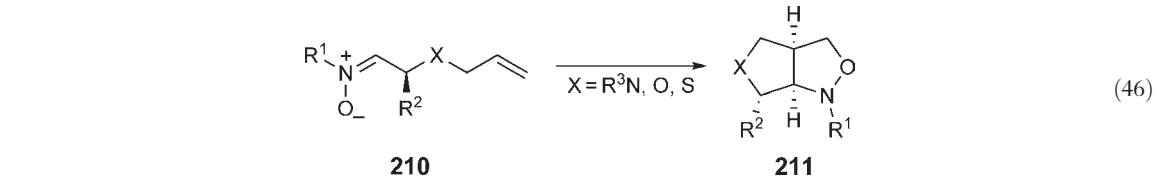


207 **208** **209**

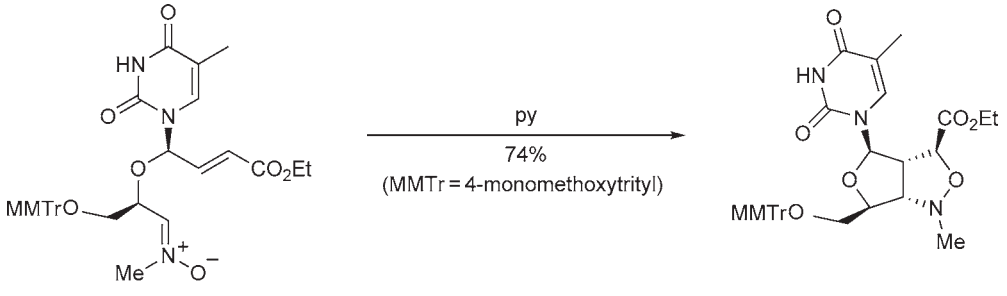
$R^1 = CO_2Me$, $R^2 = H$, $R^3 = Bz$, 90%, de > 98%
$R^1 = CN$, $R^2 = H$, $R^3 = 4\text{-}Bu^tC_6H_4$, 43%, de > 98%
$R^1 = H$, $R^2 = CN$, $R^3 = 4\text{-}Bu^tC_6H_4$, 37%, de > 98%

Scheme 35

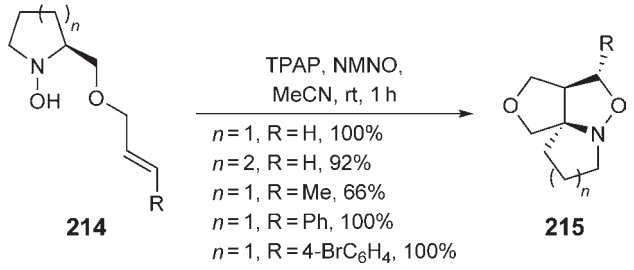
There are many literature examples in which C-5-hexenylnitrones (e.g., **210**) undergo intramolecular cycloaddition under relatively mild conditions, often with high regio- and stereoselectivities (reflecting the geometry of the olefin moieties) to afford bicyclic compounds **211** with at least three contiguous stereogenic centers (Equation 46). Intramolecular cycloaddition of alkeny1 nitrones has been elegantly employed in the synthesis of a series of novel branched, fused, and spiro-isoxazolidinyl nucleosides. For example, the 2′,3′-seconucleoside-derived nitrone **212** (prepared from thymidine over six steps) reacted at room temperature in pyridine to afford the 2′,3′-*a*-fused isoxazolidinyl nucleoside **213** in good yield (Equation 47) <1994T5279>. Oxidation of secondary hydroxylamines **214** using 5 mol% of tetrapropylammonium perruthenate (TPAP) and 1.5 equiv of *N*-methyl morpholine *N*-oxide (NMNO) gave an intermediate nitrone that underwent rapid intramolecular cyclization to form spiro compounds **215** as single diastereoisomers (Equation 48) <2004TL3659>. For further selected examples of alkenyl nitrone intramolecular cycloadditions that yield the subject heterocycles, see <1994T3929, 1994T4921, 1994T5503, 1994SL620, 1995T107, 1995T119, 1995T10497, 1998T3181, 1995T5689, 1997T17513, 1998T13997, 1999EJOC2725, 1999T1249, 2000TA897, 2002JOC4380, 2002T7821>. In an interesting variation, the enolate group of nitrones **217**, generated by treatment of **216** with lithium diisopropylamide (LDA), acted as a dipolarophile attacking the nitrone group intramolecularly with high diastereoselectivity to give the bicyclic compounds **218** (**Scheme 36**) <1995T6285>. In many cases, long and multistep synthetic routes are required to develop the two reaction sites necessary for intramolecular cycloaddition, namely the nitrone and olefin, at appropriate positions within the precursors; tandem reactions (e.g., Equation 49) <2001JOC2602, 2004JOC1475> and sequential one-pot reactions <1997TL429, 1999T12493, 2004BMC191> have, therefore, been investigated. In a noteworthy development, there is a recent report of tandem reactions involving lipase-catalyzed kinetic resolution of racemic α-hydroxynitrones, transesterification, and subsequent intramolecular 1,3-dipolar cycloaddition to afford tetrahydrofuro[3,4-*c*]isoxazole derivatives in moderate yield (>90% ee) <2005CC2369>.



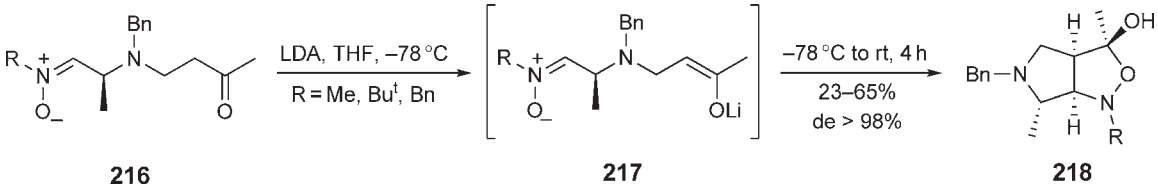
210 211 (46)



212 213 (47)

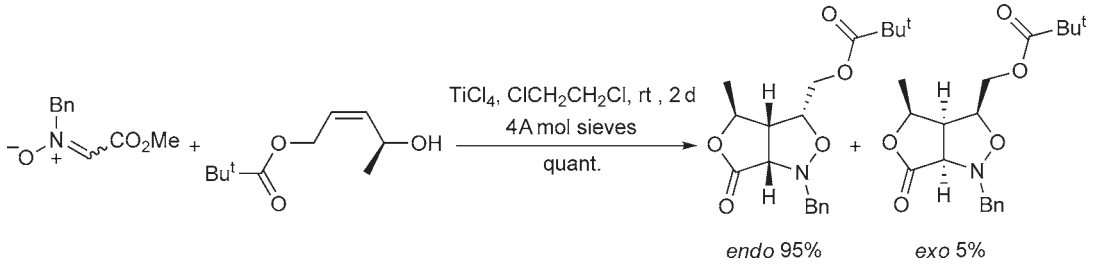


214 215 (48)



216 217 218

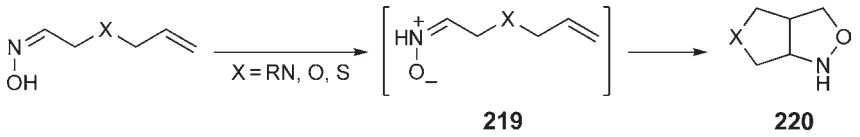
Scheme 36



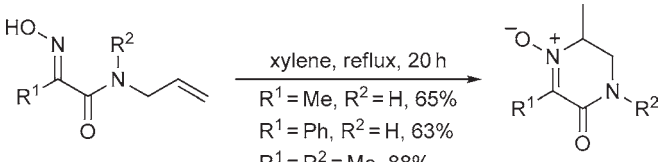
(49)

The IOOC (also known as the IOAC) can afford fused five-membered isoxazolidines, for example, **220** (**Scheme 37**); reactions often proceed with a remarkable degree of stereoselectivity and it is generally believed that oxime–olefin cycloaddition proceeds via the formation of the (*Z*)-NH nitrone, for example, **219**. In some cases, the oximes can show high configurational stability <1996CC167, 1998J(P1)341, 2003OBC1122>; for example, (*E*)-oximes **221** cyclized exclusively to nitrones **222** (Equation 50) and the corresponding (*Z*)-oximes **223** cyclized

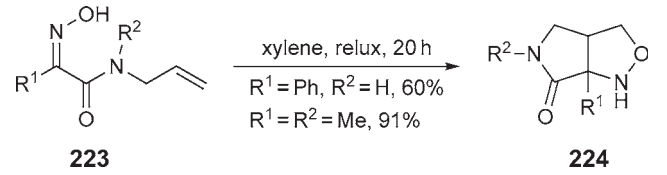
exclusively to pyrrolo[3,4-*c*]isoxazoles **224** in good yield (Equation 51) <2003OBC1122>. The thermal IOOC reaction of amidoximes **225** was highly stereoselective (**Scheme 38**) <1996T7875>; subsequent reduction of the products **226** with either Zn/AcOH or $LiAlH_4$ afforded homochiral functionalized pyrrolidin-2-ones (or a pyrrolizidin-3-one, R^1–$R^2 = (CH_2)_3$) **227** and pyrrolidines (or a pyrrolizidine, R^1–$R^2 = (CH_2)_3$) **228**, respectively. The use of bicyclic isoxazolidines as chiral auxiliaries has been demonstrated. The isoxazolidine skeleton **230** was constructed by $ZnCl_2$-catalyzed IOOC using **229**, with the major **230**-*exo* isomers readily isolated by crystyallization. Successive acylation of **230**-*exo* ($R^1 = Pr^i$) and asymmetric alkylation proceeded with high selectivities to give **231** (**Scheme 39**), as did analogous boron–aldol reactions <1997TL3261>. Subsequent transformation of **231** to chiral alcohols, aldehydes, and ketones with recovery of the auxiliary was shown to occur without loss of stereochemical integrity. In an interesting variation to the IOOC, $BF_3{\cdot}OEt_2$-promoted intramolecular cycloaddition of silyloximes, perhaps via a *N*-boranonitrone, has been utilized to access substituted hexahydrofuro[3,4-*c*]isoxazoles and hexahydropyrrolo[3,4-*c*]-isoxazoles <2005JOC10720>.



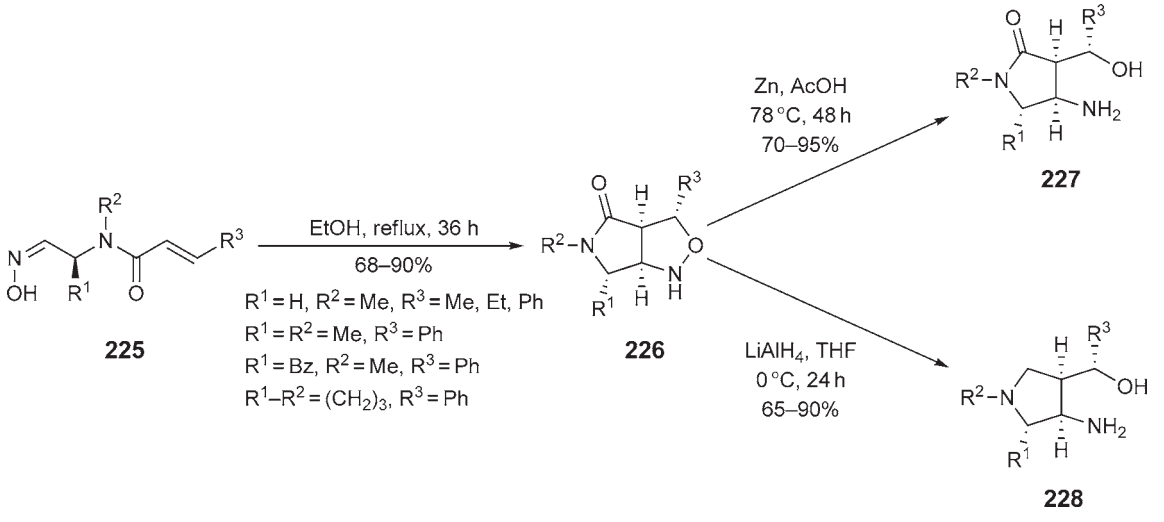
Scheme 37



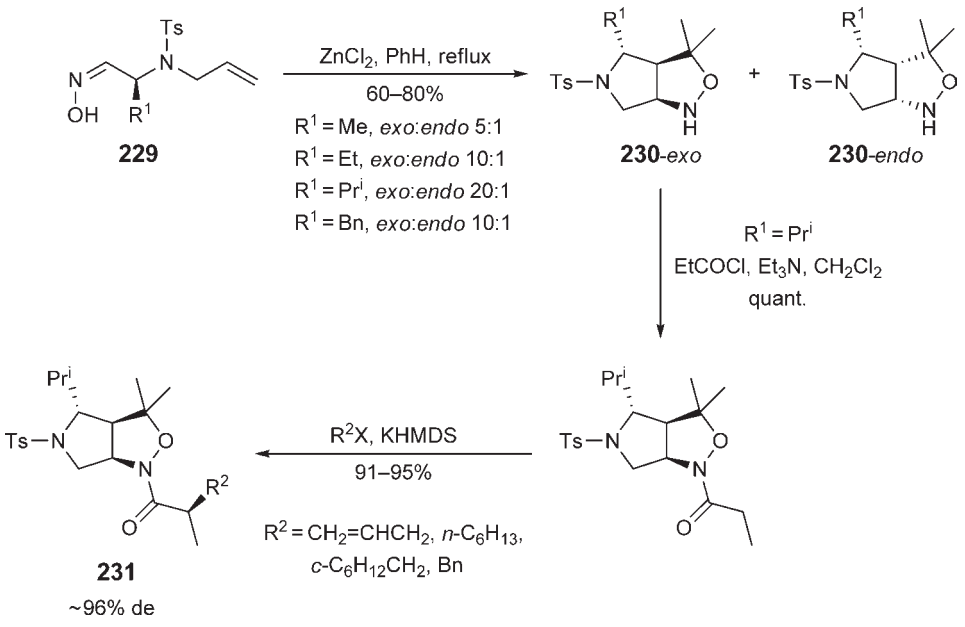
(50)



(51)

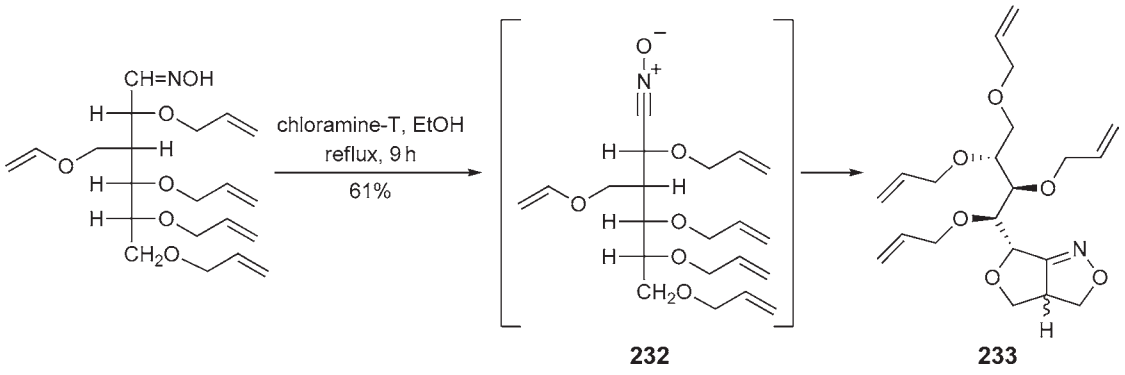


Scheme 38

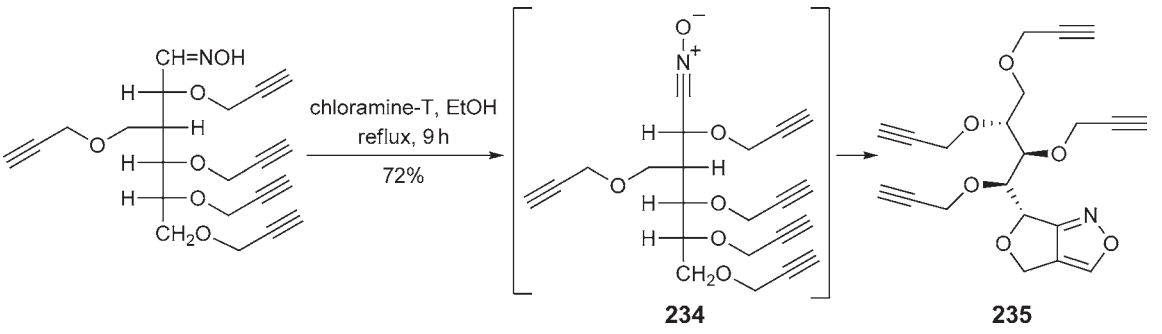


Scheme 39

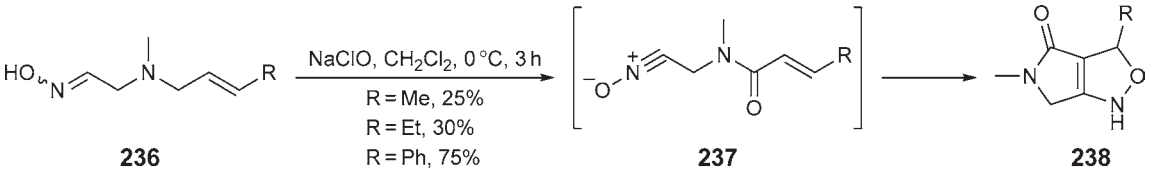
The INOC with olefins and acetylenes has found extensive use for the synthesis of isoxazolines and isoxazoles, respectively <1996CHEC-II(7)49>. The nitrile oxide **232**, generated from the corresponding pentaallyl carbohydrate oxime by treatment with chloramine-T, underwent *in situ* intramolecular cycloaddition giving rise to a separable mixture of diastereomeric dihydrofuro[3,4-*c*]isoxazoles **233** (**Scheme 40**). This approach was also suitable for preparing chiral isoxazole **235** by the intramolecular nitrile oxide cycloaddition of the corresponding *O*-pentapropargyl derivative **234** (**Scheme 41**) <2005T2999>. In a similar manner, the corresponding *N*-methyl and *N*-benzyl nitrones underwent cycloaddition to yield fused isoxazolidines <1995TL7729>. The exclusive formation of a tetrahydrofuran ring from pentaallyl nitrile oxide **232** and corresponding nitrone is a very powerful demonstration of the preferred formation of a five-membered ring to that of six- or seven-membered rings. Treatment of oximes **236** with sodium hypochlorite gave **238**, arising from initial INOC of **237** followed by a favorable 1,3-prototropic hydrogen shift, rationalized on the basis of increased thermodynamic stability of the product through extension of conjugation (**Scheme 42**) <1996TL14323>. INOC of norbornadiene-tethered nitrile oxides **240**, derived from nitro compounds **239**, were highly regio- and stereoselective giving *exo*-adducts **241** only (**Scheme 43**) <2001JOC276>. The INOC strategy has been further extended to include a smaller class of under-utilized cyclizations, the INHC in which the alkene component is either a furan or pyrrole (indole) unit <1996CHEC-II(7)49>.



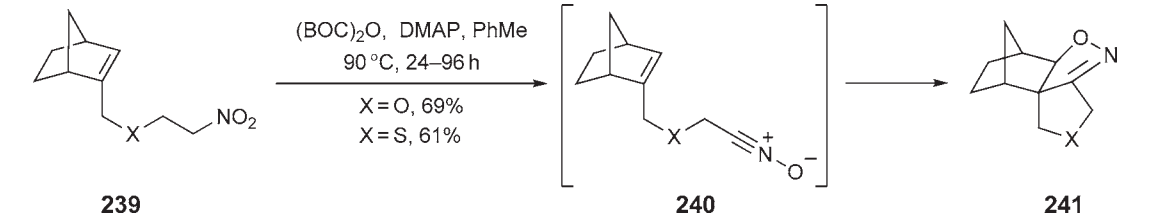
Scheme 40



Scheme 41



Scheme 42

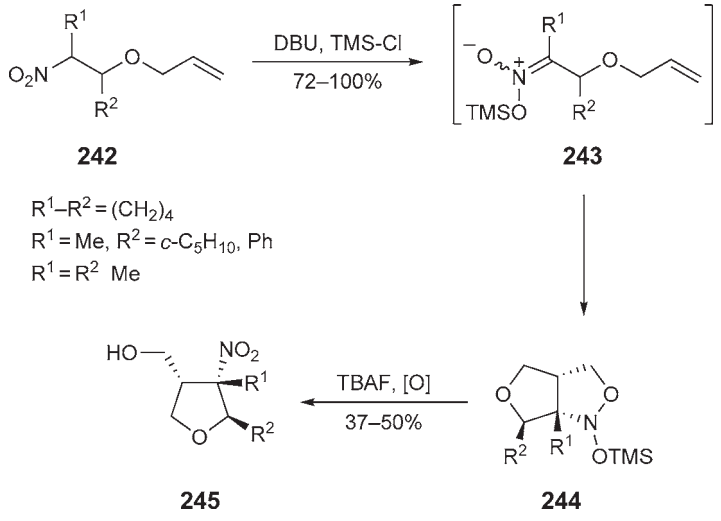


Scheme 43

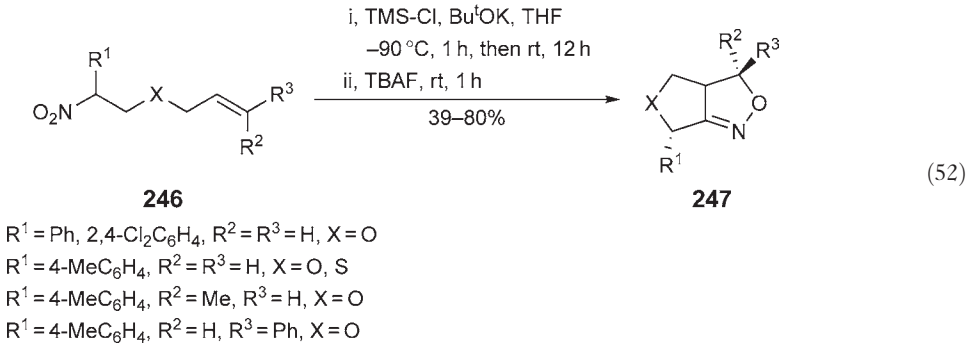
The ISOC offers a highly stereoselective alternative to the analogous INOC reaction and has been successfully applied to the synthesis of the class of heterocycle that forms the subject of this chapter. Indeed, a comparison between the diasteroselectivity of an INOC and ISOC for the synthesis of a furo[3,4-*c*]isoxazole from a common nitroether starting reagent demonstrated that the ISOC was the preferred methodology for the substrate investigated <2000JOC499>. The transformation of *β*-nitroalkyl allyl ethers **242** into their corresponding silylnitronates **243** afforded, after ISOC, *N*-trimethylsilyloxyisoxazolidines **244**; TBAF-promoted oxidative desilylation gave diastereomerically pure tetrahydrofurans **245** in moderate yield (**Scheme 44**) <2004OL2027>. Isoxazolines **247** were readily prepared in a one-pot ISOC followed by TBAF desilylation from nitro-olefins **246** (Equation 52) <1999EJOC2689>. 1,3-Dipolar cycloaddition of nitrile imines <2001SC3799, 2003PS(178)417, 2004TA1127, 2005SC249> and azomethine imines <2003T4123, 2003T4451> has been reported to give heterocycles in this class. For example, intramolecular 1,3-dipolar cycloaddition of the nitrile imines **249**, generated by base treatment of hydrazonoyl chlorides **248**, yielded, after purification, enantiopure hexahydrofuro[3,4-*c*]pyrazoles **250** and **251** with reasonable-to-excellent diasteroselectivities (**Scheme 45**) <2004TA1127>.

2,3-Dihydrofurans are probably the most common dipolarophile investigated in examples of intermolecular 1,3-dipolar cycloaddition to afford [1,2,6] adducts <1996CHEC-II(7)49, 1967BSF4179, 1995JFC189, 1998TL4851, 1998T12737, 1999JACS3845, 1999JOC2353, 1999JOM200, 2000T7817, 2003T2899, 2003JHC957>. Two representative examples are shown in **Scheme 46** <1998EJO1793> and (Equation 53) <1998JOC1064>. In a notable example, clean 1,3-dipolar cycloadditions of stable Wang resin-supported nitrile oxides have been demonstrated (Equation 54) <2002EJO1175>. Additionally, kinetic studies of 1,3-dipolar cycloaddition of benzonitrile oxides <1998JOC8801> and *C*-benzoyl-*N*-phenylnitrones <1998JOC1064> utilizing, among others, 2,3-dihydrofuran as substrate, have been investigated. 2,3-Dihydropyrroles similarly give access to [1,2,6] adducts <1996CHEC-II(7)49, 1967BSF4179>, whereas furans, 2,3-dihydrophospholes, phospholes, and thiophenes generally give access to

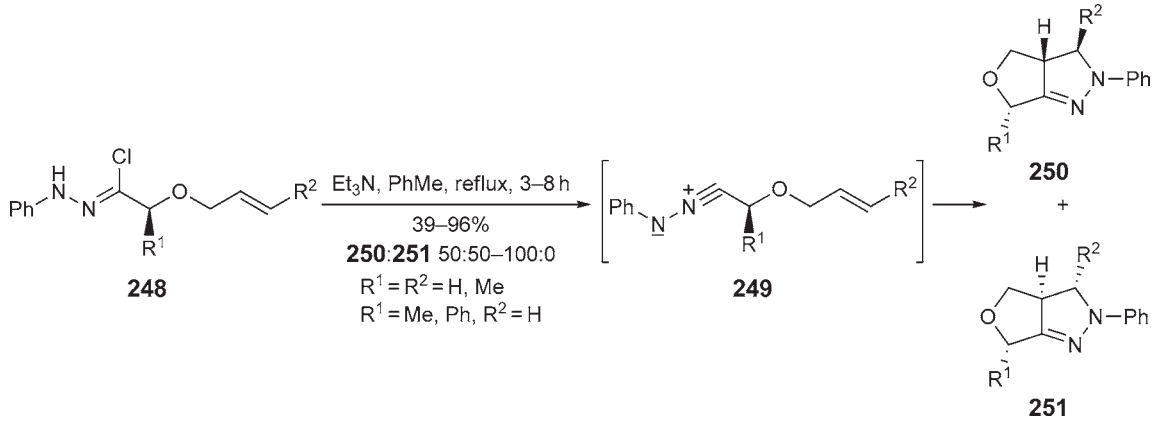
products with [1,2,4] orientation <1996CHEC-II(7)49>. *N*-Substituted maleimides have been used extensively as dipolarophiles with, for example, nitrones <2001T7951, 2000T10087, 2003T4113, 2003T9997, 1997TA1031, 2001TL6719> and nitrile oxides <2002T10437> to prepare derivatives in this class. In an applied example, 1,3-dipolar cycloadditions of bis(*N*-methylnitrones) with bis(*N*-phenylmaleimides) afforded polymeric hexahydropyrrolo[3,4-*d*]isoxazole derivatives <2003MM6340>.



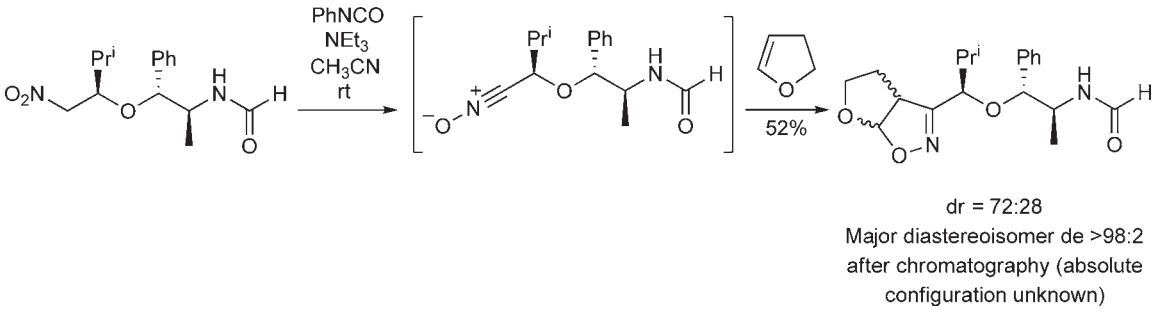
Scheme 44



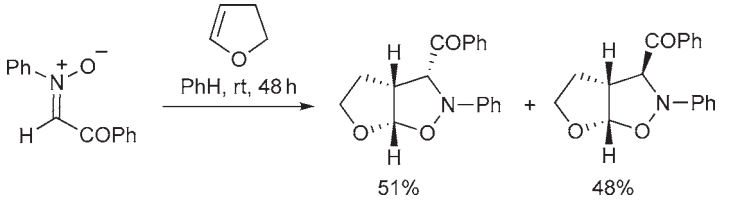
(52)



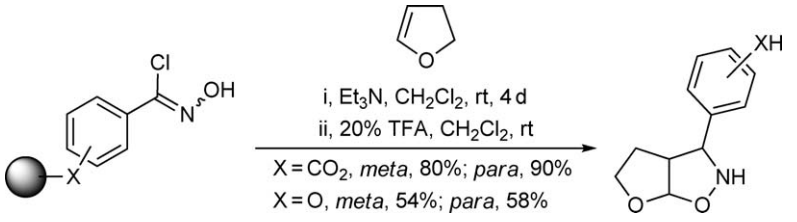
Scheme 45



Scheme 46



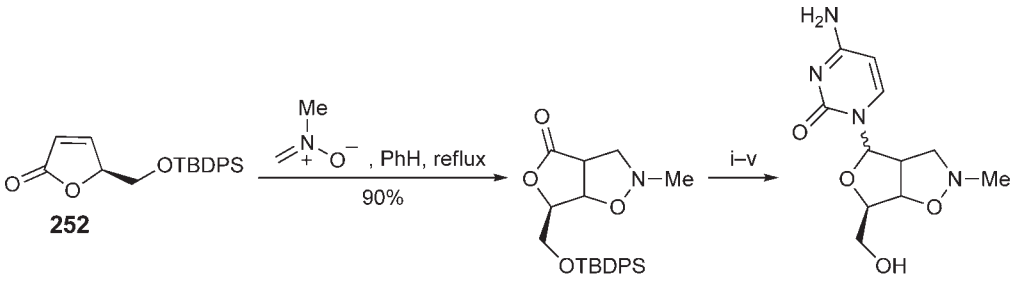
(53)



(54)

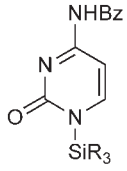
1,3-Dipolar cycloaddition to α,β-unsaturated lactones has been widely used to assemble derivatives in this class. The synthesis of modified bicyclo[3.3.0] isoxazolidinyl nucleosides **254** was investigated as part of a program aimed at the synthesis of novel anti-HIV agents (**Scheme 47**) <1996BML1475>. 1,3-Dipolar cycloaddition of lactone **252** with the nitrone derived from *N*-methylhydroxylamine and paraformaldehyde afforded **253** as a key intermediate. Subsequent manipulation over a further five steps afforded the individual anomers of pyrimidine nucleoside **254** in good yield. Cycloaddition of diazomethane occurred in a regio- and stereospecific manner in nonpolar solvents to substituted furan-2(5*H*)-ones to give dihydrofuro[3,4-*c*]pyrazol-6-one adducts in good yield <1996T1267, 1996TA1943, 2002TA1993, 2003JOC6522, 2004CEJ2237, 2005JOC8942>. In a simple example, furan-2(5*H*)-ones **255** afforded adducts **256** with diazomethane (**Scheme 48**) <1999T229>. The corresponding cycloaddition with ethyl diazoacetate occured also in a regio- and stereospecific manner to give adducts **257**, with the ester carbonyl group conjugated with the C═N (**Scheme 48**) <1999T229>. The sulfinyl group in arylsulfinylfuran-2(5*H*)ones has been shown to both enhance their dipolarophilic reactivity and modulate the stereochemical outcome in reactions with diazoalkanes <1996TA1943, 2002TA1993, 2003JOC6522>, nitrile oxides <1999T14491, 2002SL73>, and nitrones <2005JOC8825>.

Cycloaddition reactions involving pyrrole-2,3-diones have proved to be a versatile approach to a variety of heterocycles <1971CC1554, 1976H(4)1316, 1981H(16)1151, 1982H(18)229, 1982H(19)2053>. Pyrrole-2,3-diones **258** reacted with diazomethane, to give **259** and pyrrolo[2,3-*d*]pyrazole derivatives **260** (Equation 55) <1997T1813>. The reaction was stoichiometry dependent with an equimolar reaction yielding an approximately equal mixture of both products **259** and **260** (the former presumably arising due to the loss of nitrogen from the initial cycloadduct), while reaction with an excess of diazomethane gave **260** as the major products isolated. Analogously, pyrrole-2,3-diones **261** and furan-2,3-diones **262** reacted regiospecifically with nitrones, to afford pyrrolo[2,3-*d*]isoxazole and furo[2,3-*d*]isoxazole derivatives **263** and **264**, respectively (Equation 56) <1996JCM466>. However, the less sterically demanding pyrrole-2,3-diones **265** reacted with nitrones to give a mixture of both **266**-*exo* and **266**-*endo* diastereoisomers (Equation 57) <1996JCM466>.



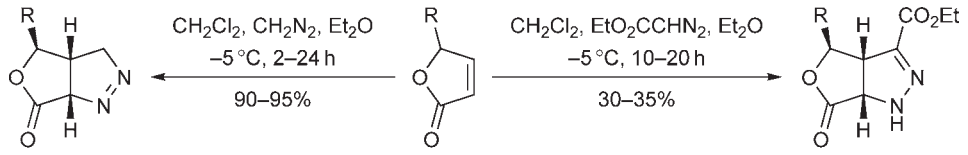
252 **253** **254**

i, DIBAL-H, CH_2Cl_2, –78 °C, 1 h; ii, AcCl, Et_3N, CH_2Cl_2, rt, 3 h, 66% (two steps)

iii,  , CH_2Cl_2, TMSOTf, rt, 12 h, 75% (α:β 4:1)

iv, TBAF, THF, rt, 0.5 h; v, NH_3, MeOH, rt, 12 h, 94% (β) or 91% (α) (two steps)

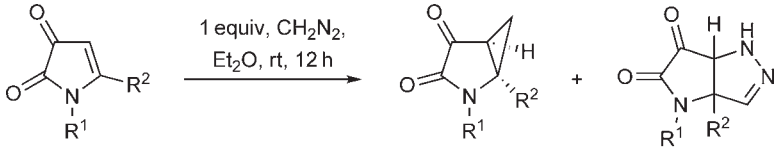
Scheme 47



256 **255** **257**

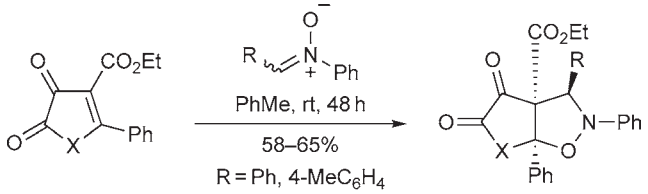
R = EtS, PhS, $EtSO_2$, $PhSO_2$

Scheme 48



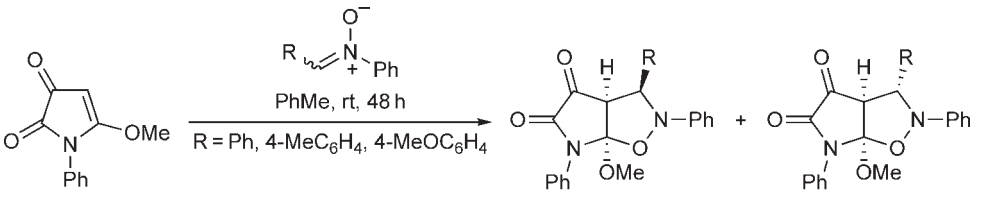
258 **259** 45–56% **260** 42–53% (55)

R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, R^2 = MeO
R^1 = Me, Ph, R^2 = MeS



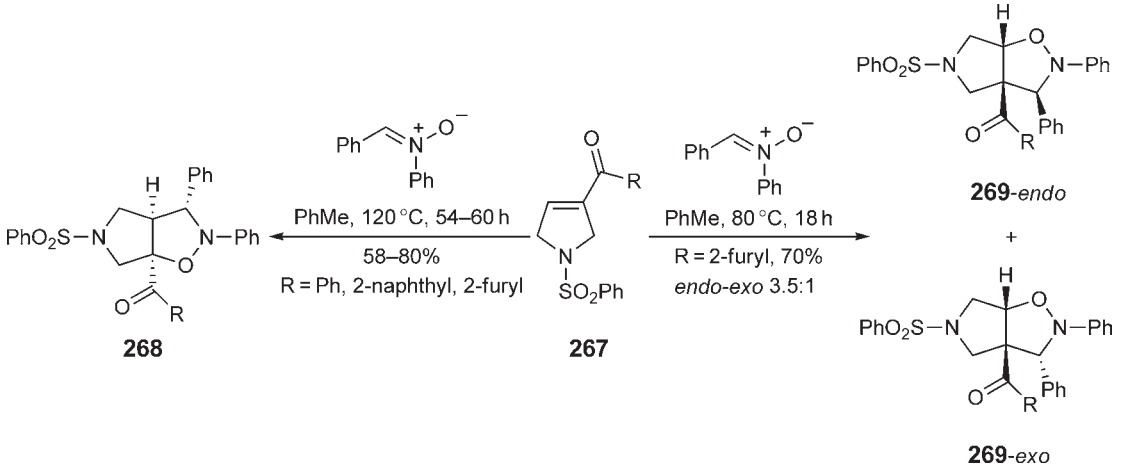
261: X = NPh
262: X = O

263: X = NPh
264: X = O (56)



(57)

In an interesting study, reaction of the five-membered heterocyclic enones **267** with diphenyl nitrone in toluene at 120 °C afforded bicyclic isoxazolidines **268** as single regio- and diastereoisomers, whereas reaction at 80 °C caused a change in regioselectivity affording a 3.5:1 mixture of diastereoisomers **269**-*endo* and **269**-*exo*, respectively (**Scheme 49**) <2005T11380>. Refluxing **269**-*endo* in toluene afforded **268** (R = 2-furyl) (presumably via a retrocycloaddition/1,3-dipolar cycloaddition). Regioisomer **268** is, therefore, thought to be favored under thermodynamic control due to the minimization of steric interactions between the 3-phenyl group of the nitrone and the aryl ketone of the enone. The first report of an aromatic cycloprop[*e*]azulene **272** utilized, as a key step, the 1,3-dipolar cycloaddition of α,β-unsaturated sulfone **270** and 2-diazopropane to give [1,2,4]-adduct **271** as the major product. Subsequent elimination of HCl, Houk–Leaver azulene synthesis and irradiation completed the synthesis of cycloprop[*e*]azulene **272** (**Scheme 50**) <2001J(P1)1579>. Notable rate enhancement was observed in arylnitrile oxide 1,3-dipolar cycloaddition to sulfones **273** and **275** in a biphasic system under sonication affording **274** and **276**, respectively (Equations 58 and 59, respectively) <1998TL4455>.



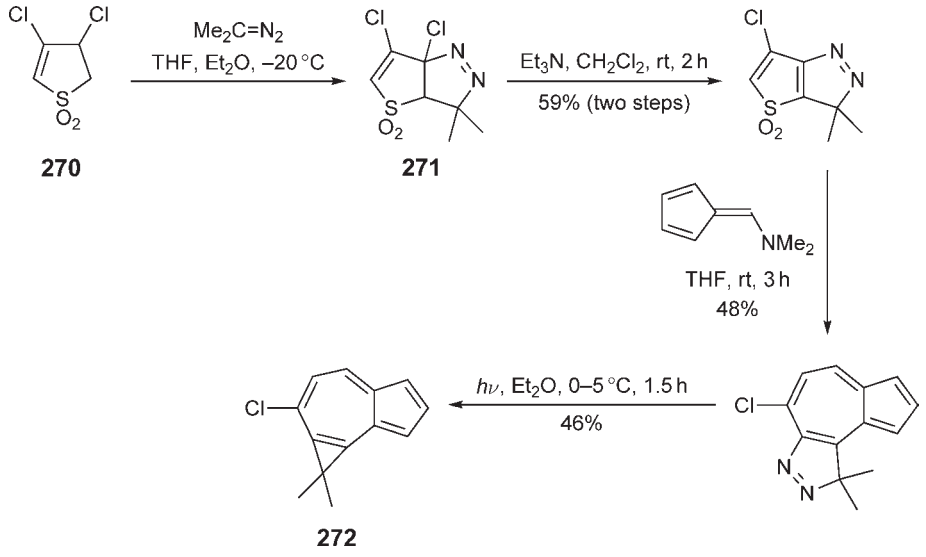
Scheme 49

10.02.9.2 Miscellaneous Methodology

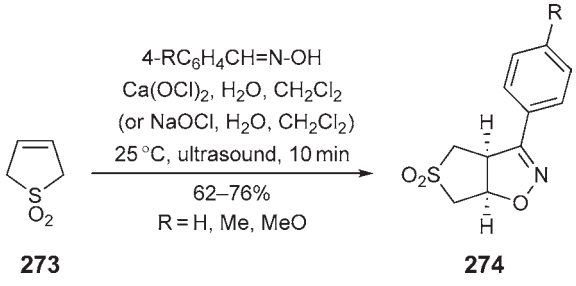
Alkyl- and aryl-substituted furo[2,3-*d*]thiazolidine derivatives **279**, with potential biological activity, have been synthesized by the reaction of methoxycarbonylmethylenetriphenylphosphorane with 4-thiazolidinone derivatives **277** (**Scheme 51**) <2001BKC476, 2003JHC721>; the reaction is suggested to proceed via the dipolar intermediate **278** with subsequent intramolecular *O*-alkylation and elimination of triphenylphosphine. An entry into furo[2,3-*d*]-thiazolidines **282**, although in relatively poor yield, has been reported by reduction of 4-thiazolidinones **280** and is suggested to proceed via iminium ion **281** and subsequent cyclization (**Scheme 52**) <2004SL1034>.

A number of efficient examples of cyclocondensations for accessing the bicyclic 5-5 heterocycles with 1:2-heteroatom orientation have been reported and representative examples utilized in investigations for the preparation of compounds with potential biological application are highlighted here. Compound **284** was prepared by condensation of hydrazine hydrate with α,γ-diketoester **283** as part of an investigation of compounds with potential as partial agonists at nicotinic receptors (Equation 60) <2003JMC3945>. A range of substituted tetrahydropyrrolo[3,4-*c*]pyrazoles **287** were developed and showed promise as Aurora kinase inhibitors <2005JMC3080> and CDK-2 inhibitors <2006BML1084>; the required common intermediate **286** was easily assembled by reaction of hydrazine

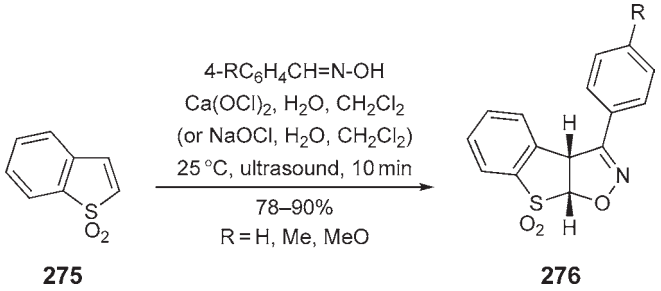
hydrochloride with α-cyanoketone **285** (**Scheme 53**). A series of derivatives **289**, for investigation as potential inhibitors of bacterial cell wall biosynthesis, were easily prepared by intramolecular cyclization of hydrazones **288** (Equation 61) <2003BML2591>. Hexahydropyrrolo[2,3-*d*]imidazole-2-thiones **292** were accessed by cyclocondensation of amines **290**, substituted ketone **291**, and potassium thiocyanate in the presence of acetic acid. Derivatives **292** were utilized as key intermediates en route to **293**, compounds of interest as inhibitors of dopamine β-hydroxylase (**Scheme 54**) <2006JMC1191>. In an alternative approach, intramolecular cyclization of **294**, bearing a tethered amine and an epoxide, afforded pyrrolo[3,2-*c*]pyrazole **295** (**Scheme 55**) <2005BML1327>. Interestingly, epoxide **294** was prepared as a mixture of *syn*- and *anti*-epoxides of which only the *anti*-epoxide underwent cyclization. Compound **295** was elaborated, in four steps, to pyrrolo[3,2-*c*]pyrazole **296**, investigated as a cysteinyl proteinase inhibitor. A similar cyclization methodology was also adopted to access a hexahydropyrrolo[3,2-*c*]isofurazole <2005BML1327>.



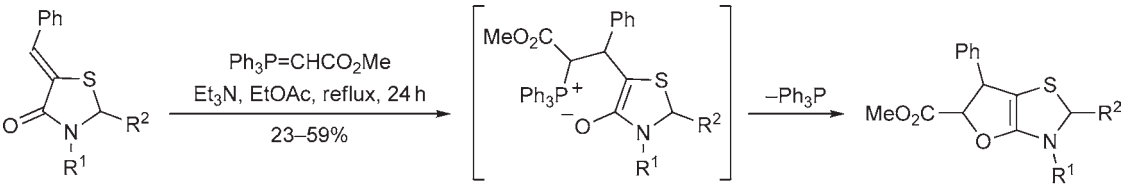
Scheme 50



(58)

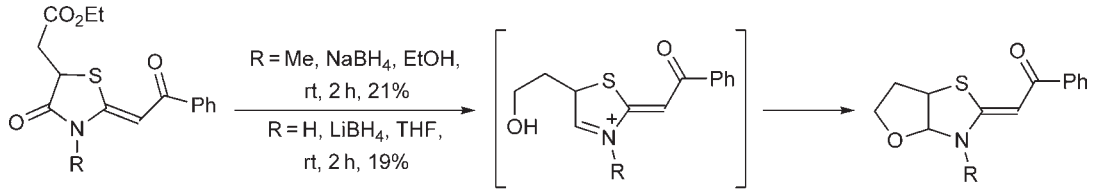


(59)

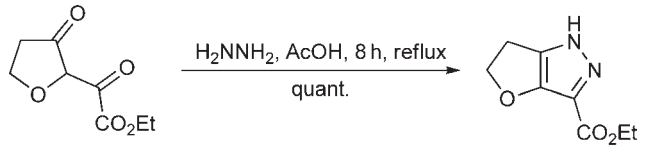


R^1 = *c*-C_6H_{12}, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$PhOC_6H_4$, R^2 = *n*-C_8H_{17}
R^1 = 4-MeC_6H_4, 4-$EtOC_6H_4$, 4-$PhOC_6H_4$, R^2 = Ph

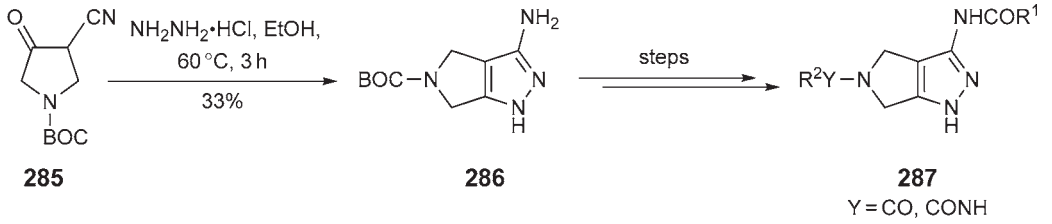
Scheme 51



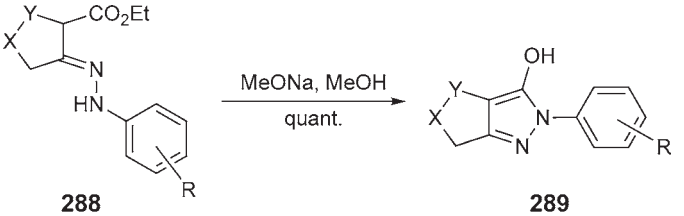
Scheme 52



(60)

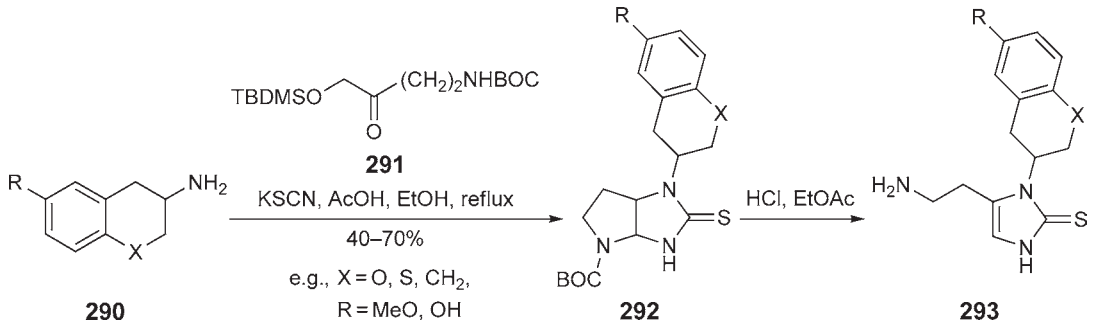


Scheme 53

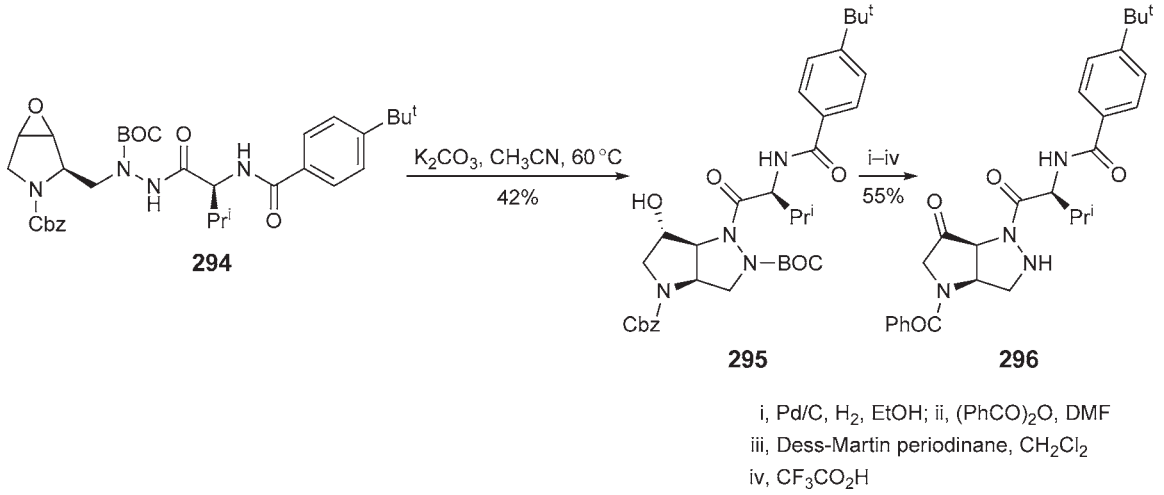


(61)

X = O, Y = CH_2, R = 4-Cl
X = S, Y = CH_2, R = 4-Cl, 3,4-Cl_2
X = CH_2, Y = S, R = H, 2-CF_3, 3-Cl, 3-CF_3, 3-CN, 3-NO_2, 4-F, 4-Cl, 4-Br, 4-CN, 4-NO_2, 4-Pr^i, 4-Bu^t, 3,4-Cl_2, 3,5-CF_3

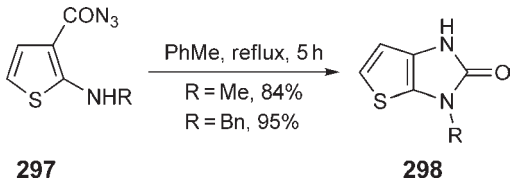


Scheme 54

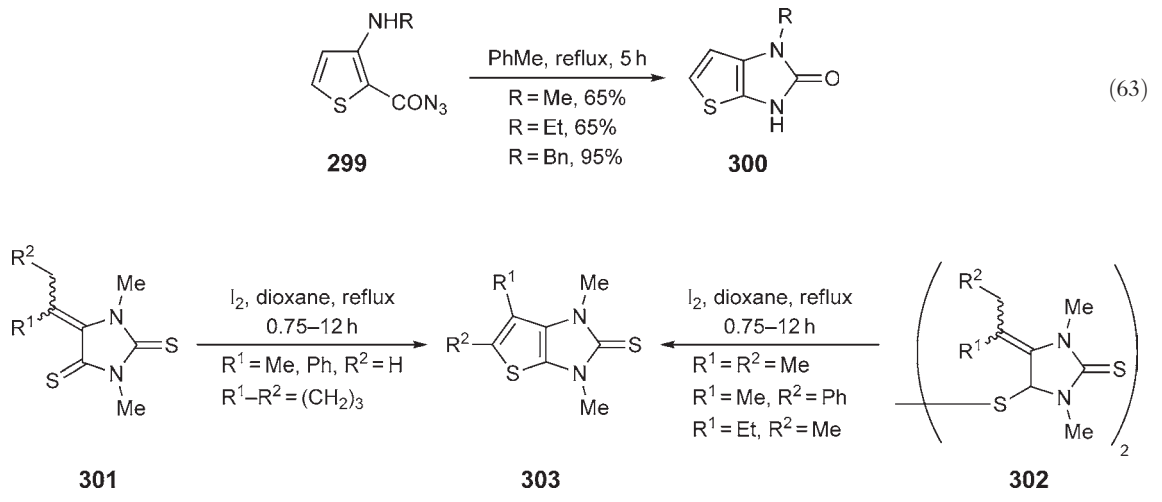


Scheme 55

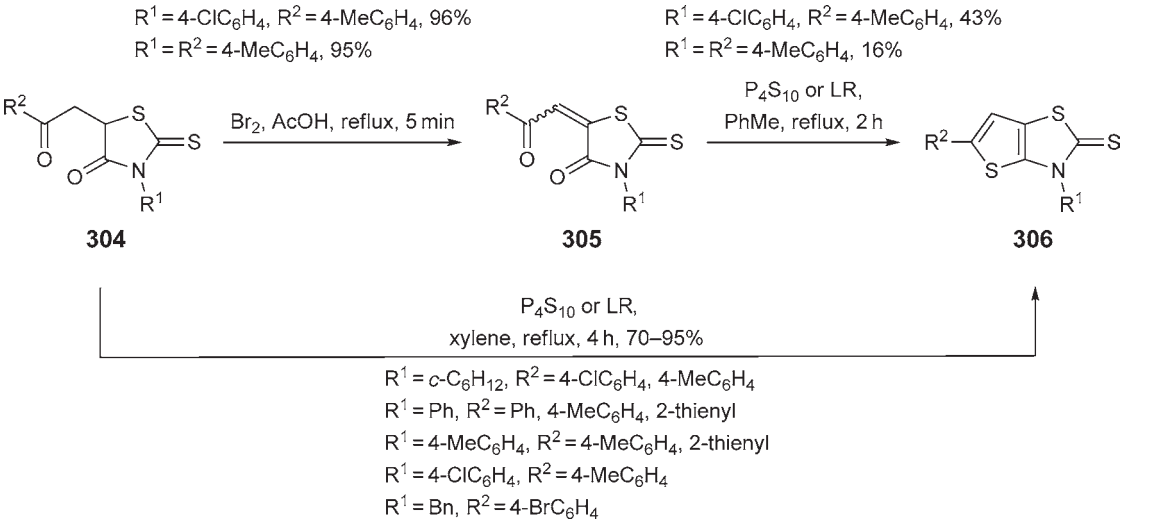
An efficient synthesis of dihydrothieno[2,3-*d*]imidazol-2-ones **298** and **300** has been reported utilizing a Curtius rearrangement of substituted thiophenecarbonylazides **297** and **299**, respectively (Equations 62 and 63) <1999T6167>. The appropriate thiophenecarbonylazides **297** and **299** were readily available from 2- and 3-thiaisatoic anhydrides by alkylation and subsequent treatment with sodium azide. Access to thieno[2,3-*d*]imidazole-2-thiones **303** was achieved by iodine oxidation of either thiohydantoin **301** or disulfide **302** (**Scheme 56**) <1999H159>. Thionation of 2-thioxo-4-oxo-1,3-thiazolidines **304** with either phosphorus pentasulfide or Lawesson's reagent (LR) in xylene afforded entry to 2,3-dihydro[2,3-*d*]-1,3-thiazole-2-thiones **306** (**Scheme 57**) <2001S413>, investigated for their nematocidal activity. A rationalization for the conversion is suggested via an initial 1,4-dithioxo derivative converting into a 1,2-dithiin and subsequent sulfur extrusion <2001S413>. An alternative approach, treating **304** with bromine in acetic acid, afforded **305** as a mixture of (*E*)- and (*Z*)-isomers and subsequent thionation gave **306**, although in poor yield (**Scheme 57**) <2001S413>.



(62)



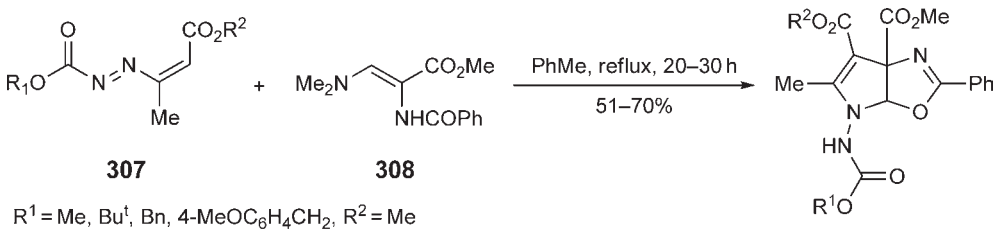
Scheme 56



Scheme 57

There are a number of interesting reactions that do not appear to have been fully exploited and there remains significant scope for their further development. Oxazoline-fused 1-aminopyrrolines **309** were directly obtained by reaction of 1,2-diaza-1,3-butadienes **307** with 3-dimethylaminopropenoates **308** (Equation 64) <2005JOC4307>. The ring opening of oxazolines **309** in acidic or basic media was investigated and shown to provide access to a range of highly substituted *N*-aminopyrroles (**Scheme 58**). Displacement of the benzotriazolyl group of *N*-(1-benzotriazolylmethyl)hydrazine **310** with 2,3-dihydrofuran in the presence of a Lewis acid gave, after cyclization, hexahydrofuro[2,3-*c*]pyrazole **311** in good yield (Equation 65) <1997JOC8210>. Substituted indoles **312** reacted with *N*-sulfonyloxaziridines **313** to give the unusual 1,3-oxazolidinoindoles **315** as a mixture of diastereoisomers (**Scheme 59**) <1997JA1159>. Based on the observed regioselectivity and crossover experiments, it was suggested that attack of the indole π-bond at the oxygen atom of the oxaziridine, followed by intramolecular nucleophilic addition of the resultant sulfonamido anion **314** occurred rather than the expected direct oxygen transfer pathway. Cyclobutanones **316** underwent, totally regiospecifically, Baeyer–Villiger oxidation using *m*-chloroperbenzoic

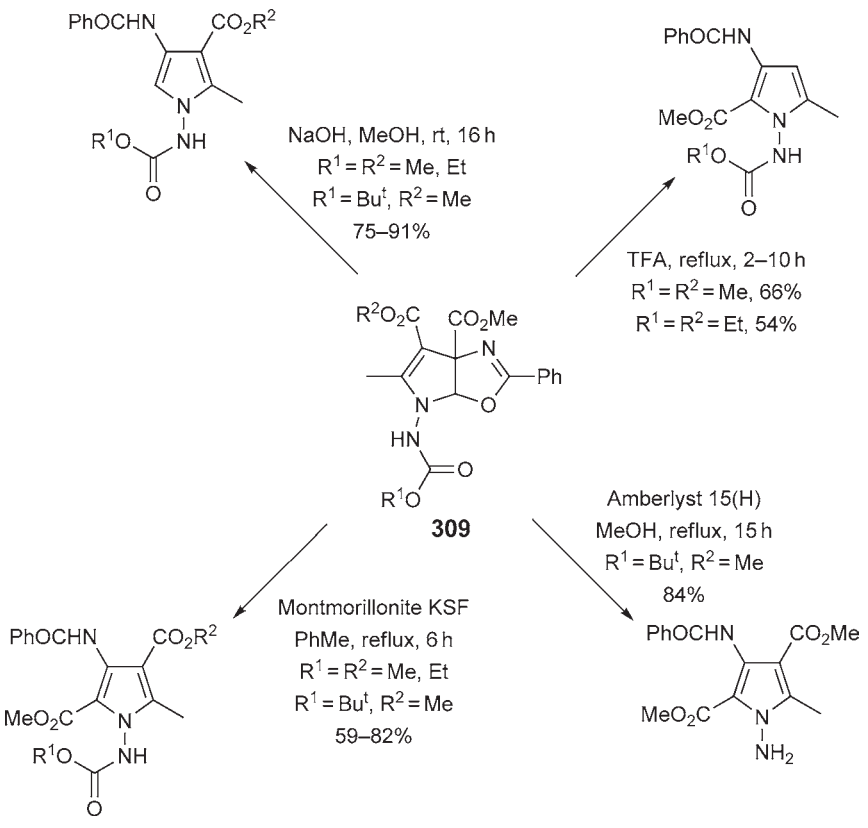
acid (MCPBA) to give the corresponding enantiopure γ-butyrolactones **317** (**Scheme 60**) <2004T7591>. Alternatively, Beckmann rearrangement with *O*-mesitylsulfonylhydroxylamine (MSH) followed by treatment with basic alumina gave the corresponding enantiopure γ-butyrolactams **318**, although in moderate yield (**Scheme 60**) <2004T7591>.



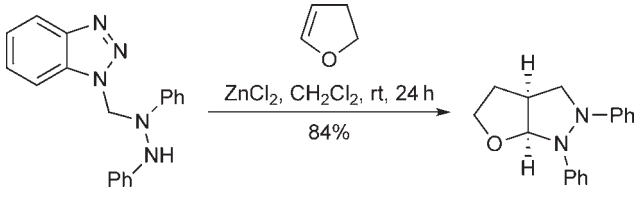
307 **308** **309**

R^1 = Me, Bu^t, Bn, 4-MeOC$_6$H$_4$CH$_2$, R^2 = Me
R^1 = Et, Bu^t, Bn, 4-MeOC$_6$H$_4$CH$_2$, R^2 = Et

(64)

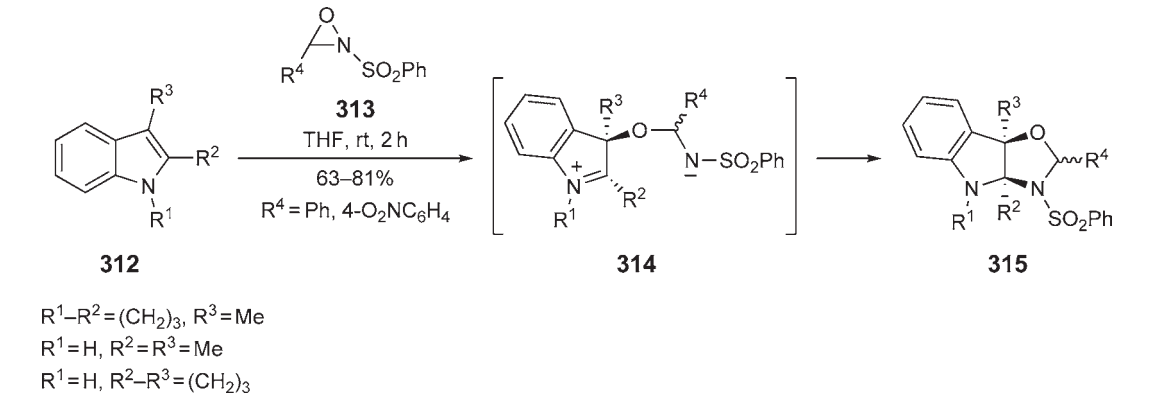


Scheme 58

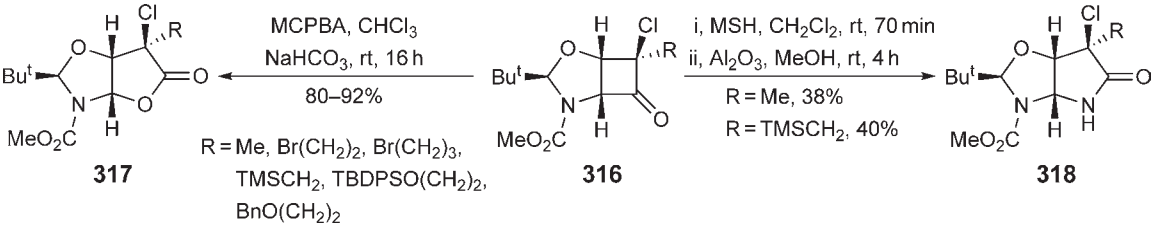


310 **311**

(65)



Scheme 59

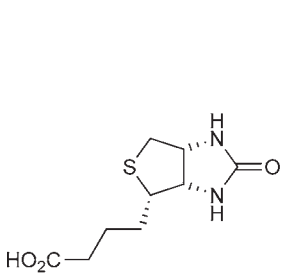


Scheme 60

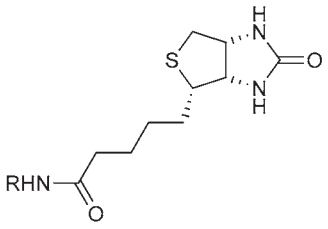
10.02.10 Important Compounds and Applications

Biotin **319**, brassilexin **48**, and sinalexin **49** are naturally occurring compounds that fall into the classification of bicyclic 5-5 heterocycles with 2:1-heteroatom orientation. Biotin is one of the water-soluble B-complex group of essential vitamins distributed widely as a cell constituent of both mammalian tissue and plant material. Biochemically, biotin functions as a cofactor for a set of enzymes that catalyze carboxylation, decarboxylation, and transcarboxylation reactions in a number of crucial metabolic processes, for example, gluconeogenesis and fatty acid synthesis <1989MI195>. Biotin and its derivatives are used, for example, in pharmaceutical preparations, drug delivery <1988ABI1>, cosmetics <2000WO044342>, immunochemistry <1989MI408>, gelators (e.g., **320**) <1997SC2203> and HIV protease inhibitors (e.g., **321**) <1996BML1371>. Biotin biosynthesis from pimeloyl-CoA has been well characterized in bacteria (e.g., *E. coli*, *B. subtilis*, and *Bacillus sphaericus*) <2001MI51> and appears to follow the same pattern in plants <1993EJB479>. There are over 40 reported total syntheses of biotin using a range of starting materials (e.g., from fumaric acid, cystine, cysteine, and sugars) and approaches (e.g., [2+2], [3+2], and [4+2] cycloadditions) <1997MI1755>. Despite this, the classical Hoffmann La Roche synthesis <1949USP2489232, 1949USP2489235, 1949USP2489238> from fumaric acid, with minor modification, remains the commercially practiced technology for large-scale manufacture of feed additives for poultry and swine.

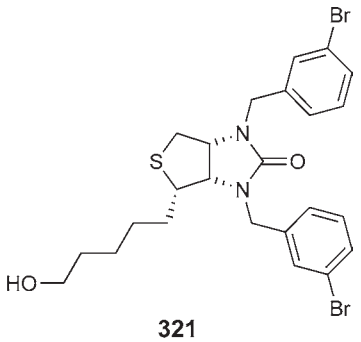
Brassilexin and sinalexin are among the most potent phytoalexins produced by economically important cruciferous plants. Brassilexin, first isolated by Devys *et al.* <1988TL6447>, appears to be involved in the defense mechanisms of *Brassica juncea* (brown mustard) and *Wasabia japonica* (wasabi) <2000P161, 2002P611, 2003P949, 2003COR1635>. Similarly, sinalexin has been implicated in the defense mechanisms of white mustard *Sinapis alba* <2001PNA747>.



319: biotin

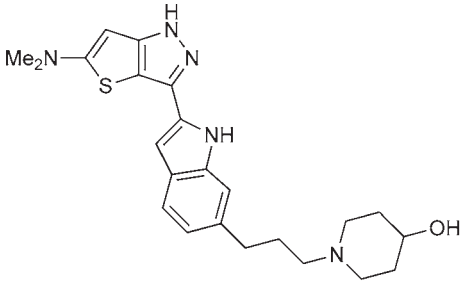


320: R = Me, C_5H_{11}, C_7H_{15}, $C_{10}H_{21}$, $C_{11}H_{23}$, $C_{15}H_{31}$

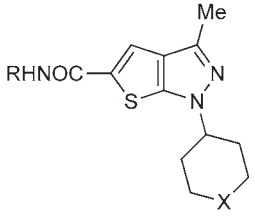


321

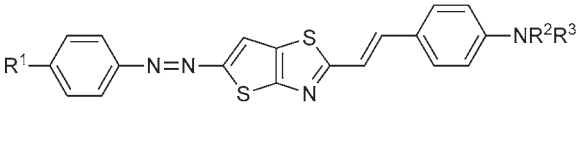
Derivatives of the bicyclic 5-5 heterocycles with 1:2-heteroatom orientation have been investigated for a wide range of applications and some are highlighted in the sections above. Additionally, patent applications have been disclosed describing (1) thienopyrazoles as (i) kinase inhibitors <2003WO101968, 2005USP026984, 2006EP1711177>, (ii) interleukin-2 inducible tyrosine kinase (ITK) inhibitors (e.g., **322**) <2005WO026175>, and (iii) selective inhibitors of PDE7 (e.g., **323**) < 2006WO004040>; (2) thienothiazoles as components in guest–host liquid crystal display devices (e.g., **324** <2000USP6039893>; (3) pyrrolo[2,3-*b*]thiazole and pyrrolo[3,2-*d*]thiazoles as inhibitors of human casein kinase Iε in the phosphorylation of the human clock protein period (hPER) for use in treating central nervous system diseases, mood and sleep disorders (e.g., **325** and **326**) <2006WO021000>; (4) thienoimidazoles, as angiotensin II antagonists (e.g., **327** and **328**) <1995USP5463073>; and, (5) pyrroloimidazole derivatives as nootropic agents <2005EP1608655>.



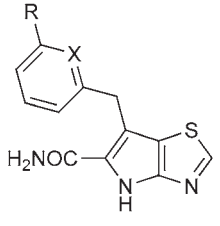
322



323: X = CH_2, O

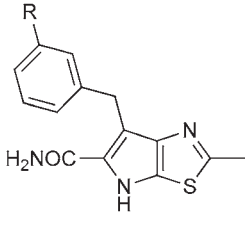


324



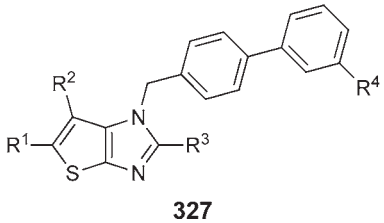
325

X = CH, R = H, F; X = N, R = H

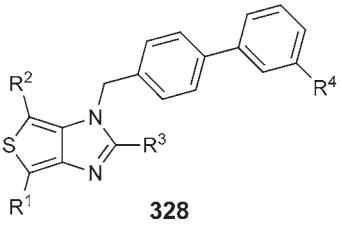


326

R = H, F, Cl, MeO, CF_3



327

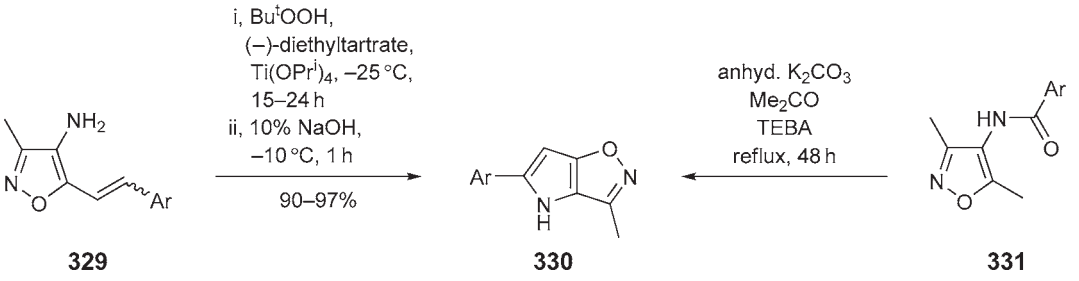


328

10.02.11 Further Developments

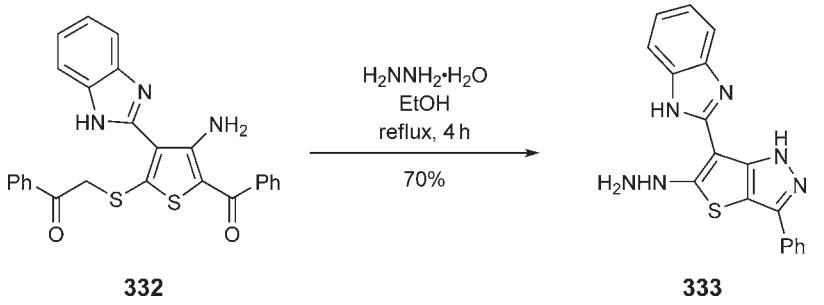
The first analogues of the previously unknown family of 4*H*-pyrrolo[2,3-*d*]isoxazoles have recently been reported <2006TL4957> (**Scheme 61**). Sharpless epoxidation of **329**, followed by treatment with 10% NaOH, resulted in the highly efficient one-pot formation of a range of 4*H*-pyrrolo[2,3-*d*]isoxazoles **330**. It is suggested that the reaction involves intramolecular ring-opening of the initially formed epoxide by the 4-amino group; subsequent base-induced dehydration affords the product **330**. An alternative approach to the same 4*H*-pyrrolo[2,3-*d*]isoxazoles **330** was also demonstrated by base treatment of **331** in the presence of triethylbenzylammonium chloride (TEBA) <2006TL4957>. In complementary approaches to those described in this chapter, there have been reports of:

(i) a thieno[3,2-*c*]pyrazole **333**, investigated for antimicrobial activity against bacterial and fungal isolates, prepared by cyclocondensation of **332** with hydrazine hydrate <2006PS(181)2051> (**Equation 66**);
(ii) a thieno[3,2-*c*]pyrazole **335**, investigated for activity at complex III of the mitochondrial respiratory chain, prepared by initial Dieckmann condensation of **334** (**Scheme 62**) <2006JMC4762>;
(iii) a series of furo[3,2-*c*]pyrazoles **337**, and their derivatives, synthesized through oxidative cyclization of **336** (**Scheme 63**) and evaluated for their cytotoxicity against HL-60 cell line <2007BMC1732>;
(iv) the synthesis of imidazo[4,5-*b*]benzothiophene **338** <2006JHC101> (**Scheme 64**); and
(v) new cyanine dye derivatives containing furo, thieno, and pyrrolo[2,3-*b*]pyrazoles that act as efficient photosensitizers <2006IJB1197>.

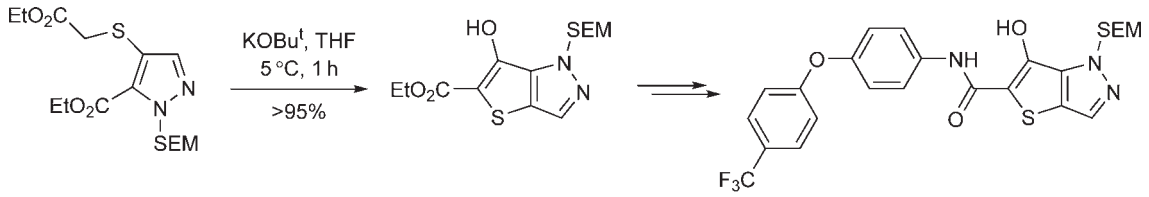


Ar = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3,4-(-OCH$_2$O-)C$_6$H$_3$, 2ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2,6-Cl$_2$C$_6$H$_3$, 2-O$_2$NC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 4Me$_2$NC$_6$H$_4$,

Scheme 61

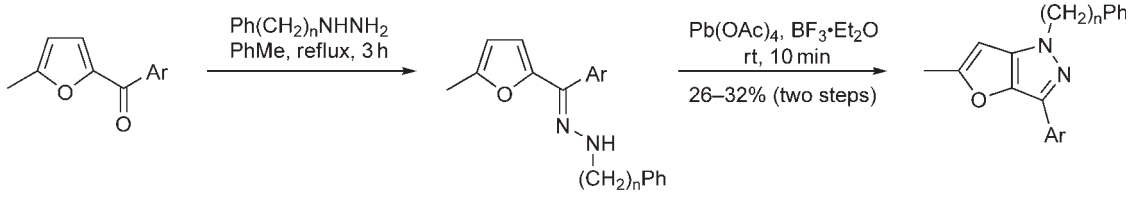


(66)



334 **335**

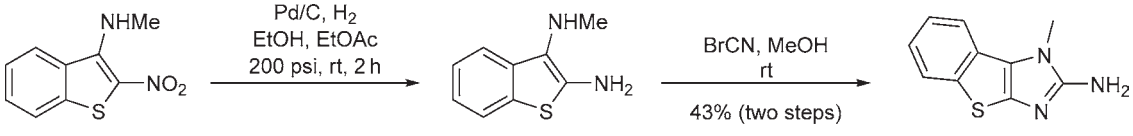
Scheme 62



336 **337**

n = 0, 1; Ar = 4-$MeO_2CC_6H_4$, 5-MeO_2Cfuryl

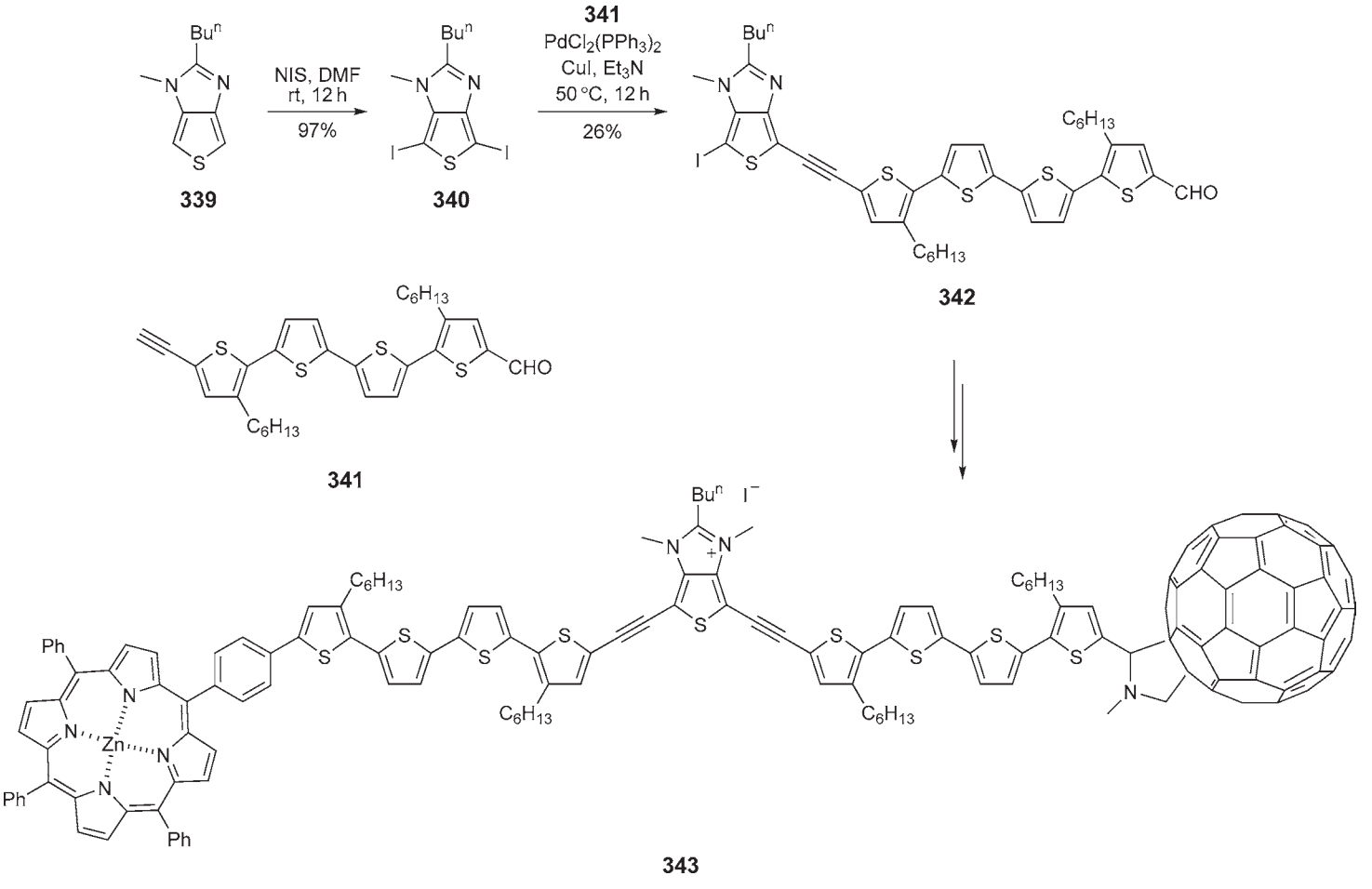
Scheme 63



338

Scheme 64

A novel zinc-porphyrin-oligothiophene-fullerene triad **343**, incorporating a central substituted thieno[3,4-*d*]imidazolium salt, has been reported as a molecular wire that exhibits controllable photoinduced intramolecular electron transfer <2006CL1366> (**Scheme 65**). Iodination of **339** using *N*-iodosuccinimide (NIS) gave **340**, which on Sonogashira reaction with oligothiophene **341** afforded **342**. Subsequent elaboration with a further Sonogashira reaction and alkylation afforded the thieno[3,4-*d*]imidazolium salt **343**.


Bu^n
NIS, DMF
rt, 12 h
97%
341
PdCl2(PPh3)2
CuI, Et3N
50 °C, 12 h
26%
339
340
342
341
343
C6H13
CHO
Ph
Zn
I^−

Scheme 65

References

1949USP2489232 M. W. Goldberg and L. H. Strenbach, *US Pat.* 2489232 (1949) (*Chem. Abstr.*, 1951, **45**, 184).
1949USP2489235 M. W. Goldberg and L. H. Strenbach, *US Pat.* 2489235 (1949) (*Chem Abstr.*, 1951, **45**, 186a).
1949USP2489238 M. W. Goldberg and L. H. Strenbach, *US Pat.* 2489238 (1949) (*Chem. Abstr.*, 1951, **45**, 186g).
1958DOK(120)1035 V. G. Zhiryakov and I. I. Levkoev, *Dokl. Akad. Nauk SSSR*, 1958, **120**, 1035.
1963CB329 G. Wittig and U. Mayer, *Chem. Ber.*, 1963, **96**, 329.
1963JOC3313 R. D. Stephens and C. E. Castro, *J. Org. Chem.*, 1963, **28**, 3313.
1965CB1210 M. Regitz, *Chem. Ber.*, 1965, **98**, 1210.
1967BSF4179 R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 1967, 4179.
1969CHE567 I. Y. Kvitko, *Chem. Heterocycl. Comp. (Engl. Transl.)*, 1969, **5**, 567.
1969KGS760 I. Y. Kvitko, *Khim. Geterotsikl. Soedin.*, 1969, **5**, 760.
1971CC1554 Y. Tsuda, K. Isobe, and A. Ukai, *J. Chem. Soc., Chem. Commun.*, 1971, 1554.
1971JOU1292 I. Y. Kvitko and A. A. Tarasenko, *J. Org. Chem. USSR (Engl. Transl.)*, 1971, **7**, 1292.
1971ZOR1253 I. Y. Kvitko and A. A. Tarasenko, *Zh. Org. Khim.*, 1971, **7**, 1253.
1972J(P1)2567 V. Calo, F. Ciminale, L. Lopez, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2567.
1972JOC2402 W. A. Mosher, P. M. Serridge, and D. W. Lipp, *J. Org. Chem.*, 1972, **37**, 2402.
1972TL4059 R. A. Abramovitch, J. Court, and E. P. Kyba, *Tetrahedron Lett.*, 1972, 4059.
1976CL287 M. Hamaguchi and T. Ibata, *Chem. Lett.*, 1976, 287.
1976CS165 S. Gronowitz, C. Westerlund, and A.-B. Hörnfeldt, *Chem. Scr.*, 1976, **10**, 165.
1976H(4)1316 T. Sano and Y. Tsuda, *Heterocycles*, 1976, **4**, 1316.
1976KGS1202 P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 1976, 1202.
1978JHC1455 A. Shafiee and A. Mazloumi, *J. Heterocycl. Chem.*, 1978, **15**, 1455.
1979CHE387 P. I. Abramenko, T. K. Ponomaryova, and G. I. Priklonskikh, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1979, **15**, 387.
1979KGS477 P. I. Abramenko, T. K. Ponomaryova, and G. I. Priklonskikh, *Khim. Geterotsikl. Soedin.*, 1979, **15**, 477.
1980BSB773 N. V. Onyamboko, R. Weber, N. Dereu, M. Renson, and C. Paulmier, *Bull. Soc. Chim. Belg.*, 1980, **89**, 773.
1981IJB930 M. G. Joshi and K. N. Wadokar, *Indian J. Chem., Sect. B*, 1981, **20**, 930.
1981H(16)1151 T. Sano, J. Toda, N. Kashiwaba, and Y. Tsuda, *Heterocycles*, 1981, **16**, 1151.
1982H(18)229 T. Sano, J. Toda, and Y. Tsuda, *Heterocycles*, 1982, **18**, 229.
1982H(19)2053 Y. Tsuda, T. Oshima, T. Sano, and J. Toda, *Heterocycles*, 1982, **19**, 2053.
1983JHC113 C. Paulmier and F. Outurquin, *J. Heterocycl. Chem.*, 1983, **20**, 113.
1984CHEC(4)741 S. Rajappa; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 4, p. 741.
1984CHEC(5)32 A. R. Katritzky and J. M. Lagowski; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 32.
1984CHEC(6)333 I. Lalezari; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 333.
1984CHEC(6)973 K. H. Pilgram; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1996, vol. 6, p. 973.
1984CHEC(6)1027 C. A. Ramsden; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1996, vol. 6, p. 1027.
1985CC1428 B. Iddon, N. Khan, and B. L. Lim, *J. Chem. Soc., Chem. Commun.*, 1985, 1428.
1985KGS223 L. V. Alan, I. Ya. Kvitko, and N. S. Fedorova, *Khim. Geterotsikl. Soedin*, 1985, 223.
1986JHC951 F. Guerrera, M. A. Siracusa, N. A. Santagati, and B. Tornetta, *J. Heterocyclic Chem.*, 1986, **23**, 951.
1987AP1010 A. O. Abdelhamid and B. Y. Riad, *Arch. Pharm. (Weinheim Ger.)*, 1987, **320**, 1010.
1987BSB407 N. V. Onyamboko, M. Renson, and C. Paulmier, *Bull. Soc. Chim. Belg.*, 1987, **96**, 407.
1987J(P1)1457 B. Iddon, N. Khan, and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1457.
1987JME574 J. B. Summers, H. Mazdiyashi, J. H. Holms, J. D. Ratajczyk, R. D. Dyer, and G. W. Carter, *J. Med. Chem.*, 1987, **30**, 574.
1987KGS410 L. D. Pinkin, V. G. Dzyubenko, P. I. Abramenko, and I. S. Shpileva, *Khim. Geterotsikl. Soedin*, 1987, 410.
1988ABI1 M. Wilcheck and E. A. Bayer, *Anal. Biochem.*, 1988, **171**, 1.
1988TL6447 M. Devys, M. Barbier, I. Loiselet, T. Rouxel, A. Sarniguet, A. Kollmann, and J. Bousquet, *Tetrahedron Lett.*, 1988, **29**, 6447.
1989MI195 J. R. Knowles, *Ann. Rev. Biochem.*, 1989, **58**, 195.
1989MI408 M. Wilcheck and E. A. Bayer, *Trends Biochem. Sci.*, 1989, **14**, 408.
1991CB2481 L. Assmann, L. Palm, M. Zander, and W. Friedrichsen, *Chem. Ber.*, 1991, **124**, 2481.
1992J(P1)973 S. Athmani, M. F. Farhat, and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 973.
1993EJB479 P. Baldet, H. Gerbling, S. Axiotis, and R. Douce, *Eur. J. Biochem.*, 1993, **217**, 479.
1994CL1873 A. Degl'Innocenti, M. Funicello, P. Scafato, and P. Spagnolo, *Chem. Lett.*, 1994, 1873.
1994CPB2036 L.-J. Huang, S.-C. Kuo, J.-P. Wang, K. Ishii, and H. Nakamura, *Chem. Pharm. Bull.*, 1994, **42**, 2036.
1994H(38)2487 B. Iddon and R. I. Ngochindo, *Heterocycles*, 1994, **38**, 2487.
1994IJB1093 A. Dandia and A. Gupta, *Indian J. Chem., Sect. B*, 1994, **33**, 1093.
1994S411 A. S. Bourlot, E. Desarbe, and J. Y. Mérour, *Synthesis*, 1994, 411.
1994SL620 O. Tamura, T. Yamaguchi, T. Okabe, and M. Sakamoto, *Synlett*, 1994, 620.
1994T3929 H. G. Aurich and J.-L. R. Quintero, *Tetrahedron*, 1994, **50**, 3929.
1994T4921 J. Rong, P. Roselt, J. Plavec, and J. Chattopadhyaya, *Tetrahedron*, 1994, **50**, 4921.
1994T5279 A. Papchikhin and J. Chattopadhyaya, *Tetrahedron*, 1994, **50**, 5279.
1994T5503 U. Chiacchio, G. Buemi, F. Casuscelli, A. Procopio, A. Rescifina, and R. Romeo, *Tetrahedron*, 1994, **50**, 5503.
1995CCC1578 R. M. Mohareb, S. M. Sherif, A. Habashi, N. I. Abdel-Sayed, and S. S. Osman, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1578.
1995H(40)1 R. Sustmann, *Heterocycles*, 1995, **40**, 1.
1995H(40)661 J.-P. Bouillon, A.-M. Frisque-Hesbain, Z. Janousek, and H. G. Viehe, *Heterocycles*, 1995, **40**, 661.

1995JA4708 M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1995, **117**, 4708.
1995JFC189 M. M. Abdul-Ghani and A. E. Tipping, *J. Fluorine Chem.*, 1995, **73**, 189.
1995JHC591 F. Guerrera, L. Salerno, M. C. Sarva, and M. A. Siracusa, *J. Heterocycl. Chem.*, 1995, **32**, 591.
1995J(P1)1475 B. Iddon, A. K. Petersen, J. Becher, and N. J. Christensen, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1475.
1995JPR472 K. Gewald, S. Rennert, R. Schindler, and H. Schaefer, *J. Prakt. Chem.*, 1995, **337**, 472.
1995PHA675 D. Briel, *Pharmazie*, 1995, **50**, 675.
1995T107 O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe, and M. Sakamoto, *Tetrahedron*, 1995, **51**, 107.
1995T119 O. Tamura, T. Okabe, T. Yamaguchi, J. Kotani, K. Gotandeq, and M. Sakamoto, *Tetrahedron*, 1995, **51**, 119.
1995T5689 U. Chiacchio, F. Casusceili, A. Corsaro, V. Librando, A. Rescifina, R. Romeo, and G. Romeo, *Tetrahedron*, 1995, **51**, 5689.
1995T6285 H. G. Aurich and H. Köster, *Tetrahedron*, 1995, **51**, 6285.
1995T10497 H. G. Aurich, C. Gentes, and K. Harms, *Tetrahedron*, 1995, **51**, 10497.
1995T12807 D. W. Hawkins, B. Iddon, and D. S. Longthorne, *Tetrahedron*, 1995, **51**, 12807.
1995TL4065 K. Bourgin, M. Soufiaoui, and M. E. Yazidi, *Tetrahedron Lett.*, 1995, **36**, 4065.
1995TL7729 R. Mukhopadhyay, A. P. Kundu, and A. Bhattacharjya, *Tetrahedron Lett.*, 1995, **36**, 7729.
1995USP5463073 N. Takehiko and I. Yoshiyuki, *US Pat.* 5463073 (1995).
1996BML1475 Y. Xiang, R. F. Schinazi, and K. Zhao, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1475.
1996BML1371 Q. Han, J. Lafontaine, L. T. Bacheler, M. M. Rayner, R. M. Klabe, V. S. Erickson, and P. Y. S. Lam, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1371.
1996CC167 C. O'Mahony and F. Heaney, *J. Chem. Soc., Chem. Commun.*, 1996, 167.
1996CHEC-II(7)49 V. J. Lee; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 49.
1996IJB715 V. K. Ahluwalia, A. Dahiya, and M. Bala, *Indian J. Chem., Sect. B*, 1996, **35**, 715.
1996JCMS466 H. A. A. El-Nabi, *J. Chem. Res. (S)*, 1996, **10**, 466.
1996KFZ37 V. S. Velezheva, A. Y. Lepeshkin, O. A. Fedotova, V. I. Shedov, and K. F. Turchin, *Khim. Farm. Zh.*, 1996, **30**, 37.
1996MI643 V. S. Velezheva, A. Y. Lepeshkin, O. A. Fedotova, V. I. Shedov, K. F. Turchin, A. L. Sedov, and O. S. Anisimova, *Pharm. Chem. J.*, 1996, **30**, 643.
1996RJC1798 Y. L. Zborovskii, V. F. Levon, and V. I. Staninets, *Russ. J. Gen. Chem. (Engl. Transl.)*, 1996, **66**, 1798.
1996T1267 R. Alibés, J. L. Bourdelande, J. Font, A. Gregori, and T. Parella, *Tetrahedron*, 1996, **52**, 1267.
1996TA1943 J. L. Garcia Ruano, A. Fraile, and M. R. Martín, *Tetrahedron Asymmetry*, 1996, **7**, 1943.
1996T7875 U. Chiacchio, A. Corsaro, V. Pistarà, A. Rescifina, G. Romeo, and R. Romeo, *Tetrahedron*, 1996, **52**, 7875.
1996TL14323 U. Chiacehio, A. Corsaro, V. Librando, A. Rescifina, R. Romeo, and G. Romeo, *Tetrahedron*, 1996, **52**, 14323.
1996ZOB1847 Y. L. Zborovskii, V. F. Levon, and V. I. Staninets, *Zh. Obshch. Khim*, 1996, **66**, 1847.
1997ACS984 C. P. Butts, L. Eberson, R. Gonzales-Luque, C. M. Hartshorn, M. P. Hartshorn, M. Merchan, W. T. Robinson, B. O. Roos, C. Vallance, and B. R. Wood, *Acta Chem. Scand.*, 1997, **51**, 984.
1997CHE698 G. G. Danagulyan, L. G. Saakyan, M. G. Zalinyan, and P. B. Terent'ev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 698.
1997G791 M. H. Elnagdi, I. El-Ghamry, E. Kandeel, A. H. Rahman, A. A. Naggar, S. Amer, and M. Riad, *Gazz. Chim. Ital.*, 1997, **127**, 791.
1997IJB668 M. J. Desai and V. H. Shah, *Indian J. Chem., Sect. B*, 1997, **36**, 668.
1997IJB813 A. Shafiee, F. Hadizadeh, and A. Foroumadi, *Indian J. Chem., Sect. B*, 1997, **36**, 813.
1997JA1159 S. Mithani, D. M. Drew, E. H. Rydberg, N. J. Taylor, S. Mooibroek, and G. I. Dmitrienko, *J. Am. Chem. Soc.*, 1997, **119**, 1159.
1997JA9641 J.-L. Wood, B. M. Stolz, H.-J. Dietrich, D. A. Pflum, and D. T. Petsch, *J. Am. Chem. Soc.*, 1997, **119**, 9641.
1997JIC206 M. K. A. Ibrahim, A. H. H. Elghandour, G. S. M. Abdel-Sayed, and A. S. M. Fattah, *J. Indian Chem. Soc.*, 1997, **74**, 206.
1997JHC549 A. Shafiee and F. Hadizadech, *J. Heterocycl. Chem.*, 1997, **34**, 549.
1997JOC8210 A. R. Katritzky, G. Qiu, and B. Yang, *J. Org. Chem.*, 1997, **62**, 8210.
1997KGS801 G. G. Danagulyan, L. G. Saakyan, M. G. Zalinyan, and P. B. Terent'ev, *Khim. Geterotsikl. Soedin.*, 1997, 801.
1997M687 S. M. Sherif and A. M. Hussein, *Monatsh. Chem.*, 1997, **128**, 687.
1997MI461 A. Shafiee, A. Zarghi, and A. R. Dehpour, *Pharm. Sci.*, 1997, **3**, 461.
1997MI1755 P. J. De Clercq, *J. Chem. Rev.*, 1997, **97**, 1755.
1997P833 M. Pedras, C. Soledade, and K. C. Smith, *Phytochemistry*, 1997, **46**, 833.
1997SC473 C. N. Johnson, R. T. Martin, H. K. A. Morgan, and M. Thompson, *Synth. Commun.*, 1997, **37**, 473.
1997SC2203 G. T. Crisp and J. Gore, *Synth. Commun.*, 1997, **27**, 2203.
1997T1813 H. A. A. El-Nabi, *Tetrahedron*, 1997, **53**, 1813.
1997T9657 E. Ceulemans, K. Vercauteren, L. K. Dyall, D. Buelens, and W. Dehan, *Tetrahedron*, 1997, **53**, 9657.
1997T17513 A. Arnone, F. Blasco, and G. Resnati, *Tetrahedron*, 1997, **53**, 17513.
1997TA1031 M. Closa, P. de March, M. Figueredo, and J. Font, *Tetrahedron Asymmetry*, 1997, **8**, 1031.
1997TL429 O. Tamura, N. Mita, N. Kusaka, H. Suzuki, and M. Sakamoto, *Tetrahedron Lett.*, 1997, **38**, 429.
1997TL3261 A. Abiko, J. F. Liu, G. Q. Wang, and S. Masamune, *Tetrahedron Lett.*, 1997, **38**, 3261.
1997TL4647 D. J. Hartley and B. Iddon, *Tetrahedron Lett.*, 1997, **38**, 4647.
1998AQ186 S. P. G. Costa, A. M. F. Oliveira-Campos, G. Kirsch, and J. Griffiths, *An. Quim.*, 1998, **94**, 186.
1998BML3037 M. Soledade, C. Pedras, A. Loukaci, and F. L. Okanga, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 3037.
1998CC1565 M. S. C. Pedras and F. I. Okanga, *J. Chem. Soc., Chem. Commun.*, 1998, 1565.
1998EJO1793 D. Enders, A. Haertwig, and J. Runsink, *Eur. J. Org. Chem.*, 1998, 1793.
1998H(48)853 S. Reck, C. Naether, and W. Friedrichsen, *Heterocycles*, 1998, **48**, 853.
1998JHC71 A. Shafiee, M. A. Ebrahimzadeh, J. Shahbazi, and S. Hamedpanah, *J. Heterocycl. Chem.*, 1998, **35**, 71.
1998JHC923 D. Binder, M. Pyerin, and H. Schnait, *J. Heterocycl. Chem.*, 1998, **35**, 923.
1998JOC1064 J. Liu, S. Niwayama, Y. You, and K. N. Houk, *J. Org. Chem.*, 1998, **63**, 1064.
1998JOC7680 S. Reck and W. Friedrichsen, *J. Org. Chem.*, 1998, **63**, 7680.

1998JOC8801 D. van Mersbergen, J. W. Wijen, and J. B. F. N. Engberts, *J. Org. Chem.*, 1998, **63**, 8801.
1998J(P1)341 F. Heaney and C. O'Mahony, *J. Chem. Soc., Perkin Trans. 1*, 1998, 341.
1998J(P1)685 A. Roessler and P. Boldt, *J. Chem. Soc., Perkin Trans. 1*, 1998, 685.
1998MI99 A. Shafiee, M. A. Ebrahimzadeh, A. Zarghi, and A. R. Dehpour, *Pharm. Pharmacol. Commun.*, 1998, **4**, 99.
1998PHA227 D. Briel, *Pharmazie*, 1998, **53**, 227.
1998RJO570 V. S. Velezheva, A. B. Tomchin, A. I. Mel'man, and V. V. Marysheva, *Russ. J. Org. Chem. (Engl. Transl.)*, 1998, **34**, 570.
1998SL407 B. Hill, M. De Vleeschauwer, and M. Belley, *Synlett*, 1998, 407.
1998T3181 H. G. Aurich, M. Geiger, C. Gentes, K. Harms, and H. Köster, *Tetrahedron*, 1998, **54**, 3181.
1998T12737 K. Hori, J. Ito, T. Ohta, and I. Furukawa, *Tetrahedron*, 1998, **54**, 12737.
1998T13997 K.-H. Kao, C.-S. Yang, J.-T. Liu, W.-W. Lin, H.-Y. Fang, C.-F. Yao, and K. Chen, *Tetrahedron*, 1998, **54**, 13997.
1998TL4455 K. Bougrin, M. Lamiri, and M. Soufiaoui, *Tetrahedron Lett.*, 1998, **39**, 4455.
1998TL4851 N. Nishiwaki, T. Uehara, N. Asaka, Y. Tohda, M. Ariga, and S. Kanemasa, *Tetrahedron Lett.*, 1998, **39**, 4851.
1998ZOR604 V. S. Velezheva, A. B. Tomchin, A. I. Mel'man, and V. V. Marysheva, *Zh. Org. Khim.*, 1998, **34**, 604.
1999EJC491 N. H. Metwally and F. M. Abdelrazek, *Egypt. J. Chem.*, 1999, **42**, 491.
1999EJO2725 M. Ferrara, F. M. Cordero, A. Goti, A. Brandi, K. Estieu, R. Paugam, J. Ollivier, and J. Salaun, *Eur. J. Org. Chem.*, 1999, 2725.
1999EJO2689 Q. Cheng, T. Oritani, T. Horiguchi, and Q. Shi, *Eur. J. Org. Chem.*, 1999, 2689.
1999H(50)159 H. Takechi, H. Takahashi, and M. Machida, *Heterocycles*, 1999, **50**, 159.
1999JA3845 K. B. Simonsen, P. Bayón, R. G. Hazell, K. V. Gothelf, and K. A. Jørgensen, *J. Am. Chem. Soc.*, 1999, **121**, 3845.
1999J(P1)3713 E. V. Tretyakov, D. W. Knight, and S. F. Vasilevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3713.
1999JOC2353 K. B. Jensen, R. G. Hazell, and K. A. Jørgensen, *J. Org. Chem.*, 1999, **64**, 2353.
1999JOC5499 M. Beres, G. Hajos, Z. Riedl, T. Soos, G. Timari, and A. Messmer, *J. Org. Chem.*, 1999, **64**, 5499.
1999JOM(586)200 E. Lukevics, V. Dirnens, N. Pokrovska, I. Zicmane, J. Popelis, and A. Kemme, *J. Organomet. Chem.*, 1999, **586**, 200.
1999PS(148)215 A. M. S. El-Sharief, Y. A. Ammar, Y. A. Mohamed, and M. S. A. El-Gaby, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **148**, 215.
1999PS(148)117 A. M. S. El-Sharief, Y. A. Ammar, Y. A. Mohamed, and M. S. A. El-Gaby, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **148**, 117.
1999SC311 P. Seneci, M. Nicola, M. Inglesi, E. Vanotti, and G. Resnati, *Synth. Commun.*, 1999, **29**, 311.
1999SC2355 Z. L. Wang, Z. Li, J. Ren, and H. Chen, *Synth. Commun.*, 1999, **29**, 2355.
1999SC3227 A. P. Misra, K. Raj, and A. P. Bhaduri, *Synth. Commun.*, 1999, **29**, 3227.
1999RJO1812 M. K. Bratenko, M. V. Vork, V. A. Chornous, and N. V. Mel'nichenko, *Russ. J. Org. Chem. (Engl. Transl.)*, 1999, **35**, 1812.
1999T229 R. Alguacil, F. Farifla, M. V. Martin, and M. C. Paredes, *Tetrahedron*, 1999, **55**, 229.
1999T1249 H. G. Aurich, M. Soeberdt, and K. Harms, *Tetrahedron*, 1999, **55**, 1249.
1999T6167 F. Fabis, S. Jolivet-Fouchet, and S. Rault, *Tetrahedron*, 1999, **55**, 6167.
1999T12493 M.-C. Yan, J.-Y. Liu, W.-W. Lin, K.-H. Kao, J.-T. Liu, J.-J. Jang, and C.-F. Yao, *Tetrahedron*, 1999, **55**, 12493.
1999T14491 J. L. García Ruano, A. Fraile, and M. R. Martín, *Tetrahedron*, 1999, **55**, 14491.
1999TL7615 E. T. Pelkey, T. C. Barden, and G. W. Gribble, *Tetrahedron Lett.*, 1999, **40**, 7615.
2000JMC4877 K. L. Seley, P. Januszczyk, A. Hagos, L. Zhang, and D. T. Dransfield, *J. Med. Chem.*, 2000, **43**, 4877.
2000JOC499 K. S.-L. E. H. Lee, M. M. Olmstead, and M. J. Kurth, *J. Org. Chem.*, 2000, **65**, 499.
2000OL519 J. J. Song and N. K. Yee, *Org. Lett.*, 2000, **2**, 519.
2000P161 M. S. C. Pedras, F. I. Okanga, I. L. Zaharia, and A. Q. Khan, *Phytochemistry*, 2000, **53**, 161.
2000PS(162)65 Z. H. Khalil, A. S. Yanni, A. M. Gaber, and S. A. Abdel-Mohsen, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **162**, 65.
2000T10087 H. Ali Dondas, R. Grigg, M. Hadjisoteriou, J. Markandu, W. A. Thomas, and P. Kennewell, *Tetrahedron*, 2000, **56**, 10087.
2000TA897 F. Pisaneschi, F. M. Cordero, A. Goti, R. Paugam, Jean Ollivier, A. Brandi, and J. Salaün, *Tetrahedron Asymmetry*, 2000, **11**, 897.
2000T7817 M. P. S. Ishar, G. Singh, K. Kumar, and R. Singh, *Tetrahedron*, 2002, **58**, 7817.
2000USP6039893 S. Arakawa, M. Matsute, and Y. Kawate, *US. Pat.* 6039893 (2000).
2000WO44342 J. Buenger, H. Driller, W. Wohlrab, L. Motitschke, C. Huschka, and R. Neubert, *PCT Int. Appl. WO* WO2000044342 (2000) (*Chem. Abstr.*, 2000, **133**, 139940).
2001ARK34 P. Stanetty, T. Dvorak, and M. D. Mihovilovic, *ARKIVOC*, 2001, **ii**, 34.
2001BKC476 F. Aydoğan, N. Öcal, and Z. Turgut, *Bull. Korean Chem. Soc.*, 2001, **22**, 476.
2001JHC205 T. Billert, R. Beckert, M. Doering, J. Wuckelt, P. Fehling, and H. Goerls, *J. Heterocycl. Chem.*, 2001, **38**, 205.
2001JHC569 J. Breinholt, C. B. Jeppesen, S. Branner, C. E. Olsen, N. Peter, H. Moeller, B. H. Nielsen, and H. S. Andersen, *J. Heterocycl. Chem.*, 2001, **38**, 569.
2001JOC276 C. Yip, S. Handerson, G. K. Tranmer, and W. Tan, *J. Org. Chem.*, 2001, **66**, 276.
2001JOC2602 O. Tamura, N. Mita, T. Okabe, T. Yamaguchi, C. Fukushima, M. Yamashita, Y. Morita, N. Morita, H. Ishibashi, and M. Sakamoto, *J. Org. Chem.*, 2001, **66**, 2602.
2001J(P1)1579 A. D. Payne and D. Wage, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1579.
2001MI51 A. Marquet, B. Tse Sum Bui, and D. Florentin, *Vitam. Horm.*, 2001, **61**, 51.
2001OL1213 M. Soledad, C. Pedras, and I. L. Zaharia, *Org. Lett.*, 2001, **3**, 1209.
2001OL3209 K. L. Seley, L. Zhang, A. Hagos, and S. Quirk, *Org. Lett.*, 2001, **3**, 3209.
2001PNA747 M. S. C. Pedras, I. L. Zaharia, Y. Gai, Y. Zhou, and D. E. Ward, *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 747.
2001S413 M. T. Omar, N. K. El-Aasar, and K. F. Saied, *Synthesis*, 2001, 413.
2001SC3799 G. Broggini, G. Molteni, T. Pilati, and G. Zecchi, *Synth. Commum.*, 2001, **31**, 3799.
2001T7951 H. A. Dondas, J. E. Cummins, R. Grigg, and M. Thornton-Pett, *Tetrahedron*, 2001, **57**, 7951.
2001TL2937 J. J. Song and N. K. Yee, *Tetrahedron Lett.*, 2001, **42**, 2937.
2001TL6719 K. Nakama, S. Seki, and S. Kanemasa, *Tetrahedron Lett.*, 2001, **42**, 6719.
2002CCS1061 H. A. Shindy, M. A. El-Maghraby, and F. M. Eissa, *J. Chin. Chem. Soc. (Taipei)*, 2002, **49**, 1061.
2002EJO1175 G. Faita, M. Mella, A. Mortoni, A. Paio, P. Quadrelli, and P. Seneci, *Eur. J. Org. Chem.*, 2002, 1175.
2002JHC367 A. Shafiee, J. S. Mojarrad, M. A. Jalili, H. R. Adhami, and F. Hadizadeh, *J. Heterocycl. Chem.*, 2002, **39**, 367.

2002JOC3365 K. L. Seley, L. Zhang, A. Hagos, and S. Quirk, *J. Org. Chem.*, 2002, **67**, 3365.

2002JOC4380 U. Chiacchio, A. Corsaro, D. Iannazzo, A. Piperno, A. Procopio, A. Rescifina, G. Romeo, and R. Romeo, *J. Org. Chem.*, 2002, **67**, 4380.

2002P611 M. S. C. Pedras, C. M. Nycholat, S. Montaut, Y. Xu, and A. Q. Khan, *Phytochemistry*, 2002, **59**, 611.

2002SL73 J. L. García Ruano, F. Bercial, A. Fraile, and M. R. Martín, *Synlett*, 2002, 73.

2002T135 H. A. El-Nabi, *Tetrahedron*, 2002, **58**, 135.

2002T7821 B. B. Snider and Q. Che, *Tetrahedron*, 2002, **58**, 7821.

2002T10437 M.-H. Shih, *Tetrahedron*, 2002, **58**, 10437.

2002TA1993 J. L. García Ruano, F. Bercial, G. Gonzalez, and M. R. Martín, *Tetrahedron Asymmetry*, 2002, **13**, 1993.

2003BML2591 Z. Li, G. D. Francisco, W. Hu, P. Labthavikul, P. J. Petersen, A. Severin, G. Singh, Y. Yang, B. A. Rasmussen, Y.-I. Lin, J. S. Skotnicki, and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2591.

2003COR1635 M. S. C. Pedras, M. Jha, and P. W. K. Ahiahonu, *Curr. Org. Chem.*, 2003, 1635.

2003JHC721 N. Öcal, F. Aydoğan, C. Yolaçan, and Z. Turgut, *J. Heterocyclic Chem.*, 2003, **40**, 721.

2003JHC957 M. Ahn, J. M. Park, I.-Y. C. Lee, and M. H. Jung, *J. Heterocyclic Chem.*, 2003, **40**, 957.

2003MM6340 L. Vretik and H. Ritter, *Macromolecules*, 2003, **36**, 6340.

2003JMC3945 T. van Herk, J. Brussee, A. M. C. H. van den Nieuwendijk, P. A. M. van der Klein, A. P. Ijzerman, C. Stannek, A. Burmeister, and A. Lorenzen, *J. Med. Chem.*, 2003, **46**, 3945.

2003JOC6522 J. L. García Ruano, A. Fraile, G. González, M. R. Martín, F. R. Clemente, and R. Gordillo, *J. Org. Chem.*, 2003, **68**, 6522.

2003FA1193 M. M. Akhavan, J. S. Mojarrad, A. Rouzrokh, S. A. Ebrahimi, M. Mahmoudian, and A. Shafiee, *Farmaco*, 2003, **58**, 1193.

2003JOC6522 J. L. Garcia Ruano, A. Fraile, G. González, M. R. Martín, F. R. Clemente, and R. Gordillo, *J. Org. Chem.*, 2003, **68**, 6522.

2003MI251 A. Zarghi, A. H. Ebrahimabadi, F. Hassanzadeh, M. R. Heydari, and A. Shafiee, *Boll. Chim. Farm.*, 2003, **142**, 251.

2003OBC1122 F. Heaney, J. Fenlon, P. McArdle, and D. Cunningham, *Org. Biomol. Chem.*, 2003, **1**, 1122.

2003P949 M. S. C. Pedras, P. B. Chumala, and M. Suchy, *Phytochemistry*, 2003, **64**, 949.

2003PS(178)417 H. M. Gaber, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 417.

2003RJO893 M. K. Bratenko, A. V. Chornous, and M. V. Vovk, *Russ. J. Org. Chem. (Engl. Transl.)*, 2003, **39**, 893.

2003RJO1161 V. N. Yarovenko, N. G. Smirnova, V. N. Bulgakova, I. V. Zavarzin, and M. M. Krayushkin, *Russ. J. Org. Chem. (Engl. Transl.)*, 2003, **39**, 1161.

2003T2899 S. Zhu, G. Jin, W. Peng, and Q. Huang, *Tetrahedron*, 2003, **59**, 2899.

2003T4113 M. Shirai, H. Kuwabara, S. Matsumoto, H. Yamamoto, A. Kakehib, and M. Noguchi, *Tetrahedron*, 2003, **59**, 4113.

2003T4123 M. Noguchi, S. Matsumoto, M. Shirai, and H. Yamamoto, *Tetrahedron*, 2003, **59**, 4123.

2003T4451 C. W. G. Fishwick, R. Grigg, V. Sridharan, and J. Virica, *Tetrahedron*, 2003, **59**, 4451.

2003T9997 H. Ali Dondas, C. W. G. Fishwick, R. Grigg, and M. Thornton-Pett, *Tetrahedron*, 2003, **59**, 9997.

2003WO101968 N. Ohi, N. Sato, M. Soejima, T. Doko, T. Terauchi, Y. Naoe, and T. Motoki, *PCT* WO101968 (2003).

2003ZOK942 M. K. Bratenko, A. V. Chornous, and M. V. Vovk, *Zh. Org. Khim.*, 2003, **39**, 942.

2003ZOK1232 V. N. Yarovenko, N. G. Smirnova, V. N. Bulgakova, I. V. Zavarzin, and M. M. Krayushkin, *Zh. Org. Khim.*, 2003, **39**, 1232.

2004BMC191 Z. Mincheva, M. Courtois, J. Crèche, M. Rideau, and M.-C. Viaud-Massuard, *Bioorg. Med. Chem.*, 2004, **12**, 191.

2004CCS785 E. A. El-Rady and F. M. A. E. Latif, *J. Chin. Chem. Soc. (Tapei)*, 2004, **51**, 785.

2004CEJ2237 B. M. Trost and M. L. Crawley, *Chem. Eur. J.*, 2004, **10**, 2237.

2004FA849 F. Campagna, F. Pallutto, A. Carotti, and E. Maciocco, *Farmaco*, 2004, **59**, 849.

2004H(63)2475 D. A. Berry, T.-C. Chien, and L. B. Townsend, *Heterocycles*, 2004, **63**, 2475.

2004IJC1355 E.-S. A. Aly, M. A. El-Borai, and M. A. Barren, *Indian J. Chem.*, 2004, **43B**, 1355.

2004IZV553 I. L. Dalinger, A. A. Zaitsev, T. K. Shkineva, and S. A. Shevelev, *Izv. Akad. Nauk SSSR Ser. Khim.*, 2004, 553.

2004JOC1475 O. Tamura, N. Iyama, and H. Ishibashi, *J. Org. Chem.*, 2004, **69**, 1475.

2004NN805 J. D. Williams, J. C. Drach, and L. B. Townsend, *Nucleos. Nucleot.*, 2004, **23**, 805.

2004OL2027 P.-Y. Roger, A.-C. Durand, J. Rodriguez, and J.-P. Dulcère, *Org. Lett.*, 2004, **6**, 2027.

2004RCB580 I. L. Dalinger, A. A. Zaitsev, T. K. Shkineva, and S. A. Shevelev, *Russ. Chem. Bull.*, 2004, **53**, 580.

2004RJO137 I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 137.

2004SAA129 V. B. Kovalskam, M. Y. Losytskyy, and S. M. Yarmoluk, *Spectrochim. Acta Part A*, 2004, **60**, 129.

2004SL1034 R. Marković, M. Baranac, and M. Stojanović, *Synlett*, 2004, 1034.

2004T7591 L. Ghosez, G. Yang, J. R. Cagnon, F. Le Bideau, and J. Marchand-Brynaert, *Tetrahedron*, 2004, **60**, 7591.

2004TA1127 L. De Benassuti, L. Garanti, and G. Molteni, *Tetrahedron Asymmetry*, 2004, **15**, 1127.

2004TL3659 I. A. O'Neil, V. E. Ramos, G. L. Ellis, E. Cleator, A. P. Chorlton, D. J. Tapolczay, and S. B. Kalindjian, *Tetrahedron Lett.*, 2004, **45**, 3659.

2004TL4143 S. Mallouk, K. Bougrin, H. Doua, R. Benhida, and M. Soufiaoui, *Tetrahedron Lett.*, 2004, **45**, 4143.

2004ZOK146 I. V. Zavarzin, N. G. Smirnova, V. N. Yarovenko, and M. M. Krayushkin, *Zh. Org. Khim.*, 2004, **40**, 146.

2005BML1327 Y. Wang, A. Benn, N. Flinn, T. Monk, M. Ramjee, J. Watts, and M. Quibell, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1327.

2005CC2369 S. Akai, K. Tanimoto, Y. Kanao, S. Omura, and Y. Kita, *J. Chem. Soc., Chem. Commun.*, 2005, 2369.

2005EP1608655 C. Farina, S. Gagliardi, C. Parini, M. Martinelli, and C. Ghelardini, *Eur. Pat.* EP1608655 (2005).

2005JCR761 N. Haider, A.-R. Farghaly, N. Al-Mekhlafi, and H. El-Kashef, *J. Chem. Res.*, 2005, 761.

2005JMC3080 D. Fancelli, D. Berta, S. Bindi, A. Cameron, P. Cappella, P. Carpinelli, C. Catana, B. Forte, P. Giordano, M. L. Giorgini, S. Mantegani, A. Marsiglio, M. Meroni, J. Moll, V. Pittalà, F. Roletto, D. Severino, C. Soncini, P. Storici, R. Tonani, M. Varasi, A. Vulpetti, and P. Vianello, *J. Med. Chem.*, 2005, **48**, 3080.

2005JOC596 A. Y. Lebedev, A. S. Khartulyari, and A. Z. Voskoboynikov, *J. Org. Chem.*, 2005, **70**, 596.

2005JOC1828 M. S. C. Pedras and M. Jha, *J. Org. Chem.*, 2005, **70**, 1828.

2005JOC4307 O. A. Attanasi, G. Favi, P. Filippone, A. Golobič, B. Stanovnik, and J. Svete, *J. Org. Chem.*, 2005, **70**, 4307.

2005JOC8825 J. L. García Ruano, A. Fraile, A. M. Martín Castro, and M. R. Martín, *J. Org. Chem.*, 2005, **70**, 8825.

2005JOC8942 J. L. Garcia Ruano, M. T. Peromingo, M. Alonso, A. Fraile, M. R. Martín, and A. Tito, *J. Org. Chem.*, 2005, **70**, 8942.

2005JOC10720 O. Tamura, T. Mitsuya, X. Huang, Y. Tsutsumi, S. Hattori, and H. Ishibashi, *J. Org. Chem.*, 2005, **70**, 10720.

2005JSC799 G. G. Pawar, P. Bineesh, P. S. R. Kumar, D. W. Rangnekar, and V. R. Kanetkar, *J. Serb. Chem. Soc.*, 2005, **70**, 799.

2005PS(180)573 A. M. S. El-Sharief, F. F. Mahmoud, N. M. Taha, and E. M. Ahmed, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 573.

2005SC249 C. Moustapha, N. A. Abdel-Riheem, and A. O. Abdelhamid, *Synth. Commun.*, 2005, **35**, 249.

2005T2999 X. S. Ghorai, R. Mukhopadhyay, A. P. Kundu, and A. Bhattacharjya, *Tetrahedron*, 2005, **61**, 2999.

2005T11380 R. Grigg, W. Martin, J. Morris, and V. Sridharan, *Tetrahedron*, 2005, **61**, 11380.

2005USPO26984 A. Bigot, F. Clerc, G. Doerflinger, S. Mignani, and H. Minoux, *US Pat.* 026984 (2005).

2005WO026175 J. G. Jurcak, M. Barrague, T. A. Gillespy, M. L. Edwards, K. Y. Musick, P. M. Weintraub, Y. Du Yan, R. M. Dharanipragada, and A. A. Parkar, *PCT* WO026175 (2005).

2006BMC714 M. Soledade, C. Pedras, and M. Suchy, *Bioorg. Med. Chem.*, 2006, **14**, 714.

2006BML96 I. Akritopoulou-Zanze, D. Darcsak, K. Sarris, K. M. Phelan, J. R. Huth, D. Song, E. F. Johnson, Y. Jia, and S. W. Djuric, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 96.

2006BML1084 P. Pevarello, D. Fancelli, A. Vulpetti, R. Amici, M. Villa, V. Pittalà, P. Vianello, A. Cameron, M. Ciomei, C. Mercurio, J. R. Bischoff, F. Roletto, M. Varasi, and M. G. Brasc, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1084.

2006CL1366 Y. Ie, T. Kawabata, T. Kaneda, and Y. Aso, *Chem. Lett.*, 2006, **35**, 1366.

2006EP1711177 D. Fancelli, S. Bindi, M. Varasi, P. Vianello, S. Vioglio, and D. Tesei, *Eur. Pat.* EP1711177, 2006.

2006IJB1197 H. A. Shindy, M. A. El-Maghraby, and F. M. Eissa, *Indian J. Chem., Sect. B*, 2006, **45**, 1197.

2006JHC101 M. Bjork and S. Grivas, *J. Heterocycl. Chem.*, 2006, **43**, 101.

2006JMC1191 A. Beliaev, D. A. Learmouth, and P. Soares-da-Silva, *J. Med. Chem.*, 2006, **49**, 1191.

2006JMC4762 S. Bolgunas, D. A. Clark, W. S. Hanna, P. A. Mauvais, and S. Pember, *J. Med. Chem.*, 2006, **49**, 4762.

2006PS(181)2051 W. W. Wardakhan, *Phosphorus, Sulfur Relat. Elem.*, 2006, **181**, 2051.

2006TL433 F. Anizon, B. Pfeiffer, and M. Prudhomme, *Tetrahedron Lett.*, 2006, **47**, 433.

2006TL4957 E. Rajanarendar, G. Mohan, P. Ramesh, and D. Karunakar, *Tetrahedron Lett.*, 2006, **47**, 4957.

2006WO004040 H. Inoue, H. Murafuji, and Y. Hayashi, *PCT* WO004040 (2006).

2006WO021000 D. M. Fink, Y. Chiang, N. D. Collar, and D. Nicola, *PCT* WO021000 (2006).

2007BMC1732 L.-C. Chou, L.-J. Huang, J.-S. Yang, F.-Y. Lee, C.-M. Teng, and S.-C. Kuo, *Bioorg. Med. Chem.*, 2007, **15**, 1732.

Biographical Sketch



Adrian Moore was born in Scarborough and studied at Durham University, where he obtained a BSc in 1986 and his PhD in 1989 under the direction of Prof. M. R. Bryce. He remained in Durham working as a postdoctoral research fellow, leaving in 1998 to become an industrial consultant in process development chemistry working for Contrachem, Ltd. He took up his present position of Senior Lecturer in the School of Health, Natural and Social Sciences at the University of Sunderland in November 2001. His scientific interests include all aspects of heterocyclic and organosulfur chemistry; in particular, their application to materials and supramolecular chemistry and the development of novel agents for cognition enhancement, treatment of depression and anti-cancer activity.

10.03
Bicyclic 5-5 Systems: Four Heteroatoms 1:3

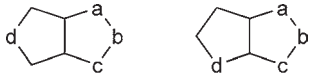
Y. A. Jackson and N. O. Townsend
University of West Indies, Jamaica, West Indies
© 2008 Elsevier Ltd. All rights reserved.

10.03.1 Introduction 130
10.03.2 Theoretical Methods 130
10.03.3 Experimental Structural and Spectroscopic Methods 131
10.03.3.1 EPR Spectroscopy 131
10.03.3.2 X-Ray Diffraction 131
10.03.3.3 Molecular Spectra 133
10.03.3.3.1 NMR spectroscopy 133
10.03.3.3.2 Mass spectrometry 133
10.03.3.3.3 IR and UV spectroscopy 134
10.03.4 Thermodynamics and Aromaticity 134
10.03.5 Reactivity of Fully Conjugated Ring Systems 134
10.03.5.1 Pyrrolo[2,3-*c*]-1,2,5-thiadiazoles 134
10.03.5.2 Thieno[2,3-*d*]-1,2,3-thiadiazoles 135
10.03.5.3 Thieno[2,3-*d*]-1,2,3-triazoles 136
10.03.5.4 Thieno[3,2-*d*]-1,2,3-thiadiazoles 136
10.03.6 Reactivity of Nonconjugated Ring Systems 136
10.03.6.1 Furo[2,3-*d*]-1,3,2-dioxathioles 136
10.03.6.2 Furo[3,4-*d*]-1,3,2-dioxathioles 137
10.03.6.3 Furo[3,4-*d*]-1,2,3-triazoles 138
10.03.6.4 Pyrrolo[2,3-*d*]-1,2,3-triazoles 138
10.03.6.5 Pyrrolo[3,4-*d*]-1,2,3-triazoles 138
10.03.6.6 Thieno[3,4-*d*]-1,3,2-dioxathioles 138
10.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms 140
10.03.8 Reactivity of Substituents Attached to Ring Heteroatoms 140
10.03.9 Ring Synthesis Classified by the Number of Ring Atoms in Each Component 140
10.03.9.1 Synthesis of the Second Heterocyclic Ring from [5+0] Atom Fragments 140
10.03.9.1.1 Furo[2,3-*d*]-1,2,3-dithiazoles 140
10.03.9.1.2 Furo[3,4-*d*]-1,2,3-triazoles 140
10.03.9.1.3 Pyrrolo[3,4-*c*]-1,2,5-oxadiazoles 141
10.03.9.1.4 Pyrrolo[3,4-*d*]-1,2,3-triazoles 141
10.03.9.2 Synthesis of the Second Heterocyclic Ring from [4+1] Atom Fragments 142
10.03.9.2.1 Furo[2,3,-*d*]-1,3,2-dioxathioles 142
10.03.9.2.2 Furo[3,4-*d*]-1,3,2-dioxathioles 142
10.03.9.2.3 Pyrrolo-[2,3-*d*]-1,2,3-thiadiazoles 144
10.03.9.2.4 Pyrrolo-[2,3-*d*]-1,2,3-triazoles 145
10.03.9.2.5 Pyrrolo[3,4-*d*]-1,3,2-dioxathioles 145
10.03.9.2.6 Thieno[2,3-*c*]-1,2,5-thiadiazoles 146
10.03.9.2.7 Thieno[2,3-*d*]-1,2,3-thiadiazoles 146
10.03.9.2.8 Thieno[3,2-*d*]-1,2,3-thiadiazoles 147
10.03.9.2.9 Thieno[3,4-*c*]-1,2,5-thiadiazoles 148
10.03.9.2.10 Thieno[3,4-*d*]-1,3,2-dioxathioles 148
10.03.9.2.11 Thieno[3,4-*d*]-1,2,3-thiadiazoles 149

10.03.9.3 Synthesis of the Second Heterocyclic Ring from [3+2] Atom Fragments 150
10.03.9.3.1 Furo[2,3-*d*]-1,2,3-oxathiazoles 150
10.03.9.3.2 Furo[3,4-*d*]-1,3,2-dioxathioles 150
10.03.9.3.3 Furo[3,4-*d*]-1,2,3-triazoles 150
10.03.9.3.4 Pyrrolo[2,3-*c*]-1,2,5-thiadiazoles 151
10.03.9.3.5 Pyrrolo[2,3-*d*]-1,2,3-triazoles 152
10.03.9.3.6 Pyrrolo[3,4-*d*]-1,2,3-triazoles 154
10.03.9.3.7 Thieno[3,2-*d*]-1,2,3-triazoles 154
10.03.10 Ring Synthesis by Transformation of Another Ring System 155
10.03.10.1 Thieno[2,3-*d*]-1,2,3-thiadiazoles 155
10.03.11 Synthesis of Particular Classes of Compounds and Comparison of the Routes Available 155
10.03.12 Important Compounds and Applications 156
References 157

10.03.1 Introduction

In CHEC-II(1996), Chapter 7.03 <1996CHEC-II(7)89> was devoted to 5-5 fused heterocyclic systems containing four heteroatoms arranged 1:3, with no heteroatoms at the bridgehead position, that is, heterocycles of general structure **1** and **2**.

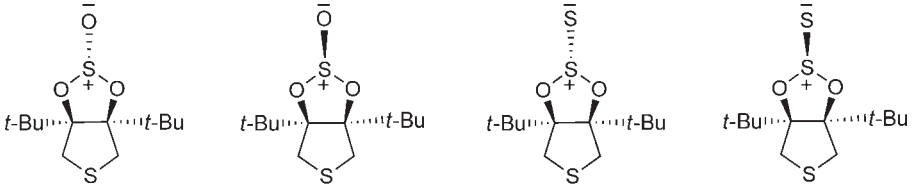


1 **2**

Both aromatic and nonaromatic systems were reviewed, and emphasis was placed on systems which had heteroatoms a, b, c, d being nitrogen, oxygen, or sulfur. This chapter follows on from that in CHEC-II(1996), covering work published since 1996.

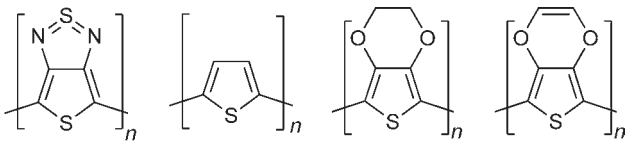
10.03.2 Theoretical Methods

No theoretical studies were reported in the previous volume <1996CHEC-II(7)89> for these 5-5 bicyclic systems. Since then a number of computational studies have been carried out. The structure and properties of cyclic sulfites **3a** and **3b** and thionosulfites **3c** and **3d** have been reported <2003HAC587, 2005HCA1451>. Density functional theoretical (DFT) calculations using the Becke's exchange with Lee, Yang, and Parr correlation functional (B3LYP/6-31G* level) have shown that the cyclic sulfite **3b** is more stable than its diastereomer **3a**.

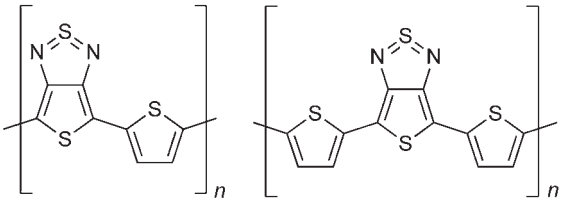


3a **3b** **3c** **3d**

DFT calculations on the polythiophene derivatives have been reported <1996JPC17327>. These calculations, used to analyze the electronic and geometric structures, revealed that polythienothiadiazole **4** is quinoid while polythiophene **5** and its derivatives **6** and **7** are aromatic. *Ab initio* studies have been performed on thienodiazole-based polymers <1996JCP5528>. These calculations, using the one-dimensional self-consistent crystal orbit (SCF-CO) method, showed that for compounds **4** and **8** there were significant differences between the geometries of the oligomers and the geometries of their corresponding polymers. However, for compound **9** the geometries of the oligomer and the polymer were very similar.

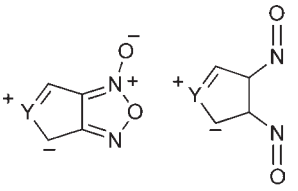


4 **5** **6** **7**



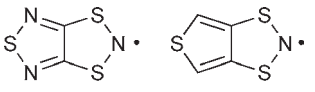
8 **9**

Using DFT studies Klenke and Friedrichsen concluded that the nonclassical furoxans **10–12** were less stable than the corresponding open chain isomers **13–15** <1998JST(451)263>.



10: Y = O **13**: Y = O
11: Y = NH **14**: Y = NH
12: Y = S **15**: Y = S

Using Neese's coupled-perturbed Kohn–Sham hybrid density functional (UPBE0, UB1LYP) techniques, the gyromagnetic (*g*) and hyperfine tensor components of the thiophene-1,3,2-dithiazoly radical (TDTA) were computed and found to be in very good agreement with values from experimental determination <2006CPL(418)30>.



TTTA **TDTA**

10.03.3 Experimental Structural and Spectroscopic Methods

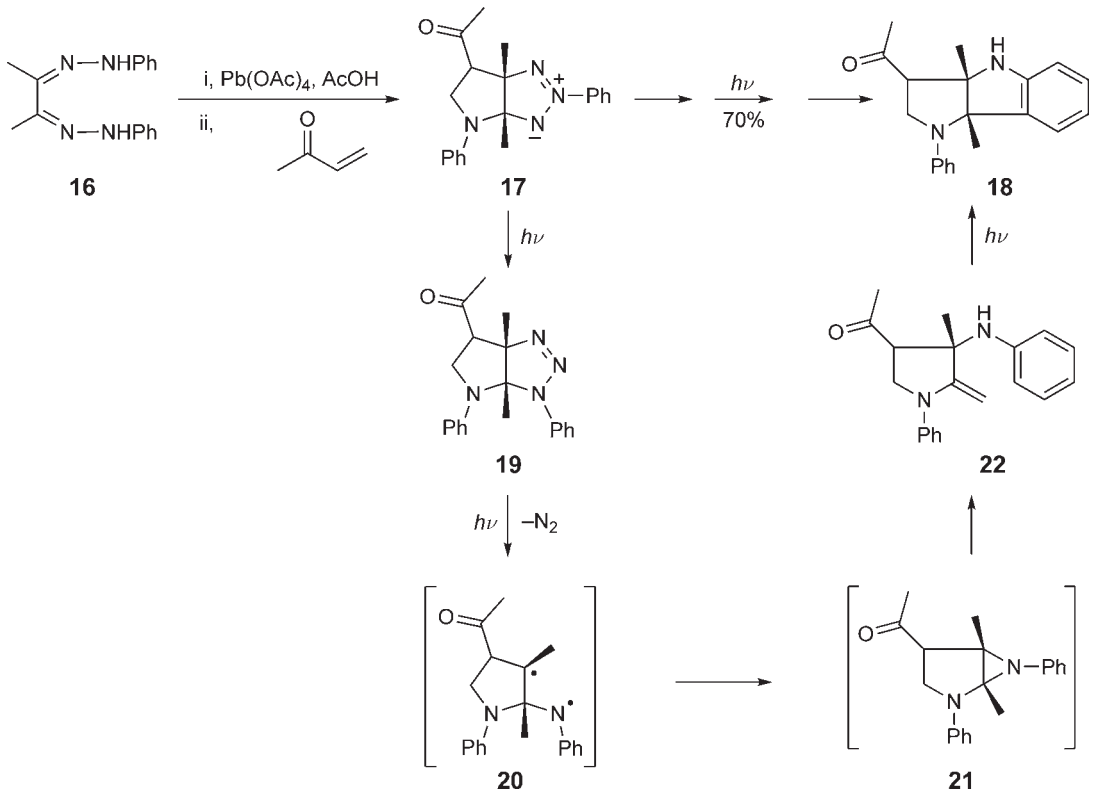
10.03.3.1 EPR Spectroscopy

Electron paramagnetic resonance (EPR) and electron-nuclear double resonance (ENDOR) studies on frozen solutions of TDTA in tetrahydrofuran (THF) allowed estimates of its spin density distribution <2005JCD3838>. A comparison with that of TTTA <2001JMC1992> determined by similar methods shows that replacement of N of TTTA by isoelectronic C–H groups results in greater localization of spin density on the dithiazolyl ring.

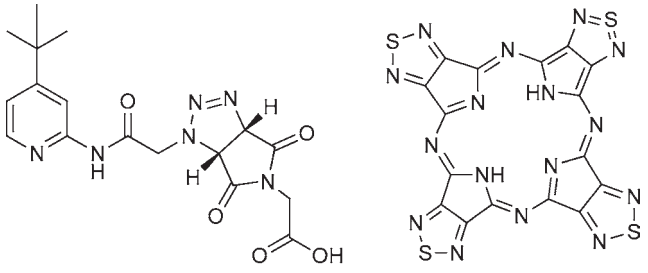
10.03.3.2 X-Ray Diffraction

X-Ray crystallographic analysis was used to investigate the mechanism by which the cyclic azimine **17** was converted into pyrrolo[3,2-*b*]indole **18** <1996CC945>. Isolation and X-ray analysis of different photolabile intermediates revealed one of them to be the fused triazoline **19** as shown in **Scheme 1**.

Single crystal X-ray crystallography has also been used to solve the structures of various compounds of interest. Triazoline **23** exists as a homodimer in the solid state <2002TL7229>. The packing motifs in tetrakis(1,2,5-thiadiazole)porphyrazine ($TTDPzH_2$) **24** and its corresponding metal derivatives (TTDPzM: M = Co, Fe, Ni, Cu, Zn) have been investigated using X-ray crystallography <2003AGE5863, 2004CEJ5158>. $TTDPzH_2$ **24** crystallizes in a monoclinic $P2_1/n$ space group with the molecules forming a layered crystal structure.

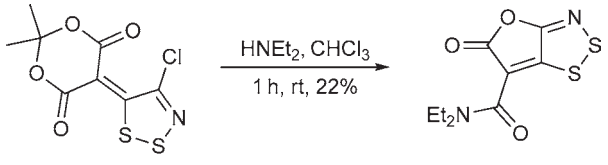


Scheme 1



23 **24**

The structure of 4-oxa-1,2-dithia-3-aza-pentalene **26**, obtained as the major product when diethylamine is reacted with Meldrum's acid derivative **25**, has been solved (Equation 1) <2000J(P1)3107>. The S–S and S–C bond lengths were found to be 2.11 and 1.69 Å, respectively. The S–S–C bond angle is 90.83°.



25 **26** (1)

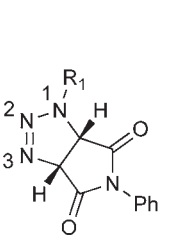
The stereochemistry of the cyclic sulfites **3a** and **3b**, and the thionosulfites **3c** and **3d** has also been determined <2003HAC587, 2005HCA1451>.

10.03.3.3 Molecular Spectra

Most of the compounds covered in this chapter have been analyzed by one or more spectroscopic method. The intention here is not to give detailed spectral data but to illustrate how these techniques have been used for structure elucidation.

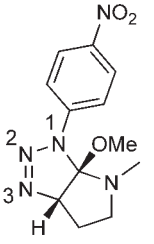
10.03.3.3.1 NMR spectroscopy

^{15}N NMR spectral data (NMR – nuclear magnetic resonance) have been reported for the triazolines **27–28** <2002J(P2)126>. The assignment of chemical shifts was aided by ^{15}N-labeling. The structure and stereochemistry of compounds **29a–e** were established using ^{1}H NMR and ^{13}C NMR analysis, including distortionless enhancement by polarization transfer (DEPT) and correlation spectroscopy (COSY) experiments <2001J(P1)1778>. Clear nuclear Overhauser effect (NOE) enhancements from 6-H to 7-CH_2 of the bridging cyclohexane ring led to assignment of *endo*-stereochemistry.

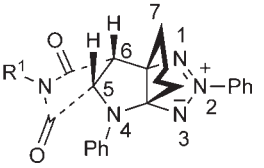


27

a: R^1 = Ph
b: R^1 = Bu



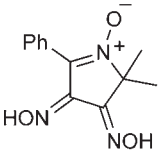
28



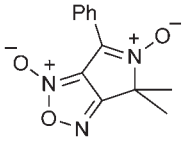
29

a: R^1 = Ph
b: R^1 = *p*-BrC_6H_4
c: R^1 = H
d: R^1 = Me
e: R^1 = CMe_3

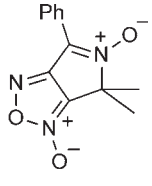
^{1}H NMR analysis was used to monitor the oxidation of dioxime **30** by manganese dioxide. Earlier work suggested that this reaction produced mainly isomer **31** <1990CHE1195>. More recent work, however, has shown that two isomeric furoxans **31** and **32** are produced in approximately equal amounts <2001RCB874>.



30



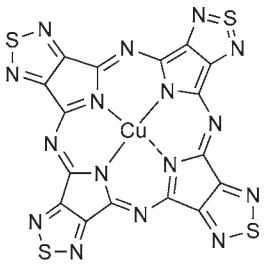
31



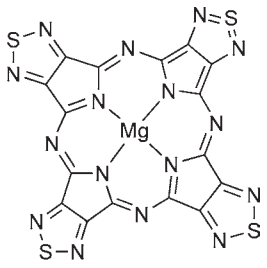
32

10.03.3.3.2 Mass spectrometry

When metalloporphyrazines **33** and **34** were analyzed using desorption electron impact (DEI) mass spectrometry, the dominant peak in each mass spectrum was due to the monomeric unit corresponding to a quarter of the molecular weight of the ligand. Only a weak signal (2%) corresponding to the molecular radical cation was observed. When matrix-assisted laser desorption/ionization (MALDI) mass spectrometry was used instead of DEI, the resulting mass spectra had the main peaks corresponding to $M^{+\bullet}$ and/or MH^+ <2002EJMS35>. These results suggested that MALDI is more accurate than DEI in determining the molecular mass of metalloporphyrazines.



33

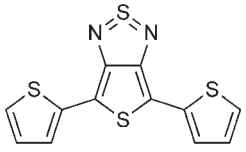


34

10.03.3.3.3 IR and UV spectroscopy

IR and UV–Vis spectroscopy (IR – infrared; UV – ultraviolet) has been used to analyze the properties of porphyrazines. The IR spectrum of $TTDPzH_2$ **24** shows medium–strong bands at 3290, 1565, and 753 cm^{-1} assigned to ν(NH), δ(NH), and γ(NH) vibrations, respectively. Comparison of the UV–Vis spectra of $TTPDPzH_2$ and its copper and magnesium derivatives TTDPzCu **33** and TTDPzMg **34**, respectively, showed main maxima in the Soret region of 330–337 nm (chlorobenzene as solvent) due mainly to B-band contributions. There are however closely lying or overlapping N and $n \rightarrow \pi^*$ transitions <1998IC1533>.

The UV–Vis spectra of compound **35** in CH_2Cl_2 show three main bands at 236, 308–360 (double peak structure), and 618 nm <2004PCB2516>. The absorption with maximum at 618 nm represents a downward shift with respect to the related absorption at 415 nm <1994H(37)693> for the parent thieno[3,4-*c*][1,2,5]thiadiazole **36**. Compound **35** displays a strong IR feature around 670–690 cm^{-1}, due mainly to the out-of-plane γ(CH) deformations of the hydrogens at the end α and ω positions of the π-conjugated skeleton. The five to six bands observed in the 780–840 cm^{-1} region have been assigned to υ(NS) stretching of the thiadiazole rings.



35



36

10.03.4 Thermodynamics and Aromaticity

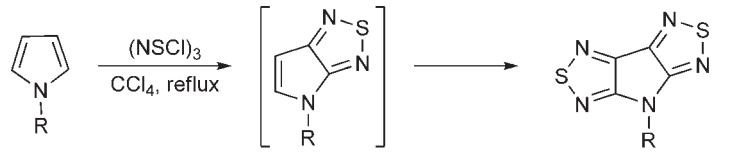
There is nothing to report in this area since CHEC-II(1996).

10.03.5 Reactivity of Fully Conjugated Ring Systems

In CHEC-II(1996) <1996CHEC-II(7)89> only one system, the thieno[2,3-*d*]-1,2,3-dithiazole, was covered in this section. Since then, there have been more examples of reactions of fully conjugated 5-5 fused heterocycles of the type being considered in this chapter. Although the number of examples of these systems has increased, most of the studies have been carried out on their synthesis rather than on their reactions.

10.03.5.1 Pyrrolo[2,3-*c*]-1,2,5-thiadiazoles

When N-substituted pyrrole **37** and trithiazyl trichloride $(NSCl)_3$ are heated at reflux in carbon tetrachloride, 7*H*-pyrrolo[2,3-*c*:4,5-*c*′]bis[1,2,5]thiadiazole **39** is formed <1997J(P1)2695>. *N*-Substituted pyrrolo[2,3-*c*]-1,2,5-thiadiazole **38** is believed to be an intermediate in this reaction (Equation 2). The enamine character of the carbon–carbon double bond of **38** is presumed to be enhanced compared to pyrrole **37**, rendering **38** more reactive toward $(NSCl)_3$.



37
a: R = Me
b: R = Ph

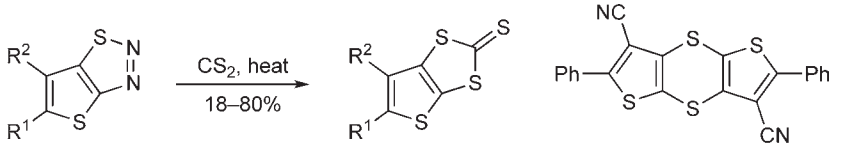
38
a: R = Me
b: R = Ph

39
a: R = Me, 31%
b: R = Ph, 43%

(2)

10.03.5.2 Thieno[2,3-*d*]-1,2,3-thiadiazoles

Thieno[2,3-*d*]-1,2,3-thiadiazoles **40a–f** heated with CS_2 in a double compartment autoclave produced thieno[2,3-*d*]-1,3-dithiol-2-thiones **41a–f** <2001MOL145>. In addition to the thermolysis product **41e**, thieno[2,3-*d*]-1,2,3-thiadiazoles **40e** also produced bisthieno[2,3-*b*:2′,3′-*e*][1,4]dithiine **42** in 36% yield (Equation 3).



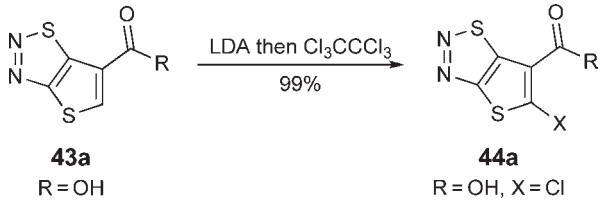
40
a: R^1 = H, R^2 = H
b: R^1 = Cl, R^2 = H
c: R^1 = Me, R^2 = H
d: R^1 = Ph, R^2 = H
e: R^1 = Ph, R^2 = CN
f: R^1 = CO_2Et, R^2 = Me

41
a: R^1 = H, R^2 = H
b: R^1 = Cl, R^2 = H
c: R^1 = Me, R^2 = H
d: R^1 = Ph, R^2 = H
e: R^1 = Ph, R^2 = CN
f: R^1 = CO_2Et, R^2 = Me

also **42** (36% from **40e**)

(3)

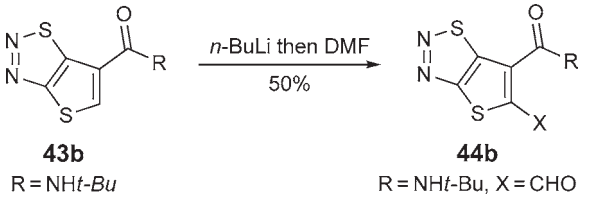
Different functional groups can be introduced at the 5-position of thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylates **43a** and **43b** by lithiation and subsequent reaction with the desired electrophile <1999JPR341>. For example, reaction of carboxylic acid **43a** with lithium diisopropylamide (LDA) followed by Cl_3CCCl_3 produced the 5-chloro product **44a** while amide **43b** treated with *n*-BuLi then dimethylformamide (DMF) gave aldehyde **44b** (Equations 4 and 5).



43a
R = OH

44a
R = OH, X = Cl

(4)

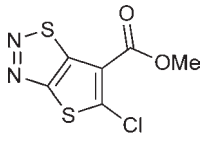


43b
R = NH*t*-Bu

44b
R = NH*t*-Bu, X = CHO

(5)

Compound **45** is susceptible to nucleophilic aromatic substitution at position 5 due to the highly electron-poor thiadiazole ring in addition to the effect of the ester functionality.

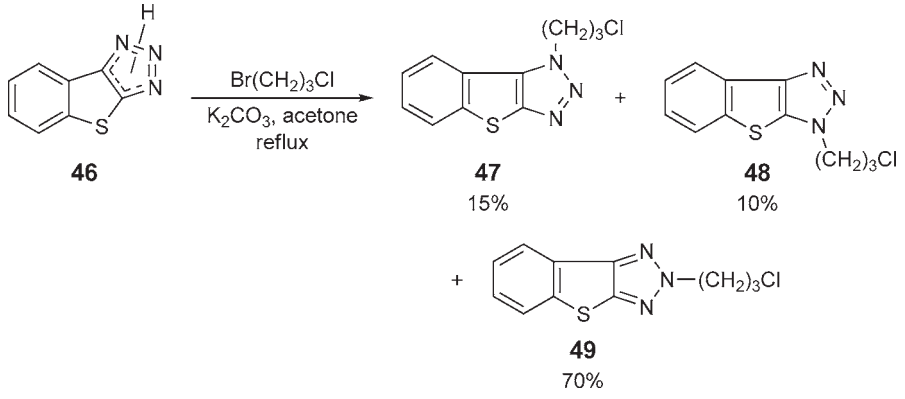


45

Nucleophiles such as benzylthiol, pyrrolidine, and morpholine effected substitution in 75–87% yields, whereas oxygen nucleophiles like methanol gave unsatisfactory results.

10.03.5.3 Thieno[2,3-*d*]-1,2,3-triazoles

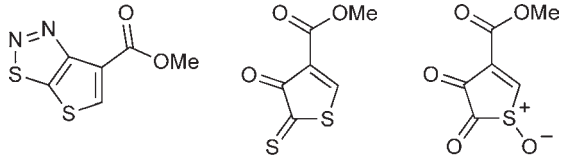
Treatment of thieno[2,3-*d*]-1,2,3-triazole **46** with alkyl halides gives alkylation at positions 1, 2, and 3 (Equation 6). Reaction of **46** with $Br(CH_2)_3Cl$ and K_2CO_3 in refluxing acetone gave a mixture of alkylated products **47–49** <1999JHC549>.



46 → $Br(CH_2)_3Cl$, K_2CO_3, acetone, reflux → **47** 15% + **48** 10% + **49** 70% (6)

10.03.5.4 Thieno[3,2-*d*]-1,2,3-thiadiazoles

Methyl thieno[3,2-*d*][1,2,3]thiadiazole-6-carboxylate (MTTC) **50** has been shown to deactivate the P450 enzyme-catalyzed oxidation of 1-phenylethanol to acetophenone <1997B7209>. It was postulated that this was due to preferential enzymatic oxidization of MTTC. GC-MS analysis of the enzymatic oxidation products of compound **50** showed the major product to have a molecular mass of 188. Compounds **51** or **52** are possible structures assigned to this molecular mass although no other analytical method had been used for confirmation.

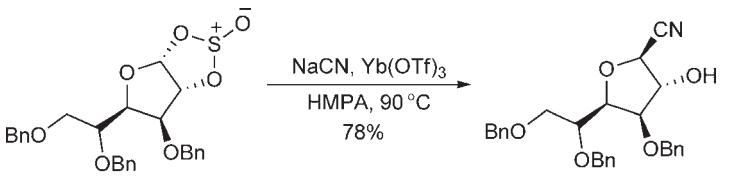


50 **51** **52**

10.03.6 Reactivity of Nonconjugated Ring Systems

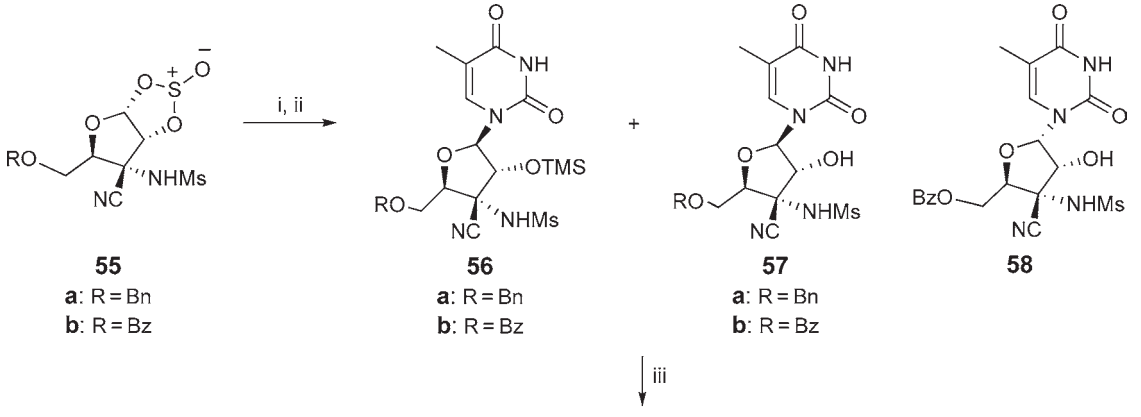
10.03.6.1 Furo[2,3-*d*]-1,3,2-dioxathioles

As outlined in CHEC-II(1996) <1996CHEC-II(7)89>, furo[2,3-*d*]-1,3,2-dioxathioles are used mainly in the synthesis of glycosides. Position 3*a* of these systems is susceptible to nucleophilic attack. Ytterbium-catalyzed cyanation of sulfite **53** using NaCN and $Yb(OTf)_3$ in hexamethylphosphoramide (HMPA) at 90 °C produced glycosyl cyanide **54** (Equation 7) <2004OL3913>.



53 54 (7)

N-Glycosylation of sulfites **55a** and **55b** using silylated thymine in dry conditions at 125 °C yielded a mixture of 2′-*O*-silylated and 2′-hydroxy-5-methyluridine derivatives **56a** and **56b**, and **57a** and **57b**, respectively (**Scheme 2**). Subjecting these mixtures to desilylation conditions tetrabutylammonium fluoride, methanol (TBAF, MeOH), gave 2′-hydroxy-5-methyluridine derivatives **57a** and **57b**. Additionally, epimer **58** was produced as a minor product (13.5%) of N-glycosylation of 5-*O*-benzoylated compound **55b** <2005JME4276>.

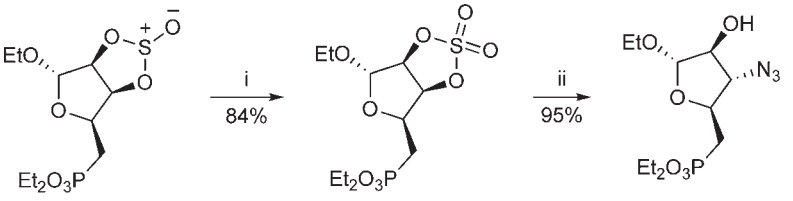


55 **a**: R = Bn **b**: R = Bz; **56** **a**: R = Bn **b**: R = Bz; **57** **a**: R = Bn **b**: R = Bz; **58**

Scheme 2

10.03.6.2 Furo[3,4-*d*]-1,3,2-dioxathioles

Oxidation of sulfite **59** using $RuCl_3$ and $NaIO_4$ yielded the cyclic sulfate **60** which is now susceptible to nucleophilic attack. Treatment of **60** with NaN_3 followed by acid hydrolysis of the intermediate 2-sulfate afforded the *trans*-3-azido-2-hydroxy derivative **61** (**Scheme 3**) <1997JOC4277>.



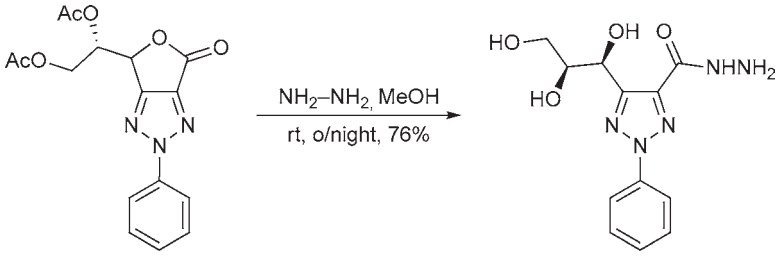
59 **60** **61**

i, $RuCl_3$, $NaIO_4$, rt, 2.5 h; ii, NaN_3, DMF, 60 °C, 2.5 h then H_2SO_4, H_2O, THF, rt, 2 h

Scheme 3

10.03.6.3 Furo[3,4-*d*]-1,2,3-triazoles

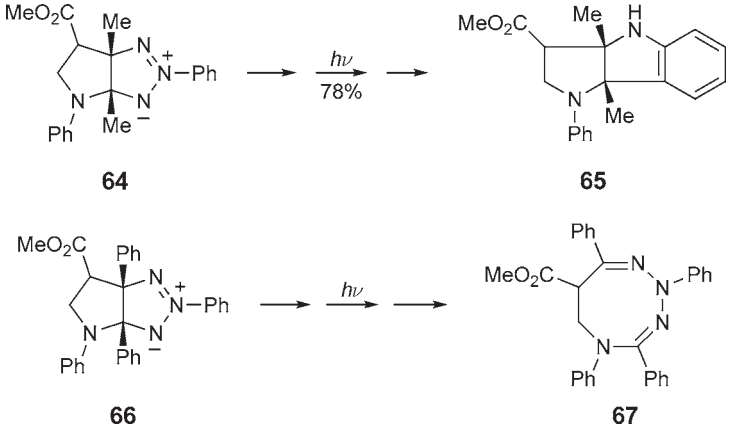
Treatment of 6-(1,2-diacetoxyethyl)-2-phenyl-2,6-dihydro-4*H*-furo[3,4-*d*]-1,2,3-triazol-4-one **62** with hydrazine hydrate in methanol resulted in opening of the lactone ring accompanied by deacetylation to produce compound **63** (Equation 8) <2000JIC168>.



62 **63** (8)

10.03.6.4 Pyrrolo[2,3-*d*]-1,2,3-triazoles

Although structurally similar, different hexahydropyrrolotriazoles are known to give quite different products on irradiation with UV light. Compound **64** underwent a series of sequential photochemical transformations to produce saturated pyrrolo[3,2-*b*]indole **65** when irradiated with UV light <1996CC945> (*cf.* **Scheme 1**). Irradiation of compound **66**, however, led to photo-induced disrotatory ring expansion yielding the 1,2,3,5-tetrazocine **67** (**Scheme 4**) <2003ARK110, 1995JCM438>.



64 **65**

66 **67**

Scheme 4

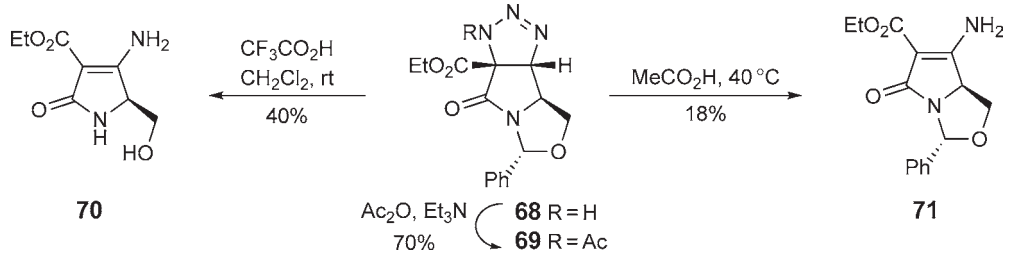
10.03.6.5 Pyrrolo[3,4-*d*]-1,2,3-triazoles

Pyrazoline **68** is converted into the *N*-acetyl derivative **69** by treatment with acetic anhydride and triethylamine at −5 °C (**Scheme 5**). Treatment of **68** with acetic acid at 40 °C caused decomposition of the dihydrotriazole ring to give the enamine **71** <1997TL5891>. Treatment with trifluoroacetic acid in dichloromethane at room temperature, however, caused decomposition of both the dihydrotriazole and the oxazolidine rings yielding the pyroglutaminol **70** <2001J(P1)2997>.

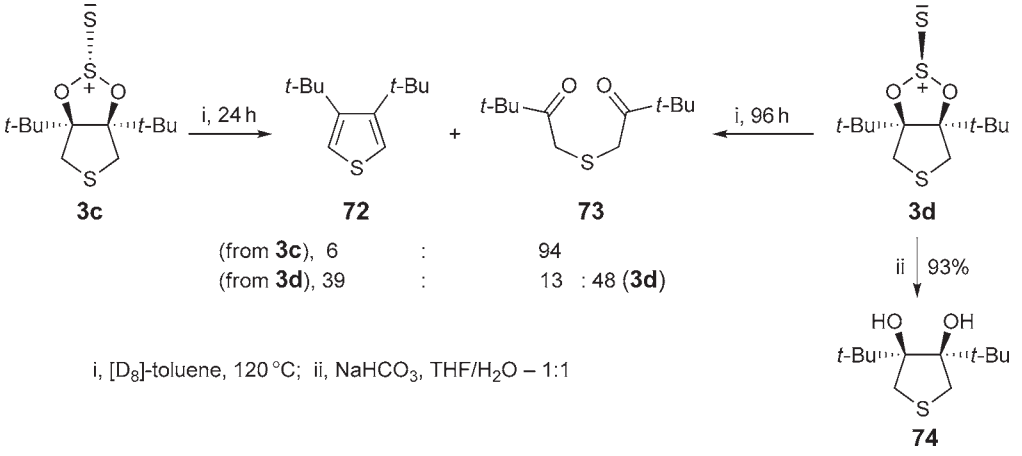
10.03.6.6 Thieno[3,4-*d*]-1,3,2-dioxathioles

Thermolysis of thionosulfite **3c** was performed by heating in [D_8]-toluene at 120 °C for 24 h. This gave thiophene **72** and sulfide **73** in a ratio of 6:94. On the other hand, heating diastereomer **3d** in [D_8]-toluene at 120 °C for 96 h gave a mixture of starting material **3d**, and decomposition products **72** and **73** in a ratio of 48:39:13. $NaHCO_3$ in a 1:1 mixture of H_2O and tetrahydrofuran (THF) hydrolyzed **3d** to the diol 74 (**Scheme 6**) <2003JA9024>.

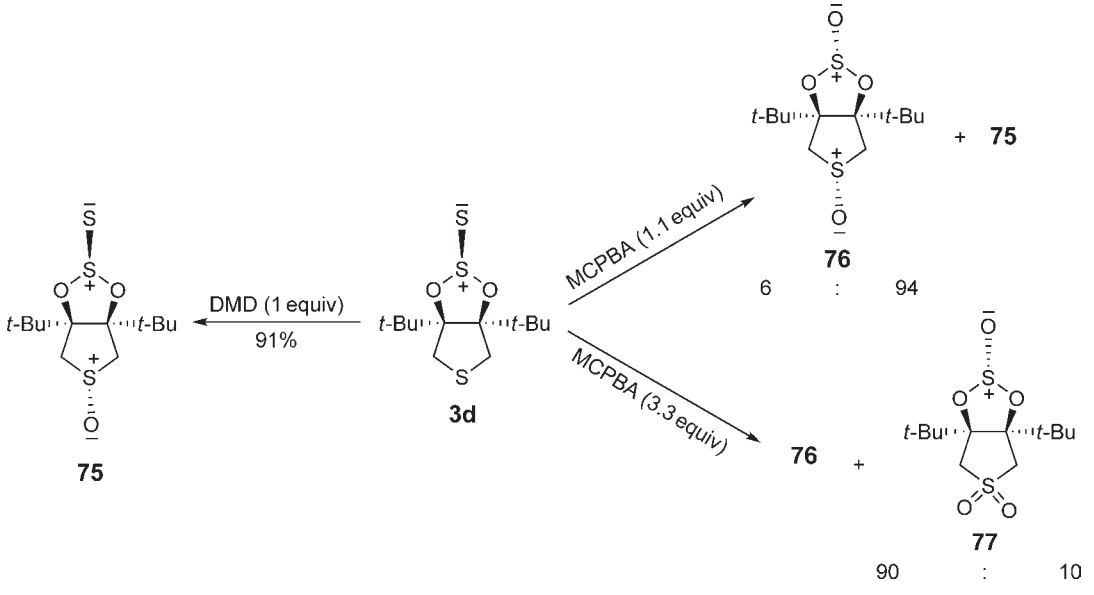
Subjecting thionosulfite **3d** to different oxidizing agents had varying results (**Scheme 7**). Dimethyldioxirane (DMD) (1 equiv) gave the sulfoxide **75** while 1.1 equiv of *m*-chloroperbenzoic acid (MCPBA) gave compounds **75** and **76** in a ratio of 94:6. An excess of MCPBA (3.3 equiv) produced a mixture of **76** and **77** (ratio 90:10). Treatment of **3c** with 1 equiv of DMD afforded **78** (Equation 9) <2005HCA1451>.



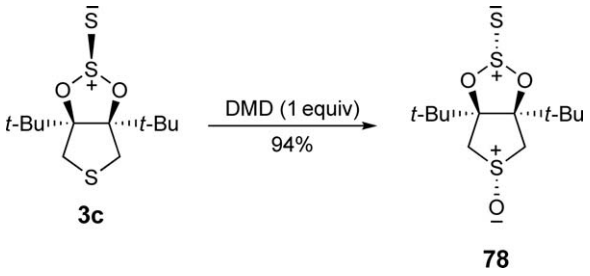
Scheme 5



Scheme 6



Scheme 7



3c 78 (9)

10.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

There is nothing to report in this area since the publication of CHEC-II(1996).

10.03.8 Reactivity of Substituents Attached to Ring Heteroatoms

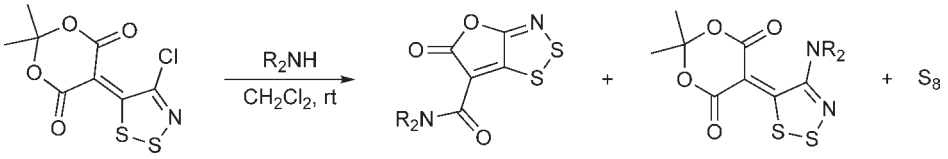
There is nothing to report in this area since the publication of CHEC-II(1996).

10.03.9 Ring Synthesis Classified by the Number of Ring Atoms in Each Component

10.03.9.1 Synthesis of the Second Heterocyclic Ring from [5+0] Atom Fragments

10.03.9.1.1 Furo[2,3-*d*]-1,2,3-dithiazoles

Reaction of Meldrum's acid derivative **25** with secondary alkylamines in dichloromethane at room temperature afforded a mixture of compounds, including furo[2,3-*d*]-1,2,3-dithiazoles **26**, the novel Meldrum's acid derivatives **79a–g**, and sulfur (**Scheme 8** and **Table 1**). Usually the reaction time is less than 6 h with yields of approximately 20%. Of note is the fact that cyclic amines such as piperidine and pyrrolidine do not produce furo[2,3-*d*]-1,2,3-dithiazoles in this way <2000J(P1)3107>.



25 26 79

Scheme 8

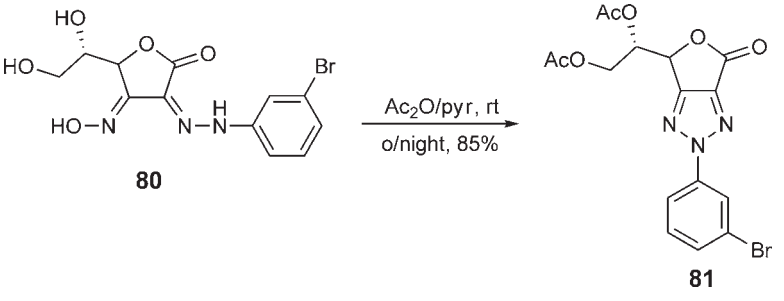
10.03.9.1.2 Furo[3,4-*d*]-1,2,3-triazoles

Boiling oxime-hydrazone **80** in acetic anhydride resulted in derivatization as well as cyclization forming the furanotriazole **81** (Equation 10) <1999JCM296>.

Table 1 Quantities of reactants, reaction times, yields of compounds **26**, **79**, sulfur (**Scheme 8**)

				Yield[a] (%)			
Entry	**25** (*mmol*)	R_2NH (*mmol*)	*Time*	**26**	**79**	S_8	*Reference*
a	0.776	R = Et 1.64	1 h	22	1	10	
b	0.826	R = *n*-Pr 1.68	1 h	22	3	8	2000J(P1)3107
c[b]	0.808	R = *i*-Pr 1.64	5 days	19	0	10	
d	0.694	R = *n*-Bu 1.42	80 min	24	4	11	
e[c]	0.740	R = *i*-Bu 1.55	5 h	2	60	6	
f	0.794	R = *n*-pentyl 1.63	1 h	28	0	6	
g	0.747	R = allyl 1.54	22 h	20	4	17	

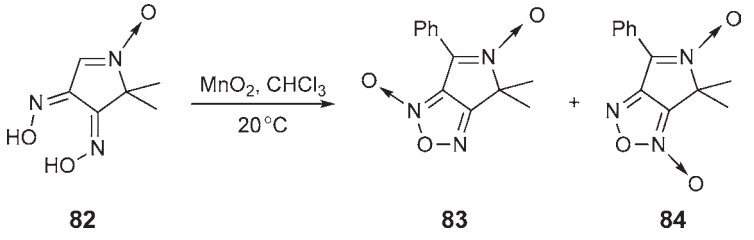
[a]Isolated yields.
[b]Compound **25** (10%) recovered.
[c]Compound **25** (22%) recovered.



(10)

10.03.9.1.3 Pyrrolo[3,4-*c*]-1,2,5-oxadiazoles

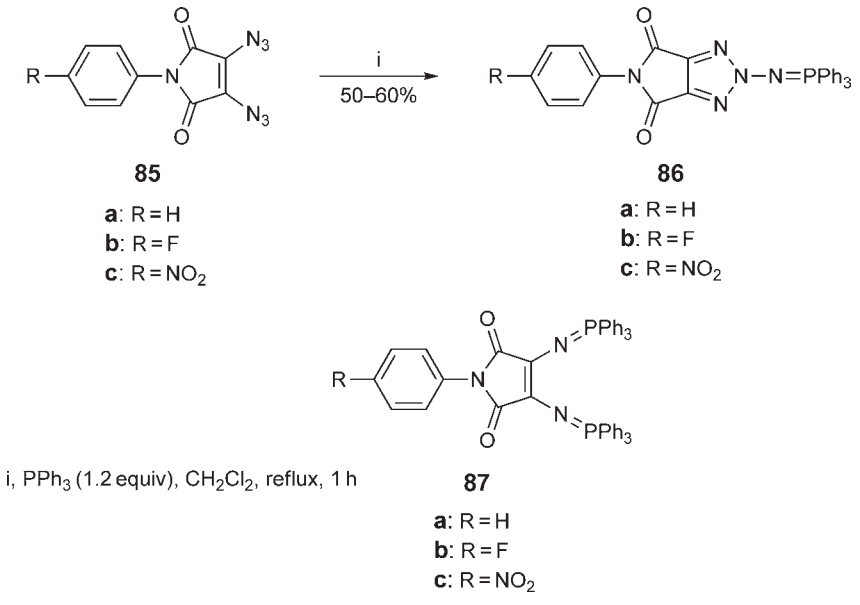
Dihydropyrrole *N*-oxide **82**, when oxidized by MnO_2 in $CHCl_3$ at 20 °C for 1 h, yielded a mixture of pyrrolo-oxodiazoles **83** and **84** in a 1:1 ratio. The ratio changed with time in favor of isomer **83**; for example, after 2 h the ratio was 1.5:1 <2001RCB874>.



(11)

10.03.9.1.4 Pyrrolo[3,4-*d*]-1,2,3-triazoles

Vicinal diazides **85a–c**, prepared by the action of sodium azide on the corresponding 3,4-dichloromaleimide, react with triphenylphosphine in refluxing dichloromethane to give 2-amino-1,2,3-triazole derivatives **86a–c** (**Scheme 9**). The stable di-Staudinger side products **87a–c** are also produced from the reaction <2005JCX385>.

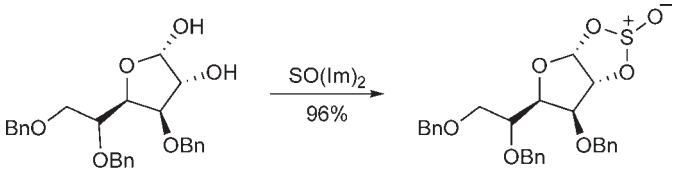


Scheme 9

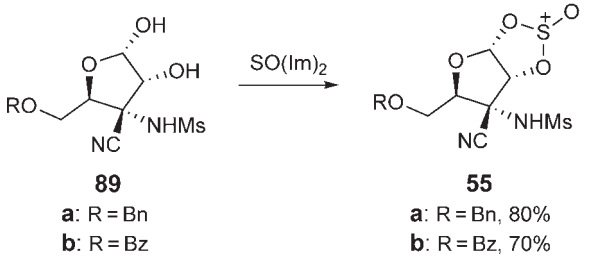
10.03.9.2 Synthesis of the Second Heterocyclic Ring from [4+1] Atom Fragments

10.03.9.2.1 Furo[2,3,-*d*]-1,3,2-dioxathioles

$SO(Im)_2$, generated from thionyl chloride and imidazole, is quite effective in the formation of cyclic sulfites from 1,2-diols. For example, furo[2,3,-*d*]-1,3,2-dioxathiole **53** was produced by reacting $SO(Im)_2$ with diol **88**. In a similar reaction, compounds **89a** and **89b** yielded **55a** and **55b**, respectively (Equations 12 and 13) <2004OL3913, 2005JME4276>.



(12)

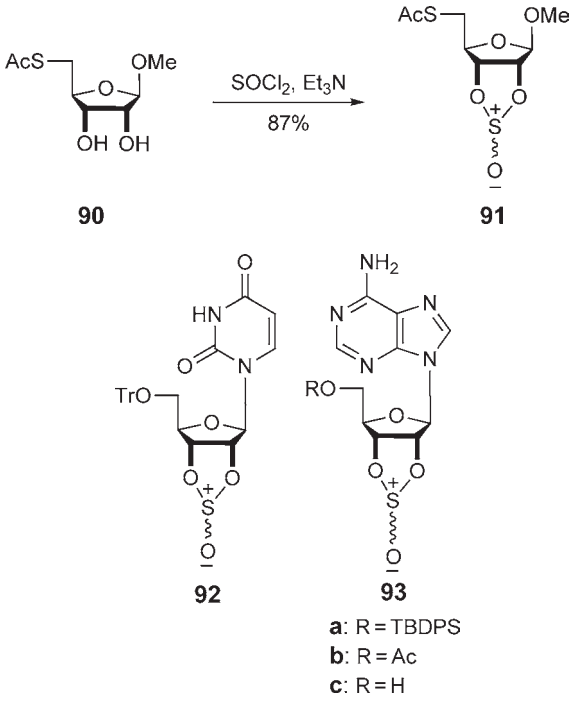


(13)

10.03.9.2.2 Furo[3,4-*d*]-1,3,2-dioxathioles

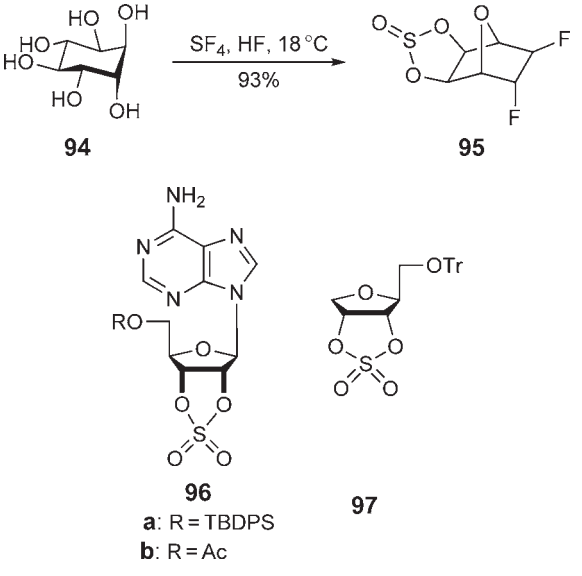
Cyclic sulfites are conveniently synthesized from vicinal diols using thionyl chloride at temperatures between −25 °C and 0 °C. Sulfite **91** was produced from diol **90** using $SOCl_2$ and triethylamine in THF at −20 °C <2001S229>. Pyridine and $SOCl_2$ in THF at −20 °C was used to produce uridine cyclic sulfite **92** from the corresponding diol in 83% yield <1996JOC7426>. Ribonucleoside cyclic sulfites **93a** and **93b** were prepared using thionyl chloride in the absence of base. Treatment of the corresponding diol with $SOCl_2$ in acetonitrile at 0 °C gave **93a** and **93b** in 67% and

81% yield, respectively. The less reactive thionyl fluoride can also be used to form cyclic sulfites from vicinal diols. To produce **93c** from the corresponding triol without replacement of the 5′ hydroxyl group with chloride, SOF_2 in acetonitrile was used to effect cyclization. Adenosine cyclic sulfite **93c** was obtained in 72% yield (Equation 14) <1998JOC7375>.



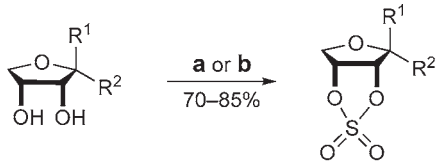
(14)

Inositol **94** when reacted with liquefied sulfur tetrafluoride and hydrogen fluoride at 18 °C produced 7-oxabicyclo[2.2.1]heptane cyclic sulfite **95** <2002JFC(115)13>. Cyclic sulfates are produced efficiently by oxidation of cyclic sulfites. The Sharpless oxidation <1988JA7538> using sodium iodate and ruthenium chloride is the most common procedure used to effect this transformation. For example, cyclic sulfite **93a** and **93b** treated with $NaIO_4$ and $RuCl_3{\cdot}3H_2O$ in acetonitrile at 0 °C produced the cyclic sulfates **96a** and **96b** in 90% and 83% yield, respectively <1998JOC7375>. Sulfate **97** was produced from the corresponding sulfite in 88% yield under similar conditions (Equation 15) <2003TL3771>.



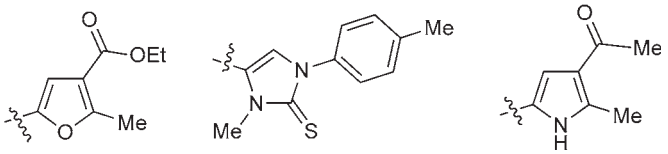
(15)

Cyclic sulfates can be made directly from vicinal diols using sulfuryl chloride. Diols **98–101** treated with SO_2Cl_2 formed the cyclic sulfates **103–105**, respectively, in good yield (**Scheme 10**). Diol **102** gave a complex mixture when reacted with SO_2Cl_2. The desired sulfate **107** was obtained in high yield using sulfuryl diimidazole <2002JOC2577>.



98: R^1 = Fur, R^2 = H
99: R^1 = H, R^2 = Fur
100: R^1 = Imi, R^2 = H
101: R^1 = H, R^2 = Imi
102: R^1 = Pyrr, R^2 = H

103: R^1 = Fur, R^2 = H; 85%
104: R^1 = H, R^2 = Fur; 72%
105: R^1 = Imi, R^2 = H; 70%
106: R^1 = H, R^2 = Imi;
107: R^1 = Pyrr, R^2 = H; 87%



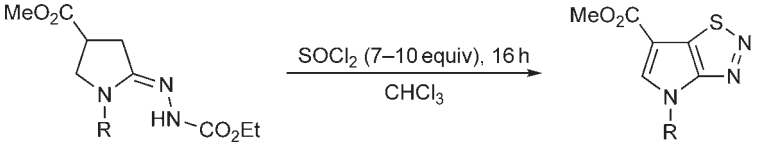
(Fur) (Imi) (Pyrr)

a for cpds. **98–101**: Cl_2SO_2/Et_3N, 0 °C, 3.5 h
b for cpd. **102**: i, NaH, DMF, 0 °C, 30 min; ii, Im_2SO_2, DMF, −40 °C, 1 h

Scheme 10

10.03.9.2.3 Pyrrolo-[2,3-*d*]-1,2,3-thiadiazoles

Pyrrolidine semicarbazones **108a** and **108b**, treated with excess thionyl chloride (Hurd–Mori reaction) in chloroform, produced pyrrolothiadiazoles **109a** and **109b**, respectively (Equation 16).



(16)

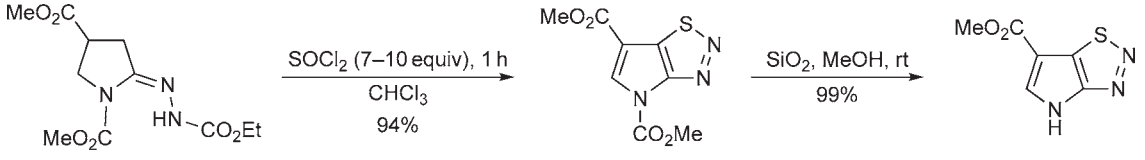
108

a: R = Bn
b: R = Me

109

a: R = Bn, 25%
b: R = Me, 15%

Changing the substituent at the nitrogen atom of the pyrrolidine ring to a methyl carboxylate group significantly increases the yield of the reaction and reduces reaction time. Compound **110** was thus converted to **111** in very good yield in 1 h allowing the convenient production of methyl pyrrolo-[2,3-*d*]-1,2,3-thiadiazole-6-carboxylate **112** on treatment of **111** with SiO_2 and methanol at room temperature for 3 days (**Scheme 11**) <2005MOL367>.

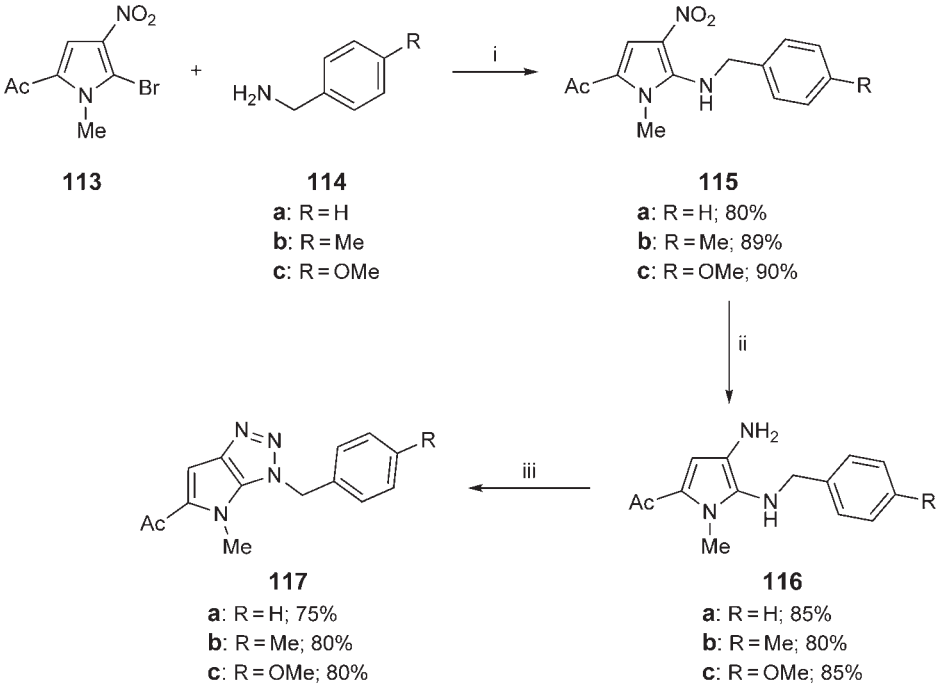


110 **111** **112**

Scheme 11

10.03.9.2.4 Pyrrolo-[2,3-*d*]-1,2,3-triazoles

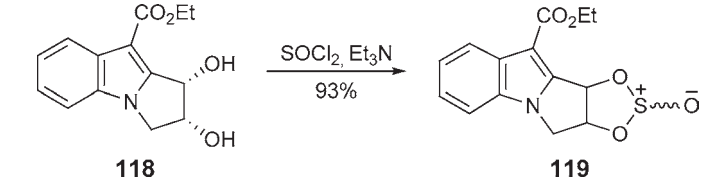
Scheme 12 shows a convenient method for producing pyrrolo[2,3-*d*]-1,2,3-triazoles from halonitropyrroles. Novel direct nucleophilic substitution of 2-bromo-3-nitropyrrole **113** by benzylamines **114a–c** gave the 2-amino-3-nitropyrroles **115a–c** in good yield. Reduction of the nitro group afforded the diaminopyrroles **116a–c** which on treatment with HNO_2 ($NaNO_2$ and AcOH) at −4 °C for 12 h installed the triazole ring **117a–c**. Diazotization using sodium nitrite and 6 M HCl instead of AcOH led to a complex mixture of products <1998H(48)1229>.



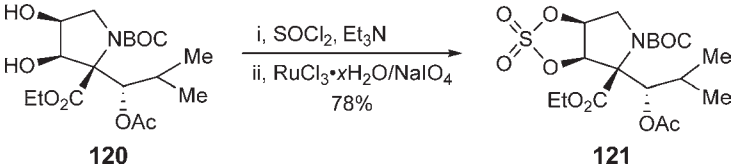
Scheme 12

10.03.9.2.5 Pyrrolo[3,4-*d*]-1,3,2-dioxathioles

The common theme of forming cyclic sulfites and cyclic sulfates from vicinal diols has also been applied in the synthesis of pyrrolo[3,4-*d*]-1,3,2-dioxathioles. Diol **118** was converted to the sulfite **119** by reaction with $SOCl_2$ and Et_3N in CH_2Cl_2 at −15 °C (Equation 17) <2001TL7513>. Similar treatment of dihydroxypyrrolidine **120**, followed by oxidation of the intermediary sulfite with $RuCl_3.xH_2O$ and $NaIO_4$, afforded the cyclic sulfate **121** (Equation 18) <2004AGE2293, 2005CEJ4227>.



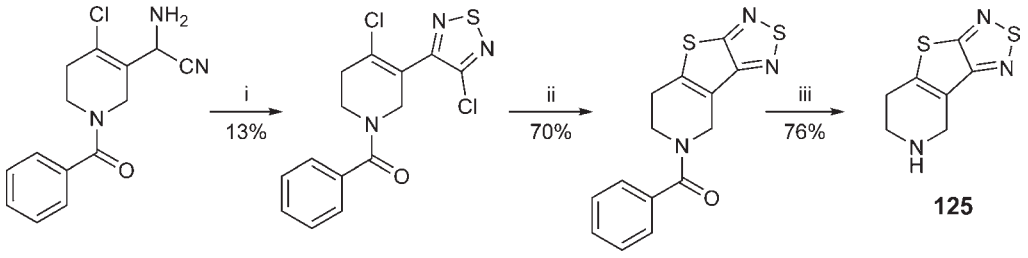
(17)



(18)

10.03.9.2.6 Thieno[2,3-*c*]-1,2,5-thiadiazoles

Synthesis of 5,6,7,8-tetrahydro[1,2,5]thiadiazolo[3′,4′:4,5]thieno[3,2-*c*]pyridine **124** was accomplished starting with α-aminonitrile **122** (**Scheme 13**). Compound **122** when reacted with sulfur monochloride produced thiadiazole **123**, although in low yield. Double halogen substitution using sodium hydrogen sulfide yielded thienothiadiazole **124** which when subjected to refluxing conc. HCl underwent cleavage of the amide bond affording compound **125** <1998JME109>.

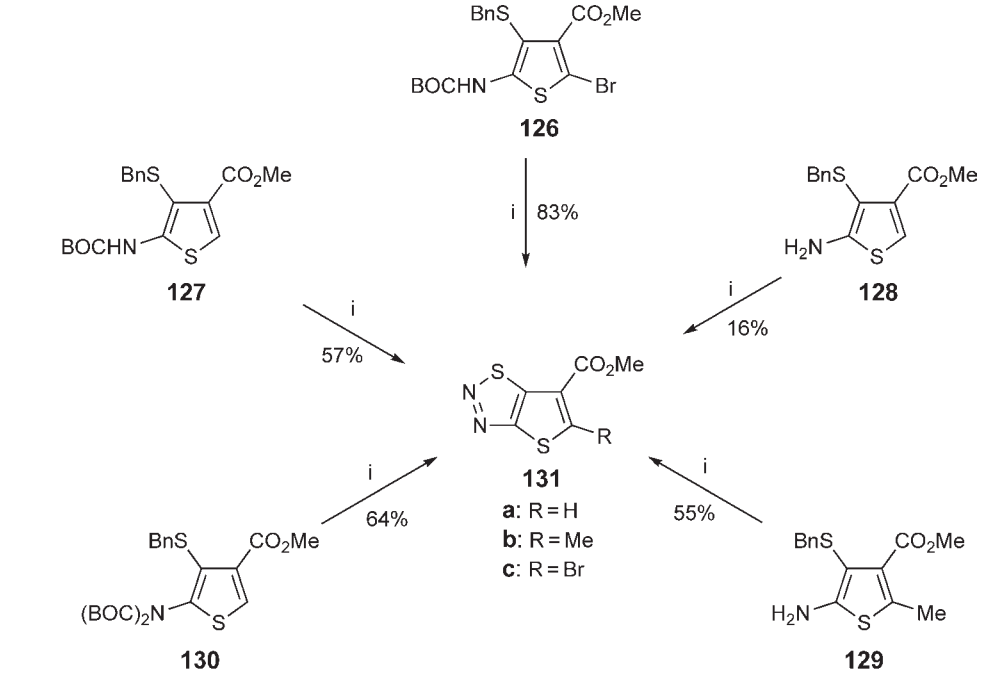


i, S_2Cl_2, DMF, rt, 8 h; ii, NaSH, DMF, K_2CO_3, rt, 3 h; iii, conc. HCl, reflux, 16 h

Scheme 13

10.03.9.2.7 Thieno[2,3-*d*]-1,2,3-thiadiazoles

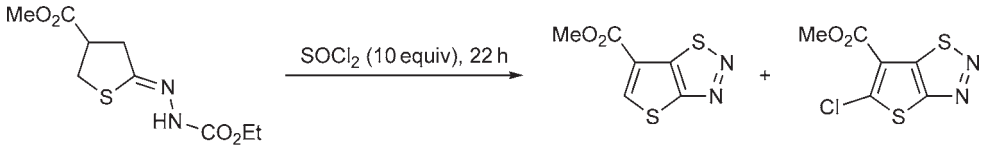
Diazotization of aminothiophene and the Hurd–Mori reaction <1955JA5359> are two popular methods for synthesis of thieno[2,3-*d*]-1,2,3-thiadiazoles. Amine **128** gave only a poor yield of methyl thieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylate **131a** when subjected to acidic diazotization conditions (**Scheme 14**). The fully substituted thiophenes **129** and **126** underwent cyclization in much greater yields under similar conditions <1999M573>. Protected amines **127** and **130** also gave a better yield of the cyclized product than the unprotected amine **128** <1999JHC761>.



i, HCl/AcOH (1:1), $NaNO_2$ (aq), <10 °C

Scheme 14

Carbazonate **132** treated with $SOCl_2$ at 25 °C (in CH_2Cl_2) gave a mixture of thienothiadiazole **131** and methyl 5-chlorothieno[2,3-*d*]-1,2,3-thiadiazole-6-carboxylate **133** in a 8:1 ratio (Equation 19). Increasing the temperature of the reaction to 80 °C ($C_2H_4Cl_2$) produced **131** as the sole product <1998J(P1)853, 1998PSI316>. As shown in **Table 2**, the yield of **131** was 60% or greater in each case.



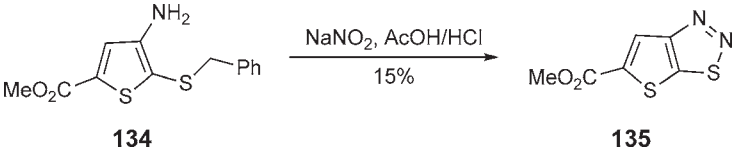
132 **131** **133** (19)

Table 2 Effects of temperature on Hurd–Mori reaction

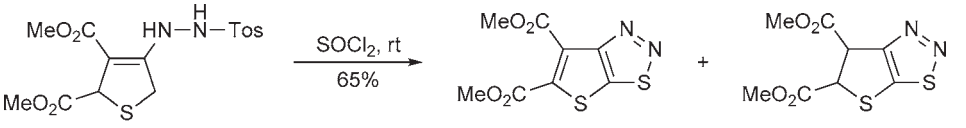
Solvent	*Temp.* (°*C*)	*Ratio* (**131**:**133**)	*Yield of* **131** (%)	*Reference*
CH_2Cl_2	25	8 : 1	60	
$C_2H_4Cl_2$	80	1 : 0	66	1998J(P1)853

10.03.9.2.8 Thieno[3,2-*d*]-1,2,3-thiadiazoles

As in the synthesis of thieno[2,3-*d*]-1,2,3-thiadiazoles, thieno[3,2-*d*]-1,2,3-thiadiazoles are made using diazotization of aminothio-substituted thiophenes and by Hurd–Mori reaction of hydrazones. Diazotization of compound **134** with $NaNO_2$ in AcOH/HCl at 0 °C produced methyl thieno[3,2-*d*]-1,2,3-thiadiazole-5-carboxylate **135** but in only low yield. Hydrazone tautomer **136** treated with excess $SOCl_2$ in CH_2Cl_2 at room temperature gave dimethyl thieno[3,2-*d*]-1,2,3-thiadiazole-5,6-dicarboxylate **137** and dimethyl 5,6-dihydrothieno[3,2-*d*]-1,2,3-thiadiazole-5,6-dicarboxylate **138** in a ratio of 3:2 (Equations 20 and 21) <1998H(48)259>.



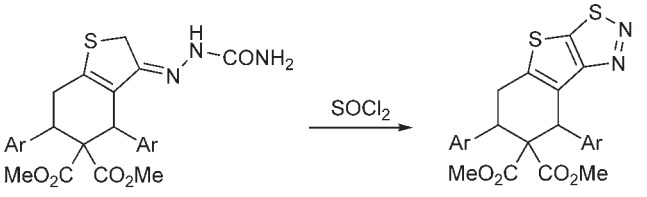
134 **135** (20)



136 **137** : **138** (21)

3 : 2

Tetrahydro[4,5]benzothieno[3,2-*d*][1,2,3]thiadiazole dicarboxylates **140a–c** were prepared by the standard Hurd–Mori reaction of the corresponding semicarbazones **139a–c** (Equation 22) <1998IJH259>. Compounds **141a–c**, under similar reaction conditions, produced benzothieno[2,3-*d*]-1′, 2′, 3′-thiadiazoles **142a–c** (Equation 23) <1999IJB308>.



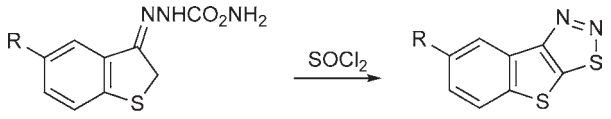
139

a: Ar = C_6H_5
b: Ar = 4-$MeOC_6H_4$
c: Ar = 4-ClC_6H_4

140

a: Ar = C_6H_5, 68%
b: Ar = 4-$MeOC_6H_4$, 65%
c: Ar = 4-ClC_6H_4, 71%

(22)



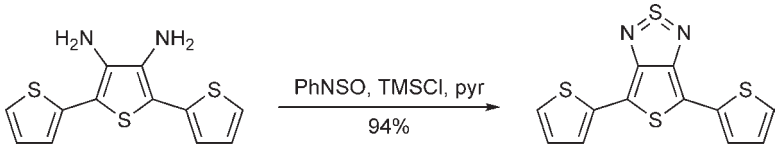
141
a: R = H
b: R = Me
c: R = Cl

142
a: R = H, 65%
b: R = Me, 70%
c: R = Cl, 68%

(23)

10.03.9.2.9 Thieno[3,4-*c*]-1,2,5-thiadiazoles

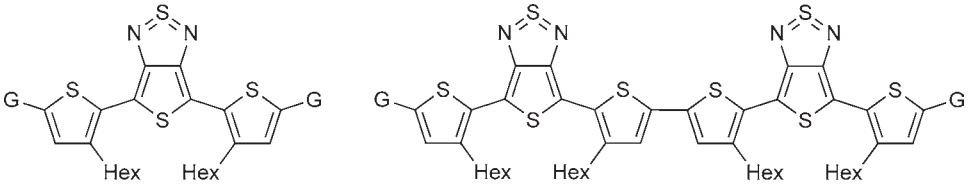
The reaction of an aryl-1,2-diamine with *N*-sulfinylaniline (PhNSO) and chlorotrimethylsilane in pyridine generates the 1,2,5-thiadiazole ring. Treatment of 2,2′:5′,2″-terthiophene-3′,4′-diamine **143** with PhNSO and chlorotrimethylsilane (TMSCl) in pyridine at room temperature for 1 h produced thieno[3,4-*c*]-1,2,5-thiadiazole **35** (Equation 24) <2004PCB2516>.



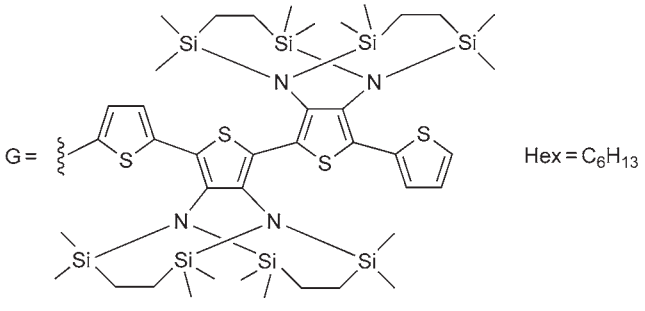
143 **35**

(24)

Oligothiophenes **144** and **145** were also prepared in an analogous reaction of the corresponding 3,4-diaminothiophene in 42% and 49% yields, respectively <2001SM(119)67>.



144 **145**



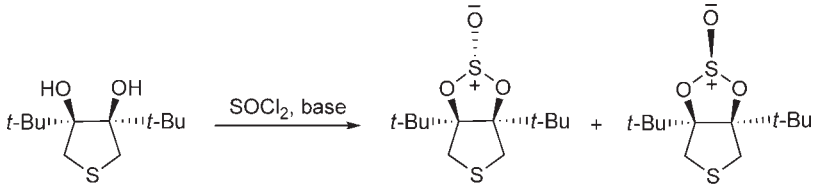
10.03.9.2.10 Thieno[3,4-*d*]-1,3,2-dioxathioles

The reaction of *cis*-3,4-di-*tert*-butylthiolone-3,4-diol **74** with thionyl chloride and base (triethylamine or pyridine) produced two diastereomeric cyclic sulfites **3a** and **3b**. The ratio of **3a** to **3b** is dependent on the solvent used (**Table 3**). These reactions are generally high yielding with a greater tendency for the formation of diastereomer **3a** (Equation 25) <2003HAC587>.

Table 3 Effect of the solvent on the ratio of **3a** : **3b** produced from **74**[a,b]

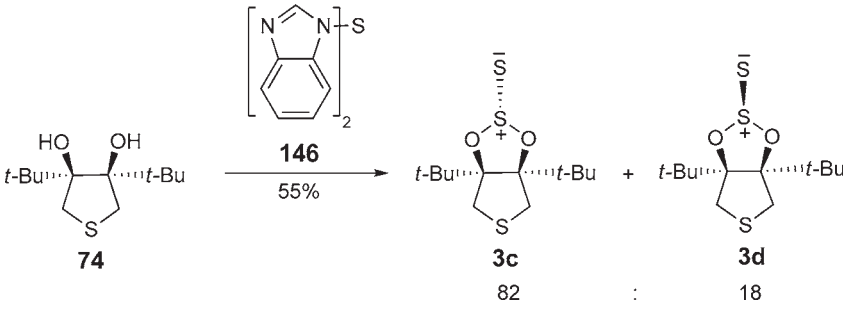
Solvent	*Yield (%)*[c]	**3a** : **3b**[d]	*Reference*
C_6H_6	91	90 : 10	
Et_2O	93	76 : 24	2003HAC587
CH_2Cl_2	95[e]	81 : 19	
CH_3CN	38[f]	79 : 21	

[a]Pyridine (4 equiv) used as base.
[b]The reaction was carried out at room temperature for 24 h.
[c]Isolated yields.
[d]The ratios determined by ^{1}H NMR analysis.
[e]The use of 2 equiv of pyridine gave **3a** and **3b** in the ratio 80:20 in 50% combined yield.
[f]**74** was recovered in 62% yield.



(25)

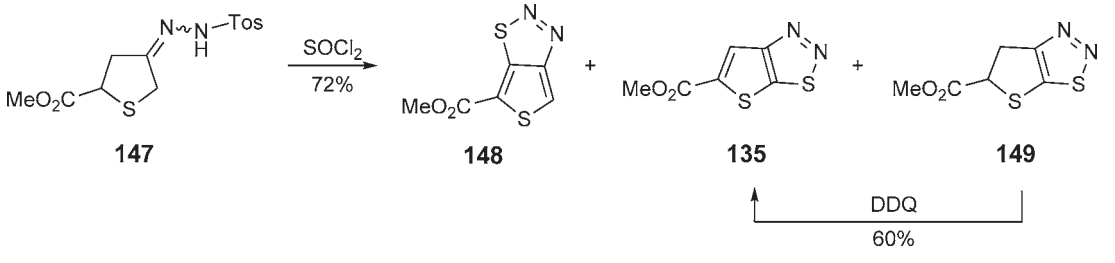
Diol **74** reacts with 4 equiv of 1,1′-thiobisbenzimidazole **146** in acetonitrile at room temperature to afford a diastereomeric mixture of thionosulfites **3c** and **3d** in the ratio 82:18. Attempts to make **3c** or **3d** by thionation of **3a** or **3b** using Lawesson's reagent were unsuccessful (Equation 26) <2003JA9024>.



(26)

10.03.9.2.11 Thieno[3,4-*d*]-1,2,3-thiadiazoles

Hurd–Mori reaction on hydrazone **147** produced methyl thieno[3,4-*d*]-1,2,3-thiadiazole-6-carboxylate **148** along with methyl thieno[3,2-*d*]-1,2,3-thiadiazole-5-carboxylate **135** and methyl 5,6-dihydrothieno[3,2-*d*]-1,2,3-thiadiazole-5-carboxylate **149** in a ratio of 1:2.6:0.5 (72% combined yield). Conversion of compound **149** to the fully aromatized **135** is accomplished by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene for 10 days (**Scheme 15**). A modified reaction mechanism for the Hurd–Mori reaction is also presented here <1998H(48)259>.

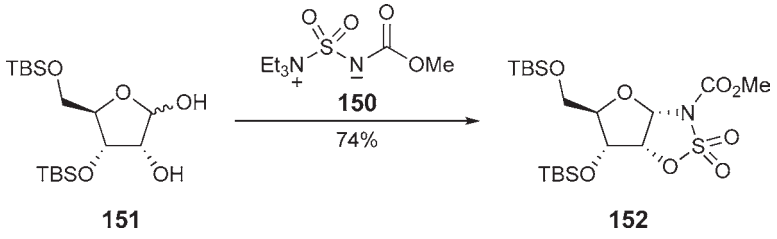


Scheme 15

10.03.9.3 Synthesis of the Second Heterocyclic Ring from [3+2] Atom Fragments

10.03.9.3.1 Furo[2,3-*d*]-1,2,3-oxathiazoles

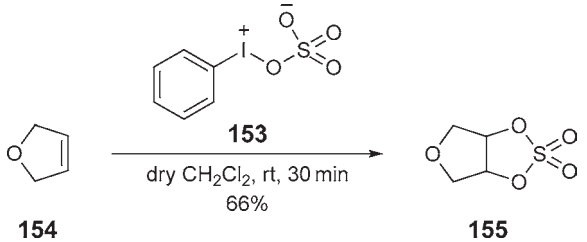
Burgess reagent **150** <1973JOC26> has been used to convert diols to sulfamidates. Heating furanose **151** with Burgess reagent **150** in THF/CH_2Cl_2 (4:1) at reflux for 6 h produced the sulfamidate **152** (Equation 27) <2004JA6234, 2004CEJ5581>.



151 **152** (27)

10.03.9.3.2 Furo[3,4-*d*]-1,3,2-dioxathioles

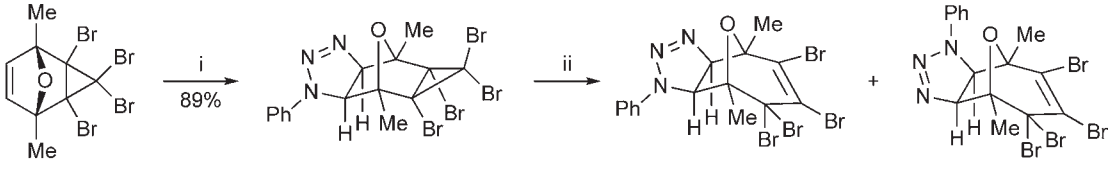
Reaction of iodosylbenzene with the dimethylformamide·sulfur trioxide adduct in dichloromethane at room temperature produces phenyliodosulfate **153** in quantitative yield. Phenyliodosulfate ($PhIOSO_3$) reacts with alkenes to form cyclic sulfates. For example, reaction with 2,5-dihydrofuran **154** in dry CH_2Cl_2 at room temperature produced tetrahydrofuro[3,4-*d*][1,3,2]dioxathiole 2,2-dioxide **155** (Equation 28) <2003TL1655>.



154 **155** (28)

10.03.9.3.3 Furo[3,4-*d*]-1,2,3-triazoles

Compound **156** (prepared by reaction of tetrabromocyclopropene and 2,5-dimethylfuran) underwent dipolar cycloaddition with phenyl azide to produce the fused triazole **157**. The reaction was carried out in dichloromethane at room temperature over 2 days. This lower reaction temperature allowed for the isolation of the adduct **157**, which was established by X-ray crystallographic analysis to be the product of *exo*-selective addition. Heating triazole **157** in benzene at reflux for 2 h resulted in ring expansion producing a 1:1 mixture of compounds **158** and **159** (**Scheme 16**) <2004JOC570>.



156 **157** **158** : **159**

i, PhN_3, CH_2Cl_2; ii, C_6H_6, reflux 1 : 1

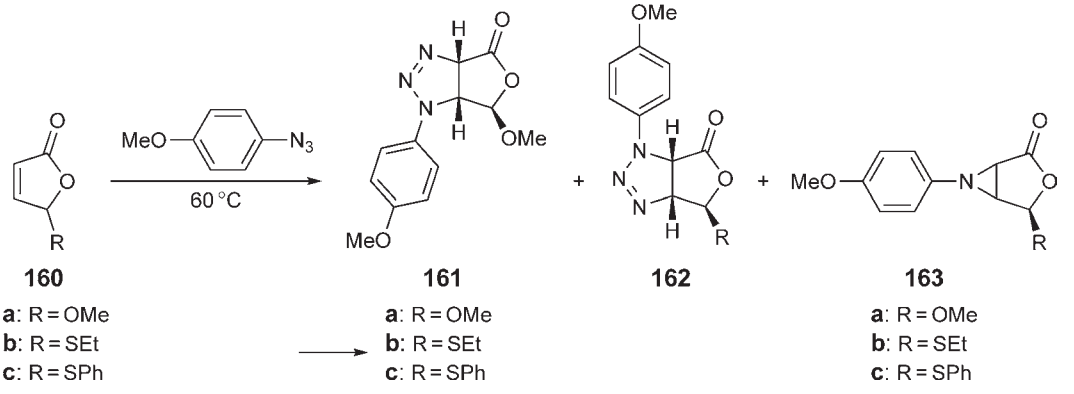
Scheme 16

Dipolar cycloaddition of *p*-methoxyphenyl azide with furanones **160a–c** conducted at 60 °C in an autoclave, in the absence of solvent, yielded the corresponding triazolines **161a–c**. The results and experimental conditions are given in **Table 4**. Only in the case of **160a** (R = OMe) were two isomeric triazolines formed (**Scheme 17**). The reactions

involving thioethers **160b** and **160c** were regiospecific. Under the reaction conditions, aziridines **163a** and **163c** were produced from **161a** and **161c**, respectively, by loss of molecular nitrogen. Compound **163b** was isolated on purification of the adduct by column chromatography. Similar cycloaddition reactions using *p*-nitrophenyl azide were also reported <2000H(52)237>.

Table 4 1,3-Dipolar cycloaddition of furanones **160a–c** with *p*-methoxyphenyl azide

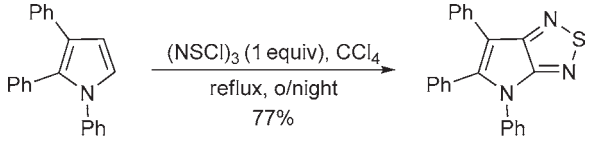
Furanone	*Time* (*h*)	*Conversion* (%)	*Triazoline* (%)	*Aziridine* (%)	*Reference*
160a	72	100	**161a**:**162** (78) 80:20	**163a** (22)	
160b	72	50	**161b** (100)	**163b** (31)	2000H(52)237
160c	96	60	**161c** (43)	**163c** (57)	



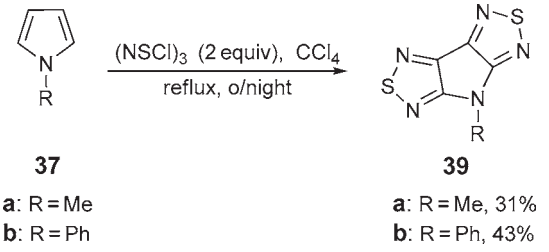
Scheme 17

10.03.9.3.4 Pyrrolo[2,3-*c*]-1,2,5-thiadiazoles

Trithiazyl trichloride – $(NSCl)_3$ – reacts with alkenes and alkynes to form 1,2,5-thiadiazoles. Heterocycles containing activated, unsubstituted C–C 'double bonds' react in a similar manner to alkenes. Heating 1,2,3-triphenylpyrrole **164** and 1 equiv of $(NSCl)_3$ in refluxing carbon tetrachloride overnight led to 4,5,6-triphenyl-4*H*-pyrrolo[2,3-*c*]thiadiazole **165**. Reaction of 1-methylpyrrole **37a** and 1-phenylpyrrole **37b** with 2 equiv of $(NSCl)_3$ under similar conditions gave pyrrolo-bisthiadiazoles **39a** and **39b**, respectively (Equations 29 and 30). Improved yields were obtained when brominated pyrroles were used in the reaction (**Table 5**) though increasing the number of bromine substituents did not improve the efficiency of the reaction <1997J(P1)2695>.

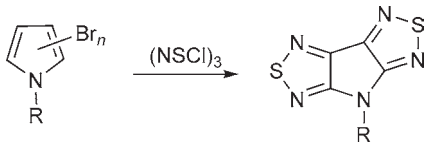


(29)



(30)

Table 5 Reaction of bromopyrroles with $(NSCl)_3$ (2 equiv) in refluxing carbon tetrachloride



R	*Pyrrole*	*Time (h)*	*Yield (%)*	*Reference*
Ph	2-Bromo[a]	2	42	
Ph	2-Bromo	4	75	
Ph	2,5-Dibromo	4	71	1997J(P1)2695
Ph	2,3,5-Tribromo	12	70	
Ph	2,3,4,5-Tetrabromo	12	62	
Me	2,5-Dibromo	4	74	

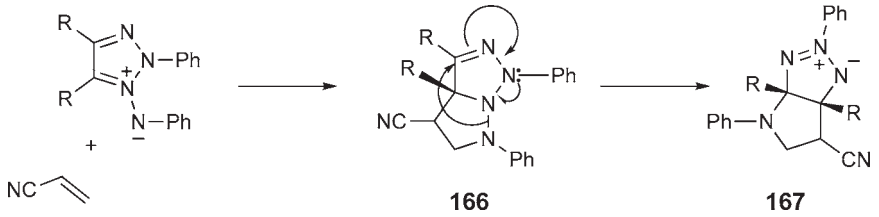
[a]1 equiv $(NSCl)_3$.

Note that for the pyrrole-$(NSCl)_3$ reactions outlined above, no 3,4-fused products are obtained. The 1,2,3-thiadiazole ring is always formed by fusion at the 2,3- and 4,5-bonds.

Treatment of benzofuran and benzothiophene with 2 equiv of $(NSCl)_3$ under these conditions resulted in no reaction. Indole, however, gave the expected 4*H*-[1,2,5]thiadiazolo[3,4-*b*] indole in 23% yield. It is suggested that benzofuran and benzothiophene are not sufficiently nucleophilic to undergo reaction with $(NSCl)_3$.

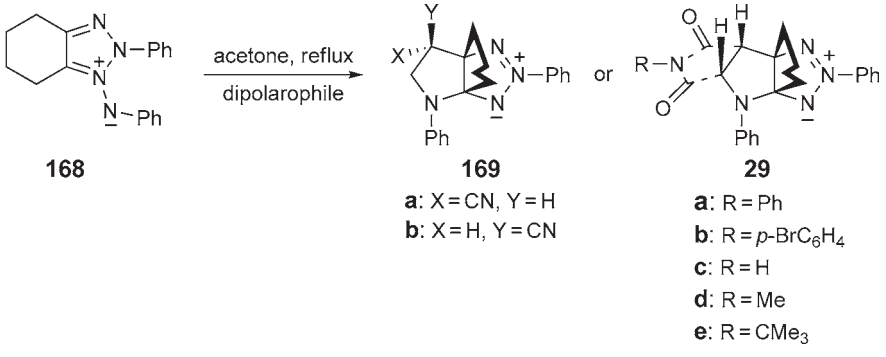
10.03.9.3.5 Pyrrolo[2,3-*d*]-1,2,3-triazoles

1,2,3-Triazolium-1-aminide 1,3-dipoles have been used extensively in the synthesis of pyrrolo-1,2,3-triazoles (**Scheme 18**). Dipolarophiles such as acrylonitrile, dimethyl acetylenedicarboxylate (DMAD), and maleimides are generally used to effect Huisgen cycloaddition <1992J(P1)1103> to give cycloadduct **166** which undergoes a 1,4-N → C rearrangement <2005HCA1611> to produce pyrrolo-1,2,3-triazole **167**.



Scheme 18

Heating of 1,2,3-triazolium-1-aminide **168** with acrylonitrile in dry acetone at reflux yielded a mixture of pyrrolo[2,3-*d*]-1,2,3-triazoles **169a** and **169b** (Equation 31), while similar reactions with different N-substituted maleimides produced only one product in each case. **Table 6** summarizes the results of these reactions <2001J(P1)1778>.

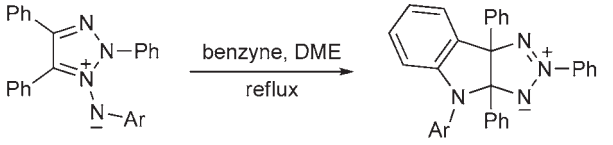


(31)

Table 6 Yields for reaction of 1,2,3-triazolium-1-aminide **168** with dipolarophiles

Dipolarophiles	*Product*	*Yield* (%)	*Reference*
Acrylonitrile	**169a**	10	
Acrylonitrile	**169b**	79	
Maleimide			2001J(P1)1778
R = Ph	**29a**	86	
R = *p*-BrC_6H_4	**29b**	90	
R = H	**29c**	78	
R = Me	**29d**	90	
R = CMe_3	**29e**	66	

Benzyne, generated *in situ* from anthranilic acid, has been successfully used as a dipolarophile in reaction with triazolium-1-aminides **170a** and **170b**. The reactions carried out in refluxing dimethoxyethane over 25 min produced indolo-1,2,3-triazoles **171a** and **171b**, respectively (Equation 32) <2003ARK110>.



170

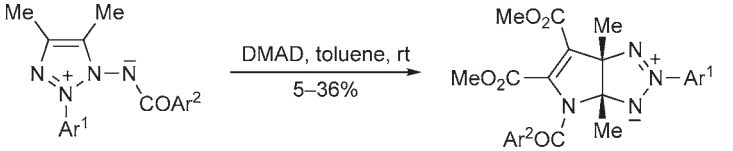
a: Ar = Ph
b: Ar = *p*-$O_2NC_6H_4$

171

a: Ar = Ph, 50%
b: Ar = *p*-$O_2NC_6H_4$, 70%

(32)

Triazolium-1-aminides **172a–e** react with DMAD in toluene at room temperature to form pyrrolo[3,4-*d*]-1,2,3-triazoles **173a–e** in varying yields (Equation 33). In refluxing toluene only two of these aminides **172b** and **172e** led to the corresponding triazoles, and only in low yields (5–8%) <2000TL10337>. Reaction of similar aminides with unsymmetrical alkyl propiolates has also been investigated <2006JOC5679, 2006TL1721>.



172

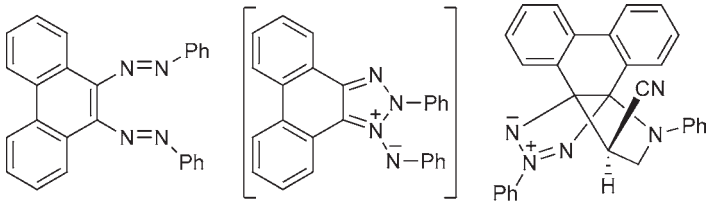
a: Ar^1 = Ph, Ar^2 = Ph
b: Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph
c: Ar^1 = Ph, Ar^2 = *p*-$O_2NC_6H_4$
d: Ar^1 = *p*-MeC_6H_4, Ar^2 = Ph
e: Ar^1 = *p*-$O_2NC_6H_4$, Ar^2 = Ph

173

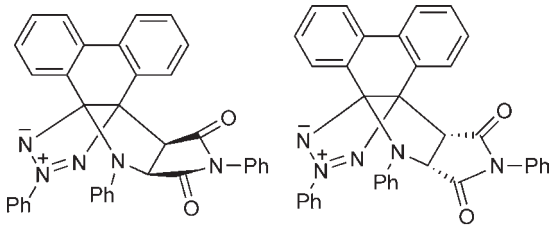
a: Ar^1 = Ph, Ar^2 = Ph
b: Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph
c: Ar^1 = Ph, Ar^2 = *p*-$O_2NC_6H_4$
d: Ar^1 = *p*-MeC_6H_4, Ar^2 = Ph
e: Ar^1 = *p*-$O_2NC_6H_4$, Ar^2 = Ph

(33)

9,10-Bis(phenylazo)phenanthrene **174**, for which the cyclic form **175** dominates reactivity at low concentrations, reacts with acrylonitrile in dry toluene at 55 °C for 48 h to give the *exo*-adduct 2,4-diphenyl-3a,6a-(biphenyl-2,2′-yl)-6-exo-cyano-1,3a,4,5,6,6a-hexahydropyrrolo[2,3-*d*]-2,3-triazol-2-ium-1-ide **176** (60%) as the only product of cycloaddition. Reaction with other alkenes, for example, *N*-phenylmaleimide, leads to a mixture of *endo*- and *exo*-products, cf. **177** and **178** <1996J(P1)1623>.



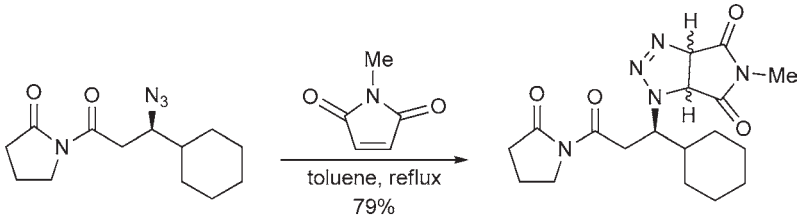
174 **175** **176**



177 **178**

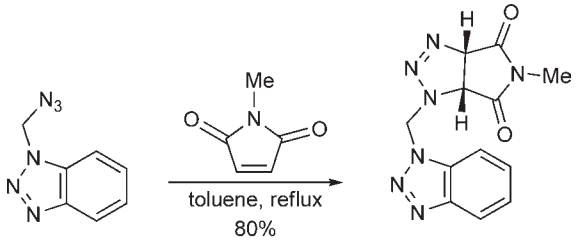
10.03.9.3.6 Pyrrolo[3,4-*d*]-1,2,3-triazoles

Pyrrolo[3,4-*d*]-1,2,3-triazoles are often synthesized by 1,3-dipolar cycloaddition of maleimides with azides. *N*-Methylmaleimide and azide **179** heated at reflux in dry toluene for 24–48 h led to triazole **180** as a 1:1 mixture of diastereomers <2002JA2134>. Benzotriazol-1-ylmethyl azide **181** formed the cycloadduct **182** with *N*-methylmaleimide after refluxing in toluene for 3 h (Equations 34 and 35) <1996JHC335>.



179 **180**
1:1 ratio of diastereomers

(34)

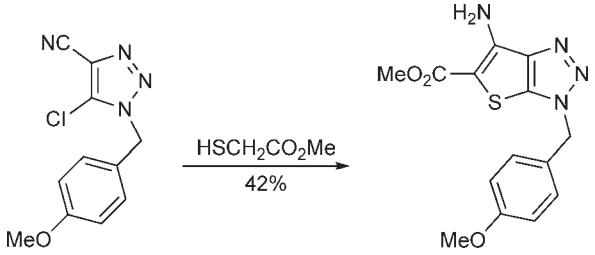


181 **182**

(35)

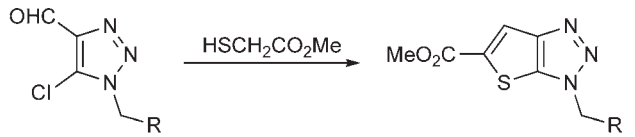
10.03.9.3.7 Thieno[3,2-*d*]-1,2,3-triazoles

Treatment of nitriles **183**, **185a**, and **185b** with methyl 2-sulfanylacetate ($HSCH_2CO_2Me$) and potassium carbonate in refluxing methanol for 2 h produced thienotriazoles **184**, **186a**, and **186b** in 42%, 60%, and 57% yield, respectively (Equations 36 and 37) <1996JCM512>.



183 **184**

(36)



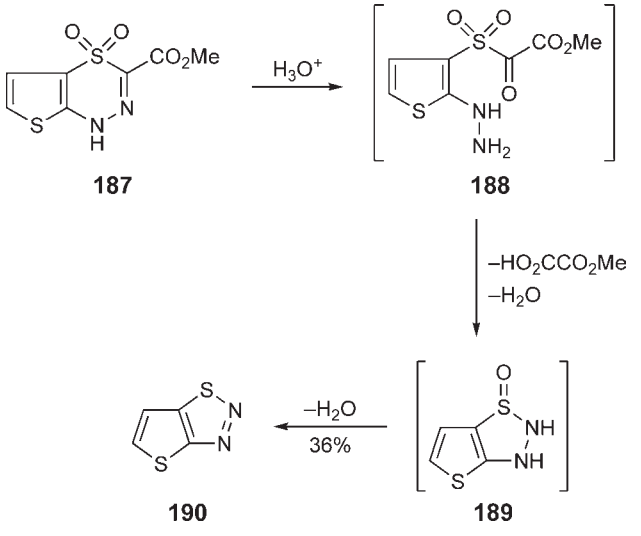
(37)

10.03.10 Ring Synthesis by Transformation of Another Ring System

10.03.10.1 Thieno[2,3-*d*]-1,2,3-thiadiazoles

A suspension of thieno-thiadiazine-4,4-dioxide **187** in a mixture of acetic acid:sulfuric acid:water (2:1:1 by volume) which had been heated at 100 °C for 4 h produced thieno[2,3-*d*]-1,2,3-thiadiazole **190** upon neutralization <2000JHC191>.

Sowell and co-workers proposed that this may have begun with acid hydrolysis of the imine group to produce hydrazine **188** (**Scheme 19**), followed by condensation to give the hydrated thienothiadiazole **189**. Pummerer-type dehydration then leads to thiadiazole **190**. The validity of this proposal, however, has not been investigated.



Scheme 19

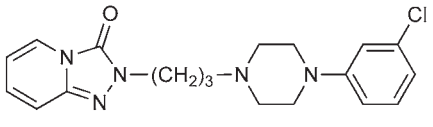
10.03.11 Synthesis of Particular Classes of Compounds and Comparison of the Routes Available

Various common routes have been used for the synthesis of many of the compounds described. Those mentioned here follow on from those reported in the previous volume <1996CHEC-II(7)89>. The Hurd–Mori reaction of hydrazones with excess thionyl chloride is the most widely used method for preparation of 1,2 3-thiadiazoles <2005MOL367, 1998J(P1)853, 1998IJH259, 1999IJB308, 1998H(48)259>.

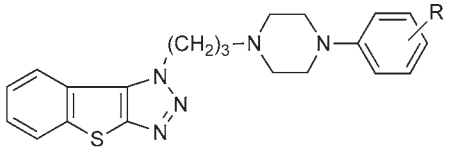
Insertion of a heteroatom into a bifunctional system is a popular method for generation of the required five-membered ring. 1,2-Diols are commonly used to form sulfites (insertion of S) by reaction with $SOCl_2$, $SO(Im)_2$, or SOF_2, whereas formation of 1,2,5-thiadiazoles can be achieved using aryl-1,2-diamines and *N*-sulfinylaniline (PhNSO). The latter group is also prepared by reaction of alkenes and alkynes with $(NSCl)_3$ <1997J(P1)2695>. 1,3-Dipolar cycloaddition of azides with varying dipolarophiles has been extensively used in formation of 1,2,3-triazoles <2004JOC570, 2001J(P1)1778, 2003ARK110, 2006JOC5679, 1996J(P1)1623, 1996JHC335>.

10.03.12 Important Compounds and Applications

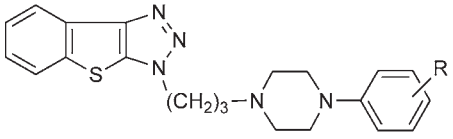
Trazodone **191** is one of the most widely used antidepressants in the world. Many analogues of Trazodone have recently been synthesized. Among these, the benzothieno[2,3-*d*]triazoles **192–194** behaved like Trazodone, with analogues **192a** and **192c** showing very similar antihistaminic activity. The ability of these analogues to inhibit serotonin-induced contractions and antiadrenergic activities was found to be less than that of Trazodone <1999JHC549>.



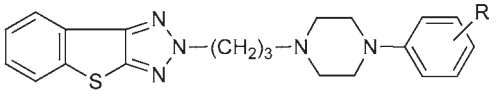
191



192



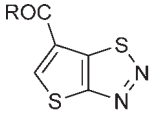
193



194

a: R = H, **b**: R = 2-Cl, **c**: R = 3-Cl

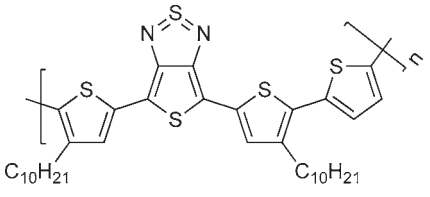
Local infection of a plant will stimulate the development of natural defense mechanisms often resulting in an immune reaction toward a variety of pathogens. Certain chemicals can also trigger the same biochemical reactions in plants. Among the chemicals found to induce this 'systemic acquired resistance' (SAR) are thieno[2,3-*d*][1,2,3]-thiadiazoles **195** <1999JPR341>.



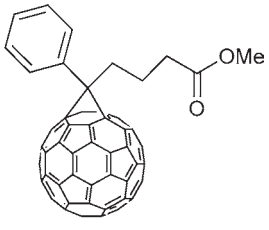
195

R = H, R = alkyl

Recently, photovoltaic cells that use a narrow band conjugated polymer PDDTT **196** as the electron donor and fullerene derivative **197** as the electron acceptor were developed. These cells show a short circuit density (J_{sc}) of 0.83 mA cm^{-2}, an open current voltage (V_{oc}) of 0.35 V, a fill factor (FF) of 38.6% under AM.5 simulator (100 mW cm^{-2}) and unprecedented photocurrent response wavelengths up to 1100 nm <2006APY081106>.

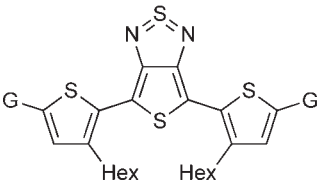


196

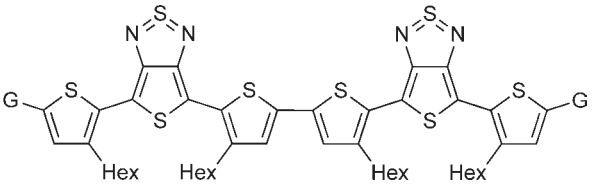


197

The nonclassical thieno[3,4-*c*]-1,2,5-thiadiazole unit **36** has become quite important in the making of synthetic metals. The oligothiophenes **144** and **145** have extended π-conjugation (5–10 nm) which is comparable in length to the inter-electrode gap currently used in nanopatterning techniques. These oligomers are potentially useful as tools for providing specific information on parameters controlling the long-distance electron tunneling through a single molecular wire <2001SM(119)67>.



144



145

Bicyclic 5-5 systems of the type being discussed in this chapter have formed the basis of many porphyrazines and metalloporphyrazines (e.g., **24**, **33**, and **34**). Compounds of this type are being investigated intensively in areas of basic research and in various applications ranging from catalysis and photochemistry to materials science. Porphyrazines have not been covered in any detail, but reviews are available <2004CEJ5158, 2003CEJ4009>.

References

1955JA5359 C. D. Hurd and R. J. Mori, *J. Am. Chem. Soc.*, 1955, **77**, 5359.
1973JOC26 E. M. Burgess, H. R. Penton, and E. A. Taylor, *J. Org. Chem.*, 1973, **38**, 26.
1988JA7538 Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538.
1990CHE1195 V. A. Reznikov, V. V. Martin, and L. B. Volodarskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1990, 1195.
1992J(P1)1103 R. N. Butler, F. A. Lysaght, and L. A. Burke, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1103.
1994H(37)693 S. Tanaka, M. Tomura, and Y. Yamashita, *Heterocycles*, 1994, **37**, 693.
1995JCM438 C. Byrne, S. M. Draper, J. P. James, and C. Long, *J. Chem. Res (S)*, 1995, 438.
1996CC945 C. Byrne, J. P. James, C. Long, and D. Wilcock, *J. Chem. Soc., Chem. Commun.*, 1996, 945.
1996CHEC-II(7)89 A. D. M. Curtis; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1995, vol. 7, p. 89.
1996JCM512 B. Iddon and M. Nicholas, *J. Chem. Res. (S)*, 1996, 512.
1996JCP5528 A. K. Bakhshi, H. Ago, K. Yoshizawa, K. Tanaka, and T. Yamabe, *J. Chem. Phys.*, 1996, **104**, 5528.
1996JHC335 A. R. Katritzky, C. N. Fali, I. V. Shcherbakova, and S. V. Verin, *J. Heterocycl. Chem.*, 1996, **33**, 335.
1996JOC7426 D. L. J. Clive, P. L. Wickens, and P. W. M. Sgarbi, *J. Org. Chem.*, 1996, **61**, 7426.
1996J(P1)1623 R. N. Butler, F. A. Lysaght, P. D. McDonald, C. S. Pyne, P. McArdle, and D. Cunningham, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1623.
1996JPC17327 G. Brocks, *J. Phys. Chem.*, 1996, **100**, 17327.
1997B7209 B. R. Babu and A. D. N. Vaz, *Biochemistry*, 1997, **36**, 7209.
1997JOC4277 P. Dauban and R. H. Dodd, *J. Org. Chem.*, 1997, **62**, 4277.
1997J(P1)2695 X.-G. Duan and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2695.
1997TL5891 P. W. H. Chan, I. F. Cottrell, and M. G. Moloney, *Tetrahedron Lett.*, 1997, **38**, 5891.
1998H(48)1229 A. Passannanti, P. Diana, P. Barraja, F. Mingoia, A. Lauria, and G. Cirrincione, *Heterocycles*, 1998, **48**, 1229.
1998H(48)259 P. Stanetty and M. Kremslehner, *Heterocycles*, 1998, **48**, 259.
1998IC1533 P. A. Stuzhin, E. M. Bauer, and C. Ercolani, *Inorg. Chem.*, 1998, **37**, 1533.
1998IJH259 D. Bhaskar Reddy, M. V. Ramana Reddy, A. Padmaja, and V. Padmavathi, *Indian J. Heterocycl. Chem.*, 1998, **7**, 259.
1998JME109 P. Sauerberg, P. H. Olesen, M. J. Sheardown, K. Rimvall, H. Thøgersen, H. E. Shannon, B. D. Sawyer, J. S. Ward, F. P. Bymaster, N. W. DeLapp, D. O. Calligaro, and M. D. B. Swedberg, *J. Med. Chem.*, 1998, **41**, 109.
1998JOC7375 M. J. Robins, E. Lewandowska, and S. F. Wnuk, *J. Org. Chem.*, 1998, **63**, 7375.
1998J(P1)853 P. Stanetty, M. Kremslehner, and H. Völlenkle, *J. Chem. Soc., Perkin Trans. 1*, 1998, 853.
1998JST(451)263 B. Klenke and W. Friedrichsen, *J. Mol. Struct.*, 1998, **451**, 263.
1998PSI316 P. Stanetty, M. Kremslehner, and M. Jaksits, *Pestic. Sci.*, 1998, **54**, 316.
1999IJB308 V. Padmavathi, A. Padmaja, and D. Bhaskar Reddy, *Indian J. Chem., Sect. B*, 1999, **38**, 308.
1999JCM296 M. A. El-Sekily, M. E. Elba, and F. S. Fouad, *J. Chem. Res. (S)*, 1999, 296.
1999JHC549 F. Guerrera, L. Salerno, M. C. Sarvà, M. A. Siracusa, A. Corsaro, V. Pistarà, R. Capasso, and G. M. Raso, *J. Heterocycl. Chem.*, 1999, **36**, 549.
1999JHC761 P. Stanetty, E. Görner, and M. Mihovilovic, *J. Heterocycl. Chem.*, 1999, **36**, 761.
1999JPR341 P. Stanetty, M. Jaksits, and M. D. Mihovilovic, *J. Prakt. Chem.*, 1999, **4**, 341.
1999M573 P. Stanetty and M. D. Mihovilovic, *Monatsh. Chem.*, 1999, **130**, 573.
2000H(52)237 G. Gonzalez, M. V. Martín, and M. Carmen Paredes, *Heterocycles*, 2000, **52**, 237.
2000JHC191 C. E. Stephens and J. W. Sowell, *J. Heterocycl. Chem.*, 2000, **37**, 191.
2000JIC168 M. A. El-Sekily, M. E. Elba, and F. S. Fouad, *J. Indian Chem. Soc.*, 2000, **77**, 168.
2000J(P1)3107 M.-K. Jeon and K. Kim, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3107.
2000TL10337 N. P. Xekoukoulotakis, C. P. Hadjiantoniou-Maroulis, and A. J. Maroulis, *Tetrahedron Lett.*, 2000, **41**, 10337.
2001JMC1992 G. D. McManus, J. M. Rawson, N. Feeder, J. van Duijn, E. J. L. McInnes, J. J. Novoa, R. Burriel, F. Palacio, and P. Oliete, *J. Mater. Chem.*, 2001, **11**, 1992.
2001J(P1)1778 R. N. Butler and L. M. Wallace, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1778.
2001J(P1)2997 P. W. H. Chan, I. F. Cottrell, and M. G. Moloney, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2997.
2001MOL145 U. Jordis, K. Bhattacharya, P. Y. Boamah, and V. J. Lee, *Molecules*, 2001, **7**, 145.
2001RCB874 V. A. Reznikov, G. I. Roshchupkina, T. V. Ribalova, and Yu. V. Gatilov, *Russ. Chem. Bull.*, 2001, **50**, 874.

2001S229 O. Schulze, J. Voss, and G. Adiwidjaja, *Synthesis*, 2001, 229.

2001SM(119)67 S. Tanaka and Y. Yamashita, *Synth. Met.*, 2001, **119**, 67.

2001TL7513 J. P. Michael, C. B. de Koning, R. L. Petersen, and T. V. Stanbury, *Tetrahedron Lett.*, 2001, **42**, 7513.

2002EJMS35 E. Mørkved, H. Kjøsen, J. Vedde, and E. Uggerud, *Eur. J. Mass. Spectrom.*, 2002, **8**, 35.

2002JA2134 D. J. Guerin and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 2134.

2002JFC(115)13 P. L. Coe, P. Maunder, C. S. Frampton, J. A. Martin, W. A. Thomas, and I. W. A. Whitcombe, *J. Fluorine Chem.*, 2002, **115**, 13.

2002JOC2577 J. Fuentes, M. Angulo, and M. Angeles Pradera, *J. Org. Chem.*, 2002, **67**, 2577.

2002J(P2)126 K. Banert, J. Lehmann, H. Quast, G. Meichsner, D. Regnat, and B. Seiferling, *J. Chem. Soc., Perkin Trans. 2*, 2002, 126.

2002TL7229 J. M. Quayle, A. M. Z. Slawin, and D. Philp, *Tetrahedron Lett.*, 2002, **43**, 7229.

2003AGE5863 M. Fujimori, Y. Suzuki, H. Yoshikawa, and K. Awaga, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5863.

2003ARK110 M. Sheridan, P. James, and C. Healy, *ARKIVOC*, 2003, **vii**, 110.

2003CEJ4009 M. P. Donzello, C. Ercolani, A. A. Gaberkorn, E. V. Kudrik, M. Meneghetti, G. Marcolongo, C. Rizzoli, and P. A. Stuzhin, *Chem. Eur. J.*, 2003, **9**, 4009.

2003HAC587 S. Tanaka, Y. Sugihara, A. Sakamoto, A. Ishii, and J. Nakayama, *Heteroatom Chem.*, 2003, **14**, 587.

2003JA9024 S. Tanaka, Y. Sugihara, A. Sakamoto, A. Ishii, and J. Nakayama, *J. Am. Chem. Soc.*, 2003, **125**, 9024.

2003TL1655 R. I. Robinson and S. Woodward, *Tetrahedron Lett.*, 2003, **44**, 1655.

2003TL3771 S. Aragonès, F. Bravo, Y. Díaz, M. I. Matheu, and S. Castillón, *Tetrahedron Lett.*, 2003, **44**, 3771.

2004AGE2293 T. J. Donohoe, H. O. Sintim, L. Sisangia, and J. D. Harling, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2293.

2004CEJ5158 Y. Suzuki, M. Fujimori, H. Yoshikawa, and K. Awaga, *Chem. Eur. J.*, 2004, **10**, 5158.

2004CEJ5581 K. C. Nicolaou, S. A. Snyder, D. A. Longbottom, A. Z. Nalbandian, and X. Huang, *Chem. Eur. J.*, 2004, **10**, 5581.

2004JA6234 K. C. Nicolaou, S. A. Snyder, A. Z. Nalbandian, and D. A. Longbottom, *J. Am. Chem. Soc.*, 2004, **126**, 6234.

2004JOC570 R. S. Orugunty, I. Ghiviriga, K. A. Abboud, M. A. Battiste, and D. L. Wright, *J. Org. Chem.*, 2004, **69**, 570.

2004OL3913 A. Benksim, D. Beaupère, and A. Wadouachi, *Org. Lett.*, 2004, **6**, 3913.

2004PCB2516 M. C. Ruiz Delgado, V. Hernández, J. T. López Navarrete, S. Tanaka, and Y. Yamashita, *J. Phys. Chem. B*, 2004, **108**, 2516.

2005CEJ4227 T. J. Donohoe, H. O. Sintim, L. Sisangia, K. W. Ace, P. M. Guyo, A. Cowley, and J. D. Harling, *Chem. Eur. J.*, 2005, **11**, 4227.

2005HCA1451 J. Nakayama, S. Yoshida (nee Tanaka), Y. Sugihara, and A. Sakamoto, *Helv. Chim. Acta*, 2005, **88**, 1451.

2005HCA1611 R. N. Butler, A. G. Coyne, W. J. Cunningham, E. M. Moloney, and L. A. Burke, *Helv. Chim. Acta*, 2005, **88**, 1611.

2005JCD3838 A. Alberola, R. D. Farley, S. M. Humphrey, G. D. McManus, D. M. Murphy, and J. M. Rawson, *J. Chem. Soc., Dalton Trans.*, 2005, 3838.

2005JCX385 Y. Mao, I. Maley, and W. H. Watson, *J. Chem. Crystallogr.*, 2005, **35**, 385.

2005JME4276 A. N. Van Nhien, C. Tomassi, C. Len, J. L. Marco-Contelles, J. Balzarini, C. Pannecouque, E. De Clercq, and D. Postel, *J. Med. Chem.*, 2005, **48**, 4276.

2005MOL367 P. Stanetty, M. Turner, and M. D. Mihovilovic, *Molecules*, 2005, **10**, 367.

2006APY081106 Y. Xia, L. Wang, X. Deng, D. Li, X. Zhu, and Y. Cao, *Appl. Phys. Lett.*, 2006, **89**, 081106.

2006CPL(418)30 S. M. Mattar, J. Sanford, and A. D. Goodfellow, *Chem. Phys. Lett.*, 2006, **418**, 30.

2006JOC5679 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham, and A. Ryder, *J. Org. Chem.*, 2006, **71**, 5679.

2006TL1721 R. N. Butler, A. M. Fahy, A. Fox, J. C. Stephens, P. McArdle, D. Cunningham, and A. Ryder, *Tetrahedron Lett.*, 2006, **47**, 1721.

Biographical Sketch



Yvette Jackson, a Jamaican, graduated with a BSc (special) degree in chemistry (1976), and a PhD in chemistry (1983), from the University of the West Indies, Mona campus (UWI, Mona). Her PhD work, under the supervision of Dr. Vernon G. S. Box, involved synthesis of rotenoids – oxygen heterocycles popularly known for their insecticidal activity. She joined the staff at UWI, Mona, in 1983 as an assistant lecturer. Since then she has done postdoctoral work (1986) and many collaborative summer research stints with Prof. Michael P. Cava and Dr. M. V. Lakshmikantham at the University of Alabama, Tuscaloosa, USA, and has risen up the ranks to professor at the University of the West Indies. Her research interests are in the areas of synthetic organic chemistry and organic reaction mechanisms.



Norman Townsend was born in Westmoreland, Jamaica on 1 February 1977. He graduated from the University of the West Indies in 2003 with a PhD in organic chemistry. Norman did postdoctoral research with Prof. Yvette Jackson at the same university between 2004 and 2006, and is currently a project officer at the Mona Institute of Applied Sciences.

10.04
Bicyclic 5-5 Systems: Four Heteroatoms 2:2

J. D. Wilden
University College London, London, UK
© 2008 Elsevier Ltd. All rights reserved.

10.04.1 Introduction 162
10.04.2 Theoretical Methods 162
10.04.2.1 Fully Conjugated Rings 162
10.04.2.2 Nonconjugated Systems 163
10.04.3 Experimental Structural Methods 163
10.04.3.1 Fully Conjugated Systems 163
10.04.3.2 Nonconjugated Systems 163
10.04.4 Thermodynamic Aspects 165
10.04.5 Reactivity of Fully Conjugated Rings 166
10.04.5.1 Thermal and Photochemical Reactions 166
10.04.5.2 Electrophilic Attack at Nitrogen 167
10.04.5.3 Electrophilic Attack at Carbon 167
10.04.5.4 Nucleophilic Attack at Carbon 167
10.04.5.5 Nucleophilic Attack at Hydrogen 168
10.04.5.6 Reduction 168
10.04.5.7 Oxidation 168
10.04.6 Reactivity of Nonconjugated Rings 169
10.04.6.1 Thermal and Photochemical Reactions 169
10.04.6.2 Electrophilic Attack at Nitrogen 169
10.04.6.3 Electrophilic Attack at Carbon 171
10.04.6.4 Nucleophilic Attack at Carbon 171
10.04.6.5 Nucleophilic Attack at Hydrogen 172
10.04.6.6 Reduction 172
10.04.6.7 Oxidation 173
10.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms 173
10.04.8 Reactivity of Substituents Attached to Ring Heteroatoms 174
10.04.9 Ring Synthesis Classified by the Number of Ring Atoms in Each Component 174
10.04.9.1 Ring Synthesis from Acyclic Compounds 174
10.04.9.2 Ring Synthesis from Monocyclic Compounds 175
10.04.9.3 Ring Synthesis via 1,3-Dipolar and Other Cycloaddition Reactions 178
10.04.10 Ring Synthesis by Transformation of Another Ring 180
10.04.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available 180
10.04.12 Important Compounds and Applications 181
10.04.12.1 Molecular Receptors Based on Glycoluril Scaffolds 181
10.04.12.2 Organic Metals and Magnets 184
10.04.12.3 Medicinal Applications 185
References 185

10.04.1 Introduction

The structural diversity associated with bicyclic 5-5 fused heterocyclic systems containing two heteroatoms in each ring has been noted previously in both CHEC(1984) <1984CHEC(6)1027> and CHEC-II(1996) <1996CHEC-II(7)115>. In recent years this diversity has also been reflected in the number of applications that have been found for these compounds which include organic metals, molecular clips and receptors and molecular magnets. These fields will be examined in due course through this chapter.

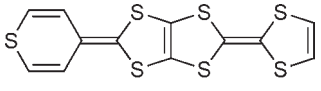
In order to provide continuity between CHEC(1984), CHEC-II(1996), and this edition, the same system of nomenclature has been adopted. Fully conjugated systems are considered prior to their partly conjugated and fully saturated counterparts. As far as possible, the general outline of CHEC-II(1996) has been followed throughout the edition. There are cases however, where the template of CHEC-II(1996) is inappropriate for this chapter. For example, many synthetic routes to fused 5-5 heterocyclic systems were established in the 1970s and 1980s and in many cases these routes have been modified but the general synthetic strategy remains the same. In this edition, compounds that have been prepared since CHEC-II(1996) by routes that have already been described in that volume have been omitted in the interests of brevity.

It is fair to say that the emphasis of the research that has been undertaken with 5-5 fused heterocycles (particularly those containing four heteroatoms in a 2:2 arrangement) has shifted from pure synthetic chemistry and methodology to more application-based research, particularly in the field of organic metals, molecular clips, and organic magnetic materials. The difference becomes evident by examining the length of the 'important compounds and applications' sections in CHEC-II(1996) and in this edition, the former comprising only a few sentences compared to here which is over four pages of this short review.

10.04.2 Theoretical Methods

10.04.2.1 Fully Conjugated Rings

As was noted in CHEC-II(1996), this heterocyclic system has proved itself to be of great value in the development of the so-called organic metals. Modified neglect of diatomic overlap (MNDO) calculations have been performed by a number of groups on systems to assess their suitability as organic metals. Misaki *et al.* <1996JOC3650> have shown by these calculations that in the highest occupied molecular orbital (HOMO) of TPDT-TTP **1** all of the sulfur atoms in the 1,3-dithiole rings have the same phase (**Figure 1**) which leads to the expected transverse intermolecular interaction in the radical cation salts which it is noted is an indispensable requirement for the realisation of 2D electronic structures.



1

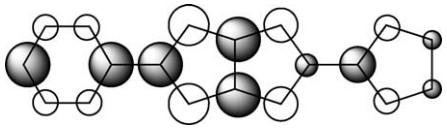
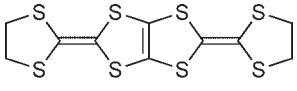


Figure 1 HOMO of TPDT-TTP **2**.

Similar results have been obtained by Yamada *et al.* for the structurally similar compound BDH-TTP as was indicated in CHEC-II(1996) (**Figure 2**).



3

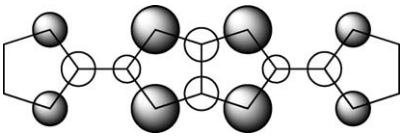


Figure 2 HOMO of BDH-TTP **4**.

10.04.2.2 Nonconjugated Systems

Little has been explored in this area in the years since CHEC-II(1996).

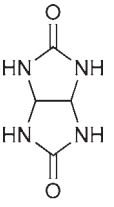
10.04.3 Experimental Structural Methods

10.04.3.1 Fully Conjugated Systems

Thiophene/thiazolothiazole co-oligomers have been investigated as organic semiconductors and their structure investigated by X-ray diffraction in reflection mode following deposition on SiO_2 surfaces at various temperatures. They conclude that thiazolothiazole derivatives have great potential as field effect transistors (see Section 10.04.12.2) <2004JMC1787>.

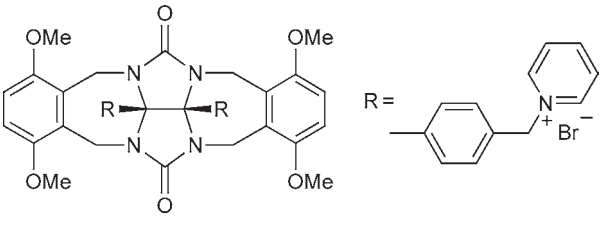
10.04.3.2 Nonconjugated Systems

The vast majority of structural methods for this category has been in the elucidation of the structure of glycoluril-based molecular clips. This rigid concave-shaped molecule **5** is an important building block for both molecular and supramolecular chemistry. Nolte and Rebek have utilized X-ray crystallography, electron microscopy, nuclear magnetic resonance (NMR) spectroscopy and computer simulations to this end which demonstrate the supramolecular architecture of structures based on substituted glycolurils where both bridgehead and heteroatom substitution differ.



5

The glycoluril derivative **6** was shown by electron microscopy to form well-defined 'razor blade-like' nanostructures in water <1996CC245>. In contrast to many X-ray descriptions of alkylated glycolurils, which show the formation of capsules and clips, Isaacs *et al.* <2002T9769> have observed that hydrogen-bonded tapes can be formed from suitably substituted glycoluril which are clearly visible in the X-ray crystal structure (**Figure 3**). They report that the molecules **7–10** all form hydrogen bonded tapes in the crystal state.



6

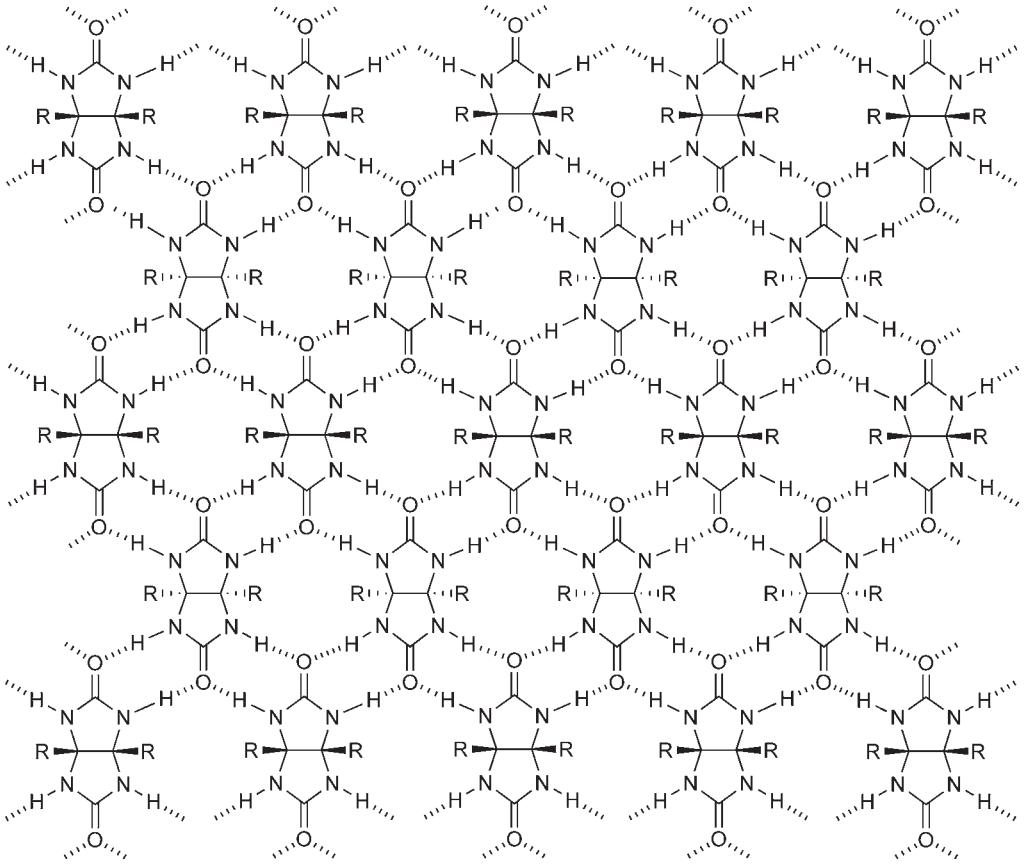
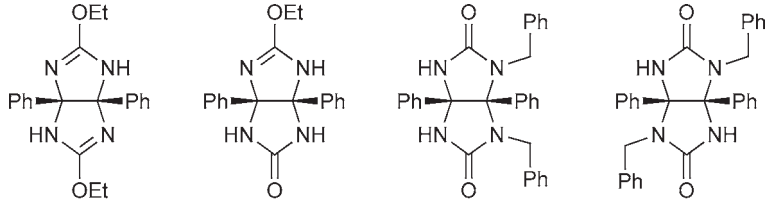
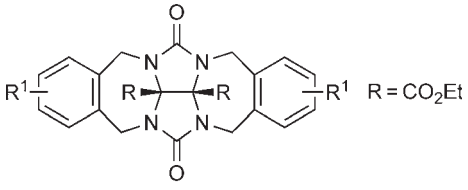


Figure 3



7 **8** **9** **10**

More recently, Wu *et al.* <2006JOC4502> have described an extensive crystallographic study of 11 different molecular clips based on the glycoluril skeleton **11**.



11

Their research has focused on examining the effect of substitution on the aromatic ring in the crystal state. Their results show that different substitution leads to different structures being formed in the crystal state. They conclude that even weak intermolecular interactions such as C–H–O hydrogen bonds can be used to control crystal packing within glycoluril systems.

10.04.4 Thermodynamic Aspects

Rebek has studied the binding of molecular hosts such as the so-called 'softball' based, once again, on the glycoluril structure <1997JA77, 1998JA66, 1998JA3650>. These are composed of molecules such as **12** which form dimers in solution and create a cavity in which small molecules such as benzene or water can bind. Indeed, it appears that in the resting state two molecules of benzene are locked within the softball (**Figure 4**).

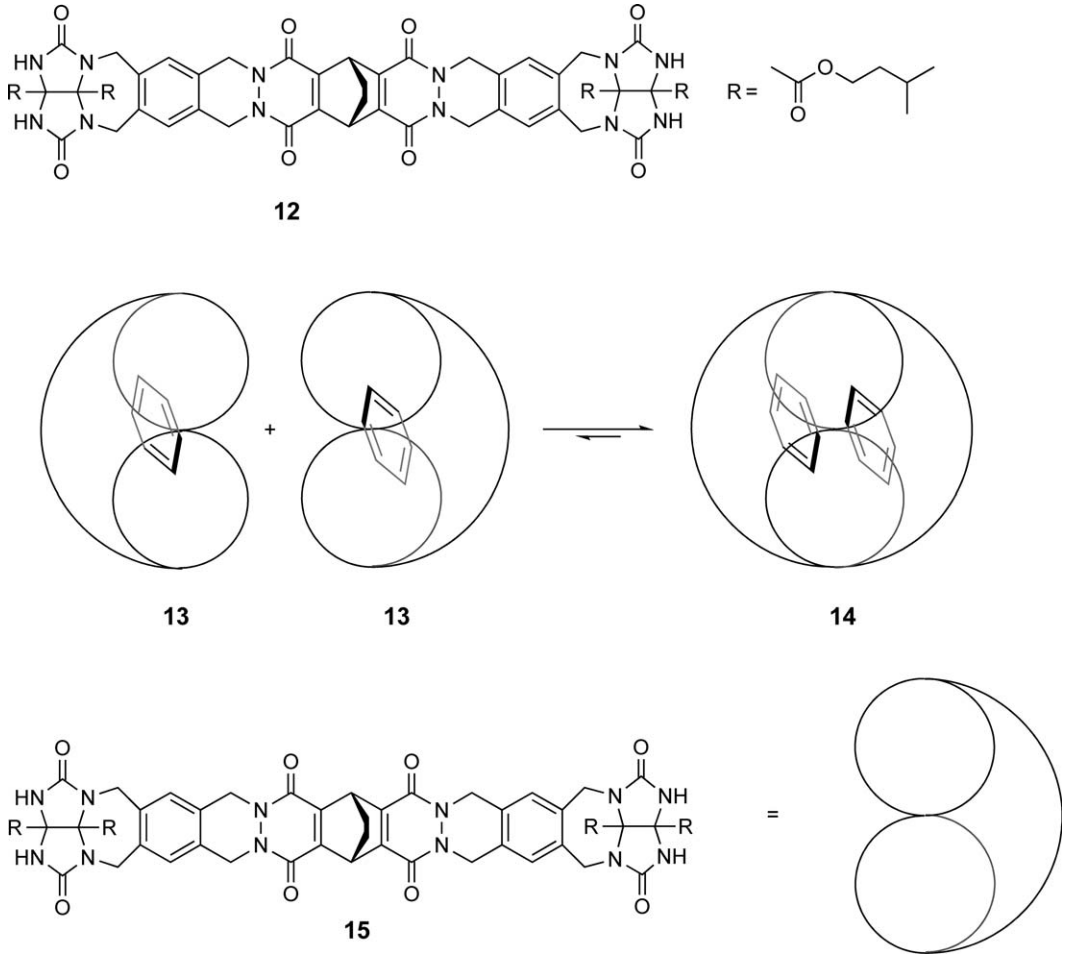


Figure 4

Encapsulation of a larger guest results in the displacement of the solvent molecules from the 'softball' (**Figure 5**).

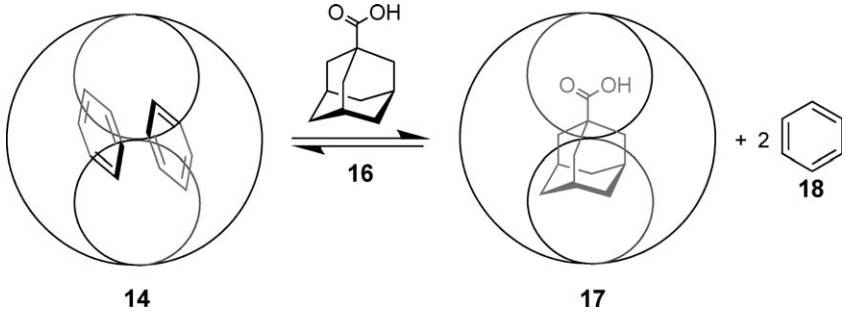


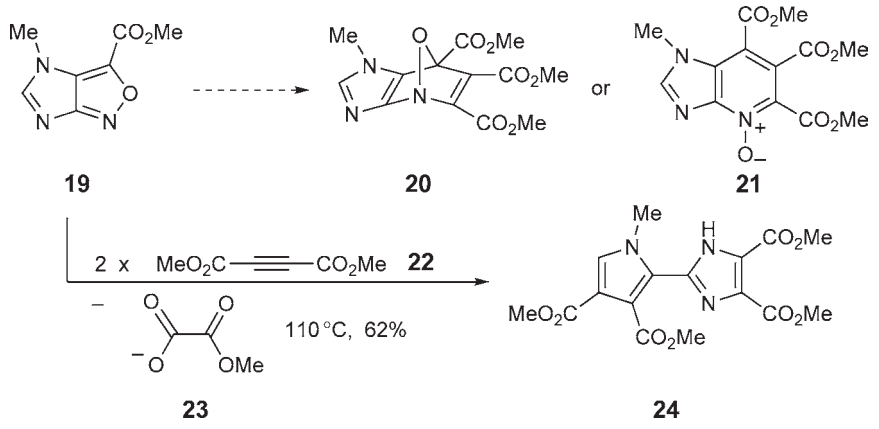
Figure 5

Their calculations indicate that binding of the larger guest such as adamantyl acid **16** is enthalpically positive, which indicates that the process is entropically driven. Their rationale is that the host contains two molecules of solvent in the resting state and that encapsulation of a single large guest liberates these solvent molecules. The resulting increase in the number of free molecules gives rise to the increase in entropy observed. It is also suggested that any solvent on the surface of the guest may also be freed to the medium on encapsulation.

10.04.5 Reactivity of Fully Conjugated Rings

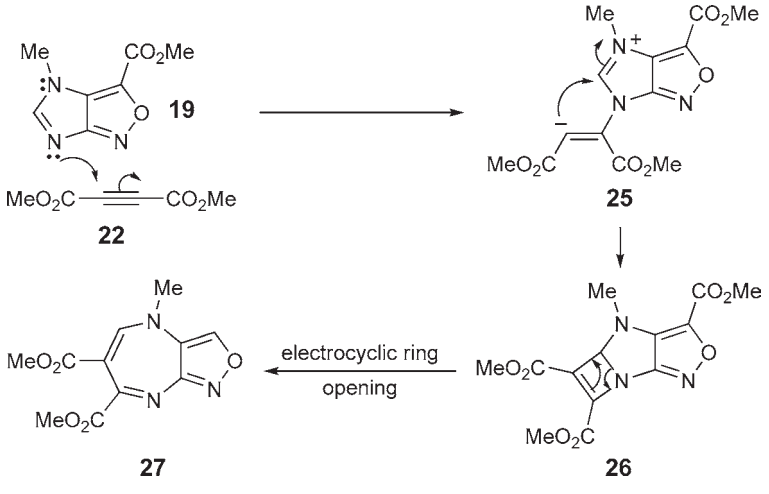
10.04.5.1 Thermal and Photochemical Reactions

Only a few of such reactions of these rings have been reported since CHEC-II(1996). However, Weaver and Tennant <1999TL8157, 2000TL9319> have demonstrated that imidazo[4,5-*c*]isoxazoles such as **19** undergo thermally driven reactions with acetylenic diesters (such as **22**) to yield, rather than the expected bridged bicyclic compound **20** or the pyridine *N*-oxide **21**, the 2-pyrrol-2-ylimidazole **24** which the authors suggest proceeds via loss of a methyl oxalate unit. The proposed pathway is outlined in **Scheme 1**.



Scheme 1

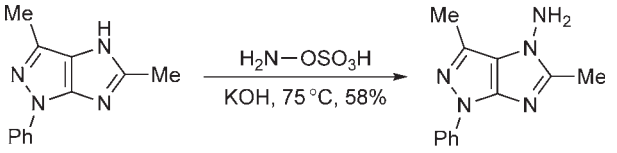
Additionally, the same authors have isolated [1,4]diazepino[2,3-*c*]isoxazoles **27** <2000TL9319> from the same reagents which they suggest proceeds via fused tricyclic compound **26** followed by an electrocyclic ring-opening reaction (**Scheme 2**), although no yield for the reaction is given in the paper.



Scheme 2

10.04.5.2 Electrophilic Attack at Nitrogen

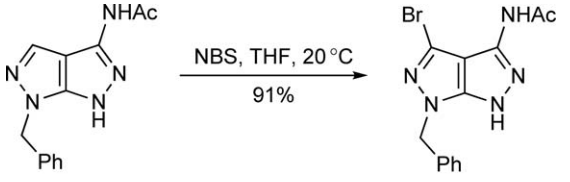
In addition to those methods described in CHEC(1984) and CHEC-II(1996) (primarily alkylation and acylation reactions), Vicentini <1996T7179> has shown that 5-methylimidazo[4,5-*c*]pyrazole **28** can undergo electrophilic attack on nitrogen by hydroxylamine *O*-sulfonic acid to yield the 4-amino species **29** (Equation 1).



28 **29** (1)

10.04.5.3 Electrophilic Attack at Carbon

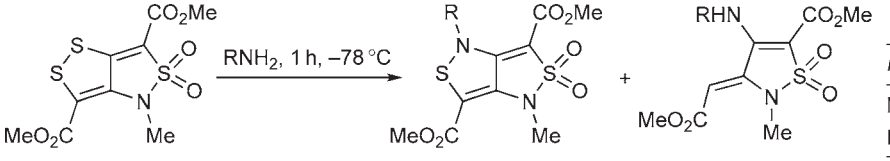
Heterocycle, **30**, is brominated at the expected position by *N*-bromosuccinimide in excellent yield (Equation 2) <2004H(63)2475>.



30 **31** (2)

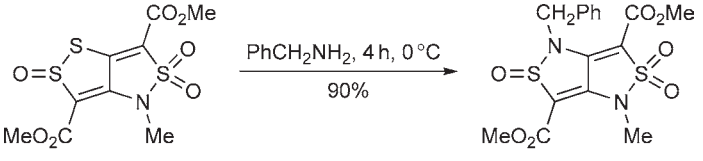
10.04.5.4 Nucleophilic Attack at Carbon

Heterocycle **32**, on exposure to various amines, undergoes nucleophilic attack at the ring junction carbon atom, giving either the bicyclic material **33** or the monocyclic product **34** <1999JHC161>. Interestingly, when the sulfur atom at the 3-position is in the lower oxidation state, the major product is the monocyclic product **34**, with the bicyclic material being isolated in low yield (Equation 3). When S-3 is oxidized however, the bicyclic material **36** is isolated in near-quantitative yields (Equation 4).



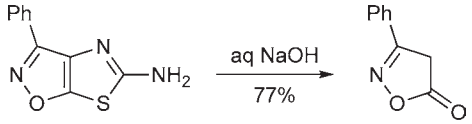
R	*Yield (%)*	
Me	5	20
$PhCH_2$	9	70

32 **33** **34** (3)



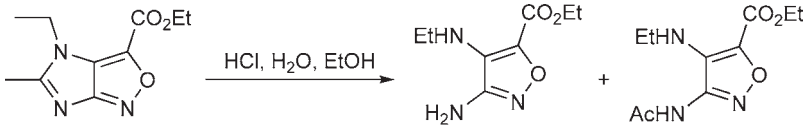
35 **36** (4)

Similarly, nucleophilic attack of hydroxide at the ring junction of heterocycle **37** results in ring cleavage and gives the monocyclic compound **38** (Equation 5) <2003IJB2625>.



37 **38** (5)

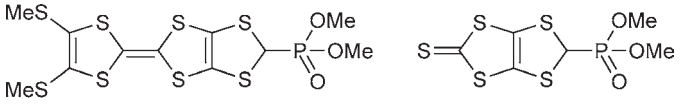
Acid-catalyzed hydrolysis of the imidazo[4,5-*c*]isoxazole leads to the the two isoxazole monocyclic compounds, **40** and **41** (Equation 6), presumably via nucleophilic attack of water at the imidazole carbon atom <1999J(P1)817>.



39 **40** 2% **41** 68% (6)

10.04.5.5 Nucleophilic Attack at Hydrogen

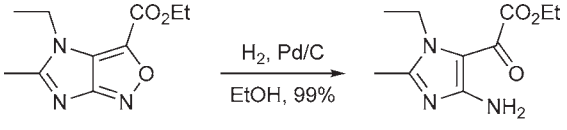
Similar applications to those reported in CHEC-II(1996) have been described for more elaborate phosphonate esters **42** and **43** which undergo Horner–Emmons reactions with carbonyl compounds following deprotonation <2000EJO51, 2002CL1002>.



42 **43**

10.04.5.6 Reduction

Imidazo[4,5-*c*]isoxazole **39** <1999J(P1)817>, first prepared by Tennant *et al.*, undergoes reduction of the N–O bond under classical hydrogenation conditions, to yield the substituted imidazole **43** in excellent yield (Equation 7).

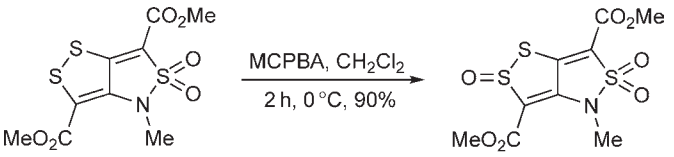


39 **43** (7)

10.04.5.7 Oxidation

Formally, reaction of the imidazopyrazole **28** with hydroxylamine *O*-sulfonic acid is an oxidation giving the hydrazine **29** as described in Section 10.04.5.2 (Equation 1).

Species **32** undergoes efficient oxidation of one sulfur atom when exposed to the common laboratory oxidant *m*-chloroperbenzoic acid (MCPBA) (Equation 8) <1999JHC161>. The high degree of chemoselectivity in this reaction is noteworthy, the product being isolated in high yield and with none of the alternative sulfur oxidation product being obtained or indeed over-oxidation to afford higher oxidation state species.



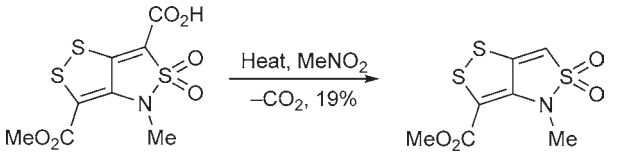
32 **35** (8)

Fully conjugated rings are, by definition, in their highest oxidation state and as such reactions in which the ring systems are maintained are rare.

10.04.6 Reactivity of Nonconjugated Rings

10.04.6.1 Thermal and Photochemical Reactions

Heterocyclic sulfonamide **36** is thermally decarboxylated in low to modest yields to give **44** (Equation 9). Inclusion of other electrophiles in the solution also allowed the replacement of the carboxylate group with Br, NO_2, and COCl as well as H <2005HCA1208>.



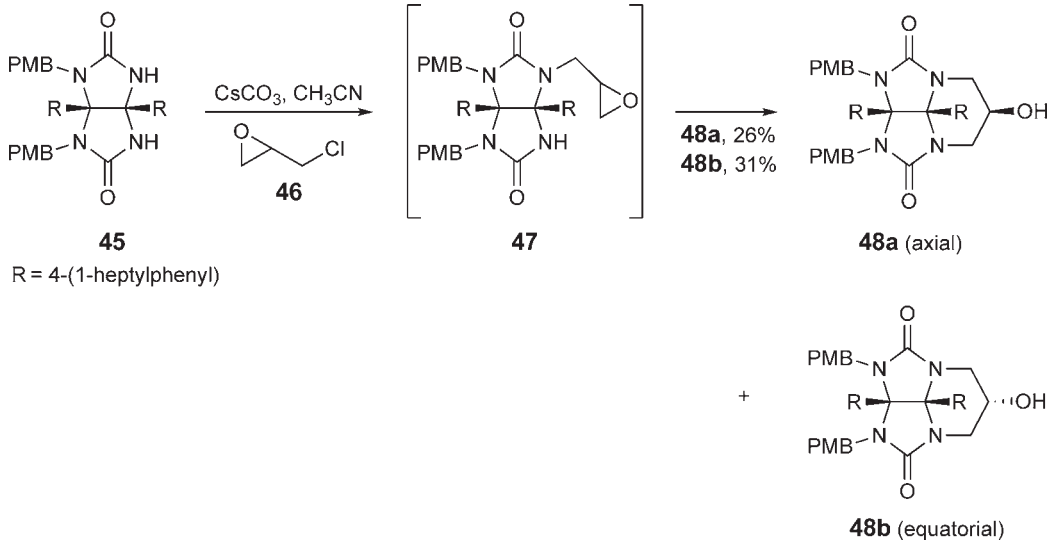
36 **44** (9)

10.04.6.2 Electrophilic Attack at Nitrogen

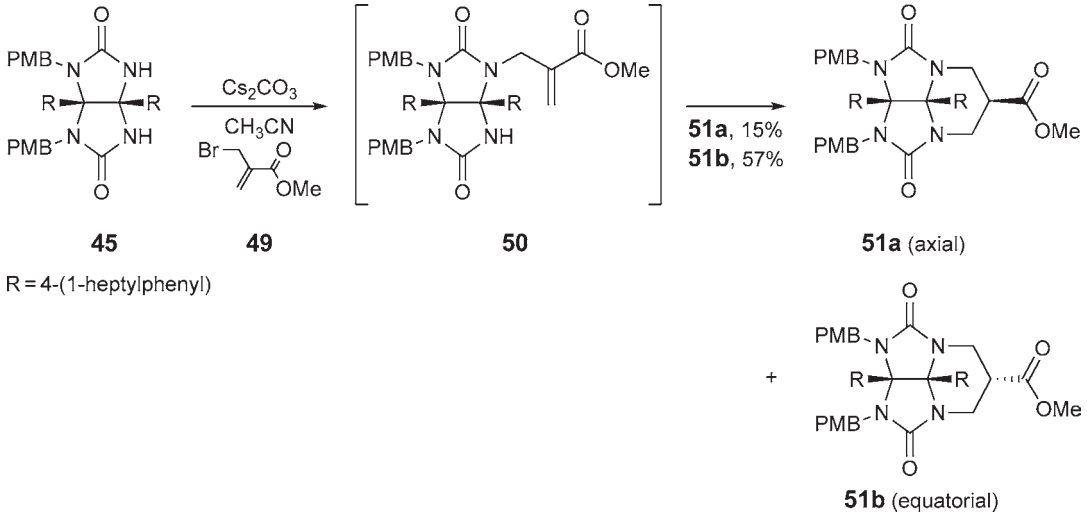
The vast majority of the reactions of the 5-5 fused systems have been the alkylation of nitrogen atoms by electrophiles and oxidants. Most of the examples have been in the alkylation of glycoluril derivatives and the general methods have been extensively covered in CHEC(1984) and CHEC-II(1996) and as such do not generally require comment here. Some of the alternative and less common methods however are outlined below.

Many macromolecular architectures have been built up by the condensation of glycoluril monomers and formaldehyde. As research in this area has intensified, so has the complexity and utility of the systems that have been synthesized <2004JA10035, 2004MM288, 2004OL1225, 2003OL3745>. Further alkylations at nitrogen have been achieved with epoxides and Michael additions to yield new clips and receptor precursors (**Schemes 3** and **4**) <2001JA11519>. Both cyclizations yielded mixtures of axial and equatorial diastereoisomers; however, these were all separable by column chromatography.

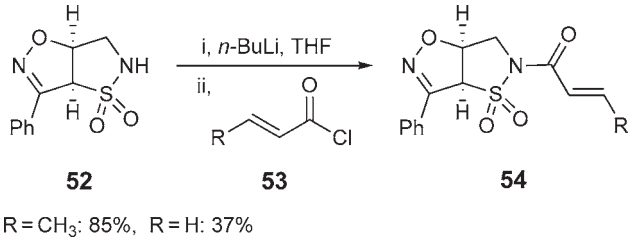
Acylation of a usually non-nucleophilic cyclic sulfonamide **52** has also been achieved under by deprotonation of the N–H by butyllithium followed by addition of various unsaturated acid chlorides (Equation 10) <2005TA761>.



Scheme 3

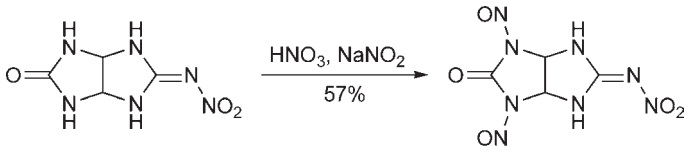


Scheme 4



(10)

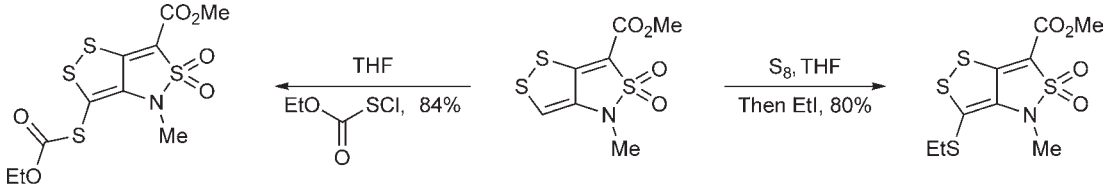
Nitrosation of glycoluril derivatives has also been reported by simple exposure to nitric acid and sodium nitrite (Equation 11) <1998RJOC34>.



55 56 (11)

10.04.6.3 Electrophilic Attack at Carbon

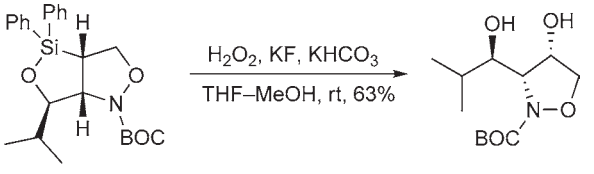
As has been mentioned above, thermal decarboxylation of heterocycle **36** can be coupled with electrophilic trapping with either bromine or nitro groups to yield the substituted analogues. The same heterocyclic system **59** can be thiolated by treatment either with elemental sulfur (followed by alkylation with an alkyl halide) to afford **60**, or the electrophilic thiolating reagent **58** to generate **57** (**Scheme 5**) <2005HCA1208>.



57 **58** **59** **60**

Scheme 5

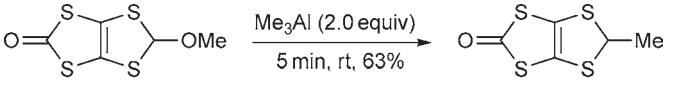
Cyclic silicon-containing compounds such as **61** undergo electrophilic attack at carbon with hydrogen peroxide to furnish the stereodefined diol **62** (Equation 12) <2003OL3875>.



61 **62** (12)

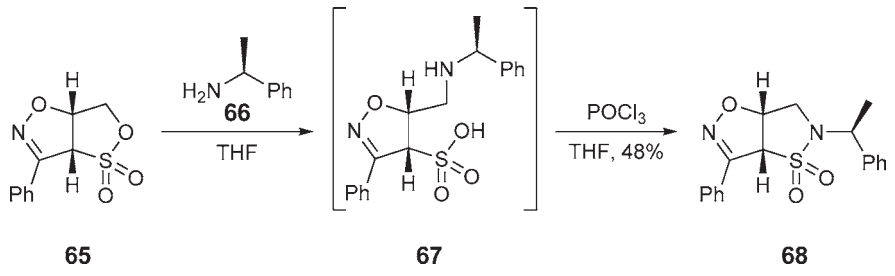
10.04.6.4 Nucleophilic Attack at Carbon

Nucleophilic displacement of alkoxide can be effected in moderate yields when the chalcogenones are treated with hard organometallic reagents such as organolithium, organozinc, and organoaluminium reagents. The best results were obtained when the compound **63** was treated with 2 equiv of trimethylaluminium which led to the product **64** in a 63% yield (Equation 13) <2001MCLC253, 1999TL6635>. Other examples however proved more difficult, yields rarely rising above 30%.



63 **64** (13)

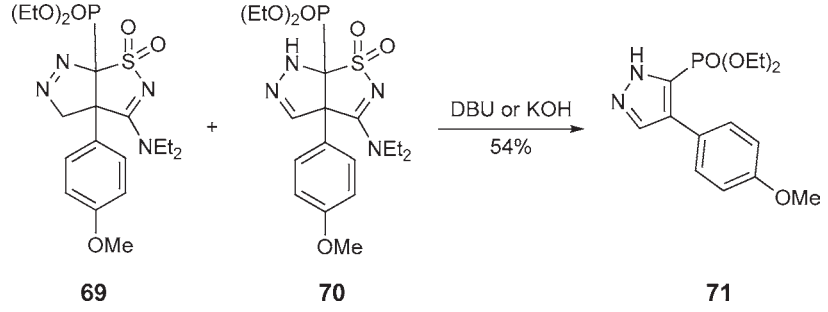
Chan and co-workers have described the nucleophilic attack of chiral amines (e.g., **66**) on the cyclic sulfonate ester **65** which yields the ring-opened compound in good yields. Treatment of the resulting sulfonic acid **67** with phosphorus oxychloride then yields the sulfonyl chloride which undergoes ring closure with 4-dimethylaminopyridine (DMAP) to give the suitably substituted heterocyclic sulfonamides **68** in good yields (**Scheme 6**) <2005TA761> which they have demonstrated to be chiral auxiliaries for asymmetric Diels–Alder reactions.



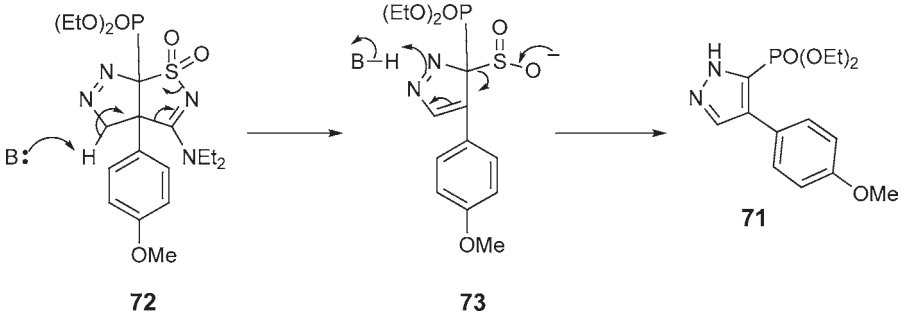
Scheme 6

10.04.6.5 Nucleophilic Attack at Hydrogen

Clerici *et al.* in their extensive work on cyclic sulfonamides have demonstrated that the compounds **69** and **70** undergo base-induced ring cleavage via elimination of diethylcyanamide and SO_2 to afford **71** (Equation 14) <2001TL5455>. Various mechanisms are feasible, however, the necessity for base in the reaction medium implies deprotonation, either at nitrogen or carbon, followed by fragmentation as outlined below (**Scheme 7**).



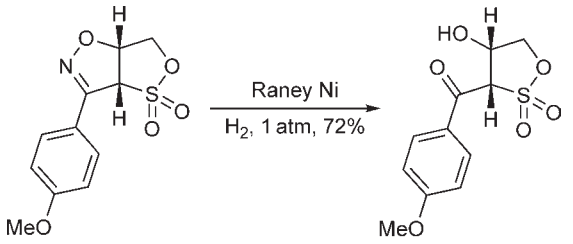
(14)



Scheme 7

10.04.6.6 Reduction

Reductions of these ring systems are common. Most often, active hydrogen techniques are employed to cleave weak heteroatom–heteroatom bonds. Reductions of the glycoluril derivatives are less common due to the lack of such a weak bond. Some recent examples include reactions by Chan *et al.* <2003TL395> who employed Raney nickel and hydrogen to effect cleavage of an N–O bond in their synthesis of new heterocyclic compounds via 1,3-dipolar cycloaddition chemistry (Equation 15).



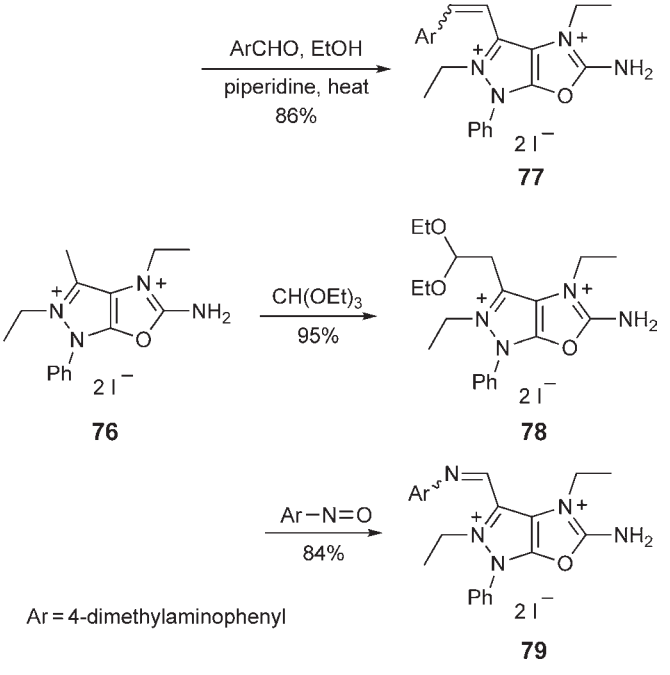
74 75 (15)

10.04.6.7 Oxidation

Treatment of the silyl compound, **61**, above with hydrogen peroxide leads to the diol **62** which formally constitutes an oxidation as well as an electrophilic attack on the carbon atom. Classically, oxidation of nonconjugated rings to furnish their conjugated (usually aromatic) analogues is achieved by treatment with nickel(II) peroxide; however, these reactions are common and have been extensively explored for a number of different heterocyclic systems in both CHEC(1984) and CHEC-II(1996) so are not discussed further here.

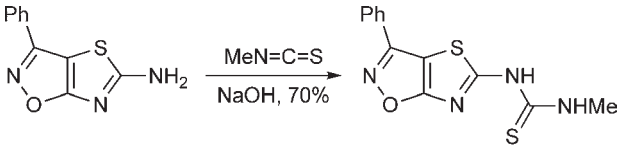
10.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Shindy *et al.* <1999JRM3001> have demonstrated that the conjugated species **76** is deprotonated at the *C*-methyl group with relatively mild bases to give a species that is, nucleophilic towards a range of electrophiles including aldehydes, orthoesters, nitroso compounds and quinolinium species. Yields of the products are generally excellent. Some examples are given below (**Scheme 8**).



Scheme 8

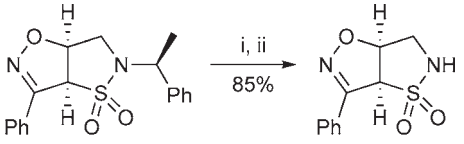
Thioureas have been formed from amino groups attached to ring carbon atoms by treatment with isothiocyanates, for example, the conversion of **80** into **81** (Equation 16) <1997IJB403>.



80 81 (16)

10.04.8 Reactivity of Substituents Attached to Ring Heteroatoms

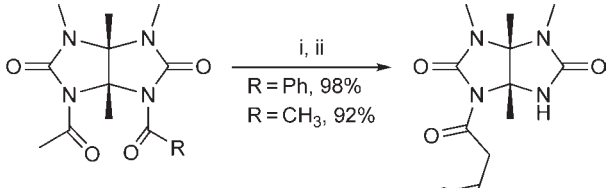
Removal of the benzyl group in heterocyclic sulfonamide **82** can be achieved by exposure to formic acid followed by ethanolic KOH (Equation 17). This method is effective where the classical method of debenzylation, namely hydrogenolysis, would result in N–O bond cleavage as outlined above <2005TA761>.



82 **83** (17)

i, HCOOH, 70 °C; ii, KOH, EtOH

Harrison *et al.* have demonstrated that bis-acyl glycoluril derivatives **84** undergo efficient Claisen ester condensation, as exemplified in Equation (18) to yield β-ketoamide derivatives **85**. A kinetic study is also presented which indicates clean, bimolecular kinetics and short half lives for the intermediates <2002CJC517>.



84 (18)

R = Ph, CH_3

i, 1:1 *t*-BuOH-THF; ii, BuLi

85

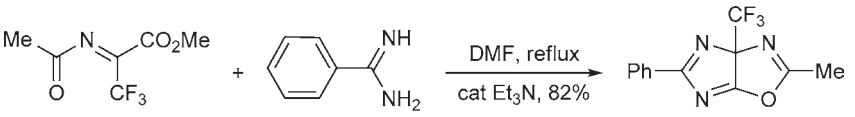
10.04.9 Ring Synthesis Classified by the Number of Ring Atoms in Each Component

Few truly new methods for the construction of these heterocycles have been reported in the years that have passed since CHEC(1984) and CHEC-II(1996). Most methods rely on classic reactions which are well defined and are robust and reliable. Nevertheless, a number of new syntheses have been reported that employ evermore ingenious and creative chemistry in the synthesis of evermore exotic and diverse compounds. The demand for these types of heterocycles, particularly in the fields of the development of new organic metals and in the continually expanding array of glycoluril receptors, as well as the classic need for small biologically active molecules for drug discovery and development has led to continued interest in this area. The vast number of synthetic routes to glycoluril derivatives (namely urea condensations) are well defined in the literature and as such, similar methods that have been employed since CHEC-II(1996) will not be covered here.

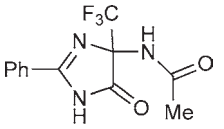
10.04.9.1 Ring Synthesis from Acyclic Compounds

There have been a few examples of acyclic compounds being converted into the heterocyclic compounds of interest in this chapter; however, these tend to employ 1,3-dipolar cycloaddition reactions, and as such will be covered in Section 10.04.9.3. The notable new synthetic routes are outlined below.

Imidazooxazole **88** is obtained from the acyclic components **86** and **87** in refluxing dimethylformamide (DMF) with sub-stoichiometric quantities of triethylamine (Equation 19). It is also noted that the monocyclic compound **89** can be converted into the same material by heating in DMF indicating that this structure is an intermediate in the one-pot synthesis <2005RCB472>.

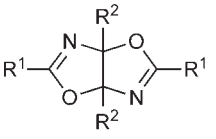


86 **87** **88** (19)



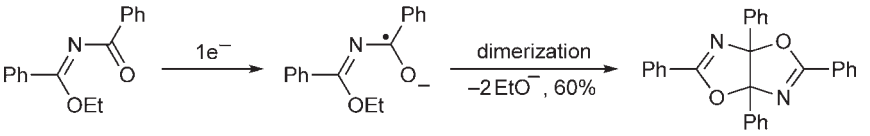
89

Boujlel *et al.* <2003SC1675> have prepared oxazolooxazoles such as **90** by the rather more unusual method of electrochemical reduction of **91** which then undergoes dimerisation giving good yields of the symmetrical heterocycles. Various substituents have been included. Their proposed mechanism involves capture of an electron to give radical anion **92** followed by dimerisation and cyclization as outlined in **Scheme 9**.



90

R^1, R^2 = Ph, *i*-Pr, Bn

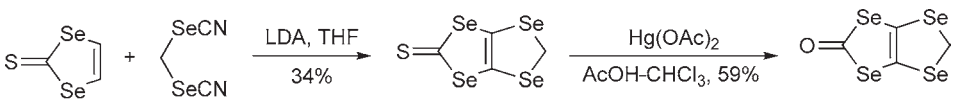


91 **92** **93**

Scheme 9

10.04.9.2 Ring Synthesis from Monocyclic Compounds

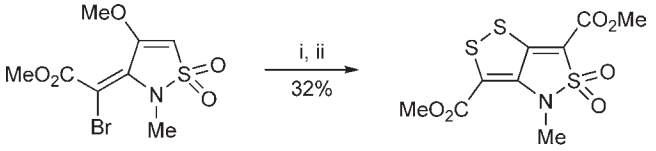
The vast majority of synthetic methods for the formation of these heterocyclic compounds fall into this class. Most syntheses rely heavily on the previous routes that are well established. New routes however are continually being devised and the structural diversity in this class of heterocyclic compounds continues to grow. In particular, the number of selenium analogues have grown greatly in recent years due to their application as organic metals and magnets (although a few examples were quoted in CHEC-II(1996)). Imakubo and co-workers have devised a synthesis of the selenium organic metal precursor **97** using the known, but previously unutilised reagent biscyanoselenatomethane which circumvents the requirement for the highly toxic reagent carbon diselenide (CSe_2) (**Scheme 10**) <2004OBC1685>.



94 **95** **96** **97**

Scheme 10

The sultam, **32**, has been prepared from the monocyclic precursor **98** followed by treatment with basic H_2S. Oxidative disulfide formation with either molecular oxygen or hydrogen peroxide then yields the product (Equation 20) <2005HCA1208>.

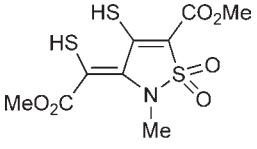


(20)

98 **32**

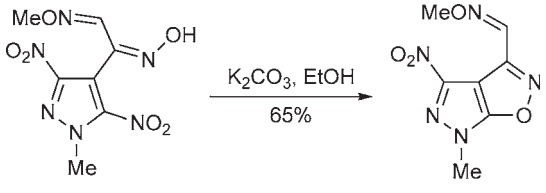
i, H_2S, Et_3N ii, H_2O_2

Presumably, 1,4-addition of sulfide to each unsaturated system occurs which is followed by elimination of methoxide and bromide leading to an intermediate such as **99**, which then cyclizes under oxidative conditions to give **32**.



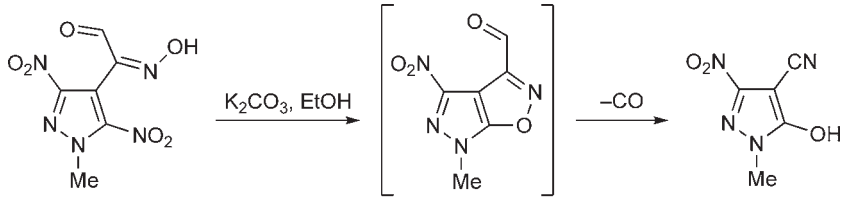
99

The pyrazolooxazole **101** has been prepared by the base-catalyzed cyclization of monocyclic compound **100** (Equation 21). It is interesting to note that the aldehyde moiety in **102** must be protected as the oxime derivative prior to cyclization. The unprotected aldehyde proceeds to form the pyrazolooxazole, but then undergoes deformylation and ring opening to give **104** (**Scheme 11**) <2005RJO1507>.



(21)

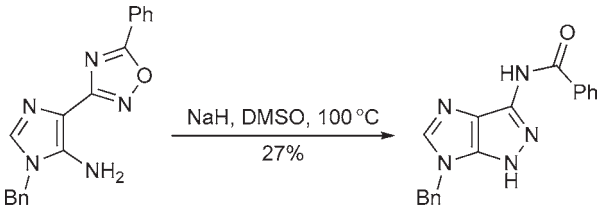
100 **101**



102 **103** **104**

Scheme 11

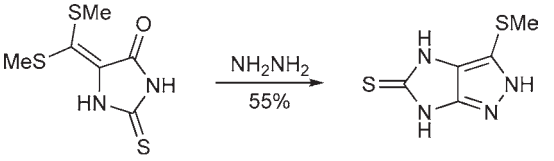
While reactions that involve nucleophilic attack of a heteroatom on a ring carbon atom in a ring synthesis are commonplace, reactions involving nucleophilic attack of one heteroatom on another (particularly on nitrogen) are rare. One exception to this observation is in the formation of compound **106**, which can be prepared by heating the bicyclic compound **105** in dimethyl sulfoxide (DMSO). The reaction involves nucleophilic attack of nitrogen on the isoxazole nitrogen atom to form the fused bicyclic system **106**. The driving force for the reaction is the generation of the carbonyl group in the product (Equation 22) <2004H(63)2475>.



(22)

105 **106**

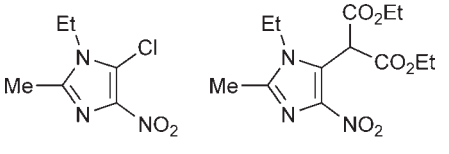
Elgemeie and co-workers have described a short synthesis of thio-substituted pyrazoloimidazoles **108** from a ketenedithioacetal precursor **107** (Equation 23) <2002SC2245>.



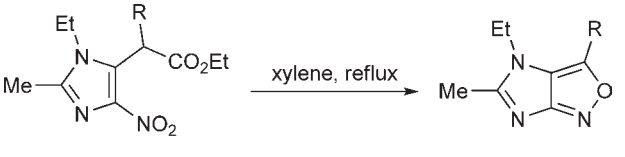
(23)

107 **108**

In a novel synthetic route as part of a wider program to identify potential adenosine receptor antagonists, Tennant *et al.* have succeeded in preparing the first examples of the imidazo[4,5-*c*]isoxazole ring system. Their studies have shown that a number of 3-substituted imidazo[4,5-*c*]isoxazoles can be prepared, bearing ester, keto, and amide groups. Their synthesis begins with substituted 4-nitro-5-chloroimidazole derivatives such as **109**. These react smoothly with malonate anions generated by deprotonation with sodium hydride, in a classic nucleophilic aromatic substitution reaction, facilitated by the strongly electron-withdrawing nitro group, to afford imidazoles such as **110** <1999J(P1)817>. Thermal cyclization of these products affords the imidazoisoxazoles **112** (Equation 24).



109 **110**



(24)

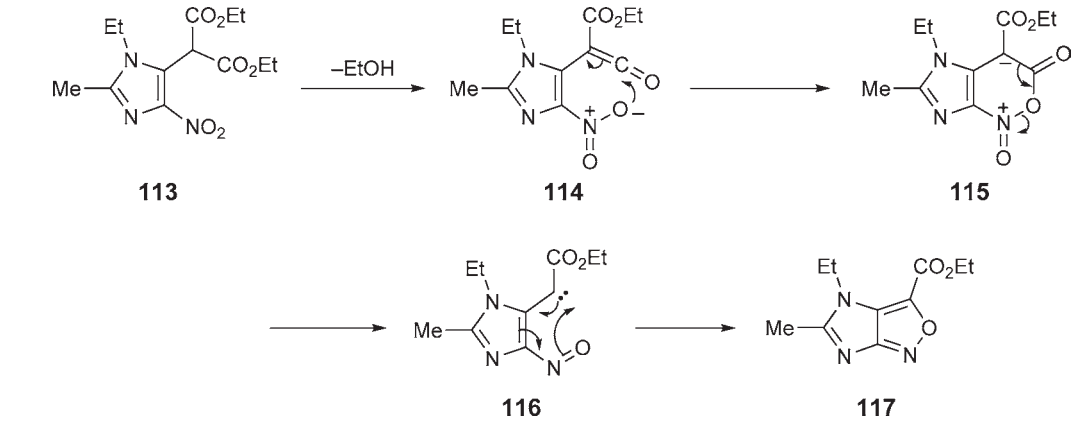
111 **112**

R = CO_2Et: 92%; COPh: 88%; COMe: 94%; $CONH_2$: 51%

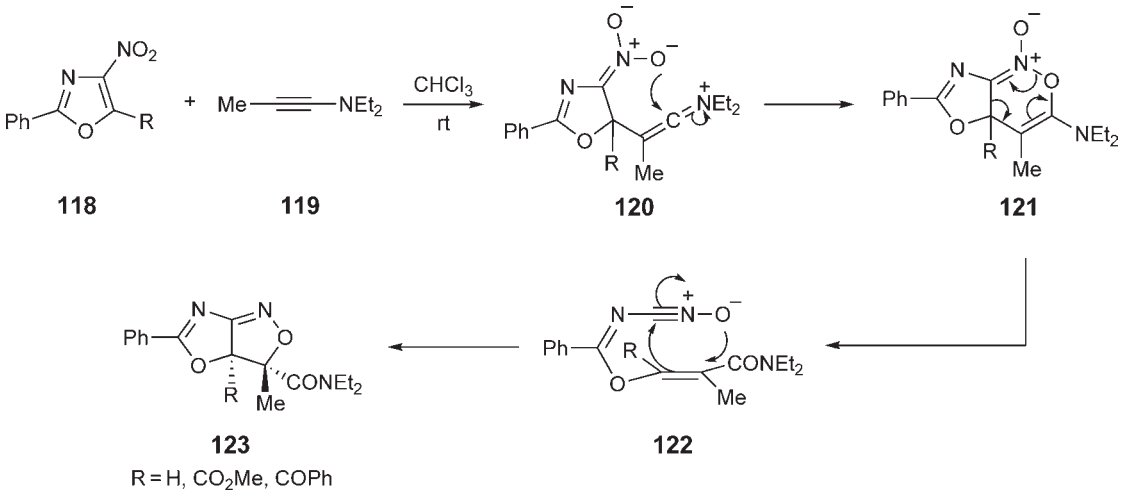
The authors propose a mechanism for the transformation which involves the formation of a ketene intermediate at elevated temperature. Cyclization involving the adjacent nitro group then yields the zwitterionic species **115** which decarboxylates to give carbene **116**. Finally, this cyclizes to yield the products (**Scheme 12**).

The hitherto unknown oxazolo[4,5-*c*]isoxazole system has been synthesized by Nesi *et al.* in their studies on isoxazoles and their reactions. Oxazole **118** reacts with 1-dimethylaminopropyne through, what the authors describe as a four-step hetero-domino sequence, which they postulate includes a 1,3-dipolar cycloaddition of intermediate nitrile oxide **122** (**Scheme 13**) <1999T13809>.

Interestingly, this synthesis could arguably fit into any one of the synthetic headings in this chapter, since it contains a conversion from another ring, a 1,3-dipolar cycloaddition, a monocyclic starting material and an acyclic intermediate!



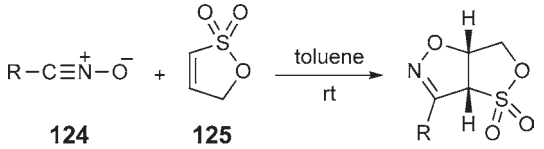
Scheme 12



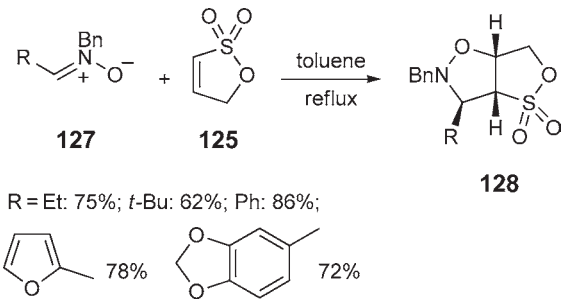
Scheme 13

10.04.9.3 Ring Synthesis via 1,3-Dipolar and Other Cycloaddition Reactions

Cycloaddition reactions are still one of the most important methods of preparing bicyclic heterocyclic compounds and new routes continue to be developed. The most common 1,3-dipoles employed in the preparation of these heterocycles tend to be nitrones, nitrile oxides, and diazoalkanes due to the attention that these reactive intermediates have received in the literature and the well-defined methods for their preparation and the high degree of regio- and stereoselectivity that is often exhibited in the reactions <1997T13855>. Extensions of reactions that have previously been described in CHEC-II(1996) such as the nitrone and nitrile oxide cycloaddition to the sultone **125** (rather than the previously reported sultam) continue to be of great synthetic utility in the preparation of heterocycles (Equations 25 and 26) <2003TL395, 2001TL5455>.

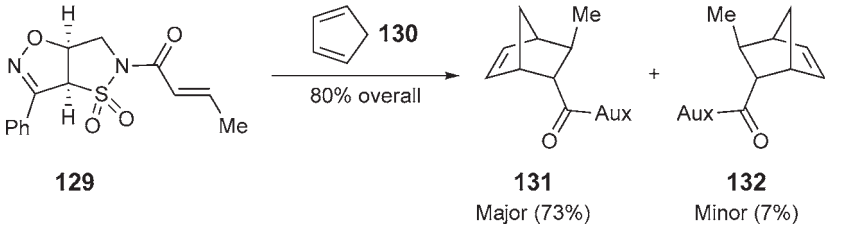


(25)



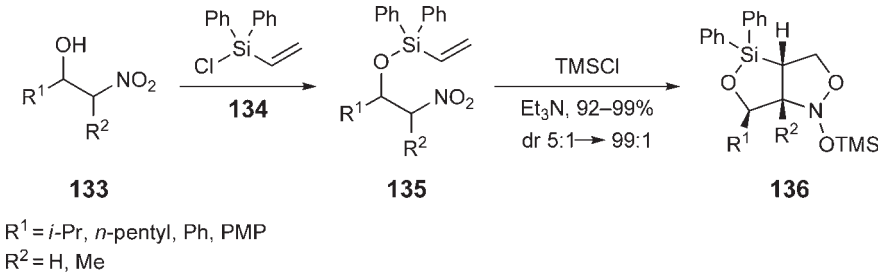
(26)

More recently, this approach has been extended to the synthesis of chiral sultams such as **129**, which have been employed as chiral auxiliaries for Diels–Alder reactions, for example, Equation (27) <2005TA761>.



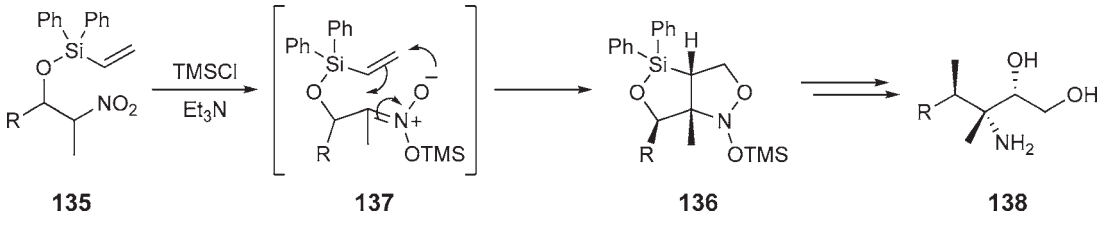
(27)

Less well-established cycloaddition chemistry has also found application in the synthesis of heterocyclic compounds in recent years. An example is the intramolecular cycloaddition of silyl nitronates that has been employed by Ishikawa and Saito to afford **136** in their synthesis of amino polyols (**Scheme 14**) <2003OL3875>.



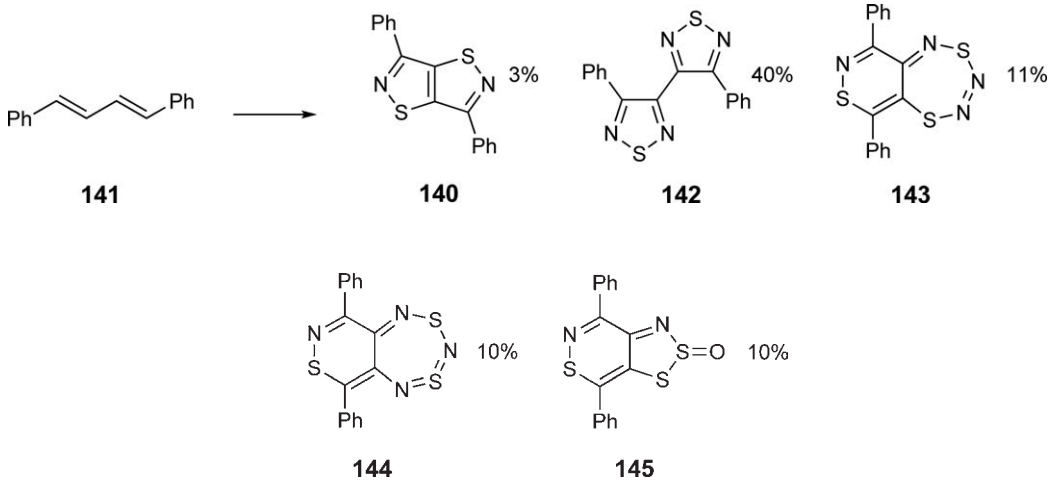
Scheme 14

The reaction mechanism involves silylation of a nitro group oxygen followed by deprotonation to give the intermediate silyl nitronate **137**, which undergoes 1,3-dipolar cycloaddition to give the product **136** in excellent yields and with diastereomeric excess ratios often exceeding 99:1 (**Scheme 15**).

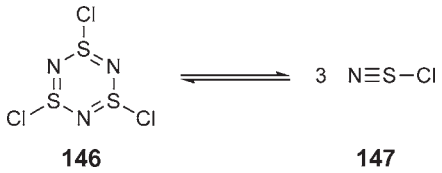


Scheme 15

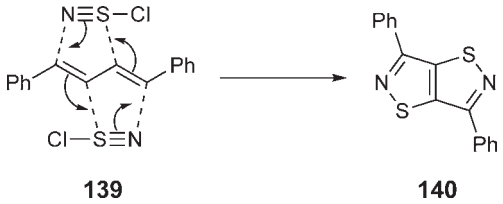
Rees and co-workers in their study of the reactions of trithiazyl trichloride in the preparations of heterocyclic compounds have noted that the isothiazolo[5,4-*d*]isothiazole compound **140** was produced in low yield on reaction with conjugated dienes, along with the other heterocyclic systems **142–145** in much higher yields (Equation 28). Since it is known that trithiazyl trichloride is in thermal equilibrium with its monomer NSCl (Equation 29), the authors propose the so-called 'criss-cross' cycloaddition reaction (Equation 30) which has been reported for azabutadienes, but this represents the first example of such a criss-cross cycloaddition to an all-carbon diene <1998CC1207>.



(28)



(29)



(30)

10.04.10 Ring Synthesis by Transformation of Another Ring

Formally, the synthetic route outlined in **Scheme 6** constitutes the preparation of a new ring system from another. Nucleophilic attack of amine on the sulfonate ester, a particularly good leaving group, leads to monocyclic compound **67**. Conversion of the sulfonic acid moiety into a sulfonyl chloride by $POCl_3$ then yields the sulfonyl chloride *in situ*, which then undergoes nucleophilic attack by the pendant amine resulting in the chiral sultam **68**.

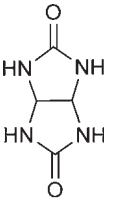
10.04.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

As was noted in CHEC-II(1996), a critical comparison of synthetic routes for this class of compounds is not a useful exercise.

10.04.12 Important Compounds and Applications

10.04.12.1 Molecular Receptors Based on Glycoluril Scaffolds

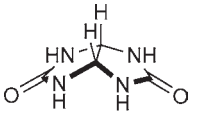
By far, the greatest interest in 5-5 heterocyclic systems containing two heteroatoms in each ring has been in the field of supramolecular chemistry and in the preparation of molecular receptors of various types. One of the most widely used heterocyclic backbones for these receptors has been glycoluril **5** and its derivatives.



5

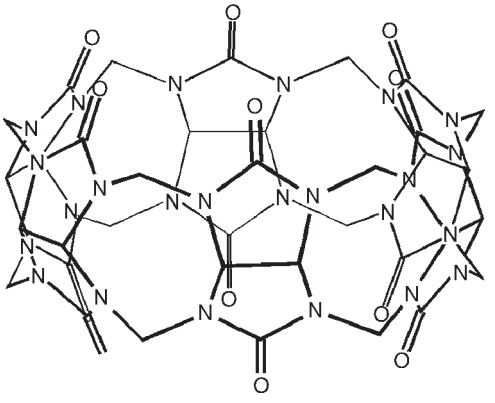
Although noted by both Nolte <1995TCC25> and Rebek <1995S1485> that these systems are ideal scaffolds for the preparation of molecular receptors, it is only in recent years that interest in these systems has increased and a number of significant advances have been made in what is now an intense field of research. In particular, Nolte noted that glycoluril possesses many desirable characteristics for elaboration into a molecular receptor including:

1. A rigid concave shape **148**.
2. Facile functionalisation of all four nitrogen atoms.
3. Two carbonyl groups which can act as hydrogen bond acceptors.



148

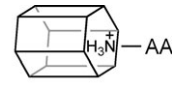
One of the major applications of glycolurils is in the preparation of the cucurbituril family of molecular receptors. Despite being known for a number of years the popularity of this molecule has grown significantly in the last decade. The most common member of the cucurbituril family is cucurbit[6]uril containing six glycoluril units linked by methylene units **149** (**Figure 6**).



149

Figure 6

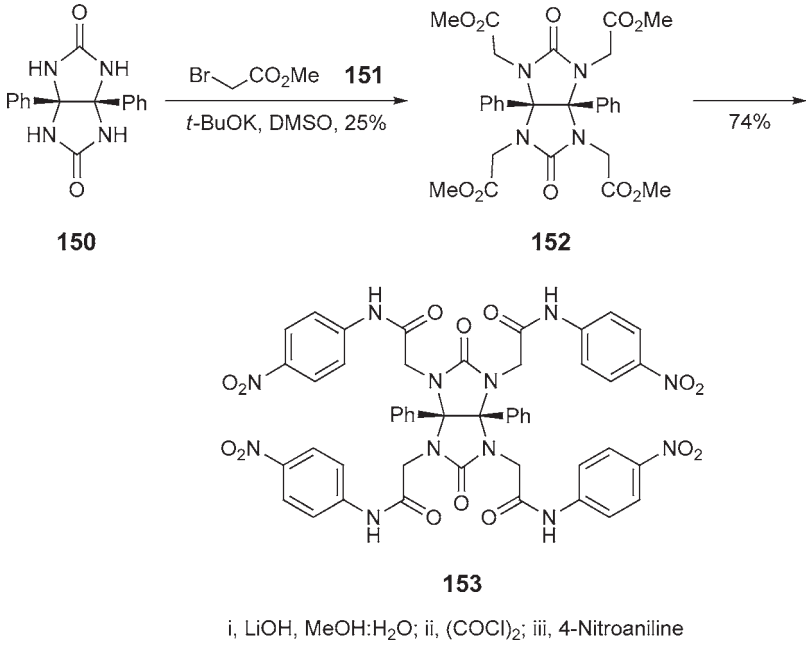
This structure has found many applications in supramolecular chemistry aside from its well-documented cation-binding affinity (which has now also been extended to the binding of lanthanide cations <2002EJI2380>). Cucurbit[6]uril has been successfully employed in catalysis, catenane formation and, most recently, has been shown to complex small peptides, probably via an exclusion complex due to unfavorable steric and polar effects prohibiting full inclusion of the peptide. A schematic representation of such an exclusion complex is given in **Figure 7** <2005JA14511, 2005THE79>.



Cucurbit[6]uril

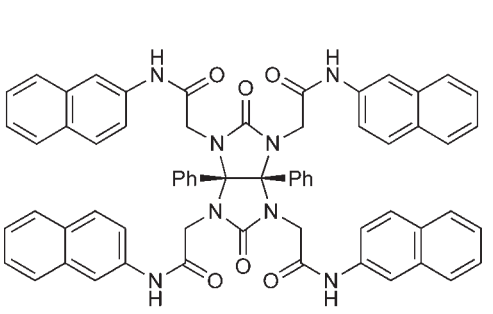
Figure 7

An intense field of research in which the glycoluril scaffold has found new applications is in the development of anion receptors. Despite many essential biochemical pathways which depend on anion complexation, the supramolecular chemistry of anion receptors is relatively unexplored compared with that of cations. Kang has reported a number of anion receptors which show selectivity for halide anions and are based on the glycoluril skeleton <2004SMC175, 2004TL5225>. Preparation of the tetra-amide derivative of glycoluril **153** by standard techniques yields a compound which shows anion-binding selectivity for fluoride and acetate anions (**Scheme 16**). The binding affinity is attributed to hydrogen bonding between the anionic guest and the four amide hydrogen atoms in the host molecule.

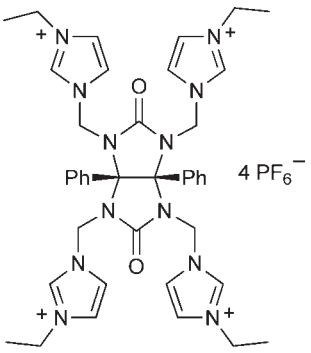


Scheme 16

Kang has also reported a bromide-selective fluorescent anion receptor **154** <2005TL1759> with a glycoluril molecular scaffold and the tetra-imidazole derivative **155** <2005TL7165> which shows affinity for fluoride and chloride anions.

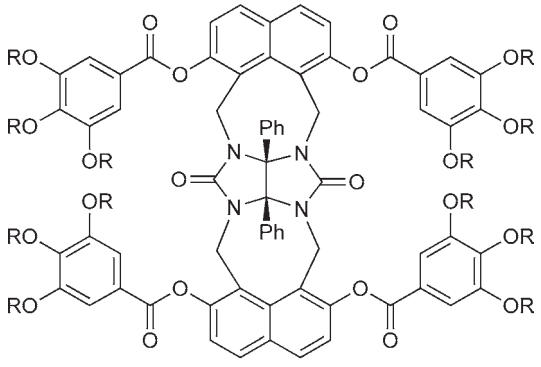


154



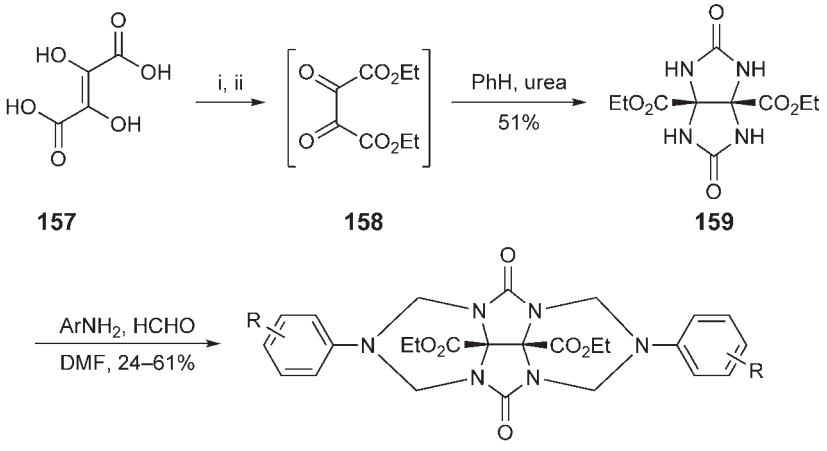
155

A similar class of receptor known as the molecular clips is also based on the glycoluril structure (most commonly two units of glycoluril known as glycoluril dimers) and can be tailored to bind a number of molecules. Again, the pioneer of this work was Nolte in the mid-1990s <1995TCC25> and in a particularly elegant experiment, he has even induced liquid crystallinity into the molecular clips such as **156** by binding of electron-rich aromatic compounds *via* π-π stacking <1997J(P2)1473>.



156

Since this work, a number of other molecular clips have been synthesised. Extensive studies in the synthesis of these compounds have been carried out by Pan and Wu who have described a new class of clips which bind aromatic guests and are soluble in nonpolar organic solvents <2006SL49>. The synthesis of this new class of molecular clip is also based on a novel synthetic pathway utilising aromatic amines outlined in **Scheme 17**.



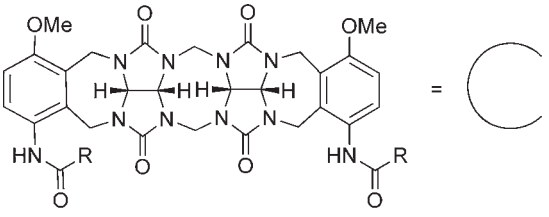
157 158 159

160

i, Br_2, AcOH, H_2O; ii, EtOH, HCl
R = H, Me, OMe, Cl, Br, I

Scheme 17

Isaacs has explored extensively the behavior of these species in various solvents. A number of molecular clip structures based on two units of glycoluril were prepared and studied using NMR analysis. It was discovered that in the series of glycoluril-dimer molecular clips bearing hydrogen bonding amides on the aromatic rings **161**, the molecules are 'C' shaped and exist as interlocking homodimers **162** in solution <2004JA10035>:



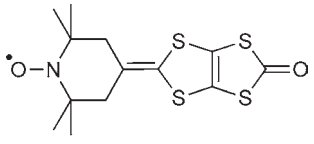
161



162

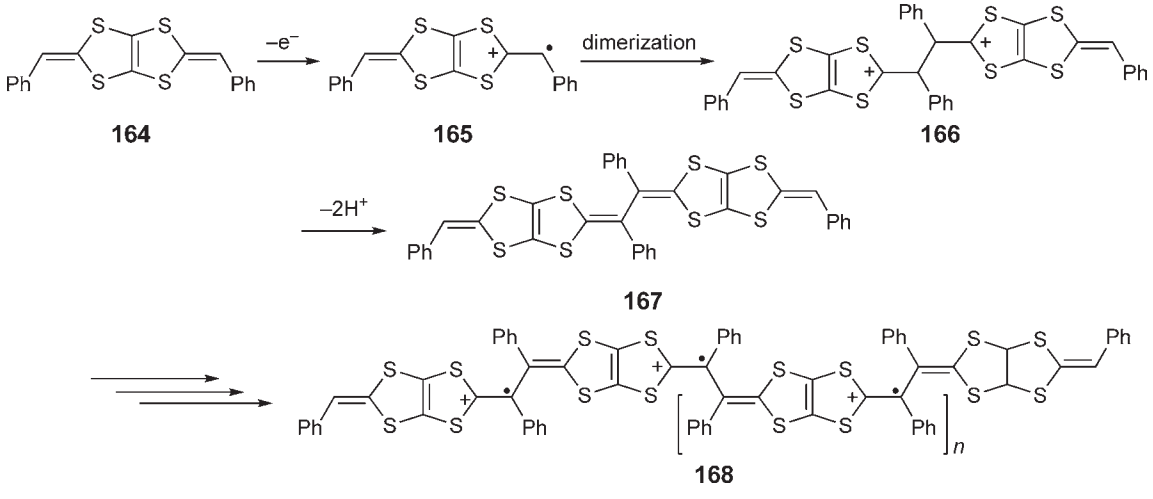
10.04.12.2 Organic Metals and Magnets

Given the number of articles that have investigated the synthesis and properties of organic metals that have appeared in the literature over the last decade, it is perhaps unsurprising that many researchers have exploited the current methodology for the preparation of the 5-5 system in the search for organic-based magnetic materials. Fujiwara *et al.* have examined the magnetic and redox properties of the stable free radical species **163** by cyclic voltammetry <1999CC2417>.



163

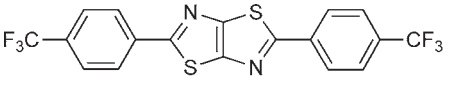
Müller and co-workers have prepared the first reported tetrathiafulvalene (TTF) main chain polymer which they suggest may improve metallic and redox properties of the material due to improved through-bond and through-space interactions in the solid state <1999CC1407>. They also report a simple synthesis of the polymeric material via a novel oxidative polymerisation sequence as outlined in **Scheme 18**.



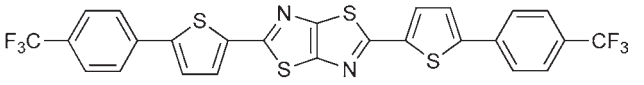
164 **165** **166** **167** **168**

Scheme 18

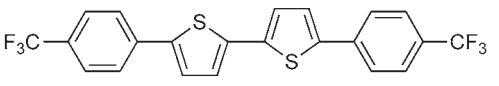
More recently, the 5-5 heterocyclic system has found application in the preparation of *n*-type organic field effect transistors, which are currently receiving much attention for applications such as flexible displays, low-cost electronic papers, and smart memory-sensor elements. The most recent examples are molecules prepared by Yamashita, who has prepared the planar, perfluorinated thiazolothiazole molecules **169–171** to this end <2004CL1170, 2005JA5336, 2004JMC1787>.



169



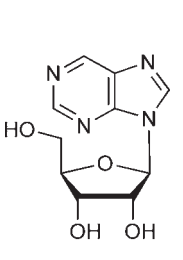
170



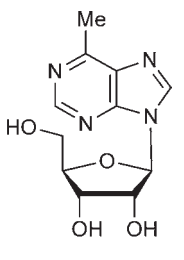
171

10.04.12.3 Medicinal Applications

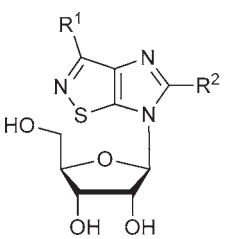
Much has been said about the application of this heterocyclic system in supramolecular chemistry and in materials chemistry, particularly in the preparation of organic conductors and superconductors. It should not be forgotten however that heterocyclic compounds in general are extremely important medicinal compounds. Although medicinal applications of this heterocyclic system have been rare in the years since CHEC-II(1996), some have been reported. Townsend and co-workers have described the preparation of imidazo[4,5-*d*]isothiazole nucleosides **174–177** and have demonstrated their properties as antiproliferative and antiviral analogues of the antibiotic nebularine **172** and the highly cytotoxic 6-methylpurine nucleoside **173** <1997JME771>.



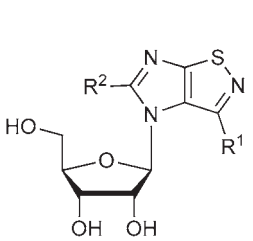
172



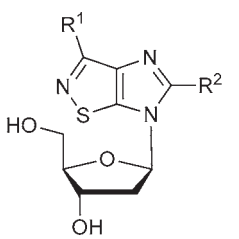
173



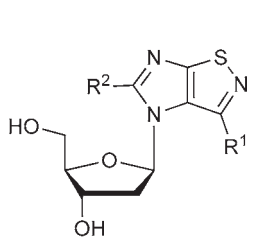
174



175



176



177

R^1 = Me, H R^2 = SMe, H

References

1984CHEC(6)1027 C. A. Ramsden; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol 6, p. 1027.

1995S1485 K. Pal, *Synthesis*, 1995, 1485.

1995TCC25 R. P. Sijbesma and R. J. M. Nolte, *Top. Curr. Chem.*, 1995, **175**, 25.
1996CC245 J. N. H. Reek, A. Kros, and R. J. M. Nolte, *J. Chem. Soc., Chem. Commun.*, 1996, 245.
1996CHEC-II(7)115 S. P. Stanforth; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol 7, p. 115.
1996JOC3650 Y. Misaki, H. Fujiwara, and T. Yamabe, *J. Org. Chem.*, 1996, **61**, 3650.
1996T7179 C. B. Vicentini, A. C. Veronese, M. Manfrini, and M. Guarneri, *Tetrahedron*, 1996, **52**, 7179.
1997IJB403 M. S. Chande and R. M. Joshi, *Indian J. Chem., Sect. B*, 1997, **36**, 403.
1997JA77 R. Meissner, X. Garcias, S. Mecozzi, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 77.
1997JME771 E. E. Swayze, J. C. Drach, L. L. Wotring, and L. B. Townsend, *J. Med Chem.*, 1997, **40**, 771.
1997J(P2)1473 J. L. M. van Nunen and R. J. M. Nolte, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1473.
1997T13855 U. Chiacchio, A. Corsaro, G. Gumina, V. Pistarà, M. Alessi, A. Piperno, G. Romeo, and R. Romeo, *Tetrahedron*, 1997, **53**, 13855.
1998CC1207 C. W. Rees and T.-Y. Yue, *J. Chem. Soc., Chem. Commun.*, 1998, 1207.
1998JA66 Y. Tokunaga and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **120**, 66.
1998JA3650 J. Kang, G. Hilmersson, J. Santamaria, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1998, **119**, 3650.
1998RJO1026 A. N. Terpigorev and S. B. Rudakova, *Russ. J. Org. Chem. (Engl. Transl.)*, 1998, **34**, 1026.
1999CC1407 H. Müller, F. Salhi, T. Narayanan, M. Lorenzen, and C. Ferrero, *J. Chem. Soc., Chem. Commun.*, 1999, 1407.
1999CC2417 H. Fujiwara and H. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1999, 2417.
1999JHC161 J. E. Schachtner, T. Zoukas, H.-D. Stachel, K. Polborn, and H. Noth, *J. Heterocycl. Chem.*, 1999, **36**, 161.
1999J(P1)817 G. Tennant, C. J. Wallis, and G. W. Weaver, *J. Chem. Soc., Perkin. Trans. 1*, 1999, 817.
1999JRM3001 H. A. Shindy, *J. Chem. Res. (M)*, 1999, 3001.
1999T13809 R. Nesi, S. Turchi, D. Giomi, and A. Danesi, *Tetrahedron*, 1999, **55**, 13809.
1999TL6635 J.-I. Yamada, K. Aoki, S'.I. Nakatsuji, H. Nishikawa, I. Ikemoto, and K. Kikuchi, *Tetrahedron Lett.*, 1999, **40**, 6635.
1999TL8157 A. Taher, A. M. Z. Slawin, and G. W. Weaver, *Tetrahedron Lett.*, 1999, **40**, 8157.
2000EJO51 M. R. Bryce, T. Finn, A. J. Moore, A. S. Batsanov, and J. A. K. Howard, *Eur. J. Org. Chem.*, 2000, 51.
2000TL9319 A. Taher, A. M. Z. Slawin, and G. W. Weaver, *Tetrahedron Lett.*, 2000, **41**, 9319.
2001JA11519 B. M. O'Leary, T. Szabo, N. Svenstrup, C. A. Schalley, A. Lutzen, M. Schafer, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2001, **123**, 11519.
2001MCLC(356)253 J.-I. Yamada, H. Akutsu, S'.I. Nakatsuji, H. Nishikawa, I. Ikemoto, and K. Kikuchi, *Mol. Cryst. Liq. Cryst.*, 2001, **356**, 253.
2001TL5455 T. Hanazawa, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, 2001, **42**, 5455.
2002CJC517 M. Rahimizadeh, K. Kam, S. I. Jenkins, R. S. McDonald, and P. H. M. Harrison, *Can. J. Chem.*, 2002, **80**, 517.
2002CL1002 K. Takahashi, H. Tanioka, H. Fueno, Y. Misaki, and K. Tanaka, *Chem. Lett.*, 2002, 1002.
2002EJI2380 D. G. Samsonenko, J. Lipkowski, O. A. Gerasco, A. V. Virovets, V. P. Fedin, J. G. Platas, R. Hernandez-Molina, and A. Mederos, *Eur. J. Inorg. Chem.*, 2002, 2380.
2002SC2245 G. H. Elgemeie, A. H. Elghandour, H. A. Ali, and A. M. Hussein, *Synth. Commun.*, 2002, **32**, 2245.
2002T9769 A. Wu, J. C. Fettinger, and L. Isaacs, *Tetrahedron*, 2002, **58**, 9769.
2003IJB2625 M. S. Chande and A. P. Amle, *Indian. J. Chem., Sect. B*, **42**, 2625.
2003OL3745 J. Lagona, J. C. Fettinger, and L. Isaacs, *Org. Lett.*, 2003, **5**, 3745.
2003OL3875 T. Kudoh, T. Ishikawa, Y. Shimizu, and S. Saito, *Org. Lett.*, 2003, **5**, 3875.
2003SC1675 I. Tapsoba, N. Adhoum, M. L. B. Khoud, R. Kossai, and K. Boujlel, *Synth. Commun.*, 2003, **33**, 1675.
2003TL395 H. Zhang, W. H. Chan, Albert, W. M. Lee, and W. Y. Wong, *Tetrahedron Lett.*, 2003, **44**, 395.
2004CL1170 S. Ando, J.-I. Nishida, E. Fujiwara, H. Tada, Y. Inoue, S. Tokito, and Y. Yamashita, *Chem. Lett.*, 2004, 1170.
2004H(63)2475 D. A. Berry, T.-C. Chien, and L. B. Townsend, *Heterocycles*, 2004, **63**, 2475.
2004JA10035 A. Wu, P. Mukhopadhyay, A. Chakraborty, J. C. Fettinger, and L. Isaacs, *J. Am. Chem. Soc.*, 2004, **126**, 10035.
2004JMC1787 S. Ando, J.-I. Nishida, Y. Inoue, S. Tokito, and Y. Yamashita, *J. Mater. Chem.*, 2004, **14**, 1787.
2004MM288 D. Tuncel and J. H. G. Steinke, *Macromolecules*, 2004, **37**, 288.
2004OBC1685 T. Shirahata and T. Imakubo, *Org. Biomol. Chem.*, 2004, **2**, 1685.
2004OL1225 S. Sasmal, M. K. Sinha, and E. Keinan, *Org. Lett.*, 2004, **6**, 1225.
2004SMC175 J. M. Kang, H. K. Ju, and J. H. Jo, *Supramol. Chem.*, 2004, **16**, 175.
2004TL5225 J. Kang, J.-H. Jo, and S. In, *Tetrahedron Lett.*, 2004, **45**, 5225.
2005HCA1208 H.-D. Stachel, B. Zimmer, E. Eckl, K. Semmlinger, W. Weigand, R. Wünsch, and P. Mayer, *Helv. Chim. Acta*, 2005, **88**, 1208.
2005JA5336 S. Ando, J.-I. Nishida, H. Tada, Y. Inoue, S. Tokito, and Y. Yamashita, *J. Am. Chem. Soc.*, 2005, **127**, 5336.
2005JA14511 M. E. Bush, N. D. Bouley, and A. R. Urbach, *J. Am. Chem. Soc.*, 2005, **127**, 14511.
2005RCB472 V. B. Sokalov, A. Y. Aksinenko, T. A. Epishina, T. V. Goreva, and I. V. Martynov, *Russ. Chem. Bull.*, 2005, **54**, 472.
2005RJO1507 A. A. Zaitsev, I. L. Dalinger, A. M. Starosotnikov, V. V. Kachala, Y. A. Strelenko, T. K. Shikineva, and S. A. Shevelev, *Russ. J. Org. Chem. (Engl. Transl.)*, 2005, **41**, 1507.
2005TA761 H.-K. Zhang, W.-H. Chan, A. W. M. Lee, W.-Y. Wong, and P.-F. Xia, *Tetrahedron Asymmetry*, 2005, **16**, 761.
2005THE79 H.-J. Buschmann, L. Mutihac, R.-C. Mutihac, and E. Schollmeyer, *Thermochim. Acta.*, 2005, **430**, 79.
2005TL1759 J. Kang and J. Kim, *Tetrahedron Lett.*, 2005, **46**, 1759.
2005TL7165 S. In and J. Kang, *Tetrahedron Lett.*, 2005, **46**, 7165.
2006JOC4502 Z.-G. Wang, B.-H. Zhou, Y.-F. Chen, G.-D. Yin, Y.-T. Li, A.-X. Wu, and L. Isaacs, *J. Org. Chem.*, 2006, **71**, 4502.
2006SL49 G. Yin, Z. Wang, Y. Chen, A. Wu, and Y. Pan, *Synlett*, 2006, 49.

Biographical Sketch



Jonathan Wilden obtained a BSc double honours degree in chemistry and biochemistry from the University of Southampton, UK where he also obtained a PhD degree in synthetic organic chemistry under the supervision of Prof. D. C. Harrowven. He then moved to the University of Sussex, Brighton, UK to undertake postdoctoral work with Prof. S. Caddick in 2000. In 2003 he moved to a postdoctoral position at University College London before being appointed to his current position as lecturer in organic chemistry and chemical biology in 2004 at the same institution.

10.05
Bicyclic 5-5 Systems: Five Heteroatoms 2:3 and Six Heteroatoms 3:3

F. Heaney and L. Doyle
National University of Ireland, Maynooth, Republic of Ireland
© 2008 Elsevier Ltd. All rights reserved.

10.05.1 Introduction 192
10.05.2 Theoretical Methods 192
10.05.2.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles 192
10.05.2.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 196
10.05.2.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 198
10.05.2.4 [1,2,3]Triazolo[4,5-*d*][1,2,3]triazoles 199
10.05.2.5 Imidazolo- and thiazaolo[4,5-*d*][1,2,3]triazoles 200
10.05.2.6 Isoxazolo[4,5-*d*][1,2,3]triazoles 200
10.05.3 Experimental Structural Methods 200
10.05.3.1 X-Ray Diffraction 200
10.05.3.1.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles 200
10.05.3.1.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 201
10.05.3.1.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]azadiphospholes 202
10.05.3.1.4 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 202
10.05.3.1.5 [1,2,3]Triazolo[4,5-*d*][1,2,3]triazoles 202
10.05.3.1.6 [1,3]Dithiolo[4,5-*d*][1,3,2]dithiaboroles 203
10.05.3.1.7 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 203
10.05.3.1.8 [1,3]Dioxolo[4,5-*c*][1,2,5]thiadiazoles 204
10.05.3.1.9 Imidazo[4,5-*c*][1,2,5]thiadiazoles 204
10.05.3.1.10 Pyrazolo[3,4-*d*][1,2,3]triazoles 205
10.05.3.1.11 Imidazo[4,5-*d*][1,2,3]triazoles 205
10.05.3.1.12 Imidazo[4,5-*d*][1,3,2]diazaborolidines 206
10.05.3.1.13 [1,2,3]Triazolo[4,5-*d*][1,3,2]thiazaphospholes 206
10.05.3.2 Molecular Spectra 206
10.05.3.2.1 Nuclear magnetic resonance spectroscopy 206
10.05.3.2.2 Mass spectrometry 211
10.05.3.2.3 UV/Vis and fluorescence spectroscopy 211
10.05.3.2.4 Raman spectroscopy 213
10.05.3.2.5 IR spectroscopy 213
10.05.3.2.6 Reflectivity spectroscopy 214
10.05.3.2.7 X-Ray photoelectron spectroscopy 214
10.05.3.2.8 Ultraviolet photoelectron spectroscopy 214
10.05.3.2.9 Surface plasmon resonance spectroscopy 214
10.05.3.2.10 Cyclic voltammetry 214
10.05.3.2.11 ESR spectroscopy 216
10.05.4 Thermodynamic Aspects 217
10.05.4.1 Magnetic Properties 217
10.05.4.1.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles 217
10.05.4.1.2 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 218
10.05.4.2 Electrical Properties 219
10.05.4.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 219

10.05.4.3 Melting Points, Boiling Points, Thermal Stability, Stability to Moisture, Solubility, R_f values 219
10.05.5 Reactivity of Fully Conjugated Rings 220
10.05.5.1 Electrophilic Attack at Nitrogen 220
10.05.5.1.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 220
10.05.5.1.2 Imidazo[4,5-*c*][1,2,5]thiadiazoles 221
10.05.5.1.3 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles 221
10.05.5.2 Nucleophilic Attack at Carbon 221
10.05.5.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 221
10.05.5.3 Oxidation 223
10.05.5.3.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 223
10.05.5.3.2 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 223
10.05.5.4 Reduction 223
10.05.5.4.1 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 223
10.05.5.5 Nucleophilic Attack at Sulfur 223
10.05.5.5.1 Imidazolo[4,5-*d*][1,2,3]dithiazoles 223
10.05.5.6 Miscellaneous Reactivity 224
10.05.5.6.1 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 224
10.05.6 Reactivity of Nonconjugated Rings 224
10.05.6.1 Electrophilic Attack at Ring Nitrogen 224
10.05.6.1.1 Pyrazolo[3,4-*d*][1,2,3]triazoles 224
10.05.6.1.2 Imidazo[4,5-*c*][1,2,5]thiadiazoles 224
10.05.6.2 Electrophilic Attack at Ring Oxygen 226
10.05.6.2.1 Oxazolo[4,5-*d*][1,2,3]triazoles 226
10.05.6.3 Reduction 226
10.05.6.3.1 Imidazo[4,5-*d*][1,3,2]diazaborolidines 226
10.05.6.4 Oxidation 226
10.05.6.4.1 Pyrazolo[3,4-*d*][1,2,3]triazoles 226
10.05.6.5 Miscellaneous Reactivity 226
10.05.6.5.1 Nitrogen extrusion – ring contraction 226
10.05.6.5.2 Fragmentation reactions 227
10.05.7 Reactivity of Substituents Attached to Ring Carbon Atoms 227
10.05.7.1 Condensation Reactions 227
10.05.7.1.1 Pyrazolo[4,3-*d*][1,2,3]oxadiazoles 227
10.05.7.2 Attack by Organometallic Reagents 228
10.05.7.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 228
10.05.8 Reactivity of Substituents Attached to Ring Heteroatoms 228
10.05.8.1 Cycloaddition 228
10.05.8.1.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 228
10.05.8.2 Elimination (Retro-Michael) 229
10.05.8.2.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 229
10.05.8.3 Nitrogen Elimination 229
10.05.8.3.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 229
10.05.8.4 Reduction 229
10.05.8.4.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 229
10.05.8.5 Oxidation 230
10.05.8.5.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 230

10.05.8.6 Condensation 230
10.05.8.6.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 230
10.05.8.7 Substitution Reactions 231
10.05.8.7.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles 231
10.05.8.8 Hydrolysis 231
10.05.8.8.1 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles 231
10.05.8.8.2 Pyrazolo[3,4-*d*][1,2,3]triazoles 232
10.05.9 Ring Syntheses Classified by Number of Ring Atoms Contributed by Each Component 232
10.05.9.1 Synthesis from Monocyclic Precursors 232
10.05.9.1.1 Synthesis from [5+0] atom fragments 232
10.05.9.1.2 Synthesis from [4+1] atom fragments 237
10.05.9.1.3 Synthesis from [3+2] atom fragments 242
10.05.9.2 Syntheses from Acyclic Precursors 245
10.05.9.2.1 [1,3]Dioxolo[4,5-*c*][1,2,5]thiadiazoles 245
10.05.9.2.2 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles 245
10.05.10 Ring Syntheses by Transformation of Another Ring 246
10.05.10.1 [1,2,3]Triazolo[4,5-*d*][1,3,2]thiazaphospholes 246
10.05.10.2 Oxazolo[4,5-*d*][1,2,3]triazoles 247
10.05.10.3 Imidazo[4,5-*d*][1,2,3]triazoles 248
10.05.10.4 Miscellaneous Syntheses 249
10.05.10.4.1 Imidazo[4,5-*d*][1,2,3]triazoles 249
10.05.10.4.2 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles 249
10.05.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available 251
10.05.12 Important Compounds and Applications 251
10.05.12.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles 251
10.05.12.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 251
10.05.12.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazolium inner salts 251
10.05.12.4 [1,3]Dithiolo[4,5-*d*][1,3,2]dithiaboroles 252
10.05.12.5 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles 252
10.05.12.6 Imidazo[4,5-*c*][1,2,5]thiadiazoles 253
10.05.12.7 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles 253
10.05.12.8 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles 253
10.05.12.9 Imidazo[4,5-*c*][1,2,3]triazoles 253
10.05.12.10 Pyrazolo[3,4-*d*][1,2,3]triazoles 253
10.05.13 Further Developments 254
10.05.13.1 [1,2,5]Oxadiazolo[3,4-*c*][1,3,2]diazaphospholes 254
10.05.13.2 Imidazo[4,5-*d*][1,2,3]oxadiazoles 255
10.05.13.3 Imidazo[4,5-*c*][1,2,5]oxadiazoles 255
10.05.13.4 Imidazo[4,5-*d*][1,3,2]diazaborolidines 255
10.05.13.5 Pyrazolo[3,4-*d*][1,2,3]triazoles 255
10.05.13.6 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles 256
10.05.13.7 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles 257
References 257

10.05.1 Introduction

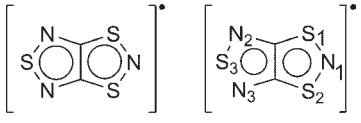
This review covers all aspects of the development of the chemistry of bicyclic 5-5 systems bearing only carbon atoms at the ring junction positions and either five heteroatoms in a 2:3 arrangement or six heteroatoms in a 3:3 arrangement since the previous review in 1996CHEC-II(7)141. In addition to material presented in the literature during the period 1996–2006, discussions from a number of articles not covered in previous review are included. While syntheses and reactivity of this class of molecules have continued to receive much attention, the most intense developments have been in the areas of theoretical analyses and X-ray diffraction (XRD) studies. One member of this class of compounds, namely the radical of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole TTTA, has received enormous attention during the review period; a driving force for much of the theoretical, experimental, and structure determination studies has been toward the development of novel organic conductive materials and molecular magnets.

10.05.2 Theoretical Methods

There have been a number of model studies on these types of compounds with computational analysis being applied to assist in the understanding of molecular structure and reactivity as well as in the estimation of the potential of molecules to act as high energetic materials or molecular building blocks.

10.05.2.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles

The potential of thiadiazolyl organic radicals as stable building blocks for conductive materials and molecular magnets underlies much of the attention dedicated to theoretical aspects of such species in the last decade. Researchers in this field wish to devise convenient computational protocols for prediction of the properties of new radicals in the belief that the availability of accurate theoretical models should provide synthetic direction. In particular, the 1,3,5-trithia-2,4,6-triazapentalenyl (TTTA) radical **1** has been extensively investigated <1996MRC913, 1999SCI261, 2000CPL(327)409, 2001PCA7615, 2001PCA7626, 2001PS145, 2002MI432, 2004MI689, 2004MI204, 2004MI3719, 2005CPL(405)382, 2005MI320>.



1

The electronic structure and isotropic hyperfine coupling constants (hfcc's) for a series of heteroaromatic compounds including TTTA have been successfully reproduced by density functional theory (DFT) <1996MRC913>. This development is significant since computations at the semi-empirical and unrestricted Hartree–Fock (UHF) levels, which while largely successful for hydrocarbons, have been unsuccessful for heteroaromatic compounds including TTTA <1991MRC625>. The calculations were performed with molecular geometry optimized by gradient-corrected DFT(UB3LYP)/6-31G* methods and isotropic hcc's were calculated through Fermi contact analysis. Discrepancies arising between the calculated and measured geometries, shown in **Table 1**, have been attributed to the fact that the experimental values are from crystal studies while the theoretical values are from the gas phase. Additionally, the antiferromagnetic interaction in the solid phase leading to dimers was also considered likely to influence the experimental geometrical parameters. The hfcc values, calculated at the DFT(UB3LYP)/TZVP level, agreed well with

Table 1 Molecular symmetry, and calculated selected geometrical parameters and hfcc's for TTTA, **1**

		a_{iso} (mT)			
Symmetry	*Geometry* (Å)	*Atom*	*Theory*	*Experiment*	*Reference*
$B_1(C_{2v})$	S–N(1) 1.679	N-1	1.030	1.121[a]	1996MRC913
	S–N(2) 1.694	N-2	0.082	0.085	
$^2B_1(C_{2v})$		N-1	1.109	1.115[b]	2000CPL(327)409
		N-2	0.084	0.084	
		S	0.276	0.329	

[a] <1989AG952>.
[b] <1991MRC625>.

experimental values, indicating the importance of the choice of basis set for predictive power. Further, computationally more demanding, and consequently at greater computational cost, *ab initio* calculations did not provide better results with the same basis sets <1996MRC913>. Subsequently the UB1LYP hybrid DFT method was shown to be a more accurate and efficient method for the computation of isotropic hfcc's of neutral bicyclic thiadiazole radicals including TTTA. For these calculations, the molecular geometry was taken from X-ray crystal structures, and the results, compared with those obtained by the (UB3LYP)/TZVP approach, are summarized in **Table 1** <2000CPL(327)409>. Kaszynski's results, on the other hand, suggest that with the introduction of appropriate scaling factors, different basis sets can be employed to most accurately relate experimental and computed hfcc's for different nuclei with the UB3LYP/cc-pVZD method at the UB3LYP/6-31G(d) geometry being optimal for ^{14}N (scaling factor 0.767) while the UHF/6-31G(d) geometry for the UB3LYP/cc-pVDZ single-point calculation are best for ^{33}S (scaling factor 1.231) <2001PCA7615>.

Electronic structure calculations have shown TTTA to be essentially planar and the residency of the unpaired electron to be largely on N_1. The SOMO, computed at the UB1LYP level, showed it to reside largely on the S–N–S moiety with a significant minor portion delocalized over the N–S–N moiety; virtually no spin density was calculated to reside over the ring C-atoms <2000CPL(327)409>. Mulliken total atomic charge density maps, calculated using the UB3LYP/6-31G* method, indicate that the electronegative nitrogen atoms display the highest electron density while the more electropositive sulfur atoms bear the most positive charge <2001PCA7615>. DFT calculations using geometry given by crystal data suggest 84% of the delocalized unpaired electron is based on the S–N–S fragment with just 22% on the N–S–N fragment. The calculated % π-electron density and % total spin density, shown in **Table 2** <2001PS145, 2001JMC1992>, are in excellent agreement with those experimentally determined by electron paramagnetic resonance (EPR) spectroscopy (see Section 10.05.3.2.11). Hulliger's laboratory has compared results from a DFT approach, using several different basis sets with the B3LYP and PW91 functionals, with those calculated with the MP2 method. Calculations were based on the MP2/cc-pVTZ-optimized geometry of the TTTA radical. DFT results using different basis sets were largely in agreement with each other; however, the MP2 results were considerably different from the others <2002MI432>. TTTA is shown to have strong electrical polarization with positive polarized charges on S and negative polarized charges on N. Calculations at the UB3LYP/6-31G* level propose it to have a dipole moment, 0.8 D <2001PCA7615>, while B3LYP/cc-pVTZ level calculations furnish a reduced value, 0.609 D <2002MI432>.

Table 2 Theoretical spin density distribution determined from DFT calculations and spin density distributions at heterocyclic N-atoms from EPR data

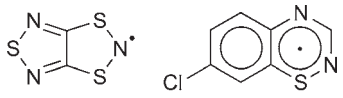
	% π-electron density		*% total spin density*		
Atom	DFT	EPR[a]	DFT	MP2	EPR[a]
N-1	47.6[a]	44.4	50.7[a] 53.5[b]	51.4	46.1
S-1	14.2[a]		16.7[a] 16.9[b]	22.3	
C	−1.9[a]		−3.1[a] −3.6[b]	9.7	
N-2	5.6[a]	3.9	5.7[a] 4.3[b]	−8.8	4.0
S-2	9.9[a]		11.1[a] 11.3[b]	2.1	

[a]Basis set not recorded <2001PS145, 2001JMC1992>.
[b]Level of calculation B3LYP/cc-pVTZ <2002MI432>.

A comparison of total hyperfine tensor component computed using the UB1LYP method, with experimental values, was found to be disappointingly poor given the accuracy of the computed isotropic components and the apparent ease of calculation of the anisotropic component. One suggestion for the disparity between calculated and experimental values is the difficulty in accurate estimation of the values from an experimental spectrum, and thus it was concluded that currently it is not possible to comment on the suitability or otherwise of the UB1LYP method for this type of calculation <2000CPL(327)409>.

The UB1LYP hybrid density functional (HDF) method has been found suitable for accurate reproduction of gyromagnetic (*g*) tensors of TTTA to within 140–750 ppm of their experimental value. The report is significant since it represent the first accurate calculation of *g* tensors of this class of radicals without using post-HF techniques <2005CPL(405)382>.

The B3LYP/6-31+G(d)//B3LYP/6-31G(d) method has been used in a theoretical assessment of redox processes of TTTA. The results suggest that TTTA has high electron-transfer ($\Delta E^1_{SCF} = 146.1\,kcal\,mol^{-1}$) and relaxation energies ($\Delta E^2_{SCF} = -8.8\,kcal\,mol^{-1}$), showing $\Sigma\Delta E_{SCF} = 137.3\,kcal\,mol^{-1}$. These values would seem to preclude it from exhibiting high conductivity, so questioning the candidacy of TTTA itself as a molecular superconductor. By way of comparison, the 1,2,4-benzothiadiazine, **2**, showing $\Sigma\Delta E_{SCF} = 122\,kcal\,mol^{-1}$, ought to be a reasonable candidate for construction of conductive materials <2001PCA7626>.

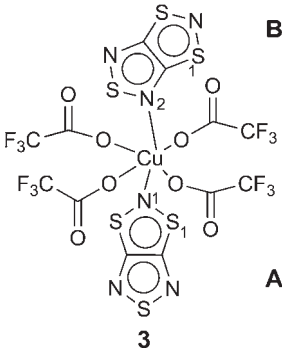


2

The TTTA radical has recently been shown to exhibit a first-order phase transition with a drastic change in magnetism and a surprisingly wide hysteresis loop over the temperature range 230–305 K. The radical has two structurally stable crystal phases, a high-temperature (HT) paramagnetic phase and a low-temperature (LT) diamagnetic phase. TTTA is observed to be thermochromic in the phase transition and the HT and LT phases are purple and green, respectively <1999SCI261>. Such properties are most attractive for molecule-based magnetic materials; thus, in addition to modeling of electronic structure and hfcc's, the structure of each phase, as well as the mechanism of the origin of the magnetism and of the magnetic interactions, have received much theoretical attention <2001MI21, 2001JMC1992, 2003MI911, 2004MI3719, 2004MI689, 2004MI204, 2005MI320>.

Structural optimization for both phases of TTTA has been conducted by means of *ab initio* molecular dynamics based on the local density approximation (LDA) in order to confirm the atomic coordinates obtained by XRD (see Section 10.05.3.1.1). The theoretical results concur with the experimental findings; the calculations predict the observed uniform, one-dimensional (1-D) radical stacking in the HT phase and strong dimerization along the stacking direction in the LT phase. A crucial difference in molecular packing in the two phases was noted; in the HT phase all molecular planes are parallel while the unit cell of the LT phase includes two molecular plane orientations, and Peierls distortion along the stacking direction appears. Volume and symmetry differences thus exist between the two phases <2004MI689, 2004MI3719>. The HT and LT phases have an estimated total energy difference of 0.31 eV <2004MI3719>.

The electronic structure of both phases of TTTA crystals has also been investigated theoretically by means of the all electron mixed basis approach, using both plane waves and atomic orbitals as a basis set, in the LDA of DFT <2003MI911, 2004MI3719>. Subsequently, DFT has been adopted for calculation of the magnetic properties and electronic band structure of TTTA <2004MI204> and the 1:1 complex of TTTA and bis(hexafluoroacetylacetonato)copper(II), [TTTA·Cu(hfac)$_2$]TTTA **3** <2005MI320>. The accurate full potential linearized augmented plane wave (FPLAPW) band structure method was used with adoption of the generalized gradient approximation (GGA) <2005MI320, 2004MI204>.



3

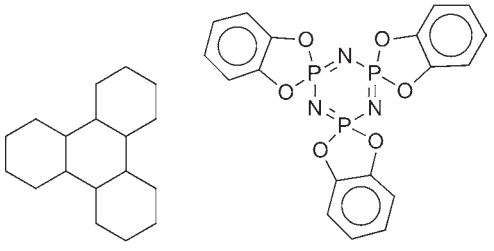
Calculated band structure of the HT phase of TTTA reveals Fermi levels exist, while in the LT phase, because of the dimerization of TTTA molecules, all twofold degenerate levels split into two separate levels with a 0.8 eV band gap. The clear distinction in the band diagrams is assumed to explain the origin of the Pauli spin paramagnetism (for a metal) in the HT phase and the closed-shell diamagnetism (for an insulator) in the LT phase. The theoretical calculation also suggests that TTTA should be a Mott insulator yet the HT phase of TTTA is not optically a metal in experiments; the apparent discrepancy can be explained by calculations based on the local spin density approximation <2003MI911, 2004MI3719>.

Electronic calculations suggest that the structural transition of TTTA from HT to LT phase takes place due to the Jahn–Teller effect, which occurs since the highest occupied molecular orbital (HOMO), a quasi-1-D system with a half-filled conduction band, is degenerate and partially occupied. The crystal is distorted spontaneously to gain energy and remove the degeneracy. The transition is regarded as a type of Peierls transition due to the quasi-1-D response of the 3-D electronic system between the HT phase having uniform stacking, and the dimerized LT phase. This explanation is in analogy to the well-known 1-D organic radical conductor, TTF–TCNQ (TTF = [1,2,5]thiadiazole-fused tetrathiafulvalene; TCNQ = tetracyanoquinodimethane) <2004MI689, 2004MI3719, 2003MI911>.

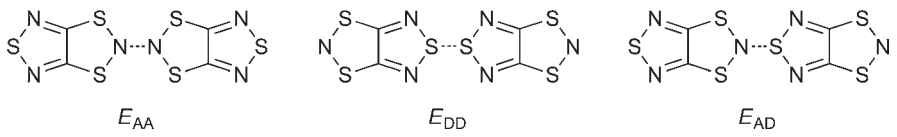
DFT investigations into the magnetism of both TTTA **1** <2004MI204, 2001JMC1992> and its $Cu(hfac)_2$ complex **3** <2005MI320> show that for TTTA the spin polarization effect and the spin exchange coupling interactions of the N-1, S-1, and S-2 atoms are responsible for the net magnetic moment. The spontaneous magnetic moments for the TTTA mainly come from the same atoms, viz. N-1, S-1, and S-2, with the N_2, N_3, and S_3 atoms making little contribution to the magnetism. The same paper reveals a ferromagnetic interaction in the intramolecular of TTTA <2004MI204>. The results for [TTTA·$Cu(hfac)_2$] **3** show that the spontaneous magnetic moments for the complex come largely from the Cu and N_1 atoms and that the magnetic interaction between them is small. It is also calculated that there would be ferromagnetic interaction between the Cu(II) ion and the N-1 atom of $TTTA^A$ and that there exists an antiferromagnetic interaction between the intramolecular organic ligands (see Section 10.05.4.1.1) <2005MI320>.

The magnetic exchange interactions of both the HT and LT phases of TTTA have been modeled by DFT using the broken symmetry approach. Calculations on the LT phase suggest it can be considered as a strongly coupled dimer with an open shell singlet state in which the exchange interaction is sufficiently strong ($2J = -2657$ K), as to render the sample essentially diamagnetic. The inter-dimer ($2J = -64$ K) and interstack interactions ($2J = -1.4$ to -7.3 K) are both of small magnitude. For the HT phase, the dominant exchange interaction is along the π-stacking direction and the singlet–triplet separation, $2J$, was estimated at -182 K. Interstack interactions are 1 or 2 orders of magnitude smaller ($2J = -12$ to $+7$ K), although significant interstack interactions were necessary to adequately model the data. The magnitude of J calculated for both phases agrees well with the observed values. The singlet and triplet energies were computed using the B3LYP nonlocal exchange and correlation functional and the LANL2DZ basis set with the geometries employed in the computations taken from crystal data <2001JMC1992>. The bistability of TTTA is attributed to an energetic match of the interstack interactions with the tendency of the π-stack to undergo a Peierls distortion <2001JMC1992>.

The concept of supramolecular motifs to obtain chains of magnetically interacting radicals in channel-type inclusion crystals lies behind the development of solid-state materials with designer properties. To this end, there has been an interest in prediction of the properties of TTTA radicals in the channels of perhydrotriphenylene (PHTP) **4** and tris(*o*-phenylenedioxy)cyclotriphosphazene (TPP) **5** <2002MI432>. *Ab initio* molecular orbital calculations, at the MP2 level of theory, have been applied to computation of the collinear intermolecular binding energies which have subsequently been used for a Markov-type prediction of the average chain length for magnetic interactions; typical synthon interaction of the three geometeries of collinear pairs of TTTA radicals, shown in **Figure 1**, up to about 6.0 kJ mol^{-1} can create unperturbed chains of about nine molecules on average. Theoretical results, shown in **Table 3**, indicate considerable variation between interaction energies (BSSE corrected) with the choice of basis set used; however, the relative energies, ΔE_A and ΔE_D vary rather little <2002MI432>. Calculations on four different arrangements of TTTA trimers (MP2/cc-pVDZ) showed a reduction in the equilibrium distance of just 5 pm, suggesting calculations for dimers are sufficient to model the supramolecular system. DFT calculations are unsuited to modeling such parameters since they have difficulties in describing the dispersion interaction.



4 **5**



E_{AA} E_{DD} E_{AD}

Figure 1 Definition of three TTTA dimer geometries.

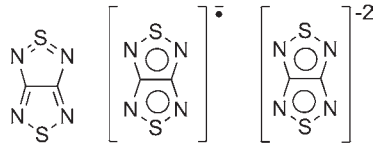
Table 3 Interaction energies, BSSE corrected, (kJ mol^{-1}), and intermolecular distances (pm) for three geometries of TTTA dimers (**Figure 1**) for different basis sets (MP2 level of theory): d_{AD}, d_{AA}, and d_{DD} are the equilibrium atomic distances between monomers; E_{AD}, E_{AA}, and E_{DD} are the interaction energies for the particular dimer geometries; and $\Delta E_f = \Delta E_A - \Delta E_D$ <2002MI432>

Basis set	d_{AD}	d_{AA}	d_{DD}	E_{AD}	E_{AA}	E_{DD}	ΔE_A	ΔE_D	ΔE_f
cc-pVDZ	3.42	3.60	3.99	−4.54	1.73	−1.01	6.27	3.53	2.74
aug-cc-pVDZ	3.35	3.54	3.72	−6.42	−0.10	−1.84	6.32	4.58	1.74
cc-pVTZ	3.43	3.72	3.95	−6.01	0.52	−1.85	6.53	4.16	2.37

The reflectivity spectrum of TTTA **1** in the LT phase <2003MI911> as well as the Raman and infrared (IR) spectra of the TTTA molecule <2004MI3719> have been calculated using a Gaussian 98 package programme with the exchange correlate of B3LYP and the basis function of atoms 6-311 g, and compared with experimental measurements. While the calculated Raman frequencies of the HT phase were found not to be in good agreement with the experimental ones, an overall correspondence with respect to peak positions and intensities was observed. The calculated reflectivity spectrum of the LT phase showed close similarity in overall behavior to the experimental reflection spectra <2002MI064434/1, 2004MI3719> although some differences in peak position and amplitude were observed <2003MI911, 2004MI3719>. The dielectric response function has been calculated for the electric field both parallel and perpendicular to the stacking direction of TTTA molecules in the LT phase. Significant differences in response were noted depending on the direction of the electric field <2003MI911, 2004MI3719>.

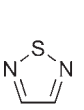
10.05.2.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

The 'carbon-poor' sulfur–nitrogen bicyclic [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6**, its radical anion **7**, and its dianion **8** have been the subject of a number of theoretical studies <1997JPO33, 2004JA11202, 2005IC7194>.

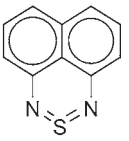


6 **7** **8**

An examination of the molecular and electronic structure of a range of cyclic and acyclic sulfur diimides employing HF-plus-correlation *ab initio* quantum chemistry and DFT using Becke's three-parameter functional along with the LYP functional has attempted to answer important structural questions, and in particular to address relationships between the structure and the excitation energies to the lowest-energy singlet and triplet excited states. A fundamental issue regarding the structure of molecules incorporating a sulfur diimide motif is whether they adopt a thiocumulene-type unit with a hypervalent sulfur atom, a dipolar resonance contributor, or a non-hypervalent spin-paired diradical structure. Calculated data for [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6**, as well as for the monocyclic **9** and the tricyclic analogue **10**, are collected in **Table 4**. Calculated d orbital occupation furnished no evidence for structures involving octet expansion of sulfur. The calculated N–S bond length of the bicycle **6**, which is in good agreement with the experimental data (162.0 pm) <1981CSC1403>, suggested the molecule takes an intermediate structure with resonance contributors exhibiting both the ═N–S–N═ and the –N═S═N– structural units. The molecular geometry taken with the calculated charge separation in the S–N bond of **6** indicates an intermediate position between the monocycle, 1,2,5-thiadiazole **9**, in which the NSN unit strongly fuses to the ethylene moiety, and naphtha[1,8-*c*,*d*][1,2,6]thiadiazine **10**, which has a short NSN bond and significant charge separation in keeping with a more or less ylidic NSN unit. Finally, a large calculated singlet/triplet gap for **6** and **9** suggests that these structures are far from being diradicaloid, while the opposite can be said of **10** with the small $\Delta E(S_o/T_1)$. *Ab initio* calculations of the lowest-energy vertical singlet–singlet and singlet–triplet transitions, which determine the position of the color band of ylidic sulfur compounds, suggest $S_1 \leftarrow S_0$ values as follows: **6** (4.18 eV, 297 nm); **9** (6.15 eV, 202 nm); **10** (2.19 eV, 566 nm). The result for the latter agrees well with the experimental absorption wavelength of the color band (642 nm) <1997JPO33>.



9

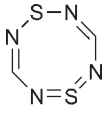


10

Table 4 Selected bond lengths, Mulliken total atomic charges, and S_0/T_1 splitting energies for sulfur diimides **6**, **9**, and **10** <1997JPO33>

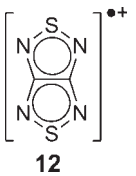
	r_{SN} (*pm*)		*DFT*		*DFT*
Compound	*DFT*	*MP2*	q_N	q_S	$\Delta E(S_0/T_1)$ (*kcal mol*$^{-1}$)
6	164.1	165.2	−0.520	+0.639	73.0
9	166.4	164.5	−0.455	+0.541	97.2
10	157.4	159.7	−0.557	+0.652	7.9

Optimization at the restricted Hartree–Fock (RHF) and DFT (B3LYP) levels in the 6-31G** basis set has also contributed to structural clarification of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6**; both approaches successfully predict that **6** ought to have planar equilibrium geometry. Direct *ab initio* ipsocentric calculations of the total π-current density map for **6** permits classification as aromatic according to magnetic criteria. It exhibits a strong and uniform diatropic perimeter circulation, of comparable intensity to the parent monocycle **11** and similar to that of naphthalene <2004JA11202>.



11

The results of DFT/(U)B3LYP/6-311+G* calculations have been used to explain structural changes involved in the experimentally known reversible electrochemical reduction of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** to the long-lived radical anion **7**, and further to the dianion **8** (see Section 10.05.5.4.1). This is an important characteristic since thiazoyl radicals are considered potential building blocks for molecular magnets and/or molecular conductors (see Section 10.05.12.2). Calculations at the same level also explain the failure of the electrochemical approach to generation of the [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazolidyl radical cation **12** (see Section 10.05.5.4.1). The four electronegative nitrogen atoms highly stabilize the HOMO of the parent bicycle **6** which is calculated to have HOMO ($-\varepsilon_i = 8.06$ eV). The singly occupied molecular orbital (SOMO) of the radical anion **7** is calculated to have $-\varepsilon_i = 0.35$ eV. The SOMO is antibonding for the S–N and nonbonding for the C–N bonds. These data explain the experimentally observed elongation of the S–N bonds and the lack of change in the C–N bond length in going from the parent to the radical anion (see Section 10.05.3.1.2). In going from the radical anion to the dianion, the SOMO of the former transforms to the HOMO of the latter, and the corresponding elongation of the S–N bonds of **8** reflects the antibonding character of this molecular orbital (**Table 5**) <2005IC7194>. The same paper reports a calculation of electron spin resonance (ESR) parameters of **6**; the hfcc $a(^{14}N \times 4)$ is calculated as 0.238 mT and g computed as 2.004 5 using the DFT/(U)B3LYP/6-311+G* method <2005IC7194>.



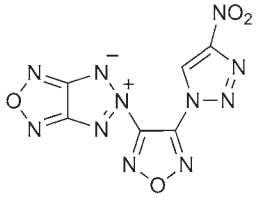
12

Table 5 Calculated values of selected bond lengths (pm) for [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6**, the radical anion **7**, and the dianion **8** <2005IC7194>

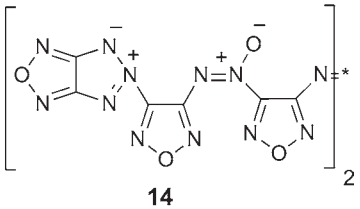
	6		**7**		**8**	
Bond (*pm*)	*XRD*	*B3LYP*	*XRD* [K(18-crown-6)]**5**	*XRD* [K(18-crown-6)]**5**·MeCN	*UB3LYP*	*B3LYP*
S–N	161.9(2)	163.8	165.2(2)	165.9(2)	169.2	171.1
C–N	135.1(3)	133.9	135.2(3)	134.2(3)	133.6	133.0

10.05.2.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

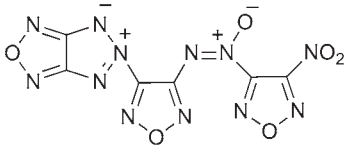
AAPF (atom–atom potential function) approaches have been found suitable for computation of several properties of [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazoles which are of use in prediction of their potential as high-energy materials. Enthalpies of formation (ΔH_f°), the molecular crystal density (ρ), and detonation velocity (D), for a number of synthesized and hypothetical members of the class of compounds **13–16**, have been computed by two different methods and the results are presented in **Table 6**. The first result in each column of the table is that computed using the set of additive schemes created at the Institute of Chemical Physics, RAN; the second result is that obtained from the methods developed at the Institute of Organic Chemistry, RAS; and there is good agreement between the results obtained by each method <1999MI1>. The diazo-linked bis-adduct **14** shows great potential as a prospective energetic compound. It has the highest enthalpy of formation and the most dense crystal packing among the synthesized compounds as well as having the record detonation velocity. The high detonation velocities calculated for the hypothetical compounds **13** and **15** suggest that they should be recommended for study as energetic materials (see Section 10.05.12.3) <1999MI1>.



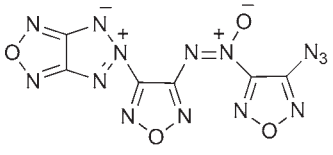
13



14



15

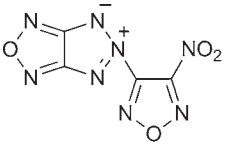


16

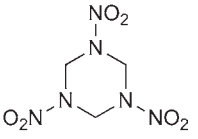
Table 6 Selected experimental and calculated characteristics for synthesized and hypothetical [1,2,3]triazolo[4,5-*c*]-[1,2,5]oxadiazole **13–17**

Compound number	*m.p.*, °*C* *Z*(*T* decomp., °*C*)	ρ ($g\,cm^{-3}$)	ΔH_f^0 ($kcal\,mol^{-1}$)	D ($km\,s^{-1}$)	*Reference*
Synthezied compounds					
13	193–194(>300)	1.87, 1.88	251, 276	8.93, 8.80	1999MI1
14	189–190(>270)	1.87, 1.84	670, 678	9.40, 8.92	1999MI1
17			202		1995JST(358)63
Hypothetical compounds					
15		1.88, 1.86	302, 310	9.43, 9.38	1999MI1
16		1.81, 1.77	378, 384	9.26, 9.10	1999MI1

A density functional procedure has been used to compute the gas-phase heat of formation of the triazolooxadiazole **17**, and the calculated value of ΔH_f° at 202 kcal mol^{-1} (903 cal g^{-1}) is more than 4 times greater than that of a leading military explosive, 1,3,5-trinitrohexahydro-1,3,5-triazine (RDX), **18** (206 cal g^{-1}), which supports the hypothesis that a high energy content is associated with nitrogen catenation <1995JST(358)63>.

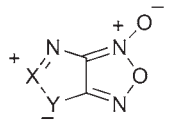


17

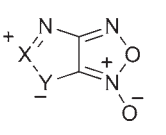


18

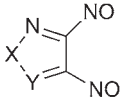
Ab initio and DFT studies have been used to predict whether nonclassical furoxans ought to adopt bicyclic structures as minima on the potential energy surface or if their open-chain dinitroso tautomers should be more stable. Theoretical analyses have been reported for the isoxazolo-, isothiazolo- , oxadiazolo-, and thiadiazolo-fused bicycles **18–28** and their open-chain tautomers **19T–23T** and **27T**, **28T**, none of which have been experimentally observed (or even trapped) <1996T743, 1998JST(451)263>. It is noted that simple RHF calculations are unsuited to determination of the equilibrium position and that the inclusion of electron correlation (MP2 level) is necessary <1996T743>. Initial results for all structures were in general agreement, with the nonclassical furoxan bicycles being found as minima using *ab initio* (RHF/6-31G*) and DFT(BLYP/6-31G*). With the inclusion of electron correlation (MP2/6-31G*//6-31G*; BLYP/6-31G*) in some cases, for example, **20/25** and **20T**, the energy difference between the nonclassical furoxan and the dinitroso tautomer was within the limit where an experimental verification of an equilibrium position would be required to provide clarity <1996T743>. However, the short endocyclic NO bond distance calculated by the RHF method and the long distance predicted by the DFT method for these molecules have cast some doubt over the results <1996T743>. The DFT method employing Becke's three-parameter exchange with the Lee, Yang, and Parr correlation functional (Becke3LYP/6-31G*) overcomes the known problem of the long N(O)–O bond distance calculated by the DFT(BLYP/6-31G*) method. Calculations at the Becke3LYP/6-31G* level suggest that the nonclassical furoxans **24–27** are less stable than the corresponding open-chain isomers **24T–27T** by 11.7–5.3 kcal mol^{-1}. Compounds **21–23** bearing one additional heteroatom are also calculated to be less stable than the tautomers **21T–23T** by 12.8–4.6 kcal mol^{-1} <1998JST(451)263>. These results contrast to those computed by the BLYP/6-31G* method which propose **22** to be more stable than **22T** by 5.1 kcal mol^{-1} <1996T743>. It is thus apparent that the BLYP functional and MP2 calculations may not be suited to nonclassical furoxans. Further support for the theoretical utility of the Becke3LYP/6-31G* method lies with the geometrical data calculated for **21–27**; in particular, the value obtained for the endocyclic NO bond distance seems more reliable than that provided by RHF or BLYP/6-31G* calculations <1998JST(451)263>.



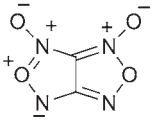
19: X = O; Y = C
20: X = S; Y = C
21: X = O; Y = N
22: X = S; Y = N
23: X = NH; Y = N



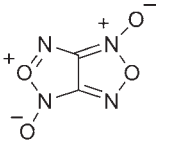
24: X = O; Y = C
25: X = S; Y = C
26: X = NH; Y = C



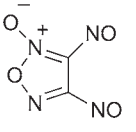
19T–23T



27



28



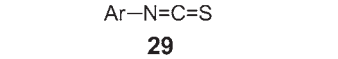
27T,**28T**

10.05.2.4 [1,2,3]Triazolo[4,5-*d*][1,2,3]triazoles

Modified intermediate neglect of differential overlap (MINDO/3) and modified neglect of differential overlap (MNDO) methods with full geometry optimization calculate triazol[4,5-*d*][1,2,3]triazole to possess antiaromatic structure with C_{2h} symmetry but not D_{2h}. In contrast, the aromatic structure with D_{2h} symmetry is found advantageous for the 2,5-dioxide derivative <1991IZV1825>.

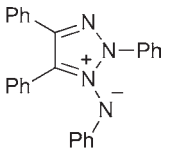
10.05.2.5 Imidazolo- and thiazaolo[4,5-*d*][1,2,3]triazoles

The observation that electron-withdrawing groups strongly orientate the cycloaddition between aryl isothiocyanates, **29** (Ar = Ph, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$), and the triazolium 1-imide, **30**, toward the C=S site has been explored theoretically. Calculations, 3-21G* and 6-31G*, suggest that linear triple-bonded canonical forms provide the explanation for the observed regioselectivity (N=C vs. S=C) (see Section 10.05.10.3) <1997J(P1)3587>.



29

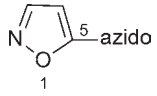
Ar = Ph, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$



30

10.05.2.6 Isoxazolo[4,5-*d*][1,2,3]triazoles

Ab initio calculations at the 6-31G(d,p)/MP2 level have lent support to the proposal, based on reaction rate studies, that the mechanism of cyclization of the transiently generated 5-azido-4-phenylazoisoxazoles involves internal capture of a nitrene (route b) rather than a π-electron reorganization with the involvement of neighboring group participation (route a) (**Scheme 27**, Section 10.05.9.1.1(iii)). Calculations on the model compound **31** find that, at the transition state, the N(1′)–N(2′) bond has stretched by 42% while the O(1)–C(5) bond has only stretched 3.7%. The calculated atomic charges show a large degree of transfer of charge from O-1 to the azido group on passing from reactant to transition state and that the C(5)–N(1') bond has developed 43% double-bond character <1996J(P2)2111>.



31

10.05.3 Experimental Structural Methods

10.05.3.1 X-Ray Diffraction

Employment of XRD studies to reveal details on the structure of a number of members of this class of bicyclic compounds has greatly increased in recent years with a large number of compounds being unambiguously characterized by this technique.

10.05.3.1.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles

A number of reports have appeared on crystal structure analyses for both the HT and LT phases of TTTA **1** <1989AG952, 1999SCI261, 2001SM(121)1767, 2001JMC1992, 2001POL1517, 2002MI432>. Awaga and co-workers obtained separate samples of both the HT and the LT phases of TTTA by annealing at 40 °C and at liquid nitrogen temperature for several hours, respectively. The same group has determined the crystal structures of both forms at room temperature <1999SCI261, 2001SM(121)1767, 2001POL1517, 2002MI064434/1> while Rawson and co-workers examined the HT phase over a range of temperatures (310, 250, and 225 K), and the LT phase at 150 K <2001JMC1992>. Both groups concluded that there were no significant differences between their analyses of the HT phase and the structure originally reported by Wolmershaser <1989AG952>. Over the temperature range studied, the HT phase was found to be monoclinic ($P2_1/c$) where one molecule is crystallographically independent; on the other hand, the LT phase is triclinic (P_1) with two molecules in the asymmetric unit, $TTTA^A$ and $TTTA^B$. In the HT phase, the TTTA molecules are planar within 0.025 Å. They form a polar 1-D regular π-stacking column along the crystallographic *b*-axis and are inclined at 21° to the stacking direction and display strong intercolumn interactions. Within the column, the stacking is regular and the overlap between neighboring molecules is slightly shifted. Each column has six neighbors with short S···N and S···S′ contacts, with distances shorter than the sums of the van der Waals radii in the intercolumn. While the molecular structure was essentially identical at all temperatures,

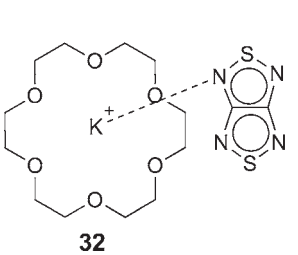
Rawson observed some slight contraction of the crystal lattice on cooling from 310 to 225 K, with slightly more contraction along the stacking axis *b* than along the *a*- or *c*-axis. Below 225 K, a large mosaic spread became apparent and the crystals showed a tendency to shatter. The LT phase has an almost identical molecular structure to the HT phase; however, there is a crucial difference in molecular packing. In the LT phase, the molecular planes are virtually parallel, while the unit cell of the HT phase comprises two molecular plane orientations. Further, in the LT phase, the TTTA molecules form discrete dimers which stack along the crystallographic *c*-axis with an eclipsed overlap between the molecular planes. In the inter-dimer arrangement, the molecular planes are not exactly parallel, being inclined at 3.5° to each other. The distance between the S–N–S moieties is 0.2 Å shorter than that between the N–S–N moieties. In the inter-dimer arrangement, there are many intermolecular and interatomic distances shorter than the sums of the van der Waals radii. With the exception of the dimerization of the π-stack in the LT phase, the intermolecular contacts in the LT and HT phases seem broadly comparable <2001JMC1992, 2002MI064434/1>. Theoretical investigations into the crystal structure of the two phases of TTTA have generally been successful in reproducing the experimental results (see Section 10.05.2.1) <2004MI689, 2004MI3719>.

The 1:1 complex TTTA·Cu(hfac)$_2$, **3**, representing the first polymeric coordination complex made from thiazyl radicals, formed deep blue, plate-like, crystals at −30 °C. The compound crystallized in the monoclinic $P2_1$ space group in which one unit of TTTA·Cu(hfac)$_2$ is crystallographically independent. The crystal structure shows Cu(hfac)$_2$ and one of the TTTA molecules – labeled TTTA^A – form the independent unit. The second TTTA, labeled TTTA^B, is obtained by the symmetry operation $(-x+1,\ y+0.5,\ -z+1)$ from TTTA^A. At each Cu(II) site, the geometry is a tetragonally distorted octahedron, the four coplanar equatorial coordination positions are occupied by oxygen atoms of the ligand, and the apical positions by nitrogen atoms of separate TTTA molecules. There is a significant difference between the two Cu–N distances with the Cu–N(1) of the dithiazoyl ring of one TTTA^A unit being 2.342(4) Å and the Cu–N(2) of the thiadiazolyl ring of the second TTTA^B unit being 2.478(5) Å. The molecular plane of the TTTA^A unit is closely orthogonal to the plane defined by the four oxygen atoms of the hfac ligand while the TTTA^B moiety slightly tilts to the plane of Cu(hfac)$_2$. There is a short distance, 3.208(4) Å, between S-1 on TTTA^B and an oxygen atom of the ligand, probably caused by an electrostatic interaction. This may suggest an overlap between the magnetic orbitals of TTTA^B and the ligand (see Section 10.05.4.1.1). TTTA bridges the distance between the Cu(II) ions creating an infinite zigzag chain along the *b*-axis. In the interchain arrangement, there are two short contacts between the sulfur atom of the dithiazolyl ring and the oxygen atoms of Cu(hfac)$_2$ <2001POL1517, 2001JA3601>.

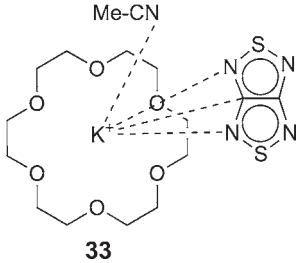
A crystallographic analysis has confirmed a hexagonal lattice for the inclusion complex between TPP **5** and TTTA **1** radicals formed from in-diffusion of TTTA in zeolite crystals of TPP–(THF)$_{0.58}$ (THF = tetrahydrofuran). Entry of the radicals into the needle-shaped crystals was accompanied by the capping faces turning blue. 'In-diffused crystals' featured strong dichroism. In the final state, the crystals were composed of TPP–(THF)$_{0.35}$–(TTTA)$_{0.16}$. Light blue crystals, also featuring dichroism, resulted from the solution co-crystallization of TTTA with biphenyl in PHTP **4** <2002MI432>.

10.05.3.1.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

[1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** and the stable radical anion salts [K(18-crown-6)][**7**] **32** and [K(18-crown-6)][**7**]·MeCN **33** have been characterized by XRD <2005IC7194>. The parent bicycle presented as monoclinic crystals ($P2_1/c$) while the salts **32** and **33** presented as triclinic $P\bar{1}$ and monoclinic ($P2_1/m$) crystals, respectively. Significant structural differences in going from the parent to the radical anions include the elongation of the S–N and C–C bonds, while very little change is observed in the C–N bond length. A DFT study has attempted to explain these observations. The crystal packing in the salts is seen to be very different with the radical anion acting as a bridging ligand in **32** and as a chelating ligand in **33**. Long distances between the radical anions exclude their interaction in the crystal, suggesting the salts to be paramagnetic (Mott) insulators; however, with smaller cation packing patterns, favorable radical interaction may become possible (see Section 10.05.2.2) <1997JPO33, 2004JA11202, 2005IC7194>.



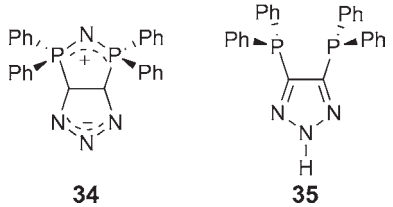
32



33

10.05.3.1.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]azadiphospholes

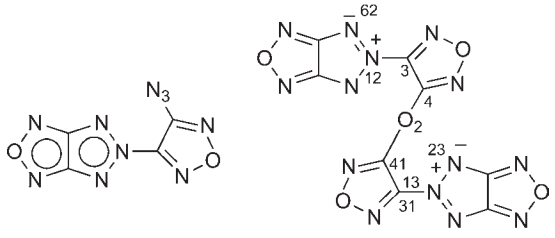
The [1,2,3]triazolo[4,5-*c*][1,2,5]azadiphosphole **34** represents a novel class of polyazapentalenes and it seems to be the first example of its kind incorporating phosphorus atoms into the pentalene ring system. It presented as monoclinic crystals with the $P2_1/c$ space group. The asymmetric unit contains two molecules of **34** and a molecule of MeCN distributed over two sites in approximately equal distribution. In agreement with the symmetry of the molecule, the P–N bond lengths are equal, measuring 1.62 Å; these distances fall between typical P–N and P═N bond lengths (1.59 and 1.68 Å, respectively). In the triazolyl moiety, the N–N bonds are slightly longer than the corresponding bond distances in **35**, its monocyclic synthetic precursor (1.33 vs. 1.35 Å), while the C–N and C–C bond lengths were essentially the same in both **35** and **34**. The linking of the two phosphorus atoms in **34** through the nitrogen atom effected a reduction in the nonbonded P···P bond distance of 0.8 Å <2003AGE3506>.



34 **35**

10.05.3.1.4 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

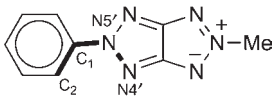
The structures of the [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazoles **36** <1993HCA1> and **37** <1999RJO1525> have been unambiguously determined by X-ray crystallographic analysis, although full details on the former structure remain to be published. The latter presented as rhombic crystals with the space group *Pcab*. As may be expected, the respective bond lengths and bond angles in the bicyclic moieties of the oxydifurazan-linked bis(triazolooxadiazole) **37** are almost equal. The dihedral angles about C(4)–C(3)–N(12)–N(62) and C(41)–C(31)–N(13)–N(23) are 13.3° and 15.1°, respectively, and these values, taken together with the relatively short C(3)–N(12) and C(31)–N(13) bond lengths, suggest some conjugation between the bicycle and the substituent oxadiazole rings (crystal numbering). As a consequence of intramolecular steric repulsion between O-2 and N-23 and N-62, the molecule is nonplanar. Intermolecular contacts have standard values and the stacking factor calculated with the use of Pauling's van der Waals radii is 0.683 <1999RJO1525>.



36 **37**

10.05.3.1.5 [1,2,3]Triazolo[4,5-*d*][1,2,3]triazoles

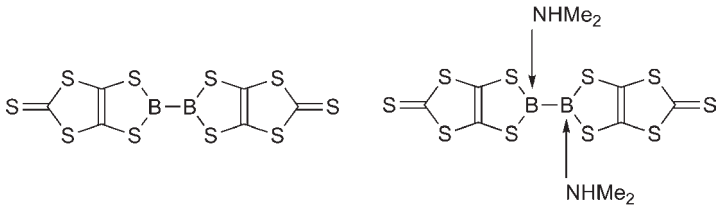
X-Ray analysis of crystals of 2-methyl-5-phenyltriazolo[4,5-*d*]triazole **38**, obtained by diffusion from methane/ethanol ($P\bar{1}$ space group), indicates there are two molecules per asymmetric unit. The first is essentially planar, with a mean deviation (non-H-atoms) of 0.03 Å and a maximum absolute torsion angle, C(2)–C(1)–N(5′)–N(4′), of 3.4°. The second molecule has a more pronounced twist with C(2A)–C(1A)–N(5′A)–N(4′A) being 9.6° <1993ZK133>.



38

10.05.3.1.6 [1,3]Dithiolo[4,5-*d*][1,3,2]dithiaboroles

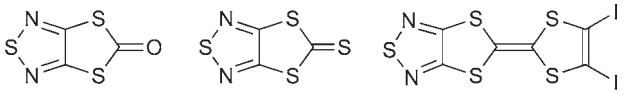
The structure of the 2,2′-bis(dimethylamino) Lewis base adduct of the bis([1,3]dithiolo[4,5-*d*][1,3,2]dithiaborole) **39**, which presented as orange needles (triclinic, $P\bar{1}$), has been described <2000AXC440>. The dimethylamine ligands are arranged in an *anti*-conformation relative to the B–B bond. The molecules are staggered rather than eclipsed about the B–B bond. The B–B bond length at 1.746(4) Å is longer than expected for a B_{sp^2}–B_{sp^2} bond; this elongation in bond length, and the angles around the B-atoms are consistent with tetrahedral geometry and a higher coordination number about the boron atoms. The BS_2C_2 rings display an envelope conformation with the B-atoms lying out of the plane of the rings. The crystal structures display a number of S···S interactions which appear to dictate the packing arrangement, which is best described as ruffled chains propagating along the *a*-direction and the interaction of S-atoms in adjacent chains creating an infinite ruffled sheet, with the sheets stacked in the *b*-direction. A number of long (3.0 Å) S···H hydrogen bonds at the sum of the van der Waals radii are also observed in the crystal structure <2000AXC440>.



39 **39**·2NHMe$_2$

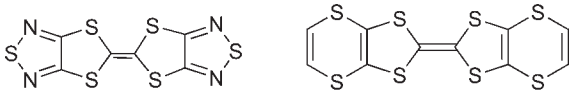
10.05.3.1.7 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The bicycles **40–42** can all be considered as TTFs and as such may have potential as component molecules for conducting organic solids. In this respect, heteroatom intermolecular S···N and S···S contacts are of special interest since they may increase the dimensionality of aggregation in the solid state, and, accordingly, much effort has been directed toward structure determination of this family of molecules <1993SM(68)1914, 1997SM(86)1871, 2003AXEo145, 2004AXEo63>.



40 **41** **42**

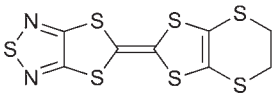
Bis(thiadiazole)tetrathiafulvalene (BTDA–TTF) **43** formed monoclinic orange crystals from trichloroethane (space group $P2_1/c$). Crystallographic analysis showed that, in contrast to bis(ethylenedithio)tetrathiafulvalene (BEDT–TTF) **44**, **43** is essentially planar. A comparison of bond lengths between BTDA–TTF and BEDA–TTF shows that the ring junction C–C bond is elongated in the former (1.416 Å) with respect to the latter (1.331 Å) while the C=C bond is 0.01 Å shorter in BTDA–TTF than the corresponding bond in BEDT–TTF. The molecules of BEDT–TTF are arranged as dimer pairs within the structure; however, the crystal data show that the molecules of BDTA–TTF pack differently forming equidistant stacks with an interstack S···S distance of 3.909(2) Å, which is greater than the van der Waals distance of 3.70 Å. It is also noted that there are a number of S···S intermolecular interstack distances of less than 3.60 Å <1993SM(68)1914>.



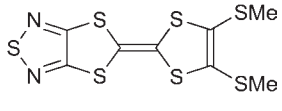
BTDA–TTF **43** BEDT–TTF **44**

The structures of the radical cation salts of the TTF derivatives were determined by X-ray crystallographic analyses <1997SM1871>. The (ClO_4) and (SbF_5) salts of **45** presented, respectively, as monoclinic (*C*2/*m* space group) and triclinic (*P*1 space group) black single crystals. A coplanar 2-D network characterized by short intermolecular S···N (3.27 Å) and S···S (3.58 Å) contacts and a column structure formed by a dimer of the donor **45** with

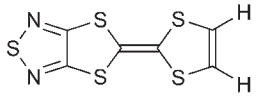
an overlap of the 1,2,5-thiadiazole ring and the dihydro-1,4-dithiin moiety exist for the ClO_4 salt. In the structure of the SbF_6 salt, two crystallographically independent donor molecules form a dimer with an overlap of the 1,2,5-thiadiazole rings; a number of short intermolecular contacts connect the donor molecules, viz. S···N (2.87–3.46 Å) and S···S (3.51–3.76 Å). A mixed stack column structure with the donor **46** and the $[Au(CN)_2]$ anion was found for the crystal of this complex, and this structural difference has consequences for its electrical conductivity (see Section 10.05.4.2.1) <1997SM(86)1871>. The dioxin analogue **48** presented as orange crystals from toluene in the $Pna2_1$ space group (orthorhombic). A large number of short intermolecular S···S contacts are observed; however, no short heteroatom contacts involving the N- or O-atoms are observed in the crystal. Two types of dimers result from the short S···S contacts, one composed of two parallel molecules and the second by a T-shaped molecular arrangement. The molecules are found to stack along the *c*-axis in a face-to-face fashion <2003AXEo145>, which contrasts with the normal trend for unsymmetrical TTF derivatives with a fused heterocyclic ring to stack in a head-to-tail fashion <2001AXEo307>. Interestingly, the packing in the diiodo derivative **42** also deviates from the norm with the molecules packing along the *b*-axis in a head-to-head fashion. The crystals of **42** presented in the $P2_1/n$ space group (monoclinic) and a crystal structure determination indicates the molecules to be planar, and to exhibit herringbone packing. The distance between the molecular planes is 3.592 Å. Introduction of the iodine atoms into the framework as expected enhanced the intermolecular contacts and a number of short intermolecular S···N, S···S, N···I, and I···I heteroatom contacts (within the sum of the Van der Waals radii) are observed <2004AXEo63>.



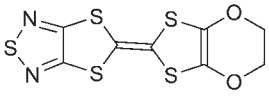
45



46



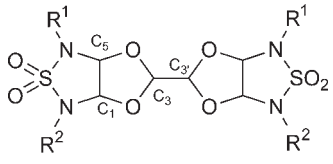
47



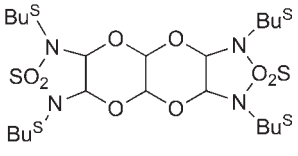
48

10.05.3.1.8 [1,3]Dioxolo[4,5-*c*][1,2,5]thiadiazoles

X-Ray diffraction of crystals of the *N*,*N*,*N*,*N*-tetra-*s*-butyl bis[1,3]dioxolo[4,5-*c*][1,2,5]thiadiazole **49a** (R = Bu^s) confirmed it to be a compound with two bicyclic units connected by a C–C bond and not the synthetic alternative, the triply annelated tetracycle **50** <2001MC138>. Orthorhombic crystals of the molecule having the *Pbca* space group were obtained. Crystal data show the bicyclic fragments to comprise *cis*-combined thiadiazolidine and dioxolane rings and to adopt the conformation of half-opened books with both the H-atoms at C-3 and C-3′ orientated inside the books. The thiadiazolidine ring has a flattened envelope conformation while the dioxolane shows a twist conformation. The relative configuration of the asymmetric centers in a bicyclic fragment are C(5)*S*, C(1)*R* and of the pseudoasymmetric atom C(3)*s*. The crystal packing shows short contacts between H-1 and H-5 of one molecule and the oxygen atoms of the sulfo group of another molecule resulting in the combination of molecules as corrugated layers parallel to the *ab* crystallographic plane <2001MC138>.



49

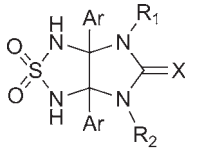


50

10.05.3.1.9 Imidazo[4,5-*c*][1,2,5]thiadiazoles

The structures of the imidazothiadiazoles **51a–g** have been confirmed by single crystal X-ray diffraction <2004JPO1091>. The study is significant since 1,2,5-thiadiazoline 1,1-dioxides had previously received very limited attention <1989JOC3077>. The crystal data show a number of general structural features (**Table 7**). The urea/thiourea groups form planar five-membered rings with the heterocyclic ring carbon atoms C–C (See Chapters in

Volumes 3 and 4 relating to the synthesis/reactivity and properties of monocyclic five-membered rings). The fused bicyclic skeletal of all compounds, except **51e**, exhibit approximate C_s symmetry with the mirror plane bisecting the ring C–C bond. The steric bulk of the ethyl groups of **51e** result in an appreciable twist from planarity for both heterocyclic fragments. For all compounds **51a–g**, the ring C–C bond is longer than may have been expected <1989JOC3077> due to the bulky aryl substituents. Interestingly, X-ray diffraction provided no evidence for the theoretically possible tautomeric equilibria for **b**, **d**, **f**, or **g**, nor was there any suggestion of the existence of asymmetric isomers which might have been expected to have formed through the attack of the HN=C(SH)–NH_2 thiourea tautomer on the reactant 1,2,5-thiadiazole 1,1-dioxides.



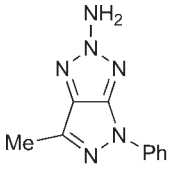
51

Table 7 Crystal form and space groups for the imidazo[4,5-*c*][1,2,5]thiadiazoles **51**

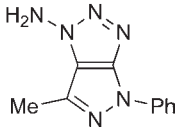
Compound	*X*	R^1	R^2	*Ar*	*Crystal type*	*Space group*
51a	O	H	H	Ph	Monoclinic	$P2_1/c$
51b	S	H	H	Ph	Orthorhombic	*Pbca*
51c	S	H	H	*p*-$MeOC_6H_4$	Monoclinic	$P2_1/n$
51d	S	Me	H	Ph	Monoclinic	$P2_1/n$
51e	S	Et	H	Ph	Monoclinic	$P2_1/n$
51f	S	Et	Et	Ph	Monoclinic	$P2_1/c$
51g	S	allyl	H	Ph	Orthorhombic	$P2_{1/c}$

10.05.3.1.10 Pyrazolo[3,4-*d*][1,2,3]triazoles

While spectroscopic data were supportive, X-ray crystallographic analysis was essential in permitting unequivocal assignment of the regioisomeric amino-substituted pyrazolotriazoles **52** and **53**. Both compounds presented as monoclinic crystals with **52** (2-amino) having the *Cc* (N.9) space group and **53** the $P2_1/n$ space group <1995H(41)2409>.



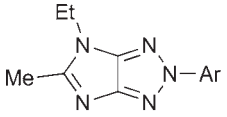
52



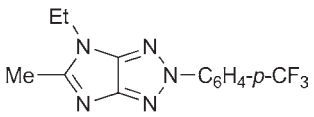
53

10.05.3.1.11 Imidazo[4,5-*d*][1,2,3]triazoles

The structures of the imidazo[4,5-*d*][1,2,3]triazoles **54a** (Ar = Ph) and **55** have been firmly established by X-ray diffraction <2002ARK80, 2002J(P1)1968>; the trifluoromethylphenyl structure **55** adopts the *P*-1 space group <2002J(P1)1968>.



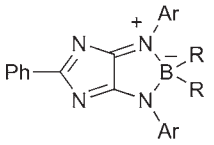
54



55

10.05.3.1.12 Imidazo[4,5-*d*][1,3,2]diazaborolidines

A single crystal structure analysis of **56a** revealed the molecule as a symmetric mesoionic betaine having a plane of symmetry (C_{2v}) with all delocalized C–N bonds being approximately the same length (1.34 Å). In this respect, the molecule can be considered as a cyanine chromophore <2004CC1860>.

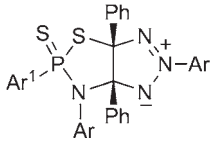


56

a: Ar = *p*-MeC_6H_4; R = F
b: Ar = *p*-MeC_6H_4; R = Ph
c: Ar = *p*-MeC_6H_4; R = Et
d: Ar = 3,5-$CF_3C_6H_3$; R = F

10.05.3.1.13 [1,2,3]Triazolo[4,5-*d*][1,3,2]thiazaphospholes

Energy-dispersive X-ray analysis (EDAX) using a scanning electron microscope confirmed the presence of sulfur and phosphorus in solid samples of the [1,2,3]triazolo[4,5-*d*][1,3,2]thiazaphospholes **57** in the expected atomic ratio of 2:1 <1997CC2149>.



57
Ar^1 = *p*-$MeOC_6H_4$

a: Ar = Ph
b: Ar = *p*-MeC_6H_4
c: Ar = *p*-BrC_6H_4
d: Ar = *p*-$NO_2C_6H_4$

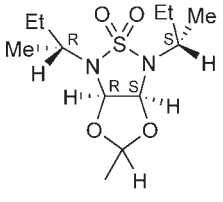
10.05.3.2 Molecular Spectra

All new ring systems have been characterized by spectroscopic data; original publications should be consulted for data pertinent to individual compounds. In the following sections, a number of points of particular interest will be discussed.

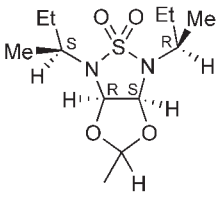
10.05.3.2.1 Nuclear magnetic resonance spectroscopy

In addition to being a fundamental tool for the structural characterization of almost all new members of this class of compounds, nuclear magnetic resonance (NMR) spectroscopy has also been central to a number of kinetic studies on the formation and reactivity of a selection of compounds in this class. As well as the more commonly reported ^{1}H and ^{13}C NMR spectra, studies on other nuclei (^{11}B, ^{19}F, ^{14}N, ^{15}N, ^{17}O, ^{31}P) have provided key structural information for a number of compounds.

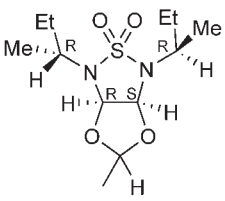
10.05.3.2.1(i) ^{1}H NMR spectroscopy



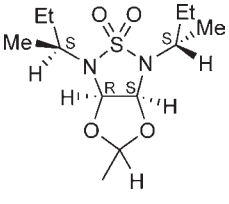
58A



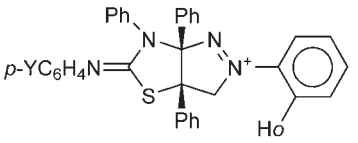
58B



58C

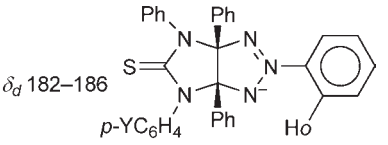


58D



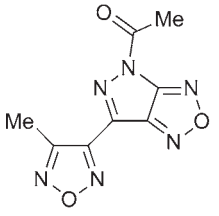
a: Y = MeO; **b**: Y = H; **c**: Y = NO_2

59

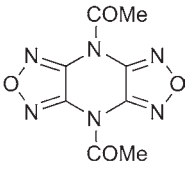


60

The acetyl proton signal of the pyrazolo[3,4-*c*][1,2,5]oxadiazole **61** resonating at 2.80 ppm appears downfield <2000RJO758> of the corresponding protons in *N*,*N*′-diacetylbis(1,2,5-oxadiazolo)[3,4-*b*:3′,4′-*e*]pyrazine **62** <1997RJO1656>.

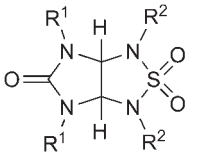


61



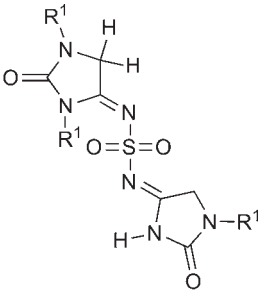
62

Analysis of ^{1}H NMR spectral data following the reaction progress of **63b** (R^1 = Et, R^2 = H) in dimethyl sulfoxide (d_6-DMSO) at 30 °C in the presence of trifluoroacetic acid (TFA) led to the proposal of a mechanism for the disproportionation of the imidazo[4,5-*c*][1,2,5]thiadiazoles **63b** to the 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **64b** and sulfamide. The important parameters in the study include the decrease in intensity of the singlet representing the protons of the CH–CH unit of the starting material **63b** at δ 5.31 ppm and the appearance of the CH_2 signal δ 4.77 ppm of the product **64b** <2003CHE784>. Similarly, monitoring the signal for the H_a proton in the ^{1}H NMR spectrum has provided kinetic data both on the rate of production of the oxazolo[4,5-*d*][1,2,3]triazoles **65** and on its acid-induced decomposition to the rare 1,3,4,5-oxatriazines **66**. Rate constants for the disappearance of **65** have been found to be first order, corresponding to a Hammett ρ-value of −1.09 (r = 0.996). Based on the kinetic data, the mechanism outlined in **Scheme 1**, involving a delocalized carbocation intermediate, is proposed to account for the formation of the oxatriazines (see Section 10.05.10.2) <1994J(P1)2797>.



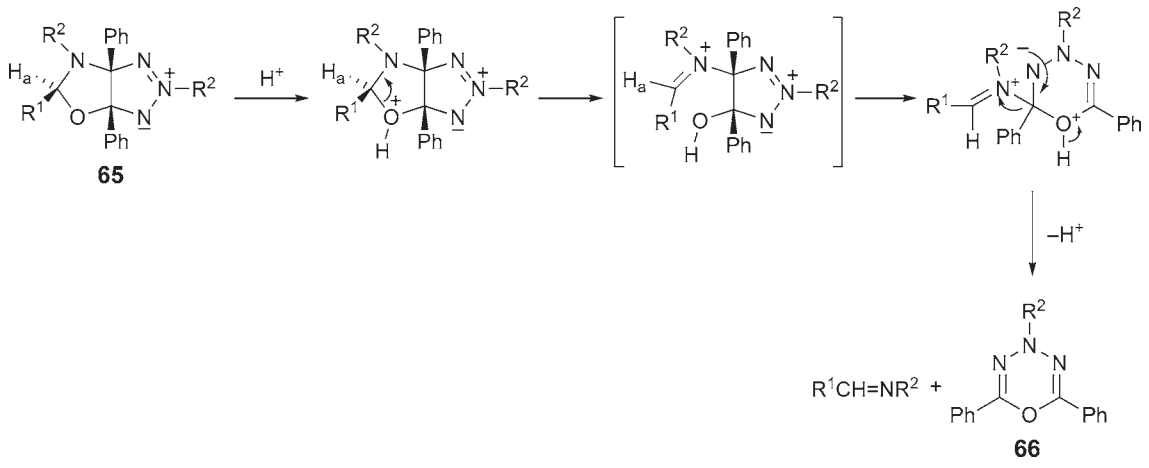
63

a: R^1 = Me; R^2 = H
b: R^1 = Et; R^2 = H
c: R^1 = R^2 = Me
d: R^1 = Et; R^2 = Me



64

a: R^1 = Me
b: R^1 = Et

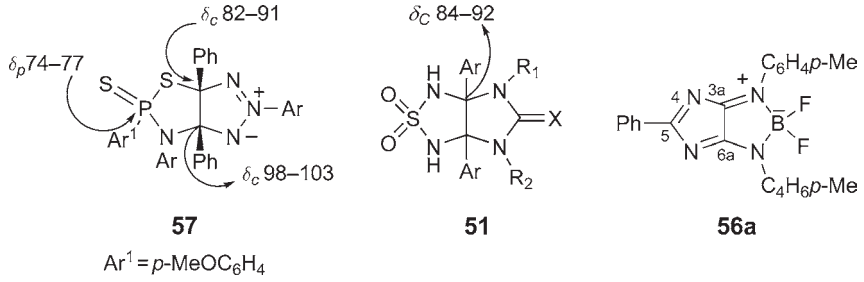


Scheme 1

10.05.3.2.1(ii) ^{13}C NMR spectroscopy

Diagnostic signals in the ^{13}C NMR spectra of the 5,5-bicyclic compounds under discussion in this chapter include the bridgehead resonance positions; for example, triazoles annelated to [1,3,2]thiazaphospholes, imidazoles, or thiazoles show quite different carbon signals <1997CC2149, 1997J(P1)3587>. The N–C–N bridgehead signal of the thiazaphospholo-fused bicycles **57** occurs at $\delta = 98$–103 ppm, while the N–C–S bridgehead occurs at $\delta = 82$–91 ppm. The quaternary bridgehead signals are particularly weak and were made more difficult to detect because of the ongoing decomposition of the products. Small splittings (3–10 Hz) of the bridgehead carbon signals were observed due to the phosphorus <1997CC2149>. The N–C–N fused bridgehead ^{13}C NMR signal for related systems without P occurs at $\delta = 95$–105 ppm and the N–C–S bridgehead occurs at $\delta = 80$–95 ppm <1990J(P1)2537, 1990J(P1)2527>. ^{13}C NMR spectra of the imidazolo[4,5-*d*][1,2,3]triazoles **60** display key quaternary N–C–N bridgehead C-atoms resonating in the range 93–106 ppm with the thioamido carbon appearing at 182–186 ppm. In the related thiazolo[4,5-*d*][1,2,3]triazoles **59b**, the bridgehead C-atoms N–C–N and S–C–N appear at 94.7 and 103.1 <1997J(P1)3587>. The bridgehead C-atoms of the imidazo[4,5-*c*][1,2,5]thiadiazoles **51** resonate in the range 84–92 ppm, while the C=O and C=S resonances are observed at ~158 or 180 ppm, respectively <2004JPO1091>.

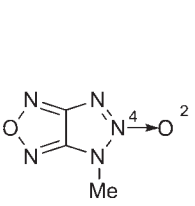
^{13}C NMR data in support of the betaine structure of the diazaborolidine **56** indicate that delocalization of the positive charge causes a downfield shift for C-5 (ca. 13 ppm) and C-3a/C-6a (ca. 4 ppm) <2004CC1860>.



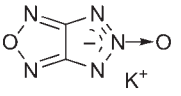
10.05.3.2.1(iii) ^{14}N, ^{15}N, and ^{17}O NMR spectroscopy

^{14}N, ^{15}N, and ^{17}O NMR spectral data have been used to characterize a number of [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazole derivatives **67–70** <1996TL8577, 2000CHE343>. In particular, the use of insensitive nuclei enhanced by polarization transfer (INEPT) and spin population transfer (SPT) pulse sequences in ^{15}N NMR investigations

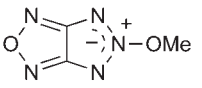
made it possible to determine the mutual arrangement of nitrogen atoms in the triazole moiety. Significantly, it has been noted that for compound **67** the ^{14}N signal for N-4 appeared at −41 ppm, while the signals for the corresponding atom in **68** and **69** were observed at −11.5 and −50 ppm, respectively. A further significant difference between the three systems was evident in the ^{17}O NMR data with the O-2 resonance signal for **67** and **69** being observed at 400 and 192 ppm, respectively <1996TL8577>. Three signals were observed in the ^{14}N NMR spectrum of the [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazolium inner salt **70** at −28.89 (NO_2), −101.24, and −155.54 ppm <2000CHE343>.



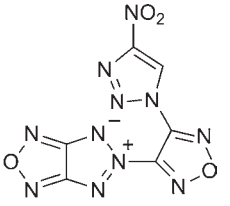
67



68



69



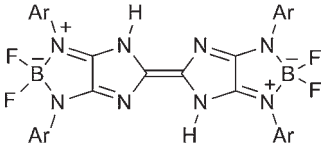
70

10.05.3.2.1(iv) ^{31}P NMR spectroscopy

^{31}P NMR spectral data for the [1,2,3]triazolo[4,5-*c*][1,2,5]azadiphosphole **34**, and the [1,2,3]triazolo[4,5-*d*][1,3,2]thiazaphospholes **57**, were instrumental in confirming their structures <1997CC2149, 2003AGE3506>. The ^{31}P NMR spectrum of **34** showed a single peak ($\delta = 22.3$ ppm) in the region characteristic of phosphorus(V) compounds <2003AGE3506>, while the ^{31}P signals for **57** appeared at $\delta = 74$–77 ppm. The P-bonded *p*-methoxyphenyl group showed the expected ^{31}P splittings; however, precise J_{PC} values could not be measured due to signal spreading caused by ongoing decomposition <1997CC2149>.

10.05.3.2.1(v) ^{19}F NMR spectroscopy

In keeping with its highly symmetric nature, the ^{19}F NMR spectrum of the imidazodiazaborole **71a** (Ar = *m*-$F_3CC_6H_4$) exhibits only two signals, a singlet at $\delta = -63.5$ ppm representing CF_3 and a double doublet at $\delta = -147.4$ ppm for the BF_2 group <2004T3847>.



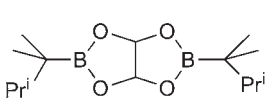
71

a: Ar = *m*-$CF_3C_6H_4$

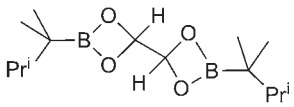
b: Ar = *p*-$Bu^tC_6H_4$

10.05.3.2.1(vi) ^{11}B NMR spectroscopy

The ^{11}B NMR data of [1,3,2]dioxaborolo[4,5-*d*][1,3,2]dioxaborole **72** showed a singlet at $\delta = 36.5$ ppm, supporting the conclusion that the compound is an alkyl-1,3,2-dioxaborolane which typically shows resonances in the range 34–40 ppm. A structural alternative to **72** might have been **72-alt**, which could not be excluded on the basis of the ^1H and ^{13}C NMR data alone; however, **72-alt** with the four-membered ring would be expected to have a more deshielded ^{11}B nucleus <1995CB751>.

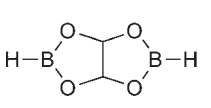


72

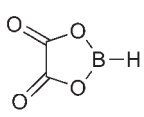


72-alt

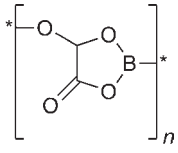
Evidence for the intermediacy of the bicyclic dioxaborolane **73**, in the reaction between oxalic acid and borane–dimethyl sulfide, is drawn from ^{11}B NMR spectral data. Reaction begins at ca. −10 °C with the appearance of two ^{11}B signals (7.8 ppm, d and 6.8 ppm, s), tentatively ascribed to a dimethyl sulfide adduct of the dioxaborolanedione **74**. At temperatures >10 °C, a doublet at $\delta = 28.9$ ppm emerged which was assigned to the bicycle **73**. A singlet at $\delta =$ 23.5 ppm, the intensity of which increased as the reaction proceeded, indicated the presence of a BO_3 moiety where the boron atom is part of a dioxaborolane ring, possibly from a compound of general structure **75**. Since the products of the reaction could not be separated all assignments are speculative <1995CB751>.



73

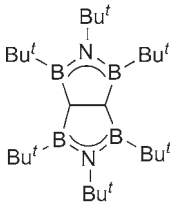


74



75

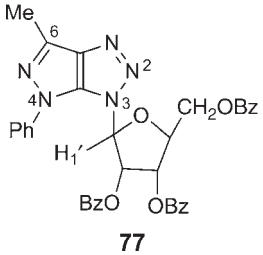
The simplicity of the ^{11}B NMR spectrum of [1,2,5]azadiborolo[3,4-*c*][1,2,5]azadiborole **76** exhibiting one signal, at $\delta = 50.2$ ppm, indicated that the molecule bears a mirror plane through NBu^t and the CC ring bond <2001ZFA1815>. Similarly the highly symmetric nature of the imidazo[4,5-*d*][1,3,2]diazaborolidines **71** is evidenced by ^{11}B NMR spectral data which show a well-separated triplet at $\delta = 10.18$ ppm, $J = 36.4$ Hz for **71a** <2004T3847>.



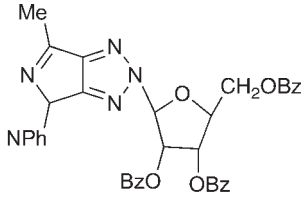
76

10.05.3.2.1(vii) ^{2}D Spectroscopy

Nuclear Overhauser enhancement spectroscopy (NOESY) experiments have helped confirm the observed regioselectivity following glycosylation of a pyrazolo[3,4-*d*][1,2,3]triazole. The regioisomeric protected nucleosides **77** and **78** showed contrasting results following irradiation of the phenyl group at the N-4 position. The N-3-*β*-isomer **77** showed a cross peak to the 1′-H on the sugar moiety, but this effect was not observed for the N-2-*β*-isomer. The failure to observe any cross peak between the C-6 methyl group and the 1′-H was taken as evidence for the lack of any N-1-substituted derivatives <1998AP269>.



77

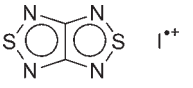


78

10.05.3.2.2 Mass spectrometry

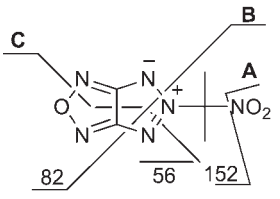
Fragmentation patterns observed in the mass spectra of a number of compounds in this class have been instrumental in assigning their structure over plausible synthetic alternatives.

In situ generation and characterization of $[C,N_2,S]^{+\cdot}$ ions (*m*/*z* 72), formed by dissociative ionization of ionized [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole $I^{+\cdot}$, **79**, has been made possible for the first time following collisional activation (CA) and neutralization–reionization (NR) mass spectrometry <1997JST(418)209>.

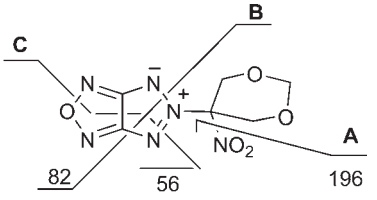


79

Mass spectrometry data reported for the first representatives of 5-nitroalkyl[1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazoles, **80** and **81**, showed low-abundance molecular ion peaks at 198 (2%) and 242 (9%) respectively. Fragmentation of **80** is believed to involve initial cleavage of the C–NO_2 bond (direction A) to form the base peak *m*/*z* 152 (100%). The fragmentation pattern is completed with the formation of an ion with *m*/*z* 82 (19%) due to the breakage of N–N and C–N in the triazole ring (direction B) and the formation of another ion with *m*/*z* of 56 (direction C) due to the cleavage of N–O and C–C in the furazan ring and N–N in the triazole ring. Compound **81** has a base peak of *m*/*z* 138, and the fragmentation pattern for **81** is the same as for **80** except where the C–NO_2 bond is cleaved (direction A) to give an ion with *m*/*z* 196 (50%) <1995IZV1315>.

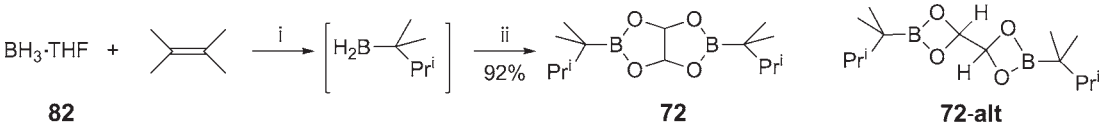


80



81

The observation that the molecular ion recorded for the [1,3,2]dioxaborolo[4,5-*d*][1,3,2]dioxaborole **72** in the mass spectrum decomposed with the loss of CH_3, C_3H_8, and C_6H_{13} leaving the $B_2O_4C_2$ unit intact provides evidence for its structure, since **72alt**, the alternative product of reaction between BH_3–THF **82** and ethene (**Scheme 2**), would have been expected to show a cleavage of the central C–C bond, which was not observed <1995CB751>.



82 **72** **72-alt**

i, 0 °C, 1 h; ii, 0.5 $(CO_2H)_2$, DME, 0 °C, 5 h then 85 °C, 8 h

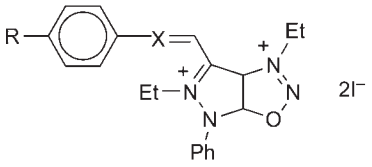
Scheme 2

The presence of intense peaks corresponding to the halved molecular weight in the mass spectra of the compounds prepared from a condensation reaction between the trimeric dihydrate of glyoxal and *N*,*N*′-dialkylsulfamides lent credence to the proposition that the products of reaction were the [1,3]dioxolo[4,5-*c*][1,2,5]thiadiazoles **49** and not the alternative tetracyclic structures **50** <2001MC138>.

10.05.3.2.3 UV/Vis and fluorescence spectroscopy

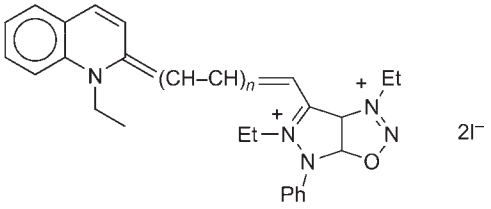
The pyrazolo[3,4-*d*][1,2,3]oxadiazoles **83** and **84**, which range in color from pale to intense violet, exhibit solvatochromic behaviour; ultraviolet (UV) spectra have been recorded in the wavelength range 300–700 nm in ethanol, 2-methylpropanol, chloroform, and dimethylformamide (DMF), as well as mixed organic solvent $CHCl_3$–DMF <1994CPA393>. Key absorption bands have been assigned to the π–π^*-transition of the unsaturated centers within the whole molecule. This band has considerable charge-transfer (CT) character depending on the substituents on a particular cyanine; this characteristic accounts for the solvatochromic behavior as summarized in **Tables 8** and **9**. Spectra recorded in aqueous

universal buffer solutions over a pH range 2.30–12.16 showed a redshift in alkaline media and a blueshift at low pH. The effectiveness of these dyes as photosensitizers increases when they are in the ionic form <1994CPA393>.



83

a: X = CH; R = OH
b: X = CH; R = $N(Me)_2$
c: X = N; R = OH



84

a: $n = 0$
b: $n = 1$

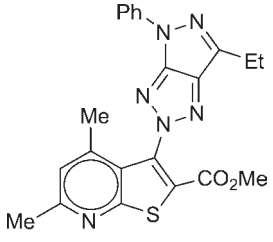
Table 8 Selected data from electronic absorption spectra of some new 1*H*-pyrazolo[4,3-*d*][1,2,3]oxadiazole cyanines in organic solvents

Compound	*EtOH*	*2-Methylpropanol* λ_{max} (nm^{-1}) $(\varepsilon_{max}/cm^2\ mol^{-1})$	$CHCl_3$	*DMF*	$CHCl_3$–*DMF*
83a	360 (19 200)	355 (17 520)	365 (8520)	365 (17 580)	
83b	350 (65 600)	340 (32 800)	340 (36 000)	340 (32 000)	
	450 (18 880)	445 (6400)	440 (8000)	450 (6500)	
83c	360 (11 400)	365 (20 880)	365 (12 920)	355 (6600)	
	440 (6400)	445 (9420)	455 (13 400)	525 (2080)	530
84a	440 (4100)	440 (16 500)	440 (8600)	440 (8400)	525
	520 (6600)			530 (6760)	
84b	455 (4100)	507 (4800)	482 (4260)	440 (4000)	
	485 (4440)	575 (4700)		515 (4160)	
	555 (4200)			565 (4000)	

Table 9 Electronic absorption spectra of **83a**, **83c**, and **84a** in aqueous universal buffer solutions

	Absorbance		
pH	$\lambda_{max} = 460\ nm$ *83a*	$\lambda_{max} = 530\ nm$ *83c*	$\lambda_{max} = 530\ nm$ *84a*
2.30	0.04	0.09	0.24
4.24	0.12	0.18	0.31
5.91	0.16	0.18	0.40
8.17	0.08	0.19	0.38
10.60	0.24	0.20	0.38
12.16	0.32	0.16	0.36

The absorption and emission maxima of the yellow-colored pyrazolo[3,4-*d*][1,2,3]triazole **85** recorded in a DMF solution presented at 340 and 401 nm, respectively, with log ε 4.01; these characteristics make **85** potentially valuable as a fluorescent brightener (see Section 10.05.12.10) <1992MI95>.



85

The ultraviolet/visible (UV/Vis) spectra have been recorded for a series of imidazo[4,5-*d*][1,3,2]diazaborolidines **56** and **71** <2004CC1860, 2004T3847>. A structured absorption band between 512 and 614 nm with a relatively high extinction coefficient (log $\varepsilon = 3.6$–4.3) characterizes the UV/Vis spectra of the intensive red imidazo[4,5-*d*][1,3,2]-diazaborolidines **56**. They show fluorescence characteristics similar to difluoroboradiaza-*s*-indacenes, a strong red fluorescence reaching into the near infrared (576–656 nm), with an unusually large fluorescence quantum yield (up to 64% in $CHCl_3$) in this spectral region <2004CC1860>. The imidazo[4,5-*d*][1,3,2]diazaborolidines **71**, also red in color, showed in their UV spectra, recorded in DMSO, three separated absorption bands typical for cyclized tetraazafulvalenes. The longest wavelength absorption at 508 nm (log $\varepsilon = 5.0$) can be shifted bathochromically to $\lambda_{max} = 557$ on changing the solvent to toluene. The trifluoromethylphenyl derivative **71a** possessed a strong orange fluorescence at 577 nm in toluene <2004T3847>.

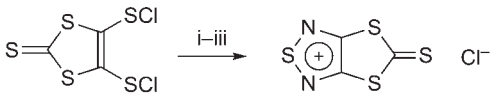
10.05.3.2.4 Raman spectroscopy

Raman spectroscopy has been shown to be a useful tool for monitoring the photoinduced magnetic phase transition of TTTA **1** from the diamagnetic LT to the paramagnetic LT phase. One report concentrated on spectral difference in the frequency region between 300 and 900 cm^{-1} where S–N vibrational modes occur <2003CPL(378)456>, while a second concentrated on the region between 1300 and 1400 cm^{-1} where the bands are considered to arise from C=N stretching in a planar molecular structure <2002MI064434/1>. In addition to recording spectra in each of the two phases, spectra were also recorded after a single-shot laser irradiation of the LT phase with different wavelengths and photon densities at 290 K. Significant differences were observed between the HT and LT Raman spectroscopy. The peak at ~1350 cm^{-1} in the LT phase shifted to slightly higher frequency with a significant reduction in intensity in going to the HT phase <2002MI064434/1>; new intense modes emerged at 752.5 and 854.7 cm^{-1} in the LT phase and some Raman modes in the HT phase became doublets in the LT phase. The latter is important since it is in keeping with the strong dimerization associated with going from HT to LT phase of TTTA <2002MI064434/1, 2003CPL(378)456>. Following a single laser shot to a TTTA sample in the LT phase, the Raman spectrum consisted of a mixture of spectra in the LT and HT phases <2003CPL(378)456>. Spectra recorded in the LT phase at 298 and 11 K and in the HT phase at 240 K confirmed the utility of Raman spectra as a diagnostic tool for monitoring TTTA phase transitions <2002MI064434/1>. Analysis of the post-irradiation data with the spectra of independent samples of TTTA in the HT and LT phases permitted calculation of the rate and extent of the phase transition as a function of irradiated photon density. A conversion efficiency from the LT to HT phase was estimated at 0.4 per proton <2003CPL(378)456>. Both photoexcitations of the CT and intramolecular π–π-transition bands induced the LT (diamagnetic) to the HT (paramagnetic) phase transition; the threshold photon density for the former was estimated at $\sim 1 \times 10^{21}/cm^3$, while no clear threshold was observed for the latter transition. A serious difficulty with the Raman analysis was the observed degradation of the TTTA crystals following the longtime laser irradiation, and consequently IR spectroscopy has been considered a superior tool for in-depth analysis of photo-induced phase transitions (PIPTs) of TTTA.

10.05.3.2.5 IR spectroscopy

PIPTs of TTTA **1** have been followed by IR reflection and transmission spectroscopy, measured by a micro-scopic Fourier transform infrared (FTIR) spectrometer. Polarized reflection spectra for the HT and LT phase crystals of TTTA have been obtained at room temperature between 650 and 850 cm^{-1}. The HT phase displayed three main vibrational modes: 681, 774, and 832 cm^{-1}. A comparison of the LT data, when the polarization of light is parallel to the stacking direction, showed the 681 cm^{-1} mode became a doublet 672 and 681 cm^{-1}. The observed doubling in periodicity, following from the zone-folding effect, is consistent with strong dimerization accompanying the magnetic phase transition of TTTA <2005MI283>. Photoexcitations of both the CT and intramolecular π–π-transition bands induce the LT (diamagnetic) to the HT (paramagnetic) phase transition but with different threshold photon densities (7×10^{19} and 7×10^{18} cm^{-3}, respectively), indicating that the PIPT, and thus the magnetic and chromic properities of TTTA, can be optically controlled. The reduced threshold compared to that obtained from photoinduced Raman scattering measurements was attributed to a difference in sample morphology <2005MI283>.

IR spectral data together with microanalytical data have been central to the suggestion that the chloride salt **87** is indeed the product of reaction between the disulfenyl dichloride **86** and trimethylsilyl azide (**Scheme 3**); characteristic absorptions in the IR spectrum include 1064 (s), 1271 (br, m), 1460 (m, br) <1994IC4537>.



86 **87**

i, Me_3SiN_3, THF, –78 °C, 5 min; ii, 90 min, rt; iii, 65 °C, 21 h

Scheme 3

10.05.3.2.6 Reflectivity spectroscopy

The polarized reflectivity *R* spectra of TTTA **1** in the HT and LT phases have been recorded with the electric vector of the lights parallel ($E_{\|}$) and perpendicular ($E_{\perp}$) to the π-stacking axis. Small peaks at 3.2 eV in both polarizations account for the purple color of the HT phase while a strong band at 2.2 eV in the $E_{\|}$ spectrum makes the LT phase green <2002MI064434/1>. The obtained reflectivity *R* spectra were converted to optical conductivity σ spectra using the Kramers–Kronig relation and the Roessler correction. Both phases exhibited bands consistent with CT and intramolecular π–π transitions. The CT bands differed greatly in the two phases. Analysis of the data for the HT phase concluded that the inter- and intracolumn interactions were comparable with each other so supporting the multidimensionality suggested by magnetic measurements; data for the LT phase suggested a much reduced dimensionality <2002MI064434/1>.

10.05.3.2.7 X-Ray photoelectron spectroscopy

X-Ray photoelectron spectroscopy (XPS) has been a useful in understanding the adsorption of TTTA molecules **1** deposited on gold surfaces by 'wet' and 'dry' processes. Temperature dependence of the S 2p spectra of TTTA film prepared by the dry process had, in general, a doublet peak due to the presence of S $2p_{1/2}$ and S $2p_{3/2}$ levels with spin–orbit splitting of 1.18 eV and area ratio of 1:2. At 135 K, two peaks were observed at 164.5 and 165.5 eV, assigned to S $2p_{3/2}$ and S $2p_{1/2}$, respectively. With reference to values observed for unbound 2,5-dimethylthiophene on gold, these signals were attributed to the unbound sulfur resulting from a physisorbed multilayer. Upon raising the temperature, most of the molecules were sublimed; however, three peaks were observed at 310 K in the S 2p region including peaks at 163.8 and 164.8 eV which are in the region expected for bound sulfur. Based on the assumption that molecules of **1** formed monolayers, the spectrum at 310 K was regarded as a superposition of the spectra of the bound and unbound sulfur, that is, one of the sulfur atoms in the molecules may have interacted with the gold surface <2005SM(153)457>.

10.05.3.2.8 Ultraviolet photoelectron spectroscopy

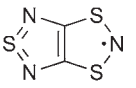
Ultraviolet photoelectron spectroscopy (UPS) has provided information about the adsorption state of TTTA **1** on gold surfaces. The density of states (DOS) for TTTA on gold agreed well with a superposition of the DOS for α- and β-spins, which suggested that the molecule could remain as a radical; the gold Fermi edge was not observed in the spectrum. Thus, it was concluded that molecules of TTTA fully cover the gold surface without degradation <2005SM(153)457>.

10.05.3.2.9 Surface plasmon resonance spectroscopy

Surface plasmon resonance (SPR) spectroscopy measurements have revealed the thickness of TTTA films and the adsorption kinetics for TTTA deposition on gold surfaces by the 'wet' process, viz. from ethanol or hexane solutions. For the film prepared from ethanol solution, the resonance angle was shifted by 0.3° toward the higher incident angle, which showed the molecules were adsorbed on the gold surface. In order to study the adsorption kinetics, the reflectivity change was monitored *in situ* by SPR. The reflectivity increased drastically after the injection, stopping after 4800 s, and it did not decrease significantly by rinsing, indicating that the TTTA molecules were strongly bound to the gold surface. The thickness of the film deposited from ethanol solution was estimated to be 1.3 nm and that deposited from hexane solution 1.8 nm, and it was thus concluded that the molecules form multilayers from the 'wet' process <2005SM(153)457>.

10.05.3.2.10 Cyclic voltammetry

Cyclic voltammetry (CV) measurements for the [1,2,5]thiadiazolo[3,4-*d*][1,3,2]dithiazole radical **1**, conducted in oxygen-free MeCN, showed a reversible wave for 0/+1 couple but not for the −1/0 couple ($E_2^{(-1/0)}$ 0.65) <2004JA8256>.

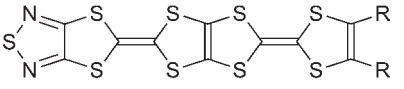


1

The [1,2,5]thiadiazolo[3,4-*d*][1,3,2]thiadiazole **6** displayed significant differences in its cyclic voltammogram compared to its 10π-electron carbon analogue, naphthalene. In contrast to the irreversible oxidation [$E_{1/2}^{ox} = 1.54$ V] and the reversible reduction [$E_{1/2}^{red} = -2.50$ V] observed for naphthalene, cyclic voltammetry on a solution of **6** in MeCN in the potential range from −2.5 to 2.5 V revealed no oxidation waves. Rather, two reversible one-electron reduction waves at −0.59 and −1.72 V corresponding to consecutive transformations of **6** into the radical anion **7** and the dianion **8** were observed, and both **7** and **8** were suggested to be rather long-lived species. The relationship of the anodic and cathodic currents suggested both **7** and **8** are involved in further reactions, although disproportionation of **7** to **6** and **8** was ruled out on the basis of an estimated equilibrium constant *K* of $\sim 10^{-19}$ <2005IC7194>.

Preliminary CV studies on BDTA–TTF, **43**, have been hindered by the low solubility of the compound in common organic solvents; measurements in tetracyanoethylene showed a single irreversible peak at +0.86 V (vs. Ag/AgCl). In contrast, BEDT–TTF, **44**, showed two reversible one-electron oxidation waves at +0.49 and +0.64 V (vs. Ag/AgCl in CH_2Cl_2) <1993SM(68)1914, 1997SM(86)1871>.

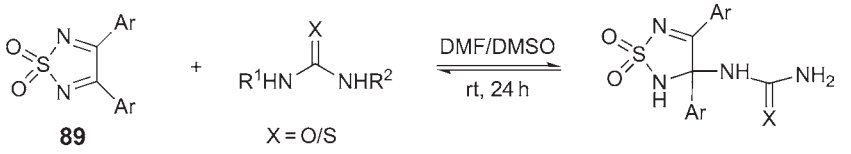
The cyclic voltammograms of thiadiazole fused [2,5-(1,3-dithiol-2-ylidene)-1,3,4,6-tetrathiapentalenes], BDT–TTPs **88**, in benzonitrile exhibited four pairs of redox waves corresponding to one-electron transfer processes at +0.60, +0.81, +1.30, and +1.47 V (vs. saturated calomel electrode (SCE)). The E1 values are a little higher than that of 4,5-bis(methylthio)-BDT–TTP (+0.49 V). The difference is attributed to the electron-withdrawing character of the fused thiadiazole ring on the bicycle <1997SM(86)1821>.



88

a: R = SMe; **b**: R = Me

Due to the absorption of UV radiation by the reactant nucleophiles and the solvent in the zone of interest, application of classical spectrophotometric methods to follow the mechanism of formation of imidazo[4,5-*c*]-[1,2,5]thiadiazoles **51** from reaction of the parent thiadiazoles 1,1-dioxides **89** and ureas/thioureas was restricted. Consequently, details of the mechanism and equilibrium constants were established by CV <2004JPO1091, 2003JPO220>. It was found that the reaction proceeded by a stepwise mechanism with an intramolecular second step as outlined in **Scheme 4**. In solution, this reaction was reversible, and the equilibrium could be shifted to the side of the reactants by a temperature increase. For example, a 3.54 mM solution of **51b** in DMF, with a 0.1 M $NaClO_4$ as supporting electrolyte, presented a featureless CV between 0.9 and −2.8 V which corroborated with the



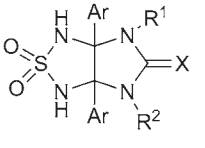
89

a: Ar = Ph
b: Ar = *p*-$MeOC_6H_4$

X = O/S

DMF/DMSO
rt, 24 h

51a: X = O; $R^1 = R^2$ = H; Ar = Ph
51b: X = S; $R^1 = R^2$ = H; Ar = Ph
51c: X = S; $R^1 = R^2$ = H; Ar = *p*-$MeOC_6H_4$
51d: X = S; R^1 = Me; R^2 = H; Ar = Ph
51e: X = S; R^1 = Et; R^2 = H; Ar = Ph
51f: X = S; $R^1 = R^2$ = Et; Ar = Ph
51g: X = S, R^1 = Allyl; R^2 = H; Ar = Ph

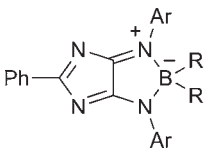


51

Scheme 4

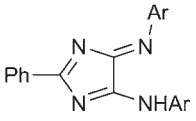
formation of a thiadiazoline since they are not voltammetrically reducible. However, after heating the solution at 105 °C for 3 h, followed by rapid cooling, the CV showed cathodic voltammetric peaks of the starting **89** and the anodic peak of the thiourea at ca. 0.3 V <2004JPO1091, 2003JPO220>.

CV experiments on the imidazo[4,5-*d*][1,3,2]diazaborolidines **56** showed clearly separated reversible one-electron reductions that, unlike the data for the parent imidazoles **90**, were not influenced by proton abstractions. The difference between the single reduction steps is much larger than those for the parent imidazole **90**, which suggested the radicals have been stabilized. Coarse tuning on the potential shifts was achievable by changing the residues on boron while fine-tuning effects were observed upon changing the amino substituents; for example, the difference in shift between the derivatives **56a** and **56c** bearing fluorine- and ethyl-substituted boron atoms was 0.72 V <2004CC1860>.



56

a: Ar = *p*-MeC_6H_4, R = F
b: Ar = *p*-MeC_6H_4, R = Ph
c: Ar = *p*-MeC_6H_4, R = Et
d: Ar = 3,5-$CF_3C_6H_3$, R = F



90

10.05.3.2.11 ESR spectroscopy

The electronic structure of TTTA radical **1** has been probed through EPR measurements, and spectra have been recorded in solution at room temperature in CH_2Cl_2/toluene mixtures <2001PS145, 2001JMC1992> and CH_2Cl_2 <2004JA8256>; additionally, frozen CH_2Cl_2/toluene solutions have been examined. The spectrum of the mixed solvent sample exhibited a well-defined 1:1:1 triplet spectrum ($g_{iso} = 2.0053$, $a_{iso}^{N(1)} = 1.12$ mT) consistent with coupling to the unique ^{14}N atom . No resolution of the hyperfine coupling to the other two N-atoms was observed and there was no improvement in resolution over the temperature range 100–240 K <2001PS145, 2001JMC1992>. The X-band spectrum of TTTA in CH_2Cl_2 showed a similar three-line pattern with parameters varying very little with the change in solvent ($g_{iso} = 2.0061$, $a_{iso}^{N(1)} = 1.115$ mT) <2004JA8256>. More detail was unveiled from measurements on frozen solutions (100 K) which exhibited rhombic EPR spectra ($g_1 = 2.0015$, $g_2 = 2.0046$, and $g_3 = 2.0105$). Only the smallest g value showed a hyperfine coupling pattern, a triplet to the unique N-atom ($a_1^{N(1)} = 2.84$ mT); this further split into 1:2:3:2:1 pentets by a smaller coupling to the two equivalent N-2 atoms of the thiadiazole ring ($a_{iso}^{N(2)} = 0.25$ mT). Hyperfine coupling to neither N-atom was observed on g_1 or g_2. The K-band spectrum showed improvement in resolution for the g values. An interesting low field resonance noted in the K-band spectra was shown by simulations to be an 'off-axis' undershoot resonance and not a principal g value. The absence of hyperfine structure to g_2 and g_3 is entirely consistent with the unpaired electron residing in a π-type orbital with g_1 co-parallel to the direction perpendicular to the plane of the molecule as has been found for other dithiazolyl radicals. An analysis of the hyperfine coupling pattern was used to map the spin density distributions on the N-atoms of **1** <2001PS145, 2001JMC1992>.

A comparison of the EPR spectra for the HT and LT phases of **1** showed a much reduced intensity for the LT phase <2001MI451, 2002MI863>, and the EPR intensity was very weak over the temperature range 140–310 K. Assuming that the ESR signal of the LT phase comes from the remaining radical monomers after the dimerization, it was estimated that ~0.5% of TTTA molecules remain as monomers <2003CPL(378)456>. Temperature dependence of the X-band EPR was monitored over the range 9–315 K and spectra have been recorded in both directions, 9 up to 315 and 315 decreasing to 9 K. Upon cooling, the paramagnetic–diamagnetic phase transition was demonstrated at about 200 K, while in the heating process the transition occured at ~300 K. These values agree with the corresponding critical temperatures determined by the paramagnetic susceptibility measurements <2001MI451>. The absence of fine structures of triplet excitons in the LT phase suggested interdimer interactions. The two phases of TTTA could be easily distinguished by EPR, providing a more sensitive analytical alternative to superconducting quantum interference device (SQUID) measurements <2001SM(121)1767, 2001MI451, 2002MI064434/1, 2002MI863, 2003CPL(378)456>.

Films of TTTA on gold surfaces showed no ESR signal at room temperature, although a signal seeming to originate from TTTA reappeared at 4 K. A comparison of this spectrum with that of the gold substrate proved that conduction electrons in gold were responsible for the signal at 4 K. It was considered that the relaxation of excited electrons was too fast to observe an ESR signal due to TTTA at this temperature <2005SM(153)457>.

Preliminary EPR spectral studies for TTTA in channels of PHTP **4** and tris(*o*-phenylenedioxy)cyclotriphosphazene **5** were hampered by difficulties in growing sufficiently large quality crystals providing close packing of the TTTA radicals. X-Band spectra from the PHTP-$(TTTA)_x$ crystals were not reproducible which suggested possible

decomposition. The Q-band spectral data of TPP–(THF)–(TTTA) crystals displayed an axial symmetry for g and A tensors, and, further, there was evidence to suggest intermolecular spin–spin coupling <2002MI064434/1>.

The radical anion of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** has been characterized by ESR spectroscopy both in solution and in the crystalline state. The experimentally determined hfcc $a(^{14}\mathrm{N} \times 4)$ is 0.314 mT, which varies slightly from the calculated value 0.238 mT. The observed g value is 2.004 5. On the basis of the ESR data, a half-life time of the electrochemically generated **6** was estimated as $\tau_{1/2} = 74.5$ s. The ESR spectra of the radical anion salts **32** and **33** were not resolved; however, those of their solutions in MeCN were found identical to the spectrum of the electrochemically generated radical anion **7** <2005IC7194>.

The electrochemical properties of the imidazo[4,5-*d*][1,3,2]diazaborolidines **56**, especially the K_{SEM} constants (10^{14}), are close to the boron-bridged violenes; indeed, the values obtained for **56** are on a par with those of the acceptor part in 'organic metals' derived from TCNQ or *N*,*N*′-dicyanochinodiimine (DCNQI) (K_{SEM} 10^7–10^{11}) <2004CC1860>.

10.05.4 Thermodynamic Aspects

10.05.4.1 Magnetic Properties

10.05.4.1.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles

Molecular bistability in its magnetic and optical properties has been observed for the organic radical TTTA **1** and some of its coordination compounds under a range of external parameters, viz. temperature, pressure, and illumination <1999SCI261, 2000MCL161, 2001JA3601, 2001POL1517, 2001MI451, 2001JMC1992, 2001SM(121)1767, 2002MI863, 2002MI432, 2003MI17403, 2003CPL(378)456, 2004CPL(393)150, 2005MI283>. Such characteristics render these species potentially interesting for application to electronic devices (see Section 10.05.12.1). The bistability, first noted by Fujita and Awaga, has been described by EPR spectroscopy <1999SCI261, 2001MI451, 2001JMC1992, 2001MI145, 2001SM(121)1767, 2002MI064434/1, 2002MI432, 2003CPL(378)456>, by diffuse correlation spectroscopy (DCS) measurements <2001MI451, 2002MI064434/1>, Raman scattering measurements <2003CPL(378)456, 2003MI17403>, polarized reflectivity spectra <2002MI863> and optical conductivity σ-spectra, polarized reflectivity IR spectra <2002MI432>, and polarized IR reflection spectra <2005MI283>. Additionally, a number of theoretical studies have attempted to explain the observed phenomena <2001JMC1992, 2003MI911, 2004MI3719, 2004MI689, 2004MI204, 2005MI320>. The experimental (see Section 10.05.3) and theoretical findings (see Section 10.05.2) are discussed earlier.

The magnetic susceptibility for a polycrystalline sample of TTTA has been examined on a SQUID susceptometer <1999SCI261, 2000MCL161, 2001JA3601, 2001MI451, 2001SM(121)1767, 2001POL1517, 2002MI064434/1>. After compensating the diamagnetism, the temperature dependence of the paramagnetic susceptibility χ_p was obtained. When the temperature was decreased from room temperature (290 K) to 230 K, χ_p decreased slightly. Below this temperature, a rapid decrease was observed and χ_p became almost zero at 180 K. A further decrease in temperature to 100 K was accompanied by a slight increase in χ_p, probably due to paramagnetic lattice defects. Upon heating from 100 to 150 K, χ_p decreased, and between 150 and 230 K, where the drastic change occurs upon cooling, a continuous change in χ_p was noted. Further warming to 305 K saw a sudden increase in χ_p – to a value almost the same as the initial value. The relationship between temperature and χ_p was reproduced following several warming and cooling cycles in the range 230–360 K. However, at temperatures above 360 K, chemical decomposition caused χ_p to irreversibly decrease to zero. The data indicate a large first-order magnetic phase transition with a surprisingly wide hysteresis loop ($T_{c\downarrow} = 230$ K and $T_{c\uparrow} = 305$ K) with a drastic change in magnetic properties. The HT phase is paramagnetic while the LT phase is diamagnetic. There are also significant differences in optical properties with the HT phase being red/purple while the LT phase is yellow/green. The two phases can coexist between 230 and 305 K.

The magnetic bistability of TTTA was stabilized by pressure with measurements made over the range 0–1.5 Gpa. The room temperature paramagnetic–diamagnetic bistability measured at ambient pressure $T_{c\downarrow} = 230$ K and $T_{c\uparrow} = 305$ K was shifted at high temperatures at higher pressures with $dT_{c\uparrow}/dp = 20 \pm 10$ and $dT_{c\downarrow}/dp = 45 \pm 20$ K Gpa^{-1} at $p = 0$ Gpa. Such behavior parallels that observed for spin-crossover complexes; however, the basis origins are likely very different. The observed dependence of pressure effects for TTTA was found to be generally explicable by the Clapeyron Equation. A second characteristic feature of the pressure effect on TTTA was the suppression of paramagnetism in the HT phase with increasing pressure. This trend was presumed to arise from an enhancement in the antiferromagnetic interactions which were estimated to have nearly doubled at 1.5 GPa from the value at 0 GPa <2004CPL(393)150>.

The magnetic properties of TTTA **1** were also observed to be tunable by laser light irradiation using the second and third harmonics of a pulsed Nd:YAG laser (532 and 355 nm). Independent photoexcitation of the HT and LT phases of TTTA showed that a nanosecond laser pulse could induce phase transition from the LT to the HT phase from both inside (296 K) and outside (11 K) the hysteresis loop. On the other hand, HT to LT transitions were not possible. Comparison of the excitation energy dependence between transition efficiency and photoconductivity suggested that the PIPT from LT to HT phase was driven by suspension of the spin-Peierls (SP) instability by accumulation of photocarriers above a critical density <2003MI17403, 2003CPL(378)456, 2005MI283>. Photoinduced HT to LT transitions failed since photoexcitation in the HT phase would produce photocarriers as well as CT excitons, and such spinless excitations never enhance the SP instability in the HT phase.

Efforts have been made to explain the magnetic properties of TTTA on the basis of the results of both molecular orbital calculations (see Section 10.05.2.1) and crystal structure data (see Section 10.05.3.1.1). Because the polar stacking column formed by the TTTA molecules in the HT phase includes short contacts between the –S–N–S– moieties on which the unpaired electron resides, the intracolumn interaction is believed to be stronger than the intercolumn interaction. The magnetic behavior of the HT phase is interpreted by the model of a 1-D antiferromagnetic chain with a modification to account for the intercolumn interactions. The difference in molecular packing between the HT and the LT phases is believed to account for the much larger estimated value of the intra-dimer exchange coupling constant as calculated by the Bleaney–Bowers method for the LT phase with respect to the HT phase. This results in an enhancement in one-dimensionality for the LT phase <1999SCI261>.

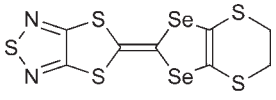
The bistability is similar to SP transition which is caused by an instability in the 1-D antiferromagnetic chains of the $S = 1/2$ Heisenberg spins toward lattice dimerization. The phase transition in TTTA is partially explained by this instability. Further, it has been proposed that cooperation between this instability and strong intercolumn interactions in TTTA may explain the first-order phase transition. An alternative explanation invoked differences in the nearest-neighbor arrangements between the HT and LT phases. The eclipsed presentation of TTTA molecules **1** in LT phase maximizes the exchange energy but causes electrostatic repulsion while the slipped overlap of the TTTA molecules in the HT phase causes this phase to be a balance between the two types of energies. The competition between the electrostatic and exchange energies in the dimers may create a potential barrier between the structures of the HT and LT phases resulting in the wide hysteresis loop <1999SCI261>. The degree of structural change between HT and LT phases explains why the transition is first and not second order as is typical for SP systems <2003MI17403>.

Magnetic measurements of the 1:1 coordination complex of TTTA and $Cu(hfac)_2$ **3** revealed a ferromagnetic dimer with a weak interdimer antiferromagnetic interaction <2001JA3601, 2001POL1517>. Temperature dependence of the paramagnetic susceptibilities χ_pT for **3** has been recorded over the range 1.8–350 K.

At the highest temperature, 300 K, the value of χ_pT at 0.793 emu K mol^{-1} was close to the ideal value (0.812) for two noninteracting $S = 1/2$ spins on $g = 2.135$ ($Cu(hfac)_2$) and 2.006 (TTTA). A gradual increase in χ_pT observed upon decreasing the temperature to 30 K was consistent with ferromagnetic coupling. After hitting a maximum at this temperature, an abrupt decrease was observed, which suggested a weak antiferromagnetic coupling between the ferromagnetic units. The magnetic data were well reproduced by the theoretical curve. The ferromagnetic coupling was ascribed to the coordination bond between $Cu(hfac)_2$ and $TTTA^A$ and the antiferromagnetic coupling to the interaction between $Cu(hfac)_2$ and $TTTA^B$ and/or interchain interactions (see Section 10.05.3.1.1) <2005MI320>.

10.05.4.1.2 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The magnetic properties of the PF_6 salt of **91** exhibit Curie-like behavior. Measurements have shown the effective magnetic moment χ_pT to suddenly decrease at the resistivity minimum temperature, ~20 K (see Section 10.05.4.2). The value of χ_pT at 0.006 emu K mol^{-1} roughly corresponded to 2% localized spins per unit cell. Since no sample dependence behavior was noted, the measurements represent genuine properties of the sample and were not considered assignable to trivial chemical impurities or lattice defects. X-Ray analyses of the TaF_6 and AsF_6 salts of the same compound proved them to be isostructural with the PF_6 salt, and further X-ray photographs show that the crystal structures are stable down to 11 K. Accordingly it is believed that the results of magnetic susceptibility, electrical resistivity, and specific heat measurements for the PF_6 salt can be considered typical of the three salts. Accordingly, the TaF_6 and AsF_6 salts of **91** are also assumed to exhibit Curie-like behavior <1997SM(86)1815>.



91

10.05.4.2 Electrical Properties

10.05.4.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

Electrical resistivity data of the SbF_6, PF_6, TaF_6, and AsF_6 salts of **91** show that some octahedral anion salts remain metallic down to ca. 20 K, and this characteristic may be useful in the exploitation of the heterocyclic donor as a component in magnetic organic materials (see Section 10.05.12.5) <1995SM(70)1157, 1997SM(86)1815>. Electrical resistance has a minimum around 20 K before rising proportionally to the logarithm of temperature followed by a saturation below ca. 2 K. It is believed the electrical behavior at low temperature may be explained by a Kondo effect; however, the origin of the spins is unknown <1997SM(86)1815>.

In spite of the 1:1 composition the radical cation salts of the [1,3]dithiolo[4,5-*c*][1,2,5]thiadiazoles **45**(ClO_4), **45**($AuBr_2$), and **45**[$Au(CN)_2$] showed moderate electrical conductivity. Data, measured at room temperature, on either single crystal or compressed pellet samples are summarized in **Table 10**. The low conductivity of **46**[$Au(CN)_2$] was in keeping with the mixed stack column structure found in the crystal of this compound while short intermolecular S···N and S···S contacts were believed to explain the high conductivity of **45**(SbF_6) <1997SM1871>. The thiadiazole fused BDT-TPPs **88** showed similar electrical conductivity <1997SM1821>.

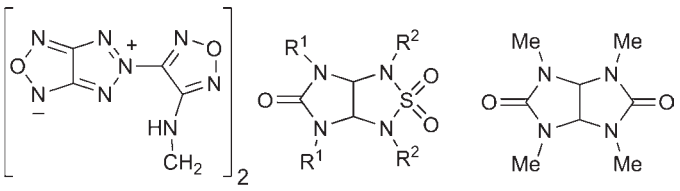
Table 10 Electrical conductivity measurements on radical cation salts of [1,3]dithiolo[4,5-*c*][1,2,5]thiadiazoles, **45**, **46**, and **88**

Salt	σ ($S\,cm^{-1}$)	E_a (*eV*)	*Reference*
45(ClO_4)	1.7×10^{-3}[a]	0.14	1997SM(86)1871
45($AuBr_2$)	3.2×10^{-3}[a]	0.13	
45[$Au(CN)_2$]	3.2×10^{-4}[a]	0.19	
45(SbF_6)	2.0×10^{-1}[a]	0.09	
46[$Au(CN)_2$]	2.7×10^{-6}[b]		
88a[TCNQ]	3×10^{-1}[b]		1997SM(86)1821
88b[TCNQ]	4.0×10^{-1}[b]	0.052	
88b(I_3)	2.0×10^{-1}[b]	0.044	

[a]Measured on single crystals.
[b]Measured on compressed pellets.

10.05.4.3 Melting Points, Boiling Points, Thermal Stability, Stability to Moisture, Solubility, R_f values

The endothermic and exothermic transition upon cooling (234 K) and heating (315 K), respectively, of TTTA **1**, has been observed by DSC measurements, and the hysteresis has been found to be in good agreement with magnetic measurements <2001MI451, 2002MI064434/1>. The [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole-centered radical anion salts **32** and **33** were observed to be thermally stable but very moisture sensitive <2005IC7194>. The [1,2,3]triazolo[4,5-*c*]-[1,2,5]azadiphosphole **34** melted at high temperature, and, unlike the very sensitive known $RPPh_2(=NSiMe_3)$ compounds, it was both moisture and air stable <2003AGE3506>. The 5,5′-[methanediamino-bis(1,2,5-oxadiazol-4,3-diyl)]bis[1*H*-[1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazolium]-bis(inner salt) **92** was found to be thermally stable above 200 °C, but the N-nitrated derivative was somewhat less stable <1995JHC1405>. Preliminary findings on the specific heat capacity of the PF_6 salt **91** of [1,3]dithiolo[4,5-*c*][1,2,5]thiadiazole under ambident conditions and under applied magnetic field suggested some unusual characteristics for this molecule; further study is to be undertaken to provide an explanation <1997SM(86)1815>. The imidazo[4,5-*c*][1,2,5]diazaborolidines **56** have displayed an extraordinary combination of properties. Despite their betaine character they were sufficiently nonpolar to be soluble in toluene, and they were stable in air and light and melted without decomposition. They were redox active and the radical anion had an unusually high thermodynamic stability <2004CC1860>. Comparative data for the sulfanamides **93** with the tetraazabicycle **94** indicated markedly lower solubility in both water and organic solvents as well as inability to form complexes with calcium salts (**Table 11**). These properties are likely to limit their biological activity <2001PCJ72>. The melting point ranges noted for the dialkyl- and tetraalkylimidazo[4,5-*c*][1,2,5]thiadiazoles **93a–d** showed a steady decline through **93a–c**, and a more significant decrease was recorded for the 2,4-dimethyl-6,8-diethyl derivative **93d** (**Table 12**). While the original article offered no explanation, the observed trend likely follows from the increased steric bulk of the substituents interfering with the packing in the solid state <2001PCJ72>. The R_f values (Silufol UV-254 plates, acetone–chloroform 1:3) noted for the same compounds **93a–d** showed a steady increase through **93a–c**, and a more significant increase was recorded for 2,4-dimethyl-6,8-diethyl derivative **93d** (**Table 12**) <2001PCJ72>.



92 **93** **94**

a: R^1 = Me; R^2 = H
b: R^1 = Et; R^2 = H
c: R^1 = Me; R^2 = Me
d: R^1 = Et; R^2 = Me

Table 11 Comparative data on the solubility of **93c** and **94** in water and some organic solvents

	Solubility, % (19 °C)				
Compound	*H_2O*	*CH_3OH*	*$(CH_3)_2CO$*	*$CHCl_3$*	*CH_2Cl_2*
93c	0.54	0.47	0.37	0.28	0.97
94	54.70	22.50	2.99	9.05	22.15

Table 12 Melting point range and R_f values for a range of di- and tetraalkylimidazo[4,5-*c*][1,2,5]thiadiazoles <2001PCJ72>

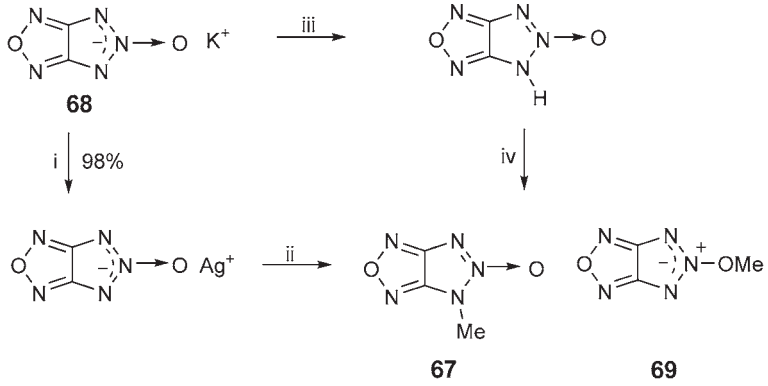
Compound	*m.p. (°C)*	R_f
93a	201–203	0.10
93b	184–185	0.14
93c	177–179	0.21
93d	85–87	0.58

10.05.5 Reactivity of Fully Conjugated Rings

10.05.5.1 Electrophilic Attack at Nitrogen

10.05.5.1.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Reaction of the potassium salt of the [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazole 2-oxide **68** with $AgNO_3$ furnished the corresponding silver salt whilst the parent bicycle was obtained on acidification <1996TL8577>. Methylation of either the silver salt, or the parent bicycle, led to mixtures of the *N*- and *O*-methylated derivatives **67** and **69**. In each case the selectivity of the reaction differed, the parent showed a 9:1 preference for the *N*-substituted derivative; however, the *O*-methylated product dominated and **67** and **69** resulted in a 4:3 ratio in the reaction starting from the silver salt (**Scheme 5**) <1996TL8577>.



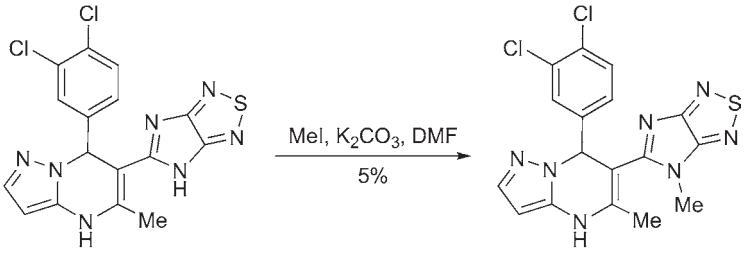
68 **67** **69**

i, $AgNO_3$; ii, MeI, MeCN, 20 °C, 8 h, **67** 86%, **69** 10%; iii, anh. HCl, $Me_2C(O)$; iv, CH_2N_2, Et_2O, **69** 52%, **67** 39%

Scheme 5

10.05.5.1.2 Imidazo[4,5-*c*][1,2,5]thiadiazoles

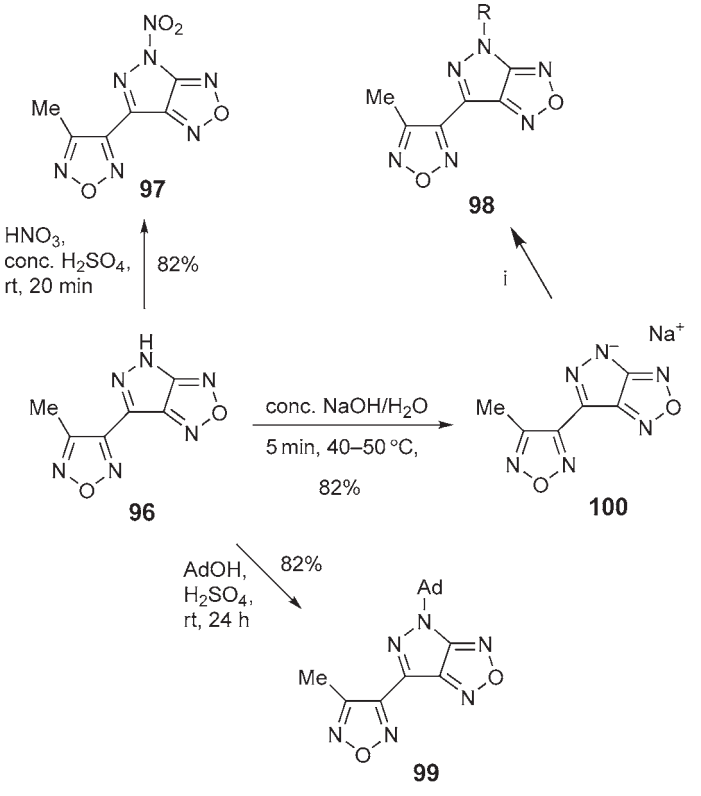
Alkylation at the N-atom of the imidazothiadiazole **95** was achieved following treatment with MeI under the influence of K_2CO_3 (Equation 1) <2001WO040231>.



95 (1)

10.05.5.1.3 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles

Nitration and adamantylation of the pyrazolo[3,4-*c*][1,2,5]oxadiazole **96** has been demonstrated, yielding **97** and **99** respectively. The alkylated derivatives **98** were formed by way of the sodium salt **100** (**Scheme 6**) <2003T1059>.



i, (a) for R = Me, MeI, KOH, EtOH, 80 °C, 1 h, 87%; (b) for R = CH_2CO_2H, $ClCH_2CO_2H$, KOH, H_2O, 100 °C, 5 h, 77%

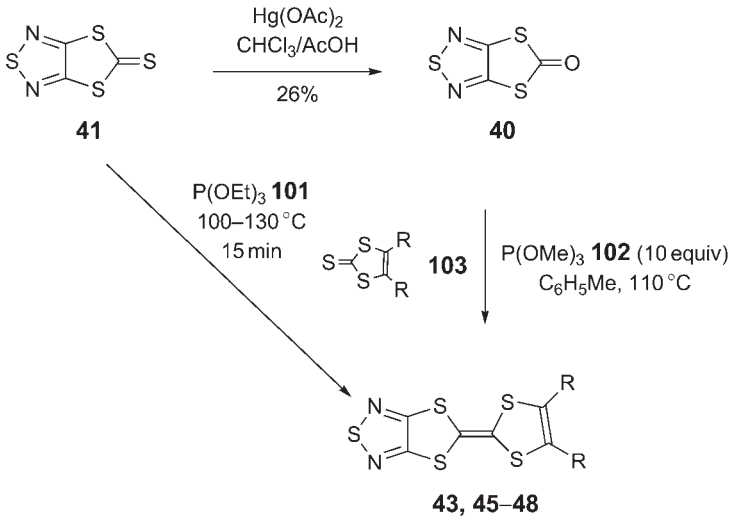
Scheme 6

10.05.5.2 Nucleophilic Attack at Carbon

10.05.5.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

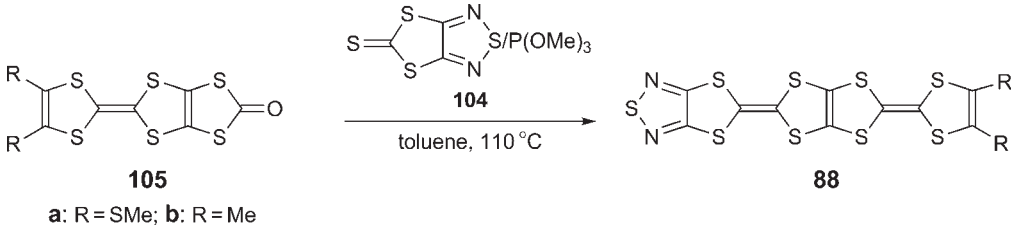
Dimerization of the dithiolothiadiazolothione **41** in the presence of triethyl phosphite, **101**, gave the bis(thiadiazole)tetrathiafulvalene **43** in low yield (3%), the same product resulted from the ketone **40** in slightly higher yield (6%)

<1993SM(68)1914>. Trimethyl phosphite **102** (10 equiv) mediated cross-coupling between the 1,3-dithiole-2-thiones **103** and the ketone **40** yielded unsymmetrical TTF derivatives **45–48**, in moderate yields (**Scheme 7**)<1997SM(86)1871>. Similar reaction between the 2-thione **104** and the TTF derivatives **105** yielded the pentacycles **88** (yields were not recorded) (Equation 2) <1997SM(86)1821>.

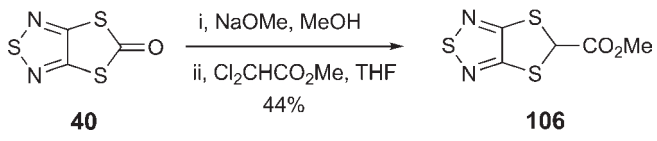


Compound	*R*	*Yield (%)*	*Reference*
43[a]	R,R = NSN	6	1993SM(68)1914
43[b]	R,R = NSN	3	1993SM(68)1914
45	R,R = SCH_2CH_2S	46	1997SM(86)1871
48	R,R = OCH_2CH_2O	23	1997SM(86)1871
46	R = SMe	42	1997SM(86)1871
47	R = H	9	1997SM(86)1871

Scheme 7



Basic cleavage of the dithiolothiadiazolone **40** followed by treatment with methyl dichloroacetate yielded the ester **106**; **106** was employed as a key starting material for synthesis of unsymmetrical TTF derivatives (**Scheme 8**) <1996JOC3987>.



Scheme 8

10.05.5.3 Oxidation

10.05.5.3.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The dithiolothiadiazolothione **41** was oxidized to the ketone **40** following reaction with mercuric acetate (**Scheme 7**) <1993SM(68)1914>.

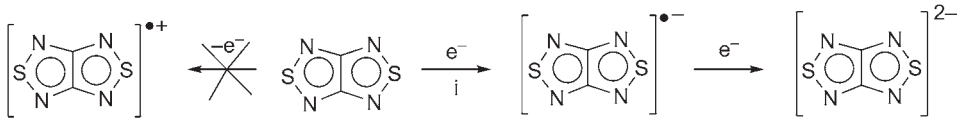
10.05.5.3.2 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The 1,3-dithiolo[4,5-*b*][1,4]dithiin **45** was subjected to electrochemical oxidation in the presence of a range of tetrabutylammonium salts in THF or CH_2Cl_2, and yielded the radical cation salts **45**(ClO_4), **45**($AuBr_2$), **45**[$Au(CN)_2$], and **45**(SbF_6). Likewise, electrolysis of the dithiol derivative **46** with *n*-$Bu_4N[Au(CN)_2]$ in THF furnished **46**[$Au(CN)_2$]. Accordingly, it was surprising that no salts of **47** or **48** could be obtained by electrolysis under any experimental conditions <1997SM(86)1871>. However, 7,7′,8,8′-tetracyanoquinodimethane (TCNQ) complexes and I_3 salts of **88** were prepared simply by mixing the donors with TCNQ or Bu_4NI_3, respectively <1997SM(86)1821>.

10.05.5.4 Reduction

10.05.5.4.1 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

Reversible electrochemical reduction of the [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** led to the long-lived radical anion **7** and further to the dianion **8**. The radical anion **7** was also obtained by the chemical reduction of the parent **6** in an ESR tube with 2 equiv of *t*-BuOK in degassed absolute MeCN at 50 °C for 20 min (**Scheme 9**). Electrochemical approaches to generation of the radical cation **12** failed <2005IC7194>.

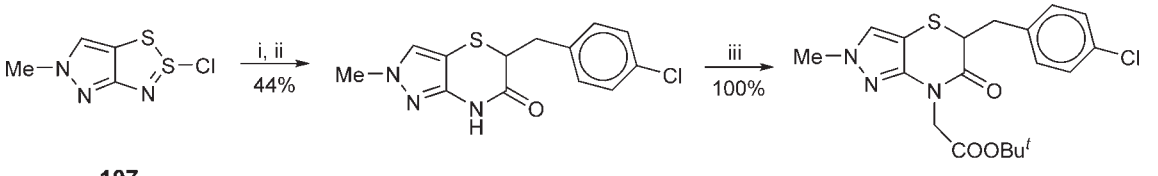


Scheme 9

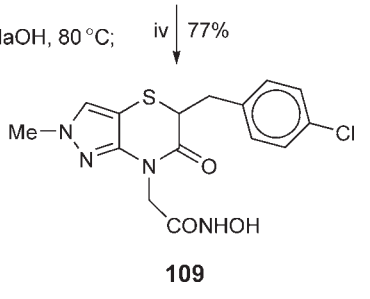
10.05.5.5 Nucleophilic Attack at Sulfur

10.05.5.5.1 Imidazolo[4,5-*d*][1,2,3]dithiazoles

Opening of the dithiazole ring of the imidazolo[4,5-*d*][1,2,3]dithiazole **107** was employed as a key step in a multistep synthesis leading to hydroxamic acid derivatives **108** and **109** which are under investigation as matrix metalloproteinase inhibitors. Following initial reaction of **107** with NaOH treatment with 2-bromo-3-(4-chlorophenyl)propionic acid *tert*-butyl ester lead to the thioethers **108** from which **109** could be obtained (**Scheme 10**). <2000WO063197>.



i, 20% $NaOH_{aq}$, 80 °C, 1 h, then 2-bromo-3-(4-chlorophenyl)propionic acid in 20% NaOH, 80 °C;
ii, acetic acid, 80 °C, 2.5 h;
iii, DMF, NaH, rt, 0.5 h, then *t*-butyl bromoacetate, rt, 15 h;
iv, TFA, rt, 2 h, then isobutyl chloroformate, THF, *N*-methylmorpholidine at −5 °C, 2 h



Scheme 10

10.05.5.6 Miscellaneous Reactivity

10.05.5.6.1 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

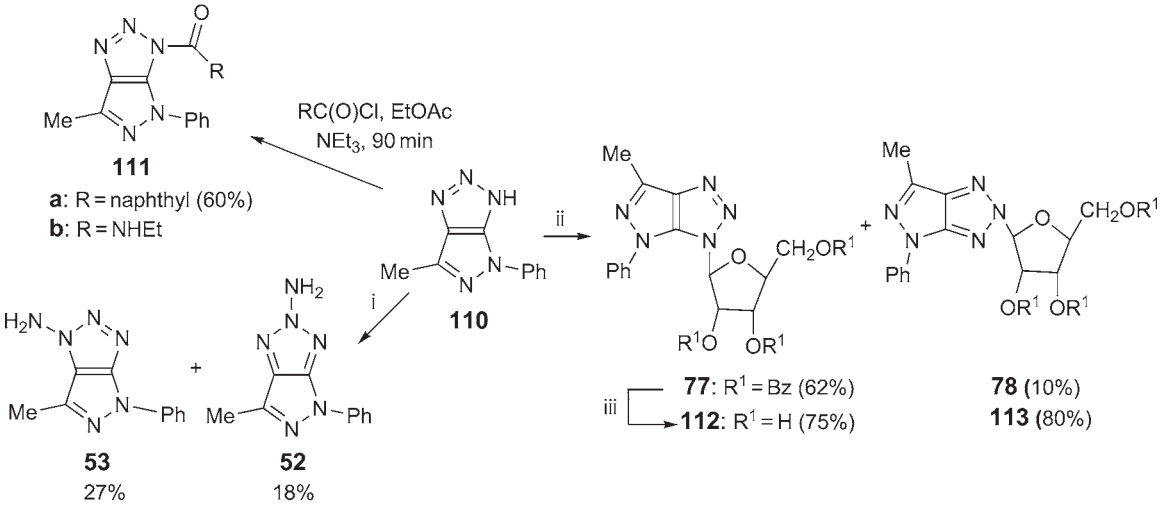
Dissociative ionization of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** was found to be an efficient preparative route to *in situ*-generated thionitrosyl cyanide and its radical cation, both of which are stable and did not undergo unimolecular rearrangement under the reaction conditions. The $[C,N_2,S]^+$ ions were characterized by mass spectrometry (*m/z* 72) (see Section 10.05.3.2.2) <1997JST(418)209>.

10.05.6 Reactivity of Nonconjugated Rings

10.05.6.1 Electrophilic Attack at Ring Nitrogen

10.05.6.1.1 Pyrazolo[3,4-*d*][1,2,3]triazoles

Reactions designed to introduce a variety of substituents at the N-3/N-1 positions of pyrazolotriazoles have been demonstrated <2000BMC2343, 1995H(41)2409, 1996USP5508154, 1998AP269, 1992FA1021>. Amination and acylation of N-3-unsubstituted pyrazolotriazole **110** have furnished new derivatives of the bicycle <1995H(41)2409, 2000BMC2343>. Treatment with naphthoyl chloride furnished **111** <2000BMC2343>, while the same substrate underwent direct amination when subjected to the Campbell procedure to yield the isomeric 1- and 2-amino derivatives **52** and **53**, as major and minor reaction products, respectively. No trace of the 3-amino isomer was detected. This is significant as attempts to form 3-aminopyrazolotriazoles by the classical procedure based on *o*-aminohydrazino pyrazoles failed <1995H(41)2409>. Glycosylation at the N-3 position of a pyrazolo[3,4-*d*][1,2,3]triazole was achieved following reaction with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose to yield the protected nucleosides **77** and **78**. The reaction proceeded with high selectivity; the *N*-3-β-isomer **77** and *N*-2-β-isomer **78** were obtained in 62% and 10% yield, respectively – only a trace amount of the *N*-3-α-isomer was detected and there was no evidence for the presence of any N-1-substituted derivatives. Deprotection was achieved with methanolic ammonia affording **112** and **113** (**Scheme 11**) <1998AP269>.



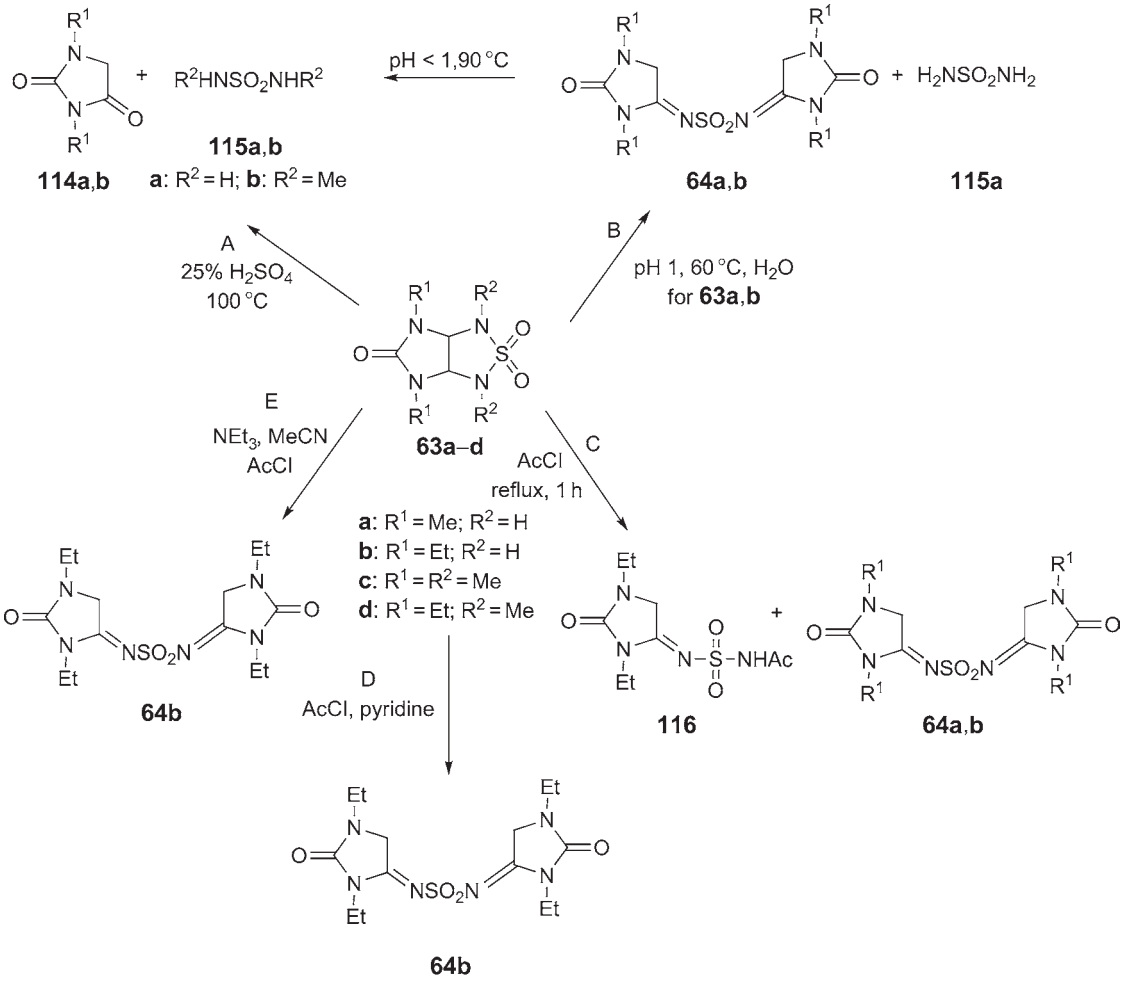
i, to a solution of **110** in KOH, H_2O at 60 °C add NH_2OSO_2H over 1 h maintain temperature of 70–75 °C;
ii, HMDS, TMSCl, TfOH, MeCN, NH_4SO_4, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose; iii, NH_3/MeOH, 4 °C, 24 h

Scheme 11

10.05.6.1.2 Imidazo[4,5-*c*][1,2,5]thiadiazoles

While the imidazo[4,5-*c*][1,2,5]thiadiazole dioxides **63a–d** were observed to be rather susceptible to hydrolysis compared to their tetraaza analogues, on treatment with refluxing 25% H_2SO_4 reaction proceeded in the same manner and **63** completely hydrolyzed to furnish 1,3-dialkylhydantoins **114a** and **114b** and sulfamides **115a** and

115b following reaction times which ranged from just 12 min to 5 h. On the other hand, under milder acid conditions (pH 1, 60 °C) or upon reaction with acetyl chloride, **63a** and **63b** disproportionated and so yielded the 4,4′-sulfonyldiiminobis(1,3-dialkylimidazolidin-2-ones) **64a** and **64b**, accompanied by the sulfamide in the case of the acid reaction and by the acetamide **116** when the reaction with AcCl was conducted at reflux temperature. Only the bisimidazolidine **64** resulted when the same reaction was repeated in either NEt_3 or pyridine. A mechanism proposed for the disproportionation is supported by observation of kinetic parameters determined by ^1H NMR spectral analysis of the reaction progress; the data indicate that the reaction is pseudo-first-order in dioxide at constant proton concentration (**Scheme 12**) (see Section 10.05.3.2.1(i)) <2003CHE784>.



Transformation	*Substrate*	*Product(s)*	*(Yield)*
A	**63a–d**	**114a,b**	**115a,b**
B	**63a**	**64a** (65–70%),	**115a**
	63b	**64b** (66–70%),	**115a**
C	**63a**	**64a** (47%)	
	63b	**64b** (44%),	**116** (19%)
D	**63b**	**64b** (43–55%)	
E	**63b**	**64b** (39%)	

Scheme 12

10.05.6.2 Electrophilic Attack at Ring Oxygen

10.05.6.2.1 Oxazolo[4,5-*d*][1,2,3]triazoles

The oxazolo[4,5-*d*][1,2,3]triazoles **65** are unstable to acid, and following heating briefly in refluxing EtOH in the presence of AcOH they are converted in high yield into the rare 1,3,4,5-oxatriazines **66** (78–93% yield); accompanying the heterocycle were the corresponding imines which rapidly solvolyzed under the reaction conditions. However, ^{1}H NMR spectral data provided compelling evidence for their existence (see Section 10.05.3.2.1(i)) (**Scheme 1**) <1994J(P1)2797>.

10.05.6.3 Reduction

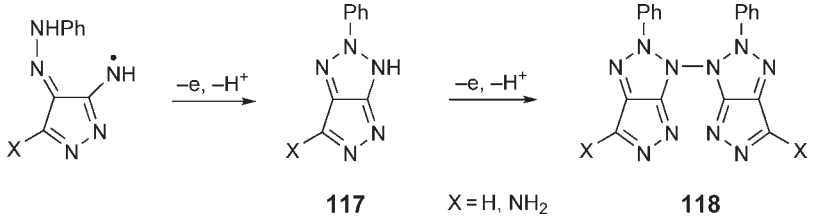
10.05.6.3.1 Imidazo[4,5-*d*][1,3,2]diazaborolidines

The boron substructure was eliminated from the imidazo[4,5-*d*][1,3,2]diazaborolidine framework **56** following ultrasonic reduction with metallic lithium in THF and anions of the imidazoles **90** formed. The observed reactivity ruled out the possibility of isolating the intermediates from these single-electron-transfer reactions <2004CC1860>.

10.05.6.4 Oxidation

10.05.6.4.1 Pyrazolo[3,4-*d*][1,2,3]triazoles

Studies on the potential of the electrochemical approach to pyrazolotriazoles **117** showed that under the conditions of bicycle synthesis from 3-amino-4-hydrazonopyrazoles the N-1-unsubstituted triazole ring of **117** was further oxidized in a one-electron peak, followed by proton removal to yield the bis-(1,1′)-2-phenylpyrazolo[3,4-*d*][1,2,3]triazoles **118**. This observation is significant, since in spite of pronounced pharmaceutical applications of pyrazoles, the redox characteristics of substituted pyrazoles have received limited attention (**Scheme 13**) <2001MI1022>.



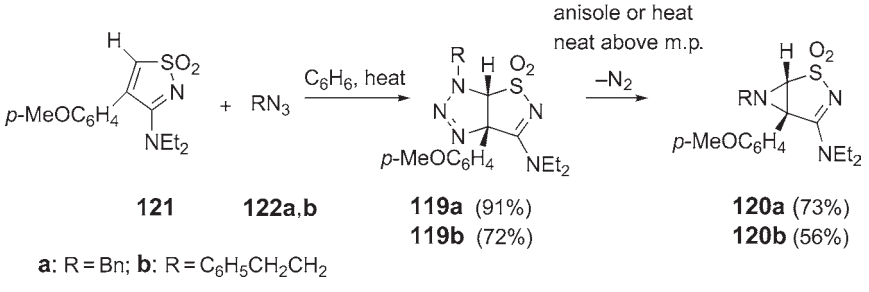
Scheme 13

10.05.6.5 Miscellaneous Reactivity

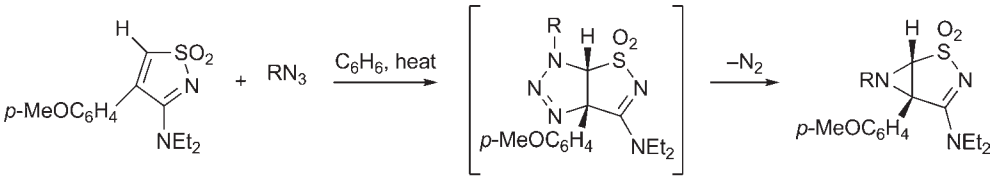
10.05.6.5.1 Nitrogen extrusion – ring contraction

10.05.6.5.1(i) Isothiazolo[4,5-*d*][1,2,3]triazoles

Thermally induced N_2 elimination from isolated samples of the isothiazolo[4,5-*d*][1,2,3]triazoles **119a** and **119b** furnished the aziridine-fused bicycles **120a** and **120b**. Parallel compounds **120c–e** were generated *in situ* from the reaction between aryl azides **122c–e** and the isothiazole **121** in refluxing benzene (**Schemes 14** and **15**) <1996T7183>.



Scheme 14



121 **122c–e** **119c–e** **120c** (74%) **120d** (51%) **120e** (50%)

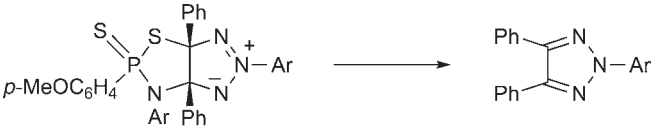
c: R = Ph; **d**: R = *p*-MeOC$_6$H$_4$; **e**: R = *p*-O$_2$NC$_6$H$_4$

Scheme 15

10.05.6.5.2 Fragmentation reactions

10.05.6.5.2(i) [1,2,3]Triazolo[4,5-*d*][1,3,2]thiazaphospholes

The [1,2,3]triazolo[4,5-*d*][1,3,2]thiazaphospholes **57**, reasonably stable in the solid state, fragmented in solution and yielded the 1,2,3-triazoles **123** and a variety of NPS compounds. Even at −30 °C in NMR solvents the bicycles lacked stability (Equation 3) <1997CC2149>.

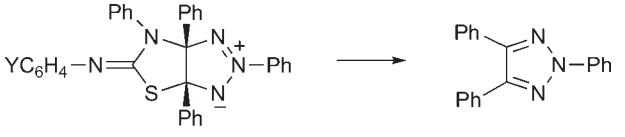


57 **123** (3)

a: Ar = Ph; **b**: Ar = *p*-MeC$_6$H$_4$; **c**: Ar = *p*-BrC$_6$H$_4$; **d**: Ar = *p*-NO$_2$C$_6$H$_4$

10.05.6.5.2(ii) Thiazaolo[4,5-*d*][1,2,3]triazoles

Under the influence of heating or upon prolonged stirring the thiazolotriazoles **59** fragmented to the triazoles **123a** (Equation 4) <1997J(P1)3587>. This observation accounts for the failure to observe thiazolotriazoles among the reaction products when reaction between triazolium 1-imides and isothiocyanates was first studied in boiling acetone <1996CHEC-II(7)141>.



59 **123a** (4)

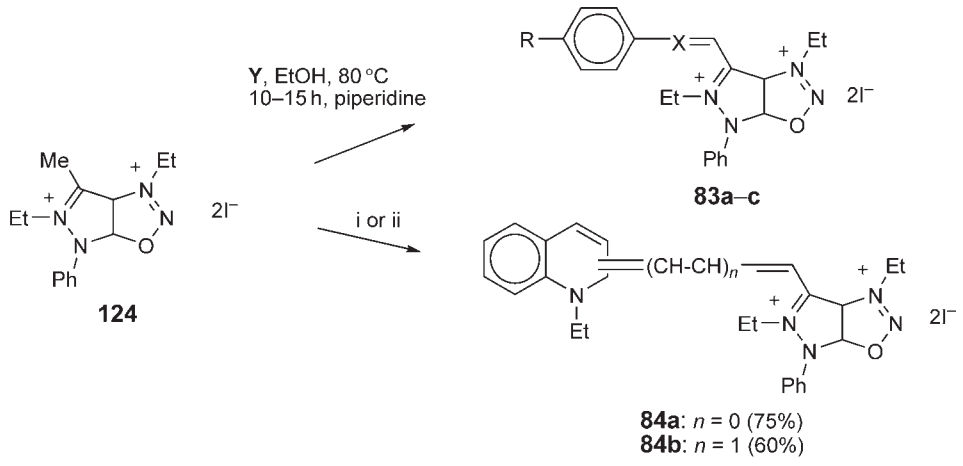
a: Y = MeO; **b**: Y = H; **c**: Y = NO$_2$

10.05.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.05.7.1 Condensation Reactions

10.05.7.1.1 Pyrazolo[4,3-*d*][1,2,3]oxadiazoles

Treatment of the pyrazolium[4,3-*d*][1,2,3]oxadiazolium diiodide **124** with *p*-hydroxy- or *p*-dimethylaminobenzaldehyde yielded the pyrazolo[4,3-*d*][1,2,3]oxadiazole styryl and azastyryl cyanines **83a** and **83b** in modest yields. Parallel reaction with *p*-nitrosophenol furnished **83c**. Reaction of **124** with 1-ethylquinolinium iodide afforded **84a** directly. However, 3-anilinocarbomylmethyl-2,4-diethyl-(N-phenylcarbomylmethyl)pyrazolium(4,3-*d*)[1,2,3]oxadiazolium diiodide **125** arising from reaction of **124** with diphenylformamidine in refluxing acetic anhydride, is the precursor to **84b** which follows from subsequent reaction with 2-methylisoquinolinium iodide (**Scheme 16**) <1994MI905-1>.



Reactant ***Y***	*X*	*R*	*Product*	*Yield (%)*	*Reference*
p-HOC_6H_4CHO	CH	OH	**83a**	52	1994CPA393
p-$Me_2NC_6H_4CHO$	CH	NMe_2	**83b**	50	
p-ONC_6H_4OH	N	OH	**83c**	45	

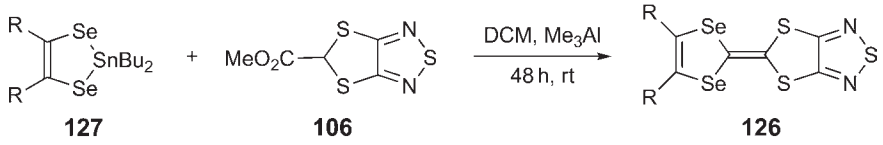
i, Leading to **84a**: 1-ethylquinolinium iodide, piperidine, reflux 3 h EtOH;
ii, Leading to **84b**: (a) PhNHCH=NPh, Ac_2O, 138 °C, 1.5 h; (b) 2-methylisoquinolium iodide, Ac_2O, 2 h

Scheme 16

10.05.7.2 Attack by Organometallic Reagents

10.05.7.2.1 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The ester bearing dithiolothiadiazole **106** has been converted into the diselenadithiafulvalene derivatives **126a** and **126b**, in 27% and 12% yield, respectively, following reaction with a preformed complex of the stable tin chalcogenides **127** and Me_3Al. It was assumed that the reaction proceeded by way of an intermediate aluminium selenolate, which formed from **127**, by Sn/Al exchange. When the same reaction was attempted at −78 °C to rt, only a 3% yield of **126a** resulted (Equation 5) <1996JOC3987>.



(5)

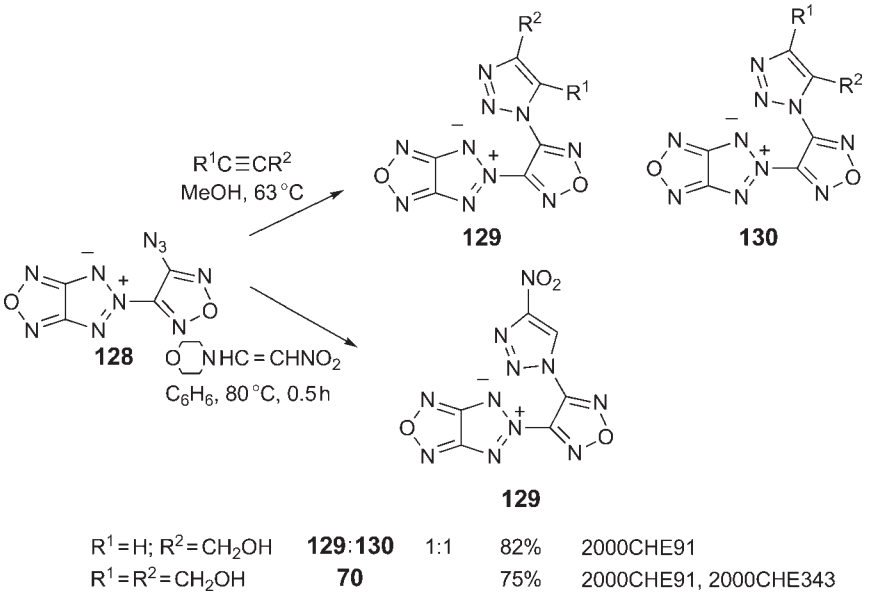
10.05.8 Reactivity of Substituents Attached to Ring Heteroatoms

10.05.8.1 Cycloaddition

10.05.8.1.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Transformations of the substituent at the 4-position of the oxadiazole ring of 5-[4-substituted] oxadiazolyltriazolooxadiazoles has led to a number of new derivatives of the bicycle <1993HCA1, 1995JHC1405, 1998MC238, 1999MI1, 1999RJO1525, 2000CHE91, 2000CHE343>. 1,3-Dipolar cycloaddition reactions between the 4-azido moiety of **128** and either morpholinonitroethene <1999MI1, 2000CHE343> or substituted acetylenes <1999MI1, 2000CHE91>

have yielded the tetracyclic compounds **70**, **129**, and **130** in reasonable yield. Reaction with propargyl alcohol furnished the regioisomeric adducts **129** and **130** in ~1:1 ratio although the data from the ^{13}C NMR spectrum show a greater than expected number of signals in the region 125–160 ppm, indicating contamination through by-products, (**Scheme 17**) <2000CHE91>. The cycloaddition with morpholinonitroethane was conducted in the presence of orthoformic ester for the removal of morpholine from the reaction medium, and without this precaution decomposition of the starting azide was observed <2000CHE343>.

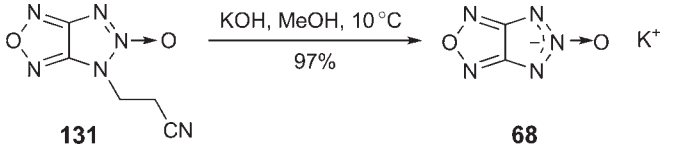


Scheme 17

10.05.8.2 Elimination (Retro-Michael)

10.05.8.2.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Potassium hydroxide-mediated elimination of cyanoethylene from the 4-cyanoethyltriazoloozadiazole **131** yielded the potassium salt **68** (Equation 6) <1996TL8577>.



(6)

10.05.8.3 Nitrogen Elimination

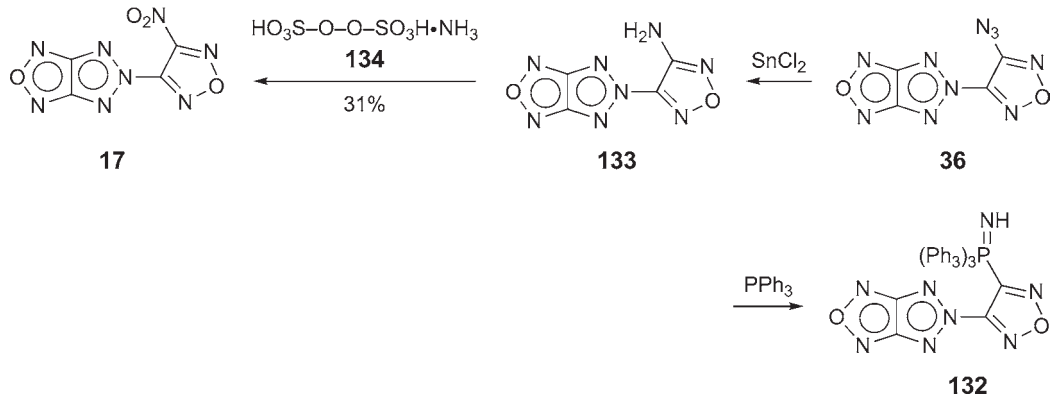
10.05.8.3.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Treatment the of 5-[4-azido]oxadiazolyltriazolooxadiazole **36** with triphenylphosphine furnished the phosphorimino derivative **132**. No experimental details were included in the publication (**Scheme 18**) <1993HCA1>.

10.05.8.4 Reduction

10.05.8.4.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Reduction of the 4-azido moiety of the 5-[4-azido]oxadiazolyltriazolooxadiazole **36** with stannous chloride yielded the amino analogue **133** (**Scheme 18**) <1993HCA1>.

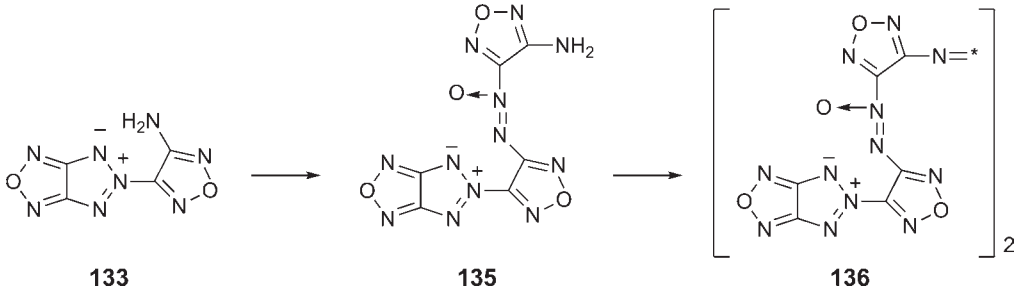


Scheme 18

10.05.8.5 Oxidation

10.05.8.5.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Ammonium persulfate **134** oxidation of the amino functionality of the 4-aminotriazolooxadiazole **133** yielded the nitro derivative **17** as a thick yellow/orange oil which exploded violently upon heating at 160 °C in a closed capillary tube (**Scheme 18**) <1993HCA1>. Oxidative transformations of **133** have also been used to access **135** and **136** containing azo and azoxy fragments, respectively (**Scheme 19**) <1999MI1>.

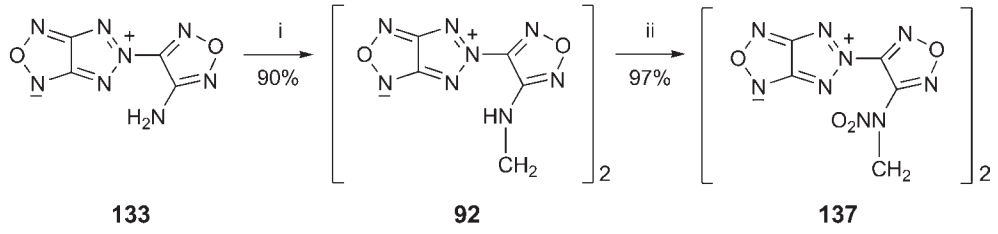


Scheme 19

10.05.8.6 Condensation

10.05.8.6.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

Condensation between the 4-amino group of the oxadiazole moiety of the triazolooxadiazolium inner salt **133** and formaldehyde furnished the methanediamino linked bis(inner salt) **92** from which the methanedinitroamine analogue **137** could be obtained on reaction with nitric acid (**Scheme 20**) <1995JHC1405>.

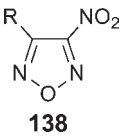


Scheme 20

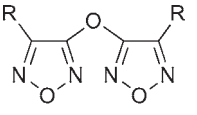
10.05.8.7 Substitution Reactions

10.05.8.7.1 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

The 4-nitro substituent on the pendant oxadiazole moiety of the triazolooxadiazole **17** has been replaced by a hydroxy group yielding **140** <1998MC238, 1999RJO1525>. In contrast to the generation of difurazanyl ether derivatives **139** from reaction of nitrofurazans **138** bearing highly electron-withdrawing groups (R) with solid anhydrous bases in dry solvents, facile regioselective replacement of the nitro group for a hydroxy group was achieved upon treatment with the solid crystalline hydrate of sodium acetate in dry MeCN. The hydroxy derivative **140** was formed from **17** in 87% yield; significantly the inclusion of 3% water in the MeCN halved the yield of **140** <1998MC238>.

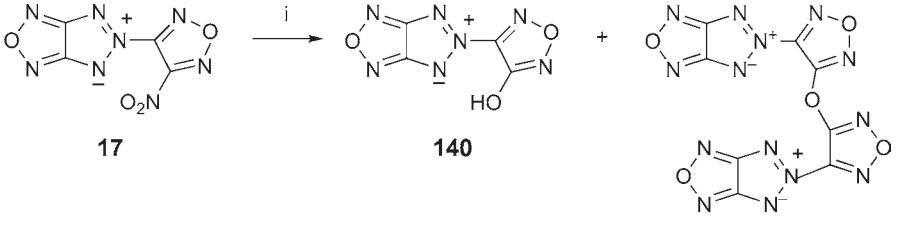


138



139

The same transformation was reported to follow treatment of **17** with excess sodium hydroxide (5 equiv), in aqueous acetone. In this case, the product yield was lower. With a reduced amount of alkali, 0.5 equiv KOH, both the hydroxy derivative **140** and the difurazanyl ether-linked bis(triazolooxadiazole) **37** resulted (**Scheme 21**) <1999RJO1525>. As a precaution it should be noted that the strongly acidic nature of hydroxyfurazans means they readily form stable salts with amines and alkali or alkaline earth metals, and such salts show a tendency to decompose with explosion on shock, friction, or fast heating, and so should be handled with care <1999RJO1525>.



17 **140** **37**

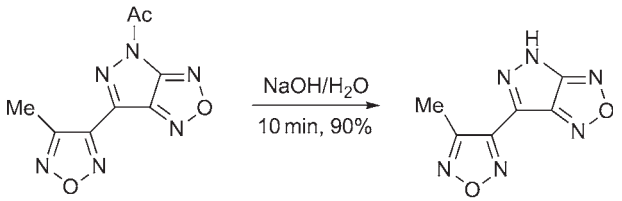
Conditions	*Product(S)*	*Yield(%)*	*Reference*
i, $NaOAc{\cdot}3H_2O$, MeCN, 75–80 °C, 35 min	**140**	37	1998MC238
i, NaOH, H_2O, Me_2CO, rt, 5 min	**140**	43	1999RJO1525
i, 0.5 equiv KOH, H_2O, MeCN, CH_2CH_2, rt, 5 min	**37**,**140**	24,31	1999RJO1525

Scheme 21

10.05.8.8 Hydrolysis

10.05.8.8.1 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles

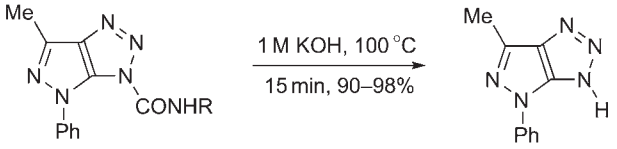
The acetyl group of **141** was readily saponified in basic media to yield **96**, which, with its acidic proton, provided a useful platform for synthesis of a number of N-3-substituted pyrazolooxadiazole derivatives (Equation 7) <2003T1059>.



141 96 (7)

10.05.8.8.2 Pyrazolo[3,4-*d*][1,2,3]triazoles

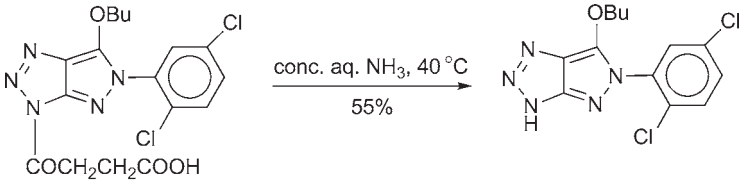
Alkaline hydrolysis of the carboxamide derivatives **142** upon heating in 1 M KOH at reflux afforded the N-3-unsubstituted bicycle **143** (Equation 8) <1992FA1021>. Methanolic ammonia has also been used to remove the N-3-substituent from **144** giving **145** (Equation 9) <1996USP5508154>.



142

R = Et, Pr, Bu, Bu^t, CH_2CO_2Et

143 (8)



144 **145** (9)

10.05.9 Ring Syntheses Classified by Number of Ring Atoms Contributed by Each Component

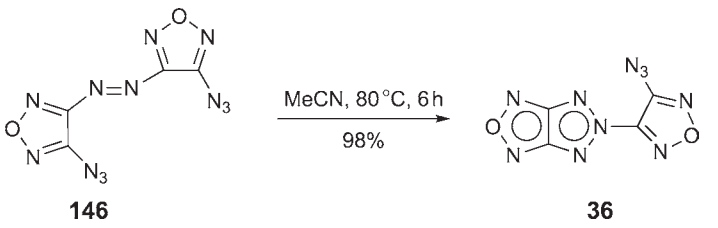
10.05.9.1 Synthesis from Monocyclic Precursors

Annulation of the second ring onto a monocyclic parent continues to be the most common synthetic route to the bicyclic systems discussed in this section. The synthetic background to the starting monocycles is, in general, not discussed in this chapter but may be found in Volumes 6 and 7 or its precursors CHEC(1984) or CHEC-II(1996).

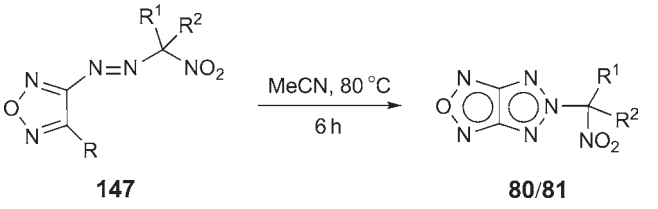
10.05.9.1.1 Synthesis from [5+0] atom fragments

10.05.9.1.1(i) [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazoles

The triazolooxadiazole **36** has been obtained, in excellent yield, following mild thermolysis of the diazidofurazan **146**, itself prepared from the diazonium salt of the corresponding diamine (Equation 10) <1993HCA1>. Thermal and oxidative cyclizations of 3-azido- or 3-amino-4-azo-1,2,5-oxadiazoles **147** were achieved upon heating in boiling benzene alone (for the azides) or in the presence of $Pb(OAc)_4$ (for the amines). In each case, a superior yield of the bicycle **80**/**81** was obtained from the azido starting material (Equation 11) <1995IZV1315>. Other triazolo[4,5-*c*]-[1,2,5]oxadiazole derivatives have been formed by cyclization of 3-amino-4-azo-1,2,5-oxadiazole derivatives by boiling in either PhCl or *o*-$Cl_2C_6H_4$, in the presence of $Pb(OAc)_4$. The same reaction has been demonstrated by treatment with $SOCl_2$. In all cases, however, low yields of isolated product rendered the reactions of limited synthetic utility <1996KGS253>.



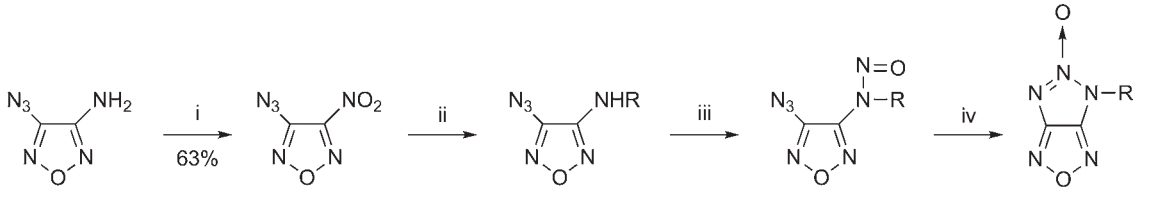
146 **36** (10)



147 **80/81** (11)

R	R^1	R^2	*Compound*	*Yield (%)*	*Reference*
N_3	Me	Me	**80**	98	1995IZV1315
NH_2	Me	Me	**80**	28	1995IZV1315
N_3	$CH_2OCH_2OCH_2$		**81**	95	1995IZV1315
NH_2	$CH_2OCH_2OCH_2$		**81**	30	1995IZV1315

Triazolooxadiazole 2-oxides **150** have been formed by cyclization between the *N*-nitroso groups and the azido groups of **149** <1996TL8577>. The synthetic sequence began with azidoaminofurazan **148**. Following oxidation and replacement of the nitro group with the desired amine nitrosation afforded **149** which cyclized to **150** in a reaction not previously described (**Scheme 22**). In the same paper, cyclization of the reactive intermediate produced on treatment of aminomethylaminooxadiazole **151**, with excess nitronium tetrafluoroborate, was reported to be a much less efficient route to **67**. The starting compound **151** was obtained by replacing the nitro group of aminonitrofurazan with methylamine (**Scheme 23**) <1996TL8577>.



148 **149** **150**

a: R = Me; **b**: R = CH_2CH_2CN

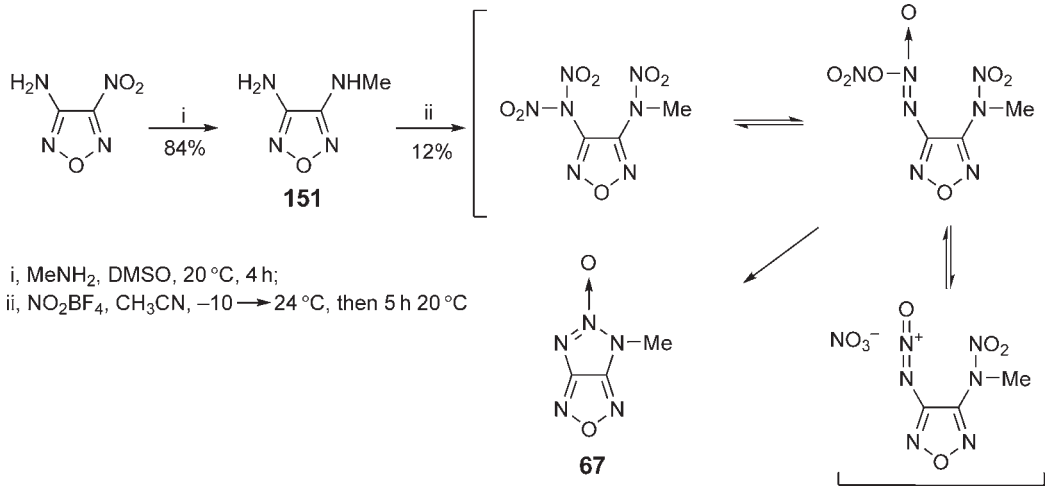
i, N_2O_5 (6 equiv), MeCN, –25 → 0 °C, then 16 h at 0 °C; ii, (a) $MeNH_2$ (aq.), MeCN, 0.5 h, 20 °C, 89% (b) $NCCH_2CH_2NH_2$ (xs), MeCN, reflux, 1 h, 70%; iii, **149a**, $NaNO_2$, HCl, H_2O/dioxane, 0 °C, 0.5 h 90% **149b**, $NaNO_2$, AcOH/H_2O, 5 °C, 1 h, 91%; iv, toluene, reflux, **150a**, 2 h, 92%; **150b**, 3 h, 70%

Scheme 22

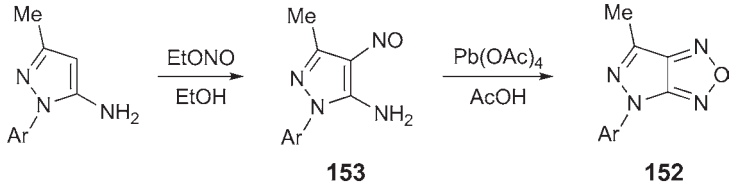
10.05.9.1.1(ii) Pyrazolo[3,4-*c*][1,2,5]oxadiazoles

A general, simple and efficient, one-pot, high-yielding synthesis of pyrazolo[3,4-*c*][1,2,5]oxadiazoles **152** involving lead tetraacetate trihydrate oxidation of 3-amino-4-nitrosopyrazolines **153** has been reported. The starting pyrazolines were available in large quantities through nitrosation of the corresponding 2*H*-pyrazol-3-ylamines with ethyl nitrite (**Scheme 24**). Reaction progress was easily monitored; the red-colored solution of the nitroso amines in glacial acetic acid solution turned deep green upon addition of lead(IV) acetate trihydrate (LTA). Other attractive features of the

reaction include the minimal workup requirement; simple dilution of the reaction mixture with water was sufficient to cause precipitation of the bicyclic products **152**, which could be obtained analytically pure from a simple recrystallization (**Scheme 24**). The mechanism advanced for the reaction, summarized in **Scheme 25**, hypothesized that LTA reacted with the oxygen atom of the nitroso group and that the adduct so furnished underwent concomitant release of lead(II) acetate in forming the observed products <2000S72>.

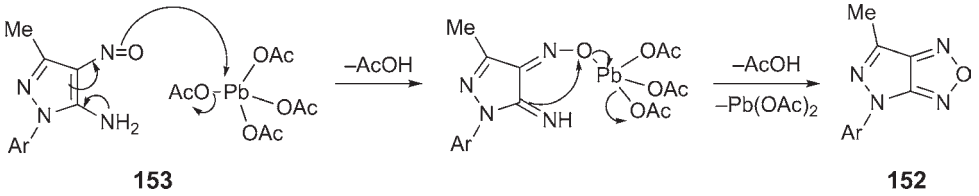


Scheme 23



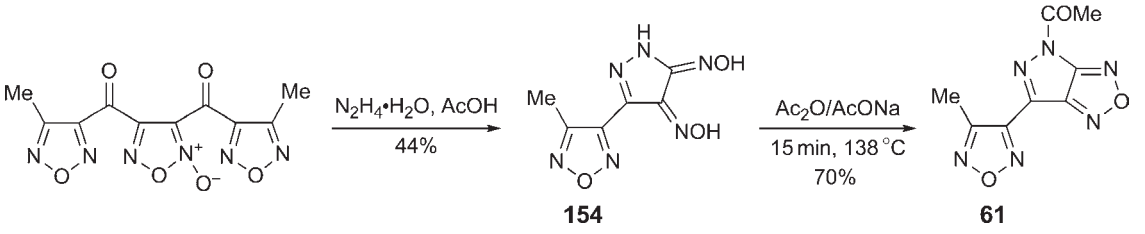
	Ar	*Yield (%)*		*Ar*	*Yield (%)*	*Reference*
152a	Ph	78	**152e**	*o*-$O_2NC_6H_4$	83	2000S72
152b	*m*-$O_2NC_6H_4$	80	**152f**	*p*-$O_2NC_6H_4$	85	
152c	*m*-ClC_6H_4	75	**152g**	3,4-$Cl_2C_6H_3$	90	
152d	2,5-$Cl_2C_6H_3$	82				

Scheme 24



Scheme 25

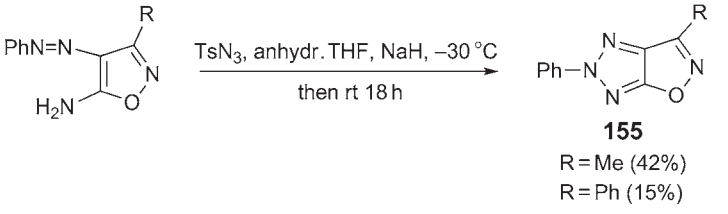
That dehydration of 4,5-bis(hydroxyimino)pyrazoles might represent a viable synthetic route to pyrazolooxadiazoles was initially alluded to when the mass spectral data of the pyrazole **154** showed an intense peak with *m*/*z* 192 corresponding to [*M*–H_2O]. It has been demonstrated that the cyclization of **154**, itself obtained from treatment of 1,2,5-oxadiazole-3,4-diylbis[(4-methyl)-1,2,5-oxadiazol-3-yl)] *N*-oxide with hydrazine, is facile upon heating with acetic anhydride in the presence of sodium acetate. Under the experimental conditions, cyclization was accompanied by N-acylation and the *N*-acyl derivative **61** resulted (**Scheme 26**) <2000RJO758, 2003T1059>. The cyclization is significant in the light of the ambiguous results following efforts to effect cyclization of similarly substituted isoxazole derivatives <2003T1059>.



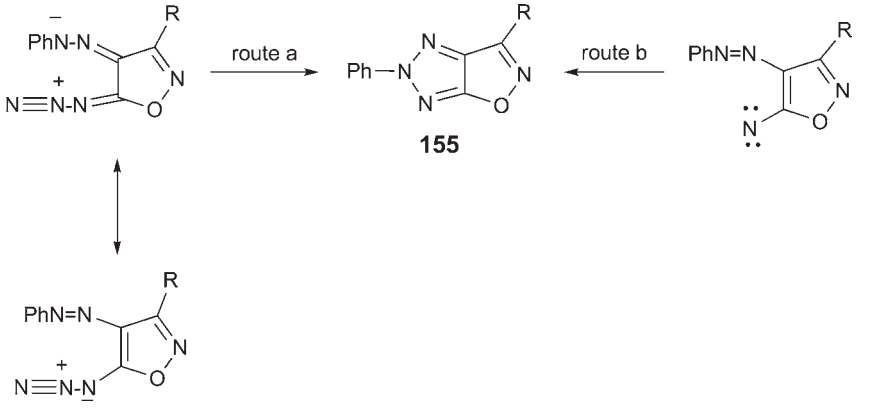
Scheme 26

10.05.9.1.1(iii) Isoxazolo[4,5-*d*][1,2,3]triazoles

The isoxazolotriazoles **155** have been synthesized starting from 3-substituted-5-amino-4-phenylazoisoxazoles by reaction with tosyl azide. The anticipated products, the 5-azido-4-phenylazo-substituted isoxazoles, were presumably too unstable to be isolated preferring to undergo immediate cyclization (Equation 12). The pathway to the cyclized products was formulated as either a π-electron reorganization with the involvement of neighboring group participation (route a) or as an internal capture of a nitrene (route b) (**Scheme 27**). Following from reaction rate and theoretical studies (see Section 10.05.2.5), the nitrene-like transition state was preferred <1996J(P2)2111>.



(12)

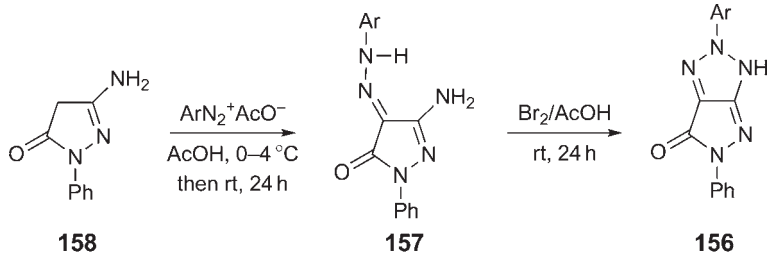


Scheme 27

10.05.9.1.1(iv) Pyrazolo[3,4-*d*][1,2,3]triazoles

Oxidation of 3-amino-4-azopyrazoles has continued to be a successful route to pyrazolo[3,4-*d*][1,2,3]triazoles. New syntheses of this bicyclic skeleton have been achieved by chemical or electrochemical oxidation <1992MI95, 2003HAC211, 2001MI1022>.

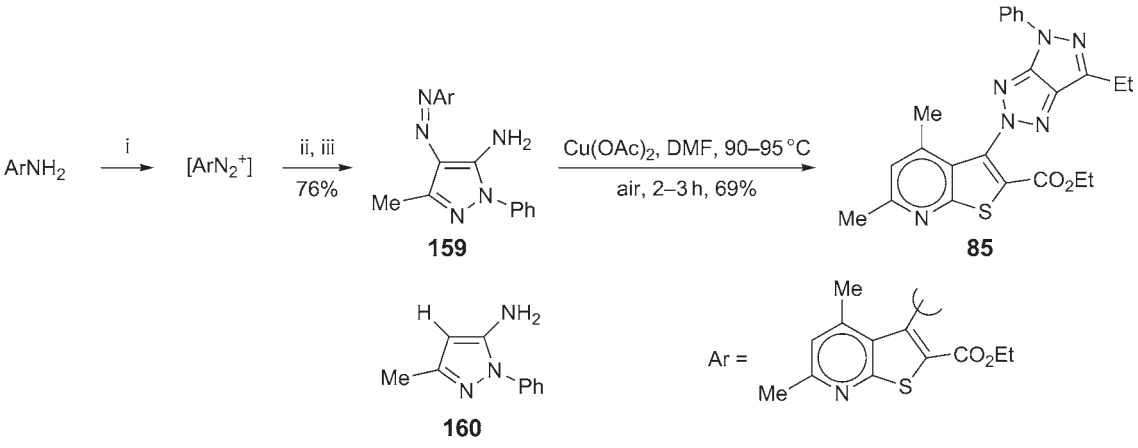
The triazolopyrazoles **156** have been synthesized in modest yield by oxidation of 3-amino-4-arylhydrazono-1-phenylpyrazol-5-ones **157**, with Br_2 in AcOH. The substrate aminohydrazones **157** were themselves obtained by coupling of the 3-aminopyrazoline-5-one **158** with diazonium acetates (**Scheme 28**) <2003HAC211>. A similar approach led to the formation of **85** following oxidative cyclization of **159** in a continuous current of air in the presence of cupric acetate (**Scheme 29**) <1992MI95>.



158 **157** **156**

a: Ar = *p*-ClC_6H_4 (65%) 68%
b: Ar = *p*-MeC_6H_4 (76%) 65%

Scheme 28



159 **85**

160

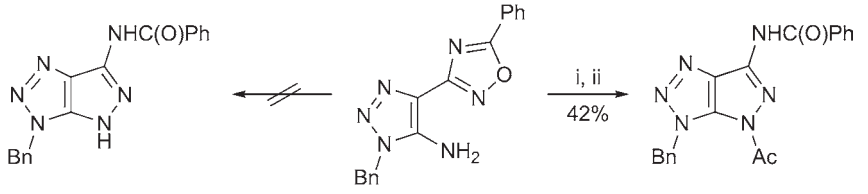
i, add $ArNH_2$ to H_3OSONO (generated from anhydr. $NaNO_2$ and CH_2SO_4) over 30 min at 10 °C, then 2 h 10 °C;
ii, add ArN_2^+ to **160** in AcOH at 10–15 °C over 30 min, then 2 h 10–15 °C;
iii, ice, NaOH (8%) to adjust pH to 5–6, then 2 h at pH 5–6, 10–15 °C

Scheme 29

The electrochemistry of pyrazole derivatives remains scarcely investigated and the formation of pyrazolotriazoles from 3-amino-4-azopyrazoles by electrochemical methods represents a novel approach to this bicycle. Electrochemical oxidation of [4-(phenylhydrazono)-4*H*-pyrazolo-3-yl]amines was conducted in air-free, anhydrous MeCN with Bu^n_4N–ClO_4 as supporting electrolyte; the working electrode was Pt and the auxiliary electrode was Pt-wire immersed in the corresponding electrolyte. The reference electrode was Ag/AgCl/Cl^-. Voltammetric data indicated that the oxidation occurred in three successive irreversible one-electron peaks. In the first peak, the loss of one electron gave the corresponding radical cation which subsequently reacted in one of two possible ways to furnish the triazole nucleus, viz., deprotonation to the radical, followed by further oxidation through the loss of the second electron and at the same time another proton, or, by loss of another electron to give the dication prior to deprotonation. Under the conditions of

the experiment, the N-1-unsubstituted triazole ring of **117** was further oxidized to the bis-(1,1′)-2-phenylpyrazolo[3,4-*d*][1,2,3]triazoles **118** (**Scheme 13**, Section 10.05.6.4.1) <2001MI1022>.

A mononuclear heterocyclic rearrangement (MHR, or Boulton–Katritzky rearrangement) has led to the pyrazolo[3,4-*d*][1,2,3]triazole **161** <2004H(63)2475>. The reaction prototype was initially demonstrated in the formation of *c*-fused 3-aminopyrazoles from ring transformation of aromatic rings bearing adjacent 5-substituted 1,2,4-oxadiazol-3-yl and amino groups. The 5-amino-4-(1,2,4-oxadiazol-3-yl)-1,2,3-triazole **162**, itself prepared in two steps from 5-amino-1,2,3-triazole-4-carbonitrile, failed to form the desired rearrangement product **162-R** upon reaction with a variety of bases, reaction solvents, and reaction temperatures. However, prior acylation of the 5-amino group facilitated the MHR and **161** resulted from **162** following treatment with NaH in DMF (**Scheme 30**). Efforts thus far to remove the acyl groups at the 3-position on the pyrazole moiety have been unsuccessful; a likely explanation lies in the relative instability of the 3-amino derivatives of the π-electron-rich bicyclic nucleus <2004H(63)2475>.



162-R **162** **161**

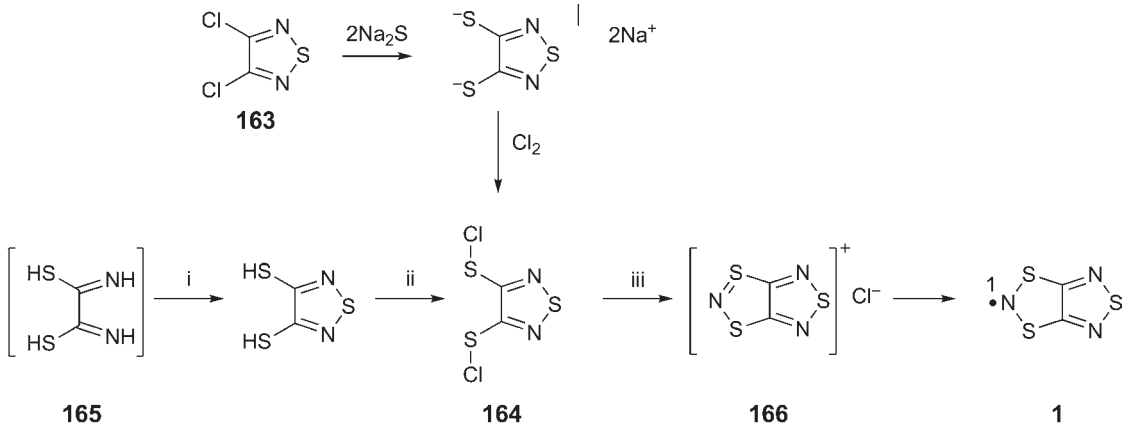
i, Ac_2O, cat. DMAP, C_5H_5N, 100 °C, 7 h; ii, NaH, DMF, 100 °C, 35 min

Scheme 30

10.05.9.1.2 Synthesis from [4+1] atom fragments

10.05.9.1.2(i) [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazole – TTTA

A number of contributions aiming to improve on the original synthesis of the thiadiazolodithiazole radical **1** have appeared. An early step in the original synthesis <1989AG952> involving the reaction of dichlorothiadiazole **163** with Na_2S to yield the disulfenyl chloride **164** as the key intermediate (**Scheme 31**) presented difficulties for some experimentalists. Accordingly, a novel synthesis of **1** starting from dithioxamide **165** has been described by Rawson and co-workers <2001JMC1992>. Condensation of **165** with SCl_2 furnished the 4,5-dithiol, subsequent chlorination ($SOCl_2$) yielded the bis(sulfenyl chloride), and finally reaction with Me_3SiN_3 provided reliable access to the disulfenyl chloride **166**. TTTA was prepared from **166** in reaction with $Na_2S_2O_4$ in MeCN followed by workup involving extraction with petroleum ether (b.p. 40–60 °C) and purification by sublimation *in vacuo* in a sealed tube (**Scheme 31**). The bicyclic radical, TTTA **1**, was prepared analytically pure and in moderate yield



163 **165** **164** **166** **1**

i, SCl_2,THF; ii, $SOCl_2$, CH_2Cl_2, 40 °C, 2 h; iii, Me_3SiN_3, CH_2Cl_2, 0 °C then 18 h, rt, 39% over 3 steps;
iv, $Na_2S_2O_4$, MeCN, 40–60 petroleum ether, 30%

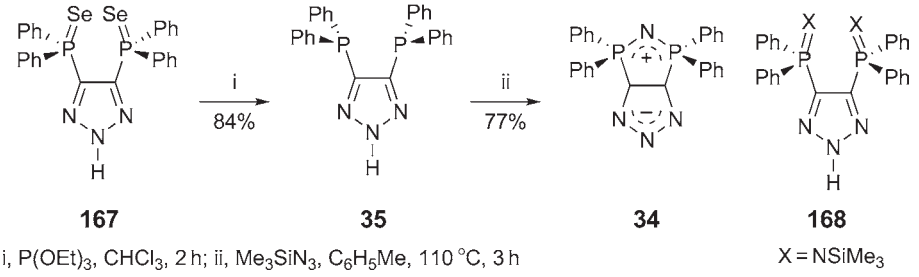
Scheme 31

<2001JMC1992>. While the conditions of this final step are identical with those reported in the original communication, Rawson reported a lower isolated yield (30% vs. 68%). The robustness of Rawson's route was further called into question in a subsequent communication which reported a failure of the salt **166** prepared according to his method to undergo reduction with $Na_2S_2O_4$. This most recent communication identified silver powder as a successful reducing agent, to be used in dry MeCN at −5 to −10 °C. Under these conditions, TTTA **1** was isolated in 15% yield. The authors believed, however, that optimization of the yield will follow from improved extraction and sublimation procedures <2002MI432>.

A 1:1 complex of TTTA·Cu(hfac)$_2$ was obtained by reaction of stoichiometric amounts of the components in hot heptane solution under a nitrogen atmosphere; the complex presents as deep blue plate-like crystals at −30 °C <2001JA3601>.

10.05.9.1.2(ii) [1,2,3]Triazolo[4,5-*c*][1,2,5]azadiphospholes

An unprecedented 'pseudo-Staudinger' reaction of 4,5-bis-(diphenylphosphino)-2*H*-1,2,3-triazole **35** with trimethylsilyl azide has led to the preparation of the novel heterocycle [1,2,3]triazolo[4,5-*c*][1,2,5]azadiphosphole **34**. Synthesis of the diphenylphosphino substrate **35**, by double deselenylation of **167**, was reported in the same paper. The expected product of reaction, the 4,5-bis[diphenyl(trimethylsilyl)phosphorimidoyl]-2*H*-1,2,3-triazole **168**, was not observed (**Scheme 32**). While the mechanism for formation of the new bicycle is not known, the authors believed that the oxidation of both the P-atoms to the pentavalent state and the resonance stabilization of the heterocycle provided the driving force for the observed selectivity; resonance forms and charge-separated structures for **34** are shown in **Figure 2**. This reaction is significant since oxidative bridging of chelating diphosphanes in reaction with Me_3SiN_3 had not previously been observed, and the net transfer of a single bridging nitrogen atom by Me_3SiN_3 appears to be truly unprecedented <2003AGE3506>.



Scheme 32

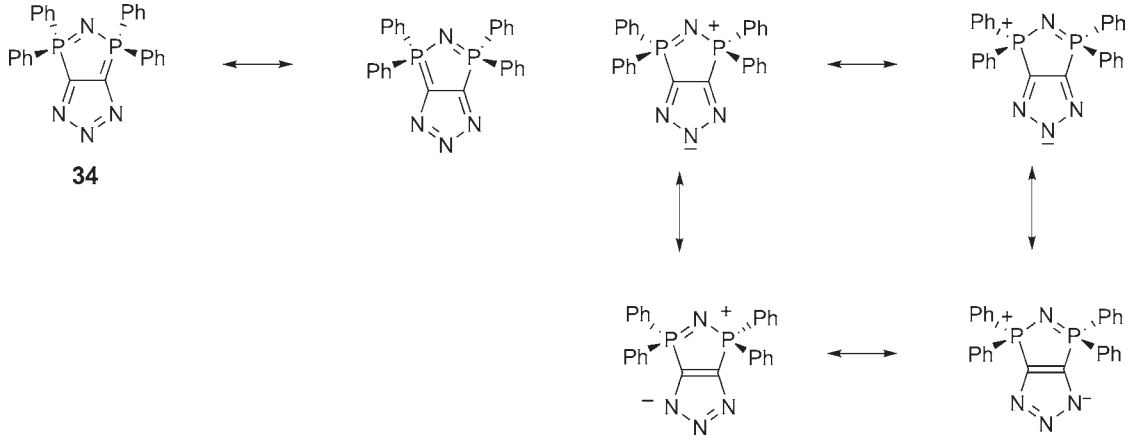
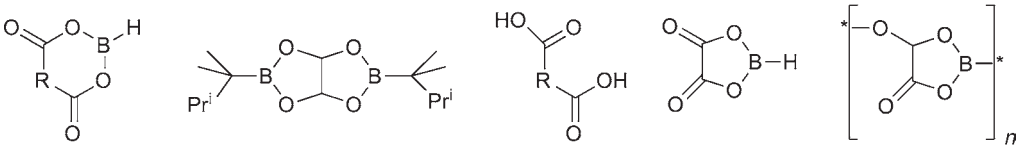


Figure 2

10.05.9.1.2(iii) [1,3,2]Dioxaborolo[4,5-*d*][1,3,2]dioxaboroles

On the basis of the observation that the acyloxy function of carboxylic acids is not readily reduced by 9-BBNH (9-borabicyclo[3.3.1]nonane), hydrogen evolution and formation of heterocycles like **169** was the expected outcome

from reaction of sterically demanding monoorganoboranes with dicarboxylic acids **170**. However, reaction between a 1:1 molar ratio of thexylborane and oxalic acid in 1,2-dimethoxyethane (DME) solution afforded an insoluble, uncharacterized product. Combining the reactants in a 2:1 ratio in THF/DME yielded, after thermally induced reduction of an intermediate THF or DME adduct, the [1,3,2]dioxaborolo[4,5-*d*][1,3,2]dioxaborole **72** in 92% yield. The heterocycle **169** was considered a likely intermediate *en route* to **72** (**Scheme 2**) <1995CB751>.



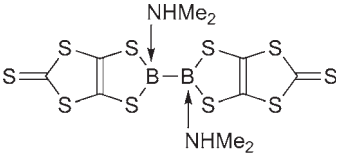
169 **72** **170** **74** **75**

a: R = CH_2
b: R = CH_2CH_2
c: R = $C(Me)_2$

The product of reaction between oxalic acid and borane–dimethyl sulfide in DME was observed to be sensitive to the experimental conditions. At −10 °C an Me_2S adduct of **74** is believed to be present, while at >10 °C the product was assigned as the bicyclic dioxaborolane **72**; finally, as the reaction progressed, oligomeric products of the type **75** were thought to be present. Support for these suggestions was drawn from ^{11}B NMR spectral analysis of the reaction progress <1995CB751>.

10.05.9.1.2(iv) [1,3]Dithiolo[4,5-*d*][1,3,2]dithiaboroles

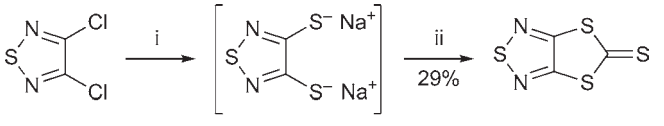
The 2,2′-bis(dimethylamino)diborane compounds **39·2NHMe$_2$** were formed from reaction between a THF solution of $[B_2Cl_4(NHMe_2)]$ and a suspension of $[NEt_4]_2[Zn(C_3S_5)_2]$ in THF. Reaction progress was followed by a color change from dark red to light yellow. Crystals of the complex were isolated following layering the reaction solution with toluene, CH_2Cl_2, and hexane <2000AXC440>.



39·2NHMe$_2$

10.05.9.1.2(v) [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

The 2-thione derivative of [1,3]dithiolo[4,5-*c*][1,2,5]thiadiazole **41** was prepared from the parent dichloride **163** following treatment of the intermediate disodium salt **171** with thiophosgene (**Scheme 33**) <1993SM(68)1914, 1997USP5703102>, while the bisthioester **103** was the precursor to the 2-one derivative **43** (**Schemes 7** and **33**) <1997SM(86)1871>.



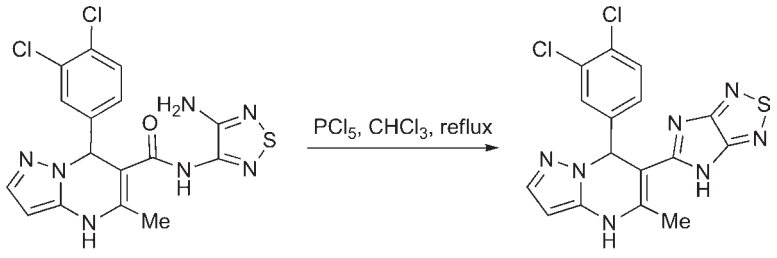
163 **171** **41**

i, $Na_2S{\cdot}9H_2O$, 70% EtOH; ii, $Cl_2C(S)$, N_2, 20 °C, 20 min

Scheme 33

10.05.9.1.2(vi) Imidazo[4,5-*c*][1,2,5]thiadiazoles

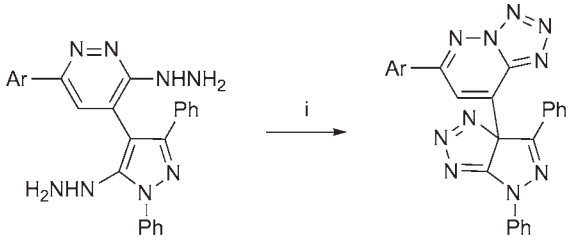
PCl_5-induced dehydrative cyclization of the amino and amide functionalities of the thiadiazole moiety of the pyrazolopyrimidine **172** led to the formation of the imidazo[4,5-*c*][1,2,5]thiadiazole substructure (Equation 13) <2001WO040231>.



172 (13)

10.05.9.1.2(vii) Pyrazolo[3,4-*d*][1,2,3]triazoles

The pyrazolo[3,4-*d*][1,2,3]triazole skeleton formed from 3-hydrazinopyrazoles **173** upon reaction with nitrous acid, and the reaction was thought to proceed by way of an intermediate azide, electrocyclization of which furnished the 5,5-bicyclic skeletal framework **174** (Equation 14) <1995M1265, 1993BCJ477>.



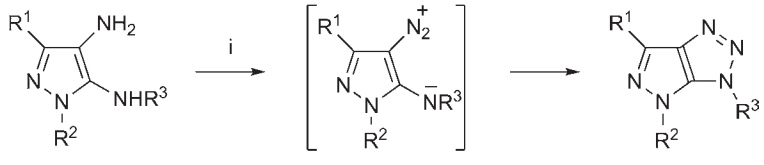
173 174

i, aq. NaN_3, DMF, 160 °C, 2 h

Ar	*Yield*(%)	*Reference*
p-$EtOC_6H_4$	45	1995M1265
p-ClC_6H_4	43	1993BCJ477
p-MeC_6H_4	45	1993BCJ477

(14)

3,4-Diaminopyrazoles **175** were also found to be suitable substrates for formation of pyrazolo[3,4-*d*][1,2,3]triazoles <1998AP269, 1993JHC129, 1996USP5508154>. In one report, due to problems with diamine stability during workup, direct reaction of diamines formed on reduction of nitroso precursors was conducted (**Scheme 35**) <1998AP269>. In other reports, isolated diamine starting materials were used <1993JHC129, 1996USP5508154>. In each case, reaction of the starting diamine with 1 equiv of sodium nitrite in either acetic acid <1998AP269, 1993JHC129> or HCl <1996USP5508154> afforded the diazo species **176**, which spontaneously cyclized to the bicycles **177** in reasonable yield (**Scheme 34**). In a variation of the same reaction, the zwitterionic



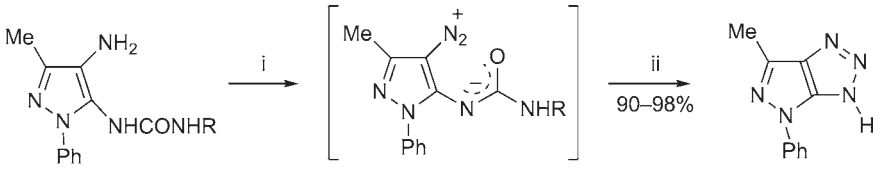
175 176 177

i, $NaNO_2$, AcOH/MeOH, rt, 1–3 h

R^1	R^2	R^3	*Yield*(%)	*Reference*
Me	Me	Et	51	1998AP69
Me	Me	Bn	62	
Me	Ph	Et	64	
Me	Ph	Bn	69	
p-MeC_6H_4	H	Et	63	1993JHC129
Ph	H	Bn	80	
p-$MeOC_6H_4$	H	Ph	72	

Scheme 34

N-alkyl-*N*′-(4-diaza-5-pyrazolo)ureas **178** upon alkaline hydrolysis formed the pyrazolo[3,4-*d*][1,2,3]triazoles **110** in essentially quantatitive yield (**Scheme 35**) <1992FA1021>. Formation of **144** by cyclization of the 3-amino-4-carboxyaminopyrazole **179** represents another variant of the same reaction (Equation 15) <1996USP5508154>.

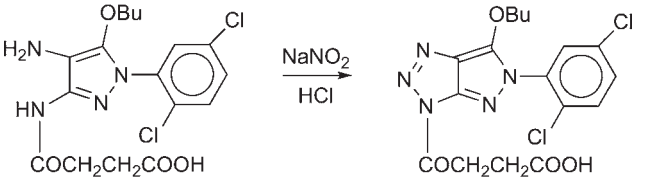


178 **110**

R = Et, Pr, Bu, Bu^t, CH_2CO_2Et

i, $NaNO_2$, HCl/MeOH, 0 °C, 2 h; ii, 1 M KOH, 100 °C, 15 min

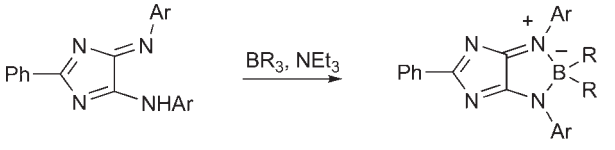
Scheme 35



179 **144** (15)

10.05.9.1.2(viii) Imidazo[4,5-*d*][1,3,2]diazaborolidines

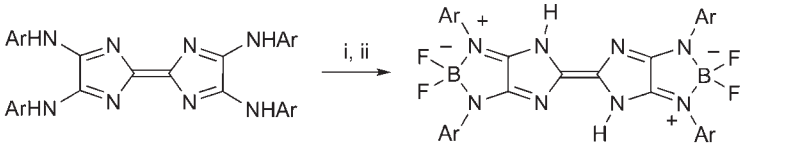
The imidazo[4,5-*d*][1,3,2]diazaborolidines **56** were formed from 4*H*-imidazoles **90** on reaction with boranes in the presence of NEt_3 (Equation 16) <2004CC1860>.



90 **56** (16)

a: Ar = *p*-MeC_6H_4; R = F (32%)
b: Ar = *p*-MeC_6H_4; R = Ph (79%)
c: Ar = *p*-MeC_6H_4; R = Et (48%)
d: Ar = 3,5-$CF_3C_6H_3$; R = F (61%)

The tetraazafulvalenes **180** reacted with $BF_3{\cdot}Et_2O$ to bridge the exocyclic nitrogen atoms, yielding, following a short reaction time, the novel bis-imidazo[4,5-*d*][1,3,2]diazaborolidines **71** as dark red crystals in good yield (**Scheme 36**) <2004T3847>.



180

71a: Ar = *m*-$CF_3C_6H_4$ (81%)
71b: Ar = *p*-Bu^tC_6H_4 (78%)

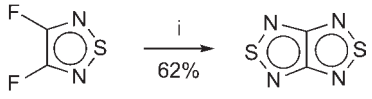
i, $BF_3{\cdot}OEt_2$, NEt_3, C_6H_5Me, 10 min, rt; ii, 90 °C, 30 min

Scheme 36

10.05.9.1.3 Synthesis from [3+2] atom fragments

10.05.9.1.3(i) [1,2,5]Thiazolo[3,4-*c*][1,2,5]thiadiazoles

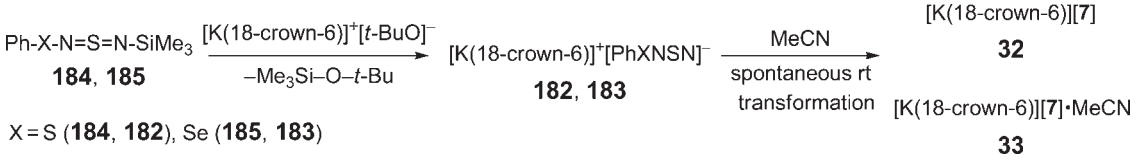
[1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** was synthesized as colorless needles by fluoride ion-induced condensation of 3,4-difluoro-1,2,5-thiadiazole **181** with $(Me_3SiN{=})_2S$ in an extension of the arylthiazylamide-based methodology to nonbenzoid systems (Equation 17) <2005IC7194>. The salts [K(18-crown-6)][**7**] and [K(18-crown-6][**7**]·MeCN, **32** and **33**, respectively, were obtained in low yield as products of a spontaneous room temperature transformation of [K(18-crown-6)][PhXNSN] salts (**182**, **183**: X = S, Se) in MeCN solution. While the mechanistic detail was not obvious, MeCN must participate in the reaction as the carbon source. Reaction with the selenium salt **183** was observed to be faster (a few tens of minutes) than that with **182** (a few days). Further, reaction with **183** was followed by ^{77}Se NMR spectroscopy, thus providing some insight into the course of the reaction which was proposed to proceed as outlined in **Scheme 38**, culminating in the formation of the diphenyl disulfide/diselenides **186**. The starting **182** and **183** were themselves obtained by desilylation of PhXN=S=NSiMe$_3$ (**184**, **185**: X = S, Se) with $[K(18\text{-crown-6})]^+[Bu^tO]^-$ (**Schemes 37** and **38**) <2005IC7194>.



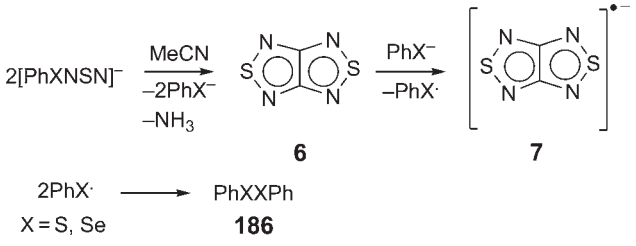
181 **6**

i, $(Me_3SiN{=})_2S$, MeCN, CsF, 2 h, 90 °C

(17)



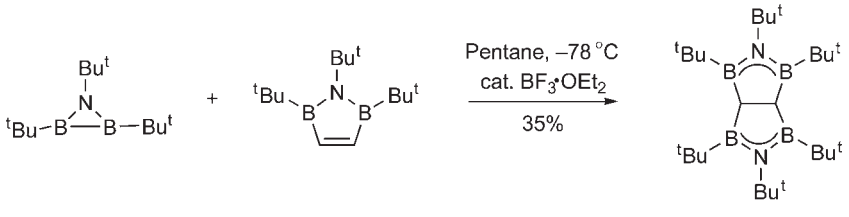
Scheme 37



Scheme 38

10.05.9.1.3(ii) [1,2,5]Azadiborolo[3,4-*c*][1,2,5]azadiboroles

Tri-*tert*-butylazadiboriridine, **187**, was observed to react with ethyne in a manner sensitive to the ratio of the reactants. When the reactants were combined in a 1:1 ratio, the heterocyclopentene, **188**, resulted. Under normal conditions, **188** did not react further with excess **187** at the C=C bond. On the other hand, [1,2,5]azabiborolo[3,4-*c*][1,2,5]azadiborole **76**, the product of a double diborylation of ethyne, was prepared by reaction of **187** and ethyne in a 2:1 ratio in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ (Equation 18) <2001ZFA1815>.



187 **188** **76**

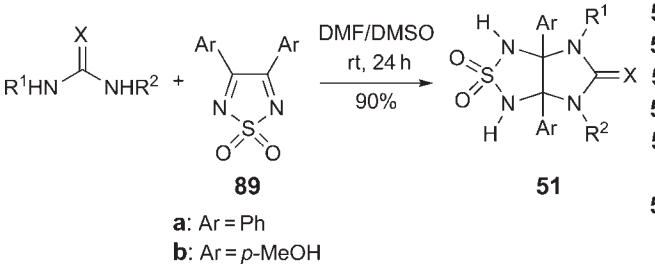
(18)

10.05.9.1.3(iii) Isothiazolo[4,5-*d*][1,2,3]triazoles

Isothiazolo[4,5-*d*][1,2,3]triazoles **119a** and **119b** have been prepared by 1,3-dipolar cycloaddition between 3-diethylamino-4-(4-methoxyphenyl)-isothiazole 1,1-dioxide **121** and benzyl azide **122a** and 2-phenylethyl azide **122b**, respectively. ^{1}H NMR spectral data of the crude reaction mixtures suggested the reactions were diastereospecific. The same substrate was trapped with aryl azides **122c–e**; however, under the reaction conditions (benzene, 80 °C), the primary cycloadducts eliminated N_2 and the aziridine-fused bicycles **120c–e** presented as the main reaction products (**Scheme 15**). In the case of **122c**, N_2 elimination was prevented by performing the reaction at room temperature, and a satisfactory yield of **119c** could be isolated after a 75 day reaction (**Schemes 14** and **15**) <1996T7183>. The relative stability of the triazolines **119a** and **119b** was as expected since it is well recognized that *N*-aryl triazolines bearing electron-withdrawing substituents on the aryl group are more susceptible to ring cleavage than their alkyl counterparts <1984AHC330>.

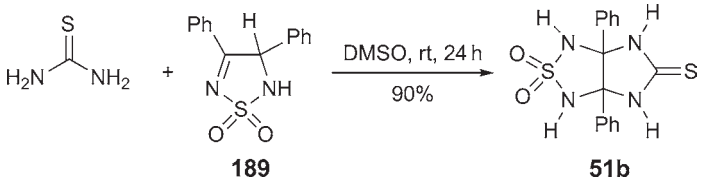
10.05.9.1.3(iv) Imidazo[4,5-*c*][1,2,5]thiadiazoles

Imidazo[4,5-*c*][1,2,5]thiadiazoles have been synthesized by annulation of the imidazole ring onto a thiadiazole core and vice versa <2003JPO220, 2004JPO1091, 2000MC28, 2001MC107, 2001PCJ72>. In spite of the observation that monofunctional nucleophiles add reversibly to only one of the two C=N bonds of 1,2,5-thiadiazole 1,2-dioxide derivatives, addition of urea to both C=N bonds of **89a** proceeded almost quantitatively and furnished the imidazo[4,5-*c*][1,2,5]thiadiazol-5-one 2,2-dioxide, **51a** (Equation 19) <2003JPO220>. Parallel reactions between thioureas and the 1,2,5-thiadiazole 1,1-dioxides **89a** and **89b** yielded the bicycles **51b–h** (**Scheme 4**) <2004JPO1091>. Significantly, the derivative **51b** was also obtained by the reaction of thiourea with 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide, **189** (Equation 20) <2004JPO1091>.



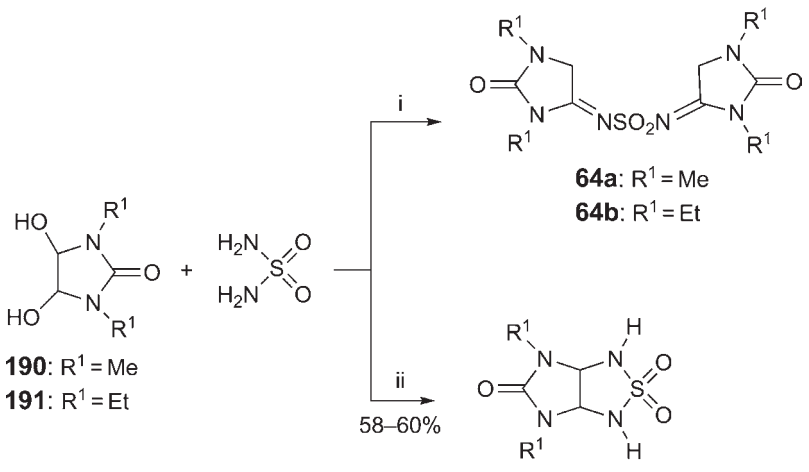
51a: X = O; R^1 = R^2 = H; Ar = Ph (93%)
51b: X = S; R^1 = R^2 = H; Ar = Ph (93%)
51c: X = S; R^1 = R^2 = H; Ar = *p*-MeOPh (93%)
51d: X = S; R^1 = Me; R^2 = H; Ar = Ph (93%)
51e: X = S; R^1 = Et; R^2 = H; Ar = Ph (94%)
51f: X = S; R^1 = R^2 = Et; Ar = Ph (95%)
51g: X = S; R^1 = Allyl; R^2 = H; Ar = Ph (81%)

(19)



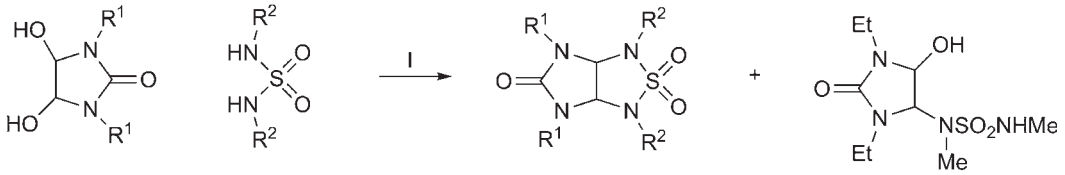
(20)

High-pressure condensation of 1,3-dialkyl-4,5-dihydroxyimidazolidin-2-ones **190** and **191**, with sulfamide and its *N*,*N*′-disubstituted derivatives, has been used as a preparative route to imidazo[4,5-*c*][1,2,5]thiadiazoles **93**. With careful control of experimental conditions, especially pH and reaction pressure, yields have been optimized <2000MC28, 2001MC107, 2001JPC72>. Thus, sulfamide reacted with **190** and **191** in conc. HCl and yielded the bis-adducts **64a** and **64b** whilst at pH 5 the products of reaction were **93a** and **93b**. *N*,*N*′-Dialkylsulfamides combined with **190** and **191** and yielded, respectively, **93c** and **93d** (7–9%, pH 2–3) together with **192** which was deemed a probable intermediate *en route* to the bicycles (**Schemes 39** and **40**) <2000MC28, 2001JPC72>. The yield of **93d** was subsequently maximized at 12% by conducting the reaction in acetone and acetic acid at 1000 mPa, reaction conditions which correspond to the liquid–solid phase transition of the solvent <2001MC107>.



i, H_2O, conc. HCl, 80 °C, 0.5 –1.5 h; ii, H_2O, pH 5, 60 °C, 0.5 h

Scheme 39



i, H_2O, pH 1 (HCl), 80–90 °C, 1–2 h

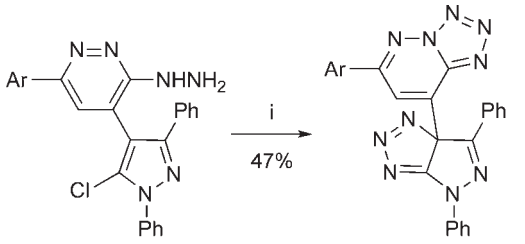
Entry	*t(h)*	*pH or acid added*	*T(°C)*	*p(MPa)*	*Solvent*	*Yield(%)* **93c**	*Yield(%)* **192**	*Reference*
1	16	1–2	12	1000	H_2O	2		2000MC28
2	16		12	1000	AcOH	5	Traces	
3	5		80	1000	AcOH	8*	Traces*	
4	16	1 drops of conc. HCl	12	1000	Me_2CO	12*	2*	
5	4.5	2 drops of AcOH	80	1000	Me_2CO	*	4*	
6	4.5	2 drops of AcOH	19	1000	Me_2CO	Traces	33.5	
7	5	2 drops of AcOH	80	1000	Dioxane	Traces	11	
8	4.5	2 drops of AcOH	100	1000	Dioxane	*	Traces*	
9	4.5	2 drops of AcOH	40	700	Dioxane	*	7.5*	

*Traces of 1,3-diethyl-2,4-dioxoimidazolidine.

Scheme 40

10.05.9.1.3(v) Pyrazolo[3,4-*d*][1,2,3]triazoles

Pyrazole **174** has been formed by electrocyclization of transient azido-substituted pyrazole **193** generated from chloropyrazoles upon treatment with sodium azide in refluxing aqueous DMF, but yields of isolated bicycles are moderate (Equation 21) <1995M1265>.



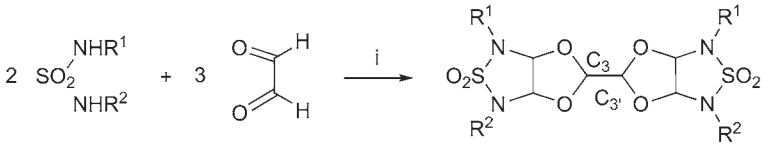
193 **174**

i, aq. NaN_3, DMF, 160 °C, 2 h **a**: Ar = *p*-$EtOC_6H_4$ (21)

10.05.9.2 Syntheses from Acyclic Precursors

10.05.9.2.1 [1,3]Dioxolo[4,5-*c*][1,2,5]thiadiazoles

The [1,3]dioxolo[4,5-*c*][1,2,5]thiadiazole heterocyclic system has been synthesized for the first time by a condensation reaction between glyoxal and *N*,*N*′-dialkylsulfamides. The use of a trimeric dihydrate of glyoxal **194** in place of aqueous glyoxal solution increased the yield of the products **49** from 5–11% to 54–85% (Equation 22). With identical substituents at the nitrogen atoms the molecule has a plane of symmetry and *meso*-forms resulted for **49a**, **49b**, and **49d–f**. In the case of structurally or configurationally different substituents, **49c** and **49g**, respectively, mixtures of diastereomeric *meso*-forms and racemates were theoretically possible. The C[3(3′)] atoms of **49g** were pseudoasymmetric, while the C-3 and C-3′ atoms of **49c** were asymmetric. While up to four racemates and two *meso*-forms are possible, **49c** gave only two peaks by HPLC, and the different forms were not resolved by ^{1}H NMR spectroscopy. Theoretically, **49g** could present as 24 stereoisomers, 12 racemates, and 12 *meso*-forms, and a number of isomers were isolated in six fractions following HPLC separation, but in this case the different forms were resolved by ^{1}H NMR spectroscopy (see Section 10.05.3.2.1) <2001MC138>.



194 **49**

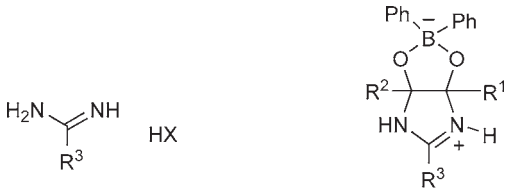
i, conc. HCl, 35–40 °C, 1–1.5 h (22)

	R^1	R^2	*Yield* (%)		R^1	R^2	*Yield* (%)	*Reference*
49a	Me	Me	81–85	**49e**	Pr^i	Pr^i	54–57	2001MC138
49b	Et	Et	54–56	**49f**	Bu^n	Bu^n	71–72	
49c	Me	Et	65–67	**49g**	CH(Me)Et	CH(Me)Et	69–71	
49d	Pr^n	Pr^n	72–74					

10.05.9.2.2 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles

The diazaboroloimidazoles **195** have been formed in modest yields by reaction between 1,2-dicarbonyl compounds, amidine salts **196** and guanidine carbonate salt, and diphenylboronic anhydride <1988CB1865>. A parallel reaction

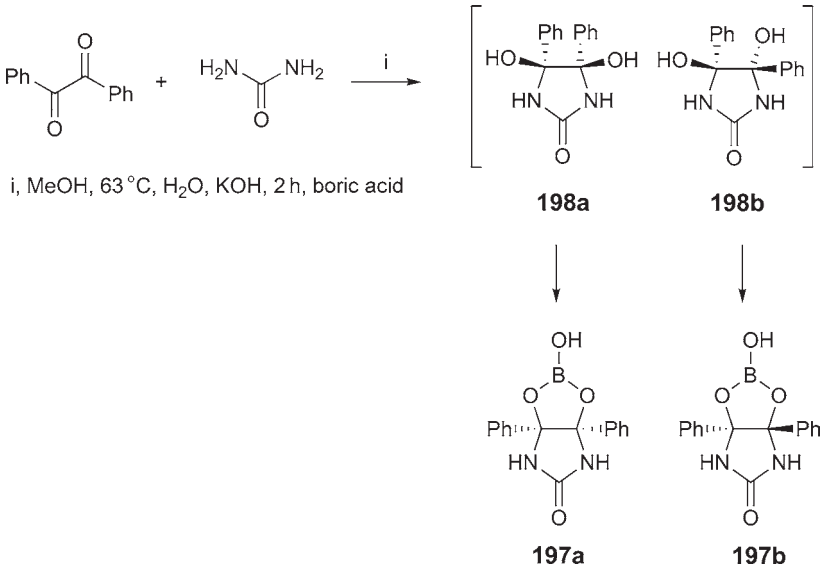
between benzil, urea, and boric acid furnished the stereoisomeric [1,3,2]dioxaborolo[4,5-*d*]imidazoles **197**. The reaction proceeded in MeOH under the influence of KOH and water; yields of the bicyclic products, which formed in a 65:35 ratio, were not recorded. The reaction was believed to proceed by way of the 4,5-dihydroxyimidazol-2-ones **198** (**Scheme 41**) <1989PHA110>.



196 **195**

X = Cl, HSO_4

R^1, R^2 = H, Me, Ph; R^3 = NH_2, Me, OMe, Ph;



198a **198b**

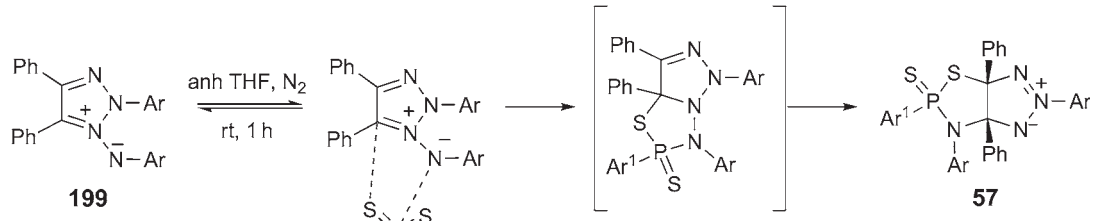
197a **197b**

Scheme 41

10.05.10 Ring Syntheses by Transformation of Another Ring

10.05.10.1 [1,2,3]Triazolo[4,5-*d*][1,3,2]thiazaphospholes

A new fused nitrogen–phosphorus–sulfur ring system has been obtained from a cycloaddition–1,4-sigmatropic rearrangement reaction sequence between triazolium imide 1,3-dipoles **199** and Lawesson's reagent, **200** (**Scheme 42**). Significantly, as a dipolarophile, Lawesson's reagent was found to be 2000 times more reactive than acrylonitrile and twice as reactive as MeSC(S)CN. The [1,2,3]triazolo[4,5-*d*][1,3,2]thiazaphospholes **57** were found to be reasonably stable in the solid state but to break down in solution in NMR solvents (see Section 10.05.3.2.1) <1997CC2149>.

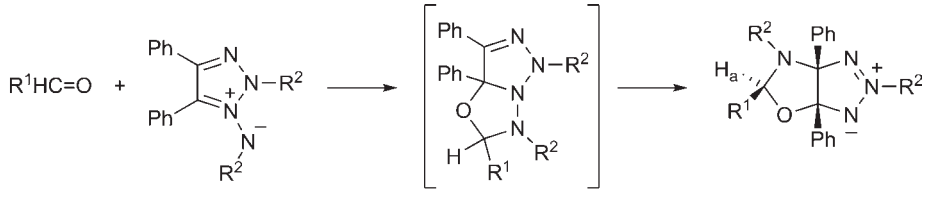


	Ar	Yield (%)
57a	Ph	83
57b	*p*-MeC_6H_4	65
57c	*p*-BrC_6H_4	84
57d	*p*-$NO_2C_6H_4$	71

Scheme 42

10.05.10.2 Oxazolo[4,5-*d*][1,2,3]triazoles

Oxazolo[4,5-*d*][1,2,3]triazoles **65** were found as rearrangement products of initially formed [3+2] adducts between 1,2,3-triazolium imides **201** and aryl aldehydes <1994J(P1)2797, 2003ARK110>. The generality of the original reaction which was initially reported with cinnamaldehyde <1996CHEC-II(7)141> has since been extended to include acetaldehyde and paraformaldehyde as well as a number of aryl aldehydes, and a range of cycloalka-1,2,3-triazoliumamidines. The products **65** which resulted from an *in situ* 1,4 N → C sigmatropic rearrangement of the primarily formed cycloadducts **202** were themselves unstable to acid (the ensuing reaction has been discussed in **Schemes 1** and **43**) (see Section 10.05.6.2.1)

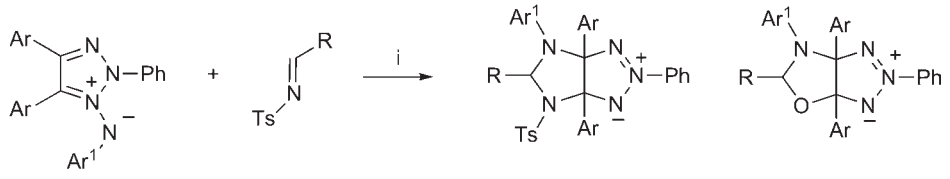


R^1	R^2	Yield (%)
Ph	Ph	80[a]
p-$MeOC_6H_4$	Ph	70[a]
p-MeC_6H_4	Ph	84[a]
p-ClC_6H_4	Ph	81[a]
p-$O_2NC_6H_4$	Ph	75[a]
H	Ph	83[b]
H	*p*-BrC_6H_4	68[b]
H	*p*-$O_2NC_6H_4$	94[b]
Me	Ph	80[c]
Me	*p*-BrC_6H_4	71[c]
Me	*p*-$O_2NC_6H_4$	80[c]

[a]anh. Me_2CO, reflux, 56 °C.
[b]CH_2O generated from paraformaldehyde upon heating in *p*-xylene 140 °C 30 min, solution cooled to 70 °C prior to dipole addition, 20 min.
[c]*p*-xylene, 70 °C, 2 h.

Scheme 43

<1994J(P1)2797>. A similar cycloaddition–rearrangement sequence accounted for the formation of oxazolo[4,5-*d*][1,2,3]triazoles **203** as side products from the reaction between triazolium imides **201** and N-substituted benzaldimines, leading to the imidazo[4,5-*d*][1,2,3]triazole **204** (Equation 23) (see Section 10.05.10.3). The oxazolotriazoles **203** were presumed to arise as a consequence of hydrolysis of the imine to the parent aldehydes under the reaction conditions <2003ARK110>.



201 **204** **203**

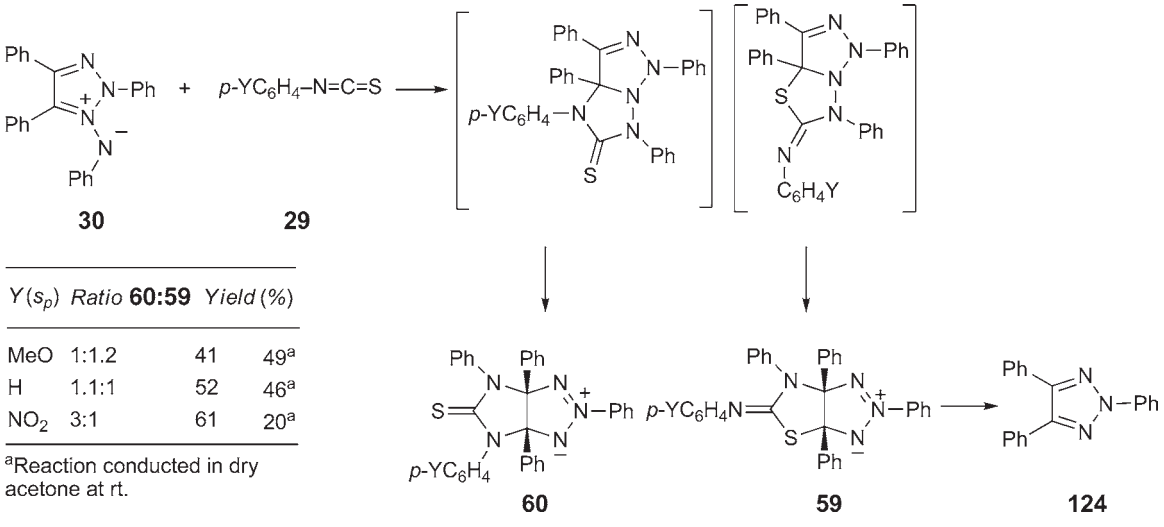
i, C_6H_6, 80 °C, 24 h

(23)

			Yield (%)	
Ar	*Ar*^{1}	*R*	**204**	**203**
Ph	Ph	CO_2Me	15	22
Ph	Ph	CO_2Et	26	25
Ph	*p*-$NO_2C_6H_4$	CO_2Et	18	30
p-ClC_6H_4	Ph	CO_2Et	10	21
p-$NO_2C_6H_4$	*p*-$NO_2C_6H_4$	CO_2Et	20	26
Ph	Ph	Ph		50
Ph	Ph	CCl_3		46

10.05.10.3 Imidazo[4,5-*d*][1,2,3]triazoles

Imidazo[4,5-*d*][1,2,3]triazoles were formed as the rearrangement products of primarily formed [3+2] adducts of triazolium 1-imides **30** with aryl isothiocyanates **29** <1997J(P1)3587> and *N*-sulfonylimines <2003ARK110>. Competitive reactivity of the aryl isothiocyanate dipolarophile **29** across the N=C or S=C bonds in cycloaddition to the triazolium 1-imide **30** has been shown to lead, by way of an immediate 1,4-sigmatropic rearrangement, to either imidazo- or thiazaolotriazoles **60** and **59**, respectively. The rearrangement was proposed to proceed via the intermediates shown in **Scheme 44** <1997J(P1)3587>. The reaction sequence yielding the



30 **29**

Y (s_p)	*Ratio* **60:59**	*Yield* (%)	
MeO	1:1.2	41	49[a]
H	1.1:1	52	46[a]
NO_2	3:1	61	20[a]

[a]Reaction conducted in dry acetone at rt.

60 **59** **124**

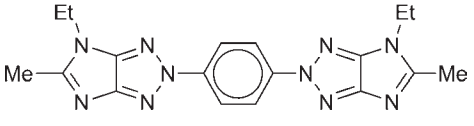
Scheme 44

imidazotriazole skeleton **60** was previously described in CHEC-II(1996) <1996CHEC-II(7)141>. A parallel sequence of reactions between *N*-sulfonylimines and triazolium imide dipoles has been observed to yield imidazotriazoles **204**, accompanied by oxazolo[5,4-*d*][1,2,3]triazoles **65** (see Section 10.05.10.2). Hydrolysis of the imine during the course of the reaction was believed to account for the formation of the oxazolo-fused bicycles. The failure of benzaldimine and the trichloroimine to furnish any imidazotriazoles reflected a more ready hydrolysis to the parent aldehyde and concomitant formation of the oxazolotriazole <2003ARK110>.

10.05.10.4 Miscellaneous Syntheses

10.05.10.4.1 Imidazo[4,5-*d*][1,2,3]triazoles

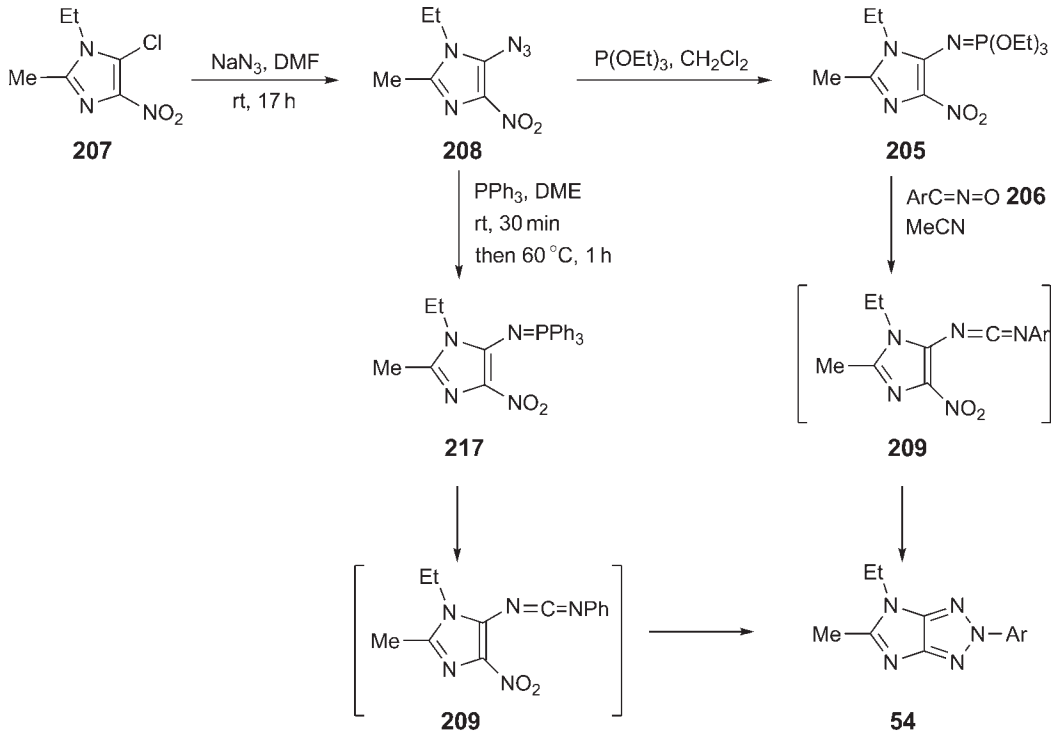
Imidazotriazoles **54** have been formed following reaction between triethyl *N*-1-ethyl-2-methyl-4-nitro-1*H*-imidazol-5-yl phosphoramidates **205** and aryl isocyanates **206** <2000TL9889, 2002J(P1)1968>. The phosphoramidates **205** were formed from the chloronitroimidazoles **207** by way of the azide derivatives **208**, and were found to be stable to rearrangement and dealkylation (**Scheme 45**). These important intermediates were characterized by ^{1}H and ^{31}P NMR data and even in one case by single crystal X-ray diffraction analysis. A complicated reaction pathway proposed to account for the annulation of the triazole ring in forming **54** is illustrated in **Scheme 46**. Initial aza-Wittig reaction between the phosphorimidate group and the isocyanate was suggested to lead to the carbodiimide-substituted nitroimidazole **209**. Intramolecular attack by the neighboring nitro group was thought to initiate a series of ring-closing and ring-opening reactions. It was believed the 5,6-bicyclic intermediate **210** ring-opened to generate the nitrosonium ion **211**, which recyclized through the nitrogen of the urea anion to form the imidazotriazene *N*-oxide **212**. Electrocyclic ring opening generated the azoxy-substituted imidazol-5-yl isocyanate **213** which cyclized to the oxadiazine **214**. Elimination of CO_2 from **214** was believed to furnish the nitrene **215** which functioned as the precursor to the imidazotriazole ring. Efforts to follow the progress of the reaction from the phosphorimidate by IR spectroscopy provided some initial evidence that the triazole ring-forming reaction proceeded by the 4-nitroimidazol-5-yl carbodiimide; however, no support for the subsequent steps of the reaction was extracted from the IR data <2002J(P1)1968>. The reaction is significant as the synthesis of only two other derivatives of this bicyclic skeleton, the 1,4-dihydro compound and a 1-hydroxy derivative, had been reported. The synthetic utility of the approach described in this paragraph is evident in its applicability to a range of aryl isocyanates including 1,4-phenylene diisocyanate which led to the bis(imidazotriazole) **216** (41%), and, in general, the isolated yields of the bicycle were moderate to good <2000TL9889, 2002J(P1)1968>. A parallel reaction with the triphenylphosphinimine **217** was reported to yield 2-phenyl-4-ethyl-5-methyl-2*H*,4*H*-imidazo[4,5-*d*]triazole in 99% yield (**Scheme 45**) <2002ARK80>.



216

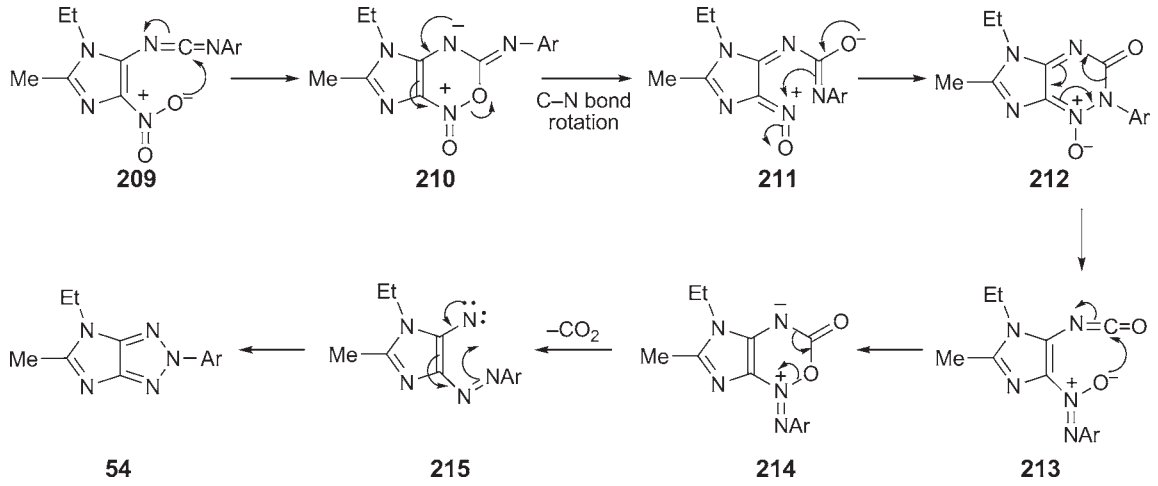
10.05.10.4.2 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles

Formation of a [1,3,2]dioxaborolo[4,5-*d*]imidazole ring skeleton **218** has been accomplished by reaction of the guanidinium side chain of protein backbone arginine residues **219** with 2,3-butanedione and a phenylboronic acid **220**. The reaction, a novel covalent arginine tagging strategy, was applied to functional probing of arginine residues in native proteins. A mass shift of 172 Da accompanied product formation following the use of phenylboronic acid and, as this mass shift is considerably larger than those from commonly observed alkali metal adducts, the conversion of arginine residues can be easily monitored, even for multiply charged proteins, making this approach experimentally attractive (Equation 24) <2005ANC4481>.

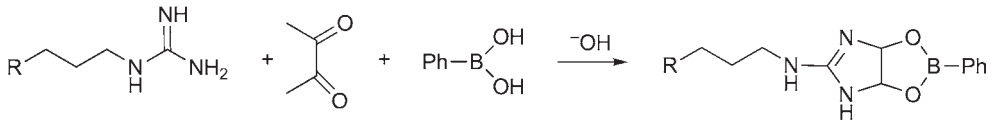


Product	*Ar*	*Yield (%)*	*Reference*	*Product*	*Ar*	*Yield (%)*	*Reference*
54a	Ph	63	2000TL9889	**54f**	*p*-$NO_2C_6H_4$	79	2000TL9889
54a	Ph	99	2002ARK80	**54g**	*p*-FC_6H_4	62	2000TL9889
54b	*p*-$CF_3OC_6H_4$	66	2002ARK80	**54h**	*p*-NCC_6H_4	61	2000TL9889
54c	*p*-$EtO_2CC_6H_4$	62	2002ARK80				
54d	2,4,6-$Me_3C_6H_2$	57	2002ARK80				
54e	*p*-$MeOC_6H_4$	64	2002ARK80				

Scheme 45



Scheme 46



219 220 218 (24)

10.05.11 Syntheses of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The syntheses of only three members of this family of compounds, viz. pyrazolo[3,4-*d*][1,2,3]triazoles, imidazo[4,5-*c*]-[1,2,5]thiadiazoles, and [1,3,2]dioxaborolo[4,5-*d*]imidazoles, have been reported by more than one approach. The pyrazolo[3,4-*d*][1,2,3]triazoles remain the most common synthetic target among this family of compounds and have been accessed from monocyclic precursors by [5+0], [4+1], and [3+2] atom fragments.

Oxidation of 3-amino-4-azopyrazoles has continued to be a successful route to pyrazolo[3,4-*d*][1,2,3]triazoles and new syntheses of this bicyclic skeleton have been achieved by chemical <1992MI95, 2003HAC211> or electrochemical oxidation <2001MI1022>. Chemical approaches include oxidation with Br_2 in AcOH <2003HAC211> or in a continuous current of air in the presence of cupric acetate <1992MI95>. The success of the electrochemical approach is significant since the electrochemistry of pyrazole derivatives has remained little investigated.

In an entirely novel example of synthesis of this bicyclic framework, an MHR (or Boulton–Katritzky rearrangement) has been illustrated; however, the reaction remains quite specific and one drawback to the synthesis of **160** is the inability to remove the acyl groups at the 3-position on the pyrazole moiety <2004H(63)2475>. Electrocyclization of intermediates produced from 3-hydrazinopyrazoles upon reaction with nitrous acid <1998AP269, 1993JHC129, 1996USP5508154, 1995M1265, 1993BCJ477> or from chloropyrazoles upon treatment with sodium azide <1991MI111, 1993BCJ477, 1995M1265> has been widely illustrated with varying yields being obtained.

Contributions aiming to improve on the original synthesis <1989AG952> of the thiadiazolodithiazole radical **1** by making the reactions more robust <2001JMC1992, 2001JMC1992> are significant since TTTA has great potential for material developments.

Facile dehydration of 4,5-bis(hydroxyimino)pyrazoles to yield pyrazolooxadiazoles is significant in the light of the ambiguous results following efforts to effect cyclization of similarly substituted isoxazole derivatives <2000RJO758, 2003T1059>.

10.05.12 Important Compounds and Applications

10.05.12.1 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles

During the last decade, the organic radicals of [1,2,5]thiadiazolo[3,4-*d*][1,3,2]dithiazole **1** and some of its coordination compounds have been extensively investigated as stable building blocks for conductive materials and molecular magnets <1996MRC913, 1999SCI261, 2000CPL(327)409, 2001PCA7615, 2001PCA7626, 2001MI145, 2002MI432, 2004MI689, 2004MI204, 2004MI3719, 2005CPL(405)382, 2005MI320>; for example, the magnetic data of TTTA·Cu(hfca)$_2$ reveal that polycyclic thiazyl radicals are useful building blocks of ferromagnetic coordination complexes <2001JA3601>.

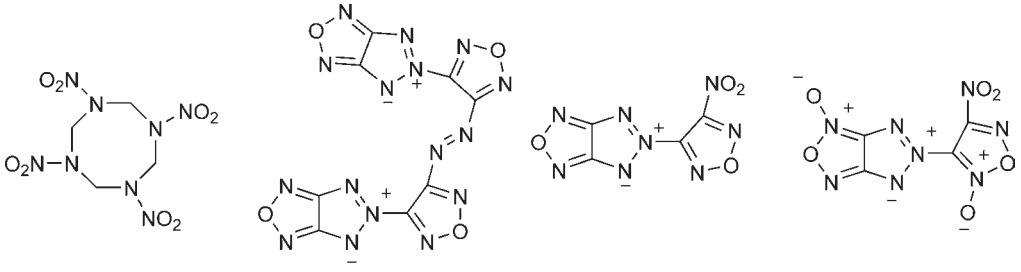
10.05.12.2 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

The radical anion of the parent bicycle is receiving attention in view of its potential value to materials science as a building block for molecular ion-based conductors and/or magnets <2005IC7194>.

10.05.12.3 [1,2,3]Triazolo[4,5-*c*][1,2,5]oxadiazolium inner salts

A number of [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazolium inner salts have been developed among a range of furazan derivatives with the potential to act as high-density, high-energetic materials <1993HCA1, 1995JHC1405, 1996MI1, 1999MI1, 2004MI75>. While the 5,5′-[methanediamino-bis(1,2,5-oxadiazol-4,3-diyl)]bis[1*H*-[1,2,3]triazolo[4,5-*c*]-

[1,2,5]oxadiazolium]-bis(inner salt) **92** was found to be shock insensitive and thermally stable above 200 °C, the N-nitrated derivative **137** was an impact-sensitive material, exploding violently with a flame when struck by a hammer <1995JHC1405>. The 5-[4-nitro-(1,2,5)oxadiazolyl] derivative **17**, indefinitely stable to storage under ordinary conditions, violently exploded when heated to 160 °C in a closed capillary tube. In a test for shock sensitivity, both **17** and its azide analogue **36** were violently brisant with an evolution of flame <1993HCA1>. Calculated values for the density, heat of formation, detonation velocity, and detonation pressure (Chapman Jouguet pressure), important parameters in accessing energetic properties, of a number of [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazolium inner salts **222–224**, are summarized in **Table 13** together with their melting points. For comparison, the values for 1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane **221** are presented (see Section 10.05.2.3).



221 **222** **223** **224**

Table 13 Energetic characteristics of a range of [1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazolium inner salts

Compound	*d* ($g\,cm^{-3}$)	ΔH^{o}_{f} ($kcal\,mol^{-1}$)	*D* ($mm\,\mu s^{-1}$)	P_{CJ} (*kbar*)	*m.p.* (°*C*)	*Reference*
222	1.85		9.4		138	1996MI1
92	1.81		8.54	340	244–245	1995JHC1405
137	1.90		9.25	407	162 dec.	1995JHC1405
17[a]	1.92		9.1	434		1993HCA1[a]
17[b]	1.69	213	8.8	366	35	1996MI1 1993HCA1[b]
76	1.87	251	8.93		193–194	1999MI1
136	1.87	670	9.40		189–190	1999MI1
223	1.91	840				2004MI75
224	1.96	760				2004MI75
221	1.90		9.1	390		B-1991M95

[a]Values for **17** as a solid.
[b]Values for **17** as a liquid.

10.05.12.4 [1,3]Dithiolo[4,5-*d*][1,3,2]dithiaboroles

The sulfur-containing diborane compounds **39** were considered of potential interest as reagents in metal-catalyzed diboration reactions <2000AXC440>.

10.05.12.5 [1,3]Dithiolo[4,5-*c*][1,2,5]thiadiazoles

Some members of this class of compounds were found to be useful antimicrobial and marine antifouling agents <1997USP5703102> while others were considered potentially interesting as magnetic organic metals <1995SM(70)1157, 2004AXEo63>.

10.05.12.6 Imidazo[4,5-*c*][1,2,5]thiadiazoles

Preliminary biological tests on the effect of imidazo[4,5-*c*][1,2,5]thiadiazolo-5-one 3,3-dioxides **93** on the acute toxicity as well as on the motional and orientational behavior in mice suggested that the combination of sulfanimide and urea structural moieties found in these compounds may elicit interesting biological activity <2000MC28>. Significantly the poor water solubility and the failure of the same compounds to form complexes with calcium salts suggested that these compounds were not likely to display similar psychotropic activity to the related imidazo[4,5-*d*]imidazole-2,5-diones (see Section 10.05.4.3) <2001PCJ72>.

10.05.12.7 [1,3,2]Dioxaborolo[4,5-*d*]imidazoles

A novel approach to differentiating between different protein conformations depending on the degree of exposure of their arginine residues was developed by Lindner and colleagues; this relied on formation of dioxaborolo[4,5-*d*]imidazole rings following reaction between exposed guanidine groups with 2,3-butanedione and phenylboronic acid. The resulting [1,3,2]dioxaborolo[4,5-*d*]imidazole-modified proteins **218** were analyzed by mass spectrometry <2005ANC4481>.

10.05.12.8 Pyrazolo[3,4-*c*][1,2,5]oxadiazoles

A series of pyrazolo[3,4-*c*][1,2,5]oxadiazoles **152** are being investigated as potential fluorescent brighteners and as antagonists of the purine P2Z receptor <2000S72>.

10.05.12.9 Imidazo[4,5-*c*][1,2,3]triazoles

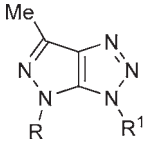
A range of triazolo-fused bicycles, including imidazo-, pyrazolo-, thiazolo-, oxazolo-, and isoxazolotriazoles have been explored as components in silver halide photographic light-sensitive materials, as developers and for use in image-forming processes <1996USP5508154>.

Compounds bearing imidazotriazole subunits have been investigated as neuropeptide Y receptor antagonists for the treatment of hyperphagia, obesity, and diabetes <2004WO050652>.

10.05.12.10 Pyrazolo[3,4-*d*][1,2,3]triazoles

Pyrazolo[3,4-*d*][1,2,3]triazoles **85**, when applied as fluorescent brighteners on polyester fibers have been found to give moderate whitening effects with a violet fluorescence, and they were categorized as grade one fluorescent brighteners <1992MI95>.

In contrast to the potent biological activity reported for many triazole-containing compounds, the series of pyrazolotriazoles **77**, **78**, and **225** showed no significant cytostatic, antiviral, antifungal, and antibacterial activity <1998APC269>. Neither did 1-amino-6-methyl-4-phenylpyrazolo[3,4-*d*][1,2,3]triazole show any potential as an antifungal substance <1999MI549>. On the other hand, the 1-(*N*-alkyl)carboxamide and 4-methyl-6-phenyl-pyrazolo[3,4-*d*][1,2,3]triazole **142** and **143**, respectively, were found to display some fungicidal activity, with the data for **143** showing most promise <1992FA1021>, while *in vitro* antibacterial activity against a range of bacteria was shown for the pyrazolotriazole **174** <1995M1265>.



a: R = Me; R^1 = Et
b: R = Me; R^1 = Bn
c: R = Ph; R^1 = Et
d: R = Ph; R^1 = Bn

225

Light-activatable DNA-cleaving ability was demonstrated for the pyrazolo[3,4-*d*][1,2,3]triazoles **111a** and **111b** – radical fragmentation of the triazole nucleus was believed to be an integral part of the biological interaction. Preliminary results suggested heterocyclic annellated triazoles may be good candidates with good potential for therapeutic use <2000BMC2343>.

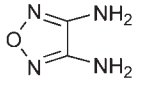
Aminals, conveniently prepared in low cost by condensation of a carbamate, an azole and either a ketone, paraformaldehyde, or trioxane in the presence of a Lewis acid and/or a Cu(II) salt were useful as intermediates for photographic couplers and organic synthesis. A number of examples incorporating pyrazolotriazole moieties have been described <1995JPP07133259>.

10.05.13 Further Developments

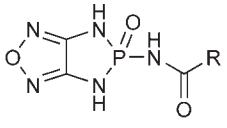
There have been a number of developments in the area since the original submission of this chapter in late 2006.

10.05.13.1 [1,2,5]Oxadiazolo[3,4-*c*][1,3,2]diazaphospholes

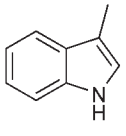
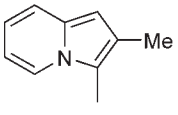
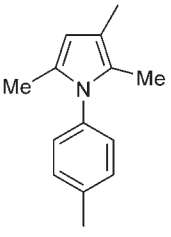
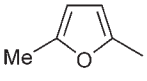
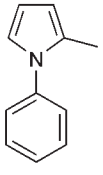
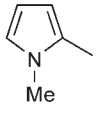
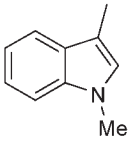
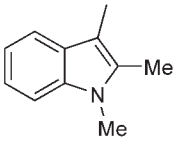
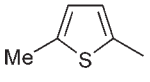
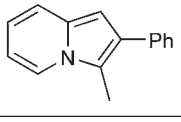
An effective and simple synthesis of a novel range of 2-(heteryl-carboxamido)-2,3-dihydro-1*H*[1,2,5]oxadiazolo[3,4-*c*]-[1,3,2]diazaphosphole-2-oxides has been reported involving reaction between 3,4-diaminooxadiazoles **226** and a range of, *in situ* generated, *N*-dichlorophosphorylheterylcarboxamides. The yields were generally quite good with the exception of **227d** and **227g**. The compounds have been fully characterized by spectroscopic methods, significantly, with the exception of **227c** and **227h** the appearance of more than one ^{31}P NMR signal suggested the molecules may exist as two or three conformers in solution. Most of the compounds exhibited moderate activity against bacteria and less against fungi; **227i** had significant antibacterial activity – even higher than the standard penicillin against *Escherichia coli* <2006ARK189>.



226

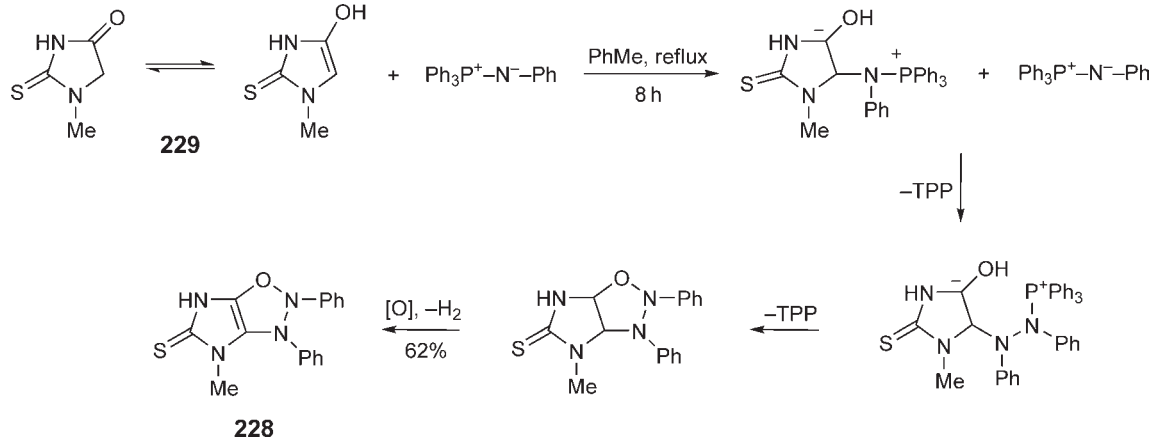


227a–j

227	*R*	*Yield* (%)	**227**	*R*	*Yield* (%)	**227**	*R*	*Yield* (%)
a		78	**b**		71	**c**		83
d		38	**e**		67	**f**		77
g		8.4	**h**		79	**i**		58
j		48						

10.05.13.2 Imidazo[4,5-*d*][1,2,3]oxadiazoles

The imidazo[4,5-*d*][1,2,3]oxadiazole-5-thione **228** has resulted from reaction between the 2-thioxoimidazolidin-4-one **229** and two equivalents of *N*-phenyliminophosphorane. The reaction also results in the formation of triphenylphosphine (TPP) and a proposed reaction mechanism is set-out in **Scheme 47** <2006PS1615>.



Scheme 47

10.05.13.3 Imidazo[4,5-*c*][1,2,5]oxadiazoles

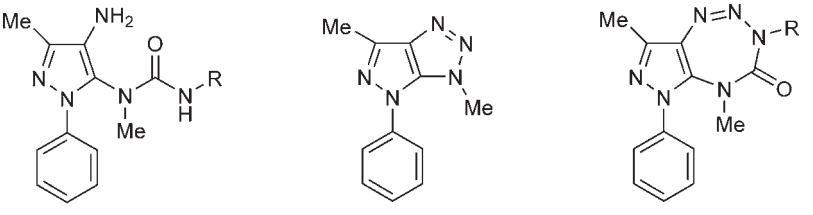
Reaction between formaldehyde and 3,4-diamino-[1,2,5]oxadiazole has been shown to lead to the parent bicycle in 89% yield <2007JHC717>.

10.05.13.4 Imidazo[4,5-*d*][1,3,2]diazaborolidines

A further example of synthesis of the imidazo[4,5-*d*][1,3,2]diazaborolidine ring system involving reaction between 4-imino-5-aminoimidazoles, analogous to **90**, and boranes has been reported (see Section 10.05.9.1.2(viii)) <2006ZN(B)437>.

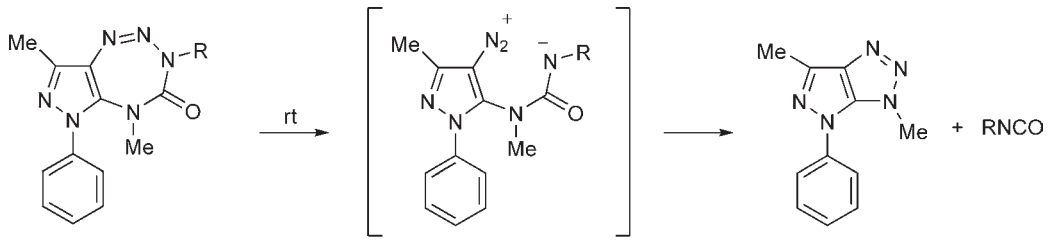
10.05.13.5 Pyrazolo[3,4-*d*][1,2,3]triazoles

New examples of the formation of pyrazolo[3,4-*d*][1,2,3]triazoles from 4-aminopyrazoloureas, described above in Section 10.05.9.1.2(vii)), have been described. The recent publication of Maggio and co-workers provides an insight into the mechanism of the reaction. It has been shown that nitrosation of **230** with nitrous acid at 0 °C followed by adjustment of the pH to 8 and room temperature extraction furnishes, from amongst a mixture of products, the 5,5-bicycle **231** whilst extraction and work-up at 0 °C yielded the 5,7-bicycle **232** as the single reaction product. The latter is the precursor to the pyrazolotriazole which results simply from room temperature solution decomposition involving loss of (m)ethyl isocyanate. The formation of the triazole **231** from the tetrazepinone **232** is rationalized as shown in **Scheme 48** <2006ARK120>.



230a,b **231** **232a,b**

a: R = CH_3; **b**: R = C_2H_5



232a,b

a: R = CH_3; **b**: R = C_2H_5

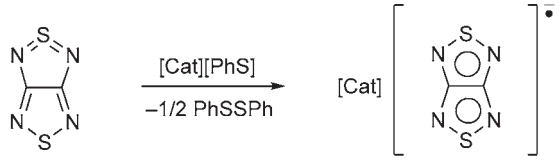
231

Scheme 48

Cyclization of 2-phenyl-[1,2,3]triazole-4-carboxaldehyde hydrazone with $POCl_3$ or $SOCl_2$ has been shown to lead to 5-phenylpyrazolo[3,4-*d*][1,2,3]triazole in the case of the former and to a mixture of the 5-phenyl and the 1-chloro-5-chlorophenylderivative <2005MI179>.

10.05.13.6 [1,2,5]Thiadiazolo[3,4-*c*][1,2,5]thiadiazoles

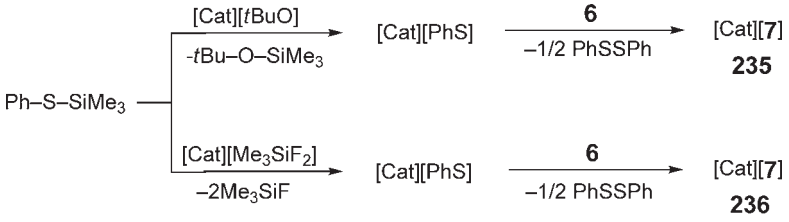
A rational preparation of thermally stable salts of the [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazolidyl radical anion **7** has been reported. The salts are MeCN soluble, and are stable in solution and in the crystalline state when stored free of air. The synthesis involves reduction of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole **6** with *in situ* generated PhS^-. PhSM, generated from $PhSSiMe_3$, served as the source of the thiolate anion (M = Li, Na, K) (Schemes 49 and 50). This synthetic procedure is attractive as it can be envisaged that salts with transition metal ions can also be generated by this approach. [Li(12-crown-4)$_2$][**7**], **233**, [Na(15-crown-5)][**7**], **234**, and [K(18-crown-6)][**7**], **235**, as well as [$(Me_2N)_3S$][**7**], **236**, have been prepared and characterized by XRD and ESR. The radical anion acts as a bridging ligand in the sodium and potassium salts. If the potassium salt, **235**, is allowed to stand in MeCN at ambient temperature for a few days, or is crystallized from the same solvent at low temperature the solvate **235.MeCN**, **237**, forms, in this structure the radical anion acts as a chelating ligand. Transformation of **237** into **235** is reversible and the procedure can be repeated at least three times. In the lithium salt **233**, the radical anion is not coordinated to the



6 **7**

[Cat] = [Li(12-crown-4)$_2$]$^+$ (**233**), 65%; [Na(15-crown-5)]$^+$ (**234**), 80%;
[K(18-crown-6)]$^+$ (**235**), 75%

Scheme 49



[Cat] = [K(18-crown-6)]$^+$ (**235**), 90%; [$(Me_2N)_3S$]$^+$ (**236**), 75%

Scheme 50

cation and can be considered a "naked" anion. In the salt **236**, with the organic cation, one of the two crystallographically independent radical anions acts as a bridging ligand whilst the other is not coordinated to the cation. Magnetic susceptibility data for the sodium and potassium salts in the temperature range 2–300 K reveal antiferromagnetic exchange interactions between paramagnetic centers **234** $J = -3.42$, $aJ = -1.12$ cm^{-1}; **235** $J = -1.22$ cm^{-1}. <2006EJI3061>.

10.05.13.7 [1,2,5]Thiadiazolo[3,4-*d*][1,3,2]dithiazoles

The potential for materials applications has continued to fuel interest in aspects of optical and solid state properties of the [1,2,5]thiadiazolo[3,4-*d*][1,3,2]dithiazol-2-yl radical **1** and a review article covering important solid-state properties *viz* magnetic properties, crystal structure, thermodynamic properties and phase control, magnetic bistability and charge doping of TTTA has appeared <2006BCJ25>. A number of additional publications have appeared in the recent months on theoretical and experimental studies of TTTA. A first-principles T-matrix calculation on multiple scatterings between electrons has shown that the intramolecular electron–electron interaction energy U is significantly reduced compared to the naïve expectation (2.9 eV and 7.3 eV respectively) due to short range correlation <2006MI1820>.

Theoretical efforts, using the Hubbard model conclude the lowest photoexcited state of TTTA is the interdimer CT exciton state and the second lowest the intradimer CT exciton state <2007MI>. Excited state dynamics of TTTA in both high and low temperature phases, has also been experimentally studied by femtosecond luminescence spectroscopy. A broad luminescence band was observed in the LT phase with a decay time constant of 1.6 ps, suggesting a large nonradiative relaxation path. Fast depolarization of luminescence suggested energy transfer between charge transfer excited states with different orientations are large and a few kinds of lattice distortation exist in the system <2006MI>. A specially designed set-up for steady-state powder photodiffraction has provided direct atomic level evidence that the photoinduced phase and the HT phase are structurally identical, the results support the model that photoexcitation suppresses the spin-Peierls instability and separation of the radical dimmers, resulting in a structure essentially identical with the unperturbed HT phase <2007JPC(A)6449>.

Relevant Websites

http://www.arkat-usa.org – ARKIVOC Journal, ARKAT USA.
http://cds.dl.ac.uk – CHC, A Comprehensive Compendium of Heterocyclic Chemistry, Chemical Database Service.
http://hetcomm.tripod.com/hetcomm.html – Heterocyclic Communications.
http://euchbf.chem.emory.edu – International Society of Heterocyclic Chemistry, ChemKey Search Database.
http://www.jhetchem.com – Journal of Heterocyclic Chemistry.
http://www.elsevier.com – Progress in Heterocyclic Chemistry (annual series), Elsevier.

References

1981CSC1403 J. Kane and R. Scheaffer, *Cryst. Struct. Commun.*, 1981, **10**, 1403.
1984AHC330 P. K. Kadaba, B. Stanovnik, and M. Tisler, *Adv. Heterocycl. Chem.*, 1984, **37**, 330.
1988CB1865 W. Kliegel and H. W. Motzkus, *Chem. Ber.*, 1988, **121**, 1865.
1989AG952 G. Wolmershaeuser and R. Johann, *Angew. Chem.*, 1989, **101**, 952.
1989JOC3077 C. Lee, J. D. Korp, and H. Kohn, *J. Org. Chem.*, 1989, **54**, 3077.
1989PHA110 F. Mergen, J. H. Poupaert, J. L. De Keyser, and P. Dumont, *Pharmazie*, 1989, **44**, 110.
1990J(P1)2527 R. N. Butler, A. M. Evans, E. M. McNeela, G. A. O'Halloran, P. D. O'Shea, D. Cunningham, and P. McArdle, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2527.
1990J(P1)2537 R. N. Butler, A. M. Evans, A. M. Gillan, J. P. James, E. M. McNeela, D. Cunningham, and P. McArdle, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2537.
1991IZV1825 K. I. Rezchikova, A. M. Churakov, V. A. Shlyapochnikov, and V. A. Tartakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1825 (*Chem. Abstr.*, 1991, **115**, 255 312).
B-1991M95 A. T. Nielsen; in 'Chemistry of Energetic Materials', G. A. Olah and D. R. Squire, Eds.; Academic Press, New York, 1991, p. 95.
1991MI111 A. A. Ismail, R. Radwan, H. A. Abdel Hamid, G. H. Sayed, and S. M. Mohamed, *J. Chem. Soc. Pak.*, 1991, **13**, 111.
1991MRC625 Y. L. Chung, J. P. B. Sandall, L. H. Sutcliffe, H. Joly, K. F. Preston, R. Johann, and G. Wolmershaeuser, *Magn. Reson. Chem.*, 1991, **29**, 625.
1992FA1021 C. B. Vicentini, V. Brandolini, M. Guarneri, and P. Giori, *Farmaco*, 1992, **47**, 1021.
1992MI95 D. W. Rangnekar and P. Y. Kamat, *Indian J. Fibre Text. Res.*, 1992, **17**, 95.
1993BCJ477 G. H. Sayed, A. Radwan, A. A. Hamed, and W. E. Boraie, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 477.

1993HCA1 A. Gunasekaran and J. H. Boyer, *Heteroatom Chem.*, 1993, **52**, 1.
1993JHC129 R. T. Chakrasali, Ch. Srinivasa Rao, H. Ila, and H. Junjappa, *J. Heterocycl. Chem.*, 1993, **30**, 129.
1993SM(68)1914 A. E. Underhill, I. Hawkins, S. Edge, S. B. Wilkes, and K. S. Varma, *Synth. Met.*, 1993, **68**, 1914.
1993ZK133 P. G. Jones and A. Chrapkowski, *Z. Kristallogr.*, 1993, **208**, 133 (*Chem. Abstr.*, 1993, **121**, 218215).
1994CPA393 A. I. M. Koraiem, R. M. Abd El-All, and R. M. Abu El-Hamd, *Chem. Pap.*, 1994, **48**, 393.
1994IC4537 C. P. Galloway, D. D. Doxsee, D. Fenske, T. B. Rauchfuss, S. R. Wilson, and X. Yang, *Inorg. Chem.*, 1994, **33**, 4537.
1994J(P1)2797 R. N. Butler and D. F. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2797.
1995CB751 A. Lang, H. Noth, and M. Schmidt, *Chem. Ber.*, 1995, **128**, 751.
1995H(41)2409 C. B. Vicentini, V. Ferretti, A. C. Veronese, and P. Giori, *Heterocycles*, 1995, **41**, 2409.
1995IZV1315 G. K. Khisamutdinov, T. A. Mratkhutzina, R. M. Gabdullin, I. S. Abdrakhmanov, S. P. Smirnov, and B. I. Ugrak, *Izv. Akad. Nauk, Ser. Khim.*, 1995, 1315 (*Chem. Abstr.*, 1995, **124**, 117188).
1995JHC1405 A. Gunasekaran, T. Jayachandran, J. H. Boyer, and M. L. Trudell, *J. Heterocycl. Chem.*, 1995, **32**, 1405.
1995JPP07133259 T. Kawagishi, H. Mizukawa, and A. Ookawa, *Jpn. Kokai Tokkoyo Koho* 07 133 259T (1995) (*Chem. Abstr.*, 1995, **123**, 340133).
1995JST(358)63 M. E. Grice and P. Politzer, *J. Mol. Struct.*, 1995, **358**, 63.
1995M1265 E. Abdel-Ghani, M. G. Assy, and H. Y. Moustafa, *Monatsh. Chem.*, 1995, **126**, 1265.
1995SM(70)1157 T. Naito, H. Tomita, A. Tateno, T. Udagawa, H. Hobayashi, and A. Kobayashi, *Synth. Met.*, 1995, **70**, 1157.
1996CHEC-II(7)141 F. Heaney; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 141.
1996J(P2)2111 G. L'abbe, L. Dyall, K. Meersman, and W. Dehaen, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2111.
1996JOC3987 J. Yamada, S. Satoki, S. Mishima, N. Akashi, K. Takahasi, N. Masuda, Y. Nishimoto, S. Takasaki, and H. Anzai, *J. Org. Chem.*, 1996, **61**, 3987.
1996KGS253 V. E. Eman, M. S. Sukhanov, O. V. Lebedev, L. V. Batog, and L. I. Khmel'nitskii, *Khim. Geterotsikl. Soedin.*, 1996, 253 (*Chem. Abstr.*, **125**, 167882).
1996MI1 A. B. Sheremetev, V. O. Kulagina, L. V. Batog, O. V. Lebedev, I. L. Yudin, and T. S. Pivina, '22nd Proceedings of the International Pyrotechnics Seminar', 1996, 377–388 (*Chem. Abstr.*, 1996, **125**, 247708).
1996MRC913 J. Gassmann and J. Fabian, *Magn. Reson. Chem.*, 1996, **34**, 913.
1996T743 B. Klenke and W. Friedrichsen, *Tetrahedron*, 1996, **52**, 743.
1996T7183 F. Clerici, F. Galletti, and D. Pocar, *Tetrahedron*, 1996, **52**, 7183.
1996TL8577 A. M. Churakov, S. L. Ioffe, Y. A. Strelenko, and V. A. Tartakosvy, *Tetrahedron Lett.*, 1996, **37**, 8577.
1996USP5508154 Y. Mizukawa and H. Kobayashi, *US Pat.* 5 508 154 (1994) (*Chem. Abstr.*, 1994, **123**, 301 449).
1997CC2149 R. N. Butler, E. C. McKenna, and D. C. Grogan, *J. Chem. Soc., Chem. Commun.*, 1997, 2149.
1997J(P1)3587 R. N. Butler, D. C. Grogan, P. D. McDonald, and L. A. Burke, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3587.
1997JPO33 T. Strassner and J. Fabian, *J. Phys. Org. Chem.*, 1997, 33.
1997JST(418)209 M. Tho Nguyen, A. W. Allaf, R. Flammang, and Y. Van Haverbeke, *J. Mol. Struct.*, 1997, **418**, 209.
1997RJO1656 I. V. Tselinskii, S. F. Mel'nikova, T. V. Romanova, S. V. Pirogov, G. Kh. Khisamutdinov, T. A. Mratkhuzina, L. V. Korolev, I. Z. Kondyukov, I. Sh. Abdrakhmanov, and S. P. Smirnov, *Russ. J. Org. Chem. (Engl. Transl.)*, 1997, **33**, 1656.
1997SM(86)1815 T. Naito, T. Inabe, E. Arai, M. Tamura, Y. Nishio, K. Kajita, R. Kato, A. Obayashi, and H. Kobayashi, *Synth. Met.*, 1997, **86**, 1815.
1997SM(86)1821 Y. Misaki, T. Miura, H. Fujiwara, K. Kawakani, T. Yamabe, T. Mori, H. Mori, and S. Tanaka, *Synth. Met.*, 1997, **86**, 1821.
1997SM(86)1871 M. Tomura and Y. Yamashita, *Synth. Met.*, 1997, **86**, 1871.
1997USP5703102 R. B. Shankar, D. R. Romer, and G. R. Pews, *US Pat.* 5 703 102 (1997) (*Chem. Abstr.*, 1997, **128**, 98950).
1998AP269 C. B. Vicentini, S. Manfredini, M. Manfrini, R. Bazzanini, C. Musiu, M. Putzolu, G. Perra, and M. E. Marongiu, *Arch. Pharm. (Weinheim, Ger.)*, 1998, **313**, 269.
1998JST(451)263 B. Klenke and W. Friedrichsen, *J. Mol. Struct.*, 1998, **451**, 263.
1998MC238 A. B. Sheremetev and N. S. Aleksandrova, *Mendeleev Commun.*, 1998, 238.
1999MI1 L. V. Batog, V. Y. Rozhkov, L. S. Konstantinova, A. N. Blinnikov, N. N. Makhova, T. S. Pivina, V. P. Lebedev, T. S. Kon'kova, and Y. N. Matyushin, 'International Annual Conference of ICT', 1999, 30th 57/1 (*Chem. Abstr.*, 1999, **132**, 8340).
1999MI549 D. Mares, C. Romagnoli, G. Sacchetti, C. C. Vicentini, and A. Bruni, *Mycoses*, 1999, **42**, 549.
1999RJO1525 A. B. Sheremetev, O. V. Kharitonova, E. V. Mantseva, V. O. Kulagina, E. V. Shatunova, N. S. Aleksandrova, T. M. Mel'nikova, E. A. Ivanova, D. E. Dmitriev, V. Eman, I. L. Yudin, V. S. Kuz'min, Y. A. Strelenko, T. S. Novikova, O. L. Lebedev, and L. I. Khmel'nitskii, *Russ. J. Org. Chem. (Engl. Transl.)*, 1999, **35**, 1525.
1999SCI261 W. Fujita and K. Awaga, *Science*, 1999, **286**, 261.
2000AXC440 N. C. Norman, A. G. Orpen, M. J. Quayle, and C. R. Rice, *Acta Crystallogr., Sect. C*, 2000, **56**, 440.
2000BMC2343 S. Menfredini, C. B. Vicentini, M. Manfrini, N. Bianchi, C. Rutigliano, C. Mischiati, and R. Gambari, *Bioorg. Med. Chem.*, 2000, **8**, 2343.
2000CHE91 L. V. Batog, L. S. Konstantinova, V. Y. Rozhkov, Y. A. Strelenko, O. V. Lebedev, and L. I. Khmel'nitskii, *Chem. Heterocycl. Compd, (Engl. Transl.)*, 2000, **36**, 91.
2000CHE343 L. V. Batog, V. Y. Rozhkov, Y. A. Strelenko, O. V. Lebedev, and L. I. Khmel'nitskii, *Chem. Heterocycl. Compd, (Engl. Transl.)*, 2000, **36**, 343.
2000CPL(327)409 S. M. Mattar and A. D. Stephens, *Chem. Phys. Lett.*, 2000, **327**, 409.
2000MC28 G. A. Gazieva, A. N. Kravchenko, K. Y. Chegaev, Y. A. Strelenko, and O. V. Lebedev, *Mendeleev Commun.*, 2000, 28.
2000MCL161 W. Fujita, Y. Torigoe, and K. Awaga, *Mol. Cryst. Liq. Cryst.*, 2000, **345**, 161.
2000RJO758 I. V. Tselinskii, S. F. Mel'nikova, S. V. Pirogov, and S. D. Shaposhnikov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2000, **36**, 758.
2000S72 P. G. Baraldi, M. J. Pineda, de las Infantas, S. Manfredini, and R. Romagnoli, *Synthesis*, 2000, 72.
2000TL9889 A. Taher, S. Eichenseher, and G. W. Weaver, *Tetrahedron Lett.*, 2000, **41**, 9889.
2000WO063197 G. R., Scarlato, R. S. S. Hadida, T. Nishimura, M. Nakatusuka, F. Samizo, Y. Kamikawa, and H. Houtigai, *PCT Int. Appl. WO* 063 197 (2000) (*Chem. Abstr.*, 2000, **133**, 321892).
2001AXEo307 M. Tomuara and Y. Yamashita, *Acta. Crystallogr., Sect. E*, 2001, **57**, o307.

2001JA3601 W. Fujita and K. Awaga, *J. Am. Chem. Soc.*, 2001, **123**, 3601.
2001JMC1992 G. D. McManus, J. M. Rawson, N. Feeder, J. van Duijn, E. J. L. McInnes, J. J. Novoa, R. Burriel, F. Palacio, and P. Oliete, *J. Mater. Chem.*, 2001, **11**, 1992.
2001MC107 G. A. Gazieva, K. A. Lyssenko, R. G. Gaziev, A. N. Kravchenko, O. V. Lebedev, and V. M. Zhulin, *Mendeleev Commun.*, 2001, 107.
2001MC138 G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, K. A. Lyssenko, M. O. Dekaprilevich, V. M. Men'shov, Y. A. Strelenko, and N. N. Makhova, *Mendeleev Commun.*, 2001, 138.
2001MI21 K. Awaga, *Nippon Kessho Gakkaishi*, 2001, **43**, 21 (*Chem. Abstr.*, 1995, **135**, 101 209).
2001MI451 W. Fujita and K. Awaga, *J. Solid State Chem.*, 2001, **159**, 451.
2001MI1022 G. M. Abou-Elenien, N. A. Ismail, A. A. El-Maghraby, and G. M. Al-abdallah, *Electroanal.*, 2001, **13**, 1022.
2001PCA7615 P. Kaszynski, *J. Phys. Chem. A*, 2001, **105**, 7615.
2001PCA7626 P. Kaszynski, *J. Phys. Chem. A*, 2001, **105**, 7626.
2001PCJ72 G. A. Gazieva, A. N. Kravchenko, O. V. Lebedev, and V. I. Abelentsev, *Pharm. Chem. J.*, 2001, **35**, 72.
2001POL1517 W. Fujita and K. Awaga, *Polyhedron*, 2001, **20**, 1517.
2001PS145 G. D. McManus, J. M. Rawson, E. J. L. McInnes, and J. Novoa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **169**, 145.
2001SM(121)1767 W. Fujita and K. Awaga, *Synth. Met.*, 2001, **121**, 1767.
2001WO040231 K. S. Atwal, W. Vaccaro, J. Lloyd, H. Finlay, L. Yan, and R. S. Bhandaru, *PCT Int. Appl.* WO 2001040231 (2001) (*Chem. Abstr.*, 2001, **135**, 19 660).
2001ZFA1815 S. Luckert, E. Eversheim, U. Englert, T. Wagner, and P. Paetzold, *Z. Anorg. Allg. Chem.*, 2001, **627**, 1815.
2002ARK80 K. J. Duffy, G. Tennant, C. J. Wallis, and G. W. Weaver, *ARKIVOC*, 2002, **iii**, 80.
2002J(P1)1968 A. Taher, S. Eichenseher, A. M. Z. Slawin, G. Tennant, and G. W. Weaver, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1968.
2002MI1 J. Takeda, Asahi Garasu Zaidan Josei Kenkyu Seika Hokoku (2002) Publisher: Asahi Garasu Zaidan, http://www.af-info.or.jp/jpn/subsidy/report2/2002/body/02B-C01-P116.TXT (Journal; Online Computer File written in Japanese) (*Chem. Abstr.* 2002, **138**, 360277).
2002MI432 H. I. Suess, T. Wuest, A. Sieber, R. Althaus, F. Budde, H.-P. Luethi, G. D. McManus, J. Rawson, and J. Hulliger, *Cryst. Eng. Commun.*, 2002, 432.
2002MI863 J. Takeda, M. Imae, S. Kurita, and T. Kodaira, *Phase Transitions*, 2002, **75**, 863.
2002MI064434/1 W. Fujita, K. Awaga, H. Matsuzaki, and H. Okamoto, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 2002, **65**, 064434/1.
2003ARK110 M. Sheridan, P. James, and C. Healy, *ARKIVOC*, 2003, **vii**, 110.
2003AGE3506 S. Trofimenko, A. L. Rheingold, and C. D. Incarvito, *Angew. Chem., Int. Ed. Engl.*, 2003, 3506.
2003AXEo145 M. Tomura and Y. Yamashita, *Acta Crystallogr., Sect. E*, 2003, **59**, o145.
2003CHE784 G. A. Gazieva, A. N. Kravchenko, Yu. A. Strelenko, O. V. Lebedev, R. G. Gaziev, and V. M. Zhulin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, 784.
2003CPL(378)456 J. Takeda, M. Imae, O. Hanado, S. Kurita, M. Furuya, K. Ohno, and T. Kodaira, *Chem. Phys. Lett.*, 2003, **378**, 456.
2003HAC211 G. A. El-Saraf, A. M. El-Sayed, and A. M. M. El-Saghier, *Heteroatom Chem.*, 2003, **14**, 211.
2003JPO220 J. A. Caram, S. L. Aimone, M. V. Mirifico, and E. J. Vasini, *J. Phys. Org. Chem.*, 2003, **16**, 220.
2003MI911 M. Furuya, K. Ohno, T. Morisato, Y. Kawazoe, and J. Takeda, *Trans. Mater. Res. Soc. Jpn.*, 2003, **28**, 911.
2003MI17403 H. Matsuzaki, W. Fujita, K. Awaga, and H. Okamoto, *Phys. Rev. Lett.*, 2003, **91**, 17403.
2003T1059 S. D. Shaposhnikov, S. V. Pirogov, S. F. Mel'nikova, I. V. Tselinsky, C. Nather, T. Graening, T. Traulsen, and W. Friedrichsen, *Tetrahedron*, 2003, **59**, 1059.
2004AXo63 M. Tomura and Y. Yamashita, *Acta Crystallogr.*, 2004, **60**, o63.
2004CC1860 T. Gebauer, R. Beckert, D. Weiss, K. Knop, C. Kaepplinger, and H. Goerls, *J. Chem. Soc., Chem. Commun.*, 2004, 1860.
2004CPL(393)150 T. Tanaka, W. Fujita, and K. Awaga, *Chem. Phys. Lett.*, 2004, **393**, 150.
2004H(63)2475 D. A. Berry, T. C. Chien, and L. B. Townsend, *Heterocycles*, 2004, **63**, 2475.
2004JA8256 J. L. Brusso, O. P. Clements, R. C. Haddon, M. E. Itkis, A. A. Leitch, R. T. Oakley, R. W. Reed, and J. F. Richardson, *J. Am. Chem. Soc.*, 2004, **125**, 8256.
2004JA11202 P. W. Fowler, C. W. Rees, and A. Soncini, *J. Am. Chem. Soc.*, 2004, **126**, 11202.
2004JPO1091 J. A. Caram, M. V. Mirifico, S. L. Aimone, O. E. Piro, E. E. Castellano, and E. J. Vasini, *J. Phys. Org. Chem.*, 2004, **17**, 1091.
2004MI75 D. B. Lempert, G. N. Nechiporenko, and S. I. Soglasnova, *Khim. Fizika*, 2004, **23**, 75 (*Chem. Abstr.*, 2004, **141**, 298159).
2004MI204 W.-D. Zou, Z.-L. Liu, M. Wu, and K.-L. Yao, *Phys. B Condens. Matter*, 2004, **351**, 204.
2004MI689 M. Furuya, Y. Kawazoe, and K. Ohno, *Sci. Technol. Adv. Mater.*, 2004, **5**, 689.
2004MI3719 M. Furuya, K. Ohno, J. Takeda, and Y. Kawazoe, *Trans. Mater. Res. Soc. Japn.*, 2004, **29**, 3719.
2004T3847 C. Kapplinger, T. Gebauer, R. Beckert, D. Weiss, W. Gunther, H. Gorls, and M. Friedrich, *Tetrahedron*, 2004, **60**, 3847.
2004WO050652 N. Otake, Y. Haga, M. Jitsuoka, and A. Kanatani, *PCT Int. Appl. WO* 050 652 (2004) (*Chem. Abstr.*, 2004, **141**, 38615).
2005ANC4481 A. Leitner and W. Lindner, *Anal. Chem.*, 2005, **77**, 4481.
2005CPL(405)382 S. M. Mattar, *Chem. Phys. Lett.*, 2005, **405**, 382.
2005IC7194 A. Yu. Makarov, I. G. Irtegova, N. V. Vasilieva, I. Yu. Bagryanskaya, T. Borrmann, Y. V. Gatilov, E. Lork, R. Mews, W. Stohrer, and A. V. Zibarev, *Inorg. Chem.*, 2005, **44**, 7194.
2005MI179 S. Kurian and K. Mohan, *Acta Ciencia Indica*, 2005, **31**(3), 179.
2005MI283 S. Oguri, O. Hanado, J. Takeda, M. Furuya, K. Ohno, S. Inoue, and T. Kodaira, *J. Luminescence*, 2005, **112**, 283.
2005MI320 W.-D. Zou, Z.-L. Liu, M. Wu, and K.-L. Yao, *J. Magnetism Magn. Mat.*, 2005, **288**, 320.
2005SM(153)457 K. Iketaki, K. Kanai, K. Tsuboi, W. Fujita, K. Awaga, M. Knupfer, Y. Ouchi, and K. Seki, *Synth. Met.*, 2005, **153**, 457.
2006ARK189 Y. H. Babu, M. A. Kumar, K. Srinivasulu, C. S. Reddy, and C. N. Raju, *ARKIVOC (Arkive for Organic Chemistry)*, 2006, **15**, 189.
2006ARK120 B. Maggio, D. Raffa, M. V. Raimondi, F. Plescia, S. Cascioferro, and G. Daidone, *ARKIVOC (Arkive for Organic Chemistry)*, 2006, **15**, 120.
2006BCJ25 K. Awaga, T. Tanaka, T. Shirai, M. Fujimori, Y. Suzuki, H. Yoshikawa, and W. Fujita, *Bull. Chem. Soc. Jpn.*, 2006, **79**(1), 25.
2006EJI3061 V. N. Ikorskii, I. G. Irtegoya, E. Lork, A. Y. Makarov, R. Mews, V. I. Oycharenko, and A. V. Zibarev, *Eur. J. Inorg. Chem.*, 2006, **15**, 3061.

2006MI	Y. Takahashi, T. Suemoto, S. Oguri, and J. Takeda, *Physical Review BB: Condensed Matter and Materials Physics*, 2006, **74**(19), 193104/1.
2006MI1820	K. Ohno, Y. Noguchi, T. Yokoi, S. Ishii, J. Takeda, and M. Furuya, *Chem. Phys. Chem.*, 2006, **7**(8), 1820.
2006PS1615	L. S. Boulos, E-S. M. Yakout, and M. H. Arsanious, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2006, **181**(7), 1615.
2006ZN(B)437	R. Beckert, C. Hippius, T. Gebauer, F. Stoeckner, C. Luedigk, D. Weiss, D. Raabe, W. Guenther, and H. Goerls, *Z. Naturforsch., Teil B*, 2006, **61**(4), 437.
2007JHC717	A. Kakanejadifard, A. Saniei, F. Delfani, M. Farnia, and G. R. Najafi, *J. Heterocycl. Chem.*, 2007, **44**(3), 717.
2007JPC(A)6449	P. Naumov, J. P. Hill, K. Sakurai, M. Tanaka, and K. Ariga, *J. Phys. Chem. A*, 2007, **111**(28), 6449.
2007MI	N. Maeshima and K. Yonemitsu (2007), Publisher: Los Alamos National Labaratory, http://aps.arxiv.org/PS_cache/arxiv/pdf/0705/0705.2303v1.pdf Journal; Online Computer File written in English. (*Chem. Abstr.* 2002, **147**, 166 409).

Biographical Sketch



Frances Heaney was born in Northern Ireland; she studied at Queen's University, Belfast, where she obtained a B.Sc. in 1986 and a Ph.D. in 1990 under the direction of Professor R. Grigg. After spending two years as a postdoctoral research fellow in the laboratories of Dr. Peter Boyle at Trinity College, Dublin, she took up her first academic position in the chemistry department at the National University of Ireland, Galway. In 1999, she took up her present position as chemistry lecturer at the National University of Ireland, Maynooth. Her scientific interests include synthetic chemistry, heterocyclic chemistry, rearrangement reactions, reaction mechanisms, and organocatalysis.



Linda Doyle studied at the National University of Ireland, Maynooth, where she obtained a first class B.Sc. (Honours) in 2005. She is currently a Ph.D. research student working with Dr. Heaney in the area of organocatalysis.

10.06
Bicyclic 5-6 Systems: Two Heteroatoms 1:1

A. R. Sherman
College of Notre Dame of Maryland, Baltimore, MD, USA
© 2008 Elsevier Ltd. All rights reserved.

10.06.1 Introduction **265**
10.06.1.1 Scope and General Reviews **265**
10.06.1.2 Isomeric Structures **265**
10.06.1.2.1 Pyrrolopyridines 265
10.06.1.2.2 Furopyridines 265
10.06.1.2.3 Thienopyridines 265
10.06.1.2.4 Pyranopyrroles 265
10.06.1.2.5 Thiopyranopyrroles 267
10.06.1.2.6 Furopyrans 267
10.06.1.2.7 Thienopyrans 268
10.06.1.2.8 Thiopyranofurans 268
10.06.1.2.9 Thienothiopyrans 268
10.06.2 Theoretical Methods **269**
10.06.2.1 *Ab Initio* Methods **269**
10.06.2.1.1 Pyrrolopyridines 269
10.06.2.1.2 Pyranopyrroles 269
10.06.2.2 Semi-Empirical Methods **269**
10.06.2.2.1 Pyrrolopyridines 269
10.06.2.2.2 Thienopyridines 270
10.06.2.2.3 Pyranopyrroles 270
10.06.3 Experimental Structural Methods **270**
10.06.3.1 X-Ray, Neutron, and Electron Diffraction Methods **270**
10.06.3.1.1 Pyrrolopyridines 270
10.06.3.1.2 Furopyridines 271
10.06.3.1.3 Thienopyridines 272
10.06.3.1.4 Furopyrans 273
10.06.3.1.5 Thienothiopyrans 273
10.06.3.2 NMR Spectroscopy **273**
10.06.3.2.1 ^{1}H NMR spectroscopy 273
10.06.3.2.2 ^{13}C NMR spectroscopy 273
10.06.3.3 Mass Spectrometry **274**
10.06.3.3.1 Pyrrolopyridines 274
10.06.3.3.2 Thienopyridines 274
10.06.3.4 UV/Fluoresence Spectroscopy **274**
10.06.3.4.1 Pyrrolopyridines 274
10.06.3.4.2 Thienopyridines 275
10.06.3.5 Dipole Moments **275**
10.06.3.5.1 Pyrrolopyridines 275
10.06.3.5.2 Thienopyridines 276
10.06.4 Thermodynamic Aspects **276**
10.06.4.1 Physical Data **276**
10.06.4.2 Solubility and Chromatographic Behavior **277**
10.06.4.3 Tautomerism, Aromaticity, and Stability **277**

10.06.5 Reactivity of Fully Conjugated Rings 278
10.06.5.1 Electrophilic Attack at N 278
10.06.5.2 Electrophilic Attack at C 278
10.06.5.3 Nucleophilic Attack at C 280
10.06.5.4 Heterogeneous Catalyzed Reactions 282
10.06.5.5 Reduction Reactions 282
10.06.5.6 Cycloaddition Reactions 282
10.06.6 Reactivity of Nonconjugated Rings 282
10.06.6.1 Equilibrium and Nonequilibrium Isomers of Fully Conjugated Rings 282
10.06.6.1.1 Dihydro derivatives 282
10.06.6.1.2 Tetrahydro derivatives 283
10.06.6.1.3 Hexahydro derivatives 285
10.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms 285
10.06.8 Ring Syntheses from Acyclic Compounds 287
10.06.8.1 Pyrrolopyridines 287
10.06.8.2 Furopyridines 288
10.06.8.3 Thienopyridines 290
10.06.8.4 Furopyrans 293
10.06.8.5 Thienopyrans 295
10.06.8.6 Thienothiopyrans 295
10.06.8.7 Pyranopyrroles 296
10.06.9 Synthesis from Monocyclic Heterocycles 296
10.06.9.1 From the Five-Membered Ring 296
10.06.9.1.1 Pyrrolopyridines 296
10.06.9.1.2 Furopyridines 298
10.06.9.1.3 Thienopyridines 299
10.06.9.1.4 Furopyrans 301
10.06.9.1.5 Thienopyrans 303
10.06.9.1.6 Thienothiopyrans 304
10.06.9.2 From the Six-Membered Ring 305
10.06.9.2.1 Pyrrolopyridines 305
10.06.9.2.2 Furopyridines 309
10.06.9.2.3 Thienopyridines 313
10.06.9.2.4 Furopyrans 317
10.06.9.2.5 Thienopyrans 319
10.06.9.2.6 Pyranopyrroles 320
10.06.10 Ring Syntheses by Transformations of Another Ring 320
10.06.10.1 Pyrrolopyridines 320
10.06.10.2 Furopyridines 321
10.06.10.3 Furopyrans 322
10.06.10.4 Pyranopyrroles 322
10.06.11 Synthesis of Particular Classes of Compounds and Critical Comparison of Available Routes 323
10.06.12 Important Compounds and Applications 323
10.06.12.1 Pyrrolopyridines 323
10.06.12.2 Furopyridines 326
10.06.12.3 Thienopyridines 327
10.06.12.4 Furopyrans 329

10.06.12.5 Thienothiopyrans 330
10.06.13 Further Developments 330
10.06.13.1 Pyrrolopyridines 330
10.06.13.2 Furopyridines 330
10.06.13.3 Thienopyridines 331
10.06.13.4 Pyranopyrroles 331
10.06.13.5 Furopyrans 331
References 331

10.06.1 Introduction

This chapter covers bicyclic ring systems consisting of a five- and a six-membered ring with each ring containing one heteroatom that is not situated at a ring junction position. Nine heterocyclic systems are covered with ring systems containing nitrogen, oxygen, and sulfur heteroatoms. Partially and fully reduced derivatives of these compounds, as well as benzo derivatives, are also treated in the chapter.

10.06.1.1 Scope and General Reviews

This chapter covers nine bicyclic ring systems; however, little or no information is available in the chemical literature for some of them. Chemical literature from 1995 to 2006 is the focus of this chapter. Literature prior to 1995 has been extensively covered previously <1984CHEC(4)497, 1996CHEC-II(7)167>. Overall, the greatest emphasis in the literature, in terms of synthetic studies, reactivity, and applications, has been placed on bicyclic ring systems containing a six-membered pyridine ring – pyrrolopyridines, furopyridines, and thienopyridines.

Some general reviews have been written for bicyclic 5-6 ring systems. A review of the synthesis and reactivity of hydrogenated pyrrolopyridines gives special attention to the tetrahydro derivatives <2002S155>. Synthesis, properties, and reactivity of furopyridines have been reviewed <1997H(45)975>. The synthesis and reactivity of thienopyridines have been reviewed recently <2003PS929, 2005RCB864>. No major reviews were found for the other bicyclic 5-6 ring systems.

10.06.1.2 Isomeric Structures

10.06.1.2.1 Pyrrolopyridines

The pyrrolopyridine isomers, shown in **Figure 1**, represent the most widely studied compounds within the bicyclic 5-6 systems discussed here. Azaindole, a common name for these compounds, is found less frequently in the literature. Each ring of the pyrrolopyridines contains a nitrogen heteroatom. The most comprehensively studied isomers are compounds **1–6**. There have been scarce, if any, references to isomers **7–12** in the period under investigation.

10.06.1.2.2 Furopyridines

The furopyridine isomers, **13–18** (shown in **Figure 2**), contain a six-membered pyridine ring and an oxygen atom in the five-membered furan ring. Among these isomers, compounds **13–16** have been most widely studied.

10.06.1.2.3 Thienopyridines

Thienopyridines, compounds **19–24** in **Figure 3**, contain a nitrogen atom in a six-membered pyridine ring fused to a five-membered thiophene ring. As with furopyridines, most emphasis has been placed on isomers **19–22**, with little reported in the literature for isomers **23** and **24**.

10.06.1.2.4 Pyranopyrroles

Pyranopyrrole isomers, shown in **Figure 4**, consist of a six-membered pyran ring fused to a five-membered pyrrole ring. Pyranopyrrolium and furopyridinium ions are known, where the oxygen in the structure bears a positive charge; however, such ionic compounds are not the focus of this chapter.

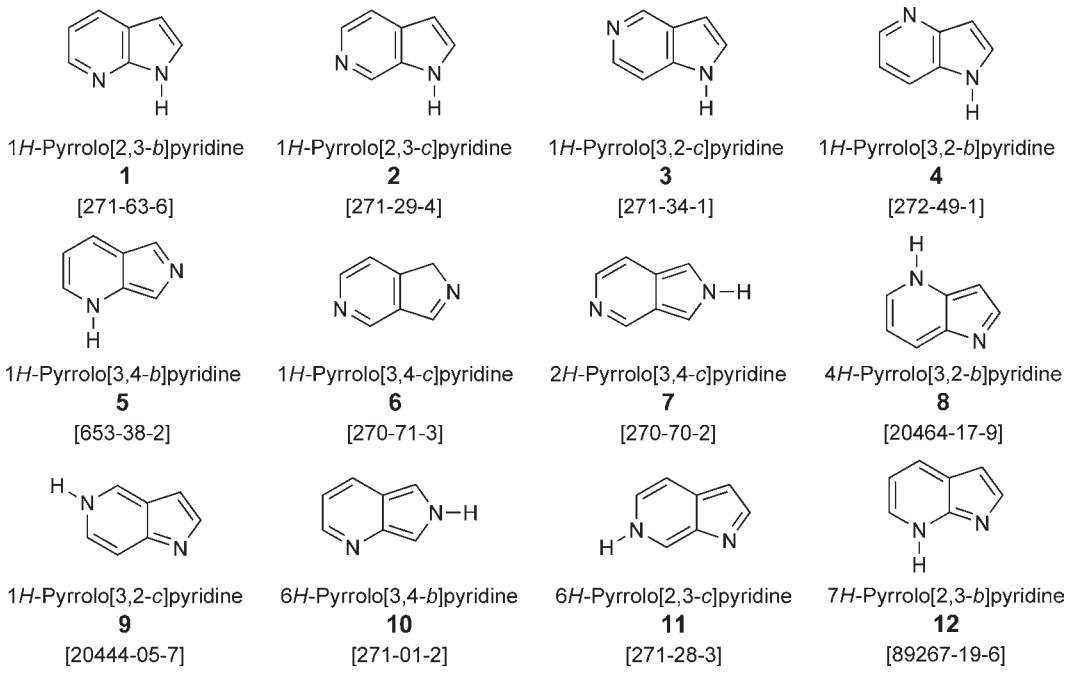


Figure 1 Pyrrolopyridine isomers.

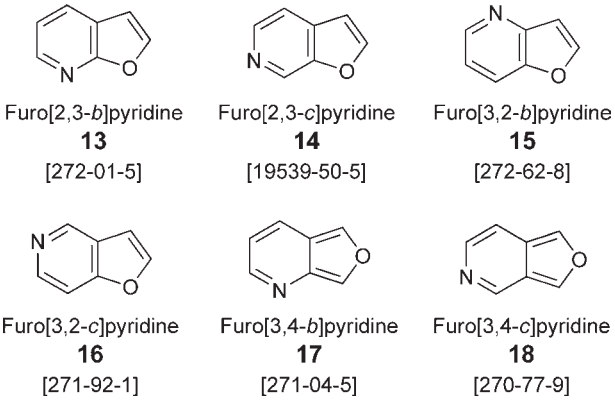


Figure 2 Furopyridine isomers.

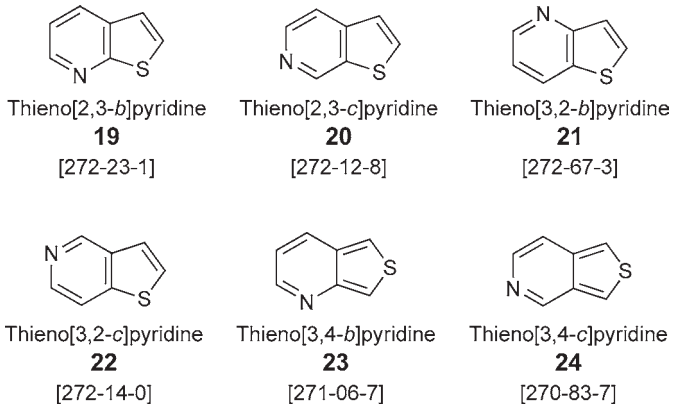


Figure 3 Thienopyridine isomers.

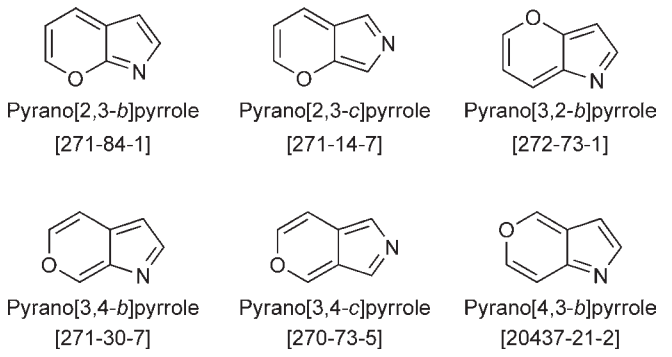


Figure 4 Pyranopyrrole isomers.

10.06.1.2.5 Thiopyranopyrroles

Thiopyranopyrrole isomers, shown in **Figure 5**, contain a six-membered thiopyran ring fused to a five-membered pyrrole ring. There are few references to these compounds in the recent chemical literature.

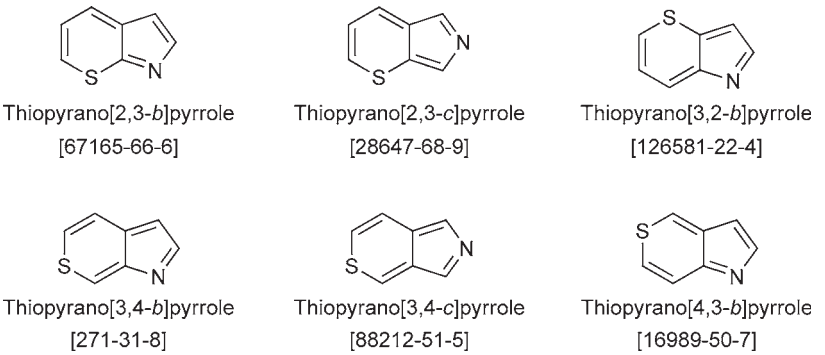


Figure 5 Thiopyranopyrrole isomers.

10.06.1.2.6 Furopyrans

Furopyrans consist of a six-membered pyran ring attached to a five-membered furan ring, as shown in **Figure 6**. Again, these isomers have not been extensively investigated in the chemical literature. A few charged furopyran compounds are known. For the ionic species, the oxygen in either ring can bear the positive charge.

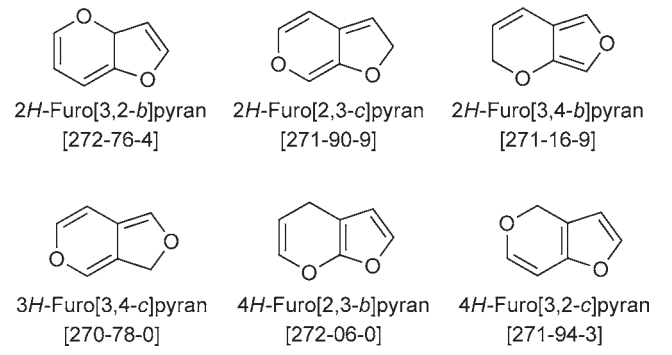


Figure 6 Furopyran isomers.

10.06.1.2.7 Thienopyrans

Figure 7 shows thienopyran isomers, which contain a six-membered pyran ring attached to a five-membered ring thiophene ring. Charged thienopyrylium isomers are known, with the oxygen in the furan ring always bearing the positive charge.

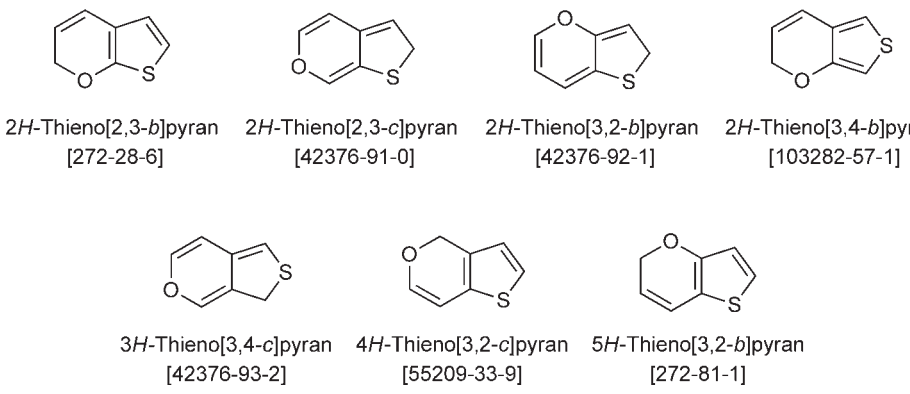


Figure 7 Thienopyran isomers.

10.06.1.2.8 Thiopyranofurans

Isomers of thiopyranofurans, shown in Figure 8, consist of a six-membered thiopyran ring fused to a five-membered furan ring. Again, the charged species always bear the positive charge on the oxygen atom.

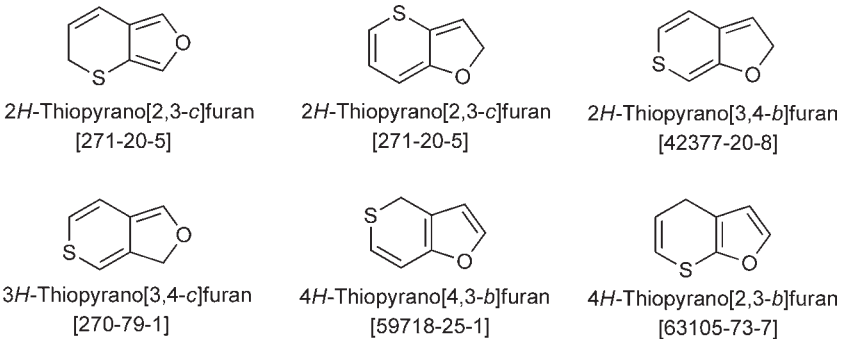


Figure 8 Thiopyranofuran isomers.

10.06.1.2.9 Thienothiopyrans

Figure 9 shows thienothiopyran isomers, containing a sulfur atom in each of the rings. The known charged species include those having positively charged sulfur in either ring.

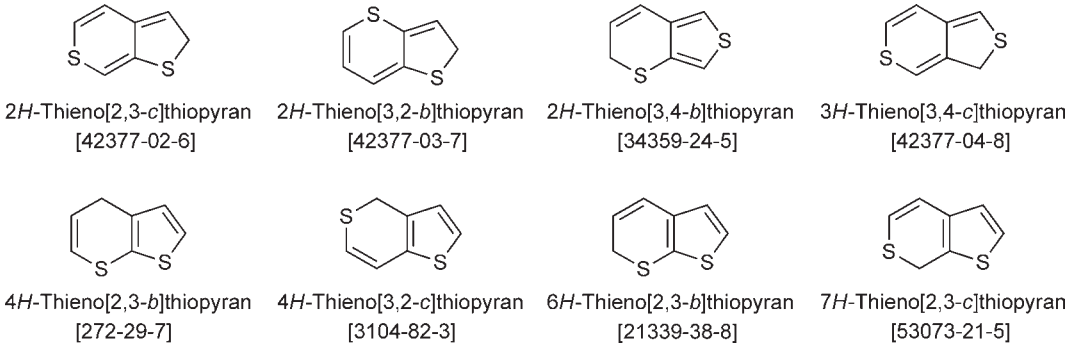


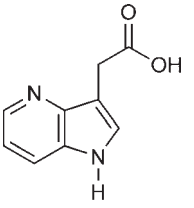
Figure 9 Thienothiopyran isomers.

10.06.2 Theoretical Methods

10.06.2.1 *Ab Initio* Methods

10.06.2.1.1 Pyrrolopyridines

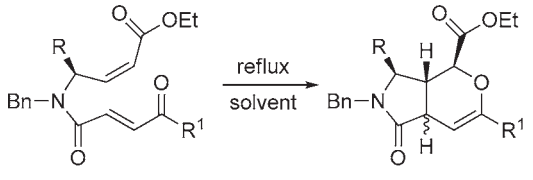
1-*H*-Pyrrolo[3,2-*b*]pyridin-3-yl acetic acid, **25**, has been the subject of RIIF/6-31G* calculations. The calculations suggest that this compound forms a kinetically stable conformer that possesses a strong intramolecular hydrogen bond which includes *anti*-orientation of the carboxyl group <2001SAA1951>.



25

10.06.2.1.2 Pyranopyrroles

Ab initio calculations of the Diels–Alder reaction leading to the formation of ethyl esters of hexahydropyrano[3,4-*c*]-pyrroles have been carried out. The calculations predicted the same reaction stereochemistry that was experimentally obtained – thermodynamically favored products resulted from an *exo*-cycloaddition reaction whereas *endo*-cycloaddition favored the kinetic products (Equation 1) <2003T8955>.



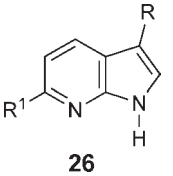
R	R^1	*Solvent*	*Ring fusion*	*Yield (%)*
Bn	Me	Benzene	*trans*	87
Bn	Me	Toluene	*cis*	91
Bn	Ph	Benzene	*trans*	78
Bn	Ph	Toluene	*cis*	85
i-Pr	Me	Benzene	*trans*	81
i-Pr	Me	Toluene	*cis*	87
$CH_2(CO_2Bn)$	Me	Benzene	*trans*	66
$CH_2(CO_2Bn)$	Me	Toluene	*cis*	72
Me	Ph	Benzene	*trans*	78
Me	Ph	Toluene	*cis*	82

(1)

10.06.2.2 Semi-Empirical Methods

10.06.2.2.1 Pyrrolopyridines

The ionization potentials of several monosubstituted pyrrolo[2,3-*b*]pyridines, **26**, have been calculated by the PM3 method. The values, shown in **Table 1**, range from 8.43 to 9.71 eV <1997JFA2345>.



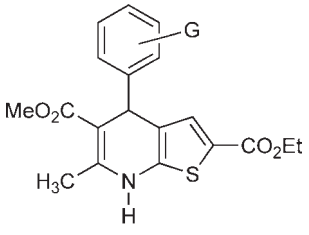
26

Table 1 Ionization potential and dipole moment data for compound **26** <1997JFA2345>

R	R^1	*Ionization potential* (*eV*)	*Dipole moment* (*D*)
H	H	8.76	1.35
H	Cl	8.59	0.97
H	Br	8.86	0.97
H	I	8.49	1.10
H	NO_2	9.71	5.14
H	NH_2	8.06	1.82
H	COMe	9.01	3.14
H	$CH{=}CH_2$	8.43	1.05
Cl	H	8.58	2.29
Br	H	8.98	2.67
I	H	8.78	2.21
NH_2	H	8.33	1.20
$C{\equiv}CH$	H	8.75	1.38
CN	H	9.14	5.06

10.06.2.2.2 Thienopyridines

Quantum-mechanical calculations using the AM1 method for a series of dihydrothieno[2,3-*b*]pyridines, **27**, have been carried out. The calculations suggest that the dihydropyridine ring is in a flattened boat conformation while there is planar geometry at the thieno portion of the molecule <1997JHC931>.



27

G = H, 2-Cl, 3-NO_2, 4-CO_2Me

10.06.2.2.3 Pyranopyrroles

Molecular modeling employing MM2 force field calculations has been carried out for inhibitors of mammalian ribonucleotide reductase based on peptide scaffolds. Calculations suggest that an octahydropyranopyrrole scaffold based on a cyclic heptapeptide inhibitor should be suitable <2005BML5146>. The pyrano[3,2-*b*]pyrrole framework can be found in natural products extracted from *Aspergillus niger*, a sponge-derived fungus. Quantum-mechanical calculations, including a molecular dynamics (MD) simulation using the MM3 force field and complete neglect of differential overlap/spectroscopic (CNDO/2S)-based circular dichroism (CD), have been used to assign absolute configurations to a few of the chiral molecules <2004JNP1532>.

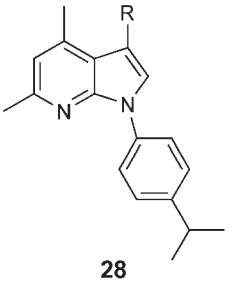
10.06.3 Experimental Structural Methods

10.06.3.1 X-Ray, Neutron, and Electron Diffraction Methods

10.06.3.1.1 Pyrrolopyridines

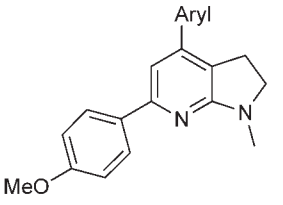
Several pyrrolopyridine derivatives, **28**, prepared for consideration as possible corticotropin-releasing hormone-1 receptor antagonists, have been studied by X-ray crystallography. The crystal structure of the pyrrolopyridine analogues compares closely to known antagonists, with excellent correlation to the calculated low-energy conformation <1999JME819>.

X-Ray crystal structures of aryl derivatives of pyrrolo[2,3-*b*]pyridines, **29**, confirm that steric interactions between the annelated ring and the electron-withdrawing substituent on the 4-position of the pyridine ring cause the pyridine ring to twist out of coplanarity <2006JOC3494>.



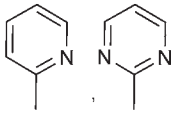
28

R = H, Ph

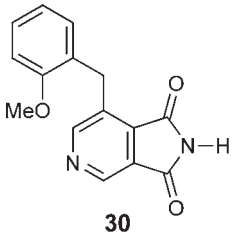


29

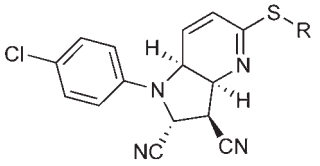
Aryl = 4-NCC$_6$H$_4$,



The structure of pyrrolo[3,4-*c*]pyridine dione derivative **30** has been determined by X-ray analysis <1998T3391>. X-Ray crystallographic analysis of reduced derivatives of pyrrolo[3,2-*b*]pyridines, **31**, confirms the *cis*-fusion of the pyridine and pyrrole rings <2003JOC5652>.



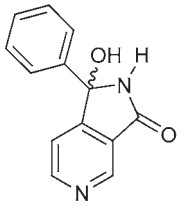
30



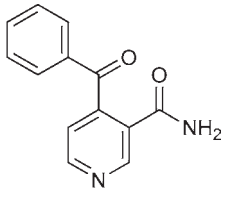
31

R = $CH_2C_6H_5$, 4-ClC_6H_4, 4-MeC_6H_4

The structure of compound **32** has been confirmed by X-ray and ^{13}C NMR analyses. These methods confirm that compound **32** exists as the cyclic hemiamidal rather than as the open intermediate **33** <2005OBC666>.



32

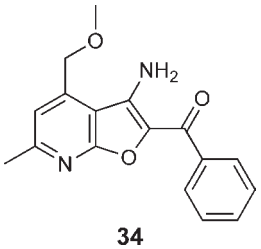


33

Pyrrolo[2,3-*b*]pyridine zinc(II) and *N*-(2-pyridyl)pyrrolo[2,3-*b*]pyridine zinc(II) compounds have been prepared and characterized by X-ray crystallography <2000IC5248>. The pyrrolo[2,3-*b*]pyridine zinc compound, formed from pyrrolo[2,3-*b*]pyridine and zinc acetate, is a stable compound that can produce a blue light in electroluminescent devices.

10.06.3.1.2 Furopyridines

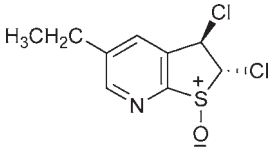
X-Ray crystallography has been used as a tool to study the structure of 3-amino-2-benzoyl-4-methoxymethyl-6-methylfuro[2,3-*b*]pyridine, **34** <2004CHE1442>. Four intramolecular contacts exist in the molecule, including an unusual intramolecular hydrogen bond involving a hydrogen atom bonded to an sp^2-hybridized carbon atom.



34

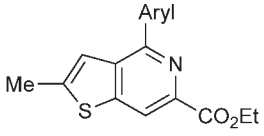
10.06.3.1.3 Thienopyridines

X-Ray crystallographic analysis of *trans*-2,3-dichloro-5-ethyl-2,3-dihydrothieno[2,3-*b*]pyridine-*syn*-1-oxide, **35**, indicates a planar pyridine ring along with a nonplanar dihydrothiophene ring tilted from the plane of the pyridine ring. ^{1}H nuclear magnetic resonance (NMR) analysis confirms the *trans*-geometry of the rings for this isomer, though additional X-ray studies are necessary for other isomers <1999JHC1077>.

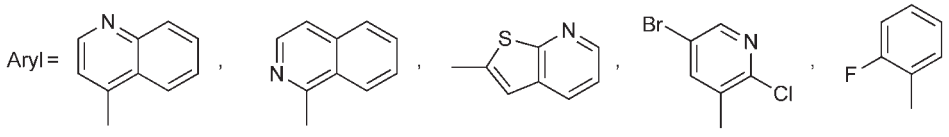


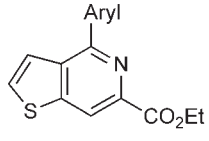
35

Using X-ray structures, 4-aryl derivatives of thienopyridines, **36** and **37**, have been studied by the PM3 method <1999SAA1035>. Energy minima were found when the torsion angle of the bond connecting the two aromatic ring systems was in the range of ±75° to ±90°.

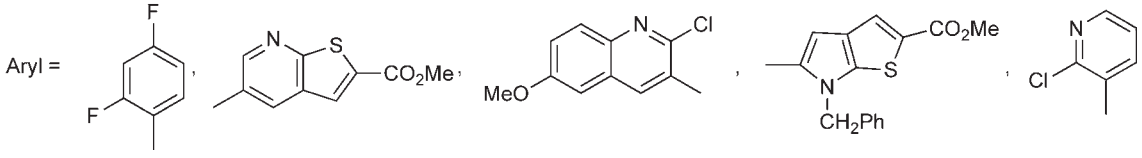


36

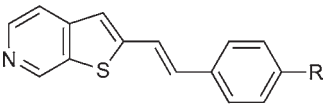




37



The X-ray crystal structure determinations of thieno[2,3-*c*]pyridine imines, **38**, have been carried out. When the imine contains weak donor and acceptor groups, as in the thioether derivative, the compound is twisted; however, the analogous bromo compound is planar <1998J(P2)437>.

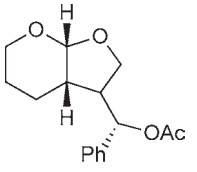


38

R = Br, SMe

10.06.3.1.4 Furopyrans

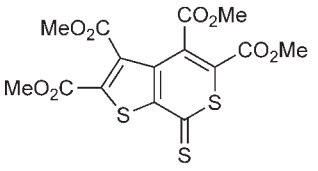
X-Ray analysis of hexahydrofuro[2,3-*b*]pyran derivative **39** shows that the tetrahydropyran ring assumes a chair conformation with the C(7a)–O(1) bond found in the axial position <1998T8753>. This conformation agrees with that obtained by analysis of the NMR spectrum of **39**.



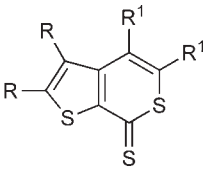
39

10.06.3.1.5 Thienothiopyrans

Several thieno[2,3-*c*]- and -[3,2-*c*]-thiopyranthione ester isomers, **40** and **41**, have been studied by X-ray analysis and their electronic spectra have been recorded <2005OL791>.



40



41

R, R^1 = CO_2Et, COPh

10.06.3.2 NMR Spectroscopy

Complete NMR spectral data, both ^1H and ^{13}C, are typically included with reports of the synthesis of the ring systems. This section is focused on NMR studies of these ring systems.

10.06.3.2.1 ^1H NMR spectroscopy

10.06.3.2.1(i) Thienopyridines

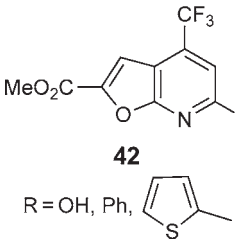
4-Aryl derivatives of thieno[3,2-*c*]pyridines, **36** and **37**, have been the subject of two-dimensional (2-D) NMR studies. Phase-sensitive nuclear Overhauser enhancement spectroscopy (NOESY) and correlation spectroscopy (COSY) experiments confirm the nonplanar conformation of the two aromatic ring systems <1999SAA1035>.

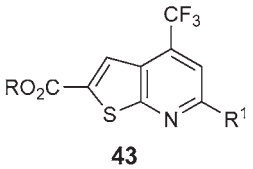
A library of trifluoromethyl-substituted thieno[2,3-*b*]pyridines has been established <2000JCO24>. Structures have been confirmed by a combination of ^1H NMR and IR spectral analysis as well as single crystal X-ray diffraction analysis.

10.06.3.2.2 ^{13}C NMR spectroscopy

10.06.3.2.2(i) Thienopyridines

Trifluoromethyl furo[2,3-*b*]pyridines, **42**, and –thieno[2,3-*b*]pyridines, **43**, have been studied by ^{13}C NMR spectroscopy. The 4-position of the CF_3 group on the ring is confirmed by both ^{13}C and ^{19}F NMR spectral methods <2003S1531>.





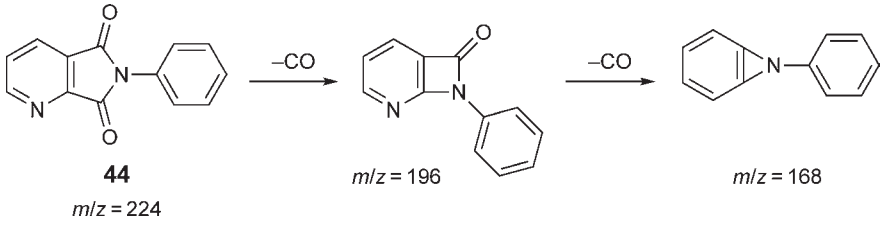
R	R^1	*Reference*
Me	Ph	2003S1531
Me	OH	2003S1531
Et	CF_3	2003S1531
Me		2003S1531

Compounds **36** and **37** have also been the subject of ^{13}C NMR studies to verify their structural conformation. All spectral data are in agreement with the X-ray crystallographic data <1999SAA1035>.

10.06.3.3 Mass Spectrometry

10.06.3.3.1 Pyrrolopyridines

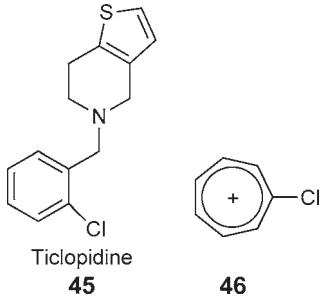
The mass spectrum of pyrrolopyridine **44**, prepared from the reaction of *N*-hydroxylquinolinimide with aryl amines at elevated temperatures (250 °C), shows interesting fragmentation patterns corresponding to the loss of CO (**Scheme 1**) <1998SC2871>.



Scheme 1

10.06.3.3.2 Thienopyridines

The metabolism of ticlopidine, **45**, has been investigated by mass spectral analysis. The principal metabolic pathways can be proposed based on supporting mass spectrometry (MS) fragmentation patterns. Chlorotropylium ion **46** ($m/z = 125$) is the base peak in the product ion mass spectrum of ticlopidine <2004MI49>.



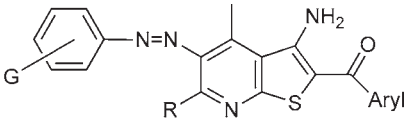
10.06.3.4 UV/Fluoresence Spectroscopy

10.06.3.4.1 Pyrrolopyridines

The ultraviolet (UV) spectra of pyrrolo[2,3-*b*]pyridine derivatives, **29**, have been recorded. The compounds absorb in the UV region between 360 and 392 nm, and they emit green fluorescent light between 466 and 469 nm <2006JOC3494>.

10.06.3.4.2 Thienopyridines

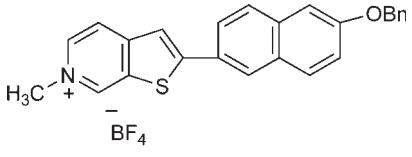
The UV–visible spectra have been recorded for a series of aryl-substituted thieno[2,3-*b*]pyridine derivatives, **47**. These compounds are of interest due to their characteristics for dyeing fabrics. Substituents on the azo aryl group have a significant effect on the absorption maxima that are recorded with maximum absorption found when substituents are electron-withdrawing groups (EWGs), such as a nitro group <2002MI365>.



47

R	*Aryl*	*G*	λ_{max} (*nm*)
CH_3	C_6H_5	4-Cl	348
CH_3	C_6H_5	3-NO_2	432
CH_3	C_6H_5	4-NO_2	431
CH_3	C_6H_5	4-OH	378
CH_3	C_6H_5	2-Cl-4-OH	380
CH_3	C_6H_5	2-Cl-4-NO_2	384
CH_3	C_6H_5	2-OH-3,5-diNO_2	268
CH_3	4-$CH_3C_6H_4$	4-Cl	388
CH_3	4-$CH_3C_6H_4$	3-NO_2	478
CH_3	4-$CH_3C_6H_4$	4-NO_2	476
CH_3	4-$CH_3C_6H_4$	4-OH	376
CH_3	4-$CH_3C_6H_4$	2-Cl-4-OH	387
CH_3	4-$CH_3C_6H_4$	2-Cl-4-NO_2	424
CH_3	4-$CH_3C_6H_4$	2-OH-3,5-diNO_2	428
C_6H_5	C_6H_5	4-NO_2	540
C_6H_5	C_6H_5	3-NO_2	542
C_6H_5	C_6H_5	2-Cl-4-OH	463
C_6H_5	C_6H_5	2-Cl-4-NO_2	484
C_6H_5	C_6H_5	2-OH-3,5-diNO_2	469
C_6H_5	4-$CH_3C_6H_4$	4-NO_2	568
C_6H_5	4-$CH_3C_6H_4$	3-NO_2	570
C_6H_5	4-$CH_3C_6H_4$	2-Cl-4- NO_2	525
C_6H_5	4-$CH_3C_6H_4$	2-Cl-4-OH	474
C_6H_5	4-$CH_3C_6H_4$	2-OH-3,5-diNO_2	463

Thieno[2,3-*c*]pyridinium salt **48** displays strong fluorescence, in agreement with a high β-value that was determined by PM3 calculations <1998J(P2)437>. UV spectroscopy of compounds **38**, **48**, and analogous thieno[2,3-*c*]- and thieno[3,4-*c*]-pyridine derivatives confirms that the thioether group serves as a superior electron donor <1996J(P2)1377>.



48

10.06.3.5 Dipole Moments

10.06.3.5.1 Pyrrolopyridines

Dipole moments for several mono- and disubstituted pyrrolo[2,3-*b*]pyridines, **26**, have been calculated using the PM3 method <1997JFA2345>. The values range from approximately 1 D for 3-halo-substituted compounds to 5.14 D for the 3-nitro derivative (see **Table 1**, Section 10.06.2.2).

10.06.3.5.2 Thienopyridines

Dipole moments that have been determined for a number of substituted dihydrothieno[2,3-*b*]pyridine derivatives, **27**, are listed in **Table 2**. The derivatives with the strongly electron withdrawing nitro group attached to the ring exhibit a higher dipole moment than derivatives containing less strongly electron withdrawing groups <1997JHC931>.

Table 2 Dipole moments of dihydrothieno[2,3-*b*]-pyridines, **27** <1997JHC931>

G	*Dipole moment* (*D*)
H	3.23
2-Cl	4.09
3-NO_2	7.69
4-CO_2Me	4.14

10.06.4 Thermodynamic Aspects

10.06.4.1 Physical Data

Parent compounds and most of the substituted derivatives of pyrrolopyridines, furopyridines, and thienopyridines are solids with melting points that range from approximately 60 to 250 °C. Detailed physical data are available for most of the compounds mentioned in this chapter. Melting point data for representative compounds for the three pyridine ring systems are given in **Tables 3–5**. Partially and fully reduced derivatives of pyrrolopyridines, furopyridines, and thienopyridines are often high boiling oils or gummy solids. Some physical data for reduced derivatives and for pyridinones are included in **Tables 3–5**.

Table 3 Melting point data for pyrrolo[2,3-*b*]pyridine derivatives

Compound	*Melting point* (°*C*)	*Reference*
3-Bromo-1-(4-methylphenylsulfonyl)pyrrolo[2,3-*b*]pyridine	133–134	1999S615
3-Bromo-1-(*t*-butyldimethylsilyl)pyrrolo[2,3-*b*]pyridine	80	1999S615
3-Chloropyrrolo[2,3-*b*]pyridine	169–170	1997JFA2345
3-(Thien-3-yl)pyrrolo[2,3-*b*]pyridine	165	1999S615
3-(4-Nitrophenyl)pyrrolo[2,3-*b*]pyridine	258–259	1999S615
6-Cyanopyrrolo[2,3-*b*]pyridine	175–177	1997JFA2345
6-Iodopyrrolo[2,3-*b*]pyridine	196–197	1997JFA2345
5-Benzoyl-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one	150–151	1997T5159
5-(1-Hydroxy-1-phenylmethyl)-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one	148–149	1997T5159
5-Vinyl-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one	164–165	1997T5159

Table 4 Melting point data for furopyridine derivatives

Compound	*Melting point range* (°*C*)	*Reference*
2,3-Dibromofuro[2,3-*b*]pyridine	85–87	1998JHC1249
3-Bromo-2-nitrofuro[2,3-*b*]pyridine	140–141.5	1998JHC1249
3-Bromo-6-cyanofuro[2,3-*b*]pyridine	203–205	1998JHC1249
5-Formylfuro[2,3-*b*]pyridine	105–110	1998JHC1305
Furo[2,3-*b*]pyridine-2-carboxamide	221–224	1998JHC1305
6-Cyano-2-methylfuro[2,3-*b*]pyridine	126–130	1998JHC1237
3-Bromo-2-nitrofuro[2,3-*c*]pyridine	94–97	1998JHC1249
3-Bromo-7-cyano[2,3-*c*]pyridine	177–179	1998JHC1249

(*Continued*)

Table 4 (Continued)

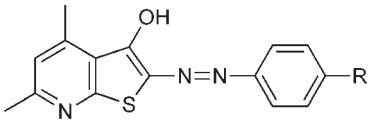
Compound	*Melting point range (°C)*	*Reference*
5-(1-Hydroxyethyl)-3-methylfuro[2,3-*c*]pyridine	56–58	1998JOC7851
2,3-Dibromofuro[3,2-*b*]pyridine	63–65	1998JHC1249
3-Bromo-2-nitrofuro[3,2-*b*]pyridine	166–169	1998JHC1249
3-Bromo-5-cyanofuro[3,2-*b*]pyridine	182–184	1998JHC1249
2-Methylfuro[3,2-*c*]pyridine 5-oxide	178–180	1999CCC539
2,3-Dimethylfuro[3,2-*c*]pyridine 5-oxide	222–225	1999CCC539
3-Bromo-2-nitrofuro[3,2-*c*]pyridine	93–95	1998JHC1249
Furo[3,2-*c*]pyridine-4-carboximidamide	80–82	1999CCC539
3-Bromo-4-chlorofuro[3,2-*c*]pyridine	139–141	1998JHC1249
trans-2,3-Diacetyl-2-methyl-2,3-dihydrofuro[2,3-*b*]pyridine	137–142	1998EJM33

Table 5 Melting point data for thienopyridine derivatives

Compound	*Melting point range (°C)*	*Reference*
3-Amino-2-(4-nitrophenyl)-6-methyl-4-methoxymethylthieno[2,3-*b*]pyridine	204–205	2000MOL1085
2-Anilino-3-cyanothieno[3,2-*c*]pyridine	247.5–248	1998S1095
Methyl-2-chloro-4,7-dihydro-4-oxo-7-phenylthieno-[2,3-*b*]pyridine-5-carboxylate	200–201	1998EJM33

10.06.4.2 Solubility and Chromatographic Behavior

Solvent effects for a series of thienopyridine derivatives, **49**, have been studied. In organic solvent/water mixtures, the pK_a values, ranging from 8.75 to 10.44, are found to be dependent on both the amount and the type of organic solvent (dimethylformamide (DMF), methanol, ethanol, and acetone) used in the mixture, with pK_a values increasing as the organic co-solvent concentration increases <2003CED1495>.



49

R = H, Me, SO_3H, NO_2

Since most of the bicyclic compounds and their derivatives considered here are solids, they are commonly purified by recrystallization. Methanol and ethanol are frequently chosen as recrystallization solvent.

10.06.4.3 Tautomerism, Aromaticity, and Stability

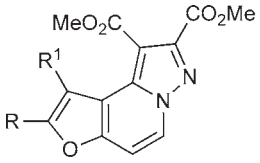
In pyrrolopyridine synthesis reactions, nitropyridines are less reactive than the corresponding nitropyridone derivatives due to the decreased aromaticity of the pyridone ring. The pyridone is more attractive for nucleophilic attack in the reaction <2002H(58)301> (see Section 10.06.5.3).

For ring systems that incorporate a pyridine ring, chemistry and reactivity of pyridone derivatives have been incorporated into Sections 10.06.5–10.06.9, wherever appropriate. For crystalline products, which represent most of the derivatives contained within this chapter, the compounds exist as the pyridone tautomer.

10.06.5 Reactivity of Fully Conjugated Rings

10.06.5.1 Electrophilic Attack at N

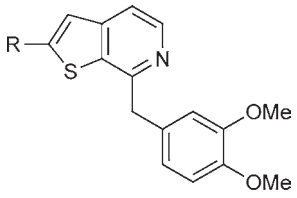
5-Aminofuro[3,2-*c*]pyridinium tosylates can be prepared from furopyridines by treatment with *O*-(4-methylbenzenesulfonyl)hydroxylamine. Treatment of the tosylate salt with base, such as potassium carbonate, leads to a pyridinium *N*-imide, **50**. Compound **50** readily undergoes 1,3-dipolar cycloaddition reactions <1999CCC539>.



50

R	R^1
H	H
Me	H
Me	Me

Thieno[2,3-*c*]pyridine derivatives, **51**, undergo methylation at the ring nitrogen with methyl iodide; however, the thieno[2,3-*c*]pyridinium salts that are produced are very labile and they are readily reduced by $NaBH_4$. Additional reaction with methyl iodide leads to quaternary ammmonium salts <2005JME4972>.



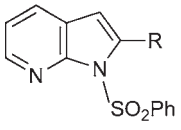
51

R = H, Me

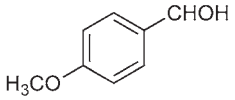
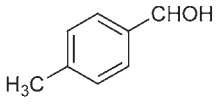
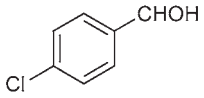
10.06.5.2 Electrophilic Attack at C

Two routes to the electrophilic fluorination of pyrrolo[2,3-*b*]pyridine *N*-oxide lead to the 4-fluoro derivative. The Balz–Schiemann reaction route, via a diazonium tetrafluoroborate salt, or a lithium/halogen-exchange reaction followed by quenching with an electrophilic fluorine source, generates the 4-fluoro product in moderate yields <2003OL5023>.

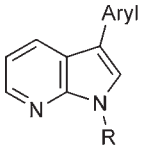
2-Substituted pyrrolo[2,3-*b*]pyridines, **52**, can be prepared in moderate to good yields by treatment of 2-lithiopyrrolo[2,3-*b*]pyridine with electrophilic reagents such as methyl iodide, carbon dioxide, or 4-substituted benzaldehydes <1997T3637>. The 2-lithio derivative is generated from pyrrolo[2,3-*b*]pyridine after placing a removable metalation directing group, such as phenylsulfonyl, in the 1-position of the ring.



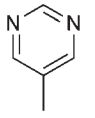
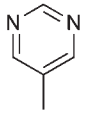
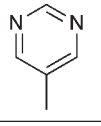
52

R	*Yield* (%)
Me	94
CO_2H	60
	62
	50
	62

3-Trimethylstannylpyrrolo[2,3-*b*]pyridines, **53**, containing an N-protecting group such as *t*-butyldimethylsilyl (TBDMS), undergo coupling reactions with a variety of aryl or heteroaryl halides to afford 3-substituted aryl- or heteroaryl-pyrrolo[2,3-*b*]pyridines in moderate yields <1999S615>.



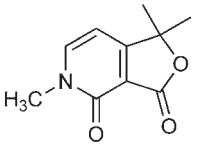
53

R	*Aryl*	*Yield (%)*
TBDMS		45
MEM		45
Ts		42
TBDMS		74
MEM		50
Ts		60

Pyrrolo[3,2-*c*]pyridine can be readily substituted with a variety of electrophiles at C-2 or C-3 after protection of the ring nitrogen atom. Derivatives can be synthesized with substituents such as iodo, methyl, trimethyltin, formyl, and allyl groups. The reactions proceed with excellent yields (47–95%) <2005S3581>.

Electrophilic substitution reactions of monosubstituted furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]-, and -[3,2-*c*]-pyridines show that the type (electron-withdrawing group (EWG) or electron-donating group (EDG)) and position of the first substituent have a significant effect on the success of the reaction. For example, bromination of 2-methyl derivatives proceeds smoothly to give 3-bromo-2-methylfuropyridines in moderate yields whereas the reaction is unsuccessful for the 2-cyano derivative. A variety of reaction conditions have been explored, including conversion to the *N*-oxide, to optimize both electrophilic and nucleophilic reactions of the furopyridines <1998JHC1249, 1998JHC1237, 1999JHC1>.

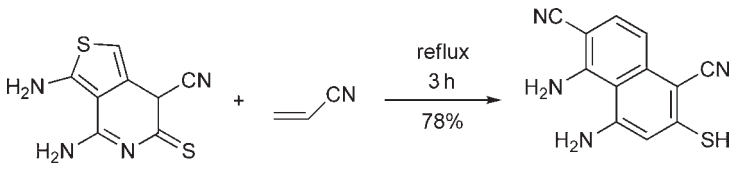
Disilylation of furo[3,4-*c*]pyridine followed by dialkylation leads to the formation of α-disubstituted derivatives in good yields (61–70%). This methodology provides a key step in the synthesis of the pyridone alkaloid cerpegin, **54** <2004OL2925>.



Cerpegin

54

Thieno[3,4-*c*]pyridines undergo an addition reaction with acrylonitrile followed by elimination of hydrogen sulfide to afford a mercaptoisoquinoline product (Equation 2) <2002CHE1342>.

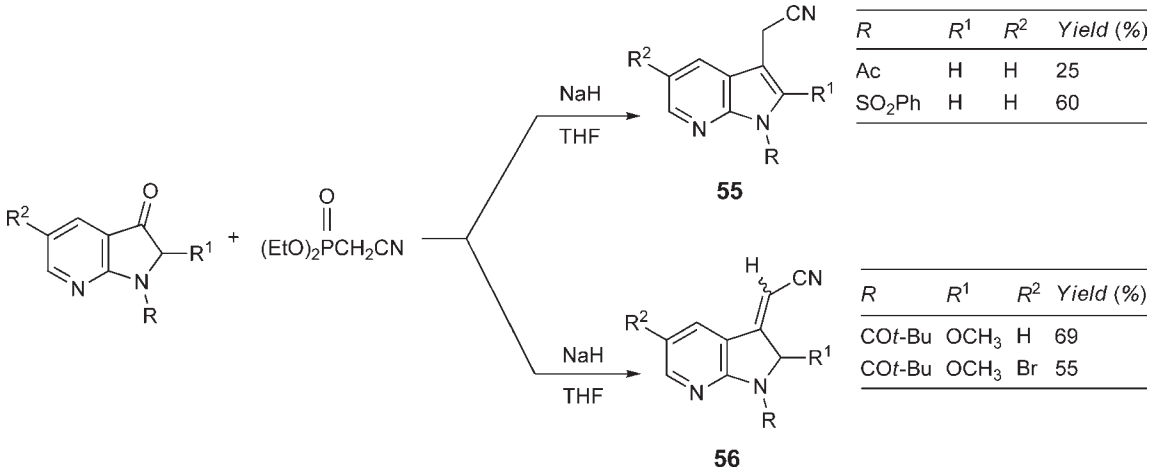


(2)

10.06.5.3 Nucleophilic Attack at C

Pyrrolo[2,3-*b*]- and -[3,2-*c*]-pyridines can be substituted at the 2-position of N-protected rings via a palladium-catalyzed reaction ($Pd(OAc)_2$) using lithium chloride and sodium acetate in DMF <2000TL919>. This reaction, which proceeds in moderate to good yields (60–92%), is especially useful for preparing 2-aryl- or 2-heteroaryl-substituted pyrrolopyridines.

Pyrrolo[2,3-*b*]pyridinones react with diethyl cyanomethanylphosphonate to give two different products, depending on the substitution pattern of the starting material. For compounds without substituents in the 2-position, pyrrolo[2,3-*b*]-pyridinyl acetonitriles, **55**, are produced. When the nitrogen atom is protected with a pivaloyl group, alkenyl nitriles, **56**, are formed (**Scheme 2**) <2001T1995>.



R	R^1	R^2	*Yield (%)*
Ac	H	H	25
SO_2Ph	H	H	60

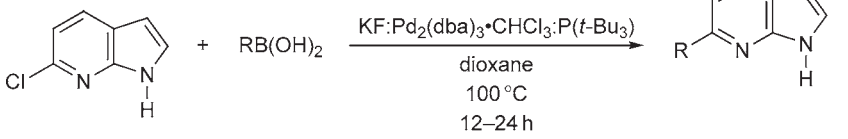
R	R^1	R^2	*Yield (%)*
CO*t*-Bu	OCH_3	H	69
CO*t*-Bu	OCH_3	Br	55

Scheme 2

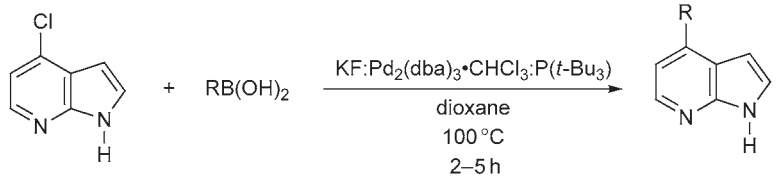
The 4- and 6-positions of pyrrolo[2,3-*b*]pyridines can be substituted via palladium-catalyzed cross-coupling reactions with the 4- or 6-halo-substituted derivatives (**Scheme 3**) <2001SL609>. Nucleophilic displacement of the 4-substituent of 6-chloro-4-nitro- and 4,6-dichloro-pyrrolo[2,3-*b*]pyridines takes place with phenols. Protection of the pyrrole nitrogen with a β-trimethylsilylethoxymethyl (SEM) group affords good yields of the aryl ethers (Equation 3) <2006TL2069>.

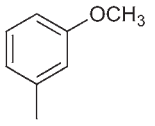
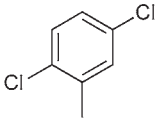
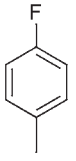
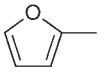
Furo[3,4-*b*]pyridine diones undergo condensation reactions with a variety of active methylene compounds such as 3-thiophenacetonitrile, creatinine, and pyrazolone to afford 7-substituted furo[3,4-*b*]pyridinones in excellent yields (70–88%) <1999SC3773>.

Thienopyridines are reported to undergo a variety of condensation reactions with reagents such as arylidene-malononitrile and ethyl ethoxymethylenecyanoacetate <2003PS2639>. Palladium-catalyzed cross-coupling reactions can be used to carry out the reaction of 7-chloro-2-iodothieno[3,2-*b*]pyridine with *N*-methyl-5-tributylstannylimidazole to afford [2-(3-methyl-3*H*-imidazol-4-yl)thieno[3,2-*b*]pyridin-7-yl]-(2-methyl-1*H*-indol-5-yl)amine, **57**. A variety of cross-coupling methods have been investigated, and a Stille coupling and Negishi cross-coupling reaction were both found to be effective <2003OPD676>.

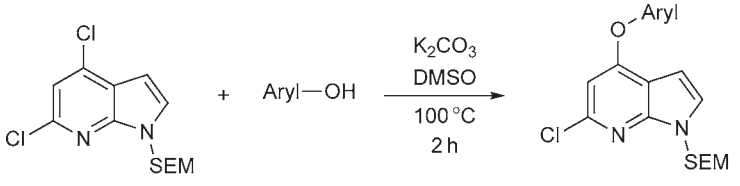


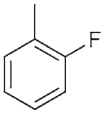
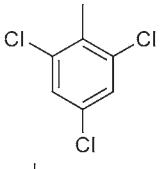
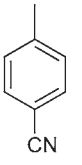
R	*Yield (%)*
Ph	76
	40



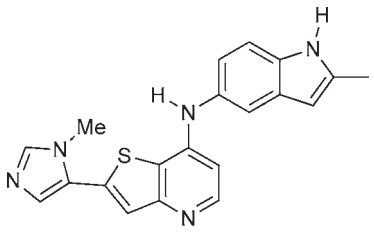
R	*Yield (%)*
Ph	85
	94
	63
	87
	47

Scheme 3



Aryl	*Yield (%)*
	91
	63
	49

(3)



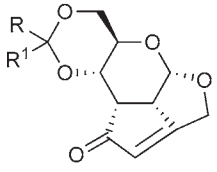
57

10.06.5.4 Heterogeneous Catalyzed Reactions

The cyano group in the side chain of pyrrolo[2,3-*b*]pyridine derivative **55** (**Scheme 2**) undergoes catalytic hydrogenation with Adams' catalyst (PtO_2) at atmospheric pressure to generate the primary amine <2001T1995>. Use of Raney nickel catalyst in this reaction has been reported to give desulfonylated nitrile as the product <1956JA1247>.

10.06.5.5 Reduction Reactions

The diisobutylaluminium hydride (DIBAL-H) reduction of perhydrofuro[2,3-*b*]pyran derivatives, **58**, is a novel entry to highly functionalized cyclopentanes containing high enantiomeric purity. The reduction targets the acetal group of the furo[2,3-*b*]pyran framework <2001CAR63>.

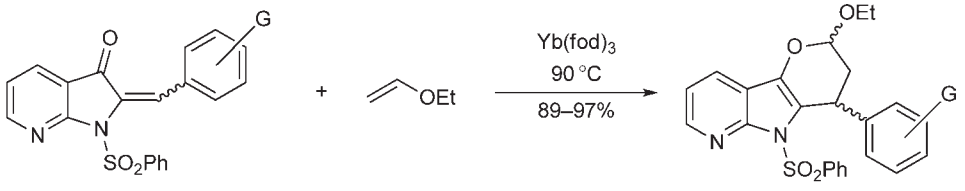


R	R^1
Me	Me
Ph	H

58

10.06.5.6 Cycloaddition Reactions

Pyrrolo[2,3-*b*]pyridinones, **59**, undergo an inverse electron demand Diels–Alder reaction with ethyl vinyl ether to generate 6-aza-*δ*-carboline products in excellent yields but low stereoselectivity (Equation 4) <1997S73>.



59

G = 4-MeO, 4-Cl, 4-NO_2, 4-Me, H, 2-CO_2Me

(4)

Cycloaddition reactions of alkynes and furo[3,2-*c*]pyridinium *N*-imides lead to furo[3,2-c]pyrazolo[1,5-*a*]pyridines, **50**, in low yields <1999CCC539>.

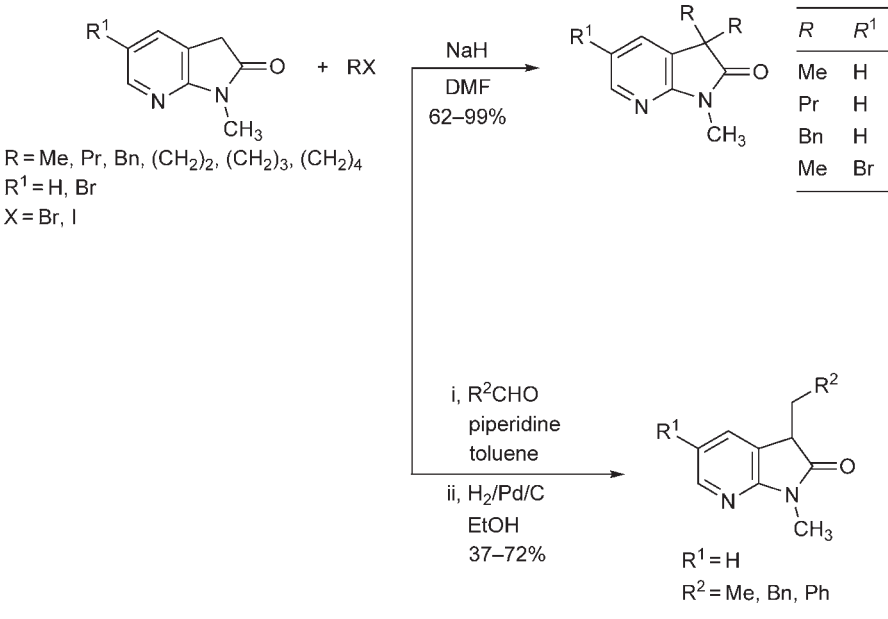
10.06.6 Reactivity of Nonconjugated Rings

10.06.6.1 Equilibrium and Nonequilibrium Isomers of Fully Conjugated Rings

10.06.6.1.1 Dihydro derivatives

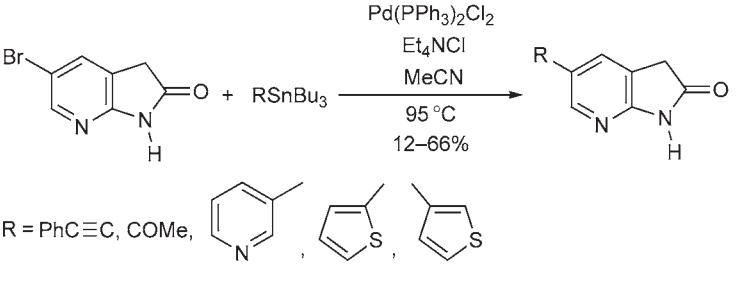
Dihydropyrrolo[2,3-*b*]pyridinones undergo alkylation reactions to give 3-disubstituted derivatives in excellent yields (**Scheme 4**) <1997SC3861>. To obtain the 3-monosubstituted derivatives, an alternate methodology has been

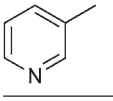
successful. Dihydropyrrolo[2,3-*b*]pyridinones can be substituted in the 5-position of the ring via palladium-catalyzed Stille coupling reactions (Equation 5) <2001H(55)1583>. Similar reactions can be carried out using Suzuki coupling and carbonylation reaction conditions.



R	R^1	*Yield (%)*	*Reference*
Me	H	81	1997SC3861
Pr	H	83	1997SC3861
Bn	H	92	1997SC3861
Me	Br	62	1997SC3861

Scheme 4



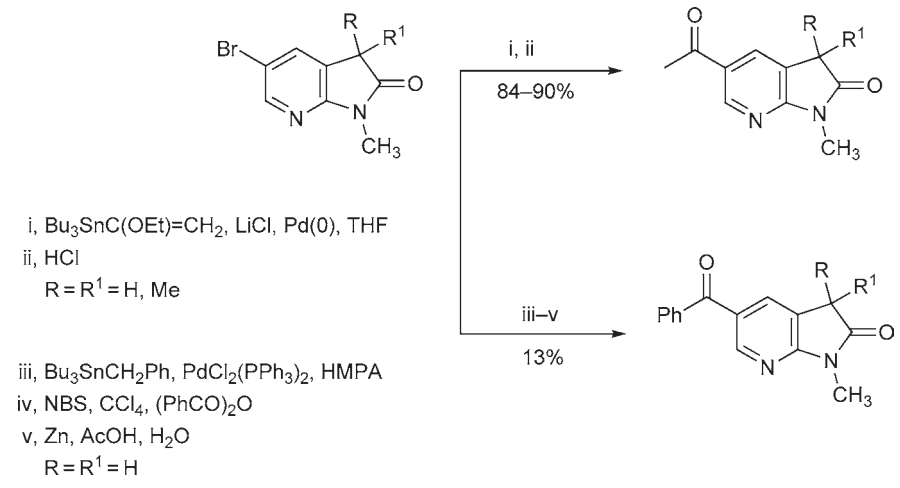
R	*Yield (%)*	*Reference*
COMe	25	2001H(55)1583
PhC≡C—	66	2001H(55)1583
	23	2001H(55)1583

(5)

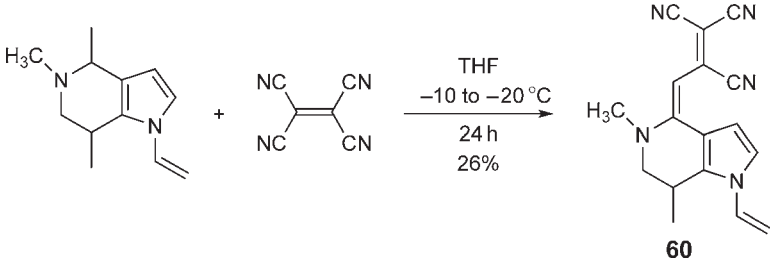
Acetyl or benzoyl groups can be introduced into the 5-position of dihydropyrrolo[2,3-*b*]pyridinones via a palladium-catalyzed reaction. The acetylation proceeds in much higher yields than the benzoylation reaction (**Scheme 5**) <1997T5159>.

10.06.6.1.2 Tetrahydro derivatives

A tetrahydropyrrolo[3,2-*c*]pyridine reacts with tetracyanoethylene to give compound **60** instead of the expected cyclobutane product found in the analogous 1-vinylpyrrole reaction (Equation 6). The ^{1}H NMR spectrum of **60** is consistent with the structure which was verified by X-ray crystallography <2001CHE1048>.

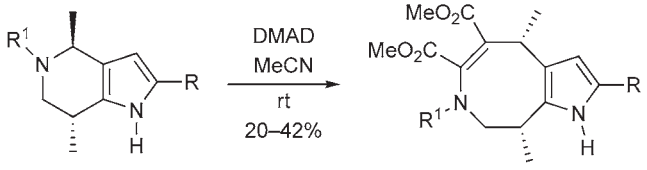


Scheme 5



60 (6)

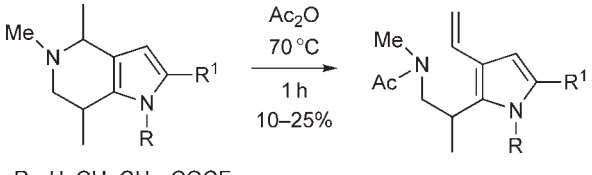
Tetrahydropyrrolo[3,2-*c*]pyridines undergo a ring-expansion reaction upon reaction with dimethyl acetylenedicarboxylate (DMAD) under mild conditions to generate tetrahydropyrrolo[2,3-*d*]azocines in low to moderate yields (Equation 7) <2002TL6767>. This synthesis represents a route to previously unreported azocines. Tetrahydropyrrolo[3,2-*c*]pyridines undergo ring opening to produce 3-vinylpyrroles upon treatment with acetic anhydride (Equation 8) <2002MC1>. Piperidine ring cleavage is also known to occur when tetrahydropyrrolo-[3,2-*c*]pyridines are treated with DMAD, generating moderate to good yields of α- and β-vinylpyrroles <2001HCO461>.



R = CHO, $COCF_3$, $=CH=C(CN)_2$
R^1 = Me, Bn

R	R^1	*Yield (%)*
$=CH=C(CN)_2$	Me	20
$COCF_3$	Me	28
$COCF_3$	Bn	42

(7)

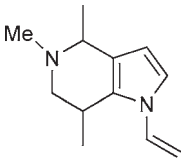


R = H, $CH=CH_2$, $COCF_3$
R^1 = H, CHO, $COCF_3$, CH=NOH, CN

R	R^1	*Yield (%)*
H	H	16
H	CHO	25
$CH=CH_2$	CN	10

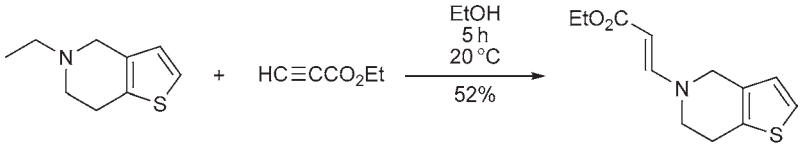
(8)

Tetrahydropyrrolo[3,2-*c*]pyridines, **61**, undergo trifluoroacetylation and aminomethylation reactions at the α-position of the pyrrole <2004CHE1477>. The reactions occur in moderate to good yields (45–80%).



61

Tetrahydrothieno[3,2-*c*]pyridine undergoes an unusual reaction with ethyl propiolate to afford compound **62** instead of the expected ring opening to give a thiophene product (Equation 9) <2004CHE519>.

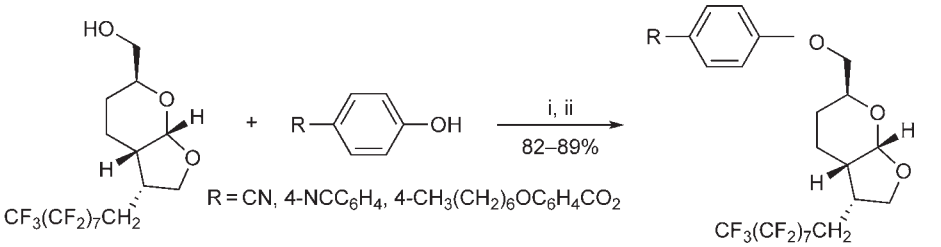


62

(9)

10.06.6.1.3 Hexahydro derivatives

Hexahydrofuro[2,3-*b*]pyran derivatives react with phenols to produce ether and ester derivatives in excellent yields (Equation 10) <1999EJO2429>. Several of these compounds exhibit liquid crystalline properties.

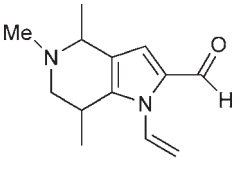


i, DEAD, PPh_2, −15 °C to rt, toluene
ii, pyridine, 0 °C to rt, CH_2Cl_2

(10)

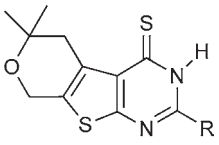
10.06.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Compound **63**, the 2-formyl derivative of compound **61**, undergoes a series of side-chain reactions at the carbonyl group including reduction with sodium borohydride and condensation reactions with hydroxylamine or malononitrile. The reactions afford the appropriately 2-substituted products in excellent yields <2004CHE1477>.



63

2-Amino-3-cyanothienopyrans undergo acylation reactions followed by treatment with hydrogen sulfide in a triethylamine/pyridine mixture to generate 2-substituted-4-thioxopyrano[4′,3′:4,5]thieno[2,3-*d*]pyrimidines, **64** <2005CHE235>. The cyclization reaction proceeds in high yields (80–83%).

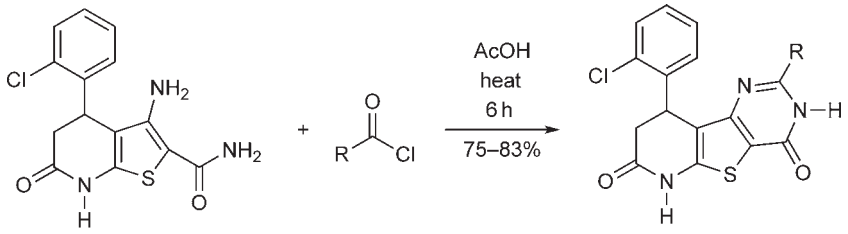


64

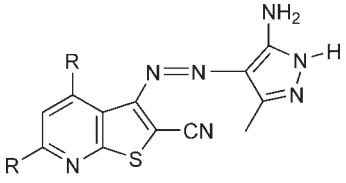
R = Et, Bu, CH_2Ph

A Sandmeyer reaction can be used to convert 5-aminofuro[2,3-*b*]pyridine derivatives to a variety of carbon substituents at the 5-position including cyano, acetyl, and formyl <1998JHC1305>.

Thienopyridine derivatives substituted with 3-amino and 2-carbamoyl groups undergo acylation followed by cyclization reactions to generate hexahydropyrido[3′2′:4,5]thieno[3,2-*d*]pyrimidines in good yields (Equation 11) <2003CHE110>. If a cyclic ketone is used in place of an acyl chloride, spiro derivatives are formed. 3-Aminothieno[2,3-*b*]pyridines can be converted into 3-(1-pyrrolyl)thieno[2,3-*b*]pyridines upon treatment with 2,5-dimethoxytetrahydrofuran <2003CHE400>. The reaction takes place with excellent yields (86–93%). 3-Amino-4,6-disubstituted thieno[2,3-*b*]-pyridines have been diazotized and further reacted to generate pyrazolylthieno[2,3-*b*]pyridines, **65**. Compound **65** can be used to synthesize pyrazolopyrimidinylthieno[2,3-*b*]pyridines, **66**, which have applications as synthetic dyes <2005DP(64)223>.

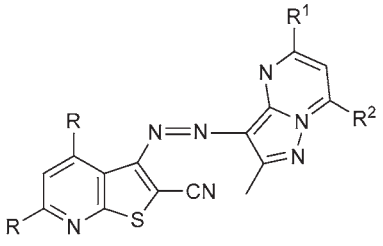


R = H, Me, CH_2Cl (11)



R = Me, Ph

65



66

R = Me, Ph

R^1 = Me, CF_3

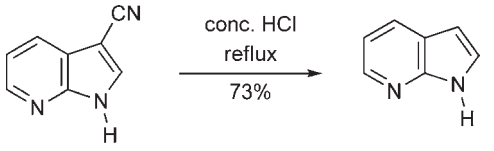
R^2 = Ph,

R	R^1	R^2
Me	Me	Ph
Me	CF_3	Ph
Ph	Me	Ph
Ph	CF_3	

10.06.8 Ring Syntheses from Acyclic Compounds

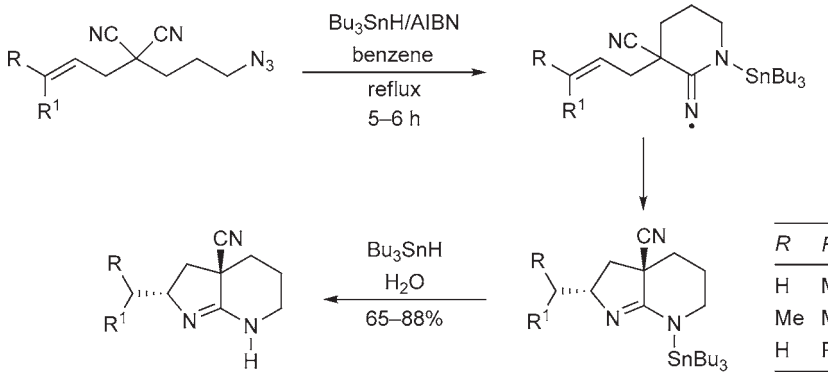
10.06.8.1 Pyrrolopyridines

A practical synthesis of pyrrolo[2,3-*b*]pyridine from succinonitrile and ethyl formate has been reported <2003OPD209>. The multistep synthesis proceeds via a substituted cyanopyrrole intermediate to give 3-cyanopyrrolo[2,3-*b*]pyridine, **67**. As shown in Equation (12), **67** can be quantitatively converted into the unsubstituted compound, **1**, by heating at reflux in concentrated acid.



67 **1** (12)

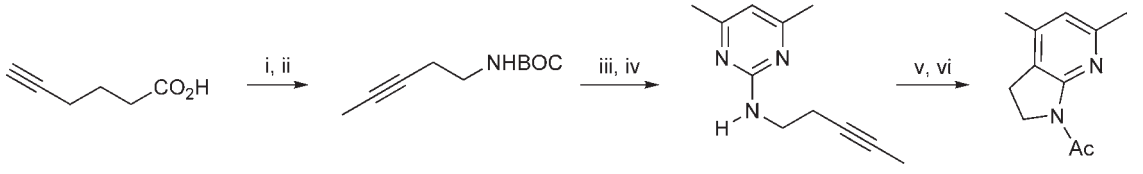
Cyclization reactions of azidopropylmalononitriles occur in *exo*-fashion under radical conditions with Bu_3SnH/2,2′-azobisisobutyronitrile (AIBN) leading to the formation of reduced pyrrolopyridines (**Scheme 6**) <2004OL417>. The reaction intermediates, nucleophilic *N*-stannylamidinyl radicals, undergo cyclization onto an alkene functional group also present in the molecule.



R	R^1	*Yield (%)*	*Reference*
H	Me	65	2004OL417
Me	Me	88	2004OL417
H	Ph	88	2004OL417

Scheme 6

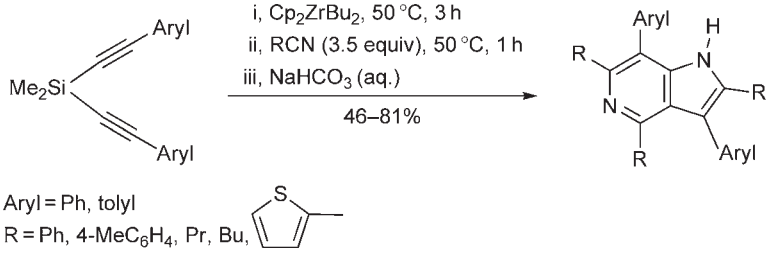
Partially hydrogenated pyrrolopyridines have been prepared through a sequence that includes an alkynyl-substituted pyrimidine ring. An initial intramolecular inverse electron demand Diels–Alder reaction is followed by a cycloreversion to form a dihydropyrrolopyridine. The pyrimidine ring is generated in four steps starting with an alkynyl carboxylic acid (**Scheme 7**) <2004JOC9215>.



i, KOH, reflux, 4 h , 80%
ii, Ph_3PON_3, Et_3N, *t*-BuOH, reflux, 79%
iii, HCl, ether, 70%
iv, 4,6-dimethylpyrimidinyl triflate, Et_3N, DMF, 1 d, 93%
v, Ac_2O, DMAP, 100 °C, 20 h, 91%
vi, Ph_2O, 1 d, reflux, 82%

Scheme 7

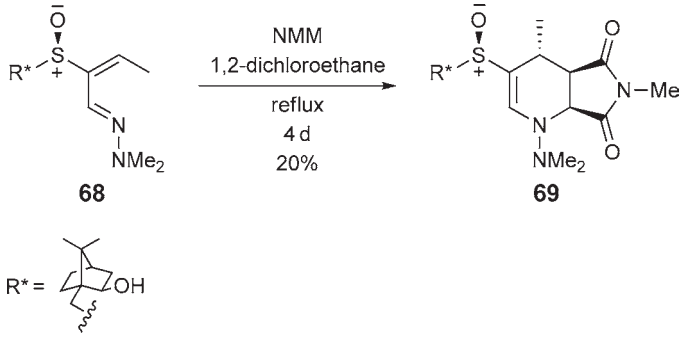
An intermolecular coupling reaction between three organonitrile molecules and a silicon-tethered diyne is reported to give good yields of pyrrolo[3,2-*c*]pyridine derivatives <2004JA7172>. The reaction is promoted by a low-valent zirconocene species (Equation 13).



Aryl	*R*	*Yield* (%)
Ph	Ph	70
Ph	Bu	64
Tolyl	Pr	67

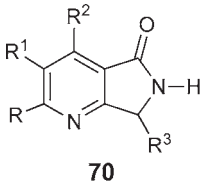
(13)

Sulfinyl hydrazones, such as **68**, reacting as 1-azabuta-1,3-dienes, undergo cycloaddition reactions with *N*-methylmaleimide (NMM), to form tetrahydropyrrolo[3,4-*b*]pyridine derivatives in low yield. The reaction occurs to form enantiomerically pure adduct **69** with complete *endo*- and facial selectivities (Equation 14) <2003S2241>.



(14)

A novel solid-phase synthesis of pyrrolo[3,4-*b*]pyridines using a sequence of Knoevenagel and Hantzsch condensation reactions has been reported <1999S1951>. The reactions lead to a variety of highly substituted pyrrolo[3,4-*b*]pyridines, **70**.



70

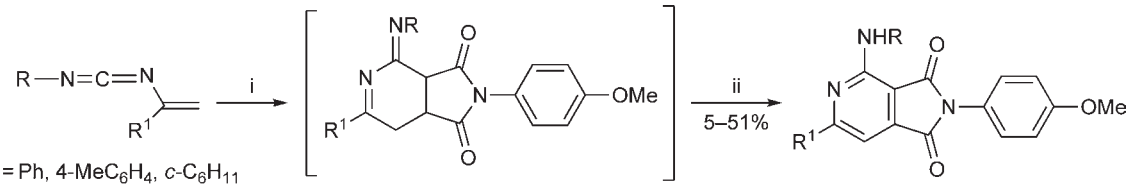
R	R^1	R^2	R^3	*Yield* (%)
Me	CO_2Et	Ph	$CH_2C_6H_5$	33
n-Pr	CO_2Et	4-Biphenyl	$CH_2C_6H_5$	39
Me	COMe	3,4-diClC_6H_3	$CH_2CH_2CO_2Bn$	26

R = Me, *n*-Pr, 4-$ClC_6H_4CH_2$
R^1 = CO_2Me, COMe, CO_2Et, CN
R^2 = Ph, 3-$Me_2NCOC_6H_4$, 4-$MeO_2CC_6H_4$, 4-Biphenyl, 4-$OCH_2C_6H_5$, 3,4-diClC_6H_3
R^3 = $CH_2C_6H_5$, *i*-Pr, $CH_2CH_2CO_2Bn$

Carbodiimides undergo a [4+2] cycloaddition reaction to form pyrrolo[3,4-*c*]pyridine derivatives <1998J(P1)3065>. Dehydrogenation of the cycloadduct in the presence of manganese dioxide gives improved yields (**Scheme 8**).

10.06.8.2 Furopyridines

Furo[2,3-*b*]pyridines are generated in a cyano [4+2] reaction that uses tungsten alkynols and aldehydes which cyclize to 1,3-dienes prior to reaction with nitriles (**Scheme 9**) <1998JA4520>. The reaction, which is activated by photolysis or with $Me_3NO{\cdot}H_2O$, works with unactivated nitriles in both intramolecular and intermolecular reactions to give moderate to good yields of product.

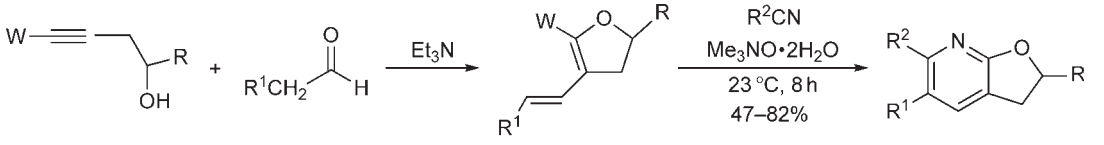


R = Ph, 4-MeC$_6$H$_4$, *c*-C$_6$H$_{11}$
R^1 = Ph, 4-MeC$_6$H$_4$

i, *N*-(*p*-methoxy)phenylmaleimide, reflux, xylene, 2–8 h
ii, heat

R	*R*^{1}	*Yield (%)*	*Reference*
Ph	Ph	41	1998J(P1)3065
c-C$_6$H$_{11}$	4-MeC$_6$H$_4$	30	1998J(P1)3065
Ph	4-MeC$_6$H$_4$	31	1998J(P1)3065

Scheme 8

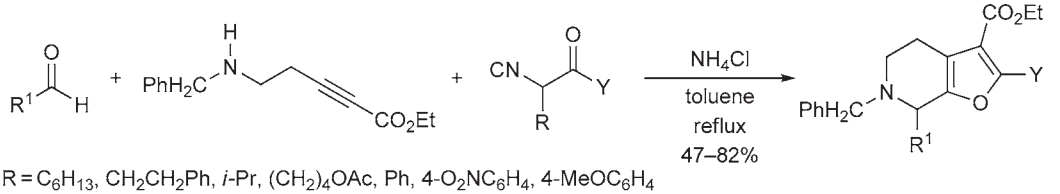


R = H, Ph
R^1 = H, Me, CHPh(CH$_2$)$_2$CN, CHPh(CH$_2$)$_3$CN
R^2 = Et, *i*-Pr, Ph

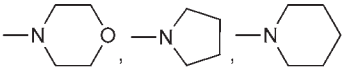
R	*R*^{1}	*R*^{2}	*Yield (%)*
H	H	*i*-Pr	58
Ph	H	Et	82
H	Me	Ph	47

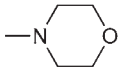
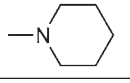
Scheme 9

A multicomponent reaction (MCR) using 5-aminopent-2-ynoates, aldehydes, and α-isocyanoacetamides produces 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines as shown in Equation (15) <2004OL115>. The reaction proceeds via oxazole intermediate **71**, which then undergoes an intramolecular Diels–Alder cycloaddition reaction with the alkyne functional group also present in the molecule to afford oxa-bridged intermediate **72**. Compound **72** fragments by a retro-Diels–Alder reaction to afford a 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine product and a nitrile. The reaction gives good yields of furopyridines with aliphatic or aromatic aldehydes and a variety of amino groups on the acetamide reagent; however, to obtain good yields, the amine must include an electronically poor dienophile.

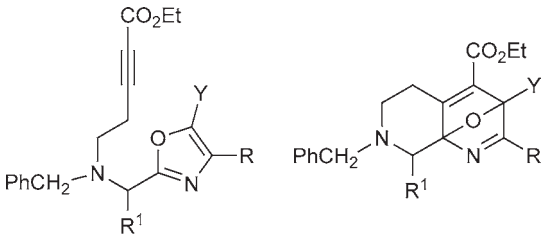


R = C$_6$H$_{13}$, CH$_2$CH$_2$Ph, *i*-Pr, (CH$_2$)$_4$OAc, Ph, 4-O$_2$NC$_6$H$_4$, 4-MeOC$_6$H$_4$

Y = NEt$_2$, 

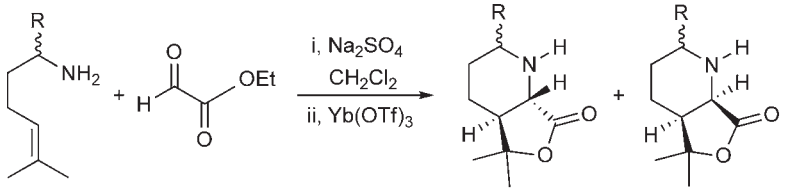
R	*Y*	*Yield (%)*
C$_6$H$_{13}$	NEt$_2$	55
(CH$_2$)$_4$OAc		61
C$_6$H$_{13}$		78

(15)



71 **72**

The electrophilic cyclization of unsaturated imines derived from glyoxalate, catalyzed by ytterbium triflate, gives reduced furo[3,4-*b*]pyridines in variable yields, but with good stereoselectivity (Equation 16) <2002TL2339>. For the 5:6 ring system, the *trans*-isomer, **73**, is the primary product formed.



73
23–72%

R	*Yield (%)*	*trans:cis* **73**
H	23	7:1
Me	72	10:1

(16)

Pyridin-2(1*H*)-ones, which can be generated from acyclic starting materials, are useful in the synthesis of furo- and thieno[3,4-*b*]pyridin-2(1*H*)-ones. Under radical conditions, the initial brominated dihydropyridinone derivatives, **74**, are converted into partially reduced furo[3,4-*b*]pyridine derivatives, whereas bromination in acetic acid leads to a dibrominated product which loses HBr to give pyridone **75**. Though compound **75** does not yield furopyridinones, the pyridone does undergo reaction with thiourea leading to a thieno[3,4-*b*]pyridine derivative (**Scheme 10**) <2004CHE862>.

A [2+2+2] cyclization reaction of acetylenes and nitriles leads to the formation of furo[3,4-*c*]pyridines under cobalt-catalyzed conditions (**Scheme 11**) <2005SL1188>.

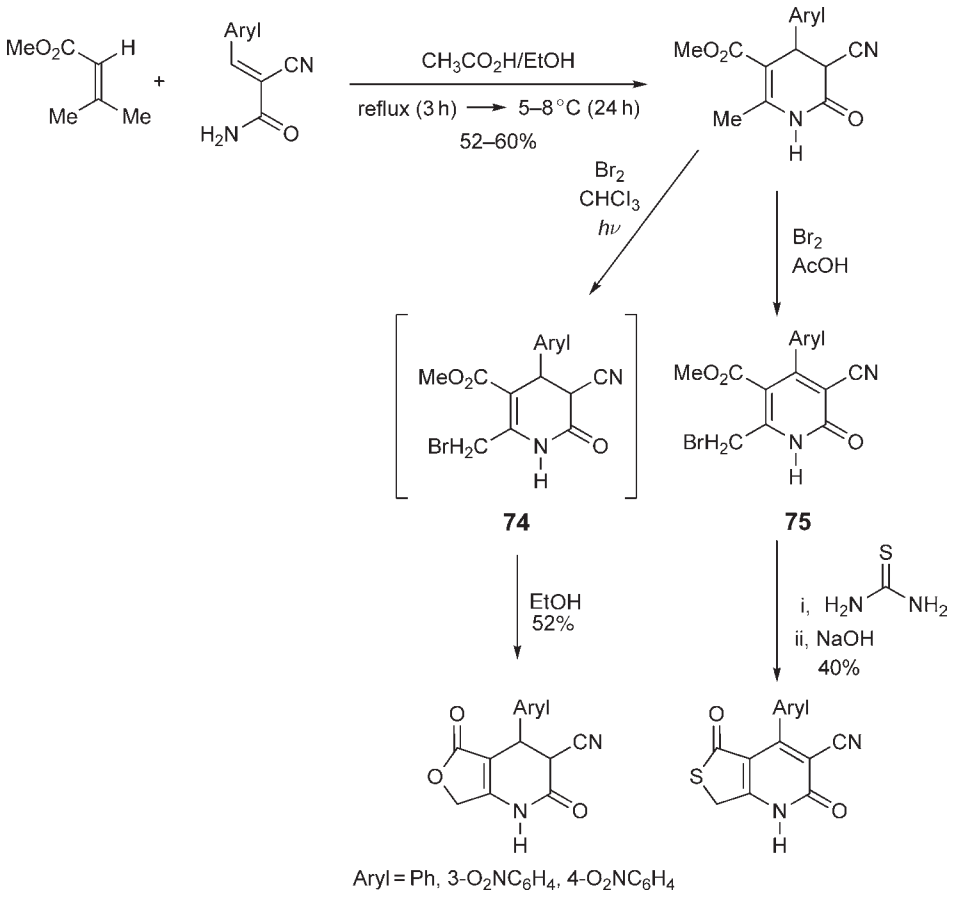
Furo[3,4-*c*]pyridine derivatives are generated from the reaction of 2,3-dihalopropenyl ketones with the ethyl ester of β-aminocrotonic acid. Initial reaction products are substituted nicotinic acids which can be partially converted into the furopyridines under harsh vacuum distillation conditions (**Scheme 12**) <2005CHE1009>.

Allenyl aldehydes undergo a ruthenium-catalyzed cycloaddition reaction with CO to afford reduced furopyridines in good yields (Equation 17) <2002AGE1584>. In a similar reaction, the furopyran derivative is formed.

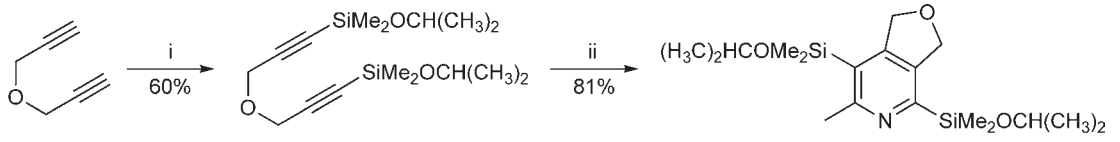
10.06.8.3 Thienopyridines

2-Pyridylsulfides, **76**, can be synthesized from cyanoesters and cyanoamides upon reaction with cyanothioacetamide and *N*-methylmorpholine followed by addition of an alkyl halide (**Scheme 13**). Treatment with base leads to cyclization to form thieno[2,3-*b*]pyridine derivatives <1998MI183, 2001CHE766, 2002RJO731, 2005JHC527, 2005RJC440>. A regioselective synthesis of trifluoromethyl-substituted cyano-2-pyridinethiones is available from cyanothioacetamide and trifluoromethylacetylacetone or its methyl derivative. Alkylation of the pyridinethiones followed by self-condensation in the presence of excess base again leads to the formation of 3-aminothieno[2,3-*b*]pyridine derivatives <1996T10841, 2000CHE1431>.

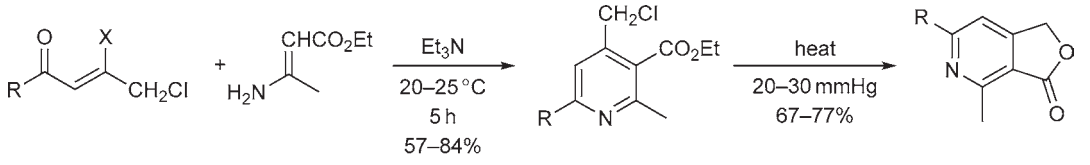
Condensation of a 1,3-dicarbonyl compound, an aldehyde, and cyanoacetamide in the presence of piperidine affords pyridine-2-thiolate derivatives. Acidification of the thiolates followed by alkylation with iodoacetamide gives a tetrahydropyridine which gives a dihydropyridine derivative upon heating in the presence of acid. Thorpe–Ziegler condensation gives thieno[2,3-*b*]pyridines in good yields <2000CHE693>. Cyanothioacetamide reacts with α,β-unsaturated carbonyl compounds to form cyanopyridinethiones which undergo alkylation and cyclization reactions to afford thieno[2,3-*b*]pyridine derivatives <2004PS2205>. Similarly, a novel synthesis of thieno[2,3-*b*]pyridines has been reported from treatment of cyanopyridinethiones directly with elemental sulfur in the presence of a base (Equation 18) <2004JHC947>.



Scheme 10

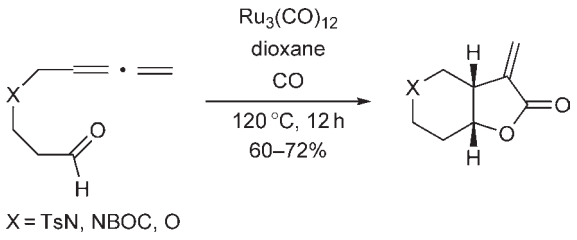


Scheme 11

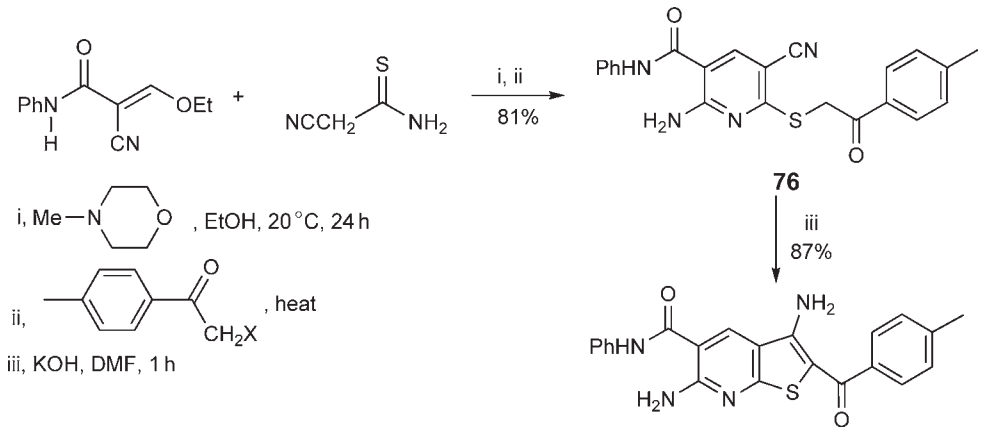


R	*Yield (%)*
Me	75
C_5H_{11}	69
Ph	71
4-ClC_6H_4	68

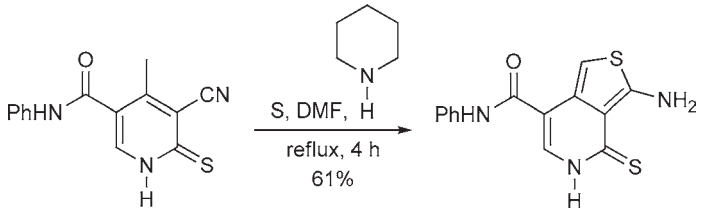
Scheme 12



(17)

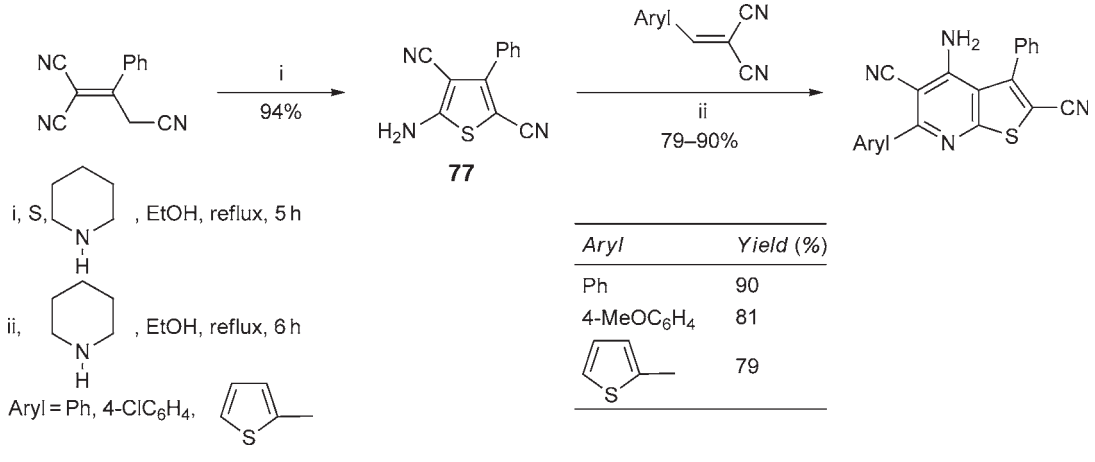


Scheme 13



(18)

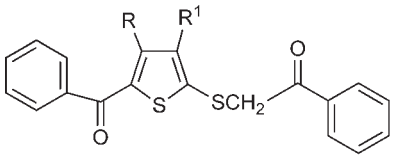
1,1,3-Tricyano-2-phenylpropene and elemental sulfur in the presence of a catalytic amount of piperidine cyclize to form 5-amino-3-phenylthiophene-2,4-dicarbonitrile, **77**. Compound **77** reacts with malononitrile derivatives affording 4-aminothieno[2,3-*b*]pyridines (**Scheme 14**) <1996HAC29>.



Aryl	*Yield (%)*
Ph	90
4-MeOC$_6$H$_4$	81
	79

Scheme 14

Thiophenes can be synthesized from a sequence involving the reaction of activated methylene compounds with carbon disulfide in base. The resulting disulfide salts, without isolation, are reacted with phenacyl bromide to afford highly substituted thiophenes, **78**. Compound **78** reacts with ethyl cyanoacetate, malononitrile, or acrylonitrile to afford thieno[3,2-*b*]pyridine derivatives <1995CCC1578>.



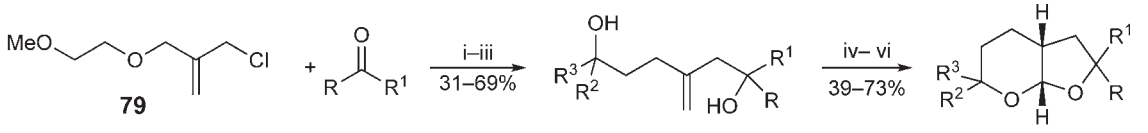
R	R^1
NH_2	$CONH_2$
OH	$COCH_3$
OH	CO_2Et

78

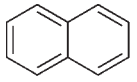
R = NH_2, OH
R^1 = $CONH_2$, $COCH_3$, CO_2Et

10.06.8.4 Furopyrans

A versatile method for the synthesis of perhydrofuropyrans begins with 2-chloromethyl-3-(2-methoxyethoxy)propene, **79**. Compound **79**, in the presence of lithium powder and a catalytic amount of naphthalene, undergoes sequential reaction with two electrophiles, first a carbonyl compound and then an epoxide, to form methylidenic diols. Hydroboration–oxidation, followed by oxidation with PCC, affords perhydrofuropyrans (**Scheme 15**) <2000TL1661, 2001SL1197, 2003T5199>.



79

i, Li,  , THF, –78 to 0 °C

ii,  , 0 °C to rt, 8 h

iii, H_2O

iv, BH_3/THF
v, H_2O_2

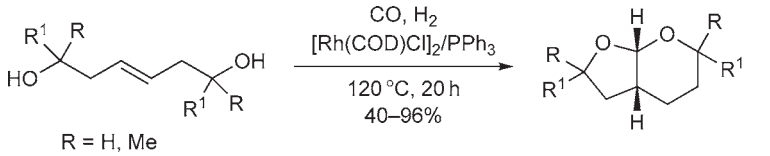
vi, PCC, CH_2Cl_2, rt, 6 h

R = R^1 = Et, $(CH_2)_4$, $(CH_2)_5$
R^2 = H, Me, Et, *n*-C_5H_{11}
R^3 = Me, Et, Ph, *n*-C_5H_{11}, *n*-C_6H_{13}

R	R^1	R^2	R^3	*Yield* (%)
Et	Et	H	Ph	63
Et	Et	Et	Et	73
$(CH_2)_4$		*n*-C_5H_{11}	*n*-C_5H_{11}	62

Scheme 15

Symmetric alkenediols undergo a hydroformylation reaction to give perhydrofuro[2,3-*b*]pyrans in the presence of a rhodium catalyst. The reaction proceeds in high yields, except in the case of the 1,6-diphenyl-3-hexene-1,6-diol (40%) (Equation 19) <2002OL289>.

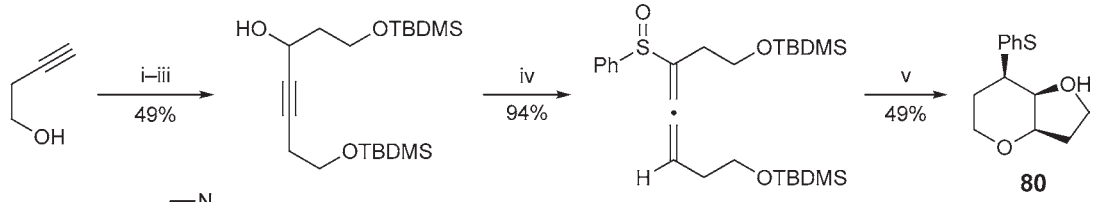


R = H, Me
R^1 = H, Me, Ph
R = R^1 = $(CH_2)_5$

R	R^1	*Yield* (%)
H	H	92
Me	Me	96
H	Ph	40

(19)

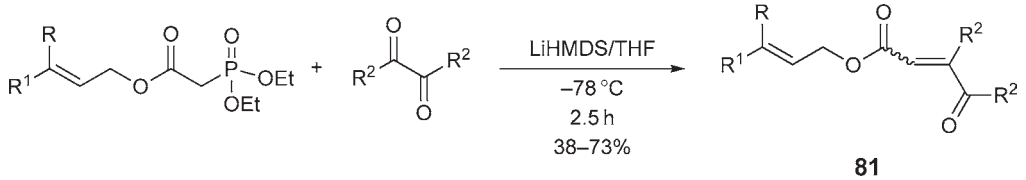
A stereoselective one-pot synthesis of furo[3,2-*b*]pyran, **80**, has been reported. The key step in the synthesis includes a double cyclization reaction along with a rearrangement (**Scheme 16**) <1998TL3605>.



i, TBDMS–Cl, , DMAP/DMF
ii, EtMgBr, Et_2O
iii,
iv, PhSCl, Et_3N
v, $HF_{(aq)}$, MeCN, 60 °C

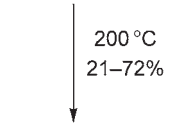
Scheme 16

Furo[3,4-*c*]pyranones are produced by an intramolecular hetero-Diels–Alder reaction of α,β-unsaturated γ-keto esters, **81**. The Horner–Wadsworth–Emmons reaction of phosphonates with α-diketones is used to assemble compounds **81** (**Scheme 17**) <2004TL4297>.



81

R = H, Me
R^1 = H, Me, Ph
R^2 = Me, Ph, 4-FC_6H_4

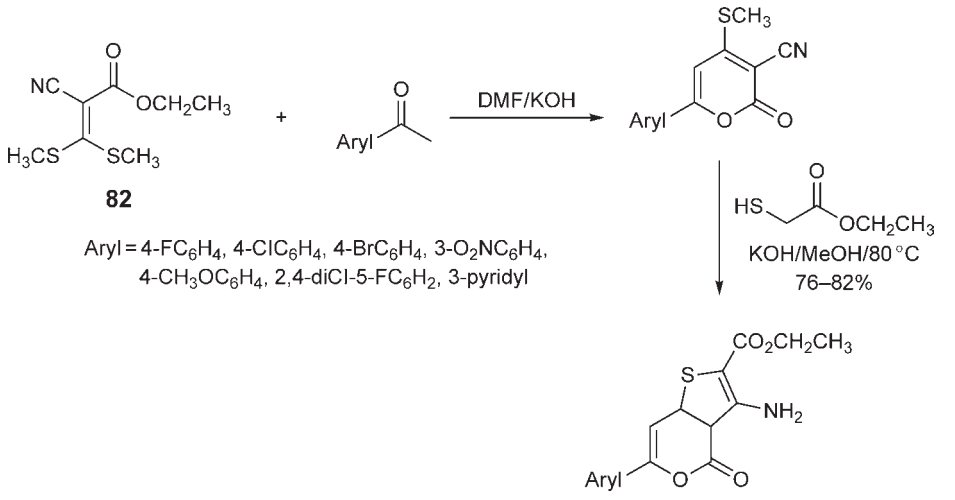


R	R^1	R^2	*Yield* (%)
Me	Me	4-FC_6H_4	64
H	Ph	Me	69 (from (*Z*)-**79**)
Me	Me	Me	37 (from (*E*)-**79**)

Scheme 17

10.06.8.5 Thienopyrans

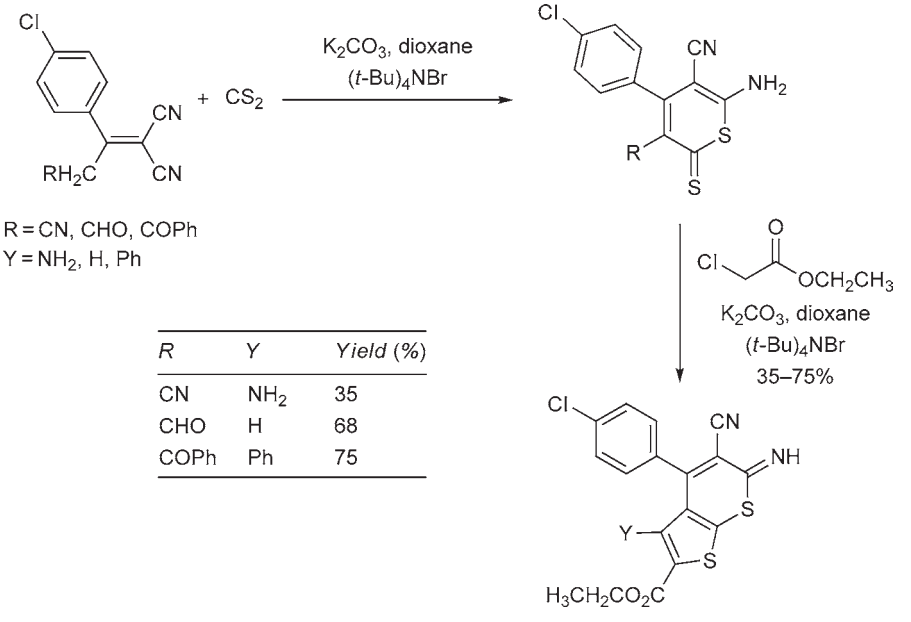
Ketene dithioacetal **82** reacts with aromatic methyl ketones to generate thiopyranones. Further reaction with ethyl mercaptoacetate leads to the formation of thieno[3,2-*c*]pyranones in good yields (**Scheme 18**) <1997BML3101>.



Scheme 18

10.06.8.6 Thienothiopyrans

Phase-transfer catalysis conditions can be used for the synthesis of thienothiopyrans from 4-chlorophenylmethylene-malononitriles in a sequence of reactions shown in **Scheme 19** <2001SC475>.



R	*Y*	*Yield (%)*
CN	NH_2	35
CHO	H	68
COPh	Ph	75

Scheme 19

10.06.8.7 Pyranopyrroles

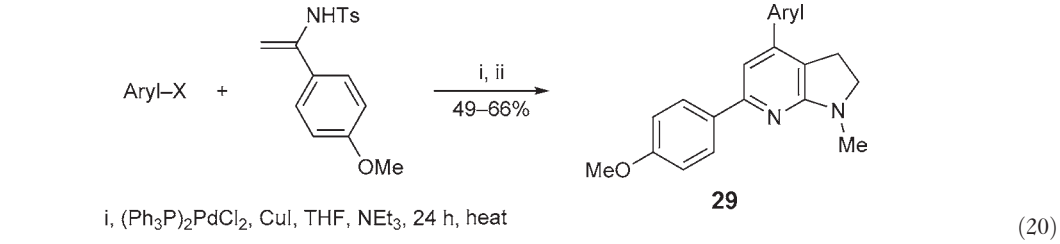
An intramolecular oxo-Diels–Alder reaction leads to the synthesis of reduced pyrano[3,4-*c*]pyrrole esters. When benzene is chosen as reflux solvent, *trans*-substituted products form, whereas *cis*-substituted derivatives are favored in refluxing toluene solvent (see Section 10.06.2.1.2) <2003T8955>.

10.06.9 Synthesis from Monocyclic Heterocycles

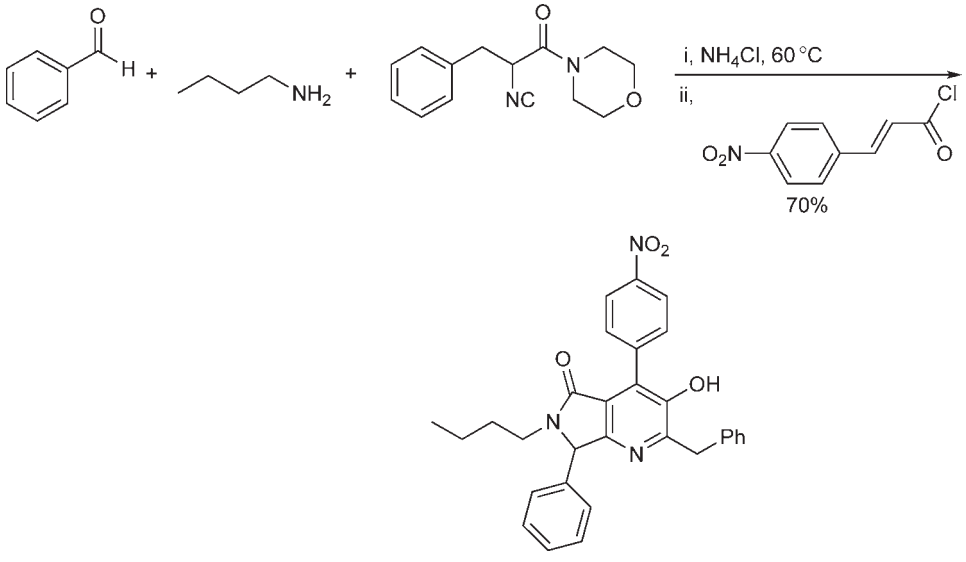
10.06.9.1 From the Five-Membered Ring

10.06.9.1.1 Pyrrolopyridines

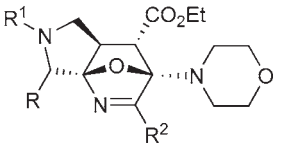
An MCR between aryl halides, propargyl *N*-tosylamines, and *N*,*S*-ketene acetals produces pyrrolo[2,3-*b*]pyridine derivatives, **29**, in moderate yields, as shown in Equation (20). The overall reaction involves a reaction sequence of the coupling-isomerization reaction (CIR) of electron-deficient heteroaryl halides and heteroarylpropargyl *N*-tosylamines, which leads to enamine formation. Treatment with a nucleophilic *N*,*S*-ketene acetal affords reduced pyrrolo[2,3-*b*]-pyridine products <2006JOC3494>. MCRs have also been applied to the synthesis of pyrrolo[3,4-*b*]pyridine-5-ones using amines, aldehydes, and isocyanides, as shown in Equation (21) <2005S161>. 5-Aminooxazole undergoes a four-component synthesis to generate pyrrolo[3,4-*b*]pyridines. The MCR, which includes a triple domino sequence, is accelerated by ammonium chloride <2001OL877, 2002JA2560>. A variation of the reaction that leads to oxa-bridged pyrrolo[3,4-*b*]pyridines, **83**, has also been developed < 2002T6351>.



(20)



(21)



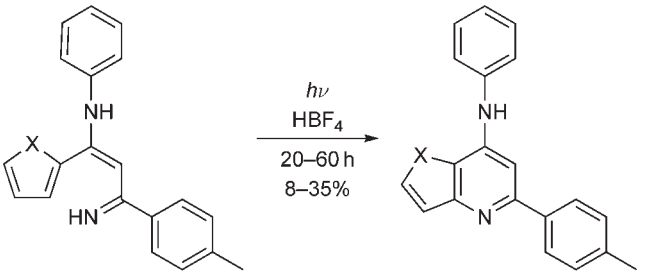
83

R = *n*-C_6H_{13}, *c*-C_8H_{17}, $(CH_2)_2C_6H_5$
R^1 = $CH_2C_6H_5$, *i*-Pr, CH_2CH_2(3,4-diOMe)C_6H_3
R^2 = $CH_2C_6H_5$, Ph

R	R^1	R^2	*Yield* (%)
n-C_6H_{13}	$CH_2C_6H_5$	$CH_2C_6H_5$	92
$(CH_2)_2C_6H_5$	$CH_2C_6H_5$	Ph	65
c-C_8H_{17}	$CH_2C_6H_5$	$CH_2C_6H_5$	82

Cyanopyrroles, formed from malononitrile and phenacyl halides, offer another route to the synthesis of pyrrolo[2,3-*b*]pyridines <2004MI15>. Treatment of the cyanopyrroles with ethyl acetoacetate leads to propenylamino-pyrroles which undergo further cyclization to form highly functionalized pyrrolo[2,3-*b*]pyridine derivatives.

A photocyclization of 3-(2-pyrrolyl)-3-amino-2-alkeneimines under acidic reaction conditions leads to the formation of pyrrolo[3,2-*b*]pyridine as shown in Equation (22) <1999T14079>. When oxygen or sulfur heteroatoms are substituted for the pyrrole ring nitrogen, the corresponding furo- and thieno[3,2-*b*]pyridines are formed. All of the photocyclizations require lengthy reaction times and the yields tend to be low, especially for the furopyridine derivatives.

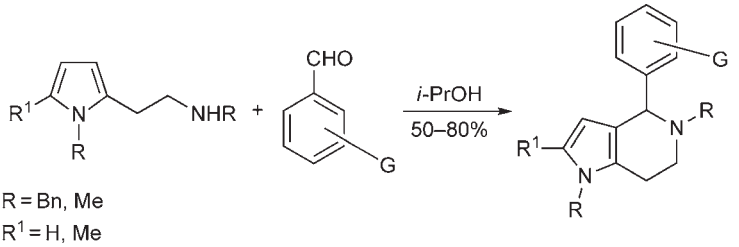


X = NCH_3, O, S

X	*Yield* (%)
NCH_3	35
O	8
S	32

(22)

Pyrrolo[2,3-*c*]- and [3,2-*c*]pyridinones can be prepared by a palladium-catalyzed cyclization of pyrrolocarboxamides under oxidative coupling conditions <2005T1077>. Alternatively, pyrrolo[1,2-*a*]pyrazine derivatives form from the same starting material in an amination reaction. Aldehydes react with methyl 2-amino-3,3-diethoxybutyrate to produce imines which can be reduced and then cyclized with titanium(IV) chloride to give pyrrolo[2,3-*c*]pyridine derivatives <1999BMC921>. *N*,*N*′-Dialkyl-2-(2-aminoethyl)pyrroles undergo a Pictet–Spengler condensation reaction with aromatic aldehydes, in the absence of a catalyst, to form tetrahydropyrrolo[3,2-*c*]pyridines (Equation 23) <2003T5265>.

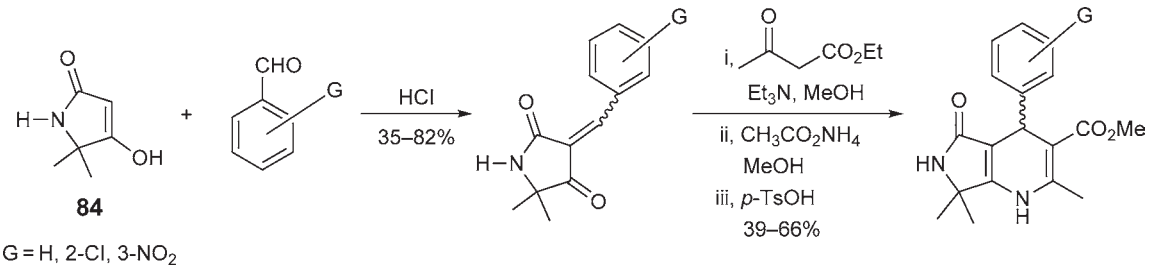


R = Bn, Me
R^1 = H, Me
G = 4-Cl, 4-F, H, 3-NO_2, 2-HO-5-NO_2

R	R^1	*G*	*Yield* (%)
Me	Me	H	50
Bn	H	4-Cl	70
Bn	Me	3-NO_2	75
Bn	Me	H	80

(23)

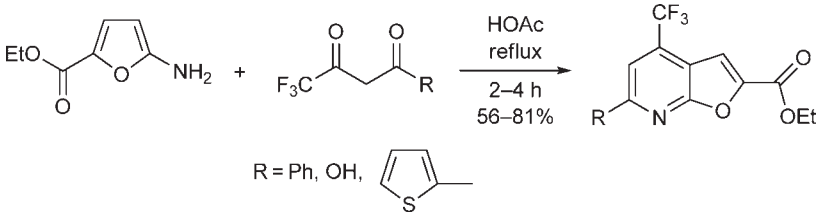
Tetrahydropyrrolo[4,3-*b*]pyridines can be synthesized from 5,5-dimethyltetramic acid, **84**, in a sequence of steps that begins with aryl aldehydes to generate arylmethylene-substituted tetramic acids. A Michael reaction with methyl acetoacetate followed by treatment with ammonium acetate yields the tetrahydropyrrolopyridine derivatives (**Scheme 20**) <2005H(65)377>. A similar reaction can be carried out with aroyl-substituted butenolides to give substituted furopyridine derivatives.



Scheme 20

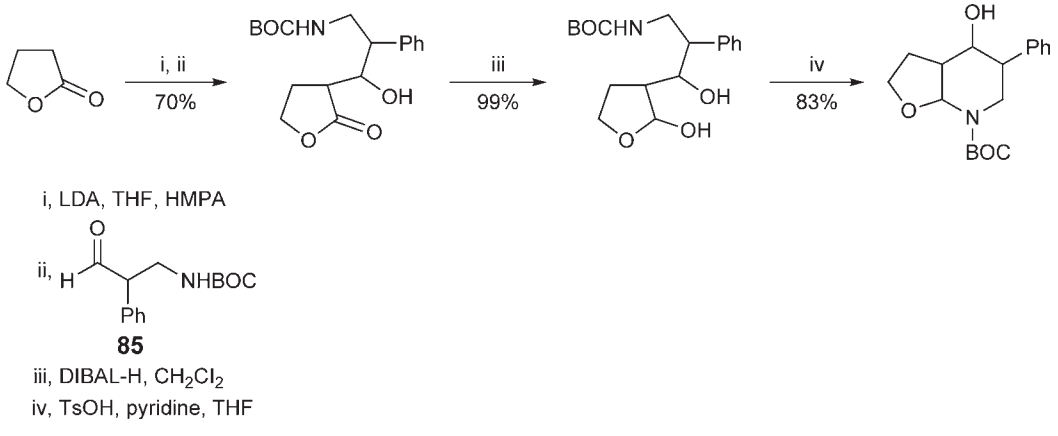
10.06.9.1.2 Furopyridines

Aminofurans undergo reaction with trifluoromethyl-substituted 1,3-dicarbonyl compounds to give furo[2,3-*b*]pyridinones in good yields under mild conditions (Equation 24). As a consequence of the amino-substituted ring double bond, which is enamine-like, initial attack on the active trifluoromethyl-substituted carbonyl group occurs at the C-nucleophilic carbon atom of the heterocycle accounting for the success of the reaction <2003S1531>. The analogous reaction with thiophene derivatives leads to the formation of thieno[2,3-*b*]pyridines. 2-Amino-3-furancarbonitriles react with α,β-unsaturated carbonyl compounds in the presence of a base to afford dihydrofuro[2,3-*b*]pyridines. Treatment with base leads to aromatization of the pyridine ring <2002JHC743>.



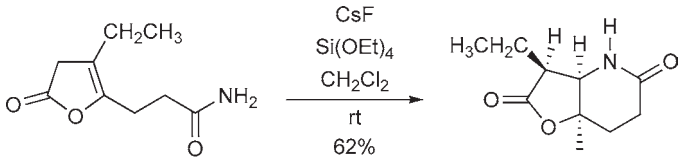
(24)

Condensation of γ-butyrolactone with aldehyde **85** followed by reduction of the lactone and ring closure affords reduced furo[2,3-*b*]pyridines (**Scheme 21**) <2003CC2062, 2004JOC1872>.



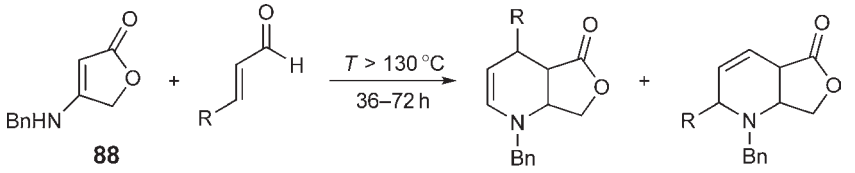
Scheme 21

Lactone **86** undergoes an intramolecular conjugate addition reaction in the presence of cesium fluoride and tetraethyl orthosilicate to give furo[3,2-*b*]pyridine dione **87** (Equation 25). After 12 h, a 1:1 mixture of 3-ethyl epimers is found; however, extending the reaction time to 72 h results in exclusively β-ethyl isomer **87** in good yield <2005JOC384>.



86 87 (25)

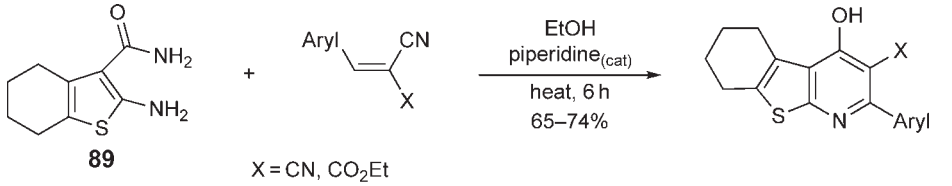
An aza-[3+3] cycloaddition reaction of tetronamide **88** with unsaturated aldehydes affords partially reduced furo[3,4-*b*]pyridines in moderate yields as shown in Equation (26) <2004JOC6732>.



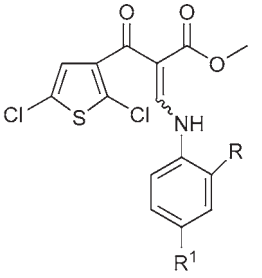
88
R = Me, *n*-Pr, Ph
25–71%
10–38% (26)

10.06.9.1.3 Thienopyridines

Compound **89**, readily synthesized from cyclohexanone, elemental sulfur, and cyanoacetamide, generates hydroxythieno[2,3-*b*]pyridine derivatives upon treatment with α-substituted cinnamonitriles in a reaction catalyzed by piperidine (Equation 27). The reaction proceeds by a Michael-type addition followed by a cyclization reaction involving loss of ammonia, and elimination of hydrogen cyanide generates the thieno[2,3-*b*]pyridine derivatives in good yields <2003HAC459>. Enaminoketo esters, **90**, undergo cyclization to afford thieno[2,3-*b*]pyridine esters or acids in high yields (78–92%) <1998EJM33>.

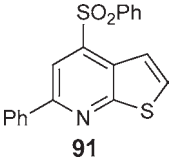


89
X = CN, CO_2Et
Aryl = Ph, 4-$CH_3OC_6H_4$, 4-ClC_6H_4 (27)



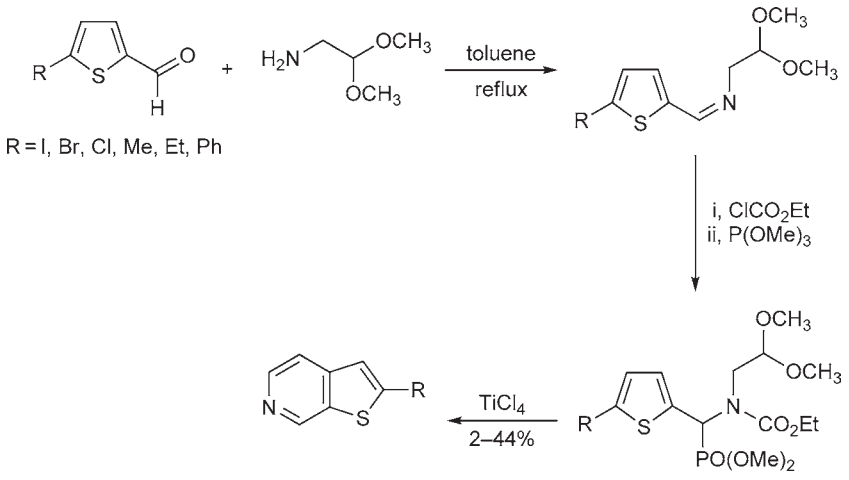
90
R = H, F, Br, Cl, OH, OCH_3, CH_3
R^1 = H, F, OCH_3, CH_3

2-Nitrothiophene reacts with a sulfone to afford 2-phenyl-4-phenylsulfonylthieno[2,3-*b*]pyridine, **91**, in low yield <1998T2607>. The phenylsulfonyl group can be readily replaced by a variety of nucleophiles.



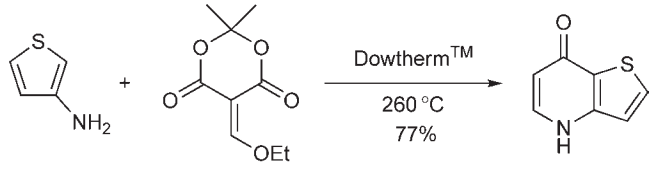
91

A modification of the Pomeranz–Fritsch synthesis <1983JOC3344> is used in the preparation of thieno[2,3-*c*]-pyridine and its 2-substituted derivatives. An aryl aldehyde undergoes condensation with aminoacetaldehyde dimethyl acetal giving a Schiff base which cyclizes to form an imine product. The imine is treated with ethyl chloroformate followed by triethyl phosphate to form an intermediate carbonate–phosphonate, which then cyclizes to the thienopyridine product (**Scheme 22**) <2004S1935>. Very low product yields (2–17%) are obtained for alkyl- and phenyl-substituted thieno[2,3-*c*]pyridines; however, the unsubstituted product and 2-halogenated derivatives give moderate yields (28–44%).



Scheme 22

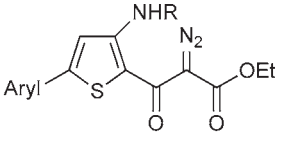
3-Aminothiophene, readily available from methyl 3-aminothiophene-2-carboxylate, undergoes a condensation reaction with compound **92**, followed by heating at elevated temperatures in Dowtherm™, to produce pyridone product (Equation 28). The pyridone can be converted into a thieno[3,2-*b*]pyridine derivative in a few straightforward steps <2004BML21>.



(28)

92

3-(3-Alkylamino-5-arylthieno-2-yl)-2-diazo-3-oxopropanoates, **93**, are useful starting materials for the synthesis of diazothieno[3,2-*b*]pyridinones. Two sets of reaction conditions have been developed for *N*-aryl- and *N*-alkyl-substituted starting materials. Additionally, the cyclization reaction rate is affected by the types of aryl substituents, with electron-donating substituents such as alkyl and methoxy groups resulting in the slowest reactions <2004JOC4867>.

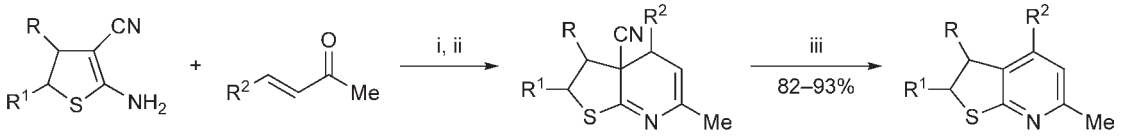


93

Aryl = Ph, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 4-BrC_6H_4
R = Me, Et, *i*-Pr, Ph, 2-$CH_3C_6H_4$, 2-NCC_6H_4, 4-$CH_3OC_6H_4$, 4-NCC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4

Aminodihydrothieno[2,3-*c*]- and [3,2-*c*]pyridines can be synthesized from 2-cyano-3-methyl-5-trimethylsilylthiophene and the imine of benzaldehyde <1998TL1227>. Substituted dihydrothiophenecarbonitriles and

α,β-unsaturated ketones in the presence of a titanium catalyst undergo a Michael addition reaction that leads to the formation of dihydrothieno[2,3-*b*]pyridines. Treatment with base leads to aromatization of the pyridine ring (**Scheme 23**) <2004JHC641>.



R, R^2 = H, Ph
R^1 = H, Me

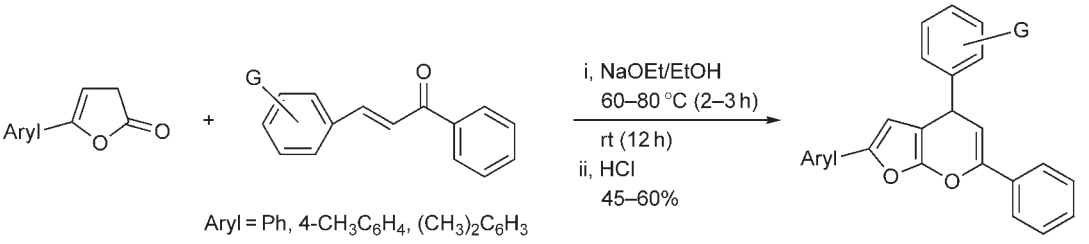
i, $TiCl_4$, CH_3Cl, rt
ii, reflux
iii, *t*-BuOK/*t*-BuOH, reflux

R	R^1	R^2	*Yield* (%)
H	H	H	90
H	Me	H	92
Ph	H	Ph	90

Scheme 23

10.06.9.1.4 Furopyrans

5-Substituted-3*H*-furan-2-ones, in the presence of a base catalyst, participate in a Michael reaction with electron-deficient α,β-unsaturated ketones to afford furo[2,3-*b*]-4*H*-pyrans. The reaction sequence involves a heterocyclization reaction followed by dehydration (Equation 29) <2003RJC655>.

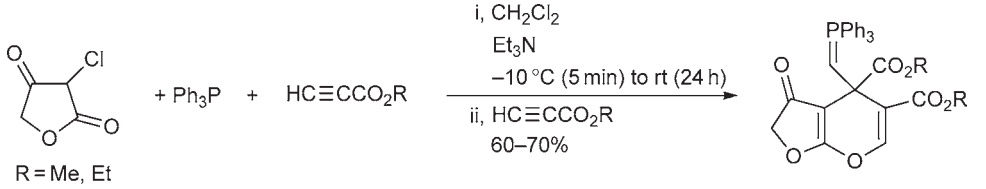


Aryl = Ph, 4-$CH_3C_6H_4$, $(CH_3)_2C_6H_3$
G = 2-OH, 4-CH_3, 2-CH_3O, 2,5-$(CH_3)_2$

(29)

Aryl	*G*	*Yield* (%)
Ph	OH	50
Ph	OCH_3	58
$CH_3C_6H_4$	OCH_3	60

Phosphorus ylides can be generated from triphenylphosphine, 3-chloro-(3*H*, 5*H*)-furan-2,4-dione, and alkynyl esters. Additional alkynyl ester, acting as a Michael acceptor, reacts with the ylides in a [4+2] cycloaddition reaction that results in the formation of furo[2,3-*b*]pyran derivatives (Equation 30) <2000T5221>.

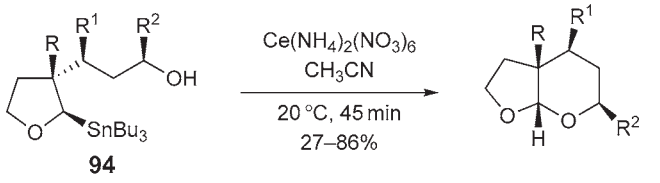


R = Me, Et

(30)

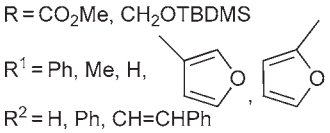
2,3-Dihydrofuran reacts with β,γ-unsaturated α-keto esters with copper or zinc complex catalysts to generate furo[2,3-*b*]pyran derivatives in good yields with high stereoselectivity. The synthesis proceeds via an inverse electron demand hetero-Diels–Alder reaction <2000CC459>.

α-Alkoxystannanes, **94**, when treated with cerium ammonium nitrate, $Ce(NH_4)_2(NO_3)_6$, produce oxonium ion intermediates by single electron transfer oxidation–fragmentation reactions, or 1,5-hydride shifts. The oxonium ions are trapped in an intramolecular reaction by the alcohol group present in the molecule to generate reduced furo[2,3-*b*]pyrans (Equation 31) <2006TL3607>.

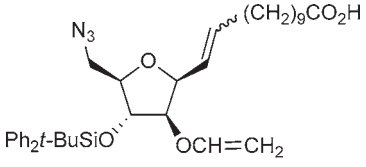


R	R^1	R^2	*Yield* (%)
CO_2Me	Ph	H	54
CO_2Me	Ph	Ph	67
$CH_2OTBDMS$	H	H	53

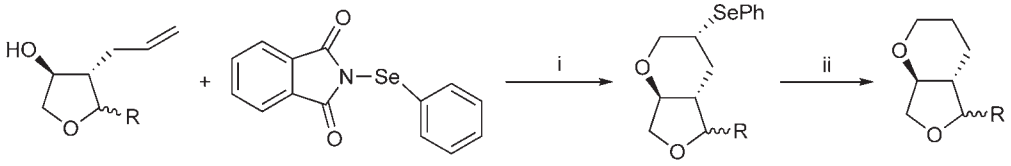
(31)



A solid-phase synthesis of furo[3,2-*b*]pyran derivatives utilizing highly functionalized sugar templates has been reported <2003JOC9406>. After incorporation of alkenes within the sugar template, such as compound **95**, the solid support is introduced via formation of the acid amide. This immobilized system then allows a ruthenium-catalyzed ring-closing metathesis that leads to the formation of the fused oxacycles.



Substituted tetrahydrofurans containing an allyl group *trans* to a hydroxyl group undergo a stereoselective cyclization reaction promoted by selenium electrophiles to afford perhydrofuro[3,4-*b*]pyrans (**Scheme 24**). If the allyl and hydroxyl groups are in a *cis*-substitution pattern, cyclization leads to perhydrofuro[3,4-*b*]furans <2004TA1949>. Reductive deselenation of the furopyrans occurs in high yields.



R = (*R*)-Ph, (*S*)-Ph

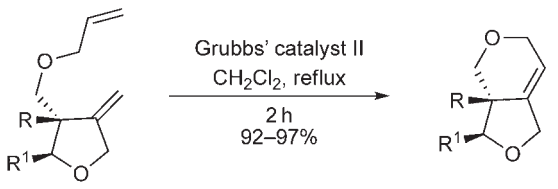
i, *N*-phenylselenophthalimide, BF_3, Et_2O, CH_2Cl_2, 0 °C, 1 h

ii, Ph_3SnH, AIBN, C_6H_6, 80 °C, 1 h

R	*Yield i* (%)	*Yield ii* (%)
(*R*)-Ph	91	86
(*S*)-Ph	75	80

Scheme 24

Exomethylene derivatives of tetrahydrofurans containing allylic ethers undergo a ring-closing metathesis reaction in the presence of Grubbs' type II catalyst to generate furo[3,4-*c*]pyrans as shown in Equation (32). Perhydrofuropyrans result from catalytic hydrogenation of the initial furopyran products <2006T4052>. The reaction is also applicable to pyranopyrrole derivatives.



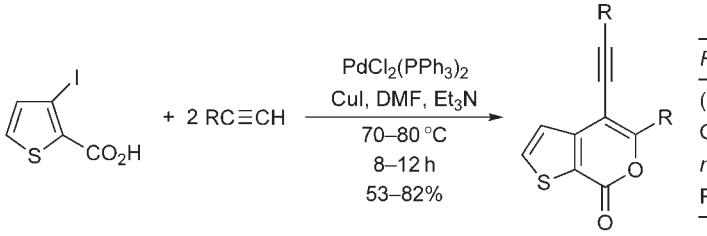
R	R^1	Yield (%)
CH_2Ph	H	92
H	4-$CH_3OC_6H_4$	97

(32)

R = $PhCH_2$, H
R^1 = H, 4-$CH_3OC_6H_4$

10.06.9.1.5 Thienopyrans

3-Iodothiophene-2-carboxylic acid and terminal alkynes, in the presence of a palladium catalyst system, produce good yields of thieno[2,3-*c*]pyran derivatives as the major product (Equation 33) <2006TL83>.

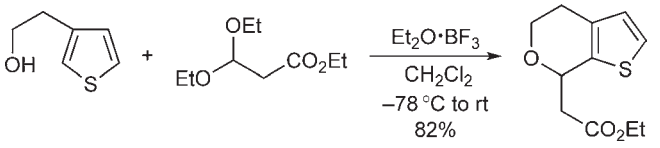


R	Yield (%)
$(CH_2)_2OH$	53
$CH(OH)CH_3$	82
n-C_4H_9	65
Ph	57

(33)

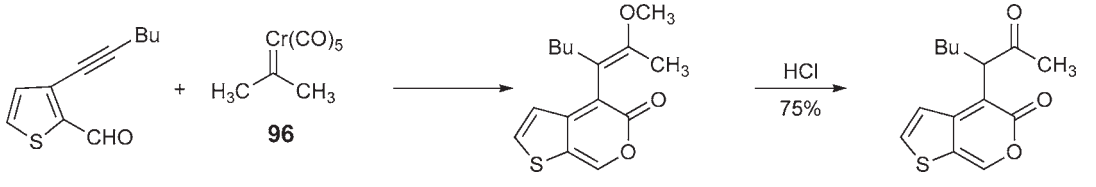
R = $C(CH_3)_2OH$, $(CH_2)_2OH$, $CH(OH)CH_3$, *n*-C_4H_9, *n*-C_6H_{13}, Ph, 4-$CH_3C_6H_4$, $CH_2OC_6H_5$

Another route to thieno[2,3-*c*]pyrans begins with 2-(3-thienyl)ethanol and ethyl 3,3-diethoxypropionate. In the presence of a Lewis acid, ethyl (4,5-dihydro-7*H*-thieno[2,3-*c*]pyran-7-yl)acetate is formed in high yield (Equation 34) <2004BMC5277>.



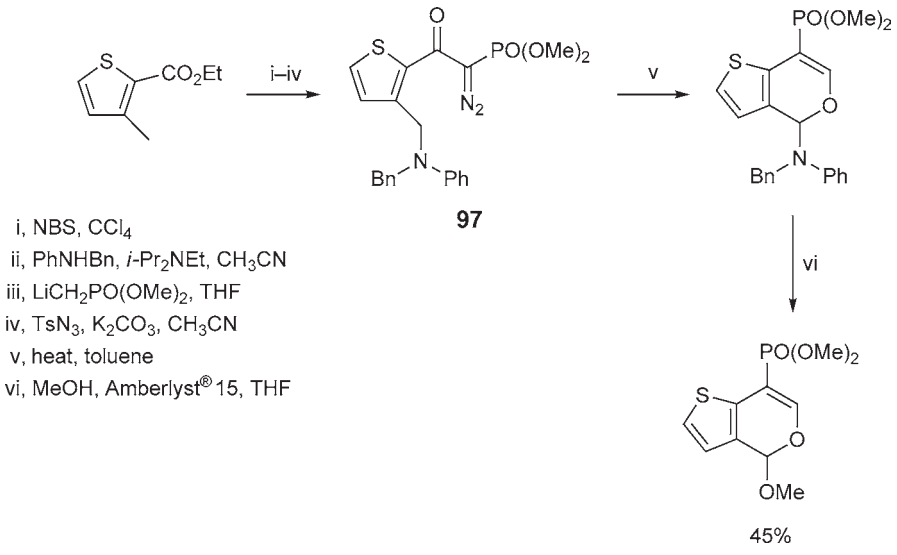
(34)

The coupling reaction of Fischer carbene complexes, **96**, with 3-alkynyl-2-thiophene carboxaldehyde leads to the formation of thieno[2,3-*c*]pyranones (**Scheme 25**) <2001TL777, 2002JOC4177>. This reaction is applicable to the oxygenated derivatives.



Scheme 25

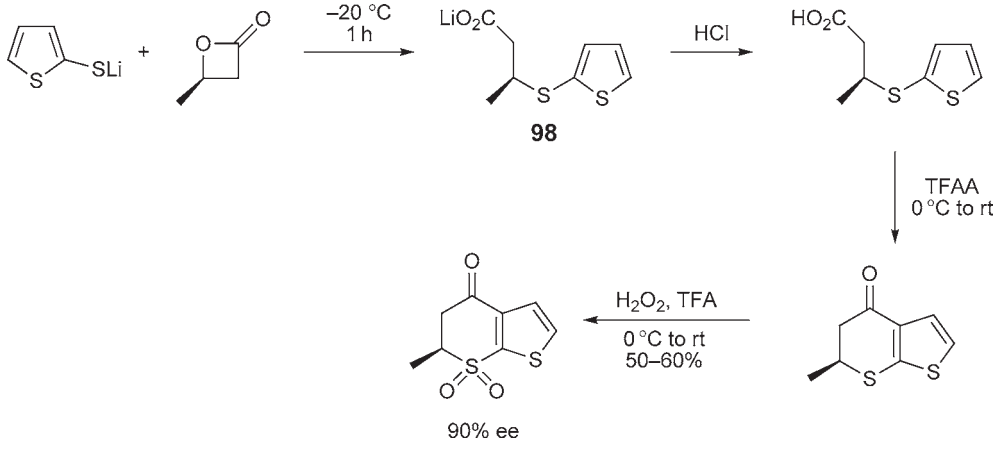
A tandem Wolff rearrangement reaction followed by cyclization leads to the formation of thieno[3,2-*c*]pyrans in moderate yields as shown in **Scheme 26** <1998T6457>. A key step of the reaction involves thermolysis of diazoketophosphonate **97**.



Scheme 26

10.06.9.1.6 Thienothiopyrans

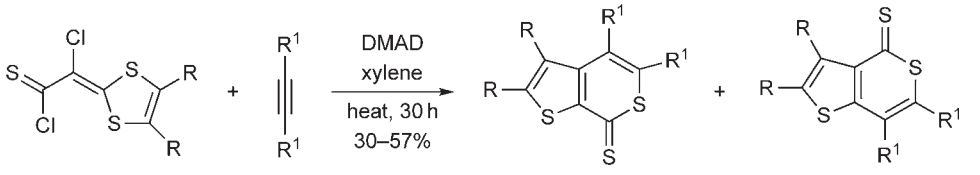
Lithium 2-thiophenethiolate, readily prepared from thiophene, *n*-butyllithium, and sulfur, reacts with *β*-butryolactone to give carboxylate derivative **98** which can be readily acidified to the free acid. Cyclization in the presence of trifluoroacetic anhydride gives thieno[2,3-*b*]thiopyran (**Scheme 27**) <1996TA2721>.



Scheme 27

Phosphonium ylides react with 1,2-dithiols in a basic medium to afford thieno[2,3-*b*]thiopyrans <2005JHC103>. This reaction represents the insertion of a carbanion species between two sulfur atoms.

Compound **99** reacts with alkynes to generate thieno[2,3-*c*]thiopyranthiones and thieno[3,2-*c*]thiopyranthiones. The ratio of isomers is typically 1:1. The reaction proceeds via a cycloaddition reaction and an unprecedented molecular rearrangement (Equation 35) <2005OL791>. Thieno[2,3-*c*]- and [3,2-*c*]thiopyrans can be prepared from thiophene-2-carbaldehyde in a multistep synthesis that leads to the thienothiopyrans in excellent yields <1999J(P1)2639>.



99

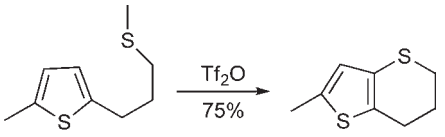
R, R^1 = CO_2Me, CO_2Et, COPh

41

(35)

R	R^1	*Yield (%)*
CO_2Me	CO_2Me	55
CO_2Me	CO_2Et	57
CO_2Et	COPh	30

Thieno[3,2-*b*]thiopyran is formed from sulfide **100** in a cyclization reaction promoted by triflic anhydride (Equation 36). The reaction proceeds in high yield <2003S1191>.



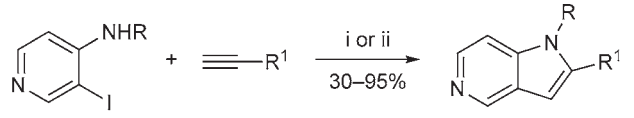
100

(36)

10.06.9.2 From the Six-Membered Ring

10.06.9.2.1 Pyrrolopyridines

Alkynes and dienes are suitable starting reagents for the preparation of pyrrolopyridines. 2-Amino-3-iodopyridines react with internal alkynes under palladium-catalyzed conditions to give 2,3-disubstituted pyrrolo[2,3-*b*]pyridines <1998TL627, 1999BML585>. Similar syntheses have been reported for other pyrrolopyridine isomers from aminohalopyridines and internal alkynes <1998TL5355, 2001TL6441>. Similarly, 2-amino-3-iodopyridines react with substituted 1,2-propadienes to give pyrrolo[2,3-*b*]pyridin-3-ones <1996TL43>. Pyrrolo[3,2-*c*]pyridines are synthesized in a cyclization reaction from 3-iodo-4-aminopyridines with alkynes in the presence of a palladium or copper catalyst (Equation 37) <1998TL5159>.



R = H, BOC, Ac R^1 = H, $Si(CH_3)_3$, CH_3, $(CH_2)_2OH$, $(CH_2)_2OTHP$, Ph

i, CuI, DMF

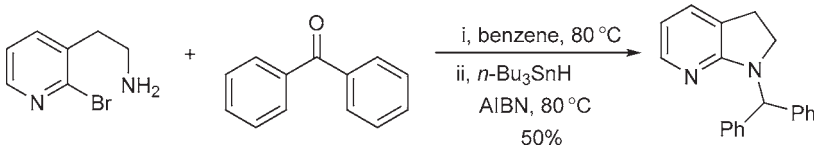
ii, $Pd(OAc)_2$, LiCl, K_2CO_3, PPh_3, DMF

R	R^1	*Method*	*Yield (%)*
BOC	H	i	30
BOC	$Si(CH_3)_3$	i	90
Ac	CH_3	ii	48

(37)

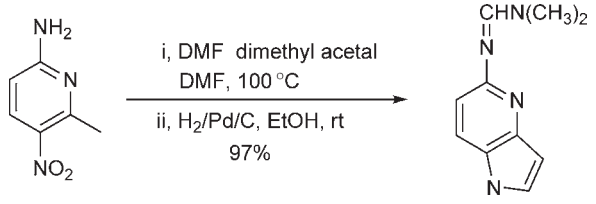
A microwave-assisted synthesis of several isomeric pyrrolopyridines ([2,3-*b*], [2,3-*c*], [3,2-*b*], and [3,2-*c*]) has been reported starting from aminohalopyridines <2005S2571>. Intramolecular palladium-catalyzed Heck reactions leading to substituted pyrrolo[3,2-*b*]pyridines from ketones and aminopyridines have been described <2003JME4702>.

A radical cyclization pathway to reduced pyrrolo[2,3-*b*]pyridines has been reported from 2-bromo-3-(2-aminoethyl)-pyridine and benzophenone in the presence of AIBN and tributyltin hydride (Equation 38) <2001OL1009>. Both electron-donating and electron-withdrawing functional groups can be present on the pyridine ring since the radical has its unpaired electron localized in a σ-orbital.

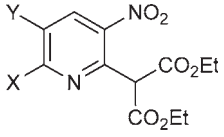


(38)

Several synthetic routes to pyrrolopyridines from nitro-substituted pyridine derivatives have been described. Starting with 3-nitro-2-[(*E*)-2-phenylethenyl]pyridine, 2-phenylpyrrolo[3,2-*b*]pyridine can be obtained in a two-step reaction <2003S1671>. This is a fairly general synthesis for pyrrolopyridines, including the [2,3-*c*], [2,3-*b*], and [3,2-*c*] isomers. The use of 6-methyl-5-nitropyridin-2-ol leads to 5-aminomethyl[3,2-*b*]pyridine in a multi-step synthesis <2003BML795>. Pyrrolo[2,3-*c*]pyridine derivatives have been synthesized from 2-amino-4-methyl-5-nitropyridine in nearly quantitative yields, while the [3,2-*b*] isomer can be generated from the 6-methyl nitropyridine derivative (Equation 39) <2003JME3060>. 2-Chloro-4-nitropyridine reacts with alkynes in a catalytic reductive annulation reaction. Alkynes containing one or more aryl or carboalkoxy groups are most reactive <2002CC484>. 2-Halogenated 3-nitropyridine derivatives react with diethyl malonate to generate substituted pyridines, **101**. Reduction of the nitro group to the amine followed by cyclization leads to the formation of pyrrolo[3,2-*b*]pyridines <1996JHC287>. An alternative method uses a vicarious nucleophilic substitution reaction of the nitropyridines to generate the pyrrolopyridine derivatives. Nitropyridine and nitropyridone derivatives can be reacted to generate pyrrolopyridines. The nitropyridone derivatives are generally more reactive toward nucleophilic attack, leading to better yields of the pyrrolopyridine products <2002H(58)301>.

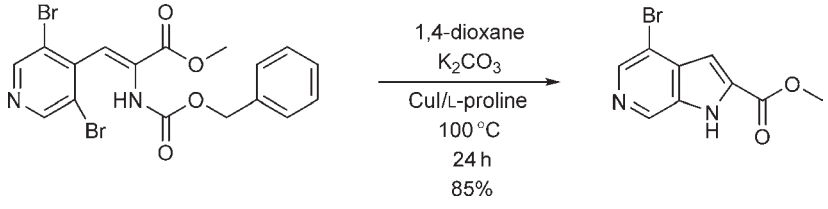


(39)



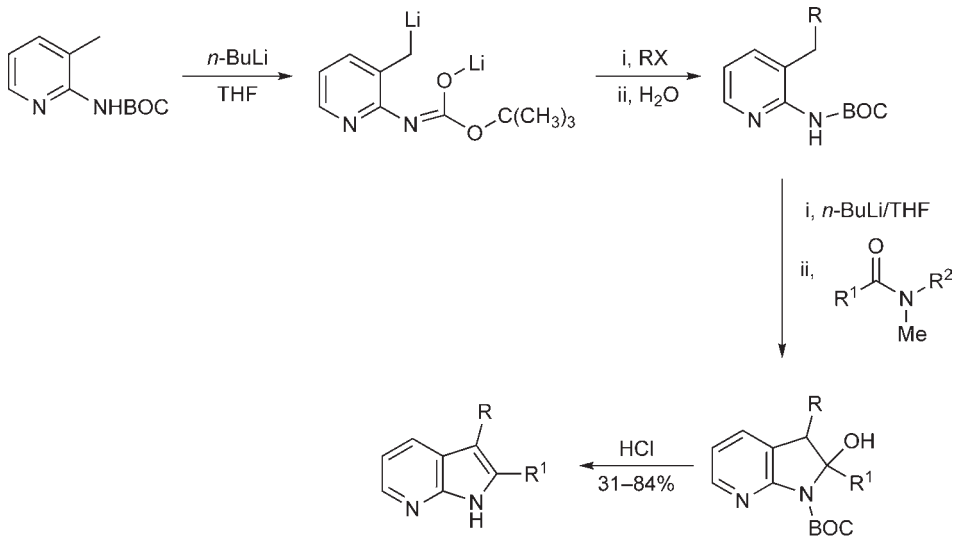
101
X = Cl, F
Y = H, Cl

A cyclization of enecarbamates leads to the synthesis of pyrrolo[2,3-*c*]pyridines (Equation 40) <2005TL8877>. The reaction is catalyzed by a copper(I) iodide/L-proline catalyst system.



(40)

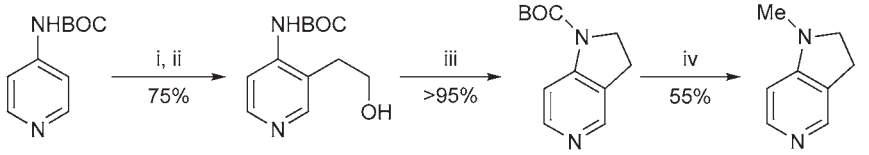
Pyrrolo[2,3-*b*]pyridines can be conveniently synthesized by a directed *ortho*-lithiation reaction from a substituted pyridyl amide derivative, available from 2-amino-3-methylpyridine, as shown in **Scheme 28** <1996S877>. Mono- or disubstituted pyrrolopyridines are formed, depending on the number of metalation/alkylation steps. Modifications of the reaction are useful in the synthesis of the isomeric [2,3-*c*]- and [3,2-*c*]pyrrolopyridines. 4-Aminopyridines, after protection of the amino nitrogen, are readily converted into reduced pyrrolo[3,2-*c*]pyridines in an efficient four-step synthesis (**Scheme 29**) <1998TL8919>. The pyrrolo[3,2-*c*]pyridine derivatives are brominated and then undergo Suzuki cross-coupling reactons. Anions resulting from lithiation of pyridine carboxamide derivatives undergo intramolecular reactions leading to the formation of polycyclic heterocycles, including pyrrolo[3,4-*c*]pyridines (Equation 41) <2005OL3673>.



R = H, Me, CH_2Ph, $CH_2CH{=}CH_2$, $(CH_2)_3N(CH_3)_2$
R^1 = H, Me, Ph
R^2 = Me, OMe

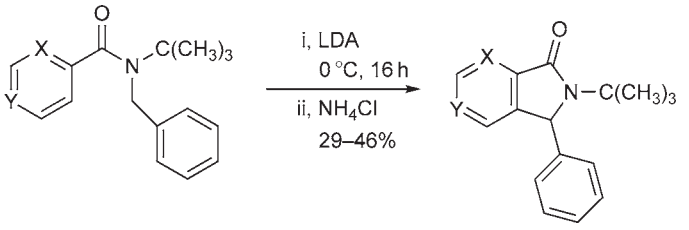
R	R^1	*Yield* (%)
H	H	84
Me	H	74
CH_2Ph	H	39
CH_3	Ph	49

Scheme 28



i, *t*-BuLi, THF, –78 → –15 °C, 3 h
ii,  , –78 °C → rt, 2 h
iii, MsCl, Et_3N, CH_2Cl_2, –10 °C → rt, 2 h
iv, DIBAL-H, CH_2Cl_2, reflux, 20 h

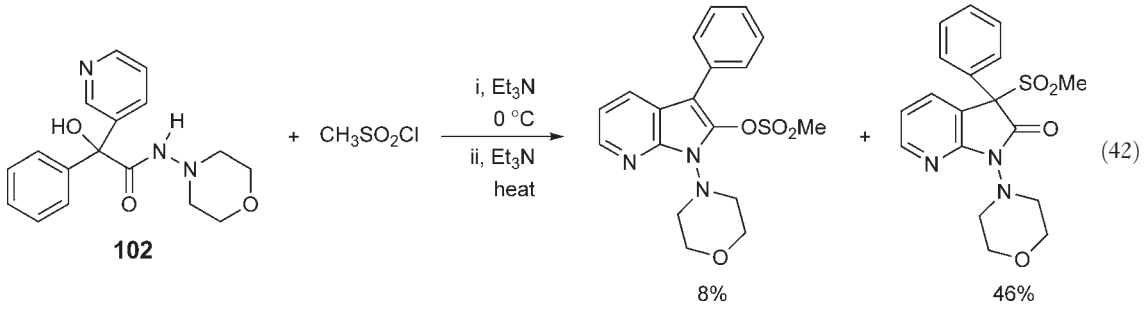
Scheme 29



X	*Y*	*Yield* (%)
N	CH	46
CH	N	29

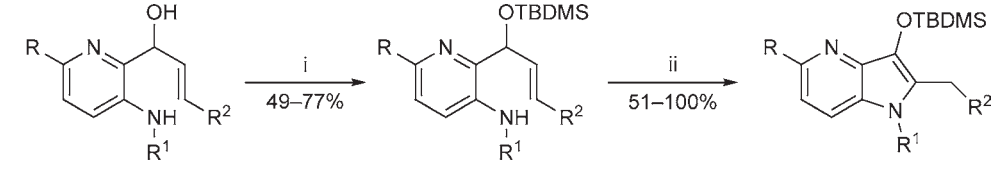
(41)

In a rearrangement reaction, 2-hydroxy-2-phenyl-2-(3-pyridinyl)acetic hydrazide, **102**, reacts with methanesulfonyl chloride to generate a mixture of pyrrolo[2,3-*b*]pyridine derivatives (Equation 42) <1998JHC145>. The proposed mechanism for the rearrangement involves intramolecular attack of compound **102** on a reactive pyridinium intermediate formed during the reaction.



(42)

2-(1-Hydroxyalkyl)-3-aminopyridines undergo a palladium-catalyzed cyclization reaction to produce pyrrolo[3,2-*b*]pyridine derivatives. After protection of the alcohol, the cyclization reaction is carried out in good yields (**Scheme 30**) <1999S1893>.



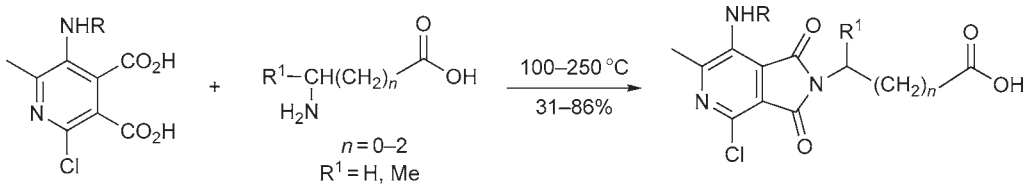
R = MeO, Cl
R^1 = Me, CH_2=$CHCH_2CH_2$
R^2 = H, Me, Ph

i, TBDMSCl
ii, $Pd(Cl_2)(CH_3CN)_2$, LiCl, K_2CO_3, benzoquinone

R	R^1	R^2	*Yield i* (%)	*Yield ii* (%)
MeO	Me	H	77	100
MeO	Me	Me	71	51
Cl	Me	Ph	70	54

Scheme 30

Pyridinedicarboxylic acids and amino acids serve as useful starting materials for the synthesis of pyrrolo[3,4-*c*]-pyridines. The reactions proceed at relatively high temperatures (Equation 43) <1996EJM49>.



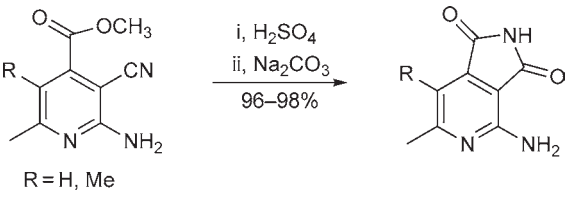
n = 0–2
R^1 = H, Me

R = H, COC_6H_5, 4-ClC_6H_4CO, 4-FC_6H_4CO, 4-$CF_3C_6H_4CO$

n	*R*	R^1	*Yield* (%)
0	H	H	64
0	COC_6H_5	H	32
1	COC_6H_5	H	82
1	4-FC_6H_4CO	H	86
0	4-FC_6H_4CO	H	31

(43)

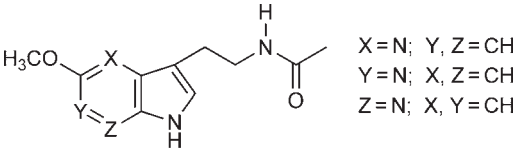
Acid hydrolysis of *ortho*-cyanopyridinecarboxylates leads to a cyclization reaction which forms pyrrolo[3,4-*c*]pyridines in nearly quantitative yields (Equation 44) <2003CHE1182>.



(44)

Pyrrolo[3,4-*c*]pyridine derivatives can be synthesized from arylacetonitriles and 5-bromonicotinamide upon reaction with lithium diisopropylamide (LDA). The reaction proceeds in moderate yields (36–54%) <1998T3391>.

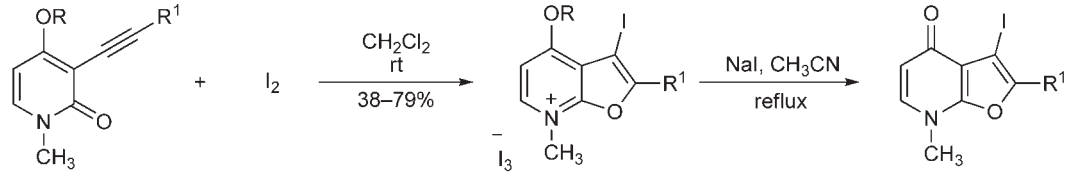
Pyrrolopyridine derivatives, **103**, can be synthesized from pyridine compounds containing amino, iodo, and/or nitro substituents <1999H(50)1065>. These compounds serve as analogues of melatonin.



103

10.06.9.2.2 Furopyridines

Furo[2,3-*b*]pyridines can be synthesized from alkynylpyridones and iodonium sources (**Scheme 31**) <2006OL1113>. Iodine proved to be much more effective at promoting the iodocyclization reaction than other iodonium sources (ICl, *N*-iodosuccinimide (NIS)). The pyridinium triiodide salt, **104**, can be converted into the corresponding pyridinone by treatment with an external source of iodide. In a variation of the reaction, a one-pot synthesis of the furopyridine derivatives **105** can be achieved, with overall yields of 79–92%, by treatment with iodine followed by sodium iodide without isolation of the triiodide salt. Another similar one-pot synthesis involves 3-iodo-2-pyridones, terminal alkynes, and organic halides in a series of two palladium cross-coupling reactions (Equation 45) <2003OL2441>. This reaction could also be carried out in a two-step sequence, but the overall reaction yields were typically improved for the one-pot method.



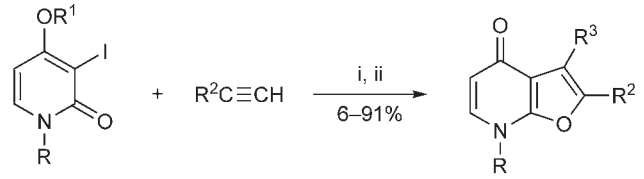
104 **105**

R = CH_3, $CH_2C_6H_5$
R^1 = Ph, 4-$MeO_2CC_6H_4$, 4-*n*-$C_6H_{13}OC_6H_4$, *n*-C_4H_9

R	R^1	*Yield* **104** (%)
CH_3	Ph	79
$CH_2C_6H_5$	Ph	72
CH_3	*n*-C_4H_9	38
CH_3	4-$MeO_2CC_6H_4$	73

Scheme 31

Alkynyl pyridinols and aryl halides generate furopyridines in good yields in the presence of a palladium catalyst system. Three isomeric 2-substituted furopyridines, the [2,3-*b*], [2,3-*c*], and [3,2-*b*] isomers, can be synthesized by this method <2002SL453>. Furo[3,2-*b*]pyridines are generated from alkynylpyridine derivatives that contain an iodo group bonded to the ring <2002OL2791, 2005EJO5296>.



R, R^1 = Me, Bn
R^2 = Ph, *n*-C_4H_9, 4-$MeO_2CC_6H_4$
R^3 = Ph, 4-$MeO_2CC_6H_4$, 4-IC_6H_4, 3-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 4-FC_6H_4

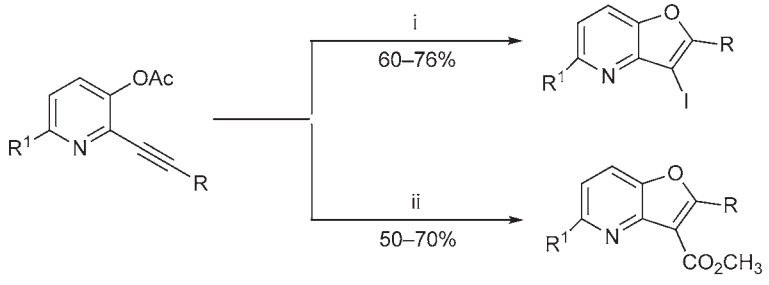
i, $PdCl_2(PPh_3)_2$, CuI, CH_3CN, Et_3N, 60 °C, 24 h
ii, R^3X, 60 °C, 48 h

R	R^1	R^2	R^3	*Yield (%)*
Me	Bn	4-$MeO_2CC_6H_4$	4-$MeO_2CC_6H_4$	83
Me	Bn	4-$MeO_2CC_6H_4$	4-$F_3CC_6H_4$	90
Me	Bn	Ph	4-$MeO_2CC_6H_4$	80
Me	Bn	*n*-C_4H_9	4-$MeO_2CC_6H_4$	61
Bn	Bn	4-$MeO_2CC_6H_4$	4-$MeO_2CC_6H_4$	58

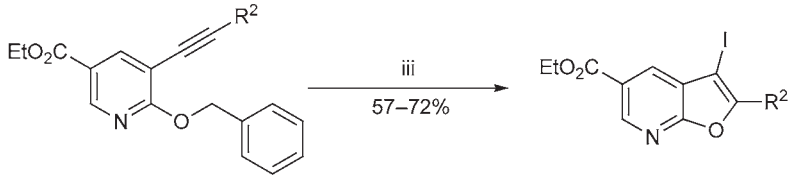
(45)

The palladium/copper-catalyzed coupling reaction of 2-iodo-3-methoxy-6-methylpyridine and terminal alkynes leads to the formation of *o*-methoxyalkynylpyridines which undergo electrophilic cyclization reactions to afford furo[3,2-*b*]pyridines in moderate yields <2005JOC10292>. A similar Pd/Cu-catalyzed reaction with hydroxypyridines and trimethylsilyl (TMS)–acetylene leads to the formation of alkynyl pyridines which cyclize to form furo[2,3-*c*]-pyridines in good yields <1998JME1357>.

The [2,3-*b*], [2,3-*c*], and [3,2-*b*] isomers of 2,3-disubstituted furopyridines can be obtained from alkynes and *o*-iodoacetoxypyridines by a palladium-catalyzed cross-coupling reaction followed by an electrophilic iodocyclization reaction or a palladium-catalyzed cyclization in the presence of CO, as illustrated in **Scheme 32** for [2,3-*b*] and [3,2-*b*] derivatives. When the pyridine ring contains strongly electron-withdrawing substituents such as carboethoxy, the reaction proceeded smoothly with benzyloxyalkynylpyridines <2002OL2409>.



R	R^1	*Method*	*Yield (%)*
Ph	H	i	76
Ph	H	ii	62
n-C_4H_9	Me	i	62
n-C_4H_9	Me	ii	67



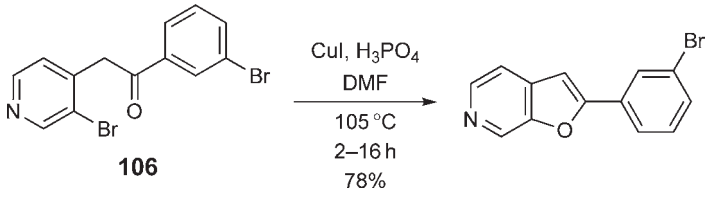
R	*Yield (%)*
Ph	72
n-C_4H_9	57

i, I_2, $NaHCO_3$, MeOH, rt
ii, K_2CO_3, NaOAc, $CuCl_2$•$2H_2O$, $PtCl_2$, MeOH, CO, rt
iii, I_2, $NaHCO_3$, EtOH

R = Ph, $CH(OEt)_2$, *n*-C_4H_9
R^1 = H, Me, $CH_3CO_2CH_2$
R^2 = Ph, *n*-C_4H_9

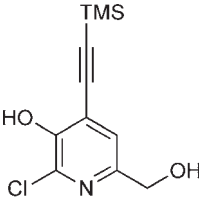
Scheme 32

The copper(I) iodide-promoted ring closure of the pyridyl bromophenyl ketone **106** leads to the formation of 2-(3′-bromophenyl)furo[2,3-*c*]pyridine as shown in Equation (46) <2005JOC6964>.

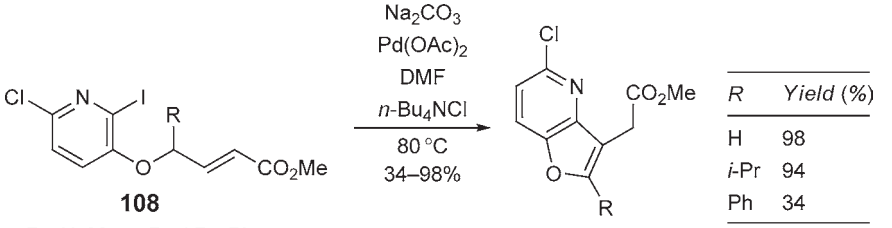


(46)

2-Chloro-3-hydroxypyridine is a readily available starting point for the synthesis of furo[2,3-*c*]pyridines via iodination followed by a palladium cross-coupling reaction with alkynes to afford alkynylpyridines, **107**. Cyclization of compound **107** leads to furo[2,3-*c*]pyridine products <1998JME1357, 1998JOC7851>. Similarly, reaction of 5-bromo-3-iodo-2-hydroxypyridine and terminal alkynes with a copper/palladium catalyst system leads to the formation of furo[2,3-*b*]pyridines <2002H(57)55>. 5-Amino-2-chloropyridine is used to generate iodopyridinyl butenoates, **108**, which undergo a palladium-catalyzed cyclization to yield 2,3,5-trisubstituted furo[3,2-*b*]pyridines (Equation 47) <2003TL725>. Alkynyl pyridines are also reagents in a solid-phase synthesis of furo[3,2-*b*]pyridines that begins with hydroxymethyl polystyrene resin <2004OL1405>.



107



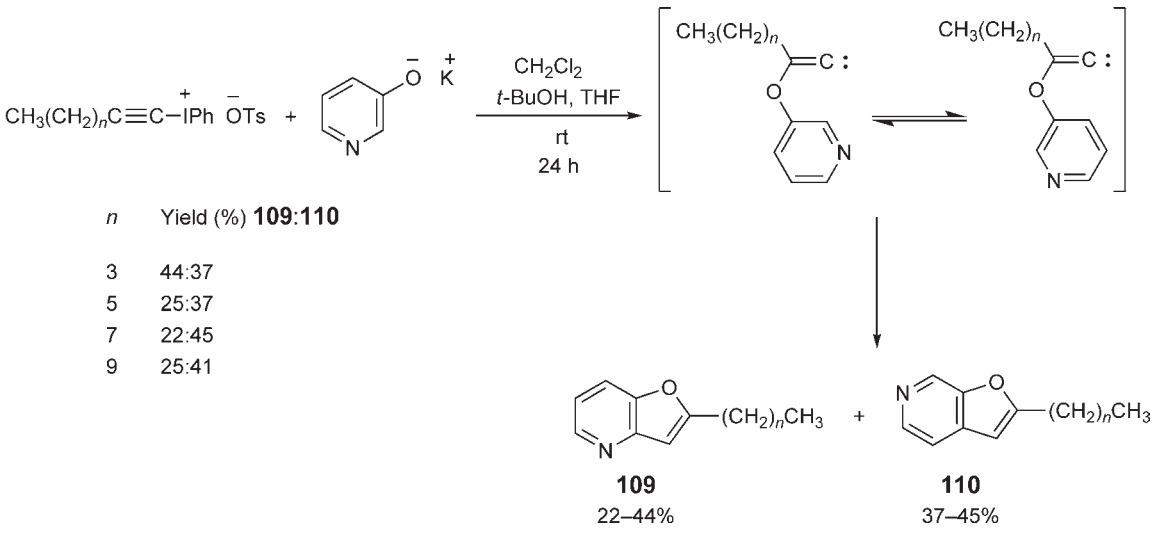
108

R = H, Me, *n*-Pr, *i*-Pr, Ph

R	*Yield (%)*
H	98
i-Pr	94
Ph	34

(47)

Alkylidenecarbenes undergo a carbon–hydrogen-insertion reaction that leads to a mixture of two isomeric products, 2-substituted furo[3,2-*b*]pyridines, **109**, and 2-substituted furo[2,3-*c*]pyridines, **110**, as shown in **Scheme 33**. The reaction is also applicable to the quinoline system <1998TL5375>.



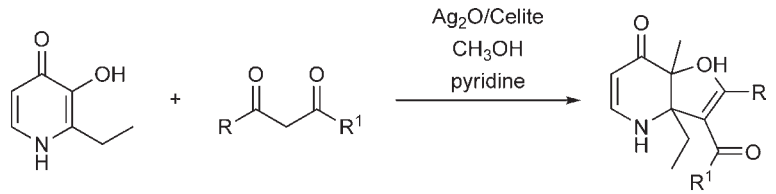
n	Yield (%) **109**:**110**
3	44:37
5	25:37
7	22:45
9	25:41

109 22–44%

110 37–45%

Scheme 33

An oxidative coupling reaction of hydroxypyridinones with β-dicarbonyl compounds leads to the formation of dihydrofuro[3,2-*b*]pyridinone derivatives (Equation 48) <2005TL5085>. The reaction is carried out as a one-pot synthesis.

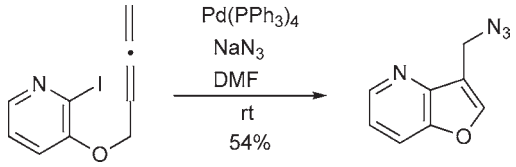


(48)

R = Me, Ph, 2-$CH_3COC_6H_4$, 2,4-$(CH_3)_2C_6H_3O$

R^1 = Me, OCH_2CH_3, Ph, 2-$CH_3C_6H_4CO$, 2-CH_3O-4-$CH_3C_6H_3$

Pyridines with an allenyl ether group and an iodine atom substituted on the ring undergo a cyclization reaction to afford furo[3,2-*b*]pyridine derivatives in moderate yields (Equation 49) <2001T7729>.



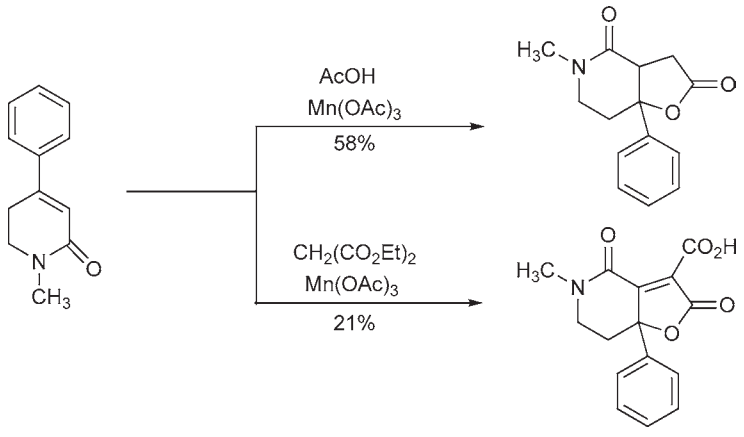
(49)

3-Hydroxypicolinic acid is converted into hexahydrofuro[3,2-*b*]pyridine-3-one derivative **111** in a nine-step stereoselective synthesis <2004BMC5689>. 3-Iodo-4-prop-2-ynyloxypicolinanilides can be converted into furo[3,2-*c*]pyridine derivatives in good yields in the presence of tri-*n*-butyltin hydride and AIBN <2004H(64)261>.



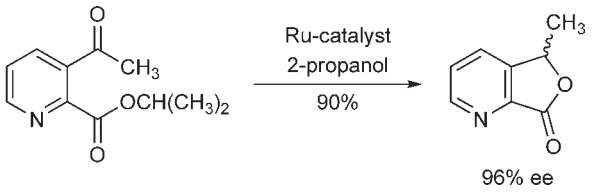
111

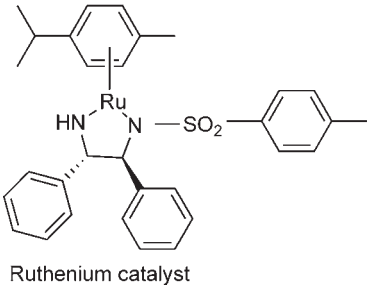
Dihydropyridinones react with acetic acid or diethyl malonate to give partially reduced furo[3,2-*c*]pyridine derivatives in low to moderate yields (**Scheme 34**) <2002CHE368>. More highly reduced products are formed with the acid starting material in the presence of manganese triacetate than with the diester under the same conditions.



Scheme 34

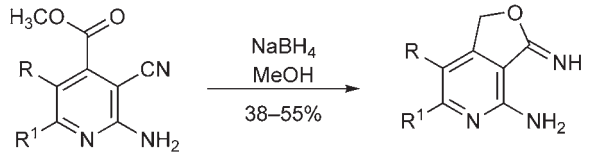
Furo[3,4-*b*]pyridines can be prepared in a stereoselective synthesis involving a ruthenium-catalyzed asymmetric transfer hydrogenation reaction <2001TL1899>. The reaction proceeds with exceptionally high yield and ee (Equation 50).





(50)

3-Cyanopyridine-4-carboxylate salts can be reduced to give dihydrofuro[3,4-*c*]pyridines (Equation 51) <2005RJO279>. Under acidic conditions, the imine fragment can be hydrolyzed to generate lactone product.

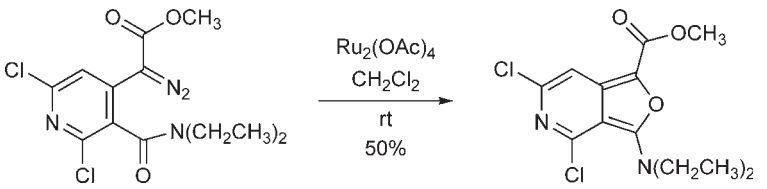


R	R^1	*Yield (%)*
CH_3	CH_3	55
H	CH_3	50
	$-(CH_2)_3-$	38
	$-(CH_2)_4-$	45

(51)

R = CH_3, H
R^1 = CH_3
R, R^1 = $(CH_2)_3$, $(CH_2)_4$

Highly functionalized furo[3,4-*c*]pyridine, **113**, can be generated in moderate yield from diazoacetic ester derivative **112** by an intramolecular rhodium-catalyzed cyclization reaction (Equation 52). Compound **113** has been shown to be a very stable molecule that has been proposed as an intermediate species in Hamaguchi–Ibata reactions <1999TL397, 2000JOC3111, 2003JOC4206>. 4-Aminofuro[3,4-*c*]pyridin-3-ones can be produced from 2-chloro-3-cyanopyridines and an appropriate primary or secondary amine nucleophile to afford aminopyridine intermediates which undergo cyclization reactions that leave the amino group in place <1999CHE58>.



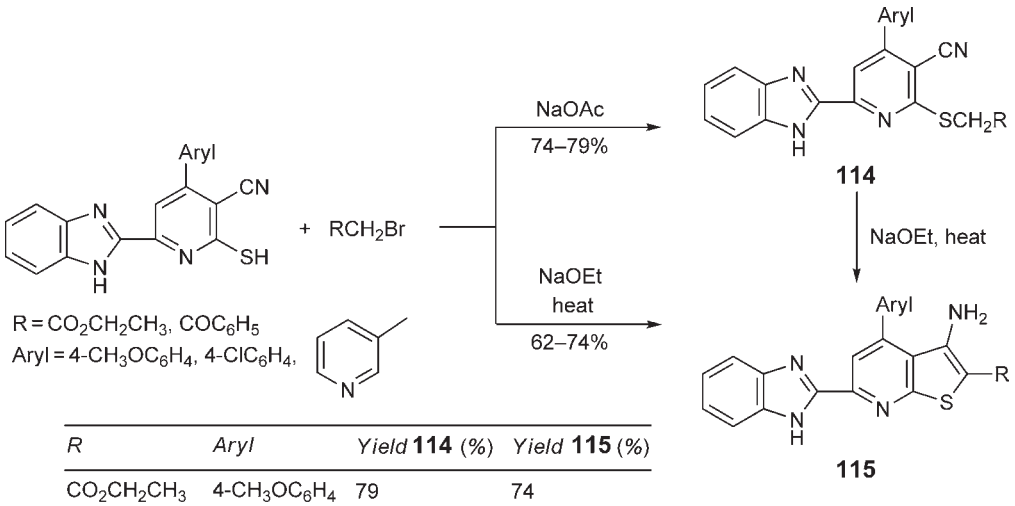
112 **113**

(52)

10.06.9.2.3 Thienopyridines

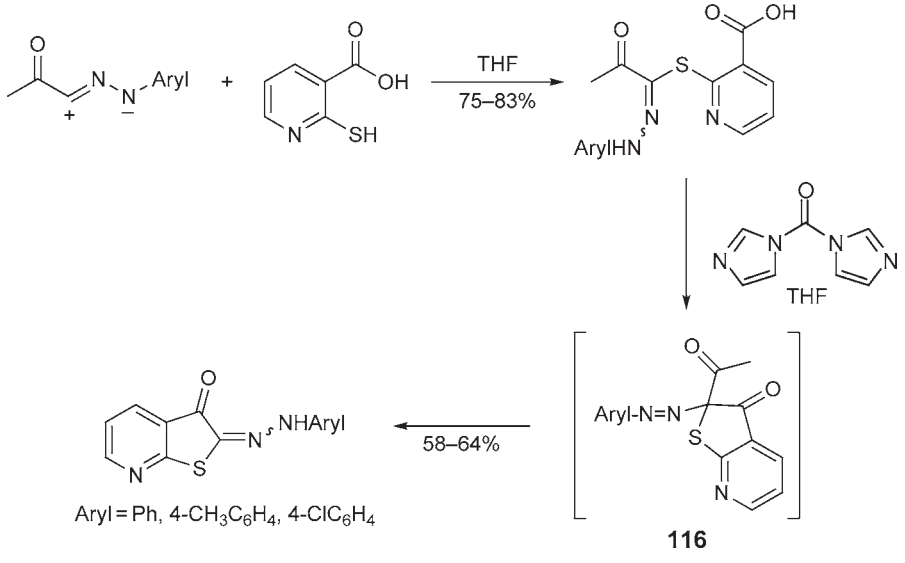
Thieno[2,3-*b*]pyridines, **115**, form via a condensation reaction with halogenated carbonyl compounds, as shown in **Scheme 35**. Depending on the base strength of the reagent and reaction conditions, intermediate **114** may be isolated <2005CCA63>.

Nitrileimines undergo addition reactions with 2-mercaptonicotinic acid to generate hydrazonomercaptonicotinic acids. These acids readily undergo cyclocondensation reactions promoted by 1,1′-carbonyldiimidazole to give oxothieno[2,3-*b*]pyridines after loss of an acetyl group from intermediate **116** (**Scheme 36**) <2005M567>.



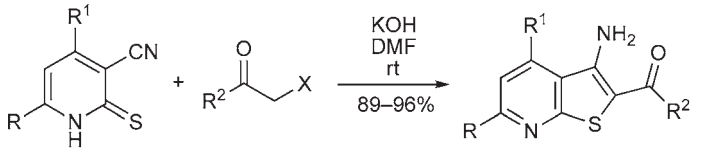
R	*Aryl*	*Yield* **114** (%)	*Yield* **115** (%)
$CO_2CH_2CH_3$	4-$CH_3OC_6H_4$	79	74
$CO_2C_6H_5$	4-ClC_6H_4	74	62

Scheme 35



Scheme 36

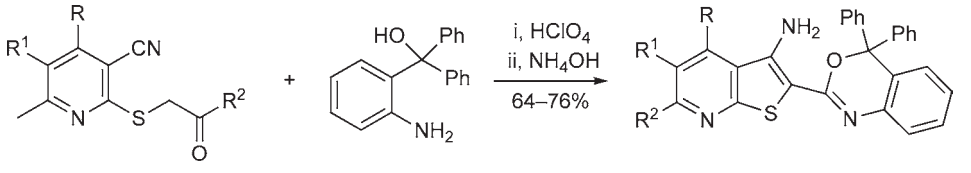
Cyanopyridinethiones react with a variety of halogenated compounds, including α-halo carbonyl compounds and ethyl 4-bromocrotonoate, in the presence of excess base to form thieno[2,3-*b*]pyridines via a Thorpe–Ziegler-type cyclization (Equation 53) <1997CHE481, 1997CHE583, 1997CHE793, 1998CHE237, 1998CHE688, 1999CHE293, 2002SC3493, 2004CHE377, 2004CHE1600>. In an analogous reaction, cyanopyridinethiones react with 4-nitrobenzyl bromide and methyl 5-chloromethyl-2-furoate followed by alkylation and cyclization to form thieno[2,3-*b*]-pyridines <2000MOL1085>. Similarly, cyanopyridin-2-ylthioacetic acids and amides are converted into thieno[2,3-*b*]pyridines, **117**, upon reaction with *o*-aminophenyl(diphenyl)carbinols (Equation 54) <2004RCB2878>. A cyclization reaction converts cyano compound **118** into a thieno[2,3-*b*]pyridine derivative. Compound **118** is available from the reaction of 2-chloro-3-cyano-4-methylamino-5-nitropyridine with pyridine (**Scheme 37**) <2003CHE328>.



R	R^1	R^2
Me	CH_2OCH_3	Ph
CH_2OCH_3	Me	Ph
Me	CH_2OCH_3	2,4-$Cl_2C_6H_3$

(53)

R, R^1 = Me, CH_2OCH_3
R^2 = Ph, 4-BrC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$F_2C_6H_3$

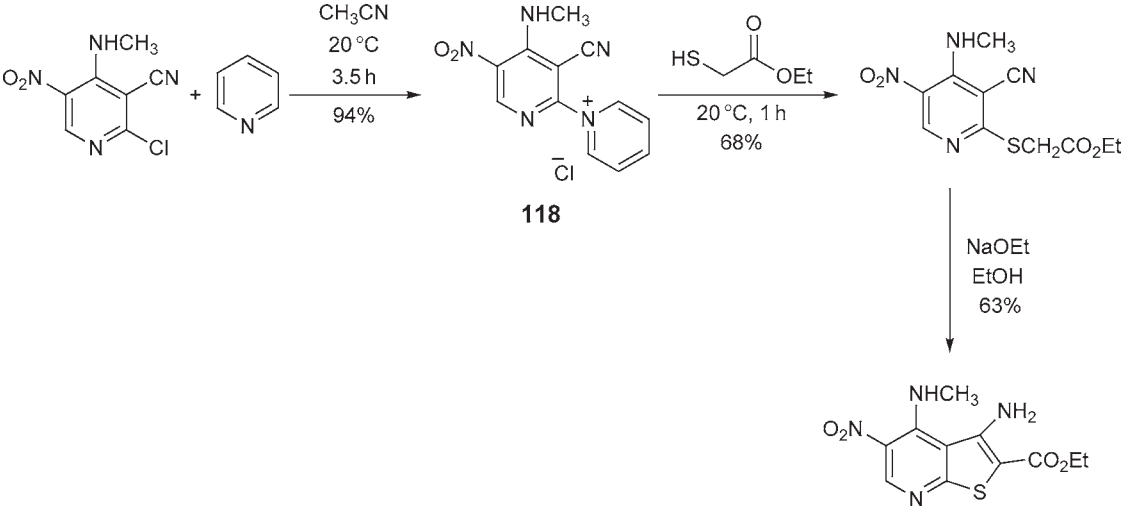


R = Me, CH_2OCH_3
R^1 = H, Cl
R^2 = OH, NH_2

117

(54)

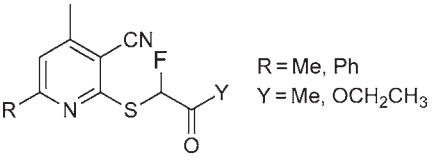
R	R^1	R^2	*Yield* (%)
Me	H	Me	64
Me	Cl	Me	76



118

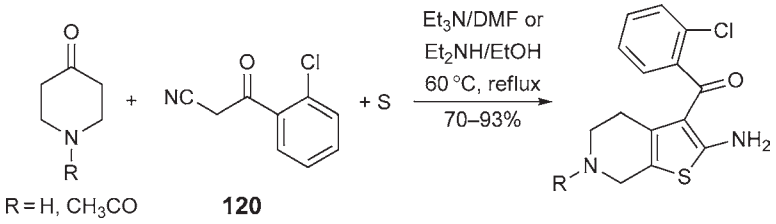
Scheme 37

Thieno[2,3-*b*]pyridines are produced in good yields (50–90%) from pyridine derivatives substituted in the 2-position with an α-fluorosulfide side chain, **119**, via an intramolecular substitution reaction. The cyclization reaction requires treatment with base <1995JOC7654>.



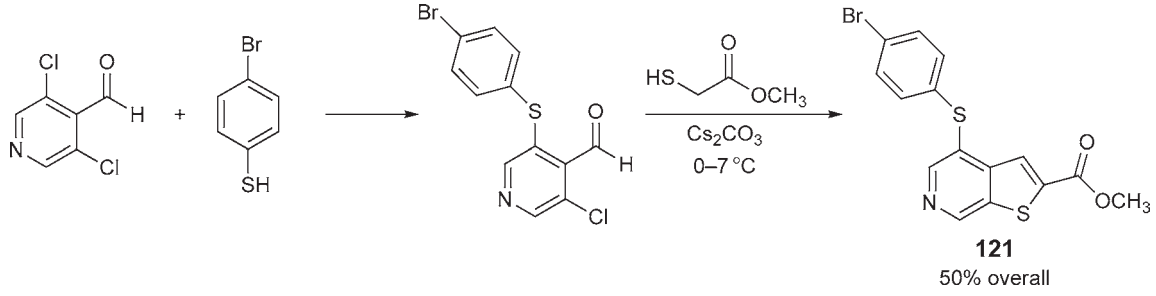
119

N-Substituted 4-piperidones react with nitrile **120** and elemental sulfur in the presence of a base such as diethylamine or triethylamine to generate tetrahydrothieno[2,3-*c*]pyridines according to the Gewald synthesis (Equation 55) <2002BML1607>. Tetrahydrothieno[2,3-*b*]pyridin-3-ones are generated from the reaction of α-brominated esters with piperidine-2-thiones <1996H(43)63>. An analogous reaction occurs with the seven-membered ring azepane-2-thiones.



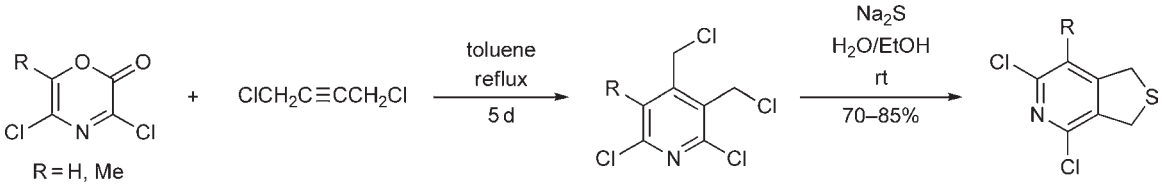
(55)

3,5-Dichloropyridine-4-carboxaldehyde reacts with thiophenol to produce a diaryl sulfide. The diaryl compound and methyl thioglycolate undergo an aldol-type cyclization reaction in the presence of a weak base to afford 4-substituted thieno[2,3-*c*]pyridine derivative **121** (**Scheme 38**) <2002JOC943>.

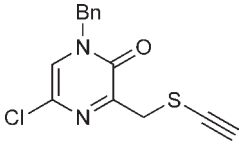


Scheme 38

Thieno[3,4-*b*] and [3,4-*c*]pyridine derivatives can be generated from a cycloaddition reaction of oxazinones with 1,4-dichloro-2-butyne to afford polyhalogenated pyridine products which cyclize to thienopyridines (**Scheme 39**) <2001T4203>. In a similar reaction, pyrazinones, **122**, containing alkynyl substituents cyclize to form thieno[3,4-*b*] and [3,4-*c*]pyridine derivatives <2002TL799, 2004T429>.



Scheme 39

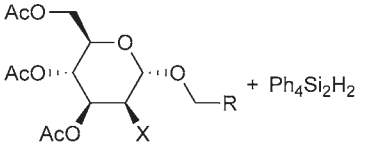


122

A variety of thienopyridine isomers can be generated in low to moderate yields from the reaction of disubstituted pyridines and phenyl isothiocyanate. The pyridine derivatives contain a halogen at position 2 or 3 of the ring, and the other substituent is either a cyanomethyl substituent (CH_2CN) or an ester (CH_2CO_2Et) <1997S949, 1998S1095>.

10.06.9.2.4 Furopyrans

A radical cyclization reaction using a stable radical reagent, 1,1,2,2-tetraphenyldisilane, has been reported to give moderate to good yields of furo[2,3-*b*]pyran derivatives (Equation 56) <2000JOC5440>. The cyclization reactions, which are initiated with Et_3B or AIBN, always produce *cis*-fused rings. A radical cyclization using halogenated allyl acetals, diethylzinc, and a mixed catalyst system, $MnBr_2$/CuCl, leads to stereoselective cyclization to afford perhydrofuro[2,3-*b*]pyran zinc reagents, **123**, in moderate yields. Compound **123** undergoes side-chain reactions to give substituted perhydrofuro[2,3-*b*]pyrans in good yield <1996TL5865>.

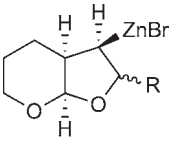


R = –CH=CH_2, –CH=CHPh, –C≡CH
X = Br, SePh

R	*X*	*Method*	*Yield (%)*
CH=CH_2	Br	i	84
CH=CH_2	Br	ii	78
CH=CH_2	SePh	i	64
CH=CH_2	SePh	ii	72

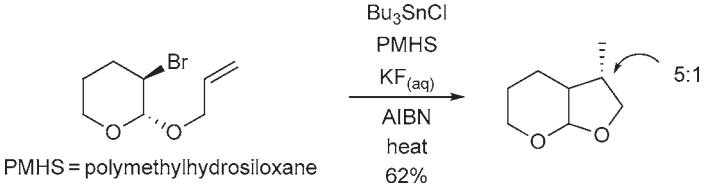
(56)

i, Et_3B, THF, EtOAc, 1 h, rt
ii, AIBN, EtOAc



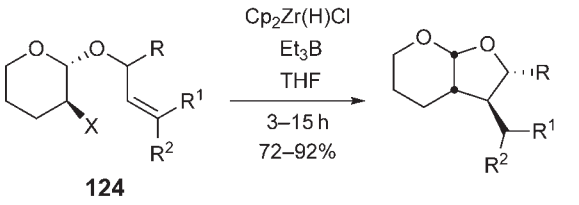
123
R = H, Ph, C_6H_{13}

Tin compounds have frequently been used for radical cyclization reactions <1996OR301>; however, due to difficulties encountered in removal of the reagent following completion of the reaction, along with health hazards associated with these compounds, alternatives for the cyclization reactions have been extensively explored. Reactions that utilize a catalytic amount of tin reagent have been developed including the radical cyclization of halogenated allyl acetals (Equation 57) <1999JOC342>. An active manganese species, generated from Li_2MnCl_4 and magnesium turnings, effectively initiates the radical cyclization reactions of 2-halogenated allyl acetals to afford perhydrofuro[2,3-*b*]pyrans in good yields. The bromoacetal derivatives are less reactive than the corresponding iodo compounds <1998SL1075>. Zirconocene complexes can be used in radical cyclization reactions of halogenated allyl acetals, **124**, to afford perhydrofuro[2,3-*b*]pyran derivatives in high yields with some stereoselectivity (Equation 58) <2002SL337, 2004BCJ1727>. An analogous reaction takes place with appropriately substituted alkynyl groups on the halogenated acetal. Cobalt catalysts have been reported in similar radical cyclization reactions <2001JA5374>. Two types of gallium reagents, dichlorogallane, $HGaCl_2$, and gallium trichloride in the presence of aluminium hydride, are also effective radical mediators in radical cyclization reactions of halogenated allyl acetals <2001OL1853>. Similarly, dichloroindium hydride, $HInCl_2$, prepared from indium trichloride and tributyltin hydride, effectively serves as a radical initiator for radical cyclization of halogenated allyl acetals in the presence of tributyltin hydride <2001TL4661>. In a less commonly explored application, the Grignard reagent, ethylmagnesium bromide, is also an effective mediator in halogenated allyl acetal cyclization reactions, affording perhydrofuro[2,3-*b*]pyran derivatives in excellent yields (84–85%) <2000OL651>.



PMHS = polymethylhydrosiloxane

(57)



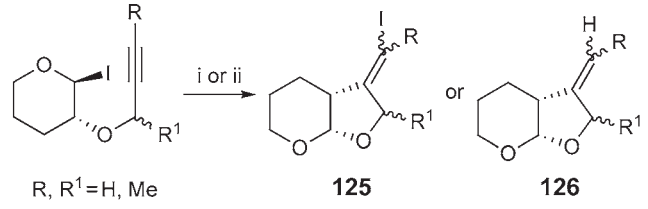
124

X	*R*	R^1	R^2	*Yield* (%) (*cis*–*trans*)
Br	H	Me	Me	92 (69:31)
I	H	Me	Me	89 (66:34)
Br	*n*-C_5H_{11}	H	H	75 (52:48)
I	*n*-C_5H_{11}	H	H	82 (56:44)

(58)

X = Br, I
R = H, *n*-C_5H_{11}
R^1 = H, Me
R^2 = H, Me, *n*-C_3H_7

Iodoalkynes, in the presence of indium species, undergo either atom-transfer cyclization or reductive cyclization reactions. The specific reaction pathway is dependent on the choice of reagents. When equivalent amounts of indium and iodine are used, the atom-transfer cyclization reaction is promoted to form (*Z*)- and (*E*)-isomers of compound **125**, whereas when the ratio of indium to iodine is 2:1, the reductive cyclization reaction predominates to give (*Z*)- and (*E*)-isomers of **126** (Equation 59) <2002TL4585>.



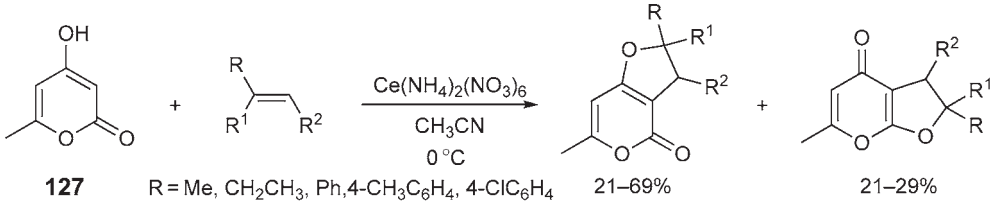
R, R^1 = H, Me **125** **126**

R	R^1	*Method*	*Yield* **125/126** (%)
Me	H	i	60/0
Me	H	ii	0/56
H	Me	i	77/0

(59)

i, In (0.5 equiv), I_2 (0.5 equiv), MeOH, 5–8 h
ii, In (2.0 equiv), I_2 (1.0 equiv), 17–27 h

Pyranone **127** reacts with alkenes in the presence of cerium ammonium nitrate via a cyclization reaction that leads to the formation of furo[2,3-*b*]- and furo[3,2-*c*]-pyranones in moderate yields (Equation 60). This reaction can be extended to the synthesis of furoquinolinones <1999H(51)2881>. Dihydropyran **128**, with either *β*-diketones or *β*-keto esters, undergoes cycloaddition reactions promoted by ceric ammonium nitrate to generate furo[2,3-*b*]pyrans in good yields (Equation 61) <1996T12495>.



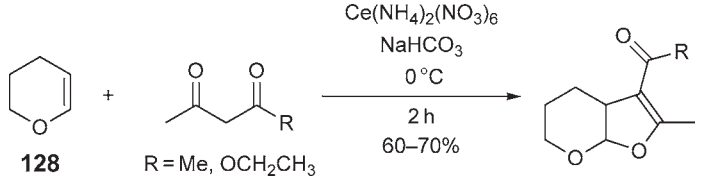
127

R = Me, CH_2CH_3, Ph,4-$CH_3C_6H_4$, 4-ClC_6H_4
R^1 = H, Me, CH_2CH_3
R^2 = H, Me

21–69% 21–29%

(60)

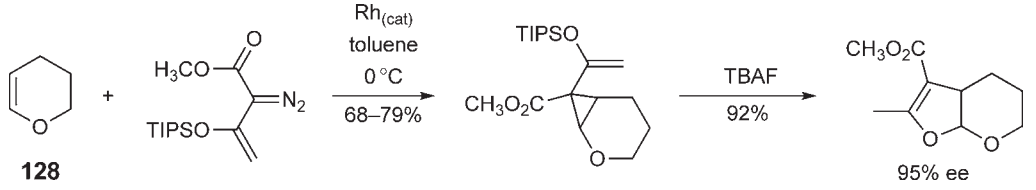
R	R^1	R^2	*Yield* [3,2-*c*]:[2,3-*b*] (%)
CH_2CH_3	CH_2CH_3	H	35:29
Me	Me	Me	21:21
Ph	H	H	69:0



128 R = Me, OCH_2CH_3

(61)

3,4-Dihydro-2*H*-pyran also undergoes a highly stereoselective cyclopropanation reaction with methyl 1-(triisopropylsiloxy)vinyldiazoacetate in the presence of a chiral rhodium catalyst. Optically active furo[2,3-*b*]pyran derivatives are generated upon desilylation of the cyclopropanes (**Scheme 40**) <2005SL1397>.

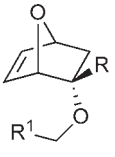


128

Scheme 40

Perhydrofuro[2,3-*b*]pyran derivatives can be synthesized in one pot via a reaction sequence involving addition and cyclization reactions. The reactants, dihydropyran and pyruvate esters, undergo a reaction which is mediated by Lewis acids such as $TiCl_4$, to afford perhydrofuro[2,3-*b*]pyran derivatives in good yields <2003SL1491>.

Perhydrofuro[3,4-*b*]pyrans can be prepared via a regioselective domino metathesis reaction of allyl- and propargyl-substituted oxanorbornenic esters, **129**. The resulting *trans*-fused perhydrofuro[3,4-*b*]pyran derivatives are formed in high yields <2000TL9777>.

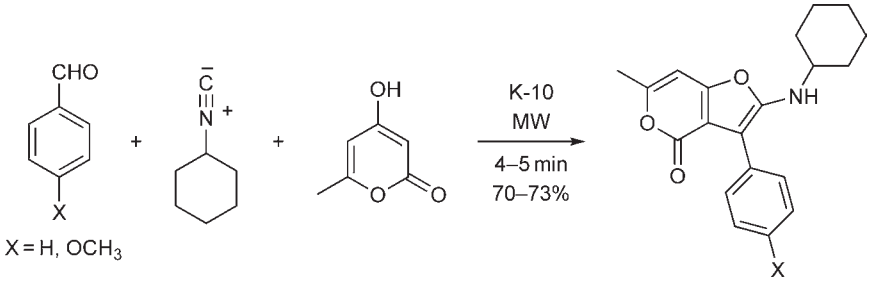


129

R = H, CH_2CH_3, Ph

R^1 = –CH=CH_2, –C≡CCH_3

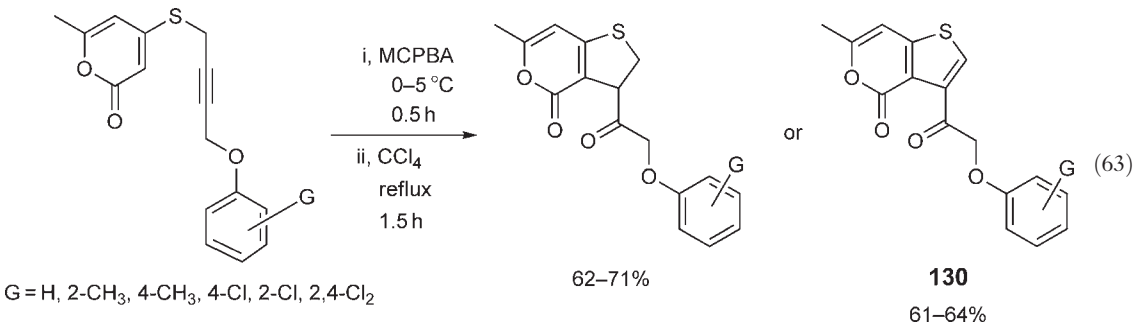
A facile one-pot synthesis of furopyrans takes place with aromatic aldehydes, cyclohexyl isocyanide, and 4-hydroxy-6-methyl-2-pyrone in the presence of a solid support such as Montmorillonite K-10 (Equation 62) <2005SC535>. The solvent-free reaction, which is enhanced by microwave irradiation, proceeds much more rapidly under these conditions than by conventional methods <2002TL2293>. The one-pot, three-component reaction is also reported to take place rapidly using water as solvent <2004M589>.



(62)

10.06.9.2.5 Thienopyrans

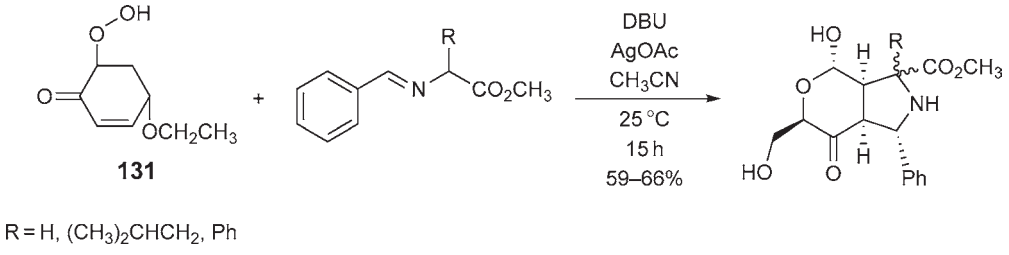
Thiopyranones containing an alkyne group, upon treatment with *m*-chloroperbenzoic acid (MCPBA), undergo a sulfoxide rearrangement to afford thieno[3,2-*c*]pyrans (Equation 63). In some cases, where the aryl group is substituted with a chlorine atom in the 2-position, or disubstituted with chlorine atoms in both 2- and 4-positions, oxidized products, **130**, were formed <2002T10309>.



(63)

10.06.9.2.6 Pyranopyrroles

A chiral enone derived from carbohydrates, **131**, undergoes a stereoselective [3+2] cycloaddition reaction with azomethine ylides to afford pyranopyrrolidines in good yields. The cycloaddition reaction is highly regio- and stereoselective (Equation 64) <2005SL587>.

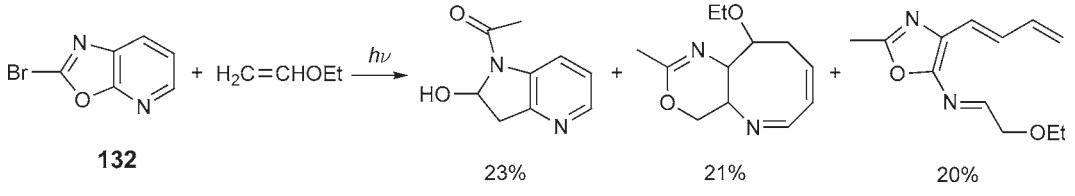


(64)

10.06.10 Ring Syntheses by Transformations of Another Ring

10.06.10.1 Pyrrolopyridines

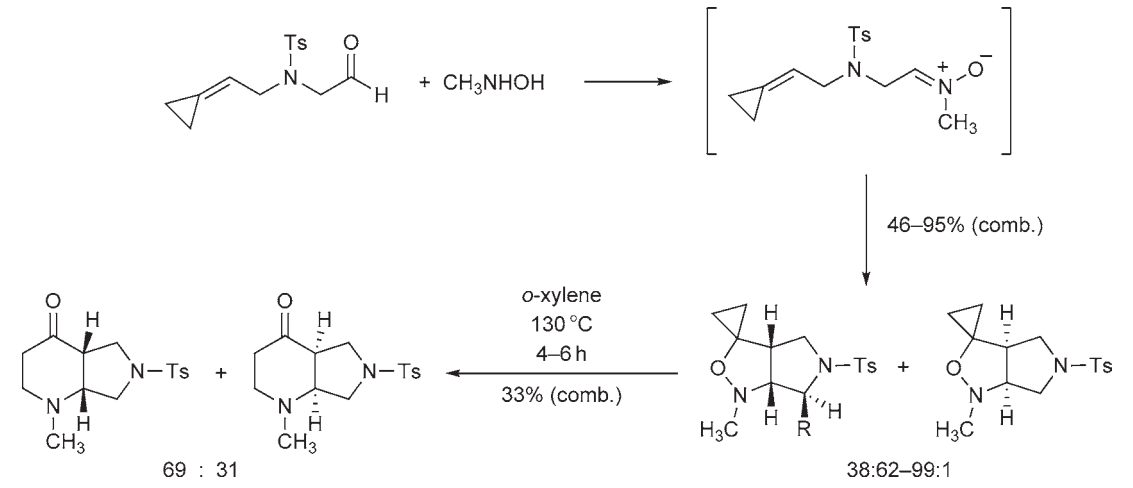
2-Methylisoxazolo[5,4-*b*]pyridine, **132**, reacts with vinyl ether in a photocyclization reaction to give a mixture of mono- and bicyclic products, including a moderate yield of the dihydropyrrolo[3,2-*b*]pyridine derivative as one of three major products shown in Equation (65) <2002EJO4211>.



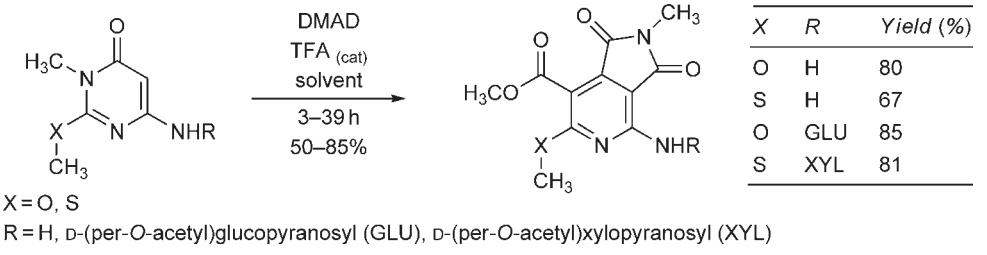
(65)

Alkylidenecyclopropane nitrones undergo intramolecular cycloaddition reactions followed by rearrangement to generate completely reduced pyrrolo[3,4-*b*]pyridine products in moderate yields (**Scheme 41**) <1997JOC8276, 1999EJO2725, 2000TA897>. The nitrone is introduced into the molecule via an aldehyde that is treated with *N*-methylhydroxylamine. The nitrone is not isolated but spontaneously undergoes the cyloaddition reaction to generate tricyclic isoxazolidine compounds. The isoxazolidines thermally rearrange to reduced pyrrolo[3,4-*b*]pyridines.

Aminopyrimidines react with DMAD in the presence of a catalytic amount of a strong acid to give pyrrolo[3,4-*c*]pyridines in a cycloaddition reaction (Equation 66) <2001SL57>. In the absence of the acid catalyst, aminopyridines are produced in the reaction.



Scheme 41

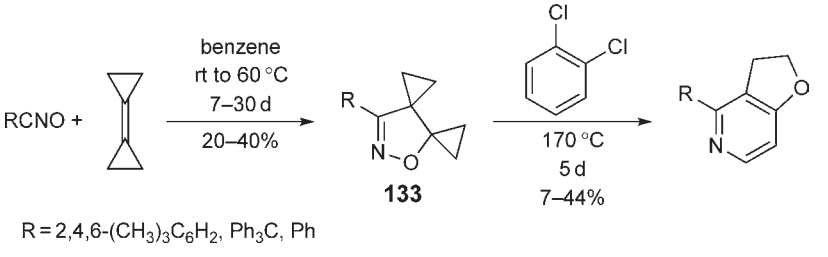


X	R	Yield (%)
O	H	80
S	H	67
O	GLU	85
S	XYL	81

(66)

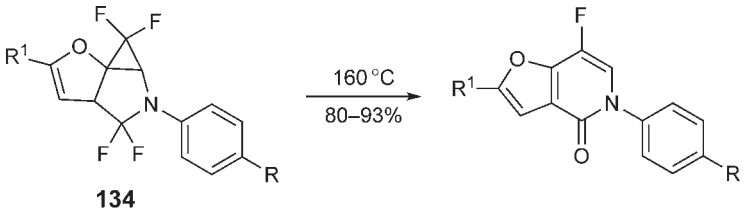
10.06.10.2 Furopyridines

Thermal rearrangements of 5-spirocyclopropaneisoxazolines, **133**, lead to dihydrofuro[2,3-*c*]pyridines (**Scheme 42**) <1996JOC1665>. Compound **133** is prepared from the reaction of bicyclopropylidene, acting as a dipolarophile, with nitrile oxides. A one-pot variation of the reaction beginning with a stable nitrile oxide and bicyclopropylidene affords higher yields of the furopyridines.



Scheme 42

Fluoro-substituted dihydrofuro[3,2-*c*]pyridinones are obtained from the thermolysis reaction of cyclopropa[*b*]-furo[2,3-*c*]pyrroles, **134**, along with the loss of HF (Equation 67) <2005SL1006>. Compound **134** is generated from pyrroles via reaction with a carbene to give an azomethine ylide which undergoes an electrocyclization reaction.



R	R^1	Yield (%)
H	H	83
Br	Me	80
OMe	4-NCC_6H_4	93
H	4-$EtO_2CC_6H_4$	86

(67)

134

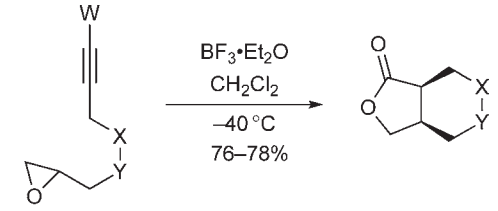
R = H, Br, OMe

R^1 = H, Me, 4-$EtO_2CC_6H_4$, 4-NCC_6H_4

Pyrazinones substituted with an alkynyloxy group at position 3 of the ring undergo an intramolecular Diels–Alder reaction to form furopyridine derivatives. The cycloaddition reaction is influenced by a variety of factors, including length of the side chain, and electron-donating ability of the oxygen in the ether link. As a consequence, high yields of furo[2,3-*b*]-, [2,3-*c*]-, [3,4-*b*]-, or [3,4-*c*]-pyridines can be generated in this reaction <1995T12463>.

10.06.10.3 Furopyrans

A tungsten-promoted intramolecular [3+2] cycloaddition reaction of an alkyne and epoxide leads to the formation of *cis*-isomers of reduced furo[3,4-*c*]pyrans, as shown in Equation (68) <2001JA7427>. The alkynyltungsten complexes were prepared in good yields from the corresponding alkynes upon treatment with $CpW(CO)_3Cl$ and diethylamine <1997JA4404>.



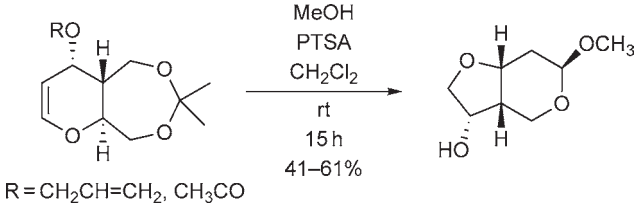
(68)

X, Y = CH_2, O

W = $CpW(CO)_3$

A [3+3] cycloaddition reaction of epoxides containing a propargyltungsten group, in the presence of Lewis acids, leads to the formation of furo[3,4-*c*]pyrans in moderate yields <2001JOC8106>. Pyranopyrroles may also be synthesized via this route.

Trioxabenzocycloheptene readily rearranges to a furo[3,2-*c*]pyran upon treatment with *p*-toluenesulfonic acid as shown in Equation (69) <2002T7951>.

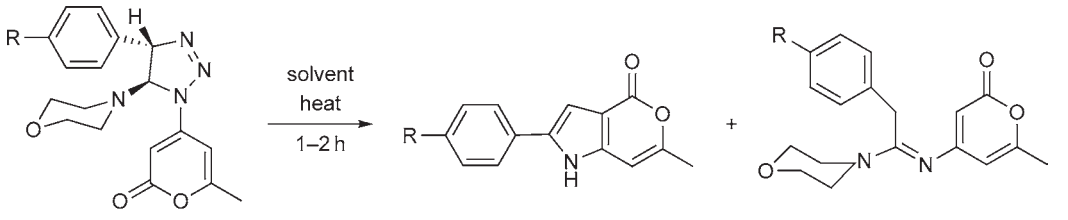


(69)

R = $CH_2CH{=}CH_2$, CH_3CO

10.06.10.4 Pyranopyrroles

Dihydrotriazoles, **135**, undergo a pyrolysis reaction to generate a mixture of pyranopyrroles, **136**, and amidines, **137** (Equation 70). 2-Aminoaziridines are proposed as key intermediates in the sequence <2001J(P1)1723>. Choice of solvent has a significant effect on the ratio of **136:137** produced.



135 → **136** 11–88% + **137** 2–88% (70)

R = H, Me, Cl, Br, F, CH_3O

Solvent = toluene (A), 1-propanol (B), toluene/BF_3•Et_2O (C)

Solvent	*R*	*Yield* **136:137** (%)
A	H	21:55
B	H	13:70
C	H	58:18
A	Me	24:46
B	Me	22:56
C	Me	77:7

10.06.11 Synthesis of Particular Classes of Compounds and Critical Comparison of Available Routes

This chapter covers nine parent ring systems. Most of the compounds discussed here are compounds that are only available synthetically. A few of the ring systems are found in naturally occurring compounds including the pyrano[3,2-*b*]-pyrrole skeleton which is incorporated in natural products found in *A. niger*, a sponge-derived fungus <2004JNP1532>. Some natural antibiotics based on furo[3,2-*c*]pyridinones have also been described recently <2002T10243>.

Most of the synthetic routes to the compounds start from a six-membered ring heterocycle. As found in the previous review <1996CHEC-II(7)167>, the focus of many of the studies has been on the pyridine series–pyrrolo-pyridines, furopyridines, and thienopyridines. Within each of these classes of compounds, the [2,3-*b*] isomers have, by far, received the most attention. Also, as found in the previous review, some of the ring systems have not been investigated at all. Since that time, there has been much interest in thienopyridines because of the wide variety of biologically active compounds that originate from derivatives of thienopyridines (see Section 10.06.12.3). Much of the chemistry of furopyrans involves partially or fully reduced derivatives. There are few literature references to the parent series listed in **Figure 6**; however, there has been considerable activity with the reduced derivatives.

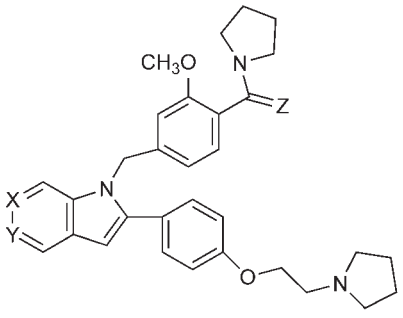
There are numerous reactions reported in the literature that produce highly functionalized derivatives of the parent bicyclic compounds. Many of those reactions have been detailed in this chapter. For several of the bicyclic systems, general synthetic routes that lead to high product yields are unavailable. Many of the known synthetic routes lead to carbonyl derivatives of the ring systems. Within this chapter, these compounds have been treated in each section according to the ring substitution pattern. Likewise, syntheses of partially and fully reduced derivatives of the compounds are included with each parent compound.

10.06.12 Important Compounds and Applications

10.06.12.1 Pyrrolopyridines

Pyrrolopyridinone **32** has been proposed as a possible precursor of simplified analogues of the isoniazid–NAD adduct, **33**. The compound may have potential use as an antituberculosis drug <2005OBC666>.

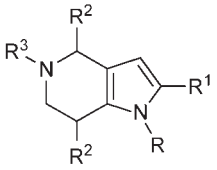
1,2-Disubstituted pyrrolo[2,3-*c*]- and [3,2-*c*]pyridine derivatives, **138**, act as thrombin inhibitors. Pyrrolo[3,2-*c*]pyridines are more active than the [2,3-*c*] isomers, possibly due to the position of the ring nitrogen and its ability to interact with the C-terminus of thrombin <2000BML2347>. 4,5,6,7-Tetrahydropyrrolo[3,2-*c*]pyridine derivatives, **139**, can act as inhibitors of platelet aggregation <2000BML581>. Tetrahydropyrrolopyridines were chosen for study because of the known platelet aggregration inhibitors that contain thienopyridine derivatives. Tetrahydropyrrolo[3,2-*c*]pyridine derivative **140** acts as a nonpeptide antagonist of the human neuropeptide Y-1 receptor <1999T11619>.



138

X, Y = C, N

Z = O, H_2



139

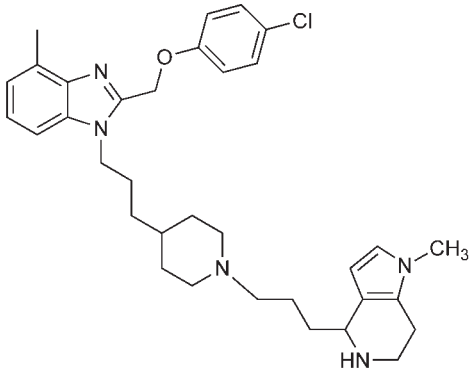
R	R^1	R^2	R^3
H	NO_2	H	$CH_2C_6H_5$
H	$CH{=}C(CN)_2$	Me	H
H	CH_2OH	Me	Me

R = H, $-CH{=}CH_2$

R^1 = NO_2, CHO, $CH{=}NCH_2CH_2OH$, $CH{=}C(CN)_2$, CH_2OH

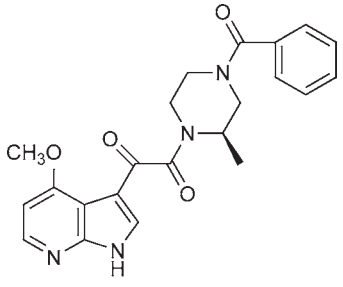
R^2 = H, Me

R^3 = H, Me, $CH_2C_6H_5$



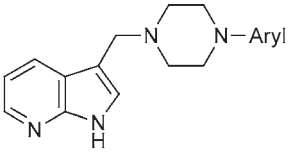
140

Pyrrolopyridines substituted at the 2-position of dipyridodiazepinones have been prepared for study as non-nucleoside inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase <1997JME2430>. Compound **141**, synthesized from pyrrolo[2,3-*b*]pyridine as a starting material, has emerged as a novel inhibitor of HIV-1. Compound **141** acts by interfering with the initial viral entry process <2003JME4236>.



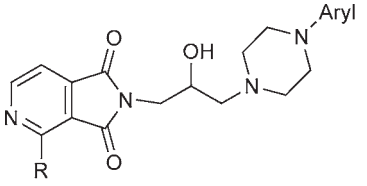
141

Piperazinylpyrrolo[2,3-*b*]pyridines, **142**, have been investigated for their effectiveness as antagonists for the human dopamine D_4 receptor (aryl group = 4-chlorophenyl) <1996JME1941>. Derivatives of **142** bearing aryl rings with fluorine groups substituted on the piperazine ring act as dopamine D_4 receptor imaging agents for positron emission tomography <2004BMC5505>. Piperazinylpyrrolo[3,4-*c*]pyridinediones, **143**, exhibit potent analgesic activity <2002FA897>.



142

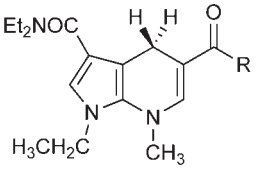
Aryl = 2-FC_6H_4, CH_2(2-HO-4-F)C_6H_3, CH_2(3-NO_2-4-F)C_6H_3, CH_2(4-CH_2F)C_6H_4, 4-ClC_6H_4



143

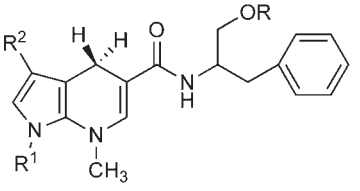
R = OCH_3, OCH_2CH_3
Aryl = Ph, 3-$CF_3C_6H_4$, 2-$CH_3OC_6H_4$

Pyrrolopyridine derivatives, such as compound **144**, in the presence of Mg^{2+} salts such as magnesium perchlorate, serve as chiral and nonchiral NADH models in the reduction of organic nitro compounds <1996JHC1211>. Similar derivatives, such as compound **145**, serve as NADH models in the asymmetric reduction of methyl benzoylformate and *N*-acetyl enamines <1997TA3309>.



144

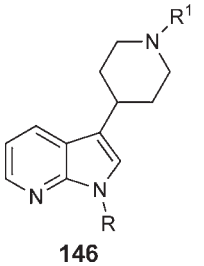
R = NEt_2, $NHCH(CH_2Ph)CH_2OH$



145

R = H, Me
R^1 = Me, CH_2CH_3
R^2 = H, $CONHCH(CH_2Ph)CH_2OR$

Indolylpiperidine compounds are known as H_1 antagonists for treatment of allergic rhinitis. Analogous piperidinylpyrrolopyridine derivatives, **146**, are under investigation for their selectivity and potency as H_1 antagonists <2005BML1165>.

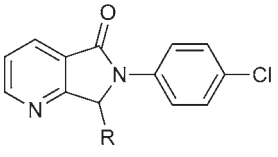


146

R = H, OCH_3, Cl
R^1 = $CH_2CH_2OCH_2CH_3$, C_4H_9

Monosubstituted pyrrolo[2,3-*b*]pyridine derivatives substituted at positions 2 or 6 of the ring system, **26**, exhibit antifungal activity against *Pyricularia oryzae*, a fungus that causes rice blast <1997JFA2345>.

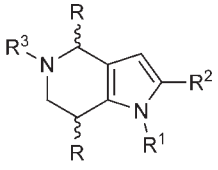
Pyrrolo[3,4-*b*]pyridine derivatives, **147**, have been prepared for comparison to the activity of alpidem, an anxiolytic imidazopyridine <1996JME4275>. The reduced derivative shows a significant affinity for the central benzodiazepine receptor. In contrast, the α,β-unsaturated derivative shows significant affinity for the peripheral benzodiazepine receptor.



147

R = =CHCON(*n*-Pr)$_2$, =CHCON(*n*-Hex)$_2$, $CH_2CON(n\text{-}Pr)_2$, $CH_2CON(n\text{-}Hex)_2$

Tetrahydropyrrolo[3,2-*c*]pyridine derivatives, **148**, inhibit platelet aggregation induced by adrenaline and ADP <2003JPL323>. Compounds such as **148** have been selected due to their lower lipophilicity compared to thienopyridine compounds used in similar applications.



148

R = H, Me

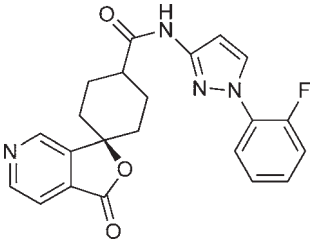
R^1 = H, $CH{=}CH_2$

R^2 = NO_2, $COCH_3$, CHO, CN, $CH{=}C(CN)_2$, $CH_2NHCH_2C_6H_5$, $CH_2NH(CH_2)_3NH_2$

R^3 = H, Me, $COCH_3$, $CH_2C_6H_5$

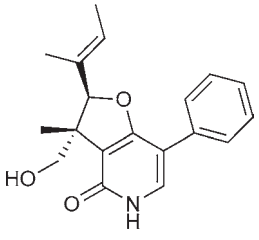
10.06.12.2 Furopyridines

A furo[3,4-*c*]pyridinone ring is incorporated in compound **149**, a neuropeptide Y antagonist. Compound **149** is currently under investigation for possible use in the treatment of obesity <2005JOC9222>.



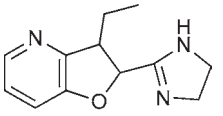
149

Cladobotryal and CJ-16,170, **150**, are natural furo[3,2-*c*]pyridinone antibiotics that have been described recently <2002T10243>. Attempts to synthesize the natural compound led to the formation of a stereoisomer of compound **150**.



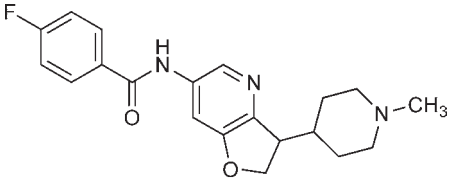
150

Compound **151** has been synthesized to study its effectiveness as an antagonist of α_2-adrenoceptors. Compound **151** is a furo[2,3-*b*]pyridine analogue of efaroxan <1998H(48)2529>.



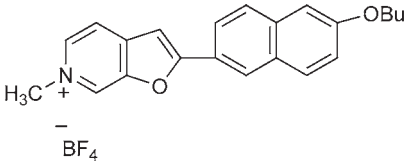
151

Substituted furo[3,2-*b*]pyridines are under investigation for use as 5-HT_{1F} receptor agonists since indole analogues are known in this application. Compound **152** may have potential as a therapeutic agent for treating migraine <2004BML167>.

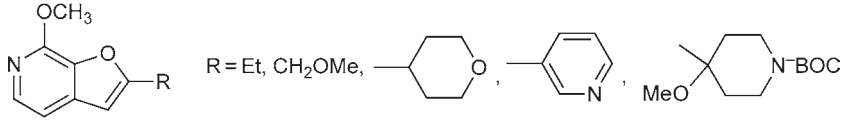


152

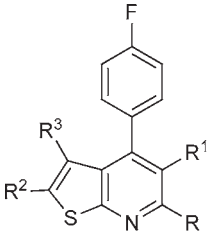
PNU-142721, **153**, a furo[2,3-*c*]pyridine derivative is reported to exhibit potent anti-HIV activity <1998JME1357, 1999SL41>. 7-Methoxyfuro[2,3-c]pyridine-4-carboxamides, **154**, act as potent inhibitors of phosphodiestearase type 4 (PDE4) <2002BML509>.



153



154



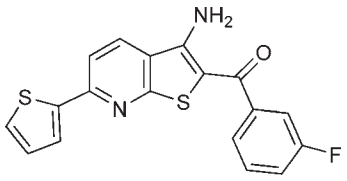
155

R = *i*-Pr, *c*-C_3H_5
R^1 = Me, CO_2R
R^2 = H, Me, *t*-Bu, Et, *i*-Pr, Ph
R^3 = H, Me, Ph, *c*-C_3H_5, 4-ClC_6H_4, *t*-Bu, 2-furyl

A series of thieno[2,3-*b*]pyridine derivatives has been studied as cytotoxic agents against a tumorigenic cell line. Compound **156** is found to be the most potent derivative in the series <2004BML3411>.

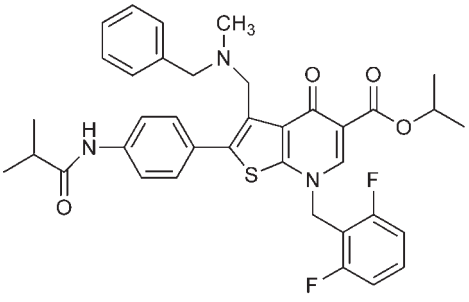
10.06.12.3 Thienopyridines

Thieno[2,3-*b*]pyridine derivatives, **155**, can be successfully used as replacements for the hexahydronaphthalene ring found in naturally occurring 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors <2001BML1285>. These compounds also display significant inhibition of cholesterol biosynthesis *in vivo*.

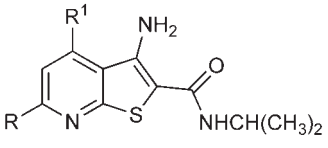


156

Thieno[2,3-*b*]pyridine derivative **157** is a potent nonpeptide antagonist of the human luteinizing hormone-releasing hormone (LHRH) receptor <1998JME4190>. Other thieno[2,3-*b*]pyridine derivatives, **158**, have also been tested as low molecular weight agonists for the luteinizing hormone receptor. These compounds mimic the mode of action of high molecular weight endogenous ligand LH; however, the thienopyridine derivatives are less active than the corresponding thienopyrimidine derivatives <2002MI1023>.



157

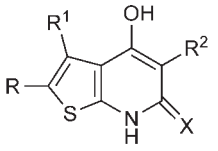


158

R = Ph, 2-naphthyl, 2-furoyl, 2-thienoyl
R^1 = Ph, 3-$MeOC_6H_4$, 2-thienyl

Thienopyridone derivatives have been prepared to study their potential activity as antibacterials. The greatest activity against *Escherichia coli* is observed for 2-chloro-7-cyclopropyl-4,7-dihydro-4-oxothieno[2,3-*b*]pyridine-5-carboxylic acid <1997H(45)255>.

Thieno[2,3-*b*]pyridinones, **159**, act as inhibitors of [^{3}H]glycine binding to the *N*-methyl-D-aspartate (NMDA) receptor. The effects of substitution patterns on reactivity have been studied, leading to thienopyridinones with activity comparable to known quinolinone antagonists <2006JME864>.



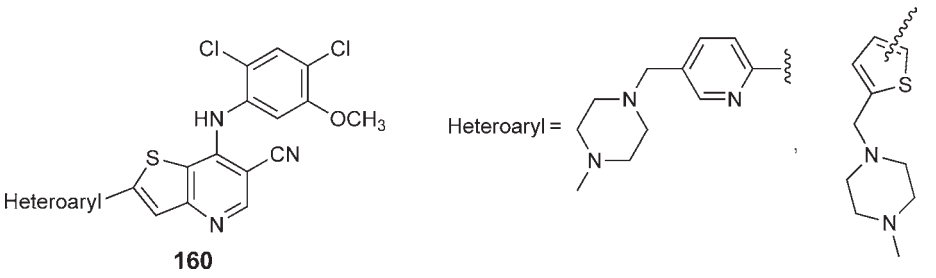
159

R = H, Br, Cl, CH_2NH_2, Me, Et
R^1 = H, $(CH_2)_2NH_2$, C_1–C_4 alkyl and cycloalkyl groups, CH_2OCH_3
R^2 = Ph, 2-thienyl, 3-$(C_6H_5O)C_6H_4$
X = O, S

Derivatives of 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines are capable of inhibiting lipopolysaccharide-stimulated production of tumor necrosis factor-α. The activity of the derivatives is linked to the substituents at positions 2 and 6.

Thienopyridines incorporated into the structures of inhibitors of coagulation factor Xa show good activity and selectivity. In addition, with the presence of heteroatoms, solubility properties of the compounds are improved <1999BML2753, 2001MI83, 2006BMC1309>.

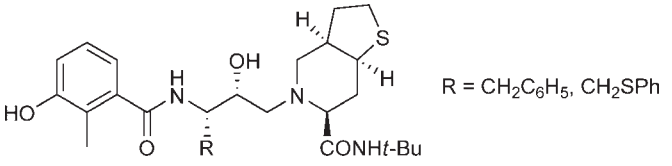
7-[(2,4-Dichloro-5-methoxyphenyl)amino]thieno[3,2-*b*]pyridine-6-carbonitriles substituted with heteroaryl groups at position C-2, **160**, have been found to inhibit Src kinase activity. The highest activity in Src and cell assays has been found with a 2,5-furan or 2,5-pyridine substituent at C-2 <2005BML4681, 2005JME3891>.



160

Compound **57** has been identified as a vascular endothelial growth factor receptor-2 (VEGFR-2) kinase inhibitor of interest for the treatment of cancer <2003OPD676>.

Tetrahydrothieno[3,2-*c*]pyridines act as effective anticonvulsants <1996CPB778>. Octahydrothienopyridines, **161**, serve as potent HIV-1 protease inhibitors and antivirals <1995BML2885, 1995BML2891>.



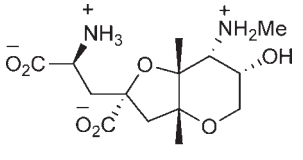
161

Since isoquinolinones are known to be very potent inhibitors of poly(ADP-ribose)polymerase (PARP), thieno[3,4-*c*]pyridin-4-ones have been studied for their potential as PARP inhibitors <1999BMC297>. Early studies indicate that the sulfur analogues also act as potent PARP inhibitors. Thienopyridine diazonium salts can be converted into heterocyclic dyes that are useful as disperse dyes for polyester fabrics <2005DP(64)223, 2006DP(70)60>.

Ticlopidine, **45**, is well known as a potent inhibitor of ADP-induced platelet aggregation (see Section 10.06.3.3) <2004MI49>.

10.06.12.4 Furopyrans

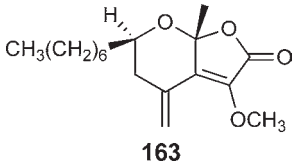
Dysiherbaine, **162**, is a biologically active compound containing the hexahydro-2*H*-furo[3,2-*b*]pyran core. Compound **162** acts as a selective agonist of non-NMDA-type glutamate receptors in the central nervous system <2003OBC772, 2003SL993>.



Dysiherbaine

162

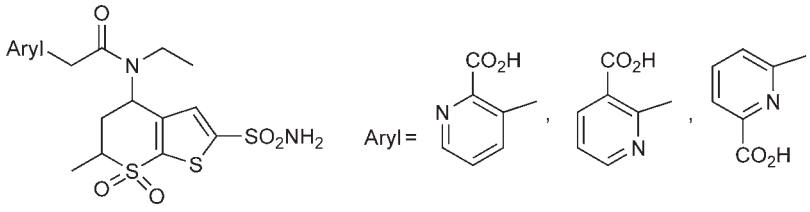
3-Methyl-2*H*-furo[2,3-*c*]pyran-2-one is a key compound recently isolated from plant-derived smoke. This compound is instrumental in promoting seed germination of a diverse range of plant species around the world <2004SCI1977, 2005TL5719>. Myxostiolide, **163**, has recently been isolated from the fungus *Myxotrichum stipitatum*. Compound **163** serves as a plant growth regulator <2002JNP621>.



163

10.06.12.5 Thienothiopyrans

Thieno[2,3-*b*]thiopyran derivatives, **164**, show effective activity as carbonic anhydrase inhibitors, especially as intraocular pressure-lowering agents <1999JME2641>.



164

10.06.13 Further Developments

No recent literature from 2006 or 2007 was found for thiopyranopyrroles, thiopyranofurans, thienothiopyrans, and thienopyrans.

10.06.13.1 Pyrrolopyridines

A recent tutorial review was published covering organometallic chemistry and its uses for synthesis and functionalization of pyrrolopyridines <2007CSR1120>.

A synthesis of pyrrolo[2,3-*b*]pyridine derivatives from nicotinic acid or 2,6-dichloropyridine affords 1,3- and 1,3,6-substituted pyrrolo[2,3-*b*]pyridines <2006JOC5538>.

2-Aminopyridines and 3-aminopyridines are used in a regioselective synthesis of pyrrolo[2,3-*b*]pyridines and pyrrolo[3,2-*b*]pyridines that proceeds via a palladium catalyzed cross-coupling reaction with aromatic alkynes <2007TL6951>.

4-Arylamino-substituted-pyrrolo[2,3-*b*]pyridines, synthesized via 4-chloropyrrolo[2,3-*b*]pyridine, have been evaluated for their biological properties on human myeloblastic leukemia cells <2007BML1934>.

Depending upon the choice of reagent, one of the methoxy groups of 4,7-dimethoxypyrrolo[2,3-*c*]pyridine can be selectively converted to a hydroxyl group in high yield. Products were confirmed by single crystal X-ray crystallography <2007TL2675>.

A one-step reaction leads to the formation of 4-thio- and 4-aminopyrrolo[3,4-*c*]pyridines. Reaction of an acetylpyruvate with compounds containing an active methylene group, followed by cyclization leads to the formation of the bicyclic ring systems in good yields <2007T4491>. An aminomethylation reaction followed by cyclization leads to the formation of 2,3-dihydropyrrolo[3,4-*c*]pyridinones <2006OL5889>.

Pyrrolo[2,3-*b*]pyridine derivatives have been synthesized for testing as cannabinoid antagonists <2006SC2797>. Derivatives of tetrahydropyrrolo[3,2-*c*]pyridinone have been shown to be cannabinoid type I (CB-1) antagonists with potential for the treatment of obesity <2007BML673>. Pyrrolo[2,3-*b*]pyridine-3-ylguanidines and thieno[2,3-*b*]pyridine-3-ylguanidines have shown promise as antidiabetic agents <2007BMC3248>. 2-Arylpyridyl derivatives of tetrahydropyrrolo[3,2-*c*]pyridionones are being studies for their activity as potent kinase inhibitors <2007JME2647>. Tetrahydropyrrolo[3,2-*c*]pyridinylethylamine derivatives have been found to be very active as gonadotropin-releasing hormone receptor antagonists (GnRH) <2007BML3845>. Similarly, thieno[2,3-*b*]pyridine-4-ones have also been found to be GnRH receptor antagonists <2006JME3809>. Oxazolidinones substituted with pyrrolo[3,4-*b*]pyridine derivatives have been tested for their antibacterial activity against Gram-positive bacteria <2006BML4537>.

10.06.13.2 Furopyridines

A single crystal X-ray analysis of 7-hydroxy-1-methoxy-6-methyl-1,3-dihydrofuro[3,4-*c*]pyridinium chloride monohydrate reveals that the bicyclic system is nearly planar, with slight skewing observed for the five-membered ring <2006AX(E)o5263>. Crystal structures of nickel complexes of furo[3,2-*c*]pyridines have been determined. The magnetic behavior of the compounds has also been studied <2006POL3261, 2007POL1523>.

3,7-Diphenyl-4-amino derivatives of furo[3,2-*c*]pyridines and thieno[3,2-*c*]pyridines have been studied as protein kinase inhibitors <2007BML250>.

10.06.13.3 Thienopyridines

Molecular modeling studies have been carried out on 4-(phenylamino)thieno[2,3-*b*]pyridines <2006BMC5765>.

A Thorpe–Ziegler intramolecular cyclization starting with 3-cyanopyridine-2-thione derivatives leads to the formation of 3-amino-2-(organylsulfinyl)thieno[2,3-*b*]pyridines in high yields <2006RCB529>.

A synthesis of thieno[3,2-*b*]pyridine derivatives beginning with 3-methylthiopyridine proceeds via a regioselective lithiation-bromination reaction <2006T6036>. Thieno[3,2-*b*]pyridinones can be synthesized from ketenimines via a [1,5]-X sigmatropic rearrangement reaction to produce a ketene intermediate. Ring closure of the ketene leads to thienopyridinones substituted at the 5-position <2007S590>. A one-pot synthesis of 7-hydroxythieno[3,2-*b*]pyridine-5-ones has been reported starting from β-chloropropenonitriles <2007S2153>. Alkylazinylcarbonitriles are useful starting materials for the synthesis of arylhydrazonothieno[3,4-*c*]pyridinediones <2007ARK213>.

2-Amino-3-aroylthieno[2,3-*c*]pyridines have been synthesized for their potential to serve as allosteric enhancers at the adenosine A_1 receptor <2006BML5530>. Thieno[3,2-*c*]pyridine derivatives have been found to be potent Lck inhibitors that are highly selective within the Src-family of tyrosine kinases <2007BML1167>. Thieno[3,2-*c*]pyridine urea compounds have been shown to be potent inhibitors of KDR kinase <2007BML1246>. Thieno[2,3-*b*]pyridine-6-one derivatives were discovered to be fairly potent inhibitors of ubiquitin C-terminal hydrolase-L1 <2007BML3729>. 7-Oxo-4,7-dihydrothieno[3,2-*b*]pyridine-6-carboxamides, classified as non-nucleoside antiviral compounds, are potent inhibitors of human cytomegalovirus DNA polymerases <2007BML3840>. 4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridine quinolines have been synthesized, and their antibacterial activity has been evaluated <2007BML1924>.

10.06.13.4 Pyranopyrroles

Polyhydroxy tetrahydropyrano[3,4-*b*]pyrroles are available in a synthesis from alkynyl carbohydrates <2007EJO3296, 2007SL403>.

10.06.13.5 Furopyrans

Perhydrofuro[2,3-*b*]pyrans can be synthesized via a ring-opening reaction of sugar derivatives containing a 1,2-cyclopropyl group <2007OL1331>.

Furo[3,4-*c*]pyranones derived from *cis*-stilbene have been shown to be potent inhibitors of proliferation in human cancer cell lines <2007MI441>.

References

1956JA1247 M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, 1956, **78**, 1247.

1983JOC3344 J. B. Hendrickson and C. Rodriguez, *J. Org. Chem.*, 1983, **48**, 3344.

1984CHEC(4)497 J. V. Greenhill; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 4, p. 497.

1995BML2885 J. E. Munroe, W. J. Hornback, J. B. Campbell, M. A. Ouellette, S. D. Hatch, M. A. Muesing, M. A. Wiskerchen, A. J. Baxter, K. Su, and K. Campanale, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2885.

1995BML2891 W. J. Hornback, J. E. Munroe, T. A. Shepherd, S. D. Hatch, M. A. Muesing, M. A. Wiskerchen, J. M. Colacino, A. J. Baxter, K. S. Su, and K. M. Campanale, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 2891.

1995CCC1578 R. M. Mohareb, S. M. Sherif, A. Habashi, N. I. Abdel-Sayed, and S. S. Osman, *Collect. Czech. Chem. Commun.*, 1995, **60**, 1578.

1995JOC7654 A. W. Erian, A. Konno, and T. Fuchigami, *J. Org. Chem.*, 1995, **60**, 7654.

1995T12463 K. J. Buysens, D. M. Vandenberghe, S. M. Toppet, and G. J. Hoornaert, *Tetrahedron*, 1995, **45**, 12463.

1996CHEC-II(7)167 A. R. Sherman; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 167.

1996CPB778 M. Ohkubo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, T. Kinoshita, and H. Takasugi, *Chem. Pharm. Bull.*, 1996, **44**, 778.

1996EJM49 A. Da Settimo, G. Primofiore, F. Da Settimo, F. Simorini, C. La Motta, A. Martinelli, and E. Boldrini, *Eur. J. Med. Chem.*, 1996, **31**, 49.

1996H(43)63 P. Marchand, C. Bellec, M.-C. Fargeau-Bellassoued, C. Nezry, and G. Lhommet, *Heterocycles*, 1996, **43**, 63.

1996HAC29 Z. E.-S. Kandeel, *Heteroatom Chem.*, 1996, **7**, 29.

1996JHC287 R. P. Robinson, K. M. Donahue, P. S. Son, and S. D. Wagy, *J. Heterocycl. Chem.*, 1996, **33**, 287.
1996JHC1211 V. Levacher, C. Valque, S. Coupa, G. Dupas, G. Quéguiner, and J. Bourguignon, *J. Heterocycl. Chem.*, 1996, **33**, 1211.
1996JME1941 J. J. Kulagowski, H. B. Broughton, N. R. Curtis, I. M. Mawer, M. P. Ridgill, R. Baker, F. Emms, S. B. Freedman, R. Marwood, S. Patel, S. Patel, C. I. Ragan, and P. D. Leeson, *J. Med. Chem.*, 1996, **39**, 1941.
1996JME4275 M. Anzini, A. Cappelli, S. Vomero, G. Giorgi, T. Langer, G. Bruni, M. R. Romeo, and A. S. Basile, *J. Med. Chem.*, 1996, **39**, 4275.
1996JOC1665 A. Goti, B. Anichini, A. Brandi, S. Kozhuskov, C. Gratkowski, and A. de Meijere, *J. Org. Chem.*, 1996, **61**, 1665.
1996J(P2)1377 M. Blenkle, P. Boldt, C. Bräuchle, W. Grahn, I. Ledoux, H. Nerenz, S. Stadler, J. Wichern, and J. Zyss, *J. Chem. Soc., Perkin Trans. 2*, 1996, 1377.
1996OR301 B. Giese, B. Kopping, T. Göbel, J. Dickhaut, G. Thoma, K. J. Kulicke, and F. Trach, *Org. React.*, 1996, **48**, 301.
1996S877 D. Hands, B. Bishop, M. Cameron, J. S. Edwards, I. F. Cottrell, and S. H. B. Wright, *Synthesis*, 1996, 877.
1996T10841 V. P. Kislyi, K. G. Nikishin, E. Ya. Kruglova, A. M. Shestopalov, V. V. Semenov, A. A. Gakh, and A. C. Buchanan, III, *Tetrahedron*, 1996, **52**, 10841.
1996T12495 S. C. Roy and P. K. Mandal, *Tetrahedron*, 1996, **52**, 12495.
1996TA2721 O. Tempkin, T. J. Blacklock, J. A. Burke, and M. Anastasia, *Tetrahedron Asymmetry*, 1996, **7**, 2721.
1996TL43 E. Desarbre and J.-Y. Mérour, *Tetrahedron Lett.*, 1996, **37**, 43.
1996TL5865 E. Riguet, I. Klement, Ch. K. Reddy, G. Cahiez, and P. Knochel, *Tetrahedron Lett.*, 1996, **37**, 5865.
1997BML3101 V. J. Ram, A. Goel, P. K. Shukla, and A. Kapil, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 3101.
1997CHE481 V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 481.
1997CHE583 S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 583.
1997CHE793 V. D. Dyachenko, S. G. Krivokolysko, Yu. A. Sharanin, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 793.
1997H(45)255 M. M. El-Abadelah, S. S. Sabri, and H. A. Al-Ashqar, *Heterocycles*, 1997, **45**, 255.
1997H(45)975 S. Shiotani, *Heterocycles*, 1997, **45**, 975.
1997JA4404 K.-W. Liang, W.-T. Li, G.-H. Lee, S.-Mi. Peng, and R.-S. Liu, *J. Am. Chem. Soc.*, 1997, **119**, 4404.
1997JFA2345 S. Minakata, T. Hamada, M. Komatsu, H. Tsuboi, H. Kikuta, and Y. Ohshiro, *J. Agric. Food Chem.*, 1997, **45**, 2345.
1997JHC931 M. Suárez, E. Ochoa, B. Pita, R. Espinosa, L. González, N. Martín, M. Quinteiro, C. Seoane, and J. L. Soto, *J. Heterocycl. Chem.*, 1997, **34**, 931.
1997JME2430 T. A. Kelly, D. W. McNeil, J. M. Rose, E. David, C.-K. Shih, and P. M. Grob, *J. Med. Chem.*, 1997, **40**, 2430.
1997JOC8276 K. Estieu, R. Paugam, J. Ollivier, J. Salaün, F. M. Cordero, A. Goti, and A. Brandi, *J. Org. Chem.*, 1997, **62**, 8276.
1997S73 E. Desarbre and J.-Y. Mérour, *Synthesis*, 1997, 73.
1997S949 D. H. Bremner, A. D. Dunn, K. A. Wilson, K. R. Sturrock, and G. Wishart, *Synthesis*, 1997, 949.
1997SC3861 V. Marie-Claude, J. Patricia, and G. Gérald, *Synth. Commun.*, 1997, **27**, 3861.
1997T3637 E. Desarbre, S. Coudret, C. Meheust, and J.-Y. Mérour, *Tetrahedron*, 1997, **53**, 3637.
1997T5159 V. Marie-Claude, J. Patricia, B. Marie-Laure, S. Laurence, and G. Gérald, *Tetrahedron*, 1997, **53**, 5159.
1997TA3309 C. Leroy, V. Levacher, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron Asymmetry*, 1997, **8**, 3309.
1998CHE237 V. L. Ivanov, V. A. Artemov, A. M. Shestopalov, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 237.
1998CHE688 A. A. Semioshkin, V. A. Artemov, V. L. Ivanov, G. M. Ptashits, P. V. Petrovskii, A. M. Shestopalov, V. I. Bregadze, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 688.
1998EJM33 M. M. El-Abadelah, M. Z. Nazer, S. F. Okasha, M. Calas, J. Bompart, and P. Mion, *Eur. J. Med. Chem.*, 1998, **33**, 33.
1998H(48)2529 P. Mayer, C. Loubat, and T. Imbert, *Heterocycles*, 1998, **48**, 2529.
1998JA4520 W.-T. Li, F.-C. Lai, G.-H. Lee, S.-M. Peng, and R.-S. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 4520.
1998JHC145 C. A. Teleha, R. A. Greenberg, and R. J. Chorvat, *J. Heterocycl. Chem.*, 1998, **35**, 145.
1998JHC1237 S. Yamaguchi, M. Kurosaki, K. Orito, H. Yokayama, Y. Hirai, and S. Shiotani, *J. Heterocycl. Chem.*, 1998, **35**, 1237.
1998JHC1249 S. Yamaguchi, K. Awajima, Y. Hirai, H. Yokoyama, and S. Shiotani, *J. Heterocycl. Chem.*, 1998, **35**, 1249.
1998JHC1305 S. Yamaguchi, M. Kurosaki, H. Yokoyama, Y. Hirai, and S. Shiotani, *J. Heterocycl. Chem.*, 1998, **35**, 1305.
1998JME1357 D. G. Wishka, D. R. Graber, L. A. Kopta, R. A. Olmsted, J. M. Friis, J. D. Hosley, W. J. Adams, E. P. Seest, T. M. Castle, L. A. Dolak, B. J. Keiser, Y. Yagi, A. Jeganathan, S. T. Schlachter, M. J. Murphy, G. J. Cleek, R. A. Nugent, S. M. Poppe, S. M. Swaney, F. Han, W. Watt, W. L. White, T.-J. Poel, R. C. Thomas, R. L. Voorman, K. J. Stefanski, R. G. Stehle, W. G. Tarpley, and J. Morris, *J. Med. Chem.*, 1998, **41**, 1357.
1998JME4190 N. Cho, M. Harada, T. Imaeda, T. Imada, H. Matsumoto, Y. Hayase, S. Sasaki, S. Furuya, N. Suzuki, S. Okubo, K. Ogi, S. Endo, H. Onda, and M. Fujino, *J. Med. Chem.*, 1998, **41**, 4190.
1998JOC7851 D. G. Wishka, D. R. Graber, E. P. Seest, L. A. Dolak, F. Han, W. Watt, and J. Morris, *J. Org. Chem.*, 1998, **63**, 7851.
1998J(P1)3065 T. Saito, T. Ohkubo, H. Kuboki, M. Maeda, K. Tsuda, T. Karakasa, and S. Satsumabayashi, *J. Chem. Soc., Perkin Trans.1*, 1998, 3065.
1998J(P2)437 H. Nerenz, M. Meier, W. Grahn, A. Reisner, E. Schmälzlin, S. Stadler, K. Meerholz, C. Bräuchle, and P. G. Jones, *J. Chem. Soc., Perkin Trans. 2*, 1998, 437.
1998MI183 S. J. Shuttleworth, M. Quimpère, N. Lee, and J. DeLuca, *Mol. Divers.*, 1998, **4**, 183.
1998S1095 D. H. Bremner, A. D. Dunn, K. A. Wilson, K. R. Sturrock, and G. Wishart, *Synthesis*, 1998, 1095.
1998SC2871 A. F. Fahmy, J. Sauer, M. S. K. Youssef, M. S. A. Halim, and M. A. Hassan, *Synth. Commun.*, 1998, **28**, 2871.
1998SL1075 J. Tang, H. Shinokubo, and K. Oshima, *Synlett*, 1998, 1075.
1998T2607 Z. Wrobel, *Tetrahedron*, 1998, **54**, 2607.
1998T3391 A. Wang, S. Tandel, H. Zhang, Y. Huang, T. C. Holdeman, and E. R. Biehl, *Tetrahedron*, 1998, **54**, 3391.
1998T6457 F. Léost, B. Chantegrel, and C. Deshayes, *Tetrahedron*, 1998, **54**, 6457.
1998T8753 S. Mayer, J. Prandi, T. Bamhaoud, S. Bakkas, and O. Guillou, *Tetrahedron*, 1998, **54**, 8753.
1998TL627 S. S. Park, J.-K. Choi, E. K. Yum, and D.-C. Ha, *Tetrahedron Lett.*, 1998, **39**, 627.
1998TL1227 H. Beaton, P. Hamley, and A. C. Tinker, *Tetrahedron Lett.*, 1998, **39**, 1227.
1998TL3605 N. Edwards, J. A. Macritchie, and P. J. Parsons, *Tetrahedron Lett.*, 1998, **39**, 3605.
1998TL5159 L. Xu, I. R. Lewis, S. K. Davidsen, and J. B. Summers, *Tetrahedron Lett.*, 1998, **39**, 5159.

1998TL5355 F. Ujjainwalla and D. Warner, *Tetrahedron Lett.*, 1998, **39**, 5355.
1998TL5375 T. Kitamura, K. Tsuda, and Y. Fujiwara, *Tetrahedron Lett.*, 1998, **39**, 5375.
1998TL8919 A. C. Spivey, T. Fekner, and H. Adams, *Tetrahedron Lett.*, 1998, **39**, 8919.
1999BMC297 A. E. Shinkwin, W. J. D. Whish, and M. D. Threadgill, *Bioorg. Med. Chem.*, 1999, **7**, 297.
1999BMC921 X. Doisy, M. Dekhane, M. LeHyaric, J.-F. Rousseau, S. K. Singh, S. Tan, V. Guilleminot, H. Schoemaker, M. Sevrin, P. George, R. Potier, and R. H. Dodd, *Bioorg. Med. Chem.*, 1999, **7**, 921.
1999BML585 N. R. Curtis, J. J. Kulagowski, P. D. Leeson, M. P. Ridgill, F. Emms, S. B. Freedman, S. Patel, and S. Patel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 585.
1999BML2753 M. R. Becker, W. R. Ewing, R. S. Davis, H. W. Pauls, C. Ly, A. Li, H. J. Mason, Y. M. Choi-Sledeski, A. P. Spada, V. Chu, K. D. Brown, D. J. Colussi, R. J. Leadley, R. Bentley, J. Bostwick, C. Kasiewski, and S. Morgan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2753.
1999CCC539 M. Bencková and A. Krutošíková, *Collect. Czech. Chem. Commun.*, 1999, **64**, 539.
1999CHE58 I. S. Arustamova and V. T. Piven, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 58.
1999CHE293 E. A. Kaigorodova, L. D. Konyushkin, S. N. Mikhailichenko, V. K. Vasilin, A. V. Sazonov, and V. G. Kul'nevich, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 293.
1999EJO2429 M. Hein and R. Miethchen, *Eur. J. Org. Chem.*, 1999, 2429.
1999EJO2725 M. Ferrara, F. M. Cordero, A. Goti, A. Brandi, K. Estieu, R. Paugam, J. Ollivier, and J. Salaün, *Eur. J. Org. Chem.*, 1999, 2725.
1999H(50)1065 D. Mazéas, G. Guillaumet, and M.-C. Viaud, *Heterocycles*, 1999, **50**, 1065.
1999H(51)2881 K. Kobayashi, K. Sakashita, H. Akamatsu, K. Tanaka, M. Uchida, T. Uneda, T. Kitamura, O. Morikawa, and H. Konishi, *Heterocycles*, 1999, **51**, 2881.
1999JHC1 S. Yamaguchi, H. Saitoh, M. Kurosaki, H. Yokoyama, Y. Hirai, and S. Shiotani, *J. Heterocycl. Chem.*, 1999, **36**, 1.
1999JHC1077 L. H. Klemm, T. J. R. Weakley, and M. Yoon, *J. Heterocycl. Chem.*, 1999, **36**, 1077.
1999JME819 C. N. Hodge, P. E. Aldrich, Z. R. Wasserman, C. H. Fernandez, G. A. Nemeth, A. Arvanitis, R. S. Cheeseman, R. J. Chorvat, E. Ciganek, T. E. Christos, P. J. Gilligan, P. Krenitsky, E. Scholfield, and P. Strucely, *J. Med. Chem.*, 1999, **42**, 819.
1999JME2641 A. Scozzafava, L. Menabuoni, F. Mincione, F. Briganti, G. Mincione, and C. T. Supuran, *J. Med. Chem.*, 1999, **42**, 2641.
1999JOC342 I. Terstiege and R. E. Maleczka, Jr., *J. Org. Chem.*, 1999, **64**, 342.
1999J(P1)2639 S. S. Mandal, J. Chakraborty, and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2639.
1999S615 M. Alvarez, D. Fernández, and J. A. Joule, *Synthesis*, 1999, 615.
1999S1893 P. Zakrzewski, M. Gowan, L. A. Trimble, and C. K. Lau, *Synthesis*, 1999, 1893.
1999S1951 A. Bhandari, B. Li, and M. A. Gallop, *Synthesis*, 1999, 1951.
1999SAA1035 R. Cruz-Almanza, E. Diaz-Torres, L. D. Miranda, D. Corona, R. Lopez-Castañares, A. Fuentes, M. R. van Calsteren, and K. Jankowski, *Spectrochim. Acta, Part A*, 1999, **55**, 1035.
1999SC3773 A. A. Fadda, H. M. Refat, M. E. A. Zaki, and H. H. Abdel Razik, *Synth. Commun.*, 1999, **29**, 3773.
1999SL41 J. Uenishi, T. Takagi, T. Ueno, T. Hiraoka, O. Yonemitsu, and H. Tsukube, *Synlett*, 1999, 41.
1999T11619 M. G. Siegel, M. O. Chaney, R. F. Bruns, M. P. Clay, D. A. Schober, A. M. Van Abbema, D. W. Johnson, B. E. Cantrell, P. J. Hahn, D. C. Hunden, D. R. Gehlert, H. Zarrinmayeh, P. L. Ornstein, D. M. Zimmerman, and G. A. Koppel, *Tetrahedron*, 1999, **55**, 11619.
1999T14079 P. J. Campos, E. Añón, M. C. Malo, and M. A. Rodriguez, *Tetrahedron*, 1999, **55**, 14079.
1999TL397 T. K. Sarkar, S. K. Ghosh, S. K. Nandy, and T. J. Chow, *Tetrahedron Lett.*, 1999, **40**, 397.
2000BML581 C. Altomare, L. Summo, S. Cellamare, A. V. Varlamov, L. G. Voskressensky, T. N. Borisova, and A. Carotti, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 581.
2000BML2347 K. Takeuchi, J. A. Bastian, D. S. Gifford-Moore, R. W. Harper, S. C. Miller, J. T. Mullaney, D. J. Sall, G. F. Smith, M. Zhang, and M. J. Fisher, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2347.
2000CC459 W. Zhuang, J. Thorhauge, and K. A. Jorgensen, *J. Chem. Soc., Chem. Commun.*, 2000, 459.
2000CHE693 A. Krauze and G. Duburs, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 693.
2000CHE1431 Ya. Yu. Yakunin, V. D. Dyachenko, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 1431.
2000IC5248 Q. Wu, J. A. Lavigne, Y. Tao, M. D'Iorio, and S. Wang, *Inorg. Chem.*, 2000, **39**, 5248.
2000JCO24 A. M. Shestopalov, V. P. Kislyi, E. Ya. Kruglova, K. G. Nikishin, V. V. Semenov, A. C. Buchanan, III, and A. A. Gakh, *J. Comb. Chem.*, 2000, **2**, 24.
2000JOC3111 T. K. Sarkar, S. K. Ghosh, and T. J. Chow, *J. Org. Chem.*, 2000, **65**, 3111.
2000JOC5440 O. Yamazaki, K. Yamaguchi, M. Yokoyama, and H. Togo, *J. Org. Chem.*, 2000, **65**, 5440.
2000MOL1085 Ye. A. Kaigorodova, V. K. Vasilin, L. D. Konyushkin, Ye. B. Usova, and G. D. Krapivin, *Molecules*, 2000, **5**, 1085.
2000OL651 A. Inoue, H. Shinokubo, and K. Oshima, *Org. Lett.*, 2000, **2**, 651.
2000T5221 I. Yavari and F. Nourmohammadian, *Tetrahedron*, 2000, **56**, 5221.
2000TA897 F. Pisaneschi, F. M. Cordero, A. Goti, R. Paugam, J. Ollivier, A. Brandi, and J. Salaün, *Tetrahedron Asymmetry*, 2000, **11**, 897.
2000TL919 S. M. Chi, J.-K. Choi, E. K. Yum, and D. Y. Chi, *Tetrahedron Lett.*, 2000, **41**, 919.
2000TL1661 E. Lorenzo, F. Alonso, and M. Yus, *Tetrahedron Lett.*, 2000, **41**, 1661.
2000TL9777 O. Arjona, A. G. Csákÿ, M. C. Murcia, and J. Plumet, *Tetrahedron Lett.*, 2000, **41**, 9777.
2001BML1285 M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Sakashita, M. Kitahara, and R. Sakoda, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1285.
2001CAR63 J. Marco-Contelles and J. Ruiz-Caro, *Carbohydr. Res.*, 2001, **335**, 63.
2001CHE766 Ya. Yu. Yakunin, V. D. Dyachenko, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 766.
2001CHE1048 A. V. Varlamov, T. N. Borisova, B. Nsabimana, G. G. Aleksandrov, L. G. Voskressensky, and A. I. Chernyshev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 1048.
2001H(55)1583 M. Cheung, R. N. Hunter, III, M. R. Peel, and K. E. Lackey, *Heterocycles*, 2001, **55**, 1583.
2001HCO461 A. V. Varlamov, T. N. Borisova, L. G. Voskressensky, B. Nsabimana, and A. I. Chernyshev, *Heterocycl. Commun.*, 2001, **7**, 461.
2001JA5374 K. Wakabayashi, H. Yorimitsu, and K. Oshima, *J. Am. Chem. Soc.*, 2001, **123**, 5374.
2001JA7427 R. J. Madhushaw, C.-L. Li, K.-H. Shen, C.-C. Hu, and R.-S. Liu, *J. Am. Chem. Soc.*, 2001, **123**, 7427.

2001JOC8106 K.-H. Shen, S.-F. Lush, T.-L. Chen, and R.-S. Liu, *J. Org. Chem.*, 2001, **66**, 8106.
2001J(P1)1723 E. Erba, D. Pocar, and P. Trimarco, *J. Chem. Soc., Perkin. Trans. 1*, 2001, 1723.
2001MI83 H. W. Pauls and W. R. Ewing, *Curr. Top. Med. Chem.*, 2001, **1**, 83.
2001OL877 X. Sun, P. Janvier, G. Zhao, H. Bienaymé, and J. Zhu, *Org. Lett.*, 2001, **3**, 877.
2001OL1009 J. N. Johnston, M. A. Plotkin, R. Viswanathan, and E. N. Prabhakaran, *Org. Lett.*, 2001, **3**, 1009.
2001OL1853 S. Mikami, K. Fujita, Y. Nakamura, H. Yorimitsu, H. Shinokubo, S. Matsubara, and K. Oshima, *Org. Lett.*, 2001, **3**, 1853.
2001SAA1951 M. Ramek and S. Tomić, *Spectrochim. Acta, Part A*, 2001, **57**, 1951.
2001SC475 A. Khodairy and A. M. El-Sayed, *Synth. Commun.*, 2001, **31**, 475.
2001SL57 C. García, M. Melguizo, J. Cobo, A. Sánchez, M. Nogueras, M. D. López, and J. N. Low, *Synlett*, 2001, 57.
2001SL609 M. Allegretti, A. Arcadi, F. Marinelli, and L. Nicolini, *Synlett*, 2001, 609.
2001SL1197 M. Yus, *Synlett*, 2001, 1197.
2001T1995 J.-Y. Mérour, P. Gadonneix, B. Malapel-Andrieu, and E. Desarbre, *Tetrahedron*, 2001, **57**, 1995.
2001T4203 P. R. Carly, T. C. Govaerts, S. L. Cappelle, F. Compernolle, and G. J. Hoornaert, *Tetrahedron*, 2001, **57**, 4203.
2001T7729 M. Gardiner, R. Grigg, M. Kordes, V. Sridharan, and N. Vicker, *Tetrahedron*, 2001, **57**, 7729.
2001TL777 Y. Zhang and J. W. Herndon, *Tetrahedron Lett.*, 2001, **42**, 777.
2001TL1899 K. Everaere, J.-L. Scheffler, A. Mortreux, and J.-F. Carpentier, *Tetrahedron Lett.*, 2001, **42**, 1899.
2001TL4661 K. Inoue, A. Sawada, I. Shibata, and A. Baba, *Tetrahedron Lett.*, 2001, **42**, 4661.
2001TL6441 F. Ujjainwalla and T. F. Walsh, *Tetrahedron Lett.*, 2001, **42**, 6441.
2002AGE1584 S.-K. Jang, K.-J. Kim, and Y.-T. Hong, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 1584.
2002BML509 G. M. Buckley, N. Cooper, R. J. Davenport, H. J. Dyke, F. P. Galleway, L. Gowers, A. F. Haughan, H. J. Kendall, C. Lowe, J. G. Montana, J. Oxford, J. C. Peake, C. L. Picken, M. D. Richard, V. Sabin, A. Sharpe, and J. B. H. Warneck, *Bioorg. Med. Chem. Lett*, 2002, **12**, 509.
2002BML1607 M. Fujita, T. Seki, H. Inada, and N. Ikeda, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1607.
2002CC484 A. Penoni and K. M. Nicholas, *J. Chem. Soc., Chem. Commun.*, 2002, 484.
2002CHE368 A. T. Soldatenkov, K. B. Polyanskii, and S. A. Soldatova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 368.
2002CHE1342 Y. M. Elkholy, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 1342.
2002EJO4211 D. Donati, S. Fusi, and F. Ponticelli, *Eur. J. Org. Chem.*, 2002, 4211.
2002FA897 H. Śladowska, B. Filipek, D. Szkatula, A. Sabiniarz, M. Kardasz, J. Potoczek, M. Sieklucka-Dziuba, G. Rajtar, Z. Kleinrok, and T. Lis, *Farmaco*, 2002, **57**, 897.
2002H(57)55 H. Van de Poël, G. Guillaumet, and M.-C. Viaud-Massuard, *Heterocycles*, 2002, **57**, 55.
2002H(58)301 T. Murashima, K. Nishi, K. Nakamoto, A. Kato, R. Tamai, H. Uno, and N. Ono, *Heterocycles*, 2002, **58**, 301.
2002JA2560 P. Janvier, X. Sun, H. Bienaymé, and J. Zhu, *J. Am. Chem. Soc.*, 2002, **124**, 2560.
2002JHC743 H. Maruoka, M. Yamazaki, and Y. Tomioka, *J. Heterocycl. Chem.*, 2002, **39**, 743.
2002JNP621 Y. Kimura, A. Shimada, M. Kusano, K. Yoshii, A. Morita, M. Nishibe, S. Fujioka, and T. Kawano, *J. Nat. Prod.*, 2002, **65**, 621.
2002JOC943 G.-D. Zhu, V. Schaefer, S. A. Boyd, and G. F. Okasinski, *J. Org. Chem.*, 2002, **67**, 943.
2002JOC4177 Y. Zhang and J. W. Herndon, *J. Org. Chem.*, 2002, **67**, 4177.
2002MC1 T. N. Borisova, L. G. Voskressensky, T. A. Soklakova, B. Nsabimana, and A. V. Varlamov, *Mendeleev Commun.*, 2002, 1.
2002MI365 G. H. Elgemeie, M. H. Helal, E. M. Abbas, and E. A. A. Mowla, *Pigm. Resin Tech.*, 2002, **31**, 365.
2002MI1023 N. C. R. van Straten, G. G. Schoonus-Gerritsma, R. G. van Someren, J. Draaijer, A. E. P. Adang, C. M. Timmers, R. G. J. M. Hanssen, and C. A. A. van Boeckel, *ChemBioChem*, 2002, **3**, 1023.
2002OL289 R. Roggenbuck, A. Schmidt, and P. Eilbracht, *Org. Lett.*, 2002, **4**, 289.
2002OL2409 A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, and F. Marinelli, *Org. Lett.*, 2002, **4**, 2409.
2002OL2791 F. Le Strat and J. Maddaluno, *Org. Lett.*, 2002, **4**, 2791.
2002RJO731 V. D. Dyachenko and R. P. Tkachev, *Russ. J. Org. Chem. (Engl. Transl.)*, 2002, **38**, 731.
2002S155 A. V. Varlamov, T. N. Borisova, and L. G. Voskressensky, *Synthesis*, 2002, 155.
2002SC3493 F. A. Abu-Shanab, Y. M. Elkholy, and M. H. Elnagdi, *Synth. Commun.*, 2002, **32**, 3493.
2002SL337 K. Fujita, H. Yorimitsu, and K. Oshima, *Synlett*, 2002, 337.
2002SL453 A. Arcadi, S. Cacchi, S. Di Giuseppe, G. Fabrizi, and F. Martinelli, *Synlett*, 2002, 453.
2002T6351 R. Gámez-Montaño, E. González-Zamora, P. Potier, and J. Zhu, *Tetrahedron*, 2002, **58**, 6351.
2002T7951 B. Schmidt, M. Pohler, and B. Costisella, *Tetrahedron*, 2002, **58**, 7951.
2002T10243 D. L. J. Clive and X. Huang, *Tetrahedron*, 2002, **58**, 10243.
2002T10309 K. C. Majumdar, U. K. Kundu, and S. Ghosh, *Tetrahedron*, 2002, **58**, 10309.
2002TL799 T. C. Govaerts, I. Vogels, F. Compernolle, and G. Hoornaert, *Tetrahedron Lett.*, 2002, **43**, 799.
2002TL2293 V. Nair, R. S. Menon, A. U. Vinod, and S. Viji, *Tetrahedron Lett.*, 2002, **43**, 2293.
2002TL2339 Q. Jia, W. Xie, W. Zhang, A. Janczuk, S. Luo, B. Zhang, J. P. Cheng, M. B. Ksebati, and P. G. Wang, *Tetrahedron Lett.*, 2002, **43**, 2339.
2002TL4585 R. Yanada, N. Nishimori, A. Matsumura, N. Fujii, and Y. Takemoto, *Tetrahedron Lett.*, 2002, **43**, 4585.
2002TL6767 A. V. Varlamov, T. N. Borisova, L. G. Voskressensky, T. A. Soklakova, L. N. Kulikova, A. I. Chernyshev, and G. G. Alexandrov, *Tetrahedron Lett.*, 2002, **43**, 6767.
2003BML795 P. E. J. Sanderson, M. G. Stanton, B. D. Dorsey, T. A. Lyle, C. McDonough, W. M. Sanders, K. L. Savage, A. M. Naylor-Olsen, J. A. Krueger, S. D. Lewis, B. J. Lucas, J. J. Lynch, and Y. Yan, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 795.
2003CC2062 D. L. J. Clive and X. Huang, *J. Chem. Soc., Chem. Commun.*, 2003, 2062.
2003CED1495 N. M. Rageh and E. M. Abdallah, *J. Chem. Eng. Data*, 2003, **48**, 1495.
2003CHE110 V. V. Dotsenko, S. G. Krivokolysko, and V. P. Litvinov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 110.
2003CHE328 E. S. Krichevsky, L. M. Alekseeva, and V. G. Granik, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 328.
2003CHE400 E. A. Kaigorodova, A. A. Osipova, V. K. Vasilin, L. D. Konyushkin, and G. D. Krapivin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 400.

2003CHE1182 A. N. Vasiliev, Ya. S. Kayukov, A. N. Lyshchikov, O. E. Nasakin, and O. V. Kayukova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 1182.

2003HAC459 R. M. Mohareb, S. M. Sherif, H. M. Gaber, S. S. Ghabrial, and S. I. Aziz, *Heteroatom Chem.*, 2003, **14**, 459.

2003JME3060 S. A. Filla, B. M. Mathes, K. W. Johnson, L. A. Phebus, M. L. Cohen, D. L. Nelson, J. M. Zgombick, J. A. Erickson, K. W. Schenck, D. B. Wainscott, T. A. Branchek, and J. M. Schaus, *J. Med. Chem.*, 2003, **46**, 3060.

2003JME4236 T. Wang, Z. Zhang, O. B. Wallace, M. Deshpande, H. Fang, Z. Yang, L. M. Zadjura, D. L. Tweedie, S. Huang, F. Zhao, S. Ranadive, B. S. Robinson, Y.-F. Gong, K. Riccardi, T. P. Spicer, C. Deminie, R. Rose, H.-G. H. Wang, W. S. Blair, P.-Y. Shi, P. Lin, R. J. Colonno, and N. A. Meanwell, *J. Med. Chem.*, 2003, **46**, 4236.

2003JME4702 A. Trejo, H. Arzeno, M. Browner, S. Chanda, S. Cheng, D. D. Comer, S. A. Dalrymple, P. Dunten, J. Lafargue, B. Lovejoy, J. Freire-Moar, J. Lim, J. Mcintosh, J. Miller, E. Papp, D. Reuter, R. Roberts, F. Sanpablo, J. Saunders, K. Song, A. Villasenor, S. D. Warren, M. Welch, P. Weller, P. E. Whiteley, L. Zeng, and D. M. Goldstein, *J. Med. Chem.*, 2003, **46**, 4702.

2003JOC4206 T. K. Sarkar, S. Basak, Z. Slanina, and T. J. Chow, *J. Org. Chem.*, 2003, **68**, 4206.

2003JOC5652 Z. Riedl, P. Kövér, T. Soós, G. Hajós, O. Egyed, L. Fábián, and A. Messmer, *J. Org. Chem.*, 2003, **68**, 5652.

2003JOC9406 M. S. M. Timmer, M. Verdoes, L. A. J. M. Sliedregt, G. A. van der Marel, J. H. van Boom, and H. S. Overkleeft, *J. Org. Chem.*, 2003, **68**, 9406.

2003JPL323 L. G. Voskressensky, M. de Candia, A. Carotti, T. N. Borisova, L. N. Kulikova, A. V. Varlamov, and C. Altomare, *J. Pharm. Pharmacol.*, 2003, **55**, 323.

2003OBC772 O. Miyata, R. Iba, J. Hashimoto, and T. Naito, *Org. Biomol. Chem.*, 2003, **1**, 772.

2003OL2441 E. Bossharth, P. Desbordes, N. Monteiro, and G. Balme, *Org. Lett.*, 2003, **5**, 2441.

2003OL5023 C. Thibault, A. L'Heureux, R. S. Bhide, and R. Ruel, *Org. Lett.*, 2003, **5**, 5023.

2003OPD209 M. Allegretti, R. Anacardio, M. C. Cesta, R. Curti, M. Mantovanini, G. Nano, A. Topai, and G. Zampella, *Org. Process Res. Dev.*, 2003, **7**, 209.

2003OPD676 J. A. Ragan, J. W. Raggon, P. D. Hill, B. P. Jones, R. E. McDermott, M. J. Munchhof, M. A. Marx, J. M. Casavant, B. A. Cooper, J. L. Doty, and Y. Lu, *Org. Process Res. Dev.*, 2003, **7**, 676.

2003PS929 E. A.-G. Bakhite, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 929.

2003PS2639 M. I. A. Moneam and A. M. K. El-Dean, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 2639.

2003RJC655 A. Yu. Egorova and Z. Yu. Timofeeva, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2003, **73**, 655.

2003S1191 N. E. Shevchenko, V. G. Nenajdenko, and E. S. Balenkova, *Synthesis*, 2003, 1191.

2003S1531 D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova, and A. A. Tolmachev, *Synthesis*, 2003, 1531.

2003S1671 D. Kuzmich and C. Mulrooney, *Synthesis*, 2003, 1671.

2003S2241 M. C. Aversa, A. Barattucci, M. C. Bilardo, P. Bonaccorsi, and P. Giannetto, *Synthesis*, 2003, 2241.

2003SL993 S. H. Kang and Y. M. Lee, *Synlett*, 2003, 993.

2003SL1491 M. C. Willis and S. E. Flower, *Synlett*, 2003, 1491.

2003T5199 F. Alonso, E. Lorenzo, J. Meléndez, and M. Yus, *Tetrahedron*, 2003, **59**, 5199.

2003T5265 M. V. Raiman, A. V. Pukin, V. I. Tyvorskii, N. De Kimpe, and O. G. Kulinkovich, *Tetrahedron*, 2003, **59**, 5265.

2003T8955 W. V. Murray, P. K. Mishra, I. J. Turchi, D. Sawicka, A. Maden, and S. Sun, *Tetrahedron*, 2003, **59**, 8955.

2003TL725 B. M. Mathers and S. A. Filla, *Tetrahedron Lett.*, 2003, **44**, 725.

2004BCJ1727 K. Fujita, H. Yorimitsu, and K. Oshima, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 1727.

2004BMC5277 A. Torrado, C. Lamas, J. Agejas, A. Jiménez, N. Díaz, J. Gilmore, J. Boot, J. Findlay, L. Hayhurst, L. Wallace, R. Broadmore, and R. Tomlinson, *Bioorg. Med. Chem.*, 2004, **12**, 5277.

2004BMC5505 S.-J. Oh, K. C. Lee, S.-Y. Lee, E. K. Ryu, H. Saji, Y. S. Choe, D. Y. Chi, S. E. Kim, J. Lee, and B.-T. Kim, *Bioorg. Med. Chem.*, 2004, **12**, 5505.

2004BMC5689 M. Quibell, A. Benn, N. Flinn, T. Monk, M. Ramjee, Y. Wang, and J. Watts, *Bioorg. Med. Chem.*, 2004, **12**, 5689.

2004BML21 M. J. Munchhof, J. S. Beebe, J. M. Casavant, B. A. Cooper, J. L. Doty, R. C. Higdon, S. M. Hillerman, C. I. Soderstrom, E. A. Knauth, M. A. Marx, A. M. K. Rossi, S. B. Sobolov, and J. Sun, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 21.

2004BML167 B. M. Mathes, K. J. Hudziak, J. M. Schaus, Y.-C. Xu, D. L. Nelson, D. B. Wainscott, S. E. Nutter, W. H. Gough, T. A. Branchek, J. M. Zgombick, and S. A. Filla, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 167.

2004BML3411 I. Hayakawa, R. Shioya, T. Agatsuma, H. Furukawa, and Y. Sugano, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3411.

2004CHE377 V. K. Vasilin, E. A. Kaigorodova, S. I. Firgang, and G. D. Krapivin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 377.

2004CHE519 L. G. Voskressensky, T. N. Borisova, S. V. Akbulatov, A. I. Chernyshev, and A. V. Varlamov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 519.

2004CHE862 Z. A. Kalme, R. A. Zhalubovskis, A. Shmidlers, J. Celmins, and G. Duburs, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 862.

2004CHE1442 E. A. Kaigorodova, V. K. Vasilin, E. A. Sidorova, V. E. Zavodnik, and G. D. Krapivin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1442.

2004CHE1477 T. N. Borisova, N. Bonifas, L. G. Voskresenskii, A. I. Chernyshev, A. V. Varlamov, and A. P. Krapivko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1477.

2004CHE1600 E. A. Kaigorodova, V. K. Vasilin, M. M. Lipunov, V. E. Zavodnik, and G. D. Krapivin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1600.

2004H(64)261 M. V. N. de Souza, Z. Yan, and R. H. Dodd, *Heterocycles*, 2004, **64**, 261.

2004JA7172 X. Sun, C. Wang, Z. Li, S. Zhang, and Z. Xi, *J. Am. Chem. Soc.*, 2004, **126**, 7172.

2004JHC641 H. Maruoka, M. Yamazaki, and Y. Tomioka, *J. Heterocycl. Chem.*, 2004, **41**, 641.

2004JHC947 T. M. A. Elmaati, *J. Heterocycl. Chem.*, 2004, **41**, 947.

2004JNP1532 J. Hiort, K. Maksimenka, M. Reichert, S. Perović-Ottstadt, W. H. Lin, V. Wray, K. Steube, K. Schaumann, H. Weber, P. Proksch, R. Ebel, W. E. G. Müller, and G. Bringmann, *J. Nat. Prod.*, 2004, **67**, 1532.

2004JOC1872 D. L. J. Clive and X. Huang, *J. Org. Chem.*, 2004, **69**, 1872.

2004JOC4867 D. J. Lee and K. Kim, *J. Org. Chem.*, 2004, **69**, 4867.

2004JOC6732 N. Sydorenko, R. P. Hsung, O. S. Darwish, J. M. Hahn, and J. Liu, *J. Org. Chem.*, 2004, **69**, 6732.

2004JOC9215 M. Wijtmans, D. A. Pratt, J. Brinkhorst, R. Serwa, L. Valgimigli, G. F. Pedulli, and N. A. Porter, *J. Org. Chem.*, 2004, **69**, 9215.

2004M589 A. Shaabani, M. B. Teimouri, and H. R. Bijanzadeh, *Monatsh. Chem.*, 2004, **135**, 589.

2004MI15 K. M. H. Hilmy, *Arch. Pharm. Pharm. Med. Chem.*, 2004, **337**, 15.

2004MI49 D. K. Dalvie and T. N. O'Connell, *Drug Metab. Dispos.*, 2004, **32**, 49.

2004OL115 A. Fayol and J. Zhu, *Org. Lett.*, 2004, **6**, 115.

2004OL417 L. Benati, G. Bencivenni, R. Leardini, M. Minozzi, D. Nanni, R. Scialpi, P. Spagnolo, G. Zanardi, and C. Rizzoli, *Org. Lett.*, 2004, **6**, 417.

2004OL1405 P. Cironi, J. Tulla-Puche, G. Barany, F. Albericio, and M. Álvarez, *Org. Lett.*, 2004, **6**, 1405.

2004OL2925 T. K. Sarkar and S. Basak, *Org. Lett.*, 2004, **6**, 2925.

2004PS2205 F. A. Attaby, S. M. Eldin, M. A. A. Elneairy, and A. K. K. El-Louh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 2205.

2004RCB2878 E. A. Kaigorodova, L. D. Konyushkin, A. A. Osipova, E. A. Gavrilova, E. V. Gromachevskaya, and G. D. Krapivin, *Russ. Chem. Bull.*, 2004, **53**, 2878.

2004S1935 A. Graulich and J.-F. Liégeois, *Synthesis*, 2004, 1935.

2004SCI977 G. R. Flematti, E. L. Ghisalberti, K. W. Dixon, and R. D. Trengove, *Science*, 2004, **305**, 977.

2004T429 T. C. Govaerts, I. A. Vogels, F. Compernolle, and G. J. Hoornaert, *Tetrahedron*, 2004, **60**, 429.

2004TA1949 M. Tiecco, L. Testaferri, L. Bagnoli, R. Terlizzi, A. Temperini, F. Marini, C. Santi, and C. Scarponi, *Tetrahedron Asymmetry*, 2004, **15**, 1949.

2004TL4297 C. Fuhrer, R. Messer, and R. Häner, *Tetrahedron Lett.*, 2004, **45**, 4297.

2005BML1165 S. Fonquerna, M. Miralpeix, L. Pagès, C. Puig, A. Cardús, F. Antón, D. Vilella, M. Aparici, J. Prieto, G. Warrellow, J. Beleta, and H. Ryder, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1165.

2005BML4681 D. H. Boschelli, B. Wu, A. C. B. Sosa, J. J. Chen, J. M. Golas, and F. Boschelli, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4681.

2005BML5146 M. J. Fuertes, J. Kaur, P. Deb, B. S. Cooperman, and A. B. Smith, III, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5146.

2005CCA63 A. Z. A. Hassanien, E.-S. I. Ibrahim, and M. E. Afifi, *Croat. Chem. Acta*, 2005, **78**, 63.

2005CHE235 A. P. Mkrtchyan, A. Sh. Oganisyan, Art. Sh. Oganisyan, and A. S. Noravyan, *Chem. Heterocyl. Compd. (Engl. Transl.)*, 2005, **41**, 235.

2005CHE1009 R. A. Gadzhili, A. G. Aliev, R. A. Nadzhafova, and R. I. Ibragimov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2005, **41**, 1009.

2005DP(64)223 Y. W. Ho, *Dyes Pigments*, 2005, **64**, 223.

2005EJO5296 F. Le Strat, H. Vallatte, L. Toupet, and J. Maddaluno, *Eur. J. Org. Chem.*, 2005, 5296.

2005H(65)377 K. Matsuo, M. Adachi, T. Takagi, S. Ueno, T. Arase, and F. Kuroi, *Heterocycles*, 2005, **65**, 377.

2005JHC103 M. D. Khidre, A. A. Kamel, and W. M. Abdou, *J. Heterocycl. Chem.*, 2005, **42**, 103.

2005JHC527 A. O. Abdelhamid and M. A. M. Alkhodshi, *J. Heterocycl. Chem.*, 2005, **42**, 527.

2005JME3891 D. H. Boschelli, B. Wu, A. C. B. Sosa, H. Durutlic, J. J. Chen, Y. Wang, J. M. Golas, J. Lucas, and F. Boschelli, *J. Med. Chem.*, 2005, **48**, 3891.

2005JME4972 A. Graulich, J. Scuvée-Moreau, V. Seutin, and J.-F. Liégeois, *J. Med. Chem.*, 2005, **48**, 4972.

2005JOC384 M. Dai, X. Zhang, S.-K. Khim, and A. G. Schultz, *J. Org. Chem.*, 2005, **70**, 384.

2005JOC6964 C. Chen and P. G. Dormer, *J. Org. Chem.*, 2005, **70**, 6964.

2005JOC9222 T. Iida, H. Satoh, K. Maeda, Y. Yamamoto, K. Asakawa, N. Sawada, T. Wada, C. Kadowaki, T. Itoh, T. Mase, S. A. Weissman, D. Tschaen, S. Krska, and R. P. Volante, *J. Org. Chem.*, 2005, **70**, 9222.

2005JOC10292 D. Yue, T. Yao, and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 10292.

2005M567 J. A. Zahra, B. A. Thaher, M. M. El-Abadelah, and H.-H. Otta, *Monatsh. Chem.*, 2005, **136**, 567.

2005OBC666 S. Broussy, V. Bernardes-Génisson, H. Gornitzka, J. Bernadou, and B. Meunier, *Org. Biomol. Chem.*, 2005, **3**, 666.

2005OL791 V. A. Ogurtsov, O. A. Rakitin, C. W. Rees, A. A. Smolentsev, P. A. Belyakov, D. G. Golovanov, and K. A. Lyssenko, *Org. Lett.*, 2005, **7**, 791.

2005OL3673 J. Clayden, S. D. Hamilton, and R. T. Mohammed, *Org. Lett.*, 2005, **7**, 3673.

2005RCB864 V. P. Litvinov, V. V. Dotsenko, and S. G. Krivokolyska, *Russ. Chem. Bull.*, 2005, **54**, 864.

2005RJC440 V. D. Dyachenko, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2005, **75**, 440.

2005RJO279 A. N. Vasil'ev, A. N. Lyshchikov, O. E. Nasakin, Ya. S. Kayukov, and V. A. Tafeenko, *Russ. J. Org. Chem. (Engl. Transl.)*, 2005, **41**, 279.

2005S161 A. Fayol, C. Housseman, X. Sun, P. Janvier, H. Bienaymé, and J. Zhu, *Synthesis*, 2005, 161.

2005S2571 N. Lachance, M. April, and M.-A. Joly, *Synthesis*, 2005, 2571.

2005S3581 M. Lefoix, J.-P. Daillant, S. Routier, J.-Y. Mérour, I. Gillaizeau, and G. Coudert, *Synthesis*, 2005, 3581.

2005SC535 A. Shaabani, M. B. Teimouri, S. Samadi, and K. Soleimani, *Synth. Commun.*, 2005, **35**, 535.

2005SL587 G. Bashiardes, C. Cano, and B. Mauzé, *Synlett*, 2005, 587.

2005SL1006 I. V. Voznyi, M. S. Novikov, and A. F. Khlebnikov, *Synlett*, 2005, 1006.

2005SL1188 A. Gutnov, V. Abaev, D. Redkin, C. Fischer, W. Bonrath, and B. Heller, *Synlett*, 2005, 1188.

2005SL1397 P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, and S. Grass, *Synlett*, 2005, 1397.

2005T1077 E. M. Beccalli, G. Broggini, M. Martinelli, and G. Paladino, *Tetrahedron*, 2005, **61**, 1077.

2005TL5085 L.-X. Pei, S.-L. Huang, Y.-D. Shen, L.-Q. An, Z.-S. Huang, Y.-M. Li, L.-Q. Gu, X.-Z. Bu, and A. S. C. Chan, *Tetrahedron Lett.*, 2005, **46**, 5085.

2005TL5719 G. R. Flematti, E. L. Ghisalberti, K. W. Dixon, and R. D. Trengove, *Tetrahedron Lett.*, 2005, **46**, 5719.

2005TL8877 C. Barberis, T. D. Gordon, C. Thomas, X. Zhang, and K. P. Cusack, *Tetrahedron Lett.*, 2005, **46**, 8877.

2006AX(E)o5263 A. Decken, R. J. Burford, D. G. Beach, and S. A. Westcott, *Acta Cryst. (E)*, 2006, **E62**, o5263.

2006BMC1309 S. Komoriya, S. Kobayashi, K. Osanai, T. Yoshino, T. Nagata, N. Haginoya, Y. Nakamoto, A. Mochizuki, T. Nagahara, M. Suzuki, T. Shimada, K. Watanabe, Y. Isobe, and T. Furugoori, *Bioorg. Med. Chem.*, 2006, **14**, 1309.

2006BMC5765 A. M. R. Bernardino, L. C. da Silva Pinheiro, C. R. Rodrigues, N. I. Loureiro, H. C. Castro, A. Lanfredi-Rangel, J. Sabatini-Lopes, J. C. Borges, J. M. Carvalho, G. A. Romeiro, V. F. Ferreira, I. C. P. P. Frugulhetti, and M. A. Vannier-Santos, *Bioorg. Med. Chem.*, 2006, **14**, 5765.

2006BML4537 S. D. Paget, C. M. Boggs, B. D. Foleno, R. M. Goldschmidt, D. J. Hlasta, M. A. Weidner-Wells, H. M. Werblood, K. Bush, and M. J. Macielag, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4537.

2006BML5530 R. Romagnoli, P. G. Baraldi, A. R. Moorman, M. A. Iaconinoto, M. D. Carrion, C. L. Cara, M. A. Tabrizi, D. Preti, F. Fruttarolo, S. P. Baker, K. Varani, and P. A. Borea, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5530.

2006DP(70)60 Y. W. Ho and W. H. Yao, *Dyes Pigments*, 2006, **70**, 60.

2006JME864 H.-P. Buchstaller, C. D. Siebert, R. Steinmetz, I. Frank, M. L. Berger, R. Gottschlich, J. Leibrock, M. Krug, D. Steinhilber, and C. R. Noe, *J. Med. Chem.*, 2006, **49**, 864.

2006JME3809 T. Imada, N. Cho, T. Imaeda, Y. Hayase, S. Sasaki, S. Kasai, M. Harada, H. Matsumoto, S. Endo, N. Suzuki, and S. Furuya, *J. Med. Chem.*, 2006, **49**, 3809.

2006JOC5538 H. Schirok, *J. Org. Chem.*, 2006, **71**, 5538.

2006JOC3494 O. G. Schramm, T. Oeser, and T. J. J. Müller, *J. Org. Chem.*, 2006, **71**, 3494.

2006OL1113 I. Aillaud, E. Bossharth, D. Conreaux, P. Desbordes, N. Monteiro, and G. Balme, *Org. Lett.*, 2006, **8**, 1113.

2006OL5889 G. Deguest, A. Devineau, L. Bischoff, C. Fruit, and F. Marsais, *Org. Lett.*, 2006, **8**, 5889.

2006POL3261 R. Ivaniková, R. Boča, L. Dlháň, H. Fuess, A. Mašlejová, V. Mráxová, I. Svoboda, and J. Titiš, *Polyhedron*, 2006, **52**, 3261.

2006RCB529 V. E. Kalugin, A. M. Shestopalov, and V. P. Litvinov, *Russ. Chem. Bull.*, 2006, **55**, 529.

2006SC2797 S. Gluszok, L. Goossens, P. Depreux, D. Barbry, and J. P. Hénichart, *Synth. Commun.*, 2006, **36**, 2797.

2006T4052 S. Gowrisanker, K. Y. Lee, and J. N. Kim, *Tetrahedron*, 2006, **62**, 4052.

2006T6036 C. Comoy, E. Banaszak, and Y. Fort, *Tetrahedron*, 2006, **62**, 6036.

2006TL83 S. Raju, V. R. Batchu, N. K. Swamy, R. V. Dev, J. M. Babu, P. R. Kumar, K. Mukkanti, and M. Pal, *Tetrahedron Lett.*, 2006, **47**, 83.

2006TL2069 S. Figueroa-Pérez, S. Bennabi, H. Schirok, and M. Thutewohl, *Tetrahedron Lett.*, 2006, **47**, 2069.

2006TL3607 M. R. Attwood, P. S. Gilbert, M. L. Lewis, K. Mills, P. Quayle, S. P. Thompson, and S. Wang, *Tetrahedron Lett.*, 2006, **47**, 3607.

2007ARK213 S. M. Al-Mousawi, I. A. Abdelhamid, and M. S. Moustafa, *ARKIVOC*, 2007, 213.

2007BMC3248 R. H. Bahekar, M. R. Jain, A. Goel, D. N. Patel, V. M. Prajapati, A. A. Gupta, P. A. Jadav, and P. R. Patel, *Bioorg. Med. Chem.*, 2007, **15**, 3248.

2007BML250 Y. Miyazaki, M. Nakano, H. Sato, A. T. Truesdale, J. D. Stuart, E. N. Nartey, K. E. Hightower, and L. Kane-Carson, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 250.

2007BML673 R. A. Smith, Z. Fathi, S. E. Brown, S. Choi, J. Fan, S. Jenkins, H. C. E. Kluender, A. Konkar, R. Lavoie, R. Mays, J. Natoli, S. J. O'Connor, A. A. Ortiz, B. Podlogar, C. Taing, S. Tomlinson, T. Tritto, and Z. Zhang, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 673.

2007BML1167 L. Abbott, P. Betschmann, A. Burchat, D. J. Calderwood, H. Davis, P. Hrnciar, G. C. Hirst, B. Li, M. Morytko, K. Mullen, and B. Yang, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1167.

2007BML1246 H. R. Heyman, R. R. Frey, P. F. Bousquet, G. A. Cunha, M. D. Moskey, A. A. Ahmed, N. B. Soni, P. A. Marcotte, L. J. Pease, K. B. Glaser, M. Yates, J. J. Bouska, D. H. Albert, C. L. Black-Schaefer, P. J. Dandliker, K. D. Stewart, P. Rafferty, S. K. Davidsen, M. R. Michaelides, and M. L. Curtin, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1246.

2007BML1924 B. K. Srivastava, M. Solanki, B. Mishra, R. Soni, S. Jayadev, D. Valani, M. Jain, and P. R. Patel, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1924.

2007BML1934 J. Guillard, M. Decrop, N. Gallay, C. Espanel, E. Boissier, O. Herault, and M.-C. Viaud-Massuard, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1934.

2007BML3729 A. H. Hermerian, A. Case, R. L. Stein, and G. D. Cuny, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3729.

2007BML3840 S. D. Larsen, Z. Zhang, B. A. DiPaulo, P. R. Manninen, D. C. Rohrer, M. J. Hageman, T. A. Hopkins, M. L. Knechtel, N. L. Oien, B. D. Rush, F. J. Schwende, K. J. Stefanski, J. L. Wieber, K. F. Wilkinson, K. M. Zamora, M. W. Wathen, and R. J. Brideau, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3840.

2007BML3845 M. Chen, Z. Guo, M. C. Lanier, L. Zhao, S. F. Betz, C. Q. Huang, C. J. Loweth, N. J. Ashweek, X.-J. Liu, R. S. Struthers, M. J. Bradbury, J. W. Behan, J. Wen, Z. O'Brien, J. Saunders, and Y.-F. Zhu, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3845.

2007CSR1120 J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, and C. H. Senanayake, *Chem. Soc. Rev.*, 2007, **36**, 1120.

2007EJO3296 S. Naud, M. Pipelier, G. Viault, A. Adjou, F. Huet, S. Legoupy, A.-M. Aubertin, M. Evain, and D. Dubreuil, *Eur. J. Org. Chem.*, 2007, 3296.

2007JME2647 D. R. Anderson, M. J. Meyers, W. F. Vernier, M. W. Mahoney, R. G. Kurumbail, N. Caspers, G. I. Poda, J. F. Schindler, D. B. Reitz, and R. J. Mourey, *J. Med. Chem.*, 2007, **50**, 2647.

2007MI441 C. A. Fuhrer, E. Grüter, S. Ruetz, and R. Häner, *ChemMedChem*, 2007, **2**, 441.

2007OL1331 S. D. Haveli, P. R. Sridhar, P. Suguna, and S. Chandrasekaran, *Org. Lett.*, 2007, **9**, 1331.

2007POL1523 J. Titiš, R. Boča, L. Dhláň, T. Ďurčeková, H. Fuess, R. Ivaniková, V. Mrázová, B. Papánková, and I. Svoboda, *Polyhedron*, 2007, **26**, 1523.

2007S590 M. Alajarín, Á. Vidal, and M.-M. Ortín, *Synthesis*, 2007, 590.

2007S2153 D. Thomae, G. Kirsch, P. Seck, and T. Kaminiski, *Synthesis*, 2007, 2153.

2007SL403 S. Naud, M. Pipelier, C. Chaumette, G. Viault, F. Huet, S. Legoupy, and D. Dubreuil, *Synlett*, 2007, 403.

2007T4491 V. S. Berseneva, V. A. Bakulev, W. Dehaen, S. Toppet, and M. Borovkova, *Tetrahedron*, 2007, **63**, 4491.

2007TL2675 K. Gesenberg, P. P. Deshpande, A. Pullockaran, F. Xu, D. Wu, Q. Gao, C. Pathirana, J. Castoro, N. Soundararajan, and A. Staab, *Tetrahedron Lett.*, 2007, **48**, 2675.

2007TL6951 K. C. Majumdar and S. Mondal, *Tetrahedron Lett.*, 2007, **48**, 6951.

Biographical Sketch



Angela Sherman was born in Baltimore, Maryland. Angela graduated from Johns Hopkins University in 1979, and in 1984 she obtained her Ph.D. in organic chemistry at Purdue University under the direction of Professor Robert Benkeser. Angela worked at Reilly Industries (now Vertellus) in Indianapolis, Indiana, for nine years, beginning as a research chemist, and advancing to the position of Section Head in Research & Development. Since 1996, Angela has been at College of Notre Dame of Maryland, where she currently holds the position of Associate Professor in the Chemistry Department. Since 2002, Angela has served as a technical editor on the control board of *ARKIVOC*, the online journal *Archives of Organic Chemistry*.

10.07
Bicyclic 5-6 Systems: Three Heteroatoms 1:2

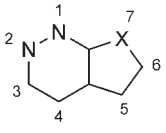
T. J. Delia
Central Michigan University, Mt. Pleasant, MI, USA
© 2008 Elsevier Ltd. All rights reserved.

10.07.1 Introduction **340**
10.07.2 Theoretical Methods **342**
10.07.3 Experimental Structural Methods **342**
10.07.4 Thermodynamic Aspects **342**
10.07.5 Reactivity of the Bicyclic Rings and Ring Substituents **343**
10.07.5.1 Pyrrolopyridazines **343**
10.07.5.2 Pyrrolopyrimidines **343**
10.07.5.3 Pyrrolopyrazines **345**
10.07.5.4 Furopyridazines **345**
10.07.5.5 Furopyrimidines **345**
10.07.5.6 Furopyrazines **346**
10.07.5.7 Thienopyridazines **346**
10.07.5.8 Thienopyrimidines **351**
10.07.5.9 Thienopyrazines **352**
10.07.6 Ring Syntheses **352**
10.07.6.1 Pyrrolopyridazines **352**
10.07.6.1.1 Pyrrolo[2,3-*c*]pyridazines 352
10.07.6.1.2 Pyrrolo[2,3-*d*]pyridazines 353
10.07.6.1.3 Pyrrolo[3,4-*c*]pyridazines 354
10.07.6.1.4 Pyrrolo[3,4-*d*]pyridazines 355
10.07.6.1.5 Pyrrolo[3,2-*c*]pyridazines 356
10.07.6.2 Pyrrolopyrimidines **356**
10.07.6.2.1 Pyrrolo[2,3-*d*]pyrimidines 356
10.07.6.2.2 Pyrrolo[3,2-*d*]pyrimidines (9-deazapurines) 370
10.07.6.2.3 Pyrrolo[3,4-*d*]pyrimidines 378
10.07.6.3 Pyrrolopyrazines **379**
10.07.6.3.1 Pyrrolo[2,3-*b*]pyrazines 379
10.07.6.3.2 Pyrrolo[3,4-*b*]pyrazines 381
10.07.6.4 Furopyridazines **381**
10.07.6.4.1 Furo[2,3-*c*]pyridazines 381
10.07.6.4.2 Furo[2,3-*d*]pyridazines 382
10.07.6.4.3 Furo[3,4-*c*]pyridazines 382
10.07.6.4.4 Furo[3,4-*d*]pyridazines 383
10.07.6.4.5 Furo[3,2-*c*]pyridazines 383
10.07.6.5 Furopyrimidines **384**
10.07.6.5.1 Furo[2,3-*d*]pyrimidines 384
10.07.6.5.2 Furo[3,4-*d*]pyrimidines 390
10.07.6.5.3 Furo[3,2-*d*]pyrimidines 391
10.07.6.6 Furopyrazines **392**
10.07.6.6.1 Furo[2,3-*b*]pyrazines 392
10.07.6.6.2 Furo[3,4-*b*]pyrazines 393

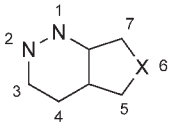
10.07.6.7 Thienopyridazines 393
10.07.6.7.1 Thieno[2,3-*c*]pyridazines 393
10.07.6.7.2 Thieno[2,3-*d*]pyridazines 395
10.07.6.7.3 Thieno[3,4-*c*]pyridazines 395
10.07.6.7.4 Thieno[3,4-*d*]pyridazines 395
10.07.6.7.5 Thieno[3,2-*c*]pyridazines 396
10.07.6.8 Thienopyrimidines 396
10.07.6.8.1 Thieno[2,3-*d*]pyrimidines 396
10.07.6.8.2 Thieno[3,4-*d*]pyrimidines 406
10.07.6.8.3 Thieno[3,2-*d*]pyrimidines 408
10.07.6.9 Thienopyrazines 415
10.07.6.9.1 Thieno[2,3-*b*]pyrazines 415
10.07.6.9.2 Thieno[3,4-*b*]pyrazines 417
10.07.7 Important Compounds and Applications 418
10.07.8 Further Developments 418
10.07.8.1 Fused Pyridazines 418
10.07.8.2 Fused Pyrimidines 418
10.07.8.2.1 Furo pyrimidines 418
10.07.8.2.2 Pyrrolo pyrimidines 418
10.07.8.2.3 Thieno pyrimidines 419
10.07.8.3 Fused Pyrazines 420
References 420

10.07.1 Introduction

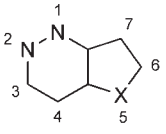
CHEC-II(1996) <1996CHEC-II(7)229> went a long way toward consolidating the material to be described in this chapter. As with the contents of the previous chapter in CHEC-II(1996), the emphasis will be on fused diazines, especially those containing the pyrimidine ring. All of the possible ring systems are shown in **Figures 1–4**. **Figure 1** illustrates all of the possible structures that contain a fused pyridazine. Similarly, **Figure 2** describes the pertinent fused pyrimidines while **Figure 3** contains the fused pyrazines. In keeping with the format of CHEC-II(1996), this is the order in which these classes of compounds will be discussed. Finally, under a category that may be called miscellaneous fused systems, **Figure 4** illustrates the many possibilities that exist for rings that contain either one or no nitrogen atoms in the six-membered ring. **Figure 5** rounds out the possibilities in which only



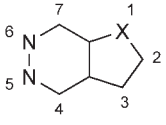
X = N: pyrrolo[2,3-*c*]pyridazine
X = O: furo[2,3-*c*]pyridazine
X = S: thieno[2,3-*c*]pyridazine



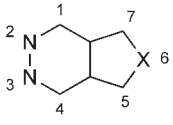
X = N: pyrrolo[3,4-*c*]pyridazine
X = O: furo[3,4-*c*]pyridazine
X = S: thieno[3,4-*c*]pyridazine



X = N: pyrrolo[3,2-*c*]pyridazine
X = O: furo[3,2-*c*]pyridazine
X = S: thieno[3,2-*c*]pyridazine



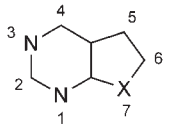
X = N: pyrrolo[2,3-*d*]pyridazine
X = O: furo[2,3-*d*]pyridazine
X = S: thieno[2,3-*d*]pyridazine



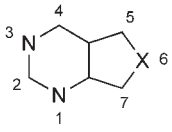
X = N: pyrrolo[3,4-*d*]pyridazine
X = O: furo[3,4-*d*]pyridazine
X = S: thieno[3,4-*d*]pyridazine

Figure 1 Fused pyridazines.

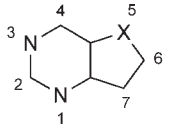
nitrogen is present in the five-membered ring. There are far fewer examples described in the literature for many of these structures. The substantial increase in the volume of the literature associated with the diazines (see below) has created limitations on what may be covered as miscellaneous fused systems. Therefore none of these ring systems, that were formerly included in CHEC-II(1996), is covered here. Investigators in these fields are encouraged to consult CHEC-II(1996).



X = N: pyrrolo[2,3-*d*]pyrimidine
X = O: furo[2,3-*d*]pyrimidine
X = S: thieno[2,3-*d*]pyrimidine

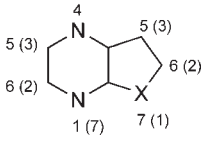


X = N: pyrrolo[3,4-*d*]pyrimidine
X = O: furo[3,4-*d*]pyrimidine
X = S: thieno[3,4-*d*]pyrimidine

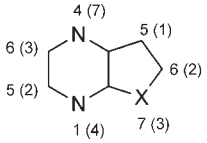


X = N: pyrrolo[3,2-*d*]pyrimidine
X = O: furo[3,2-*d*]pyrimidine
X = S: thieno[3,2-*d*]pyrimidine

Figure 2 Fused pyrimidines.

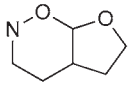


X = N: pyrrolo[2,3-*b*]pyrazine
X = O: furo[2,3-*b*]pyrazine
X = S: thieno[2,3-*b*]pyrazine

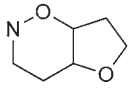


X = N: pyrrolo[3,4-*b*]pyrazine
X = O: furo[3,4-*b*]pyrazine
X = S: thieno[3,4-*b*]pyrazine

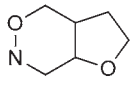
Figure 3 Fused pyrazines.



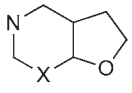
Furo[3,2-*e*]-1,2-oxazine



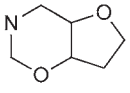
Furo[2,3-*e*]-1,2-oxazine



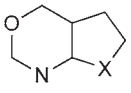
Furo[2,3-*d*]-1,2-oxazine



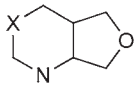
X = O: furo[3,2-*e*]-1,3-oxazine
X = S: furo[3,2-*e*]-1,3-thiazine



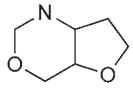
Furo[2,3-*c*]-1,3-oxazine



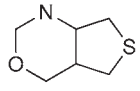
X = O: furo[2,3-*d*]-1,3-oxazine
X = S: thieno[2,3-*d*]-1,3-oxazine



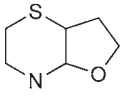
X = O: furo[3,4-*d*]-1,3-oxazine
X = S: furo[3,4-*d*]-1,3-thiazine



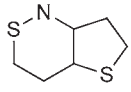
Furo[3,2-*d*]-1,3-oxazine



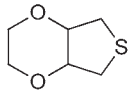
Thieno[3,4-*d*]-1,3-oxazine



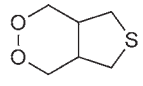
Furo[3,2-*b*]-1,4-thiazine



Thieno[2,3-*e*]-1,2-thiazine



Thieno[3,4-*b*]-1,4-dioxin



Thieno[3,4-*d*]-1,2-dioxin

Figure 4 Fused oxazines and thiazines.

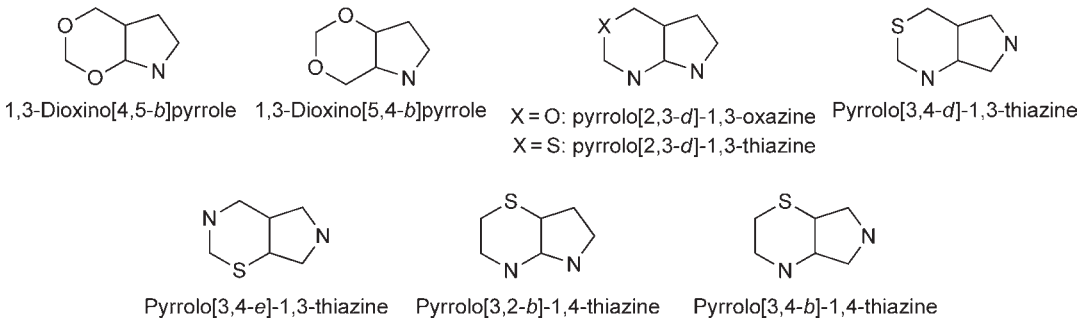


Figure 5 Pyrrolo-fused systems.

Having been involved with the preparation of the equivalent chapter in CHEC-II(1996), this author can attest to the fact that the literature since 1993 (the last year to be fully included in CHEC-II(1996)) has more than doubled (to over 5000 references).

With a goal of trying to be as comprehensive as possible considerable numbers of references have been included, along with much more detail than was present in CHEC-II(1996). Nevertheless, space constraints have dictated that virtually all of the patent literature be excluded.

10.07.2 Theoretical Methods

The trend continues in the literature to focus on synthetic methodology. Undoubtedly this is driven by either biomedical applications or potential commercial uses in the field of polymers.

Polythieno[3,4-*d*]pyridazines have enjoyed success as polymers with potential commercial applications. Because of this, two quantum-chemical investigations have been carried out to elicit geometric and electronic structures and stabilities of such molecules <1995SM691, 2000JPC7106>.

The potential tautomerism of 1,2,3,4-tetrahydro-5,7-dimethyl-6*H*-pyrrolo[3,4-*d*]pyridazine-1,4-diones has been examined by AM1 semi-empirical methods <1998JMT(434)7, 1998JMT(427)65, 1998JMT(430)85>.

In recent years, there has been a greater interest in joining certain heterocyclic systems to [60]-fullerene with pyrimidine-fused 3-sulfolenes as one such case. Three derivatives have been examined in membrane model environments and the aggregation of these derivatives has been studied <2000J(P2)301>. Similar studies have been carried out on furo[2,3-*d*]pyrimidines <1996JST(385)55>.

Additional theoretical studies have been conducted in order to develop better structures for biological activity <2001MI497, 2005CCA55>.

10.07.3 Experimental Structural Methods

Standard structural methods are reported with the syntheses of the bicyclic compounds within the purview of this chapter and are not revisited here.

A wide array of spectroscopic methods have contributed to the establishment of structures of the bicyclic compounds covered here. These spectral studies include electron spin resonance (ESR) <1998JMT(424)21>, Raman <1995MM2922, 1995SM593>, and vibrational techniques <1995MI281, 1997JCP5541>.

Crystallographic analysis has been used quite effectively to solidify structural determinations. Several examples include dihydrofolate reductase complexes <B-1997MI399>, nucleosides <1999AXC1335, 1999AXC1560>, zopiclone <2001CC2204>, and immucillin inhibitors <2003BBR917>.

10.07.4 Thermodynamic Aspects

Topological resonance energy studies of the three isomeric thienopyrimidines show that while all of the ring systems are aromatic, the thieno[3,4-*d*]pyrimidine class of compounds is less aromatic by approximately 20%. Correspondingly this system is believed to be considerably more reactive than its isomers <1997CCA841>.

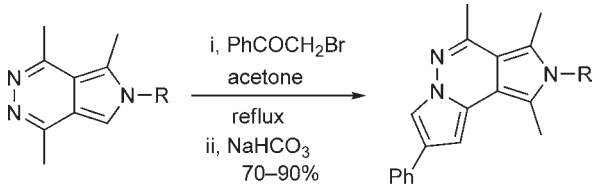
The formation of pyrrolo-, furo-, and thieno[2,3-*d*]pyridazines has been predicted on the basis of thermodynamic studies <2005JOC998>.

10.07.5 Reactivity of the Bicyclic Rings and Ring Substituents

There has been very little novel chemistry either of substituents on the various ring systems or of the ring systems themselves. Consequently, the sections that follow are more illustrative than exhaustive and the comments focus primarily on unusual reactions with limited attention paid to standard reactions, readily expected by practicing chemists. It also seems prudent to follow the format of CHEC-II(1996) by consolidating the various isomers into a broader category.

10.07.5.1 Pyrrolopyridazines

Alkylation of a ring nitrogen on **1** with an acyl bromide leads to a cyclization reaction producing a tricyclic compound **2** (Equation 1) <2003CHE669>.



(1)

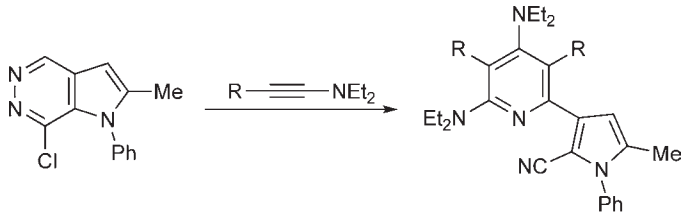
1

a: R = Me

b: R = 4-MeC$_6$H$_4$

2

Fused pyridazines, such as **3**, that have a chloro substituent α to the nitrogen in the pyridazine ring react with electron-rich ynamines in a reaction sequence including an inverse electron demand Diels–Alder process to give the corresponding pentasubstituted pyridines (Equation 2) <1994CPB2219>. Another isomer of the pyrrolopyridazine as well as a furopyridazine behaved similarly <1994CPB2219>.



(2)

3

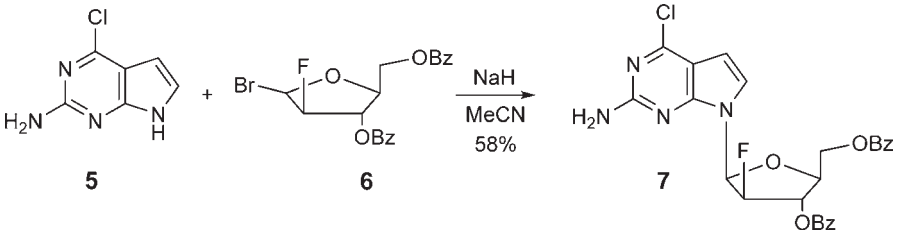
4

a: R = Me (54%)

b: R = Et (48%)

10.07.5.2 Pyrrolopyrimidines

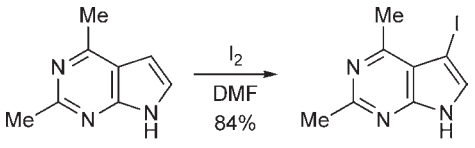
Not surprisingly, one of the most common reactions of pyrrolo[2,3-*d*]pyrimidines is nucleoside formation. Typical of the process is the reaction of **5** with the fluorine-containing carbohydrate moiety **6** to produce the nucleoside **7** (**Scheme 1**) <1995JME3957>. Numerous other reports are described in the literature but the number is too large to be cited here.



5 **6** **7**

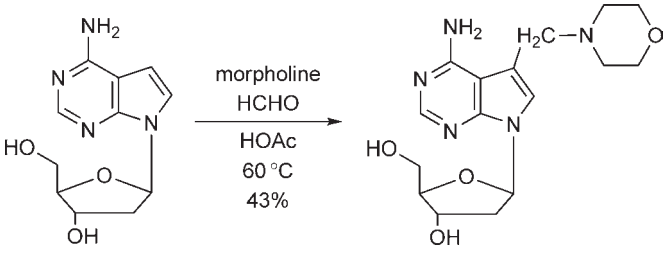
Scheme 1

Iodo derivatives of pyrrolo[2,3-*d*]pyrimidines have been sought due to their ease of replacement in Pd-catalyzed carbon–carbon bond formation, so when a relatively simple iodination process is achieved there is considerable interest. Elemental iodine reacts easily with **8** to produce **9** in good yield (Equation 3) <1996J(P1)459>. In contrast, nucleoside analogs of this ring system have been brominated using *N*-bromosuccinimide (NBS) at the adjacent position 6 instead <1997CC695>.



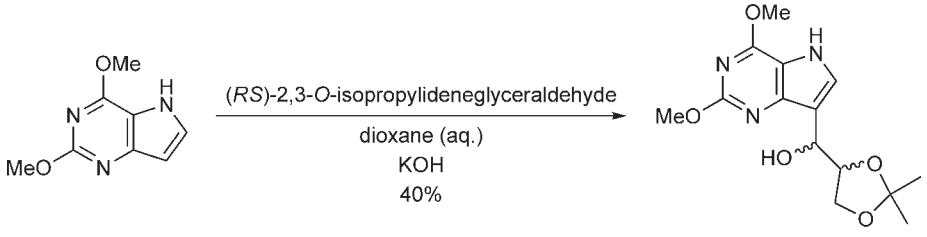
8 **9** (3)

Alkylation at position 5 of a pyrrolo[2,3-*d*]pyrimidine occurs via a Mannich reaction. The nucleoside **10** is transformed into the morpholinomethyl derivative **11** in modest yield (Equation 4) <1997S1067>.



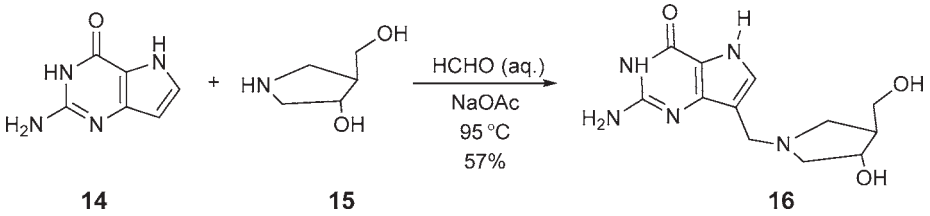
10 **11** (4)

Interest in preparing *C*-nucleoside compounds has prompted syntheses involving C-alkylation. Thus, **12** reacts with (*RS*)-2,3-*O*-isopropylideneglyceraldehyde to give only **13** (Equation 5) <1996MI549>.



12 **13** (5)

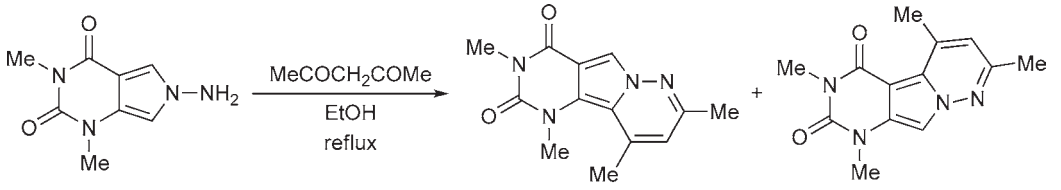
A rather unusual, and quite specific, Mannich reaction occurs when the pyrrolo[3,2-*d*]pyrimidine **14** undergoes reaction with (3*R*,4*R*)-3-hydroxy-4-(hydroxymethyl)pyrrolidine **15** and formaldehyde to produce the pseudonucleoside **16** (**Scheme 2**) <2003OL3639>.



14 **15** **16**

Scheme 2

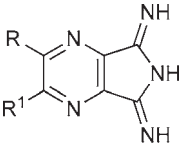
Most cyclizations described in this chapter involve a carbon–nitrogen bond as the final step. However, the *N*-amino compound **17** offers an example of a carbon–carbon bond formation to complete ring formation. Treatment of **17** with $MeCOCH_2COMe$ gives a mixture of products **18** and **19** (Equation 6) <2003CHE953>, with **19** obtained in very small amounts.



17 **18** 72% **19** 2% (6)

10.07.5.3 Pyrrolopyrazines

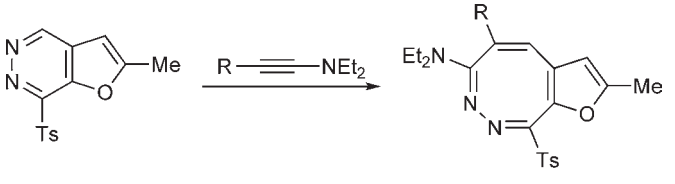
A number of examples of **20** have been prepared with the sole purpose of converting this structure into porphyrin-like structures commonly referred to as azaphthalocyanines <1999MI417, 1996JOC5706, 1997JME3897>.



20

10.07.5.4 Furopyridazines

Upon reaction with ynamines 2-methyl-7-tosylfuro[2,3-*d*]pyridazine **21** undergoes [2+2] cycloaddition–ring-expansion reactions to afford **22** (Equation 7) <1996H(43)199> as one of three products isolated.

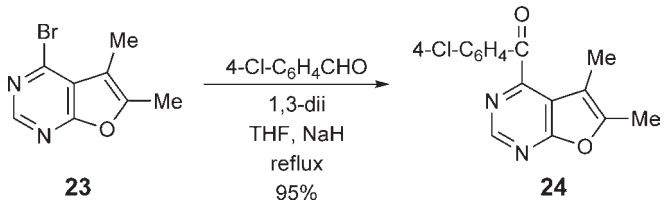


21 **22**

a: R = Me (20%)
b: R = Et (14%) (7)

10.07.5.5 Furopyrimidines

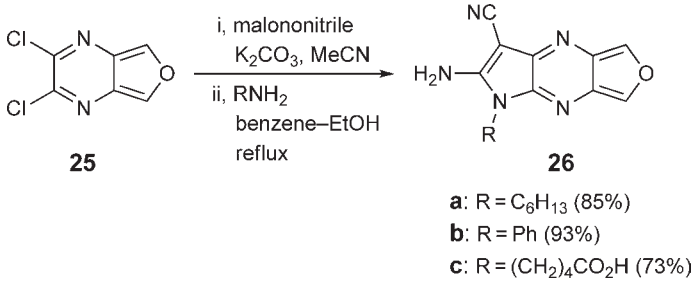
Normally acylation reactions would be considered standard chemistry but replacing an aryl bromide with a ketone under relatively mild conditions warrants attention. Here **23** is treated with 1,3-dimethylimidazolium iodide (1,3-dii) in refluxing THF leading to the formation of the ketone **24** (Equation 8) <1997H(45)2159>.



(8)

10.07.5.6 Furopyrazines

While ring annulation is not uncommon, the formation of a five-membered ring onto an existing pyrazine is somewhat unique. Thus, **25** reacts with malononitrile and then with an amine to form the tricyclic product **26** (Equation 9) <2001MC152>. Thiophene and pyrrole analogs of **25** react similarly. Note that **26** is suitably substituted to add yet another ring.

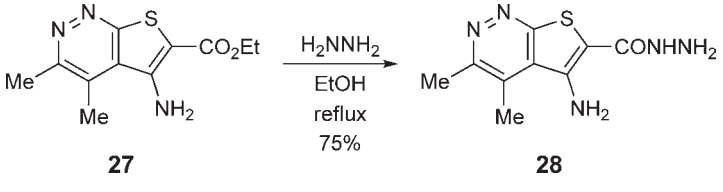


(9)

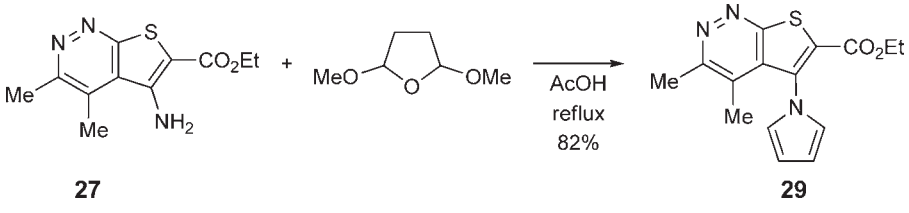
10.07.5.7 Thienopyridazines

By far the largest body of the literature of thienopyridazines involves the reactions of thieno[2,3-*c*]pyridazines. There are two main types of reactions on such systems: (1) simple chemistry of existing functional groups and (2) reactions involving cyclization to give tricyclic (and higher) ring systems.

Examples of the simple reactions include the conversion of the ester group of **27** into hydrazides (Equation 10), such as **28** <2004JCCS1325>, and replacement of the amino moiety of **27** with the pyrrole ring via reaction with 2,5-dimethoxytetrahydrofuran to produce **29** (**Scheme 3**) <2004JCCS1325>. Identical chemistry has been conducted on the corresponding diphenyl derivative <1994PS(89)193>.

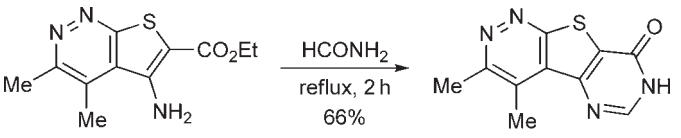


(10)



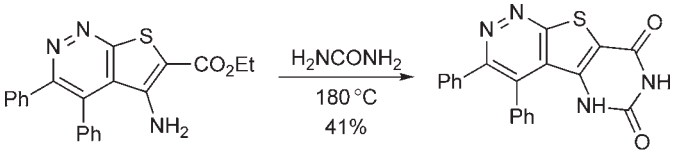
Scheme 3

There is, however, a larger body of literature describing the formation of tricyclic ring systems from suitably substituted bicyclic systems. One such approach commences with the enamino ester arrangement present in structure **27**. Heating this compound to reflux in the high boiling solvent/reactant formamide is a standard method for producing the fused pyrimidine structure shown in **30** (Equation 11) <2005PS(180)413>. The analogous product has been obtained by heating **31** under identical conditions <2000PS(163)153>.



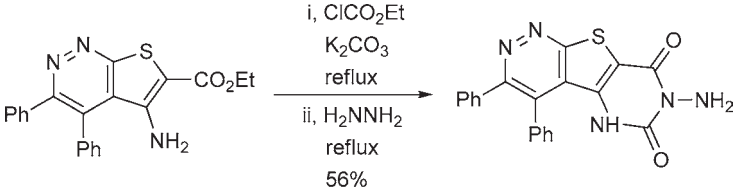
27 **30** (11)

The pyrimidinedione **32** is formed similarly by heating **31** with urea until a melt is obtained (Equation 12) <2004PS(179)2245>.



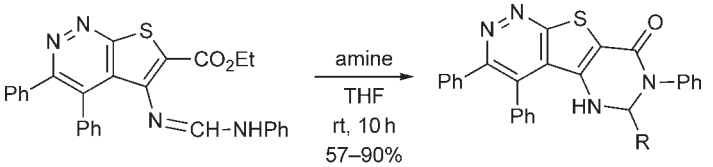
31 **32** (12)

A variation on this procedure is observed when **31** is initially treated with ethyl chloroformate and then with hydrazine (Equation 13). The resulting product is an *N*-amino derivative **33** <2004PS(179)2245>.



31 **33** (13)

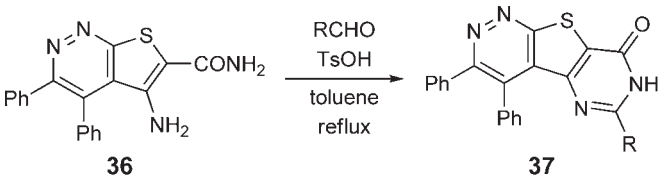
In a multistep process, compound **34**, formed from reacting the amino group in **31** first with PPh_3 and then with PhNCO, reacts with a variety of amines to give a series of compounds **35** (Equation 14) <1997H(45)1319>.



34 **35** (14)

a: R = diethylamino
b: R = piperidino
c: R = 4-Me-piperazino
d: R = morpholino

The corresponding amide **36**, undoubtedly obtained in most cases from the ester, serves well as a precursor for a series of substituted pyrimidinones **37a–g** (Equation 15) <1996M537>. Compound **37h** has been prepared by treatment of **36** with acetic anhydride in 65% yield <2005JCM270>.

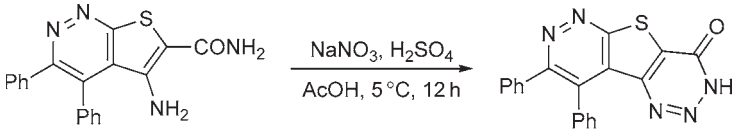


36 → **37**

a: R = Ph (81%)
b: R = 4-$O_2NC_6H_4$ (65%)
c: R = 4-ClC_6H_4 (50%)
d: R = 2-$MeOC_6H_4$ (72%)
e: R = 3,4-methylenedioxyphenyl (80%)
f : R = 2,6-$Cl_2C_6H_3$ (70%)
g: R = 4-MeC_6H_4 (80%)
h: R = Me (65%)

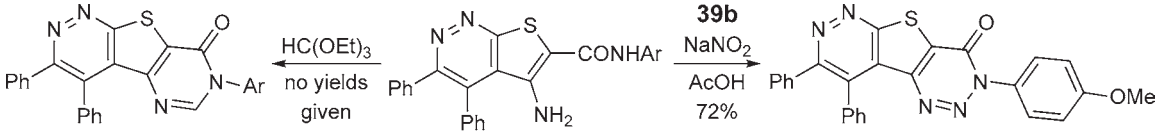
(15)

An unusual adaptation of this cyclization reaction provides the triazine **38**, by treatment of **36** with HONO (Equation 16) in 65% yield <1996M1037> or in 83% yield <2005PS(180)591>.



36 → **38** (16)

Aryl-substituted amides **39**, when treated with triethyl orthoformate, give the corresponding N-arylated pyrimidine-fused rings **40** (**Scheme 4**) <2000PS(164)299> as well as one example of the triazine **41** <2000PS(164)299>.

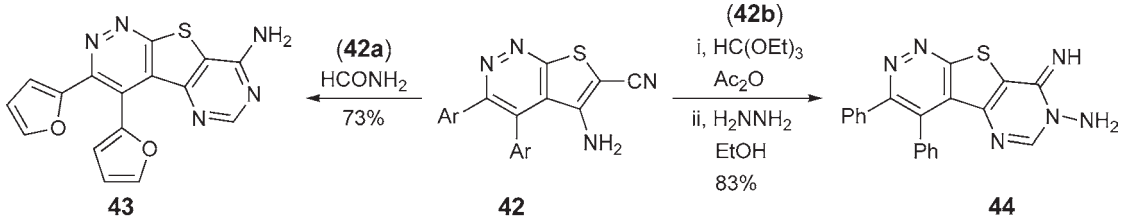


40 ← **39** → **41**

a: Ar = Ph
b: Ar = 4-$MeOC_6H_4$
c: Ar = 4-ClC_6H_4

Scheme 4

Having a cyano group and an amino group *ortho* to each other on a ring is another system that has led to the formation of fused pyrimidine ring systems. In this case, an aminopyrimidine is the result. Compound **42** in **Scheme 5** is one such structure. Treatment of **42a** with formamide leads to the amino derivative **43** <1999PS(155)175>. Alternatively **42b** provides **44** after treatment with triethyl orthoformate followed by hydrazine <1999PS(155)175>.

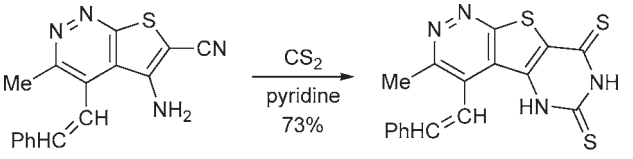


43 ← **42** → **44**

a: Ar = 2-furyl
b: Ar = Ph

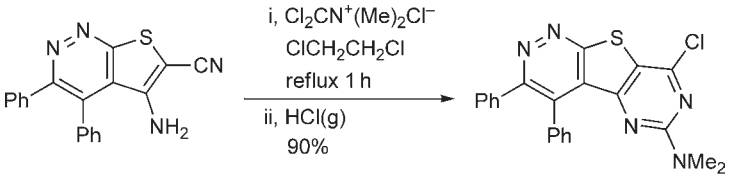
Scheme 5

While the usual method for preparing a fused pyrimidinedione involves cyclization of *ortho* amino and carboethoxy groups (see Equation 12), an unusual synthesis of a fused pyrimidinedithione **46** has been obtained by treating the *ortho* amino and cyano compound **45** with CS_2 (Equation 17) <2003BKC1181>.



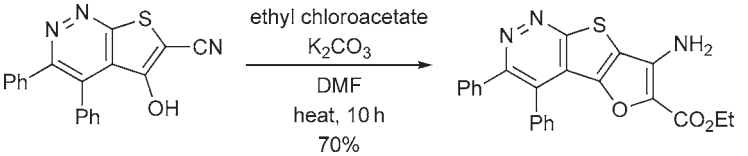
45 **46** (17)

The synthesis of **47** was accomplished through the initial reaction of **42b** with *N*, *N*-dimethyldichloromethyleneiminium chloride. The resulting intermediate was cyclized by heating after the introduction of HCl gas (Equation 18) <1996M739>.



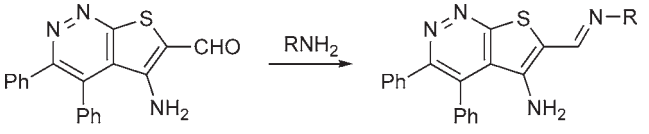
42b **47** (18)

Other rings have been fused onto thieno[2,3-*c*]pyridazines. The reaction of **48** with ethyl chloroacetate provides a fused furan derivative **49** (Equation 19) <1999M1117>.



48 **49** (19)

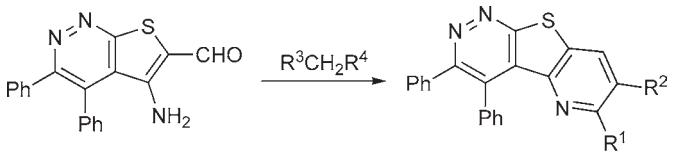
The aldehyde moiety of **50** can be condensed with either amines or active methylene compounds. In the case of reactions with amines, the aldehyde **50** (presumably obtained by reduction of the cyano group with diisobutylaluminium hydride (DIBAL-H)) forms simple Schiff bases **51** (Equation 20) <1998J(P1)3557>.



50 **51** (20)

a: R = Ph (93%)
b: R = 4-BrC_6H_4 (92%)
c: R = Bu (79%)

Friedländer condensation of **50** with a variety of active methylene compounds affords a variety of substituted fused pyridothieno[2,3-*c*]pyridazines **52** (Equation 21) <1996H(43)1073>. A solution of **50**, the appropriate active methylene compound, and a small amount of alcoholic KOH under reflux led to all of the products except **52f** and **52h**.



50 **52**

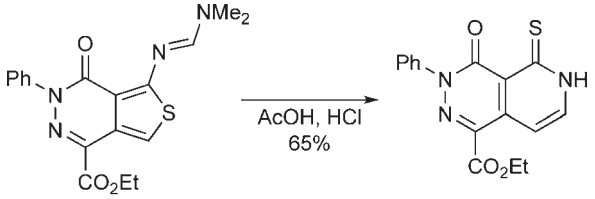
	R^3	R^4	R^1	R^2	*Yield* (%)
a	H	PhCO	Ph	H	50
b	H	4-ClC_6H_4CO	4-ClC_6H_4	H	40
c	H	2-PyridylCO	2-Pyridyl	H	55
d	H	MeCO	Me	H	62
e	Me	MeCO	Me	Me	60
f	MeCO	MeCO	Me	MeCO	34
g	MeCO	CO_2Et	Me	CO_2Et	67
h	CN	CN	NH_2	CN	90
i	CN	Ph	NH_2	Ph	57
j	CN	CO_2Et	NH_2	CO_2Et	36
k	CN	CO_2Et	OH	CN	47

(21)

Compounds **52f** and **52h** were prepared from **50** and 2,4-pentadienone and malononitrile, respectively, in tetrahydrofuran (THF) with a few drops of piperidine added.

The only other group of compounds that has exhibited unusual reactions is the thieno[3,4-*d*]pyridazines. The types of reaction involve either ring expansion (or addition) and introduction of a functional group onto the ring.

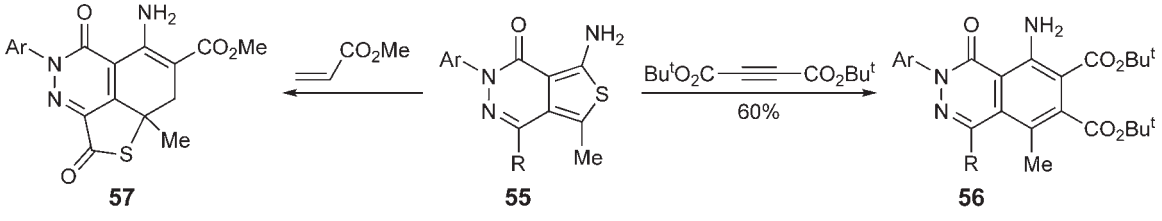
A simple case of ring expansion involves converting an amino group into a dimethylaminomethyleneamino moiety **53** by reaction with DMF–DMA (dimethylformamide–dimethylacetamide). Treatment of this compound with acid causes ring opening and recyclization to give **54** (Equation 22) <2005JCM23>.



53 **54**

(22)

Thieno[3,4-*d*]pyridazines such as **55a** readily undergo [4+2] cycloaddition reactions. Such a reaction with di-*t*-butyl acetylenedicarboxylate gives the phthalazine **56** (**Scheme 6**) with concomitant loss of sulfur <2000MI389>. Similar cycloaddition reactions involving maleic anhydride and *N*-phenylmaleimide have also been reported <1994PS(88)147, 2003JKC591>. Meanwhile compound **55b** reacts with methyl acrylate, under reflux, to yield **57** (no yield given) that results from addition, followed by methanol elimination <1998CJC1038>.

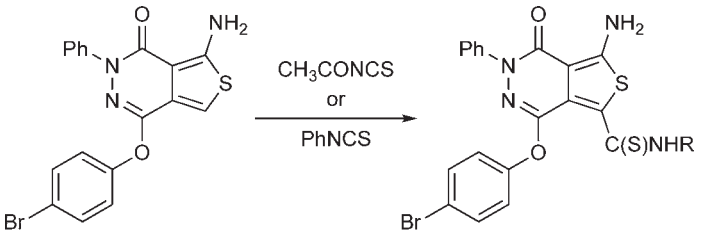


57 **55** **56**

a: Ar = 4-MeC_6H_4; R = CO_2Et
b: Ar = 4-MeC_6H_4; R = CO_2Me

Scheme 6

An acylation on the thiophene ring occurs when **58** is allowed to react with either acetyl isothiocyanate or phenyl isothiocyanate to form the corresponding thiocarbamoyl derivatives **59a** and **59b**, respectively (Equation 23) <1997IJB612>.



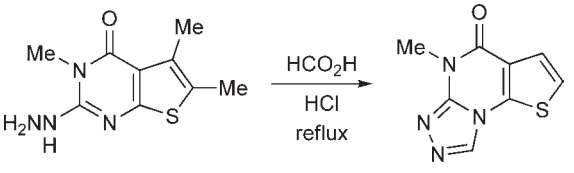
58 **59**

a: R = CH_3CO (65%)
b: R = Ph (60%)

(23)

10.07.5.8 Thienopyrimidines

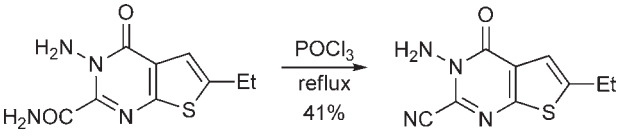
While cyclization to form a third ring onto compounds covered in this chapter is not novel, it is included here because there are numerous examples described in the literature. Illustrating this reaction is the cyclization of **60** in the presence of formic acid to give the tricyclic product **61** (no yield given) (Equation 24) <2000MOL835>.



60 **61**

(24)

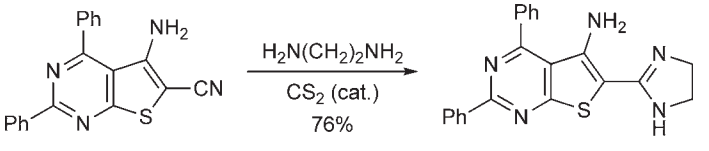
Although the conversion of an amide to a nitrile may be considered a standard reaction, the conversion of **62** to **63** by treatment with $POCl_3$ represents the synthesis of one of the very few examples of such a nitrile derivative (Equation 25) <2004IZV1257>.



62 **63**

(25)

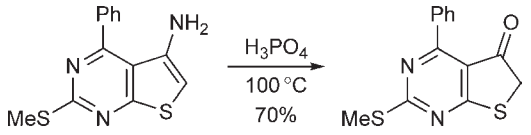
It is possible to introduce a heterocyclic ring as a substituent by addition to a cyano group. Adding ethylenediamine to **64** in the presence of a trace amount of CS_2 allows the formation of **65** in good yield (Equation 26) <1997PHA500>.



64 **65**

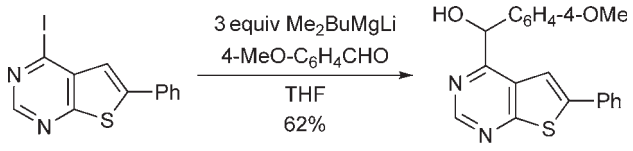
(26)

Destroying the aromatic character of the thiophene ring has been accomplished by heating the 5-aminothieno[2,3-*d*]-pyrimidine **66** with orthophosphoric acid (Equation 27); the 5-oxo product **67** is obtained <2005CHJ211>.



66 67 (27)

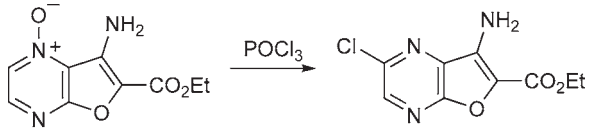
Organometallic reagents are better known for their involvement in the alkylations at ring nitrogen atoms in many heterocycles. However, under proper circumstances, they can promote addition to carbonyl groups. Such is the case when **68** is allowed to react with an excess of $Me_2BuMgLi$ at 0 °C. The secondary alcohol **69** is obtained in fair yield (Equation 28) <2004OL1991>.



68 69 (28)

10.07.5.9 Thienopyrazines

Although not novel chemistry, it is worth noting the formation of chloro derivatives from *N*-oxides. The *N*-oxide **70** is easily converted into the chloro thienopyrazine **71** with $POCl_3$ (no yield given) (Equation 29) <2000JME1586>.



70 71 (29)

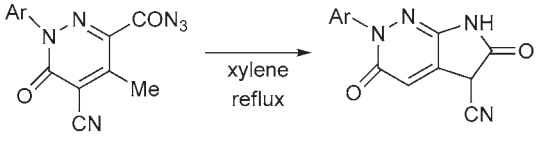
10.07.6 Ring Syntheses

10.07.6.1 Pyrrolopyridazines

10.07.6.1.1 Pyrrolo[2,3-*c*]pyridazines

Two specific processes have been described leading to the formation of this fused ring system, both starting with a substituted pyridazine.

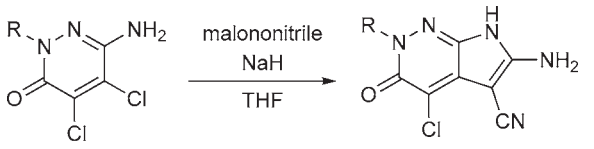
Commencing with the pyridazine **72**, the pyrrolo[2,3-*c*]pyridazine **73** is formed under thermal conditions (Equation 30) <1995PJC1642, 1995PHA788>.



72 73 (30)

a: Ar = Ph (65%)
b: Ar = 4-$MeOC_6H_4$ (70%)
c: Ar = 4-MeC_6H_4 (60%)
d: Ar = 4-ClC_6H_4 (80%)

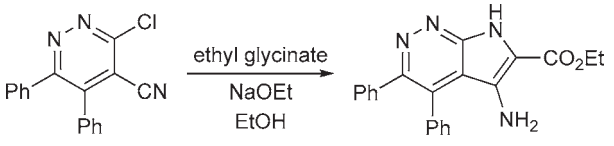
A related synthesis involves the conversion of **74** into **75** by treatment with malononitrile followed by cyclization (Equation 31) <2000JHC5, 2001JHC1179>.



74 **75** (31)

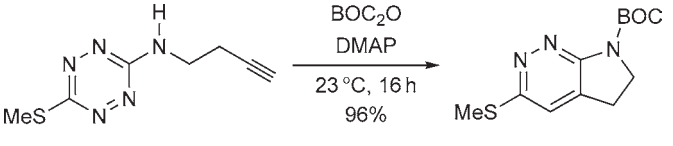
a: R = Me (91%)
b: R = Et (80%)
c: R = *n*-Pr (62%)
d: R =  (72%)

Yet another variation of this approach is the treatment of **76** with ethyl glycinate, followed by cyclization in ethoxide solution to afford **77** (no yield given) (Equation 32) <1999BAP135>.



76 **77** (32)

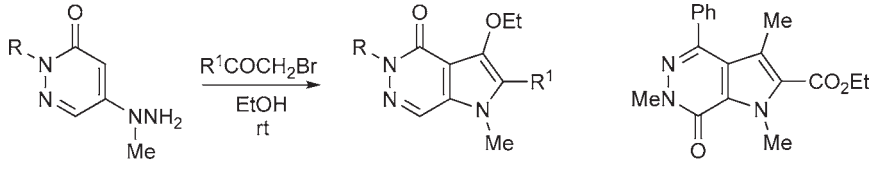
As reported previously in CHEC-II(1996) <1996CHEC-II(7)229>, intramolecular Diels–Alder cyclization is useful for the preparation of the partially reduced pyrrolopyridazine **79** (Equation 33) <1998JOC6329, 2000JOC9120>.



78 **79** (33)

10.07.6.1.2 Pyrrolo[2,3-*d*]pyridazines

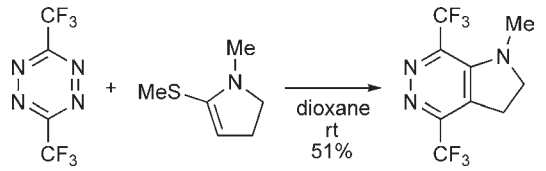
The synthesis of pyrrolo[2,3-*d*]pyridazines can be achieved by starting either with pyridazine, a tetrazine, or a pyrrole. Pyridazinone **80** reacts with bromomethyl derivatives to give poor yields of **81** <1996H(43)1863> (Equation 34), while 5-acetyl-2-methyl-4-nitro-6-phenyl-3(2*H*)-pyridazinone, after treatment with sarcosine ethyl ester for a brief time at room temperature, followed by acid hydrolysis afforded a good yield of **82** (70%) <1994S669>.



80 **81** **82** (34)

a: R = H; R^1 = CO_2Et (14%)
b: R = Me; R^1 = CO_2Et (23%)
c: R = Ph; R^1 = CO_2Et (19%)
d: R = H; R^1 = Ph (19%)
e: R = Me; R^1 = Ph (24%)
f: R = R^1 = Ph (29%)

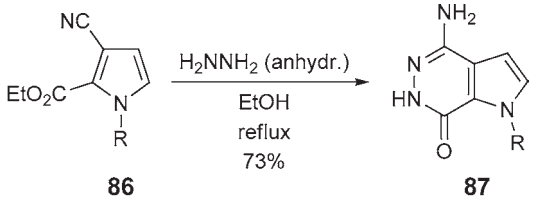
The inverse electron demand Diels–Alder reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **83** with dihydropyrrole **84** leads to the partially reduced structure **85** (**Scheme 7**) <1994H(38)1845>.



83 **84** **85**

Scheme 7

Commencing with the pyrrole nucleoside **86**, the corresponding pyrrolo[2,3-*d*]pyridazine nucleoside **87** was prepared upon treatment with hydrazine (Equation 35) <1997JME794>.



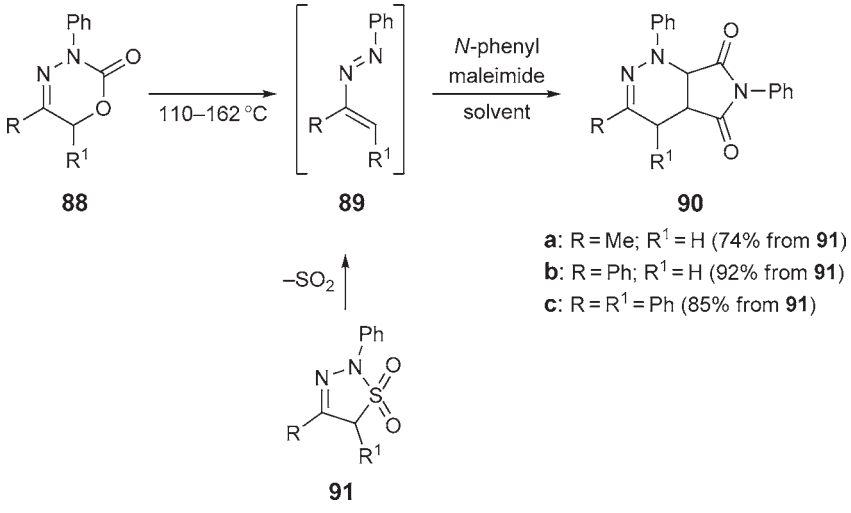
86 **87**

R = 2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl

(35)

10.07.6.1.3 Pyrrolo[3,4-*c*]pyridazines

Only two examples of the synthesis of pyrrolo[3,4-*c*]pyridazines that begin with a pyridazine have been reported. The first involves a Diels–Alder reaction. Thus pyridazine **88** under thermal conditions provides the heterodiene **89** intermediate with loss of CO_2, which is trapped *in situ* with *N*-phenyldiazamaleimide to form **90** in the yields shown (**Scheme 8**) <2001OL3647>. Alternatively, the thiadiazole 1,1-dioxide **91** can produce **89** by loss of SO_2.



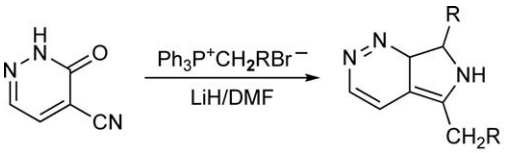
88 **89** **90**

a: R = Me; R^1 = H (74% from **91**)
b: R = Ph; R^1 = H (92% from **91**)
c: R = R^1 = Ph (85% from **91**)

91

Scheme 8

The second example involves the reaction of the anion of **92** with phosphonium bromides to give **93** in moderate yields (Equation 36) <2005HAC56>.

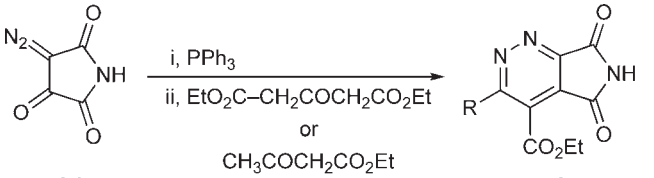


92 93

a: R = H (43%)
b: R = Me (47%)

(36)

In a one-pot, multistep reaction, the diazosuccinimide **94** and a keto ester affords pyrrolo[3,4-*c*]pyridazines **95** (Equation 37) <1995JHC1457>.

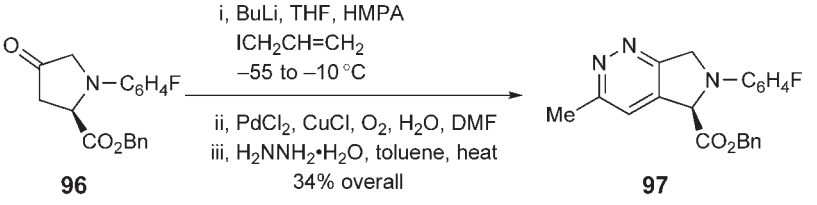


94 95

a: R = CH_2CO_2Et
b: R = Me

(37)

A single compound is reported to arise from the conversion of (2*S*)-4-oxo-*N*-(C_6H_4F)-proline benzyl ester **96** into **97** in three steps (Equation 38) <2004JOC4656>.



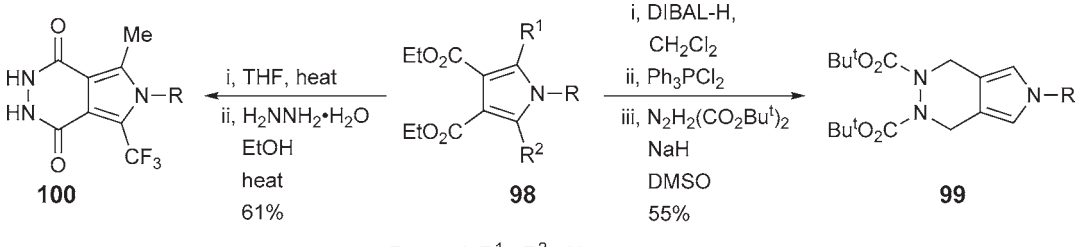
96 97

PhF = 9-(9-phenylfluorenyl)

(38)

10.07.6.1.4 Pyrrolo[3,4-*d*]pyridazines

The synthesis of this ring system has been largely limited to cyclization reactions involving a pyrrole as the starting material. Hence, structures such as **98a**, upon reduction of the esters, chlorination of the alcohols, and treatment with a hydrazine derivative, lead to N-protected pyrrolo[3,4-*d*]pyridazines **99** <1997JA1406>; without ester reduction, **98b** leads to **100** (**Scheme 9**) <2001S1837>. Similar reactions occur when diacetyl groups have replaced the diester groups in **98** <2004BML2031>.



100 98 99

a: R = tosyl; $R^1 = R^2 = H$
b: R = PhNHCONH; R^1 = Me; $R^2 = CF_3$

Scheme 9

10.07.6.1.5 Pyrrolo[3,2-*c*]pyridazines

No syntheses of this ring system have been reported. This continues the lack of interest shown in this class of compound exhibited in both CHEC(1984) and CHEC-II(1996).

10.07.6.2 Pyrrolopyrimidines

10.07.6.2.1 Pyrrolo[2,3-*d*]pyrimidines

10.07.6.2.1(i) Syntheses from pyrimidines

The investigations that describe the syntheses of pyrrolo[2,3-*d*]pyrimidines from pyrimidines, with very few exceptions, have nitrogen functionality at the 4/6-position of the pyrimidine ring. Primarily this nitrogen-containing group is an amine moiety. Even within these limits, the major type of pyrimidine precursor has no substituent at position 5.

In the simplest case, 2,4-diamino-6-oxopyrimidine, **101**, has been used to prepare a variety of derivatives that have substituents on either the 5- or 6-position of the fused ring system or even no substituent at all. Equation (39) illustrates the generality of this approach. Treatment of **101** with chloroacetaldehyde affords **102a** in good yield <2002JHC833>. Changing to chloroacetone in this reaction leads to the corresponding 6-methyl derivative **102b** <2005JHC165, 2005BML2225>. Other investigators report the formation of **102b** accompanied by the new [2,3-*d*]pyrimidine **103a** <1995JME4495, 1996JME4563>.



101 **102**

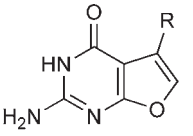
Entry	*R*	*R*^{1}	*Yield (%)*	*Conditions*
a	H	H	82	i
b	H	Me	70	ii
c	H	$(CH_2)_4C_6H_4$-4-CO_2Me	38	iii
d	H	CH_2CO_2Et	54	iv
e	H	CH_2Ph	59	v
f	$CH_2C_6H_4$-4-CO_2Bu^t	H	41	vi
g	CH_2thiophene-2-CO_2Bu^t	H	31	vii
h	CN	H	72	viii
i	CO_2Me	H	93	ix
j	$(CH_2)_2C_6H_4$-4-CO_2H	H	57	x
k	$(CH_2)_2OBn$	H	79	xi
l	$(CH_2)_2Ph$	Me	68	xii[a]
m	$(CH_2)C_6H_4$-4-CO_2Et	Me	65	xii[a]

(39)

[a]Compounds prepared from **105** using conditions xii below.

i, $ClCH_2CHO$, NaOAc, H_2O, 100 °C
ii,$ClCH_2COCH_3$, NaOAc, H_2O, 100 °C
iii, $ClCH_2CO(CH_2)_4C_6H_4$–4-CO_2Me, DMF, 40–45 °C, 3 d
iv, $ClCH_2COCH_2CO_2Et$, NaOAc, H_2O
v, $BrCH_2COCH_2Ph$, DMF, rt, 3 d
vi, $BrCH(CHO)CH_2C_6H_4CO_2Bu^t$, K_2CO_3, DMSO
vii, 5-$(BrCH(CHO)CH_2)$–thiophene-2-CO_2Bu^t, K_2CO_3, DMSO
viii, ClCH(CN)CHO, NaOMe, toluene
ix, $ClCH(CO_2Me)CHO$, NaOAc, H_2O, reflux
x, (a) $O_2NCH{=}CH(CH_2)_2C_6H_4CO_2Et$ (b) NaOH, rt (c) H_2SO_4, 0 °C (d) NaOH to pH 7; (e) HOAc
xi, (a) EtOAc/H_2O, 50 °C, $O_2NCH{=}CH(CH_2)_2OBn$ (b) $SnCl_2$/PhSH, Et_3N, MeCN (c) H_2O, Dowex-50, reflux
xii, 10 mol% $PdCl_2(CH_3CN)_2$, benzoquinone, LiCl, THF, reflux, 3 h

Another example of the simultaneous formation of both the pyrrolo and furo compounds has been observed. Nearly identical yields of **102c** and **103b** were isolated <2005JME5329>. Nonetheless, other 6-substituted derivatives of pyrrolo[2,3-*d*]pyrimidines have been prepared without complication, for example, **102d** <2001JHC349> and a variety of arylmethyl compounds, illustrated by **102e** <2003BMC5155>.



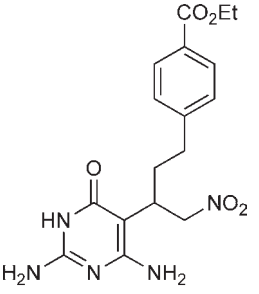
103

a: R = Me

b: R = $(CH_2)_4C_6H_4$-4-CO_2Me

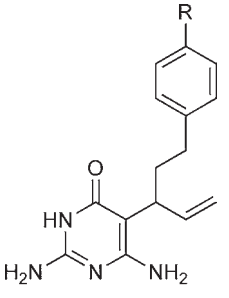
The introduction of substituents at position 5 of the pyrrolo[2,3-*d*]pyrimidine ring system has been spurred on by the quest for biologically active compounds, especially as inhibitors of folate-dependent enzymes. Thus, treatment of **101** with the appropriate bromoaldehyde provided **102f** and **102g** <2001CPB1280>. The 5-cyano derivative **102h** <1996SC3317, 2001JME1993> and the 5-carbomethoxy derivative **102i** <2001JME1993> have also been generated using chloroaldehydes. In the latter case, the corresponding 6-carbomethoxyfuro[2,3-*d*]pyrimidine was also obtained.

The introduction at position 5 of the pyrimidine ring of the desired substituent along with the necessary atoms to provide the framework for the pyrrole component of these compounds has been effected through appropriate nitroalkenes. Allowing **101** to react with such nitroalkenes leads to intermediate structures such as **104**. Nef reaction conditions provides **102j** <1999TL4023> and **102k** <2000TL8581>.



104

A structure similar to **104** has been constructed. This alkene **105** undergoes an intramolecular palladium-catalyzed amination reaction to provide the 5,6-disubstituted compounds **102l** and **102m** <1998SC3885>.

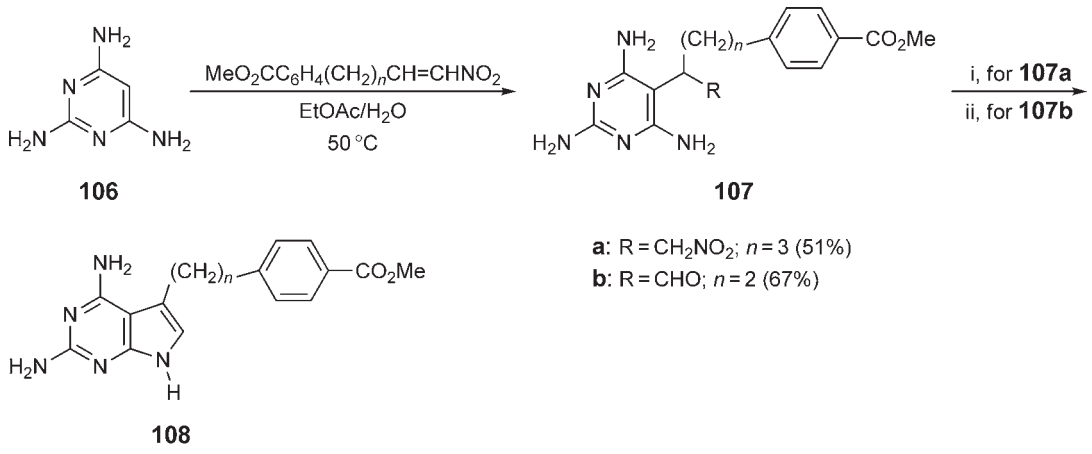


105

a: R = H

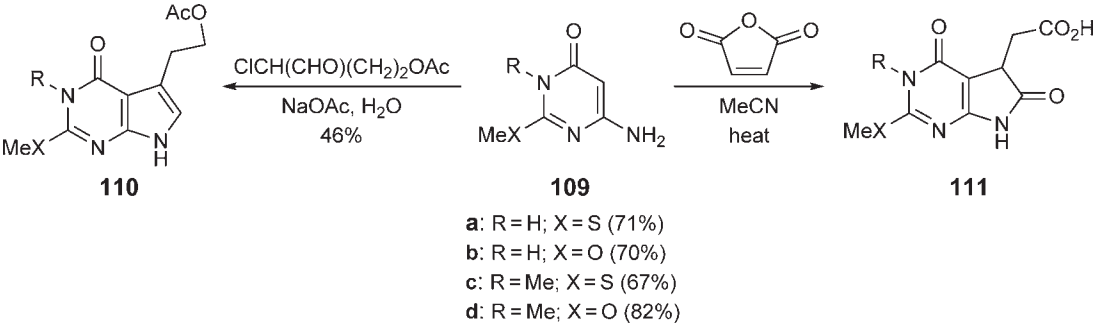
b: R = CO_2Et

Parallel chemistry has been employed with **106** to afford the diaminopyrrolopyrimidines **107**. Michael addition of a nitroalkene with **106** gives intermediate **107a** (**Scheme 10**), which undergoes a Nef reaction to produce **107b** and thence **108** <1999TL4027>. An alternative route is the reaction of **106** with an α-bromoaldehyde to form **108** <1999OPD184>.



Scheme 10

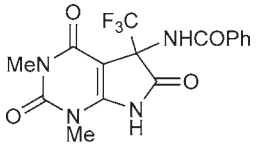
Other pyrimidines with variations at positions 2 and 4 have also been used to generate specific pyrrolo[2,3-*d*]-pyrimidines. The condensation of 6-amino-4-hydroxy-2-methylthiopyrimidine **109a** with 2-chloro-4-acetoxybutanal in aqueous NaOAc gives the fused ring product **110** (**Scheme 11**) <1998J(P1)3565>.



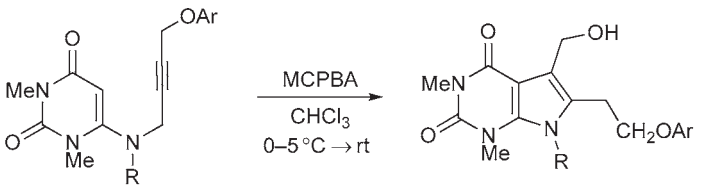
Scheme 11

However, treatment of **109a–d** with maleic anhydride leads to the appropriately substituted oxo derivatives **111a–d** <1998T5753>. 6-Aminouracil and the *N*-methyl or *N*,*N*′-dimethyl analogs proceed under identical conditions to form the corresponding *N*-methylated analogs of **111** <1998T5753>.

Heating 6-amino-1,3-dimethyluracil with PhC(O)N=C(CF_3)CO_2Et and Et_3N in DMF gives compound **112** in 98% yield <2001IZV1113>.



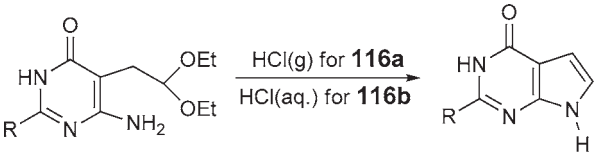
Finally, an unusual approach to pyrrolo[2,3-*d*]pyrimidines is seen in Equation (40). The dimethyluracil **113** is presumed to form the *N*-oxide at the exocyclic nitrogen atom. This then undergoes a [2,3]-sigmatropic rearrangement followed by a [3,3]-sigmatropic rearrangement, tautomerization, and cyclization to give **114** <2005S1164>.



113 **114** (40)

Compd.	*R*	*Ar*	*Yield (%)*	*Compd.*	*R*	*Ar*	*Yield (%)*
a	Me	3-MeC_6H_4	82	**e**	Me	4-Cl-3,5-$Me_2C_6H_2$	75
b	Me	2,4-$Cl_2C_6H_3$	76	**f**	Me	4-$Bu^tC_6H_4$	78
c	Me	2-Me-4-ClC_6H_3	78	**g**	Et	3-MeC_6H_4	80
d	Me	4-BrC_6H_4	80	**h**	Et	2,4-$Cl_2C_6H_3$	76

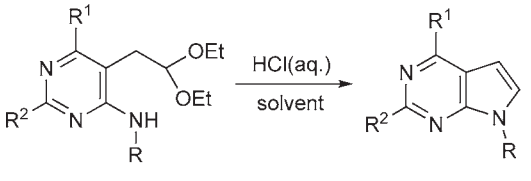
Pyrimidines with a functionalized alkyl group at position 5 have also been used as precursors to pyrrolo[2,3-*d*]-pyrimidines. In particular, the 2,2-diethoxyethyl group has been the subject of much activity. In an efficient process, **115a** was hydrolyzed in acidic media to form an aldehyde *in situ* which subsequently cyclized to **116a** in excellent yield (Equation 41) <2004BML5247, 1998EJO827>. Aqueous hydrolysis of **115b**, followed by cyclization of the intermediate aldehyde, affords **116b** <1995MI756>.



115 **116** (41)

a: R = SH (92%)
b: R = H (86%)

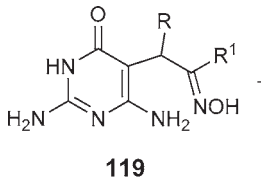
Other pyrimidines bearing the acetal moiety at position 5 have been employed in similar synthetic efforts. Much of this work involves carbohydrate rings attached to the amino group. Thus, **117a** readily undergoes acid hydrolysis and cyclization to the corresponding **118a** (Equation 42) <1996TL8147>. Additional examples include **117b** to **118b** <1997NN495>, **117c** to **118c** <2004NN1929>, and **117d** to **118d** <1997T3831>.



117 **118** (42)

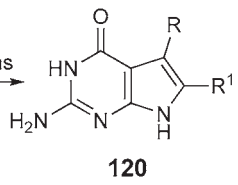
a: R = anhydrohexitol; R^1 = Cl; R^2 = NH_2 (76%)
b: R = 2-benzyloxymethyltetrahydrofuranyl; R^1 = Cl; R^2 = H (48%)
c: R = 2-cyclopentenylmethanol; R^1 = Cl; R^2 = H (60%)
d: R = 2-dimethoxymethyl-3-hydroxytetrahydrofuran-4-yl; R^1 = Cl; R^2 = H (81%)

Some related syntheses of pyrrolo[2,3-*d*]pyrimidines have utilized a variety of C-5 carbon moieties in order to provide the requisite atoms for cyclization. Equation (43) illustrates the use of oxime intermediates in this role. The oxime **119a**, formed by reduction of a nitro group, is cyclized to **120a** <2003OBC4166>. Oxime **119b** undergoes thermal cyclization to **120b**, while oxime **119c**, as one of several examples of this method, gives **120c** <1998J(P1)3025>. A report that focused on preparing similar compounds with a substituent on the pyrrolo nitrogen atom demonstrated, among others, the formation of the ring nitrogen derivative of **120c**, ethyl 2-amino-7-(2,3-dihydroxypropyl)-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidine-6-carboxylate <2004T943>.



119

conditions



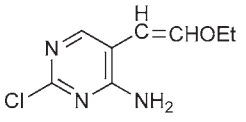
120

Entry	*R*	*R*^{1}	*Yield (%)*	*Conditions*
a	$(CH_2)_3OBn$	H	91	i
b	H	CF_3	43	ii
c	H	CO_2Et	60	ii

(43)

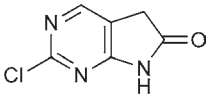
i, Dowex-50, H_2O, 60 °C
ii, HCl (conc.), H_2O, EtOH, PhCHO, reflux

The synthesis of 2-chloro-5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidine-6-one, **122**, was accomplished by heating the alkenyl pyrimidine, **121**, in acidic media (Equation 44) <2001TL999>.



121

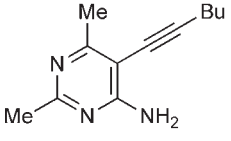
i, conc. HCl, MeOH, reflux (70%)
ii, C_5H_5NHBr, Br_2, Bu^tOH (90%)
iii, Zn, NH_4Cl, THF (80%)



122

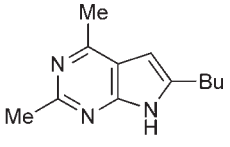
(44)

A number of examples were shown to undergo amine addition to an adjacent carbon–carbon triple bond to give indole-like products. One such example shows pyrimidine **123** being converted to **124** in strong base (Equation 45) <2000AGE2488>.



123

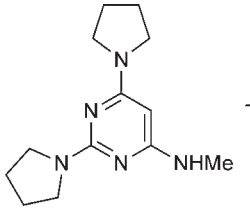
$KOBu^t$
NMP
rt
78%



124

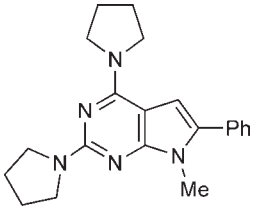
(45)

Treatment of the triaminopyrimidine **125** with phenacyl bromide, under mildly basic conditions, gives the tetrasubstituted product **126** (Equation 46), presumably via alkylation at position 5 <1995JME4161, 2001JLR797, 2000JHC1471>.



125

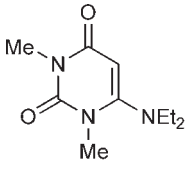
$PhCOCH_2Br$
$(Pr^i)_2NEt$
MeCN
85%



126

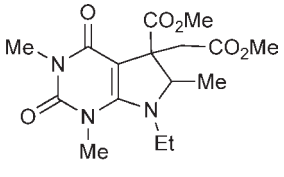
(46)

The tertiary amine **127** undergoes an interesting reaction with dimethyl acetylenedicarboxylate to produce the partially reduced pyrrolo[2,3-*d*]pyrimidine **128** (Equation 47) <1996TL1853, 1998JCM2025>.



127

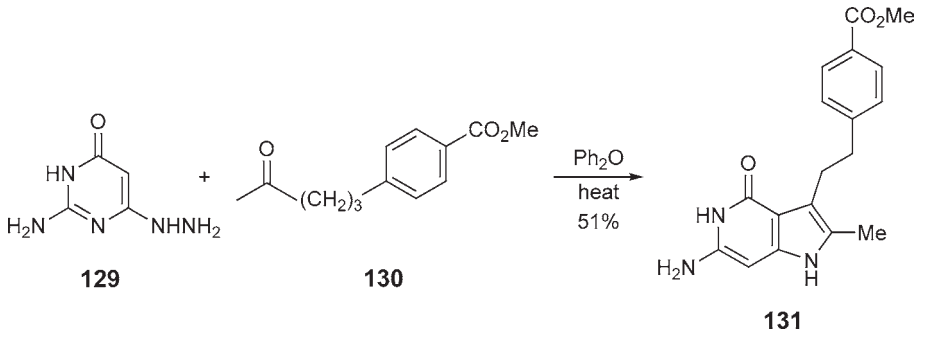
$MeO_2C{\equiv}CO_2Me$
EtOH
reflux
85%



128

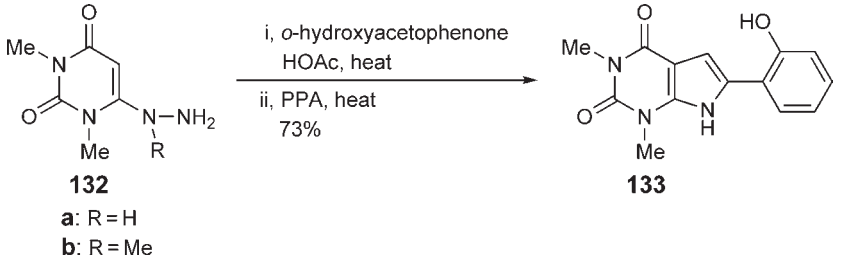
(47)

A hydrazine or substituted hydrazine in lieu of the amino group on the pyrimidine precursor is also an effective species. In what may be described as a Fischer indole-type reaction, 2-amino-6-hydrazino-4(3*H*)-oxopyrimidine **129** undergoes thermolytic cyclization when heated with compounds **130** (**Scheme 12**). The resultant product **131** is obtained in modest yield <1996H(43)323, B-2002MI439>.



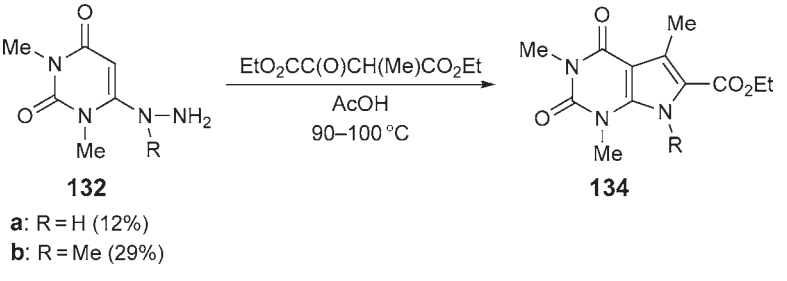
Scheme 12

Similarly, the hydrazine analog of dimethyluracil **132a** produces **133** when treated first with *o*-hydroxyacetophenone in hot acetic acid and the intermediate hydrazone heated in polyphosphoric acid (Equation 48) <1997AF958>.



(48)

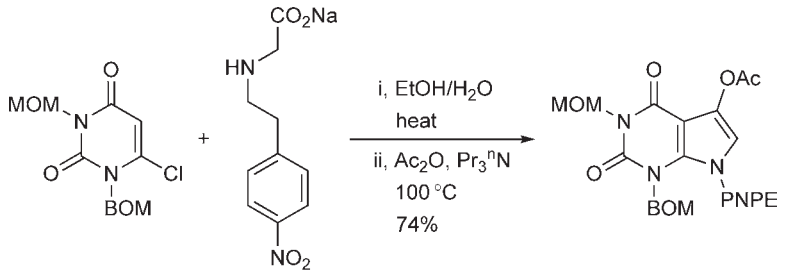
The *N*-methylhydrazine **132b**, however, does not fare so well. Reaction of **132b** with diethyl oxalpropionate in acetic acid heated to ~90 °C gives poor yields of cyclized products **134a** and **134b** (Equation 49) <1998H(47)315>.



(49)

6-Chlorouracil, in its protected form, can be formally viewed as a precursor in pyrrolo[2,3-*d*]pyrimidine preparations. Thus **135** is treated with **136**, which presumably gives a 6-amino intermediate by displacing the chloro group, and subsequently cyclizes to **137** (**Scheme 13**) <1995JOC5069>.

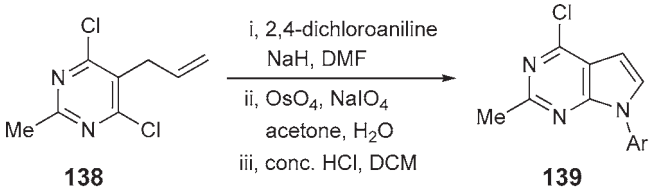
In similar fashion, the chloropyrimidine **138** is first aminated with 2,4-dichloroaniline and cyclized upon oxidation of the allyl group to give the pyrrolopyrimidine **139** (Equation 50) <2004H(62)191>.



135 **136** **137**

BOM = benzyloxymethyl
PNPE = *p*-nitrophenethyl

Scheme 13

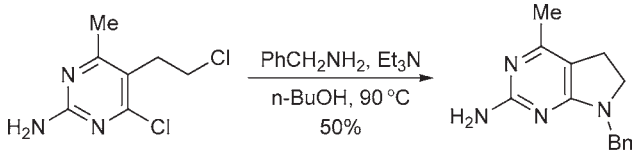


138 **139**

Ar = 2,4-$Cl_2C_6H_3$ (53%)

(50)

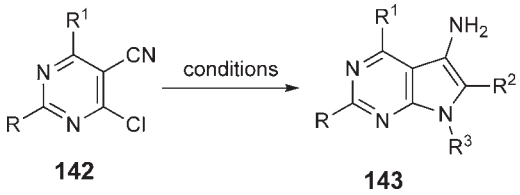
There are several examples of the synthesis of pyrrolo[2,3-*d*]pyrimidines in which the pyrrole ring is first obtained in a reduced form. The transformation of **140** (Equation 51) illustrates the general approach for this type of compound. Treatment of **140** with benzylamine leads to replacement of the 6-chloro group accompanied by cyclization to **141** <2000JME3837>. Comparable approaches bearing different functionalized substituents at position 5 of the pyrimidine ring produce analogous reduced pyrrolo[2,3-*d*]pyrimidines <2005BML1829, 2005BML3713>.



140 **141**

(51)

As with the synthesis of pyrimidine rings containing an amino substituent, the cyano group is likewise employed when an amino group at position 5 of the pyrrolo[2,3-*d*]pyrimidine is desired. One laboratory has studied this method extensively. Compound **142a** is allowed to react with sarcosine methyl ester to form an intermediate 6-substituted aminopyrimidine. This is immediately cyclized to the bicyclic product **143a** (Equation 52) <1999CHE1381>. Other amino acids have been incorporated in similar ways. Thus **142b** leads to **143b** <2000CHE841>, and **142c** gives **143c** <2003PJC1275, 2003S1377>.



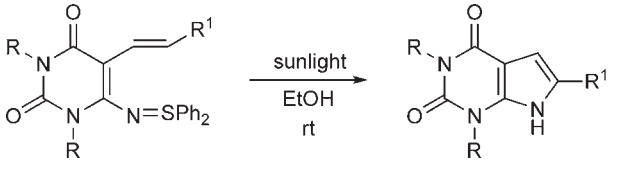
142 **143**

Entry	*R*	R^1	R^2	R^3	*Yield (%)*	*Condtions*
a	MeS	NHBu	CO_2Me	Me	55	i
b	MeS	NHMe	CO_2Me	H	60	ii
c	MeS	Cl	CO_2Me	Me	48	i

i, sarcosine methyl ester hydrochloride, Na_2CO_3 (or Et_3N), MeOH, reflux
ii, glycine methyl ester, MeOH, reflux

(52)

Additional examples of syntheses illustrate some of the more unusual tactics taken to produce pyrrolo[2,3-*d*]-pyrimidines. Recently a group of sulfilimines, **144**, have been converted to products **145** under the influence of sunlight (Equation 53) <2005TL5551>.

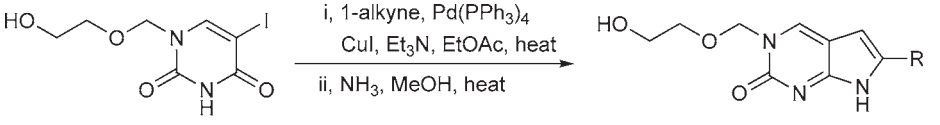


144 **145**

(53)

a: R = Me; R^1 = COF_3 (88%)
b: R = Pr^i; R^1 = COF_3 (96%)
c: R = Me; R^1 = Ph (91%)
d: R = Me; R^1 = 4-MeC_6H_4 (89%)
e: R = Me; R^1 = 4-ClC_6H_4 (84%)

The attachment of a carbohydrate ring or acyclic form of a carbohydrate onto one of the pyrimidine nitrogen atoms leads to unusual 'nucleoside-like' structures. One such example is illustrated in Equation (54). The iodinated acyclic pyrimidine **146** undergoes initial carbon–carbon bond formation with an alkyne, replacing the iodine. Further reaction with ammonia results in ring cyclization to give **147** <2005JME4690>. Other examples of carbohydrate moieties occupying the same ring position have been reported <1995NN291, 1999HCA2028> besides acyl groups <2003NN1029>.



146 **147**

(54)

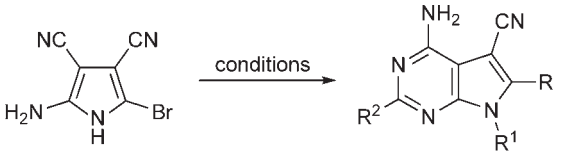
a: R = H (60%)
b: R = Bu (53%)
c: R = C_5H_{11} (30%)
d: R = C_6H_{13} (35%)
e: R = C_7H_{15} (74%)
f: R = C_8H_{17} (36%)
g: R = C_9H_{19} (72%)
h: R = $C_{10}H_{21}$ (84%)
i: R = $C_{11}H_{23}$ (53%)

10.07.6.2.1(ii) Syntheses from pyrroles

As with other series involving the annulation of a pyrimidine ring onto a five-membered ring, the usual requirement is to have two adjacent functional groups, one of which is an amine. The use of a cyano group as the other functional group occupies the majority of examples in such syntheses. Therefore, it is not surprising that this situation holds in the syntheses of pyrrolo[2,3-*d*]pyrimidines from pyrroles.

One of the driving forces for syntheses of this class of compound is the search for analogs of toyocamycin and related antiviral compounds. The aglycone of toyocamycin **148a** has been the starting point for such investigations (Equation 55). Therefore derivatives in which additional substituents have been incorporated, either to be retained or later removed, have been developed. One of the most popular pyrroles has been **149** which is readily prepared from tetracyanoethylene. Debromination of **149** followed by treatment with chlorformamidine gives **148a** in good yield <1995JME2158>. Subsequently **148b** was prepared under less harsh conditions from **149** <1998SC3835, 1999NN153>. A series of 7-substituted analogs of **148b** have been prepared in a similar fashion from **149**. One of these derivatives, **148c**, illustrates the method <1996JME873>. If, however, triethyl orthoacetate is used instead of triethyl orthoformate, the 2-methyl derivative **148d** can be produced <2003NN2171>. Two reports have appeared in which the imidate of **149** is the starting material and a carbohydrate ring is attached to the pyrrole nitrogen. Ring

cyclization proceeds in the usual way to give the 2′-deoxy-2′-fluoro-β-D-arabinofuranosyl derivative of **148b** (90% yield) <1995CC115, 1995JME4106>. A third report begins with an imidate and, in the first step, introduces an aromatic amine that subsequently appears at position 4 of the bicyclic product <2005JME6430>.

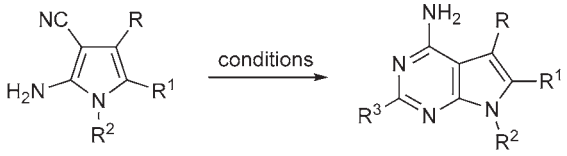


149 **148**

a: R = R^1 = R^2 = H (79%); conditions i
b: R = Br; R^1 = R^2 = H (72%); conditions ii
c: R = Br; R^1 = Bn; R^2 = H (43%); conditions iii
d: R = Br; R^1 = H; R^2 = Me (78%); conditions iv (55)

i, chlorformamidine/Dowtherm-A, heat
ii, (a) $(EtO)_3CH$, MeCN, reflux (b) NH_3, EtOH, 105 °C
iii, (a) $(EtO)_3CH$, MeCN, reflux; NaH, BnX, MeCN (b) NH_3, MeOH
iv, (a) $(EtO)_3CCH_3$, MeCN (b) NH_3, EtOH

Pyrroles bearing the same amino/cyano group combination but having a variety of other substituents around the ring also play a role in the syntheses of 4-amino-pyrrolo[2,3-*d*]pyrimidines. A series of diaryl compounds **151a–f** were made simply from **150a–f** (Equation 56) <1999JHC729>. An extensive study of similar derivatives as adenosine receptor antagonists has been conducted. One example, **151g**, illustrates the range of compounds described <2000JME4636>. Another series has been prepared, of which the formation of **151h** is one example <2001BML849>.



150 **151**

Entry	*R*	R^1	R^2	R^3	*Yield (%)*	*Conditions*
a	Ph	H	4-F-C_6H_4	H	48	i
b	Ph	H	2-Cl-4-FC_6H_3	H	65	i
c	4-MeOC_6H_4	H	4-FC_6H_3	H	55	i
d	4-MeOC_6H_4	H	2-Cl-4-FC_6H_3	H	72	i
e	4-ClC_6H_4	H	4-FC_6H_4	H	77	i
f	4-ClC_6H_4	H	2-Cl-4-FC_6H_3	H	66	i
g	Me	Me	PhCH(Me)	2-Pyridyl	21	ii
h	Ph	H	PhCH(CH_2OH)	H		iii
i	H	H	Bn	H	56	iv
j	PhOC_6H_4	H	*c*-Pentyl	H	31	v
k	CN	Ph	H	H	74	vi
l	CN	4-MeOC_6H_4	H	H	38	vi
m	CN	4-BrC_6H_4	H	H	72	vi

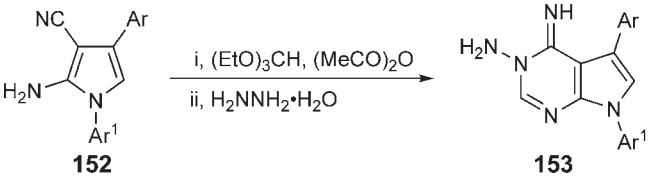
(56)

i, $HCONH_2$, DMF, HCO_2H
ii, 2-pyridylcarbonitrile, NaOMe, 2-PrOH
iii, (a) $(EtO)_3CH$, 80 °C; NH_3, MeOH, rt (b) NaOEt, EtOH, 80 °C; HCl, MeOH
iv, (a) diethoxymethyl acetate, Bu_4NHSO_4, MeCN, reflux (b) NH_3, MeOH, 60 °C
v, $HCONH_2$, NH_3(g), 200 °C
vi, $HCONH_2$, reflux

The synthesis of 7-substituted 5,6-unsubstituted pyrrolo[2,3-*d*]pyrimidines can be accomplished under similar conditions. For example, **151i** is produced in modest yield from **150i** <2004OL2857>. Carbocyclic rings have also been introduced. **151j** is generated in poor yield in this way <2000BML2167>.

An interesting synthesis of this type of compound uses the Schiff base of the amino group attached to the pyrrole as an intermediate. Loss of the aromatic aldehyde from the Schiff base leads to respectable yields of the 4-amino-6-aryl-5-cyanopyrrolo[2,3-*d*]pyrimidines **151k–l** <1997CHE1450>.

In many of the previous examples, ammonia was used in the final cyclization step. However, hydrazine has also been used, leading to a different type of product. Reaction of **152** with triethyl orthoformate gives the intermediate imidate, which, when treated with hydrazine, produces the corresponding 4-iminopyrrolo[2,3-*d*]pyrimidines **153** (Equation 57) <1997JCM452, 2000JHC757, 2002MOL554>.



152 **153**

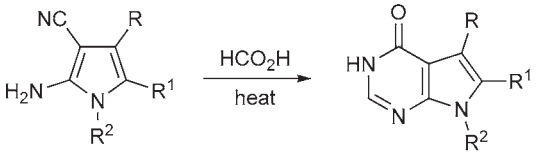
a: Ar = 4-ClC$_6$H$_4$; Ar^1 = 4-MeC$_6$H$_4$
b: Ar = Ph; Ar^1 = 4-ClC$_6$H$_4$ (89%)
c: Ar = 4-MeOC$_6$H$_4$; Ar^1 = Ph (88%)
d: Ar = Ar^1 = 4-MeOC$_6$H$_4$ (84%)
e: Ar = 4-ClC$_6$H$_4$; Ar^1 = Ph (86%)
f: Ar = Ar^1 = 4-ClC$_6$H$_4$ (70%)
g: Ar = Ph; Ar^1 = 4-MeOC$_6$H$_4$ (87%)
h: Ar = Ph; Ar^1 = 4-BrC$_6$H$_4$ (72%)
i: Ar = Ph; Ar^1 = 4-IC$_6$H$_4$ (60%)
j: Ar = 4-MeOC$_6$H$_4$; Ar^1 = 4-BrC$_6$H$_4$ (71%)
k: Ar = 4-MeOC$_6$H$_4$; Ar^1 = 4-IC$_6$H$_4$ (80%)
l: Ar = 4-ClC$_6$H$_4$; Ar^1 = 4-BrC$_6$H$_4$ (86%)
m: Ar = 4-ClC$_6$H$_4$; Ar^1 = 4-IC$_6$H$_4$ (88%)

(57)

By simply using formic acid as the cyclization reagent, pyrrolo[2,3-*d*]pyrimidin-4-ones (7-deazahypoxanthines) can be obtained. A few examples of this reaction are shown in Equation (58). An appropriately substituted pyrrole **154** is cyclized in formic acid, usually heated, to the corresponding product **155**. In this way, **155a** and **155b** <1995JCM314>, **155c–g** <1996JME2285, 2001OPD581, 2004C640>, **155h** <1996JME2482>, **155i–k** <2002AFF147>, and **155l–t** <1998JHC1295> have been prepared. Cyclization of **154u** in 85% phosphoric acid provided **155u** in good yield <1997JME1749>.

Reduced forms of the pyrrole bearing the amino/cyano combination have, in a limited way, been incorporated into pyrrolo[2,3-*d*]pyrimidines. Heating **156a–c** with formamide gives **157a–c** (**Scheme 14**), as expected <2002FA613>. However, when **156d–g** was heated with triethyl orthoformate or orthoacetate, followed by stirring with hydrazine, the 3-amino derivatives **158d–g** were isolated <2004EJC565>.

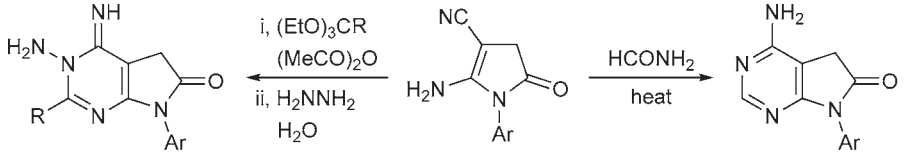
While still on the subject of rings with adjacent amino and cyano groups, there is a special case in which the original ring is a furan rather than a pyrrole. In all of the examples reported, the furan **159** is treated with guanidine or the appropriate amidine to produce the corresponding 4-aminopyrrolo[2,3-*d*]pyrimidine **160** (Equation 59). Although this chemistry is not novel, it has seen a resurgence in the past decade. A few descriptive examples are given. Compounds **159a–d**, when reacted with guanidine, benzamidine, or acetamidine, provide the expected structures **160a–d** <1995JOC6684>. As part of a total synthesis of a DHFR inhibitor, TNP-351, **160e** was prepared from **159e** <1996JOC7973, 2003JOC9938>. Similar structures, such as **160f** and **160g** <2001JHC1197>, **160h** <2003BMC59>, and **160i–k** <2005JHC1127>, are representative examples of compounds that have also been prepared.



154 **155**

Entry	*R*	R^1	R^2	*Yield (%)*
a	4-ClC_6H_4	H	4-MeC_6H_4	
b	4-FC_6H_4	H	4-MeC_6H_4	
c	Me	Me	Bn	60
d	–$(CH_2)_4$–		Bn	
e	Ph	Ph	Bn	
f	Ph	Me	Bn	
g	Me	Ph	Bn	
h	Me	Me	PhCH(Me)	79
i	H	Ph	Ph	48
j	H	Ph	4-ClC_6H_4	51
k	H	Ph	4-MeC_6H_4	65
l	Ph	H	4-$MeOC_6H_4$	79
m	Ph	H	4-BrC_6H_4	59
n	Ph	H	4-IC_6H_4	50
o	4-$MeOC_6H_4$	H	4-BrC_6H_4	80
p	4-$MeOC_6H_4$	H	4-IC_6H_4	76
q	4-ClC_6H_4	H	4-MeC_6H_4	80
r	4-ClC_6H_4	H	4-$MeOC_6H_4$	79
s	4-ClC_6H_4	H	4-BrC_6H_4	76
t	4-ClC_6H_4	H	4-IC_6H_4	81
u	Me	H	2,4,6-$Me_3C_6H_2$	81

(58)



158 **156** **157**

d: Ar = 4-FC_6H_4; R = H (55%)
e: Ar = 2-MeO-4-$NO_2C_6H_4$; R = H (60%)
f: Ar = 4-FC_6H_4; R = Me (51%)
g: Ar = 2-MeO-4-$NO_2C_6H_3$; R = Me (74%)

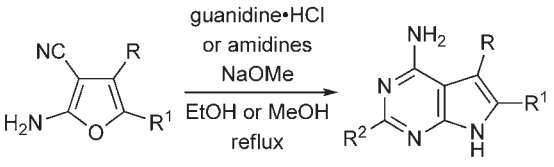
a: Ar = $PhSO_2NH_2$ (75%)
b: Ar = $PhSO_2NH$-2-pyrimidyl (72%)
c: Ar = $PhSO_2NH$-(4-Me-2- pyrimidyl) (76%)

Scheme 14

Another furan precursor **161** has been used to generate a series of pyrrolo[2,3-*d*]pyrimidine triones **162** (Equation 60); the furandiones react with aryl isocyanates, releasing 2 mol of carbon dioxide, to form compounds **162a–f** <2004ASJ877>.

When an amino group is adjacent to a carboxamide group, annulation usually leads to a pyrrolo[2,3-*d*]pyrimidin-4-one **164**. Such is the case when **163** is allowed to react with aliphatic carboxylic esters (Equation 61) <1996H(42)691>.

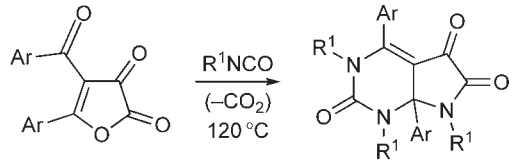
The same may be said of an amine function adjacent to a ketone, although with a 4-substituted pyrrolo[2,3-*d*]-pyrimidine **166** as the end product. Equation (62) illustrates this type of reaction, where **165** is heated with ammonium acetate <1996IZV1720>.



159 160

Entry	R	R^1	R^2	Yield (%)
a	Me	H	NH_2	67
b	Ph	H	NH_2	42
c	Me	H	Ph	30
d	Me	H	Me	46
e	4-$MeO_2CC_6H_4(CH_2)_3$	H	NH_2	42
f	4-ClC_6H_4	H	NH_2	51
g	Bn	H	NH_2	37
h	3,4,5-$(MeO)_3C_6H_2(CH_2)_2$	H	NH_2	44
i	2,5-$Cl_2C_6H_3(CH_2)_3$	H	NH_2	68
j	2,5-$(MeO)_2C_6H_3(CH_2)_3$	H	NH_2	53
k	$Ph(CH_2)_3$	H	NH_2	47

(59)

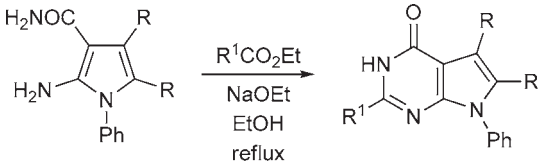


161
Ar = 4-$MeOC_6H_4$

162

a: R^1 = Ph (70%)
b: R^1 = 4-MeC_6H_4 (65%)
c: R^1 = 4-ClC_6H_4 (75%)
d: R^1 = naphthyl (80%)
e: R^1 = 4-$MeOC_6H_4$ (65%)
f: R^1 = 3,5-$Me_2C_6H_3$ (60%)

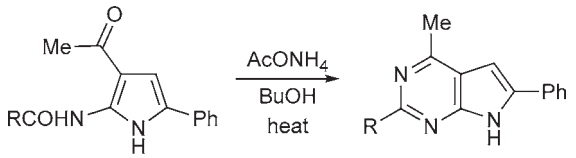
(60)



163 164

a: R = Me; R^1 = H (90%)
b: R = R^1 = Me (92%)
c: R = Me; R^1 = Et (84%)
d: R = Ph; R^1 = H (92%)

(61)

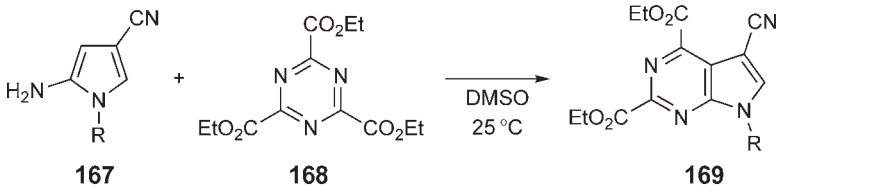


165 166

a: R = Ph (98%)
b: R = Me (56%)

(62)

There are examples where only an amino group is present on the pyrrole ring in order to form an annulated pyrimidine ring. The formation of a pyrrolo[2,3-*d*]pyrimidine is accomplished via an inverse electron demand Diels–Alder reaction involving a 1,3,5-triazine. A series of *N*-alkylpyrroles **167** were treated with 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine, **168**, at room temperature to afford the corresponding bicyclic products **169** (**Scheme 15**) <2002JOC8703, 2005JOC998>.

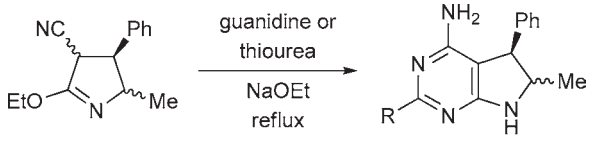


167 **168** **169**

a: R = Bn (96%)
b: R = neopentyl (95%)
c: R = Ph (92%)
d: R = cyclopentyl (92%)
e: R = 1-(2-methylthio)ethyl (93%)

Scheme 15

The presence of an alkoxy group on the pyrrole in place of the amino group also works if the alkoxy group can be displaced by a suitable nitrogen-containing species. Heating **170** with either guanidine or thiourea produced *cis*/*trans*-mixtures of **171** (no yields given) (Equation 63) <1998MI187>. Similar chemistry is reported to occur with ethyl 2-ethoxy-(3,4,5-trimethoxyphenyl)-1-pyrroline-3-carboxylate <1996BMC593>.

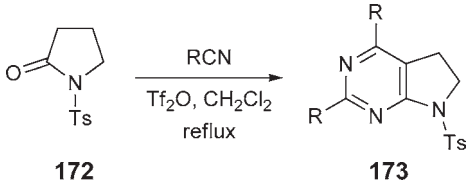


170 **171**

a: R = NH_2
b: R = SH

(63)

There remains a collection of syntheses from relatively uncommon precursors. One that has seen a modest amount of exploration involves the use of pyrrolidones as precursors. Thus the *N*-tosyl-2-pyrrolidone **172** reacts with nitriles to give partially reduced pyrrolo[2,3-*d*]pyrimidines **173** (Equation 64) <1996T7973>.

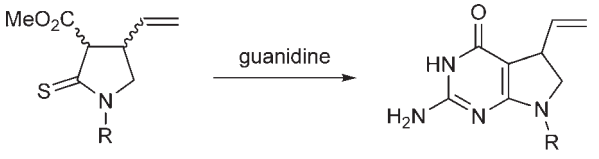


172 **173**

a: R = Me (34%)
b: R = SMe (35%)

(64)

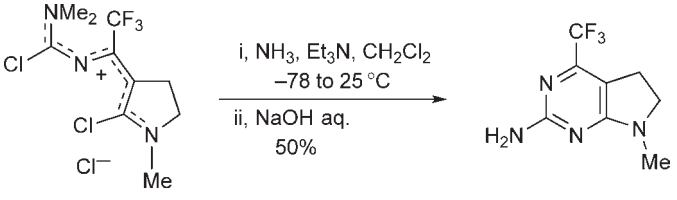
Pyrrolidinones that are thiated to give compounds such as **174** have also been converted to deazaguanine intermediates by condensation with guanidine. The vinyl derivatives **175** are thus obtained (Equation 65) <1999TL5291, 2001JOC3726>.



174 **175** (65)

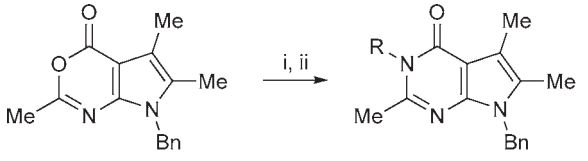
a: R = CH(Me)Ph
b: R = Bn
c: R = 4-MeOC$_6$H$_4$CH$_2$
d: R = 3,4-(MeO)$_2$C$_6$H$_3$CH$_2$

In addition to pyrrolidinones and pyrrolidinethiones, chloropyrrolidines have found use in preparing reduced pyrrolo[2,3-*d*]pyrimidines. The conjugated structure **176** undergoes cyclization to **177** in modest yield (Equation 66) <1996BSF501>.



176 **177** (66)

Two further unusual examples involve a different bicyclic system and an acyclic system as precursors. In the first instance, use is made of the reactivity of a pyrrolo[2,3-*d*]-1,3-oxazin-4-one **178** (Equation 67). Treatment of this compound with hydrazine hydrate afforded the 3-amino derivative **179a** while reaction with 4-methoxyaniline produced **179b** <2000IJB764>.

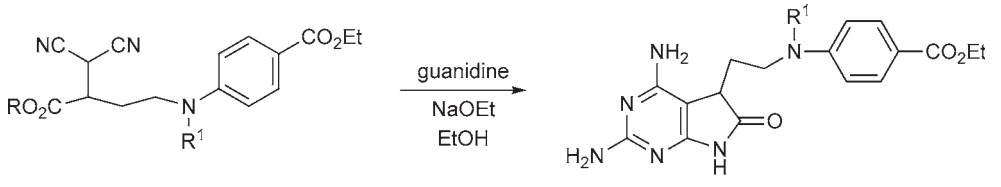


178 **179** (67)

a: R = NH$_2$ (55%)
b: R = 4-MeOC$_6$H$_4$ (75%)

i, H_2NNH_2, AcOH, NaOAc, reflux
ii, *p*-anisidine, AcOH, NaOAc, reflux

Perhaps the most unique synthesis of a pyrrolo[2,3-*d*]pyrimidine arises from a completely acyclic precursor. Thus, **180**, upon reaction with guanidine in basic media, produces both rings, although undoubtedly one ring is formed first *in situ* (Equation 68). Good yields of **181** were obtained <1995CPB256>.



180 **181** (68)

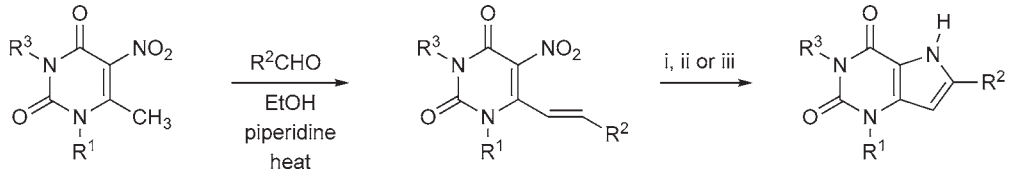
a: R = R^1 = Me (74%)
b: R = Et; R^1 = BOC (85%)

10.07.6.2.2 Pyrrolo[3,2-*d*]pyrimidines (9-deazapurines)

Deaza analogs of purines continue to be a major topic of interest to heterocyclic chemists, and especially those with a research focus on biological activity. The synthetic approaches divide, nearly equally, between using pyrimidines or pyrroles as precursors.

10.07.6.2.2(i) Syntheses from pyrimidines

The obvious value of 5-nitro-6-methylpyrimidines as precursors in the syntheses of pyrrolo[3,2-*d*]pyrimidines continues since last reported in CHEC-II(1996) <1996CHEC-II(7)229>. Perhaps the most prolific molecule is the *N*,*N*′-dialkyluracil structure **182** (**Scheme 16**). The effect the nitro group has on acidifying a hydrogen atom on the methyl group allows a variety of chemical reactions to occur. In order to form a pyrrolopyrimidine with a substituent, most often aryl, at position 8, compound **182** is readily condensed with an aromatic aldehyde to form the vinyl intermediate **183** <1994JME1526, 2003TL2121, 2004EJM879>. Hence reduction of the nitro group is followed immediately by cyclization to the appropriate 9-deazaxanthine analog **184**. Compounds **184e–q** are reported to form in excellent yields (95–99%), though not specifically attributed to individual compounds <2003TL2121>. Additional examples, formed in the same manner, have also been reported <2004EJM879>.



182 **183** **184**

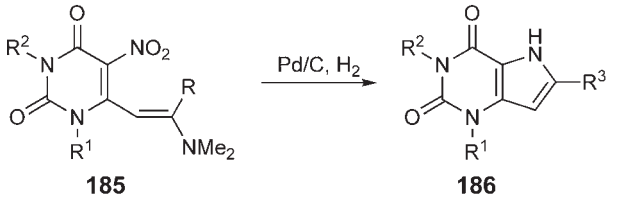
	R^1	R^2	R^3	*Yield (%)*	*Conditions*		R^1	R^2	R^3	*Yield (%)*	*Conditions*
a:	H	Ph	Me	6	i	**j**:	Pr^n	4-$MeOC_6H_4$	Pr^n		iii
b:	H	Ph	Pr^n	21	i	**k**:	Pr^n	4-$AcNHC_6H_4$	Pr^n		iii
c:	Me	Ph	Me	16	ii	**l**:	Pr^n	2-BrC_6H_4	Pr^n		iii
d:	Pr^n	Ph	Pr^n	11	ii	**m**:	Pr^n	2-FC_6H_4	Pr^n		iii
e:	Pr^n	4-MeC_6H_4	Pr^n		iii	**n**:	Pr^n	4-$Pr^iC_6H_4$	Pr^n		iii
f:	Me	4-MeC_6H_4	Me		iii	**o**:	Pr^n	2-thienyl	Pr^n		iii
g:	Pr^n	Ph	Pr^n		iii	**p**:	Pr^n	2-furyl	Pr^n		iii
h:	Pr^n	2-MeC_6H_4	Pr^n		iii	**q**:	Pr^n	4-AcC_6H_4	Pr^n		iii
i:	Pr^n	4-$Me_2NC_6H_4$	Pr^n		iii						

i, $P(OEt)_3$, heat
ii, sodium dithionite, HCO_2H, heat
iii,$SnCl_2$, DMF, heat

Scheme 16

Treatment of the appropriate 5-nitrouracils with DMF diethyl acetal in DMF afforded the corresponding 6-[(dimethylamino)vinyl]uracils **185** (Equation 69). Ring closure to unsubstituted products **186a–d** was effected by reduction with Pd/C in an H_2 atmosphere <1994JME1526>. Poor yields were observed in each case and **186e** was also isolated along with **186d** <1994JME1526>.

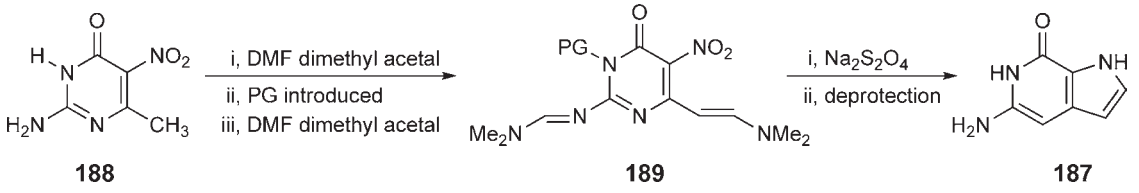
Compounds **185f** and **185g** were cyclized using Zn in acetic acid <1994CHE1077>. Additional examples involving identical chemistry have been described <2000CHE307>. In this report, a variety of amino groups have been employed in place of the NMe_2 in compound **185**.



Entry	R	R^1	R^2	R^3	Yield (%)
a	H	Me	H	H	21
b	H	Pr^n	H	H	14
c	H	Me	Me	H	36
d	H	Pr^n	Pr^n	H	16
e	H	Pr^n	Pr^n	NMe_2	22
f	H	Me	Me	H	65
g	Me	Me	Me	Me	27

(69)

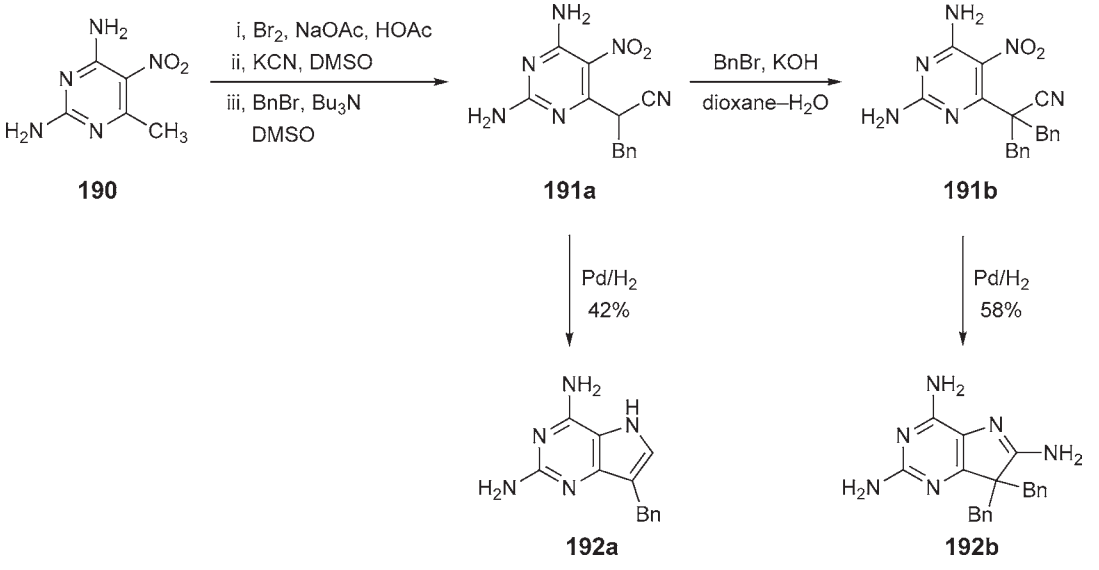
Developing a good synthesis of 9-deazaguanine **187** has been the goal of several laboratories since the work reported in CHEC-II(1996) <CHECII(7)229>. The process begins, in all cases, with 5-nitro-6-methylguanine **188** (**Scheme 17**). The major variation lies in the protecting group needed at N-3. The initial reaction involves treatment of **188** with DMF dimethyl acetal which acts on the 2-amino group. This is followed by protecting N-3 by reaction with chloromethyl pivalate <1995JOC7947>, benzyl bromide <1999NN363>, or pivaloyloxymethyl chloride <1999JOC8411, 2002SC3797>. With N-3 protected, an additional quantity of DMF dimethyl acetal afforded the intermediate **189**. Reduction was accomplished in all cases using sodium dithionite. Deprotection at N-3 afforded **187** in yields ranging from 48% to 90%.



Scheme 17

One example of the formation of intermediate **189** (without a protecting group) has also been described <2003JME3060>.

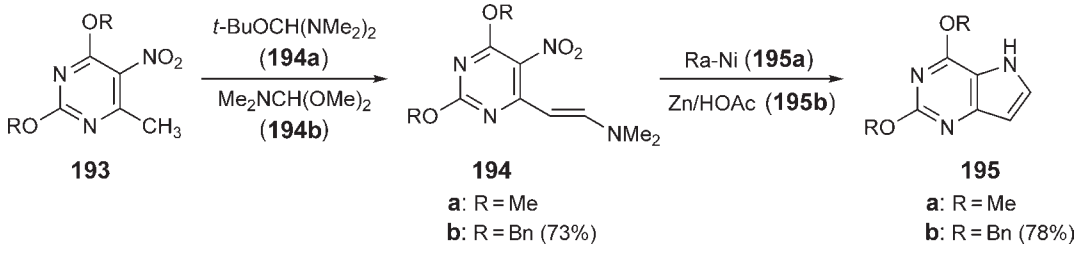
Structure **190** has been converted into key intermediates **191a** and **191b** via bromination, cyanide displacement, and benzylation (**Scheme 18**). Cyclization of **191** occurs upon reduction of the nitro group to give **192** <2004BMC3187>. The N^2,N^4-dibenzyl derivative of **190** leads to similar products <2004JME3187>.



Scheme 18

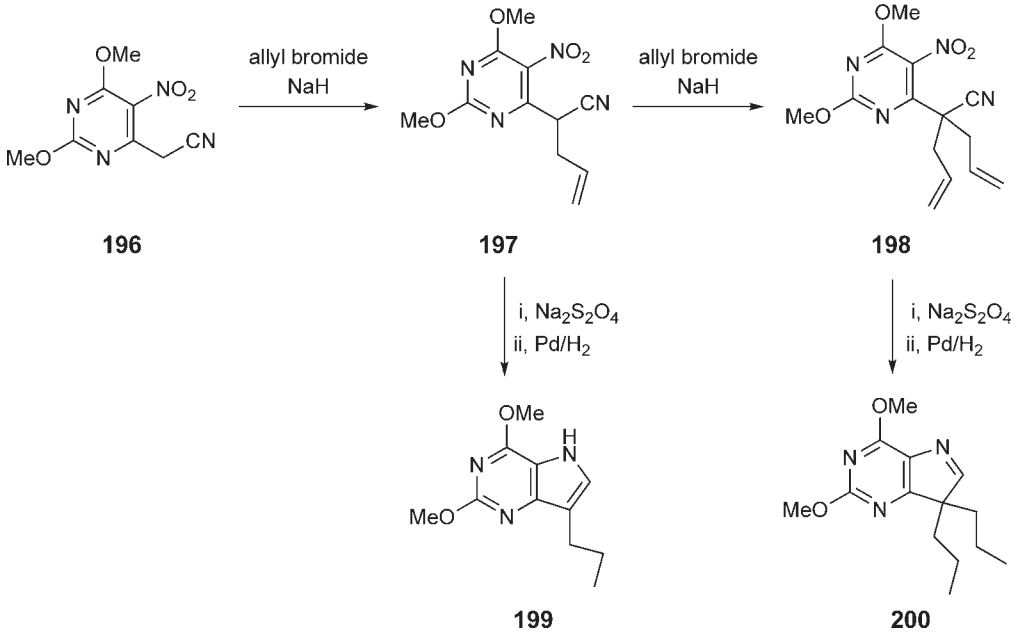
The 4-oxo analog of **191a** has also been reduced with Pd/H_2 to give the corresponding guanine analog of **192a** <1996TL5829>. In addition, a 3-thiophenylmethyl analog of 9-deazaguanine has been reported <2001OPD216>. The dimethoxy analogs of **191a** and **191b** provide analogous pyrrolo[3,2-*d*]pyrimidines <1998T2931>.

6-Methyl-5-nitrouracil is protected by chlorination and replacement of the resultant dichloropyrimidine with alkoxide to give **193** (**Scheme 19**). As previously described, treatment of **193a** with *t*-butoxybis(dimethylamino)-methane or of **193b** with DMF dimethyl acetal leads to the corresponding enamino compounds **194**. Reduction of **194a** affords **195a** while **194b** gives **195b** which can be converted into the 9-deazaxanthine product <2001JOC5723>.



Scheme 19

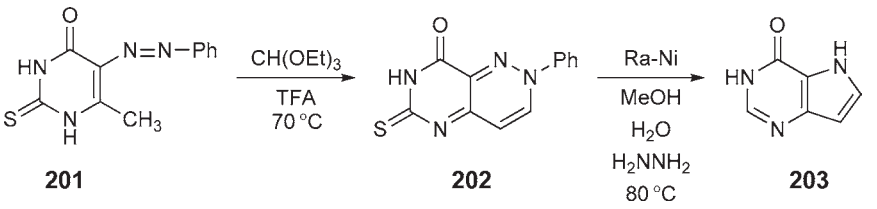
Unsaturated side chains have been introduced into pyrrolo[3,2-*d*]pyrimidines by similar chemistry to that shown in **Scheme 18**. Commencing with **196**, one or two allyl side chains are introduced to provide **197** or **198** (**Scheme 20**). Reduction of the nitro group with $Na_2S_2O_4$ followed by catalytic hydrogenation of **197** or **198** caused both cyclization and saturation of the double bond giving **199** and **200**, respectively <1996CC49, 1997T391>.



Scheme 20

There are several unique methods that have been employed for the synthesis of pyrrolo[3,2-*d*]pyrimidines. The following examples illustrate these approaches.

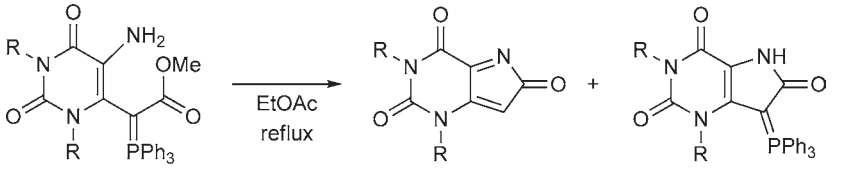
The phenylazo moiety, in place of the nitro group, can be used in conjunction with an adjacent methyl group to form a pyrrolo[3,2-*d*]pyrimidine. Thus **201** undergoes cyclization with triethyl orthoformate to give a pyrimidopyrazine **202** (**Scheme 21**). The subsequent ring opening and recyclization to form the pyrrolopyrimidine ring system **203** is accompanied by desulfurization in the presence of Raney nickel <2002CPB364>.



201 **202** **203**

Scheme 21

6-Azidouracils have been transformed into the triphenylphosphorane intermediate **204** (Equation 70). Cyclization is accompanied by loss of PPh_3 to afford a mixture of **205** and **206** <2002HAC357>.

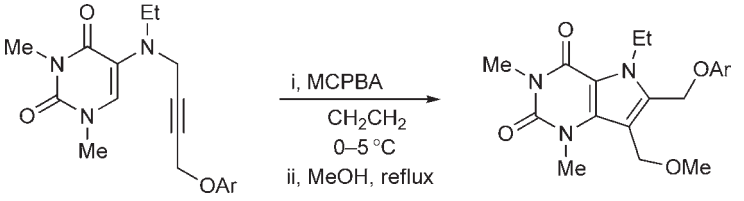


204 **205** **206**

a: R = Me
b: R = Et

(70)

Several pyrrolo[3,2-*d*]pyrimidines **208** were synthesized in excellent yields from the corresponding 5-substituted uracils **207** (Equation 71) <1998JOC3550>.

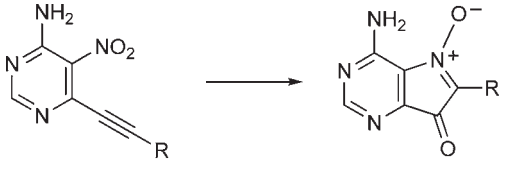


207 **208**

a: Ar = 2-ClC_6H_4 (94%)
b: Ar = 4-ClC_6H_4 (92%)
c: Ar = Ph (93%)
d: Ar = 4-$MeOC_6H_4$ (93%)
e: Ar = 4-MeC_6H_4 (95%)
f: Ar = 2-MeC_6H_4 (95%)

(71)

Cyclization of 6-acetylenic derivatives constitutes yet another approach to pyrrolo[3,2-*d*]pyrimidines. A series of 6-substituted acetylenes **209**, prepared by alkynylation of the chloropyrimidine, undergo cyclization to the *N*-oxides **210** when heated briefly in pyridine (Equation 72) <2003SL1151, 2004CHE1335>.

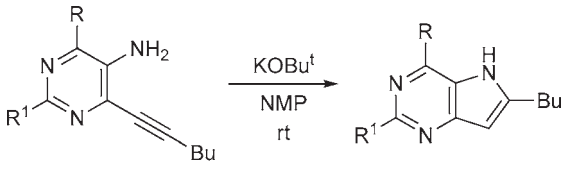


209 **210**

a: R = Ph (95%)
b: R = 4-MeC_6H_4 (90%)
c: R = 4-FC_6H_4 (87%)
d: R = Bu (92%)

(72)

If, however, there is an amino group adjacent to the acetylene substituent, cyclization occurs in basic media to afford the fused ring without the *N*-oxide function (Equation 73). So, **211** leads to moderate yields of **212** <2000AGE2488>.

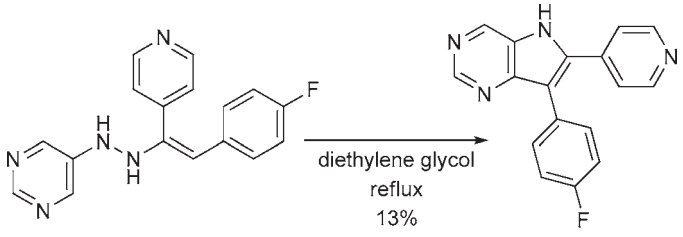


211 **212**

a: R = Cl; R^1 = H (78%)
b: R = R^1 = Me (61%)

(73)

An approach to this type of ring system that has been classified as a diazaindole is shown in Equation (74). Here **213** has been prepared in two steps from 5-bromopyrimidine. Heating this compound at reflux in diethylene glycol affords **214** in very poor yield <2003JME4702>.



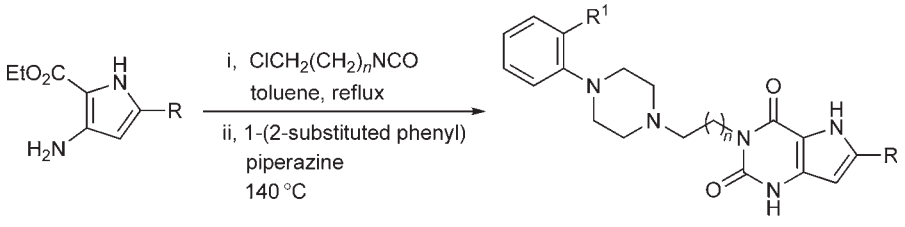
213 **214**

(74)

10.07.6.2.2(ii) Synthesis from pyrroles

The most common approach to the synthesis of a fused pyrimidine ring involves condensation reactions between adjacent carboalkoxy and amino groups. Therefore, it is not surprising that the majority of pyrrolo[3,2-*d*]pyrimidines that involve a pyrrole precursor follow this pathway.

Very recently, a series of N^1-substituted 9-deazaxanthines **216** have been described as originating from **215**, some of which are illustrated below (Equation 75) <2005JME2420>.

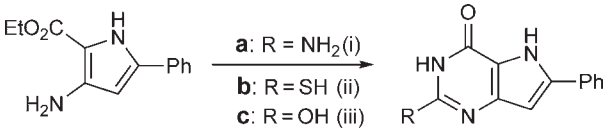


215 **216**

Entry	*n*	*R*	R^1	*Yield (%)*	*Entry*	*n*	*R*	R^1	*Yield (%)*
a	1	H	MeO	79	**g**	2	Ph	MeO	67
b	1	H	Cl	85	**h**	2	Ph	Cl	54
c	2	H	MeO	70	**i**	1	2-ClC_6H_4	MeO	50
d	2	H	Cl	89	**j**	1	2-ClC_6H_4	Cl	43
e	1	Ph	MeO	50	**k**	1	3-ClC_6H_4	MeO	51
f	1	Ph	Cl	59	**l**	1	4-ClC_6H_4	MeO	39

(75)

Compound **215e**, as one example, can be converted to a variety of pyrrolo[3,2-*d*]pyrimidines **217** depending on the condensing agent (no yields given) (Equation 76) <2000JME4288>.

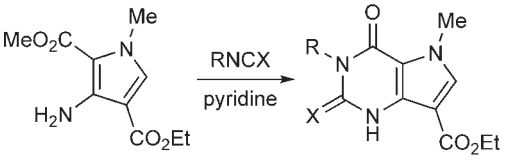


215e **217**

(76)

i, (a) H_2NCN, HCl (conc.) dioxane, reflux (b) NaOH(aq.), reflux
ii, (a) $S{=}C{=}NCO_2Et$, benzene, reflux (b) KOH(aq.), reflux
iii, (a) KNCO, HOAc, H_2O (b) NaOH(aq.), reflux

Additional examples of 9-deazaxanthines can be obtained from pyrrole **218** by treatment with a group of isocyanates or isothiocyanates to give the corresponding compound **219** (Equation 77) <1994H1087>. Compounds **219b**, **219e**, and **219f** were prepared in acetonitrile with KOH and water added.

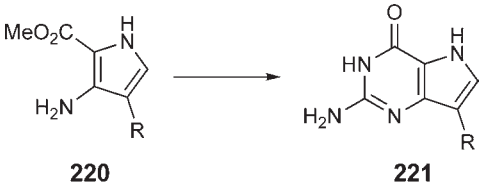


218 **219**

Entry	*R*	*X*	*Yield (%)*
a	Me	S	66
b	Et	O	58
c	Et	S	60
d	Allyl	S	50
e	Bn	O	73
f	Ph	O	85
g	Ph	S	85
h	4-MeC_6H_4	S	51

(77)

More than a little effort has been devoted to preparing 9-deaza-9-substituted guanine derivatives (7-substituted pyrrolo[3,2-*d*]pyrimidines) **221**. In each case, the appropriate 2-alkoxycarbonyl-3-amino-4-substituted pyrrole **220** (Equation 78) has been prepared. However, each product was accessed under different conditions. Thus **220a**, upon treatment with 1,3-bis(methoxycarbonyl)-*S*-methylisothiourea in HOAc, gave **221a** <1996TL4339>. Compound **220b**, prepared in eight steps, was allowed to react with cyanamide in aqueous ethanolic HCl to give **221b** <2002JOC6612>. **220c** was prepared with deuterium in the pyridine ring and cyclized to **221c** using 1,3-dimethoxycarbonyl-*O*-methylisourea <1999JLR1235>. The condensation of **220d** with 1,3-dicarbomethoxy-2-methyl-2-thiopseudourea was unsuccessful until excess AcOH in MeOH was employed to provide a mild acid catalysis. In this way, **221d** could be obtained <1997JOC8071>.

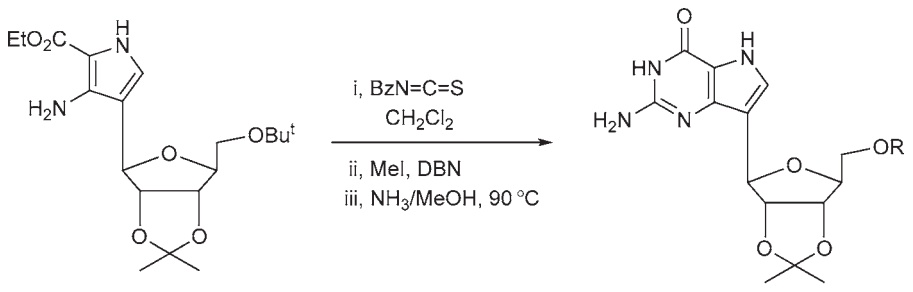


220 **221**

(78)

a: R = CO_2Me (57%)
b: R = 2-(2-fluorophenyl)-1-oxoethyl (53%)
c: R = 3-pyridinylmethyl (80%)
d: R = Ph (75%)

It is not surprising that pyrrolo[3,2-*d*]pyrimidines bearing a carbohydrate moiety should be included in this area of research. The construction of a pyrrole ring with an attached carbohydrate ring serves as a useful precursor in the synthesis of this type of molecule. Compound **222**, prepared in seven steps from D-γ-ribolactone, is transformed into **223a** (Equation 79). Deblocking of **223a** to the nucleoside **223b** was accomplished by warming in CF_3CO_2H/H_2O at 50 °C <2001JOC4852>. Pyrroles, similar to **222**, bearing a substituent on the pyrrole nitrogen atom have also been transformed into pyrrolo[3,2-*d*]pyrimidines <2003JME3412, 2000T3053>.

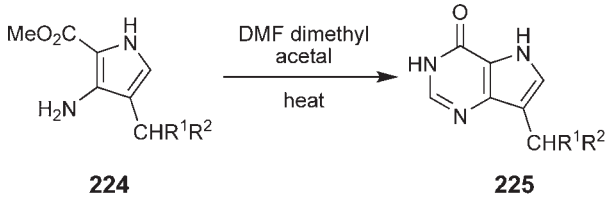


222 **223**

a: R = Bu^t (57%)
b: R = H (68%)

(79)

The syntheses of 9-deazahypoxanthines **225** from pyrroles **224** have been carried out by allowing the amino group of **224** to react with DMF dimethyl acetal (Equation 80). The intermediate amidine readily undergoes cyclization to give **225** <1994JME2477>. Other examples following this type of reaction are known <2000CHE1409>.

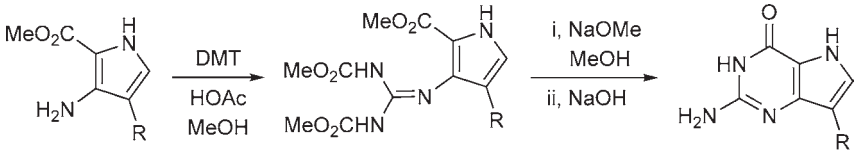


224 **225**

Entry	R^1	R^2	*Yield (%)*
a	H	$c\text{-}C_5H_{11}$	72
b	H	3-pyridyl	78
c	CH_2CN	$3\text{-}ClC_6H_4$	88
d	H	Ph	39
e	H	$3\text{-}PhCH_2OC_6H_4$	12
f	H	3-Thienyl	27
g	H	4-Pyridyl	94

(80)

Guanylation of pyrrole **226** was accomplished with 1,3-dimethoxycarbonyl-2-methyl-2-thiopseudourea (DMT) under mild acid catalysis to give adduct **227** (**Scheme 22**). Cyclization and deprotection to produce **228** was accomplished in basic media <2000NN379>.

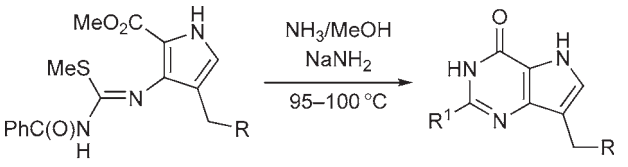


226 **227** **228**

a: R = N(Ph)CO_2Et (76%)
b: R = N(cyclohexyl)carbobenzoxy
c: R = Ph-O (30%)
d: R = $3\text{-}MeC_6H_4O$ (29%)
e: R = PhS (43%)
f: R = 3-pyridylO (47%)

Scheme 22

Another report describing the activation of the pyrrole amino group has appeared. Compounds **229** are transformed into **230** and **231** in 45–55% and 15–30% yields, respectively (Equation 81) <2000OPD129>.

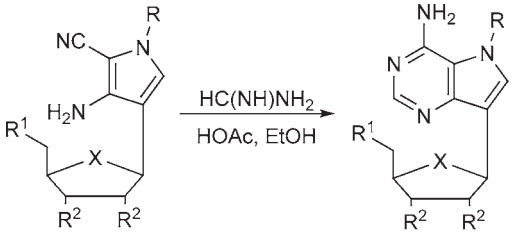


229a: R = 3-pyridyl
229b: R = cyclopentyl
229c: R = 3-furanyl

230a–c: $R^1 = NH_2$
231a–c: R^1 = SMe

(81)

There have been a number of reports describing the synthesis of 'nucleoside' analogs of 9-deazaadenine. All begin with a pyrrole bearing adjacent amino and cyano functional groups. Typically these compounds have the structure **232** and are converted to the fused system **233** by treatment with formamidine. The dideoxyribose derivative of pyrrole **232a** is transformed into **233a** in this manner (Equation 82) <1996NN1223, 1996NN1821>. Similarly, the protected ribosyl compound **232b** gives **233b** <1997CAR33>. Replacement of the oxygen atom in the carbohydrate moiety results in the formation of **233c** from **232c** <2004JME1322, 2004JME3275>. Additional variations of N-containing 'nucleosides' are described <2000T3053, 2003JME155>. Finally, replacement of the heteroatom in the carbohydrate component of **232** with a methylene group gives the cyclopentyl analog **232d**, which also undergoes cyclization to give the corresponding **233d** <1999TL3309>. In all cases, mild acidic hydrolysis affords the deprotected 'nucleoside'.

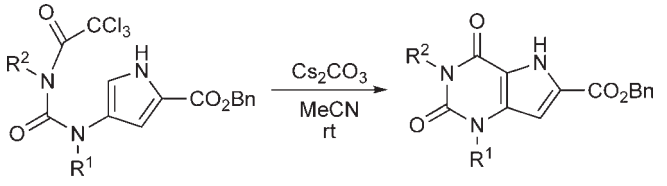


232 **233**

a: R = H; R^1 = TrO; R^2 = H; X = O (95%)
b: R = H; R^1 = TrO; $R^2 = OCMe_2O$; X = O (95%)
c: R = H; R^1 = MeS; $R^2 = OCMe_2O$; X = NBOC (quant.)
d: R = H; $R^1 = Bu^tO$; $R^2 = OCMe_2O$; $X = CH_2$ (81%)

(82)

One other synthetic approach that does not utilize adjacent functional groups in the precursor has been reported. Pyrrole **234** has been constructed in such a way that a cyclization to **235** is the preferred course of the reaction (Equation 83). This represents the lone approach envisioned in this series <2003JOC6984>. A related synthesis using solid-phase techniques has been described <2005JCO977>.

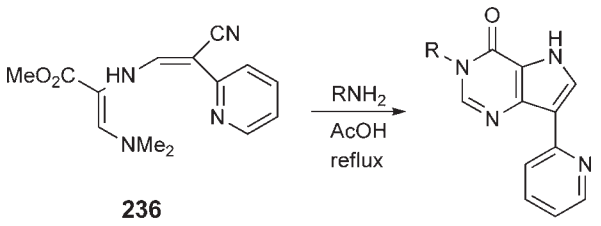


234 **235**

a: R^1 = Bn; R^2 = Et (75%)
b: R^1 = Bn; R^2 = allyl (70%)
c: R^1 = Bn; R^2 = Ph (59%)
d: $R^1 = Pr^i$; R^2 = Et (67%)
e: $R^1 = Pr^i$; R^2 = allyl (66%)
f: $R^1 = Pr^i$; R^2 = Ph (53%)
g: R^1 = allyl; R^2 = Et (79%)
h: $R^1 = R^2$ = allyl (76%)
i: R^1 = allyl; R^2 = Ph (69%)

(83)

Although strictly speaking this example does not begin with a preformed ring, the explanation for the conversion of **236** into pyrrolo[3,2-*d*]pyrimidines **237** by heating with an amine appears to proceed via an unisolated pyrrole (Equation 84) <2000H(53)805>. This process can be explained by cyclization of **236** into 3-dimethylamino-4-(2-pyridinyl)pyrrole-2-carboxylate followed by reaction with another molecule of **236** in which the dimethylamino group is substituted by the aminopyrrole derivative.



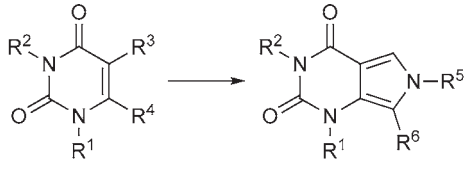
236 **237**

a: R = $PhCH_2$ (42%)
b: R = 4-$MeOC_6H_4CH_2$ (32%)
c: R = Me (25%)

(84)

10.07.6.2.3 Pyrrolo[3,4-*d*]pyrimidines

The literature describing the synthesis of pyrrolo[3,4-*d*]pyrimidines since the publication of CHEC-II(1996) <1996CHEC-II(7)229> involves both pyrimidine and pyrrole precursors almost evenly. Extensive use of uracil derivatives has been made in order to generate a variety of compounds of this class. Equation (85) illustrates some of the approaches to their syntheses. Treatment of the dibenzyluracil **238a** with 3 equiv of NaH and 1.5 equiv of tosylmethyl isocyanide (TOSMIC) generated **239a** <2000H(53)205>. Protection of the ring nitrogen atoms with 4-methoxybenzyl groups **238b** allowed this molecule to react with ethyl isocyanoacetate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **239b** <2002H(58)301>.



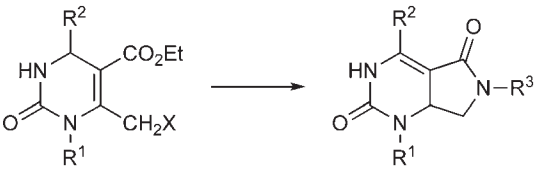
238 **239**

(85)

Entry	R^1	R^2	R^3	R^4	R^5	R^6	*Yield* (%)
a	$PhCH_2$	$PhCH_2$	H	H	H	H	91
b	4-$MeOC_6H_4CH_2$	4-$MeOC_6H_4CH_2$	NO_2	H	H	CO_2Et	88
c	Me	CH_2CHMe_2	CHO	Me	$PhCH_2$	H	
d	CH_2CHMe_2	CH_2CHMe_2	CN	Me	NaphthylCH_2	H	

Bromination of the methyl group in **238c** gave the bromomethyl compound, which underwent reaction with benzylamine. Ring closure of the resulting intermediate afforded **239c** <1995JME2557>. In essentially the same process, **238d** was reduced by Ra-Ni in HCO_2H. This was followed by bromination, amination, and ring closure <1995JME2557>. No yields were given for these two compounds and many additional examples are described in the cited reference.

The presence of a carboxylic ester at position 5 of a pyrimidine ring contributes to a series of fused pyrroles containing a carbonyl group (Equation 86). The pyrimidine **240a** is heated at reflux with cyclohexylamine for 8 h providing **241a** <2001JHC1051>.



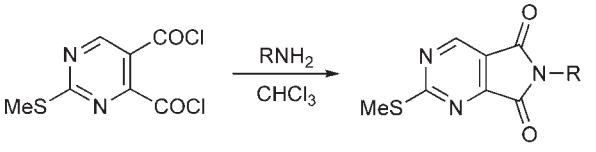
Entry	R^1	R^2	R^3	X	Yield (%)
a	Me	4-$O_2NC_6H_4$	C_6H_{11}	Br	36
b	Me	4-$O_2NC_6H_4$	Me	Br	53
c	H	Ph	n-Pr	Cl	NA

(86)

240 **241**

The same reaction involving **240a** and methylamine proceeds at room temperature producing **241b** <2001JHC1051>. Solid-phase synthesis of **241c** from **240c** is one of but many examples of this approach to the pyrrolo[3,4-*d*]pyrimidines <2002JCO501>.

2-Methylthiopyrimidine-4,5-dicarbonyl chloride **242**, obtained by hydrolysis of the diester followed by reaction with oxalyl chloride, serves as a suitable starting material for the formation of **243** (Equation 87). The corresponding aniline and benzylamine were employed in the synthesis of **243a** and **243b** <2000MI19>.



(87)

242 **243**

a: R = 3,5-$(CF_3)_2C_6H_3$ (25%)

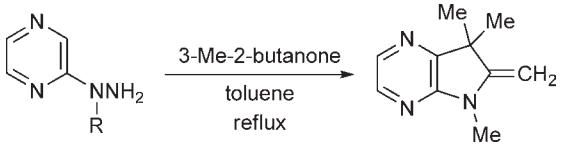
b: R = 3,5-$(CF_3)_2C_6H_3CH_2$ (68%)

10.07.6.3 Pyrrolopyrazines

10.07.6.3.1 Pyrrolo[2,3-*b*]pyrazines

All of the synthetic approaches to the pyrrolo[2,3-*b*]pyrazines originate with a suitably substituted pyrazine. Furthermore, all but one of these approaches have a chloropyrazine as the initial precursor.

In the simplest example, 2-chloropyrazine can be treated with methylhydrazine to afford **244a**. Commencing with **244a**, treatment with 3-methyl-2-butanone gives an enamine, which, after thermal Fischer-type cyclization, leads to **245** (Equation 88) <1994MI17>.



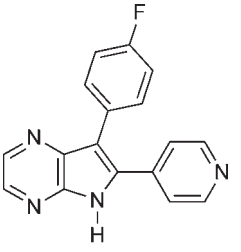
(88)

244 **245**

a: R = Me (46%)

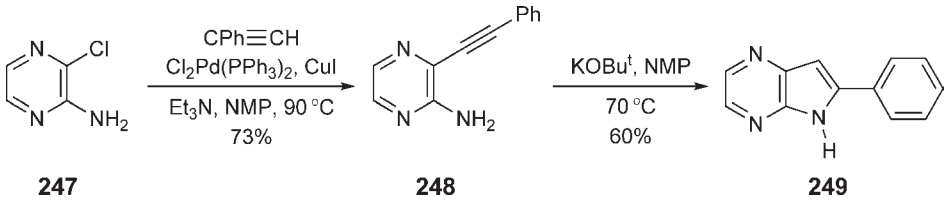
b: R = H

Similarly, **244b** reacts with 4-fluorobenzyl 4-pyridyl ketone to give an enamine intermediate that also undergoes thermal cyclization producing the aromatic product **246**. Details regarding this compound were published in a subsequent paper <2003JME4702>.



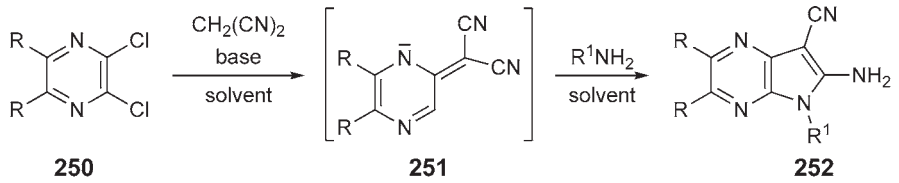
246

The readily available 2-amino-3-chloropyrazine **247** has been coupled with phenylacetylene using palladium-catalyzed conditions to give 2-amino-3-phenylethynylpyrazine **248**, which subsequently is cyclized to pyrrolo[2,3-*b*]pyrazine **249** (**Scheme 23**) <2004TL8087, 2004TL8631, 2005TL1845>.



Scheme 23

Replacement of a chloro group on the pyrazine by nucleophilic substitution with the anion of an activated methylene species is the major pathway in the synthesis of pyrrolo[2,3-*b*]pyrazines. The symmetrical pyrazine **250a** undergoes reaction with malononitrile and K_2CO_3 in acetonitrile to form **251a** (**Scheme 24**). Reaction of this intermediate with benzylamine in acetonitrile affords **252a** <2001MC152>.

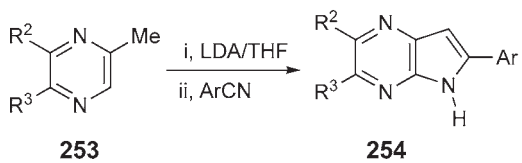


Entry	*R*	R^1	*Yield* (%)	*Entry*	*R*	R^1	*Yield* (%)
a	Cl	$PhCH_2$	70	**g**	CN	morpholino-CH_2CH_2	96
b	CN	$PhCH_2$	75	**h**	CN	morpholino-$CH_2CH_2CH_2$	88
c	CN	$PhCH_2CH_2$	80	**i**	CN	CH_2=$CHCH_2$	77
d	CN	3,4-$(MeO)_2C_6H_3CH_2CH_2$	92	**j**	CN	THF-CH_2	83
e	CN	$Me_2NCH_2CH_2$	70	**k**	CN	3-$MeOC_6H_4$	69
f	CN	$MeOCH_2CH_2$	74	**l**	CN	2-furyl-CH_2	86

Scheme 24

The same reaction of malononitrile with **250b** and NEt_3 in DMF produced a series of products **252b–d** when a variety of amines were employed <2002CHE219>. Other examples, such as **252e–l**, made from **250b** in a similar fashion have also been described <1998JCM284, 2000CHE1349, 2001DP133, 2002CHE336>.

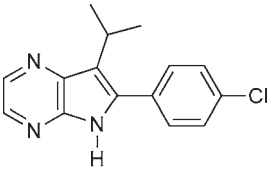
A somewhat different approach to this series of compounds involves the reaction between a carbanion and an aromatic nitrile. Thus, a series of methylpyrazines **253** is first treated with lithium diisopropylamide (LDA) to generate an anion at the methyl group. Addition of an aromatic nitrile produces **254** (Equation 89) <2003JME222, 2004EUP1388541>. Many other examples have been reported <2003JME222>, including some with substituents at the open position in structure **254**.



Entry	R^2		R^3	*Ar*	*Yield* (%)
a	H		H	2-Furyl	6
b	H		H	2-Thienyl	8
c	H		H	3-Thienyl	6
d	H		H	2-Pyridyl	8
e	H		H	Ph	37
f	H		H	1-Naphthyl	17
g		–(CH_2)–		Ph	44
h	H		Me	Ph	26
i	H		H	1-(4-ClC_6H_4)-*c*-Pr	41

(89)

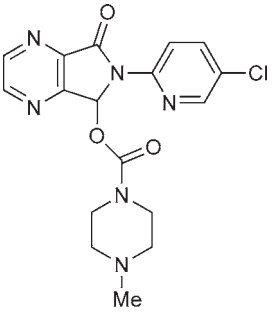
The motivation for synthesizing structures of this type appears to be the generation of derivatives of aloisine **255** <2004BML413>.



255

10.07.6.3.2 Pyrrolo[3,4-*b*]pyrazines

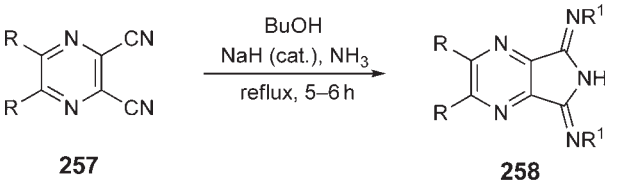
Interest in the synthesis and reactions of pyrrolo[3,4-*b*]pyrazines is focused on two goals. The first is the development of analogs of zopiclone **256**, a hypnotic agent <2001MI27>. Analogs of **256** are typically prepared from pyrazine-2,3-dicarboxylic anhydride (a furo[3,4-*b*]pyrazine) and a variety of aliphatic or aromatic amines <1996MI26, 1997MI28>.



256

The lipase from *Candida antarctica* catalyzes the resolution of the key intermediate in the formation of zopiclone, and presumably derivatives of zopiclone <1997TA995>.

The second, and perhaps more widespread, focus is on phthalocyanin analogs. The key intermediate for the synthesis of tetrapyrazinoporphyrazines is structure **258**. 5,6-Dichloropyrazine-2,3-dicarbonitrile, prepared from diaminomaleonitrile, reacts with secondary amines to form the pyrazines **257**. Treatment of **257a–d** with NaH and NH_3 leads to the corresponding **258a–d** (Equation 90) <1999MI417>. Compound **258e** was prepared from **257e** by treatment with 2-(4-fluorophenyl)ethylamine and elemental sulfur at 50 °C <2001BML2817>.



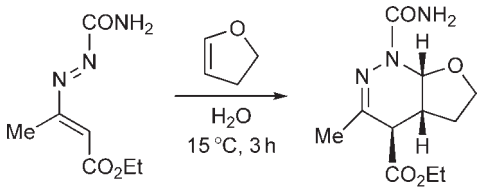
257 → **258** (90)

R^1 = H	**a**: R = morpholino (97%)
R^1 = H	**b**: R = thiomorpholino (74%)
R^1 = H	**c**: R = piperidino (<20%)
R^1 = H	**d**: R = pyrrolidino (65%)
R^1 = 4-$FC_6H_4(CH_2)_2$	**e**: R = H (32%)

10.07.6.4 Furopyridazines

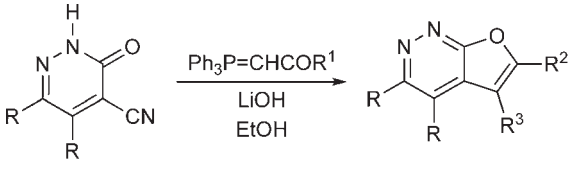
10.07.6.4.1 Furo[2,3-*c*]pyridazines

In CHEC-II(1996) <1996CHEC-II(7)229>, intermolecular Diels–Alder reactions were conducted with furan to give nonaromatic species. This example explores the reaction of the diene **259** with dihydrofuran. The reaction proceeds with 100% conversion to give a mixture of stereoisomeric products, one of which, **260**, is obtained in pure form (Equation 91) <2001HCA513, 2005EJO1142>.



259 **260** (91)

Treatment of the pyridazinone **261** with ester ylides affords **262a** and **262b** while the reaction with keto ylides produces **262c** and **262d**, although none in very good yield (Equation 92) <2005HAC56>.



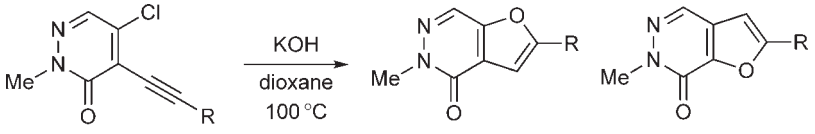
261 **262**

	R	R^1	R^2	R^3	*Yield* (%)
a	2-Furyl	OMe	CO_2Me	NH_2	~26
b	2-Furyl	OEt	CO_2Et	NH_2	~26
c	2-Furyl	Me	Me	H	~18
d	2-Furyl	Ph	Ph	H	~18

(92)

10.07.6.4.2 Furo[2,3-*d*]pyridazines

Limited research on these isomers of the furopyridazine series of compounds continues to be the case. Two examples of the synthesis of furo[2,3-*d*]pyridazines illustrate what has been described recently in the literature. Treatment of the pyridazines **263** with KOH provided a series of 2-substituted derivatives **264** in yields ranging from 3% to 79% (Equation 93) <2002H(57)2115>. The isomeric **265** was obtained when the regioisomer of **263** was used <2002H(57)2115>. The poor yields associated with both reactions using **263b** or its regioisomer is attributed to the acidity of the propargylic protons.

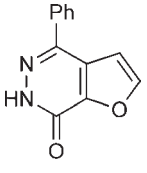


263 **264** **265**

a: R = Ph	50%	80%
b: R = C_3H_7	3%	4%
c: R = Bu^t	52%	65%

(93)

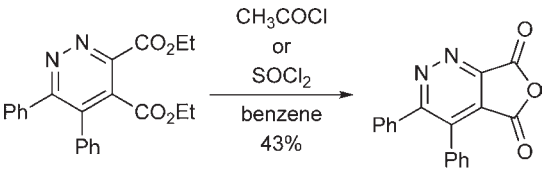
A multistep process beginning with 3-furancarboxylic acid is reported to produce **266** <1995JAP07033773>.



266

10.07.6.4.3 Furo[3,4-*c*]pyridazines

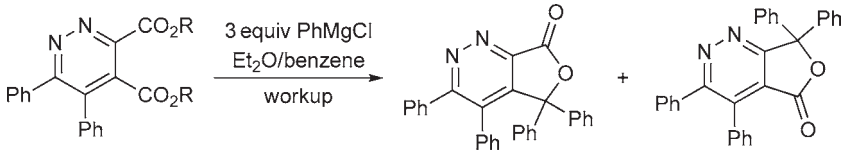
The dicarboxylic acid derivative **267a** is converted directly to the anhydride **268** by treatment with either acetyl chloride or thionyl chloride (Equation 94) <1999SC4141>.



267
a: R = H
b: R = Et

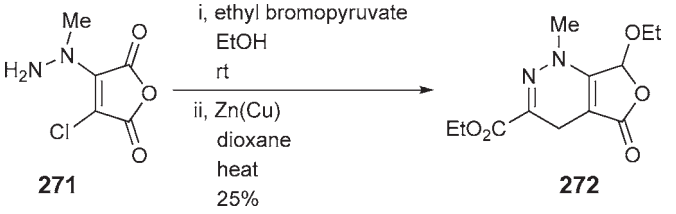
268 (94)

If, however, the corresponding ester **267b** is allowed to react with 3 mol of phenylmagnesium bromide, a pair of isomers **269** and **270** is obtained (Equation 95) <2002SC989>.



267b **269** 34% **270** 13% (95)

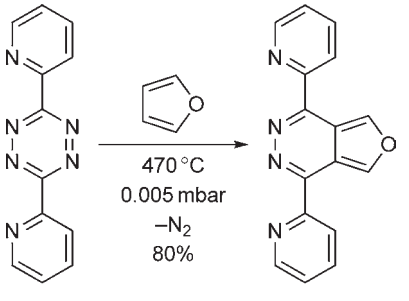
The hydrazinofuranone **271** is allowed to react with ethyl bromopyruvate to generate a hydrazone, which, upon heating in the presence of Zn(Cu), affords the product **272** in poor yield <1996H(43)1863> (Equation 96).



271 **272** (96)

10.07.6.4.4 Furo[3,4-*d*]pyridazines

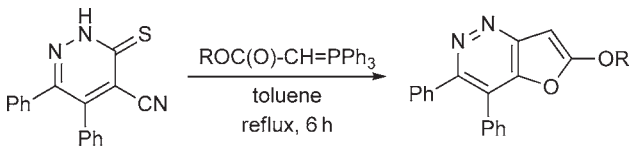
Apart from a very unconventional synthesis of **274** via fragmentation of the tetrazine **273** in the presence of furan (Equation 97) <2003AJC811>, interest in the furo[3,4-*d*]pyridazines has waned since the coverage in CHEC-II(1996) <1996CHEC-II(7)229>.



273 **274** (97)

10.07.6.4.5 Furo[3,2-*c*]pyridazines

Only two examples of an aromatic species of this isomer of fused pyridazine have been reported. The furo[3,2-*c*]-pyridazine, **276**, has been prepared in modest yield from the pyridazine **275** upon treatment with carboalkoxymethyl-triphenylphosphoranes (Equation 98) <2004PS(179)97>. The structure was confirmed by spectroscopic evidence and results by rearrangement of an intermediate alkylidene structure.



275 **276**

R = Me (65%)
R = Et (60%)

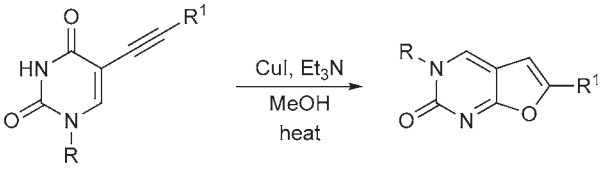
(98)

10.07.6.5 Furopyrimidines

10.07.6.5.1 Furo[2,3-*d*]pyrimidines

10.07.6.5.1(i) Syntheses from pyrimidines

The synthesis of furo[2,3-*d*]pyrimidines can originate either from a furan or pyrimidine precursor, in similar fashion to almost all other systems described in this chapter. In this case, the dominant precursor in synthetic studies is the pyrimidine ring. Furthermore, the large majority of pyrimidine precursors are uracil nucleosides that have an acetylenic function at the 5-position of the pyrimidine. Almost without exception the carbon–carbon triple-bond moiety was introduced via Pd-catalyzed replacement of the 5-iodouracil compound. Therefore, we will commence our discussion with the acetylenic intermediate. It should also be noted that, with one exception, the carbohydrate component of the precursor possesses the 2-deoxyribose or arabinose configuration. In a few cases, the hydroxyl functions are protected, but for simplicity we shall present the precursor in the nonprotected form. So, compound **277** is typically treated with copper(I) iodide and triethylamine in methanol to give the corresponding furo[2,3-*d*]pyrimidine **278** (Equation 99). For brevity, only a few selected examples have been shown. In this way, **278a** and **278b** <1999JME4479>, **278c** <2000NN851>, **278d** <2000BML1215>, **278e** and **278f** <2000JME4993>, **278g** and **278h** <2001NN1063>, **278i** and **278j** <2001BML391, 2001NN763>, **278k** and **278l** <2001NN653>, **278m** and **278n** <2001NN287, 2005BM1231>, **278o** <2002CEJ2891>, **278p** <2003TL3387, 2003HCA1193, 2004TL2457>, **278q** <2003NN931>, **278r** <2003BML4511>, **278s** <2004SL2406>, **278t** <2004NN183>, **278u** <2004NN1>, **278v** <2004CC1304>, **278w** and **278x** <2005BML3791>, **278y** <2005CC2555>, **278z** <2005JME7012>, **278aa** and **278bb** <2004JME1847, 2005TL6511>, and **278cc** <2003NN935> were prepared in varying yields.



277 **278**

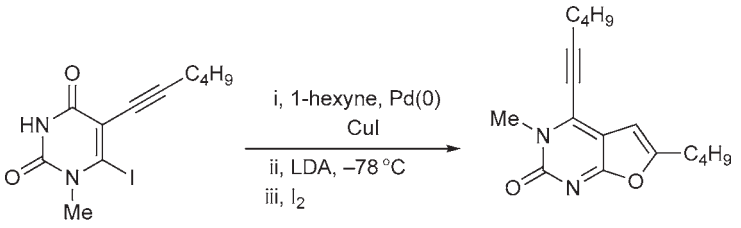
R =

a: X = OH; $R^1 = C_5H_{11}$ (68%)
b: X = OH; $R^1 = C_{12}H_{25}$ (49%)
c: X = OH; R^1 = 4-$Me_2NC_6H_4$ (20%)
d: X = OH; $R^1 = (CH_2)_9Cl$ (70%)
e: X = OH; R^1 = Ph (16%)
f: X = OH; R^1 = 4-BrC_6H_4 (19%)
g: X = OH; R^1 = 4-$MeOC_6H_4$ (43%)
h: X = OH; R^1 = 4-$CH_3(CH_2)_2OC_6H_4$ (59%)
i: X = OH; $R^1 = (CH_2)_3CH{=}CH_2$ (73%)
j: X = OH; $R^1 = (CH_2)_3C{\equiv}C$ (4%)
k: X = OH; $R^1 = (CH_2)_4Ph$ (81%)
l: X = OH; $R^1 = (CH_2)_3OPh$ (48%)
m: X = OH; R^1 = 4-MeC_6H_4 (71%)
n: X = OH; R^1 = 4-EtC_6H_4 (14%)
o: X = OH; R^1 = ferrocenyl (35%)
p: X = OH; R^1 = Me (50%)
q: X = Cl; R^1 = 4-$CH_3(CH_2)_4C_6H_4$ (23%)
r: X = OH; $R^1 = C_4H_9OC_9H_{18}$ (42%)
s: X = OH; $R^1 = PhC_5H_{11}$ (20%)
t: X = OH; $R^1 = MeOCH_2$ (29%)
u: X = F; $R^1 = C_8H_{17}$ (86%)
v: X = OH; R^1 = fluorescein (74%)
w: X = OH; $R^1 = Me_2CH$ (63%)
x: X = OH; R^1 = But (52%)
y: X = OH; $R^1 = (CH_2)_3NPhth$ (69%)
z: X = OH; $R^1 = CH_3(CH_2)_2$ (48%)
aa: X = H; $R^1 = C_6H_{13}$ (45%)
bb: X = H; $R^1 = C_{10}H_{21}$ (81%)
cc: X = OH (xylo); $R^1 = C_8H_{17}$ (75%)

(99)

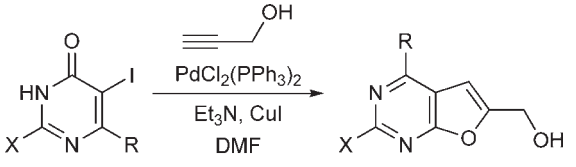
Other related examples of **278** include having an azido group in lieu of both hydroxyl groups <2003NN1939>, and the 4-iodo and bromo derivatives of **278m** <2003JOC6788> have been described. Examples of 'acyclic nucleosides' have also been reported <2002JME2032, 2005TL6511, 2005BMC1239>.

The expected compound in the carbon–carbon coupling reaction of **279** with 1-hexyne was found in only minor amounts (Equation 100). The major product of this reaction is the bicyclic compound **280** (no yield given) <2000TL8741>.



279 **280** (100)

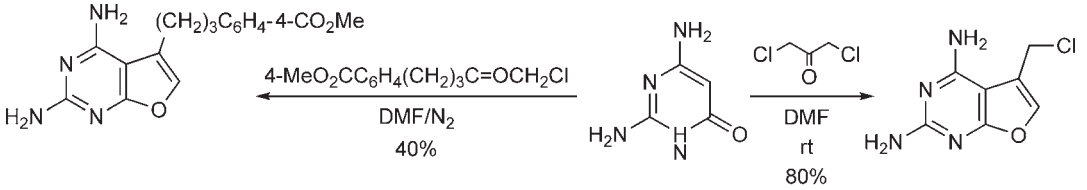
A microwave-enhanced coupling reaction of 5-iodopyrimidines **281** proceeds to the expected furo[2,3-*d*]pyrimidines **282** via the unisolated 5-alkynyl intermediate (Equation 101) <2003TL9181>.



281 **282** (101)

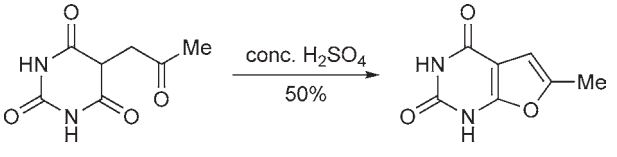
a: X = MeO; R = Me (80%)
b: X = MeS; R = Me (82%)
c: X = MeS; R = H (82%)

Introducing a β-keto alkyl group at position 5 of a pyrimidine ring has been explored as a means of obtaining 5-substituted furo[2,3-*d*]pyrimidines. The most popular choice of alkylating agent has been 1,3-dichloroacetone (Equation 102). Under very mild conditions, alkylation of **283** and subsequent cyclization to give **284** has been achieved <1995JME3798, 2000JHC935, 2000JME3125, 2002JME1942, 2005BMC5475>. Compound **285** is obtained, along with the corresponding pyrrolo[2,3-*d*]pyrimidine from a similar reaction <2004JME6893>. Ethyl bromopyruvate and 3-bromo-1,1,1-trifluoropropanone behave similarly <1997CC371>.



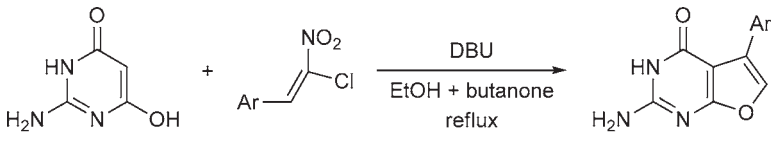
285 **283** **284** (102)

The alkylated barbituric acid **286** readily undergoes dehydration in conc. H_2SO_4 to produce the 6-methyl compound **287** (Equation 103) <1995H(41)937>.



286 **287** (103)

A substantial number of 5-arylfuro[2,3-*d*]pyrimidines have been generated by similar chemistry. In this case, a nitroethenylphenyl moiety is used. Thus 6-aminouracil **288** is allowed to react with **289** in mild, basic medium to generate a series of **290**, of which several are illustrated (**Scheme 25**) <1999CPB156>.

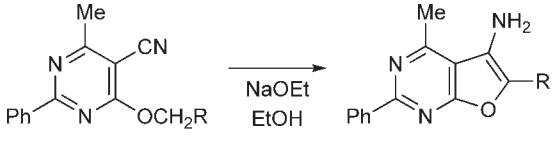


288 **289** **290**

a: Ar = Ph (61%)
b: Ar = 4-$MeOC_6H_4$ (54%)
c: Ar = 3,4-$(MeO)_2C_6H_3$ (54%)
d: Ar = 4-FC_6H_4 (68%)

Scheme 25

Having a carbonyl group β to an ether oxygen provides a suitable arrangement for producing 6-substituted furo[2,3-*d*]pyrimidines. The presence of an adjacent cyano group makes the formation of an amino-substituted furo[2,3-*d*]pyrimidine an easy accomplishment. So, **291**, upon treatment with base, readily undergoes cyclization to **292** (Equation 104) <2004JCCS1357>.

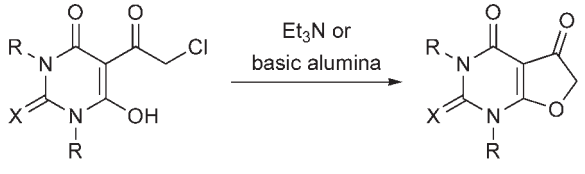


(104)

291 **292**

a: R = $COCH_3$ (76%)
b: R = COPh (73%)
c: R = CO_2Et (74%)

Pyrimidines acylated at position 5 offer another route to furo[2,3-*d*]pyrimidines. In this situation, a 5-oxo derivative is produced. Barbituric acid structures **293**, obtained by acylation with chloroacetyl chloride, are readily transformed into furo[2,3-*d*]pyrimidines **294** (Equation 105). The use of triethylamine leads to **294a** <1999HCO107, 2001JHC359> and to **294b** <2001JHC359>, while basic alumina under microwave-enhanced conditions gives excellent yields of **294c–h** <2002IJB2414>.

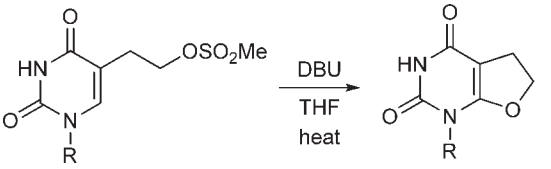


(105)

293 **294**

a: X = O; R = Me (89%)
b: X = S; R = Et (72%)
c: X = S; R = Ph (90%)
d: X = S; R = 4-ClC_6H_4 (92%)
e: X = S; R = 4-BrC_6H_4 (94%)
f: X = S; R = 2-$MeOC_6H_4$ (90%)
g: X = S; R = 2-MeC_6H_4 (90%)
h: X = S; R = 3-MeC_6H_4 (93%)

The syntheses of furo[2,3-*d*]pyrimidines with a completely saturated furan ring can be effected if the alkyl group that is introduced into position 5 of the pyrimidine ring bears no carbonyl function. Thus, **295a** is readily converted into **296a** (Equation 106). The protected 2′-deoxy-ribose analog **295b** was also transformed into the corresponding nucleoside **296b** in very good yield <1995JHC211>.

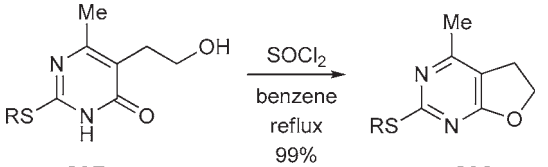


(106)

295 **296**

a: R = H (85%)
b: R = 2′-deoxyribose (87%)

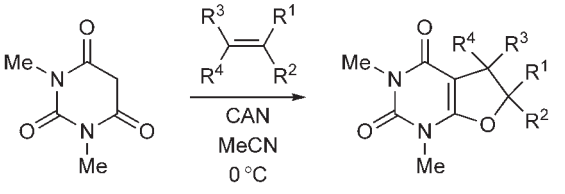
Pyrimidones such as **297** behave similarly if a good leaving group has been introduced. Thus **297** is chlorinated with thionyl chloride and cyclized under reflux conditions to **298** (Equation 107) in quantitative yield <1996JHC229>.



(107)

297 **298**

An alternative, but effective, method for preparing furo[2,3-*d*]pyrimidines with the potential for polysubstitution in the furan ring is shown in Equation (108). Here *N*,*N*′-dimethylbarbituric acid **299** is treated with a variety of alkenes in MeCN containing cerium(IV) ammonium nitrate to produce **300** with complete regioselectivity (Equation 108) <2000SC4277>.



(108)

299 **300**

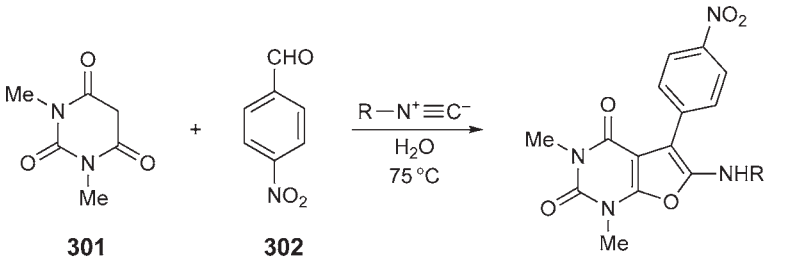
a: $R^1 = R^2 = Et$; $R^3 = R^4 = H$ (49%)
b: $R^1 = Me$; $R^2 = Ph$; $R^3 = R^4 = H$ (66%)
c: $R^1 = R^2 = Ph$; $R^3 = R^4 = H$ (80%)
d: $R^1 = R^2 = R^3 = Me$; $R^4 = H$ (52%)
e: $R^1 = R^2 = R^3 = R^4 = Me$ (49%)
f: $R^1 = n$-Bu; $R^2 = R^3 = R^4 = H$ (25%)
g: $R^1 = R^3 = (CH_2)_4$; $R^2 = R^4 = H$ (28%)
h: $R^1 = OAc$; $R^2 = Me$; $R^3 = R^4 = H$ (36%)
i: $R^1 = CO_2Me$; $R^2 = Me$; $R^3 = R^4 = H$ (26%)
j: $R^1 = CH_2OH$; $R^2 = Me$; $R^3 = R^4 = H$ (27%)
k: $R^1 = CH_2Cl$; $R^2 = Me$; $R^3 = R^4 = H$ (49%)

Finally, a one-pot, three-component condensation reaction in water provides an efficient procedure for the synthesis of furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **303** (**Scheme 26**). *N*,*N*′-Dimethylbarbituric acid **301** and 4-nitrobenzaldehyde **302** are reacted with a series of isocyanides to give good yields of the 6-amino products **303** <2002TL9151, 2005SC535>.

10.07.6.5.1(ii) Syntheses from furans

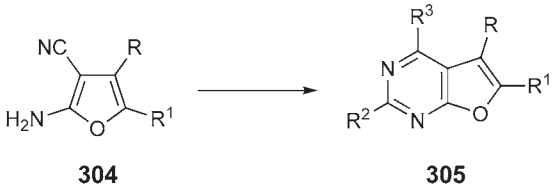
As with other systems discussed in this chapter, the standard method for annelating a pyrimidine ring is the use of adjacent amino and cyano groups. So it is not surprising that this chemistry is the method of choice in preparing furo[2,3-*d*]pyrimidines from furans. From a 2-amino-3-cyanofuran with additional substituents at position 4 and/or 5, **304** (Equation 109), a variety of amino **305** or oxo/thioxo **306** products have been obtained. Phosgene iminium chloride converts **304a** and **304b** into the corresponding furo[2,3-*d*]pyrimidines **305a** and **305b** <1996JHC659>.

More usual, formamide acts as both reagent and solvent. In this situation, **304c** undergoes ring cyclization to **305c** <2001IZV2424>. Using approximately the same conditions, **304d–g** gives **305d–g** <2004BML3907, 2005BML2203>. With identical aryl groups on the furan ring, **304h** and **304i** generate the 4-amino derivatives **305h** and **305i** when heated in formamide <1995IJH191>. However, heating **304h** and **304i** with urea or thiourea produces the respective 2-substituted compounds **305j** and **305k** <1995IJH191>.



a: R = But (77%)
b: R = cyclohexyl (89%)
c: R = Bn (81%)
d: R = 2,6-$Me_2C_6H_3$ (73%)
e: R = *N*-morpholinoethyl (74%)

Scheme 26

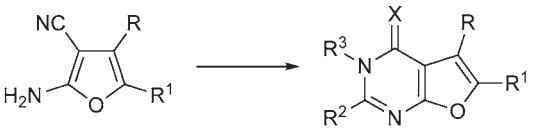


Entry	*R*	R^1	R^2	R^3	*Yield* (%)	*Conditions*
a	Me	Me	Me_2N	Cl	41	i
b	Et	Et	Me_2N	Cl	54	i
c	2,5-Me_2-thiophene		H	NH_2	63	ii
d	H	4-$MeOC_6H_4$	H	NH_2		iii
e	H	Ph	H	NH_2		iii
f	H	4-ClC_6H_4	H	NH_2		iii
g	H	4-MeC_6H_4	H	NH_2		iii
h	Ph	Ph	H	NH_2		iii
i	3,4,5-$(MeO)_3C_6H_2$		H	NH_2	50	iii
j	3,4,5-$(MeO)_3C_6H_2$		OH	NH_2	60	iv
k	3,4,5-$(MeO)_3C_6H_2$		SH	NH_2	55	iv

(109)

A number of structures, **306**, have also been obtained from **304l–r** by use of different cyclizing agents. For instance, **306a** is produced from **304a** upon treatment with carbon disulfide (Equation 110) <1995IJH191>. A 6-substituted amino phenyl analog of **306a** was formed under identical conditions <1997MI610>. Using a series of acid chlorides converts **304b** into the corresponding 4-oxo compounds <2003BCJ203>.

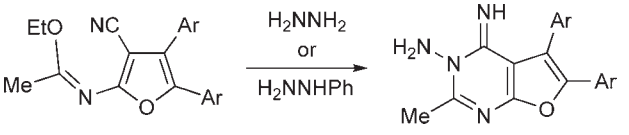
Compounds such as **304**, when treated with triethyl orthoacetate, produce the ethoxyethylideneamino derivative **307** (Equation 111), which can also serve to generate furo[2,3-*d*]pyrimidines such as **308** when allowed to react with cold hydrazine <1995MI177, 1998IJH147>. Treatment of **307b** with phenylhydrazine affords the *N*-phenyl analog of **308b** (65%) <1995MI177>.



304 306

Entry	R	R^1	R^2	R^3	X	Yield (%)	Conditions
l	3,4,5-MeO_3-C_6H_2	3,4,5-MeO_3-C_6H_2	SH	H	S	50	i
m	Ph	Ph	Ph	H	O	82	ii
n	Ph	Ph	Me	H	O	74	ii
o	Ph	Ph	CH_2Cl	H	O	80	ii
p	Ph	Ph	C_7H_{15}	H	O	73	ii
q	Ph	Ph	$C_{11}H_{25}$	H	O	81	ii
r	Ph	Ph	3-pyridyl	H	O	85	ii

(110)

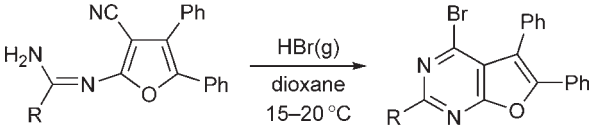


307 308

a: Ar = Ph (70%)
b: Ar = 2-furyl (61%)

(111)

Other chemically modified amino groups have found use as precursors to furo[2,3-*d*]pyrimidines. The imino structure **309** has been successfully transformed into 4-bromo products **310** (Equation 112) <1999H(51)2723>.

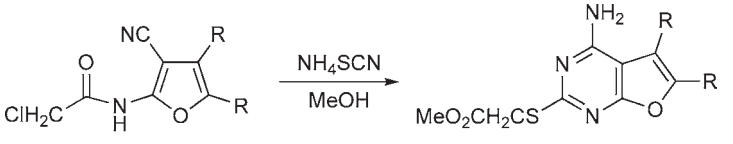


309 310

a: R = CH_2Cl (58%)
b: R = $CHCl_2$ (34%)

(112)

The corresponding amides, **311**, upon treatment with ammonium thiocyanate give **312**, presumably through an intermediate thiazolidone species (Equation 113) <2001JHC507>.

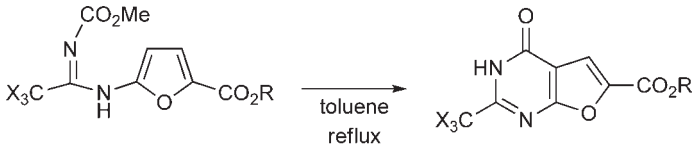


311 312

a: R = Me (63%)
b: R = Ph (72%)

(113)

If a suitable functionality can be incorporated into the amine component of the furan ring, then the adjacent cyano group is not necessary for ring closure. Such is the case with **313** (Equation 114) where all of the requisite atoms for formation of a pyrimidine ring are present. It is sufficient to simply heat **313** in toluene to effect ring closure to **314** <2002SC3749>. A poor yield of the 2-morpholino-4-thione analog of **314** is described in a two-step process commencing with *N*-(5-methoxycarbonyl-2-furyl)-4-morpholinecarboximidoyl chloride <1997MI501>.

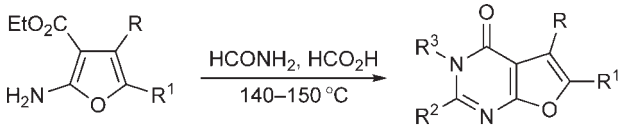


313 **314**

(114)

a: X = F; R = Me (81%)
b: X = Cl; R = Me (86%)
c: X = F; R = Et (79%)
d: X = Cl; R = Et (83%)
e: X = F; R = Pr^i (86%)
f: X = Cl; R = Pr^i (89%)

Having a carboethoxy group in lieu of the cyano group on the furan ring has been used to generate 4-oxo derivatives. Thus **315** in hot formamide/formic acid is transformed into **316a** and **316b** (Equation 115) <2004HCA956>. The microwave-assisted reaction of **315c** with substituted thioureas generated a series of **316** in quite good yields, of which several are listed <2005IJB581>.



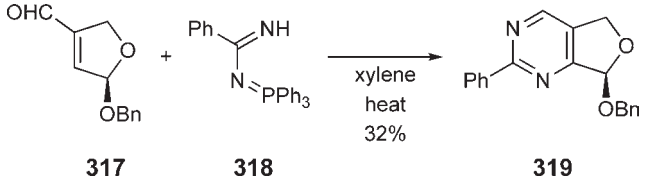
315 **316**

(115)

a: R = CO_2Et; R^1 = 4-$O_2NC_6H_4$; $R^2 = R^3$ = H (21%)
b: R = CO_2Et; R^1 = 3-$O_2NC_6H_4$; $R^2 = R^3$ = H (46%)
c: R = R^1 = Ph; R^2 = SH; R^3 = 4-ClC_6H_4 (87%)
d: R = R^1 = Ph; R^2 = SH; R^3 = 4-MeC_6H_4 (79%)
e: R = R^1 = Ph; R^2 = SH; R^3 = 4-$MeOC_6H_4$ (91%)
f: R = R^1 = Ph; R^2 = SH; R^3 = 4-$O_2NC_6H_4$ (92%)

10.07.6.5.2 Furo[3,4-*d*]pyrimidines

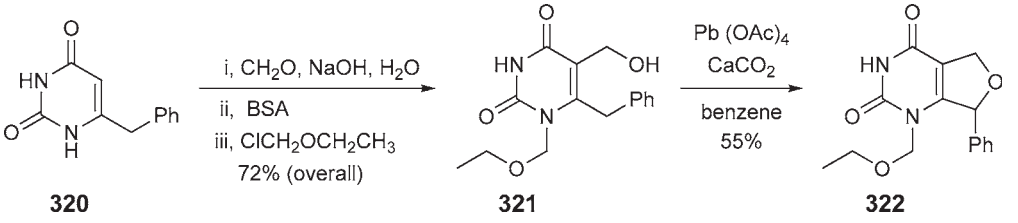
None of the examples cited in this section contains an aromatic furan ring. With one exception all of the compounds here were obtained by annulating the oxygen-containing five-membered ring onto a suitably substituted pyrimidine ring. The exception involves the condensation of (*R*)-2-(benzyloxy)-2,5-dihydrofuran-4-carboxaldehyde **317** with *N*-triphenylphosphoranilidebenzamidine **318**, under thermal conditions, to give the new fused pyrimidine **319** in low yield (**Scheme 27**) <1999SL1265>.



317 **318** **319**

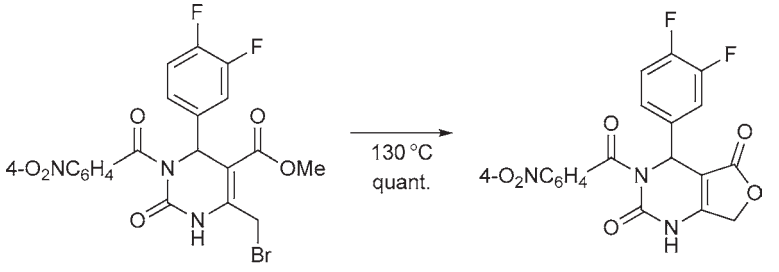
Scheme 27

Furoannelated analogs of uracil acyclic nucleosides were prepared as compounds with potential as anti-HIV agents (HIV = human immunodeficiency virus). Hence, 6-benzyluracil **320** is converted to the precursor **321** first by hydroxymethylation, silylation *in situ* with bis(trimethylsilyl)acetamide (BSA), then by alkylation (**Scheme 28**) <2001S559>. Ring closure to **322** was effected by treatment with lead tetraacetate and calcium carbonate <2004AP148>.



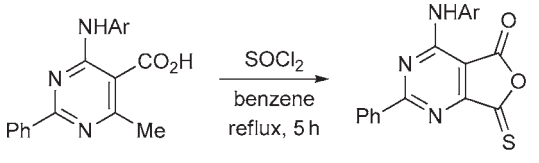
Scheme 28

An unusual approach to the synthesis of furo[3,4-*d*]pyrimidinones is shown in Equation (116). Structure **323** is transformed into **324** by heating the compound neat in an oil bath in near-quantitative yield <2000BML175>.



(116)

In what may be the simplest reaction in this section, a series of pyrimidine-5-carboxylic acids **325** were heated with thionyl chloride to produce **326** (Equation 117) in which a yield is reported only for **326f** <1994APH55>.

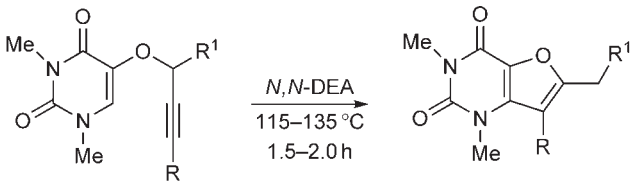


(117)

a: Ar = Ph
b: Ar = 4-ClC_6H_4
c: Ar = 2-ClC_6H_4
d: Ar = 4-$EtOC_6H_4$
e: Ar = 4-MeC_6H_4
f: Ar = 4-HOC_6H_4 (78%)

10.07.6.5.3 Furo[3,2-*d*]pyrimidines

There are two synthetic pathways to the very few examples of this class of compound. The first follows a scheme shown in CHEC-II(1996) <1996CHEC-II(7)229> in which a propynyloxy precursor **327** undergoes a [3,3]-sigmatropic rearrangement, followed by enolization and cyclization in hot *N*,*N*-diethylaniline (*N*,*N*-DEA) to give the furopyrimidines **328** (Equation 118) <1998JOC9997, 1997JCM309>. In the latter study, yields were described as between 80% and 90% but not specifically assigned to a structure.

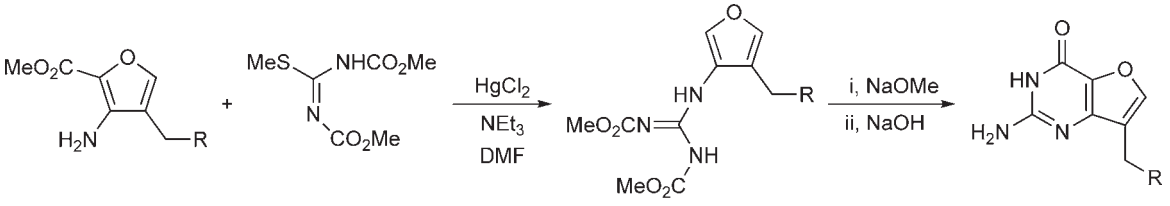


327 **328**

(118)

Entry	R	R^1	Yield (%)	Entry	R	R^1	Yield (%)
a	$PhOCH_2$	H	80	**f**	H	H	
b	$4\text{-}ClC_6H_4OCH_2$	H	75	**g**	H	Me	
c	$2\text{-}MeC_6H_4OCH_2$	H	72	**h**	CH_2OH	H	
d	$2,4\text{-}Me_2C_6H_3OCH_2$	H	80	**i**	CH_2Cl	H	
e	$2,3\text{-}Me_2C_6H_3OCH_2$	H	72				

An alternative, though less efficient, method for the synthesis of furo[3,2-*d*]pyrimidines commences with a furan with adjacent amino and ester functionalities. Compound **329** serves as this precursor (**Scheme 29**). The amino group was remarkably resistant to guanylation using standard methodology. The more reactive 1,3-bis(carbomethoxy)-2-methyl-2-thiopseudourea **330** effected condensation to give the adduct **331**. While **331** could be isolated, it was found to be more convenient to carry out both cyclization and hydrolysis steps without isolation of intermediates to provide the desired **332** <1999JHC423>.



329 **330** **331** **332**

a: R = 3-pyridyl (yield not given)
b: R = Ph (36%)

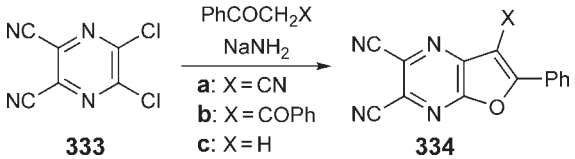
Scheme 29

10.07.6.6 Furopyrazines

The relatively small attention being paid to furopyrazines continues, as shown by the limited amount of research describing these compounds.

10.07.6.6.1 Furo[2,3-*b*]pyrazines

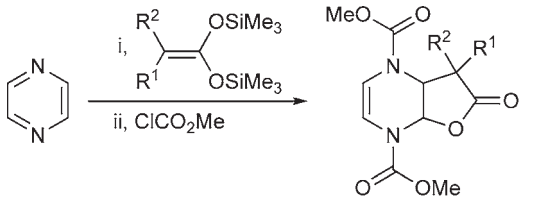
One of the very few reports in this area is an extension of work seen previously in the synthesis of pyrrolo[2,3-*b*]pyrazines. If the pyrazine **333** is permitted to react with activated methylene compounds bearing at least one α-carbonyl group, the oxygen analogue **334** is produced (Equation 119) instead of the nitrogen system (no yields given) <1998JCM284>.



333 **334**

(119)

The use of an unsubstituted heterocycle as a precursor in synthetic reactions is relatively rare. For this reason, the reaction described in Equation (120) is shown. Unsubstituted pyrazine **335** is first treated with bis(trimethylsilyl)-ketene acetals, followed by treatment with methyl chloroformate. The result is the nonaromatic products **336** <2005EJO3724, 2005TL3449>.



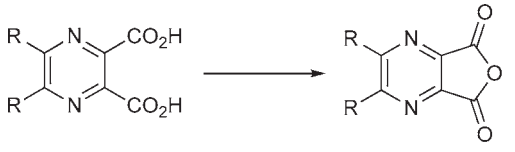
335 336

a: $R^1 = R^2 = Me$ (47%)
b: $R^1 = R^2 = (CH_2)_5$ (58%)
c: $R^1 = H$; $R^2 = Pr^i$ (36%)

(120)

10.07.6.6.2 Furo[3,4-*b*]pyrazines

This class of compound continues to be largely ignored in the chemical literature. Whatever interest there is in the furo[3,4-*b*]pyrazines is focused on formation of cyclic anhydrides. Equation (121) portrays the syntheses of **338** commencing from the intermediate dicarboxylic acid **337**. Thus **337a** is heated in acetic anhydride to give the known **338a** (no yield given) <1996SC617>, while **337b** is heated with oxalyl chloride in THF, with a trace amount of pyridine, to give the corresponding **338b** <2003HCA2149>.



337 338

a: R = H
b: R = Cl (49%)

(121)

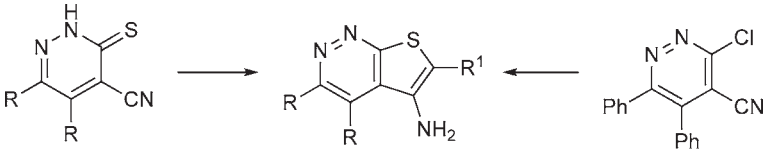
The interest in compounds of this type appears to be in their reactivity as anhydrides.

10.07.6.7 Thienopyridazines

A review describing the syntheses of thieno[2,3-*c*]pyridazines, thieno[3,2-*c*]pyridazines, thieno[2,3-*d*]pyridazines, and thieno[3,4-*d*]pyridazines has been published recently <2004PS(179)321>.

10.07.6.7.1 Thieno[2,3-*c*]pyridazines

Perhaps the most common approach to a wide variety of thieno[2,3-*c*]pyridazine derivatives involves the reaction of a cyano pyridazinethione such as **339** with a functionalized alkylating agent, followed by cyclization in the basic medium, to give compounds of structure **340** (Equation 122). Thus **339a** gives **340a** (no yield given) <1994PS(86)203>, **339b** gives **340b** <1996M537>, **339c** affords **340c** <1996M739>, **339d** produces **340d** (no yield given) <2004JCCS1325, 2005MI413>, and **339e** provides the corresponding example of **340e** <2005JCM270>.



339 340 341

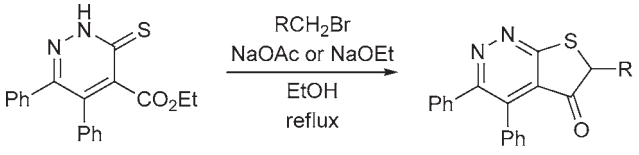
a: R = 2-furyl; $R^1 = CO_2Et$
b: R = Ph; $R^1 = CONH_2$ (75%)
c: R = Ph; $R^1 = CN$ (70%)
d: R = Me; $R^1 = CO_2Et$
e: R = 2-pyridyl; $R^1 = COMe$ (75%)
f: R = Ph; $R^1 = CO_2Et$

(122)

Additional examples of similar reactions involving two different substituents (R) on the pyridazine ring have also been reported <2003BKC1181>.

An alternative route begins with **341** which is treated with ethyl thioacetate in the presence of K_2CO_3 and the resulting intermediate is cyclized to give **340f** <1997H(45)1319>; a monophenyl derivative (56%) is prepared in the same way <2005JHC661>.

In a parallel sequence, the pyridazine derivative **342** reacts with bromomethyl derivatives to give **343** (Equation 123) <1999M1117>.

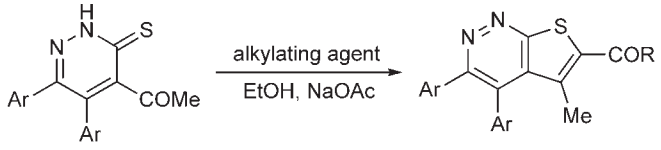


342 **343**

a: R = PhCO (90%)
b: R = 4-BrC_6H_4CO (95%)
c: R = PhCONH (84%)
d: R = 4-MeC_6H_4CONH (86%)
e: R = 4-ClC_6H_4CONH (84%)
f: R = CN (70%)
g: R = CO_2Et (74%)
h: R = COMe (69%)

(123)

If, however, the ketone **344** is used instead of the ester **342**, reaction with ethyl bromoacetate produces the fully aromatic **345** (Equation 124) <2004EJC427>. Compound **344a** has been alkylated with ethyl chloroacetate and 4-chlorophenacyl chloride to give **345a** (52%) and 2-(4-chlorobenzoyl)-3-methyl-4,5-diphenylthieno[2,3-*c*]pyridazine **345b** (50%), respectively <1998PHA839>. Similarly **344**, upon treatment with phenacyl bromide, leads to the corresponding **345** <2004EJC427>. Specific yields of products were not given.

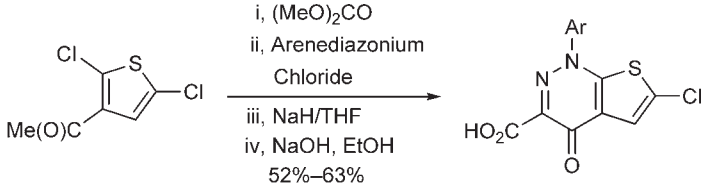


344 **345**

a: Ar = Ph; R = OEt
b: Ar = Ph; R = 4-ClC_6H_4
c: Ar = 4-$MeOC_6H_4$; R = OEt
d: Ar = Ph; R = Ph
e: Ar = 4-ClC_6H_4; R = Ph
f: Ar = 4-$MeOC_6H_4$; R = Ph

(124)

Although the majority of syntheses of this ring system use a substituted pyridazine as the precursor, there is one example of a synthesis that starts with a thiophene such as **346** and leads to **347** in three steps (Equation 125) <1997JPR284>.



346 **347**

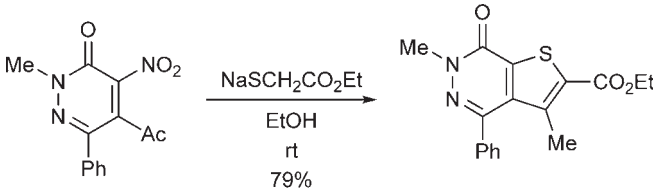
a: Ar = Ph (55%)
b: Ar = 4-FC_6H_4 (52%)
c: Ar = 4-ClC_6H_4 (60%)
d: Ar = 4-BrC_6H_4 (63%)
e: Ar = 4-$MeOC_6H_4$ (52%)
f: Ar = 4-MeC_6H_4 (56%)

(125)

10.07.6.7.2 Thieno[2,3-*d*]pyridazines

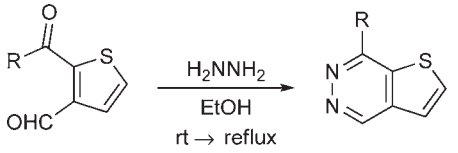
The chemistry of this series parallels that of the nitrogen and oxygen analogs. Hence the synthesis of thieno[2,3-*d*]pyridazines can be accomplished from either a pyridazine or thiophene ring precursor.

Reaction of **348** with the ethyl thioglycolate anion affords ethyl thieno[2,3-*d*]pyridazine-2-carboxylate **349** in excellent yield <1994S669> (Equation 126).



348 **349** (126)

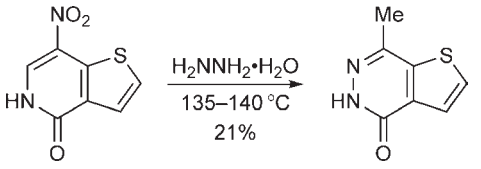
A two-step synthesis of **351** has been accomplished from thiophene **350** in excellent yields (Equation 127) <1999JOC394>.



350 **351** (127)

a: R = 3-thienyl (94%)
b: R = 4-MeOC$_6$H$_4$ (92%)

One example of the formation of a thieno[2,3-*d*]pyridazine **353** via rearrangement of thienopyridine **352** has been accomplished, albeit in poor yields, by treatment with hydrazine (Equation 128) <1995RJO273>.



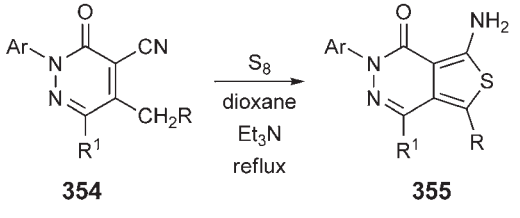
352 **353** (128)

10.07.6.7.3 Thieno[3,4-*c*]pyridazines

There have been no reports of the synthesis of compounds in this class of ring system.

10.07.6.7.4 Thieno[3,4-*d*]pyridazines

Clearly the most common approach to the synthesis of thieno[3,4-*d*]pyridazines, such as **355**, proceeds via the reaction of a suitably substituted pyridazine **354** and elemental sulfur (Equation 129) <1995T12745,1995JCM488, 1996PJC589, 1997HAC29, 1997IJB612, 1999JCM648, 2001JHC685>.



354 **355** (129)

Entry	*R*	*R*$_1$	*Ar*	*Yield (%)*
a	Me	CO_2Me	Ph	77
b	Me	CO_2Me	4-MeC_6H_4	61
c	Me	CO_2Me	4-$MeOC_6H_4$	69
d	Me	CN	Ph	88
e	H	CO_2Et	4-$MeOC_6H_4$	62
f	H	CO_2Et	Ph	

The thio analog of **355** can be obtained by commencing with a pyridazinethione <2000MI389>.

10.07.6.7.5 Thieno[3,2-*c*]pyridazines

There were no reports of the synthesis of compounds in this class of ring system.

10.07.6.8 Thienopyrimidines

10.07.6.8.1 Thieno[2,3-*d*]pyrimidines

10.07.6.8.1(i) Syntheses from pyrimidines

In nearly all cases of syntheses from pyrimidines, the presence of a sulfur atom at position 6 is a prerequisite. Having either a cyano group or a carboalkoxy group at position 5 represents the majority of compounds used in the preparation of thieno[2,3-*d*]pyrimidines.

The elaboration of products that contain nonfunctional groups at positions 2 and 4 has been one of the more frequent approaches. Thus, pyrimidines **356** lead to 5-amino products **357**. Compound **356a** is first alkylated at sulfur with chloroacetonitrile and then cyclized in basic medium to give **357a** (Equation 130) <1997PHA500>. Similarly **356a** can be alkylated with a variety of activated methylene compounds and cyclized in base to give **357b–f** <2005PS(180)375, 1999PHA858>. Fluorine can be introduced into position 6 by alkylating **356a** with $ClCH(F)CO_2Et$ followed by cyclization to **357g** <1998BCJ2387>. 4-Methylpyrimidines **356h** are converted to **357h** and **357i** in an analogous manner <1998M523>. Similarly, **357j–l** are obtained from **356h** <2002PS(177)303> as are **357m** and **357n** from **356m** and **356n** <2003PS(178)737>.



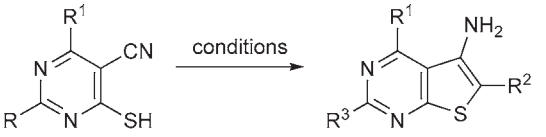
356 **357**

Entry	*R*	*R*^{1}	*Yield (%)*	*Conditions*	*Entry*	*R*	*R*^{1}	*Yield (%)*	*Conditions*
a	Ph	CN	60	i	**h**	Me	CN	88	iv
b	Ph	CO_2Et	85	ii	**i**	Me	$CONH_2$	82	iv
c	Ph	$COCH_3$	81	ii	**j**	Me	COMe	77	v
d	Ph	$CONH_2$	83	ii	**k**	Me	COPh	86	v
e	Ph	COPh	85	ii	**l**	Me	CO_2Et	80	v
f	Ph	CONHPh	85	ii	**m**	Me	CN	70	vi
g	Ph	F	60	iii	**n**	Me	NHPh	73	vi

(130)

i, (a) $ClCH_2CN$, NaOAc, EtOH (b) NaOEt, EtOH
ii, (a) R^1CH_2X, NaOAc (b) NaOEt, EtOH
iii, (a) $ClCH(F)CO_2Et$, TEA, THF (b) TEA, EtOH
iv, (a) $ClCH_2CN$ or $ClCH_2CCO_2Et$, NaOEt; (b) NaOEt, EtOH
v, (a) $ClCH_2R^{1'}$, K_2CO_3, EtOH, heat
vi, (a) $ClCH_2CN$ or $ClCH_2CONHPh$, NaOAc, EtOH; (b) NaOEt, EtOH

The chemistry is essentially the same with pyrimidines bearing one or two groups at positions 2 and 4 that are not either an alkyl or aryl moiety. So **358a** is converted to **359a** (Equation 131) <2003MI11>, **358b** produces **359b** <2003MI72>, **358c** gives **359c** <2004JCCS1381, 2005CHJ211>. If **358d** is treated with an activated chloromethyl compound, both of the thione groups are alkylated. In the cyclization process, obviously, only the group at position 6 participates to give **359d–j** <2002JHC863, 2005JHC841>. Similar products, in which the pyrimidine ring bears a 2-amino substituent, have been described <1998CHE688, 2003IZV2063>. In addition, 2-alkoxy derivatives **358k–m** are transformed into **359k–m** without isolation of the intermediate alkylated compounds <1998H(48)1157>. Examples of 2-aryl-4-thiomethyl products have also been described <2005PHA75>.



358 **359**

Entry	*R*	R^1	R^2	R^3	*Yield (%)*	*Conditions*
a	SEt	2-Thienyl	CO_2Et	SEt	44	i
b	SMe	2-Furanyl	COMe	SMe	35	ii
c	SMe	4-BrC_6H_4-4-oxazolyl	CO_2Et	SMe	83	iii
d	SH	SMe	CO_2Bu^t	$SCH_2CO_2Bu^t$	48	iv
e	SH	SMe	$CON(CH_2)_2O$	$SCH_2CON(CH_2)_2O$	56	iv
f	SH	SMe	$CONH_2$	SCH_2CONH_2	55	iv
g	SH	SMe	CO_2Me	SCH_2CO_2Me	37	iv
h	SH	SMe	CN	SCH_2CN	54	iv
i	SH	SMe	COPh	SCH_2COPh	33	iv
j	SH	SMe	COC_6H_4-4-Br	$SCH_2COC_6H_4$-4-Br	48	iv
k	OMe	Ph	$CONH_2$	OMe	33	v
l	OEt	Ph	CO_2Et	OEt	58	v
m	OPr^i	Ph	CN	OPr	65	v

(131)

i, $ClCH_2CO_2Et$, acetone, K_2CO_3, heat
ii, $ClCH_2COCH_3$, acetone, K_2CO_3, heat
iii, (a) $ClCH_2CO_2Et$, NaOAc (b) NaOEt, EtOH
iv, (a) $ClCH_2R_2$, TEA or NaOMe (b) NaOMe, MeOH, heat
v, $ClCH_2R_2$, K Rhodanide, NaOEt, heat

The use of a chloro group at position 6 of the pyrimidine ring in lieu of a sulfur-containing group has been exploited extensively. Ultimately the difference is merely how the sulfur atom is introduced. Here the sodium salt of a sulfur component is used to displace the chlorine atom. Equation (132) illustrates this approach to the synthesis of thieno[2,3-*d*]pyrimidines. In some of these examples, the chloro group at position 4 is ultimately replaced by an amino group. So, **360a** is first aminated at position 4 and this intermediate is reacted with the sodium salt of ethyl thioacetate and cyclized to form the diamino products **361a–c** <1995JCM286, 1995LA1703>. The same process utilizing aromatic amines in the first stage has produced **361d–i** <1999C140, 2000C127>. Similar chemistry has produced **361j** in which both chlorines have been displaced by the sodium salt of ethyl thioacetate.



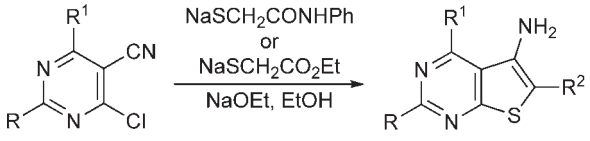
360 **361**

Entry	*R*	*Yield (%)*	*Conditions*	*Entry*	*R*	*Yield (%)*	*Conditions*
a	NHMe	90	i	**f**	NHC_6H_4-4-F	79	i
b	$NHPr^i$	84	i	**g**	NHC_6H_4-3-CF_3	65	i
c	$NHBu^n$	80	i	**h**	NHC_6H_3-2,4-F_2	70	i
d	NHC_6H_4-2-F	86	i	**i**	NHPh	68	i
e	NHC_6H_4-3-F	76	i	**j**	SCH_2CO_2Et	70	ii

(132)

i, (a) R_2NH_2, EtOH (b) $NaSCH_2CO_2Et$, EtOH (c) NaOEt, EtOH, heat
ii, (a) $NaSCH_2CO_2Et$, EtOH (b) NaOEt, EtOH

Two other examples involving a 6-chloropyrimidine have been reported. The chloropyrimidine **362a** reacted with the sodium salt of mercaptoacetic acid anilide. Cyclization to **363a** occurs in the usual manner (Equation 133) <1996MI83>. Likewise, **363b** is produced from **362b** in good yield <2000S255>.

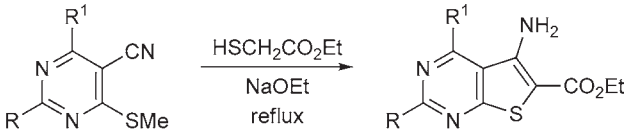


362 **363**

(133)

a: R = SMe; R^1 = H; R^2 = CONHPh (82%)
b: R = NMe_2; R^1 = NH_2; R^2 = CO_2Et (93%)

The thiomethyl group has also been employed as a leaving group. Treatment of **364a–f** with the anion of ethyl mercaptoacetate followed by sodium ethoxide generates **365a–f** (Equation 134) <2003JIC311>.

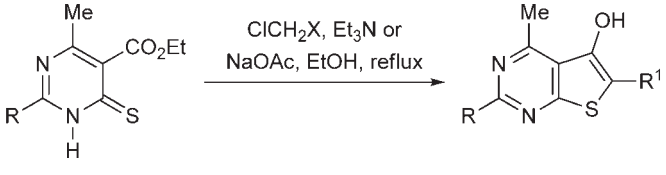


364 **365**

(134)

a: R = H; R^1 = OH
b: R = Me; R^1 = OH
c: R = CF_3; R^1 = OH
d: R = Ph; R^1 = NH_2
e: R = 2-pyridyl; R^1 = NH_2
f: R = 4-pyridyl; R^1 = NH_2

Replacing the cyano group at position 5 with a carboethoxy group allows cyclization to generate 5-hydroxy derivatives. As in previous examples, a sulfur atom at position 6 of the pyrimidine ring is necessary for reaction. The precursor may be the thione (and subsequently alkylated) or a thioalkyl moiety introduced by displacing a chlorine atom. For convenience, the precursors here will be assumed to be the pyrimidinethione. Thione **366a** is alkylated with chloroacetonitrile and cyclized, without isolation of the intermediate, to **367a** (Equation 135) <1995PJC1033>. Alkylation of **366b** with a variety of activated methylene compounds gives **367b–e** <2001BKC311>. In similar fashion, **367f–h** were produced from **366f** <2002JCCS1057, 2002PS(177)2745>. A pyrimidine with a phenylthiazole group at position 4 also proceeds to give similar structures <1999JPC147>.

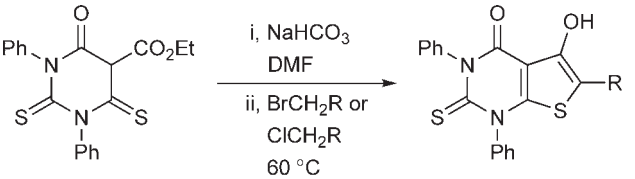


366 **367**

(135)

Entry	*R*	R^1	*Yield* (%)	*Entry*	*R*	R^1	*Yield* (%)
a	PhCH=CH	CN	60	**e**	4-ClC_6H_4	COPh	60
b	4-ClC_6H_4	CO_2Et	60	**f**	Ph	CO_2Et	
c	4-ClC_6H_4	$CONH_2$	70	**g**	Ph	COPh	
d	4-ClC_6H_4	CONHPh	75	**h**	Ph	4-ClC_6H_4	

N,*N*′-Diphenylbarbituric acid derivative **368** (Equation 136) can be monoalkylated at one of the thiones and cyclized in the usual way to **369** <1997FA547>.

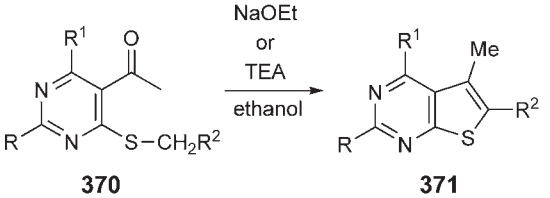


368 → **369**

a: R = CN (95%)
b: R = COMe (96%)
c: R = CO_2Et (97%)

(136)

Much as does the carboethoxy group on the pyrimidine ring, the acetyl group serves as a suitable condensation partner, along with the 5-methylene group in an adjacent position. Base-promoted condensation of **370a–d** afforded **371a–d** in yields of 50–60% (Equation 137) <1995PJC887>, while the 2-thienylpyrimidine **370e** produced **371e** <1997JIC58>. Compounds **371f** and **371g** were obtained from **370f** and **370g** in identical fashion <2003EJC>. The phenylethenyl analogs **371h** and **371i** have also been prepared <2002MI64>. Without isolation of the intermediate acetyl compound **370i**, obtained by acetylation, **371i** is formed <1997JME3694>. If the phenyl ring at position 2 is connected to two pyrimidine rings, cyclization occurs to give a 'dimeric' structure analogous to **371b** <1995PS(102)65, 1998PJC61>.

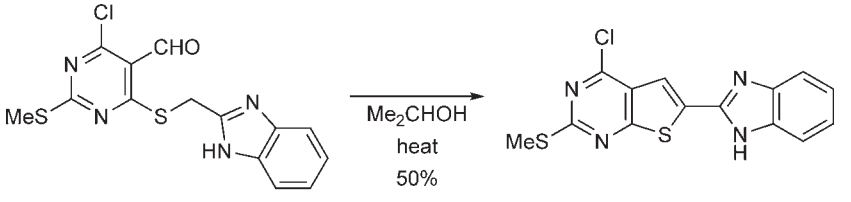


370 → **371**

Entry	*R*	R^1	R^2	*Yield (%)*	*Conditions*
a	Ph	Me	CH_2CONH_2		NaOEt
b	Ph	Me	CH_2CO_2Et		NaOEt
c	4-ClC_6H_4	Me	CH_2CONH_2		NaOEt
d	4-ClC_6H_4	Me	CH_2CO_2Et		NaOEt
e	2-Thienyl	Me	CO_2Et	60	NEt_3
f	4-BrC_6H_4	Me	CO_2Et	50	NEt_3
g	4-BrC_6H_4	Me	CONHPh	60	NEt_3
h	PhCH=CH	Me	COPh	65	NEt_3
i	PhCH=CH	Me	CO_2Et	70	NEt_3
j	NH_2	NH_2	H	77	$KHCO_3$

(137)

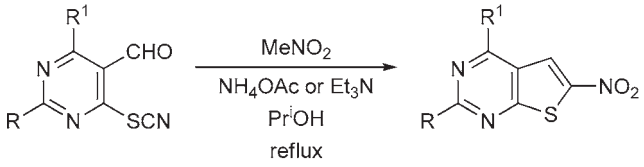
Not surprisingly, the formyl group at position 5 has been employed to produce thieno[2,3-*d*]pyrimidines with no substituent at position 5 of the bicyclic product. Structures such as **372**, generated from the chloropyrimidine and (benzimidazol-2-yl)methanethiol, undergo cyclization to **373** (Equation 138) <2003HCO89>.



372 → **373**

(138)

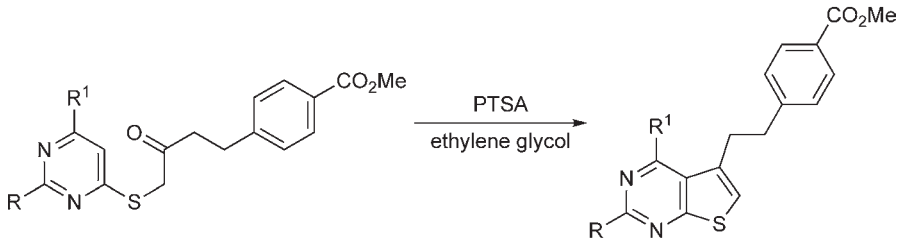
A series of thiocyanates **374** are condensed with nitromethane which cyclizes immediately to **375** (Equation 139) <2004CHE1352>.



374 **375** (139)

a: R = H; R^1 = NMe_2 (50%)
b: R = H; R^1 = piperidino (42%)
c: R = MeS; R^1 = NMe_2 (67%)
d: R = MeS; R^1 = piperidino (54%)
e: R = MeS; R^1 = Cl (10%)

A cyclization reaction occurs when **376** is heated with *p*-toluenesulfonic acid (PTSA) to give the folate analog **377** (Equation 140) <1996H(43)349>.



376 **377** (140)

a: R = NH_2; R^1 = OH (74%)
b: R = R^1 = NH_2 (55%)

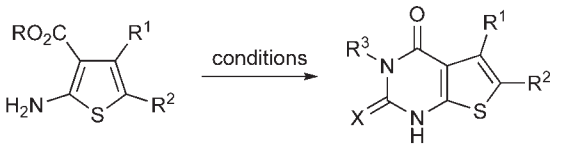
10.07.6.8.1(ii) Syntheses from thiophenes

As with other syntheses originating from a five-membered heterocycle, annulation of a pyrimidine ring occurs readily when an amino group is adjacent to a carbonyl-containing functional group. Therefore the majority of examples in this section have a precursor with these structural characteristics. All examples, without exception, have a 4-oxo group in the product. Some have an oxo (or thioxo) group at position 2. This structural type will be described first. Structure **378** is readily converted to **379** by means of a variety of reagents (Equation 141).

The reaction of **378a** with KSCN affords **379a** in good yield <1995EJH627>. If, however, **378b–d** are allowed to react with ethyl isocyanatoacetate followed by cyclization in base, **379b–d** are formed in very good yield <1998CPB1724>. On the other hand, alkyl or aryl isocyanates or isothiocyanates allow formation of **379e–i** from **378e** <1999EJC469>. Additional examples using this method have also been described <2003JME113, 2005BML1885, 2001BML1119>. An extension of this method using other aryl isothiocyanates leads to the formation of **379j–n** from **378j–n** <2002MI717>.

An alternative to *N*-aryl derivatives described above is the use of *N*-aryl thioureas as the cyclization reagent. In this case, a microwave-assisted reaction gave significantly higher yields of **379o–q** from **378o–q** <2003BKC1038>. Only a few representative examples are provided here.

The following examples, although formally the same as those described above, are considered separately because of the reagents used to effect cyclization and the similarity of the product structures. Treatment of **380a** with CS_2, then Me_2SO_4, followed by hydrazine, leads to the corresponding structure **381a** (Equation 142) <1997IJB566, 2003IJH336, 2000AF904>. The initial intermediate is a dithiocarbamate, which, upon methylation, gives the dithiocarbamate ester. A tetramethylene analog was also prepared <2000AF904>.

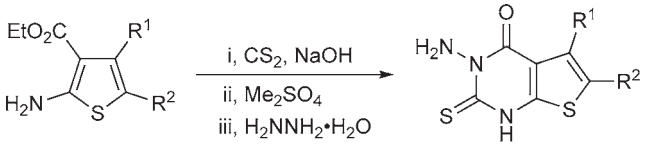


378 **379**

Entry	*R*	R^1	R^2	R^3	*X*	*Yield (%)*	*Conditions*
a	Et	Me	Ph	H	S	70	i
b	Et	Me	4-$MeOC_6H_4$	CH_2CO_2Et	O	96	ii
c	Et	Me	2-$MeOC_6H_4$	CH_2CO_2Et	O	81	ii
d	Et	Me	Ph	CH_2CO_2Et	O	86	ii
e	Et	2-Thienyl	H	Et	O	65	iii
f	Et	2-Thienyl	H	Ph	O	60	iii
g	Et	2-Thienyl	H	Me	S	75	iii
h	Et	2-Thienyl	H	Et	S	70	iii
i	Et	2-Thienyl	H	Bu^n	S	60	iii
j	Et	Me	Me	4-ClC_6H_4	S	85	iv
k	Et	Me	Me	4-MeC_6H_4	S	79	iv
l	Me	H	H	Ph	S	89	iv
m	Me	H	H	4-ClC_6H_4	S	90	iv
n	Me	H	H	Me	S	90	iv
o	Et	Me	CO_2Et	Ph	S	82	v
p	Et	Me	CO_2Et	4-$MeOC_6H_4$	S	82	v
q	Et	Me	CO_2Et	4-O_2N-C_6H_4	S	93	v

(141)

i, (a) KSCN, HCl, dioxane, reflux (b) HOAc, reflux
ii, (a) $OCNCH_2CO_2Et$, pyridine (b) NaOEt, EtOH
iii, appropriate isocyanate or isothiocyanate, pyridine, reflux
iv, (a) SCNAr, EtOH, reflux (b) KOH (c) HCl
v, *N*-arylthiourea, EtOH, K_2CO_3 (solid), MW



380 **381**

(142)

a: $R^1 = R^2 =$ Me (80%)
b: $R^1 =$ H; $R^2 =$ Pr (58%)
c: $R^1 =$ H; $R^2 =$ Ph (50%)
d: $R^1 =$ Me; $R^2 = CO_2Et$ (22%)
e: $R^1 =$ H; $R^2 =$ Et (40%)

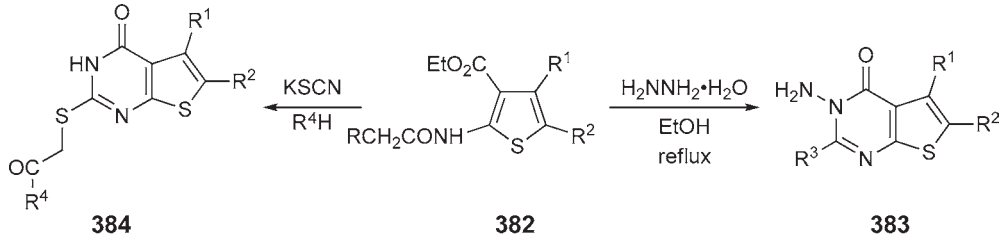
Another report has appeared that follows the same chemical pathway, but there is insufficient information to accurately portray the actual structures produced <1999MI37>.

The use of di-2-pyridylthiocarbonate in lieu of CS_2/Me_2SO_4 accomplishes the same reaction <2002AF448>.

Another reagent has been employed for the preparation of **381a** <1997JME574>. In this case, ammonium thiocyanate provides the structural components for cyclization to occur. A number of other compounds (not shown here) were obtained in this way.

A variation of this method employs thiophosgene in place of CS_2 and Me_2SO_4. Thus **380b** undergoes similar reactions to produce **381b** <2000PHA500> while **381c** is obtained from **380c** <2003JHC869>. Additional examples include the preparation of **381d** and **381e** <2000EJM677>.

Other *N*-amino thieno[2,3-*d*]pyrimidines that possess neither an oxygen nor a sulfur atom at position 2 have been reported. One general approach involves acylation of the amino group on the thiophene precursor. Three different acylating reagents are involved, namely acetyl chloride <2001MI17>, acetic anhydride <2003EJM89>, and chloroacetyl chloride <1997MI105>. These acetylated precursors **382** (Equation 143), when treated with hydrazine, afford the corresponding compounds **383**. For example, **382a** yields **383a** <2001MI17> and **382b** gives **383b** <2003EJM89>. When the chloromethyl intermediate **382c** is allowed to react with a variety of anilines, compounds **382c–f** are formed and the final products are arylaminomethyl derivatives such as **383c–f** <1997MI105>. Additional examples are described.



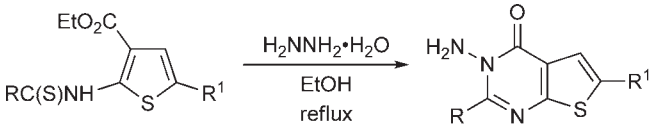
384 **382** **383**

a: R = H; $R^1 = R^2 = R^3$ = Me (76%)
b: R = R^2 = H; R^1 = 2-furanyl; R^3 = Me (57%)
c: R = Cl; $R^1 = R^2$ = Me; $R^3 = PhNHCH_2$ (49%)
d: R = Cl; $R^1 = R^2$ = Me; $R^3 = 4\text{-}MeC_6H_4NHCH_2$ (48%)
e: R = Cl; $R^1 = R^2$ = Me; $R^3 = 4\text{-}MeOC_6H_4NHCH_2$ (51%)
f: R = Cl; $R^1 = R^2$ = Me; $R^3 = 4\text{-}ClC_6H_4NHCH_2$ (49%)
g: $R^1 = R^2$ = Me; R^4 = OEt (34%)
h: $R^1 = R^2$ = Me; R^4 = OH (28%)
i: $R^1 = R^2$ = Me; $R^4 = N(CH_2CH_2)_2O$ (41%)

(143)

If, on the other hand, **382d** is treated only with KSCN, the corresponding **384g–i** are reportedly produced <2000H(53)2363>.

Two other types of *N*-aminothieno[2,3-*d*]pyrimidines fall within the scope of this review. Both involve a thiocarbonyl intermediate, illustrated by **385** (Equation 144). Thus **385a–c** afford respectable yields of **386a–c** upon treatment with hydrazine <1996PHA7>. Other products are described in this citation. Other reports describe similar chemistry <1995FA605, 1995AP231, 2000EJM1065, 2000BML1089, 2001JHC973, 2001JCM817, 2001EJM287, 2003MI89>. Carboxamide derivatives **386d–f** likewise are produced from precursors **385d–f** <2004IZV1257>.

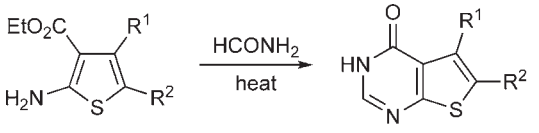


385 **386**

a: R = PhNH; R^1 = Ph (60%)
b: R = 4-MeC_6H_4NH; R^1 = Ph (65%)
c: R = 4-$MeOC_6H_4NH$; R^1 = Ph (60%)
d: R = $CONH_2$; R^1 = Et (61%)
e: R = CONHPh; R^1 = Et (55%)
f: R = $CONHC_6H_4$-4-Cl; R^1 = Et (60%)

(144)

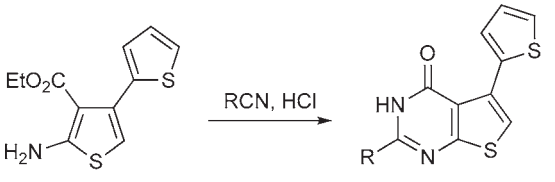
Perhaps the most classical, and most widely used, method for annelating a pyrimidine ring involves cyclization by heating a compound with *ortho*-disposed amino and carboalkoxy groups in formamide. This strategy has been employed in the synthesis of thieno[2,3-*d*]pyrimidines that are devoid of substituents at position 2 on the pyrimidine ring. Equation (145) gives an overview of this method. One straightforward example is **387a** yielding **388a** <1996SC3733> while the isomeric **388b** is produced in quantitative yield <2004OL1991>. Other aryl derivatives are possible, such as **388c** <1999HCO463>. Finally, the ubiquitous dimethyl thiophene **387d** provides **388d** in good yield <2003MI43>.



387 **388** (145)

a: R^1 = Ph; R^2 = H (63%)
b: R^1 = R^2 = Ph (100%)
c: R^1 = 2-benzothiazolyl; R^2 = H (76%)
d: R^1 = R^2 = Me (72%)

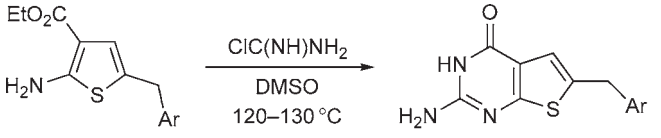
On the other hand, if a substituent at position 2 is desired, other reagents are required for cyclization. Nitriles have proven useful in this instance. If compound **389** is treated with nitriles such as chloroacetonitrile <1999JCM646>, acetonitrile, phenylacetonitrile, malononitrile, and ethyl cyanoacetate <1999APH49>, the corresponding products **390a–e** are formed (Equation 146). An additional report using this method has appeared where the 4-oxo product was not isolated, but rather converted into the 4-chloro derivative *in situ* <2001S2119>. One report cites the use of benzoyl isothiocyanate instead of a nitrile to produce similar structures <2004BMC3891>.



389 **390** (146)

a: R = CH_2Cl
b: R = Me (92%)
c: R = $PhCH_2$ (80%)
d: R = $NCCH_2$ (77%)
e: R = EtO_2CCH_2 (80%)

Another standard method of producing a fused pyrimidine ring is reaction with formamidine, which always provides for no substituent at position 2. However **391** reacts with chloroformamidine, obtained by reaction of cyanamide and HCl, to produce a variety of benzyl derivatives **392** (Equation 147) <2004JHC941> that mimic guanine analogs.

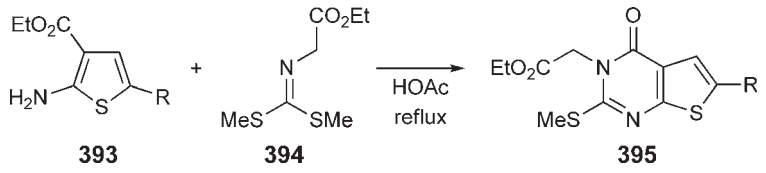


391 **392** (147)

a: Ar = Ph (34%)
b: Ar = 2-MeC_6H_4 (65%)
c: Ar = 2-ClC_6H_4 (24%)
d: Ar = 2-$MeOC_6H_4$ (59%)
e: Ar = 2,4-$Me_2C_6H_3$ (61%)
f: Ar = 2,4-$Cl_2C_6H_3$ (56%)
g: Ar = 2,4-$(MeO)_2C_6H_3$ (63%)
h: Ar = 4-$EtO_2CC_6H_4$ (51%)

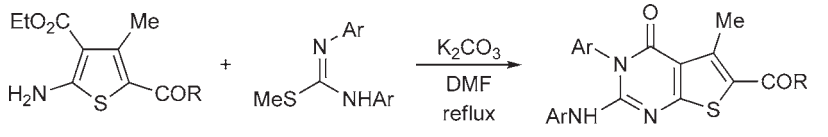
Before leaving the discussion of annulations involving unaltered amino/carboethoxy-substituted thiophenes, there are several lesser-explored reagents that deserve a mention. Early on BMMA reagents (*N*-bis(methylthio)methylene amino esters) were described as a novel method for forming thieno[2,3-*d*]pyrimidines. An example illustrates the use of this reagent (**Scheme 30**). The cyclocondensation of **393** with **394** proceeds smoothly to give **395** <1995H(40)851>.

Cyclocondensation of **396** with alkylthioureas **397** produced a significant number of products **398**, of which a few examples are shown (**Scheme 31**) <2000IJH93>.



393 394 395

Scheme 30

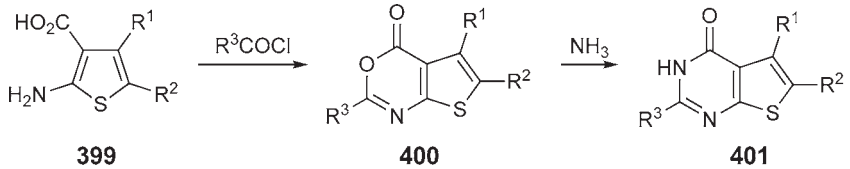


396 397 398

a: R = Me; Ar = 2-EtOC$_6$H$_4$ (59%)
b: R = PhNH; Ar = Ph (53%)
c: R = EtO; Ar = 4-MeC$_6$H$_4$ (76%)

Scheme 31

It is not necessary for the carbonyl functionality on the thiophene ring to be an ester. The carboxylic acid **399**, shown in **Scheme 32**, is converted by reaction with a variety of acid chlorides (or acid anhydrides) into thieno-oxazinones **400**. Reaction of **400** with dry ammonia generates **401** in average yields <2002JCM5>.

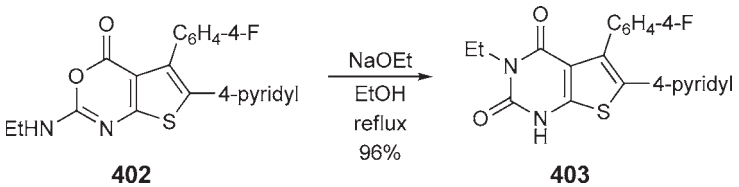


399 400 401

a: $R^1 = R^2 = -(CH_2)_4-$; R^3 = Me (55%)
b: $R^1 = R^2 = R^3$ = Me (52%)
c: $R^1 = R^2$ = Me; R^3 = Et (60%)
d: $R^1 = R^2$ = Me; R^3 = Ph (68%)

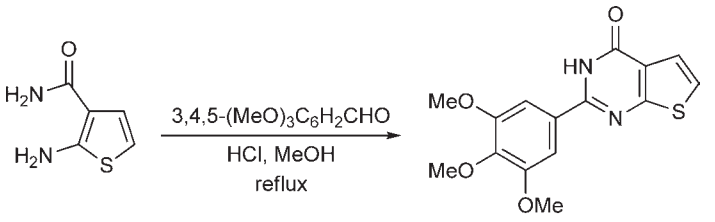
Scheme 32

Although **402** was prepared in a slightly different way than **400**, it also undergoes ring opening and recyclization in basic media to afford an excellent yield of **403** (Equation 148) <2002BMC3113>.



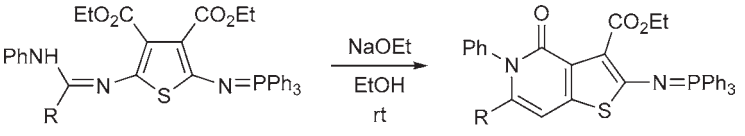
402 403 (148)

An aromatic aldehyde serves as the connecting atom between the two nitrogen atoms in **404** to produce the simple structure **405** in Equation (149) (no yield given) <2005BML3763>.



404 **405** (149)

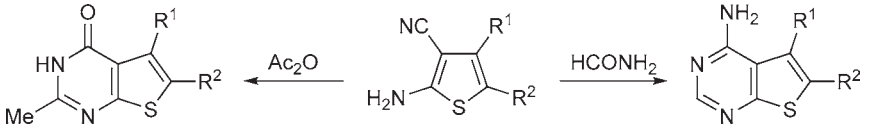
Conversion of the amino group into a Schiff base intermediate offers yet another method for preparing thieno[2,3-*d*]-pyrimidines. Such intermediates **406** are readily cyclized with alkoxide to produce **407** (Equation 150) <2004JOC8366>.



406 **407** (150)

a: R = piperidino (81%)
b: R = morpholino (77%)

When the amino group is left unchanged but the carboethoxy group has been replaced by a cyano group, the products are usually 4-amino derivatives of thieno[2,3-*d*]pyrimidines. Equation (151) features a select group of examples that illustrate this chemistry. So, **408a** undergoes ring annulation when heated in formamide to give **409a** <1996PS271>, **408b** affords **409b** <1996HAC29>, **408c** produces **409c** <1997IJB1126>, **408d** provides **409d** <2003PJS95>, and **408e** gives **409e** <2005JME6066>. If nitriles are used instead of formamide, a substituent at position 2 of the pyrimidine ring is introduced, depending on the nature of the nitrile <1996PS271, 1996HAC29, 1997M687, 2003PJS95>.

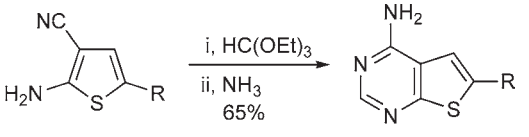


410 **408** **409** (151)

410	408	409
78%	**a**: R^1 = Ph; R^2 = H	66%
62%	**b**: R^1 = Ph; R^2 = CN	80%
82%	**c**: R^1 = Me; R^2 = Bn	85%
	d: $R^1 = R^2$ = Me	76%
	e: R^1 = 4-$O_2NC_6H_4$; R^2 = Me	98%

A 4-oxo-thieno[2,3-*d*]pyrimidine is obtained, however, when acetic anhydride is the cyclization reactant. Here **410a** <1996PS271>, **410b** <1996HAC29>, and **410c** <1997IJB1126> were obtained from the corresponding thiophenes. Other reagents have been employed to give 4-oxo derivatives (ethyl cyanoacetate) <2002JHC877> or 4-thioxo derivatives (CS_2) <2000HAC94>.

One laboratory has made use of triethyl orthoformate as an effective cyclizing agent as shown by the conversion of **411** to **412** (Equation 152) <2001CHC681, 2003CHC171, 2005CAR547>, although the nature of the carbohydrate moiety has been varied.

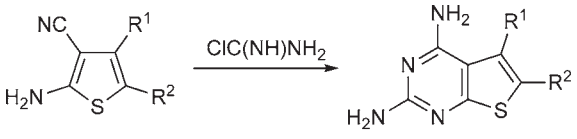


411 **412** (152)

R = α-D-glucopyranosyl

Chloroacetylation of the amino group provides an intermediate that can be cyclized to 2-substituted-4-amino thieno[2,3-*d*]pyrimidines upon treatment with KSCN <1996JPR206>.

Chloroformamidine is also a useful reagent that leads to cyclization of thiophene **413a** to the diamino product **414a** (Equation 153) <1996JHC1959>; **413b** gives **414b** <2003EJM605> and **413c** provides **414c** <1997BML1629>.

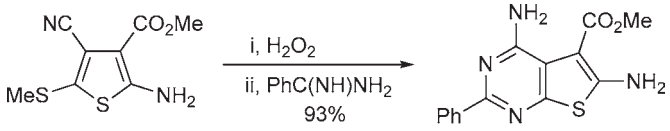


413 **414**

(153)

a: R^1 = Me; R^2 = 2-Br-3,4,5,-$(MeO)_3C_6H$ (23%)
b: R^1 = Me; R^2 = $PhCH_2CH_2$ (45%)
c: $R^1 = R^2$ = 4-$BnOC_6H_4$ (44%)

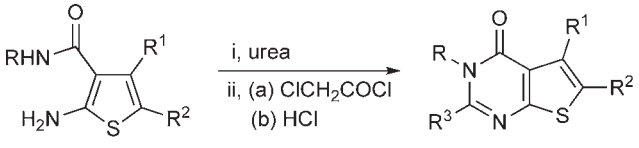
Oxidation of the methylthio group in **415** provides a good leaving group so that the amidine can be introduced to form **416** (Equation 154) <1998PHA227>.



415 **416**

(154)

As seen in another series, an amino group adjacent to a carboxamide group provides a suitable precursor for cyclization. Hence, **417a** upon reaction with urea gives the xanthine analog **418a** (Equation 155) <1995JHC953>. The substituted amide **417b** is first treated with chloroacetyl chloride and then with HCl to afford **418b** <1996AF981>.



417 **418**

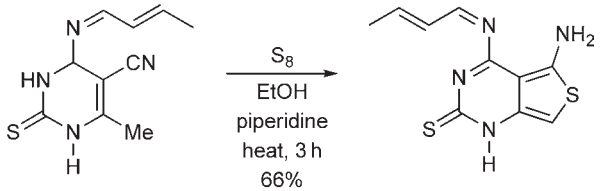
(155)

a: R = R^1 = H; R^2 = Ph; R^3 = OH (75%)
b: R = Ph; $R^1 = R^2$ = Me; R^3 = CH_2Cl (60%)

Isolated examples of syntheses of thieno[2,3-*d*]pyrimidines commencing with either amino- or nitrothiophene possessing no other functionality have been described <2004CHE370, 1996J(P1)417, 1996J(P1)1403>.

10.07.6.8.2 Thieno[3,4-*d*]pyrimidines

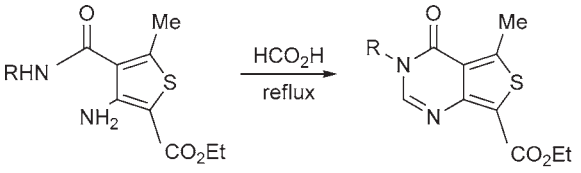
Surprisingly, only one example of the synthesis of thieno[3,4-*d*]pyrimidines has been described starting from a pyrimidine ring. In CHEC-II(1996) <1996CHEC-II(7)229>, substituted 5-cyanouracils, upon reaction with elemental sulfur, led to the formation of compounds in this class. Now the use of a 5-cyanopyrimidino-2-thione **419** under similar conditions (Equation 156) leads to the thienopyrimidine **420** <1997HCO151>.



419 **420**

(156)

The Thorpe–Ziegler reaction has been employed in the synthesis of thieno[3,4-*d*]pyrimidines by providing the thiophene **421**. Heating this compound under reflux in formic acid leads to a series of thienopyrimidines **422** (Equation 157) <2002IZK854>.

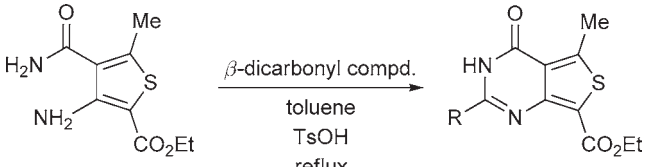


421 **422**

a: R = H (80%)
b: R = $PhCH_2$ (78%)
c: R = *cyclo*-C_6H_{11} (84%)
d: R = O N -$CH_2CH_2CH_2$ (75%)

(157)

If, however, **421a** is allowed to react with a β-dicarbonyl compound, 2-substituted analogs of **422** can be obtained. Thus **421a** with acetylacetone affords **423a** while **421a** with $PhCOCH_2CO_2Et$ leads to **423b** (Equation 158) <2002IZK1879>.

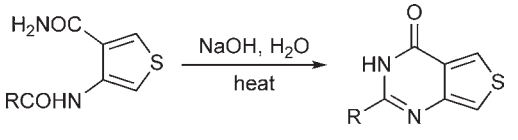


421a **423**

a: R = Me (86%)
b: R = Ph (20%)

(158)

Rather simpler structures have been described for this series of fused ring compounds. Thiophenes **424**, lacking substituents at positions 2 and 5, follow the same pathway. Hence **424** has been cyclized to **425** in the presence of base (Equation 159) <1999BMC297>.

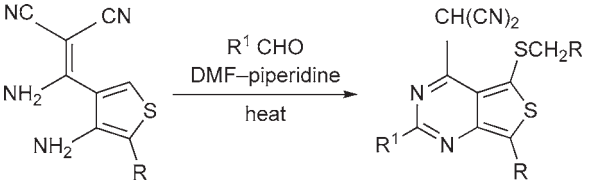


424 **425**

a: R = Me (57%)
b: R = Ph (43%)

(159)

Compound **426** can be readily converted into the thieno[3,4-*d*]pyrimidine **427** by refluxing the corresponding aldehyde in DMF solution (Equation 160) <1994JCM484>.

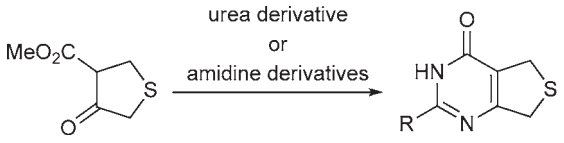


426 **427**

a: R = PhCO; R^1 = Ph (59%)
b: R = CO_2Et; R^1 = H (63%)
c: R = CO_2Et; R^1 = Ph (55%)

(160)

The β-dicarbonyl configuration of **428** has been successfully condensed with either urea or amidine components (Equation 161) to give fused pyrimidine structures **429**. Thus **429a** was obtained from 5-ethylthiourea in methanolic KOH <1995JHC953>, **429b** from urea in DMF at 200 °C <1995JHC953>, **429c** from acetamidine in ethanolic NaOEt <1996T1723>, and **429d** from benzamidine in ethanolic NaOEt <1996T1723>.



428 **429**

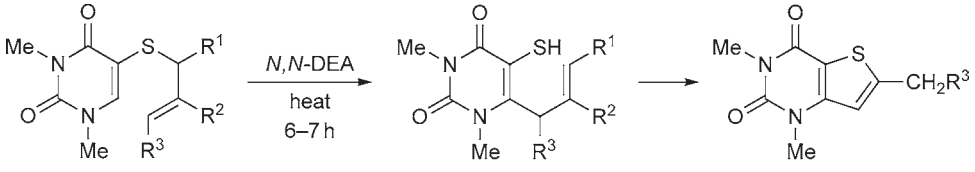
a: R = EtS (83%)
b: R = HO (61%)
c: R = Me (96%)
d: R = Ph (65%)

(161)

10.07.6.8.3 Thieno[3,2-*d*]pyrimidines

Although only a relatively few examples of thieno[3,2-*d*]pyrimidines were described in CHEC-II(1996) <1996CHEC-II(7)229>, there has been a significant interest shown in this series since then. While the vast majority of syntheses originate with a suitably substituted thiophene, some approaches involving pyrimidine precursors have also been reported.

The lone approach to thieno[3,2-*d*]pyrimidines involving a pyrimidine precursor has an unsaturated aliphatic chain tethered to the 5-position of the pyrimidine through a sulfur atom. **Scheme 33** shows a propenylthio derivative **430** that undergoes a thermal [3,3]-sigmatropic rearrangement when heated in *N*,*N*-diethylamine (*N*,*N*-DEA) to give **431**. Cyclization of this compound affords the bicyclic product **432a** <2001SC2979>. Compound **432b** is obtained from an alternative pathway commencing with **430b**.

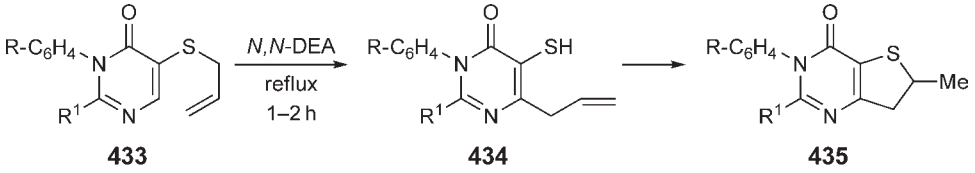


430 **431** **432**

a: $R^1 = R^3 = H$, $R^2 = Cl$ (80%)
b: $R^1 = R^2 = H$, $R^3 = Me$ (92%)

Scheme 33

A similar type of reaction occurs with a monooxo pyrimidine **433**, giving a series of products **435** (**Scheme 34**) <2005T10774>.

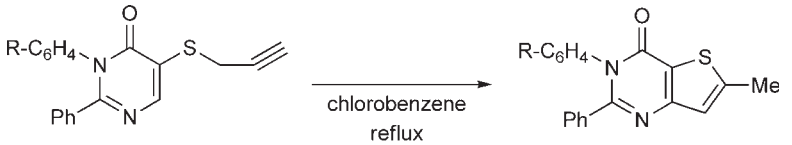


433 **434** **435**

Entry	*R*	R^1	*Yield (%)*	*Entry*	*R*	R^1	*Yield (%)*
a	4-Me	SMe	77	**e**	2-Me	Ph	78
b	H	SMe	82	**f**	4-Me	Ph	81
c	4-Me	SMe	76	**g**	H	Ph	85
d	4-Cl	SMe	80	**h**	4-MeO	Ph	76

Scheme 34

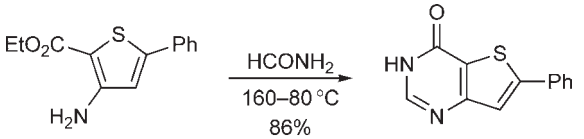
If the side chain contains an alkynyl moiety a similar process occurs, as seen in Equation (162). The propynylthiopyrimidines **436** undergo thermal rearrangement and cyclization to give quite good yields of **437** <2004TL6075>.



(162)

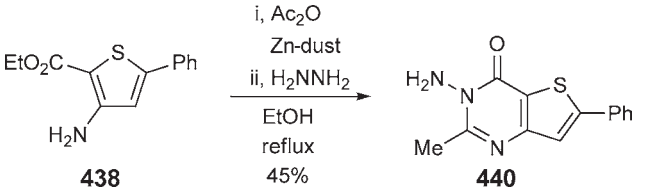
a: R = 4-Me (77%)
b: R = H (78%)
c: R = 4-Me (78%)
d: R = 4-MeO (75%)
e: R = 4-Cl (80%)

The formation of thieno[3,2-*d*]pyrimidines beginning with adjacent amino and carboxy ester groups on a thiophene ring has been extensively employed. In the simplest cases, treatment with formamide to produce the fused pyrimidine ring is a classical method. Thus, Shah *et al.* have described the process in which thiophene **438** is heated in formamide to give the expected fused ring system **439** (Equation 163) <2002OJC159, 1998IJB73>.



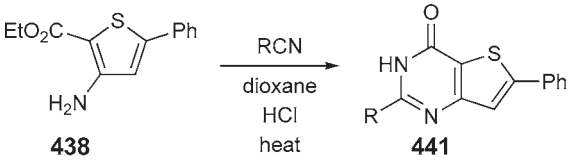
(163)

Additionally, **438** undergoes cyclization when acetylated and heated with hydrazine in EtOH to give the *N*-amino derivative **440** (Equation 164) <1995MI136>.



(164)

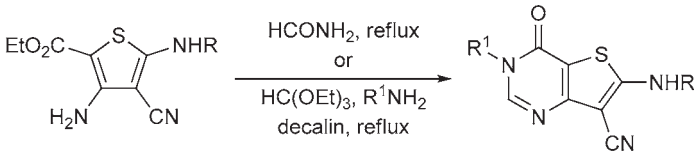
Furthermore, treatment of **438** with a series of nitriles effects cyclization to a variety of 2-substituted compounds **441** in low to modest yields (Equation 165) <1994IJB436>.



a: R = Me (45%)
b: R = CH_2Cl (40%)
c: R = CO_2Et (25%)
d: R = CH_2CO_2Et (38%)
e: R = CH_2CH_2Cl (41%)
f: R = Ph (35%)
g: R = $PhCH_2$ (32%)
h: R = 4-$ClC_6H_4CH_2$ (38%)
i: R = 4-$O_2NC_6H_4CH_2$ (52%)
j: R = Ph-CH=CH (55%)

(165)

More highly substituted thiophenes, in particular those containing other functional groups, also undergo ring closure when heated in formamide. Equation (166) illustrates this process quite well. Here heating **442** in $HCONH_2$ or heating with triethyl orthoformate in the presence of an additional amine produces a series of products **443** <2001MI11>, albeit in poor to modest yields.

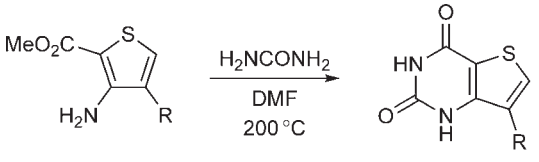


442 **443**

Entry	*R*	R^1	*Yield (%)*	*Entry*	*R*	R^1	*Yield (%)*
a	C_6H_{11}	H	25	**m**	C_6H_{11}	3-MeC_6H_4	65
b	Ph	H	30	**n**	C_6H_{11}	4-MeC_6H_4	60
c	Et	Et	28	**o**	Ph	Et	28
d	Et	Pr^n	25	**p**	Ph	Pr^n	35
e	Et	Ph	40	**q**	Ph	Bu^n	33
f	Et	4-MeC_6H_4	45	**r**	Ph	$PhCH_2$	30
g	Et	4-$MeOC_6H_4$	50	**s**	Ph	Ph	50
h	C_6H_{11}	Et	25	**t**	Ph	3-MeC_6H_4	60
i	C_6H_{11}	Pr	20	**u**	Ph	4-MeC_6H_4	60
j	C_6H_{11}	Bu^n	20	**v**	Ph	4-$MeOC_6H_4$	50
k	C_6H_{11}	$PhCH_2$	30	**w**	Ph	4-$HO_2CC_6H_4$	30
l	C_6H_{11}	Ph	60				

(166)

Other annulations involving urea as the cyclization reagent have been reported, as in the conversion of **444** into **445** (Equation 167) <1994JHC305>. Alternatively, these same products can be formed by treating the thiophene derivative **444** with KCNO in aqueous HOAc at room temperature for ~12 h. However, the yields are considerably less (29–45%) <1994JHC305>. One example shows the prior conversion of **444g** into the *N*-formyl derivative, which, upon heating in formamide, affords the corresponding **441g** <2004BML21>.

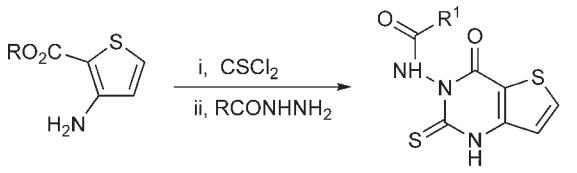


444 **445**

a: R = Me (77%)
b: R = Ph (80%)
c: R = 4-MeC_6H_4 (62%)
d: R = 4-$MeOC_6H_4$ (65%)
e: R = 4-FC_6H_4 (64%)
f: R = 4-ClC_6H_4 (69%)
g: R = H

(167)

Combinatorial methods have been employed to convert the very simple thiophene precursor **446a** into a variety of N-substituted products **447**. The process first involves conversion of the amino group into the isothiocyanate followed by treatment with substituted hydrazides (Equation 168) <2004JCO573>. Other derivatives have been prepared using similar chemistry.



(168)

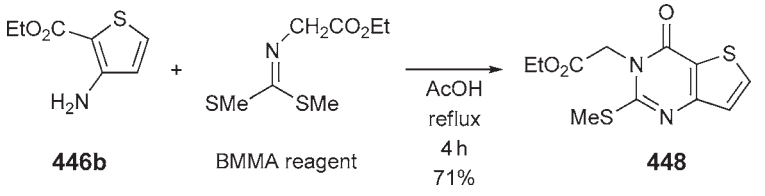
446

a: R = Me
b: R = Et

447

a: R^1 = Ph (76%)
b: R^1 = 3-$MeOC_6H_4$ (74%)
c: R^1 = 3-BrC_6H_4 (80%)

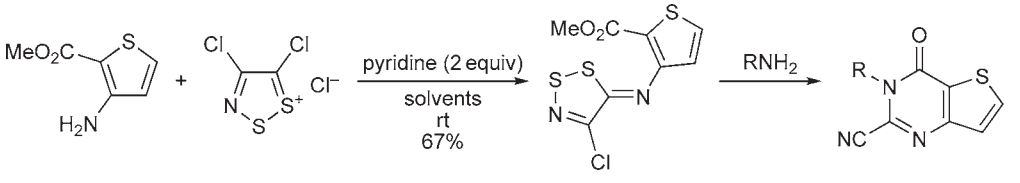
An unusual BMMA reagent, *N*-[bis(methylthio)methylene]aminoacetic acid ethyl ester, leads to the annulation of **446b**, thereby forming compound **448** (**Scheme 35**) <1995H(40)851>.



446b BMMA reagent **448**

Scheme 35

The reaction of **446a** with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) in the presence of 2 equiv of pyridine formed the intermediate **449**, which, upon treatment with aliphatic amines, afforded the desired thieno-pyrimidines **450** (**Scheme 36**) <1998JHC659, 2002H(57)1471>.

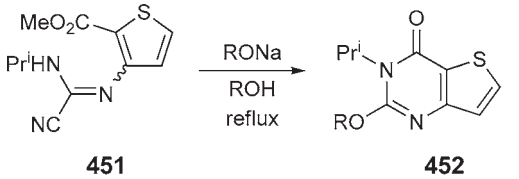


446a **449** **450**

a: R = Me (80%)
b: R = Et (84%)
c: R = Pr^i (52%)
d: R = *n*-C_5H_{11} (83%)
e: R = $PhCH_2$ (64%)
f: R = piperonyl (71%)
g: R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (NA)

Scheme 36

Alkoxy analogs of **450** were also prepared from **451**, undoubtedly obtained as a by-product in the formation of **450c**. Two examples of the formation of **452** in this way are shown in Equation (169) <1998JHC659>.

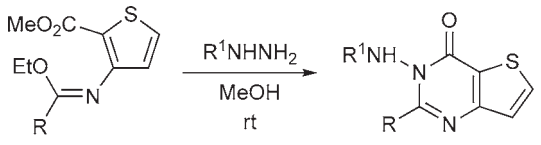


(169)

451 **452**

a: R = Me (91%)
b: R = Et (86%)

Other imine-like structures such as **453**, when allowed to react with hydrazines at room temperature, produce similar fused thienopyrimidines **454** (Equation 170) <2000JFC(105)83>.

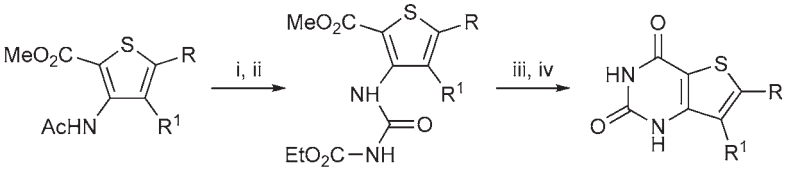


453 **454**

(170)

a: R = Me; $R^1 = C_6F_5$ (50%)
b: R = Me; $R^1 = CH_2CF_3$ (45%)
c: R = Et; $R^1 = C_6F_5$ (77%)
d: R = Et; $R^1 = CH_2CF_3$ (74%)

The examples above open up synthetic approaches that involve manipulating either the amino or carboalkoxy moieties. The following examples illustrate the variety of ways in which these transformations have been used to synthesize thieno[3,2-*d*]pyrimidines. **Scheme 37** describes one such method in which an intermediate urea derivative **456** is formed from **455** by reaction with ethyl isothiocyanatoformate. Cyclization to **457** occurs upon heating in an ethanolic alkoxide medium <2003BML107>.



455 **456** **457**

a: R = H; $R^1 = NO_2$ (87%)
b: R = NH_2; R^1 = H (85%)

a: R = H; $R^1 = NH_2$ (86%)
b: R = NH_2; R^1 = H (85%)

i, HCl (conc.), MeOH, heat; ii, ethyl isocyanatoformate, $CHCl_3$, heat; iii, Fe(S), AcOH, EtOH, heat; iv, NaOMe, MeOH, heat

Scheme 37

Analogs of **457** that possess a sulfur atom at position 2 have also been prepared in a similar way <2002MI717>.

The use of thiophene isothiocyanates has also been valuable in the formation of thieno[3,2-*d*]pyrimidines. Treatment of **458** with (*S*)-(+)-2-amino-1-propanol at reflux in the presence of $KOBu^t$ produces **459a** (Equation 171).



458 **459**

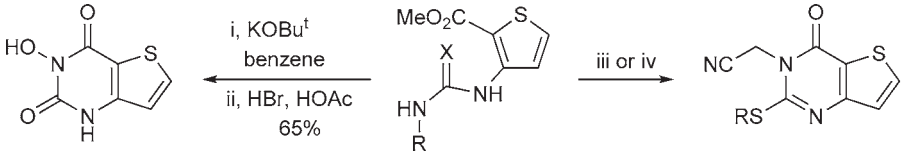
Entry	*R*	*R^1*	*Yield (%)*	*Conditions*
a	$CH_2CH(Me)CH_2OH$	HS	59	i
b	NH_2	NH_2NH	64	ii
c	CH_2CN	MeS	89	iii
d	CH_2CN	Pr^nS	91	iii
e	CH_2CN	$PhCH_2S$	71	iii
f	CH_2CN	$Bu^tO_2CCH_2S$	62	iii

(171)

i, $KOBu^t$, THF; ii, $H_2NNH_2 \cdot H_2O$, EtOH, reflux; iii, (a) H_2NCH_2CN (b) RX

A heated solution of **458** in dry EtOH containing hydrazine gives **459b** <1995JHC69>. The thienopyrimidine-acetonitriles **459c–f** were prepared from **458** through an initial reaction with malononitrile to form a thioureido intermediate, followed by treatment with alkyl halides <2001JHC419>.

Other urea or thiourea derivatives of thiophene have been used to generate similar structures (Equation 172). Hence, **460a** affords **461** in good yield <1994S846>. Meanwhile **460b**, using different conditions, produces a short series of **462** <2001JOC4723>.



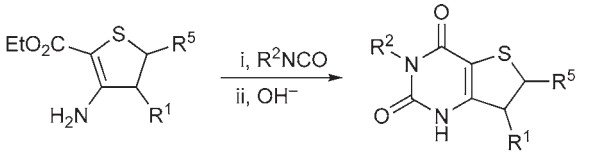
461 **460** **462** (172)

a: X = O; R = BnO
b: X = S; R = CH_2CN

iii, RX, 1 M NaOH, acetone, rt for **462a,b**
iv, RCl, KI, Na_2CO_3, DMF, 100 °C for **462c–e**

a: R = Pr
b: R = Bn
c: R = CH_2COOH
d: R = CH(Me)COOH
e: R = CH_2CH_2COOH

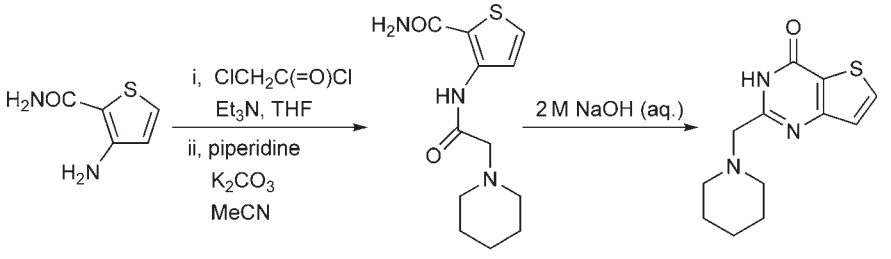
The amino group of **463** is transformed initially into carbamate compounds by treatment with several isocyanates. The carbamate intermediates were readily cyclized in base to give dihydrothieno[3,2-*d*]pyrimidines **464** (Equation 173) <1996MI597, 1995JOC1461>.



463 **464** (173)

Entry	R^1	R^2	R^5	*Yield (%)*	*Entry*	R^1	R^2	R^5	*Yield (%)*
a	SH	Ph	H		**e**	SMe	*n*-Pr	H	65
b	SH	Ph	Me	87	**f**	SMe	*c*-C_3H_5	H	71
c	SH	3-$CF_3C_6H_4$	Ph		**g**	SMe	Ph	H	
d	SMe	3-$CF_3C_6H_4$	H	79	**h**	H	Ph	H	87

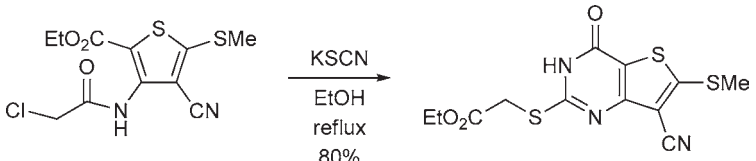
If the amide moiety, in lieu of the carboalkoxy group, is used, then a monooxy derivative is obtained. Thus, the simple thiophene **465** is first acylated on the amine using chloroacetyl chloride. Subsequent treatment with piperidine affords intermediate **466**. Cyclization in alkali produces the thienopyrimidine **467** (no yield given) (**Scheme 38**) <1998JME4021>.



465 **466** **467**

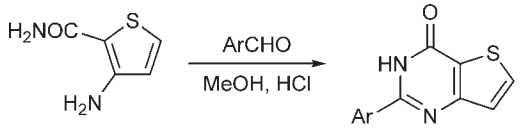
Scheme 38

A similar product, **469**, is formed when the acylated thiophene **468** is heated with KSCN in EtOH (Equation 174) <2000H(53)2363>.



468 **469** (174)

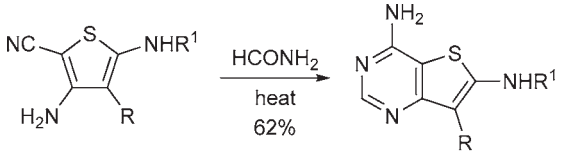
Under different conditions, **465** reacts with aromatic aldehydes (Equation 175) to give the corresponding 2-arylpyrimidine analogues **460** but no yields were provided <2005BML3763>.



465 **470** (175)

a: Ar = 4-MeOC$_6$H$_4$ **b**: Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$

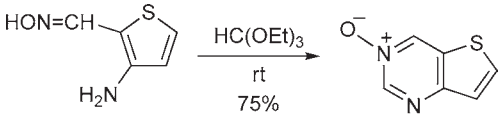
Although the most common approach to the formation of a fused pyrimidine ring involves adjacent amino and acid functional groups, other functional groups have been used instead of the acid moiety. The following examples describe some of this chemistry. A cyano group adjacent to an amine functional has long been used to produce aminopyrimidines. This approach has also been used to generate thieno[3,2-*d*]pyrimidines. Typical of this chemistry are the reactions of the substituted thiophenes **471** with formamide to produce the expected products **472** (Equation 176) <1996M955, 2002MOL756>.



471 **472** (176)

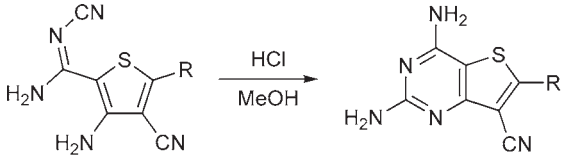
a: R = benzothiazol-2-yl; R^1 = H
b: R = CN; R^1 = Ph (92%)

The use of aldehyde derivatives serves in lieu of the carboalkoxy group in cyclization reactions. The oxime **473**, when allowed to react with triethyl orthoformate, gives the *N*-oxide **474** (Equation 177) <1996H(43)389>.



473 **474** (177)

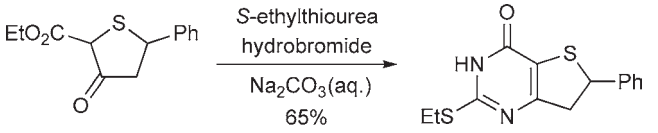
The cyanoacetamidine derivative **475** can be readily cyclized to the thienopyrimidines **476** (Equation 178) <1996T1011>.



475 **476** (178)

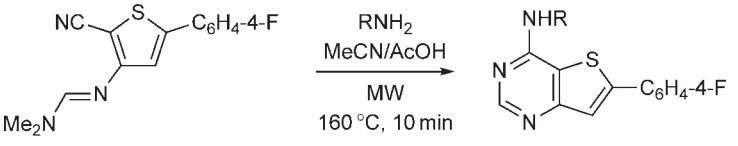
a: R = NHCH$_2$CH=CH$_2$ (82%)
b: R = SMe (93%)

There is one example of annulation of a pyrimidine ring to a saturated thiophene ring. Ketone **477** is condensed with *S*-ethylthiourea·HBr at room temperature in water over 18 h. The product is the reduced thienopyrimidine **478** (Equation 179) <1994NN1135>.



477 **478** (179)

Despite the extensive use of microwave-enhanced reactions in order to effect syntheses, very little has been explored in the synthesis of thieno[3,2-*d*]pyrimidines. One example of this newer technology being applied to heterocyclic systems involves the conversion of the formamidine **479** into **480** when treated with an amine under high-temperature microwave conditions (Equation 180) <2004OL1523>.



479 **480** (180)

a: R = 2-ClC$_6$H$_4$CH$_2$ (78%)
b: R = 3-CF$_3$OC$_6$H$_4$CH$_2$ (96%)
c: R = 2-MeOCH$_2$CH$_2$ (91%)

While considering more modern technologies, there are several reports of syntheses being effected through the use of resin-bound starting materials <2003TL5041, 1997TL1729>.

10.07.6.9 Thienopyrazines

10.07.6.9.1 Thieno[2,3-*b*]pyrazines

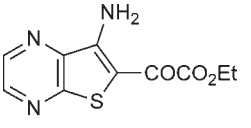
Ethyl thioglycolate has been a common reagent used to introduce the sulfur atom into pyrazine precursors for the synthesis of thieno[2,3-*b*]pyrazines. Typically this involves displacement of a chloro group on the pyrazine. Thus **481a** prepared in this way can be transformed into **482a** by heating in EtOH containing piperidine (Equation 181) <1994SC1895>. Likewise **481b** is converted into **482b** by heating in EtOH containing NaOAc <1994SC1895>. No yields were given for **482a** and **482b**. Similar syntheses have also been reported <2000JME1586>.



481 **482** (181)

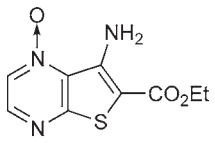
a: R = Et; R^1 = CN; R^2 = NH$_2$
b: R = Me; R^1 = CN; R^2 = NH$_2$

If mercaptopyruvate is used instead of a thioglycolate, **483** can be prepared <2005JHC661>.



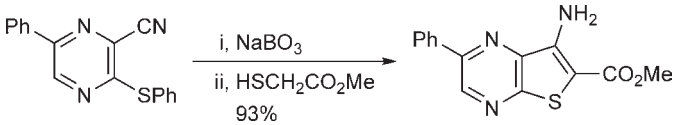
483

Oxidation of one of the nitrogen atoms of 2-chloro-3-cyanopyrazine to form a mono-*N*-oxide allows for an identical sequence of reactions to generate the corresponding *N*-oxide **484** <1999WO9957122, 2000JME1586>.



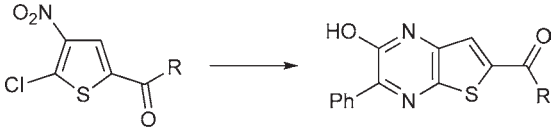
484

If the sulfur atom has been introduced in another way in order to form, for example, **485**, oxidation of the sulfur atom by treatment with sodium borate leads to a mixture of the corresponding sulfoxides and sulfones (major product) in a total yield of 95%. Now treatment with methyl thioglycolate in basic medium gives **486** (Equation 182) <2001SC725>.



485 **486** (182)

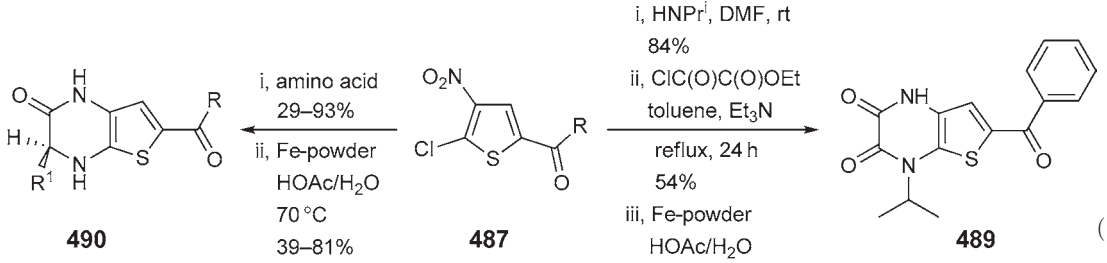
Starting with the thiophene precursor **487**, three different products have been obtained, depending on reagents and conditions. Reaction of **487a** with α-phenylgycine methyl ester leads to replacement of the chlorine atom. Reduction of the nitro group with iron powder/acetic acid is followed by cyclization to a lactam. Subsequent aromatization to give **488a** proceeds via an acetylation/deacetylation sequence (Equation 183) <2003H(60)337>.



487 **488** (183)

a: R = Me (53%)
b: R = Ph

Replacement of the chlorine in **487b** with isopropylamine is accomplished, then the secondary amine product is acylated with ethyl oxalyl chloride (Equation 184). Again reduction of the nitro group allows cyclization to **489** to occur <2001H(55)1963>.



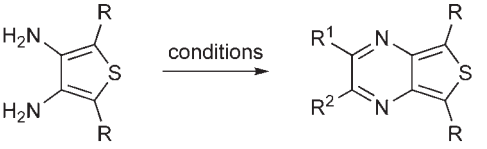
490 **487** **489** (184)

a: R = Me; R^1 = Me (64%)
b: R = Me; R^1 = $PhCH_2$ (81%)
c: R = Me; R^1 = CH_2CH_2SMe (56%)
d: R = Me; R^1 = CH_2SCH_3 (39%)
e: R = Me; R^1 = H (50%)
f: R = Ph; R^1 = H (65%)
g: R = Ph; R^1 = Me (51%)
h: R = Ph; R^1 = $PhCH_2$ (65%)

Finally the chloro group of **487a** or **487b** is displaced by one of several amino acid derivatives including L-phenylalanine ethyl ester, L-phenylalanine, L-methionine methyl ester, *S*-methyl-L-cysteine, and glycine ethyl ester. Reduction of the nitro group is followed immediately by cyclization to give the series **490**, where R^1 results from the specific amino acid utilized <2002H(57)97>.

10.07.6.9.2 Thieno[3,4-*b*]pyrazines

Whereas it was reported in CHEC-II(1996) <1996CHEC-II(7)229> that examples of this system were rare, the increase in synthetic activity since then has been significant. Such compounds can be obtained using either a thiophene or a pyrazine precursor. Virtually all of the molecules prepared from thiophene precursors follow the pathway shown in Equation (185). The appropriate diaminothiophenes **491**, usually obtained by reduction of the corresponding nitro groups, are condensed with the desired 1,2-dicarbonyl compound under generally mild conditions to yield **492**.



491 **492**

Entry	*R*	R^1	R^2	*Entry*	*R*	R^1	R^2
a	2-Thienyl	H	H	**j**	H	C_6H_{13}	C_6H_{13}
b	2-Thienyl	Me	Me	**k**	H	C_8H_{17}	C_8H_{17}
c	2-Thienyl	C_6H_{13}	C_6H_{13}	**l**	H	$C_{10}H_{21}$	$IC_{10}H_{21}$
d	2-Thienyl	$C_{13}H_{27}$	$C_{13}H_{27}$	**m**	H	$C_{12}H_{25}$	$C_{12}H_{25}$
e	2-Thienyl	$C_{16}H_{13}$	$C_{16}H_{13}$	**n**	4-$Bu^tC_6H_4$	Bu^t	Bu^t
f	H	Ph	Ph	**o**	4-$Bu^tC_6H_4$	OMe	OMe
g	2-Thienyl	Ph	Ph	**p**	4-$Bu^tC_6H_4$	CN	CN
h	H	H	H	**q**	4-$Bu^tC_6H_4$	CN	Bu^t
i	H	Me	Me	**r**	4-$Bu^tC_6H_4$	Br	Br

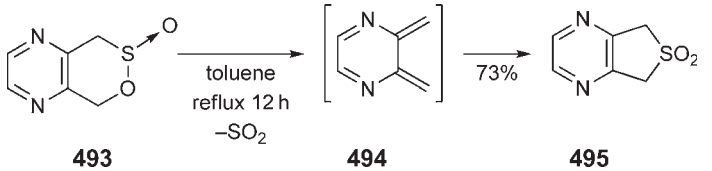
(185)

Conditions

a–e: $(R^1R^2CO)_2$, MeOH or $(HCO)_2$, Na_2CO_3(aq.), 68–85% <1994CC1585>
f: $(PhCO)_2$, MeOH, AcOH, 60 °C, MW, 5 min; 72% <2004TL4873>
g: $(PhCO)_2$, MeOH, 60 °C; 54% <2005SM53>
h–m: $(R^1R^2CO)_2$, EtOH, rt; 37–97% <2002JOC9073>
n–r: $(R^1R^2CO)_2$, *p*-TsOH, $CHCl_3$, reflux overnight; 74–96% <2002AM822>

One of the earliest reports shows the conversion of **491a–e** to the corresponding series of alkyl-substituted products **492a–e** <1994CC1585>. Ten years later, the interest in microwave-assisted reactions provided improved yields and purity, due to avoidance of polymerization, in the formation of **492f** from **491f** <2004TL4873>. Benzil has quite recently been employed with a terthiophene molecule **491g** to give the fully substituted **492g** <2005SM53>. Additional examples in which aliphatic dicarbonyl compounds have been condensed with **491g** have been described <1996CM570> as well as condensation with $(HCO)_2$ <1995SM599>. It has been found that greatly improved yields can be achieved by allowing the condensation reaction to proceed at room temperature over longer periods of time. These conditions drastically reduce unwanted polymerization, leading to pure isolated products. Compounds **492a–c** and **492f** as well as **492h–n** were obtained in this way <2002JOC9073>.

Pyrazino sulfolenes **495** have been derived from a cycloaddition reaction of intermediate **494** with SO_2. This intermediate is produced by the thermal decomposition of the sulfine **493** (**Scheme 39**) <2000JOC3395>.



493 **494** **495**

Scheme 39

10.07.7 Important Compounds and Applications

The interest in certain classes of compounds frequently stems from a desire to improve on the biological activity of a lead molecule, usually a natural product. Such has been the case during the past ten or so years. A few of these seminal substances are mentioned here. For details an independent search of the literature is recommended.

A compound that has driven a considerable amount of synthetic effort is zopiclone **256** <1997TA995, 2001CC2204, 2001MI27>, a compound that displays behavior similar to the benzodiazepines.

Aloisines **255** are glycogen synthase kinase-3 (GSK-3) inhibitors that have provoked more than a little interest in producing synthetic analogs <2004BML413>.

A class of compounds, called immucillins <2003BBR917>, are potent transition-state analogs of purine nucleoside phosphorylase. As such these pyrrolo[3,2-*d*]pyrimidines have been the target of much exploration.

Finally, toyocamycin <1995JME2158>, a powerful natural product with exceptional biological activity, has been a model for extensive syntheses of pyrrolo[2,3-*d*]pyrimidines.

A number of other molecules with nonbiological commercial applications may be found among the patent literature.

10.07.8 Further Developments

10.07.8.1 Fused Pyridazines

[4+2] Cycloaddition of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate with EWG-substituted primary ketene N,O-acetals provides a tetrasubstituted pyridazine, methyl 4-amino-5,7-dioxo-6,7-dihydro-5*H*-pyrrolo[3,4-*c*]pyridazine-3-carboxylate <2006S1513>.

A series of 3-chloro-4-arylacetylenic pyridazines have been cyclized to the corresponding 5-aryl-furo(or pyrrolo or thia)[2,3-*c*]pyridazinones <2006TL6125, 2006JMC3753>.

Two thieno[3,4-*d*]pyridazines were prepared *via* reaction of suitably substituted pyridazinones under microwave conditions <2006PS1755>.

10.07.8.2 Fused Pyrimidines

10.07.8.2.1 Furo pyrimidines

Treatment of a furan with ortho amino and cyano groups continues to be a viable route to fused pyrimidines. Thus, 2-amino-4,5-di-(2-furanyl)furano-3-carbonitrile produces 5,6-di-(2-furyl)furo[2,3-*d*]pyrimidin-4(*H*)-ones in 72% yield upon cyclization in acetic anhydride/formic acid <2006JHC1129>.

The use of a pyrimidine precursor continues to be the more popular approach to furo pyrimidines. The one-pot three-component condensation reactions of alkyl or aryl isocyanides with *N*,*N*′-dimethylbarbituric acid in the presence of terephthaldialdehyde proceeded spontaneously at room temperature in DMF to give good yields of the corresponding 1,4-bis(6-alkyl or arylamino-1,3-dimethylfurano[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione-5-yl)benzenes <2006BMCL3697>.

Aryl acetylenic derivatives continue to exhibit interest as precursors for fused ring systems. Foe example, treatment of 1-methyl-5-(trimethylsilylethynyl)uracil with ammonium fluoride leads to 3-methylfuro[2,3-*d*]pyrimidin-2(3*H*)-one in good yield <2006JMC391>.

Reaction of 2,4-diamino-6-oxo-pyrimidine with methyl 4-(3-chloro-2-oxopropyl)benzoate gives a mixture of 5- and 6-benzyl furo[2,3-*d*]pyrimidines in 27% yield and 23%, respectively <2006BMC8590>.

10.07.8.2.2 Pyrrolo pyrimidines

The majority of reactions involving nucleosides previously seen continued to evoke interest in 2006. Hence conversion of pyrrolo[2,3-*d*]pyrimidines (7-deazapurines) into nucleosides has been described <2006JOC81, 2006BMCL285, 2006OBC1131, 2006S2005>. Reactions at either the pyrrolopyrimidine ring <2006JOC3248, 2006S3280, 2006TL4149> or the carbohydrate moiety <2006JOC3077> have also been reported.

Again there is an equal effort given to synthesizing pyrrolopyrimidines commencing with either pyrimidine or pyrrole precursors.

10.07.8.2.2(i) Syntheses from pyrimidines

A useful pyrimidine precursor is 2,4-diamino-6-oxo-pyrimidine. Heating a mixture of this pyrimidine and 1-bromo-2-butanone in DMF afforded 2-amino-6-ethyl-3,4-dihydro-4-oxo-7(*H*)-pyrrolo[2,3-*d*]pyrimidine in modest yield <2006JMC1055>.

Rigidins, a class of marine natural products, have been synthesized. The pyrrolo[2,3-*d*]pyrimidine skeleton is obtained from 6-chlorouracils and protected glycines in a two-step process <2006T8243>.

Condensation of N^1,N^3-dilkyl-6-methyl-5-nitrouracils with benzaldehyde produces a 6-styryl derivative. Reduction of the nitro group leads to spontaneous cyclization to the corresponding N^1,N^3-dialkyl-6-phenyl-pyrrolo[3,2-*d*]pyrimidin-2,4-diones <2006BMCL3642>.

The Paal Knorr reaction provides an efficient synthesis of 1,3,7-triaryl-6-phenyl-2-thioxo-1,2,3,7-tetrahydropyrrolo[2,3-*d*]pyrimidin-4-one derivatives from 2-thiobarbituric acids under microwave conditions <2006JHC1231>.

Several 7*H*-pyrrolo[2,3-*d*]pyrimidin-2(*H*)-ones, *via* domino cross-coupling and cyclization reactions, were prepared from N^4-benzoyl-5-iodo-cytosine <2006H1325>.

An unusual synthesis of 7-deazaguaninyl-β-amino acid occurs via an intermediate β-lactam structure <2006EJOC2410>.

Finally, 5-bromo-2,4-dichloropyrimidines has been used in the synthesis of several examples of pyrrolo[2,3-*d*]-pyrimidines. Displacement of the 4-chloro group with liquid ammonia gives the expected 4-amino derivative. Palladium-catalyzed cross-coupling of this intermediate with vinyl stannane gave the corresponding vinyl ether, which was cyclized to furnish 2-chloropyrrolo[2,3-*d*]pyrimidine <2006BMCL2173>. Other examples following the same pathway have been described in which an aniline <2006BMCL2689> or cyclohexylamine <2006BMCL5778> have been incorporated into the pyrimidine ring *in lieu* of ammonia.

10.07.8.2.2(ii) Synthesis from pyrroles

Pyrroles bearing *ortho* amino/cyano groups are standard precursors in the formation of 4-oxo-pyrrolopyrimidines. Thus, 4-(4-oxo-5-phenyl-3,4-dihydro-pyrrolo[2,3-*d*]pyrimidin-7-yl)benzenesulfonamide is prepared by cyclization of the appropriately substituted 2-amino-3-cyanopyrrole in refluxing formic acid <2006AF301, 2006AF405>. Meanwhile the same pyrrole in refluxing formamide leads to the 4-amino analogue <2006AF405>. Similarly 6-phenyl-7-(substituted phenyl)-3,7-dihydroxypyrrolo[2,3-*d*]pyrimidin-4-ones are obtained from the corresponding pyrroles *via* cyclization in refluxing formic acid <2006PHA174>.

Likewise 3-amino-2-cyano-4-(3-methoxyphenyl)-*N*-carboethoxypyrrole is converted into 7-(3-methoxyphenyl)-pyrrolo[3,2-*d*]pyrimidin-4-one by, first decarboxylation, and then cyclization in refluxing formic acid <2006BMCL2091>. Replacing the 3-methoxyphenyl group on the pyrrole with a reduced pyrrole (a mimic of a ribofuranose ring) leads to a 4-aminopyrrolo[3,2-*d*]pyrimidine when treated with formamidine acetate <2006BMCL2662>.

Finally, *ortho* aminoesters have been used to produce 7-deazaxanthines. For example ethyl 2-amino-5-phenyl-1*H*-pyrrole-3-carboxylate is first treated with 2-chloroethyl isocyanate in refluxing toluene. The resulting urea derivative is then allowed to react with 1-(2-methoxyphenyl)piperazine and cyclized to the expected pyrrolo[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione <2006BMCL150>.

10.07.8.2.3 Thieno pyrimidines

One example of the synthesis of a thienopyrimidine commencing with a pyrimidine precursor appeared in 2006. Thus, 4-chloro-5-cyano-6-aryl-2-methylthiopyrimidines react with either ethyl (or *t*-butyl) 2-mercaptoacetate to afford 5-amino-4-aryl-2-methylthiothieno[2,3-*d*]pyrimidine-6-carboxylic acids <2006JMC3888>.

A number of examples of synthetic approaches to thienopyrimidines are reported, most following standard chemical reactions previously seen. For example the classic annelation of a pyrimidine ring arising from *ortho* amino/ester groups continues. Condensation of the commercially available methyl 3-amino-5-(4-chlorophenyl)thiophene-2-carboxylate with DMF-dimethylacetal afforded the expected amidine. Reaction of this amidine with a variety of 5-amino-1*H*-benzimidazoles gave the corresponding thieno[3,2-*d*]pyrimidinones <2006BMCL4994>. The ethyl ester precursor reacts with a quinolinylmethyl amine in a similar way <2006BMCL5207>. A series of new thieno[2,3-*d*]pyrimidin-4(3*H*)-ones and thieno[3,2-*d*]pyrimidin-4(3*H*)-ones were synthesized by cyclocondensation of alkyl isothiourea ethers of *sym*-diarylthioureas with 4-phenylthiophene *o*-esters in DMF <2006IJHC271>.

Several examples begin with ethyl 4,5-disubstituted-2-aminothiophene-3-carboxylates. So, reaction with naproxenoyl chloride <2006IJC(B)450> or 4-chlorophenylisothiocyanate <2006MI498> or $CSCl_2$, followed by ethanolamine <2006AF553> or $CSCl_2$ followed by methylamine <2006PS1935> lead to intermediates that are cyclized to

give the corresponding thieno[2,3-*d*]pyrimidines. In addition reaction of the thiophene precursor with formamide also provides a thieno[2,3-*d*]pyrimidine 2006MI37>. Coupling of 5-bromo-4-nitro-thiophene-2-carboxylic acid with 3-methoxy-4-(2-pyrrolidin-1-ylethoxy)aniline gave the expected amide. Subsequent reduction of the nitro group and cyclization in refluxing formic acid provided the corresponding thieno[2,3-*d*]pyrimidinone <2006BMCL4723>.

A further example of the formation of a fused pyrimidine by reaction of *ortho* amino/cyano groups is illustrated by condensation of 2-amino-4-(4-nitrophenyl)-3-thiophenecarbonitrile with formamide in the presence of Ph_3P at elevated temperature <2006T11311>.

10.07.8.3 Fused Pyrazines

The reaction of 2-(3-chloropyrazin-2-yl)-1-phenylbutan-1-one with either primary amines or hydrazines, catalyzed by acid, at high temperatures provided the corresponding pyrrolo[2,3-*b*]pyrazine <2006T9919>.

Reaction of 3-benzenesulfonylpyrazine-2-carbonitrile with ethyl 2-mercaptoacetate and sodium carbonate gave 97% of ethyl 3-aminothieno[2,3-*b*]pyrazine-2-carboxylate <2006T11124>.

Interest in the natural product aloisines continues to spark activity in the synthesis of protein kinase inhibitors. New 5,7-disubstituted 6-aminopyrrolo[2,3-*d*]pyrazine-2,3-dicarbonitriles were prepared in excellent yields in a two-stage nucleophilic reaction on 5,6-dichloropyrazine-2,3-dicarbonitrile <2006EJM727>.

References

1994APH55 J. Pluta, M. Flendrich, J. Cieplik, and Z. A. Krolicki, *Acta Polon. Pharm. Drug Res.*, 1994, **51**, 55.
1994CC1585 C. Kitamura, S. Tanaka, and Y. Yamashita, *J. Chem. Soc., Chem. Commun.*, 1994, 1585.
1994CHE1077 E. B. Tsupak, Y. N. Tkachenko, and A. F. Pozharskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1994, **30**, 1077.
1994CPB2219 E. Oishi, K. Iwamoto, T. Okada, S. Suzuki, K. Tanji, A. Miyashita, and T. Higashino, *Chem. Pharm. Bull.*, 1994, **42**, 2219.
1994H(38)1845 N. Haider, K. Mereiter, and R. Wanko, *Heterocycles*, 1994, **38**, 1845.
1994IJB436 C. J. Shishoo, U. S. Pathak, K. S. Jain, I. T. Devani, and M. T. Chhabria, *Indian J. Chem., Sect. B.*, 1994, **33**, 436.
1994JCM484 R. M. Mohareb and S. M. Sherif, *J. Chem. Res. (S)*, 1994, **12**, 484.
1994JHC305 F. Jourdan, D. Laduree, and M. Robba, *J. Heterocycl. Chem.*, 1994, **31**, 305.
1994JME1526 B. Grahner, S. Winiwarter, W. Lanzner, and C. E. Mueller, *J. Med. Chem.*, 1994, **37**, 1526.
1994JME2477 S. Niwas, P. Chand, V. P. Pathak, and J. A. Montgomery, *J. Med. Chem.*, 1994, **37**, 2477.
1994MI17 M. Rickwood, S. D. Marsden, M. E. Ormsby, A. L. Staunton, D. W. Wood, J. D. Hepworth, and C. D. Gabbutt, *Mol. Cryst. Sci. Technol. Sect. A*, 1994, **246**, 17.
1994NN1135 J. Renault, D. Laduree, and M. Robba, *Nucleos. Nucleot.*, 1994, **13**, 1135.
1994PS(86)203 M. S. Abbady and S. M. Radwan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **86**, 203.
1994PS(88)147 A. H. H. Elghandour, M. K. A. Ibrahim, B. Ed-Badry, and H. K. Waly, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **88**, 147.
1994PS(89)193 S. M. Radwan, M. S. Abbady, and H. S. El-Kashef, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1994, **89**, 193.
1995AP231 M. Guetschow, K. Droessler, and S. Leistner, *Arch. Pharm.*, 1995, **328**, 231.
1995CC115 B. K. Bhattacharya and G. R. Revankar, *J. Chem. Soc., Chem. Commun.*, 1995, 115.
1995CPB256 K. Aso, T. Hitaka, K. Yukishige, K. Ootsu, and H. Akimoto, *Chem. Pharm. Bull.*, 1995, **43**, 256.
1995EJC627 A. M. A. Fattah, A. S. Aly, F. A. Motti, N. A. Hassan, and H. A. H. Aly, *Egypt. J. Chem.*, 1995, **38**, 627.
1995FA605 A. Santagati, M. Modica, M. Santagati, V. Cutuli, D. Amore, and A. Caruso, *Farmaco*, 1995, **50**, 605.
1995H(40)851 F. Sauter, J. Froehlich, K. Blasl, and K. Gewald, *Heterocycles*, 1995, **40**, 851.
1995H(41)937 J. Renault, F. Jourdan, D. Laduree, and M. Robba, *Heterocycles*, 1995, **41**, 937.
1995IJH191 M. M. Ali, M. A. Zahran, Y. A. Ammar, Y. A. Mohamed, and A. T. Seleim, *Indian J. Heterocycl. Chem.*, 1995, **4**, 191.
1995JAP07033773 N. Iwase and M. Ooshima, Jpn. Kokai Tokkyo Koho JP 07033773 (1995) (*Chem. Abstr.*, 1995, **122**, 290874).
1995JCM286 S. Tumkevicius and R. Pupeikyte, *J. Chem. Res. (S)*, 1995, 286.
1995JCM314 K. A. M. El-Bayouki, W. M. Basyouni, H. Hosni, and A. S. El-Deen, *J. Chem. Res. (S)*, 1995, 314.
1995JCM488 F. A. Abu-Shanab, B. Wakefield, F. Al-Omran, M. M. A. Khaled, and H. Elnagdi, *J. Chem. Res. (S)*, 1995, 488.
1995JHC69 U. Urleb, *J. Heterocycl. Chem.*, 1995, **32**, 69.
1995JHC211 K. Eger, M. Jalalian, and M. Schmidt, *J. Heterocycl. Chem.*, 1995, **32**, 211.
1995JHC953 F. Jourdan, J. Renault, A. Karamat, D. Ladurie, and M. Robba, *J. Heterocycl. Chem.*, 1995, **32**, 953.
1995JHC1457 H. Poschenrieder and H. Stachel, *J. Heterocycl. Chem.*, 1995, **32**, 1457.
1995JME2158 A. Gangjee, F. Mavandadi, S. F. Queener, and J. J. McGuire, *J. Med. Chem.*, 1995, **38**, 2158.
1995JME2557 W. F. Michne, J. D. Schroeder, J. W. Guiles, A. M. Treasurywala, and C. A. Weigelt, *J. Med. Chem.*, 1995, **38**, 2557.
1995JME3798 A. Gangjee, R. Devraj, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 1995, **38**, 3798.
1995JME3957 B. K. Bhattacharya, J. O. Ojwang, R. F. Rando, J. H. Huffma, and G. R. Revankar, *J. Med. Chem.*, 1995, **38**, 3957.
1995JME4106 S. H. Krawczyk, M. R. Nassiri, L. S. Kucera, E. R. Kern, R. G. Ptak, L. L. Wotring, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 1995, **38**, 4106.
1995JME4161 G. L. Bundy, D. E. Ayer, L. S. Banitt, K. L. Belonga, S. A. Mizsak, J. P. Palmer, J. M. Tustin, J. E. Chin, E. D. Hall, K. L. Linesmars, I. M. Richards, H. M. Scherch, F. F. Sun, P. A. Yonkers, P. G. Larson, J. M. Lin, G. E. Padbury, C. S. Aaron, and J. K. Mayo, *J. Med. Chem.*, 1995, **38**, 4161.
1995JME4495 A. Gangjee, R. Devray, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 1995, **38**, 4495.
1995JOC1461 P. G. Baraldi, B. Cacciari, S. Manfredini, G. P. Pollini, D. Simoni, G. Spalluto, and V. Zanirato, *J. Org. Chem.*, 1995, **60**, 1461.
1995JOC5069 E. D. Edstrom and Y. Wei, *J. Org. Chem.*, 1995, **60**, 5069.

1995JOC6684 E. C. Taylor, H. H. Patel, and J.-G. Jun, *J. Org. Chem.*, 1995, **60**, 6684.
1995JOC7947 E. C. Taylor and W. B. Young, *J. Org. Chem.*, 1995, **60**, 7947.
1995LA1703 S. Tumkevicius, *Liebigs Ann. Chem.*, 1995, 1703.
1995MI136 J. R. Desai, A. R. Parikh, and N. A. Chauhan, *J. Inst. Chem. (India)*, 1995, **67**, 136.
1995MI177 A. S. Aly, N. M. Fathy, S. A. Swelam, and F. M. E. Abdel-Megeid, *Egypt. J. Pharm. Sci.*, 1995, **36**, 177.
1995MI281 L. Cuff and M. Kertesz, *Polym. Mat. Sci. Eng.*, 1995, 281.
1995MI756 A. V. Tsytovich, D. V. Shamshin, V. B. Burkosvskii, and V. I. Shvets, *Russ. J. Bioorg. Chem.*, 1995, **21**, 756.
1995MM2922 J. Kastner, H. Kuzmany, D. Vegh, M. Landl, L. Cuff, and M. Kertesz, *Macromolecules*, 1995, **28**, 2922.
1995NN291 D. Loakes and D. M. Brown, *Nucleos. Nucleot.*, 1995, **14**, 291.
1995PHA788 A. M. Hussein, A. A. Atalla, and A. M. K. El-Dean, *Pharmazie*, 1995, **50**, 788.
1995PJC887 M. G. Assy, A. El-Kafrawy, and M. M. Hassanien, *Pol. J. Chem.*, 1995, **69**, 887.
1995PJC1033 M. G. Assy, *Pol. J. Chem.*, 1995, **69**, 1033.
1995PJC1642 A. M. Hussein, A. A. Atalla, and A. M. K. El-Dean, *Pol. J. Chem.*, 1995, **69**, 1642.
1995PS(102)65 M. G. Assy, M. M. Hassaniem, and G. A. Ahmed, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1995, **102**, 65.
1995PTR90 A. Lang, C. Dunn, K. Paulini, C. L. Gibson, M. J. Rice, and C. J. Suckling, *Pteridines*, 1995, **6**, 90.
1995RJO273 Y. M. Yutilov, N. N. Smolyar, and S. V. Gres'ko, *Russ. J. Org. Chem.*, 1995, **31**, 273.
1995SM593 J. Kastner, H. Kuzmany, D. Vegh, M. Landl, L. Cuff, and M. Kertesz, *Synth. Met.*, 1995, **69**, 593.
1995SM599 S. Tanaka and Y. Yamashita, *Synth. Met.*, 1995, **69**, 599.
1995SM691 C. Quattrocci, R. Lazzaroni, R. Kiebooms, D. Vanderzande, J. Gelan, and J. L. Bredas, *Synth. Met.*, 1995, **69**, 691.
1995T12745 H. Al-Awadhi, F. Al-Omran, M. H. Elnagdi, L. Infantes, C. Foces-Foces, N. Jagerovic, and J. Elguero, *Tetrahedron*, 1995, **51**, 12745.
1996AF981 A. K. Gadad, S. G. Kapsi, R. I. Anegundi, S. R. Pattan, C. S. Mahajanshetti, and C. J. Shishoo, *Arzneim. Forsch.*, 1996, **46**, 981.
1996BMC593 L. F. Kuyper, J. M. Garvey, D. P. Baccanari, J. N. Champness, D. K. Stammers, and C. R. Beddell, *Bioorg. Med. Chem.*, 1996, **4**, 593.
1996BSF501 J.-P. Bouillon, Z. Janousek, and H. G. Viehe, *Bull. Soc. Chim. Fr.*, 1996, **133**, 501.
1996CCC49 M. Otmar, M. Masojidkova, and A. Holy, *Collect. Czech. Chem. Commun.*, 1996, **61**, S49.
1996CHEC-II(7)229 T. J. Delia and D. T. Hurst; in 'Comprehensive Hetrocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 8, p. 229.
1996CM570 C. Kitamura, S. Tanaka, and Y. Yamashita, *Chem. Mater.*, 1996, **8**, 570.
1996H(42)691 A. Miyashita, K. Fujimoto, T. Okada, and T. Higashino, *Heterocycles*, 1996, **42**, 691.
1996H(43)199 K. Iwamoto, S. Suzuki, E. Oishi, A. Miyashita, and T. Higashino, *Heterocycles*, 1996, **43**, 199.
1996H(43)323 E. C. Taylor and B. Hu, *Heterocycles*, 1996, **43**, 323.
1996H(43)349 E. C. Taylor, H. H. Patel, G. Sabitha, and R. Chaudhari, *Heterocycles*, 1996, **43**, 349.
1996H(43)389 S. Ostrowski, *Heterocycles*, 1996, **43**, 389.
1996H(43)1073 M. C. Veiga, M. J. Quintela, and C. Peinador, *Heterocycles*, 1996, **43**, 1073.
1996H(43)1863 T. Yamasaki, M. Oda, Y. Okamoto, T. Okawara, and M. Furukawa, *Heterocycles*, 1996, **43**, 1863.
1996HAC29 Z. E. Kandeel, *Heteroatom Chem.*, 1996, **7**, 29.
1996J(P1)417 N. Ono, H. Hironaga, K. Ono, S. Kaneko, T. Murashima, T. Ueda, C. Tsukamura, and T. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1996, 417.
1996J(P1)459 T. Sakamoto, Y. Kondo, S. Sato, and H. Yamanaka, *J. Chem. Soc., Perkin Trans. 1*, 1996, 459.
1996J(P1)1403 T. Murashima, K. Fujita, K. Ono, T. Ogawa, H. Uno, and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1403.
1996JHC229 E. A. M. Badawey, *J. Heterocycl. Chem.*, 1996, **33**, 229.
1996JHC659 C. G. Lockhart and J. W. Sowell, *J. Heterocycl. Chem.*, 1996, **33**, 659.
1996JHC1959 A. Rosowsky, C. E. Mota, and S. F. Queener, *J. Heterocycl. Chem.*, 1996, **33**, 1959.
1996JME873 T. E. Renau, L. L. Wotring, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 1996, **39**, 873.
1996JME2285 P. M. Traxler, P. Furet, H. Mett, E. Buchdunger, T. Meyer, and N. Lydon, *J. Med. Chem.*, 1996, **39**, 2285.
1996JME2482 C. E. Mueller, U. Geis, B. Grahner, W. Lanzner, and K. Eger, *J. Med. Chem.*, 1996, **39**, 2482.
1996JME4563 A. Gangjee, F. Mavandadi, R. L. Kisliuk, J. J. McGuire, and S. F. Queener, *J. Med. Chem.*, 1996, **39**, 4563.
1996JOC5706 S. V. Kudrevich, S. Gilbert, and J. E. van Lier, *J. Org. Chem.*, 1996, **61**, 5706.
1996JOC7973 E. C. Taylor and Z. Mao, *J. Org. Chem.*, 1996, **61**, 7973.
1996JPR206 K. Gewald, H. Achaefer, K. Eckert, and T. Jeschke, *J. Prakt. Chem.*, 1996, **338**, 206.
1996JST(385)55 O. V. Shishkin and D. M. Antonov, *J. Mol. Struct.*, 1996, **385**, 55.
1996M537 J. M. Quintela, M. C. Veiga, R. Alzarez-Sarandes, and C. Peinador, *Monatsh. Chem.*, 1996, **127**, 537.
1996M739 J. M. Quintela, M. C. Veiga, S. Conde, and C. Peinador, *Monatsh. Chem.*, 1996, **127**, 739.
1996M955 S. M. Sherif, *Monatsh. Chem.*, 1996, **127**, 955.
1996M1037 J. M. Quintela, M. C. Veiha, R. Alvarez-Sarandes, L. Gonzalez, and C. Peinador, *Monatsh. Chem.*, 1996, **127**, 1037.
1996MI26 D. Zuo, Y. Zhang, J. Shen, and Y. Li, *Zhongjuo Yaowu Huaxue Zazhi*, 1996, **6**, 26 (*Chem. Abstr.*, 1996, **120**, 167917).
1996MI83 S. Tumkevicius, *Chemija*, 1995, 83.
1996MI597 P. G. Baraldi, B. Cacciari, R. Romagnoli, G. Spalluto, L. Garuti, M. Roberti, A. Pani, G. Perra, F. Scintu, N. Pinna, C. Musiu, and P. La Colla, *Anti-Cancer Drug Des.*, 1996, **11**, 597.
1996NN1223 C. S. Lee, J. Du, and C. K. Chu, *Nucleos. Nucleot.*, 1996, **15**, 1223.
1996NN1821 Y. Xiang, J. Du, and C. K. Chu, *Nucleos. Nucleot.*, 1996, **15**, 1821.
1996PHA7 M. Santagati, M. Modica, A. Santagati, F. Russo, and S. Spampinato, *Pharmazie*, 1996, **51**, 7.
1996PJC589 A. M. Hussein, A. A. Atalla, I. S. Abdel-Hafez, and M. H. Elnagdi, *Pol. J. Chem.*, 1996, **70**, 589.
1996PS271 F. M. Abdelrazek, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, 271.
1996RCB1720 A. V. Komkov, V. S. Bogdanov, and V. A. Dorokhov, *Russ. Chem. Bull.*, 1996, **45**, 1720.
1996SC617 J. J. Chen, J. M. Hinkley, D. S. Wise, and L. B. Townsend, *Synth. Commun.*, 1996, **26**, 617.
1996SC3317 M. T. Migawa, J. M. Hinkley, G. C. Hoops, and L. B. Townsend, *Synth. Commun.*, 1996, **26**, 3317.

1996SC3733 Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Bahab, and S. A. Ahmed, *Synth. Commun.*, 1996, **26**, 3733.
1996T1011 V. A. Artyomov, L. A. Rodinovskaya, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1996, **52**, 1011.
1996T1723 A. C. Tome, J. A. S. Cavaleiro, and R. C. Storr, *Tetrahedron*, 1996, **52**, 1723.
1996T7973 A. G. Martinez, A. H. Fernandez, F. M. Jimenez, P. J. M. Martinez, A. Cristina, and L. R. Subramanian, *Tetrahedron*, 1996, **52**, 7973.
1996TL1853 P. J. Bhuyan, J. S. Sandhu, and A. C. Ghosh, *Tetrahedron Lett.*, 1996, **37**, 1853.
1996TL4339 A. J. Elliott, J. A. Montgomery, and D. A. Walsh, *Tetrahedron Lett.*, 1996, **37**, 4339.
1996TL5829 A. J. Elliott, P. L. Kotian, J. A. Montgomery, and D. A. Walsh, *Tetrahedron Lett.*, 1996, **37**, 5829.
1996TL8147 M. W. Andersen, S. M. Daluge, L. Kerremans, and P. Herdewijn, *Tetrahedron Lett.*, 1996, **37**, 8147.
1997AF958 H. H. Zoorob, M. A. Elzahab, M. Abdel-Mogib, M. A. Ismail, and M. Abdel-Hamid, *Arzneim.-Forsch.*, 1997, **47**, 958.
1997BML1629 M. Zhang and R. W. Harper, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1629.
1997CAR33 C. Liang, T. Ma, J. S. Cooperwood, J. Du, and C. K. Chu, *Carbohydr. Res.*, 1997, **303**, 33.
1997CC371 C. L. Gibson, K. Paulini, and C. J. Suckling, *Chem. Commun.*, 1997, 371.
1997CC695 V. C. Bailey, J. K. Sethi, A. Galione, and B. V. L. Potter, *Chem. Commun.*, 1997, 695.
1997CCA841 A. Juric, S. Nikolic, and N. Trinajstic, *Croat. Chem. Acta*, 1997, **70**, 841.
1997CHE1450 O. E. Nasakin, A. N. Lyshchikov, P. M. Lukin, V. A. Tafeenko, and A. K. Bulai, *Chem. Heterocycl. Compd.*, 1997, **33**, 1450.
1997FA547 A. Ranise, O. Bruno, S. Schenone, F. Bondavalli, G. Falcone, W. Filippeli, and S. Sorrentino, *Farmaco*, 1997, **52**, 547.
1997H(45)1319 J. M. Quintela, R. Alvarez-Sarandes, M. C. Veiga, and C. Peinador, *Heterocycles*, 1997, **45**, 1319.
1997H(45)2159 A. Miyashita, K. Obae, Y. Suzuki, E. Oishi, K. Iwamoto, and T. Higashino, *Heterocycles*, 1997, **45**, 2159.
1997HAC29 A. M. Hussein, A. A. Atalla, I. S. Abdel-Hafez, and M. H. Elnagdi, *Heteroatom Chem.*, 1997, **8**, 29.
1997HCO151 Y. M. Elkholy, A.-Z. Abdel-Aziz Elassar, and M. H. Elnagdi, *Heterocycl. Commun.*, 1997, **3**, 151.
1997IJB566 U. S. Pathak, I. S. Rathod, K. S. Jain, N. S. Laddha, and K. S. Kolhe, *Indian J. Chem., Sect. B*, 1997, **36**, 566.
1997IJB612 M. K. A. Ibrahim, A. H. H. Elghandour, and B. el-Badry, *Indian J. Chem., Sect. B*, 1997, **36**, 612.
1997IJB1126 S. El-Maligie, *Indian J. Chem., Sect. B*, 1997, **36**, 1126.
1997JA1406 L. C. Bush, R. B. Heath, X. W. Feng, P. A. Wang, L. Maksimovic, A. In Song, W.-S. Chung, A. B. Berinstain, J. C. Scaiano, and J. A. Berson, *J. Am. Chem. Soc.*, 1997, **119**, 1406.
1997JCP5541 L. Cuff and M. Kertesz, *J. Chem. Phys.*, 1997, **106**, 5541.
1997JCM309 K. C. Majumdar and U. Das, *J. Chem. Res. (S)*, 1997, **9**, 309.
1997JCM452 W. M. Baqsyouni, H. M. Hosni, and K. A. M. El-Bayouki, *J. Chem. Res. (S)*, 1997, 452.
1997JIC58 M. G. Assy, *J. Indian Chem. Soc.*, 1997, **74**, 158.
1997JME574 M. Modica, M. Santagati, F. Russo, L. Parotti, L. De Gioia, C. Selvaggini, M. Salmona, and T. Menneni, *J. Med. Chem.*, 1997, **40**, 574.
1997JME794 E. A. Meade, L. L. Wotring, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 1997, **40**, 794.
1997JME1749 Y. L. Chen, R. S. Mansbach, S. M. Winter, E. Brooks, J. L. Collins, M. L. Corman, A. R. Dunaiskis, W. S. Faraci, R. J. Gallaschun, A. Schmidt, and D. W. Schulz, *J. Med. Chem.*, 1997, **40**, 1749.
1997JME3694 A. Rosowsky, A. T. Papoulis, and S. F. Queener, *J. Med. Chem.*, 1997, **40**, 3694.
1997JME3897 S. Kudrevich, N. Brasseur, C. La Madeleine, S. Gilbert, and J. E. van Lier, *J. Med. Chem.*, 1997, **40**, 3897.
1997JOC8071 A. J. Elliott, P. E. Morris, S. L. Petty, and C. H. Williams, *J. Org. Chem.*, 1997, **62**, 8071.
1997JPR284 M. M. El-Abadelah, M. R. Kamal, and W. M. Tokan, *J. Prakt. Chem./Chem. Ztg.*, 1997, **339**, 284.
1997M687 S. M. Sherif and A. M. Hussein, *Monatsh. Chem.*, 1997, **128**, 687.
1997MI28 D. Zuo, D. Lu, Y. Liu, and Y. Zhang, *J. Chin. Pharm. Sci.*, 1997, **6**, 28.
1997MI105 C. J. Shishoo, V. S. Shirsath, I. S. Rathod, S. B. Brahmbhatt, U. S. Pathak, and K. S. Jain, *Drug Des. Discov.*, 1997, **15**, 105.
B-1997MI399 V. Cody, N. Galitsky, J. R. Luft, W. Pangborn, A. Gangjee, and S. F. Queener; in 'Proceedings of Intl. Symposium on Pteridines and Folates: Chemistry and Biology of Pteridines and Folates', 11th edn., W. Pfleiderer and H. Rokos, Eds.; Blackwell, Berlin, 1997, p. 399.
1997MI501 L. M. Osborne and T. W. Miyakawa, *J. Liquid Chromatogr. Related Tech.*, 1997, **20**, 501.
1997MI610 M. T. Omar, *Archives Pharm. Res.*, 1997, **20**, 610.
1997NN495 R. R. Talekar and R. H. Wightman, *Nucleos. Nucleot.*, 1997, **16**, 495.
1997PHA500 A. A. Geies, *Pharmazie*, 1997, **52**, 500.
1997S1067 F. Seela, Y. Chen, and M. Zulauf, *Synthesis*, 1997, 1067.
1997T391 M. Otmar, M. Masojidkova, and A. Holy, *Tetrahedron*, 1997, **53**, 391.
1997T3831 R. R. Talekar and R. H. Wightman, *Tetrahedron*, 1997, **53**, 3831.
1997TA995 V. Gotor, F. Limeres, R. Garcia, M. Bayod, and R. Brieva, *Tetrahedron Asymmetry*, 1997, **8**, 995.
1997TL1729 M. F. Gordeev, H. C. Hui, E. M. Gordon, and D. V. Patel, *Tetrahedron Lett.*, 1997, **38**, 1729.
1998BCJ2387 A. W. Erian and F. A. Abu-Shanab, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 2387.
1998CHE688 A. A. Semioshkin, V. A. Artemov, V. L. Ivanov, G. M. Ptashits, P. V. Petrovskii, A. M. Shestopalov, V. I. Bregadze, and V. P. Litvinov, *Chem. Heterocycl. Compd.*, 1998, **34**, 688.
1998CJC1038 A. W. Erian, E. A. A. Hafex, E. S. Darwish, and M. H. Elnagdi, *Can. J. Chem.*, 1998, **76**, 1038.
1998CPB1724 N. Cho, Y. Nara, M. Harada, T. Sugo, Y. Masuda, A. Abe, K. Kusimoto, Y. Itoh, T. Ohtaki, T. Watanabe, and S. Furuya, *Chem. Pharm. Bull.*, 1998, **46**, 1724.
1998EJO827 U. Diederichsen and H. W. Schmitt, *Eur. J. Org. Chem.*, 1998, 827.
1998H(47)315 T. Yamasaki, K. Nishida, Y. Okamoto, T. Okawara, and M. Furukawa, *Heterocycles*, 1998, **47**, 315.
1998H(48)1157 M. Rehwald and K. Gewald, *Heterocycles*, 1998, **48**, 1157.
1998IJB73 M. Shah, P. Patel, and H. Parekh, *Indian J. Chem., Sect. B*, 1998, **37**, 73.
1998IJH147 S. A. Swelam, *Indian J. Heterocycl. Chem.*, 1998, **8**, 147.
1998JCM284 J. Jaung, M. Matsuoka, and K. Fukunishi, *J. Chem. Res. (S)*, 1998, **6**, 284.
1998JCM2025 P. J. Bhuyan, K. C. Lekhok, and J. S. Sandhu, *J. Chem. Res. (S)*, 1998, 2025.
1998JHC659 H.-S. Lee, Y.-G. Chang, and K. Kim, *J. Heterocycl. Chem.*, 1998, **35**, 659.
1998JHC1295 C. G. Dave and R. D. Shah, *J. Heterocycl. Chem.*, 1998, **35**, 1295.

1998JME4021 M. L. Crespo, L. Pages, A. Vega, V. Segarra, M. Lopez, G. Spalluto, and V. Zanirato, *J. Med. Chem.*, 1998, **41**, 4021.
1998JMT(424)21 J. A. Berson, *THEOCHEM*, 1998, **424**, 21.
1998JMT(427)65 A. Guven and C. Ogretic, *THEOCHEM*, 1998, **427**, 65.
1998JMT(430)85 A. Guven and C. Ogretic, *THEOCHEM*, 1998, **430**, 85.
1998JMT(434)7 A. Guven and C. Ogretir, *THEOCHEM*, 1998, **434**, 7.
1998JOC3550 K. C. Majumdar, U. Das, and N. K. Jana, *J. Org. Chem.*, 1998, **63**, 3550.
1998JOC6329 D. L. Boger, R. P. Schaum, and R. M. Garbaccio, *J. Org. Chem.*, 1998, **63**, 6329.
1998JOC9997 K. C. Majumdar and U. Das, *J. Org. Chem.*, 1998, **63**, 9997.
1998J(P1)3025 C. L. Gibson, K. Ohta, K. Paulini, and C. J. Suckling, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3025.
1998J(P1)3557 J. M. Quintela, R. Alvarez-Sarandes, and C. Peinador, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3557.
1998J(P1)3565 D. M. Williams, D. Loakes, and D. M. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3565.
1998M523 A. M. D. El-Dean, *Monatsh. Chem.*, 1998, **129**, 523.
1998MI187 S. Y. Sung and K. S. Sin, *Arch. Pharm. Res.*, 1998, **21**, 187.
1998PHA227 D. Briel, *Pharmazie*, 1998, **53**, 227.
1998PHA839 A. M. K. El-Dean and S. M. Radwan, *Pharmazie*, 1998, **53**, 839.
1998SC3835 A. R. Porcari and L. B. Townsend, *Synth. Commun.*, 1998, **28**, 3835.
1998SC3885 S. E. Watson, F. Khandkar, M. Bui, A. Markovich, and E. C. Taylor, *Synth. Commun.*, 1998, **28**, 3885.
1998T2931 H. Otmar, M. Masojidkova, M. Budesinsky, and A. Holy, *Tetrahedron*, 1998, **54**, 2931.
1998T5753 J. Cobo, A. Sanchez, and M. Nogueras, *Tetrahedron*, 1998, **54**, 5753.
1999APH49 H. M. Hosni, W. M. Basyouni, and K. A. M. El-Bayouki, *Acta Poloniae Pharm.*, 1999, **56**, 49.
1999AXC1335 F. Seela, C. Wei, H. Reuter, and G. Kastner, *Acta Crystallogr., Sect. C*, 1999, **55**, 1335.
1999AXC1560 F. Seela, M. Zulauf, H. Reuter, and G. Kastner, *Acta Crystallogr., Sect. C*, 1999, **55**, 1560.
1999BAP135 A. M. K. El-Dean, A. A. Geies, and S. M. Radwan, *Bull. Pol. Acad. Sci.*, 1999, **47**, 135.
1999BMC297 A. E. Shinkwin, W. J. D. Whish, and M. D. Threadgill, *Bioorg. Med. Chem.*, 1999, **7**, 297.
1999CHE1381 S. Tumkevicius and V. Masyavicius, *Chem. Heterocycl. Compd.*, 1999, **35**, 1381.
1999CPB156 F. Wahid, C. Monneret, and D. Dauzonne, *Chem. Pharm. Bull.*, 1999, **47**, 156.
1999EJC469 H. M. Hosni, *Egypt. J. Chem.*, 1999, **42**, 469.
1999H(51)2723 M. T. Chhabria and C. J. Shishoo, *Heterocycles*, 1999, **51**, 2723.
1999HCA2028 D. Loakes, R. Bazzanini, and D. M. Brown, *Helv. Chim. Acta*, 1999, **82**, 2028.
1999HCO107 L. Strekowski, M. A. Ismail, and H. H. Zoorob, *Heterocycl. Commun.*, 1999, **5**, 107.
1999HCO463 M. A. Khalil, M. A. Raslan, K. M. Dawood, and S. M. Sayed, *Heterocycl. Commun.*, 1999, **5**, 463.
1999JCM646 H. M. Hosni, W. M. Basyouni, and H. A. El-Nahas, *J. Chem. Res. (S)*, 1999, 646.
1999JCM648 A. A. Al-Naggar, M. M. Abdel-Khalik, and M. H. Elnagdi, *J. Chem. Res. (S)*, 1999, 648.
1999JHC423 P. E. Morris, A. J. Elliott, and J. A. Montgomery, *J. Heterocycl. Chem.*, 1999, **36**, 423.
1999JHC729 C. G. Dave and N. D. Desai, *J. Heterocycl. Chem.*, 1999, **36**, 729.
1999JLR1235 T. L. Hutchison and P. E. Morris, *J. Labelled Cmpd. Radiopharm.*, 1999, **42**, 1235.
1999JME4479 C. McGuigan, C. J. Yarnold, G. Jones, S. Velazquez, H. Barucki, A. Brancale, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *J. Med. Chem.*, 1999, **42**, 4479.
1999JOC394 S. Yang and J. Fang, *J. Org. Chem.*, 1999, **64**, 394.
1999JOC8411 R. H. Furneaux and P. C. Tyler, *J. Org. Chem.*, 1999, **64**, 8411.
1999JPC147 A. W. Erian, *J. Prakt. Chem.*, 1999, **34**, 147.
1999M1117 S. M. Radwan and E. A. Bakhite, *Monatsh. Chem.*, 1999, **130**, 1117.
1999MI37 U. S. Pathak and V. Alagarsamy, *Acta Pharm. Turcica*, 1999, **4**, 37.
1999MI140 S. Tumkevicius and A. Kaminskas, *Chemija*, 1999, **10**, 140.
1999MI417 E. H. Morkved, H. Kjosen, H. Ossletten, and N. Erchak, *J. Porphyrins Phthalocyanines*, 1999, **3**, 417.
1999NN153 A. R. Porcari and L. B. Townsend, *Nucleos. Nucleot.*, 1999, **18**, 153.
1999NN363 E. S. Gibson, K. Lesiak, K. A. Watanabe, L. J. Gudas, and K. W. Pankiewicz, *Nucleos. Nucleot.*, 1999, **18**, 363.
1999OPD184 C. J. Barnett, T. M. Wilson, and M. E. Kobierski, *Org. Process Res. Dev.*, 1999, **3**, 184.
1999PHA858 D. Briel, *Pharmazie*, 1999, **54**, 858.
1999PS(155)175 S. M. Radwan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1999, **155**, 175.
1999SC4141 A. A. Shalaby, M. El-Shahawi, N. A. Shams, and S. Batterjee, *Synth. Commun.*, 1999, **29**, 4141.
1999SL1265 E. Rossi, G. Abbiati, and E. Pini, *Synlett*, 1999, 1265.
1999TL3309 B. K. Chun and C. K. Chu, *Tetrahedron Lett.*, 1999, **40**, 3309.
1999TL4023 E. C. Taylor and B. Liu, *Tetrahedron Lett.*, 1999, **40**, 4023.
1999TL4027 E. C. Taylor and B. Liu, *Tetrahedron Lett.*, 1999, **40**, 4027.
1999TL5291 E. C. Taylor and B. Liu, *Tetrahedron Lett.*, 1999, **40**, 5291.
1999WO9957122 P. P. Ehrlich, J. W. Ralston, J. F. Daanen, and M. D. Meyer, *PCT* WO 99 57 122 (1999) (*Chem. Abstr.*, 1999, **131**, 337029).
2000AF904 M. R. Prasad, U. S. Pathak, and A. R. R. Rao, *Arzneim.-Forsch.*, 2000, **50**, 904.
2000AGE2488 A. L. Rodriguez, C. Koradin, W. Dohle, and P. Knochel, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2488.
2000BML175 B. Lagu, D. Tian, G. Chiu, D. Nagarathnam, J. Fang, W. Shen, C. Forray, R. W. Ranson, R. S. L. Chang, K. P. Vyas, and K. Zhang, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 175.
2000BML1089 M. Modica, M. Santagati, A. Santagati, F. Russo, A. Cagnotto, M. Goegan, and T. Mennini, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1089.
2000BML1215 A. Brancale, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1215.
2000BML2167 L. D. Arnold, D. J. Calderwood, R. W. Dixon, P. N. Johnston, J. S. Kamens, R. Munschauer, P. Rafferty, and S. E. Ratnofsky, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2167.
2000CHE841 S. Tumkevicius, A. Urbonas, and P. Vainilavicius, *Chem. Heterocycl. Compd.*, 2000, **36**, 841.
2000CHE1349 Y. M. Volovenko and G. G. Dubinina, *Chem. Heterocycl. Compd.*, 2000, **36**, 1349.
2000CHE1409 S. A. Ryndina, A. V. Kadushkin, N. P. Solov'eva, and V. G. Granik, *Chem. Heterocycl. Compd.*, 2000, **36**, 1409.

2000EJM677 M. Modica, M. Santagati, F. Russo, C. Selvaggini, A. Cagnotto, and T. Mennini, *Eur. J. Med. Chem.*, 2000, **35**, 677.

2000EJM1065 M. Modica, M. Santagati, S. Guccione, F. Russo, A. Cagnotto, M. Goegan, and T. Mennini, *Eur. J. Med. Chem.*, 2000, **35**, 1065.

2000H(53)205 M. N. Zimmerman, N. H. Nemeroff, and C. W. Bock, *Heterocycles*, 2000, **53**, 205.

2000H(53)805 L. Jukic, J. Svete, A. Golobic, L. Golic, and B. Stanovnik, *Heterocycles*, 2000, **53**, 805.

2000H(53)2363 M. Gruner, M. Rahwald, K. Eckert, and K. Gewald, *Heterocycles*, 2000, **53**, 2363.

2000HAC94 M. A. Raslan, S. M. Sayed, M. A. Khalil, and A. M. Farag, *Heteroatom Chem.*, 2000, **11**, 94.

2000IJB764 H. M. Hassan and S. M. Bayomi, *Indian J. Chem., Sect. B.*, 2000, **39**, 764.

2000IJH93 I. S. Rathod, A. S. Pillai, and V. S. Shirsath, *Indian J. Heterocycl. Chem.*, 2000, **10**, 93.

2000JFC(105)83 M. Kammoun, A. M. Khemakhem, and B. Hajjem, *J. Fluorine Chem.*, 2000, **105**, 83.

2000JHC5 J.-W. Park, D.-H. Kweon, and Y.-J. Yoon, *J. Heterocycl. Chem.*, 2000, **37**, 5.

2000JHC757 C. G. Dave and R. D. Shah, *J. Heterocycl. Chem.*, 2000, **37**, 757.

2000JHC935 A. Gangjee, N. P. Dubash, and S. F. Queener, *J. Heterocycl. Chem.*, 2000, **37**, 935.

2000JHC1471 G. L. Bundy, T. M. Schwartz, J. R. Palmer, L. S. Banitt, and W. Watt, *J. Heterocycl. Chem.*, 2000, **37**, 1471.

2000JME1586 M. D. Meyer, R. J. Altenbach, F. Z. Basha, W. A. Carroll, S. Condon, S. W. Elmore, J. F. Kerwin, K. B. Sippy, K. Tietje, M. D. Wendt, A. A. Hancock, M. E. Brune, S. A. Buckner, and I. Drizin, *J. Med. Chem.*, 2000, **43**, 1586.

2000JME3125 A. Gangjee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2000, **43**, 3125.

2000JME3837 A. Gangjee, J. Yu, J. J. McGuire, V. Cody, N. Galitsky, R. L. Kisliuk, and S. F. Queener, *J. Med. Chem.*, 2000, **43**, 3837.

2000JME4288 M. H. Norman, N. Chen, Z. Chen, C. Fotsch, C. Hale, N. Han, R. Hurt, T. Jenkins, J. Kincaid, L. Liu, Y. Lu, O. Moreno, V. J. Santora, J. D. Sonnenberg, and W. Karbon, *J. Med. Chem.*, 2000, **43**, 4288.

2000JME4636 S. Hess, C. E. Mueller, W. Frobenius, U. Reith, K. Klotz, and K. Eger, *J. Med. Chem.*, 2000, **43**, 4636.

2000JME4993 C. McGuigan, H. Barucki, S. Blewett, A. Carangio, J. T. Erichsen, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *J. Med. Chem.*, 2000, **43**, 4993.

2000JOC9120 D. L. Boger and S. E. Wolkenberg, *J. Org. Chem.*, 2000, **65**, 9120.

2000J(P2)301 J. M. Janot, E. Bienvenuee, P. Seta, R. V. Bensasson, A. C. Tome, R. F. Enes, J. A. S. Cavaleiro, S. Leach, X. Camps, and A. Hirsch, *J. Chem. Soc., Perkin Trans. 2*, 2000, 301.

2000JPC7106 O. Kwon and M. L. McKee, *J. Phys. Chem.*, 2000, **104**, 7106.

2000MI19 M. S. S. Palanki, P. E. Erdman, M. E. Goldman, C. Suto, and M. J. Suto, *Med. Chem. Res.*, 2000, **10**, 19.

2000MI127 S. Tumkevicius, Z. Sarakauskaite, and A. Urbonas, *Chemija*, 2000, **11**, 127.

2000MI389 Y. A. Issac, M. S. Ali, and A. W. Erian, *Sci. Pharm.*, 2000, **68**, 389.

2000MOL835 A. B. A. El-Gazzar and N. A. Hassan, *Molecules*, 2000, **5**, 835.

2000NN379 P. E. Morris, A. J. Elliott, S. P. Walton, C. H. Williams, and J. A. Montgomery, *Nucleos. Nucleot.*, 2000, **19**, 379.

2000NN851 C. E. Kerr, B. E. Eaton, and T. L. Netzel, *Nucleos. Nucleot.*, 2000, **19**, 851.

2000OPD129 V. P. Pathak, *Org. Process Res. Dev.*, 2000, **4**, 129.

2000PHA500 M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangano, and A. Caruso, *Pharmazie*, 2000, **55**, 500.

2000PS(163)153 S. M. Radwan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **163**, 153.

2000PS(164)299 S. M. Radwan and A. M. K. El-Dean, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **164**, 299.

2000S255 Z. Wang, R. Neidlein, and C. Krieger, *Synthesis*, 2000, 255.

2000SC4277 K. Kobayashi, H. Tanaka, K. Tanaka, K. Yoneda, O. Morikawa, and H. Konishi, *Synth. Commun.*, 2000, **30**, 4277.

2000T3053 G. B. Evans, R. H. Fumeaux, G. J. Gainsford, V. L. Schramm, and P. C. Tyler, *Tetrahedron*, 2000, **56**, 3053.

2000TL8581 D. Edmont and D. M. Williams, *Tetrahedron Lett.*, 2000, **41**, 8581.

2000TL8741 E. S. Kumarasinghe, M. A. Peterson, and M. J. Robins, *Tetrahedron Lett.*, 2000, **41**, 8741.

2001BKC311 H. A. Saad, H. Y. Moustafa, M. G. Assy, and M. A. Sayed, *Bull. Korean Chem. Soc.*, 2001, **22**, 311.

2001BML391 S. Srinivasan, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 391.

2001BML849 L. Widler, J. Green, M. Missbach, M. Susa, and E. Altmann, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 849.

2001BML1119 W. A. Carroll, K. B. Sippy, T. A. Esbenshade, S. A. Buckner, A. A. Hancock, and M. D. Meyer, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1119.

2001BML2817 E. B. Grant, D. Guiadeen, M. Singer, D. Argentieri, D. J. Hlasta, and M. Wachter, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2817.

2001CC2204 N. Shankiand, W. I. F. David, K. Shankland, A. R. Kennedy, C. S. Frampton, and A. J. Florence, *Chem. Commun.*, 2001, 2204.

2001CHC681 I. Garcia, H. Feist, R. Cao, M. Michalik, and K. Peseke, *J. Carbohydr. Chem.*, 2001, **20**, 681.

2001CPB1280 K. Aso, Y. Imai, K. Yukishige, K. Ootsu, and H. Akimoto, *Chem. Pharm. Bull.*, 2001, **49**, 1280.

2001DP133 J.-Y. Jaung, S. H. Jeong, and S. H. Kim, *Dyes Pigments*, 2001, **48**, 133.

2001EJM287 M. Modica, M. Santagati, S. Guccione, F. Russo, A. Cagnotto, M. Goegan, and T. Mennini, *Eur. J. Med. Chem.*, 2001, **36**, 287.

2001H(55)1963 T. Erker and K. Trinkl, *Heterocycles*, 2001, **55**, 1963.

2001HCA513 O. A. Attanasi, L. De Crescentini, P. Filipone, F. Fringuelli, F. Mantellini, M. Matteucci, O. Piermatti, and F. Pizzo, *Helv. Chim. Acta*, 2001, **84**, 513.

2001JCM817 A. Santagati, G. Granata, and M. Santagati, *J. Chem. Res. (S)*, 2001, 817.

2001JHC269 H. Mauroka, K. Yamagata, and M. Yamazaki, *J. Heterocycl. Chem.*, 2001, **38**, 269.

2001JHC349 A. Gangjee, N. P. Dubash, and R. L. Kisliuk, *J. Heterocycl. Chem.*, 2001, **38**, 349.

2001JHC359 H. H. Zoorob, M. A. Ismail, and L. Strekowski, *J. Heterocycl. Chem.*, 2001, **38**, 359.

2001JHC419 M. Guetschow and J. C. Powers, *J. Heterocycl. Chem.*, 2001, **38**, 419.

2001JHC507 S. Demirayak and U. A. Mohsen, *J. Heterocycl. Chem.*, 2001, **38**, 507.

2001JHC685 M. H. Mohamed, M. M. Abdel-Khalik, and M. H. Elnagdi, *J. Heterocycl. Chem.*, 2001, **38**, 685.

2001JHC973 M. Modica, M. Santagati, and A. Santagati, *J. Heterocycl. Chem.*, 2001, **38**, 973.

2001JHC1051 H. Namazi, Y. R. Mirzaei, and H. Azamat, *J. Heterocycl. Chem.*, 2001, **38**, 1051.

2001JHC1179 S.-G. Lee, D.-H. Kweon, and Y.-J. Yoon, *J. Heterocycl. Chem.*, 2001, **38**, 1179.

2001JHC1197 A. Rosowsky, H. Fu, and S. F. Queener, *J. Heterocycl. Chem.*, 2001, **38**, 1197.

2001JLR797 J. A. Easter and W. T. Stolle, *J. Labelled Compd. Radiopharm.*, 2001, **44**, 797.
2001JME1993 A. Gangjee, A. Vidwans, E. Elzein, J. J. McGuire, S. F. Queener, and R. L. Kisliuk, *J. Med. Chem.*, 2001, **44**, 1993.
2001JOC3726 E. C. Taylor and B. Liu, *J. Org. Chem.*, 2001, **66**, 3726.
2001JOC4723 M. Guetschow and J. C. Powers, *J. Org. Chem.*, 2001, **66**, 4723.
2001JOC4852 B. K. Chun, G. Y. Song, and C. K. Chu, *J. Org. Chem.*, 2001, **66**, 4852.
2001JOC5723 G. B. Evans, R. H. Furneaux, T. L. Hutchison, H. S. Kezar, P. E. Morris, V. L. Schramm, and P. C. Tyler, *J. Org. Chem.*, 2001, **66**, 5723.
2001MC152 I. L. Yudin, S. M. Aronova, A. B. Sheremetev, B. B. Averkiev, and M. Y. Antipin, *Mendeleev Commun.*, 2001, 152.
2001MI11 M. K. Abd El-Hamed, M. M. Kandeel, S. M. A. Roshdy, and F. El-Telbany, *Bull. Fac. Pharm.*, 2001, **39**, 11.
2001MI17 A. K. El-Ansary and A. H. Omar, *Bull. Fac. Pharm.*, 2001, **39**, 17.
2001MI27 M. Bayod, F. Fernandex-Mari, L. Llavona, I. Llorente, C. Ribas, and V. M. Sanchez-Pedregal, *Recent Res. Dev. Org. Chem.*, 2001, **5**, 27.
2001MI497 M. Rarey and M. Stahl, *J. Comput.-Aided Mol. Des.*, 2001, **15**, 497.
2001NN287 C. McGuigan, H. Barucki, A. Carangio, S. Blewett, S. Srinivasan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2001, **20**, 287.
2001NN653 A. Carangio, C. McGuigan, D. Cahard, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2001, **20**, 653.
2001NN763 S. Srinivasan, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2001, **20**, 763.
2001NN1063 S. Blewett, C. McGuigan, H. Barucki, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2001, **20**, 1063.
2001OL3647 R. K. Boeckman, Jr., P. Ge, and J. E. Reed, *Org. Lett.*, 2001, **3**, 3647.
2001OPD216 R. L. De Jong, J. G. Davidson, G. J. Dozeman, P. J. Fiore, P. Giri, M. E. Kelly, T. P. Puls, and R. E. Seamans, *Org. Process Res. Dev.*, 2001, **5**, 216.
2001OPD581 R. W. Fischer and M. Misun, *Org. Process Res. Dev.*, 2001, **5**, 581.
2001RCB1113 V. B. Sokolov, A. Y. Aksinenko, and I. V. Martynov, *Russ. Chem. Bull.*, 2001, **50**, 1113.
2001RCB2424 M. M. Krayushkin, S. N. Ivanov, A. Y. Martynkin, B. V. Lichitsky, A. A. Dudinov, and B. M. Uzhinov, *Russ. Chem. Bull.*, 2001, **50**, 2424.
2001S559 L. Petersen, E. B. Petersen, and C. Nielsen, *Synthesis*, 2001, 559.
2001S1837 O. A. Attanasi, P. Filippone, B. Guidi, F. Mantellini, and S. Santeusanio, *Synthesis*, 2001, 1837.
2001S2119 M. R. Prasad, A. R. R. Rao, P. S. Rao, and K. S. Rajan, *Synthesis*, 2001, 2119.
2001SC725 W. Zhang, A. R. Haight, K. L. Ford, and S. I. Parekh, *Synth. Commun.*, 2001, **31**, 725.
2001SC2979 K. C. Majumdar, N. K. Jana, A. Bandyopadhyay, and S. K. Ghosh, *Synth. Commun.*, 2001, **31**, 2979.
2001TL999 M. Cheung, P. A. Harris, and K. E. Lackey, *Tetrahedron Lett.*, 2001, **42**, 999.
2002AF448 A. Santagati, G. Granata, M. Santagate, V. Cutuli, V. G. Mangano, and A. Caruso, *Arzneim. Forsch.*, 2002, **52**, 448.
2002AFF147 K. M. H. Hilmy, *Afinidad*, 2002, **59**, 147.
2002BMC3113 M. Fujita, T. Hirayama, and N. Ikeda, *Bioorg. Med. Chem.*, 2002, **10**, 3113.
2002CEJ2891 A. R. Pike, L. C. Ryder, B. R. Horrocks, W. Clegg, M. R. J. Elsegood, B. A. Connolly, and A. Houlton, *Chem. Eur. J.*, 2002, **8**, 2891.
2002CHE219 Y. M. Volovenko and G. G. Dubinina, *Chem. Heterocycl. Compd.*, 2002, **38**, 219.
2002CHE336 Y. M. Volovenko and G. G. Dubinina, *Chem. Heterocycl. Compd.*, 2002, **38**, 336.
2002CPB364 H. Shin, H. B. Cottam, and D. A. Carson, *Chem. Pharm. Bull.*, 2002, **50**, 364.
2002FA613 M. S. A. El-Gaby, A. M. Gaber, A. A. Atalla, and K. A. A. Al-Wahab, *Farmaco*, 2002, 613.
2002H(57)97 T. Erker and K. Trinkl, *Heterocycles*, 2002, **57**, 97.
2002H(57)1471 P. K. Mohanta and K. Kim, *Heterocycles*, 2002, **57**, 1471.
2002H(57)2115 O. R'kyek, B. U. W. Maes, G. L. F. Lemiere, and R. A. Dommisse, *Heterocycles*, 2002, **57**, 2115.
2002H(58)301 T. Murashima, K. Nishi, K. Nakamoto, and A. Kato, *Heterocycles*, 2002, **58**, 301.
2002HAC357 W. M. Abdou, A. F. M. Fahmy, and A. A. Kamel, *Heteroatom Chem.*, 2002, **13**, 357.
2002IJB2414 M. Kidwai, B. Dave, and R. Venkataramanan, *Indian J. Chem., Sect. B*, 2002, **41**, 2414.
2002IZK854 S. A. Ryndina, A. V. Kadushkin, N. P. Solov'eva, and V. G. Granik, *Izv. Akad. Nauk. Ser. Khim.*, 2002, **51**, 789.
2002IZK1879 S. A. Ryndina, A. V. Kadushkin, N. P. Solov'eva, and V. G. Granik, *Izv. Akad. Nauk. Ser. Khim.*, 2002, **51**, 1879.
2002JCCS1057 A. M. K. El-Dean and M. E. Abdel-Moneam, *J. Chin. Chem. Soc.*, 2002, **49**, 1057.
2002JCM5 M. R. Prasad, A. R. Rao, P. S. Rao, and K. S. Rajan, *J. Chem. Res. (S)*, 2002, 5.
2002JCO501 R. Perez, T. Beryozkina, O. I. Zbruyev, W. Haas, and O. C. Kappe, *J. Comb. Chem.*, 2002, **4**, 501.
2002JHC833 A. Gangjee, J. Yu, and R. L. Kisliuk, *J. Heterocycl. Chem.*, 2002, **39**, 833.
2002JHC863 D. Briel, T. Franz, and B. Dobner, *J. Heterocycl. Chem.*, 2002, **39**, 863.
2002JHC877 F. Al-Omran, R. M. Mohareb, and A. A. El-Khair, *J. Heterocycl. Chem.*, 2002, **39**, 877.
2002JME1942 A. Gangjee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2002, **45**, 1942.
2002JME2032 R. Kumar, M. Nath, and D. L. J. Tyrrell, *J. Med. Chem.*, 2002, **45**, 2032.
2002JOC6612 M. Prashad, D. Har, L. Chen, H.-Y. Kim, O. Repic, and T. J. Blacklock, *J. Org. Chem.*, 2002, **67**, 6612.
2002JOC8703 Q. Dang and J. E. Gomez-Galeno, *J. Org. Chem.*, 2002, **67**, 8703.
2002JOC9073 D. D. Kenning, K. A. Mitchell, T. R. Calhoun, M. R. Funfar, D. J. Sattler, and S. C. Rasmussen, *J. Org. Chem.*, 2002, **67**, 9073.
2002MI64 N. H. Ouf, *Aswan Sci. Tech. Bull.*, 2002, 64.
B-2002MI439 A. Gangjee, Y. Zeng, J. J. McGuire, R. L. Kisliuk, and E. Chu; in 'Proceedings of the International Symposium on Pteridines and Folates: Chemistry and Biology of Pteridines and Folates', 12th edn., S. Milstien, Ed.; Academic Publishers, Bethesda, MD, 2002, p. 439.
2002MI717 N. A. Santagati, O. Prezzavento, E. Bousquet, G. Ronsisvalle, and S. Spampinato, *J. Pharm. Pharmacol.*, 2002, **54**, 717.
2002MOL554 C. G. Dave and R. D. Shah, *Molecules*, 2002, **7**, 554.
2002MOL756 A. M. M. El-Saghier, *Molecules*, 2002, **7**, 756.
2002OJC159 M. Shah, P. Patel, and H. Parekh, *Orient. J. Chem.*, 2002, **18**, 159.
2002PS(177)303 E. A. Bakhite, A. A. Geies, and H. S. El-Kashef, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 303.

2002PS(177)2745 A. M. K. El-Dean and M. E. Abdel-Moneam, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 2745.
2002SC989 A. A. Shalaby, M. M. El-Shahawi, N. A. Shams, and S. Batterjee, *Synth. Commun.*, 2002, **32**, 989.
2002SC3749 M. V. Vovk, A. V. Bol'but, A. V. Dorokhov, and V. V. Pyrozhenko, *Synth. Commun.*, 2002, **32**, 3749.
2002SC3797 Mao-Chin Liu, Mei-Zhen Luo, D. E. Mozdziesz, and A. C. Sartorelli, *Synth. Commun.*, 2002, **32**, 3797.
2002TL9151 A. Shaabani, M. B. Teimouri, and H. R. Bijanzadeh, *Tetrahedron Lett.*, 2002, **43**, 9151.
2003AJC811 R. N. Warrener, D. N. Butler, and D. Margetic, *Aust. J. Chem.*, 2003, **56**, 811.
2003BBR917 W. F. de Azevedo, F. Canduri, D. M. dos Santos, J. H. Pereira, M. V. B. Dias, R. G. Silva, M. A. Mendes, L. A. Basso, M. S. Palma, and D. S. Santos, *Biochem. Biophys. Res. Commun.*, 2003, **309**, 917.
2003BCJ203 M. Kidwai, S. Rastogi, and R. Venkataramanan, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 203.
2003BKC1038 M. Kidwai and A. D. Mishra, *Bull. Korean Chem. Soc.*, 2003, **24**, 1038.
2003BKC1181 M. S. A. El-Gaby, A. M. K. El-Dean, A. E. M. Gaber, H. A. Eyada, and A. S. N. Al-Kamali, *Bull. Korean Chem. Soc.*, 2003, **24**, 1181.
2003BMC59 A. Rosowsky, H. Chen, H. Fu, and S. F. Queener, *Bioorg. Med. Chem.*, 2003, **11**, 59.
2003BMC5155 A. Gangjee, J. Yang, M. A. Ihnat, and S. Kamat, *Bioorg. Med. Chem.*, 2003, **11**, 5155.
2003BML107 M. L. P. Price, W. C. Guida, T. E. Jackson, J. A. Nydick, P. L. Gladstone, J. C. Juarez, F. Donate, and R. J. Ternansky, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 107.
2003BML4511 C. McGuigan, A. Brancale, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4511.
2003CHC171 L. Herrera, H. Feist, J. Quincoces, M. Michalik, and K. Peseke, *J. Carbohydr. Chem.*, 2003, **22**, 171.
2003CHE669 V. G. Arsen'ev, M. Y. Arsen'eva, D. V. Shopin, and L. P. Olekhnovich, *Chem. Heterocycl. Compd.*, 2003, **39**, 669.
2003CHE953 E. B. Tsupak, M. A. Shevchenko, A. F. Pozharskii, and Y. N. Tkachenko, *Chem. Heterocycl. Compd.*, 2003, **39**, 953.
2003EJC11 G. A. Ahmed, H. Y. Mostafa, M. G. Assy, and N. S. Mansor, *Egypt. J. Chem.*, 2003, **46**, 11.
2003EJM89 R. V. Chambhare, V. G. Khadse, A. S. Bobde, and R. H. Bahekar, *Eur. J. Med. Chem.*, 2003, **38**, 89.
2003EJM605 I. O. Donkor, H. Li, and S. F. Queener, *Eur. J. Med. Chem.*, 2003, **38**, 605.
2003H(60)337 T. Erker, K. Trinkl, and F. Pertlik, *Heterocycles*, 2003, **60**, 337.
2003H(60)2471 O. R'kyek, B. U. W. Maes, G. L. F. Lemiere, and R. A. Dommisse, *Heterocycles*, 2003, **60**, 2471.
2003HCA1193 D. Loakes, D. M. Brown, S. A. Salisbury, M. G. McDougall, C. Neagu, S. Nampalli, and S. Kumar, *Helv. Chim. Acta*, 2003, **86**, 1193.
2003HCA2149 V. A. Azov, F. Diederich, Y. Lill, and B. Hecht, *Helv. Chim. Acta*, 2003, **86**, 2149.
2003HCO89 S. Tumkevicius, A. Kaminskas, V. Bucinskaite, and L. Labanauskas, *Heterocycl. Commun.*, 2003, **9**, 89.
2003IJH336 V. Alagarsamy, U. S. Pathak, S. Meena, K. V. Rameshu, R. Revathi, S. Amuthalakshmi, K. Thirumurugan, and V. Rajasolomon, *Indian J. Heterocycl. Chem.*, 2003, **12**, 335.
2003JHC869 A. Santagati, A. Marrazzo, and G. Granata, *J. Heterocycl. Chem.*, 2003, **40**, 869.
2003JIC311 A. S. Saxena, A. Goel, and V. J. Ram, *J. Indian Chem. Soc.*, 2003, **80**, 311.
2003JKC591 K. Al-zaydi and M. H. Elnagdi, *J. Korean Chem. Soc.*, 2003, **47**, 591.
2003JME113 S. Sasaki, N. Cho, Y. Nara, M. Harada, S. Endo, N. Suzuki, S. Furuya, and M. Fujino, *J. Med. Chem.*, 2003, **46**, 113.
2003JME155 G. B. Evans, R. H. Furneaux, G. J. Gainsford, J. C. Hanson, G. A. Kicska, A. A. Sauve, V. L. Schramm, and P. C. Tyler, *J. Med. Chem.*, 2003, **46**, 155.
2003JME222 Y. Mettey, M. Gmpel, V. Thomas, M. Garnier, M. Leost, I. Ceallos-Picot, M. Noble, J. Endicott, J.-M. Vierfond, and L. Meijer, *J. Med. Chem.*, 2003, **46**, *222*.
2003JME3060 S. A. Filla, B. M. Mathes, K. W. Johnson, L. A. Phebus, M. L. Cohen, D. L. Nelson, J. M. Zgombick, J. A. Erickson, K. W. Schenck, D. B. Wainscott, T. A. Branchek, and J. M. Schaus, *J. Med. Chem.*, 2003, **46**, 3060.
2003JME3412 G. B. Evans, R. H. Furneaux, A. Lewandowicz, V. L. Schramm, and P. C. Tyler, *J. Med. Chem.*, 2003, **46**, 3412.
2003JME4702 A. Trejo, H. Arzeno, M. Browner, S. Chanda, S. Cheng, D. D. Comer, S. A. Dalrymple, P. Dunten, J. Lafargue, B. Lovejoy, J. Freire-Moar, J. Lim, J. Meintosh, J. Miller, E. Papp, D. Reuter, R. Roberts, F. Sanpablo, J. Saunders, K. Song, A. Villasenor, S. D. Warren, M. Welch, P. Weller, P. E. Whiteley, L. Zeng, and D. M. Goldstein, *J. Med. Chem.*, 2003, **46**, 4702.
2003JOC6788 M. S. Rao, N. Esho, C. Sergeant, and R. Dembinski, *J. Org. Chem.*, 2003, **68**, 6788.
2003JOC6984 F. Marcotte, F. J. R. Rombouts, and W. D. Lubell, *J. Org. Chem.*, 2003, **68**, 6984.
2003JOC9938 E. C. Taylor and B. Liu, *J. Org. Chem.*, 2003, **68**, 9938.
2003MI43 M. M. Kandeel and A. H. Omar, *Bull. Fac. Pharm.*, 2003, **41**, 43.
2003MI72 G. A. Ahmed, S. El-Bahai, Nasser, and M. A. El-Salam, *Boll. Chim. Farm.*, 2003, **142**, 72.
2003MI89 F. E. M. Al-Baih, *J. Saudi Chem. Soc.*, 2003, **7**, 89.
2003MI115 G. A. Ahmed and N. M. A. El-Salam, *Boll. Chim. Farm.*, 2003, **142**, 115.
2003NN931 G. Luoni, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2003, **22**, 931.
2003NN935 A. Carangio, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2003, **22**, 935.
2003NN1029 R. H. E. Hudson, R. D. Viirre, N. McCourt, and J. Tse, *Nucleos. Nucleot.*, 2003, **22**, 1029.
2003NN1939 I. Lavandera, S. Fernandez, M. Ferrero, E. De Clercq, and V. Gotor, *Nucleos. Nucleot.*, 2003, **22**, 1939.
2003NN2171 A. R. Porcari, R. G. Ptak, K. Z. Borysk, J. M. Breitenbach, J. C. Drach, and L. B. Townsend, *Nucleos. Nucleot.*, 2003, **22**, 2171.
2003OBC4166 D. M. Hammond, D. Edmont, A. R. Homillo-Araujo, and D. M. Williams, *Org. Biomol. Chem.*, 2003, **1**, 4166.
2003OL3639 G. B. Evans, R. H. Furneaux, P. C. Tyler, and V. L. Schramm, *Org. Lett.*, 2003, **5**, 3639.
2003PJC1275 S. Tumkevicius and Z. Sarakauskaite, *Pol. J. Chem.*, 2003, **77**, 1275.
2003PJS95 K. M. M. Rahman, A. Z. M. S. Chowdhury, M. M. H. Bhuiyan, M. K. Hossain, and M. K. Uddin, *Pak. J. Sci. Ind. Res.*, 2003, **46**, 95.
2003PS(178)737 M. I. A. Moneam, A. A. Geies, G. M. El-Naggar, and S. M. Mussa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 737.
2003RCB2063 A. E. Fedorov, A. M. Shestopalov, and P. A. Belyakov, *Russ. Chem. Bull.*, 2003, **52**, 2063.
2003S1377 S. Tumkevicius, Z. Sarakauskaite, and V. Masevicius, *Synthesis*, 2003, 1377.
2003TL2121 A. Stefanachi, F. Leonetti, A. Cappa, and A. Carotti, *Tetrahedron Lett.*, 2003, **44**, 2121.
2003TL3387 D. Loakes, D. M. Brown, S. A. Salisbury, M. G. McDougall, C. Neagu, S. Nampalli, and S. Kumar, *Tetrahedron Lett.*, 2003, **44**, 3387.

2003TL5041 G. L. Adams, T. L. Graybill, R. M. Sanchez, V. W. Magaard, G. Burton, and R. A. Rivero, *Tetrahedron Lett.*, 2003, **44**, 5041.
2003TL9181 E. Petricci, M. Radi, F. Corelli, and M. Botta, *Tetrahedron Lett.*, 2003, **44**, 9181.
2004AP148 M. Wamberg, E. B. Pedersen, and C. Nielsen, *Arch. Pharm. (Weinheim, Ger.)*, 2004, **337**, 148.
2004ASJ877 M. Sacmaci and Y. Akcamuv, *Asian J. Chem.*, 2004, **16**, 877.
2004BMC3187 M. Otmar, M. Masojidkova, I. Votruba, and A. Holy, *Bioorg. Med. Chem.*, 2004, **12**, 3187.
2004BMC3891 M. Modica, G. Romeo, L. Materia, F. Russo, A. Cagnotto, T. Mennini, R. Gaspar, G. Falkay, and F. Fulop, *Bioorg. Med. Chem.*, 2004, **12**, 3891.
2004BML21 M. J. Munchhof, J. S. Beebe, J. M. Casavant, B. A. Cooper, J. L. Doty, R. C. Higdon, S. M. Hillerman, C. I. Soderstrom, E. A. Knauth, M. A. Marx, A. M. K. Rossi, S. Sobolov, and J. Sun, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 21.
2004BML413 C. Kunick, K. Lauenroth, M. Leost, L. Meijer, and T. Lemcke, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 413.
2004BML2031 T. Hu, B. A. Stearns, B. T. Campbell, J. M. Arruda, C. Chen, J. Aiyar, R. E. Bezverkov, A. Santini, H. Schaffhauser, W. Lu, S. Venkatraman, and B. Munoz, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2031.
2004BML3907 Y. Maeda, M. Nakano, H. Sato, Y. Miyazaki, S. L. Schweider, J. L. Smith, and A. T. Truesdale, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3907.
2004BML5247 P. Reigan, A. Gbaj, E. Chinje, I. J. Stratford, K. T. Douglas, and S. Freeman, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5247.
2004C640 S. J. Mickel, R. Fischer, and W. Marterer, *Chimia*, 2004, **58**, 640.
2004CC1304 G. Jiao and K. Burgess, *Chem. Commun.*, 2004, 1304.
2004CHE370 M. V. Vovk, A. V. Bolbut, V. I. Boiko, V. V. Pirozhenko, A. N. Chernega, and A. A. Tolmachev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 370.
2004CHE1335 S. Tumkevicius, I. Susvilo, and A. Brukstus, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1335.
2004CHE1352 O. B. Ryabova, M. I. Evstratova, V. A. Makaro, V. A. Tajeenko, and V. G. Granik, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1352.
2004EJC427 F. A. Yassin, *Egypt. J. Chem.*, 2004, **47**, 427.
2004EJC565 S. A. Swelam and N. M. Fawzy, *Egypt J. Chem.*, 2004, **47**, 565.
2004EJM879 A. Carotti, A. Stefanachi, E. Ravina, E. Sotelo, M. I. Loza, M. I. Cadavid, N. B. Centeno, and O. Nicolotti, *Eur. J. Med. Chem.*, 2004, **39**, 879.
2004EUP1388541 L. Meijer, J.-M. Vierfond, and Y. Mettey, *Eur. Pat.* 1 388 541(*Chem. Abstr.*, 2004, **140**, 163892).
2004H(62)191 B. Dyck and J. R. McCarthy, *Heterocycles*, 2004, **62**, 191.
2004HCA956 A. Martin-Kohler, J. Widmer, G. Bold, T. Meyer, U. Sequin, and P. Traxler, *Helv. Chim. Acta*, 2004, **87**, 956.
2004JCCS1325 A. E. M. Gaber, M. S. A. El-Gaby, A. M. K. El-Dean, H. A. Eyada, and A. S. N. Al-Kamali, *J. Chin. Chem. Soc. (Taipei)*, 2004, **51**, 1325.
2004JCCS1357 M. I. A. Moneam, A. A. Geies, G. M. El-Naggar, and S. M. Mousa, *J. Chin. Chem. Soc. (Taipei)*, 2004, **51**, 1357.
2004JCCS1381 A. A. Aly, *J. Chin. Chem. Soc. (Taipei)*, 2004, **51**, 1381.
2004JCO573 A. Ivachtchenko, S. Kovalenko, O. V. Tkachenko, and O. Parkhomenko, *J. Comb. Chem.*, 2004, **6**, 573.
2004JHC941 A. Gangjee, Y. Qiu, and R. L. Kisliuk, *J. Heterocycl. Chem.*, 2004, **41**, 941.
2004JME1322 V. P. Kamath, S. Ananth, S. Bantia, and P. E. Morris, *J. Med. Chem.*, 2004, **47**, 1322.
2004JME1847 C. McGuigan, R. N. Pathirana, R. Snoeck, G. Andrei, E. De Clercq, and J. Balzarini, *J. Med. Chem.*, 2004, **47**, 1847.
2004JME3275 G. B. Evans, R. H. Furneaux, V. L. Schramm, V. Singh, and P. C. Tyler, *J. Med. Chem.*, 2004, **47**, 3275.
2004JME6893 A. Gangjee, Y. Zeng, J. J. McGuire, F. Mehraein, and R. L. Kisliuk, *J. Med. Chem.*, 2004, **47**, 6893.
2004JOC4656 G. Jeannotte and W. D. Lubell, *J. Org. Chem.*, 2004, **69**, 4656.
2004JOC8366 M. Ding, S. Xu, and J. Zhao, *J. Org. Chem.*, 2004, **69**, 8366.
2004NN1 C. McGuigan, A. Carangio, R. Snoeck, G. Andrei, E. De Clercq, and J. Balzarini, *Nucleos. Nucleot.*, 2004, **23**, 1.
2004NN183 S. Guenther and V. Nair, *Nucleos. Nucleot.*, 2004, **23**, 183.
2004NN1929 K. S. Gudmundsson, Z. Wang, S. M. Daluge, L. C. Johnson, R. Hazen, L. D. Condreay, and C. McGuigan, *Nucleos. Nucleot.*, 2004, **23**, 1929.
2004OL1523 D. S. Yoon, Y. Han, T. M. Stark, J. C. Haber, B. T. Gregg, and S. B. Stankovich, *Org. Lett.*, 2004, **6**, 4775.
2004OL1991 F. D. Therkelsen, M. Rottlaender, N. Thorup, and E. Bjerregaard Pedersen, *Org. Lett.*, 2004, **6**, 1991.
2004OL2857 T.-C. Chien, E. A. Meade, J. M. Hinkley, and L. Townsend, *Org. Lett.*, 2004, **6**, 2857.
2004PS(179)97 L. S. Boulos and H. A. Abdel-Malek, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 97.
2004PS(179)321 A. M. K. El-Dean, A. E. M. Gaber, M. S. A. El-Gaby, H. A. Eyada, and A. S. N. Al-Kamali, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 321.
2004PS(179)2245 A. Deeb, M. Kotb, and M. El-Abbasy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **179**, 2245.
2004RCB1257 I. V. Zavarzin, N. G. Smirnova, E. I. Chernoburova, V. N. Yarovenko, and M. M. Krayushkin, *Russ. Chem. Bull.*, 2004, **53**, 1257.
2004SL2406 V. Aucagne, F. Amblard, and L. A. Agrofoglio, *Synlett*, 2004, 2406.
2004T943 C. L. Gibson, S. L. Rosa, K. Ohta, P. H. Boyle, F. Leurquin, A. Lemacon, and C. J. Suckling, *Tetrahedron*, 2004, **60**, 943.
2004TL2457 D. A. Berry, K. Jung, D. S. Wise, A. D. Sercel, W. H. Pearson, H. Mackie, J. B. Randolph, and R. L. Somers, *Tetrahedron Lett.*, 2004, **45**, 2457.
2004TL4873 Z. Zhao, D. D. Wisnoski, S. E. Wolkenberg, W. H. Leister, Y. Wang, and C. W. Lindsley, *Tetrahedron Lett.*, 2004, **45**, 4873.
2004TL6075 C. Mohan, V. Kumar, and M. P. Mahajan, *Tetrahedron Lett.*, 2004, **45**, 6075.
2004TL8087 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 8087.
2004TL8631 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2004, **45**, 8631.
2005BMC1231 N. Esho, J. Desaulniers, B. Davies, H. M. Chui, M. S. Rao, C. S. Chow, S. Szafert, and R. Dembinski, *Bioorg. Med. Chem.*, 2005, **13**, 1231.
2005BMC1239 F. Amblard, V. Aucagne, P. Guenot, R. F. Schinazi, and L. A. Agrofoglio, *Bioorg. Med. Chem.*, 2005, **13**, 1239.
2005BMC5475 A. Gangjee, Y. Zeng, M. Ihnat, L. A. Warnke, D. W. Green, R. L. Kisliuk, and F. Lin, *Bioorg. Med. Chem.*, 2005, **13**, 5475.
2005BML1829 J. Kempson, W. J. Pitts, J. Barbosa, J. Guo, O. Omotoso, A. Watson, K. Stebbins, G. C. Starling, J. H. Dodd, J. C. Barrish, R. Felix, and K. Fischer, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1829.
2005BML1885 E. Duval, A. Case, R. L. Stein, and G. D. Cuny, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1885.

2005BML2203 Y. Miyazaki, S. Matsunaga, J. Tang, Y. Maeda, M. Nakano, R. J. Philippe, M. Shibahara, W. Liu, H. Sato, L. Wang, and R. T. Nolte, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2203.

2005BML2225 A. Gangjee, H. D. Jain, and R. L. Kisliuk, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2225.

2005BML3713 Y. St-Denis, R. Di Fabio, G. Bernasconi, E. Castiglioni, S. Contini, D. Donati, E. Fazzolari, G. Gentile, D. Ghirlanda, C. Marchionni, F. Messina, F. Micheli, F. Pavone, A. Pasquarello, F. M. Sabbatini, M. G. Zampori, R. Arban, and G. Vitulli, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3713.

2005BML3763 Y. D. Wang, S. Johnson, D. Powell, J. P. McGinnis, M. Miranda, and S. K. Rabindran, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3763.

2005BML3791 G. Luoni, C. McGuigan, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3791.

2005CAR547 I. Otero, H. Feist, L. Herrera, M. Michalik, J. Quincoces, and K. Peseke, *Carbohydr. Res.*, 2005, **340**, 547.

2005CC2555 R. T. Ranasinghe, D. A. Rusling, V. E. C. Powers, K. R. Fox, and T. Brown, *Chem. Commun.*, 2005, 2555.

2005CCA55 V. Lather and A. K. Madan, *Croat. Chem. Acta*, 2005, **78**, 55.

2005CHJ211 A. A. Aly, *Chin. J. Chem.*, 2005, **23**, 211.

2005EJO1142 F. Palacios, D. Aparicio, Y. Lopez, J. M. De, los Santos, and C. Alonso, *Eur. J. Org. Chem.*, 2005, **6**, 1142.

2005EJO3724 H. Rudler, B. Denise, Y. Xu, A. Parlier, and J. Vaissermann, *Eur. J. Org. Chem.*, 2005, **17**, 3724.

2005HAC56 W. M. Abdou, N. A. Ganoub, A. F. Fahmy, and A. M. Shaddy, *Heteroatom Chem.*, 2005, **16**, 56.

2005IJB581 M. Kidwai, A. D. Mishra, and S. Saxena, *Indian J. Chem., Sect. B*, 2005, **44**, 581.

2005JCO977 G. Fridkin and W. D. Lubell, *J. Comb. Chem.*, 2005, **7**, 977.

2005JCM23 B. Al-Saleh, M. M. Abdelkhalik, M. A. El-Apasery, and M. H. Elnagdi, *J. Chem. Res. (S)*, 2005, 23.

2005JCM270 F. A. Yassin, *J. Chem. Res. (S)*, 2005, 270.

2005JHC165 A. Gangjee, H. D. Jain, J. Phan, and R. L. Kisliuk, *J. Heterocycl. Chem.*, 2005, **42**, 165.

2005JHC661 S. Hu, Y. Huang, M. A. Poss, and R. G. Gentles, *J. Heterocycl. Chem.*, 2005, **42**, 661.

2005JHC841 D. Briel, S. Drescher, and B. Dobner, *J. Heterocycl. Chem.*, 2005, **42**, 841.

2005JHC1127 A. Gangjee, Z. Ye, and S. F. Queener, *J. Heterocycl. Chem.*, 2005, **42**, 1127.

2005JME2420 E. Patane, V. Pittala, F. Guerrera, L. Salerno, G. Romeo, M. A. Siracusa, F. Russo, F. Manetti, M. Botta, I. Mereghetti, A. Cagnotto, and T. Mennini, *J. Med. Chem.*, 2005, **48**, 2420.

2005JME4690 Z. Janeba, J. Balzarini, G. Andrei, R. Snoeck, E. De Clercq, and M. J. Robins, *J. Med. Chem.*, 2005, **48**, 4690.

2005JME5329 A. Gangjee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2005, **48**, 5329.

2005JME6066 Y. Dai, Y. Guo, R. R. Frey, Z. Ji, M. L. Curtin, A. A. Ahmed, D. H. Albert, L. Arnold, S. S. Arries, T. Barlozzari, J. L. Bauch, J. J. Bouska, P. F. Bousquet, G. A. Cunha, K. B. Glaser, J. Guo, J. Li, P. A. Marcotte, K. C. Marsh, M. D. Moskey, L. J. Pease, K. D. Stewart, V. S. Stoll, P. Tapang, N. Wishart, S. K. Davidsen, and M. R. Michaelides, *J. Med. Chem.*, 2005, **48**, 6066.

2005JME6430 S. H. Boyer, B. G. Ugarkar, J. Solbach, J. Kopcho, M. C. Matelich, K. Ollis, J. E. Gomez-Galeno, R. Mendonca, M. Tsuchiya, A. Nagahisa, M. Nakane, J. B. Wiesner, and M. D. Erion, *J. Med. Chem.*, 2005, **48**, 6430.

2005JME7012 D. Rai, M. Johar, T. Manning, B. Agrawal, D. Y. Kunimoto, and R. Kumar, *J. Med. Chem.*, 2005, **48**, 7012.

2005JOC998 Z. X. Yu, Q. Dang, and Y. D. Wu, *J. Org. Chem.*, 2005, **70**, 998.

2005PHA75 D. Briel, *Pharmazie*, 2005, **60**, 75.

2005PS(180)375 M. I. Abdel Moneam, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 375.

2005PS(180)413 A. M. K. El-Dean, M. S. A. El-Gaby, A. M. Gaber, H. A. Eyada, and A. S. N. Al-Kamali, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 413.

2005PS(180)591 A. Deeb, M. Kotb, and M. El-Abbasy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 591.

2005S1164 K. C. Majumdar, A. Biswas, and P. P. Mukhopadhyay, *Synthesis*, 2005, 1164.

2005SC535 A. Shaabani, M. B. Teimouri, S. Samadi, and K. Soleimani, *Synth. Commun.*, 2005, **35**, 535.

2005SM53 E. Perzon, X. Wang, F. Zhang, W. Mammo, J. L. Delgado, P. de la Cruz, O. Inganaes, F. Langa, and M. R. Andersson, *Synth. Met.*, 2005, **154**, 53.

2005T10774 C. Mohan, P. Singh, and M. P. Mahajan, *Tetrahedron*, 2005, **61**, 10774.

2005TL1845 C. R. Hopkins and N. Collar, *Tetrahedron Lett.*, 2005, **46**, 1845.

2005TL3449 H. Rudler, B. Denise, Y. Xu, and J. Vaissermann, *Tetrahedron Lett.*, 2005, **46**, 3449.

2005TL5551 N. Matsumoto and M. Takahashi, *Tetrahedron Lett.*, 2005, **46**, 5551.

2005TL6511 V. Valdivia, A. Hernandez, A. Rivera, F. Sartillo, A. Loukaci, J. Fourrey, and L. Quintero, *Tetrahedron Lett.*, 2005, **46**, 6511.

2006AF301 M. M. F. Ismail, M. M. Ghorab, E. Noaman, Y. A. Ammar, H. I. Heiba, and M. Y. Sayed, *Arzneim. Forsch.*, 2006, **56**, 301.

2006AF405 M. M. Ghorab, E. Noaman, H. I. Heiba, Y. A. Ammar, and M. Y. Sayed, *Arzneim. Forsch.*, 2006, **56**, 405.

2006AF553 M. M. Ghorab, F. A. Ragab, E. Noaman, H. I. Heiba, and M. Galal, *Arzneim. Forsch.*, 2006, **56**, 553.

2006BMC8590 A. Gangjee, J. Yang, J. J. McGuire, and R. L. Kisliuk, *Bioorg. Med. Chem.*, 2006, **14**, 8590.

2006BMCL150 V. Pittala, G. Romeo, L. Salerno, M. A. Siracusa, M. Modica, L. Materia, I. Mereghetti, A. Cagnotto, T. Mennini, G. Marucci, P. Angeli, and F. Russo, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 150.

2006BMCL285 B. Arumgham, H.-J. Kim, M. N. Prichard, E. R. Kern, and C. K. Chu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 285.

2006BMCL2091 T. L. Smalley, A. J. Peat, J. A. Boucheron, S. Dickerson, D. Garrido, F. Preugschat, S. L. Schweiker, S. A. Thomson, and T. Y. Wang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2091.

2006BMCL2173 H. S. Choi, Z. Wang, W. Richmond, X. He, K. Yang, T. Jiang, T. Sim, D. Karanewsky, X.-J. Gu, V. Zhou, Y. Liu, O. Ohmori, J. Caldwell, N. Gray, and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2173.

2006BMCL2662 V. P. Kamath, J. Zhang, P. E. Morris, and Y. S. Babu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2662.

2006BMCL2689 H.-S. Choi, Z. Wang, W. Richmond, X. He, K. Yang, T. Jiang, D. Karanewsky, X.-J. Gu, V. Zhou, Y. Liu, J. Che, C. C. Lee, J. Caldwell, T. Kanazawa, I. Umemura, N. Matsura, O. Ohmori, T. Honda, N. Gray, and Y. He, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2689.

2006BMCL3642 C. Esteve, A. Nueda, J. L. Diaz, J. Beleta, A. Cardenas, E. Lozoya, M. I. Cadavid, M. I. Loza, H. Ryder, and B. Vidal, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3642.

2006BMCL3697 M. B. Teimouri and R. Bazhrang, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3697.

2006BMCL4723 D. L. Hertzog, K. A. Al-Barazanji, E. C. Bigham, M. J. Bishop, C. S. Britt, D. L. Carlton, J. P. Cooper, A. J. Daniels, D. M. Garrido, A. S. Goetz, M. K. Grizzle, Y. C. Guo, A. L. Handlon, D. M. Ignar, R. O. Morgan, A. J. Peat, F. X. Tavares, and H. Zhou, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4723.

2006BMCL4994 A. J. Carpenter, K. A. Al-Barazanji, K. K. Barvian, M. J. Bishop, C. S. Britt, J. P. Cooper, A. S. Goetz, M. K. Grizzle, D. L. Hertzog, D. M. Ignar, R. O. Morgan, G. E. Peckham, J. D. Speake, and W. R. Swain, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4994.

2006BMCL5207 N. C. Warshakoon, J. Sheville, R. T. Bhatt, W. Ji, J. L. Mendez-Andino, K. M. Meyers, N. Kim, J. A. Wos, C. Mitchell, J. L. Paris, B. B. Pinney, O. Reizes, and X. E. Hu, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5207.

2006BMCL5778 K. J. Moriarty, H. K. Koblish, T. Garrabrant, J. Maisuria, E. Khalil, F. Ali, I. P. Petrounia, C. S. Crysler, A. C. Maroney, D. L. Johnson, and R. A. Galemmo, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 5778.

2006EJM727 G. G. Dubinina, M. O. Platonov, S. M. Golovach, P. O. Borysko, A. O. Tolmachov, and Y. M. Volovenko, *Eur. J. Med. Chem Chim. Ther.*, 2006, **41**, 727.

2006EJOC2410 P. Chakraborty, A. M. Brueckner, and U. Diederichsen, *Eur. J. Org. Chem.*, 2006, 2410.

2006H1325 R. H. E. Hudson and A. K. Dambenieks, *Heterocycles*, 2006, **68**, 1325.

2006IJC(B)450 A. G. M. Al-Sehemi, A. M. S. El-Sharief, and Y. A. Ammar, *Indian J. Chem. Sect. B*, 2006, **45**, 450.

2006JHC1129 J. I. Pyo, S. H. Lee, and C. S. Cheong, *J. Heterocycl. Chem.*, 2006, **43**, 1129.

2006JHC1231 M. Kidwai, K. Singhal, and S. Rastogi, *J. Heterocycl. Chem.*, 2006, **43**, 1231.

2006JMC391 M. J. Robbins, K. Miranda, V. K. Rajwanshi, M. A. Peterson, G. Andrei, R. Snoeck, E. De Clercq, and J. Balzarini, *J. Med. Chem.*, 2006, **49**, 391.

2006JMC1055 A. Gangjee, H. D. Jain, J. Phan, X. Lin, X. Song, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2006, **49**, 1055.

2006JMC3753 B. Dyck, S. Markison, L. Zhao, J. Tamiya, J. Grey, M. W. Rowbottom, M. Zhang, T. Vickers, K. Sorensen, C. Norton, J. Wen, C. E. Heise, J. Saunders, P. Conlon, A. Madan, D. Schwarz, and V. S. Goodfellow, *J. Med. Chem.*, 2006, **49**, 3753.

2006JMC3888 S. Moore, H. Jaeschke, G. Kleinau, S. Neumann, S. Costanzi, J.-K. Jiang, J. Childress, B. M. Raaka, A. Colson, R. Paschke, G. Krause, C. J. Thomas, and M. C. Gershengorn, *J. Med. Chem.*, 2006, **49**, 3888.

2006JOC81 F. Seela and X. Peng, *J. Org. Chem.*, 2006, **71**, 81.

2006JOC3077 I. Nowak, C. T. Jones, and M. J. Robbins, *J. Org. Chem.*, 2006, **71**, 3077.

2006JOC3248 Q. Meng, D. H. Kim, X. Bai, L. Bi, N. J. Turro, and J. Ju, *J. Org. Chem.*, 2006, **71**, 3248.

2006MI37 R. O. Bora, I. S. Rathod, and S. S. Toshniwal, *International Journal of Chemical Sciences*, 2006, **4**, 37.

2006IJH271 I. S. Rathod and H. U. Patel, *Ind. J. Heterocycl. Chem.*, 2006, **15**, 271.

2006MI498 F. E. M. El-Baih, H. A. S. Al-Blowy, and H. M. Al-Hazimi, *Molecules*, 2006, **11**, 498.

2006OBC1131 K. Clinch, G. B. Evans, G. W. J. Fleet, R. H. Furneaux, S. W. Johnson, D. H. Lenz, S. P. H. Mee, P. R. Rands, V. L. Schramm, E. A. Taylor Ringia, and P. C. Tyler, *Org. Biomol. Chem.*, 2006, **4**, 1131.

2006PHA174 K. M. H. Hilmy, *Archiv der Pharmazie*, 2006, **339**, 174.

2006PS1755 S. Al-Mousawi, A.-Z. Elassar, and M. El-Apasery, *Phosphorus Sulfur Silicon Relat. Elem.*, 2006, **181**, 1755.

2006PS1935 M. M. Ghorab, A. N. Osman, E. Noaman, H. I. Heiba, and N. H. Zaher, *Phosphorus Sulfur Silicon Relat. Elem.*, 2006, **181**, 1935.

2006S1513 J. Mueller and R. Troschuetz, *Synthesis*, 2006, 1513.

2006S2005 F. Seela, K. Xu, and P. Chittepu, *Synthesis*, 2006, 2005.

2006S3280 T. Kawate, B. H. Wang, C. R. Allerson, and J. L. Wolfe, *Synthesis*, 2006, 3280.

2006T8243 J. T. Gupton, E. J. Banner, A. B. Scharf, B. K. Norwood, R. F. P. Kanters, R. N. Dominey, J. E. Hempel, A. Kharlamova, I. Bluhn-Chertudi, C. R. Hickenboth, B. A. Little, M. D. Sartin, M. B. Coppock, K. E. Krumpe, B. S. Burnham, H. Holt, K. X. Du, K. M. Keertikar, A. Diebes, S. Ghassemi, and J. A. Sikorski, *Tetrahedron*, 2006, **62**, 8243.

2006T9919 D. S. Chekmarev, S. V. Shorshnev, A. E. Stepanov, and A. N. Kasatkin, *Tetrahedron*, 2006, **62**, 9919.

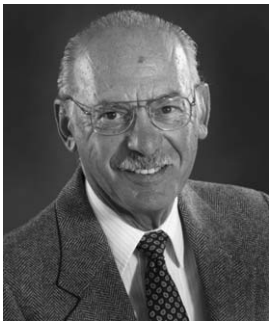
2006T11124 G. Blanco, N. Segui, J. M. Quintela, C. Peinador, M. Chas, and R. Toba, *Tetrahedron*, 2006, **62**, 11124.

2006T11311 D. M. Barnes, A. R. Height, T. Hameury, M. A. McLaughlin, J. Mei, J. S. Tedrow, and J. Dalla Riva Toma, *Tetrahedron*, 2006, **62**, 11311.

2006TL4149 M. V. Voronkov, K. Gu, S. D. P. Baugh, and M. R. Becker, *Tetrahedron Lett.*, 2006, **47**, 4149.

2006TL6125 J. X. de Araujo, M. Schmitt, P. Benderitter, and J.-J. Bourguignon, *Tetrahedron Lett.*, 2006, **47**, 6125.

Biographical Sketch



Thomas J. Delia was born in Brooklyn, NY, and studied at the College of the Holy Cross, where he obtained his B.S. degree in chemistry. His graduate studies were conducted at the Virginia Polytechnic Institute where he received both the M.S. (1959) and Ph.D. (1962) under the direction of Professor Frank Vingiello. After a one year postdoctoral appointment at the University of Virginia (with Professor Alfred Burger), he took a research associate appointment at the Sloan-Kettering Institute for Cancer Research in Rye, NY. After four years at the SKI, he took a faculty position at Central Michigan University in Mt. Pleasant, MI, in 1966. The remainder of his professional career was spent at CMU where he rose to the rank of professor. During this period, he served twice as department chair. While at CMU he held a National Academy of Science, Exchange Scientist position at the Institute for Organic Chemistry and Biochemistry in Prague (1971–72) and a Fulbright Scholar award at the Australian National University (1982–83). He retired in 2000 and was granted professor emeritus status. His scientific interests have focused on nitrogen heterocyclic chemistry, in particular synthesis of pyrimidine derivatives with potential biological applications.

10.08
Bicyclic 5-6 Systems: Three Heteroatoms 2:1

B. R. Buckley
Loughborough University, Loughborough, UK
© 2008 Elsevier Ltd. All rights reserved.

10.08.1 Introduction 433
10.08.2 Theoretical Methods 437
10.08.3 Experimental Structural Methods 438
10.08.3.1 X-Ray Determinations 438
10.08.3.1.1 Isothiazolo[4,5-*b*]pyridines 439
10.08.3.1.2 Dithiazolo[4,5-*c*]pyridines 440
10.08.3.2 NMR Spectroscopy 441
10.08.3.2.1 Proton NMR spectroscopy 441
10.08.3.2.2 Carbon-13 NMR spectroscopy 441
10.08.3.3 Mass Spectrometry 444
10.08.3.3.1 1,3-Dithiolo[4,5-*c*]pyridines 444
10.08.3.4 UV and Visible Spectroscopy 444
10.08.3.5 IR Spectroscopy 445
10.08.4 Thermodynamic Aspects 447
10.08.4.1 General Discussion 447
10.08.4.2 Solubilities and Chromatographic Behavior 449
10.08.4.3 Conformations and Tautomerism 449
10.08.5 Reactivity of Fully Conjugated Rings 449
10.08.5.1 Imidazo[4,5-*b*]pyridines 449
10.08.5.2 Imidazo[4,5-*c*]pyridines 449
10.08.5.3 Pyrazolo[3,4-*c*]pyridines 450
10.08.5.4 Pyrazolo[4,3-*c*]pyridines 450
10.08.5.5 Oxazolo[4,5-*c*]pyridines 450
10.08.5.6 Oxazolo[4,5-*b*]pyridines 450
10.08.5.7 Isoxazolo[5,4-*b*]pyridines 451
10.08.5.8 Isoxazolo[4,5-*c*]pyridines 452
10.08.5.9 Isoxazolo[5,4-*b*]pyridines 453
10.08.5.10 Isoxazolo[4,5-*b*]pyridines 454
10.08.5.11 Isothiazolo[4,3-*c*]pyridines 454
10.08.5.12 Isothiazolo[5,4-*b*]pyridines 454
10.08.5.13 Isothiazolo[4,5-*c*]pyridines 454
10.08.5.14 3*H*-1,2-Dithiolo[4,3-*c*]pyridines 454
10.08.6 Reactivity of Nonconjugated Rings 454
10.08.6.1 3*H*-1,2-Dithiolo[3,4-*b*]pyridines 454
10.08.6.2 Isothiazolo[5,4-*b*]pyridines 455
10.08.7 Reactivity of Substituents Attached to Ring Carbon Atoms 455
10.08.7.1 Imidazo[4,5-*b*]pyridines 455
10.08.7.2 Pyrazolo[3,4-*b*]pyridines 455

10.08.7.3 Pyrazolo[4,3-*c*]pyridines 456
10.08.7.4 Oxazolo[4,5-*b*]pyridines 457
10.08.7.5 Isoxazolo[4,3-*c*]pyridines 458
10.08.7.6 Isoxazolo[5,4-*b*]pyridines 459
10.08.7.7 Isothiazolo[5,4-*b*]pyridines 460
10.08.7.8 3*H*-1,2-Dithiolo[3,4-*b*]pyridines 460
10.08.8 Reactivity of Substituents Attached to Ring Heteroatoms 461
10.08.8.1 Oxazolo[4,5-*b*]pyridines 461
10.08.9 Ring Synthesis Classified by Formation of the Second Heterocyclic Ring 461
10.08.9.1 Imidazo[4,5-*b*]pyridines 461
10.08.9.1.1 Closure of the imidazole ring 461
10.08.9.1.2 Closure of the pyridine ring 464
10.08.9.2 Imidazo[4,5-*c*]pyridines 465
10.08.9.2.1 Closure of the imidazole ring 465
10.08.9.2.2 Closure of the pyridine ring 467
10.08.9.3 Imidazo[4,5-*b*]quinolin-2-ones 468
10.08.9.4 Pyrazolo[3,4-*b*]pyridines 468
10.08.9.4.1 Closure of the pyrazole ring 468
10.08.9.4.2 Closure of the pyridine ring 470
10.08.9.5 Pyrazolo[4,3-*c*]pyridines 472
10.08.9.6 Pyrazolo[3,4-*c*]pyridines 472
10.08.9.7 Oxazolo[4,5-*b*]pyridines 474
10.08.9.8 Oxazolo[5,4-*b*]pyridines 474
10.08.9.8.1 Closure of the oxazole ring 474
10.08.9.8.2 Closure of the pyridine ring 475
10.08.9.9 Isoxazolo[5,4-*c*]pyridines 475
10.08.9.10 Isoxazolo[5,4-*b*]pyridines 475
10.08.9.10.1 Closure of the isoxazole ring 475
10.08.9.10.2 Closure of the pyridine ring 475
10.08.9.11 Isoxazolo[4,5-*c*]pyridines 476
10.08.9.12 Isoxazolo[4,5-*b*]pyridines 476
10.08.9.12.1 Closure of the isoxazole ring 476
10.08.9.12.2 Closure of the pyridine ring 476
10.08.9.13 Isoxazolo[3,4-*b*]pyridines 476
10.08.9.14 Thiazolo[4,5-*b*]pyridines 476
10.08.9.15 Thiazolo[5,4-*b*]pyridines 476
10.08.9.16 Isothiazolo[4,3-*b*]pyridines 477
10.08.9.17 Isothiazolo[5,4-*b*]pyridines 477
10.08.9.18 Isothiazolo[4,5-*b*]pyridines 478
10.08.9.19 Isothiazolo[5,4-*c*]pyridines 478
10.08.9.20 1,3-Dithiolo[4,5-*c*]pyridines 478
10.08.9.21 1,3-Dithiolo[4,5-*b*]pyridines 478
10.08.9.22 3*H*-1,2-Dithiolo[3,4-*b*]pyridines 478
10.08.9.23 3*H*-1,2-Dithiolo[3,4-*c*]pyridines 479
10.08.9.24 3*H*-1,2-Dithiolo[4,3-*c*]pyridines 479
10.08.9.25 3*H*-1,2-Dithiolo[4,3-*b*]pyridines 479
10.08.9.26 Thiopyrano[4,3-*d*]isoxazoles 479

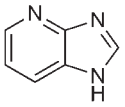
10.08.9.27 Thiopyrano[3,4-*c*]pyrazoles 479
10.08.9.28 Thiopyrano[4,3-*c*]pyrazoles 479
10.08.9.29 Thiopyrano[2,3-*c*]pyrazoles 479
10.08.9.30 Selenopyrano[2,3-*c*]pyrazoles 480
10.08.10 Synthesis by Transformation of Another Bicyclic Ring System 480
10.08.10.1 Imidazo[4,5-*c*]pyridines 480
10.08.10.2 Pyrazolo[3,4-*c*]pyridines 480
10.08.10.3 Pyrazolo[4,3-*c*]pyridines 480
10.08.10.4 Pyrazolo[3,4-*b*]pyridines 480
10.08.10.5 Oxazolo[4,5-*b*]pyridines 481
10.08.10.6 Oxazolo[4,5-*c*]pyridines 482
10.08.10.7 Oxazolo[5,4-*c*]pyridines 482
10.08.10.8 Oxazolo[5,4-*b*]pyridines 482
10.08.10.9 Isoxazolo[4,5-*c*]pyridines 482
10.08.10.10 Thiazolo[5,4-*b*]pyridines 482
10.08.10.11 Isothiazolo[5,4-*b*]pyridines 482
10.08.10.12 Isothiazolo[5,4-*c*]pyridines 482
10.08.10.13 Isothiazolo[4,5-*c*]pyridines 483
10.08.11 Synthesis from Acyclic Precursors 483
10.08.11.1 Pyrazolo[4,3-*c*]pyridines 483
10.08.12 Important Compounds and Applications 483
10.08.13 Further Developments 487
10.08.13.1 Imidazo[4,5-*b*]pyridines 487
10.08.13.2 Imidazo[4,5-*c*]pyridines 487
10.08.13.3 Pyrazolo[3,4-*c*]pyridines 487
10.08.13.4 Pyrazolo[4,3-*c*]pyridines 487
10.08.13.5 Oxazolo[4,5-*c*]pyridines 487
10.08.13.6 Oxazolo[4,5-*b*]pyridines 488
10.08.13.7 Isothiazolo[5,4-*b*]pyridines 488
References 488

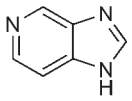
10.08.1 Introduction

The first review of this category of compounds as a group was in Chapter 7.08 of <1996CHEC-II(7)283>, and independent reviews of imidazopyridines <1984CHEC(5)607>, pyrazolopyridines <1984CHEC(5)305>, oxazolopyridines <1984CHEC(6)613>, isoxazolopyridines <1984CHEC(6)613>, thiazolopyridines <1984CHEC(6)613>, and isothiazolopyridines <1984CHEC(6)613> were presented in CHEC(1984). This chapter serves as an update to the original chapter and endeavors to inform the reader of the various syntheses available and the most recent theoretical and experimental techniques used for structure elucidation. General review articles can be found in <1996CHEC-II(7)283> and <B-2000MI1>.

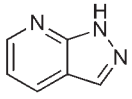
This chapter reviews 5:6 ring-fused heterocyclic ring systems with no bridgehead heteroatoms. More specifically, these ring systems have two heteroatoms in the five-membered ring and one in the fused six-membered ring. Many structural combinations have been reported and some are shown in the structures below. Many of these substances exhibit significant biological activity or are themselves intermediates for biologically active compounds. Thus, there is a vast number of publications in this area; a search of the patent literature alone (from 1995 to 2005) reported over 1000 hits for the important heterocyclic bicyclic systems presented in this chapter. The reactions reviewed here are therefore by no means exhaustive but offer an overview of the area and highlight significant examples. Not included in this chapter are bicyclic systems derived from carbohydrates. IUPAC nomenclature is used throughout this chapter.

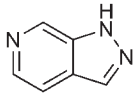
Imidazopyridines

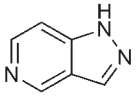

Imidazo[4,5-*b*]pyridine

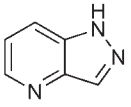

Imidazo[4,5-*c*]pyridine

Pyrazolopyridines

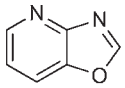

Pyrazolo[3,4-*b*]pyridine

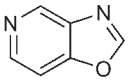

Pyrazolo[3,4-*c*]pyridine

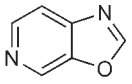

Pyrazolo[4,3-*c*]pyridine

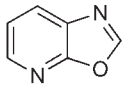

Pyrazolo[4,3-*b*]pyridine

Oxazolopyridines

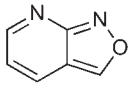

Oxazolo[4,5-*b*]pyridine

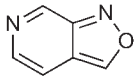

Oxazolo[4,5-*c*]pyridine

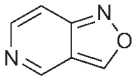

Oxazolo[5,4-*c*]pyridine

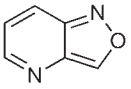

Oxazolo[5,4-*b*]pyridine

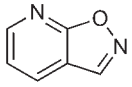
Isoxazolopyridines

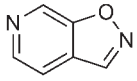

Isoxazolo[3,4-*b*]pyridine

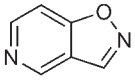

Isoxazolo[3,4-*c*]pyridine

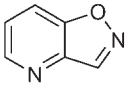

Isoxazolo[4,3-*c*]pyridine


Isoxazolo[4,3-*b*]pyridine

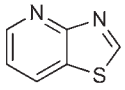

Isoxazolo[5,4-*b*]pyridine

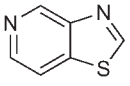

Isoxazolo[5,4-*c*]pyridine

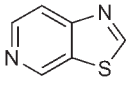

Isoxazolo[4,5-*c*]pyridine

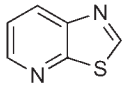

Isoxazolo[4,5-*b*]pyridine

Thiazolopyridines

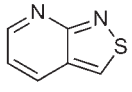

Thiazolo[4,5-*b*]pyridine

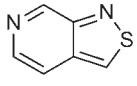

Thiazolo[4,5-*c*]pyridine

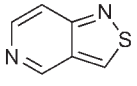

Thiazolo[5,4-*c*]pyridine

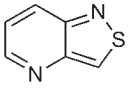

Thiazolo[5,4-*b*]pyridine

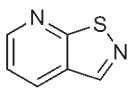
Isothiazolopyridines

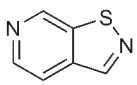

Isothiazolo[3,4-*b*]pyridine

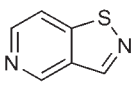

Isothiazolo[3,4-*c*]pyridine

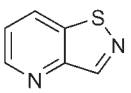

Isothiazolo[4,3-*c*]pyridine


Isothiazolo[4,3-*b*]pyridine

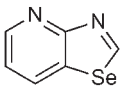

Isothiazolo[5,4-*b*]pyridine

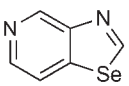

Isothiazolo[5,4-*c*]pyridine

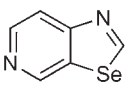

Isothiazolo[4,5-*c*]pyridine

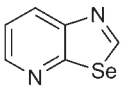

Isothiazolo[4,5-*b*]pyridine

Selenazopyridines

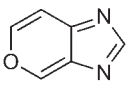

Selenazo[4,5-*b*]pyridine

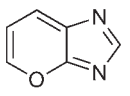

Selenazo[4,5-*c*]pyridine


Selenazo[5,4-*c*]pyridine

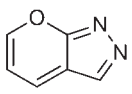

Selenazo[5,4-*b*]pyridine

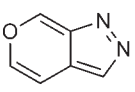
Pyranoimidazoles

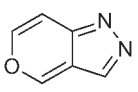

Pyrano[3,4-*d*]imidazole]

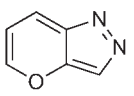

Pyrano[2,3-*d*]imidazole]

Pyranopyrazoles

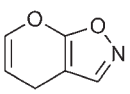

Pyrano[2,3-*c*]pyrazole

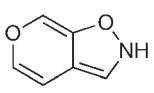

Pyrano[3,4-*c*]pyrazole

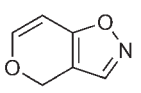

Pyrano[4,3-*c*]pyrazole

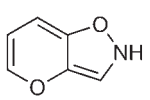

Pyrano[3,2-*c*]pyrazole

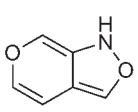
Pyranoisoxazoles

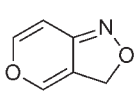

4*H*-Pyrano[2,3-*d*]isoxazole


2*H*-Pyrano[4,3-*d*]isoxazole

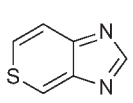

4*H*-Pyrano[3,4-*d*]isoxazole

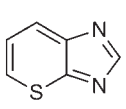

2*H*-Pyrano[2,3-*d*]isoxazole


1*H*-Pyrano[3,4-*d*]isoxazole

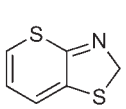

3*H*-Pyrano[3,4-*c*]isoxazole

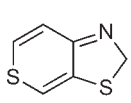
Thiopyranoimidazoles

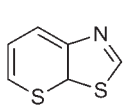

Thiopyrano[3,4-*d*]imidazole

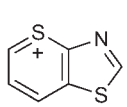

Thiopyrano[2,3-*d*]imidazole

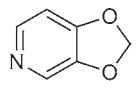
Thiopyranothiazoles


2*H*-Thiopyrano[2,3-*d*]thiazole

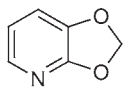

2*H*-Thiopyrano[4,3-*d*]thiazole


5*H*-Thiopyrano[3,2-*d*]thiazole

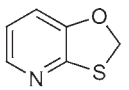

Thiopyrano[3,4-*d*]thiazol-4-ium



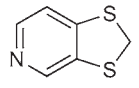
2*H*-1,3-Dioxolo[4,5-*c*]pyridine



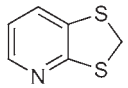
2*H*-1,3-Dioxolo[4,5-*b*]pyridine



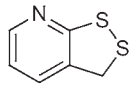
2*H*-1,3-oxathiolo[4,5-*b*]pyridine



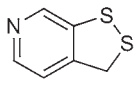
2*H*-1,3-Dithiolo[4,5-*c*]pyridine



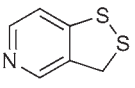
2*H*-1,3-Dithiolo[4,5-*b*]pyridine



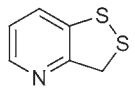
3*H*-1,2-Dithiolo[3,4-*b*]pyridine



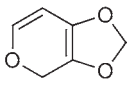
3*H*-1,2-Dithiolo[3,4-*c*]pyridine



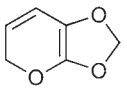
3*H*-1,2-Dithiolo[4,3-*c*]pyridine



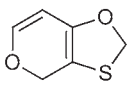
3*H*-1,2-Dithiolo[4,3-*b*]pyridine



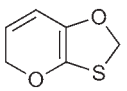
2*H*,4*H*-1,3-Dioxolo[4,5-*c*]pyran



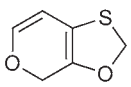
2*H*,5*H*-1,3-Dioxolo[4,5-*b*]pyran



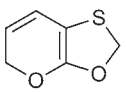
2*H*,4*H*-1,3-oxathiolo[4,5-*c*]pyran



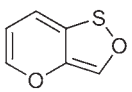
2*H*,5*H*-1,3-oxathiolo[4,5-*b*]pyran



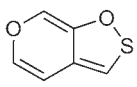
2*H*,4*H*-1,3-oxathiolo[5,4-*c*]pyran



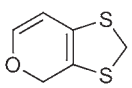
2*H*,5*H*-1,3-oxathiolo[5,4-*b*]pyran



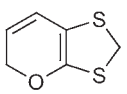
1,2-Oxathiolo[4,3-*b*]pyran



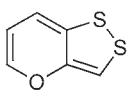
1,2-Oxathiolo[5,4-*c*]pyran



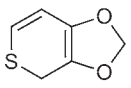
2*H*,4*H*-1,3-Dithiolo[4,5-*c*]pyran



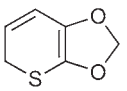
2*H*,5*H*-1,3-Dithiolo[4,5-*b*]pyran



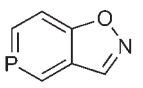
1,2-Dithiolo[4,3-*b*]pyran



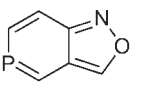
4*H*-1,3-Dioxolo[4,5-*c*]thiopyran



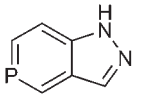
4*H*-1,3-Dioxolo[4,5-*b*]thiopyran



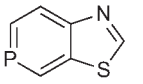
Isoxazolo[4,5-*c*]phosphorine



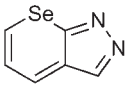
Isoxazolo[4,3-*c*]phosphorine



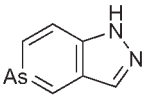
Pyrazolo[4,3-*c*]phosphorine



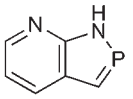
Thiazolo[5,4-*c*]phosphorine



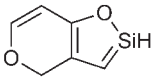
Selenino[2,3-*c*]pyrazole



1*H*-Arsenino[4,3-*c*]pyrazole



1*H*-1,2-Azaphospholo[5,4-*b*]pyridine



4*H*-1,2-Oxasilolo[4,5-*c*]pyran

10.08.2 Theoretical Methods

As reported in <1996CHEC-II(7)283>, there are very few theoretical studies of the various classes of compounds in this chapter. Some methods were discussed in the original chapter and several more recent examples are described below. The site of electrophilic attack on pyrazolo[3,4-*c*]pyridines has been predicted by theoretical calculations <B-2000MI1>. Molecular modeling using MM2-optimized model structures of the (cyanomethyl)pyridine moiety (conducted using the Chem-3D-Plus program and *N*-acetylpiperidine torsional parameters from <1989JOC3779>) showed that a third coordination site close to the pyridine sp^2 nitrogen in platelet-activating factor antagonists may increase potency <1996JME487>. Imidazo[4,5-*c*]pyridines were identified as possible targets and an overlay diagram of a (cyanomethyl)pyridine and a imidazo[4,5-*c*]pyridine is shown in **Figure 1**. Several imidazo[4,5-*c*]pyridines were synthesized and **1** was found to be a potent platelet-activating factor antagonist.

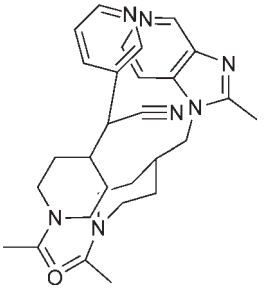
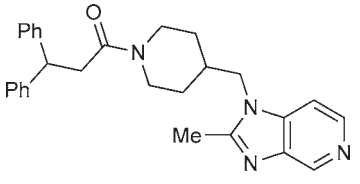


Figure 1



1

The molecular design of a new series of adenosine A_{2A} antagonists (adenosine acts at specific membrane G protein receptors positively (A_{2A}, A_{2B}) or negatively (A_1, A_3) <2005JMC6887>) was carried out using 52 structures from the literature: in particular three classes with different selectivity for A_1 and A_{2A} subtypes. The reference molecules were built and optimized using semi-empirical quantum-mechanics method AM1 (ChemX software, Chemical Design Ltd., Oxford Molecular Group, the Magdalene Centre, Oxford Science Park, Oxford OX4 4GA, UK); electrostatic potential maps were used to compare the electronic features of the molecules and to investigate the different alignments between compounds related or unrelated to the xanthine ring system. These alignments identified three common pharmacophoric points showing one H-bond donor and two H-bond acceptors that represent the minimum requirement to interact with both A_1 and A_{2A} receptors. An exclusion zone, representing an unfavorable steric interaction in the A_{2A} active site, and an additional exclusion zone, representing an unfavorable steric interaction in the A_1 active site (**Figure 2**). From these studies, several biologically active compounds were identified and synthesized including the imidazo[4,5-*c*]pyridine **2**.

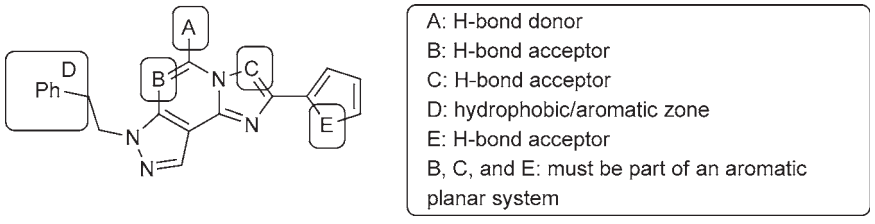
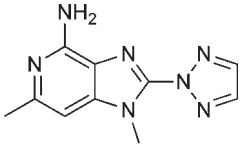
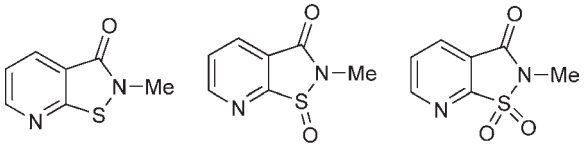


Figure 2



2

The performance of several semi-empirical (modified neglect of diatomic overlap (MNDO), AM1, PM3, and SAM1) and *ab initio* (Hartree–Fock (HF) and MP2/6-31G*) methods for determining structural and electronic factors of a series of isothiazolo[5,4-b]pyridines was compared by Martinez-Merino *et al.* <1996T8947>. They found that most of the semi-empirical methods calculated reasonable molecular structures when compared to the actual X-ray structures (compounds **3–5**) (see, for example, **Table 1** for selected bond lengths of compound **3**). However, the dipole moments were not reproducible using these methods.



3 **4** **5**

10.08.3 Experimental Structural Methods

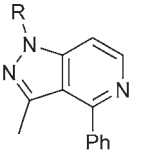
10.08.3.1 X-Ray Determinations

As mentioned in <1996CHEC-II(7)283>, there are very few X-ray studies of the various classes of compounds in this chapter. In general, the crystal structures published provide supporting evidence for structure elucidation. For example, the X-ray crystal structure of pyrazolo[4,3-*c*]pyridine **6** was reported to confirm its structure and that of its analogues (**7** and **8**) by comparison of other spectral data <2004T933>.

Table 1 Theoretical vs. actual selected bond lengths of compound **3** <1996T8947>

Internal coord.	*MNDO*	*AM1*	*PM3*	*SAM1*	*6-31G**	*X-Ray*
S(1)–N(2) (Å)	1.665	1.667	1.778	1.710	1.719	1.719
N(2)–C(3) (Å)	1.424	1.403	1.451	1.414	1.365	1.364
C(3)–C(4) (Å)	1.489	1.480	1.480	1.513	1.475	1.450
C(5)–C(5) (Å)	1.429	1.429	1.412	1.450	1.382	1.396
C(5)–S(1) (Å)	1.684	1.710	1.760	1.788	1.753	1.747
N(2)–C(7) (Å)	1.460	1.422	1.470	1.437	1.448	1.452
C(3)–O(6) (Å)	1.222	1.239	1.214	1.257	1.200	1.230
C(5)–S(1)–N(2) (°)	94.0	94.8	91.9	92.3	90.0	89.7
S(1)–N(2)–C(3) (°)	114.6	114.0	119.9	115.9	116.6	117.0
N(2)–C(3)–C(4) (°)	108.0	108.9	109.9	109.4	108.2	108.1
C(3)–C(4)–C(5) (°)	111.4	112.7	113.6	111.9	113.6	113.8
C(4)–C(5)–S(1) (°)	111.8	109.4	112.2	110.5	111.5	111.3
S(1)–N(2)–C(3)–C(7) (°)	177.0	−179.4	144.6	−179.3	179.9	−177.5

Reproduced with permission: Molecular modelling of the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one derivatives; V. Martínez-Merino *et al*. 1996 © Elsevier Limited.



6: R = Ph
7: R = 4-$O_2NC_6H_4$
8: R = 3-$O_2NC_6H_4$

10.08.3.1.1 Isothiazolo[4,5-*b*]pyridines

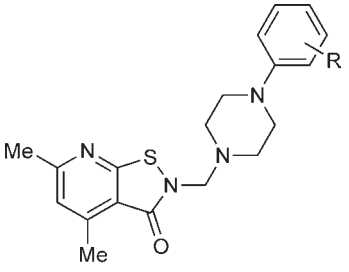
Karczmarzyk *et al.* have reported their studies on 2-substituted derivatives of isothiazolo[4,5-*b*]pyridines <1998AX(C)992, 2001FES905, 2004JCC453>. Spectral analysis of compound **9** revealed that it existed in solution as two tautomeric forms (Equation 1). X-Ray crystallography revealed a H-atom in the vicinity of the N-atom and the C–O bond length (1.249 Å) was typical of a carbonyl group, thus confirming that the equilibrium in Equation (1) lies to the left in the solid state.



(1)

9

During studies by Karczmarzyk and co-workers on new analgesic agents, compounds **10–15** were synthesized, several discrepancies were found in their biological activities, and this instigated a structure–activity relationship (SAR) study. Bond lengths and angles were very similar for compounds **10–15** and differed significantly from those of compound **9**. A direct comparison of selected geometrical data for **9** and **11** is shown in **Table 2**.



10: R = H
11: R = 2-OMe
12: R = 2-Cl
13: R = 2-F
14: R = 3-CF_3
15: R = 4-NO_2

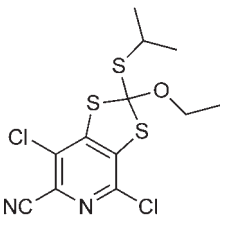
Table 2 Direct comparison of selected geometrical data for **9** and **11** <2004JCC453>

Coordinate	**9**	**11**
Bond distances (Å)		
S(1)–N(2)	1.691(2)	1.703 3(13)
S(1)–C(8)	1.737(2)	1.738 1(14)
O(3)–C(3)	1.249(2)	1.224(2)
N(2)–C(3)	1.352(2)	1.377(2)
N(7)–C(8)	1.339(2)	1.333(2)
N(7)–C(6)	1.343(2)	1.340(2)
C(3)–C(9)	1.463(2)	1.469(2)
C(4)–C(5)	1.392(2)	1.389(2)
C(4)–C(9)	1.401(2)	1.394(2)
C(4)–C(10)	1.501(3)	1.495(2)
C(5)–C(6)	1.402(3)	1.397(2)
C(6)–C(11)	1.503(2)	1.498(2)
C(8)–C(9)	1.394(2)	1.386(2)
Bond angles (°)		
N(2)–S(1)–C(8)	90.33(8)	90.18(6)
C(3)–N(2)–S(1)	116.34(12)	116.40(9)
C(8)–N(7)–C(6)	114.9(2)	115.03(12)
O(3)–C(3)–N(2)	122.9(2)	123.32(13)
O(3)–C(3)–C(9)	127.2(2)	128.19(14)
N(2)–C(3)–C(9)	109.87(14)	108.47(12)
C(5)–C(4)–C(9)	115.9(2)	115.90(13)
C(5)–C(4)–C(10)	121.3(2)	121.55(14)
C(9)–C(4)–C(10)	122.8(2)	122.54(13)
C(4)–C(5)–C(6)	121.4(2)	121.42(14)
N(7)–C(6)–C(5)	122.9(2)	122.75(13)
N(7)–C(6)–C(11)	116.1(2)	116.17(14)
C(5)–C(6)–C(11)	121.0(2)	121.08(14)
N(7)–C(8)–C(9)	126.5(2)	126.53(13)
N(7)–C(8)–S(1)	121.44(13)	121.10(11)
C(9)–C(8)–S(1)	112.03(12)	112.36(10)
C(8)–C(9)–C(4)	118.2(2)	118.37(12)
C(8)–C(9)–C(3)	111.40(14)	112.57(13)
C(4)–C(9)–C(3)	130.4(2)	129.06(13)
Torsion angles (°)		
S(1)–N(2)–C(12)–N(21)		89.5(2)
C(22)–N(21)–C(12)–N(2)		64.0(2)
C(26)–N(21)–C(12)–N(2)		−65.9(2)
C(23)–N(24)–C(31)–C(32)		−93.3(2)

Reproduced with permission: Structure of 4,6-dimethylisothiazolo[5,4-*b*]pyridin-3(2H)-one and its 2-[4-(2-methylphenyl) piperazin-1-ylmethyl] derivative; Z. Karczmarzyk *et al.* 2004 © Springer Science & Business Media.

10.08.3.1.2 Dithiazolo[4,5-*c*]pyridines

The X-ray structure of 4,7-dichloro-2-isopropylthio-6-cyano-2-ethoxy-1,3-dithiolo[4,5-*c*]pyridine **16** was reported to elucidate its structure and it was found that the dithiole fragment of the molecule is not planar along the S–S line by 26.8°. The plane of the EtO group is orthogonal to the plane of the three S–C–S atoms and its torsion angle is 64.1° <1998CHE297>.



16

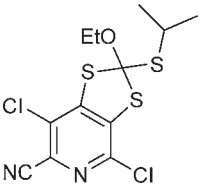
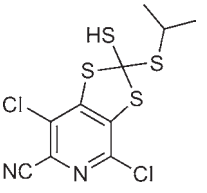
X-Ray data for imidazo[4,5-*b*]pyridines, imidazo[4,5-*c*]pyridines, pyrazolo[3,4-*c*]pyridines, oxazolo[5,4-*b*]pyridines, and isoxazolo[5,4-*b*]pyridines can be found in <1996CHEC-II(7)283>; no further reports in these areas have been found since the publication of the original chapter.

10.08.3.2 NMR Spectroscopy

10.08.3.2.1 Proton NMR spectroscopy

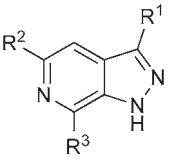
Several proton nuclear magnetic resonance (NMR) studies on certain 5:6 bicyclic ring systems were summarized in <1996CHEC-II(7)283>, including the characteristic ^{1}H NMR spectra signals for isothiazolo[5,4-*b*]pyridines. In the majority of cases, ^{1}H NMR spectroscopy has been used as an invaluable tool for structural elucidation; however, for these classes of compounds, ^{1}H NMR spectroscopy is perhaps not the ideal tool due to the general lack of protons in the majority of reported compounds. For example, the ^{1}H NMR spectra of compounds **16** and **17** have been reported and are shown in **Table 3** <1998CHE297>, but far more information can be gathered from the ^{13}C NMR spectrum (see Section 10.08.3.2.1). The ^{1}H NMR data for 18 different pyrazolo[3,4-*c*]pyridines have been reported by Volochnyuk *et al.* <2003S1531>.

Table 3 ^{1}H NMR spectra of compounds **16** and **17** <1998CHE297>

Compound	*δ (ppm)*
 **16**	1.25 (3H, t, Me), 1.39 (6H, d, Me), 3.49 (1H, q, CH), 3.71 (2H, q, CH_2)
 **17**	1.42 (6H, d, Me), 4.09 (1H, q, CH)

10.08.3.2.2 Carbon-13 NMR spectroscopy

The first ^{13}C NMR spectroscopic study of 1*H*-pyrazolo[3,4-*c*]pyridine derivatives **18–26** has been reported by Gueiffier and co-workers <1999H(51)1661>. The chemical shift values, obtained in dimethyl sulfoxide (DMSO-d_6), are shown in **Table 4**, and coupling constants can be found in <1999H(51)1661>.



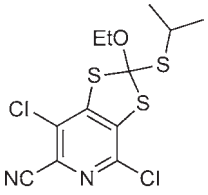
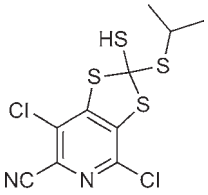
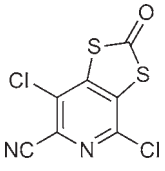
18: R^1, R^2, R^3 = H
19: R^1, R^3 = H; R^2 = Cl
20: R^1, R^2 = H; R^3 = Cl
21: R^1 = Cl; R^2, R^3 = H
22: R^1, R^2 = Cl; R^3 = H
23: R^1 = Br; R^2, R^3 = H
24: R^1 = Br; R^2 = Cl; R^3 = H
25: R^1 = NO_2; R^2, R^3 = H
26: R^1 = NO_2; R^2 = Cl; R^3 = H

Table 4 Selected ^{13}C NMR spectral data (ppm) for compounds **18–22**, **25**, and **26** <1999H(51)1661>

Compound	*C-3*	*C-3a*	*C-4*	*C-5*	*C-7*	*C-7a*
18	133.1	[126.3]	114.6	138.3	135.2	[137.1]
19	[132.8]	[129.5]	114.2	[139.3]	134.7	[136.5]
20	133.4	[128.3]	114.9	137.6	[134.7]	[135.3]
21	[137.9]	[123.2]	112.4	139.2	135.9	[132.2]
22	[137.4]	[126.1]	112.2	[140.2]	135.0	[131.7]
25	[148.9]	[120.3]	113.7	140.9	138.0	[141.7]
26	[144.0]	[122.1]	113.3	Not Determined	137.1	[137.8]

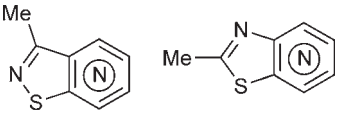
The ^{13}C NMR spectra of compounds **16**, **17**, and **27** have been reported <1997CHE1306, 1998CHE297> and, not surprisingly, the chemical shift of the carbon at C-2 is further downfield for compound **27** than for compounds **16** and **17** (**Table 5**).

Table 5 ^{13}C NMR spectra of compounds **16**, **17**, and **27**

	Selected ^{13}C NMR chemical shifts δ (ppm)					
Compound	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Reference*
 **16**	149.6	127.4	139.9	139.1	126.3	1998CHE297
 **17**	146.8	135.6	143.4	135.6	146.8	1998CHE297
 **27**	151.8	129.3	141.2	139.9	126.0	1997CHE1306

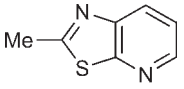
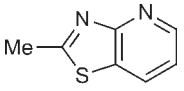
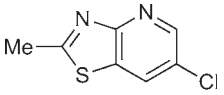
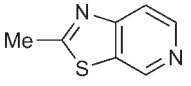
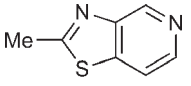
Chimichi *et al.* have reported the synthesis and spectroscopic data for all four thiazolopyridine isomers in order to examine how the differently substituted fused five-membered heterocycle influences the chemical and spectroscopic properties <1997MRC601>. The unambiguous assignment of the ^{13}C chemical shifts of these systems was reported and ^{13}C–^{1}H coupling constants showed that azole ring fusion on the pyridine system is responsible for a significant increase in all one-bond couplings. The authors also suggest that ^{13}C NMR spectroscopy is more useful than other common spectroscopic techniques (mass spectrometry (MS), infrared (IR), and ^{1}H NMR) in distinguishing between

the isomers of **28** and **29**. The chemical shift data for thiazolopyridines **30–34** are shown in **Table 6**. The resonances were assigned on the basis of two-dimensional (2-D) heteronuclear correlation (HETCOR) and correlation through long-range coupling (COLOC) experiments.



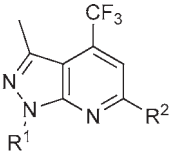
28 **29**

Table 6 ^{13}C NMR chemical shift (ppm) data for thiazolopyridines **30–34** <1997MRC601>

Compound	*C-2*	*C-3a*	*C-4*	*C-5*	*C-6*	*C-7*	*C-7a*	*CH_3*
 **30**	168.11	146.33	129.22	121.01	146.55		159.00	20.93
 **31**	170.59	164.15		147.70	119.38	132.15	129.02	20.68
 **32**	171.33	162.47		146.88	127.62	129.90	129.90	20.84
 **33**	172.64	158.26	116.85	145.62		143.81	132.86	20.35
 **34**	168.08	149.98	144.29		143.40	116.21	143.69	20.05

Reproduced with permission: Carbon-13 NMR Studies on Azolopyridines. 4. The Thiazolopyridine Systems; S. Chimichi *et al.* 1997 © John Wiley & Sons, Ltd.

The ^{19}F and ^{13}C NMR data for several pyrazolo[3,4-*c*]pyridines **35–39** have been reported by Volochnyuk *et al.* (**Table 7**) <2003S1531>.



35: R^1 = Ph; R^2 = 3-pyridyl
36: R^1 = Ph; R^2 = CF_3
37: R^1 = Me; R^2 = 2-thiophene
38: R^1 = Me; R^2 = CF_3

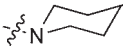
39: R^1 = Ph; R^2 = 

Table 7 ^{19}F and ^{13}C NMR chemical shift (ppm) data for pyrazolo[3,4-*c*]pyridines **35–39** <2003S1531>

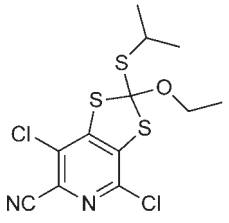
		^{13}C NMR δ (ppm)							
	^{19}F NMR δ (ppm)	Me at C-3	C-3	C-3a	C-4	C-5	C-6	C-7a	CF_3
35	−62.1	13.3	140.0	109.3	131.3	109.7	153.3	151.5	121.6
36	−62.1	14.5	140.5	108.6	130.3	114.8	151.8	151.5	123.2
37	−62.5	14.3	143.3	107.1	130.8	109.4	151.8	151.6	123.2
38	−61.8 −68.0	14.1	139.8	111.1	133.2	108.6	146.7	151.2	122.2
39	−62.3	14.6	140.8	102.3	131.8	101.6	157.8	152.0	123.4

10.08.3.3 Mass Spectrometry

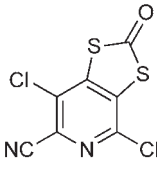
As reported in <1996CHEC-II(7)283>, no specific study on the mass spectra of these classes of compounds has been reported, although this analytical method has only been used as a tool for structure elucidation or reference without critical analysis. Some examples are reported in <1996CHEC-II(7)283>. Further information on the MS of heterocycles can be found in <2001MI1>. The mass spectral data for imidazopyridines, pyrazolo[3,4-*b*]pyridines, oxazolopyridines, ioxazolopyridines, isothiazolopyridines, 3*H*-1,2-dithiolo[3,4-*b*]pyridines, and 1,3-dithiolo[4,5-*b*]pyridines were reported in <1996CHEC-II(7)283>, but there have been no further reports in this area.

10.08.3.3.1 1,3-Dithiolo[4,5-*c*]pyridines

The molecular ion (M^+) of **16** was reported in <1998CHE297> and was shown to be unstable and dissociates in a number of directions. The most stable ion has *m*/*z* 262, and high-resolution MS showed that this ion is formed by removal of the isopropyl group and ethyl radicals from M^+. To determine the structure of this ion, the collision-activation spectrum was recorded and was found to be compound **27** <1997CHE1306>.



16

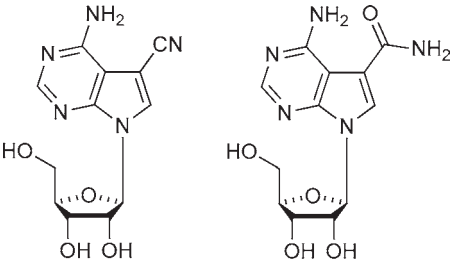


27

10.08.3.4 UV and Visible Spectroscopy

The ultraviolet (UV) spectra of several ring systems presented in this chapter and the previous review are presented in <1996CHEC-II(7)283>, besides a report on the UV spectra of tetrahydroisoxazole[4,5-*c*]pyridines.

In order to prepare toyocamycin **40** and sangivamycin **41** analogues, Gueiffier and co-workers were interested in the preparation of 3-cyano derivatives of 1*H*-pyrazolo[3,4-*c*]pyridines <1999H(51)1661>. However, all attempts to substitute the halogens in compounds **21**, **22**, and **24** failed and even the Sandmeyer reaction on compound **42** failed; this was explained by studying the effect of pH on the structure of the diazo compounds by monitoring the UV spectra. The UV spectra of **42** at pH 7 showed four maxima at 199, 238, 260, and 336 nm. The pH was varied from pH 1 to pH 11 (**Table 8**) and hypsochromic <1994PAC1088, 1996PAC2230> and bathochromic <1994PAC1124, 1996PAC2247> effects were observed, suggesting that the suitable form of **42** for nucleophilic substitution exists only under acidic conditions (Equation 2).

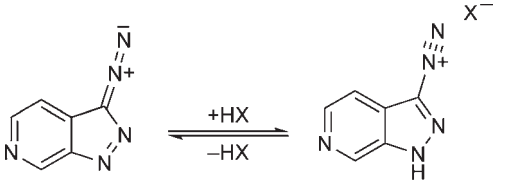


Toyocomycin
40

Sangivamycin
41

Table 8 UV spectra of **42** at varying pH <1999H(51)1661>

pH	λ_{max1} (ε) [nm]	λ_{max2} (ε) [nm]	λ_{max3} (ε) [nm]	λ_{max4} (ε) [nm]
1	205 (14 500)	241 (31 500)	300 (10 000)	317 (10 250)
2	200 (15 000)	241 (31 500)	300 (10 000)	320 (10 250)
5	199 (23 000)	239 (24 000)	260 (9600)	338 (10 500)
7	199 (21 500)	238 (22 600)	260 (9600)	336 (10 000)
8	201 (19 250)	238 (23 250)	250 (10 000)	336 (10 250)
11	ND	238 (22 250)	263 (7800)	335 (9600)

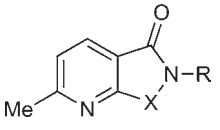


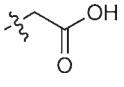
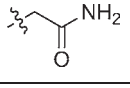
42 (2)

10.08.3.5 IR Spectroscopy

No definitive studies on IR spectroscopy in this group have been found since the publication of Chapter 7.08 in <1996CHEC-II(7)283>. IR structural observations have only been used as supporting evidence for structure elucidation. For example, the IR spectra of 2-substituted-3-oxoisothiazolo[5,4-*b*]pyridines **43–58** have been reported (**Table 9**) <1998FES504>. The IR data for imidazo[4,5-*b*] and imidazo[4,5-*c*]pyridines were reported in <1996CHEC-II(7)283>.

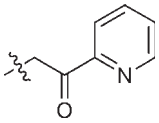
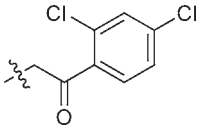
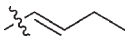
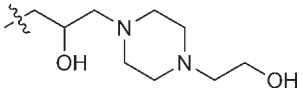
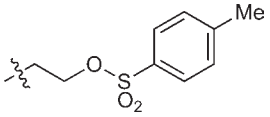
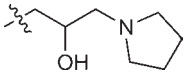
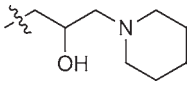
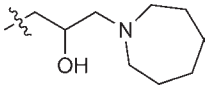
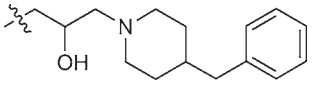
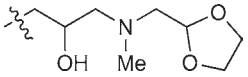
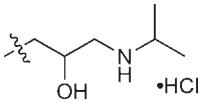
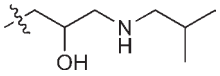
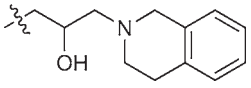
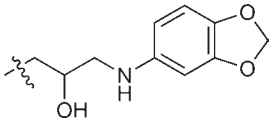
Table 9 IR spectra of 2-substituted-3-oxoisothiazolo[5,4-*b*]pyridines <1998FES504>



Compound	*X*	*R*	*IR* (cm^{-1})
43	S		3200–2400 (OH) 1710, 1670 (C═O)
44	S		3330, 3180 (NH) 1720, 1680 (C═O)

(*Continued*)

Table 9 (Continued)

Compound	*X*	*R*	*IR* (cm^{-1})
45	SO_2		1710 (C═O)
46	SO_2		1710 (C═O)
47	SO_2		3230 (═CH) 1730 (C═O)
48	S		3350 (OH) 1650 (C═O)
49	S		1670 (C═O)
50	S		3350–3150 (OH) 1670 (C═O)
51	S		3350–3150 (OH) 1670 (C═O)
52	S		3350–3150 (OH) 1670 (C═O)
53	S		3350 (OH) 1670 (C═O)
54	S		3400–3200 (OH) 1670 (C═O)
55	S		3300 (OH) 3100–2600 (hydrochloride) 1670 (C═O)
56	S		3300–2550 (NH, OH) 1670 (C═O)
57	S		3400–3200 (OH) 1670 (C═O)
58	S		3250–3000 (NH, OH) 1670 (C═O)

Reproduced with permission: 2-Substituted-3-oxoisothiazolo [5,4-*b*] pyridines as potential central nervous system and antimycobacterial agents; W. Malinka *et al.* 1998 © Elsevier Limited.

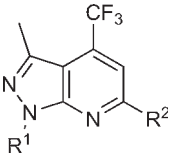
10.08.4 Thermodynamic Aspects

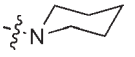
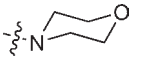
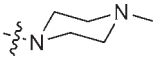
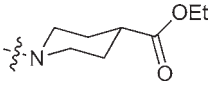
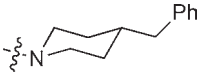
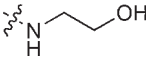
10.08.4.1 General Discussion

As mentioned in <1996CHEC-II(7)283>, the correlation of melting points, chromatographic and solubility properties for all of the ring systems presented in this chapter is not possible. However, several studies of imidazo[4,5-*b*]pyridines, imidazo[4,5-*c*]pyridines, oxazolo[4,5-*b*]pyridines, and thiazolo[4,5-*b*]pyridines can be found in <1996CHEC-II(7)283> and a few more recent examples are presented below.

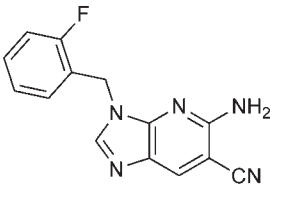
The melting points for a large number of fluorinated pyrazolo[3,4-*b*]pyridines have been reported by Volochnyuk *et al.* (**Table 10**) <2003S1531>.

Table 10 Melting points of several fluorinated pyrazolo[3,4-*b*]pyridines <2003S1531>

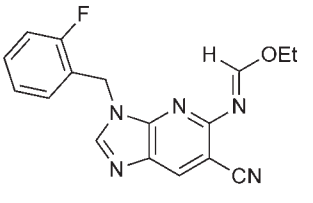


Compound	R^1	R^2	*m.p.* (°*C*)
35	Ph	3-Pyridyl	142–143
36	Ph	CF_3	74–75
37	Me	2-Thienyl	119–120
38	Me	CF_3	Oil
39	Ph		126
59	Ph	Ph	144
60	Ph	2-Thienyl	151–152
61	Ph	Me	58–59
62	Ph	OH	179–181
63	Ph	OTs	151–153
64	Ph	$OPOCl_2$	110
65	Ph	$OPO(OPh)_2$	68–70
66	Ph		137–139
67	Ph		87
68	Ph		112
69	Ph		109
70	Ph		174–176

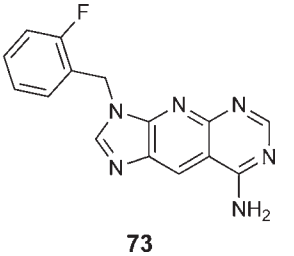
The imidazo[4,5-*b*]pyridines **71** and **72** have been prepared and a significant difference in melting points was observed: compound **71** decomposed at 214 °C, the imine **72** at 122 °C, and the cyclized product **73** at 150 °C <2001S2393>.



71



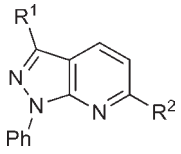
72



73

A large range of melting points for a variety of pyrazolo[3,4-*b*]pyridines **74–79** has also been reported by Zheng *et al.*, and interestingly the melting points appear to be independent of the substitution pattern at R^2, as no trend is observed when changing the substitution pattern α to nitrogen (R^1) (**Table 11**) <2006SC1549>.

Table 11 Selected melting points for a variety of pyrazolo[3,4-*b*]pyridines <2006SC1549>

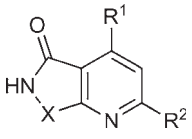


Compound	R^1	R^2	*m.p.* (°C)
74	Me	Ph	128–129
75	Me	4-MeC_6H_4	84–85
76	Me	4-$MeOC_6H_4$	102–103
77	Ph	Ph	135–146
78	Ph	4-MeC_6H_4	162–163
79	Ph	4-$MeOC_6H_4$	178–179

Reproduced with permission: One-Pot and Convenient Conversion of 5-Azidopyrazole-4-carboxaldehyde to Pyrazolo[3,4-*b*]pyridines; A. Zheng *et al.* 2006 © Taylor & Francis Ltd.

A general trend is observed when isoxazolo[5,4-*b*]pyridines and pyrazolo[5,4-*b*]pyridines are compared; in all cases, lower melting points for the corresponding pyrazolo[5,4-*b*]pyridines were observed (**Table 12**) <1997SC2217>.

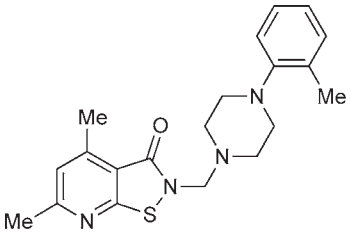
Table 12 Melting points of several isoxazolo[5,4-*b*]pyridines and pyrazolo[5,4-*b*]pyridines <1997SC2217>



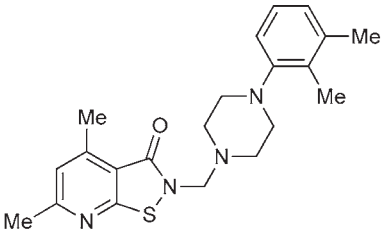
Compound	*X*	R^1	R^2	*m.p.* (°C)
80	O	CF_3	C_2H_5	197
81	O	CF_3	4-$CH_3C_6H_4$	211
82	O	CF_3	4-ClC_6H_4	216
83	O	H	CF_3	163
84	NH	CF_3	C_2H_5	176
85	NH	CF_3	4-$CH_3C_6H_4$	194
86	NH	CF_3	4-ClC_6H_4	187
87	NH	H	CF_3	155

Reproduced with permission: A Novel Method for the Synthesis of Isoxazolo and Pyrazolo Pyridines Using Hypervalent Iodine Reagent; A. C. S. Reddy *et al.* 1997 © Taylor & Francis Ltd.

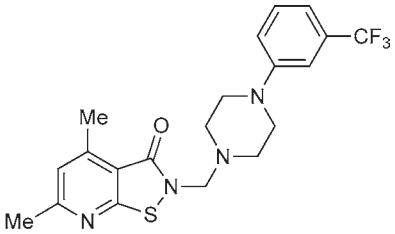
The melting points for a variety of isothiazolo[5,4-*b*]pyridine derivatives have been reported by Karczmarzyk and co-workers, and interestingly for compounds **88** and **89** the melting point increases quite significantly (from 108–110 °C to 158–160 °C) by introduction of an extra methyl group in the 3-position of the pendant aryl ring. Introduction of a CF_3 group in the 3-position **90** also increased the m.p. (145–148 °C) <2001FES905>.



88



89

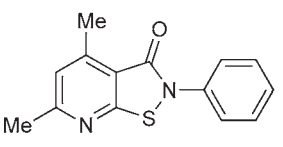


90

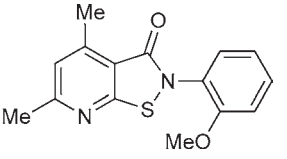
10.08.4.2 Solubilities and Chromatographic Behavior

Some general observations for 4-nitroimidazo[4,5-*c*]pyridin-2-ones, imidazo[4,5-*b*]pyridine-2-thiones, imidazo[4,5-*c*]pyridine-2-thiones, imidazo[4,5-*b*]quinolin-2-ones, isothiazolo[5,4-*b*]pyridine-2-thiones, and 3*H*-1,2-dithiolo[4,3-*c*]pyridine-3-thiones are reported in <1996CHEC-II(7)283>. The majority of compounds in this review have been isolated using standard chromatographic techniques.

The lipophilicity data for a range of isothiazolo[5,4-*b*]pyridine derivatives have been reported by Karczmarzyk and co-workers during their biological studies toward compounds with behavioral central nervous system (CNS) activity. They found that the lipophilicity, expressed as log P_{calc}, for compounds **91** and **92** did not differ significantly (4.43 and 4.18, respectively) <2001FES905>. It was noted that pK_a values for simple 1-arylpiperazines are typically within the range 7.94–9.14 and this suggested that compounds **91** and **92** may be protonated at pH 7.4. Therefore, a study to confirm this was conducted by measuring the ionization constant of both **91** and **92**. Compounds **91** and **92** are sparingly soluble in water and are unstable in acidic media, so the measurements were carried out in a 33% alcohol–water solution (37 °C). pK_a values of 7.15 **91** and 7.55 **92** were obtained and showed that *in vivo* about 50–60% of the compounds may be positively charged species.



91



92

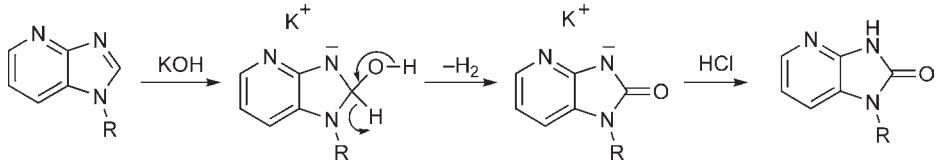
10.08.4.3 Conformations and Tautomerism

The conformations and tautomerisms of the various ring systems are discussed in the body of this chapter and in the original chapter <1996CHEC-II(7)283>.

10.08.5 Reactivity of Fully Conjugated Rings

10.08.5.1 Imidazo[4,5-*b*]pyridines

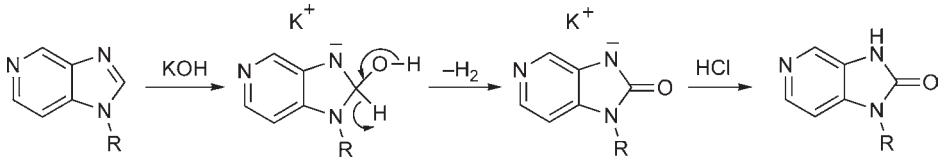
Imidazo[4,5-*b*]pyridines are exclusively hydroxylated in the imidazole ring; however, no yield was reported (Equation 3) <B-2000MI1>. N-Alkylation, N-deprotection, palladium-catalyzed cross-coupling, and thionation of imidazo[4,5-*b*]pyridines were reviewed in <1996CHEC-II(7)283>.



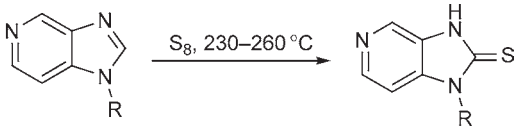
(3)

10.08.5.2 Imidazo[4,5-*c*]pyridines

Imidazo[4,5-*c*]pyridines are also exclusively hydroxylated in the imidazole ring; again no yield was reported for this transformation (Equation 4) <B-2000MI1>. Thionation of imidazo[4,5-*c*]pyridines can also be carried out with elemental sulfur; however, no yield was reported for this transformation (Equation 5) <B-2000MI1>.



(4)



(5)

10.08.5.3 Pyrazolo[3,4-*c*]pyridines

No further advances in the reactions of pyrazolo[3,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.5.4 Pyrazolo[4,3-*c*]pyridines

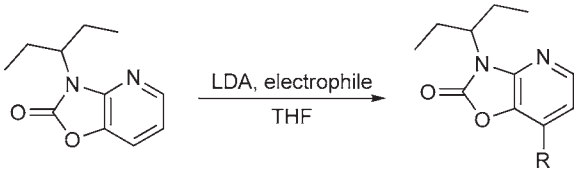
As found in the original chapter <1996CHEC-II(7)283>, no examples of reactions of fully conjugated pyrazolo[4,3-*c*]pyridines have been reported.

10.08.5.5 Oxazolo[4,5-*c*]pyridines

Other than the catalytic hydrogenation and the ring-opening reaction with hydroxide reported in the original chapter, no further advances in the synthesis of oxazolo[4,5-*c*]pyridines has been reported since 1996CHEC-II(7)283.

10.08.5.6 Oxazolo[4,5-*b*]pyridines

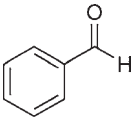
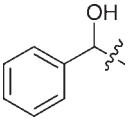
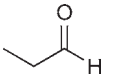
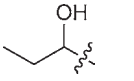
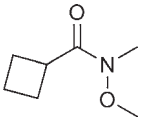
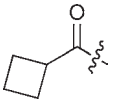
An attempt to directly couple **93** with bromobenzene via a Negishi coupling reaction resulted in a low yield of the desired product (Equation 6; **Table 13**) <2005TL1683>. Regioselective metalation with *t*-BuLi resulted in the formation of a mixture of the desired lithium anion at the 4-position of the pyridine ring as well as addition of *t*-BuLi to the oxazolidinone carbonyl group. Deprotonation with lithium diisopropylamide (LDA) followed by the addition of dibromoethane cleanly afforded desired bromide **94** (R = Br). The intermediate lithium anion was subjected to additional electrophiles, as shown in **Table 13**. Addition of methyl iodide, several aldehydes, and a Weinreb amide each proceeded in good yield. Not unexpectedly, treatment with ethyl iodide resulted only in recovery of protonated starting material due to competing elimination.



93 **94**

(6)

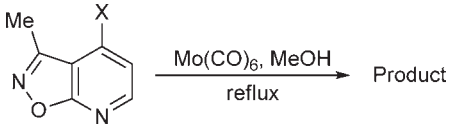
Table 13 Reaction of compound **93** and LDA with various electrophiles <2005TL1683>

Electrophile	*R*	*Yield* (%)
$BrCH_2CH_2Br$	Br	65
MeI	Me	78
		89
		73
		76
PhBr	Ph	11

Reproduced with permission: Synthesis of 2-amino-3-hydroxy-4-substituted pyridines via regioselective metalation of 3-(1-ethylpropyl)-[1,3]oxazolo[4,5-*b*]pyridin-2(3*H*)-one and application to corticotropin releasing factor$_1$ receptor ligands; R. A. Hartz *et al.* 2005 © Elsevier Limited.

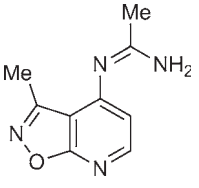
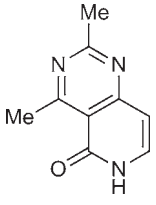
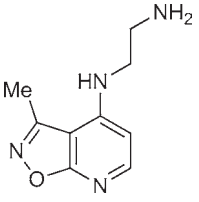
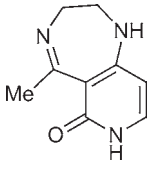
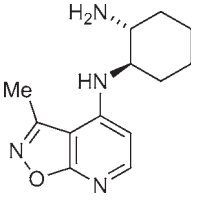
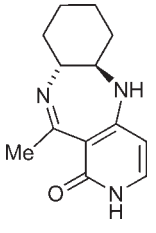
10.08.5.7 Isoxazolo[5,4-*b*]pyridines

A range of isoxazolo[5,4-*b*]pyridines have been treated with $Mo(CO)_6$ in methanol to afford a range of products (Equation 7; **Table 14**) <2003S2518>.



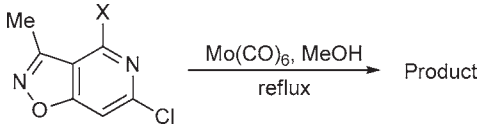
(7)

Table 14 Treatment of isoxazolo[5,4-*b*]pyridines with $Mo(CO)_6$ (Equation 7) <2003S2518>

Starting material	*Product*	*Yield* (%)
		65
		55
		75

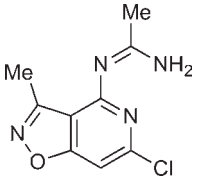
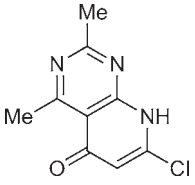
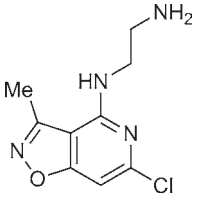
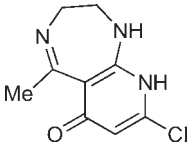
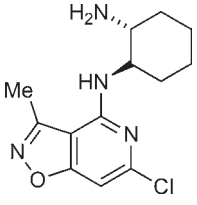
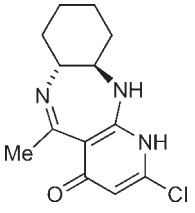
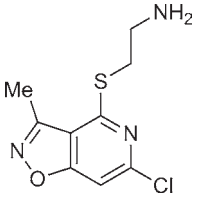
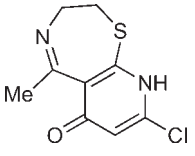
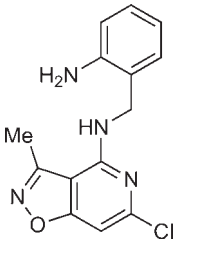
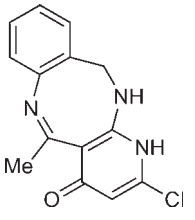
10.08.5.8 Isoxazolo[4,5-*c*]pyridines

A range of isoxazolo[4,5-*c*]pyridines have also been treated with $Mo(CO)_6$ in methanol to afford a range of products (Equation 8; **Table 15**) <2003S2518>.



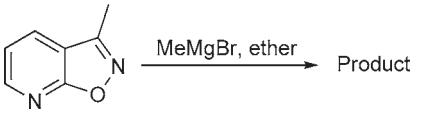
(8)

Table 15 Treatment of isoxazolo[4,5-*c*]pyridines with $Mo(CO)_6$ (Equation 8) <2003S2518>

Starting material	*Product*	*Yield* (%)
		65
		35
		41
		67
		46

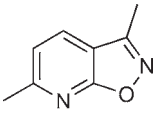
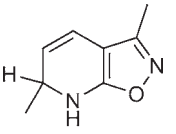
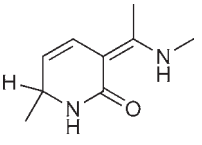
10.08.5.9 Isoxazolo[5,4-*b*]pyridines

Isoxazolo[5,4-*b*]pyridine **95** reacted in the dark to give different addition products **96–98** (Equation 9; **Table 16**), depending on the number of equivalents of organometallic compound and on the reaction temperature <2002TL9527>. The same authors found that sodium malonate, thermally unreactive toward the isoxazolo[5,4-*b*]-pyridine **95**, can be used as a photochemical trapping agent <2002TL9527>.

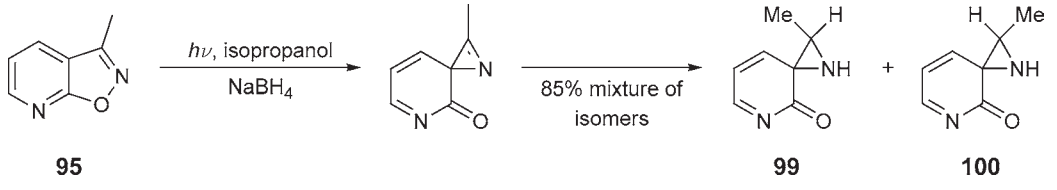


95 (9)

Table 16 Reaction of isoxazolo[5,4-*b*]pyridine **95** with varying equivalents of MeMgBr <2002TL9527>

MeMgBr (*equiv*)	*Temp*	*Product*	*Yield* (%)
1.0	rt	 **96**	80
1.0	−80 °C	 **97**	92
6.0	rt	 **98**	90

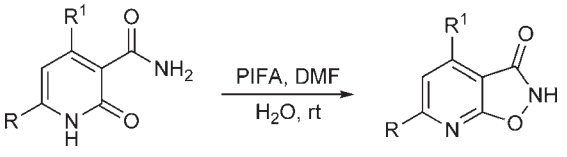
Treatment of the irradiated isoxazolo[5,4-*b*]pyridine **95** with sodium borohydride, a reagent which is also thermally inert toward **95**, traps the spiroazirine intermediate giving diastereoisomeric spiroaziridines **99** and **100** (**Scheme 1**).



95 **99** **100**

Scheme 1

Isoxazolo[5,4-*b*]pyridines have been synthesized via cyclization under oxidative conditions using phenyliodine(III) bis(trifluoroacetate) (PIFA) (Equation 10; **Table 17**) <1997SC2217>.



(10)

Table 17 Formation of isoxazolo[5,4-*b*]pyridines using oxidative conditions (Equation 10) <1997SC2217>

R	R^1	*Yield* (%)
CH_3	CF_3	71
C_2H_5	CF_3	76
C_6H_5	CF_3	80
4-$CH_3C_6H_4$	CF_3	69
4-ClC_6H_4	CF_3	72
CF_3	H	65

Reproduced with permission: A Novel Method for the Synthesis of Isoxazolo and Pyrazolo Pyridines Using Hypervalent Iodine Reagent; A. C. S. Reddy *et al.* 1997 © Taylor & Francis Ltd.

10.08.5.10 Isoxazolo[4,5-*b*]pyridines

No further advances in the reactions of isoxazolo[4,5-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.5.11 Isothiazolo[4,3-*c*]pyridines

No further advances in the reactions of isoxazolo[4,3-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.5.12 Isothiazolo[5,4-*b*]pyridines

No further advances in the reactions of isoxazolo[5,4-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.5.13 Isothiazolo[4,5-*c*]pyridines

No further advances in the reactions of isothiazolo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

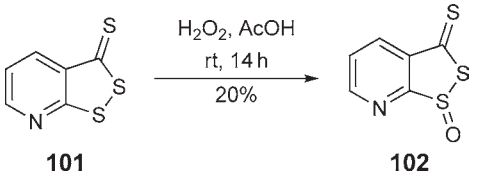
10.08.5.14 3*H*-1,2-Dithiolo[4,3-*c*]pyridines

No further advances in the reactions of 3*H*-1,2-dithiolo[4,3-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

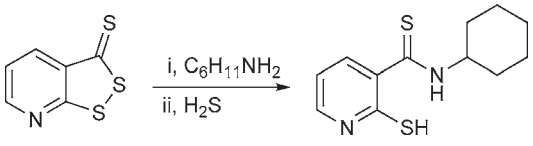
10.08.6 Reactivity of Nonconjugated Rings

10.08.6.1 3*H*-1,2-Dithiolo[3,4-*b*]pyridines

One of the sulfur atoms in 3*H*-1,2-dithiolo[3,4-*b*]pyridine **101** can be selectively oxidized to the sulfoxide derivative **102** using hydrogen peroxide and acetic acid, presumably mediated by peracetic acid generated *in situ* (Equation 11) <2003FA995>. It has been reported that 3*H*-1,2-dithiolo[3,4-*b*]pyridines can be ring-opened using primary amines, although no yields were reported for this process (Equation 12) <2000JME199>.



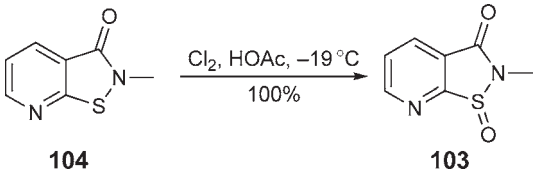
101 **102** (11)



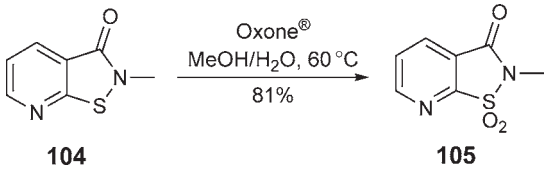
(12)

10.08.6.2 Isothiazolo[5,4-*b*]pyridines

2-Methylisothiazolo[5,4-*b*]pyridin-3-(2*H*)-one-1-oxide **103** was quantitatively obtained by treating **104** with chlorine in aqueous acetic acid (Equation 13). The oxidation of **104** with Oxone® at 60 °C in aqueous methanol gave 2-methylisothiazolo[5,4-*b*]pyridin-3-(2*H*)-one 1,1-dioxide **105** in a single step (Equation 14). No C-halogenation or N-oxidation products were detected under these reaction conditions <1996T8947>.



104 **103** (13)

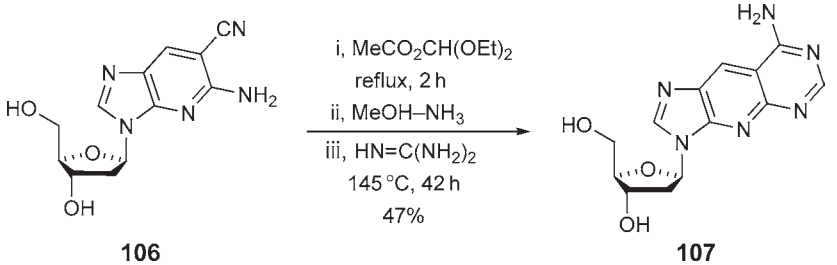


104 **105** (14)

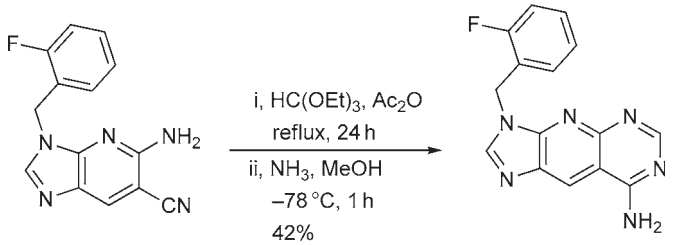
10.08.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.08.7.1 Imidazo[4,5-*b*]pyridines

Conversion of the imidazo[4,5-*b*]pyridine **106** to stretched 2′-deoxyadenine **107** was achieved without isolation of any intermediates in 47% yield (Equation 15) <2002SL1483>. A similar cyclization of **108** was achieved using triethyl orthoformate and ammonia (Equation 16) <2001S2393>.



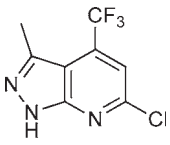
106 **107** (15)



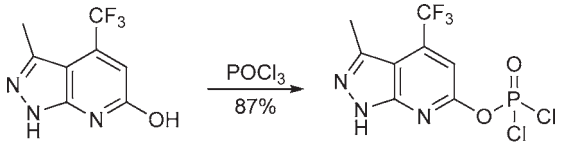
108 (16)

10.08.7.2 Pyrazolo[3,4-*b*]pyridines

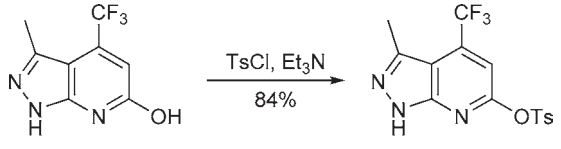
In the attempted synthesis of α-chloropyridines, for example **109**, alcohol **62** was treated with $POCl_3$, but only compound **64** was isolated (Equation 17) <2003S1531>. It was also found that **62** could be tosylated (Equation 18) and displaced with a secondary amine (Equation 19; **Table 18**).



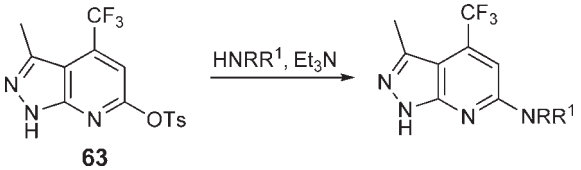
109



62 **64** (17)

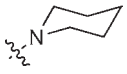
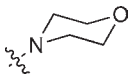
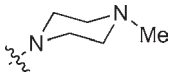
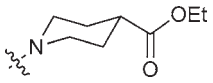
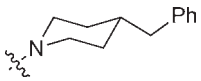
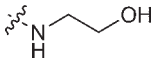


62 **63** (18)



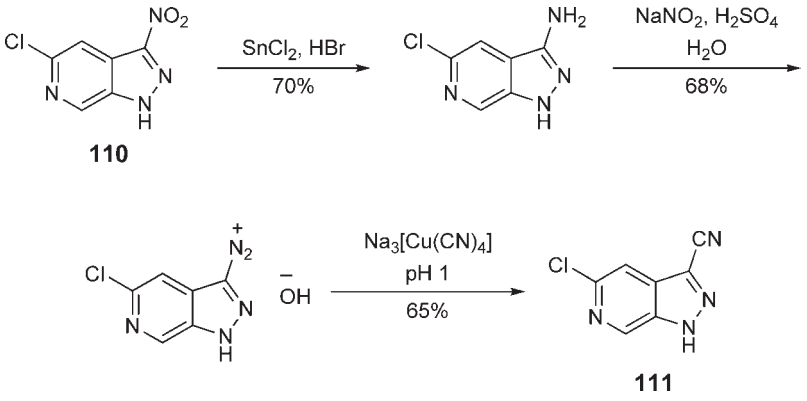
63 (19)

Table 18 Displacement of the tosylate group in **63** with secondary amines (Equation 19) <2003S1531>

NRR[1]	*Yield* (%)
	68
	72
	53
	62
	63
	43

10.08.7.3 Pyrazolo[4,3-*c*]pyridines

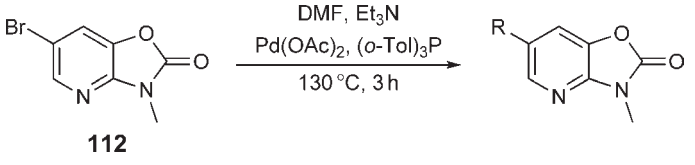
Conversion of the nitro to cyano group in compound **110** involved a number of reactions of substituents attached to ring carbon atoms (**Scheme 2**) <1999H(51)1661>. Diozatization under typical conditions followed by reaction with $Na_3[Cu(CN)_4]$ at pH 1 afforded the cyano derivative **111**.



Scheme 2

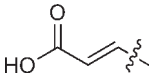
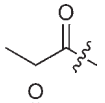
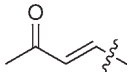
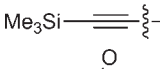
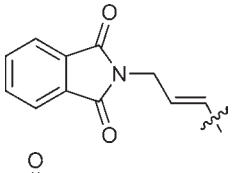
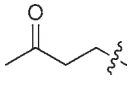
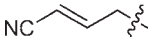
10.08.7.4 Oxazolo[4,5-*b*]pyridines

An attempt to functionalize position 6 of the oxazolo[4,5-*b*]pyridine **112** was unsuccessful when using *n*-butyllithium and an electrophile at −78 °C; however, successful Heck coupling was achieved using palladium(II) acetate and tri-*o*-tolylphosphine in dimethylformamide (DMF) with triethylamine as base (Equation 20; **Table 19**) <1996TL2409, 1997T5159, 1998BMC1963>. The Stille (Equation 21; **Table 20**) and Suzuki couplings were also found to be successful (Equation 22).

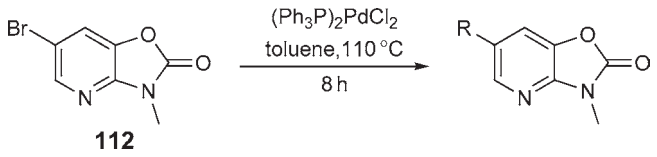


(20)

Table 19 Heck reaction of **112** with a range of coupling partners (Equation 20) <1996TL2409>

Reagent	*R*	*Yield* (%)
Acrylic acid		70
Butyl vinyl ether		90
Ethyl 1-propenyl ether		40
3-Buten-2-one		85
Trimethylsilylacetylene		92
N-Allylphthalimide		69
3-Buten-2-ol		73
Acrylonitrile		65

Reproduced with permission: Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones: functionalization at 6-position; V. Marie-Claude *et al*. 1996 © Elsevier Limited.

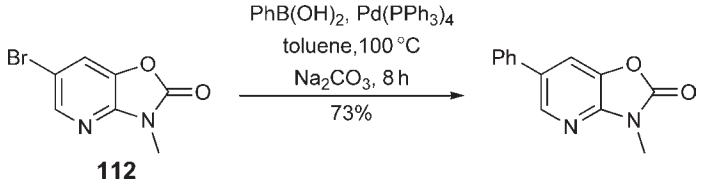


(21)

Table 20 Stille coupling using compound **112** (Equation 21) <1996TL2409>

Reagent	*R*	*Yield* (%)
Tetramethyltin	CH_3	72
Tetrabutyltin	CH_2=CH	62
Tributylvinyltin	CH_3–$(CH_2)_3$	86

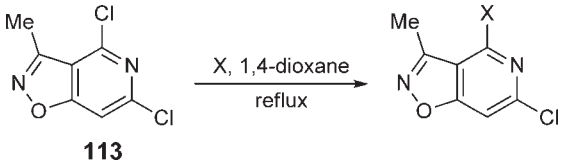
Reproduced with permission: Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones: functionalization at 6-position; V. Marie-Claude *et al.* 1996 © Elsevier Limited.



(22)

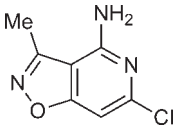
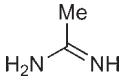
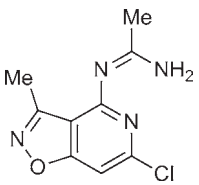
10.08.7.5 Isoxazolo[4,3-*c*]pyridines

Substitution of one of the Cl-bonds in the isoxazolo[4,3-*c*]pyridine **113** with a variety of nucleophiles has been reported by Ponticelli and co-workers (Equation 23; **Table 21**) <2003S2518>.



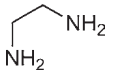
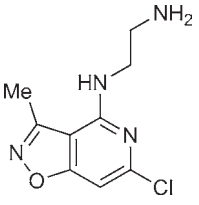
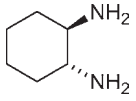
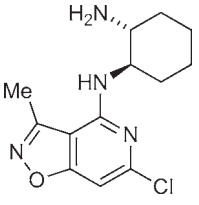
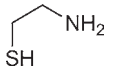
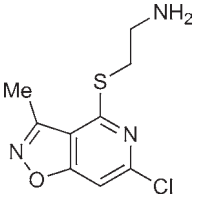
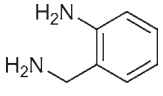
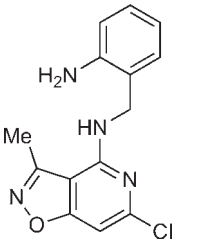
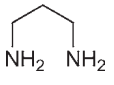
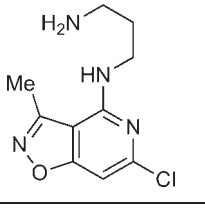
(23)

Table 21 Nucleophilic substitution of isoxazolo[4,3-*c*]pyridine **113** (Equation 23) <2003S2518>

X	*Product*	*Yield* (%)
NH_3		70
		65

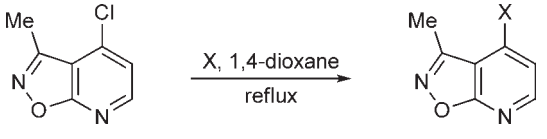
(*Continued*)

Table 21 (Continued)

X	*Product*	*Yield* (%)
		54
		55
		85
		63
		63

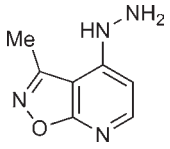
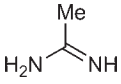
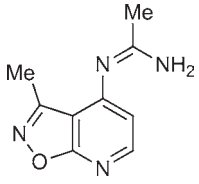
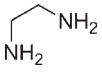
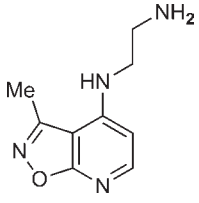
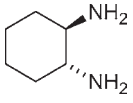
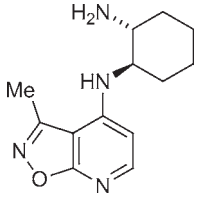
10.08.7.6 Isoxazolo[5,4-*b*]pyridines

Ponticelli and co-workers also reported the synthesis of isoxazolo[5,4-*b*]pyridines using the methodology described in Section 10.08.7.5 (Equation 24; **Table 22**) <2003S2518>.



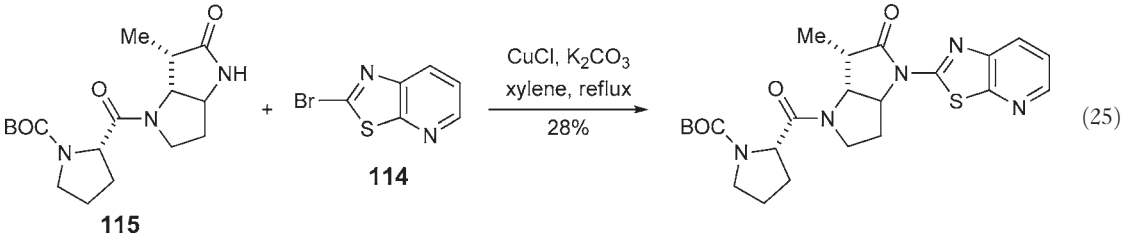
(24)

Table 22 Nucleophilic substitution of isoxazolo[5,4-*b*]pyridines (Equation 24) <2003S2518>

X	*Product*	*Yield* (%)
H_2NNH_2		65
		85
		76
		60

10.08.7.7 Isothiazolo[5,4-*b*]pyridines

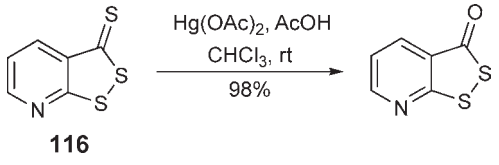
Coupling of the isothiazolo[5,4-*b*]pyridine **114** with compound **115** affords useful compounds as serine protease inhibitors (Equation 25) <2003JME4428>.



(25)

10.08.7.8 3*H*-1,2-Dithiolo[3,4-*b*]pyridines

Mercuric acetate can be used to substitute sulfur to oxygen in compound **116** (Equation 26) <2000JME199>.

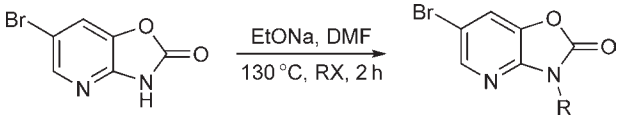


(26)

10.08.8 Reactivity of Substituents Attached to Ring Heteroatoms

10.08.8.1 Oxazolo[4,5-*b*]pyridines

N-Alkylation of oxazolo[4,5-*b*]pyridines can be achieved in a number of ways. Viaud *et al.* have reported direct N-alkylation by reaction with alkyl halides (Equation 27; **Table 23**) or Michael condensation with a range of olefins (Equation 28; **Table 24**) <1996TL2409>, both methods affording the desired products in good yields.

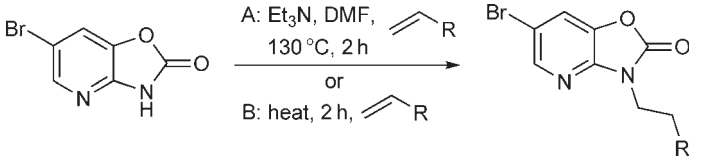


(27)

Table 23 N-Alkylation of oxazolo[4,5-*b*]pyridines (Equation 27) <1996TL2409>

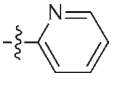
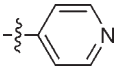
R	*Yield* (%)
CH_3	85
CH_2CN	82
CH_2COOMe	74
CH_2CH_2Ph	78
CH_2Ph	56

Reproduced with permission: Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones: functionalization at 6-position; V. Marie-Claude *et al*. 1996 © Elsevier Limited.



(28)

Table 24 Michael condensation of oxazolo[4,5-*b*]pyridines (Equation 28) <1996TL2409>

R	*Method*	*Yield* (%)
$COOCH_3$	A	52
CN	A	81
	B	87
	B	65

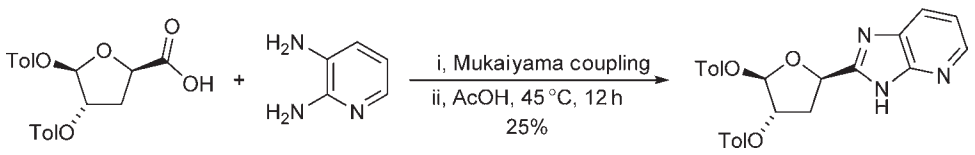
Reproduced with permission: Substituted oxazolo[4,5-*b*]pyridin-2(3*H*)-ones: functionalization at 6-position; V. Marie-Claude *et al.* 1996 © Elsevier Limited.

10.08.9 Ring Synthesis Classified by Formation of the Second Heterocyclic Ring

10.08.9.1 Imidazo[4,5-*b*]pyridines

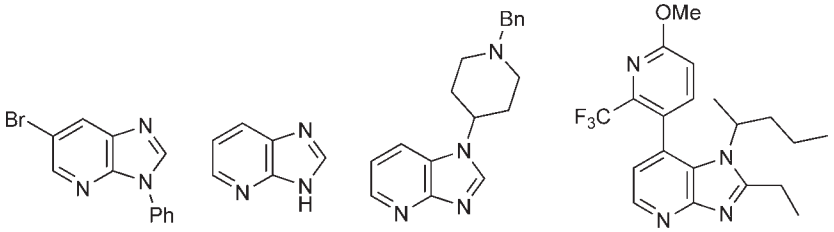
10.08.9.1.1 Closure of the imidazole ring

Imidazo[4,5-*b*]pyridines can be synthesized by a large number of routes, from which condensation of the appropriate carboxylic acid or acid chloride with the corresponding diaminopyridine, sometimes requiring cyclization of the intermediate amide with strong acid, appears to be the most widely used method <1996CHEC-II(7)283>. A recent example has been reported for the synthesis of pyridoimidazole C-nucleosides, and although the yield in this particular case was low, no epimerization at the C-1′ stereocenter was observed (Equation 29) <2003TL5807>.

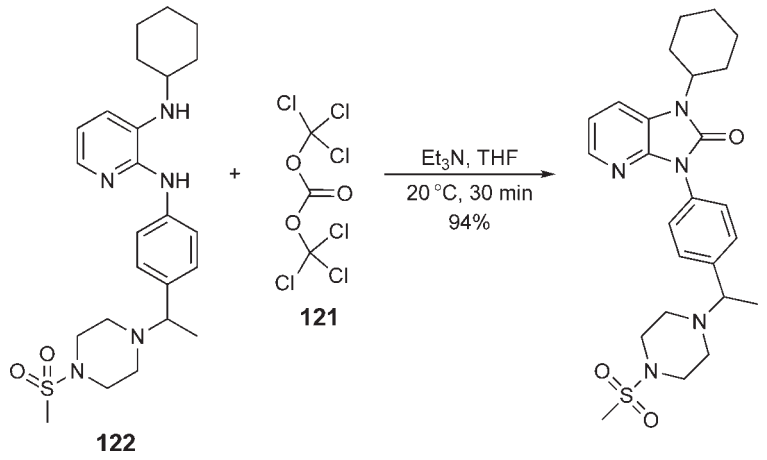


(29)

Imidazo[4,5-*b*]pyridines **117** <2003BML2485>, **118** <2004BML3165>, **119** <2005BML2129>, and **120** <2003BML289> have been prepared from the corresponding diaminopyridine and the appropriate trialkyl orthoformate or, in the case of **120**, triethyl orthopropionate. However, in each case, the authors fail to report product yields.

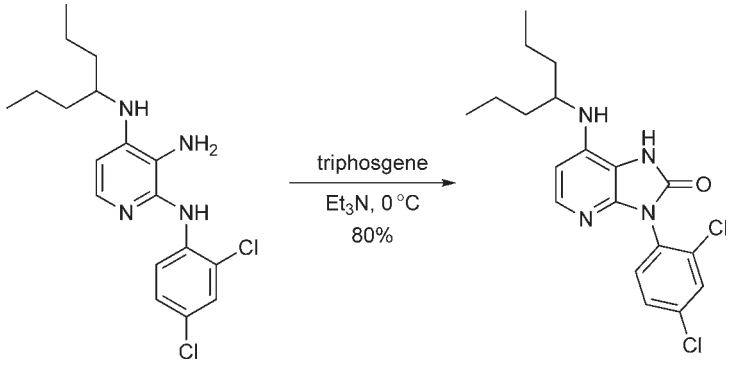


Cyclization of 2,3-diaminopyridines to afford 1*H*,3*H*-imidazo[4,5-*b*]pyridin-2-ones and related compounds can be achieved using a variety of reagents, including phosgene, urea, carbonyldiimidazole, their sulfur analogues, etc. <1996CHEC-II(7)283>. Other examples include the use of carbonic acid bis-trichloromethyl ester **121**, which reacted with the bis-amine **122** in excellent yield (Equation 30) <2004JOC7752>. Guo *et al.* have used this approach to prepare a large number of biologically active imidazo[4,5-*b*]pyridines <2005JME5104>.

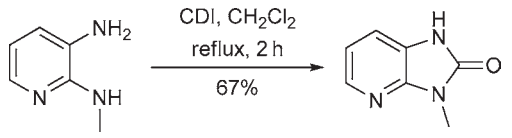


(30)

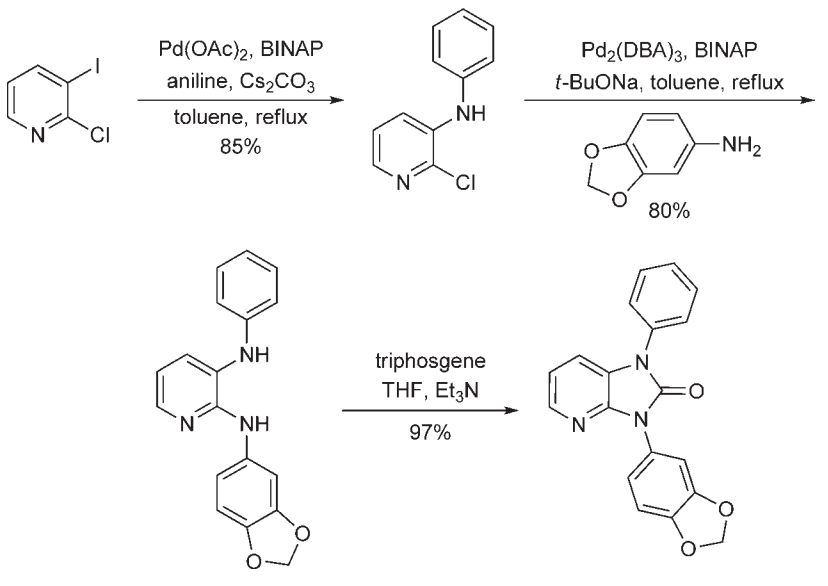
A range of imidazo[4,5-*b*]pyridine-2-ones, which are active corticotropin-releasing factor-1 antagonists, have been prepared by cyclization using triphosgene in good yield, for example Equation (31) <2005JME5104>. Similar systems can be prepared in good yield using carbonyldiimidazole (CDI) (Equation 32) <2000JME3052>. Several symmetrical and unsymmetrical imidazo[4,5-*b*]pyridine-2-ones have been prepared using a sequential Buchwald–Hartwig coupling approach; an example is shown in **Scheme 3** <2004JOC7752>.



(31)

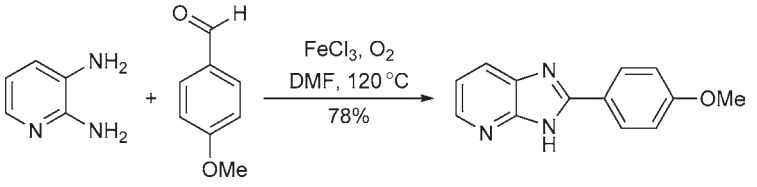


(32)

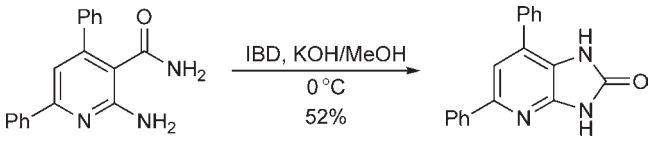


Scheme 3

The above examples report perhaps the most well used routes to imidazo[4,5-*b*]pyridines; however, there are many other less well known methods. For example, treatment of 2,3-diaminopyridines with aryl aldehydes and subsequent oxidation with sulfur affords the corresponding imidazo[4,5-*b*]pyridines in good yield <1996CHEC-II(7)283>. A catalytic Fe(III)/Fe(II) redox cycle approach to imidazopyridines has been reported (Equation 33) <2000S1380>. A hypervalent iodine oxidative rearangement of 2-aminopyridinecarboxamides has also been reported <2001S541>. Treatment of 2-amino-4,6-diphenyl-3-pyridinecarboxamide **123** with iodobenzene diacetate (IBD) in KOH/MeOH afforded the pyridin-2-one **124** (Equation 34).



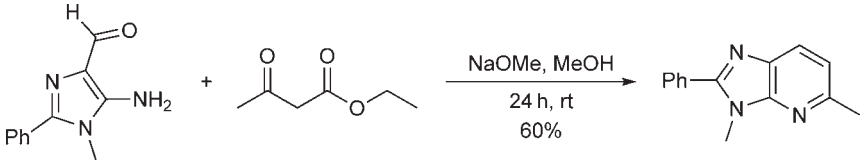
(33)



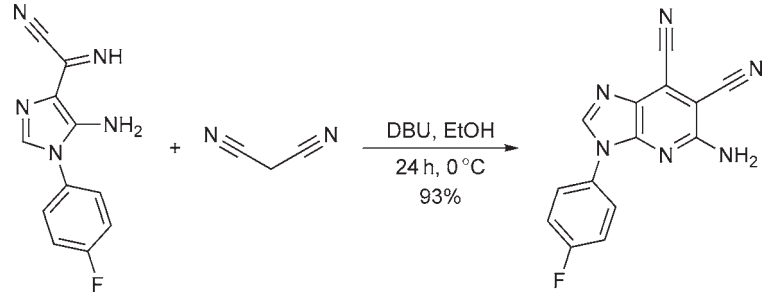
123 **124** (34)

10.08.9.1.2 Closure of the pyridine ring

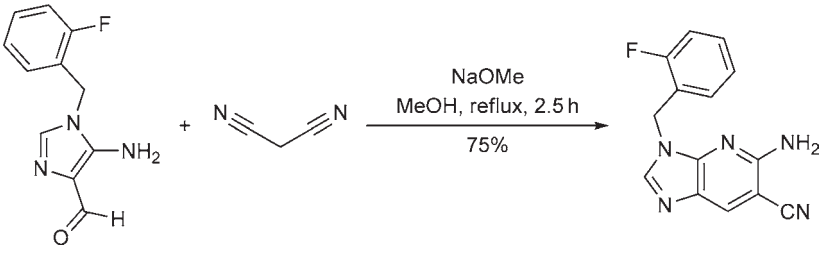
Formation of imidazo[4,5-*b*]pyridines by closure of the pyridine ring is perhaps not the obvious synthetic route; however, there are several reports regarding the synthesis of these compounds using this approach in good to excellent yield (Equations 35) <1997JHC107>, (36) <2003JOC276>, (37) <2001S2393>, and (38) <2000T7909>). All of these methods start from the appropriately functionalized imidazole. Reaction of the primary amine with a soft electrophile and subsequent dehydration affords the corresponding imidazo[4,5-*b*]pyridine.



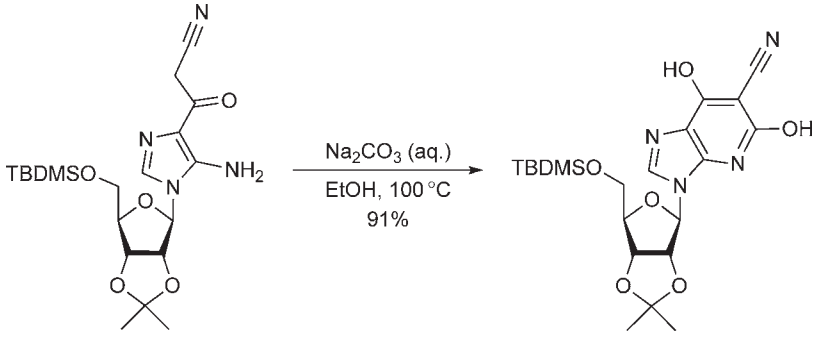
(35)



(36)

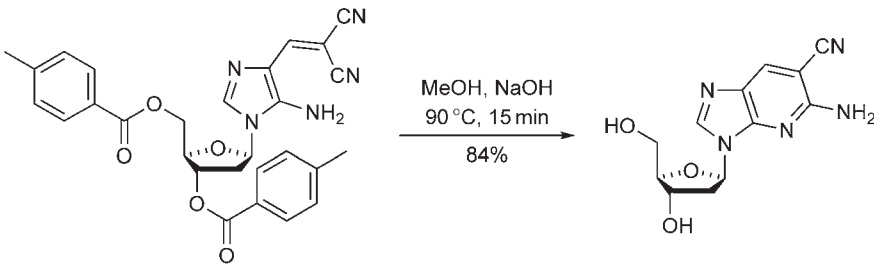


(37)



(38)

Simultaneous cyclization and deprotection of **125** with MeOH–NaOH afforded the imidazo[4,5-*b*]pyridine **126** in good yield (Equation 39) <2002SL1483>.

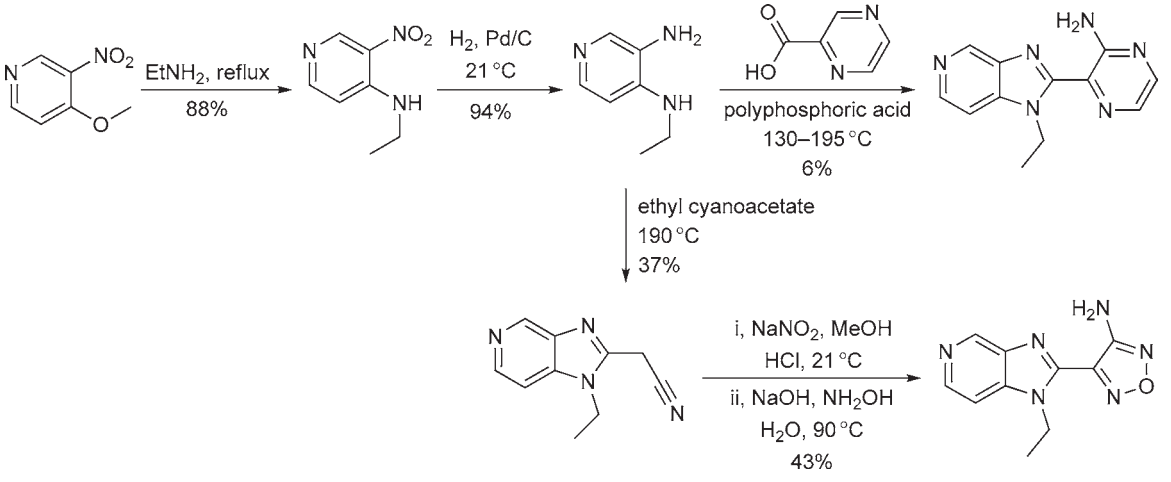


(39)

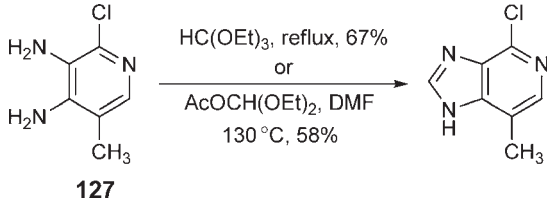
10.08.9.2 Imidazo[4,5-c]pyridines

10.08.9.2.1 Closure of the imidazole ring

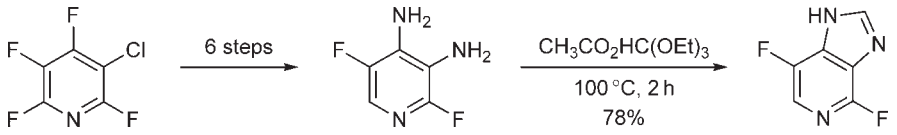
Several imidazo[4,5-*c*]pyridines, which are potent MSK-1 inhibitors, have been prepared from commercially available 4-methoxy-3-nitropyridine following the sequence shown in **Scheme 4** <2005BML3402>. *anti*-Fixed 3-methyl-3-deaza-20-deoxyadenosine and other related imidazo[4,5-*c*]pyridines have been synthesized by Irani *et al.* using the diamino pyridine **127**, which on treatment with diethoxymethyl acetate or triethyl orthoformate affords the corresponding ring-closed product (Equation 40) <2005NN737>. 3-Fluoro-3-deazaadenosine analogues have been prepared using an imidazo[4,5-*c*]pyridine as a key intermediate, synthesized from commercially available 3-chloro-2,4,5,6-tetrafluoropyridine (**Scheme 5**) <2005TL3883>. Several imidazo[4,5-*c*]pyridines, which have potent activity toward methicillin-resistant *Staphylococcus aureus* (MRSA), have been synthesized from the amino pyridine **128** (**Scheme 6**) <2004BMC4211>. Inhibitors of the metalloprotease neprilysin have been synthesized from the thioether **129** (**Scheme 7**) <2005HCA731>.



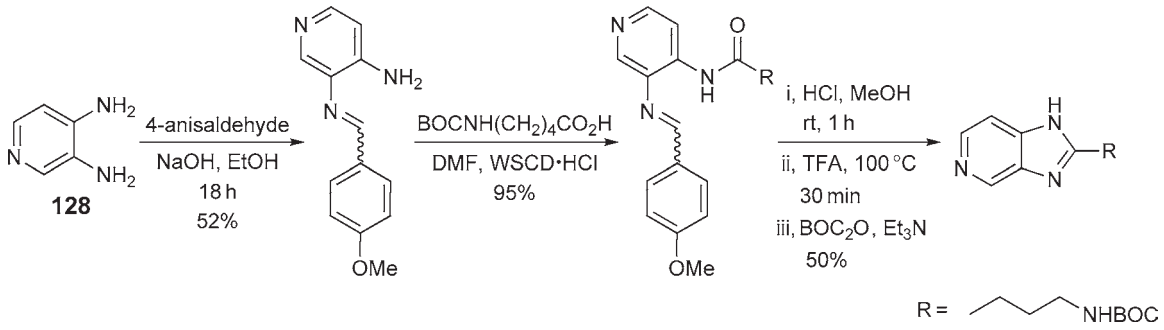
Scheme 4



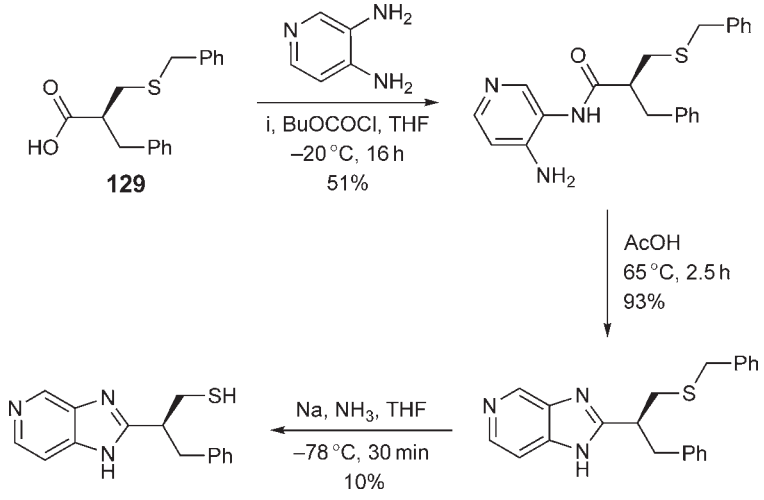
(40)



Scheme 5

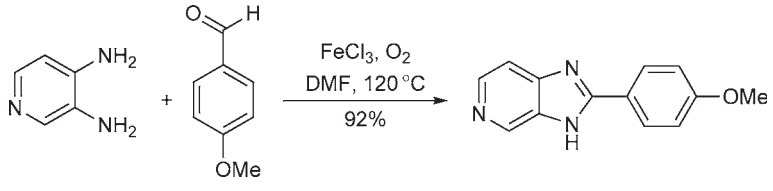


Scheme 6

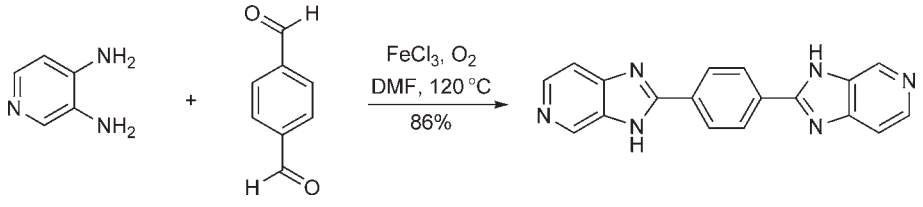


Scheme 7

A catalytic Fe(III)/Fe(II) redox cycling approach to imidazopyridines has also been reported for the synthesis of imidazo[4,5-*c*]pyridines (Equations 41 and 42) <2000S1380>.

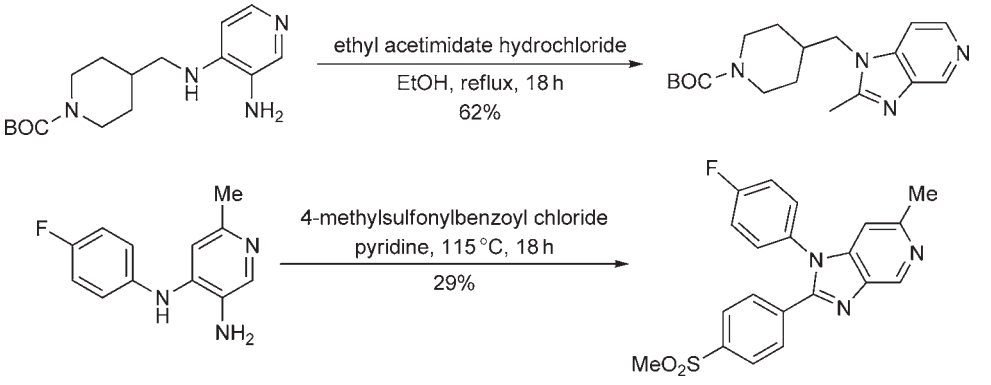


(41)



(42)

Imidazo[4,5-*c*]pyridines have also been prepared through cyclization of the requisite diamine with ethyl acetimidate hydrochloride (Equation 43) <1996JME487> or by cyclization with 4-methylsulfonylbenzoyl chloride (Equation 44) <2001JME350>. Further examples of this type can be found in <1996CHEC-II(7)283>.

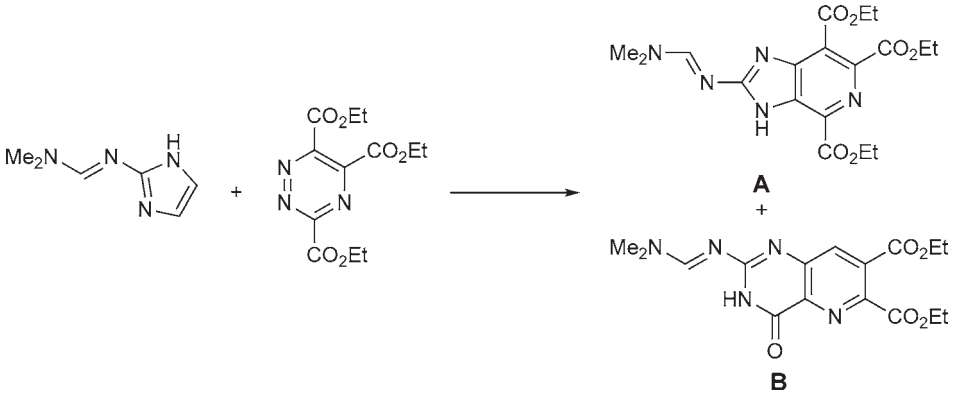


(43)

(44)

10.08.9.2.2 Closure of the pyridine ring

The inverse electron demand Diels–Alder reaction can be utilized to form imidazo[4,5-*c*]pyridines, through the reaction of imidazoles with 1,2,4-triazines. However, a mixture of products is observed, imidazo[4,5-*c*]pyridines and pyrido[3,2-*d*]pyrimid-4-ones (compounds **A** and **B** in Equation (45), respectively). Either can be the main product depending on the triazine substituents. The cycloadditions are limited in that they require a strong electron-donating C-2 substituent on the imidazole as well as strong electron withdrawing substituents on the triazine (Equation 45; **Table 25**) <1997TL7495, 2003JOC4345>.

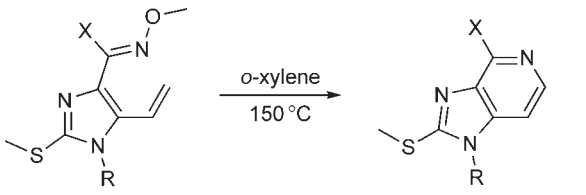


(45)

Table 25 Synthesis of imidazo[4,5-*c*]pyridines and pyrido[3,2-*d*]pyrimid-4-ones (Equation 45) <2003JOC4345>

Solvent	*Temp.*	*Time* (*h*)	*Yield A* (%)	*Yield B* (%)
THF	rt	60	32	55
Dioxane	rt	60	43	47
CH_2Cl_2	rt	60	25	60
THF	Reflux	10	17	72
Dioxane	Reflux	5	13	77

It was found that heating a dilute solution of imidoyl chloride **130** in *o*-xylene afforded the chloroimidazopyridine **131** in 73% yield. The yield of **131** could be improved slightly to 81% if the electrocyclization was run in a microwave reactor, but because of scale-up problems this procedure was not normally used. In the case of imidoyl bromide **132**, the electrocyclization afforded only a modest 46% yield of bromopyridine **133**, along with about 13% of recovered starting material. With the benzyloxymethyl (BOM)-protected imidoyl chloride **134**, chloropyridine **135** was obtained in 84% isolated yield upon heating in *o*-xylene (Equation 46) <2006OL1443>.



130 = PMB: X = Cl
132 = PMB: X = Br
134 = BOM: X = Cl

131 = PMB: X = Cl (73%)
133 = PMB: X = Br (46%)
135 = BOM: X = Cl (84%)

(46)

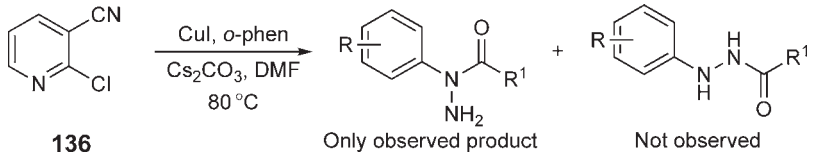
10.08.9.3 Imidazo[4,5-*b*]quinolin-2-ones

No further advances in the synthesis of imidazo[4,5-*b*]quinolin-2-ones have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.4 Pyrazolo[3,4-*b*]pyridines

10.08.9.4.1 Closure of the pyrazole ring

Reaction of 2-chloro-3-cyanopyridine **136** with hydrazines gave only one isomer (Equation 47) <2004TL2389>. This process was then applied to the synthesis of 3-amino-pyrazolo[3,4-*b*]pyridines. Reaction of 2-chloro-3-cyanopyridine **136** with excess hydrazines, 5/10 mol% of CuI/*o*-phenanthroline, and cesium carbonate in DMF afforded 1-substitued-3-amino-pyrazolo[3,4-*b*]pyridines in reasonable yields (Equation 48; **Table 26**). Strongly nucleophilic hydrazines such as aliphatic derivatives gave higher yields and cleaner reactions than aromatic ones. Deactivated hydrazines such as 4-cyanophenylhydrazine and 2,4-dinitrophenylhydrazine did not afford the desired products, yielding only recovered starting material. A range of iodo-substituted pyrazolo[3,4-*b*]pyridines has also been reported by the use of an analogous procedure <2004TL6633>.

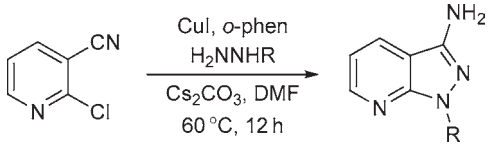


136

Only observed product

Not observed

(47)



(48)

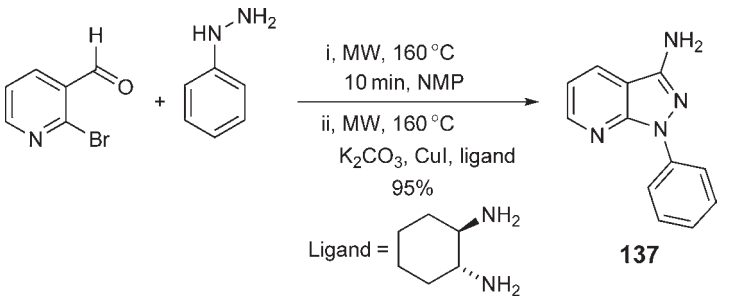
Table 26 Reaction of 2-chloro-3-cyanopyridine **136** with excess hydrazines (Equation 48) <2004TL2389>

R (*product*)	*Yield* (%)
Ph	50
Me	93
H	70
Et	86
4-Tolyl	53
4-Methoxyphenyl	61
Benzyl	72

Reproduced with permission: Synthesis and functionalisation of 1*H*-pyrazolo[3,4-*b*]pyridines involving copper and palladium-promoted coupling reactions; G. Lavecchia *et al.* 2004 © Elsevier Limited.

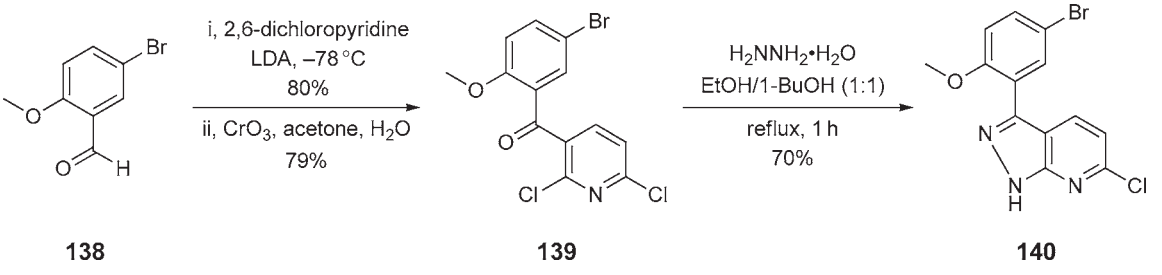
A highly efficient one-pot, two-step microwave procedure has been developed for the synthesis of 1-aryl-1*H*-indazoles. Microwave heating of 2-halobenzaldehydes or 2-haloacetophenones with phenylhydrazines at 160 °C for 10 min quantitatively yielded the arylhydrazones, which were further cyclized to give 1-aryl-1*H*-indazoles via CuI/diamine-catalyzed

N-arylation under microwave heating (160 °C, 10 min). Good to excellent yields were observed for hydrazones of 2-iodo-, 2-bromo-, and 2-chlorobenzaldehydes. Notably, a yield of 87% was achieved for a hydrazone of unactivated 2-chlorobenzaldehyde, whereas using the previously reported palladium catalysis the yield was less than 1% for the same substrate. Application of this methodology afforded the pyrazolo[3,4-*b*]pyridine **137** in excellent yield (Equation 49) <2005TL7553>.



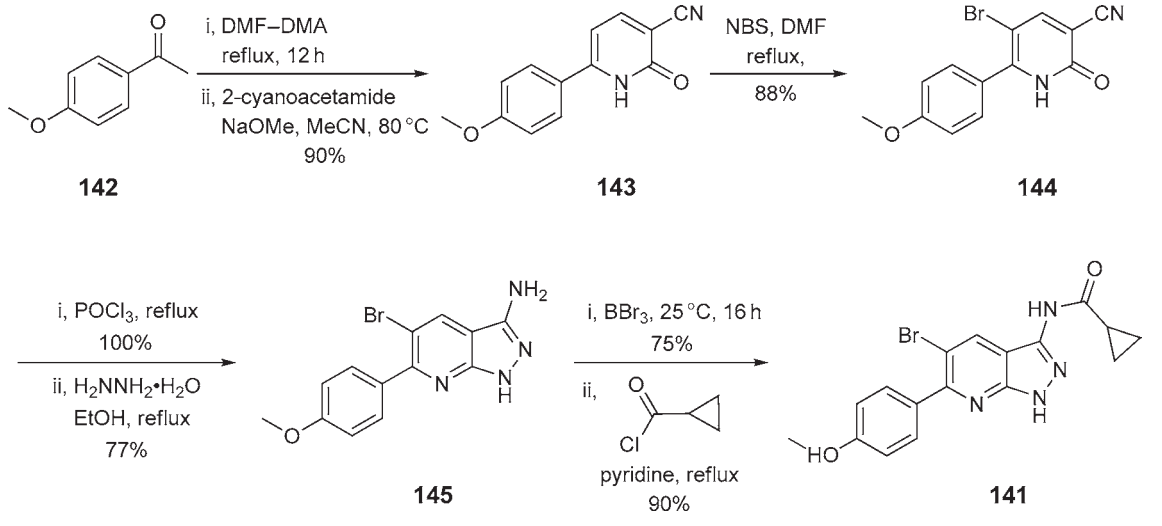
(49)

The synthesis of pyrazolo[3,4-*b*]pyridines can be achieved by reaction of 2,6-dichloro-3-lithiopyridine with 5-bromo-2-methoxybenzaldehyde **138** to provide the alcohol, which after Jones oxidation gave ketone **139**. Treatment of the ketone with hydrazine furnished the desired pyrazolo[3,4-*b*]pyridine **140** (**Scheme 8**) <2006BML262>.



Scheme 8

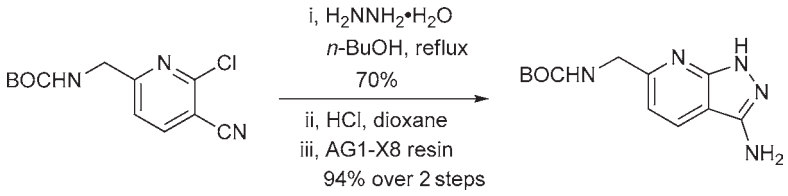
6-Aryl-pyrazolo[3,4-*b*]pyridines are potent inhibitors of glycogen synthase kinase-3 (GSK-3) and several analogues have been prepared following the general procedure outlined for **141** in **Scheme 9** <2003BML3055>. Treatment of the commercially available ketone **142** with DMF–DMA at reflux afforded the intermediate dimethylaminopropenone, which was cyclized without purification to afford the pyridone **143** (DMA = dimethylacetamide). Selective bromination at the 3-position of the pyridone employing *N*-bromosuccinimide (NBS) at reflux afforded **144** in excellent yield. Subsequent treatment with phosphorus oxychloride at reflux, followed by cyclization of the intermediate chloronitrile



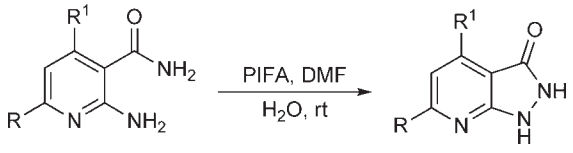
Scheme 9

with hydrazine afforded the amine **145**. Demethylation employing BBr_3 followed by subsequent selective N-3-acylation afforded the desired pyrazolo[3,4-*b*]pyridine **141** in excellent overall yield.

Pyrazolo[3,4-*b*]pyridines have also been formed by reaction of the appropriate chloronitrile pyridine (Equation 50) <2002BML2925>. Pyrazolo[3,4-*b*]pyridines can be prepared by oxidative cyclization with PIFA (Equation 51; **Table 27**) <1997SC2217>.



(50)



(51)

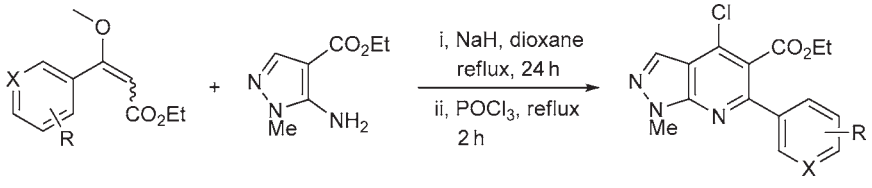
Table 27 Pyrazolo[3,4-*b*]pyridines prepared by oxidative cyclization (Equation 51) <1997SC2217>

R	R^1	*Yield* (%)
C_2H_5	CF_3	73
4-$CH_3C_6H_4$	CF_3	69
4-ClC_6H_4	CF_3	72
CF_3	H	63

Reproduced with permission: A Novel Method for the Synthesis of Isoxazolo and Pyrazolo Pyridines A. Zheng *et al.* 2006 © Taylor & Francis Ltd.

10.08.9.4.2 Closure of the pyridine ring

Condensation of the intermediates **146–151** with either ethyl 5-amino-1-methylpyrazole-4-carboxylate or ethyl 2-aminothiophene-3-carboxylate using sodium hydride in refluxing dioxane gave the corresponding 4-hydroxy-1-methyl-pyrazolopyridine or 4-hydroxythienylpyridine esters, respectively (Equation 52; **Table 28**) <2003BMC2991>.

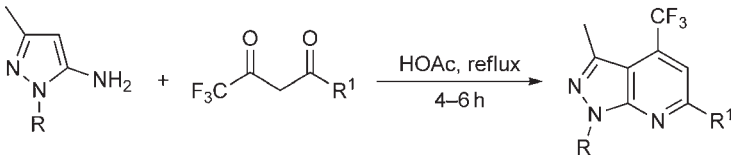


(52)

Table 28 Condensation of the intermediates **146–151** (Equation 52) <2003BMC2991>

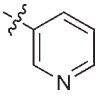
Compound	*X*	*R*	*Yield* (%)
146	CH	3-CN	95
147	CH	3-Br	57
148	N	3-Br	65
149	CH	H	60
150	CH	4-F	73
151	N	H	44

A range of trifluoromethyl-containing pyrazolo[3,4-*b*]pyridines have been prepared, in good yield, from the reaction of 4,4,4-trifluoro-3-oxobutanoates with electron-rich amino pyrazoles (Equation 53; **Table 29**) <2003S1531>.

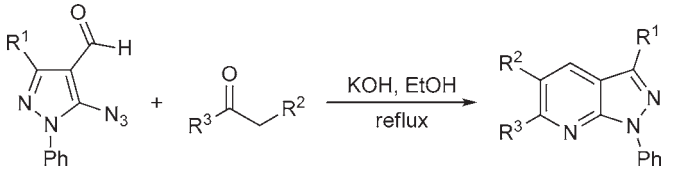


(53)

Table 29 Pyrazolo[3,4-*b*]pyridines prepared from 4,4,4-trifluoro-3-oxobutanoates (Equation 53) <2003S1531>

R	R^1	*Yield* (%)
Ph	Ph	85
Ph		92
Ph		94
Ph	CF_3	91
Ph	Me	88
Me		74
Ph	OH	86

A one-pot, two-step synthesis of a wide variety of pyrazolo[3,4-*b*]pyridines has been reported by Zheng *et al.*; *in situ* diazo transfer followed by Friedländer cyclization affords good yields of the desired products (Equation 54; **Table 30**) <2006SC1549>.



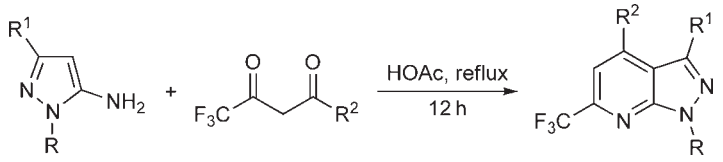
(54)

Table 30 Synthesis of a wide variety of pyrazolo[3,4-*b*]pyridines (Equation 54) <2006SC1549>

R^1	R^2	R^3	*Time* (*h*)	*Yield* (%)
CH_3	H	Ph	3	88
CH_3	H	4-$CH_3C_6H_4$	3	86
CH_3	H	4-$CH_3OC_6H_4$	3	80
CH_3	H	CH_3	2	78
CH_3	Ac	CH_3	2	70
CH_3	Ac	Ph	3	75
CH_3	–$(CH_2)_3$–		2	87
CH_3	–$(CH_2)_4$–		3	68
CH_3	–$CO(CH_2CMe_2CH_2)_4$–		12	15
CH_3	–$(CH_2)_2C_6H_4$–		4	75
Ph	H	Ph	3	68
Ph	H	4-$CH_3C_6H_4$	3	60
Ph	H	4-$CH_3OC_6H_4$	4	73
Ph	H	CH_3	3	78
Ph	–$(CH_2)_3$–		3	92
Ph	–$(CH_2)_4$–		4	75
Ph	–$(CH_2)_2C_6H_4$–		4	65

Reproduced with permission: One-Pot and convenient conversion of 5-azidopyrazole-4-carboxaldehyde to pyrazolo[3,4-*b*]pyridines; S. P. Singh *et al.* 2006 © Taylor & Francis Ltd.

A range of fluorinated pyrazolo[3,4-*b*]pyridines have been prepared by cyclization of pyrazoles with β-diketones (Equation 55; **Table 31**) <2004SC4359>.



(55)

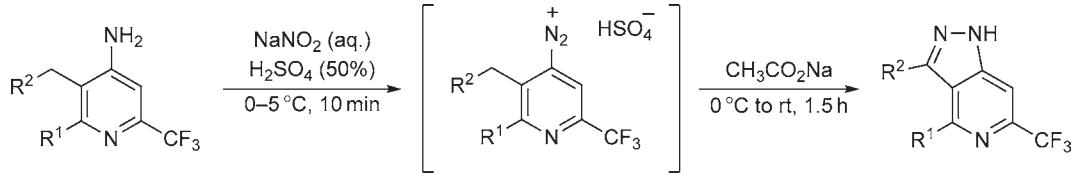
Table 31 Fluorinated pyrazolo[3,4-*b*]pyridines (Equation 55) <2004SC4359>

R	R^1	R^2	*Yield* (%)
H	C_6H_5	2-Thienyl	80
H	4-$CH_3OC_6H_4$	C_6H_5	76
H	C_6H_4	2-Thienyl	73
2-Benzothiazoyl	C_6H_5	2-Thienyl	68
2-Benzothiazoyl	C_6H_5	C_6H_5	59
C_6H_5	4-$CH_3OC_6H_4$	2-Thienyl	74
C_6H_5	4-$CH_3OC_6H_4$	C_6H_5	72
C_6H_5	C_6H_5	CF_3	70

Reproduced with permission: Synthesis of Some Novel Fluorinated Pyrazolo[3,4-*b*]Pyridines; S. P. Singh *et al.* 2006 © Taylor & Francis Ltd.

10.08.9.5 Pyrazolo[4,3-*c*]pyridines

5-Alkyl-4-aminopyridines were diazotized using sodium nitrite in sulfuric acid (50%). Treatment of the diazonium salts with aqueous sodium acetate solution afforded the desired trifluoromethylated pyrazolo[4,3-*c*]pyridines **152–154**. Analysis of the crude materials also revealed the presence of the diazo coupling product, derived from coupling of the product with starting material. In order to minimize this side reaction, the diazonium salts were slowly added to a large excess of cold, vigorously stirred aqueous sodium acetate, affording the pyrazolopyridines (**Scheme 10**; **Table 32**) <2001T2051>.



Scheme 10

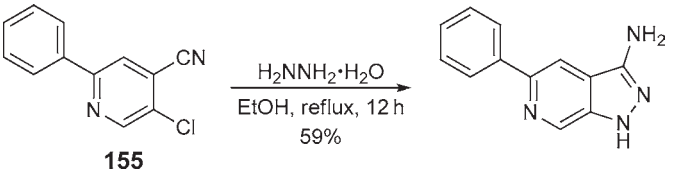
Table 32 Formation of trifluoromethylated pyrazolo[4,3-*c*]-pyridines **152–154** (**Scheme 10**) <2001T2051>

Compound	R^1	R^2	*Yield* (%)
152	H	H	64
153	Me	H	77
154	H	Me	40

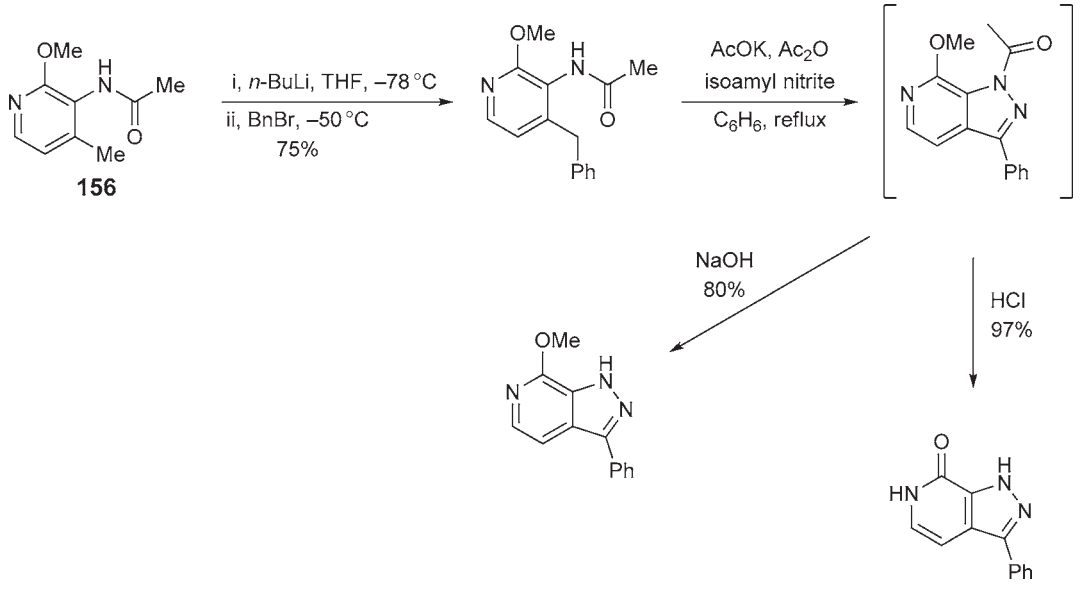
10.08.9.6 Pyrazolo[3,4-*c*]pyridines

Pyrazolo[3,4-*c*]pyridines have been formed by cyclization of the chloronitrile **155** with hydrazine hydrate in good yield (Equation 56) <2003BML1581>. Townsend and co-workers have reported the preparation of 3-substituted

pyrazolo[3,4-*c*]pyridines starting from 3-acetamido-2-methoxy-4-methylpyridine **156** (**Scheme 11**) <1997SL561>. Depending on the workup of the reaction, both pyrazolo[3,4-*c*]pyridines or pyrazolo[3,4-*c*]pyridones can be prepared.



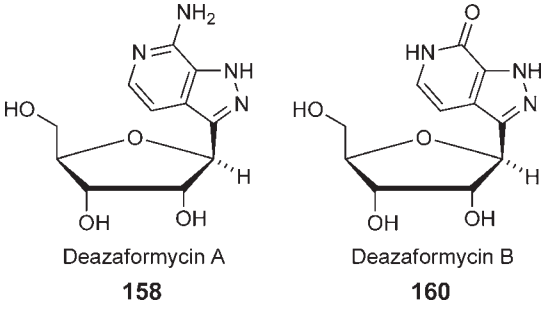
(56)

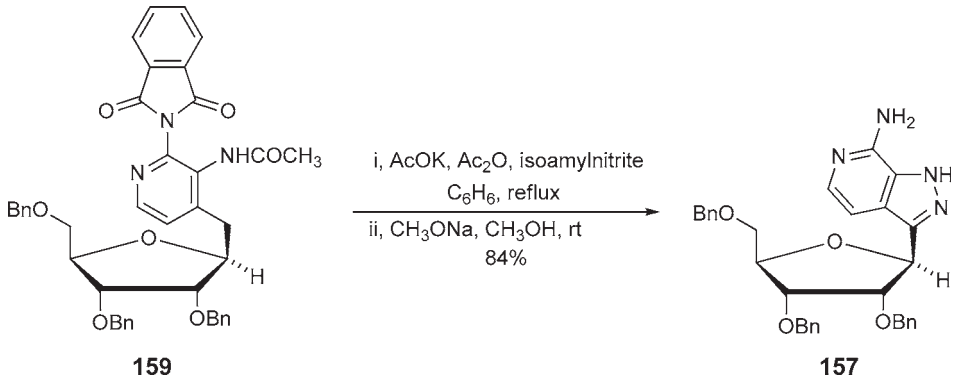


Scheme 11

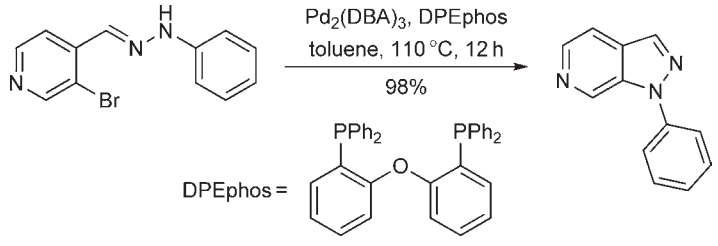
The pyrazolo[3,4-*c*]pyridine **157** was a key intermediate in the synthesis of 4-deazaformycin A **158** (Equation 57) <2003JOC6466>. Compound **157** was synthesized in good yield by cyclization of the intermediate nitroso compound derived from **159** on treatment with potassium acetate, acetic anhydride, and isoamyl nitrite. This methodology was also applied to the synthesis of deazaformycin B **160** <2002SL1479>.

Pyrazolo[3,4-*c*]pyridines can also be synthesized through an intramolecular Buchwald–Hartwig reaction in excellent yield (Equation 58) <2005JOC596>.





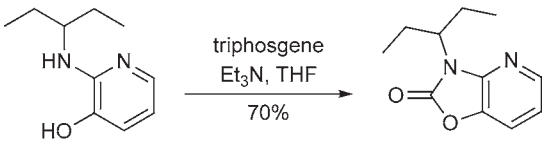
159 157 (57)



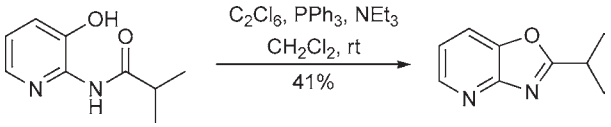
(58)

10.08.9.7 Oxazolo[4,5-*b*]pyridines

Treatment of the 2-amino-3-hydroxypyridine **161** with triphosgene resulted in the formation of the 1,3-oxazolo[4,5-*b*]-pyridin-2(3*H*)-one **162**, an intermediate in the formation of CRF-1 receptor ligands (Equation 59) <2005TL1683>. Oxazolo[4,5-*b*]pyridines have been synthesized using a triphenylphosphine–hexachloroethane combination, with the triphenylphosphonium halide being formed prior to addition of the amide (Equation 60) <2005TL9001>.

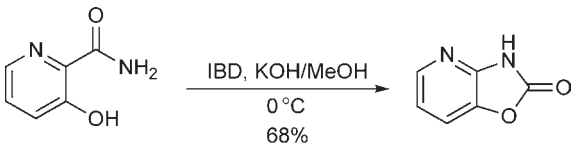


161 162 (59)



(60)

Treatment of 3-hydroxy-2-pyridinecarboxamide **163** with IBD afforded the oxazolo[4,5-*b*]pyridine **164** in good yield (Equation 61) <2001S541>.

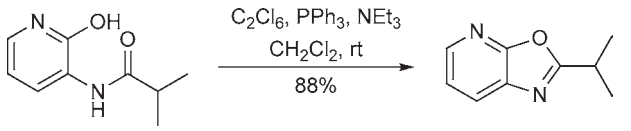


163 164 (61)

10.08.9.8 Oxazolo[5,4-*b*]pyridines

10.08.9.8.1 Closure of the oxazole ring

The triphenylphosphine–hexachloroethane system was also used to form oxazolo[5,4-*b*]pyridines (Equation 62). The reaction conditions tolerated a wide variety of substituents in the 2-position, and even a sterically bulky group did not decrease dramatically the yield of desired products <2005TL9001>.



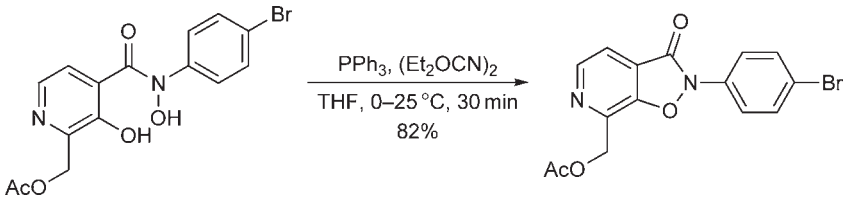
(62)

10.08.9.8.2 Closure of the pyridine ring

No further advances in the synthesis of oxazolo[5,4-*b*]pyridines by closure of the pyridine ring have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.9 Isoxazolo[5,4-*c*]pyridines

Isoxazolo[5,4-*c*]pyridines have been synthesized in good yield under Mitsunobu conditions (Equation 63) <2000TL2295>.

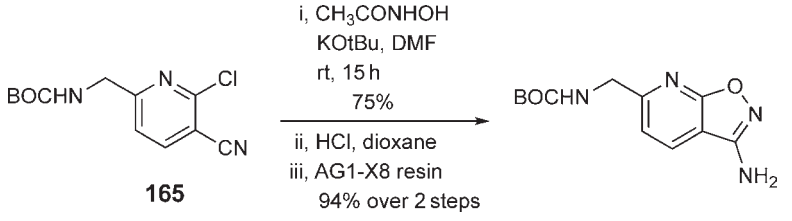


(63)

10.08.9.10 Isoxazolo[5,4-*b*]pyridines

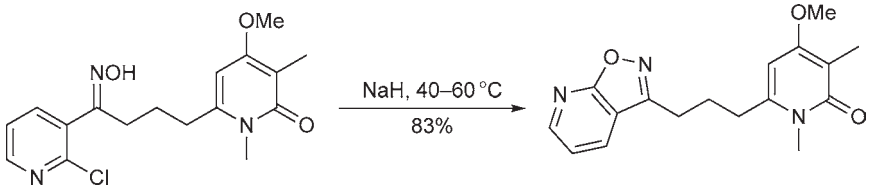
10.08.9.10.1 Closure of the isoxazole ring

Synthesis of isoxazolo[5,4-*b*]pyridines can be carried out from the corresponding chloronitrile intermediate **165** (Equation 64) <2002BML2925> or by deprotonation of an oxime with subsequent cyclization and expulsion of chloride (Equation 65) <1996JA10803>. Ring closure onto the nitrile in **166** by treatment with sodium hydroxide affords the isoxazolo[5,4-*b*]pyridine **167** in low yield (Equation 66) <1999JOC8479>.

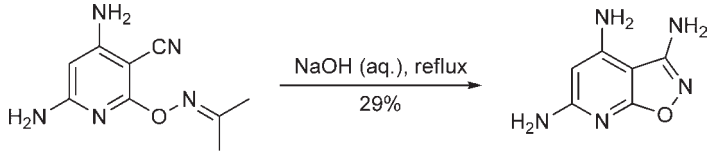


165

(64)



(65)

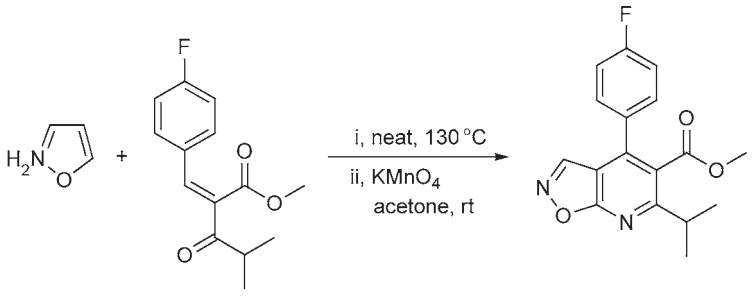


166 **167**

(66)

10.08.9.10.2 Closure of the pyridine ring

Isoxazolo[5,4-*b*]pyridines have also been synthesized by condensation of an aminoisoxazole with the appropriate benzylidene ketoester; however, no yields were reported (Equation 67) <2001BML1285>.



(67)

10.08.9.11 Isoxazolo[4,5-*c*]pyridines

No further advances in the synthesis of isoxazolo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

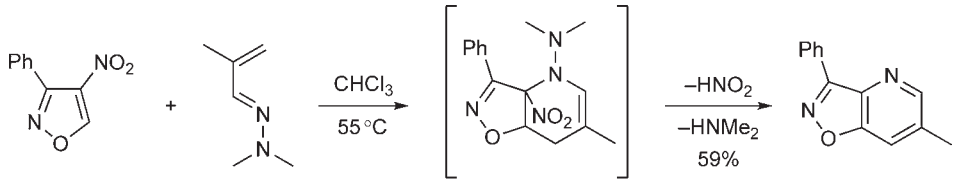
10.08.9.12 Isoxazolo[4,5-*b*]pyridines

10.08.9.12.1 Closure of the isoxazole ring

No further advances in the synthesis of isoxazolo[5,4-*b*]pyridines by closure of the isoxazole ring have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.12.2 Closure of the pyridine ring

Reaction of the isoxazole **168** with the azadiene **169** afforded the isoxazolo[4,5-*b*]pyridine **170** through the spontaneous loss of nitrous acid and dimethylamine from the unstable adduct **171** (**Scheme 12**) <1995T7085>.



168 **169** **171** **170**

Scheme 12

10.08.9.13 Isoxazolo[3,4-*b*]pyridines

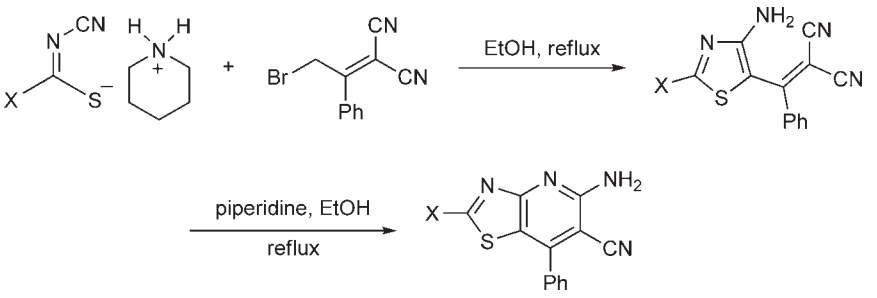
No further advances in the synthesis of isoxazolo[3,4-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.14 Thiazolo[4,5-*b*]pyridines

Thiazolo[4,5-*b*]pyridines have been prepared by reaction of 2-bromo-1-phenylethylidinemalonitrile with a range of thiolatonitriles (**Scheme 13**; **Table 33**) <1997T13351>.

10.08.9.15 Thiazolo[5,4-*b*]pyridines

No further advances in the synthesis of thiazolo[5,4-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.



Scheme 13

Table 33 Synthesis of thiazolo[4,5-*b*]pyridines <1997T13351>

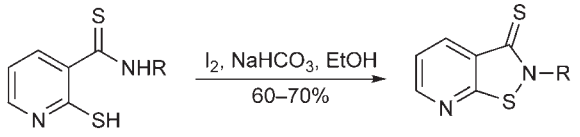
X	*Yield* (%)
NHPh	59
NHEt	67
$NHCH_2CH{=}CH_2$	70
SCH_3	74

10.08.9.16 Isothiazolo[4,3-*b*]pyridines

No further advances in the synthesis of isothiazolo[4,3-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.17 Isothiazolo[5,4-*b*]pyridines

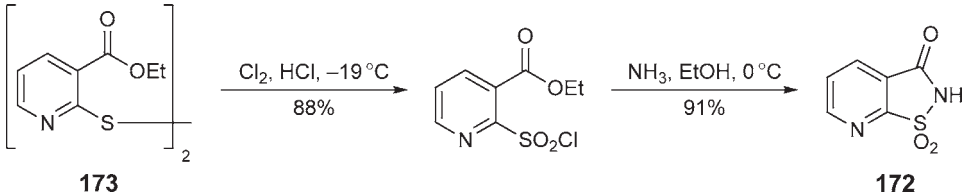
A range of isothiazolo[5,4-*b*]pyridines were prepared by cyclization of thiopyridines with iodine/sodium carbonate (Equation 68) <2000FA669>.



(68)

R = *n*-C_3H_7, *n*-C_4H_7, *n*-C_5H_{11}, *n*-C_6H_{13}, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_3Ph$

In the attempted synthesis of isothiazolo[5,4-*b*]pyridin-3(2*H*)-one 1,1-dioxide **172**, direct oxidation of isothiazolo[5,4-*b*]pyridin-3(2*H*)-one with either Oxone®/MeOH, 3-chloroperoxybenzoic acid/CH_2Cl_2, or $KMnO_4$/AcOH did not afford the desired product. However, this compound was synthesized in good yield by treatment of **173** with chlorine in aqueous HCl and subsequent reaction with ammonia in ethanol (**Scheme 14**) <1996T8947>.

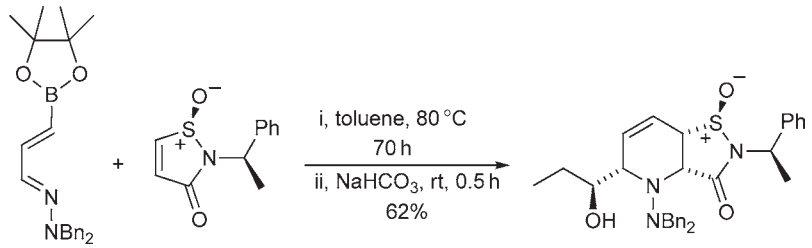


173 **172**

Scheme 14

10.08.9.18 Isothiazolo[4,5-*b*]pyridines

The aza-Diels–Alder reaction has been used to form isothiazolo[4,5-*b*]pyridines <1996CHEC-II(7)283> in a highly diastereoselective manner (Equation 69) <2004AGE2001, 2004JOC8429>.



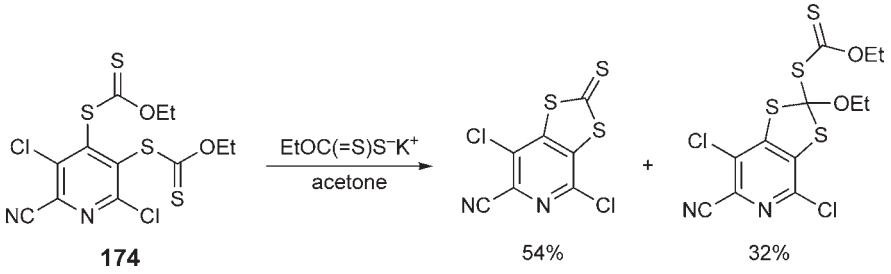
(69)

10.08.9.19 Isothiazolo[5,4-*c*]pyridines

No further advances in the synthesis of isothiazolo[5,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.20 1,3-Dithiolo[4,5-*c*]pyridines

Two compounds were formed upon treatment of **174** with potassium ethyl xanthate (Equation 70) <1997CHE1306, 1998CHE297>.



174

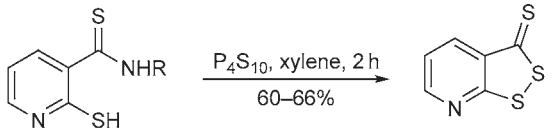
(70)

10.08.9.21 1,3-Dithiolo[4,5-*b*]pyridines

No further advances in the synthesis of 1,3-dithiolo[4,5-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

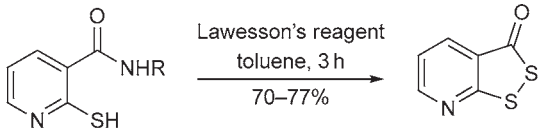
10.08.9.22 3*H*-1,2-Dithiolo[3,4-*b*]pyridines

A range of 3*H*-1,2-dithiolo[3,4-*b*]pyridines were prepared by cyclization of thiopyridines with P_4S_{10} in xylene (Equation 71) <2000FAS669>. 3*H*-1,2-Dithiolo[3,4-*b*]pyridines can also be prepared using Lawesson's reagent (Equation 72) <2000FA669>.



(71)

R = *n*-C_3H_7, *n*-C_4H_7, *n*-C_5H_{11}, *n*-C_6H_{13}, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_3Ph$



(72)

R = *n*-C_3H_7, *n*-C_4H_7, *n*-C_5H_{11}, *n*-C_6H_{13}, CH_2Ph, $(CH_2)_2Ph$, $(CH_2)_3Ph$

10.08.9.23 3*H*-1,2-Dithiolo[3,4-*c*]pyridines

No further advances in the synthesis of 3*H*-1,2-dithiolo[3,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.24 3*H*-1,2-Dithiolo[4,3-*c*]pyridines

No further advances in the synthesis of 3*H*-1,2-dithiolo[4,3-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.25 3*H*-1,2-Dithiolo[4,3-*b*]pyridines

No further advances in the synthesis of 3*H*-1,2-dithiolo[4,3-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.26 Thiopyrano[4,3-*d*]isoxazoles

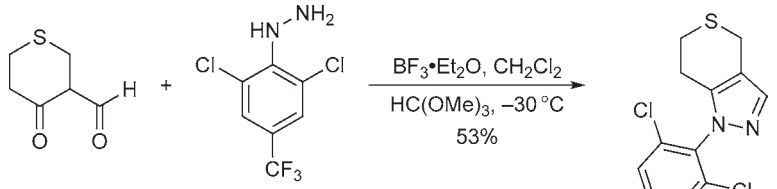
No further advances in the synthesis of thiopyrano[4,3-*d*]isoxazoles have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.27 Thiopyrano[3,4-*c*]pyrazoles

No further advances in the synthesis of thiopyrano[3,4-*c*]isoxazoles have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.9.28 Thiopyrano[4,3-*c*]pyrazoles

The thiopyrano[4,3-*c*]pyrazole **175** was prepared by treatment of the aldehyde **176** with the arylhydrazine **177** (Equation 73) <2002TL8639>.

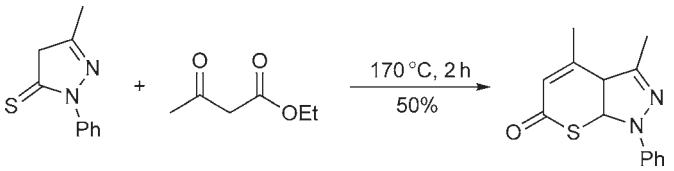


176 **177** **175**

(73)

10.08.9.29 Thiopyrano[2,3-*c*]pyrazoles

Condensation of 3-methyl-1-phenylpyrazole-5-thione with acetoacetic ester **178** afforded the thiopyrano[2,3-*c*]-pyrazol-6-one **179** (Equation 74) <2003CHE1115>.



178 179 (74)

10.08.9.30 Selenopyrano[2,3-*c*]pyrazoles

No further advances in the synthesis of selenopyrano[2,3-*c*]pyrazoles have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10 Synthesis by Transformation of Another Bicyclic Ring System

10.08.10.1 Imidazo[4,5-*c*]pyridines

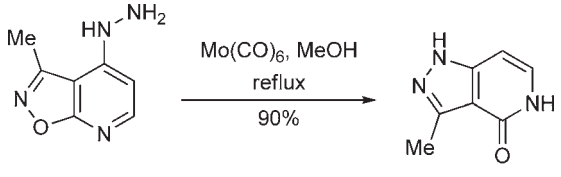
No further advances in the synthesis of imidazo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.2 Pyrazolo[3,4-*c*]pyridines

No further advances in the synthesis of pyrazolo[3,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.3 Pyrazolo[4,3-*c*]pyridines

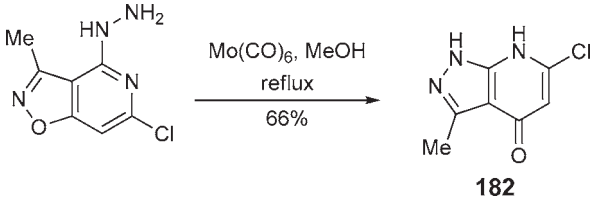
Treatment of the hydrazine **180** with $Mo(CO)_6$ in methanol affords the pyrazolo[4,3-*c*]pyridine **181** in excellent yield (Equation 75) <2003S2518>.



180 181 (75)

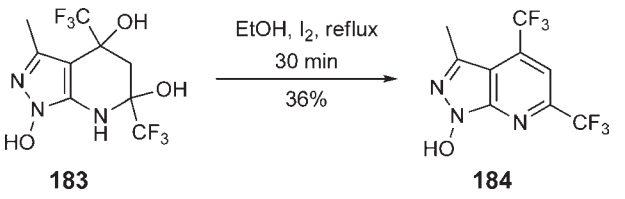
10.08.10.4 Pyrazolo[3,4-*b*]pyridines

Using the same method as for the synthesis of the pyrazolo[4,3-*c*]pyridine **181**, Ponticelli and co-workers also prepared the corresponding pyrazolo[3,4-*b*]pyridine **182** (Equation 76) <2003S2518>.



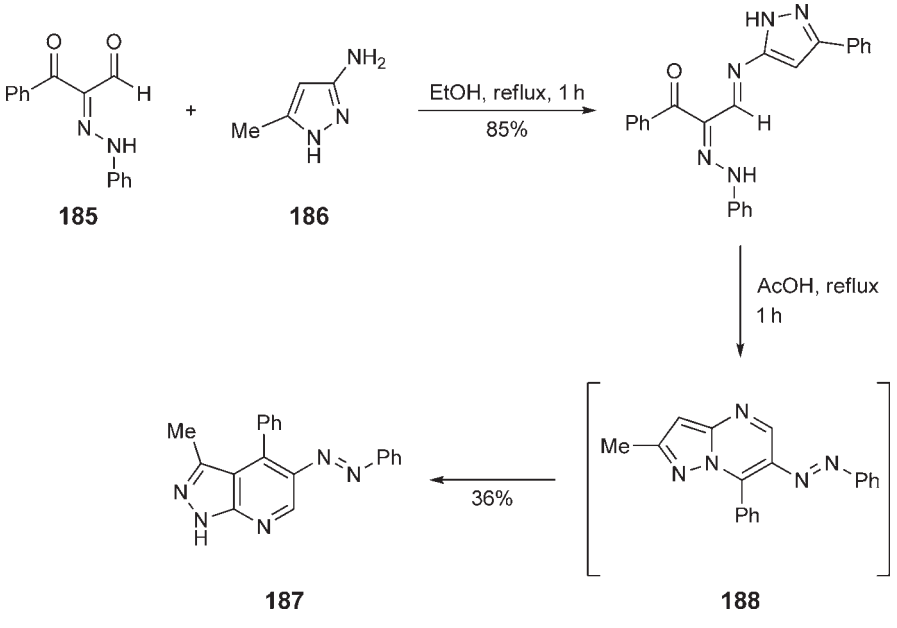
182 (76)

Aromatization of **183** in refluxing ethanol affords the corresponding unsaturated system **184** (Equation 77) <2003S1531>.



183 184 (77)

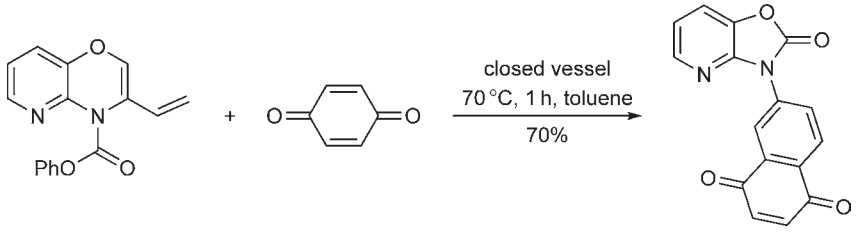
Treatment of compound **185** with the pyrazole **186**, and subsequent cyclization with acetic acid, afforded a mixture of products **187** and **188** in a ratio of 3:2 (**Scheme 15**). Trituration of the mixture in acetonitrile induced dissolution of one of the two products, and the remaining product was found to be **187**; a pure sample of **188** was not isolated upon evaporation of the solvent as rearrangement to **187** had occurred. Thus, **188** is believed to be the kinetic product and **187** the thermodynamic product.



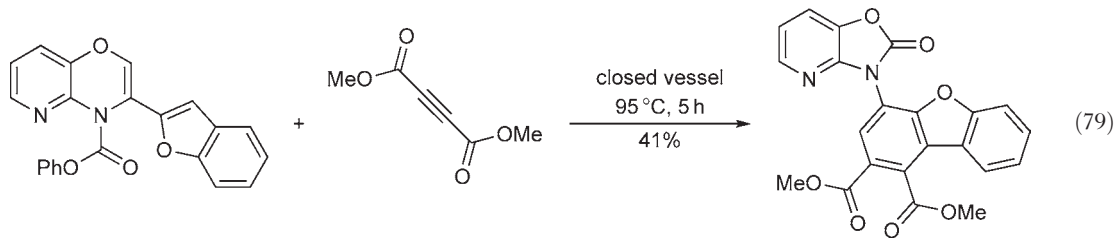
Scheme 15

10.08.10.5 Oxazolo[4,5-*b*]pyridines

An interesting Diels–Alder cycloaddition of pyridooxazinic dienes affords the corresponding oxazolo[4,5-*b*]pyridines in moderate yield after subsequent rearrangement (Equations 78 and 79) <2004TL8257>.



(78)



(79)

10.08.10.6 Oxazolo[4,5-*c*]pyridines

No further advances in the synthesis of oxazolo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.7 Oxazolo[5,4-*c*]pyridines

No further advances in the synthesis of oxazolo[5,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.8 Oxazolo[5,4-*b*]pyridines

No further advances in the synthesis of oxazolo[5,4-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.9 Isoxazolo[4,5-*c*]pyridines

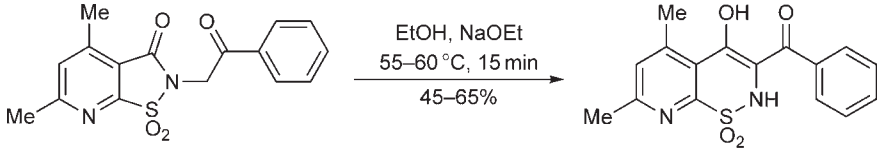
No further advances in the synthesis of isoxazolo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.10 Thiazolo[5,4-*b*]pyridines

No further advances in the synthesis of thiazolo[5,4-*b*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.10.11 Isothiazolo[5,4-*b*]pyridines

Reaction of isothiazolo[5,4-*b*]pyridines, such as **189**, affords the corresponding pyridothiazines **190** by rearrangement, although only general yields were reported (Equations 80) <2002FA737>.



189 **190**

(80)

10.08.10.12 Isothiazolo[5,4-*c*]pyridines

No further advances in the synthesis of isothiazolo[5,4-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

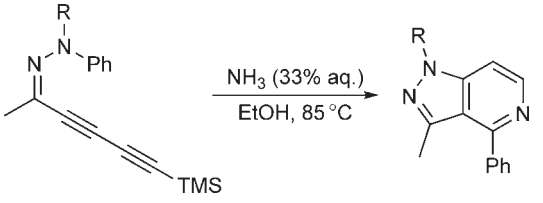
10.08.10.13 Isothiazolo[4,5-*c*]pyridines

No further advances in the synthesis of isothiazolo[4,5-*c*]pyridines have been reported since the original chapter in 1996CHEC-II(7)283.

10.08.11 Synthesis from Acyclic Precursors

10.08.11.1 Pyrazolo[4,3-*c*]pyridines

A new synthesis of the pyrazolo[4,3-*c*]pyridine core based on an unusual one-step tandem ring closure and rearrangement of bisacetylenic N-acylated hydrazones using aqueous ammonia has been reported (Equation 81; **Table 34**) <2004T933>.



(81)

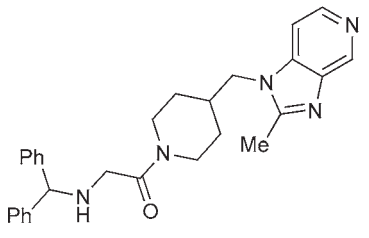
Table 34 Synthesis of pyrazolo[4,3-*c*]pyridines (Equation 81) <2004T933>

R	*Yield* (%)
2-$O_2NC_6H_4$	Degradation
4-$O_2NC_6H_4$	71
Ph	36
3-$O_2NC_6H_4$	56

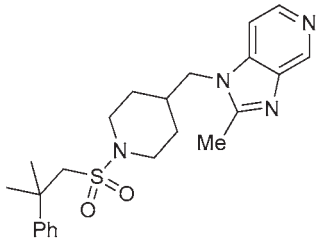
10.08.12 Important Compounds and Applications

Not surprisingly, many of the structural architectures presented in this chapter are either key intermediates for compounds with significant and useful biological activities or are themselves biologically active. Thus, there is a vast number of publications in the patent literature which contain the important heterocyclic systems presented in this chapter. Presented here, together with some highlights from scientific papers are some illustrative examples.

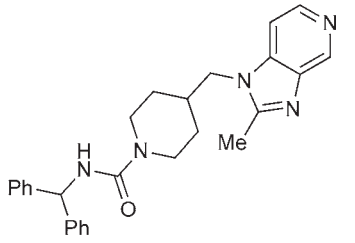
The replacement of the polar head group of a range of piperazines by a 2-methylimidazo[4,5-*c*]pyridine group provided efficient orally active platelet-activating factor antagonists, for example, compounds **191–193** <1996JME487>.



191



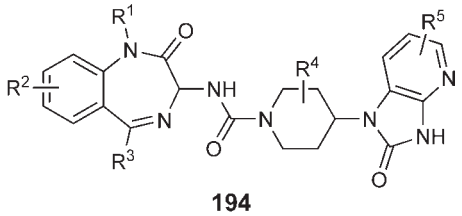
192



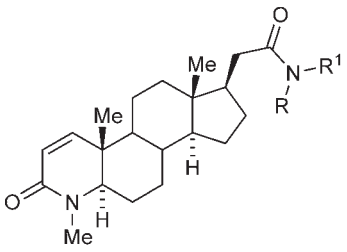
193

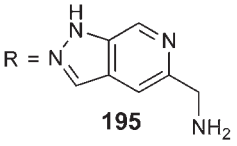
Merck and Co., Inc., have patented imidazo[4,5-*b*]pyridines of the general structure **194**, which have been found to be antagonists of calcitonin gene-related peptide (CGRP) receptors, which are useful for the treatment of the symptoms for headache, migraine, and cluster headaches <2005WO013894>. Merck have also patented the

imidazo[4,5-*b*]pyridine and pyrazolo[3,4-*c*]pyridines **195** and **196**, which are modulators of the androgen receptor and are useful in the enhancement of weakened muscle tone as well as a variety of other disorders <2005WO005606>. The imidazo[4,5-*b*]pyridine **197** has also been patented and is a modulator of c-Met and is expected to be useful in the treatment of c-Met-related diseases such as cancer <2005WO004607>.



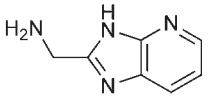
194



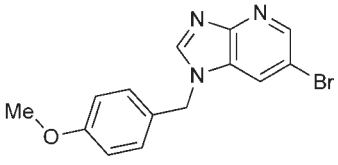


195

or

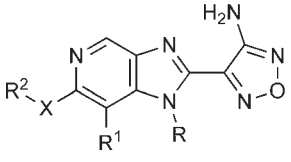


196

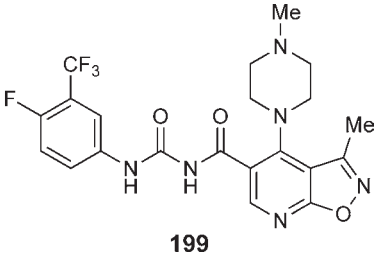


197

The Glaxo group have patented imidazo[4,5-*c*]pyridines of the general structure **198** as they have been found to be useful kinase inhibitors <2005WO034866>.

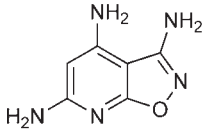


198

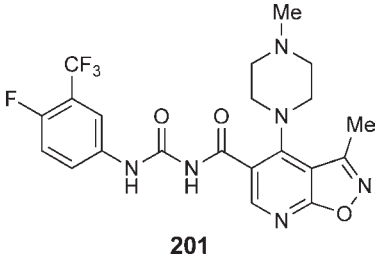


199

The isoxazole **200** is an important intermediate in the synthesis of a guanine–cytosine (G–C) DNA base hybrid <1999JOC8479> and the isoxazole **201** is an antagonist of the monocyte chemoattractant protein-1 (MCP-1) function <2002WO060900>.

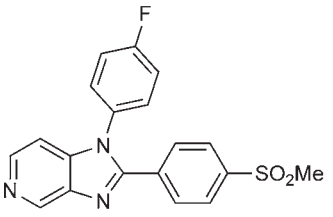


200

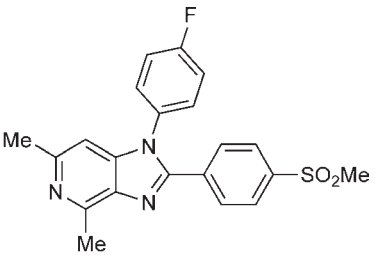


201

Several cyclooxygenase-2 (COX-2) selective inhibitors have been based on imidazo[4,5-c]pyridines, for example, compounds **202** and **203** <2001JME350>.

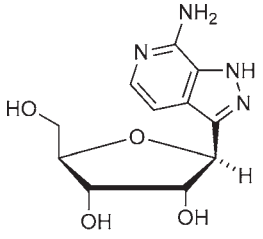


202



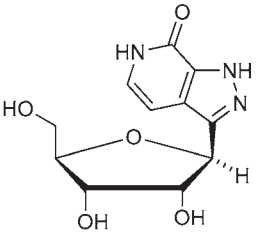
203

4-Deazaformycin A **158** and B **160** have been synthesized and are possible mimics for the naturally occurring nucleosides adenosine and inosine <2002SL1479, 2003JOC6466>.



Deazaformycin A

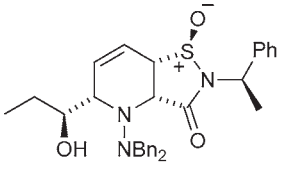
158



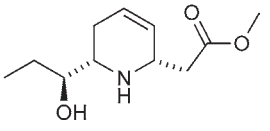
Deazaformycin B

160

The isothiazolo[4,5-*b*]pyridine **204** has been utilized as a important intermediate in the asymmetric synthesis of (−)-methyl palustramate **205** <2004JOC8429>.

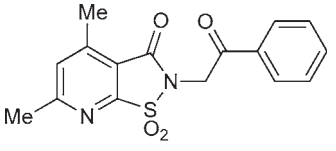


204



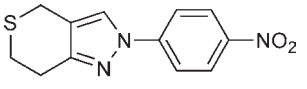
205

Isothiazolo[5,4-*b*]pyridines, such as **189**, are key intermediates in the synthesis of pyridothiazine 1,1-dioxides, which have CNS antioxidant properties <2002FA737>.



189

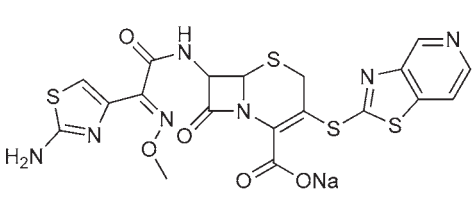
The thiopyrano[4,3-*c*]pyrazole **206** has been found to be a good inhibitor of bacterial cell wall biosynthesis <2003BML2591>.



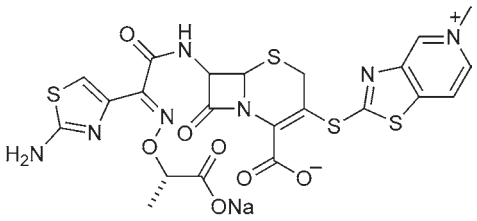
206

The cephalosporin derivative **207** has shown strong antibacterial activity against Gram-positive bacteria, including MRSA; however, only weak activity against Gram-negative bacteria was observed <1998BMC1009, 1998BMC1641>.

Activity of this compound was increased by quaternization of the nitrogen atom in the pyridyl ring to give, for example, compound **208**.

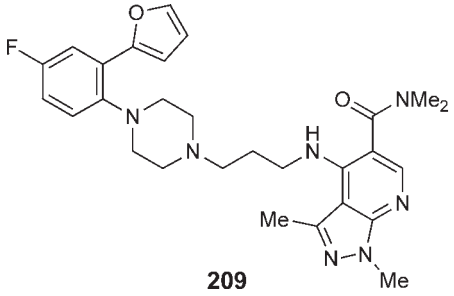


207

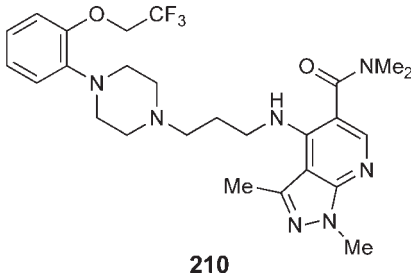


208

Several uroselective α_1-adrenoceptor antagonists have been based on the pyrazolo[3,4-*b*]pyridines **209** and **210** <1997JME2674>. These compounds have nanomolar affinity at the α_1-AR subtype in the human lower urinary tract.

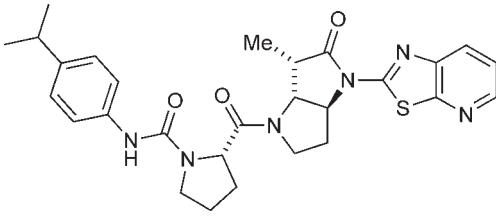


209



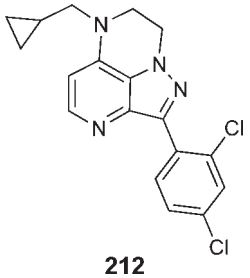
210

A range of chiral (*S*)-proline derivatives, for example **211**, have been shown to be active serine protease inhibitors and are active antivirals of human cytomegalovirus (HCMV) <2003JME4428>.



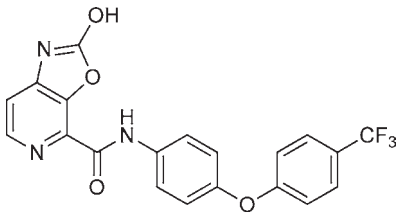
211

Compound **212**, NBI 35965, has been identified as a high-affinity antagonist of the CRF, which may be useful in treating stress and anxiety-related disorders <2005JME5780>.



212

The oxazolo[5,4-*c*]pyridine **213** is just one example of a series of compounds which have antifungal activity <2003EUP1275653>.



213

10.08.13 Further Developments

Since the preparation of this review several publications have been reported, a summary of the 2007 literature is shown below.

10.08.13.1 Imidazo[4,5-*b*]pyridines

Bavetsias *et al.* have reported several imidazo[4,5-*b*]pyridines as inhibitors of Aurora kinases <2007BML6567>. Imidazo[4,5-*b*]pyridines have also been repoted to act as calcitonin gene-related peptide (CGRP) antagonists <2007WO120592>. The liquid chromatography-tandem mass spectrometry analysis of 2-amino-1-methyl-6-(4-hydroxyphenyl) imidazo[4,5-*b*]pyridine has been reported by Busquets *et al.* <2007JAFC9318>. The unusual nitrenium chemistry of 2-amino-1-methyl-6-phenyl-1*H*-imidazo [4,5-*b*]pyridine has been reported by Nguyen and Novak <2007JOC4698>. The synthesis and antiproliferative activity of several new tricyclic 2-thioxo-1*H*,3*H*-imidazo [4,5-*b*]pyridine derivatives has been examined by Liszkiewicz *et al.* <2007PS199>.

10.08.13.2 Imidazo[4,5-*c*]pyridines

Antiviral 2,5-disubstituted imidazo[4,5-*c*]pyridines have been reported for the treatment of hepatitis C <2007BML390, 2007BML5111>. A method for the preparation of substituted 1*H*-imidazo[4,5-*c*]pyridines as immune response modifiers has been reported <2007WO092641>. 6-Phenyl-1*H*-imidazo[4,5-*c*]pyridine-4-carbonitrile derivatives have been reported to act as cathepsin K and S inhibitors <2007USP179138>. Imidazo[4,5-*c*]pyridine derivatives have also been prepared as C3A receptor antagonists <2007WO034277>.

10.08.13.3 Pyrazolo[3,4-*c*]pyridines

Tetrahydropyrazolo[3,4-*c*]pyridines have been prepared as cannabinoid modulators <2007WO112399>. The pyrazolo[3,4-*c*]pyridine, Apixaban (BMS-562247), has been found to be a highly potent, selective, efficacious, and orally bioavailable inhibitor of blood coagulation factor xa <2007JMC5339>. Several pyrazolo[3,4-*c*]pyridines have been found to be potent inhibitors of human eosinophil phosphodiesterase <2007JMC344>.

10.08.13.4 Pyrazolo[4,3-*c*]pyridines

Pyrazolo[4,3-*c*]pyridines have been reported as IGF-1R inhibitors <2007WO099166, 2007WO068619>.

10.08.13.5 Oxazolo[4,5-*c*]pyridines

4-Carboxypyrazoles have been prepared as antivirals for treatment of hepatitis C virus (HCV) infection <2007WO039146>.

10.08.13.6 Oxazolo[4,5-*b*]pyridines

The fluorescence properties of derivatives of oxazolo[4,5-*b*]pyridine has been reported by Mac *et al.* <2007JPP(A)188>. Martin *et al.* have reported the preparation of oxazolo[4,5-*b*]pyridine derivatives as inducible nitric oxide synthase inhibitors <2007WO045622>.

10.08.13.7 Isothiazolo[5,4-*b*]pyridines

Azabicyclic derivatives of isothiazolopyridines have been used for therapeutic use as a 7-nACh receptor activators <2007WO038367>.

No further reports were found for isoxazolo[5,4-*b*]pyridines, isoxazolo[4,5-*c*]pyridines, isoxazolo[4,5-*b*]pyridines, isothiazolo[4,3-*c*]pyridines, isothiazolo[5,4-*b*]pyridines, isothiazolo[4,5-*c*]pyridines, dithiolo[4,3-*c*]pyridines, dithiolo[4,3-*b*]pyridines, dithiolo[3,4-*b*]pyridines, dithiolo[3,4-*b*]pyridines, thiopyrano[4,3-*d*]isoxazoles, thiopyrano[3,4-*c*]pyrazoles, thiopyrano[4,3-*c*]pyrazoles, thiopyrano[2,3-*c*]pyrazoles or selenopyrano[2,3-*c*]pyrazoles.

References

1984CHEC(5)305 J. V. Greenhill; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 305.

1984CHEC(5)607 J. A. Montgomery and J. A. Secrist; III, in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 5, p. 607.

1984CHEC(6)613 K. Undheim; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 613.

1989JOC3779 D. M. Schnur, Y. H. Yuh, and D. R. A. Dalton, *J. Org. Chem.*, 1989, **54**, 3779.

1994PAC1088 P. Muller, *Pure Appl. Chem.*, 1994, **66**, 1088.

1994PAC1124 P. Muller, *Pure Appl. Chem.*, 1994, **66**, 1124.

1995T7085 S. Turchi, D. Giomi, and R. Nesi, *Tetrahedron*, 1995, **51**, 7085.

1996CHEC-II(7)283 L. B. Townsend and D. S. Wise; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 283.

1996JA10803 S. McN. Sieburth, J. Chen, K. Ravindran, and J.-L. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 10803.

1996JME487 E. Carceller, M. Merlos, M. Giral, D. Balsa, J. García-Rafanell, and J. Forn, *J. Med. Chem.*, 1996, **39**, 487.

1996PAC2230 G. P. Moss, *Pure Appl. Chem.*, 1996, **68**, 2230.

1996PAC2247 G. P. Moss, *Pure Appl. Chem.*, 1996, **68**, 2247.

1996T8947 V. Martinez-Merino, J. I. Garcia, J. A. Mayoral, M. J. Gil, J. M. Zabalza, J. P. Fayet, M. C. Vertut, A. Carpy, and A. González, *Tetrahedron*, 1996, **52**, 8947.

1996TL2409 M.-C. Viaud, P. Jamoneau, L. Savelon, and G. Guillaumet, *Tetrahedron Lett.*, 1996, **37**, 2409.

1997CHE1306 A. M. Sipyagin, V. V. Kolchanov, A. T. Lebedev, and N. K. Karakhanova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 1306.

1997JHC107 F. Perandones and J. L. Soto, *J. Heterocycl. Chem.*, 1997, **34**, 107.

1997JME2674 T. R. Elworthy, A. P. D. W. Ford, G. W. Bantle, D. J. Morgans, Jr., R. S. Ozer, W. S. Palmer, D. B. Repke, M. Romero, L. Sandoval, E. B. Sjogren, F. X. Talamás, A. Vazquez, H. Wu, N. F. Arredondo, D. R. Blue, Jr., A. DeSousa, L. M. Gross, M. S. Kava, J. D. Lesnick, R. L. Vimont, T. J. Williams, Q.-M. Zhu, J. R. Pfister, and D. E. Clarke, *J. Med. Chem.*, 1997, **40**, 2674.

1997MRC601 S. Chimichi, P. Tedeschi, S. Calvietti, and F. Ponticelli, *Magn. Reson. Chem.*, 1994, **35**, 601.

1997SC2217 C. S. Reddy, B. Narsaiah, and R. V. Venkataratnam, *Synth. Commun.*, 1997, **27**, 2217.

1997SL561 P. Marakos, N. Pouli, D. S. Wise, and L. B. Townsend, *Synlett*, 1997, 561.

1997T5159 M.-C. Viaud, P. Jamoneau, M.-L. Baudin, L. Savelon, and G. Guillaumet, *Tetrahedron*, 1997, **53**, 5159.

1997T13351 V. A. Artyomov, V. L. Ivanov, A. M. Shestopalov, and V. P. Litvinov, *Tetrahedron*, 1997, **53**, 13351.

1997TL7495 Z. Wan and J. K. Snyder, *Tetrahedron Lett.*, 1997, **38**, 7495.

1998AX(C)992 Z. Karczmarzyk and W. Malinka, *Acta Crystallogr. Part C*, 1998, (7), 992.

1998BMC1009 M. Tsushima, K. Iwamatsu, A. Tamura, and S. Shibahara, *Bioorg. Med. Chem.*, 1998, **6**, 1009.

1998BMC1641 M. Tsushima, Y. Kano, E. Umemura, K. Iwamatsu, A. Tamura, and S. Shibahara, *Bioorg. Med. Chem.*, 1998, **6**, 1641.

1998BMC1963 L. Savelon, J. G. Bizot-Espiard, D. H. Caignard, B. Pfeiffer, P. Renard, M. C. Viauda, and G. Guillaumet, *Bioorg. Med. Chem.*, 1998, **6**, 1963.

1998CHE297 A. M. Sipyagin, V. V. Kolchanov, Z. G. Aliev, N. K. Karakhanova, and A. T. Lebedev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 297.

1998FES504 W. Malinka, S. Ryng, M. Sieklucka-Dziuba, G. Rajtar, A. Glowniak, and Z. Kleinrok, *Il Farmaco*, 1998, **53**, 504.

1999H(51)1661 J.-C. Milhavet, A. Gueiffier, L. Bernal, and J.-C. Teulade, *Heterocycles*, 1999, **51**, 1661.

1999JOC8479 M. Mascal, N. M. Hext, R. Warmuth, J. R. Arnall-Culliford, M. H. Moore, and J. P. Turkenburg, *J. Org. Chem.*, 1999, **64**, 8479.

B-2000MI1 A. R. Katritzky and A. F. Pozharskii, 'Handbook of Heterocyclic Chemistry', 2nd edn. 2000.

2000FA669 M. Pregnolato, M. Terreni, D. Ubiali, G. Pagani, P. Borgna, F. Pastoni, and F. Zampollo, *Farmaco*, 2000, **55**, 669.

2000JME199 G. Pagani, M. Pregnolato, D. Ubiali, M. Terreni, C. Piersimoni, F. Scaglione, F. Fraschini, A. Rodríguez Gascón, and J. L. P. Muñoz, *J. Med. Chem.*, 2000, **43**, 199.

2000JME3052 M. Oguchi, K. Wada, H. Honma, A. Tanaka, T. Kaneko, S. Sakakibara, J. Ohsumi, N. Serizawa, T. Fujiwara, H. Horikoshi, and T. Fujita, *J. Med. Chem.*, 2000, **43**, 3052.

2000S1380 M. P. Singh, S. Sasmal, W. Lu, and M. N. Chatterjee, *Synthesis*, 2000, 1380.

2000T7909 N. Kojima, N. Minakawa, and A. Matsuda, *Tetrahedron*, 2000, **56**, 7909.

2000TL2295 G.-Q. Shi, *Tetrahedron Lett.*, 2000, **41**, 2295.

2001BML1285 M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Sakashita, M. Kitaharac, and R. Sakoda, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1285.

2001FES905 W. Malinka, Z. Karczmarzyk, M. Sieklucka-Dziuba, M. Sadowski, and Z. Kleinrok, *Il Farmaco*, 2001, **56**, 905.

2001JME350 C. Almansa, A. F. de Arriba, F. L. Cavalcanti, L. A. Gómez, A. Miralles, M. Merlos, J. García-Rafanell, and J. Forn, *J. Med. Chem.*, 2001, **44**, 350.

2001MI1 V. G. Zaikin, A. V. Valamov, A. I. Mikaya and N. S. Prostakov,'*Osnovy mass-spectrometrii organicheskikh soedinenii*, (in Russian)', MAIK in '*Nauk Interperiodika*', Moscow (2001).

2001S541 O. Prakash, H. Batra, H. Kaur, P. K. Sharma, V. Sharma, S. P. Singh, and R. M. Moriarty, *Synthesis*, 2001, 541.

2001S2393 B. L. Booth, R. A. Carpenter, G. Morlock, Z. Mahmood, and R. B. Pritchard, *Synthesis*, 2001, 2393.

2001T2051 V. I. Tyvorskii, D. N. Bobrov, O. G. Kulinkovich, K. A. Tehrani, and N. De Kimpe, *Tetrahedron*, 2001, **57**, 2051.

2002BML2925 J. J. Cui, G.-L. Araldi, J. E. Reiner, K. M. Reddy, S. J. Kemp, J. Z. Ho, D. V. Siev, L. Mamedova, T. S. Gibson, J. A. Gaudette, N. K. Minami, S. M. Anderson, A. E. Bradbury, T. G. Nolan, and J. E. Semple, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2925.

2002FA737 W. Malinka, M. Kaczmarz, B. Filipek, J. Sapa, and B. Glod, *Farmaco*, 2002, **57**, 737.

2002SL1479 V. N. Kourafalos, P. Marakos, N. Pouli, and L. B. Townsend, *Synlett*, 2002, 1479.

2002SL1483 R. Clayton, M. L. Davis, W. Fraser, W. Li, and C. A. Ramsden, *Synlett*, 2002, 1483.

2002TL8639 S. K. Meegalla, D. Doller, R. Liu, D. Sha, R. M. Soll, and D. S. Dhanoa, *Tetrahedron Lett.*, 2002, **43**, 8639.

2002TL9527 D. Donati, S. Fusi, and F. Ponticelli, *Tetrahedron Lett.*, 2002, **43**, 9527.

2002WO060900 E. Laborde, L. Robinson, F. Meng, B. T. Peterson, H. Villar, S. E. Anuskiewicz, Y. Ishiwata, S. Yokochi, Y. Matsumoto, T. Kakigami, H. Inagaki, T. Jomori, and K. Matsushima, *PCT Int. Appl. WO*, 0 609 00 (2002).

2003BMC2991 N. J. Green, J. Xiang, J. Chen, L. Chen, A. M. Davies, D. Erbe, S. Tama, and J. F. Tobin, *Bioorg. Med. Chem.*, 2003, **13**, 2991.

2003BML289 A. G. Arvanitis, C. R. Arnold, L. W. Fitzgerald, W. E. Frietze, R. E. Olson, P. J. Gilligan, and D. W. Robertson, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 289.

2003BML1581 J. Witherington, V. Bordas, D. Haigh, D. M. B. Hickey, R. J. Ife, A. D. Rawlings, B. P. Slingsby, D. G. Smith, and R. W. Ward, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1581.

2003BML2485 M. T. Bilodeau, A. M. Cunningham, T. J. Koester, P. A. Ciecko, K. E. Coll, W. R. Huckle, R. W. Hungate, R. L. Kendall, R. C. McFall, X. Z. Mao, R. Z. Rutledge, and K. A. Thomas, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2485.

2003BML2591 Z. Li, G. D. Francisco, W. Hu, P. Labthavikul, P. J. Perersen, A. Severin, G. Singh, Y. Yang, B. A. Ramussen, Y.-I. Lin, J. D. Skotnicki, and T. S. Mansour, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2591.

2003BML3055 J. Witherington, V. Bordas, A. Gaiba, N. S. Garton, A. Naylor, A. D. Rawlings, B. P. Slingsby, D. G. Smith, A. K. Takle, and R. W. Ward, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3055.

2003CHE1115 N. L. Nam and I. I. Grandberg, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2003, **39**, 1115.

2003EUP1275653 B. Muller and B. Hartmann, *Eur. Pat.*, EP 1275653 (2003).

2003FA995 R. Salvetti, G. Martinetti, D. Ubiali, M. Pregnolato, and G. Pagani, *Farmaco*, 2003, **58**, 995.

2003JME4428 A. D. Borthwick, D. E. Davies, P. F. Ertl, A. M. Exall, T. M. Haley, G. J. Hart, D. L. Jackson, N. R. Parry, A. Patikis, N. Trivedi, G. G. Weingarten, and J. M. Woolven, *J. Med. Chem.*, 2003, **46**, 4428.

2003JOC276 M. E. A. Zaki, M. Proenca, and B. L. Booth, *J. Org. Chem.*, 2003, **68**, 276.

2003JOC4345 B. R. Lahue, Z.-K. Wan, and J. K. Snyder, *J. Org. Chem.*, 2003, **68**, 4345.

2003JOC6466 V. N. Kourafalos, P. Marakos, N. Pouli, and L. B. Townsend, *J. Org. Chem.*, 2003, **68**, 6466.

2003S1531 D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova, and A. A. Tolmachev, *Synthesis*, 2003, 1531.

2003S2518 D. Donati, S. Ferrini, S. Fusi, and F. Ponticelli, *Synthesis*, 2003, 2518.

2003TL5807 M. Jazouli, D. Guianvarc'h, M. Soufiaoui, K. Bougrin, P. Vierling, and R. Benhida, *Tetrahedron Lett.*, 2003, **44**, 5807.

2004AGE2001 B. B. Touré and D. G. Hall, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 2001.

2004BMC4211 H. Yoshizawa, T. Kubota, H. Itani, H. Ishitobi, H. Miwa, and Y. Nishitani, *Bioorg. Med. Chem.*, 2004, **12**, 4211.

2004BML3165 M. E. Tedder, Z. Nie, S. Margosiak, S. S. Chu, V. A. Feher, R. Almassy, K. Appelt, and K. M. Yager, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3165.

2004JCC453 Z. Karczmarzyk and W. Malinka, *J. Chem. Cryst.*, 2004, **34**, 453.

2004JOC7752 J. T. Kuethe, A. Wong, and I. W. Davies, *J. Org. Chem.*, 2004, **69**, 7752.

2004JOC8429 B. B. Touré and D. G. Hall, *J. Org. Chem.*, 2004, **69**, 8429.

2004SC4359 S. P. Singh, R. Naithani, R. Aggarwal, and O. Prakash, *Synth. Commun.*, 2004, **34**, 4359.

2004T933 L. Commeiras, S. C. Woodcock, J. E. Baldwin, R. M. Adlington, A. R. Cowley, and P. J. Wilkinson, *Tetrahedron*, 2004, **60**, 933.

2004TL2389 G. Lavecchia, S. Berteina-Raboin, and G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 2389.

2004TL6633 G. Lavecchia, S. Berteina-Raboin, and G. Guillaumet, *Tetrahedron Lett.*, 2004, **45**, 6633.

2004TL8257 F. Lepifre, C. Buon, P.-Y. Roger, P. Bouyssou, and G. Coudert, *Tetrahedron Lett.*, 2004, **45**, 8257.

2005BML2129 D. Kim, L. P. Wang, J. J. Hale, C. L. Lynch, R. J. Budhu, M. MacCross, S. G. Mills, L. Malkowitz, S. L. Gould, J. A. DeMartino, M. S. Springer, D. Hazuda, M. Miller, J. Kessler, R. C. Hrin, G. Carver, A. Carella, K. Henry, J. Lineberger, W. A. Schleif, and E. A. Emini, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2129.

2005BML3402 M. J. Bamford, M. J. Alberti, N. Bailey, S. Davies, D. K. Dean, A. Gaiba, S. Garland, J. D. Harling, D. K. Jung, T. A. Panchal, C. A. Parr, J. G. Steadman, A. K. Takle, J. T. Townsend, D. M. Wilson, and J. Witherington, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3402.

2005HCA731 S. Sahli, B. Frank, W. B. Schweizer, F. Dieterich, D. Blum-Kaelin, J. D. Aebi, H.-J. Böhm, C. Oefner, and G. E. Dale, *Helv. Chim. Acta*, 2005, **88**, 731.

2005JMC6887 P. Minetti, M. O. Tinti, P. Carminati, M. Castorina, M. A. Di Cesare, S. Di Serio, G. Gallo, O. Ghirardi, F. Giorgi, L. Giorgi, G. Piersanti, F. Bartoccini, and G. Tarzia, *J. Med. Chem.*, 2005, **48**, 6887.

2005JME5104 ZGuo, J. E. Tellew, R. S. Gross, B. Dyck, J. Grey, M. Haddach, M. Kiankarimi, M. Lanier, B.-F. Li, Z. Luo, J. R. McCarthy, M. Moorjani, J. Saunders, R. Sullivan, X. Zhang, S. Zamani-Kord, D. E. Grigoriadis, P. D. Crowe, T. K. Chen, and J. P. Williams, *J. Med. Chem.*, 2005, **48**, 5104.

2005JME5780 R. S. Gross, Z. Guo, B. Dyck, T. Coon, C. Q. Huang, R. F. Lowe, D. Marinkovic, M. Moorjani, J. Nelson, S. Zamani-Kord, D. E. Grigoriadis, S. R. J. Hoare, P. D. Crowe, J. Han Bu, M. Haddach, J. McCarthy, J. Saunders, R. Sullivan, T. Chen, and J. P. Williams, *J. Med. Chem.*, 2005, **48**, 5780.

2005JOC596 A. Y. Lebedev, A. S. Khartulyari, and A. Z. Voskoboynikov, *J. Org. Chem.*, 2005, **70**, 596.

2005NN737 R. J. Irani and J. SantaLucia, Jr., *Nucleos. Nucleot. Nucleic Acids*, 2005, **21**, 737.

2005TL1683 R. A. Hartz, K. K. Nandab, and C. L. Ingalls, *Tetrahedron Lett.*, 2005, **46**, 1683.

2005TL3883 K. Sakthivel and P. D. Cook, *Tetrahedron Lett.*, 2005, **46**, 3883.

2005TL7553 C. Pabba, H.-J. Wang, S. R. Mulligan, Z.-J. Chen, T. M. Stark, and B. T. Gregg, *Tetrahedron Lett.*, 2005, **46**, 7553.

2005TL9001 S. Heuser, M. Keenanb, and A. G. Weichert, *Tetrahedron Lett.*, 2005, **46**, 9001.

2005WO004607 J. Cui and I. Botrous, *PCT Int. Appl.*, WO 0046 07 (2005).

2005WO005606 W. P. Dankulich, M. L. Kaufman, R. S. Meissner, and H. J. Mitchell, *PCT Int. Appl.*, WO 0056 06 (2005).

2005WO013894 C. S. Burgey, C. A. Stump, and T. M. Williams, *PCT Int. Appl.*, WO 0 138 94 (2005).

2005WO034866 D. Lee and R. A. Stavenger, *PCT Int. Appl.*, WO 0 348 66 (2005).

2006BML262 L. Revesz, E. Blum, F. E. Di Padova, T. Buhl, R. Feifel, H. Gram, P. Hiestand, U. Manning, U. Neumann, and G. Rucklin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 262.

2006OL1443 M. L. Meketa and S. M. Weinreb, *Org. Lett.*, 2006, **8**, 1443.

2006SC1549 A. Zheng, W. Zhang, and J. Pan, *Synth. Commun.*, 2006, **36**, 1549.

2007BML390 G. Puerstinger, J. Paeshuyse, De Clercq, and J. Neyts, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 390.

2007BML5111 G. Puerstinger, J. Paeshuyse, S. Heinrich, J. Mohr, N. Schraffl, E. De Clercq, and J. Neyts, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5111.

2007BML6567 V. Bavetsias, C. Sun, N. Bouloc, J. Reynisson, P. Workman, S. Linardopoulos, and E. McDonald, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6567.

2007JAFC9318 R. Busquets, L. Puignou, M. T. Galceran, K. Wakabayashi, and K. Skog, *J. Ag. Food Chem.*, 2007, **55**, 9318.

2007JMC344 A. J. Duplantier, E. L. Bachert, J. B. Cheng, V. L. Cohan, T. H. Jenkinson, K. G. Kraus, M. W. McKechney, J. D. Pillar, and J. W. Watson, *J. Med. Chem.*, 2007, **50**, 344.

2007JMC5339 D. J. P. Pinto, M. J. Orwat, S. Koch, K. A. Rossi, R. S. Alexander, A. Smallwood, P. C. Wong, A. R. Rendina, J. M. Luettgen, R. M. Knabb, K. He, B. Xin, R. R. Wexler, and, and P. Y. SLam, *J. Med. Chem.*, 2007, **50**, 5339.

2007JOC4698 T.-H. Nguyen and M. Novak, *J. Org. Chem.*, 2007, **72**, 4698.

2007JPP(A)188 M. Mac, W. Baran, T. Uchacz, B. Baran, M. Suder, and S. Lesniewski, *J. Photochem. and Photobiology, A: Chemistry*, 2007, **192**, 188.

2007PS199 H. Liszkiewicz, M. W. Kowalska, and J. Wietrzyk, *Phosphorus, Sulfur and related elements*, 2007, **182**, 199.

2007USP179138 J. Cai, Z. Rankovic, P. S. Jones, D. J. Bennett, I. Cumming and J. Gillespie *U.S. Pat.* 179138 (2007).

2007WO034277 T. W. Butler, *PCT Int. Appl.*, 2007 WO 034277 (2007).

2007WO038367 R. Schumacher, M. D. Danca, J. Ma, B. Herbert, T. M. Nguyen, W. Xie, and A. Tehim, *PCT Int. Appl.*, 2007 WO 038367 (2007).

2007WO039146 G. Bravi, A. G. Cheasty, J. A. Corfield, R. M. Grimes, D. Harrison, C. D. Hartley, P. D. Howes, K. J. Medhurst, M. L. Meeson, J. E. Mordaunt, P. Shah, M. J. Slater, and G. V. White, *PCT Int. Appl.*, 2007 WO 039146 (2007).

2007WO045622 T. Martin, W.-R. Ulrich, T. Fuchss, R. Boer, C. Hesslinger, A. Strub, M. Eltze, and M. Lehner, *PCT Int. Appl.*, 2007 WO 045622 (2007).

2007WO068619 T. Bandiera, A. Lombardi Borgia, P. Polucci, M. Villa, M. Nesi, M. Angiolini, and M. Varasi, *PCT Int. Appl.*, 2007 WO 068619 (2007).

2007WO092641 B. M. Zimmermann, J. F. Dellaria, L. T. Dressel, and D. T. Amos, *PCT Int. Appl.*, 2007 WO 092641 (2007).

2007WO099166 T. Bandiera, E. Perrone, A. Lombardi Borgia, and M. Varasi, *PCT Int. Appl.*, 2007 WO 099166 (2007).

2007WO112399 M. Xia, M. Wachter, M. Pan, F. Liotta, and Fina,, *PCT Int. Appl.*, 2007 WO 112399 (2007).

2007WO120592 K. Belyk, *PCT Int. Appl.*, 2007 WO 120592 (2007).

Biographical Sketch



Benjamin R. Buckley was born in Nottingham; he studied at Manchester Metropolitan University, from where he obtained a B.Sc. in 1999, and Loughborough University, from where he obtained his Ph.D. in 2003 under the supervision of Professor Philip C. Bulman Page. Following this, he worked as postdoctoral research associate with Professor Philip C. Bulman Page for one more year and took up his present position as a research fellow at Loughborough University in January 2004. His scientific interests include all aspects of asymmetric synthesis, in particular asymmetric organocatalysis.

10.09
Bicyclic 5-6 Systems: Four Heteroatoms 1:3

M. C. Elliott
Cardiff University, Cardiff, UK
© 2008 Elsevier Ltd. All rights reserved.

10.09.1 Introduction 493
10.09.2 Theoretical Methods 494
10.09.3 Experimental Structural Methods 494
10.09.3.1 X-Ray Diffraction 494
10.09.3.2 NMR Studies 494
10.09.3.3 Mass Spectrometry 495
10.09.3.4 Infrared Spectroscopy 495
10.09.4 Thermodynamic Aspects 495
10.09.5 Reactivity of Fully Conjugated Rings 495
10.09.6 Reactivity of Nonconjugated Rings 496
10.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms 499
10.09.8 Reactivity of Substituents Attached to Ring Heteroatoms 499
10.09.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component 500
10.09.9.1 Synthesis of the Six-Membered Ring 500
10.09.9.1.1 From [6+0] atom fragments 500
10.09.9.1.2 From [5+1] atom fragments 502
10.09.9.1.3 From [4+2] atom fragments 504
10.09.9.1.4 From [3+3] atom fragments 504
10.09.9.1.5 From [2+2+2] atom fragments 504
10.09.9.2 Synthesis of the Five-Membered Ring 504
10.09.9.2.1 From [5+0] atom fragments 504
10.09.9.2.2 From [4+1] atom fragments 505
10.09.9.2.3 From [3+2] atom fragments 505
10.09.10 Ring Syntheses by Transformations of Another Ring 506
10.09.11 Important Compounds and Applications 506
10.09.12 Further Developments 506
References 507

10.09.1 Introduction

This review continues the coverage in CHEC-II(1996) <1996CHEC-II(7)351>. Although the stated period of literature coverage is 1995–2007, the previous chapter does not cover literature after 1990. The intervening years are covered herein. Apart from nucleoside phosphates and their derivatives, there are relatively few reports of 5-6 fused systems with one heteroatom in the five-membered ring and three heteroatoms in the six-membered ring. These nucleoside cyclic phosphates have been mainly studied as a result of their biological activity, and the actual formation/reactivity of the resulting furo[3,2-*d*]-1,3,2-dioxaphosphorin ring is generally straightforward. As a result, coverage of this ring system has been restricted to structural studies which provide leading references.

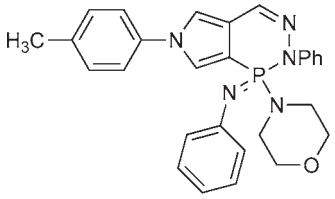
10.09.2 Theoretical Methods

The conformations of various cyclic phosphate derivatives of 2-deoxyribose (e.g., compound **6**, Section 10.09.3.2) have been studied using density functional theory (DFT) methods <2005JOC7107>.

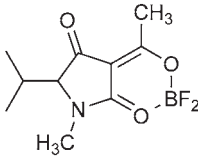
10.09.3 Experimental Structural Methods

10.09.3.1 X-Ray Diffraction

Single crystal X-ray diffraction data have been reported for compounds **1** <2001HAC658>, **2** <1990J(P1)1959>, and **70** (Section 10.09.9.1.5). The bond lengths and angles in these compounds are in line with expectations. Crystal structures of two examples of the more general structure **5** (Section 10.09.3.2) were determined, as well as other cyclic phosphate derivatives of ribose and 2-deoxyribose <2005JOC1620, 2005JOC7107>.



1

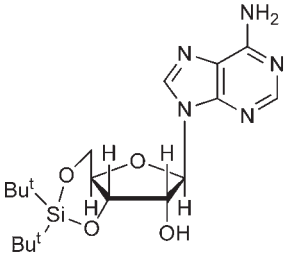


2

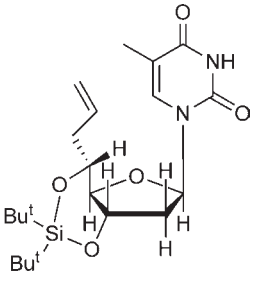
10.09.3.2 NMR Studies

All of the compounds discussed below have, presumably, been characterized at least by ^{1}H NMR spectroscopy and usually also by ^{13}C NMR spectroscopy. In some instances, other pulse sequences have been used to deduce structure and/or stereochemistry. These techniques have largely become routine and warrant no further discussion.

The conformations of a number of silyl-tethered nucleosides typified by 3′,5′-*O*-(di-*tert*-butylsilanediyl)-adenosine **3**, have been studied by NMR spectroscopy <1993MRC1039>. The conformational bias in such systems was used to determine the stereochemistry of compound **4** by NOE studies <1998NN1033>.



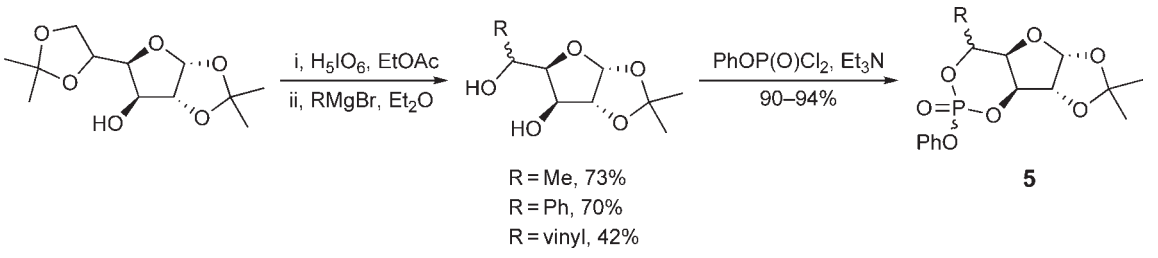
3



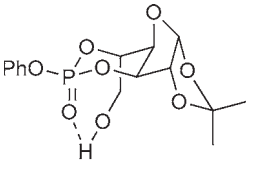
4

The solution conformation of cyclic phosphates such as cAMP and cGMP is crucial to their biological properties. Much of the seminal work in this area was carried out prior to the period of coverage of this chapter <1987JA4058>. More recent studies have focused on the conformations of modified cyclic phosphates, for example fused phosphates of general structure **5** which have additional conformational constraints. The additional alkyl groups, introduced in the sequence shown in **Scheme 1**, were valuable in providing additional coupling constant data which assisted in the structure determination <2004T4077>.

The chair conformation of the six-membered ring in such compounds can be stabilized by hydrogen bonding by incorporation of an additional hydroxyl group, for example, compound **6** <2005JOC7107>.



Scheme 1



6

10.09.3.3 Mass Spectrometry

While molecular and fragment ions have been reported for a number of the compounds described, little discussion is generally given.

10.09.3.4 Infrared Spectroscopy

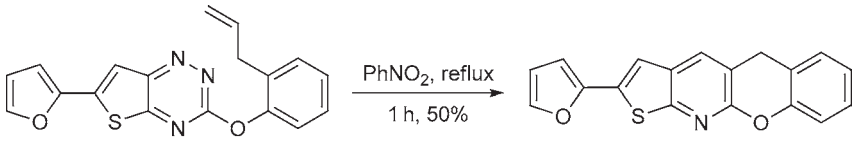
Infrared data for the compounds described below, where reported, are generally in line with expectations and are seldom discussed in the original reports.

10.09.4 Thermodynamic Aspects

Bicyclic heterocycles consisting of a fused 5-6 ring system have relatively little strain, so that their stability is broadly in line with what would be expected. Where thermodynamic properties are relevant to the chemical reactivity, these are discussed in the appropriate sections below.

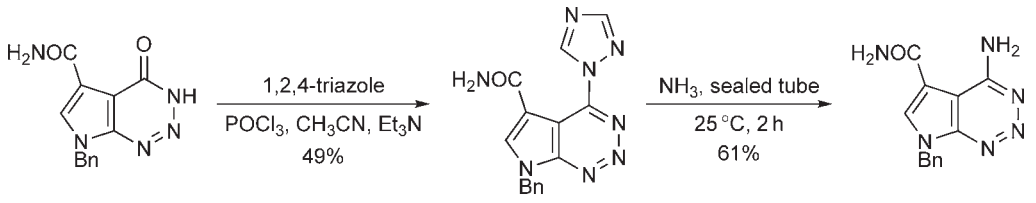
10.09.5 Reactivity of Fully Conjugated Rings

There are relatively few fully conjugated heterocycles within the scope of this chapter. Compound **7** is one of a number of similar structures which undergo an intramolecular aza-Diels–Alder reaction followed by extrusion of molecular nitrogen to give fused pyridine derivatives such as **8** (Equation 1) <2003T8489>.



7 **8** (1)

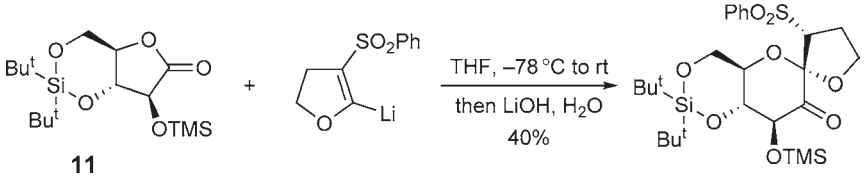
Compound **9** undergoes ready substitution with 1,2,4-triazole upon treatment with $POCl_3$ to give compound **10**. The triazole itself can then be removed by substitution with ammonia (**Scheme 2**) <2001JOC4776, 2005JME3840>.



Scheme 2

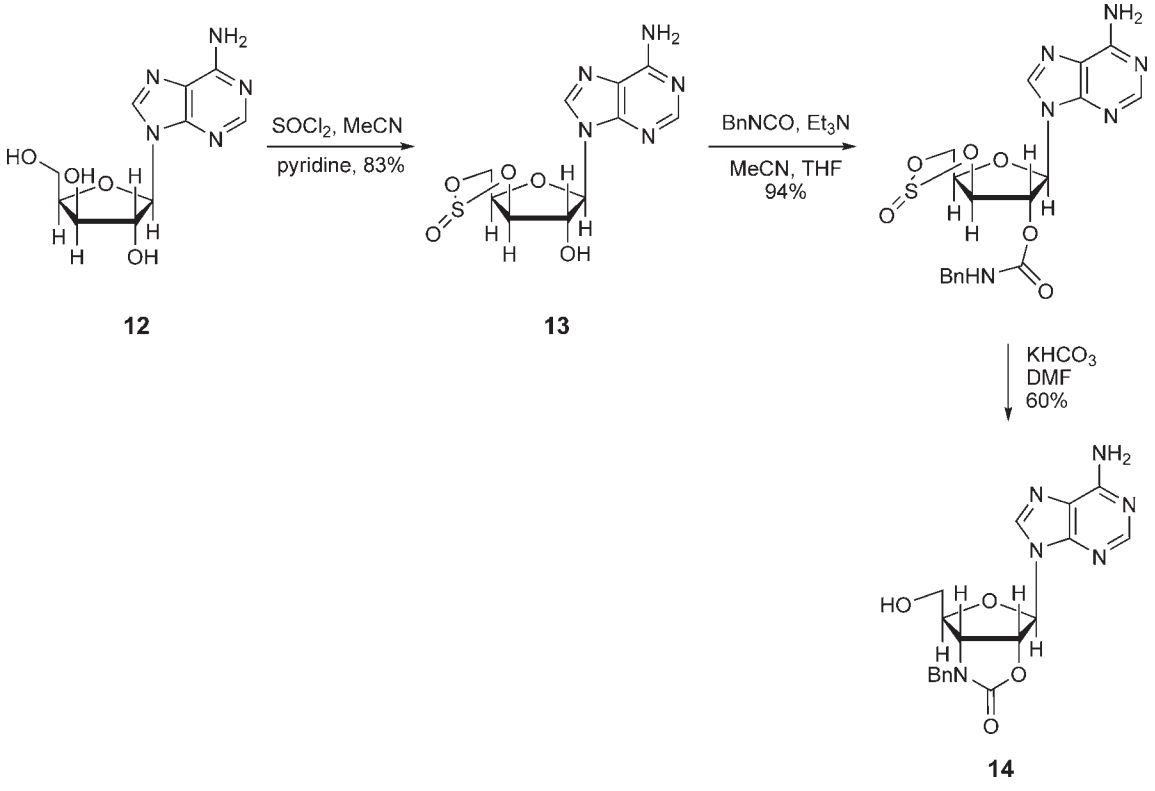
10.09.6 Reactivity of Nonconjugated Rings

A recent approach to the papulacandin spiroketal features an elegant pinacol-type ring expansion of lactone **11** as shown in Equation (2) <1999T15159>.



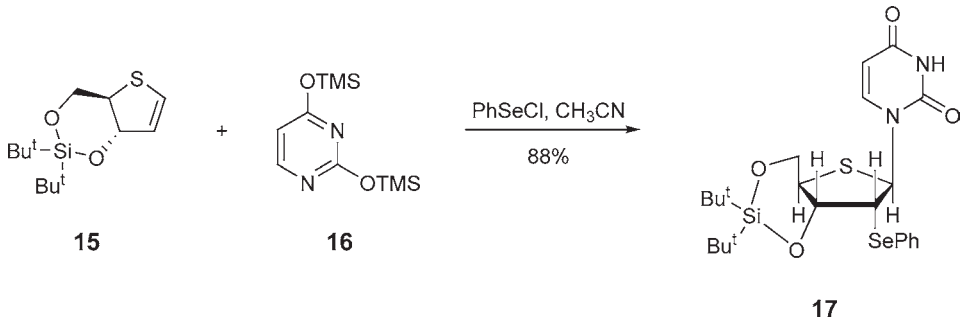
(2)

Takatsuki and co-workers have recently introduced the 3′,5′-*O*-sulfinyl group which has the dual purpose of protection and activation in nucleoside chemistry. For example, compound **13**, prepared by protection of **12** as shown in **Scheme 3**, underwent reaction with benzyl isocyanate followed by intramolecular displacement of the sulfinate to give the product **14** <2004TL137>. A similar approach has also been used to prepare thioglycoside epoxides <2004CAR2895>.



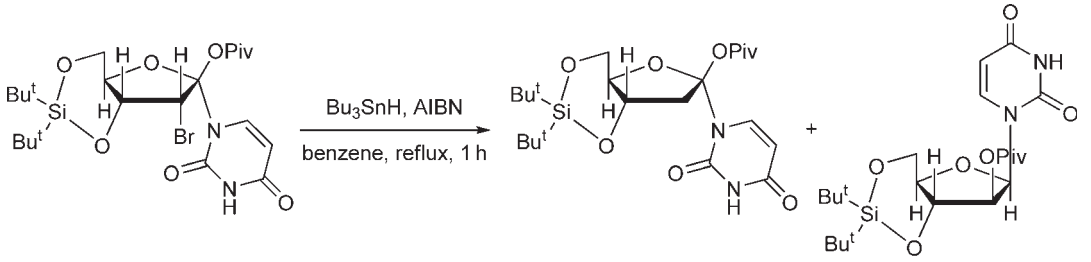
Scheme 3

Thionucleosides are of considerable interest, and can be prepared stereoselectively by the electrophile-initiated addition of the base to a thiofuranoid glycal. For example, reaction of substrate **15** with the protected uracil **16** and phenylselenenyl chloride gave compound **17** as the sole detectable stereoisomer (Equation 3) <1998TL3713, 2002JOC5959, 2003NN763, 2004OL2645>.



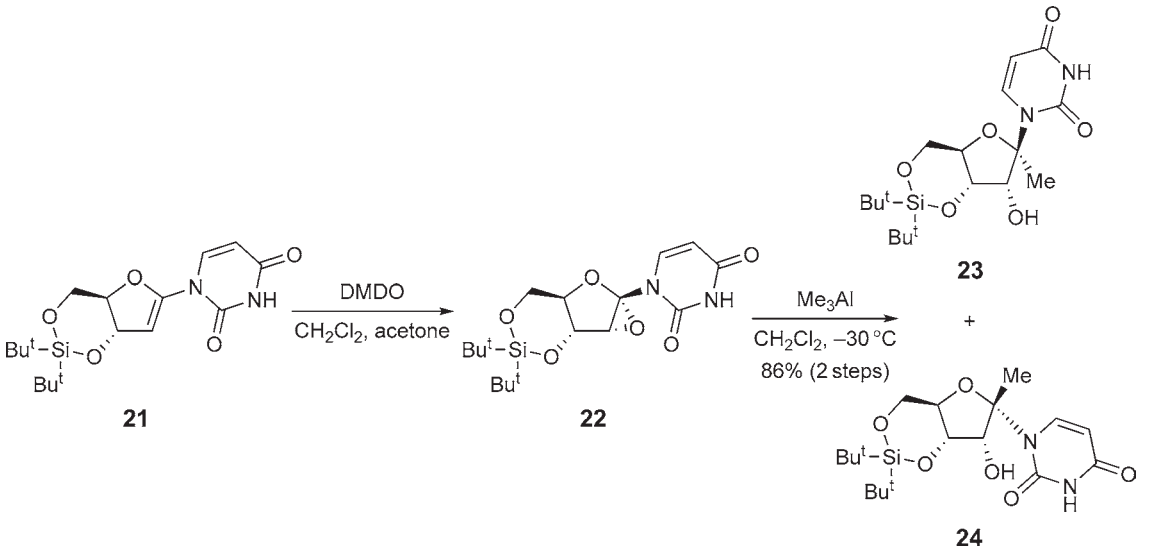
(3)

Compound **18**, prepared by a modification of this method, underwent free-radical dehalogenation as shown in Equation (4) to give the product of radical migration **20** as well as the expected product **19** <1995TL3867>.



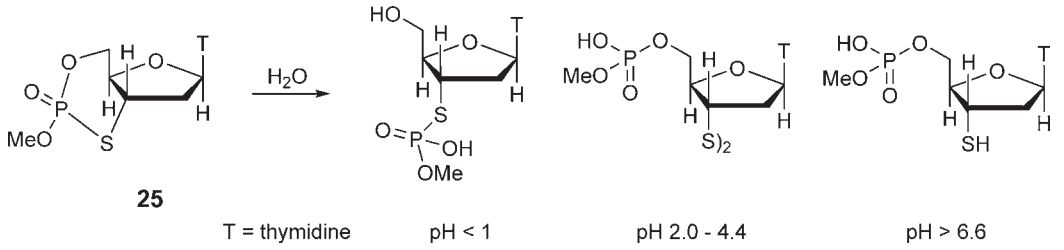
(4)

In related work from the same group, dehydro-nucleoside **21** underwent stereospecific epoxidation with dimethyldioxirane (DMDO) to give epoxide **22**. The ring opening of this compound with trimethylaluminium is presumably a predominantly S_N1 process giving isomers **23** and **24** in a 5:1 ratio (**Scheme 4**) <2004JOC1831>.



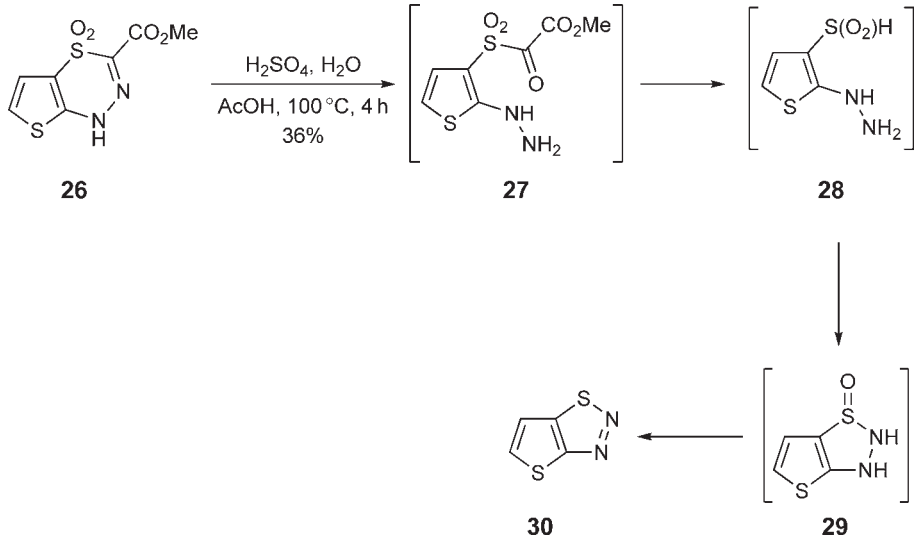
Scheme 4

Nucleoside phosphates are pivotal in a number of important biological processes, and so the detailed mechanisms of the reactivity of these compounds have been widely studied. A recent study has shown that the major product of hydrolysis of the cyclic thiophosphate analogue **25** varies according to pH as shown in Equation (5). The detailed hydrolysis pathway has implications for the use of such compounds as therapeutic agents <2000EJO1987>.



25 (5)

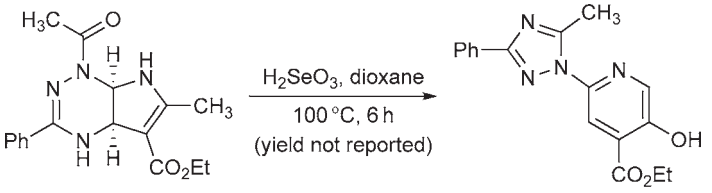
Compound **26**, prepared as described in Section 10.09.9.1.2, was shown to undergo the novel hydrolytic decomposition shown in **Scheme 5** <2000JHC191>. Treatment with aqueous acid presumably initiates a hydrolysis to give compound **27**. Further hydrolysis then results in loss of the glyoxylate fragment to give sulfinic acid **28**, self-condensation of which will provide sulfoxide **29**. Finally, loss of water will give the observed 10π-aromatic product **30**.



26 **27** **28** **29** **30**

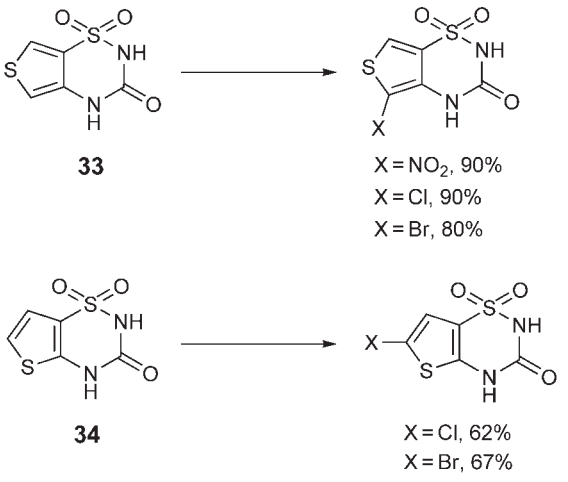
Scheme 5

Compound **31**, the synthesis of which is described in Section 10.09.9.2.3, undergoes a substantial rearrangement upon oxidation with selenious acid, giving 1,2,4-triazole **32** (Equation 6). A plausible mechanism for this transformation is presented in the original report <2003RCB1740>.



31 **32** (6)

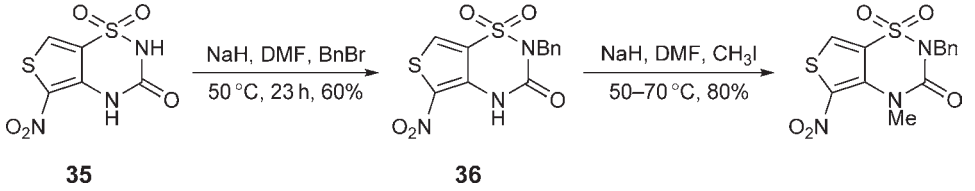
Thieno[3,4-*e*]-1,2,4-thiadiazine dioxide **33** and thieno[2,3-*e*]-1,2,4-thiadiazine dioxide **34** (prepared as shown in **Scheme 8** and Equation (10), Section 10.09.9.1.1) undergo electrophilic substitution on the thiophene ring regioselectively as shown in **Scheme 6** <1997H(45)1767>.



Conditions: Nitration (HNO_3, H_2SO_4, 0–5 °C); chlorination (NCS, THF or dioxane, reflux); bromination (NBS, THF, reflux)

Scheme 6

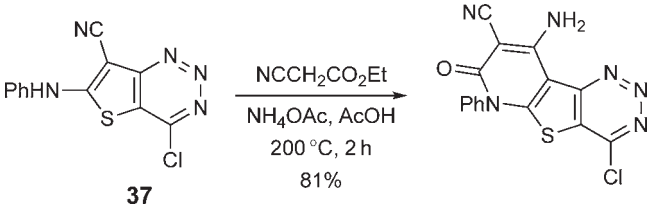
The parent thieno[3,4-*e*]-1,2,4-thiadiazine dioxide **35** undergoes regioselective alkylation at N-2 to give, for example, compound **36**. This can then be followed by alkylation at N-4 (**Scheme 7**) <1999BMC2811, 2000EJM751>.



Scheme 7

10.09.7 Reactivity of Substituents Attached to Ring Carbon Atoms

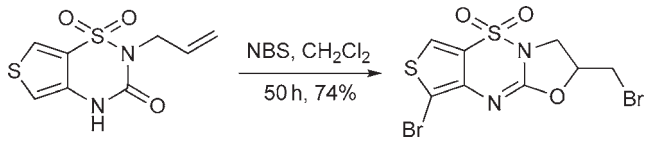
Compound **37**, prepared as described in Section 10.09.9.1.2, underwent further annulation upon treatment with ethyl cyanoacetate (Equation 7) <2002MOL756>.



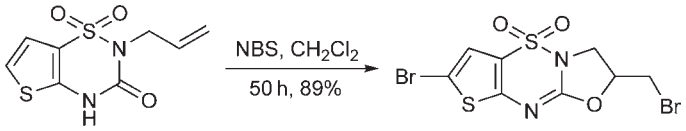
(7)

10.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

Compounds **38** and **40**, prepared by the method shown in **Scheme 7** (Section 10.09.6), undergo ready bromocyclization to give oxazolo-fused derivatives **39** and **41** (Equations 8 and 9) <2005JHC755>. In this case, bromination of the thiophene 2-position precedes bromocyclization. Further elaborations are then possible by displacement of the alkyl bromide <2005JHC763>.



38 39 (8)



40 41 (9)

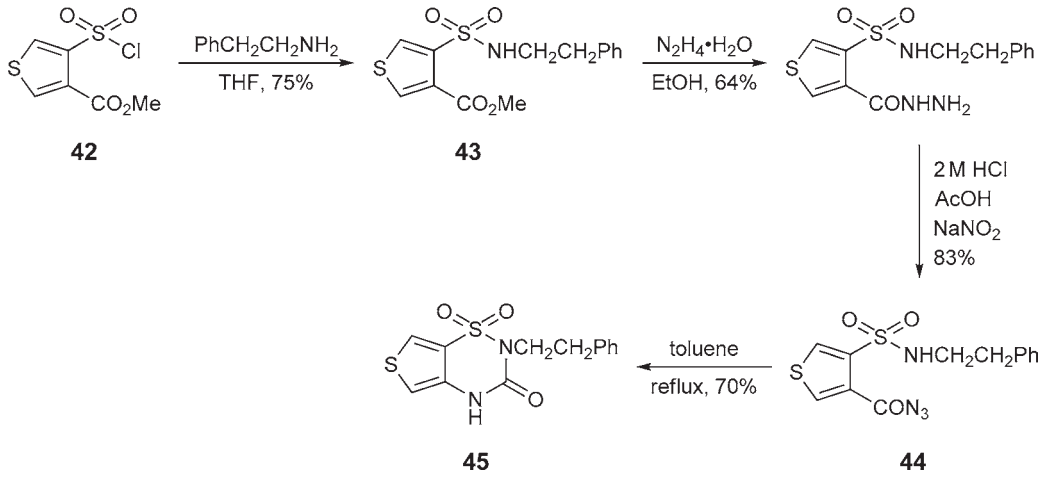
10.09.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Syntheses have been classified according to the last-formed ring, since it is this which defines the 5,6-fused system. In some cases, especially with multistep syntheses, the number of atoms within each fragment differ according to what one considers to be the key step. Although most reactions are classified according to the actual ring-forming step, reactions of a similar type have been grouped together in some instances.

10.09.9.1 Synthesis of the Six-Membered Ring

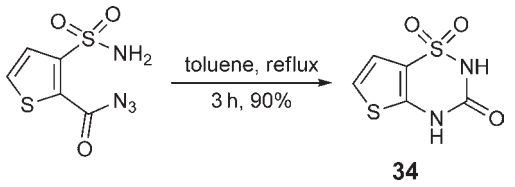
10.09.9.1.1 From [6+0] atom fragments

The reactivity of thieno[3,4-*e*]-1,2,4-thiadiazines and thieno[2,3-*e*]-1,2,4-thiadiazines has been discussed in Sections 10.09.6 and 10.09.8. These compounds, along with the [2,3-*e*]-1,2,4-thiadiazines, are relatively straightforward to prepare from thiophene derivatives. Although regioselective alkylation at N-2 is possible, the synthesis shown in **Scheme 8** has the advantage that different substituents can be directly introduced at this position during the ring synthesis. Sulfonyl chloride **42** underwent ready sulfonamide formation to give compound **43**. A two-step formation of acyl azide **44** was followed by Curtius rearrangement with concomitant cyclization to give the desired heterocycle **45**. An essentially identical route was used in the formation of the parent thieno[2,3-*e*]-1,2,4-thiadiazine **34** (Equation 10). For the formation of the [3,2-*e*] fused system, a directed lithiation was used to introduce the carboxylic acid group into compound **46**. From this point, the formation and rearrangement of the azide was accomplished in a single step to give compound **47** accompanied by a moderate amount of the unrearranged five-membered heterocycle **48** (**Scheme 9**). Approximately 40 derivatives of these compounds were evaluated for HIV-1 reverse transcriptase activity, with submicromolar activity being observed in a number of compounds <1998JME4109, 1997H(45)1767>.



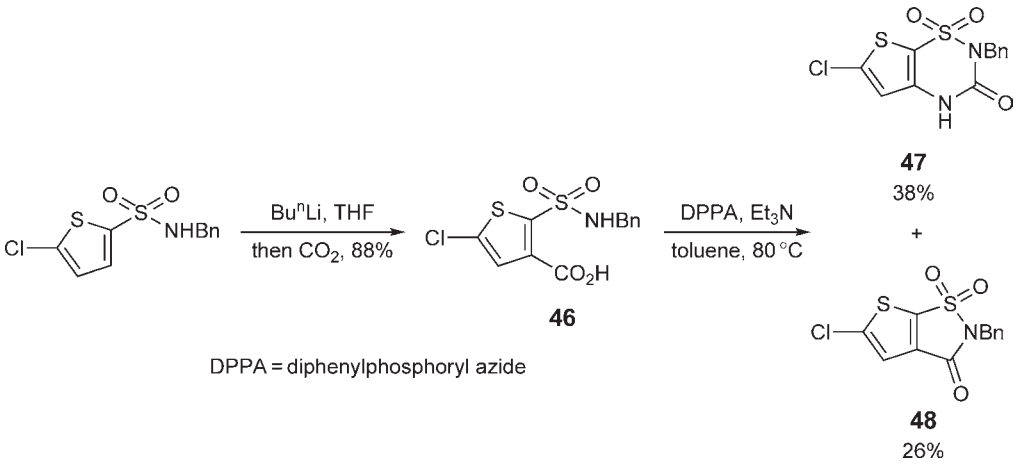
42 43 44 45

Scheme 8



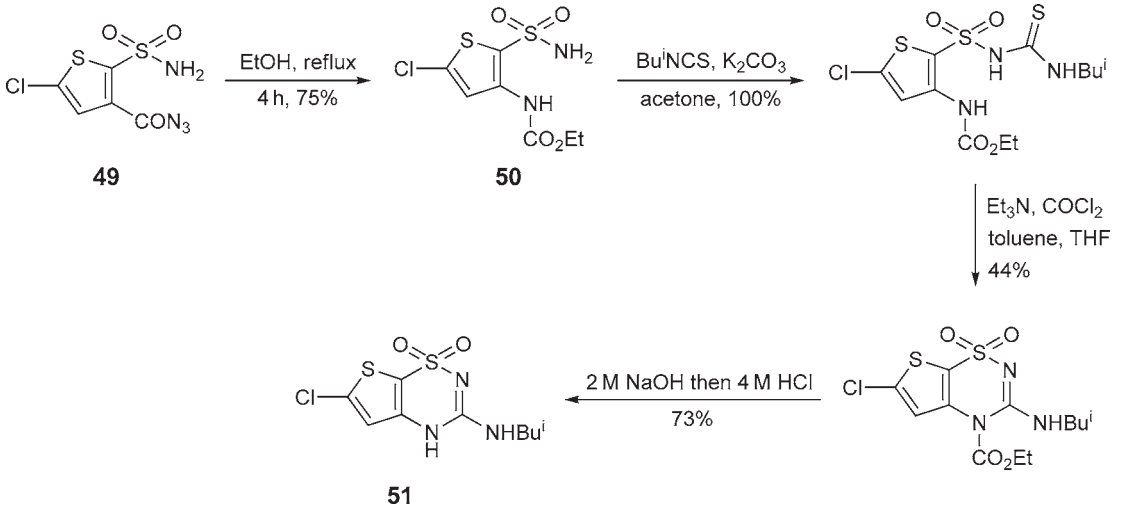
(10)

34



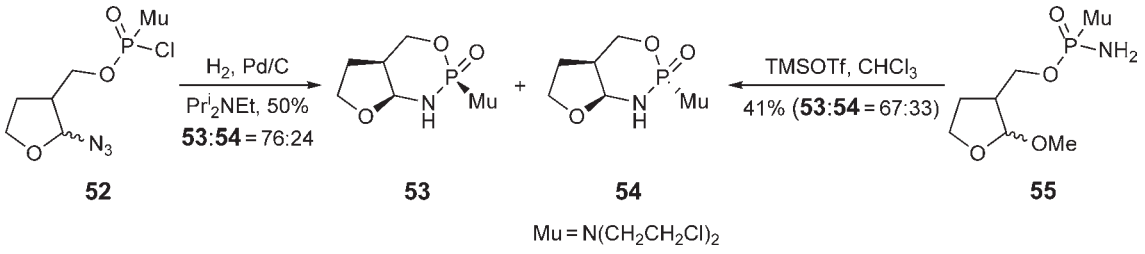
Scheme 9

The activation of ATP-sensitive potassium channels of pancreatic β-cells has important implications for the treatment of type 2 diabetes. A range of similar compounds to those shown above has been prepared by an essentially identical method. In one particular modification to the approach shown above, sulfonamide azide **49** underwent Curtius rearrangement without cyclization upon heating in ethanol to give compound **50**. Reaction with isobutyl isothiocyanate was then followed by cyclization of the carbamate nitrogen onto the thiourea. Acid hydrolysis of the carbamate then gave bicyclic guanidine **51** in moderate overall yield (**Scheme 10**) <2002JME4171>.



Scheme 10

The reductive cyclization of a mixture of epimers of compound **52** gave a 76:24 mixture of stereoisomers **53** and **54** in 50% overall yield. The exclusive formation of the *cis* ring junction was attributed to ready isomerization of the hemiaminal. A similar mixture was also prepared by cyclization of acetal **55** (**Scheme 11**) <1998TL2315>.

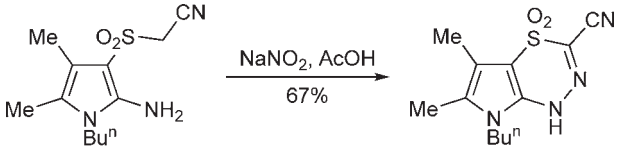


52 **53** **54** **55**

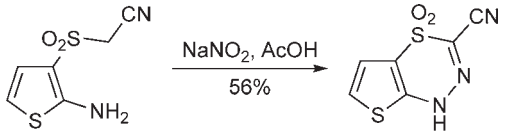
Scheme 11

10.09.9.1.2 From [5+1] atom fragments

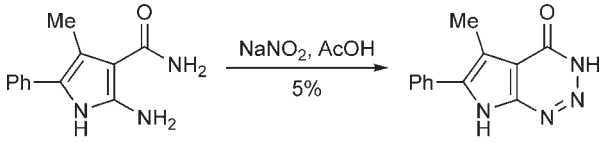
The most commonly used general method within this category is the diazotization of 2-aminopyrrole and 2-aminothiophene derivatives followed by intramolecular nucleophilic trapping. For example, reaction of compound **56** gave compound **57** as one of a number of compounds prepared in this manner (Equation 11) <1996JHC1615>. Although only one example of the corresponding thieno[2,3-*e*]-1,3,4-thiadiazine ring system **58** was reported <1998JHC927>, there is no obvious reason why this reaction should not be general (Equation 12). The reactions work just as well with an ester as electron-withdrawing group in place of the nitrile <1998JHC933>. A primary amide can also act as the nucleophile, leading to isolation of pyrrolo[2,3-*d*]-1,2,3-triazine **59** in low yield (Equation 13) <1999S2082>. The chemistry of compounds **9** and **10**, prepared by this method, has been discussed in Section 10.09.5 <2001JOC4776>.



56 **57** (11)



58 (12)

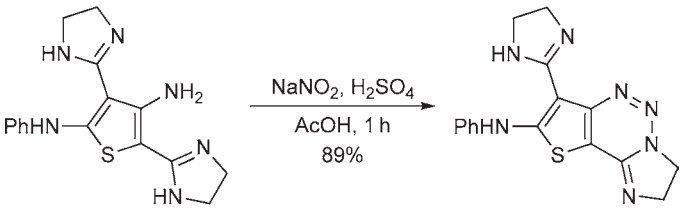


59 (13)

A further modification of the same process is shown in Equation (14). Using an iminoyl chloride, generated *in situ* from a nitrile, as the nucleophilic trap leads to the exclusive formation of regioisomer **37**. The same regiochemistry was observed in the formation of compound **60** (Equation 15) <2002MOL756>.



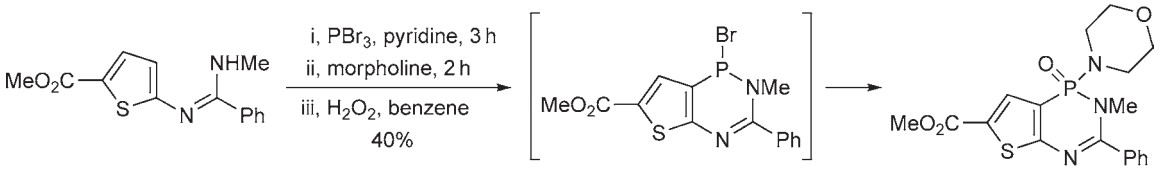
37 (14)



(15)

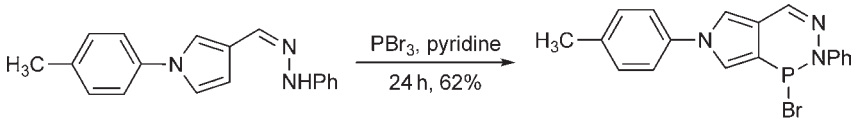
60

The heterocyclic system in compound **63** was prepared in 40% yield from amidine **61** as shown in **Scheme 12** <2001CHE1183>. Although the intermediate **62** was not isolated on this occasion, related compounds, for example, **64**, can be isolated if care is taken to exclude moisture (**Scheme 13**) <2001HAC658>.



61 **62** **63**

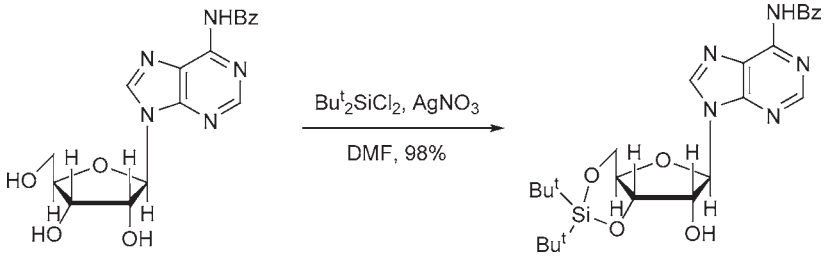
Scheme 12



64

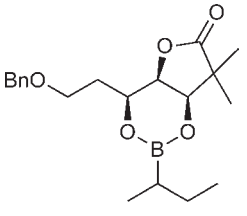
Scheme 13

The di-*t*-butylsilylene protecting group is rapidly becoming ubiquitous within nucleoside chemistry, allowing the simultaneous protection of the 3′- and 5′-hydroxy groups. This protecting group is generally introduced using the dichlorosilane in the presence of silver nitrate (Equation 16) <1995TL1683> although the corresponding triflate has also been used <2003NN1007>. Selected applications of this protecting group have already been discussed in Sections 10.09.3.2 and 10.09.6.



(16)

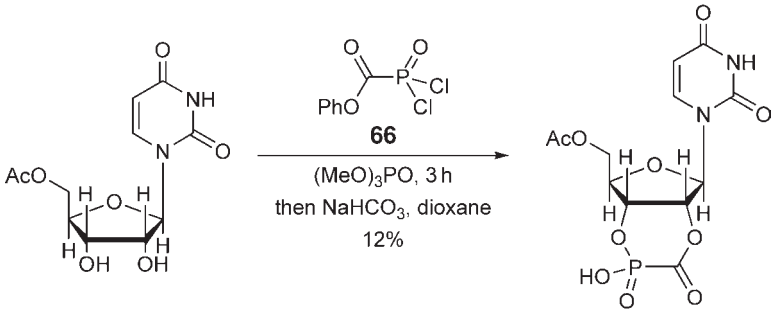
During studies toward the synthesis of calyculin C, Karisalmi and Koskinen noted the particular stability of boronate ester **65**, although details were not given <2004S1331>.



65

10.09.9.1.3 From [4+2] atom fragments

Phosphonoformate derivative **66** is a useful reagent for the synthesis of 1,4,2-dioxaphosphorin derivatives. 5′-Acetyluridine derivative **67** was prepared in this way, albeit in low yield (Equation 17) <2000JOC1218>.



(17)

10.09.9.1.4 From [3+3] atom fragments

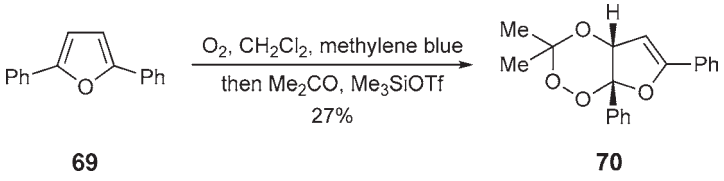
Boron trifluoride-mediated acylation of pyrrolidine-2,4-dione **68** led to the isolation of the neutral boron difluoride complex **2**, which was sufficiently stable to be purified by column chromatography (Equation 18). This compound has been characterized crystallographically as noted above <1990J(P1)1959>.



(18)

10.09.9.1.5 From [2+2+2] atom fragments

Furano[3,2-*e*]-1,2,4-trioxane **70** has been prepared by the photooxygenation of 2,5-diphenylfuran **69** followed by addition of acetone (Equation 19) <1997H(44)367>.

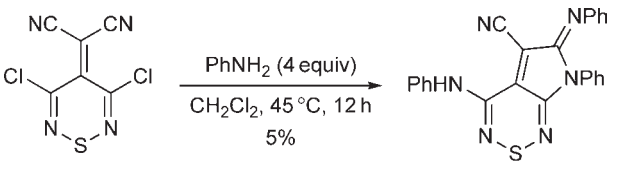


(19)

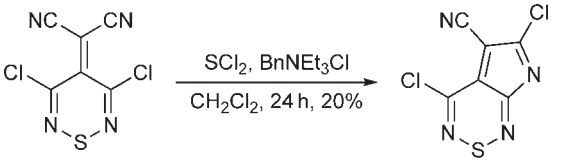
10.09.9.2 Synthesis of the Five-Membered Ring

10.09.9.2.1 From [5+0] atom fragments

The chemistry of thiadiazine **71** has been investigated by Koutentis and Rees. During the course of this work, a number of annulation reactions were discovered. For example, treatment of compound **71** with an excess of aniline gave compound **72**, albeit in poor yield (Equation 20). Compound **71** is formed by reaction of tetracyanoethene (TCNE) with SCl_2. Further reaction with SCl_2 gave compound **73** (Equation 21) <2000J(P1)1081, 2000J(P1)1089>.



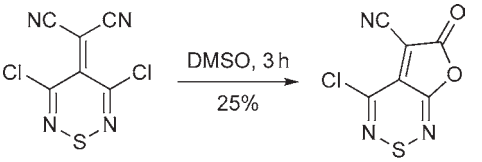
71 72 (20)



71 73 (21)

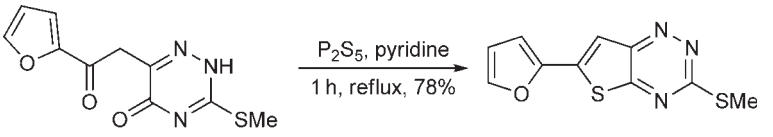
10.09.9.2.2 From [4+1] atom fragments

Also from the work of Koutentis and Rees is the reaction of compound **71** with dimethyl sulfoxide (DMSO) to give compound **74** as the major product (Equation 22) <2000J(P1)1081, 2000J(P1)1089>.



71 74 (22)

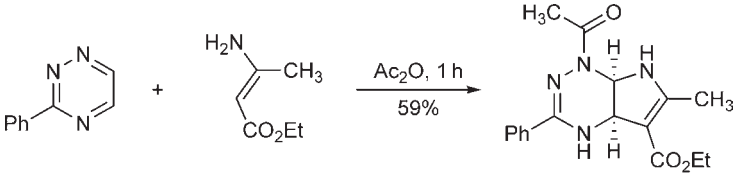
The thiophene ring in compound **76** was prepared in fairly straightforward manner by reaction of the immediate precursor **75** with phosphorus pentasulfide in line with a previously reported procedure (Equation 23). Further annulation reactions of these compounds have already been discussed in Section 10.09.5 <2003T8489>.



75 76 (23)

10.09.9.2.3 From [3+2] atom fragments

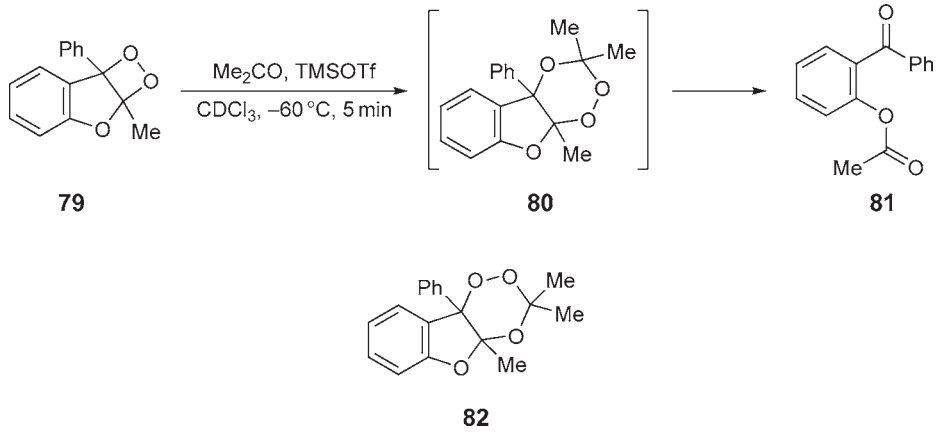
The 1,2,4-triazine ring is an ambident electrophile, and reacts with enamine-type nucleophiles. For example, addition of enamine **78** to a solution of triazine **77** in acetic anhydride furnished the pyrrolotriazine **31** (Equation 24) <2003TL2421>.



77 78 31 (24)

10.09.10 Ring Syntheses by Transformations of Another Ring

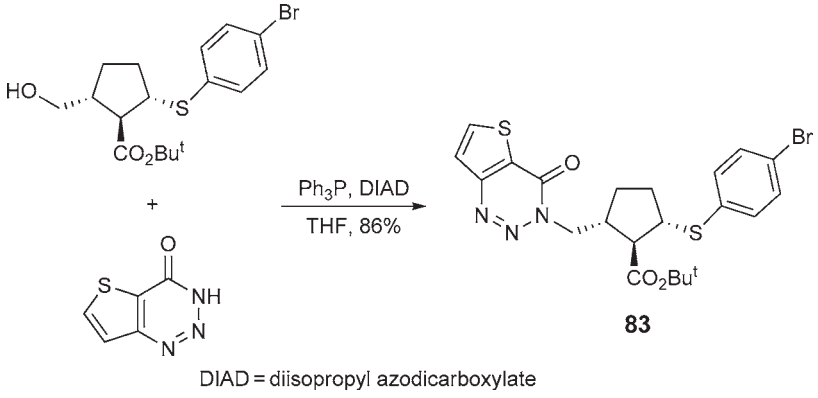
During the acetone-mediatated decomposition of dioxetane **79** to give ketoester **81**, a compound having ^{1}H and ^{13}C NMR data consistent with the 1,2,4-trioxane **80** was observed (**Scheme 14**). Although not isolable, this intermediate was stable in solution for a few days. In the opinion of the present author, it would be difficult to distinguish compound **80** from the regioisomeric trioxane **82**, and this could also account for the formation of compound **81** <1994T8393>.



Scheme 14

10.09.11 Important Compounds and Applications

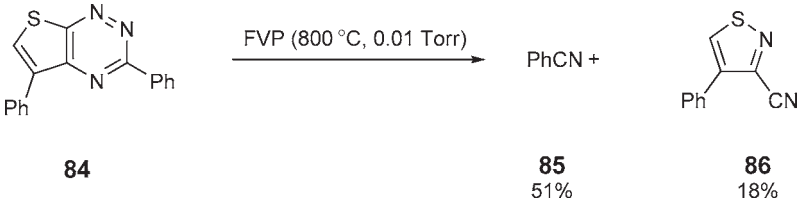
Most applications of compounds of this class have been noted during the preceding discussion. The [6,5] fused heterocycle in compound **83** was introduced in one step using a Mitsunobu reaction (Equation 25). This compound, and a number of related structures, showed activity as inhibitors of matrix metalloproteinase <2003JME3840>.



(25)

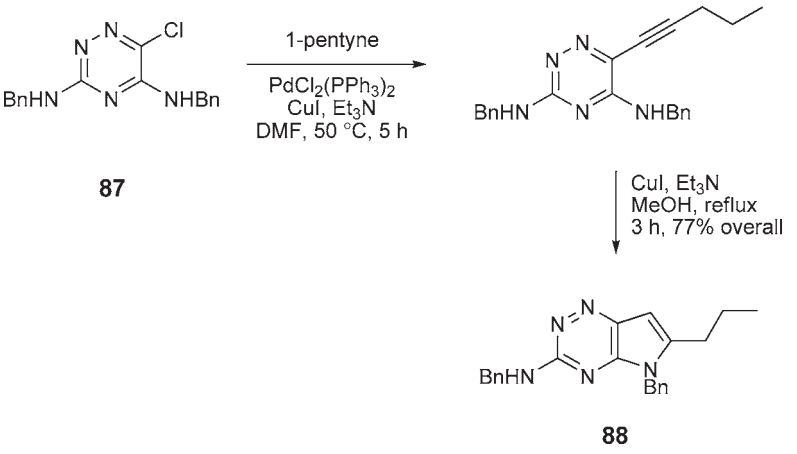
10.09.12 Further Developments

The chemistry of compound **7** was discussed in Section 10.09.5. The pyrolysis of related compound **84** has also been reported, with benzonitrile **85** and compound **86** being the major of a number of products (Equation 26) <2004T9121>.



(26)

The 1,2,4-triazine **87** underwent a one-pot Sonagashira coupling followed by cyclization to give pyrrole[2,3-*e*]-1,2,4-triazine **88** in good overall yield (**Scheme 15**) <2007TL5069>.



Scheme 15

References

1987JA4058 K. A. Nelson, W. G. Bentrude, W. N. Setzer, and J. P. Hutchinson, *J. Am. Chem. Soc.*, 1987, **109**, 4058.
1990J(P1)1959 R. C. F. Jones, M. J. Begley, G. E. Peterson, and S. Sumaria, *J. Chem. Soc., Perkin Trans. 1*, 1990, 1959.
1993MRC1039 T. Katsura, K. Ueno, and K. Furusawa, *Magn. Reson. Chem.*, 1993, **31**, 1039.
1994T8393 W. Adam and M. Sauter, *Tetrahedron*, 1994, **50**, 8393.
1995TL1683 T. Wada, M. Tobe, T. Nagayama, K. Furusawa, and M. Sekine, *Tetrahedron Lett.*, 1995, **36**, 1683.
1995TL3867 Y. Itoh, K. Haraguchi, H. Tanaka, K. Matsumoto, K. T. Nakamura, and T. Miyasaka, *Tetrahedron Lett.*, 1995, **36**, 3867.
1996CHEC-II(7)351 S. T. Mullins; Bicyclic 5-6 Systems: Four Heteroatoms 1:3, in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 351.
1996JHC1615 C. E. Stephens and J. W. Sowell, Sr., *J. Heterocycl. Chem.*, 1996, **33**, 1615.
1997H(44)367 C. W. Jefford, S.-j. Jin, J.-C. Rossier, S. Kohmoto, and G. Bernardinelli, *Heterocycles*, 1997, **44**, 367.
1997H(45)1767 M. E. Arranz, S. Vega, and J. A. Díaz, *Heterocycles*, 1997, **45**, 1767.
1998JHC927 C. E. Stephens and J. W. Sowell, Sr., *J. Heterocycl. Chem.*, 1998, **35**, 927.
1998JHC933 C. E. Stephens and J. W. Sowell, Sr., *J. Heterocycl. Chem.*, 1998, **33**, 933.
1998JME4109 E. Arranz, J. A. Diaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clercq, and S. Vega, *J. Med. Chem.*, 1998, **41**, 4109.
1998NN1033 G. Wang and P. J. Middleton, *Nucleos. Nucleot.*, 1998, **17**, 1033.
1998TL2315 P. Maynard-Faure, C. Gonser, V. Vaime, and D. Bouchu, *Tetrahedron Lett.*, 1998, **39**, 2315.
1998TL3713 K. Haraguchi, A. Nishikawa, E. Sasakura, H. Tanaka, K. T. Nakamura, and T. Miyasaka, *Tetrahedron Lett.*, 1998, **39**, 3713.
1999BMC2811 M. E. Arranz, J. A. Díaz, S. T. Ingate, M. Witvrouw, C. Pannecouque, J. Balzarini, E. De Clercq, and S. Vega, *Bioorg. Med. Chem.*, 1999, **7**, 2811.
1999S2082 P. Diana, P. Barraja, A. Lauria, A. M. Almerico, G. Dattolo, and G. Cirrincione, *Synthesis*, 1999, 2082.
1999T15159 J. C. Carretero, J. E. de Diego, and C. Hamdouchi, *Tetrahedron*, 1999, **55**, 15159.
2000EJM751 E. Arranz, J. A. Díaz, S. Vega, M. Campos-Toimil, F. Orallo, I. Cardelús, J. Llenas, and A. G. Fernández, *Eur. J. Med. Chem.*, 2000, **35**, 751.
2000EJO1987 M. I. Elzagheid, K. Mattila, M. Oivanen, B. C. N. M. Jones, R. Cosstick, and H. Lönnberg, *Eur. J. Org. Chem.*, 2000, 1987.
2000JHC191 C. E. Stephens and J. W. Sowell, Sr., *J. Heterocycl. Chem.*, 2000, **37**, 191.
2000JOC1218 C. G. Ferguson, B. I. Gorin, and G. R. J. Thatcher, *J. Org. Chem.*, 2000, **65**, 1218.
2000J(P1)1081 P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1081.
2000J(P1)1089 P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1089.
2001CHE1183 S. A. Kovaleva, N. G. Chubaruk, A. A. Tolmachev, and A. M. Pinchuk, *Chem. Heterocycl. Compd. (Eng. Transl.)*, 2001, **37**, 1183.
2001HAC658 S. P. Ivonin, A. A. Tolmachev, A. A. Chaikovskaya, T. N. Kudraya, A. A. Anischenko, E. B. Rusanov, A. N. Chernega, and A. M. Pinchuk, *Heteroatom Chem.*, 2001, **12**, 658.
2001JOC4776 M. T. Migawa and L. B. Townsend, *J. Org. Chem.*, 2001, **66**, 4776.
2002JME4171 F. E. Nielsen, T. B. Bodvarsdottir, A. Worsaae, P. MacKay, C. E. Stidsen, H. C. M. Boonen, L. Pridal, P. O. G. Arkhammar, P. Wahl, L. Ynddal, F. Junager, N. Dragsted, T. M. Tagmose, J. P. Mogensen, A. Koch, S. P. Treppendahl, and J. B. Hansen, *J. Med. Chem.*, 2002, **45**, 4171.
2002JOC5959 K. Haraguchi, H. Takahashi, N. Shiina, C. Horii, Y. Yoshimura, A. Nishikawa, E. Sasakura, K. T. Nakamura, and H. Tanaka, *J. Org. Chem.*, 2002, **67**, 5959.
2002MOL756 A. M. M. El-Saghier, *Molecules*, 2002, **7**, 756.

2003RCB1740 V. N. Charushin, N. N. Mochul'skaya, A. A. Andreiko, M. I. Kodess, D. V. Beskrovnyi, I. A. Litvinov, O. G. Sinyashin, and O. N. Chupakhin, *Russ. Chem. Bull.*, 2003, **52**, 1740.

2003JME3840 T. Le Diguarher, A.-M. Chollet, M. Bertrand, P. Hennig, E. Raimbaud, M. Sabatini, N. Guilbaud, A. Pierré, G. C. Tucker, and P. Casara, *J. Med. Chem.*, 2003, **46**, 3840.

2003NN763 K. Haraguchi, H. Takahashi, and H. Tanaka, *Nucleos. Nucleot.*, 2003, **22**, 763.

2003NN1007 V. Serebryany and L. Beigelman, *Nucleos. Nucleot.*, 2003, **22**, 1007.

2003T8489 Y. A. Ibrahim, B. Al-Saleh, and A. A. A. Mahmoud, *Tetrahedron*, 2003, **59**, 8489.

2003TL2421 V. N. Charushin, N. M. Mochulskaya, A. A. Andreiko, V. I. Filyakova, M. I. Kodess, and O. N. Chupakhin, *Tetrahedron Lett.*, 2003, **44**, 2421.

2004CAR2895 J. N. Tilekar and T. L. Lowary, *Carbohydr. Res.*, 2004, **339**, 2895.

2004JOC1831 K. Haraguchi, Y. Kubota, and H. Tanaka, *J. Org. Chem.*, 2004, **69**, 1831.

2004OL2645 K. Haraguchi, N. Shiina, Y. Yoshimura, H. Shimada, K. Hashimoto, and H. Tanaka, *Org. Lett.*, 2004, **6**, 2645.

2004S1331 K. Karisalmi and A. M. P. Koskinen, *Synthesis*, 2004, 1331.

2004T4077 F. Sartillo-Piscil, S. Cruz, M. Sánchez, H. Höpfl, C. A. de Parrodi, and L. Quintero, *Tetrahedron*, 2004, **59**, 4077.

2004T9121 Y. A. Ibrahim, A. A. Al-Awadi, and M. R. Ibrahim, *Tetrahedron*, 2004, **60**, 9121.

2004TL137 K.-i. Takatsuki, M. Yamamoto, S. Ohgushi, S. Kohmoto, K. Kishikawa, and H. Yamashita, *Tetrahedron Lett.*, 2004, **45**, 137.

2005JHC755 S. Vega, M. E. Arranz, and V. J. Arán, *J. Heterocycl. Chem.*, 2005, **42**, 755.

2005JHC763 S. Vega, M. E. Arranz, and V. J. Arán, *J. Heterocycl. Chem.*, 2005, **42**, 763.

2005JME3840 M. T. Migawa, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 2005, **48**, 3840.

2005JOC1620 I. Le Clézio, H. Gornitzka, J.-M. Escudier, and A. Vigroux, *J. Org. Chem.*, 2005, **70**, 1620.

2005JOC7107 S. Cruz-Gregorio, M. Sanchez, A. Clara-Sosa, S. Bèrnes, L. Quintero, and F. Sartillo-Piscil, *J. Org. Chem.*, 2005, **70**, 7107.

2007TL5069 C. Nyffenegger, G. Fournet, and B. Joseph, *Tetrahedron Lett.*, 2007, **48**, 5069.

Biographical Sketch



Mark Elliott was born in Doncaster. He studied in Loughborough, where he obtained a BSc in 1991 and a PhD in 1994 working with Prof. C. J. Moody on transition-metal-catalyzed reactions of diazo compounds. After postdoctoral work with Prof. A. Pfaltz, initially in Basel under the auspices of a Royal Society European Exchange Fellowship, and later at the Max-Planck Institute in Mülheim, he returned to the UK in 1996 to take up his current position as lecturer in chemistry at Cardiff. His reseach interests include asymmetric heterocyclic chemistry, asymmetric catalysis, and natural product chemistry.

10.10
Bicyclic 5-6 Systems: Four Heteroatoms 3:1

B. R. Buckley and S. P. Neary
Loughborough University, Loughborough, UK
© 2008 Elsevier Ltd. All rights reserved.

10.10.1 Introduction 512
10.10.2 Theoretical Methods 512
10.10.3 Experimental Structural Methods 513
10.10.4 Thermodynamic Aspects 513
10.10.5 Reactivities of Fully Conjugated Rings 513
10.10.5.1 Triazolo[4,5-*b*]pyridines and Triazolo[4,5-*c*]pyridines 513
10.10.5.1.1 Ring substitution 513
10.10.5.1.2 Photochemistry and thermolysis 514
10.10.5.2 *N*-Amino[1,2,3]triazolopyridines 514
10.10.5.3 [1,2,3]Thiadiazolo[3,4-*b*]pyridines and [1,2,3]Thiadiazolo[3,4-*c*]pyridines 515
10.10.5.4 [1,2,5]Thiadiazolo[3,4-*b*]pyridines, [1,2,5]Thiadiazolo[3,4-*c*]pyridines, [1,2,5]Selenadiazolo[3,4-*b*]pyridines, and [1,2,5]Selenadiazolo[3,4-*c*]pyridines 515
10.10.5.5 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]Oxadiazolo[3,4-*c*]pyridines and Their Oxides 515
10.10.6 Reactivities of Nonconjugated Rings 515
10.10.7 Reactivities of Substituents Attached to Ring Carbon Atoms 515
10.10.7.1 Triazolopyridines 515
10.10.8 Reactivities of Substituents Attached to Ring Heteroatoms 516
10.10.8.1 *N*-Hydroxy[1,2,3]triazolo[4,5-*b*]pyridines 516
10.10.9 Ring Synthesis from Monocyclic Heterocycles 517
10.10.9.1 Synthesis by Formation of the Five-Membered Ring 517
10.10.9.1.1 Triazolopyridines 517
10.10.9.1.2 Triazolopyridine N-oxides and N-hydroxytriazolopyridines 518
10.10.9.1.3 N-Amino[1,2,3]triazolopyridines 518
10.10.9.1.4 [1,2,3]Thiadiazolopyridines 518
10.10.9.1.5 [1,2,5]Thiadiazolopyridines and [1,2,5]selenadiazolopyridines 518
10.10.9.1.6 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]oxadiazolo[3,4-*c*]pyridines, and N-oxides 519
10.10.9.2 Synthesis by Formation of the Six-Membered Ring 519
10.10.9.2.1 Triazolopyridines 519
10.10.9.2.2 [1,2,5]Thiadiazolopyridines, [1,2,5]selenadiazolo[4,5-*c*]pyridines, and [1,2,5]oxadiazolo[4,5-*c*]pyridines 520
10.10.10 Ring Synthesis by Transformation of Another Ring 520
10.10.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available 521
10.10.12 Important Compounds and Applications 521
References 522

10.10.1 Introduction

The first review of this category of compounds as a group was in Chapter 7.10 <1996CHEC-II(7)363>. The present chapter will serve as an update to the original chapter and endeavors to inform the reader of the various syntheses available and the most recent theoretical and experimental techniques used for structure elucidation. General review articles can be found in <2002AHC(83)2, 1996CHEC-II(7)363, 1984CHEC(6)400, 1984CHEC(6)415, 1984CHEC(6)524, 1984CHEC(6)712, 1984CHEC(6)731>, and <1983AHC(34)79>.

The nomenclature of this class of heterocycles was discussed in 1996CHEC-II(7)363. As many triazolopyridines are prepared as nucleoside mimics, they are often described in the literature using the nucleoside, rather than the systematic IUPAC nomenclature. The reactions reviewed here are by no means exhaustive but offer an overview of the area and highlight significant examples. The compounds presented in this review have a wide variety of applications; this includes analogues of the well-documented peptide coupling reagent *N*-hydroxy[1,2,3]triazolo[4,5-*b*]pyridine (HOAt). Many of these substances exhibit significant biological activity or are themselves intermediates for biologically active compounds. The synthesis section is split into synthesis by formation of the five-membered ring and then synthesis of the six-membered ring. These sections are then further divided according to the class of heterocyclic system. A critical review of these methods is presented in Section 10.10.11.

Some of the interesting structural architectures to be reviewed and their names are presented in **Figure 1**.

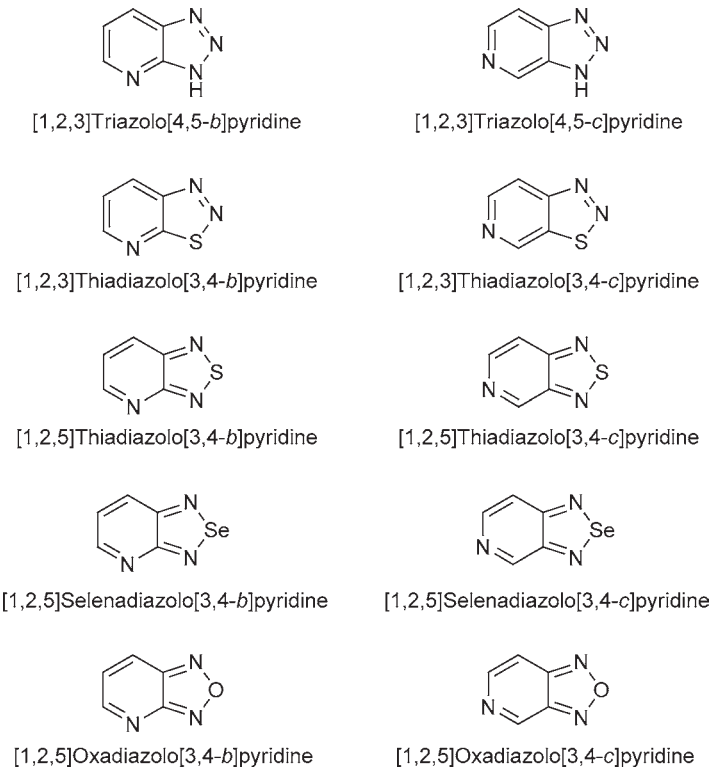
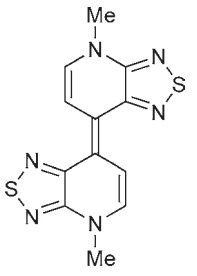


Figure 1

10.10.2 Theoretical Methods

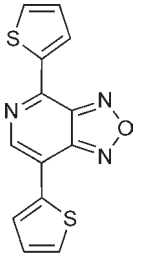
The comparative ionization potentials of various triazolopyridines and [1,2,3]-thiadiazolopyridines were discussed in <1996CHEC-II(7)363>. A review of several theoretical methods for determination of the preferred site of alkylation and structural conformations can be found in <2002AHC(83)2>. Pergolese and Bigotto have also reported computational studies for the surface-enhanced Raman spectroscopy of 1*H*-1,2,3-triazolo[4,5-*b*]pyridine on silver sols <2001JRS109>. The highest occupied molecular orbital (HOMO) and net atomic charges of **1** have been calculated using the PM3 method <1997CC1851>.



1

10.10.3 Experimental Structural Methods

Extensive nuclear magnetic resonance and ultraviolet spectroscopy methods were reviewed in <1996CHEC-II(7)363>, as well as mass spectral fragmentation patterns of [1,2,3]triazolo[4,5-*b*]pyridines (Section 7.10.8.1). More recently, furoxan rearrangement of some pyridofuroxan derivatives has been studied by ^{1}H, ^{13}C, ^{14}N, ^{15}N, and ^{17}O NMR spectroscopy <2000JPO480>. The X-ray crystallographic data of a series of electron donors containing 1,2,5-thiadiazole and 1,1′-dihydro-4,4′-bi(pyridylidene) units have been reported <1997CC1851>. The fluoresence spectroscopic characterization of 4,7-bis(2-thienyl)-1,2,5-oxadiazolo[3,4-*c*]pyridine **2** has also been reported <2002CPL(354)173>.



2

10.10.4 Thermodynamic Aspects

No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

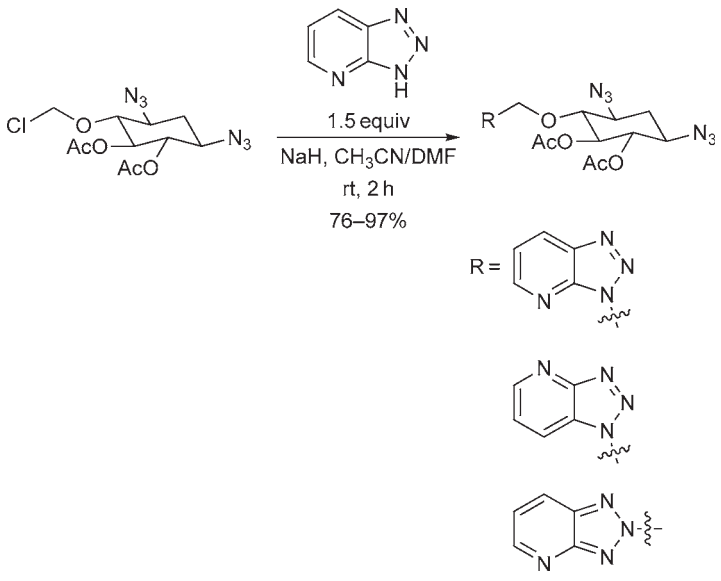
10.10.5 Reactivities of Fully Conjugated Rings

General chemical properties of triazolopyridines, such as oxidations, reductions, reaction with electrophiles, reactions with nucleophiles, homolytic reactions, ring-opening reactions, and photochemical reactions can be found in <2002AHC(83)2>.

10.10.5.1 Triazolo[4,5-*b*]pyridines and Triazolo[4,5-*c*]pyridines

10.10.5.1.1 Ring substitution

Functionalization of triazolopyridines was discussed in <1996CHEC-II(7)363> and it was concluded that there is no predominant factor which determines the site of N-functionalization. A recent example of this can be found in the report by Ding *et al.* of their synthesis of paromomycin-related heterocycle-substituted aminoglycoside mimics (Equation 1) <2003AGE3409>.



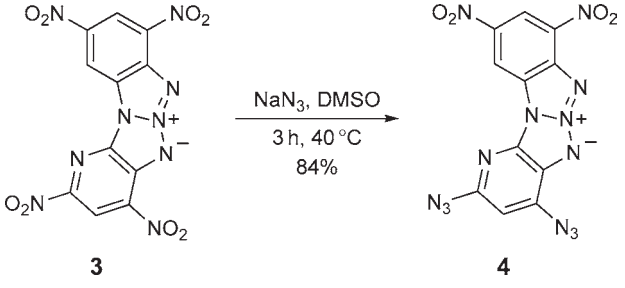
(1)

10.10.5.1.2 Photochemistry and thermolysis

No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

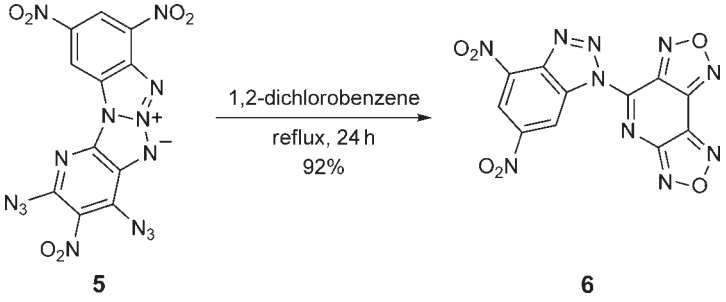
10.10.5.2 *N*-Amino[1,2,3]triazolopyridines

A study on the electrophilic addition on the benzene ring of tetraazapentalenes was reported in <1996CHEC-II(7)363>. A recent report has shown that two of the nitro groups in **3** can be substituted with the azide moiety affording compound **4** which, perhaps not too surprisingly, was extremely sensitive to sparks, friction, and impact (Equation 2). A range of other substitution patterns were explored and compound **5** was converted into **6** in good yield (Equation 3) <2005AGE7089>.



3 **4**

(2)



5 **6**

(3)

10.10.5.3 [1,2,3]Thiadiazolo[3,4-*b*]pyridines and [1,2,3]Thiadiazolo[3,4-*c*]pyridines

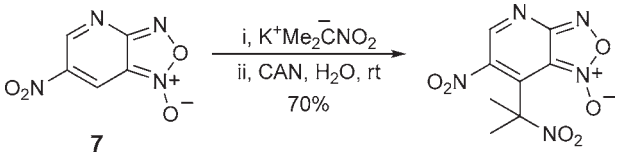
No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

10.10.5.4 [1,2,5]Thiadiazolo[3,4-*b*]pyridines, [1,2,5]Thiadiazolo[3,4-*c*]pyridines, [1,2,5]Selenadiazolo[3,4-*b*]pyridines, and [1,2,5]Selenadiazolo[3,4-*c*]pyridines

No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

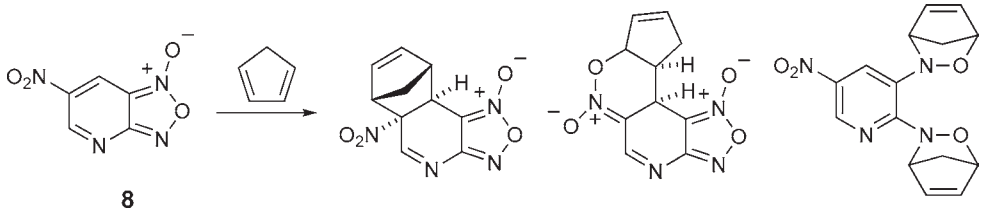
10.10.5.5 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]Oxadiazolo[3,4-*c*]pyridines and Their Oxides

From the range of heterocycles studied in this and the original chapter it can be seen that the pyridofuroxans show the least aromatic character. A range of examples to support this conclusion can be found in <1996CHEC-II(7)363>. Terrier and co-workers have reported the reaction of 6-nitro[2,1,3]oxadiazolo[4,5-*b*]pyridine **7** with 2-nitropropenide ion and subsequent oxidation (Equation 4) <2003OBC2192>. Their results highlighted the existence of an inverse relationship between the ease of oxidation and stability of the σ-adducts. Ranking of electrophilicity of a range of heteroaromatics including [1,2,5]oxadiazolo[3,4-*b*]pyridines has been reported <2005JOC6242>.



7 (4)

Reaction of 6-nitro[1,2,3]oxadiazolo[4,5-*b*]pyridine-1-oxide **8** under Diels–Alder conditions resulted in the formation of several adducts, a normal Diels–Alder adduct, a hetero-Diels–Alder adduct, and a di-adduct, which is believed to arise from the minor dinitroso tautomer of **8**; unfortunately, no yields were reported for these products (Equation 5) <2000JOC7391>.



8 (5)

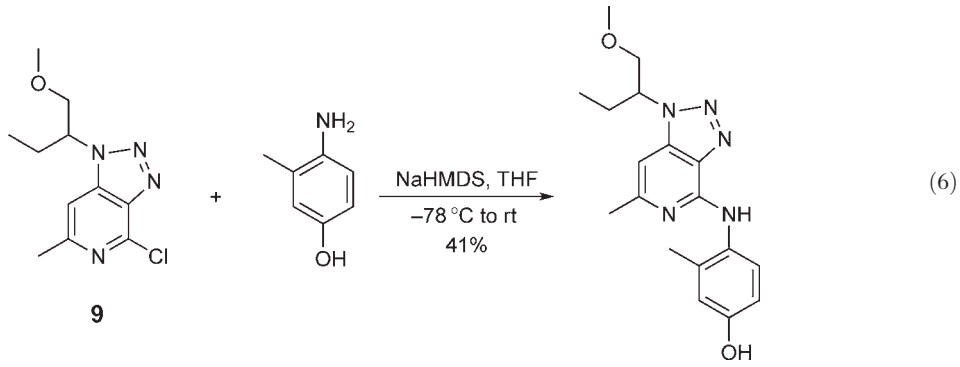
10.10.6 Reactivities of Nonconjugated Rings

No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

10.10.7 Reactivities of Substituents Attached to Ring Carbon Atoms

10.10.7.1 Triazolopyridines

Substitution of a suitable leaving group α- to nitrogen can occur readily on the pyridine ring of compounds such as **9** (Equation 6) (see, e.g., <2006BMC4029>).



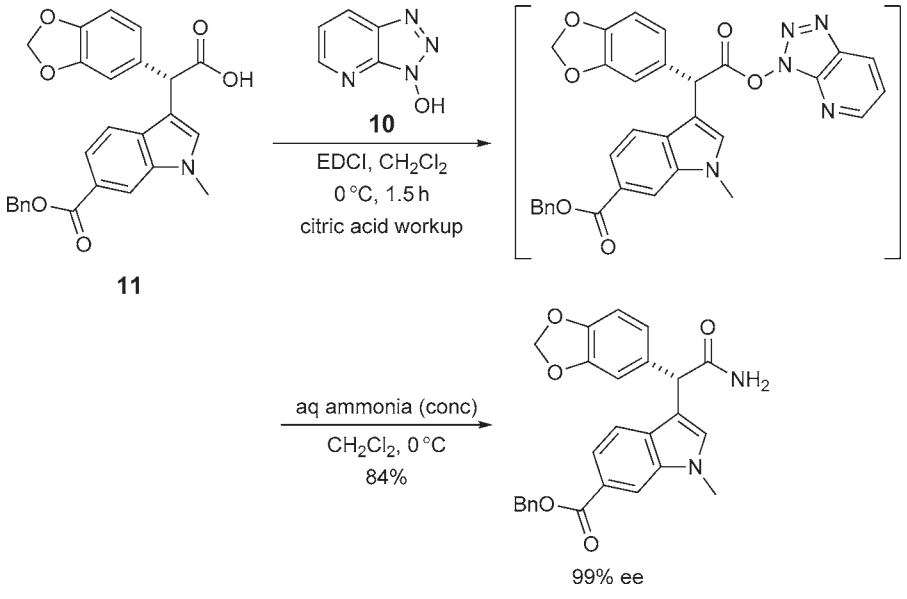
(6)

10.10.8 Reactivities of Substituents Attached to Ring Heteroatoms

10.10.8.1 *N*-Hydroxy[1,2,3]triazolo[4,5-*b*]pyridines

N-Hydroxybenzotriazole is perhaps one of the most popular amide coupling reagents used today; however, problems with the racemization of certain substrates have resulted in the structurally related *N*-hydroxy[1,2,3]triazolo[4,5-*b*]-pyridine (HOAt) **10** attracting recent attention due to its ability to suppress the level of racemization for a range of amide coupling reactions. The ability of these reagents to suppress racemization is believed to be due to the anchimeric assistance effect of HOAt <2000T4437>. Several review articles have been published in this area and a lot of this work has been carried out by Carpino and co-workers (see, e.g., <2002AHC(83)2, 1998JPR581, 1998JOC9678>).

For example, racemization-free synthesis of chiral acylsulfonamides has been effectively achieved using *N*-hydroxy[1,2,3]triazolo[4,5-*b*]pyridine. *N*-Hydroxybenzotriazole is a common coupling reagent for forming acylsulfonamides but racemization occurs readily when using this reagent. It was found that, in contrast to the corresponding reaction of *N*-hydroxybenzotriazole, coupling of **11** with *N*-hydroxy[1,2,3]triazolo[4,5-*b*]pyridine **10** afforded a configurationally stable adduct which could be washed to remove the basic urea by-product (**Scheme 1**) <2001TA1589>. Other recent examples in this area include <2001OL1621, 2004JOC62, 2003JOC2290, 2006EJO1563, and 2005CC4922>.



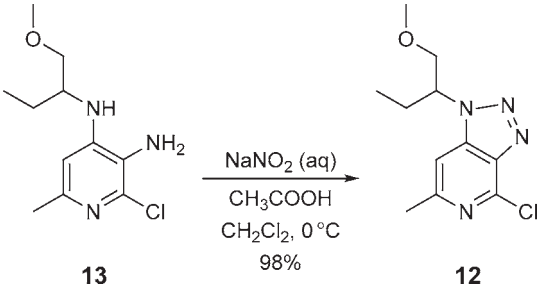
Scheme 1

10.10.9 Ring Synthesis from Monocyclic Heterocycles

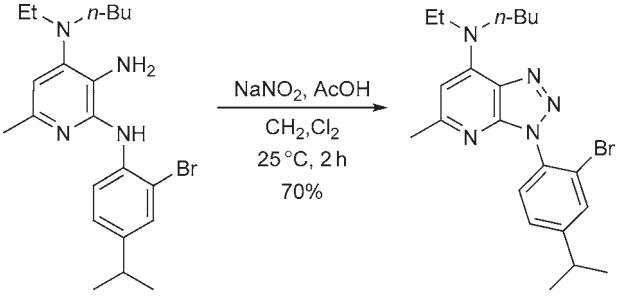
10.10.9.1 Synthesis by Formation of the Five-Membered Ring

10.10.9.1.1 Triazolopyridines

The synthesis of a large number of triazolopyridines using the original Chichibabin approach was reported in <1996CHEC-II(7)363>. Recent examples include Kumar's synthesis of the triazolopyridine **12** by treatment of the pyridine **13** with sodium nitrite and formic acid (Equation 7) <2006BMC4029>, and Chorvat and Bakthavatchalam's synthesis of **14** (Equation 8) <1999JME833>.

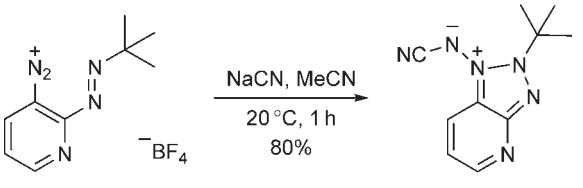


13 **12** (7)



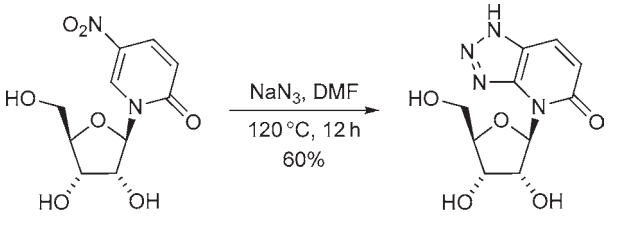
14 (8)

A novel method for the production of triazolopyridines has been reported by Churakov <2004EJO4797>. Treatment of the tetrafluoroborate salt **15** with sodium cyanide affords the product **16** in good yield (Equation 9).



15 **16** (9)

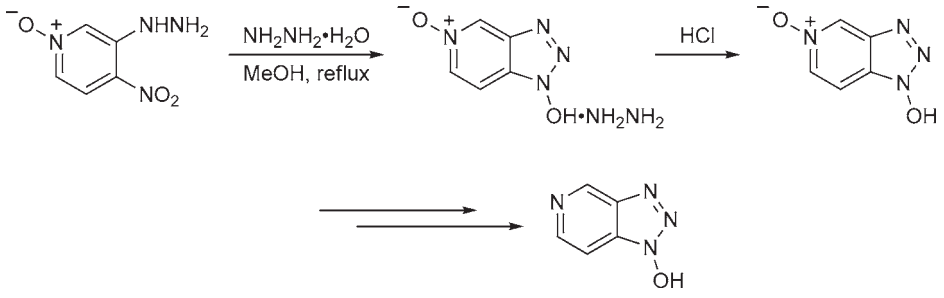
Another useful route for the formation of triazolopyridines and triazolopyridones involves the treatment of nitropyridone **17** with sodium azide to afford **18** (Equation 10) <2005JME6454>.



17 **18** (10)

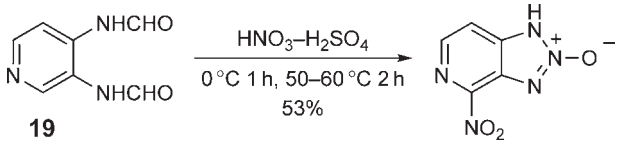
10.10.9.1.2 Triazolopyridine N-oxides and N-hydroxytriazolopyridines

A related approach to the synthesis of triazolopyridone **18** has been used in the formation of 5- and 6-HOAt <2000OL2253>. Treatment of a nitrophenylhydrazine with hydrazine hydrate affords the corresponding triazolopyridine *N*-oxide, and addition of acid and subsequent manipulations afford the *N*-hydroxytriazolopyridine; unfortunately, no yields were reported for these reactions (**Scheme 2**). The 6-isomer was prepared in a similar manner; however, in this case protection of the pyridine nitrogen as the *N*-oxide was not required.



Scheme 2

Reaction of the bis-formamide **19** with nitric acid in concentrated sulfuric acid has been reported by Yutilov and Smolyar <2004RJO1526>. Interestingly, the product is reported to decompose by explosion above 225 °C (Equation 11).



(11)

10.10.9.1.3 N-Amino[1,2,3]triazolopyridines

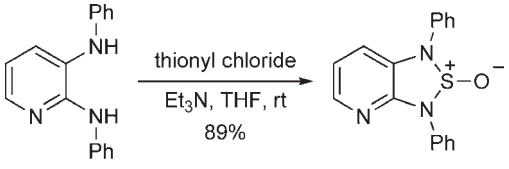
No further advances in this area have been reported since the publication of <1996CHEC-II(7)363>.

10.10.9.1.4 [1,2,3]Thiadiazolopyridines

No further advances in this area have been reported since the publication of <1996CHEC-II(7)363> (see for a new example <2006PS(181)533>).

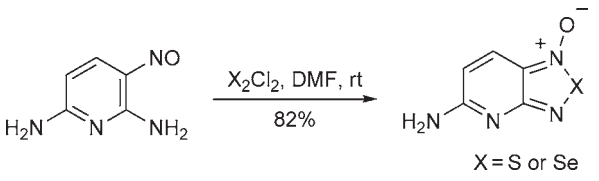
10.10.9.1.5 [1,2,5]Thiadiazolopyridines and [1,2,5]selenadiazolopyridines

1,2-Diphenylthiadiazolo[3,4-*b*]pyridin-2-one **20** has been prepared in good yield by treatment of the bis-amine **21** with thionyl chloride (Equation 12) <2004JOC7753>.



(12)

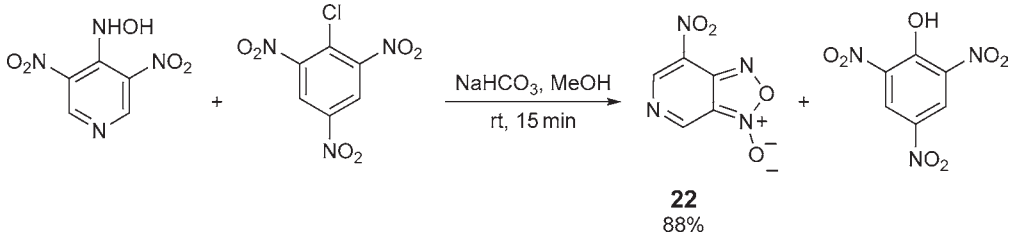
A range of 1,2,5-thia- and -selenadiazole *N*-oxides have been prepared from nitroso- and isonitrosopyrimidines and diazolopyridines (Equation 13) <2005RJC457>.



(13)

10.10.9.1.6 [1,2,5]Oxadiazolo[3,4-*b*]pyridines, [1,2,5]oxadiazolo[3,4-*c*]pyridines, and N-oxides

Reaction of 3,5-dinitro-4-hydroxyaminopyridine with picryl chloride in the presence of base affords the oxadiazolopyridine **22** and picric acid (Equation 14) <2000CHE1003>.



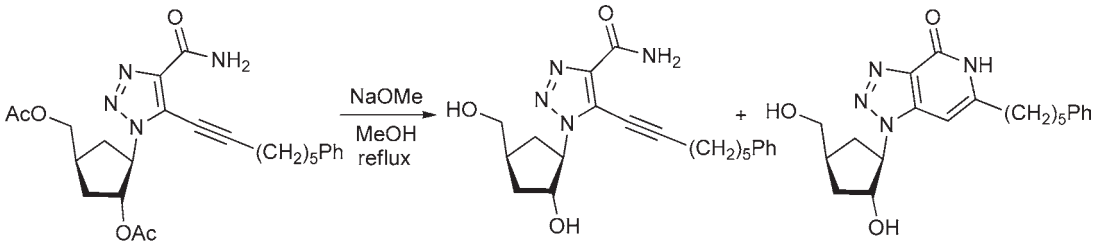
22
88%

(14)

10.10.9.2 Synthesis by Formation of the Six-Membered Ring

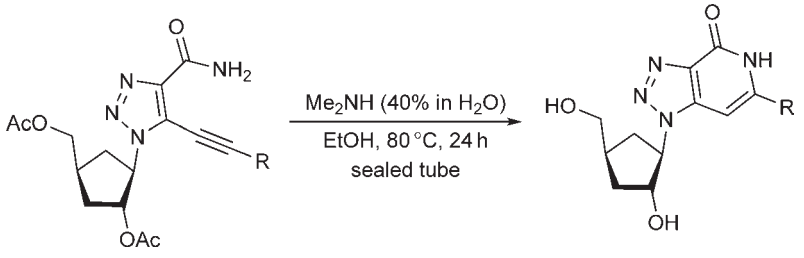
10.10.9.2.1 Triazolopyridines

A triazolopyridone has been prepared from substituted 1,2,3-triazoles using sodium methoxide, with the deprotected deoxycarbanucleosides **23** being the original desired product (Equation 15) <2005T11744>. Modification of the reaction conditions using dimethylamine in a sealed tube, under Minakawa's conditions produced a range of triazolopyridones (Equation 16 and **Table 1**).



23
63%

(15)

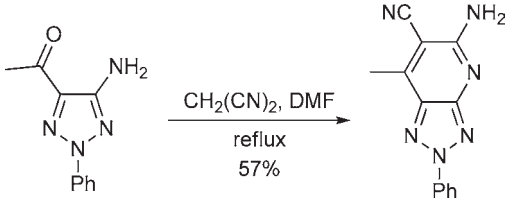


(16)

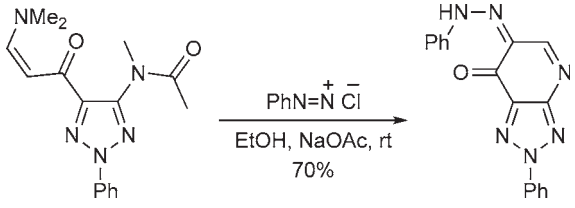
Table 1 Formation of a range of triazolopyridone deoxycarbanucleosides (Equation 16)

R	*Yield* (%)
C_3H_7	56
C_4H_9	60
C_5H_{11}	62
C_8H_{17}	51
Ph	72
$PhCH_2$	51
$Ph(CH_2)_3$	66
$Ph(CH_2)_5$	67

Several 1,2,3-triazolo[4,5-*b*]pyridines have been prepared by Al-Mousawi and Moustafa by treatment of the corresponding triazole with either malononitrile (Equation 17) or benzenediazonium chloride (Equation 18), respectively <2007BJO12>.



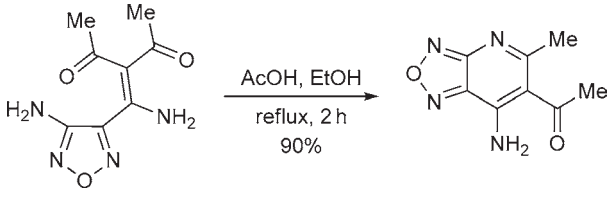
(17)



(18)

10.10.9.2.2 [1,2,5]Thiadiazolopyridines, [1,2,5]selenadiazolo[4,5-*c*]pyridines, and [1,2,5]oxadiazolo[4,5-*c*]pyridines

There have been no further advances in the area of [1,2,5]thiadiazolopyridines, [1,2,5]selenadiazolo[4,5-*c*]pyridines, and [1,2,5]oxadiazolo[4,5-*c*]pyridines since the publication of <1996CHEC-II(7)363>. However, Sheremetev and Dorokhov have reported the synthesis of a range of oxadiazolopyridines by cyclization of the corresponding enaminodione with acetic acid (Equation 19) <2001RCB1280>.



(19)

10.10.10 Ring Synthesis by Transformation of Another Ring

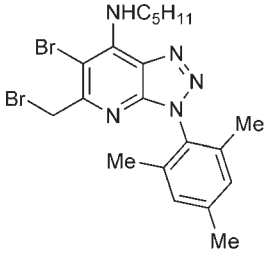
Several examples for the synthesis of triazolo- and thiadizolopyridines by transformation of another ring were reported in <1996CHEC-II(7)363>. There have been no further advances in this area since the publication of <1996CHEC-II(7)363>.

10.10.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

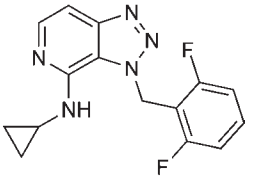
As reported by Jones in <2002AHC(83)2> the most versatile route to 1,2,3-triazolo[4,5-*b*] and [1,2,3]-triazolo[4,5-*c*]pyridines is through the diaozatization of 2,3-diamines, (see Section 10.10.9.1.1). The corresponding *N*-oxides are perhaps most conveniently synthesized from 2,3-nitrohydrazines, which installs the *N*-oxide bond without the need to oxidize the corresponding amine (see e.g., Section 10.10.9.1.2). There are very few reports on the synthesis of [1,2,3]thiadiazolopyridines and the most convenient method for the synthesis of this class of compounds appears to be through electrocyclization of *ortho*-diazonium thiolates generated *in situ* (see Section 7.10.9.1.4; <1996CHEC-II(7)363>). [1,2,5]Thiadiazolopyridines and [1,2,5]selenadiazolopyridines are more common and can easily be prepared from diaminopyridines. Perhaps the most convenient method for the synthesis of either the sulfur or selenium derivatives is through condensation of the corresponding sulfur or selenium dichloride and the required diaminopyridine (Equation 13) <2005RJC457>. Oxadiazolopyridines can be generally prepared by two methods: (1) thermolysis of *ortho*-azidonitropyridines or (2) oxidative cyclization of *ortho*-nitroamines, both of which can give excellent product yields (see Section 7.10.9.1.6; <1996CHEC-II(7)363>).

10.10.12 Important Compounds and Applications

Several of the heterocyclic systems presented in this and the original chapter have found use as, or have been intermediates for, important compounds with biological activity. Compounds such as **24** have been used as corticotropin-releasing factor (CRF) receptor antagonists <1998WO08847> and **25** has been used to study CRF receptor binding <1999JME833>.

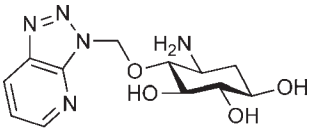


24



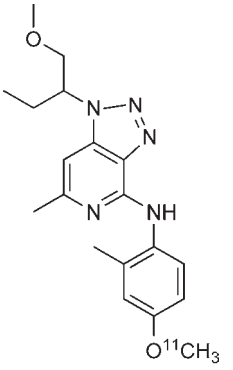
25

Several neamine mimetics (**26** for example) for RNA recognition have been prepared which show lower toxicity than neomycin B <2001OL1621>.



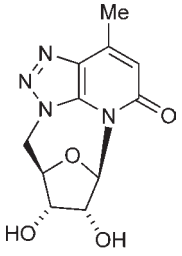
26

Radiolabeled [^{11}C]SN003 **27** has been evaluated as a photoelectron transfer (PET) ligand for CRF_1 receptors <2006BMC4029>.



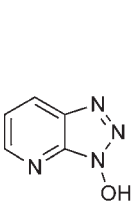
27

Several ribofuranosyl triazolopyridines have been screened against the hepatitis C virus (HCV) and **28** was found to be more effective in a HCV subgenomic replicon cell-based assay than the known lead compound <2005JME6454>. Several triazolopyridines have also been used as herbicides and microbiocides <2002AHC(83)2>.

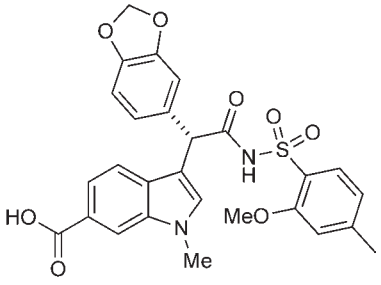


28

HOAt, as mentioned in <1996CHEC-II(7)363>, is still used as an excellent peptide coupling reagent. The recent publication <2001TA1589> discussed in Section 10.10.8.1, highlighting the suppression of racemization in a range of coupling reactions will only serve to increase the number of reports using this reagent. For example, the selective endothelin-A antagonist **29** was prepared using HOAt **10** <2001TA1589>.

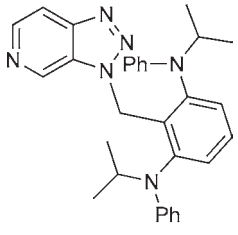


10



29

Compound **30** has been used as a catalyst for polymerization <1998WO40420>.



30

References

1983AHC(34)79 G. Jones and D. R. Sliskovic; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1983, vol. 34, p. 79.

1984CHEC(6)400 R. M. Paton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 400.

1984CHEC(6)415 R. M. Paton; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 415.

1984CHEC(6)524 L. M. Weinstock and I. Shinkai; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 524.

1984CHEC(6)712 K. Undheim; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 712.

1984CHEC(6)731 K. Undheim; in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 6, p. 731.

1996CHEC-II(7)363 V. J. Lee; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 363.

1997CC1851 Y. Yamashita, K. Ono, M. Tomura, and K. Imaeda, *Chem. Commun.*, 1997, 1851.

1998JOC9678 F. Albericio, J. M. Bofill, A. El-Faham, and S. A. Kates, *J. Org. Chem.*, 1998, **63**, 9678.

1998JPR581 A. Speicher, T. Klaus, and T. Eicher, *J. Prakt. Chem.*, 1998, **340**, 581.

1998WO08847 Y. L. Chen (Pfizer Inc., Y. Y. Chen USA) *PCT Int. Appl.*, WO 08847 (1998) (*Chem. Abstr.*, 1998, **128**, 204902s).

1998WO40420 C. M. Killian, J. P. Medevitt, P. B. MacKenzie, L. S. Moody, and J. A. Ponasik, Jr., (Eastman Chemical Co. USA). *PCT Int. Appl.*, WO 40420 (1998) (*Chem. Abstr.*, 1998, **129**, 261037h].

1999JME833 R. J. Chorvat, R. Bakthavatchalam, J. P. Beck, P. J. Gilligan, R. G. Wilde, A. J. Cocuzza, F. W. Hobbs, R. S. Cheeseman, M. Curry, J. P. Rescinito, P. Krenitsky, D. Chidester, J. A. Yarem, J. D. Klaczkiewicz, C. N. Hodge, P. E. Aldrich, Z. R. Wasserman, C. H. Fernandez, R. Zaczek, L. W. Fitzgerald, S.-M. Huang, H. L. Shen, Y. N. Wong, B. M. Chien, C. Y. Quon, and A. Arvanitis, *J. Med. Chem.*, 1999, **42**, 833.

2000CHE1003 O. R. Klyuchnikov, F. G. Khairutdinov, V. V. Golovin, and I. F. Falyakhov, *Chem. Heterocycl. Comp.* (*Engl. Transl.*), 2000, **36**, 1003.

2000JOC7391 F. Terrier, M. Sebban, R. Goumont, J. C. Hallé, G. Moutiers, I. Cangelosi, and E. Buncel, *J. Org. Chem.*, 2000, **65**, 7391.

2000JPO480 P. Cmoch, B. Kamienski, K. Kamienska-Trela, L. Stefaniak, and G. A. Webb, *J. Phys. Org. Chem.*, 2000, **13**, 480.

2000OL2253 L. A. Carpinoa, H. Imazumia, B. M. Foxman, M. J. Vela, P. Henklein, A. El-Faham, J. Klosed, and M. Bienert, *Org. Lett.*, 2000, **2**, 2253.

2000T4437 P. Li and J-C. Xu, *Tetrahedron*, 2000, **56**, 4437.

2001JRS109 B. Pergolese and A. Bigotto, *J. Raman Spectrosc.*, 2001, **32**, 109.

2001OL1621 Y. Ding, S. A. Hofstadler, E. E. Swayze, and R. H. Griffey, *Org. Lett.*, 2001, **3**, 1621.

2001RCB1280 L. S. Vasil'ev, A. B. Sheremetev, N. K. Khoa, Z. K. Dem'yanets, and V. A. Dorokhov, *Russ. Chem. Bull.*, 2001, **50**, 1280.

2001TA1589 D. Ellis, *Tetrahedron Asymmetry*, 2001, **12**, 1589.

2002AHC(83)2 G. Jones; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Elsevier, Amsterdam, 2002, vol. 83, p. 2.

2002CPL(354)173 T. Koga, A. Takase, S. Yashuda, S. Yamashita, H. Gorohmaru, T. Thiemann, S. Mataka, and K. Takahashi, *Chem. Phys. Lett.*, 2002, **354**, 173.

2003AGE3409 Y. Ding, S. A. Hofstadler, E. E. Swayze, L. Risen, and R. H. Griffey, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3409.

2003JOC2290 S. Thust and B. Koksch, *J. Org. Chem.*, 2003, **68**, 2290.

2003OBC2192 R. Goumont, E. Jan, M. Makosza, and F. Terrier, *Org. Biomol. Chem.*, 2003, **1**, 2192.

2004EJO4797 D. L. Lipilin, O. Y. Smirnov, A. M. Churakov, Y. A. Strelenko, A. Y. Tyurin, S. L. Ioffe, and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2004, 4794.

2004JOC62 L. A. Carpino, J. Xia, C. Zhang, and A. El-Faham, *J. Org. Chem.*, 2004, **69**, 62.

2004JOC7753 J. T. Kuethe, A. Wong, and I. W. Davies, *J. Org. Chem.*, 2004, **69**, 7752.

2004RJO1526 Y. M. Yutilov and N. N. Smolyar, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 1526.

2005AGE7089 M. H. V. Huynh, M. A. Hiskey, D. E. Chavez, and R. D. Gilardi, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 7089.

2005CC4922 S. R. Vogel, C. Deck, and C. Richert, *J. Chem. Soc., Chem. Commun.*, 2005, 4922.

2005JME6454 P. Wang, J. Du, S. Rachakonda, B.-K. Chun, P. M. Tharnish, L. J. Stuyver, M. J. Otto, R. F. Schinazi, and K. A. Watanabe, *J. Med. Chem.*, 2005, **48**, 6454.

2005JOC6242 F. Terrier, S. Lakhdar, T. Boubaker, and R. Goumont, *J. Org. Chem.*, 2005, **70**, 6242.

2005RJC457 A. A. Yavolovskii, V. D. Kishichenco, O. A. Olinichenko, and E. I. Ivanov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2005, **75**, 1526.

2005T11744 N. Joubert, R. F. Schinazi, and L. A. Agrofoglio, *Tetrahedron*, 2005, **61**, 11744.

2006BMC4029 J. S. D. Kumar, V. J. Majo, G. M. Sullivan, J. Prabhakaran, N. R. Simpson, R. L. Van Heertum, J. J. Mann, and R. V. Parsey, *Bioorg. Med. Chem.*, 2006, **14**, 4029.

2006EJO1563 A. El-Faham, S. N. Khattab, M. Abdul-Ghani, and F. Alberico, *Eur. J. Org. Chem.*, 2006, 1563.

2006PS(181)533 S. H. B. Naik, M. S. Ramesha, B. V. Swetha, and T. R. Roopa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2006, **181**, 533.

2007BJO12 S. M. Al-Mousawi and M. S. Moustafa, *Beilstein J. Org. Chem.*, 2007, **3**, 12.

Biographical Sketch



Benjamin R. Buckley was born in Nottingham and studied at Manchester Metropolitan University, where he obtained a BSc in 1999 and Loughborough University where he obtained his PhD in 2003 under the supervision of Prof. Philip C. Bulman Page. Following this he worked as postdoctoral research associate and as a research fellow at Loughborough University before being appointed to his present position as lecturer in organic chemistry (RCUK Fellow) in 2007. His scientific interests include all aspects of asymmetric synthesis, in particular asymmetric organocatalysis.



Stephen P. Neary was born in Letterkenny and studied at Dublin City University obtaining first class honours in applied chemistry. In 2007 he began his PhD at Loughborough University under the supervision of Dr. Benjamin Buckley.

10.11
Bicyclic 5-6 Systems: Purines

I. Collins and J. J. Caldwell
The Institute of Cancer Research, Sutton, UK
© 2008 Elsevier Ltd. All rights reserved.

10.11.1 Introduction 526
10.11.2 Theoretical Methods 527
10.11.3 Experimental Structural Methods 528
10.11.3.1 X-Ray Diffraction 528
10.11.3.2 Proton NMR Spectra 528
10.11.3.3 Carbon-13 NMR Spectra 530
10.11.3.4 Nitrogen-15 NMR Spectra 530
10.11.3.5 UV and UV Photoelectron Spectra 532
10.11.3.6 IR and Raman Spectra 532
10.11.3.7 Mass Spectra 532
10.11.3.8 EPR Spectra 533
10.11.4 Thermodynamic Aspects 533
10.11.4.1 Tautomerism 533
10.11.4.2 Thermochemistry 533
10.11.5 Reactivity of Fully Conjugated Rings 533
10.11.5.1 Thermal and Photochemical Reactions 533
10.11.5.2 Reactions with Electrophiles 534
10.11.5.2.1 N-Alkylation and arylation 534
10.11.5.2.2 C-Alkylation and arylation 543
10.11.5.2.3 Nitration 543
10.11.5.2.4 Oxidation of ring atoms 543
10.11.5.2.5 Halogenation 545
10.11.5.2.6 Metal complexes 547
10.11.5.3 Reactions with Nucleophiles 549
10.11.5.3.1 Reduction 549
10.11.5.3.2 Amination and hydrolysis 549
10.11.5.3.3 Reaction with carbon nucleophiles 551
10.11.5.3.4 Deprotonation (nucleophilic attack at hydrogen) 551
10.11.5.4 Reactions with Free Radicals 553
10.11.5.5 Intermolecular Cyclic Transition State Reactions 554
10.11.6 Reactivity of Nonconjugated Rings 554
10.11.7 Reactivity of Substituents Attached to Ring Carbon Atoms 554
10.11.7.1 Alkyl, Alkenyl, and Alkynyl Derivatives 554
10.11.7.2 Cyanopurines 557
10.11.7.3 Aminopurines 558
10.11.7.3.1 Alkylation and arylation 558
10.11.7.3.2 Displacement reactions 559
10.11.7.4 Halopurines 561
10.11.7.4.1 Displacement by heteroatom nucleophiles 561
10.11.7.4.2 Carbon–carbon bond formation 569
10.11.7.5 Thiopurines 575

10.11.7.6 Purines with a Fused Heterocyclic Ring System 577
10.11.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms 578
10.11.9 Ring Synthesis from Acyclic Precursors 579
10.11.10 Ring Synthesis by Transformation of Another Ring 580
10.11.10.1 Synthesis from Imidazoles 580
10.11.10.2 Synthesis from Pyrimidines 582
10.11.10.3 Synthesis from Triazines 585
10.11.11 Critical Comparison of Synthetic Routes 586
10.11.12 Important Compounds and Applications 587
10.11.12.1 Naturally Occurring Purines 587
10.11.12.2 Purines in Drug Design 588
10.11.13 Further Developments 590
References 590

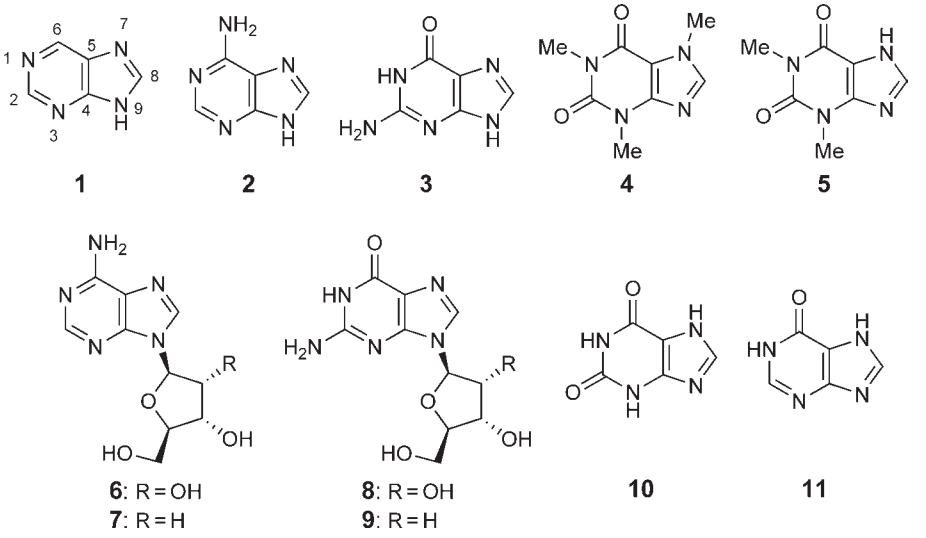
10.11.1 Introduction

The chemistry of purine nucleosides and nucleotides continues to be central to the exploration of the structure, biochemistry, and biological function of polynucleotides and nucleic acids. Moreover, the purine bicycle continues to increase in importance as a structural component in the development of new synthetic pharmacological and therapeutic agents. Arguably there has been a renaissance in the field of purine synthesis since the preceding account in this area was published in CHEC-II(1996) <1996CHEC-II(7)397>, driven in large part by the requirement for substantial numbers of new, polysubstituted purine ligands for basic biomedical research, and by the search for appropriate synthetic routes to prepare them. This chapter concentrates particularly on these synthetic methods and on the increased understanding of purine reactivity that has developed in parallel with the synthetic procedures. The applications of purines in the important contemporary field of structure-based drug design are also highlighted. There have been further improvements in the experimental methods used for the determination of the structure of synthetic purines, newly isolated natural products, and purines incorporated into polynucleotides, especially in the use of heteronuclear NMR experiments. Continuing advances in theoretical chemistry have been applied to better characterize the tautomeric behavior of purines. The chemistry of nucleosides and nucleotides is a large area, much of which is beyond the scope of this work. The focus here is on the behavior, transformations, and preparations of the purine bicycle. Although examples where this occurs in the context of simple nucleosides and nucleotides have been incorporated to illustrate general principles, the chemistry of the sugar moieties of nucleosides is not addressed here (see Volume 3). Selected reviews describing specific areas in more detail are collated in **Table 1**.

Table 1 Purine reviews 1995–2006

Subject	*Author(s)*	*Reference*
NMR	Marek and Sklenar	2005MI201
Tautomerism	Sigel	2004PAC1869
Synthesis	Seela *et al.*	2004SOS945
Synthesis	Ewing and Mackenzie	B-1999MI127
Library generation	Bork *et al.*	2004MI245
Pd-cat. C–N bond formation	Lakshman	2005CSY83
Nucleoside synthesis	Vorbruggen and Ruh-Polenz	2000OR1
Enzymatic modifications	Ferrero and Gotor	2000CRV4319
Nucleosides	Ichikawa and Kato	2001CME385
Nucleosides	Ferrier *et al.*	2002MI275
Carbonucleosides	Schneller	2002MI1087
Carbonucleoside synthesis	Crimmins	1998T9229
Natural products	Rosemeyer	2004CBI361
Receptors	Ralevic and Burnstock	1998MI413
Biological activity	Legraverend and Grierson	2006BMC3987
Biological activity	Haystead	2006MI1117
Purine Hsp90 ligands	Chiosis	2006MI1183

The purine ring-numbering scheme, **1**, and structures of some simple purines, viz. adenine **2**, guanine **3**, caffeine **4**, theophylline **5**, adenosine **6**, 2′-deoxyadenosine **7**, guanosine **8**, 2′-deoxyguanosine **9**, xanthine **10**, and hypoxanthine **11**, are shown.



10.11.2 Theoretical Methods

The mechanism of the inverse electron demand Diels–Alder reaction of 1,3,5-triazines with amino-substituted imidazoles to form purines was examined in both the gas and the solution phase at the MP2/6-311++G**//B3LYP/6-31G* level <2005JOC998, 2001JOC6029>. Two proposed stepwise mechanisms were studied, with an initial Diels–Alder reaction followed by ammonia extrusion and finally a retro-Diels–Alder pathway shown to be favored by as much as 50 kcal mol^{-1} over an alternative Diels–Alder–retro-Diels–Alder–ammonia-extrusion route. A reason for the relatively low reactivity of purine to electrophilic substitution reactions was postulated based on density functional theory (DFT)/B3LYP methods <2005TL6333>. Assuming frontier orbital control for the reaction, calculations showed the highest occupied molecular orbital (HOMO) of purine to be a σ-orbital, in contrast to more reactive 9-methyladenine or 9-methylxanthine where the HOMOs in both instances were calculated to be π-orbitals. The basicities of adenine derivatives were estimated using combined gas-phase DFT and polarizable continuum model calculations <2002JOC790>. The parameters developed in this approach were found to accurately predict the pK_a values of ATP derivatives determined experimentally by ^{15}N nuclear magnetic resonance (NMR) methods (see Section 10.11.3.4). An unusual geometric arrangement observed in crystallographic studies of human purine nucleoside phosphorylase with several transition state analogues, which showed three oxygen atoms lying in a close stack, was investigated using molecular dynamics (MD) and combined quantum-mechanical/molecular mechanical molecular dynamics (QM/MM-MD) methods <2004JA15720>. The studies showed that the close proximity of the three oxygen atoms, two from the ribosyl unit and one from a phosphate group, allowed electron density to be pushed toward the purine ring resulting in stabilization of the incipient oxacarbenium transition state.

The tautomerization of xanthine oxidase substrates, in particular hypoxanthine, was studied from a semi-empirical and *ab initio* level, as well as DFT/B3LYP <1996JOC5964>. The relative stability of the tautomers of hypoxanthine suggested that the bioactive species was the N(1)–H,N(9)–H keto tautomer, an interpretation supported by subsequent work on the interaction of substrates and inhibitors with xanthine oxidase <1997JA3007>. A study on the intramolecular proton transfer in monohydrated and dehydrated tautomers of guanine was conducted using an initial Hartree–Fock level of theory at the standard 6-31G(d) basis set, followed by single point calculations <1998JA5024>. As well as obtaining structural parameters for N(9)–H guanine monohydrate in good correspondence with experimental data, it was shown that water had a key role in controlling the nonplanarity of the hydroxy forms of guanine as well as the oxo tautomers. An example of the importance of free energy of hydration calculations in drug design has been shown, where the increased susceptibility of 8-aza-9-methylpurine riboside to hydration over 9-methylpurine riboside, with a $\Delta\Delta G_{hyd}$ of -7.1 kcal mol^{-1}, correlated well with the increased potency of the 8-aza analogue as an adenosine deaminase inhibitor

when the relative free energy of binding was also taken into consideration <1998JA3295>. The differences in free energy of hydration were calculated using a combined quantum-mechanical and free energy perturbation approach.

10.11.3 Experimental Structural Methods

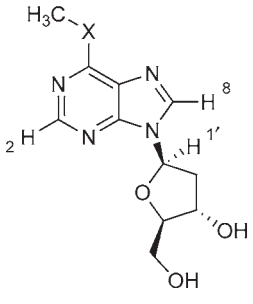
10.11.3.1 X-Ray Diffraction

A major updated statistical survey was compiled of the geometric parameters of neutral and protonated purine high-resolution structures in the Cambridge Crystallographic Database <1996JA509>. Eighty-four new purine-containing structures were analyzed and compared with an earlier data set, with the distribution of bond lengths and angles observed to be consistent with that seen before. The study provided target values for purine bond lengths and angles that should be useful in the constrained refinement of nucleic acid structures, or for parametrization of molecular modeling force fields. In general, the large number of purine structures solved in the past decade has produced parameters for the purine rings that show coplanarity of the purine ring atoms with unremarkable bond lengths and angles. However, distortions of the expected geometry have sometimes been observed. For example, a comparison of 9-(carboxymethyl)-2,6-chloropurine <1995AXC2383>, 7-(carboxymethyl)-6-chloropurine <1998AXC1316>, and 9-(carboxymethyl)-6-chloropurine <1998AXC1907> showed alternating changes in the internal bond angles, particularly of the six-membered ring, of between 0.4° and 4° depending on the substitution pattern. A comparison of the structures of guaninium dichloride (2-amino-1,6-dihydro-6-oxo-9*H*-purine-3,7-diium dichloride) with the monohydrochloride <1999AXC467> showed that the additional protonation at N-3 led to an increase in the C(2)–N(3) and N(3)–C(4) bond lengths of 0.025 and 0.017 Å, respectively. The internal angle at N-3 increased by 5.3°, while the internal angles at C-2 and C-4 correspondingly decreased by 3.9° and 4.9°. A distortion of the bond lengths and angles of the purine bicycle was observed when an additional imidazole ring was fused to the six-membered ring in the acyclovir analogue 3-[(2-hydroxyethoxy)methyl)]-6-methyl-3*H*-imidazolo[1,2-*a*]purin-9(5*H*)-one, although the tricycle retained planarity <2001AXC767>. The observation of a coplanar conformation of the two heterocycles in several unsubstituted 6-(azolyl)purines, for example, 6-(1,2,4-triazol-1-yl)purine with an interplanar angle of 1.4°, was proposed as a basis for developing a selective alkylation protocol for alkylation of N-9 versus N-7 where coplanarity leads to the shielding of N-7 by an azolic C–H bond <2006JOC4216, 2006JOC7773, 2006JOC8901>; see Section 10.11.5.2.1.

The first structures of anhydrous, uncomplexed theophylline <1997AXC777> and theobromine <1998AXC1980> were determined, in which the purines displayed typical geometries. The tautomeric structure of 1,3-dimethylisoguanine (6-amino-1,3-dimethyl-1*H*-purin-2(3*H*)-one), isolated from several natural sources (see Section 10.11.12.1) was reassigned as a result of a crystallographic structure determination which defined the correct positioning of both hydrogens on the exocyclic amino group <1999AXC1585>. The refinement of both hydrogens to the amino functionality was supported by the intermolecular hydrogen-bonding patterns seen within the unit cell.

10.11.3.2 Proton NMR Spectra

The effect of the sulfur oxidation state on the proton NMR resonances of 6-methylthiopurine deoxyribonucleosides has been reported <1996T10737>, showing that the chemical shifts of the ring protons moved downfield as the oxidation state increased and the substituent became more electron-withdrawing (**Figure 1**). Similarly, the effect on purine proton resonances of 8-fluoro substitution has been detailed <1996JA10408>.

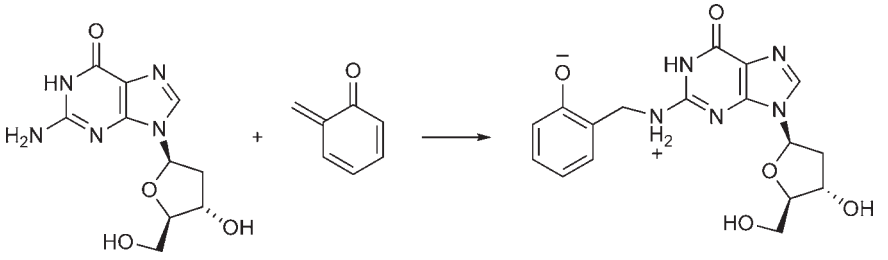


	Chemical shift δ (ppm)		
X	*H*-1′	*H*-2	*H*-8
S	6.45	8.75	8.65
SO	6.54	9.13	8.95–8.96*
SO_2	6.57	9.17	9.07

*Racemic mixture of *R*- and *S*-sulfoxides.

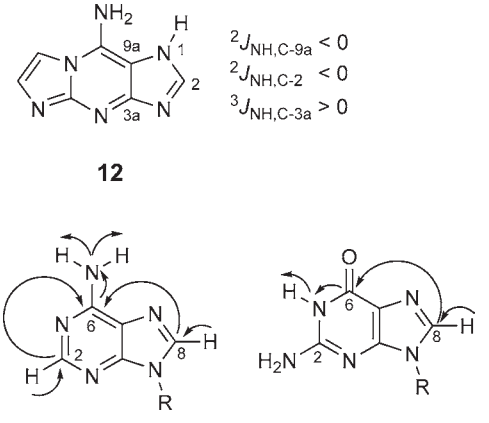
Figure 1

The acquisition of long-range $^{1}H–^{13}C$ heteronuclear correlation data to elucidate the substitution patterns in purine products has become routine, and many of the synthetic chemistry papers discussed in this chapter make use of this technique. Although individual examples are too numerous to catalog here, the utility of this approach can be seen in early papers concerned with regioselective cross-coupling reactions to 2,6-dichloropurines, where heteronuclear multiple bond correlation (HMBC) and heteronuclear multiple quantum correlation (HMQC) experiments determined the position of monosubstitution following Stille reactions <1995TL1945, 1996T5625>. Similarly, the preparation of 2-(tributylstannyl)-6-chloro-9-(tetrahydropyran-2-yl)purine by regioselective lithiation of 6-chloro-9-(tetrahydropyran-2-yl)purine was confirmed through three-bond correlation of the remaining protons on the purine to the ring carbon atoms <2004OBC665>. The sites of alkylation of 2′-deoxyadenosine and 2′-deoxyguanosine by a reactive quinone methide were clarified by HMBC experiments, showing in both cases that reaction occurred at the exocyclic amino substituent (Equation 1) <1999JA6773>.



(1)

A modification of the HMBC experiment was devised to distinguish $^{2}J_{H,C}$ and $^{3}J_{H,C}$ couplings from the signs and magnitudes of the cross-peaks in the correlation spectrum. This procedure allowed the unambiguous assignment of the major tautomer of tricyclic compound **12** in dimethyl sulfoxide (DMSO) as that bearing a proton on N-1 <2004OL2673>. A modified HCCNH-TOCSY pulse sequence was used to assign the exchangeable protons of adenine and guanine bases within nonhelical RNA oligomers (TOCSY = total correlated spectroscopy) <1996JA689>. In this process, demonstrated on a ^{13}C, ^{15}N uniformly labeled RNA 14-mer, magnetization was transferred from the independently assigned H-8/C-8 and/or H-2/C-2 resonances of the purines through C-6 to the imino and amino NH protons (**Figure 2**). Correlations and assignments for all of the guanine/adenine residues (six in total) in the 14-mer were observed. Monitoring of the chemical shift of the exchangeable amino protons of guanine allowed the spectroscopic titration of a simple guanosine nucleoside and a synthetic 8-(pyrrol-2-yl)guanosine nucleoside, providing evidence of a Hoogsteen-type three-point hydrogen-bonding interaction in the hetero-dimeric complex <2004JA11460>. Time-dependent saturation transfer nuclear Overhauser effect (NOE) experiments were used to assign the exchangeable OH and NH resonances of the inhibitor [^{15}N-1]-6-hydroxyl-1,6-dihydropurine ribonucleoside when bound to the enzyme adenosine deaminase, showing that the O(6)–H and N(1)–H protons were strongly hydrogen-bonded to the enzyme, consistent with the proposed enzymic mechanism <2004JA1952>.

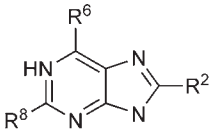


12

Figure 2

10.11.3.3 Carbon-13 NMR Spectra

An exhaustive set of trisubstituted purines bearing combinations of methyl or phenyl groups at C-2, C-6, and C-8 was characterized by HMBC and NOE experiments, from which a straightforward correlation of the substitution pattern with the ^{13}C chemical shifts of the methyl group or the *ipso*-carbons of the phenyl substituents was observed (**Figure 3**) <2004S2869>. The methyl carbons resonated at ca. 16, 19, or 26 ppm when attached through positions 8, 6, or 2, respectively. The *ipso*-carbons of the phenyl groups appeared at ca. 130, 134–136, or 138 ppm when the group was attached through positions 8, 6, or 2, respectively. The chemical shifts of the C-2, C-5 and C-6 carbons of 2′-deoxyguanosine were observed to shift in the presence of palladium(II) acetate and tris(2,4-xylyl)phosphine, indicating coordination of the palladium–ligand complex by the purine base <2005JOC6378>. The magnitude of the shifts was greatest for C-2 ($\Delta\delta = -5.7$ ppm), followed by C-6 ($\Delta\delta = -2.0$ ppm), implying that coordination was through N-1 and/or O-6 of the purine. The observation of this coordination was important in the context of interpreting the inhibitory effects of purine substrates in some palladium-catalyzed cross-coupling reactions (see Section 10.11.7.4.2).



R^2, R^6, R^8 = Me or Ph

	Chemical shift δ (ppm)	
	$\delta\ ^{13}C_{Me}$	$\delta\ ^{13}C_{ipso\text{-}Ph}$
R^2	~26	~138
R^6	~19	~134–136
R^8	~16	~130

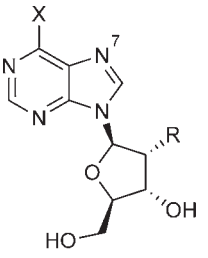
Figure 3

The incorporation of a ^{13}C label into 3,9-dimethyl[5-^{13}C]uric acid was used to elucidate the structure of the products arising from chlorination of 3,9-dimethyluric acid <2003OL4265> (see Section 10.11.6). The increasing availability of specifically ^{13}C- and ^{15}N-labeled nucleosides through chemical synthesis (see Sections 10.11.10.1 and 10.11.10.2) has provided additional means to distinguish and assign the NMR resonances of individual purine bases within DNA or RNA oligomers, and hence to make deductions about the three-dimensional (3-D) structure. For example, the complete two- and three-bond H–C, N–C, and H–N coupling constants have been reported for 2′-β-deoxy-[8-^{13}C; amino,9-$^{15}N_2$]adenosine <1999JOC4685>. Comparison of nucleic acid oligomers containing either [1,3,NH_2-$^{15}N_3$]- or [2-^{13}C-1,3,NH_2-$^{15}N_3$]-purine nucleosides allowed the ^{13}C-2 label to function as a direct tag where present <1999JOC6575>. By this means, the ^{15}N-1 and ^{15}N-3 atoms of the residues containing the ^{13}C-2 label could be unambiguously differentiated from those in untagged bases within DNA or RNA fragments using ^{15}N NMR spectroscopy. Alternatively, the introduction of a ^{13}C-8 label into ^{15}N-7-labeled purine nucleosides served as an indirect tag for the presence of the ^{15}N-labeled residue <2003JOC8657>. Here the C(8)–N(7) coupling was too small (<1 Hz) for reliable direct observation, but 2-D ^{1}H–^{15}N NMR experiments clearly showed the couplings of H-8 to C-8 and N-7 when the ^{13}C-8 label was present.

10.11.3.4 Nitrogen-15 NMR Spectra

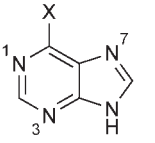
As discussed above, a number of purines bearing single or multiple specific ^{15}N labels have been prepared, allowing the ^{15}N resonances of ring nitrogens to be determined directly (**Figure 4**) <1995JA11669, 2001JOC5463, 2001JOC6472>. Values were determined indirectly for analogues of the tricylic tetrahydro[1,4]diazepino[1,2,3-*gh*]purine core of the asmarine natural products using ^{15}N–^{1}H HMBC experiments <2003T6493, 2005JOC199> (see Section 10.11.12.1). As well as being essential for structure elucidation, these measurements distinguished between the tautomeric forms (and hybridization state) of the ring nitrogens, for example $\delta_{N\text{-}1} = 136.9$ in an sp^3-hybridized C–N–H tautomer, while $\delta_{N\text{-}1} = 238.0$ in the corresponding sp^2-hybridized C=N tautomer. The ^{15}N spectra of fully ^{15}N labeled adenine suggested the presence of an N(3)–H tautomer, as well as the expected N(9)–H (major) and N(7)–H (minor) tautomers <2001JOC5463>. Among other examples, ^{15}N–^{1}H HMBC and HMQC connectivities were used to establish the regioselectivity of Suzuki couplings to 2,6-dichloro-9-isopropylpurine <2003T607>, determine the structure of the marine natural product mucronatine <2001TL7257> (see Section

10.11.12.1), prove the coordination of the anticancer compound *trans*-[$PtCl_2${(*E*)-HN=C(OMe)Me}$_2$] to adenine N-3 and guanine N-7 in dinucleotides <2002JA12854>, and investigate the structures and tautomeric states of intermediates in a synthesis of the natural product agelasine F <2005OBC1025>. In this last case, the chemical shifts of the ring nitrogen atoms in purinium cations and betaines were also deduced from the 2-D experiments (**Figure 5**).



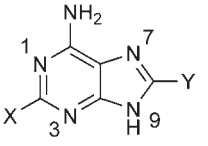
δ(ppm) relative to HNO_3 (DMSO-d_6, 40.5 MHz)

X	*R*	*N-7*
Cl	H	231.6
Cl	OH	244.7
NH_2	H	244.2
NH_2	OH	244.2



δ(ppm) relative to NH_3 (DMSO-d_6, 60.8 MHz)

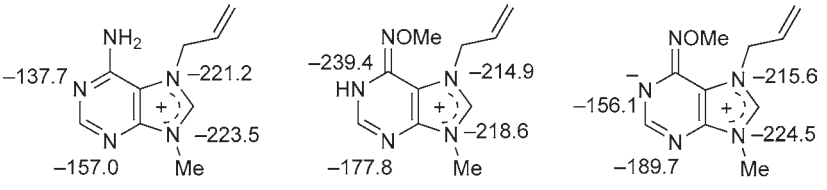
X	*N-1*	*N-3*	*N-7*	NH_2
Cl	255.2	273.5	230.4	
OH	172.6	225.9	224.8	
NH_2	234.8	227.9		79.5



δ (ppm) relative to $MeNO_2$ (DMSO-d_6, 60.8 MHz)

X, *Y*	*N-1*	*N-3*	*N-7*	*N-9*	NH_2
X, Y = H	–145.7	–151.5	–140.3	–222.6	–301.2
X = H; Y = Br	–144.8	–151.5	–139.4	–224.2	–305.1
X = $C_6H_{13}S$; Y = H	–154.5	–163.4	–140.3	–225.0	–300.3

Figure 4



^{15}N chemical shifts (relative to $MeNO_2$, 50 MHz) deduced from ^{15}N–^{1}H HMBC

Figure 5

A new heteronuclear NMR pulse sequence, the quantitative Γ(HCN) experiment, was developed to measure the glycosidic torsion angles in ^{13}C, ^{15}N-labeled oligonucleotides <2004JA1962>. This procedure, using cross-correlated relaxation rates (Γ), was found to be more accurate than proton NOE methods, leading to determinations of the glycosidic torsion angles in an RNA 14-mer of known geometry to within an accuracy of 10°. The pK_a values of 2- and 8-substituted ATP analogues were determined experimentally from measurement of ^{15}N resonances (natural abundance) as a function of pH titration <2002JOC790>. The preferred protonation site was N-1 of the purine in all the compounds studied, although for 2-thioether derivatives a mixed population of N-1 and N-7 single protonation was observed. The analogues were found to be between 0.4–1 log units less basic than ATP, except 2-chloro-ATP which was 4 orders of magnitude less basic. Good correlation with *ab inito*-calculated values of the adenine pK_a values was observed (see Section 10.11.2). The observation of chemically induced dynamic nuclear polarization (CIDNP) effects

in the ^{15}N NMR spectrum during the nitration of 6-chloropurine with trifluoroacetyl nitrate indicated the involvement of a heterolytic dissociation and radical recombination step (predominantly intermolecular) in the reaction mechanism <2005JA5957> (see Section 10.11.5.2.3).

10.11.3.5 UV and UV Photoelectron Spectra

Ultraviolet (UV) spectra have been used to distinguish between N- and S-substituents at C-6 of purine 2′-deoxyribonucleosides <1998T187>. Thus, simple 6-(thioalkyl) substituents gave characteristic λ_{max} (water) = 282–292 nm, compared to λ_{max} (water) = 277 nm for a 6-(methanesulfoxy)purine and λ_{max} (water) = 266 nm for N-bonded 6-(cysteinyl)purine. The conversion of 6-methylthiopurine incorporated within oligoribonucleotides into 6-(methanesulfoxy)purine and 6-azidopurine was followed by UV using these characteristic spectra <1996T10737>. The UV absorbtion spectra of 8-(2-arylalkyn-1-yl)purines, potential fluorescence probes for studying nucleic acid structure, depended on the electronic properties of the aryl substituents <2006TL3529>. Both electron-donating and electron-withdrawing functionality on the terminal phenyl ring red-shifted the spectra relative to the unsubstituted phenyl analogue, reflecting the expected decrease in the HOMO–LUMO gap. A tetracyclic 8-(3*H*-[1,2,3]triazol-4-yl)adenosine derivative with an extended π-system showed strong fluorescence, although a significant shift toward the UV region was seen between the excitation and emission spectra ($\lambda_{max,\ excitation} = 307$ nm, $\lambda_{max,\ emission} = 380$ nm) <2005TL6745>. Purine-containing cyanines were developed as possible fluorescent staining dyes for DNA to be used as diagnostic markers for the presence of malaria parasites <1997T12595>. The UV spectra (λ_{max}) of these materials depended primarily on the length of the conjugated system. The intensity of fluorescence was greatest in very rigid, planar analogues where dissipation of the electronic excitation energy through internal vibration and rotation modes of the aromatic components was minimized. The UV spectra and fluorescent properties of tricyclic and tetracyclic 2,6-diaminopurine etheno derivatives were examined, but the presence of the additional double bonds in the fused imadazole rings did not significantly change the UV spectral properties from those of the parent 2,6-diaminopurine <2005OBC2924>.

The excited triplet state of the *N*-(9-methylpurin-6-yl)pyridinium cation was studied by laser flash and steady-state photolysis, resulting in an assignment of transient absorption spectra to the excited triplet state (λ_{max} (water) = 550 nm) and to the *N*-(9-methylpurin-6-yl)pyridinyl radical (λ_{max} (water) = 610 nm) formed during quenching of the triplet state by sulfur-containing amino acids <1995JA127>. The near-UV spectra for 2-aminopurine, 7-methyladenine, and 9-methyladenine were each resolved into contributions from five electronic transitions, using a combination of linear dichroism, fluorescence anisotropy, and ordinary and magnetic circular dichroism techniques <1997JA3114, 1997JA12240>. The character of the lowest excited state of 2-aminopurine ($\pi\pi^*$) was found to be different to that of purine ($n\pi^*$), suggesting a basis for the different photophysics of the two compounds <1997JA3114>.

10.11.3.6 IR and Raman Spectra

The vibration spectrum of the first excited state of guanine was measured using laser desorption jet-cooled resonance-enhanced multiphoton ionization (REMPI) spectrometry <1999JA4896>. The millimeter wave spectrum of purine was collected using a free jet spectrometer, and the observed rotational spectrum was assigned to the N(9)–H tautomer <1996CPL189>.

10.11.3.7 Mass Spectra

The use of tandem liquid chromatography–mass spectrometry (LC–MS) instrumentation is now routine in synthetic chemistry laboratories, and many of the synthesis papers cited in this chapter report data on purine-containing compounds obtained in this way. Tandem LC–MS has proved particularly valuable for the high-throughput analysis (or purification by mass-directed high-performance liquid chromatography (HPLC)) of large compound libraries prepared by parallel synthesis techniques (see Sections 10.11.7.4.1 and 10.11.7.4.2). The methodology is also suited to the investigation of mixtures of complex materials, as seen in the analysis of purine-containing cyclic peptidomimetics prepared through intramolecular S_NAr reactions <2001JOC507>. Mass spectrometric fragmentation patterns have continued to be useful for determination of the structure of new natural products, as for example 3,7-dimethylisoguanine <1995TL7893> and 1,3-dimethylisoguanine <1997JNP727, 1997JNP729> isolated from marine sources (see Section 10.11.12.1).

10.11.3.8 EPR Spectra

N-tert-Butylaminoxyl radicals have been incorporated into ribo- and deoxyribonucleosides in order to introduce new spin-labeled residues into nucleic acids for use in conjunction with electron paramagnetic resonance (EPR) spectroscopy <2001JOC3513, 2005OL303>. For both 8-(*N-tert*-butylaminoxyl)- and 2-(*N-tert*-butylaminoxyl)purine ribonucleosides, the hyperfine structures of the EPR spectra were affected by the electron densities of the purine rings and varied as substituents on the ring were changed. Furthermore, the EPR spectra of 2-(*N-tert*-butylaminoxyl)-6-oxopurine deoxyribonucleoside showed a marked pH dependence between pH 6.10 and pH 10.41 <2005OL303>. The changes in the EPR spectra as pH increased were accurately simulated by assuming an increase in electron density on the nitrogen atom of the aminoxyl radical corresponding to the presence of a greater proportion of the deprotonated purine. ^{13}C electron-nuclear double resonance (ENDOR) measurements of the EPR spectrum of the unpaired electron on the catalytic molybdenum atom of the enzyme xanthine oxidase during the reaction with [^{13}C-8]-2-hydroxy-6-methylpurine have provided evidence that the enzymic mechanism does not involve formation of a direct Mo–C(8) bond <2001JA2658>.

10.11.4 Thermodynamic Aspects

10.11.4.1 Tautomerism

The tautomerization of the guanyl radical has been studied by radiolytic methods as well as by DFT calculations <2006JA13796>. The DFT calculations, at the B1B95/6-31+G** level, show tautomerization from the iminic to aminic form of the guanyl radical to occur by water-assisted proton transfer, with a calculated energy barrier of 21.3 kJ mol^{-1}, whereas direct tautomerization was calculated to be 183.7 kJ mol^{-1}, considerably higher than the measured activation energy of 23.0 kJ mol^{-1}. The tautomeric states of adenine have been addressed using ^{15}N NMR spectroscopy, which as well as confirming the N(9)–H isomer to be the major and the N(7)–H isomer the minor tautomer present in solution, also showed the existence of the N(3)–H isomer <2001JOC5463> (see Section 10.11.3.4). The existence of the N(3)–H isomer was supported by DFT calculations, taking into account solvent effects using the polarizable continuum model (PCM) and Poisson–Boltzmann self-consistent reaction field (SCRF-PB) models. NMR spectroscopy has been used to measure the levels of tautomerism of purines at temperatures of −60 °C <2004TL6259>. *N*,*N*-Dimethyl-*N*′-(7(9)*H*-purin-6-yl)formamidine was found to have an N(7)–H population of 71% and N(9)–H of 29%, whereas 6-methoxypurine had an N(7)–H presence of 18% and N(9)–H of 82%. 6-Chloropurine failed to resolve adequately at this temperature to allow an absolute determination. As part of a study on the gas-phase acidity of various sites of adenine derivatives, an analysis of the tautomeric states of the molecules showed that while adenine, 9-ethyladenine, 3-methyladenine, and *N*,*N*-dimethyladenine existed as the amino tautomer, 1-methyladenine adopted the imino form <2004JOC7018>.

10.11.4.2 Thermochemistry

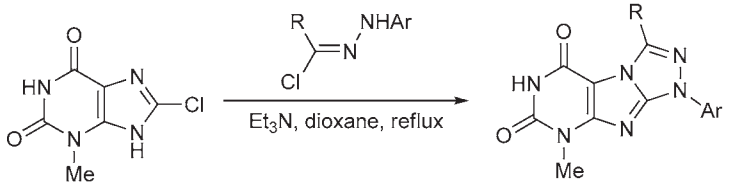
Isolobal reaction schemes were used to calculate heats of formation for azole, azine, and benzoazole, with the results, obtained as an average over a set of possible isolobal schemes, compared to experimental values <1997JST9>. A comparison to calculated semi-empirical heats of formation (using three methods: MNDO, AM1, PM3) resulted in the generation of correction terms, allowing heats of formation to be predicted for a number of other systems, including purine. Thus at the *ab initio* level the N(7)–H tautomer of purine gave a heat of formation of 73.2 kcal mol^{-1}, compared to a semi-empirical value of 73.0 kcal mol^{-1} calculated using the PM3 method, found to be the most accurate of the three studied. The N(9)–H tautomer gave an *ab initio* value of 68.3 kcal mol^{-1} and a value of 69.5 kcal mol^{-1} obtained from the modified PM3 method. Group additivity parameters have been devised to allow the prediction of heats of formation for azine heterocycles <1996T14335>. A value of 70.1 kcal mol^{-1} was obtained for the N(9)–H tautomer of purine.

10.11.5 Reactivity of Fully Conjugated Rings

10.11.5.1 Thermal and Photochemical Reactions

8-Chlorotheophylline reacted with the nitrilium imides generated *in situ* from amidrazones treated with triethylamine to give [1,2,4]triazolo[3,4-*f*]purines as single regioisomers in very high yield (**Scheme 1**) <2001JOC4055>. The

mechanism of the reaction may be described as a [3+2] cycloaddition of the nitrilium imide to the C═N bond of the theophylline, followed by elimination of hydrogen chloride, but the degree of synchronicity of the cycloaddition has not been determined. Other 8-substituted theophylline derivatives were able to take part equally well in the cycloaddition–elimination, for example, 8-nitrotheophylline and 8-(methylthio)theophylline (pyridine, reflux). The photoexcited triplet state of the *N*-(methylpurine-6-yl)pyridinium cation was found to be an efficient photosensitizer for the oxidation of thiol-containing amino acids to dithianes <1995JA127>.



R	*Ar*	*Yield (%)*
Ph	Ph	82
Me	4-$O_2NC_6H_4$	80
CH_3CO	Ph	75
PhNHCO	Ph	80
EtOCO	Ph	76

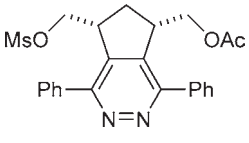
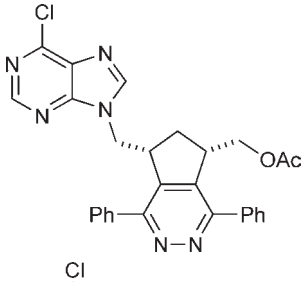
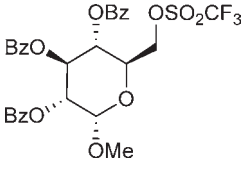
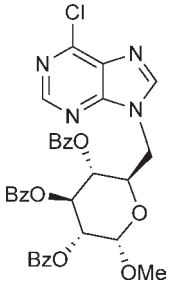
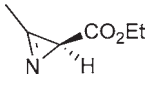
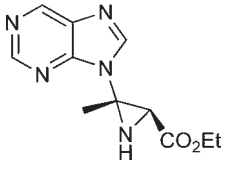
Scheme 1

10.11.5.2 Reactions with Electrophiles

10.11.5.2.1 N-Alkylation and arylation

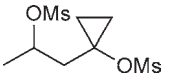
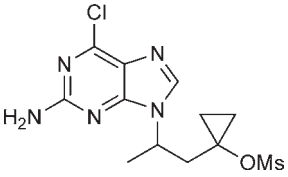
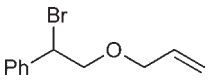
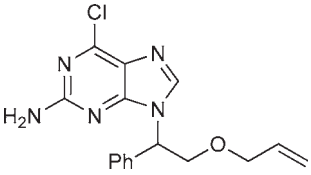
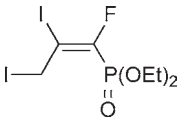
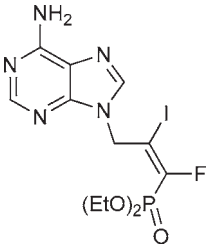
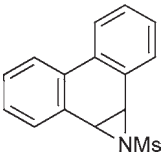
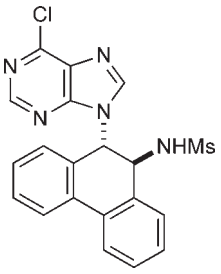
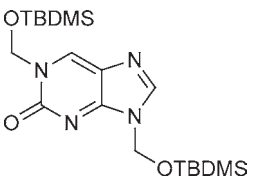
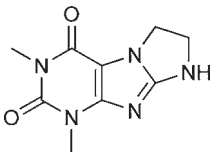
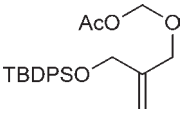
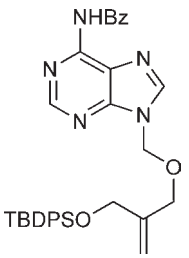
Direct S_N2 and S_N1 *N*-alkylation reactions using purines have been documented previously <1996CHEC-II(7)397>. As stated, N-9 products tend to predominate; however, mixtures are often obtained with N-7 as the secondmost nucleophilic center, with N-1 and N-3 products occasionally present to a lesser degree (**Table 2**).

Table 2 S_N2 and S_N1 N-alkylation of purine ring nitrogens

Electrophile	*Major product*	*Yield (%)*	*Reference*
		28	2004S2855
		81 4:1 N-9:N-7	1998EJO2931
		68 2:1 N-9:N-7	2003TL6277

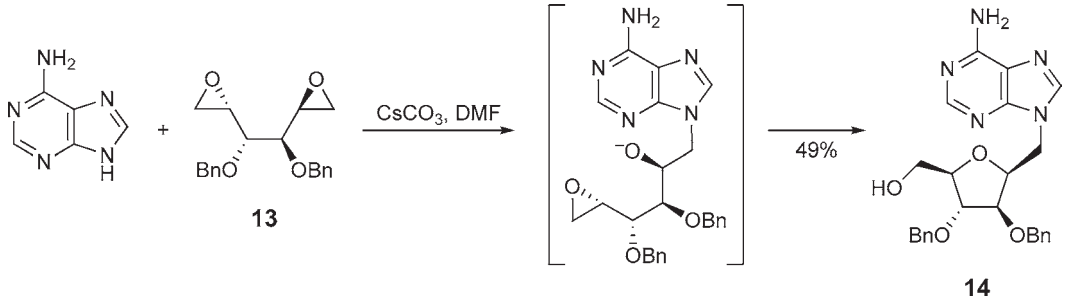
(*Continued*)

Table 2 (Continued)

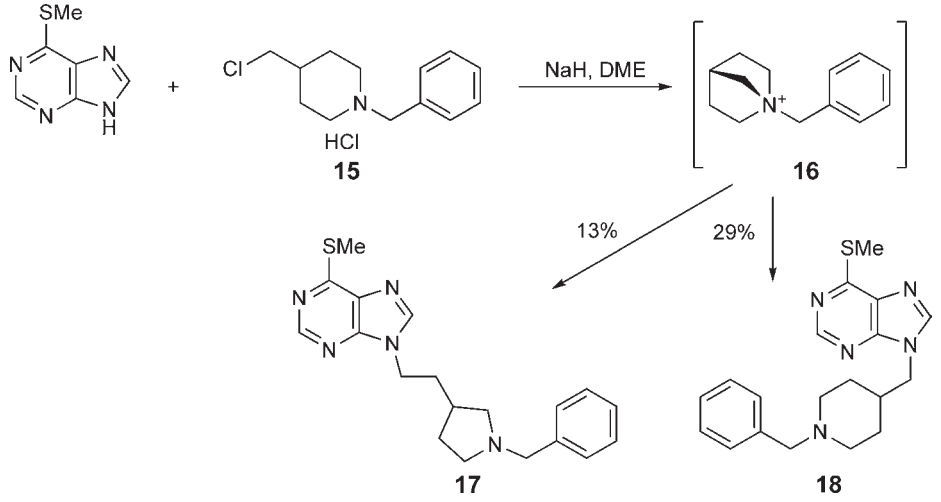
Electrophile	*Major product*	*Yield (%)*	*Reference*
		77	2000JOC9245
		84 3:1 N-9:N-7	2003OL637
		60	2000JOC227
		72	1996JHC681
$ClCH_2OTBDMS$		38	2001J(P1)1662
$BrCH_2CH_2Br$		93	1998JHC135
		49 1:1 N-9:N-1	2003T9635

Bisalkylation (N7, 8-NH_2) of 8-aminopurine starting material.

Nucleophilic addition of purines to bisepoxides has been shown to lead to the formation of homonucleosides (**Scheme 2**) <2006EJO2403>. For example, adenine was stirred in the presence of cesium carbonate in dimethylformamide (DMF) and epoxide **13**. Initial epoxide ring opening gave an intermediate, which when heated to 110 °C underwent *5-exo-tet*-cyclisation to give homonucleoside **14**. Reaction of 6-methylsulfanylpurine with chloride **15** in the presence of sodium hydride in 1,2-dimethoxyethane (DME) led to the formation of two N-9-alkylated products, **17** and **18** (**Scheme 3**) <2002S911>. The two products were proposed to arise from divergent α-attack of the purine anion onto intermediate **16**, formed *in situ* from the free amine of **15**.



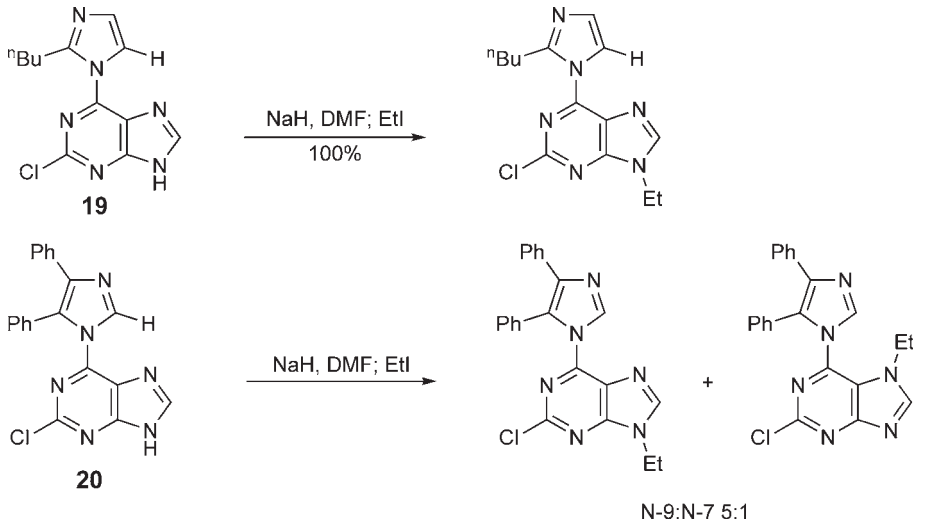
Scheme 2



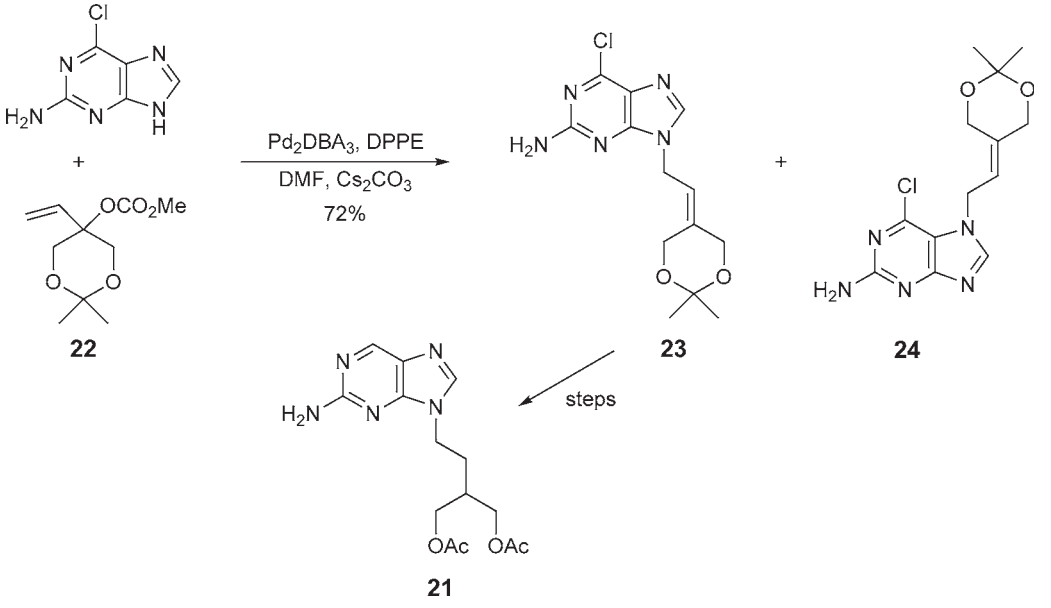
Scheme 3

Regiospecific N-9-alkylation has been achieved by shielding the N-7 position with a proximal heteroaryl C–H bond (**Scheme 4**; see Section 10.11.3.1) <2006JOC7773, 2006JOC8901>. Formation of the anion of 6-(2-butylimidazol-1-yl)-2-chloropurine **19** with sodium hydride in DMF followed by alkylation with ethyl iodide gave exclusively the N-9-alkylated isomer in quantitative yield. In contrast, treatment of **20** under similar conditions gave a 5:1 ratio of N-9- to N-7-alkylation. A solid-supported reagent, polymeric BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine), has been used to construct a library of N-7/N-9-alkylated regioisomers from O^6-benzyl-2-aminopurine, with the N-7 isomer subsequently removed by chemoselective separation <2000TL3573>.

The Tsuji–Trost reaction, more commonly applied to carbocyclic nucleoside synthesis, has been used in the synthesis of famciclovir **21** (**Scheme 5**) <2000T4589>. Reaction of 2-amino-6-chloropurine with allylic carbonate **22** in the presence of Pd_2DBA_3 and bis(diphenylphosphino)ethane (DPPE) gave a 1:1 ratio of **23** to **24** after 1 h (DBA = dibenzylideneacetone). However, a ratio of >95:5 in favor of the thermodynamically favored N-9 isomer **23** was subsequently obtained upon further stirring, highlighting the reversibility of the reaction in this specific instance.

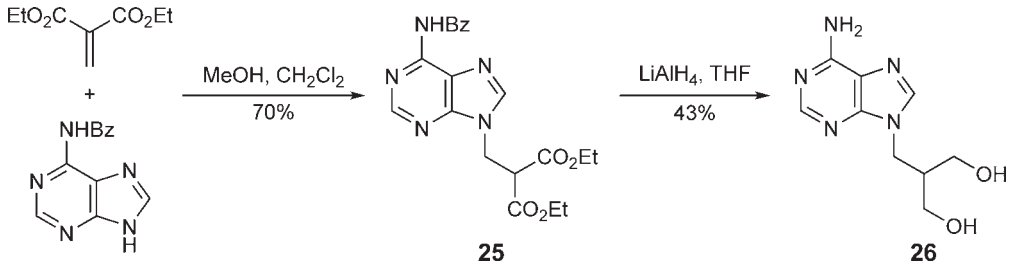


Scheme 4



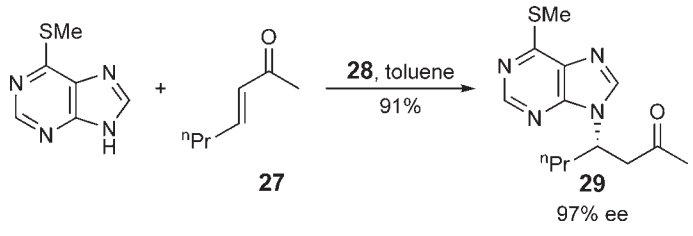
Scheme 5

The Michael addition of N^6-benzoyladenine to diethyl methylenemalonate provided access to acyclic carbonucleosides such as **25** (**Scheme 6**) <2003T2177>. Subsequent reduction with lithium aluminium hydride gave penciclovir analogue **26**. The conjugate addition approach was applied to the synthesis of acyclic phosphonate nucleosides <1996TL4701, 1999EJO931>. Michael additions using purines have also been performed using microwave heating <2005S419>. An enantioselective addition was developed, giving the desired adducts in high yield and ee <2005AGE2393>. For example, the addition of 6-methylsulfanylpurine to α,β-unsaturated enone **27** using *N*,*N*′-bis(salicylaldehydo)ethylenediamine (salen) catalyst **28** gave a 91% yield (97% ee), with only the N-9 adduct **29** observed (Equation 2).



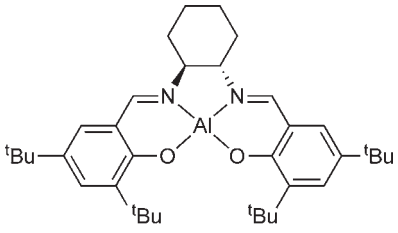
25 **26**

Scheme 6



27 **29**
97% ee

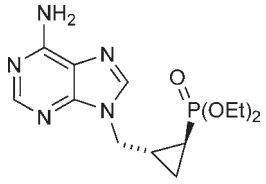
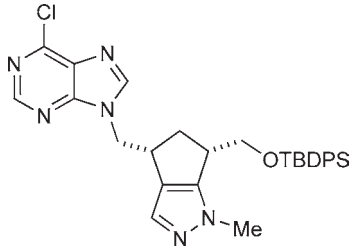
(2)



28

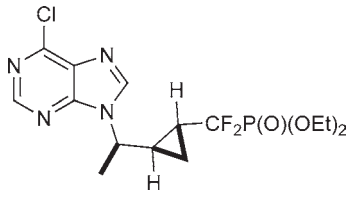
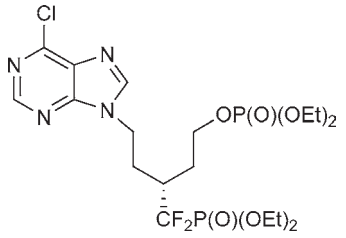
The Mitsunobu reaction has been well documented for the N-alkylation of purines (**Table 3**). A solid-phase approach, incorporating a Mitsunobu reaction, has been used to construct small libraries of general structure **30** <1997TL1161>. As an example, coupling of supported purine **31** with 2-(3-thienyl)ethanol using diethyl azodicarboxylate (DEAD) and PPh_3 in tetrahydrofuran (THF)–dichloromethane gave **32** after cleavage (**Scheme 7**). When retained on the resin, further displacement with butylamine gave aniline **33** after cleavage.

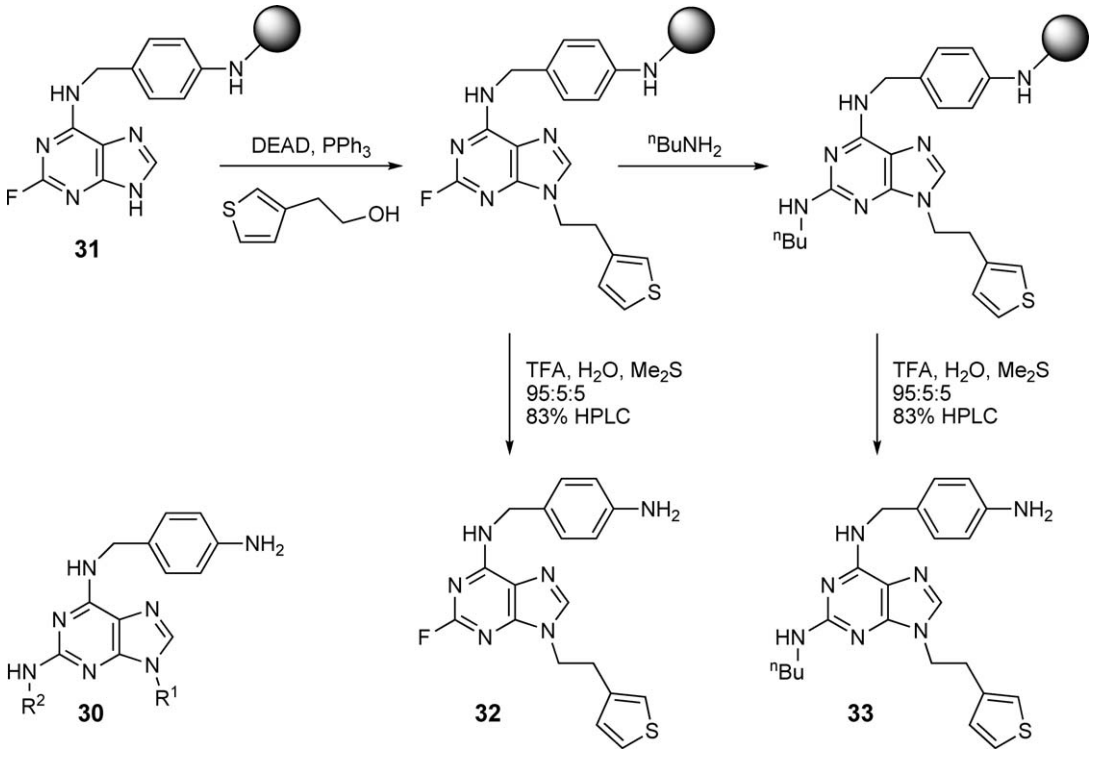
Table 3 Carbonucleosides prepared by Mitsunobu coupling to acyclic alcohols

Conditions	*Product*	*Yield (%)*	*Reference*
PPh_3, DEAD, THF, −10 °C		46%	1999TL8235
PPh_3, DEAD, THF		62%	2006S73

(*Continued*)

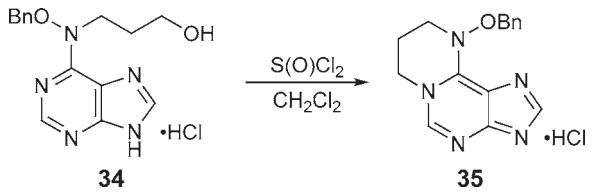
Table 3 (Continued)

Conditions	*Product*	*Yield (%)*	*Reference*
PPh_3, DEAD, THF, rt		43% (20% N-7)	2000T7099
PPh_3, DIAD, THF, 0 °C		88%	2003T10223



Scheme 7

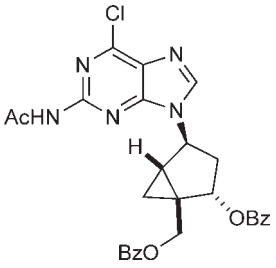
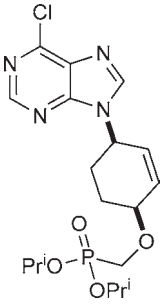
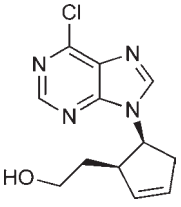
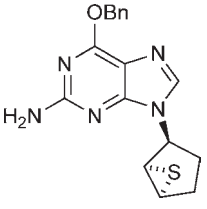
Alcohol **34** has been used in an intramolecular N-alkylation (Equation 3) <2001TL5941>. Treatment of **34** with refluxing thionyl chloride in dichloromethane gave tricyclic **35** as the HCl salt.



(3)

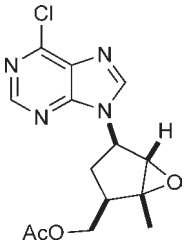
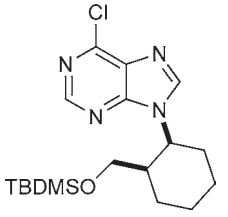
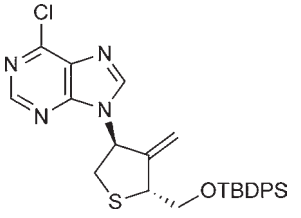
The synthesis of carbocyclic nucleosides has received much attention in recent years due to their interesting biological profiles and the replacement of the metabolically labile glycosidic linkage present in nucleosides. Two preferred methods have emerged for the formation of carbocyclic nucleosides, namely Mitsunobu couplings and the Tsuji–Trost reaction. General conditions for the Mitsunobu couplings from the appropriate carbocyclic alcohol are summarized in **Table 4**. Entry 2 shows the reaction of 6-chloropurine giving a mixture of N-9-, N-7-, and N-3-alkylation <1995JOC1531>; however, the product of reaction at N-9 predominates in most instances.

Table 4 Cyclic carbonucleosides prepared by Mitsunobu coupling

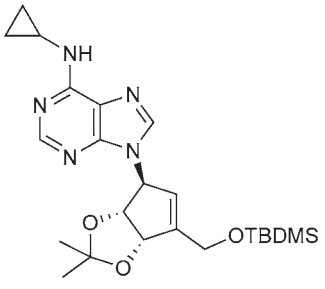
Conditions	*Product*	*Yield* (%)	*Reference*
PPh_3, DEAD, THF, rt		80	2000OL3793
PPh_3, DEAD, dioxane, rt		40 (10% N-7, 5% N-3)	1995JOC1531
i, PPh_3, DEAD, dry THF, rt; ii, TBAF		67 (2 steps)	1996T8407
PPh_3, DEAD, THF, rt		28	2006EJO4473

(*Continued*)

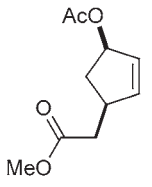
Table 4 (Continued)

Conditions	*Product*	*Yield (%)*	*Reference*
PPh_3, DIAD, THF, 0 °C to rt		66	2006SL2215
PPh_3, DEAD, THF, rt		41	2005T473
PPh_3, DEAD, THF, 0 °C		55	2004JOC3208

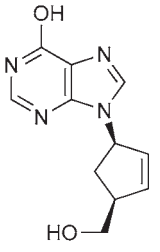
The Tsuji–Trost reaction provides a rapid access to carbocyclic nucleosides. The reaction of 6-cyclopropylaminopurine with the appropriate acetate using a $Pd(PPh_3)(DPPF)$ catalyst and Et_3Al as base gave **36** in 55% yield (DPPF = 1,1′bis(diphenylphosphino)ferrocene) <2004T8397>. The N-7 versus N-9 selectivity for the reaction has been observed to be substrate dependent. Whereas reaction of 6-chloropurine with acetate **37** using $Pd(P(OPr^i)_3)_4$ and Et_3Al gave the desired N-9 product exclusively in 67% yield, N^6-benzoyladenine gave an 81% yield of the N-9 product and 7% yield of the N-7 product <1998T1439>. One of the main applications of the Tsuji–Trost reaction to construct carbocyclic nucleosides has been in the synthesis of carbovir **38** <1996JOC4192, 1997JOC1580>, a selective inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase, and derivatives thereof <1996T799, 1996T2789, 1996T8969>, including a solid-phase synthetic approach <2000OL1065>; see Section 10.11.12.2.



36

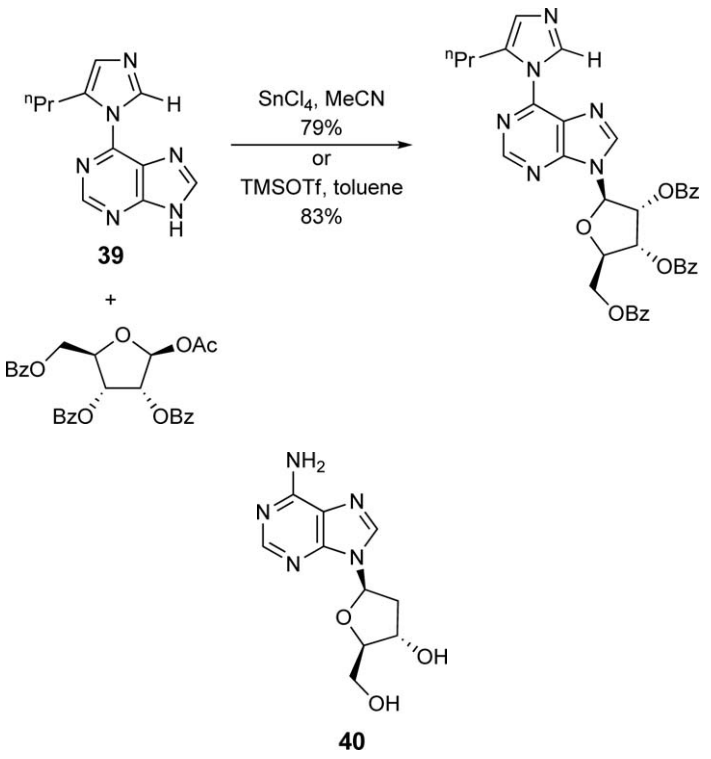


37



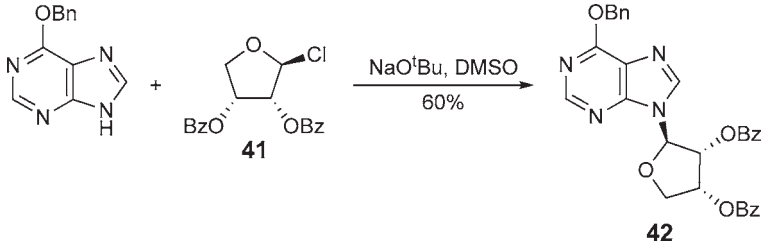
38

The synthesis of nucleosides has been reviewed extensively <2000OR1>. Nucleosides have been constructed by displacement/Vorbruggen-type addition <1998HCA145, 1998TL4437, 2003TL9327, 2004JOC5555, 2006OL491>, enzymatic <2003TL2899, 2003TL2605>, and Mitsunobu coupling <2002T4865>. Regiospecificity has been obtained using Vorbruggen-type couplings, where the imidazole group at the 6-position of substrates such as **39** blocks N-7 glycosylation to give exclusively N-9 nucleosides in a similar manner to that used in **Scheme 4** (Equation 4) <2005OL4601>. This methodology has been applied to the synthesis of cladribine **40** <2006JOC7773>.



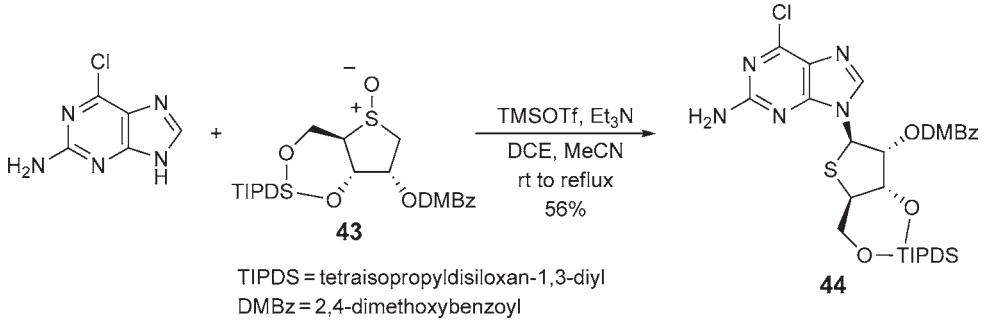
(4)

A method to form nucleosides from chlorofuranoses was shown to be highly β-selective (Equation 5) <2000TL8207>. For example, the reaction of 6-(benzyloxy)purine with **41** provided nucleoside **42** with a >99:1 ratio of β- to α-anomers. Product distribution was found to be independent of the anomeric ratio of the chlorofuranose starting materials.



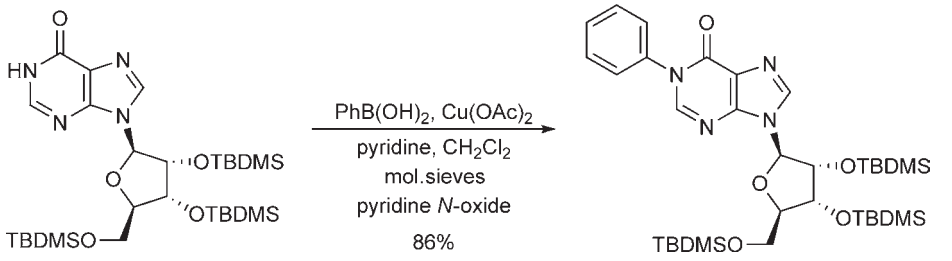
(5)

The Pummerer reaction has been used to construct thioribonucleosides <2000JA7233, 2005JOC5655>. The reaction of 6-chloro-2-aminopurine with sulfoxide **43** in the presence of TMSOTf gave thionucleoside **44** (Equation 6).



(6)

Direct arylations of purines have been achieved by copper-mediated couplings. Thus, 1-aryl inosines and guanosines were made directly from the corresponding N(1)–H derivative by reaction with a range of aryl boronic acids in the presence of copper(II) acetate in good yield (Equation 7) <2005TL5699>. Copper has also been used in the arylation of purine, where iodobenzene in the presence of copper(I) iodide and a diamine ligand gave 9-phenylpurine (66% yield) <2004JOC5578>. Copper(II) acetate and arylboronic acids in the presence of phenanthroline in dichloromethane have been used to form N-9-arylated species in a regioselective fashion on a range of 2- and/or 6-substituted purines <2003TL3359>. No arylation at the 6-position was observed.



(7)

10.11.5.2.2 C-Alkylation and arylation

In general, reactive carbon electrophiles have been shown to react preferentially at the nitrogen atoms of the purine bicycle (see Section 10.11.5.2.1). However, 9-(2,3,5-tris-*O*-*tert*-butyldimethylsilyl)-α-D-ribofuranosyl-6-chloro-2-(tributylstannyl)purine reacted with benzoyl chloride to substitute the 2-tributylstannyl group (PhCOCl, pyridine, toluene, 60% yield) <1997JOC6833>. Indirect C-alkylations have been achieved through deprotonation and alkylation; see Section 10.11.5.3.4. The major routes to *C*-alkyl and *C*-aryl substitution are through nucleophilic displacement or transition metal-catalyzed reactions of halopurines; see Sections 10.11.7.4.1 and 10.11.7.4.2.

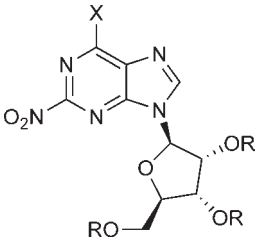
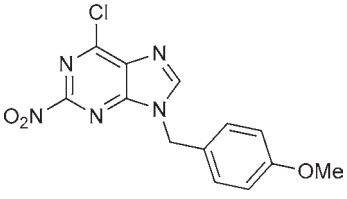
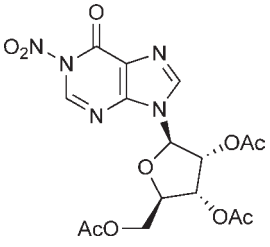
10.11.5.2.3 Nitration

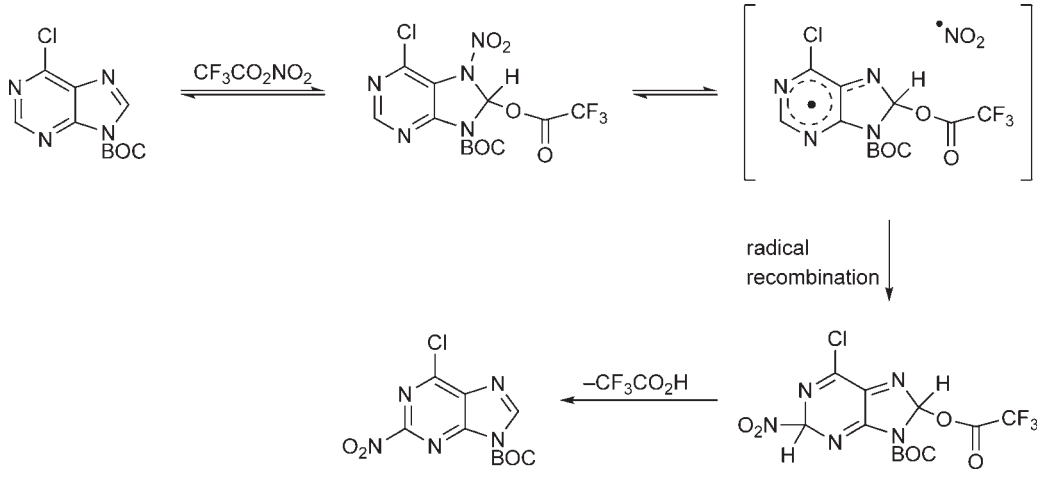
The nitration of purines using trifluoroacetyl nitrate, made *in situ* from tetrabutylammonium nitrate and trifluoroacetic anhydride, has proved a useful method for the introduction of nitro groups at carbon and nitrogen atoms of the bicycle (**Table 5**) <1995TL7875, 1995JA3665, 2006S2993>. When all hydroxyl and amino substituents in the substrates were protected, and C-6 of the purine bore a substituent, then nitration was directed to C-2 of the purine. Although originally postulated as a purely radical reaction, the mechanism was subsequently shown through extensive NMR investigations of the reaction of 6-chloro-9-(*tert*-butyloxycarbonyl)purine (see Section 10.11.3.4) to proceed through electrophilic attack to generate an 8-(trifluoroacetoxy)-7-nitramine <2005JA5957>. Heterolytic dissociation of the nitramine was followed by radical readdition at C-2 and elimination of trifluoroacetic acid to regenerate the purine (**Scheme 8**). If unprotected ribonucleosides were used, highly polar products resulted from a mixture of competing N-nitration, O-nitration, and glycosidic bond cleavage. However, suitably protected inosine derivatives gave good yields of the N-1-nitroso purines (**Table 5**) <1995JA3665> which were good substrates for subsequent ring-opening–ring-closing aminolysis reactions (see Section 10.11.5.3.2). A facile displacement of 2-nitropurines by fluoride (tetrabutylammonium fluoride (TBAF), THF, DMF, rt, 67–78% yield) was demonstrated <2006S2993>.

10.11.5.2.4 Oxidation of ring atoms

The oxidation of purines is of particular interest for understanding the mechanism and chemical consequences of oxidative damage to purine bases in DNA, which occurs predominantly at C-8. The metabolism of xanthine-containing drugs, such as caffeine and analogues, also involves oxidation at C-8 of the embedded purine ring system. A mild and direct oxidation at C-8 of caffeine and adenosine derivatives was achieved using dimethyldioxirane (DMDO) (**Scheme 9**) <1995TL2665>. The reaction was highly selective, with no other oxidation products observed, and was presumed to occur through formation and rearrangement of the 8,9- or 7,8-oxaziridines. Protection of the C-2′-hydroxyl group of adenosine was necessary to suppress concomitant cleavage of the sugar residue. A high-yielding (isolated yields > 95%) biocatalytic method for the oxidation of caffeine derivatives at C-8 was developed using a mixed bacterial culture containing *Klebsiella* and *Rhodococcus* strains <1999J(P1)677>. This process also oxidized adenine to 8-oxo-6-aminopurine (70% yield), provided *N*-methylmaleimide was included in the incubation mixture as a thiol-reactive compound to prevent further metabolism of the product.

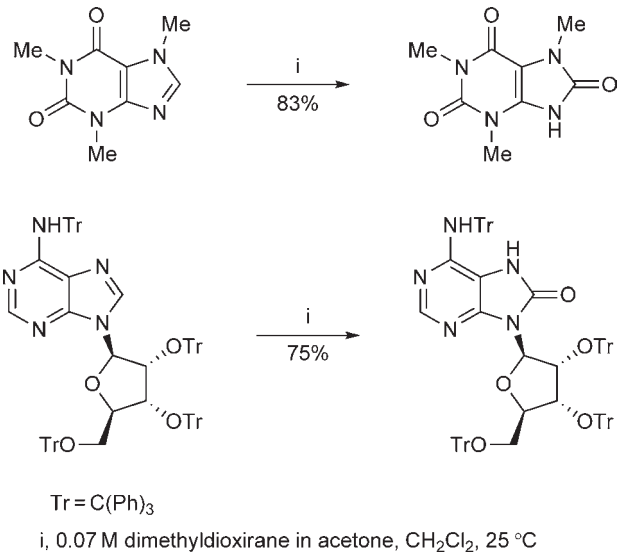
Table 5 C- and N-Nitrated purines prepared using trifluoroacetyl nitrate

Nitropurine			*Yield (%)*	*Reference*
	X	R		
	Cl	Ac	71	2000TL1291
	$N(Ac)_2$	Ac	55	2000TL1291
	$N(c\text{-}C_5H_{11})Ac$	Ac	48	2000TL1291
	$N(Bz)_2$	Bz	84	2006S2993
			55	2006S2993
			70	1995JA3665

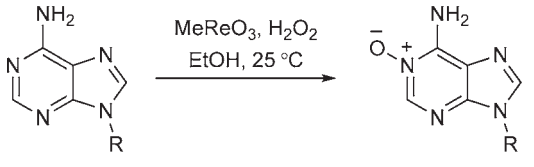


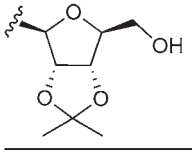
Scheme 8

Selective oxidation of N-1 of adenine derivatives is typically carried out with peracids <1998JOC3213>, but has also been achieved with hydrogen peroxide and catalytic methyltrioxorhenium (**Scheme 10**) <2000T10031>. The inclusion of pyridazine-2-carboxylic acid as a stabilizer for reactive rhenium peroxides led to increased yields. Caffeine did not react under these conditions.



Scheme 9



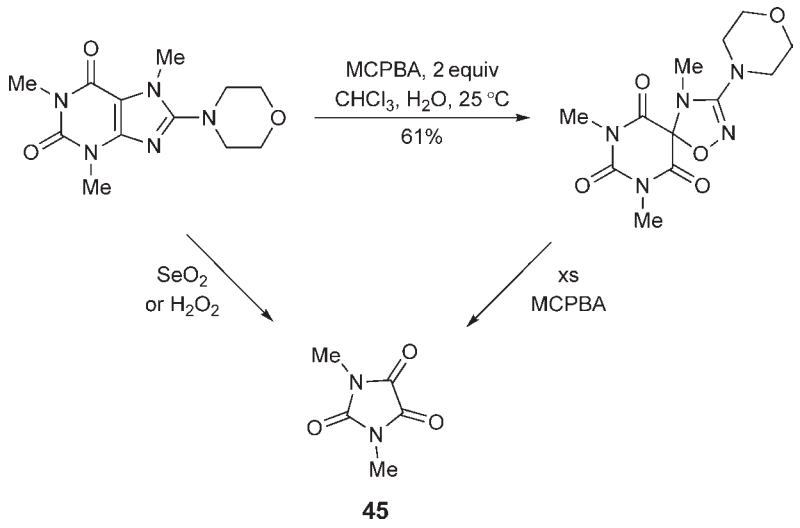
R	*Yield (%)*
$(CH_2)_5CH_3$	83
$(CH_2)_4OH$	85
$(CH_2)_4OAc$	89
	93

Scheme 10

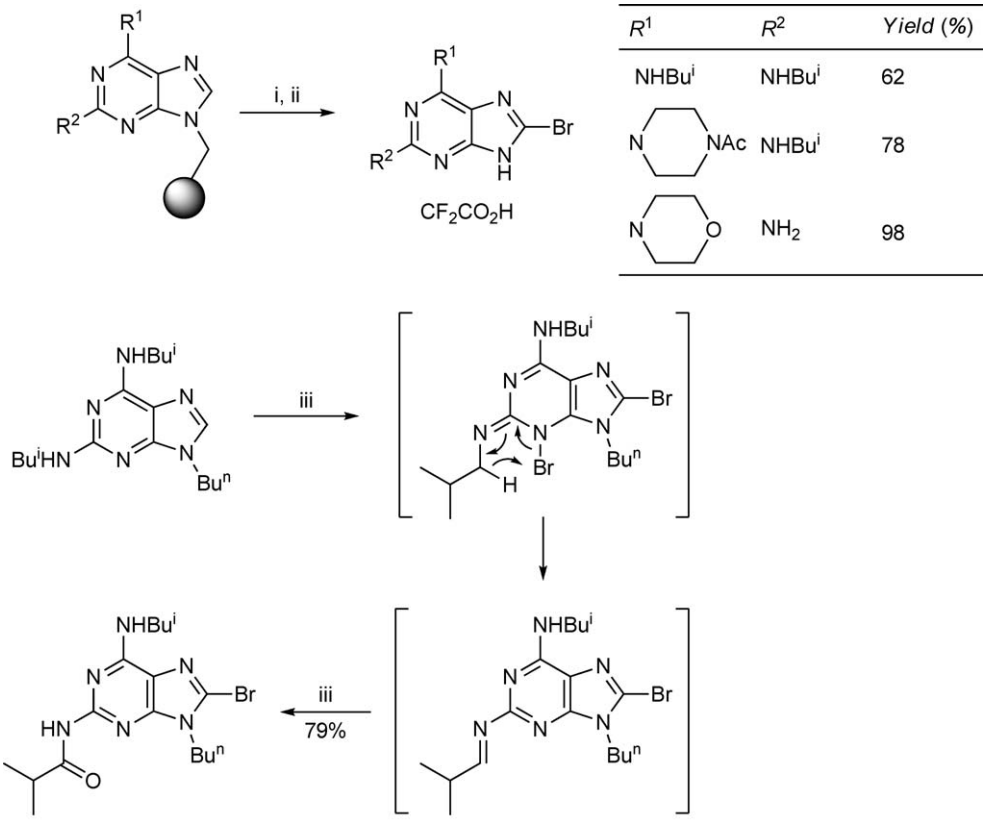
A double oxidation at the 5,6-carbon–carbon double bond and N-9 by 2 equiv of *m*-chloroperbenzoic acid (MCPBA) was postulated as the mechanism for the oxidative rearrangement of 8-dialkylaminoxanthines to novel 1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones <1999EJO2419>. The presence of an electron-donating 8-amino substituent was essential for this reaction to occur. Further oxidation of the products gave 1,3-dimethylparabenic acid **45**, which was also produced directly when selenium dioxide or hydrogen peroxide were used (**Scheme 11**).

10.11.5.2.5 Halogenation

Direct halogenation of purines occurs predominantly in the fused imidazole ring at C-8 <1996CHEC-II(7)397>. The popularity of substituted purine scaffolds for medicinal chemistry applications (see Section 10.11.12.2) has generated significant interest in solid-phase syntheses. The charge-transfer complex of bromine and 2,6-lutidine was shown to be an effective reagent for the bromination of resin-linked 2,6-diaminopurines <2001TL6279, 2001TL6515>. The reaction was best conducted in *N*-methyl-2-pyrrolidone (NMP) as solvent, where competing dissociation of the charge-transfer complex to an unreactive species was moderate, whereas more polar solvents such as DMF gave no reaction. In benzene, the reagent was still more reactive and gave concomitant oxidation of the 2-aminoalkyl substituent, presumably by initial bromination at N-3 of the purine (**Scheme 12**) followed by further oxidation of the imine product.



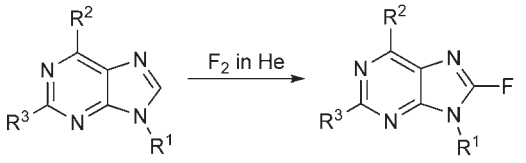
Scheme 11

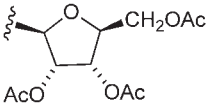


R^1	R^2	*Yield* (%)
$NHBu^i$	$NHBu^i$	62
	$NHBu^i$	78
	NH_2	98

Scheme 12

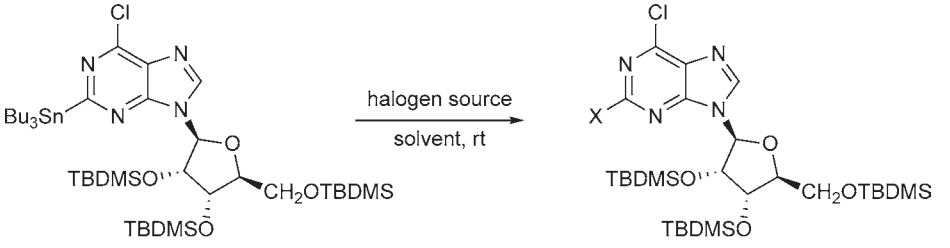
Fluorination of adenine derivatives using elemental fluorine (1% F_2 in He delivered at a rate of 5–10 μmol F_2 min^{-1}) gave the C-8 fluoro analogues in moderate yields <1996JA10408>. Although chloroform was the optimum solvent, this was not suitable for less-soluble, unprotected compounds and ethanol was substituted, although a reduction in yield was observed (**Scheme 13**).



R^1	R^2	R^3	*Solvent*	*Yield* (%)
$CH_2OCH_2CH_2OH$	NH_2	OH	EtOH	10
$CH_2OCH_2CH_2OAc$	NHAc	OH	$CHCl_3$	28
	NHAc	OH	$CHCl_3$	30

Scheme 13

An alternative to direct halogenation involves the introduction of a directing trialkylstannyl or trialkylsilyl group through regioselective deprotonation (see Section 10.11.5.3.4), followed by electrophilic halogen–metal exchange. Thus the 2-(tributylstannyl)purine **46** (**Scheme 14**) was transformed to the 2-halopurines, including the 2-fluoro compound, by reaction with electrophilic halogen sources <1997JOC6833>. Similarly, the reaction of 6-chloro-9-(tetrahydropyran-2-yl)-2-tributylstannyl-9*H*-purine with iodine gave 6-chloro-2-iodo-9-(tetrahydropyran-2-yl)-9*H*-purine (95% yield) <2001TL8161, 2004OBC665>.



46

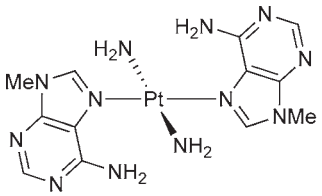
Reagents	*Solvent*	*X*	*Yield* (%)
I_2	THF	I	97
NBS	THF	Br	92
NCS	THF	Cl	95
XeF_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine	CH_2Cl_2	F	85

Scheme 14

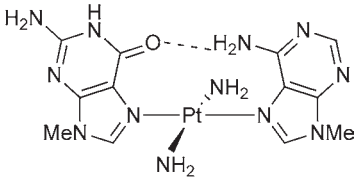
10.11.5.2.6 Metal complexes

The reaction of purines with cationic metal complexes has been of particular interest for understanding and exploiting the mechanisms by which anticancer organometallic compounds interact with DNA. A number of bis(purine) *trans*-diamino-platinum complexes, for example, **47** and **48**, of adenine and guanine were prepared and studied by X-ray crystallography and NMR spectroscopy <1996JA4124>. In general, the heterocycles adopted coplanar relative conformations, with intramolecular hydrogen bonding seen when an adenine and guanine were present in the same complex. The species **47** and **48** were capable of further aggregation or complexation of additional metal centers and purines or pyrimidines. The cationic ruthenium(II) complex (η^6-biphenyl)-$Ru(NH_2CH_2CH_2NH_2)(Cl)(PF_6)$ has anticancer activity <2001JME3616> and has been shown to react with guanine-containing compounds <2002JA3064>. The resulting complexes, for example **49**, were investigated by crystallography and nuclear Overhauser enhancement spectroscopy (NOESY) studies, and showed coordination of

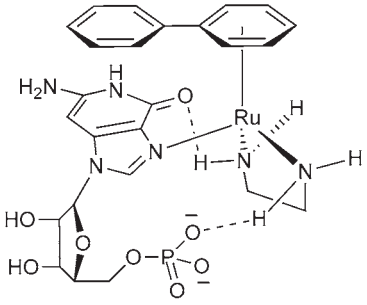
the metal by the purine N-7 and hydrogen bonding between the guanine O-6 and the ethylenediamine ligand. The observation of a hydrophobic interaction between the biphenyl ligand and the complexed purine suggested that ruthenium species of this type may be capable of simultaneous coordination and intercalation to DNA.



47

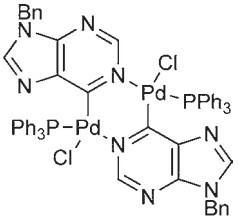


48



49

The reaction of neutral bis(7-methylpurin-8-yl)methane with divalent metal acetate salts generated air-stable and water-soluble metal chelates with a 2:1 ligand:metal stoichiometry (69–93% yields) <1998JOC436> (see Section 10.11.7.1). These complexes were prepared more readily than those with bis(benzimidazole)methanes, reflecting a more extensive delocalization of the negative charge formed upon deprotonation of the central methano carbon atom. The dimeric palladium complex **50** was isolated and characterized from the reaction of 6-chloro-9-benzylpurine with tetrakis(triphenylphosphine) palladium(0) <1996ACS462>. The complex **50** cross-coupled with an excess of organostannanes, and was also capable of catalyzing (5 mol%) the cross-coupling of 6-chloro-9-benzylpurine with organostannanes, suggesting that such species may play a role in the mechanism of palladium-catalyzed reactions of halopurines. Aggregation and complexation of intermediate organopalladium species by the nitrogen-rich purine heterocycle has been invoked to explain the difficulties sometimes observed when conducting palladium-catalyzed cross-coupling reactions of halopurines <2001JA7779> (see Section 10.11.7.4.2). The coordination of unprotected guanine to palladium under basic conditions through either N-1 or O-6, or both, was shown by ^{31}P and ^{13}C NMR studies (see Section 10.11.3.3), and correlated with a slowing of the rate of palladium-catalyzed Suzuki couplings to 8-bromoguanosines <2005JOC6378>. The reaction of the purine ring with a cationic rhodium(I) complex to form an N-heterocyclic carbene species was involved in the initial step of the coupling of alkenes to C-8 of purines through C–H activation <2002JA13964, 2004JOC7329> (see Section 10.11.5.3.3).

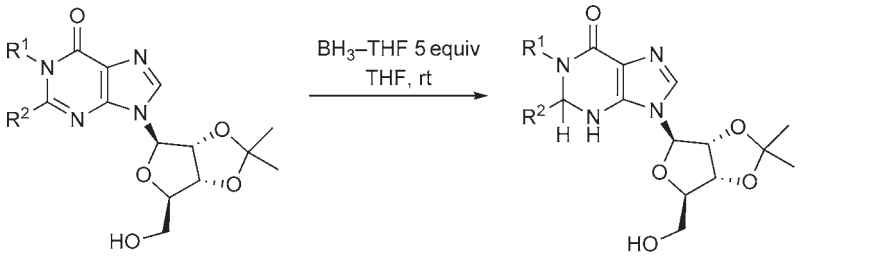


50

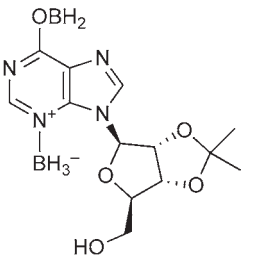
10.11.5.3 Reactions with Nucleophiles

10.11.5.3.1 Reduction

A novel, regioselective partial reduction of inosine derivatives to 2,3-dihydroinosines was achieved using borane–THF at room temperature <2002TL653>. These compounds were sensitive to reoxidation in air, with approximately 10–20% regeneration of the starting materials observed after 7 days. The regioselectivity was attributed to prior coordination of borane to the N-3 position. Consistent with this, the introduction of a methyl substituent at C-2 suppressed the reaction. The reduction was most efficient for N-1-alkylated compounds, while N-1-unsubstituted inosine derivatives gave substantial unreacted starting material (**Scheme 15**). This was attributed to the formation of the less-reactive aromatic complex **51** through reaction with an additional equivalent of borane.



R^1	R^2	*Yield (%)*
H	H	49
Me	H	92
Bn	H	75
H	Me	0
Me	Me	30

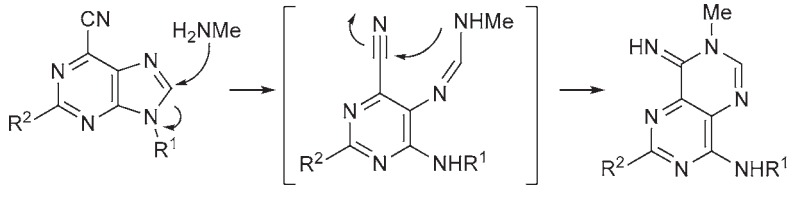


51

Scheme 15

10.11.5.3.2 Amination and hydrolysis

Two major modes of attack by amino or hydroxy nucleophiles on the conjugated rings of purines are commonly observed in the absence of halide leaving groups. Nucleophilic addition to unsubstituted C-8 is one path, and is usually accompanied by opening of the imidazole ring. Alternatively, addition to C-2 may occur when N-1 is substituted with electron-deficient arenes, nitro, amino, or alkoxy groups. Subsequent ring opening of the pyrimidine may be followed by Dimroth rearrangement if C-6 bears an amino group, or by loss of the substituted N-1 functionality. Addition to C-8 was observed when 6-cyanopurines were exposed to excess methylamine at low temperatures (0 °C to rt) <2001J(P1)2532>. Imidazole ring opening produced a formamidine which cyclized onto the nitrile substituent to form 4-imino-pyrimido[5,4-*d*]pyrimidines (**Scheme 16**). The identity of the new heterocycles was proven by X-ray crystallography. In contrast to earlier reports on similar systems, no evidence was found for the formation of isomeric 6-carboxamidinopurines resulting from attack of the methylamine on the nitrile (see Section 10.11.7.2). The hydrolysis of a 6-(*N*-tosylcarboxamidino)-2-oxo-9-purine by glacial acetic acid in refluxing DMF also led, via nucleophilic attack on C-8, to rearrangement to the 4-imino-pyrimido[5,4-*d*]pyrimidine (38% yield)

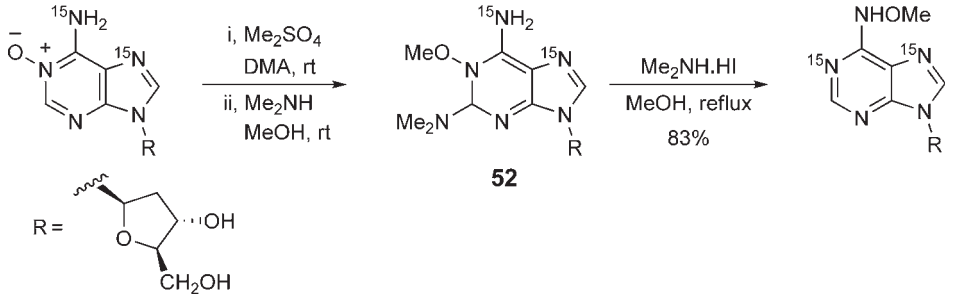


R^1	R^2	*Yield (%)*
4-$MeOC_6H_4$	H	86
4-$MeOC_6H_4$	Et	72
4-NCC_6H_4	H	99

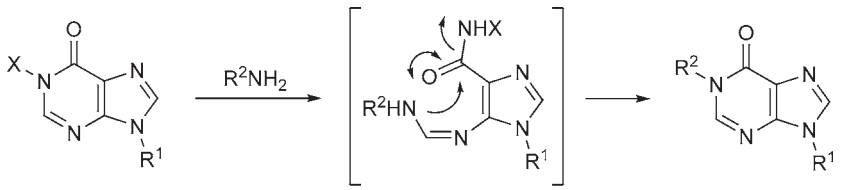
Scheme 16

<2001J(P1)1241>. Opening of the imidazole ring of 2′-deoxyadenosine and 2′-deoxyguanosine by formamide, ultimately yielding the pyrimidine fragments, was the basis of studies into improving chemical sequencing procedures for DNA <1996JA5615>.

In an example of the other prevalent pathway for purine aminolysis, dimethylamine was seen to attack at C-2 of ^{15}N-labeled adenosines activated by N-1 methoxy substitution <1998JOC3213>. In the presence of dimethylamine hydrogen iodide, functioning as a weak acid, a Dimroth rearrangement of the intermediate **52** occurred, where the C(2)–N(1) bond was broken and the ring reclosed with the labeled 6-amino group now incorporated into the purine bicycle (**Scheme 17**). In contrast, 1-aminoadenosine nucleosides showed a competition between the Dimroth rearrangement and a different ring-opening–ring-closing rearrangement when reacted with hydrazine hydrate <1996JHC1115>. The presence of excess methanol in the reaction mixture promoted the Dimroth process to give predominantly the rearranged 6-hydrazinopurines. However, significant quantities of 4-(4-amino-1,2,4-triazol-3-yl)imidazoles were also isolated, and became the dominant or sole products as the methanol content of the reaction was reduced. The pathway for the formation of these products, although not fully elucidated, appeared to involve the intramolecular transfer of a formyl-hydrazone equivalent within the first ring-opened intermediate, before ring closure to give the triazole. 1-Nitro- and 1-(4-nitrophenyl)inosines underwent ring opening through attack of amines at C-2, followed by ring closure to reform the purine ring system with loss of the original N-1 functionality (**Scheme 18**) <1995JA3665, 1997J(P1)2079>. Such reactions were useful for the introduction of ^{15}N labels at N-1 <1995JA3665>.

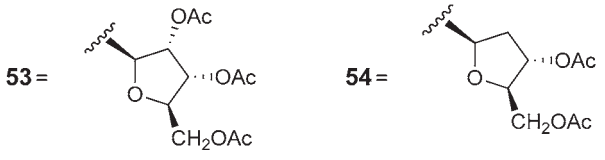


Scheme 17



X	R^1	R^2	*Yield (%)*	*Reference*
NO_2	**53**	Bn	91	1995JA3665
NO_2	**53**	(*S*)-CH(Me)CO_2Me	80	1995JA3665
NO_2	**53**	(*S*)-CH(^{i}Pr)CO_2Me	20	1995JA3665
4-$O_2NC_6H_4$	**54***	$(CH_2)_6NH_2$	92	1997J(PI)2079
4-$O_2NC_6H_4$	**54***	$(CH_2)_2OH$	90	1997J(PI)2079
2,4-$(O_2N)_2C_6H_3$	**54***	OH	75	1997J(PI)2079

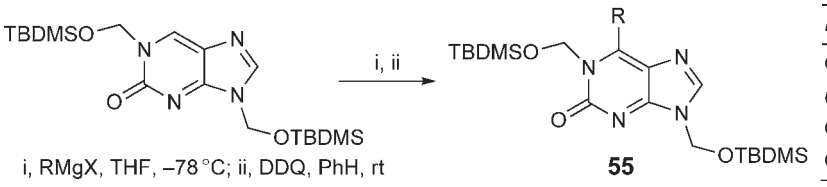
*Concomitant deacetylation of the ribofuranose under reaction conditions.



Scheme 18

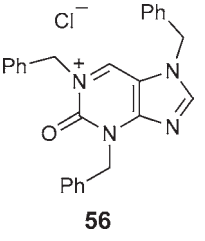
10.11.5.3.3 Reaction with carbon nucleophiles

The known reaction of purine with malononitrile was optimized for the synthesis of 5-amino-3*H*-imidazo[4,5-*b*]-pyridine-6-carbonitrile (90% yield) through addition of malononitrile to C-6 followed by ring-opening–ring-closing <1996JHC319>. Alkyl, alkenyl, and alkynyl Grignard reagents also added regioselectively to C-6 of N-protected purin-2-ones <2001J(P1)1662> to give the 6-substituted purin-2-ones **55** after reoxidation of the crude products with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; **Scheme 19**). The silyloxymethyl protecting groups were readily removed using tetramethylammonium fluoride and acetic acid (68–90% yields). The tribenzylated 2-oxopurinium salt **56** also underwent regioselective addition of a range of Grignard reagents to the 6-position to generate 6-substituted-1,3,6,7-tetrahydro-1,3,7-tribenzyl-2H-purin-2-ones <1995T3655>. The attack of methyl cyanoacetate at C-8 of some 6-(methoxyformidoyl)purines and 6-enaminopurines, leading to ring-opening–ring-closing rearrangement to form pyrimidopyrimidines, was a complicating factor in the syntheses of these materials <2004OBC2340>.

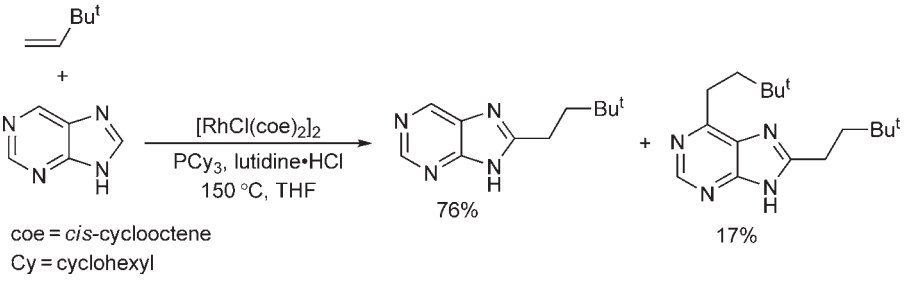


R	*Yield* (%)
CH_2CH_2Ph	66
(*E*)-CH=CHPh	67
$CH=CH_2$	63
C≡CPh	76

Scheme 19



As an alternative to addition of anionic nucleophiles followed by reoxidation, rhodium(I)-catalyzed C–H activation allowed the nucleophilic addition of alkenes to the intermediate Rh(I) carbene complex <2002JA13964, 2004JOC7329>. Purine behaved anomalously compared to other heterocycles, for which selective monoalkylation was observed, and underwent sequential substitution first at C-8 and then at C-6 (Equation 8). Caffeine was monoalkylated at C-8 in low yield (15%). Selectivity for C-8-arylation was also observed in the palladium-catalyzed C–H activation of 6-phenyl-9-benzylpurine (aryl iodides, 0.05 equiv $Pd(OAc)_2$, 3 equiv CuI, 2.5 equiv Cs_2CO_3, DMF, 160 °C, 60 h, 48–95% yields) <2006OL5389>.

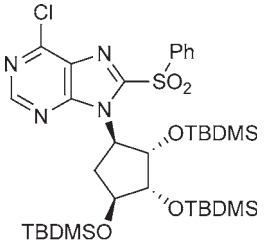


(8)

10.11.5.3.4 Deprotonation (nucleophilic attack at hydrogen)

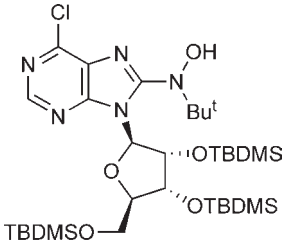
The deprotonation of purines at C-8 to generate the lithium anions is well precedented <1996CHEC-II(7)397> and was used in an attempt to introduce fluorine to C-8 by reaction with *N*-fluorobenzenesulfonimide <2005OL3889>. However, the 8-phenylsulfonyl-substituted purine **57** (78% yield) was produced instead of the

expected 8-fluoro compound. The generation of **57** was rationalized as occurring through a single electron transfer between the 8-lithiopurine and *N*-fluorobenzenesulfonimide, followed by decomposition to form a phenylsulfonyl radical which recombined with the purine C-8 radical. The C-8 lithium anions formed from 9-(tetrahydropyran-2-yl)-6-chloropurine or protected ribofuranosyl purines reacted smoothly with hexachloroethane, 1,2-dibromotetrachloroethane, cyanogen bromide, or cyanogen iodide to give the 8-halopurines in generally very high yields (78–99%) <1998SC4303>.



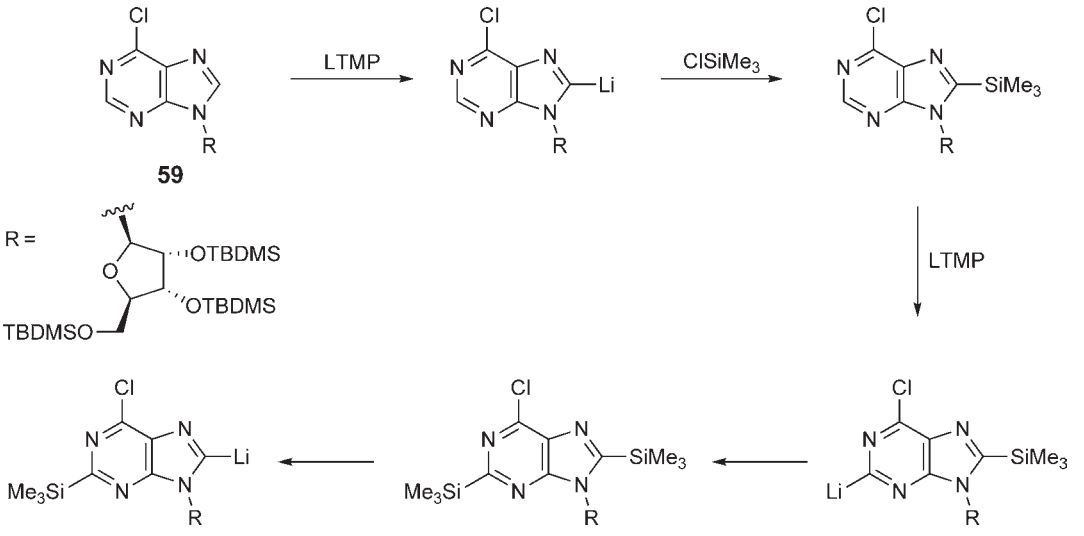
57

Deprotonation of a protected 6-chloropurine nucleoside (6 equiv LDA, −78 °C) also gave the C-8 anion, which reacted with 2-methyl-2-nitroisopropane to give the 8-(*N-tert*-butylhydroxylamine) derivative **58** (56% yield). This was subsequently oxidized to access a variety of spin-labeled ribonucleosides bearing an *N-tert*-butylaminoxyl radical at C-8 <2001JOC3513>.

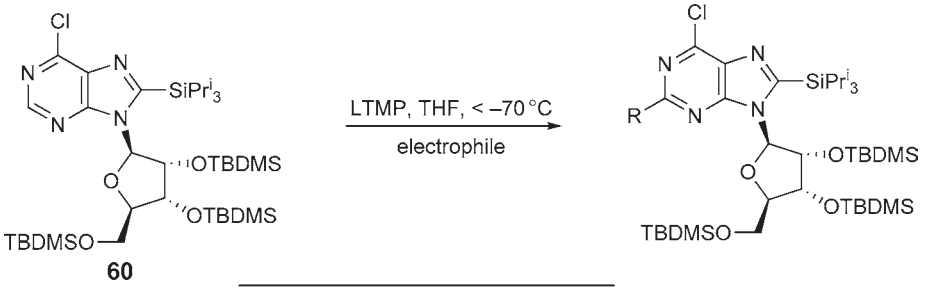


58

Whereas deprotonation of the ribonucleoside **59** with lithium 2,2,6,6-tetramethylpiperidide and reaction with iodine gave exclusively the 8-iodo derivative in a high yield (90%), treatment of the lithiated species with chlorotrimethylsilane or chlorotributylstannane led to mixtures of starting material, C-8- and C-2-silylated (or -stannylated) products <1995TL6507, 1997JOC6833>. Deuterium-quenching experiments showed the exclusive formation of the C-8 anion when 1.2 equiv of base was used, while additional deuteration at C-2 was observed when an excess (5 equiv) was employed. The distribution of the silylated products supported an intermolecular silyl-migration mechanism (**Scheme 20**). The addition of hexamethylphosphoramide (HMPA) to the reaction mixture and the use of 5 equiv of lithium 2,2,6,6-tetramethylpiperidide (LTMP) as base promoted the migration to give optimal yield and selectivity for the C-2-silylated (83% yield) and -stannylated (90% yield) products. 6-Chloro-9-(tetrahydropyran-2-yl)-9*H*-purine gave 2-tributylstannyl-6-chloro-9-(tetrahydropyran-2-yl)-9*H*-purine (100% yield) under similar conditions <2001TL8161, 2004OBC665>. The intermolecular silyl migration was prevented when the bulky triisopropylsilyl group (but not the triethylsilyl group) was introduced at C-8, to give a high isolated yield (99%) of the 8-silylated nucleoside **60** <1999JOC7773>. Subsequent low-temperature deprotonation of **60** occurred at C-2 and a variety of electrophiles were successfully introduced (**Scheme 21**). Quantitative desilylation was achieved with TBAF, or occurred simultaneously with ammonolysis of the 6-chloro substituent (ammonia–methanol, sealed tube, 65–99% yield). The presence of a blocking phenyl substituent at C-8, introduced through a Stille coupling to the 8-stannyl derivative, also directed lithiation to C-2. Deprotonation was also directed away from C-8 to the lateral position in 6-methyl-9-(tetrahydropyran-2-yl)purine when potassium or sodium bases were used in preference to lithium, leading to syntheses of 6-fluoromethylpurines after quenching the anion with *N*-fluorobenzenesulfonamide <2003NN747>.



Scheme 20

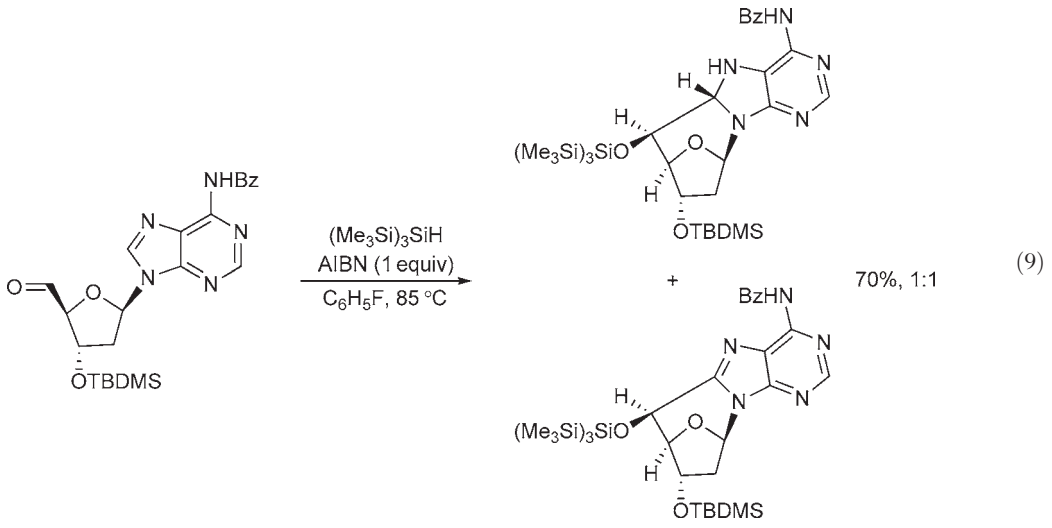


Electrophile	*R*	*Yield* (%)
I_2	I	78
$ClCO_2Me$	CO_2Me	46
$C_6H_{11}CHO$	$CH(OH)C_6H_{11}$	97
HCO_2Me	CHO	98

Scheme 21

10.11.5.4 Reactions with Free Radicals

Perfluoroalkyl radicals generated by indirect electrochemical reduction of the corresponding halides have been shown to undergo $S_{RN}1$ substitution at C-8 of various 6-substituted purine tetramethylammonium salts <1996JOC1331, 2000T2655>. Good yields were generally obtained; for example, tetramethylammonium adenine afforded 8-nonafluorobutyladenine in 60% yield. A contrasting regioselectivity was seen when 9-benzylpurine was reacted with simple alkyl and acyl radicals produced by the Minisci redox procedure <1995TL7875>. In all cases, selective substitution at C-6 was observed (36–61%). The generation of a carbon radical at C-5′ of purine deoxyribonucleosides led to cyclization onto C-8 (Equation 9) <2005EJO4640>. The initial product mixture contained both the addition product and the oxidized cyclopurine, indicating that the intermediate purine radical underwent competing further radical processes under the reaction conditions. The addition product was shown by NMR studies to be a single isomer corresponding to stereoselective cyclization through a chair-like transition state. Oxidation of the product mixture with chloranil gave the cyclopurine, of interest as a model for the lesions caused by some DNA damaging agents and radiation.



(9)

The successful nitration of purines by trifluoroacetyl nitrate was originally presumed to proceed through heterolytic dissociation of the reagent into nitroso and trifluoroacetyl radicals, followed by radical attack on the purine <1995TL7875>. However, detailed investigation has shown the reaction mechanism to be a combination of electrophilic and radical steps (see Section 10.11.5.2.3).

10.11.5.5 Intermolecular Cyclic Transition State Reactions

The reaction of 8-chlorotheophyllines with nitrilium imides to give [1,2,4]triazolo[3,4-*f*]purines may be described as a [3+2] cycloaddition process <2001JOC4055>; see Section 10.11.5.1. The purine bicycle has been prepared through the Diels–Alder–retro-Diels–Alder reaction of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine with 5-amino-1-benzylimidazole <1999JA5833>; see Section 10.11.10.3.

10.11.6 Reactivity of Nonconjugated Rings

The reactivity of purine scaffolds containing a single nonconjugated ring, such as xanthines, 2-, 6-, and 8-oxopurines, has been covered in the preceding sections. The oxidation of 3,9-dimethyluric acid by chlorine gas was revisited and studied in detail using product degradation and position-specific ^{13}C labeling in conjunction with NMR spectroscopy <2003OL4265>. Initial attack of the chlorine electrophile was shown to occur at C-5 of the bicycle to generate a transient amidinium species that predominantly underwent ring-opening–ring-closing rearrangement of the six-membered ring to give 7a-chloro-6-methyl-7-methyliminodihydroimidazo[1,5-*c*]imidazole-1,3,5-trione. A major side reaction was interception of the amidinium intermediate by solvent nucleophiles and spiro contraction of the six-membered ring to give 1,6-dimethyl-1,3,6,8-tetraazaspiro[4.4]nonane-2,4,7,9-tetraone. The regiochemical divergence of the acid-catalyzed ring opening of *cis*-fused 4,5-dimethoxytetrahydropurine-2,6,8-triones was rationalized by considering the two isomeric ring-twisted conformers of the unconjugated starting material, which led to opening of the five- or six-membered ring dependent on the preferred conformer <1997JHC477>. The structures of uric acid glycol half-ethers, originally postulated as purine rings incorporating angular acid aminal functionality, were revised to monocyclic structures where the six-membered ring has been opened <1995TL8885>.

10.11.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.11.7.1 Alkyl, Alkenyl, and Alkynyl Derivatives

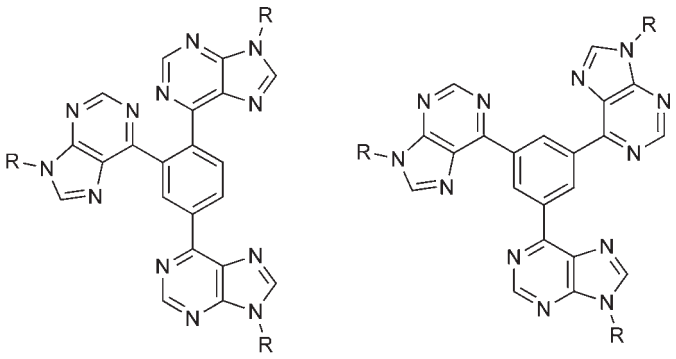
Bis(7-methylpurin-8-yl)methane underwent a high-yielding nitrosation and also reacted with dimethylformamide dimethylacetal under mild conditions at the exocyclic carbon, reflecting the high acidity of the hydrogens on the bridging carbon <1998JOC436>; see Section 10.11.5.2.6. The introduction of 6-fluoromethyl and 6-difluoromethyl

substituents to simple purines and purine nucleosides has been comprehensively investigated, starting from 6-(hydroxymethyl)purines <2005OBC3001, 2006S1848>. The use of standard fluorinating reagents for the one-step transformation on protected 6-(hydroxymethyl)purine nucleosides gave low to moderate yields of the 6-(fluoromethyl)purine derivatives, for example, (diethylamino)sulfur trifluoride (18% yield), perfluoro-1-butanesulfonyl fluoride and Hünig's base (13–31% yields), and [bis-(2-methoxyethyl)amino]sulfur trifluoride (41–46% yield). In contrast, a multistep protocol via transformation of the alcohols to the iodides (88–91% yields) allowed a higher-yielding fluorination by a Finkelstein-type reaction with silver(I) fluoride (AgF, Dowex, THF, rt, 72–81% yields), which exploited the poorer solubility of silver(I) iodide in THF compared to that of silver(I) fluoride <2005OBC3001>. For the preparation of 6-(difluoromethyl)purines, the 6-(hydroxymethyl)purine starting materials were first oxidized to the 6-formylpurines using the Dess–Martin periodinane (93–98% yields). These aldehydes were found to be very prone to hydration even in the presence of trace amounts of water <2006S1848>. Treatment of the aldehydes with [bis-(2-methoxyethyl)amino]sulfur trifluoride (−20 °C, CH_2Cl_2, 48–52% yields) gave reasonable yields of the 6-(difluoromethyl)purines. Deprotonation of the lateral position in 6-methyl-9-(tetrahydropyran-2-yl)purine, rather than C-8, was observed when potassium or sodium bases were used in preference to lithium, leading to 6-fluoromethylpurines after quenching with *N*-fluorobenzenesulfonamide <2003NN747>; see Section 10.11.5.3.4.

The reactions of a number of *C*-alkenyl-substituted purines have been studied. Various 6-(1-ethoxyvinyl)purines were made through Stille coupling of (1-ethoxyvinyl)tributyl stannane to 6-chloropurines, and were subsequently hydrolyzed to give the 6-acetylpurines (HCl aq., acetone, reflux, 65–93% yields). This method was substantially more efficient than other means to generate the 6-acetylpurines, for example, addition of methylmagnesium iodide to 6-cyanopurines <1997T2291>. Further manipulation of the 6-acetylpurines to 6-(1-aminoethyl)purines was achieved by reductive amination under standard conditions (amine HCl salts, $NaCNBH_3$, MeOH, 11–42% yields). 2′,3′-Di-*O*-acetyl-6-vinyl-2′-deoxyguanosine was converted into the corresponding 6-(2-*N*-acetylaminoethyl) derivative starting with an azidophenylselenation of the vinyl substituent (Me_3SiN_3, *N*-phenylselenophthalimide, CH_2Cl_2, rt, 71% yield) that delivered the azide to the terminal carbon of the vinyl group <1996TL8857>. Subsequent Staudinger reduction of the azide (PPh_3, Ac_2O) and hydrogenolytic deselenation with Raney nickel gave the 6-(2-*N*-acetylaminoethyl) product (80% yield), whereas attempted simultaneous hydrogenolysis of both groups led to competing overreduction to the 6-ethylpurine. 6-Vinyl-9-(tetrahydropyran-2-yl)purine was further elaborated at the vinyl terminus by Heck reactions with aryl and alkenyl halides ($Pd(OAc)_2$, $^iPr_2NEt$, DMF, 60–85 °C, 52–85% yields) <1999T211>. 6-Vinyl-9-(tetrahydropyran-2-yl)purine and 6-vinyl-9-benzylpurine underwent conjugate addition of amine, alkoxide, and thiolate nucleophiles to the vinyl terminus in THF or EtOH as solvent (40–98% yields) <2006EJO5083>.

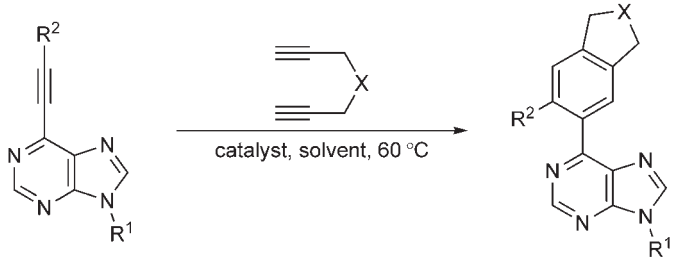
C-Alkynylpurines have been shown to undergo a number of synthetically useful functionalizations at the pendant alkynyl group. Unprotected 2-ethynyladenosine was coupled to a range of cyclic enol triflates under Sonogashira conditions (CuI, $Pd(PPh_3)_4$, LiCl, Et_3N, DMF, 80 °C, 23–87% yields) to afford the corresponding 2-(2-cycloalkenylethynyl)adenosines <1997T6747>. Hydrogenation of 6-(substituted 3-en-1-ynyl)purines with the Lindlar catalyst combination (Pd on $CaCO_3$ poisoned with lead and quinoline) gave either predominantly the 6-(*Z*-1,3-dienyl)purines or the completely reduced 6-alkylpurines depending on the exact nature of the substituents <1999T211>. The conjugate nucleophilic addition of amines to 6-vinyl-9-(tetrahydropyran-2-yl)purine and 6-vinyl-9-benzylpurine gave the corresponding 6-aminovinylpurines (45–97% yields) <2006EJO5083>. Secondary amines provided the (*E*)-configured enamines, whereas mixtures of (*E*)- and (*Z*)-enamines were produced by primary amines.

The participation of purine *C*-alkynyl substituents in [2+2+2] cyclotrimerization reactions was exploited to construct covalently linked purine trimers as models for Hoogsteen-type nucleobase triplet hydrogen-bonding structures <2001TL519>. Simple 6-ethynyl-9-benzylpurine and 6-ethynyl-9-(tetrahydropyran-2-yl)purine were successfully cyclotrimerized to the 1,3,5-tri(purinyl)benzenes **61** with an active nickel catalyst ($Ni(COD)_2$, PPh_3, THF, rt, 50–66% yields; COD = cyclooctadiene). Minor amounts of the regioisomers **62** (5–8% yields), separable by chromatography, were also isolated. Other common catalyst systems for this reaction, such as $TaCl_5$, Grubbs' catalyst, Wilkinson's catalyst, and $Ni(CO)_2(PPh_3)_2$, gave only unchanged starting material. This methodology was extended to cover the co-cyclotrimerization between 6-alkynylpurines and α,ω-diynes <2003TL785, 2004JOC9224>. A greater range of effective catalysts were observed for this process, but generally superior results were achieved using $NiBr_2(DPPE)_2$/Zn or $CoBr(PPh_3)_3$ (**Scheme 22**). A strong dependence for the success of the transformation on the degree and type of phosphorus ligation of the metal center (e.g., $Ni(PPh_3)_4$ was ineffective), as well as considerable variation in yield dependent on the linker in the diyne component were observed. It was speculated that the generally low activity of many group VIII metal catalysts (Co, Rh, Ir) in the reaction was attributable to the formation of cordinatively saturated, and thus catalytically inactive, complexes with the purine heterocyclic nitrogens <2004JOC9224> (see Sections 10.11.7.4.2 and 10.11.5.2.6).



61
R = Bn, THP

62
R = Bn, THP

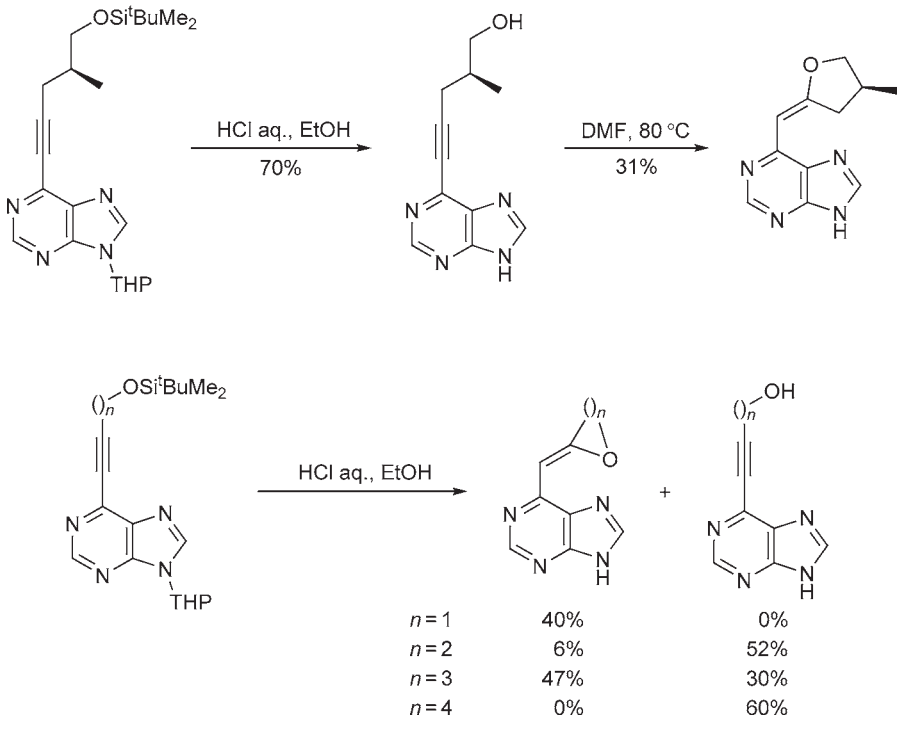


Catalyst	*Solvent*	R^1	R^2	*X*	*Yield (%)*
$CoBr(PPh_3)_3$	Toluene	Bn	H	O	55
$NiBr_2(DPPE)_2$/Zn	MeCN	Bn	Bu	O	55
$NiBr_2(DPPE)_2$/Zn	MeCN	Bn	Ph	O	88
$NiBr_2(DPPE)_2$/Zn	MeCN	Bn	Bu	$C(C(O)CH_3)_2$	59
$NiBr_2(DPPE)_2$/Zn	MeCN	Bn	Ph	$C(CO_2Et)_2$	64
$NiBr_2(DPPE)_2$/Zn	MeCN	THP	Ph	$C(CO_2Et)_2$	67
$NiBr_2(DPPE)_2$/Zn	MeCN	THP	Ph	CH_2	33

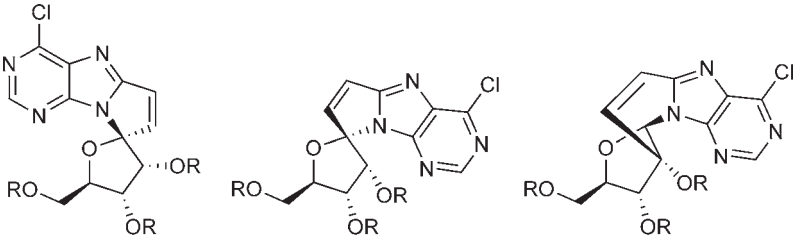
Scheme 22

The outcome of intramolecular cyclization of 6-(hydroxyalkyn-1-yl)purines was found to be complex and highly dependent on the chain length separating the alkyne and alcohol, and also on the degree of substitution of the chain <2005EJO4988>. 6-(*S*-5-Hydroxy-4-methylpent-1-yl)purine was isolable and cyclized smoothly on heating through the 5-*exo-dig*-mode to generate the 6-(*E*-tetrahydrofuranylmethylidene)purine (31% yield). However, the corresponding unsubstituted three-carbon linker gave spontaneous partial cyclization upon desilylation of the alcohol, giving the 6-(*Z*-tetrahydrofuranylmethylidene)purine and the uncyclized deprotected hydroxyalkyne. Interestingly, heating of the uncyclized alcohol in this case did not lead to cyclization, whereas heating the 6-(*Z*-tetrahydrofuranylmethylidene)purine isomerized this to the (*E*)-isomer. Longer carbon chains showed no cyclization, while the one- and two-carbon linkers gave the (*Z*)-allene oxide and traces of the (*Z*-oxetanylmethylidene)purine, respectively (**Scheme 23**).

A 6-chloro-8-(2,2-dibromovinyl)purine nucleoside gave rise to an exocyclic vinyl radical when treated with tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) under slow addition conditions <1999JOC7081>. The initially formed vinyl radical was capable of both 1,5-hydrogen abstraction and, to a lesser extent, 1,6-hydrogen abstraction, generating carbon-centered radicals on the furanose which added back to the C-8 bromovinyl substituent. Elimination of HBr gave rise to the isolated products **63** (18% yield), **64** (14% yield), and **65** (5% yield) after chromatography. Little diastereofacial selectivity was seen for the cyclization of the C-1′ furanose radical to the C-8 vinyl group, in contrast to the related cyclizations of uridine nucleosides where a strong directing effect of the 2′-alkoxy group was observed.



Scheme 23



10.11.7.2 Cyanopurines

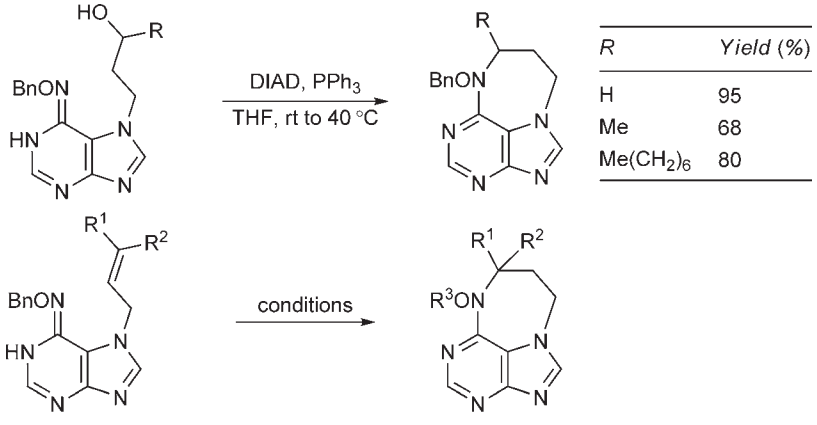
Attempts to produce 6-carboxamidinopurines from 6-cyanopurines by nucleophilic attack of ammonia or amines usually fail, giving instead the pyrimido[5,4-*d*]pyrimidine-rearrangement products <2001J(P1)2532>. However, 9-methyl- or 9-aryl-6-cyanopurines did generate the 6-(methoxyformidoyl)purines when treated with catalytic 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol at reflux (65 °C, 88–97% yields) <2004OBC1019>. Higher temperatures, or the use of ethanol at reflux, led instead to nucleophilic displacement of the 6-cyano substitutent to give 6-alkoxypurines (46–97% yields). The 6-(methoxyformidoyl)purines were converted to 6-carboxamidinopurines by reaction with methylamine hydrochloride in methanol–dichloromethane (reflux, 86–92% yields). In contrast, when the 6-(methoxyformidoyl)purines were stirred with aqueous methylamine at room temperature, these more basic conditions gave rearrangement to pyrimido[5,4-*d*]pyrimidines through nucleophilic attack at C-8, opening of the five-membered ring, and reclosure onto the imidate.

10.11.7.3 Aminopurines

10.11.7.3.1 Alkylation and arylation

8-Aminotheophylline underwent a two-step reductive amination on the exocyclic amine with 2-carboxybenzaldehyde (neat mixture, 120 °C then $NaBH_4$, MeOH, 0 °C, 39% yield) to give 8-[*N*-(2-carboxyphenyl)methyl]aminotheophylline <1999JHC639>. Heating this material at 300 °C formed a novel tetracyclic 2,4-benzodiazepinopurine ring system (36% yield) through intramolecular amide formation to N-7. 8-Aminotheophylline was also the starting material for the preparation of tricycles through alkylation on N-7 with bifunctional alkylating agents, followed by intramolecular alkylation or acylation of the 8-amino substituent <1998JHC135> (see Section 10.11.5.2.1). The Sharpless asymmetric aminohydroxylation reaction was used in an efficient, direct preparation of *cis*-opened diol epoxide adducts of O-protected deoxyadenosine and *trans*-7,8-dihydroxy-7,8-dihydrobenzo[α]pyrene <1998JA3520>. These products were previously difficult to prepare by the customary routes involving S_NAr reaction of amine-functionalized pyrenes and halopurines. The adducts are monomeric models of the alkylation products formed between purine bases in DNA and metabolically activated, carcinogenic polyaromatic hydrocarbons. The alkylation of nucleosides and DNA with the simple quinone methide derived from *O*-(*tert*-butyldimethylsilyl)-2-bromomethylphenol (KF, DMF, 37–50 °C) was investigated as a model system for studying the mechanism and selectivity of DNA alkylation by common metabolically activated drugs and xenobiotics, for example, the mitomycins and anthracyclins <1999JA6773>. 2′-Deoxyadenosine formed the stable C-6 amine benzylation product when incubated at 50 °C (43% yield), and an identical mode of reactivity was observed with 2′-deoxyadenosine in single-strand (ss DNA) and double-strand DNA (ds DNA). Likewise, 2′-deoxyguanosine reacted through the exocyclic C-2 amino group (31% yield). The relative reactivity of the two isolated purine nucleosides was found to be dG:dA 4.6:1, but this selectivity increased to 19:1 when the nucleosides were incorporated into dsDNA. The greater propensity for deoxyguanosine alkylation mirrored the known specificity of anticancer antibiotics binding in the minor groove of dsDNA for alkylation of the guanine bases.

The intramolecular alkylation of 6-(benzyloxy)iminopurines by electrophiles tethered to N-9 was studied during studies toward the total synthesis of the cytotoxic marine alkaloid asmarine A <2001TL5941, 2003T6493, 2005JOC199>. For alkylation using primary and secondary alcohols, a Mitsunobu procedure was successful to yield the [6,5,7]tricycle <2001TL5941, 2003T6493>. However, to introduce the tertiary center present in the natural product, other methods involving electrophilic activation of a triply substituted alkene were required (**Scheme 24**)



R	*Yield* (%)
H	95
Me	68
$Me(CH_2)_6$	80

R^1	R^2	R^3	*Conditions*	*Yield* (%)
Me	Me	Bn	i, $Hg(OAc)_2$, THF, 40 °C	
			ii, $NaBH_4$, NaOH	69
Me	Me	Bn	i, I_2, $NaHCO_3$, EtOH, rt	
			ii, Bu_3SnH, $h\eta$, THF, reflux	61
Me	Me	H	i, 15% HBr/AcOH, rt	
			ii, 30% HBr/AcOH, 100 °C	68
Me	Pr	H	i, 15% HBr/AcOH, 100 °C	
			ii, 30% HBr/AcOH, 100 °C	33

Scheme 24

<2005JOC199>. Aminomercuration or aminoiodination, both followed by reduction steps to remove the electrophile, were only suitable for uncongested 1,1-dimethyl alkenes. To prepare systems bearing larger substituents, activation of the double bond by protonation using HBr in AcOH was more successful, and was applied to the synthesis of asmarine analogues <2003T6493, 2005JOC199>. These conditions were also applicable to the cyclization of tertiary alcohols <2005JOC199>.

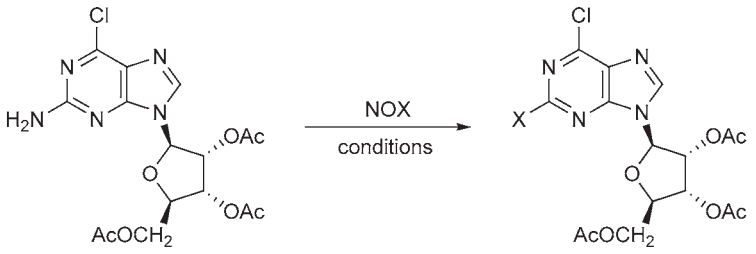
N-Arylation of 2-amino-6-chloro-9-benzylpurine with arylboronic acids at room temperature was achieved using stoichiometric quantities of copper(II) acetate to promote the coupling (2 equiv $Cu(OAc)_2$, cat. 4-dimethylaminopyridine (DMAP), 2 equiv Et_3N, $CHCl_3$, 49–67% yields) <2004TL195>. More conventional Buchwald conditions using catalytic palladium were applicable to the cross-coupling of protected 2′-deoxyadenosine or 2′-deoxyguanosine at the exocyclic amines to halopurine nucleosides (10 mol% $Pd(OAc)_2$, 15 mol% 2,2-bis(diphenyl-phosphanyl)-1,1-binaphthyl (BINAP), Cs_2CO_3, 24–90% yields) <2000OL293> (see Section 10.11.7.4.2). 8-Aminocaffeine was arylated on the 8-amino substituent by Ullman reaction with 2-chlorobenzoic acid (Cu, K_2CO_3, DMF, reflux, 40% yield) <1995JHC941>. In the absence of the N-7 methyl substituent, the Ullman coupling to 8-aminotheophylline occurred at N-7 instead.

2,6-Diaminopurine reacted regioselectively at the C-6 amino group with 1,2-bis[(dimethylamino)methylene]hydrazine to form 2-amino-6-(1,2,4-triazol-4-yl)purine as a single product (85% yield) <2000TL7211>. The conversion to the 1,2,4-triazolyl group was useful in directing subsequent purine N-alkylation specifically to N-9 (vs. N-7) (see Sections 10.11.3.1 and 10.11.5.2.1). Displacement of the triazole by aqueous hydroxide ions gave 9-alkylguanines in high yield. The use of 1,2,4-triazol-4-yl substituents as pseudohalides for S_NAr reactions and transition metal-catalyzed coupling reactions has been demonstrated (see Section 10.11.7.3.2).

10.11.7.3.2 Displacement reactions

There are three common approaches to the displacement of amine substituents from purines. First, diazotization and dediazoniation have been used to replace amine substituents, primarily with hydrogen or hydroxyl, carboxyl, and halide functionalities. Second, the S_NAr reactions of quaternary ammonium substituents have provided useful synthetic adjuncts to the displacement reactions of halopurines. Finally, of increasing importance has been the conversion of aminopurines (or oxopurines) to N-linked 1,2,4-triazoles (and other azoles), which function as pseudohalogens and can be displaced by nucleophiles or take part in transition metal-catalyzed reactions.

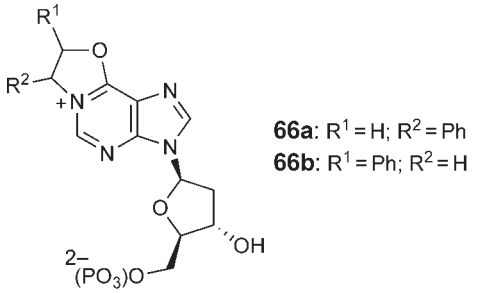
There remains uncertainty over the relative contribution of cationic versus radical intermediates during the diazotization and displacement reactions of aminopurines <2002JOC6788>. Mechanistic studies on the reaction of 9-propylpurin-6-yl diazotate (formed by treating 6-amino-9-propylpurine with an alkyl nitrite in the presence of a strong base) with acetic acid in various solvents showed a product distribution that supported rapid evolution of a heteroaryl cation intermediate and reaction with available nucleophiles through homolytic processes <1999OL1957>. In particular, trapping of the putative cation by benzene was observed, leading to the 6-phenylpurine. Theoretical and experimental studies on the diazotization of guanosines provided evidence for the generation of a cation at C-2 that ring-opened to a ketene–carbodimide species capable of reclosure to give a rearranged oxanosine <1999OL273, 1999JA6108>. The inclusion of iodoacetic acid as a selective radical trap in the diazotization of 2-amino-6-chloropurine nucleosides by nitrite salts, and quaternary ammonium halides or antimony(III) halides suggested that competing heterolytic and homolytic processes were operating at room temperature <2002JOC6788>. The small amount of hydro-dediazoniation product produced in the absence of iodoacetic acid was eliminated when the radical trap was introduced, accompanied by an increase in the amount of 2-iodo-6-chloropurines relative to other 2-halo-6-chloropurines. It is likely therefore that C-2 and C-6 purinediazonium cations fragment by both heterolytic and homolytic processes. Optimized procedures for the clean halo-dediazonation using antimony trihalides as catalysts were determined <2002JOC6788>. An alternative methodology avoiding the use of the toxic antimony compounds was developed, involving several convenient routes for the *in situ* generation of nitrosyl chloride or nitrosyl bromide (**Scheme 25**) <2003JOC666>. The diazotization of 3′,5′-diacetyl-6-aminopurine-2′-deoxyribonucleoside using *tert*-butyl nitrite in bromoform at 65 °C gave the corresponding 6-bromopurine nucleoside (57% yield) <2001JOC8592>. A 2,6-diaminopurine nucleoside was selectively acylated at the C-2 amine with isobutyryl chloride <2000T1047>. This served to protect the C-2 amino substituent in a subsequent diazotization and hydrolysis of the 6-amino group ($NaNO_2$, AcOH, H_2O, 88% yield). A 2-amino-6-methoxypurine nucleoside was transformed to purin-2-yl carboxylates when diazotization was carried out in the presence of the appropriate acids (isoamyl nitrite, CH_2Cl_2, rt; benzoic acid, 38%; *N*-BOC-L-valine, 49%), although hydrolysis, hydro-dediazoniation, and chloro-dediazoniation side products were also formed in substantial quantities (BOC = *t*-butoxycarbonyl) <2005TL8225>.



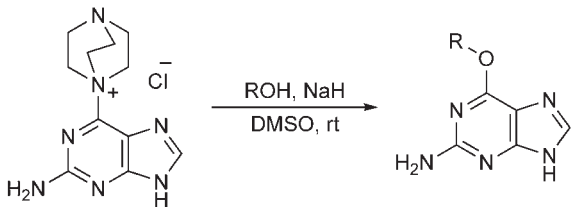
Conditions	*X*	*Yield (%)*
9 equiv Me_3SiCl, 3 equiv $BnNEt_3{\cdot}NO_2$, CH_2Cl_2, rt	Cl	83
3.5 equiv Me_3SiCl, 1.5 equiv $BnNEt_3{\cdot}NO_2$, 5 equiv $NaNO_2$, CH_2Cl_2, rt	Cl	86
9 equiv Me_3SiCl, 20 equiv $BnNEt_3{\cdot}NO_2$, CH_2Br_2, rt	Br	85
5 equiv AcCl, 5 equiv $BnNEt_3{\cdot}NO_2$, CH_2Cl_2, 5 °C	Cl	83

Scheme 25

The generation of intermediate trialkylammonio purine species can be used to increase the rate of nucleophilic displacement of 6-chloropurines. The addition of catalytic DMAP was found to enhance the reactivity of 2-amino-*N*,*N*,*N*-trimethyl-9*H*-purine-6-ylammonium chloride to nucleophilic displacement by alkoxides <2002S538>. This methodology was applied to the synthesis of an [^{18}F]-labeled inhibitor of O^6-methylguanine-DNA methyltransferase <2002TL6301>. The bicyclic tertiary amine 1,4-diazabicyclo[2.2.2]octane (DABCO) was found to be a useful alternative to trimethylamine, with the intermediate 6-(1-azonia-4-azabicyclo[2.2.2]oct-1-yl)purine salts readily isolated <1997J(P1)185>. The quaternary ammonium salts were readily displaced by alkoxide nucleophiles (**Scheme 26**). The salt formed from DABCO and 6-chloro-2-aminopurine was also used to construct 6-aryloxy- and 6-alkoxyguanine adducts related to the anticipated DNA-damage products resulting from exposure to styrene <2006EJO507>. 6-Chloropurine nucleosides were reacted with trimethylamine to generate the quaternary trimethylammonium salts *in situ*, that reacted with tetrabutylammonium triphenyldifluorosilicate as a source of nucleophilic fluoride ion to give 6-fluoropurine nucleosides (59–72% yields) <1999NN2327>. Styrene 7,8-oxide is a carcinogenic epoxide that reacts predominantly with DNA through alkylation of N-7 of guanine, with some reactivity toward N-1 and N-6 also seen. The N-1 adducts deaminate through attack of the terminal alcohol onto C-6 of the purine with loss



66a: R^1 = H; R^2 = Ph
66b: R^1 = Ph; R^2 = H

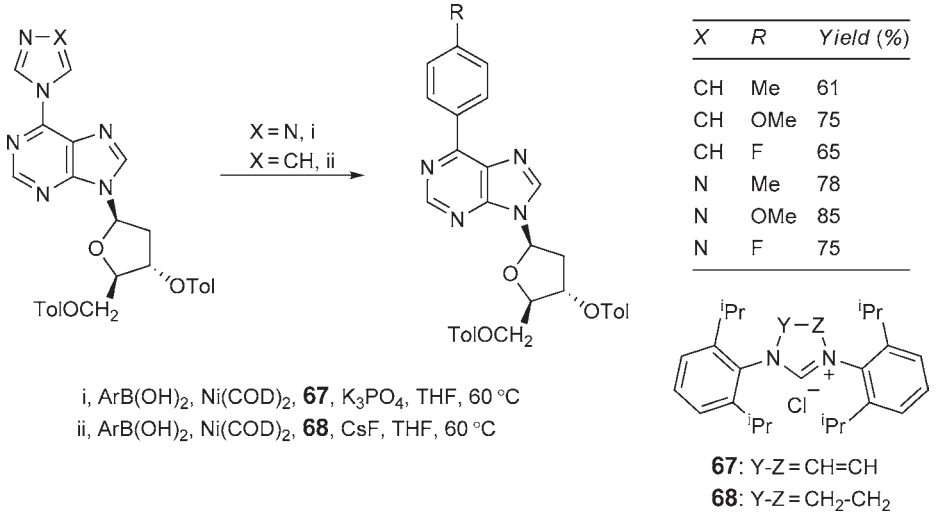


R	*Yield (%)*
Me	88
$H_2C{=}CHCH_2$	87
Bn	81
$(c\text{-}C_6H_{11})CH_2$	51

Scheme 26

of ammonia to give cyclic intermediates **66**, followed by hydrolysis to yield 7-alkylinosine derivatives <1999OL1233>. Two separate hydrolysis pathways exist, corresponding to water attacking directly at C-6 for the intermediate **66a** or at the benzylic carbon for isomeric compound **66b**.

The conversion of purine exocyclic amines to 1,2,4-triazol-4-yl substituents was readily achieved using 1,2-bis[(dimethylamino)methylene]hydrazine <1995JA5951, 2000TL7211>. Alternatively, N-linked triazole, tetrazole, or imidazole rings have been introduced as substituents by forming activated phosphonium species from 6-oxopurines followed by reaction with the heteroarenes <1995TL91, 2000OL3497>. The azoles were readily displaced by hydroxide <2000TL7211>, succinimide or phthalimide <1995TL91>, amines <1995JA5951, 2000OL3497, 2006JOC7773>, alkoxides and thiols <1995JA5951>. This process therefore provided a simple substitution of aminopurines by other heteroatom nucleophiles without the need for diazotization. Furthermore, 6-(imidazol-1-yl)-, 6-(benzimidazol-1-yl)-, and 6-(1,2,4-triazol-4-yl)purine nucleosides were competent electrophilic coupling partners in a nickel-catalyzed cross-coupling with arylboronic acids, leading to the 6-arylpurine derivatives (**Scheme 27**) <2004OL3421>.



X	R	Yield (%)
CH	Me	61
CH	OMe	75
CH	F	65
N	Me	78
N	OMe	85
N	F	75

Scheme 27

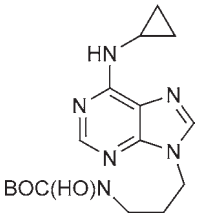
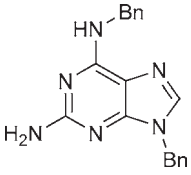
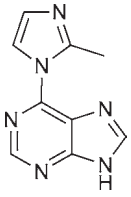
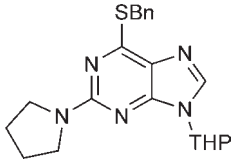
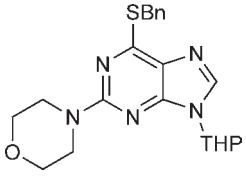
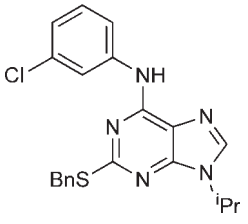
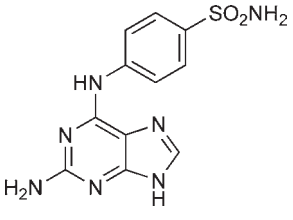
10.11.7.4 Halopurines

10.11.7.4.1 Displacement by heteroatom nucleophiles

Substitution of halopurines at C-2 and C-6 has become a well-developed synthetic process, with a wide variety of nucleophilic aromatic substitution and palladium-catalyzed C–N or C–O bond formations exemplified in the literature. The use of selective, sequential substitution reactions on polyhalopurine scaffolds is the basis of an increasing number of combinatorial syntheses of polysubstituted purines, both in solution and on solid phase. The introduction of N-, O-, or S-substituents has often been combined with transition metal-catalyzed C–C bond-forming reactions (see Section 10.11.7.4.2) and selective N-alkylation (see Section 10.11.5.2.1) to provide versatile routes to purines with multiple, diverse substituents.

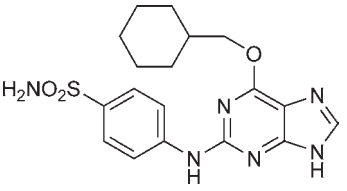
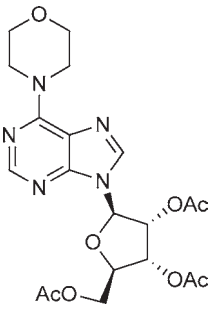
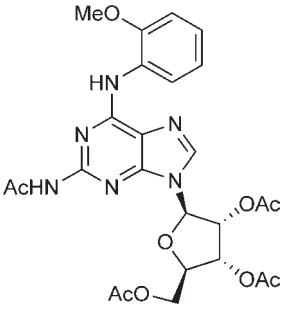
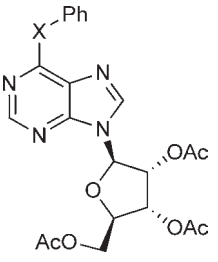
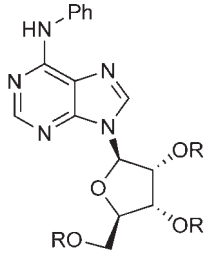
The direct nucleophilic aromatic substitution of purines and purine nucleosides bearing a single halogen substituent has been achieved with a range of reaction conditions, usually with very high yields. For nucleophilic amines, azoles, and alkoxides reacting with 6-chloropurines, no additional catalyst is generally required: see <1996CHEC-II(7)397> and, for example, <1995JME2582, 1998TL1827, 1998T6605>, and **Table 6**. Pyrrolidine displaced the halide from 2-iodo-6-benzylsulfanyl-9-(tetrahydropyran-2-yl)purine at room temperature when used as solvent <2001TL8165> but more typical conditions for displacements at this position involved higher temperatures <2002T7911>. A range of novel 8-(dialkylamino)xanthines were prepared by the known direct displacement of 8-bromoxanthines <1999EJO2419>. The copper(I)-mediated Ullman reaction (CuBr, DMSO, 180 °C, 45% yield) of 8-bromotheophylline with ethyl 2-aminobenzoate gave displacement of the xanthine 8-bromo substituent by the aniline, and was accompanied by acylation of the xanthine N-7 to produce a tetracyclic purino[8,7-*b*]quinazoline <1995JHC941>. The substitution of 6-chloroxanthine nucleosides with nitrogen, sulfur, and oxygen nucleophiles was conducted either directly, or through the formation and isolation of a 6-(1-pyridinium) salt <1995J(P1)15>.

Table 6 Displacement reactions of halopurines

Reacting halogen	*Conditions*	*Product*	*Yield (%)*	*Reference*
6-Cl	(*c*-Pr)NH_2, THF, 25 °C		100	1998T6605
6-Cl	$BnNH_2$ (1.05 equiv), Et_3N, DMF, 80–100 °C		95[a]	1998TL1827
6-Cl	2-Methylimidazole (4 equiv), BuOH, reflux		84	1995JME2582
2-I	Pyrrolidine (neat), 20 °C		n.d.[b]	2001TL8165
2-I	Morpholine, $^nPrN_3$, DMA, 120 °C		91	2002T7911
6-Cl	3-Cl(C_6H_4)NH_2, HCl, BuOH, 120 °C		98	2005EJO939
6-Cl	4-SO_2NH_2-(C_6H_4)NH_2 (2 equiv), CF_3CO_2H (5 equiv), CF_3CH_2OH, reflux		77	2003CC2802

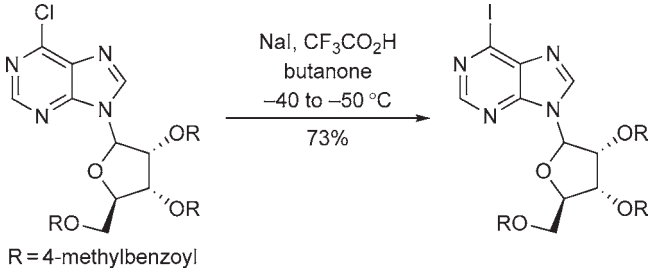
(*Continued*)

Table 6 (Continued)

Reacting halogen	*Conditions*	*Product*	*Yield (%)*	*Reference*
2-F	4-$SO_2NH(C_6H_4)NH_2$ (2 equiv), CF_3CO_2H (5 equiv), CF_3CH_2OH, reflux		91	2003CC2802
6-Br	Morpholine, (2.5 equiv), DME, 25 °C		91	2001JOC8592
6-Br	2-MeO(C_6H_4)-NH_2, MeOH, 65 °C		95	2001JOC8592
6-Br	PhSH or PhOH, DBU, MeCN, 25 °C		X = S 92 X = O 82	2001JOC8592
6-I	$PhNH_2$, MeCN, 70 °C	 R = (4-methylbenzoyl)	80	2004OL2917

[a]Yield for two-steps: C-6 S_NAr followed by N9 benzylation.
[b]Yield not given.

Weakly basic amines, particularly anilines with electron-withdrawing substituents, often fail to react with halopurines under simple conditions and significant research effort has been directed to overcome this. Anilines were found to be efficiently introduced by acid-mediated processes, where the purine was activated to nucleophilic attack by protonation at a ring nitrogen <2005EJO939, 2003CC2802>. A combination of trifluoroacetic acid in 2,2,2-trifluoroethanol as solvent was particularly effective for the displacement of the halide from 6-cyclohexylmethoxy-2-fluoropurine and 2-amino-6-chloropurine by anilines <2003CC2802>. Contrary to the expected sequence for S_NAr reactivity (F > Cl > Br > I), it was found that 6-bromo and 6-iodopurine nucleosides were more reactive to nucleophilic aromatic substitution than the corresponding 6-chloro derivatives, and were readily displaced by anilines and weakly basic amines without additional activation <2001JOC8592, 2004OL2917>, see **Table 6**. For the 6-bromopurines, substitution with anilines was only successful when highly polar solvents (alcohols, DMF) were used. In contrast, a 6-iodopurine nucleoside reacted with aniline in acetonitrile. Furthermore, a marked decrease in reactivity of the 6-bromonucleosides was seen when acetyl protecting groups on the sugar were replaced by *t*-butyldimethylsilyl (TBDMS) groups <2001JOC8592>. The 6-bromopurine nucleosides were prepared by bromination of the corresponding 6-hydroxy compounds (hexamethylphosphoric triamide (HMPT), *N*-bromosuccinimide (NBS), LiBr, MeCN) <2000TL1695> or by diazotization–bromination of the 6-aminopurines (^tBuONO, $CHBr_3$, 65 °C) <2001JOC8592>. The 6-iodo substituent was introduced by a novel low-temperature aromatic Finkelstein reaction of the corresponding 6-chloro compound, where trifluoroacetic acid was essential to promote the halogen exchange by protonation of the purine (Equation 10) <2004OL2917>.

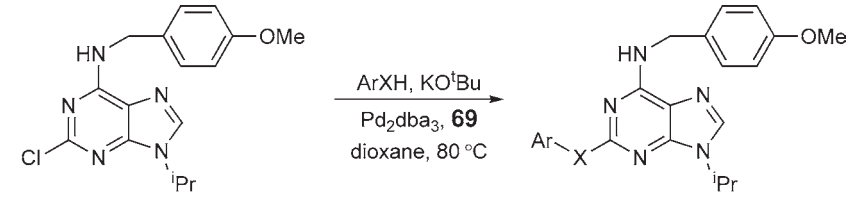


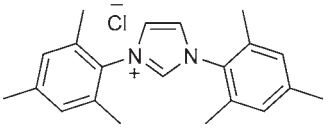
(10)

The palladium-catalyzed amination of halopurines has emerged as a useful alternative for the introduction of aniline substituents, reviewed in <2005CSY83>. The metal-mediated process may offer advantages even when uncatalyzed S_NAr is possible, as in some cases the uncatalyzed reactions have been shown to be slow to reach completion, for example, if there are existing amino substituents on the purine. This can then render the direct S_NAr reactions unsuitable for use in combinatorial, solid-phase synthetic approaches <1999CBO361, 2001TL8751>. Much of the elucidation of the optimum conditions for palladium-catalyzed amination of halopurines was carried out in the context of generating dimeric purine species linked through an exocyclic nitrogen that represent the cross-links formed when DNA is exposed to nitrous acid <2000JOC2959, 2000OL293>. Typical conditions used the Buchwald–Hartwig catalyst combinations ($Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3) <2000OL293> and similar reagents were also suitable for the substitution of 6-chloro-9-(4-methoxylbenzyl)purine by mannopyranosylamines (Pd_2DBA_3, (−)-BINAP, KO^tBu, 140 °C) <1999TL2573>. A comparison of 6-iodo and 6-chloro derivatives in the latter study showed no difference in reactivity. An efficient synthesis of 2-anilino and 2-aryloxypurines by palladium-catalyzed reactions of 2-chloropurines was realized using an N-heterocylic carbene ligand (**Scheme 28**) <2001TL8751>. Although very high yielding, this catalyst combination was not suitable for introducing haloanilines, other than fluoroanilines, due to competing reaction of the aryl halide.

For the amination of 6-bromopurine nucleosides with 4-methylaniline, a marked improvement in efficiency was seen with bis-coordinating ligands compared to monocoordinate phosphines <1999JA6090, 2001JA7779>. For example, bidentate (2′-dicyclohexylphosphanylbiphenyl-2-yl)dimethylamine led to a 2.5-fold increase in the yield of the product when compared to the monodentate biphenyl-2-yl-dicyclohexylphosphane (ligand, Pd_2DBA_3, K_3PO_4, DME, 80 °C). Good yields of a variety of 6-anilinopurine nucleosides were obtained (52–69% yields) <1999JA6090>. Interestingly, no such differentiation in ligand suitability was seen for the related coupling of 4-methylaniline to 2-bromopurine nucleosides <2001JA7779>. The difference in behavior was rationalized as reflecting the different possibilities for palladium coordination. Amination at C-6 introduced a site for stable complexation of the metal between N-7 and the aniline in a five-membered ring, tending to remove the metal from the catalytic cycle unless a bidentate ligand was present, whereas amination at C-2 produced a less-stable four-membered complexation between the aniline and N-1. When the optimum catalyst conditions were applied to the coupling of aminopyrenes to

6-bromopurine nucleosides, significant over-reaction of the product to couple to a further equivalent of the bromopurine was observed, producing a purine dimer. This behavior was not seen with the equivalent reactions of 2-bromopurine nucleosides <2003JOC6020>. 2′-Deoxy-2-bromoinosine was efficiently coupled to a variety of alkyl and aryl amines using Buchwald–Hartwig conditions ($Pd(OAc)_2$, Cs_2CO_3, BINAP, toluene, 80 °C, 40–94% yields) <2000TL7281>. The bidentate phosphine ligand Xantphos was found to be optimum for the amination of 6-bromo- and 6-chloropurine nucleosides with azole heterocycles (**Scheme 29**) <2006AGE3660>. Exclusion of palladium from this reaction resulted in no formation of product, eliminating the possibility of a competing S_NAr mechanism.

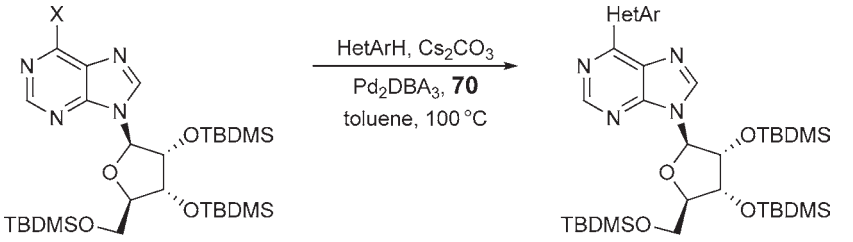


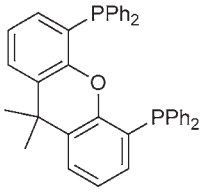


69

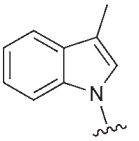
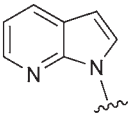
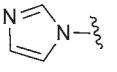
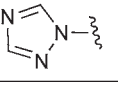
Ar	*X*	*Yield (%)*
Ph	NH	95
Ph	NMe	97
4-$CH_3C_6H_4$	O	90
2-$CH_3C_6H_4$	O	90

Scheme 28



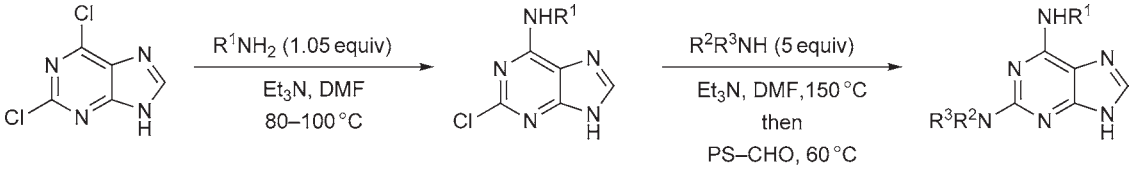


70

X	*HetAr*	*Yield (%)*
Br		91
Br		72
Cl		45
Cl		85

Scheme 29

2,6-Dihalopurines have been widely studied in the context of achieving selective, sequential S_NAr reactions. The 6-halo substituent has been found to be substantially more reactive. Thus, 2,6-dichloropurine underwent monosubstitution with imidazoles to generate 2-chloro-6-(imidazol-1-yl)purines (imidazole 6 equiv, DMF, 65 °C, 66–72% yields) <2006JOC4216>. The reactions of 2,6-dichloropurine with 1 equiv of primary or secondary amines gave good yields of the isolated 2-chloro-6-aminopurines (47–92% yields, **Scheme 30**) <1998TL1827>. However, subsequent displacement of the 2-chloro substituent required an excess (5 equiv) of amine and higher temperature to force the reaction to completion. The reduction in reactivity toward nucleophilic displacement of 2-halopurines when substituted at C-6 with amines or other strongly electron donating groups has been a complicating factor in many synthetic routes based on sequential S_NAr of 2,6-dihalopurines. In this case, the synthesis was adapted for solution-phase parallel synthesis by using a formyl-polystyrene resin to scavenge the excess amine necessary for the second displacement, so achieving high yields and purities of the 2,6-diaminopurine products (**Scheme 30**). By combining this sequence with selective alkylation at N-9 (see Section 10.11.5.2.1), a library of 2,6,9-trisubstituted purines was produced <1998TL1827>.



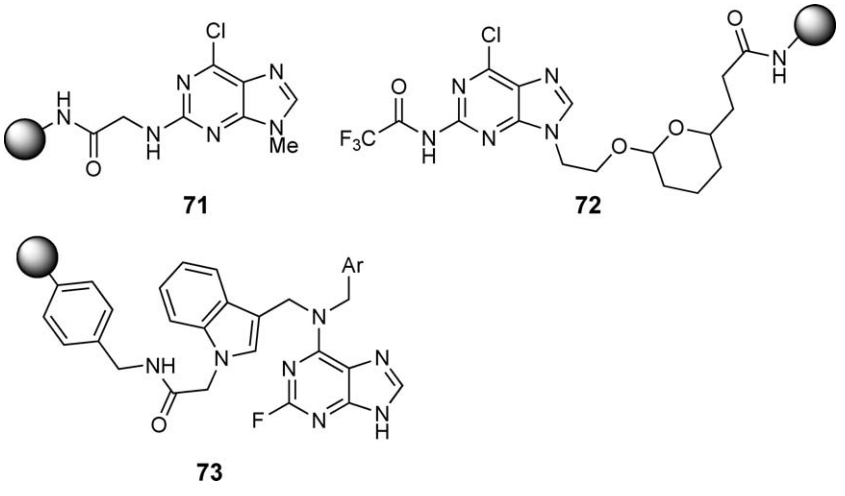
R^1	R^2	R^3	*Yield* (%)	*Purity* (%)
$PhCH_2$	$PhCH_2$	H	77	95
$PhCH_2$	Morpholino		62	98
c-C_6H_{11}	$PhCH_2$	H	62	87

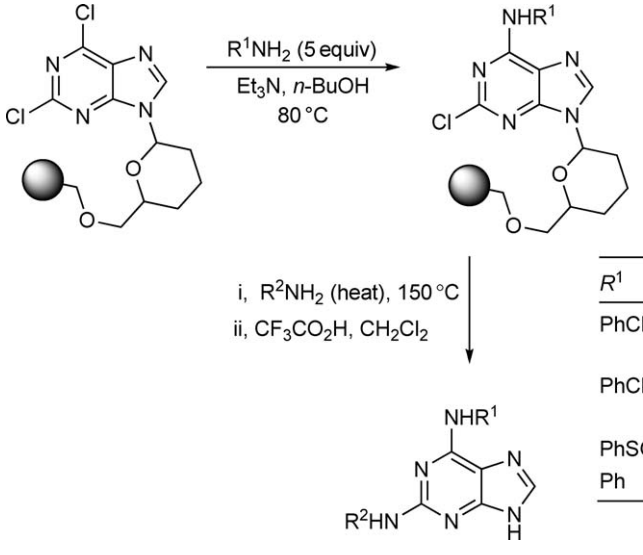
Scheme 30

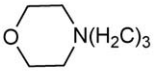
6-Chloro-2-iodo-9-(tetrahydropyran-2-yl)purine underwent selective S_NAr reaction at C-6 with benzyl thiol under mild conditions ($PhCH_2SH$, Et_3N, 60 °C, 82% yield) to give 6-benzylsulfanyl-2-iodo-9-(tetrahydropyran-2-yl)purine <2001TL8161>. Subsequent displacement of the 2-iodo substituent with amines was possible (piperidine-2-methanol, $^iPr_3N$, DMA, 110 °C, 100% yield). For 6-chloro-2-iodo-9-isopropylpurine, selective substitution of the 6-chloro group with benzylamines and anilines was achieved at temperatures below 40–50 °C, while further reaction of the 2-iodo substituent with pyrrolidine-2-methanol required much harsher conditions (140 °C) <2001JHC299>. The S_NAr reaction of 2,6,8-trichloro-7-methylpurine with the terminal amino group of an immobilized H-Ala-Phe-(BOC)Lys-NH-cellulose tripeptide, followed by deprotection of the lysine side chain and cyclization, led to one major cyclic product when the reaction was carried out with heating under microwave irradiation <2001JOC507>. Although the cyclic product was not characterized fully, it was anticipated based on the reactivity of simple purines that cyclization had occurred between C-8 (initial displacement) and C-6.

Driven by the proven utility of purine-based compound libraries in drug discovery <1998SCI533, 1999CBO361> (see Section 10.11.12.2), there has been a focus of interest on combinatorial synthesis of polysubstituted purines both in solution and on solid supports. Since the starting materials are generally 2,6-dihalopurines, there has been significant effort to produce hybrid synthetic routes that combine halide displacement by heteroatom nucleophiles with palladium-catalyzed C–C bond-forming reactions and/or selective purine N-alkylation on these substrates <1997TL1161, 1997T6747, 1998TL1827, 2001TL2771, 2001TL6515, 2001TL8161, 2001TL8169, 2001JOC8273, 2002T7911, 2002TL6169>. For example, 2,6-dichloropurine attached via N-9 to a Rink polystyrene resin was subject to displacement of both halides under vigorous conditions (amines 26 equiv, NMP, 125 °C) <2001TL6515>. Bromination of the resin-bound 2,6-diaminopurines at C-8 was followed by Stille couplings (see Section 10.11.7.4.2). In contrast, (4-(2,6-dichloropurin-9-yl)cyclopent-2-enyl)methanol attached through the carbocycle to a resin underwent selective displacement of the 6-chloro substituent (5 equiv amine, 5 equiv Et^iPr_2N, *n*-BuOH, 80 °C) <2000OL1065>. 4-Aminobenzyl-(2-fluoro-9*H*-purin-6-yl)amine, linked to a solid support through the terminal aniline, was subject to selective N-alkylation at N-9 under Mitsunobu conditions followed by S_NAr reaction of the 2-fluoro substituent with amines <1997TL1161>.

Two resin-attachment strategies were developed for the combinatorial preparation of large libraries of 2-(acylamino)- and 2-(alkylamino)-6-aminopurines <1996JA7430>. In the first, the 6-chloro-2-amino-9-methylpurine was linked by a glycinamide at the C-2 amine to a Rink resin **71**. Acylation of the exocyclic amine was followed by S_NAr substitution of the 6-chloro substituent (amines, DMF:DMSO 1:1, 4 °C) where low temperature and extended reaction time (16 h) were necessary to prevent competitive deacylation of the 2-acylamino groups. A library of 348 purines (6 × 58 2-acetamido × 6-amino) was prepared in this way. Alternatively, 2-(trifluoroacetylamino)-6-chloro-9-(2-hydroxyethylamino)purine was attached to an aminoalkyl solid support via an acid-labile tetrahydropyran linker **72**. Mitsunobu alkylation at the 2-acylamino substituent was followed by displacement of the 6-chloro group (amines, DMSO, 70 °C) with concomitant deacetylation. 2,6-Dichloropurine linked by a tetrahydropyran to Merrifield resin was also used to prepare a library of analogues of the kinase inhibitor olomoucine (**Scheme 31**) <1997JOC201>; see Section 10.11.12.2. Selective displacement of the 6-chloro substituent took place under moderate conditions (amines 5 equiv, DMF, Et_3N, 80 °C) and was also successful for benzyl alcohols and hydrazines. Amination of the 2-chloro group required much harsher conditions (neat amine, 150 °C). Although the resin, linker, and 6-amino substituents tolerated this regime, 6-benzyloxy and 6-hydrazino substituents did not. The selective displacement of 2-fluoro-6-chloropurine at the 6-chloro group (Et^iPr_2N, THF, 60 °C) was used to load the purine scaffold onto the functionalized indole-linked resin **73** <2001TL2771>. Mitsunobu alkylation at N-9 was followed by displacement of the 2-fluoro substituent (amines, BuOH:DMSO 4:1, 120 °C).

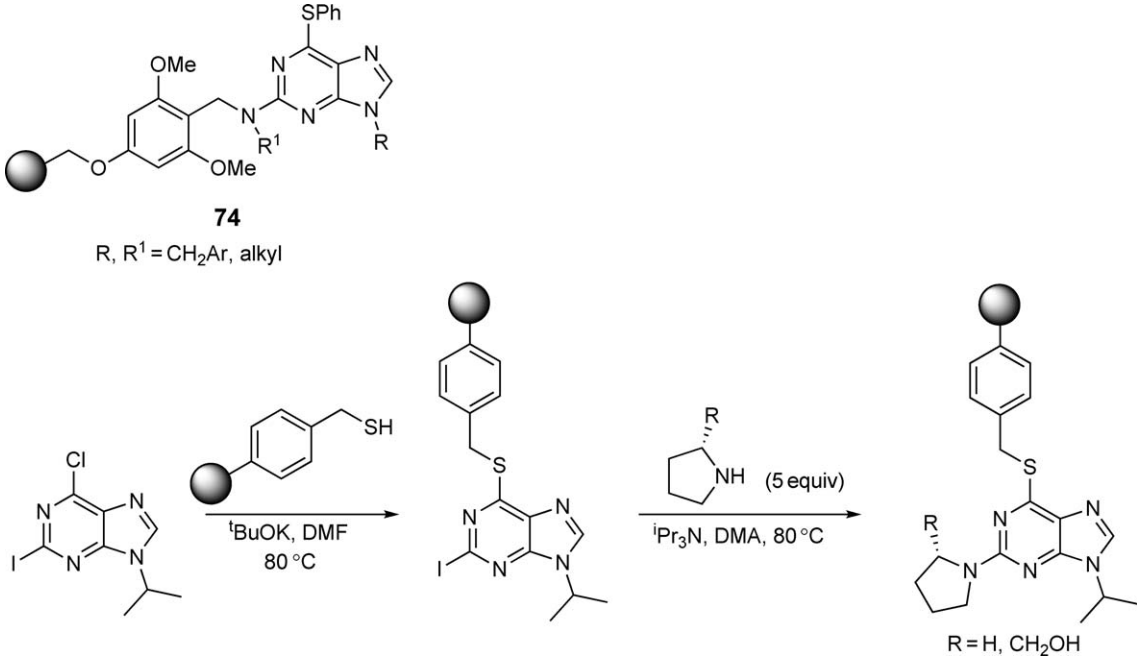




R^1	R^2	*Yield (%)*	*Purity (%)*
$PhCH_2$	$HOCH_2CH_2$	90	92
$PhCH_2$		62	98
$PhSO_2$	$HOCH_2CH_2$	91	89
Ph	$HOCH_2CH_2$	85	90

Scheme 31

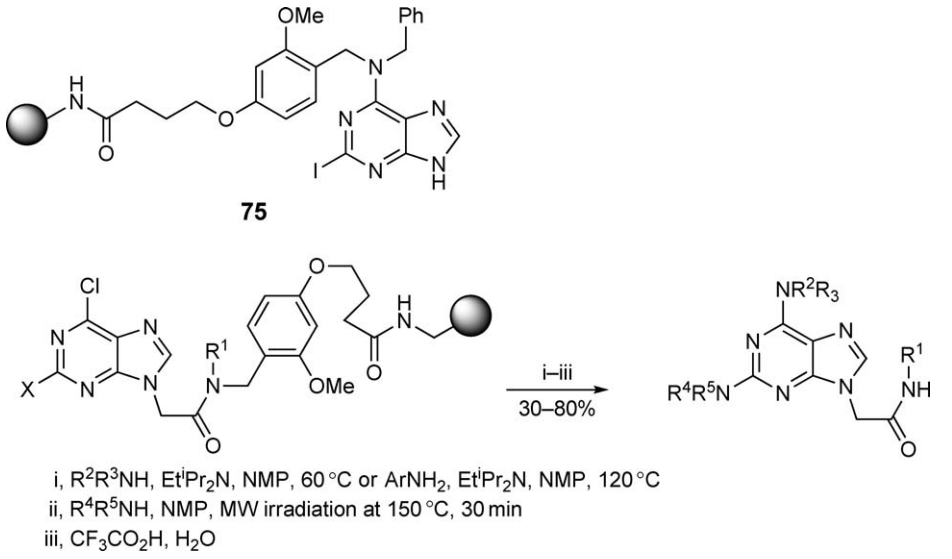
The presence of a 6-thiol substituent has been observed to permit more facile S_NAr reactions of 2-halopurines compared to analogous 6-amino-substituted compounds <2001JOC8273>. This was developed into a traceless combinatorial solid-phase synthesis of 2,6-diaminopurines where 2-fluoro-6-phenylsulfenyl-9-alkylpurines were loaded onto a functionalized aminoalkyl resin **74** through displacement of the 2-fluoro substituent. The resin-bound 6-phenylsulfanylpurines **74** were elaborated by oxidation to the sulfone and displacement with amines (see Section 10.11.7.5), followed by acidic cleavage from the solid support. Other solid-phase syntheses have linked the purine to the resin through a 6-thiol substituent (**Scheme 32**) <2001TL8165, 2002T7911>. 6-Chloro-2-iodo-9-isopropylpurine reacted with a Merrifield-SH resin. In solution, subsequent displacement of the 2-iodo group by amines was possible with a 1:1 stoichiometry of amine and purine (amines 1–1.5 equiv, Pr^i_3N, DMA, 100–120 °C; **Table 6**) while on the solid phase an excess of amine was necessary to drive the reaction to completion (amines 5 equiv, Pr^i_3N, DMA, 80 °C).



Scheme 32

Microwave heating accelerated the S_NAr reaction of resin-bound 2-halopurines <2002TL6169, 2005TL2873>. 6-Chloro-2-iodopurine was loaded onto the functionalized resin **75** by selective displacement of the 6-chloro substituent (Et^iPr_2N, NMP, 60 °C). Mitsunobu alkylation at N-9 was followed by amination of the 2-iodo group (amines, NMP, microwave irradiation at 200 °C, 30 min) and acidic cleavage from the resin <2002TL6169>. Alternatively, resin-bound purines linked through N-9 underwent selective chloride displacement at C-6 under standard thermal conditions followed by microwave-assisted S_NAr at C-2 (**Scheme 33**). A 20 000-member library of purin-9-yl acetamides was prepared using this strategy. Comparison of different halogen substituents at C-2 revealed that under the microwave heating conditions, the order of reactivity toward displacement with amines was I > F >> Cl, and that electron-donating C-6 substituents further retarded the reaction. Other studies have shown the improved reactivity of 2-fluoropurines over 2-chloropurines for S_NAr reactions <1997TL1161>.

It is important to note that S_NAr displacement reactions of heteroatom functional groups other than halides have been demonstrated on purine substrates, including mesitylenesulfonates <2000OL927>, sulfones (see Section 10.11.7.5), nitro substituents <2006S2993>, and *N*-azoles (see Section 10.11.7.3.2). Halopurines have been reduced using sodium naphthalenide <1997T6295>.



Scheme 33

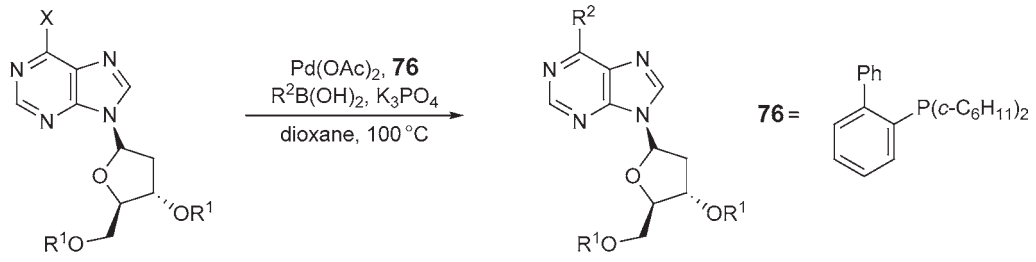
10.11.7.4.2 Carbon–carbon bond formation

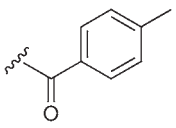
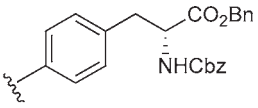
As envisaged in CHEC-II(1996) <1996CHEC-II(7)397>, carbon–carbon bond formation through transition metal-mediated cross-coupling reactions to halopurines has increased in significance and is now the basis of several versatile synthetic routes to polysubstituted purines and purine nucleosides, often in combination with aromatic nucleophilic substitution reactions (see Section 10.11.7.4.1). Transition metal-catalyzed cross-coupling reactions of organostannanes, organozincs, alkynes, and boronic acids have been demonstrated for a wide variety of 2-, 6-, and 8-halopurine substrates, as reviewed in <2005T2245> and <2003EJO245>. More recently, the introduction of imidazol-1-yl and 1,2,4-triazol-4-yl groups as pseudohalogen substituents capable of undergoing transition metal-catalyzed cross-couplings has widened the scope of this approach to substituted purines (see Section 10.11.7.3.2).

There is often a need for specific catalysts and reaction conditions for the optimal reaction of halopurines in C–C bond-forming reactions. Thus, efficient Suzuki coupling of arylboronic acids to 9-benzyl-6-chloropurine required anhydrous conditions for neutral or electron-rich aryl groups, while electron-deficient aryl or alkenyl substituents proceeded more effectively in aqueous media <1999SL1145, 2001S1704>. A similar pattern was observed in the reactions of 9-benzyl-8-bromoadenine <2001S1704>. Comparison of the reactivity of a 6-chloro- and a 6-bromopurine nucleoside showed the chloropurine to give superior yields with both electron-rich and electron-deficient boronic acids (**Scheme 34**). The optimum conditions were anhydrous, using potassium phosphate as the base and the catalyst formed from palladium acetate and 2-(dicyclohexylphosphino)biphenyl **76** <2001JA7779>. Interestingly, C–C bond formation to these substrates was less sensitive to the catalyst used than related transition metal-catalyzed C–N bond-forming reactions (see Section 10.11.7.4.1). The same conditions also gave good yields for the coupling of 4-boronophenylalanines to 6-halopurine nucleosides (**Scheme 34**) <2005JOC8001>. Some racemization of the amino acid chiral center was observed, which was avoided by using the analogous 4-(trimethylstannyl)phenylalanines in a Stille reaction catalyzed by dipalladium tris(dibenzylideneacetone) and triphenylarsine.

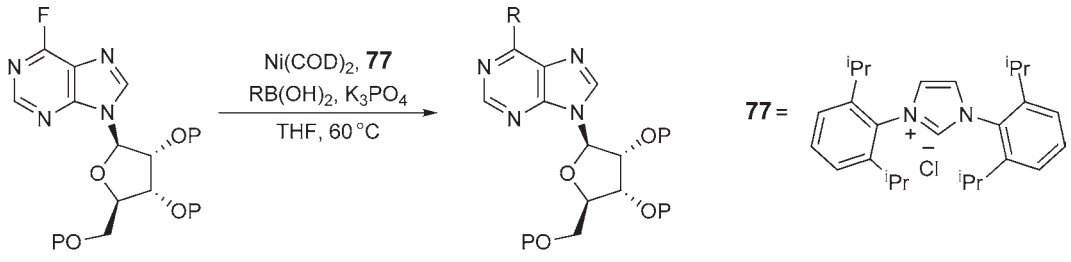
An N-heterocyclic carbene ligand, formed from 1,3-bis-(2,4,6-trimethylphenyl)-3*H*-imidazol-1-ium chloride and cesium carbonate, with dipalladium tris(dibenzylideneacetone) gave excellent yields (93–96% yields) in the Suzuki coupling of 2-chloropurines and arylboronic acids in anhydrous dioxane <2001TL8751>. The combination of an imidazolium-carbene and nickel(0) bis(cyclooctadiene) formed a catalyst capable of insertion into the C–F bond of 6-fluoropurine nucleosides (**Scheme 35**) <2005OL1149>.

In general, cross-coupling reactions of N-unprotected halopurines or unprotected halopurine nucleosides have had limited success, possibly reflecting coordination by the substrates leading to nonproductive transition metal complexes <2005JOC6378> (see Section 10.11.5.2.6). Sequestration of the metal may also cause difficulties in product purification. For example, a low catalyst loading (1 mol% $(PPh_3P)_2Cl_2$ and 2 mol% CuI) was critical for the Sonogashira alkynylation of unprotected 8-bromoguanosine and 8-bromoadenosine <2006TL3529>. Good yields were obtained from ethynylbenzenes with electron-donating aromatic substituents (52–85% yields) while electron-poor substrates



R^1	R^2	X	*Yield (%)*	*Reference*
TBDMS	4-Methoxyphenyl	Cl	83	2001JA7779
TBDMS	4-Methoxyphenyl	Br	69	
TBDMS	4-Acetylphenyl	Cl	84	
TBDMS	4-Acetylphenyl	Br	49	
		I	73	2005JOC8001

Scheme 34



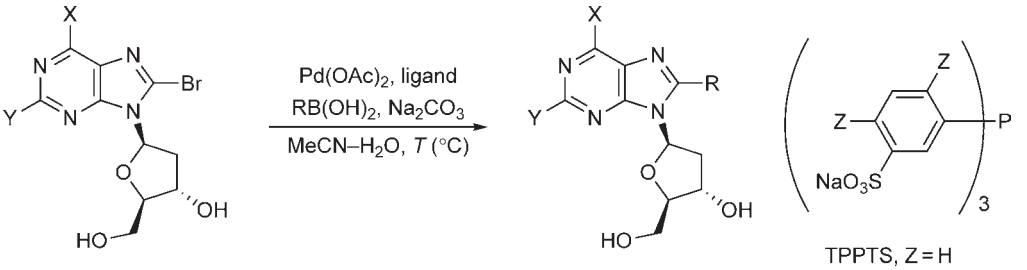
P = 2,4,6-trimethylbenzoyl

R	*Yield (%)*
Phenyl	84
4-Methoxyphenyl	84
4-Fluorophenyl	73

Scheme 35

sometimes failed to react. The addition of higher proportions of catalyst gave low yields of poorer-purity products, believed to be due in part to complexation of the metals by the purines. An alternative approach to successfully using unprotected halopurines and nucleosides in coupling reactions involved a water-soluble palladium catalyst formed from palladium(II) acetate and tris(3-sulfonatophenyl)phosphine (TPPTS) or tris(4,6-dimethyl-3-sulfonatophenyl)phosphine (TXPTS) in an aqueous reaction medium. Good yields were obtained for the reaction of arylboronic acids with 8-bromo-2′-deoxyadenosine, 8-bromo-2′-deoxyguanosine, and other unprotected halopurine nucleosides (**Scheme 36**) <2003JOC6767, 2005JOC6378>. The addition of 2′-deoxyguanosine, but not 1-methyl-2′-deoxyguanosine, to the reaction medium was found to inhibit the formation of the active palladium(0) species and slow the reaction. ^{13}C and ^{31}P NMR spectroscopy data suggested that coordination of the unprotected guanine heterocycle to the metal through N-1 or O-6, or both, underlay the difficulties experienced with transition metal-coupling reactions to these substrates <2005JOC6378>. Similar aqueous conditions allowed the coupling of enantiopure phenylalanine boronic acids to 6-chloropurine and a range of unprotected halopurine nucleosides in good yield (63–97%) without racemization. The reactions required high temperatures (125–150 °C) which were achieved with conventional or microwave heating

<2006OBC2278>. Aqueous Suzuki reactions conducted with microwave heating were also successful for the coupling of diverse aryl- and alkenylboronic acids to unprotected 2-, 6-, or 8-halopurines <2006S3515>.



X	Y	R	Ligand	T (°C)	Yield (%)
OH	NH_2	Ph	TPPTS	80	82
OH	NH_2	4-F-C_6H_4	TPPTS	80	82
NH_2	H	Ph	TPPTS	80	87
OH	NH_2	4-MeO-C_6H_4	TXPTS	23	99
NH_2	H	Ph	TXPTS	23	50

Scheme 36

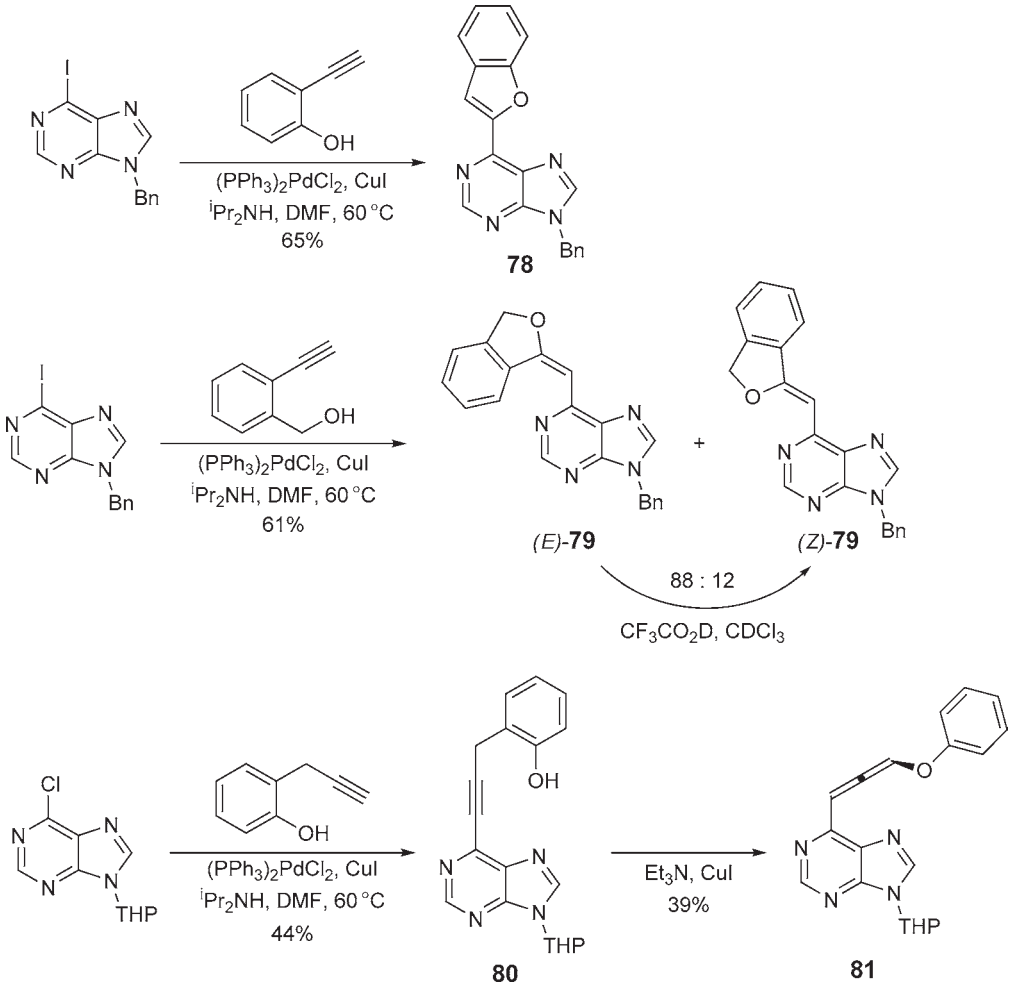
A useful tandem coupling–cyclization occurred when 2-ethynylphenol and 2-(hydroxymethyl)ethynylbenzene reacted with 6-iodo-9-benzylpurine under catalysis with palladium(II) and copper(I), generating 6-(2-benzofuryl)purine **78** and 6-(isobenzofuran-1(3*H*)-ylidinemethyl)purine **79**, respectively <2006T6121>. The initial mixture of (*E*)- and (*Z*)-**79** was isomerized in acid to the (*Z*)-isomer (**Scheme 37**). From the mechanism of analogous tandem sequences, it is likely that the product **78** resulted from cyclization promoted by Ar–Pd–I species followed by cross-coupling. In contrast, when 2-propynylphenol was coupled to 6-chloro-9-(tetrahydropyranyl)purine under similar conditions, the simple 6-alkynylpurine **80** was isolated. Treatment of purified **80** with triethylamine and copper(I) iodide led to an unusual rearrangement to give the 6-allenylpurine **81**.

Many of the reported carbon–carbon bond-forming reactions of halopurines have involved the introduction of sp^2-hybridized carbon substituents. In contrast, cuprates derived from primary, secondary, and tertiary alkyl Grignard reagents and copper(I) iodide, but not copper(I) cyanide, were found to add to 6-chloro-9-(tetrahydropyran-2-yl)purine to afford the 6-alkyl derivatives in moderate to good yields (**Scheme 38**) <1996TL1285>. Both nickel- and iron-catalyzed cross-couplings of alkyl and aryl Grignard reagents to 6-chloropurines also proceeded effectively <1995JME2582, 2002JA13856>. The palladium-catalyzed cross-coupling of alkylzinc reagents to protected 6-iodo- and 6-chloropurine derivatives, both simple bases and nucleosides, provided a straightforward synthesis of 6-methylpurines <2000NN1123>, 6-(hydroxymethyl)purines and (purin-6-yl)alanines <2004OL3225, 2004JOC7985>, where enantiopure iodozincalanines reacted without racemization.

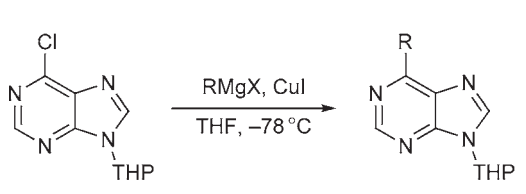
Heck reactions of 9-benzyl-6-halopurines with alkenes failed under conventional conditions (butyl acrylate, $Pd(PPh_3)_2Cl_2$, Et_3N, DMF), ascribed to the formation of stable purine–palladium compexes which prevent β-elimination of hydrogen and remove the metal from the catalytic cycle <2004TL273>. It was hypothesized that including an excess of formate in the reaction mixture would lead to transmetalation (with H^-) and reductive elimination to free the metal catalyst, and this indeed resulted in moderate yields of the 6-alkylpurine substitution products. However, the regioselectivity of the coupling was low compared to the classical Heck reaction and a mixture of linear and branched products was produced in all cases (**Scheme 39**). Substitution of the alkene at the α-position was tolerated, but substitution at the β-position gave only reduction of the halopurine.

An alternative means to introduce alkyl substituents at C-6 was devised through halogen–metal exchange of 6-iodo-9-benzylpurine (^{i}PrMgCl, THF–toluene, 0 °C) and subsequent quenching with aromatic and aliphatic aldehydes to give the alcohols **84** (25–91% yields) <2003OL4289>. Other C-electrophiles, such as carboxylate esters and nitriles, did not react with the magnesiopurine reagent. When these conditions were applied to 2-iodo-6-chloro-9-benzylpurine, selective magnesiation at C-2 occurred, provided the reaction was carried out at −80 °C, and reaction with aldehydes gave the alcohols **85** (48–85% yields) <2006OL1291>. However, when the halogen–metal exchange

was conducted at 0 °C, migration of the metal to C-8 was observed. For the related substrate 6-iodo-2-chloro-9-benzylpurine, a strikingly different behavior was observed (**Scheme 40**). While halogen–metal exchange at −80 °C again gave the straightforward 6-hydroxymethylpurine products, the use of 2 equiv of Grignard reagent at 0 °C led to addition at C-6 and displacement of the iodo substituent. Subsequent chloride–metal exchange was observed at C-2, and the intermediate magnesiopurine could be quenched with water to produce 6-alkylpurines, or further reacted with aldehydes to generate 2,6-dialkyl derivatives. 6-Zincated purines were prepared from 6-iodopurine nucleosides by direct insertion of the metal (zinc dust, THF, 70 °C) and underwent palladium(0)-catalyzed reaction with aryl iodides to introduce 6-aryl substituents <1996TL8375, 1997T7237>.

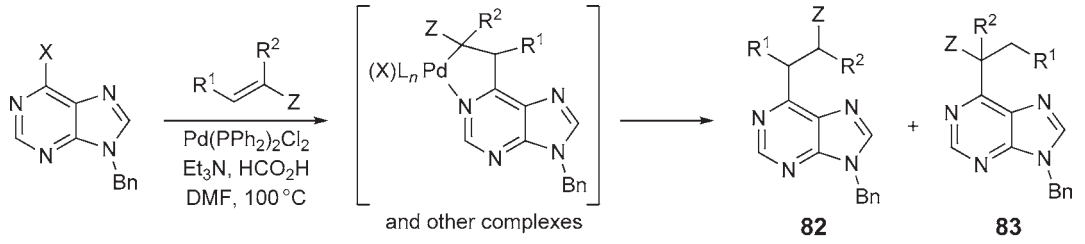


Scheme 37



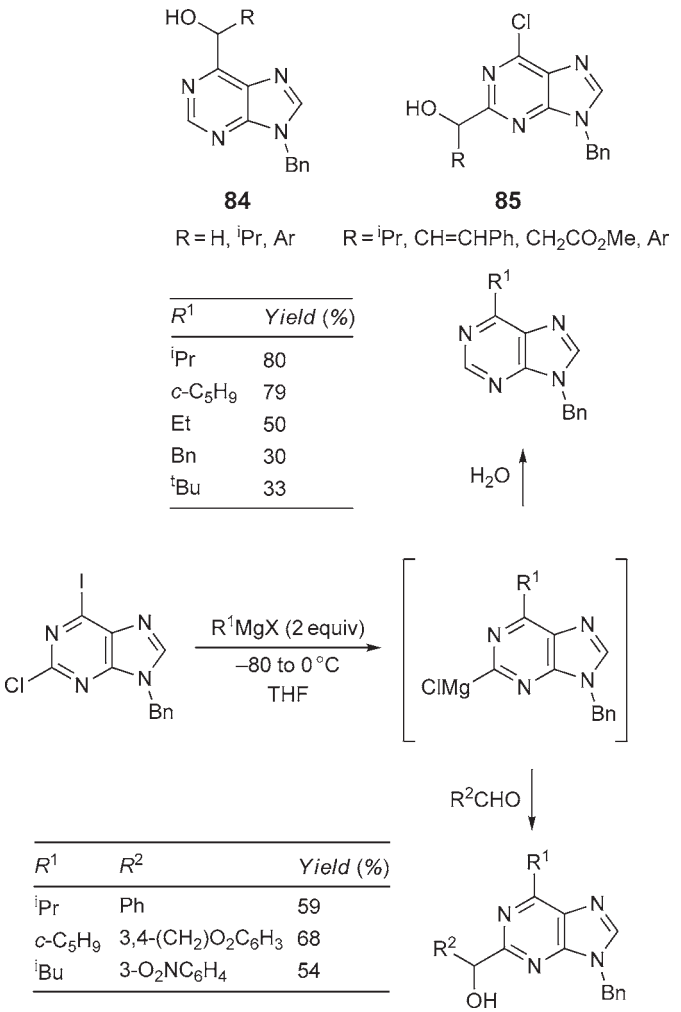
R	*X*	*Yield (%)*
Me	I	19
^{i}Pr	Br	67
c-C_6H_{11}	Br	67
^{t}Bu	Cl	40
Ph	Br	10

Scheme 38



				Yield (%)	
X	*Z*	R^1	R^2	**82**	**83**
Cl	CO_2Bu	H	H	27	46
I	CO_2Bu	H	H	22	53
I	CN	H	H	22	23
I	Ph	H	H	27	29
I	CO_2Me	H	Me	16	9

Scheme 39

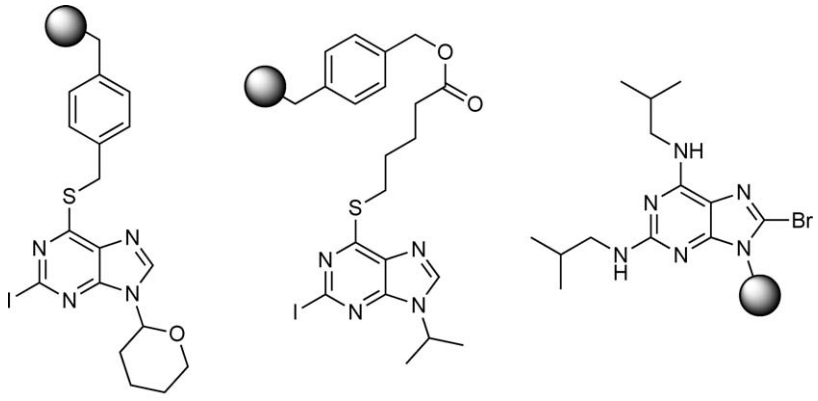


R^1	*Yield (%)*
^{i}Pr	80
c-C_5H_9	79
Et	50
Bn	30
^{t}Bu	33

R^1	R^2	*Yield (%)*
^{i}Pr	Ph	59
c-C_5H_9	3,4-$(CH_2)O_2C_6H_3$	68
^{i}Bu	3-$O_2NC_6H_4$	54

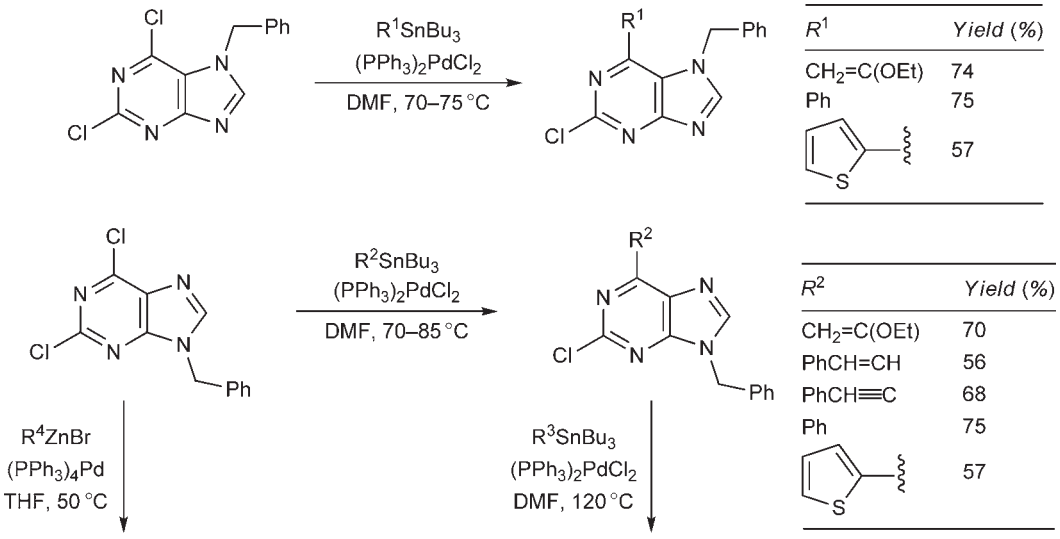
Scheme 40

The adaptation of transition metal-catalyzed C–C bond-forming reactions to purines for solid-phase synthesis has become an area of significant interest. In solution, Suzuki and Sonogashira couplings to 6-benzylsulfanyl-2-iodo-9-(tetrahydropyran-2-yl)-9*H*-purine proceeded in good yield without complications <2001TL8161, 2002T7911>. In contrast, direct attachment of the 6-thiol substrate to the Merrifield-Cl resin, as in **86**, led to complete failure of the Sonogashira reaction under standard conditions (alkyne, $Pd(PPh_3)_2Cl_2$, CuI, Pr^i_2NEt, 80 °C) with the formation of deposits of palladium black observed on the resin <2001TL8169>. One explanation for this is the probable coordination of the palladium between the 6-thio group and N-7. Although this can occur in solution as well, for the resin-bound substrate **86** the steric bulk of the solid phase may promote dissociation of the phosphine ligands and thus disfavor the decomplexation of the metal from the purine to regenerate the catalytically active palladium species. Accordingly, the use of more tightly bound chelating phosphine ligands, for example, bis(diphenylphosphino)ethane, did permit isolation of the coupled products (20–25% yields after cleavage from the resin). The introduction of the 5-thiovaleric acid linker **87**, to relieve steric congestion around the purine due to the resin, further increased the efficiency of both Sonogashira and Suzuki reactions on the solid phase (50–58% yields after cleavage from the resin) <2001TL8169, 2002T7911>. Similar difficulties were encountered in Stille reactions of the 8-bromopurine **88** attached to the Rink resin, where lack of reaction and competing hydro-dehalogenation were significant problems <2001TL6515>. In this case, the specific combination of a chelating phosphine ligand, bis(diphenylphosphino)propane, and copper(I) oxide as a cocatalyst led to satisfactory yields and purities of the coupled products ($Pd(OAc)_2$, Cu_2O, 1,3-bis(diphenylphosphino)propane (dppp), NMP, 100 °C; 68–98% yields after cleavage from the resin).



86 **87** **88**

The first selective palladium-catalyzed cross-couplings of organotin and organozinc reagents to 2,6-dichloropurines were reported in 1995 <1995TL1945>. Both 9-benzyl- and 7-benzyl-2,6-dichloropurine showed exclusive or highly selective reaction of the 6-chloro substituent, despite the greater steric hindrance in the latter compound. The selectivity of the Stille reactions was temperature dependent, and coupling of a second organostannane to the remaining 2-chloro group was achieved by increasing the temperature from 70 to 120 °C, allowing for a one-pot synthesis of differentially 2,6-disubstituted purines (**Scheme 41**) <1996T5625>. In contrast, monocoupling of organostannanes to both 9-benzyl-2-iodo-6-chloropurine and 9-benzyl-2-bromo-6-chloropurine at lower temperatures (40–65 °C) using a more reactive palladium catalyst occurred selectively at the 2-iodo or 2-bromo group <1996T5625>. Selective reaction of the 2-iodo group was also observed for the coupling of alkynes to various 2-iodo-6-chloro-8-aryl-9-methylpurines <2001JME170> and in the Stille reaction of isopropenyl acetate and 2-iodo-6-chloro-tri-*O*-acetylpurine riboside <2005TL1165>. The same balance of chemo- and regioselectivity was evident for Suzuki couplings, where reaction of benzeneboronic acid with 9-benzyl-2,6-dichloropurine gave selectively 9-benzyl-2-chloro-6-phenylpurine (77% yield) while 9-benzyl-2-iodo-6-chloropurine afforded 9-benzyl-6-chloro-2-phenylpurine (81% yield) <2001S1704>. This controlled sequential reactivity of 2,6-dihalopurines was exploited for the synthesis of truncated carba analogues of the synthetic antimitotic purine myoseverin through sequential Suzuki and Negishi couplings to 9-isopropyl-2,6-dichloropurine <2003T607>. The palladium-catalyzed coupling of benzeneboronic acid and 9-(tetrahydropyran-2-yl)-6,8-dichloropurine was also selective for reaction at the 6-chloro substituent <2004S889>. A combination of selective, sequential metal-catalyzed cross-couplings to 2,6-dichloro-9-benzylpurine and subsequent functionalization at C-8 through palladium-catalyzed C–H activation and arylation was used to prepare 2,6,8-trisubstituted purines <2006OL5389> (see Section 10.11.5.3.3).



R^1	Yield (%)
CH_2=C(OEt)	74
Ph	75
	57

R^2	Yield (%)
CH_2=C(OEt)	70
PhCH=CH	56
PhCH≡C	68
Ph	75
	57

R^4	Yield (%)
Ph	50
Bn	75
Me	69
Bu	63

R^2	R^3	Yield (%)
PhCH=CH	CH_2=C(OEt)	57
PhCH=CH	Ph	63
CH_2=C(OEt)	PhCH=CH	69
Ph	PhCH=CH	62

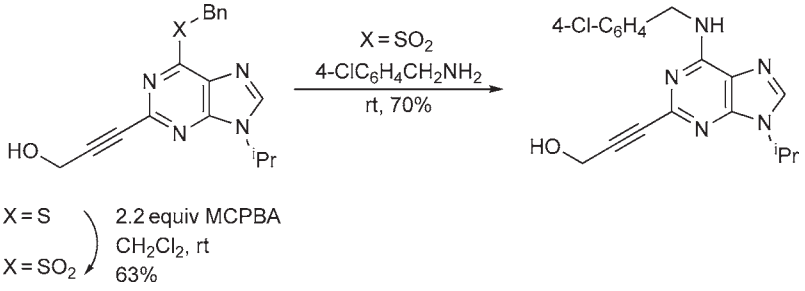
Scheme 41

Palladium-catalyzed double methylation of 9-(tetrahydropyran-2-yl)-2,6-dichloropurine with trimethylaluminium occurred in high yield, whereas selective monomethylation was achieved at C-6 through iron-catalyzed coupling of methylmagnesium chloride, provided a 1:1 stoichiometry of reagents was used <2003JOC5773>. The iron-mediated reaction was also successful with protected furanose substituents at N-9 of the purine, constituting a route to 6-methyl-2-substituted purine nucleosides. Unusually, monomethylation of 9-(tetrahydropyran-2-yl)-6,8-dichloropurine with these reagents occurred at C-8, in place of the more common reactivity of the 6-chloro group in this substrate <2004S889>. Application of the iron-catalyzed coupling of methylmagnesium chloride to 9-(tetrahydropyran-2-yl)-2,6,8-trichloropurine generally led to mixtures of isomers of mono-, di-, and trisubstituted products, although useful selectivity (46% isolated yield) was observed for the monocoupling of benzeneboronic acid to C-6 through Suzuki reaction <2004S2869>.

10.11.7.5 Thiopurines

The principal use of thiopurines in recent years has been as surrogates for halopurines in S_NAr reactions through oxidation of the sulfanyl group and displacement with nucleophiles. This has often contributed an important element to the combinatorial reaction sets required for the preparation of polysubstituted purines, both in solution and on solid phase (see Sections 10.11.7.4.1 and 10.11.7.4.2). Most commonly, 6-benzylthiopurines have been oxidized with 2 equiv of MCPBA to the corresponding sulfones, which are sufficiently activated to undergo substitution by aryl and alkyl amines (see, for example, **Scheme 42**) <2001TL8161>. An advantage of this methodology over simple halopurine displacements was the ability to carry the unactivated thiopurine through several steps before activation.

The transformation was applied to the solid-phase synthesis of purines by further linking the 6-benzylthio substituent to a resin <2001TL8165, 2002T7911>. Oxidation and substitution using amines provided a traceless cleavage of the 6-amino purines from the the resin. An alternative linking strategy used a longer, less bulky thiovaleric acid linker at C-6 to provide a less sterically congested environment around the purine scaffold <2001TL8169, 2002T7911>. This offered advantages in improved reactivity of other sites on the purine bicycle during the solid-phase synthesis (see Section 10.11.7.4.2). Other solid-phase combinatorial syntheses of purines have linked the purine to the resin through C-2 amines, but used a 6-phenylthio-group for the on-resin oxidation–displacement (10 equiv MCPBA, 10 equiv NaOH, then 2 equiv amine, 80 °C) <2001JOC8273>. 2-(Benzylthio)-6-(3-chlorophenylamino)-9-isopropylpurine was also successfully oxidized to the sulfone and displaced with valinol during the synthesis of purine Cyclin-dependent Kinase (CDK) inhibitors <2005EJO939>. The incorporation of 6-(methanethio)purine nucleosides into DNA oligomers allowed the selective oxidation of the methansulfanyl groups with MCPBA or magnesium monoperoxyphthalic acid (MMPP) to the sulfinyl or sulfonyl analogues. These were displaced, within the intact DNA oligomers, by simple amines (e.g., ammonia, methylamine), water, azide anion, or amino acids <1996T10737, 1998T187>.

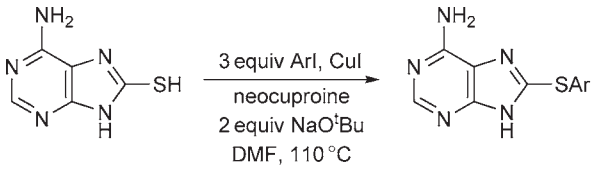


Scheme 42

A one-pot procedure for the transformation of 6-thiopurine nucleosides to 6-aminopurines was developed using DMDO as the oxidant in the presence of a stoichiometric amount of various amines <1996T6759>. For example, 6-thio-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribosyl)purine was readily converted to the 6-alkylamino derivatives (6-amino, 75% yield; 6-methylamino, 55% yield). Similarly, *N*-6-acetyl-8-thio-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribosyl)adenosine was converted to *N*-6-acetyl-8-methylamino-9-(2′,3′,5′-tri-*O*-acetyl-β-D-ribosyl)adenosine (DMDO, methylamine, CH_2Cl_2, 25 °C, 83% yield). Less nucleophilic 2-mercaptopurine derivatives did not undergo the displacement reaction, however, and only the products of dithiane formation and desulfurization were isolated.

The activation of thiopurines to the sulfoxide or sulfone derivatives is not always necessary for subsequent displacement reactions to occur. 9-(4-Hydroxy-(3-hydroxymethyl)butyl)-2-amino-6-[(4-chlorophenyl)sulfanyl]-7*H*-purine was hydrolyzed directly to the 9-alkylguanine antiviral agent, penciclovir, on refluxing in 2 M hydrochloric acid (95% yield) <1999T5239>. Hydrogenolysis of the 6-(4-chlorophenylthio) substituent to give a related antiviral drug, famcyclovir, was achieved with Raney nickel (87%). The 6-(4-chlorophenylthio) groups were conveniently installed onto simple guanines through O-mesylation and displacement with thiols. The presence of the 6-arylthio substituent was found to have a beneficial effect on the degree of regioselectivity of N-9 alkylation (vs. N-7) during the synthesis. Cyanine dyes were prepared by the displacement of the 6-methylthio group from 3,7-dimethyl-6-(methylthio)purinium *p*-toluenesulfonate by heterocyclic methylene bases <1997T12595>.

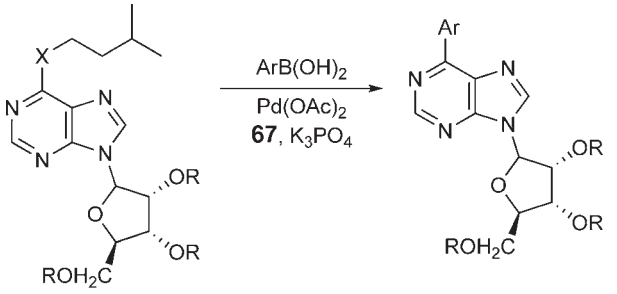
The Ullman coupling of 2-bromo-(hetero)aryl-1-carboxylates and 8-mercaptotheophylline was reported to proceed in moderate yield under standard conditions (cat. CuI, K_2CO_3, DMF, 120 °C; 2-bromobenzoic acid, 47%; 2-bromopyridine-3-carboxylic acid, 39%) <1998JHC57>. Formation of the C–S bond was accompanied by condensation of the acid and N(7)–H to yield tetracyclic purino[8,7-*b*][1,3]benzothiazines and pyrido[3′2′:5,6][1,3]thiazino[3,2-*f*]purines. On heating alone in DMF exposed to air, 8-mercaptotheophylline dimerized to give 8,8′-dithiotheophylline (58% yield). More generally, 8-mercaptoadenine was coupled to aryl iodides using copper(I) catalysis with neocuproine as an essential additive for successful reaction (**Scheme 43**) <2004JOC3230>. The reactions were carried out under inert atmosphere to prevent dithiane formation, and no evidence was seen of this or of the alternative copper-catalyzed arylation of the 6-amino substituent. The choice of solvents was limited to DMF and DMSO due to the poor solubility of 8-mercaptoadenine.



Ar	*Yield (%)*
2-$MeOC_6H_4$	36
4-$MeOC_6H_4$	62
2-ClC_6H_4	57
2-$HOCH_2C_6H_4$	79
3,5-$Me_2C_6H_3$	67

Scheme 43

Both 6-alkanesulfanyl- and 6-alkanesulfonylpurines proved competent coupling partners in the palladium-catalyzed Suzuki reaction with boronic acids when an imidazolium carbene ligand was used <2005OL1149>. The sulfones were found to be significantly more reactive (60 °C, THF) than the thioethers (90 °C, toluene) (**Scheme 44**).

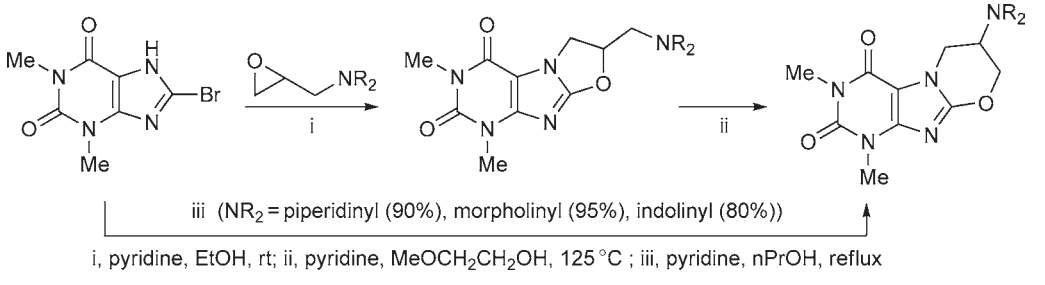


X	*R*	*Ar*	*Conditions*	*Yield (%)*
S	Tol	4-MeC_6H_4	toluene, 90 °C	69
S	Ac	4-$MeOC_6H_4$	toluene, 90 °C	78
SO_2	Mes	4-$MeOC_6H_4$	THF, 60 °C	81

Scheme 44

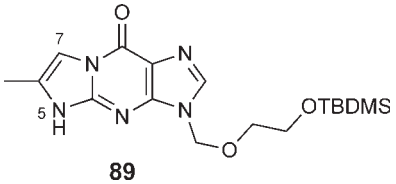
10.11.7.6 Purines with a Fused Heterocyclic Ring System

Although isolable by chromatography, 6,7-dihydrooxazolo[2,3-*f*]theophyllines formed from the alkylation of 8-bromotheophylline with aminomethyloxiranes were found to be unstable, undergoing easy ring-opening–ring-closing in the presence of base to yield oxazino[2,3-*f*]theophyllines (**Scheme 45**) <2005TL3561>. The rearrangement was specific to 6,7-dihydrooxazolo[2,3-*f*]theophyllines bearing 7-aminomethyl functionality, suggesting a mechanism involving formation of an intermediate aziridinium cation that is attacked by the 8-oxo group on the less-substituted carbon to form the six-membered dihydrooxazine ring.



Scheme 45

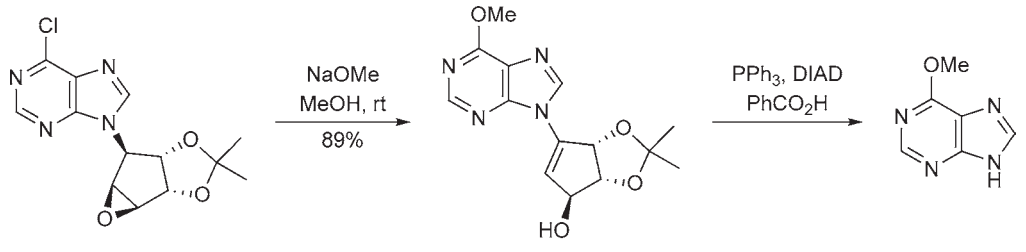
3,9-Dihydro-3-[(2-hydroxyethoxy)methyl]-6-methyl-9-oxo-5*H*-imidazo[1,2-*a*]purine, a tricyclic analogue of the antiviral drug acyclovir, behaved anomalously during a straightforward tritylation reaction designed to protect the N-5 nitrogen of the fused (nonpurine) imidazole ring of **89** <1998T2941>. Instead of the *N*-trityl analogue, C-tritylation at C-7 of the fused ring was observed. This appeared to be a consequence of steric congestion by the adjacent C-6 methyl substituent, since removal of this group gave predominantly the expected N-tritylation.



89

10.11.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms

As described in Section 10.11.1, the subject of modifications to the sugars of purine nucleosides is not considered in this chapter. However, there have been a number of reports describing modifications to simpler ring nitrogen substituents, or to sugar groups where the purine base has played a significant mechanistic role. For example, the hydrolysis of 8-arylaminopurine nucleosides was investigated <2002JOC2303>. These are the major class of adducts formed in the reactions of purine bases in DNA with the active metabolites of mutagenic aromatic amines. Compared to unmodified purine nucleosides, the 8-arylaminopurine nucleosides showed considerably greater susceptibility to hydrolysis. Thus, a slow spontaneous cleavage of the sugar–N(9) bond was seen in neutral aqueous media that was not exhibited by simple 2′-deoxyguanosine. In mildly acidic media ($6 > pH > 3$), rate enhancements of 40–1300-fold were seen for the 8-arylaminopurine nucleosides compared to 2′-deoxyguanosine. The enhanced reactivity to hydrolysis was ascribed to the additional steric compression between the C-8 arylamino substituent and the N-9 sugar group, and the electron-donating properties of the arylamines which stabilize the cationic intermediates of acid-catalyzed hydrolysis. The 6-chloropurine carbonucleoside **90** (**Scheme 46**) underwent S_NAr displacement and rearrangement of the epoxide on treatment with sodium methoxide to generate the *N*-cyclopentenyl derivative **91** <2004T3451>. The diasteroisomeric epoxide, where both epoxide and the proton to be removed were on the same face of the carbocycle, required more vigorous conditions to achieve the rearrangement (NaOMe, MeOH, reflux, 93% yield). Attempts to invert the stereochemistry of the C-3′ hydroxyl in **91** using the Mitsunobu conditions led only to cleavage of the carbocycle from the purine. This was rationalized as resulting from hydroxyl activation followed by S_N2' attack to generate an unstable hemiaminal that decomposed by release of the purine. However, oxidation (pyridinium chlorochromate (PCC), Celite, CH_2Cl_2, 88% yield) followed by Luche reduction ($NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 85% yield) provided an efficient means of epimerizing the alcohol **91**.



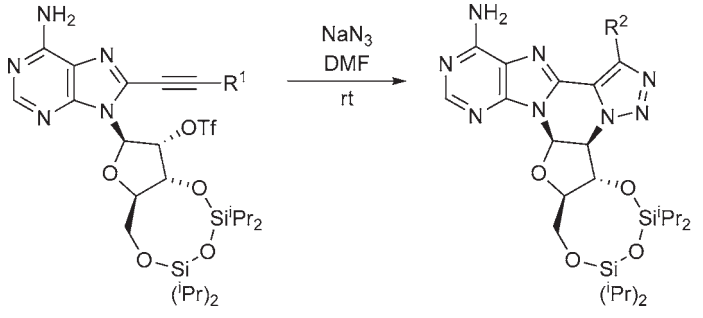
90 **91**

Scheme 46

As part of an investigation into new synthetic routes to the important acyclic nucleoside class of antiviral drugs, the cross metathesis of 9-allyl-6-chloropurine with 2,2-dimethyl-4-vinyl-1,3-dioxolane was attempted <2003TL9177>. The reaction was confounded by the coordination of the ruthenium metathesis catalyst with the purine heterocyclic nitrogens. This was overcome to some extent by using the *p*-toluenesulfonic acid or hydrogen chloride salts of the

purine for the reaction, leading to low recovery (14% yield) of the desired cross metathesis product. A higher-yielding strategy involved construction of a fully functionalized allylic acetate by cross metathesis, followed by attachment to the purine N-9 through a palladium-catalyzed allylation (see Section 10.11.5.2.1).

Displacement of a 2′-triflate by azide from 8-(2-silylethyn-1-yl)adenosine nucleosides resulted in a tandem [3+2] cycloaddition generating the novel fluorescent 8-(3*H*-[1,2,3]triazol-4-yl)-9*H*-purine heterocyclic ring system (**Scheme 47**) <2005TL6745>. The mild conditions for the cycloaddition were a reflection of the intramolecular nature of this process. The corresponding intermolecular reaction between a simple adenosine nucleoside bearing a 2′-azide and an 8-alkynyladenosine nucleoside required high temperatures (120 °C) for the cycloaddition, generating a mixture of the two possible [3+2] cycloadducts (18% and 31% yield). However, copper(I) catalysis of the same intermolecular process yielded a single regioisomer (73% yield) with the reaction proceeding at room temperature. The generation of a 2′-mesylate from 7-(2-hydroxy-2-phenylethyl)theophylline and attempted displacement with amines led to involvement of the adjacent 6-oxo group in trapping the nascent carbocation and the formation of a transient tricyclic species <2000T7685>. In the reaction with ammonia, a mixture of products was isolated containing the desired 7-(2-amino-2-phenylethyl)theophylline (3% yield), 7-(2-hydroxy-2-phenylethyl)-1,3-dimethyl-1,2,3,6-tetrahydro-6-imino-2-oxo-7*H*-purine (40% yield), and 7-(2-phenylvinyl)theophylline (31% yield).



R^1	R^2	*Yield* (%)
$SiMe_3$	H	75
TBDMS	TBDMS	30

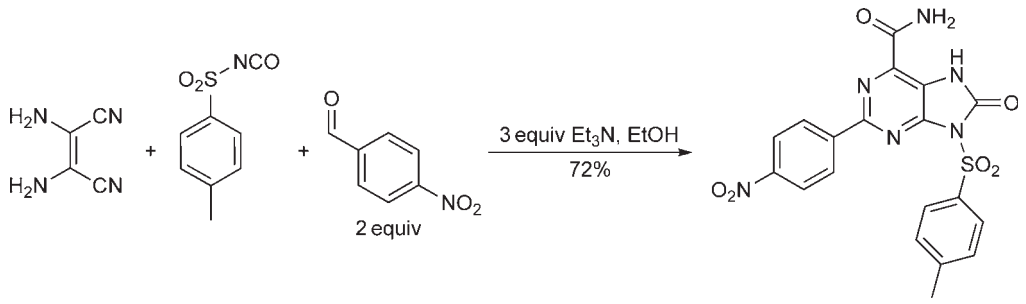
Scheme 47

Adenosine analogues where the furanose ring was replaced with alternative dihydro- and tetrahydrofurans were prepared from 6-chloro-9-(4-methylenetetrahydrofuran-3-yl)-9*H*-purine <2002T4865>. Of particular interest was the transformation of the exocyclic alkene on the THF ring first by dihydroxylation, then elimination to yield (4-(6-aminopurin-9-yl)-2,5-dihydrofuran-3-yl)methanol after amination of the purine ring at C-6. This *N*-alkenylpurine was reduced (Pd/C, H_2, 25 psi, 73% yield) to provide the tetrahydrofuran-3-yl derivative.

10.11.9 Ring Synthesis from Acyclic Precursors

Reports of the synthesis of purines from totally acyclic precursors are scarce, with the majority of synthetic routes involving the anulation of imidazoles or pyrimidines to form the bicycle (see Section 10.11.10). The proposed prebiotic synthesis of purine bases through polymerization of hydrogen cyanide, and the subsequent generation of nucleic acids from these precursors, has been reviewed <1997T11493>. 9-Aryl-6-cyanopurines were formed in moderate to good yields from the cyclization of (*Z*)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-arylformamidines upon treatment with dimethylformamide dimethylacetal (1–3 equiv DMF–DMA, MeCN, rt, 28–81% yields), although in all cases the purines were accompanied by the formation of pyrrole by-products (DMA = dimethylacetamide) <1997JHC739>. The reaction was shown to proceed through initial intramolecular cyclization to generate 1-aryl-5-amino-4-(cyanoformimidoyl)imidazoles followed by cyclocondensation with DMF–DMA. Carrying out these two steps separately avoided the formation of the pyrrole by-products. A further improvement on this methodology was seen when the (*Z*)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-arylformamidines were refluxed with an excess of triethyl orthoformate. The 6-cyanopurines were isolated in generally high yields by simple filtration upon cooling, or by precipitation with petroleum ether (69–96% yields). Treatment of *N*-((*Z*)-2-amino-1,2-dicyanovinylcarbamoyl)-*p*-toluenesulfonamide, formed *in situ* from diaminomaleonitrile and tosyl isocyanate, with 4-nitrobenzaldehyde led to the production of 7,8-dihydro-2-(4-nitrophenyl)-8-oxo-9-tosylpurine-6-carboxamide (Equation 11) <2001JHC939>. Again, mechanistic studies indicated an initial cyclization to an imidazolone followed by condensation with the

aldehyde to give an unstable 1,2-dihydro-8-oxopurine which was oxidized by air on isolation, or under the conditions of the reaction, to the 8-oxopurine. Also of interest in this mechanism was the concomitant generation of the 6-carboxamido substituent from a nitrile during the condensation of the aldehyde with the cyanoformamide.

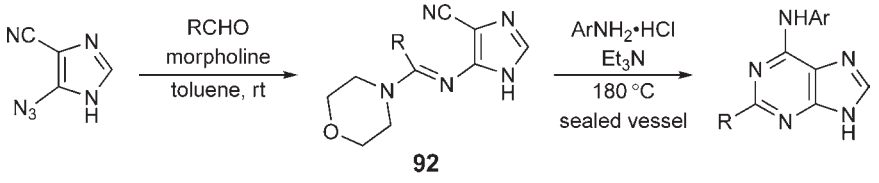


(11)

10.11.10 Ring Synthesis by Transformation of Another Ring

10.11.10.1 Synthesis from Imidazoles

A major route for the synthesis of purines starts from imidazoles and forms the fused six-membered pyrimidine ring. Depending on the substitution of the imidazole, three categories of cyclization can be distinguished, corresponding to the introduction of 0–2 ring atoms from external reagents in the bicycle-forming step (also see Volume 4). Cyclization of the imidazoloamidines **92**, which contained all the atoms of the nascent purine bicycle, was triggered by nucleophilic attack of anilines to the nitrile at high temperature and pressure (**Scheme 48**) <1997J(P1)3021>. The amidine starting materials were made from 4-azido-5-cyanoimidazole, morpholine, and simple aldehydes through the intermediacy and thermal rearrangement of a 1,2,3-triazoline.



R	*Ar*	*Yield (2 steps) (%)*
Et	4-MeOC$_6$H$_4$	22
Pr	Ph	20

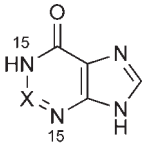
Scheme 48

Treatment of 1-methyl-4-cyano-5-aminoimidazole with phosgeniminium chloride produced an imidazoloamidine (64% yield) that cyclized when exposed to dry hydrogen chloride gas (95% yield) to give 6-chloro-2-dimethylamino-9-methylpurine <1997T8269>. Elaboration of this material led to the first synthesis of the natural product purine heteromine A (see Section 10.11.12.1).

1-Alkyl-4-cyanoformimidoyl-5-aminoimidazoles reacted with acetone or pentan-3-one to give stable 6-carbamoyl-2,2-dialkyl-1,2-dihydropurines (88–92% yields) where the ketone carbonyl provided the final ring atom of the bicycle (<1995J(P1)669>; see also Section 10.11.9). When pentane-2,3-dione was used, however, elimination of acetone followed the cyclization to yield the 6-carbamoyl-2-methylpurine (57% yield). Alternatively, the reaction of 1-(2-hydroxyethyl)-4-cyanoformimidoyl-5-aminoimidazole with ethyl chloroformate and DBU led to the formation of 1-(2-hydroxyethyl)-6-cyano-2-oxopurine (50% yield) <1996JHC855>. Interestingly, in this case, hydrolysis of the 6-cyano group to the carboxamide was not observed during the cyclization. Nucleophilic attack by malononitrile on related 1-aryl-4-cyanoformimidoyl-5-aminoimidazoles occurred at the cyanoformimidine group to afford 4-(1′-amino-2′,2′-dicyanovinyl)imidazoles, which were further cyclized to 6-(cyanomethylidene)purines upon exposure to triethyl orthoformate or acetic anhydride <2003JOC276>. 1-Aryl-4-cyanoformimidoyl-5-aminoimidazoles were found to be

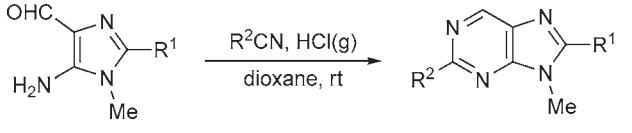
intermediates in the formation of 6-cyanopurines from (*Z*)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-arylformamidines (see Section 10.11.9), and were converted to 6-cyanopurines by an excess of triethyl orthoformate or triethyl orthopropionate (reflux, 65–91% yields) <2001J(P1)2532>. Alternatively, reaction of the 1-aryl-4-cyanoformimidoyl-5-aminoimidazoles with a slight excess of tosyl isocyanate at room temperature led to 6-(*N*-tosylcarboxamidino)-2-oxopurines (85–99% yields) <2001J(P1)1241>. Elucidation of the mechanism suggested that initial condensation occurred at the cyanoformimidine to generate an imidazol-2-one. Subsequent opening of this new heterocycle with participation of the 5-amino substituent on the imidazole led to formation of the fused pyrimidine ring of the purine, and accounted for the concomitant formation of the 6-(*N*-tosylcarboxamidino) functionality. An analogous pathway was proposed for the reaction of 1-substituted-4-cyanoformimidoyl-5-aminoimidazoles with ethoxymethylenemalononitrile or ethoxymethylene cyanoacetate, in which conjugate addition of the imino nitrogen to the activated alkene and cyclization of the resulting malonate enolate onto the nitrile led to a spectroscopically observable imidazopyrrolidine intermediate <2004OBC2340>. Ring opening of the pyrrolidine and reclosure gave 9-substituted-6-(1-amino-2,2-dicyanovinyl)- or 9-substituted-6-(1-amino-2-cyano-2-methoxycarbonylvinyl)purines as the final products (29–95% yields).

Syntheses of purines from imidazoles have been used for the introduction of multiple ^{15}N and ^{13}C atoms into the bicycle. This has provided several spin-labeled intermediates for incorporation into DNA, allowing structural studies of nucleic acid oligomers by NMR spectroscopy <1999JOC6575, 2001JOC6472>. [NH_2, $CONH_2$-$^{15}N_2$]-5-Amino-4-imidazolecarboxamide was prepared in six steps from imidazole-4,5-dicarboxylic acid, with the amide ^{15}N introduced as $^{15}NH_3$ and the amino ^{15}N originating from $Na^{15}NO_2$ via a diazo coupling <1999JOC6575>. Cyclocondensation with diethoxymethyl acetate gave the doubly ^{15}N-labeled hypoxanthine **93**, which was further transformed into multiply labeled adenine nucleosides through chlorination of the 6-oxo substituent and displacement with $^{15}NH_3$. An additional ^{13}C spin label was introduced at C-2 of the purine through reaction of [NH_2, $CONH_2$-$^{15}N_2$]-5-amino-4-imidazolecarboxamide with labeled sodium ethyl xanthate ($NaS^{13}CSOEt$). Desulfurization led to the triple-labeled hypoxanthine **94**. Alternatively, oxidation of the methanethiol and displacement by $^{15}NH_3$ gave triple- or quadruple-labeled purines **95** and **96**. A similar synthetic route starting from imidazole-3-carboxylic acid used nitration with $NH_4{}^{15}NO_3$ to introduce a labeled N1 to hypoxanthine <2001JOC6472>.



93: X = ^{12}C-H
94: X = ^{13}C-H
95: X = ^{12}C-$^{15}NH_2$
96: X = ^{13}C-$^{15}NH_2$

Purine formation from 1-methyl-4-amino-5-imidazolecarbaldehydes by introduction of two ring atoms in the cyclization step was achieved in moderate yields using simple alkyl and aryl nitriles as the two-atom component when the mixture was exposed to dry hydrogen chloride gas at room temperature (**Scheme 49**) <1997JHC1459>. By analogy with other pyrimidine ring-forming reactions, the mechanism presumably involved amidine formation between the amino substituent and the nitrile, followed by intramolecular attack of the amidine on the protonated aldehyde. Both formamide and formamidine acetate could be used in place of the nitriles to generate purines unsubstituted at C-2 (52–79% yields), but other amidines, for example acetamidine and benzamidine, did not react. 1-Substituted-5-cyano-4-aminoimidazoles reacted with tosyl isocyanate as the two-atom component to give unstable 5-(tosylureido)imidazoles which cyclized to isoguanines on warming (MeCN, −15 °C to room temperature, 53–77% yields) <1996JHC855>.



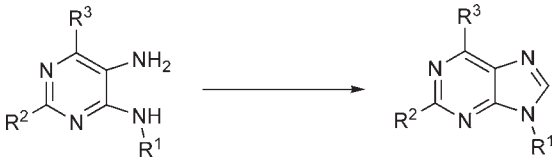
R^1	R^2	*Yield (%)*
Me	Me	44
Me	Ph	46
Ph	Et	22
Ph	Ph	33

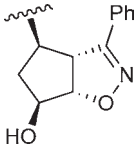
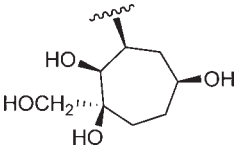
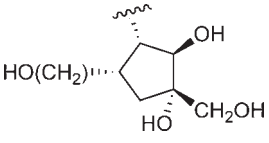
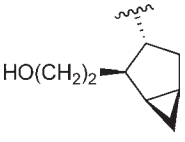
Scheme 49

10.11.10.2 Synthesis from Pyrimidines

The synthesis of purines by formation of an imidazole ring on a suitably functionalized pyrimidine has been the most popular route for recent syntheses (also see Volume 7). In particular, the addition of a single ring carbon atom to 4,5- or 5,6-diaminopyrimidines forms the majority of recently reported syntheses, although procedures where two or three atoms of the imidazole ring are introduced in the cyclization step are known (see below). The reaction of diaminopyrimidines with alkyl orthoformates or formic acid has been used to assemble simple purines, and to construct nucleosides where the sugar groups, or carbocyclic analogues, were already attached to the pyrimidine <1999T8075, 1999JOC2304, 2002S2445, 2004T3643, 2006JOC5980> (for selected examples, see **Table 7**). An attraction of this procedure is that unprotected hydroxyl groups in the substituents are often well tolerated. This route has been successful both in solution and on the solid phase <2001JME170, 2002TL8071, 2003TL8361, 2005EJO939>. Dialkoxymethyl acetates have been widely used as alternatives to orthoformates in the ring closure <1995JA11669, 1995TL3499, 1998T5883>. Other one-carbon electrophiles used for the annulation of diaminopyrimidines include trialkyl orthoacetates <2003TL8361>, formamides <2000JCO249, 2002T7607, 2001JOC5463>, and xanthates <2003JOC8657, 2006TL775>. The required 4,5- or 5,6-diaminopyrimidine starting materials often arise from reduction of *ortho*-aminonitropyrimidines. Typical reducing conditions were hydrogenation over palladium catalysts, or reduction using tin(II) chloride, chromium(II) chloride, or aluminium hydrides, and the crude reduction products have often been taken straight into the ring-forming reactions. Alternatively, S_NAr displacement by amines of the halide from *ortho*-chloroaminopyrimidines, or *ortho*-chloronitropyrimidines followed by reduction, has given the diaminopyrimidine precursors, a protocol particularly useful for combinatorial strategies.

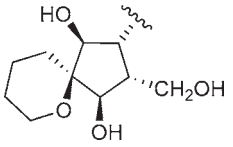
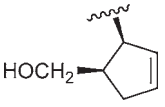
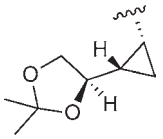
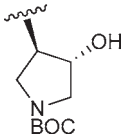
Table 7 Preparation of purines from 4,5-diaminopyrimidines and formate equivalents



R^1	R^2	R^3	*Conditions*	*Yield* (%)	*Reference*
	H	Cl	$CH(OEt)_3$, 12 M HCl(aq), 25 °C $CH(OEt)_3$, Ac_2O, 100 °C, 20 h $CH(OEt)_3$, *p*-TsOH, 25 °C, 8 d	0 39 91	2004T3643
	H	Cl	$CH(OEt)_3$, *p*-TsOH, DMF, 20 °C	69	1999JOC2304
	H	Cl	$CH(OEt)_3$, *p*-TsOH, DMF, 20 °C	53	1999JOC2304
	H	Cl	$CH(OEt)_3$, 12 M HCl(aq), rt	56[a]	1999T8075

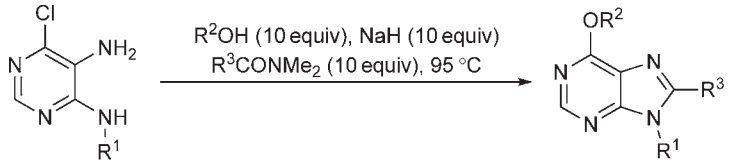
(*Continued*)

Table 7 (Continued)

R^1	R^2	R^3	*Conditions*	*Yield (%)*	*Reference*
	H	Cl	$CH(OEt)_3$, *p*-TsOH, DMF, 10 °C	32	2006JOC5980
	H NH_2	Cl Cl	$CH(OEt)_3$, 12 M HCl(aq), rt	93 55	2002S2445
Me	SMe	N(Bn)-CH_2-resin	$(MeO)_3CH$, $MeSO_3H$, 80 °C	n.a.[b]	2002TL8071
Me	NHAc	Cl	$(EtO)_3CH$, HCl, MeOH, 80 °C	89	2001JME170
H	SBn	OH	$(MeO)_3CH$, Cl, DMF, rt	92	2005EJO939
H	H	OH	$AcOCH(OEt)_2$, HCO_2H, DMF, 13 °C	88[c]	1995JA11669
	H	Cl	$AcOCH(OEt)_2$, 120 °C	n.a.[b]	1995TL3499
	H	Cl	$AcOCH(OEt)_2$, 110 °C then *p*-TsOH, toluene, rt	35	1998T5883
H	H	$^{15}NH_2$	$AcOCH(OEt)_2$	80[d]	2001JOC5463
n-C_5H_{11}	H	Cl	$Me_2NCH(OMe)_2$, 95 °C $Me_2NCH(OMe)_2$, DMF, 130 °C	65 68	2002T7607
n-Butyl *n*-Pentyl *n*-Hexyl	H	NH-resin	$HCONH_2$, 160 °C	n.a.[b]	2000JCO249
H	SH	OH	$NaS^{13}CSOEt$, DMF, reflux	90[c]	2003JOC8657

[a]Yield for 2 steps including reduction of precursor *ortho*-nitroaminopyrimidine.
[b]Yield for this step not described.
[c]^{15}N incorporated at purine N-7.
[d]^{15}N incorporated at adenine N-1, N-3, N-7, N-9, and 6-NH_2.

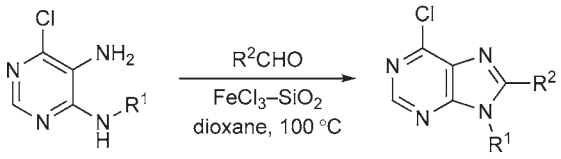
The reaction of a large excess of *N*,*N*-dimethylalkaneamides and alkoxide anions with 6-chloro-4,5-diaminopyrimidines gave rise to 6,8,9-trisubstituted purines, where condensation of the amide with the diamine to form the five-membered ring was accompanied by S_NAr displacement of the chloro substituent by the alkoxide (**Scheme 50**) <2002T7607>. No purines were formed from the diaminopyrimidine and the alkyl amides in the absence of alkoxides, suggesting the mechanism was through initial reaction of the alkoxide and amide to give the acetals of the amide, to which the diaminopyrimidine then added. The formation of 8-mercaptoxanthines from 5,6-diaminouracils and potassium ethyl xanthate was significantly accelerated by microwave heating (120 °C, 10 min, 73–97% yields) <2006TL775>. 6-Chloro-4[amino-^{15}N],5-diaminopyrimidine was selectively formylated on the ^{15}N-labeled 4-amino group by [^{13}C]formic trimethylacetic anhydride <1999JOC4685>. Cyclodehydration to give the doubly labeled purine was effected using an unusual reagent combination of triethyl phosphate and $TiCl_2(^iPrO)_2$ (88% yield). 7,9-Disubstituted-2-chloro-8-oxopurines were formed in generally high yields in the condensation of 2-chloro-4,5-diaminopyrimidines with triphosgene (triphosgene, Et_3N, THF, 0 °C to rt, 50–100% yields) <2005S2227>.



R^1	R^2	R^3	*Yield* (%)
H	Et	H	34
^{i}Pr	Bn	H	38
Bu	Et	Me	33
^{i}Pr	Et	Et	29

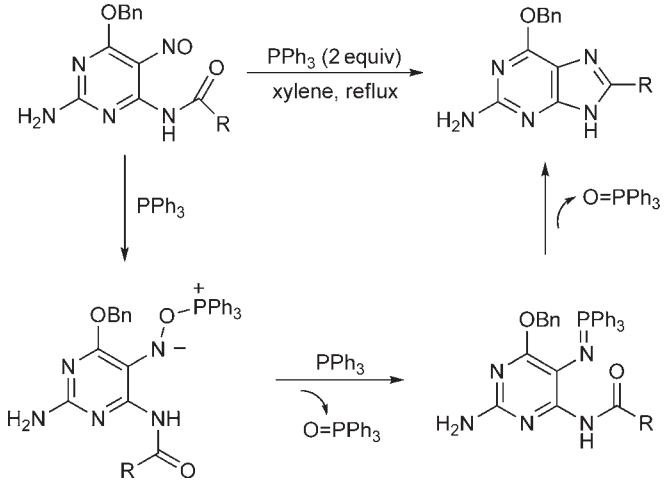
Scheme 50

The condensation of aldehydes and diaminopyrimidines has been used to prepare purines when the condensation is coupled with an oxidation step. Thus, 6-chloro-4-alkylamino-5-aminopyrimidines and alkyl, alkenyl, and aryl aldehydes afforded the 8-substituted purines when reacted in the presence of silica-supported iron(III) chloride in a variant of the Traube xanthine synthesis (**Scheme 51**) <2000TL6559>. Related methodology using iron(III) chloride in solution was applied to prepare 2-amino-8-aryl-9-methyl-6-chloropurines as intermediates in the synthesis of adenosine receptor antagonists <2001JME170>. A similar transformation, involving condensation with an aldehyde followed by oxidative cyclization with thionyl chloride, was used to prepare tricyclic pyrimido[1,2,3-*cd*]purinediones <2003T47>. If no oxidation step is included, dihydropurines may result, as was seen in the reaction of 6-chloro-4-anilino-5-aminopyrimidine with benzaldehyde to give 6-chloro-8,9-diphenyl-8,9-dihydro-7*H*-purine (57% yield) <2006T2563>. Alternatively, 4-amino-5-nitrosopyrimidines have been converted into 8-substituted guanines through acylation of the 4-amino substituent with mixed anhydrides or acid chlorides, followed by reductive cyclization to form the imidazole ring using 2 equiv of triphenylphosphine (**Scheme 52**) <2003CC1452>. Purine formation was presumed to occur through reduction of the nitroso group to an iminophosphorane which underwent aza-Wittig condensation with the adjacent amide.



R^1	R^2	*Yield* (%)
$Ph(CH_2)_2$	2-Furanyl	85
$Ph(CH_2)_2$	PhCH=CH	55
^{i}Bu	Me	88
Cyclopropyl	2-Furanyl	48

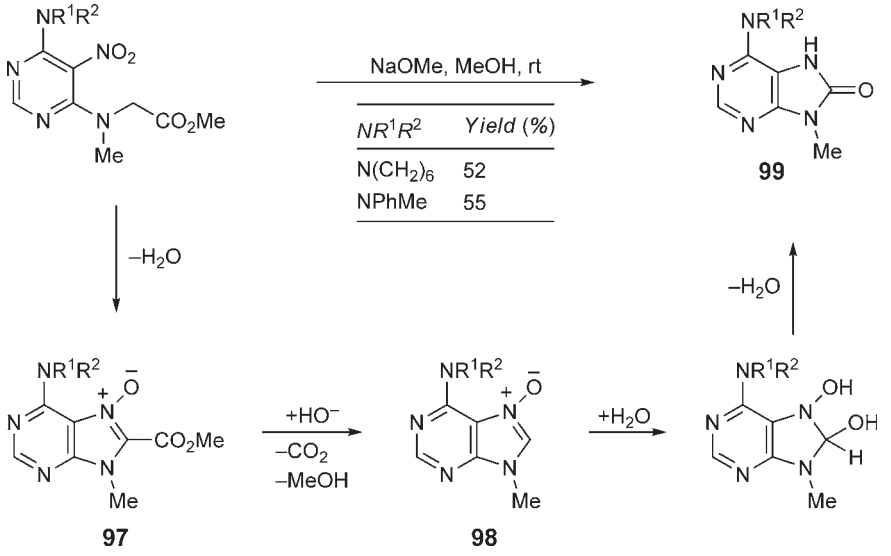
Scheme 51



R	*Yield* (%)
Me	82
Ph	90
Bn	40
CH=CHPh	86
3-pyridyl	92

Scheme 52

An unusual nonreductive cyclisation-rearrangement of an exocyclic enolate onto a nitropyrimidine was involved in the construction of 8-oxopurines from 4,6-diamino-5-nitropyrimidines <2005TL1841, 2006SL1422>. Intramolecular condensation of the enolate and the nitro group led to an intermediate **97** that underwent hydroxide addition to the ester and decarboxylation to give the purine *N*-oxide **98** (**Scheme 53**). Addition–elimination of water to **98** was proposed to explain the rearrangement of the *N*-oxide to the 8-oxopurine **99**. The procedure only generated purines when a dialkylamino substituent was present at C-6 of the purine, otherwise 4,5-diamino-5-nitrosopyrimidines were produced. Interestingly, when the pyrimidine N-4 substituent was changed from methylamine to benzylamine, a dependence on the nature of the alkoxide was observed <2006SL1422>. While lithium, sodium, and potassium ethoxides in ethanol gave the expected 8-oxopurines (45–81% yields), the equivalent methoxides in methanol gave the 8-methoxy-9*H*-purines instead (57–91% yields), indicative of competition between hydroxide and methoxide for attack on **98**. Various bases in aprotic solvents failed to give any reaction of the nitropyrimidines, for example, NaOMe in DMF, and lithium diisopropylamide (LDA) in THF.

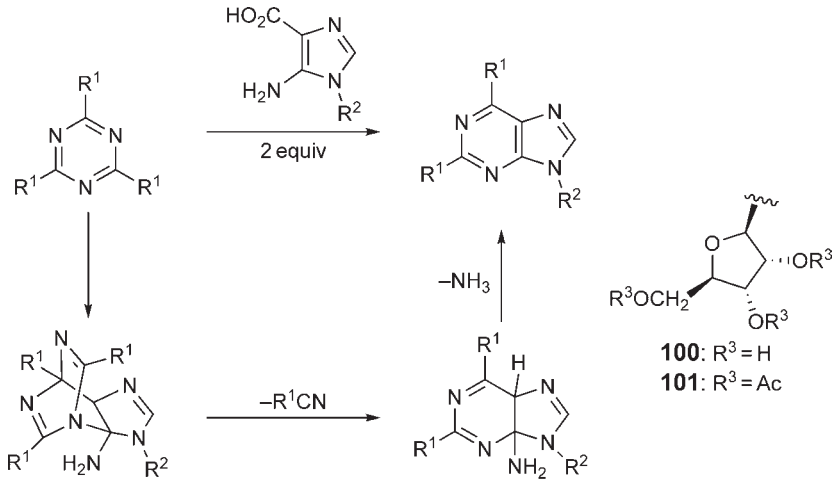


Scheme 53

8-Amino- and 8-phenylxanthines were prepared from 5-bromo-6-methoxy-1,3-dimethyl-1*H*-pyrimidine-2,4-dione by a two-step condensation where amidines or guanidines provided the three atoms of the fused imidazole ring <2005OL1833>. Although the initial S_NAr reaction was straightforward, neither acidic, basic, nor palladium-mediated conditions would effect the cyclization, but ring closure was achieved using catalytic copper(I) iodide and sodium hydride (53–82% yields).

10.11.10.3 Synthesis from Triazines

The well-known application of 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine as a diene in inverse electron demand Diels–Alder cyclizations was adapted for the synthesis of purines <1999JA5833>. The unstable, electron-rich dienophile 5-amino-1-benzylimidazole was generated *in situ* by decarboxylation of 5-amino-1-benzyl-4-imidazolecarboxylic acid under mildly acidic conditions (**Scheme 54**). Collapse of the Diels–Alder adduct by retro-Diels–Alder reaction and elimination of ethyl cyanoformate, followed by aromatization by loss of ammonia, led to the purine products. The reactions proceeded at room temperature if left for sufficient periods (e.g., 25 °C, 7 days, 50% yield) but were generally more efficient at higher temperatures (80–100 °C, 2–24 h). The inverse electron demand Diels–Alder cyclization of unsubstituted 1,3,5-triazine was also successful. This synthesis had the advantage of constructing the simple purine heterocycle directly in the presence of both protected and unprotected furanose substituents (also see Volume 8).



R^1	R^2	*Conditions*	*Yield (%)*
CO_2Et	Bn	80 °C, DMF, 2 h	83
CO_2Et	**100**	80 °C, DMF–AcOH, 24 h	81
CO_2Et	**101**	90 °C, DMSO, 6 h	75
H	**100**	90 °C, DMSO, 6 h	40
H	**101**	90 °C, DMSO, 6 h	65

Scheme 54

The 1,2,4-triazin-3-one ring of 6,8-dimethyl-2,8-dihydropyrimido[5,4-*e*][1,2,4]triazine-3,5,7-trione (fervenulone) underwent ring contraction upon alkylation with *tert*-butyl bromoacetate to yield a 1,3-dimethyl-2,6,8-trioxo-1,2,3,6,8,9-hexahydropurine <1995JOC7063>. The mechanism for the transformation was proposed to proceed through N-alkylation of the triazinone followed by an anion-accelerated sigmatropic rearrangement to open the six-membered ring, that reclosed to form the five-membered ring of the trioxopurine.

10.11.11 Critical Comparison of Synthetic Routes

A major advance in the synthetic chemistry of purines since the preceding survey in this series <1996CHEC-II(7)397> has been the development of routes to polysubstituted purines involving the reactions of halopurines, particularly through nucleophilic aromatic substitution and transition metal-catalyzed cross-couplings (see Sections 10.11.7.4.1 and 10.11.7.4.2). In many instances, such strategies are now the method of choice for the preparation of highly substituted purines. Although regioselective transition metal-catalyzed couplings to various dihalopurines are now well established for sp^2–sp^2 bond formations, the formation of sp^2–sp^3 bonds by this method has generally received less attention. The construction of trihalopurines and the control of the regioselectivity of their reactions promises to be an interesting area for further study. The chemistry of regioselectively metalated purines also provides opportunities for further exploration.

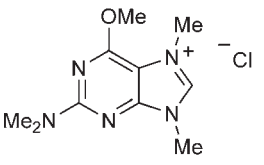
Advances have been made in the selective N-alkylation of purine ring nitrogens, with Mitsunobo and palladium-catalyzed allylation methodologies demonstrating high versatility (see Section 10.11.5.2.1). The introduction of 6-azole substituents as directing groups for N-9-versus N-7-alkylation, and also as pseudohalogens for displacement or cross-coupling reactions, is a potentially powerful development in this area. The reactions of halopurines and thiopurines have been effectively combined with the various N-alkylation procedures into parallel synthesis strategies both in solution and on the solid phase. This has led to the efficient preparation of large compound libraries, particularly of 2,6,9-trisubstituted purines (see Section 10.11.12.2). In contrast to the foregoing methodologies, the functionalization of purines by inter- or intramolecular radical reactions has not been extensively investigated, although the examples reported suggest that high selectivities can be achieved (see Section 10.11.5.4).

De novo purine ring synthesis most frequently involves the annulation of functionalized imidazoles and pyrimidines, and these routes are highly developed. The use of Diels–Alder–retro-Diels–Alder reactions of triazines to generate the purine bicycle is a useful but less explored alternative (see Section 10.11.10.3). There are few reports of multicomponent reactions to assemble the purine nucleus. If realized, such a strategy could provide a valuable means of preparing polysubstituted purines complementary to the methodology developed around polyhalopurines, as has been seen with other heteroaromatic systems <2002J(P1)1921>.

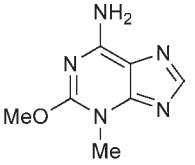
10.11.12 Important Compounds and Applications

10.11.12.1 Naturally Occurring Purines

A number of new purine-containing natural products have been identified in both terrestrial and marine sources. Several of these are purinium salts, such as heteromine A (6-methoxy-7,9-dimethyl-2-*N*,*N*-dimethylaminopurinium chloride) **102**, which was isolated from the climbing plant *Heterosperma brownie*, and showed cytotoxicity toward K562 and HL-60 cell lines <1996H(43)781>. The total synthesis of heteromine A has been described <1997T8269 (see Section 10.11.10.1). Simple purines have been isolated from marine sponges, including mucronatine (2-methoxy-3-methyl-3*H*-purin-6-ylamine) **103**, which showed antifoulant properties <2001TL7257>. The structure of mucronactine was elucidated by 2-D NMR spectroscopy, where a ^{15}N–^{1}H HMQC experiment established the 6-aminopurine tautomer in preference to the 6-iminopurine. This corresponded with the structure of 1,3-dimethylisoguanine previously isolated from other sponges <1997JNP727, 1997JNP729>, which was shown by X-ray crystallography to adopt the 6-amino tautomer <1999AXC1585>.

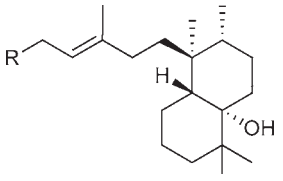


102

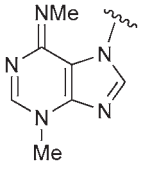


103

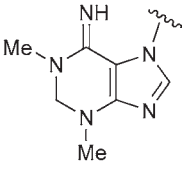
3,7-Dimethylisoguanine was isolated from a sponge of the genus *Agelas* <1995TL7893>. *Agelas* species have proved a rich source of more complex bioactive purine natural products, such as the cytotoxic adenine-related diterpenoids agelasimine A **104** and B **105**, whose structures and absolute configurations were confirmed by total synthesis <1996JA8250, 1997T16977>. The purine was installed by two complementary regioselective alkylation routes. Additionally, it was found that oxidation of **104** (DDQ) followed by acid-base treatment gave **105** through a ring-opening–ring-closing rearrangement, suggesting a possible biosynthetic transformation of **104** to **105**.



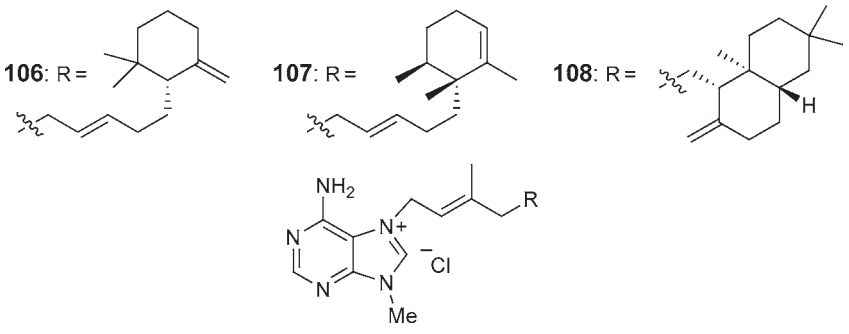
104: R =



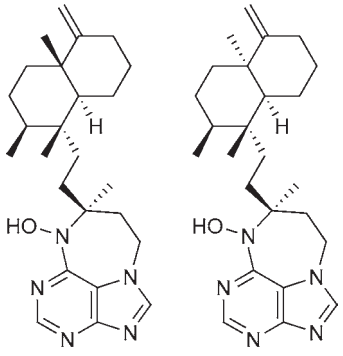
105: R =



The agelasines are a family of diterpenoid 7,9-dialkylpurinium salts, also isolated from marine *Agelas* species, that have a range of biological activites including cytotoxic and antimicrobial effects. Agelasine A was prepared by alkylation of 7-methyl-3,7-dihydropyrrolo[2,3-*d*]pyrimidin-4-one *O*-methyloxime <1995J(P1)963>. Agelasine D **106**, agelasine E **107**, and numerous non-natural analogues were synthesized by regioselective alkylation of N^6-methoxy-9-methyl-9*H*-purine-6-amine with allyl bromides and subsequent reductive cleavage of the N(6)–O bond <2004TL4233, 2005OBC1025>. Surprisingly, in contrast to data reported for agelasine F **108**, the natural product and 6-aminopurines most similar to it did not display activity against mycobacterium tuberculosis, whereas some *N*-6-methoxy synthetic intermediates did have significant antimycobacterial activity. *epi*-Agelasine C was found to have antimicroalgal, but not antibacterial, properties <1997JNP411>.

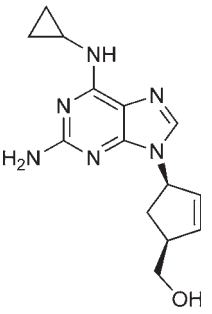


The tricyclic marine sponge metabolites asmarine A **109** and B **110** showed toxicity to human tumor cell lines <1998TL1445, 2000JNP299>, and a number of simpler analogues have been prepared <2003T6493>; see Section 10.11.7.3.1.



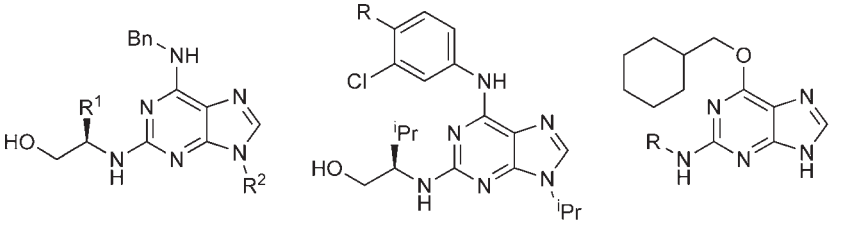
10.11.12.2 Purines in Drug Design

The purine bases adenine and guanine are essential molecular components of living organisms, and are incorporated within macromolecules (nucleic acids) and small molecules (enzyme cofactors: e.g., ATP, SAM; signaling molecules: e.g., adenosine, cyclic AMP). A very large number of proteins involve purine-containing ligands in their function, including nucleic acid polymerases, kinases, nucleotide phosphorylases, purine-recognizing receptors, and the enzymes responsible for purine metabolism and biosynthesis. It is therefore unsurprising that the chemistry of purines has been widely exploited in biomedical and therapeutic applications <1999CBO361, 2006BMC3987, 2006MI1117>. The purine scaffold is a chemically stable motif containing a high N:C ratio (4:5) relative to other common heterocyclic drug scaffolds, providing multiple opportunities for specific hydrogen-bonding interactions between the scaffold and biological targets. The potential for generating neutral molecules with up to four substituents (from C-2, C-6, C-8, N-7, or N-9) well distributed around the perimeter of the bicycle allows the easy exploration of chemical space along vectors in all directions emanating within the plane of the heterocycle. Thus a major exercise in the past decade has been the construction of diverse, often large, libraries of polysubstituted purines as materials for biological research <1998SCI533, 1999CBO361>; see Sections 10.11.7.4 and 10.11.10. The very widespread occurrence of purines as biologically active agents in the biomedical literature has been recently reviewed <2006BMC3987, 2006MI1117> and is not covered here. The development of antiviral purine carbonucleosides, where medicinal chemists have sought to replace the nucleoside sugar ring with metabolically more stable moieties that are still recognized by the enzymic targets, has continued to deliver successful therapies such as the inhibitor of HIV replication, abacavir **111** <1997AAC1082>.



111

Two additional areas where endogenous purines have provided the basis for recent successful drug design are highlighted here: the discovery of purine-derived CDK inhibitors, and the identification of purines as inhibitors of the heatshock protein 90 (HSP90) molecular chaperone. The chemistry of purines has been central to the development of inhibitors of protein kinases. These enzymes function by transferring the terminal phosphate group of the cofactor ATP to the hydroxyl group of a serine, threonine, or tyrosine in protein substrates. The importance of protein kinases in cellular signaling processes regulating growth, replication, and metabolism has led to this protein family becoming a major current drug target <2002MI309>. The discovery of kinase inhibitors has involved the design of scaffolds based on the purine-containing cofactor <1996JA7430, 1998SCI533, 2005JME710>, as well as biochemical screening of other diverse heterocyclic chemical libraries. Structure-based drug design using crystallographic screening to identify small molecule fragments that bind to target enzymes has also generated purine derivatives as kinase inhibitors <2007JME2289>. The use of ligand-enzyme X-ray crystallography has contributed extensively to the understanding of the binding of ATP and inhibitors to the ATP-binding site of kinases, and the high degree of conservation of sequence and 3-D structure in the ATP-binding site across the kinome has been widely exploited <2004CME663, 2004SCI1800>. A key example of structure-based design in this area was the development of purine-based inhibitors of the CDK family of cell-cycle regulatory enzymes, reviewed in <2002MI1037>, beginning with the identification of olomoucine **112** as a lead inhibitor selective for CDKs over other kinases <1994EJB771>. Comparison of the crystallographically determined binding modes of olomoucine and ATP in CDK2 showed the purines occupying similar spaces but with an approximately 160° rotation of the olomoucine heterocycle relative to the adenosine of ATP, and therefore using different functionality to fulfil the conserved hydrogen-bonding interactions to the kinase <1995MI378>. Further work led to the identification of roscovitine **113** <1997EJB518, 1997EJB527>, which was subsequently developed as a clinical candidate (seleciclib) for the treatment of various tumors. Extensive application of structure-based design and combinatorial library synthesis, especially of 2,6,9-trisubstituted purines, has led to the discovery of many other purine inhibitors of CDK family members; see, for example, <1997BML2697, 1997JME408, 1999BMC1281, 1999CBO361, 2000JME1282, 2002BML3283, 2002JME3381, 2003BML2993>, and <2004JME3710>, including purvalanol A **114**, purvalanol B **115** <1998SCI533>, NU2058 **116** <2000JME2797>, and NU6102 **117** <2002MI745>.



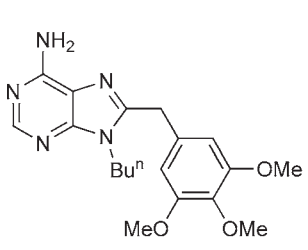
112: R^1 = H; R^2 = Me
113: R^1 = Et; R^2 = ^{i}Pr

114: R = H
115: R = CO_2H

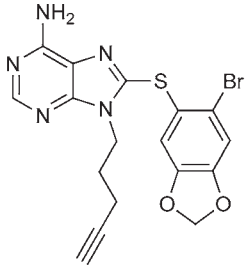
116: R = H
117: R = 4-(C_6H_4)SO_2NH_2

The molecular chaperone HSP90 contains an ATPase domain essential to its function of mediating and stabilizing the correct folding of client proteins. The 3-D structure of the ATP-binding site is quite distinct from that of kinases, but has also proved amenable to structure-based drug design, including modifications of the adenine nucleotide cofactor <2006CME1091>. The development of purine-based inhibitors of HSP90 has been reviewed in <2006MI1183>. The prototype inhibitor PU3 **118** was designed to match the structural features of the ATP-binding

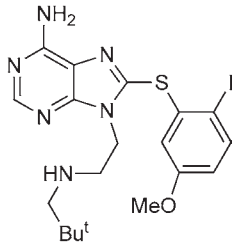
pocket <2001CBO289> and was followed by more potent compounds identified from screening purine libraries based on the PU3 structure <2002BMC3555>. The binding of PU3 and analogues to the HSP90 ATPase domain was determined crystallographically <2004BML325, 2004CBO775>. Further potent analogues of PU3 have been developed <2005JME2892, 2006JME381, 2006JME817, 2006JME5352>, including 8-arylsulfanyladenines such as **119** and related orally bioavailable compounds, for example, **120**.



118



119



120

10.11.13 Further Developments

Several noteable publications have appeared in the literature since the compilation of this review. An efficient method to construct isoguanines from the parent imidazole template (see Section 10.11.10.1) has been achieved <2007SL1231>. A large library of 2,6,8,9-tetrasubstituted purines was prepared by construction of a resin-bound 2,4,5,6-tetraaminopyrimidine and subsequent purine ring formation using orthoacetates <2007TL2823> (see Section 10.11.10.2). Alkylation of protected guanines and other purines with simple alcohols under modified Mitsunobu conditions (DIAD, PPh_3, THF, 70 °C) gave good yields of the N-9 alkylation products with complete stereochemical control when chiral alcohols were used <2007JO5012> (see Section 10.11.5.2.1). Mitsunobu conditions were less successful in the coupling of a carbocyclic alcohol to N-9 of 6-chloropurine during the synthesis of the natural product (−)-neplanocin F, where displacement of a homoallylic secondary triflate was more productive <2007T7165>. Microwave promoted Michael additions to prepare acyclic nucleosides, discussed in Section 10.11.5.2.1, have been performed using water as solvent <2007SL721>, and the rapid Vorbruggen glycosylation of purines conducted under microwave heating formed the first step of a high-throughput synthesis of a nucleoside library <2007JO173>. Microwave heating was also applied to the displacement of the halogens in 6-chloropurine and 2-amino-6-chloropurine by oxygen, nitrogen, and sulfur nucleophiles <2007T5323> (see Section 10.11.7.4.1). A comprehensive study on such S_NAr reactions of 6-halopurine nucleosides has resulted in a proposed set of halogen displacement reactivity orders, which were dependent on the nature of the nucleophile <2007JA5962>. Interestingly, displacement using anilines as the nucleophilic component was found to be autocatalytic, requiring significant induction periods, which could be overcome by the addition of trifluoroacetic acid. Further derivatization at the 6-position of halopurines has also been demonstrated by the formation of (purin-6-yl)acetates from the coupling of 6-chloropurines with the Reformatsky reagent ($BrZnCH_2CO_2Et$) under palladium catalysis <2007TL5589> (see Section 10.11.7.4.2). A chemical genetics approach has been applied to the construction of a small purine based library with the aim of generating potent and selective inhibitors of mutant kinases <2007T5832>, again highlighting the importance of purines as privileged structures in drug design (see Section 10.11.12.2).

References

1994EJB771 J. Vesely, L. Havlicek, M. Strnad, J. J. Blow, A. Donella-Deana, L. Pinna, D. S. Letham, J. Kato, L. Detivaud, S. Leclerc, and L. Meijer, *Eur. J. Biochem.*, 1994, **224**, 771.

1995AXC2383 D. M. C. Chan, C. H. Schwalbe, G. Sood, and W. Fraser, *Acta Crystallogr.*, 1995, **51**, 2383.

1995JA127 B. Marciniak, G. L. Hug, J. Rozwadowski, and K. Bobrowski, *J. Am. Chem. Soc.*, 1995, **117**, 127.

1995JA3665 X. Ariza, V. Bou, and J. Vilarrasa, *J. Am. Chem. Soc.*, 1995, **117**, 3665.

1995JA5951 R. W. Miles, V. Samano, and M. J. Robins, *J. Am. Chem. Soc.*, 1995, **117**, 5951.

1995JA11669 A. R. Pagano, W. M. Lajewski, and R. A. Jones, *J. Am. Chem. Soc.*, 1995, **117**, 11669.

1995JHC941 A. Da Settimo, G. Primofiore, B. M. Cristina, F. Da Settimo, and A. M. Marini, *J. Heterocycl. Chem.*, 1995, **32**, 941.

1995JME2582 K. G. Estep, K. A. Josef, E. R. Bacon, P. M. Carebateas, S. Rumney, IV G. M. Pilling, D. S. Krafte, W. A. Volberg, K. Dillon, N. Dugrenier, G. M. Briggs, P. C. Canniff, W. P. Gorczyca, G. P. Stankus, and A. M. Ezrin, *J. Med. Chem.*, 1995, **38**, 2582.

1995JOC1531 M.-J. Perez-Perez, J. Rozenski, R. Busson, and P. Herdewijn, *J. Org. Chem.*, 1995, **60**, 1531.
1995JOC7063 M. M. Mehrotra, D. D. Sternbach, R. D. Rutkowske, and P. L. Feldman, *J. Org. Chem.*, 1995, **60**, 7063.
1995J(P1)15 L. de Napoli, D. Montesarchio, G. Picciali, C. Santacroce, and M. Varra, *J. Chem. Soc., Perkin Trans. 1*, 1995, 15.
1995J(P1)669 B. L. Booth and P. R. Eastwood, *J. Chem. Soc., Perkin Trans. 1*, 1995, 669.
1995J(P1)963 E. Piers, M. L. Breau, Y. Han, G. L. Plourde, and W. Yeh, *J. Chem. Soc., Perkin Trans. 1*, 1995, 963.
1995MI378 U. Schulze-Gahmen, J. Brandsen, H. D. Jones, D. O. Morgan, L. Meijer, and S. H. Kim, *Proteins*, 1995, **22**, 378.
1995T3655 G. Andresen, L. Gundersen, M. Lundmark, F. Rise, and S. Sundell, *Tetrahedron*, 1995, **51**, 3655.
1995TL91 K. Kamaike, M. Takahashi, K. Utsugi, K. Tomizuka, and Y. Ishido, *Tetrahedron Lett.*, 1995, **36**, 91.
1995TL1945 L. Gundersen, G. Langli, and F. Rise, *Tetrahedron Lett.*, 1995, **36**, 1945.
1995TL2665 R. Saladino, C. Crestini, R. Bernini, E. Mincione, and R. Ciafrino, *Tetrahedron Lett.*, 1995, **36**, 2665.
1995TL3499 M. Lee, D. Lee, Z. Zhao, M. G. Newton, M. W. Chun, and C. K. Chu, *Tetrahedron Lett.*, 1995, **36**, 3499.
1995TL6507 K. Kato, H. Hayakawa, H. Tanaka, H. Kumamoto, and T. Miyasaka, *Tetrahedron Lett.*, 1995, **36**, 6507.
1995TL7875 L. Desaubry and J. Bourgignon, *Tetrahedron Lett.*, 1995, **36**, 7875.
1995TL7893 F. Cafieri, E. Fattorusso, A. Mangoni, and O. Taglialatela-Scafati, *Tetrahedron Lett.*, 1995, **36**, 7893.
1995TL8885 N. Poje and M. Poje, *Tetrahedron Lett.*, 1995, **36**, 8885.
1996ACS462 L. Gundersen, *Acta Chem. Scand.*, 1996, **50**, 462.
1996CHEC-II(7)397 G. Shaw; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 397.
1996CPL189 W. Caminati, G. Maccaferri, P. G. Favero, and L. B. Favero, *Chem. Phys. Lett.*, 1996, **251**, 189.
1996H(43)781 Y. Lin, H. Lee, J. Ou, and Y. Kuo, *Heterocycles*, 1996, **43**, 781.
1996JA509 L. Clowney, S. C. Jain, A. R. Srinivasan, J. Westbrook, W. K. Olson, and H. M. Berman, *J. Am. Chem Soc.*, 1996, **118**, 509.
1996JA689 R. Fiala, F. Jiang, and D. J. Patel, *J. Am. Chem. Soc.*, 1996, **118**, 689.
1996JA4124 A. Schreiber, M. S. Lüth, A. Erxleben, E. C. Fusch, and B. Lippert, *J. Am. Chem. Soc.*, 1996, **118**, 4124.
1996JA5615 R. Saladino, E. Mincione, C. Crestini, R. Negri, E. Di Mauro, and G. Costanzo, *J. Am. Chem. Soc.*, 1996, **118**, 5615.
1996JA7430 T. C. Norman, N. S. Gray, J. Y. Koh, and P. G. Schultz, *J. Am. Chem. Soc.*, 1996, **118**, 7430.
1996JA8250 M. Ohba, N. Kawase, and T. Fujii, *J. Am. Chem. Soc.*, 1996, **118**, 8250.
1996JA10408 J. R. Barrio, M. Namavari, M. E. Phelps, and N. Satyamurthy, *J. Am. Chem. Soc.*, 1996, **118**, 10408.
1996JHC319 P. A. Harris and W. Pendergast, *J. Heterocycl. Chem.*, 1996, **33**, 319.
1996JHC681 Y. Shalom, R. G. Harvey, and J. Blum, *J. Heterocycl. Chem.*, 1996, **33**, 681.
1996JHC855 A. M. Dias, M. F. J. R. P. Proenca, and B. L. Booth, *J. Heterocycl. Chem.*, 1996, **33**, 855.
1996JHC1115 S. Asano, K. Itano, Y. Yamagata, and K. Kohda, *J. Heterocycl. Chem.*, 1996, **33**, 1115.
1996JOC1331 M. Medebielle, M. A. Oturan, J. Pinson, and J. Saveant, *J. Org. Chem.*, 1996, **61**, 1331.
1996JOC4192 M. T. Crimmins and B. W. King, *J. Org. Chem.*, 1996, **61**, 4192.
1996JOC5964 B. Hernandez, F. J. Luque, and M. Orozco, *J. Org. Chem.*, 1996, **61**, 5964.
1996T799 M. J. Konkel and R. Vince, *Tetrahedron*, 1996, **52**, 799.
1996T2789 L. B. Akella and R. Vince, *Tetrahedron*, 1996, **52**, 2789.
1996T5625 G. Langli, L. Gundersen, and F. Rise, *Tetrahedron*, 1996, **52**, 5625.
1996T6759 R. Saladino, E. Mincione, C. Crestini, and M. Mezzetti, *Tetrahedron*, 1996, **52**, 6759.
1996T8407 L. B. Akella and R. Vince, *Tetrahedron*, 1996, **52**, 8407.
1996T8969 M. J. Konkel and R. Vince, *Tetrahedron*, 1996, **52**, 8969.
1996T10737 Y. Xu, *Tetrahedron*, 1996, **52**, 10737.
1996T14335 C. W. Bird, *Tetrahedron*, 1996, **52**, 14335.
1996TL1285 H. Dvorak, D. Dvorak, and A. Holy, *Tetrahedron Lett.*, 1996, **37**, 1285.
1996TL4701 H. B. Lazrek, H. Khaïder, A. Rochdi, J.-L. Barascut, and J.-L. Imbach, *Tetrahedron Lett.*, 1996, **37**, 4701.
1996TL8375 T. M. Stevenson, A. S. B. Prasad, J. R. Citineni, and P. Knochel, *Tetrahedron Lett.*, 1996, **37**, 8375.
1996TL8857 S. Czernecki, A. Hoang, and J. Valery, *Tetrahedron Lett.*, 1996, **37**, 8857.
1997AAC1082 S. M. Dalgue, S. S. Good, M. B. Faletto, W. H. Miller, M. H. St. Clair, L. R. Boon, M. Tisdale, N. R. Parry, J. E. Reardon, R. E. Dornsife, D. R. Averett, and T. A. Krenitsky, *Antimicrob. Agents Chemother.*, 1997, **41**, 1082.
1997AXC777 Y. Ebisuzaki, P. D. Boyle, and J. A. Smith, *Acta Crystallogr., Sect. C*, 1997, **53**, 777.
1997BML2697 S. R. Schow, R. L. Mackman, C. L. Blum, E. Brooks, A. G. Horsma, A. Joly, S. S. Kerwar, G. Lee, D. Schiffman, G. Marek, X. Wang, W. M. Wick, X. Xiaoming, and R. T. Lum, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2697.
1997EJB518 W. F. De Azevedo, S. Leclerc, L. Meijer, L. Havlicek, M. Strnad, and S. H. Kim, *Eur. J. Biochem.*, 1997, **243**, 518.
1997EJB527 L. Meijer, A. Borgne, O. Mulner, J. P. J. Chong, J. J. Blow, N. Inagaki, M. Inagaki, J. G. Delcros, and J. P. Molynoux, *Eur. J. Biochem.*, 1997, **243**, 527.
1997JA3007 G. Rastelli, L. Costantino, and A. Albasini, *J. Am. Chem. Soc.*, 1997, **119**, 3007.
1997JA3114 A. Holmen, B. Norden, and B. Albinsson, *J. Am. Chem. Soc.*, 1997, **119**, 3114.
1997JA12240 A. Holmen, A. Broo, B. Albinsson, and B. Norden, *J. Am. Chem. Soc.*, 1997, **119**, 12240.
1997JHC477 N. Poje, A. Palkovic, and M. Poje, *J. Heterocycl. Chem.*, 1997, **34**, 477.
1997JHC739 M. J. Alves, M. A. Carvalho, M. F. J. R. P. Proenca, B. L. Booth, and R. G. Pritchard, *J. Heterocycl. Chem.*, 1997, **34**, 739.
1997JHC1459 F. Perandones and J. L. Soto, *J. Heterocycl. Chem.*, 1997, **34**, 1459.
1997JME408 L. Havlicek, J. Hanus, J. Vesely, S. Leclerc, L. Meijer, G. Shaw, and M. Strnad, *J. Med. Chem.*, 1997, **40**, 408.
1997JNP411 T. Hattori, K. Adachi, and Y. Shizuri, *J. Nat. Prod.*, 1997, **60**, 411.
1997JNP727 S. S. Mitchell, A. B. Whitehill, H. G. Trapido-Rosenthal, and C. M. Ireland, *J. Nat. Prod.*, 1997, **60**, 727.
1997JNP729 C. C. Cehade, R. L. A. Dias, R. G. S. Berlinck, A. G. Ferreira, L. V. Costa, M. Rangel, E. L. A. Malpezzi, J. C. de Freitas, and E. Hadju, *J. Nat. Prod.*, 1997, **60**, 729.
1997JOC201 D. A. Nugiel, L. A. M. Cornelius, and J. W. Corbett, *J. Org. Chem.*, 1997, **62**, 201.
1997JOC1580 N. Katagiri, M. Takebayashi, H. Kokufuda, C. Kaneko, K. Kanehira, and M. Torihara, *J. Org. Chem.*, 1997, **62**, 1580.
1997JOC6833 K. Kato, H. Hayakawa, H. Tanaka, H. Kumamoto, S. Shindoh, S. Shuto, and T. Miyasaki, *J. Org. Chem.*, 1997, **62**, 6833.
1997J(P1)185 N. K. Lembicz, S. Grant, W. Clegg, R. J. Griffin, S. L. Heath, and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1997, 185.

1997J(P1)2079 L. De Napoli, A. Messere, D. Montesarchio, G. Piccialli, and M. Varra, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2079.
1997J(P1)3021 E. Erba and D. Sporchia, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3021.
1997JST9 C. I. Williams and M. A. Whitehead, *J. Mol. Struct.*, 1997, 9.
1997T2291 M. Hocek, M. Masojidkova, and A. Holy, *Tetrahedron*, 1997, **53**, 2291.
1997T6295 E. Lewandowska, V. Neschadimenko, S. F. Wnuk, and M. J. Robins, *Tetrahedron*, 1997, **53**, 6295.
1997T6747 S. A. Adah and V. Nair, *Tetrahedron*, 1997, **53**, 6747.
1997T7237 A. S. B. Prasad, T. M. Stevenson, J. R. Citineni, V. Nyzam, and P. Knochel, *Tetrahedron*, 1997, **53**, 7237.
1997T8269 C. Peinador, J. M. Quintela, and M. J. Moreira, *Tetrahedron*, 1997, **53**, 8269.
1997T11493 J. D. Sutherland and J. N. Whitfield, *Tetrahedron*, 1997, **53**, 11493.
1997T12595 W. Moreda and A. R. Forrester, *Tetrahedron*, 1997, **53**, 12595.
1997T16977 M. Ohba, K. Iizuka, H. Ishibashi, and T. Fujii, *Tetrahedron*, 1997, **53**, 16977.
1997TL1161 N. S. Gray, S. Kwon, and P. G. Schultz, *Tetrahedron Lett.*, 1997, **38**, 1161.
1998AXC1316 G. Sood, C. H. Schwalbe, and W. Fraser, *Acta Crystallogr., Sect. C*, 1998, **54**, 1316.
1998AXC1907 G. Sood, C. H. Schwalbe, and W. Fraser, *Acta Crystallogr., Sect. C*, 1998, **54**, 1907.
1998AXC1980 K. A. Ford, Y. Ebisuzaki, and P. D. Boyle, *Acta Crystallogr., Sect. C*, 1998, **54**, 1980.
1998EJO2931 H. Franzyk, J. H. Rasmussen, R. A. Mazzei, and S. R. Jensen, *Eur. J. Org. Chem.*, 1998, 2931.
1998HCA145 R. Volpini, E. Camaioni, S. Vittori, L. Barboni, C. Lambertucci, and G. Cristalli, *Helv. Chim. Acta*, 1998, 145.
1998JA3295 M. D. Erion and M. R. Reddy, *J. Am. Chem. Soc.*, 1998, **120**, 3295.
1998JA3520 A. S. Pilcher, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, 1998, **120**, 3520.
1998JA5024 L. Gorb and J. Leszczynski, *J. Am. Chem. Soc.*, 1998, **120**, 5024.
1998JHC57 A. Da Settimo, A. M. Marini, G. Primofiore, F. Da Settimo, and D. Bertini, *J. Heterocycl. Chem.*, 1998, **35**, 57.
1998JHC135 T. Ueda, R. Oh, S. Nagai, and J. Sakakibara, *J. Heterocycl. Chem.*, 1998, **35**, 135.
1998JOC436 A. Abbotto, A. Facchetti, S. Bradamante, and G. A. Pagani, *J. Org. Chem.*, 1998, **63**, 436.
1998JOC3213 A. R. Pagano, H. Zhaou, A. Shallop, and R. A. Jones, *J. Org. Chem.*, 1998, **63**, 3213.
1998MI413 V. Ralevic and G. Burnstock, *Pharmacol. Rev.*, 1998, **50**, 413.
1998SC4303 J. M. J. Nolsoe, L. Gundersen, and F. Rise, *Synth. Commun.*, 1998, **28**, 4303.
1998SCI533 N. S. Gray, L. Wodicka, A. W. H. Thunnissen, T. C. Norman, S. Kwon, F. H. Espinoza, D. O. Morgan, G. Barnes, S. LeClerc, L. Meijer, S. Kim, D. J. Lockhart, and P. G. Schultz, *Science*, 1998, **281**, 533.
1998T187 Y. Xu, *Tetrahedron*, 1998, **54**, 187.
1998T1439 H. Kapeller, C. Marschner, M. Weißenbacher, and H. Griengl, *Tetrahedron*, 1998, **54**, 1439.
1998T2941 J. Zeidler and B. Golankiewicz, *Tetrahedron*, 1998, **54**, 2941.
1998T5883 H. Miyabe, S. Kanehira, K. Kume, H. Kandori, and T. Naito, *Tetrahedron*, 1998, **54**, 5883.
1998T6605 M. J. Mulvihill and M. J. Miller, *Tetrahedron*, 1998, **54**, 6605.
1998T9229 M. T. Crimmins, *Tetrahedron*, 1998, **54**, 9229.
1998TL1445 T. Yosief, A. Rudi, Z. Stein, I. Goldberg, G. M. D. Gravalos, M. Schleyer, and Y. Kashman, *Tetrahedron Lett.*, 1998, **39**, 1445.
1998TL1827 M. T. Fiorini and C. Abell, *Tetrahedron Lett.*, 1998, **39**, 1827.
1998TL4437 Y. Choi, K. Lee, J. H. Hong, R. F. Schinazi, and C. K. Chu, *Tetrahedron Lett.*, 1998, **39**, 4437.
1999AXC467 D. Matkovic-Calogovic and K. Sankovic, *Acta Crystallogr., Sect. C*, 1999, **55**, 467.
1999AXC1585 M. T. do Prado Gambardella, R. Luis, A. Dias, C. C. Chehade, and R. G. de Sousa Berlinck, *Acta Crystallogr., Sect. C*, 1999, **55**, 1585.
1999BMC1281 M. Legraverend, O. Ludwig, E. Bisagni, S. Leclerc, L. Meijer, N. Giocanti, R. Sadri, and V. Favaudon, *Bioorg. Med. Chem.*, 1999, **7**, 1281.
1999CBO361 Y. Chang, N. S. Gray, G. R. Rosania, D. P. Sutherlin, S. Kwon, T. C. Norman, R. Sarohia, M. Leost, L. Meijer, and P. G. Schultz, *Chem. Biol.*, 1999, **96**, 361.
1999EJO931 A. Esposito, M. G. Perino, and M. Taddei, *Eur. J. Org. Chem.*, 1999, 931.
1999EJO2419 H. Zimmer, A. Amer, F. M. Baumann, M. Haecker, C. G. M. Hess, D. Ho, H. J. Huber, K. Koch, K. Mahnke, C. Schumacher, and R. C. Wingfield, *Eur. J. Org. Chem.*, 1999, 2419.
1999JA4896 E. Nir, L. Grace, B. Brauer, and M. S. de Vries, *J. Am. Chem. Soc.*, 1999, **121**, 4896.
1999JA5833 Q. Dang, Y. Liu, and M. D. Erion, *J. Am. Chem. Soc.*, 1999, **121**, 5833.
1999JA6090 M. K. Lakshman, J. C. Keeler, J. H. Hilmer, and J. Q. Martin, *J. Am. Chem. Soc.*, 1999, **121**, 6090.
1999JA6108 R. Glaser, S. Rayat, M. Lewis, M. Son, and S. Meyer, *J. Am. Chem. Soc.*, 1999, **121**, 6108.
1999JA6773 P. Pande, J. Shearer, J. Yang, W. A. Greenberg, and S. E. Rokita, *J. Am. Chem. Soc.*, 1999, **121**, 6773.
1999JHC639 A. Da Settimo, G. Primofiore, A. M. Marini, F. Da Settimo, C. La Motta, and S. Salerno, *J. Heterocycl. Chem.*, 1999, **36**, 639.
1999JOC2304 A. Roy, K. Chakrabarty, P. K. Dutta, N. C. Bar, N. Basu, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 1999, **64**, 2304.
1999JOC4685 C. C. Orji, R. Michalcyzk, and L. A. P. Silks, III, *J. Org. Chem.*, 1999, **64**, 4685.
1999JOC6575 J. Abad, B. L. Gaffney, and R. A. Jones, *J. Org. Chem.*, 1999, **64**, 6575.
1999JOC7081 A. Kitaka, T. Asakura, T. Kuze, H. Tanaka, N. Yamada, K. Nakamura, and T. Miyasaki, *J. Org. Chem.*, 1999, **64**, 7081.
1999JOC7773 H. Kumamoto, H. Tanaka, R. Tsukioka, Y. Ishida, A. Nakamura, S. Kimura, H. Hayakawa, K. Kato, and T. Miyasaka, *J. Org. Chem.*, 1999, **64**, 7773.
1999J(P1)677 K. M. Madyastha and G. R. Sridhar, *J. Chem. Soc., Perkin Trans. 1*, 1999, 677.
B-1999MI127 D. F. Ewing and G. Mackenzie; in 'Rodd's Chemistry of Carbon Compounds', M. Sainsbury, Ed.; Elsevier, Amsterdam, 1999, p. 127.
1999NN2327 V. Gurvich, H. Y. Kim, R. P. Hodge, C. M. Harris, and T. M. Harris, *Nucleos. Nucleot.*, 1999, **18**, 2327.
1999OL273 R. Glaser and M. Lewis, *Org. Lett.*, 1999, **1**, 273.
1999OL1233 M. Koskinen and K. Hemminki, *Org. Lett.*, 1999, **1**, 1233.
1999OL1957 F. Song, V. R. St. Hilaire, and E. H. White, *Org. Lett.*, 1999, **1**, 1957.
1999SL1145 M. Havelkova, M. Hocek, M. Cesnek, and D. Dvorak, *Synlett*, 1999, 1045.
1999T211 A. Brathe, L. Gundersen, F. Rise, A. B. Eriksen, A. V. Vollsnes, and L. Wang, *Tetrahedron*, 1999, **55**, 211.
1999T5239 B. Brand, C. B. Reese, Q. Song, and C. Visintin, *Tetrahedron*, 1999, **55**, 5239.

1999T8075 L. A. Agrofoglio, C. Demaison, and L. Toupet, *Tetrahedron*, 1999, **55**, 8075.
1999TL2573 N. Chida, T. Suzuki, S. Tanaka, and I. Yamada, *Tetrahedron Lett.*, 1999, **40**, 2573.
1999TL8235 J. H. Hah, J. M. Gil, and D. Y. Oh, *Tetrahedron Lett.*, 1999, **40**, 8235.
2000CRV4319 M. Ferrero and V. Gotor, *Chem. Rev.*, 2000, **100**, 4319.
2000JA7233 T. Naka, N. Minakawa, H. Abe, D. Kaga, and A. Matsuda, *J. Am. Chem. Soc.*, 2000, **122**, 7233.
2000JCO249 R. Di Lucrezia, I. H. Gilbert, and C. D. Floyd, *J. Comb. Chem.*, 2000, **2**, 249.
2000JME1282 M. Legraverend, P. Tunnah, M. Noble, P. Ducrot, O. Ludwig, D. S. Grierson, M. Leost, L. Meijer, and J. Endicott, *J. Med. Chem.*, 2000, **43**, 1282.
2000JME2797 C. E. Arris, F. T. Boyle, A. H. Clavert, N. J. Curtin, J. A. Endicott, E. F. Garman, A. E. Gibson, B. T. Golding, S. Grant, R. J. Griffin, P. Jewsbury, L. N. Johnson, A. M. Lawrie, D. R. Newell, M. E. M. Noble, E. A. Sausville, R. Schulz, and W. Yu, *J. Med. Chem.*, 2000, **43**, 2797.
2000JNP299 T. Yosief, A. Rudi, and Y. Kashman, *J. Nat. Prod.*, 2000, **63**, 299.
2000JOC227 A. J. Zapata, Y. Gu, and G. B. Hammond, *J. Org. Chem.*, 2000, **65**, 227.
2000JOC2959 E. A. Harwood, P. B. Hopkins, and S. T. Sigurdsson, *J. Org. Chem.*, 2000, **65**, 2959.
2000JOC9245 A. Esposito and M. Taddei, *J. Org. Chem.*, 2000, **65**, 9245.
2000NN1123 A. E. Hassan, R. A. Abou-Elkair, J. A. Montgomery, and J. A. Secrist, III, *Nucleos. Nucleot. Nucleic Acids*, 2000, **19**, 1123.
2000OL293 F. De Riccardis and F. Johnson, *Org. Lett.*, 2000, **2**, 293.
2000OL927 M. K. Lakshman, F. N. Ngassa, J. C. Keeler, Y. Q. V. Dinh, J. H. Hilmer, and L. M. Russon, *Org. Lett.*, 2000, **2**, 927.
2000OL1065 M. T. Crimmins and W. J. Zuercher, *Org. Lett.*, 2000, **2**, 1065.
2000OL3497 X. Lin and M. J. Robins, *Org. Lett.*, 2000, **2**, 3497.
2000OL3793 H. R. Moon, H. Ford, Jr and V. E. Marquez, *Org. Lett.*, 2000, **2**, 3793.
2000OR1 H. Vorbruggen and C. Ruh-Pohlenz, *Org. React.*, 2001, **55**, 1.
2000T1047 L. Beigelman, P. Haeberli, D. Sweeler, and A. Karpeisky, *Tetrahedron*, 2000, **56**, 1047.
2000T2655 M. Medebielle, S. Fujii, and K. Kato, *Tetrahedron*, 2000, **56**, 2655.
2000T4589 R. Freer, G. R. Geen, T. W. Ramsay, A. C. Share, G. R. Slater, and N. M. Smith, *Tetrahedron*, 2000, **56**, 4589.
2000T7099 T. Yokomatsu, T. Yamagishi, K. Suemune, H. Abe, T. Kihara, S. Soeda, H. Shimeno, and S. Shibuya, *Tetrahedron*, 2000, **56**, 7099.
2000T7685 S. Kozai, K. Ogimoto, and T. Maruyama, *Tetrahedron*, 2000, **56**, 7685.
2000T10031 R. Saladino, P. Carlucci, M. C. Danti, C. Crestini, and E. Mincione, *Tetrahedron*, 2000, **56**, 10031.
2000TL1291 P. Y. F. Deghati, M. J. Wanner, and G. Koomen, *Tetrahedron Lett.*, 2000, **41**, 1291.
2000TL1695 E. A. Veliz and P. A. Beal, *Tetrahedron Lett.*, 2000, **41**, 1695.
2000TL3573 W. McComas, L. Chen, and K. Kim, *Tetrahedron Lett.*, 2000, **41**, 3573.
2000TL6559 Q. Dang, B. S. Brown, and M. D. Erion, *Tetrahedron Lett.*, 2000, **41**, 6559.
2000TL7211 K. Alarcon, A. Martelli, M. Demeunynck, and J. Lhomme, *Tetrahedron Lett.*, 2000, **41**, 7211.
2000TL7281 R. R. Bonala, I. G. Shishkina, and F. Johnson, *Tetrahedron Lett.*, 2000, **41**, 7281.
2000TL8207 R. W. Scott, D. E. Fox, and D. K. Williams, *Tetrahedron Lett.*, 2000, **41**, 8207.
2001AXC767 K. Suwinska, B. Golankiewicz, and W. Zielenkiewicz, *Acta Crystallogr., Sect. C*, 2001, **C57**, 767.
2001CBO289 G. Chiosis, M. N. Timaul, B. Lucas, P. N. Munster, F. F. Zheng, L. Sepp-Lorenzino, and N. Rosen, *Chem. Biol.*, 2001, **8**, 289.
2001CME385 E. Ichikawa and K. Kato, *Curr. Med. Chem.*, 2001, **8**, 385.
2001JA2658 P. Manikandan, E. Choi, R. Hille, and B. M. Hoffman, *J. Am. Chem. Soc.*, 2001, **123**, 2658.
2001JA7779 M. K. Lakshman, J. H. Hilmer, J. Q. Martin, J. C. Keeler, Y. Q. V. Dinh, F. N. Ngassa, and L. M. Russon, *J. Am. Chem. Soc.*, 2001, **123**, 7779.
2001JHC299 M. Legraverend, O. Ludwig, S. Lecter, and L. Meijer, *J. Heterocycl. Chem.*, 2001, **38**, 299.
2001JHC939 A. S. Hamad and H. A. Y. Derbala, *J. Heterocycl. Chem.*, 2001, **38**, 939.
2001JME170 H. Harada, O. Asano, Y. Hoshino, S. Yoshikawa, M. Matsukura, Y. Kabasawa, J. Niijima, Y. Kotake, N. Watanabe, T. Kawata, T. Inoue, T. Horizoe, N. Yasuda, H. Minami, K. Nagata, M. Murakami, J. Nagaoka, S. Kobayashi, I. Tanaka, and S. Abe, *J. Med. Chem.*, 2001, **44**, 170.
2001JME3616 R. E. Morris, R. E. Aird, P. del S. Murdoch, H. Chen, J. Cummings, N. D. Hughes, S. Parsons, A. Parkin, G. Boyd, D. I. Jodrell, and P. J. Sadler, *J. Med. Chem.*, 2001, **44**, 3616.
2001JOC507 D. Scharn, L. Gemeroth, J. Schneider-Mergener, and H. Wenschuh, *J. Org. Chem.*, 2001, **66**, 507.
2001JOC3513 M. Aso, T. Ikeno, K. Norihisa, M. Tanaka, N. Koga, and H. Suemune, *J. Org. Chem.*, 2001, **66**, 3513.
2001JOC4055 A. S. Shawali, M. A. N. Mosselhi, and N. M. Tawfik, *J. Org. Chem.*, 2001, **66**, 4055.
2001JOC5463 A. Laxer, D. T. Major, H. E. Gottlieb, and B. Fischer, *J. Org. Chem.*, 2001, **66**, 5463.
2001JOC6029 Z.-X. Yu, Q. Dang, and Y.-D. Wu, *J. Org. Chem.*, 2001, **66**, 6029.
2001JOC6472 M. L. Jain, Y. Tsao, N. Ho, and J. Cheng, *J. Org. Chem.*, 2001, **66**, 6472.
2001JOC8273 S. Ding, N. S. Gray, Q. Ding, and P. G. Schultz, *J. Org. Chem.*, 2001, **66**, 8273.
2001JOC8592 E. A. Veliz and P. A. Beal, *J. Org. Chem.*, 2001, **66**, 8592.
2001J(P1)1662 G. Andresen, A. B. Eriksen, B. Dalhaus, L. Gundersen, and F. Rise, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1662.
2001J(P1)1241 B. L. Booth, I. M. Cabral, A. M. Dias, A. P. Freitas, A. M. M. Beja, M. F. Proenca, and M. R. Silva, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1241.
2001J(P1)1662 G. Andresen, A. B. Eriksen, B. Dalhus, L.-L. Gundersen, and F. Rise, *J. Chem. Soc., Perkin Trans 1*, 2001, 1662.
2001J(P1)2532 A. Al-Azmi, B. L. Booth, R. A. Carpenter, A. Carvalho, E. Marrelec, R. G. Pritchard, and M. F. J. R. P. Proenca, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2532.
2001S1704 M. Havelkova, D. Dvorak, and M. Hocek, *Synthesis*, 2001, 1704.
2001TL519 M. Hocek, I. G. Stara, I. Stary, and H. Dvorakova, *Tetrahedron Lett.*, 2001, **42**, 519.
2001TL2771 P. H. Dorf and R. S. Garigipati, *Tetrahedron Lett.*, 2001, **42**, 2771.
2001TL5941 D. Pappo, A. Rudi, and Y. Kashman, *Tetrahedron Lett.*, 2001, **42**, 5941.
2001TL6279 W. K.-D. Brill and C. Rivia-Toniolo, *Tetrahedron Lett.*, 2001, **42**, 6279.

2001TL6515 W. K.-D. Brill and C. Rivia-Toniolo, *Tetrahedron Lett.*, 2001, **42**, 6515.
2001TL7257 M. Bourguet-Kondracki, M. Martin, J. Vaclet, and M. Guyot, *Tetrahedron Lett.*, 2001, **42**, 7257.
2001TL8161 V. Brun, M. Legraverend, and D. S. Grierson, *Tetrahedron Lett.*, 2001, **42**, 8161.
2001TL8165 V. Brun, M. Legraverend, and D. S. Grierson, *Tetrahedron Lett.*, 2001, **42**, 8165.
2001TL8169 V. Brun, M. Legraverend, and D. S. Grierson, *Tetrahedron Lett.*, 2001, **42**, 8169.
2001TL8751 S. Ding, N. S. Gray, Q. Ding, and P. G. Schultz, *Tetrahedron Lett.*, 2001, **42**, 8751.
2002BMC3555 G. Chiosis, B. Lucas, A. Shtil, H. Huezo, and N. Rosen, *Biorg. Med. Chem.*, 2002, **10**, 3555.
2002BML3283 V. Krystof, R. Lenobel, L. Havlicek, M. Kuzma, and M. Strnad, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3283.
2002JA3064 H. Chen, J. A. Parkinson, S. Parsons, R. A. Coxall, R. O. Gould, and P. J. Sadler, *J. Am. Chem. Soc.*, 2002, **124**, 3064.
2002JA12854 Y. Liu, J. Vinje, C. Pacifico, G. Natile, and E. Sletten, *J. Am. Chem. Soc.*, 2002, **124**, 12854.
2002JA13856 A. Fürstner, A. Leitner, M. Mendez, and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856.
2002JA13964 K. L. Tan, R. G. Bergman, and J. A. Ellman, *J. Am. Chem. Soc.*, 2002, **124**, 13964.
2002JME3381 A. E. Gibson, C. E. Arris, J. Bentley, F. T. Boyle, N. J. Curtin, T. G. Davies, J. A. Endicott, B. T. Golding, S. Grant, R. J. Griffin, P. Jewsbury, L. N. Johnson, V. Mesguiche, D. R. Newell, M. E. M. Noble, J. A. Tucker, and H. J. Whitfield, *J. Med. Chem.*, 2002, **45**, 3381.
2002JOC790 D. T. Major, A. Laxer, and B. Fischer, *J. Org. Chem.*, 2002, **67**, 790.
2002JOC2303 M. Novak, M. Ruenz, S. Kazerani, K. Toth, T. Nguyen, and B. Heinrich, *J. Org. Chem.*, 2002, **67**, 2303.
2002JOC6788 P. Francom, Z. Janeba, S. Shibuya, and M. J. Robins, *J. Org. Chem.*, 2002, **67**, 6788.
2002J(P1)1921 I. Collins, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1921.
2002MI1037 J. Haesslein and N. Jullian, *Curr. Top. Med. Chem.*, 2002, **2**, 1037.
2002MI1087 S. W. Schneller, *Curr. Top. Med. Chem.*, 2002, **2**, 1087.
2002MI275 R. J. Ferrier, R. Blattner, R. A. Field, R. H. Furneaux, J. M. Gardiner, J. O. Hoberg, K. P. R. Kartha, D. M. G. Tilbrook, P. C. Tyler, and R. H. Wightman, *Carbohydr. Chem.*, 2002, 275.
2002MI309 P. Cohen, *Nat. Rev. Drug Discov.*, 2002, **1**, 309.
2002MI745 T. G. Davies, J. Bentley, C. E. Arris, F. T. Boyle, N. J. Curtin, J. A. Endicott, A. E. Gibson, B. T. Golding, R. J. Griffin, I. R. Hardcastle, P. Jewsbury, L. N. Johnson, V. Mesguiche, D. R. Newell, M. E. M. Noble, J. A. Tucker, L. Wang, and H. J. Whitfield, *Nat. Struct. Biol.*, 2002, **9**, 745.
2002S538 R. Schirmacher, B. Wangler, E. Schirmacher, T. August, and R. Rosch, *Synthesis*, 2002, 538.
2002S911 M. I. Rodriquez-Franco and M. I. Fernandez-Bachiller, *Synthesis*, 2002, 911.
2002S2445 P. Besada, M. J. Gonzalez-Moa, C. Teran, L. Santana, and E. Uriate, *Synthesis*, 2002, 2445.
2002T4865 S. Bera and V. Nair, *Tetrahedron*, 2002, **58**, 4865.
2002T7607 P. G. Baraldi, A. U. Broceta, M. J. P. de las Infantas, J. J. D. Mochun, A. Espinosa, and R. Romagnoli, *Tetrahedron*, 2002, **58**, 7607.
2002T7911 V. Brun, M. Legraverend, and D. S. Grierson, *Tetrahedron*, 2002, **58**, 7911.
2002TL653 K. Horota, H. Sajiki, R. Hattori, Y. Monguchi, G. Tanabe, and O. Muraoka, *Tetrahedron Lett.*, 2002, **43**, 653.
2002TL6169 R. E. Austin, J. F. Okonya, D. R. S. Bond, and F. Al-Obeidi, *Tetrahedron Lett.*, 2002, **43**, 6169.
2002TL6301 R. Schirrmacher, U. Mühlhausen, B. Wängler, E. Schirrmacher, J. Reinhard, G. Nagel, B. Kaina, M. Piel, M. Wießler, and F. Rösch, *Tetrahedron Lett.*, 2002, **43**, 6301.
2002TL8071 L. G. J. Hammarstrom, D. B. Smith, F. X. Talamas, S. S. Labadie, and N. E. Krauss, *Tetrahedron Lett.*, 2002, **43**, 8071.
2003BML2993 J. Moravec, V. Krystof, J. Hanus, L. Havlicek, D. Moravcova, K. Fuksova, M. Kuzma, R. Lenobel, M. Otyepka, and M. Strnad, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2993.
2003CC1452 M. Xu, F. De Giacomo, D. E. Paterson, T. G. George, and A. Vasella, *J. Chem. Soc., Chem. Commun.*, 2003, 1452.
2003CC2802 H. J. Whitfield, R. J. Griffin, I. R. Hardcastle, A. Henderson, J. Meneyrol, V. Mesguiche, K. L. Sayle, and B. T. Golding, *J. Chem. Soc., Chem. Commun.*, 2003, 2802.
2003EJO245 M. Hocek, *Eur. J. Org. Chem.*, 2003, 245.
2003JOC276 M. E. A. Zaki, M. F. Proenca, and B. L. Booth, *J. Org. Chem.*, 2003, **68**, 276.
2003JOC666 P. Francom and M. J. Robins, *J. Org. Chem.*, 2003, **68**, 666.
2003JOC5773 M. Hocek and H. Dvorakova, *J. Org. Chem.*, 2003, **68**, 5773.
2003JOC6020 M. K. Lakshman, F. N. Ngassa, S. Bae, B. G. Buchanan, H. Hahn, and H. Mah, *J. Org. Chem.*, 2003, **68**, 6020.
2003JOC6767 E. C. Western, J. R. Daft, E. M. Johnson, II, P. M. Gannett, and K. H. Shaughnessy, *J. Org. Chem.*, 2003, **68**, 6767.
2003JOC8657 A. J. Shallop, B. L. Gaffney, and R. A. Jones, *J. Org. Chem.*, 2003, **68**, 8657.
2003NN747 A. E. Hassan, W. B. Parker, P. W. Allan, J. A. Montgomery, and J. A. Secrist, III, *Nucleos. Nucleot. Nucleic Acids*, 2003, **22**, 747.
2003OL637 J. Novak, I. Linhart, H. Dvorakova, and V. Kubelka, *Org. Lett.*, 2003, **5**, 637.
2003OL4265 N. Poje and M. Poje, *Org. Lett.*, 2003, **5**, 4265.
2003OL4289 T. Tobrman and D. Dvorak, *Org. Lett.*, 2003, **5**, 4289.
2003T47 S. Weyler, A. M. Hayallah, and C. E. Muller, *Tetrahedron*, 2003, **59**, 47.
2003T607 M. Hocek, I. Votruba, and H. Dvorakova, *Tetrahedron*, 2003, **59**, 607.
2003T2177 S. Guillarme, S. Legoupy, A.-M. Aubertin, C. Olicard, N. Bourgougnon, and F. Huet, *Tetrahedron*, 2003, **59**, 2177.
2003T6493 D. Pappo and Y. Kashman, *Tetrahedron*, 2003, **59**, 6493.
2003T9635 S. Guillarme, S. Legoupy, N. Bourgougnon, A.-M. Aubertin, and F. Huet, *Tetrahedron*, 2003, **59**, 9635.
2003T10223 T. Murano, Y. Yuasa, H. Kobayakawa, T. Yokomatsu, and S. Shibuya, *Tetrahedron*, 2003, **59**, 10223.
2003TL785 P. Turek, M. Kotora, M. Hocek, and I. Cisarova, *Tetrahedron Lett.*, 2003, **44**, 785.
2003TL2605 J. A. Trelles, M. Fernandez, E. S. Lewkowicz, A. M. Iribarren, and J. V. Sinisterra, *Tetrahedron Lett.*, 2003, **44**, 2605.
2003TL2899 H. Komatsu and T. Araki, *Tetrahedron Lett.*, 2003, **44**, 2899.
2003TL3359 A. K. Bakkestuen and L.-L. Gundersen, *Tetrahedron Lett.*, 2003, **44**, 3359.
2003TL6277 M. J. Alves, A. G. Fortes, and L. F. Goncalves, *Tetrahedron Lett.*, 2003, **44**, 6277.
2003TL8361 L. G. J. Hammarstrom, M. E. Meyer, D. B. Smith, and F. X. Talamas, *Tetrahedron Lett.*, 2003, **44**, 8361.
2003TL9177 F. Amblard, S. P. Nolan, I. Gillaizeau, and L. A. Agrofoglio, *Tetrahedron Lett.*, 2003, **44**, 9177.
2003TL9327 M. Zhong and M. J. Morris, *Tetrahedron Lett.*, 2003, **44**, 9327.

2004BML325 B. Dymock, X. Barril, M. Beswick, A. Collier, N. Davies, M. Drysdale, A. Fink, C. Fromont, R. E. Hubbard, A. Massey, A. Surgenor, and L. Wright, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 325.

2004CBI361 H. Rosemeyer, *Chem. Biodiver.*, 2004, **1**, 361.

2004CBO775 L. Wright, X. Barril, B. Dymock, L. Sheridan, A. Surgenor, M. Beswick, M. Drysdale, A. Collier, A. Massey, N. Davies, A. Fink, C. Fromont, W. Aherne, K. Boxall, S. Sharp, P. Workman, and R. E. Hubbard, *Chem. Biol.*, 2004, **11**, 775.

2004CME663 M. Cherry and D. H. Williams, *Curr. Med. Chem.*, 2004, **11**, 663.

2004JA1952 H. Deng, S. Cahill, L. Kurz, and R. Callender, *J. Am. Chem. Soc.*, 2004, **126**, 1952.

2004JA1962 E. Duchardt, C. Richter, O. Ohlenschlager, M. Gorlach, J. Wohnert, and H. Schwalbe, *J. Am. Chem. Soc.*, 2004, **126**, 1962.

2004JA11460 J. L. Sessler, J. Jayawickramarajah, C. L. Sherman, and J. S. Brodbelt, *J. Am. Chem. Soc.*, 2004, **126**, 11460.

2004JA15720 S. Nunez, D. Antoniou, V. L. Schramm, and S. D. Schwartz, *J. Am. Chem. Soc.*, 2004, **126**, 15720.

2004JME3710 I. R. Hardcastle, C. E. Arris, J. Bentley, F. T. Boyle, Y. Chen, N. J. Curtin, J. A. Endicott, A. E. Gibson, B. T. Golding, R. J. Griffin, P. Jewsbury, J. Menyerol, V. Mesguiche, D. R. Newell, M. E. M. Noble, D. J. Pratt, L. Wang, and H. J. Whitfield, *J. Med. Chem.*, 2004, **47**, 3710.

2004JOC3208 P. Gunaga, M. Baba, and L. S. Jeong, *J. Org. Chem.*, 2004, **69**, 3208.

2004JOC3230 H. He, L. Llauger, N. Rosen, and G. Chiosis, *J. Org. Chem.*, 2004, **69**, 3230.

2004JOC5555 L. A. Paquette, A. L. Kahane, and C. K. Seekamp, *J. Org. Chem.*, 2004, **69**, 5555.

2004JOC5578 J. C. Antilla, J. M. Baskin, T. E. Barder, and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578.

2004JOC7018 S. Sharma and J. K. Lee, *J. Org. Chem.*, 2004, **69**, 7018.

2004JOC7329 K. L. Tan, S. Park, J. A. Ellman, and R. C. Bergman, *J. Org. Chem.*, 2004, **69**, 7329.

2004JOC7985 P. Capek, R. Pohl, and M. Hocek, *J. Org. Chem.*, 2004, **69**, 7985.

2004JOC9224 P. Turek, M. Kotora, I. Tislerova, M. Hocek, I. Votruba, and I. Cisarova, *J. Org. Chem.*, 2004, **69**, 9224.

2004MI245 J. T. Bork, J. W. Lee, and Y.-T. Chang, *QSAR Comb. Sci.*, 2004, **23**, 245.

2004OBC665 D. Taddei, P. Kilian, A. M. Z. Slawin, and J. D. Woolins, *Org. Biomol. Chem.*, 2004, **2**, 665.

2004OBC1019 M. A. Carvalho, T. M. Esteves, M. F. Proenca, and B. L. Booth, *Org. Biomol. Chem.*, 2004, **2**, 1019.

2004OBC2340 M. A. Carvalho, M. E. A. Zaki, Y. Alvares, M. F. Proenca, and B. L. Booth, *Org. Biomol. Chem.*, 2004, **2**, 2340.

2004OL2673 M. U. Roslund, P. Virta, and K. D. Klika, *Org. Lett.*, 2004, **6**, 2673.

2004OL2917 J. Liu, Z. Janeba, and M. J. Robins, *Org. Lett.*, 2004, **6**, 2917.

2004OL3225 P. Silhar, R. Pohl, I. Votruba, and M. Hocek, *Org. Lett.*, 2004, **6**, 3225.

2004OL3421 J. Liu and M. J. Robins, *Org. Lett.*, 2004, **6**, 3421.

2004PAC1869 H. Sigel, *Pure Appl. Chem.*, 2004, **76**, 1869.

2004S889 M. Hocek, D. Hockova, and H. Dvorakova, *Synthesis*, 2004, 889.

2004S2855 O. Caamano, G. Gomez, F. Fernandez, M. D. Garcia, X. Garcia-Mera, and E. De Clercq, *Synthesis*, 2004, 2855.

2004S2869 M. Hocek and R. Pohl, *Synthesis*, 2004, 2869.

2004SCI1800 M. E. M. Noble, J. A. Endicott, and L. N. Johnson, *Science*, 2004, **303**, 1800.

2004SOS945 F. Seela, N. Ramzaeva, and H. Rosemeyer; in 'Science of Synthesis', Y. Yamamoto, Ed.; Thieme, Stuttgart, 2004, vol. 16, pp. 945–1108.

2004T3451 X. Yin and S. W. Schneller, *Tetrahedron*, 2004, **60**, 3451.

2004T3643 P. Quadrelli, R. Scrocchi, P. Caramella, A. Rescifina, and A. Piperno, *Tetrahedron*, 2004, **60**, 3643.

2004T8397 L. A. Agrofoglio, F. Amblard, S. P. Nolan, S. Charamon, I. Gillaizeau, T. A. Zevaco, and P. Guenot, *Tetrahedron*, 2004, **60**, 8397.

2004TL195 R. A. Joshi, P. S. Patil, M. Muthukrishnan, C. V. Ramana, and M. K. Gurjar, *Tetrahedron Lett.*, 2004, **45**, 195.

2004TL273 T. Toberman and D. Dvorak, *Tetrahedron Lett.*, 2004, **45**, 273.

2004TL4233 B. T. Utenova and L. Gundersen, *Tetrahedron Lett.*, 2004, **45**, 4233.

2004TL6259 P. Seckarova, R. Marek, K. Malinakova, E. Kolehmainen, D. Hockova, M. Hocek, and V. Sklenar, *Tetrahedron Lett.*, 2004, **45**, 6259.

2005AGE2393 M. Ganelman and E. N. Jacobsen, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 2393.

2005CSY83 M. K. Lakshman, *Curr. Org. Synth.*, 2005, **2**, 83.

2005EJO939 D. Taddei, A. M. Z. Slawin, and J. D. Woolins, *Eur. J. Org. Chem.*, 2005, 939.

2005EJO4640 M. L. Navacchia, A. Manetto, P. C. Montevecchi, and C. Chatgiliaoglu, *Eur. J. Org. Chem.*, 2005, 4640.

2005EJO4988 T. C. Berg, L. Gundersen, A. B. Eriksen, and K. E. Malterud, *Eur. J. Org. Chem.*, 2005, 4988.

2005JA5957 B. Rodenko, M. Koch, A. M. van der Burg, M. J. Wanner, and G. Koomen, *J. Am. Chem Soc.*, 2005, **127**, 5957.

2005JME710 S. A. Laufer, D. M. Domeyer, T. R. F. Scior, W. Albrecht, and D. R. J. Hauser, *J. Med. Chem.*, 2005, **48**, 710.

2005JME2892 L. Llauger, H. He, J. Kim, J. Aguirre, N. Rosen, U. Peters, P. Davies, and G. Chiosis, *J. Med. Chem.*, 2005, **48**, 2892.

2005JOC199 D. Pappo, S. Shimony, and Y. Kashman, *J. Org. Chem.*, 2005, **70**, 199.

2005JOC998 Z.-X. Yu, Q. Dang, and Y.-D. Wu, *J. Org. Chem.*, 2005, **70**, 988.

2005JOC5655 L. A. Paquette and S. Dong, *J. Org. Chem.*, 2005, **70**, 5655.

2005JOC6378 E. C. Western and K. H. Shaugnessy, *J. Org. Chem.*, 2005, **70**, 6378.

2005JOC8001 P. Capek, R. Pohl, and M. Hocek, *J. Org. Chem.*, 2005, **70**, 8001.

2005MI201 R. Marek and V. Sklenar, *Annu. Rep. NMR Spectrosc.*, 2005, **54**, 201.

2005OBC1025 A. K. Bakkestuen, L. Gundersen, D. Petersen, B. T. Utenova, and A. Vik, *Org. Biomol. Chem.*, 2005, **3**, 1025.

2005OBC2924 P. Virta, A. Koch, M. U. Roslund, P. Mattjus, E. Kleinpeter, L. Kronberg, R. Sjoholm, and K. D. Klika, *Org. Biomol. Chem.*, 2005, **3**, 2924.

2005OBC3001 P. Silhar, R. Pohl, I. Votruba, and M. Hocek, *Org. Biomol. Chem.*, 2005, **3**, 3001.

2005OL303 T. Kaneko, M. Aso, N. Koga, and H. Suemune, *Org. Lett.*, 2005, **7**, 303.

2005OL1149 J. Liu and M. J. Robbins, *Org. Lett.*, 2005, **7**, 1149.

2005OL1833 B. G. Szczepankiewicz, J. J. Rhode, and R. Kurukulasuriya, *Org. Lett.*, 2005, **7**, 1833.

2005OL3889 A. Roy and S. W. Schneller, *Org. Lett.*, 2005, **7**, 3889.

2005OL4601 M. Zhong, I. Nowak, and M. J. Robins, *Org. Lett.*, 2005, **7**, 4601.

2005S419 A. Khalafi-Nezhad, A. Zarea, M. N. Soltani Rad, B. Mokhtari, and A. Parhami, *Synthesis*, 2005, 419.

2005S2227 C. Gaulon, H. P. Dijkstra, and C. J. Springer, *Synthesis*, 2005, 2227.
2005T473 D. Vina, L. Santana, E. Uriarte, and C. Teran, *Tetrahedron*, 2005, **61**, 473.
2005T2245 S. Schröter, C. Stock, and T. Bach, *Tetrahedron*, 2005, **61**, 2245.
2005TL1165 M. Gupta and V. Nair, *Tetrahedron Lett.*, 2005, **46**, 1165.
2005TL1841 I. Susvilo, A. Brukstus, and S. Tumkevicius, *Tetrahedron Lett.*, 2005, **46**, 1841.
2005TL2873 R. E. Austin, C. Waldraff, and F. AL-Obeidi, *Tetrahedron Lett.*, 2005, **46**, 2873.
2005TL3561 M. T. Cegla, J. Potaczek, M. Zylewski, and L. Strekowski, *Tetrahedron Lett.*, 2005, **46**, 3561.
2005TL5699 J. J. Strouse, M. Jeselnik, F. Tapaha, C. B. Jonsson, W. B. Parker, and J. B. Arterburn, *Tetrahedron Lett.*, 2005, **46**, 5699.
2005TL6333 M. D'Auria, *Tetrahedron Lett.*, 2005, **46**, 6333.
2005TL6745 G. O'Mahony, E. Ehrman, and M. Grotli, *Tetrahedron Lett.*, 2005, **46**, 6745.
2005TL8225 T. Maruyama, N. Moriwaka, Y. Demizu, and M. Ohtsuka, *Tetrahedron Lett.*, 2005, **46**, 8225.
2006AGE3660 P. Lagisetty, L. M. Russon, and M. K. Lakshman, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 3660.
2006BME3987 M. Legraverend and D. S. Grierson, *Bioorg. Med. Chem.*, 2006, 3987.
2006CME1091 E. McDonald, P. Workman, and K. Jones, *Curr. Med. Chem.*, 2006, **6**, 1091.
2006EJO507 J. Novak, Z. Hasnik, and I. Linhart, *Eur. J. Org. Chem.*, 2006, 507.
2006EJO2403 P. Busca, I. McCort, T. Prange, and Y. Le Merrer, *Eur. J. Org. Chem.*, 2006, 2403.
2006EJO4473 E. Elhalem, M. J. Comin, and J. B. Rodriguez, *Eur. J. Org. Chem.*, 2006, 4473.
2006EJO5083 M. Kuchar, R. Pohl, I. Votruba, and M. Hocek, *Eur. J. Org. Chem.*, 2006, 5083.
2006JA13796 C. Chatgilialoglu, C. Caminal, A. Altieri, G. C. Vougioukalakis, Q. G. Mulazzani, T. Gimisis, and M. Guerra, *J. Am. Chem. Soc.*, 2006, **128**, 13796.
2006JME381 H. He, D. Zatorska, J. Kim, J. Aguirre, L. Lauger, Y. She, N. Wu, R. M. Immormino, D. T. Gewirth, and G. Chiosis, *J. Med. Chem.*, 2006, **49**, 381.
2006JME817 M. A. Biamonte, J. Shi, K. Hong, D. C. Hurst, L. Zhang, J. Fan, D. J. Busch, P. L. Karjian, A. A. Maldonado, J. L. Sensintaffar, Y. Yang, A. Kamal, R. E. Lough, K. Lundgren, F. J. Burrows, G. A. Timony, M. F. Boehm, and S. R. Kasibhatla, *J. Med. Chem.*, 2006, **49**, 817.
2006JME5352 L. Zhang, J. Fan, K. Vu, K. Hong, Y. Le Brazidec, J. Shi, M. A. Biamonte, D. J. Busch, R. E. Lough, R. Grecko, Y. Ran, J. L. Sensintaffar, A. Kamal, K. Lundgren, F. J. Burrows, R. Mansfield, G. A. Timony, E. H. Ulm, S. R. Kasibhatla, and M. F. Boehm, *J. Med. Chem.*, 2006, **49**, 5532.
2006JOC4216 M. Zhong, I. Nowak, J. F. Cannon, and M. J. Robins, *J. Org. Chem.*, 2006, **71**, 4216.
2006JOC5980 S. Sahabuddin, A. Roy, M. G. B. Drew, B. G. Roy, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 2006, **71**, 5980.
2006JOC7773 M. Zhong, I. Nowak, and M. J. Robins, *J. Org. Chem.*, 2006, **71**, 7773.
2006JOC8901 M. Zhong and M. J. Robins, *J. Org. Chem.*, 2006, **71**, 8901.
2006MI1117 T. A. Haystead, *Curr. Top. Med. Chem.*, 2006, **6**, 1117.
2006MI1183 G. Chiosis, *Curr. Top. Med. Chem.*, 2006, **6**, 1183.
2006OBC2278 P. Capek, R. Pohl, and M. Hocek, *Org. Biomol. Chem.*, 2006, **4**, 2278.
2006OL491 R. Alibes, A. Alvarez-Larena, P. de March, M. Figueredo, J. Font, T. Parella, and A. Rushtullet, *Org. Lett.*, 2006, **8**, 491.
2006OL1291 T. Tobrman and D. Dvorak, *Org. Lett.*, 2006, **8**, 1291.
2006OL5389 I. Cerna, R. Pohl, B. Klepetarova, and M. Hocek, *Org. Lett.*, 2006, **8**, 5389.
2006S73 M. D. Garcia, O. Caamano, F. Fernandez, P. Abeijon, and J. M. Blanco, *Synthesis*, 2006, 73.
2006S1848 P. Silhar, R. Pohl, I. Votruba, and M. Hocek, *Synthesis*, 2006, 1848.
2006S2993 M. Braendvang and L. Gundersen, *Synthesis*, 2006, 2993.
2006S3515 P. Caprek, M. Vilan, Z. Hasnik, R. Pohl, and M. Hocek, *Synthesis*, 2006, 3515.
2006SL1422 I. Susvilo, A. Brukstus, and S. Tumkevicius, *Synlett*, 2006, 1422.
2006SL2215 Y. Aubin, G. Audran, and H. Monti, *Synlett*, 2006, 2215.
2006T2563 X. Che, L. Zhang, Q. Dang, and X. Bai, *Tetrahedron*, 2006, **62**, 2563.
2006T6121 T. C. Berg, V. Bakken, L. Gundersen, and D. Petersen, *Tetrahedron*, 2006, **62**, 6121.
2006TL775 L. Zhang and Y. J. Zhang, *Tetrahedron Lett.*, 2006, **47**, 775.
2006TL3529 A. G. Firth, I. J. S. Fairlamb, K. Darley, and C. G. Baumann, *Tetrahedron Lett.*, 2006, **47**, 3529.
2007JA5962 J. Liu and M. J. Robins, *J. Am. Chem. Soc.*, 2007, **129**, 5962.
2007JME2289 A. Donald, T. McHardy, M. G. Rowlands, L. J. Hunter, T. G. Davies, V. Berdini, R. G. Boyle, G. W. Aherne, M. D. Garrett, and I. Collins, *J. Med. Chem.*, 2007, **50**, 2289.
2007JO173 B. C. Bookser and N. B. Raffaele, *J. Org. Chem.*, 2007, **72**, 173.
2007JO5012 W. Lu, S. Sengupta, J. L. Petersen, N. G. Akhmedov, and X. Shi, *J. Org. Chem.*, 2007, **72**, 5012.
2007SL721 G. Qu, Z. Zhang, M. Geng, R. Xia, L. Zhao, and H. Guo, *Synlett*, 2007, 721.
2007SL1231 A. M. Dias, S. Vila-Cha, I. M. Cabral, and M. F. Proenca, *Synlett*, 2007, 1231.
2007T5323 L. Huang, Y. Cherng, Y. Cheng, J. Jang, Y. Chao, and Y. Cherng, *Tetrahedron*, 2007, **63**, 5323.
2007T5832 C. Zhang and K. M. Shokat, *Tetrahedron*, 2007, **63**, 5832.
2007T7165 S. Rodriguez, D. Edmont, C. Mathe, and C. Perigaud, *Tetrahedron*, 2007, **63**, 7165.
2007TL2823 L. G. J. Hammarstrom, D. B. Smith, and F. X. Talamais, *Tetrahedron Lett.*, **48**, 2823.
2007TL5589 Z. Hasnik, P. Silhar, and M. Hocek, *Tetrahedron Lett.*, 2007, **48**, 5589.

Biographical Sketch



John Caldwell was born in Ayrshire, Scotland. He obtained his B.Sc. in chemistry at the University of Strathclyde in 1996, where he also obtained his Ph.D. in 2000 in the group of Professor W. J. Kerr, studying organometallic-mediated natural product synthesis. After a post-doctoral period working in the research group of Professor D. Craig at Imperial College London, he took up his current position at The Institute of Cancer Research, Surrey, in 2003. His research interests include organometallic chemistry, natural product synthesis, and medicinal chemistry.



Ian Collins was born in Essex, England. He received a B.A. and M.A. in natural sciences from Pembroke College, Cambridge University. In 1991, he obtained his Ph.D. at Cambridge University in the group of Professor A. B. Holmes, studying the asymmetric synthesis of hydroxylated alkaloid natural products through intramolecular dipolar cycloadditions. Following his Ph.D. studies, he joined the medicinal chemistry department at the Neuroscience Research Centre of Merck & Co. in Harlow, UK. He took up his current position as a team leader (faculty) at The Institute of Cancer Research, Surrey, in 2003. His research interests are centered on drug discovery and medicinal chemistry, particularly the application of structure-based design, and the synthesis of heterocyclic compounds.

10.12
Bicyclic 5-6 Systems: Other Four Heteroatoms 2:2

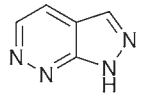
M. H. Elnagdi
Cairo University, Giza, Egypt
N. Al-Awadi
University of Kuwait, Safat, Kuwait
I. A. Abdelhamid
Cairo University, Giza, Egypt
© 2008 Elsevier Ltd. All rights reserved.

10.12.1 Introduction 600
10.12.2 Theoretical Methods 603
10.12.3 Experimental Structural Methods 604
10.12.3.1 X-Ray Diffraction 604
10.12.3.2 Proton NMR Spectroscopy 606
10.12.3.3 Carbon-13 NMR Spectroscopy 608
10.12.3.4 Nitrogen-15 NMR Spectroscopy 608
10.12.3.5 Mass Spectrometry 609
10.12.3.6 UV Spectroscopy 609
10.12.4 Thermodynamic Aspects 610
10.12.4.1 Melting Points 610
10.12.4.2 Solubility 611
10.12.4.3 Chromatographic behavior 611
10.12.4.4 Aromaticity 612
10.12.4.5 Other Physical Data 612
10.12.4.6 Tautomerism 612
10.12.4.6.1 Prototropic tautomerism 612
10.12.4.6.2 Functional group tautomerism (amino, oxo, and thioxo derivatives) 612
10.12.5 Reactivity of Fully Conjugated Rings 613
10.12.5.1 General Considerations 613
10.12.5.2 Thermal and Photochemical Processes 613
10.12.5.3 Electrophilic Attack at Nitrogen 614
10.12.5.3.1 Alkylation and glycosylation 614
10.12.5.4 Electrophilic Attack at Carbon 617
10.12.5.5 Nucleophilic Attack at Carbon 617
10.12.5.5.1 Reactions with carbon nucleophiles 618
10.12.5.5.2 Reactions with nitrogen nucleophilies 619
10.12.5.5.3 Reaction with oxygen nucleophiles 623
10.12.5.6 Radical Reactions, Oxidation and Reduction 623
10.12.6 Reactivity of Nonconjugated Rings 623
10.12.7 Reactivity of Substituents 626
10.12.7.1 Halogen Substituents 626
10.12.7.2 Carboxylic Acid and Carboxylic Acid Derivatives 626

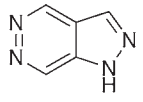
10.12.7.3 Amino, Diazo, and Hydrazo Substituents 627
10.12.7.4 Aldehydes, Oxo and Thioxo Derivatives 629
10.12.8 Ring Synthesis 630
10.12.8.1 Synthesis of Six-Membered Rings by Formation of Two Bonds 630
10.12.8.1.1 From [3+3] atom fragments 630
10.12.8.1.2 From [4+2] atom fragments 630
10.12.8.1.3 From [5+1] atom fragments 635
10.12.8.2 Synthesis of Six-Membered Rings by Formation of One Bond 638
10.12.8.2.1 Bond formation α to a heteroatom 638
10.12.8.2.2 Bond formation γ to a heteroatom 640
10.12.8.3 Synthesis of Five-Membered Rings by Formation of Two Bonds 641
10.12.8.3.1 From [4+1] atom fragments 641
10.12.8.3.2 From [3+2] atom fragments 643
10.12.8.4 Synthesis of Five-Membered Rings by Formation of One Bond 646
10.12.8.4.1 Bond formation α to a heteroatom 646
10.12.9 Important Compounds and Applications 646
10.12.9.1 Viagra Synthesis and biological activity 646
10.12.9.2 ALP: Further Developments 649
10.12.9.3 Formycin A and B 649
10.12.9.4 Other Compounds with Promising Biological Activities 649
10.12.9.5 Organic Metals: Conducting Organic Solids 652
10.12.10 Further Developments 653
References 654

10.12.1 Introduction

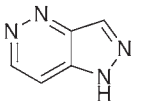
As mentioned in CHEC-II <1996CHEC-II(7)431>, large number of ring systems are possible within the title of this chapter. In this chapter, we will update the treatment for systems **1–50** in CHEC-II (with exclusion of purine **40**, which is discussed separately in Chapter **10.11**). In addition, systems like **51–59** are also known, and their chemistry will be also described in light of their interesting potential as conducting organic metals.



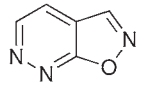
1*H*-Pyrazolo[3,4-*c*]pyridazine
1



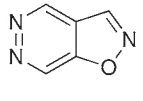
1*H*-Pyrazolo[3,4-*d*]pyridazine
2



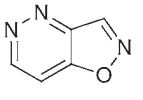
1*H*-Pyrazolo[4,3-*c*]pyridazine
3



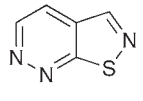
Isoxazolo[5,4-*c*]pyridazine
4



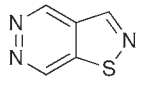
Isoxazolo[4,5-*d*]pyridazine
5



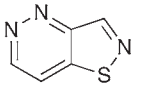
Isoxazolo[4,5-*c*]pyridazine
6



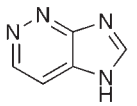
Isothiazolo[5,4-*c*]pyridazine
7



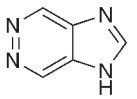
Isothiazolo[4,5-*d*]pyridazine
8



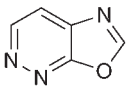
Isothiazolo[4,5-*c*]pyridazine
9



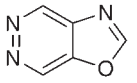
5*H*-Imidazo[4,5-*c*]pyridazine
10



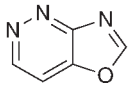
1*H*-Imidazo[4,5-*d*]pyridazine
11



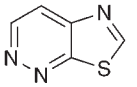
Oxazolo[5,4-*c*]pyridazine
12



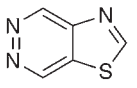
Oxazolo[4,5-*d*]pyridazine
13



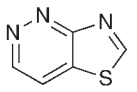
Oxazolo[4,5-*c*]pyridazine
14



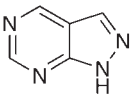
Thiazolo[5,4-*c*]pyridazine
15



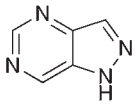
Thiazolo[4,5-*d*]pyridazine
16



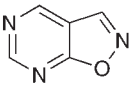
Thiazolo[4,5-*c*]pyridazine
17



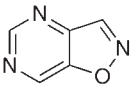
1*H*-Pyrazolo[3,4-*d*]pyrimidine
18



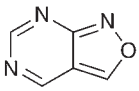
1*H*-Pyrazolo[4,3-*d*]pyrimidine
19



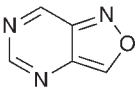
Isoxazolo[5,4-*d*]pyrimidine
20



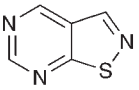
Isoxazolo[4,5-*d*]pyrimidine
21



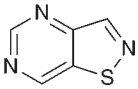
Isoxazolo[3,4-*d*]pyrimidine
22



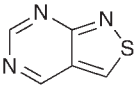
Isoxazolo[4,3-*d*]pyrimidine
23



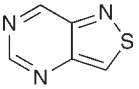
Isothiazolo[5,4-*d*]pyrimidine
24



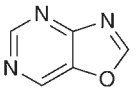
Isothiazolo[4,5-*d*]pyrimidine
25



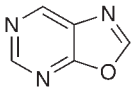
Isothiazolo[3,4-*d*]pyrimidine
26



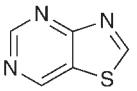
Isothiazolo[4,3-*d*]pyrimidine
27



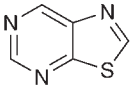
Oxazolo[4,5-*d*]pyrimidine
28



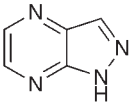
Oxazolo[5,4-*d*]pyrimidine
29



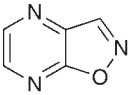
Thiazolo[4,5-*d*]pyrimidine
30



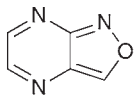
Thiazolo[5,4-*d*]pyrimidine
31



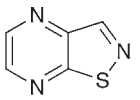
1*H*-Pyrazolo[3,4-*b*]pyrazine
32



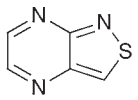
Isoxazolo[4,5-*b*]pyrazine
33



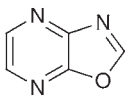
Isoxazolo[3,4-*b*]pyrazine
34



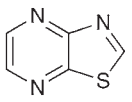
Isothiazolo[4,5-*b*]pyrazine
35



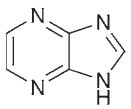
Isothiazolo[3,4-*b*]pyrazine
36



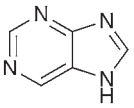
Oxazolo[4,5-*b*]pyrazine
37



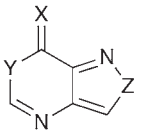
Thiazolo[4,5-*b*]pyrazine
38



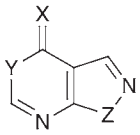
1*H*-Imidazo[4,5-*b*]pyrazine
39



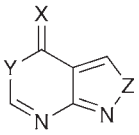
Purine
40



41

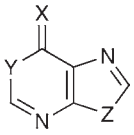


41a

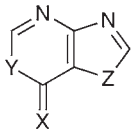


42

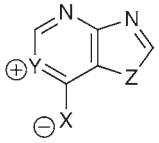
X = O, S, N; Y = O, S



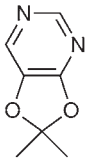
43



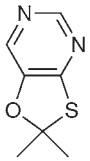
44



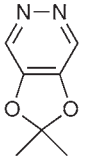
45



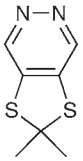
[1,3]Dioxolo[4,5-*d*]pyrimidine
46



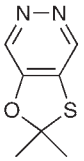
[1,3]Oxathiolo[4,5-*d*]pyrimidine
47



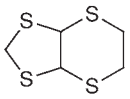
[1,3]Dioxolo[4,5-*d*]pyridazine
48



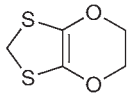
[1,3]Dithiolo[4,5-*d*]pyridazine
49



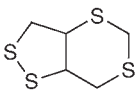
[1,3]Oxathiolo[4,5-*d*]pyridazine
50



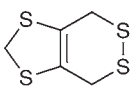
Dihydro-[1,3]dithiolo[4,5-*b*][1,4]dithiine
51



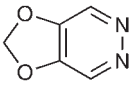
Dihydro-[1,3]
dithiolo[4,5-*b*][1,4]dioxine
52



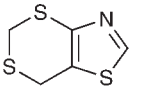
Tetrahydro-[1,2]
dithiolo[4,3-*d*][1,3]dithiine
53



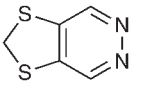
1,3-Dithiolo[4,5-d]
[1,2]dithine
54



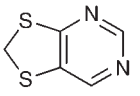
[1,3]Dioxolo[4,5-*d*]pyridazine
55



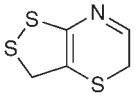
7*H*-[1,3]Dithiino[4,5-*d*]thiazole
56



[1,3]Dithiolo[4,5-*d*]pyridazine
57



[1,3]Dithiolo[4,5-*d*]pyrimidine
58



3*H*,4*H*-[1,2]dithiolo[3,4-b][1,4]thiazine
59

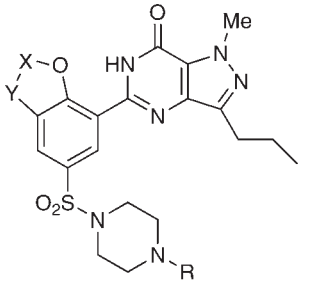
The literature on these ring systems in the last 10 years is vast. An Internet search alone provides 3500 citations for sildenafil (**60a**, Viagra). Not only Viagra is of medical interest; allopurinol (ALP) **61**, the classical treatment of gout arthritis, is still of interest, and pyrazolopyridazines and thiazolopyridazines have also been shown to be of biological importance. These activities extend beyond an interest in the synthesis and chemistry of these compounds indicated by the large number of patented potential applications.

Despite this interest, the literature of these compounds has not been reviewed in the covered survey period with exception of a review on 1,3-dithiolo[4,5-*d*]pyrimidines (system **58**) as well as its oxo, dioxo, and aminooxo derivatives <B-2004MI357>.

10.12.2 Theoretical Methods

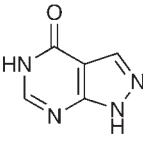
Calculations for π-electron density of pyrazolo[3,4-*d*]pyrimidines and their tautomers were discussed in CHEC-II <1996CHEC-II(7)431>.

Ab initio calculations indicated that introduction of a cyclic ether to the phenyl group of sildenafil derivatives **60** might enhance coplanarity of the molecule. The torsional angles were calculated to be 2–3° for sildenafil analogues with a five-membered ether ring and 12–16° for the derivatives of **60** with a six-membered ether ring. The least planar molecules are the most active enzyme inhibitors <2001BMC1609>.



60

a: X = C_2H_4; R = CH_3
b: X, Y = $(CH_2)_2$, $(CH_2)_3$
R = Me, $(CH_2)_2OH$



61

To gain insight into the physicochemical properties of ALP **61**, a density functional theory (DFT) study of anionic forms of ALP was reported <2003JST91>. Full geometric optimization and total molecular energy theoretical calculations of six possible monomeric tautomers and allopurinol^{2-} were performed by employing two different functionals and basis sets. For the first three most stable allopurinol^{1-} tautomers and allopurinol^{2-}, several molecular and electronic structure properties were calculated. Also, thermodynamic properties concerning heterocyclic protonic transfer and tautomeric processes and the infrared (IR) vibrational spectra were obtained. Among other theoretical results, the N(1)–H species was considered as the energetically most stable allopurinol^{1-} tautomer in the gas phase with the comparatively higher stabilization of N(5)–H species operating in aqueous solutions of allopurinol^{1-}. Several

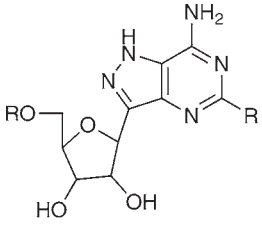
of the molecular and electronic structure properties are strongly sensitive to tautomerism and the anionic state of ALP. The heterocycle shows an increase of its π-type Lewis basicity and also a decrease of its π-type Lewis acidity upon ascending the anionic state. The identity of the atoms proposed to be favored in electronic charge density donating processes is suggested to be independent of both the tautomerism and anionic state. Comparative σ-type Lewis basicities are suggested for the electron donor sites of the heterocycle, the lowest one corresponding to the exocyclic oxygen atom. Several IR spectral features characterize allopurinol^{n-}, one of these corresponding to the energy decrease of the $\nu_{C=O}$ vibrational mode with the increase of the anionic state. A number of theoretical properties are in overall concordance with the experimental behavior shown by ALP in the condensed phase. These show correspondence with those shown by the purine derivative hypoxanthine. Similar treatments for natural ALP as well as allopurinol^{2+} were performed <2001JMT243, 2003JST91, 2002SM129>.

10.12.3 Experimental Structural Methods

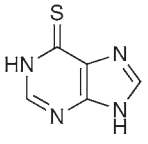
10.12.3.1 X-Ray Diffraction

X-Ray data for ALP **61**, formycine A **62**, as well as the pyrazolopyrimidine derivatives **63** and oxazinopyrimidine **64** have been discussed in CHEC-II.

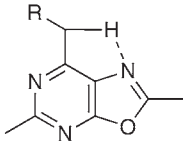
X-Ray crystal structure determinations of N2-furanosylpyrazolo[3,4-*d*] pyrimidines have been reported. X-Ray data indicated that the furanosyl moiety adopt an *anti*-conformation with an angle of ~100° <1996CHEC-II(7)431>. X-Ray crystal data of 2*H*-pyrazolo[3,4-*d*] pyridazine **65** indicated that although both rings are planar the molecule is not planar with a dihedral angle between pyrazolo[3,4-*d*]pyridazine rings of 2.6° <2004AXE807, 2002AXE1021>. An X-ray crystal structure determination confirmed the structure of 3-hydroxy-5,5,6,7,7-pentamethyl-3-phenyl-3,5,6,7-tetrahydro-isoxazolo[4,3-*d*]pyrimidine <2004JSTC356>.



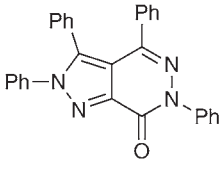
62



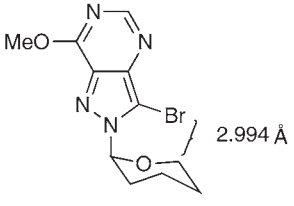
63



64



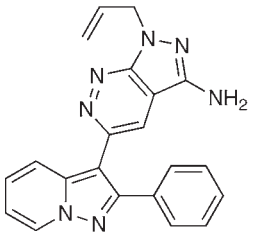
65



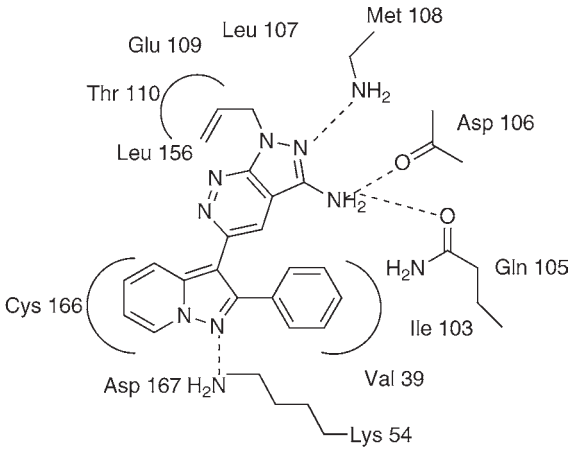
66

In 3-bromo-7-methoxy-2-tetrahydropyran-2-ylpyrazolo[1,5-*a*]pyrimidine **66**, the pyrimidine and pyrazole rings make a dihedral angle of 3.8°. The tetrahydropyran ring is in a chair conformation and its mean plane makes an interplanar angle of 52.5° with the pyrazole ring. There is a short Br···O intramolecular contact of 2.994 Å <2004JSTC356>.

The crystal structure of ERK2 complexed with **67** was determined. It is believed that the molecule can recognize small hydrophobic substituents but not hydrophilic ones <2006BML55>.The structure of the complex is shown in formula **68**.



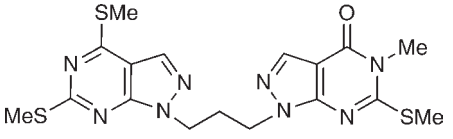
67



68

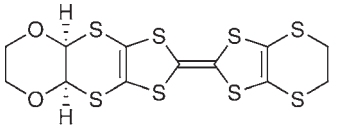
The ternary complex of purine nucleoside phosphorylase from *Escherichia coli* with formycine B and a sulfate or phosphate ion is crystallized in hexagonal space group *P*622 with unit cell dimension of $a = 123.11$, $c = 241.22$. The biologically active hexamer is formed through twofold crystallographic symmetry constituting a trimer of dimers. High-resolution X-ray diffraction data were collected using synchrotron radiation. The crystal structure of a tertiary complex of hexameric purine nucleoside phosphorylase PNP from *E. coli* with formycine B was also determined <1998JMB153, 2002JMB351>.

X-Ray diffraction studies of 1-(4,6-dimethylethylsulfanyl-1-*H*-pyrazolo[3,4-*d*]pyrimidinyl)-3-(5-methyl-6-methylsulfanyl-4-oxo-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-1-ylpropane **69**, the 'Leonard' trimethylene linker, showed unusual U-moieties formed due to intramolecular π−π stacking interactions, CH···N, CH···S, and S···S interactions <2006JST106>.

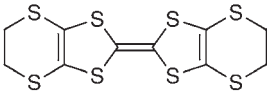


69

Several X-ray studies on organic conductors have recently been published <2000CC1117, 1998JOC3952>. A single crystal of BEDT-TFF **70** was obtained by recrystallization from CS_2 <1998JOC3952>. It was shown that the molecule is nonplanar. The dioxane ring is forced to incline toward the outer ethylene group linking two S atoms. The whole molecule is bulkier than that of **71** but the dioxane ring added to the skeleton resulted in no significant deformation of the molecule <1996TL7603>.



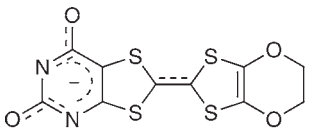
70



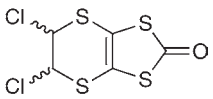
71

The X-ray crystal structure of the tetrabutylammonium (TBA) salt of anion **72** revealed complementary hydrogen bonds leading to homo-intermolecular diene as a building unit <2003SM669>.

An X-ray crystal structure of **73** indicated that the molecule is located on an mm2 site in which the two chlorine atoms adopt an axial position while the carbon atoms are disordered, a consequence of the (*R*,*R*)- and (*S*,*S*)-racemic mixture <2000CC1117>.

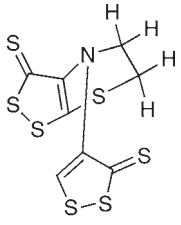


72



73

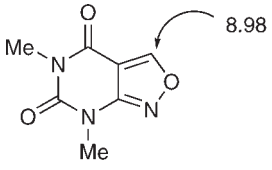
Compound **74** was found to have the partial saturated structure. The thiazine ring has a 'sofa' conformation with C-5 lying 0.7 Å out of the plane of the remaining five atoms (which are coplanar to within 0.07 Å). The geometry at nitrogen is pyramidal, N-4 being 0.28 Å out of the plane of its substituents. The two dithiole rings are oriented approximately orthogonally (ca. 80°), thus minimizing interactions between them. A comparison of the pattern of bonding in these two rings shows that the C(3A)–C(7A) fusion between one of them and the thiazine ring results only in changes in the bond lengths of this bond (1.371(4) Å) and its immediately adjacent neighbor C(7A)–S(1) (1.729(3) Å) <1999JOC5010>.



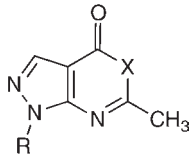
74

10.12.3.2 Proton NMR Spectroscopy

Although it has been stated in CHEC-II <1996CHEC-II(7)431> that many of the reported data have not been unequivocally assigned, the data could be discussed to indicate deshielding of ring CH as a result of ring π-deficiency. Reported nuclear magnetic resonance (NMR) data of new derivatives of ring systems **1–45** attest to this fact. Thus the CH signal in isoxazolo[3,4-*d*]pyrimidine **75** appeared at δ 8.98 ppm <2002T10073>.

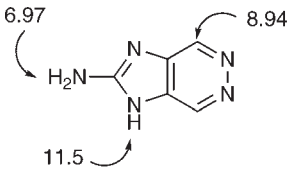


75

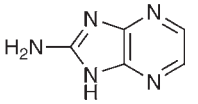


76a: X = O
76b: X = NMe

The CH in azoloazines **76** has been reported to resonate at δ 8.31 in **76a** and at δ 8.2 ppm in **76b** <2006BMC2040>. The cytotoxic marine natural product zarzissine <1994MI1455> was assumed to have structure **77**. Synthetic **77** showed the signals for H-4 and H-7 at δ 8.8 ppm which is a typical value for other imidazo[4,5-*d*]-pyridazines <1998J(P2)1839>. This is not in agreement with a δ 8.09 value reported for the natural product, and led to suggested structure **78** for the natural product. The latter was also synthesized and showed a non-D_2O exchangeable proton at δ 8.09 which is typical for that reported for zarzissine. However, the need to confirm this conclusion by obtaining NMR data for zarzissine under the same conditions seemed mandatory as the ^{13}C NMR and ultraviolet (UV) data of synthesized **78** were different from those reported for zarzissine <1994MI1455, 2001T5497>.

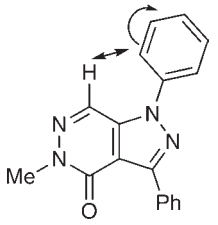


77



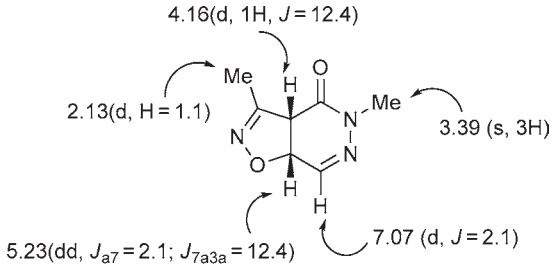
78

Nuclear Overhauser effect (NOE) difference measurements were used to assign structure **79** for the product of reaction of diphenylnitrile imine with 5-ethylsulfonyl-2-methyl(2*H*)pyridazinone. Thus in the ^{1}H NMR spectrum the *ortho*-protons of the arylhydrazino moiety (which were identified by two-dimensional heteronuclear multiple quantum correlation (2-D HMQC) spectroscopy) were shown in differential NOE (DNOE) experiment to be significantly enhanced on irradiation of pyridazine hydrogen H-7, proving their steric proximity <2000JST13>.



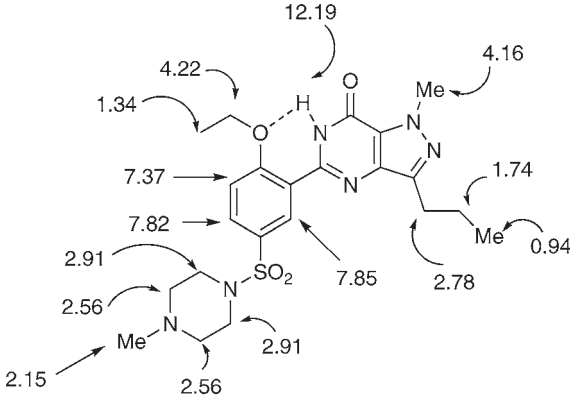
79

^{1}H NMR data for **80** could be used to assign a *cis*-arrangement for H-3a and H-7a as a coupling of 12.4 Hz was observed for these protons <2001T4389>.



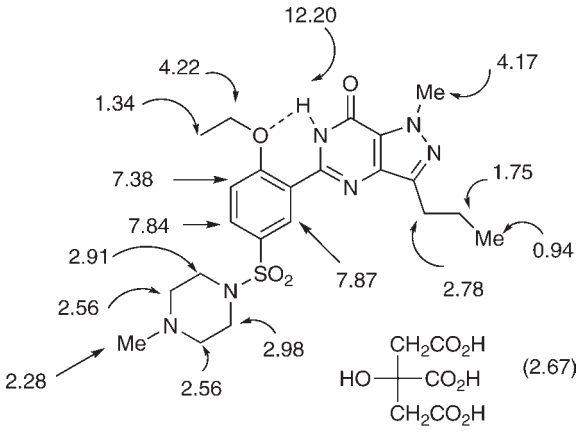
80

^{1}H NMR spectra of sildenafil **81** and its citrate **82** showed that differences in data for **81** and **82** are only significant for the piperazine fragment. It is thus believed that the most probable site for protonation is the piperazine <2005JPBA865>.



81

The ^{1}H NMR data of base and citrate suggest existence of an N(6)–H···OEt hydrogen bond in **81** and **82** <2005JPBA865>.

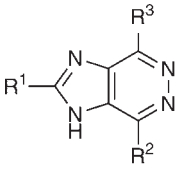


82

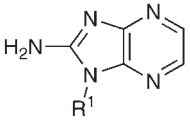
10.12.3.3 Carbon-13 NMR Spectroscopy

In CHEC-II <1996CHEC-II(7)431>, it was stated that data were not unequivocally interpreted. The situation has now changed as use of 2-D NMR spectroscopy enables better data interpretation. The ^{13}C NMR spectra of pure base and citrate of sildenafil in the solid state were measured and data were assigned based on liquid-state values as well as dipolar dephasing and variable contact time experiments. The most interesting are the differences in chemical shifts $D = \delta_{liq} - \delta_{sol}$ since these values are identical for rigid and conformationally fixed fragments of the molecule (the latter are expected to undergo larger changes). Compared to the averaged value in the liquid state, the signals of ethyl and *N*-propyl carbons are shifted remarkably (+1.0 to −5.1 ppm). A ^{13}C CPMAS NMR method has been proposed for identification and quantization of Viagra in its pharmaceutical preparation <2005JPBA865>.

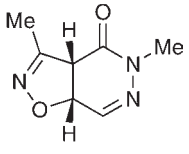
^{13}C NMR spectra of **83** and **84** have been reported but were not interpreted <2001T5497>. On the other hand, data for **85** were interpreted but the rationale for such interpretation was not given <2004BMC265>.



83



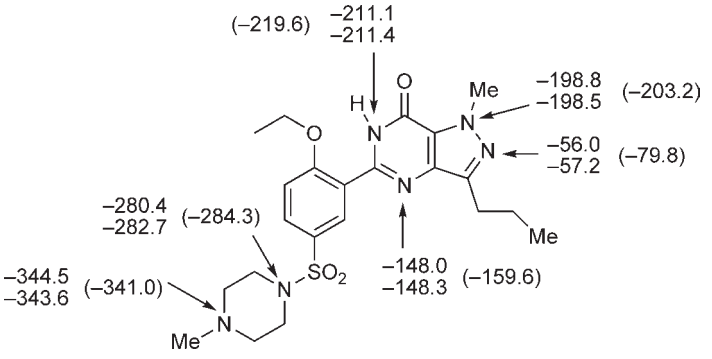
84



85

10.12.3.4 Nitrogen-15 NMR Spectroscopy

^{15}N NMR data for sildenafil and its citrate salt in solution (DMSO-d_6) as well as that of the salt in the solid state are reported for **81**. Most interesting is the large shift obtained in solution and in the solid state for N-2 and N-4 linked to a double bond (21.6 and 11.3).



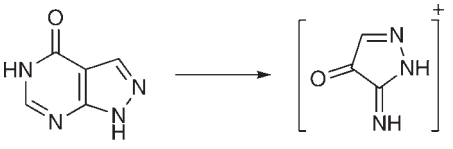
81

The nitrogen double bonds are very sensitive to intermolecular interactions and shifts of about 10–20 ppm were observed, for example, for pyrazoles upon formation of hydrogen bonds. It is probable that hydroxyl groups of the citrate anion act as hydrogen bond donors and OH···N(1) and OH···N(4) and exist in the solid state <2005JPBA865>.

10.12.3.5 Mass Spectrometry

In CHEC-II <1996CHEC-II(7)431>, fragmentation by two pathways was discussed. Although there is no specific mass spectrometry (MS) investigation, MS both by electron-transfer (ET) and configuration interaction methods of plenty of derivatives of these ring systems have been reported. Almost all fully conjugated systems revealed an intense $M^{+\cdot}$ peak reflecting their stability.

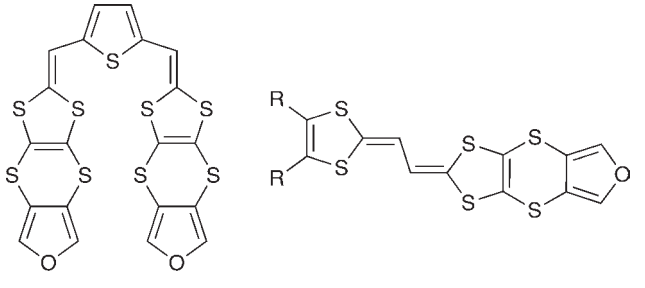
Mass spectral data for ALP **86** have been reported using low-resolution electron impact. In addition to the molecular ion, a peak at *m*/*z* 109 for ion radical **87** was detected <2001MI15>.



86 **87**

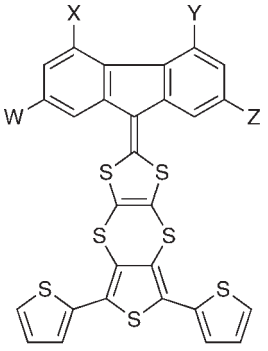
10.12.3.6 UV Spectroscopy

In CHEC-II <1996CHEC-II(7)431>, UV spectral studies on several biologically interesting pyrazolo[3,4-*d*]pyrimidine and pyrazolo[4,3-*d*]pyrimidines were discussed. The UV spectra of several extended conjugated organic metals have been reported. Thus, compounds **88** and **89** present two main absorption bands, namely λ_{max} and λ_{o-o}. These well-resolved lines at ~400 and 420 nm are characteristic of a rigid extended system. The rigidification of **89** is enhanced by intramolecular S···S interaction between the central thiophene ring and end-capped 1,3-dithiole cycles <2003TL1623>.

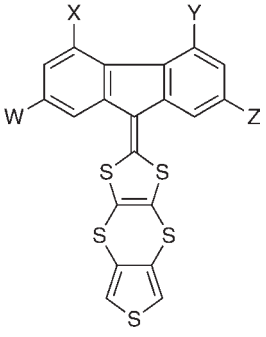


88 **89**

Electronic absorption studies were performed on compounds **90** and **91** in dimethylformamide (DMF); the longest wavelength maxima at ~503–567 nm arising from intramolecular charge transfer (ITC) are shifted bathochromically with an increase in the sum of the nucleophilic constant 6π-attached to the fluorene ring. An equation to enable calculation of this effect was devised <2001MM2232>.



90

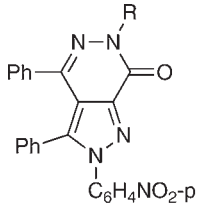


91

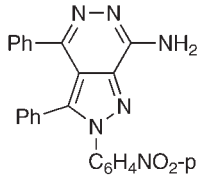
10.12.4 Thermodynamic Aspects

10.12.4.1 Melting Points

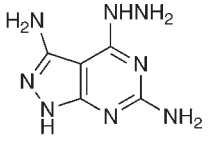
As indicated in CHEC-II <1996CHEC-II(7)431>, aromatic ring systems **1–42** are high-melting compounds, and melting points (m.p.) are generally increased with potential for formation of intermolecular hydrogen bonding. These conclusions are evidenced through inspecting reported m.p. for new derivatives of these ring systems. For example, **92a** is reported to have m.p. of 302 °C while **92b** melts at only 168 °C <2002JHC869>. Amino derivative **93** has m.p. of 281 °C, compound **94** has m.p. of 319 °C, while **95** has m.p. of 239 °C <2000JHC707>.



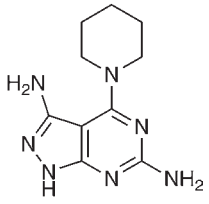
92a: R = H
92b: R = C_6H_5



93

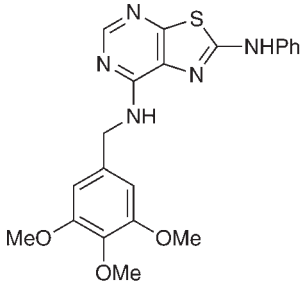


94

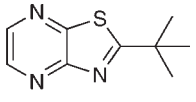


95

2-Azido-1-methoxymethylimidazo[4,5-*b*]pyrazine has m.p. of 91–93 °C, reflecting the effect of absence of potential for hydrogen bonding and perhaps molecular geometry <2001T5497>. In the light of these considerations, it seems difficult to interpret reported m.p.'s for some azolopyrimidines: as an example **96** is reported to melt only at 110–111 °C <2005JOC10194> although one may suggest that this is a result of molecular geometry that hinders molecular stacking and perhaps preference for intramolecular rather than intermolecular hydrogen bonding. The effect of long alkyl chains as well as lack of potential for hydrogen bonding is demonstrated by **97** for which m.p. < 50 °C is reported <2002JHC1077>.



96



97

Software systems and methods for predicting the melting temperature (T_m) and other characteristics of oligonucleotides containing pyrazole[3,4-*d*]pyrimidines have been invented <2003USP235822>.

The drug ALP has m.p. 305 °C and sublimes in a zero-order process. Activation energy for the process was calculated using zero-order kinetics. An Arrhenius plot showed an activation energy of 132.6 kJ mol^{-1} for this process <2001MI15>.

10.12.4.2 Solubility

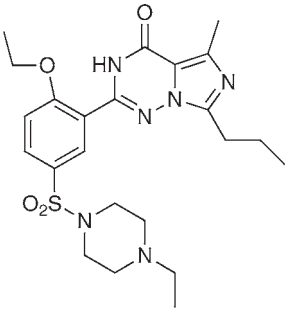
As indicated in CHEC-II <1996CHEC-II(7)431>, azoloazines are generally soluble in polar solvents. Recently reported compounds were crystallized from methanol <2002JHC1077> or ethanol <2001BMC715>.

10.12.4.3 Chromatographic behavior

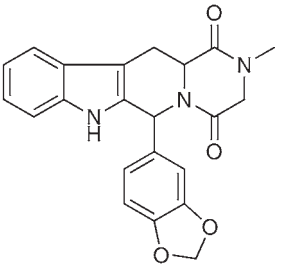
High-performance liquid chromatography (HPLC) <2005JCH118> and HPLC–MS <2005JCH89> were developed for determination of sildenafil in biological fluids. Reverse-phase high-performance liquid chromatography (RP-HPLC) has been used for quantitative analysis of sildenafil citrate in pure form and its pharmaceutical formulations <2002MI743>. An HPLC method coupled with UV detection and electrospray ionization mass spectrometry, HPLC–UV–ESI-MS, was developed for determination of sildenafil **82**, vardenafil **98**, and tadalafil **99** in dietary supplements. The separation was achieved on a C_{18} column with acetonitrile and an aqueous solution containing 20 mmol NH_4OAc and 0.2% formic acid as mobile phase. UV detection was at 292 nm. The detection range was 0.8–80 μg mol^{-1} for sildenafil, 2.25–225 μg mol^{-1} for vardenafil, and 1.1–110 μg mol^{-1} for tadalafil. The standard deviation varied from 2.0 to 5.6 % <2005JCH89>.

A method is described for extraction and determination of sildenafil citrate and its metabolites in human serum by micellar electrokinetic capillary chromatography (MEKC) coupled with sample stacking and polarity switching <2002JCH279>.

Liquid chromatography–electrospray ionization mass spectrometry (LC–ESI-MS) for analysis of sildenafil has also been developed and applied to 40 botanical products. About half of the analyzed samples proved to contain undeclared additives of the three drugs sildenafil, vardenafil, and tadalafil <2004JPBA525>. A similar electrokinetic capillary chromatography method to that proposed for the determination of sildenafil **82** has been reported for vardenafil **98** and tadalafile **99**. Statistical evaluation of the electrophoretic results was achieved. The described method is thought to be rapid and sensitive <2004JCH231>.



Vardenafil
98



Tadalafil
99

A simple and sensitive capillary zone electrophoresis method with UV absorbance detection has been described for the quantification of ALP and its metabolite oxypurinol in aqueous solution. This method could be applied for analyzing these compounds in serum and ALP concentration in pharmaceutical preparations <2003JCH231, 2001ANA121, 2003JC(B)303>.

An accurate HPLC method for the determination of formycin A (FA) in plasma utilizing a Liichromsorb RP-18 column has been described and successfully applied <1999JCH383>.

10.12.4.4 Aromaticity

As has been indicated in CHEC-II <1996CHEC-II(7)431>, aromatic compounds are those polyenes that prefer to react by substitution rather than addition to retain their characteristic polyene structure. In this respect, all unsaturated derivatives of ring systems **1–50** as well as their oxo and thioxo derivatives are aromatic in character. In fact aromatic character is higher in systems **1–50** than that in π-excessive furan and pyrrole where intermediate π-adducts live long enough to be intercepted by nucleophiles giving rise to addition products. Friedel–Crafts acylation has never been reported for **1–50** or their derivatives. Reported X-ray spectral data indicate that fully unsaturated derivatives and their oxo and thioxo derivatives are planar and that bond lengths are intermediate between those of single and double bonds. Moreover, both ^{13}C NMR and ^{1}H NMR data indicate deshielding in both the five- and six-membered rings as a result of ring currents.

10.12.4.5 Other Physical Data

As would be expected, the most intensively studied physical property of ring systems is their electrical conductivity <2002MI608, 2003SM353, 2003TL1623, 2003SM193>. Sildenafil has been determined by analysis of UV spectra <2006JPBA857>. Near-IR measurements of Viagra have been analyzed to enable detection of imitations of Viagra. Small peaks in the spectral region 6200–5700 cm^{-1} originate from sildenafil citrate so that active ingredients can be measured <2006MI840>. Fourier transform infrared (FTIR) and FT-Raman spectra of 4-aminopyrazolo[3,4-*d*]-pyrimidines were recorded and observed frequencies were assigned to various modes of vibration <2001MI383>.

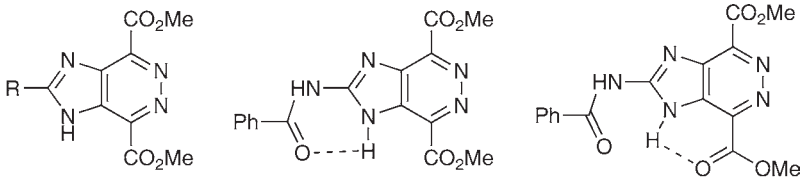
Very recently, the electrochemiluminescent (ECL) response of ALP was studied in aqueous media in wide pH range (pH 2–13) using ignition (FI) analysis. It was revealed that ALP itself had no ECL activity but could greatly enhance the ECL of $Ru(bpy)_3^{2+}$ in alkaline media giving rise to a sensitive FI-ECL response <2006TAL1544>.

Fluorescence and phosphorescence emission spectroscopy were employed to study the interaction of *E. coli* purine nucleoside phosphorylase (PNP) with its specific inhibitor, FA. The results show, for the first time, the application of phosphorescence spectroscopy to the identification of the tautomeric form of the inhibitor bound by the enzyme <2004MI377>.

10.12.4.6 Tautomerism

10.12.4.6.1 Prototropic tautomerism

The only discussed system in CHEC-II <1996CHEC-II(7)431> is pyrazolo[3,4-*d*]pyrimidine. Interestingly, the ^{1}H NMR spectrum of **100a** ($CDCl_3$, room temperature) showed two distinct broad singlets for the methoxy resonance (δ 4.15 and 3.5, both s, 3H) indicative of N-1 and N-3 tautomers, presumably due to intramolecular hydrogen bonding with the aromatic carbonyl as in **100A**. However, possible hydrogen bonding with the ester carbonyl as in **100B** cannot be excluded. Coalescence of resonance occurred at 50 °C (δ 4.05). In contrast, the methoxy resonance of **100b** appeared as one sharp singlet (δ 4.10; s, 6H), indicative of a more rapid equilibrium <2001T5497>.

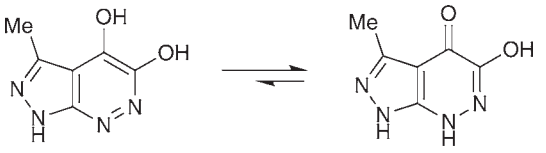


100a: R = NHCOPh
100b: R = Ph

100A **100B**

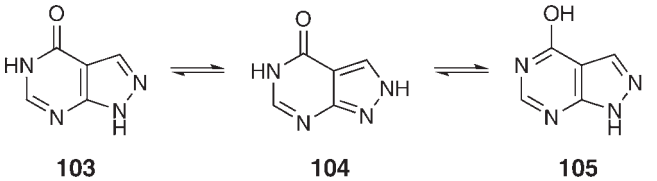
10.12.4.6.2 Functional group tautomerism (amino, oxo, and thioxo derivatives)

Little investigation of tautomerism in amino, oxo, and thioxo compounds has been undertaken. However, in all published work on these derivatives, amino, oxo, and thioxo structures were assigned with the exception of **101** (which was assumed to exist in the dihydroxy form). However, the data presented <2001BMC715> cannot be used to exclude completely structures like **102**.

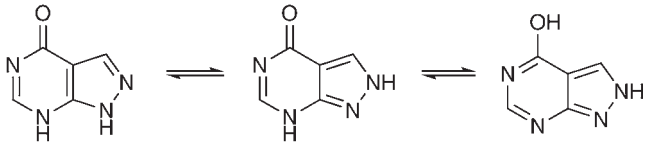


101 102

The tautomerism of ALP is determined by the position of two labile hydrogen atoms in the molecule. For this compound, there are six possible tautomers **103–108** <2001BMC715>.



103 104 105



108 107 106

The structure of crystalline ALP has been established by X-ray diffraction to be **103** and hydrogen bonding may be responsible for the preferred protonation sites <1996CHEC-II(7)431>. Electronic absorption, dispersed fluorescence, and fluorescence excitation spectra were measured for this compound in aqueous solutions of different pH's <1996SAA1547>. These studies revealed that in water solution the molecules of ALP adopt oxo tautomeric forms. The Raman and IR spectra recorded for crystalline ALP indicated the presence of oxo tautomers **103** as in the solid state <2003JST91>. Coexistence of the oxo-N(1)–H and oxo-N(2)–H tautomers **103** and **104** was suggested on the basis of ^{13}C NMR spectroscopy <1973JHC431>. The relative energies of the tautomeric forms of ALP were calculated at the DFT(B3L4P) and MP2 levels. These calculations predict that the oxo tautomer **103** is the most stable. The oxo form **104** is higher in energy by 11.4 kJ mol^{-1} (MP2). The energy difference between the most stable hydroxyl tautomers and **103** is considerably higher <2006MI123>, and calculations made at lower levels of theory agreed well with these calculations <1996JOC5964>.

10.12.5 Reactivity of Fully Conjugated Rings

10.12.5.1 General Considerations

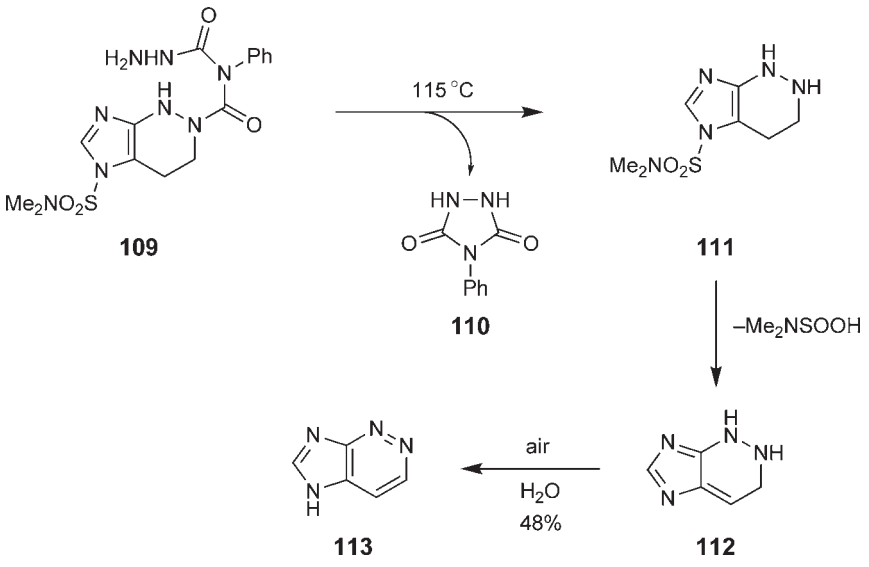
It has been indicated in CHEC-II <1996CHEC-II(7)431> that these systems tend to react by substitution rather than addition. Electrophilic reagents attack ring nitrogen atoms while, as is typical for π-deficient heteroaromatics, nucleophiles replace good leaving substituents especially at activated positions. However, to our knowledge, direct replacement of proton as with azines has not yet been observed.

10.12.5.2 Thermal and Photochemical Processes

Several precyclic and photochemical processes for pyrazolo[3,4-*d*]pyridazines, isoxazolo[4,5-*d*]pyridazines, and formycene-N6-oxide were discussed in CHEC-II <1996CHEC-II(7)431>.

UV illumination of monomers of ALP **103** isolated at low temperature resulted in transformation into the hydroxyl tautomers **105** or **106** <2006MI123>.

Thermolysis of **109** at 115 °C afforded **113**. It is believed that **111** and **112** are intermediates. The molecule initially eliminates 4-phenyltriazolidine-3,5-dione **110** to yield **111**, that further eliminates a sulfonamide derivative yielding intermediate **112** that is oxidized in air into **113** <1998TL4561> (**Scheme 1**).

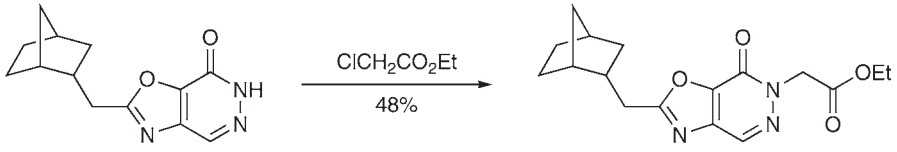


Scheme 1

10.12.5.3 Electrophilic Attack at Nitrogen

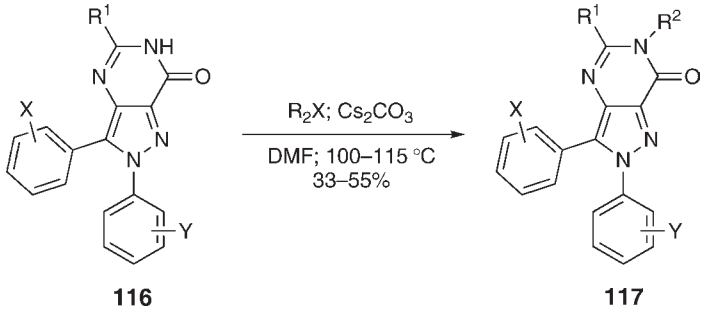
10.12.5.3.1 Alkylation and glycosylation

In CHEC-II <1996CHEC-II(7)431>, the reactivity of pyrazolo[3,4-*d*]pyrimidine derivatives toward alkylating agents and on glycosylation has been fully discussed. Several investigations on the behavior of pyrazolo[3,4-*d*]pyrimidine-7-one <2006BMC2040>, imidazopyridazinones <1993BML1019>, pyrazolopyridazinones <2006BML731>, and oxazolo[4,5-*d*]pyridazinones <2004TL4693> have been reported. *N*-Alkylation rather than *O*-alkylation has always been observed <2004CHE1039>. For example, alkylation of **114** with ethyl chloroacetate afforded only **115** (Equation 1) <2004TL4693>.



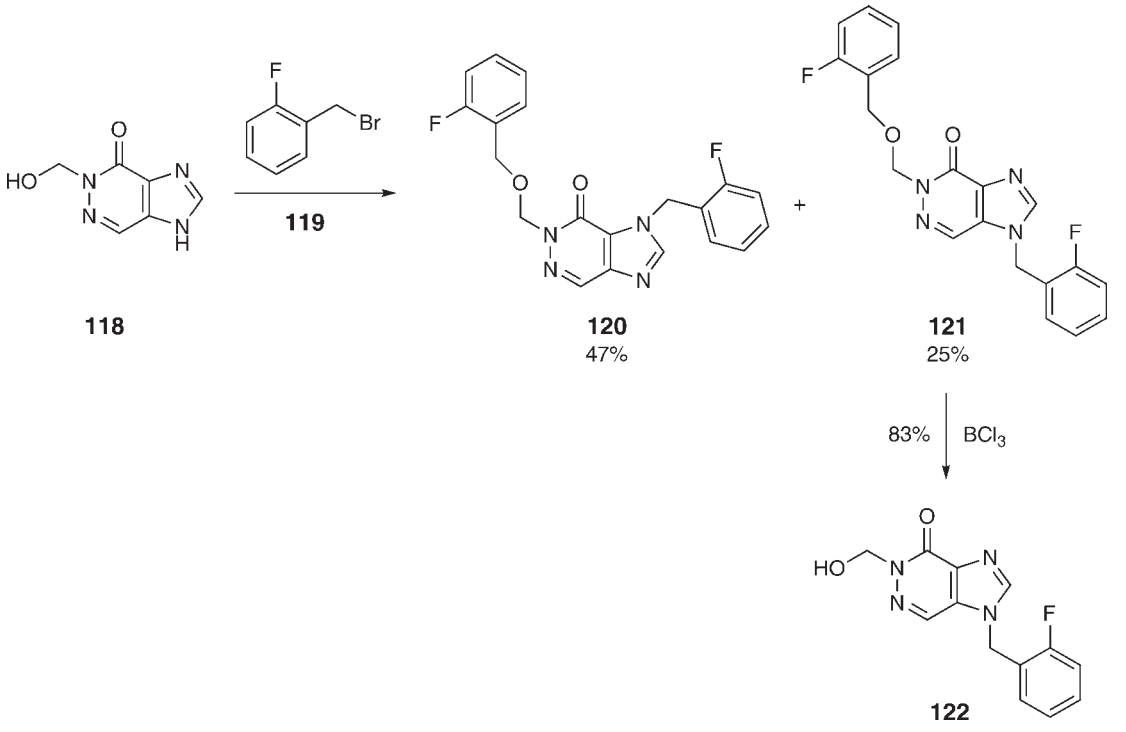
(1)

Also, alkylation of **116** with alkyl halides in DMF solution and in the presence of $CsCO_3$ afforded *N*-alkylated derivatives **117** (Equation 2).



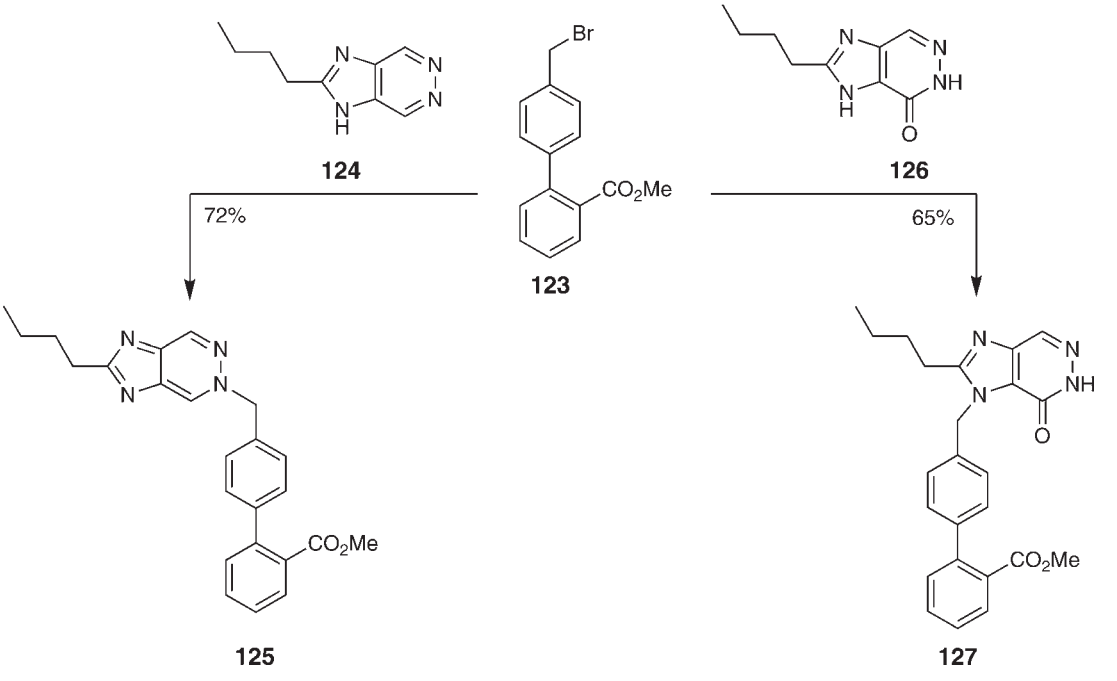
(2)

Treatment of **118** with 2-fluorobenzyl bromide **119** afforded a mixture of **120** and **121**. The mixture was separated by flash chromatography. The *N*-protective group in **118** was removed to yield **122** upon treatment of **121** with boron trichloride (**Scheme 2**) <1995JHC1423>. Alkylation of azolopyridazin-7-ones with alkyl halides in DMF in the presence of potassium carbonate afforded the corresponding 6-alkyl derivatives in 55–72% yield <2002FA89>.



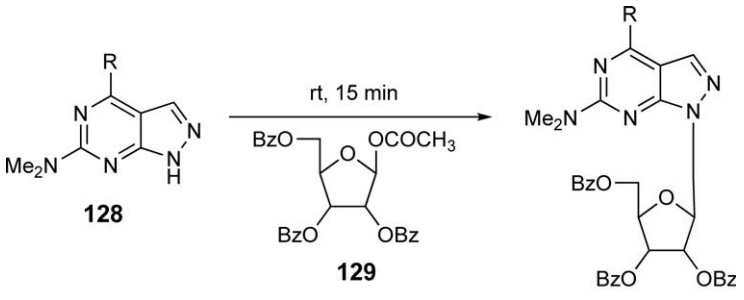
Scheme 2

While **124** is alkylated to give **125** on treatment with **123**, the pyridazinone **126** is converted into **127** upon treatment with the same reagent (**Scheme 3**) <1993BML1019>.

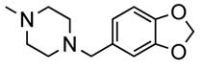


Scheme 3

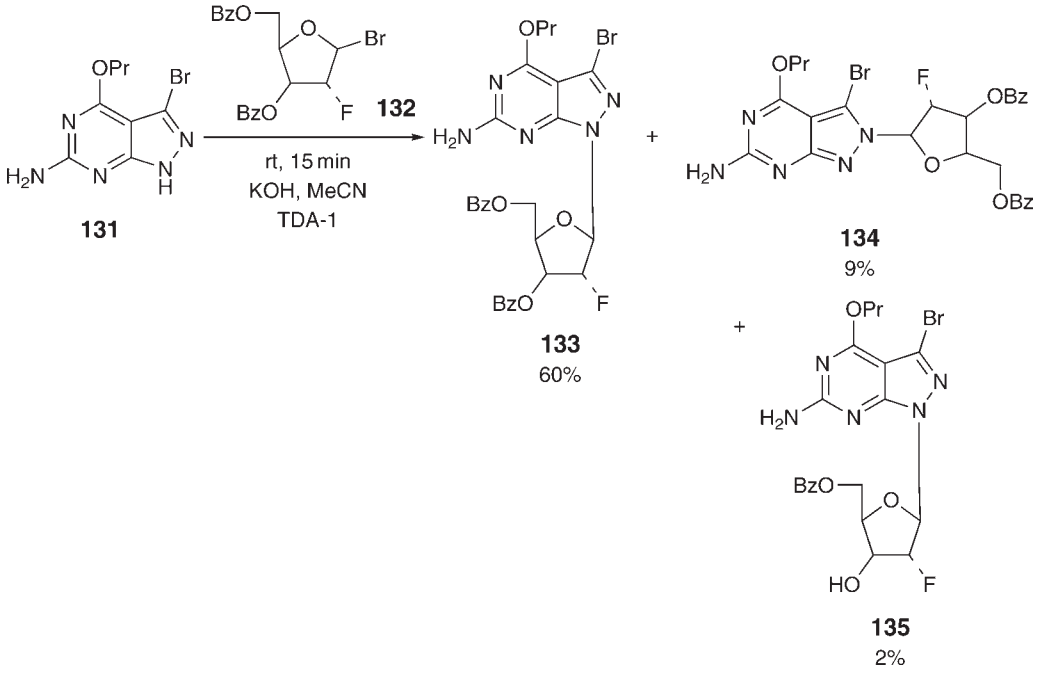
The pyrazolo[3,4-*d*]pyrimidine **128** was regioselectively glycosylated with 1-*O*-acetyl-3,4,5-tri-*O*-benzoylfuranose **129** in the presence of $SnCl_4$ to yield the N-1-glycosylated derivatives **130** (Equation 3) <2001EJM321>.



(3)

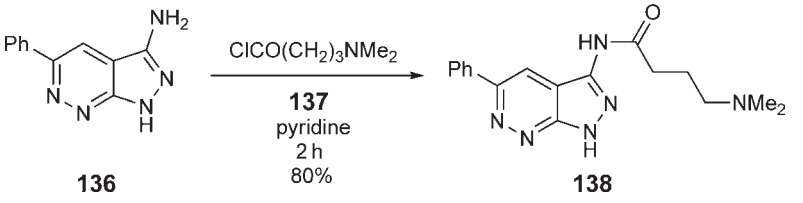
	R	*Yield* (%)	*Reference*
a	OMe	50	2001EJM321
b	$NHCH_2C_6H_5$	43	2001EJM321
c		60	2001EJM321
d		5	2001EJM321

Condensing **131** with **132** in acetonitrile in the presence of powdered KOH and tris[2-(2-methoxyethoxy)ethyl]-amine (TDA-1) for 20 min at room temperature resulted in formation of **133** <2003JOC5519> along with **134** and a trace amount of **135**. Note that formation of an N-2-isomeric glycoside was not accompanied by dehalogenation, which is different to a closely related glycosylation procedure for **131** (Equation 4) <1998S207>.



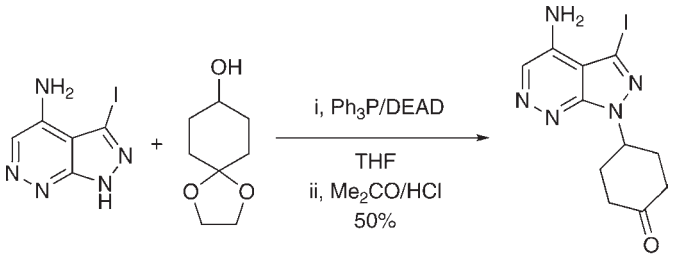
(4)

Acylation of **136** at the exocyclic amino function with 4-dimethylaminobutanoyl chloride **137** has been reported to afford **138** (Equation 5) <2003BML1581>.



136 138 (5)

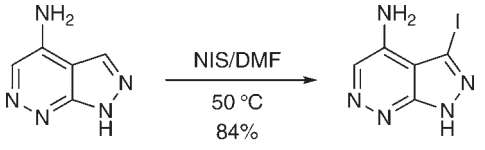
Treatment of **139** with **140** in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) in tetrahydrofuran (THF) and then with Me_2CO/HCl gives **141** (Equation 6) <2002BML1687>.



139 140 141 (6)

10.12.5.4 Electrophilic Attack at Carbon

As indicated in CHEC-II <1996CHEC-II(7)431>, reactions of this type are rather rare as ring carbons are generally π-deficient; however, iodination of **142** by *N*-iodosuccinimide (NIS) affords **139**. This reaction may proceed by a radical mechanism (Equation 7) <2002BML1687>.



142 139 (7)

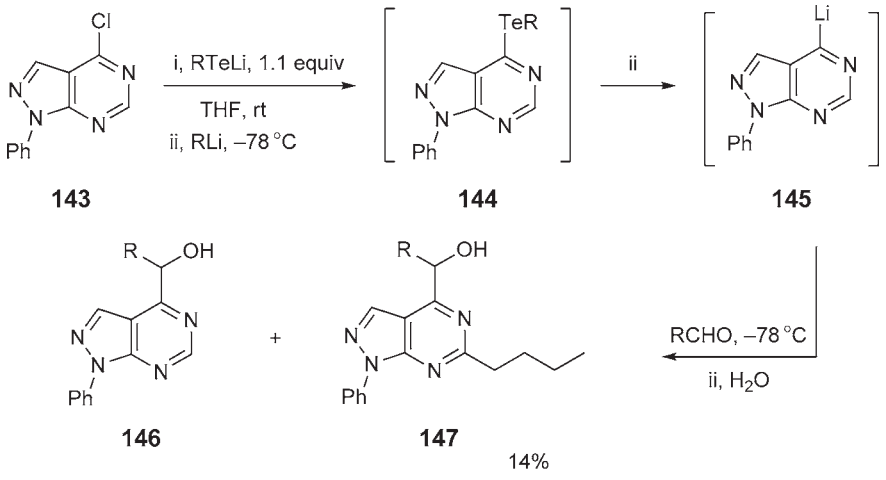
Treatment of **143** with alkyl lithium tellurate then with alkyl lithium afforded lithio derivatives **144** and **145**. The latter reacted with carbonyl compounds to yield the hydroxyl compounds **146** and **147** (**Scheme 4**) <1999TL2139>.

Pyrazolopyrimidine **148** reacted with magnesium to yield the corresponding Grignard reagent **149** that reacted with pivaldehyde to yield the corresponding C-alkylated derivative **150** (**Scheme 5**) <2003JOC2054>.

Treatment of **151a** and **151b** with tosyl azide in the presence of lithium diisopropylamide (LDA) afforded a mixture of **152a**,**b** and **153a**,**b** (Equation 8) <2001T5497>.

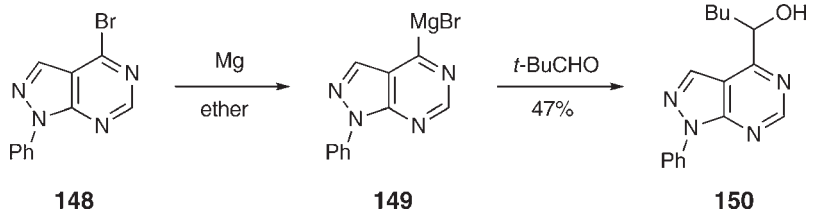
10.12.5.5 Nucleophilic Attack at Carbon

As indicated in CHEC-II <1996CHEC-II(7)431>, displacement of a good leaving substituent by a nucleophile is readily accomplished. In several cases, ring opening and recyclization in an ANRORC mode (addition of nucleophile by ring opening and recyclization) occurs.

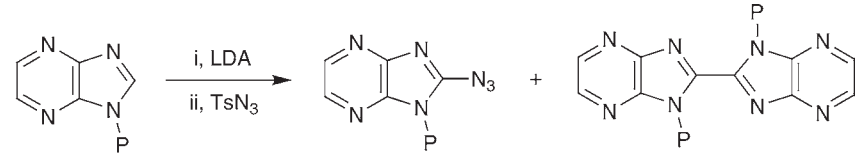


	R	Yield (%)	Reference
a	*t*-Bu	74	1999TL2139
b	Ph	61	1999TL2139

Scheme 4



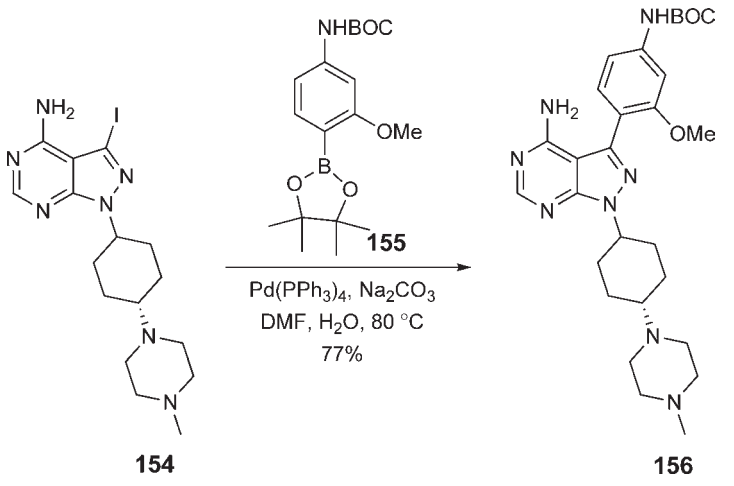
Scheme 5



(8)

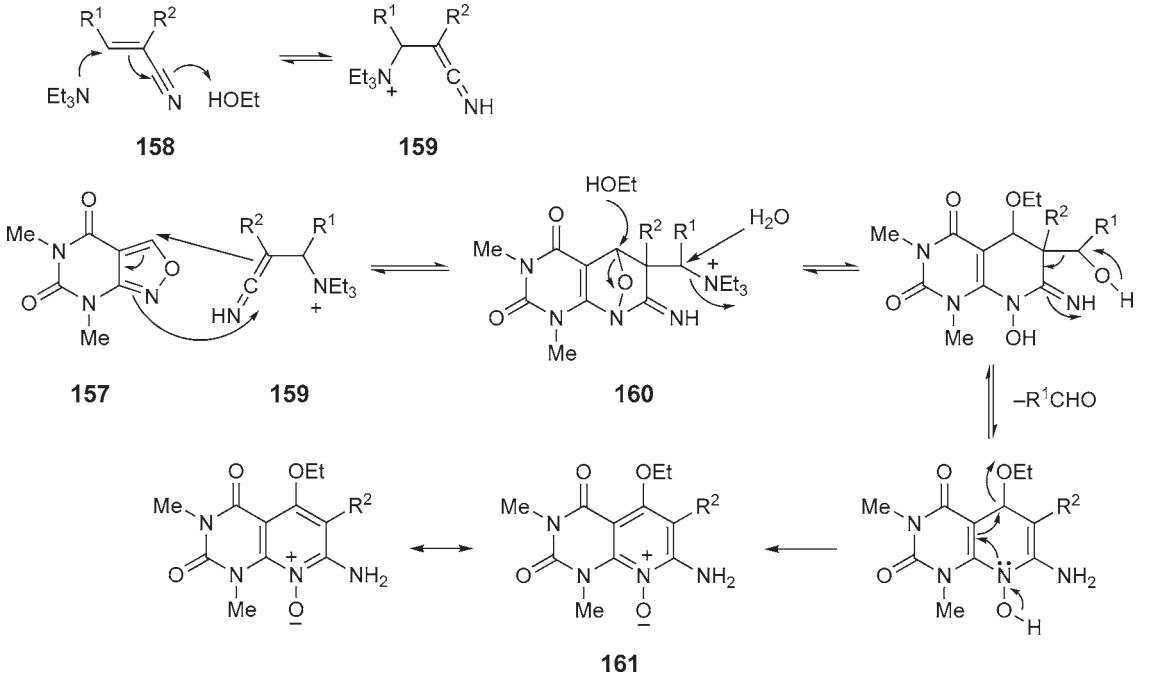
10.12.5.5.1 Reactions with carbon nucleophiles

It has been demonstrated in CHEC-II <1996CHEC-II(7)431> that halogen substituents as well as other good leaving substituents can be readily replaced by carbon nucleophiles, for example, cyanide ion or active methylene compounds. Also, direct cyanation of 1-phenylpyrazolo[3,4-*d*]pyrimidine was demonstrated. Since then, reactivity toward carbon nucleophiles has not received much attention. However, a few interesting reactions with carbon electrophiles have been reported in the last few years. Thus, reacting **154** with **155** affords **156** (Equation 9) <2002BML1687>.



(9)

The reaction of **157** with **158** in the presence of triethylamine has afforded **161** in excellent yield. A mechanism involving initial addition of triethylamine to **158** yielding **159** that then added **157** to afford **160**, that is converted into **161** *via* the intermediacy of an *N*-hydroxypyridopyrimidine intermediate, has been proposed (**Scheme 6**) <2003TL1847>.

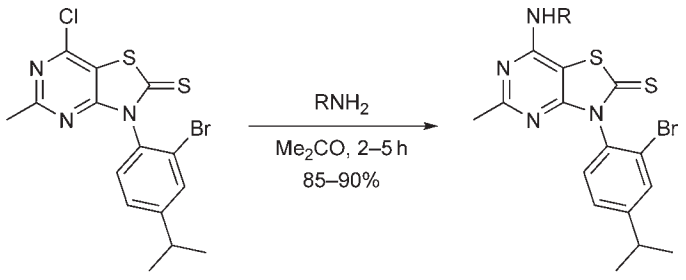


Scheme 6

10.12.5.5.2 Reactions with nitrogen nucleophiles

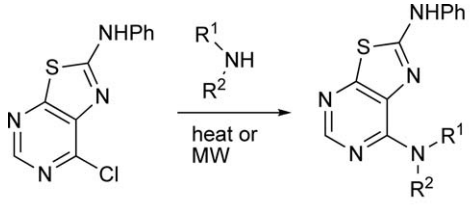
As indicated in CHEC-II <1996CHEC-II(7)431>, replacement of halogen, alkylthio, and alkoxy functions with nitrogen nucleophiles is readily effected under mild conditions <2002BML1687, 1999BML1185, 1999JHC321, 2001EJM321, 2005JOC10194, 2001BMC715>. Replacement of CN by nitrogen nucleophiles has also been reported

<2003OL507>. Thus **162** reacted with amines in refluxing acetone to yield amine **163** (Equation 10) <1999BML1185>; yields of individual derivatives were not given.



162 **163** (10)

Replacement of chlorine in **164** by aliphatic or aromatic primary amines as well as secondary amines has been investigated. Aliphatic amines reacted with **164** under basic conditions to yield **165**, whereas aromatic amines required mildly acidic conditions to undergo this transformation. Primary and secondary aliphatic amines reacted smoothly to yield the corresponding diamines in good to excellent yields. Even the weakly nucleophilic *t*-butylamine produced the corresponding product in modest yield (20%). The conditions employed for aliphatic amine displacement were not suitable for aromatic amines; the latter required a slight excess of glacial acetic acid and microwave heating to enable this displacement. Under these conditions, amination with aniline occurred readily affording the corresponding 7-anilino products. However, both electronic and steric factors influenced this reaction as evidenced from the moderate yield for substitution with 4-nitroaniline (20%) and with *N*-methylaniline (60%) (Equation 11) <2005JOC10194>.

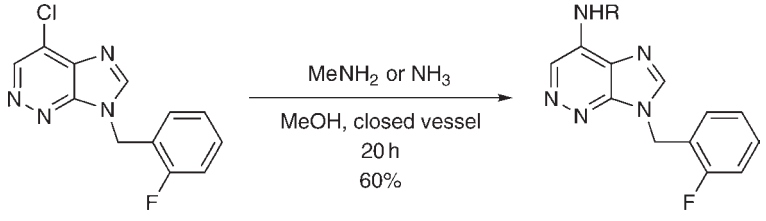


164 **165**

	R^1	R^2	*Yield* (%)	*Reference*
a	3,4,5-$(MeO)_3C_6H_2$	H	90	2005JOC10194
b	-$(CH_2)_2$-NMe-(CH_2)-		85	2005JOC10194
c	Me-$(CH_2)_3$-	H	90	2005JOC10194
d	*t*-Butyl-	H	20	2005JOC10194
e	*p*-$MeOC_6H_4$-	H	93	2005JOC10194

(11)

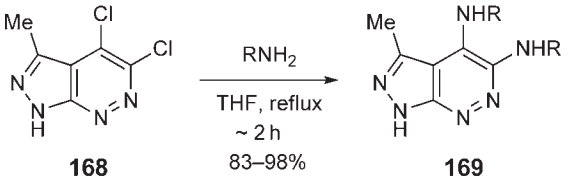
Amination of **166** with methylamine or ammonia in methanol at 125 °C produced the amino derivatives **167** (Equation 12) <1995JHC1423>.



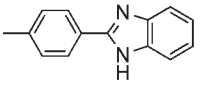
166 **167**
R = Me, or H

(12)

Both halogen atoms in **168** are readily replaced by amines in THF to yield **169** (Equation 13) <2001BMC715>.



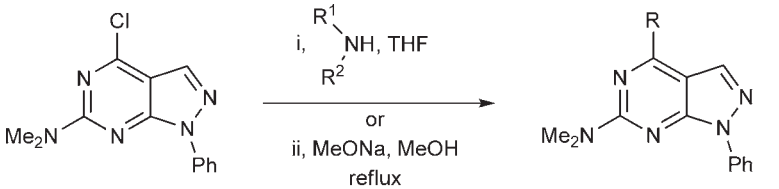
168 169

	R	Yield (%)	Reference
a	4-CH_3-C_6H_4	83	2001BMC715
b	4-$HO_2CC_6H_4$	98	2001BMC715
c	-COC_6H_5	87	2001BMC715
d		85	2001BMC715

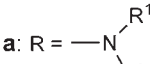
(13)

Treatment of 3-(2-methoxy-5-bromophenyl)-1*H*-pyrazolo[3,4-*b*]pyrazine-6-chloride with 2,4-difluoroanisole affords 3-(2-methoxy-5-bromophenyl)-6-(2,4-difluorophenylamino)-1*H*-pyrazolo[3,4-*b*]pyrazine <2006BML262>.

Similar to the established behavior of 4-chloropyrazolo[3,4-*d*]pyrimidines discussed in CHEC-II(1996) <1996CHEC-II(7)431>, the chlorine substituent in **170** is readily converted into amine **171a** upon treatment with aliphatic primary or secondary amines (Equation 14) <2001EJM321>. Substitution with methoxide leads to **171b**.

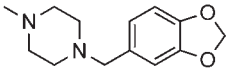


170 171

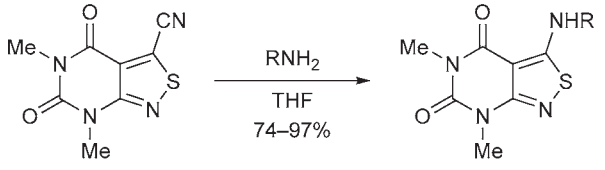
a: R = 

b: R = OMe

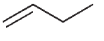
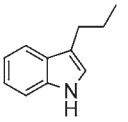
(14)

	R	Yield (%)	Reference
a	OMe	70	2001EJMC321
b	$NHCH_2C_6H_5$	40	2001EJMC321
c	Piperidino	94	2001EJMC321
d		70	2001EJMC321

The cyano function in **172** is readily replaced by amines to yield **173** (Equation 15) <2003OL507>.

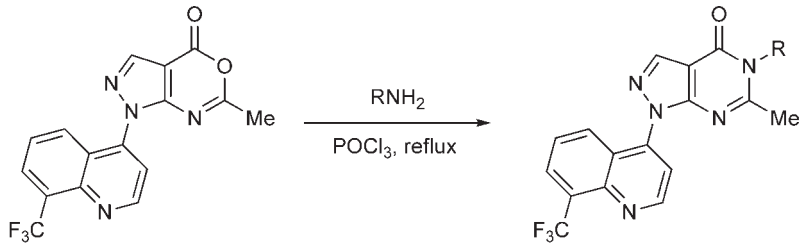


172 173

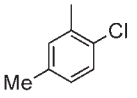
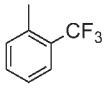
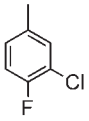
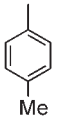
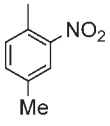
	R	Yield (%)	Reference
a	*n*-Pr-	97	2003OL507
b		94	2003OL507
c		74	2003OL507

(15)

Ring opening and recyclization of **174** into **175** by the action of amines has been reported (Equation 16) <2006BMC2040>.

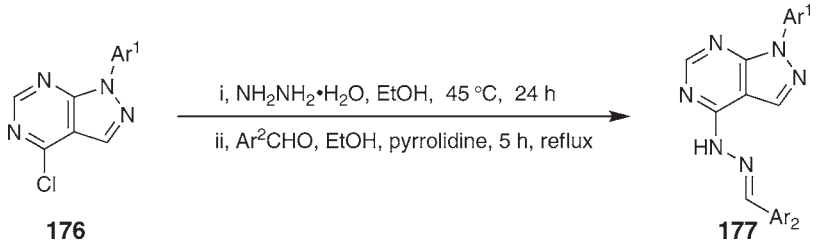


174 175

175	R	Yield (%)	Reference	R	Yield (%)	Reference
a		57	2006BMC2040	d		52	2006BMC2040
b		55	2006BMC2040	e		50	2006BMC2040
c		64	2006BMC2040	f		54	2006BMC2040

(16)

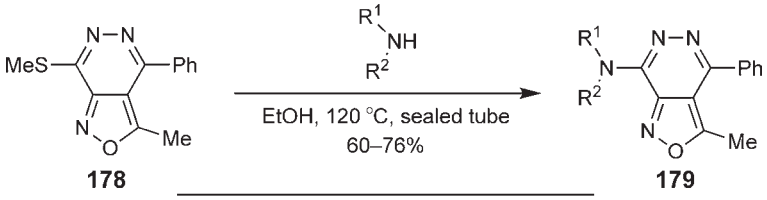
Treatment of **176** with hydrazine hydrate then with aromatic aldehydes afforded **177** (**Scheme 7**) <2004BML2121>; yields were not given.



176 177

Scheme 7

Replacement of the alkylthio moiety in **178** with aliphatic primary amines and with piperidine to yield **179** could be effected in ethanol at 110–120 °C in a sealed tube (Equation 17) <2002FA89>.



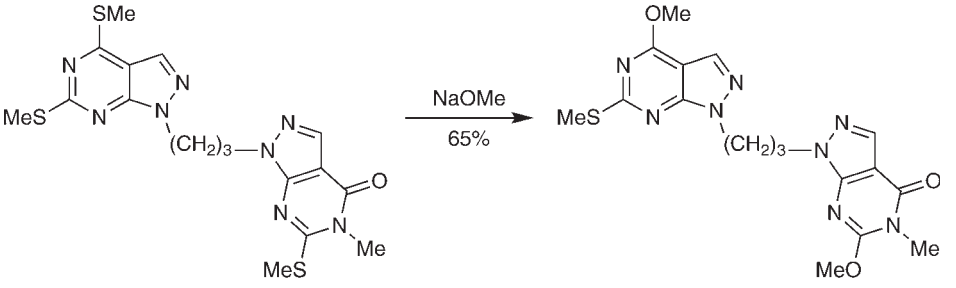
178 179

	R^1	R^2	Yield (%)	Reference
a	Me	H	60	2002FA89
b	Et	H	70	2002FA89
c	*n*-Pr	H	80	2002FA89
d	*n*-But	H	67	2002FA89
e	$(CH_2)_5$		76	2002FA89

(17)

10.12.5.5.3 Reaction with oxygen nucleophiles

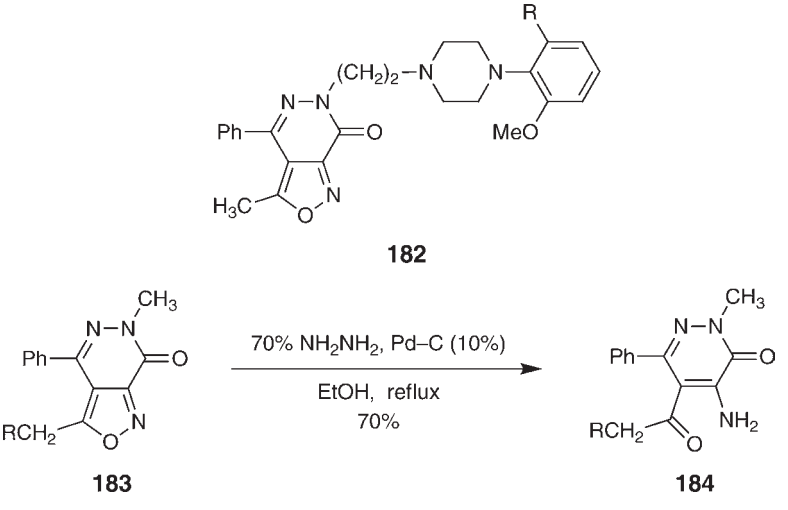
Treatment of **180** with sodium methoxide affords **181** (Equation 18) <2006JST106>.



180 **181** (18)

10.12.5.6 Radical Reactions, Oxidation and Reduction

We have pointed out earlier in CHEC-II <1996CHEC-II(7)431> that an amine can be replaced an aryl group on treatment with an aryl nitrite. Ring reduction of isoxazolo[3,4-*d*]pyrimidines and ring cleavage of pyrazole[3,4-*d*] pyrimidinones was also reported in this article. Further examples of reduction and ring opening could be effected by hydrazine hydrate. Thus, whereas attempted reduction of **182** with hydrazine hydrate and Pd–C (10%) always brought about parallel loss of the alkyl piperazinyl moiety at N-6, **183** could be successfully reduced into **184** on similar treatment (Equation 19) <1998BMC925>. This type of reductive cleavage has been observed using a diversity of reducing agents <2004COR1463>.



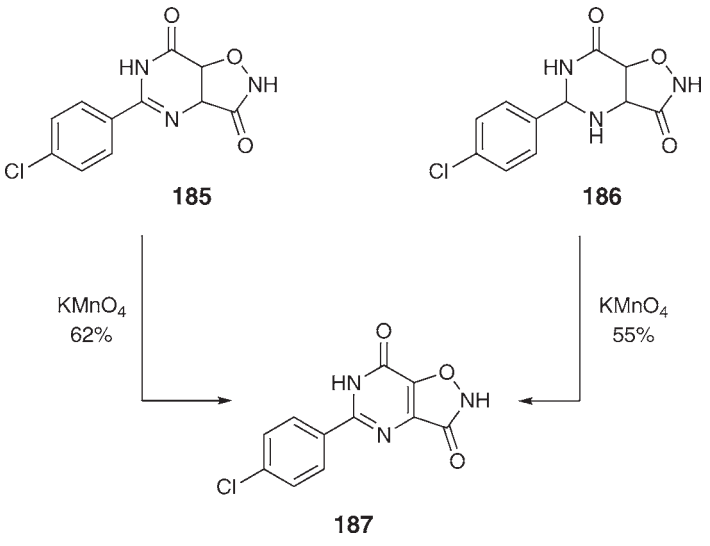
182

183 **184** (19)

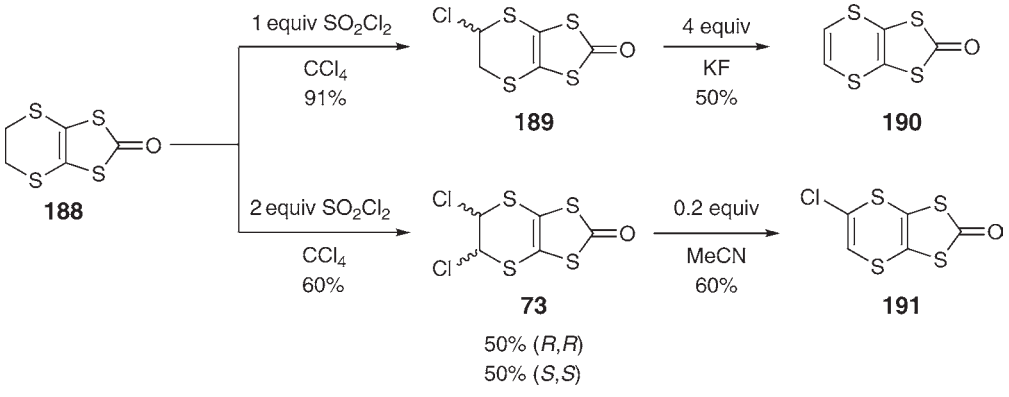
10.12.6 Reactivity of Nonconjugated Rings

Little has been discussed on this topic in CHEC-II <1996CHEC-II(7)431>. The isoxazolo[4,5-*d*]pyrimidin-3,7-diones **185** or **186** are converted into **187** upon oxidation with potassium permanganate in acetone (**Scheme 8**) <2004BMC265>.

The chemistry of nonaromatic condensed 1,3-dithiolanes has received considerable interest due to the reported interesting conductivity properties. Some of this chemistry has been recently reviewed <1995S215>. The chlorination of **188** was efficiently performed with 1 equiv of SO_2Cl_2 in refluxing carbon tetrachloride to afford racemic **189**; with 2 equiv of sulfuryl chloride, *trans*-5,6-dihydro-5,6-dichloro-1,3-dithiolo[4,5-*b*][1,4]dithiene-2-one **73** was obtained as a racemic mixture of (*R*,*R*)- and (*S*,*S*)-enantiomers without any (*R*,*S*)-diastereoisomer, as confirmed by the presence of a single ^{1}H NMR signal. Dehydrochlorination of **189** and **73** into **190** and **191**, respectively, could be effected as shown in **Scheme 9** <2000CC1117>.

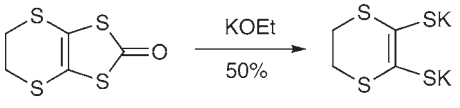


Scheme 8



Scheme 9

Being formally a derivative of carbonic acid, 4,5-bis(ethylenedithio)-1,3-dithiol-2-one **188** is opened into the dipotassium salt **192** by the action of potassium ethoxide in THF (Equation 20) <1974JOC511>.

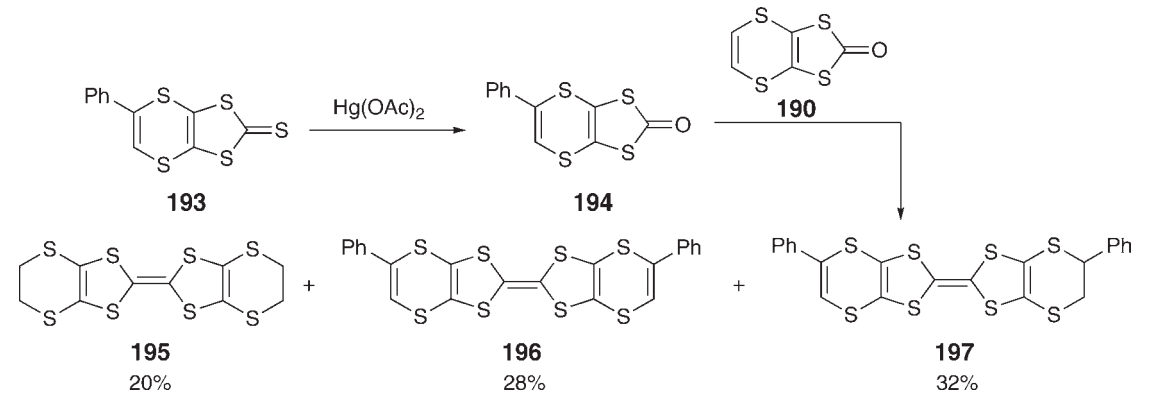


(20)

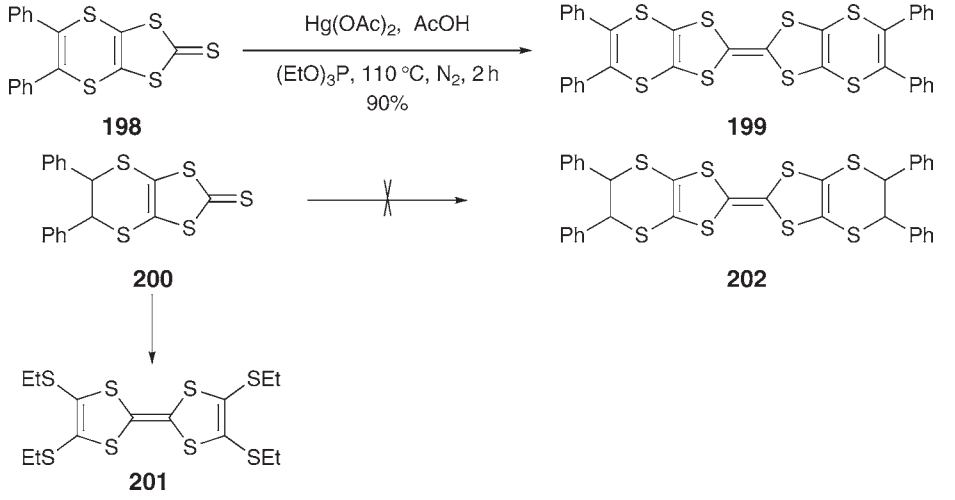
The thione **193** is converted into **194** on treatment with $Hg(OAc)_2$. This product when reacted with **190** yields a mixture of **195–197** (**Scheme 10**) <1996TL284>.

The thione sulfur atom in **198** was converted into oxygen with mercuric acetate in quantitative yield. Subsequent heating of the reaction product in triethyl phosphite (110 °C) for 2 h resulted in a yellow precipitate of **199**. This contrasts with results reported for the coupling of saturated analogue **200**, which gave **201** rather than its self-coupled product **202**. This suggests that the unsaturated dithiin ring contributes to the stability of the molecule through conjugation (**Scheme 11**) <2000CC2039>.

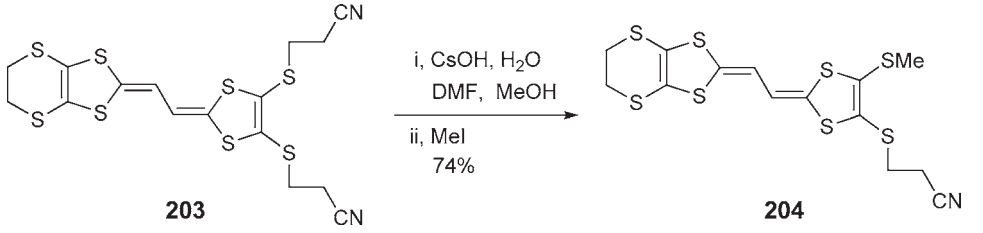
Dealkylation of **203** by the action of CsOH followed by methylation gives **204** as 1:1 mixture of geometric isomers (Equation 21) <1994S809>.



Scheme 10

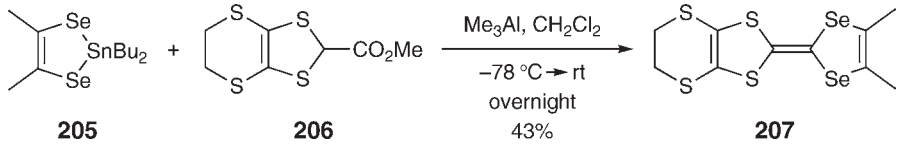


Scheme 11



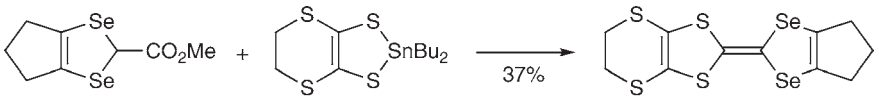
(21)

The ester **205** condensed with **206** when left overnight in the presence of trimethylaluminium at −78 °C to yield **207** (Equation 22) <1996JOC3987>.



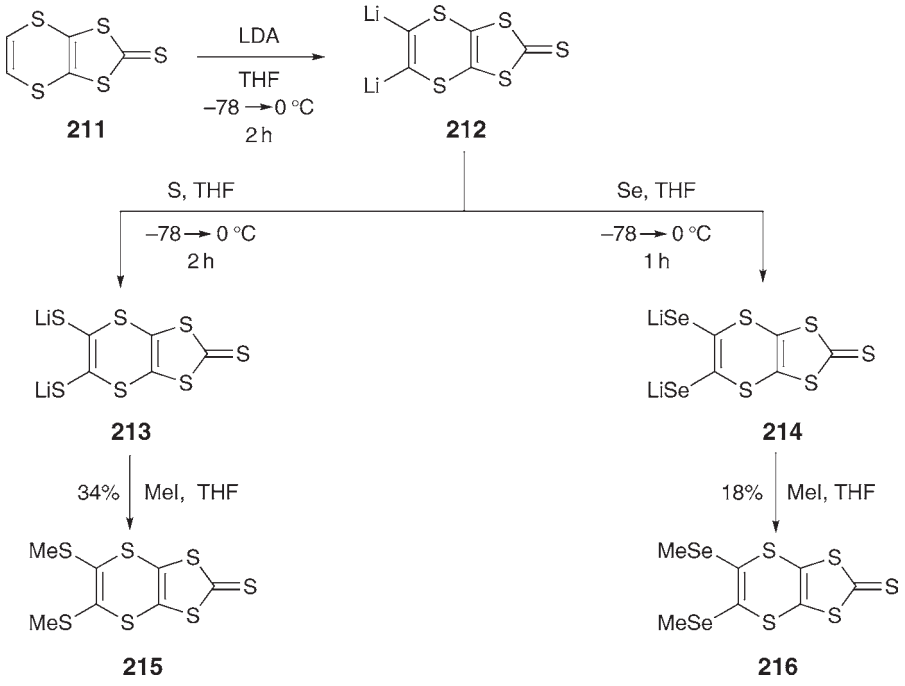
(22)

Alternatively, reacting **208** with **209** under similar conditions gives **210** (Equation 23) <1996JOC3987>.



208 **209** **210** (23)

The dithiolodithione **211** is easily lithiated by LDA and the lithium salt **212** is then converted into **213** and **214** that were subsequently alkylated to give **215** and **216** as shown in **Scheme 12** <1987CL1317, 1988BCJ2973>.



Scheme 12

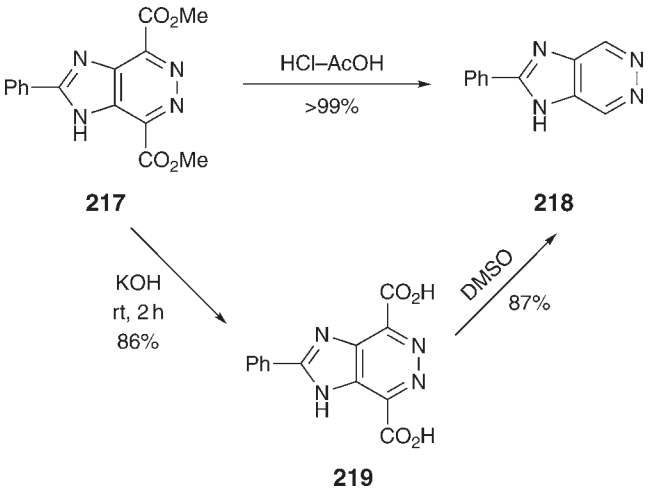
10.12.7 Reactivity of Substituents

10.12.7.1 Halogen Substituents

The reactivity of such a substituent has been discussed earlier in CHEC-II <1996CHEC-II(7)431>. Generally, and as a result of π-deficiency of the six-membered ring, a halogen substituent on a six-membered moiety is readily replaced by nucleophiles. This type of reaction has been dealt with when discussing reactivity of the considered ring systems toward nucleophiles. On the other hand, halogens on the azole side of the ring can be displaced only with difficulty if displaceable at all.

10.12.7.2 Carboxylic Acid and Carboxylic Acid Derivatives

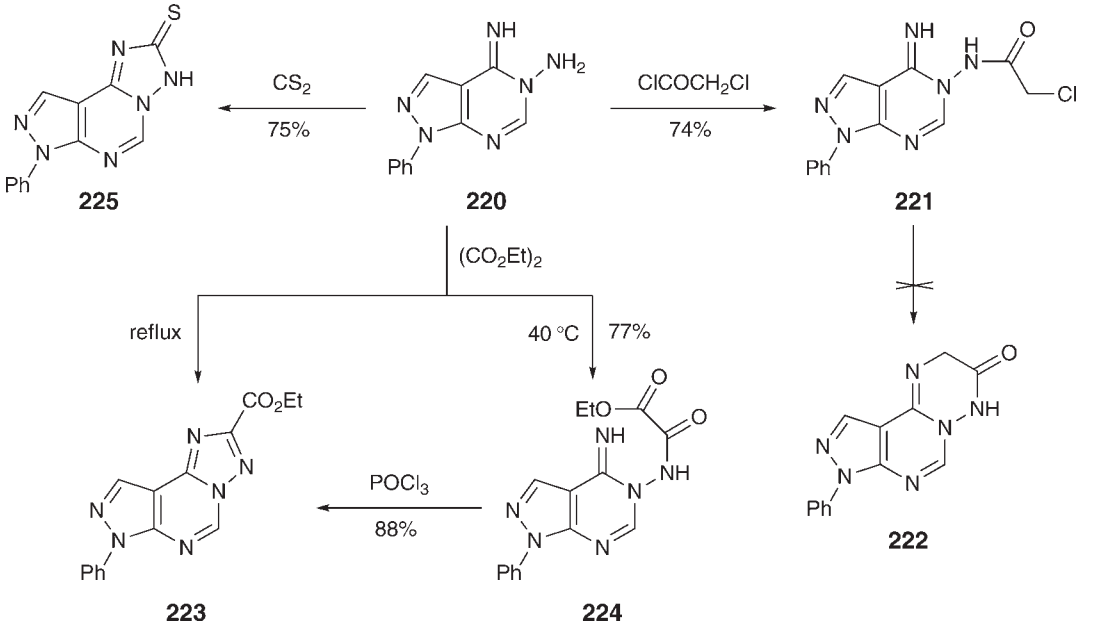
In CHEC-II <1996CHEC-II(7)431>, it was shown that the cyano function in 3-cyanopyrazolo[3,4-*d*]pyrimidines can be converted into an amide by hydrogen peroxide and that 3-carboxylic acid derivatives readily decarboxylate at 200 °C. Wan *et al.* <2001T5497> have reported that treatment of **217** with an acetic acid–hydrochloric acid mixture affords **218**. Compound **218** was also obtained upon heating **219** in DMSO for 2 h. Compound **219** was obtained in turn via heating **217** in KOH (**Scheme 13**). It has been pointed out earlier that a CN function is readily replaced by amines.



Scheme 13

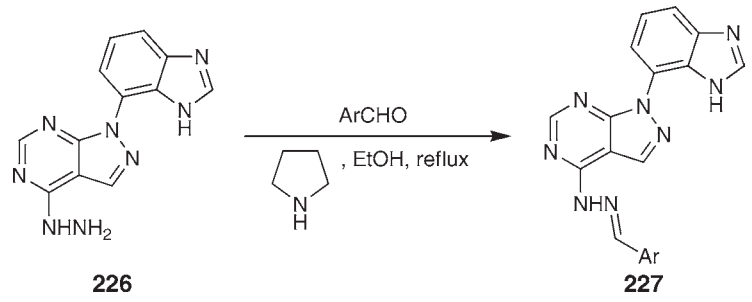
10.12.7.3 Amino, Diazo, and Hydrazo Substituents

The reactivity of amino functions on diazotization and condensation with dimethylformamide dimethyl acetal has been discussed in CHEC-II <1996CHEC-II(7)431>. The diamine **220** is readily converted into a variety of tricyclic pyrazolo[3,4-*d*]pyrimidines under a variety of conditions <2004T5093>. Thus with chloroacetyl chloride the chloroacetyl derivative **221** was formed. This could not be further cyclized into **222**. Refluxing **220** with diethyl oxalate afforded **223** while **224** was formed when the reaction was conducted at 40 °C. Treatment of **224** with $POCl_3$ afforded **223**. Reacting **220** with carbon disulfide afforded **225** (**Scheme 14**) <2004T5093>.



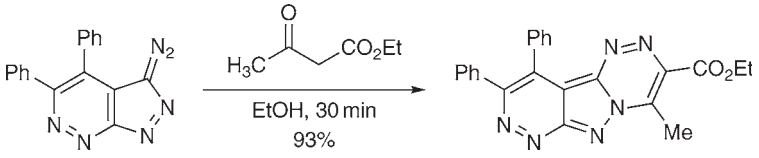
Scheme 14

The hydrazinopyrazolo[3,4-*d*]pyrimidine **226** readily condensed with aromatic aldehydes in refluxing ethanol in the presence of catalytic amounts of pyrrolidine, to form the hydrazones **227** in 33–81% yields (Equation 24) <2004BML2127>; yields of individual derivatives were not given.



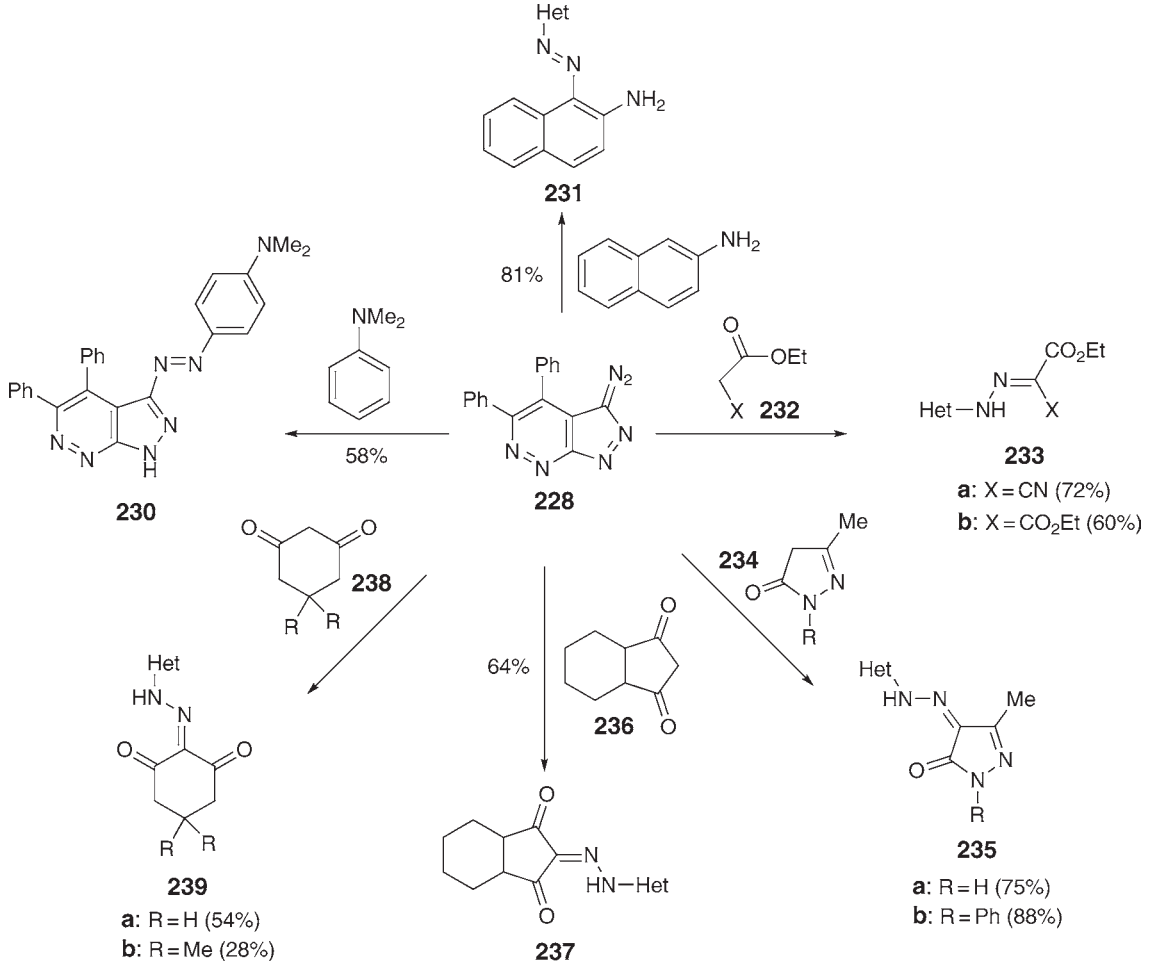
226 **227** (24)

Treatment of the diazo compound **228** with ethyl acetoacetate affords **229** (Equation 25) <2004BMCL5013>.



228 **229** (25)

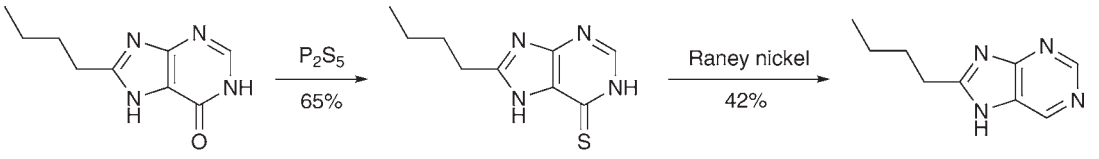
Coupling of compound **228** with dimethylaniline and with 2-naphthylamine afforded the azo derivatives **230** and **231**. Compound **228** also coupled with active methylene reagents, such as pyrazolone **234**, indan-1,3-dione **236**, and cyclohexane-1,3-dione **238**, to yield the corresponding arylhydrazones **235**, **237**, and **239**, respectively <2004H(63)1143, 2004BMCL5013> (**Scheme 15**).



Scheme 15

10.12.7.4 Aldehydes, Oxo and Thioxo Derivatives

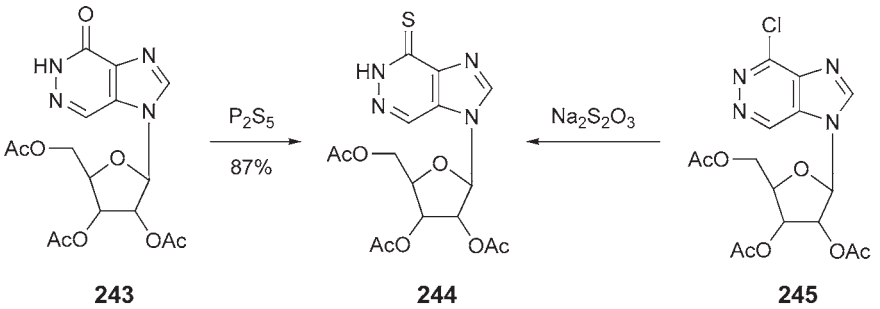
In addition to reactivities reported in CHEC-II <1996CHEC-II(7)431>, the imidazopyridazinone **240** is converted into thioxo derivative **241** which was then converted into **242** upon treatment with Raney nickel <1993BML1019>. Most likely, the thione moiety is initially reduced to a mercapto function and the latter then aromatized via H_2S elimination (**Scheme 16**).



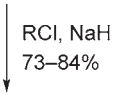
240 **241** **242**

Scheme 16

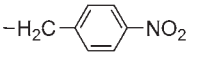
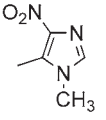
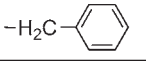
Treatment of **243** with P_2S_5 in pyridine affords the thioxo compound **244** which was directly formed on reacting **245** with $Na_2S_2O_3$ in butanol. Alkylation of **244** by alkyl halides in THF in the presence of sodium hydride gives **246** <1996BMC1725> (**Scheme 17**).



243 **244** **245**

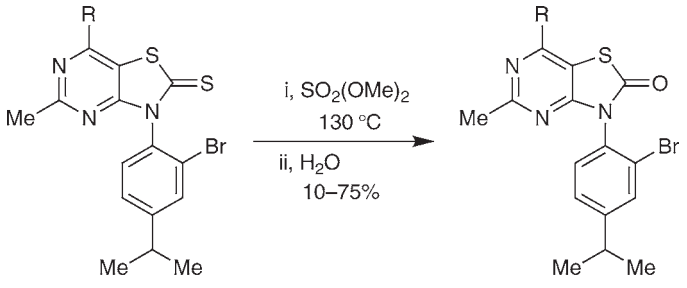


246

	R	*Yield (%)*	*Reference*
a		76	1996BMC1725
b		73	1996BMC1725
c		73	1996BMC1725
d		84	1996BMC1725

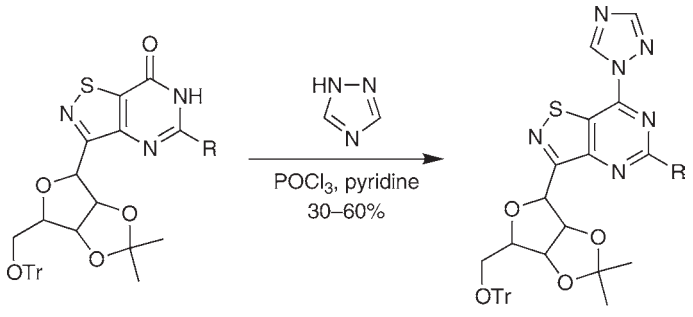
Scheme 17

Treatment of **247** with dimethyl sulfate at 130 °C followed by refluxing by heating the resulting product in water under reflux affords **248** (Equation 26) <1999BML1185>; yields of individual derivatives were not given.



247 248 (26)

Interestingly, treatment of **249** with 1*H*-1,2,4-triazole and phosphorus oxychloride in pyridine results in formation of the 7-triazol-1-ylisothiazolopyrimidine **250** in yields depending on the nature of the substituents (Equation 27) <2001NN229>.



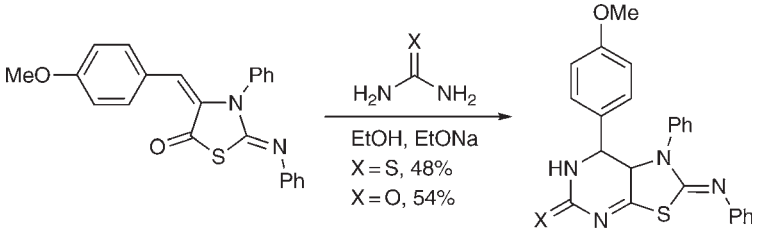
249 250 (27)

10.12.8 Ring Synthesis

10.12.8.1 Synthesis of Six-Membered Rings by Formation of Two Bonds

10.12.8.1.1 From [3+3] atom fragments

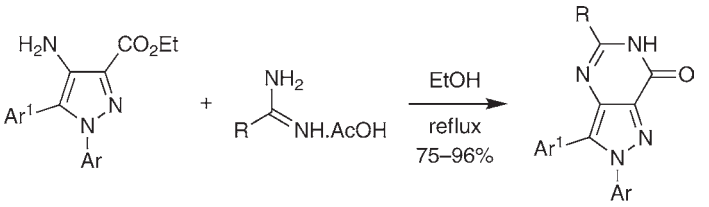
Azoloazines are synthesized by this route, as indicated in CHEC-II <1996CHEC-II(7)431>. Reaction of **251** with urea or thiourea in refluxing ethanolic sodium ethoxide afforded **252** (Equation 28).



251 252 (28)

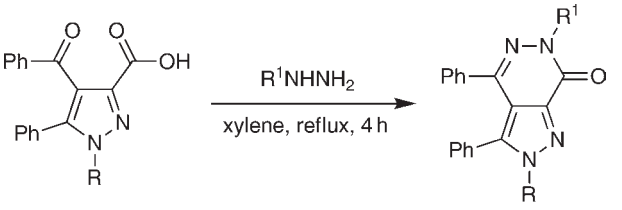
10.12.8.1.2 From [4+2] atom fragments

Plenty of such routes devoted to the synthesis of pyrazolo[3,4-*d*]pyrimidines, pyrazolo[4,3-*d*]pyrimidines, as well as pyrazolopyridazines are described in CHEC-II <1996CHEC-II(7)431>. This route is still extensively utilized. Thus, reacting **253** with the amidine acetate **254** in refluxing ethanol yielded **255** (Equation 29) <2006BML731>; yields of individual derivatives were not given.



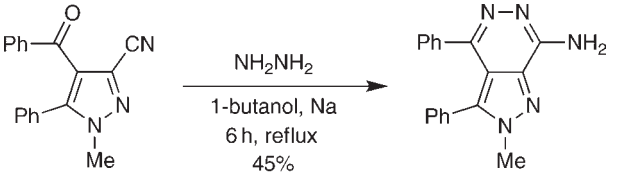
253 254 255 (29)

Pyrazolo[3,4-*d*]pyridazines are readily obtained from reaction of pyrazoles having 4,5-dicarbonyl or carboxy substituents <1997OPPI285, 2003T5869>. For example, reacting **256** with hydrazines affords **257** (Equation 30); again, yields of individual derivatives were not given.



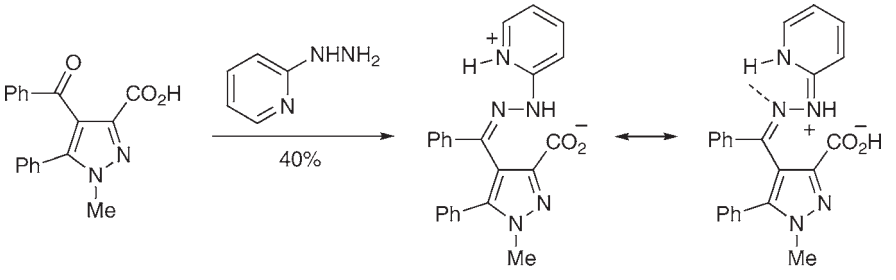
256 257 (30)

Similarly **258** gives **259** when treated with hydrazine hydrate (Equation 31).



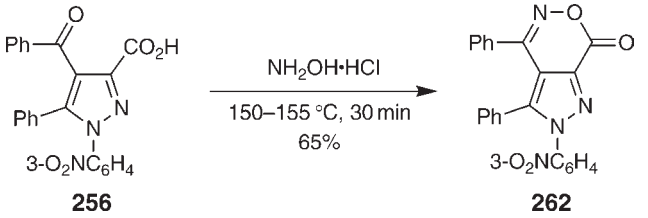
258 259 (31)

Attempted reaction of **256** (R = Me) with 2-pyridylhydrazine afforded only a carboxylic hydrazone **260**, which is believed to be stabilized by hydrogen bonding in its resonance form **261** (Equation 32) <2005EJM401>.



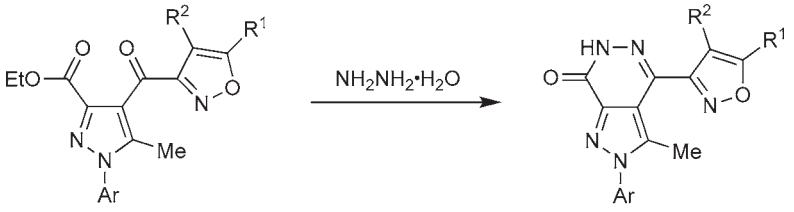
256 260 261 (32)

Similar results were reported on reacting *N*-aryl-substituted **256** with hydrazine. Reacting an aryl **256** derivative with hydroxylamine hydrochloride gives **262** (Equation 33) <2002JHC869>.



256 262 (33)

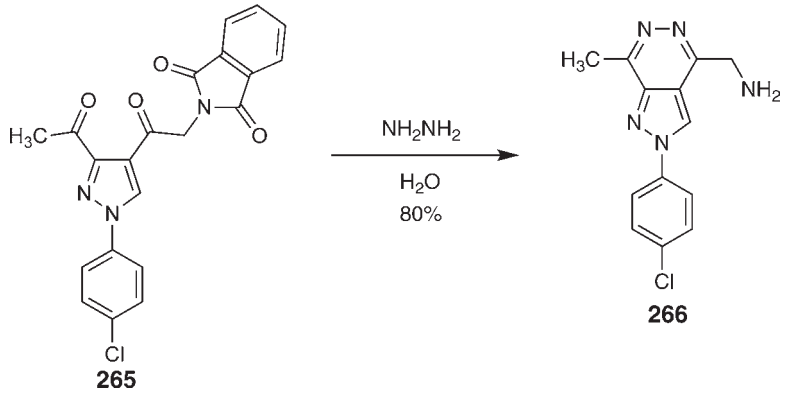
The isoxazoloylpyrazole ester **263** reacts with hydrazine hydrate to yield the pyrazolo[4,5-*d*]pyridazines **264** (Equation 34) <1997MI617>.



(34)

	R^1	R^2	*Yield* (%)	*Reference*
a	$COCH_3$	CH_3	74	1997MI617
b	$COCH_3$	Ph	67	1997MI617
c	COPh	Ph	71	1997MI617
d	CN	NH_2	62	1997MI617
e	SO_2Ph	Ph	61	1997MI617

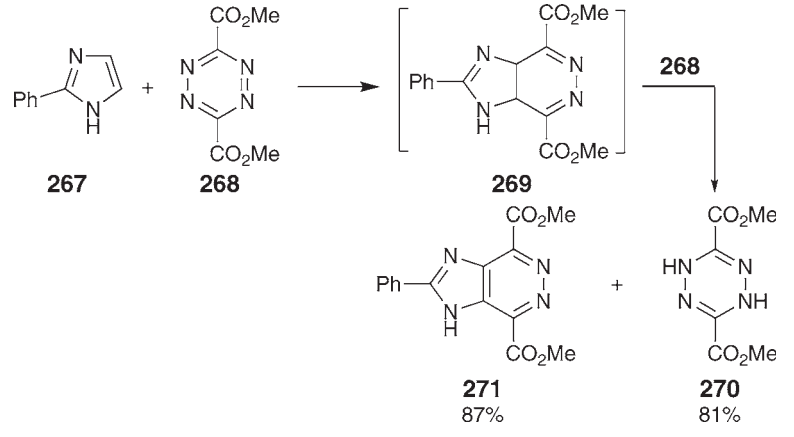
An interesting application of this synthetic methodology is the conversion of **265** into **266** upon reflux with hydrazine hydrate (Equation 35) <2004ZNB1132>.



(35)

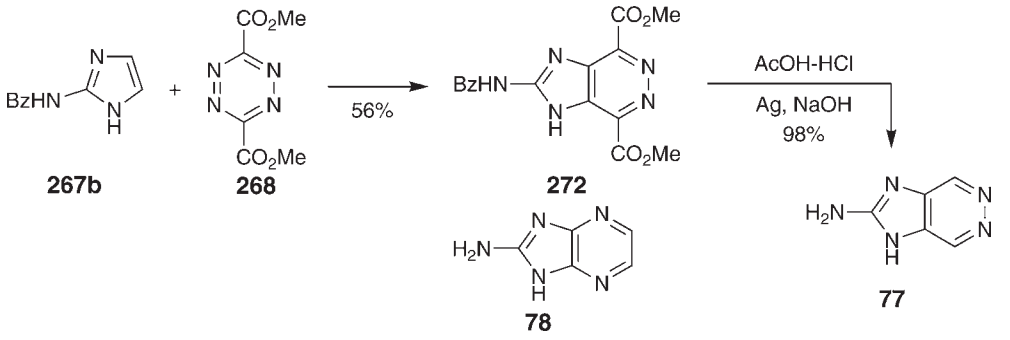
Several other azolopyridazine ring systems have been prepared by similar approaches <2002FA89, 2002JHC329, 2001MOL203, 2000MOL1187>. For example, 6-substituted imidazo[4,5-*d*]pyridazin-7-ones are obtained from the reaction of 1,2-disubstituted 4-aroylimidazole-5-carboxylates and hydrazines <2002JHC329>.

The inverse electron demand Diels–Alder [4+2]-cycloaddition of imidazoles to electron-poor dienes to yield imidazo[4,5-*d*]pyridazines, reported in CHEC-II(1996), has been further developed. It was reported that the reaction of **267** with tetrazines **268** was fruitless. However, **267** reacted with excess of **268** to yield aromatic **271** along with 1,4-dihydrotetrazine **270**. Most likely, **271** arose from dehydrogenation of first-formed **269** by an extra equivalent of **268** <2001T5497> (**Scheme 18**).



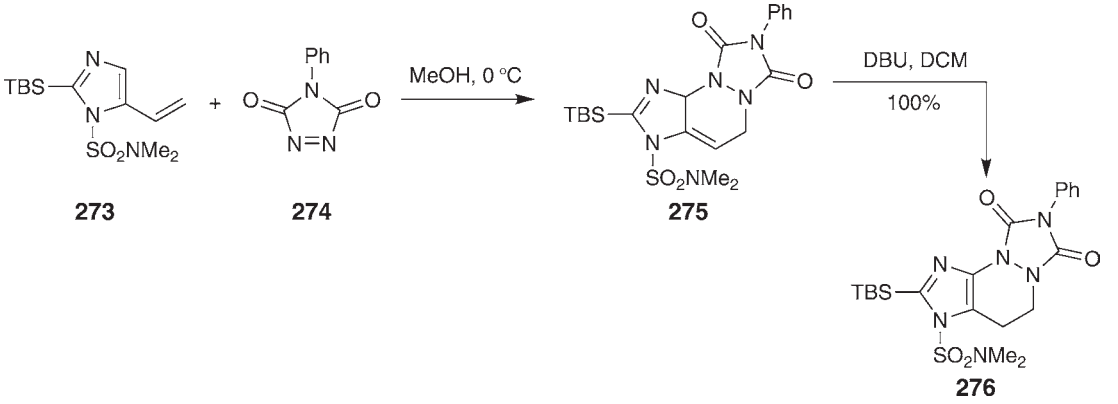
Scheme 18

Adopting this chemistry enabled synthesis of **77** from **267b** and **268**. Thus, reacting **267b** and **268** gave **272**, which was hydrolyzed and decarboxylated to give **77**. Structure **77** was believed to be the cytotoxic marine natural product zarzissine, but, as mentioned earlier, differences in the ^{1}H and ^{13}C NMR spectra of **77** and those reported for zarzissine led to structure **78** being proposed for the latter (**Scheme 19**) <2001T5497>.



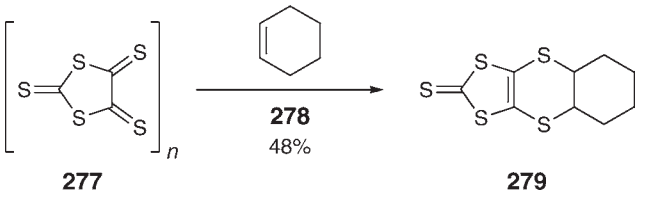
Scheme 19

The addition of 1-phenyl-3,5-triazolidendione **274** to vinylimidazole **273** afforded **275**, which can be converted into **276** (**Scheme 20**) <1998TL4561>.



Scheme 20

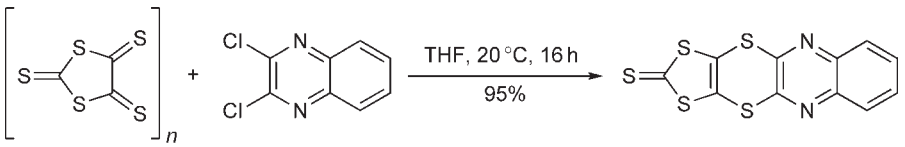
The principal reaction described above (i.e., the Diels–Alder cycloaddition) has been employed with great success to prepare 1,3-dithiolo[3,4-*b*]-1,4-dithiones. For example, reacting **277** with cyclohexene **278** affords **279** (Equation 36) <1991KGS1317>. The molecule is active toward both electron-poor and electron-rich dienophiles <1998RUP95252, 2003TL3127>.



(36)

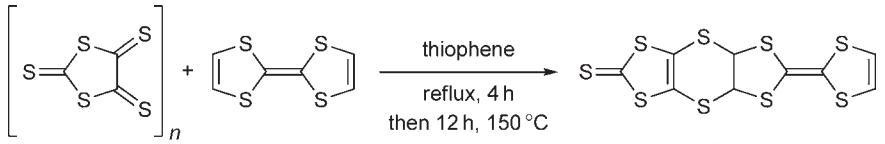
Monomeric 1,3-dithiole-2,4,5-trithione, generated *in situ* from **268** by thermal depolymerization, is believed to be the active species participating in these reactions. Generally, excess **268** is refluxed with the dienophile in aprotic solvent until the dienophile disappears.

A further example of the applicability of this approach is the reaction of **277** with **280** to yield **281** (Equation 37) <1990J(P1)2563>.



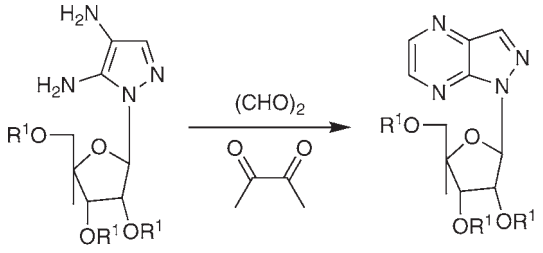
277 **280** **281** (37)

Another example is the reaction of **277** with tetrathiafulvene (TTF) **282** to yield **283** (Equation 38) <1992S1071>.



277 **282** **283** (38)

3,4-Pyrazoldiamines were reported in CHEC-II to react with hydroxy ketones to yield pyrazolo[3,4-*b*]pyrazines. Similar to this, pyrazolopyrazines **285** are obtained at room temperature from reaction of **284** with glyoxal (and butane-2,3-dione) in good yield (Equation 39) <2004TL4105>.

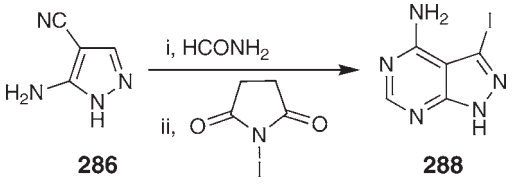


284 **285**

a: R^1 = H (76%)
b: R^1 = Me (71%)

(39)

Ready formation of pyrazolo[3,4-*d*]pyrimidines from reaction of 5-aminopyrazole-4-carboxylic acid derivatives is a well-established route to derivatives of this ring system. A recent application is the conversion of **286** into **288** by reaction with formamide and NIS **287** (Equation 40) <2002BML1687>.

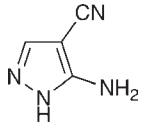


286 **287** **288**

84%

(40)

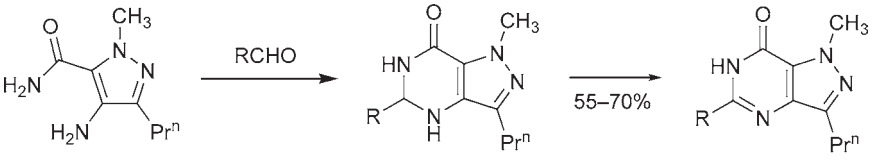
Several pyrazolo[3,4-*d*]pyrimidine derivatives were prepared via reaction of **289** with reagents that can furnish an N–C fragment, for example, urea, thiourea, and formamide <2002BML1687>.



289

10.12.8.1.3 From [5+1] atom fragments

This route is extensively utilized for biologically interesting pyrazolo[4,3-*d*]pyrimidines and pyrazolo[3,4-*d*]pyrimidines and to a lesser extent thiazolo and isothiazolopyrimidines, imidazooxazines, and isoxazolopyrimidines. Generally the 5-atom fragments are obtained from acylaminocarboxylic acid derivatives <1996CHEC-II(7)431>. This methodology is still widely used as both pyrazolo[4,3-*d*]pyrimidines and pyrazolo[3,4-*d*]pyrimidines are biologically interesting molecules. Thus, a facile one-pot synthesis of **291** from reaction of **290** with 4-(*N*,*N*-dimethylamino)benzaldehydes in acetic acid in the presence of *p*-toluenesulfonate at room temperature is reported to yield **291**, which is readily dehydrated into **292** upon reflux in acetic acid <2005JHC751>. Compound **292** was readily formed when an arylidene aniline was used instead of aromatic aldehydes; yields were dependent on the synthetic method used (**Scheme 21**).



290 **291** **292**

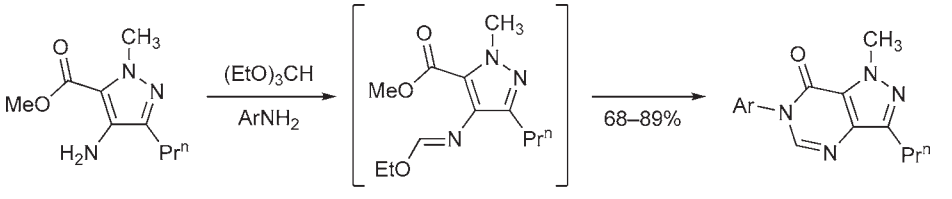
	R	*Yield* (%)	*Reference*
a	4-$Me_2NC_6H_4$	60	2005JHC751
b	4-$CH_3C_6H_4$	58	2005JHC751
c	4-$CH_3OC_6H_4$	61	2005JHC751
d	4-ClC_6H_4	75	2005JHC751

Scheme 21

Reaction of 5-amino-1-phenyl-1*H*-pyrazole-1-carboxamide with aromatic aldehydes in the presence of heteropolyacid $H_{14}[NaP_5W_{30}MoO_{10}]$ gave derivatives of 6-aryl-1-pyrazolo[3,4-*d*]pyrimidin-4-[5*H*]ones <2006MI1>.

A rapid and high yielding synthesis of pyrazolo[3,4-*d*]pyrimidinones by reaction of aromatic aldehydes with 4-amino-1-methyl-3-propyl-1*H*-pyrazole-5-carboxamide intermediates in the presence of copper chloride has recently been reported for the synthesis of Viagra analogues <2005H(65)1821>.

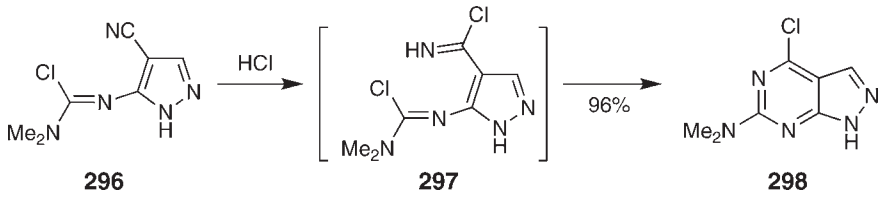
Reacting **293** with arylamines and triethyl orthoformate affords **295**. The iminoether **294** is a possible intermediate (Equation 41) <2004OPP92>.



293 **294** **295** (41)

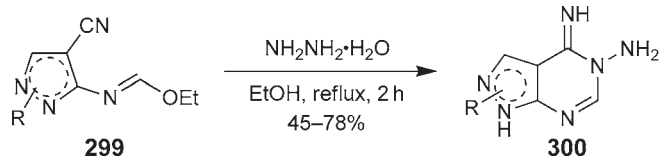
	Ar	*Yield* (%)	*Reference*
a	4$CH_3C_6H_4$	78	2004OPP92
b	C_6H_5	76	2004OPP92
c	3-$CH_3OC_6H_4$	74	2004OPP92
d	2-ClC_6H_4	68	2004OPP92

Treatment of **296** with hydrochloric acid in dichloromethane affords **298**. It is believed that **297** is an intermediate (Equation 42) <2001EJM321>.



296 **297** **298** (42)

Heating **299** with hydrazine hydrate in ethanol at reflux for 2 h affords **300** (Equation 43) <2004T5093>.

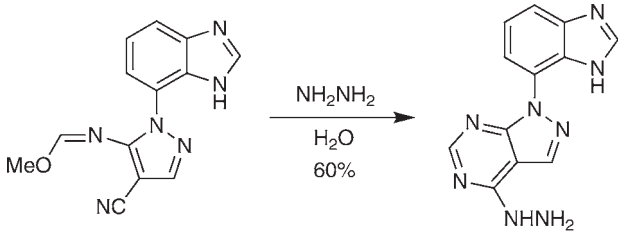


299 **300**

	R	*Yield (%)*	*Reference*
a	-NHPh	78	2004T5093
b	-NEtPh	66	2004T5093
c	-NMe2	45	2004T5093

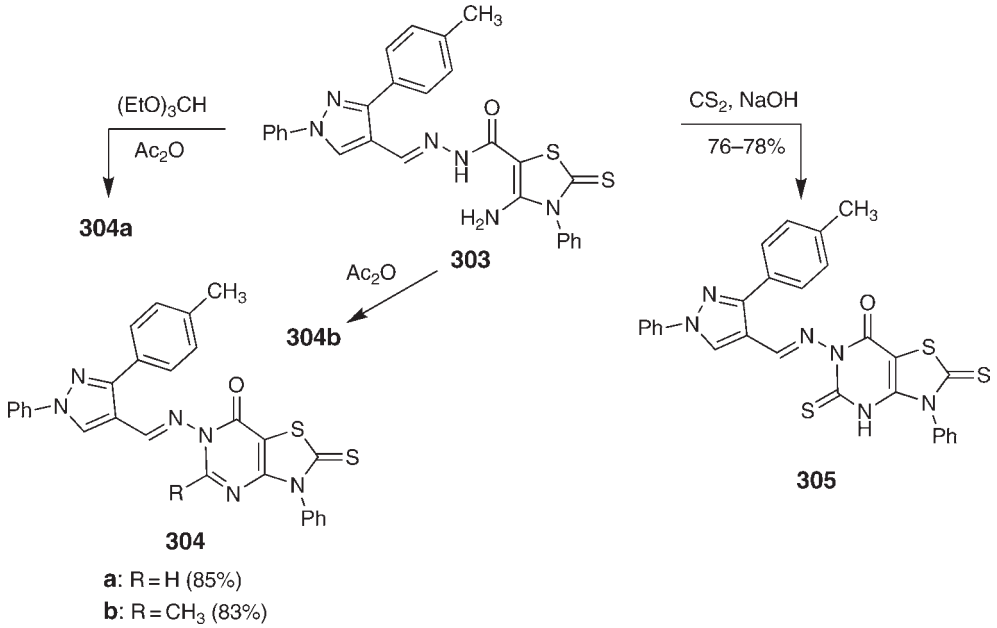
(43)

Similarly, reacting **301** with hydrazine in ethanol gives **302** (Equation 44) <2004BML2127>.



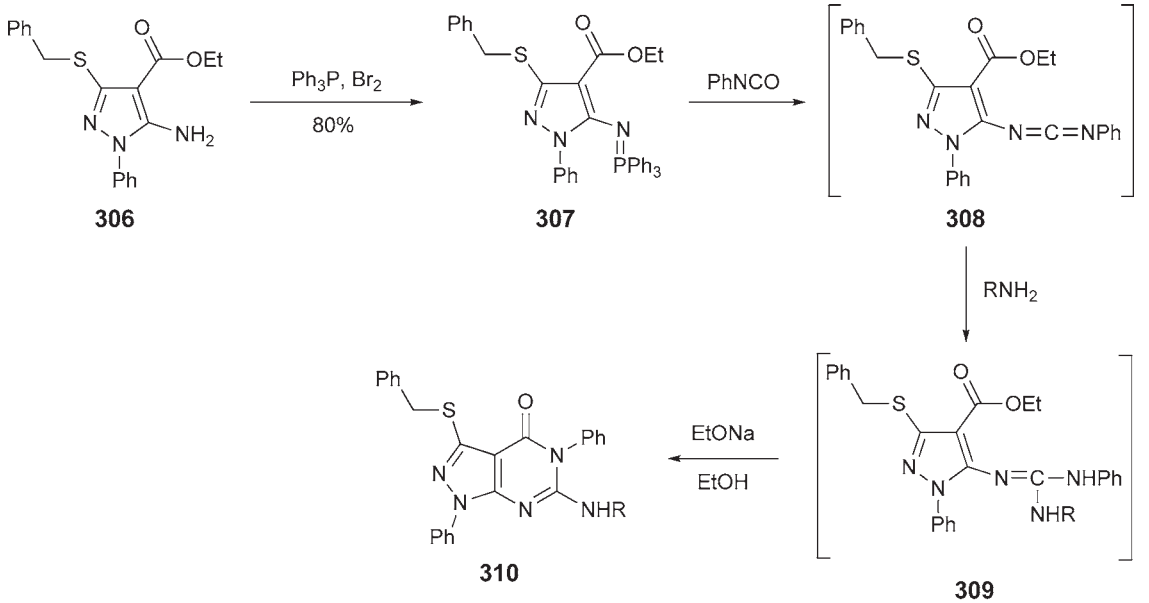
301 **302** (44)

The reaction of **303** with triethyl orthoformate in acetic anhydride gives **304a**. On refluxing **303** with acetic anhydride, **304b** is produced. Reaction of **303** with carbon disulfide in the presence of sodium hydroxide gives **305** (**Scheme 22**) <2003EJM27>. A series of thiazolo[4,5-*d*]pyrimidinethiones were prepared *via* cyclization of 4-amino-2-thioxo-3-thiazole-5-carboxylic acids <1999BML1185>.



Scheme 22

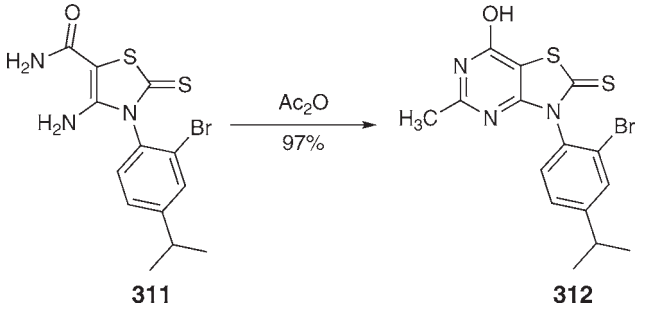
A series of pyrazolo[3,4-*d*]pyrimidines **310** were obtained *via* reacting carbodiimide **308** with amines. Carbodiimide **308** was obtained by reacting ester **306** with triphenylphosphine and bromine, and then reacting the so-formed **307** with phenyl isocyanate. The intermediacy of **309** is suggested (**Scheme 23**) <2004JHC393>.



	R	*Yield (%)*	*Reference*
a	*n*-Pr	86	2004JHC393
b	*i*-Pr	93	2004JHC393
c	*n*-Bu	66	2004JHC393
d	*i*-Bu	53	2004JHC393
e	2-$CH_3C_6H_4CH_2$	80	2004JHC393
f	4-$CH_3C_6H_4CH_2$	66	2004JHC393

Scheme 23

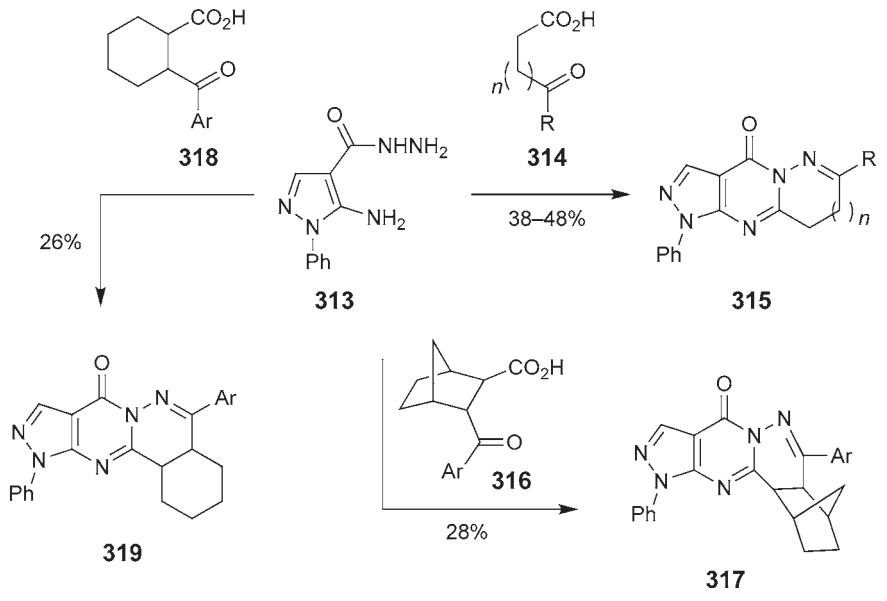
Refluxing **311** in acetic anhydride for 2.5 h afforded **312** (Equation 45) <1999BML1185>.



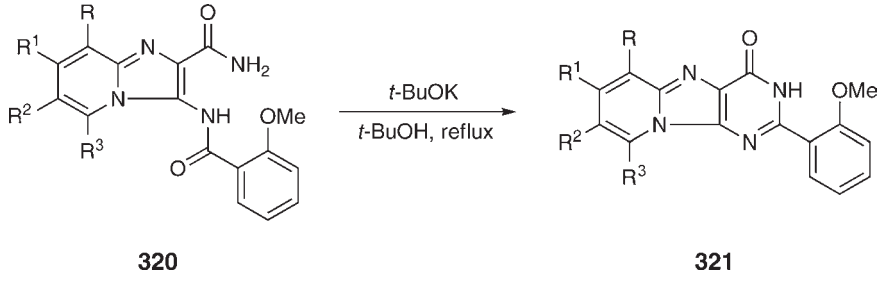
(45)

The tricyclic system **315** is formed in moderate yields from reaction of **313** with **314**. The reactions of **313** with **316** and **318** give **317** and **319**, respectively (**Scheme 24**) <2002JST41>.

The tricyclic system **321** is formed in good yield on heating **320** with potassium *t*-butoxide in *t*-butanol (Equation 46) <2005BMC2790>; yields for particular examples are not given.



Scheme 24



(46)

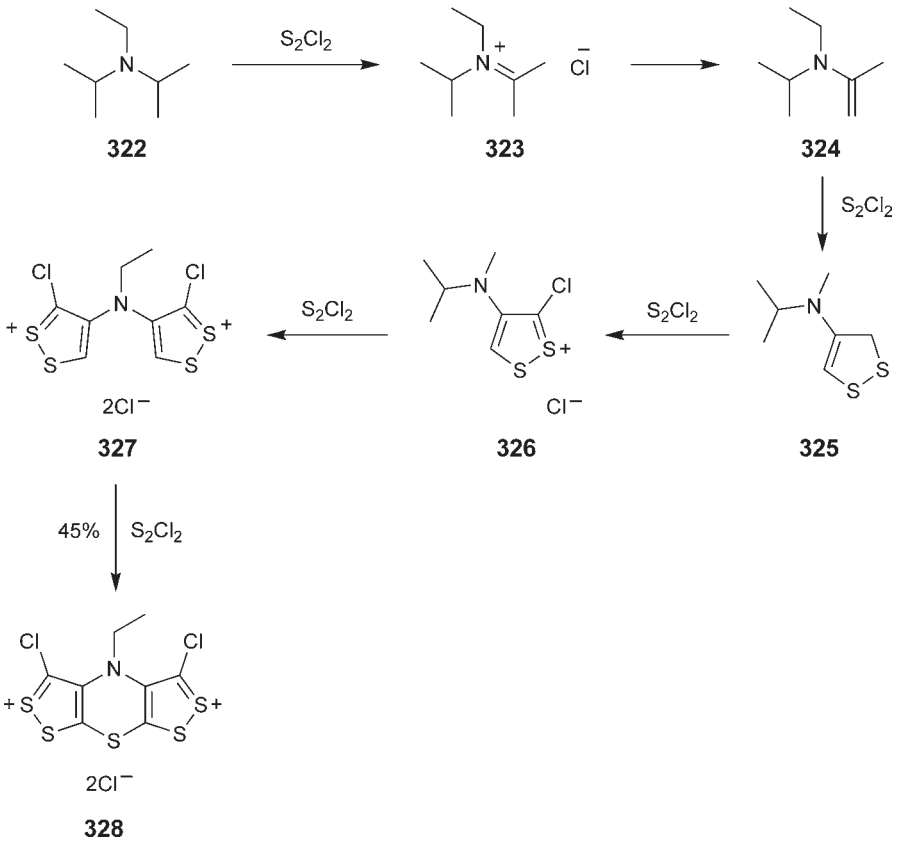
A new simple synthesis of bis[1,2]dithiolo[1,4]thiazines from Hünig's base has been described <1998JOC2189, 1997AG281>. It is proposed that the first step in this reaction is oxidation of Hünig's base **322** with S_2Cl_2 (or its more reactive DABCO complex) to give stable iminium ion **323**. Proton loss from **323** gives **324** that reacts with S_2Cl_2 to give **325**; the latter then affords **326** that is converted into **327**. Finally, with S_2Cl_2, compound **328** is produced (**Scheme 25**).

10.12.8.2 Synthesis of Six-Membered Rings by Formation of One Bond

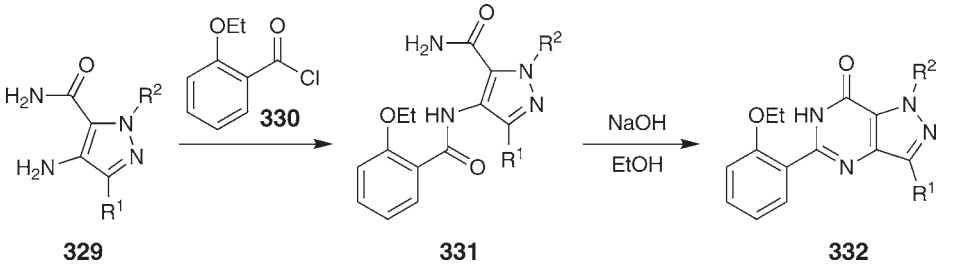
10.12.8.2.1 Bond formation α to a heteroatom

Cyclization of acylamino acids or aminoacyl acid amides into azoloazines has been discussed in CHEC-II <1996CHEC-II(7)431>. Several precursors to sildenafil derivatives are prepared in this way; for example, treatment of **329** with **330** gives **331**. This is readily cyclized by ethanolic sodium hydroxide into **332** <2005BML3900>. Other derivatives of **332** were obtained similarly (**Scheme 26**) <2001BML895, 2001BMC1609, 2005BML3900, 2006MI468>. Details for individual derivatives are not given.

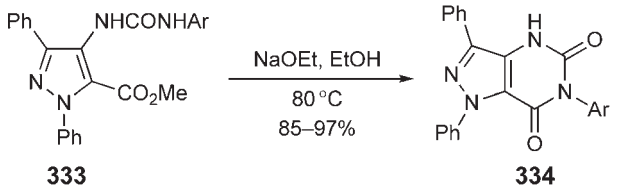
The pyrazole ester **333** is converted into **334** upon treatment with sodium ethoxide in ethanol at 80 °C (Equation 47) <2000JHC1247>.



Scheme 25



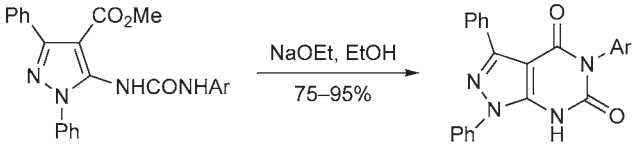
Scheme 26



	Ar	*Yield* (%)	*Reference*
a	C_6H_5	85	2000JHC1247
b	2-$CH_3C_6H_4$	87	2000JHC1247
c	3-EtC_6H_4	93	2000JHC1247
d	3-ClC_6H_4	97	2000JHC1247
e	4-$CH_3OC_6H_4$	95	2000JHC1247
f		85	2000JHC1247

(47)

Isomeric compounds **335** are similarly converted into **336** (Equation 48) <2000JHC1247, 2003PS1413>.

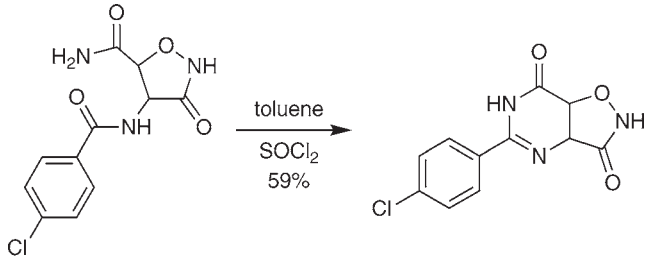


335 **336**

	Ar	Yield (%)	Reference
a	C_6H_5	89	2000JHC1247
b	2-$CH_3C_6H_4$	92	2000JHC1247
c	3-EtC_6H_4	92	2000JHC1247
d	3-ClC_6H_4	95	2000JHC1247
e		85	2000JHC1247

(48)

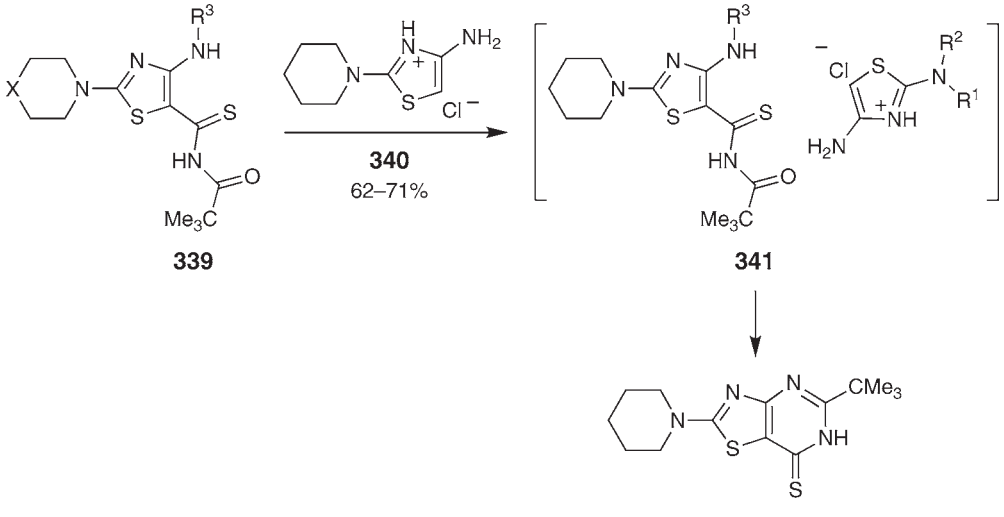
Similarly, the hexahydroisoxazolopyrimidine derivative **338** is prepared via heating **337** in toluene at reflux for 8 h in the presence of thionyl chloride (Equation 49) <2004BMC265>.



337 **338**

(49)

Thiazolo[4,5-*d*]pyrimidines **342** are obtained *via* cyclizing **339** by the action of **340**. The intermediacy of **341** is postulated (Equation 50) <2003HCA1949>.



339 **341** **342**

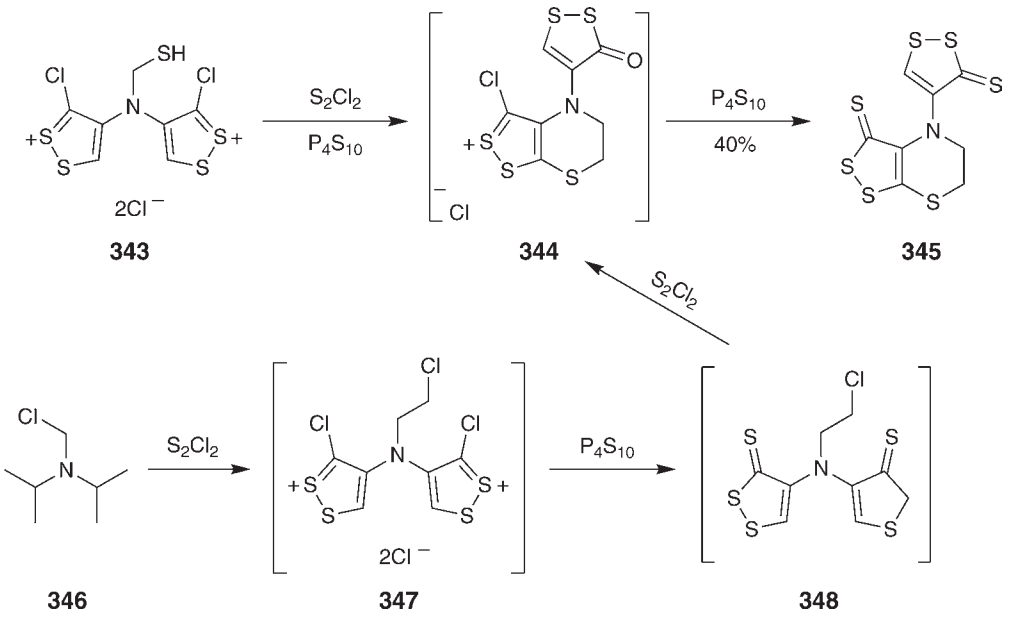
(50)

Reacting **343** with S_2Cl_2 and P_4S_{10} affords **344** which upon treatment with P_4S_{10} affords **345**. Compound **344** is also formed via converting **346** into **347** by the action of S_2Cl_2 and treating the latter product with P_4S_{10} to yield **348** that is converted into **344** by S_2Cl_2, (yield is not given) (**Scheme 27**). The complete reaction scheme is probably quite complex and other pathways can be envisioned <1999JOC5010>.

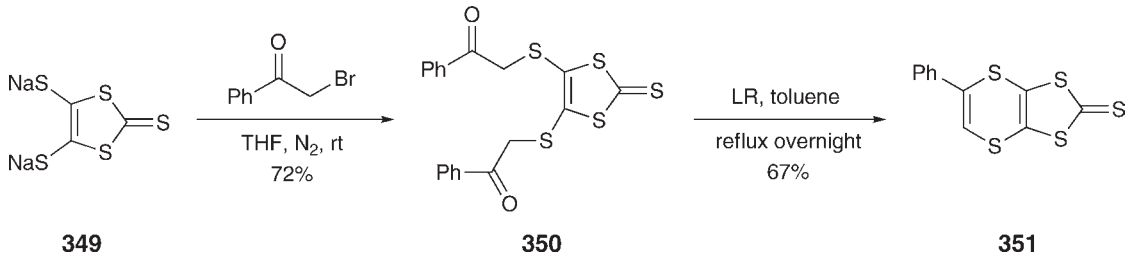
10.12.8.2.2 Bond formation γ to a heteroatom

Reaction of disodium dithiolate salt **349** with phenacyl bromide affords **350**. Treatment of the latter with Lawesson's reagent (LR) gives **351** (**Scheme 28**) <1996TL2821>.

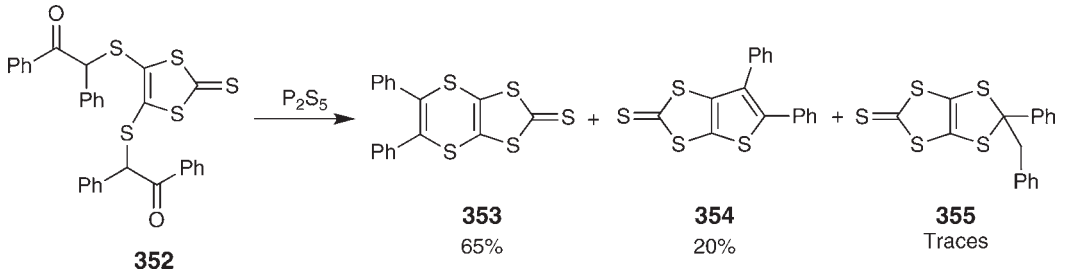
Similarly, **352** cyclized into **353** on heating with P_2S_5 at reflux in toluene in the dark for 3 h; thiophene **354** and a trace of **355** were also isolated (Equation 51) <2000CC2039>.



Scheme 27



Scheme 28



(51)

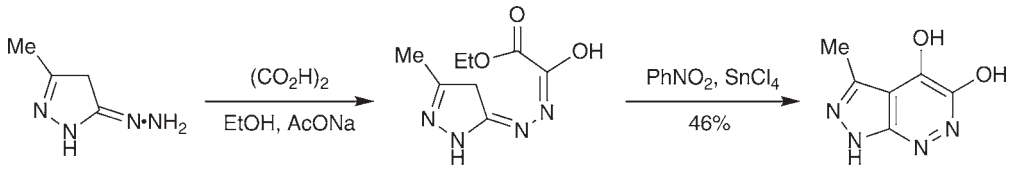
It has been reported that **357**, prepared via condensing **356** with oxalic acid (no yield was given), cyclizes into pyrazolo[3,4-*c*]pyrimidinone **358** on reflux in nitrobenzene in the presence of stannic chloride (**Scheme 29**) <2001BMC715>.

10.12.8.3 Synthesis of Five-Membered Rings by Formation of Two Bonds

10.12.8.3.1 From [4+1] atom fragments

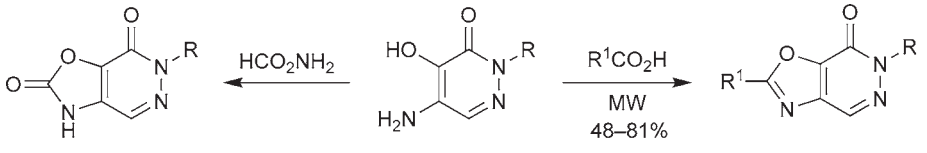
Azines with two adjacent heteroatomic substituents readily cyclize into azoloazines using a variety of reagents <1996CHEC-II(7)431>. A convenient and versatile synthetic approach to substituted 1,3-oxazolo[4,5-*d*]pyridazinones was developed utilizing **359** as starting material. Thus, condensing **359** with organic acids under microwave

irradiation gives **360**, while reaction of **359a** and **359b** with ammonium formate gives **361a** and **361b** (**Scheme 30**) <2004TL4693>.



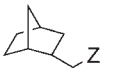
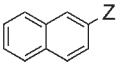
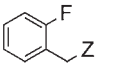
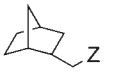
356 **357** **358**

Scheme 29



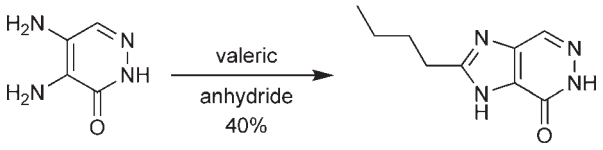
361 **359** **360**

a: R = H (42%)
b: R = Ph (93%)

	R	R^1	Yield (%)	Reference
a	H		75	2004TL4693
b	H		81	2004TL4693
c	H		63	2004TL4693
d	$-CH_2CO_2Et$		48	2004TL4693

Scheme 30

Similarly, reacting **362** with valeric anhydride gives **363** in good yield (Equation 52) <1993BML1019>.

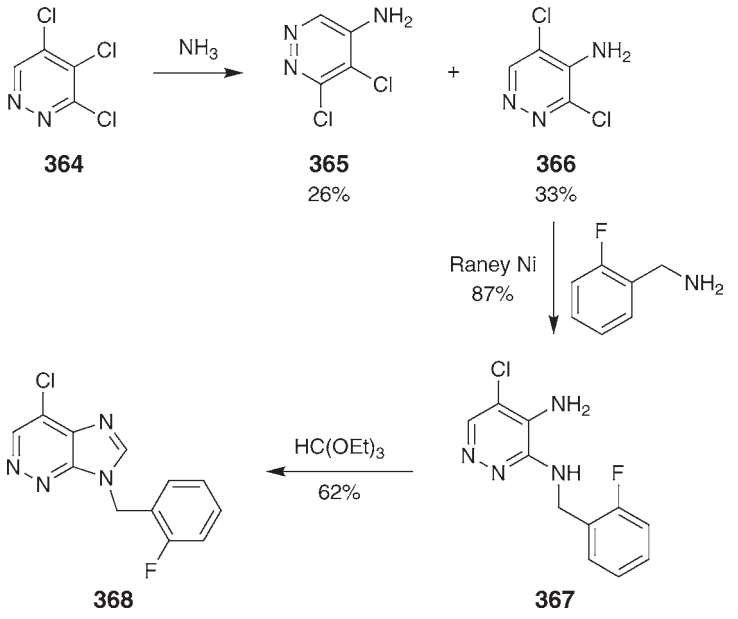


362 **363**

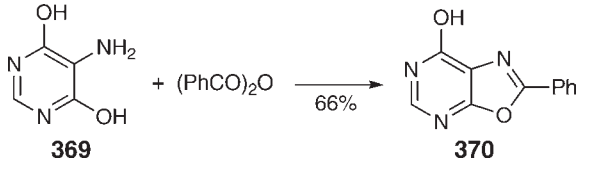
(52)

Treatment of **364** with ammonia gives **365** and **366**. Compound **366** reacted with 2-fluorobenzylamine to yield **367** that reacted with triethyl orthoformate yielding **368** (**Scheme 31**) <1995JHC1423>.

Treatment of **369** with benzoic anhydride affords **370** in high yield (Equation 53) <2004BML1997>.



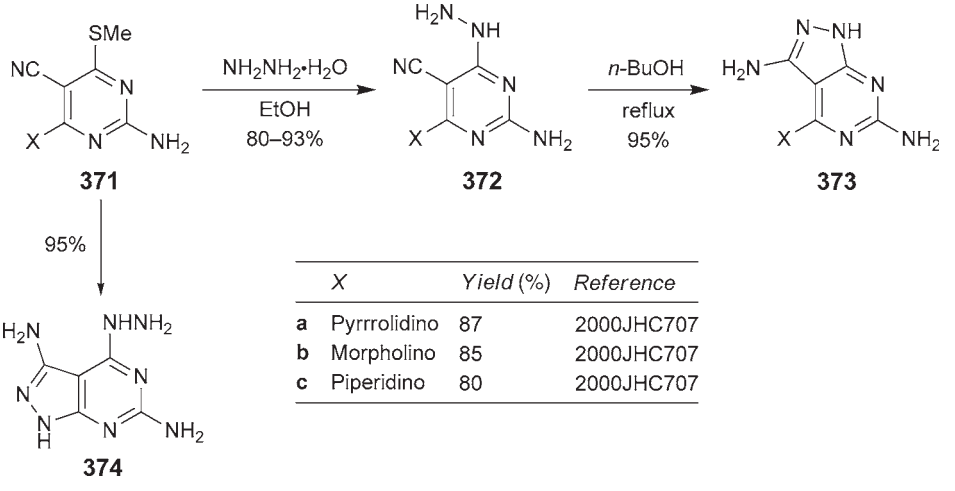
Scheme 31



(53)

10.12.8.3.2 From [3+2] atom fragments

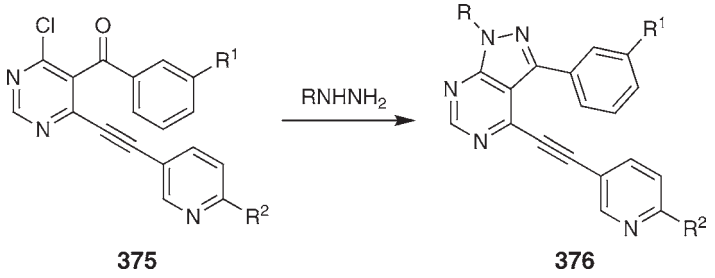
The pyrimidine **371** reacts with hydrazine hydrate in refluxing ethanol to yield **372**. This cyclized to **373** on reflux in *n*-butanol. Compound **374** was formed directly upon treatment of **371** with excess hydrazine hydrate (**Scheme 32**) <2000JHC707>.



	X	Yield (%)	Reference
a	Pyrrrolidino	87	2000JHC707
b	Morpholino	85	2000JHC707
c	Piperidino	80	2000JHC707

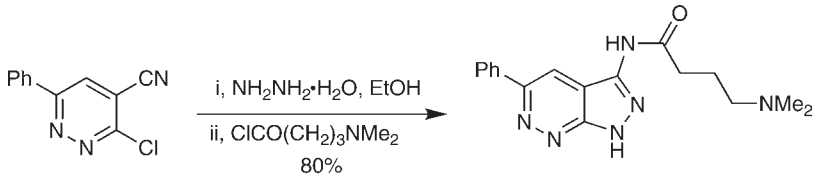
Scheme 32

Treatment of **375** with hydrazine hydrate in dichloromethane gives **376** (Equation 54) <2004BML4165>. Yields for compounds **376** were not given.



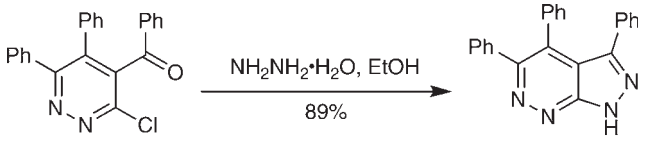
375 **376** (54)

The pyrazolopyridazine **378** is obtained via treatment of **377** with hydrazine hydrate and $ClCO(CH_2)_3NMe_2$ (Equation 55) <2003BML1581>.



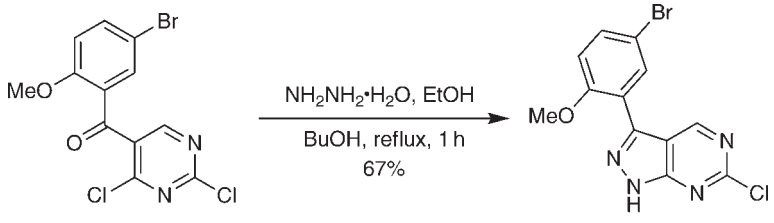
377 **378** (55)

Quite similar is the reported conversion of **379** into **380** upon reflux in EtOH with hydrazine hydrate (Equation 56) <2003PS199>.



379 **380** (56)

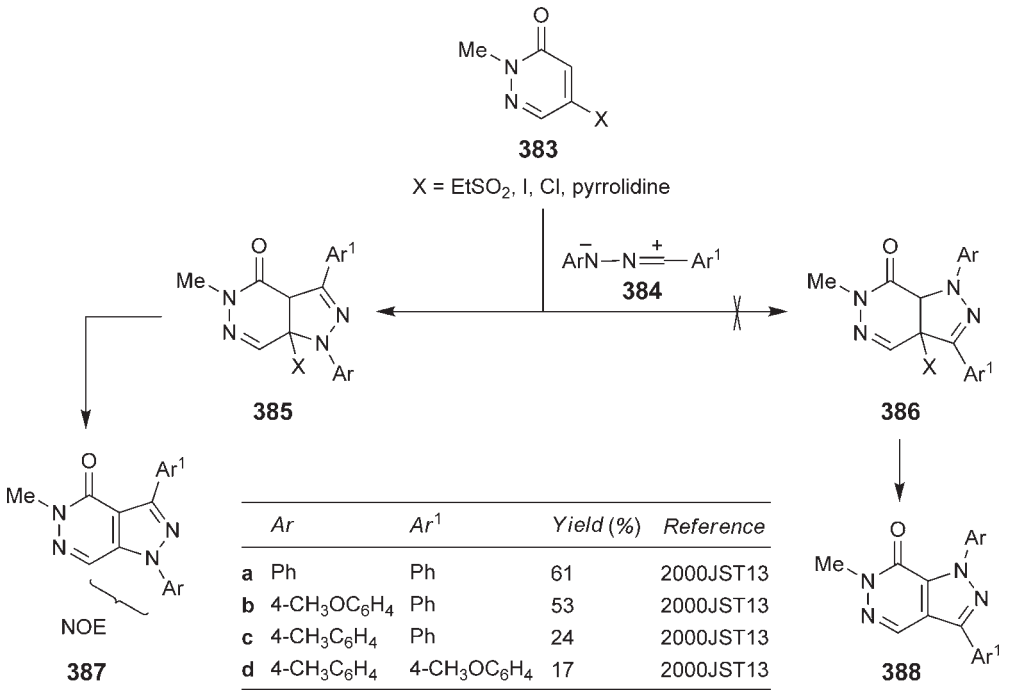
Similarly, aroylpyrazines are converted into pyrazolopyrazines. For example, reacting **381** with 2 equiv of hydrazine hydrate in refluxing methanol gives **382** (Equation 57) <2006BML262>.



381 **382** (57)

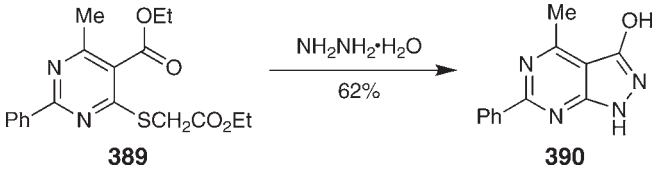
The reaction of the 5-substituted-2-methyl-3(2-*H*)pyridazinone **383** with nitrile imine **384** generated *in situ* from the corresponding hydrazonoyl halide has been shown to afford **387** rather than **388**. The formation of **387** is believed to proceed via the intermediacy of **385** (**Scheme 33**) <2000JST13>.

The reaction of **389** with hydrazine hydrate resulted in replacement of the thioether moiety by hydrazine and formation of **390** (Equation 58) <2002PS2745>.



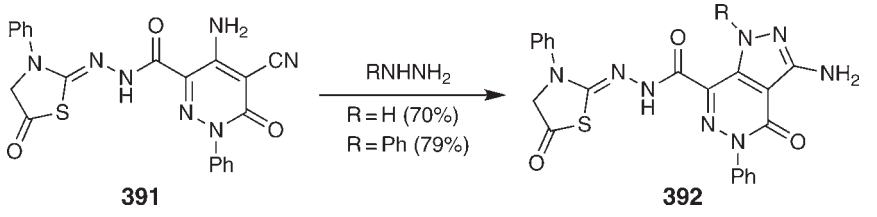
	Ar	Ar1	Yield (%)	Reference
a	Ph	Ph	61	2000JST13
b	4-$CH_3OC_6H_4$	Ph	53	2000JST13
c	4-$CH_3C_6H_4$	Ph	24	2000JST13
d	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	17	2000JST13

Scheme 33



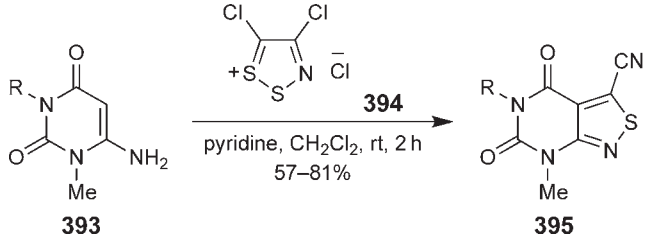
(58)

Treatment of **391** with hydrazine affords **392** (Equation 59) <2002HAC258>.



(59)

A novel synthesis of isothiazolo[3,4-*d*]pyrimidines **395** in high yields *via* reaction of **393** with **394** in dichloromethane in the presence of pyridine at room temperature has been reported (Equation 60) <2003OL507>.

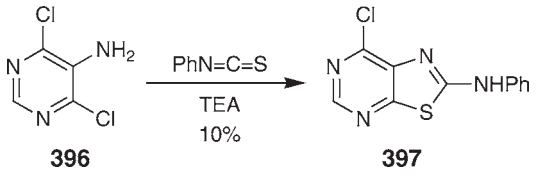


	R	Yield (%)	Reference
a	Me	80	2003OL507
b	Et	74	2003OL507
c	*i*-Pr	81	2003OL507
d	*n*-Bu	57	2003OL507

(60)

The reaction of 4,6-dichloro-5-aminopyrimidine **396** with phenyl isothiocyanate in the presence of triethylamine afforded directly 7-substituted aminothiazolo[5,4-*d*]pyrimidines **397** in a modest yield (Equation 61). Better yields

were obtained by using Cs_2CO_3; the yield improvement is believed to result from the so-called 'cesia effect' <2005JOC10194>.

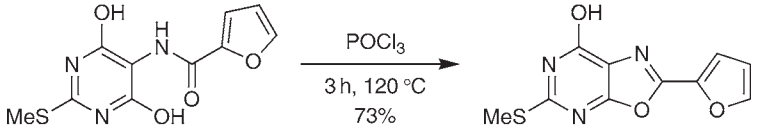


396 397 (61)

10.12.8.4 Synthesis of Five-Membered Rings by Formation of One Bond

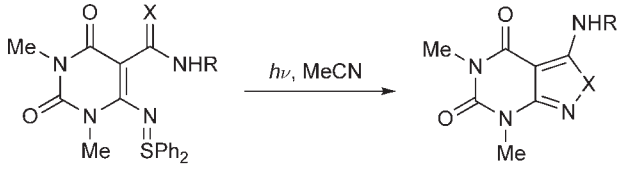
10.12.8.4.1 Bond formation α to a heteroatom

Treatment of **398** with phosphorus oxychloride affords **399** (Equation 62) <2006EJM7>.



398 399 (62)

The amides **400a** are cyclized into aminoisoxazolopyrimidines **401** when thioamides **400b** are heated; the aminoisothiazolopyrimidines **401b** are formed (Equation 63) <2002T10073>.

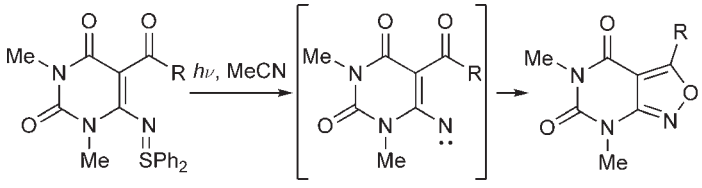


400 401

	X	R	Yield (%)	Reference
a	O	Ph	12	2002T10073
b	S	Me	59	2002T10073
c	S	Benzyl	52	2002T10073
d	S	Ph	76	2002T10073

(63)

Similar photolysis of **402** affords isoxazoles **404**. The nitrene **403** is assumed as an intermediate, and yields varied depending on the nature of R (Equation 64) <2002T10073>.



402 403 404

	R	Yield (%)	Reference
a	H	91	2002T10073
b	Me	88	2002T10073
c	*cyclo*-Pr	54	2002T10073
d	Ph	78	2002T10073

(64)

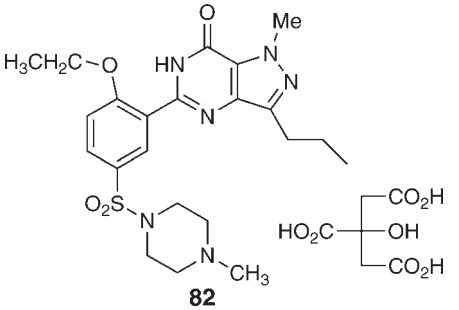
10.12.9 Important Compounds and Applications

10.12.9.1 Viagra Synthesis and biological activity

1-(3-(6,7-Dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenylsulfonyl)-4-methylpiperazine **81** (sildenafil) is used to treat male erectile dysfunction. Male erectile dysfunction is a common and important medical problem <1994MI151>. According to a random community-based sample study, over half of the males at 40–70 years of age suffer from erectile dysfunction <1994MI151>. Compound **81** is a potent and selective phosphodiesterase type 5 (PDE-5) inhibitor <2005JCH118>. In addition to the original synthesis, a synthesis from reaction of 2-ethoxy-5-methylpiperazin-1-ylsulfonylbenzaldehyde with 4-amino-3-propylpyrazolo-5-carboxamide has been patented.

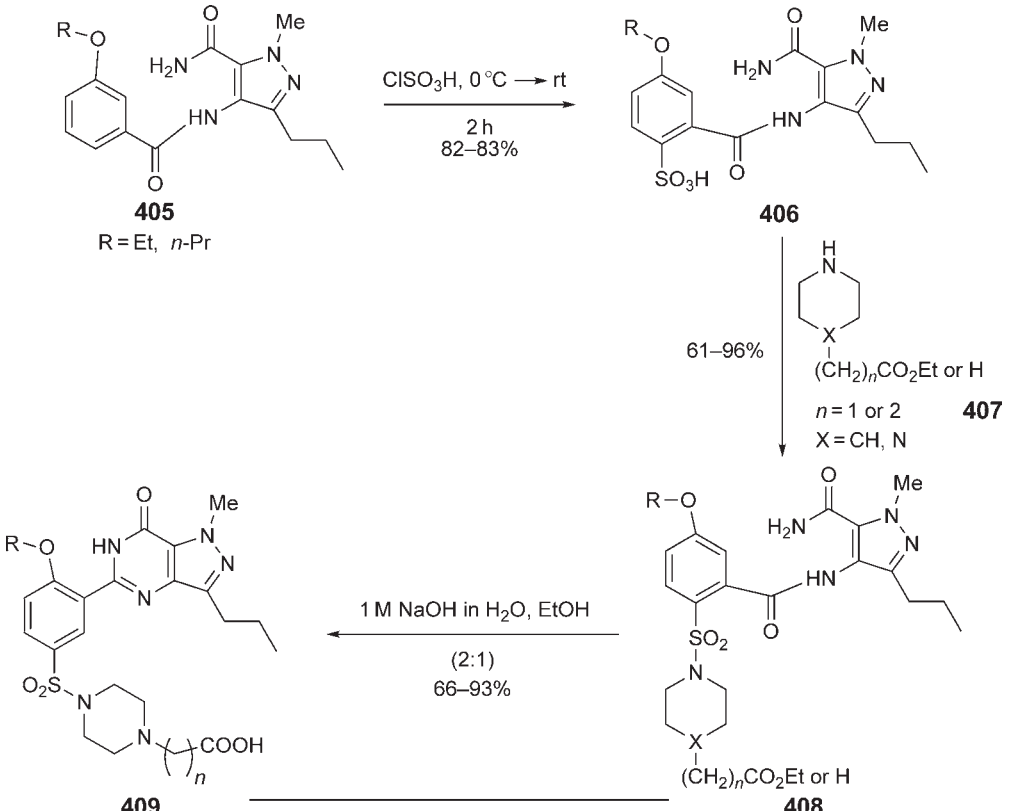
Since its approval by the FAD on 27 March 1998, it has been widely utilized and is available in 25, 50, and 100 mg tablets. Many techniques have been used to determine sildenafil citrate in pharmaceutical samples <2002TAL757, 2000JLC1377, 2003MI2897, 2001MI483>. A liquid chromatographic method to determine sildenafil in rat serum

with a basic mobile phase has recently been described <2006MI952>, and there are many methods to trace sildenafil in dietary supplements as well as in the tablets to cope with doping <2006MI840>.



82

The behavior of **82** on electro-oxidation on a glassy carbon electrode between pH 2 and pH 8 was investigated. Measurement of the peak current enables rapid determination of sildenafil <2004ANA227>. There are some notable drawbacks associated with use of Viagra. Clinically significant adverse effects such as headache (16%), dyspepsia (7%), and visual disturbances (3%) have been reported and their incidence is dose dependent <2001BMC3013>. In the light of this, several authors have reported the synthesis of compounds structurally related to Viagra with the hope of eliminating as far as possible undesirable side effects <2001BMC3013>. Thus, sulfonating **405** with chlorosulfonic acid affords **406**. The latter condensed with **407** to yield **408**. Cyclization of **408** with sodium hydroxide gave **409**, which is claimed to be more potent in inhibiting PDE-5 (**Scheme 34**) <2001BMC3013>.

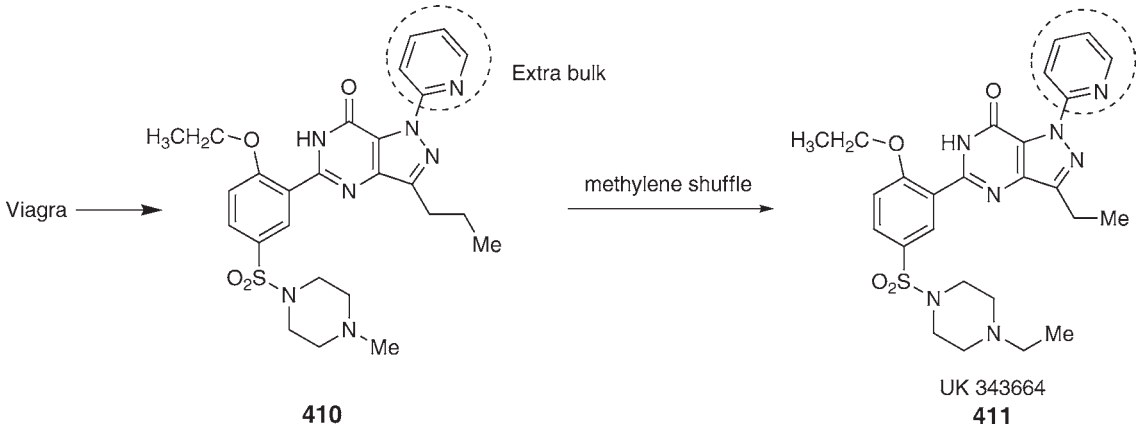


	R	X	n	Yield (%)	Reference
a	Et	CH	0	68	2001BMC3013
b	Et	CH	1	84	2001BMC3013
c	Et	CH	2	93	2001BMC3013
d	Et	CH	3	91	2001BMC3013
e	Et	N	1	83	2001BMC3013

Scheme 34

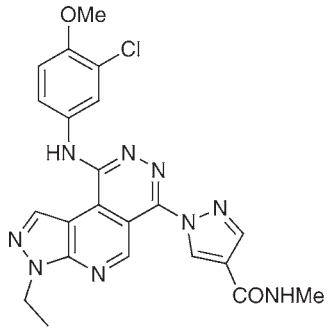
'Methylene shuffles' have been used to modify the hydrophobicity of sildenafil. It was found that adding extra bulk on the right-hand side of the molecule, as in **410**, increased the selectivity of the drug for its target. However, this also made the drug too lipophilic. Therefore, a methylene shuffle was carried out such that the propyl and methyl groups were altered to two ethyl groups. UK343664 **411** was subjected to clinical trials (**Scheme 35**) <B-2001MI1>.

Novel pyrazolopyridopyridazine derivatives **412–415** were synthesized and are suggested to be more potent and selective PDE-5 inhibitors than sildenafil <2001BML2461, 2003BMC457>.

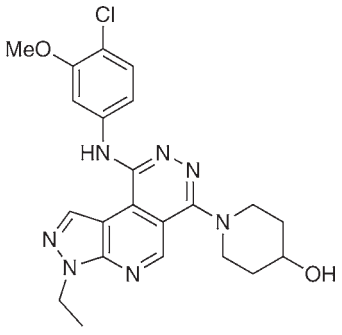


410 **411**

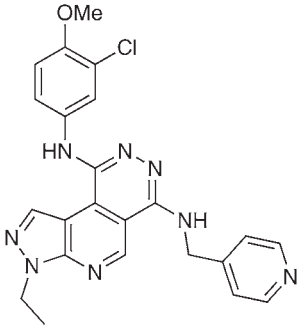
Scheme 35



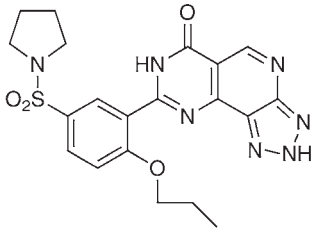
412



413



414



415

Some compounds having quite similar pyrazolo[4,3-*d*]pyrimidine structures have been claimed in the patent literature to be potent phosphodiesterase inhibitors. Some are claimed to act also upon female sexual dysfunctions.

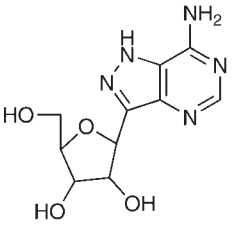
10.12.9.2 ALP: Further Developments

1*H*-4,5-Dihydropyrazolo[3,4-*d*]pyrimidine is a well-known compound used as a pharmaceutical and marketed under the name allopurinol or Zyloric. It is still one of the drugs of choice for the treatment of gout and arthritis despite some reported side effects. The chemistry of ALP and its synthesis have been dealt with in CHEC-II(1996) <1996CHEC-II(7)431>. This drug still attracts attention from both theoretical and pharmaceutical viewpoints. Analytical methods for the determination of allopurinol and its active metabolites have been described earlier. Tautomerism of ALP has also been described. It seems that ALP will find new applications <2005MI407>. There is growing evidence that ALP therapy in heart failure confers significant benefits with regard to performance and vacuolar function. As the safety of ALP is already established in patients with gout, it seems attractive to investigate these claims further. It has been indicated that ALP is ineffective in reduction of oxidative stress in diabetic patents <2004MI546>.

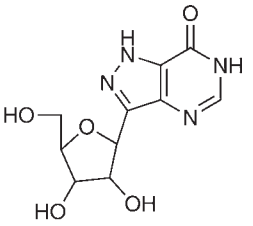
ALP, an inhibitor of the xanthine oxidase enzyme, is reported to provide protection against free radical-mediated damage by various mechanisms, including free radical scavenging and metal chelation, that is, Cu(II). To obtain a wider insight into the molecular aspects of the beneficial action, ALP and the Cu(II)–ALP system were investigated by radiochemical and spectroscopic studies. The results suggest that ALP may inhibit oxidative damage both through the direct conversion of radicals, such as ·OH, into less-reactive transient species, and the capture of copper ions, which play a relevant role in the metal-catalyzed generation of reactive oxygen species, and may prove beneficial for cell protection <2003MI533>.

10.12.9.3 Formycin A and B

Formycin A **62** and B **416** are two naturally occurring nucleosides possessing significant antitumor activity. The chemistry of both antibiotics has been discussed earlier in CHEC-II(1996) <1996CHEC-II(7)431>. The ionization constant of FA **61** was found to be 4.4 for protonation at N-3 and 9.6 for deprotonation at N-7. Formycin B **416** has a pK_a of 8.8 corresponding to deprotonation at N-1 and of 10.4 corresponding to deprotonation at N-7. A third ionization constant for formycin B was found to be 1.3 corresponding to protonation at N-3 <1997T6903>.



61

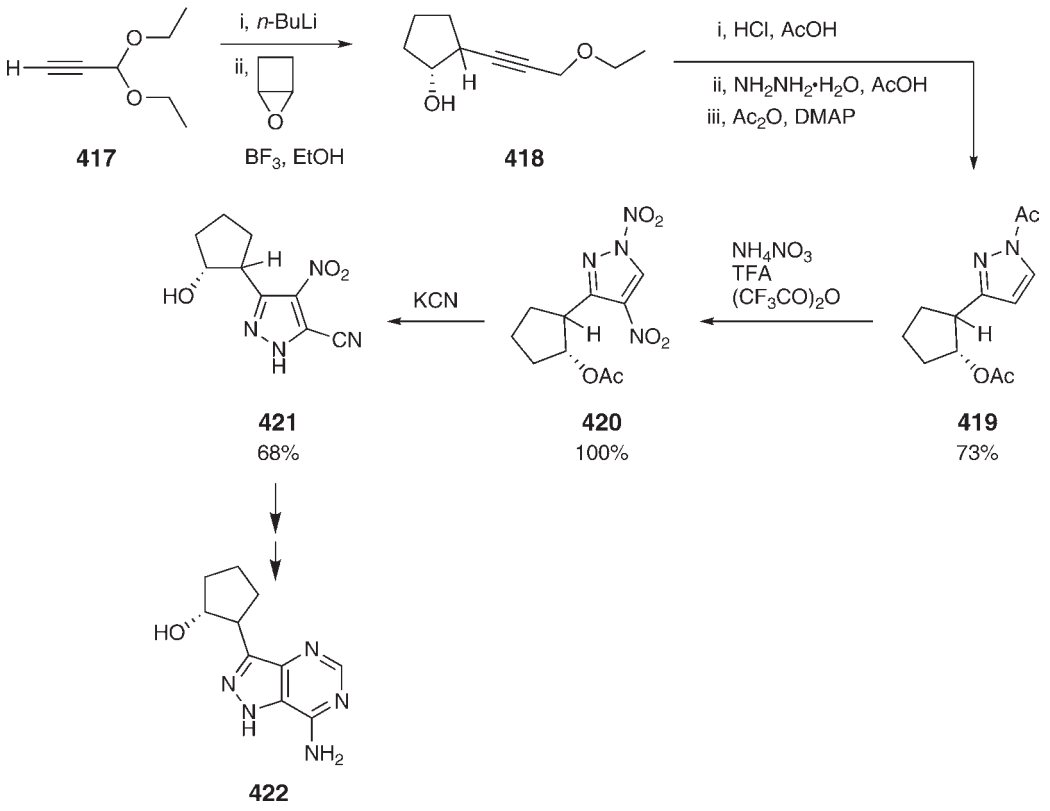


416

Steady-state and time-resolved emission spectroscopy was used to study the interaction of *E. coli* PNP with its specific inhibitors formycin B, FA, and *N*-1-methylformycin A. Complexation was found to induce tautomeric shifts <2000BBA1467>. Carbocyclic analogues of formycin A and B have been recently synthesized <2004T8233>. The synthesis utilized **417** as starting material which was converted into **418** *via* a multistage synthesis. The latter could be converted into the formycin analogue (**Scheme 36**) <2004TL8233>.

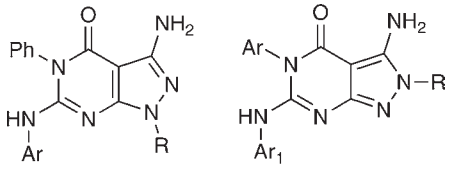
10.12.9.4 Other Compounds with Promising Biological Activities

Plenty of biological activities have been attributed to derivatives of ring systems **1**–**50** in the patent and published literature. New substituted pyrazolo[4,3-*d*]pyrimidines have been synthesized and claimed to be useful for treatment of male erectile dysfunction due to the inhibitory action they exerted on phosphodiesterase enzymes <1998EPP995750, 2000USP6066722>. Diverse biological activities have been attributed to pyrazolo[3,4-*d*]pyrimidines



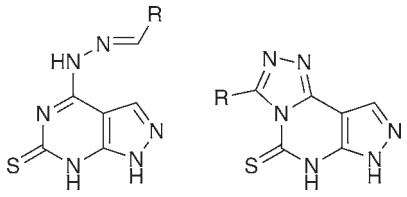
Scheme 36

<2002WO0276990>. Thus, compounds **423** and **424** have been claimed to exhibit significant analgesic activity superior to that of aspirin, free radical-scavenging activity, as well as carcinogenic potential <1999IJB1075>.



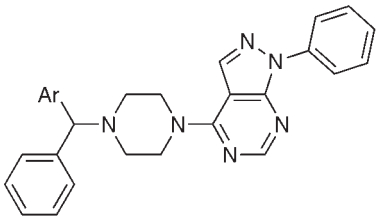
423 **424**

The pyrazolo[3,4-*d*]pyrimidines **425** and **426** are claimed to be useful as pharmaceuticals for treatment of hyperuricemia and prevention of gout.

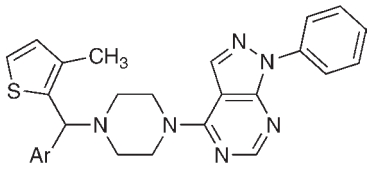


425 **426**

Pyrazolo[3,4-*d*]pyrimidines **427** and **428** were synthesized and their antiviral activity was evaluated in a plaque reduction assay. It is very interesting that this class of compounds provide remarkable evidence that they are very specific for human enteroviruses, in particular coxsackie viruses <2004BML2519>.

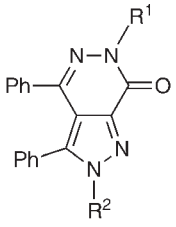


427



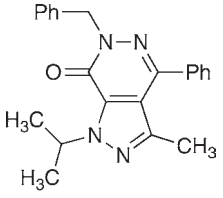
428

The pyrazolo[3,4-*d*]pyridazines **429** were reported to be potent tyrosine kinase inhibitors. Several pyrazolo[3,4-*d*]-pyridazines derivatives were tested for antimicrobial activity against Gram-positive bacteria and fungi; the compounds **429a** and **429b** had the highest antibacterial activity with minimum inhibitory concentrations in the range 0.31–0.0024 mg ml^{-1} <2005EJM401>.



429a: $R^1 = C_6H_3Cl_2(2,5)$; R^2 = pyridine
429b: $R^1 = C_6H_2Cl_3(2,4,6)$; $R^2 = CH_3$

A series of pyrazolo[3,4-*d*]pyridazinones **430** and analogues, potentially useful as peripheral vasodilators, were synthesized and evaluated as inhibitors of PDE5 extracted from human platelets. Several of them showed IC_{50} values in the range 0.14–1.4 μM. A good activity and selectivity profile versus PDE6 was found for compound **430** (6-benzyl-3-methyl-1-isopropyl-4-phenylpyrazolo[3,4-*d*]pyridazin-7(6*H*)-one). Structure–activity relationship studies demonstrated the essential role played by the benzyl group at position 6 of the pyrazolopyridazine system. Other types of pyridazinones fused with five- and six-membered heterocycles (pyrrole, isoxazole, pyridine, and dihydropyridine), as well as some open-chain models were prepared and evaluated. Besides the pyrazole, the best of the fused systems proved to be isoxazole and pyridine <2002MI227>.



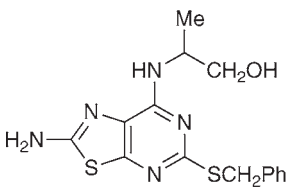
430

Aminothiazolo[5,4-*d*]pyrimidine **431** is claimed to be a modulator of chemokine receptor activity. The compound is claimed to be useful for treatment of chemokine-mediated diseases such as psoriasis <2001WO0158960>.

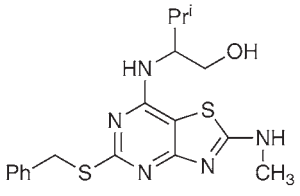
A thiazolo[4,5-*d*]pyrimidine **432** is claimed to act as CX3CR1 receptor antagonist <2002WO0276990>.

Compound **433** exemplifies novel analogues of known pyrazolopyrimidine template-based srokinase enzyme inhibitors that incorporate bone-targeting group modifications designed to provide tissue (bone) selectivity and

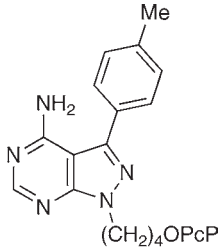
diminished side effects <2003BML3063>. A series of 1-aryl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl-arylhydrazones were discovered as novel inhibitors of glucogen synthesis kinase 3 (GSK3) <2004BML2121>.



431

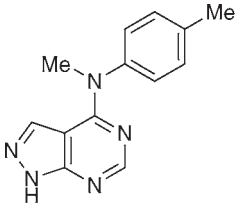


432

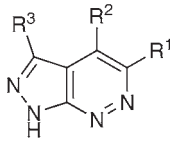


433

Pyrazolodiazines of general formula **434** and **435** were reported to be useful for the treatment of diabetes <2003MIP292257r>.

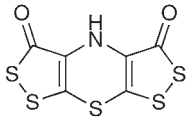


434

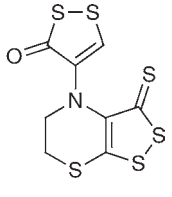


435

Compounds **436** and **437** have been tested by the National Cancer Institute (NCI) at Bethesda in a disease-oriented *in vitro* anticancer screening program against 60 human tumor cell lines, showing moderate activity <2004JOC3672>.



436

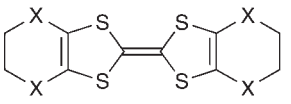


437

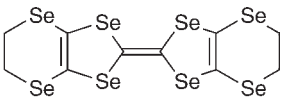
10.12.9.5 Organic Metals: Conducting Organic Solids

The discovery of metallic conductivity in organic solids stands as a major scientific discovery of the twentieth century <1995S215>. From a total of several organic π-donors described in the literature, five (**438a–c**, **439**, and **440**) are four-heteroatom bicyclic 5:6 systems with two heteroatoms in each moiety.

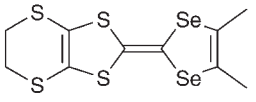
Such ring systems are obtained either *via* a [4+2]-cycloaddition of electron-poor olefins or acetylene to **441**, or alkylation followed by cyclization. These syntheses are described in their appropriate place in the text. As nonaromatics, ring opening occurs readily as well as several substitution reactions. The chemistry of these derivatives is the major sector of Section 10.12.6 (dealing with the chemistry of nonaromatic rings) <1996TL2821>. The synthesis, electrochemical properties, and molecular structures of new organic conductors have been described <1989ZOR658, 2003TL1623>.



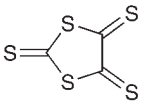
438a: X = O
438b: X = S
438c: X = Se



439

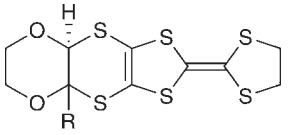


440



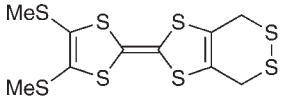
441

Compound **442** (commonly termed DoDHT), which possesses only one 1,3-dithiolylidene unit as a π-electron system, has been investigated.

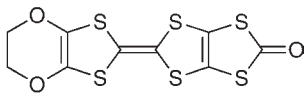


442

The AsF_6^- and PF_6^- salts of DoDHT are isostructural and exhibit a superconducting transition under 16.5 kbar <2003SM193>. The crystal structures of $(DoDHT)_2AsF_6$ and $(DoDHT)_2BF_4 \cdot H_2O$ were investigated both at room and low temperatures. In the AsF_6^- salt, the lattice constant of the *b*-axis is minimized around 25 K, while other constants contract on decreasing temperature. In the BF_4^- salt, thermal movement of the anion is observed at room temperature, but stops at low temperature. The relationship between the change in the crystal structure of the salts and their electrical behavior has been discussed <2003SM1199>. Organic conductors from other ring systems and their salts have been prepared and their structures as well as potential as organic conductors and as superconductors were investigated <2002SM129, 2002MI608, 2003SM899>. Radical cation salts of, for example, **443** and **444** were prepared.

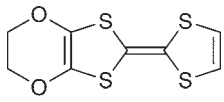


443



444

Ethylene dioxytetrathiafalvulene (EDO) **445** PF_6^- salt shows a first-order metal insulator transition at around 280 K <2003SM643>. The subject is expanding, and plenty of other reports on such compounds have been made <2003SM377, 2003BCJ89, 2003SM899, 2003SM365>.

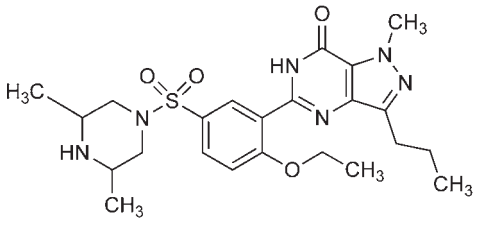


EDO
445

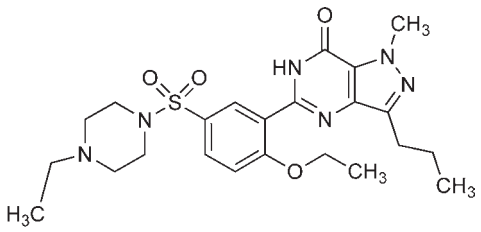
10.12.10 Further Developments

Chemistry and pharmaceutical activities of pyrazolo[4,3-*d*]pyrimidines, pyrazolo[3,4-*d*]pyrimidines and to a lesser extent thiazolopyrimidines have in the last two years been actively investigated. Two new sildenafil analogues namely aildenafil (methiosildenafil as named in the by USA) **446** and homosildenafil **447** has been identified in China <2007MI231>, USA <2007MI1615>, and in Taiwan <2006MI19>. As sildenafil analogues are still illegally

added to dietary supplements marketed for erectile dysfunction, several new analytical methods have been developed to identify these derivatives including liquid chromatography, tandem mass spectrometry, and 2D NMR <2007MI231, 2007MI1615, 2006MI19>. X-ray powder diffraction method for fast screening of sildenafil tablets has been recently developed <2007MI1514>.

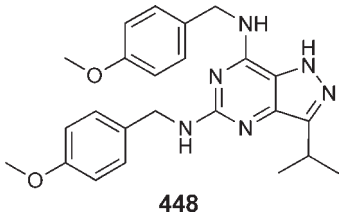


446



447

High performance liquid chromatography (HPLC) coupled with electrochemical detection was developed for simultaneous determination of sildenafil and its metabolites, *N*-Demethyl sildenafil <2007MI613> guest–host interactions of sildenafil have been investigated using phase solubility diagrams (PSD), differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), ^{1}H NMR, and molecular mechanical modeling (MM^+) <2007MI857>. The hydrophobic character of sildenafil was found to provide 39% of the driving force for complex stability <2007MI857>. New promising biological activities of pyrazolo[4,3-*d*]pyrimidines have been reported <2007MI857, 2006EJM1405, 2006BMCL5176>. Surprisingly compound **448** may be used as the lead for developing a novel class of antiproliferative agents <2006EJM1405>.



448

A new route to 1-aryl-4-aminopyrazole-5-carboxylic acid derivatives via reacting arylhydrazononitriles with halocarboxylic acid derivatives has recently been reported. The pyrazoles so obtained were used for synthesis of arylazolo[4,3-*d*]-pyrimidines, some of which proved inhibitors of coagulation factor Xa <2006BMCL3755, 2007MI1467>.

Heteropolyacids $H_{14}[NaP_5W_{29}MoO_{110}]$ and $H_3PMO_{12}O_4$ have been shown to be efficient catalysts for consecutive condensation of aldehydes with 5-aminopyrazole-4-carboxamide and cyclization into pyrazolo[3,4-*d*]pyrimidines <2007MI1467>. The reaction of ethyl 5-acylaminopyrazoles with hexachloroethane and triphenylphosphine in the presence of a base has been recently reported to afford an imidoyl chloride that reacted *in situ* with ethylamine yielding an amidine in 71% yield that cyclized readily in DMF in the presence of potassium carbonate to yield pyrazolopyrimidines in 65% yield <2007TL3983>.

Ethyl 5-aminopyrazole-4-carboxylates are converted into pyrazolo[3,4-*d*]pyrimidines via condensation with Ph_3P/Br_2; subsequent reaction with an arylazocyanate and further reacting two carbodiimide with amines. Yields ranged from 13 to 65% dependant on the substituent <2006MI1584, 2007BMCL2203>. A similar approach was used for synthesis of triazolo[4,5-*d*]pyrimidine-7(6)ones from ethyl 4-aminothiazolo-5-carboxylates <2007MIxx>.

References

1973JHC431 M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Heterocycl. Chem.*, 1973, **10**, 431.
1974JOC511 S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, 1974, **39**, 511.
1987CL1317 H. Nakano, T. Nakamito, T. Nogami, and Y. Shirota, *Chem. Lett.*, 1987, 1317.
1988BCJ2973 H. Nakano, T. Nogami, and Y. Shirota, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2973.
1989ZOR658 O. Y. Neilands, Y. Y. Katsens, and Y. N. Kreitzberga, *Zh. Org. Khim.*, 1989, **85**, 658.
1990J(P1)2563 K. S. Varma, S. Edge, A. E. Underhill, J. Becher, and G. J. Bojesen, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2563.
1991KGS1317 R. S. Medne, Y. Y. Katsens, I. L. Krapsha, and O. Y. Neilands, *Khim. Geterotsikl. Soedin.*, 1991, 1317.
1992S1071 V. Y. Khodorkovsky, J. Y. Becker, and J. Bernstein, *Synthesis*, 1992, 1071.

1993BML1019 K. H. Gibson, R. Wood, A. A. Oldhan, and J. S. Major, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1019.
1994MI151 H. A. Feldman, I. Goldstein, D. G. Hatzichristou, R. J. Krane, and J. B. McKinlay, *J. Urol.*, 1994, **54**, 151.
1994MI1455 N. Bouaicha, P. Amade, D. Puel, and C. Roussakis, *Nat. Prod.*, 1994, **57**, 1455.
1994S809 N. Sventrup, K. M. Rasmussen, T. K. Hansen, and J. Becher, *Synthesis*, 1994, 809.
1995JHC1423 J. L. Kelley, J. B. Thompson, U. L. Styles, F. E. Soroko, and B. R. Cooper, *J. Heterocycl. Chem.*, 1995, **32**, 1423.
1995S215 N. Svenstrap and J. Becher, *Synthesis*, 1995, 215.
1996BMC1725 J. C. Bussolari, J. D. Stoeckler, and R. P. Panzica, *Bioorg. Med. Chem.*, 1996, **4**, 1725.
1996CHEC-II(7)431 M. H. Elnagdi, N. Al-Awadi, and A. W. Erian; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 431.
1996JOC3987 Y.-I. Yamada, S. Satoki, S. Mishima, N. Akashi, K. Takhishi, N. Musuda, Y. Nishimoto, S. Takasaki, and H. Azai, *J. Org. Chem.*, 1996, **61**, 3987.
1996JOC5964 B. Hernadez, F. J. Luque, and M. Orozco, *J. Org. Chem.*, 1996, **61**, 5964.
1996SAA1547 M. K. Shukla and P. C. Mishra, *Spectrochim. Acta, Part A*, 1996, **52**, 1547.
1996TL2821 T. Ozturk, *Tetrahedron Lett.*, 1996, **37**, 2821.
1996TL7603 D. Y. Noh, H. J. Lee, J. Hong, and A. E. Underhill, *Tetrahedron Lett.*, 1996, **37**, 7603.
1997AG281 C. F. Marcose, C. Polo, T. Torroba, and C. W. Rees, *Angew. Chem.*, 1997, **36**, 281.
1997MI617 H. F. Zohdi, T. A. Osman, and A. O. Abdelhamid, *J. Chin. Chem. Soc.*, 1997, **44**, 617.
1997OPPI285 F. Al-Omran, N. Al-Awadi, A. a. El-Khair, and M. H. Elnagdi, *Org. Prep. Proced. Int.*, 1997, 285.
1997T6903 I. Luyten, C. Thibaudeau, and J. Chattopadhyaya, *Tetrahedron*, 1997, **53**, 6903.
1998BMC925 F. Montesaneo, D. Barlocco, V. DalPiaz, A. Leonerdi, E. Poggesi, F. Fanelli, and P. De Bendedetti, *Bioorg. Med. Chem.*, 1998, **6**, 926.
1998EPP995750 A. Wood, *Eur. Pat.* 995750 (1998) (*Chem. Abstr.*, 2000, **132**, 293774).
1998JMB153 G. Koellner, M. Luic, D. Shugar, W. Saenger, and A. Bzowska, *J. Mol. Biol.*, 1998, **280**, 153.
1998JOC2189 C. W. Rees, A. J. P. White, D. J. Williams, O. A. Rakitin, C. F. Marcos, C. Polo, and T. Torroba, *J. Org. Chem.*, 1998, **63**, 2189.
1998JOC3952 J.-I. Yamada, S. Tanaka, J. Segawa, M. Hamasaki, K. Hagiya, H. Anzai, H. Nishikawa, I. Ikemoto, and K. Kikuchi, *J. Org. Chem.*, 1998, **63**, 3952.
1998J(P2)1839 P. Barraclough, D. Firmin, R. Lyer, W. R. King, J. C. Lindon, M. S. Nobbs, S. Smith, C. J. Wharton, and J. M. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1839.
1998RUP95252 O. Y. Neilands, Y. Y. Katsens, and Ya. N. Kreitsberga, *Russ. Pat.* Su 1428753 (1998) *Chem. Abstr.*, **110**, 95252
1998S207 F. Seela and G. Becher, *Synthesis*, 1998, 207.
1998TL4561 P. Y. F. Deghati, M. J. Wanner, and G. Koomen, *Tetrahedron Lett.*, 1998, **39**, 4561.
1999BML1185 J. P. Beek, M. A. Curry, R. O. Chorvat, L. W. Fitzgerald, P. J. Cilligen, R. Zaczet, and G. L. Trainol, *Bioorg. Med. Chem. Lett*, 1999, **9**, 1185.
1999IJB1075 C. J. Shishoo, T. Ravikumar, Kstain, I. S. Rathod, T. P. Gandhi, and M. C. Satia, *Indian J. Chem., Sect. B*, 1999, 1075.
1999JCH383 G. Misztal, B. Paw, J. S. Skierski, and E. Jangiello-Wojtowicz, *J. Chromatogr., Part B*, 1999, **731**, 383.
1999JHC321 K. Makino, H. S. Kim, and Y. Kurusawa, *J. Heterocycl. Chem.*, 1999, **36**, 321.
1999JOC5010 C. W. Rees, A. J. P. White, and D. J. Williams, *J. Org. Chem.*, 1999, **64**, 5010.
1999TL2139 O. Sugimoto, M. Sudo, and K. Tanji, *Tetrahedron Lett.*, 1999, **40**, 2139.
2000BBA1467 B. Kierdaszak, A. Modrak-Wojcik, J. Wierzchowski, and D. Shugar, *Biochim. Biophys. Acta*, 2000, **109**, 1467.
2000CC1117 O. J. Dautel, J. Larson, and M. Fourmigue, *J. Chem. Soc., Chem. Commun.*, 2000, 1117.
2000CC2039 E. Ertas and T. Dzturk, *J. Chem. Soc., Chem. Commun.*, 2000, 2039.
2000JHC707 M. T. Cocco, C. Congiu, and V. Onnis, *J. Heterocycl. Chem.*, 2002, **37**, 707.
2000JHC1247 M. El-Haddad, M. Soakri, S. Lazar, A. Bennamara, G. Guillaumet, and M. Akssira, *J. Heterocycl. Chem.*, 2000, **37**, 1247.
2000JLC1377 A. Segall, M. Vitale, V. Perez, M. Palacios, and M. Pizzono, *J. Liq. Chromatogr.*, 2000, **23**, 1377.
2000JST13 G. Krajsovszky, A. Gaal, N. Haider, and P. Matyus, *J. Mol. Struct.*, 2000, **528**, 13.
2000MOL1187 H.-M. Chen and R. S. Hosmane, *Molecules*, 2000, **5**, 1187.
2000USP6066722 R. H. Furneaux, P. C. Tyler, and V. L. Schramm, *US Pat.* 6066722 (2000) (*Chem. Abstr.*, 2000, **132**, 334726).
2001ANA121 X. Sun, W. Cao, X. Bai, X. Yang, and E. Wang, *Anal. Chimi. Acta*, 2001, **442**, 121.
2001BMC1609 D.-K. Kim, N. Lee, J. Y. Lee, D. H. Ryu, J.-S. Kim, S.-H. Lee, J.-Y. Choi, K. Chang, Y.-W. Kim, G.-J. Im, *et al.*, *Bioorg. Med. Chem.*, 2001, **9**, 1609.
2001BMC715 A. K. Tewari and A. Mishra, *Biorg. Med. Chem.*, 2001, **9**, 715.
2001BMC3013 D.-K. Kim, J. Y. Lee, N. Lee, D. Hyun Ryu, J.-S. Kim, S. Lee, J.-Y. Choi, J.-H. Ryu, N.-H. Kim, G.-J. Im, *et al.*, *Bioorg. Med. Chem.*, 2001, **9**, 3013.
2001BML895 D. Kim, D. H. Ryu, N. Lee, J. Y. Lee, J. S. Kim, S. Lee, J. Y. Choi, J. H. Ryu, N. H. Kim, G. J. Im, *et al.*, *Bioorg. Med. Chem. Lett.*, 2001, **9**, 1895.
2001BML2461 Y. Bi, P. Stoy, L. Adam, B. He, J. Krupinski, D. Notmandin, R. Pongrac, L. Seliger, A. Watson, and J. E. Macor, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2461.
2001EJM321 J. M. Quintela, C. Peinador, M. J. Moreira, A. Alfonso, L. M. Botana, and Riguera, *Eur. J. Med. Chem.*, 2001, **36**, 321.
2001JMT243 M. E. Costas and R. Acevedo-Chavez, *J. Mol. Struct. Theochem*, 2001, **543**, 243.
B-2001MI1 G. L. Patrick, 'An Introduction to Medicinal Chemistry', 2nd edn., Oxford University Press, Oxford, 2001.
2001MI383 V. Krishnakumar and M. Arivazhagen, *Asian J. Chem.*, 2001, **13**, 383.
2001MI483 N. Daraghmch, M. Al-Omari, A. Badwan, and A. Jaber, *J. Pharm. Biomed. Anal.*, 2001, **35**, 483.
2001MI15 L. Burnhan, D. Dollimole, and K. Alexander, *Thermochim. Acta*, 2001, **367–368**, 15.
2001MI1 A. Gibson, *Eur. J. Pharma.*, 2001, **411**, 1.
2001MM2232 P. J. Skabura, I. M. Serebrqov, I. F. Perepichlca, N. Sariciftci, H. Neugebauer, and A. Cravion, *Macromolecules*, 2001, **34**, 2232.
2001MOL203 H.-M. Chen and R. S. Hosmane, *Molecules*, 2001, **6**, 203.
2001NN229 H. Wamhoff, A. Bamberg, and P. Sohar, *Nucleosides & Nucleotides*, 2001, **20**, 229.
2001T4389 F. Delgado, M. R. Martin, and M. V. Martin, *Tetrahedron*, 2001, **57**, 4389.
2001T5497 Z. Wan, G. H. C. Woo, and J. K. Snyder, *Tetrahedron*, 2001, **57**, 5497.

2001WO0158960 R. Bonnert, F. Hunt, and P. Willis, *PCT Int. Appl. WO* 0158960, (2001) *(Chem. Abstr.*, 2001, **135**, 180778).

2002AXE1021 G. T. Gainsford and G. B. Evans, *Acta Crystallogr., Sect. E*, 2002, **58**, 1021.

2002BML1687 A. F. Burchat, D. J. Calderwood, M. M. Friedman, G. C. Hirst, B. L. P. Rafferty, K. Ritta, and B. S. Skinner, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1687.

2002FA89 V. D. Piaz, A. Rascon, M. E. Dubra, M. P. Giovannoni, C. Vergetli, and M. C. Castellana, *Farmaco*, 2002, **57**, 89.

2002HAC258 R. M. Mohareb and D. H. Fleita, *Heteroatom Chem.*, 2002, **13**, 258.

2002JCH279 J. J. B. Nevado, J. R. Flores, G. C. Penalvo, and N. R. Farinas, *J. Chromatogr., Part A*, 2002, **953**, 279.

2002JHC329 U. Eilitiz, C. Bottcher, L. Hennig, and K. Burger, *J. Heterocycl. Chem.*, 2002, **39**, 329.

2002JHC869 A. Sener, R. Kasimogullari, M. K. Sener, I. Bildnicl, and Y. Akcamme, *J. Heterocycl. Chem.*, 2002, **39**, 869.

2002JHC1077 C. Fruit, A. Turck, N. Ple, and G. Quequiner, *J. Heterocycl. Chem.*, 2002, **39**, 1077.

2002JMB351 G. Koellner, A. Bzowska, B. W. Kutrowska, M. Luic, T. Steiner, W. Saenger, and J. Stepinski, *J. Mol. Biol.*, 2002, **315**, 351.

2002JST41 F. Miklos, I. Kanizsai, P. Sohar, and G. Stajer, *J. Mol. Struct.*, 2002, **610**, 41.

2002MI227 V. DalPiaz, M. C. Castellana, C. Vergell, M. P. Giovannoni, A. Gavalda, V. Segarra, J. Beleta, H. Ryder, and J. M. Palacios, *Bioorg. J. Enzyme Inhib. Med. Chem.*, 2002, **17**(4), 2002, 227.

2002MI743 N. D. Dinesh, B. K. Vishukumar, P. Nagaraja, N. M. Made Gowda, and K. S. Rangappa, *J. Pharma. Biomed. Anal.*, 2002, **29**, 743.

2002MI608 Y. Misaki, M. Taniguchi, K. Tanaka, K. Takimiya, A. Morikami, T. Otsubo, and T. Mori, *Solid State Chem.*, 2002, **168**, 608.

2002PS2745 A. M. Kamal El-Dean and M. E. Abdel-Moneam, *Phosphorus, Sulfur and Silicon and Related Elements*, 2002, **177**, 2745.

2002SM129 S. L. Moustarder, N. Mercier, P. Hudhomme, N. Gallego-Planas, A. Gorgues, and A. Riou, *Synth. Met.*, 2002, **130**, 129.

2002T10073 N. Matsumoto and M. Makahashi, *Tetrahedron*, 2002, **58**, 10073.

2002TAL757 N. D. Dinesh, P. Nagaraja, N. M. Made Gowda, and K. S. Rangappa, *Talanta*, 2002, **57**, 757.

2002WO0276990 S. Hanson and G. Nordeall, *PCT Int. appl. WO* 0276990 (2002) (*Chem. Abstr.*, 2002, **137**, 263057d).

2003BCJ89 S. Kimura, H. Nii, H. Kurai, T. Takeuch, M. Katsuhara, and T. Mori, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 89.

2003BMC457 C. Yu, H. Mason, X. Wu, J. Wang, S. Chong, B. Beyer, A. Henubod, R. Pongrac, L. Seliger, B. He, *et al.*, *Bioorg. Med. Chem.*, 2003, **46**, 457.

2003BML1581 J. Witherington, V. Bordas, D. Haigh, D. M. B. Hickey, R. J. Ife, A. D. Rawlings, B. P. Slingsby, D. G. Smith, and R. W. Ward, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1581.

2003BML3063 R. Swdaramoorthi, W. C. Shakespeare, T. P. Keenan, C. A. Metcalf, III, Y. Wang, U. Mani, M. Taylor, S. Liu, R. S. Bohacek, S. S. Narula, *et al.*, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3063.

2003EJM27 A. A. Bekhit, H. T. Y. Fahmy, S. A. F. Rostom, and A. M. Baraka, *Eur. J. Med. Chem.*, 2003, **38**, 27.

2003HCA1949 C. Hahnemann and H. Hartmann, *Helv. Chim. Acta*, 2003, **86**, 1949.

2003JC(B)303 T. Perez-Ruiz, C. Martinez-Loazno, V. Tomas, and R. Galera, *J. Chromatogr., Part B*, 2003, **798**, 303.

2003JCH231 J. R. Flores, J. J. B. Nevado, G. C. Penalvo, and N. M. Diez, *J. Chromatogr., Part B*, 2004, **881**, 231.

2003JOC2054 O. Sugimoto, S. Yamada, and K. I. Tanji, *J. Org. Chem.*, 2003, **68**, 2054.

2003JOC5519 J. He, I. Mikhailopulo, and F. Seela, *J. Org. Chem.*, 2003, **68**, 5519.

2003JST91 A. Torreggiani, M. Tamba, A. Trinchero, and G. Fini, *J. Mol. Struct.*, 2003, **651–653**, 91.

2003JST91 R. A. Gevedo-Chavez, J. Robles, and M. E. Costas, *J. Mol. Struct.*, 2003, **664–665**, 91.

2003MI2897 H. Y. Aboul-Enein and J. Hefnawy, *J. Liq. Chromatogr. Relat. Technol.*, 2003, **26**, 2897.

2003MI533 M. Tamba and A. Torreggiani, *Res. Chem. Intermed.*, **29**(6) 2003, 533.

2003MIP292257r J. Witherington and R. W. Ward, Appl. No. WO/2003/080616 (*Chem. Abstr.*, 2003, **139**, 292257r).

2003OL507 Y. G. Chang, H. S. Cho, and K. Kim, *Organic Letters*, 2003, **5**, 507.

2003PS199 A. A. Shalaby, *Phosphorus, Sulfur Silicon Related Elements*, 2003, **178**, 199.

2003PS1413 M. Abass, *Phosphorus, Sulfur Silicon and Silicon and Related Elements*, 2003, **178**, 1413.

2003SM193 H. Nishikawa, T. Morimoto, T. Kodama, I. Ikemoto, K. Kikuchi, J. Yamada, H. Yoshino, and K. Murata, *Synth. Met.*, 2003, **133–134**, 193.

2003SM353 K. Balodis, S. Khasanov, C. Chong, M. Macsato, H. Yamochi, G. Saito, and O. Neilands, *Synth. Met.*, 2003, **133–134**, 353.

2003SM365 S. Kimura, H. Nii, H. Kurai, and T. Mori, *Synth. Met.*, 2003, **133–134**, 365.

2003SM377 I. Malfant, C. Faulmann, L. Kushch, M.-E. Sanchez, L. Pilia, B. G. de Bonneval, P. Cassoux, and M.-L. Doublet, *Synth. Met.*, 2003, **133–134**, 377.

2003SM643 A. Ota, H. Yamochi, and G. Saito, *Synth. Met.*, 2003, **135–136**, 643.

2003SM669 Y. Misaki, T. Nakayashiki, S. Yoshida, K. Tanaka, and T. Mori, *Synth. Met.*, 2003, **135–136**, 669.

2003SM1199 K. Kikuchi, H. Nishikawa, T. Morimoto, T. Kodama, I. Ikemoto, and J. Yamada, *Synth. Met.*, 2003, **137**, 1199.

2003T5869 J. M. Chezal, E. Moreau, O. Chavignon, C. Lartigue, Y. Blache, and J. C. Teulade, *Tetrahedron*, 2003, **59**, 5869.

2003TL1623 P. Leriche, S. Royuet, N. Pillerei, G. Mobon, and P. Frere, *Tetrahedron Lett.*, 2003, **44**, 1623.

2003TL1847 P. J. Bhuyan, H. N. Borhan, and R. C. Boruah, *Tetrahedron Lett.*, 2003, **44**, 1847.

2003TL3127 J.-P. Griffiths, R. J. Brown, P. Day, C. J. Matthews, B. Vital, and J. D. Wallis, *Tetrahedron Lett.*, 2003, **44**, 3127.

2003USP235822 S. G. Lokhov, I. V. Katyavin, R. O. Dempey, A. A. Gall, I. A. Afrina, M. J. Singer, and N. M. J. Vermeulen, *US Pat.* 2003 235 822 (2003) (*Chem. Abstr.*, 2004, **140**, 544579).

2004ANA227 S. A. Ozkan, B. Uslu, and P. Zuman, *Anal. Chim. Acta*, 2004, **501**, 227.

2004AXE807 M. Dincer, N. Ozdemir, I. Yildirim, E. Demir, Y. Akcamer, and S. Isik, *Acta Crystallogr., Sect. E*, 2004, **60**, 807.

2004BMC265 E. Wagner, L. Bccan, and E. Nowakowska, *Bioorg. Med. Chem.*, 2004, **12**, 265.

2004BMCL5013 A. Deeb, F. El-Mariah, and M. Hosny, *Bioorg. Med. Chem.*, 2004, **14**, 5013.

2004BML1997 M. Bauser, G. Delapierre, M. Hauswald, T. Flessner, D. D. Urso, A. Hermann, B. Beyreuther, J. De Vry, P. Spreyer, E. Reissmuller, *et al.*, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1997.

2004BML2121 A. J. Peat, J. A. Boucheron, S. H. Dickerson, D. D. Garrido, W. Mills, J. Peackham, F. Preugschat, T. Smalley, S. L. Schweiker, J. R. Wilson, *et al.*, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2121.

2004BML2127 A. T. Peat, D. Garrido, J. A. Boucheron, S. L. Schweiller, S. H. Dickerson, J. R. Wilson, T. Y. Wang, and S. A. Thomson, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2127.

2004BML2519 J.-H. Chern, K.-S. Shia, T.-A. Hsu, C.-L. Tai, C.-C. Lee, Y.-C. Lee, C.-S. Chang, S.-N. Tseng, and S.-R. Shih, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2519.

2004BML4165 A. Gomtsyan, S. Didomenico, C.-H. Lee, A. O. Stewart, S. S. Bhagwat, E. A. Kowaluk, and M. F. Jarris, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4165.

2004BMCL5013 A. Deeb, F. El-Mariah, and M. Hosny, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5013.

2004CHE1039 A. Sener, R. Kasimogullari, M. K. Sener, and H. Gene, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 1039.

2004COR1463 S.-G. Lee, J.-J. Kim, H.-K. Kim, D.-H. Kweon, Y.-J. Kang, S.-D. Cho, S.-K. Kim, and Y.-H. Yoon, *Curr. Org. Chem.*, 2004, **8**, 1463.

2004H(63)1143 A. Deeb and M. Kotb, *Heterocycles*, 2004, **63**, 1143.

2004JCH231 J. R. Flores, J. J. B. Nevado, G. C. Penalvo, and N. M. Diaz, *J. Chromatogr., Part B*, 2004, **811**, 231.

2004JHC393 J. H-Q. Wang, Z.-J. Liu, Li-M. Yang, and M. W. Ding, *J. Heterocycl. Chem.*, 2004, **41**, 393.

2004JOC3672 S. Barriga, P. Fuertes, C. F. Marcos, and T. Torroba, *J. Org. Chem.*, 2004, **69**, 3672.

2004JPBA525 S. R. Gratz, C. L. Flurer, and K. A. Wolnik, *J. Pharma. Biochem. Anal.*, 2004, **36**, 525.

2004JSTC356 G. I. Roschupkina, T. V. Rybalova, Y. V. Gatilov, and V. A. Reznikov, *J. Struct. Chem.*, 2004, **4**, 356.

B-2004MI357 O. Neilorad; 'Khimiya Biologischeskaya Aktivnust Kislorod, Serusodrzhashikh Getero Sirlov', 2nd edn., Mosko, Russian Federation, 2003, 357 *(Chem. Abstr.*, 2004, **141**, 225336).

2004MI377 J. Wlodarczyk, G. S. Galitonov, and B. Kierdazzuk, *Eur. Biophys. J.*, 2004, **33**, 377.

2004MI546 M. Afshari, B. Larijani, A. Rezaic, A. Mojtahedi, M. J. Zaman, F. Astanehi-Asghari, S. Mostafalou, A. Hosseinnezhad, R. Heshmat, and M. Abdollahi, *Biomed. Pharmaco.*, 2004, **58**, 546.

2004OPP92 N. R. Reddy, G. M. Reddy, and P. Reddy, *Org. Prep. Proced. Int.*, 2004, **36**, 92.

2004PS2067 M. A. Metwally, E. M. Keshk, A. Fekry, and H. A. Etman, *Phosphorus, Sulfur and Silicon and Related Elements*, 2004, **179**, 2067.

2004T8233 J. Zhou, M. Yang, and S. W. Schneller, *Tetrahedron*, 2004, **45**, 8233.

2004T5093 P. G. Baraldi, H. El-Kashef, A. Farghaly, P. Vanelle, and F. Fruttarolo, *Tetrahedron*, 2004, **60**, 5093.

2004TL4105 T.-C. Chiem, R. A. Smaldone, and L. B. Townsend, *Tetrahedron Lett.*, 2004, **45**, 4105.

2004TL4693 E. B. Frolor, F. J. Lakner, and A. V. Irachtchenko, *Tetrahedron Lett.*, 2004, **45**, 4693.

2004TL8233 J. Zhou, M. Yang, and S. W. Schneller, *Tetrahedron Lett.*, 2004, 8233.

2004ZNB1132 H. M. E. Hassaneen, H. M. Hassaneen, and M. H. Elnagdi, *Z. Naturforsch, B*, 2004, **59b**, 1132.

2005BMC2790 G. Xia, J. Li, A. Peng, S. Lai, S. Zhang, J. Shen, Z. Lia, X. Chan, and R. Ji, *Bioorg. Med. Chem.*, 2005, **15**, 2790.

2005BML3900 H. Haning, U. Niewohner, T. Schenke, T. Lampe, A. Hillish, and E. Bischoff, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3900.

2005EJM401 E. Akbas and I. Derber, *Eur. J. Med. Chem.*, 2005, **40**, 401.

2005H(65)1821 R. J. Abdel-Jalile, M. Khanfar, S. Al-Gharabli, M. M. El-Abadelah, K. Eichele, M. U. Anwar, and W. Voelter, *Heterocycles*, 2005, **65**, 1821.

2005JCH89 X. Zhu, S. Xiao, B. Chen, F. Zhang, S. Yao, Z. Wan, D. Yang, and H. Han, *J. Chromatogr., Part A*, 2005, **1060**, 89.

2005JCH118 Y. Wang, J. Wang, Y. Cui, J. Fawcett, and J. Ga, *J. Chromatogr., Part B*, 2005, **828**, 118.

2005JHC751 N. R. Reddy, G. M. Reddy, B. S. Reddy, and P. P. Reddy, *J. Heterocycl. Chem.*, 2005, **42**, 751.

2005JOC10194 J. Liu, R. J. Patch, C. Schubert, and M. R. Playa, *J. Org. Chem.*, 2005, **70**, 10194.

2005JPBA865 I. Wawer, M. Pisklata, and Z. Chilmoczyk, *J. Pharm. Biochem. Anal.*, 2005, **38**, 865.

2005MI407 S. D. Prabha, *J. Mol. Cell. Cardio.*, 2005, **39**, 407.

2006BMC2040 B. S. Holla, M. Mahalinga, M. S. Karthikeqan, P. M. Akeveali, and N. S. Shetty, *Bioorg. Med. Chem.*, 2006, **16**, 2040.

2006BMCL3755 J. M. Fevig, J. Cacciola, J. B. Jr, K. A. Rossi, J. Jona, R. M. Knabb, J. M. Luettgen, P. C. Wong, S. A. Bai, R. R. Wexler, and P. Y. S. Lam, *Bioorg. and Med. Chem. Lett.*, 2006, **16**, 3755.

2006BMCL5176 Y.-L. Li, J. M. Fevig, J. Cacciola, J. B. Jr, K. A. Rossi, J. Jona, R. M. Knabb, J. M. Luettgen, P. C. Wong, S. A. Bai, R. R. Wexler, and P. Y. S. Lam, *Bioorg. and Med. Chem. Lett.*, 2006, **16**, 5176.

2006BML55 T. Kinoshita, M. Warizaya, M. Ohori, K. Sato, M. Neya, and T. Fujii, *Bioorg. Med. Chem. Lett.*, 2006, **16(5)**, 55.

2006BML262 L. Revesz, E. Blun, F. E. Dipadova, T. Buhl, R. Feifel, H. Gram, P. Hiestand, U. Manning, U. Neumann, and G. Hucklin, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 262.

2006BML731 P. A. Carpino, D. A. Griffitr, S. Sakya, R. L. Dow, S. C. Black, J. R. Hadcock, P. A. Iredale, P. O. Scott, M. N. Fichtner, C. R. Rose, *et al.*, *Chem. Lett.*, 2006, **16**(3), 2006, 731.

2006EJM7 M. H. Holschbach, D. Bier, S. Stusyen, W. W. W. Sihver, H. H. Coenen, and R. A. Olsson, *Eur. J. Med. Chem.*, 2006, **41**, 7.

2006EJM1405 V. Krystof, D. Moravcova, M. Paprskarova, P. Barbier, V. Peyrot, A. Hlobilkova, L. Havlicek, and M. Strnad, *Eur. J. Med. Chem.*, 2006, **41**, 1405.

2006JST106 K. Avasthi, S. M. Faroog, R. Raghunandan, and P. R. Maulik, *J. Mol. Struct.*, 2006, **785**, 106.

2006MI19 K.-C. Lai, Y.-C. Liu, M.-C. Tseng, and J. Hueilin, *J. Food and Drug Anal.*, 2006, **14**, 19.

2006MI468 Y.-F. Zhao, X. Zhai, J.-Y. Chen, S.-C. Guo, and P. Gong, *Chem. Res. Chin.*, 2006, **22(4)**, 468.

2006MI840 M. J. Vredenbkegt, L. Blok-Jip, R. Hoognerbrugge, D. M. Barends, and D. deKaste, *J. Pharm. Biomed. Anal.*, 2006, **40**, 840.

2006MI1584 H. Liu, H.-Q. Wang, M.-W. Ding, Z.-J. Liu, and W.-J. Xiao, *J. Fluorine Chem.*, 2006, **127**, 1584.

2006JPBA857 M. M. Al-Omari, M. B. Zaghal, J. E. Davies, and A. A. Badwan, *J. Pharm. Biochem. Anal.*, 2006, **40**, 857.

2006MI952 M. H. Guermouche and K. Bensalah, *J. Pharm. Biomed. Anal.*, 2006, **40**, 952.

2006MI123 A. Gerega, L. Lapinski, I. Reva, H. Rostkowska, and M. J. Nowak, *Biophys. Chem.*, 2006, **122**, 123.

2006MI1 M. M. Heravi, R. Motamedi, N. Seifi, and F. F. Bamoharram, *J. Mol. Catal., Part A*, 2006, **249**, 1.

2006TAL1544 Y. Chi, J. Xie, and G. Chen, *Talanta*, 2006, **68**, 1544.

2007BMCL2203 H. Liu, H.-Q. Wang, and Z.-J. Liu, *Bioorg. and Med. Chem. Lett.*, 2007, **17**, 2203.

2007MI231 J. Wang, Y. Jang, Y. Wang, X. Zhao, Y. Cui, and J. Gu, *J. Pharm. Biomed. Anal.*, 2007, **44**, 231.

2007MI613 M. Al-Ghazawi, M. Tutunji, and S. AbuRuz, *J. Pharm. Biomed. Anal.*, 2007, **43**, 613.

2007MI857 M. M. AlOmari, M. B. Zughul, J. E. D. Davies, and A. A. Badwan, *J. Pharm. Biomed. Anal.*, 2006, **41**, 857.

2007MI1467 M. M. Heravi, R. Motamedi, F. F. Bamoharram, and N. Seify, *Cat. Commun.*, 2007, **8**, 1471.

2007MI1514 J. K. Maurin, F. Plucinski, A. P. Mazurek, and Z. Fijalek, *J. Pharm. Biomed. Anal.*, 2007, **43**, 1514.

2007MI1615 J. C. Reepmeyer, J. T. Woodruff, and D. A. D'Avignon, *J. Pharm. Biomed. Anal.*, 2007, **43**, 1615.

2007MIxx Y. Liang, S. Fan, W. Y. Mo, and H. W. He, *J. Fluorine Chem.*, 2007.

2007TL3983 N. D. Adams, S. J. Schmidt, S. D. Knight, and D. Dhanak, *Tetrahedron Lett.*, 2007, **48**, 3983.

Biographical Sketch



Mohamed Hilmy Elnagdi was born in Egypt in September 1941. He graduated from the Faculty of Science at Cairo University in 1962; since that date, Prof. Elnagdi has worked at Cairo University, Faculty of Science, in the Chemistry Department. Prof. Elnagdi obtained his M.Sc. in 1966, Ph.D. in 1969, and D.Sc. in 1982. He has also been awarded a Diploma in Applied Chemistry from Tokyo Institute of Technology in 1973. Prof. Elnagdi has been professor of organic chemistry at Cairo University since 1980. He worked as professor of organic chemistry at Kuwait University from 1993 to 1999, then as visiting professor at the same university in 2003. Since March 2007 Prof. Elnagdi has shifted back to the University of Kuwait with intention to end his career there. Prof. Elnagdi has received fellowships from several institutions, including those from the Royal Norwegian Council for Scientific and Industrial Research, taken at University of Oslon (1977); Visiting Associate Professor at the University of Utah in 1976 with Prof. L. B. Townsend; Alexander von Humboldt Fellowship at University of Bonn with Profs. H. Wamhoff and R. Regitz. The Alexander von Humbolt Foundation has continually supported his activities in Germany, enabling him to cooperate with many German colleagues including Profs. K. Hafner, K. S. Hartki, M. Hoffmann, and H. H. Otto. Prof. Elnagdi has specialized in the synthesis of polyfunctional heterocycles and has published around 300 papers in this area as well as 15 review articles. In addition, Prof. Elnagdi is cooperating with the Al-Awadi group at Kuwait University, where he is co-author on 30 papers. He has received several national and regional awards for his research output, including the TWAS Chemistry and COMESTECH awards.



Nouria Al-Awadi was born in Kuwait and obtained her B.Sc. from the Faculty of Science at Kuwait University in 1976 and Ph.D. from the University of Kent, UK, in 1979. She held a postdoctoral fellowship at the University of Sussex (1981–82). Prof. Al-Awadi is FRCS and chartered scientist of RSC. She has been professor of organic chemistry at the University of Kuwait since 1992. Prof. Al-Awadi has held several administrative positions at Kuwait University: Vice dean of the College of Graduate Studies at Kuwait University (1984–90); Head of the Chemistry Department (1992–95); dean of Faculty of Science (1995–2001); Prof. Al-Awadi since September 2006 until now is vice-president of Kuwait University for academic affairs. Prof. Al-Awadi has specialized in studying kinetics and mechanisms of gas-phase reactions and their potential utility as green methodologies in organic chemistry. She has more than 95 published papers and one patent. She is author of three review articles.



Ismail Abdelshafy was born in Egypt in 1978 and obtained his B.Sc. from the Faculty of Science at Cairo University in 2001 and M.Sc. in 2005. He was due to finish his Ph.D. in 2006. Ismail Abdelshafy has specialized in heterocyclic chemistry and has published eight papers and has five papers submitted for publication. Ismail Abdelshafy is now an assistant lecturer at Cairo University, Faculty of Science, in the Chemistry Department.

10.13
Bicyclic 5-6 Systems: Five Heteroatoms 2:3 or 3:2

F. Aldabbagh
National University of Ireland, Galway, Republic of Ireland
© 2008 Elsevier Ltd. All rights reserved.

10.13.1 Introduction **662**
10.13.2 Theoretical Methods **663**
10.13.3 Experimental Structural Methods **664**
10.13.3.1 Nuclear Magnetic Resonance **664**
10.13.3.2 UV Spectroscopy and Fluorescence **667**
10.13.3.3 X-Ray Crystallography **667**
10.13.4 Thermodynamic Aspects **667**
10.13.5 Reactivity of Fully Conjugated Rings **668**
10.13.5.1 Electrophilic Attack at Nitrogen **668**
10.13.5.1.1 Azoloazines 668
10.13.5.1.2 Thiazoloazines and azolothiazines 670
10.13.5.2 Electrophilic Attack at Carbon **670**
10.13.5.3 Nucleophilic Attack at Carbon **670**
10.13.5.3.1 Azoloazines 670
10.13.5.3.2 Oxazoloazines and azolooxazines 675
10.13.5.3.3 Other heterocycles 675
10.13.5.4 Nucleophilic Attack at Sulfur or Selenium **676**
10.13.6 Reactivity of Nonconjugated Rings **676**
10.13.6.1 Oxidative Aromatization **676**
10.13.6.1.1 Thiazoloazines and azothiazines 676
10.13.6.2 Electrophilic Attack at Sulfur **677**
10.13.6.2.1 Other heterocycles 677
10.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms **677**
10.13.7.1 Azoloazines **677**
10.13.7.1.1 Pyrazolo[4,3-*e*][1,2,4]triazines 677
10.13.7.1.2 [1,2,3]Triazolo[4,5-*d*]pyridazines and [1,2,3]triazolo[4,5-*d*]pyrimidines 678
10.13.7.2 Thiazoloazines and Azolothiazines **679**
10.13.7.2.1 [1,2,5]-Thiadiazolo[3,4-*b*]pyrazines 679
10.13.8 Reactivity of Substituents Attached to Ring Heteroatoms **679**
10.13.8.1 Azoloazines **679**
10.13.8.1.1 [1,2,3]Triazolo[4,5-*d*]pyridazines 679
10.13.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component **680**
10.13.9.1 Synthesis of the Fused Six-Membered Ring **680**
10.13.9.1.1 Azoloazines 680
10.13.9.1.2 Oxazoloazines and azolooxazines 683
10.13.9.1.3 Other heterocycles 685
10.13.9.1.4 New heterocyclic systems 685
10.13.9.2 Synthesis of the Fused Five-Membered Ring **686**
10.13.9.2.1 Azoloazines 686

10.13.9.2.2 Oxazoloazines and azolooxazines 690
10.13.9.2.3 Thiazoloazines and azolothiazines 691
10.13.9.2.4 Other heterocycles 693
10.13.10 Ring Synthesis by Transformation of Another Ring 693
10.13.10.1 Azoloazines 693
10.13.10.1.1 Pyrazolo[3,4-*e*][1,2,4]triazines 693
10.13.10.1.2 Pyrazolo[3,4-*d*][1,2,3]triazines 694
10.13.10.1.3 [1,2,3]Triazolo[4,5-*d*]pyridazines 694
10.13.10.2 Oxazoloazines and Azolooxazines 695
10.13.10.2.1 [1,2,5]Oxadiazolo[3,4-*d*]pyrimidines 695
10.13.10.3 Thiazoloazines and Azolothiazines 695
10.13.10.3.1 [1,2,5]Thiadiazolo[3,4-*b*]pyrazines 695
10.13.11 Synthesis of Particular Classes of Compounds and Critical Comparisons of the Various Routes Available 695
10.13.11.1 Azoloazines 696
10.13.11.2 Oxazoloazines and Azolooxazines 696
10.13.12 Important Compounds and Applications 696
10.13.12.1 Azoloazines 696
10.13.12.1.1 Imidazo[4,5-*d*][1,2,3]triazines and pyrazolo[3,4-*d*][1,2,3]triazines 696
10.13.12.1.2 Pyrazolo[4,3-*e*][1,2,4]triazines 696
10.13.12.1.3 [1,2,3]Triazolo[4,5-*d*]pyrimidines and [1,2,3]triazolo[4,5-*d*]pyridazines 697
10.13.12.2 Oxazoloazines and Azolooxazines 697
10.13.12.2.1 Isoxazolo[5,4-*d*][1,2,3]triazines 698
10.13.12.2.2 [1,2,5]Oxadiazolo[3,4-*d*]pyridazines 698
10.13.12.2.3 [1,2,5]Oxazolo[3,4-*b*]pyrazines 698
10.13.12.3 Thiazoloazines and Azolothiazines 698
10.13.12.3.1 Imidazo[4,5-*c*][1,2,6]thiadiazines 698
10.13.13 Further Developments 698
10.13.13.1 Reactivity of Fully Conjugated Rings [1,2,3]Triazolo[4,5-*d*]pyrimidine 698
10.13.13.2 Synthesis of the Fused Five-Membered Ring [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine 699
References 699

10.13.1 Introduction

This chapter contains 52 heterocyclic systems possessing a bicyclic 5-6 system with five heteroatoms distributed 2:3 or 3:2 among the two fused rings. Heterocycles with heteroatoms at ring junctions are not included. The present chapter focuses on advances made since these systems were first reviewed as a collective by Knowles in 1996 <1996CHEC-II(7)489>. **Figures 1–4** give the 49 heterocyclic systems included in the Knowles review (plus pyrazolo[3,4-*d*][1,3,2]diazaphosphinine), and **Figure 5** gives two new systems reported since then <2000JHC1269>.

There are ten heterocyclic systems containing only nitrogen heteroatoms referred to as azoloazines (**Figure 1**), which are the most frequently studied bicyclic 2:3 or 3:2 systems in the literature. Less common are the 12 heterocyclic systems containing one oxygen and four nitrogen atoms referred to as oxazoloazines and azolooxazines (**Figure 2**). Eighteen heterocyclic systems contain one sulfur and four nitrogen atoms, and are referred to as thiazoloazines and azolothiazines (**Figure 3**). Ten heterocyclic systems are given in **Figure 4**, which are classified as other heterocycles in this chapter. Note, that the pyrazolo[3,4-*d*][1,3,2]diazaphosphinine system was not included in the Knowles review <1996CHEC-II(7)489> but was first reported in 1991; thus, it is not classified as a new heterocyclic system <1991MI132>. However, many of the heterocyclic systems in **Figures 2–4** have not been studied since 1996 and do not appear in this chapter. Compounds in this chapter are grouped according to the classifications and IUPAC names shown in **Figures 1–5**. Some of the reactions discussed in this review have appeared in a recent review by Döpp and Döpp of 1,2,3-triazines and phosphorus analogs <2004SOS223>.

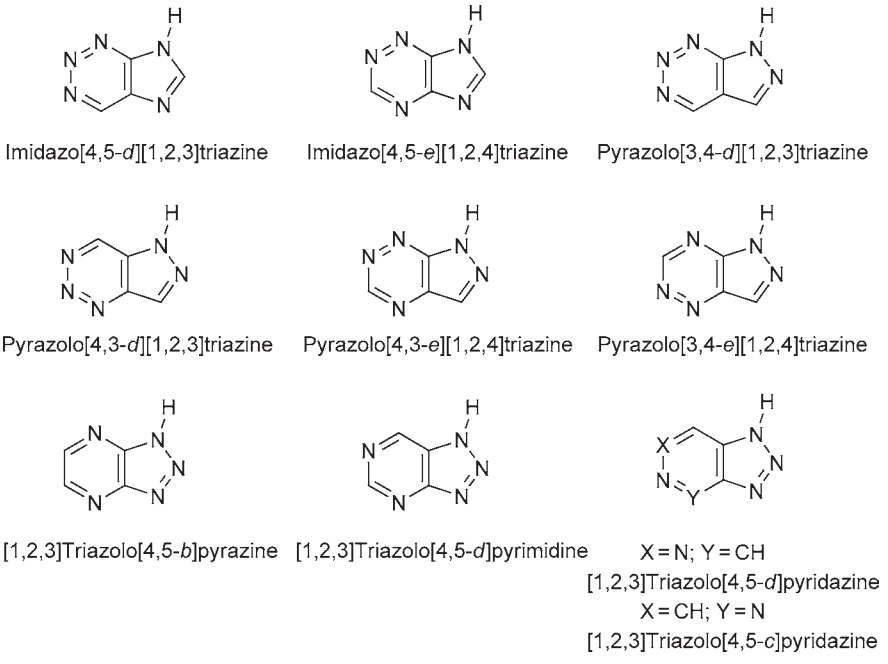


Figure 1 Azoloazines.

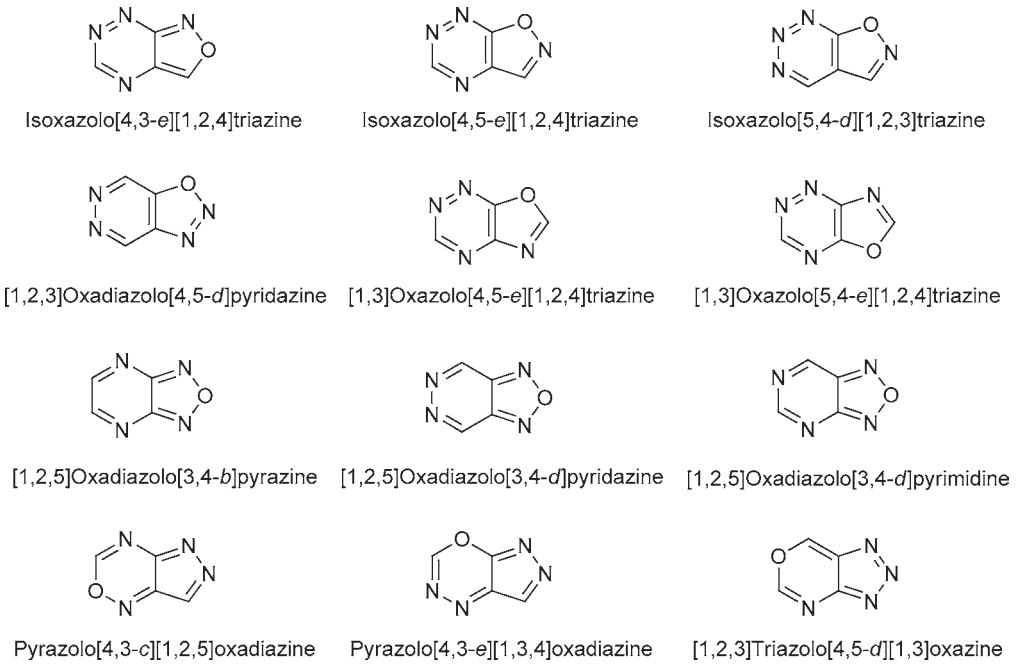


Figure 2 Oxazoloazines and azolooxazines.

10.13.2 Theoretical Methods

Several older theoretical studies are included in the review by Knowles <1996CHEC-II(7)489>, and little has been reported since. Nagy *et al.* carried out quantum calculations on several [1,2,3]triazolo[4,5-*d*]pyridazines to reveal electron distributions in the ground and the excited state using the semi-empirical Hückel molecular orbital (MO) method to explain the fluorescence of such compounds (see Section 10.13.3.2) <2002JPH83>.

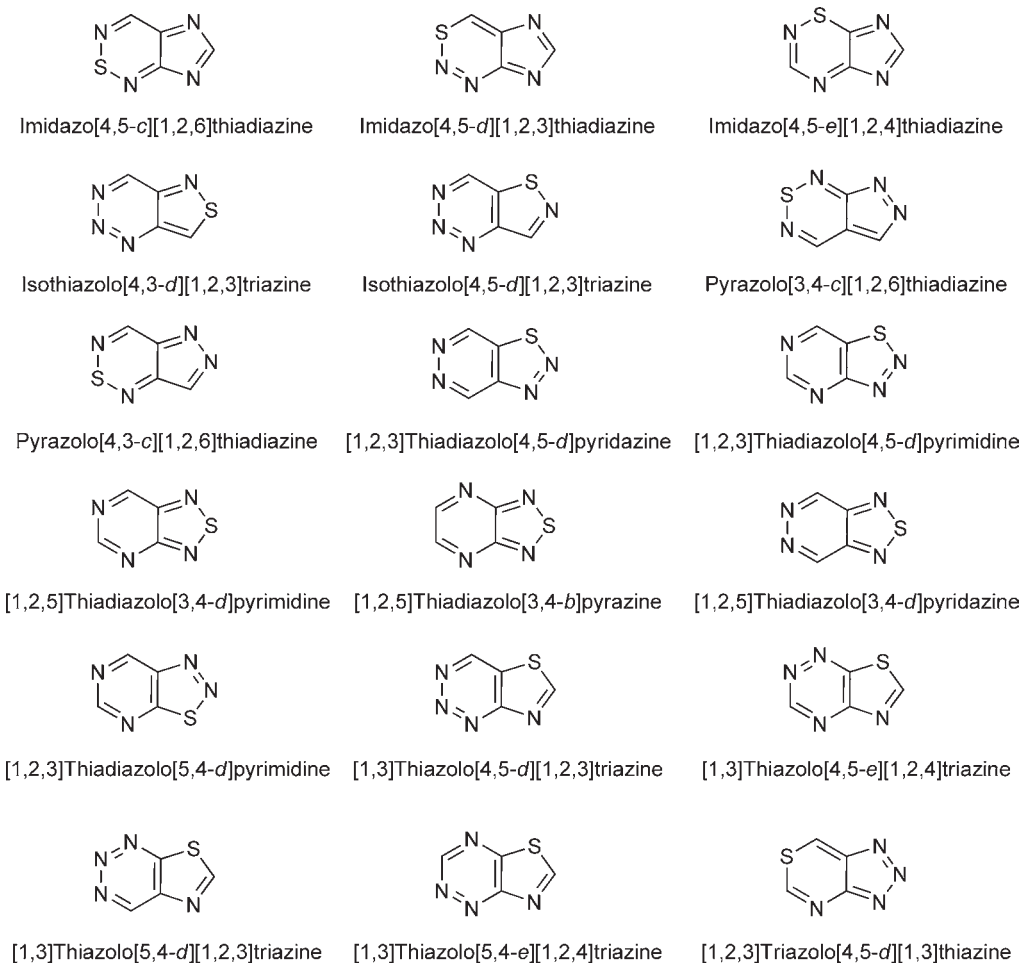


Figure 3 Thiazoloazines and azolothiazines.

To gain more insight into the experimentally observed structure–activity relationships for monosaccharide-linked inhibitors of O^6-methylguanine-DNA methyltransferase (MGMT), and [1,2,3]triazolo[4,5-*d*]pyrimidine derivatives, three-dimensional (3-D) models were constructed using molecular dynamics simulations of MGMT–ligand complex (including associated solvent molecules) <2001JME4050>. The latter class of compounds has been used as mimics of natural nucleosides (see Section 10.13.12.1.3); however, discussion of computational studies is beyond the scope of this chapter.

10.13.3 Experimental Structural Methods

The format of this section is similar to that of the review by Knowles <1996CHEC-II(7)489>, where only the main structure elucidation techniques are reviewed. None of the heterocyclic systems included in this chapter exists as radicals; thus, electron spin resonance (ESR) spectroscopy is not included. Mass spectrometry is also omitted from discussion, as this technique is always used in conjunction with other analytical techniques to ensure full characterization of compounds. Nevertheless, mass spectra for most of the compounds in this chapter have been reported, although assignments of fragmentation patterns are rarely given.

10.13.3.1 Nuclear Magnetic Resonance

^{1}H Nuclear magnetic resonance (NMR) spectroscopy tends not to be useful, as there is a maximum of two methylenes (four protons) in every ring system, although it can be valuable as a diagnostic tool for substituents. As expected, greater

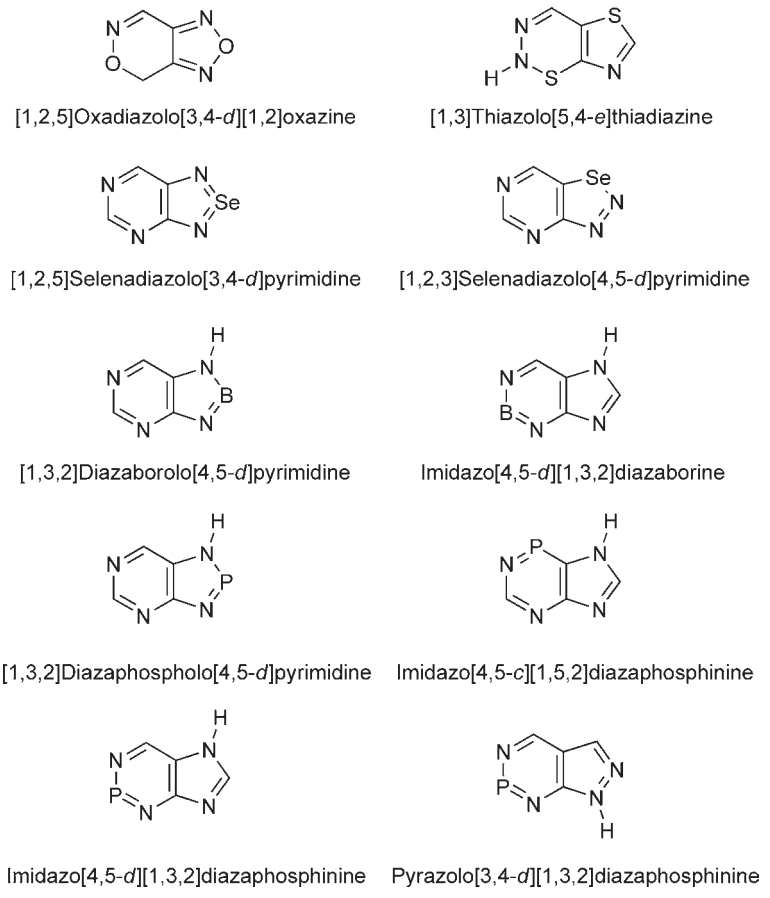


Figure 4 Other heterocycles.

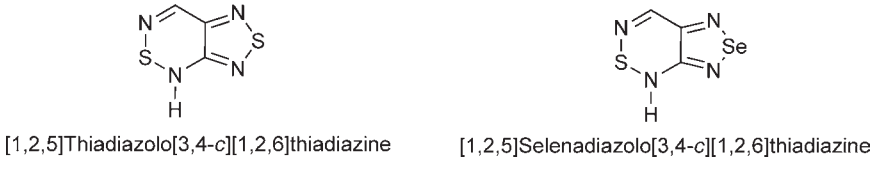


Figure 5 New heterocycles.

use of ^{13}C and ^{15}N NMR spectroscopy has been made for structure determination of unknown compounds. ^{13}C NMR chemical shifts (δ) with assignments exist for imidazo[4,5-*e*][1,2,4]triazines and [1,2,5]oxadiazolo[3,4-*d*]pyridazines <1996CHEC-II(7)489>, pyrazolo[3,4-*d*][1,2,3]triazine nucleosides <2004JOC4695>, thiazolo[4,5-*e*][1,2,4]trazines <2004RCB1279>, [1,2,3]triazolo[4,5-*d*]pyrimidines <1996CHEC-II(7)489> and [1,2,3]triazolo[4,5-*d*]pyrimidine nucleosides <2005HCA751>.

Caution is recommended when comparing ^{15}N-δ, as reference compounds used can sometimes vary. However use of a concentric capillary tube containing pure liquid nitromethane as an external reference is becoming standard practice. The choice of nitromethane has the consequence that most δ values are negative, although some authors will adopt other references, such as liquid ammonia. The use of the latter as an external reference will give ^{15}N resonances downfield from the liquid ammonia signal. However, an arbitrary value for nitromethane shift relative to liquid ammonia (e.g., 380.2 ppm) can be used <1986AGE383>, although δ values given in this chapter have not been adjusted from the sourced articles.

Assignments for ^{15}N-δ for imidazo[4,5-*e*][1,2,4]triazines and [1,2,5]oxadiazolo[3,4-*d*]pyridazines exist <1996CHEC-II(7)489>. More recently, the ^{15}N NMR spectrum of 2-azahypoxanthine (imidazo[4,5-*d*][1,2,3]triazine (**Figure 6**) has been recorded with assignments (δ, ppm, NMR spectra were recorded in DMSO-d_6 at 305 K with nitromethane as external reference) for N-1, N-2, and N-3 given as −35.3, 22.4, and −142.0, respectively <2002MRC300>. Surprisingly, the N(5,7)-atoms in 2-azahypoxanthine were not observed, possibly owing to a combination of signal broadening, and the effect of exchange of hydrogen atoms between both nitrogen sites of the imidazole ring.

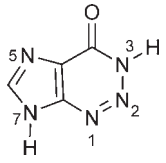
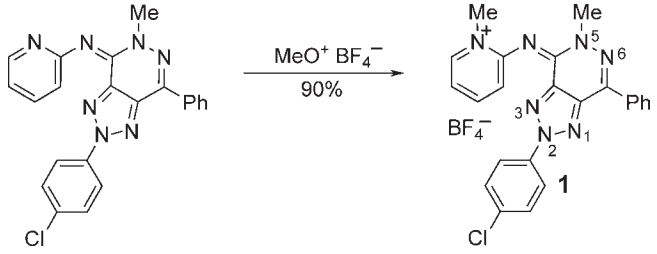
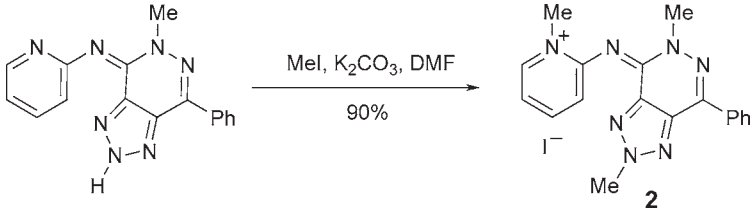


Figure 6

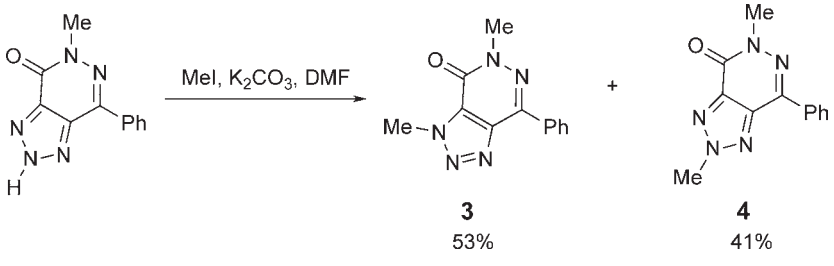
Product elucidation of trimethyloxonium tetrafluoroborate and methyl iodide reactions with [1,2,3]triazolo[4,5-*d*]-pyridazines (**Schemes 1–3**) using mainly 2-D heteronuclear multiple bond correlation (HMBC). ^{1}H–^{15}N NMR correlation experiments have been carried out <2002JST73>. The assignments obtained for ^{15}N-δ for methylated derivatives **1–4** are shown in **Table 1**.



Scheme 1



Scheme 2



Scheme 3

Table 1 ^{15}N NMR assignments for compounds **1** (DMSO-d_6), **2** ($CDCl_3$–CD_3OD, 1:1), **3**, and **4** (both in $CDCl_3$)

Compound	*N-1*	*N-2*	*N-3*	*N-5*	*N-6*	*α-N*	*Py-N*
1	314.9 (overlapping)	273.4	314.9 (overlapping)	185.5	329.6	209.9	183.8
2	325.3 (overlapping)	268.8	325.3 (overlapping)	188.4	325.3 (overlapping)	202.0	180.1
3	231.0	383.8	Unassigned	195.7	323.6		
4	325.3 and 329.2 interchangeable with N-3	264.5	325.3 and 329.2 interchangeable with N-1	192.4	327.2		

All chemical shifts are in ppm, and liquid ammonia was the external reference used.

10.13.3.2 UV Spectroscopy and Fluorescence

Ultraviolet (UV) spectroscopy does not tend to be the method of choice for structure determination, but a list of UV absorptions was given in the review by Knowles <1996CHEC-II(7)489>. Fluorescence properties and triplet yields of [1,2,3]triazolo[4,5-*d*]pyridazines in various solvents have been reported <2002JPH83>. These heterocyclic systems were found to be photochemically very stable. In a recent paper, Wierzchowski *et al.* studied the fluorescence emission properties of 8-azaxanthine ([1,2,3]triazolo[4,5-*d*]pyrimidine-5,7-dione) and its *N*-alkyl derivatives at various pH's <2006JPH276>. For the 8-azaxanthines, an important characteristic of emission spectra in aqueous solutions was the unusually large Stokes shift. Since 8-azaxanthine is a substrate for purine nucleoside phosphorylase II from *Escherichia coli*, the reaction is now monitored fluorimetrically. The fluorescence properties of [1,2,3]triazolo[4,5-*d*]-pyrimidine ribonucleosides were earlier described by Seela *et al.* <2005HCA751>.

10.13.3.3 X-Ray Crystallography

As most compounds tend to be crystalline, X-ray crystallography remains the most popular analytical technique for structure elucidation, and many of the heterocyclic systems described in this chapter have been analyzed by this method <1996CHEC-II(7)489>. More recently, crystal structures of 7-deaza-2,8-diazaadenosine **103** (**Scheme 79**) <2005OBC1714>, pyrazolo[4,3-*e*][1,2,4]triazines **84** (**Scheme 60**) <2000H(53)2175>, thiazolo[4,5-*e*][1,2,4]trazines **38**, **40** (**Schemes 26** and **27**) <2004RCB1279> and [1,2,3]triazolo[4,5-*d*]pyridazine **60** (**Scheme 40**) <2000CC1785> have been reported. Not included in the Knowles review <1996CHECII-(7)489> was the work of Chen *et al.* to obtain an X-ray crystal structure of pyrazolo[3,4-*d*][1,3,2]diazaphosphorin-6-one (**Figure 7**) <1991MI132>.

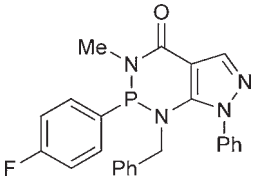


Figure 7

10.13.4 Thermodynamic Aspects

In agreement with Knowles <1996CHEC-II(7)489>, the diversity of the structures included in this chapter makes melting point and solubility studies impossible to consider. Haque and Stewart have reported new methods for the isocratic determination of dacarbazine [5-(3,3-dimethyl-1-triazene)imidazole-4-carboxamide] (a clinically used anti-neoplastic agent for the treatment of various carcinomas) from common impurities 2-azahypoxanthine (photochemical degradation product, **Figure 6**) and 5-aminoimidazole-4-carboxamide (metabolic degradation product) using high-performance liquid chromatography (HPLC) on an avidin protein column <1999MI933>.

Although no pK_a or tautomerism studies have been carried out since 1995, such studies have been earlier reported for 8-azaxanthine ([1,2,3]triazolo[4,5-*d*]pyrimidine-5,7-dione) and the 2-methyl analog (not covered by Knowles <1996CHEC-II(7)489>). 8-Azaxanthine (pK_a = 4.9) in neutral aqueous media exists as a monoanion due to the acidity of the triazole-2-hydrogen; conversely, the 2-methyl analog is considerably less acidic (pK_a = 7.2) <1965CB1060>.

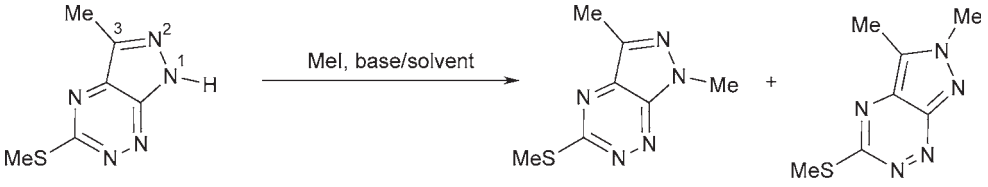
10.13.5 Reactivity of Fully Conjugated Rings

10.13.5.1 Electrophilic Attack at Nitrogen

10.13.5.1.1 Azoloazines

10.13.5.1.1(i) Pyrazolo[4,3-*e*][1,2,4]triazines

Mojzych and Rykowski carried out a series of alkylation reactions on pyrazolo[4,3-*e*][1,2,4]triazine **5** using methyl iodide with various base/solvent combinations. In all cases, a mixture of the respective 1,3- and 2,3-dimethyl derivatives **6** and **7** was obtained (**Scheme 4**), but the isomers were readily separated by column chromatography. The highest yield of **6** was 70%, obtained when the alkylation was carried out in the presence of sodium hydride or potassium *tert*-butoxide in dimethylacetamide (DMA) at room temperature. The highest yield of **7** was 57%, obtained when the alkylation was carried out with potassium carbonate in DMA or ethanol. When ethyl iodide, propyl and benzyl chloride, butyl bromide, 4-bromo-1-butene, and methyl chloroacetate were used as alkylating agents, mixtures of 1- and 2-alkylated derivatives were obtained with alkylation at N-1 always predominating. For the latter alkylations, potassium *tert*-butoxide in DMA was used. All alkylations were carried using 2 equiv of alkyl halide at room temperature <2003PJC1797>.

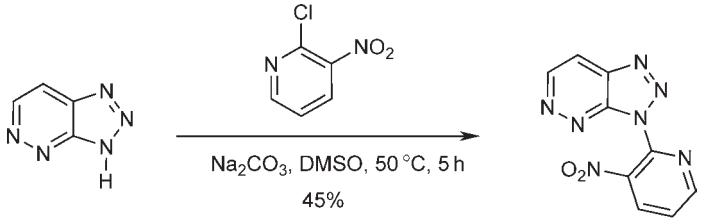


5 **6** **7**

Scheme 4

10.13.5.1.1(ii) [1,2,3]Triazolo[4,5-*c*]pyridazines and [1,2,3]triazolo[4,5-*d*]pyrimidines

Trudell and co-workers reported the N-arylation with 2-chloro-3-nitropyridine of [1,2,3]triazolines fused onto [4,5-*c*]pyridazine (**Scheme 5**) and [4,5-*d*]pyrimidine (**Scheme 6**) <2000JHC1597>. Substitution at the 2-position of the pyridine ring was confirmed by X-ray crystallographic analysis of products **8** and **9**. Similarly, [1,2,3]triazolo[4,5-*d*]pyrimidine gave **10** in low yield, after nucleophilic substitution of the chloro substituent activated by the nitro group in 2-chloronitrobenzene (**Scheme 6**).

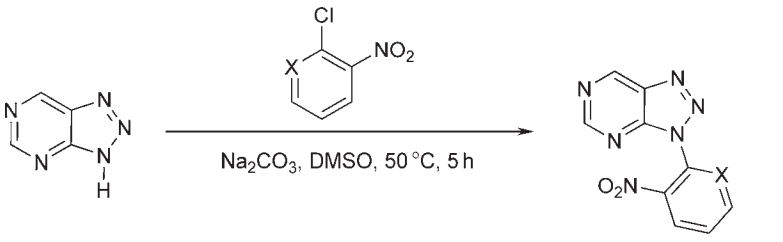


8

Scheme 5

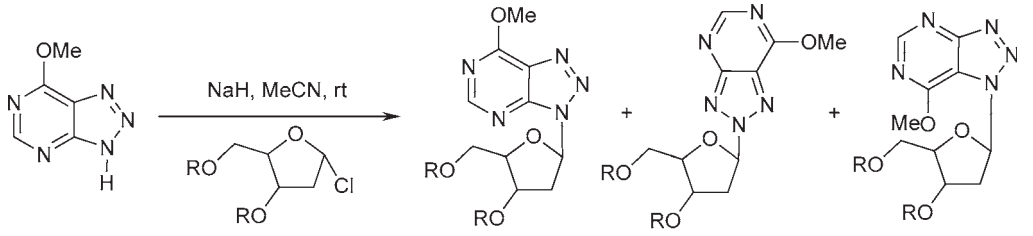
There has been consistent interest in coupling [1,2,3]triazolo[4,5-*d*]pyrimidines with sugar derivatives, as such systems act as isosteres of purines <1996CHEC-II(7)489>. Electrophilic attack on halo-sugars has been reported at several nitrogen atoms <1996CHEC-II(7)489>, as demonstrated by a recent example by Seela *et al.* involving glycosylation of 7-methoxy-3*H*-triazolo[4,5-*d*]pyrimidine with 2′-deoxy-3,5-bis-*O*-(4-methylbenzoyl)-α-D-*erythro*-pentofuranosyl chloride to give regioisomers N-3 **11**, N-2 **12**, and N-1 **13** (**Scheme 7**) <2005HCA751>.

Under different basic conditions, glycosylation of guanine derivative **14** was reported to give only triazoline N-3 adduct **15** (**Scheme 8**) <2001JME4050>.



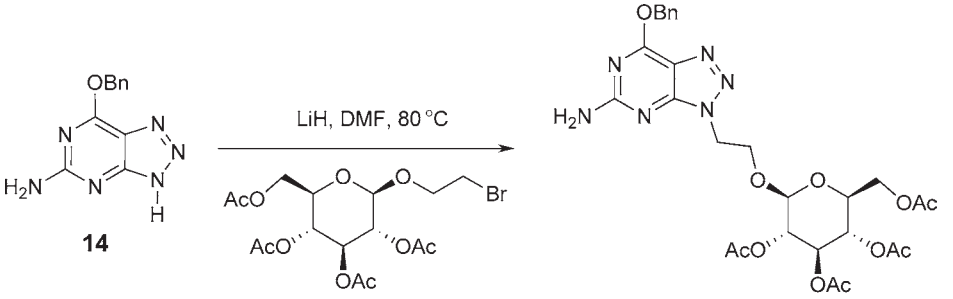
9: X = N (60%)
10: X = CH (10%)

Scheme 6



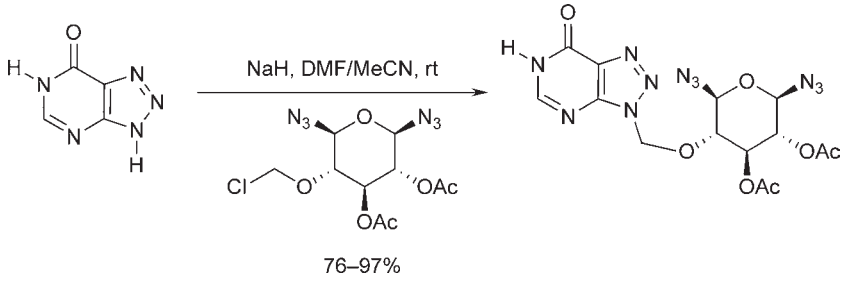
11 29%
12 32%
13 23%

Scheme 7



Scheme 8

Scheme 9 shows an example of selective electrophilic substitution at N-3 of [1,2,3]triazolo[4,5-*d*]pyrimidin-7-one reported by Ding *et al.*, who showed that glycosylation can occur at the 4-position of diazido-2-deoxystreptamine derivative, if the alkyl halide is appropriately substituted at this position <2003AGE3409>.



76–97%

Scheme 9

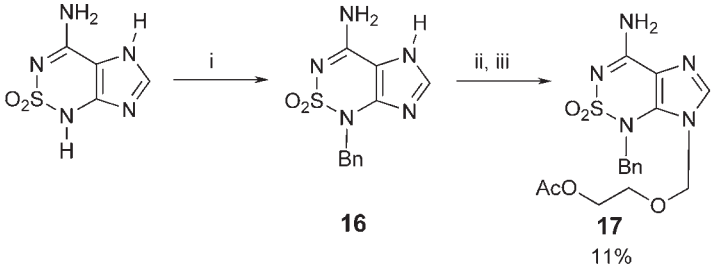
10.13.5.1.1(iii) [1,2,3]Triazolo[4,5-*d*]pyridazines

Methylations of [1,2,3]triazolo[4,5-*d*]pyridazines are shown in **Schemes 1–3** <2002JST73>. The reaction in **Scheme 3** is nonselective, highlighting the steric influence of the pyridylimino moiety on alkylations, although electrophilic attack seems to be most favored at the N-2 of the fused triazole.

10.13.5.1.2 Thiazoloazines and azolothiazines

10.13.5.1.2(i) Imidazo[4,5-*c*][1,2,6]thiadiazines

The *1-NH* is the most acidic hydrogen of imidazothiazine dioxide allowing introduction of the benzyl group preferentially at this position to give 1-benzyl derivative **16** <1981H(16)525>. The N-1 blocked compound **16** was first silylated with hexamethyldisilizane, and treatment with acetoxymethyl ether yielded the N-1,N-7-disubstituted compound **17** (**Scheme 10**) <1999BMC1617>. Subsequent hydrogenolysis (H_2/Pd–C) of the benzyl moiety of **17** afforded an SO_2 analog of acyclovir (**Scheme 78**) <1999BMC1617>.



i, Na_2CO_3 (aq.), BnBr; ii, $Me_3SiNHSiMe_3$, py; iii, $AcO(CH_2)_2OCH_2OAc$, $BF_3{\cdot}OEt_2$

Scheme 10

10.13.5.2 Electrophilic Attack at Carbon

There are no reports since 1996, although lithiation of [1,2,3]triazolo[4,5-*d*]pyrimidine at the 7-position followed by reaction with electrophiles was briefly covered in the review by Knowles <1996CHEC-II(7)489>.

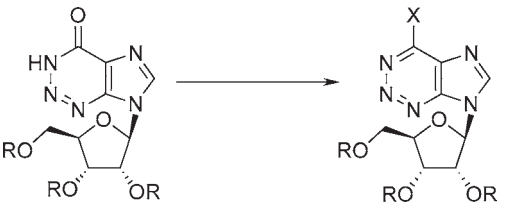
10.13.5.3 Nucleophilic Attack at Carbon

Knowles reviewed several examples of nucleophilic attack at a carbon atom of the six-membered ring fused onto a stable and deactivated fused five-membered ring containing three heteroatoms <1996CHEC-II(7)489>. The examples reported since 1996 similarly all occur at the six-membered ring, but the five-membered ring does not necessarily contain three heteroatoms (e.g., imidazo[4,5-*d*][1,2,3]triazine and pyrazolo[3,4-*d*][1,2,3]triazine). In most cases, nucleophilic attack at the carbon is facilitated by the attachment of a good leaving group at this position.

10.13.5.3.1 Azoloazines

10.13.5.3.1(i) Imidazo[4,5-*d*][1,2,3]triazines and pyrazolo[3,4-*d*][1,2,3]triazines

Krawczyk *et al.* reported the preparation of various 4-substituted 7-(β-D-ribofuranosyl)-1-imidazo[4,5-*d*][1,2,3]triazines **19** from the triazin-4-ones **18** using various nucleophile–$POCl_3$ combinations (**Scheme 11**; **Table 2**) <2000NN39>. The nucleophilic substitution was found to be strongly influenced by the choice of base and reaction conditions. Treatment of **18a** with triethylamine and $POCl_3$ in chloroform at reflux was expected to give the 4-chloro derivative, but instead diethylamine was substituted in 49% yield. Previous attempts at forming the 4-chloro intermediate of imidazo[4,5-*d*][1,2,3]triazine have led to degradation of the triazine ring (**Scheme 12**) <1995JHC1417>. 4-Dimethylaminopyridine (DMAP) was used to give 4-(dimethylamino)pyridinium intermediates, which can be readily displaced by nucleophiles to give substitution products **19**, analogous to nucleophilic substitution at the 4-position of pyrazolo[3,4-*d*]triazines (**Scheme 13**) <1995JHC1417>. In **Table 2**, quenching the reaction with methanolic ammonia for 1 h at 0 °C was expected to give the 4-amine (X = NH_2), but instead led to isolation of

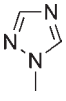


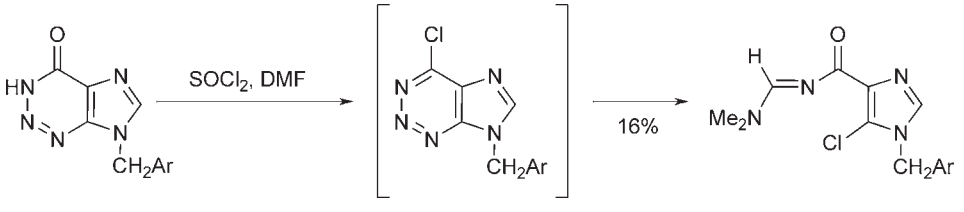
18a: R = Ac
18b: R = TBDMS

19

Scheme 11

Table 2 Synthesis of **19** from **18** in Scheme 11

Substrate	*Reagents*	*X*	*Yield of* **19** (%)
18a	$POCl_3$, Et_3N	$N(Et)_2$	49
18a	$POCl_3$, DMAP MeOH, NH_3	MeO	27
18a	$POCl_3$, Et_3N 1,2,4-triazole		30
18b	$POCl_3$, Py MeOH, NH_3	NH_2	59
18b	$POCl_3$, DMAP MeOH, NH_3	MeO	51
18b	$POCl_3$, DMAP $MeNH_2$	NHMe	24
18b	$POCl_3$, DMAP MeOH, NaOMe	MeO	41
18b	$POCl_3$, Et_3N 1,2,4-triazole		31

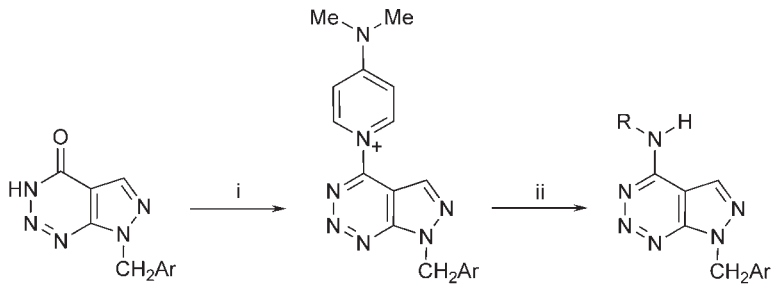


Scheme 12

the 4-methoxy derivative. Extending the reaction time to 24 h gave some 2-azaadenosine derivative (X = NH_2) in an unspecified yield. Replacing DMAP with pyridine gave a pyridinium intermediate susceptible to ring cleavage involving nucleophilic attack at the pyridinium α-carbons (the so-called Zincke reaction <1995JHC1417, 2001JOC4776>) giving the 4-amine (X = NH_2) from **18b**. Various other nucleophiles, such as 1,2,4-triazole and methylamine, were also substituted in the presence of either $POCl_3$/DMAP or $POCl_3$/Et_3N (**Table 2**).

Unlike imidazo[4,5-*d*][1,2,3]triazin-4-ones (**Scheme 11**), the DMAP adduct **20** of pyrazolo[3,4-*d*][1,2,3]triazin-4-one is sufficiently stable to be isolated, and treatment with the appropriate amine or ammonium hydroxide gave 4-amines **21** in good yields (**Scheme 13**) <1995JHC1417>.

Krawczyk *et al.* found that a combination of $POCl_3$/pyridine with hydrogen sulfide gave higher yields of the [1,2,3]triazin-4-thione **22** from the triazin-4-one than application of the more conventional Lawesson's reagent (**Figure 8**), as shown in **Scheme 14**. Reductive elimination of the sulfur was achieved in low yield using Raney nickel <2000NN39>.



i, $ClC_6H_4POCl_2$, DMAP, MeCN; ii, RNH_2 (**21**: R = Me (71%), Et (49%)); ii, NH_4OH (**21**: R = H (83%)); Ar = 2-F-C_6H_4

Scheme 13

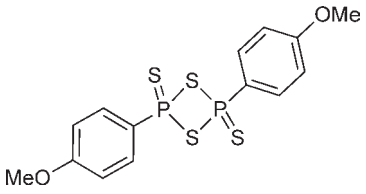
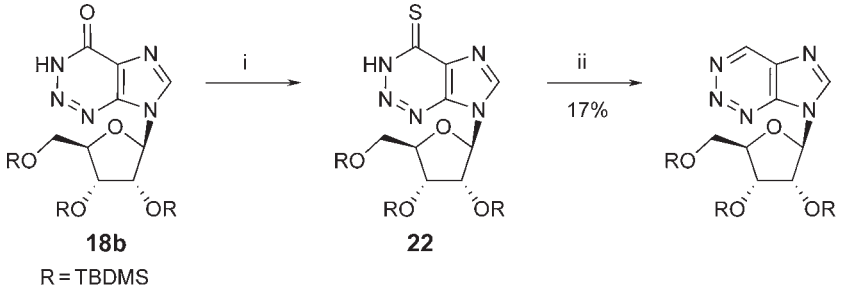


Figure 8



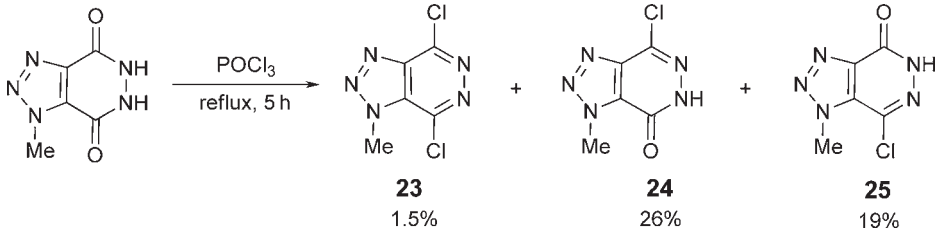
R = TBDMS

i, Lawesson's reagent (35% for **22**) or $POCl_3$, py, H_2S (42% for **22**); ii, Raney Ni, EtOH

Scheme 14

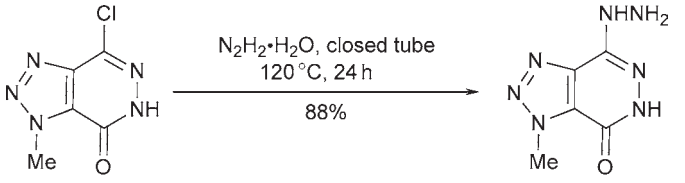
10.13.5.3.1(ii) [1,2,3]Triazolo[4,5-*d*]pyridazines

Chlorination with phosphorus oxychloride under conditions which minimize dichlorination was reported to give a mixture of products consisting of dichloride **23** and two respective isomeric monochlorides, 4-chloro and 7-chloro **24** and **25** (**Scheme 15**) <2002JHC889>.



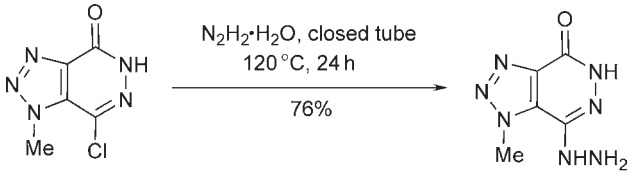
Scheme 15

The 4- and 7-monochlorides **24** and **25** were reacted with hydrazine hydrate in a closed tube to give the hydrazino derivatives **26** and **27**, as shown in **Schemes 16** and **17**, respectively <2002JHC889>.



24 **26**

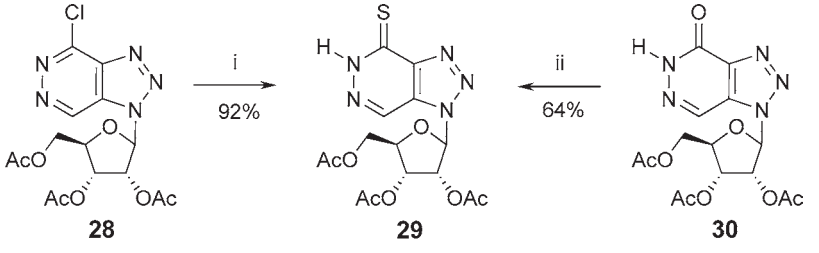
Scheme 16



25 **27**

Scheme 17

Two methods for the preparation of [1,2,3]triazolo[4,5-*d*]pyridazine-4-thione **29** were reported by Bussolari *et al.* involving nucleophilic substitution of sulfur by displacement of the 4-chloro substituent from **28** and of the oxygen atom of 4-lactam derivative **30** using sodium thiosulfate and phosphorus pentasulfide, respectively (**Scheme 18**) <1996BMC1725>.

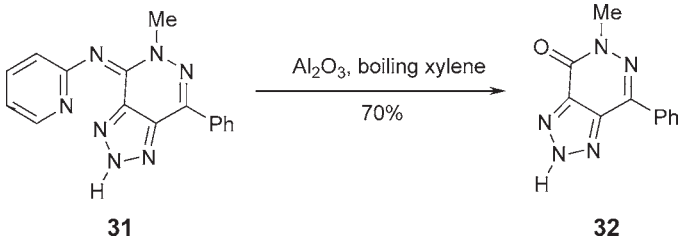


28 **29** **30**

i, $Na_2S_2O_3$, BuOH, H_2O, EtOH; ii, P_2S_5

Scheme 18

The Schiff base side chain of [1,2,3]triazolo[4,5-*d*]pyridazine **31** was easily hydrolyzed in the presence of alumina at high temperatures to give triazolopyridazinone **32** (**Scheme 19**) <2000CC1785>.

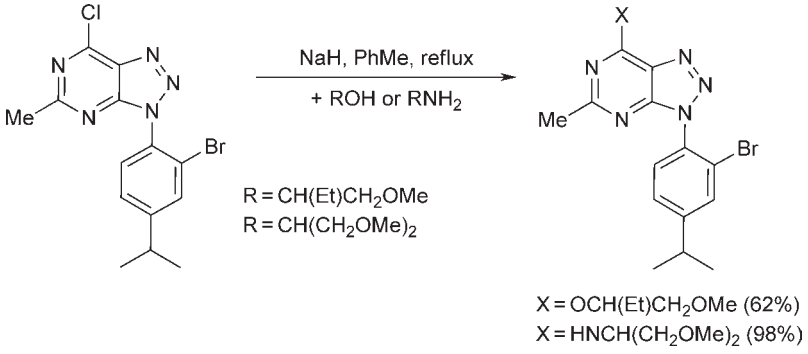


31 **32**

Scheme 19

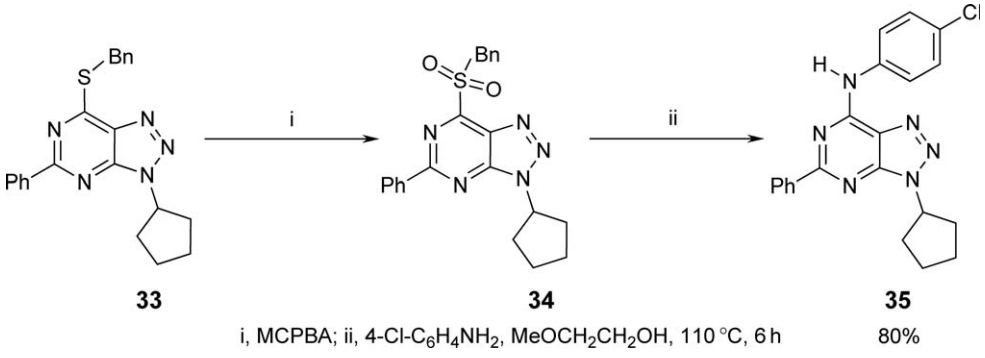
10.13.5.3.1(iii) [1,2,3]Triazolo[4,5-*d*]pyrimidines

Various nitrogen <1998JME668, 1999EJM867, 1999JME833, 2001BMC1357, 2003JCO653, 2005BMC5399> and oxygen <1999JME833> nucleophiles have been used to displace the 7-chloro substituent in [1,2,3]triazolo[4,5-*d*]-pyrimidine derivatives. Two representative examples are given in **Scheme 20** <1999JME833>.



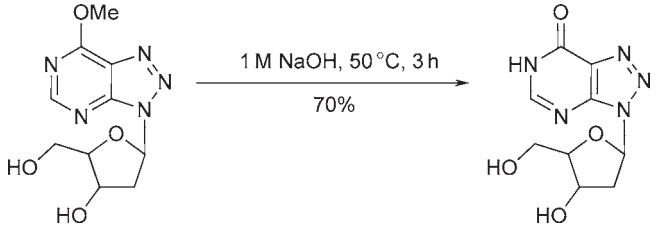
Scheme 20

An alternative nucleophilic attack at the 7-position is given in **Scheme 21**. The oxidation of the 7-benzylsulfanyl substituent of **33** with *m*-chloroperbenzoic acid (MCPBA) resulted in the corresponding sulfone **34**. The 7-sulfones were found to be unstable, and used immediately to facilitate a nucleophilic substitution by various primary amines or ammonia. The transformation of sulfide **33** into 7-amino compound **35** was accomplished in 80% overall yield <2004JHC575>.



Scheme 21

7-Methoxy[1,2,3]triazolo[4,5-*d*]pyrimidine nucleosides are susceptible to nucleophilic displacement by hydroxide ions, as represented by the example in **Scheme 22** <2005HCA751>.

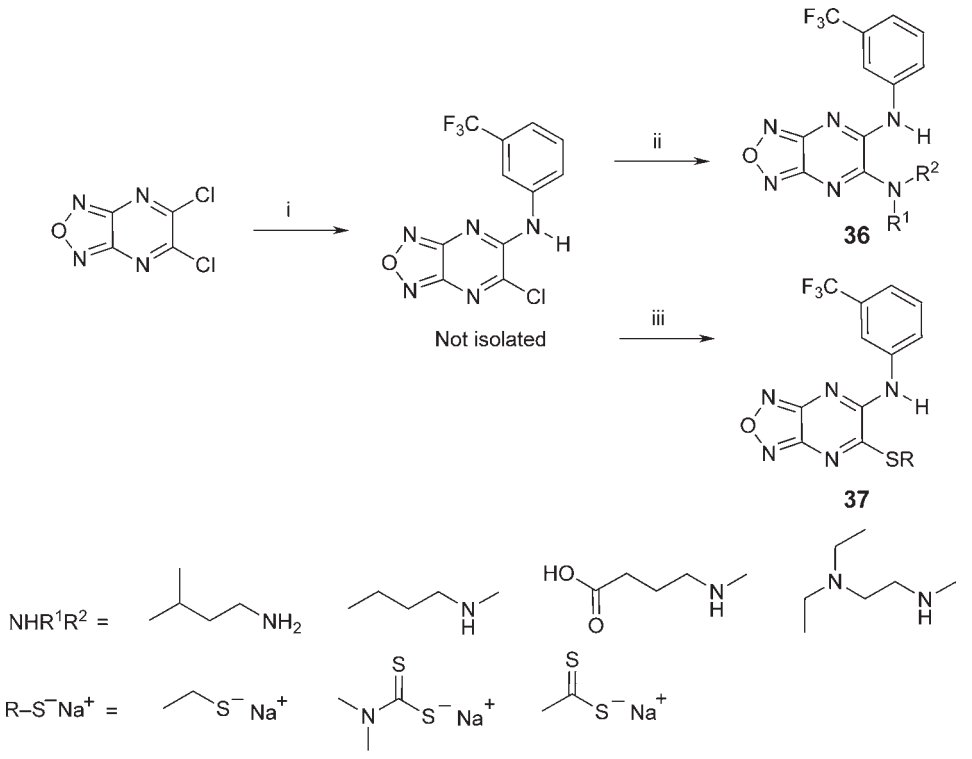


Scheme 22

10.13.5.3.2 Oxazoloazines and azolooxazines

10.13.5.3.2(i) [1,2,5]Oxadiazolo[3,4-*b*]pyrazines

Fernández *et al.* reported the solid-phase synthesis of a library of asymmetrically disubstituted [1,2,5]oxadiazolo[3,4-*b*]pyrazines by stepwise displacement of two chlorine atoms in 5,6-dichloro derivatives using various nitrogen nucleophiles <2002TL4741>. The preliminary solution-phase reaction is shown in **Scheme 23** (yields not given) in which the displacement of one chlorine atom was partially controlled by using weak bases such as anilines, acting as both hydrogen chloride acceptors and hindered nucleophiles. The second nucleophile added was either a primary or secondary aliphatic amine or a sodium thiolate. However, in these solution reactions, tedious chromatography was required to separate the required products **36** and **37** from symmetrical derivatives. In contrast, selectivity problems were largely avoided when inserting the aniline building block attached to a solid-phase resin.

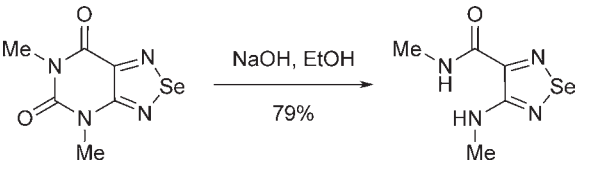


Scheme 23

10.13.5.3.3 Other heterocycles

10.13.5.3.3(i) [1,2,5] Selenadiazolo[3,4-*d*]pyrimidines

4,6-Dimethyl[1,2,5]selenadiazolo[3,4-*d*]pyrimidine-5,7-dione was hydrolyzed using 5% aqueous sodium hydroxide in ethanol to give 4-methylamino-3-(*N*-methylcarbamoyl)[1,2,5]selenadiazole in good yield (**Scheme 24**)

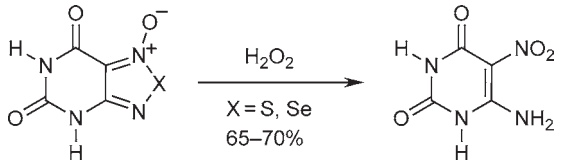


Scheme 24

<2000JHC1269>. An analogous basic hydrolysis of the fused pyrimidinone ring in these heterocyclic systems had been previously reviewed by Knowles <1996CHEC-II(7)489>.

10.13.5.4 Nucleophilic Attack at Sulfur or Selenium

A vigorous reaction occurs when 1,2,5-thia- and selena-diazole *N*-oxides annulated onto pyrimidine rings are treated with 10–30% hydrogen peroxide resulting in the formation of 6-amino-5-nitrouracils (**Scheme 25**) <2000CHE1359>.



Scheme 25

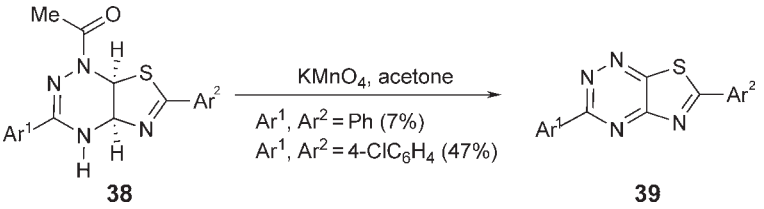
10.13.6 Reactivity of Nonconjugated Rings

10.13.6.1 Oxidative Aromatization

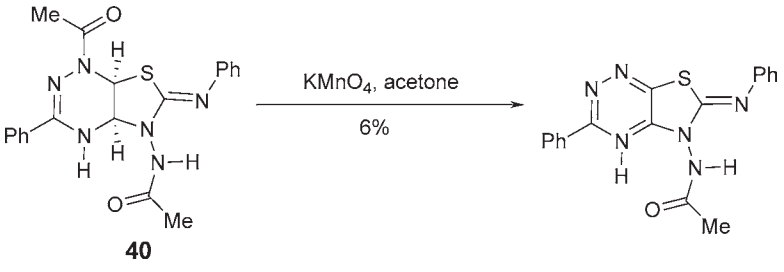
10.13.6.1.1 Thiazoloazines and azothiazines

10.13.6.1.1(i) [1,3]Thiazolo[4,5-*e*][1,2,4]triazines

Oxidation of 1-acetyl-1,4,4*a*,7*a*-tetrahydrothiazolotriazines **38** with potassium permanganate in acetone at room temperature resulted in dehydrogenation accompanied by elimination of the *N*-acetyl group to give the conjugated aromatic system, [1,3]thiazolo[4,5-*e*][1,2,4]triazines **39** (**Scheme 26**) <2004RCB1279>. A similar oxidative deacetylation and rearomatization occurred for related heterocycle **40**, although the isolated product yields were low (**Scheme 27**) <2004RCB1279>.



Scheme 26



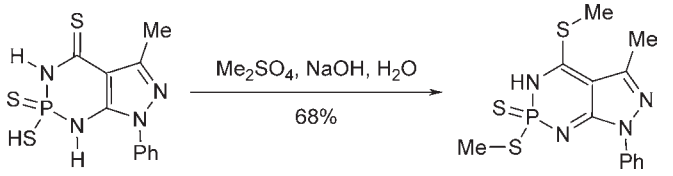
Scheme 27

10.13.6.2 Electrophilic Attack at Sulfur

10.13.6.2.1 Other heterocycles

10.13.6.2.1(i) Pyrazolo[3,4-*d*][1,3,2]diazaphosphinines

Scheme 28 shows the alkylation of the thioamides to give alkyl sulfides of pyrazolo[3,4-*d*][1,3,2]diazaphosphinine ring system <1998KFZ16>.



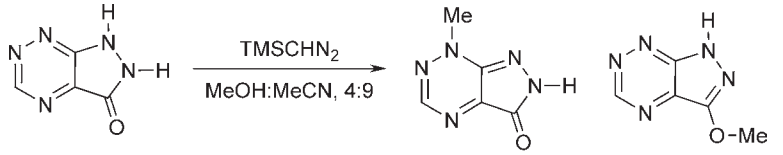
Scheme 28

10.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms

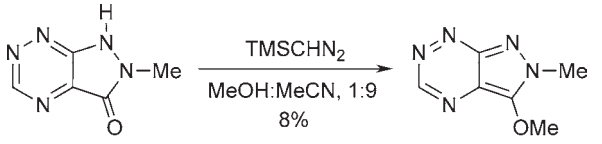
10.13.7.1 Azoloazines

10.13.7.1.1 Pyrazolo[4,3-e][1,2,4]triazines

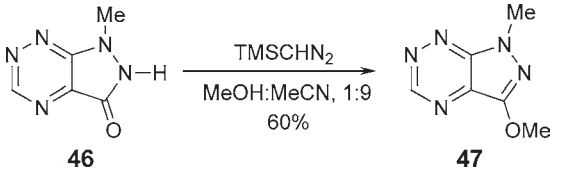
The products obtained from attempted O-methylation of pyrazolo[4,3-*e*][1,2,4]triazin-3-ones with the oxophilic reagent, (trimethylsilyl)diazomethane, were found to be highly dependent upon existing substitution patterns on nitrogen atoms <2006JA5646>. Unsubstituted compound **41** gave a mixture of 7-*N*-methyl **42** and *O*-methyl-substituted derivative **43** (**Scheme 29**). N-2 and N-1 methyl-substituted derivatives **44** (**Scheme 30**) and **46** (**Scheme 31**) respectively gave exclusive O-methylated products **45** in poor yield and **47** in good yield. The reactions given in **Schemes 29–31** form part of natural product elucidation studies described in more detail in Section 10.13.12.1.2.



Scheme 29



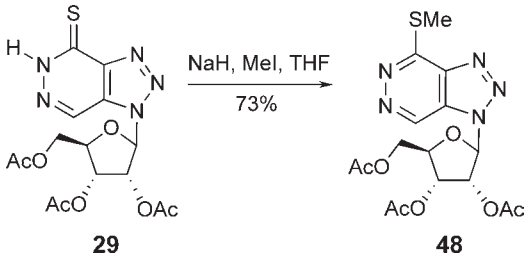
Scheme 30



Scheme 31

10.13.7.1.2 [1,2,3]Triazolo[4,5-*d*]pyridazines and [1,2,3]triazolo[4,5-*d*]pyrimidines

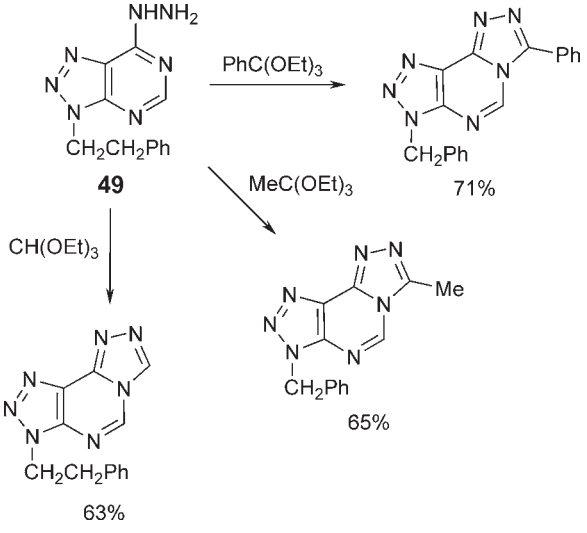
Alkylations of the 4-thione substituent of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)triazolo[4,5-*d*]pyridazine-4-thione **29** were carried out using sodium hydride and various alkyl halides, and the reaction with methyl iodide to give methylthio derivative **48** is shown in **Scheme 32** <1996BMC1725>.



29 **48**

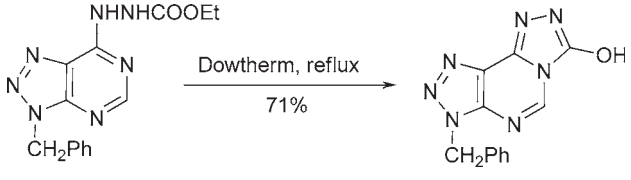
Scheme 32

Triazole rings can be built using hydrazine substituents attached to carbon or nitrogen atoms <1996CHEC-II(7)489>. Livi and co-workers fused 1,2,4-triazole rings onto [1,2,3]triazolo[4,5-*d*]pyrimidines by condensation of the 7-hydrazine derivatives (e.g., **49**) with triethyl orthoformate, triethyl orthoacetate, or triethyl orthobenzoate, to give various tricyclic compounds in good yields (**Scheme 33**) <1999JHC1195>.



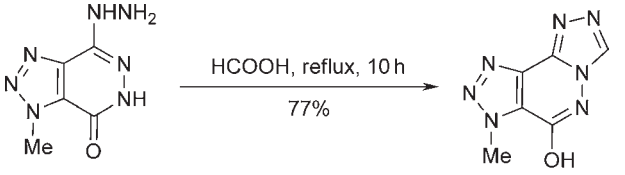
Scheme 33

An analogous transformation can be achieved thermally using [1,2,3]triazolo[4,5-*d*]pyrimidine bearing an ethoxycarbonylhydrazino substituent at the 7-position, which induced a cyclization with the elimination of ethanol (**Scheme 34**) <1999JHC1195>.



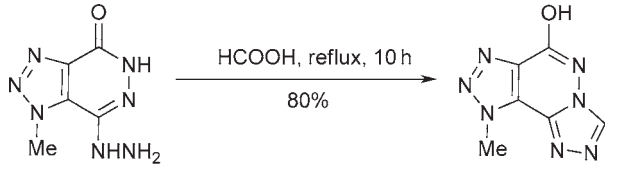
Scheme 34

A similar condensation of 2,3-triazolo[4,5-*d*]pyridazine 4- and 7-hydrazino derivatives **50** and **52** with formic acid gave [1,2,3]triazolo[4,5-*d*][1,2,4]triazolo[4,3-*b*]pyridazin-4-ols **51** and **53** in high yields, as shown in **Schemes 35** and **36**, respectively <2002JHC889>.



50 **51**

Scheme 35



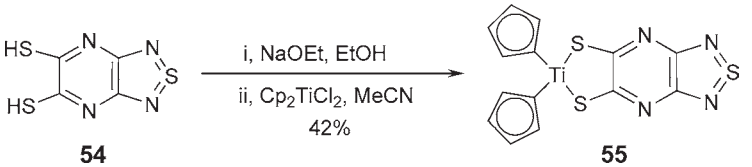
52 **53**

Scheme 36

10.13.7.2 Thiazoloazines and Azolothiazines

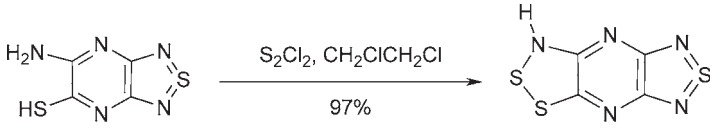
10.13.7.2.1 [1,2,5]-Thiadiazolo[3,4-*b*]pyrazines

Oakley and co-workers reported the transformation of 1,2,5-thiadiazolo[3,4-*b*]pyrazines into tricyclic rings **55** and **57**. Titanocene **55** was prepared by reaction of 5,6-dithiol derivative **54** with Cp_2TiCl_2 under basic conditions (**Scheme 37**) <1998JA352>, and 6-amino-5-thiol **56** was condensed with sulfur monochloride to give the 1,2,3-dithiazolidine derivative **57** in excellent yield (**Scheme 38**) <1999JA969>.



54 **55**

Scheme 37



56 **57**

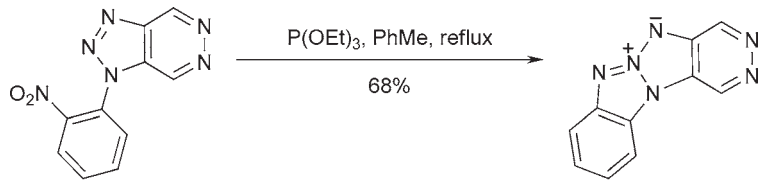
Scheme 38

10.13.8 Reactivity of Substituents Attached to Ring Heteroatoms

10.13.8.1 Azoloazines

10.13.8.1.1 [1,2,3]Triazolo[4,5-*d*]pyridazines

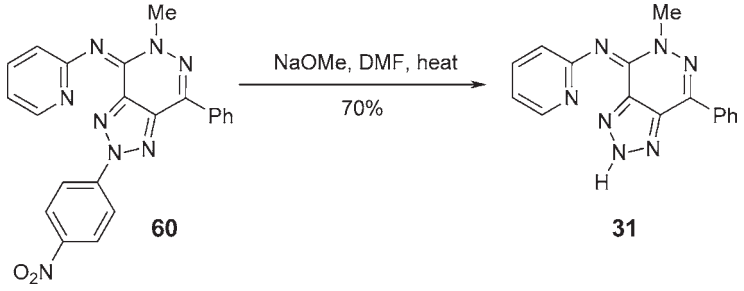
The tetrazapentalene ring system **59** was constructed by reductive cyclization of *N*-(2-nitrophenyl)[1,2,3]triazolo[4,5-*d*]-pyridazine **58** with triethyl phosphite in toluene at 120 °C (**Scheme 39**) <2000JHC1597>.



58 59

Scheme 39

The 4-nitrophenyl substituent of [1,2,3]triazolo[4,5-*d*]pyridazine **60** was readily displaced by sodium methoxide to afford the unsubstituted triazole **31**, as shown in **Scheme 40** <2000CC1785>.



60 31

Scheme 40

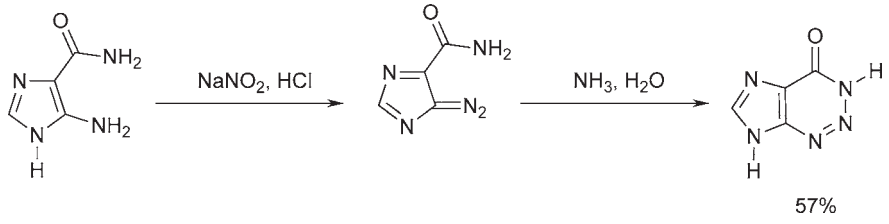
10.13.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

10.13.9.1 Synthesis of the Fused Six-Membered Ring

10.13.9.1.1 Azoloazines

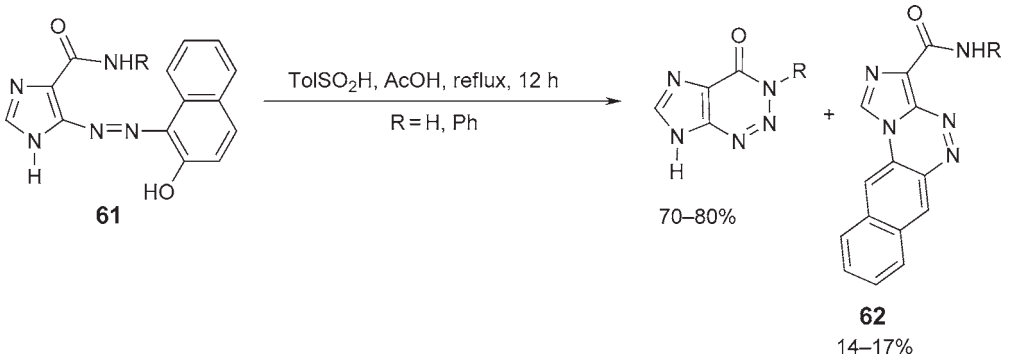
10.13.9.1.1(i) Imidazo[4,5-*d*][1,2,3]triazines

There have been several preparations of imidazo[4,5-*d*][1,2,3]triazin-4-one (2-azahypoxanthine) <1996CHEC-II(7)489, 1996BML185, 1997JOC7288, 2002MRC300>, but all are modifications of a well-established diazotization procedure dating back to the early 1960s <1962JOC2150>. These reactions involve treatment of 5(4)-aminoimidazole-4(5)-carboxamide with nitrous acid, as shown in **Scheme 41** <1996BML185>.



Scheme 41

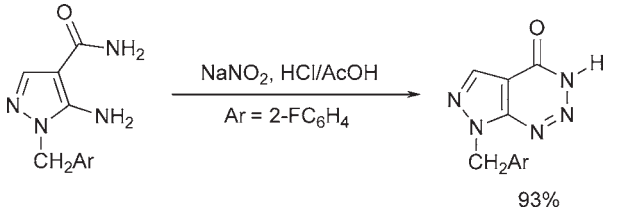
Azo compounds **61** under acidic conditions were reported to undergo a cyclization with elimination of 2-naphthol to give imidazo[4,5-*d*][1,2,3]triazin-4-ones as unexpected major products with relatively little of the expected imidazole-*N*-1 cyclization products **62** isolated (**Scheme 42**) <2000CHE465>.



Scheme 42

10.13.9.1.1(ii) Pyrazolo[3,4-*d*][1,2,3]triazines

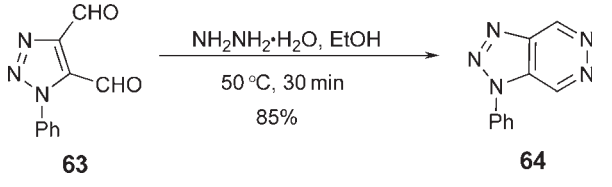
Analogous to the synthesis of imidazo[4,5-*d*][1,2,3]triazin-4-ones (**Scheme 41**), diazotization is the method of choice for making this ring system, and involves treatment of the 5-aminopyrazole-4-carboxamides with nitrous acid (**Scheme 43**) <1995JHC1417, 1996CHEC-II(7)489>.



Scheme 43

10.13.9.1.1(iii) [1,2,3]Triazolo[4,5-*d*]pyridazines

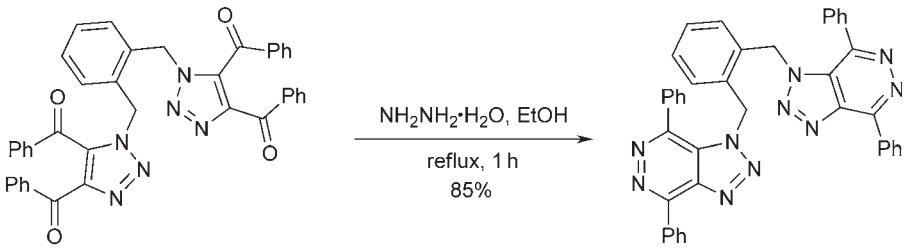
The traditional approach to this ring system involves adding hydrazine to [1,2,3]triazole-4,5-dialdehyde to condense the fused pyridazine ring <1996CHEC-II(7)489>. For example, Trudell and co-workers reported the conversion of dialdehyde **63** into the fused pyridazine ring compound **64** by reaction with hydrazine monohydrate at 50 °C (**Scheme 44**) <2000JHC1597>.



Scheme 44

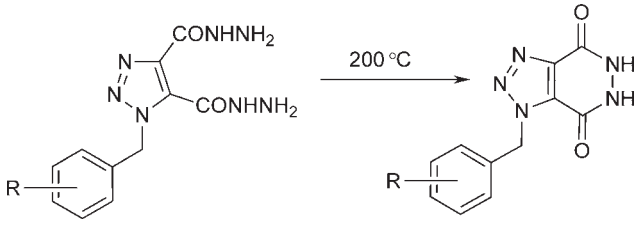
Abu-Orabi *et al.* used the condensation of hydrazine with bis(triazole) diketone **65** to form bis(triazolopyridazine) **66** (**Scheme 45**) <1999MI774>.

The same group reported the formation of the fused pyridazine dione ring without the addition of hydrazine <2000HCO443>. [1,2,3]Triazolo[4,5-*d*]pyridazine-4,7-diones **68** were formed in moderate yields by heating dicarboxyhydrazides **67** at 200 °C in the absence of solvent for 4–5 h (**Scheme 46**; **Table 3**) <2000HCO443>. Analogous dicarboxyhydrazides were reported to give [1,2,3]triazolo[4,5-*d*]pyridazine-4,7-diones in improved yields by Livi and co-workers with the cyclization induced by 10% hydrochloric acid solution <2002JHC889>.



65 66

Scheme 45



67 68

Scheme 46

Table 3 Yields for the synthesis of **68** from **67** in **Scheme 46**

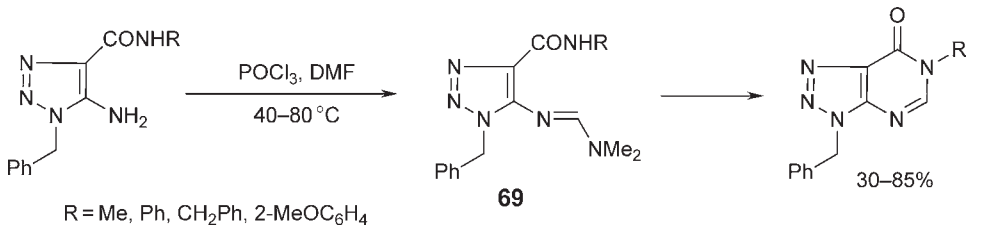
R	*Yield of* **68** (%)
H	60
4-Me	57
3-Me	55
4-MeO	52
2-Cl	56
3-Cl	51
4-Cl	55
2-Br	56
3-Br	53
4-Br	52
$4\text{-}O_2N$	49
2-F	47
3-F	53
$2,6\text{-}Cl_2$	48
$2,3,4,5,6\text{-}(Me)_5$	52

10.13.9.1.1(iv) [1,2,3]Triazolo[4,5-*d*]pyrimidines

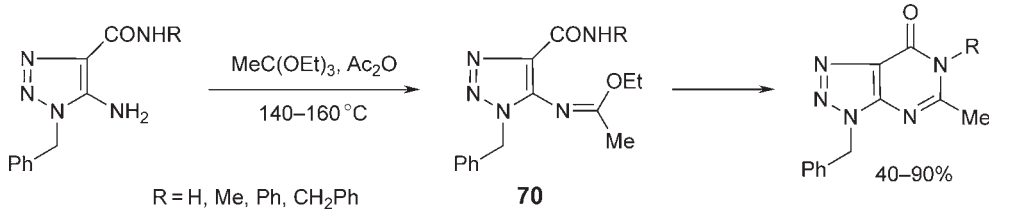
Kislyi *et al.* facilitated the formation of [1,2,3]triazolo[4,5-*d*]pyrimidin-7-ones from 5-amino-1,2,3-triazole-4-carboxamides under Vilsmeier conditions (**Scheme 47**) or using triethyl orthoacetate and acetic anhydride (**Scheme 48**) <2003RCB1770>. These methods could be used to isolate the respective 5-formamidine **69** and 5-imidoate **70** reaction intermediates, if lower temperatures and shorter reaction times were employed.

A more recent synthesis of [1,2,3]triazolo[4,5-*d*]pyrimidin-7-ones involved the elimination of ethanol from a base-catalyzed cyclization of a 5-urea derivative onto the 4-ester substituent of, for example, guanidine **71** (**Scheme 49**) <2005S2544>.

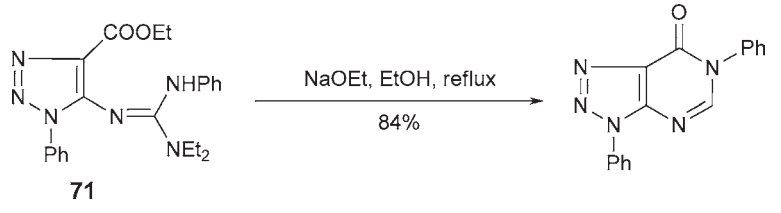
The preparation of [1,2,3]triazolo[4,5-*d*]pyrimidine **73** was reported from 1,2,3-triazole **72** using sodium methoxide in refluxing methanol. The mechanism presumably involves the addition of base to the 4-carbonitrile substituent of



Scheme 47

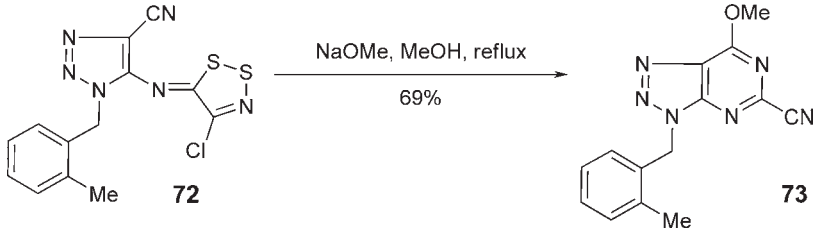


Scheme 48



Scheme 49

72, with subsequent nucleophilic cyclization onto the adjacent 5-imine substituent leading to collapse of the dithiazole ring to give the 5-carbonitrile substituent of **73** with elimination of chlorine and sulfur (**Scheme 50**) <2002BMC449>.

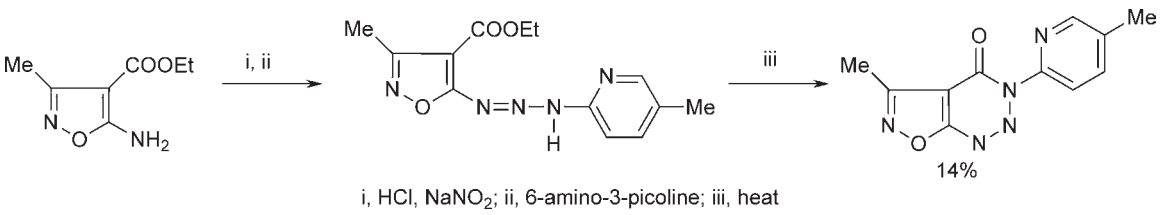


Scheme 50

10.13.9.1.2 Oxazoloazines and azolooxazines

10.13.9.1.2(i) Isoxazolo[5,4-*d*][1,2,3]triazines

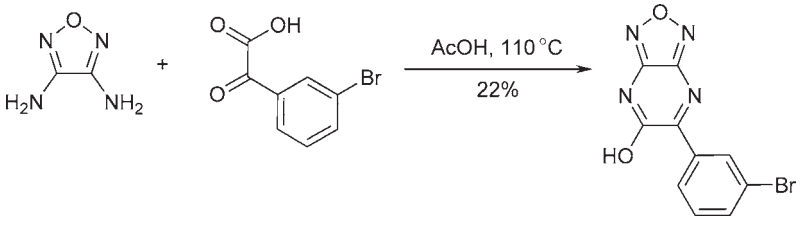
The preparation of isoxazolo[5,4-*d*][1,2,3]triazine-4-ones is usually achieved via diazotization <1988JP11509, 2003MI147>. For example, 5-amino-3-methylisoxazole-4-ethanoate formed the diazonium salt that was not isolated, and underwent spontaneous cyclizations upon heating to give the isoxazolo[5,4-*d*][1,2,3]triazine-4-one in modest yield (**Scheme 51**) <1997FA105>.



Scheme 51

10.13.9.1.2(ii) [1,2,5]Oxadiazolo[3,4-*b*]pyrazines

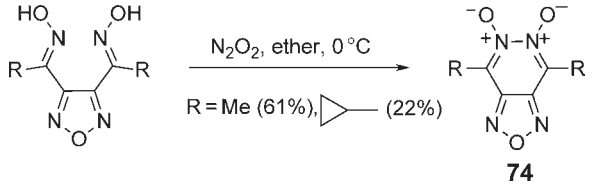
The established procedure for the synthesis of the fused pyrazine ring involves condensation of the oxadiazole diamine with 1,2-dicarbonyl compounds <1978JOC341>. The latter procedure was used by Beebe *et al.* to make a series of [1,2,5]oxadiazolo[3,4-*b*]pyrazines for evaluation as antibacterial agents <2003BML3133>. An example is shown in **Scheme 52**, which involved heating the diamine with (3-bromophenyl)oxoacetic acid in glacial acetic acid at 110 °C to give the [1,2,5]oxadiazolo[3,4-*b*]pyrazine.



Scheme 52

10.13.9.1.2(iii) [1,2,5]Oxadiazolo[3,4-*d*]pyridazines

Ring closure of 1,6-dioximes by treatment with dinitrogen tetroxide in dry ether has been previously used to give the fused pyridazine ring in this heterocyclic system <1996CHEC-II(7)489>, and was used more recently to give the *N*,*N*′-dioxides **74** (**Scheme 53**) <2000CHE1091>.

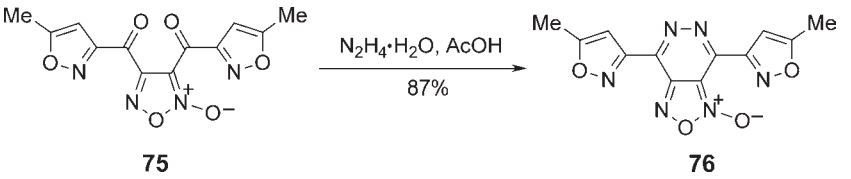


Scheme 53

Acidic condensation of hydrazine with 3,4-diacyloxadiazole **75** was reported to give the pyridazine-fused compound **76** in high yield, as shown in **Scheme 54** <2003T1059>.

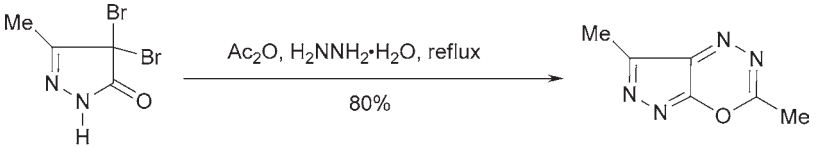
10.13.9.1.2(iv) Pyrazolo[4,3-*e*][1,3,4]oxadiazines

A novel approach to the formation of the fused [1,3,4]oxadiazine ring in this heterocyclic system involved treatment of pyrazol-3-one **77** with acetic anhydride and hydrazine hydrate to give oxadiazine **78** in high yield (**Scheme 55**) <2002IJB664>.



75 **76**

Scheme 54



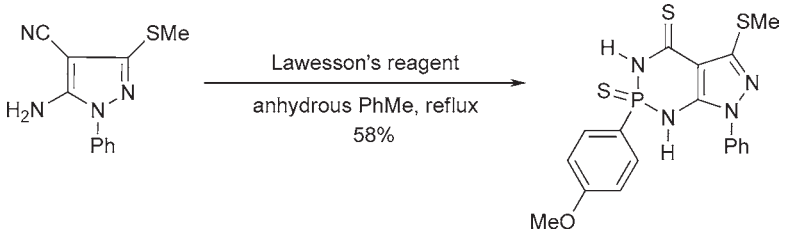
77 **78**

Scheme 55

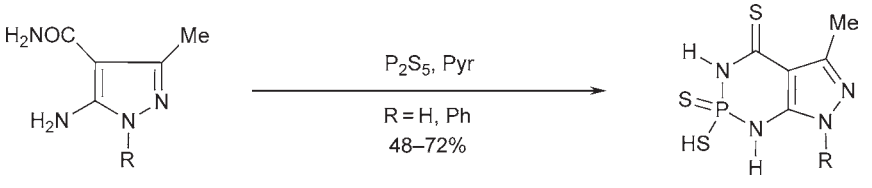
10.13.9.1.3 Other heterocycles

10.13.9.1.3(i) Pyrazolo[3,4-*d*][1,3,2]diazaphosphinines

Scheme 56 shows a reported preparation of this heterocyclic system from 5-amino-4-cyano-3-methylthia-1-phenylpyrazole upon treatment with Lawesson's reagent (**Figure 8**) <2001S2445>. The proposed mechanism of this reaction involves condensation of Lawesson's reagent with the amine and addition of P–SH onto the nitrile with subsequent rearrangement. A similar six-membered ring formation from 5-amino-3-methylpyrazole-4-carboxamides using P_2S_5 had been earlier reported (**Scheme 57**) <1998KFZ16>.



Scheme 56

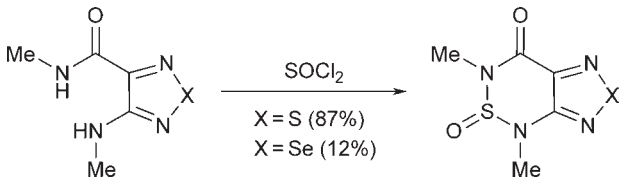


Scheme 57

10.13.9.1.4 New heterocyclic systems

10.13.9.1.4(i) [1,2,5]Thiadiazolo[3,4-*c*][1,2,6]thiadiazines and [1,2,5]selenadiazolo[3,4-*c*][1,2,6]thiadiazines

The synthesis of novel heterocyclic systems [1,2,5]thia(or selena)diazolo[3,4-*c*][1,2,6]thiadiazine was reported by Ueda *et al.* by treatment of 4-methylamino-3-(*N*-methylcarbamoyl)[1,2,5]thia(selena)diazole with thionyl chloride (**Scheme 58**) <2000JHC1269>.



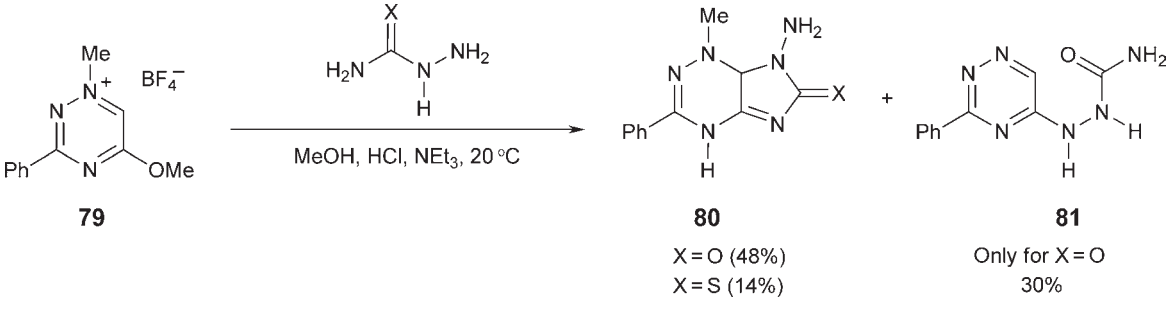
Scheme 58

10.13.9.2 Synthesis of the Fused Five-Membered Ring

10.13.9.2.1 Azoloazines

10.13.9.2.1(i) Imidazo[4,5-*e*][1,2,4]triazines

Neunhoeffer and co-workers have fused the imidazole ring onto 1,2,4-triazines by activation of the latter as N-1 salts with subsequent reaction with *N*,*N*′-bis-nucleophiles, such as urea, thiourea, semicarbazide, thiosemicarbazide, and alkylated derivatives <2001JHC901>. The reactions of semicarbazide (X = O) and thiosemicarbazide (X = S) with 1-methyl-5-methoxy-1,2,4-triazinium tetrafluoroborate **79** are given in **Scheme 59**. In the thiosemicarbazide case, the isolation of mainly intermediate **82a** and **82b** (**Figure 9**) shortly after commencing the reaction indicated that nucleophilic attack at the unsubstituted 6-position of **79** occurred first followed by displacement of the 5-methoxy substituent to give the final cyclization product **80** (X = S). The semicarbazide reaction gave the 1,2,4-triazine **81** via competitive *ipso*-substitution, as well as the required cyclization product **80** (X = O). The imidazo[4,5-*e*][1,2,4]triazine ring system has been prepared earlier *via* a similar reaction between 5,6-dichloro-1,2,4-triazine and benzenecarboximidamide with substitution at the 5-position followed by nucleophilic cyclization to displace the 6-chloro substituent <1996CHEC-II(7)489>.



79

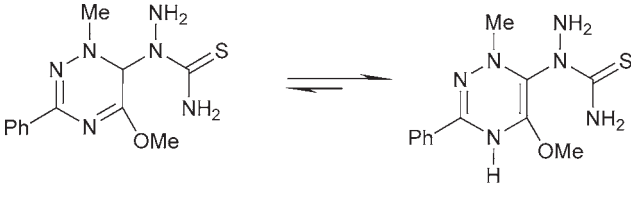
80

X = O (48%)
X = S (14%)

81

Only for X = O
30%

Scheme 59



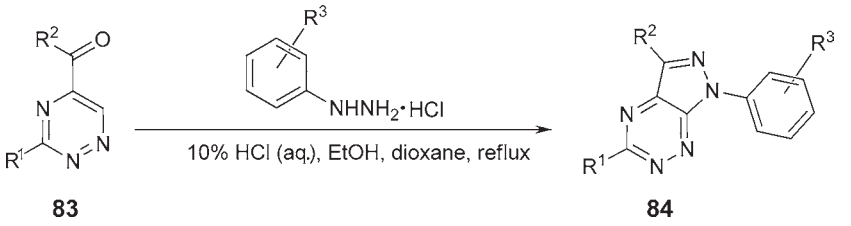
82a **82b**

Figure 9

10.13.9.2.1(ii) Pyrazolo[4,3-*e*][1,2,4]triazines

Most ring synthesis methods focus on formation of the five-membered pyrazole through cyclizations involving condensation of hydrazine with carbonyl moieties attached to the [1,2,4]triazine <1996CHEC-II(7)489>. A typical synthesis of the pyrazole ring to give various pyrazolo[4,3-*e*][1,2,4]triazines **84** was reported by Rykowski *et al.* using a

one-pot conversion of 5-acyl-1,2,4-triazines **83** into hydrazones *in situ* by reaction with phenylhydrazine hydrochlorides, and subsequent five-membered cyclization under slightly acidic conditions (**Scheme 60**; **Table 4**) <2000H(53)2175>.



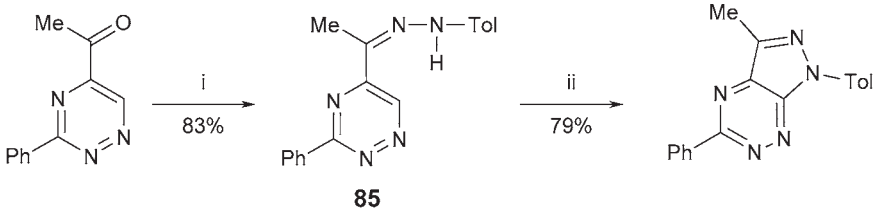
83 **84**

Scheme 60

Table 4 Yields for the synthesis of **84** from **83** in **Scheme 60**

R^1	R^2	R^3	*Yield of* **84** (%)
Ph	Me	3-Cl	86
Ph	Me	4-O_2N	52
Ph	Me	2-Me	60
Ph	Me	3-Me	78
SMe	Et	H	67

This Polish group isolated the hydrazone in some cases in the reaction given in **Scheme 60** by preparing the hydrazone at room temperature rather than at reflux. An alternative two-step procedure is shown in **Scheme 61**, where hydrazone **85** was isolated <2000H(53)2175>.



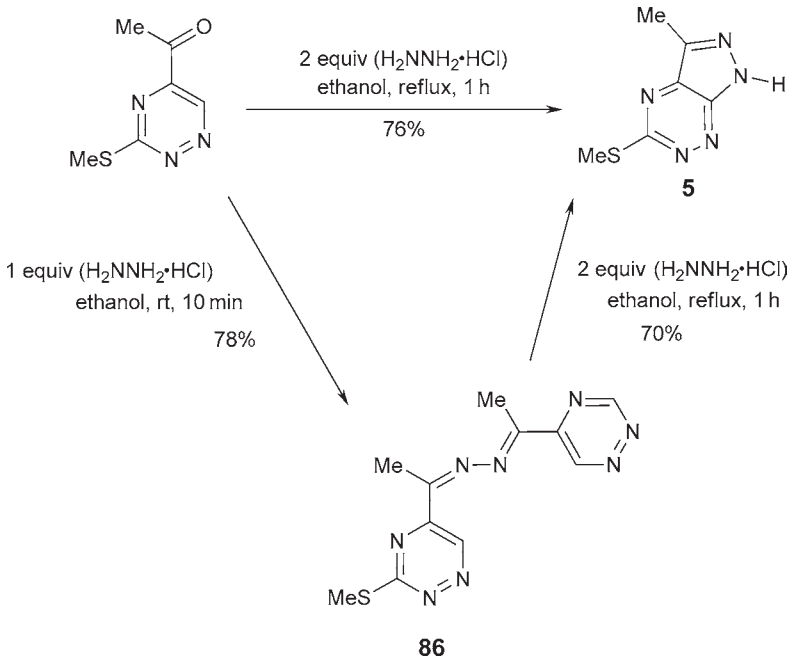
85

i, 4-MeC$_6$H$_4$NHNH$_2$·HCl, 10% HCl (aq.), EtOH, dioxane, rt; ii, 10% HCl (aq.), EtOH, dioxane, reflux

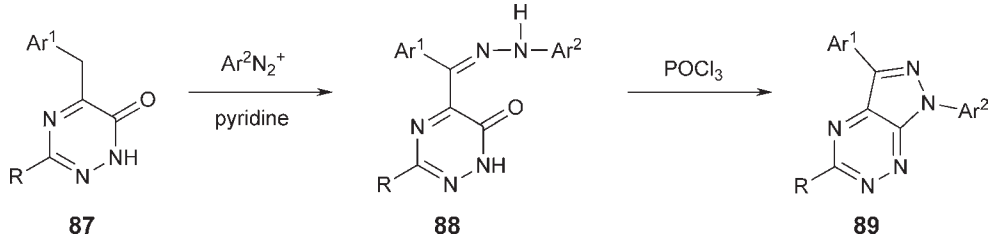
Scheme 61

In a later report, Mojzych and Rykowski showed that pyrazolo[4,3-*e*][1,2,4]triazine **5** could be obtained using a condensation between hydrazine hydrochloride and 5-acetyl-3-(methylsulfanyl)-1,2,4-triazine (**Scheme 62**). When 1 rather than 2 equiv of hydrazine hydrochloride was used, and the reaction temperature was kept at room temperature, azine intermediate **86** was isolated <2003PJC1797>.

An alternative acidic five-membered nucleophilic cyclization of hydrazone to give the pyrazole ring was reported by Gucký *et al.* <2002HCO613>. This involved prior preparation of aryl hydrazones **88** by coupling the activated benzylic position of 1,2,4-triazin-6-one **87** with aryl diazonium salts. Aryl hydrazones **88** were cyclized onto the triazine carbonyl in hot $POCl_3$ to give pyrazoles **89** (**Scheme 63**). The overall yields for transforming **87** into **89** are shown in **Table 5**. The aryl diazonium salts ($Ar^2N_2^+$) were prepared using traditional hydrochloric acid/sodium nitrite aqueous mixture, and were stored on an ice bath prior to addition to **87**. This Czech group used the same $POCl_3$



Scheme 62



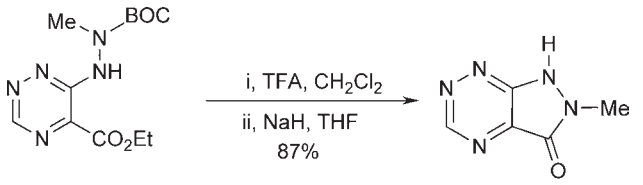
Scheme 63

Table 5 Overall yields for the synthesis of **89** (**Scheme 63**) and **92** (**Scheme 68**) from **87**

R	Ar^1	Ar^2	*Yield of* **89** (%)	*Yield of* **92** (%)
Me	Ph	Ph	61	
Me	Ph	4-$O_2NC_6H_4$	69	
Me	Ph	4-ClC_6H_4	82	
Me	Ph	2-$MeOC_6H_4$	84	
Me	4-ClC_6H_4	Ph	57	
Me	4-ClC_6H_4	4-$O_2NC_6H_4$	61	
Me	4-ClC_6H_4	4-ClC_6H_4	78	
Ph	Ph			85
Ph	4-ClC_6H_4			77
Me	4-ClC_6H_4			72

conditions to convert oximes into isoxazolo[4,5-*e*][1,2,4]triazines (**Scheme 68**). El Massry reported an analogous condensation of 6-benzoyl-[1,2,4]triazine-3,5-dione with aryl hydrazines to form hydrazones *in situ*, that cyclized to give pyrazolo[4,3-*e*][1,2,4]triazines <2003PS1143>.

Hydrolysis of the hydrazine BOC-protecting group of **90** followed by treatment with sodium hydride gave pyrazolo[4,3-*e*][1,2,4]triazine-3-one **44** by nucleophilic cyclization onto the 5-ethoxycarbonyl group (**Scheme 64**) <2006JA5646>.

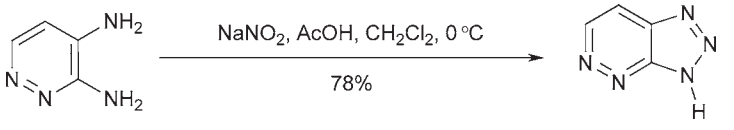


90 44

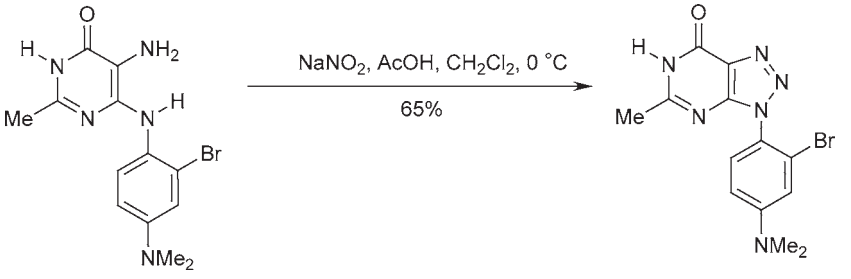
Scheme 64

10.13.9.2.1(iii) [1,2,3]Triazolo[4,5-*c*]pyridazines

[1,2,3]Triazolo[4,5-*c*]pyridazine synthesis dates back to the early 1960s <1964JHC247>, and involves the formation of the fused [1,2,3]triazole ring by treatment of 3,4-diaminopyridazine with sodium nitrite in dilute acid at 0 °C. A more recent synthesis is shown in **Scheme 65** <2000JHC1597>, and was carried out under the same reaction conditions as the nitrosation given in **Scheme 66** to form [1,2,3]triazolo[4,5-*d*]pyrimidines.



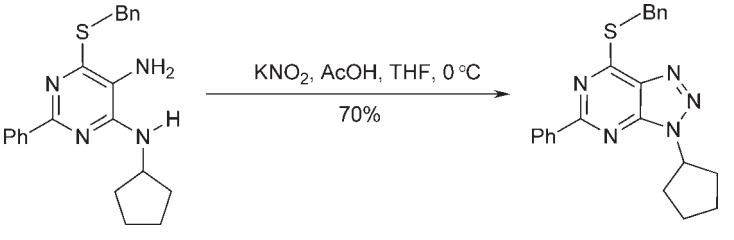
Scheme 65



Scheme 66

10.13.9.2.1(iv) [1,2,3]Triazolo[4,5-*d*]pyrimidines

The fused triazole ring is most commonly prepared by nitrosation followed by cyclization involving treatment of diaminopyrimidines with either sodium or potassium nitrite in dilute acid <1996CHEC-II(7)489, 2003JCO653>, as shown in the examples in **Schemes 66** <1999JME833> and **67** <2004JHC575>.

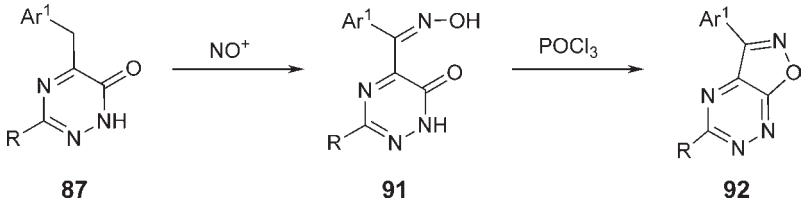


Scheme 67

10.13.9.2.2 Oxazoloazines and azolooxazines

10.13.9.2.2(i) Isoxazolo[4,5-*e*][1,2,4]triazines

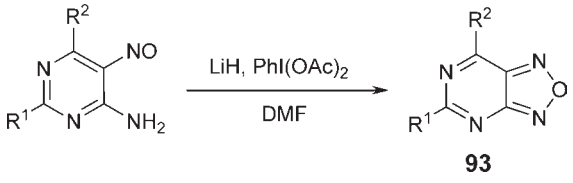
Gucký *et al*. prepared oximes **91** by nitrosation of the activated methylene group of **87** using nitrosylsulfuric acid and sodium nitrite in concentrated sulfuric acid (**Scheme 68**) <2002HCO613>. Oximes **91** were treated with hot $POCl_3$ to induce a five-membered cyclization to provide the fused isoxazole ring in **92**. The overall yields for transforming **87** to **92** are shown in **Table 5**.



Scheme 68

10.13.9.2.2(ii) [1,2,5]Oxadiazolo[3,4-*d*]pyrimidines

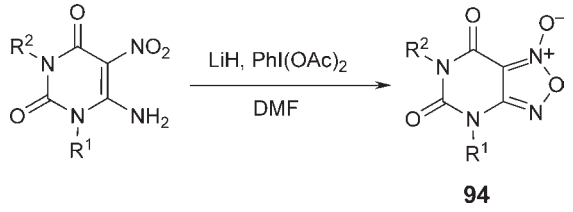
Oxidative cyclizations of the 6-amino substituent onto the adjacent nitroso group to give **93** (**Scheme 69**; **Table 6**) <1997S1255> and nitro group to give **94** (**Scheme 70**; **Table 7**) <1998JOC6947> attached to respective pyrimidine and pyrimidine-2,4-dione rings were used to fuse the 1,2,5-oxadiazole ring. The transformation in **Scheme 69** has more recently been reported in acidic media, and intermediate tri- and tetraoximes isolated <2005RJC493>.



Scheme 69

Table 6 Yields for the synthesis of **93** in **Scheme 69**

R^1	R^2	*Yield of* **93** (%)
OH	OH	92
H	NH_2	90
NH_2	NH_2	89
NH_2	OBn	89

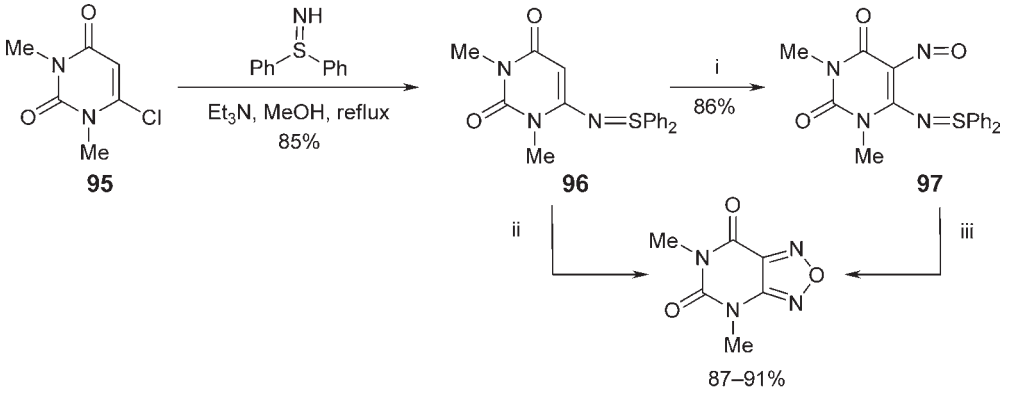


Scheme 70

The synthesis of 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione was reported by Matsumoto and Takahashi starting from 6-chlorouracil **95** (**Scheme 71**) <2002T10073>. Displacement of the chlorine substituent

Table 7 Yields for the synthesis of **94** in **Scheme 70**

R^1	R^2	*Yield of* **94** (%)
Me	Me	95
Me	H	72
H	Me	85
H	H	97



i, isopentyl nitrite, PhMe, reflux, 5 min; ii, isopentyl nitrite, PhMe, reflux, 3.5 h; iii, PhMe, reflux, 6 h

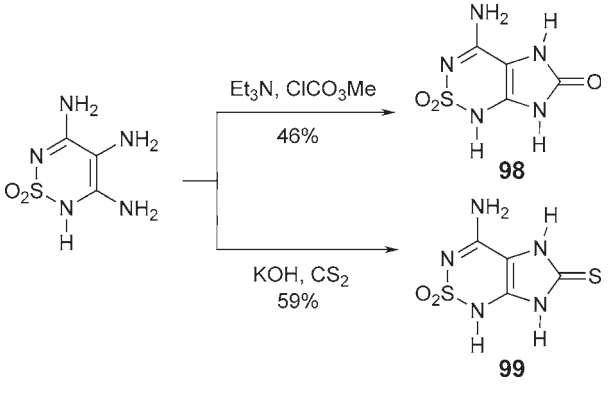
Scheme 71

of **95** by *S*,*S*-diphenylsulfimine gave sulfimine **96** in high yield. The nitroso adduct **97** was prepared by reaction of **96** with isopentyl nitrite, and extension of the reaction time gave the fused 1,2,5-oxadiazole ring directly in high yield. Alternatively, 4,6-dimethyl[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione was obtained by thermolysis of **97**.

10.13.9.2.3 Thiazoloazines and azolothiazines

10.13.9.2.3(i) Imidazo[4,5-*c*][1,2,6]thiadiazines

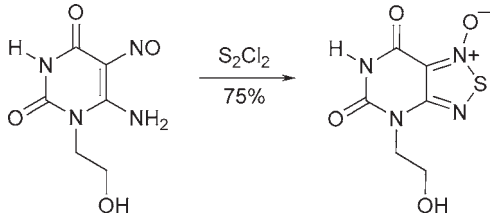
The synthesis of this ring system by condensation of 3,4,5-triamino-1,2,6-thiadiazine-1,1-dioxide with formic acid equivalents to give the fused imidazole ring dates back to the review by Montgomery and Secrist <1984CHEC(5)607>. This methodology was extended to cyclocondensation reactions of 3,4,5-triamino-1,2,6-thiadiazine-1,1-dioxide with electrophiles such as methyl chloroformate and carbon disulfide to yield 6-oxo **98** and 6-thioxo **99** derivatives of 4-aminoimidazo[4,5-*c*]-1,2,6-thiadiazine-2,2-dioxide respectively (**Scheme 72**) <1999BMC1617>.



Scheme 72

10.13.9.2.3(ii) [1,2,5]Thiadiazolo[3,4-*d*]pyrimidines

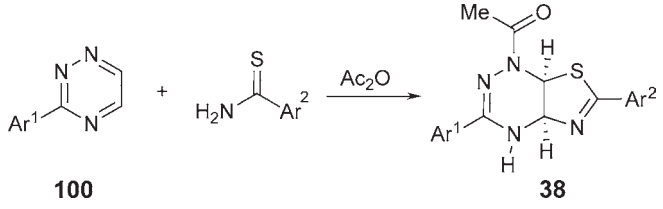
Scheme 73 shows the reaction of 1-hydroxyethyl-6-aminouracil with sulfur monochloride giving the [1,2,5]thiadiazolo[3,4-*d*]pyrimidine-*N*-oxide in good yield <2005RJC493>. An analogous transformation with selenium monochloride was reported in the same paper, and is given in **Scheme 77**.



Scheme 73

10.13.9.2.3(iii) Thiazolo[4,5-*e*][1,2,4]triazines

The reaction of 3-aryl-1,2,4-triazines **100** with thioamides in acetic anhydride was reported to occur regioselectively at room temperature resulting in simultaneous *N*-acetylation and annelation of the thiazole ring to form 1,4,4*a*,7*a*-tetrahydrothiazolo[4,5-*e*][1,2,4]triazines **38** (**Scheme 74**; **Table 8**) <2004RCB1279>.

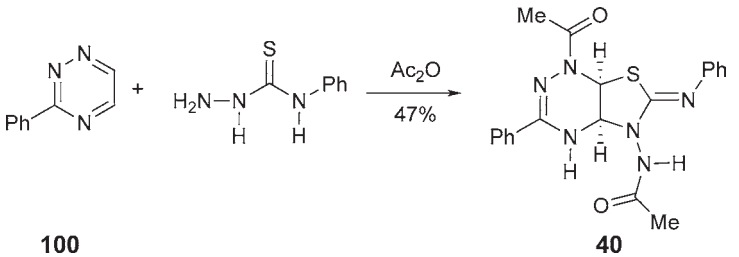


Scheme 74

Table 8 Yields for the synthesis of **38** from **100** in **Scheme 74**

Ar^1	Ar^2	*Yield of* **38** (%)
Ph	Ph	58
4-$MeOC_6H_4$	Ph	51
4-$O_2NC_6H_4$	Ph	15
4-ClC_6H_4	Ph	44
4-MeC_6H_4	Ph	44
Ph	4-ClC_6H_4	54
4-MeC_6H_4	4-ClC_6H_4	64
4-ClC_6H_4	4-ClC_6H_4	47
Ph	2-C_5H_4N	17
4-MeC_6H_4	2-C_5H_4N	48
4-MeC_6H_4	4-C_5H_4N	28
Ph	4-C_5H_4N	35

This Russian group reacted **100** (Ar^1 = Ph) with 4-phenylthiosemicarbazide under the same conditions as in **Scheme 74** to afford acetamide cycloadduct **40**, as shown in **Scheme 75** <2004RCB1279>.



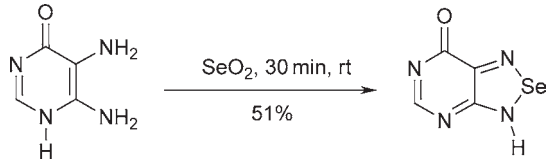
100 40

Scheme 75

10.13.9.2.4 Other heterocycles

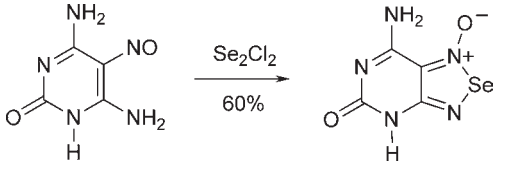
10.13.9.2.4(i) [1,2,5]Selenadiazolo[3,4-*d*]pyrimidines

Solvent-free selenium dioxide oxidation of 5,6-diaminopyrimidin-4-one was reported to give the [1,2,5]selenadiazolo[3,4-*d*]pyrimidin-7-one <2004MI289> as shown in **Scheme 76**. The fused selenadiozole ring may be alternatively formed by reacting the diamine in **Scheme 76** with H_2SeO_3 <1996CHEC-II(7)489>.



Scheme 76

Yavolovskii *et al*. have reported the synthesis of several [1,2,5]selenadiazolo[3,4-*d*]pyrimidines (e.g., **Scheme 77**) and [1,2,5]thiadiazolo[3,4-*d*]pyrimidines (e.g., **Scheme 73**) using respective sulfur and selenium monochloride reactions with nitrosopyrimidinamines <2005RJC493>.



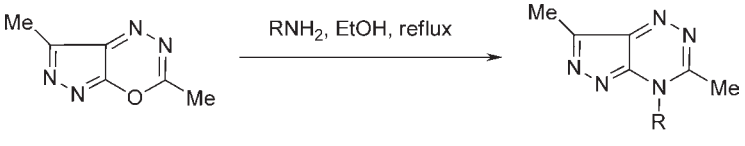
Scheme 77

10.13.10 Ring Synthesis by Transformation of Another Ring

10.13.10.1 Azoloazines

10.13.10.1.1 Pyrazolo[3,4-e][1,2,4]triazines

Pyrazolo[4,3-*e*][1,3,4]oxadiazine **78**, whose preparation is given in Section 10.13.9.1.2(iv), was condensed with various amines to give pyrazolo[3,4-*e*][1,2,4]triazines **101** (**Scheme 78**; **Table 9**) <2002IJB664>. This ring system was earlier reported by synthesis of the fused six-membered ring, through condensation onto pyrazolediones <1996CHEC-II(7)489>.



78 101

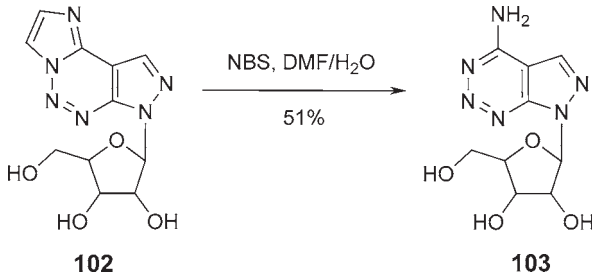
Scheme 78

Table 9 Yields for the synthesis of **101** from **78** in **Scheme 78**

R	*Yield of* **101** (%)
CH_2COOH	87
Tol	72
4-$H_2NC_6H_4$	67
4-$HOOCC_6H_4$	47

10.13.10.1.2 Pyrazolo[3,4-*d*][1,2,3]triazines

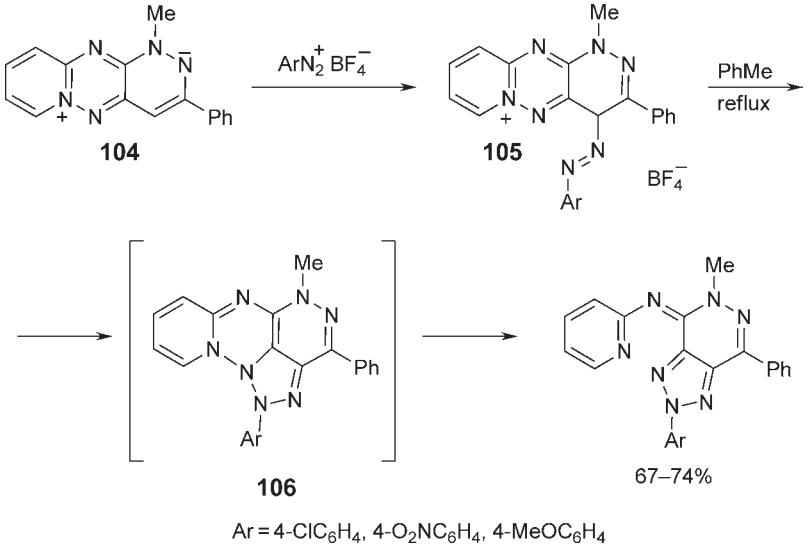
The removal of the *N*-etheno group from the fused imidazole ring of tricycle **102** was achieved using *N*-bromosuccinimide (NBS) in 1:1 DMF–water to yield the 2-azanucleoside (pyrazolo[3,4-*d*][1,2,3]triazine) **103** (**Scheme 79**) <2004JOC4695, 2005OBC1714>. An analogous tricycle transformation to imidazo[4,5-*d*][1,2,3]triazines has been reported earlier <1996CHEC-II(7)489>.



Scheme 79

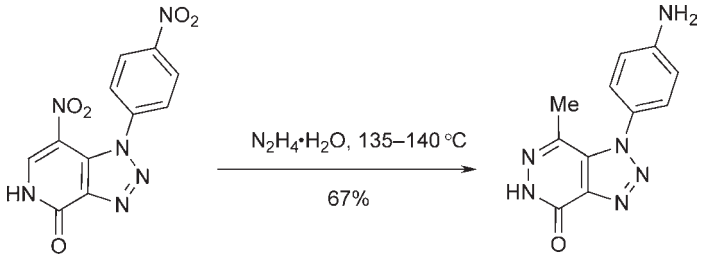
10.13.10.1.3 [1,2,3]Triazolo[4,5-*d*]pyridazines

Kövér *et al.* treated tricyclic zwitterion **104** with aryl diazonium salts, and observed changes in colors from green to bright red indicating azo coupling to give **105** (**Scheme 80**) <2000CC1785>. Salt **105** decomposed on heating to give yellow [1,2,3]triazolo[4,5-*d*]pyridazines. The required ring closure to give the fused pyridazine ring may have proceeded *via* the *peri*-fused tetracycle **106** formed *via* 1,5-dipolar cyclization after deprotonation of **105**.



Scheme 80

Yutilov *et al.* reported the formation of the [1,2,3]triazolo[4,5-*d*]pyridazin-4-one ring system with simultaneous conversion of the 7-nitro into a methyl substituent, and reduction of the aryl nitro group to an amino substituent on treatment of [1,2,3]triazolo[4,5-*c*]pyridin-4-one **107** with hydrazine at elevated temperatures (**Scheme 81**) <2004RJOC1015>.



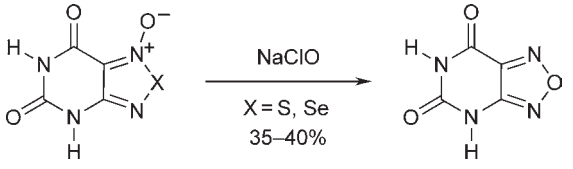
107

Scheme 81

10.13.10.2 Oxazoloazines and Azolooxazines

10.13.10.2.1 [1,2,5]Oxadiazolo[3,4-*d*]pyrimidines

When 1,2,5-thia- and selena-diazolo[3,4-*d*]pyrimidine-5,7-dione *N*-oxides are treated with sodium hypochlorite, the respective S or Se atom is replaced by O to give 1,2,5-oxadiazoles, as shown in **Scheme 82** (precise yields not given) <2000CHE1359>. A more vigorous oxidation leads to ring-opening of the fused five-membered ring (see Section 10.13.5.4).

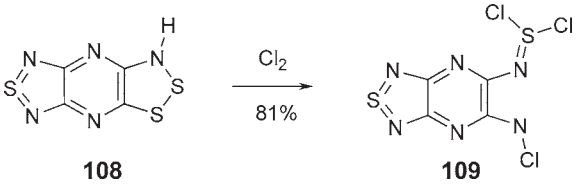


Scheme 82

10.13.10.3 Thiazoloazines and Azolothiazines

10.13.10.3.1 [1,2,5]Thiadiazolo[3,4-*b*]pyrazines

Chlorine gas was reported to rupture the disulfide bond of the fused 1,2,3-dithiazolidine ring of tricycle **108** to give [1,2,5]thiadiazolo[3,4-*b*]pyrazine **109** (**Scheme 83**) <1999JA969>.



108 **109**

Scheme 83

10.13.11 Synthesis of Particular Classes of Compounds and Critical Comparisons of the Various Routes Available

This section provides a critical evaluation of synthetic methods available for the preparation of the most common compounds. Most heterocyclic systems included in this review are made by only one of the following protocols: synthesis of the fused six-membered ring (Section 10.13.9.1), synthesis of the fused five-membered ring (Section

10.13.9.2), and synthesis by ring transformation of another ring (Section 10.13.10). Only three ring systems have been prepared using two of the latter protocols, [1,2,3]triazolo[4,5-*d*]pyrimidines (synthesis of the fused five- and six-membered ring), [1,2,3]triazolo[4,5-*d*]pyridazines (synthesis of the fused six-membered ring and ring synthesis by transformation from another ring), and [1,2,5]oxadiazolo[3,4-*d*]pyrimidines (synthesis of the fused five-membered ring and ring synthesis by transformation from another ring).

10.13.11.1 Azoloazines

When the synthesis of a heterocyclic system containing a diazole fused onto 1,2,3-triazin-4-one (e.g., imidazo[4,5-*d*][1,2,3]triazin-4-one (Section 10.13.9.1.1(i)) and pyrazolo[3,4-*d*][1,2,3]triazin-4-one (Section 10.13.9.1.1(ii))) or 1,2,3-triazole fused onto pyrimidin-4(7)-(di)one (e.g., [1,2,3]triazolo[4,5-*d*]pyrimidin-4(7)-(di)one (Section 10.13.9.1.1(iv))) is required, the synthesis of the six-membered ring is the most reliable method. There are several recent accounts of six-membered annulations onto 1,2,3-triazoles to give [1,2,3]triazolo[4,5-*d*]pyrimidines (Section 10.13.9.1.1(iv)), which are valuable alternatives to 1,2,3-triazole annulation using nitrosation techniques <1996CHEC-II(7)489>.

The synthesis of fused 1,2,3-triazoles is nearly always achieved by treating 1,2-diamines attached to diazines with nitrous acid (e.g., [1,2,3]triazolo[4,5-*c*]pyridazine (Section 10.13.9.2.1(iii)) and [1,2,3]triazolo[4,5-*d*]pyrimidine (Section 10.13.9.2.1(iv)), <1996CHEC-II(7)489>). When a heterocyclic system containing a diazole fused onto 1,2,4-triazine is required, annulation of the five-membered heterocycle is nearly always the most facile route (e.g., imidazo[4,5-*e*][1,2,4]triazine (Section 10.13.9.2.1(i)) and pyrazolo[4,3-*e*][1,2,4]triazine (Section 10.13.9.2.1(ii))). In support of the latter, the synthesis of the fused six-membered ring of pyrazolo[3,4-*e*][1,2,4]triazine from the pyrazoledione was reported as low yielding <1996CHEC-II(7)489>.

The removal of the *N*-etheno group from the fused imidazole ring of tricycles, diimidazo[1,2-*c*:4′,5′-*e*][1,2,3]triazines and imidazo[1,2-*c*]pyrazolo[4,3-*e*][1,2,3]triazines, is a reliable method for making imidazo[4,5-*d*][1,2,3]triazines <1996CHEC-II(7)489> and pyrazolo[3,4-*d*][1,2,3]triazines, respectively (Section 10.13.10.1.2).

[1,2,3]Triazolo[4,5-*b*]pyrazines are the only azoloazines without a preparative method included in this chapter, and are prepared by a six-membered ring synthesis of the fused pyrazine ring <1972JOC4124>.

10.13.11.2 Oxazoloazines and Azolooxazines

Isoxazolo[5,4-*d*][1,2,4]triazine-4-ones are prepared by six-membered cyclizations of diazonium salts onto adjacent ester or amide substituents on the isoxazole ring (Section 10.13.9.1.2(i)). [1,2,5]Oxadiazolo[3,4-*b*]pyrazines (Section 10.13.9.1.2(ii)) and [1,2,5]oxadiazolo[3,4-*d*]pyridazines (Section 10.13.9.1.2(iii)) are traditionally accessed by reliable six-membered condensation reactions to give the fused pyrazine and pyridazine rings, respectively.

The other heterocycles tend to be less frequently reported; thus, there are no regularly used protocols for their synthesis.

10.13.12 Important Compounds and Applications

The following section describes compounds that have found applications or had their uses extended since the review by Knowles <1996CHEC-II(7)489>.

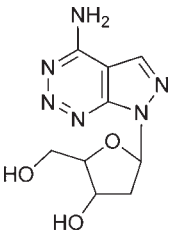
10.13.12.1 Azoloazines

10.13.12.1.1 Imidazo[4,5-*d*][1,2,3]triazines and pyrazolo[3,4-*d*][1,2,3]triazines

Base-pairing studies on 2-azapurine (imidazo[4,5-*d*][1,2,3]triazine) <2000CEJ369> nucleosides and pyrazolo[3,4-*d*][1,2,3]triazine **110** (**Figure 10**) <2004JOC4695> showed that these adenine nucleoside analogs form strong 'purine–purine' base pairs with dG but not with pyrimidine dT. Synthetic nucleoside mimics can be incorporated into viral DNA <1996CHEC-II(7)489>, and 2-azapurine nucleosides have been shown to have antiviral activity <2000NN39>.

10.13.12.1.2 Pyrazolo[4,3-*e*][1,2,4]triazines

This ring system provides the only naturally occurring compounds included in this review, and has the distinction of being one of only two naturally occurring ring skeletons containing more nitrogen than carbon atoms <2006JA5646>.



110

Figure 10

The proposed structures of natural products, pseudoiodinine **45** <1996CHEC-II(7)489>, nostocine A **42** <1996H(43)1513>, and fluviol A **43** <1996H(43)1513>, are given in **Schemes 29** and **30**. **Figure 11** gives the assigned structures for fluviols B, C, D, and E <1997MI357>. Kelly and co-workers recently reported the first total synthesis and structure confirmation of nostocine A and fluviol A, and reassigned the structure of pseudoiodinine from **45** to that previously assigned to fluviol C <2006JA5646> (**Figure 11**). The compounds in **Figure 11** were isolated from *Pseudomonas fluorescens* var. *pseudoiodinum*, and are all highly colored (e.g., pseudoiodinine is red and fluviol E is violet) <1997MI357>.

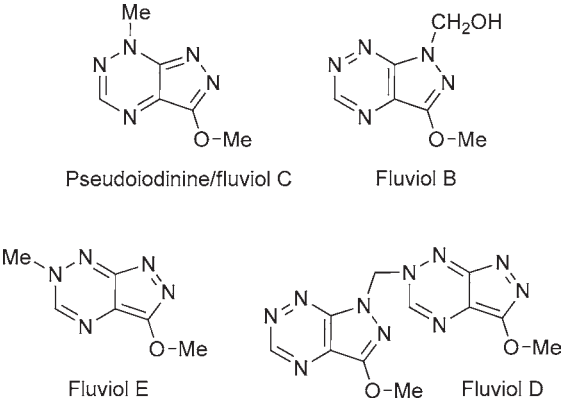


Figure 11

Among the pyrazolo[4,3-*e*][1,2,4]triazine natural products, fluviol E has the widest spectrum of antimicrobial activity <1997MI357>. It was reported to inhibit the growth of Gram-positive and Gram-negative bacteria, with somewhat weak activity against fungi also reported. At doses found to be toxic to white mice, and the growth of the ascetic form of Ehrlich carcinoma was found to be inhibited by 40% in these animals. Greater antitumor activity, but less toxicity, was exhibited by fluviols A and C toward white mice.

10.13.12.1.3 [1,2,3]Triazolo[4,5-*d*]pyrimidines and [1,2,3]triazolo[4,5-*d*]pyridazines

[1,2,3]Triazolo[4,5-*d*]pyrimidines are known as 8-azapurines <1996CHEC-II(7)489>, and derivatives have been widely tested as isosteres for purines and associated nucleosides <1996BMC1725, 1999JME833, 2001JME4050, 2005HCA751>. The 1,2,3-triazole fused compounds show activity against tumor proliferation <2005BMC5399> and high affinity toward adenosine receptors <1998JME668, 1999EJM867, 1999FA615>.

10.13.12.2 Oxazoloazines and Azolooxazines

[1,2,5]Oxadiazole fused compounds (furoxanes) are very good nitric oxide donors. Many such compounds show relatively low stability to bases and nucleophilic reagents, and decompose under the action of thiolate anions

(however, note the selective substitution reported at the fused pyrazine ring in Section 10.13.5.3.2(i)). This is thought to give such compounds important biological activities <2002MI523>.

10.13.12.2.1 Isoxazolo[5,4-*d*][1,2,3]triazines

Ryng *et al*. have investigated the cytostatic <1997FA105> and immunological <2003MI147> effects of this class of compounds. The compounds investigated were more potent than the reference drug, dacarbazine <1997FA105>, toward mouse P-388 leukemia cell lines <1997FA105>.

10.13.12.2.2 [1,2,5]Oxadiazolo[3,4-*d*]pyridazines

The tris-*N*-oxide shown in **Figure 12** has been reported to possess vasodilator activity <2002MI523>.

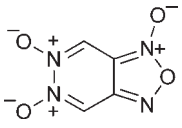


Figure 12

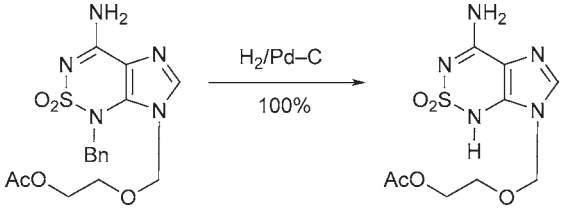
10.13.12.2.3 [1,2,5]Oxazolo[3,4-*b*]pyrazines

This class of compounds has been recently shown to have antibacterial activity against *Haemophilus influenza* <2003BML3133>.

10.13.12.3 Thiazoloazines and Azolothiazines

10.13.12.3.1 Imidazo[4,5-*c*][1,2,6]thiadiazines

The synthesis of the first imidazothiadiazine dioxide acyclonucleosides (SO_2–purine analogs), and their associated antiviral activities, were reported by Martínez *et al*. <1999BMC1617>. **Scheme 84** shows the hydrogenolysis of **17**, which afforded **111** in quantitative yield; this is the first SO_2 analog of acyclovir (a clinically used antiherpetic drug). The imidazothiadiazine compounds screened showed interesting anti-HIV as well as activity against cytomegalovirus (CMV) strains, and were proposed as new lead compounds for drug discovery.



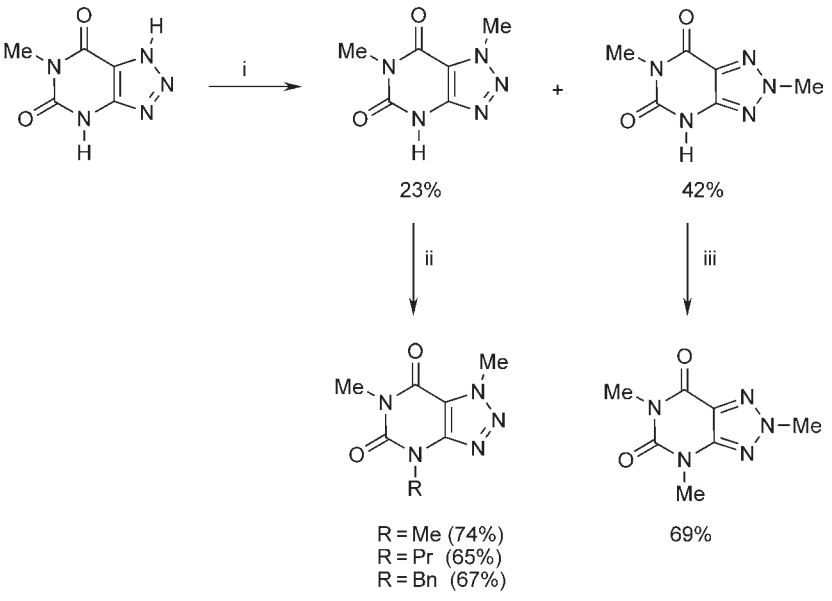
17 **111**

Scheme 84

10.13.13 Further Developments

10.13.13.1 Reactivity of Fully Conjugated Rings [1,2,3]Triazolo[4,5-*d*]pyrimidine

Islam and Nagamatsu reported that the alkylation on the triazole ring in the presence of anhydrous potassium carbonate took place simultaneously at the 1- and 2-position, with the 2-position taking priority (e.g., methylation in **Scheme 85**) <2006S4167>. Addition of further alkylating agent gave alkylation on the pyrimidine ring. The [1,2,3]triazolo[4,5-*d*]pyrimidine-5,7-diones (8-azaxanthines) were accessed via the previously discussed cyclization of the appropriate 5,6-diaminouracil with nitrous acid (Section 10.13.9.2.1(iv)).

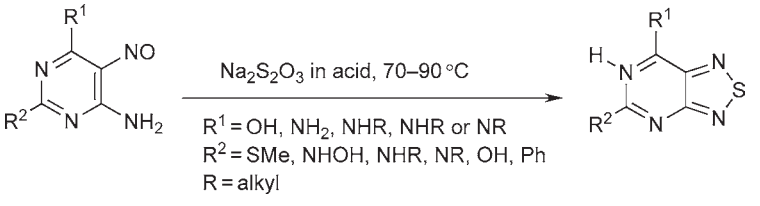


i, MeI, K_2CO_3, DMF, reflux; ii, R-I, K_2CO_3, DMF, rt or reflux; iii, MeI, K_2CO_3, DMF, rt

Scheme 85

10.13.13.2 Synthesis of the Fused Five-Membered Ring [1,2,5]Thiadiazolo[3,4-*d*]pyrimidine

The workers who reported the chemistry described in **Scheme 85**, also reported a new preparation of this 8-thiapurine ring system via reaction of 6-amino-5-nitrosopyrimidine with sodium thiosulfate in acidic media (**Scheme 86**), and extended this methodology to the synthesis of 4-β-D-ribofuranosyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidines <2007H(72)573>. The latter article includes the facile synthesis of these compounds, as well as the evaluation of antitumor and antiviral activity.



Scheme 86

References

1962JOC2150 Y. F. Shealy, C. A. Krauth, and J. A. Montgomery, *J. Org. Chem.*, 1962, **27**, 2150.
1964JHC247 A. G. Gerhardt and R. N. Castle, *J. Heterocycl. Chem.*, 1964, **1**, 247.
1965CB1060 G. Nubel and W. Pfleiderer, *Chem. Ber.*, 1965, **98**, 1060.
1972JOC4124 C. A. Lovelette and L. Long, Jr., *J. Org. Chem.*, 1972, **37**, 4124.
1978JOC341 N. Sato and J. Adachi, *J. Org. Chem.*, 1978, **43**, 341.
1981H(16)525 P. Goya, C. Ochoa, and M. Stud, *Heterocycles*, 1981, **16**, 525.
1984CHEC(5)607 J. A. Montgomery and J. A. Secrist, III, in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees Eds.; Pergamon, Oxford, 1984, vol. 5, part 4A, p. 607.
1986AGE383 W. von Philipsborn and R. Müller, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 383.
1988J(P1)1509 A. J. Boulton, M. Kiss, and J. D. K. Saka, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1509.
1991MI132 R. Chen, J. Wang, H. Wang, and X. Yao, *Jiegou Huaxue*, 1991, **10**, 132.
1995JHC1417 J. L. Kelley, D. C. Wilson, V. L. Styles, F. E. Soroko, and B. R. Cooper, *J. Heterocycl. Chem.*, 1995, **32**, 1417.
1996BMC1725 J. C. Bussolari, J. D. Stoeckler, and R. P. Panzica, *Bioorg. Med. Chem.*, 1996, **4**, 1725.

1996BML185 Y. Wang and M. F. G. Stevens, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 185.

1996CHEC-II(7)489 P. Knowles; in 'Comprehensive Heterocyclic Chemistry-II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven Eds.; Pergamon, Oxford, 1996, vol. 7, p. 489.

1996H(43)1513 K. Hirata, H. Nakagami, J. Takashina, T. Mahmud, M. Kobayashi, Y. In, T. Ishida, and K. Miyamoo, *Heterocycles*, 1996, **43**, 1513.

1997JOC7288 Y. Wang, M. F. G. Stevens, T-m. Chan, D. DiBenedetto, Z-x. Ding, D. Gala, D. Hou, M. Klugelman, W. Leong, S.-c. Kuo, *et al.*, *J. Org. Chem.*, 1997, **62**, 7288.

1997FA105 S. Ryng, W. Malinka, and D. Duś, *Farmaco*, 1997, **52**, 105.

1997MI357 V. V. Smirnov, E. A. Kiprianova, A. D. Garagulya, S. E. Esipov, and S. A. Dovjenko, *FEMS Microbiol. Lett.*, 1997, **153**, 357.

1997S1255 M. Sako, S. Oda, K. Hirota, and G. P. Beardsley, *Synthesis*, 1997, 1255.

1998JA352 T. M. Barclay, A. W. Cordes, N. A. George, R. C. Haddon, M. E. Itkis, M. S. Mashuta, R. T. Oakley, G. W. Patenaude, R. W. Reed, J. F. Richardson, *et al.*, *J. Am. Chem. Soc.*, 1998, **120**, 352.

1998JME668 L. Betti, G. Biagi, G. Giannaccini, I. Giorgi, O. Livi, A. Lucacchini, C. Manera, and V. Scartoni, *J. Med. Chem.*, 1998, **41**, 668.

1998JOC6947 M. Sako, S. Oda, S. Ohara, K. Hirota, and Y. Maki, *J. Org. Chem.*, 1998, **63**, 6947.

1998KFZ16 D. B. Nilov, N. P. Solov′eva, I. S. Nikolaeva, V. V. Peters, L. Y. Krylova, T. A. Gus′kova, and V. G. Granik, *Khim. Farm. Zh.*, 1998, **32**, 16.

1999BMC1617 A. Martínez, A. I. Esteban, A. Herrero, C. Ochoa, G. Andrei, R. Snoeck, J. Balzarini, and E. De Clercq, *Bioorg. Med. Chem.*, 1999, **7**, 1617.

1999EJM867 L. Betti, G. Biagi, G. Giannaccini, I. Giorgi, O. Livi, A. Lucacchini, C. Manera, and V. Scartoni, *Eur. J. Med. Chem.*, 1999, **34**, 867.

1999JA969 T. M. Barclay, A. W. Cordes, R. C. Haddon, M. E. Itkis, R. T. Oakley, R. W. Reed, and H. Zhang, *J. Am. Chem. Soc.*, 1999, **121**, 969.

1999JHC1195 G. Biagi, I. Giorgi, O. Livi, C. Manera, and V. Scartoni, *J. Heterocycl. Chem.*, 1999, **36**, 1195.

1999JME833 R. J. Chorvat, R. Bakthavatchalam, J. P. Beck, P. J. Gilligan, R. G. Wilde, A. J. Cocuzza, F. W. Hobbs, R. S. Cheeseman, M. Curry, J. P. Rescinito, *et al.*, *J. Med. Chem.*, 1999, **42**, 833.

1999FA615 G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, L. Betti, G. Giannaccini, and A. Lucacchini, *Farmaco*, 1999, **54**, 615.

1999MI774 S. T. Abu-Orabi, R. Al-Hamdany, A. Atfah, A. A. S. Ali, and K. Abu-Shandi, *Asian J. Chem.*, 1999, **11**, 774.

1999MI933 A. Haque and J. T. Stewart, *J. Liq. Chrom. Rel. Technol.*, 1999, **22**, 933.

2000CC1785 P. Kövér, G. Hajós, Z. Riedl, L. Párkányi, and G. Kollenz, *J. Chem. Soc., Chem. Commun.*, 2000, 1785.

2000CHE465 M. A. Bezmaternykh, V. S. Mokrushin, and E. V. Sadchikov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 465.

2000CHE1091 O. A. Ivanova, E. B. Averina, T. S. Kuznestsova, and N. S. Zefirov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 1091.

2000CHE1359 A. A. Yavolovsky, E. I. Ivanov, and R. Y. Ivanova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 1359.

2000CEJ369 T. Sugiyama, E. Schweinberger, Z. Kazimierczuk, N. Ramzaeva, H. Rosemeyer, and F. Seela, *Chem. Eur. J.*, 2000, **6**, 369.

2000H(53)2175 A. Rykowski, M. Mojzych, and Z. Karczmarzyk, *Heterocycles*, 2000, **53**, 2175.

2000HCO443 S. T. Abu-Orabi, R. Al-Hamdany, S. Shahateet, and K. Abu-Shandi, *Heterocycl. Commun.*, 2000, **6**, 443.

2000JHC1269 T. Ueda, W. Doi, S.-i. Nagi, and J. Sakakibara, *J. Heterocycl. Chem.*, 2000, **37**, 1269.

2000JHC1597 K. C. V. Ramanaiah, E. D. Stevens, M. L. Trudell, and P. F. Pagoria, *J. Heterocycl. Chem.*, 2000, **37**, 1597.

2000NN39 S. Krawczyk, M. T. Migawa, J. C. Drach, and L. B. Townsend, *Nucleosides and Nucleotides*, 2000, **19**, 39.

2001BMC1357 T. Kumagai, T. Okubo, H. Kataoka-Okubo, S. Chaki, S. Okuyama, and A. Nakazato, *Bioorg. Med. Chem.*, 2001, **9**, 1357.

2001JHC901 O. N. Chupakhin, G. L. Rusinov, D. G. Beresnev, V. N. Charushin, and H. Neunhoeffer, *J. Heterocycl. Chem.*, 2001, **38**, 901.

2001JME4050 J. Reinhard, W. E. Hull, C.-w. von der Leith, U. Eichhorn, H.-c. Kliem, B. Kaina, and M. Wiessler, *J. Med. Chem.*, 2001, **44**, 4050.

2001JOC4776 M. T. Migawa and L. B. Townsend, *J. Org. Chem.*, 2001, **66**, 4776.

2001S2445 S. –l. Deng and D.–z. Liu, *Synthesis*, 2001, 2445.

2002BMC449 P. G. Baraldi, M. G. Pavani, M. del Carmen Nunez, P. Brigidi, B. Vitali, R. Gambari, and R. Romagnoli, *Bioorg. Med. Chem.*, 2002, **10**, 449.

2002IJB664 A. K. Tewari, L. Mishra, H. N. Verma, and A. Mishra, *Indian J. Chem., Sect. B*, 2002, **41**, 664.

2002HCO613 T. Gucký, K. Nálepa, and I. Wiedermannová, *Heterocycl. Commun.*, 2002, **8**, 613.

2002JHC889 G. Biagi, F. Ciambrone, I. Giorgi, O. Livi, V. Scartoni, and P. L. Barili, *J. Heterocycl. Chem.*, 2002, **39**, 889.

2002JST73 A. Csámpai, P. Kövér, G. Hajós, and Z. Riedl, *J. Mol. Struct.*, 2002, **616**, 73.

2002JPH83 K. Nagy, L. Biczók, A. Demeter, P. Kövér, and Z. Riedl, *J. Photochem. Photobiol. A*, 2002, **153**, 83.

2002MI523 V. G. Granik, M. É.Kaminka, N. B. Grigor'ev, I. S. Severina, M. A. Kalinkina, V. A. Makarov, and V. I. Levina, *Pharm. Chem. J.*, 2002, **36**, 523.

2002MRC300 K. Vaughan, D. E. V. Wilman, R. T. Wheelhouse, and M. F. G. Stevens, *Magn. Reson. Chem.*, 2002, **40**, 300.

2002T10073 N. Matsumoto and M. Takahashi, *Tetrahedron*, 2002, **58**, 10073.

2002TL4741 E. Fernández, S. García-Ochoa, S. Huss, A. Mallo, J. M. Bueno, F. Micheli, A. Paio, E. Piga, and P. Zarantonello, *Tetrahedron Lett.*, 2002, **43**, 4741.

2003AGE3409 Y. Ding, S. A. Hofstadler, E. E. Swayze, L. Risen, and R. H. Griffey, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 3409.

2003BML3133 X. Beebe, A. M. Nilius, P. J. Merta, N. B. Soni, M. H. Bui, R. Wagner, and B. A. Beutel, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3133.

2003JCO653 N. Baindur, N. Chadha, and M. R. Player, *J. Comb. Chem.*, 2003, **5**, 653.

2003MI147 M. Maczynski, A. Jezierska, M. Zimecki, and S. Ryng, *Acta Pol. Pharm.*, 2003, **60**, 147.

2003PJC1797 M. Mojzych and A. Rykowski, *Pol. J. Chem.*, 2003, **77**, 1797.

2003PS1143 A. M. El Massry, *Phosphorus, Sulfur and Silicon and Related Elements*, 2003, **178**, 1143.

2003RCB1770 V. P. Kislyi, E. B. Danilova, and V. V. Semenov, *Russ Chem. Bull.*, 2003, **52**, 1770.

2003T1059 S. D. Shaposhnikov, S. V. Mel'nikova, I. V. Tselinsky, C. Näther, T. Graening, T. Traulsen, and W. Friedrichsen, *Tetrahedron*, 2003, **59**, 1059.

2004JHC575 G. Biagi, I. Giorgi, O. Livi, F. Pacchini, V. Scartoni, and O. L. Salerni, *J. Heterocycl. Chem.*, 2004, **41**, 575.

2004JOC4695 F. Seela, M. Lindner, V. Glaçon, and W. Lin, *J. Org. Chem.*, 2004, **69**, 4695.

2004SOS223 H. Döpp and D. Döpp, *Science of Synthesis*, 2004, **17**, 223.

2004MI289 J.-h. Zou, F. Yang, W.-j. Zheng, Y. Bai, and Y.-q. Li, *Huaxue Shiji*, 2004, **26**, 289.

2004RCB1279 N. N. Mochul′skaya, A. A. Andreiko, E. B. Vasil′eva, V. I. Filyakova, A. T. Gubaidullin, I. A. Litvinov, O. G. Sinyashin, G. G. Aleksandrov, and V. N. Charushin, *Russ. Chem. Bull.*, 2004, **53**, 1279.

2004RJO1015 Y. M. Yutilov, N. N. Smolyar, A. B. Eres'ko, and S. V. Gres'ko, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 1015.
2005BMC5399 L. Havlicek, K. Fuksova, V. Krystof, M. Orsag, B. Vojtesek, and M. Strnad, *Bioorg. Med. Chem.*, 2005, **13**, 5399.
2005HCA751 F. Seela, A. M. Jawalekar, and I. Münster, *Helv. Chim. Acta*, 2005, **88**, 751.
2005OBC1714 W. Lin, H. Li, X. Ming, and F. Seela, *Org. Biomol. Chem.*, 2005, **3**, 1714.
2005RJC493 A. A. Yavolovskii, V. D. Kishichenko, O. A. Oliinichenko, and E. I. Ivanov, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2005, **75**, 493.
2005S2544 J.-f. Zhao, C. Xie, M. –w. Ding, and H.-w. He, *Synthesis*, 2005, 2544.
2006JA5646 T. R. Kelly, E. L. Elliott, R. Lebedev, and J. Pagalday, *J. Am. Chem. Soc.*, 2006, **128**, 5646.
2006JPH276 J. Wierzchowski, J. Sepiol, D. Sulikowski, B. Kierdaszuk, and D. Shugar, *J. Photochem. Photobiol. A*, 2006, **179**, 276.
2006S4167 R. Islam and T. Nagamatsu, *Synthesis*, 2006, 4167.
2007H(72)573 T. Nagamatsu, R. Islam, and N. Ashida, *Heterocycles*, 2007, **72**, 573.

Biographical Sketch



Fawaz Aldabbagh was born in Baghdad, Iraq, in 1971, and studied in the UK at Brunel University (B.Sc., 1994) and at Loughborough University (Ph.D., 1997, under the direction of Professor W. R. Bowman). He spent two years working as a postdoctoral research fellow with Professors I. D. Jenkins and W. K. Busfield at Griffith University, Brisbane, Australia, before taking his current position as a lecturer in chemistry at the National University of Ireland, Galway, in April 2000. Fawaz has a variety of research interests including controlled radical polymerizations and the synthesis of biologically active heterocyclic systems using radical cyclizations. More recently, his research has focused on the synthesis of new benzimidazolequinone antitumor agents. To date, Fawaz has published 30 refereed primary research papers, plus major reviews and book chapters in materials science, medicinal chemistry, and organic synthesis, which have received almost 250 citations.

10.14
Bicyclic 5-6 Systems: Six and Seven Heteroatoms

C. A. Ramsden
Keele University, Keele, UK
© 2008 Elsevier Ltd. All rights reserved.

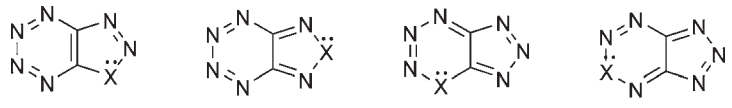
10.14.1 Introduction **703**
10.14.2 Theoretical Methods **705**
10.14.3 Experimental Structural Methods **706**
10.14.3.1 X-Ray Diffraction **706**
10.14.3.2 NMR Spectroscopy **706**
10.14.3.3 Mass Spectrometry **707**
10.14.3.4 IR and UV Spectroscopy **707**
10.14.3.5 Dipole Moments **707**
10.14.4 Thermodynamic Aspects **707**
10.14.5 Reactivity of Fully Conjugated Rings **707**
10.14.6 Reactivity of Nonconjugated Rings **708**
10.14.7 Reactivity of Substituents Attached to Ring Carbon Atoms **708**
10.14.8 Reactivity of Substituents Attached to Ring Heteroatoms **708**
10.14.9 Ring Synthesis from Two Components **708**
10.14.9.1 Seven Heteroatoms (10π) **708**
10.14.9.1.1 Oxadiazolo[3,4-*e*][1,2,3,4]tetrazines **11** 708
10.14.9.2 Six Heteroatoms (10π) **709**
10.14.9.2.1 Pyrazolo[3,4-*e*][1,2,3,4]tetrazines **14** 709
10.14.9.2.2 1,3-Thiazolo[5,4-*e*][1,3,4,2]oxadiazaborolium **17** 710
10.14.9.3 Six Heteroatoms (12π) **710**
10.14.9.3.1 1,2,5-Thiadiazolo[3,4-*c*][1,2,6]thiadiazines **21** 710
10.14.9.3.2 1,2,5-Selenadiazolo[3,4-*c*][1,2,6]thiadiazines **22** 710
10.14.9.4 Six Heteroatoms (14π) **710**
10.14.9.4.1 1,3-Dithiolium[4,5-*e*][1,2,3,4]tetrathiane **23** 710
10.14.10 Ring Synthesis by Transformation of Another Ring **711**
10.14.11 Important Compounds and Applications **711**
References **711**

10.14.1 Introduction

This chapter reviews progress since 1994 in the chemistry of bicyclic 5-6 heterosystems that have a total of six or seven ring heteroatoms. Systems with bridgehead heteroatoms are not included and these are covered in Volumes 10 and 11. When this area of chemistry was reviewed in 1994 in Chapter 7.14 of CHEC-II(1996), it was described as being in its infancy <1996CHEC-II(7)513>. Since then, little progress toward maturity has been made.

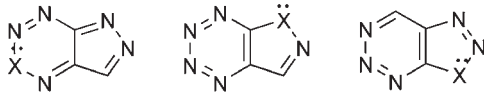
This chapter is structured in the same way as the corresponding chapter in CHEC-II(1996) <1996CHEC-II(7)513>. For a full coverage of the subject, the two chapters must be considered together. In addition to subdivision according to the number of ring heteroatoms (six or seven), these bicyclic 5,6-heterosystems are also conveniently further subdivided according to the number of π-electrons (10, 12, or 14) in the fully-conjugated parent system. Structures **1–4** show the four possible 10π-electron systems with seven heteroatoms (4:3). If the

heteroatoms X are restricted to O, S, or NR, then 12 heterocyclic systems are possible. Replacement of the nitrogen atoms (–N═) by other heteroatoms (e.g. –B═, –HSi═) leads to additional parent systems.



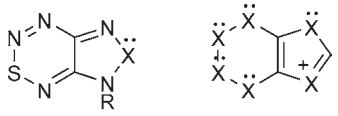
1 **2** **3** **4**

Using a similar analysis, it can be shown that there are 63 possible 10π-electron six-heteroatom systems (4:2 or 3:3) if X is restricted to O, S, or NR. In practice only derivatives of the generalised systems **5–7** have been reported. This number is further increased if –N═ is replace by –B═, –HSi═, etc., and three examples of this type are known (see **Figure 1**).



5 **6** **7**

A large number of parent bicyclic 4:3, 4:2, and 3:3 heterocycles having 12π-electrons are possible but few derivatives have been reported and these are all derived from the generalized system **8**. Finally, one example of a system that can be regarded as being derived from the 14π-electron system **9** is known.



8 **9**

Figure 1 shows the parent structures of all the known compounds that fall within the scope of this chapter together with their systematic names. All compounds are named as derivatives of these parent structures **10–23**.

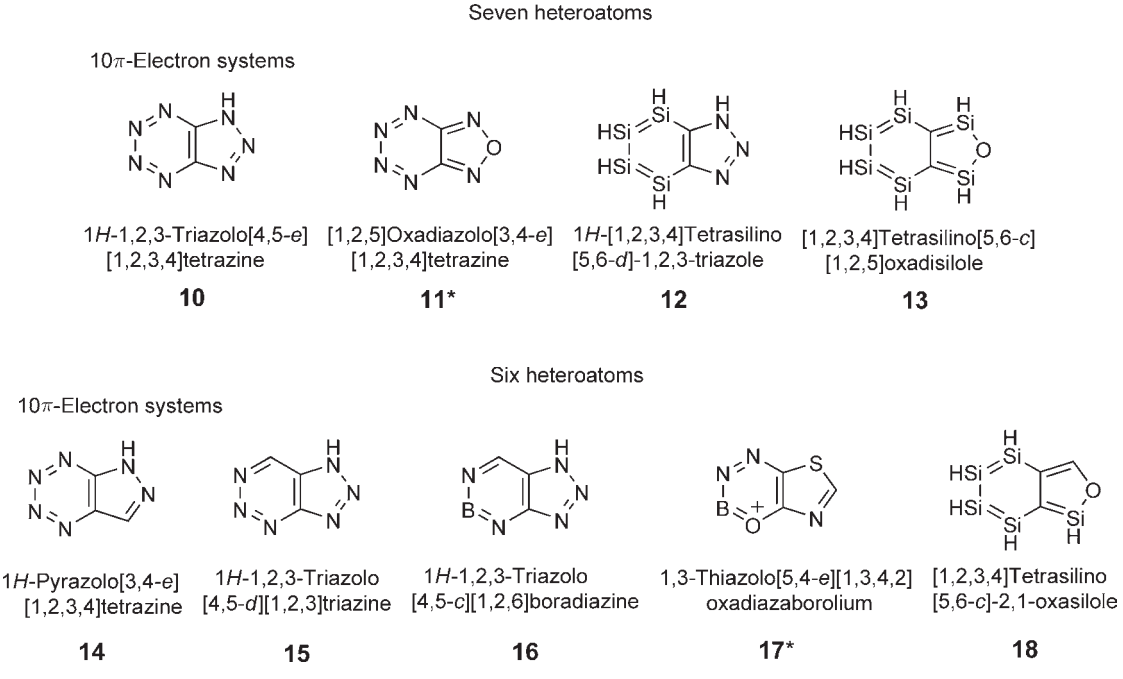
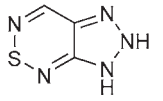


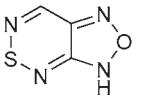
Figure 1 (*Continued*)

12π-Electron systems



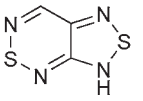
1,2,3-Triazolo[4,5-*c*] [1,2,6]thiadiazine

19



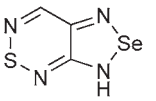
[1,2,5]Oxadiazolo[3,4-*c*] [1,2,6]thiadiazine

20



[1,2,5]Thiadiazolo[3,4-*c*] [1,2,6]thiadiazine

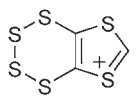
21



[1,2,5]Selenadiazolo[3,4-*c*] [1,2,6]thiadiazine

22*

14π-Electron systems



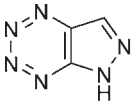
1,3-Dithiolium[4,5-*e*] [1,2,3,4]tetrathiane

23*

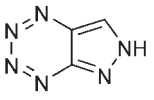
Figure 1 Parent fully conjugated ring systems of known compounds. The asterisk indicates systems described since the publication of CHEC-II(1996).

10.14.2 Theoretical Methods

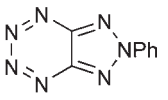
A systematic investigation of the relative energies of azaindazole tautomers including the isomeric pyrazolo[3,4-*e*]-[1,2,3,4]tetrazines **24** and **25** has been reported. Both AM1 and density functional theory (DFT) *ab initio* calculations indicate that the 1*H*-tautomer **24** is more stable: the calculated energy differences are 18.8 (AM1) and 27.8 kJ mol^{-1} (B3LYP/6-31G*) <2005JPO719>. The AM1 calculation appears to underestimate the energy difference and this is attributed to inadequate treatment of the multiple lone pair–lone pair integrals. Previous workers have noted that for calculations on 2-phenyl-1,2,3-triazolo[4,5-*e*][1,2,3,4]tetrazine **26**, the AM1 method underestimates the C–C double bond character <1991AXC590>, and this may be attributed to overestimation of core repulsion energies in multi-nitrogen systems <1992J(P1)2779>.



24



25

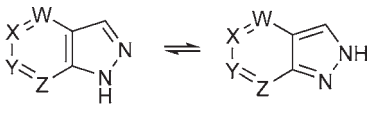


26

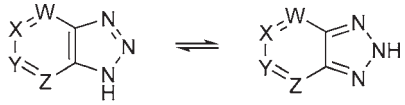
A statistical analysis of the calculated 1*H*- and 2*H*-tautomer energy differences for a series of indazole derivatives reveals that aza substitutions make the following contributions (kJ mol^{-1}) to the energy differences: 4-N (-4.4 ± 1.0); 5-N (-3.3 ± 1.2); 6-N (-5.1 ± 1.1); 7-N ($+9.8 \pm 1.0$) <2005JPO719>. A 7-aza atom favors the 1*H*-tautomer, whereas 4-, 5-, and 6-aza atoms favor the 2*H*-tautomer but the effect is not large enough to shift the equilibrium in favor of the 2*H*-structure. The same analysis indicated that 3-NO_2 and 3-CO_2Me substituents contribute to stabilization of the 2*H*-tautomers (3-NO_2 (-11.4 ± 2.8 kJ mol^{-1}) and 3-CO_2Me (-13.0 ± 2.8 kJ mol^{-1})). This study did not include 3-aza derivatives but an extension of the AM1 study suggests that 3-aza substitution strongly favors the 1*H*-tautomer (3-N ($+24.8$ kJ mol^{-1} (average))) <2006UP1>. **Table 1** shows the calculated AM1 energy differences ($\Delta\Delta E$) for a series of polyazaindazole tautomers **27a,b** and **28a,b**. In all cases, the 1*H*-tautomer is more stable ($\Delta\Delta E$ positive). However, the relative stability is consistently greater for the 3-aza derivatives **28** and the stabilization attributed to the 3-aza atom (Δ 3-N) is large and consistent, and averages 24.8 kJ mol^{-1} (**Table 1**). This effect is in interesting contrast with the relative destabilizing effect of 3-NO_2 and 3-CO_2Me substituents <2005JPO719>.

As part of an investigation of the binding of adenosine analogues to an active site of mammalian adenosine deaminase, the structure and conformations of 2,8-diazaadenosine **29**, and other isoteric analogs of adenosine **30**, have been modeled using *ab initio* calculations and molecular mechanics (MM+) <2003MI152>.

Table 1 Calculated AM1 energy differences ($\Delta\Delta E$) for polyazaindazole tautomers



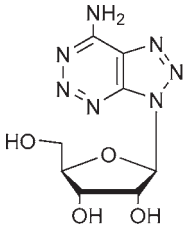
27a **27b**



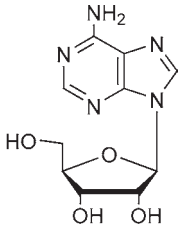
28a **28b**

W	*X*	*Y*	*Z*	$\Delta\Delta E$[a,b]	*W*	*X*	*Y*	*Z*	$\Delta\Delta E$[a,c]	$\Delta 3$-*N*[a,c]
CH	N	N	N	27.91	CH	N	N	N	53.23	25.32
N	CH	N	N	25.36	N	CH	N	N	49.22	23.86
N	N	CH	N	27.53	N	N	CH	N	52.29	24.76
N	N	N	CH	13.35	N	N	N	CH	39.06	25.71
N	N	N	N	18.79	N	N	N	N	43.13	24.34

[a] kJ mol^{-1}.
[b] <2005JPO719>.
[c] <2006UP1>.



29

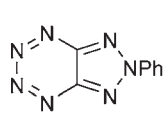


30

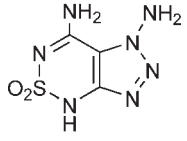
10.14.3 Experimental Structural Methods

10.14.3.1 X-Ray Diffraction

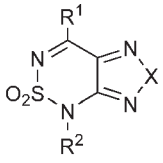
No new structures of compounds belonging to this class have been determined using X-ray crystallography. Previously, the structures of triazolotetrazine **31**, triazolothiadiazine **32**, several bicyclic thiadiazines **33** ($R^1 = NH_2$, O^-K^+; R^2 = H, Me; X = NH, O, S), and the tetrasilinooxadisilole **34** have been reported and are discussed in CHEC-II(1996) <1996CHEC-II(7)513>.



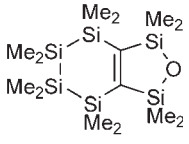
31



32



33



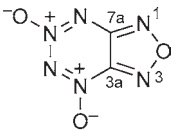
34

10.14.3.2 NMR Spectroscopy

^{15}N and ^{13}C chemical shifts have previously been reported for the derivatives **32** and **33** and are tabulated in CHEC-II(1996) <1996CHEC-II(7)513>.

The ^{13}C, ^{14}N, ^{15}N, and ^{17}O nuclear magnetic resonance (NMR) spectra of the oxadiazolotetrazine 4,6-di-*N*-oxide **35** have been reported <1995MC227>. The ^{13}C signals at δ 143.5 (C-3a) and 155.8 (C-7a) are comparable to those reported for the triazolotetrazine **31** (δ 145.7 (C-3a) and 145.7 (C-7a)) <1996CHEC-II(7)513>. The ^{15}N signals in the di-*N*-oxide **35** occur at δ 35.0 (N-1), 38.2 (N-3), 8.0 (N-5), −43.9 (N-6), −52.8 (N-4), and −106.0 (N-7). A study of

^{15}N-enriched samples of compound **35** in combination with the natural isotope spectrum enabled the unambiguous assignment of the structure.



35

10.14.3.3 Mass Spectrometry

Nothing of special significance has been reported since the publication of CHEC-II(1996).

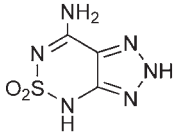
10.14.3.4 IR and UV Spectroscopy

Ultraviolet (UV) spectra of the derivatives **32** and **33** and two triazolotriazine derivatives have been reported and are tabulated in CHEC-II(1996) <1996CHEC-II(7)513>. No new UV spectra have been reported.

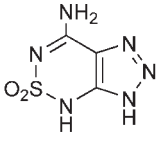
A detailed study, including the use of isotopic substitution, of the infrared (IR) and Raman spectra of the triazolotetrazine-4,6-di-*N*-oxide **35** has been reported <1995MC100, 1995IZV2187>, and characteristic vibration frequencies of the tetrazine dioxide fragment have been identified.

10.14.3.5 Dipole Moments

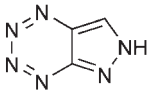
No experimental dipole moments have been reported for the compounds covered by this chapter. Previously, on the basis of calculations, the greater stability of the tautomers **36**, relative to isomers **37**, has been ascribed to the significantly larger dipole moments (calc. 5.08 D vs. 2.97 D) which leads to greater solvation <1996CHEC-II(7)513>. More recently *ab initio* calculations (B3LYP/6-31G*) indicate a similar difference in the calculated dipole moments of the tautomers **38** and **39** ($\Delta\mu$ 2.84 D), suggesting that polar solvents would favor the tautomer **38** <2005JPO719>.



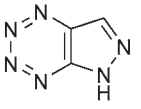
36



37



38



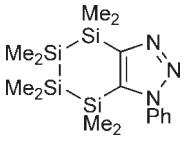
39

10.14.4 Thermodynamic Aspects

There is nothing new to report in this area. Some pK_a values of compounds with structures **33** ($R^1 = NH_2$; $R^2 = H$; X = O, S, NR) have been measured and these were tabulated in CHEC-II(1996) <1996CHEC-II(7)513>.

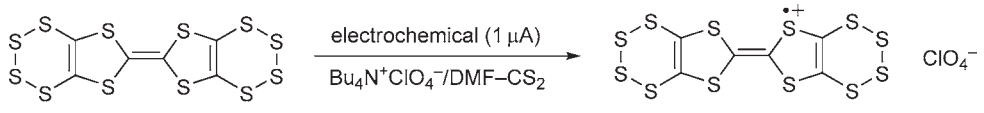
10.14.5 Reactivity of Fully Conjugated Rings

Previously there have been limited studies on: (1) the thermal decomposition of compounds **31** and **40**; (2) N-alkylation of the five-membered ring of the amine **33** (X = O; $R^1 = NH_2$; $R^2 = H$) and N-amination of the amine **33** (X = NH; $R^1 = NH_2$; $R^2 = H$); and (3) reduction of the derivatives of the amine **33** (X = O) to 3,4,5-triamino-1,2,6-thiadiazine-1,1-dioxides. A full discussion of these transformations can be found in CHEC-II(1996) <1996CHEC-II(7)513>.



40

The only new chemistry concerns electrochemical oxidation of the tetrathiafulvene derivative **41** to the radical cation perchlorate **42** (Equation 1) <2005MCL575>. The salt **42** was formed electrochemically as a dense thin film on the electrode surface and shown to be a conducting cation-radical salt that behaves like an organic metal. The electrical conductivity shows an interesting variation with temperature which may be related to a phase transition at 102 K <2005MCL575>.



41 **42** (1)

10.14.6 Reactivity of Nonconjugated Rings

Earlier studies have described N-alkylations of the six-membered rings of the derivatives **33** ($R^2 = H$) and reaction of the derivatives **33** ($R^1 = NH_2$; $R^2 = H$) with amines resulting in either transamination or ring opening to furazans <1996CHEC-II(7)513>.

No new reactions have been reported since 1996.

10.14.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Apart from a simple N-formylation of the oxadiazolothiadiazine derivative **33** ($R^1 = NHMe$; $R^2 = Me$; X = O) <1996CHEC-II(7)513>, reactions of substituents have not been studies and there are no new results.

10.14.8 Reactivity of Substituents Attached to Ring Heteroatoms

No reactions in which the heterocyclic system plays an influential role in determining the product have been reported.

10.14.9 Ring Synthesis from Two Components

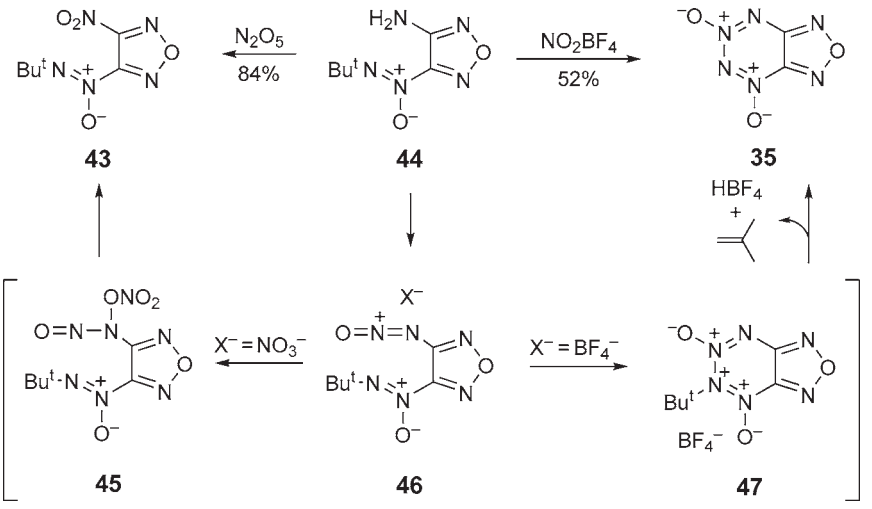
The synthesis of the diverse systems covered by this chapter are discussed in the same order as their parent structures are presented in **Figure 1** (see Section 10.14.1). Only systems for which preparative studies have been reported since 1994 are included in this section. All earlier work is described in CHEC-II(1996) <1996CHEC-II(7)513>.

10.14.9.1 Seven Heteroatoms (10π)

10.14.9.1.1 Oxadiazolo[3,4-*e*][1,2,3,4]tetrazines **11**

Oxadiazolo[3,4-*e*][1,2,3,4]tetrazine 4,6-di-*N*-oxide **35** is obtained as a yellow crystalline compound (m.p. 110–112 °C (decomp.)) by reaction of the amine **44** with excess nitronium tetrafluoroborate in acetonitrile at −20 °C (**Scheme 1**). Compound **35** is very sensitive to shock and, although it can be stored for long periods at 0 °C, it should be handled with care. The authors propose the mechanism shown in **Scheme 1** to account for the formation of compound **35**. When the counterion is tetrafluoroborate, the intermediate **46** cyclizes to the bicyclic cation **47**, which liberates

isobutene and HBF_4. Interestingly, treatment of the amine **44** with dinitrogen pentoxide gives the nitro derivative **43** and it is proposed that under these conditions the intermediate **46** reacts with nitrate ion leading to the nitrofurazan *via* the intermediate **45** <1995MC102, 1995MC227>.

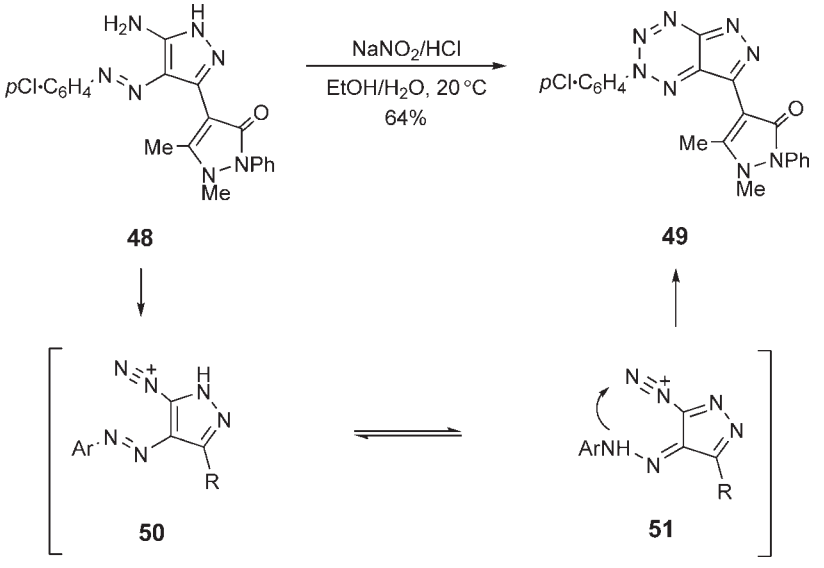


Scheme 1

10.14.9.2 Six Heteroatoms (10π)

10.14.9.2.1 Pyrazolo[3,4-*e*][1,2,3,4]tetrazines **14**

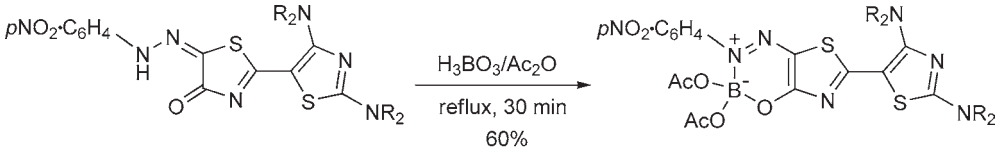
The pyrazolo[3,4-*e*][1,2,3,4]tetrazine derivative **49** has been reported to be formed by treatment of the hydrochloride salt of the amine **48** with sodium nitrite in aqueous ethanol at room temperature. Only a single example was described. Compound **49** was obtained as red crystals (m.p. > 300 °C). The product is presumed to form from the diazonium cation **50** which cyclizes via the hydrazone tautomer **51** (**Scheme 2**) <1998MI11>.



Scheme 2

10.14.9.2.2 1,3-Thiazolo[5,4-*e*][1,3,4,2]oxadiazaborolium **17**

The derivative **53** (m.p. 297–300 °C) has been prepared by heating the hydrazone **52** with 1 equiv of boric acid in hot acetic anhydride (Equation 2). No other derivatives were described <2003HCA1949>.



52 **53**

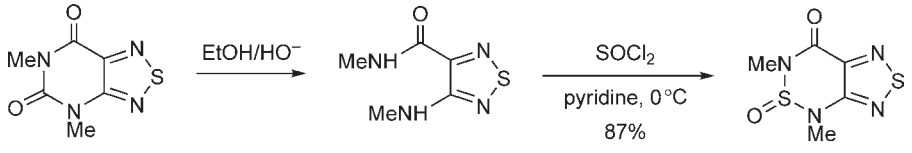
R_2N = morpholinyl

(2)

10.14.9.3 Six Heteroatoms (12π)

10.14.9.3.1 1,2,5-Thiadiazolo[3,4-*c*][1,2,6]thiadiazines **21**

The novel derivative **56** (m.p. 127–128 °C) has been prepared in high yield by reaction of the 1,2,5-thiadiazole **55** with thionyl chloride (**Scheme 3**) <2000JHC1269>. The intermediate **55** is made by alkaline hydrolysis of 4,6-dimethyl[1,2,5]thiadiazolo[3,4-*d*]pyrimidine-5,7(4*H*,6*H*)-dione **54** <2000JHC1269>.

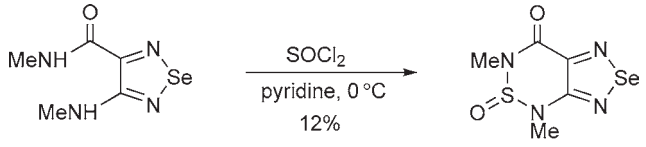


54 **55** **56**

Scheme 3

10.14.9.3.2 1,2,5-Selenadiazolo[3,4-*c*][1,2,6]thiadiazines **22**

Reaction of a pyridine solution of the 1,2,5-selenadiazole **57** with thionyl chloride at 0 °C gave a low yield of the novel selenadiazolo[3,4-*c*][1,2,6]thiadiazine **58** (m.p. 208–210 °C) (Equation 3). The precursor **57** was prepared from the corresponding selenadiazolo[3,4-*d*]pyrimidine, in a similar procedure to that used for compound **55** <2000JHC1269>.



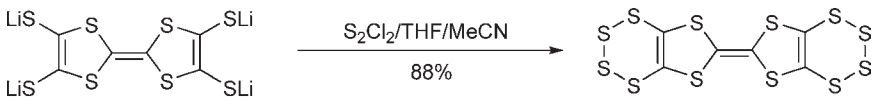
57 **58**

(3)

10.14.9.4 Six Heteroatoms (14π)

10.14.9.4.1 1,3-Dithiolium[4,5-*e*][1,2,3,4]tetrathiane **23**

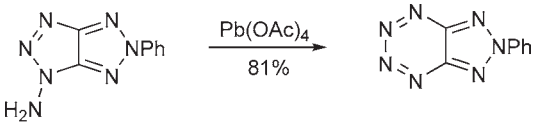
The compound **60** (C_6S_{12}) has been reported to be formed by reaction of the tetralithium salt **59** with sulfur monochloride at room temperature (Equation 4). In an alternative procedure, the tetrasodium salt was used. Similar procedures gave the C_6S_{10} and C_6S_{14} analogues. Products were obtained as solvates and were not recrystallized <2005MCL575>.



59 60 (4)

10.14.10 Ring Synthesis by Transformation of Another Ring

The only ring synthesis in this category is formation of the triazolotetrazine **26** by oxidation of the 1-aminotriazolotriazole **61** (Equation 5), and this was discussed in CHEC-II(1996) <1996CHEC-II(7)513>.



61 26 (5)

10.14.11 Important Compounds and Applications

A number of the compounds described in this chapter and the corresponding chapter in CHEC-II(1996) <1996CHEC-II(7)513> have been made because of their structural relationship to purines. Although some biological activities have been reported no useful applications have emerged. Some of the polyaza derivatives are of potential interest as explosives and high-energy oxidizing agents <1992MI1109, 1995MC100, 2004MI75>. More recently, there has been some preliminary interest in polysulfur derivatives as organic metals <2005MCL575>.

References

1991AXC590 K. Yamaguchi, T. Kaihoh, T. Itoh, and A. Ohsawa, *Acta Crystallogr., Sect. C*, 1991, **47**, 590.

1992J(P1)2779 A. H. M. Al-Shaar, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan, and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2779.

1992MI1109 G. N. Marchenko, T. S. Pivina, and V. A. Shlyapochnikov, *Proc. Int. Pyrotech. Semin.*, 1992, 1109 (*Chem. Abstr.*, 1994, **119**, 75818g).

1995MC227 A. M. Churakov, S. L. Ioffe, and V. A. Tartakovsky, *Mendeleev Commun.*, 1995, 227.

1995MC100 K. I. Rezchikova, A. M. Churakov, V. A. Shlyapochnikov, and V. A. Tartakovskii, *Mendeleev Commun.*, 1995, 100.

1995IZV2187 K. I. Rezchikova, A. M. Churakov, V. A. Shlyapochnikov, and V. A. Tartakovskii, *Izv. Akad. Nauk SSSR, Ser. Khimi.*, 1995, 2187.

1995MC102 A. M. Churakov, S. E. Semenov, S. L. Ioffe, Y. A. Strelenko, and V. A. Tartakovskii, *Mendeleev Commun.*, 1995, 102.

1996CHEC-II(7)513 C. A. Ramsden; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 513.

1998MI11 F. M. A. El-Taweel, *Alex. J. Pharm. Sci.*, 1998, **12**, 11.

2000JHC1269 T. Ueda, W. Doi, S. Nagai, and J. Sakakibara, *J. Heterocycl. Chem.*, 2000, **37**, 1269.

2003HCA1949 C. Hahnemann and H. Hartmann, *Helv. Chim. Acta*, 2003, **86**, 1949.

2003MI152 Y. P. Zarubin, D. V. Mirgorodsky, P. P. Purygin, I. A. H'icheva, and V. L. Florent'ev, *Vestnik Samarskogo Gosudarstvennogo Universiteta, Estestvennonauchnaya Seriya*, 2003, 152 (*Chem. Abstr.*, 2004, **141**, 420020).

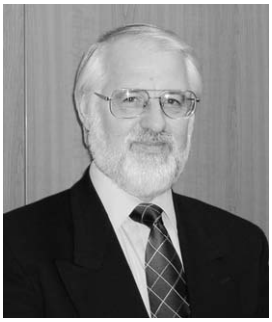
2004MI75 D. B. Lempert, G. N. Nechiporenko, and S. I. Soglasnova, *Khimicheskaya Fizika*, 2004, **23**, 75. (*Chem. Abstr.*, 2004, **141**, 298159.)

2005MCL575 V. Starodub, A. Kravchenko, V. Bondarenko, and A. Kazachkov, *Mol. Cryst. Liq. Cryst.*, 2005, **427**, 575.

2005JPO719 I. Alkorta and J. Elguero, *J. Phys. Org. Chem.*, 2005, **18**, 719.

2006UP1 C. A. Ramsden, Unpublished results.

Biographical Sketch



Chris Ramsden was born in Manchester, UK in 1946. He is a graduate of Sheffield University and received his PhD (W. D. Ollis) in 1970 and DSc in 1990. After post-doctoral work at the University of Texas (M. J. S. Dewar) (1971–73) and University of East Anglia (A. R. Katritzky) (1973–76), he worked in the pharmaceutical industry. He moved to Keele University as Professor of Organic Chemistry in 1992. His research interests are heterocycles, *ortho*-quinones and three-center bonds, and applications of their chemistry to biological problems.

10.15
Bicyclic 6-6 Systems: Two Heteroatoms 1:1

A. P. Dobbs
Queen Mary, University of London, London, UK
© 2008 Elsevier Ltd. All rights reserved.

10.15.1 Introduction 714
10.15.2 Theoretical Methods 714
10.15.3 Experimental Structural Methods 714
10.15.3.1 NMR Spectroscopy 714
10.15.3.2 X-Ray Crystallography 715
10.15.3.3 Dipole Moments 715
10.15.3.4 Photochemistry 715
10.15.4 Thermodynamic Aspects 715
10.15.4.1 Tautomerism 715
10.15.4.2 Aromaticity 715
10.15.4.3 Thermal Isomerization Reactions 715
10.15.5 Reactivity of Fully Conjugated Rings 716
10.15.5.1 Electrophilic Attack at Carbon 717
10.15.5.2 Nucleophilic Attack at Carbon 717
10.15.5.3 Nucleophilic Attack at Hydrogen 718
10.15.5.4 Reduction 719
10.15.5.5 Miscellaneous 719
10.15.6 Reactivity of Nonconjugated Rings 719
10.15.6.1 Electrophilic Attack at Nitrogen 719
10.15.6.2 Nucleophilic Attack at Carbon 719
10.15.6.3 Oxidation 720
10.15.7 Reactivity of Substituents Attached to Ring Carbon Atoms 720
10.15.7.1 Carbon Substituents 720
10.15.7.2 Oxygen and Sulfur Substituents 721
10.15.7.3 Halogen Substituents 722
10.15.7.4 Miscellaneous Substituents 723
10.15.8 Reactivity of Substituents Attached to Ring Heteroatoms 723
10.15.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component 723
10.15.9.1 Synthesis by Construction of the Second Heterocyclic Ring onto an Existing Heterocycle 724
10.15.9.1.1 Heteroatom in a new ring adjacent to a bridgehead position 724
10.15.9.1.2 Heteroatom in new ring remote from a bridgehead position 730
10.15.9.2 Synthesis from Acyclic Precursors 735

10.15.10 Ring Syntheses by Transformations of Another Ring 739
10.15.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available 743
10.15.12 Important Compounds and Applications 744
References 749

10.15.1 Introduction

This chapter is designed to build on the excellent previous two chapters in CHEC(1984) and CHEC-II(1996) on bicyclic 6-6 fused ring systems with two heteroatoms <1996CHEC-II(7)527, 1984CHEC(2)581>. Therefore, this contribution has been written in the same style and format as the previous editions, in order to make the information as accessible to the reader as possible, and also to keep the continuity between the editions.

10.15.2 Theoretical Methods

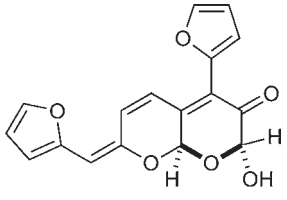
Little has been reported in the way of theoretical methods or studies since the previous volumes, and the reader is directed to these <1996CHEC-II(7)527, 1984CHEC(2)581>.

The preparation and study of tautomers derived from 2-(2′-pyridyl)indole, 2-(2′-pyrrolo)[1,8]naphthyridine, and related heterocycles has been undertaken using ultraviolet (UV) and nuclear magnetic resonance (NMR) spectroscopy and also by molecular orbital (MO) calculations <1998JOC4055>.

10.15.3 Experimental Structural Methods

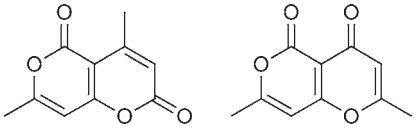
10.15.3.1 NMR Spectroscopy

As part of extensive studies lasting over 30 years on the structures of chromophores involved in nonenzymatic browning reactions, two intensely orange, previously unknown, compounds have been identified: (2*R*,8a*R*)-**1** and (2*S*, 8a*R*)-4-(2-furyl)-7-[(2-furyl)methylidene]-2-hydroxy-2*H*,7*H*,8a*H*-pyrano[2,3-*b*]pyran-3-one <1998CAR215>. Additional studies on the single Maillard reaction products of these compounds have also been reported <1998JFA3912>.



1

The Lewis acid-mediated condensation reaction of α,β-unsaturated carboxylic acids with 4-hydroxy-2-pyrones has been utilized to prepare Fleischmann's α,α-bispyrone **2** and Praill's α,γ-bispyrone **3** and confirm their assignments <2000TL1901>.



α,α-Bispyrone α,γ-Bispyrone

2 **3**

The synthesis and conformational properties of 1,5-dioxa-*cis*-decalins (and heterocycle-fused derivatives) have been studied and they have been found to exist in conformations where the oxygen atoms are predominantly in a

gauche-arrangement <1997LA1143>. The synthesis and conformational properties of *N*-monoalkyl 1,5-diaza-*cis*-decalins have also been studied and the conformational equilibrium between the chair–chair inversion forms of various derivatives measured and related to the size of the *N*-alkyl group <2001TL6451, 2001JOC1103, 2001T4537, 2002JOC3072>. The same group has prepared and utilized chiral 1,5-diaza-*cis*-decalins as ligands for various asymmetric reactions. Preparation and separation of the racemic ligands is straightforward and high yielding <2000OL875> and best results have been obtained in asymmetric lithiation–substitution reactions <2000OL875> and in the enantioselective oxidative biaryl coupling of substituted 2-naphthol derivatives <2001OL1137>. Using a 1,5-diaza-*cis*-decalin copper(I) iodide complex with singlet oxygen gave the biaryl products in 85% yield and up to 93% ee.

10.15.3.2 X-Ray Crystallography

The novel X-ray crystal structures of the following have all been reported: 5-amino-4-(4-methoxyphenyl)-2-phenyl-7-(pyrrolidin-1-yl)-[1,6]naphthyridine-8-carbonitrile <1999AXC1670>, 5-amino-4-(4-diethylaminophenyl)-2-(4-hydroxyphenyl)-7-(pyrrolidin-1-yl)[1,6]naphthyridine-8-carbonitrile <2001AXC726>, 5-amino-4-(4-diethylaminophenyl)-2-phenyl-7-(pyrrolidin-1-yl)[1,6]naphthyridine-8-carbonitrile <2000AXC80>, and rotenone α-oxime <2003AXC392>.

The crystal structure of [1,8]-naphthyridinium-1-tetraphenylborate has been reported and has shown, contrary to the usual pyramidalization of nitrogen, a flattened, spatially distorted molecular structure <1996M391>.

10.15.3.3 Dipole Moments

[1,6]Naphthyridines exhibit second harmonic generation on excitation using a Nd-YAG laser (1064 nm). Solvatochromisn has been used to estimate the enhancement in dipole moments on excitation and the values of β, the first-order hyperpolarisability. Photophysical studies have shown that the compounds have a fluorescence lifetime of about 10 ns and fluorescence quantum yield of ~0.05–0.1 in different solvents <2002SAA1535>.

10.15.3.4 Photochemistry

The water-soluble compound 2-amino[1,8]naphthyridine is a novel DNA-binding photosensitizer, which may be employed for the one-electron oxidation of DNA. It is also reported to be an excellent chromophore for the design of artificial electron-accepting nucleobases <1999TL6029>.

10.15.4 Thermodynamic Aspects

10.15.4.1 Tautomerism

The author is directed to the previous volumes for a comprehensive treatment of tautomerism in this class of compounds <1996CHEC-II(7)527, 1984CHEC(2)581>.

The preparation and study of tautomers derived from 2-(2′-pyridyl)indole, 2-(2′-pyrrolo)[1,8]naphthyridine, and related heterocycles has been undertaken using UV and NMR spectroscopy and also by MO calculations <1998JOC4055>.

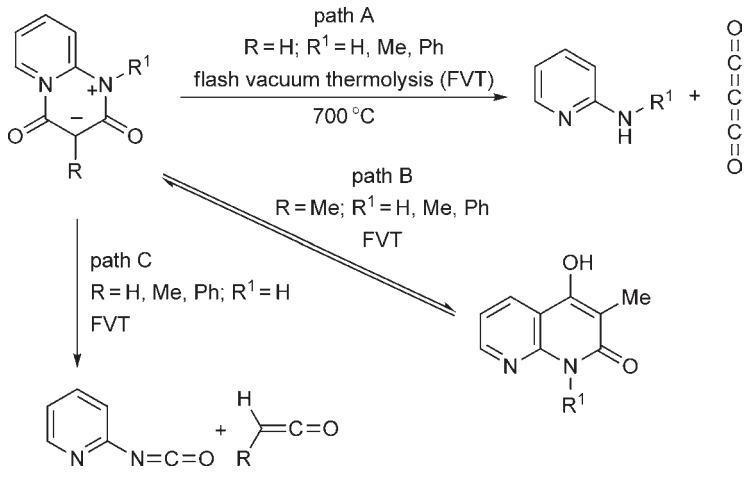
10.15.4.2 Aromaticity

The air oxidation and aromatization of substituted 6,7-dihydro-5*H*-[1,6]naphthyridin-8-ones to substituted 8-hydroxy-[1,6]naphthyridines has been reported <2003JME453>.

The formation of a series of thioethers from 2-thioxo-1,2,5,6,7,8-hexahydro- or from 3-thioxo-2,3,5,6,7,8-hexahydro-[2,7]naphthyridine, with the establishment of aromaticity, has been reported <1997PCJ34, 2003IZK2069>.

10.15.4.3 Thermal Isomerization Reactions

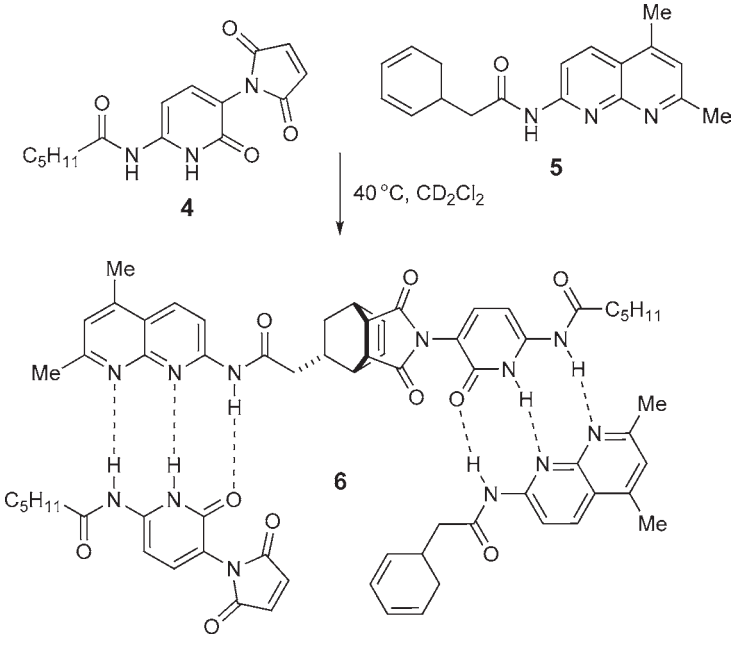
The ketene valence isomers of mesoionic pyrimidinylium olates have been shown to undergo three different reaction pathways (**Scheme 1**): either retro-ene-type fragmentation to give C_3O_2 and 2-aminopyridine (path A), electrocyclization to a naphthyridine (path B), or cycloreversion to 2-pyridyl isocyanate and a ketene (path C) <2000J(P2)1841>. The exact nature of the product varied with the substituents present.



Scheme 1

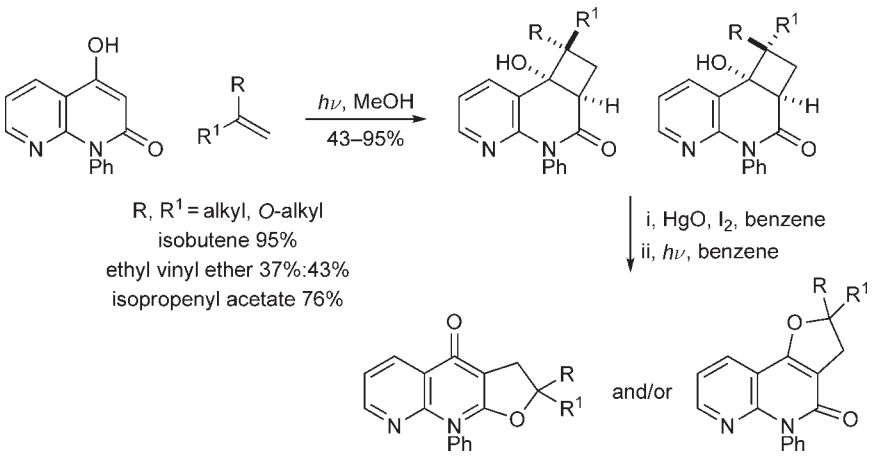
10.15.5 Reactivity of Fully Conjugated Rings

The product **6** of the Diels–Alder reaction between **4** and **5** shows sigmoidal characteristics, indicating that self-replication is taking place, that is, the product formed is an efficient catalyst for the original Diels–Alder reaction (**Scheme 2**) <1997CC1495>.



Scheme 2

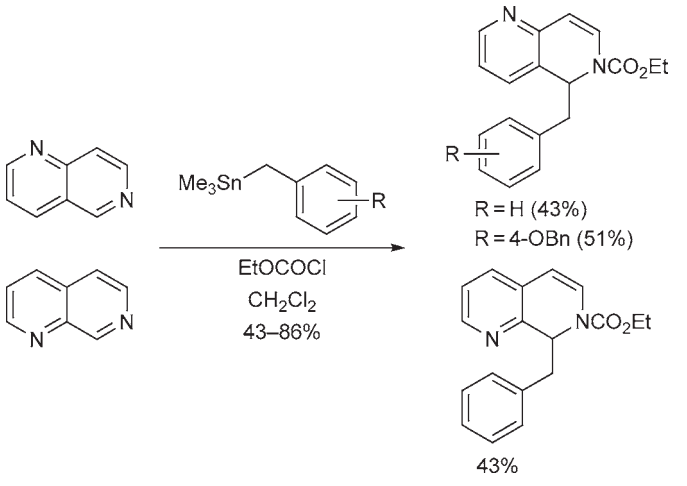
Only the head-to-tail adducts were obtained in the [2+2] photoaddition of 4-hydroxy-1-phenyl[1,8]naphthyridin-2(1*H*)-one with various alkenes in methanol (**Scheme 3**). The photolysis of the hypoiodites generated by the *in situ* reaction of the cycloadducts with excess mercury(II) oxide–iodine reagent in benzene induced a regioselective scission of the non-ring junction bond of the alkoxyl radical to give substituted 3,9-dihydro-9-phenylyfuro[2,3-*b*][1,8]naphthyridin-4(2*H*)-one and/or 3,5-dihydro-5-phenylfuro[3,2-*c*][1,8]naphthyridin-4-(2*H*)-ones <1996T6125>.



Scheme 3

10.15.5.1 Electrophilic Attack at Carbon

The regioselective alkylation of [1,6]- and [1,7]-naphthyridines using benzylstannane and ethyl chloroformate has been described <2000TL8053> as an excellent route to give substituted dihydronaphthyridines (**Scheme 4**).

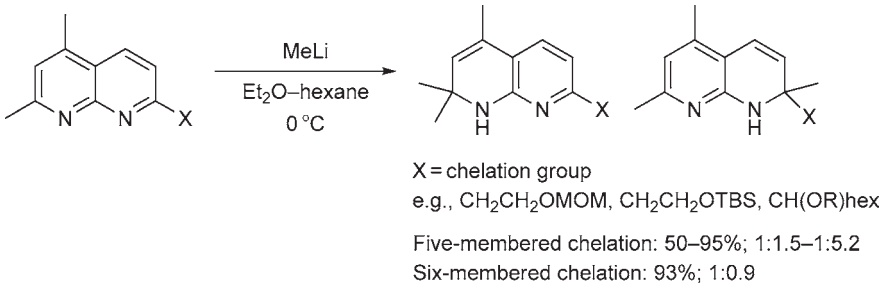


Scheme 4

4-Aryl[1,8]naphthyridin-2(1*H*)-ones have been prepared by the Suzuki coupling of 4-halo[1,8]naphthyridin-2(1*H*)-ones with arylboronic acids in the presence of $Pd(PPh_3)_4$ and cesium carbonate <2003TL6021>. The products were useful as potential acyl-CoA-cholesterol acyltransferase inhibitors. The same researchers found that extending these structures to *N*-phenyl-*N*′-[3-(4-phenylnaphthylidinoyl)]urea derivatives gave improved activity <2004BML1309>.

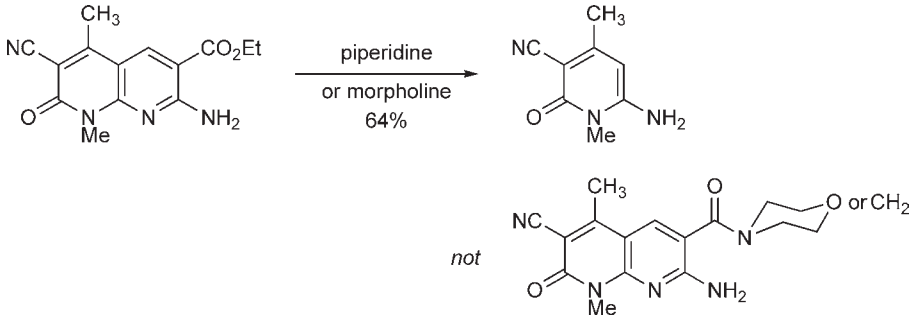
10.15.5.2 Nucleophilic Attack at Carbon

The nucleophilic addition of *n*-alkyllithiums to α,α'-disubstituted [1,8]naphthyridines has been achieved in a nonpolar diethyl ether–hexane mixed solvent (**Scheme 5**); note that when performed in a more polar solvent such as tetrahydrofuran (THF), the alkyllithium acts as a base <2005S1397>. A group capable of five-membered ring chelation at the α-position gave excellent selectivity for that site over an α-position without a chelating group.



Scheme 5

The reaction of 7-amino-6-carbethoxy-3-cyano-1,4-dimethyl[1,8]naphthyridin-2(1*H*)-one with piperidine or morpholine does not afford the corresponding substituted [1,8]naphthyridin-2-ones but instead leads to thermal decomposition to give 6-amino-3-cyano-1,4-dimethylpyridin-2(1*H*)-one (**Scheme 6**) <2001S103>.

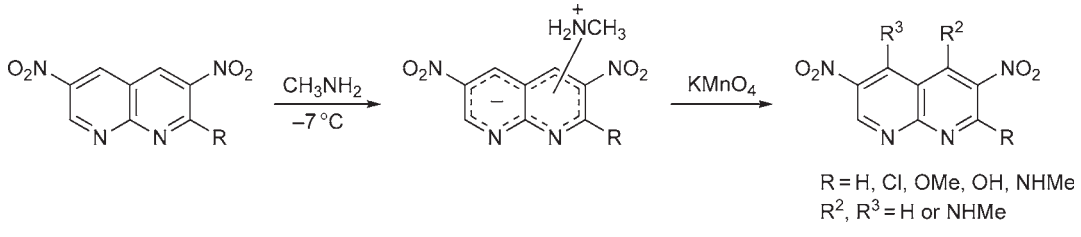


Scheme 6

A common method for the preparation of [2,7]naphthyridines is first to form the corresponding naphthyridinones and to treat them with phosphorus oxyhalides, to give an *O*-acyl intermediate followed by nucleophilic substitution by the halogen. This is then followed by dehalogenation to give the naphthyridine. A detailed study on the mechanism of these halogenation and dehalogenation reactions of the [2,7]naphthyridine ring has been published <2001RRC1139>.

10.15.5.3 Nucleophilic Attack at Hydrogen

3,6-Dinitro[1,8]naphthyridine and its 2-substituted derivatives are dehydro-methylaminated with a solution of potassium permanganate in liquid methylamine to afford the corresponding mono- or bis-methylamino-3,6-dinitro[1,8]naphthyridines (**Scheme 7**) <2000CJC950>. When the 2-substituent is either chlorine or OMe, then some substitution by $NHCH_3$ also occurs. Quantum-chemical calculations have shown that the reaction is controlled by the interaction of the frontier MOs.



Scheme 7

10.15.5.4 Reduction

Specific attention has been drawn to the generation and synthetic use of heteroaryl radicals (cf. aryl radicals) during the period of this review. For example, radicals have been generated from substituted 3-bromo-7,8-dihydro[1,7]-naphthyridines <2001JLRS283>; used in a sequential amination/annelation/aromatisation process to functionalized and fused pyridines <2003JOC6959>; generated photochemically from 7-amino-6-fluoroquinolines and related heterocycles <2001EJO391>; and used in the synthesis of fused pyridines from 2-pyridyl radicals <2002J(P1)1769>.

[2,7]Naphthyridine has been reduced with hydrogen and palladium on $CaCO_3$ to 1,2,3,4-tetrahydro[2,7]naphthyridine <1996EJM875>. [1,6]Hydronaphthyridines may be reduced to 1,6-diazadecalins in good yields and as a single diastereomer using $NaBH_4$ in a mixed AcOH/EtOH/THF solvent system <2003SL2301>. A reductive cyclization of nitropyridones to bicyclic bispyridones has been reported <2000BML1069>.

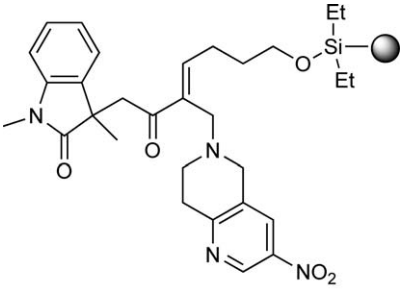
10.15.5.5 Miscellaneous

The aza-Diels–Alder reaction of a variety of amino-aza-heterocycles to yield cyclic amidines and isothioureas has been reported <1996TL2619>.

10.15.6 Reactivity of Nonconjugated Rings

10.15.6.1 Electrophilic Attack at Nitrogen

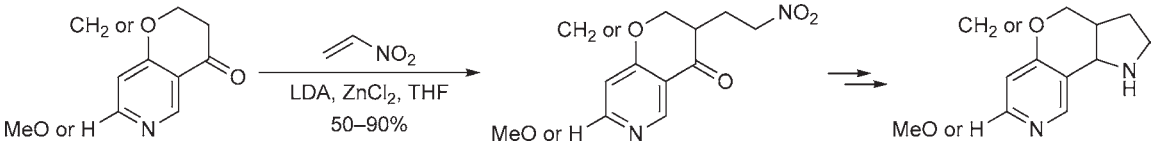
The chemo- and regiospecific palladium-catalyzed four-component reaction of aryl iodides followed by incorporation of carbon monoxide, a polymer-supported allene, and a range of secondary cyclic amines has been reported as a short and high-yielding route to complex heterocycles with three points of diversity, such as **7** <2000CC2241>.



7

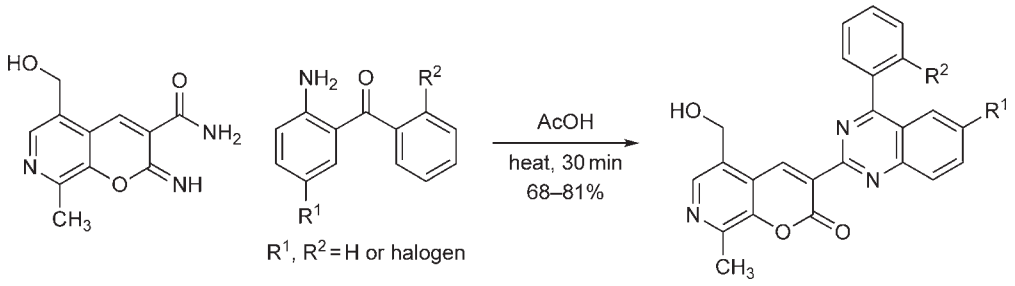
10.15.6.2 Nucleophilic Attack at Carbon

A series of conformationally restricted analogues of nicotine and anabasine have been prepared as part of a program studying models of Parkinson's disease and pain (**Scheme 8**). Transformations of the heterocyclic ketone were key to the program, including cyclization to a third heterocyclic ring <1998BML2173>.



Scheme 8

The reaction of 2-imino-2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide with substituted 2-aminobenzophenones proceeds via ring opening and recyclization to give 3-(4-arylquinazolyn-2-yl)-2*H*-pyrano[2,3-*c*]pyridin-2-ones (**Scheme 9**) <2005SC1641>.

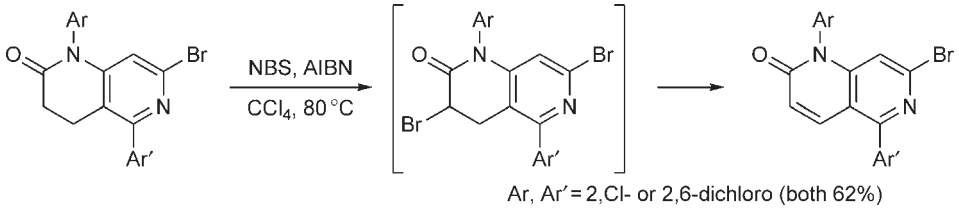


Scheme 9

The aqueous methanolysis of 3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridinium α-D-*N*-acetylneuraminoate has been studied and is believed to proceed via dissociative transition states with no intramolecular nucleophilic participation by the anomeric carboxylate group <2004JPO478>. The synthesis of the starting substituted sugar is also reported.

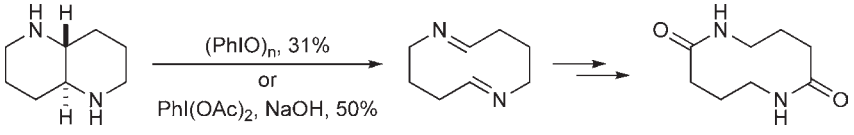
10.15.6.3 Oxidation

It is possible to perform regiospecific benzylic radical bromination of 3,4-dihydro-1*H*-[1,6]naphthyridin-2-ones, followed by spontaneous elimination, to form quinolinones (**Scheme 10**). The products were used as part of a programme aimed at novel p38 inhibitors <2003BML467>.



Scheme 10

It has been reported that [1,5]diaza-*cis*-decalins undergo an oxidative rearrangement, at the more hindered position, followed by fragmentation to give the ring expanded bis-lactam (**Scheme 11**). If the *N*-BOC-protected compound was used, oxidation occurred at the less hindered position to give a route to 2,6-substituted-1,5-diaza-*cis*-decalins <2002TL3747>.



Scheme 11

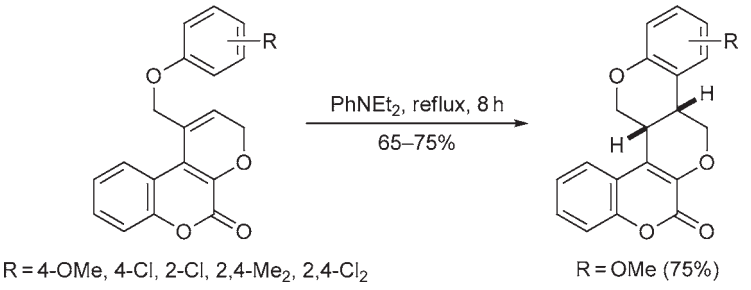
10.15.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.15.7.1 Carbon Substituents

A microwave-assisted SeO_2 oxidation of heteroaromatic methyl groups to give the corresponding heteroaromatic aldehydes has been reported <2003SC475>.

2-Amino-5,6,7,8-tetrahydro[1,6]naphthyridine-3-carbonitriles have been further cyclized with guanidine hydrochloride to give tetraazaanthracenes <2002JME5173>.

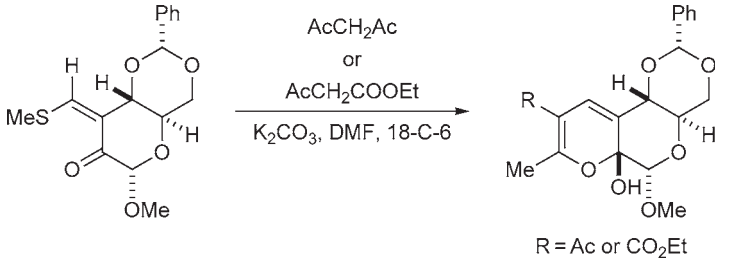
On heating in *N*,*N*-dimethylaniline, 1-aryloxymethylpyrano[2,3-*c*]benzopyran-5(3*H*)-ones undergo a [3,3]-sigmatropic rearrangement, followed by enolization and unusual internal [1,6]-Michael addition to give [6*c*,12*b*-*cis*]-6c,7,12b,13-tetrahydro-1*H*-chromenopyrano[2,3-*c*]chromen-1-ones (**Scheme 12**) <1998TL7147>.



Scheme 12

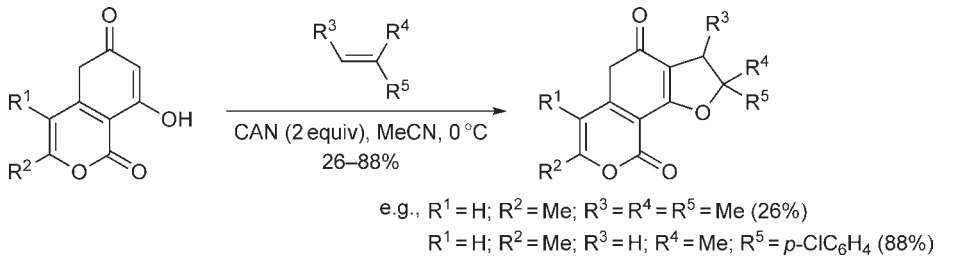
10.15.7.2 Oxygen and Sulfur Substituents

The reactions of fused and unfused α-pyrones with magnesium alkoxides, sodium alkoxides, and water as the nucleophile have been studied in depth, particularly with respect to the effects of chelation <1996J(P1)2715>. The annelation reactions of pyranose derivatives, with acetylacetone and ethyl acetoacetate, to give a variety of annelated fused pyrans have been reported, with the products obtained as single diastereoisomers (**Scheme 13**) <1997LA1019>.



Scheme 13

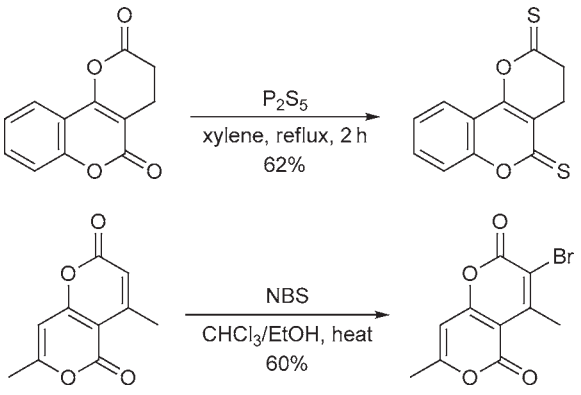
Furopyranopyrandiones have been prepared by the cerium(IV) ammonium nitrate-mediated reaction of 4-hydroxy-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-diones with alkenes (**Scheme 14**) <2003H(60)939>.



Scheme 14

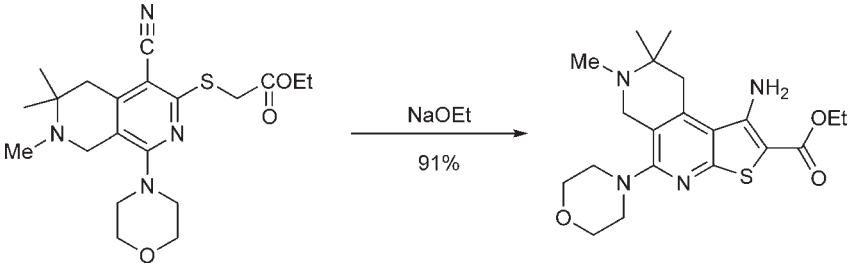
3,4-Dihydropyrano[3,2-*c*]chromene-2,5-diones are readily converted into the corresponding dithione with P_2S_5 (**Scheme 15**) <1997CHE39>. Bromination of the related pyranopyran-2,5-dione using *N*-bromosuccinimide (NBS) under thermal conditions gives exclusively the monobrominated product <1998JIC590>.

The reaction of 2- and 4-pyridones, fused as part of a variety of 6,6-heterocyclic systems, is a recurring theme in many publications: for example, conversion of diethyl 4-oxo-1,5,7,8-tetrahydro-4*H*-[1,6]naphthyridine 3,6-dicarboxylate into the 4-chloro derivative <2004BML3441>, and others will appear through the chapter.

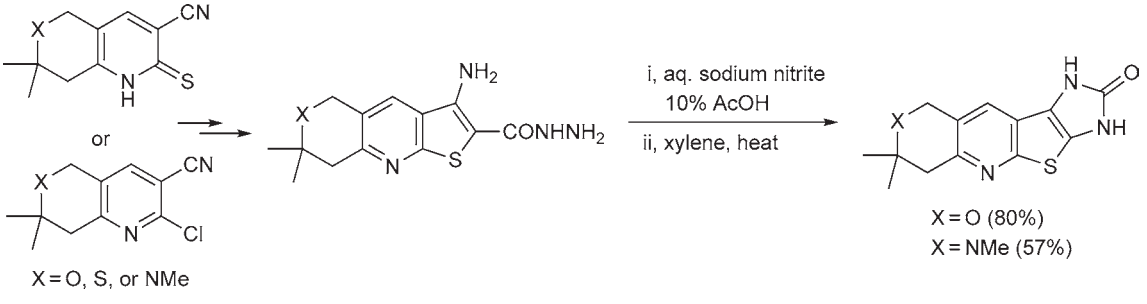


Scheme 15

There are many examples of substituents on the heterocyclic systems under discussion being cyclized to give further (hetero)cyclic rings, such as cyclization to give a 6,7,8,9-tetrahydro-3-thia-4,7-diazacyclopenta[*a*]naphthalene (**Scheme 16**) <1997PCJ540> and the cyclization of 3-amino-2-hydrazinocarbonyl-7,7-dimethyl-7,8-dihydro-5*H*-pyrano[3,4-*e*]thieno-[2,3-*b*]pyridine to give 7,7-dimethyl-2-oxo-1,2,6,7-tetrahydro-9*H*-pyrano[3′,4′-*e*]imidazo[4″5″:2,3]thieno[5,4-*b*]pyridines (**Scheme 17**), a previously unreported heterocyclic system <1997CHE741>. Other examples will become apparent through the chapter.



Scheme 16

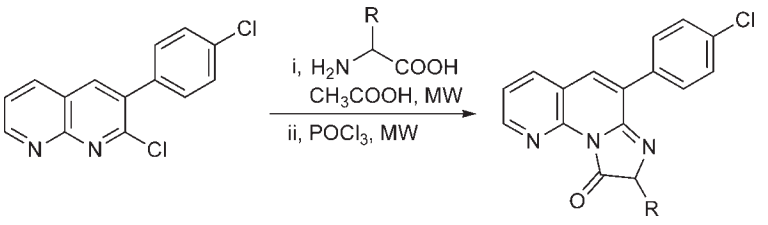


Scheme 17

10.15.7.3 Halogen Substituents

2-Chloro[1,8]naphthyridine-3-carbonitriles readily undergo nucleophilic substitution at the C-2 by 4-substituted piperazines under microwave irradiation <2004BML5179>. The product 2-(4-substituted piperazin-1-yl)[1,8]naphthyridine-3-carbonitriles were 5-HT_3 antagonists.

The microwave-assisted synthesis of imidazo[1,2-*a*][1,8]naphthyridin-1(2*H*)-ones from 2-chloro[1,8]naphthyridine derivatives has been reported (**Scheme 18**) <2002SC857>.



Scheme 18

The same group has reported a mild and efficient synthesis of related compounds, 1,2,4-triazolo[4,3-*a*][1,8]naphthyridines, using iodobenzene diacetate in the solid state <2002SC2377>.

10.15.7.4 Miscellaneous Substituents

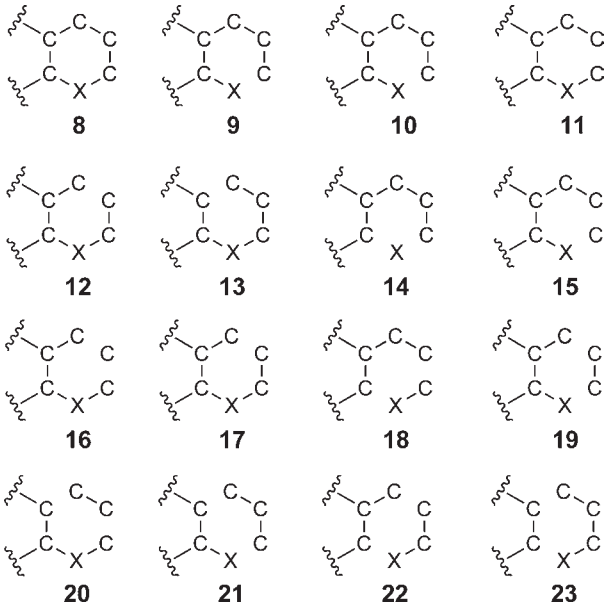
3-Nitro functions attached to 5,6,7,8-tetrahydro[1,6]naphthyridines may easily be reduced to the corresponding amine employing hydrogen with palladium-on-carbon as the catalyst <2001SC787>.

10.15.8 Reactivity of Substituents Attached to Ring Heteroatoms

Chloramine-T reacts with (2-oxo-3-phenyl-2*H*-[1,8]naphthyridine-1-yl)acetic acid arylidenehydrazides to generate 1-(5-aryl-[1,3,4]-oxadiazol-2-ylmethyl)-3-phenyl-1*H*-[1,8]naphthyridin-2-ones <2004IJB2014>.

10.15.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The same system of classification will be used here as in CHEC(1984) and CHEC-II(1996), that is, classification of ring synthesis by the location of the heteroatom within the new ring and then by the number of atoms contributed by each reaction component (**Scheme 19**). This is explained in detail in CHEC-II(1996) and will not be repeated here.



Scheme 19

A comprehensive review of the palladium-catalyzed reactions of propargylic compounds, including in heterocycle synthesis, has been published <1995AGE2589>. Larock has reported numerous examples of the synthesis of many of the heterocycles covered within this chapter from palladium-mediated alkynes, involving in particular palladium <2001OL4035, 2002JOC86, 2003JOC920, 2003JOC980, 2004JOC6772> or electrophilic <2001OL2973, 2002JOC3437> ring-closing reactions.

It is worthwhile commenting that the one method that has really seen an explosion in its use for heterocycle formation since the publication of CHEC-II(1996) is olefin metathesis, with the various metathesis catalysts now readily commercially available. It is beyond the scope of this review to discuss the mechanism and nature of metathesis catalysts and the reader is directed to alternative texts for this <2004CRV2199, 2004CRV2239>.

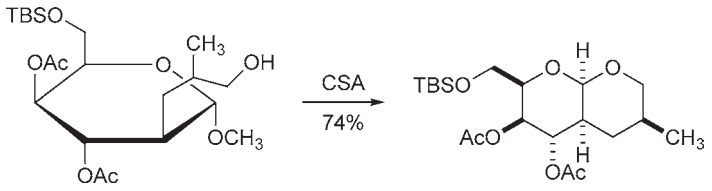
10.15.9.1 Synthesis by Construction of the Second Heterocyclic Ring onto an Existing Heterocycle

10.15.9.1.1 Heteroatom in a new ring adjacent to a bridgehead position

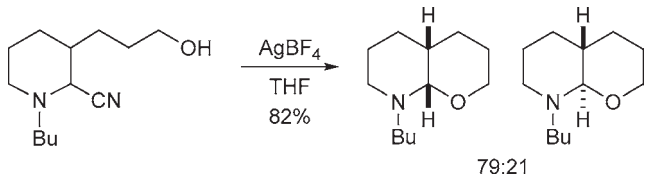
The *ortho*-hydroxyalkylation and cyclization of aminopyridines has given rise to a large range of heterocycles, including naphthyridines, dihydronaphthyridines, and tetrahydronaphthyridines <1999S1893>.

10.15.9.1.1(i) Synthesis of the second ring from [6+0] atom fragments

D-Camphor-10-sulfonic acid (CSA) has been utilized to form *cis*-fused bicyclic acetals from hexopyranosides (**Scheme 20**) <1997TL849>. A silver tetrafluoroborate-promoted cyclization of a series of 3-hydroxyalkyl-2-cyanopiperidines has been used to prepare the octahydropyrano[2,3-*b*]pyridine of 'upenamide' (**Scheme 21**) <2004EJO1057>. Related pyranopyridines have been prepared using an intramolecular Wadsworth–Emmons cyclization <2003TL8545>.

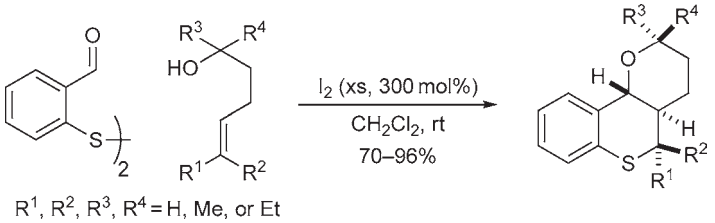


Scheme 20



Scheme 21

An intramolecular hetero-Diels–Alder reaction of *o*-thiobenzoquinone methides, generated *in situ* from bis(2-formylphenyl)disulfide and alkenols in the presence of iodine, has been used to prepare thiochromans (**Scheme 22**) <2003TL6513>.

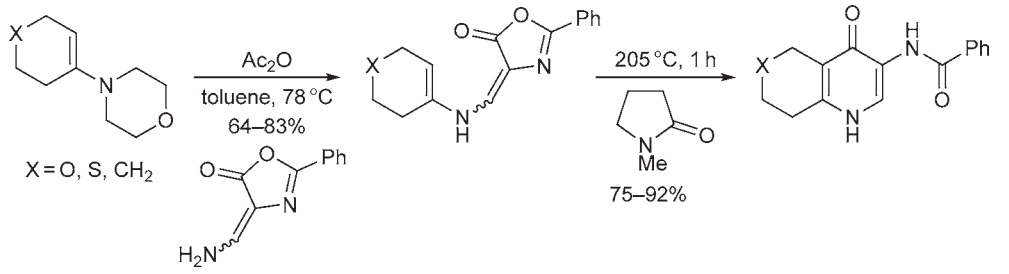


Scheme 22

A related cycloaddition approach of *ortho*-thioquinone methides promoted by Lewis acids has also been reported <2005SL469>.

The condensation of 6-substituted 4-hydroxypyrones with 1-cyclohexenecarboxaldehydes in the presence of L-proline gives the initial 1,2-addition addition product of the pyrone with the aldehydes, followed immediately by a 6π-electrocyclic process to give substituted oxopyrano[4,3-*b*][1]benzopyrans <1997JOC6888>.

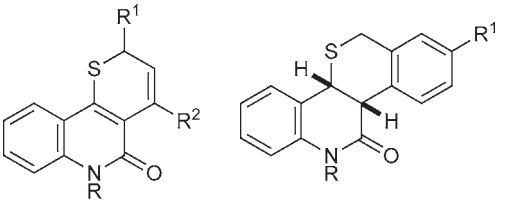
A novel intermolecular alkenyl transfer of enamines has been developed and utilized in the preparation of cycloalkenylaminomethyleneoxazolones, which could subsequently be cyclized to fused pyridones (**Scheme 23**) <1996TL8871>.



Scheme 23

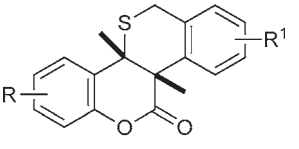
A range of enantiomerically pure (*R*)- and (*S*)-, (*E*)- or (*Z*)-oxime ethers of 2,3-dihydro[1,8]naphthyridine have been prepared from 2-amino-6-methylpyridine <2000EJM815>. The selective acetylation of the same compounds in the 1-, 4-, or 1,4-positions has also been reported <1996JHC1185>.

2*H*-Thiopyrano[3,2-*c*]quinolin-5(6*H*)-ones **24** have been prepared by what is in effect overall a thio-Claisen rearrangement: substituted 4-mercaptoquinolin-2(1*H*)-ones were reacted with various prop-2-ynylic halides which cyclized upon heating via an initial [3,3]-sigmatropic shift to form an intermediate allene, followed by enolization to form an ene-thiol, a 1,5-H shift and electrocyclic ring closure to give the product <2002TL2111>. More recently, the same group have formed quinoline-annelated sulfur heterocycles by aryl radical cyclizations <2005TL6655>. Many sulfur-fused pyridine systems **25** have also been prepared by the reaction of *N*-methylmorpholinium 4-(hetero)aryl-5-cyana-2-oxo-1,2,3,4-tetrahydropyridine-6-thiolates with malononitrile and acetone in ethanol <2003IZK969>.



24 **25**

A simple synthesis of *cis*-benzothiapyrano[3,2-*c*]benzopyran-7(2*H*)ones **26** has been reported through 6-*endo*-*trig*-aryl radical cyclizations <2003S2385>. Further, related, fused heterocycles have also been reported by the same group by sequential Claisen rearrangement and pyridine hydrotribromide-mediated 6-*endo*-cyclizations <2002OL2629>. They have also reported the syntheses of a range of thiopyrano[2,3-*b*]thiochromen-5(2*H*)-ones via a similar method <2003T5289>.



26

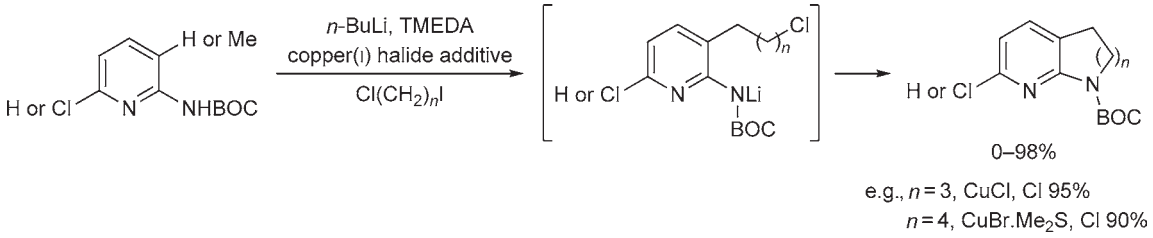
R, R^1 = H, alkyl, *O*-alkyl

Rhode and Hoffmann have investigated sequential radical-mediated cyclizations of enynes as a method for the stereocontrolled synthesis of heteroannular acetals. The sequence generally followed a 5-*exo*-*trig*,6-*endo*-*dig*-pathway and gave the products in a stereocontrolled manner <2000T6479>.

A samarium iodide–water–amine mixture has been shown to be effective for cyclizations of *O*-cyclohexenyliodophenols and pyridines into heterocycles <2003OBC2423>.

The three-component coupling of arylacetaldehydes, secondary amines, and (hetero)aryl azides in refluxing benzene gave triazolines which underwent thermal rearrangement to quinolines and [1,7]naphthyridines <1996J(P1)1359>.

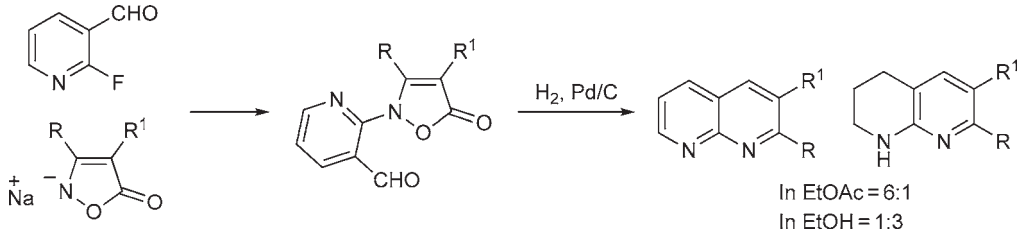
BOC-protected 2-aminopyridines undergo *ortho*-alkylation with α,ω-dihaloalkanes followed by an *in situ* cyclization to give bicyclic adducts in excellent yield (**Scheme 24**) <2004TL1721>.



Scheme 24

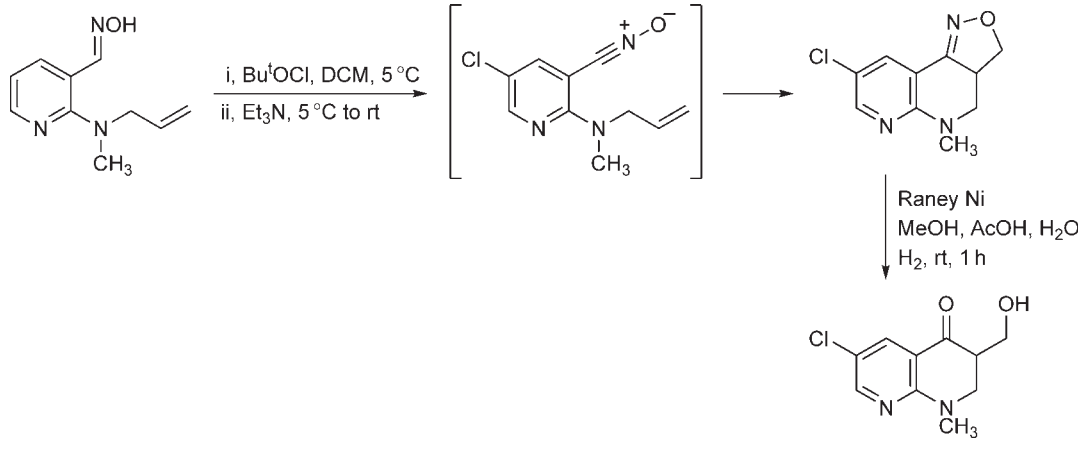
2-Aryl-1,2-dihydro-3-nitro[1,8]naphthyridines have been obtained by the 6π-thermal electrocyclization of 1-(2-arylideneamino-3-pyridyl)-2-nitroethylenes, obtained *in situ* from aromatic aldehydes and 1-(2-amino-3-pyridyl)-2-nitroethylene in xylene <2002SC747>. 2-Chlorotetrahydro[1,8]naphthyridines have also been obtained from 2,6-dichloropyridines using a free radical xanthate-mediated cyclization <2004OL3671>.

Catalytic hydrogenation of pyridine 2-isoxazolones gives, surprisingly, a mixture of [1,8]naphthyridine and [1,8]tetrahydronaphthyridine, the exact ratio depending upon the solvent used to perform the hydrogenation (**Scheme 25**) <2003T9887>.



Scheme 25

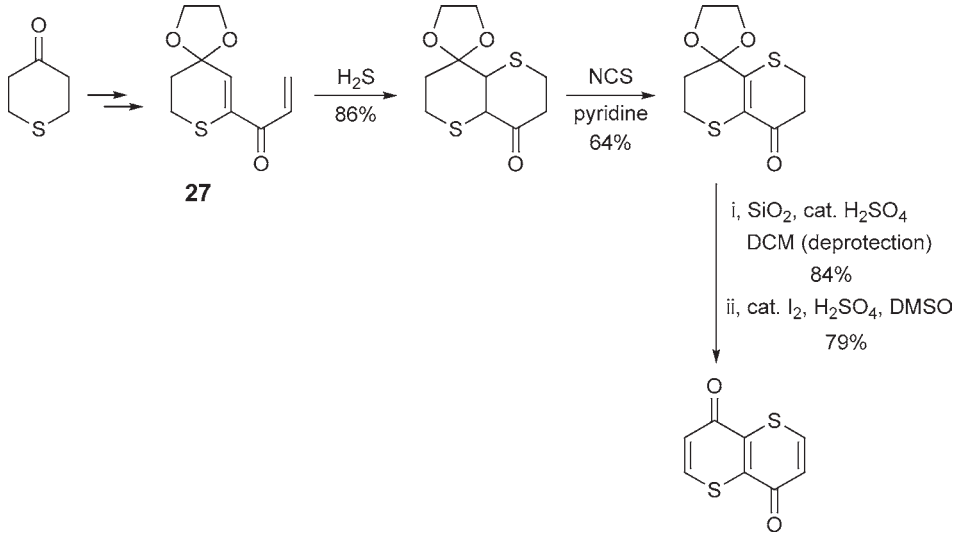
[1,8]Naphthyridines have been prepared via palladium-assisted nucleophilic amination <2002H(56)443>, and 5,6,7,8-tetrahydronaphthyridines by a one-pot double Suzuki reaction of 2,5-dibromopyridine with phthalimide-protected allylamine followed by an intramolecular Chichibabin reaction <2001TL6811>. An intramolecular nitrone cycloaddition has been highly effective in the preparation of [1,8]naphthyridin-5-one derivatives (**Scheme 26**) <1995JHC1595>.



Scheme 26

10.15.9.1.1(ii) Synthesis of the second ring from [5+1] atom fragments

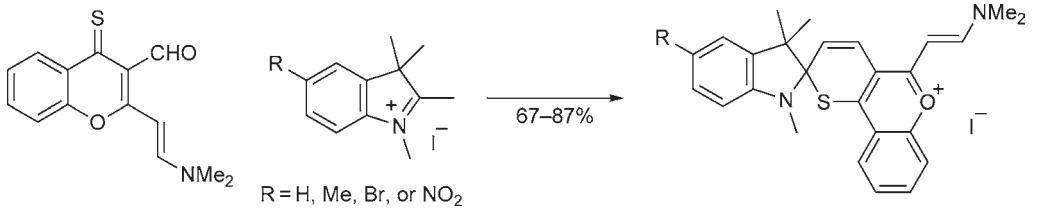
An eight-step synthesis of 4*H*,8*H*-thiopyrano[3,2-*b*]thiopyrano-4,8-dione has been reported starting from tetrahydrothiopyran-4-one in 25% overall yield. The key step was the cyclization of an unstable 'divinyl ketone' **27**, used immediately upon generation, with hydrogen sulfide to give the new heterocycle (**Scheme 27**). The dione could also be converted into the dithione on treatment with Lawesson's reagent; both of these products are of interest as new materials with potential conducting and magnetic properties <1998EJO1989>.



Scheme 27

10.15.9.1.1(iii) Synthesis of the second ring from [4+2] atom fragments

A novel indolinospirothiopyran dye, 2-*N*,*N*-dimethylaminoethenyl-(1″,3″,3″-trimethylindoline-2″-spiro-2′-2′*H*-1′-thiopyrano)[5′,6′-*c*]benzo[*b*]pyrylium iodide, has been prepared by the condensation of 1,2,3,3-tetramethylindolium iodide and 2-*N*,*N*-dimethylaminoethenyl-3-formyl-4*H*-1-benzopyran-4-thione (**Scheme 28**) <1999JMC2991, 2000S247>.



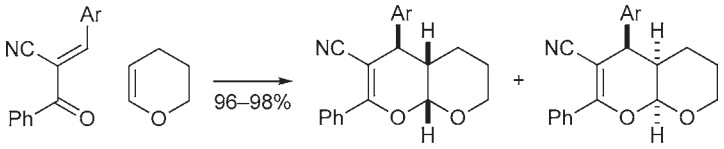
Scheme 28

3-(3-Carboxy-2-pyridylthio)propionic acids, prepared by the reaction of 2-mercatopyridin-3-carboxylic acid with 3-bromopropionic acid in aqueous KOH, undergo cyclization upon treatment with anhydrous sodium acetate and acetic anhydride to afford 2,3-dihydrothiopyrano[2,3-*b*]pyridin-4(4*H*)-ones. These products undergo further reaction with phenylhydrazine to give the phenylhydrazone (isolated) and then Fischer indole cyclization to give novel 5*H*,11*H*-pyrido[2′,3′:2,3]thiopyrano[4,3-*b*]indoles <2000JHC379>.

1,2-Dihydro-5*H*-[1]benzopyrano[4,3-*b*]pyridine-2,5-diones have been prepared from 4-alkylaminocoumarin-3-carbaldehydes and 5-(4*H*)-oxazolinones (azlactones) derived from *N*-acetylglycine and hippuric acid in an Erlenmeyer–Ploechl reaction <2005JHC857>. Related substituted 3-(5-amino[1,3,4]thiadiazolo-2-yl)-2*H*-pyrano[2,3-*c*]-pyridin-2-ones have been prepared by a Knoevenagel condensation of pyridoxal hydrochloride with cyanoacetamide to give 2*H*-pyrano[2,3-*c*]pyridine-3-carboxamide followed by reaction with N-4-substituted thiosemicarbazides <2004JHC517>. An efficient one-pot synthesis of 7-azacoumarins has been reported via a Knoevenagel reaction of

pyridoxal hydrochloride and acetonitriles in water as reaction medium <1997H(45)1715>. A three-component tandem Knoevenagel/hetero-Diels–Alder reaction has been employed in the synthesis of pyrano[3,2-*c*]coumarins and the total synthesis of (±)-preethulia coumarin <2001EJO3711>.

Bismuth(III) chloride catalyzes the intramolecular hetero-Diels–Alder reaction of aldimines, generated *in situ* from aromatic amines and the *N*-allyl derivative of *o*-aminobenzaldehyde, in acetonitrile at reflux to generate [1,6]naphthyridine derivatives <2002TL1573>. The hetero-Diels–Alder reaction of 3-aryl-2-benzoyl-2-propenenitriles and enol ethers yields 2-alkoxy-4,6-diaryl-3,4-dihydro-2*H*-pyran-5-carbonitriles (**Scheme 29**) <1997M1157>.



Ar = C_6H_5 (1:1.5)
Ar = *p*-$NO_2C_6H_4$ (1:1.3)
Ar = *p*-$CH_3C_6H_4$ (1:2)

Scheme 29

7-Substituted-3-aryl[1,6]naphthyridin-2-amines and 7-substituted-3-aryl[1,6]naphthyridin-2(1*H*)-ones have been prepared by diazotization of 3-aryl[1,6]naphthyridine-2,7-diamines, themselves obtained by the condensation cyclization of 4,6-diaminonicotinaldehyde and phenylacetonitrile <2000J(P1)1843>. Derivatives of cyanoacetic acid have rarely been used in the synthesis of naphthyridines, although a recent study has shown that they may be reacted with 4-piperidone derivatives to give [1,6]naphthyridines <2000CHE496>.

Several different and novel modifications of the Friedländer reaction have been reported. A small library of substituted [1,8]naphthyridines was prepared from 2-alkoxy-6-amino-3-cyano-5-formyl-4-phenylpyridine by the Friedländer condensation with aldehydes, ketones, and other active methylene compounds <1995H(41)1001>. They have extended their method to the synthesis of polycondensed [1,8]naphthyridine derivatives <1996H(43)53>. Solvent-free Friedländer condensations of various active methylene compounds with 2-aminonicotinaldehyde in the presence of piperidine at room temperature rapidly give [1,8]naphthyridines in high yields after only a few minutes <2001IJB713>. Sodium fluoride catalyzes the Friedländer condensation of 2-aminonicotinaldehyde with carbonyl compounds bearing an α-methylene group in the solid state to give [1,8]naphthyridines in high yield <2003SC3131>. The solid state *p*-toluensulfonic acid-promoted Friedländer condensation of active methylene compounds with 2-aminonicotinaldehyde has also been reported, giving the corresponding [1,8]naphthyridines <2003IJB1170>. Amines, such as (substituted) pyrrolidines, piperidines, and bicyclic amines, have also been found to catalyze the Friedländer reaction, with 1,3,3-trimethyl-6-azabicyclo[3.2.1]octane (TABO) in particular giving particularly high yields of [1,8]naphthyridines <2003JOC467>. The Friedländer reaction has also been utilized in the preparation of a $\alpha_V\beta_3$ antagonist <2004JOC1959>, the [1,8]naphthyridine prepared subsequently being reduced to a tetrahydronaphthyridine moiety.

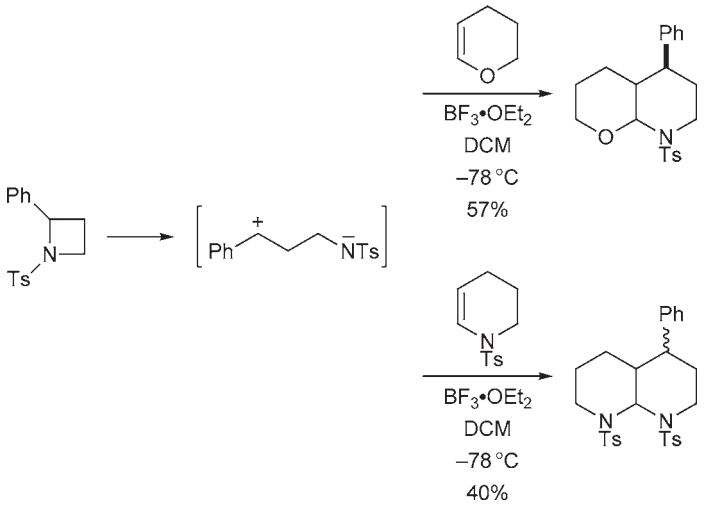
N-Tosylaziridine and *N*-tosylazetidine act as masked 1,3- and 1-4 dipoles with electron-rich alkenes to give adducts useful in the preparation of substituted piperidines (**Scheme 30**) <2001TL6087>.

Photolysis of pyridoxine (vitamin B_6) in aqueous solution at 254, 266, or 308 nm generates an *o*-quinone that may be trapped by ethyl vinyl ether in a Diels–Alder reaction <1998CC491>.

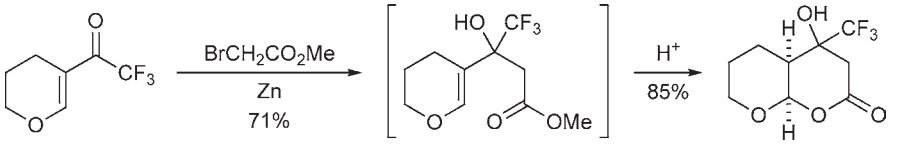
10.15.9.1.1(iv) Synthesis of the second ring from [3+3] atom fragments

Alkyl bromides have been shown to add to 5-trifluoroacetyl-3,4-dihydro-2*H*-pyrans in the presence of zinc powder (**Scheme 31**). When $BrCH_2CO_2Me$ is employed as the alkyl bromide, after the initial addition, the ester may easily be cleaved under acidic conditions and the product undergoes spontaneous cyclization to afford a bicyclic lactone <1999JFC141>.

A detailed study of the [3+3] cycloaddition reaction of 4-hydroxy-2-pyrones and 1,3-diketones has been reported and is useful for the construction of 2*H*-pyranyl heterocycles <2003JOC1729>. It was found that using α,β-unsaturated iminium salts gave exclusively the 2*H*-pyrans. The same group has also reported on the problems of direct epoxidation of the endocyclic olefin in 2*H*-pyrans fused to 2-pyrones, leading to the development of novel methods for the *cis*- (OsO_4, $K_3Fe(CN)_6$, K_2CO_3, H_2O/*t*-BuOH) and *trans*- (magnesium monoperoxyphthalate, H_2O_2, *i*-PrOH) dihydroxylation of these olefinic systems <2001OL2141>.



Scheme 30



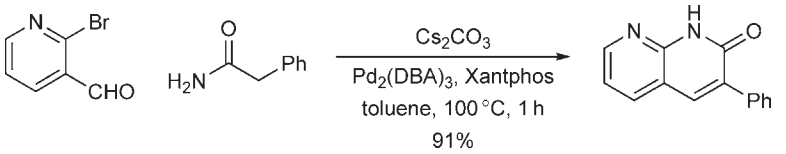
Scheme 31

Pyrano-fused heterocycles, namely pyrano[3,2-*c*]quinoline-2,5(6*H*)-diones, pyrano[3,2-*c*]benzopyran-2,5(6*H*)-dione, and pyrano[3,2-*c*]pyridine-2,5(6*H*)-diones, have been efficiently prepared by the condensation of 4-hydroxy-2-(1*H*)-quinolines, 4-hydroxycoumarin, or 4-hydroxy-(1*H*)-pyridone with α-acetyl-γ-butyrolactone or the sodium salt of α-formyl-γ-butyrolactone in the presence of ammonium acetate <1999JHC467>.

The reaction of triphenylphosphine and dimethyl acetylenedicarboxylate (DMAD) in the presence of either 2-, 3-, or 4-aminophenol and 2-amino-3-hydroxypyridine gives a vinylphosphonium salt which undergoes Michael addition to give a range of highly functionalized heterocyclic systems <2002T6895>.

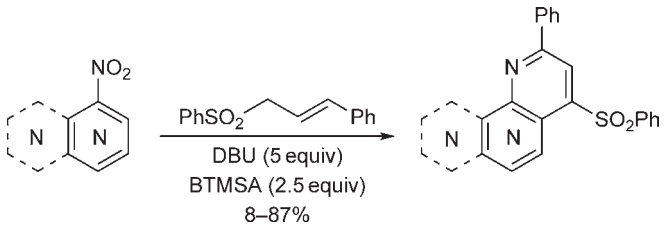
A facile synthesis of substituted 2-hydroxy-3-dimethylaminopropenoates has been reported. These undergo addition with cyclic 1,3-diketones and (hetero)aromatic hydroxyl compounds to afford either 3-hydroxytetrahydro-2*H*-1-benzopyran-2-ones, benzo- and naphthopyran-2-ones, and azolo- and azinopyran-2-ones <1998T9799>.

A palladium-catalyzed amidation of halo(hetero)aromatics substituted in the *ortho*-position by a carbonyl function with a primary or secondary amine has been introduced as an alternative to the Friedländer condensation for the synthesis of naphthyridinones (and quinolinones) (**Scheme 32**) <2004OL2433>.



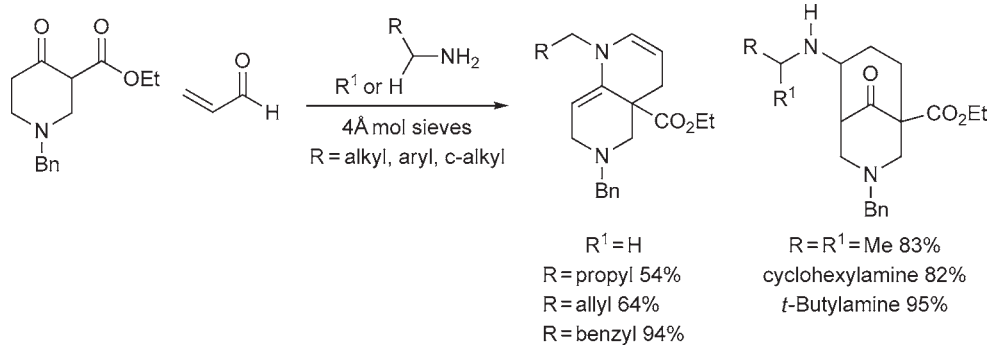
Scheme 32

The DBU/bis(trimethylsilyl)acetamide (BTMSA) double condensation of nitro(hetero)arenes with cinnamyl-based sulfones yields 2-aryl-4-arylsulfonyl heterocycles in good to excellent yields (DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene; **Scheme 33**) <1997TL4913, 1998T2607>.



Scheme 33

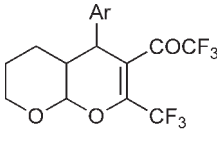
4-Hydroxy-2-pyridones react with diethyl *N*,*N*-dimethylaminomethylenemalonate to give a mixture of isomeric fused pyranones <1996JHC1041>. The three-component domino reaction of *β*-keto esters with acrolein and primary amines in presence of 4 Å molecular sieves gives either [1,6]hydronaphthyridines or aminoazabicyclo[3.3.1]nonanes, depending on the nature of the primary amine, in a one-pot sequence (**Scheme 34**) <2003SL2301>.



Scheme 34

10.15.9.1.1(v) Synthesis of the second ring from [2+4] atom fragments

β, *β*-Di(trifluoroacetyl)ethylene derivatives, $(CF_3CO)_2C{=}CR^1R^2$, react with many nucleophiles and also as heterodienes with dienophiles such as 3,4-dihydro-2*H*-pyran to give highly fluorinated pyranopyran products, **28** <1995JFC167>.



28

The condensation reactions of mono- and bicyclic 4-piperidones has proven a popular method for the preparation of substituted 5,6,7,8-tetrahydro[1,6]naphthyridines, with several different examples being reported <2001SC787, 2003BML1627, 2004JME5167>.

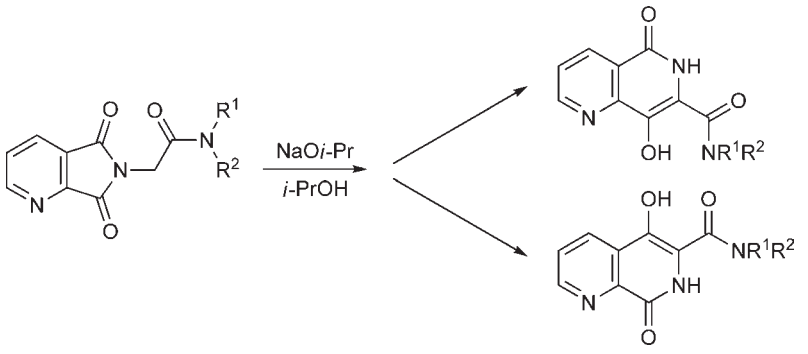
10.15.9.1.2 Heteroatom in new ring remote from a bridgehead position

10.15.9.1.2(i) Synthesis of the second ring from [6+0] atom fragments

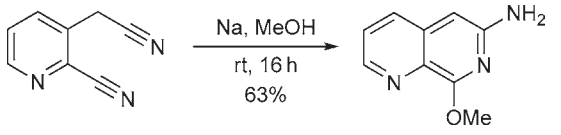
An asymmetric cyanosilylation followed by hydrolysis and cyclization has been used by Curran and co-workers as the key step in the asymmetric synthesis of camptothecin <2001JA9908, 2003H(59)369>.

[1,6]- and [1,7]-Naphthyridines have been synthesized by the alkoxide-induced rearrangement of quinolinimidoacetamide (**Scheme 35**) <2005JHC493>. [1,7]Naphthyridines have also been obtained from the regioselective cyclization of pyridine dinitriles (**Scheme 36**) <2000JME675, 2002BML233>. The ultimate products of this investigation were potent and selective phosphodiesterase-type 4D inhibitors. 5-Phenyl-5,6,7,8-tetrahydro[1,6]naphthyridines and related compounds of varying levels of unsaturation have been prepared via acid-promoted intramolecular imine

formation and cyclization <2004JHC857>. The products were screened as potential D1 receptor ligands. Finally, the hydrogen halide-promoted cyclization of 2-dicyanomethylene-1,2-dihydropyridine-3-carbonitriles has been reported to give 5-amino-7-halo-substituted [1,6]naphthyridines <1995H(41)1013>. A detailed mechanistic rationalization of the direction of cyclization has since been published <1999H50739>.

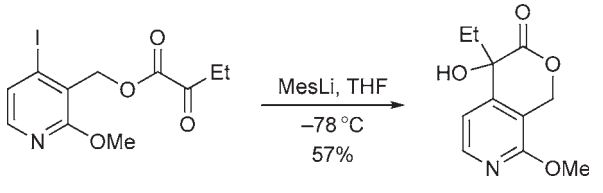


Scheme 35



Scheme 36

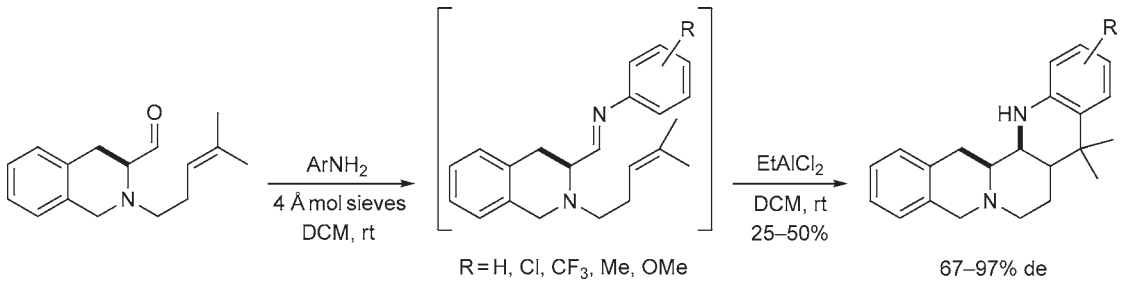
A series of 3-crotyl ether-substituted 4-iodopyridines underwent Heck-type cyclization using a tris-(triphenylphosphine)rhodium(I) acetate/palladium(II) acetate couple to give oxygen-containing pyridine-fused heterocyclic products <1999JOC3461>. Mesityllithium has been demonstrated to be an excellent lithiation reagent for 3-alkoxycarbonyl 4-iodopyridines, giving lactone products (**Scheme 37**) <2001OL13>. On treatment with an *N*-nucleophile, such as ammonia or hydrazine, 5-acetyl-3-benzoylamino-6-(2-dimethylamino-1-ethenyl)-2*H*-pyran-2-one undergoes rearrangement to pyrano[2,3-*b*]pyridine <1996JHC1303>.



Scheme 37

The N-acylation product of the reaction of enaminones with either 2-chloronicotinoyl chloride or 2,6-dichloro-5-fluoronicotinoyl chloride readily undergoes cyclization (either directly or on treatment with sodium hydride) to give high yields of 8-acyl-7-alkyl[1,6]naphthyridin-5(6*H*)-ones, which themselves are attractive precursors for elaboration to naphtho[2,3-*h*][1,6]naphthyridin-5-ones and pyrido[2,3-*c*][1,6]naphthyridin-6-ones <2002T58>.

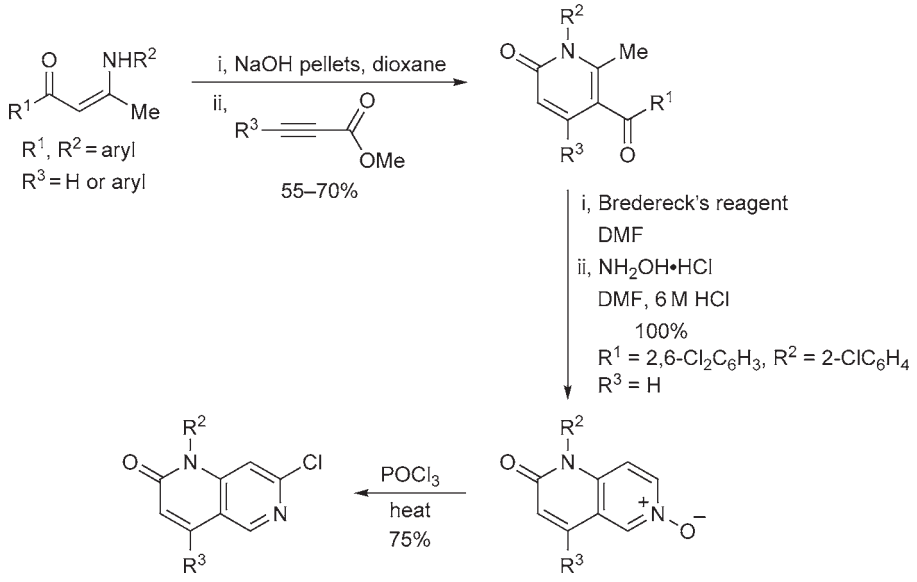
An intramolecular hetero-Diels–Alder reaction has been used to prepare octahydro-14*H*-benzo[*g*]quinolino[2,3-*a*]-quinolidines (**Scheme 38**) <1998BML2881>. The same researchers have published a major study on the mechanism of this hetero-Diels–Alder reaction and have shown that under Lewis acid-catalyzed conditions it proceeds via a stepwise mechanism <1996T955>.



Scheme 38

10.15.9.1.2(ii) Synthesis of the second ring from [5+1] atom fragments

A versatile and flexible route to naphthyridines, containing an isoquinolinic nitrogen, and their corresponding *N*-oxides, has been reported from various *o*-bromopyridinecarbaldehydes and ammonia <1999S306>. Highly functionalized naphthyridones (and quinolines) have been prepared from a common *N*-aryl pyridinone template (**Scheme 39**) <2002OL2071>.



Scheme 39

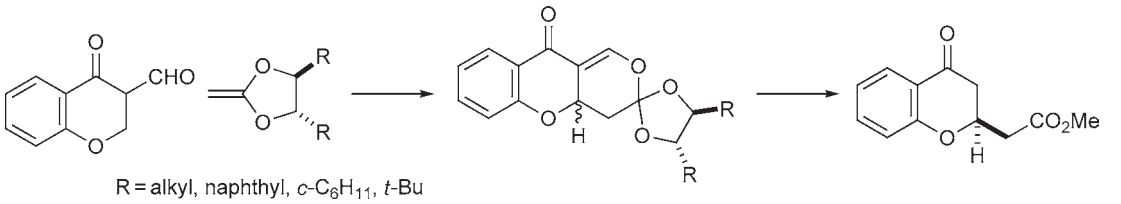
10.15.9.1.2(iii) Synthesis of the second ring from [4+2] atom fragments

There have been many reported examples of (hetero)aryl halides undergoing palladium-catalyzed couplings with acetylenes followed by electrophilic cyclization to yield heterocycles: 2*H*-[2,6]naphthyridin-1-one <2005JOC1432> and Sonogashira coupling of *β*-chloroacroleins followed by iminoannelation of the internal acetylene to give a range of fused pyridines <2003S717>.

Diels–Alder reactions have featured heavily during the period of review. *N*-Vinyl-2-oxazolidinone has been reported as a dienophile for the first time, including the preparation of various tetrahydro-2*H*,7*H*-pyrano[4,3-*b*]pyrans <2002SL952>. The heterodiene cycloaddition reaction of 3-formylchromone with a series of ketene acetals formed from C_2-symmetric 1,2-diarylethane-1,2-diols is completely diastereoselective (**Scheme 40**) <1995J(P1)2293>.

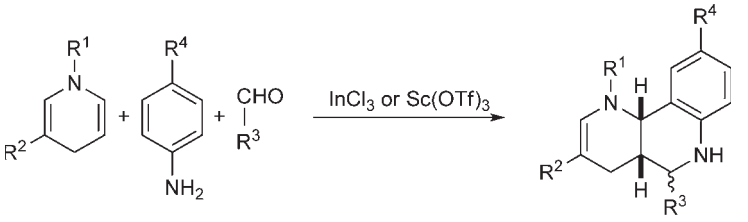
An inverse electron demand Diels–Alder reaction of substituted [1,2,4]triazines with various 1,2,3,6-tetrahydropyridines has been utilized to prepare 5,6,7,8-tetrahydro[2,6]naphthyridines <1997PJC83>. A hetero-Diels–Alder approach utilizing divinyl thioketones has been used to give polyring-fused tetrahydrothiapyrans <1996CC811, 2000H(53)1685>. Various heterocyclic aldehydes (from pyrazole, pyrimidine, pyridine, indole, and thiazole) have been subjected to a Knoevenagel condensation with an aldehyde followed by an intramolecular hetero-Diels–Alder

reaction to give fused heterocyclic rings containing four to seven rings but all featuring either a central 2,7-*O*,*O*, *O*,*S*, or *O*,*N*-fused heterocyclic core <2002T531>. *p*-Toluenesulfonyl cyanide has been used as a dienophile in the Diels–Alder reaction with 5,6-dimethylene-2(1*H*)-pyridinone *ortho*-quinodimethanes to generate [1,6]- and [1,7]-naphthyridines <2003T5481, 2004T429>.



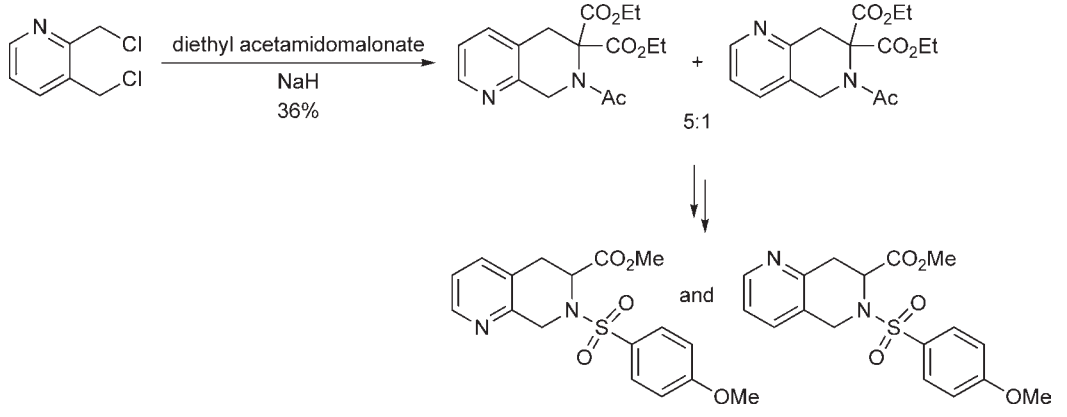
Scheme 40

The Lewis acid-catalyzed three-component reaction of dihydropyridines, aldehydes, and *p*-substituted anilines efficiently yields highly substituted tetrahydroquinolines in a stereoselective manner, through a mechanism believed to be imine formation followed by formal [4+2] cycloaddition (**Scheme 41**). The 1,4-dihydropyridine starting materials were also prepared *in situ* by the nucleophilic addition of cyanide to pyridinium salts, creating in effect a one-pot four-component reaction <2003OL717>.



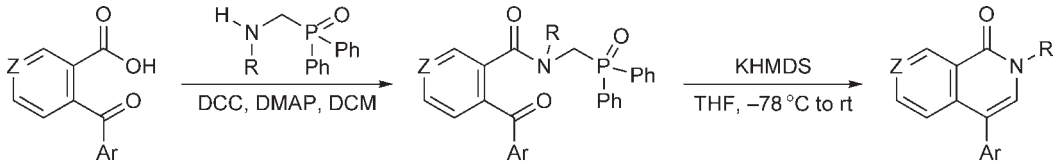
Scheme 41

Mixtures of different regioisomeric tetrahydronaphthyridines have been obtained on cyclization of 2,3-bis(chloromethyl)pyridine with diethyl acetamidomalonate and sodium hydride (**Scheme 42**). After further modifications, these regioisomers were separable and developed as part of a program aimed toward modified hydroxamic acids as HB-EGF (heparin-binding EGF-like growth factor; EGF = epidermal growth factor) shedding inhibitors <2003BMC433>.



Scheme 42

The coupling of *o*-aroylbenzoic or nicotinic acids with phosphorylated amines using dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP) followed by deprotonation with potassium bis(trimethylsilylamide) and cyclization gave isoquinolines or naphthyridinones in good yields (**Scheme 43**) <1996T4433>.



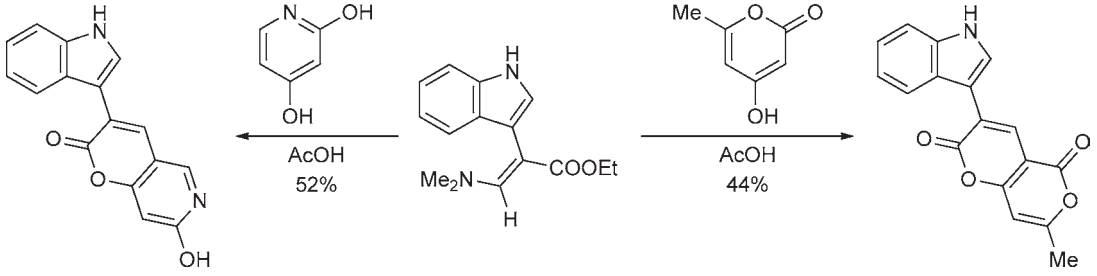
Z = CH; Ar = Ph (90%)	90%
Z = CH; Ar = 4-MeOC$_6$H$_4$ (86%)	90%
Z = CH; Ar = 2-furyl (82%)	65%
Z = N; Ar = Ph (81%)	85%
and other examples	

Scheme 43

N-Substituted amides derived from 2-chloro- or 4-chloronicotinic acid react with CH-acidic nitriles in the presence of base to yield amino derivatives of [1,6]naphthyrid-5(6*H*)-ones and [2,7]naphthyrid-1(2*H*)-ones <1997JHC397>. 3-(1-Alkylamino)pyridines react with electron-deficient alkynes (acetylene dicarboxylates) in the presence of acid to give 1,2-dihydro[2,7]naphthyridine-3,4-dicarboxylates in up to 72% yield; compounds unsubstituted at C-1 were readily oxidized with potassium permanganate to naphthyridine-1-ones <2005TL3953>.

10.15.9.1.2(iv) Synthesis of the second ring from [3+3] atom fragments

Alkyl 3-dimethyl-2-(1*H*-indol-3-yl)propenoates have found an important role in the synthesis of 3-heteroarylindoles as part of a program aimed at the total synthesis of aplysinopsins and related cytotoxic compounds (**Scheme 44**) <2004T4601>.

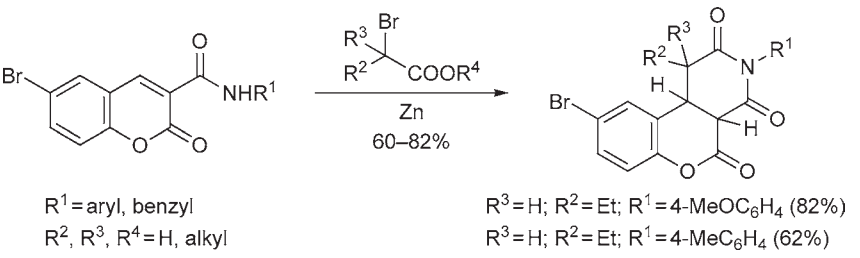


Scheme 44

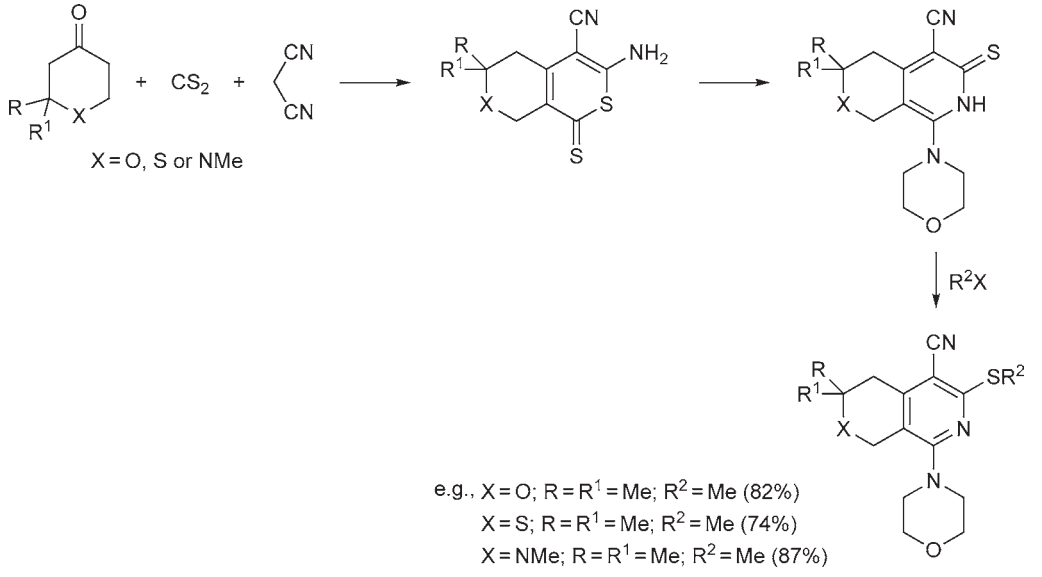
4-Chloro-2-aryl-2*H*-chromene-3-carbaldehydes, formed from the reaction of flav-4-ones with dimethylformamide (DMF)/$POCl_3$, react with ethyl 3-aminocrotonate under Hantzsch conditions to give ethyl 2-methyl-5-aryl-5H-chromen[3,4-*c*]pyridine carboxylates in good yields <2001SC2589>.

The Reformatsky reactions of ethyl α-bromopropionate and related esters with N-substituted 6-bromo-2-oxochromene-3-carboxamides in a mixed diethyl ether–benzene–HMPA–THF solvent system give substituted 9-bromo-2,3,4,4a,5,10b-hexahydro-1*H*-chromeno[3,4-*c*]pyridine-2,4,5-triones (HMPA = hexamethylphosphoramide; **Scheme 45**) <2004RJO892>. Without the THF present in the mixed-solvent system, the reaction stops at the intermediate *N*-benzyl-6-bromo-4-(1-alkoxycarbonylalkyl)-2-oxochroman-3-carboxamide stage.

The one-pot reaction of a piperidin-4-one, carbon disulfide, and 1,1-dicyanomethane generates condensed thiopyranthiones (**Scheme 46**). These products are reactive to ring opening and react with amines to give condensed pyridines and ultimately [2,7]naphthyridines <1999CHE799>.

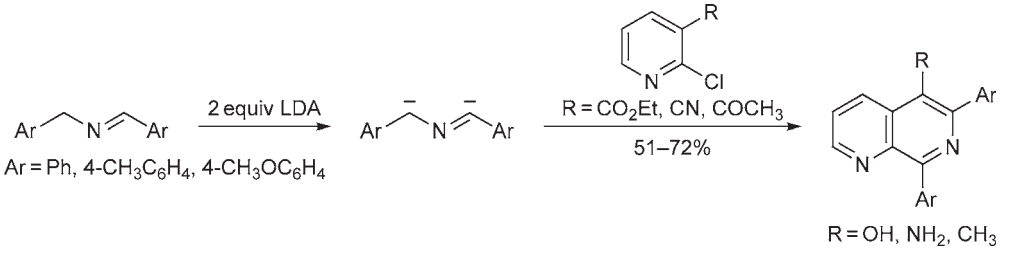


Scheme 45



Scheme 46

2-Azaallyl anions, generated by treatment of arylmethylidene(arylmethylamines) with lithium diisopropylamide (LDA), react with 2-halogenopyridines to give a variety of substituted [1,7]naphthyridines (**Scheme 47**) <1995J(P1)2643>.

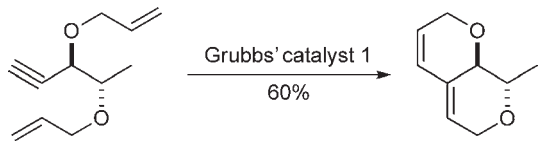


Scheme 47

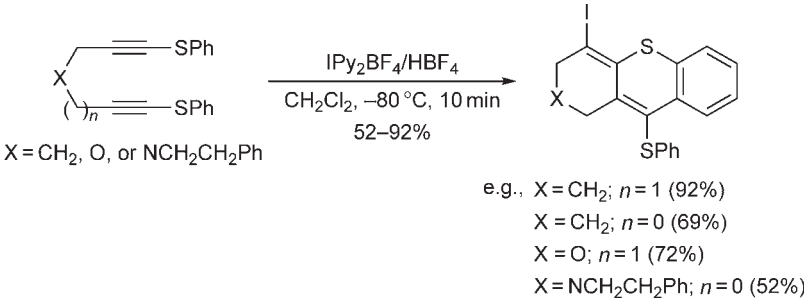
10.15.9.2 Synthesis from Acyclic Precursors

Double sequential ene-yne ring-closing metathesis on a series of chiral 3,4-bisallyloxybut-1-ynes using both Grubbs' catalysts has been used to generate chiral dioxabicyclo[4.4.0]decanes (**Scheme 48**) <2003JOC7889>.

An *exo–endo*-cyclisation of α,ω-diynes promoted by bis(pyridyl)iodonium(I) tetrafluoroborate (IPy_2BF_4) has been described for the first time and is an excellent route for accessing a variety of sulfur-containing heterocycles when employing alkynyl sulfides (**Scheme 49**) <1998AGE3136>.



Scheme 48

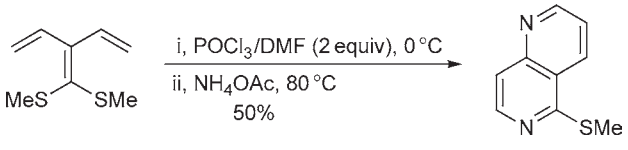


Scheme 49

Bonfanti and Craig have reported the synthesis of dihydrobenzothiopyrans and dihydrobenzopyrans by cation-mediated cyclization reactions <2005TL3719>.

Solid-phase syntheses have become increasingly popular during the period of this review, with examples including the synthesis of 5,6,7,8-tetrahydro[1,6]naphthyridines from Meldrum's acids derived from β-amino alcohols via Hantzsch condensation and cyclization with cyclative cleavage from the resin (using 70% trifluoroacetic acid (TFA)/dichloromethane (DCM) followed by 5% triethylamine/DCM) <1999S1951> and also of isoquinolinones and 5-oxo-5,6-dihydro-[1,6]naphthyridines <1995JOC5748>.

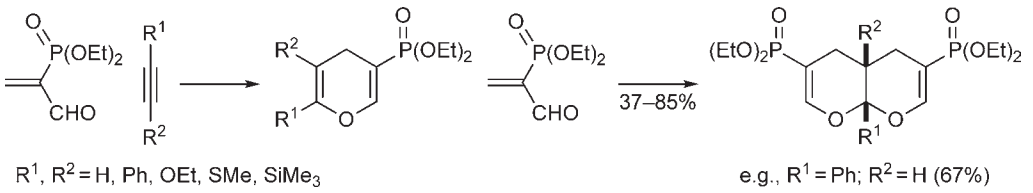
N-Sulfinyl δ-amino-β-keto ester enaminones have been developed as novel sulfinimine-derived chiral building blocks which will undergo a one-pot intramolecular Michael addition followed by retro-Michael-type elimination to give enantiopure 2,4,5-trisubstituted piperidines. In addition to obtaining the desired piperidines, it was found that 5,6,7,8-tetrahydro[1,6]naphthyridines could also be obtained from the same starting material in moderate to good yields <2005JOC5413>. The Vilsmeier–Haack reaction of acyclic ketene *S*,*S*-acetals bearing an α-acetyl, vinyl, or ethynyl group has been used to access substituted pyridines and naphthyridines (**Scheme 50**) <2004SL1731>.



Scheme 50

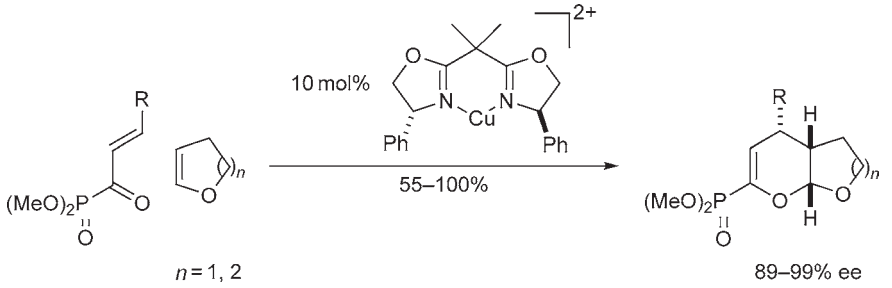
Highly substituted [1,6]naphthyridines have been prepared by the Michael addition and subsequent Thorpe–Ziegler cyclization of a series of chalcones with malononitrile in the presence of pyrrolidine, over extended periods of heating <1999SC3881>. Attempts to reduce the reaction times using microwave irradiation gave mixtures of products <2002SC2903>.

Diels–Alder reactions, in various disguises, have proven to be a popular method for preparing a range of heterocycles. 5-(Phenylthio)pyrano[3,2-*c*][1]benzopyrans have been prepared in high yield from the reaction of 5-phenylthio-4-penten-1-ol and salicylaldehyde in the presence of *p*-toluenesulfonic acid and trimethyl orthoformate <2000TL2643>. The first synthesis of phosphonoacrolein has been reported and this has been utilized as a heterodiene in the Diels–Alder reaction with alkynes, first to give phosphono-substituted pyrans and then a second cycloaddition to give pyranopyrans (**Scheme 51**) <2002JOC7303>.



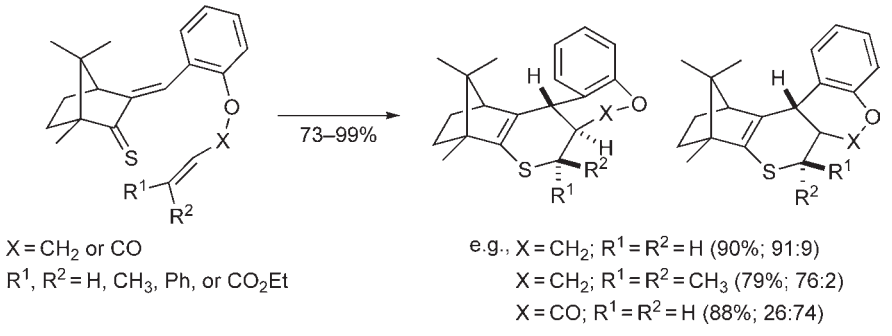
Scheme 51

Evans has reported that the cationic C_2-symmetric chiral Lewis acid Cu(II)bis(oxazoline) complex promotes the hetero-Diels–Alder reaction of α,β-unsaturated acyl phosphonates with enol ethers to give the cycloadducts with excellent ee (**Scheme 52**). As well as simple dihydropyrans, various fused bis-dihydropyrans are also reported <1998JA4895, 2000JA1635>.



Scheme 52

The hetero-Diels–Alder reaction of homochiral camphor-derived thiabutadienes has given, for the first time, optically active bornene ring-fused dihydrothiopyrans with high diastereoselectivity (**Scheme 53**) <2000H(53)1685>. The *exo*:*endo*-ratio varied with the nature of substituent, varying from 91:9 (X = CH_2, $R^1 = R^2 = H$) to 1:99 (X = CO, $R^1 = CO_2Et$, $R^2 = H$).

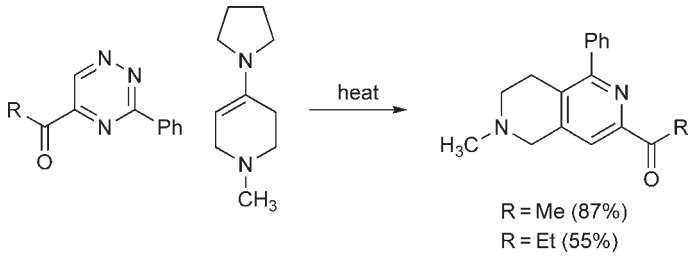


Scheme 53

Hanessian and Compain have also reported a Lewis acid-promoted inverse electron demand hetero-Diels–Alder reaction between dihydrofurans and dihydropyrans with α-keto-β,γ-unsaturated phosphonates to give structurally related products <2002T6521>. High-pressure *endo*-selective hetero-Diels–Alder reactions between α,β-unsaturated aldehydes and enol ethers in the presence of lanthanide catalysts have also been reported and give 3,4-dihydro-2*H*-pyrans. Examples include the use of cyclic enol ethers to give 2,3,4,4a,5,8a-hexahydro-2*H*,5*H*-pyrano[2,3-*b*]pyrans <1995T8383>.

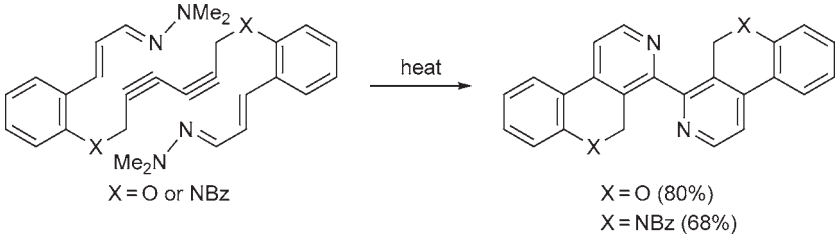
The adducts from the Diels–Alder reaction of 2(1*H*)-pyrazinones with 3-butynylaminomethyl side chains undergo thermolysis to give either [1,7]naphthyridinones or [2,7]naphthyridines <1996T9161>. The intramolecular

trimethylene-tethered inverse electron demand Diels–Alder reaction between imidazoles and 1,2,4-triazene gives 1,2,3,4-tetrahydro-[1,5]naphthyridines in excellent yields <1997TL7499, 2004JOC7171>. Cyclic (and noncyclic) enamines undergo inverse electron demand (hetero-) Diels–Alder reactions with 5-acyl-1,2,4-triazines to give a variety of heterocycles, including acyl-substituted 5,6,7,8-tetrahydro[2,6]naphthyridines (**Scheme 54**) <1997PJC83>.



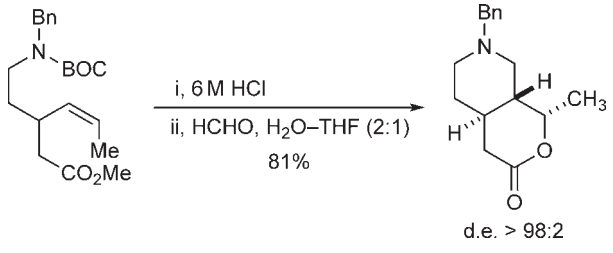
Scheme 54

Double intramolecular Diels–Alder reactions of α,β-unsaturated hydrazones have been used to prepare 2,2′-bipyridines (**Scheme 55**) <1999CC793, 2001J(P1)2183>.



Scheme 55

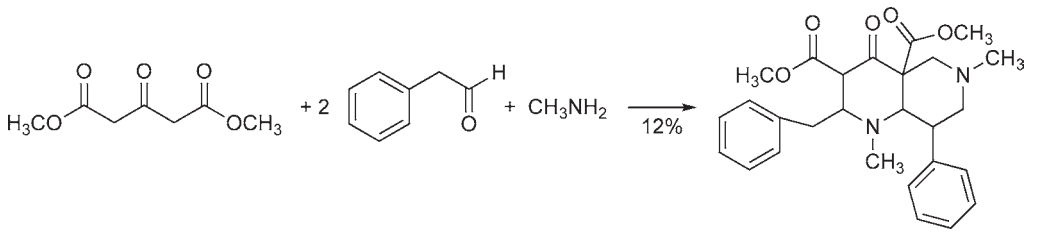
Overman and co-workers have reported Mannich bis-cyclizations (carboxylate-terminated *N*-acyliminium ion bis-cyclizations; **Scheme 56**) and employed these in the total synthesis of (−)-ajmalicine <1995JA9139>.



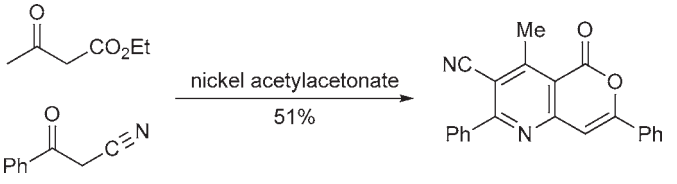
Scheme 56

A similar vinylogous Mannich reaction has been used by Martin in the total syntheses of the heteroyohimboid alkaloids (−)-ajmalicine and (−)-tetrahydroalstonine <1995JOC3236>. An attempted synthesis of an opioid analgesic 2,4-dibenzyl-3,7-diazabicyclo[3.3.1]nonan-9-one-1,5-dicarboxylate (piperidone) by a double Mannich reaction of oxoglutarate, 2 equiv of phenylacetaldehyde, and methylamine did not give the expected product but instead gave rise to an unexpected [1,6]naphthyridine derivative (**Scheme 57**) <1998PHA442>.

Ethyl acetoacetate reacts with benzoylacetonitrile in the presence of a catalytic amount of nickel acetylacetonate to give substituted 3-cyano[4,3-*b*]pyridin-5-ones (**Scheme 58**) <1997RCB1041>.



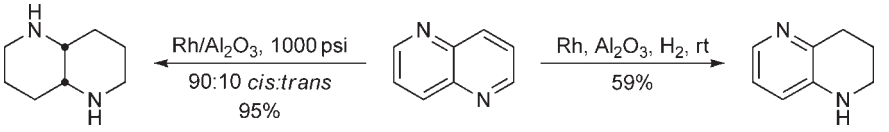
Scheme 57



Scheme 58

10.15.10 Ring Syntheses by Transformations of Another Ring

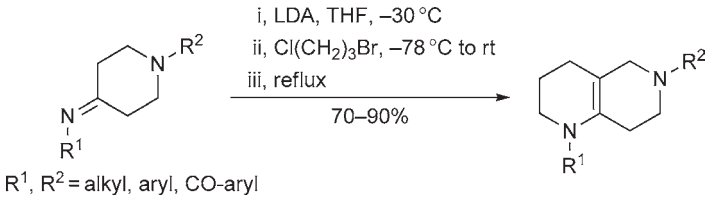
Reduction of an aromatic ring has been a popular theme for the preparation of saturated heterocycles. For example, the reduction of [1,5]naphthyridine leads to either 1,2,3,4-tetrahydro[1,5]naphthyridine or [1,5]diaza-*cis*- and *trans*-decalins using rhodium (**Scheme 59**) <2001TL6451>. Also, [1,6]hydronaphthyridines may be reduced to [1,6]diazadecalins in good yields and as a single diastereomer using $NaBH_4$ in a mixed AcOH/EtOH/THF solvent system <2003SL2301>. The [1,8]naphthyridine prepared from a Friedländer reaction has subsequently been reduced to a tetrahydronaphthyridine as a key stage in the preparation of an $\alpha_V\beta_3$ antagonist <2004JOC1959>.



Scheme 59

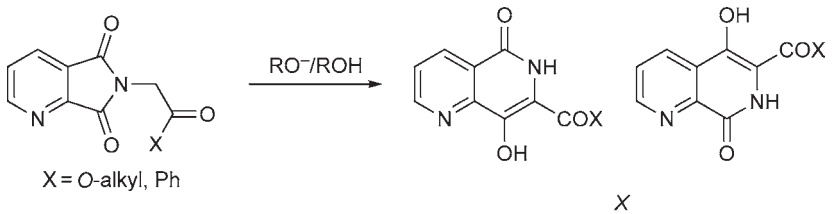
Aryl amines react with an excess of an endocyclic ene-carbamate, including *tert*-butyl 1,2,3,4-tetrahydro-1-pyridinecarboxylate, on the surface of Montmorillonite KSF clay to give 4-aminobutyloctahydrobenzo[*h*][1,6]naphthyridines in excellent yields and moderate diastereoselectivity <2004TL7947>.

4-Piperidinoimines may be α-metallated and alkylated in one pot and subsequently cyclized to give 1,2,3,4,5,6,7,8-octahydro[1,6]naphthyridines (**Scheme 60**) <1998TL7767>.



Scheme 60

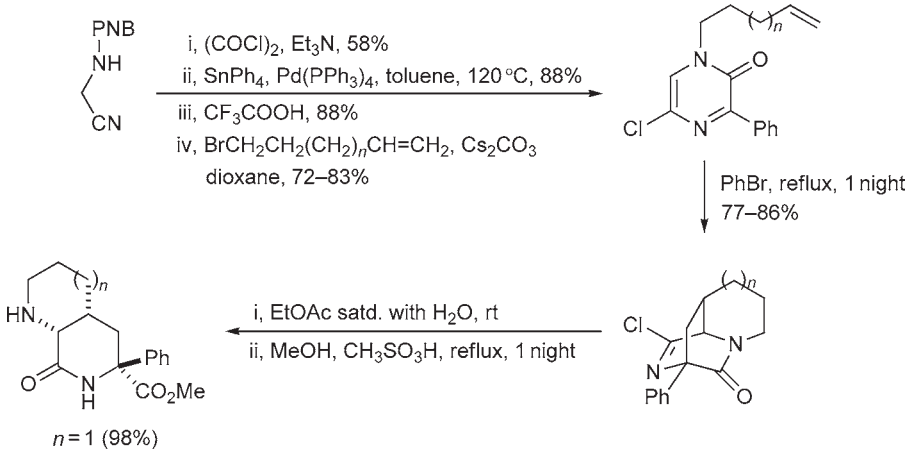
Although the alkoxide-induced rearrangement of N-substituted phthalimides is well documented, little has been reported concerning N-substituted quinolinimides. It has been found that N-substituted quinolinimides react with sodium alkoxides to give mixtures of [1,6]- and [1,7]-naphthyridines, often with transesterification (**Scheme 61**) <1996JHC361, 1999JHC979>.



	X	
40%	OEt	18%
42%	OMe	18%
40%	O*i*Pr	20%
45%	Ph	19%

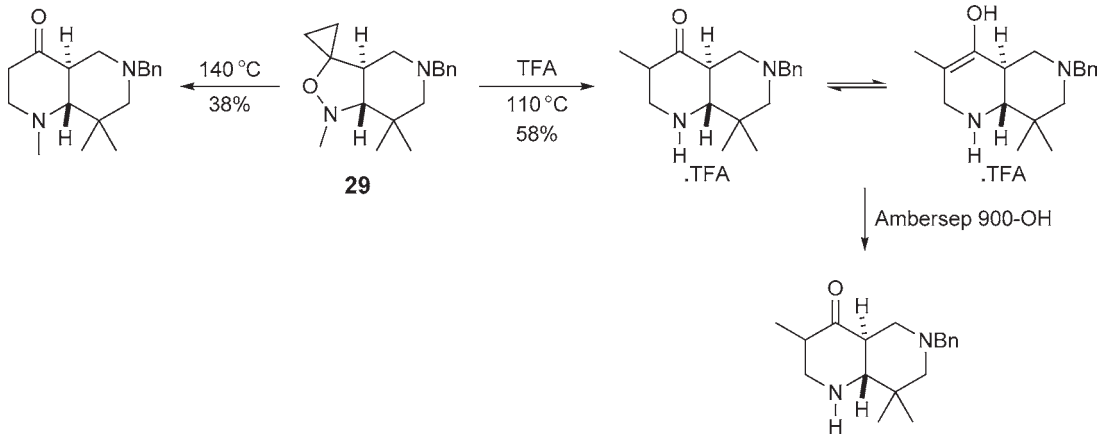
Scheme 61

The intramolecular Diels–Alder reaction of 1-(*N*-ω-alkenyl)-2(1*H*)-pyrazinones generates *cis*-[1,7]naphthyridines in good yields (**Scheme 62**) <2001TL7397>. This method has been used in the development of a *cis*-[1,7]naphthyridine-based scaffold on which to build a type VI external β-turn mimic <2003EJO1868>, and for the synthesis and conformational analysis of [1,7]naphthyridine-based substance P antagonist analogues <2003T4721>.



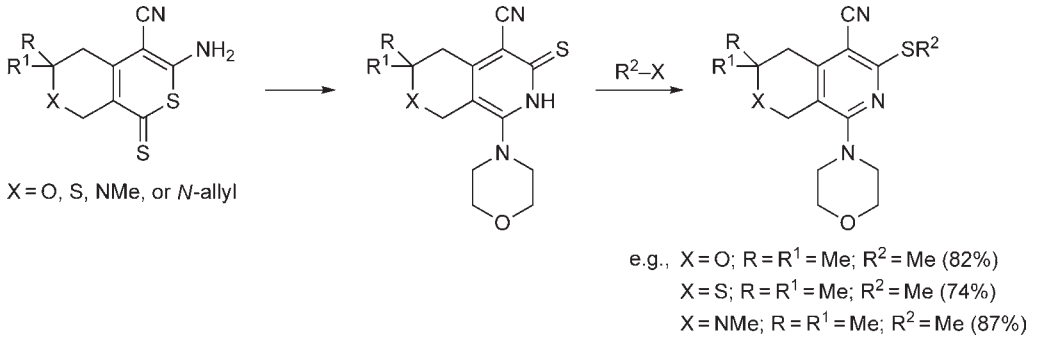
Scheme 62

Thermolysis of 3,4-*cis*- ring-fused 5-spirocyclopropane isoxazolidines **29** in the presence of a protic acid has yielded a variety of heterocycles, including [1,6]naphthyridines, with the concomitant extrusion of ethane (**Scheme 63**) <2003JOC3271>.



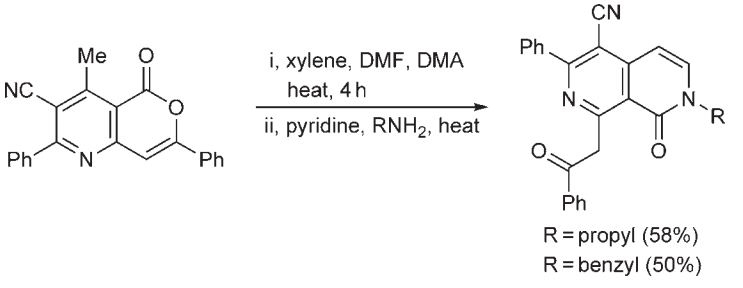
Scheme 63

Various heterocycles, but particularly thiopyrans, ring-open and reclose when reacted with amines to give a variety of condensed heterocycles, including [2,7]naphthyridines (**Scheme 64**) <1999CHE799>.



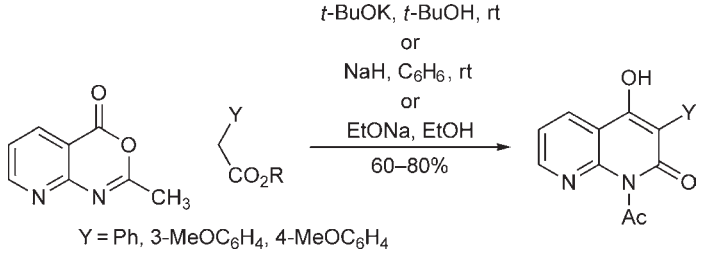
Scheme 64

Along the same lines, 3-cyanopyrano[4,3-*b*]pyridin-5-ones ring open and reclose when reacted with DMF followed by pyridine and a primary amine to give 5-cyano[2,7]naphthyridin-1-ones (**Scheme 65**) <1997RCB1041>.



Scheme 65

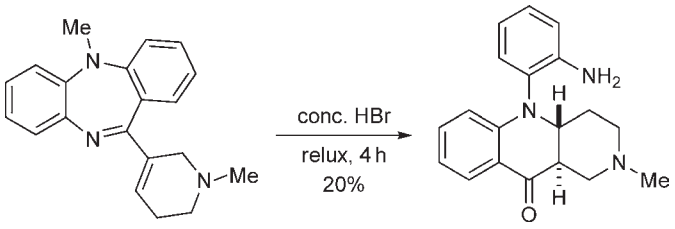
Pharmaceutically important 3-substituted-[1,8]naphthyridine-2,4-diones have been prepared by the reaction of 2-methyl-4*H*-pyrido[2,3-*d*][3,1]oxazin-4-one with active methylene compounds (**Scheme 66**) <1997J(P1)1487, 2003JOC4567> and by the same group via an intramolecular azadiene–ketene electrocyclization reaction of amino-nicotinic acid derivatives in a related process <2001JOC4413>.



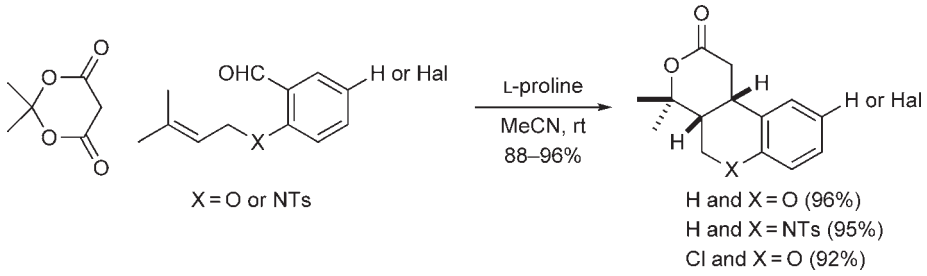
Scheme 66

Various diazepines undergo rearrangement on treatment with concentrated hydrobromic acid to give naphthyridines in one step (**Scheme 67**) <2002TL1583>.

A novel one-pot synthesis of various fused lactones has been achieved via a domino sequence of Knoevenagel/hetero-Diels–Alder/elimination reactions of *N*- and *O*-prenyl aryl aldehyde derivatives with Meldrum's acid in the presence of D- or L-proline with high diastereoselectivity (**Scheme 68**) <2005MI1353>.

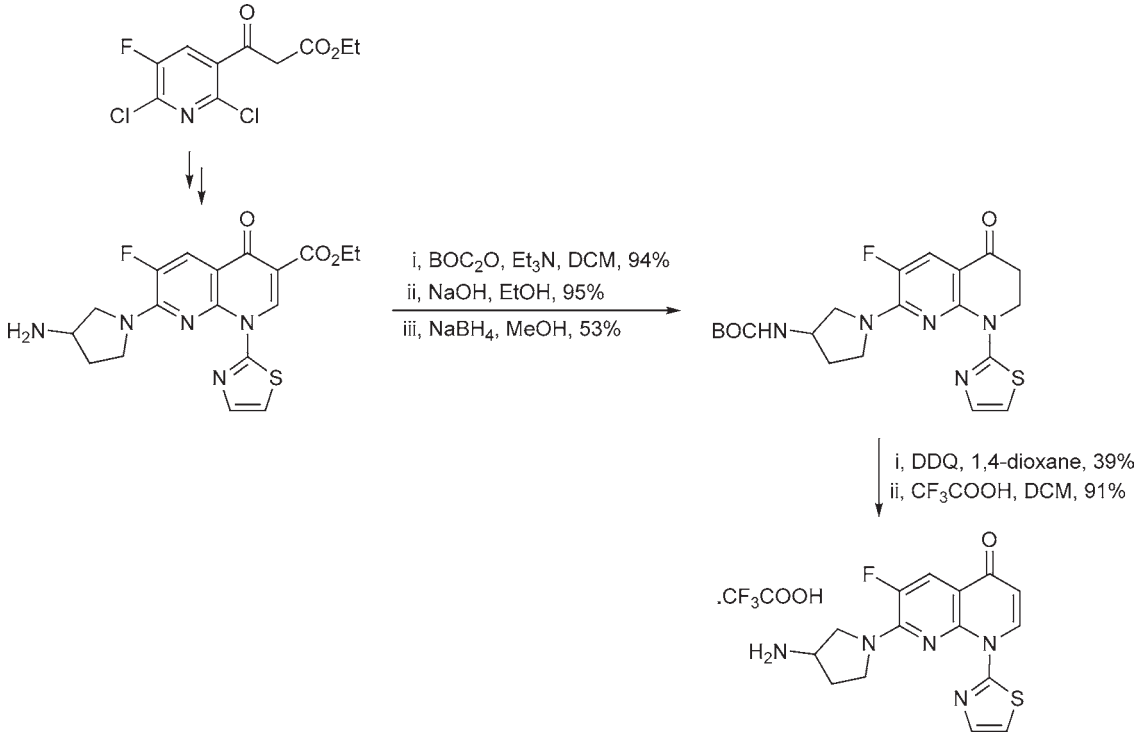


Scheme 67



Scheme 68

In an excellent piece of heterocyclic chemistry, manipulations of the [1,8]naphthyridine system between various oxidation levels have led to the synthesis of novel antitumor agents based around 3-substituted 1,4-dihydro-4-oxo-1-(2-thiazolyl)[1,8]naphthyridines (**Scheme 69**) <2004BML3189>.

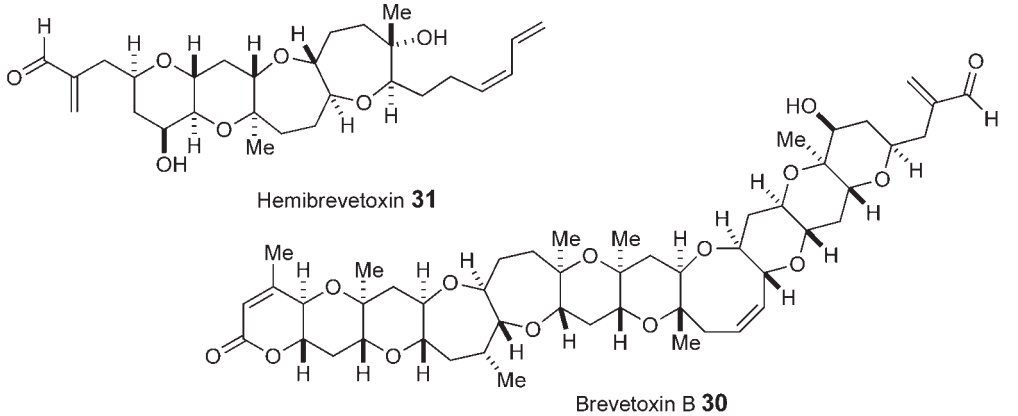


Scheme 69

Candida antarctica lipase B has been employed to resolve kinetically a series of bicyclic 1-heteroaryl primary amines by enantioselective acetylation <2003JOC3546>.

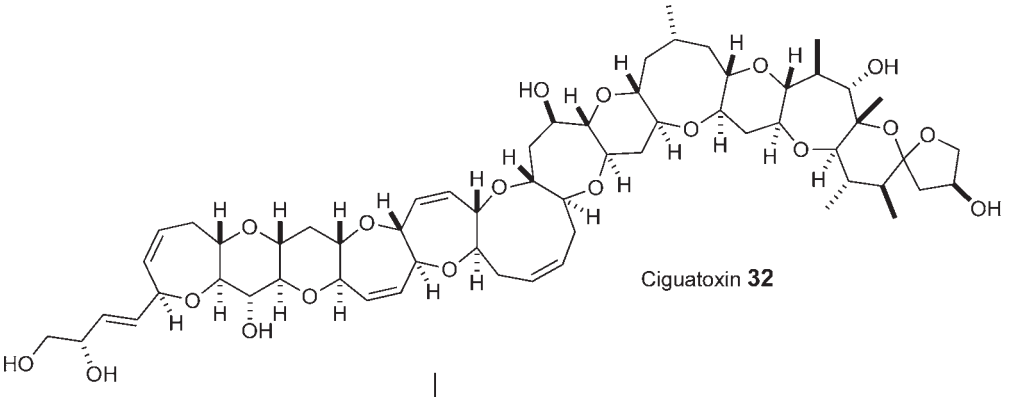
10.15.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

Interest in the total synthesis of polycyclic ether natural products has increased rapidly over the period of review and it is impossible to do justice here to this vast amount of work. Instead, the reader is directed to an excellent review <2005CRV4314>. Highlights worthy of note, but certainly not an exhaustive list, include: brevetoxin **30** – total synthesis <1995JA10252, 1997JSO686, 1998NAT264, 1999CEJ646, 2004JA14374, 2005JA9246>, synthesis by metathesis/hydroboration <1997TL123, 1999T8231>, synthesis and biological studies <2002T1921>; hemibrevetoxin **31** – AB-ring by *endo*-selective alkynol cycloisomerization <1997JOC6432>, formal synthesis by an oxiranyl anion strategy <1998JOC6200>, and total synthesis <1995JSO284, 1995TL5777, 1996MGM361, 1996TL6365, 1998JOC6597, 1998JSO940, 2001JOC1380, 2003JA7822>; ciguatoxin **32** <1997CC1289, 1998T21, 2001SCI1904, 2003JSO562, 2004ACR961, 2004PNA12013, 2004SL577, 2005MI240, 2006JA9352>; prymnesins <2001TL5725>; synthesis of the *trans*-dioxadecalin subunit <1997TL2899> and the total synthesis of okadaic acid **33** <1997JA8381, 1998J(P1)3907, 1999AGE2258>; isolation and determination of stereochemistry of maitotoxin <1995TL9011, 1996JA7946> and efforts toward its total synthesis <1996JA10335>; and tetrodotoxin <2003JA8798>.

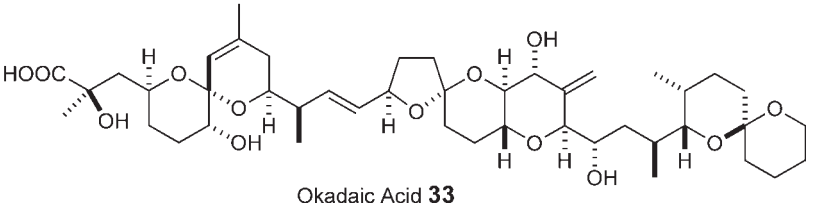


Hemibrevetoxin **31**

Brevetoxin B **30**



Ciguatoxin **32**



Okadaic Acid **33**

It is also worthwhile now summarizing some of the excellent methodology that has been developed over the last decade toward preparing parts of these complex ring structures, some of which has already been touched upon elsewhere in this chapter.

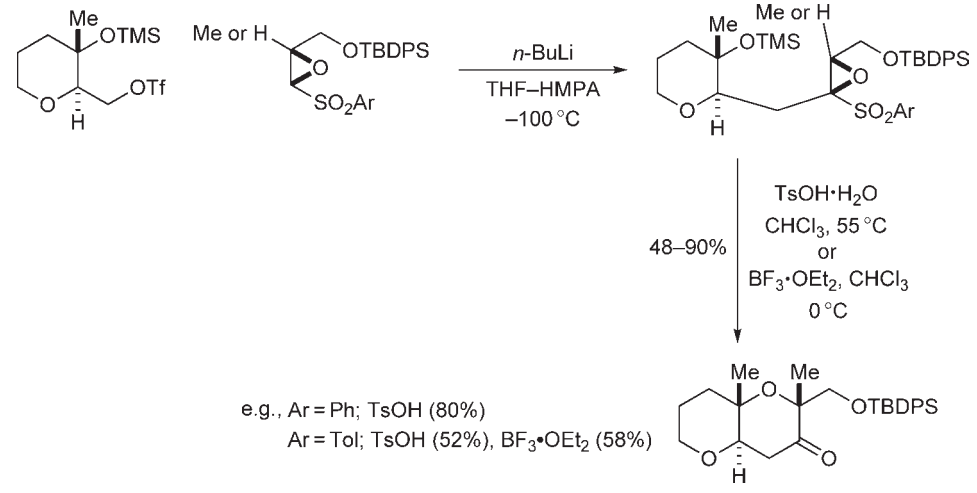
There are reports of many iterative cyclization strategies for the synthesis of fused polycyclic ethers related to marine natural products, for example, an SmI_2-induced reductive cyclization <1999TL2811, 2002T1853>; cyclic

enol ether epoxidation followed by ring opening and cyclization (metathesis) to a new cyclic enol ether <1998JOC5310>; rhodium carbenoid insertion <2002T2027>; endocyclization of 1-alkyn-5-ols in the presence of tungsten pentacarbonyl–THF complex <1998JOC3680>; palladium-catalyzed couplings of ketene acetal triflates and organozinc reagents <2002JOC3494>; and an electron-transfer-initiated heterogenerative cascade under non-acidic conditions <2002OL2489>.

The dicobalt octacarbonyl-promoted Nicholas reaction has been used in the preparation of polycyclic ethers related to the marine polyethers ciguatoxin **32** and gambiertoxin <1999JOC37>.

2-Alkoxy-3-oxoalkyl-tetrahydropyrans and -tetrahydrofurans have become useful synthetic intermediates in the synthesis of many oxa- and aza-annelation products <1995J(P1)2103>.

A stereocontrolled synthesis of methyl-substituted *trans*-fused tetrahydropyrans, with the methyl groups being adjacent to the ring oxygen atoms, has been described by Mori, using a coupling reaction of a sulfonyl-stabilized oxiranyl anion with triflates and the subsequent 6-*endo*-cyclisation of the product (**Scheme 70**) <1999TL8019, 2003T8767>.



Scheme 70

The use of epoxides as cyclization precursors has also featured in synthesis of fused cyclic polyethers in work by Markó *et al.* <1997TL2899>, Murai and co-workers (AgOTf-promoted epoxide cascades <1996TL6173> and a more biomimetic approach employing an epoxide cascade <1997T12425>), Floreancig and co-workers <2002OL2489>, and Rainier and co-workers (synthesis of C-glycosides from epoxides, followed by ring-closing metathesis and acid-mediated annelation reactions <2002T1997>).

As in most areas of synthesis, ring-closing metathesis has also featured prominently in synthetic sequences toward *cis*- and *trans*-fused pyranopyrans and other related heterocycles <1997SL1263, 1999T8253, 2002T1997, 2002TL7095>. Nicolaou has reported the development of *cis*-3,4-dichlorocyclobutene as a novel synthon for metathesis reactions, including the preparation of complex polycyclic systems with high stereospecificity <2001AGE4441>.

The use of various heteroatom-directed cyclization methods has also been a recurring theme, including the use of boron- <1995TL1431>, silicon- <1997T12425, 1999TL8019>, sulfur- <1996TL2865, 1998TL8325, 2003T9767>, and tin-based methods (radical cyclizations: <1999J(P1)3395, 2005T8589>). Diisobutylaluminium hydride (DIBAL-H) has also, surprisingly, been used as a mechanistic probe to look at spiroketal rearrangement <2004TL8165>.

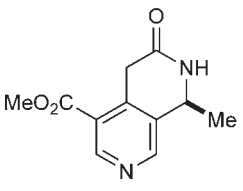
Other miscellaneous methods have included spiroketal rearrangements <2000JOC8822, 2004TL8165>, intramolecular hetero-Michael additions <1997JOC4570>, ring expansion and subsequent cyclization of furan derivatives <2003TL8227>, and cyclization of esters or enol ethers <1998T13557, 2005T8177>.

10.15.12 Important Compounds and Applications

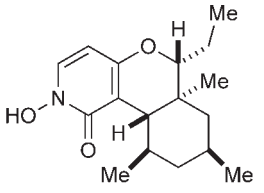
There have been many reports of novel natural products being isolated containing fused rings of the types discussed in this chapter. For example a range of glucosides, such as clitoriacetal 11-*O*-β-D-glucopyranoside <1998P121>, dalcochinin-8'-*O*-β-D-glucoside <1999P739>; rotenoids, isoflavones, and chalcones from *Millettia usaramensis*

<1998P295>, *Derris malaccensis* <2001H(55)1121>, and cube resin <1997JOC350>; fused aromatic compounds meshimakobnol A and B from *Phellinus linteus* <2004TL5931>; (−)-neuchromenin (2,3-dihydro-8,9-dihydroxy-2-methyl-4*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-4-one) from *Eupenicillium javanicum* var. *meloforme* <2001EJO1963>; and trichodion (a bis-pyrone) from *Trichosporiella* species <2000JAN1401>.

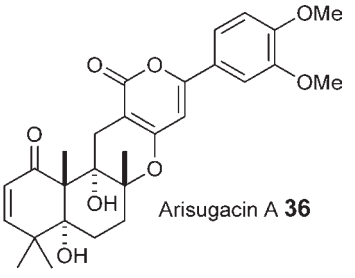
The first (or novel) total synthesis of the following compounds has been reported: jasminine **34** <2004T6785>; the cytotoxic *N*-hydroxypyridone natural product (±)-fusaricide **35** <2001SC2667>; tetrodotoxin <2003JA8798>; (±)-deoxypenostatin A <2000JOC8490>; (20*S*)-camptothecin <1998CEJ67>; irinotecan <1997JOC6588>; (±)-arisugacin **36** <2002OL367, 2002TL3341, 2002TL8791, 2003T311>; (±)-matrine <1998AGE1128> and neozeylanicine **37** <1995LA645>; rotenoids <1998TL881> and ^{3}H- <1996JLR215>, ^{11}C- <1999JLR641> and ^{18}F- <1999JLR1039> labeled rotenoids (for use as a positron emission tomography (PET) probe of mitochondrial complex 1 activity).



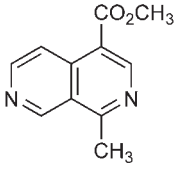
Jasminine **34**



Fusaricide **35**

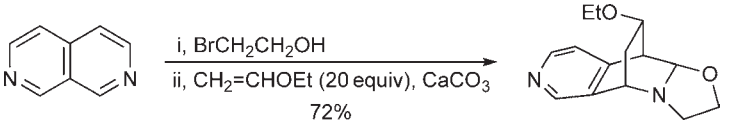


Arisugacin A **36**



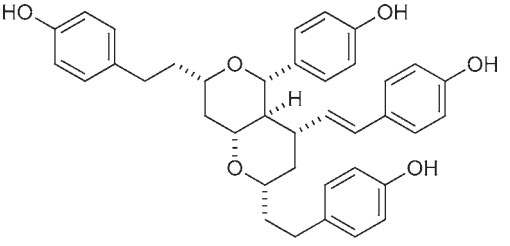
Neozeylanicine **37**

Langlois and co-workers have developed a Bradsher cycloaddition route, involving a [2,7]naphthyridinium salt toward the tricyclic core of manzamine A (**Scheme 71**) <1995TL9475, 1998TL837, 2000TL9251>.



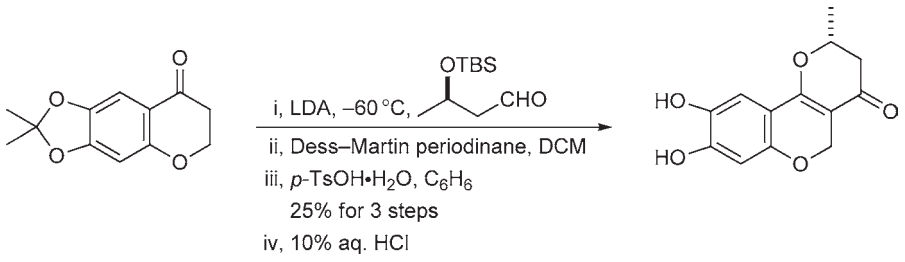
Scheme 71

Synthetic effort is going on toward the unique diarylheptanoid blepharocalyxin D, **38**, which has shown considerable *in vitro* antiproliferative activity against human fibrosarcoma HT-1080 cells, although this postulated structure for blepharocalyxin D is yet to be confirmed by synthesis <2003TL6351>.



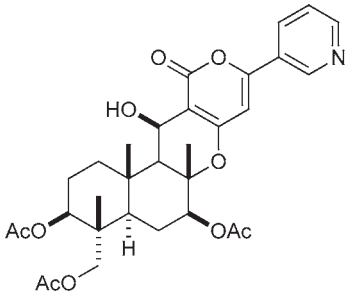
38

A concise synthesis and determination of absolute configuration of (−)-neuchromenin, a neurotrophic metabolite of *E. javanicum* var. *meloforme*, has been described (**Scheme 72**) <2001EJO1963>.



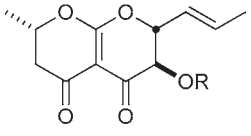
Scheme 72

Many of the heterocyclic systems discussed have found use in medicinal chemistry discovery programs. Highlights among O-containing systems include: various syntheses of radicinin and its analogues <1995T8983>; structure–activity relationships (SARs) of pyripyropenes <1995JAN749, 1996JAN1133, 1997JAN229> and analogues of pyripyropene A, **39**, and (±)-GERI-BP001 as acyl-CoA:cholesterol acyltransferase inhibitors <1995JOC5726, 1995JOC8126, 1997CL935, 2000BML1315>; N,N-disubstituted 1-amino-2-phenyl-3*H*,12*H*-naphtho[1,2-*b*]pyrano[2,3-*d*]pyran-3-ones, which have demonstrated anti-arrhythmic and analgesic properties <1996FA665>; homopterocarpane derivatives with antitumor and anti-AIDS activity (AIDS = acquired immune deficiency syndrome) <1997FA13>; tricyclic pyrones with an appended adenine moiety as compounds that ameliorate the toxicity of amyloid-β peptides <2003T4795>; azacoumarins <1998JME2436>, pyranocoumarins, and coumarinopyranopyrimidines <2000JCM26>, and the synthesis and biological activity of pyrano[3,2-*c*]coumarins <1996PHA148>; polysubstituted 2(1*H*)-quinolinone and coumarin derivatives <1995BCJ905>; asymmetric hetero-Diels–Alder approach to coumarin anticoagulants <2001TA707>; homopterocarpane derivatives (6a,12a-dihydro-6*H*,7*H*-[1]-benzopyran-[4,3-*b*]-benzopyran derivatives), which are active on the human breast cancer cell line MCF-7 <2005FA135>; and the isolation of a bis-pyrone, trichodion, **40**, from *Trichosporiella* species, which inhibits interferon gamma (IFN-γ)-mediated expression of the reported gene secreted alkaline phosphatase and the expression of a human tumor necrosis factor alpha (TNF-α) promoter-driven luciferase reported gene <2000JAN1401>.



(+)-Pyripyropene A

39

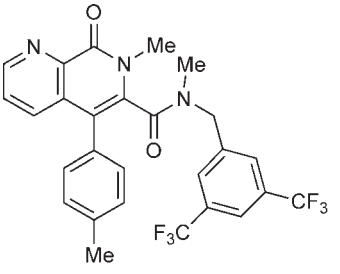


Trichodion

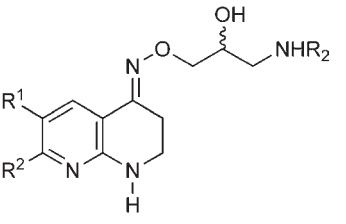
40

Highlights from N-containing heterocycles include: tricyclic fused (hetero)aryl and (hetero)cyclic dihydropyridines (and in particular sulfonyl-containing) as K_{ATP} openers that inhibit bladder contractions *in vitro* <2004JME3163, 2004JME3180>; many different (fused) bicyclic azacompounds as acetylcholinesterase inhibitors <2000JHC799>; a series of 5-, 6-, 7-, and 8-aza analogues of 3-aryl-4-hydroxyquinolin-2(1*H*)-one as *N*-methyl-D-aspartate (NMDA)/glycine receptor antagonists, the most successful of which, 5-aza-7-chloro-4-hydroxy-3-(3-phenoxyphenyl)quninolin-2-(1*H*)-one, was also an anticonvulsant <2001BMC2061>; [1,5]naphthyridine derivatives as potent and selective transforming growth factor beta (TGF-β)-type I receptor inhibitors <2004JME4494> and 1,3-biarylureas incorporating a [1,5]naphthyridine, found to be selective nonpeptide antagonists of the orexin-1 receptor <2001BML1907>; 5,6,7,8-tetrahydro[1,6]naphthyridines <2004JME5167>; 8,8-dimethyl[1,6]naphthyridines <2003BML1627>; 1,6-naphthyridines <1999BML2583, 1999JME3023, 2001BML103> and macrocycles derived from and containing [1,6]naphthyridines <2005BML1693> as anti-human cytomegalovirus inhibitors; 3-aryl[1,6]naphthyridine-2,7-diamines and related 2-ureas as inhibitors of fibroblast growth factor (FGF) receptor-1 tyrosine kinase <2000JME4200> and vascular endothelial growth factor receptor-2 tyrosine kinases <2005JME4628>; an SAR study, performed on novel [1,6]naphthyridines and naphthyridinones as potent inhibitors of spleen tyrosine kinase (SYK)

<2003BML1415>; the introduction of substituted 5,6-dihydrouracil functions to the 5-position of *N*-(4-fluorobenzyl)-8-hydroxy[1,6]naphthyridine-7-carboxamide, leading to a series of highly active human immunodeficiency virus 1 (HIV-1) integrase inhibitors <2005BML4550>; conversion of 3-bromo[1,6]naphthyridin-2(1*H*)-ones into thiazolo[4,5-*b*][1,6]naphthyridin-2(1*H*)-ones, giving a ninefold increase in cyclic adenosine monophosphate (cAMP) phosphodiesterase III inhibition <1995JME2546>; the rapid synthesis of [1,6]- and [1,7]-naphthyridines aimed toward β_3 adrenergic receptor agonists (useful in the treatment of obesity) <2000TL8053>; [1,7]- and [2,7]-naphthyridines as potent and highly specific PDE5 inhibitors <2003BML2341>; [1,7]-naphthyridines, found to be potent and selective phosphodiesterase-type 4D inhibitors <2002BML233> and [1,7]- and [1,8]-naphthyridine-3-carbonitriles, which inhibit the kinase activity of epidermal growth factor receptor (EGFR) <2004BML1411>; 5,6,7,8-tetrahydro[1,8]naphthyridines <2003JME4790>; 5,6,7,8-tetrahydro[1,8]naphthyridine derivatives, which have formed the basis of a major body of synthetic and biological work (11 published parts at the time of writing) as nonpeptide $\alpha_v\beta_3$ antagonists <2000JME3736, 2002BML25, 2004JME4829>; 5-substituted indol-1-ylpropionic acids, substituted at the C-5 with 5,6,7,8-tetrahydro[1,8]naphthyridine derivatives <2005BML2679>, and the related piperidine derivatives (in place of the indole moiety) <2004BML5227>, and 5,6,7,8-tetrahydro[1,8]naphthyridine phenylbutyrate derivatives <2003BML1483>, all used as nonpeptidic $\alpha_v\beta_3$ antagonists; indole naphthyridinones also used as inhibitors of the bacterial enoyl-ACP (acyl carrier protein) reductases FabI and FabK <2003JME1627>; pyrano(thiopyrano)[3,4-*c*]pyridine and [2,7]naphthyridine derivatives, reported as anticonvulsants <2002PCJ465>; axially chiral [1,7]naphthyridine-6-carboxamides, developed as orally active tachykinin NK1 receptor antagonists <1998JME4232, 1999JME3982>; a series of 6*H*-[1,6]naphthyridin-5-ones <1998BML2635> and [1,8]naphthyridin-2(1*H*-one) derivatives <2002CPB1050> as PDE4 inhibitors; (*R*)- or (*S*)-(*E*)-oxime ethers of 2,3-dihydro[1,8]naphthyridine, **42**, as antihypertensive agents <2000EJM815>; aza-thiopyranoindazoles <2000BML305>; compounds with a piperazine unit fused to a [1,8]naphthyridine, shown to be novel antiprotozoals, being active against *Philasterides dicentrarchi*, the causative agent of scuticociliatosis in farmed turbot and Black Sea bass/bream <2003EJM265>, and keeping the piperazine theme, 2-piperazinyl[1,8]naphthyridine <1998EJM383> and 4-piperazinyl[1,8]naphthyridine <1999EJM505> derivatives are potential anti-hypertensive agents, as are (*E*)- and (*Z*)-4(1*H*)-[1-(3-alkylamino-2-hydroxypropyl)oximino]-2,3-dihydro[1,8]naphthyridines <1997EJM955>; 2-phenyl[1,8]naphthyridines with C-4 and C-7 substituents as potent antagonists for the A1 adenosine receptor subtype <2000JME2814>; the synthesis and antibacterial properties of a library of [1,8]naphthyridinyl-4-thiazolidinones <2001IJB336> and 1′,2′,4′-triazolyl/1′,3′,4′-thiadiazolyl/1′,3′,4′-oxadiazolyl[1,8]naphthyridines <1996IJB339>; the synthesis and diuretic properties of a range of fused heterocycles, focusing on tetrahydro [1,8]naphthyridines <2000EJM227>; 4-phenyl[1,8]naphthyridines and their tetrahydro analogues as antimycobacterial agents <1998FA741>; a range of 2,4,6-heterocycle-substituted triazines as antimalarial agents <2005BML531>; 11*H*-indolo[3,2-*c*][1,8]naphthyridines as potential antitumor agents <2002EJM475>; the affinity profile of [1,8]naphthyridine derivatives toward native human and bovine adenosine receptors <2004JME3019>; complex N-substituted 5-amino-*N*,*N*-diethyl-9-isopropyl [1,2,4]triazolo[4,3-*a*]-[1,8]naphthyridine-6-carboxamides as potent anti-inflammatory and/or analgesic agents which are devoid of acute gastrolesivity <2005EJM155>; (*R*,*S*)-(*E*)-oxime ethers of 2,3-dihydro[1,8]naphthyridine and 2,3-dihydrothiopyrano-[2,3-*b*]-pyridine as β_3-antagonists <2003BML4921>; [1,8]naphthyridin-4-ones derivatives as A_{2A} adenosine receptor ligands <2005BCML4604>; [1,8]naphthyridin-4(1*H*)-one-3-carboxamide derivatives as cannabinoid receptor ligands <2004BML1921>; novel 3-heterocycle-fused thiopyranylthiovinyl cephalosporins which showed antibacterial activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* <2000JAN551>.



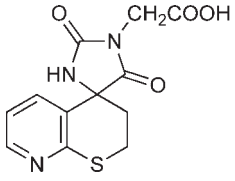
41



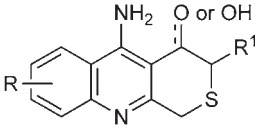
42

A variety of 5,6,7,8-tetrahydronaphthylidine (and 5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine) derivatives have been prepared and reported as HB-EGF shedding inhibitors – effective against a variety of human skin diseases <2003BMC433>.

Spirohydantoin derivatives of thiopyran[2,3-*b*]pyridin-4(4*H*)-one, **43**, have been reported to be potent *in vitro* and *in vivo* aldose reductase inhibitors <2005BMC491>. A series of thia-velnacrine analogues have been prepared as potential agents for treating Alzheimer's disease <2001BMC2921>. Thiolactone pyridines have been prepared as potential A3 adenosine receptor antagonists <1999JME706>. Aza-thioxanthones have been shown to exhibit significant cytotoxicity in the leukemic MOLT-4 line and pronounced activity in the non-small lung cancer cell line HOP-92. The compounds were prepared from 2-aminopyridine via an Ullmann condensation and Friedel–Crafts ring closure <1996BML861, 1996BML865>.

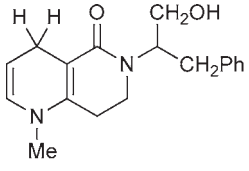


43

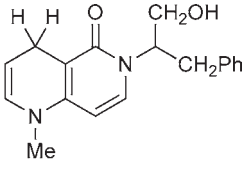


44

A range of heterocycles, including **45** and **46**, have been developed as chiral NADH models <2001T9101>. Similarly, a number of unnatural DNA base pairs have been prepared and their hydrogen-bonding ability and polymerase recognition investigated <2002AGE3841>.

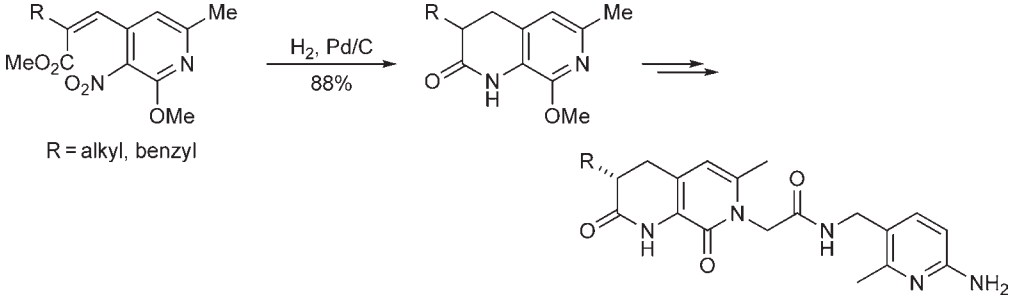


45



46

Bicyclic pyridones have been prepared (**Scheme 73**) and found to be potent orally bioavailable thrombin inhibitors <2000BML1069>.

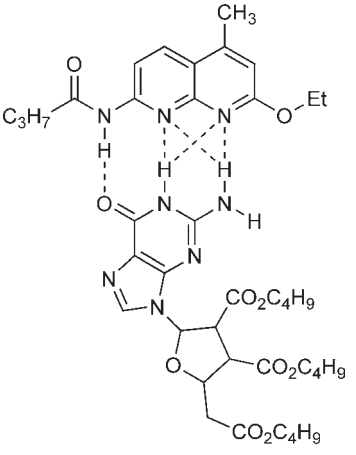


Scheme 73

The synthesis and preliminary biological activity of substituted 7-alkylseleno-1,4-dihydro[1,6]naphthyridines have been reported <2000DOC218> along with their further synthetic transformations <2001RCB122>. There have also been reports of the preparation of selenium-containing fused heterocycles. The C═O function in benzothiophen-3-ones, 3,4-dihydrothiopyrano[3,2-*b*]benzothiophen-4(2*H*)-ones, and 3,4-dihydro-2*H*,5*H*-thiopyrano[2′,3′:4,5]thiopyrano[3,2-*b*]benzothiophen-4-ones reacts with selenium dioxide and thionyl chloride to give fused 1,2,3-selena and thiadiazoles via their semicarbazones <1999IJB308>.

There have been a number of examples of the heterocycles discussed being employed as multidentate ligands, for example, based on the [1,8]naphthyridine system (<2000T8245> (general multidentate dinucleating ligands), <1997JCD4561> (ruthenium complexes) and <1995JPR451> (benzo-condensed crown ethers containing [1,8]naphthyridine units and their complexation with organic guest molecules)); [1,8]naphthyridine-2,7-dicarboxaldehyde and their 2,7-dimethimine derivatives <2002JHC829>; chiral 2,7-bis(dihydrooxazolyl)-[1,8]naphthyridines <1998HCA491>;

[2,7]naphthyridine <2003CC336>; and chiral 1,5-diaza-*cis*-decalins <2000OL875>. [1,8]Naphthyridines have been employed as a hydrogen-bonding unit at the core of self-assembling dendrimers using the DDA-AAD hydrogen-bonding motif <2002JA13757>, and related dendrimers have been shown to control their aggregation <1998JA2172>. It has been observed that the hydrogen-bonded complex between guanosine and a 7-amido-2-alkoxy[1,8]naphthyridine, containing the DAA-ADD motif, is of low stability due to a conformational steric effect <1995TL7627>. [1,8]Naphthyridines have also been utilized in the preparation of a novel quadruply bound heterodimer DDAD-AADA and used to investigate the association process <2002EJO4054>. [1,8]Naphthyridines have been found in the center of a quadruple hydrogen-bonding unit in supramolecule copolymer, **47** <2005JA810>. [1,8]Naphthyridin-2,7-(1,8*H*)-dione is an effective mimic of protonated cytosine in peptide nucleic acid triplex recognition systems <2002BML3121>. The synthesis of two novel peptide nucleic acids (PNAs) based on [1,8]naphthyridin-2(1*H*)-one and benzo[b][1,8]naphthyridin-2(1*H*)-one has been reported, along with their incorporation into oligomers of PNA and evaluation as substitutes for thymine, with the former compound being the more effective mimic <2001EJO1781>.



47

References

1984CHEC(2)581 P. A. Lowe; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 581.

1995AGE2589 J. Tsuji and T. Mandai, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2589.

1995BCJ905 F. M. A. A. El-Taweel, S. Z. A. Sowellim, and A. G. A. Elagamey, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 905.

1995H(41)1001 J. M. Quintela, J. Vilar, C. Peinador, C. Veiga, and V. Ojea, *Heterocycles*, 1995, **41**, 1001.

1995H(41)1013 P. Victory, N. Busquets, J. I. Borrell, J. Teixidó, B. Serra, J. L. Matallana, H. Junek, and H. Sterk, *Heterocycles*, 1995, **41**, 1013.

1995JA9139 M. Lögers, L. E. Overman, and G. S. Welmaker, *J. Am. Chem. Soc.*, 1995, **117**, 9139.

1995JA10252 K. C. Nicolaou, F. P. J. T. Rutjes, E. A. Theodorakis, J. Tiebes, M. Sato, and E. Untersteller, *J. Am. Chem. Soc.*, 1995, **117**, 10252.

1995JAN749 R. Obata, T. Sunazuka, Z. Li, H. Tomoda, and S. Ōmura, *J. Antiobiot.*, 1995, **48**, 749.

1995JFC167 S. Zhu, B. Xu, and J. Zhang, *J. Fluorine Chem.*, 1995, **74**, 167.

1995JHC1595 M. W. Read and P. S. Ray, *J. Heterocycl. Chem.*, 1995, **32**, 1595.

1995JME2546 B. Singh, E. R. Bacon, G. Lesher, S. Robinson, P. O. Pennock, D. C. Bode, E. D. Pagani, R. G. Bentley, M. J. Connell, L. T. Hamel, and P. J. Silver, *J. Med. Chem.*, 1995, **38**, 2546.

1995JOC3236 S. F. Martin, C. W. Clark, and J. W. Corbett, *J. Org. Chem.*, 1995, **60**, 3236.

1995JOC5726 K. A. Parker and L. Resnick, *J. Org. Chem.*, 1995, **60**, 5726.

1995JOC5748 D. A. Goff and R. N. Zuckermann, *J. Org. Chem.*, 1995, **60**, 5748.

1995JOC8126 T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y. Harigaya, and S. Ōmura, *J. Org. Chem.*, 1995, **60**, 8126.

1995J(P1)2103 P. Duhamel, A. Deyine, G. Dujardin, G. Plé, and J.-M. Poirier, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2103.

1995J(P1)2293 T. W. Wallace, I. Wardell, K.-D. Li, P. Leeming, A. D. Redhouse, and S. R. Challand, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2293.

1995J(P1)2643 A. Couture, P. Grandclaudon, C. Simion, and P. Woisel, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2643.

1995JPR451 E. Weber and H.-J. Köhler, *J. Prakt. Chem.*, 1995, **337**, 451.

1995JSO284 F. Sato, *J. Synth. Org. Chem. Jpn.*, 1995, **53**, 284.

1995LA645 F. Bracher and K. Mink, *Liebigs Ann. Chem.*, 1995, 645.

1995T8383 D. A. L. Vandenput and H. W. Scheeren, *Tetrahedron*, 1995, **51**, 8383.

1995T8983 M. Eh, D. Schomburg, K. Schicht, and M. Kalesse, *Tetrahedron*, 1995, **51**, 8983.

1995TL1431 R. W. Hoffmann and I. Münster, *Tetrahedron Lett.*, 1995, **36**, 1431.

1995TL5777 I. Kadota, P. Jungyoul, N. Koumura, G. Pollaud, Y. Matsukawa, and Y. Yamamoto, *Tetrahedron Lett.*, 1995, **36**, 5777.
1995TL7627 T. J. Murray and S. C. Zimmerman, *Tetrahedron Lett.*, 1995, **36**, 7627.
1995TL9011 M. Sasaki, N. Matsumori, M. Murata, K. Tachibana, and T. Yasumoto, *Tetrahedron Lett.*, 1995, **36**, 9011.
1995TL9475 E. Magnier, Y. Langlois, and C. Mérienne, *Tetrahedron Lett.*, 1995, **36**, 9475.
1996BML861 A. Varvaresou, A. Tsotinis, A. Papadaki-Valiraki, and T. Siatra-Papastaikoudi, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 861.
1996BML865 A. Varvaresou, A. Tsotinis, T. Siatra-Papastaikoudi, A. Papadaki-Valiraki, D. E. Thurston, T. C. Jenkins, and L. R. Kelland, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 865.
1996CC811 T. Saito, H. Kensuke, K. Sakamaki, T. Karakasa, and S. Moriyama, *J. Chem. Soc., Chem. Commun.*, 1996, 811.
1996CHEC-II(7)527 S. P. Stanforth; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriuen, Eds.; Pergamon, Oxford, ch. 7.15, p. 527.
1996H(43)53 J. M. Quintela, R. M. Arcas, C. Veiga, C. Peinador, J. Vilar, and V. Ojea, *Heterocycles*, 1996, **43**, 53.
1996IJB339 G. Rama Rao, K. Mogilaiah, and B. Sreenivasulu, *Indian J. Chem., Sect. B*, 2001, **35**, 339.
1996JA7946 W. Zheng, J. A. DeMattei, J.-P. Wu, J. J.-W. Duan, L. R. Cook, H. Oinuma, and Y. Kishi, *J. Am. Chem. Soc.*, 1996, **118**, 7946.
1996JA10335 K. C. Nicolaou, M. H. D. Postema, E. W. Yue, and A. Nadin, *J. Am. Chem. Soc.*, 1996, **118**, 10335.
1996JAN1133 R. Obata, T. Sunazuka, Z. Li, Z. Tian, Y. Harigaya, N. Tabata, H. Tomoda, and S. Ōmura, *J. Antibiot.*, 1996, **49**, 1133.
1996JHC361 M. Blanco, G. Lorenzo, I. Perillo, and C. B. Schapira, *J. Heterocycl. Chem.*, 1996, **33**, 361.
1996JHC1303 S. Strah, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem.*, 1996, **33**, 1303.
1996JHC1185 P. L. Ferrarini, C. Mori, and S. Belfiore, *J. Heterocycl. Chem.*, 1996, **33**, 1185.
1996JHC1041 M. Kušar, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem.*, 1996, **33**, 1041.
1996JLR215 J. P. O'Neil, H. F. VanBrocklin, H. Morimoto, and P. G. Williams, *J. Labelled Compd. Radiopharm.*, 1996, **39**, 215.
1996J(P1)1359 E. M. Beccalli, E. Erba, M. L. Gelmi, and D. Pocar, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1359.
1996J(P1)2715 L. Crombie, D. E. Games, and A. W. G. James, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2715.
1996M391 H. Bock, T. T. H. Van, and H. Schödel, *Monatsh. Chem.*, 1996, **127**, 391.
1996MGM361 I. Kadota and Y. Yamamoto, *Main Group Met. Chem.*, 1996, **19**, 361.
1996FA665 M. Longobardi, A. Bargagna, E. Mariani, W. Filippelli, G. Falcone, and I. Marabese, *Farmaco*, 1996, **51**, 665.
1996EJM875 M. Dukat, W. Fiedler, D. Dumas, and B. R. Martin, *Eur. J. Med. Chem.*, 1996, **31**, 875.
1996PHA148 R. M. Shaker, *Pharmazie*, 1996, **51**, 148.
1996T955 F. Linkert, S. Laschat, S. Kotila, and T. Fox, *Tetrahedron*, 1996, **52**, 955.
1996T4433 A. Couture, E. Deniau, P. Grandclaudon, and P. Woisel, *Tetrahedron*, 1996, **52**, 4433.
1996T6125 H. Senboku, M. Takashima, M. Suzuki, K. Kobayashi, and H. Suginome, *Tetrahedron*, 1996, **52**, 6125.
1996T9161 K. J. Buysens, D. M. Vandenberghe, and G. J. Hoornaert, *Tetrahedron*, 1996, **52**, 9161.
1996TL2619 J. M. Mellor and H. Rataj, *Tetrahedron Lett.*, 1996, **37**, 2619.
1996TL2865 E. Alvarez, M. Delgado, M. T. Diaz, L. Hanxing, R. Pérez, and J. D. Martin, *Tetrahedron Lett.*, 1996, **37**, 2865.
1996TL6173 N. Hayashi, K. Fujiwara, and A. Murai, *Tetrahedron Lett.*, 1996, **37**, 6173.
1996TL6365 M. Morimoto, H. Matsukura, and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6365.
1996TL8871 M. Adachi, T. Sasatani, N. Chomei, and S. Takada, *Tetrahedron Lett.*, 1996, **37**, 8871.
1997CC1289 T. Oishi, K. Maeda, and M. Hirama, *J. Chem. Soc., Chem. Commun.*, 1997, 1289.
1997CC1495 B. Wang and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1997, 1495.
1997CHE39 A. A. Avetisyan, I. L. Aleksanyan, and A. G. Alvandzhyan, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 39.
1997CHE741 V. Dabaeva, A. S. Noravyan, V. N. Madakyan, and B. D. Enokyan, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 741.
1997CL935 R. Obata, T. Sunazuka, Z. Tian, H. Tomoda, Y. Harigaya, S. Ōmura, and A. B. Smith, III, *Chem. Lett.*, 1997, 935.
1997EJM955 P. L. Ferrarini, C. Mori, M. Badawneh, C. Manera, G. Saccomanni, V. Calderone, R. Scatizzi, and P. L. Barili, *Eur. J. Med. Chem.*, 1997, **32**, 955.
1997FA13 P. Valenti, G. Fabbri, A. Rampa, A. Bisi, and F. Belluti, *Farmaco*, 1997, **52**, 13.
1997H(45)1715 G. Brufola, F. Fringuelli, O. Piermatti, and F. Pizzo, *Heterocycles*, 1997, **45**, 1715.
1997JA8381 C. J. Forsyth, S. F. Sabes, and R. A. Urbanek, *J. Am. Chem. Soc.*, 1997, **119**, 8381.
1997JAN229 R. Obata, T. Sunazuka, Z. Tian, H. Tomoda, Y. Harigaya, and S. Ōmura, *J. Antiobiot.*, 1997, **50**, 229.
1997JCD4561 A. E. M. Boelrijk, T. X. Neenan, and J. Reedijk, *J. Chem. Soc., Dalton Trans.*, 1997, 4561.
1997JHC397 A. Nemazany and N. Haider, *J. Heterocycl. Chem.*, 1997, **34**, 397.
1997JOC350 N. Fang and J. E. Casida, *J. Org. Chem.*, 1997, **62**, 350.
1997JOC4570 J. M. Betancort, V. S. Martín, J. M. Padrón, J. M. Palazón, M. A. Ramírez, and M. A. Soler, *J. Org. Chem.*, 1997, **62**, 4570.
1997JOC6432 M. M. Gleason and F. E. McDonald, *J. Org. Chem.*, 1997, **62**, 6432.
1997JOC6588 K. E. Henegar, S. W. Ashfrod, T. A. Baughman, J. C. Sih, and R.-L. Gu, *J. Org. Chem.*, 1997, **62**, 6588.
1997JOC6888 D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freeman, J.-P. Perchellet, and P. K. Chiang, *J. Org. Chem.*, 1997, **62**, 6888.
1997J(P1)1487 V. Delieza, A. Detsi, V. Bardakos, and O. Igglessi-Markopoulou, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1487.
1997JSO686 M. Sato, *J. Synth. Org. Chem. Jpn.*, 1997, **55**, 686.
1997LA1019 K. Peseke, G. Thiele, M. Michalik, and D. R. Powell, *Liebigs Ann. Chem.*, 1997, 1019.
1997LA1143 R. W. Hoffmann and I. Münster, *Liebigs Ann. Chem.*, 1997, 1143.
1997M1157 K. Bogdanowicz-Szwed and A. Pałasz, *Monatsh. Chem.*, 1997, **128**, 1157.
1997PCJ540 E. G. Paronikyan, G. V. Mirzoyan, A. S. Noravyan, E. M. Arzanunts, R. S. Sukasyan, I. S. Sarkisyan, I. M. Nazaryan, and I. A. Ozhagatspanyan, *Pharm. Chem. J.*, 1997, **31**, 540.
1997PJC83 A. Rykowski and T. Lipinska, *Pol. J. Chem.*, 1997, **71**, 83.
1997RCB1041 V. A. Dorokhov, A. Y. Yagodkin, V. S. Bogdanov, and S. V. Baranin, *Russ. Chem. Bull.*, 1997, **46**, 1041.
1997SL1263 M. A. Leeuwenburgh, H. S. Overkleeft, G. A. van der Marel, and J. H. van Boom, *Synlett*, 1997, 1263.
1997T12425 N. Hayashi, K. Fujiwara, and A. Murai, *Tetrahedron*, 1997, **53**, 12425.
1997TL123 J. S. Clark and J. G. Kettle, *Tetrahedron Lett.*, 1997, **38**, 123.
1997TL849 H. Shimizu, Y. Shimada, A. Tomita, and O. Mitsunobu, *Tetrahedron Lett.*, 1997, **38**, 849.
1997TL2899 I. E. Markó, A. P. Dobbs, V. Scheirmann, F. Chellé, and D. J. Bayston, *Tetrahedron Lett.*, 1997, **38**, 2899.

1997TL4913 Z. Wróbel, *Tetrahedron Lett.*, 1997, **38**, 4913.
1997TL7499 C. E. Neipp, P. B. Ranslow, Z. Wan, and J. K. Snyder, *Tetrahedron Lett.*, 1997, **38**, 7499.
1998AGE1128 L. Boiteau, J. Boivin, A. Liard, B. Quiclet-Sire, and S. Z. Zard, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 1128.
1998AGE3136 J. Barluenga, G. P. Romanelli, L. J. Alvarez-García, I. Llorente, J. M. González, E. García-Rodríguez, and S. García-Granda, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3136.
1998BML2173 J.-M. Vernier, H. Holsenback, N. D. P. Cosford, J. P. Whitten, F. Menzaghi, R. Reid, T. S. Rao, A. I. Scaan, G. K. Lloyd, C. M. Suto, L. E. Chavez-Noriega, M. S. Washburn, A. Urrutia, and I. A. McDonald, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2173.
1998BML2635 J. G. Montana, G. M. Buckley, N. Cooper, H. J. Dyke, L. Gowers, J. P. Gregory, P. G. Hellwell, H. J. Kendall, C. Lowe, R. Maxey, J. Miotla, R. J. Naylor, K. A. Runcie, B. Tuladhar, and J. B. H. Warneck, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2635.
1998BML2881 A. Monsees, S. Laschat, M. Hotfilder, and P. G. Jones, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2881.
1998CAR215 T. Hofmann, *Carbohydr. Res.*, 1998, **313**, 215.
1998CC491 D. Brousmiche and P. Wan, *J. Chem. Soc., Chem. Commun.*, 1998, 491.
1998CEJ67 H. Josien, S.-B. Ko, D. Bom, and D. P. Curran, *Chem. Eur. J.*, 1998, **4**, 67.
1998EJM383 P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, L. Calzolari, T. Loffredo, E. Martinotti, and G. Saccomanni, *Eur. J. Med. Chem.*, 1998, **33**, 383.
1998EJO1989 M. Hemmerling, S. Hünig, M. Kemmer, and K. Peters, *Eur. J. Org. Chem.*, 1998, 1989.
1998FA741 P. L. Ferrarini, C. Manera, C. Mori, M. Badawneh, and G. Saccomanni, *Farmaco*, 1998, **53**, 741.
1998HCA491 C. J. Fahrni and A. Pfaltz, *Helv. Chim. Acta*, 1998, **81**, 491.
1998JA2172 S. C. Zimmerman, Y. Wang, P. Bharathi, and J. S. Moore, *J. Am. Chem. Soc.*, 1998, **120**, 2172.
1998JA4895 D. A. Evans and J. S. Johnson, *J. Am. Chem. Soc.*, 1998, **120**, 4895.
1998JFA3912 T. Hofmann, *J. Agric. Food Chem.*, 1998, **46**, 3912.
1998JIC590 S. K. Talapatra, P. Pal, K. Biswas, A. Shaw, R. Chaakrabarti, and B. Taalapatra, *J. Indian Chem. Soc.*, 1998, **75**, 590.
1998JME2436 G. A. Wächter, M. C. Davis, A. R. Martin, and S. G. Franzblau, *J. Med. Chem.*, 1998, **41**, 2436.
1998JME4232 Y. Ikeura, Y. Ishichi, T. Tanaka, A. Fujishima, M. Murabayashi, M. Kawada, T. Ishimaru, I. Kamo, T. Doi, and H. Natsugari, *J. Med. Chem.*, 1998, **41**, 4232.
1998JOC3680 J. L. Bowman and F. E. McDonald, *J. Org. Chem.*, 1998, **63**, 3680.
1998JOC4055 F. Wu, J. Hardesty, and R. P. Thummel, *J. Org. Chem.*, 1998, **63**, 4055.
1998JOC5310 J. D. Rainer and S. P. Allwein, *J. Org. Chem.*, 1998, **63**, 5310.
1998JOC6200 Y. Mori, K. Yaegashi, and H. Furukawa, *J. Org. Chem.*, 1998, **63**, 6200.
1998JOC6597 I. Kadota and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 6597.
1998J(P1)3907 S. V. Ley, A. C. Humphries, H. Eick, R. Downham, A. R. Ross, R. J. Boyce, J. B. J. Pavey, and J. Pietruszka, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3907.
1998JSO940 T. Nakata, *J. Synth. Org. Chem. Jpn.*, 1998, **56**, 940.
1998NAT264 K. C. Nicolaou, Z. Yang, G. Q. Shi, J. L. Gunzner, K. A. Agrios, and P. Gartner, *Nature*, 1998, **392**, 264.
1998P121 B. P. Da Silva, R. R. Bernardo, and J. P. Parent, *Phytochemistry*, 1998, **47**, 121.
1998P295 A. Yenesew, J. O. Midiwo, and P. G. Waterman, *Phytochemistry*, 1998, **47**, 295.
1998PHA442 T. Siener, U. Müller, M. Jansen, and U. Holzgrabe, *Pharmazie*, 1998, **53**, 442.
1998T21 T. Oka, K. Fujiwara, and A. Murai, *Tetrahedron*, 1998, **54**, 21.
1998T2607 Z. Wróbel, *Tetrahedron*, 1998, **54**, 2607.
1998T9799 J. Smodiš and B. Stanovnik, *Tetrahedron*, 1998, **54**, 9799.
1998T13557 F. Simart, Y. Brunel, S. Robin, and G. Rousseau, *Tetrahedron*, 1998, **54**, 13557.
1998TL837 E. Magnier and Y. Langlois, *Tetrahedron Lett.*, 1998, **39**, 837.
1998TL881 C. D. Gabbutt, J. D. Hepworth, B. M. Heron, and J.-L. Thomas, *Tetrahedron Lett.*, 1998, **39**, 881.
1998TL7147 K. C. Majumdar, P. Chatterjee, and S. Saha, *Tetrahedron Lett.*, 1998, **39**, 7147.
1998TL7767 E. L. Gaidarova, A. A. Borisenko, T. I. Chumakov, A. V. Mel'nikov, I. S. Orlov, and G. V. Grishina, *Tetrahedron Lett.*, 1998, **39**, 7767.
1998TL8325 D. Craig, A. H. Payne, and P. Warner, *Tetrahedron Lett.*, 1998, **39**, 8325.
1999AGE2258 A. B. Dounay, R. A. Urbanek, S. F. Sabes, and C. J. Forsyth, *Angew. Chem., Int. Ed. Engl.*, 1998, **38**, 2258.
1999AXC1670 R. Sankaranarayanan, S. Shanmuga, S. Raj, D. Velmurugan, H.-K. Fun, V. Raghukumar, and V. T. Ramakrishnan, *Acta Crystallogr. Sect. C*, 2000, **C55**, 1670.
1999BML2583 L. Chan, H. Jin, T. Stefanac, W. Wang, J.-F. Lavallée, J. Bédard, and S. May, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2583.
1999CC793 N. Bushby, C. J. Moody, D. A. Riddick, and I. R. Waldron, *J. Chem. Soc., Chem. Commun.*, 1999, 793.
1999CEJ646 K. C. Nicolaou, J. L. Gunzner, G. Q. Shi, K. A. Agrios, P. Gartner, and Z. Yang, *Chem. Eur. J.*, 1999, **5**, 646 (and preceeding articles).
1999CHE799 E. G. Paronikyan and A. S. Noravyan, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 799.
1999EJM505 P. L. Ferrarini, C. Mori, V. Calderone, L. Calzolari, P. Nieri, G. Saccomanni, and E. Martinotti, *Eur. J. Med. Chem.*, 1999, **34**, 505.
1999H(50)739 J. Teixidó, J. I. Borrell, B. Serra, J. L. Matallana, C. Colominas, F. Carrión, R. Pascual, J. L. Falcó, and X. Batllori, *Heterocycles*, 1999, **50**, 739.
1999IJB308 V. Padmavathi, A. Padmaja, and D. Bhaskar Reddy, *Indian J. Chem., Sect. B*, 1999, **38**, 308.
1999JFC141 S. Zhu, C. Qin, G. Xu, Q. Chu, and Q. Huang, *J. Fluorine Chem.*, 1999, **99**, 141.
1999JHC467 R. B. Toche, M. N. Jachak, R. W. Sabnis, and T. Kappe, *J. Heterocycl. Chem.*, 1999, **36**, 467.
1999JHC979 M. M. Blanco, I. A. Perillo, and C. B. Schapira, *J. Heterocycl. Chem.*, 1999, **36**, 979.
1999JLR641 S. E. Snyder, P. S. Sherman, T. J. Desmond, K. A. Frey, and M. R. Kilbourn, *J. Labelled Compd. Radiopharm.*, 1999, **42**, 641.
1999JLR1039 L. Martarello, T. Greenamyre, and M. M. Goodman, *J. Labelled Compd. Radiopharm.*, 1999, **42**, 1039.
1999JMC2991 S. Yagi, K. Maeda, and H. Nakazumi, *J. Mater. Chem.*, 1999, **9**, 2991.
1999JME706 A.-H. Lu, S. Moro, N. Forsyth, N. Melman, X.-D. Ji, and K. A. Jacobson, *J. Med. Chem.*, 1999, **42**, 706.
1999JME3023 L. Chan, H. Jin, T. Stefanac, J.-F. Lavallée, G. Falardeau, W. Wang, J. Bédard, S. May, and L. Yuen, *J. Med. Chem.*, 1999, **42**, 3023.
1999JME3982 H. Natsugari, Y. Ikeura, I. Kamo, T. Ishimaru, Y. Ishichi, A. Fujishima, T. Tanaka, F. Kasahara, M. Kawada, and T. Doi, *J. Med. Chem.*, 1999, **42**, 3982.

1999JOC37 S. Hosokawa and M. Isobe, *J. Org. Chem.*, 1999, **64**, 37.
1999JOC3461 D. Bankston, F. Fang, E. Huie, and S. Xie, *J. Org. Chem.*, 1999, **64**, 3461.
1999J(P1)3395 E. Lee, H. Y. Song, and H. J. Kim, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3395.
1999P739 J. Svasti, C. Srisomsap, S. Techasakul, and R. Surarit, *Phytochemistry*, 1999, **50**, 739.
1999S306 A. Numata, Y. Kondo, and T. Sakamoto, *Synthesis*, 1999, 306.
1999S1893 P. Zakrzewski, M. Gowan, L. A. Trimble, and C. K. Lau, *Synthesis*, 1999, 1893.
1999S1951 A. Bhandari, B. Li, and M. A. Gallop, *Synthesis*, 1999, 1951.
1999SC3881 P. Murugan, V. Raghukumar, and V. T. Ramakrishnan, *Synth. Commun.*, 1999, **29**, 3881.
1999T8231 J. S. Clark and J. G. Kettle, *Tetrahedron*, 1999, **55**, 8231.
1999T8253 M. A. Leeuwenburgh, C. Kulker, H. I. Duynstee, H. S. Overkleeft, G. A. van der Marel, and J. H. van Boom, *Tetrahedron*, 1999, **55**, 8253.
1999TL2811 N. Hori, H. Matsukura, G. Matsuo, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2811.
1999TL6029 K. Nakatani, S. Sando, K. Yoshida, and I. Saito, *Tetrahedron Lett.*, 1999, **40**, 6029.
1999TL8019 Y. Mori, H. F. Uruta, T. Takase, S. Mitsunoka, and H. Furukawa, *Tetrahedron Lett.*, 1999, **40**, 8019.
2000AXC80 L. Govindasamy, D. Velmurugan, V. Raghukumar, I.-H. Suh, and V. T. Ramakrishnan, *Acta Crystallogr. Sect. C*, 2000, **56**, 80.
2000BML305 A. P. Krapcho, S. N. Haydar, S. Truong-Chiott, M. P. Hacker, E. Menta, and G. Beggiolin, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 305.
2000BML1069 C. A. Coburn, D. M. Rush, P. D. Williams, C. Homnick, E. A. Lyle, S. D. Lewis, B. J. Lucas, Jr., J. M. Di Muzio-Mower, M. Juliano, J. A. Krueger, K. Vastag, I.-W. Chen, and J. P. Vacca, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1069.
2000BML1315 R. Obata, T. Sunazuka, K. Otoguro, H. Tomoda, Y. Harigaya, and S. Ōmura, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1315.
2000BML1069 C. A. Coburn, D. M. Rush, P. D. Williams, C. Homnick, E. A. Lyle, S. D. Lewis, B. J. Lucas, Jr., J. M. Di Muzio-Mower, M. Juliano, J. A. Krueger, K. Vastag, I.-W. Chen, and J. P. Vacca, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1069.
2000CC2241 R. Grigg, W. MacLachlan, and M. Rasparini, *J. Chem. Soc., Chem. Commun.*, 2000, 2241.
2000CHE496 V. V. Shelyakin and M. O. Lozinsky, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **33**, 496.
2000CJC950 M. Woźniak, M. Grzegożek, and P. Suryło, *Can. J. Chem.*, 2000, **78**, 950.
2000DOC218 V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Dokl. Chem. (Engl. Transl.)*, 2000, **374**, 218.
2000EJM227 K. Nishijima, H. Nishida, Y. Yamashita, M. Ito, Y. Onuki, M. Mizota, and S. Miyano, *Eur. J. Med. Chem.*, 2000, **35**, 227.
2000EJM815 P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, R. Greco, C. Manera, A. Martinelli, P. Nieri, and G. Saccomanni, *Eur. J. Med. Chem.*, 2000, **35**, 815.
2000H(53)1685 T. Saito, H. Furuie, Y. Ishigooka, I. Watanabe, and K. Kobayashi, *Heterocycles*, 2000, **53**, 1685.
2000JA1635 D. A. Evans, J. S. Johnson, and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635.
2000JAN551 H. Yamazaki, Y. Tsuchida, H. Satoh, S. Kawashima, H. Hanaki, and K. Hiramatsu, *J. Antibiot.*, 2000, **53**, 551.
2000JAN1401 G. Erkel, J. Rether, T. Anke, and O. Sterner, *J. Antibiot.*, 2000, **53**, 1401.
2000JCM26 A. M. El-Agrody, M. S. Abd El-Latif, A. H. Fakery, and A. H. Bedair, *J. Chem. Res. (S)*, 2000, 26.
2000JHC379 A. Da Settimo, A. M. Marini, G. Primofiore, F. Da Settimo, S. Salerno, C. La Motta, G. Pardi, P. L. Ferrarini, and C. Mori, *J. Heterocycl. Chem.*, 2000, **37**, 379.
2000JHC799 A. Borioni, M. R. Del Guidice, C. Mustazza, and F. Gatta, *J. Heterocycl. Chem.*, 2000, **37**, 799.
2000JME675 R. Hersperger, K. Bray-French, L. Mazzoni, and T. Müller, *J. Med. Chem.*, 2000, **43**, 675.
2000JME2814 P. L. Ferrarini, C. Mori, C. Manera, A. Martinelli, F. Mori, G. Saccomanni, P. L. Barili, L. Betti, G. Giannaccini, L. Trincavelli, and A. Lucacchini, *J. Med. Chem.*, 2000, **43**, 2814.
2000JME3736 M. E. Duggan, L. T. Duong, J. E. Fisher, T. G. Hamill, W. F. Hoffman, J. R. Huff, N. C. Ihle, C.-T. Leu, R. M. Nagy, J. J. Perkins, S. B. Rodan, G. Wesolowski, D. B. Whitman, A. E. Zartman, G. A. Rodan, and G. D. Hartman, *J. Med. Chem.*, 2000, **43**, 3736.
2000JME4200 A. M. Thompson, C. J. C. Connolly, J. M. Hamby, S. Boushelle, B. G. Hartl, A. M. Amar, A. J. Kraker, D. L. Driscoll, R. W. Steinkampf, S. J. Patmore, P. W. Vincent, B. J. Roberts, W. L. Elliott, W. Klohs, W. R. Leopold, H. D. H. Showalter, and W. A. Denny, *J. Med. Chem.*, 2000, **43**, 4200.
2000JOC8490 B. B. Snider and T. Liu, *J. Org. Chem.*, 2000, **65**, 8490.
2000JOC8822 C. Betancor, R. L. Dorta, R. Freire, T. Prangé, and E. Suárez, *J. Org. Chem.*, 2000, **65**, 8822.
2000J(P1)1843 A. M. Thompson, H. D. H. Showalter, and W. A. Denn, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1843.
2000J(P2)1841 A. Fiksdahl, C. Plüg, and C. Wentrup, *J. Chem. Soc., Perkin Trans. 2*, 2000, 1841.
2000OL875 X. Li, L. B. Schenkel, and M. C. Kozlowski, *Org. Lett.*, 2000, **2**, 875.
2000S247 S. Yagi, K. Maeda, and H. Nakazumi, *Synthesis*, 2000, 247.
2000T6479 O. Rhode and H. M. R. Hoffmann, *Tetrahedron*, 2000, **56**, 6479.
2000T8245 C. He and S. J. Lippard, *Tetrahedron*, 2000, **56**, 8245.
2000TL1901 L. R. Zehnder, J. W. Dahl, and R. P. Hsung, *Tetrahedron Lett.*, 2000, **41**, 1901.
2000TL2643 H. Miyazaki, Y. Honda, K. Honda, and S. Inoue, *Tetrahedron Lett.*, 2000, **41**, 2643.
2000TL8053 V. J. Colandrea and E. M. Naylor, *Tetrahedron Lett.*, 2000, **41**, 8053.
2000TL9251 D. Urban, E. Duval, and Y. Langlois, *Tetrahedron Lett.*, 2000, **41**, 9251.
2001AGE4441 K. C. Nicolaou, J. A. Vega, and G. Vassilikogiannakis, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 4441.
2001AXC726 R. Sankaranarayanan, D. Velmurugan, S. Shanmuga, S. Raj, and H.-K. Fun, *Acta Crystallogr. Sect. C*, 2001, **57**, 726.
2001BML103 L. Chan, T. Stefanac, J.-F. Lavallée, H. Jin, J. Bédard, S. May, and G. Falardeau, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 103.
2001BMC2061 Z.-L. Zhou, J. M. Navratil, S. X. Cai, E. R. Whittemore, S. A. Espitia, J. E. Hawkinson, M. Tran, R. M. Woodward, E. Weber, and J. F. W. Keana, *Bioorg. Med. Chem.*, 2001, **9**, 2061.
2001BMC2921 O. Tabarrini, V. Cecchetti, A. Temperini, E. Filipponi, M. G. Lamperti, and A. Fravolini, *Bioorg. Med. Chem.*, 2001, **9**, 2921.
2001BML1907 R. A. Porter, W. N. Chan, S. Coulton, A. Johns, M. S. Hadley, K. Widdowson, J. C. Jerman, S. J. Brough, M. Coldwell, D. Smart, F. Jewitt, P. Jeffrey, and N. Austin, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1907.
2001EJO391 E. Fasani, M. Mella, S. Monti, and A. Albina, *Eur. J. Org. Chem.*, 2001, 391.
2001EJO1781 A. B. Eldrup, B. B. Nielsen, G. Haaima, H. Rasmussen, J. S. Kastrup, C. Christensen, and P. E. Nielsen, *Eur. J. Org. Chem.*, 2001, 1781.
2001EJO1963 Y. Tanada and K. Mori, *Eur. J. Org. Chem.*, 2001, 1963.

2001EJO3711 G. Appendino, G. Cravotto, A. Minassi, and G. Palmisano, *Eur. J. Org. Chem.*, 2001, 3711.
2001H(55)1121 N. Thasana, M. Chuankamnerdkarn, and S. Ruchirawat, *Heterocycles*, 2001, **55**, 1121.
2001IJB336 K. Mogilaiah, R. Babu Rao, and G. Rama Sudhakar, *Indian J. Chem., Sect. B*, 2001, **40B**, 336.
2001IJB713 K. Mogilaiah and R. Babu Rao, *Indian J. Chem., Sect. B*, 2001, **40B**, 713.
2001JA9908 K. Yabu, S. Masumoto, S. Yamasaki, Y. Hamashima, M. Kanai, W. Du, D. P. Curran, and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 9908.
2001JLRS283 C. Gueret, M. D. Le Bas, C. Perrio, F. Dauphin, M. Dilly, L. Chazalviel, P. Emond, S. Chalon, S. Tymciu, D. Guilloteau, M.-C. Lasne, and L. Barre, *J. Labelled Compd. Radiopharm.*, 2001, **44**, S283.
2001JOC1103 B. Ganguly, D. A. Freed, and M. C. Kozlowski, *J. Org. Chem.*, 2001, **66**, 1103.
2001JOC1380 J. D. Rainer, S. P. Allwein, and J. M. Cox, *J. Org. Chem.*, 2001, **66**, 1380.
2001JOC4413 A. L. Zografos, C. A. Mitsos, and O. Igglessi-Markopoulou, *J. Org. Chem.*, 2001, **66**, 4413.
2001J(P1)2183 N. Bushby, C. J. Moody, D. A. Riddick, and I. R. Waldron, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2183.
2001OL13 Y. Kondo, M. Asai, T. Miura, M. Uchiyama, and T. Sakamoto, *Org. Lett.*, 2001, **3**, 13.
2001OL1137 X. Li, J. Yang, and M. C. Kozlowski, *Org. Lett.*, 2001, **3**, 1137.
2001OL2141 L. R. Zehnder, L.-L. Wei, R. P. Hsung, K. P. Cole, M. J. McLaughlin, H. C. Shen, H. M. Sklenicka, J. Wang, and C. A. Zificsak, *Org. Lett.*, 2001, **3**, 2141.
2001OL2973 Q. Huang, J. A. Hunter, and R. C. Larock, *Org. Lett.*, 2001, **3**, 2973.
2001OL4035 G. Dai and R. C. Larock, *Org. Lett.*, 2001, **3**, 4035.
2001RCB122 S. V. Roman, V. D. Dyachenko, and V. P. Litvinov, *Russ. Chem. Bull.*, 2001, **50**, 122.
2001RRC1139 E. Barbu and F. Cuiban, *Rev. Roum. Chim.*, 2001, **46**, 1139.
2001S103 R. A. Mekheimer, *Synthesis*, 2001, 103.
2001SC787 J. D. Harling, F. P. Harrington, and M. Thompson, *Synth. Commun.*, 2001, **31**, 787.
2001SC2589 M. Venkati and G. L. D. Krupadanam, *Synth. Commun.*, 2001, **31**, 2589.
2001SC2667 B. B. Snider and R. B. Smith, *Synth. Commun.*, 2001, **31**, 2667.
2001SCI1904 M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Guri, and M. Satake, *Science*, 2001, **294**, 1904.
2001T4537 M. C. Kozlowski, Z. Xu, and A. G. Santos, *Tetrahedron*, 2001, **57**, 4537.
2001T9101 C. Vitry, J. Bédat, Y. Prigent, V. Levacher, G. Dupas, I. Salliot, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, 2001, **57**, 9101.
2001TA707 G. Cravotto, G. M. Nano, G. Palmisano, and S. Tagliapietra, *Tetrahedron Asymmetry*, 2001, **12**, 707.
2001TL5725 M. Sasaki, T. Shida, and K. Tachibana, *Tetrahedron Lett.*, 2001, **42**, 5725.
2001TL6087 I. Ungureanu, P. Klotz, A. Schoenfelder, and A. Mann, *Tetrahedron Lett.*, 2001, **42**, 6087.
2001TL6451 X. Xie, D. A. Freed, and M. C. Kozlowski, *Tetrahedron Lett.*, 2001, **42**, 6451.
2001TL6811 M. Palucki, D. L. Hughes, N. Yasuda, C. Yang, and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 6811.
2001TL7397 F. J. R. Rombouts, W. De Borggraeve, S. M. Toppet, F. Compernolle, and G. J. Hoornaert, *Tetrahedron Lett.*, 2001, **42**, 7397.
2002AGE3841 C. Yu, A. A. Henry, F. E. Romesberg, and P. G. Schultz, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3841.
2002BML25 R. S. Meissner, J. J. Perkins, L. T. Duong, G. D. Hartman, W. F. Hofmann, J. R. Huff, N. C. Ihle, C.-T. Leu, R. M. Nagy, A. Naylor-Olsen, G. A. Rodan, S. B. Rodan, D. B. Whitman, G. A. Wesolowski, and M. E. Duggan, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 25.
2002BML233 R. Hersperger, J. Dawson, and T. Mueller, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 233.
2002BML3121 C. Christensen, A. B. Eldrup, G. Haaima, and P. E. Nielsen, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3121.
2002CPB1050 K. Takayama, M. Iwata, H. Hisamichi, Y. Okamoto, M. Aoki, and A. Niwa, *Chem. Pharm. Bull.*, 2002, **50**, 1050.
2002EJM475 L. Dalla Via, O. Gia, S. M. Magno, A. Da Settimo, G. Primofiore, F. Da Settimo, F. Simorini, and A. M. Marini, *Eur. J. Med. Chem.*, 2002, **37**, 475.
2002EJO4054 S. Brammer, U. Lüning, and C. Kühl, *Eur. J. Org. Chem.*, 2002, 4054.
2002H(56)443 U. N. Rao and E. R. Biehl, *Heterocycles*, 2002, **56**, 443.
2002JA13757 Y. Ma, S. V. Kolotuchin, and S. C. Zimmerman, *J. Am. Chem. Soc.*, 2002, **124**, 13757.
2002JHC829 C. Vu, D. Walker, J. Wells, and S. Fox, *J. Heterocycl. Chem.*, 2002, **39**, 829.
2002JME5173 A. Gangjee, Y. Zeng, J. J. McGuire, and R. L. Kisliuk, *J. Med. Chem.*, 2002, **45**, 5173.
2002JOC86 K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 86.
2002JOC3072 Z. Xu and M. C. Kozlowski, *J. Org. Chem.*, 2002, **67**, 3072.
2002JOC3437 Q. Huang, J. A. Hunter, and R. C. Larock, *J. Org. Chem.*, 2002, **67**, 3437.
2002JOC3494 I. Kadota, H. Takamura, K. Sato, and Y. Yamamoto, *J. Org. Chem.*, 2002, **67**, 3494.
2002JOC7303 S. Arimori, R. Kouno, T. Okauchi, and T. Minami, *J. Org. Chem.*, 2002, **67**, 7303.
2002J(P1)1769 S. Maiti, B. Achari, R. Mukhopadhyay, and A. K. Banerjee, *J. Chem., Soc. Perkin Trans. 1*, 2002, 1769.
2002PCJ465 E. G. Paronikyan, A. S. Noravyan, I. A. Dzhagatspanan, I. M. Nazaryan, and R. G. Paronikyan, *Pharm. Chem. J.*, 2002, **36**, 465.
2002OL367 T. Sunazuka, M. Handa, K. Nagai, T. Shirahata, Y. Harigaya, K. Otoguro, I. Kuwajima, and S. Ōmura, *Org. Lett.*, 2002, **4**, 367.
2002OL2071 C. G. Savarin, J. A. Murry, and P. G. Dormer, *Org. Lett.*, 2002, **4**, 2071.
2002OL2489 V. S. Kumar, D. L. Aubele, and P. E. Floreancig, *Org. Lett.*, 2002, **4**, 2489.
2002OL2629 K. C. Majumdar, U. K. Kundu, and S. K. Ghosh, *Org. Lett.*, 2002, **4**, 2629.
2002SAA1535 V. K. Indirapriyadharshini, P. Ramamurthy, V. Raghukumar, and V. T. Ramakrishnan, *Spectrochim. Acta, Part A*, 2002, **58**, 1535.
2002SC747 K. Mogilaiah and R. Babu Rao, *Synth. Commun.*, 2002, **32**, 747.
2002SC857 K. Mogilaiah, D. Srinivasa Chowdary, and P. Raghotham Reddy, *Synth. Commun.*, 2002, **32**, 857.
2002SC2377 K. Mogilaiah, H. Ramesh Babu, and N. Vasudeva Reddy, *Synth. Commun.*, 2002, **32**, 2377.
2002SC2903 E. Veverková, M. Nosková, and Š. Toma, *Synth. Commun.*, 2002, **32**, 2903.
2002SL952 C. Gaulon, P. Gizecki, R. Dhal, and G. Dujardin, *Synlett*, 2002, 952.
2002T58 M. Valès, V. Lokshin, G. Pèpe, R. Guglielmetti, and A. Samat, *Tetrahedron*, 2002, **58**, 8543.
2002T531 E. Ceulemans, M. Voets, S. Emmers, K. Uytterhoeven, L. Van Meervelt, and W. Dehaen, *Tetrahedron*, 2002, **58**, 531.
2002T1853 N. Hori, H. Matsukuri, G. Matsuo, and T. Nakata, *Tetrahedron*, 2002, **58**, 1853.
2002T1921 M. L. Candenas, F. M. Pinto, C. G. Cintado, E. Q. Morales, I. Brouard, M. T. Díaz, M. Rico, E. Rodríguez, R. M. Rodríguez, R. Pérez, R. L. Pérez, and J. D. Martìn, *Tetrahedron*, 2002, **58**, 1921.

2002T1997 S. P. Allwein, J. M. Cox, B. E. Howard, H. W. B. Johnson, and J. D. Rainier, *Tetrahedron*, 2002, **58**, 1997.
2002T2027 F. P. Marsäter, J. A. Vanecko, and F. G. West, *Tetrahedron*, 2002, **58**, 2027.
2002T6521 S. Hanessian and P. Compain, *Tetrahedron*, 2002, **58**, 6521.
2002T6895 I. Yavari, M. Adib, and L. Hojabri, *Tetrahedron*, 2002, **58**, 6895.
2002TL1573 G. Sabitha, E. V. Reddy, C. Maruthi, and J. S. Yadav, *Tetrahedron Lett.*, 2002, **43**, 1573.
2002TL1583 J. Cairns, T. R. Clarkson, J. A. M. Hamersma, and D. R. Rae, *Tetrahedron Lett.*, 2002, **43**, 1583.
2002TL2111 K. C. Majumdar, M. Ghosh, M. Jana, and D. Saha, *Tetrahedron Lett.*, 2002, **43**, 2111.
2002TL3341 K. P. Cole, R. P. Hsung, and X.-F. Yang, *Tetrahedron Lett.*, 2002, **43**, 3341.
2002TL3747 X. Li, Z. Xu, E. F. DiMauro, and M. C. Kozlowski, *Tetrahedron Lett.*, 2002, **43**, 3727.
2002TL7095 M. H. D. Postema and J. L. Piper, *Tetrahedron Lett.*, 2002, **43**, 7095.
2002TL8791 K. P. Cole and R. P. Hsung, *Tetrahedron Lett.*, 2002, **43**, 8791.
2003AXC392 S.-P. Yang, X.-B. Yu, J.-G. Huang, and H.-H. Xu, *Acta Crystallogr., Sect. C*, 2003, **59**, 392.
2003BMC433 K. Yoshiizumi, M. Yamamoto, T. Miyasaka, Y. Ito, H. Kumihara, M. Sawa, T. Kiyoi, T. Yamamoto, F. Nakajima, R. Hirayama, H. Kondo, E. Ishibushi, H. Ohmoto, Y. Inoue, and K. Yoshino, *Bioorg. Med. Chem.*, 2003, **11**, 433.
2003BML467 J. A. Hunt, F. Kallashi, R. D. Ruzek, P. J. Sinclair, I. Ita, S. X. McCormick, J. V. Pivnichny, C. E. C. A. Hop, S. Kumar, Z. Wang, S. J. O'Keefe, E. A. O'Neill, G. Porter, J. E. Thompson, A. Woods, D. M. Zaller, and J. B. Doherty, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 467.
2003BML1415 C. L. Cywin, B.-P. Zhao, D. W. McNeil, M. Hrapchak, A. S. Prokopowicz, III, D. R. Goldberg, T. M. Morwick, A. Gao, S. Jakes, M. Kashem, R. L. Magolda, R. M. Soll, M. R. Player, M. A. Bobko, J. Rinker, R. L. DesJarlais, and M. P. Winters, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1415.
2003BML1483 W. H. Miller, P. J. Manley, R. D. Cousins, K. F. Erhard, D. A. Heerding, C. Kwon, S. T. Ross, J. M. Samanen, D. T. Takata, I. N. Uzinskas, C. C. K. Yuan, R. C. Haltiwanger, C. J. Gress, M. W. Lark, S.-M. Hwang, I. E. James, D. J. Rieman, R. N. Willette, T.-L. Yue, L. M. Azzarano, K. L. Sayers, B. R. Smith, K. W. Ward, K. O. Johanson, and W. F. Huffman, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1483.
2003BML1627 N. E. Austin, M. S. Hadley, J. D. Harling, F. P. Harrington, G. J. MacDonald, D. J. Mitchell, G. J. Riley, T. O. Stean, G. Stemp, S. C. Stratton, M. Thompson, and N. Upton, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1627.
2003BML2341 T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, Y. Moritani, K. Saruta, T. Higashijima, J. Kotera, K. Fujishige, M. Takagi, K. Kikkawa, and K. Omori, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2341.
2003BML4921 G. Saccomanni, M. Badawneh, B. Adinolfi, V. Calderone, T. Cavallini, P. L. Ferrarini, R. Greco, C. Manera, and L. Testai, *Bioorg. Med. Chem. Lett.*, 2003, **11**, 4921.
2003CC336 J. P. Plante, P. D. Jones, D. R. Powell, and T. E. Glass, *J. Chem. Soc., Chem. Commun.*, 2003, 336.
2003EJM265 J. M. Quintela, C. Peinador, L. González, R. Iglesias, A. Paramá, F. Álvarez, M. L. Sanmartín, and R. Riguera, *Eur. J. Med. Chem.*, 2003, **38**, 265.
2003EJO1868 F. J. R. Rombouts, W. M. De Borggraeve, D. Delaere, M. Froeyen, S. M. Toppet, F. Compernolle, and G. J. Hoornaert, *Eur. J. Org. Chem.*, 2003, 1868.
2003H(59)369 K. Yabu, S. Matumoto, M. Kanai, W. Du, D. P. Curran, and M. Shibasaki, *Heterocycles*, 2003, **59**, 369.
2003H(60)939 K. Kobayashi, K. Nagase, O. Morikawa, and H. Konishi, *Heterocycles*, 2003, **60**, 939.
2003IJB1170 K. Mogilaiah and G. R. Sudhakar, *Indian J. Chem., Sect. B*, 2003, **42**, 1170.
2003IZK969 V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega, and V. P. Litvinov, *Izv. Akad. Nauk Ser. Khim.*, 2003, 918 (English translation: *Russ. Chem. Bull. Int. Ed.*, 2003, **52**, 969).
2003IZK2069 L. A. Rodinovskaya, A. M. Shestopalov, and A. V. Gromova, *Izv. Akad. Nauk Ser. Khim.*, 2003, 2069 (English translation: *Russ. Chem. Bull. Int. Ed.*, 2003, **52**, 2185).
2003JA7822 A. Zakaraian, A. Batch, and R. A. Holton, *J. Am. Chem. Soc.*, 2003, **125**, 7822.
2003JA8798 N. Ohyabu, T. Nishikawa, and M. Isobe, *J. Am. Chem. Soc.*, 2003, **125**, 8798.
2003JME453 L. Zhuang, J. Wai, M. W. Embrey, T. E. Fisher, M. S. Egbertson, L. S. Payne, J. P. Guare, J. P. Vacca, D. J. Hazuda, P. J. Felock, A. L. Wolfe, K. A. Stillmock, M. V. Witmer, G. Moyer, W. A. Schleif, L. J. Gabryelski, Y. M. Leonard, J. J. Lynch, Jr., S. R. Michelson, and S. D. Young, *J. Med. Chem.*, 2003, **46**, 453.
2003JME1627 M. A. Seefeld, W. H. Miller, K. A. Newlander, W. J. Burgess, W. E. DeWolf, Jr., P. A. Elkins, M. S. Head, D. R. Jakas, C. A. Janson, P. M. Keller, P. J. Manley, T. D. Moore, D. J. Payne, S. Pearson, B. J. Polizzi, X. Qiu, S. F. Rittenhouse, I. N. Uzinskas, N. G. Wallis, and W. F. Huffman, *J. Med. Chem.*, 2003, **46**, 1627.
2003JME4790 J. H. Hutchinson, W. Halczenko, K. M. Brashear, M. J. Breslin, P. J. Coleman, L. T. Duong, C. Fernandez-Metzler, M. A. Gentile, J. E. Fisher, G. D. Hartman, J. R. Huff, D. B. Kimmel, C.-T. Leu, R. S. Meissner, K. Merkle, R. Nagy, B. Pennypacker, J. J. Perkins, T. Prueksaritanont, G. A. Rodan, S. L. Varga, G. A. Wesolowski, A. E. Zartman, S. B. Rodan, and M. E. Duggan, *J. Med. Chem.*, 2003, **46**, 4790.
2003JOC467 P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey, J. C. McWilliams, P. J. Reider, J. W. Sager, and R. P. Volante, *J. Org. Chem.*, 2003, **68**, 467.
2003JOC920 G. Dai and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 920.
2003JOC980 Q. Huang and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 980.
2003JOC1729 H. C. Shen, J. Wang, K. P. Cole, M. J. McLaughlin, C. D. Morgan, C. J. Douglas, R. P. Hsung, H. A. Coverdale, A. I. Gerasyuto, J. M. Hahn, J. Liu, H. M. Sklenicka, L.-L. Wei, L. R. Zehnder, and C. A. Zificsak, *J. Org. Chem.*, 2003, **68**, 1729.
2003JOC3271 F. M. Cordero, F. Pisaneschi, M. Salvati, V. Paschetta, J. Ollivier, J. Salaün, and A. Brandi, *J. Org. Chem.*, 2003, **68**, 3271.
2003JOC3546 K. A. Skupinska, E. J. McEachern, I. R. Baird, R. T. Skerlj, and G. J. Bridger, *J. Org. Chem.*, 2003, **68**, 3546.
2003JOC4567 C. A. Mitsos, A. L. Zografos, and O. Igglessi-Markopoulou, *J. Org. Chem.*, 2003, **68**, 4567.
2003JOC6959 G. Abbiati, A. Arcadi, G. Bianchi, S. Di Giuseppe, F. Marinelli, and E. Rossi, *J. Org. Chem.*, 2003, **68**, 6959.
2003JOC7889 C.-J. Wu, R. J. Madhushaw, and R.-A. Liu, *J. Org. Chem.*, 2003, **68**, 7889.
2003JSO562 T. Oishi, *J. Synth. Org. Chem. Jpn.*, 2003, **61**, 562.
2003OBC2423 A. Dahlén, A. Petersson, and G. Hilmersson, *Org. Biomol. Chem.*, 2003, **1**, 2423.
2003OL717 R. Lavilla, M. C. Bernabeu, I. Carranco, and J. L. Díaz, *Org. Lett.*, 2003, **5**, 717.
2003S717 S. Hesse and G. Kirsch, *Synthesis*, 2003, 717.

2003S2385 K. C. Majumdar, A. Biswas, and P. P. Mukhopadhyay, *Synthesis*, 2003, 2385.
2003SC475 S. Goswami and A. K. Adak, *Synth. Commun.*, 2003, **33**, 475.
2003SC3131 K. Mogliaiah and C. S. Reddy, *Synth. Commun.*, 2003, **33**, 3131.
2003SL2301 C. Simon, F. Lieby-Muller, J.-F. Peyronel, T. Constantieux, and J. Rodrigues, *Synlett*, 2003, 2301.
2003T311 R. P. Hsung, K. P. Cole, L. R. Zehnder, J. Wang, L.-L. Wei, X.-F. Yang, and H. A. Coverdale, *Tetrahedron*, 2003, **59**, 311.
2003T4721 F. J. R. Rombouts, J. Van den Bossche, S. M. Toppet, F. Compernolle, and G. J. Hoornaert, *Tetrahedron*, 2003, **59**, 4721.
2003T4795 D. H. Hua, X. Huang, M. Tamura, Y. Chen, M. Woltkamp, L.-W. Jin, E. M. Perchellet, J.-P. Perchellet, P. K. Chiang, I. Namatame, and H. Tomoda, *Tetrahedron*, 2003, **59**, 4795.
2003T5289 K. C. Majumdar, A. Bandyopadhyay, and A. Biswas, *Tetrahedron*, 2003, **59**, 5289.
2003T5481 T. C. Govaerts, I. A. Vogels, F. Compernolle, and G. J. Hoornaert, *Tetrahedron*, 2003, **59**, 5481.
2003T8767 H. Furuta, T. Takase, H. Hayashi, R. Noyori, and Y. Mori, *Tetrahedron*, 2003, **59**, 9767.
2003T9767 H. Furuta, T. Takase, H. Hayashi, R. Noyori, and Y. Mori, *Tetrahedron*, 2003, **59**, 9767.
2003T9887 G. Abbiati, E. M. Beccalli, G. Broggini, and C. Zoni, *Tetrahedron*, 2003, **59**, 9887.
2003TL6021 H. Ban, M. Muraoka, and N. Ohashi, *Tetrahedron Lett.*, 2003, **44**, 6021.
2003TL6351 W. Li, K. T. Mead, and L. T. Smith, *Tetrahedron Lett.*, 2003, **44**, 6351.
2003TL6513 T. Saito, T. Horikoshi, T. Otani, Y. Matsuda, and T. Karakasa, *Tetrahedron Lett.*, 2003, **44**, 6513.
2003TL8227 U. M. Krishna, G. S. C. Srikanth, and G. K. Trivedi, *Tetrahedron Lett.*, 2003, **44**, 8227.
2003TL8545 J. M. Bartoloméa, J. Alcázar, J. I. Andrés, M. De Bruyn, J. Fernández, E. Matesanz, and K. Van Emelen, *Tetrahedron Lett.*, 2003, **44**, 8545.
2004ACR961 M. Inoue and M. Hirama, *Acc. Chem. Res.*, 2004, **37**, 961.
2004BML1309 S. Ohnuma, M. Muraoka, K. Ioriya, and N. Ohashi, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1309.
2004BML1411 A. Wissner, P. R. Hamann, R. Nilakantan, L. M. Greenberger, F. Ye, T. A. Rapuano, and F. Loganzo, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1411.
2004BML1921 P. L. Ferrarini, V. Calderone, T. Cavallini, C. Manera, G. Saccomanni, L. Pani, S. Ruiu, and G. L. Gessa, *Bioorg. Med. Chem. Lett.*, 2004, **12**, 1921.
2004BML3189 Y. Tsuzuki, K. Tomita, Y. Sato, S. Kashimoto, and K. Chiba, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3189.
2004BML3441 A. Mitchinson, J. R. Atack, P. Blurton, R. W. Carling, J. L. Castro, K. S. Curley, M. G. N. Russell, G. Marshall, R. M. McKernan, K. W. Moore, R. Narquizian, A. Smith, L. J. Street, S.-A. Thompson, and K. Wafford, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3441.
2004BML5179 R. Mahesh, R. Venkatesha, V. Perumal, and P. V. Pandi, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5179.
2004BML5227 B. L. De Corte, W. A. Kinney, L. Liu, S. Ghosh, L. Brunner, W. J. Hoekstra, R. J. Santulli, R. W. Tuman, J. Baker, C. Burns, J. C. Proost, B. A. Tounge, B. P. Damiano, B. E. Maryanoff, D. L. Johnson, and R. A. Galemmo, Jr., *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5227.
2004CRV2199 A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
2004CRV2239 M. D. McReynolds, J. M. Dougherty, and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239.
2004EJO1057 A. A. Maia, S. Mons, R. Pereira de Freitas Gil, and C. Marazano, *Eur. J. Org. Chem.*, 2004, 1057.
2004IJB2014 K. Mogilaiah, K. Srinivas, and G. Rama Sudhakar, *Indian J. Chem., Sect. B*, 2004, **43**, 2014.
2004JA14374 G. Matsuo, K. Kawamura, N. Hori, H. Matsukura, and T. Nakata, *J. Am. Chem. Soc.*, 2004, **126**, 14374.
2004JHC517 I. O. Zhuravel, S. M. Kovalenko, A. V. Ivachtchenko, V. P. Chernykh, and P. E. Shrinkarenkio, *J. Heterocycl. Chem.*, 2004, **41**, 517.
2004JHC857 T. Hussenether and R. Troschütz, *J. Heterocycl. Chem.*, 2004, **41**, 857.
2004JME3019 P. L. Ferrarini, L. Betti, T. Cavallini, G. Giannaccini, A. Lucacchini, C. Manera, A. Martinelli, G. Ortore, G. Saccomanni, and T. Tuccinardi, *J. Med. Chem.*, 2004, **47**, 3019.
2004JME3163 W. A. Carroll, R. J. Altenbach, H. Bai, J. D. Brioni, M. E. Brune, S. A. Buckner, C. Cassidy, Y. Chen, M. J. Coghlan, A. V. Daza, I. Drizin, T. A. Fey, M. Fitzgerald, M. Gopalakrishnan, R. J. Gregg, R. F. Henry, M. W. Holladay, L. L. King, M. E. Kort, P. R. Kym, I. Milicic, R. Tang, S. C. Turner, K. L. Whiteaker, L. Yi, H. Zhang, and J. P. Sullivan, *J. Med. Chem.*, 2004, **47**, 3163.
2004JME3180 W. A. Carroll, K. A. Agrios, R. J. Altenbach, S. A. Buckner, Y. Chen, M. J. Coghlan, A. V. Daza, I. Drizin, M. Gopalakrishnan, R. F. Henry, M. E. Kort, P. R. Kym, I. Milicic, J. C. Smith, R. Tang, S. C. Turner, K. L. Whiteaker, H. Zhang, and J. P. Sullivan, *J. Med. Chem.*, 2004, **47**, 3180.
2004JME4494 F. Gellibert, J. Woolven, M.-H. Fouchet, N. Mathews, H. Goodland, V. Lovegrove, A. Laroze, V.-L. Nguyen, S. Sautet, R. Wang, C. Janson, W. Smith, G. Krysa, V. Bouliay, A.-C. de Gouville, S. Huet, and D. Hartley, *J. Med. Chem.*, 2004, **47**, 4494.
2004JME4829 P. J. Coleman, K. M. Bashear, B. C. Askew, J. H. Hutchinson, C. A. McVean, L. T. Duong, B. P. Feuston, C. Fernandez-Metzler, M. A. Gentile, G. D. Hartman, D. B. Kimmel, C.-T. Leu, L. Lipfert, K. Merkle, B. Pennypacker, T. Prueksaritanont, G. A. Rodan, G. A. Wesolowski, S. B. Rodan, and M. E. Duggan, *J. Med. Chem.*, 2004, **47**, 4829.
2004JME5167 N. Haginoya, S. Kobayashi, S. Komoriya, T. Yoshino, M. Suzuki, T. Shimada, K. Watanabe, Y. Hirokawa, T. Furugori, and T. Nagahara, *J. Med. Chem.*, 2004, **47**, 5167.
2004JOC1959 N. Yasuda, Y. Hsiao, M. S. Jensen, N. R. Rivera, C. Yang, K. M. Wells, J. Yau, M. Palucki, L. Tan, P. G. Dormer, R. P. Volante, D. L. Hughes, and P. J. Reider, *J. Org. Chem.*, 2004, **69**, 1959.
2004JOC6772 D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772.
2004JOC7171 B. R. Lahue, S.-M. Lo, Z.-K. Wan, G. H. C. Woo, and J. K. Snyder, *J. Org. Chem.*, 2004, **69**, 7171.
2004JPO478 T. L. Knoll and A. J. Bennet, *J. Phys. Org. Chem.*, 2004, **17**, 478.
2004OL2433 P. J. Manley and M. T. Bilodeau, *Org. Lett.*, 2004, **6**, 2433.
2004OL3671 E. Bacqué, M. El Qacemi, and S. Z. Zard, *Org. Lett.*, 2004, **6**, 3671.
2004PNA12013 M. Inoue, K. Miyazaki, H. Uehara, M. Maruyama, and M. Hirama, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 12013.
2004RJO892 V. V. Shchepin, D. V. Fotin, and M. I. Vakhrin, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 892.
2004SL577 M. Inoue and M. Hirama, *Synlett*, 2004, 577.
2004SL1731 S. Sun, Y. Liu, Q. Liu, Y. Zhao, and D. Dong, *Synlett*, 2004, 1731.
2004T429 T. C. Govaerts, I. A. Vogels, F. Compernolle, and G. J. Hoornaert, *Tetrahedron*, 2004, **60**, 429.
2004T4601 R. Jakše, J. Svete, B. Stanovnik, and A. Golobič, *Tetrahedron*, 2004, **60**, 4601.

2004T6785 M.-L. Bennasar, T. Roca, E. Zulaica, and M. Monerris, *Tetrahedron*, 2004, **60**, 6785.

2004TL1721 A. J. Davies, K. M. J. Brands, C. J. Cowden, U.-H. Dolling, and D. R. Lieberman, *Tetrahedron Lett.*, 2004, **45**, 1721.

2004TL5931 A. Nagatsu, S. Itoh, R. Tanaka, S. Kato, M. Haruna, K. Kishimoto, H. Hirayama, Y. Goda, H. Mizukami, and Y. Ogihara, *Tetrahedron Lett.*, 2004, **45**, 5931.

2004TL7947 J. S. Yadav, B. V. Subba Reddy, V. Sunitha, K. S. Reddy, and K. V. S. Ramakrishna, *Tetrahedron Lett.*, 2004, **45**, 7947.

2004TL8165 X. Meng, Y. Zhang, M. Sollogoub, and P. Sinaÿ, *Tetrahedron Lett.*, 2004, **45**, 8165.

2005BMC491 F. D. Settimo, G. Primofiore, C. La Motta, S. Salerno, E. Novellino, G. Greco, A. Lavecchia, S. Laneri, and E. Boldrini, *Bioorg. Med. Chem.*, 2005, **13**, 491.

2005BML531 A. Agarwal, K. Srivastava, S. K. Puri, and P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 531.

2005BML1693 G. Falardeau, H. Lachance, A. St-Pierre, C. G. Yannopoulos, M. Drouin, J. Bédard, and L. Chan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1693.

2005BML2679 K. Leonard, W. Pan, B. Anaclerio, J. M. Gushue, Z. Guo, R. L. DesJarlais, M. A. Chaikin, J. Lattanze, C. Crysler, C. L. Manthey, B. E. Tomczuk, and J. J. Marugan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2679.

2005BML4550 M. W. Embrey, J. S. Wai, T. W. Funk, C. F. Homnick, D. S. Perlow, S. D. Young, J. P. Vacca, D. J. Hazuda, P. J. Felock, K. A. Stillmock, M. V. Witmer, G. Moyer, W. A. Schleif, L. J. Gabryelski, L. Jin, I.-W. Chen, J. D. Ellis, B. K. Wong, J. H. Lin, Y. M. Leonard, N. N. Tsou, and L. Zhuang, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4550.

2005BML4604 C. Manera, L. Betti, T. Cavallini, G. Giannaccini, A. Martinelli, G. Ortore, G. Saccpmanni, L. Trincavelli, T. Tuccinardi, and P. L. Ferrarini, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4604.

2005CRV4314 T. Nakata, *Chem. Rev.*, 2005, **105**, 4314.

2005EJM155 G. Grossi, M. Di Braccio, G. Roma, V. Ballabeni, M. Tognolini, and E. Barocelli, *Eur. J. Med. Chem.*, 2005, **40**, 155.

2005FA135 A. Rampa, A. Bisi, F. Belluti, S. Gobbi, L. Piazzi, P. Valenti, A. Zampiron, A. Caputo, K. Varani, P. A. Borea, and M. Carrara, *Farmaco*, 2005, **60**, 135.

2005JA810 G. B. W. Ligthart, H. Ohkawa, R. P. Sijbesma, and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 810.

2005JA9246 I. Kadota, H. Takamura, H. Nishii, and Y. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 9246.

2005JHC493 M. M. Blanco, C. B. Schapira, G. Levin, and I. A. Perillo, *J. Heterocycl. Chem.*, 2005, **42**, 493.

2005JHC857 I. C. Ivanov, T. N. Glasnov, and D. Heber, *J. Heterocycl. Chem.*, 2005, **42**, 857.

2005JME4628 A. M. Thompson, A. M. Delaney, J. M. Hamby, M. C. Schroeder, T. A. Spoon, S. M. Crean, H. D. H. Showalter, and W. A. Denny, *J. Med. Chem.*, 2005, **48**, 4628.

2005JOC1432 T. Yao and R. C. Larock, *J. Org. Chem.*, 2005, **70**, 1432.

2005JOC5413 F. A. Davis, J. Zhang, Y. Li, H. Xu, and C. DeBrosse, *J. Org. Chem.*, 2005, **70**, 5413.

2005MI240 M. Hirama, *Chem. Rec.*, 2005, **5**, 240.

2005MI1353 G. Sabitha, N. Fatima, E. V. Reddy, and J. S. Yadav, *Adv. Synth. Catal.*, 2005, **347**, 1353.

2005S1397 T.-G. Nam, M. Wijtmans, D. A. Pratt, and N. A. Porter, *Synthesis*, 2005, 1397.

2005SC1641 I. O. Zhuravel, S. M. Kovalenko, A. V. Ivachtchenko, V. P. Chernykh, and P. E. Shinkarenko, *Synth. Commun.*, 2005, **35**, 1641.

2005SL469 S. Inoue, P. Wang, M. Nagao, Y. Hoshino, and K. Honda, *Synlett*, 2005, 469.

2005T8177 R. Carrillo, V. S. Martín, M. López, and T. Martín, *Tetrahedron*, 2005, **61**, 8177.

2005T8589 N. Hiramatsu, N. Takahashi, R. Noyori, and Y. Mori, *Tetrahedron*, 2005, **61**, 8589.

2005TL3719 J.-F. Bonfanti and D. Craig, *Tetrahedron Lett.*, 2005, **46**, 3719.

2005TL3953 V. Y. Vvedensky, Y. V. Ivanov, V. Kysil, C. Williams, S. Tkachenko, A. Kiselov, A. V. Khvat, and A. V. Ivachtchenko, *Tetrahedron Lett.*, 2005, **46**, 3953.

2005TL6655 K. C. Majumdar, P. P. Mukhopadhyay, and A. Biswas, *Tetrahedron Lett.*, 2005, **46**, 6655.

2006JA9352 M. Inoue, K. Miyazaki, Y. Ishihara, A. Tatami, Y. Ohnuma, Y. Kawada, K. Komano, S. Yamashita, N. Lee, and M. Hirama, *J. Am. Chem. Soc.*, 2006, **128**, 9352.

Biographical Sketch



Adrian Dobbs was born in Bromley, Kent (UK), and studied at King's College London, obtaining a B.Sc. in 1992 and a Ph.D. in 1996, working under the guidance of Professor Keith Jones. He then undertook postdoctoral research for two years with Professor Istvan Markó at the Université Catholique de Louvain, at Louvain-la-Neuve, Belgium, under a Royal Society Research Fellowship. On returning to the UK, he joined the process chemistry department of Glaxo SmithKline (Tonbridge, Kent), before taking up his first academic position at the Open University at the end of 1999. He moved to a lectureship in organic chemistry at the University of Exeter in 2001 and remained there until the department was suddenly closed by the university in July 2005. He then moved to his current position as a lecturer in organic chemistry at Queen Mary, University of London. His research interests encompass the development of new synthetic methodologies for the synthesis of complex heterocyclic systems and their application to the total synthesis of natural products. Within this broad area, Lewis acid-promoted cyclizations such as the Prins reaction, radical cyclization reactions, and organosilicon and organofluorine reagents feature prominently.

10.16
Bicyclic 6-6 Systems: Three Heteroatoms 1:2

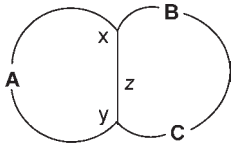
E. S. H. El Ashry and N. Rashed
Alexandria University, Alexandria, Egypt
© 2008 Elsevier Ltd. All rights reserved.

10.16.1 Introduction 760
10.16.2 Theoretical Methods 760
10.16.3 Experimental Structural Methods 762
10.16.3.1 X-Ray Diffraction 762
10.16.3.2 NMR Spectroscopy 764
10.16.4 Thermodynamic Aspects 765
10.16.4.1 Conformation 765
10.16.4.2 Tautomerism 766
10.16.5 Reactivity of Fully Conjugated Rings 767
10.16.5.1 Pyrido[*x*,*y*-*z*]pyridazines 767
10.16.5.2 Pyrido[*x*,*y*-*z*]pyrimidines 768
10.16.5.3 Pyrido[*x*,*y*-*z*]pyrazines 771
10.16.6 Reactivity of Nonconjugated Rings 773
10.16.6.1 Pyrido[*x*,*y*-*z*]pyridazines 773
10.16.6.1.1 Electrophilic attack at ring carbons 773
10.16.6.1.2 Electrophilic attack at ring nitrogens 773
10.16.6.1.3 Nucleophilic attack at ring carbons 773
10.16.6.1.4 Ring contraction 774
10.16.6.2 Pyrido[*x*,*y*-*z*]pyrimidines 775
10.16.6.2.1 Electrophilic attack at ring carbons 775
10.16.6.2.2 Electrophilic attack at ring nitrogens 776
10.16.6.2.3 Nucleophilic attack at ring carbons 779
10.16.6.3 Pyrido[*x*,*y*-*z*]pyrazines 782
10.16.6.3.1 Electrophilic attack at ring carbons 782
10.16.6.3.2 Electrophilic attack at ring nitrogen 783
10.16.6.3.3 Nucleophilic attack at ring carbons 783
10.16.6.4 Pyrido[2,3-*d*][1,3]oxazines 784
10.16.6.5 Pyrano(thiopyrano)[*x*,*y*-*z*]diazines 784
10.16.6.5.1 Pyrano[3,2-*c*]pyridazines 784
10.16.6.5.2 Thiopyrano[2,3-*d*]pyrimidines 785
10.16.6.6 Pyrano[*x*,*y*-*z*][1,*n*]dioxanes 785
10.16.6.6.1 Pyrano[4,3-*d*][1,3]dioxanes 785
10.16.6.6.2 Pyrano[2,3-*b*][1,4]dioxanes 785
10.16.7 Reactivity of Substituents 786
10.16.7.1 Pyrido[*x*,*y*-*z*]diazines 786
10.16.7.1.1 Electrophilic attack 786
10.16.7.1.2 Nucleophilic attack 787
10.16.8 Synthesis 788
10.16.8.1 Synthesis of Pyrido[*x*,*y*-*z*]pyridazines 788
10.16.8.1.1 Synthesis of pyrido[*x*,*y*-*c*]pyridazines 788
10.16.8.1.2 Synthesis of pyrido[*x*,*y*-*d*]pyridazines 788

10.16.8.2 Synthesis of Pyrido[*x*,*y*-*z*]pyrimidines 795
10.16.8.2.1 Synthesis of pyrido[2,3-*d*] and [3,2-*d*]pyrimidines 795
10.16.8.2.2 Synthesis of pyrido[3,4-*d*] and [4,3-*d*]pyrimidines 824
10.16.8.3 Synthesis of Pyrido[*x*,*y*-*z*]pyrazines 827
10.16.8.3.1 Synthesis of pyrido[2,3-*b*]pyrazines 827
10.16.8.3.2 Synthesis of pyrido[3,4-*b*]pyrazines 832
10.16.8.3.3 Special compounds 833
10.16.8.4 Synthesis of Pyrido[*x*,*y*-*z*][1,*n*]oxazines 833
10.16.8.5 Synthesis of Pyrano and Thiopyrano[*x*,*y*-*z*][1,*n*]diazines 834
10.16.8.5.1 Synthesis of pyrano and thiopyrano[*x*,*y*-*z*]pyridazines 834
10.16.8.5.2 Synthesis of pyrano and thiopyrano [*x*,*y*-*z*]pyrimidines 836
10.16.8.6 Synthesis of Pyrano[*x*,*y*-*z*][1,*n*]dioxane and -Dithiane 837
10.16.9 Important Compounds and Applications 838
References 839

10.16.1 Introduction

This chapter covers advances in the chemistry of bicyclic 6-6 systems containing three heteroatoms with ratio 1:2, which updates Chapter 16 in Volume 7 in CHEC-II(1996) <1996CHEC-II(7)561>. In general, it includes references until the end of 2005 on those fused heterocycles with two six-membered rings having either nitrogen, oxygen, or sulfur as heteroatoms. Compounds with bridge heteroatoms are not included herein. Consequently, a general presentation for these heterocycles can be shown by **1–4**, which are shown in **Figure 1**, whose A, B, and C represent the heteroatoms. The relative locations of the heteroatoms in the two rings have been clearly identified from the site of fusion of the ring having one heteroatom, denoted by the atom labels *x* and *y*, onto the side of the ring, having the two heteroatoms, that is denoted by the letter *z*. The arrangement of the chapter into sections and subsections is dependent on the general instructions for the series and the compounds with similar heteroatoms, followed by analogues with different ones.

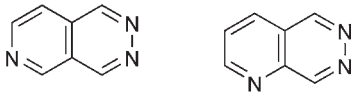


1 A = B = C
2 A = B ≠ C
3 A ≠ B = C
4 A ≠ B ≠ C
A, B, C = N, O or S

Figure 1

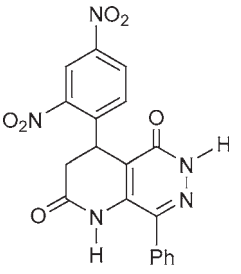
10.16.2 Theoretical Methods

The slightly lower lowest unoccupied molecular orbital (LUMO) energy of pyrido[3,4-*d*]pyridazine **5** compared to its isomer [2,3-*d*] **6**, calculated by the AM1 method <1985JA3902>, explained the shorter time required for the pyrido[3,4-*d*]-pyridazine to complete the [4+2] cycloaddition reaction with cyclic enamines of different ring sizes <1995M211, 2001ARK21>.



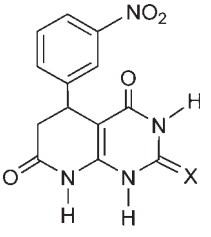
LUMO energy	–1.215 eV	–1.122 eV
	5	**6**

Semi-empirical molecular orbital calculations (AM1) of 4-(2,4-dinitrophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine **7** indicated the presence of two favored conformations. In both conformers, the pyrid-2(1*H*)-one ring has a twisted boat conformation, the pyridazinone ring is essentially planar, and the phenyl group is orthogonal to this plane. In the first conformation, the aryl constituent at C-4 lies in the pseudoaxial position which is in agreement with the X-ray analysis, while in the second the aryl group occupies the pseudoequatorial one. The calculated heats of formation for compound **7** indicated that the difference in stability between the two favored conformations is approximately 2 kcal mol^{-1} <2000T2473>.



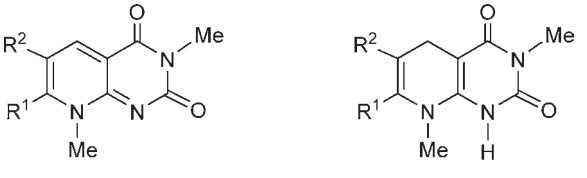
7

Semi-empirical calculations for 5-(3-nitrophenyl)-2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-*d*]pyrimidine **8** and its 2-thioxo derivative **9** using the AM1 method indicated that they have the same favored conformations. In both, the pyridone system exhibits a twisted conformation with the phenyl ring bisecting the pyridone moiety by the dihedral angle (108.85° and 113.55°, respectively). The charge density values for the olefinic carbons C-4a and C-8a (−0.323 to −0.305 and 0.268 to 0.248, respectively) confirm the observed electronic push–pull effect in the ^{13}C nuclear magnetic resonance (NMR) data where C-4a appeared at higher field at δ_c 88.6 for **8** and 93.2 ppm for **9**, while their C-8a appeared at lower field at δ_c 144.8 and 148.0 ppm <1996JHC45>.



8: X = O
9: X = S

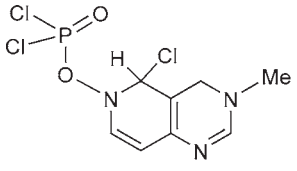
The correlation of the reduction potential of pyrido[2,3-*d*]pyrimidine derivatives and their reduction with $Na_2S_2O_4$ indicated that compounds having less negative reduction potentials (−1.43 to −1.62 V) could be reduced by $Na_2S_2O_4$, while those having more negative reduction potentials (−1.84 to −1.94 V) could not be reduced <1986T961, 2001JOC1590>. Thus, compounds **10** having reduction potentials from −1.67 to −1.76 V were reduced by $Na_2S_2O_4$ to the corresponding 1,5-dihydro derivatives **11** <2004H(63)1393>.



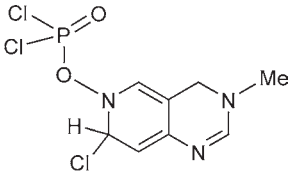
10 **11**

R^1 = Me, Ph
R^2 = H, CO_2Et, CONHCH(Me)Ph

Quantum-mechanical calculations for the 5-chloro and 7-chloro, intermediate model compounds **12** and **13** showed a significantly lower energy for **12** than **13**. The calculated values for the energy difference (**13** – **12**) at different levels of theory are 38 kJ mol^{-1} (RHF/6-31G*), 28 kJ mol^{-1} (B3LYP/6-31G*), and 43 kJ mol^{-1} (MP2/6-31G*) (RHF = restricted Hartree–Fock) <B-1982MI1, B-2001MI1, 2004TL3737>.

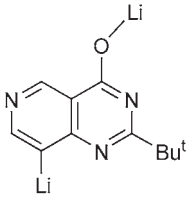


12



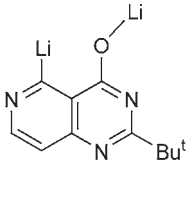
13

The heats of formation of the lithiated derivatives **14** and **15** calculated by the semi-empirical Li/PM3 method indicated that the C-5-lithiated intermediate **15** is the more stable isomer. This was in agreement with the result obtained from their reaction with various electrophiles to give regioselectively the respective thermodynamically preferred 5-substituted pyridopyrimidinone at higher temperature and longer reaction time, while the second 8-substituted isomer needed milder conditions <2004T4107>.



14

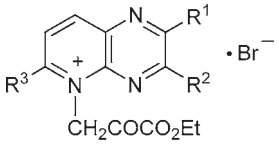
ΔH_f = +3.21 kcal mol^{-1}



15

ΔH_f = –4.18 kcal mol^{-1}

The proton affinities of the pyrido[2,3-*b*]pyrazine system for N-1 = 205.56, N-4 = 212.02, and N-5 = 216.32 kcal mol^{-1} showed that the most basic site is at N-5, which is in agreement with the formation of the quaternary salt derivatives **16**–**19** as intermediates for the synthesis of imidazopyridopyrazine fused rings <1994H(38)283, 1991JCC675>.



16: $R^1 = R^2 = R^3 = H$
17: R^1 = Me; $R^2 = R^3 = H$
18: $R^1 = R^3 = H$; R^2 = Me
19: $R^1 = R^2 = H$; R^3 = Me

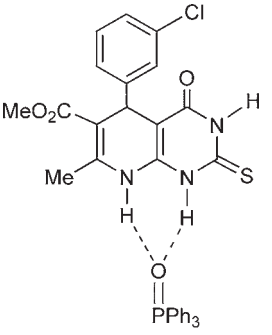
10.16.3 Experimental Structural Methods

10.16.3.1 X-Ray Diffraction

X-Ray crystallographic analysis of 4-(2,4-dinitrophenyl)-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazine **7** is in agreement with the semi-empirical molecular orbital calculation (AM1) <2000T2473>.

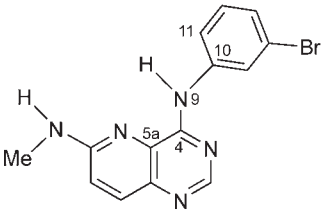
The X-ray crystallographic analysis of methyl 5-(3-chlorophenyl)-7-methyl-4-oxo-2-thioxo-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylate **20** in the presence of triphenylphosphine oxide showed molecular complexes

formed by one molecule of triphenylphosphine oxide linked to one molecule of **20** <1994T8085>. The bonding takes place through the oxygen atom of the triphenylphosphine oxide and the N-1 and N-8 atoms of **20** via two hydrogen bonds. In the solid state of **20**, the heterocyclic moiety is nearly planar with a dihedral angle between the two rings of 3.3°, although the dihydropyridine ring confers a flattened boat conformation with both N-8 and C-5 atoms slightly above the main plane of the molecule. The aryl ring is in a pseudoaxial position and almost orthogonal to the main plane of the bicyclic system (93.2°). The *meta*-chloro substituent is in an *anti*-periplanar (*ap*) orientation with respect to H-5 and points toward the dihydropyridine ring. Many X-ray structural analyses of dihydropyridines show that the *syn*-periplanar (*sp*) form is favored in the crystalline state, with a few exceptions, and the *ap*-conformation has been postulated in less active bicyclic dihydropyridines <1991AGE1559>. The preference for the *ap*-form in derivative **20** may be a consequence of the co-crystallization with triphenylphosphine oxide, which forces the *ap*-conformation over the *sp*, although an intrinsic preference for the *ap*-form in the solid state of compound **20** cannot be ruled out. The ester group lies above the plane of the bicyclic system (18.79°) with the carbonyl group in the *trans*-conformation with respect to the double bond of the dihydropyridine ring. Finally, the 4-oxo and 2-thioxo forms are also favored in the pyrimidine ring rather than the corresponding tautomeric forms <1994T8085>.

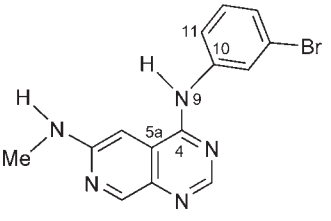


20 : Ph_3PO
1 : 1

X-Ray crystal structures for the two isomers pyrido[3,2-*d*]- and pyrido[3,4-*d*]pyrimidine derivatives **21** and **22** showed that the C(5a)–C(4) bond in **22** is lengthened to 1.46 Å, compared to 1.43 Å in **21**, to relieve the nonbonded interaction between C-5 and N-9 protons. The length of the C(4)–N(9) bonds in both analogues is quite short (1.34 and 1.35 Å for **21** and **22**, respectively), suggesting a considerable degree of conjugation and a consequent resistance to torsional twisting to relieve that nonbonded interaction. This is supported by the C(5a)–C(4)–N(9)–C(10) torsion angle for **22**, which is close to 180°, indicating an essentially coplanar geometry. The torsion angle for C(4)–N(9)–C(10)–C(11) of **22** is nearly 30°, indicating an out-of-plane rotation of the phenyl group, whereas in **21** the corresponding torsion angle is 1.5°. The bromine atom in **22** is *anti* with respect to the methylamino substituent, which in turn is *anti* to the aniline ring, whereas in **21** the conformation is *syn* <1997JME1820>.



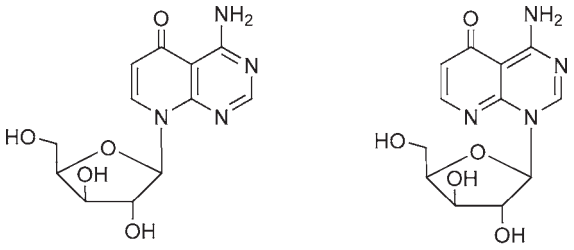
21
[3,2-*d*]



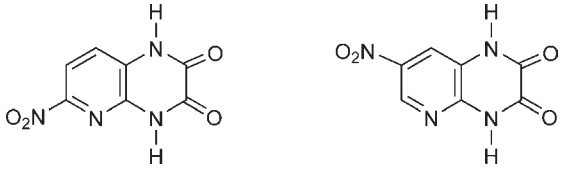
22
[3,4-*d*]

Upon formation of the nucleosides from 5-aminopyrido[2,3-*d*]pyrimidin-5(8*H*)-one, the major isomeric nucleoside product was found to be the 4-amino-5-oxo-8-(β-D-xylofuranosyl)pyrido[2,3-*d*]pyrimidine and the minor is the 1-xylosyl isomer as proved by X-ray crystallographic studies. They showed that the bond length of C(1′)–N(8) is

1.497 Å and the torsion angle of O(4′)–C(1′)–N(8)–C(9) is −171.38°, which indicates an *anti*-orientation of the pyrido[2,3-*d*]pyrimidine base. The pseudorotation phase angle *p* is 23.6° <2000JME3704>.

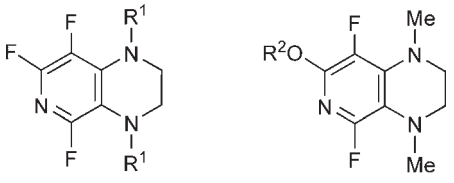


X-Ray crystallographic studies of the 6-nitropyrido[2,3-*b*]pyrazine-2,3(1*H*,4*H*)-dione **23** showed that the nitro group and the aromatic ring exhibited a dihedral angle of 130°, while those of the isomeric structure **24** were a nearly planar 179°. The conjugation between the nitro group and aromatic ring constrains the conformation of **24** to be coplanar, whereas Coulombic repulsion between the lone pair of the pyridine nitrogen atom and the nitro group oxygen atom led to the twisted conformation of **23** <1996JME1331>.



23 **24**

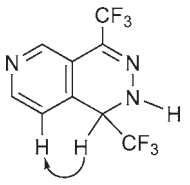
The X-ray crystallography of tetrahydropyrido[3,4-*b*]pyrazines **25** and **26** showed some common geometrical features: the N-1 atom is planar, the N-4 atom has a pyramidal configuration of the bonds, and the N(1)–C(8a) bonds (mean 1.367 Å) are significantly shorter than the N(4)–C(4a) bonds (mean 1.414 Å). In molecules **25**, the N(6)–C(7) bond is shorter than N(6)–C(5), whereas in molecules **26** this bond distribution has been reversed, indicating the involvement of the oxygen atoms in the delocalization of the charge <2005JOC7208>.



25: R^1 = Me, Bn **26**: R^2 = Me, Et

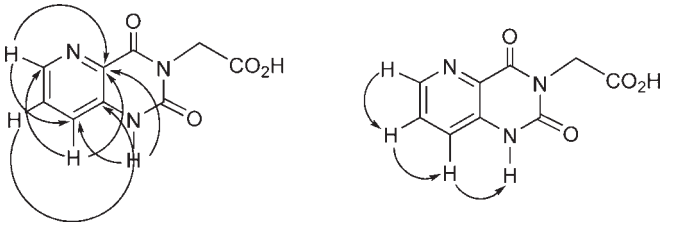
10.16.3.2 NMR Spectroscopy

The isolated dihydropyrido[3,4-*d*]pyridazine intermediate obtained during the dehydrogenation of its 5,6,7,8-tetrahydro analogue was assigned as the 1,2-dihydro structure **27** from its ^{1}H NMR spectrum, where one of the two hydrogen atoms could be easily identified as an NH (by D_2O exchange) while the other hydrogen appeared as a quartet at $\delta = 4.94$ ppm with a coupling constant $^3J_{H-F} = 7.6$ Hz which was assigned to a CH–CF_3. Irradiation of the signal at δ 4.94 ppm led to significant nuclear Overhauser enhancement (NOE) for the doublet of H-8 at δ 7.26 ppm <1994H(38)1845>.

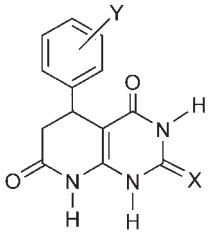


27

The heteronuclear multiple bond correlation (HMBC) NMR spectrum of 3-carboxymethyl-1,2,3,4-tetrahydro[3,2-*d*]-pyrimidine-2,4-dione showed long-range correlations between the NH proton and C-8 signal, the NH proton and C-4a signal, the H-6 and C-8 signals, the H-6 and C-4a signals, the H-8 and C-4a signals, the H-8 and C-6 signals, and the H-7 and C-8a signals <2003TL2745>. The NOE spectrum resulting from irradiation of the NH proton and H-6 provided signal enhancement of H-8 and H-7, respectively, while low-power irradiation of H-8 provided signal enhancement of the NH proton and H-7 <2003TL2745>.



In the ^{13}C NMR spectra, a push–pull effect of octahydropyrido[2,3-*d*]pyrimidine **28** was observed in the olefinic C-4a and C-8a due to the electronic behavior of their substituents. Thus, C-4a appears at low δ values (88–93 ppm) and C-8a gives peaks at lower field (146.0–148.5 ppm) <1996JHC45>.



28

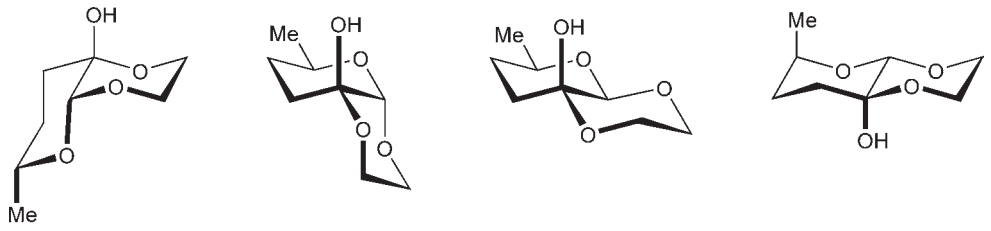
X = O, S

Y = 2-NO_2, 3-NO_2, 2-Cl

10.16.4 Thermodynamic Aspects

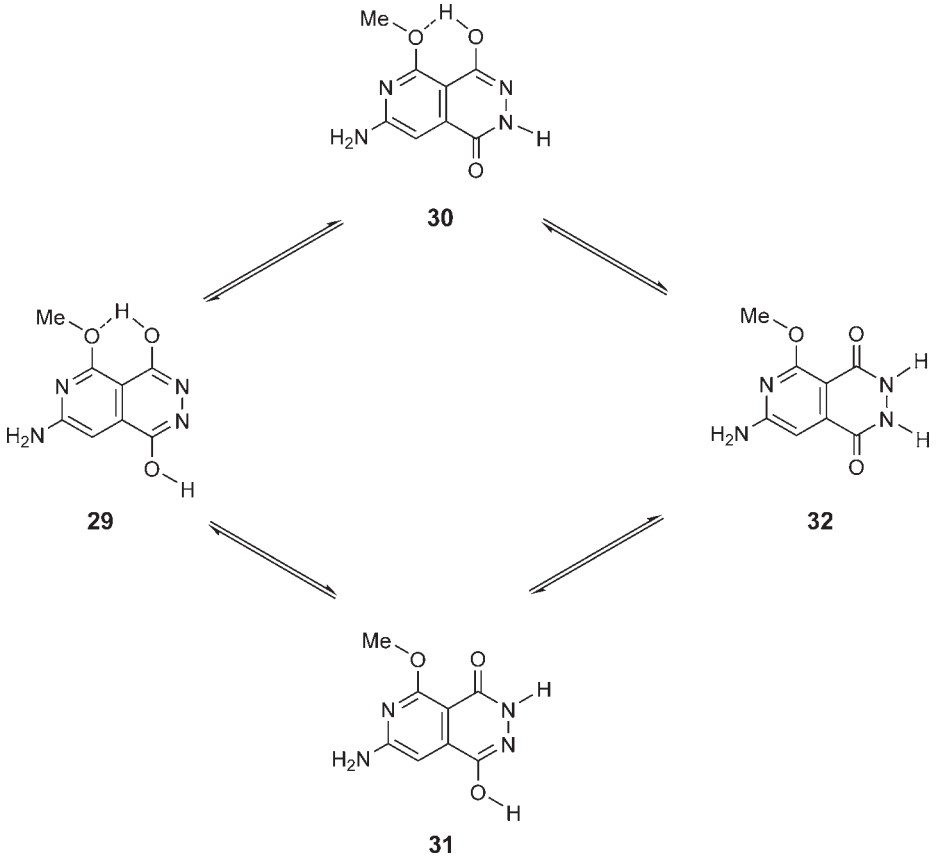
10.16.4.1 Conformation

The force field calculations of the enthalpies ($\Delta\Delta H$) of the four hemiketals of 6-methylpyrano[2,3-*b*]dioxane-8a-ols clearly indicate that the β-*cis*-fused link is the most favored, followed by the α-*cis*- and β-*trans*-isomers, while the α-*trans*-compound, due to the pyranoid ring being forced into $^1C_4$ conformation with an axial methyl group, is the least likely to be formed <1991MI235>.



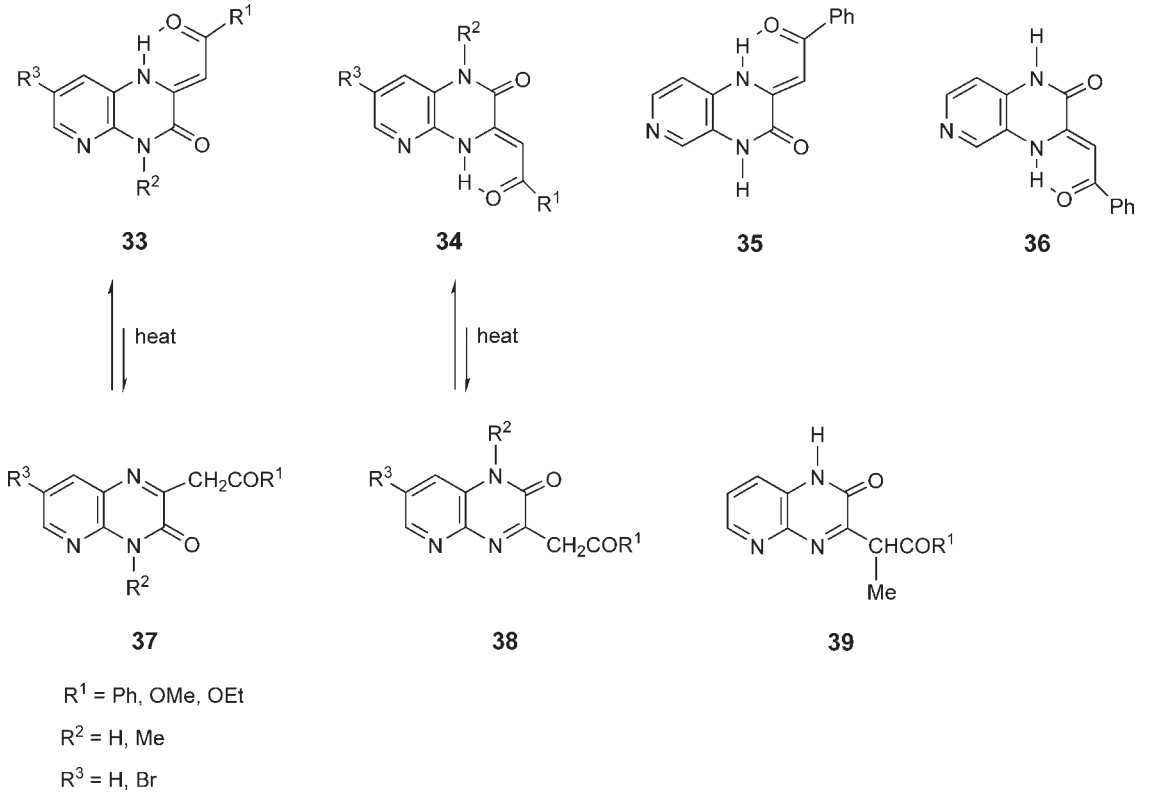
10.16.4.2 Tautomerism

7-Amino-5-methoxypyrido[3,4-*d*]pyridazine-1,4-(2*H*,3*H*)-dione could exist in different tautomeric forms **29–31** besides the dilactam form **32**. The forms **29** and **30** are the preferred tautomers based on the chemical shift for the hydroxyl group which is consistent with the presence of intramolecular hydrogen bonding that could stabilize such lactim forms <1997T8225>.



Pyrido[2,3-*b*]- and [3,4-*b*]pyrazinone derivatives having the alkoxycarbonylmethylene or phenacylidene groups at C-2 or C-3 exist predominantly in the enamine forms **33–36**. The enamine structures were supported by the signals for =CH– instead of $–CH_2–$ in their ^1H NMR spectra, as well as the appearance of those of the hydrogen-bonded –NH– at lower field <1994JHC1065, 1995JHC1071>. The imine–enamine equilibrium is influenced by elevated temperature, and it gradually shifts from enamine forms **33** and **34** to the imine forms **37** and **38**, respectively. The isomeric enamine **34** shows less temperature effect than **33** due to the small steric compression between the *peri*-hydrogen atom at the 8-position in **33** and the hydrogen bond which destabilizes the enamine form, whereas the hydrogen bond in **34** has no

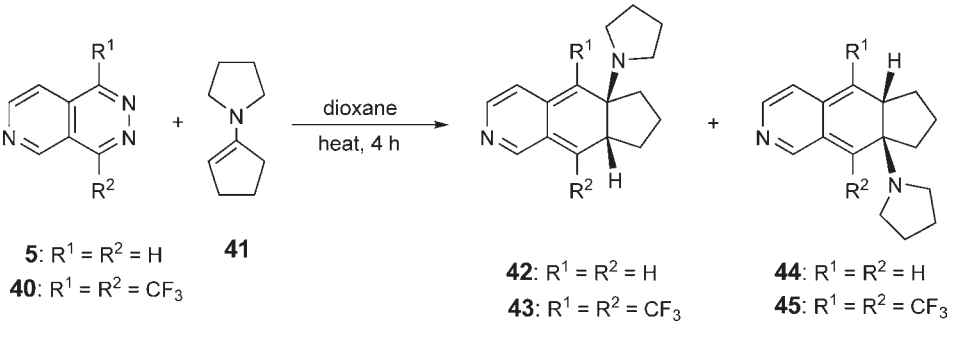
steric interaction with the neighboring nitrogen lone pair. The enamines **35** and **36** show no temperature effect. 3-(1-Benzoyl/1-ethoxycarbonyl)ethyl-1*H*-pyrido[2,3-*b*]pyrazin-2-ones **39** exist only in the imine form due to the steric effect of the methyl substituent <1997JHC773>.



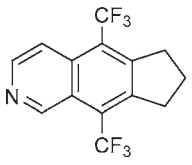
10.16.5 Reactivity of Fully Conjugated Rings

10.16.5.1 Pyrido[*x*,*y*-*z*]pyridazines

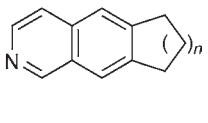
Pyrido[3,4-*d*]pyridazine **5** as an electron-deficient azadiene in a [4+2] cycloaddition reaction using 1-pyrrolidino-1-cyclopentene **41** as the dienophile in boiling dioxane under an argon atmosphere gave a 7:1 mixture of the two isomeric cycloadducts **42** and **44**, respectively, together with a small amount of isoquinoline **47**. The reaction was completed after 4 h of refluxing, compared to 20 h in the case of pyrido[2,3-*d*]pyridazine. Six-, seven-, and eight-membered cyclic enamines gave directly the cycloalkene-fused isoquinolines **48** <1995M211, 2001ARK21>. The reaction of the 1,4-bis(trifluoromethyl) derivative **40** under the same reaction conditions for 1 h furnished the cyclopentene-fused isoquinoline **46**, according to ^{1}H NMR spectroscopy and mass spectrometry as well as elemental analysis, via 1,2-elimination of the pyrrolidine moiety from the two regioisomeric intermediates **43** and **45** (Equation 1) <1994H(38)1845>.



(1)

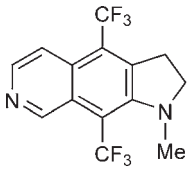


46: 48%

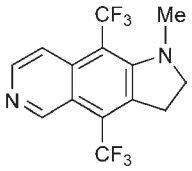


47: n = 1
48: n = 2–4

The pyrido[3,4-*d*]pyridazine **40** was also reacted with 1-methyl-2-methylthio-2-pyrroline, at room temperature within 30 min, to give the two isomeric pyrroline-annulated isoquinolines **49** and **50**, in an overall yield of 65% with ratio 1:2.3, via elimination of nitrogen and methanethiol from the initially formed cycloadducts <1994H(38)1845>.



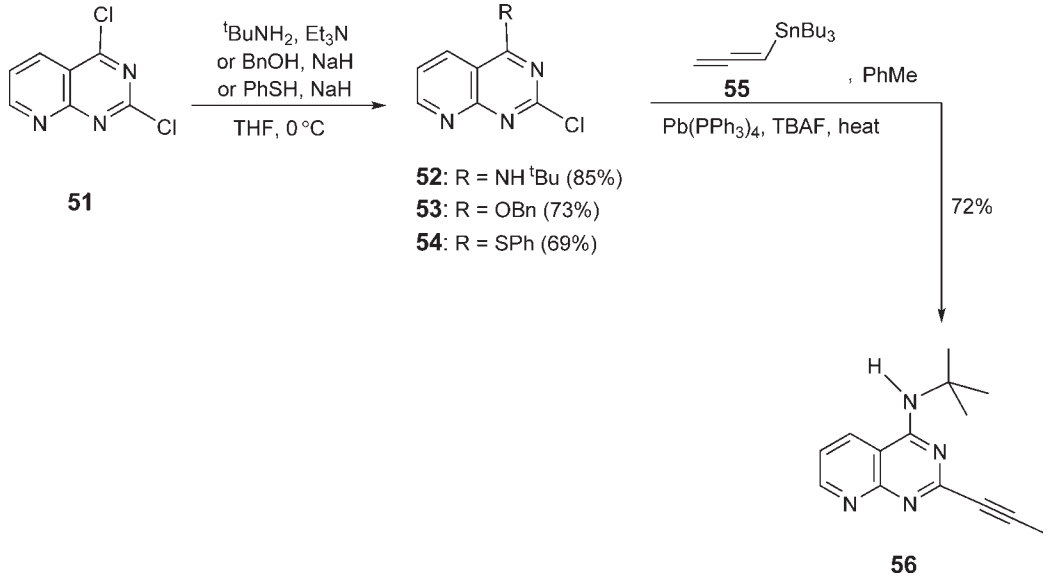
49



50

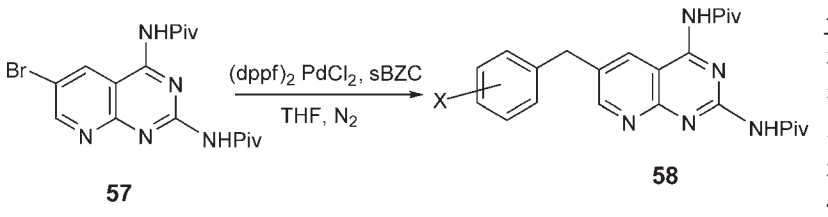
10.16.5.2 Pyrido[*x*,*y*-*z*]pyrimidines

The reactivity of C-4 in the pyrimidine ring in 4,6-dihalogenopyridopyrimidine toward nucleophilic substitution reaction was noted <1997USP5654307, 1999WO9935146>. 2,4-Dichloropyrido[2,3-*d*]pyrimidine **51** was easily substituted with higher selectivity at position 4 than position 2 to form the 4-substituted derivatives **52–54** upon reaction with *tert*-butylamine, benzyl alcohol, or thiophenol as nucleophiles in the presence of a base in tetrahydrofuran (THF). The introduction of the *tert*-butylamino group required Et_3N rather than NaH as a base. The 2-alkyne derivative **56** was obtained using palladium-promoted cross-coupling of **52** with allenyl tin derivative **55** via thermal isomerization of the coupling intermediate (**Scheme 1**) <2005TL5851>.



Scheme 1

6-(5-Indanylamino)pyrido[2,3-*d*]pyrimidine was obtained as its hydrochloride salt from reaction of 6-chloropyrido[2,3-*d*]-pyrimidine with 5-aminoindane <1997WO9718212>. The 6-(substituted benzyl)pyrido[2,3-*d*]pyrimidines **58** were prepared via condensation of 2,4-dipivaloylamino-6-bromo derivative **57** with substituted benzylzinc chloride (sBZC) in the presence of a catalytic amount of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)·CH_2Cl_2 [$(dppf)_2PdCl_2 \cdot CH_2Cl_2$] in THF under nitrogen (Equation 2) <2003BMC59>.

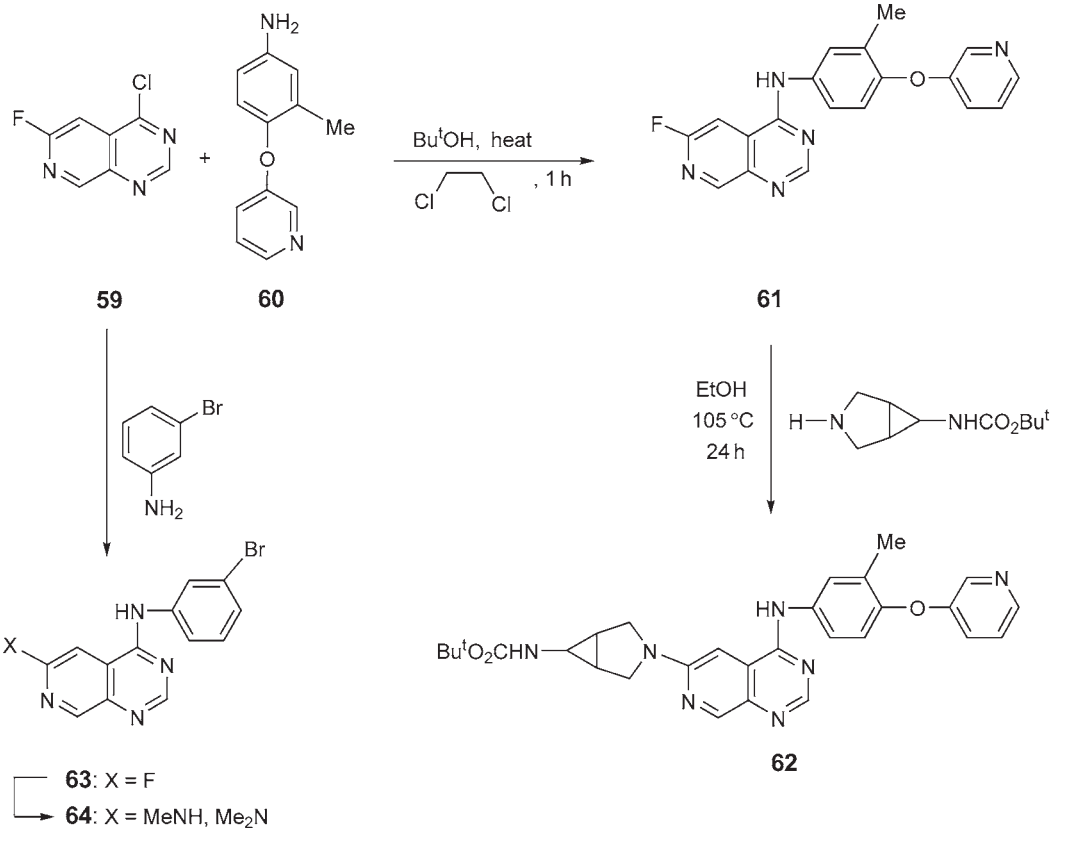


57 58

X	*Yield* (%)
2,5-$(OMe)_2$	48
3,4-$(OMe)_2$	58
3,5-$(OMe)_2$	56
2-Cl	54
4-F	76

(2)

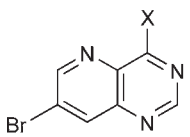
Reaction of 4-chloro-6-fluoropyrido[3,4-*d*]pyrimidine **59** with [3-methyl-4-(pyridin-3-yloxy)phenyl]amine **60**, followed by coupling the formed amine **61** with (3-azabicyclo[3.1.0]hex-6-yl)carbamic acid *tert*-butyl ester, afforded the substituted derivative **62** <2002EPP1249451>. Compound **59** was also reacted with 3-bromoaniline to give the 4-anilino derivative **63** that upon treatment with either methyl- or dimethylamine gave the corresponding 4,6-diamino derivatives **64** (**Scheme 2**) <1997WO9726259, 1995WO9519774>.



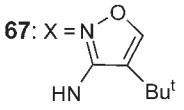
Scheme 2

Similar reactivity was observed upon halogenation of 7-bromopyrido[3,2-*d*]pyrimidine **65** with $POCl_3$ and subsequent amination of the resulting 4-chloro derivative **66** with 3-amino-4-(*tert*-butyl)isoxazole to afford the

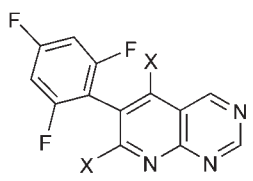
isomeric secondary amine **67** <2005WO2005042498>. Halogenation of 6-(2,4,6-trifluorophenyl)pyrido-[2,3-*d*]pyrimidine-5,7-diol **68** with $POCl_3$ and PCl_5 at 130 °C gave the respective 5,7-dichloro derivative **69** <2005WO200501000>. The amino derivative **70** was prepared via amination of 2-methanesulfinyl-6,7-diphenylpyrido[2,3-*d*]pyrimidine with 4-(2-diethylaminoethoxy)aniline in the presence of toluene at reflux for 14 h <2002WO2002090360>.



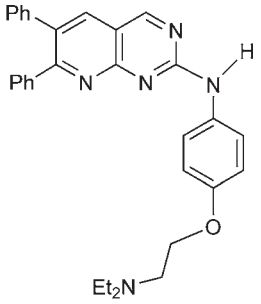
65: X = H
66: X = Cl



67: X =

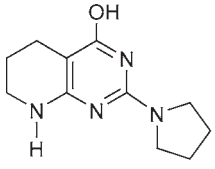


68: X = OH
69: X = Cl (95%)

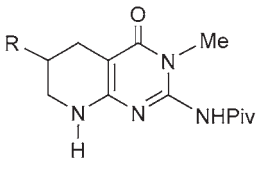


70

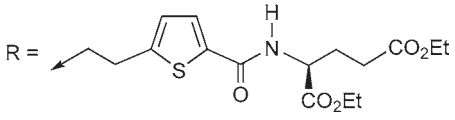
Catalytic hydrogenation of the pyridine ring of 4-hydroxy-2-pyrrolidinopyrido[2,3-*d*]pyrimidine in the presence of H_2/PtO_2 in HCl gave **71**. 2-(Pivaloylamino)-6-substituted pyrido[2,3-*d*]pyrimidin-4(3*H*)-one gave the 5,6,7,8-tetrahydro derivative **72** via similar catalytic reduction conditions in the presence of trifluoroacetic acid (TFA) at 800 psi hydrogen pressure for 40 h <1996WO9603406>.



71
90%

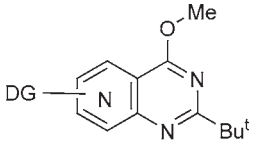


72

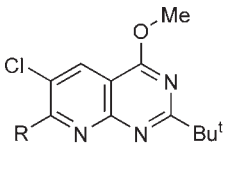


R =

Functionalization by lithiation of the pyridine moiety of 2-*tert*-butyl-4-methoxypyridopyrimidine derivatives has been examined. Several parameters may be taken into account to explain the regioselectivity of metalation: the *peri*-directing nitrogen atom N-1 of the pyrimidine moiety, the α-directing effect of the nitrogen atom of the pyridine moiety, and the *ortho*-directing substituent such as chlorine or a methoxy group. It has been noted that their effects were in the order *ortho*-effect of substituent > *peri*-effect of pyrimidine N-1 > α-effect of pyridine nitrogen > *peri*-effect of OMe group <2004T4107, 2004T6353>. Thus, direct lithiation of 2-*tert*-butyl-4-methoxypyridopyrimidine derivatives **73–76** was carried out using 4 equiv of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) at −78 °C in THF for 1 h followed by addition of the electrophile (4 equiv) to give the substituted pyridopyrimidine products **77–80**, respectively <2004T6353>.

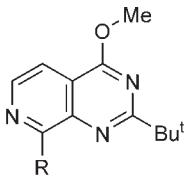


DG = Directing group



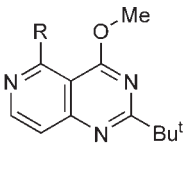
73: R = H
77: R = SPh

R	*Yield (%)*
MeCH(OH)	93
PhCH(OH)	76
PhS	94
Bu_3Sn	60
I	86



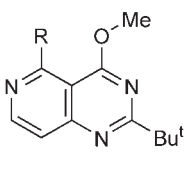
74: R = H
78

R	*Yield (%)*
MeCH(OH)	68
PhCH(OH)	69
PhS	65
Bu_3Sn	75
I	76



75: R = H
79

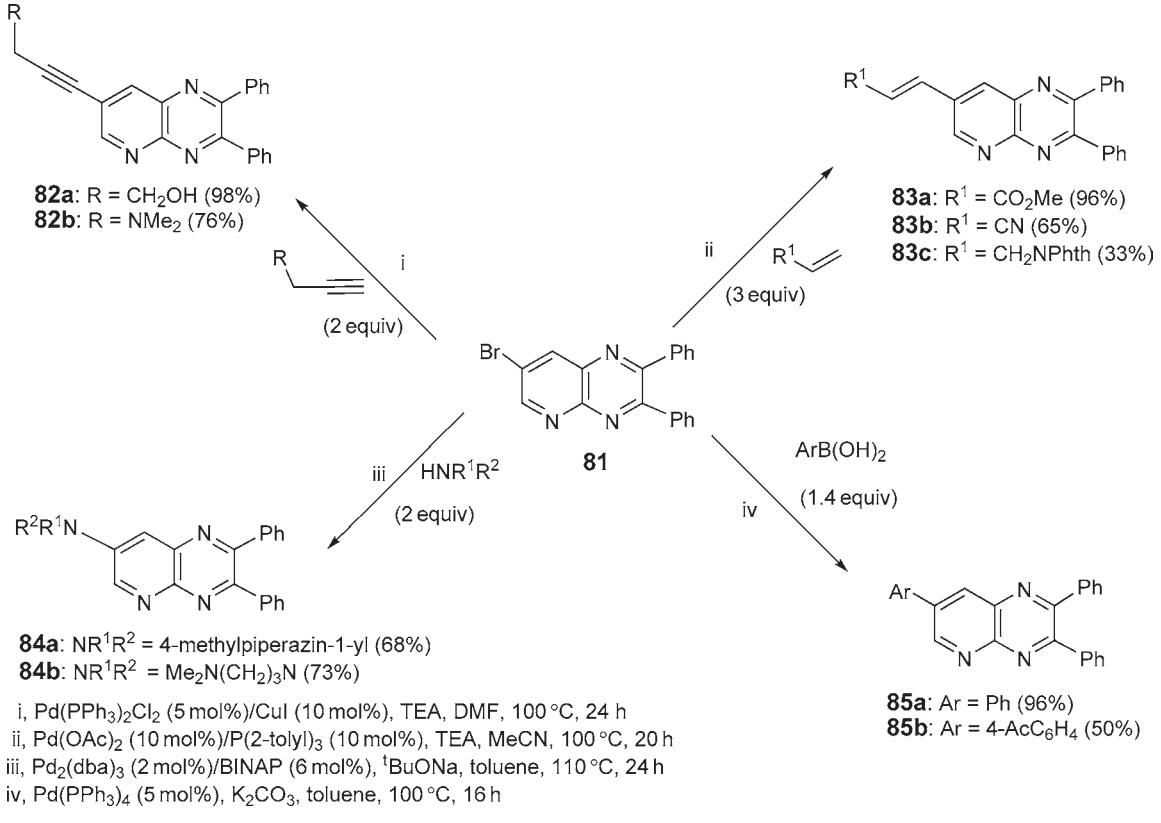
R	*Yield (%)*
MeCH(OH)	28
PhCH(OH)	31
PhS	27
Bu_3Sn	21
I	24



76: R = H
80

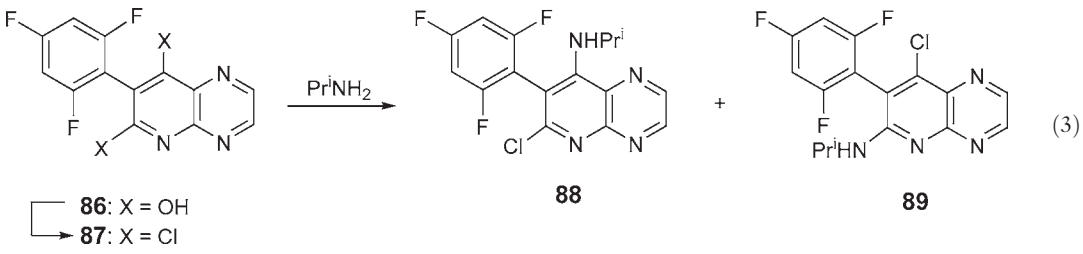
10.16.5.3 Pyrido[*x*,*y*-*z*]pyrazines

Several uncatalyzed nucleophilic substitution reactions on 7-bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine **81** have been reported <1976BSF251, 1992IJB92>, but such reactions provide mixtures of the regioisomeric products due to an elimination/addition mechanism where addition often competes with substitution to give low yields of the products; moreover, palladium-catalyzed Sonogashira, Heck, Buchwald–Hartwig, and Suzuki cross-couplings of **81** with acetylenes, olefins, secondary amines, and areneboronic acids gave the corresponding 7-substituted-2,3-diphenylpyrido[2,3-*b*]pyrazines **82–85**, respectively, as single products in good yields (**Scheme 3**) <2005S1345>.

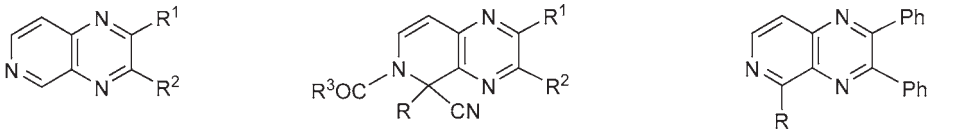


Scheme 3

Chlorination of the dihydroxypyridopyrazine derivative **86** followed by amination of the resulting 6,8-dichloro derivative **87** with isopropylamine afforded a mixture of aminochloro isomers **88** and **89** (Equation 3) <2004WO2004056825>.



2,3-Disubstituted pyrido[3,4-*b*]pyrazines **90** were reacted with equivalent amounts of trimethylsilyl cyanide and acyl chlorides or chloroformates in the presence of a catalytic amount of $AlCl_3$ in CH_2Cl_2 to give the Reissert compounds **91**, where the reactions occurred across the C-5,N-6 bond <1994JHC819>. On the other hand, treatment of **90** ($R^1 = R^2 = Ph$) with benzenesulfonyl chloride and trimethylsilyl cyanide in the presence of a catalytic amount of $AlCl_3$ gave 5-cyanopyridopyrazine **93**. Reaction of H-5 in **91** ($R^1 = R^2 = Ph$) with NaH in the presence of iodomethane or benzyl bromide gave the Reissert compound **92** or the alkylated pyridopyrazine derivative **94** depending upon the nature of R^3; when $R^3 = Ph$, the product was **94**, whereas $R^3 = OEt$ gave **92** <1994JHC819>.

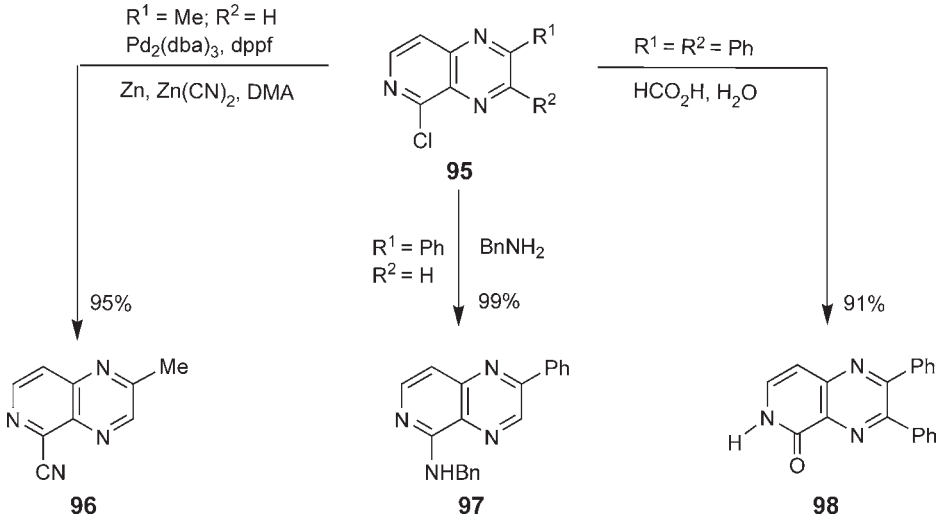


90: R^1, R^2 = H, Ph

91: R = H; R^3 = Ph, OEt (35–78%)
92: R = Me (89%), Bn (95%); R^3 = OEt

93: R = CN (50%)
94: R = Me (46%), Bn (27%)

Pd-catalyzed cyanation of 2-methylpyrido[3,4-*b*]pyrazine **95** with $Zn(CN)_2$ in the presence of $Pd_2(dba)_3$ and dppf gave the 5-cyano derivative **96** (dba = dibenzylideneacetone). Amination, without using any base, with benzylamine converted **95** into adduct **97** in excellent yield. Hydrolysis of **95** in aqueous formic acid provided the 5-oxo derivative **98** (**Scheme 4**) <2003H(60)925>.



Scheme 4

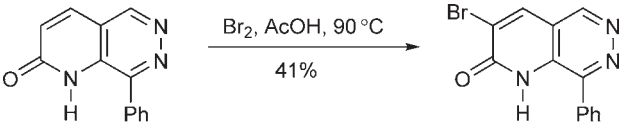
Pyrido[2,3-*b*]pyrazine and its 2-, 3-, or 6-methyl derivatives were reacted with ethyl bromopyruvate in dimethylformamide (DMF) to give 5-ethoxalylmethylpyrido[2,3-*b*]pyrazinium bromides **16–19**, indicating the preferential nucleophilicity at N-5. This is in agreement with the theoretical values of proton affinities of the pyrido[2,3-*b*]pyrazine ring system <1991JCC675, 1994H(38)283>.

10.16.6 Reactivity of Nonconjugated Rings

10.16.6.1 Pyrido[*x*,*y*-*z*]pyridazines

10.16.6.1.1 Electrophilic attack at ring carbons

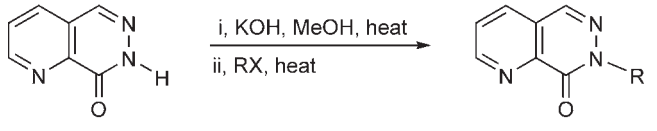
Bromination of 8-phenylpyrido[2,3-*d*]pyridazin-2-(1*H*)-one **99** using Br_2 in AcOH was found to be sluggish, requiring several days of heating to achieve a modest yield of the corresponding 3-bromo derivative **100** (Equation 4) <2006TL2257>.



99 **100** (4)

10.16.6.1.2 Electrophilic attack at ring nitrogens

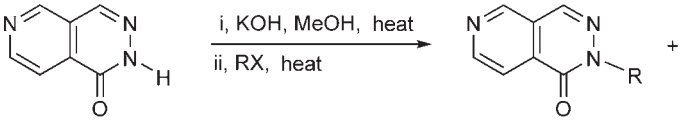
Alkylation of pyrido[2,3-*d*]pyridazin-8(7*H*)-one **101** with alkyl halides in the presence of KOH in MeOH gave the *N*-alkyl derivatives **102** (Equation 5) <1996T3261>.



R	*Yield (%)*
Me	55
	30
Bn	28

101 **102** (5)

Similarly, alkylation of the potassium salt of pyrido[3,4-*d*]pyridazin-1(2*H*)-one **103** with methyl iodide or allyl bromide gave the N-alkylated derivatives **104** and **105**, respectively. On the other hand, benzylation of **103** with benzyl bromide afforded a mixture of *N*-benzyl **106** and *O*-benzyl derivatives **107** (Equation 6) <1996T3261>.



103

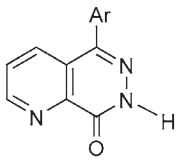
104: R = Me (61%)
105: R =  (59%)
106: R = Bn (38%)

107: R = Bn (17%)

(6)

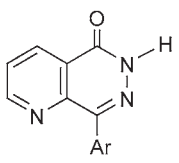
10.16.6.1.3 Nucleophilic attack at ring carbons

Chlorination of pyrido[2,3-*d*]pyridazines **108** and **109** with $POCl_3$ in pyridine at 110 °C afforded the respective 8- and 5-chloro derivatives **110** and **112**, which upon reaction with hydrazine hydrate in boiling ethanol gave the hydrazine derivatives **111** and **113**, respectively <1998SC2871>.



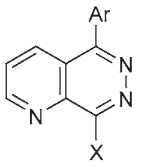
108

Ar = C_6H_5, 4-MeC_6H_4



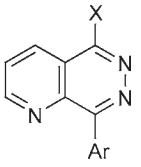
109

Ar = C_6H_5, 4-MeC_6H_4



110: X = Cl (73–78%)

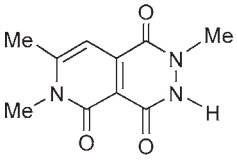
111: X = $NHNH_2$ (80–86%)



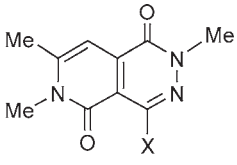
112: X = Cl (63–73%)

113: X = $NHNH_2$ (70–74%)

Under the same conditions, the trioxo analogue **114** gave the chloro derivative **115**, which upon boiling in anhydrous xylene with a series of cyclic secondary amines gave the amines **116** <1998FA475>.

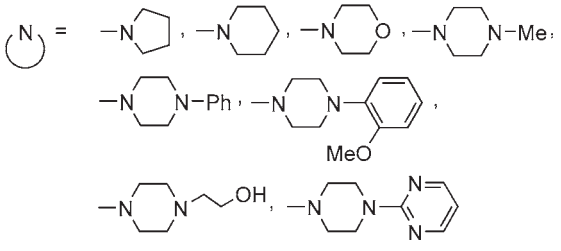


114

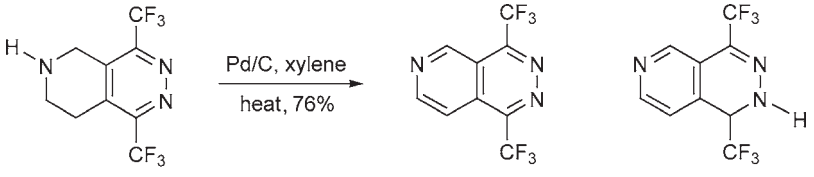


115: X = Cl (50%)

116: X = N (40–85%)



Dehydrogenation of 1,4-bis(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyridazine **117** by refluxing in xylene in the presence of 10% Pd/C afforded the oxidized product **40**. From a large-scale reaction, the 1,2-dihydropyrido[3,4-*d*]-pyridazine intermediate **27** was isolated (Equation 7) <1994H(38)1845>.

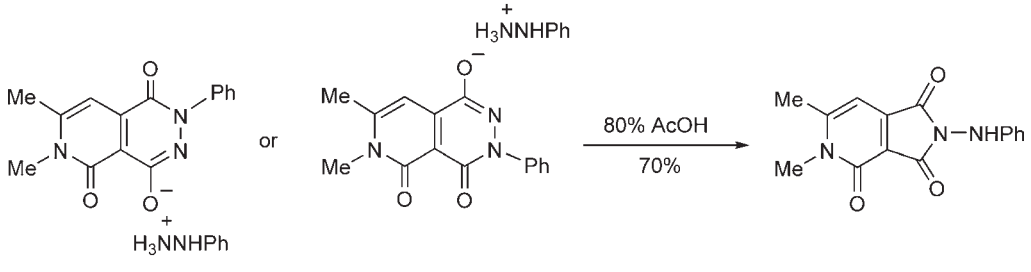


117 **40** **27**

(7)

10.16.6.1.4 Ring contraction

Ring contraction of *N*-phenylpyridopyridazine hydrazonium salts **118** or **119** into *N*-phenylaminoimide **120** was performed by boiling in 80% AcOH (Equation 8) <1998FA468>.



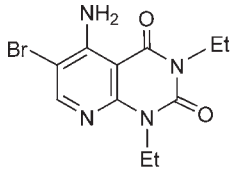
118 **119** **120**

(8)

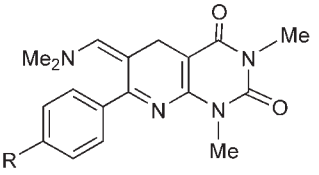
10.16.6.2 Pyrido[*x*,*y*-*z*]pyrimidines

10.16.6.2.1 Electrophilic attack at ring carbons

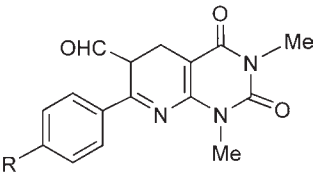
The more reactive center toward electrophilic substitution in pyrido[2,3-*d*]pyrimidine rings was found to be at C-6. Thus, 1,3-diethyl-5-aminopyrido[2,3-*d*]pyrimidine-2,4-dione was treated with bromine in the presence of pyridine in CCl_4 to give **121** <1995CAP2151971>. The 6-substituted pyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-diones **122** and **123** could be synthesized using Vilsmeier reaction on the corresponding 5,6-dihydropyrido[2,3-*d*]pyrimidine(1*H*,3*H*)-2,4-dione at room temperature and 80 °C <2004T11511>.



121



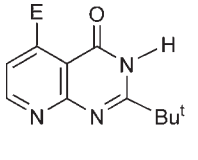
122



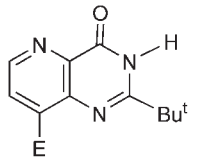
123

R	**122**	**123**
H	51%	71%
Me	61%	70%
Br	63%	87%

Regioselective lithiation of the pyridine moiety in pyridopyrimidinone derivatives may depend upon several factors: the *ortho*-directing effect of the substituent on the pyridine ring > *peri*-effect of pyrimidine N-1 > α-effect of pyridine nitrogen > *peri*-effect of amide group <2004T4107, 2004T6353>. Thus, the metalation of 2-*tert*-butylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one was directed to the C-5 position, with 8 equiv of LiTMP in THF at 0 °C for 1 h, followed by reaction with various electrophiles to form the 5-substituted products **124**. On the other hand, the [3,2-*d*] analogue in which the pyridine nitrogen atom was at the 5-position, *peri* to the carbonyl group of the lactam function, afforded under the same conditions at −78 °C the 8-substituted derivatives **125** <2004T4107>. The [4,3-*d*] analogue, under the same reaction conditions at various temperatures, was treated with benzaldehyde as electrophile to give a mixture of **126** and **127**. It was observed that the regioselectivity was dependent on the temperature and reaction time, where compound **126** that was obtained at higher temperature with longer reaction time could be the thermodynamic product while compound **127** was obtained under milder conditions and could be the kinetic product <2004T4107>.

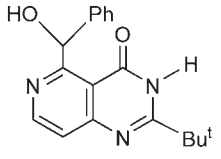


124

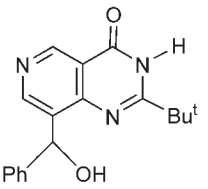


125

E	**124**	**125**
MeCH(OH)	95%	89%
PhCH(OH)	96%	89%
Ph	84%	80%
I	75%	31%



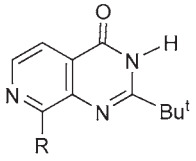
126



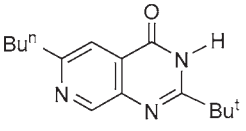
127

2-*tert*-Butylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one **128** also exhibited a regioselective metalation at C-5 at the *peri*-position to the carbonyl of the lactam function when an excess (4 equiv) of *n*-butyllithium was used in THF at −78 °C, followed by reaction with diphenyl disulfide as the electrophile to afford the addition products **129**, **131**, and **132**. Compound **129** and **131** resulted from an addition of BuLi at the α-position of the pyridine nitrogen, whereas the main product **132** resulted from an addition of *n*-butyllithium at C-8 followed by reaction with electrophile at C-5. When the reaction was performed with phenyllithium at −10 °C, **130** and **133** were obtained. Using a less-nucleophilic metalating agent such LiTMP (8 equiv) and various electrophiles afforded 5-substituted derivatives

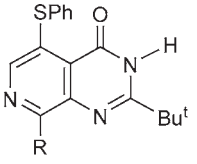
134 in excellent yields. When the 5-position was occupied with a chlorine atom, lithiation using LiTMP at −20 °C for 1 h followed by reaction with benzaldehyde gave the 6- and 8-substituted products **135** and **136**, respectively <2004T4107>.



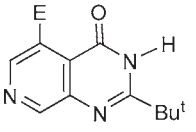
128: R = H
129: R = Bu^n (18%)
130: R = Ph (40%)



131
17%

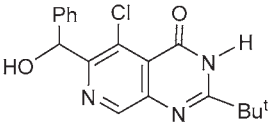


132: R = Bu^n (56%)
133: R = Ph (29%)

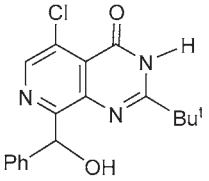


134

E = SPh	(97%)
E = MeCH(OH)	(96%)
E = PhCH(OH)	(96%)
E = I	(75%)
E = Cl	(82%)

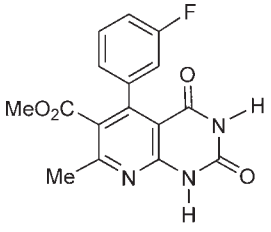


135
35%

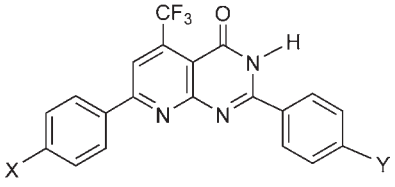


136
35%

Methyl 5-(3-fluorophenyl)-7-methyl-1,2,3,4,5,8-hexahydropyrido[2,3-*d*]pyrimidine-2,4-dione-6-carboxylate was oxidized to the tetrahydro derivative **137** by the action of sodium nitrite in acetic acid <1994T8085>. Oxidation of 2,7-disubstituted-5-trifluoromethyl-1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones using active MnO_2 in CH_2Cl_2 gave the corresponding pyridopyrimidin-4(3*H*)-ones **138** <1995IJB587>.



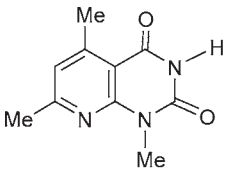
137
81%



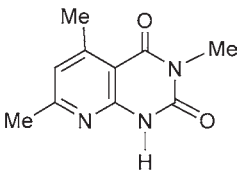
138
X = H, Me, OMe, Cl
Y = H, OMe
67–81%

10.16.6.2.2 Electrophilic attack at ring nitrogens

The nucleophilicity of the two nitrogen atoms in the pyrimidine ring of 5,7-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione toward electrophilic substitution has been found to be different. Thus, alkylation of its lithium salt with dimethyl sulfate gave the methylated products **139** and **140** in a 4.8:1 ratio. The ratio decreased to 2:1 in case of the sodium salt, whereas when the potassium salt was used, the main product was **140** <1996DOK33>.

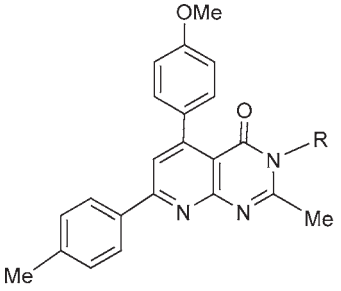


139

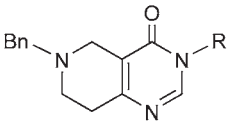


140

Compound **142** was prepared by reacting **141** with chloroacetic acid under basic conditions which were accompanied by the loss of CO_2. Acetylation and benzoylation of **141** with boiling Ac_2O or benzoyl chloride in pyridine yielded the corresponding 3-acetyl(benzoyl) derivatives **143** and **144**, respectively <1994H(38)57>. Alkylation of 6-benzyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-one **145** with 1-(2-methoxyphenyl)-4-(2-chloroethyl)piperazine afforded the 3-substituted derivative **146** <2000DEP19900544>.

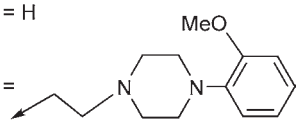


141: R = H
142: R = Me (77%)
143: R = Ac (58%)
144: R = Bz (71%)

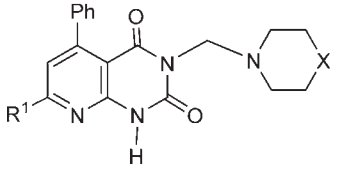


145: R = H

146: R =

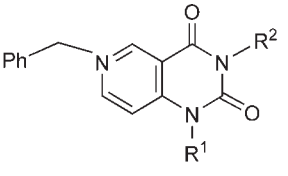


Mannich reaction of 5-phenyl-7-substituted pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones using piperidine, morpholine, and *N*-methylpiperazine in aqueous formaldehyde led to the mono-Mannich base derivative **147** at the more-acidic N-3 position of the pyrimidine ring <1995MI55>. Methylation of *N*-benzylpyrido[4,3-*d*]pyrimidine-2,4-dione **148** with MeI/Na_2CO_3 gave **149–151**, which were separated chromatographically <1994JHC1569>. In one pot, the 1,3-dialkylated derivative **152** was obtained from 1,2,3,4-tetrahydro-2,4-dioxopyrido[2,3-*d*]pyrimidine by reaction with prop-2-yn-1-yl alcohol under Mitsunobu conditions <1993M1217>.

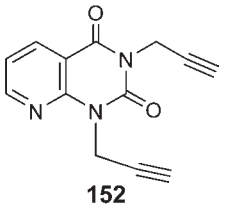


147

X = CH_2, O, NMe
R^1 = Me, Ph
55–77%

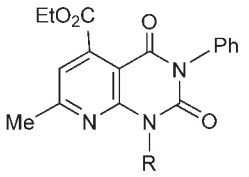


148: $R^1 = R^2 = H$
149: R^1 = Me; R^2 = H (14%)
150: R^1 = H; R^2 = Me
151: $R^1 = R^2$ = Me

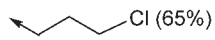


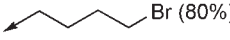
152

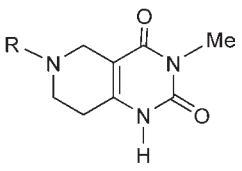
The potassium salt of 7-methyl-3-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate **153** was condensed with 1-bromo-3-chloropropane or 1,4-dibromobutane in anhydrous DMF at room temperature to afford the *N*-1-alkyl derivatives **154** and **155**, respectively <1994FA499>. The corresponding *N*-1-piperazinylalkyl derivatives of **153** were also prepared in more than 40% yield. Debenzylation of 6-benzyl-3-methylpyrido[4,3-*d*]pyrimidine **156** by Pd/C-catalyzed hydrogenolysis in AcOH gave the analogue **157** <1994JHC1569>.



153: R = H

154: R =  Cl (65%)

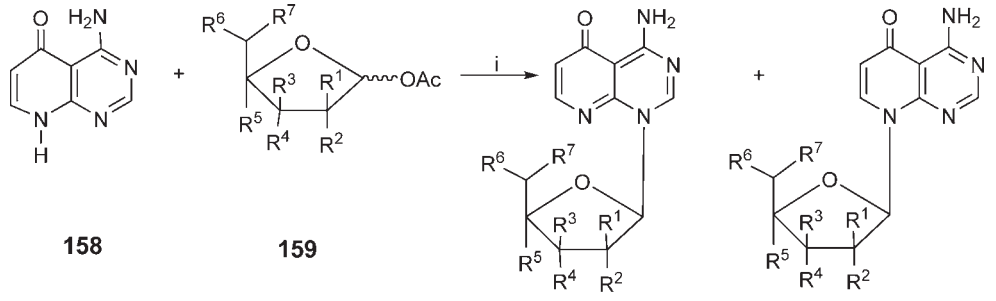
155: R =  Br (80%)



156: R = Bn

157: R = H (90%)

Condensation of the silylated derivative of **158**, in a one-pot reaction, with more than 20 derivatives of 1-O-acylated sugars **159** gave a mixture of two isomers, **160** (minor) and **161** (major), having the β-configuration, resulting from the coupling at N-1 and N-8 of **158**, respectively. The N-1-coupled products were formed first and then slowly converted into N-8 analogues during heating, where an equilibrium was reached after 2–3 days (Equation 9) <2000JME3704>.

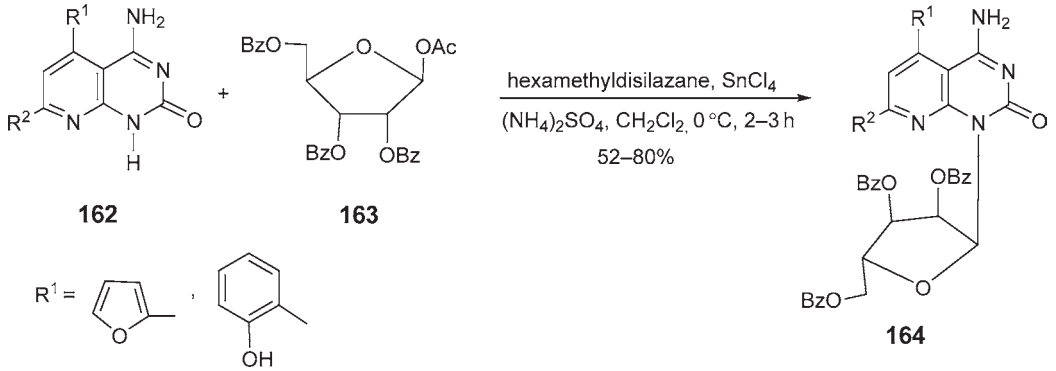


158 **159** **160** 20–30% **161** 40–60% (9)

R^1–R^7 = H, OH, Me, Et,  ,  , CH_2OH

i, BSA, $Cl(CH_2)_2Cl$, TMSOTf, reflux, 3 d

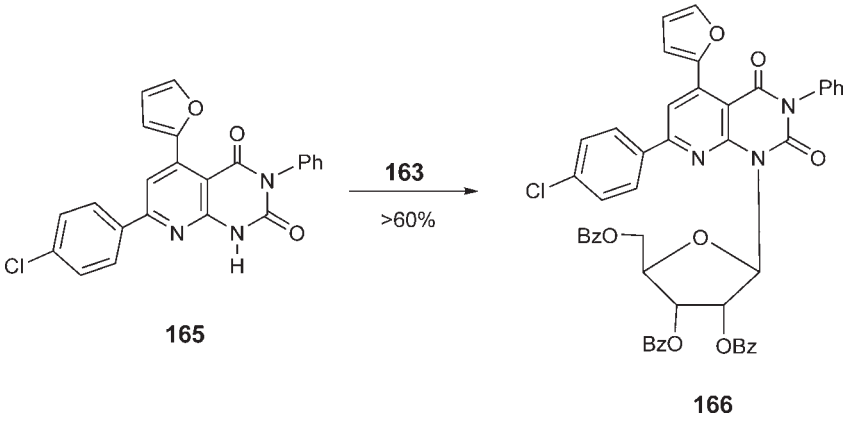
Condensation of trimethylsilyl derivatives of 4-amino-5,7-disubstituted pyrido[2,3-*d*]pyrimidin-2(1*H*)-ones **162** with 1-*O*-acetyl-2,3,4-tri-*O*-benzoyl-β-D-ribofuranose **163** in the presence of $SnCl_4$ in CH_2Cl_2 at 0 °C for 2–3 h afforded the corresponding α-ribonucleoside derivatives **164** (Equation 10) <2002IJB430>. In a previous report on the synthesis of β-ribonucleosides, high temperature and a long reaction time (10 h) were required <1998IJB517>. The condensation of the trimethylsilyl derivative of 3,5,7-trisubstituted pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **165** with **163** gave the nucleoside derivative **166** (Equation 11) <1997IJH237>.



162 **163** hexamethyldisilazane, $SnCl_4$; $(NH_4)_2SO_4$, CH_2Cl_2, 0 °C, 2–3 h; 52–80% **164** (10)

R^1 =

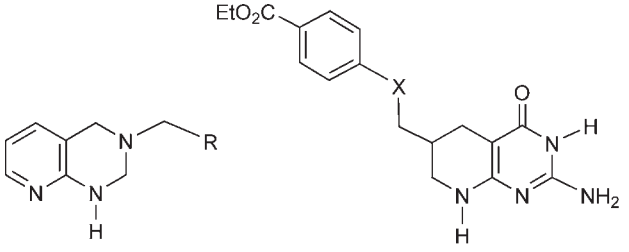
R^2 = 2-FC_6H_4, 3-BrC_6H_4, 3-$H_2NC_6H_4$



165 166 (11)

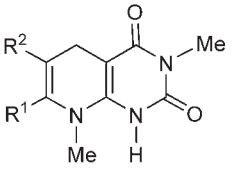
10.16.6.2.3 Nucleophilic attack at ring carbons

Reduction of 22 derivatives of 3-substituted pyrido[2,3-*d*]pyrimidin-4(3*H*)-one with $LiAlH_4$ afforded the respective 1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine derivatives **167** in >55% yield <1995PHA719>. On the other hand, a selective reduction of the 7-oxo group in 6-substituted 2-amino-5,6-dihydropyrido[2,3-*d*]pyrimidine-4,7(3*H*,8*H*)-diones was carried out by employing 1 M BH_3·THF at reflux for 24 h to afford compound **168**, the 4-oxo group and the ester group remaining unaltered <2000H(52)1207>. Reduction of 3,8-dimethyl-2,4-dioxo-6,7-disubstituted 2,3,4,8-tetrahydropyrido[2,3-*d*]pyrimidines with $Na_2S_2O_4$ gave the corresponding 1,2,3,4,5,8-hexahydro products **169–172** <2004H(63)1393>.



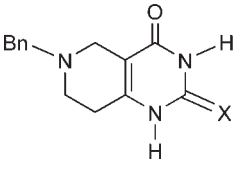
167
>55%

168
X = CH_2, NH, NMe
52–79%

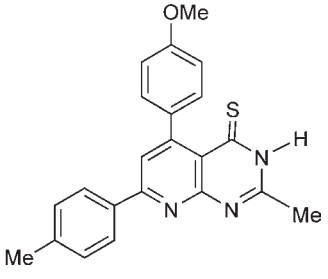


169: R^1 = Me; R^2 = CO_2Et (60%)
170: R^1 = Ph; R^2 = CO_2Et (100%)
171: R^1 = Ph; R^2 = CONHCH(Me)Ph (100%)
172: R^1 = Ph; R^2 = H (60%)

The thioxopyrido[4,3-*d*]pyrimidine **173** was oxidized with H_2O_2 in NaOH solution to give the corresponding dioxo derivative **174** <1994JHC1569>. Thiation of 2-methyl-5-methoxyphenyl-7-tolylpyridopyrimidin-4(3*H*)-one was achieved by the action of P_2S_5 in boiling dry xylene to yield the 4-thioxo analogue **175** <1994H(38)57>.

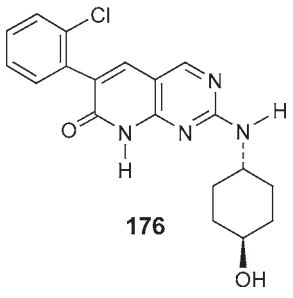


173: X = S
174: X = O (67%)

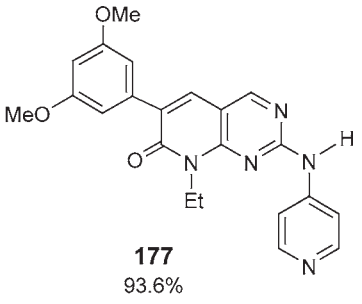


175
50%

Ozone oxidation of 6-aryl-2-methylthiopyrido[2,3-*d*]pyrimidin-7(8*H*)-one followed by displacement of the resulting methyl sulfone with *trans*-4-aminocyclohexanol afforded the amino pyridopyrimidinone derivative **176** <2002WO2002018380>. Amination of 6-dimethoxyphenyl-8-ethyl-2-methylthiopyrido[2,3-*d*]pyrimidin-7-one with 4-aminopyridine and $LiNH_2$ in THF at 50 °C produced the 2-[(4-pyridyl)amino] derivative **177** <2003WO2003027110>.

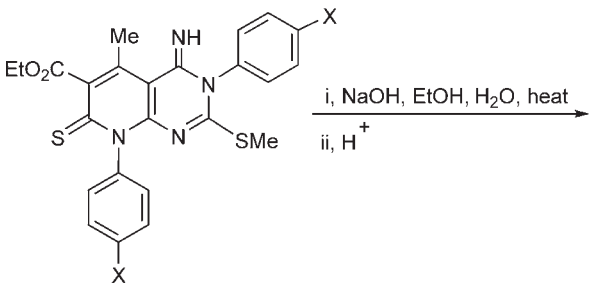


176



177
93.6%

Hydrolysis of **178** with H_2O/EtOH/NaOH produced **179**, whereby the *S*-methyl group was hydrolyzed (Equation 12) <1993JHC887>.



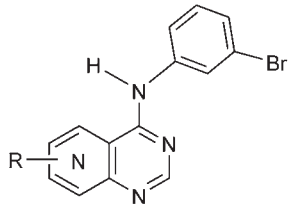
X	Yield (%)
H	50
Cl	52

(12)

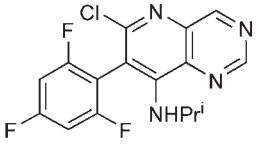
178: X = H, Cl

179

Halogenation of 6-(7)-substituted pyrido[2,3-*d*], -[3,2-*d*], -[3,4-*d*], and -[4,3-*d*] pyrimidin-4(3*H*)-ones by refluxing in $POCl_3$ or $SOCl_2$ followed by amination of the resulting 4-chloro intermediates with 3-bromoaniline gave the respective amino derivatives **180** <1996JME1823>. Chlorination/aromatization of 6,8-dioxo-7-(2,4,6-trifluorophenyl)pyrido[3,2-*d*]pyrimidines and subsequent amination of the obtained dichloropyridopyrimidine by isopropylamine gave selectively the 6-chloro-8-amino derivative **181** <2004WO2004056826>.

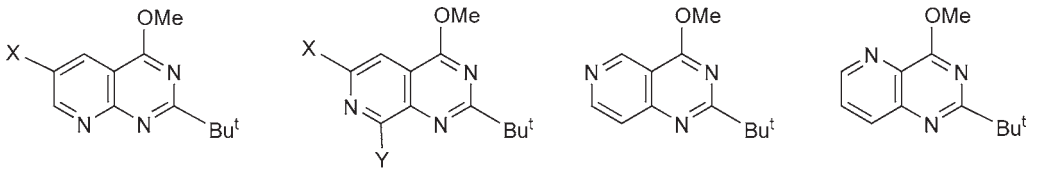


180
R = NHMe, NMe_2, Cl, F, OMe
52–94%



181

Seven 4-methoxypyridopyrimidines, **182–188**, have been prepared by converting the respective 2-*tert*-butylpyridopyrimidin-4(3*H*)-ones using phosphorus oxychloride into their 4-chloro derivatives, which upon reaction with sodium methoxide gave the corresponding 4-methoxy analogues <2004T6353>.



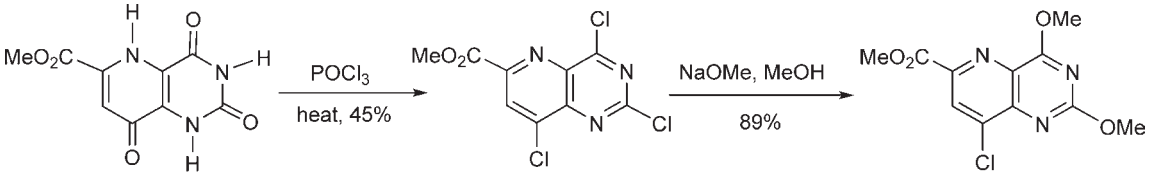
182: X = H (97%)
183: X = Cl (90%)

184: X = Y = H (77%)
185: X = OMe; Y = H (82%)
186: X = H; Y = OMe (64%)

187 79%

188 65%

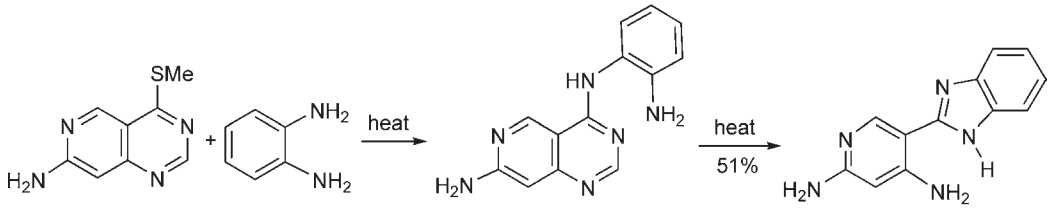
Similarly, chlorination of 2,4,8-trioxopyrido[3,2-*d*]pyrimidine **189** afforded the trichloro derivative **190**, which upon treatment with sodium methoxide gave 2,4-dimethoxy derivative **191** where the chlorine atom at position 8 was not displaced (**Scheme 5**) <1993JME3103, 1995JME2615>.



189 **190** **191**

Scheme 5

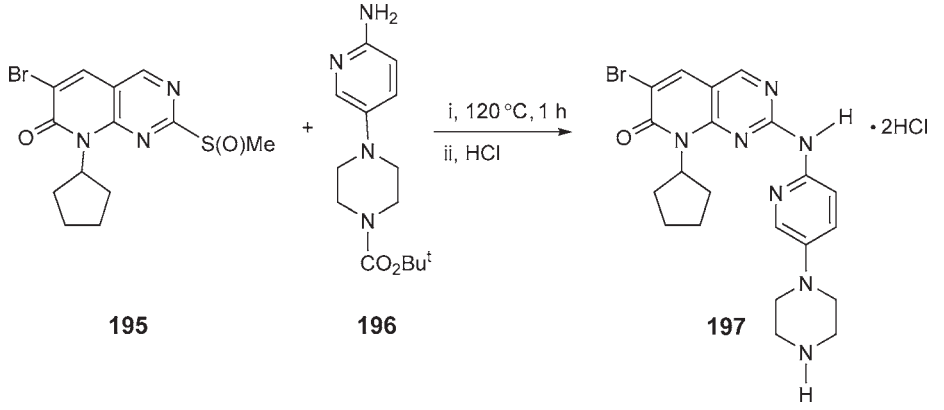
Amination of 4-methylthiopyrido[4,3-*d*]pyrimidine derivative **192** with 1,2-phenylenediamine at a high temperature (150 °C) in the absence of solvent gave only the benzimidazole **194**. Conducting the reaction at a lower temperature (115 °C), a 1:1 mixture of **193** and its rearrangement product **194** were obtained (32%). They were separated by high-performance liquid chromatography (HPLC) to give 13% and 19% yield, respectively (Equation 13) <1995JME3780>. The formation of **194** can be explained due to the nucleophilic attack of the second amino group, in the diamine **193**, on C-4 followed by opening of the pyrimidine ring and elimination of an HCN molecule.



(13)

192 **193** **194**

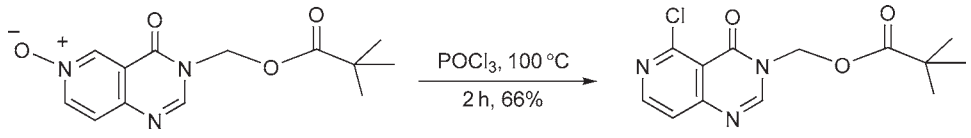
Solventless reaction of 6-bromo-8-cyclopentyl-2-methylsulfinyl-8*H*-pyrido[2,3-*d*] pyrimidin-7-one **195** with *tert*-butyl 4-(6-aminopyridin-3-yl)piperazine-1-carboxylate **196** at 120 °C for 1 h followed by deprotection in the presence of gaseous HCl afforded the amine derivative **197** (Equation 14) <2003WO2003062236>.



(14)

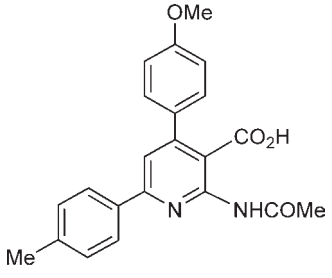
195 **196** **197**

Regioselective chlorination at C-5 of 3-pivaloyloxymethylpyrido[4,3-*d*]pyrimidine *N*-oxide **198** with $POCl_3$ (100 °C/2 h) gave **199** via a Meisenheimer *N*-oxide rearrangement (Equation 15)<2004TL3737>.



198 **199** (15)

Hydrolysis of 5-(4-methoxyphenyl)-7-(4-tolyl)-2-methyl-3-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one in boiling aqueous pyridine was accompanied by ring fission to give the pyridine derivative **200** <1994H(38)57>.

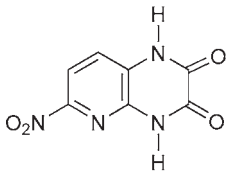


200
73%

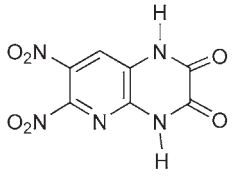
10.16.6.3 Pyrido[*x*,*y*-*z*]pyrazines

10.16.6.3.1 Electrophilic attack at ring carbons

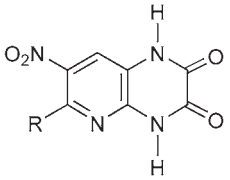
The reactivity of the pyridine nucleus in pyrido[*x*,*y*-*z*]pyrazines at position 6 and 7 toward electrophilic substitution could be deduced from the results of nitration of pyrido[2,3-*b*]pyrazine-2,3-(1*H*,4*H*)-dione or its 7-nitro derivatives with fuming HNO_3 in $AcOH/Ac_2O$ to give the 6-nitro and 6,7-dinitro derivatives **23** and **201**, respectively. On the other hand, 6-substituted pyridopyrazinediones furnished the 7-nitro derivatives **202** using $HNO_3/AcOH/Ac_2O$ for **202a**, KNO_3/H_2SO_4 for **202b**, and NO_2BF_4/tetramethylenesulfone for **202c**, respectively <1996JME1331>.



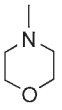
23
28%



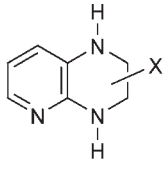
201
45%



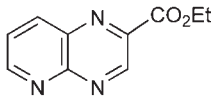
202

Compound	*R*	*Yield (%)*
a	OMe	62
b		57
c		65

Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) converted ethyl 1,2,3,4-tetrahydropyrido[2,3-*b*]-pyrazine-2-carboxylate **203** into the conjugated pyridopyrazine **205**, while the 3-isomer **204** could not be oxidized to the corresponding aromatic heterocycle <2002T5241>.



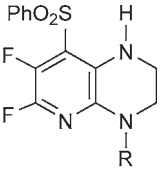
203: X = 2-CO_2Et
204: X = 3-CO_2Et



205
23%

10.16.6.3.2 Electrophilic attack at ring nitrogen

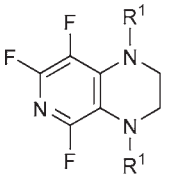
Acetylation of the pyrazine ring in **206** by boiling Ac_2O produced selectively the 4-acetyl derivative **207**, indicating the greater nucleophilicity of this site as compared to N-1 <2005JOC9377>.



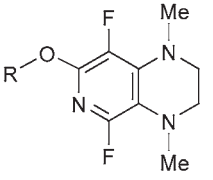
206: R = H
207: R = Ac (66%)

10.16.6.3.3 Nucleophilic attack at ring carbons

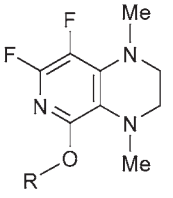
The regioselectivity of nucleophilic substitution in **25** may be explained by consideration of the activating influences of the ring nitrogen and the fluorine substituents at the pyridine ring. The pyridine nitrogen significantly activates the *ortho*-positions of the pyridine ring, C-5 and C-7. The 7-position is attacked preferentially because of activation by the *ortho*- and *meta*-fluorine atoms, whereas the 5-position is activated only by a *meta*-fluorine and significantly deactivated by a *para*-fluorine atom. In addition, the neighboring N–R^1 group may hinder to some extent the attack at the 5-position <2005JOC7208>. Thus, when 1,4-dimethyl-5,7,8-trifluoro-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (**25**: R^1 = Me) was reacted with NaOMe or NaOEt in MeCN by boiling or microwave irradiation, it produced **26a**, **208a** or **26b**, **208b** with ratios of 10:1 and 8:1, respectively, arising from substitution at sites that are *ortho* to the pyridine ring nitrogen with a high degree of control; the regioselectivity may be due to the activating influences of ring nitrogen and the fluorine substituents. The minor products **208a** and **208b** were identified by ^{19}F NMR and gas chromatography–mass spectrometry (GC–MS) analysis but could not be isolated. The reaction of **25** with $KOBu^t$ gave essentially **26c** and with potassium phenoxide under microwave irradiation gave a mixture of **26d**, **208d**, and **209** in 65% yield with a ratio 4.9:1.0:1.2, respectively, which could not be separated <2005JOC7208>. Similarly, nitrogen and sulfur nucleophilic substitution occurred preferentially at C-7, and to a lesser extent at C-5 in a competing process <2005JOC7208>.



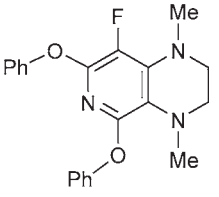
25



26a: R = Me (76%)
26b: R = Et (80%)
26c: R = ^{t}Bu (66%)
26d: R = Ph

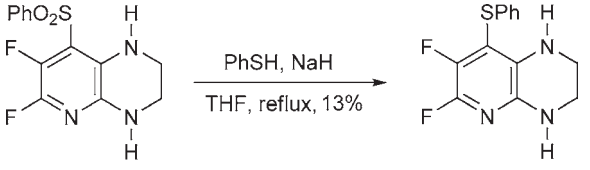


208a: R = Me
208b: R = Et
208d: R = Ph



209

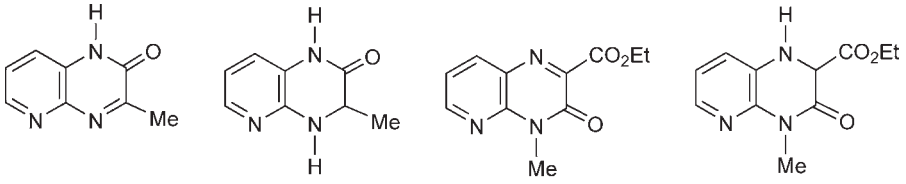
Reaction of 6,7-difluoro-8-phenylsulfonyl-1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazine **206** with sodium thiophenoxide led to the 8-phenylsulfanyl derivative **210** (Equation 16) <2005JOC9377>.



206 **210**

(16)

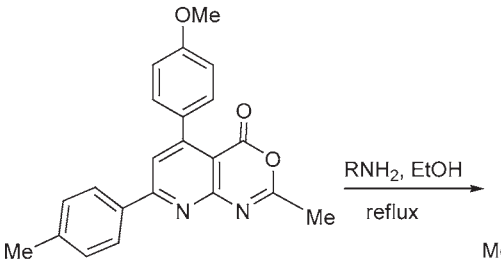
Hydrogenation of 3-methylpyrido[2,3-*b*]pyrazin-2(3*H*)-one **211** by the action of $NaBH_4$ in NaOH gave **212** <1995JHC703>. On the other hand, the tetrahydro analogue **214** was obtained from **213** by the action of H_2/Raney-Ni in THF <1996JHC1737>.



211 **212** 47% **213** **214** 74%

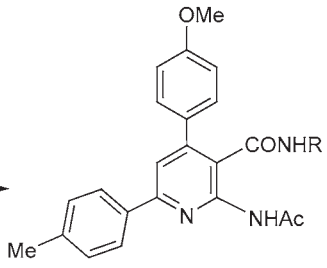
10.16.6.4 Pyrido[2,3-*d*][1,3]oxazines

Reaction of the pyrido[2,3-*d*][1,3]oxazin-4-one **215** with hydrazines and various primary amines in boiling ethanol yielded the corresponding 2-acetylaminopyridine derivatives **216** (Equation 17) <1994H(38)57>.



215

RNH_2, EtOH, reflux



216

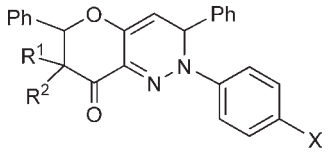
R	*Yield* (%)
NH_2	60
NHPh	65
OH	71
Bn	63
4-MeC_6H_4	50
Ph	67
Et	79

(17)

10.16.6.5 Pyrano(thiopyrano)[*x*,*y*-*z*]diazines

10.16.6.5.1 Pyrano[3,2-*c*]pyridazines

Condensation of 3,6-diphenylpyrano[3,2-*c*]pyridazinone derivatives **217** with PhCHO afforded the 7-benzylidene derivatives **218** <1989IJB167>.



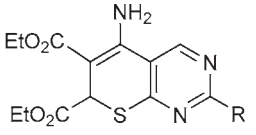
217: $R^1 = R^2 = H$

218: R^1, R^2 = CHPh

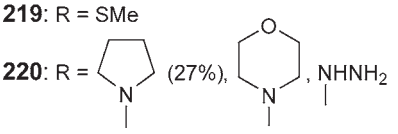
X = H, Br, NO_2

10.16.6.5.2 Thiopyrano[2,3-*d*]pyrimidines

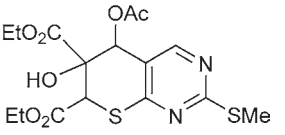
Displacement of the methylthio group in thiopyrano[2,3-*d*]pyrimidine **219** with pyrrolidine, morpholine, and hydrazine gave the 2-substituted derivatives **220**. Diazotization of **219** with $NaNO_2$ in AcOH followed by hydrolysis of the resulting diazonium salt gave the acetyl derivative **221** <1977JHC361>.



219: R = SMe



220: R = (27%), , $NHNH_2$

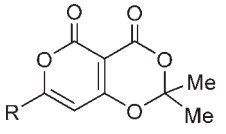


221
83%

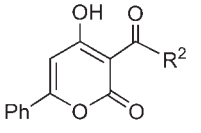
10.16.6.6 Pyrano[*x*,*y*-*z*][1,*n*]dioxanes

10.16.6.6.1 Pyrano[4,3-*d*][1,3]dioxanes

7-Substituted 2,2-dimethylpyrano[4,3-*d*][1,3]dioxane-4,5-dione derivatives **223** were prepared from the 7-chloro derivative **222** by reaction with a variety of aromatic and alkyl tributyltin reagents in the presence of bis(triphenylphosphine)palladium(II) chloride in THF. Palladium-catalyzed cross-coupling methodology in the transformation of **222** to **223** offered a significant improvement over known literature methods <1979JOC1613>. Reaction of 2,2-dimethyl-7-phenylpyrano[4,3-*d*]dioxane-4,5-dione **223** (R = Ph) with benzylamine or ethanol in refluxing xylene afforded the amide **224** and ester **225**, respectively <1997SL895>.



222: R = Cl
223: R = R^1

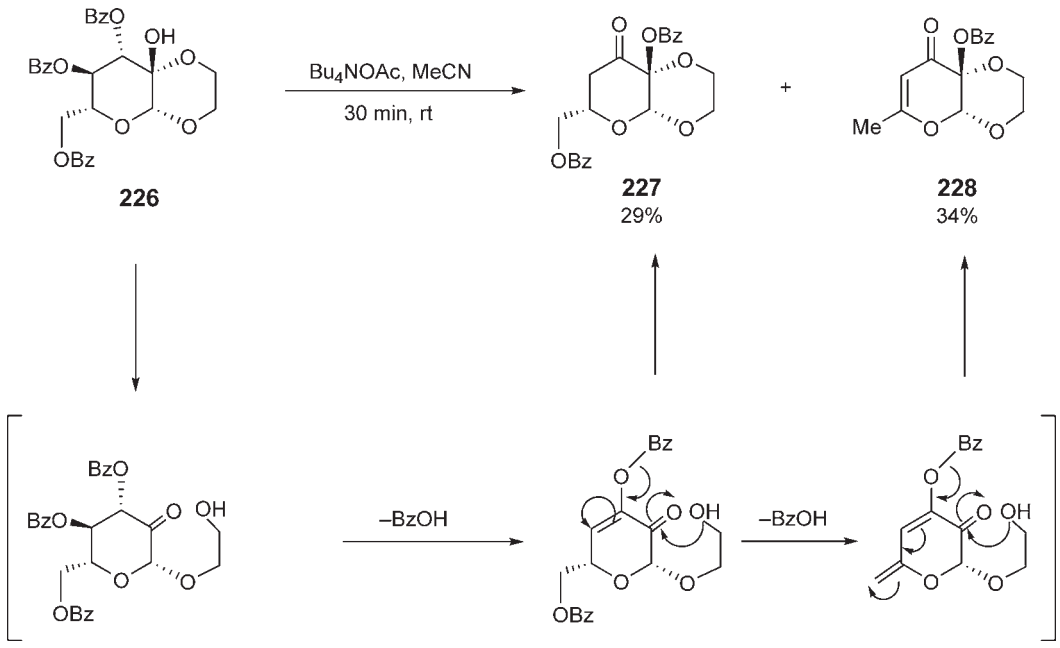


224: R^2 = NHBn (28%)
225: R^2 = OEt (87%)

223: *R* = R^1	*Yield* (%)
Ph	33
2-Furyl	77
2-Thienyl	56
4-$PhOC_6H_4$	72
^{n}Bu	62
4-Biphenyl	42
3-Biphenyl	36
β-Styryl	44
Ethynylphenyl	39

10.16.6.6.2 Pyrano[2,3-*b*][1,4]dioxanes

The dioxanoid hemiketal link in sugar derivative *cis*-pyrano[2,3-*b*][1,4]dioxane **226** showed a pronounced tendency to be opened to the 2-uloside derivative under slightly basic conditions with tetrabutylammonium acetate in MeCN to afford an approximate 1:1 mixture of **227** and **228**. Thus, elimination of one and two benzoic acid molecules from the open dioxane intermediate and subsequent cycloketal formation (Equation 18) had taken place. In the case of a less polar solvent such as CH_2Cl_2 in the presence of Ag_2CO_3, the rearranged product **227** was obtained in 82% yield <2004EJO4901>.



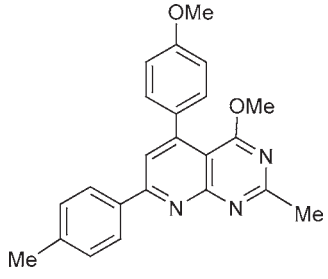
(18)

10.16.7 Reactivity of Substituents

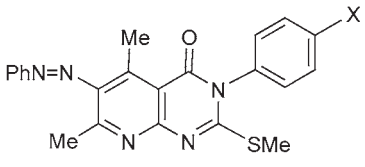
10.16.7.1 Pyrido[*x*,*y*-*z*]diazines

10.16.7.1.1 Electrophilic attack

Methylation of 2-methyl-5-methoxyphenyl-7-tolylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one with MeI in the presence of anhydrous K_2CO_3 in boiling acetone afforded the *O*-methyl derivative **229** rather than the *N*-methyl analogue <1994H(38)57>. The 2-methylthio products **230** were obtained upon methylation of 3-aryl-5,7-dimethyl-6-phenylazo-2-thioxopyrido[2,3-*d*]pyrimidin-4(3*H*)-ones with Me_2SO_4 under alkaline conditions <2000IJB210>. Also, methylation of polysubstituted 2,7-dithioxopyrido[2,3-*d*]pyrimidines by MeI in the presence of sodium ethoxide led to monomethylthio derivative **178** where the ester group remained without hydrolysis <1993JHC887>.

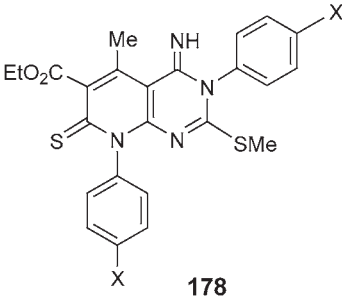


229
83%



230

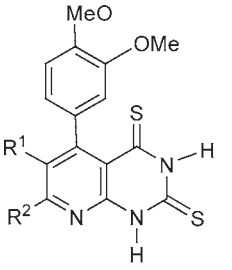
X	*Yield (%)*
H	75
Me	83
OMe	70
Cl	88



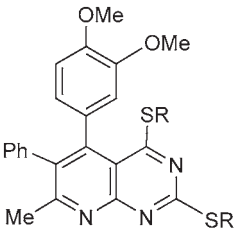
178

X	*Yield (%)*
H	96
Cl	97

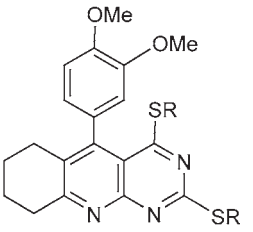
The dialkylthio derivatives **233–236** were prepared by the alkylation of the respective dithiones **231** and **232** with MeI or EtI in presence of NaOMe in absolute MeOH <1994MI203>.



231: R^1 = Ph; R^2 = Me
232: R^1, R^2 = –$(CH_2)_4$–

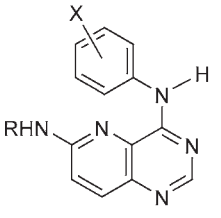


233: R = Me (83%)
234: R = Et (84%)

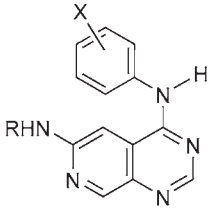


235: R = Me (90%)
236: R = Et (83%)

Acylation of 6-aminopyrido[3,2-*d*]- and pyrido[3,4-*d*]pyrimidines **237** and **239** with acryloyl chloride in the presence of base afforded their acrylamido derivatives **238** and **240**, respectively <1999JME1803>.



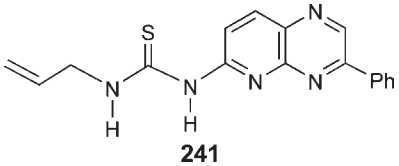
237: R = H
238: R =  (26–57%)



239: R = H
240: R =  (24–79%)

X = 3-Br, 3-Me, 3-Br-4-F, 3-Cl-4-F

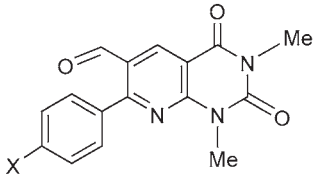
Treatment of 6-amino-3-phenylpyrido[2,3-*b*]pyrazine with allyl isothiocyanate afforded the thioureido derivative **241** <2004WO2004104003>.



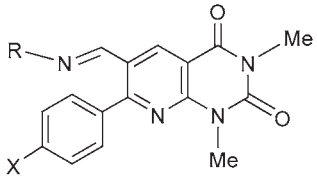
241

10.16.7.1.2 Nucleophilic attack

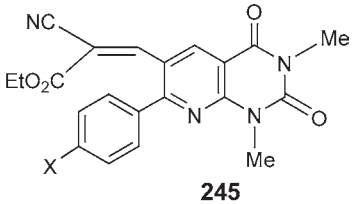
Reaction of the carbaldehyde **242** with primary amines afforded the imines **243** and **244**, and with ethyl cyanoacetate, in the presence of piperidine/AcOH, gave the acrylates **245** <2004T11511>.



242



Compound	*X*	*R*	*Yield (%)*
243a	H	Me	57
243b	Me	Me	60
244a	H	Ph	63
244b	Me	Ph	58

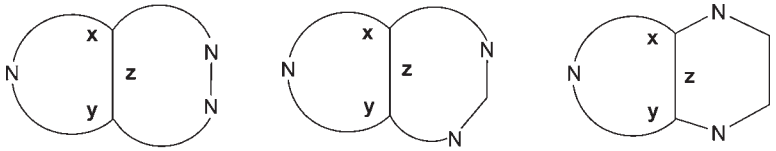


245

X	*Yield (%)*
H	63
Me	65

10.16.8 Synthesis

The synthesis of pyridodiazine ring systems can be classified according to the relative location of nitrogen atoms in the diazine nucleus of the fused ring system as shown in formulas **246–248** for pyrido[*x*,*y*-*z*]pyridazines, pyrido[*x*,*y*-*z*]pyrimidines, and pyrido[*x*,*y*-*z*]pyrazines, respectively (**Figure 2**). Such fused ring systems have been subdivided according to the site of fusion *z*, that is, whether it is b–d.



246 **247** **248**

Figure 2

10.16.8.1 Synthesis of Pyrido[*x*,*y*-*z*]pyridazines

10.16.8.1.1 Synthesis of pyrido[*x*,*y*-*c*]pyridazines

Condensation of malononitrile dimer **249** (X = CN) with the phenylhydrazono derivative of acetylacetonitrile **250** afforded the polyfunctionally substituted pyridine derivative **253**, which upon condensation with benzaldehyde gave the pyrido[3,4-*c*]pyridazine **255** <1998PJS81>. The isomeric pyrido[2,3-*c*]pyridazine derivative **254** could also be formed from condensation of the dimer **249** (X = CN) with the phenylhydrazono derivative of acetylacetone **251** <1998PJS81>. Alternatively, reaction of 2-arylhydrazono-1,3-dicarbonyl compounds **252** with active methylene reagents **249** in refluxing EtOH with a few drops of piperidine gave the pyrido[2,3-*c*]pyridazine derivatives **258** via intermediates **256** and **257** (**Scheme 6**) <1998JCM26, 2004MOL910, 2004ZNB721>.

Cycloaddition of azodicarboxylates to 2-vinylpyridine in the presence of a biocatalyst (*Saccharomyces cerevisiae*) proceeded in a highly selective fashion to afford only pyrido[3,2-*c*]pyridazine derivatives **259** in >80% yield compared to that found in the literature when the reaction was carried out in an organic medium to give a mixture of **259** in <20% yield and its isomer pyrido[1,2-*c*]triazine derivatives **260** <1979T2027, 1993BCJ2429>. Similarly, 1,2,3,4-tetrahydropyrido[3,4-*c*]pyridazine-1,2-dicarboxylate **261** was obtained under the same reaction conditions in >60% yield by using 4-vinylpyridine.

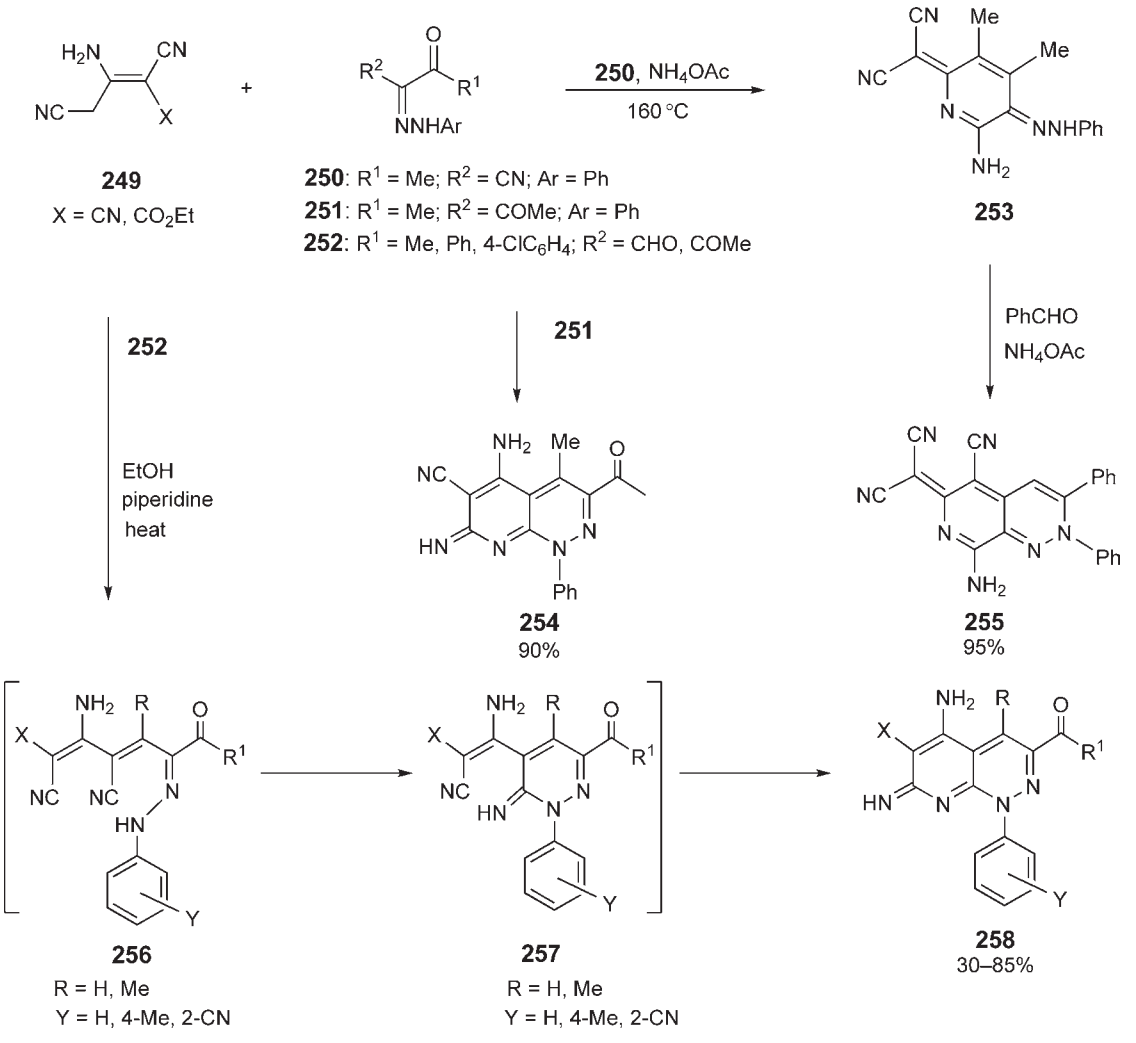
α-Acylation of ethyl diazoacetate with 2-chloro-6-trifluoromethylnicotinic acid, followed by cyclization in the presence of triphenylphosphine, gave 4-hydroxy-7-trifluoromethylpyrido[2,3-*c*]pyridazine derivative **262** <2004WO2004039802>. When ethyl 1-aryl-5-cyano-1,6-dihydro-4-methyl-6-oxopyridazine-3-carboxylate **263** was allowed to react with PhCHO in refluxing EtOH in the presence of a catalytic amount of piperidine followed by reaction with $NH_2NH_2 \cdot H_2O$, the corresponding styrylcarbohydrazide **264** was obtained. The latter underwent cyclization followed by autoxidation to 2,6-diaryl-7-amino-3,8-dioxopyrido[3,4-*c*]pyridazine-4-carbonitrile **265** by the action of cuprous chloride <1995JCM488, 1995PHA788>.

10.16.8.1.2 Synthesis of pyrido[*x*,*y*-*d*]pyridazines

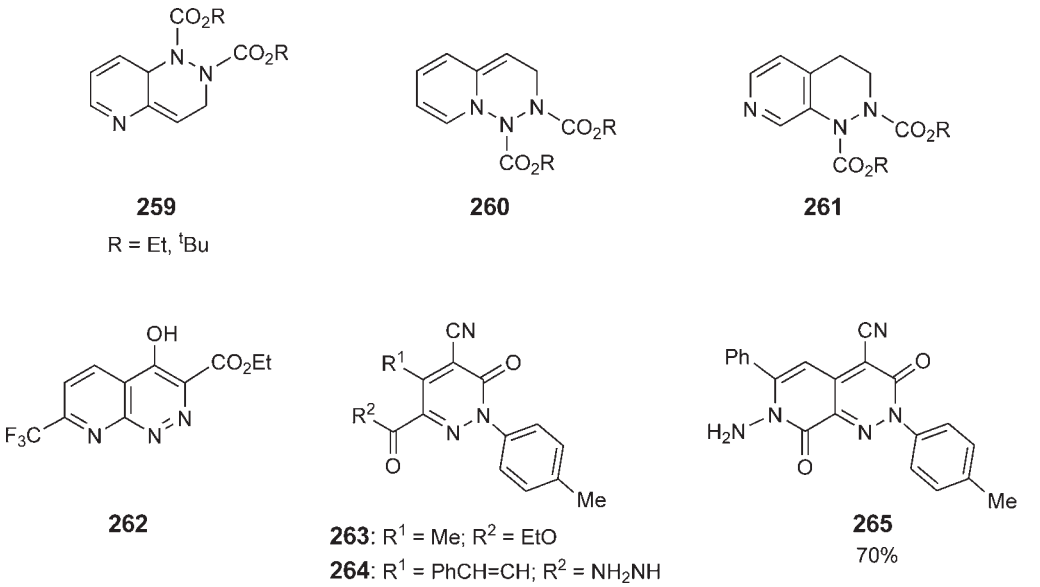
Two complementary routes to the synthesis of pyrido[*x*,*y*-*d*]pyridazines have been developed, the first of which begins by constructing the pyridine ring, and the second by constructing the pyridazine ring. In addition, ring transformations of pyrrolopyridine, pyridooxazine, pyridopyrimidine, and tetrazine derivatives to the pyrido[*x*,*y*-*d*]pyridazines have also been reported.

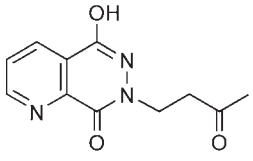
10.16.8.1.2(i) From pyridine intermediates

Michael-type reaction of quinolinic acid hydrazide and methyl vinyl ketone yielded a mixture of two isomers, 5-hydroxypyrido[2,3-*d*]pyridazin-8(7*H*)-one **266** and 8-hydroxy pyrido[2,3-*d*]pyridazin-5(6*H*)-one **267**, in a 2:1 ratio <2002M1177>. Cyclocondensation of hydrazine derivatives with 2-aroylnicotinic acid in the presence of Et_3N in refluxing toluene afforded the corresponding pyridopyridazinone derivatives **268** <1993WO19939307146, 1993CAP2086898, 1995EPP634413>.

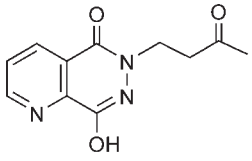

249
X = CN, CO2Et
250: R1 = Me; R2 = CN; Ar = Ph
251: R1 = Me; R2 = COMe; Ar = Ph
252: R1 = Me, Ph, 4-ClC6H4; R2 = CHO, COMe
250, NH4OAc
160 °C
253
252
EtOH
piperidine
heat
251
PhCHO
NH4OAc
254
90%
255
95%
256
R = H, Me
Y = H, 4-Me, 2-CN
257
R = H, Me
Y = H, 4-Me, 2-CN
258
30–85%

Scheme 6

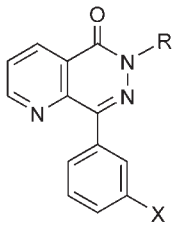

259
R = Et, tBu
260
261
262
263: R1 = Me; R2 = EtO
264: R1 = PhCH=CH; R2 = NH2NH
265
70%



266



267

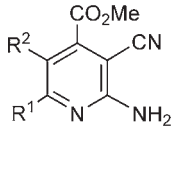


268

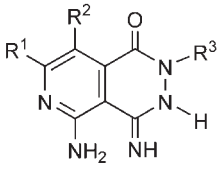
X = H, NO_2

R = H, Ph, 4-FC_6H_4

Polyfunctionalized pyrido[3,4-*d*]pyridazines **270** and **272** could be prepared by cyclization of pyridine derivatives **269** with R^3NHNH_2 <2002RJO1548> and coupling 5-(*trans*-pyrazolylazo)pyridine **271** with *p*-chlorobenzenediazonium chloride, respectively <2000IJH135>.

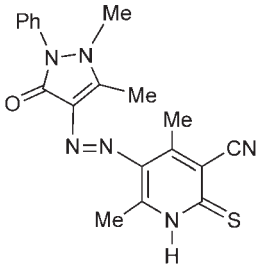


269

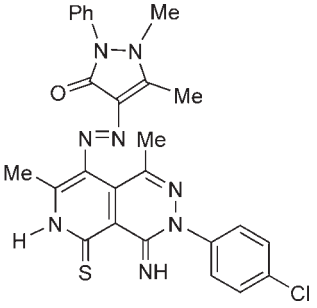


270

R^1, R^2, R^3 = H, Me

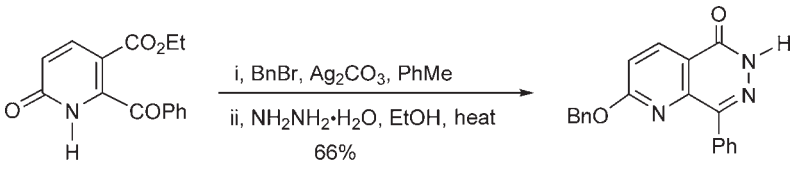


271



272

Selective *O*-benzylation of pyridone **273** using Ag_2CO_3 as a base in toluene followed by cyclization of the ketoester functional groups with hydrazine hydrate afforded the fused pyridopyridazine derivative **274** (Equation 19) <2006TL2257>.



(19)

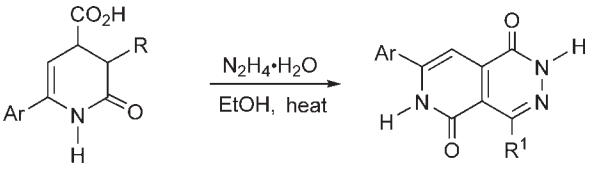
273 **274**

Condensation of 3-ethoxycarbonyl-, 3-acetyl-, or 3-cyano-1,2,3,4-tetrahydropyridine-4-carboxylic acid derivatives **275–277** with hydrazine hydrate in boiling ethanol afforded the pyrido[3,4-*d*]pyridazine derivatives **278–280**, respectively (Equation 20) <2002PS1359>.

Similarly, reaction of hydrazine hydrate with pyridinedicarboxylates **281** in boiling alcohol, followed by cyclization of the resulting dihydrazides **282**, gave the pyrido[3,4-*d*]pyridazine-1,4-diones **283**, where deacetylation has occurred during the formation of **282** (Equation 21) <1997T8225>.

10.16.8.1.2(ii) From pyridazine intermediates

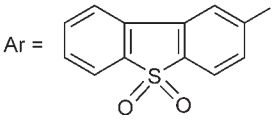
Cyclocondensation of 3-(2-fluorophenyl)-4-aminopyridazine-5-carbaldehyde **284** with phenylacetyl chloride gave the tetrahydropyridopyridazine derivative **285**, which upon dehydration with *p*-toluenesulfonic acid gave **286** (**Scheme 7**) <2006TL2257>.

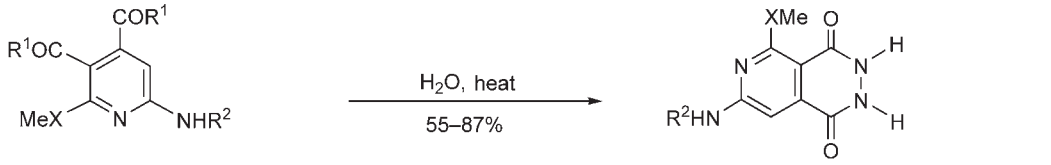


275: R = CO_2Et
276: R = COMe
277: R = CN

278: R^1 = OH (73%)
279: R^1 = Me (70%)
280: R^1 = NH_2 (68%)

(20)



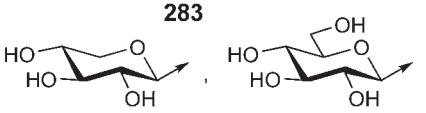


283

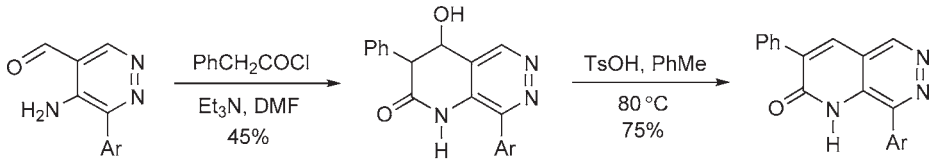
(21)

281: R^1 = OMe; R^2 = H, sugar acetate
282: R^1 = $NHNH_2$; R^2 = H, unprotected sugar

R^2 =



X = O, S



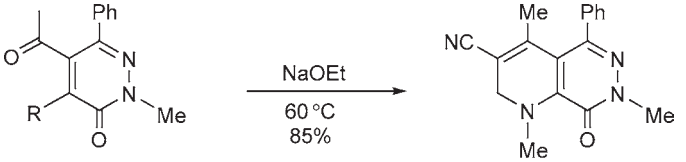
284
Ar = 2-FC_6H_4

285

286

Scheme 7

On the other hand, reaction of 5-acetyl-2-methyl-4-nitro-6-phenyl-3(2*H*)-pyridazinone **287** with *N*-methyl-*β*-alaninenitrile afforded the 4-(2-cyanoethyl) derivative **288**, which was cyclized by heating with sodium ethoxide in ethanol to the pyrido[2,3-*d*]pyridazine **289** (Equation 22) <1994S669>.



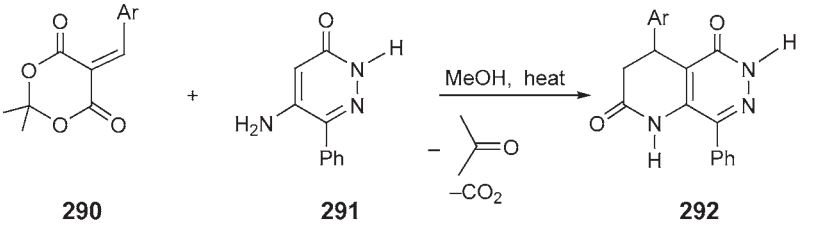
289

(22)

287: R = NO_2
288: R = $MeN(CH_2)_2CN$

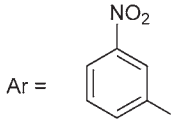
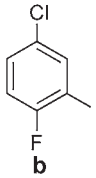
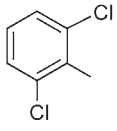
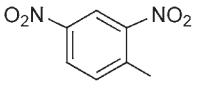
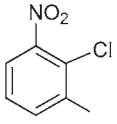
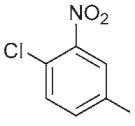
Arylidene-substituted Meldrum's acids **290** were reacted with 5-amino-6-phenyl-3(2*H*)-pyridazinone **291** to yield 4-aryl-2,5-dioxo-8-phenyl-1,2,3,4,5,6-hexahydropyrido[2,3-*d*]pyridazines **292** in one step in good yields

<2000T2473>. The reaction time for completion of the reaction was found to be dependent on the nature of the substituent in the aryl group. Thus, strongly electron-withdrawing groups decreased the required reaction time (Equation 23).

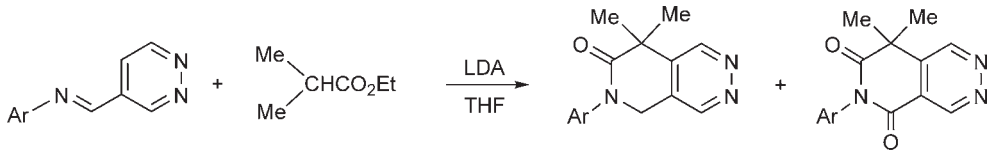


290 + **291** → **292**

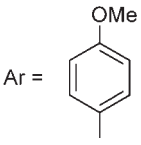
292	*Yield* (%)
a	90
b	88
c	70
d	89
e	90
f	70

Ar =  **a**,  **b**,  **c**,  **d**,  **e**,  **f** (23)

Lithium ester enolate-imine condensation has been used for the preparation of β-lactam rings via addition at the imine moiety <1996H(43)1057>. But treatment of imino derivatives of the pyridazine **293** with the lithium enolate of ethyl α,α-dimethylacetate **294** in THF led to the formation of the pyrido[3,4-*d*]pyridazine **295** and its oxidized form **296**. Compound **295** was obtained by nucleophilic attack of the carbanion species at C-5 of the pyridazine ring followed by cyclization (Equation 24) <1996JHC1731>.

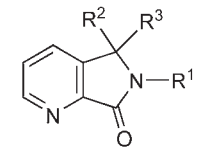


293 + **294** → **295** (35%) + **296** (7%) (24)

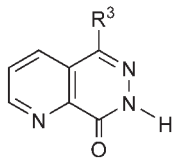
Ar = 

10.16.8.1.2(iii) Ring transformation of other heterocycles

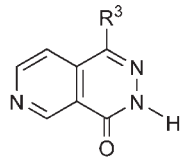
Pyrrolo[*x*,*y*-*z*]pyridine derivatives were found to be converted to the pyridopyridazine rings by the action of boiling hydrazine hydrate, via opening of the pyrrole ring followed by cyclization to the new ring structure. Thus, the pyrido[2,3-*d*]pyridazine derivatives **300–302** were obtained from the pyrrolo[3,4-*b*]pyridines **297–299**, respectively <1996T3261, 2001S221>. Analogue **302** was also formed by refluxing **299** with hydrazine hydrate in acetic acid <1998SC2871>. Similarly, the pyrido[3,4-*d*]pyridazinones **303** and **304** were prepared from [3,4-*c*] analogues of **297** and **298**, respectively <2001S221>.



297: R^1 = Ph; R^2 = OH; R^3 = H
298: R^1 = NMe_2; R^2 = OH; R^3 = Ar
299: R^1 = OH; R^2,R^3 = O

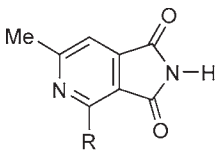


300: R^3 = H (63%)
301: R^3 = Ph (91%), 4-MeC_6H_4 (98%)
302: R^3 = OH (92%)

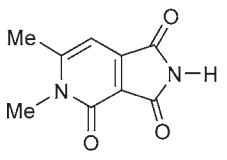


303: R^3 = H (75%)
304: R^3 = Ph (86%), 4-MeC_6H_4 (98%)

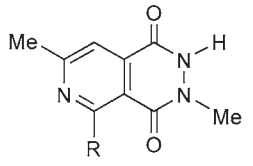
Regioselectivity was observed when the reaction was extended to the use of substituted hydrazines, where the reaction of 3,4-pyridinedicarboximide derivatives **305** or **306** with methylhydrazine in boiling ethanol gave the corresponding 3-methyl-1,4-dioxo-1,2,3,4-tetrahydropyrido[3,4-*d*]pyridazine **307** and 2-methyl-1,4,5-trioxo-1,2,3,4,5,6-hexahydro analogue **308**, respectively, via opening of the imide ring and evolution of ammonia gas <1995FA37>.



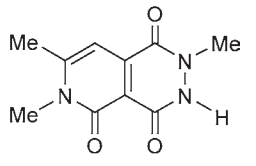
305



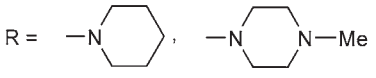
306



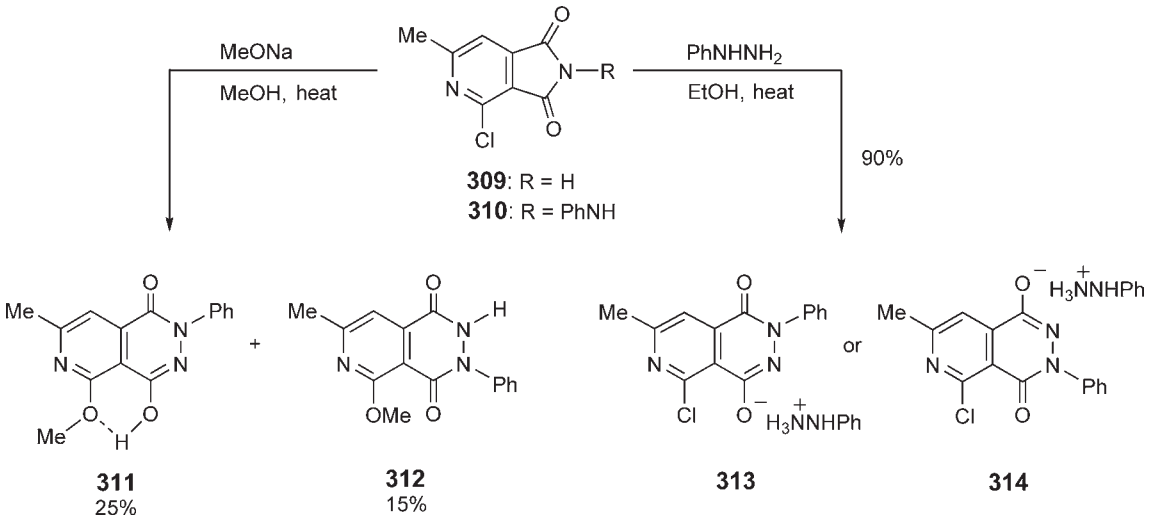
307
50% each



308
35%

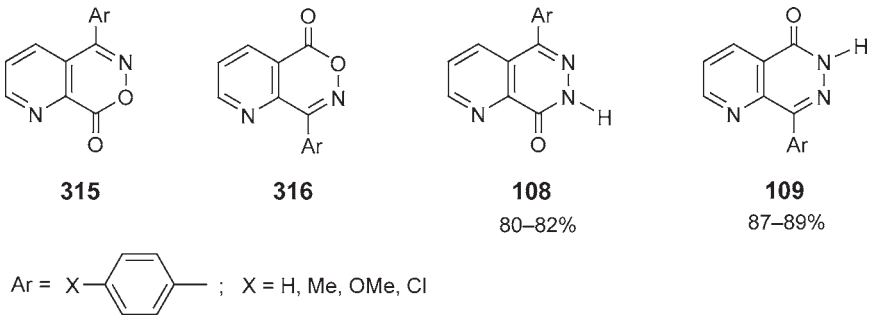
R = 

On the other hand, 2-chloro-6-methyl-3,4-pyridinedicarboximide **309** was reacted with phenylhydrazine to yield the salt of *N*-phenylpyrido[3,4-*d*]pyridazine **313** or **314**. The *N*-phenylaminoimide **310** was isomerized to the corresponding 2- and 3-phenyl isomers **311** and **312** under the influence of heating in methanolic solution of MeONa (**Scheme 8**) <1998FA468>.

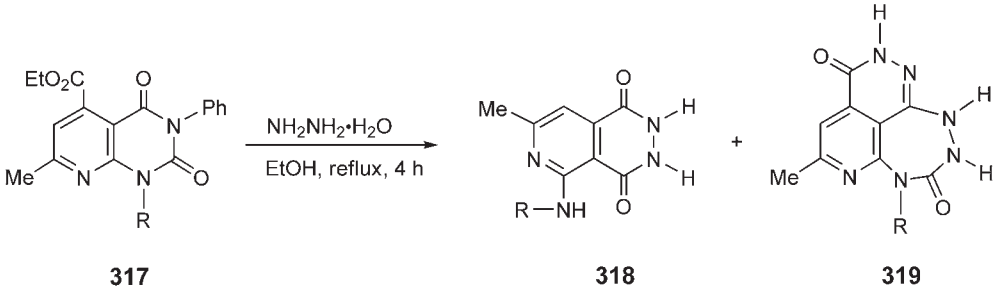


Scheme 8

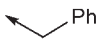
5-Arylpyrido[2,3-*d*]pyridazin-8(7*H*)-ones **108** and 8-arylpyrido[2,3-*d*]pyridazin-5(6*H*)-ones **109** were prepared via ring transformation of 5-arylpyrido[3,2-*d*][1,2]oxazin-8-one **315** and 8-arylpyrido[2,3-*d*][1,2]oxazin-5-one **316** by the action of hydrazine in presence of AcOH <1998SC2871>.

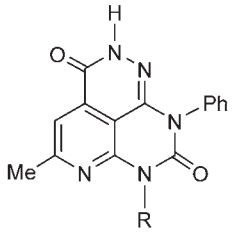


Ring transformation of ethyl 2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylates **317** with 80% hydrazine hydrate in boiling ethanol gave a mixture of 5-methyl/allyl/benzylamino-1,2,3,4-tetrahydro-1,4-dioxopyrido[3,4-*d*]pyridazines **318**, pyrido[2,3,4-*ed*]pyridazino[3,4-*f*][1,2,4]triazepines **319**, and a low yield of 2,3,4,6,7-pentaazaphenalene **320**. The reaction of **317** with hydrazine hydrate was also performed without a solvent in an oil bath at 125 °C for 1 h to give the same products, but higher yields of **318** and lower yield of **319** as well as traces of **320** were obtained (Equation 25) <1997FA657>.

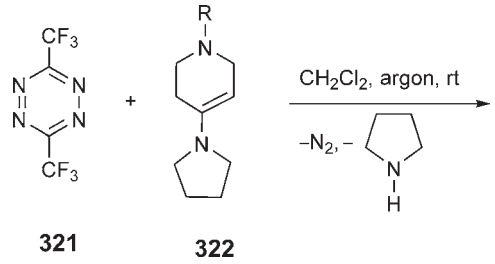


(25)

	Yield with solvent (*without solvent*) (%)		
R	**318**	**319**	**320**
Me	17 (40)	65 (40)	7.5 (30)
	19 (2.6)	60 (2.5)	8.5 (2.5)
	20 (30)	50 (35)	5.5 (55)



[4+2] Cycloaddition of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **321** with 1-methyl(acetyl)-1,2,5,6-tetrahydro-4-pyrrolidinopyridine **322** led to the formation of *N*-methyl(acetyl)pyridopyridazine **323** (Equation 26) <1994H(38)1845>.



R	*Yield* (%)
Me	59
Ac	76

(26)

10.16.8.2 Synthesis of Pyrido[*x*,*y*-*z*]pyrimidines

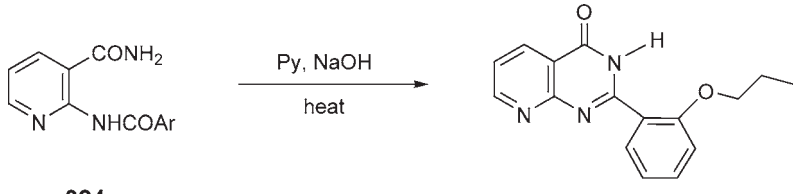
10.16.8.2.1 Synthesis of pyrido[2,3-*d*] and [3,2-*d*]pyrimidines

Pyrido[2,3-*d*]pyrimidine bicyclic systems represent interesting fused heterocyclic compounds having pharmacological and biological properties. Their syntheses are well documented in the literature. The pyridine or pyrimidine rings have been used as precursors for constructing the second heterocyclic ring.

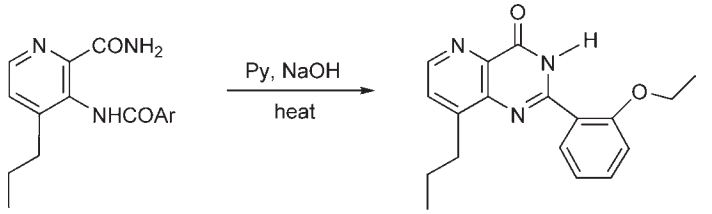
10.16.8.2.1(i) Synthesis from pyridine intermediates

10.16.8.2.1(i)(a) Formation of the pyrimidine ring from [6+0] atom fragments

The pyrimidine rings in the pyrido[2,3-*d*]- and [3,2-*d*]pyrimidinones **325** and **327** were formed by heating the corresponding amides **324** and **326** at reflux in pyridine and aqueous NaOH, respectively (Equations 27 and 28) <1994WO9405661, 2000USP6060477>.

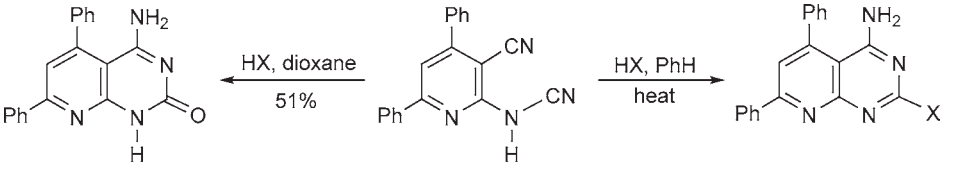


324 **325** (27)



326 **327** (28)

Cyclization of 2-cyanoamino-4,6-diphenylpyridine-3-carbonitrile **328** by using hydrogen halide in benzene led to the 4-amino-2-halogenopyrido[2,3-*d*]pyrimidine **329**. The reaction was regiospecific and the other possible 2-amino-4-halogeno derivative was not detected. The cyclization was much faster when hydrogen bromide was used. When dioxane was used as the solvent, the nonhalogenated compound **330** was obtained as the hydrolysis product of **329** (**Scheme 9**) <1995T10253>.

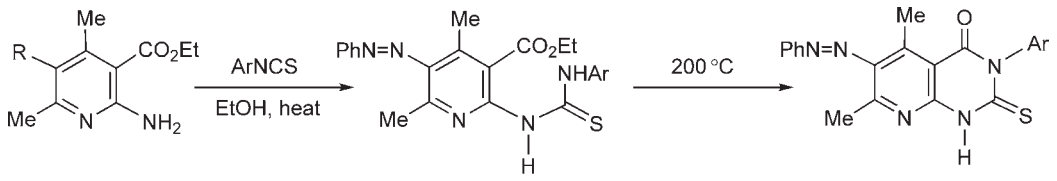


330 **328** **329**

X	*Yield* (%)
Br	75
Cl	34

Scheme 9

The diazo-coupling reaction of 2-amino-3-carbethoxy-4,6-dimethylpyridine **331** with phenyldiazonium chloride followed by reaction of the resulting 5-phenylazo derivative **332** with aryl isothiocyanate gave the pyridothioureas **333**. Thermal cyclization of the latter by heating in an oil bath at 200 °C afforded the pyrido[2,3-*d*]pyrimidine derivatives **334** in good yields (60–80%), while cyclization in boiling pyridine gave **334** in lower yields (40–43%) (**Scheme 10**) <2000IJB210>.



331: R = H
332: R = PhN_2

$PhN_2^+Cl^-$
HCl
66%

333
70–93%

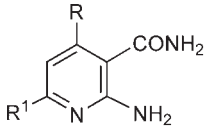
334

	Yield (%)	
Ar (**334**)	*No solvent*	*Pyridine*
Ph	60	40
4-MeC_6H_4	65	43
4-$MeOC_6H_4$	80	43
4-ClC_6H_4	70	40

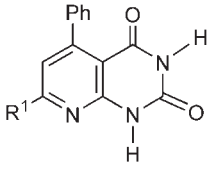
Scheme 10

10.16.8.2.1(i)(b) Formation of the pyrimidine ring from [5+1] atom fragments

Reaction of 2-amino-4-phenyl-6-substituted pyridine-3-carboxamides **335** with ethyl chloroformate in dry pyridine afforded the corresponding 1*H*,3*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione derivatives **337** <1995MI55>. Cyclization of 2-amino-3-carboxamido-4-trifluoromethyl-6-substituted pyridines **336** with benzaldehyde or 4-anisaldehyde in refluxing AcOH gave eight 2,7-disubstituted 1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **338** <1995IJB587>.

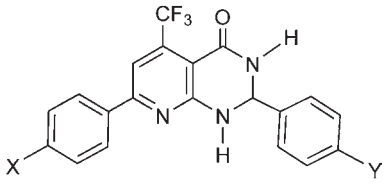


335: R = Ph
336: R = CF_3



337

R^1	*Yield (%)*
Me	71
Ph	88

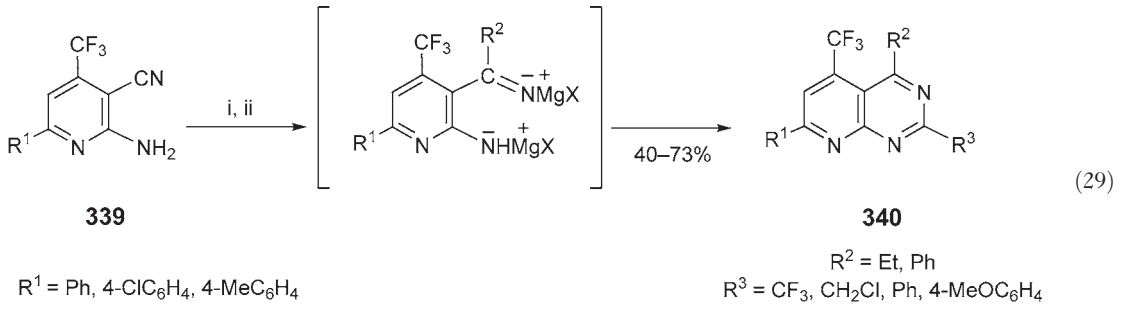


338
X = H, Me, OMe, Cl
Y = H, OMe
65–98%

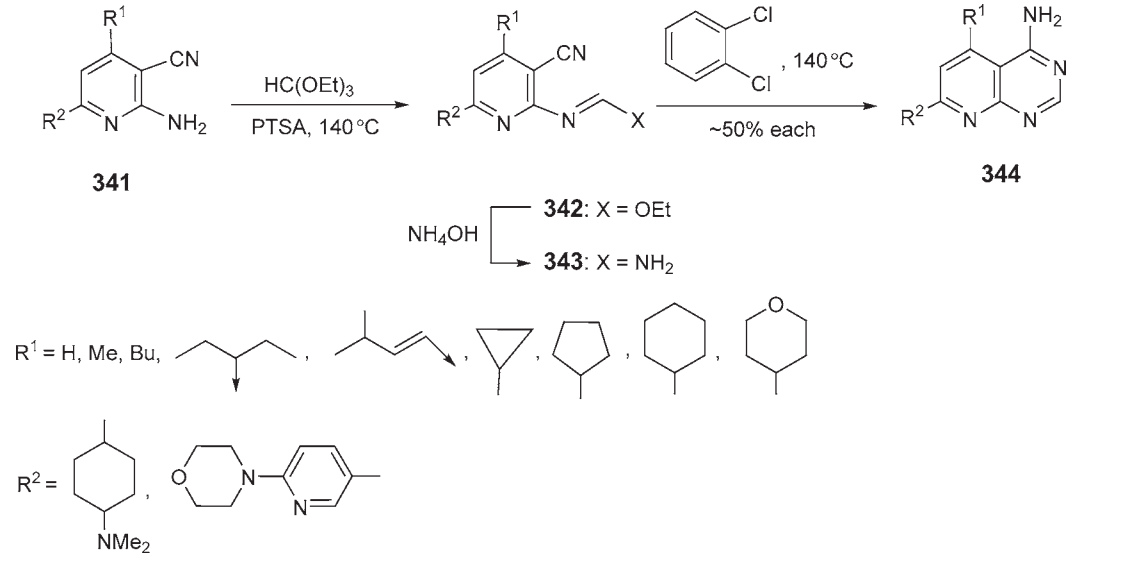
Ten fluorinated 2,4,7-trisubstituted pyrido[2,3-*d*]pyrimidines **340** were synthesized by reacting 2-amino-3-cyano-4-trifluoromethylpyridines **339** with a Grignard reagent followed by condensation with trifluoroacetic anhydride or chloroacetyl chloride at room temperature in a single pot. The reaction took place via the attack of the nucleophile on the nitrile carbon, with subsequent acylation and cyclization. Phenyl Grignard reagent gave higher yields than the ethyl reagent, which was attributed to the destabilization of the anion by the phenyl group. 2-Arylpyrido[2,3-*d*]-pyrimidine derivatives **340** were also synthesized from **339** by reaction with Grignard reagent followed by reaction with aromatic aldehydes under reflux (Equation 29) <2004SC4463>.

5-Alkylpyrido[2,3-*d*]pyrimidine derivatives **344** were synthesized in three steps from 2-amino-3-cyanopyridine intermediates **341** by heating with $HC(OEt)_3$ to produce the iminoether **342** followed by stirring with aqueous NH_3 to give the amidine **343** which was then thermally cyclized to produce **344** (**Scheme 11**) <2001BML83>.

Cyclization of 2-amino-3-cyanopyridine derivatives with CS_2 in the presence of KOH in DMF afforded the corresponding dithioxopyrido[2,3-*d*]pyrimidines **345–349** <1993PHA221, 1994MI203, 2002IJB430>. The spiro analogue **350** was prepared by reacting the generated 2-amino-6-aryl-3-cyano-4-spiro-indole-1,4-dihydropyridine with CS_2 using basic alumina as solid support under microwave irradiation for 2 min <2005ARK80>.



(29)



Scheme 11

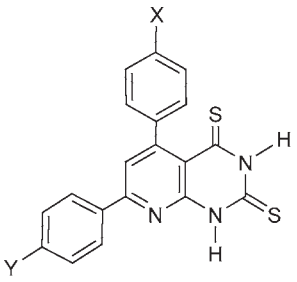
Cyclocondensation of 2-amino-5-nitro-3-pyridinecarboxamide with 4-hydroxybenzaldehyde in the presence of $ZnCl_2$ in refluxing diethylene glycol dimethyl ether gave the pyridopyrimidine **351** <1994MIP2056742>. Reaction of ethyl 2-(1-ethoxyethylidene)amino-4,5,6-trisubstituted-3-pyridinecarboxylate with *N*-(2-aminoethyl)morpholine in the presence of HCl gave the polysubstituted pyridopyrimidin-4(3*H*)-one **352** <1997WO9719946>.

10.16.8.2.1(i)(c) Formation of the pyrimidine ring from [4+2] atom fragments

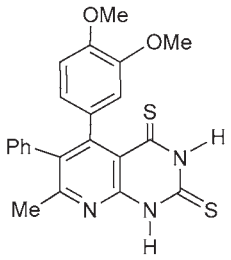
One-pot reaction of 2-aminonicotinic acid **353** with benzoyl chloride and benzylamine under microwave irradiation gave the disubstituted pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **356** <2005TL1241>. Condensation of **354** with phenyl isocyanate or isothiocyanate in the presence of Ph_2O gave the cyclized product **357** and **358**, respectively <1993IJH259, 1997IJH237>. Chlorosulfonyl isocyanate afforded upon reaction with **355** in aqueous $NaHCO_3$ the diethyl analogue **359** <1997WO9719078>.

Cycloaddition of 2-amino-3-cyano-4,5,6-trisubstituted pyridine **360** with formamidine acetate in the presence of diglyme produced the 4-pyridopyrimidinylamine **361** as its hydrochloride salt (Equation 30) <2000USP6030969>.

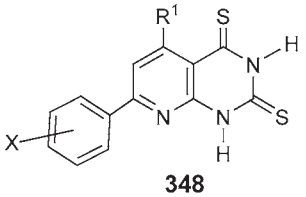
Condensation of 2-amino-3-cyano-4,6-disubstituted pyridine with urea, thiourea, or formamide afforded the pyrido[2,3-*d*]pyrimidines **362** and **363**, respectively <1993PHA221>. Different analogues of **362** (X = O) with 7-[2-(F or OH), 3-(NH_2 or Br), and 4-methylphenyl] and 5-[2-furyl and 2-hydroxyphenyl] groups were also prepared under the same reaction conditions in 72–80% yield <2002IJB430>. Spiro(indolepyrido[2,3-*d*]pyrimidines) **364** were prepared under microwave irradiation by the *in situ* reaction of the generated 2-amino-6-aryl-3-cyano-4-spiro-indole-1,4-dihydropyridine with urea using basic alumina as solid support or a few drops of DMF as homogenizer to increase the reaction temperature. Excellent yields and higher purity were achieved using a 4 min irradiation <2005ARK80>.



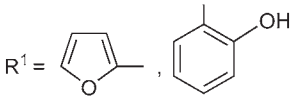
345: X = H; Y = NH_2 (64%)
346: X = MeO; Y = Br (72%)



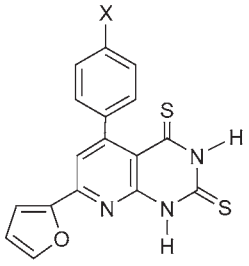
347
98%



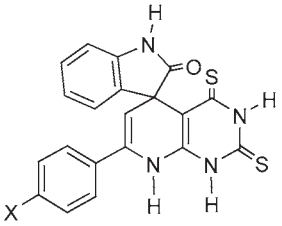
348
68–73%



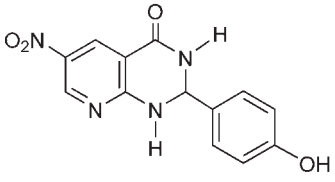
X = 2-F, 2-OH, 3-NH_2, 3-Br, 4-Me



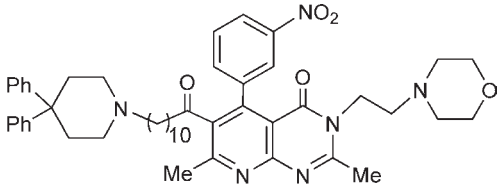
349
X = 2-F, 2-OH, 3-NH_2, 3-Br, 4-Me



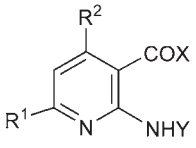
350
X = F (64%)
X = Me (72%)
X = MeO (87%)



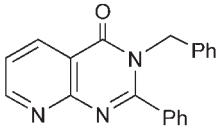
351
68%



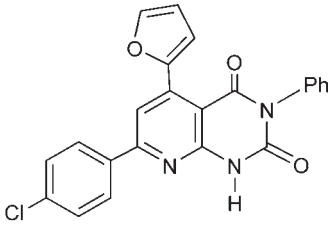
352



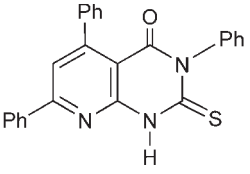
353: X = OH; Y = H
354: X = NH_2; Y = H
355: X = 3-ClC_6H_4; Y = Et
R^1, R^2 = H, Et, Ph, 4-ClC_6H_4, 2-furyl



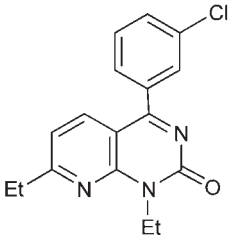
356



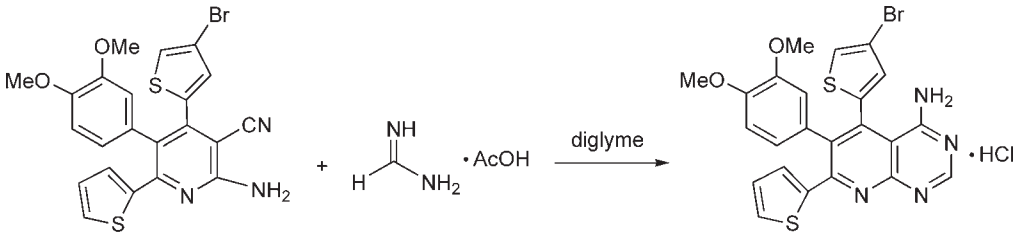
357



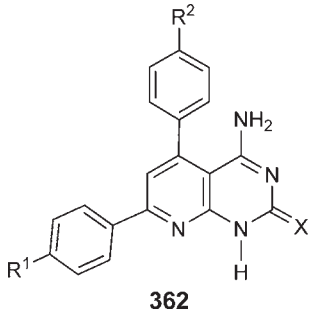
358



359

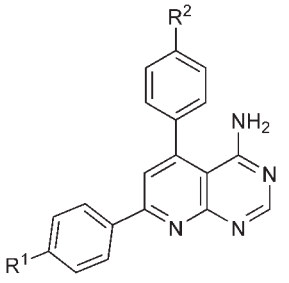


(30)



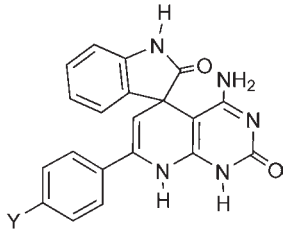
362

R^1	R^2	X	Yield (%)
NH_2	H	O	80
Br	MeO	O	75
NH_2	H	S	78
Br	MeO	S	80



363

R^1	R^2	Yield (%)
NH_2	H	60
Br	MeO	62



364

Y	Yield (%)
F	89
Me	86
MeO	90

Reaction of 2-amino-3,5-dicyano-6-substituted pyridine derivatives with formamide led to pyridopyrimidines **365** <1993JHC253>.

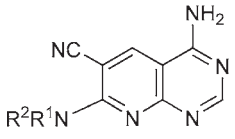
The pyrido[3,2-*d*]pyrimidines **370** were prepared from 2,3-pyridinedicarboxylic acid anhydride **366** by the action of boiling MeOH to give the stable isomer of half-ester **367**. Subsequent treatment with ethyl chloroformate in presence of Et_3N and NaN_3 formed the azide **368** that was transformed by Curtius rearrangement into the isocyanate **369**. Reaction of **369** with a series of amino acids under mild conditions gave adducts **370** (**Scheme 12**) <2003TL2745>.

Cyclocondensation of ethyl 2-aminonicotinate in presence of $HC(OEt)_3$ and various primary amines gave 22 3-substituted pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **371** <1995PHA719>. Fourteen 3,5,7-triarylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **372** have been prepared from the reaction of either 2-amino-3-cyano-4,6-diarylpyridines or the 3-carboxamido products of alcoholic KOH hydrolysis, with aryl isocyanates; better yields were obtained from the amides <1995IJB740>. 4-Aminopyrido[2,3-*d*]pyrimidin-5(8*H*)-one **158** was synthesized by treatment of 2-amino-3-cyano-4-methoxypyridine with trimethylsilyl iodide to give the corresponding pyridin-4(1*H*)-one, which was refluxed with formamidine acetate in ethoxyethanol to effect the cyclization <2000JME3704>.

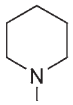
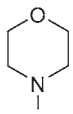
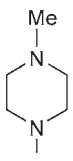
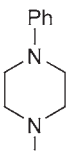
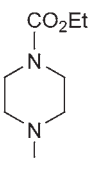
10.16.8.2.1(i)(d) Formation of the pyrimidine ring from [3+3] atom fragments

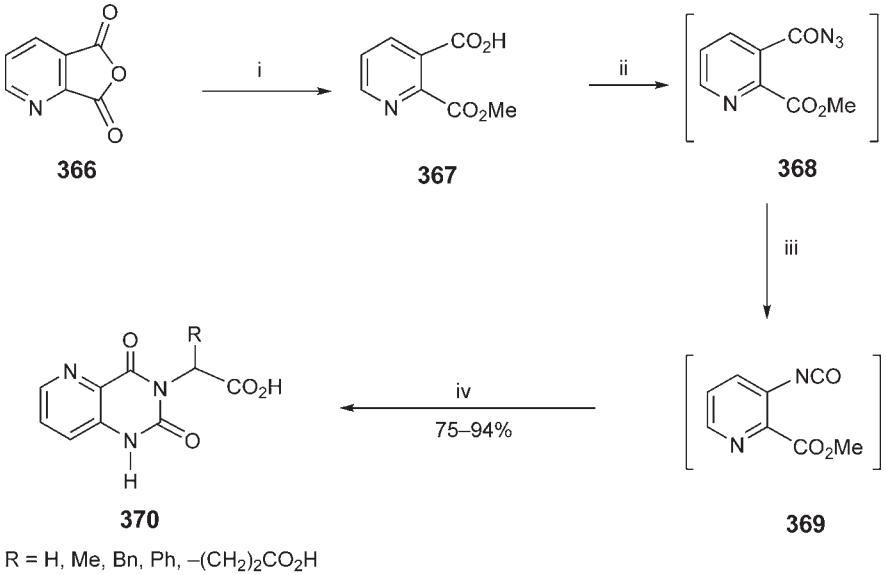
Pyrimidine annulation of 2-chloro-3-cyanopyridine **373** with guanidine in dimethyl sulfoxide (DMSO) at 130 °C afforded the diaminopyrido[2,3-*d*]pyrimidine **374** (Equation 31) <2001H(55)1679>.

^{14}C-Guanidine hydrochloride was also used to afford the labeled diaminopyridopyrimidine derivative **375** via its reaction with 5-benzyl-2-bromo-3-cyano-4-methylpyridine <1993JLR1119>. The 2-thioxo-3-ethoxycarbonylpiperidine derivative was reacted with guanidine hydrochloride to give the tetrahydro analogue **376** <1994EUP593286>. Similar cyclocondensation reaction of 2,6-difluoronicotinic acid with 2-fluoro-5-chlorobenzamidine gave the trihalogenated pyridopyrimidine derivative **377** <2005WO2005065416>.



365

R^2R^1N	Yield (%)
	98
	65
	98
	98
	65
	65

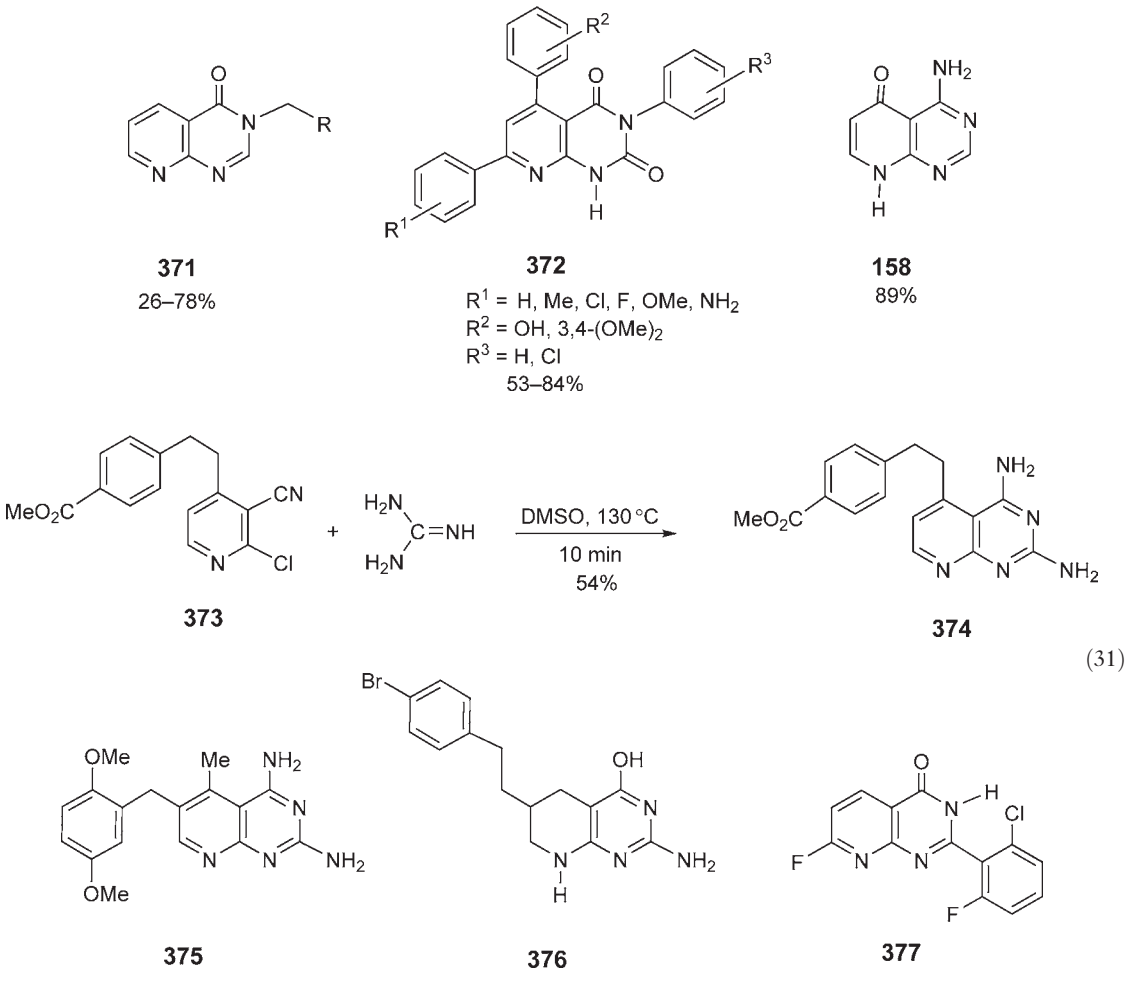


366 **367** **368** **369** **370**

R = H, Me, Bn, Ph, $-(CH_2)_2CO_2H$

i, MeOH, reflux; ii (a), $ClCO_2Et$, Et_3N, THF, −10 °C (b), NaN_3, H_2O, −10 °C; iii, PhMe, reflux; iv, amino acid, NaOH (1 M), H_2O

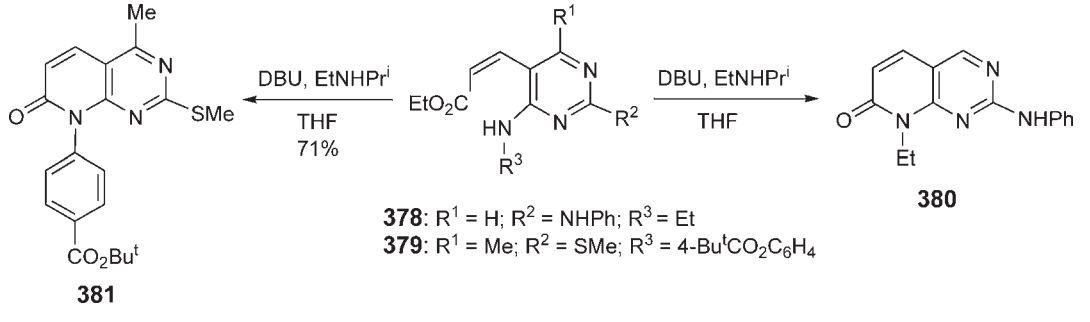
Scheme 12



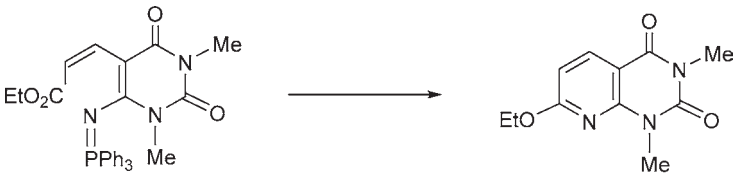
10.16.8.2.1(ii) From pyrimidine intermediates

10.16.8.2.1(ii)(a) Formation of the pyridine ring from [6+0] atom fragments

The pyrido[2,3-*d*]pyrimidinones **380** and **381** were thermally obtained from boiling the ethyl acrylate derivatives **378** and **379**, respectively, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and EtNHPr^i in THF (**Scheme 13**) <2001WO2001055148, 2004USP2004009993>. The acrylates were obtained from reaction of the corresponding pyrimidine-5-carbaldehyde with (carbethoxymethylene)triphenylphosphorane. On the other hand, acrylate **382** was converted into **383** via aza-Wittig cyclization (Equation 32) <1997LA1619>.



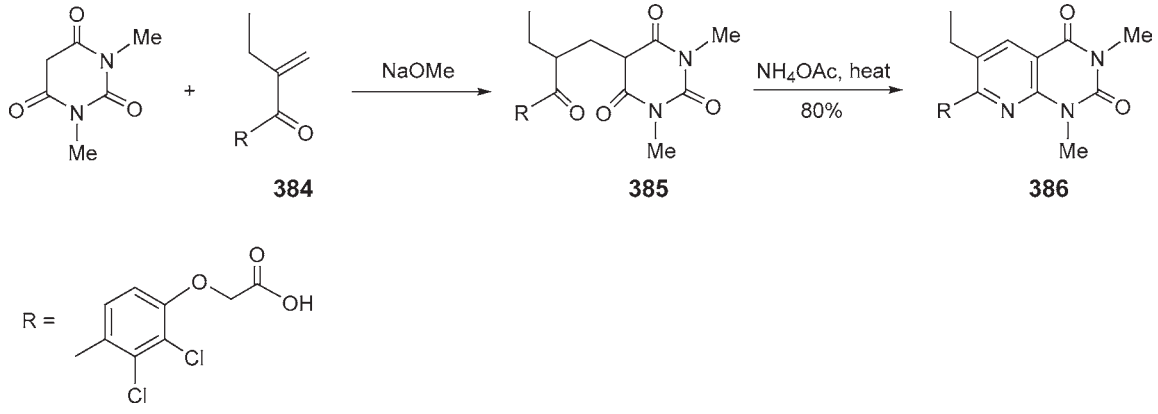
Scheme 13



382 **383** (32)

10.16.8.2.1(ii)(b) Formation of the pyridine ring from [5+1] atom fragments

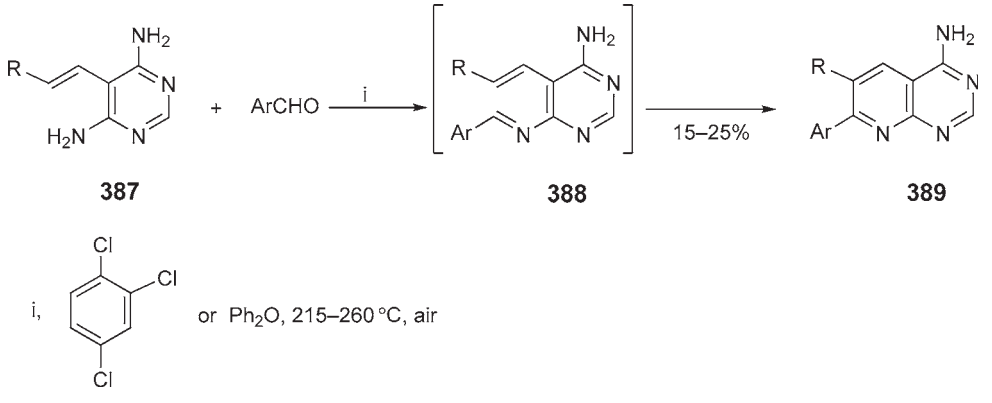
Michael addition of 1,3-dimethylbarbituric acid to etacrynic acid **384** gave the addition product **385**, which upon fusion with ammonium acetate yielded the annulated pyridopyrimidinedione **386** (**Scheme 14**) <1997PHA97>.



384 **385** **386**

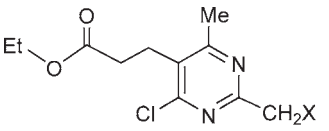
Scheme 14

Thirty-two derivatives, **389**, of 6,7-disubstituted-4-aminopyrido[2,3-*d*]pyrimidine were synthesized by cyclization of alkenylpyrimidines **387** with aryl aldehydes at high temperature in 1,2,4-trichlorobenzene or Ph_2O, via intermediate **388** (Equation 33) <2001WO2001057040, 2005BML2803>.

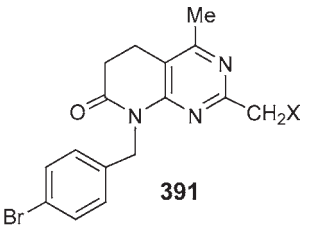


387 **388** **389** (33)

Displacement of the chlorine atom in ethyl (4-chloro-2,6-disubstituted-pyrimidin-5-yl)propionates **390** with 4-bromobenzylamine hydrochloride by refluxing in Bu^nOH in the presence of $NaHCO_3$, followed by cyclization, afforded **391** <1995USP5466692>.



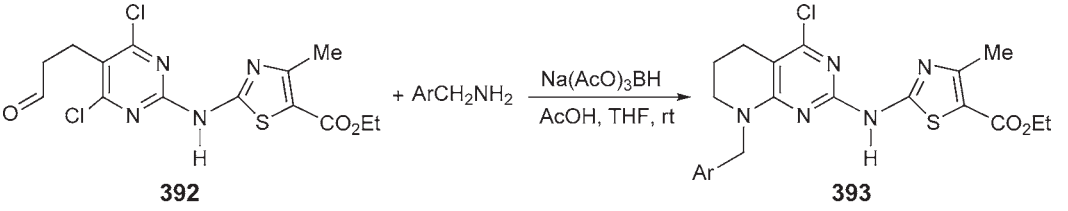
390



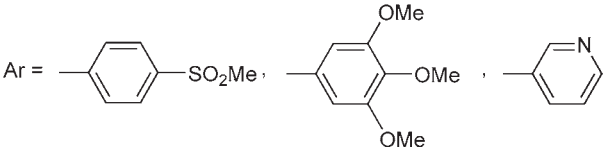
391

X = H, OMe

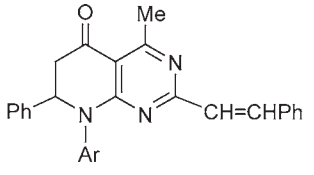
A reductive amination/cyclization step was performed on the aldehyde **392** upon reaction with a variety of amines in the presence of sodium triacetoxyborohydride in THF/AcOH at room temperature to give the tetrahydropyrido[2,3-*d*]pyrimidine **393** (Equation 34) <2005BML1829>.



392 **393** (34)

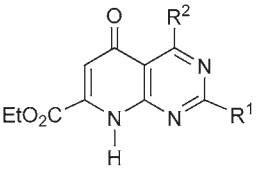
Ar = 

The tetrahydropyridopyrimidine **394** was obtained via condensation of 5-acetyl-4-arylamino-6-methyl-2-styrylpyrimidine with benzaldehyde <1997PJC1232>. The 5,8-dihydropyrido[2,3-*d*]pyrimidine derivatives **395** could be obtained from condensing 5-acetyl-4-amino-2,6-disubstituted pyrimidines with ethyl oxalate in the presence of alkoxide; by-products of Friedländer self-condensation of **395** were also obtained <2002RCB1875>.



394

Ar = Ph, 4-MeC_6H_4, 2-OHC_6H_4

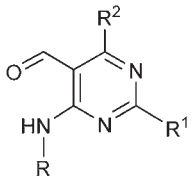


395

R^1, R^2 = Me, Ph, CCl_3, 4-ClC_6H_4, 4-$NO_2C_6H_4$

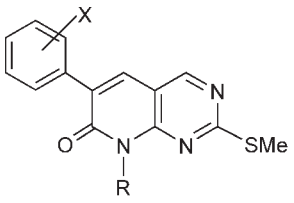
10.16.8.2.1(ii)(c) Formation of the pyridine ring from [4+2] atom fragments

The solid-supported reagent KF/Al_2O_3 in DMF mediated the condensation of 2-methylthiopyrimidine derivatives **396** (R^1 = SMe) with ethyl arylacetate for the preparation of substituted pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **397** <2006TL3177, 2002WO2002018380>. Similarly, the cyclocondensation of 2-amino derivative **396** ($R^1 = NH_2$) with (2,6-dimethylphenyl)acetonitrile gave pyrido[2,3-*d*]pyrimidinimine **398** <1996WO9634867>. Bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate in the presence of 18-crown-6 and bis(trimethylsilyl)amide in THF were used for the conversion of the 6-phenylaminopyrimidine derivative of **396** into the pyridopyrimidine **399** <2002WO2002059083>. Also, the 7-amino-2-oxo analogue **400** was synthesized by reaction of 6-amino-5-formyl-2,3-dihydro-2-oxopyrimidine with $(EtO)_2P(O)CH_2CN$ in the presence of sodium hydroxide <1997JPP09263584>.



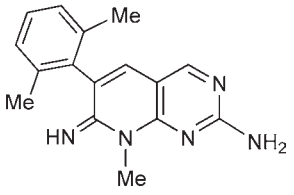
396

R = H, Me, Et, Ph
R^1 = SMe, NH_2
R^2 = H, Ph

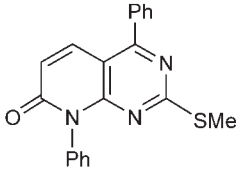


397

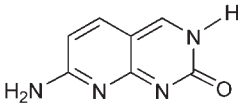
X = H, 2-Me, 2-Cl, 4-OH, 4-MeO, 4-Bu^t, 2,5-$(MeO)_2$, 2,6-Cl_2
56–87%



398

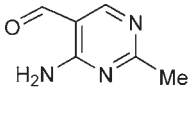


399

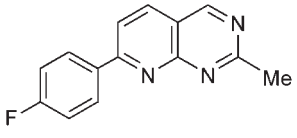


400
14%

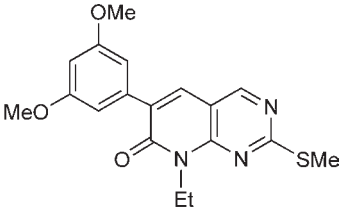
Cyclocondensation of 4-amino-5-formylpyrimidine **401** with 4-fluoroacetophenone furnished 7-substituted 2-methylpyridopyrimidine **402** <1993CAP2078469>, and **396** (R = Et, R^1 = SMe) with ethyl 3,5-dimethoxyphenylacetate in DMSO/DBU at 50 °C gave **403** <2003WO2003027110>.



401

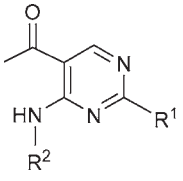


402

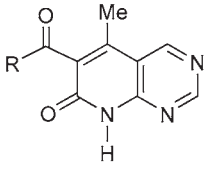


403
84%

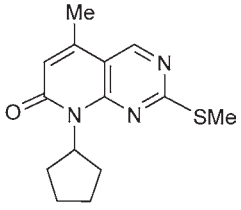
The condensation of 5-acetyl derivative **404** instead of the corresponding 5-formyl compound, with ethyl acetoacetate, ethyl benzoylacetate, and diethyl acetone-1,3-dicarboxylate, by heating in the absence of base gave the respective 6-acylpyrido[2,3-*d*]pyrimidin-7(8*H*)-ones **406**. The reaction of **404** with diethyl malonate afforded the 6-carboxylate **407** <2005RCB784>. Reaction of **405** with triethyl phosphonoacetate yielded **408** <2001WO2001070741>.



404: R^1 = R^2 = H
405: R^1 = SMe; R^2 =

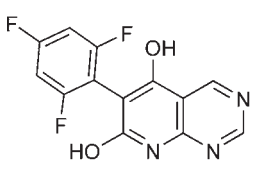


406: R = Me, Ph, $EtOCOCH_2$
407: R = OEt

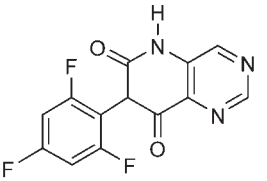


408

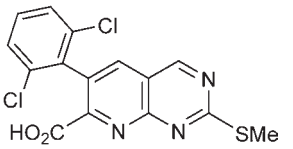
Heating ethyl 4-aminopyrimidine-5-carboxylate with ethyl 2,4,6-trifluorophenylacetate in NaOEt at 130 °C gave dihydroxypyridopyrimidine **409** <2005WO2005010000>, while reaction of the isomeric ethyl 5-aminopyrimidine-4-carboxylate with 2,4,6-trifluorophenylacetyl chloride afforded the tautomeric analogue **410** <2004WO2004056826>. Cyclocondensation of 4-amino-2-(methylsulfanyl)pyrimidine-5-carbaldehyde with a substituted phenylpyruvic acid gave the condensed pyridopyrimidine derivative **411** <2005WO2005090344>.



409
30%

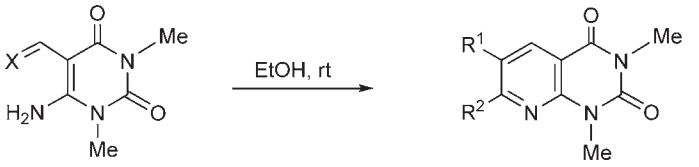


410



411

6-Amino-1,3-dimethyl-5-thioformyluracil **412** has much higher reactivity toward nucleophiles than the corresponding aldehyde **413**. Thus, reactions of **412** with carbanions derived from malononitrile, ethyl cyanoacetate, and diethyl malonate, as well as (cyanomethylene)triphenylphosphorane in alcoholic solution in presence of Et_3N at room temperature gave the cyclized products **414a–d**, respectively <1997CPB542>. The corresponding 5-formyluracil **413** possessed much lower reactivity toward these nucleophiles (Equation 35) <1976JOC1095, 1980H(14)407, 1981JOC846, 1984CPB122, 1984H(22)513, 1984JHC1543, 1985JHC345, 1992AHC(55)129>.

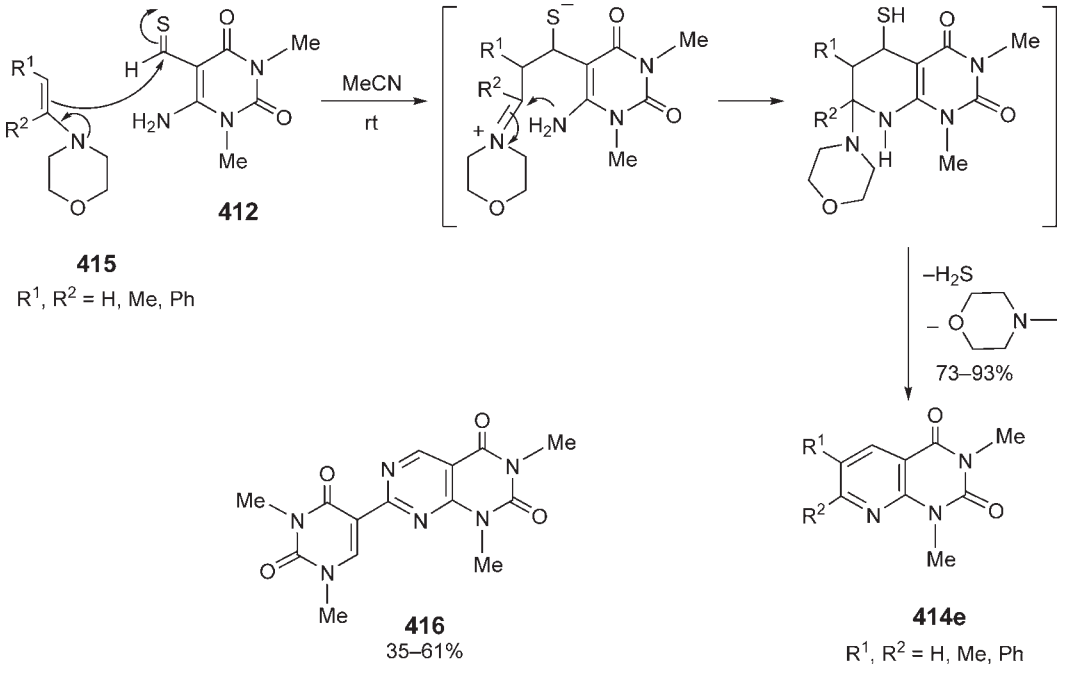


412: X = S
413: X = O

414a: R^1 = CN; R^2 = NH_2 (97%)
414b: R^1 = CO_2Et; R^2 = NH_2 (59%)
414c: R^1 = CO_2Et; R^2 = OH (91%)
414d: R^1 = H; R^2 = NH_2 (73% from **412**, 39% from **413**)

(35)

Reaction of 6-amino-1,3-dimethyl-5-thioformyluracil **412** with morpholino enamines **415** in anhydrous acetonitrile proceeded regiospecifically to give pyrido[2,3-*d*]pyrimidine derivatives **414e** via a nucleophilic attack of the electron-rich enamine **415** on the thioformyl group of **412**, followed by cyclization with the elimination of H_2S and morpholine. On the other hand, the reaction of **412** with phenyl-substituted enamines **415** (R^1 or R^2 = Ph) in boiling acetonitrile gave a by-product **416** together with the expected products **414e** (Equation 36) <1997JOC2999>.



415
R^1, R^2 = H, Me, Ph

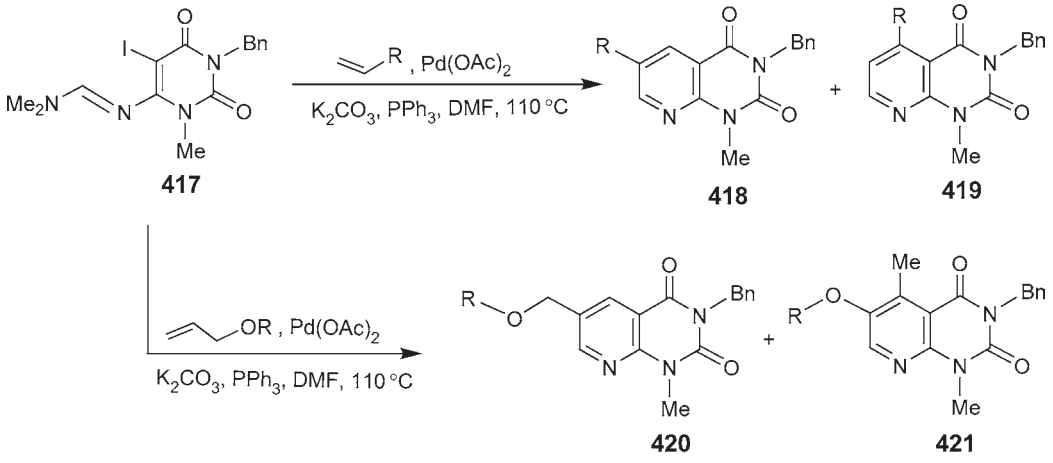
412

416
35–61%

414e
R^1, R^2 = H, Me, Ph

(36)

A series of pyrido[2,3-*d*]pyrimidine-2,4-diones bearing substituents at C-5 and/or C-6 were synthesized using palladium-catalyzed coupling of uracil derivative **417** with vinyl substrates or allyl ethers to give the regioisomeric mixtures of **418**/**419** and **420**/**421**, respectively. The ratio of the isomeric structures was dependent on the substituent R. In the case of the reaction with *n*-butyl vinyl ether, only the product **419** was obtained. However, the reactions with acrylonitrile, ethyl acrylate, 2-trifluoromethylstyrene, and 3-nitrostyrene afforded only **418**. Also, reaction with allyl phenyl ether gave only **420**. The key intermediate **417** was prepared by the reaction of 6-amino-1-methyluracil with DMF–DMA (DMA = dimethylacetamide), followed by N-benzylation with benzyl chloride and vinyl iodination with *N*-iodosuccinimide (NIS) (**Scheme 15**) <2001BML611>.

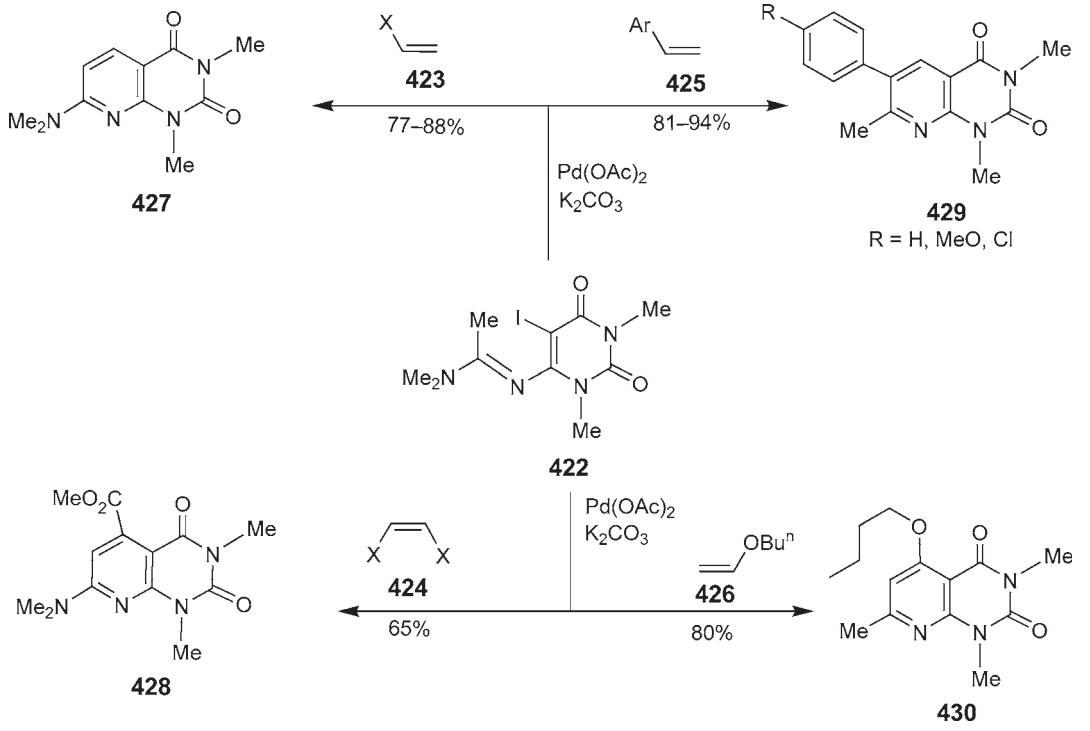


R	Pr^n	Bu^nO	*CN*	CO_2Et	*Ph*	4-ClC_6H_4	4-FC_6H_4	2-FC_6H_4	3-$NO_2C_6H_4$	Bn
418			73%	78%	28%	45%	78%	41%	70%	42%
419		74%			11%	55%	22%	38%		20%
420	17%				25%					22%
421	9%									12%

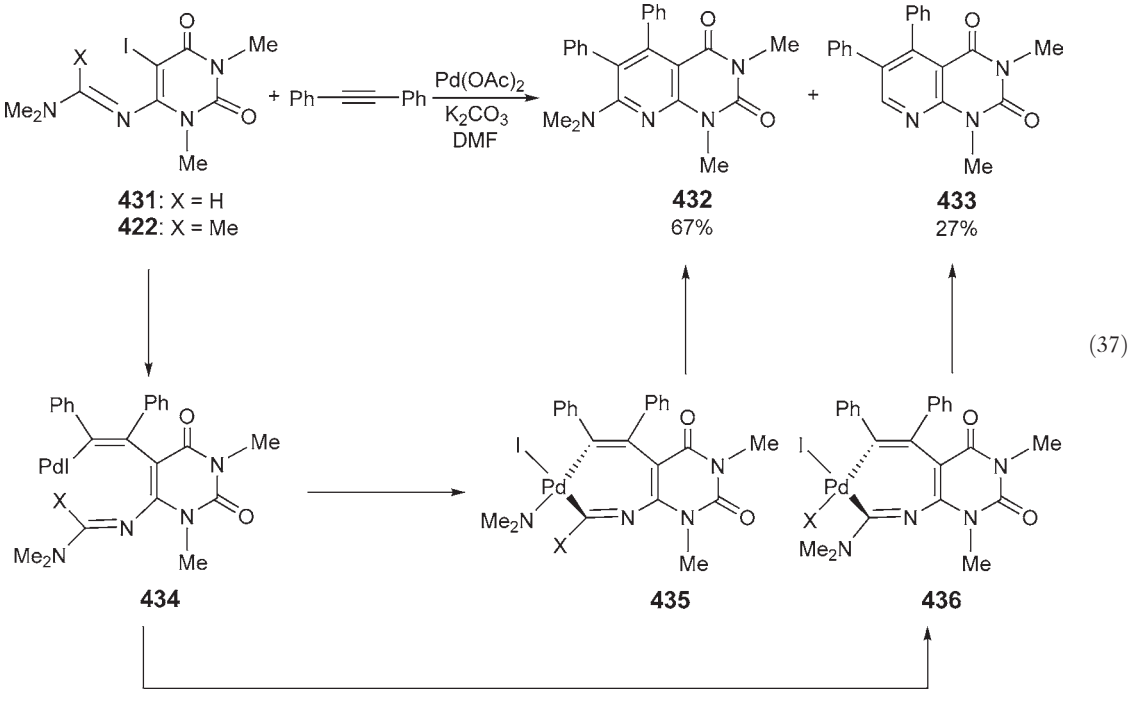
Scheme 15

Similarly, the reaction of iodouracil **422** with styrenes **425** or *n*-butyl vinyl ether **426** gave the deaminated pyrido[2,3-*d*]pyrimidines **429** and **430**, respectively, with a methyl group at the C-7 position. Although the methyl group of the acetamidine moiety is not a good leaving group, the reaction of **422** with ethyl acrylate, acrylonitrile, methyl vinyl ketone (**423**: X = CO_2Et, CN, COMe), or dimethyl maleate (**424**: X = CO_2Me) in the presence of a catalytic amount of $Pd(OAc)_2$ using K_2CO_3 as a base in DMF gave the demethylated pyrido[2,3-*d*]pyrimidines **427** and **428**, respectively (**Scheme 16**) <2000SC81>.

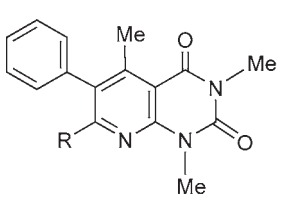
Diphenylacetylene has also been reacted with iodouracil **431** having a formamidine moiety under similar conditions to afford the dehydrogenated product **432** and the deaminated product **433** via intermediates **435** and **436**, respectively. The selectivity increased in the presence of lithium chloride, whereby 93% of **432** with a trace amount of **433** were obtained. The lithium cation prevents the insertion of palladium into intermediate **434** to form intermediate **436**, which is necessary to form **433**. The reaction of **431** with asymmetric acetylenes in the presence of lithium chloride afforded the dehydrogenated pyridopyrimidines **437** and **439**. However, reaction of **422** with acetylenic compounds in the absence of lithium chloride afforded the deaminated pyridopyrimidines **438** and **440** (Equation 37) <2000TL5899>.


427
423
77–88%
425
81–94%
429
R = H, MeO, Cl
Pd(OAc)2
K2CO3
422
428
424
65%
426
80%
430

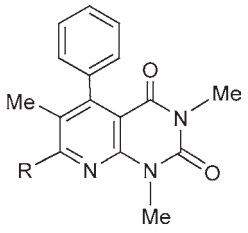
Scheme 16


431: X = H
422: X = Me
Pd(OAc)2
K2CO3
DMF
432
67%
433
27%
434
435
436

(37)

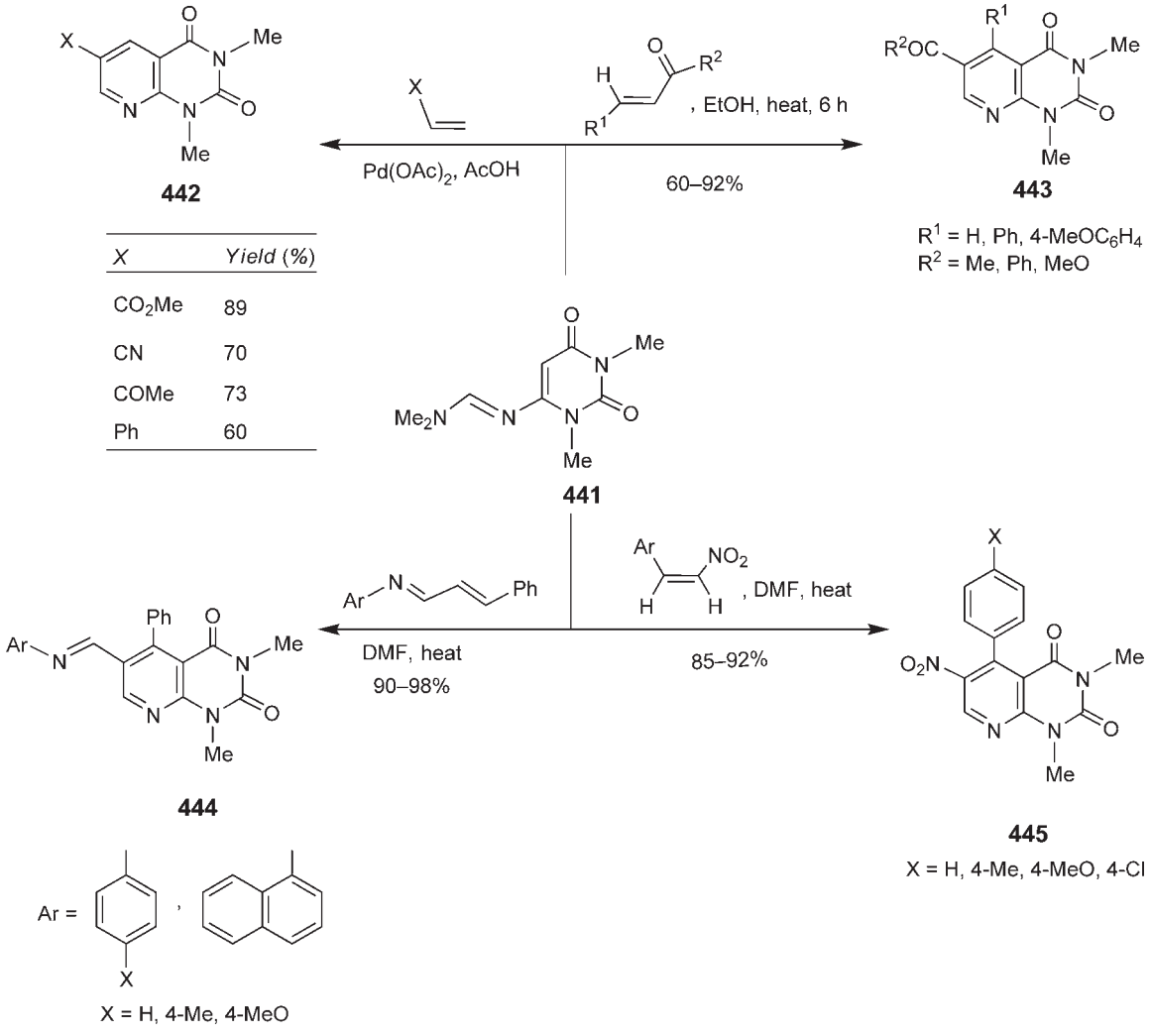


437: R = NMe_2 (60%)
438: R = Me (48%)



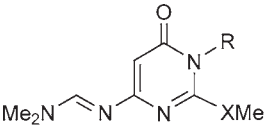
439: R = NMe_2 (36%)
440: R = Me (18%)

Treatment of 6-[(dimethylamino)methylene]amino-1,3-dimethyluracil **441** with an equimolar amount of an α,β-unsaturated carbonyl compound in dry EtOH under reflux (6 h) gave after elimination of dimethylamine from the 1:1 cycloadduct the pyridopyrimidines **443** as the only products. The regioselectivity was due to the electron-donating effect of the dimethylamine substituent which increased the nucleophilicity of the C-5 position. The reaction time could be reduced to 4 min when this reaction was carried out in a microwave oven <2002IJB804>. Treatment of **441** with methyl acrylate, acrylonitrile, methyl vinyl ketone, and styrene in the presence of a stoichiometric amount of palladium acetate in refluxing acetic acid instead of acetonitrile produced the corresponding 6-substituted pyrido[2,3-*d*]pyrimidines **442** in good yield <1994H(37)563>. Uracil **441** was reacted with conjugated imines and α,β-unsaturated nitro compounds in refluxing DMF to afford the pyrido[2,3-*d*]pyrimidines **444** and **445**, respectively (**Scheme 17**) <2001SL1299>.

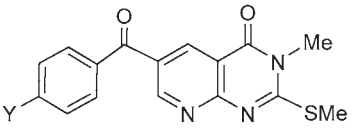


Scheme 17

Treatment of 6-dimethylaminomethyleneaminopyrimidine **446** with *β*-dimethylaminopropiophenone hydrochloride [$ArCO(CH_2)_2NMe_2 \cdot HCl$] in hot DMF gave the corresponding 6-aroylpyrido[2,3-*d*]pyrimidine derivatives **448**, while cyclization of **447** under the same conditions led to the loss of the C-2 methyl group to form the analogues **449** <1999JHC501>.

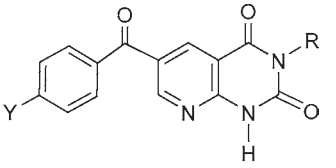


446: X = S; R = Me
447: X = O; R = H, Me



448

Y	*Yield* (%)
Cl	55
Br	58
NO_2	66

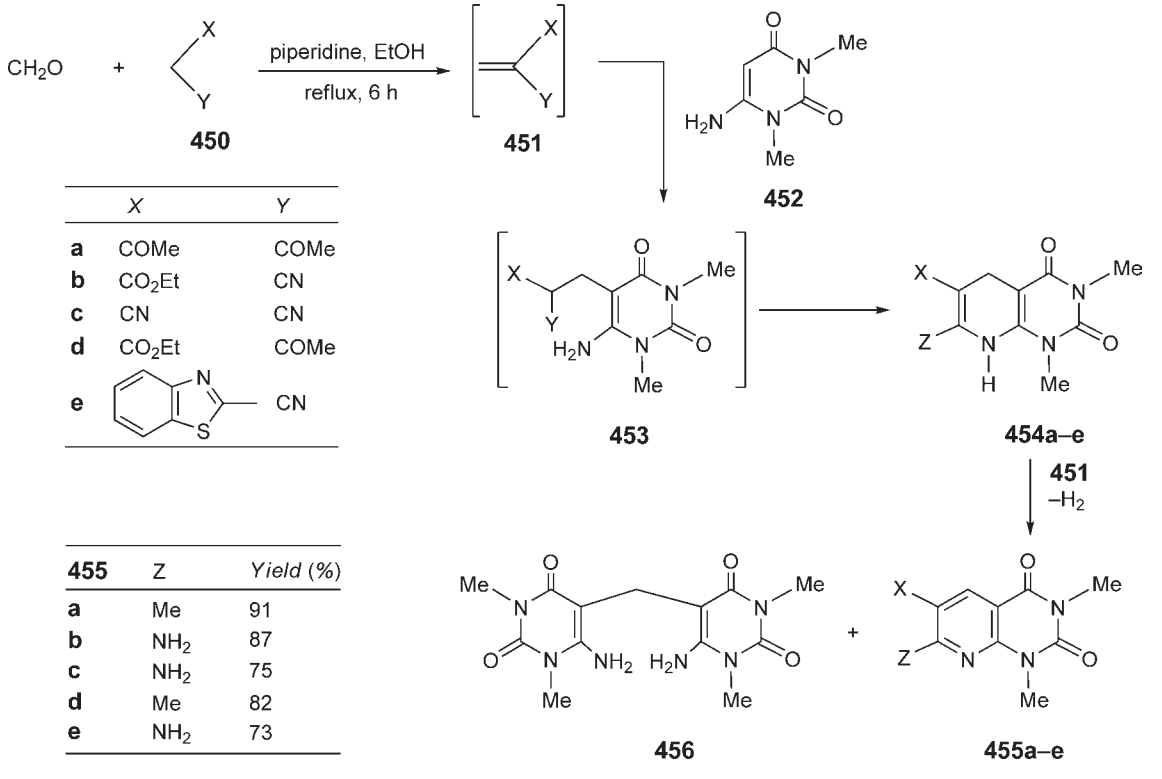


449

Y	*R*	*Yield* (%)
H	H	48
Cl	H	57
NO_2	H	70
H	Me	50
NO_2	Me	68

10.16.8.2.1(ii)(d) Formation of the pyridine ring from [3+3] atom fragments

Several heterocyclization reactions using 6-aminouracil derivatives have been described for the synthesis of pyridopyrimidines. Thus, a one-pot reaction of a 2:2:1 mixture of active methylene compounds **450a–e**, formaldehyde, and 6-amino-1,3-dimethyluracil **452** in boiling ethanol containing a catalytic amount of piperidine gave the pyrido[2,3-*d*]-pyrimidine derivatives **455a–e** in high yields. The reaction proceeds *via* the *in situ* formation of methylene derivative **451**, which then reacted with **452** to yield the Michael adduct **453** that spontaneously cyclized into the dihydropyridine intermediate **454**, which subsequently oxidized to give **455**. The yields were decreased when equimolar amounts of reactants were employed under the same reaction conditions. The dipyrimidinyl derivative **456** was isolated from the reaction mixture as a by-product (**Scheme 18**) <2001H(55)1315>.

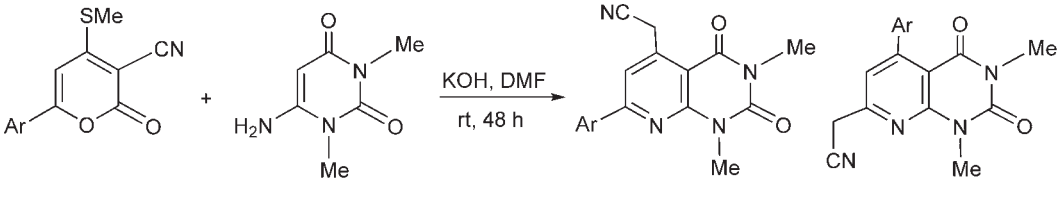


	X	*Y*
a	COMe	COMe
b	CO_2Et	CN
c	CN	CN
d	CO_2Et	COMe
e		CN

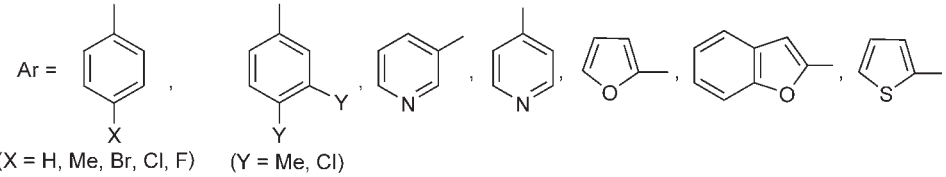
455	Z	*Yield* (%)
a	Me	91
b	NH_2	87
c	NH_2	75
d	Me	82
e	NH_2	73

Scheme 18

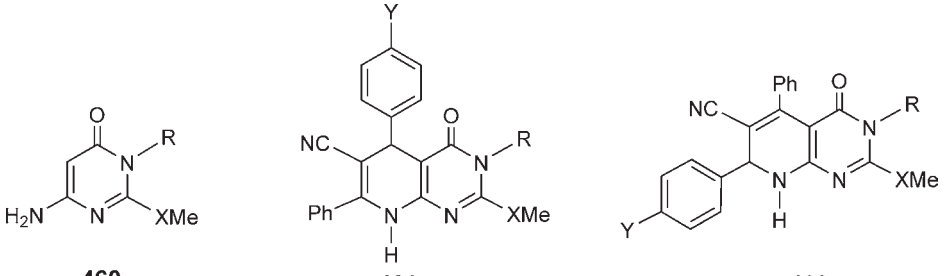
The 7-aryl-5-cyanomethyl-1,3-dimethyl-2,4-dioxopyrido[2,3-*d*]pyrimidines **458** have been regioselectively synthesized through the nucleophilic attack of the amino groups in 6-amino-1,3-dimethyluracil **452** on the highly electrophilic center at C-6 in 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones **457**. Ring opening of **457** followed by decarboxylation and recyclization with the elimination of methylmercaptan gave **458** with no detection of the 5-aryl-7-cyanomethyl isomers **459** (Equation 38) <2000S541>.



457 **452** **458** 66–78% **459** (38)



Microwave irradiation, for 15–20 min under solvent-free conditions, promoted the regiospecific three-component one-step cyclocondensation of benzoylacetonitrile, an aromatic aldehyde, and aminopyrimidinones **460** to give 6-cyano-5,8-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **461** rather than the isomers **462**. The formation of **461** proceeds via a Michael-type addition of C-5 in aminopyrimidine **460** to the activated double bond of the arylidene-benzoylacetonitrile intermediate followed by cyclization with the removal of a water molecule. Compounds **461** were also prepared conventionally by refluxing the reactants in absolute ethanol for 40–48 h <2001TL5625>.

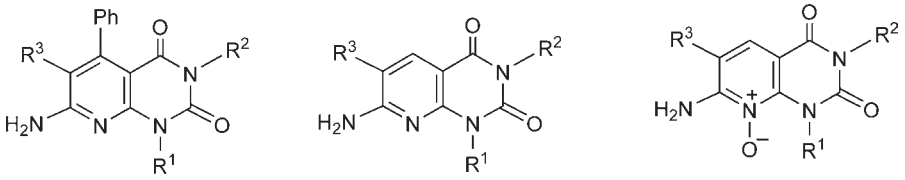


460 R = H, Me; X = O, S

461 70–75%

462 Y = H, MeO, Cl

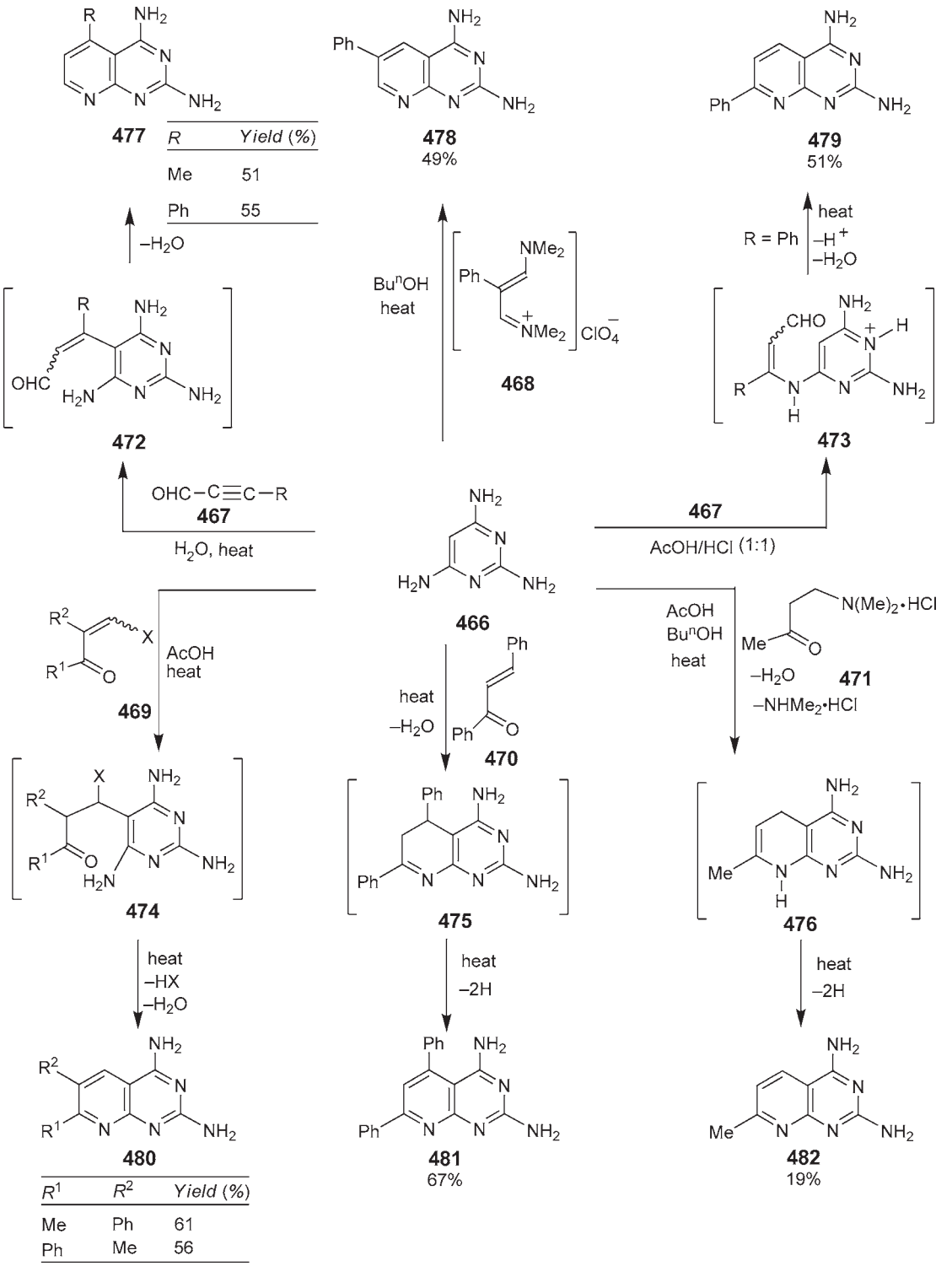
Microwave-assisted multicomponent reaction of 6-amino- or hydroxy-aminouracil derivatives with benzaldehyde and malononitrile or ethyl cyanoacetate in the solid state in the absence or presence of Et_3N for 5–8 min afforded the pyridopyrimidine derivatives **463** <2003TL8307>. Similarly, 6-aminouracil derivatives or 6-hydroxyamino analogues were reacted with $HC(OEt)_3$ and active methylene compounds [$CH_2(CN)_2$ or $NCCH_2CO_2Et$] in the presence of AcOH under microwave-assisted conditions to give the pyrido[2,3-*d*]pyrimidines **464** and their *N*-oxides **465** within 2 or 8 min, respectively. The reaction proceeded under thermal conditions in ethanol or without solvent for 1–4 h to give **464** and **465** in 45–70% and 35–50% yield, respectively <2004SL283>.



463 **464** 85–95% **465** 55–60%

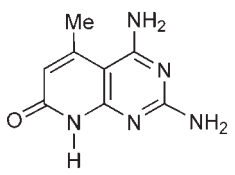
R^1, R^2 = H, Me; R^3 = CN, CO_2Et

An improved synthesis of substituted pyrido[2,3-*d*]pyrimidine-2,4-diamines **477–482** can be carried out by cycloaddition of 2,4,6-triaminopyrimidine **466** with the 1,3-biselectrophiles **467–471** via intermediates **472–476** (**Scheme 19**) <1994AP221>.

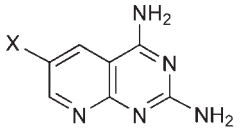


Scheme 19

The triaminopyrimidine **466** was also reacted with ethyl acetoacetate in Ph_2O or dioxane under thermal conditions to form the diamino-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one **483** <1999JOC634>. Its reaction with bromo(nitro)-malonaldehyde in boiling EtOH in the presence of HCl afforded the corresponding 6-bromo(nitro) analogues **484** and **485**, respectively <1996JME1438, 1997JME470>.

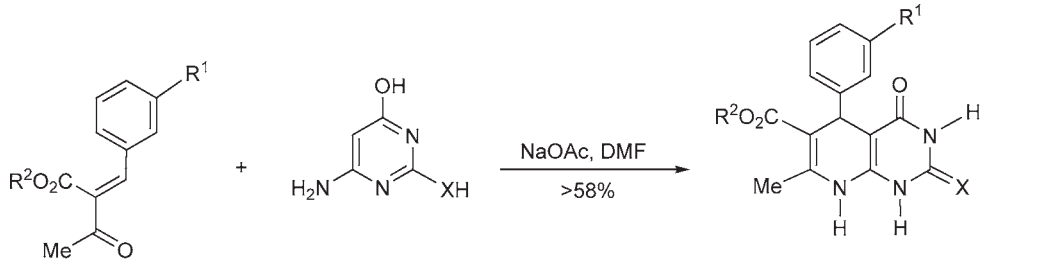


483
51%



484: X = Br
485: X = NO_2 (76%)

It is notable that for 4-aminopyrimidines bearing a 2-hydroxy, 2-mercapto, or 2-amino group as well as the 6-hydroxy substituent, these substituents play an important role in the success of their condensation. Thus, the condensed hexahydropyrido[2,3-*d*]pyrimidine derivatives **488** were prepared by reacting the 4-amino-2,6-disubstituted pyrimidines **487** with arylmethylenacetoacetate **486** (Equation 39) <1994T8085>.



(39)

486

487

X = O, S, NH

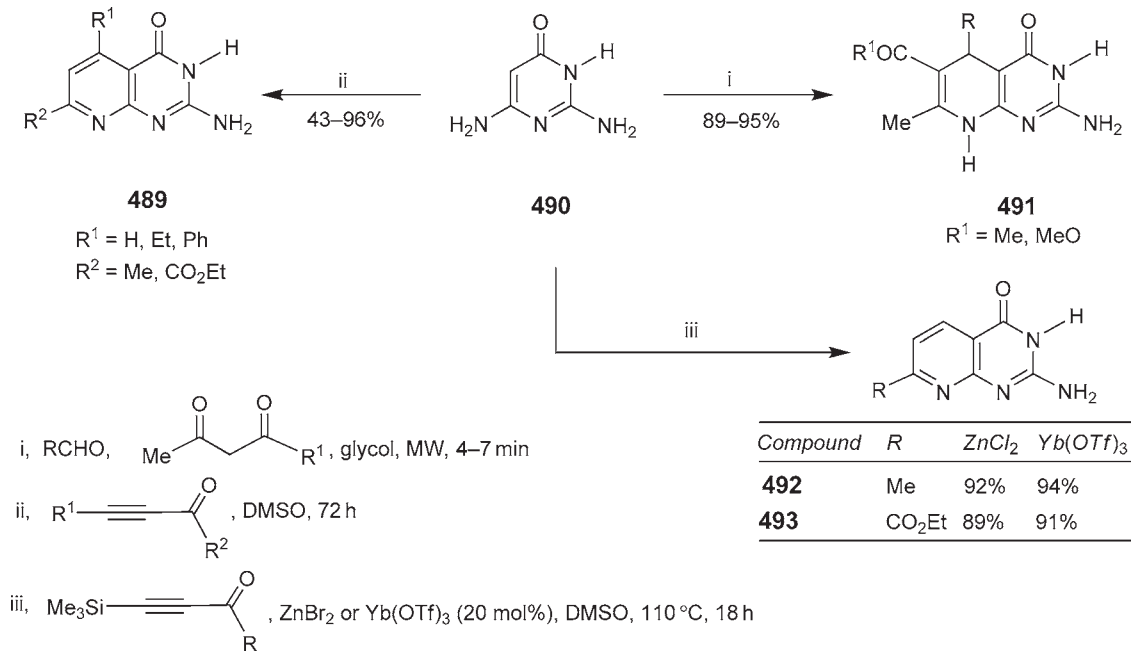
488

R^1 = H, Br, Cl, F, NO_2
R^2 = Me, Et, Pr^i, MeO

One-pot condensation of 2,6-diaminopyrimidin-4(3*H*)-one **490** with an alkyl (aryl) aldehyde and acyclic 1,3-dicarbonyl compounds in glycol under microwave irradiation without catalyst afforded 15 5,6-disubstituted-7-methyl-5,8-dihydropyridopyrimidines **491** <2005ARK76>. The Michael addition and subsequent cyclodehydration of **490** with α-ketoalkynones provided the pyrido[2,3-*d*]pyrimidines **489** in excellent yields. The reaction was run in a range of different solvents at room temperature or 60 °C, where the most reliable reaction conditions involved stirring for 72 h at either room temperature or 60 °C in DMSO <2001TL6585>. The reaction of **490** with either 4-trimethylsilylbut-3-yn-2-one or ethyl 2-oxo-4-(trimethylsilyl)but-3-ynoate in DMSO in the presence of zinc(II) bromide or ytterbium(III) triflate as Lewis acids catalyzed the Bohlmann–Rahtz heteroannulation reaction to give pyridopyrimidine derivatives **492** and **493**, respectively (**Scheme 20**) <2001SL1523>.

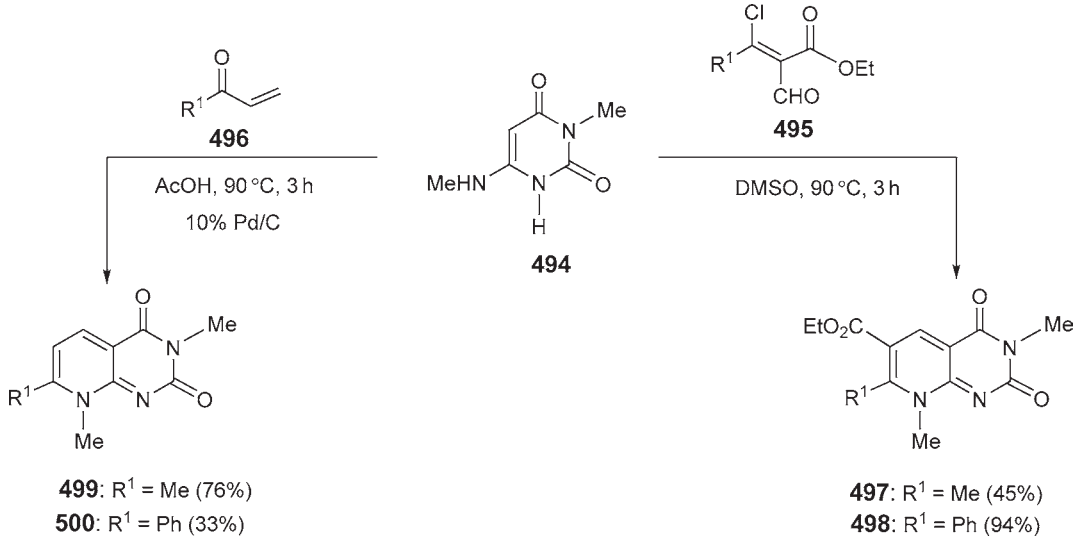
Reaction of 3-methyl-6-methylaminouracil **494** with **495**, obtained by the Vilsmeier reaction of ethyl acetoacetate and ethyl benzoylacetate, or with vinyl ketones **496** under a modified procedure previously described <1984CPB1699, 2002H(57)491>, afforded the pyrido[2,3-*d*]pyrimidine derivatives **497–500** (**Scheme 21**) <2004H(63)1393>.

Reaction of 3-(5-acetoxyhexyl)-6-amino-1-methyluracil with diketene in boiling dichloroethane gave the cyclized pyrido[2,3-*d*]pyrimidine-2,4,5-trione **501** <2002WO2002094824>. Also, reaction of 6-amino-1-phenyluracil with methoxyvinyl cyanide gave 7-amino-tetrahydropyrido[2,3-*d*]pyrimidinedione **502** <2001EPP1145716>. The cyano



Compound	R	$ZnCl_2$	$Yb(OTf)_3$
492	Me	92%	94%
493	CO_2Et	89%	91%

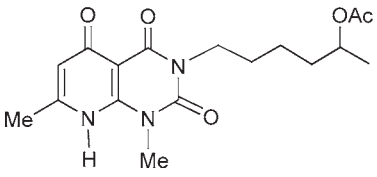
Scheme 20



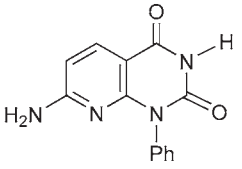
Scheme 21

analogues **503** were prepared via initial Michael addition of 4-aminouracil to cinnamonitrile ($ArCH{:}C(CN)_2$) followed by cyclization to give a 5,8-dihydro intermediate which subsequently underwent oxidation to the fully aromatized **503** in boiling DMF <1996JIC623>. Twelve 2,4-dihydroxy tautomeric analogues of **503** were prepared by reacting substituted benzaldehydes with malonitrile and 4-amino-2,6-dihydroxypyrimidine in EtOH at 80 °C with $KF–Al_2O_3$ as catalyst; the 1,3-dihydro derivatives were not detected <2004SC4331>. The analogues **504** were prepared from the reaction of 2-oxindolin-3-ylidenemalonitriles with 6-amino-1,3-dimethyluracil in boiling EtOH. The structure of

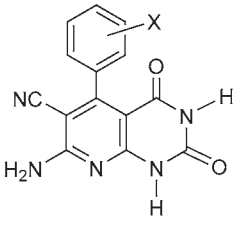
the spiro product **504** was confirmed by one-pot unequivocal synthesis via reaction of isatin with malononitrile and 6-amino-1,3-dimethyluracil in refluxing EtOH in the presence of a catalytic amount of piperidine <2000SC2223>. On the other hand, one-step reaction of 6-amino-2-methoxy or methylthiopyrimidin-4(3*H*)-one with a 4-substituted benzaldehyde and ethyl cyanoacetate gave 5-aryl-6-cyano-3*H*,8*H*-pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives **505** <1999JHC113>.



501

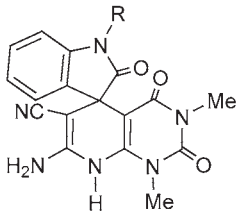


502



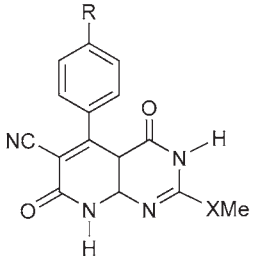
503

X = H, 2-Cl, 4-Cl



504

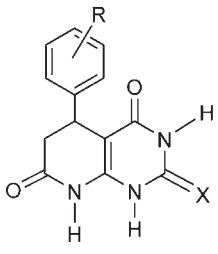
R	*Yield (%)*
H	80
Me	87



505

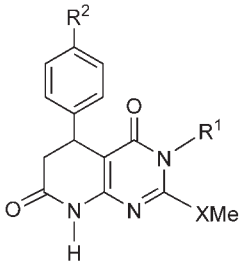
X	*R*	*Yield (%)*
O	H	65
O	Cl	68
O	NO_2	70
S	H	65
S	Cl	70
S	NO_2	68

Reaction of 6-amino-uracil or thiouracil with an arylidene-substituted Meldrum's acid in boiling AcOH afforded the corresponding octahydropyrido[2,3-*d*]pyrimidines **506** <1996JHC45>. Similar cyclization using 6-amino-2-methoxy or methylthiopyrimidin-4-one derivatives in boiling nitrobenzene led to **507** <1997JHC521>.



506

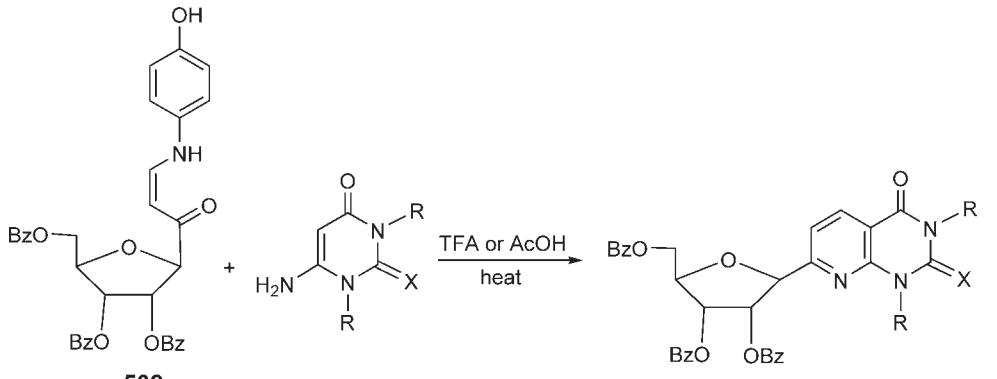
X	*R*	*Yield (%)*
O	2-NO_2	54
S	2-NO_2	52
O	3-NO_2	50
S	3-NO_2	48
O	2-Cl	60
S	2-Cl	54



507

X	*R^1*	*R^2*	*Yield (%)*
S	H	H	70
S	Me	H	68
O	H	Cl	76
S	H	Cl	77
S	Me	Cl	78
O	Me	NO_2	72
S	H	NO_2	84
S	Me	NO_2	82

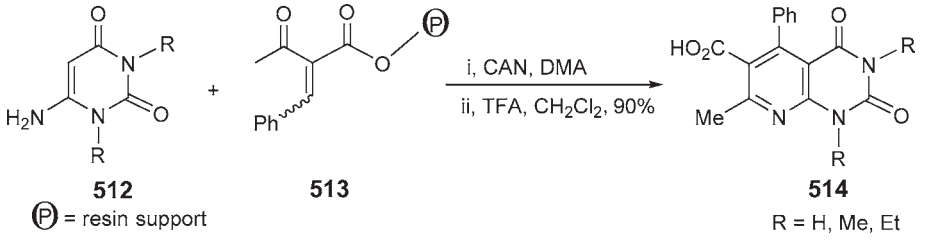
Rare C-nucleosides were observed via cyclocondensation of the glycosyl enaminone **508** with 6-amino derivatives of uracil, thioxouracil, and 1,3-dimethyluracil to give the 7-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)pyrido[2,3-*d*]pyrimidine derivatives **509–511**, respectively (Equation 40) <1996CAR71>.



(40)

Compound	R	X	Yield (%)
509	H	O	64
510	H	S	77
511	Me	O	87

Solid-phase synthesis of pyrido[2,3-*d*]pyrimidines **514** was achieved by Hantzsch condensation of Wang resin-supported Knoevenagel derivative **513** with 6-aminouracil derivatives **512** as an α-oxo enamine component in the presence of ceric ammonium nitrate (CAN) in DMA followed by hydrolysis with TFA in CH_2Cl_2. Compound **513** was prepared by treatment of a hydroxylated polymer, such as Wang or Sasrin resin, with diketene, followed by condensation with benzaldehyde (Equation 41) <1996TL4643>.



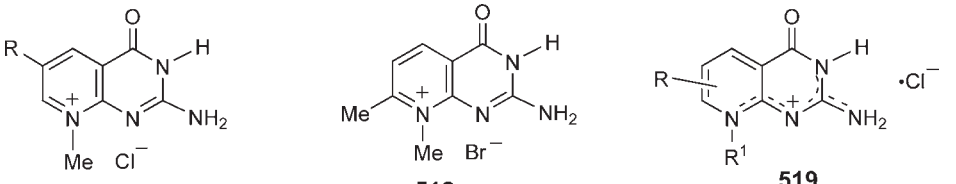
512
Ⓟ = resin support

513

514
R = H, Me, Et

(41)

Condensation of 2-amino-6-methylaminopyrimidin-4(3*H*)-one with freshly sublimed triformylmethane in aqueous or methanolic hydrochloric acid under nitrogen yielded the pyridopyrimidinium salt **515** and **516**, respectively. On the other hand, the condensation under $H_2O/HCl/O_2$ conditions gave the 6-carboxylic acid derivative **517**. The dimethylpyridopyrimidine salt **518** was prepared from the reaction with freshly distilled 2-(2-bromoethyl)-2-methyl-1,3-dioxolane under N_2 at 60 °C <1993JOC1104>. An improved condensation reaction of malonaldehyde bis(dimethylacetal), methacrolein, methyl vinyl ketone, or crotonaldehyde with 6-alkylamino-2-aminopyrimidin-4(3*H*)-ones in the presence of $NaHSO_3$ in mild acidic solution at room temperature gave 8-alkyl-2-aminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one hydrochlorides and their monomethyl analogues at the 6-, 7- and 5-positions **519** <1994JHC1385> in better yields than reported earlier <1993JOC1104>.

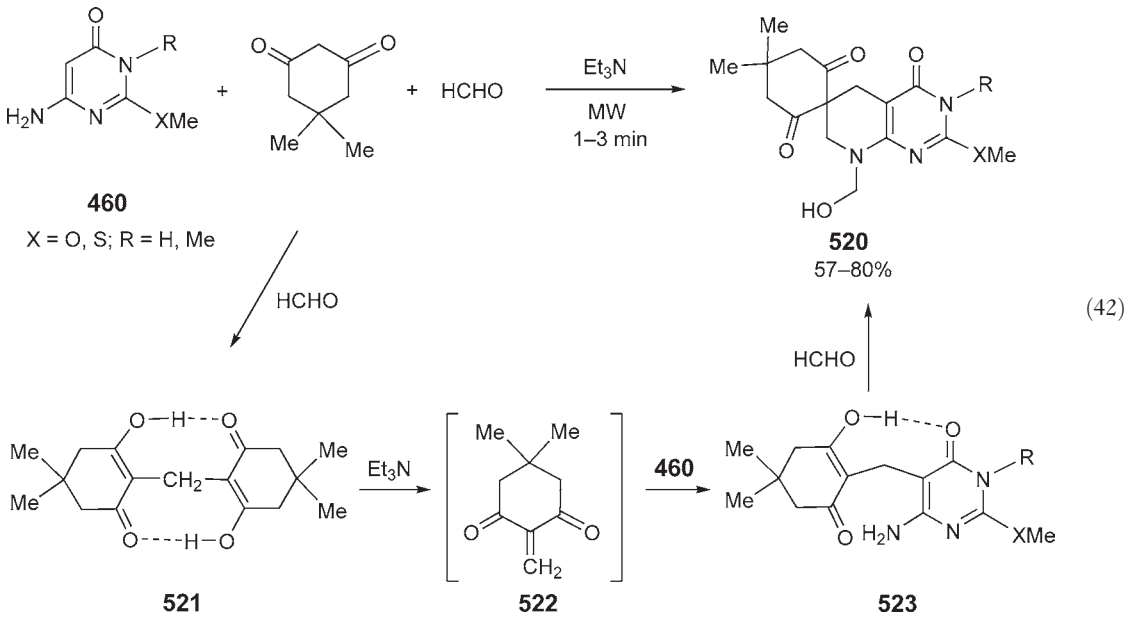


515: R = CHO (57%)
516: R = $CH(OMe)_2$ (70%)
517: R = CO_2H (46%)

518
70%

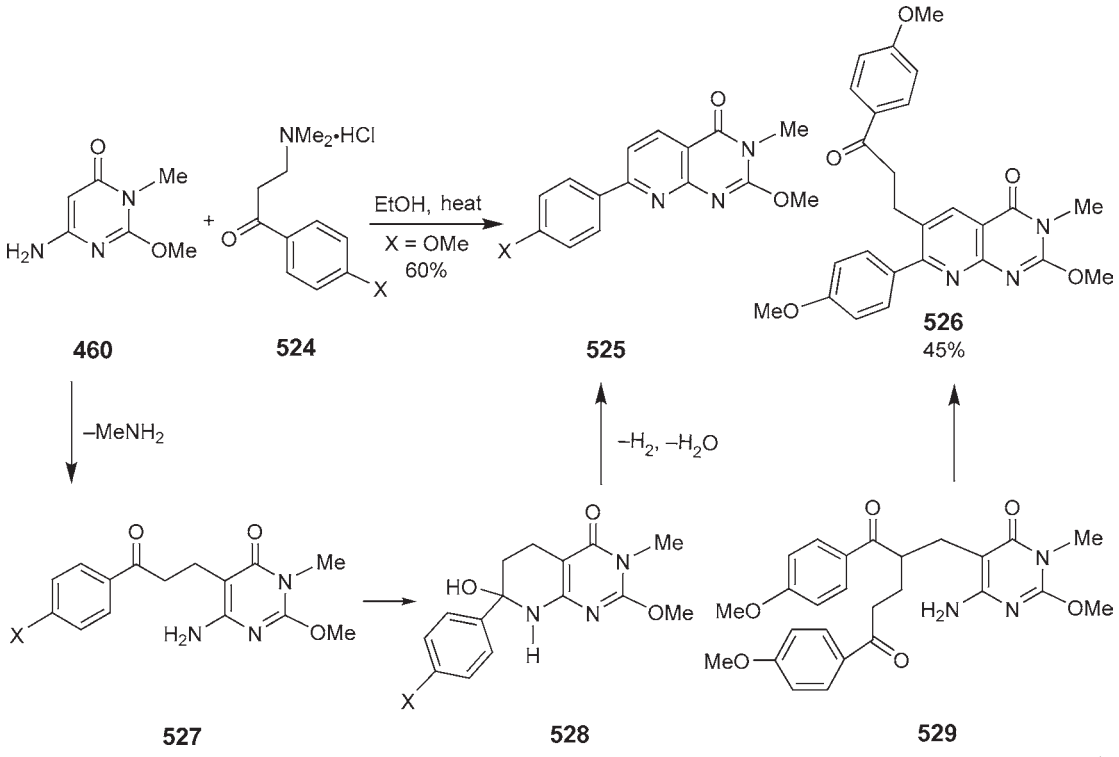
519
R = H, Me
R^1 = Me, Et, Pr^n, Pr^i, Bu^i
32–99%

The unexpected 8-hydroxymethylhexahydropyrido[2,3-*d*]pyrimidine-6-spiro-1′-cyclohexane-2′,4,6′-triones **520** were obtained from microwave-assisted cyclocondensation of equimolar amounts of 6-aminopyrimidin-4-ones **460** and dimedone with a large excess of formaldehyde (37% in water) in the presence of Et_3N as a catalyst <2006TL27>. The reaction proceeded via an initial formation of the 2:1 dimedone/formaldehyde adduct **521** that gave intermediate **522** and **523** which could undergo cyclocondensation with excess formaldehyde to give **520** (Equation 42) <2006TL27>.



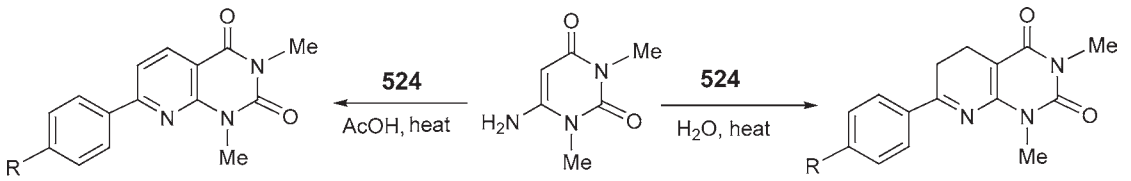
(42)

When 6-aminopyrimidinone **460** (R = Me, X = O) was reacted with an equimolar amount of 3-dimethylaminopropiophenone hydrochlorides **524** in boiling ethanol, it gave selectively the 7-arylpyrido[2,3-*d*]pyrimidines **525** in moderate to good yields. The Michael adducts **527** and the derived hemiacetals **528** were isolated in some cases. Similarly, reaction of **460** with **524** (X = OMe), in 2:1 molar ratio, led to **525** (X = OMe) in 60% yield, whereas, when the molar ratio was 1:1, the product **526** was formed via formation of the intermediate **529** that resulted from a second alkylation of the initial Michael adduct on the active methylene group (Equation 43) <2002T4873>.



(43)

Reaction of 6-amino-1,3-dimethyluracil with the Mannich base **524** under nitrogen in boiling H_2O gave 5,6-dihydropyrido[2,3-*d*]pyrimidine-(1*H*,3*H*)-2,4-diones **531** rather than their oxidized analogues **530**. The latter could be obtained by boiling the reactants in AcOH (**Scheme 22**) <2004T11511>.



530

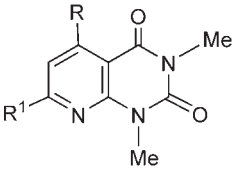
R	*Yield* (%)
H	54
Me	49
Br	66

531

R	*Yield* (%)
H	50
Me	61
Br	66

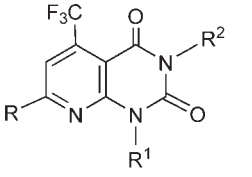
Scheme 22

Reactions of substituted α-ketoalkynes ($RC{\equiv}CCOR^1$) with 6-amino-1,3-dimethyluracil and a water-soluble nickel catalytic system [$Ni(CN)_2$–CO–KCN–NaOH] afforded 2,4-dioxopyrido[2,3-*d*]pyrimidine derivatives **532** under very mild conditions (room temperature and atmospheric pressure). The mechanism involved a nucleophilic attack by Ni(0), formed *in situ*, onto the triple bond of the substrate. The reaction terminates within 30 min, giving ~98% of **532**, while in the absence of this catalytic system the reaction took a longer time (10 h) to reach a maximum yield of ~30% <2001J(P1)2341>. A regioselective interaction of 6-aminouracil derivatives with CF_3COCH_2COR in boiling AcOH afforded the cyclized 5-trifluoromethylpyrido[2,3-*d*]pyrimidines **533** <2003S1531>.



532

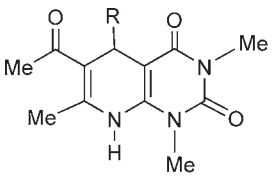
$R = Bu^n$, Ph
R^1 = Me, Et, Pr
95–98%



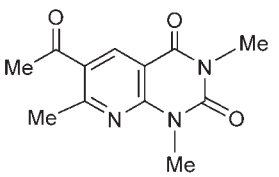
533

R = Me, CF_3, Ph, 
R^1 = Me, Bn
R^2 = H, Me
73–95%

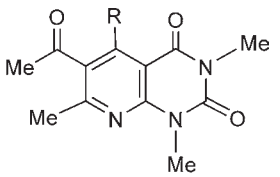
A 5-desubstitution occurred during dehydrogenation in a one-step synthesis of dihydropyrido[2,3-*d*]pyrimidines **534** (14 derivatives). Thus, when a mixture of 6-amino-1,3-dimethyluracil, an aromatic(aliphatic) aldehyde, and acetylacetone was heated in acetic acid for 8 h, high yields (70–90%) of dihydropyrido[2,3-*d*]pyrimidines **534** were obtained. The oxidized products **535** and **536** were formed in some cases in small amounts. As the reaction time was increased to 48 h, dehydrogenation of **534** took place and the dearylated/alkylated product **535** along with the normal products **536** were increased. The percentage yield of **535** was greater with electron-releasing and bulkier groups, whereas the percentage of **536** was greater for groups having electron-withdrawing capacity. Fast atom bombardment mass spectrometry (FABMS) of the crude reaction mixture showed the presence of ROAc, indicating loss of R^+ during the course of oxidation <2004SC4447>.



534
8–40%



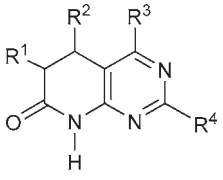
535
10–44%



536
14–44%

10.16.8.2.1(iii) From acyclic precursors

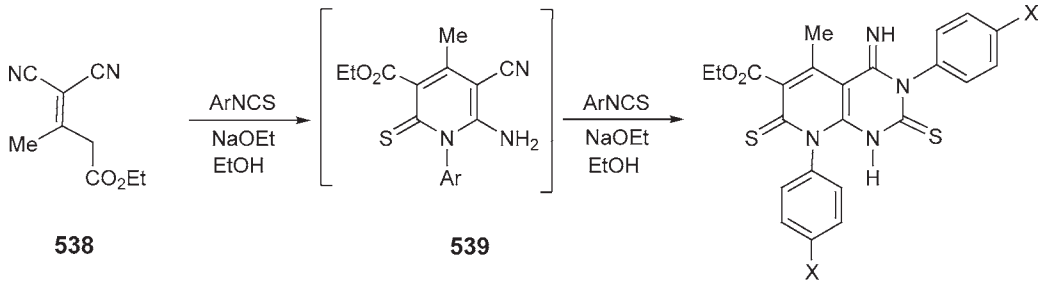
Synthesis of tetrahydropyrido[2,3-*d*]pyrimidin-7-ones **537** in a microwave-assisted one-pot cyclocondensation of α,β-unsaturated esters with active methylene compounds (malononitrile or methyl cyanoacetate) and amidine salts (guanidine or benzamidine) in NaOMe/MeOH for 10 min has been reported <2003TL5385>.



537

R^1, R^2 = H, Me, Ph
R^3 = NH_2, OH
R^4 = NH_2, Ph
53–98%

Addition of arylisothiocyanates to the active methylene compound **538** led to the formation of pyrido[2,3-*d*]pyrimidines **540** and **541**, resulting from the initial addition to form the pyridine intermediates **539** followed by a second addition to give the products (Equation 44) <1993JHC887>.



538 **539**

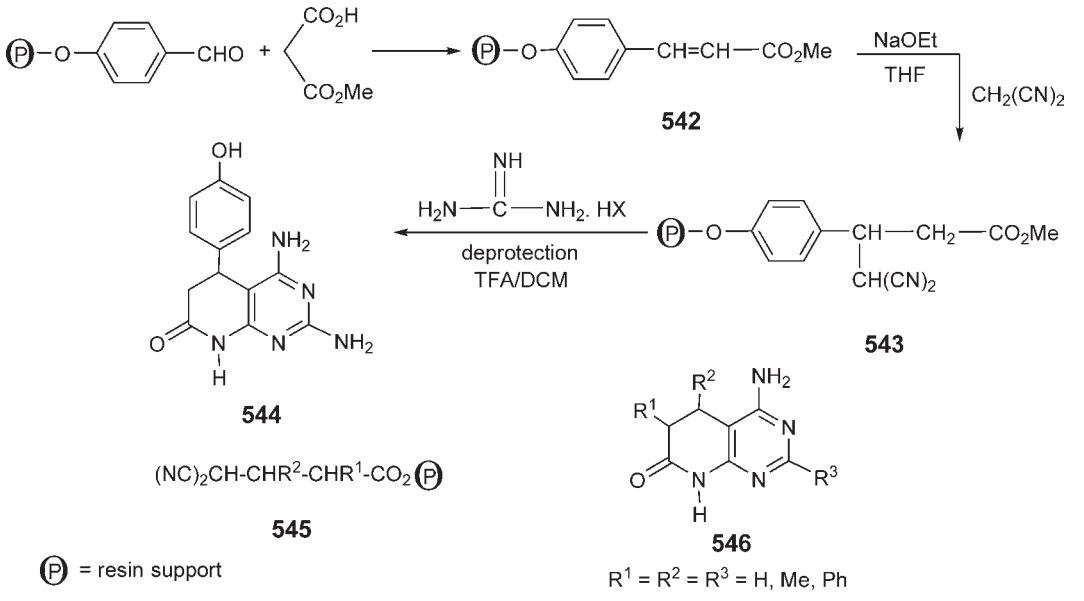
540: X = H (91%)
541: X = Cl (93%)

(44)

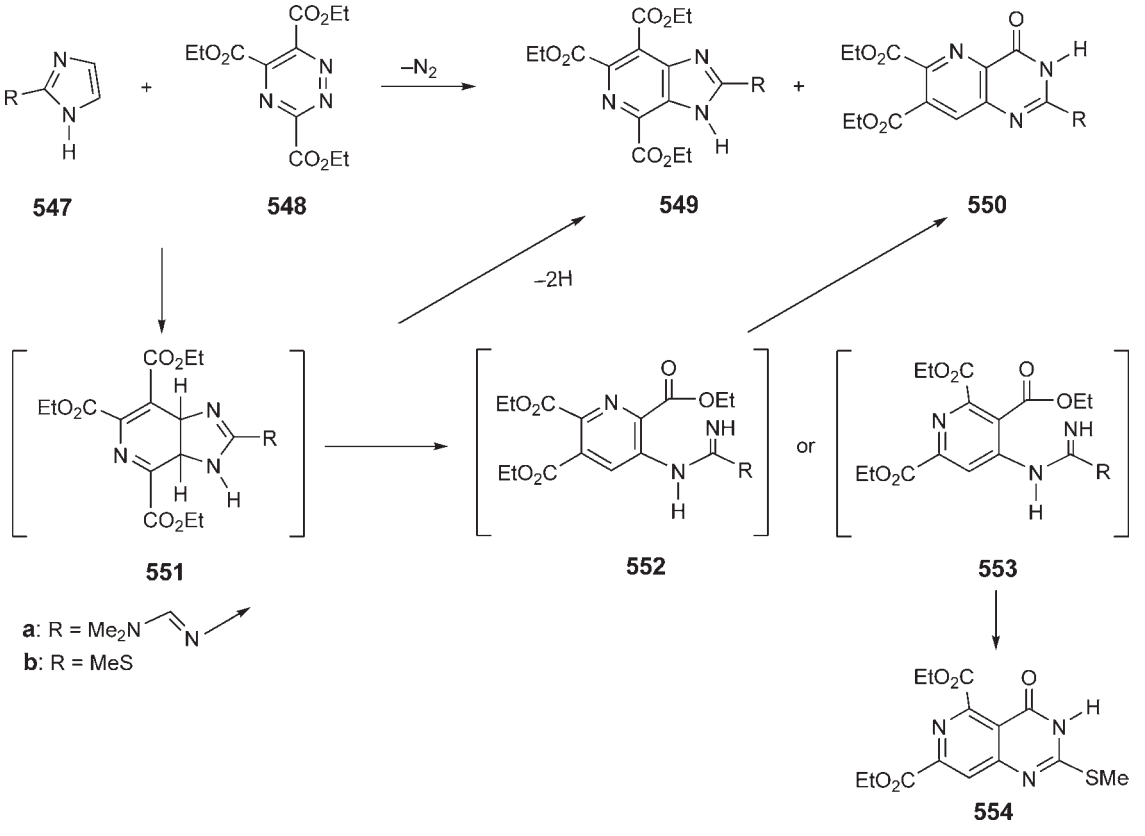
The reaction of Wang resin-supported 4-hydroxybenzaldehyde with propanedioic acid monomethyl ester afforded 3-(4-hydroxyphenyl)-2-propenoic acid methyl ester **542**, which upon treatment with malononitrile gave Wang resin-supported β-(dicyanomethyl)-4-hydroxybenzenepropanoic acid methyl ester **543**. Cyclocondensation of ester **543** with guanidine yielded, after cleavage from the resin, 2,4-diamino-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-one derivative **544** (**Scheme 23**) <2003MI85>. The procedure can also be started by attaching an α,β-unsaturated acid to the Wang resin using dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine in THF followed by converting the resulting resin ester into the Michael adduct **545** by treatment with malononitrile and MeONa in THF. Treatment of **545** with amidine HN=C(NH_2)R^3 in MeOH yielded the corresponding pyridopyrimidine, **546** <2003MI85>.

10.16.8.2.1(iv) Ring transformation of other heterocycles

Intermolecular inverse electron demand Diels–Alder reactions of 2-substituted imidazoles **547a** with 1,2,4-triazine **548** produced both imidazo[4,5-*c*]pyridine **549a** and pyrido[3,2-*d*]pyrimidin-4(3*H*)-one **550a**. The cycloadditions require a strong electron-donating C-2 substituent on the imidazoles and a strong electron-withdrawing substituent on the triazine ring. The ratio of **549**:**550** was controlled by the reactant substituents and reaction temperature, but only slightly dependent upon the solvent. In boiling dioxane, the pyrido[3,2-*d*]pyrimidin-4(3*H*)-one **550a** was produced in excellent yield (77%) in a 6:1 ratio with **549a**. The less electron-rich 2-(methylthio)imidazole **547b** required extended reaction time as well as higher temperature (156 °C, refluxing bromobenzene, 69 h) to react with triazine **548** to give product **550b** (72%) accompanied by another rearranged pyrido[4,3-*d*]pyrimidin-4(3*H*)-one **554** (13%) in addition to a small amount (7%) of imidazopyridine **549b** <2003JOC4345>. The formation of pyrido[3,2-*d*]- and pyrido[4,3-*d*]pyrimidine ring systems was achieved via deprotonation of H-3a or H-7a from intermediate **551**, followed by opening of the imidazole ring to intermediate **552** or **553** and subsequent ring closure (**Scheme 24**) <2003JOC4345>.

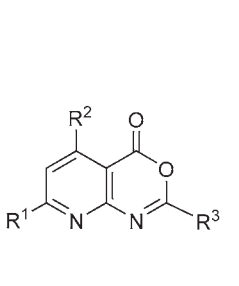


Scheme 23



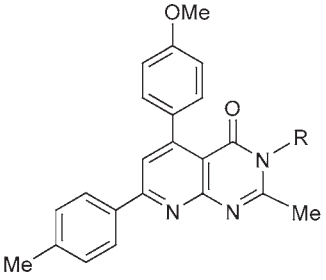
Scheme 24

Fusion of 2-methylpyrido[2,3-*d*][1,3]oxazin-4-one **555** with ammonium acetate, hydrazine hydrate, benzylamine, and aniline in the presence of anhydrous zinc chloride at 150–160 °C gave the pyrido[2,3-*d*]pyrimidines **556** <1994H(38)57>. Also, amination of the 2-isopropyl or isobutyl analogues of **555** ($R^1 = R^2 = H$) with benzylamine in ethylene glycol in presence of sodium hydroxide gave the pyrido[2,3-*d*]pyrimidine derivatives **557** <2003WO2003103575, 2004WO2004039774>.



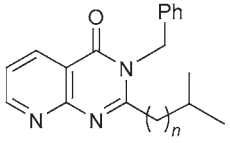
555

R^3 = Me,



556

R	*Yield (%)*
H	85
NH_2	83
Bn	80
Ph	69

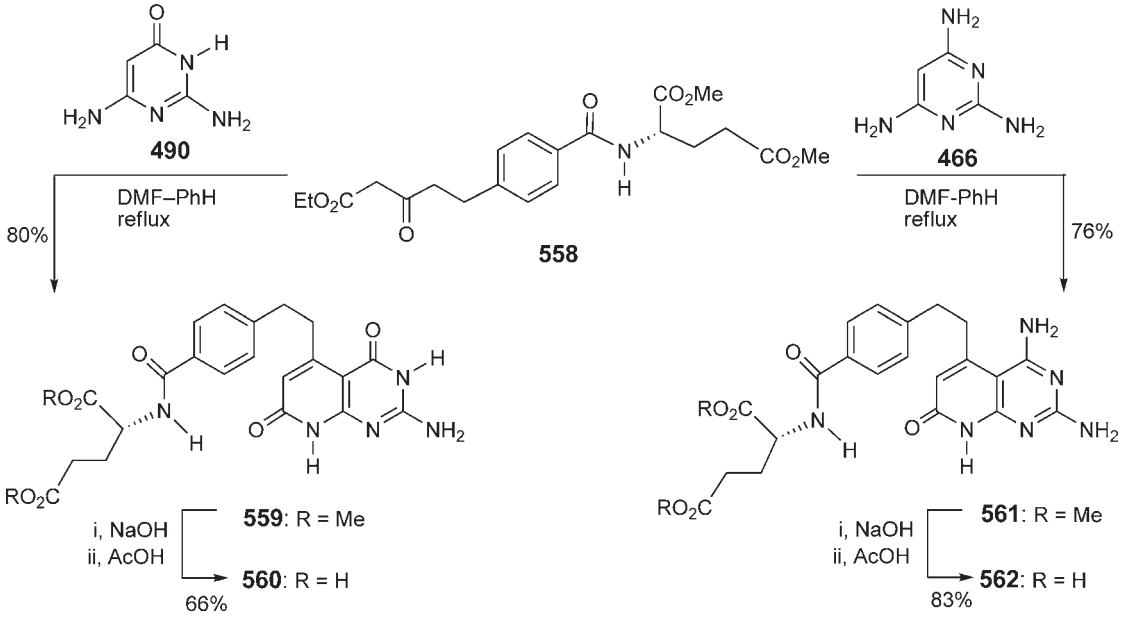


557

n = 0, 1

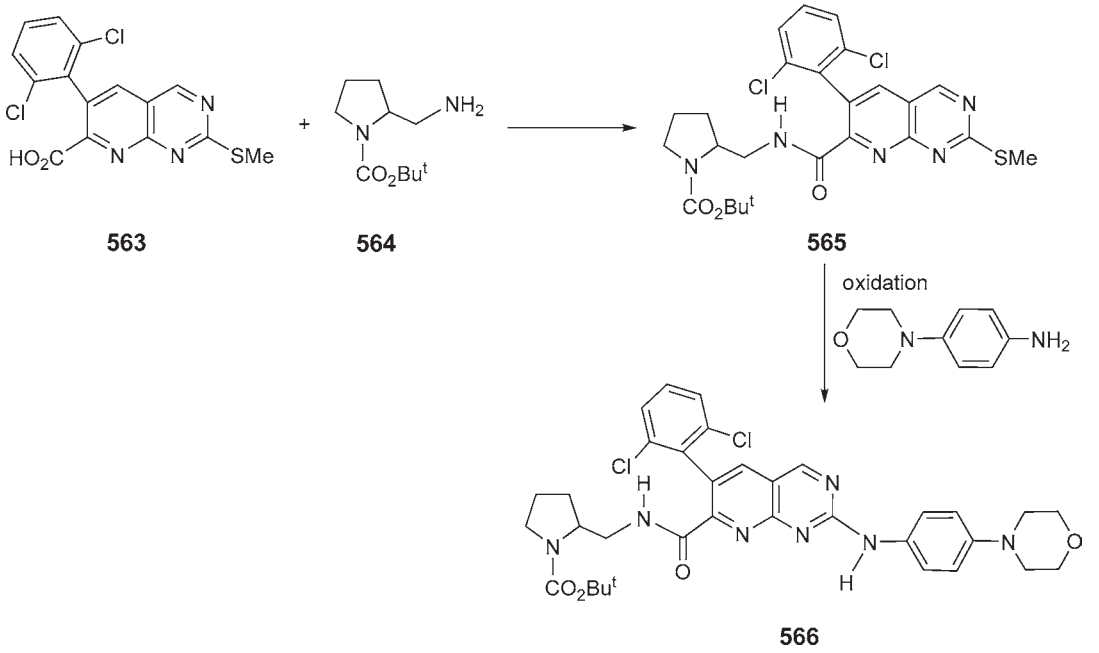
10.16.8.2.1(v) Special compounds

The pyrido[2,3-*d*]pyrimidines **560** and **562** were prepared as analogues of the multitargeted antifolate (MTA) by the reaction of *β*-keto ester **558** with either 2,4-diamino-6(1*H*)pyrimidinone **490** or 2,4,6-triaminopyrimidine **466**, followed by saponification of the resulted glutamate products **559** and **561**, respectively (**Scheme 25**) <1997H(45)2229>.



Scheme 25

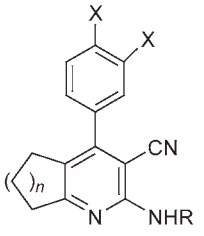
The carboxylic group of 6-aryl-2-methylthiopyrido[2,3-*d*]pyrimidine-7-carboxylic acid **563** was amidated with (*R*)-2-(aminomethyl)-1-(*tert*-butoxycarbonyl)pyrrolidine **564**, followed by sulfide oxidation of the resulting amide **565** and reaction with 4-morpholinoaniline to give the substituted pyridopyrimidine **566** as a kinase inhibitor (**Scheme 26**) <2005WO2005090344>.



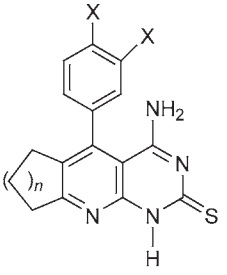
Scheme 26

10.16.8.2.1(vi) Fused pyrido[2,3-*d*]pyrimidines

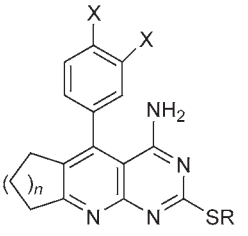
During the period of this review, this section includes mainly an additional fused cycloalkane ring at the [*b*]-side of the pyridine moiety. Thus, cycloalkane ring-fused pyridine derivatives are precursors for constructing these heterocycles. Few examples were prepared from pyrimidine ring derivatives. Reaction of 2-amino-3-cyanopyridine derivatives **567** with benzoyl isothiocyanate in acetone gave the corresponding ureido derivatives **568**, which were cyclized by the action of alkali with subsequent elimination of the benzoyl moiety to yield 4-aminopyrido[2,3-*d*]pyrimidine-2(1*H*)-thiones **569–571**. A series of alkylthio analogues **572** were prepared by treatment of **568** with the proper alkyl halide in a 1 M NaOH–EtOH mixture <1994MI203>. Also, treatment of hexahydroquinoline derivatives **573** with benzoyl isothiocyanate in refluxing dioxane afforded the pyrimido[4,5-*b*]quinolines **574** via a thioureido intermediate <1996JIC623>.



567: R = H
568: R = C(S)NHCOPh

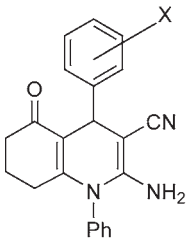


569: *n* = 1; X = H (92%)
570: *n* = 2; X = H (89%)
571: *n* = 2; X = OMe (68%)

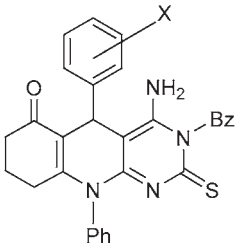


572

X = H, OMe
R = Me, Et, Bu^t, Ph(CH$_2$)$_2$–, PhCOCH$_2$
60–98%

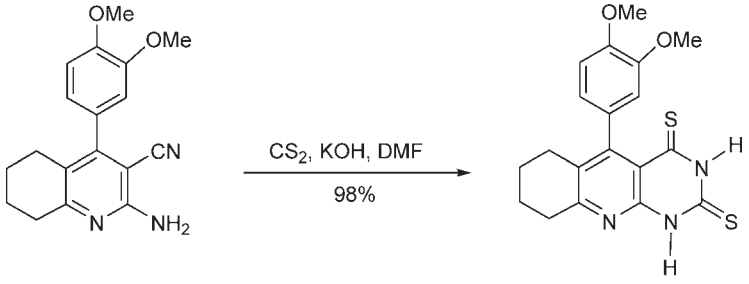


573



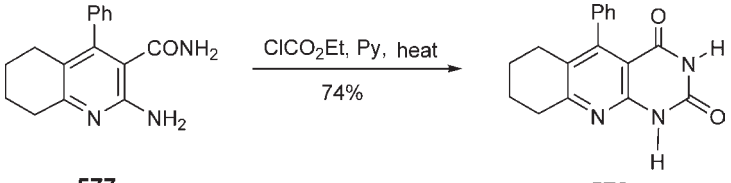
574: X = H, 2-Cl, 3-Cl, 4-Cl, 4-MeO

Treatment of 2-amino-3-cyano-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydroquinoline **575** with CS_2 and KOH in DMF led to the dithioxopyrimido[4,5-*b*]quinoline derivative **576** (Equation 45) <1994MI203>. The dioxopyrimido[4,5-*b*]quinoline **578** was prepared via cyclocondensation of aminocarboxamide **577** with ethyl chloroformate in boiling pyridine (Equation 46) <1995MI55>.



(45)

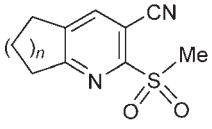
575 **576**



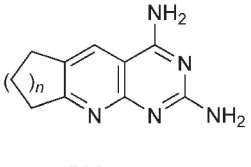
(46)

577 **578**

Cycloalkane ring-fused 2,4-diaminopyrido[2,3-*d*]pyrimidine **580** was obtained by direct treatment of sulfone **579** with guanidine carbonate in boiling diphenyl ether. Sulfoxide **579** was prepared by perbenzoic acid oxidation of the methylthio derivative <1994T199>.



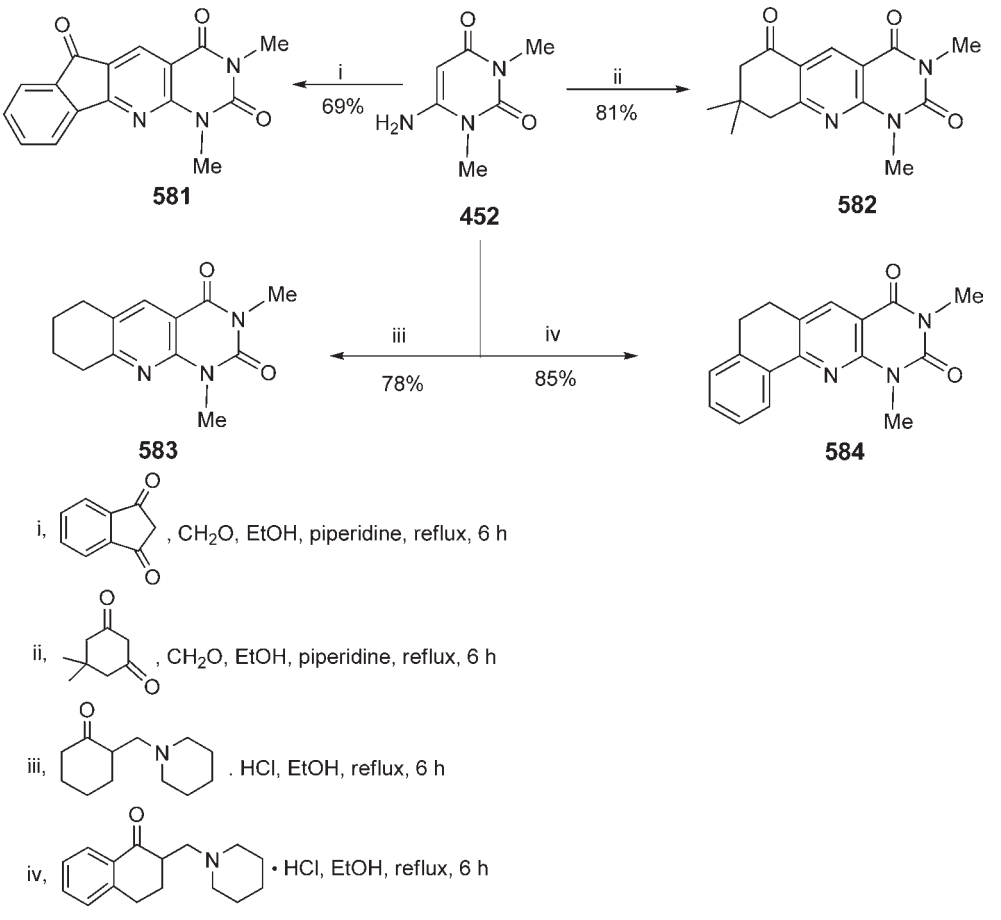
579



580

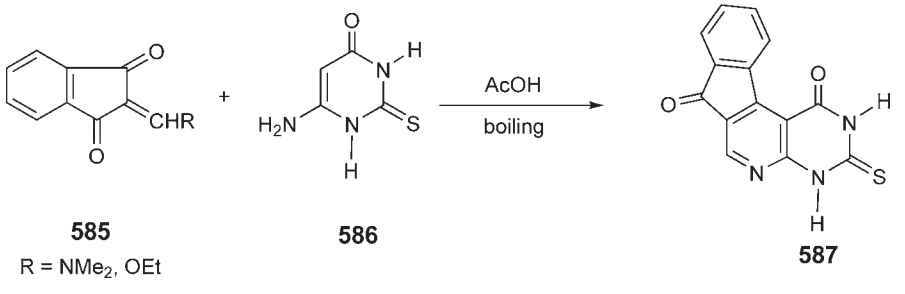
n	*Yield* (%)
3	50
4	50
5	40
6	50
8	50

One-pot syntheses of indenopyrido[2,3-*d*]pyrimidine derivatives **581** and pyrimido[4,5-*b*]quinoline derivative **582** were achieved by refluxing a 2:2:1 mixture of indane-1,3-dione or dimedone, formaldehyde, and 6-amino-1,3-dimethyluracil **452** in ethanol containing a catalytic amount of piperidine. The reactions proceed via the anticipated Michael adducts <2001H(55)1315>. The fused pyridopyrimidine derivatives **583** and **584** were prepared from reaction of **452** with the corresponding ketonic Mannich bases in refluxing ethanol (**Scheme 27**) <1997JOC2999, 2001H(55)1315>.



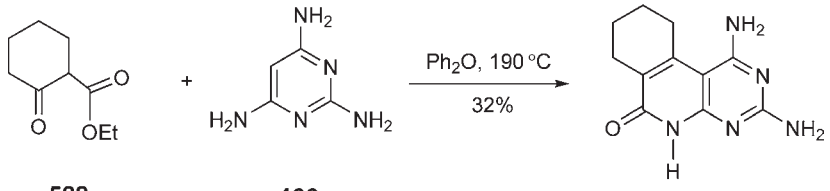
Scheme 27

The 2-thioxo-1,3-dihydroindeno[3,2-*d*]pyrimido[4,5-*b*]pyridine-4,9-dione **587** was obtained by reaction of 2-dimethylaminomethylene- and 2-ethoxymethylene-1,3-indenedione **585** with 6-amino-2-thioxopyrimidin-4(3*H*)-one **586** in boiling acetic acid (Equation 47) <2003HAC491>.



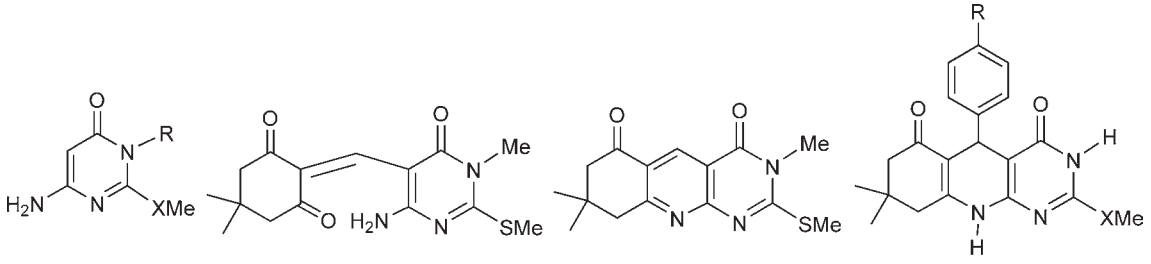
(47)

The thermal cyclization reaction of 2,4,6-triaminopyrimidine **466** with ethyl 2-cyclohexanonecarboxylate **588** in Ph_2O at 190 °C gave the tetrahydropyrimido[4,5-*c*]isoquinolin-6(5*H*)-one **589** as the sole product (Equation 48) <1999JOC634>.



588 **466** **589** (48)

The analogous reaction to that described in Equation (42) using paraformaldehyde in equimolar amount to dimedone (instead of a large excess) was irradiated for 3 min to yield pyrimido[4,5-*b*]quinoline-4,6-dione **591** via formation of intermediate adduct **590** <2006TL27>. The 5-aryl-5,6,7,8,9,10-hexahydropyrimido[4,5-*b*]quinolines **592** were also prepared by the cyclocondensation reaction of 6-aminopyrimidine **460** with dimedone and 4-substituted benzaldehydes by boiling in absolute ethanol for 30 min <1998JHC231>.



460
R = H, Me
X = O, S

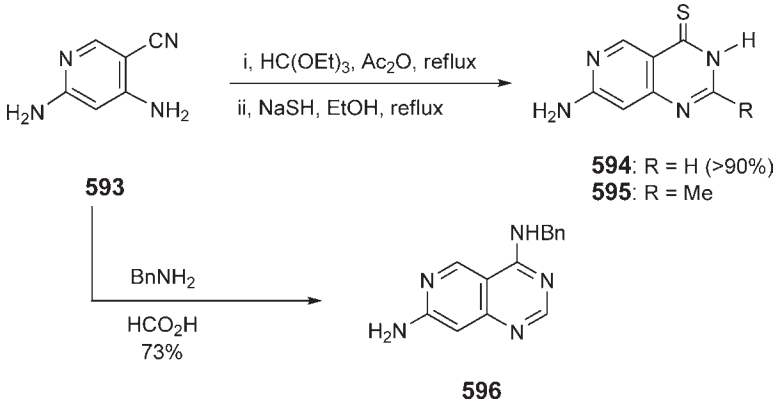
590

591
45%

592
75–88%
R = H, OMe, Cl, NO_2

10.16.8.2.2 Synthesis of pyrido[3,4-*d*] and [4,3-*d*]pyrimidines

Fused [3,4-*d*]- and [4,3-*d*]pyridopyrimidines have been mainly synthesized via annulation of the pyrimidine nucleus onto a pyridine precursor through [5+1], [4+2], and [3+3] cyclizations. Thus, treatment of 4,6-diamino-3-cyanopyridine **593** with $HC(OEt)_3/Ac_2O$ followed by ethanolic NaSH gave pyrido[4,3-*d*]pyrimidine derivative **594** contaminated with its 2-methyl derivative **595**, which was attributed to competing acetylation of **593** with Ac_2O. Treatment of **593** with benzylamine in refluxing formic acid led to 4,7-diaminopyrido[4,3-*d*]pyrimidine **596** (**Scheme 28**) <1995JME3780>.



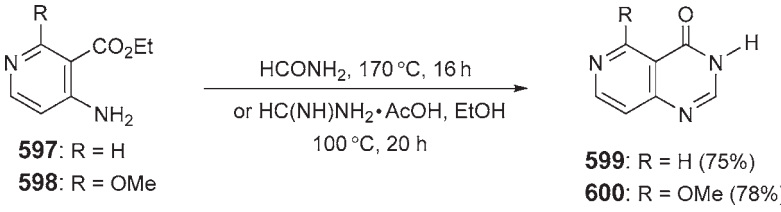
593

594: R = H (>90%)
595: R = Me

596

Scheme 28

Cyclization of either nicotinic acid derivatives **597** by heating with neat formamide (170 °C/16 h) <2004TL3737> or **598** with formamidine acetate in ethanol (100 °C/20 h) <2004TL3737> gave the corresponding pyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **599** and **600** (Equation 49).

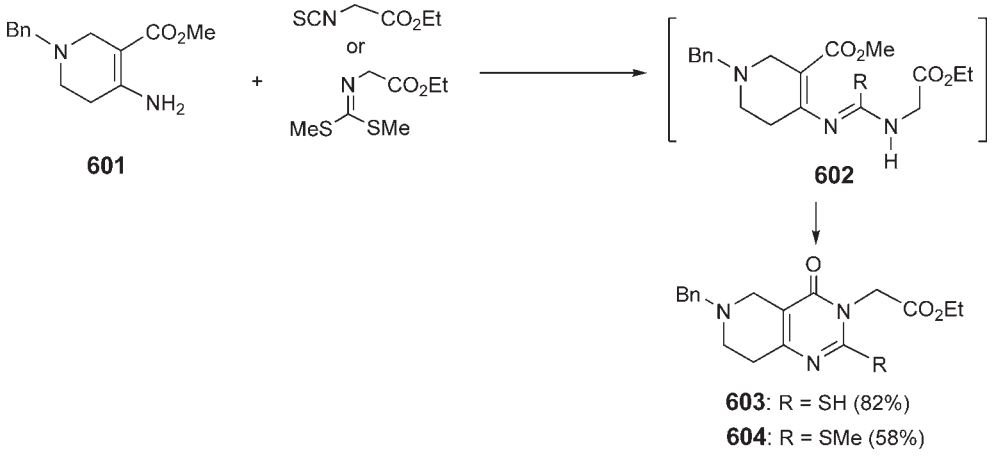


597: R = H
598: R = OMe

599: R = H (75%)
600: R = OMe (78%)

(49)

Reaction of methyl 4-amino-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate **601** with ethyl isothiocyanoacetate in refluxing pyridine or ethyl *N*-[bis(methylthio)methylene]glycinate (BMMA reagent) in AcOH at reflux temperature gave the pyrido[4,3-*d*]pyrimidines **603** and **604**, respectively, via intermediate **602** (Equation 50) <2001H(55)115>.



601

602

603: R = SH (82%)
604: R = SMe (58%)

(50)

Reaction of 3,5-bisarylmethylene-1-ethyl-4-piperidone with thiourea or guanidine hydrochloride in alcoholic KOH afforded the pyrido[4,3-*d*]pyrimidine derivatives **605** and **606**, respectively <2001IJB213>.

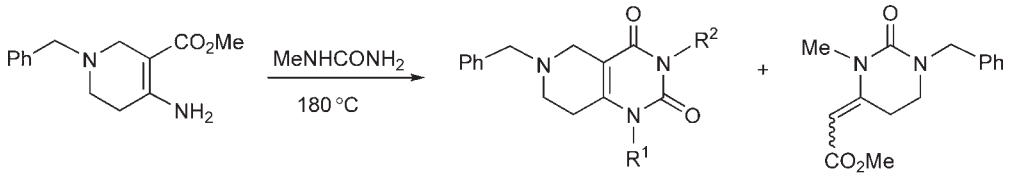


605
70–85%

606
55–62%

Ar = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 2,5-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$

The synthesis of pyrido[4,3-*d*]pyrimidine-2,4-diones was carried out by thermal fusion of enamine **601** with *N*-methylurea at 180 °C to give the pyridopyrimidines **156** and **607** in addition to the unexpected α,β-unsaturated esters **608**, which were separated chromatographically in very poor yield (Equation 51). Alternatively, **156** was obtained in 59% yield by treatment of **601** with methyl isocyanate and Et_3N to give the corresponding uriedo intermediate which was cyclized *in situ* with NaOH <1994JHC1569>.



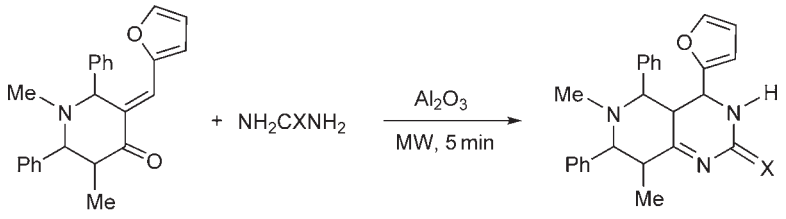
601

156: R^1 = H; R^2 = Me (1.1%)
607: R^1 = Me; R^2 = H (0.03%)

608 3.7%

(51)

Microwave irradiation of 3-(fur-2′-ylmethylene)-1,5-dimethyl-2,6-diphenylpiperidin-4-one **609** with urea/thiourea using neutral alumina gave 4,4a,5,6,7,8-hexahydro-3*H*-pyrido[4,3-*d*]pyrimidine derivatives **610** and **611**, respectively (Equation 52) <2005IJB2527>.

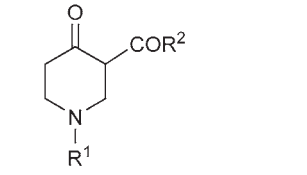


609

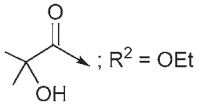
610: X = O (75%)
611: X = S (70%)

(52)

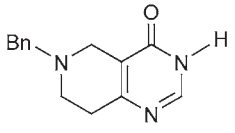
The 6-benzylpyrido[4,3-*d*]pyrimidine **145** was prepared by cyclizing the methyl carboxylate **612** with formamidine hydrochloride <2000DEP19900544>. The 2-butyl-6-(2-hydroxy-2-methyl-1-oxopropyl) analogue **615** was also prepared from cyclocondensation of ethyl ester **613** with BuC(NH)NH_2 <1994USP5281602>. The trisubstituted analogue **616** was obtained from the reaction of 2-guanidino-4-(4-fluorophenyl)thiazole hydrobromide with *N*,3-dibenzoyl-4-piperidone **614** <1995USP5405848>.



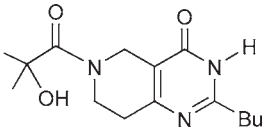
612: R^1 = Bn; R^2 = OMe

613: R^1 =  ; R^2 = OEt

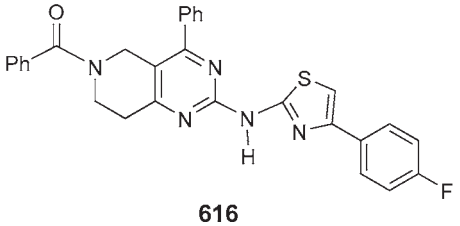
614: R^1 = COPh; R^2 = Ph



145

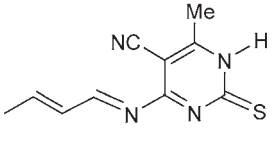


615

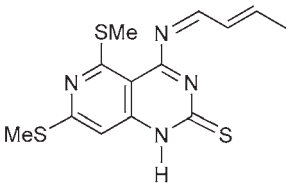


616

Two examples were reported starting from a pyrimidine nucleus for building this fused ring. The first example was achieved by reaction of **617** with CS_2 in benzene containing NaH followed by treatment with MeI to give the pyrido[4,3-*d*]pyrimidine derivative **618** <1997HCO151>.

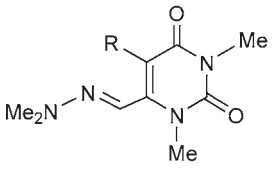


617



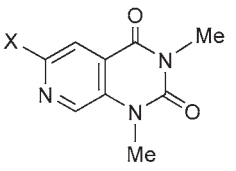
618

The second method using the pyrimidine nucleus for preparing 6-substituted pyrido[3,4-*d*]pyrimidines **621** and **622** has been achieved via coupling of 1,3-dimethyluracil-6-carbaldehyde dimethylhydrazone **619** with styrene and 4-chlorostyrene, respectively, in presence of a stoichiometric amount of $Pd(OAc)_2$ in refluxing MeCN. The analogues **623** and **624** were prepared from coupling of **619** with methyl acrylate and acrylonitrile followed by cyclization of the formed azatriene intermediate **620** in presence of AcOH in boiling chlorobenzene. When methyl vinyl ketone was employed in the above reaction, in presence of $Pd(OAc)_2$, 7,8-dihydropyrido[3,4-*d*]pyrimidine derivative **625** was obtained <1994H(37)563>.

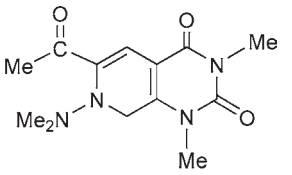


619: R = H

620: R = 

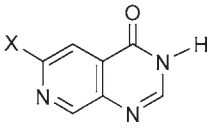


621: X = Ph (40%)
622: X = 4-ClC_6H_4 (50%)
623: X = CO_2Me (99%)
624: X = CN (95%)



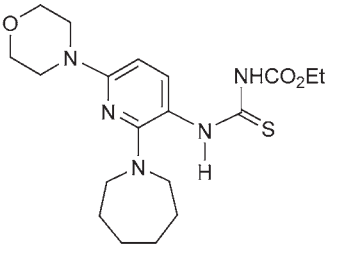
625
68%

The synthesis of 6-substituted derivatives **626** was achieved via reaction of 2-substituted-5-aminopyridine-4-carboxylic acids and formamidine acetate in boiling 2-methoxyethanol <1996J(P1)2221>. The pyrido[3,4-*d*]pyrimidinone **628** was prepared by amination of the thioureido derivative **627** with diisopropylamine followed by cyclization in boiling DMF <2004FRP2846657>. Pyridine **627** was prepared from the corresponding 3-amino derivative with ethoxycarbonyl isothiocyanate in DMF.

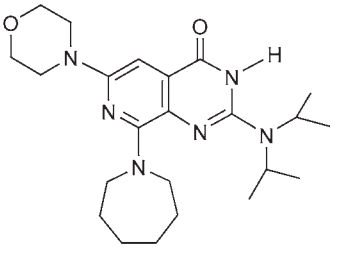


626

X	*Yield* (%)
Cl	86
F	89
OMe	90



627



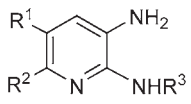
628

10.16.8.3 Synthesis of Pyrido[*x*,*y*-*z*]pyrazines

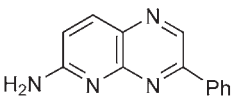
Two pyridopyrazine-fused heterocycles can be presented here, having either a [2,3-*b*] or a [3,4-*b*] junction; more work has been published on the first type than on the second one. *o*-Diaminopyridine derivatives are the main starting materials used for constructing such fused ring systems by condensation with α-dicarbonyl compounds.

10.16.8.3.1 Synthesis of pyrido[2,3-*b*]pyrazines

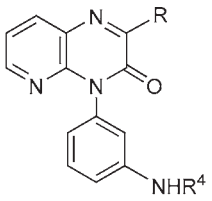
Condensation of 2,3,6-triaminopyridine **629** with monophenyl glyoxal gave the pyridopyrazine **633** <2004WO2004104002, 2004WO2004104003>, while cyclization of **630** with α-ketocarboxylic acids formed pyridopyrazinone **634** <1996GBP2291422, 1996WO9601825, 1997WO9724355>. On the other hand, condensation of oxalic acid with **631** and **632** in boiling 4 M HCl yielded the pyridopyrazines **635** and **636**, respectively. Under the same conditions, the [3,4-*b*] analogue **637** was prepared using 3,4-diaminopyridine <1996JME1331>.



629: $R^1 = R^3 = H$; $R^2 = NH_2$
630: $R^1 = R^2 = H$; $R^3 = 3\text{-}R^4HNC_6H_4$
631: $R^1 = R^3 = H$; $R^2 = R$
632: $R^1 = R$; $R^2 = R^3 = H$

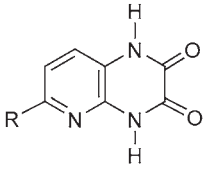


633



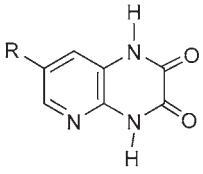
634

R = Bu^i, Bn, 3-pyridyl
R^4 = H, CONHAr



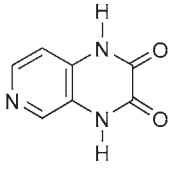
635

R	*Yield (%)*
MeO	57
MeS	56
MeNH	61
	32



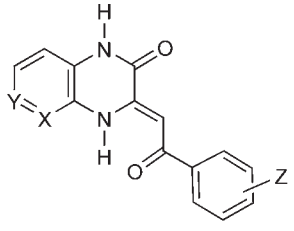
636

R	*Yield (%)*
Me	81
NO_2	74

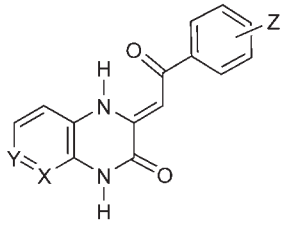


637
48%

Cyclocondensation of 2,3-diaminopyridine with substituted benzoylpyruvates in AcOH/EtOH solution gave mainly 3-phenacylidenepyrido[2,3-*b*]pyrazine derivatives **638**. The isomers **640** were obtained in H_2SO_4/EtOH. Both isomers exist in the enamine form, as evidenced by their ^{1}H NMR and IR spectra <1995JHC347>. Similarly, the phenacylidene derivatives **639** and **641** were prepared under the same reaction conditions using 3,4-diaminopyridine <1994JHC1065>.



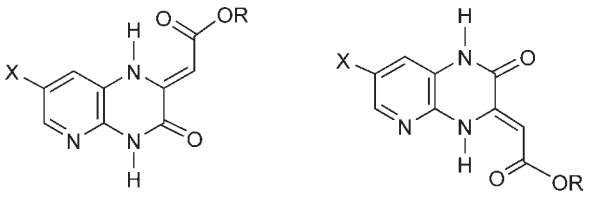
638: X = N; Y = CH (59–81%)
639: X = CH; Y = N (22–81%)



640: X = N; Y = CH (23–60%)
641: X = CH; Y = N (23–82%)

Z = H, 4-OMe, 4-OH, 4-Br, 4-Me, 3-OMe, 2-OMe, 2-OH

Similarly, when dialkyl acetylenedicarboxylates were condensed with 2,3-diaminopyridine in ethanol, the 2-carboxy-carbonylmethylene-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-ones **33** were obtained. The isomers **34** were formed when acidified ethanolic solution was employed <1995JHC1071>.

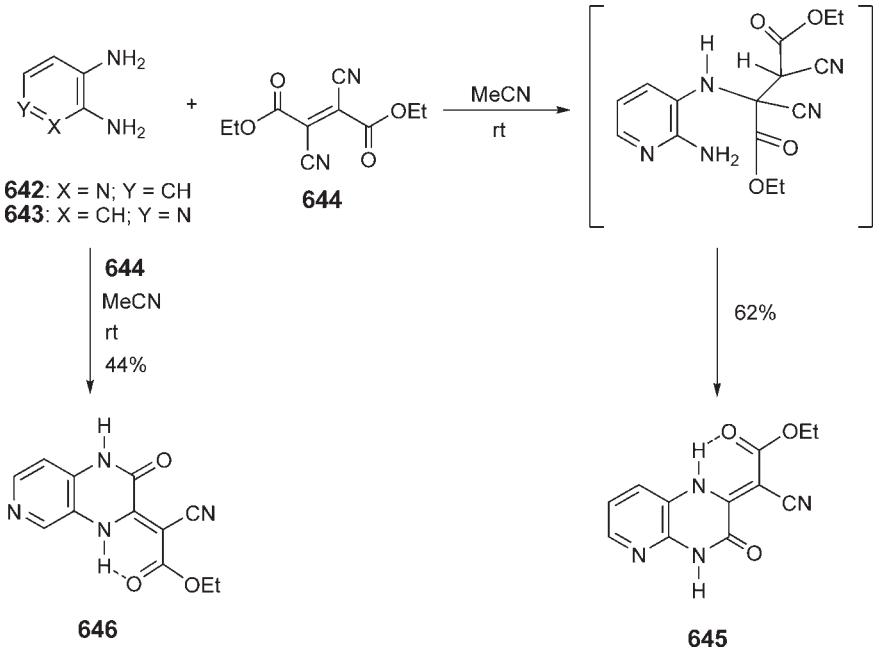


33
43–78%

X = H, Br; R = Me, Et

34
24–36%

Furthermore, 2,3-diaminopyridine **642** was reacted with diethyl (*E*)-2,3-dicyanobutendioate **644** in acetonitrile at room temperature to give regioselectively the isomer (*Z*)-2-(α-cyano-α-ethoxycarbonylmethylene)-1,2-dihydro-4*H*-pyrido[2,3-*b*]pyrazin-3-one **645** via the attack of the β-amino group in **642** on the ethylene double bond of **644**, followed by cyclization between the second amino group and the ester group with the elimination of EtOH and HCN molecules. Compound **646** was regioselectively prepared from **643** (**Scheme 29**) <1998JHC1389>.



642: X = N; Y = CH
643: X = CH; Y = N

644

MeCN
rt

644
MeCN
rt
44%

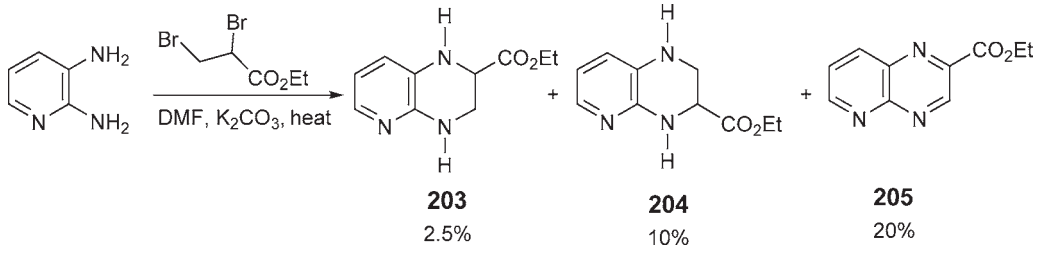
62%

646

645

Scheme 29

Reaction of 2,3-diaminopyridine with ethyl 2,3-dibromopropionate in boiling DMF in the presence of K_2CO_3 provided the pyridopyrazine-2-carboxylate **205** as the major product along with a mixture of tetrahydro isomers **203** and **204**. The small quantity of isomer **203** was attributed to spontaneous oxidation to the product **205** (Equation 53) <2002T5241>.



DMF, K_2CO_3, heat

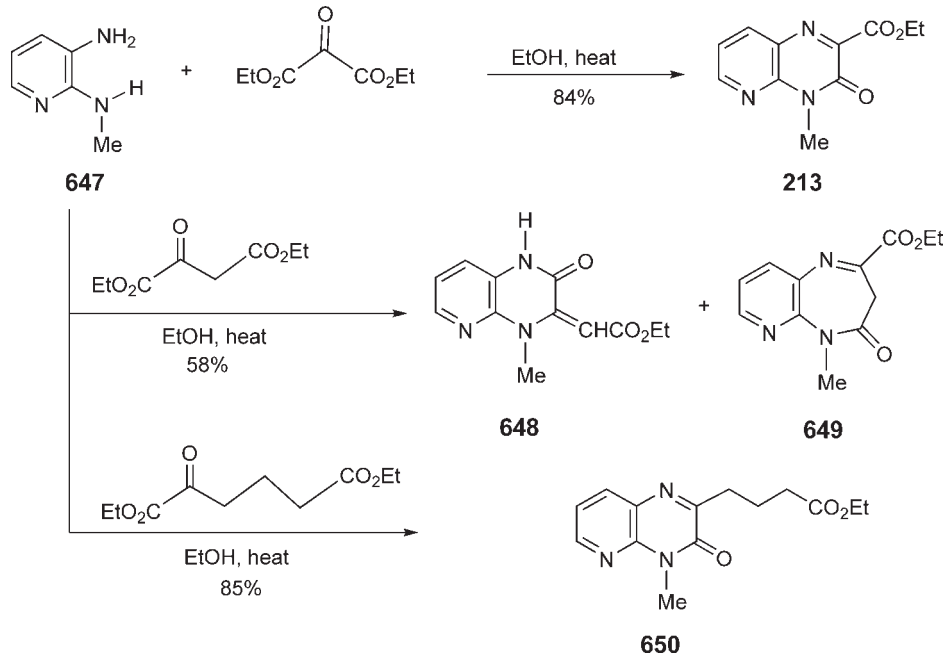
203
2.5%

204
10%

205
20%

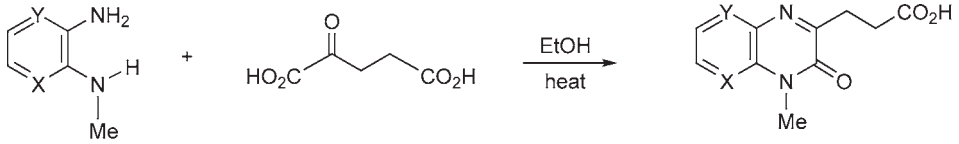
(53)

Condensation of 3-amino-2-(methylamino)pyridine **647** with diethyl 2-oxomalonate in boiling ethanol afforded 2-carbethoxy-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one **213** <1996JHC1737>. On the other hand, condensation of **647** with diethyl oxaloacetate gave ethyl [2(1*H*)-oxopyrido[2,3-*b*]pyrazine-3(4*H*)-ylidene]carboxylate **648** in addition to the formation of pyridodiazepine **649** as a by-product <1996JHC1737>. However, the condensation of **647** with diethyl 2-oxoadipate gave the 2-ethoxycarbonylpropyl analogue **650** (**Scheme 30**) <1994FA259>.



Scheme 30

Cyclocondensation of 3-amino-2-methylaminopyridine **647** or 2-amino-3-methylaminopyridine **651** with 2-ketoglutaric acid gave 2-carboxyethyl-4-methylpyrido[2,3-*b*]pyrazin-3(4*H*)-one **652** and its 3-carboxyethyl-2(1*H*)-one isomer **653**, respectively (Equation 54) <1994FA259>.



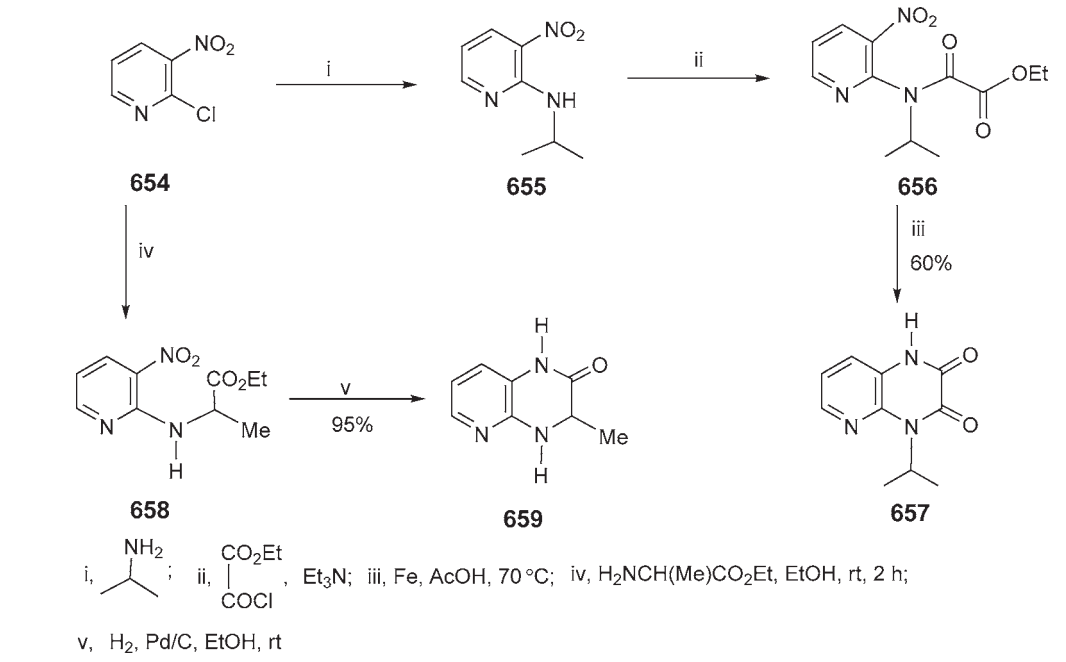
647: X = N; Y = CH
651: X = CH; Y = N

652: X = N; Y = CH (88%)
653: X = CH; Y = N (60%)

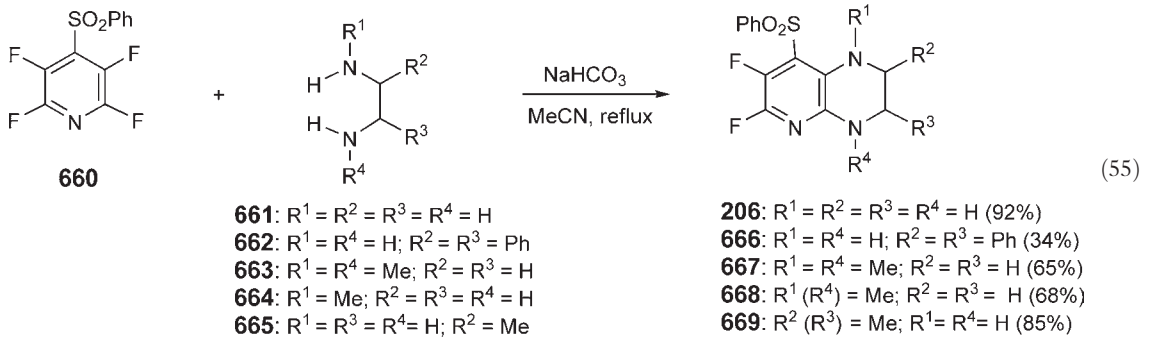
(54)

A synthesis of pyridopyrazines has been developed using 2-chloro-3-nitropyridine **654** as a starting material. Thus, 4-isopropyl-1,4-dihydropyrido[2,3-*b*]pyrazine-2,3-dione **657** was synthesized by reaction of **654** with isopropylamine followed by acylation of the resulting 2-isopropylamino derivative **655** with ethyl oxalyl chloride in the presence of Et_3N to give the amide **656**. Reduction of **656** with iron powder in glacial AcOH at 70 °C afforded **657** <2002M653>. Furthermore, condensation of **654** with alanine ethyl ester in EtOH followed by catalytic hydrogenation of ethyl 2-(3-nitro-2-pyridyl)aminopropionate **658** gave the tetrahydropyrido[2,3-*b*]pyrazin-2-one **659** (**Scheme 31**) <1995JHC703>.

The tetrahydropyrido[2,3-*b*]pyrazine derivatives **206** and **666–669** could be synthesized via reaction of 4-phenylsulfonyltetrafluoropyridine **660** with diamines **661–665**, respectively, in the presence of $NaHCO_3$ in boiling MeCN (Equation 55) <2005JOC9377>.

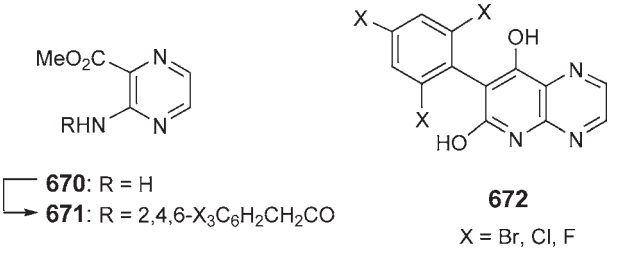


Scheme 31

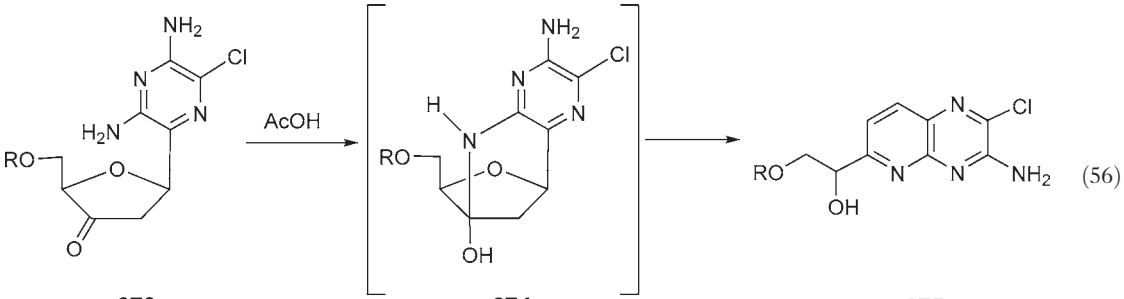


(55)

Two examples were reported for the synthesis of the pyrido[2,3-*b*]pyrazine moiety using pyrazine precursors. Thus, amidation of methyl 2-aminopyrazine-3-carboxylate **670** with a substituted acetyl chloride followed by heterocyclization of the formed amide **671** gave 6,8-dihydroxy pyridopyrazine **672** <2004WO2004056825>.

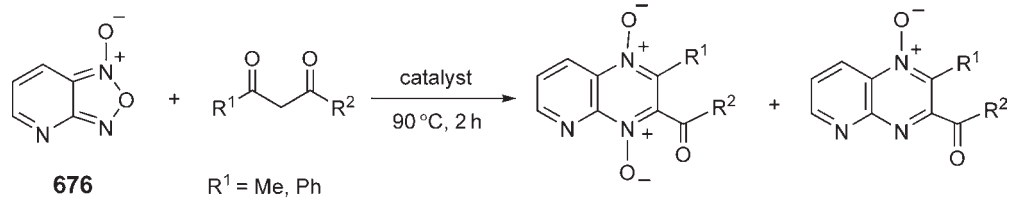


A unique acyclic C-nucleoside containing the pyrido[2,3-*b*]pyrazine nucleus **675** was prepared by the action of AcOH, whereby rearrangement of 3′-keto-2′-deoxypyrazine C-nucleoside derivatives **673** occurs via the intramolecular aminal intermediate **674**, followed by furanose ring opening and subsequent aromatization (Equation 56) <1996JA8953, 1997YZ126>.



(56)

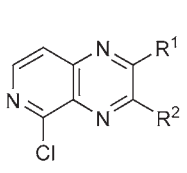
Ring transformation of pyrido[2,3-*c*]furoxan **676** with 1,3-diketones or *β*-keto esters was catalyzed by silica gel, alumina, or molecular sieves to give mainly the corresponding pyrido[2,3-*b*]pyrazine 1,4-dioxides **677** in addition to pyrido[2,3-*b*]pyrazine 1-oxides **678** in a low yield (Equation 57) <1997H(45)107>.



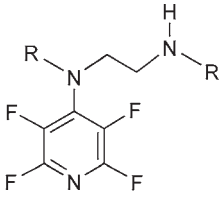
(57)

10.16.8.3.2 Synthesis of pyrido[3,4-*b*]pyrazines

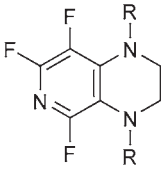
The syntheses of such [3,4-*b*] fused analogues are almost the same as those utilized in the case of the [2,3-*b*] isomers, but using 3,4-diaminopyridine in place of the 2,3-derivative. Thus, 5-chloropyrido[3,4-*b*]pyrazines **679** were prepared from symmetrical disubstituted 1,2-dicarbonyl compounds and 2-chloro-3,4-diaminopyridine in refluxing EtOH. Condensation with methyl glyoxal provided a mixture of two regioisomers **680** and **681**; the 2-substituted isomer was the major product. The regiochemistry resulted from attack of the more-nucleophilic 3-amino group on the more-electrophilic formyl function <2003H(60)925>. In the case of phenylglyoxal, 5-chloro-2-phenylpyrido[3,4-*b*]pyrazine **682** was the only product obtained. Cyclization between pentafluoropyridine and *N*,*N*′-dimethyl-1,2-ethylenediamine in the presence of $NaHCO_3$ as base in refluxing MeCN afforded the tetrahydropyrido[3,4-*b*]pyrazine **684** in excellent yield. In the case of diisopropyl- and dibenzylethylenediamine, low yields of **685** and **686** were found due to the formation of uncyclized adduct **683** as a major product <2005JOC7208>.



679: $R^1 = R^2 = H$ (82%), Me (60%), Ph (91%)
680: R^1 = Me; R^2 = H (82%)
681: R^1 = H; R^2 = Me (12%)
682: R^1 = Ph; R^2 = H (79%)

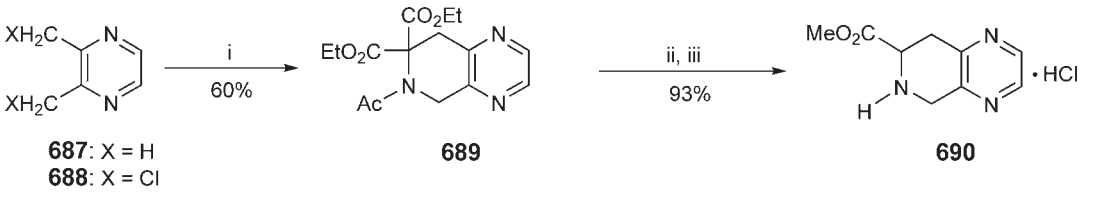


683



684: R = Me (97%)
685: R =  (26%)
686: R = Bn (33%)

A tetrahydropyrido[3,4-*b*]pyrazine nucleus was constructed from 2,3-dimethylpyrazine **687** by chlorination with *N*-chlorosuccinimide (NCS) to give 2,3-bis(chloromethyl)pyrazine **688**, followed by cyclization with diethyl acetamidomalonate to pyridopyrazine **689**. Hydrolysis and decarboxylation of **689** in hydrochloric acid, then esterification by action of thionyl chloride in methanol gave methyl 5,6,7,8-tetrahydropyrido[3,4-*b*]pyrazine-7-carboxylate hydrochloride **690** (**Scheme 32**) <2003BMC433>.



687: X = H
688: X = Cl

689

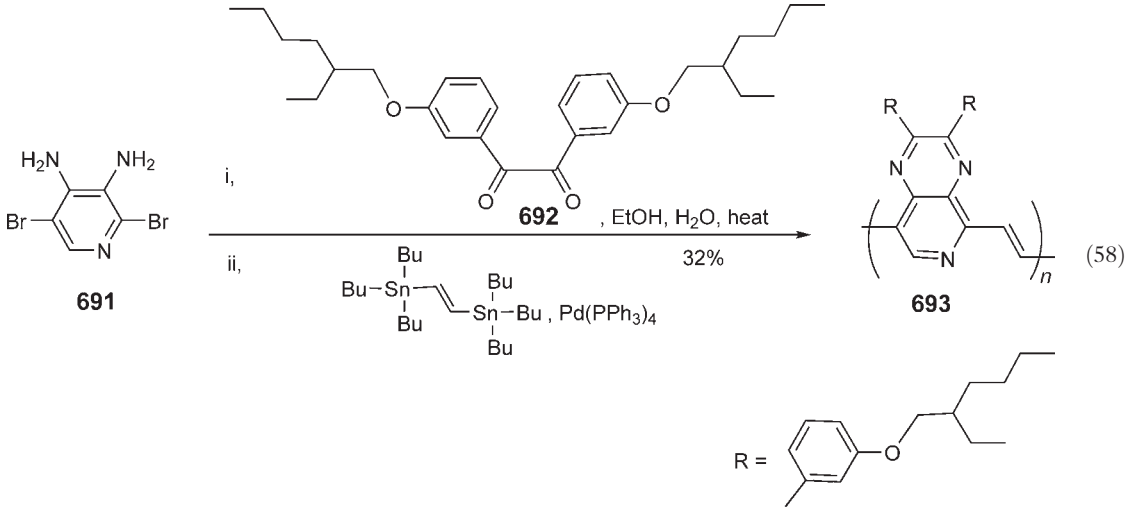
690

i, $(EtO_2C)_2$ CHNHAc, Cs_2CO_3; ii, HCl; iii, $SOCl_2$, MeOH

Scheme 32

10.16.8.3.3 Special compounds

Poly(pyrido[3,4-*b*]pyrazine vinylene) **693** has been synthesized via condensation of 3,4-diamino-2,5-dibromopyridine **691** with 1,2-bis[3-(2′-ethylhexyloxy)phenyl]-ethane-1,2-dione **692** followed by coupling with 1,2-bis(tri-*n*-butylstannyl)ethylene in DMF at 110 °C in the presence of tetrakis(triphenylphosphine)palladium. The vinylene polymer **693** showed improved stability toward photooxidation compared with similar polymers with purely aliphatic side chains and also had smaller band gaps (Equation 58) <2002SM(131)53>.



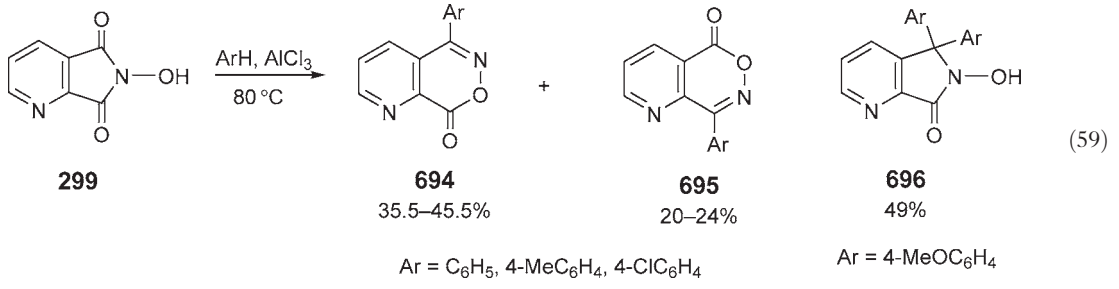
691

693

(58)

10.16.8.4 Synthesis of Pyrido[*x*,*y*-*z*][1,*n*]oxazines

The literature on such ring systems is limited, and includes only the use of pyridine derivatives as starting materials. Thus, reaction of *N*-hydroxyquinolinimide **299** with benzene, toluene, and chlorobenzene in the presence of anhydrous $AlCl_3$ gave a mixture of 5-arylpyrido[3,2-*d*][1,2]oxazin-8-one **694** and the 8-arylpyrido[2,3-*d*][1,2]oxazin-5-one isomer **695**. The same reaction with anisole afforded a low yield (6%) of **695** (Ar = 4-$MeOC_6H_4$) in addition to pyrrolopyridine derivative **696** as the main product, and none of the isomer **694** (Ar = 4-$MeOC_6H_4$) was observed (Equation 59) <1998SC2871>.



299

694
35.5–45.5%

695
20–24%

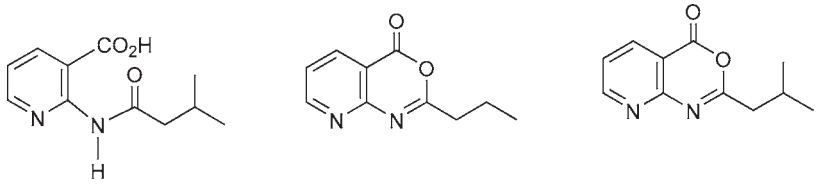
696
49%

Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4

Ar = 4-$MeOC_6H_4$

(59)

Cyclization of 2-aminonicotinic acid with butyric anhydride gave the 2-propyl-4*H*-pyrido[2,3-*d*][1,3]oxazin-4-one **698** <2004WO2004039774>, while the 2-isobutyl analogue **699** was prepared via the cyclization of amide **697**, obtained from acylation of 2-aminonicotinic acid with isovaleryl chloride, in Ac_2O at 120 °C <2003WO2003103575>.

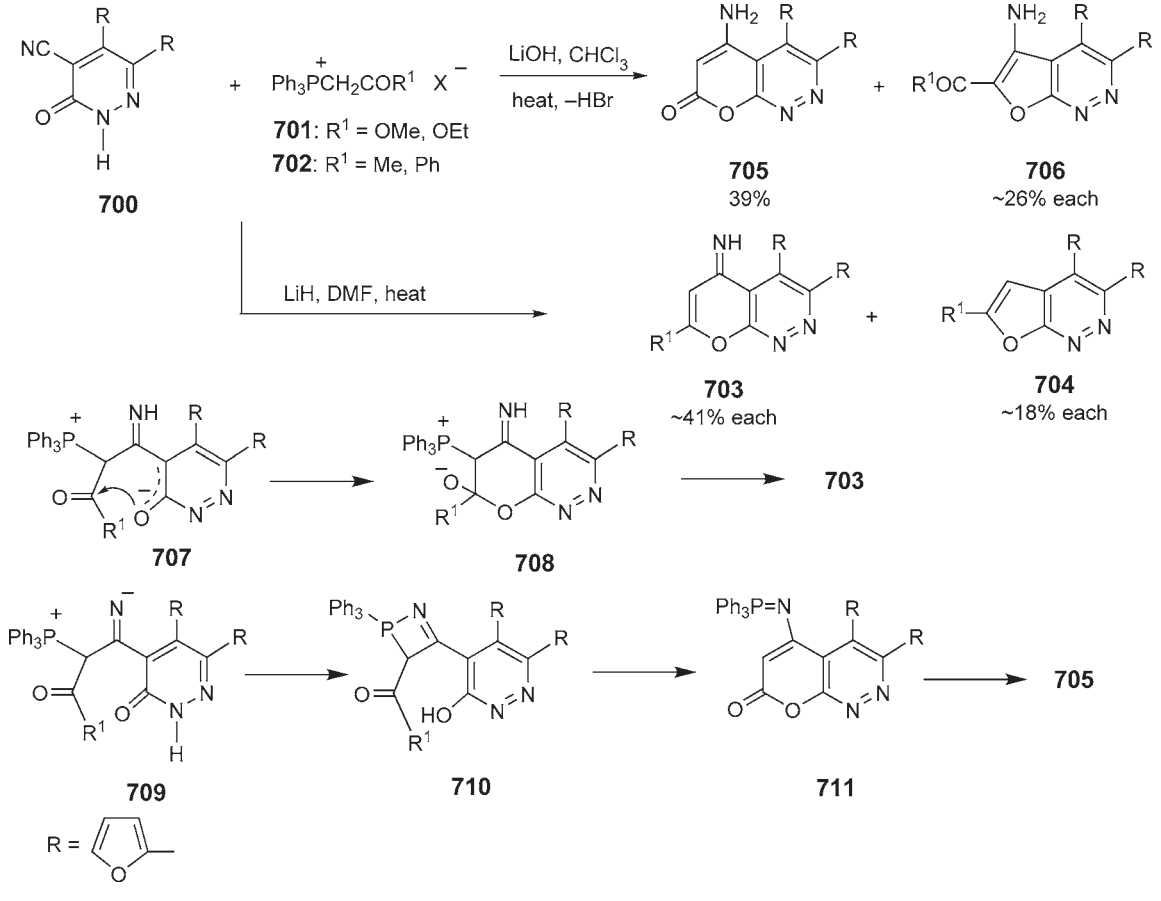


697 **698** **699**

10.16.8.5 Synthesis of Pyrano and Thiopyrano[*x*,*y*-*z*][1,*n*]diazines

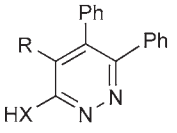
10.16.8.5.1 Synthesis of pyrano and thiopyrano[*x*,*y*-*z*]pyridazines

The formation of this ring system via construction of the pyrano or thiopyrano ring on diazine precursors is known. Two examples were reported using pyran or thiopyran as precursors, in addition to another example from acyclic derivatives. Thus, regioselective condensation of phosphoranes **701** with 5,6-(difur-2-yl)-3-oxo-2,3-dihydropyridazine-4-carbonitrile **700** in the presence of a base (LiOH) in boiling $CHCl_3$ afforded a mixture of pyrano[2,3-*c*]pyridazine **705** and fused furans **706**. Under more drastic conditions, a mixture of **700** and **702**, in boiled DMF in the presence of LiH, gave the fused pyran(furan) derivatives **703** and **704**. The mechanism of formation of **703** and **705** involved a series of sequential intermediates, viz. **707** → **708** → **703** or intermediates **709** → **710** → **711** → **705** (**Scheme 33**) <2004PS2373>.

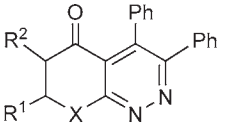


Scheme 33

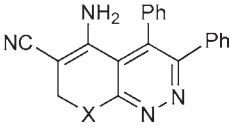
Treatment of 4-acetyl-5,6-diphenyl-3-hydroxypyridazine **712** with aromatic aldehydes in the presence of piperidine as a catalyst in refluxing ethanol afforded 7-arylpyrano[2,3-*c*]pyridazinone derivative **715** <1997G787>. On the other hand, high-temperature reaction of vinyl cyanide with 3-hydroxy(mercapto)pyridazine derivatives **713** gave the corresponding pyrano(thiopyrano)[2,3-*c*]pyridazines **717**. However, the ethoxycarbonyl derivatives **714** gave **716** <1989JPR757>.



712: R = COMe
713: R = CN
714: R = CO_2Et

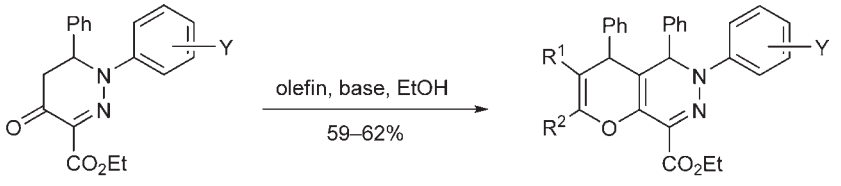


715: R^1 = Ar; R^2 = H; X = O
716: R^1 = H; R^2 = CN; X = O or S



717: X = O or S

Reaction of 1-aryl-3-carbethoxy-6-phenyl-1,4,5,6-tetrahydropyridazin-4-ones **718** with activated olefins such as benzalacetophenone, benzalacetone, 3-benzylideneacetylacetone, diethyl 2-benzylidenemalonate, and α-cyano-β-phenylacrylic acid in the presence of an organic base like pyrrolidine, morpholine, piperidine, or triethylamine gave the corresponding 2,8-dihydro-1*H*-pyrano[2,3-*d*]pyridazines **719–723**, respectively. The 1-oxo- and 1-imino derivatives of the pyrano[2,3-*d*]pyridazine ring system were also prepared from the respective 6-oxo or 6-imino derivative of the starting pyridazine **718** under the same conditions (Equation 60) <1989IJB733>.

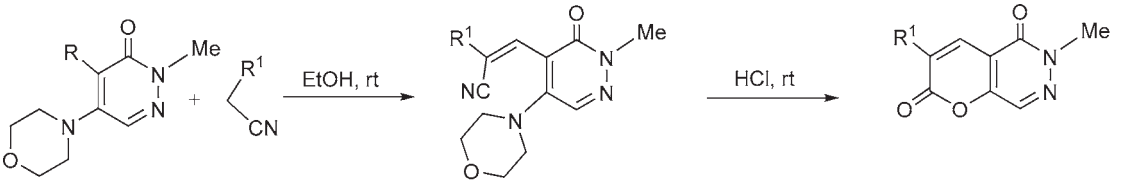


(60)

718
Y = H, 4-NO_2, 4-Br, 2,4,6-Br_3

719: R^1 = H; R^2 = Ph
720: R^1 = H; R^2 = Me
721: R^1 = COMe; R^2 = Me
722: R^1 = CO_2Et; R^2 = OH
723: R^1 = CO_2H; R^2 = NH_2

Transformation of both the ester and nitrile derivatives **726** or **727** into pyrano[2,3-*d*]pyridazines **728** or **729**, respectively, by treatment with dilute HCl at room temperature involved nucleophilic displacement of the morpholino group by the hydroxyl group with an acidic hydrolysis followed by intramolecular iminolactonization and then hydrolysis of the formed imino group to a carbonyl group. Compounds **726** and **727** were prepared by Vilsmeier–Haack formylation of 2-methyl-5-morpholino-3(2*H*)-pyridazinone **724** followed by condensation of the resulting product **725** with either ethyl α-cyanoacetate or malononitrile in EtOH (**Scheme 34**) <1994H(37)171>.



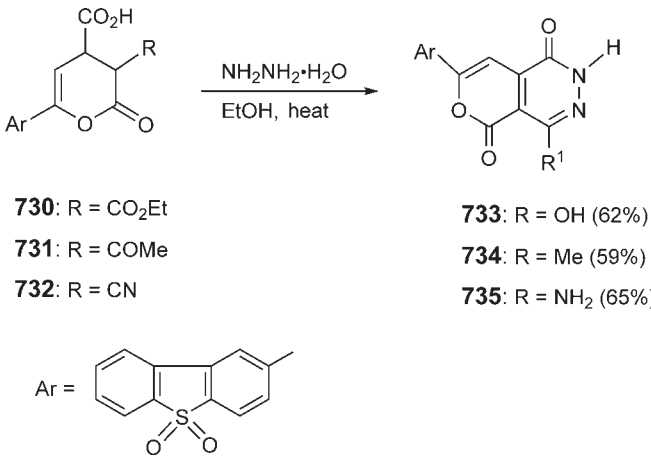
724: R = H
725: R = CHO

726: R^1 = CO_2Et
727: R^1 = CN

728: R^1 = CO_2Et (62%)
729: R^1 = CN (73%)

Scheme 34

Pyrano[3,4-*d*]pyridazine derivatives **733–735** were prepared by cyclocondensation reactions of 6-aryl-3-(ethoxycarbonyl, acetyl, or cyano)-2-oxo-2*H*,3*H*,4*H*-pyran-4-carboxylic acids **730–732**, respectively, with hydrazine hydrate in boiling ethanol (Equation 61) <2002PS1359>.



730: R = CO_2Et
731: R = COMe
732: R = CN

733: R = OH (62%)
734: R = Me (59%)
735: R = NH_2 (65%)

(61)

Ar =

Pyrano(thiopyrano)[3,4-*c*]pyridazine-4-carbonitrile derivatives **737** and **738** were obtained by cyclocondensation of 3-(phenylhydrazono)derivatives **736** with malononitrile or ethyl cyanoacetate, respectively, in DMSO in the presence of morpholine (Equation 62) <1996KGS1410, 2002WO2002026743>.



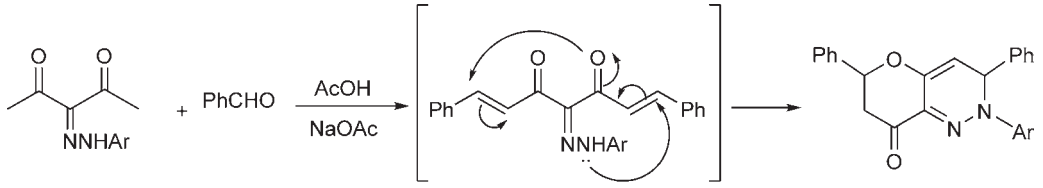
736
R = H, Me
X = O, S

Z = CN, CO_2Et

737: Y = NH (91% if R = H)
738: Y = O

(62)

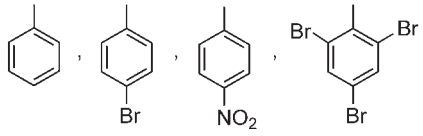
Tetrahydropyrano[3,2-*c*]pyridazinone derivatives **741** were prepared from the reaction of arylhydrazonoacetylacetone **739** and PhCHO in glacial AcOH in the presence of NaOAc, in a single synthetic step, via the formation of diphenylheptadienearylhydrazone intermediate **740** (Equation 63) <1989IJB167>.



739 **740** **741**

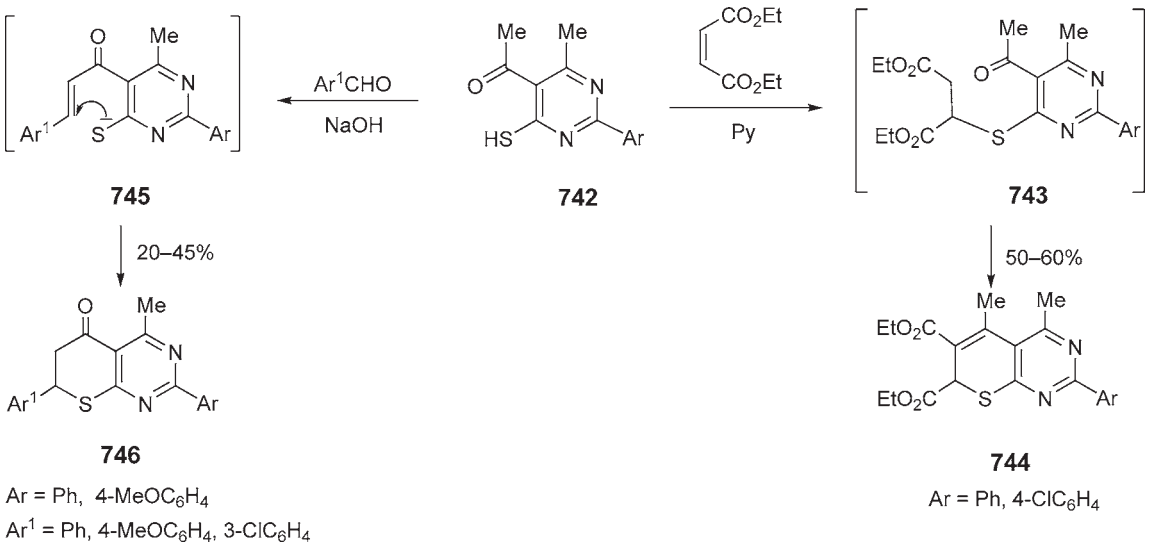
(63)

Ar =



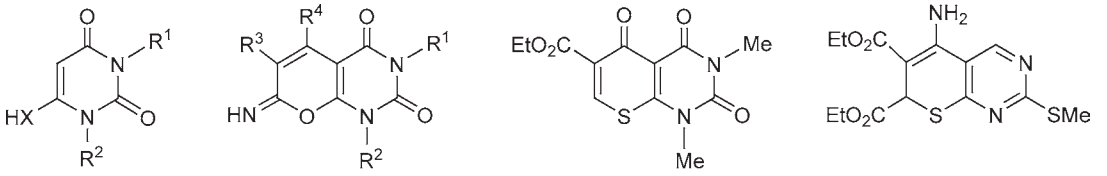
10.16.8.5.2 Synthesis of pyrano and thiopyrano [*x*,*y*-*z*]pyrimidines

Pyrano- and thiopyranopyrimidines are interesting as annulated uracils and pyrimidine derivatives. Thus treatment of 5-acetyl-2-aryl-4-mercapto-6-methylpyrimidine **742** with diethyl maleate in refluxing pyridine formed the cyclized thiopyrano[2,3-*d*]pyrimidine derivative **744** via the formation of the Michael-type product **743** <1990PHA792>, which then undergoes dehydration to give **744**. On the other hand, 2,7-diaryl-4-methyl-6,7-dihydrothiopyrano[2,3-*d*]pyrimidin-5-ones **746** were prepared by condensation of **742** with Ar^1CHO in ethanolic solution containing equivalent amounts of NaOH. The reaction proceeds through the formation of condensation product **745** followed by Michael addition of the thiolate to the cinnamoyl moiety (**Scheme 35**) <1990JCCS497, 1990PHA62>.



Scheme 35

Three-component cyclocondensation of barbituric acid **747** with $HC(OEt)_3$ and malononitrile or ethyl cyanoacetate in the presence of Ac_2O proceeds with microwave assistance to give pyrano[2,3-*d*]pyrimidines **749** in 5 min. This reaction under thermal conditions in ethanol or without solvent needed 1.5–6 h to give **749** in 45–55% yield <2004SL283>. Also, microwave-assisted cyclocondensation of **747** with PhCHO and either malononitrile or ethyl cyanoacetate (in the absence or presence of Et_3N in DMF or solvent free) gave the 7-amino-5*H* derivative of **750**; the use of a solvent led to a poor yield and took more time <2003TL8307>. Reaction of 1,3-dimethyl-6-mercaptouracil **748** ($R^1 = R^2 = Me$) with diethyl ethoxymethylenemalonate in refluxing $CHCl_3$ for 2 h gave the 6-ethoxycarbonyl-5-oxothiopyrano[2,3-*d*]pyrimidine derivative **751** <1976CPB1390>. Cyclocondensation of 4-chloro-5-cyano-2-methylthiopyrimidine with diethyl mercaptosuccinate in refluxing EtOH in the presence of Na_2CO_3 afforded diethyl 5-amino-2-(methylthio)-7*H*-thiopyrano[2,3-*d*]pyrimidine-6,7-dicarboxylate **752** <1977JHC361>.



747: X = O
748: X = S
R^1, R^2 = H, Me

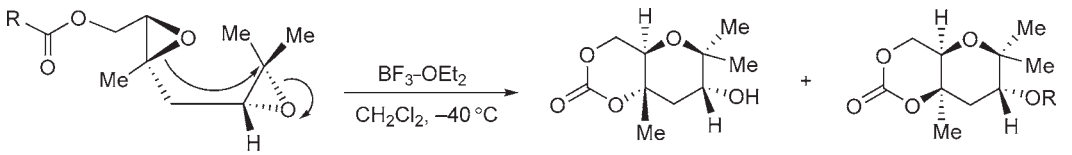
749: R^4 = H (75–80%)
750: R^4 = Ph (75–95%)
R^3 = CN, CO_2Et

751
73%

752
69%

10.16.8.6 Synthesis of Pyrano[*x*,*y*-*z*][1,*n*]dioxane and -Dithiane

This ring system is rarely reported in the literature, where only two examples were observed during this period. Thus, selective oxacyclization of a 0.05 M solution of 1,4-diepoxides **753** with 1 equiv of $BF_3{\cdot}OEt_2$ at −40 °C gave a mixture of *trans*-**754** and *cis*-**755** diastereoisomers depending upon the nature of the terminal nucleophile. In case of *tert*-butyl carbonate **753a**, a trace amount of **754** (<4%), **755** as the major product (56%), and **756** as a minor product (12%) were obtained. The production of by-product **756** was diminished by conducting the reaction in boiling CH_2Cl_2. Although the *N*-phenylcarbamate **753b** gave only the *cis*-fused product **755** (70% yield) after hydrolysis of the initial iminocarbonate, the *N*,*N*-dimethylcarbamate **753c** provided 55% yield of *trans*-fused product **754** at room temperature with an additional 21% yield of the *cis*-fused byproduct **755** <2003OL2123>. It was therefore concluded that increasing the nucleophilicity of the terminating carbonyl might favor the inversion of stereoselectivity to form the *trans*-fused diastereomer (Equation 64).



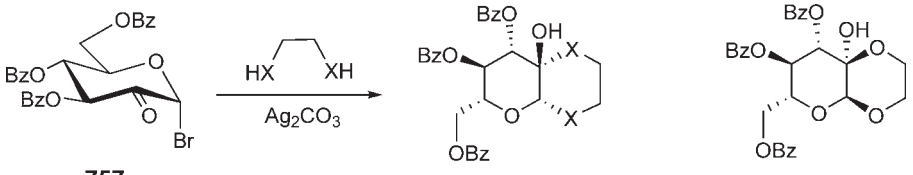
753a: R = Bu^{t}O
753b: R = PhNH
753c: R = Me_2N

754
trans-Fused

755: R = H
756: R = Bu^t
cis-Fused

(64)

β-Specific glucosidations of glycos-2-ulosyl bromide **757** with glycol or 1,2-ethanedithiol and subsequent intramolecular hemiketalization afforded the β-*cis*-pyrano[2,3-*b*][1,4]dioxane **226** and the dithiane analogue **758**, respectively. No *trans*-fused products could be detected. When the glycosidation of **757** with glycol was carried out by stirring in DMF, a mixture of β-*cis*- **226** and α-*cis*-isomer **759** was obtained (Equation 65) <2004EJO4901>.



757

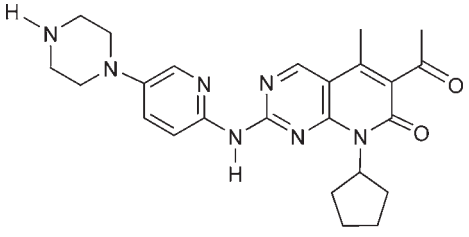
226: X = O (92%)
758: X = S (79%)
β-*cis*

759
α-*cis*
36%

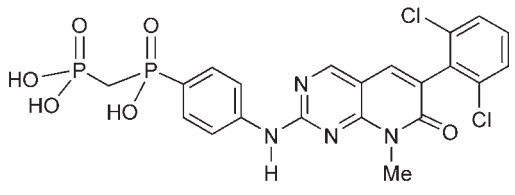
(65)

10.16.9 Important Compounds and Applications

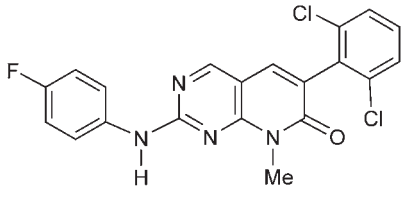
A wide range of biological activity has been observed for compounds containing pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones, including cyclin-dependent kinase 4 (CDK4) inhibition by **760** <2005WO2005005426>, Src and Abl tyrosine kinase inhibition by **761** <2003BML3071>, tyrosine kinase inhibition by PD-173956 **762** <2000BP885>, P38MAP kinase inhibition by **763** and **764** <2002WO2002018379, 2002WO2002064594>, hepatitis C polymerase inhibition <2004USP2004167123>, phosphodiesterase V (PDE V) inhibition <2004JPP2004083587>, telomerase inhibition <2004USP2004009993>, and serine/threonine kinase inhibition <2004WO2004018419>. Furthermore, this ring system has been found in a variety of interesting compounds including the angiotensin-2 antagonist tasosartan by **765** <1998JME4251>.



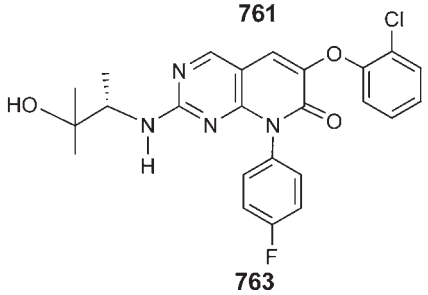
760



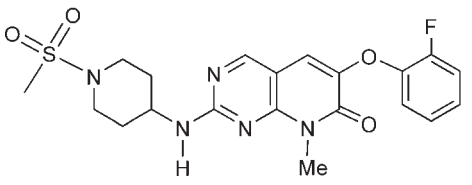
761



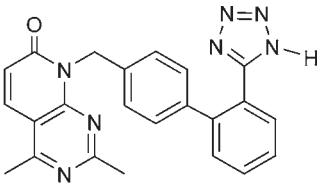
762



763

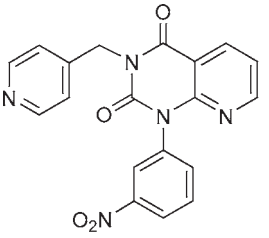


764



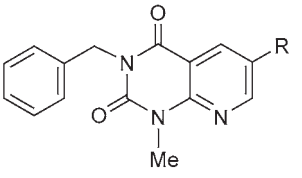
765

It has been reported that compounds bearing the pyrido[2,3-*d*]pyrimidine moiety such as RS-25344 **766** exhibited excellent PDE 4 inhibitory activity <1994MI510>. Pyridopyrimidine analogues **767** bearing substituents at C-3 and/or C-4 positions on the pyridine ring were found to be potent PDE 4 inhibitors <2001BML611>.



RS-25344

766

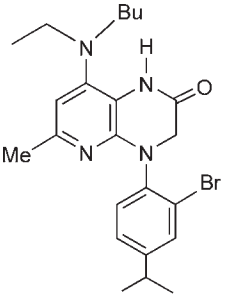


R = OBu^n, CN, CO_2Et, Ph, 4-Cl/FC_6H_4

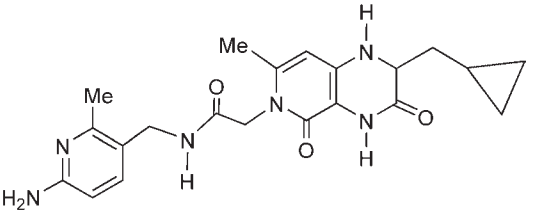
767

.

A series of 3,4-dihydro-1*H*-pyrido[2,3-*b*]pyrazine-2-ones were found to be very potent receptor antagonists of corticotropin-releasing factor-1; among them, **768** has $IC_{50} = 0.7$ nM <2004JME5783>. Polysubstituted hexahydropyrido[3,4-*b*]pyrazinone derivatives **769** inhibit human thrombin with $K_i < 0.1$ nM <1999USP5869487>.



768



769

Relevant Websites

http://www.cas.org– Chemical Abstracts Service.
http://www.sciencedirect.com– Science Direct.

References

1976BSF251 M. Vinot and P. Maitte, *Bull. Soc. Chim. Fr.*, 1976, 251.
1976CPB1390 T. Itoh, M. Honma, and H. Ogura, *Chem. Pharm. Bull.*, 1976, **24**, 1390.
1976JOC1095 A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.*, 1976, **41**, 1095.
1977JHC361 A. A. Santilli and A. C. Scotese, *J. Heterocycl. Chem.*, 1977, **14**, 361.
1979JOC1613 D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613.
1979T2027 G. Jones and P. Rafferty, *Tetrahedron*, 1979, **35**, 2027.

1980H(14)407 K. Hirota, Y. Kitade, and S. Senda, *Heterocycles*, 1980, **14**, 407.
1981JOC846 K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanebe, and J. J. Fox, *J. Org. Chem.*, 1981, **46**, 846.
B-1982MI1 In 'Modern Quantum Chemistry, Introduction to Advanced Electronic Structure Theory', A. Szabo and N. S. Ostlund, Eds.; Macmillan, New York, 1982, p. 1.
1984CPB122 Y. Tominaga, S. Kohra, H. Okuda, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.*, 1984, **32**, 122.
1984CPB1699 T. Nagamatsu, M. Koga, and F. Yoneda, *Chem. Pharm. Bull.*, 1984, **32**, 1699.
1984H(22)513 P. Matyus, P. Sohar, and H. Wamhoff, *Heterocycles*, 1984, **22**, 513.
1984JHC1543 T. L. Su and K. A. Watanabe, *J. Heterocycl. Chem.*, 1984, **21**, 1543.
1985JA3902 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
1985JHC345 K. Hirota, Y. Kitade, and S. Senda, *J. Heterocycl. Chem.*, 1985, **22**, 345.
1986T961 A. Ohno, M. Kashiwagi, Y. Ishihara, S. Ushida, and S. Oka, *Tetrahedron*, 1986, **42**, 961.
1989IJB167 H. V. Patel and P. S. Fernandes, *Indian J. Chem., Sect. B*, 1989, **28**, 167.
1989IJB733 H. V. Patel and P. S. Fernandes, *Indian J. Chem., Sect. B*, 1989, **28**, 733.
1989JPR757 N. A. Shams, A. M. Kaddah, E. I. Enayat, A. A. Shalaby, and A. M. Youssef, *J. Prakt. Chem.*, 1989, **33**, 757.
1990JCCS497 S. El-Bahaie and M. G. Assy, *J. Chin. Chem. Soc.*, 1990, **37**, 497.
1990PHA62 S. El-Bahaie, *Pharmazie*, 1990, **45**, 62.
1990PHA792 M. G. Assy, M. M. Hassanien, and S. Abdel-Rahman, *Pharmazie*, 1990, **45**, 792.
1991AGE1559 S. Goldmann and J. Stoltefus, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1559.
1991JCC675 M. Szafran and J. Kopat, *J. Comput. Chem.*, 1991, **8**, 675.
1991MI235 A. E. Smith and H. J. Lindner, *J. Comput.-Aided Mol. Des.*, 1991, **5**, 235.
1992AHC(55)129 H. Wamhoff, J. Dzenis, and K. Hirota; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Academic Press, New York, 1992, vol. 55, p. 129.
1992IJB92 S. Kumari, P. Ghai, and A. Sexsena, *Indian J. Chem., Sect. B*, 1992, **31**, 92.
1993BCJ2429 R. R. Kakulapati, B. Nanduri, and N. R. Kota, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 2429.
1993CAP2078469 M. Bratz, R. Kober, R. Seele, T. Saupe, N. Meyer, N. Walker, A. Landes, and H. Walter, *Can. Pat.* 2078469 AA (1993) (*Chem. Abstr.*, 1993, **120**, 77293).
1993CAP2086898 R. Hewett, S. N. Pettit, and P. Smith, *Can. Pat.* 2086898 AA (1993) (*Chem. Abstr.*, 1993, **121**, 9415).
1993IJH259 S. Shukla, S. A. Gupta, and L. Prakash, *Indian J. Heterocycl. Chem.*, 1993, **2**, 259.
1993JHC253 M. T. Cocco, C. Congiu, A. Maccioni, and V. Onnis, *J. Heterocycl. Chem.*, 1993, **30**, 253.
1993JHC887 D. G. Hehemann and W. Winnik, *J. Heterocycl. Chem.*, 1993, **30**, 887.
1993JLR1119 J. A. Hill, J. C. Wisowaty, Darnofall, and E. Michael, *J. Labelled Compd. Radiopharm.*, 1993, **33**, 1119.
1993JME3103 A. Rosowsky, C. E. Mota, J. E. Wright, J. H. Freisheim, J. J. Heusner, J. J. McCormack, and S. F. Queener, *J. Med. Chem.*, 1993, **36**, 3103.
1993JOC1104 M. J. Koen and J. E. Gready, *J. Org. Chem.*, 1993, **58**, 1104.
1993M1217 J. Reisch, K. R. R. Rao, and C. O. Usifoh, *Monatsh. Chem.*, 1993, **124**, 1217.
1993PHA221 R. Sharma, S. Shukla, and R. D. Goyal, *Pharmazie*, 1993, **48**, 221.
1993WO(1993)9307146 R. S. Wilhelm, B. E. Loe, B. H. Devens, R. Alvarez, and M. G. Martin, *PCT Int. Appl. WO Pat.* 19939307146 A1 (1993) (*Chem. Abstr.*, 1993, **119**, 180830).
1994AP221 R. Troschütz and T. Dennstedt, *Arch. Pharm. (Weinheim Ger.)*, 1994, **327**, 221.
1994EUP593286 C. J. Barnett and T. M. Wilson, *Eur. Pat.* 593286 A2 (1994) (*Chem. Abstr.*, 1994, **121**, 35635).
1994FA259 F. Savelli, A. Boido, M. Satta, A. Peana, and C. Marzano, *Farmaco*, 1994, **49**, 259.
1994FA499 H. Śladowska, M. Sieklucka-Dziuba, L. Staniak, and Z. Kleinrok, *Farmaco*, 1994, **49**, 499.
1994H(37)171 P. Mátyus, K. Fuji, and K. Tanaka, *Heterocycles*, 1994, **37**, 171.
1994H(37)563 K. Hirota, H. Kuki, and Y. Maki, *Heterocycles*, 1994, **37**, 563.
1994H(38)57 H. M. F. Madkour, M. A. I. Salem, T. M. Abdel-Rahman, and M. E. Azab, *Heterocycles*, 1994, **38**, 57.
1994H(38)283 Y. Blache, A. Gueiffier, O. Chavignon, A. Elhakmaoui, H. Viols, J. C. Teulade, J. C. Milhavet, G. Dauphin, and J. P. Chapat, *Heterocycles*, 1994, **38**, 283.
1994H(38)1845 N. Haider, K. Mereiter, and R. Wanko, *Heterocycles*, 1994, **38**, 1845.
1994JHC819 F. F. Duarte and F. D. Popp, *J. Heterocycl. Chem.*, 1994, **31**, 819.
1994JHC1065 T. Seki and Y. Iwanami, *J. Heterocycl. Chem.*, 1994, **31**, 1065.
1994JHC1385 M. T. G. Ivery and J. E. Gready, *J. Heterocycl. Chem.*, 1994, **31**, 1385.
1994JHC1569 H. Furrer, H.-W. Fehlhaber, and R. Wagner, *J. Heterocycl. Chem.*, 1994, **31**, 1569.
1994MI203 N. H. Eshba, M. M. El-Semary, M. F. M. Abdel-Kreem, and R. M. Shafik, *Alex. J. Pharm. Sci.*, 1994, **8**, 203.
1994MI510 R. Alvarez, R. S. Wilhelm, E. R. Shelton, D. V. Daniels, D. Yang, K. Kelly, and R. M. Eglen, *Can. J. Physiol. Pharmacol.*, 1994, **72**, 510.
1994MIP2056742 V. A. Monge, M. V. Martinez, and G. C. Sanmartin, A. M. A. Simon, *ES. Pat.* 2056742 A1 (1994) (*Chem. Abstr.*, 1994, **122**, 105912).
1994S669 V. Dal Piaz, G. Ciciani, and M. P. Giovannoni, *Synthesis*, 1994, 669.
1994T199 G. E. H. Elgemeie and B. A. W. Hussain, *Tetrahedron*, 1994, **50**, 199.
1994T8085 A. Pastor, R. Alajarin, J. J. Vaquero, J. Alvarez-Builla, M. Fau de Casa-Juana, C. Sunkel, J. Priego, I. Fonseca, and J. Sanz-Aparicio, *Tetrahedron*, 1994, **50**, 8085.
1994USP5281602 H. Newman, *US Pat.* 5281602 A (1994) (*Chem. Abstr.*, 1994, **120**, 270443).
1994WO9405661 A. S. Bell and N. K. Terratt, *PCT Int. Appl. WO Pat.* 940566 A1 (1994) (*Chem. Abstr.*, 1994, **121**, 57528).
1995CAP2151971 K. Furukawa and T. Hasegawa, *Can. Pat.* 2151971 AA (1995) (*Chem. Abstr.*, 1995, **124**, 289568).
1995EPP634413 B. D. G. Haylor and P. H. G. Smith, *Eur. Pat.* 634413 A1 (1995) (*Chem. Abstr.*, 1995, **122**, 214088).
1995FA37 H. Śladowska, J. Potoczek, M. Siekluck-Dziuba, G. Rajtar, M. Mlynarczyk, and Z. Kleinrok, *Farmaco*, 1995, **50**, 37.
1995IJB587 U. T. Bhalerao and A. Krishnaiah, *Indian J. Chem., Sect. B*, 1995, **34**, 587.
1995IJB740 A. K. Sharma, A. K. Yadav, and L. Prakash, *Indian J. Chem., Sect. B*, 1995, **34**, 740.
1995JCM488 F. A. Abu-Shanab, B. Wakefield, F. Al-Omran, M. M. A. Khaled, and H. Elnagdi, *J. Chem. Res. (S)*, 1995, 488.

1995JHC347 T. Seki, H. Sakata, and Y. Iwanami, *J. Heterocycl. Chem.*, 1995, **32**, 347.
1995JHC703 T. Seki, H. Sakata, and Y. Iwanami, *J. Heterocycl. Chem.*, 1995, **32**, 703.
1995JHC1071 T. Seki and Y. Iwanami, *J. Heterocycl. Chem.*, 1995, **32**, 1071.
1995JME2615 A. Rosowsky, R. A. Forsch, and S. F. Queener, *J. Med. Chem.*, 1995, **38**, 2615.
1995JME3780 A. M. Thomson, A. J. Bridges, D. W. Fry, A. J. Kraker, and W. A. Denny, *J. Med. Chem.*, 1995, **38**, 3780.
1995M211 N. Haider and W. Staschek, *Monatsh. Chem.*, 1995, **126**, 211.
1995MI55 R. M. Shafik, N. H. Eshba, M. M. El-Semary, and M. F. M. Abdel-Kreem, *Alex. J. Pharm. Sci.*, 1995, **9**, 55.
1995PHA719 G. Hou, D. Gravier, F. Casadebaig, J.-P. Dupin, H. Bernard, and M. Boisseau, *Pharmazie*, 1995, **50**, 719.
1995PHA788 A. M. Hussein, A. A. Atalla, and A. M. K. El-Dean, *Pharmazie*, 1995, **50**, 788.
1995T10253 P. Victory, J. Cirujeda, and A. Vidal-Ferran, *Tetrahedron*, 1995, **51**, 10253.
1995USP5405848 P. J. Sanfilippo, M. P. Bonner, and J. J. Mcnally, *US Pat.* 5405848 A (1995) (*Chem. Abstr.*, 1995, **123**, 55912).
1995USP5466692 J. W. Ellingboe, *US Pat.* 5466692 A1 (1995) (*Chem. Abstr.*, 1995, **124**, 176134).
1995WO9519774 A. J. Bridges, W. A. Denny, D. Fry, A. Kraker, R. Meyer, G. W. Rewcastle, and A. M. Thompson, *PCT Int. Appl. WO Pat.* 9519774 A1 (1995) (*Chem. Abstr.*, 1995, **124**, 8839).
1996CAR71 I. Maeba, Y. Nishiyama, M. Wakimura, and T. Tabata, *Carbohydr. Res.*, 1996, **290**, 71.
1996CHEC-II(7)561 E. S. H. El Ashry and N. Rashed; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 561.
1996DOK33 K. U. Khuzhaniezov, V. A. Urakov, and Kh. M. Shokhidoyatov, *Dokl. Akad. Nauk SSSR*, 1996, **10**, 33.
1996GBP2291422 N. Shimazaki, S. Watanabe, A. Sawada, and K. Hemmi, *Br. Pat.* 2291422 A1 (1996) (*Chem. Abstr.*, 1996, **125**, 10857).
1996H(43)1057 G. Heinisch, T. Langer, J. Tonnel, K. Mereiter, and K. Wurst, *Heterocycles*, 1996, **43**, 1057.
1996JA8953 J. J. Chen, D. S. Wise, and L. B. Townsend, *J. Am. Chem. Soc.*, 1996, **118**, 8953.
1996JHC45 N. Martin, M. Quinteiro, C. Seoane, and J. Soto, *J. Heterocycl. Chem.*, 1996, **33**, 45.
1996JHC1731 G. Heinisch, T. Langer, and J. Tonnel, *J. Heterocycl. Chem.*, 1996, **33**, 1731.
1996JHC1737 F. Savelli, A. Boido, and G. Damonte, *J. Heterocycl. Chem.*, 1996, **33**, 1737.
1996JIC623 M. G. Assy, M. El-Kafrawy, and M. O. Ghareeb, *J. Indian Chem. Soc.*, 1996, **73**, 623.
1996JME1331 J. Ohmori, H. Kubota, M. Shimizu-Sasamata, M. Okada, and S. Sakamoto, *J. Med. Chem.*, 1996, **39**, 1331.
1996JME1438 A. Gangjee, A. Vasudevan, S. F. Queener, and R. L. Kisliuk, *J. Med. Chem.*, 1996, **39**, 1438.
1996JME1823 G. Rewcastle, B. D. Palmer, A. M. Thompson, A. J. Bridges, D. R. Cody, H. Zhou, D. W. Fry, A. McMichael, and W. A. Denny, *J. Med. Chem.*, 1996, **39**, 1823.
1996J(P1)2221 G. W. Rewcastle, W. A. Denny, R. T. Winters, N. L. Colbry, and H. D. Hollis Showalter, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2221.
1996KGS1410 E. G. Paronikyan, A. S. Noravyan, and A. P. Engoyan, *Khim. Geterotsikl. Soedin.*, 1996, **10**, 1410.
1996T3261 J. Z. Brzeziński, H. B. Bzowski, and J. Epsztajn, *Tetrahedron*, 1996, **52**, 3261.
1996TL4643 M. F. Gordeev, D. V. Patel, J. Wu, and E. M. Gordon, *Tetrahedron Lett.*, 1996, **37**, 4643.
1996WO9601825 K. D. Hemmi, N. Shimazaki, S. Watanabe, and A. Sawada, *PCT Int. Appl. WO Pat.* 9601825 A1 (1996) (*Chem. Abstr.*, 1996, **124**, 317209).
1996WO9603406 M. D.Varney and W. H. Romines, *PCT Int. Appl. WO Pat.* 9603406 A1 (1996) (*Chem. Abstr.*, 1996, **125**, 34163).
1996WO9634867 C. J. Blankley, D. H. Boschelli, A. M. Doherty, J. M. Hamby, S. Klutchko, and R. L. Panek, *PCT Int. Appl. WO Pat.* 9634867 A1 (1996) (*Chem. Abstr.*, 1996, **126**, 59965).
1997CPB542 K. Hirota, K. Kubo, and H. Sajiki, *Chem. Pharm. Bull.*, 1997, **45**, 542.
1997FA657 H. Śladowska, M. Bodetko, M. Sieklucka-Dziuba, G. Rajtar, D. Źolkowska, and Z. Kleinrok, *Farmaco*, 1997, **52**, 657.
1997G787 M. F. Ismail, H. A. Y. Derbala, and H. S. E. Abul-Yazeed, *Gazz. Chim. Ital.*, 1997, **127**, 787.
1997H(45)107 T. Takabatake, T. Miyazawa, and M. Hasegawa, *Heterocycles*, 1997, **45**, 107.
1997H(45)2229 E. C. Taylor and K. Lee, *Heterocycles*, 1997, **45**, 2229.
1997HCO151 Y. M. Elkholy, E. A. Abdel-Aziz, and M. H. Elnagdy, *Heterocycl. Commun.*, 1997, **3**, 151.
1997IJH237 A. K. Yadav, H. Agrawal, A. Singh, and L. Prakash, *Indian J. Heterocycl. Chem.*, 1997, **6**, 237.
1997JHC521 J. Quiroga, A. Hormaza, B. Insuasty, M. Nogueras, A. Sánchez, N. Hanold, and H. Meier, *J. Heterocycl. Chem.*, 1997, **34**, 521.
1997JHC773 T. Seki, Y. Iwanami, Y. Kuwatani, and M. Iyoda, *J. Heterocycl. Chem.*, 1997, **34**, 773.
1997JME470 A. Gangjee, R. Devraj, and S. F. Queener, *J. Med. Chem.*, 1997, **40**, 470.
1997JME1820 G. W. Rewcastle, A. J. Bridges, D. W. Fry, J. R. Rubin, and W. A. Denny, *J. Med. Chem.*, 1997, **40**, 1820.
1997JOC2999 K. Hirota, K. Kubo, H. Sajiki, Y. Kitade, M. Sako, and Y. Maki, *J. Org. Chem.*, 1997, **62**, 2999.
1997JPP09263584 K. Ataka, H. Miyata, and A. Takama, *Jpn. Pat.* 09263584 A2 (1997) (*Chem. Abstr.*, 1997, **127**, 331502).
1997LA1619 H. Wamhoff and V. Kramer-Hoss, *Leibigs Ann. Chem.*, 1997, 1619.
1997PHA97 K. Gorlitzer and K. Diers, *Pharmazie*, 1997, **52**, 97.
1997PJC1232 M. G. Assy and H. Y. Moustafa, *Pol. J. Chem.*, 1997, **71**, 1232.
1997SL895 P. D. May and S. D. Larsen, *Synlett*, 1997, 895.
1997T8225 J. Cobo, A. Sánchez, M. Nogueras, and E. De Clerq, *Tetrahedron*, 1997, **53**, 8225.
1997USP5654307 A. J. Bridges, W. A. Denny, D. Fry, A. Kraker, R. F. Meyer, G. W. Rewcastle, and A. M. Thompson, *US Pat.* 5654307 A (1997) (*Chem. Abstr.*, 1997, **127**, 220667).
1997WO9718212 F. Buzzetti, M. G. Brasca, A. Longo, and D. Ballinari, *PCT Int. Appl. WO Pat.* 9718212 A1 (1997) (*Chem. Abstr.*, 1997, **127**, 65645).
1997WO9719078 K. Takayama, H. Hisamichi, M. Iwata, H. Kubota, and M. Aoki, *PCT Int. Appl. WO Pat.* 9719078 A1 (1997) (*Chem. Abstr.*, 1997, **127**, 65784).
1997WO9719946 T. Bar, P. Zimmermann, R. Boer, V. Gekeler, W. Lse, H. Boss, and W.-R. Ulrich, *PCT Int. Appl. WO Pat.* 9719946 A1 (1997) (*Chem. Abstr.*, 1997, **127**, 81463).
1997WO9724355 N. Shimazaki, A. Sawada, and S. Watanabe, *PCT Int. Appl. WO Pat.* 9724355 A1 (1997) (*Chem. Abstr.*, 1997, **127**, 149156).
1997WO9726259 H. D. H. Showalter, R. T. Winter, G. W. Rewcastle, and W. A. Denny, *PCT Int. Appl. WO Pat* 9726259 A1 (1997) (*Chem. Abstr.*, 1997, **127**, 176432).
1997YZ126 T. Miyazawa, T. Takabatake, and M. Hasegawa, *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)*, 1997, **117**, 126.

1998FA468 H. Śladowska, J. Potoczek, M. Sokolowska, G. Rajtar, M. Sieklucka-Dziuba, T. Kocki, and Z. Kleinrok, *Farmaco*, 1998, **53**, 468.

1998FA475 H. Śladowska, J. Stanasiuk, M. Sieklucka-Dziuba, T. Saran, and Z. Kleinrok, *Farmaco*, 1998, **53**, 475.

1998IJB517 G. Singh, Swati, A. K. Mishra, and L. Prakash, *Indian J. Chem., Sect. B*, 1998, **37**, 517.

1998JCM26 M. H. Elnagdi, M. A. Barsy, F. M. Abdel-Latif, and K. U. Sadek, *J. Chem. Res. (S)*, 1998, 26.

1998JHC231 A. J. Ortíz, A. Sánchez, and M. Nogueras, *J. Heterocycl. Chem.*, 1998, **35**, 231.

1998JHC1389 Y. Yamada and H. Yasuda, *J. Heterocycl. Chem.*, 1998, **35**, 1389.

1998JME4251 J. W. Ellingboe, M. D. Collini, D. Quagliato, J. Chen, M. Antane, J. Schmid, D. Hartupee, V. Whate, C. H. Park, T. Tanikella, and J. F. Bagli, *J. Med.Chem.*, 1998, **41**, 4251.

1998PJS81 S. M. El-Kousy, R. M. Mohareb, M. Riad, and M. H. Elnagdi, *Pak. J. Sci. Ind. Res.*, 1998, **41**, 81.

1998SC2871 A. F. Fahmy, J. Sauer, M. S. K. Youssef, M. S. Abdel Halim, and M. A. Hassan, *Synth. Commun.*, 1998, **28**, 2871.

1999JHC113 J. Quiroga, M. Alvarado, B. Insuasty, M. Nogueras, A. Sánchez, and M. D. López, *J. Heterocycl. Chem.*, 1999, **36**, 113.

1999JHC501 J. Quiroga, G. Viveros, B. Insuasty, M. Nogueras, A. Sánchez, and J. Cobo, *J. Heterocycl. Chem.*, 1999, **36**, 501.

1999JME1803 J. B. Smaill, B. D. Balmer, G. W. Rewcastle, W. A. Denny, D. J. McNamara, E. M. Dobrusin, A. J. Bridges, H. Zhou, H. D. H. Showalter, R. T. Winters, W. R. Leopold, D. W. Fry, J. M. Nelson, V. Slintak, W. L. Elliot, B. J. Roberts, P. W. Vincent, and S. J. Patmore, *J. Med. Chem.*, 1999, **24**, 1803.

1999JOC634 A. Vasudevan, F. Mavandadi, L. Chen, and A. Gangjee, *J. Org. Chem.*, 1999, **64**, 634.

1999USP5869487 C. Coburn, C. Kolatac, D. M. Rush, and J. P. Vacca, *US Pat.* 5869487 A (1999) (*Chem. Abstr.*, 1999, **130**, 168393).

1999WO9935146 M. C. Carter, G. S. Cockerill, S. B. Guntrip, K. E. Lackey, and K. J. Smith, *PCT Int. Appl. WO Pat.* 9935146 A1 (1999) (*Chem. Abstr.*, 1999, **131**, 102288).

2000BP885 A. J. Kraker, B. G. Hartl, A. M. Amar, M. R. Barvian, H. D. H. Showalter, and C. W. Moore, *Biochem. Pharmacol.*, 2000, **60**, 885.

2000DEP19900544 G. Steiner, K. Schellhaas, W. Lubisch, U. Holzenkamp, D. Starck, L. Szabo, F. Emling, F. J. Garcia-Ladona, H.-P. Hofmann, and L. Unger, *Ger. Pat.* 19900544 A1 (2000) (*Chem. Abstr.*, 2000, **133**, 89540).

2000H(52)1207 J. I. Borrell, J. Teixido, J. L. Matallana, B. Martinez-Teipel, and E. Couceiro, *Heterocycles*, 2000, **52**, 1207.

2000IJB210 C. G. Dave and M. C. Shukla, *Indian J. Chem., Sect. B*, 2000, **39**, 210.

2000IJH135 A. A. Elbahnsawy, M. K. A. Ibrahim, G. F. Ahmed, and A. F. Sayed, *Indian J. Heterocycl. Chem.*, 2000, **10**, 135.

2000JME3704 J.-L. Girardet, E. Gunic, C. Esler, D. Cieslak, Z. Pietrzkowski, and G. Wang, *J. Med. Chem.*, 2000, **43**, 3704.

2000S541 P. Srivastava, A. S. Saxena, and V. J. Ram, *Synthesis*, 2000, 541.

2000SC81 Y. H. Roh, J. W. Bae, G. S. Nam, J. H. Kim, S. H. Kim, and C. M. Yoon, *Synth. Commun.*, 2000, **30**, 81.

2000SC2223 A. S. El-Ahl, *Synth. Commun.*, 2000, **30**, 2223.

2000T2473 B. Pita, E. Sotelo, M. Suárez, E. Raviña, E. Ochoa, Y. Verdecia, H. Novoa, N. Blaton, C. deRanter, and O. M. Peeters, *Tetrahedron*, 2000, **56**, 2473.

2000TL5899 J. W. Bae, S. H. Lee, Y. J. Cho, Y. J. Jung, H.-J. Hwang, and C. M. Yoon, *Tetrahedron Lett.*, 2000, **41**, 5899.

2000USP6030969 S. S. Bhagwat, R. J. Perner, and Y. G. Gu, *US Pat.* 6030969 A (2000) (*Chem. Abstr.*, 2000, **132**, 180592).

2000USP6060477 G. A. Piazza and R. Pamukcu, *US Pat.* 6060477 A (2000) (*Chem. Abstr.*, 2000, **132**, 321870).

2001ARK21 E. Abdel-Rehem and N. Haider, *ARKIVOC*, 2001, **ii**, 21.

2001BML83 M. Cowart, C.-H. Lee, G. A. Gfesser, E. K. Bayburt, S. S. Bhagwat, A. O. Stewart, H. Yu, K. L. Kohlhaas, S. McGaraughty, C. T. Wismer, J. Mikusa, C. Zhu, K. M. Alexander, M. F. Jarvis, and E. A. Kowaluk, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 83.

2001BML611 G. Nam, C. M. Yoon, E. Kim, C. K. Rhee, J. H. Kim, J. H. Shin, and S. H. Kim, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 611.

2001EPP1145716 H. Yoshii and A. Fujita, *Eur. Pat.* 1145716 A2 (2001) (*Chem. Abstr.*, 2001, **135**, 308891).

2001H(55)115 A. Z. M. S. Chowdhury and Y. Shibata, *Heterocycles*, 2001, **55**, 115.

2001H(55)1315 A. S. El-Ahl, S. A. A. El Bialy, and M. A. Ismail, *Heterocycles*, 2001, **55**, 1315.

2001H(55)1679 F. Schöfeld and R. Troschütz, *Heterocycles*, 2001, **55**, 1679.

2001IJB213 A. G. Hammam, M. A. Sharaf, and N. A. Abd El-Hafez, *Indian J. Chem., Sect. B*, 2001, **40**, 213.

2001JOC1590 Y. Mikata, K. Mizukami, K. Hayashi, S. Yano, N. Yamazaki, and A. Ohno, *J. Org. Chem.*, 2001, **66**, 1590.

2001J(P1)2341 N. Rosas, P. Sharma, C. Alvarez, A. Cabrera, R. Ramírez, A. Delgado, and H. Arzoumanian, *J. Chem. Soc., Perkin. Trans. 1*, 2001, 2341.

B-2001MI1 In 'A Chemist's Guide to Density Functional Theory', 2nd edn., W. Koch and M. C. Holthausen, Eds.; Wiley-VCH, Weinheim, 2001, p. 1.

2001S221 Y. Saito, T. Sakamoto, and Y. Kikugawa, *Synthesis*, 2001, 221.

2001SL1299 A. J. Thakur, P. Saikia, D. Prajapati, and J. S. Sandhu, *Synlett*, 2001, 1299.

2001SL1523 M. C. Bagley, J. W. Dale, D. D. Hughes, M. Ohnesorge, N. G. Phillips, and J. Bower, *Synlett*, 2001, 1523.

2001TL5625 J. Quiroga, C. Cisneros, B. Insuasty, R. Abonía, M. Nogueras, and A. Sánchez, *Tetrahedron Lett.*, 2001, **42**, 5625.

2001TL6585 M. C. Bagley, D. D. Hughes, R. Lloyd, and V. E. C. Powers, *Tetrahedron Lett.*, 2001, **42**, 6585.

2001WO2001055148 R. J. Booth, A. Chatterjee, and T. C. Malone, *PCT Int. Appl. WO Pat.* 2001055148 A1 (2001) (*Chem.Abstr.*, 2001, **135**, 152818).

2001WO2001057040 S. S. Bhagwat, C. H. Lee, R. J. Perner, and Y. G. Gu, *PCT Int. Appl. WO Pat.* 2001057040 A1 (2001) (*Chem. Abstr.*, 2001, **135**, 152822).

2001WO2001070741 R. J. Booth, E. M. Dobrusin, P. L. Toogood, and S. N. Vanderwel, *PCT Int. Appl. WO Pat.* 2001070741A1 (2001) (*Chem. Abstr.*, 2001, **135**, 272982).

2002EPP1249451 S. K. Bhattacharya, J. C. Kath, and J. Morris, *Eur. Pat.* 1249451 A2 (2002) (*Chem. Abstr.*, 2002, **137**, 294972).

2002H(57)491 M. Nitta and H. Kanda, *Heterocycles*, 2002, **57**, 491.

2002IJB430 G. Singh, G. Singh, A. K. Yadav, and A. K. Mishra, *Indian J. Chem., Sect. B*, 2002, **41**, 430.

2002IJB804 P. Saikia, A. J. Thakur, D. Prajapati, and J. S. Sandhu, *Indian J. Chem., Sect. B*, 2002, **41**, 804.

2002M653 M. Weber, H. Bartsch, and T. Erker, *Monatsh. Chem.*, 2002, **133**, 653.

2002M1177 E. Gossnitzer, A. Krbavcic, W. Wendélin, and M. Krbavcic, *Monatsh. Chem.*, 2002, **133**, 1177.

2002PS1359 A. A. F. Wasfy, M. S. Amine, M. M. H. Arief, S. G. Donia, and A. A. Aly, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1359.

2002RCB1875 A. V. Komkov and V. A. Dorokhov, *Russ. Chem. Bull.*, 2002, **51**, 1875.

2002RJO1548 A. N. Vasil'ev, A. N. Nikolaev, A. N. Lyschikov, O. E. Nasakin, and Ya. S. Kayukov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2002, **38**, 1548.

2002SM(131)53 M. Jonforsen, T. Johansson, L. Spjuth, O. Inganäs, and M. R. Andersson, *Synth. Met.*, 2002, **131**, 53.

2002T4873 J. Quiroga, H. Insuasty, B. Insuasty, R. Abonía, J. Cobo, A. Sánchez, and M. Nogueras, *Tetrahedron*, 2002, **58**, 4873.

2002T5241 M. Mateu, A. S. Capilla, Y. Harrak, and M. D. Pujol, *Tetrahedron*, 2002, **58**, 5241.

2002WO2002018379 H. B. Arzeno J. J. Chen, J. P. Dunn, D. M. Goldstein, and J. A. Lim *PCT Int. Appl. WO Pat.* 2002018379 A2 (2002) (*Chem. Abstr.*, 2002, **136**, 216763).

2002WO2002018380 J. J. Chen, J. P. Dunn, D. M. Goldstein, and J. A. Lim, *PCT Int. Appl. WO Pat.* 2002018380 A1 (2002) (*Chem. Abstr.*, 2002, **136**, 232316).

2002WO2002026743 E. Barker, S. Bystroem, E. Desarbre, J. Duffy, S. James, C. Liljebris, and J. Martinsson, *PCT Int. Appl. WO Pat.* 2002026743 A1 (2002) (*Chem. Abstr.*, 2002, **136**, 279464).

2002WO2002059083 J. L. Adams, J. C. Bochm, R. Hall, Q. Jin, J. Kasparec, D. J. Silva, and J. J. Taggart, *PCT Int. Appl. WO Pat.* 2002059083 A2 (2002) (*Chem. Abstr.*, 2002, **137**, 140533).

2002WO2002064594 J. J. Chen, J. P. Dunn, D. M. Goldstein, and C. M. Stahl, *PCT Int. Appl. WO Pat.* 2002064594 A2 (2002) (*Chem. Abstr.*, 2002, **137**, 185502).

2002WO2002094824 M. J. Mckennon, J. P. Klein, and M. Coon, *PCT Int. Appl. WO Pat.* 2002094824 A1 (2002) (*Chem. Abstr.*, 2002, **138**, 4609).

2002WO2002090360 C. A. Barrish, M. A. Lago, and M. A. Semones, *PCT Int. Appl. WO Pat.* 2002090360 A1 (2002) (*Chem. Abstr.*, 2002, **137**, 370104).

2003BMC59 A. Rosowsky, H. Chen, H. Fu, and S. F. Queener, *Bioorg. Med. Chem.*, 2003, **11**, 59.

2003BMC433 K. Yoshiizumi, M. Yamamoto, T. Miyasaka, Y. Ito, H. Kumihara, M. Sawa, T. Kiyoi, T. Yamamoto, F. Nakajima, R. Hirayama, H. Kondo, E. Ishibushi, H. Ohmoto, Y. Inoue, and K. Yoshino, *Bioorg. Med. Chem.*, 2003, **11**, 433.

2003BML3071 C. B. Vu, G. P. Luke, N. Kawahata, W. C. Shakespeare, Y. Wang, R. Sundaramoorthi, C. A. Metcalf, T. P. Keenan, S. Pradeepan, E. Corpuz, T. Merry, R. S. Bohacek, D. C. Dalgarno, S. S. Narula, M. R. Van Schravendijk, M. K. Ram, S. Adams, S. Liou, J. A. Keats, S. M. Violette, W. Guan, M. Weigele, and T. K. Sawyer, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3071.

2003H(60)925 W. W. K. R. Mederski, D. Kux, M. Knoth, and M. J. Schwarzkopf-Hofman, *Heterocycles*, 2003, **60**, 925.

2003HAC491 H. M. Hassaneen, T. A. Abdallah, H. A. Abdhadi, H. M. E. Hassaneen, and R. M. Pagni, *Heteroatom Chem.*, 2003, **14**, 491.

2003JOC4345 B. R. Lahue, Z.-K. Wan, and J. K. Snyder, *J. Org. Chem.*, 2003, **68**, 4345.

2003MI85 L. J. Falco, J. I. Borrell, and J. Teixido, *Mol. Divers.*, 2003, **6**, 85.

2003OL2123 F. Bravo, F. E. McDonald, W. A. Neiwert, B. Do, and K. I. Hardcastle, *Org. Lett.*, 2003, **5**, 2123.

2003S1531 D. M. Volochnyuk, A. O. Pushechnikov, D. G. Krotko, D. A. Sibgatulin, S. A. Kovalyova, and A. A. Tolmachev, *Synthesis*, 2003, 1531.

2003TL2745 R. Mamouni, M. Aadil, M. Akssira, J. Lasri, and J. Sepulveda-Arques, *Tetrahedron Lett.*, 2003, **44**, 2745.

2003TL5385 N. Mont, J. Teixido, J. I. Borrell, and C. O. Kappe, *Tetrahedron Lett.*, 2003, **44**, 5385.

2003TL8307 I. Devi, B. S. D. Kumar, and P. J. Bhuyan, *Tetrahedron Lett.*, 2003, **44**, 8307.

2003WO2003027110 H. I. Tjiong and R. T. Winters, *PCT Int. Appl. WO Pat.* 2003027110 A2 (2003) (*Chem. Abstr.*, 2003, **138**, 287695).

2003WO2003062236 M. R. Barvian, R. J. Booth, J. Quin, J. T. Repine, D. J. Sheehan, P. L. Toogood, S. N. Vanderwel, and H. Zhou, *PCT Int. Appl. WO Pat.* 2003062236 A1 (2003) (*Chem. Abstr.*, 2003, **139**, 149646).

2003WO2003103575 D. Dhanak, S. D. Knight, P. Lu, D. J. Morgans, and B. Yao, *PCT Int. Appl. WO Pat.* 2003103575 A2 (2003) (*Chem. Abstr.*, 2003, **140**, 42200).

2004EJO4901 E. Cuny, F. W. Lichtenthaler, and H. J. Lindner, *Eur. J. Org. Chem.*, 2004, 4901.

2004FRP2846657 S. Rault, J. C. Lancelot, M. Kopp, D. H. Caignard, B. Pfeiffer, and P. Renard, *Fr. Pat.* 2846657 A1 (2004) (*Chem. Abstr.*, 2004, **140**, 375180).

2004H(63)1393 S. Naya, K. Shibayama, and M. Nitta, *Heterocycles*, 2004, **63**, 1393.

2004JME5783 C. D. Dzierba, A. G. Takvorian, M. Rafalski, P. Kasireddy-Polam, H. Wong, T. F. Molski, G. Zhang, Y. W. Li, S. Lelas, Y. Peng, J. F. McElroy, R. C. Zaczek, R. A. Taub, A. P. Combs, P. J. Gilligan, and G. L. Trainor, *J. Med. Chem.*, 2004, **47**, 5783.

2004JPP2004083587 K. Yamada, M. Hikota, Y. Koga, K. Yoshikawa, and K. Omori, *Jpn. Pat.* 2004083587 A2 (2004) (*Chem. Abstr.*, 2004, **140**, 247112).

2004MOL910 K. M. Al-Zaydi, R. M. Borik, and M. H. Elnagdi, *Molecules*, 2004, **9**, 910.

2004PS2373 W. M. Abdou, A. F. M. Fahmy, and A. A. M. Shaddy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, **180**, 2373.

2004SC4331 X.-S. Wang, Z.-S. Zeng, D.-Q. Shi, X.-Y. Wei, and Z.-M. Zong, *Synth. Commun.*, 2004, **34**, 4331.

2004SC4447 A. Agarwal and P. M. S. Chauhan, *Synth. Commun.*, 2004, **34**, 4447.

2004SC4463 S. Ravikanth, G. V. Reddy, D. Maitraie, V. R. Rao, P. S. Rao, and B. Narsaiah, *Synth. Commun.*, 2004, **34**, 4463.

2004SL283 I. Devi and P. J. Bhuyan, *Synlett*, 2004, 283.

2004T4107 J. Audoux, N. Plé, A. Turk, and G. Quéguiner, *Tetrahedron*, 2004, **60**, 4107.

2004T6353 J. Audoux, N. Plé, A. Turk, and G. Quéguiner, *Tetrahedron*, 2004, **60**, 6353.

2004T11511 U. Girreser, D. Heber, and M. Schütt, *Tetrahedron*, 2004, **60**, 11511.

2004TL3737 E. J. Williams, P. W. Kenny, J. G. Kettle, and P. G. Mwashimba, *Tetrahedron Lett.*, 2004, **45**, 3737.

2004USP2004009993 M. Angiolini, D. Ballinari, D. F. Bassini, L. Bonomini, M. Gude, M. Menichincheri, J. Moll, and J. Y. Trosset, *US Pat.* 2004009993 A1 (2004) (*Chem. Abstr.*, 2004, **140**, 94058).

2004USP2004167123 J. K. Pratt, D. A. Betebenner, P. L. Donner, B. E. Green, D. J. Kempf, K. F. McDaniel, C. J. Maring, V. S. Stoll, and R. Zhang, *US Pat.* 2004167123 (2004) (*Chem. Abstr.*, 2004, **141**, 207236).

2004WO2004018419 P. A. Barsanti, D. Bussiere, S. D. Harrison, C. C. Heise, J. M. Jansen, E. Jazan, T. D. Machajewski, C. Ncbride, W. R. McCrea, S. Ng, Z. J. Ni, S. Pecchi, K. Pfister, S. Ramurthy, P. A. Renhowa, C. M. Shafer, J. B. Silver, A. Wagman, and M. Weismann, *PCT Int. Appl. WO Pat.* 2004018419 (2004) (*Chem. Abstr.*, 2004, **140**, 235711).

2004WO2004039774 P. J. Coleman, M. E. Fraley, and W. F. Hoffman, *PCT Int. Appl. WO Pat.* 2004039774 A2 (2004) (*Chem. Abstr.*, 2004, **140**, 406814).

2004WO2004039802 S. C. Goodacre and D. J. Hallet, *PCT Int. Appl. WO Pat.* 2004039802 A1 (2004) (*Chem. Abstr.*, 2004, **140**, 406813).

2004WO2004056825 P. J. Crowley, M. Dobler, U. Mueller, and J. Williams, *PCT Int. Appl. WO Pat.* 2004056825 A1 (2004) (*Chem. Abstr.*, 2004, **141**, 89117).

2004WO2004056826 P. J. Crowley, M. Dobler, U. Mueller, and J. Williams, *PCT Int. Appl. WO Pat.* 2004056826 A1 (2004) (*Chem. Abstr.*, 2004, **141**, 89106).

2004WO2004104002 E. Guenther, E. Claus, I. Seipelt, U. R. Rapp, and L. Wixler, *PCT Int. Appl. WO Pat.* 2004104002 A1 (2004) (*Chem. Abstr.*, 2004, **142**, 23311).

2004WO2004104003 E. Guenther, E. Claus, I. Seipelt, U. R. Rapp, and L. Wixler, *PCT Int. Appl. WO Pat.* 2004104003 A1 (2004) (*Chem. Abstr.*, 2004, **142**, 23312).

2004ZNB721 K. M. Al-Zaydi and M. H. Elnagdi, *Z. Naturforsch., B*, 2004, **59**, 721.

2005ARK80 A. Dandia, K. Arya, S. Khaturia, and P. Yadav, *ARKIVOC*, 2005, **xiii**, 80.

2005ARK76 S. Tu, J. Zhang, Z. Xiang, F. Fang, and T. Li, *ARKIVOC*, 2005, **xiv**, 76.

2005BML1829 J. Kempson, W. J. Pitts, J. Barbosa, J. Guo, O. Omotoso, A. Watson, K. Stebbins, G. C. Starling, J. H. Dodd, J. C. Barrish, R. Felix, and K. Fischer, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1829.

2005BML2803 R. J. Perner, C. H. Lee, M. Jiang, Y. G. Gu, S. DiDomenico, E. K. Bayburt, K. M. Alexander, K. L. Kohlhaas, M. F. Jarvis, E. L. Kowaluk, and S. S. Bhagwat, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2803.

2005IJB2527 V. Padmavathi, T. V. R. Reddy, K. A. Reddy, A. Padmaja, and D. B. Reddy, *Indian J. Chem., Sect. B*, 2005, **44**, 2527.

2005JOC7208 G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, and A. Vong, *J. Org. Chem.*, 2005, **70**, 7208.

2005JOC9377 A. Baron, G. Sandford, R. Slater, D. S. Yufit, J. A. K. Howard, and A. Vong, *J. Org. Chem.*, 2005, **70**, 9377.

2005RCB784 A. V. Komkov, I. P. Yakovlev, and V. A. Dorokhov, *Russ. Chem. Bull.*, 2005, **54**, 784.

2005S1345 L. Yin and J. Liebscher, *Synthesis*, 2005, 1345.

2005TL1241 J. F. Liu, J. Lee, A. M. Dalton, G. Bi, L. Yu, C. M. Baldino, E. McElory, and M. Brown, *Tetrahedron Lett.*, 2005, **46**, 1241.

2005TL5851 G. Lavecchia, S. Berteina-Raboin, and G. Guillaumet, *Tetrahedron Lett.*, 2005, **46**, 5851.

2005WO200501000 O. Wagner, T. Grote, C. Blettner, M. Gewehr, W. Grammenos, A. Gypser, B. Mueller, J. Rheinheimer, P. Schaefer, F. Schieweck, A. Schwoegler, I. B. J. Tormo, A. Akers, J. B. Speakman, M. Rack, R. Stierl, M. Scherer, S. Strathmann, and U. Schoefl, *PCT Int. Appl. WO Pat.* 200501000 A2 (2005) (*Chem. Abstr.*, 2005, **142**, 198091).

2005WO2005005426 V. G. Beylin, A. C. Blackburn, D. T. Erdman, and P. L. Toogood, *PCT Int. Appl. WO Pat.* 2005005426 A1 (2005) (*Chem. Abstr.*, 2005, **142**, 134616).

2005WO2005042498 R. Bakthavatchalam, C. A. Blum, H. Brielmann, T. M. Caldwell, D. N. Cortright, K. J. Hodgetts, J. M. Peterson, and X. Zheng, *PCT Int. Appl. WO Pat.* 2005042498 A2 (2005) (*Chem. Abstr.*, 2005, **142**, 463742).

2005WO2005065416 S. Chakravarty, S. Dugar, R. Tester, and A. Conte, *PCT Int. Appl. WO Pat.* 2005065416 A2 (2005) (*Chem. Abstr.*, 2005, **143**, 133391).

2005WO2005090344 K. Honold, W. Schaefer, and S. Scheiblich, *PCT Int. Appl. WO Pat.* 2005090344 A1 (2005) (*Chem. Abstr.*, 2005, **143**, 347193).

2006TL27 J. Quiroga, S. Cruz, B. Insuasty, R. Abonía, M. Nogueras, and J. Cobo, *Tetrahedron Lett.*, 2006, **47**, 27.

2006TL2257 A. Mitchinson, W. P. Blackaby, S. Bourrain, W. R. Carling, and R. T. Lewis, *Tetrahedron Lett.*, 2006, **47**, 2257.

2006TL3177 B. E. Blass, K. Coburn, N. Fairweather, M. Sabat, and L. West, *Tetrahedron Lett.*, 2006, **47**, 3177.

Biographical Sketch



El Sayed Helmy El Ashry studied chemistry at Alexandria University (B.Sc. 1963, M.Sc. 1966, Ph.D. 1969, and D.Sc. 1997). He was awarded the Alexander von Humboldt and Fulbright Fellowships. He has been a visiting professor at Tokyo Institute of Technology, Ohio State University, Michigan Technological University, New York State University, Darmstadt Institute of Organic Chemistry, UmAlqura University, and Konstanz University. He has given lectures at various universities, institutes, companies, and conferences around the world. He is currently a professor of organic chemistry at Alexandria University after being the head of the department for the last four years. He has supervised more than 70 M.Sc. and Ph.D. students and published about 300 publications and review articles in highly renowned journals in the field of carbohydrates and nucleosides, a major area of research in the series '*Heterocycles from Carbohydrate Precursors*' and author of a book, '*Synthesis of Naturally Occurring Nitrogen Heterocycles from Carbohydrates*' (2005). He is also an editor for various international journals. He has received many awards of recognition and distinction, in particular 'Excellence' and '1st class Ribbon of Science and Arts' awards from the President of Egypt.



Nagwa Rashed graduated from Alexandria University in 1974 (M.Sc. in 1977 and Ph.D. in 1981 under the supervision of Professor E. S. H. El Ashry). She currently works on the chemistry of carbohydrates, nucleosides, and heterocycles. She has to her credit about 80 publications besides 10 review articles.

10.17
Bicyclic 6-6 Systems: Four Heteroatoms 1:3

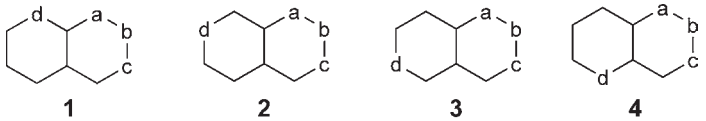
P. W. Groundwater and R. J. Anderson
University of Sunderland, Sunderland, UK
M. Nyerges
Technical University of Budapest, Budapest, Hungary
© 2008 Elsevier Ltd. All rights reserved.

10.17.1 Introduction 848
10.17.2 Theoretical Methods 849
10.17.3 Experimental Structural and Spectroscopic Methods 850
10.17.3.1 X-Ray Diffraction 850
10.17.3.2 Molecular Spectra 851
10.17.3.2.1 NMR spectroscopy 851
10.17.3.2.2 Mass spectrometry 851
10.17.3.2.3 IR spectroscopy 852
10.17.3.2.4 Other analytical methods 852
10.17.4 Thermodynamic Aspects and Aromaticity 852
10.17.5 Reactivity of Fully Conjugated Ring Systems 853
10.17.5.1 2*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazines 853
10.17.5.2 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines 853
10.17.6 Reactivity of Nonconjugated Ring Systems 853
10.17.6.1 Pyrano[3,2-*d*]-1,3,2-dioxathiins 853
10.17.6.2 1*H*,6*H*-Pyrano[3,4-*c*]-1,5,2-dioxazines 858
10.17.6.3 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines 859
10.17.6.4 Pyrido[3,2-*d*]-1,2,6-oxathiazines 861
10.17.7 Reactivity of Substituents Attached to Ring Carbon Atoms 862
10.17.7.1 2*H*-Pyrano[2,3-*d*]-1,2,3-triazines 862
10.17.7.2 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines 863
10.17.7.3 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines 880
10.17.7.4 Pyrido[3,2-*e*]-1,2,4-triazines 881
10.17.7.5 Pyrido[2,3-*e*]-1,2,4-trioxines 881
10.17.8 Reactivity of Substituents Attached to Ring Heteroatoms 882
10.17.8.1 Pyrano[2,3-*d*]-1,2,3-triazines 882
10.17.8.2 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines 882
10.17.8.3 2*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazines 882
10.17.8.4 Pyrido[3,2-*e*]-1,2,4-triazines 882
10.17.8.5 Pyrido[2,3-*e*]-1,2,4-trioxines 883
10.17.9 Ring Syntheses Classified by the Number of Ring Atoms Contributed by Each Component 885
10.17.9.1 Synthesis of the Second Heterocyclic Ring from [6+0] Fragments 885
10.17.9.1.1 1*H*-Pyrano[4,3-*e*]-1,2,4-triazines 885
10.17.9.1.2 2*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazines 886
10.17.9.1.3 Pyrido[4,3-*e*]-1,2,4-thiadiazines 886
10.17.9.1.4 Pyrido[2,3-*e*]-1,2,4-triazines 886
10.17.9.1.5 Pyrido[3,2-*e*]-1,2,4-triazines 886

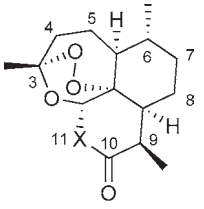
10.17.9.2 Synthesis of the Second Heterocyclic Ring from [5+1] Fragments 889
10.17.9.2.1 Pyrano[3,2-*d*]-1,3,2-dioxathiins 889
10.17.9.2.2 Pyrano[2,3-*d*]-1,2,3-triazines 892
10.17.9.2.3 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines 892
10.17.9.2.4 2*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazines 893
10.17.9.2.5 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines 895
10.17.9.2.6 1*H*-Pyrido[4,3-*c*]-1,2,6-thiadiazines 896
10.17.9.2.7 Pyrido[2,3-*d*]-1,2,3-triazines 897
10.17.9.3 Synthesis of the Second Heterocyclic Ring from [4+2] Fragments 898
10.17.9.3.1 3*H*,6*H*-Pyrano[3,4-*e*]-1,3,4-oxadithiins 898
10.17.9.3.2 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines 899
10.17.9.3.3 Pyrido[3,2-*d*]-1,2,3-oxathiazines 902
10.17.9.3.4 Pyrido[2,3-*e*]-1,2,4-triazines 902
10.17.9.3.5 Pyrido[2,3-*e*]-1,2,4-trioxines 902
10.17.9.4 Synthesis of the Second Heterocyclic Ring from [3+3] Fragments 904
10.17.9.5 Synthesis of the Second Heterocyclic Ring by Miscellaneous Routes 904
10.17.10 Ring Syntheses by Transformation of Another Bicyclic System 904
10.17.10.1 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines 904
10.17.11 Synthesis of Particular Classes of Compounds and Comparison of Routes Available 905
10.17.12 Important Compounds and Applications 905
10.17.13 Further Developments 905
References 907

10.17.1 Introduction

This chapter describes 6,6-fused heterocyclic systems, general structures **1–8**, with no heteroatoms occupying a bridgehead position. Both aromatic and nonaromatic derivatives will be discussed, with the emphasis on those structures which contain only N, O, and S as the heteroatoms. The chapter concentrates on work published since 1995 but any key references prior to this, including those from CHEC-II(1996) <1996CHEC-II(7)625>, are included.



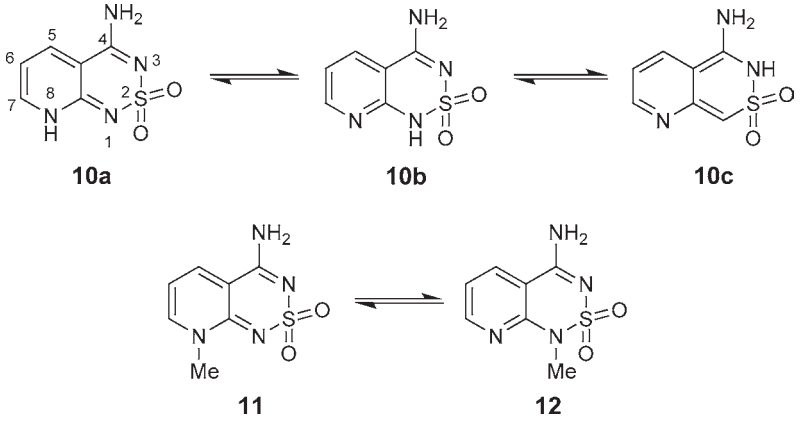
A very well-studied compound which falls within the remit of this chapter is the natural product, artemisinin **9a**, the traditional Chinese medicine known as qinghaosu. In this chapter, as in the CHEC-II(1996) chapter <1996CHEC-II(7)625>, we will not attempt to provide a full account of artemisinin research, but the main features of its unique, 3*H*,6*H*-pyrano[2,3-*e*]-1,2,4-trioxine, ring system will be summarized.



9a: X = O
9b: X = NH

10.17.2 Theoretical Methods

The tautomerism of 4-aminopyrido[2,3-*c*]-1,2,6-thiadiazine-2,2-dioxide, an acid with a pK_a of 5.85, has been investigated by Páez *et al.* (**Scheme 1**). The 8*H*-tautomer **10a** is characterized by an ultraviolet (UV) maximum at 365 nm and the 1*H*-tautomer **10b** by a band at 320 nm, thus allowing the determination of the tautomeric equilibrium by UV spectroscopy. This conclusion that the aminopyridothiadiazinedioxide **10** exists as the 8*H*-tautomer in aqueous and dimethyl sulfoxide (DMSO) solutions was based upon a comparison with the UV spectra of the 8-methyl derivative **11** (λ_{max} 365 nm) and the 1-methyl derivative **12** (λ_{max} 322 nm) <2004JST83>.



Scheme 1

These workers also calculated the relative stability of the tautomers **10a–c** in the gas phase by *ab initio* and density functional theory (DFT) methods and in solution using several continuum solvation models such as self-consistent reaction fields (SCRF) and the Poisson–Boltzmann method. These results showed good agreement between the experimental and theoretical approaches.

In order to understand the relationship between the physicochemical properties and the antimalarial activities of artemisinin analogs, molecular docking simulations were performed to probe the interactions of these analogs with hemin. In the most stable docked configuration, the endoperoxide bridge is in close proximity to the hemin iron <1995MI215>. Three-dimensional quantitative structure–activity relationship (3D-QSAR) studies on the basis of the docking models, employing comparative molecular force field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA), were also described <2002BMC2883>. CoMFA and hologram QSAR (HQSAR) were utilized, starting from a series of 211 artemisinin analogs with known *in vitro* antimalarial activity <2002JME292>.

Artemisinin **9a** has been studied at the *ab initio* self-consistent field (SCF), Hartree–Fock (HF), and DFT levels with 6-31G* basis sets <1999JST103>. The geometries of artemisinin and the radical anions and neutral species generated by rearrangement, after reduction of the peroxide bond, were fully optimized with the AM1 and PM3 semi-empirical methods, in order to characterize the intermediates formed during this process <2002JST207, 2003MI180>. The electrostatic potential of artemisinin **9a** was also calculated by the PM3 method <2001JST267>.

Ab initio calculations using DFT have shown that the reactions which occur between artemisinin and some metal ions and complexes lead to a series of radicals which are probably responsible for its therapeutic activity. In particular, it has been shown that the interaction of Fe(II) with artemisinin **9a** causes the O–O bond to be broken, as do Fe(III) and Cu(I), but not Zn(II) <2004JST95>. DFT calculations have been carried out on the interactions of artemisinin and several other endoperoxides with the hexaaquaferrous ion $[Fe(H_2O)_6]^{2+}$ and heme <2005JST87>.

In another DFT study, the reductive decomposition of artemisinin **9a** was investigated by the DFT B3LYP method, together with the 6-31G(d) and 6-31+G(d,p) basis sets <2006BMC1546>.

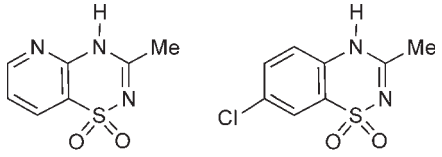
Calculations on the singlet and triplet states of artemisinin were carried out, using several levels of theory, in order to study its singlet–triplet excitations. It was concluded that HF theory is not sufficient to estimate the adiabatic transition of this endoperoxide and that correlated calculations are required <1998JST87>.

The calculated nuclear quadrupole coupling constants (NQCCs) of ^{17}O in artemisinin **9a** and some of its derivatives and the effects of charge density due to the nature of ligands on the NQCC of ^{17}O were described. All calculations were performed at the HF/3-21G level <2005MI366>.

10.17.3 Experimental Structural and Spectroscopic Methods

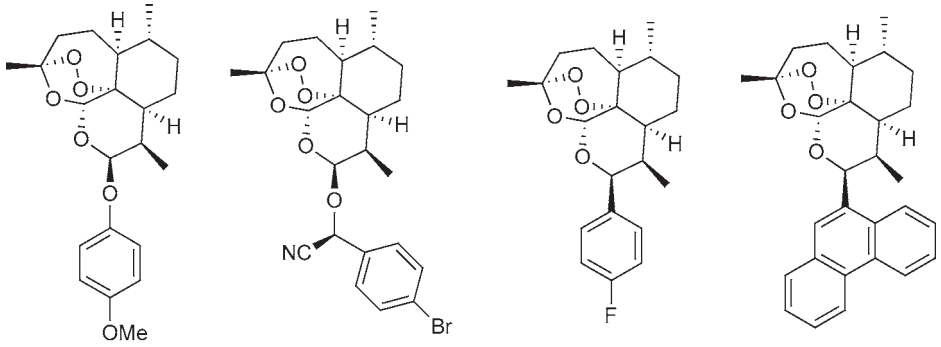
10.17.3.1 X-Ray Diffraction

The single crystal X-ray structure of 3-methyl-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1,-dioxide **13** was compared to that of diazoxide **14** in order to determine the predominant tautomeric form and it was found that both these thiadiazine-dioxides exist in the 4*H* tautomeric form in the solid state <1995AXC2064>.

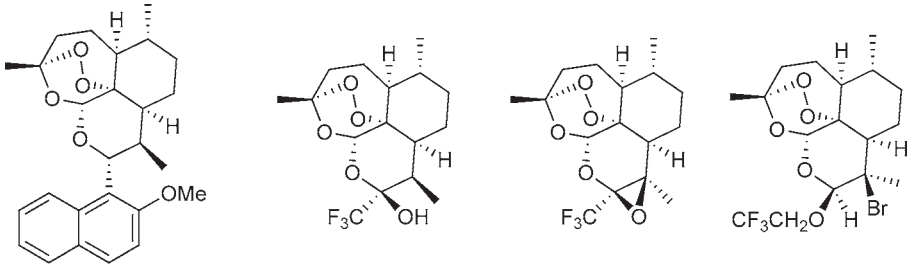


13 **14**

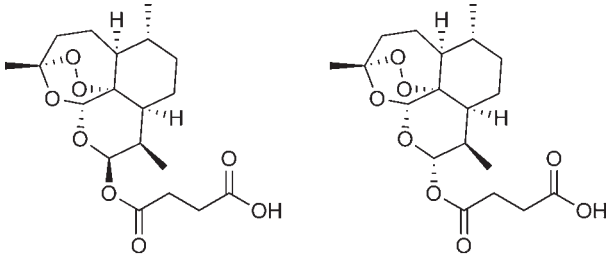
X-Ray crystallographic studies have confirmed the discovery of a new polymorphic artemisinin crystal, belonging to the triclinic space group, *P*1 <1997P1209>. The structures of the following artemisinin analogs have also been determined using X-ray crystallography: **15** <1999TL9129>, **16** <2001BML5>, **17–19** <2003EJO2098>, **20–22** <2002JOC1253>, **23** and **24** <2002EJO113>, **25** <2006AXE1898>, and **26** <2006AXC281>.



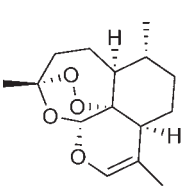
15 **16** **17** **18**



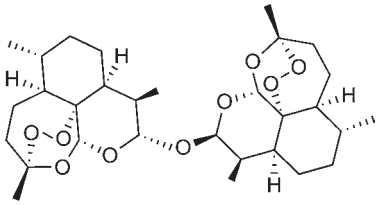
19 **20** **21** **22**



23 **24**



25

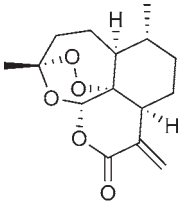


26

10.17.3.2 Molecular Spectra

10.17.3.2.1 NMR spectroscopy

Full nuclear magnetic resonance (NMR) assignments for artemisitene **27** were reported for the first time <2001J(P1)2421> and the NMR characterization of covalent adducts obtained by the alkylation of heme with artemisinin **9a** and its derivatives has been described <2002ICA488, 2005AGE2060>.



27

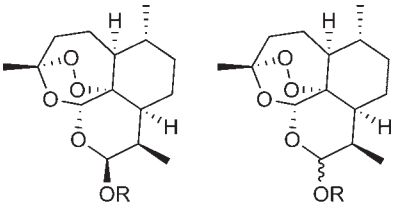
The NMR analysis of N-substituted 11-azaartemisinin analogs **9b** was enhanced by additional data acquired by preparing the ^{15}N-labeled 11-azaartemisinin from artemisinin and $^{15}NH_3$ <1995JME5045>, which showed ^{1}J C–N coupling to C-12 and C-10 and a long range (^{3}J) coupling to C-9.

10.17.3.2.2 Mass spectrometry

A new analytical method for high-sensitivity, direct detection, quantitation, and isotopomer analysis of artemisinin has been described using high-performance liquid chromatography (HPLC)-electrospray ionization mass spectrometry (MS), without pre- or post-column derivatization. This method has been shown to be particularly suitable for the analysis of artemisinin in biosynthetic stable isotope labeling experiments and for the quantitative analysis, in the nanogram range, of crude biological samples <1998ANC3084>. A previously established HPLC system with post-column derivatization for the analysis of artemisinin **9a** was coupled to an ADS (alkyl diol silica) pre-column, allowing direct and repetitive injection of protein-rich fluids such as plasma <2000JCH(B)155>.

An LC-MS pre-column method with selected ion monitoring (SIM) was recently developed and validated for the analysis and standardization of artemisinin **9a** in *Artemisia annua* L. <2005MI7010>, and the densitometric thin layer chromatographic determination of artemisinin **9a** and artemether **28a** and arteether **28b** has also been described <2003MI359>.

A new gas chromatography (GC) method was developed to characterize artemether **28a** and its metabolites in body fluids. The extracts were derivatized and then separated on an optimized capillary GC system and identified by chemical ionization MS using ammonia as the reagent gas <1998JCH(B)101>. A sensitive, selective, and reproducible GC–MS–SIM method has also been developed for the determination of artemether **28a** and dihydroartemisinin **29a** in plasma, using artemisinin **9a** as an internal standard <1999JCH(B)251>.



28a: R = Me
28b: R = Et

29a: R = H
29b: R = Ac
29c: R = Bz

10.17.3.2.3 IR spectroscopy

3-Aminomethylpyrido[4,3-*e*]thiadiazine-1,1-dioxide **30** has been shown to exist as an equilibrium between the uncharged **30a** and zwitterionic **30b** forms by IR spectroscopy (Equation 1), with N^+–H stretches present between 3000 and 2400 cm^{-1} <1997BSB781>. An equilibrium between the uncharged and zwitterionic forms is also seen for the 3-imidazol-1-yl analogs <1998T4935>.

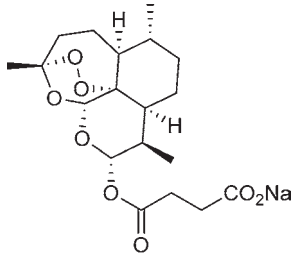


30a **30b** (1)

Fourier transform infrared spectroscopy has been used to monitor the Fe(III)-and Fe(II)-mediated activation of artemisinin **9a** <2001JME3150>. Circular dichroism studies on artemisinin **9a** and epiartemisinin and their *β*-cyclodextrin complexes have been reported <2004HCA2368>.

10.17.3.2.4 Other analytical methods

An HPLC method using electrochemical detection in the reductive mode for the determination of artemether **28a** and its metabolite dihydroartemisinin **29a** <1997JCH(B)145> and for the simultaneous quantification of artesunate **31** and dihydroartemisinin **29a** in plasma has been developed <1997JCH(B)259, 1998JCH(B)201>. An effective reversed-phase HPLC method using electrochemical and UV detection has been developed for the simultaneous determination in plant extracts of artemisinin and its bioprecursors such as arteannuin B **32a**, and artemisitene **27** <1995JNP798, 2001JIC489>.



31

Artemisinin **9a** has been extracted from *Artemisia annua* L. by supercritical fluid extraction and analyzed by supercritical fluid chromatography (SFC) using a capillary column coupled with a flame ionization detector <1997JCH(A)353>. The SFC method has also been used for the determination of artemisinin in whole blood <1995JCH(B)183>.

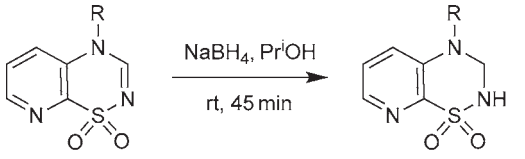
10.17.4 Thermodynamic Aspects and Aromaticity

There has been no work published in this area since CHEC-II(1996) <1996CHEC-II(7)625>.

10.17.5 Reactivity of Fully Conjugated Ring Systems

10.17.5.1 2*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazines

Reduction of the 1,2,4-thiadiazine 1,1-dioxides **32** with sodium borohydride in isopropanol gives the dihydro derivatives **33** (Equation 2) <1998JME2946>.



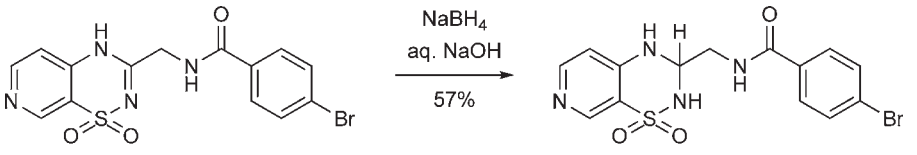
(2)

32

33a: R = Me (90%)
33b: R = Et (87%)
33c: R = Pr^i (50%)

10.17.5.2 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

The reduction of 3-(4-bromobenzamidoaminomethyl)-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **34** with sodium borohydride in aqueous sodium hydroxide gave the 2,3-dihydro derivative **35** (Equation 3) <1997BSB781>.



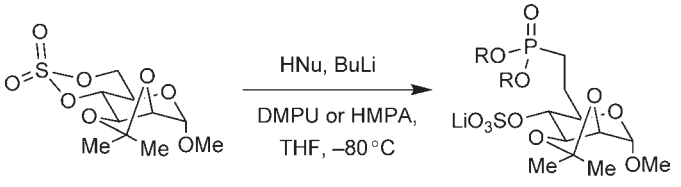
(3)

34 **35**

10.17.6 Reactivity of Nonconjugated Ring Systems

10.17.6.1 Pyrano[3,2-*d*]-1,3,2-dioxathiins

Dialkyl methyl phosphonate derivatives **37a–c** of mannopyranosides may be prepared from cyclic sulfate **36** by reaction with the appropriate lithiated methylphosphonate, prepared by titration of the corresponding methylphosphonate with butyllithium in the presence of 1,1-diphenylethylene as indicator (Equation 4) <2002TL4017>.



(4)

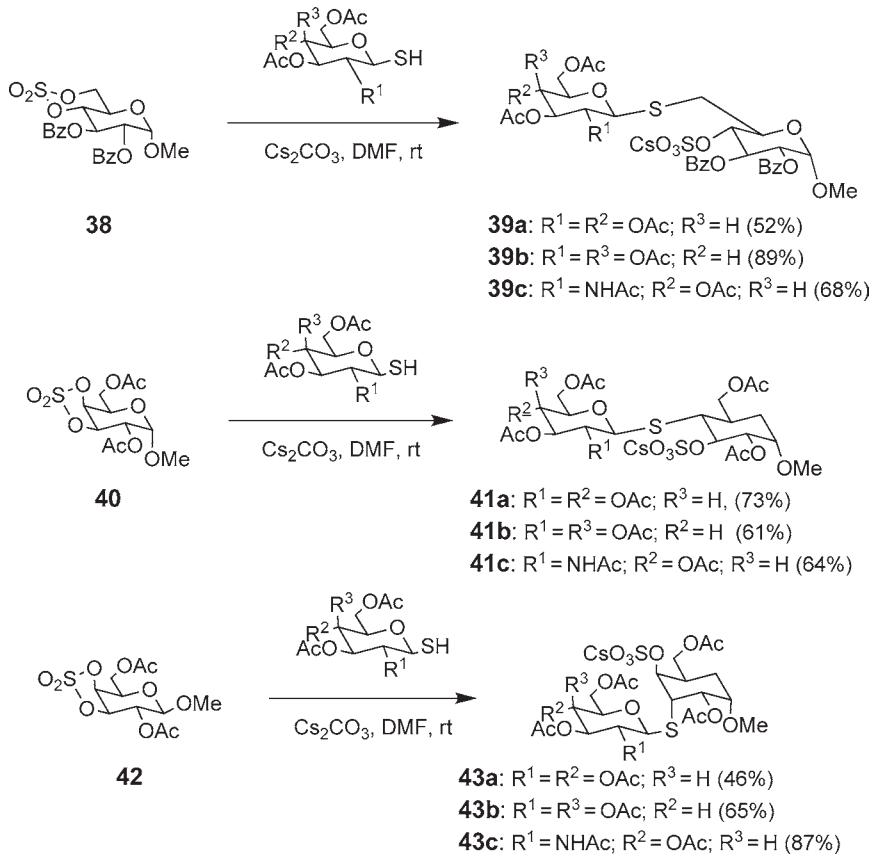
36

37a: R = Pr^i (~50%)
37b: R = Et (~10%)
37c: R = Me (~10%)

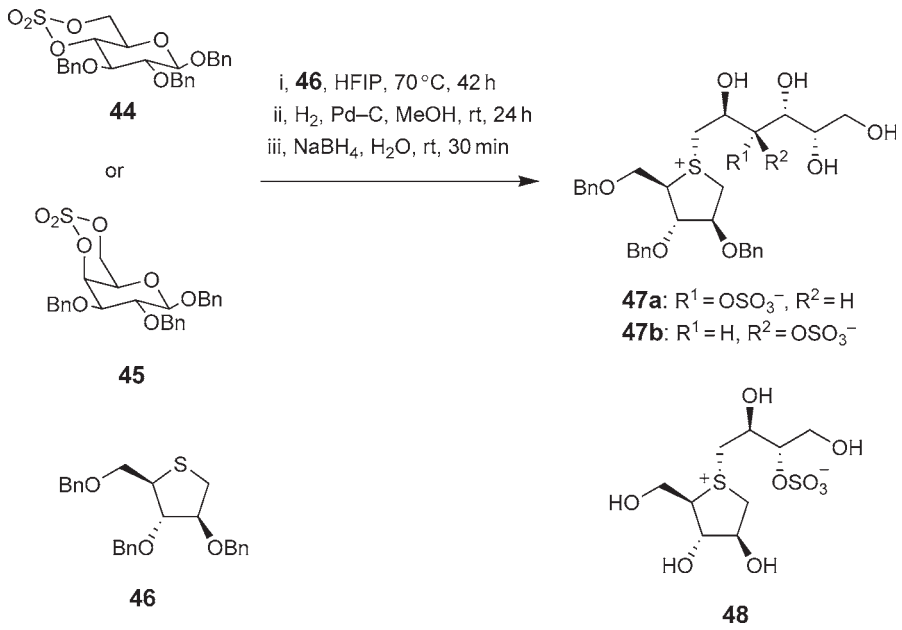
The cyclic sulfate monosaccharides **38**, **40**, and **42** may be used as intermediates to achieve the corresponding thio-linked disaccharides **39**, **41**, and **43** (**Scheme 2**) <1997JP11079>.

Reaction of benzyl α-D-glucopyranosyl cyclic sulfate **44** or benzyl α-D-galactopyranosyl cyclic sulfate **45** with 1,4-anhydro-2,3,5-tri-*O*-benzyl-4-thio-D-arabinol **46**, followed by debenzylation and reduction, gave novel sulfonium sulfate derivatives **47a** and **47b**, respectively, which were used to prepare homologs of salacinol **48**, a natural human maltase glucoamylase inhibitor, as lead candidates for the treatment of type 2 diabetes (**Scheme 3**) <2006JOC1111>.

A study was conducted into the regioselectivity of the reactions of cyclic sulfate galactopyranoside **49**. Under aqueous tetrahydrofuran (THF) conditions and using the hard nucleophile, hydroxide anion, consistently low regioselectivity was

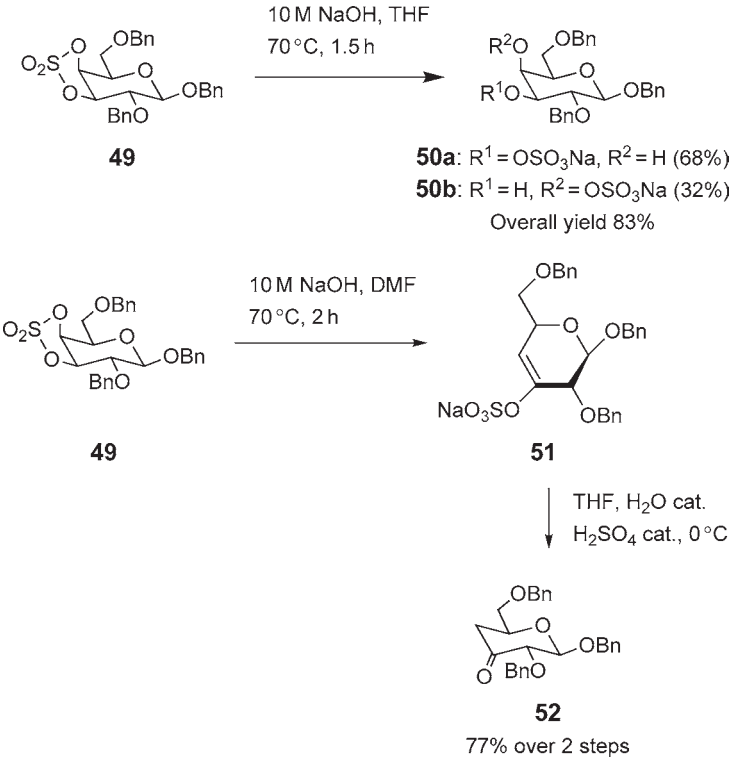


Scheme 2



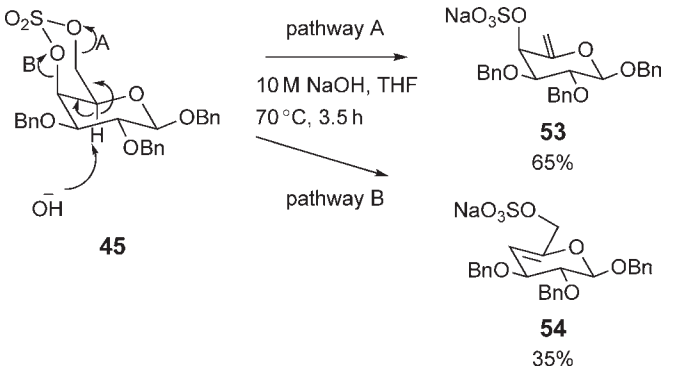
Scheme 3

achieved with **49**; the ratio of products **50a** and **50b** was in the range 65–70:30–35 in favor of attack at C-4, as indicated by ^{13}C NMR spectroscopy. Hydrolysis of **51** with aqueous sodium hydroxide in dimethylformamide (DMF) gave only a trace of **50** (5%), leading instead to the unsaturated sulfate **51**, via deprotonation at C-3, which was hydrolyzed to the corresponding ketone **52** in good yield over the two steps (**Scheme 4**) <2000MI311>.



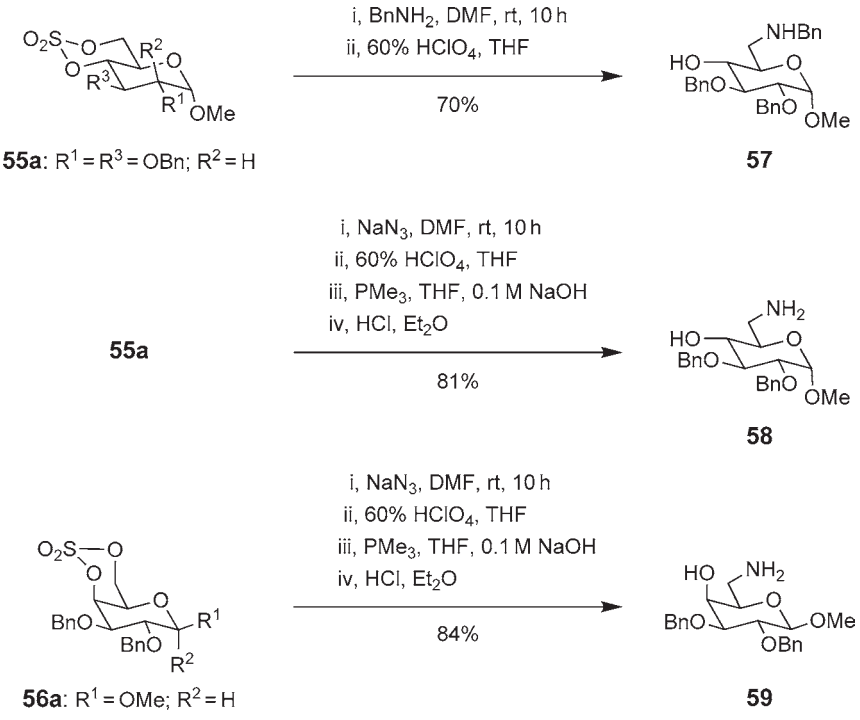
Scheme 4

Surprisingly, monohydrolysis of **45** with 10 M sodium hydroxide in either aqueous THF or DMF gave none of the expected monosulfates, but instead gave a mixture of the exocyclic and endocyclic elimination products **53** and **54**, both products arising through deprotonation at C-5, in a ratio of 65:35 and overall yield of 93% (**Scheme 5**) <2000MI311>.



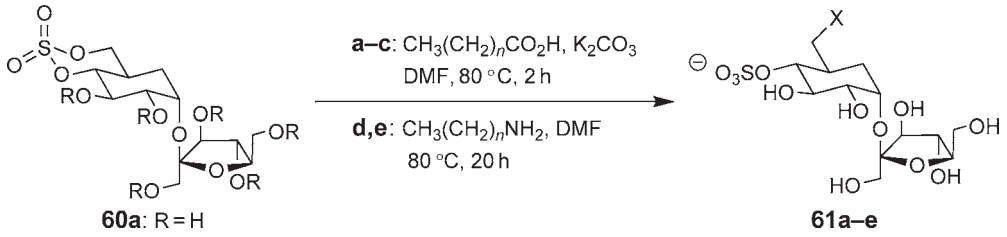
Scheme 5

Both **55a** and **56a** have been used in the synthesis of 1,3-hydroxyamines **57**, **58**, and **59** as molecular recognition motifs (**Scheme 6**) <1997AGE95>.



Scheme 6

Regioselective nucleophilic attack on the cyclic sulfate **60a** by O-nucleophiles gave anionic sucrose-based surfactants **61a–c** in good yield, while attack by N-nucleophiles afforded amphoteric sucrose-based surfactants **61d** and **61e** in reasonable yield (Equation (5); **Table 1**) <1998CAR189>.

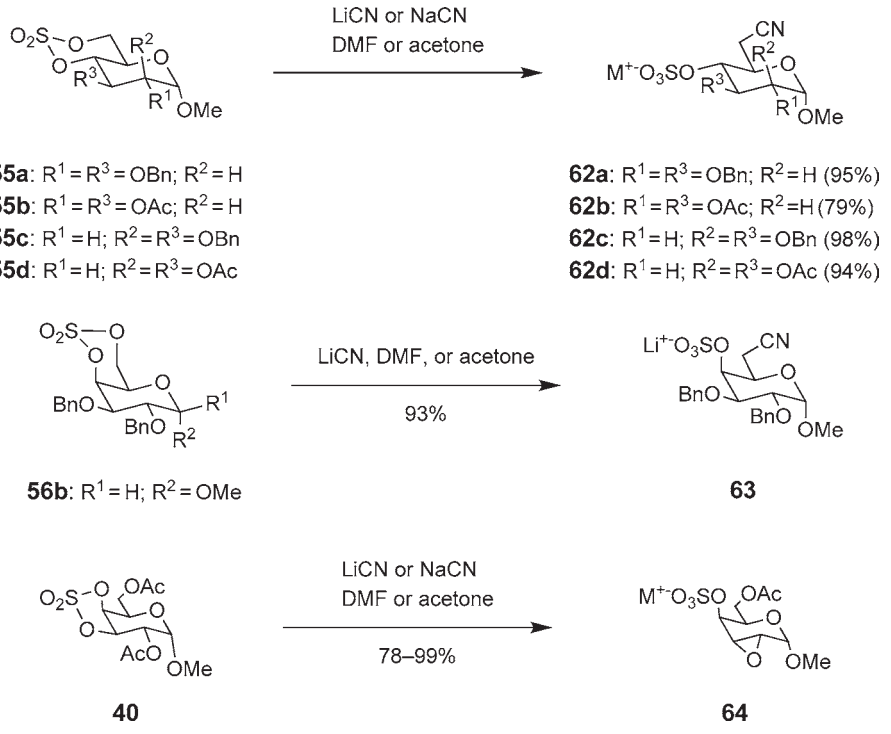


(5)

Table 1 Preparation of sucrose-based surfactants **61a–e** from pyrano[3,2-*d*]-1,3,2-dioxathiin 1,1-dioxide **60a** <1998CAR189>

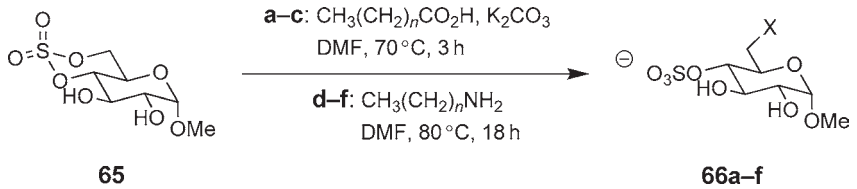
Product **61**	*Nucleophile*	*X*	*Yield (%)*
a	$CH_3(CH_2)_{14}CO_2H$	$-OCO(CH_2)_{14}CH_3$	75
b	$CH_3(CH_2)_{16}CO_2H$	$-OCO(CH_2)_{16}CH_3$	72
c	$CH_3(CH_2)_{18}CO_2H$	$-OCO(CH_2)_{18}CH_3$	60
d	$CH_3(CH_2)_{15}NH_2$	$-NH_2^+(CH_2)_{15}CH_3$	76
e	$CH_3(CH_2)_{17}NH_2$	$-NH_2^+(CH_2)_{17}CH_3$	60

The reaction of lithium or sodium cyanide with mannopyranoside and glucopyranoside 4,6-cyclic sulfates **55a–d** and the galactopyranoside 4,6-cyclic sulfate **56b** was found to be high yielding and consistently gave the corresponding 6-cyano-4-sulfate products **62a–d** and **63**, respectively, while the less reactive 3,4-cyclic sulfate **40** gave the 2,3-anhydro derivative **64** (**Scheme 7**) <1998S1778>.



Scheme 7

Similar surfactants based upon glucopyranose were synthesized via the reaction of cyclic sulfate **65** with fatty acids or long-chain aliphatic amines, which proceeds regioselectively at the least hindered cyclic sulfate carbon, to give a range of methyl sulfoglucopyranosyl surfactants **66a–f** (Equation 6, **Table 2**) <1999S621>.

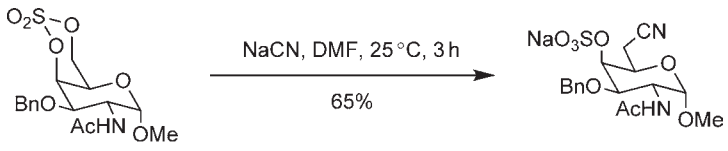


(6)

Table 2 Preparation of glucopyranose-based surfactants **66a–f** from pyrano[3,2-*c*]-1,2,6-thiadioxane 1,1-dioxide **65** <1999S621>

Product **68**	*Nucleophile*	*X*	*Yield (%)*
a	$CH_3(CH_2)_{10}CO_2H$	$-OCO(CH_2)_{10}CH_3$	85
b	$CH_3(CH_2)_{12}CO_2H$	$-OCO(CH_2)_{12}CH_3$	91
c	$CH_3(CH_2)_{14}CO_2H$	$-OCO(CH_2)_{14}CH_3$	87
d	$CH_3(CH_2)_5NH_2$	$-NH_2^+(CH_2)_5CH_3$	53
e	$CH_3(CH_2)_9NH_2$	$-NH_2^+(CH_2)_9CH_3$	51
f	$CH_3(CH_2)_{13}NH_2$	$-NH_2^+(CH_2)_{13}CH_3$	54

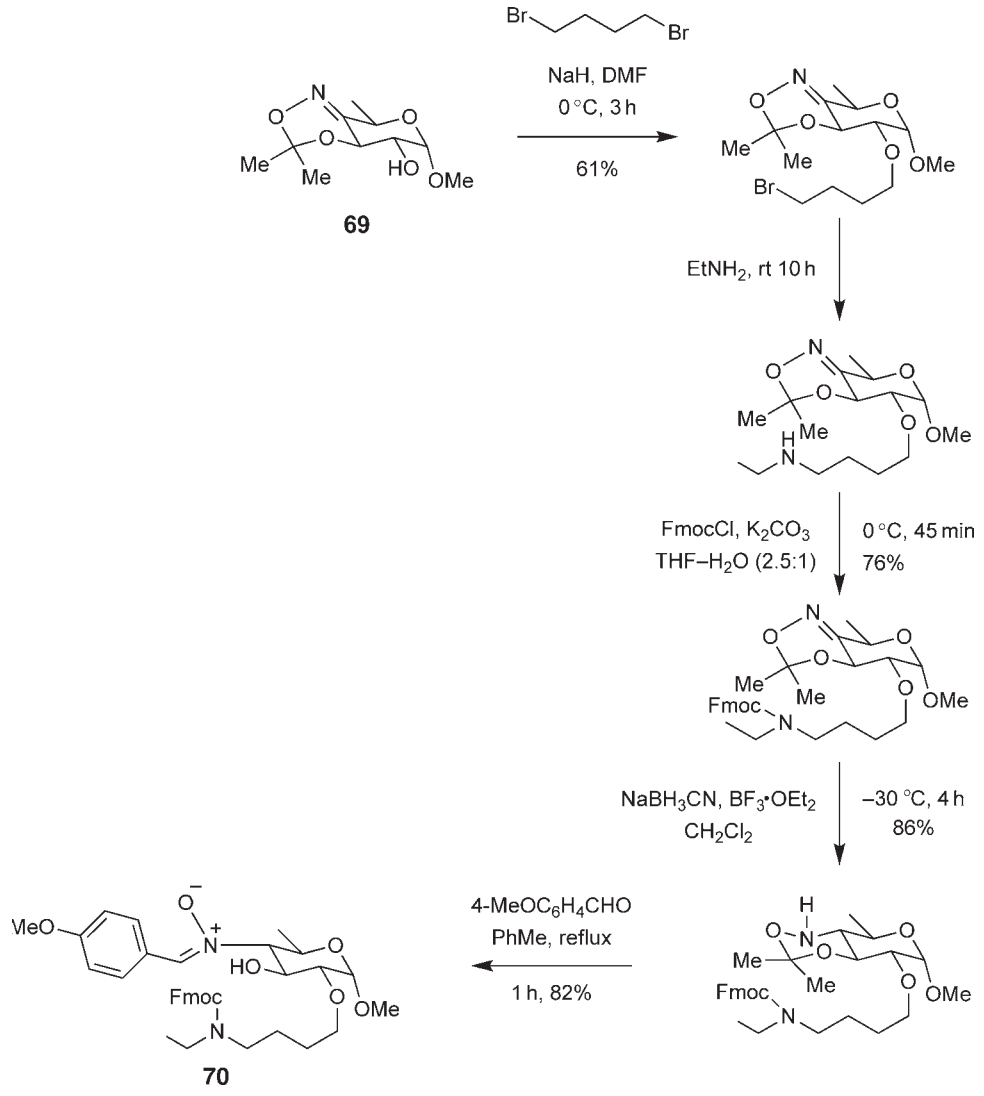
Regioselective ring opening of **67** at C-6 with sodium cyanide was achieved in high yield to furnish the cyanosulfate **68** <2003AGE5209>, which provides a high-yielding route to one-carbon extended carbohydrate derivatives (Equation 7).



67 68 (7)

10.17.6.2 1*H*,6*H*-Pyrano[3,4-*c*]-1,5,2-dioxazines

In the synthesis of analogues of calicheamicin γ_1^I and esperamicin A_{1B}, Moutel and Prandi employed the glycosylation of a nitrone with a trichloroacetimidate as a key step – β-N–O glycosidic bond formation. Preparation of the nitrone begins with the alkylation of the known alcohol **69** <1992CC1494> with 1,4-dibromobutane in the presence of sodium hydride. Subsequent aminoalkylation, amine protection with 9-fluorenylmethoxycarbonyl (Fmoc), and reduction with $NaBH_3CN$ were followed by nitrone **70** formation with 4-methoxybenzaldehyde (**Scheme 8**) <2001J(P1)305>.



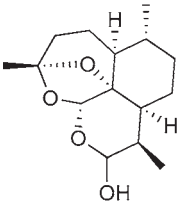
69 70

Scheme 8

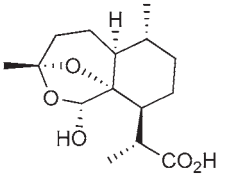
10.17.6.3 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines

As *Plasmodium falciparum* is rich in hemin, hemozoin, and free iron, the Fe-stimulated rearrangement of artemisinin **9a** and its analogs has been widely studied in the hope of defining a mechanistic feature which could be exploited in analog design <1995JA5885, 1996JME1885, 1997JA5968, 1998J(P1)2163, 2000CC2193, 2001CPB1541, 2001HCA928, 2003HCA3074, 2004AGE1381>. In some cases, the preparation of covalent adducts between **9a** and heme models has been described <2002ICA488, 1997JA5968, 2002CC414, 2003BML1059, 2005AGE2060>.

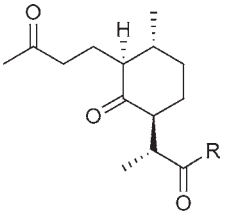
With hemin in MeCN–H_2O at pH 7.8, artemisinin **9a** was converted into acid **72** in 23% yield. Dihydroartemisinin **29a** reacted in a different way giving a 1:1 mixture of the 3-deoxo-derivative **71** and the diketoaldehyde **73a** <1996TL253>.



71

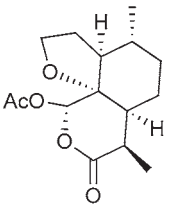


72

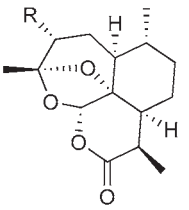


73a: R = H
73b: R = OH
73c: R = OMe

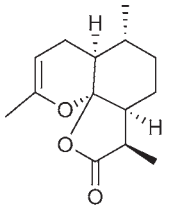
Under non-aqueous conditions, artemisinin **9a** reacted with tetraphenylporphine iron(III) chloride and *N*-acetylcysteine to give the tetrahydrofuran (THF) **74** in 74% yield together with arteannuin D **75a** (2%) <1996TL253>. The same transformation was observed with hemin/benzenethiol in THF <1995JA5885>. Whereas artemisinin **9a** reacts slowly in the presence of hemin[Fe(III)], the $FeCl_3$-induced reaction proceeds much more rapidly. By changing the solvent polarity and the amount of catalyst used, it is possible to selectively enhance formation of THF **74**, arteannuin D **75a** or the diketo acid **73b** and enol lactone **76** <1996TL257>, all of which have already been characterized as products of the thermal decomposition of **9a** <1985JOC4504>. The reduction of artemisinin **9a** by ferrous sulfate in aqueous acetonitrile gave, in 1% yield, the unstable epoxide **77**, a compound which was previously postulated as the species responsible for the antimalarial activity. The main products were the previously known compounds **74** (25%) and **75a** (67%) <1996CC2213, 1998JA3316>. Similar degradation was observed for the carba analog in $FeSO_4$/MeCN/H_2O <2001J(P1)605>.



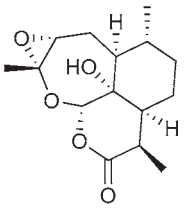
74



75a: R = OH
75b: R = H

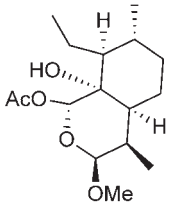


76

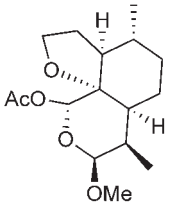


77

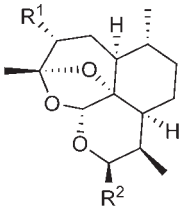
Reaction of artemether **28a** and a catalytic amount of ferrous ion in the presence of excess cysteine gave three rearrangement products, **78** (10%), **79** (26%), and **80a** (44%), and two water-soluble adducts, **81** (1.4%) and **82** (3.2%), of the amino acid <2003BML1645>.



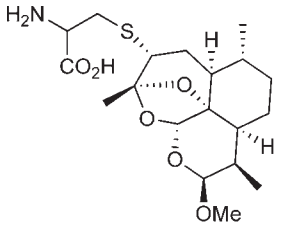
78



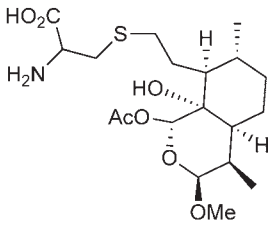
79



80a: R^1 = OH; R^2 = Me
80b: R^1 = R^2 = H



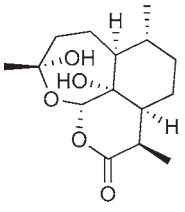
81



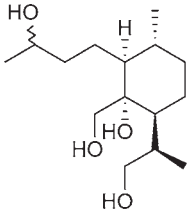
82

Hydrogenation of artemisinin **9a** in the presence of palladium on carbon or calcium carbonate gives deoxyartemisinin **75b**, an inactive compound containing one fewer oxygen atoms <1997JNP325>. This reduction is proposed to proceed via a dihydroxy intermediate **83**, which may be obtained immediately after work-up and then cyclized to compound **76b** on standing. Reduction of **9a** <1979MI129, 2001BML5> and its analogs <2002TL7837, 2002BMC227> with zinc–acetic acid also gives this type of compound. Dihydroartemisinin **29a** reacted similarly, by hydrogenation in the presence of palladium on calcium carbonate, to give deoxydihydroartemisinin **80b** <2002JNP184>.

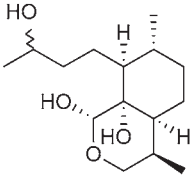
The $LiAlH_4$ reduction of artemisinin **9a** has been reported to result in complete reduction to compound **84** and partial reduction to the cyclic hemiacetal **85**, along with two rearrangement products **86a** and **86b** <1986MI153, 1997T7493>.



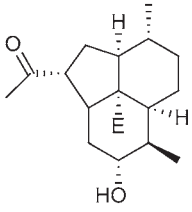
83



84



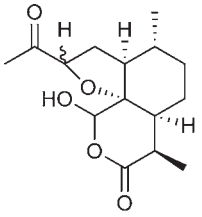
85



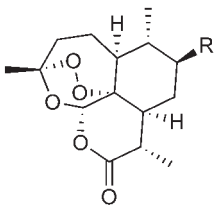
86a: E = OOH
86b: E = OH

The electrochemical reduction of **9a** gave **29a** in only 5% yield, beside the recovered **9a**; however, artemisitene **27** was rapidly degraded in the presence of EDTA-Fe^{3+} to give predominantly compounds **74**, **75a**, and **87**, the same products as those obtained from the chemical reaction of **9a** with ascorbic acid and $FeCl_3$ or $CuSO_4$ systems <2000JP14279>.

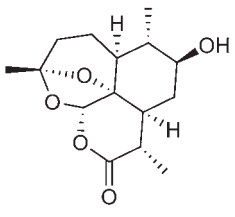
Studies on the microbial transformation of artemisitene **27** by *Aspergillus niger* yielded 11-*epi*-artemisinin **88a**, 9β-hydroxydeoxy-11-*epi*-artemisinin **89**, and 9β-hydroxy-11-*epi*-artemisinin **88b**. These metabolites were characterized on the basis of their spectral data <1999P257>. When artemisinin **9a** was transformed by *Mucor polymorphosporus* or *A. niger*, five products were identified as 9β-hydroxyartemisinin **90**, 3β-hydroxyartemisinin **91**, deoxyartemisinin **75b**, 3β-hydroxydeoxyartemisinin **75a**, and 1α-hydroxydeoxyartemisinin **92** <2002JNP1693>.



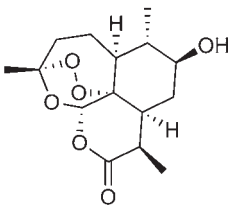
87



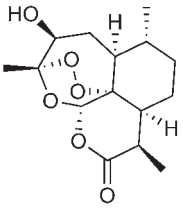
88a: R = H
88b: R = OH



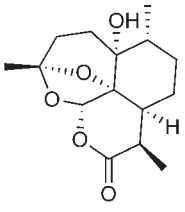
89



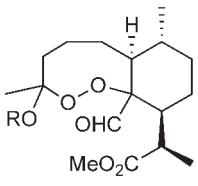
90



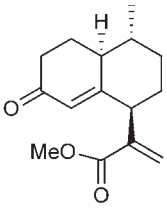
91



92



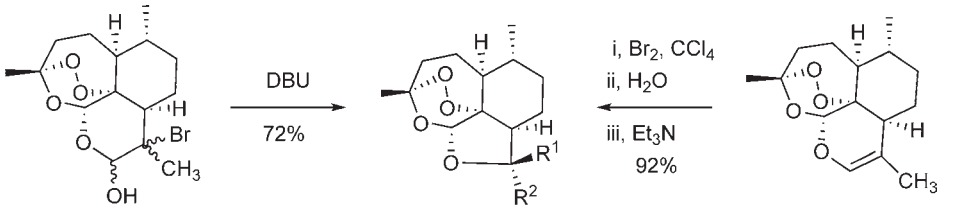
93a: R = H
93b: R = Me



94

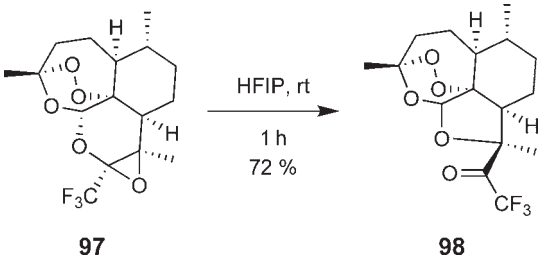
The acid degradation of artemisinin **9a** has also been studied in detail. In an ice-cooled methanolic solution of H_2SO_4, endoperoxide **93a** was obtained in 50% yield. The use of these strongly acidic conditions at room temperature gives the diketoester **9a** in 70–75% yield. Short reaction times prevent the epimerization at the C-1 and C-7 <1997J(P1)3435, 2001T8481>. The acid degradations of artemisetene **27** can also give a wide variety of products, but conditions which result in decalenone methyl ester **94** in 70% yield have been reported <2001J(P1)2421>.

The bromoacetal **95** undergoes ring contraction to the relatively unstable aldehyde **96a** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or triethyamine (**Scheme 9**) <1995JME1922>. This aldehyde **96a** has been obtained in a one-pot process from anhydrodihydroartemisinin **25** in excellent yield. The stereoselectivity of the reaction with iodine is opposite to that with bromine, and allows the preparation of the isomeric aldehyde **96b**, with conservation of the configuration of the starting artemisinin at C-9 <2001TL2125>.



Scheme 9

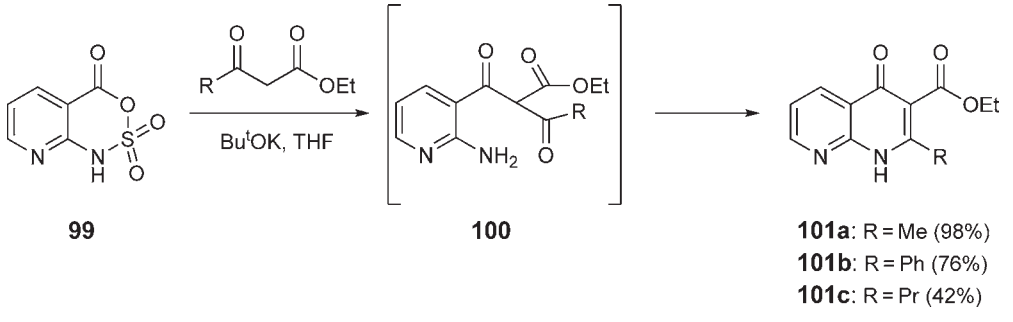
Treatment of the epoxy ether **97** with hexafluoro-2-propanol (HFIP) or trifluoroethanol provided the rearranged trifluoromethyl ketone **98** as a single stereoisomer. NMR data for **98** did not allow the unambiguous determination of the configuration at C-9, which was confirmed by the single crystal X-ray structure (Equation 8) <2002JOC1253>.



(8)

10.17.6.4 Pyrido[3,2-*d*]-1,2,6-oxathiazines

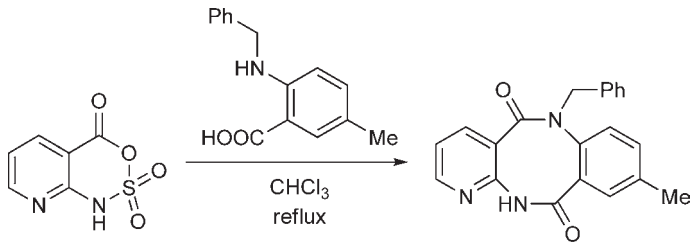
Azathioisatoic anhydride **99** has been employed as an acylating agent in the preparation of 1,8-naphthyridones **101** by Igglessi-Markopoulou and co-workers (**Scheme 10**) <2001JOC4413>. Reaction of the sulfinamide lactone **99** with



Scheme 10

β-ketoesters gives C-acylated diketo intermediates **100**, which subsequently cyclize via the condensation of the 2-amino group with a keto group to give the 1,8-naphthyridin-4-ones **101**.

The same acylating agent **99** reacts with substituted anthranilic acids to give a non-symmetrical dibenzodiazocinedione **102** in an unreported yield (Equation 9) <2004TL1377>.

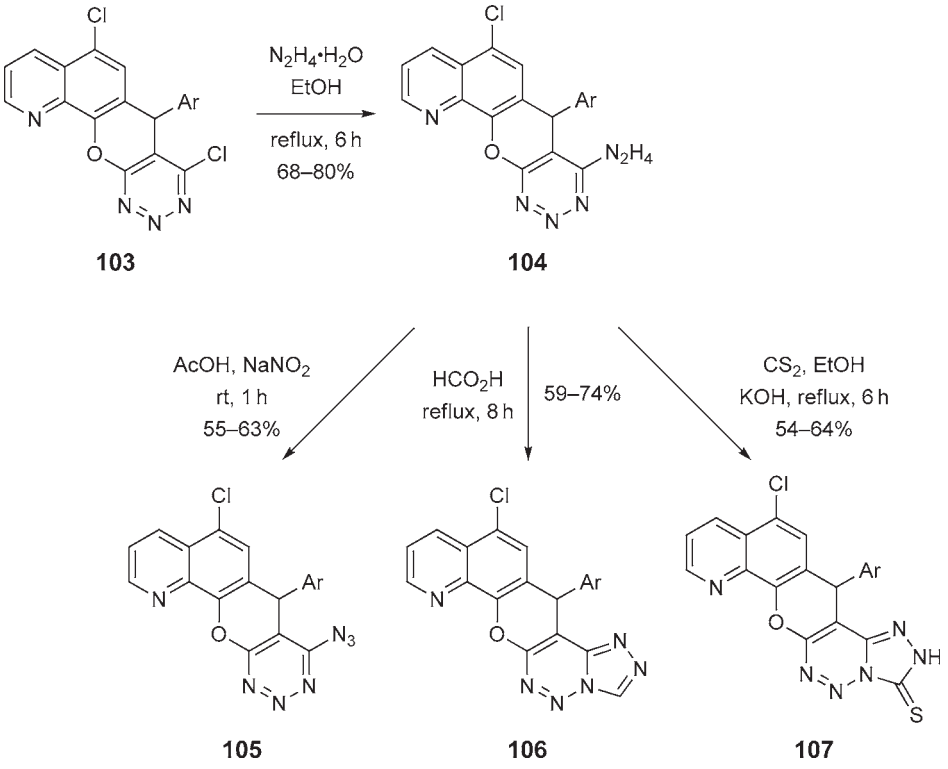


(9)

10.17.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.17.7.1 2*H*-Pyrano[2,3-*d*]-1,2,3-triazines

Nucleophilic substitution of the 4-chloro group of the 4-pyranotriazines **103** with hydrazine gives the 4-hydrazinotriazines **104**, which can be further elaborated to the corresponding azides **105** or cyclized upon reaction with formic acid or carbon disulfide to give the triazolotriazines **106** or thioxotriazolotriazines **107**, respectively (**Scheme 11**) <2005HCO495>.

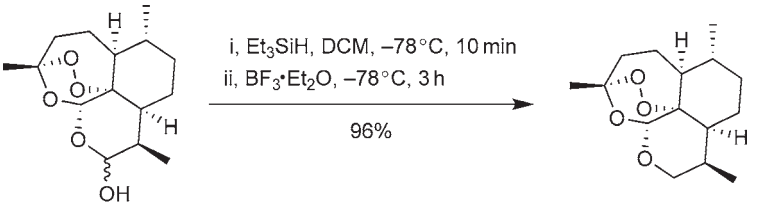


Scheme 11

10.17.7.2 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines

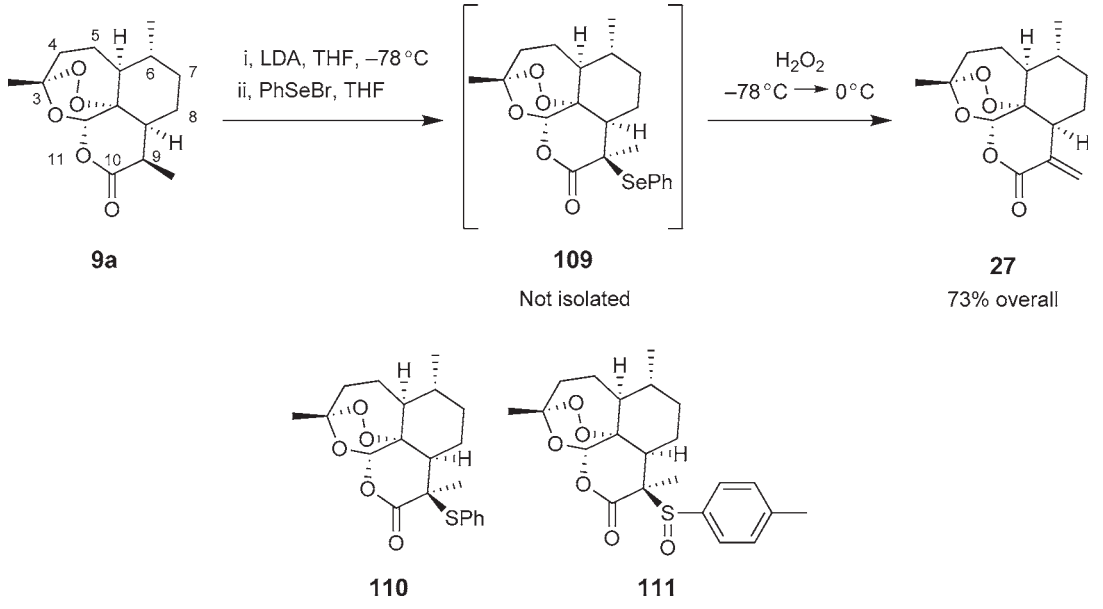
Dihydroartemisinin **29a**, which is easily prepared from artemisinin **9a** in one step, is an important starting material for many artemisinin derivatives. The lactone group of **9a** is most often reduced to the lactol with sodium borohydride in methanol at 0 °C, but other hydride reagents have also been reported <1988JME645, 1995JME764, 1995JME1911, 1996P97, 1999TL8543, 2000BMC2739, 2000JME1635, 2000JME4228, 2002TL7235, 2002JME4321>. The reduction with $NaBH_4$–$BF_3{\cdot}Et_2O$ gives deoxo-derivative **108** <1979MI1, 1989TL5973, 1990JME1516> and this method was applied, with modifications, to obtain C-3 and C-9 modified analogs <1996JME4149>. While artemisinin **9a** could not be reduced directly to 10-deoxoartemisinin **108** with Et_3SiH/BF_3, dihydroartemisinin **29a** was smoothly converted at low temperature into the desired tetrahydropyran **108** (Equation 10) <1996JME4149, 2002JME4321>.

A one-pot preparation of artemether **28a**, arteether **28b**, and related O-alkylated compounds from artemisinin **9a** and the appropriate hydroxy compound, using $NaBH_4$/Amberlyst-15 as reagent, has been described <2002TL7235, 2002IJC2185>.



29a **108** (10)

A straightforward, regiospecific, one-pot conversion of artemisinin **9a** to artemisitene **27** involving selenoxide elimination from the intermediate **109** has been reported yielding **27** as the sole product (**Scheme 12**) <1997JME633>. Later, several selenium-free routes were developed, one of them via **110** in 52% overall yield <2002JME4321, 2003JME4244>, while the synthesis via the sulfinyl derivative **111** gives an 86% yield after recrystallization <2003SC1855>.



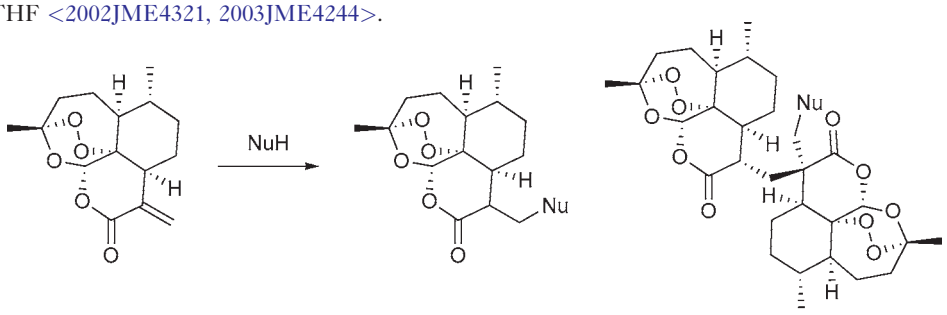
9a **109** Not isolated **27** 73% overall

110 **111**

Scheme 12

The unique structural feature of artemisitene **27**, the exocyclic α,β-unsaturated ketone moiety, presents an opportunity for nucleophilic attack via a 1,4-addition reaction and **27** reacts readily with sulfur, nitrogen, and carbon nucleophiles to give the corresponding Michael adducts **112** (Equation 11; **Table 3**). The reactions of **27** with Grignard reagents as alternative Michael donors also provided reasonable amounts of the C-9 stereoisomers of **112** and a dimer **113**, resulting from further reaction of the enolate intermediate with another molecule of **27** <1997JME633, 2000BML1601, 2001TL2843, 2001JME4688>. Radical-induced Michael addition of artemisitene

has also been reported and the 9α-substituted analogs formed can be converted into the 9β-epimers by refluxing with DBU in THF <2002JME4321, 2003JME4244>.



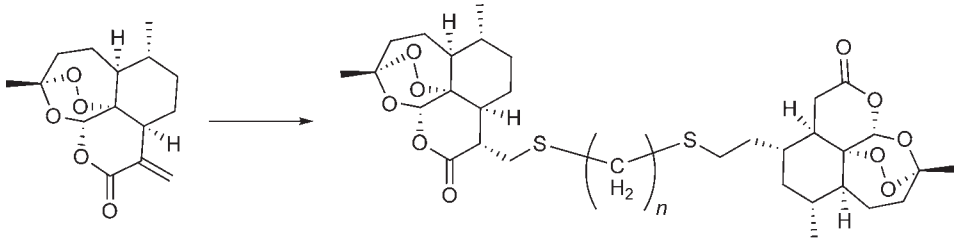
27 **112** **113** (11)

Table 3 Michael adducts **112** of artemisitene **27**

NuH	*Reagent*	*C-9*	*Yield (%)*	*Reference*
PhSH	BuLi	β	72	1997JME633
Imidazole		α:β 1:1	77	1997JME633
CH_2=C(OTMS)Bu^t	$TiCl_4$	α:β 2:1	n.r.[b]	2000BML1601
TMSCN	$TiCl_4$	n.r.	52	2000BML1601
1,2,4-Triazole		α:β 1:1	40	2001TL2843
Benzotriazole		α:β 2:1	60	2001TL2843
Benzimidazole	KF–Al_2O_3	α:β 2:3	64	2001TL2843
$PhCOCH_3$	LDA	α	44	2001JME4688
Me_2CHCO_2Me	LDA	α	82	2001JME4688
2-Acetylpyrrole	LDA	α:β 1.6:1	73	2001JME4688
EtMgBr	CuBr	α:β 3.4:1	79 (+9% **113**)	2001JME4688
BuMgBr	CuBr	α:β 3.7:1	70 (+21% **113**)	2001JME4688
$Ph(CH_2)_3MgBr$	CuBr	α:β 4.4:1	43 (+35% **113**)	2001JME4688
$PhCH_2CH_2Br$	Bu_3SnH, AIBN[a]	α:β 3:2	51	2003JME4244
p-MeS-$C_6H_4CH_2CH_2Br$	Bu_3SnH, AIBN	α:β 2.2:1	55	2003JME4244
p-Me_2N-$C_6H_4CH_2CH_2Br$	Bu_3SnH, AIBN	α:β 1:1	62	2003JME4244
m-F_3C-$C_6H_4CH_2CH_2I$	AIBN	n.r.	58	2002JME4321
m-$ClC_6H_4CH_2CH_2I$	AIBN	n.r.	62	2002JME4321
$TMSO(CH_2)_3MgBr$	CuBr	n.r.	3	2002JME4321
$CF_3(CH_2)_3MgBr$	CuBr	n.r.	52	2002JME4321

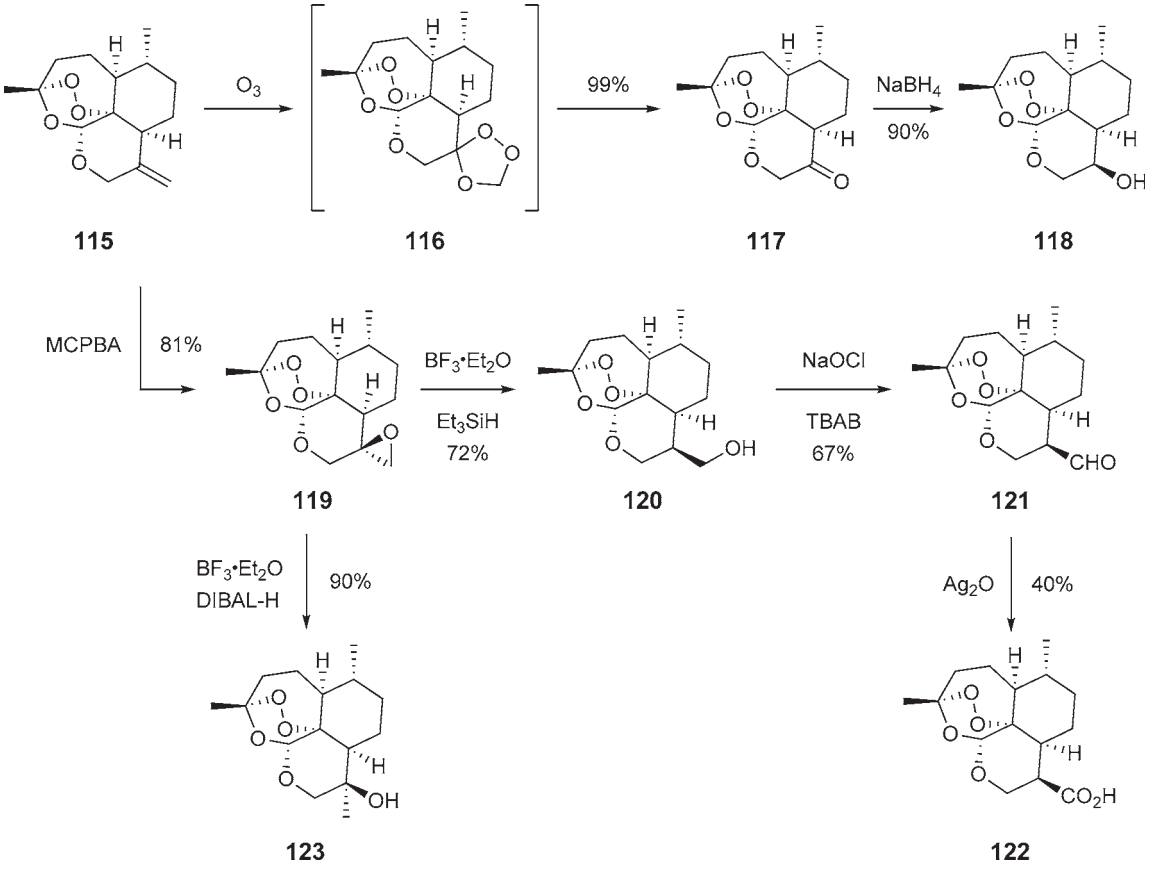
[a]AIBN = azobisisobutyronitrile.
[b]n.r. = not reported.

Related nucleophilic addition reactions between artemisitene **27** and bifunctional nucleophiles have also been investigated. Dimeric artemisinin analogs **114a–d** (Equation 12) with linkers of various lengths were obtained (n = 2, 86%; n = 3, 91%; n = 4, 97%; n = 5, 93%). Reaction of bifunctional Grignard reagents with artemisitene at −78 °C yielded a complex mixture of seven artemisinin derivatives including dimers, trimers, and tetrakis-adducts, which were separated by HPLC and characterized by spectroscopic methods <2001JME4688>.



27 **114** (12)

Deoxoartemisitene **115** is a versatile intermediate for the preparation of a variety of C-11 derivatives of deoxoartemisinin. Ozonolysis of **115** afforded deoxoartemisitone **117** via the self-cleavage of the ozonide ring of **116** without the need for a reducing agent. Reduction of **117** with sodium borohydride led exclusively to alcohol **118**. Epoxidation of alkene **115** with *m*-chloroperbenzoic acid (MCPBA) and $NaHCO_3$ gave the (11*S*)-epoxide **119** and its (*R*)-epimer in a 1.7:1 ratio. Ring-opening of the (11*S*)-epoxide **119** with triethylsilane gave the primary alcohol **120**, and with DIBAL-H gave the tertiary alcohol **123**, both in the presence of $BF_3{\cdot}Et_2O$. Sodium hypochlorite oxidation of alcohol **120** in the presence of tetrabutylammonium bromide led cleanly to the aldehyde **121**. Further oxidation of **121** with silver oxide at room temperature afforded demethyldeoxoartemisininylic acid **122** (**Scheme 13**) <2001TL3997, 2004BML2001>.

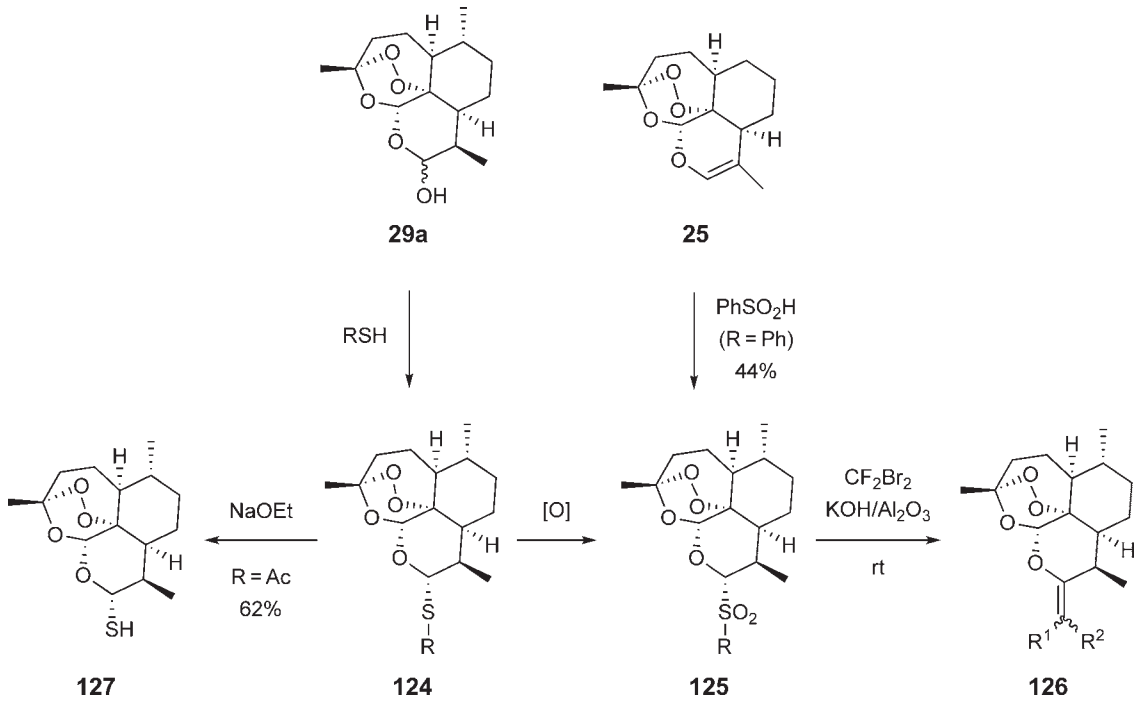


Scheme 13

Various thioethers **124** (e.g., R = Me, Et, *n*-Bu, Bn) of dihydroartemisinin were prepared by treating **29a** with thiols in the presence of $BF_3{\cdot}Et_2O$ (**Scheme 14**; **Table 4**). Unlike the O-acetalization of dihydroartemisinin **29** using various alcohols under the same conditions, the S-acetalization of **29** produced the α-anomers as the major products, which were separated from the minor, C-10β, diastereoisomers <2003BML3665>. The thioethers **124** can be further oxidized to the respective sulfoxides **125** by MCPBA <1995EJM697> or H_2O_2/urea complex <2002TL2891, 2003BML3665>. 10-*exo*-Alkylidene deoxoartemisinin derivatives **126** with anti-angiogenic activity were synthesized from these sulfoxides using a highly efficient, mild, and simple Ramberg–Bäcklund rearrangement (**Table 5**), which produced an (*E*)- and (*Z*)-mixture of products **126** <2004BML3683, 2004JOC984>.

In the reaction of **25** and benzenesulfinic acid, the sulfone **125** was formed directly, as a single diastereomer <2000BMC1361>.

The S-acetal analog **127** was prepared from the base-catalyzed deacetylation of thioether **124** (R = Ac) <2003BML3665, 2004BMC3783, 2004BML3683>.



Scheme 14

Table 4 Synthesis of thioacetals **124** (α-anomers) from dihydroartemisinin **29a**

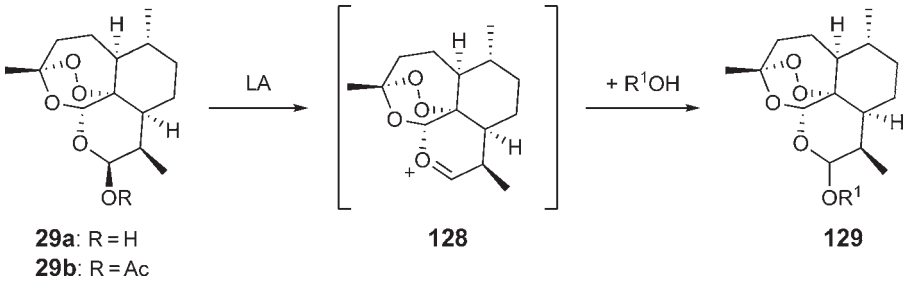
R	*Yield* **124** *(%)*	*Reference*
Me	41 (+32% β)	2004JOC984
Et	86 (+6% β)	2004JOC984
Bu	74 (+10% β)	2004JOC984
Pr^i	80 (+5% β)	2004JOC984
Bn	82 (+8% β)	2004JOC984
Allyl	70 (+11% β)	2004JOC984
Cyclohexyl	62 (+10% β)	1995EJM697
β-Naphthyl	20 (+20% β)	1995EJM697

Table 5 Olefination of **125** by Ramberg–Bäcklund rearrangement <2004JOC984>

R	*Product* **126**	*E/Z ratio*	*Yield (%)*
M	$R^1 = H$; $R^2 = Br$	50:50	74
Et	$R^1 = Me$; $R^2 = Br$	84:16	76
Bu	$R^1 = Pr$; $R^2 = Br$	92:8	84
Pr^i	$R^1 = R^2 = Me$	n/a	26
Bn	$R^1 = H$; $R^2 = Ph$	70:30	78

The Lewis acid-mediated glycoside coupling has been applied to the synthesis of a large number of artemisinin-ether derivatives **129** from **29a**, but does not always give good results, primarily due to the fragile endoperoxide and/or the formation of other side-products. The initial approach used $BF_3{\cdot}Et_2O$ as a catalyst, but in many cases **25** was obtained as a major product. This suggests the involvment of an oxonium ion intermediate **128**, which either reacts with an -OH group or loses a proton to give the by-product **25**. Further studies involving the use of the Mitsunobu

conditions (diethyl azodicarboxylate (DEAD), Ph_3P) gave high stereoselectivity but sometimes low overall yield <2002EJO113>. Later, the use of TMSOTf/$AgClO_4$ catalysis was explored. In every published case, the reaction provided excellent yields with good stereoselectivity in favour of the β-isomers (**Scheme 15**) <2001JME58>. Selected examples from the hundreds of reactions described are collected in **Table 6**.



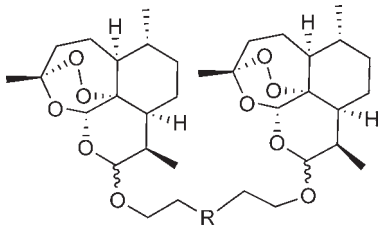
Scheme 15

Table 6 Synthesis of of artemisinin-ether derivatives **129**

129	*R*	R^1	*Lewis acid (LA)*	*Yield (%)*	α:β[a]	*Reference*
a	H	Bn(Pr)CH- (*R*:*S* 1:2.7)	$BF_3{\cdot}Et_2O$	73	β	1995JME764
b	H	CH_3(*p*-$F_3CC_6H_4$)CH- (*R*)	$BF_3{\cdot}Et_2O$	60	β	1995JME764
c	H	EtO_2CCH_2-	$BF_3{\cdot}Et_2O$	n.r.[b]	n.r.	1996P97
d	H	(*p*-$HOCH_2C_6H_4$)CH_2-	$BF_3{\cdot}Et_2O$	78	β	1996JME4511
e	H	HC≡CCH_2-	$BF_3{\cdot}Et_2O$	90	1:4	1996J(P1)1015
f	H	H_2C=CCH_2-	$BF_3{\cdot}Et_2O$	76	1:3.75	1996J(P1)1015
g	H	$HO_2CCH_2CH_2$(*p*-FC_6H_4)CH-	$BF_3{\cdot}Et_2O$	85	β	1997JME1396
h	H	Ph-	TMSOTf/$AgClO_4$	68	1:4	1999TL9129
i	H	$BrCH_2CH_2$-	$BF_3{\cdot}Et_2O$	60	β	2000JME1635
j	H	$BrCH_2CH_2CH_2$-	$BF_3{\cdot}Et_2O$	90	β	1995JME2311
k	H	NC(*p*-BrC_6H_4)CH-	$BF_3{\cdot}Et_2O$	57	β	2001BML5
l	H	NC(*p*-BrC_6H_4)CH-	$BF_3{\cdot}Et_2O$	24	β	2003BMC977
m	H	*p*-$MeOC_6H_4$-	TMSOTf/$AgClO_4$	73	1:4	2001JME58
n	H	*p*-FC_6H_4-	TMSOTf/$AgClO_4$	60	1:3	2001JME58
o	H	*p*-$(HOCH_2)C_6H_4CH_2$-	$BF_3{\cdot}Et_2O$	78	β	2002JME1052
p	H	$H_2NCH_2CH_2$-	$BF_3{\cdot}Et_2O$	14	β	95EJM697
q	H	*p*-$AcC_6H_4CH_2$	$BF_3{\cdot}Et_2O$	68	β	2003BMC4363
r	H	$HOCH_2CH_2$-	$BF_3{\cdot}Et_2O$	13	β	2005JNP1274
s	H	(*o*-FC_6H_4)CH_2-	$BF_3{\cdot}Et_2O$	76	β	2002EJO113
t	H	CF_3CH_2-	$BF_3{\cdot}Et_2O$	29	β	2002EJO113
u	H	*p*-HSC_6H_4-	$BF_3{\cdot}Et_2O$	13	β	2005JNP1274
v	Bn	2-Naphthyloxy-	$BF_3{\cdot}Et_2O$	98	β	2003EJO2098
w	Ac	$BrCH_2CH_2$-	TMSOTf	84	1:9	2004JOC3242
x	H	$CF_3CF_2CH_2$-	$BF_3{\cdot}Et_2O$	43	3:97	1998JME4101
y	H	$CF_3CF_2CH_2$-	TMSCl	54	3:97	1998JME4101
z	H	$CF_3CF_2CH_2$-	DEAD, PPh_3	80	7:93	1998JME4101
aa	H	C_6F_5	DEAD, PPh_3	50	6:94	1998JME4101
ab	H	1-Naphthyl-	DEAD, PPh_3	27	1:1.7	2002EJO113
ac	H	1-Naphthyl-	Cl_3CCN, DBU	73	β	2002EJO113
ad	H	2-Naphthyl-	DEAD, PPh_3	16	2.2:1	2002EJO113
ae	H	2-Naphthyl-	Cl_3CCN, DBU	77	β	2002EJO113
af[c]	H	$Fc(CH_2)_3$-	$BF_3{\cdot}Et_2O$	n.r.	25:75	2000BMC2739
ag	Ac	*m*-$(MeO_2CCH_2CH_2)C_6H_4$-	TFA	36	β	2005JME4608
ah	Ac	*p*-$(MeO_2CCH_2)C_6H_4$-	TFA	30	β	2005JME4608

[a] β = only the β-isomer reported.
[b] n.r. = not reported.
[c] Fc = ferrocenyl.

Synthesis of dihydroartemisinin polyethylene-glycol dimers **130** may be achieved easily in one chemical operation starting with dihydroartemisinin **29a** and the corresponding bifunctional alcohol or thiol under acidic conditions (**Table 7**) <1997BMC1257>.



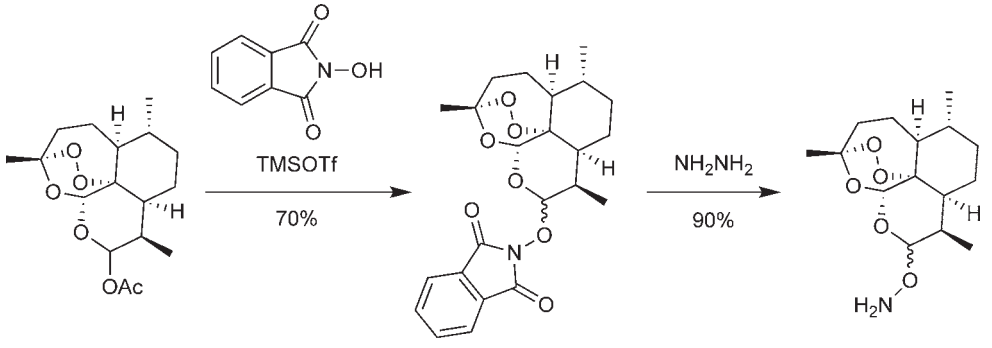
130

Table 7 Synthesis of dihydroartemisinin polyethylene-glycol dimers **130**

R	*Yield (%)*	
OCH_2CH_2O	4.2	α,α
OCH_2CH_2O	31.8	β,β
OCH_2CH_2O	13.0	α,β
$(CH_2)_4$	36	β,β
S-S	27[a]	β,β

[a]In a two-step operation.

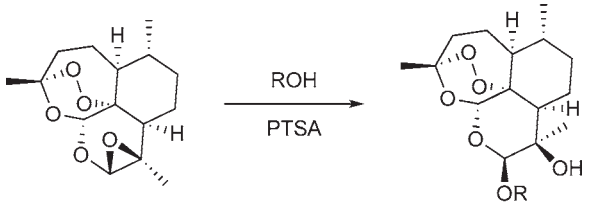
O-Aminodihydroartemisinin **132** was synthesized via the TMSOTf-catalyzed coupling reaction of *O*-acetyldihydroartemisinin **129** (R = Ac), followed by treatment of **131** with hydrazine. This compound reacts readily with benzaldehyde to give the corresponding oxime derivative (**Scheme 16**) <2004JOC3242>.



129 **131** **132**

Scheme 16

Several fluorinated aryl ethers **134** were prepared from the reaction of the 11,12β-oxirane **133** <1994TL2129> with substituted benzyl alcohols (Equation 13; **Table 8**) <1995JME4120>.

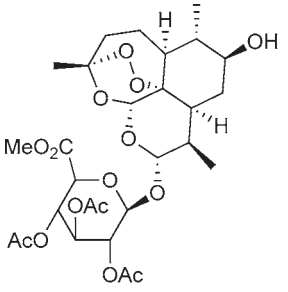


133 **134** (13)

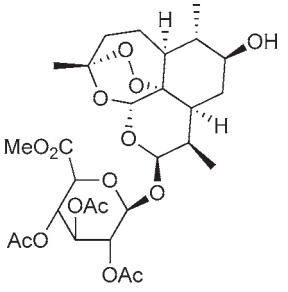
Table 8 Synthesis of fluorinated aryl ethers **134** <1995JME4120>

R	*Yield (%)*
o-Fluorobenzyl	59
m-Fluorobenzyl	63
p-Fluorobenzyl	69
Pentafluorobenzyl	67

The search for new water-soluble analogs of artemisinin **9a** more suitable for intravenous use led to the synthesis of the glucuronide conjugates. Using the classical Königs–Knorr reaction, condensation of dihydroartemisinin **29a** (a mixture of both α- and β-isomers in solution) with acetobromo-α-D-glucuronic acid methyl ester in the presence of Ag_2CO_3 as catalyst at room temperature in benzene gave almost exclusively the β-glucuronide of α-dihydroartemisinin **135a**. Condensation of the α-OH sugar and dihydroartemisinin **29a** in the presence of $BF_3{\cdot}Et_2O$ as catalyst gave the β-glucuronide of dihydroartemisinin **135b** in 17% yield <1995JME1911>. New and greatly improved preparations of the glucuronides of **29a** have been reported using anomeric hydroxy and imidate glucuronate intermediates; reaction of the hydroxy glucuronate under DCE/$ZnCl_2$ catalysis gave the 12β, 1′β-isomer in 31% yield, while the glucuronic trichloroacetimidate gave the 12α, 1′β-isomer in 32% yield (with 15% of the 12β, 1′β-isomer) <1997JCM370, 2001JME1467>.

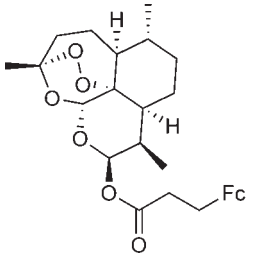


135a

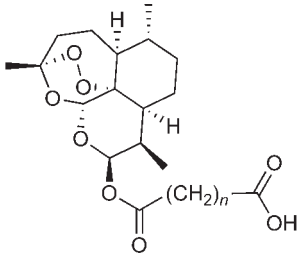


135b

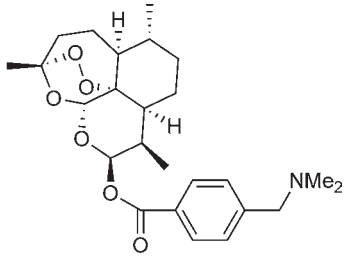
Dihydroartemisinin **29a** reacts with carboxylic acids to yield different esters **136–138** in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) <1997BML1091, 1997H(45)1055, 2001EJM469, 2000BMC2739>.



136
62%

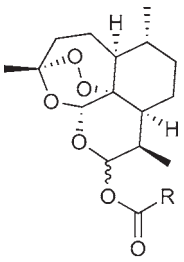


137a: $n = 4$ (50%)
137b: $n = 5$ (55%)
137c: $n = 7$ (45%)



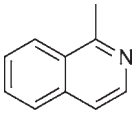
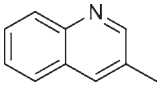
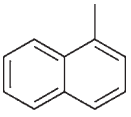
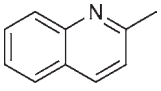
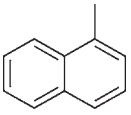
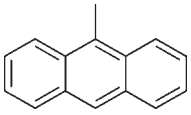
138
62%

Hydroxy activation of **29a** using the Mitsunobu reaction gave the corresponding β-ester derivatives **139**. The Schmidt procedure was also superior (**Table 9**) <2002EJO113>.



139

Table 9 Mitsunobu preparation of artemisinin β-ester derivatives **139** <2002EJO113>

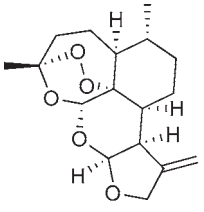
R	*Method*	*Yield (%)*	*R*	*Method*	*Yield (%)*
Ph	Ph_3P, DEAD	53		Ph_3P, DEAD	25
Ph	Cl_3CCN, DBU	80		Ph_3P, DEAD	5
	Ph_3P, DEAD	38		Ph_3P, DEAD	55
	Cl_3CCN,DBU	85		Ph_3P, DEAD	63

Dihydroartemisinin **29a** and anhydrides or acyl chlorides in the presence of DMAP, pyridine, or triethylamine gave the α-esters **139**; the base thus has no effects on the stereochemistry of the acyl substituent (**Table 10**) <2002EJO113>.

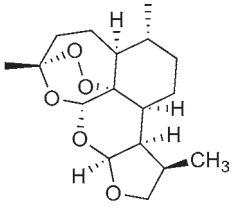
Table 10 Synthesis of artemisinin α-esters **139** <2002EJO113>

R **139**-α	*Method*	*Yield (%)*
CH_3	Ac_2O, DMAP	90
p-$O_2NC_6H_4$	*p*-$O_2NC_6H_4COCl$, Et_3N	82
Ph-	PhCOCl, Et_3N	71
Ph-	PhCOOH, DCC	35

Heating the propynyldihydroartemisinin derivatives **129e** (**Table 6**) or the corresponding allyl ether **129f** (**Table 6**) with Bu_3SnH–AIBN in toluene gave the 5-*exo-trig* products **140** (82%) and **141** (70%), respectively <1996JP11015>.



140

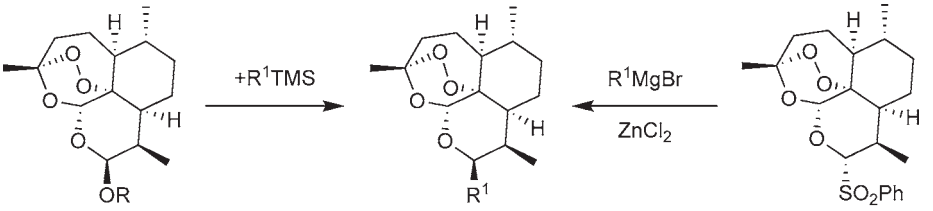


141

A popular approach to improving the metabolic stability of O-glycoside derivatives of dihydroartemisinin is to replace the C–O linkage at C-10 with a C–C linkage. These derivatives generally showed better bioavailability, as well as lower toxicity, when compared to the corresponding C–O derivatives <1998BML1003>.

Several groups prepared carba artemisinins by the reaction of dihydroartemisinin **29a** or its derivatives with silanes in the presence of a Lewis acid such as $BF_3{\cdot}Et_2O$ or $TiCl_4$ (**Scheme 17**, **Table 11**). In this reaction, it is proposed that the product is derived by axial attack of the R^1TMS (TMS = trimethylsilyl) as a carbon nucleophile. The often modest yield of carba derivatives was attributed to the competing dehydration reaction and subsequent formation of anhydroartemisinin **25**, which makes the purification of the desired material extremely difficult on a large scale <1995JME613, 1999JME5487>. O'Neill and his group improved the yield of this reaction using zinc chloride as a milder Lewis acid for the coupling reaction with C-10α-benzoate **29c** <2001J(P1)2682>. The C-10 allyl-substituted dihydroartemisinin **142** (R^1 = allyl) is an often-used starting material for the synthesis of further monomeric and dimeric analogs <2004JME1290, 2006BML1227>.

Direct substitution reaction of **125** <1995EJM697> with organozinc reagents derived from allyl, benzyl, phenyl, vinyl, and *n*-butyl Grignard reagents stereoselectively produced C-10-substituted deoxoartemisinins **142** in good to moderate yields (**Scheme 17**; **Table 12**) <2002TL2891>.



29a–c **142** **125**

Scheme 17

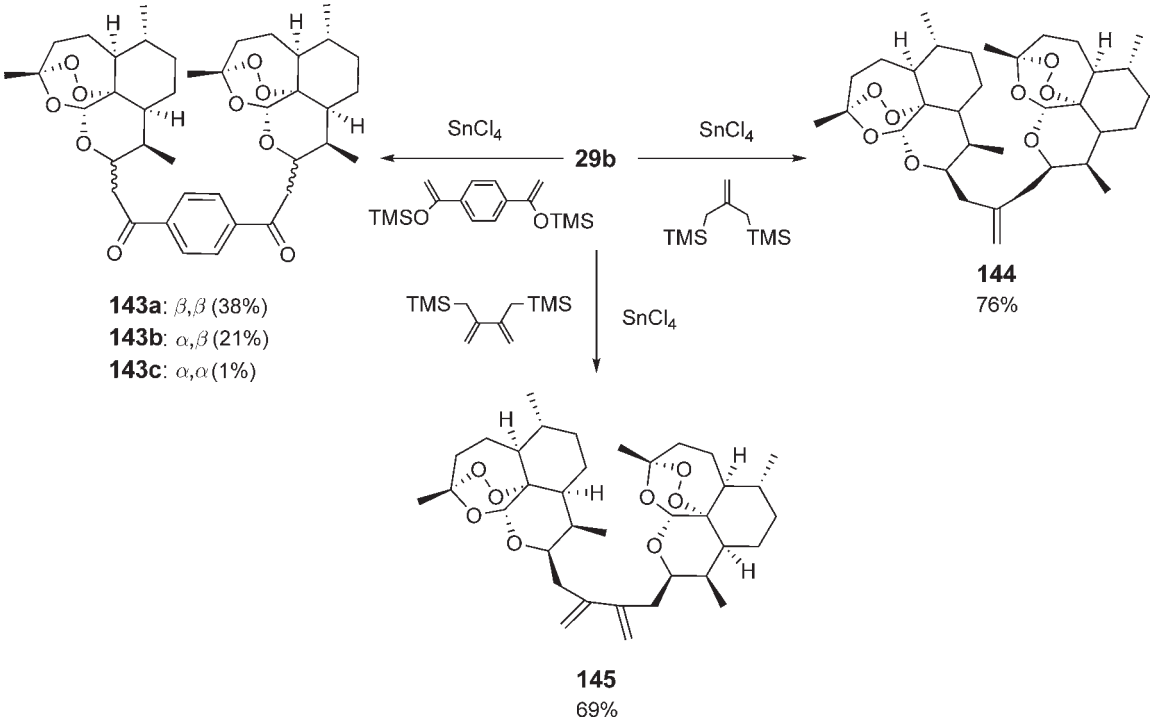
Table 11 Lewis acid-catalyzed synthesis of carba-artemisinins **142**

R	R^1	*Conditions*	*Yield of* **142** *(%)*	*Reference*
H	Allyl	$BF_3.Et_2O$, CH_2Cl_2, −55 °C	50 + 23% **25**	1995JME613
Ac	CN	$TiCl_4$, CH_3CN, −40 °C	76	1999TL8543 2000JME4228
Ac	$PhCOCH_2$-	$TiCl_4$, CH_3CN, −40 °C	72	2000JME4228
Ac	$OHCCH_2$-	$TiCl_4$, CH_3CN, −40 °C	30	2000JME4228
Bz	Allyl	$ZnCl_2$, DCE, 0 °C	90	2001JP12682 2002JME1052, 2004JME1290, 2005BML2629, 2005TL4243
Bz	Allyl	$ZnCl_2$, DCM, 0 °C	90	2005OL1561
Bz	CH_2=C(Ph)CH_2-	$ZnCl_2$, DCE, 0 °C	91	2001JP12682
Bz	CH_2=C(*m*-$F_3CC_6H_4$)CH_2-	$ZnCl_2$, DCE, 0 °C	94	2001JP12682
Bz	CH_2=C(*p*-FC_6H_4)CH_2-	$ZnCl_2$, DCE, 0 °C	86	2001JP12682
Bz	CH_2=C(*o*-FC_6H_4)-CH_2-	$ZnCl_2$, DCE, 0 °C	70	2001JP12682

Table 12 Direct substitution of sulfone intermedates **125** with various organozinc reagents <2002TL2891>

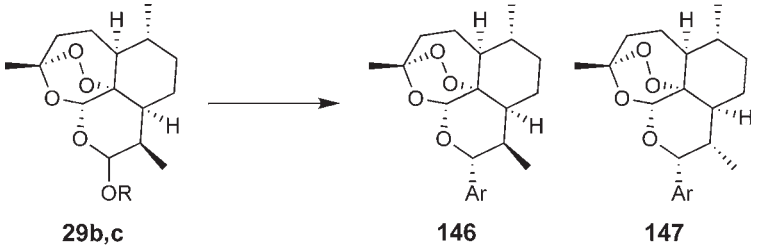
R^1	*Yield (%)*
Allyl	84
Benzyl	69
Phenyl	91
Vinyl	73
n-Butyl	48

Dihydroartemisinin α-acetate **29b** undergoes mild $SnCl_4$-promoted double coupling with the bis-enol trimethylsilyl ether of *p*-diacetylbenzene to produce the β,β-dimer **143a**, obtained previously from artemether **28a** using $TiCl_4$ <1999JME4275>. The reproducibility and yield were better with $SnCl_4$ than with $TiCl_4$, giving **143a** in 38% yield; the α,β-dimer **143b** and α,α-dimer **143c** were also obtained <2002BMC227>. In a similar manner and in the presence of $SnCl_4$, the allylic bis-silane converted **29b** on a gram scale into dimer **144**. This new, very stable dimer was then transformed easily in one additional step into a number of different dimers <2003JME1060, 2004JME1299>. Recently, **29b** was converted into a C-10-carba-trioxane-conjugated diene dimer **145** (**Scheme 18**) <2006JME2731>.



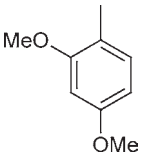
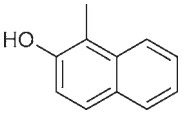
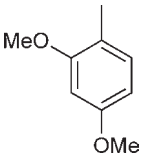
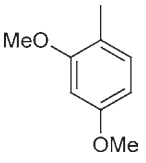
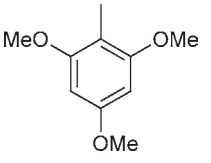
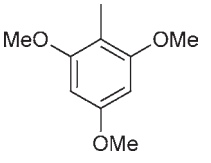
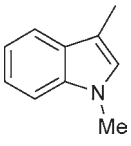
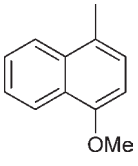
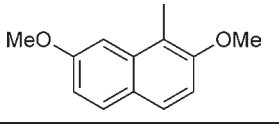
Scheme 18

A number of arylated products were obtained from the reaction of artemisinin benzoate **29c** or acetate **29b** with activated aromatics in the presence of $BF_3{\cdot}Et_2O$ or $SnCl_4$. The β-benzoate was found to be a more effective donor than the α one. In many cases, the glycal **25** was formed as a by-product, together with varying amounts of the dimeric acetal **26**. The latter compound can be prepared from **29a** in the presence of *p*-toluenesulfonyl chloride and triethylamine. The outcome of the reactions of the β-benzoate **29c** with 1,3-dimethoxybenzene was more complicated than the other cases; a disubstituted aryl product **146** and an aromatic regioisomer **147** were isolated, beside the standard products, in varying amounts depending upon the reaction conditions (**Table 13**; Equation 14) <2003EJO2098>.



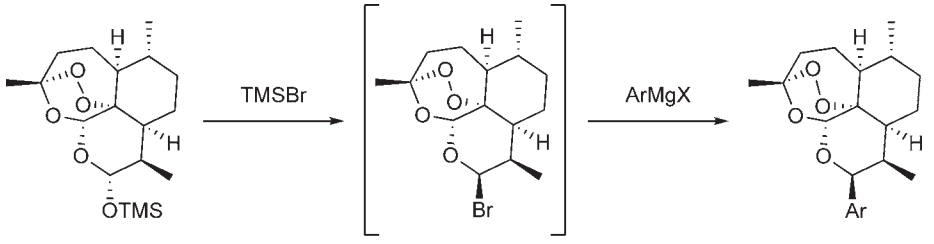
29b,c **146** **147** (14)

Table 13 Relative yields of aryl carba-artemisinin analogs **146** and **147**, the dehydro product **25**, and the dimeric acetal **26** <2003EJO2098>

R	*Ar*	*Reagent*	**146**	**147**	**25**	**26**	*Reference*
α-Ac		$BF_3{\cdot}Et_2O$	26%	9%	[a]		2001J(P1)605
α-Ac		$BF_3{\cdot}Et_2O$	68% (α:β 1:1)				1999J(P1)1827
β-Bz[b]		$BF_3{\cdot}Et_2O$	25%		33%	10%	2003EJO2098
β-Bz[c]		$SnCl_4$	20%		19%		2003EJO2098
β-Bz		$BF_3{\cdot}Et_2O$	71%		11%	5%	2003EJO2098
α-Bz		$BF_3{\cdot}Et_2O$	57%		12%	3%	2003EJO2098
β-Bz[d]		$SnCl_4$	73%				2003EJO2098
β-Bz		$SnCl_4$	13%		30%		2003EJO2098
β-Bz[c]		$SnCl_4$	44%				2003EJO2098

[a]Major product, exact yield not given.
[b]10% other arylated products.
[c]36% other arylated products.
[d]No attempt was made to isolate other products.

Treatment of **148** <2002EJO113> with TMSBr resulted in the formation of the 10β-bromide **149** (not isolated) and subsequent reaction with arylmagnesium halides gave the *C*-aryl glycosides **150** in acceptable yield (**Scheme 19**; **Table 14**). It was not possible to suppress formation of the glycal **25** <2003EJO2098>.



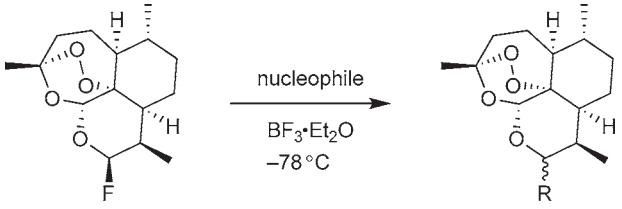
148 **149** **150**

Scheme 19

Table 14 Synthesis of *C*-aryl glycosides **150** <2003EJO2098>

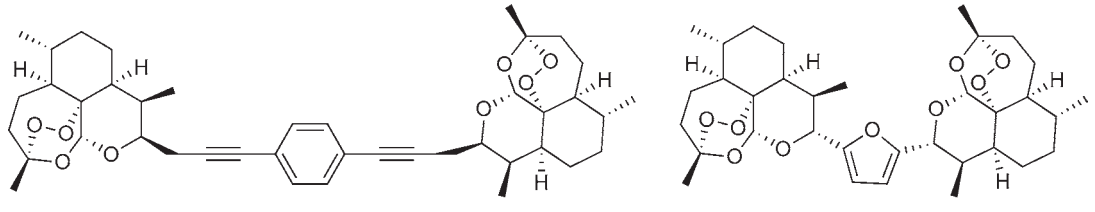
Ar	*Yield (%)*	*Ar*	*Yield (%)*
Ph	45	2-Naphthyl	43
4-FC_6H_4-	39	2,4,6-$Me_3C_6H_2$-	55
4-$(CH_2{=}CH)C_6H_4$-	68	2,4,5-$Me_3C_6H_2$-	55
2-$MeOC_6H_4$-	59	9-Phenanthryl	37
2,4,6-$(MeO)_3C_6H_2$-	46	4-(1-morpholino)C_6H_4-	51

Fluorination of **29a** with Et_2NSF_3 (DAST) proceeded in 82% yield on a gram scale to form a mixture of anomeric fluorides **151**, with the β-fluoride predominating and easily separated from the α-fluoride by column chromatography on Florisil. Coupling of either the α- or the β-fluoride **151** with Me_3Al gave the 10β-methyl derivative **152** (R = Me) with almost complete stereoselectivity. Several dimethylaluminium acetylides also coupled smoothly in the presence of boron trifluoride-etherate to form exclusively the 10β-acetylenic derivatives. In stereochemical contrast, electron-rich aromatics coupled to produce exclusively the 10α-oriented derivatives in a boron trifluoride-promoted Friedel–Crafts alkylation (Equation (15); **Table 15**) <1998TL1533, 1999JME300>.



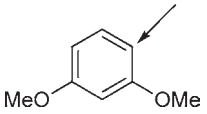
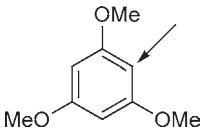
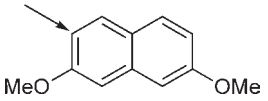
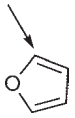
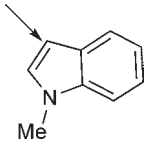
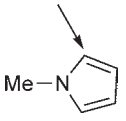
151 **152** (15)

Saturated non-acetal dimers, such as **153** and **154**, can be prepared from **151** via aluminium acetylide condensations or Friedel–Crafts reactions. Although the acetylenic dimer **153** is β-linked to C-10 of the artemisinin skeleton, the aryl dimer **154** is α-linked <1999JME4275>.



153 **154**

Table 15 Coupling of artemisinin fluorides **151**

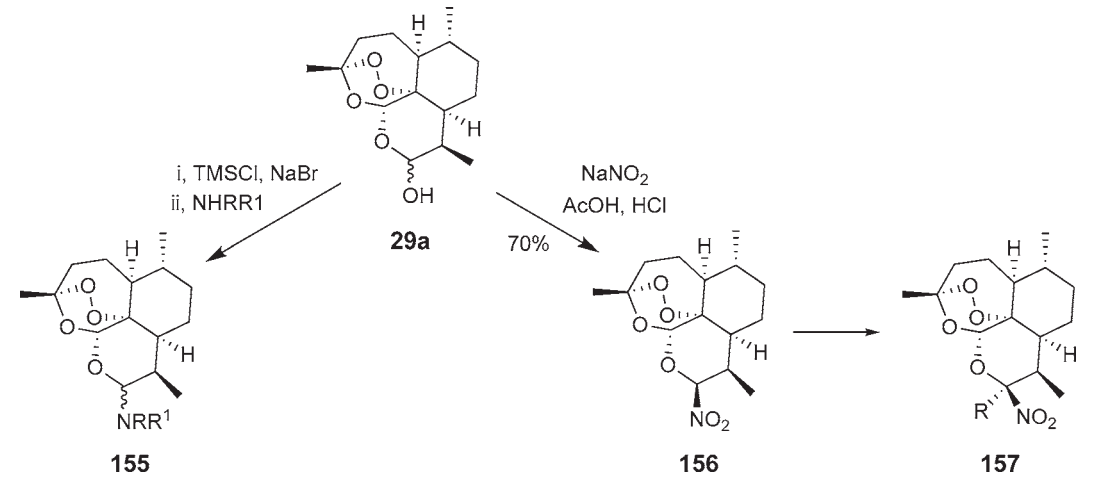
Nucleophile[a]	*10-R*	*Yield (%)*
Me_3Al	β-Me	57
Et_3Al	β-Et	51
Me_2AlR	β-C≡CPh	70
Me_2AlR	β-C≡C(p-ClC_6H_4-)	69
Me_2AlR	β-C≡CC_6H_{13}	77
Me_2AlR	β-C≡C$SiMe_3$	80
	α-Ar	71
	α-Ar	60
	α-Ar	80
	α-Ar	86
	α-Ar	72
	α-Ar	31

[a]Where appropriate, the direction of electrophilic aromatic substitution is indicated by an arrow.

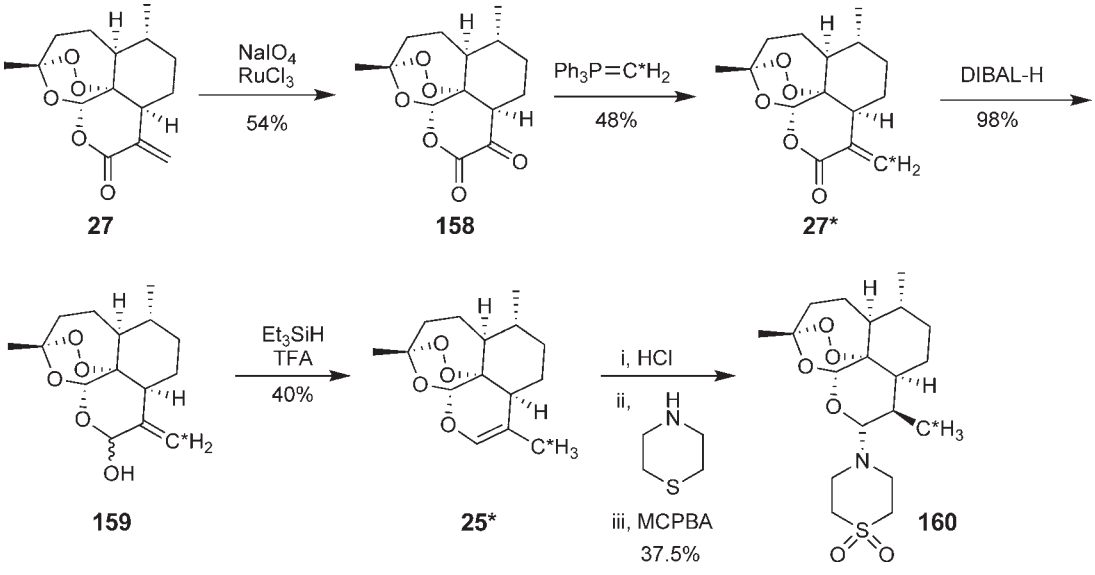
Various alkylamino-artemisinins **155** were synthesized by the nucleophilic displacement of bromoartemisin **149**, which was prepared *in situ* from **148** (**Scheme 19**), followed by reaction with alkylamines <2004AGE1381>. A more direct route involved treatment of **29a** firstly with a mixture of NaBr and TMSCl and then with the amine <2006AGE2082>. HFIP can be used as an additive in the amination step to increase the yield <2005AGE2060>. Similar aminoartemisinins **155** (where $NRR^1 = NHAr$) were prepared by reacting **29a** with anilines, in the presence of a catalytic amount of pyridinium sulfate in pyridine, in good yields (e.g., Ar = Ph, 93%; p-ClC_6H_4, 72%; m-$MeOC_6H_4$, 85%) (**Scheme 20**) <1995BML1791>. This reaction could not be applied to the synthesis of alkylamino derivatives due to their differences in basicity.

The conversion of the 10-hydroxy group on **29a** into 10-nitro by the action of HNO_2 has been reported and the 10α-nitro-derivative **156** so formed reacted with a variety of electrophiles, in the presence of base, to give the corresponding addition products **157** (R = $CH_3CH(OH)$-, $CH_3C(OH)(CH_3)$-, $OHCCH_2CH_2$-, $NCCH_2CH_2$) (**Scheme 20**) <2001IJC(B)1125>.

A labeled aminoartemisinin **160** has been prepared from artemisitene **27**, via the dioxo derivative **158**, for the purpose of metabolic studies (**Scheme 21**) <2006AGE2082>. The synthesis of various other labeled artemisinin derivatives, **27***, **159**, and **25***, has also been described <1996MI249, 1996MI263>.



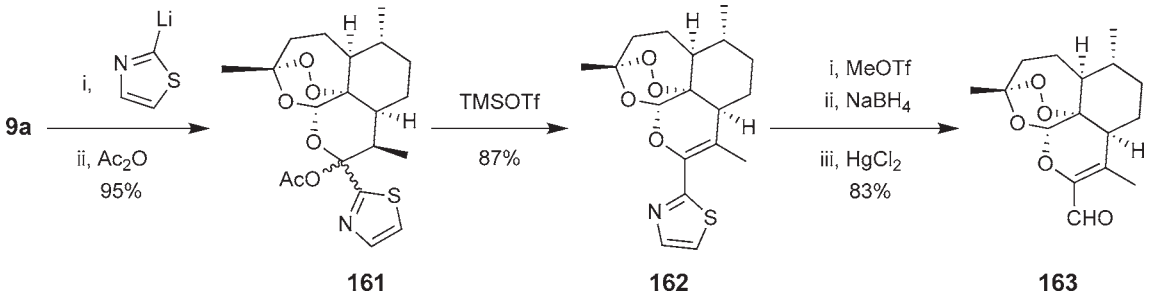
Scheme 20



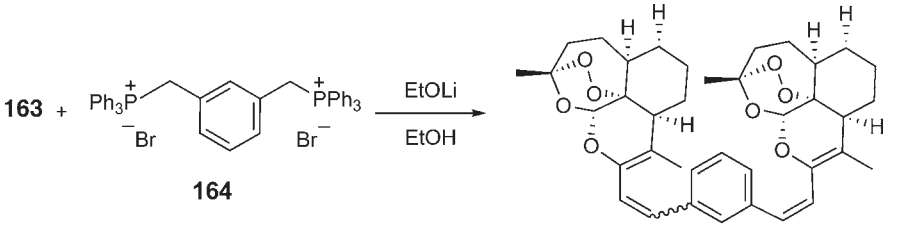
Scheme 21

When artemisinin **9a** was treated with 2-lithiothiazole followed by *in situ* O-acetylation, the thiazole carbonyl adduct **161** was formed chemoselectively in good yield (**Scheme 22**); the same reaction with PhLi produced a mixture of uncharacterized products. When this acetyl adduct **161** was exposed to TMSOTf, the corresponding elimination product **162** was formed, which was converted in three steps without purification of intermediates into aldehyde **163**. This was reacted with high chemoselectivity in reactions with organometallics (*n*-BuLi, PhMgBr) and with phosphonium ylides in a Wittig procedure <1999T3625>.

Dimers **165a–c** were prepared in high overall yield and in a novel manner via a bis-Wittig coupling reaction with aldehyde **163**. The coupling reaction was optimized to almost quantitative yield by generating the bis-phosphonium ylide reagent via the *in situ* deprotonation of the corresponding bis-phosphonium bromide salt **164** in the presence of aldehyde **163** using *in situ*-generated lithium ethoxide as base (Equation 16). The three geometric isomers **165a–c** were separated <1999JME4275>.



Scheme 22



(16)

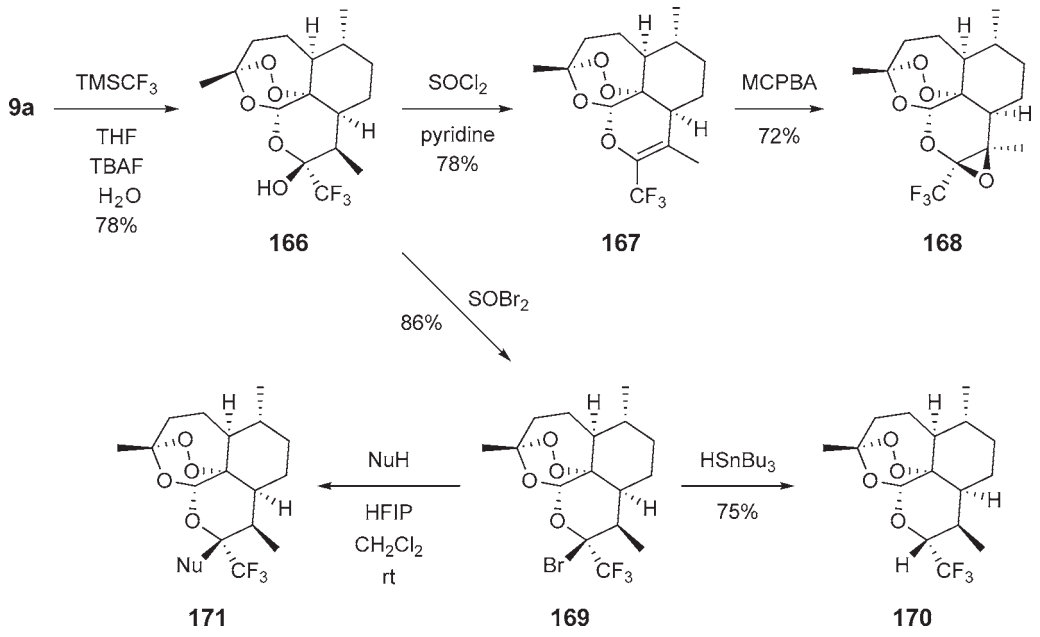
165a: *trans, trans* (27%)
165b: *trans, cis* (54%)
165c: *cis, cis* (18%)

Trifluoromethylated hemiketal **166** was prepared from artemisinin **9a** by treatment with 2 equiv of $TMSCF_3$ in the presence of $TBAF{\cdot}3H_2O$ (0.1 equiv) at room temperature (TBAF = tetrabutylammonium fluoride); desilylation occurred upon the addition of water. The reaction was stereoselective and led to hemiketal **166** in high yield (**Scheme 23**) <1996BML2717>. The glycal **167** could be obtained in good yield by treatment of **166** with thionyl chloride and pyridine. Epoxidation of **167** using MCPBA gave only one stereoisomer of epoxy ether **168** (**Scheme 23**) with no indication of the presence of the other stereoisomer <2002JOC1253>. The nucleophilic substitution of the hydroxy group of the hemiketal **166** with bromine proceeds in good yield with retention of configuration. A novel, nonacetal deoxoartemisinin **170** was prepared by debromination of bromide **169** in the presence of tributyltin hydride at reflux in toluene, without alteration of the endoperoxide bridge (**Scheme 23**) <2002OL757>. In replacement reactions with nucleophiles, **169** was activated by the addition of a strong hydrogen bond donor of low nucleophilicity, such as HFIP. The completely diastereoselective substitution of bromide **169** with various nucleophiles under mild conditions gave access to new artemisinin C-10-substituted analogs **171** (**Scheme 23**; **Table 16**) <2003JOC9763, 2004JME2694>.

The reactivity of **25** and of its 10-trifluoromethyl analog **167** <2002JOC1253> toward brominating reagents was explored with the aim of preparing C-16 allylic bromides **172** and **173**. The glycals **25** and **167** react with *N*-bromosuccinimide (NBS) to provide compounds **172** and **173**, respectively, both in 90% yield (**Scheme 24**). Allylic bromination of the trifluoromethyl analog **167** also occurred in 70% yield with Br_2 in CCl_4. The products **172** and **173** react easily with N-, O-, and C-nucleophiles to provide substituted derivatives **174** (**Scheme 24**; **Table 17**) <2002TL7837, 2004JME1423>. Nucleophilic substitution of the allylic bromides **172** and **173** can also occur at C-10 under solvolytic conditions, yielding substituted analogs **175**; the use of HFIP further increases this selectivity. Primary alcohols reacting with **173** via allylic substitution can give **174** exclusively <2004JME1423>. With amines as nucleophiles, the selectivity of substitution is dependent on their nucleophilicity, but attack at the exocyclic carbon is always favored to yield **174** as the major product (**Scheme 24**; **Table 17**) <2006JOC3082>.

The allylic alcohol **176**, prepared by the hydrolysis of allylic bromide **173** <2004JME1423>, was oxidized with MnO_2 to the corresponding aldehyde **177**, which reacted easily with allyl bromide in the presence of zinc under Barbier's conditions to give the adduct **178** (**Scheme 25**). Of particular note is the fact that the peroxide bridge was not sensitive to Zn under these reaction conditions <2005OL5219>.

Arteether **28b** and 10-deoxoartemisinin **108** were used as substrates for microbial fermentation to obtain new hydroxy derivatives <1995JNP751, 1996JNP251>. Using *Cunninghamella elegans*, 7β-hydroxyarteether **179** was



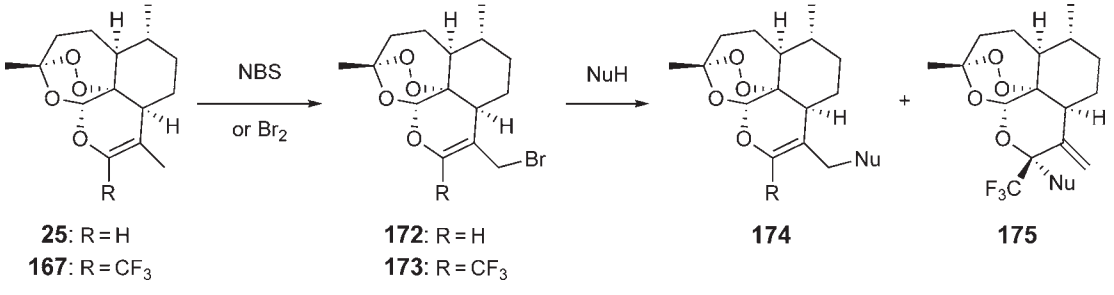
Scheme 23

Table 16 Substitution of bromide **169** with nucleophiles <2003JOC9763, 2004JME2694>

Nucleophile	*Yield* **171** *(%)*	*Yield* **167** *(%)*
H_2O	87	12
MeOH	79	5
p-$(MeO_2C)C_6H_4CH_2OH$	76	6
$CH_2{=}CHCH_2OH$	73	5
$HOCH_2CH_2OH$	89	2
CF_3CH_2OH	46	12
H_2O_2 (UHP)[a]	83	0
$HO_2CCH_2CH_2CO_2H$	68	5

[a]UHP = urea hydrogen peroxide.

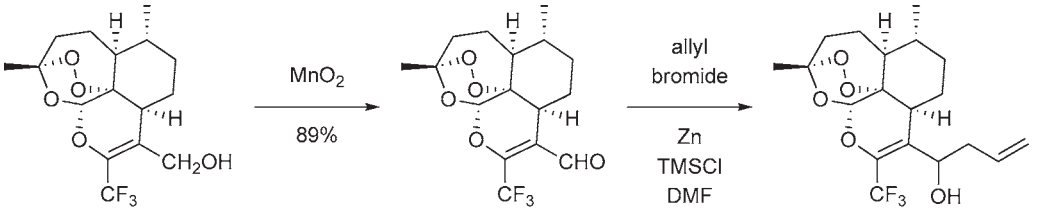
obtained in 40% yield from arteether **28b** <1995JME1911>, while 10-deoxoartemisinin **108** was transformed to **183b** (84%), along with some minor products <2004JNP1595>. Fermentation with *Streptomyces lavendulae* arteether **28b** was also used to prepare 7α-hydroxyarteether **180**, 5α-hydroxyarteether **181**, and 15-hydroxyarteether **182** <1995JME1911>. 10-Deoxoartemisinin **108** was transformed to 7β-hydroxy deoxoartemisinin **183b** by *Mucor*



Scheme 24

Table 17 Nucleophilic substitution of the allylic bromides **172** and **173**

R	*Nucleophile*	*Product ratio 174:175*	*Yield (%)*	*Reference*
H	Morpholine	50:50	82	2002TL7837
H	EtOH, NaH	10:90	36	2002TL7837
CF_3	Morpholine	100:0	90	2004JME1423
CF_3	EtOH, NaH	100:0	98	2004JME1423
CF_3	BnOH, NaH	100:0	97	2004JME1423
CF_3	EtOH (solvent)	13:87	92	2006JOC3082
CF_3	CF_3CH_2OH (solvent)	20:80	52	2006JOC3082
CF_3	Piperidine	100:0	80	2006JOC3082
CF_3	Aniline	83:17	75	2006JOC3082
CF_3	Dimethyl malonate, NaH	100:0	90	2004JME1423

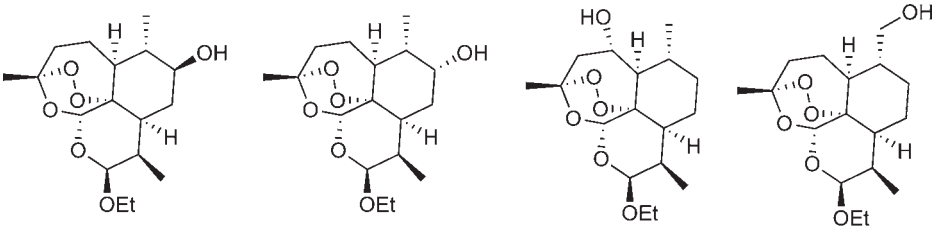


176 **177** **178**

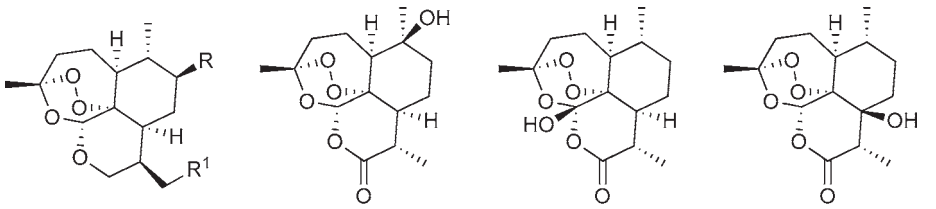
Scheme 25

ramannianus in 45% yield <2002BTL937>. The microbial hydroxylation of **108** with *A. niger* gave 16-hydroxy-10-deoxoartemisinin **183c** (26%) and **183b** (69%) as the major products <2004BTL607>.

In a preparative scale fermentation of **9a** by *Cunninghamella echinulata*, 6β-hydroxyartemisinin **184** was obtained in 50% yield <2002TL4519>. Transformation of artemisinin **9a** by the fungi *Eurotium amstelodami* and *A. niger* was investigated; 12β-hydroxyartemisinin **185** and 8aβ-hydroxyartemisinin **186** were isolated in 63% and 32% yields, respectively, from the extract of *E. amstelodami*, and 80% and 19%, respectively, from the extract of *A. niger* <2006MI349>.



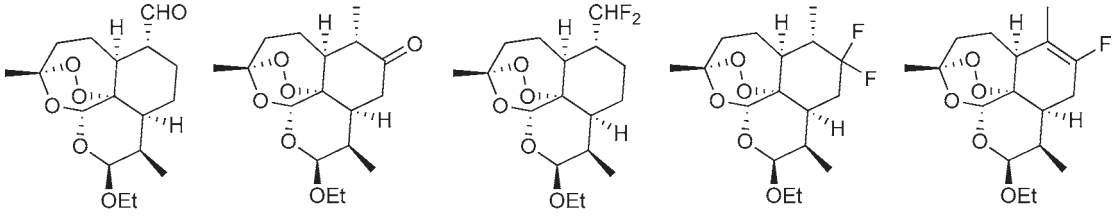
179 **180** **181** **182**



183a: R = R^1 = H
183b: R = OH; R^1 = H
183c: R = H; R^1 = OH

184 **185** **186**

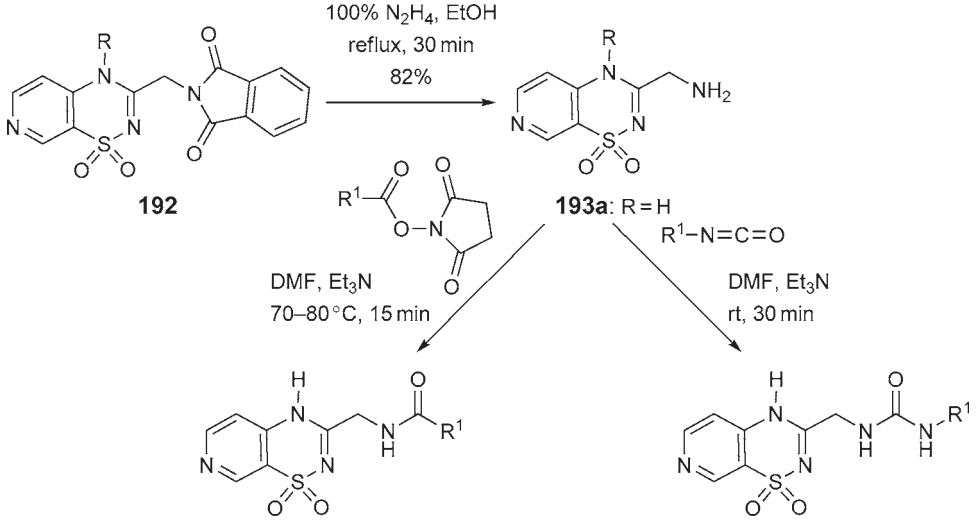
From the study of a microbially mediated oxidation of arteether **28b**, sufficient quantities of 7α-hydroxy **180** and 15-hydroxy derivatives **182** were obtained to employ them as intermediates for the preparation of fluorinated compounds. The hydroxyl groups were oxidized to the corresponding aldehyde **187**, or ketone **188**, with catalytic quantities of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of excess *N*-methylmorpholine *N*-oxide. On reaction with DAST, **187** and **188** were converted into the corresponding geminal difluoro derivatives, **189** (63%) and **190** (42%). In addition to **190**, a monofluoro olefin **191** was obtained in 25% yield from **188** on reaction with DAST <1995JME4120>.



187 **188** **189** **190** **191**

10.17.7.3 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

Hydrazinolysis of the 3-phthalimidomethylpyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxides **192** gave the 3-aminomethyl derivative **193a** only when R = H. When N-4 was substituted by either methyl or phenyl groups **192** (R = Me or Ph), this hydrazinolysis led to decomposition of the thiadiazine 1,1-dioxide ring (**Scheme 26**) <1997BSB781>. Reaction of the 3-aminomethyl derivative **193a** with isocyanates gave the corresponding ureas **194a–c**, while reaction with *N*-succinimidyl esters gave the amides **195a–c**.



192

193a: R = H

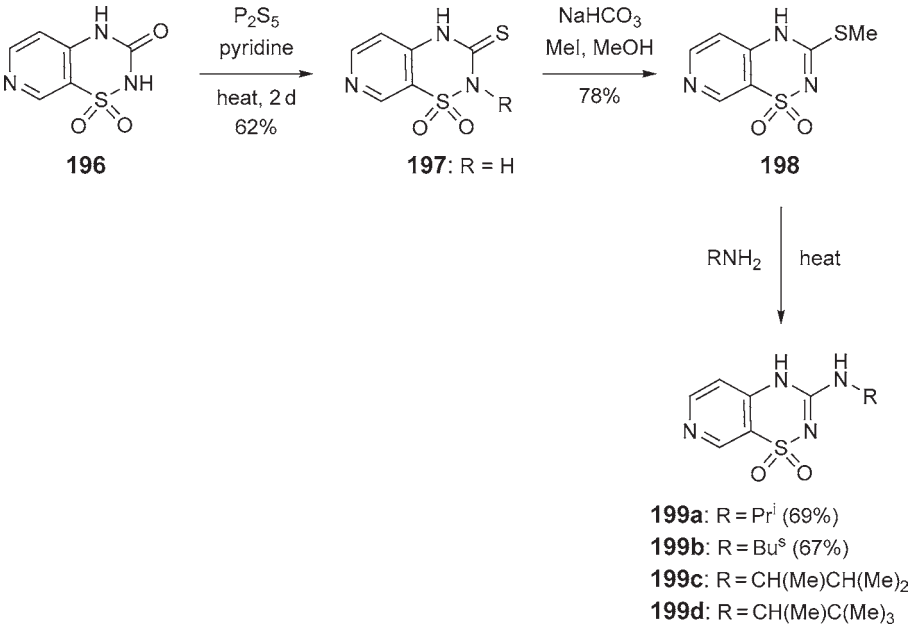
195a: R^1 = 1*H*-indol-2-yl (45%)
195b: R^1 = 4-BrC_6H_4 (54%)
195c: R^1 = naphth-2-yl (71%)

194a: R^1 = 4-ClC_6H_4 (64%)
194b: R^1 = 3-MeC_6H_4 (51%)
194c: R^1 = 3-MeOC_6H_4 (60%)

Scheme 26

Treatment of the 3-oxo derivative **196** with P_2S_5 gives the thione analog **197**, which can be methylated with sodium hydrogen carbonate and methyl iodide to give the thioether **198**. Nucleophilic substitution of the methylsulfinyl group by a range of amines gives the 3-alkylamino derivatives **199a–d** (**Scheme 27**) <1993JME3211,

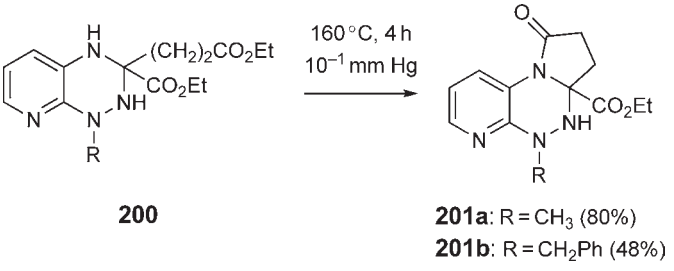
1996JME937>. Nucleophilic substitution of a 3-imidazolyl group also gives the 3-alkylamino derivatives **199** <1997MI463, 1998T4935>.



Scheme 27

10.17.7.4 Pyrido[3,2-*e*]-1,2,4-triazines

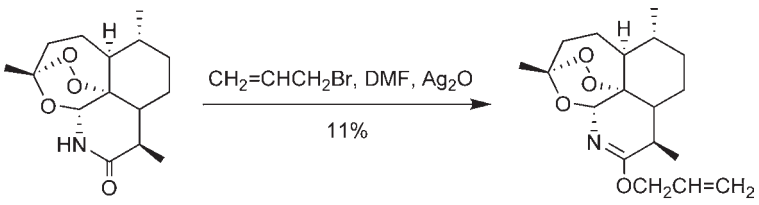
The tetrahydropyrido[3,2-*e*]-1,2,4-triazines **200** with an ethoxycarbonylethyl substituent in the 3-position cyclize to their tricyclic analogs **201** when heated under reduced pressure (**Scheme 28**) <1999JHC857>.



Scheme 28

10.17.7.5 Pyrido[2,3-*e*]-1,2,4-trioxines

The first attempts to access N-substituted 11-azaartemisinin derivatives directly from 11-azaartemisinin were unsuccessful; reaction of 11-azaartemisinin **9b** with allyl bromide in the presence of silver oxide gave the *O*-allyl-substituted analog **202** (*O*-allyl-11-azaartemisinin) in low yield (Equation 17) <1995JME5045, 1997TL731>.

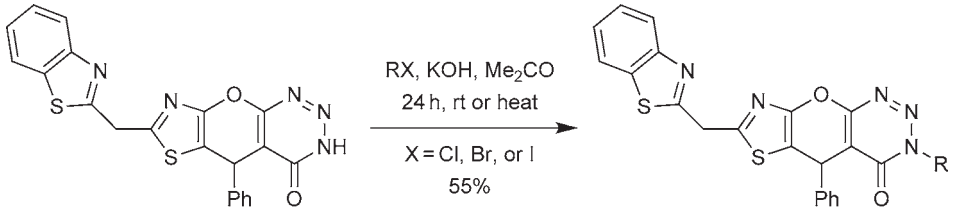


9b 202 (17)

10.17.8 Reactivity of Substituents Attached to Ring Heteroatoms

10.17.8.1 Pyrano[2,3-*d*]-1,2,3-triazines

Alkylation of pyrano[2,3-*d*]-1,2,3-triazine **203** with a number of electrophiles in 15% potassium hydroxide/acetone solution gave the substituted triazines **204** in a remarkably consistent 55% yield (Equation 18) <2003MI1061>.

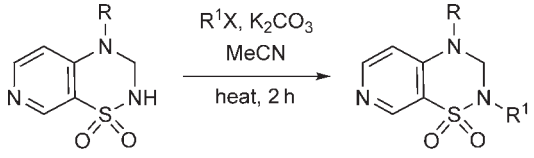


203 (18)

204a: R = Me
204b: R = CH_2CN
204c: R = CH_2COPh

10.17.8.2 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

Alkylation of N-2 of the dihydrothiadiazine ring of **205** gives a range of dialkylated derivatives **206a–c** (Equation 19) <1998JME2946>.



205 (19)

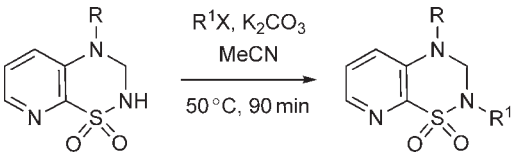
206a: R = R^1 = Me (65%)
206b: R = Me; R^1 = $(CH_2)_2Me$ (55%)
206c: R = $CHMe_2$; R^1 = Me (53%)

10.17.8.3 2*H*-Pyrido[3,2-*e*]-1,2,4-thiadiazines

Similar methodology to that employed above gave dialkylated dihydropyrido[3,2-*e*]thiadiazines **207a–c** (**Scheme 29**), while alkylation of the oxidized form **208** gave the *N*-monoalkyl derivatives **209a–c** <1998JME2946>.

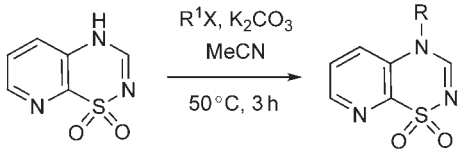
10.17.8.4 Pyrido[3,2-*e*]-1,2,4-triazines

The 1-methyltetrahydropyrido[3,2-*e*]-1,2,4-triazine **210** reacts with chloroacetyl chloride in the presence of dimethylamine to give the 4-chloroacetyl derivative **211** (Equation 20) <1999JHC857>.



33a

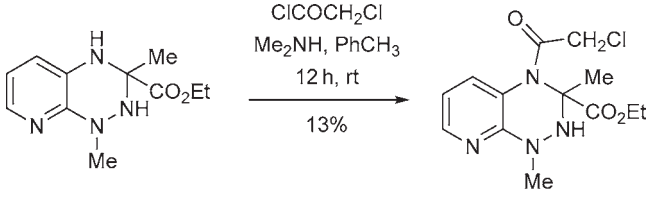
207a: R = R^1 = Me (54%)
207b: R = Et; R^1 = Me (65%)
207c: R = R^1 = Et (45%)



208

209a: R = Me (yield not reported)
209b: R = Et (70%)
209c: R = CHMe$_2$ (33%)

Scheme 29

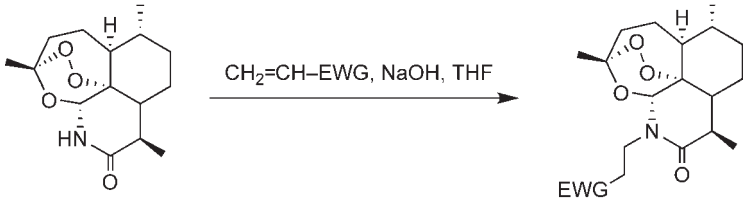


(20)

210 **211**

10.17.8.5 Pyrido[2,3-*e*]-1,2,4-trioxines

11-Azaartemisinin **9b** reacts with acrylates substituted with an electron-withdrawing group (EWG) to furnish a range of N-substituted 11-azaartemisinin analogs **212a–j** in good yield (Equation 21; **Table 18**) <2000BMC1111, 1997TL731>.



(21)

9b **212a–j**

Table 18 Synthesis of N-substituted 11-azaartemisinin analogs **212a–j**

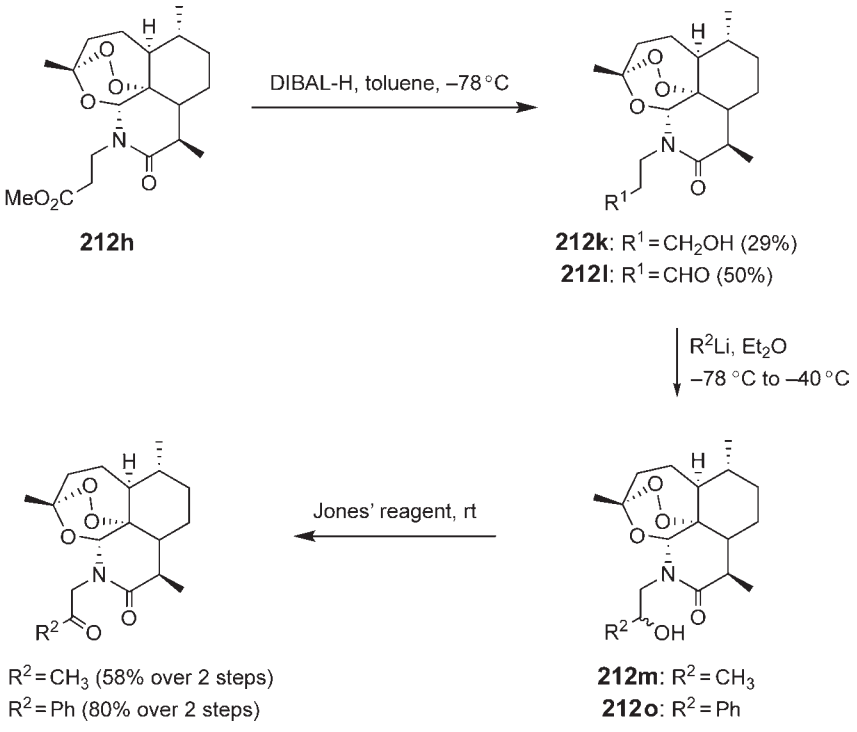
Product **212**	*EWG*	*Yield (%)*	*References*
a	CO_2Et	86	1997TL731 2000BMC1111
b	CN	88	1997TL731 2000BMC1111
c	SO_3Ph	80	1997TL731 2000BMC1111

(*Continued*)

Table 18 (Continued)

Product **212**	*EWG*	*Yield (%)*	*References*
d	SO_2Ph	90	1997TL731 2000BMC1111
e	SOPh	76	1997TL731
f	$CO_2C(CH_3)_3$	80	2000BMC1111
g	$CH(CO_2Et)CH_2CO_2Et$	78	2000BMC1111
h	CO_2Me	85	2000BMC1111 1999BML2969
i	COMe	73	2000BMC1111 1999BML2969
j	$CON(CH_3)_2$	n.r.	1999BML2969

Further functionalization was achieved through reduction and elaboration of **212h** to provide ketones **212n** and **212p**; compounds **212a–j**, **212n**, and **212p** were also tested for their antimalarial activity (**Scheme 30**) <2000BMC1111>.



212h

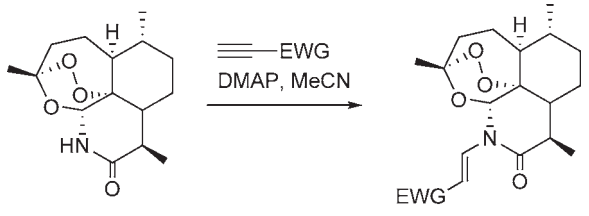
212k: $R^1 = CH_2OH$ (29%)
212l: $R^1 = CHO$ (50%)

212n: $R^2 = CH_3$ (58% over 2 steps)
212p: $R^2 = Ph$ (80% over 2 steps)

212m: $R^2 = CH_3$
212o: $R^2 = Ph$

Scheme 30

Unsaturated N-substituted 11-azaartemisinin analogs **213a–e** may be likewise prepared from 11-azaartemisinin **9b** through reaction with terminal acetylenes conjugated with EWGs; in most cases, the (*E*)-stereoisomer was formed exclusively (Equation 22; **Table 19**) <2000BMC1111>.



9b **213a–e** (22)

Table 19 Synthesis of unsaturated N-substituted 11-azaartemisinin analogs **213** <2000BMC1111>

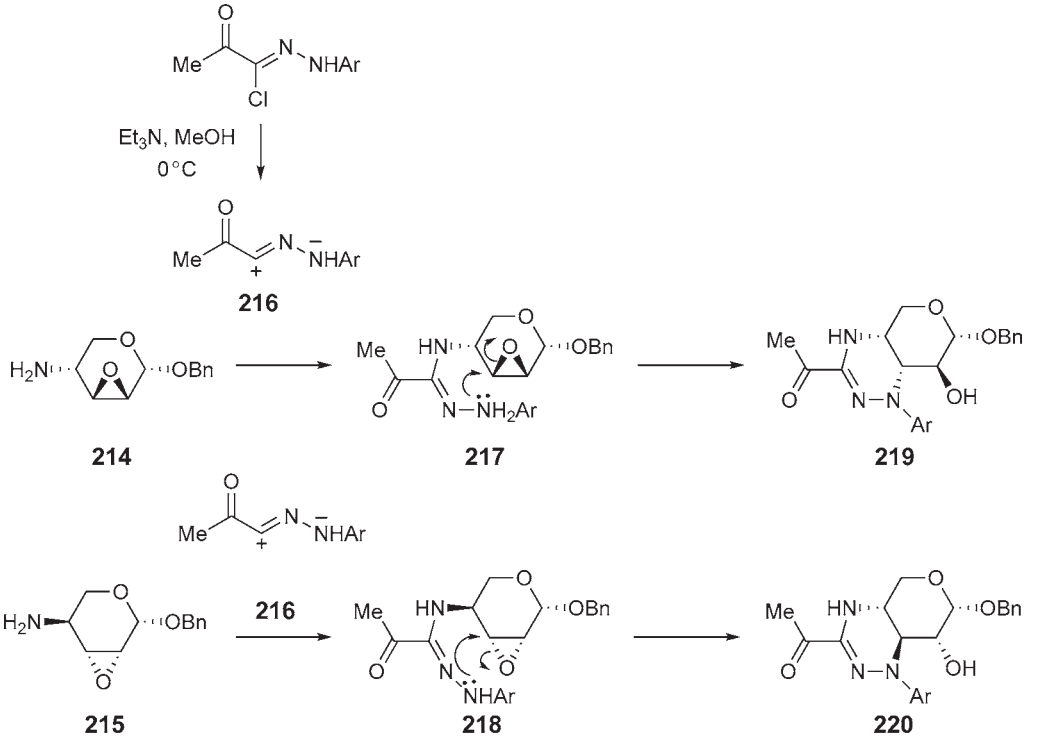
Product **213**	*EWG (stereochemistry of alkene)*	*Yield (%)*
a	CO_2Me (*E*)	56
b	$COCH_3$ (*E*)	56
c	$CON(CH_3)_2$ (*E*)	47
d	CN (*E*)	40
e	CN (*Z*)	4

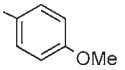
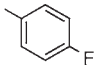
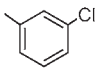
10.17.9 Ring Syntheses Classified by the Number of Ring Atoms Contributed by Each Component

10.17.9.1 Synthesis of the Second Heterocyclic Ring from [6+0] Fragments

10.17.9.1.1 1*H*-Pyrano[4,3-*e*]-1,2,4-triazines

Reaction of benzyl β-L- and α-D-4-amino-2,3-anhydro-4-deoxylyxopyranosides **214** and **215** with the nitrilimines **216**, generated *in situ* from the hydrazonyl chloride and triethylamine in methanol at 0 °C, gave the transient amidrazone adducts **217** and **218**, which undergo cyclization by nucleophilic attack of the hydrazono group on the epoxide ring to give the pyrano[4,3-*e*]-1,2,4-triazines **219** and **220**, respectively, in good to excellent yields (**Scheme 31**) <2001CL660>.

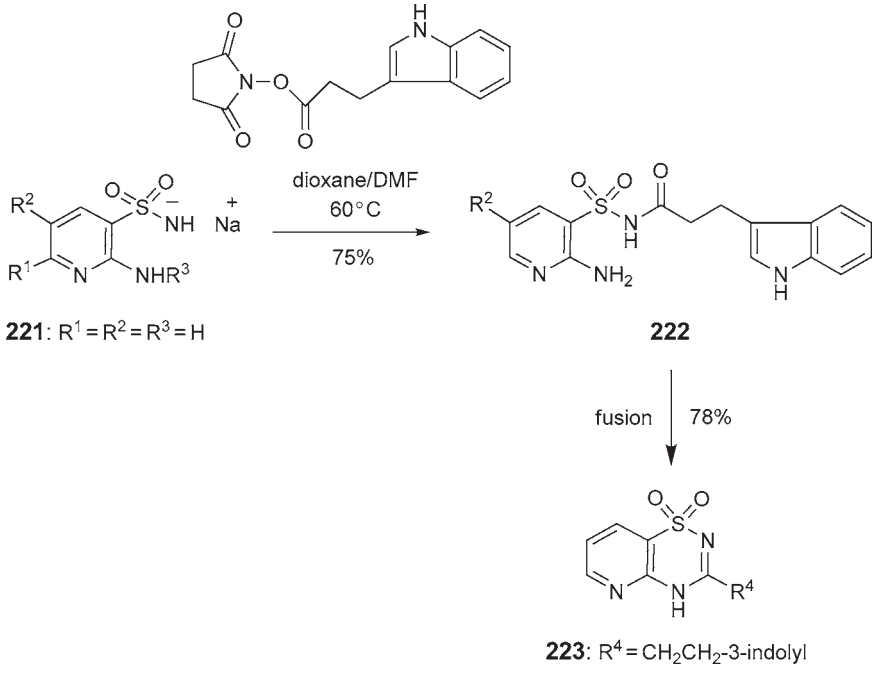


Yields	*a*	*b*	*c*	*d*
Ar				
219	85%	80%	78%	72%
220	79%	85%	77%	70%

Scheme 31

10.17.9.1.2 2*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazines

The reaction of the sodium salt of 2-aminopyridine-3-sulfonamide **221** ($R^1 = R^2 = R^3 = H$) with succinimidyl 3-(1*H*-indol-3-yl)propionate gives the amide **222**, which cyclizes on fusion to the 3-[2-(1*H*-indol-3-ylethyl)]-4*H*-pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **223** (**Scheme 32**) <1997MI463>.



221: $R^1 = R^2 = R^3 = H$

222

223: $R^4 = CH_2CH_2$-3-indolyl

Scheme 32

10.17.9.1.3 Pyrido[4,3-*e*]-1,2,4-thiadiazines

Fusion has also been employed in the synthesis of 3-cyclopentylpyrido[4,3-*e*]thiadiazine 1,1-dioxide **226** from the corresponding amide **225** (**Scheme 33**) <1996JME937>.

Cyclization of an amide has also been employed in the synthesis of 3-aminomethylpyrido[4,3-*e*]thiadiazine 1,1-dioxides **227a–c**. The phthalimidoacetamides were prepared from the sulfonamides **227a–c** and phthalimidoacetyl chloride under Schotten–Baumann conditions, then cyclized in $POCl_3$, via the imidoyl chloride intermediates **229a–c**, to give the 3-phthalimidomethyl derivatives **192a–c** (**Scheme 34**) <1997BSB781>. Amide cyclization via the imidoyl chlorides has also been employed to give the trifluoromethyl derivative <1996JME937>.

An alternative synthesis of this ring system involves the conversion of the pyridine-3-sulfonic acid **229** into the pyridylsulfonylguanidine **230**, then cyclization with K_2CO_3 in DMF (**Scheme 35**) <1993JME3211>.

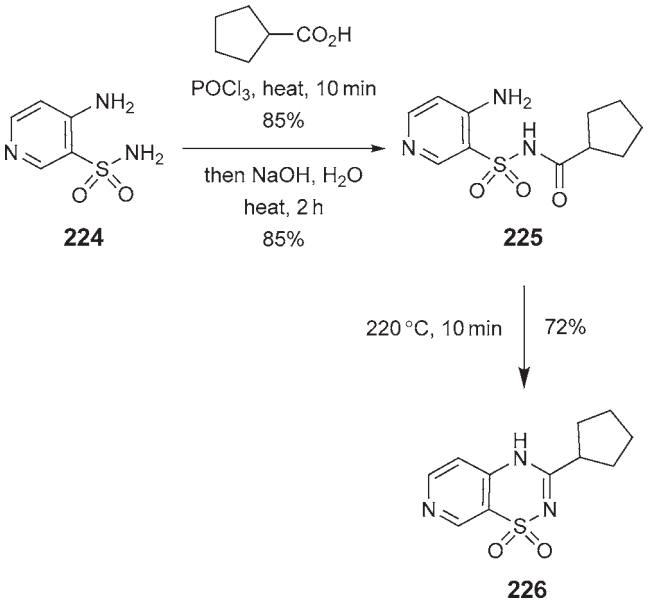
10.17.9.1.4 Pyrido[2,3-*e*]-1,2,4-triazines

Reaction of the dicyanoindenone **231** with pyrazole or 1,2,3-triazole diazonium salts gives deeply colored aminotriazines **232** and **233**, which cyclize upon pyrolysis to give the pentacyclic compounds **234** and **235** containing the pyrido[2,3-*e*]-1,2,4-triazine nucleus (**Scheme 36**) <2003JRM1161>.

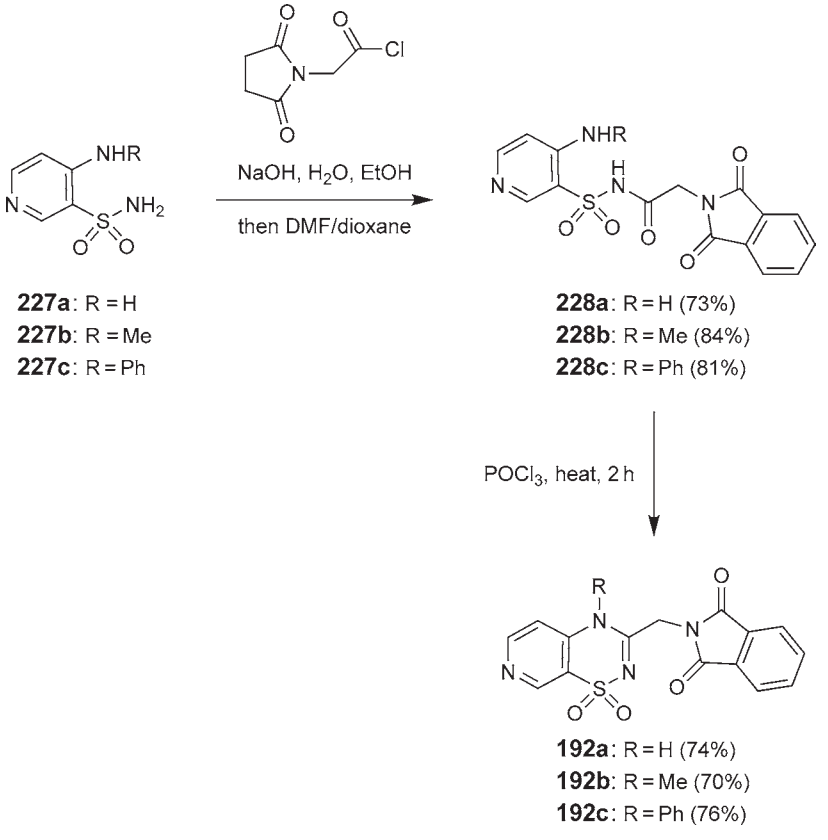
10.17.9.1.5 Pyrido[3,2-*e*]-1,2,4-triazines

Savelli, Boido, and Ciarallo prepared a series of hydrazones from the reaction of nitropyridylhydrazines **236** with α-keto esters. Upon reduction of the nitro group, the amino group of **237** cyclized onto the pendant hydrazone group to give the tetrahydropyridotriazines **238** in unreported yields (**Scheme 37**) <1999JHC857>.

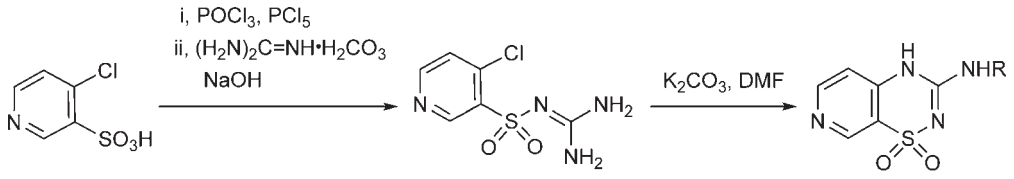
Kidwai *et al.* reported the preparation of a series of 3-substituted quinolino[3,2-*e*]-1,2,4-triazines **240a–f** by the nitrosation of the hydrazones **239** with sodium nitrite in acetic acid under microwave irradiation or reflux, leading to ring closure (Equation 23) <1998IJB1063>.



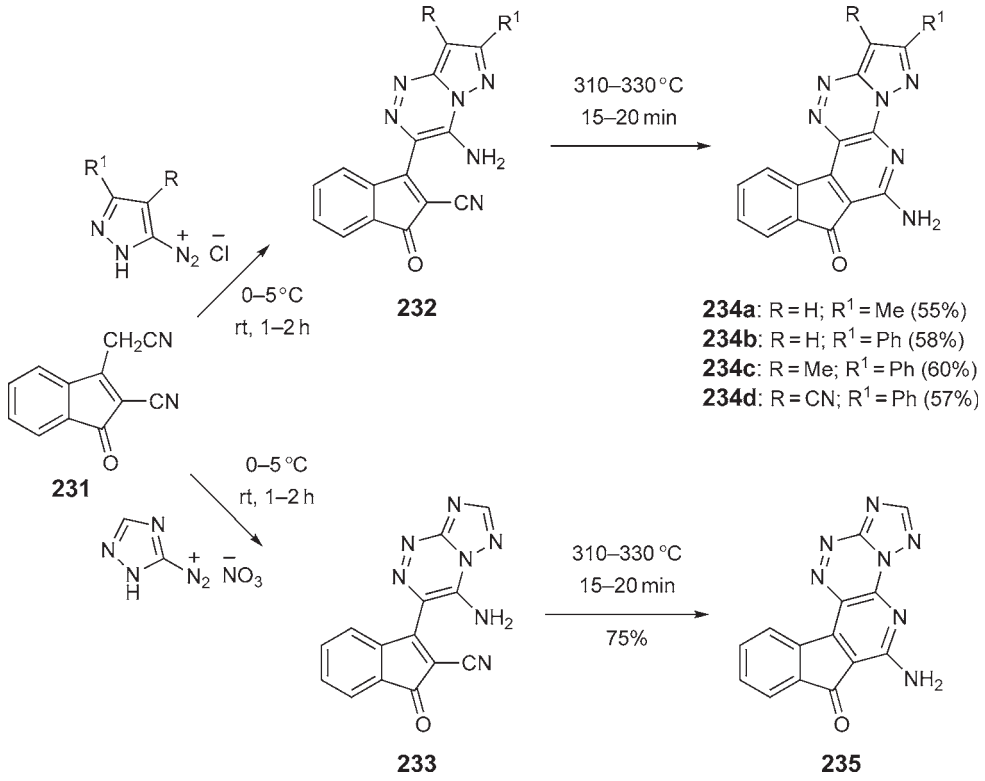
Scheme 33



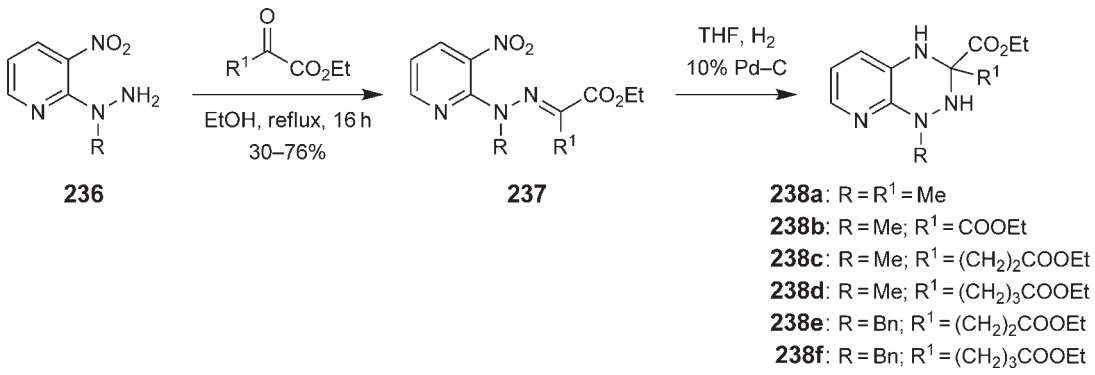
Scheme 34



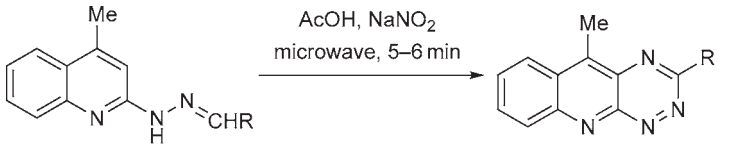
Scheme 35



Scheme 36



Scheme 37



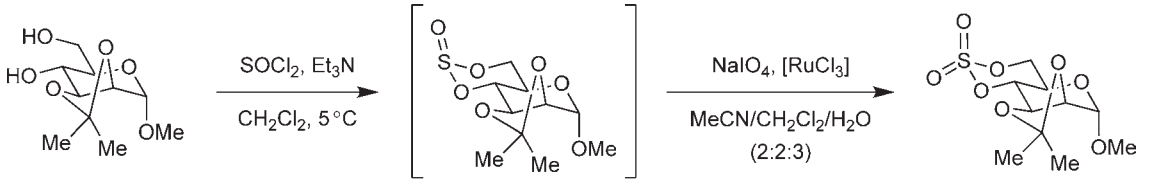
239

240a: R = Ph (70%)
240b: R = 3-$O_2NC_6H_4$ (68%)
240c: R = 2-$O_2NC_6H_4$ (80%)
240d: R = 4-ClC_6H_4 (88%)
240e: R = 4-$MeOC_6H_4$ (75%)
240f: R = 2-HOC_6H_4 (72%) (23)

10.17.9.2 Synthesis of the Second Heterocyclic Ring from [5+1] Fragments

10.17.9.2.1 Pyrano[3,2-*d*]-1,3,2-dioxathiins

Pyrano[3,2-*d*]-1,3,2-dioxathiins are most commonly found in organic synthesis as their sulfate analogs, pyrano[3,2-*d*]-1,3,2-dioxathiin 1,1-dioxides, such as the cyclic sulfate **36**, which are used as electrophilic intermediates in the synthesis of saccharide derivatives. The cyclic sulfate moiety may be attacked by a variety of nucleophiles, with regioselectivity for the least hindered carbon, to provide saccharide derivatives with a wide range of functionality. The cyclic sulfate intermediates may be prepared in good yield, even on a large scale, according to the general procedure of Gao and Sharpless <1988JA7538>. For example, cyclic sulfate **36** is obtained from methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside **241** and thionyl chloride under mild basic conditions, followed by *in situ* oxidation of the resultant sulfite **242** (**Scheme 38**) <2002TL4017>.



241

242
Not isolated

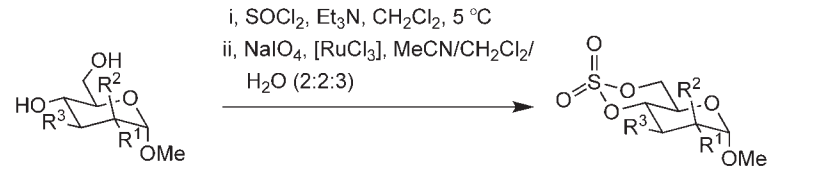
36
85% overall yield

Scheme 38

The analogous methyl α-D-glucopyranosyl **38**, **55a**, and **55b**, methyl α-D-mannopyranosyl **55c** and **55d**, and methyl α-D-galactopyranosyl **56b** and **40** cyclic sulfates may be prepared from appropriately protected methyl α-D-glucopyranosides **243a**, **243b** and **244**, methyl α-D-mannopyranosides **243c** and **243d**, and methyl α-D-galactopyranosides **245** and **246**, respectively, with minor adaptations to the Gao and Sharpless method (**Scheme 39**) <1997J(P1)1079, 1998S1778>.

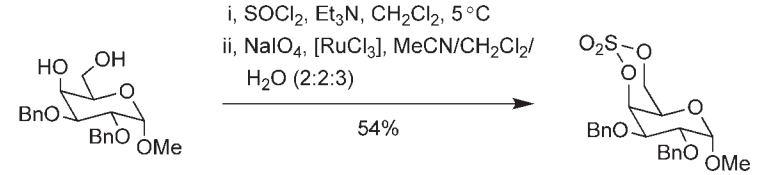
The corresponding benzyl β-D-galactopyranosyl cyclic sulfates **49** and **45**, prepared from the appropriately protected benzyl β-D-galactopyranoside **247** using the method of Gao and Sharpless <1988JA7538>, were used to study the regioselectivity of sulfate ring opening in these systems (**Scheme 40**) <2000MI311>.

Benzyl β-D-glucopyranosyl cyclic sulfate **44** can also be prepared using this methodology from the benzyl-protected β-D-glucopyranoside **248a** (Equation 24) <2006JOC1111>.

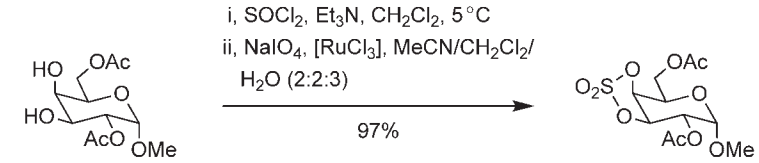


243a: $R^1 = R^3 = OBn$; $R^2 = H$
243b: $R^1 = R^3 = OAc$; $R^2 = H$
243c: $R^2 = R^3 = OBn$; $R^1 = H$
243d: $R^2 = R^3 = OAc$; $R^1 = H$
244: $R^1 = R^3 = OBz$; $R^2 = H$

55a: $R^1 = R^3 = OBn$; $R^2 = H$ (68%)
55b: $R^1 = R^3 = OAc$; $R^2 = H$ (92%)
55c: $R^2 = R^3 = OBn$; $R^1 = H$ (85%)
55d: $R^2 = R^3 = OAc$; $R^1 = H$ (90%)
38: $R^1 = R^3 = OBz$; $R^2 = H$ (68%)

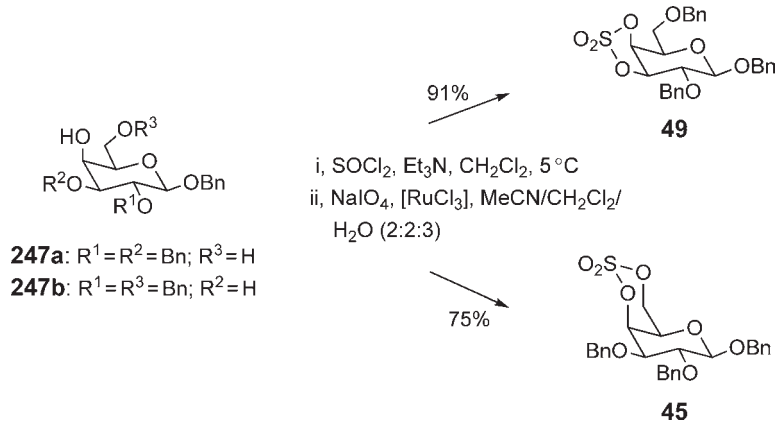


245 **56b**



246 **40**

Scheme 39

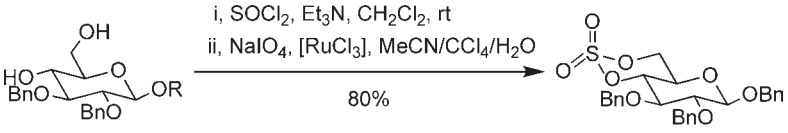


247a: $R^1 = R^2 = Bn$; $R^3 = H$
247b: $R^1 = R^3 = Bn$; $R^2 = H$

49

45

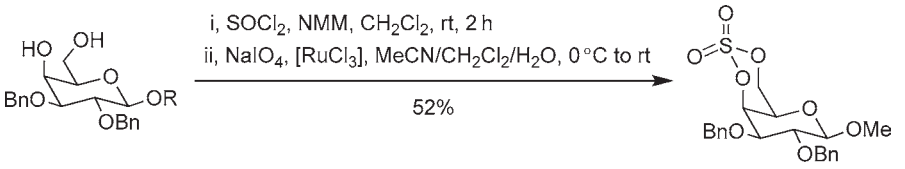
Scheme 40



248a: R = Bn **44**

(24)

The benzyl protected methyl β-D-galactoside cyclic sulfate **56** can be prepared similarly from methyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside **248b** (Equation 25) <1992S1035>.

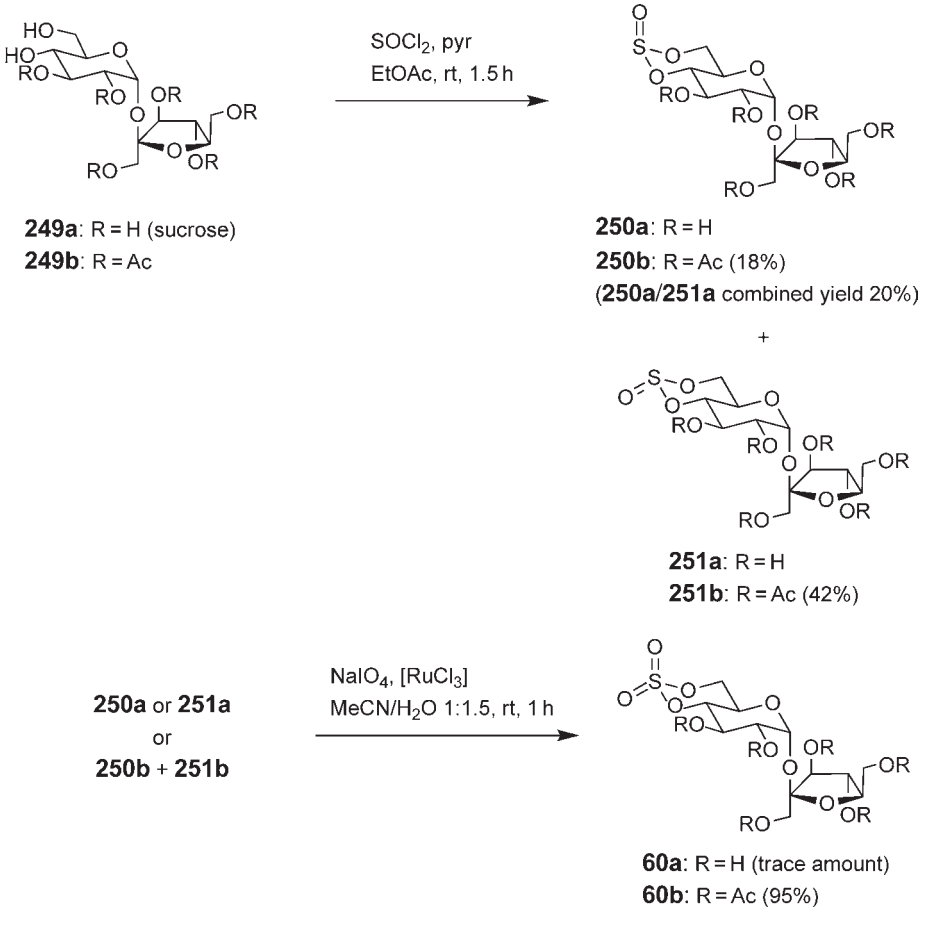


(25)

248b: R = Me

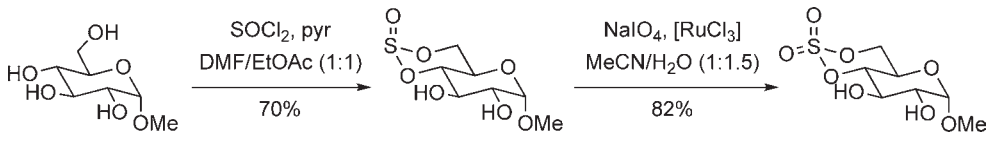
56

A range of sucrose-based surfactants **61a–e** was synthesized through the cyclic sulfite and sulfate intermediates; the cyclic sulfite diastereoisomers **250b** and **251b** were prepared from selectively acetylated sucrose **249b**. The configuration of the sulfoxide group was confirmed by ^{1}H NMR spectroscopy. Subsequent oxidation of the cyclic sulfite diastereoisomers with periodate gave the acetylated cyclic sulfate **60b**, which was deacetylated to give the glucopyranosyl 4,6-cyclic sulfate of sucrose **60a**, both in excellent yield. The same cyclic sulfate **60a** could be obtained in trace amounts from unprotected sucrose **249a**, through the sulfite diastereoisomers **250a** and **251a**, using the same preparative methods (**Scheme 41**) <1998CAR189>.



Scheme 41

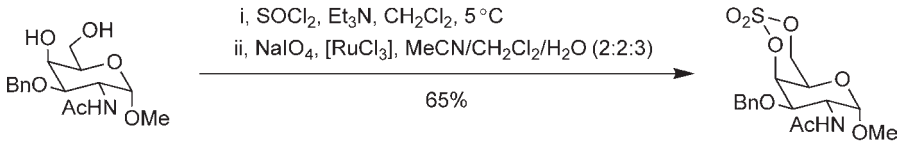
Similar surfactants based upon glucopyranose were synthesized using the Gao and Sharpless procedure for preparation of the cyclic sulfate from methyl α-D-glucopyranoside **252**; using a mixture of DMF and ethyl acetate (1:1) as solvent, the axial cyclic sulfite **253** was formed exclusively, as indicated by ^{1}H NMR spectroscopy, from which the cyclic sulfate **65** was obtained in good yield (**Scheme 42**) <1999S621>.



252 **253** **65**

Scheme 42

The methodology of Gao and Sharpless <1988JA7538> is equally applicable to glycosamines; the cyclic sulfate of methyl α-D-*N*-acetylgalactosamine **67** was prepared from methyl α-D-*N*-acetylgalactosamine **254** (Equation 26) <2003AGE5209>.

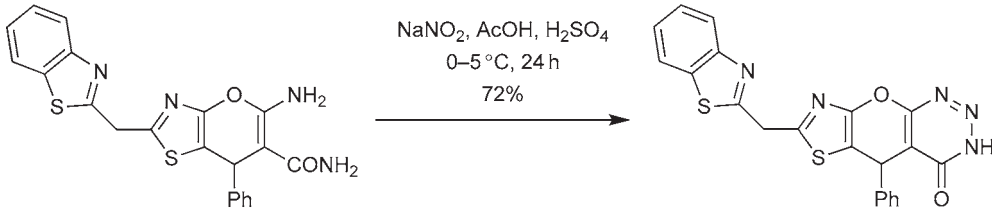


(26)

254 **67**

10.17.9.2.2 Pyrano[2,3-*d*]-1,2,3-triazines

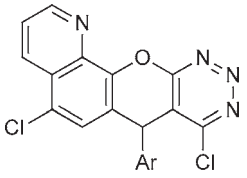
Nitrosation of pyranocarboxamide **255** with sodium nitrite in acetic acid gave the pyrano[2,3-*d*]-1,2,3-triazine **256** (Equation 27) <2003MI1061>.



(27)

255 **256**

Similar methodology gave the chlorotriazine **257** <2005HCO495>.



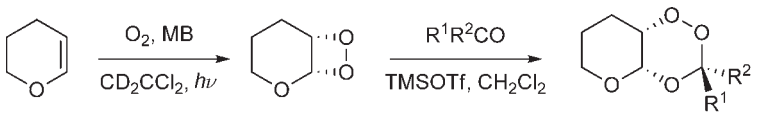
257

10.17.9.2.3 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines

Pyrano[2,3-*e*]-1,2,4-trioxines **260a–c** arise in low yield from the reaction of the appropriate alkene, 3,4-dihydro-2*H*-pyran **258**, with singlet oxygen in the presence of methylene blue (MB), followed by condensation of the intermediate oxetane **259** with acetaldehyde or acetone as appropriate (**Scheme 43**) <1997H(46)451>.

The analogous reaction of the bicyclic alkene, 5,6,7,8-tetrahydrochroman **261**, gave an epimeric mixture of the tricyclic pyrano-1,2,4-trioxane diastereoisomers **262a** and **262b** in a ratio of 1.5:1 (**Scheme 44**) <1997H(46)451>.

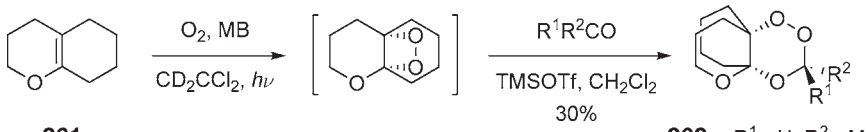
The tricyclic pyrano-1,2,4-trioxanes **264a** and **264b** were likewise achieved from the photo-oxygenation of 2-oxabicyclo[4.6.0]dodec-1(6)-ene **263**, as an epimeric mixture (**Scheme 45**) <1997H(46)451>.



258 **259**

260a: R^1 = H; R^2 = Me (16%)
260b: R^1 = Me; R^2 = H (14%)
260c: R^1 = Me; R^2 = Me (12%)

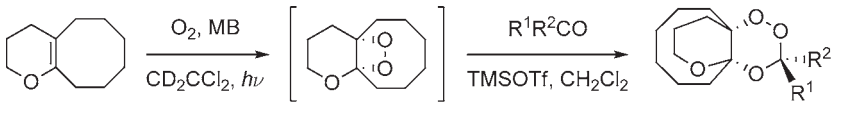
Scheme 43



261

262a: R^1 = H; R^2 = Me
262b: R^1 = Me; R^2 = H

Scheme 44



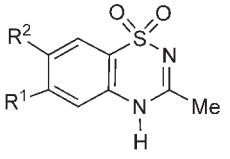
263

264a: R^1 = H; R^2 = Me
264b: R^1 = Me; R^2 = H
(overall yield 43%)

Scheme 45

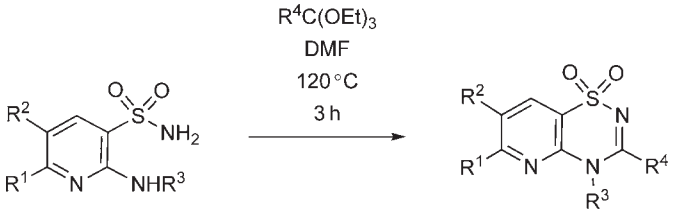
10.17.9.2.4 2*H*-Pyrido[2,3-*e*]-1,2,4-thiadiazines

1,2,4-Benzothiadiazines, such as chlorothiazide **265a** and diazoxide **265b**, have diuretic and anti-hypertensive properties <1995T3221, 1998T13645>. The anti-hypertensive activity of these compounds is increased by the presence of EWGs in the benzene ring; so a number of research groups have attempted to prepare more potent analogs through the replacement of this benzene ring by a pyridine ring, thus giving rise to the pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-oxides and their structural analogs.



265a: R^1 = Cl; R^2 = SO_2NH_2
265b: R^1 = H; R^2 = Cl

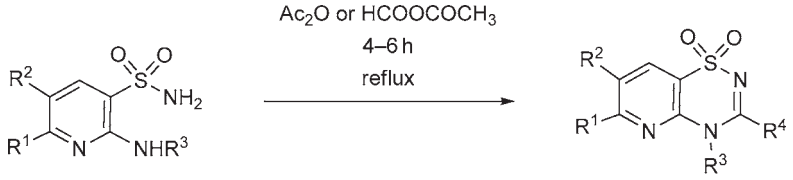
The pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-oxides **267** are readily prepared by the reaction of 2-aminopyridine-3-sulfonamides **266** with sources of C-1 units such as orthoesters (Equation 28; **Table 20**), <1998T13645, 2003S1603> and anhydrides (Equation 29; **Table 21**) <1995T3221, 2000JME1456>.



266 **267** (28)

Table 20 Pyrido[2,3-e]-1,2,4-thiadiazine 1,1-oxides **267** from the reaction of 2-aminopyridine-3-sulfonamides **266** with orthoesters

R^1	R^2	R^3	R^4	*Yield (%)*	*Reference*
H	Me	H	H	50	1998T13645
H	Me	H	Me	32	1998T13645
H	Me	H	Ph	21	1998T13645
Me	H	H	H	87	2003S1603
Me	H	H	Me	38	2003S1603

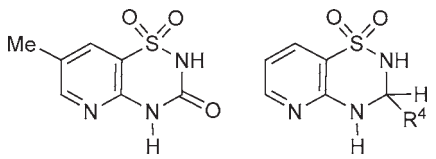


266 **267** (29)

Table 21 Pyrido[2,3-e]-1,2,4-thiadiazine 1,1-oxides **267** from the reaction of 2-aminopyridine-3-sulfonamides **266** with anhydrides

R^1	R^2	R^3	R^4	*Yield (%)*	*Reference*
H	H	H	Me	75	1995T3221
H	H	Me	Me	70	1995T3221
H	H	H	H	95	1995T3221
H	Cl	H	Me	65	2000JME1456

The 3-oxo derivative **268** has been prepared, in 29% yield, by the reaction of 2-amino-5-methylpyridine-3-sulfonamide **266** ($R^1 = R^3 = H$, $R^2 = Me$) with urea at 210 °C<1998T13645>, while the dihydro derivatives **269** are obtained from the reaction of the aminopyridinesulfonamide **266** ($R^1 = R^2 = R^3 = H$) with aldehydes in refluxing 2-propanol and ethyl acetate saturated with HCl (**Table 22**) <1998JME2946>.

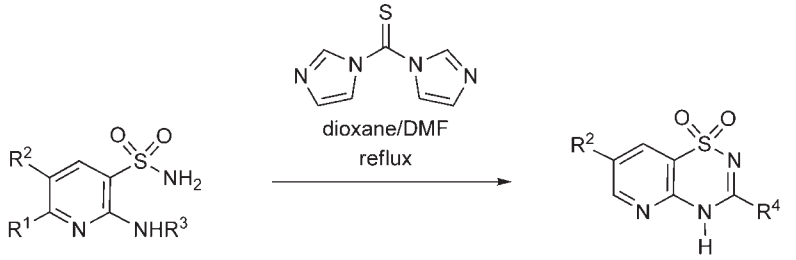


268 **269**

Table 22 Preparation of 3-substituted 3,4-dihydropyrido-[2,3-*e*]-1,2,4-thiadiazine 1,1-oxides **269** <1998JME2946>

R^4	*Yield (%)*
H	75
Me	76
Et	80
Pr	75
Pr^i	82
1′-Ethylpropyl	80
Cyclohexyl	80
Ph	75

The reaction of the aminopyridinesulfonamides **266** ($R^1 = R^3 = H$, $R^2 = H$ or Cl) with thiocarbonyl-1,1′-diimidazole in dioxane/DMF gives the 3-imidazolyl-substituted products **267** (Equation 30) <2000JME1456>.



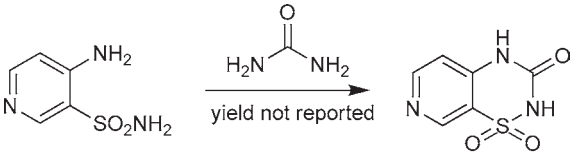
266: $R^1 = R^3 = H$; $R^2 = H$ or Cl

267a: $R^2 = H$; R^4 = 1-imidazolyl (67%)
267b: $R^2 = Cl$; R^4 = 1-imidazolyl (80%)

(30)

10.17.9.2.5 2*H*-Pyrido[4,3-*e*]-1,2,4-thiadiazines

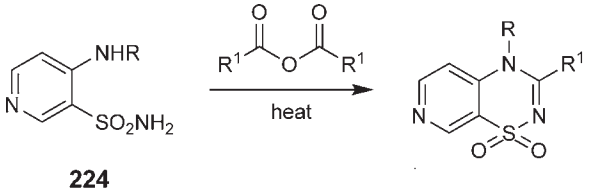
Using the same methodology as they employed in the synthesis of the 3-oxopyrido[2,3-*e*]-1,2,4-thiadiazines **268** <1998T13645>, Pirotte *et al.* prepared the 3-oxopyrido[4,3-*e*]-1,2,4-thiadiazines **196** from the 4-aminopyridine-3-sulfonamide **224** and urea (Equation 31) <1993JME3211>.



224 **196**

(31)

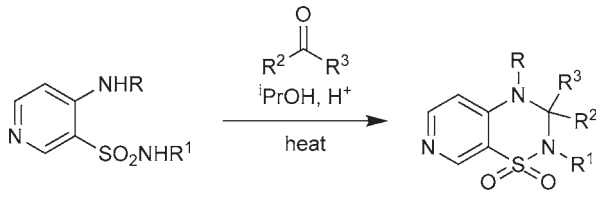
This group also prepared a number of substituted pyrido[4,3-*e*]-1,2,4-thiadiazines **197**, **269**, **270**, and **271** by the reaction of suitably substituted aminopyridinesulfonamides **224** with a range of C-1 units, such as anhydrides (Equation 32), <1996JME937> aldehydes (Equation 33, **Table 23**) <1998JME2946>, and 1,1′-thiocarbonyldiimidazole (**Scheme 46**) <1998T4935>.



224

269a: R = R^1 = Me (n.r.)
269b: R = $CHMe_2$; R^1 = Me (80%)
269c: R = *cyclo*-C_6H_{11}; R^1 = Me (65%)
269d: R = *cyclo*-C_8H_{15}; R^1 = Me (65%)
269e: R = morpholinyl; R^1 = Me (70%)
269f: R = *N*-azabicyclooctyl; R^1 = Me (60%)
269g: R = H; R^1 = Me (n.r.)
269h: R = H; R^1 = Et (50%)
269i: R = H; R^1 = Pr (55%)
269j: R = H; $R^1 = Pr^i$ (45%)
269k: R = H; $R^1 = Bu^t$ (45%)

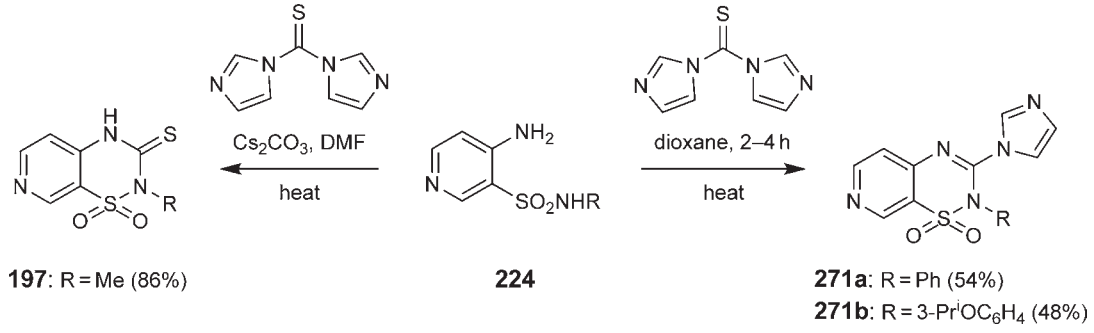
(32)



224 **270** (33)

Table 23 Substituted aminopyridinesulfonamides **270** from 4-aminopyridine-3-sulfonamides **224** and aldehydes

R	R^1	R^2	R^3	*Yield (%)*
H	H	H	H	75
H	H	H	Me	76
H	H	H	Et	80
H	H	H	Pr	75
H	H	H	Pr^i	82
H	H	H	$CHEt_2$	80
H	H	H	*cyclo*-C_6H_{11}	80
H	H	H	Ph	75
H	Me	H	H	45
H	Pr^i	H	H	60
H	C_5H_{11}	H	H	55
H	*cyclo*-C_6H_{11}	H	H	63
H	Ph	H	H	35
H	Me	H	Me	65
Me	H	H	H	66
Et	H	H	H	90
CH_2CF_3	H	H	H	75
Pr^i	H	H	H	85
Bu	H	H	H	80
C_5H_{11}	H	H	H	72
cyclo-C_6H_{11}	H	H	H	81
Me	H	H	Me	50
Me	H	H	Et	41

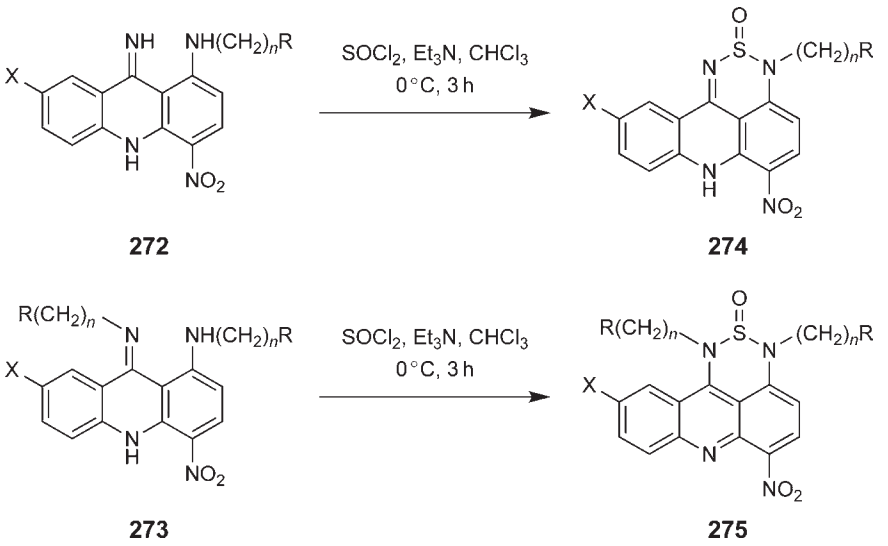


197: R = Me (86%) **224** **271a**: R = Ph (54%)
271b: R = 3-$Pr^iOC_6H_4$ (48%)

Scheme 46

10.17.9.2.6 1*H*-Pyrido[4,3-*c*]-1,2,6-thiadiazines

The 1,2,6-thiadiazino[3,4,5-*kl*]acridine analogs **274** and **275** of the pyrimido[4,5,6-*kl*]acridine DNA-binding antitumor agents were prepared by the reaction of the alkylaminoiminodihydroacridines **272** or their 9-alkylimino analogs **273** with thionyl chloride in $Et_3N/CHCl_3$ at 0 °C. These novel DNA binders show a preference for A–T binding sites (**Scheme 47**, **Table 24**) <2003BMC399>.



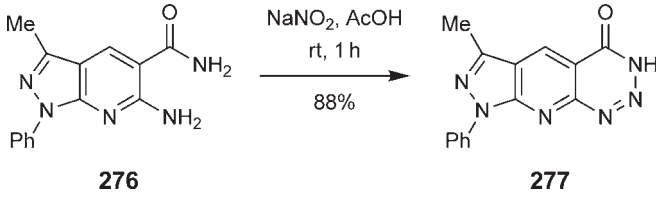
Scheme 47

Table 24 1,2,6-Thiadiazino[3,4,5-*kl*]acridine analogs **274** and **275** from the reaction of the alkylaminoiminodihydroacridines **272** or their 9-alkylimino analogs **273**

Compound	*X*	*n*	*R*	*Yield (%)*
274a	OMe	2	NMe_2	59
274b	OMe	3	NMe_2	77
274c	OMe	2	NEt_2	69
274d	H	2	NMe_2	50
274e	H	3	NMe_2	49
274f	H	2	NEt_2	29
274g	H	2	Piperidino	34
274h	Me	2	NMe_2	73
274i	Me	3	NMe_2	54
274j	Me	2	NEt_2	59
274k	Me	2	Piperidino	40
275a	OMe	2	NMe_2	65
275b	OMe	3	NMe_2	47

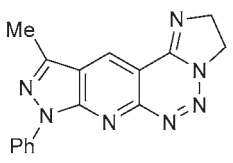
10.17.9.2.7 Pyrido[2,3-*d*]-1,2,3-triazines

Nitrosation of the aminonicotinamide **276** with sodium nitrite in acetic acid gave the pyridotriazine **277** (Equation 34) <1998JRM231>.

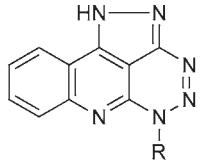


(34)

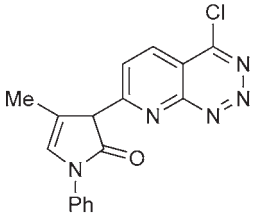
This group and others have extended this methodology to the preparation of the imidazolopyrazolopyridine **278** <2000PHA356> and pyridotriazines **279**, <2001SC1971> **280**, <2002JHC309> and **281** <2005JHC567>.



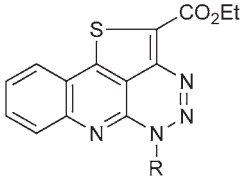
278



279



280

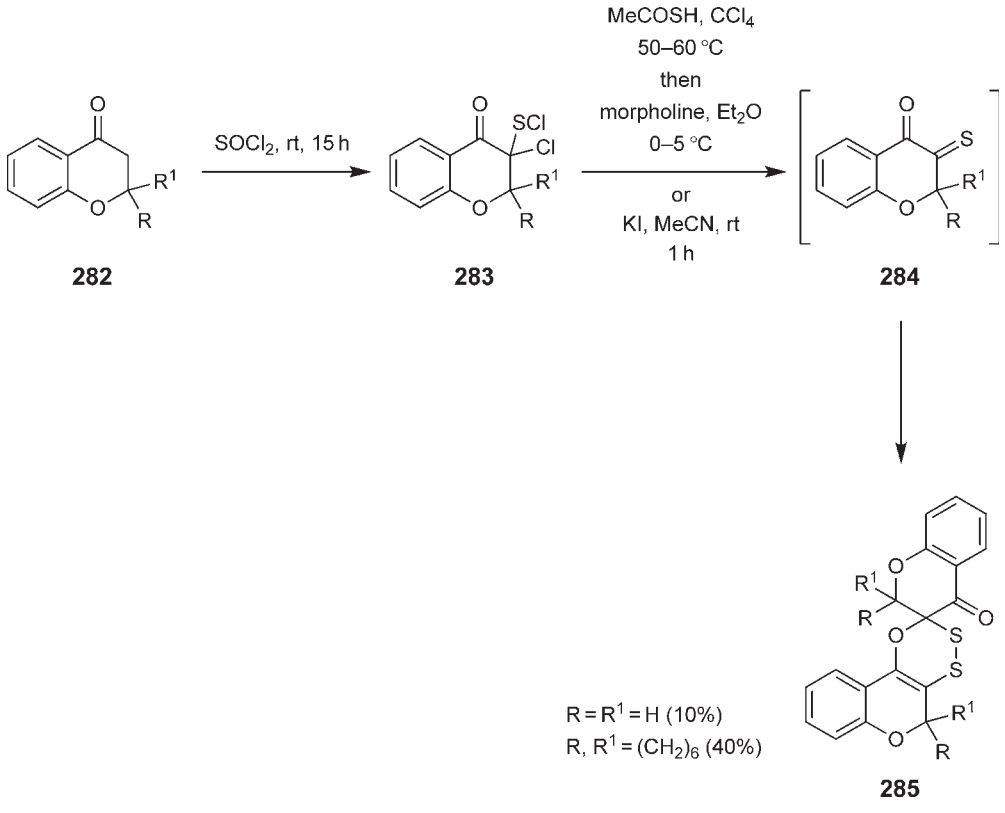


281a: R = Bu (77%)
281b: R = *c*-C_6H_{11} (89%)
281c: R = Bu^i (73%)

10.17.9.3 Synthesis of the Second Heterocyclic Ring from [4+2] Fragments

10.17.9.3.1 *3H,6H*-Pyrano[3,4-*e*]-1,3,4-oxadithiins

The reaction of 4-oxochromanones **282** with thionyl chloride gives α-chlorosulfenyl chlorides **283**. Treatment of these sulfenyl chlorides with potassium iodide or thioacetic acid followed by morpholine gives rise to the chroman-4-one thiosulfine intermediates **284**, which can dimerize in a Diels–Alder reaction to give the chromeno[3,4-*e*]-1,3,4-oxadithiin-4-one **285**, for example, R, $R^1 = (CH_2)_6$, R = R^1 = H, in low yield (**Scheme 48**) <1998JOC9840, 2002ZNB922>.



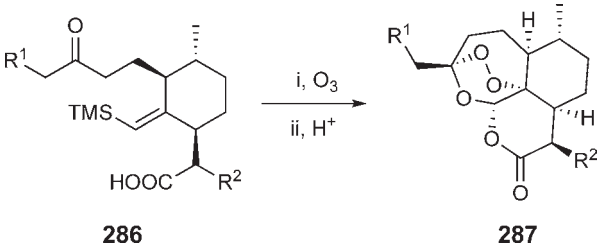
282 283 284 285

Scheme 48

10.17.9.3.2 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines

Exposure of keto acids **286** to ozone at low temperature followed by purging with excess ozone and the addition of silica gel and aqueous sulfuric acid led, over several days, to the clean formation of the desired tetracyclic artemisinin analogs **287** modified at C-3 and C-9 (Equation 35; **Table 25**) <1996JME2900>.

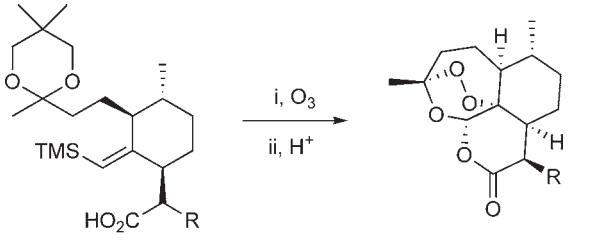
Similar transformations were described in which ozonolysis of the keto-protected carboxylic acid **288** gave C-9-modified artemisinin analogs **289** (Equation 36; **Table 26**) <2002JME4321>.



286 **287** (35)

Table 25 Synthesis of artemisinin analogs **287** <1996JME2900>

R^1	R^2	*Yield (%)*	R^1	R^2	*Yield (%)*
Me	H	62	Me	*n*-Bu	26
Et	H	58	$PhCH_2$	*n*-Bu	25
n-Pr	H	55	*n*-Pr	*n*-Bu	29
$MeOCH_2CH_2$-	H	49	$EtOCH_2CH_2$-	*n*-Bu	21
$EtOOCCH_2$-	H	26	$PhCH_2CH_2CH_2$-	*n*-Bu	27
p-$ClC_6H_4CH_2CH_2$-	H	63	*p*-$ClC_6H_4CH_2CH_2$-	*n*-Bu	27
$PhCH_2CH_2CH_2$-	H	44			

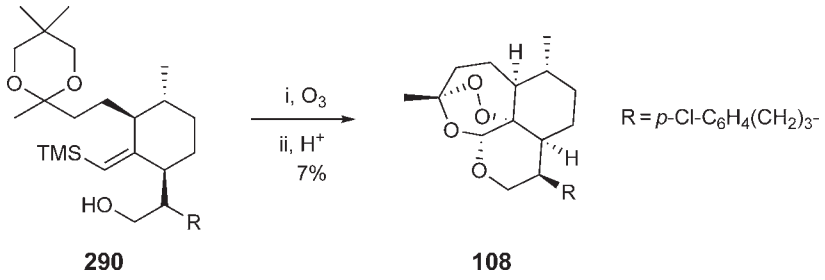


288 **289** (36)

Table 26 Synthesis of C-9-modified artemisinin analogs **289** <2002JME4321>

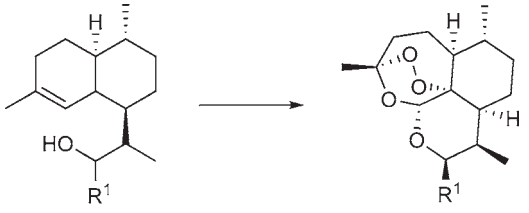
R	*Yield (%)*	*R*	*Yield (%)*
n-Bu-	27	*p*-$FC_6H_4(CH_2)_2$-	25
$Ph(CH_2)_2$-	28	*p*-$MeOC_6H_4(CH_2)_2$-	34
p-$ClC_6H_4(CH_2)_2$-	39	2,3-$Cl_2C_6H_3(CH_2)_2$-	31

The ozonolysis/cyclization of the corresponding alcohol **290** to give the less-oxidized 10-deoxoartemisinin **108** has been accomplished, but only in a suprisingly low yield (Equation 37) <1996JME4149>.



290 **108** (37)

Photooxidative cyclization of alcohols **291**, in the presence of oxygen and rose bengal using a 500 W tungsten lamp at −40 °C, followed by treatment with trifluoroacetic acid (TFA), gave various C-10-substituted dihydroartemisinin analogs **142** (Equation 38; **Table 27**) <1997BML1091, 2002JME4940, 2003JME987>.



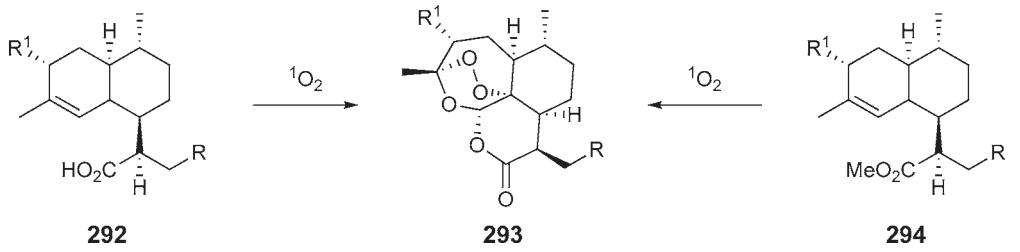
291 **142** (38)

Table 27 Photooxidative cyclization of alcohols **291** to give C-10-substituted dihydroartemisinin analogs **142**

R^1	*Yield (%)*	*Reference*
Et	n.r.[a]	1997BML1091
n-Bu	n.r.	1997BML1091
$PhCH_2$	n.r.	1997BML1091
$CH_2{=}CHMe_2$	n.r.	1997BML1091
$HO_2C(CH_2)_3$	n.r.	1997BML1091
4-$(CH_2{=}CH)C_6H_4CH_2CH_2$	35	2002JME4940
$CH_2{=}CH(CH_2)_2$	41	2003JME987
$Br(CH_2)_2$	40	2003JME987

[a]n.r. = not reported.

Oxidation of acid **292** (R = *n*-C_4H_9, R^1 = H) and phenylpropyl acid **292** (R = $C_6H_5(CH_2)_2$, R^1 = H) using singlet oxygen, followed by acid treatment, gave 9β-pentyl artemisinin **293** (R = *n*-C_4H_9, R^1 = H) (40%) and 9β-propylphenylartemisinin **293** ($C_6H_5(CH_2)_2$, R^1 = H) (38%) <1997TL6173, 1998SC1555>. The same method was used for the synthesis of artemisinin itself **9a** (R = R^1 = H) <1996SC321>. 3β-Hydroxyartemisinin **293** (R = H, R^1 = OH) was synthesised from **292** (R = H, R^1 = OH) via singlet oxygen oxidation followed by aerial (triplet oxygen) oxidation <1999JNP790>. Dihydroartemisinic acid **292** (R = R^1 = H) was converted into artemisinin when exposed to light and air, catalyzed by chlorophyll a, in mineral oil, suggesting that this process might be a non-enzymatic conversion in plants <1999JNP430>. Photooxygenation of modified 12-methyl artemisinate derivatives **294** yielded eight new artemisinin analogs **293** (**Scheme 49**; **Table 28**) <2001JNP1201>.



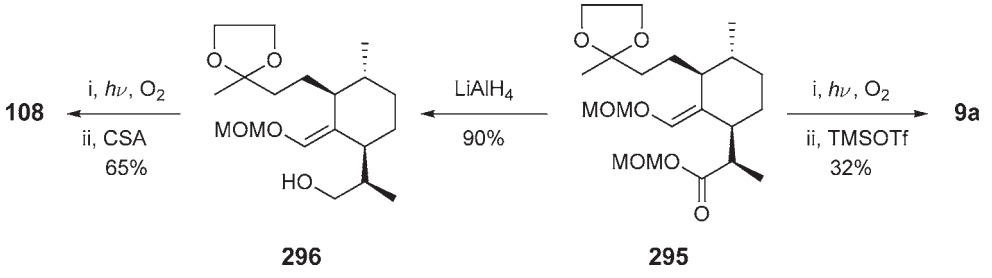
292 293 294

Scheme 49

Table 28 Photooxygenation of methyl artemisinate derivatives **294** <2001JNP1201>

Precursor	R^1	*R*	*Yield* **293** *(%)*	*Precursor*	R^1	*R*	*Yield* **293** *(%)*
294a	H	CN	5	**294e**	H	CH_2NO_2	10
294b	H	CO_2Me	4	**294f**	H	$CH(CH_3)NO_2$	27
294c	H	OMe	24	**294g**	OH	H	8
294d	H	SO_2Et	6	**294h**	OAc	H	3

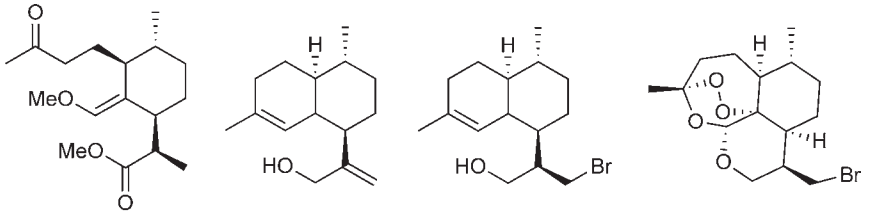
An improved preparation of artemisinin **9a** and 10-deoxoartemisinin **108** has been described which uses the photooxygenation of protected keto ester **295** and alcohol **296**, respectively (**Scheme 50**) <1998JNP633, 1998T319>. The mechanism of these cyclizations has been investigated.



296 295

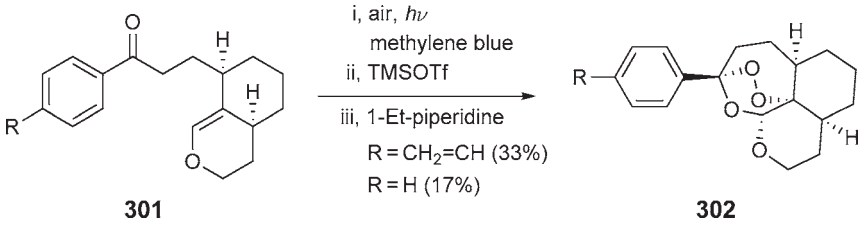
Scheme 50

The photoxidation of methyl vinyl ether **297** followed by treatment with $HClO_4$ formed artemisinin **9a** in 10% yield <2003ARK125, 2003TL387>, while photooxidative cyclization of the alcohol **298** with oxygen, rose bengal, and irradiation, followed by *in situ* treatment with TFA, gave deoxoartemisitene **115** in 35% yield. Similar photooxidation of **299** gave 13-bromodeoxoartemisinin **300** smoothly in 30% yield <2001TL3997, 2004BML2001>.



297 298 299 300

The successful photooxygenation of keto vinyl ether **301** to styryltrioxane **302**, with exclusive formation of the 12*R*-pyran stereoisomers, has been reported (Equation 39) <2002JME3824>.

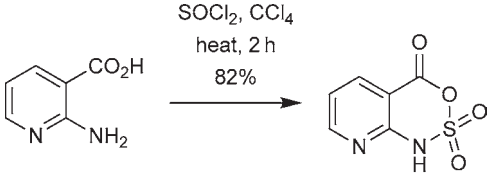


301 **302** (39)

Dihydroartemisinic acid **292** undergoes slow spontaneous autooxidaton to artemisinin **9a** and other products reported from *A. annua*. The mechanism of this complex process has been investigated in detail <2002T897, 2004T1125> and the role of the 12-carboxylic acid group elucidated <2002T909>.

10.17.9.3.3 Pyrido[3,2-*d*]-1,2,3-oxathiazines

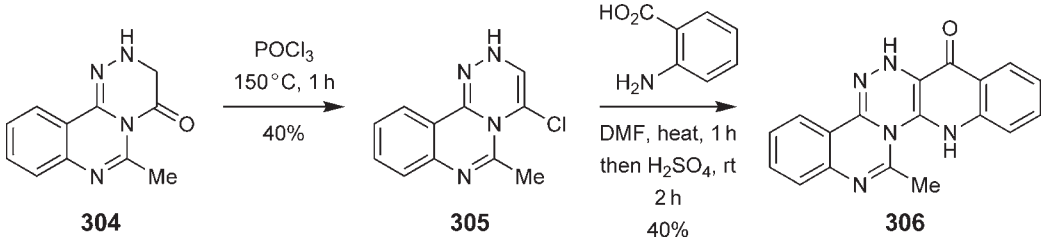
The azathio isatoic anhydride **99** has been prepared by the reaction of 2-aminonicotinic acid **303** and thionyl chloride in CCl_4 <2001JOC4413>, benzene, or cyclohexane as the solvent (Equation 40) <2004TL1377>.



303 **99** (40)

10.17.9.3.4 Pyrido[2,3-*e*]-1,2,4-triazines

Chlorination of the known triazinone **304** <1989IJB647>, followed by reaction with anthranilic acid, gave the benzopyrido[2′,3′:5,6]-1,2,4-triazino[4,3-*c*]quinazolinone **306** (**Scheme 51**) <1996IJB1026>.

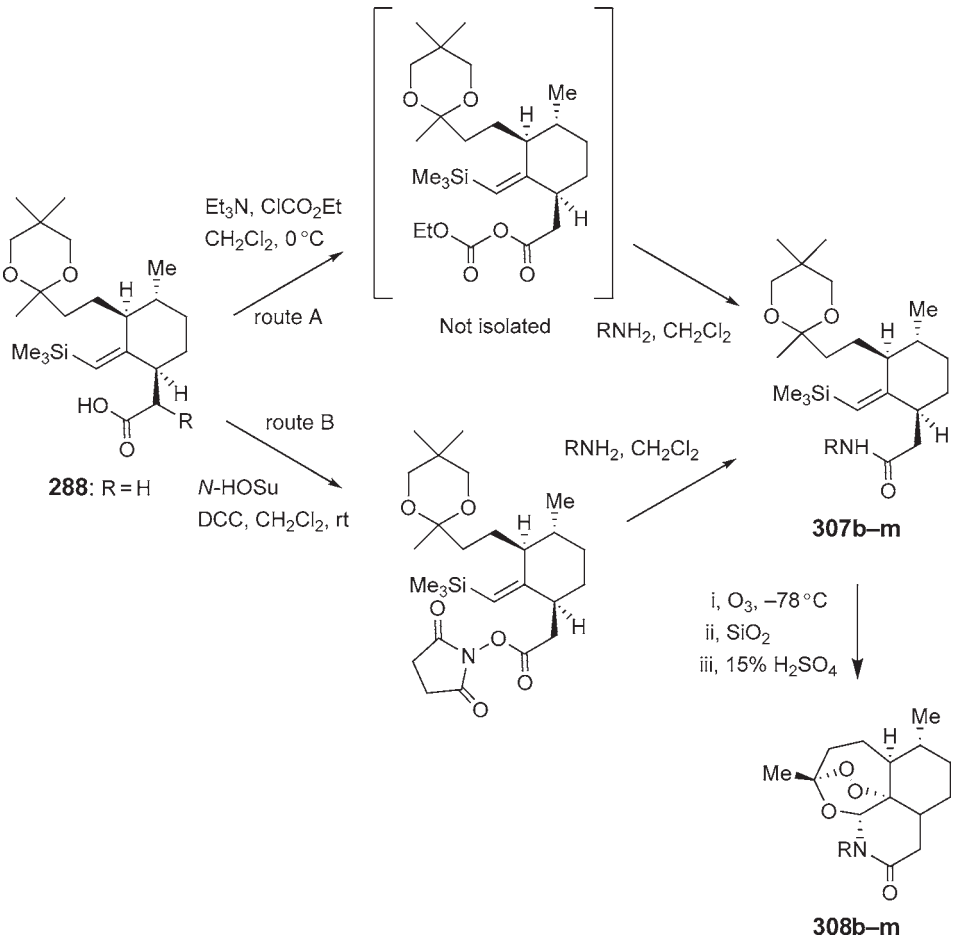


304 **305** **306**

Scheme 51

10.17.9.3.5 Pyrido[2,3-*e*]-1,2,4-trioxines

In an analogous manner to artemisinin **9a**, 11-azaartemisinin and 11-aza-9-desmethylartemisinin **308a** (R = H) were obtained from an entirely synthetic route <1992JA974>, which was subsequently used to prepare a number of N-substituted analogs of 11-aza-9-desmethylartemisinin **308b–m** via the amides **307b–m** from the synthetic carboxylic acid intermediate **288** (R = H) (**Scheme 52**; **Table 29**) <1995JME5038>. The loss of the 9-methyl group did not cause any substantial loss of activity, while increased potency over artemisinin was achieved with some of the N-substituted 11-azaartemisinin analogs **308b–m** <1995JME5038>.



Scheme 52

Table 29 Synthesis of amide precursors **307b–m** for the synthesis of 11-aza-9-desmethylartemisinin derivatives **308b–m** <1995JME5038>

Amide **307**	*R*	*Route*	*Yield (2steps) (%)*	*Product* **308**	*Yield (%)*
b	CH_3	B	87	**b**	n.r.[a]
c	$CH_2CH_2CH_3$	A	81	**c**	24
d	*i*-C_4H_9	A	84	**d**	61
e	*n*-C_5H_{11}	A	91	**e**	51
f	*i*-C_5H_{11}	A	78	**f**	65
g	$CH_2CH_2N(CH_3)_2$	A	71	**g**	n.r.
h	$CH_2CO_2C(CH_3)_3$	A	n.r.	**h**	35
i	$CH_2C_6H_5$	A	95	**i**	25
j	$CH_2C_6H_4$-*p*-Cl	A	82	**j**	42
k	$(CH_2)_2C_6H_5$	A	78	**k**	83
l	$(CH_2)_3C_6H_5$	A	80	**l**	78
m	$(CH_2)_5CO_2H$	B	n.r.	**m**	n.r.
	CH_2CO_2H			**n** (from **308h**)	n.r.

[a]n.r. = not reported.

10.17.9.4 Synthesis of the Second Heterocyclic Ring from [3+3] Fragments

There has been no work published in this area since CHEC-II(1996) <1996CHEC-II(7)625>.

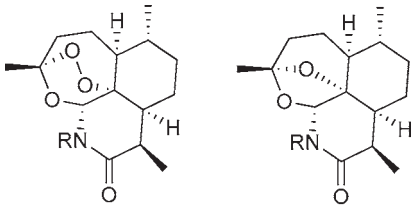
10.17.9.5 Synthesis of the Second Heterocyclic Ring by Miscellaneous Routes

There has been no work published in this area since CHEC-II(1996) <1996CHEC-II(7)625>.

10.17.10 Ring Syntheses by Transformation of Another Bicyclic System

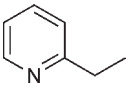
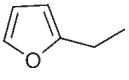
10.17.10.1 3*H*,6*H*-Pyrano[2,3-*e*]-1,2,4-trioxines

A complex mixture of products results from the reaction of a methanolic solution of artemisinin **9a** with ammonia or alkylamines, which, on treatment with dilute H_2SO_4/SiO_2, yielded the appropriate 11-azaartemisinins **309** along with some 10-azadeoxyartemisinine **310** as a minor product (**Table 30**) <1995TL829, 1995JME5045, 2003MOL901, 1999JNP54>. In CH_2Cl_2 in the presence of benzylamine, artemisinin **9a** transfers an oxygen atom from the intermediate, ring-opened, hydroperoxide to tertiary amines (e.g., Et_3N) to form *N*-oxides and *N*-benzyl-11-azadeoxyartemisinin **310** (R = Bn) selectively <1999TL4715>.



309 **310**

Table 30 Synthesis of N-substituted 11-azaartemisinin analogs **309**

R	*Yield* **309** *(%)*	*Yield* **310** *(%)*	*Reference*
H	45	9	1995TL829
Isobutyl	45	4	1995TL829
Allyl	45	15	1995TL829, 2000H(53)261
Methyl	17	8	1995JME5045
Benzyl	65		1995JME5045
$HOCH_2CH_2$	10		2003MOL901
	39	5	1995JME5045
	28		1995JME5045

Ozonolysis of the *N*-allyl-substituted product **309** (R = allyl) gave *N*-(2′-acetaldehydo)-11-azaartemisinin in 60% yield, which showed significantly higher antimalarial activity than artemisinin <1995JME5045>.

10.17.11 Synthesis of Particular Classes of Compounds and Comparison of Routes Available

The compounds belonging to this class which have been the most studied are artemisinin (a 3*H*,6*H*-pyrano[2,3-*e*]-1,2,4-trioxine) and its 11-aza analog (a pyrido[2,3-*e*]-1,2,4-trioxine) and the various routes to these classes of compounds have been described in detail in Sections 10.17.9.2.3, 10.17.9.3.2, and 10.17.9.3.5.

10.17.12 Important Compounds and Applications

As stated earlier, we have not attempted to provide a full account of the large amount of published work on artemisinin **9a** but have concentrated on the main features of this unique ring system. More details of the large number of derivatives synthesized and the mode of action, etc., are available from the following published reviews: <1995MI569, 1999MI1125, 1999JHC1599, 1999H(51)1681, 1999PAC1139, 2001COR601, 2001PAC1173, 2001CME1803, 2001CME1827, 2002ACR167, 2002ACR255, 2003CME2197, 2003COR1231, 2004CME1265, 2004ACR397, 2004JME2945, 2004MI503, 2005MI509, 2006OPP1>.

The 3-alkylamino-4*H*-pyrido[4,3-*e*]-1,2,4-thiadiazine 1,1,-dioxides, BPDZ44 **199c** and BPDZ62 **199d**, are exceedingly potent drugs acting on pancreatic K_{ATP} (adenosine triphosphate sensitive K^+ channels) and strongly inhibit insulin release as a result of their K_{ATP} channel-opening properties <1998T4935>.

10.17.13 Further Developments

Since this chapter was prepared, the only chemical developments in compounds belonging to this class have involved artemisinin and its derivatives, and some of these will be summarized here. Using combustion calorimetry, Liu and co-workers have determined the standard molar enthalpies of formation of artemisinin **9a**, artemether **28a** and artesunate **31** as −1493, −2420 and −3320 kJ mol^{-1}, respectively, and the thermal stabilities of these compounds were also investigated by thermal analysis in combination with FT-IR <2007MI1045>.

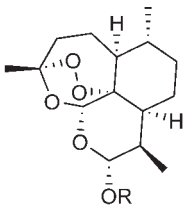
A high performance thin layer chromatography (HPTLC) method has been developed for artemether **28a**, employing silica gel 60F_{254} as the stationary phase and toluene–ethyl acetate–formic acid (8:2:0.3) as the mobile phase <2007MI839>, while a method for the determination of artemisinin **9a** from *Artemisia annua* L. has been developed involving reverse phase HPLC in combination with evaporative light scattering <2006MI487>. A range of solvents have been evaluated for the extraction of artemisinin from *Artemisia annua* L. and it was concluded that hydrofluorocarbons and ionic liquids could compete with hexane in terms of cost effectiveness and efficiency <2006JNP1653>.

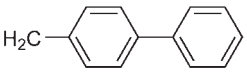
The mechanism of the anti-malarial activity of artemisinin **9a** has been the subject of a number of investigations, <2006BMC2082, 2006BMC2972, 2006MI562> while the use of artemisinin as a lead in anti-cancer, anti-viral, and anti-fungal drug discovery has been reviewed <2007MI411>, and a quantitative structure activity relationship developed for 3*H*,6*H*-pyrano[2,3-*e*]-1,2,4-trioxine anti-malarial agents. <2006BMC2333>.

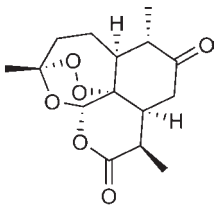
Most studies have concentrated on the synthesis of new active artemisinin analogs. A series of highly lipophilic ether derivatives have been prepared and tested and the two most active compounds **311a**,**b** provided 100% protection to *Plasmodium yoelii nigeriensis* infected mice <2006JME7227>.

Other new ethers have been prepared and tested for their cytotoxicity towards lymphocytes <2006BMC8043>; a new ketone, artemisitone-9 **312** has been obtained from the biotransformation of artemisinin by *Streptomyces griseus* <2006BML1909>, four new non-acetal, hydrolytically stable derivatives **313** have been prepared and tested as inhibitors of *Toxoplasma gondii* <2006AAC4206>, a new isoxazoline cycloadduct **314** has been prepared in low yield <2007MOL395>; and a library of C-16 modified analogs has been prepared and tested for their antiparasitic activity <2006MI729>.

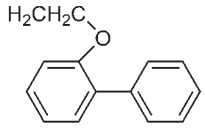
Finally, gem-difluoromethylene analogs, e.g., **315** and **316**, designed to mimic artemisinin, have been prepared by the treatment of the trifluoromethyl derivatives **169** and **173** with 2 equiv of MeLi in THF at −78 °C, and their anti-malarial activity investigated (**Scheme 53**) <2006JFC637>.

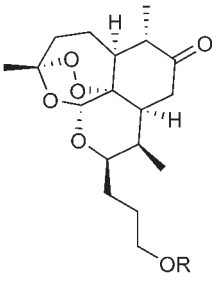


311a R = 

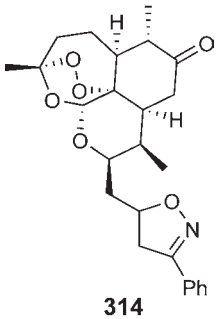


312

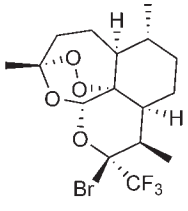
311b R = 



313 R = H, COPh, $CO_2C_6H_4Br$-2, $CH_2CH_2CH(Me)CH_2CH_2CH{=}CMe_2$

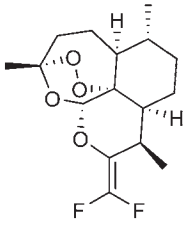


314

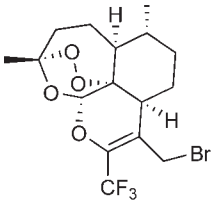


169

MeLi
2 equiv.
THF, –78 °C

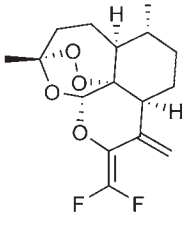


315



173

MeLi
2 equiv.
THF, –78 °C



316

Scheme 53

References

1979MI129 J.-M. Liu, M.-Y. Ni, J.-F. Fan, Y.-Y. Tu, Z.-H. Wu, Y.-L. Wu, and W.-S. Chou, *Huaxue Xuebao*, 1979, **37**, 129 (*Chem. Abstr.*, 1980, **92**, 94594w).
1985JOC4504 A. J. Lin, D. L. Klayman, J. M. Hoch, J. V. Silverton, and C. F. George, *J. Org. Chem.*, 1985, **50**, 4504.
1986MI153 Y.-L. Wu and J.-L. Zhang, *Youji Huaxue*, 1986, 153 (*Chem. Abstr.*, 1986, **105**, 191426n).
1988JA7538 Y. Gao and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 7538.
1988JME645 A. Brossi, B. Venugopalan, L. Dominguez Gerpe, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. Milhous, and W. Peters, *J. Med. Chem.*, 1988, **31**, 645.
1989IJB647 Z. El-Gendy and R. M. Abdel-Rahman, *Indian J. Chem., Sect. B*, 1989, **28**, 647.
1989TL5973 M. Jung, X. Li, D. A. Bostos, H. N. ElSohly, and J. D. McChesney, *Tetrahedron Lett.*, 1989, **30**, 5973.
1990JME1516 M. Jung, X. Li, D. Bustos, H. ElSohly, J. McChesney, and W. K. Milhous, *J. Med. Chem.*, 1990, **33**, 1516.
1992CC1494 T. Bamhaoud, J. M. Lancelin, and J. M. Beau, *J. Chem. Soc., Chem. Commun.*, 1992, 1494.
1992JA974 M. A. Avery, W. K. M. Chong, and C. Jennings-White, *J. Am. Chem. Soc.*, 1992, **114**, 974.
1992S1035 B. B. Lohray, *Synthesis*, 1992, 1035.
1993JME3211 B. Pirotte, P. de Tullio, P. Lebrun, M.-H. Antoine, J. Fontaine, B. Masereel, M. Schynts, L. Dupont, A. Herchuelz, and J. Delarge, *J. Med. Chem.*, 1993, **36**, 3211.
1994TL2129 Y. M. Pu, B. Yagen, and H. Ziffer, *Tetrahedron Lett*, 1994, **35**, 2129.
1995AXC2064 L. Dupont, B. Pirotte, P. de Tullio, B. Masereel, and J. Delarge, *Acta Cryst., Sect. C*, 1995, **51**, 2064.
1995BML1791 Y.-H. Yang, Y. Li, Y.-L. Shi, J.-D. Yang, and B.-A. Wu, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1791.
1995EJM697 B. Venugopalan, P. J. Karnik, C. P. Bapat, D. K. Chatterjee, N. Iyer, and D. Lepcha, *Eur. J. Med. Chem.*, 1995, **30**, 697.
1995JA5885 G. H. Posner, J. N. Cumming, P. Ploypradith, and C. H. Oh, *J. Am. Chem. Soc.*, 1995, **117**, 5885.
1995JCH(B)183 D. L. Mount, G. D. Todd, and V. Navaratnam, *J. Chromatogr. B*, 1995, **666**, 183.
1995JME613 Y. M. Pu and H. Ziffer, *J. Med. Chem.*, 1995, **38**, 613.
1995JME764 A. J. Lin and R. E. Miller, *J. Med. Chem.*, 1995, **38**, 764.
1995JME1911 K. Ramu and J. K. Bakert, *J. Med. Chem.*, 1995, **38**, 1911.
1995JME1922 B. Venugopalan, C. P. Bapat, P. J. Karnik, D. K. Chatterjee, N. Iyer, and D. Lepchat, *J. Med. Chem.*, 1995, **38**, 1922.
1995JME2311 S. Kamchonwongpaisan, S. Paitayatat, Y. Thebtaranonth, P. Wilairat, and Y. Yuthavong, *J. Med. Chem.*, 1995, **38**, 2311.
1995JME4120 Y. M. Pu, D. S. Torok, H. Ziffer, X.-Q. Pan, and S. R. Meshnick, *J. Med. Chem.*, 1995, **38**, 4120.
1995JME5038 M. A. Avery, J. D. Bonk, W. K. M. Chong, S. Mehrotra, R. Miller, W. Milhous, D. K. Goins, S. Venkatesan, C. Wyandt, I. Khan, and B. A. Avery, *J. Med. Chem.*, 1995, **38**, 5038.
1995JME5045 D. S. Torok, H. Ziffer, S. R. Meshnick, X.-Q. Pan, and A. Ager, *J. Med. Chem.*, 1995, **38**, 5045.
1995JNP751 C. D. Hufford, S. I. Kheufa, K. Y. Orabi, F. T. Wigges, R. Kumar, R. D. Rogers, and C. F. Campana, *J. Nat. Prod.*, 1995, **58**, 751.
1995JNP798 D. R. Vanderberghe, A. N. Vergauwe, M. van Montagu, and E. G. van den Eeckhout, *J. Nat. Prod.*, 1995, **58**, 798.
1995MI215 K. L. Shukla, T. M. Gund, and S. R. Meshnick, *J.Mol. Graph.*, 1995, **13**, 215.
1995MI569 Y. L. Wu and Y. Li, *Med. Chem. Res.*, 1995, **5**, 569.
1995T3221 P. de Tullio, B. Pirotte, L. Dupont, B. Masereel, D. Laeckmann, T. Podona, O. Diouf, P. Lebrun, and J. Delarge, *Tetrahedron*, 1995, **51**, 3221.
1995TL829 D. S. Torok and H. Ziffer, *Tetrahedron Lett.*, 1995, **36**, 829.
1996BML2717 A. Abouabdellah, J. P. Bégué, D. Bonnet-Delpon, J. C. Gantier, T. T. Thanh Nga, and T. Dinh Thac, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 2717.
1996CC2213 W.-M. Wu, Z.-J. Yao, Y.-L. Wu, K. Jiang, Y.-F. Wang, H.-B. Chen, F. Shan, and Y. Li, *J. Chem. Soc., Chem. Commun.*, 1996, 2213.
1996CHEC-II(7)625 A. D. M. Curtis; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, Vol. 7, p. 625.
1996IJB1026 H. A. Allimony, H. M. El-Shaaer, S. G. Abdel-Hamide, S. A. Abdel-Aziz, and R. M. Abdel-Rahman, *Indian J. Chem., Sect. B*, 1996, **35**, 1026.
1996J(P1)1015 B. Venugopalan, P. J. Karnik, and S. Shinde, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1015.
1996MI249 M. A. Avery, J. D. Bonk, and S. Mehrotra, *J. Labelled Comp.*, 1996, **38**, 249.
1996MI263 M. A. Avery, J. D. Bonk, and J. Bupp, *J. Labelled Comp.*, 1996, **38**, 263.
1996JME937 P. de Tullio, B. Pirotte, P. Lebrun, J. Fontaine, L. Dupont, M.-H. Antoine, R. Ouedraogo, S. Khelili, C. Maggetto, B. Masereel, *et al.*, *J. Med. Chem.*, 1996, **39**, 937.
1996JME1885 M. A. Avery, P. Fan, J. M. Karle, J. D. Bonk, R. Miller, and D. K. Goins, *J. Med. Chem.*, 1995, **39**, 1885.
1996JME2900 M. A. Avery, S. Mehrotra, J. D. Bonk, J. A. Vroman, D. K. Goins, and R. Miller, *J. Med. Chem.*, 1996, **39**, 2900.
1996JME4149 M. A. Avery, S. Mehrotra, T. L. Johnson, J. D. Bonk, J. A. Vroman, and R. Miller, *J. Med. Chem.*, 1996, **39**, 4149.
1996JME4511 P. M. O'Neill, L. P. Bishop, R. C. Storr, S. R. Hawley, J. L. Maggs, S. A. Ward, and B. K. Park, *J. Med. Chem.*, 1996, **39**, 4511.
1996JNP251 E. A. Abourashed and C. D. Hufford, *J. Nat. Prod.*, 1996, **59**, 251.
1996P97 J. F. S. Ferreira and J. Janick, *Phytochemistry*, 1996, **41**, 97.
1996SC321 M. G. Constantino, M. Beltrame, and G. V. J. daSilva, *Synth. Commun.*, 1996, **26**, 321.
1996TL253 R. K. Haynes and S. C. Vonwiller, *Tetrahedron Lett.*, 1996, **37**, 253.
1996TL257 R. K. Haynes and S. C. Vonwiller, *Tetrahedron Lett.*, 1996, **37**, 257.
1997AGE95 M. Hendrix, P. B. Alper, E. S. Priestley, and C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 95.
1997BMC1257 G. H. Posner, P. Ploypradith, W. Hapangama, D. Wang, J. N. Cumming, P. Dolan, T. W. Kensler, D. Klinedinst, T. A. Shapiro, Q. Yi Zheng, *et al.*, *Bioorg. Med. Chem.*, 1997, **5**, 1257.
1997BML1091 M. Jung, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1091.
1997BSB781 B. Pirotte, P. de Tullio, P. Neven, D. Dewalque, J. Delarge, D.-H. Caignard, and P. Renard, *Bull. Soc. Chim. Belg.*, 1997, **106**, 781.
1997H(46)451 C. W. Jefford, M. F. Deheza, and J. B. Wang, *Heterocycles*, 1997, **46**, 451.

1997H(45)1055 M. Jung and S. Lee, *Heterocycles*, 1997, **45**, 1055.
1997JA5968 A. Robert and B. Meunier, *J. Am. Chem. Soc.*, 1997, **119**, 5968.
1997JCH(B)145 N. Sandrenan, A. Sioufi, J. Godbillon, C. Netterb, M. Danker, and C. van Valkenburg, *J. Chromatogr. B*, 1997, **691**, 145.
1997JCH(B)259 J. Karbwang, K. Na-Bangchang, P. Molunto, V. Banmairuroi, and K. Congpuong, *J. Chromatogr. B*, 1997, **690**, 259.
1997JCH(A)353 M. Kohler, W. Haerdi, P. Christen, and J.-L. Veuthey, *J. Chromatogr. A*, 1997, **785**, 353.
1997JCM370 R. T. Brown, F. Scheinmann, and A. V. Stachulski, *J. Chem Res. (S)*, 1997, 370.
1997JME633 S. Paitayatat, B. Tarnchompoo, Y. Thebtaranonth, and Y. Yuthavong, *J. Med. Chem.*, 1997, **40**, 633.
1997JME1396 A. J. Lin, A. B. Zikry, and D. E. Kyle, *J. Med. Chem.*, 1997, **40**, 1396.
1997JNP325 A. C. Beekman, A. R. W. Barentsen, H. J. Woerdenbag, W. Van Uden, N. Pras, A. W. T. Konings, F. S. El-Feraly, A. M. Galal, and H. V. Wikstrom, *J. Nat. Prod.*, 1997, **60**, 325.
1997MI463 P. de Tullio, B. Pirotte, P. Neven, B. Masereel, D. Dewalque, O. Diouf, T. Podona, D. Caignard, P. Renard, and J. Delarge, *J. Pharm. Pharmacol.*, 1997, **49**, 463.
1997P1209 K.-L. Chan, K.-H. Yuen, H. Takayanagi, S. Janadasa, and K.-K. Peh, *Phytochemistry*, 1997, **46**, 1209.
1997J(P1)1079 J. A. Calvo-Asin, F. G. Calvo-Flores, J. M. Exposito-López, F. Hernández-Mateo, J. J. Garcia-López, J. Isac-Garcia, F. Santoyo-González, and A. Vargas-Berenguel, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1079.
1997J(P1)3435 S.-M. Hui, K.-S. Ngo, and G. D. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3435.
1997T7493 L.-K. Sy, S.-M. Hui, K.-K. Cheung, and G. D. Brown, *Tetrahedron*, 1997, **53**, 7493.
1997TL731 B. Mekonnen and H. Ziffer, *Tetrahedron Lett.*, 1997, **38**, 731.
1997TL6173 J. A. Vroman, I. A. Khan, and M. A. Avery, *Tetrahedron Lett.*, 1997, **38**, 6173.
1998ANC3084 P. Sahai, R. A. Vishwakarma, S. Bharel, A. Gulati, M. Z. Abdin, P. S. Srivastava, and S. K. Jain, *Anal. Chem.*, 1998, **70**, 3084.
1998BML1003 M. Jung and S. Lee, *Biorg. Med. Chem. Lett.*, 1998, **8**, 1003.
1998CAR189 H. G. Bazin, T. Polat, and R. J. Linhardt, *Carbohydr. Res.*, 1998, **309**, 189.
1998IJB1063 M. Kidwai, S. Kohli, A. K. Goel, and M. P. Dubey, *Indian J. Chem., Sect. B*, 1998, **37**, 1063.
1998JA3316 W.-M. Wu, Y. Wu, Y.-L. Wu, Z.-J. Yao, C.-M. Zhou, Y. Li, and F. Shan, *J. Am. Chem. Soc.*, 1998, **120**, 3316.
1998JCH(B)101 W. Blum, U. Pfaar, and J. Kuhnol, *J. Chromatogr. B*, 1998, **710**, 101.
1998JCH(B)201 K. Na-Bangchang, K. Congpuong, L. N. Hung, P. Molunto, and J. Karbwang, *J. Chromatogr. B*, 1998, **708**, 201.
1998JRM231 A. M. Hussein and T. I. El-Emary, *J. Chem. Res (M)*, 1998, 231.
1998JME2946 B. Pirotte, T. Podona, O. Diouf, P. de Tullio, P. Lebrun, L. Dupont, F. Somers, J. Delarge, P. Morain, P. Lestage, *et al.*, *J. Med. Chem.*, 1998, **41**, 2946.
1998JME4101 T. T. Thanh Nga, C. Menage, J.-P. Begue, D. Bonnet-Delpon, J.-C. Gantier, B. Pradines, J.-C. Doury, and T. Dinh Thac, *J. Med. Chem.*, 1998, **41**, 4101.
1998J(P1)2163 S. Bharel, R. A. Vishwakarma, and S. K. Jain, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2163.
1998JST87 S. Tonmunphean, S. Irle, S. Kokpol, V. Parasuk, and P. Wolschann, *J. Mol. Struct.*, 1998, **454**, 87.
1998JNP633 S. Bharel, A. Gulati, M. Z. Abdin, P. S. Srivastava, R. A. Vishwakarma, and S. K. Jain, *J. Nat. Prod.*, 1998, **61**, 633.
1998JOC9840 F. A. G. El-Essawy, S. M. Yassin, I. A. El-Sakka, A. F. Khattab, I. Søtofte, J. Ø.Madsen, and A. Senning, *J. Org. Chem.*, 1998, **63**, 9840.
1998S1778 A. Vargas-Berenguel, F. Santoyo-González, J. Calvo-Asín, F. G. Calvo-Flores, J. M. Expósito-López, F. Hernández-Mateo, J. Isac-García, and J. J. Giménez-Martínez, *Synthesis*, 1998, 1778.
1998SC1555 J. A. Vroman, H. N. ElSohly, and M. A. Avery, *Synth. Commun.*, 1998, **28**, 1555.
1998T319 D. M. Nowak and P. T. Lansbury, *Tetrahedron*, 1998, **54**, 319.
1998T4935 P. deTullio, B. Pirotte, F. Somers, S. Boverie, F. Lacan, and J. Delarge, *Tetrahedron*, 1998, **54**, 4935.
1998T13645 C. G. Neill, P. N. Preston, and R. H. Wightman, *Tetrahedron*, 1998, **54**, 13645.
1998TL1533 S. H. Woo, M. H. Parker, P. Ploypradith, J. Northrop, and G. H. Posner, *Tetrahedron Lett.*, 1998, **39**, 1533.
1999BML2969 E. Katz, J. Ma, D. Kyle, and H. Ziffer, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2969.
1999H(51)1681 A. K. Bhattacharya and R. P. Sharma, *Heterocycles*, 1999, **51**, 1681.
1999JCH(B)251 S. S. Mohamed, S. A. Khalid, S. A. Ward, T. S. M. Wan, H. P. O. Tang, M. Zheng, R. K. Haynes, and G. Edwards, *J. Chromatogr. B*, 1999, **731**, 251.
1999JHC857 F. Savelli, A. Boido, and G. Ciarallo, *J. Heterocycl. Chem.*, 1999, **36**, 857.
1999JHC1599 S. Ekthawatchai, M. Isaka, and P. Kittakoop, *J. Heterocycl. Chem.*, 1999, **36**, 1599.
1999JME300 G. H. Posner, M. H. Parker, J. Northrop, J. S. Elias, P. Ploypradith, S. Xie, and T. A. Shapiro, *J. Med. Chem.*, 1999, **42**, 300.
1999JME4275 G. H. Posner, P. Ploypradith, M. H. Parker, H. O'Dowd, S.-H. Woo, J. Northrop, M. Krasavin, P. Dolan, T. W. Kensler, S. Xie, *et al.*, *J. Med. Chem.*, 1999, **42**, 4275.
1999JME5487 P. M. O'Neill, N. L. Searle, K.-W. Kan, R. C. Storr, J. L. Maggs, S. A. Ward, K. Raynes, and B. K. Park, *J. Med. Chem.*, 1999, **42**, 5487.
1999JNP54 A. M. Galal, M. S. Ahmad, F. S. El-Feraly, and A. T. McPhail, *J. Nat. Prod.*, 1999, **62**, 54.
1999JNP430 T. E. Wallaart, W. van Uden, H. G. M. Lubberink, H. J. Woerdenbag, N. Pras, and W. J. Quax, *J. Nat. Prod.*, 1999, **62**, 430.
1999JNP790 N. Acton, *J. Nat. Prod.*, 1999, **62**, 790.
1999J(P1)1827 D. Y. Wang, Y. K. Wu, Y. L. Wu, Y. L. Ying, and F. Shan, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1827.
1999JST103 J. Gu, K. Chen, H. Jiang, and R. Ji, *J. Mol. Struct.*, 1999, **459**, 103.
1999MI125 M. A. Avery, M. Alvim-Gaston, and J. R. Woolfrey, *Adv. Med. Chem.*, 1999, **4**, 125.
1999P257 K. Y. Orabi, A. M. Galal, A.-R. Ibrahim, F. S. El- Feraly, S. I. Khalifa, and H. N. El-Sohly, *Phytochemistry*, 1999, **51**, 257.
1999PAC1139 Y. L. Wu, H. B. Chen, and K. Jiang, *Pure Appl. Chem.*, 1999, **71**, 1139.
1999S621 H. G. Bazin and R. J. Linhardt, *Synthesis*, 1999, 621.
1999T3625 H. O'Dowd, P. Ploypradith, S. Xie, T. A. Shapiro, and G. H. Posner, *Tetrahedron*, 1999, **55**, 3625.
1999TL4715 R. K. Haynes, H. H. Pai, and A. Voerste, *Tetrahedron Lett.*, 1999, **40**, 4715.
1999TL8543 J. Ma, E. Katz, and H. Ziffer, *Tetrahedron Lett.*, 1999, **40**, 8543.
1999TL9129 P. M. O'Neill, A. Miller, S. A. Ward, B. K. Park, F. Scheinmann, and A. V. Stachulski, *Tetrahedron Lett.*, 1999, **40**, 9129.
2000BMC1361 G. H. Posner, J. P. Maxwell, H. O'Dowd, M. Krasavin, S. Xieb, and T. A. Shapiro, *Bioorg. Med. Chem.*, 2000, **8**, 1361.
2000BMC2739 L. Delhaes, C. Biot, L. Berry, L. A. Maciejewski, D. Camus, J. S. Brocard, and D. Dive, *Bioorg. Med. Chem.*, 2000, **8**, 2739.

2000BMC1111 B. Mekonnen, E. Weiss, E. Katz, J. Ma, H. Ziffer, and D. E. Kyle, *Bioorg. Med. Chem.*, 2000, **8**, 1111.
2000BML1601 J. Ma, E. Weiss, D. E. Kyleb, and H. Ziffer, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1601.
2000CC2193 D. Y. Wang and Y. L. Wu, *J. Chem. Soc., Chem. Commun.*, 2000, 2193.
2000H(53)261 M. Jung and J. Bae, *Heterocycles*, 2000, **53**, 261.
2000JCH(B)155 T. Gordi, E. Nielsen, Z. Yu, D. Westerlund, and M. Ashton, *J. Chromatogr. B*, 2000, **742**, 155.
2000JME1456 B. Pirotte, R. Ouedraogo, P. de Tullio, S. Khelili, F. Somers, S. Boverie, L. Dupont, J. Fontaine, J. Damas, and P. Lebrun, *J. Med. Chem.*, 2000, **43**, 1456.
2000JME1635 Y. Li, Y.-M. Zhu, H.-J. Jiang, J.-P. Pan, G.-S. Wu, and J.-M. Wu, *J. Med. Chem.*, 2000, **43**, 1635.
2000JME4228 J. Ma, E. Katz, D. E. Kyle, and H. Ziffer, *J. Med. Chem.*, 2000, **43**, 4228.
2000J(P1)4279 W.-M. Wu and Y.-L. Wu, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4279.
2000MI311 F. Dagron and A. Lubineau, *J. Carbohydr. Chem.*, 2000, **19**, 311.
2000PHA356 T. I. El-Emary, A. M. Hussein, and H. S. El-Kashef, *Pharmazie*, 2000, **55**, 356.
2001BML5 Y. Li, F. Shan, J.-M. Wu, G.-S. Wu, J. Ding, D. Xia, W.-Y. Yang, G. Atassi, S. Léonce, D.-H. Caignardd, *et al.*, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 5.
2001CL660 M. Saeed, R. J. Abdel-Jalil, W. Voelter, and M. M. El-Abadelah, *Chem. Lett.*, 2001, 660.
2001CPB1541 N. Sibmooh, R. Udomsangpetch, and A. Kijjoa, *Chem. Pharm. Bull.*, 2001, **49**, 1541.
2001COR601 K. J. McCullough and M. Nojima, *Curr. Org. Chem.*, 2001, **5**, 601.
2001EJM469 J.-M. Wu, F. Shan, G.-S. Wu, Y. Li, J. Ding, D. Xiao, J.-X. Han, G. Atassi, S. Leonce, D.-H. Caignard, *et al.*, *Eur. J. Med. Chem.*, 2001, **36**, 469.
2001HCA928 Y. K. Wu, Z. Y. Yue, and H. H. Liu, *Helv. Chim. Acta*, 2001, **84**, 928.
2001IJB1125 B. Kalita, G. Bez, A. Barua, and N. C. Barua, *Indian. J. Chem. Sect. B.*, 2001, **40**, 1125.
2001JIC489 B. L. Singh, D. V. Singh, and R. K. Verma, *J. Indian Chem. Soc.*, 2001, **78**, 489.
2001JME58 P. M. O'Neill, A. Miller, L. P. D. Bishop, S. Hindley, J. L. Maggs, S. A. Ward, S. M. Roberts, F. Scheinmann, A. V. Stachulski, G. H. Posner, *et al.*, *J. Med. Chem.*, 2001, **44**, 58.
2001JME1467 P. M. O'Neill, F. Scheinmann, A. V. Stachulski, J. L. Maggs, and B. K. Park, *J. Med. Chem.*, 2001, **44**, 1467.
2001JME3150 S. Kapetanaki and C. Varotsis, *J. Med. Chem.*, 2001, **44**, 3150.
2001JME4688 S. Ekthawatchai, S. Kamchonwongpaisan, P. Kongsaeree, B. Tarnchompoo, Y. Thebtaranonth, and Y. Yuthavong, *J. Med. Chem.*, 2001, **44**, 4688.
2001JST267 A. G. Taranto, J. W. de M. Carneiro, and F. G. Oliveira, *J. Mol. Struct.*, 2001, **539**, 267.
2001JNP1201 J. Han, J.-G. Lee, S.-S. Min, S.-H. Park, C. K. Angerhofer, G. A. Cordell, and S.-U. Kim, *J. Nat. Prod.*, 2001, **64**, 1201.
2001JOC4413 A. L. Zografos, C. A. Mitsos, and O. Igglessi-Markopoulou, *J. Org. Chem.*, 2001, **66**, 4413.
2001CME1803 C. W. Jefford, *Curr. Med. Chem.*, 2001, **8**, 1803.
2001CME1827 P. Christen and J. L. Veuthey, *Curr. Med. Chem.*, 2001, **8**, 1827.
2001J(P1)305 S. Moutel and J. Prandi, *J. Chem. Soc., Perkin Trans 1*, 305.
2001J(P1)605 D.-Y. Wang, Y.-L. Wu, Y. Wu, J. Liang, and Y. Li, *J. Chem. Soc., Perkin Trans. 1*, 2001, 605.
2001J(P1)2421 L.-K. Sy and G. D. Brown, *J. Chem. Soc., Perkin Trans 1*, 2001, 2421.
2001J(P1)2682 P. M. O'Neill, M. Pugh, A. V. Stachulski, S. A. Ward, J. Davies, and B. K. Park, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2682.
2001PAC1173 A. Robert, F. Benoit-Vical, and O. Dechy-Cabaret, *Pure Appl. Chem.*, 2001, **73**, 1173.
2001SC1971 R. A. Mekheimer, *Synth. Commun.*, 2001, **31**, 1971.
2001T8481 L.-K. Sy, K.-K. Cheung, N.-Y. Zhu, and G. D. Brown, *Tetrahedron*, 2001, **57**, 8481.
2001TL2125 F. Grellepois, D. Bonnet-Delpon, and J.-P. Begue, *Tetrahedron Lett.*, 2001, **42**, 2125.
2001TL2843 X.-B. Liao, J.-Y. Han, and Y. Li, *Tetrahedron Lett.*, 2001, **42**, 2843.
2001TL3997 M. Jung, K. Lee, and H. Jung, *Tetrahedron Lett.*, 2001, **42**, 3997.
2002ACR167 A. Robert, O. Dechy-Cabaret, J. Cazelles, and B. Meunier, *Acc. Chem. Res.*, 2002, **35**, 167.
2002ACR255 Y. K. Wu, *Acc. Chem. Res.*, 2002, **35**, 255.
2002BMC227 G. H. Posner, J. Northrop, I.-H. Paik, K. Borstnik, P. Dolan, T. W. Kensler, S. Xiec, and T. A. Shapiro, *Bioorg. Med. Chem.*, 2002, **10**, 227.
2002BMC2883 F. Cheng, J. Shen, X. Luo, W. Zhu, J. Gu, R. Ji, H. Jiang, and K. Chen, *Bioorg. Med. Chem.*, 2002, **10**, 2883.
2002BTL937 S. F. de Medeiros, M. A. Avery, B. Avery, S. G. F. Leite, A. C. C. Freitas, and J. S. Williamson, *Biotechnol. Lett.*, 2002, **24**, 937.
2002CC414 A. Robert, Y. Coppel, and B. Meunier, *J. Chem. Soc., Chem. Commun.*, 2002, 414.
2002EJO113 R. K. Haynes, H.-W. Chan, M.-K. Cheung, W.-L. Lam, M.-K. Soo, H.-W. Tsang, A. Voerste, and I. D. Williams, *Eur. J. Org. Chem.*, 2002, 113.
2002JHC309 R. A. Ahmed, M. M. Kandeel, M. S. Abbady, and M. S. K. Youssef, *J. Heterocycl. Chem.*, 2002, **39**, 309.
2002ICA488 A. Robert, Y. Coppel, and B. Meunier, *Inorg. Chim. Acta*, 2002, **339**, 488.
2002IJC2185 C. Singh and P. Tiwari, *Indian J. Chem.*, 2002, **41**, 2185.
2002JME292 M. A. Avery, M. Alvim-Gaston, C. R. Rodrigues, E. J. Barreiro, F. E. Cohen, Y. A. Sabnis, and J. R. Woolfrey, *J. Med. Chem.*, 2002, **45**, 292.
2002JME1052 S. Hindley, S. A. Ward, R. C. Storr, N. L. Searle, P. G. Bray, B. K. Park, J. Davies, and P. M. O'Neill, *J. Med. Chem.*, 2002, **45**, 1052.
2002JME3824 G. H. Posner, H. B. Jeon, P. Ploypradith, I.-H. Paik, K. Borstnik, S. Xie, and T. A. Shapiro, *J. Med. Chem.*, 2002, **45**, 3824.
2002JME4321 M. A. Avery, M. Alvim-Gaston, J. A. Vroman, B. Wu, A. Ager, W. Peters, B. L. Robinson, and W. Charman, *J. Med. Chem.*, 2002, **45**, 4321.
2002JME4940 M. Jung, K. Lee, H. Kendrick, B. L. Robinson, and S. L. Croft, *J. Med. Chem.*, 2002, **45**, 4940.
2002JST207 A. G. Taranto, J. W. Carneiro, M. de F. G. de Oliveira, M. T. de Araujo, and C. R. Correa, *J. Mol. Struct.*, 2002, **580**, 207.
2002JNP184 A. M. Galal, S. A. Ross, M. A. ElSohly, H. N. ElSohly, F. S. El-Feraly, M. S. Ahmed, and A. T. McPhail, *J. Nat. Prod.*, 2002, **65**, 184.
2002JNP1693 J.-X. Zhan, Y.-X. Zhang, H.-Z. Guo, J. Han, L.-L. Ning, and D.-A. Guo, *J. Nat. Prod.*, 2002, **65**, 1693.
2002JOC1253 F. Grellepois, F. Chorki, B. Crousse, M. Ourevitch, D. Bonnet-Delpon, and J.-P. Begue, *J. Org. Chem.*, 2002, **67**, 1253.

2002OL757 F. Chorki, F. Grellepois, B. Crousse, V. D. Hoang, N. V. Hung, D. Bonnet-Delpon, and J.-P. Bégué, *Org. Lett.*, 2002, **4**, 757.
2002T897 L.-K. Sy and G. D. Brown, *Tetrahedron*, 2002, **58**, 897.
2002T909 L.-K. Sy and G. D. Brown, *Tetrahedron*, 2002, **58**, 909.
2002TL2891 S. Lee and S. Oh, *Tetrahedron Lett.*, 2002, **43**, 2891.
2002TL4017 N. A. Khanjin and J.-L. Montero, *Tetrahedron Lett.*, 2002, **43**, 4017.
2002TL4519 J. Zhan, H. Guo, J. Dai, Y. Zhang, and D. Guoa, *Tetrahedron Lett.*, 2002, **43**, 4519.
2002TL7235 C. Singh and P. Tiwari, *Tetrahedron Lett.*, 2002, **43**, 7235.
2002TL7837 F. Grellepois, F. Chorki, M. Ourevitch, B. Crousse, D. Bonnet-Delpon, and J.-P. Begue, *Tetrahedron Lett.*, 2002, **43**, 7837.
2002ZNB922 M. I. Hegab, A. E. A. Amr, and F. M. E. Abdel-Megeid, *Z. Naturforsch., B*, 2002, **57**, 922.
2003AGE5209 Z. Abdallah, G. Doisneau, and J.-M. Beau, *Angew. Chem., Int. Ed. Engl.*, 2003, **42**, 5209.
2003ARK125 J. S. Yadav, R. S. Babu, and G. Sabitha, *ARKIVOC*, 2003, **Part 3**, 125.
2003BMC399 I. Antonini, P. Polucci, A. Magnano, D. Cacciamani, M. T. Konieczny, J. Paradziej-Łukowicz, and S. Martelli, *Bioorg. Med. Chem.*, 2003, **11**, 399.
2003BMC977 Y. Li, J.-M. Wu, F. Shan, G.-S. Wu, J. Ding, D. Xiao, J.-X. Han, G. Atassi, S. Leonce, D.-H. Caignard, *et al.*, *Bioorg. Med. Chem.*, 2003, **11**, 977.
2003BMC4363 Y. Li, Z.-S. Yang, H. Zhang, B.-J. Cao, F.-D. Wang, Y. Zhang, Y.-L. Shi, J.-D. Yang, and B.-A. Wu, *Bioorg. Med. Chem.*, 2003, **11**, 4363.
2003BML1059 M. Rodriguez, D. Bonnet-Delpon, J.-P. Begue, A. Robert, and B. Meunier, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1059.
2003BML1645 W.-M. Wu, Y.-L. Chen, Z. Zhai, S.-H. Xiao, and Y.-L. Wu, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1645.
2003BML3665 S. Oh, I. H. Jeong, W.-S. Shin, and S. Lee, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3665.
2003CME2197 Y. Li and Y. L. Wu, *Curr. Med. Chem.*, 2003, **10**, 2197.
2003COR1231 G. Bez, B. Kalita, P. Sarmah, N. C. Barua, and D. K. Dutta, *Curr. Org. Chem.*, 2003, **7**, 1231.
2003EJO2098 R. K. Haynes, H.-W. Chan, M.-K. Cheung, S. T. Chung, W.-L. Lam, H.-W. Tsang, A. Voerste, and I. D. Williams, *Eur. J. Org. Chem.*, 2003, 2098.
2003HCA3074 Y. K. Wu and H. H. Liu, *Helv. Chim. Acta*, 2003, **86**, 3074.
2003JME987 M. Jung, S. Lee, J. Ham, K. Lee, H. Kim, and S. K. Kim, *J. Med. Chem.*, 2003, **46**, 987.
2003JME1060 G. H. Posner, I.-H. Paik, S. Sur, A. J. McRiner, K. Borstnik, S. Xie, and T. A. Shapiro, *J. Med. Chem.*, 2003, **46**, 1060.
2003JME4244 M. A. Avery, K. M. Muraleedharan, P. V. Desai, A. K. Bandyopadhyaya, M. M. Furtado, and B. L. Tekwani, *J. Med. Chem.*, 2003, **46**, 4244.
2003JOC9763 G. Magueur, B. Crousse, M. Ourevitch, J.-P. Begue, and D. Bonnet-Delpon, *J. Org. Chem.*, 2003, **68**, 9763.
2003JRM1161 A. Z. A. Hassanien and Z. E. Kandeel, *J. Chem. Res. (M)*, 2003, 1161.
2003MI180 A. G. Taranto, J. W. M. Carneiro, and M. T. Araujo, *Braz. J. Pharm. Sci.*, 2003, **39**, 180.
2003MI359 M. Gabriels and J. A. Plaizier Vercammen, *J. Chromatogr. Sci.*, 2003, **41**, 359.
2003MI1061 S. M. Sayed, *J. Chin. Chem. Soc.*, 2003, **50**, 1061.
2003MOL901 M. M. Al-Oqail, A. M. Galal, M. S. Ahmad, A. M. Al-Fishawi, and F. S. El-Feraly, *Molecules*, 2003, **8**, 901.
2003S1603 M. Fischer and R. Troschütz, *Synthesis*, 2003, 1603.
2003SC1855 S. Ekthawatchai, J. Lertvorachon, P. Meepowpan, T. Thongpanchang, Y. Thebtaranonth, and Y. Yuthavong, *Synth. Commun.*, 2003, **33**, 1855.
2003TL387 J. S. Yadav, R. Satheesh Babu, and G. Sabitha, *Tetrahedron Lett.*, 2003, **44**, 387.
2004ACR397 G. H. Posner and P. M. O'Neill, *Acc. Chem. Res.*, 2002, **37**, 397.
2004AGE1381 R. K. Haynes, W.-Y. Ho, H.-W. Chan, B. Fugmann, J. Stetter, S. L. Croft, L. Vivas, W. Peters, and B. L. Robinson, *Angew. Chem., Int. Ed. Engl.*, 2004, **43**, 1381.
2004BMC3783 S. Oh, I. H. Jeong, C. M. Ahn, W.-S. Shin, and S. Lee, *Bioorg. Med. Chem.*, 2004, **12**, 3783.
2004BML2001 M. Jung, K. Lee, H. Jung, H. Kendrick, V. Yardley, and S. L. Croft, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2001.
2004BML3683 S. Oh, I. H. Jeong, W.-S. Shin, and S. Lee, *Bioorg. Med. Chem. Lett.*, 2004, **12**, 3683.
2004BTL607 I. A. Parshikov, B. Miriyala, M. A. Avery, and J. S. Williamson, *Biotechnol. Lett.*, 2004, **26**, 607.
2004CME1265 M. Jung, K. Lee, and H. Kim, *Curr. Med. Chem.*, 2003, **11**, 1265.
2004HCA2368 G. Marconi, S. Monti, F. Manoli, A. D. Esposti, and A. Guerrini, *Helv. Chim. Acta*, 2004, **87**, 2368.
2004JME1290 J. P. Jeyadevan, P. G. Bray, J. Chadwick, A. E. Mercer, A. Byrne, S. A. Ward, B. K. Park, D. P. Williams, R. Cosstick, J. Davies, *et al.*, *J. Med. Chem.*, 2004, **47**, 1290.
2004JME1299 G. H. Posner, A. J. McRiner, I.-H. Paik, S. Sur, K. Borstnik, S. Xie, T. A. Shapiro, A. Alagbala, and B. Foster, *J. Med. Chem.*, 2004, **47**, 1299.
2004JME1423 F. Grellepois, F. Chorki, M. Ourévitch, S. Charneau, P. Grellier, K. A. McIntosh, W. N. Charman, B. Pradines, B. Crousse, D. Bonnet-Delpon, *et al.*, *J. Med. Chem.*, 2004, **47**, 1423.
2004JME2694 G. Magueur, B. Crousse, S. Charneau, P. Grellier, J.-P. Bégué, and D. Bonnet-Delpon, *J. Med. Chem.*, 2004, **47**, 2694.
2004JME2945 P. M. O'Neill and G. H. Posner, *J. Med. Chem.*, 2004, **47**, 2945.
2004JST83 N. E. Campillo, C. Montero, and J. A. Páez, *J. Mol. Struct.*, 2004, **678**, 83.
2004JST95 M. G. B. Drew, J. Metcalfe, and F. M. D. Ismail, *J. Mol. Struct.*, 2004, **711**, 95.
2004JNP1595 I. A. Parshikov, K. M. Muraleedharan, B. Miriyala, M. A. Avery, and J. S. Williamson, *J. Nat. Prod.*, 2004, **67**, 1595.
2004JOC984 S. Oh, I. H. Jeong, and S. Lee, *J. Org. Chem.*, 2004, **69**, 984.
2004JOC3242 B. J. Kim and T. Sasaki, *J. Org. Chem*, 2004, **69**, 3242.
2004MI503 D. Sriram, V. S. Rao, K. V. G. Chandrasekhar, and P. Yogeeswari, *Nat. Prod. Res.*, 2004, **18**, 503.
2004T1125 G. D. Brown and L. K. Sy, *Tetrahedron*, 2004, **60**, 1125.
2004TL1377 A. Hassner, B. Sun, G. Gellermann, and S. Meir, *Tetrahedron Lett.*, 2004, **45**, 1377.
2005AGE2060 S. A.-L. Laurent, A. Robert, and B. Meunier, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 2060.
2005BML2629 V. T. Khac, T. N. Van, and S. T. Van, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2629.
2005HCO495 A. A. A. Hafez and N. M. Nahas, *Heterocycl. Commun.*, 2005, **11**, 495.
2005JHC567 R. A. Mekheimer, K. U. Sadek, H. A. A. El-Nabi, A. A. E. Mohamed, E. A. Ebraheem, and M. B. Smith, *J. Heterocycl. Chem.*, 2005, **42**, 567.

2005JME4608 Z. S. Yang, W. L. Zhou, Y. Sui, J. X. Wang, J. M. Wu, Y. Zhou, Y. Zhang, P. L. He, J. Y. Han, W. Tang, Y. Li and J. P. Zuo, *J. Med. Chem.*, 2005, **48**, 4608.

2005JST87 M. G. B. Drew, J. Metcalfe, and F. M. D. Ismail, *J. Mol. Struct.*, 2005, **756**, 87.

2005JNP1274 A. M. Galal, S. A. Ross, M. Jacob, and M. A. ElSohly, *J. Nat. Prod.*, 2005, **68**, 1274.

2005MI366 M. A. Rafiee, N. L. Hadipour, and H. Naderi-Manesh, *J. Chem. Inf. Model.*, 2005, **45**, 366.

2005MI509 J. P. Begue and D. Bonnet-Delpon, *Drugs of the Future*, 2005, **30**, 509.

2005MI7010 M. F. Wang, C. H. Park, Q. L. Wu, and J. E. Simon, *J. Agr. Food Chem.*, 2005, **53**, 7010.

2005OL1561 Y. G. Liu, V. K. W. Wong, B. C. B. Ko, M. K. Wong, and C. M. Che, *Org. Lett.*, 2005, **7**, 1561.

2005OL5219 F. Grellepois, B. Crousse, D. Bonnet-Delpon, and J.-P. Begue, *Org. Lett.*, 2005, **7**, 5219.

2005TL4243 V. T. Khac, V. N. Van, and T. N. Van, *Tetrahedron Lett.*, 2005, **46**, 4243.

2006AAC4206 L. Jones-Brando, J. D'Angelo, G. H. Posner, and R. Yolken, *Antimicrob. Agents Chemother.*, 2006, **50**, 4206.

2006AXC281 Z. Y. Yue, S. H. Li, P. Gao, J. H. Zhang, and P. F. Yan, *Acta Crystallogr. Sect. C*, 2006, **62**, 281.

2006AXE1898 S. H. Li, Z. Y. Yue, P. Gao, and P. F. Yan, *Acta Crystallogr. Sect. E* ., 2006, **62**, O1898.

2006AGE2082 R. K. Haynes, B. Fugmann, J. Stetter, K. Rieckmann, H.-D. Heilmann, H.-W. Chan, M.-K. Cheung, W.-L. Lam, H.-N. Wong, S. L. Croft, *et al.*, *Angew. Chem., Int. Ed. Engl.*, 2006, **45**, 2082.

2006BMC1546 A. G. Taranto, J. W. DCarneiro, and M. T. de Araujo, *Bioorg. Med. Chem.*, 2006, **14**, 1546.

2006BMC2082 S. Tonmunphean, V. Parasuk, and S. Kokpol, *Bioorg. Med. Chem.*, 2006, **14**, 2082.

2006BMC2333 A. R. Katritzky, O. V. Kulshyn, I. Stoyanova-Slavova, D. A. Dobchev, M. Kuanar, D. C. Fara, and M. Karelson, *Bioorg. Med. Chem.*, 2006, **14**, 2333.

2006BMC2972 L. Messori, C. Gabbiani, A. Casini, M. Siragusa, F. F. Vincieri, and A. R. Bilia, *Bioorg. Med. Chem.*, 2006, **14**, 2972.

2006BMC8043 Z.-S. Yang, J.-X. Wang, Y. Zhou, J.-P. Zuo, and Y. Li, *Bioorg. Med. Chem.*, 2006, **14**, 8043.

2006BML1227 M. Jung, J. Tak, W. Y. Chung, and K. K. Park, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1227.

2006BML1909 J.-H. Liu, Y.-G. Chen, B.-Y. Yu, and Y.-J. Chen, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1909.

2006JFC637 G. Magueur, B. Crousse, M. Ourèvitch, D. Bonnet-Delpon, and J.-P. Bégué, *J. Fluor. Chem.*, 2006, **127**, 637.

2006JME2731 I.-H. Paik, S. Xie, T. A. Shapiro, T. Labonte, A. A. Narducci Sarjeant, A. C. Baege, and G. H. Posner, *J. Med. Chem.*, 2006, **49**, 2731.

2006JME7227 C. Singh, S. Chaudhary, and S. K. Puri, *J. Med. Chem.*, 2006, **49**, 7227.

2006JNP1653 A. A. Lapkin, P. K. Plucinski, and M. Cutler, *J. Nat. Prod.*, 2006, **69**, 1653.

2006JOC1111 B. D. Johnston, H. H. Jensen, and B. M. Pinto, *J. Org. Chem.*, 2006, **71**, 1111.

2006JOC3082 C. Chollet, B. Crousse, M. Ourevitch, and D. Bonnet-Delpon, *J. Org. Chem.*, 2006, **71**, 3082.

2006MI349 I. A. Parshikov, B. Miriyala, K. M. Muraleedharan, M. A. Avery, and J. S. Williamson, *J. Ind. Microbiol. Biotech.*, 2006, **33**, 349.

2006MI487 A. R. Bilia, P. Melillo de Malgalhaes, M. C. Bergonzi, and F. F. Vincieri, *Phytomedicine*, 2006, **13**, 487.

2006MI562 A. Robert, C. Bonduelle, S. A.-L. Laurent, and B. Meunier, *J. Phys. Org. Chem.*, 2006, **19**, 562.

2006MI729 R. B. Menon, M. M. Kannoth, B. L. Tekwani, J. Gut, P. J. Rosenthal, and M. A. Avery, *Combin. Chem. & High Throughput Screening*, 2006, **9**, 729.

2006OPP1 B. J. Kim and T. Sasaki, *Org. Prep. Proced. Int.*, 2006, **38**, 1.

2007MI411 S. Lee, *Mini-Rev. Med. Chem.*, 2007, **7**, 411.

2007MI839 N. G. Tayade and M. S. Nagarsenker, *J. Pharm. Biomed. Analysis*, 2007, **43**, 839.

2007MI1045 J. X. Dong, Z. D. Qi, Z. H. Zhang, and Y. Liu, *J. Chem. Engineer. Data*, 2007, **52**, 1045.

2007MOL395 T. Van Neck, S. Van Mierloo, and W. Dehaen, *Molecules*, 2007, **12**, 395.

Biographical Sketch



Miklós Nyerges was born in Budapest in 1967 and gained his M.Sc. degree from the Technical University of Budapest in 1991 and his Ph.D. from the same institution in 1996 (on research done partly at Cardiff University). He was a postdoctoral associate with Paul Groundwater at Sunderland University and then with Prof. Sir Derek Barton at Texas A&M. After a short visit to the Korean Research Institute of Chemical Technology, South Korea (C.S. Pak), in 1999, he returned to Sunderland as a NATO postdoctoral fellow. Currently, he is a senior scientific researcher in the Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest. His research interests involve cycloaddition approaches to synthesis of natural products. He was a recipient of the Zoltán Földi award for Innovative Organic Chemistry (1995), a junior award of the Hungarian Academy of Sciences in Organic Chemistry (1997), the Géza Zemplén award (2000), and a János Bólyai plaquette (2002).



Paul Groundwater was born in Edinburgh in 1962 and gained his B.Sc. (1983) and Ph.D. (1987) degrees from the University of Edinburgh. He was a postdoctoral fellow at the Australian National University, Canberra, with Prof. Ron Warrener; he then returned to the UK to join Prof. Malcolm Stevens at the Cancer Research Campaign Experimental Chemotherapy Research Group, Aston University. In 1989, he was appointed to a lectureship in the Department of Chemistry, Cardiff University. In 1996, he was appointed to a readership in organic chemistry in the Institute of Pharmacy and Chemistry at the University of Sunderland and was promoted to professor, in the Sunderland Pharmacy School, in 2001. He is the center director of ChemiSPEC, a business providing spectroscopic services to industry, and is currently the team leader of the Drug Design and Analysis Group in the Sunderland Pharmacy School. His research interests include the generation and reactivity of dipolar intermediates, the design and synthesis of novel medicinal agents, the identification of the active principle of medicinal plants, and new assays for disease markers.



Roz Anderson is a graduate of the University of Newcastle, where she obtained both her B.Sc. (1984) and Ph.D. (for work on the chemistry of cobaloximes, under the supervision of Prof. Bernard Golding) degrees. She then moved to Sunderland University to a postdoctoral position with Prof. Jeff Brown in the School of Pharmaceutical Sciences. In 1990, she was appointed to a lectureship in organic chemistry and was promoted to senior lecturer in 1993 and principal lecturer in 2003. Her research interests include the synthesis of novel chromogenic agents for enhanced bacterial detection, the investigation into the role of tryptophan hydroxylase in autism and the possible role of environmental factors in the symptomology, the design and synthesis of improved cysteamine prodrugs, and molecular modeling in drug design and reaction mechanisms.

10.18
Bicyclic 6-6 Systems: Pteridines

C. Suckling, C. Gibson, and J. Huggan
University of Strathclyde, Glasgow, UK
© 2008 Elsevier Ltd. All rights reserved.

10.18.1 Introduction **916**
10.18.1.1 Brief Historical Survey 916
10.18.1.2 Nomenclature and Literature 917
10.18.2 Theoretical Methods **917**
10.18.3 Experimental Structural Methods **918**
10.18.4 Thermodynamic Properties **920**
10.18.5 Reactivity of Fully Conjugated Rings **921**
10.18.5.1 Introduction 921
10.18.5.2 Photochemical Reactions 921
10.18.5.3 Electrophilic Attack at Carbon 921
10.18.5.4 Electrophilic Attack at Nitrogen 921
10.18.5.5 Nucleophilic Attack at Carbon 922
10.18.5.6 Radical Attack at Carbon 922
10.18.5.7 Other Reactions of Fully Conjugated Pteridines 923
10.18.6 Reactivity of Nonconjugated Rings **923**
10.18.6.1 Introduction 923
10.18.6.2 Reactivity of Dihydropteridines 923
10.18.6.3 Tetrahydro Derivatives 924
10.18.7 Reactivity of Substituents Attached to Ring Carbon Atoms **925**
10.18.7.1 General Survey of Substituents on Carbon 925
10.18.7.2 Nucleophilic Displacement 925
10.18.7.3 Electrophilic Attack 927
10.18.7.4 Metal-Catalyzed Substitution 928
10.18.7.5 Oxidation Reactions 929
10.18.7.6 Reduction Reactions 931
10.18.7.7 Side-Chain Reactions 931
10.18.8 Reactivity of Substituents Attached to Nitrogen **933**
10.18.8.1 *N*-Oxides 933
10.18.8.2 Metal Complexes 933
10.18.9 Ring Syntheses **934**
10.18.9.1 Ring Syntheses from Pyrimidines 934
10.18.9.2 Ring Syntheses from Pyrazines 941
10.18.10 Ring Syntheses by Transformation of Other Rings **947**
10.18.11 Critical Comparisons of the Various Routes Available **947**
10.18.12 Important Compounds and Applications **948**
10.18.12.1 Synthesis of Special Classes of Pteridines 948
10.18.12.2 Photochemistry 949
10.18.12.3 Metal Complexes 949

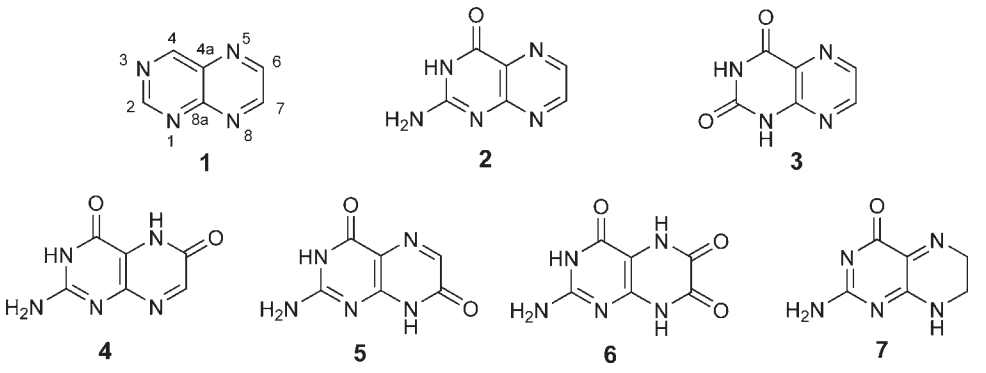
10.18.12.4 Nucleoside and Nucleotide Analogues 951
10.18.12.5 Natural Products 956
10.18.12.6 Biosynthetic Pathways 957
10.18.12.7 Chemical Mechanism of Action of Pteridine-Synthesising or -Transforming Enzymes 959
10.18.12.8 Medicinal Chemistry 962
10.18.12.9 Toxicology 966
10.18.12.10 Nanochemistry 966
10.18.13 Further Developments 967
10.18.13.1 Physicochemical Properties 967
10.18.13.2 Reactivity of Conjugated Pteridines 967
10.18.13.3 Reactions of Substituents 967
10.18.13.4 Synthesis from Pyrimidines 967
10.18.13.5 Synthesis from Pyrazines 967
10.18.13.6 Medicinal Chemistry 967
10.18.13.7 Enzyme Mechanisms 968
References 968

10.18.1 Introduction

10.18.1.1 Brief Historical Survey

Pteridines, **1**, have occupied a niche in the specialized literature of heterocyclic chemistry for over a century, especially in the form of their 2-amino-4-oxo derivatives, known as pterins, **2**, and 2,4-dioxo derivatives, known as lumazines, **3** <1996CHEC-II(7)679>. The first chemical syntheses of pteridines date from 1857 <1857LA117, 1857LA200>, but the rational development of pteridine chemistry took place in the 1890s and early 1900s when the synthetic methods that are the forerunners of today's methods were first described by Kühling <1894CB2116, 1895CB1968>, Gabriel and Colman <1901CB1234>, Isay <1906CB250>, and Sachs and Meyerheim <1908CB3957>. The study of pteridines as natural products began in 1889 with Hopkins' isolation of yellow purine-like pigments from the wings of the common English brimstone butterfly <1889PCS117, 1889NAT335>. Continuation of this work led to the identification of several pteridine-based pigments <1891NAT197, 1892NAT581, 1894PRS5, 1895MI661> such as xanthopterin, **4**, <1925CB2178>, isoxanthopterin, **5**, <1933LA226>, and leucopterin, **6**, <1926CB2067>. A further member of this class, erythropterin, was later described <1936LA49>. However, the unusual physical properties of pteridines and severe difficulties with elemental analyses delayed the structural elucidation of these pigments until the 1940s <1940LA182, 1940LA98, 1941LA284>. It was not until 1959 that some of the earliest prepared pteridines were recognized as lumazine derivatives <1959CB2468>. This knowledge subsequently initiated much work in isolating new natural pteridines as well as many synthetic approaches to this heterocyclic nucleus, as exemplified by the vitamin folic acid and methotrexate, an antileukemia drug <1949JA1753>. The importance of this interdisciplinary field was recognized as early as 1952 by Polonovski, who organized the first symposium. By 1995, 10 periodic international congresses and many more symposia on specific aspects of pteridines had followed.

Since 1995, the interdisciplinary character of the field has assumed still greater importance and the impact of pteridine chemistry has extended broadly through biology into medicine. In addition to the established drugs such as methotrexate, the relevance of pteridines to disease states such as phenylketonuria and cardiovascular disorders has become significant. Moreover, the detailed biosynthetic pathways leading to pteridine cofactors have been elucidated. These discoveries have depended upon an ever-increasing coupling between pteridine chemistry and biochemistry, pharmacology, and medicine. The molecular aspects of this research form an increased proportion of this chapter compared with previous editions.

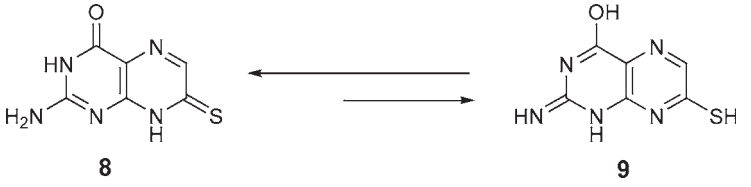


10.18.1.2 Nomenclature and Literature

The term 'pteridine' describes the pyrazino[2,3-*d*]pyrimidine nucleus, as proposed by Wieland <1941LA83> in 1941, and originates from the Greek word *pteron* meaning wing. The numbering of this ring system **1** follows the IUPAC rules; however, the central C═C bond may be substituted. It has generally been agreed to name 2-amino-4(3*H*)-pteridinone **2** 'pterin' <1963AG993> since most naturally occurring pteridines show the same pattern of substituents at the pyrimidine moiety of the nucleus. Thus, this term is also commonly used as the characteristic part of the trivial name of the natural pteridine derivatives. Similarly, 2,4(1*H*,3*H*)-pteridinedione derivatives **3** are called 'lumazines'. Reduced compounds are indicated by the prefixes 'dihydro-', 'tetrahydro-', and so on, with numerals showing the positions of the additional hydrogen atoms.

Further details of specialized nomenclature can be found in <1996CHEC-II(7)679>. A three-letter code has been proposed to achieve consistency in nomenclature for the future <1990PTR129>.

Tautomerism is common in pteridine derivatives and the favored tautomers should be represented by the structural formulas. Amino groups exist as such and not in the iminodihydro form whereas the hydroxy and thiol functions **9** located adjacent or *para* to a ring nitrogen atom prefer the thermodynamically more stable amide (lactam) and thioamide (thioxo) configuration **8** (**Scheme 1**) <B-1976MI1>.



Scheme 1

The pteridine literature has been reviewed several times. The excellent monograph by Brown covers for the first time the entire chemistry of this heterocycle <B-1988MI1> and more specialized chapters are found in various books <B-1988MI1, B-1985MI1, B-1987MI1, B-1992MI1>. The proceedings of two International Symposia on the Chemistry and Biology of Pteridines and Folates <B-1997MI1, B-2001MI1> as well as a series of ten winter workshops <2005MI1, 2004MI1, 2003MI1, 2002MI1, 2001MI2, 2000MI1, 1999MI1, 1998MI1, 1997MI2, 1996MI1> contain specific information about newer developments in the field.

10.18.2 Theoretical Methods

The great advance in the capacity of modern computers has contributed to a major expansion in the detail of theoretical investigations of small molecules and also an expansion of the size of systems suitable for study. Pteridine chemistry has aspects of both. In small molecule work, it is important to establish the appropriateness of a number of possible basis sets for *ab initio* calculations to yield useful results. For vibrational spectra of pteridines and related tetraazanaphthalenes, the B3LYP/6-31G* basis set has been reported to give the best correlation between theory and experiment but the smaller 4-31G basis set also gave acceptable results <2000PCA7386>. Calculations relevant to

the vibrational spectra of lumazine in water have shown that the spherical cavity model of solvation is adequate to reproduce the spectra of N-protonated lumazines <2003PCB2139>. This work has significance for probing the reaction mechanisms of enzymes that use pteridine or isoalloxazine cofactors and is notable for its inclusion of water in the model. Solvation properties have also been a concern of semi-empirical studies of the tautomeric forms of 2-thiolumazine <2002JMM246>. In view of the practical difficulty of determining tautomeric positions, the results of this study are interesting; they show distinct differences between basicity of atoms in the gas phase and in solution. In the gas phase, the order of increasing basicity was N-5 < N-8 < O-4 < S-2 < N-1 < N-3, whereas in the aqueous phase a very different order was found, S-2 < O-4 = N-5 < N-8 < N-1 < N-3. These data were interpreted as being consistent with the sulfur atom exisiting in the thiol form and the oxygen atom in the keto form in aqueous solution. Fluorescence spectra have been investigated <1999MI359>. The properties of N(5)–O(4) complexes of pteridin-4(3*H*)-ones have been investigated by PM3 calculations which served to emphasize the importance of chelation in these compounds <2000JMM433>.

Turning to biological applications, *ab initio* calculations on pterin and its di- and tetrahydro reduced derivatives showed, not surprisingly, that the electronic structures of the three compounds are profoundly different <1998PTR85>. Whereas in pterin, N-8 has pyridine-like character, in both the di- and tetrahydro oxidation states it has pyrrole-like character with the nonbonded electrons conjugated with the pyrimidine ring. This result reflects the normal reactivity of 4-oxopteridines in which N-8 is both weakly basic and poorly nucleophilic. Similarly, *ab initio* calculations (6-31GX**) of model compounds for tetrahydrobiopterin and its analogues as cofactors of nitric oxide synthase (NOS) showed that the electronic properties of tetrahydrolumazine, tetrahydropterin, the 4-amino analogue of tetrahydropterin, and *N*-5-methyltetrahydropterin differ significantly. The lumazine, the pterin, and the 4-amino pterin analogue were all distinct but the *N*-5-methylpterin was indistinguishable from pterin itself <1999PTR91>. This unsurprising outcome was interpreted to support an electronic interaction between the 'pyrimidine' ring of the cofactor and the heme at the active site.

The intrinsic properties of pterins have also been investigated in the context of the molybdenum cofactor, in particular the population of tautomers <1997J(P2)1529>. A polar continuum model including water suggested that several possible tautomers were of similar energy and that only an *ortho*-quinonoid tautomer (the 5,6-dihydro-(3*H*) tautomer) was too high in energy to play a role.

Where covalent bonding in enzyme inhibitors might be anticipated, a theoretical study of relative hydration free energy differences in heteroaromatic compounds including pteridines can be expected to be useful. Such a case concerns adenosine and cytosine deaminases <1998JA3295>. A combination of thermodynamic and quantum-mechanical calculations produced calculated $\Delta\Delta G$(hydration) values that correlated well with experimentally determined equilibrium constants for hydration over a range of greater than 10^3. Hydration was argued to be dependent not only upon local substituent effects, as is typically the case with carbonyl compounds, but also upon the loss of aromaticity in forming a covalent hydrate. While other factors such as desolvation and electrostatic interactions contribute to inhibitor binding, it was possible to separate out a contribution associated with hydration and to argue that hydration free energies have value in drug design.

Combined quantum-mechanical and molecular-mechanical calculations have now moved into the field of enzyme mechanisms with dihydrofolate reductase a favored test case. In agreement with experimental data, the transition state for the hydride-transfer step has been shown to relate to two primary features of catalysis, namely a conformational pressure by the enzyme to move the substrate toward the transition state structure and the indirect transfer of a proton from the active site acidic amino acid to N-5 <1999JA12140, 2003PCB14036>. However, agreement between experimental and theoretical results is not always found. In a study of the pH-dependent inhibition of dihydrofolate reductase by methotrexate using Poisson–Boltzmann calculations supported by electrostatic and quantum-mechanical calculations, it was found that Asp27 (*Escherichia coli* numbering) was not deprotonated when methotrexate was bound, directly the opposite of what is normally accepted <1997JMB656>. Undeterred, the estimation of inhibitor potency by calculation has been encouraged in studies of pteridines and related quinazolines binding to dihydrofolate reductase <1998MI119>.

10.18.3 Experimental Structural Methods

Crystallographic studies have made a substantial contribution to knowledge of the structures of pteridinyl metal complexes <1999CCR323>. As noted in Section 10.18.2, the commonest coordination pattern of pterins and lumazines is O(4)–N(5) chelation of the metal, two of which ligands typically form the equatorial plane of a distorted octahedron; the axial ligands are commonly water, or other solvent. Under appropriate conditions, the *cis*-isomers of octahedrally coordinated metal ions can be obtained, for example, the diaquo complex of copper(II) with two perpendicular dimethyllumazine ligands <1999JCX571>. With softer metal cations, additional coordination by

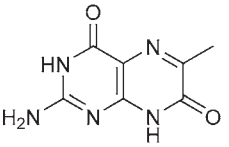
anions such as nitrate leads to higher coordination numbers. d^8 Metal cations such as palladium(II) form the expected square planar configurations, such as dihalo bis-pterin complexes <2003POL483>. The three-dimensional (3-D) layout of the unit cell is often determined by hydrogen-bonding networks involving water. These general properties are shown by 1,3-dimethyllumazine complexes of copper(II) <1997POL607>. Varying the methylation on a lumazine did not substantially change the coordination chemistry; cobalt(II), nickel(II), zinc(II), and cadmium(II) complexes all adhered to the general rules outlined above <2002POL1961, 2003ICA(342)209>. The spin states of complexes of 2-(dimethylamino)-4-(3*H*)-pteridinone with iron(II), cobalt(II), and copper(II) have been shown to be high spin with octahedral configurations and methanol as the axial ligand <1997IC3869>. Evidence for supramolecular aggregations has been found with nickel(II) and cadmium(II) complexes of pteridines and ethylene diamine; surprisingly, water-soluble compounds were obtained <2005CGD1597>.

Very large transition metal species such as tetrabromoaurate do not form complexes with direct pteridine ligation of the metal; instead, the planar tetrabromoaurate anions are linked loosely in the crystal to two dimethyllumazine molecules <1998JCX565, 2004STC159>. In platinum complexes, 4-hydroxy-2-mercaptopteridine has been shown to form bridges between two metal ions through a nitrogen atom of a pyrazine ring <2000ICC231>; this is in total contrast to the normal chelating behavior of O-4 and N-5. 6-Acetyl-1,3,7-trimethyllumazine has been found to form complexes with rhenium(I) in which the standard coordination mode is found <2001ICA(325)65>; the complex was shown to undergo reversible one-electron reduction by electrochemical measurements.

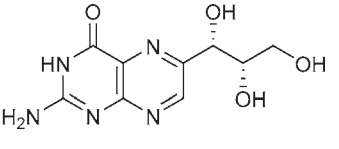
In connection with the structure of the molybdenum cofactor, the cobalt complex of a typical alkene-1,2-dithiolate ligand has been prepared and characterized <1997AXC213>. Molybdopterin complexes themselves have been studied in detail and, like the cobalt complex, have been shown to ligate the metal through the sulfur atoms of the dithiolene. A characteristic of the molybdenum ion is its ability to expand its coordination number with additional ligands, especially oxygen and sulfur, ligands that can be provided either by small molecules or by amino acid side chains in proteins <1997JIS773>, 1997JCD3909>. Complexes of molybdenum with simple, non-sulfur-containing pterins such as 6,7-dimethylpterin, have also been described <1999IC2600> and their properties investigated by X-ray photoelectron spectroscopy in order to determine the oxidation states of the metal <1999IC2607>. The point of particular interest was the ability of pterin ligands to interact with the metal electronically; evidence was adduced to show that with a high-oxidation-state starting material (Mo(VI)) reduced pterins can act as powerful electron donors, while with lower oxidation states (Mo(IV)) pterins act as electron acceptors, indicating that a substantial degree of delocalization across the whole molybdenum–pteridine framework is possible.

Fluorescence spectra have become especially important because of the increasing applications of pterins in analogues of nucleosides and nucleotides. As would be expected, these spectra are pH sensitive and their study has made the determination of several pK_a's possible <2003PCA178>. For example, 6,7-dimethylisoxanthopterin had pK_a's of 8.3 and 8.5 associated with the ionizations at N-3 and N-6. Fluorescence lifetime measurements have been made with pteridines incorporated into oligonucleotides and as monomers <1997ABI86>. Lifetimes of between 0.87 and 6.54 ns were found for the most fluorescent compounds, which had quantum yields greater than 0.15. The highest quantum yield was found for **10** with a value of 0.88. Not surprisingly, the incorporation of pteridine nucleotides into DNA causes fluorescence quenching, especially when the pteridines were close in sequence to purines. Double strands with unchanged T_ms were obtained indicating that the pteridine did not significantly perturb the double helical structure.

The establishment of the absolute configuration of 6-(1-hydroxyalkyl)pterins has been demonstrated by the highly sensitive method of fluorescence-detected circular dichroism (CD) <2002H(56)387>. For example, the major pterin from *E. coli* was shown to be L-monapterin **11** <2001H(54)283>. The use of CD spectra of fully acetylated tetrahydropterins including tetrahydro-D-monapterin and related heterocyclic compounds to establish configurational relationships has been described <2005H(65)2917>. Fluorescence correlation spectroscopy has been used to probe the molecular motion of neopterin in solution <2001PTR147>. The conformations of dihydro- and tetrahydropterin in solution have been investigated by nuclear magnetic resonance (NMR) spectroscopy <2000PTR32>; the reduced rings were found to have the expected near-planar conformations. Further examples of NMR spectroscopy, together with optical spectroscopy and mass spectrometry, can be found in CHEC-II(1996) <1996CHEC-II(7)679>.



10

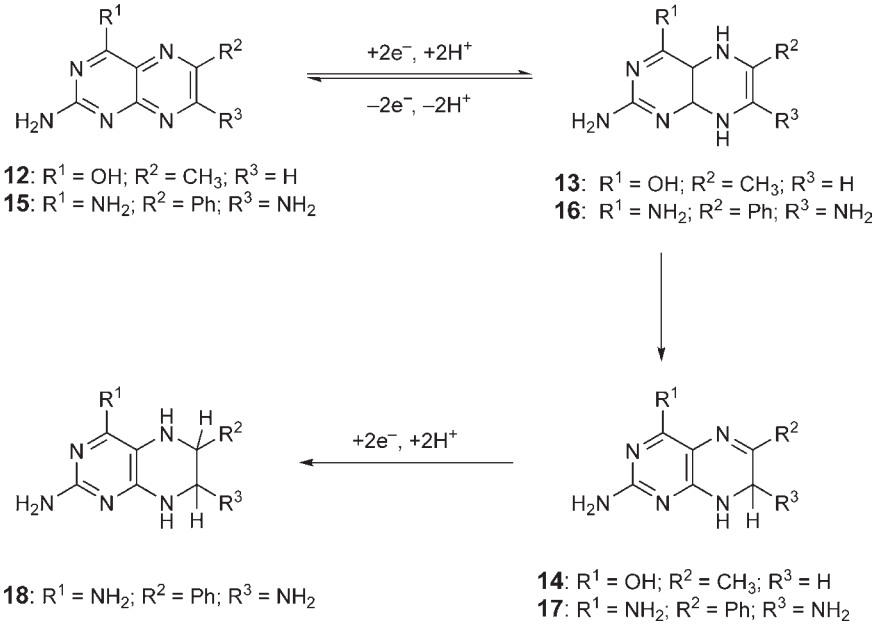


11

10.18.4 Thermodynamic Properties

The measurement of the pK_a of isoxanthopterin was noted above <2003PCA178>. The pK_a's of a number of fluorinated pterins have been reported measured in methanol solution <1996T13017>. Under these conditions, there was little difference between the observed pK_a's and those of comparable non-fluorine-containing pterins; thus a pK_a between 2.2 and 2.4 was found for conjugated pterins and 7.5–7.9 and 2.3–2.7 for dihydropterins (see also Section 10.18.9.1). The pK_as of a wide range of 6- and 7-acyl pteridines have been reported together with their ultraviolet (UV) spectra <2004PTR129>. In the case of 2,4-diaminopteridines, a 7-acyl group caused a reduction in the pK_a from 5.32 to 4.59; the introduction of an additional basic side chain caused the pK_a of the pteridine to fall to between 2.4 and 3.7 depending upon the substituent as a consequence of the cation in the side chain. The pK_a of 1,3-dimethyllumazines reflects the structure and properties of the pyrazine ring <1996PTR113>. For example, the 7-amino-6-thione had an acidic pK_a of 5.49; the 7-hydroxy analogue had two acidic pK_a's, 2.56 reflecting OH ionization and 8.38 reflecting NH5 ionization to give a dianion. Remarkably, the 7-thiol-6-thione was shown to be one of the strongest pteridine acids known with a pK_a of 1.96.

An important study of the electrochemistry of pterin cofactors and inhibitors of NOS has appeared <2001MI176>. Consistent with its role as an electron donor in the reaction catalyzed by NOS, tetrahydrobiopterin was found to be easily oxidized at a potential of +0.27 V (vs. normal hydrogen electrode) and reduced after reversing the potential at −0.16 V. Other pterins that are capable of sustaining nitric oxide production by NOSs showed similar behavior. On the other hand, sepiapterin, and other related 7,8-dihydropterins that do not support nitric oxide production, required much higher potentials for oxidation (0.82–1.04 V) and reduction was not observed between +1.2 and −0.8 V. An electron-transfer role for tetrahydrobiopterin in catalysis by NOSs is supported by these results. Interestingly, a number of 7,7-dimethyl-7,8-dihydropterins have been found to support nitric oxide synthesis in cells and tissues <2005PTR112P56>; like sepiapterin, these compounds were not readily oxidized but the 6-acetyl derivative was shown to undergo reversible electrochemical reduction in ethanolic solution at a potential of −0.42 V <2005PTR112P57>. It is therefore possible that these compounds might undergo reduction either at the active site of NOS to permit subsequent electron transfer to heme or undergo intracellular reduction to the tetrahydro compounds which, as tetrahydrobiopterin analogues, are the active compounds. Direct current polarography (DCP) of many pteridine derivatives related to folic acid has been studied <1996CPB1115>. These studies revealed that the two-electron reduction product of 2-amino-4-hydroxy-6-methylpteridine **12** was 2-amino-4-hydroxy-6-methyl-7,8-dihydropteridine **14**. The reaction path was assumed to be reduction of **12** to 2-amino-4-hydroxy-6-methyl-5,6,7,8-tetrahydropteridine **13**, which tautomerized to **14** (**Scheme 2**). To this end, interest in triamterene (6-phenyl-2,4,7-triaminopteridine) **15**, a diuretic, was raised because of its significant structural difference from naturally occurring pteridines.



Scheme 2

The electrode reaction of triamterene **15** was elucidated by means of DCP, Tast polarography, cyclic voltammetry, microcoulometry, controlled potential electrolysis, and spectroscopy (ultraviolet/visible (UV/Vis), NMR). Two steps of reduction independent of pH were observed; two-electron reduction of **15** resulted in the formation of **17**. The first reduction wave of **15** was assumed to be due to irreversible two-electron reduction forming unstable **16**, which tautomerized to **17**, and the second reduction wave was ascribed to two-electron reduction of **17** to the tetrahydro product, **18** (**Scheme 2**).

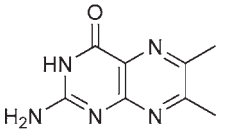
10.18.5 Reactivity of Fully Conjugated Rings

10.18.5.1 Introduction

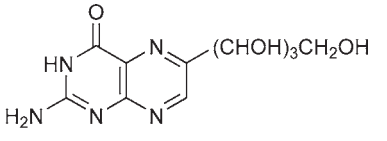
The pyridine-like nitrogen atoms of pteridines all substantially reduce the electron density of the conjugated rings compared with typical carbocyclic aromatic compounds. The obvious consequence of this fundamental property is a very limited electrophilic chemistry in pteridines, except where several strongly electron-donating substituents are present. On the other hand, the highly polar C═N bonds lend themselves to nucleophilic addition, radical addition, and one-electron reduction. While such reactions break the conjugation of either the pyrimidine or the pyrazine ring, the ring not attacked usually retains its delocalization. The presence of several electron-withdrawing nitrogen atoms leads to weak basicity and nucleophilicity (including acting as a ligand in metal complexes), but such reactions are characteristic of pteridines substituted with electron-donating substituents. Indeed the chemistry of pteridines is dominated by the effect of such substituents, especially in the pyrimidine ring, as found in the natural products, pterins and lumazines. The validity of these broad generalizations will become abundantly clear with the examples cited below.

10.18.5.2 Photochemical Reactions

Pteridines play a role in blue light photoreceptors and their ability to mediate the formation of singlet oxygen has been studied as a model for putative biological reactions <1999MI1117>. Pterins **19** and **20** were shown to be effective photosensitizers for singlet oxygen production but the quantum yields (0.16 and 0.20) were typically 2.5-fold less than the fused benzopteridines, riboflavin and flavine mononucleotide (FMN). Photoreduction of **19** and **20** in aqueous solution has been investigated and a sequential reduction *via* the dihydro to the tetrahydro oxidation state was observed and a mechanism *via* the triplet excited state of the pterins was preferred <1997JPH43>. The reduction of methotrexate by NADPH at the active site of dihydrofolate reductase has been reported to be stimulated by illumination <1999MI77>. Perhaps more significantly, the phototoxicity of methotrexate has been investigated <2002MI467>, and it was suggested that oxidation at guanosine residues is the major damage to DNA. The direct agent of this damage appeared not to be methotrexate itself but 2,4-diamino-6-hydroxymethylpteridine, the photo-oxidation product of methotrexate.



19



20

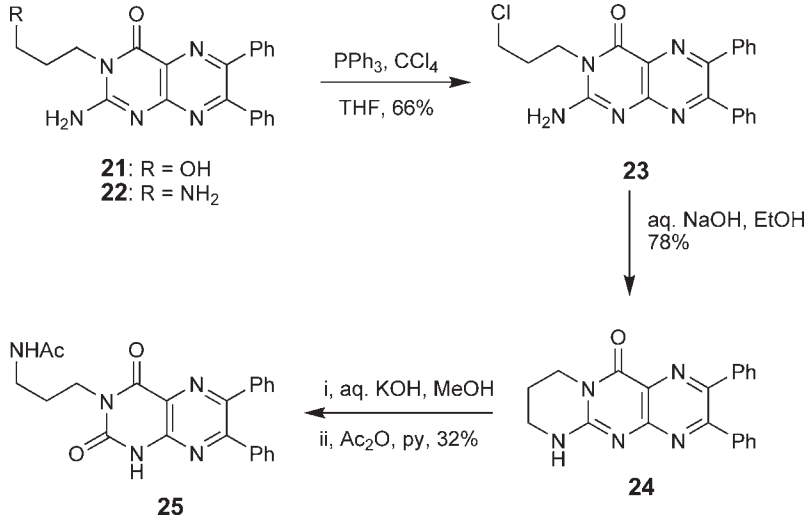
10.18.5.3 Electrophilic Attack at Carbon

As polyazaheterocycles with pyridine-like nitrogen atoms, pteridines are not noted for ready electrophilic substitution <1996CHEC-II(7)679>. No significant new examples appear to have been reported during the period covered by this chapter.

10.18.5.4 Electrophilic Attack at Nitrogen

A major recent growth point in substitution reactions has been the synthesis of pteridine glycosides, especially ribosides for study as probes in DNA chemistry taking advantage of the fluorescent properties of pteridines (see Section 10.18.12.4). Typically these reactions are developments of standard methods of glycosylation used with purines and pyrimidines as nucleophiles. In these and in other cases, the ambident nucleophiles within the pterin

structure especially can lead to complications. Control can be established by the use of protecting groups, as described in Section 10.18.12.4. In some cases, intramolecular reactions have been observed (**Scheme 3**). In a study of the synthesis of pteridine-bearing oligonucleotides that required the attachment of the pterin through N-3 or the 2-amino group, the conversion of the 3-hydroxypropyl pterin **21** into the 3-aminopropyl pterin **22** was of interest. Treatment of **21** with triphenylphosphine and carbon tetrachloride in tetrahydrofuran (THF) afforded the 3-chloropropyl pterin **23**, which readily cyclized to the tricyclic pteridine **24** <2004OBC3588>. Amidine **24** was not a precursor for the required pterin **22** but gave the unstable 3-aminopropyl lumazine on hydrolysis with with methanolic potassium hydroxide, which was characterized as its acetamide **25**.



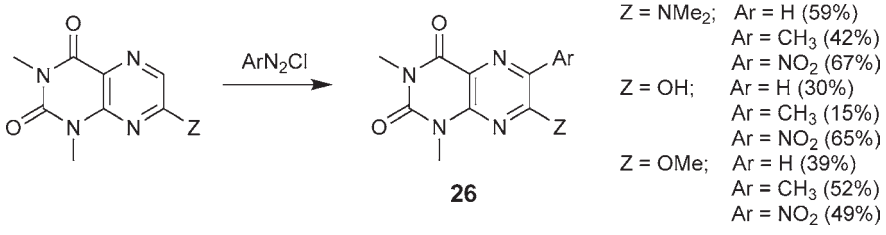
Scheme 3

10.18.5.5 Nucleophilic Attack at Carbon

Nucleophilic attack at carbon in pteridines can be expected at any of the unsubstituted positions because all are activated by adjacent nitrogen atoms. Such reactions are of limited synthetic use unless a leaving group is present (see Section 10.18.7.2).

10.18.5.6 Radical Attack at Carbon

In the case of substituted 1,3-dimethyllumazines **26**, arylation with arene diazonium salts in mildly alkaline solution has been demonstrated <1997PTR188, 1997H(45)765>. In simple lumazines without substituents Z, substitution was selective at C-7 but yields were poor (14–37%). When the electron-donating group (MeO or Me_2N) is at C-7, substitution was unambiguously at C-6. *N*-Oxides also behave as electron-donating groups, the 5-*N*-oxide directing exclusively to the 6-aryl products and the 8-*N*-oxide directing predominantly to the 7-aryl products. Removal of the *N*-oxide was effected with tributylphosphine. Evidence for the involvement of aryl radicals in these reactions was adduced from the isolation of small quantities of 4′-arylated derivatives of the required 6-arylpteridine products. Aryl groups included 4-methyl-, 4-chloro-, and 4-nitrophenyl (**Scheme 4**).

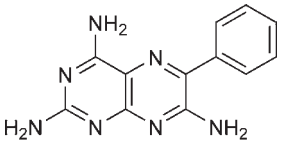


Scheme 4

The introduction of substituents into position 7 of a 2,4-disubstituted pteridine can be effected very cleanly by the use of acyl radicals typically and has been known for many years. Treatment of aldehydes with *t*-butyl hydroperoxide and iron(II) generates acyl radicals which add selectively to the 7-position. A recent exploitation of this chemistry has provided a large number of new examples including both aryl and alkyl acyl radicals as reagents <2004PTR129>; pK_a data have been compiled (Section 10.18.4) and many nucleophilic substitution reactions of the 7-acylated pteridines and functional group modifications have been described (Section 10.18.7.2).

10.18.5.7 Other Reactions of Fully Conjugated Pteridines

Reduced pterins in the folic acid series are important cofactors in biosynthesis in which the active diastereoisomer has the (6*S*)-configuration. Attempts continue to be made to optimize the stereoselective hydrogenation of folic acid using chiral rhodium–phosphane complexes immobilized on silica gel as catalysts <2000M1371>. It is unlikely that such methods will displace the current commercial routes based upon selective crystallization in the folate series, although they may have value for other substrates. The reduction of pteridines has also been studied by several electrochemical methods supported by spectroscopic characterization <1996CPB1115>. As described in Section 10.18.4, a fully conjugated pteridine such as the diuretic triamterene **15** showed two reductive waves, the first affording the 5,8-dihydro derivative, which, under the conditions of the experiment, tautomerized to the 7,8-dihydro derivative. This in turn was reduced to the corresponding tetrahydropteridine, which on oxidation afforded 2,4-diamino-6-phenylpteridine.



15

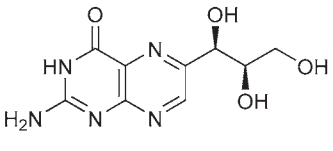
10.18.6 Reactivity of Nonconjugated Rings

10.18.6.1 Introduction

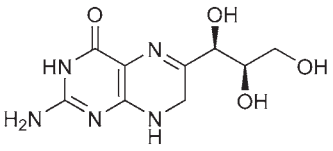
The importance of the dihydro and tetrahydro oxidation states of pterins in biology has stimulated interest in the study of the chemical properties of these compounds, especially with respect to electron-transfer and radical reactions. It has become apparent, perhaps unsurprisingly, that the stability and reactivity of these oxidation states are very sensitive to substituent effects and the much greater stability of the fully conjugated pteridines is most evident. The oxidation of tetrahydropterins and the reduction of dihydropterins have become especially important in the chemistry of nitric oxide production in nature and in oxidative stress but the accumulation of relevant facts has not led so far to a detailed understanding of the chemical property relationships. Relevant information is summarized in the following section.

10.18.6.2 Reactivity of Dihydropteridines

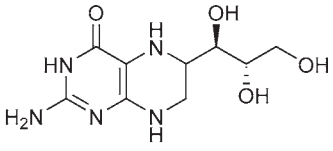
7,8-Dihydroneopterin **28** has been compared with neopterin **27** as a radical scavenger using electron spin resonance (ESR) spin trap techniques <1997BBR774> and rate constants for the reaction of 7,8-dihydropterin with both superoxide (10^3 $M^{-1}s^{-1}$) and peroxyl radicals (10^7 $M^{-1}s^{-1}$) determined. In contrast, neopterin showed no radical scavenging properties. Dihydroneopterin has also been shown to be effective in scavenging large organic radicals such as diphenylpicrylhydrazyl and 2,2′-azinodi[3-ethylbenzthiazoline sulfonate] <2000PTR90>. However, the properties of 7,8-dihydroneopterin depend very much upon reaction conditions. In addition to scavenging radicals, dihydroneopterin and related compounds have also been shown to promote hydroxyl radical production in aqueous solution <2000HCA954>. Ten 7,8-dihydropterins were studied (**28**, **30–32**) and it was found that the oxidizability of the dihydropterin and its ability to coordinate iron were important in determining the extent of hydroxyl radical formation.



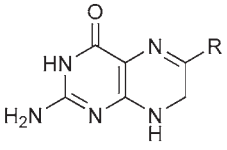
27



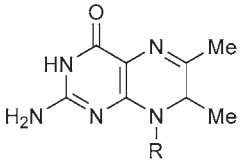
28



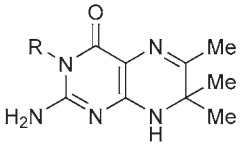
29



30: R = CH_2OH, CH_3, $COCH(OH)CH_3$, COEt, CHO



31: R = H, Me



32: R = H, Me

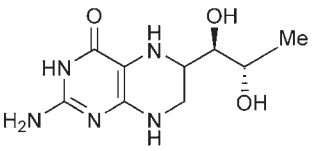
In the case of 7,8-dihydroneopterin itself, the production of superoxide in air-saturated water has been investigated and the pterin was shown to promote substantially the formation of superoxide even at low iron(II) concentrations, from which it was suggested that the radical-promoting activity of 7,8-dihydroneopterin is physiologically more important than its radical-scavenging properties <2000PTR60>. A sequel to this study has investigated the interaction of 7,8-dihydroneopterin with peroxynitrite, which is implicated as a major mediator of damage to cells under oxidative stress <2004BBR379>. Luminescence and spin probe oxidation were used as analytical techniques to dissect a complex cluster of reactions. These test reactions induced by peroxinitrite were both inhibited by dihydroneopterin as was the nitration of tyrosine by peroxynitrite. On the other hand, hydroxylation reactions were promoted by dihydroneopterin, indicating the capacity of dihydropterins to have demonstrably different effects on the reactivity of various radicals.

Pteridines have been emphasized as important in radical processes in cells <2002BBA124>. For example, it is believed that neopterin and dihydroneopterin acting together have a role in modulating the redox environment of cells, especially those associated with oxidative properties in cells such as macrophages. The demonstration that dihydroneopterin is oxidized by hypochlorous acid to neopterin without cleavage of the side chain (in contrast to oxidation by oxygen which causes side-chain cleavage) has been interpreted to indicate that a similar transformation *in vivo* might provide a mechanism for increasing the oxidative power by removing the dihydroneopterin, which, as evidenced by the studies mentioned above, has antioxidant properties <2000BBR307>. Neopterin has also been discussed as a mediator of the cellular immune response <2004PTR107>.

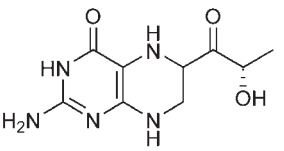
Further chemical transformations of possible biological relevance mediated by dihydrobiopterin include cleavage of heme in hemoproteins <2002BBA124, 2002PTR115>. In air-saturated water, 7,8-dihydroneopterin was shown to promote the formation of carbon monoxide and free iron from metmyoglobin and methemoglobin by cleavage of the heme. The mechanism proposed gave 7,8-dihydroneopterin the role of a reducing agent affording the iron(II) hemoproteins which then subsequently underwent autoxidation leading to heme cleavage.

10.18.6.3 Tetrahydro Derivatives

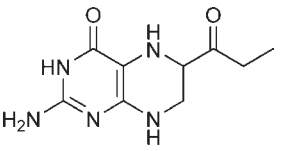
The heme cleavage reaction mentioned above has also been shown to be promoted by tetrahydroneopterin <2002PTR115>. In an important study, the electrochemistry of pterin cofactors and inhibitors of NOS has been described <2001MI176>. Tetrahydrobiopterin, the natural cofactor for NOSs, tetrahydroneopterin, and 6,7-dimethyltetrahydropterin, which can both substitute for tetrahydrobiopterin **33** as cofactor, all showed an oxidative signal (+0.27 V vs. normal hydrogen electrode) in cyclic or square wave voltammetry and this was connected with a reductive signal (−0.16 V) associated with the regeneration of tetrahydrobiopterin from its oxidation product. On the other hand, compounds that are not effective cofactors including 7,8-dihydrobiopterin, sepiapterin **34**, and 2′-deoxysepiapterin **35** required much higher potentials for oxidation (+0.82–1.04 V). The results were interpreted to be consistent with the one-electron oxidation of tetrahydrobiopterin to the trihydrobiopterin radical during catalysis by NOSs. Interestingly, in tissue and cellular preparations and *in vivo*, a range of dihydropterins has been shown to promote nitric oxide synthesis but the mechanism has not yet been established <2005PTR112P57>. The radical enzymology of tetrahydrobiopterin has been reviewed in detail <2003CRV2365>.



33



34



35

Recently, the possibility of using tetrahydrobiopterin as a therapeutic agent has been investigated taking advantage of its electron-donating properties. To establish the molecular basis of this possibility, a study of the reaction of tetrahydrobiopterin with superoxide by electron paramagnetic resonance (EPR) spectroscopy was undertaken <2001MI975>. The measured rate constants for the reaction of tetrahydrobiopterin and superoxide at pH 7.4 were suggested to be too slow for this reaction to be significant physiologically. Ascorbate was shown not to reduce dihydro to tetrahydrobiopterin and to have no effect on the production of nitric oxide by endothelial NOS. The study concluded that a better explanation of the beneficial physiological effects of tetrahydrobiopterin used as a drug was its direct interaction with NOS itself avoiding the so-called uncoupling phenomenon.

10.18.7 Reactivity of Substituents Attached to Ring Carbon Atoms

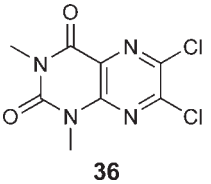
10.18.7.1 General Survey of Substituents on Carbon

In general, most substituents attached to pteridine rings behave in the manner expected of simpler paradigms in pyridine chemistry. However, pteridines of synthetic interest are often polyfunctional, especially in the pterin series. In order to gain control of the course of synthetic reactions, it is either necessary to expend effort on selective protection or to devise sequential strategies that obviate the need for additional protecting groups. Both approaches have been widely used. For reactions of substituents attached to the pyrazine ring, 1,3-dimethyllumazines have frequently been used as substrates. Although such compounds are not closely related to biologically active pteridines that are of interest in many synthetic studies, the absence of weakly acidic protons on the pyrimidine ring and the improved solubility afforded by the absence of hydrogen-bonding groups gives these compounds many practical advantages in exploring the reactivity of substituents attached to carbon in pteridines.

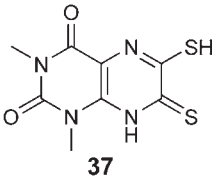
10.18.7.2 Nucleophilic Displacement

The substitution of pteridines at positions adjacent to the pyridine-like nitrogen atoms in either the pyrimidine or the pyrazine is a well-established synthetic procedure and remains an important contributor to the synthesis of complex substituted pteridines. Significant extensions of these methods have been described at both the pyrimidine and pyrazine rings.

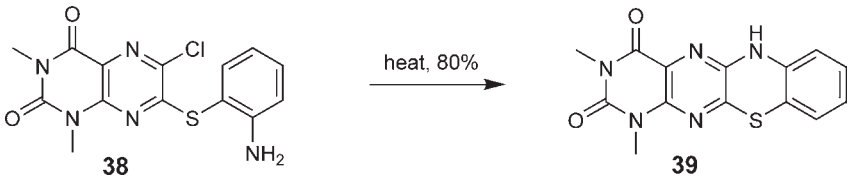
6,7-Dichloro-1,3-dimethyllumazine **36** has been known for many years to favor nucleophilic substitution at C-7, reflecting the more extensive delocalization of the intermediate adduct onto O-4 compared with attack at C-6. An exception to this generalisation is mercaptide, which affords lumazine-6-thiols if C-7 bears a substituent (typically N, O, or S). It has now been found that alkylthiolate anions in general displaced chloride at C-6 in 65–81% yield <1996PTR113>. The alkylthio groups lend themselves to further alkylation and derivatization. Alkylthio derivatives such as **37** were converted into ribosides and oxidation of benzyl thioethers to sulfones converted the thioether into a good leaving group for further nucleophilic substitution (see below). In one case, a non-sulfur nucleophile was shown to be able to displace the 6-chloro substituent in an intramolecular reaction (**38** that led to the tetracyclic 1,3-dimethylbenzo-1,4-thiazino[3,2-*g*]lumazine **39**) in good yield.



36

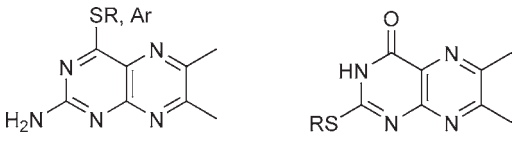


37



38 **39**

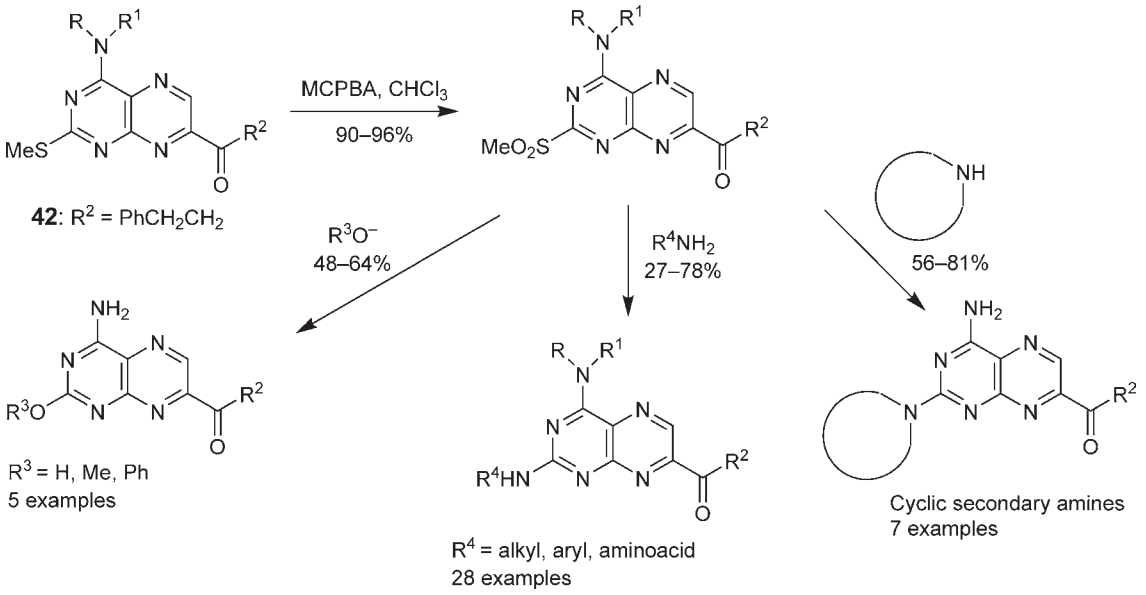
Alkylthio derivatives have also been developed as the basis for the preparation of libraries of pteridines and related heterocyclic compounds <2004T943, 2003OBC664>. In the 2- or 4-position, various alkyl- and arylthiopteridines (**40**, **41**) undergo nucleophilic substitution by primary aromatic or aliphatic amines and secondary aliphatic amines under vigorous conditions to afford the corresponding amino derivatives in moderate yields. Oxidation of the sulfur with *m*-chloroperbenzoic acid or dimethyldioxirane (DMDO) affords intermediate sulfones which undergo substitution under much milder conditions and in higher yields at the cost of a more complex workup. The significance of this approach for the synthesis of libraries was demonstrated by the unexpected identification of some 2-*N*-alkyl compounds as inhibitors of GTP cyclohydrolase 1 (GTPCH 1) <2004T943> (see also Section 10.18.12).



40: R = CH_2Ph; Ar = 4-C_6H_4Me

41: R = Me, CH_2Ph

Other examples of the use of this reaction have yielded diverse collections of pteridines from **42**, produced by acyl radical attack (see Section 10.18.5.6) on 2,4-disubstituted pteridines with a free 7-position <2004PTR129> (**Scheme 5**; **Table 1**).



42: R^2 = $PhCH_2CH_2$

Scheme 5

The ready alkylation of heterocyclic thiols lends this link to applications in solid-phase synthesis. Although much more work has been done in other heterocyclic systems, a prototype solid-phase synthesis has been described in which the pteridine is built from a 2- or 4-alkylthiopyrimidine attached to a cross-linked polystyrene support <2003OBC1909, 2003TL1267> Oxidative cleavage was preferred using DMDO to avoid unwanted by-products

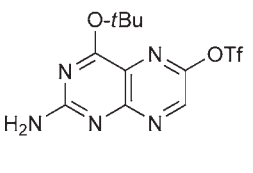
Table 1 2-Substituted pteridines by nucleophilic displacement of 2-sulfones ($R^2 = CH_2CH_2Ph$) (**Scheme 5**) <2004PTR129>

Nucleophile	*Yield* (%)
R^3O	
OH	57
OMe	64
OPh	48
R^4NH_2	
Me	78
i-Pr	35
CH_2CO_2H	63
Ph	60
Cyclic amine	
Piperidine	78
Morpholine	81

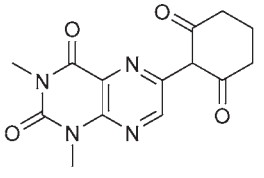
associated with peracids. 4,6-Dichloro-5-nitropyrimidine has been used as a precursor in the solid-state synthesis of 4-aminopteridin-6(5*H*)-ones through nucleophilic substitution of chloride by an amino acid Wang resin derivative <2000TL8177>.

Examples of substitution at C-6 have been greatly extended by the development of methods for the preparation of triflates such as **43** <1999H(50)117, 2002H(57)1841>. *N*-Oxides typically serve as precursors. In the case of pterins, 4-butoxypterin-8-oxide reacted with triflic anhydride to afford the 6-triflate **43**; the course of this conversion parallels that of 8-*N*-oxides being transformed into 6-chloro compounds by acetyl chloride in the presence of trifluoroacetic acid (TFA) <1999AXC254). Compound **43** underwent substitution by many nucleophiles bearing a variety of functional groups including *β*-dicarbonyl carbanions, thiolates, and *umpolung* reagents (cyanohydrins and thioacetals).

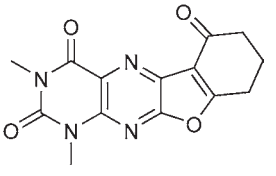
In the case of 1,3-dimethyllumazines, the 6-triflate can be prepared from the 5-*N*-oxide using triflic anhydride (86%); similarly, the 6-chloro (96%) and 6-bromo (76%) compounds can be obtained by reacting the *N*-oxide with acetyl chloride and acetyl bromide, respectively <1997PTR1>. Substitution by simple nitrogen, oxygen, and sulfur nucleophiles was successful in yields ranging from 37 to 83%; the most reactive nucleophile investigated was the phenylselenide anion which afforded a 95% yield. More interesting in synthetic terms is substitution by the anions of 1,3-dicarbonyl compounds to afford the corresponding C-alkylated pteridine, for example **44** <1999H(50)117, 2002H(57)1841>; in this case, a further oxidative cyclization of the enolate anion adding to C-7 took place affording the tetracyclic structure **45**.



43



44



45

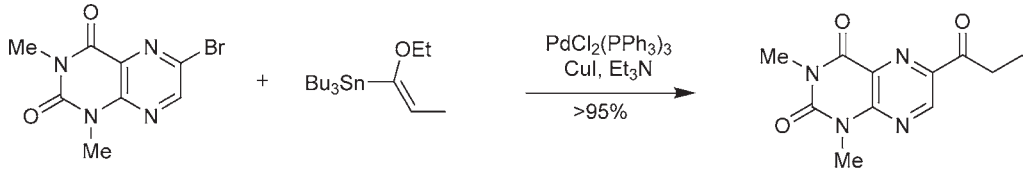
Selectivity in the reactions described above relies upon the different reactivity of leaving groups. However the intrinsic reactivity of chloride as a leaving group in nucleophilic substitution differs greatly from position to position. In the course of the synthesis of inhibitors of a cyclic adenosine monophosphate (cAMP)-specific phosphodiesterase, it was shown that the order of reactivity for secondary amine nucleophiles is C-4 > C-7 > C-2 > C-6 <1998JME4733>. Further medicinal chemical examples of these nucleophilic substitution reactions have been reported <1999JME4108, 2005BML675> (see Section 10.18.12.8).

10.18.7.3 Electrophilic Attack

Electrophilic attack on the pteridine nucleus is not a common reaction and no new examples of significance have been reported during the period under review; earlier examples can be found in CHEC-II(1996) <1996CHEC-II(7)679>.

10.18.7.4 Metal-Catalyzed Substitution

Organometallic coupling reactions have assumed great importance in all fields of chemistry and their applications in pteridine chemistry are increasing. As found in purine chemistry, the success of individual reactions can depend upon the availability of competing coordination sites for the catalytic metal ion, the common 2-amino-4-oxo substitution pattern being frequently associated with low reactivity. However, in cases where chelation is not possible, such as in 1,3-dimethyllumazines, yields can approach quantitative <2000J(P1)89> (**Scheme 6**). For example, the 6-bromolumazine **46** undergoes a Stille coupling in the presence of catalytic copper(I) with the tri-*n*-butyltin enolate to afford the 6-(1-propanoyllumazine) **47**. Similar reactions were also demonstrated with 1,3-unsubstituted, and with 1- and 3-methyllumazines. On the other hand, coupling with ethyne was only possible on a pyrazine precursor to the lumazines. Phenylacetylene has been shown to couple successfully with 6-chloro-1,3-dimethyllumazine <2001BKC141>.

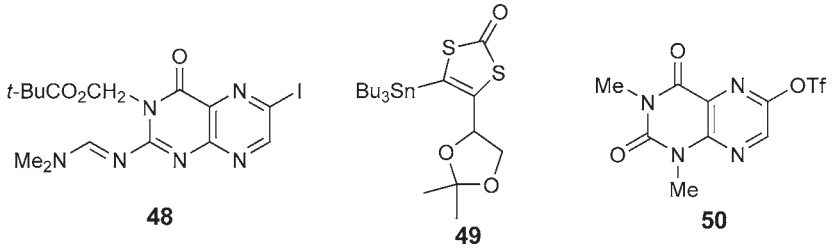


46 **47**

Scheme 6

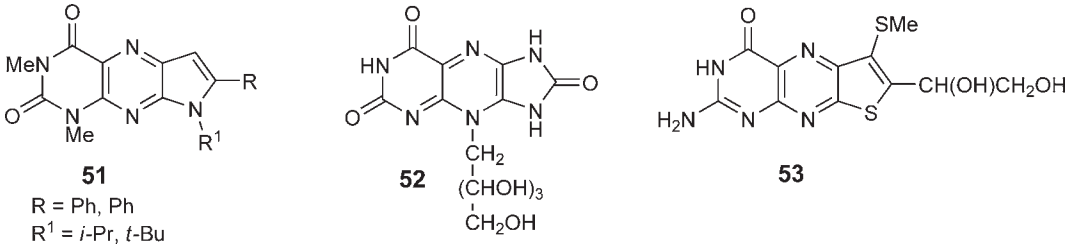
A major advantage of these reactions in general is their ability to tolerate an exceptionally wide range of substituents in the coupling partners. Thus, the synthesis of intermediates relating to the molybdenum cofactor has been possible by Stille coupling of 6-iodopterins **48** with complex stannyl reagents such as **49** <1998T9559>. The extension of this coupling reaction to the preparation of the organic ligand of the molybdenum cofactor in protected form has also been reported <2001J(P1)3239>. Sonogashira cross-coupling reactions with 6-chloro-1,3-dimethyllumazines as substrates are also effective for forming pteridinyl-6-alkynes <2003RCB1403>.

Regioselective oxidative coupling with copper alkynides to the 1,3-dimethyllumazine 6-triflate to form the 7-alkynyl-6-triflates (**50**, 20–72% yield, six examples) has been demonstrated; further elaboration by nucleophilic substitution of the triflate was also described <2000H(53)1259>. 1,3-Dimethyllumazine-6-alkynes have been selectively hydrated to give the 6-(β-oxo) derivatives using mercuric sulfate in aqueous TFA in yields approaching quantitative <2000J(P1)89>; the resulting ketones showed typical carbonyl reactivity such as reduction and C-α nitrosation, properties similar to those found for 4-amino-2-methylthiopteridine 7-ketones <2004PTR129>.



48 **49** **50**

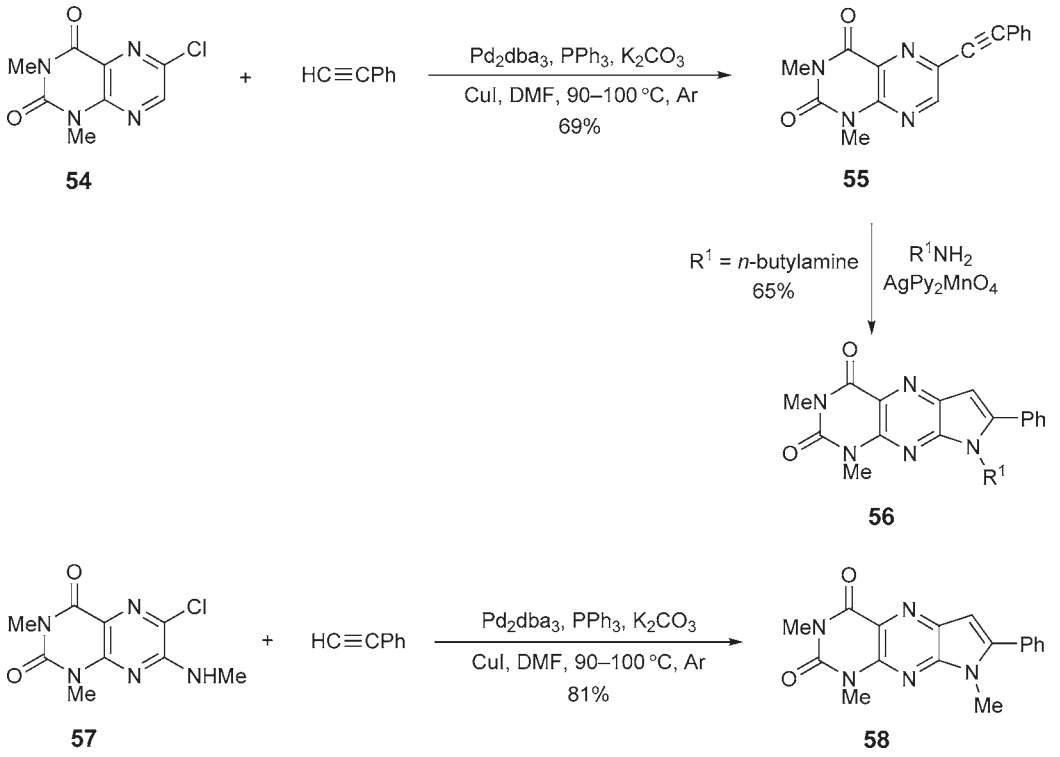
Substitution by alkynes using organometallic reagents has been used as the first step in the synthesis of fused-tricyclic pteridine derivatives **51–53** using oxidative S_N^H reaction of 6-alkyn-1-yl derivatives <2003RCB1403>. This method of annelation is of particular use in the synthesis of analogues of natural pteridines, for example, of the yellow pigment russupteridine **52** and the metabolite of the molybdenum cofactor, urothione **53**.



51
R = Ph, Ph
R^1 = *i*-Pr, *t*-Bu

52 **53**

Thus 6-chloro-1,3-dimethyllumazine **54** reacted with terminal alkynes, such as phenylacetylene in dimethylformamide (DMF), under Sonogashira conditions, to give **55**. Oxidative amination of the 6-(alkyn-1-yl)lumazine **55** with primary alkylamines such as *n*-butylamine in the presence of $AgPy_2MnO_4$ afforded the pyrrolo[3,2-*g*]pteridine-5,7(6*H*,8*H*)dione **56** in good yield (**Scheme 7**) <2003RCB1403>. The ease of oxidative amination and subsequent heterocyclization was dependent on the bulkiness of the amine and the nature of the substituent R^1. Alternatively, 6-chloro-7-methylaminolumazine **57** reacting with phenylacetylene gave directly pyrrolopteridine **58** in good yield. Using a similar procedure and sulfur nucleophiles, it was possible to prepare pteridines such as **53** with a thiophene ring in place of the pyrrole ring.



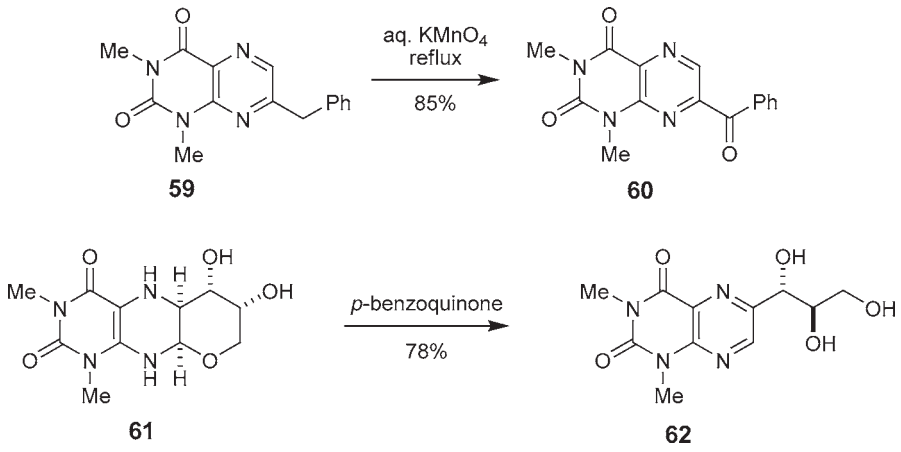
Scheme 7

10.18.7.5 Oxidation Reactions

Alkyl groups attached to carbon atoms in pteridines show many of the typical oxidation characteristics of benzylic groups, the electron-deficient heterocyclic rings being largely resistant to oxidation (**Scheme 8**). Thus potassium permanganate smoothly oxidized the 7-benzyllumazine **59** to the corresponding 7-phenylketone **60** <2001BKC141>. The same reaction was practical for the 6-isomer and for both the corresponding pterins. Similarly, many side-chain functional groups susceptible to oxidation can be transformed in preparatively useful yields.

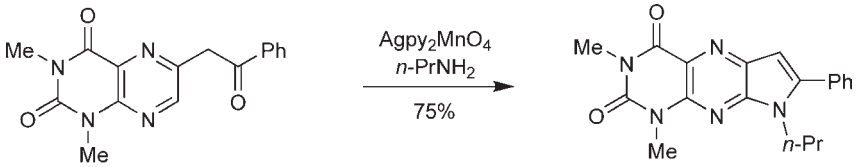
Dihydroxypyranopteridines are well known to undergo oxidative cleavage to 6-formyl pteridines with periodic acid; interestingly, it has been reported that with a very mild oxidizing agent, *p*-benzoquinone, oxidation of the tetrahydropyranopteridine **61** afforded the 1,2,3-trihydroxypropyl substituted analogue **62** <2001JHC727>.

Not all reactions, however, proceed as smoothly as might be expected. In compounds related to those in **Scheme 7**, the 6-phenylethynyllumazine **63** afforded only 10% of the expected 6-(2-oxophenylethyl)lumazine together with a small quantity of pyrimidine cleavage product when oxidized with bispyridinesilver permanganate <2003RCB1403>. On the other hand, if the reaction was carried out in the presence of propylamine, the pyrrolopteridine **64** was obtained in good yield (**Scheme 9**).



59 **60** **61** **62**

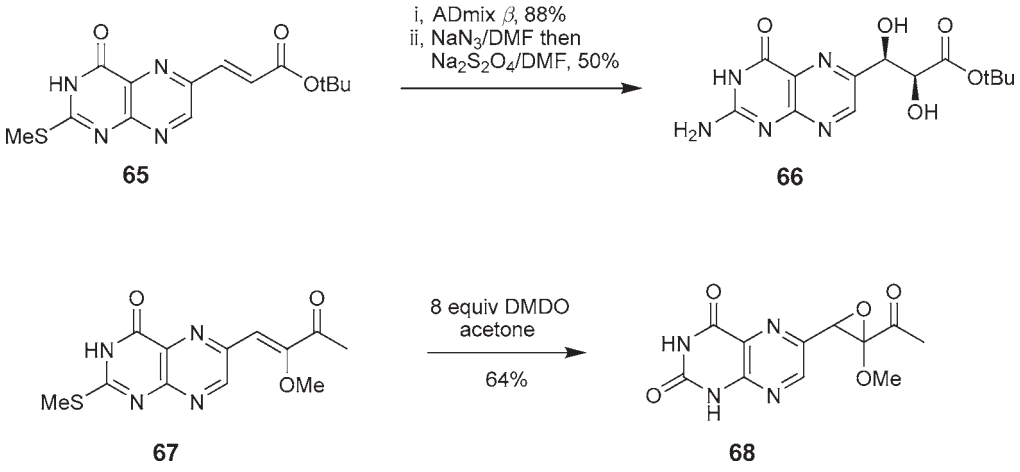
Scheme 8



63 **64**

Scheme 9

This problem may, however, be a special case because the oxidation of pteridine alkenes in the presence of sensitive substituents such as alkylthio was shown to be possible using ligand-assisted catalysis with osmium tetraoxide or DMDO (**Scheme 10**). In the case of pteridine **65**, a clean series of transformations to afford the pterin **66** was possible <2003OBC664, 2005PTR53O04/04>. However, if oxidation was carried out under moist conditions, the corresponding 2-oxopteridine (lumazine) was always obtained as illustrated by the conversion of **67** into the epoxide **68**.



65 **66** **67** **68**

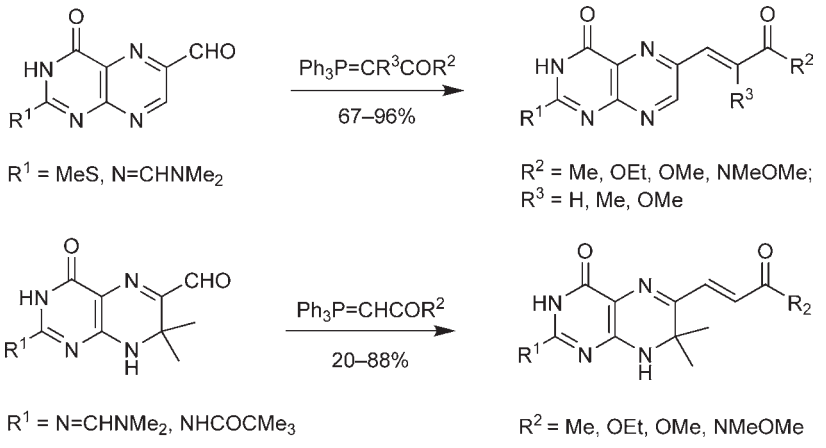
Scheme 10

10.18.7.6 Reduction Reactions

No new reactions of significance appear to have been published during the period of this review; earlier examples can be found in CHEC-II(1996) <1996CHEC-II(7)679>.

10.18.7.7 Side-Chain Reactions

The alkene substrates required for the oxidation reactions cited in Section 10.18.7.5 were obtained by Wittig reactions of the corresponding 6-aldehyde. This is a very general reaction and is successful with a wide range of stabilized Wittig reagents using either the 2-pivaloylamino, 2-formamidino, or 2-alkylthiopteridine-6-aldehydes as substrates (**Scheme 11**) <2003OBC664; 1999J(P1)163>. Examples in the lumazine series have also been described (**Table 2**) <2004PTR10>.

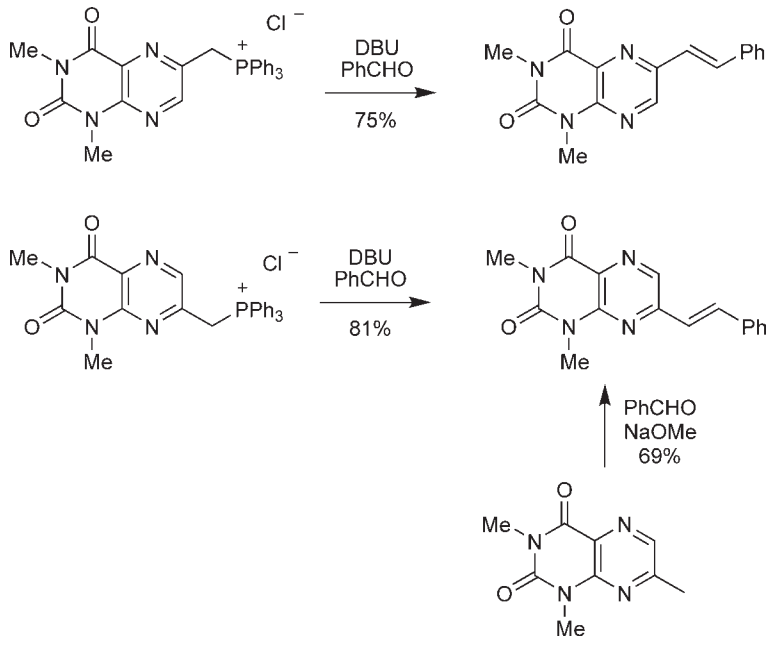


Scheme 11

Table 2 Examples of Wittig alkenylations (**Scheme 11**) <2003OBC664, 1999J(P1)163>

	R^1	R^2	R^3	*Yield* (%)
From 7-unsubstituted pteridines	MeS	OMe	Me	78
	MeS	OMe	Me	76
	MeS	Me	H	71
	N=CHNMe$_2$	NMeOMe	H	92
	N=CHNMe$_2$	OMe	H	97
	N=CHNMe$_2$	OEt	H	67
From 7,7-dimethyl-7,8-dihydropteridines	N=CHNMe$_2$	NMeOMe	H	88
	N=CHNMe$_2$	OMe	H	74
	NHCOCMe$_3$	NMeOMe	H	34
	NHCOCMe$_3$	OMe	H	54
	NHCOCMe$_3$	OEt	H	20

Turning the Wittig reaction the other way round, pteridinyl-6- and -7-phosphonium salts have been studied as donors to benzaldehydes to afford styryl derivatives (**Scheme 12**) <2004PTR10>. Conversion of the phosphonium salt into the phosphonium ylide was achieved using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This reaction has been used for the synthesis of potent anticancer agents (see Section 10.18.12.8 <2000JME1620>). Also, in the field of carbanion chemistry, 6-methyllumazines were shown to be substrates for Claisen ester condensations with alkyl esters bearing electron-withdrawing substituents as the acceptor such as ethyl oxalate. In the absence of such groups, the reaction is complicated by the addition of a C-6 carbanion to C-7 of another lumazine molecule leading to dimerization. 7-Styryllumazines can be prepared by aldol condensation of benzaldehyde with 1,3,7-trimethyllumazine in the presence of sodium methoxide in 75–85% yield, a reaction that fails with the 6-methyl isomer; however, as noted above, both isomers can be obtained using Wittig reactions.

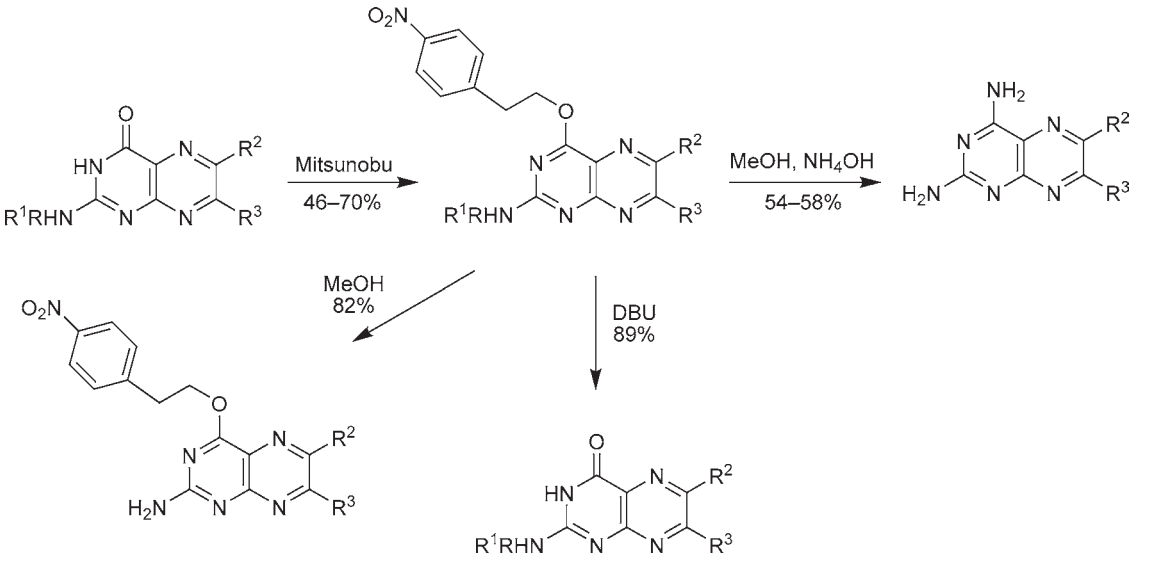


Scheme 12

6-Haloalkyl-substituted pteridines are also practical substrates for many nucleophilic substitution reactions, as implied by the phosphonium salt chemistry above. In the case of 6-bromomethylpteridines, a wide range of ring substituents are tolerated; both 2,4-diamino and 2-amino-4-oxo compounds undergo nucleophilic substitution with O-, S-, and N-nucleophiles <1999PTR79>. Twenty-one examples of the substitution of 2,4-diamino-6-bromomethylpteridine in yields of 40–70%, mostly by alcohols and alkoxides, but also by ammonia, primary and secondary amines, and methanethiol, were presented. The hydrolysis of the 4-amino group by either acid or base led readily to the corresponding pterins. There are also many applications of this chemistry in the synthesis of biologically active compounds, especially folate and methotrexate analogues (see Section 10.18.12.8). Related acylation reactions have also been reported: 1,3-dimethyllumazine-6-carbonyl chlorides were found to acylate the magnesium salts of β-dicarbonyl compounds and their cyano analogues in good yields <2004PTR10>.

Although some recent studies have sought to minimize the presence of protecting groups <2003OBC664>, control of pteridine chemistry can be greatly improved by using protecting groups for the ring substituents, thereby allowing successful transformations of side chains. As in all fields of chemistry, the removal of a protecting group can be troublesome; in the case of pteridine pivalamides, it has been shown that this group can be conveniently cleaved using iron(III) nitrate in methanol at room temperature <2004TL5643>. However, a particularly thorough study that builds upon nucleoside chemistry has recommended the use of the 2-(4-nitrophenyl)ethyl (NPE) group for the protection of O-4 <2003HCA1>. For 2-acetamido or isobutyramido pteridines, the NPE group can be put on using Mitsunobu conditions in 60–90% yield, a reaction that was also successful with 2-dimethylamino pteridines (**Scheme 13**; **Table 3**). Selectivity in cleaving protecting groups was possible: *N*-acetyl was selectively removed in the presence of NPE using methanol at 50 °C and DBU selectively cleaved the NPE group. If ammonia in methanol were used, both the acetamide was cleaved and the 4-ONPE group underwent nucleophilic substitution to afford a 2,4-diaminopteridine. An alternative 2-amino protecting group that gave access to similar chemistry was (dimethylamino)methylene; in this case, however, the Mitsunobu reaction placed the NPE protecting group on N-3.

A study of pterins in the context of biologically reactive oxygen species was facilitated by protecting groups for nitrogen, 2-(dimethylaminomethylene) and 3-acyl (especially pivaloyl); interestingly, both groups were put on together in a one-pot reaction in 52–95% yield in DMF solution using the required acid chloride and 6-formylpterin as substrate <2006OBC1811>. New selective protecting groups have also figured prominently in the synthesis of photoaffinity labels for tetrahydrobiopterin-dependent enzymes <2000HCA2738> (see also Section 10.18.12.2). While inevitably increasing the number of steps in a synthesis, protecting groups make both simple and complex side-chain manipulation practical in pteridine chemistry as these contributions show. For an example in complex



Scheme 13

Table 3 Examples of Mitsunobu reactions (**Scheme 13**) <2003HCA1>

R	R^1	R^2	R^3	*Yield* (%)
Ac	H	Me	H	46
Ac	H	CH_2OAc	H	70
Ac	H	Ph	H	68
Ac	H	Ph	Ph	69
H	H	CH_2OH	H	54
H	H	Ph	Ph	58

natural product synthesis, appropriately protected pterins readily underwent standard functional group interconversion, as shown by the sequence 6-CHO to 6-CO_2H to 6-amino to 6-iodo, that was required in the synthesis of compounds related to the molybdenum cofactor <1998T9559>.

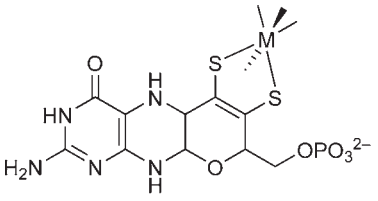
10.18.8 Reactivity of Substituents Attached to Nitrogen

10.18.8.1 *N*-Oxides

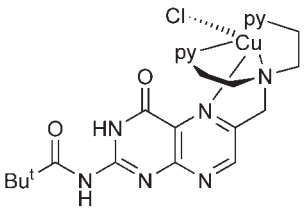
In a modern version of well-established *N*-oxide chemistry, 1,3-dimethyllumazine-5-oxide was converted into the corresponding 6-triflate using trifluoromethanesulfonic anhydride thereby opening the way to many reactions mentioned in Section 10.18.7.2 <1997PTR1> <2002H(57)1841>. Similar reactions with acetyl chloride and acetyl bromide afforded the corresponding 6-chloro- and 6-bromolumazines.

10.18.8.2 Metal Complexes

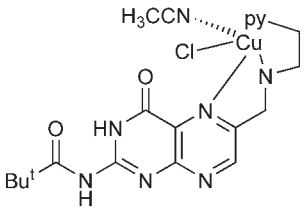
Lumazines have been extensively studied as ligands for both main group and transition metal ions but other pteridines are also important as ligands, one of the most significant being the molybdenum cofactor in which a dithiolene substituent acts as a ligand for molybdenum or tungsten (**69**; see also Sections 10.18.3 and 10.18.12.3). An extensive review of the field has appeared which highlights the fact that N-5 in pteridines is an important donor as is also the case in related flavin complexes <1999CCR323>. Unsubstituted pterins rarely form stable complexes because of their weak donor and poor solubility properties. However, if additional side-chain substituents are present as in *N*-alkyllumazines or protected pterins, the coordination chemistry is rich as illustrated by **70** and **71**.



69: M = Mo, W



70



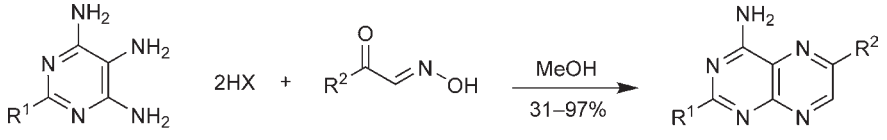
71

10.18.9 Ring Syntheses

Progress in the ring synthesis of pteridines has been characterized by an increase in the range and complexity of substituents that have been accommodated. The basic strategies use either pyrimidine or pyrazine building blocks as would be expected. Also apparent is an increased emphasis on syntheses that lead to potential diversity in libraries of pteridines in support of modern medicinal chemistry. This is typified by the extensive range of alkylthio substituents that can be replaced by nucleophiles either directly or following oxidation (see Section 10.18.7.2). However, such variations can lead to substantial changes in chemical reactivity of the pyrimidine or pyrazine ring; generality should therefore be claimed with caution. A review has appeared collecting information on pteridine synthesis to early 1998 <1998H(48)1255>.

10.18.9.1 Ring Syntheses from Pyrimidines

As noted in the introduction, the classical methods for syntheses of pteridines from pyrimidines developed by Isay and Gabriel, Timmis, Polonovsky-Boon, and Taylor have been known for many years <1996CHEC-II(7)679>. Recent developments focus on improvements in scope and selectivity. For example, the Isay and Gabriel methods involve the condensation of a 5,6-diaminopyrimidine with 1,2-dicarbonyl compounds, a reaction that commonly affords mixtures of products depending upon the reactivity of the reacting partners. By converting an aldehyde into its oxime, it has been found that the reactivity difference in α-dicarbonyl compounds can be magnified to afford single products in condensation reactions (**Scheme 14**; **Table 4**). The regioselective, one-step synthesis of 2,6-disubstituted-4-aminopteridines **72** from 2-substituted-4,5,6-triaminopyrimidine dihydrohalides **73** and α-ketoaldoximes **74** has been demonstrated <1997TL6835>. The oxime methodology has also been used in a large study of inhibitors of NOS (<1999JME4108>; see Section 10.18.12.8).



73 **74** **72**

R^1 = H, NH_2, SCH_3, C_6H_5
X = Cl, Br
R^2 = CH_3, CH_2CH_3, CH_2X, C_6H_5, *p*-CH_3-C_6H_4

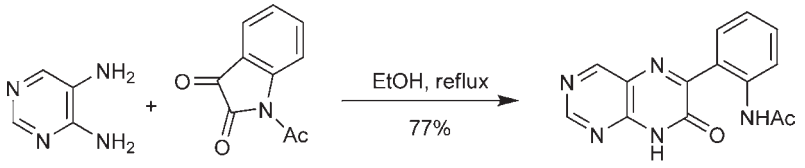
Scheme 14

An alternative differentiation in reactivity is to use an α-ketoamide (**Scheme 15**). Thus 4,5-diaminopyrimidine reacted with the *N*-acetylindolone **75** to afford the 6-arylpteridin-7-one **76** in good yield presumably *via* initial acylation of the 5-amino group by **75** <1996RTC31>.

α,β-Unsaturated carbonyl compounds also offer sites for nucleophilic attack with differential reactivity and these have been exploited in the regioselective synthesis of pteridines (**Scheme 16**; **Table 5**). 5,6-Diaminopyrimidines **77** reacted with dimethyl acetylenedicarboxylate (DMAD) to afford the corresponding pteridines **78** on reflux in

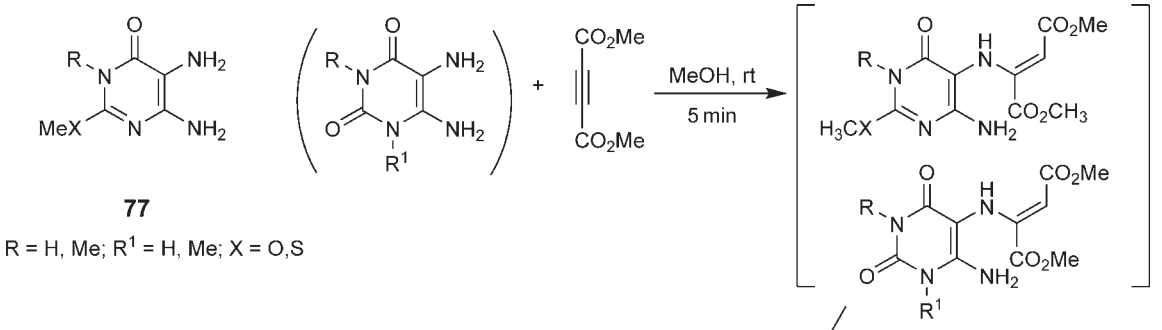
Table 4 Examples of acetoxime-ketone synthesis of pteridines <1997TL6835>

R^1	R^2	*Yield* (%)
NH_2	Me	81
NH_2	Ph	93
H	Me	31
H	Ph	88
MeS	Me	47
MeS	Ph	97
Ph	Me	61
Ph	Ph	88



75 **76**

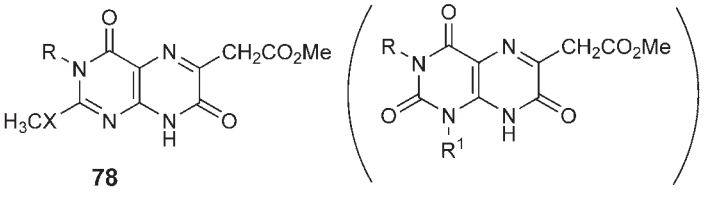
Scheme 15



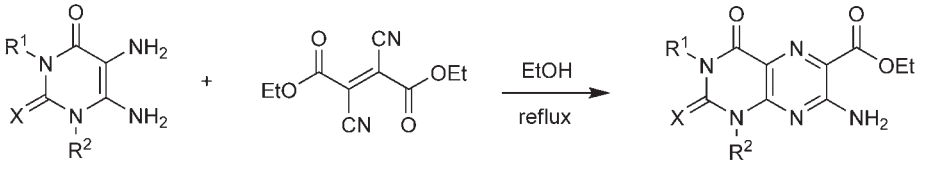
77

R = H, Me; R^1 = H, Me; X = O,S

79



78



81 **80** **82**

Scheme 16

Table 5 Synthesis of pteridines by Michael addition of 5,6-diaminopyrimidines (**Scheme 16**) <1999JHC435>

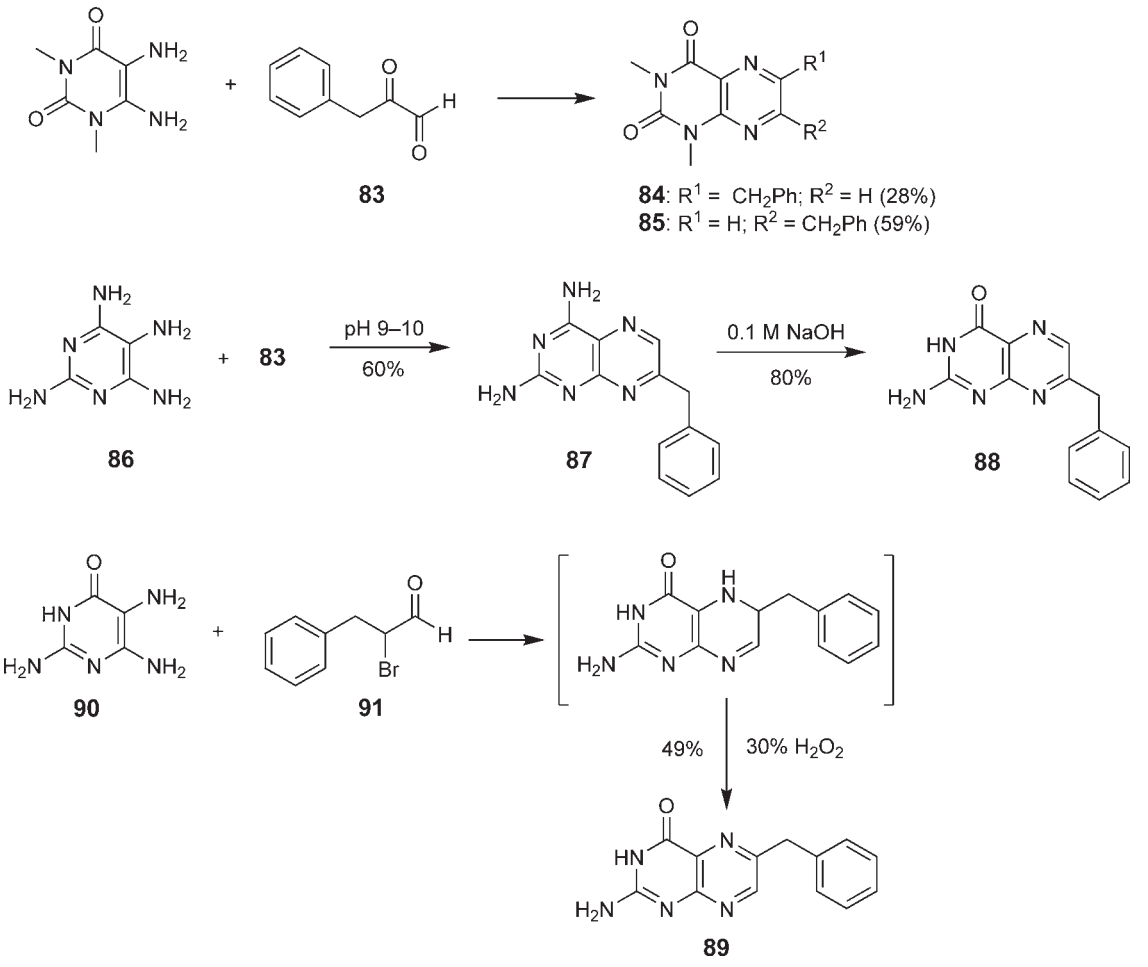
Compound	*R*	R^1	*X*	*Yield* (%)
79	H		O	88
	H		S	91
	Me		O	90
	Me		S	91
	H	H		63
	Me	H		61
	Me	Me		88
	H	Me		89
78	H		O	91
	H		S	92
	Me		O	92
	Me		S	85
	H	H		90
	Me	H		88
	Me	Me		75
	H	Me		66
82	Me	Me	O	65
	Et	Et	O	62
	Pr	Pr	O	60
	Bu	Bu	O	36
	Me	Me	S	34
	Et	Et	S	33
	Pr	Pr	S	35
	Bu	Bu	S	46

methanol in one step <1999JHC435>. The intermediate **79** was also isolable after 5 min if the reaction was carried out at room temperature. Even more activated α,β-unsaturated carbonyl compounds such as diethyl (*E*)-2,3-dicyanobutenedioate **80** were used as Michael acceptors for 1,3-dialkyl-5,6-diaminouracils **81** as donors to give the corresponding ethyl 7-aminopteridine-6-carboxylates **82** <1999JHC1317>. The structure of the single isomer **82** formed in this regioselective reaction was confirmed by 1-D and 2-D NMR techniques.

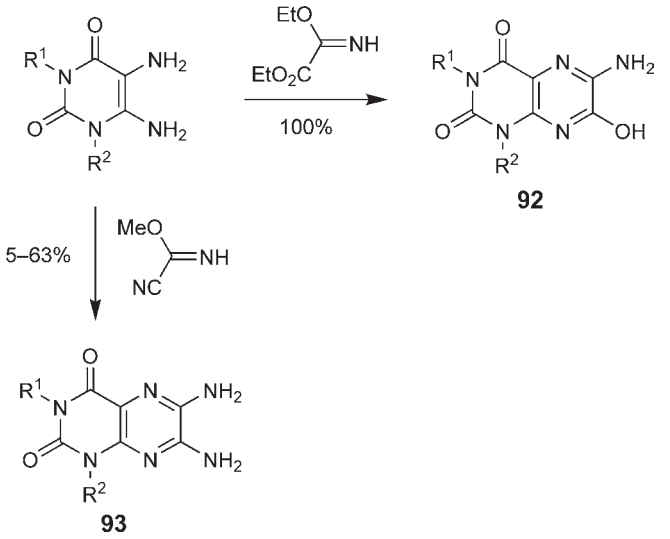
Reaction conditions can also play a role in determining the regioselectivity of condensation (**Scheme 17**). The reaction of 4,5-diamino-1,3-dimethyluracil with benzylglyoxal **83** gave a mixture of pteridines **84** and **85**, which were separated by column chromatography <2001BKC141>. However, when 2,4,5,6-tetraaminopyrimidine **86** reacted with benzylglyoxal at pH 9–10, only the 7-benzylpteridine **87** was obtained, which on hydrolysis afforded the corresponding 4-oxopteridine **88**. On the other hand, if the reaction was carried out at a pH below 8, a mixture of 6- and 7- benzylpteridines formed. In yet another method for introducing differentiated reactivity at carbon, the 6-benzylpteridine **89** was obtained selectively by the reaction of 2,4,5-triaminopyrimidin-5(1*H*)-one **90** with 2-bromo-3-phenylpropanal **91**.

Other reagents with differentiated reactivity used in partnership with 5,6-diaminopyrimidines include imidates (**Scheme 18**; **Table 6**) <1998PTR175>. High-yielding condensation reactions afforded 6,7-disubstituted derivatives that, in the case of the 7-hydroxy derivative **92**, were further modified *via* the 7-chloro compound and nucleophilic substitution. Also notable is that 6,7-diaminolumazines such as **93** can be prepared, products that are not available by direct nucleophilic substitution of 6- and 7-chloro derivatives as noted above. Microwave irradiation has been shown to promote the condensation of α-ketoaldehydes with 5,6-diaminouracils to give 6- and 7-substituted-tetrahydropteridine-2,4-diones with good regioselectivity <2006RJO136>.

The syntheses of 7- and 9-difluoro-substituted pterins from vicinal diaminopyrimidines and fluorine-containing aliphatic precursors have been reported <1996T13017>. The 7,7-difluoropterins can be considered as blocked dihydropterins because of their resistance toward the autoxidation at positions 7 and 8. 2,4,5-Triaminopyrimidine-5(1*H*)-one **90** reacted with aliphatic fluorinated precursors to give the pterins **94–96**. In the case of bromotrifluoroacetone as the aliphatic precursor, the pyrimidooxazine **97** was also isolated. 2-Amino-6-chloro-5-nitropyrimidin-4(3*H*)one reacted with amino alcohol **98** to give the 6-substituted pyrimidine **99** which on activation of the OH group with mesyl chloride and reduction of the nitro group with H_2/Pd gave the 6-trifluoromethylpterin **100** (**Scheme 19**). The synthesis of the required aliphatic precursors and UV and pK_a properties of fluoropterins were also reported.



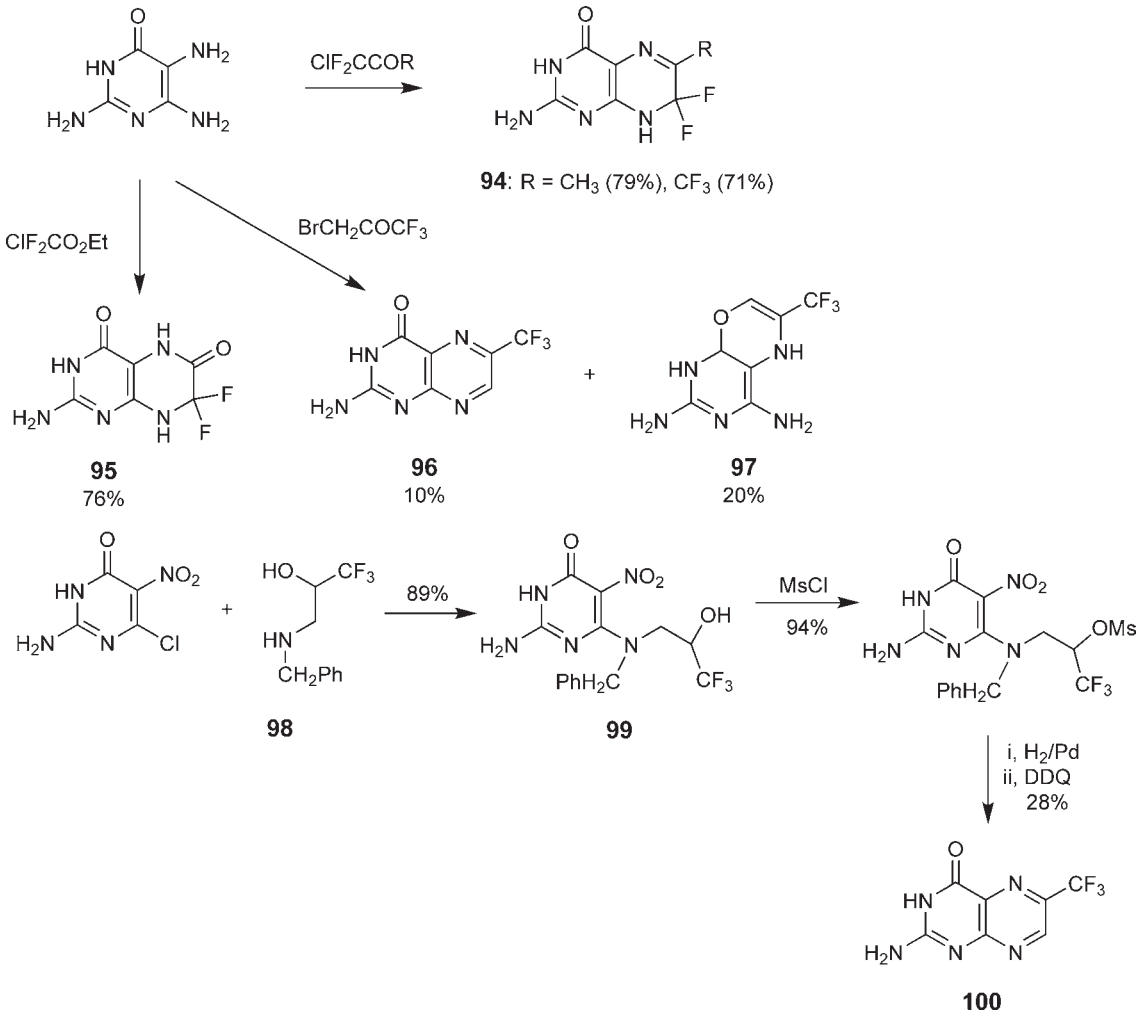
Scheme 17



Scheme 18

Table 6 Pteridine synthesis by imidate condensation with 5,6-diaminopyrimidine (**Scheme 18**) <2006RJO136>

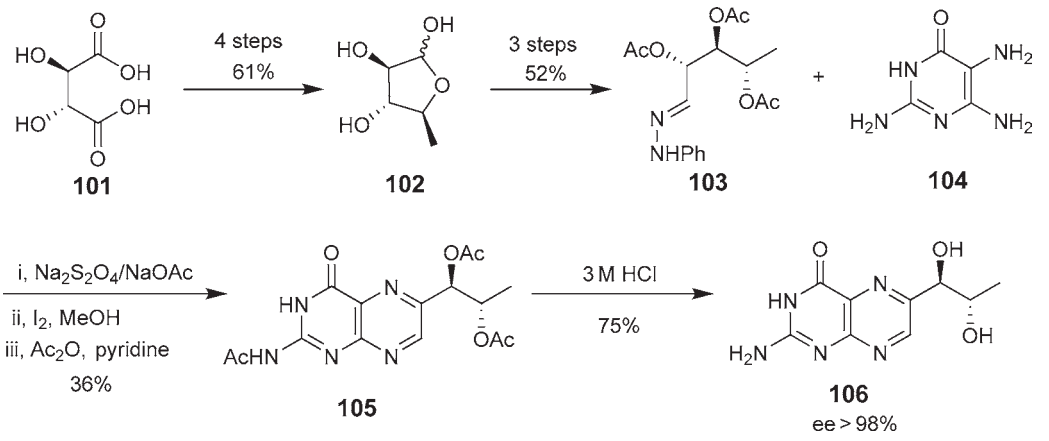
R^1	R^2	*Yield* (%)
Me	Me	66
H	H	62
Me	H	53
H	Me	63



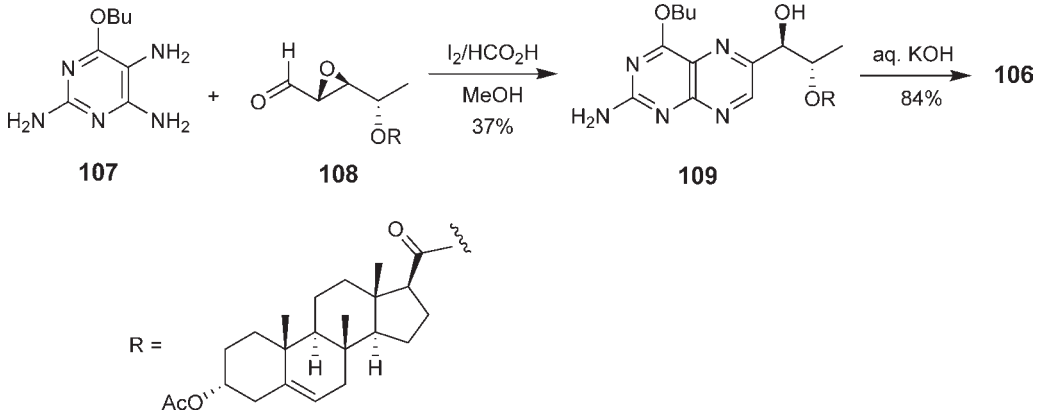
Scheme 19

In a wider context than fluoropterins, α-bromoketones have been shown to react with diaminopyrimidines to form mixtures of dihydro and conjugated pteridines but with good selectivity for the position of substituents on the ring. For example, phenacyl bromide reacted with 2,4,5-aminopyrimidin-6-one to give a mixture of 7,8-dihydro and fully conjugated 2-amino-7-phenylpteridin-4(3*H*)one <2001CHE755>. With 4,5-diaminopyrimidin-6-one and other aryl acyl bromides, only the fully conjugated product was isolated <2003CCC965>.

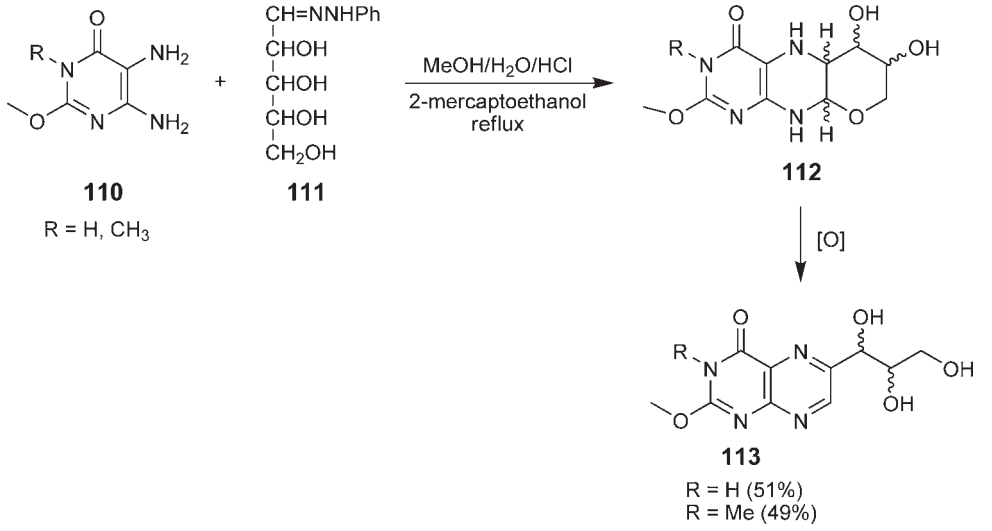
With carefully selected aliphatic precursors, the synthesis of single stereoisomers of side-chain-substituted pteridines has been achieved (**Schemes 20–22**). The synthesis of L-biopterin **106** requires 5-deoxy-L-arabinose **102** as a key intermediate preparable from the expensive sugars L-rhamnose and L-arabinose. Alternatively, the readily



Scheme 20



Scheme 21



Scheme 22

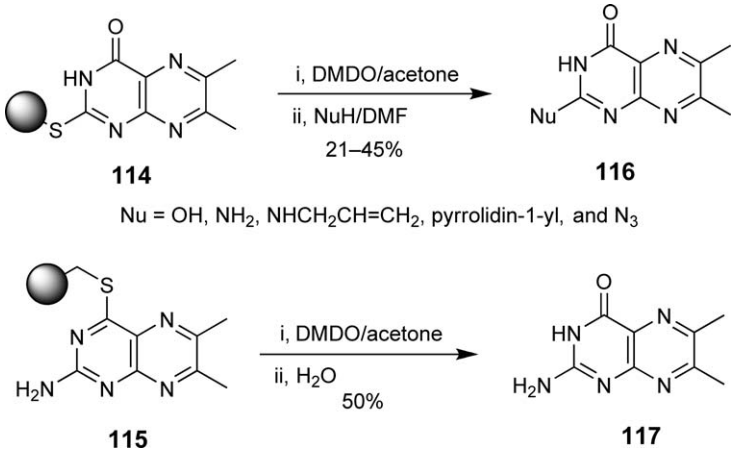
available L-tartaric acid **101** was used to prepare **102** which was then converted into its phenylhydrazone derivative **103** to condense with 2,5,6-triamino-4-pyrimidinol **104** <1996JOC8698>. Initial condensation of the pyrimidine C-5 amino group occurs at the phenylhydrazone imine and subsequent tautomerism creates the second carbonyl group for cyclocondensation at the adjacent carbon atom, thereby providing for regioselectivity of condensation and retaining the stereochemical integrity of the remaining carbon atoms.

An alternative route to such 6-(1-hydroxyalkyl)-substituted pteridines including **106** is from 2,4,5-triamino-6-butoxypyrimidine **107** and 2-formyloxiranes **108** in which the stereochemical properties are emphasized by the inclusion of the 17-steroidal ester <1992S303>. L-Biopterin **106** was synthesized from the oxirane **108** and **107** via a 5,6-dihydropteridine intermediate which was oxidized *in situ* to afford the product (**Scheme 21**). Syntheses of oxiranes and the condensation mechanism in the context of molecular orbital calculations were discussed. The field has been reviewed <1998H(48)1255>.

The use of sugar phenylhydrazones as precursors for the synthesis of L-neopterin has been referred to in the context of oxidation reactions in Section 10.18.7.5. This is an example of a well-established method and further cases with a variety of pyrimidines have been described (**Scheme 22**). The 5,6-diamino-2-methoxypyrimidin-4(3*H*)-ones **110** were condensed with protected pentose phenylhydrazones of both D- and L-series **111** such as D-ribose, D- and L-xylose, D- and L-arabinose to give corresponding pyrano[3,2-*g*]pteridines **112**. These pteridines on oxidation either in buffer solution (sodium carbonate/sodium bicarbonate pH = 10) with bubbling oxygen (where R = H) or in water with *p*-benzoquinone (where R = CH_3) gave corresponding polyhydroxypteridines **113** <2001JHC727>. The relative configurations at the stereocenters of the acetyl derivatives of **112** and **113** were determined by NMR and X-ray analysis. Other examples of this synthetic strategy include 4-amino-L-*erythro*-biopterin in a one-pot process <2002ACT343>, and intermediates in the synthesis of pteridinyl-6-alkenes described in Section 10.18.7.7 <2003OBC664>.

Despite all of the activity in pyrimidine-based synthesis, only one study has emerged of solid-phase versions of these reactions <2003TL1267, 2003OBC1909>. This chemistry was based upon condensation of dicarbonyl compounds with resin-bound pyrimidine-5,6-diamines through a 2-alkylthio link and oxidative cleavage as described in Section 10.18.7.2. The value of alkylthio substituents in the synthesis of complex substituted pterins has also been demonstrated in the synthesis of nucleic acid conjugates <2004OBC3588> (see Section 10.18.12.4).

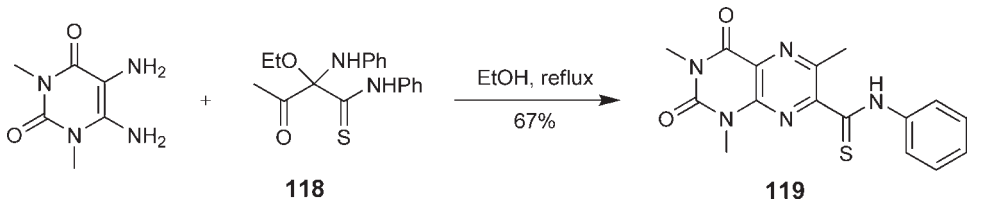
In modern medicinal chemistry, the creation of diversity on a structural framework is important. In principle, diversity at positions 2, 4, 6, 7, and 8 of pteridines can be achieved using such solid-phase chemistry. This prototype solid-phase synthesis involved nitrosation of the resin-bound pyrimidine, reduction of nitroso group with sodium dithionite, and subsequent cyclization with biacetyl to afford pteridines **114** and **115**. Cleavage from the resin by nucleophilic substitution of the oxidized sulfur linker using *m*-chloroperbenzoic acid or DMDO led to the pteridine products **116** and **117** (**Scheme 23**).



114 **116** **115** **117**

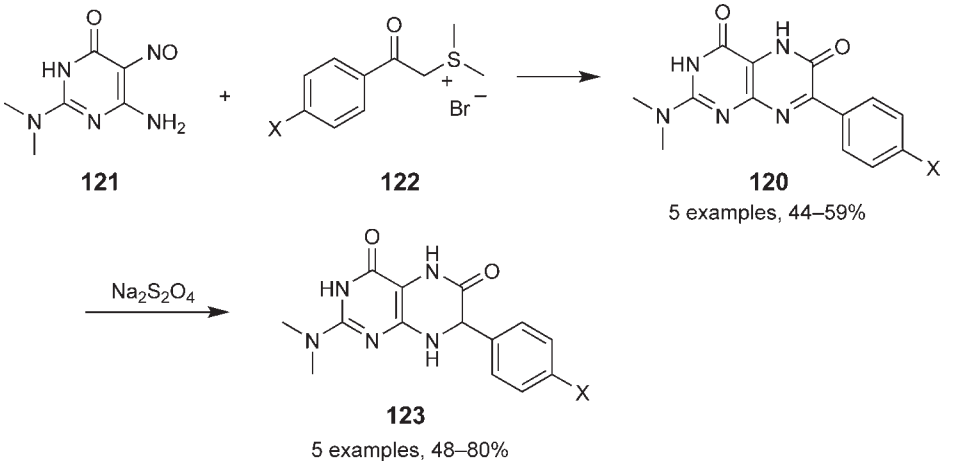
Scheme 23

An unusual rearrangement following cyclization using a masked α-carbonyl equivalent, 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **118**, to form 6,7-disubstituted pteridine **119** by simply refluxing in ethanol for 3 h was reported (**Scheme 24**) <2002JOC4526>. The synthesis of pyridopyrazine and related compounds using **39** was also discussed.



Scheme 24

As a final example of regioselective control (**Scheme 25**), sulfonium ylides usually give nitrones when reacted with nitroso groups *via* oxaziridine intermediates. However, 7-aryl-2-dimethylamino-3,4,5,6-tetrahydropteridine-4,6-diones **120** were directly formed when nitrosopyrimidine **121** reacted with dimethylphenacylsulfonium bromides **122** instead of the isomeric 5-oxides <1996H(43)437>. It was also reported that the resulting pteridines were reduced to give 7,8-dihydro derivatives **123** with sodium dithionite (**Table 7**).



Scheme 25

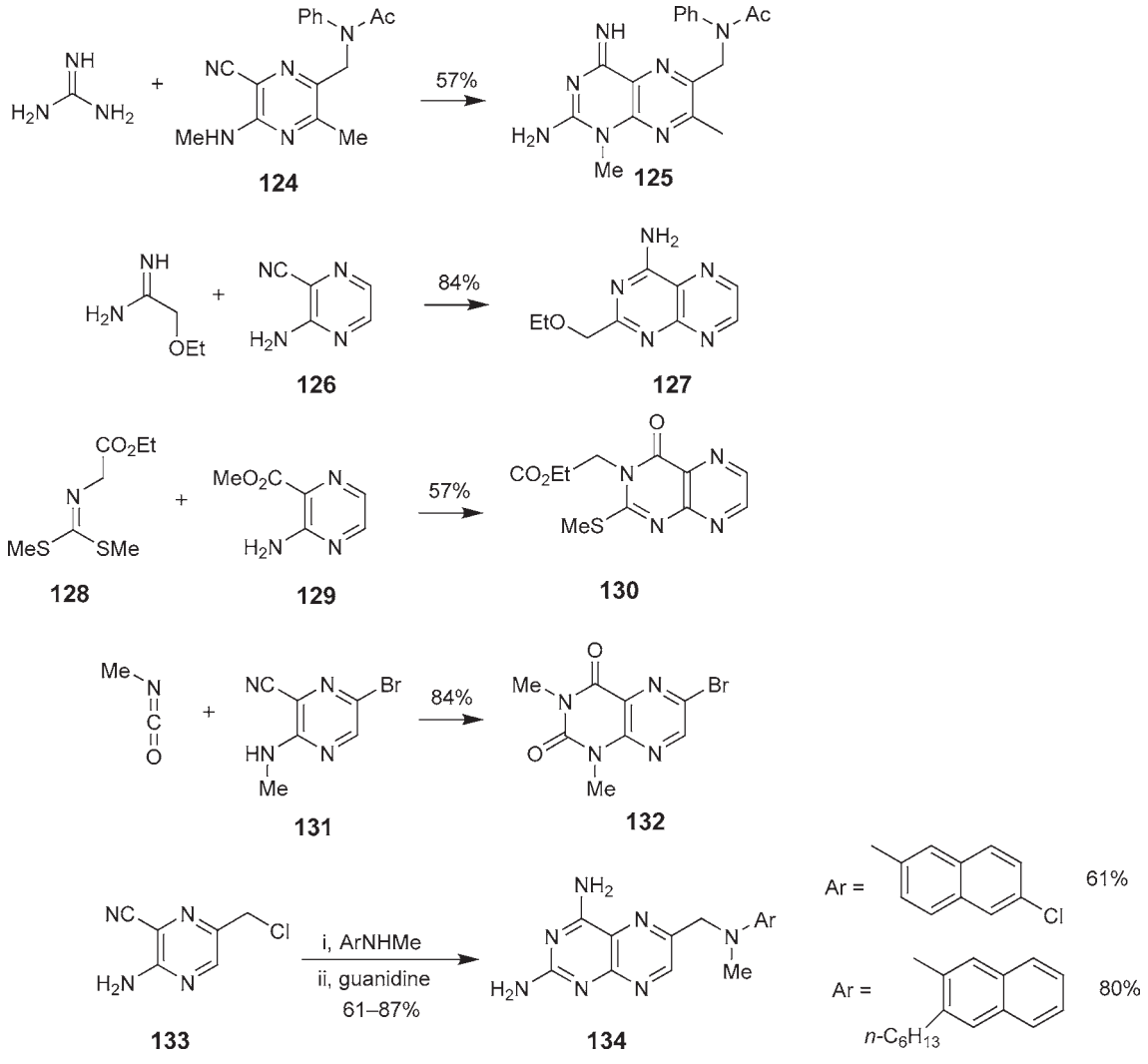
Table 7 Pteridine synthesis using 2-oxosulfonium salts as precursors (**Scheme 25**) <1996H(43)437>

Compound	*X*	*Yield* (%)
120	H	44
	Br	46
	Cl	59
	MeO	49
	Me	46
123	H	80
	Br	70
	Cl	52
	MeO	66
	Me	48

10.18.9.2 Ring Syntheses from Pyrazines

Although more recent than ring syntheses based on pyrimidines, the pioneering work of Taylor <1996CHEC-II(7)679> has established the condensation of aminocyanopyrazines and their derivatives with amidine equivalents as viable and general routes to the synthesis of pteridines. One advantage of this synthetic strategy is that the

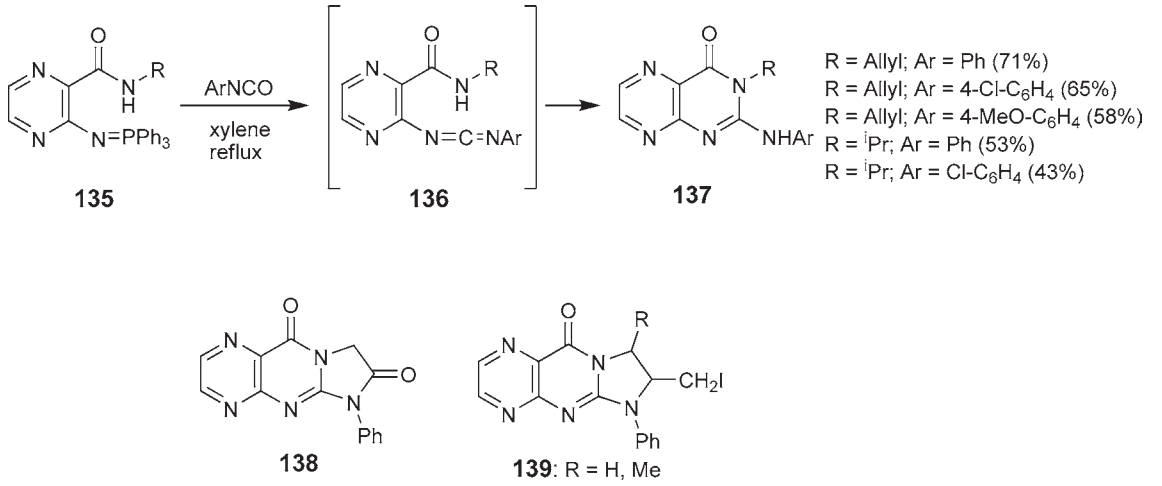
structure of the products is usually unambiguous. With guanidine itself (**Scheme 26**), the side-chain amide-substituted pyrazine **124** was shown to condense under basic conditions to afford the 4-iminopteridine **125** in moderate yield; the acetyl group remained intact <1997JHC973>. Substituted amidines have been found to react in good yield to give 6,7-unsubstituted pteridines **127** from the corresponding pyrazine **126**. Similarly, methyl 2-aminopyrazine-3-carboxylate **129** condensed, this time under acidic conditions, with the bis(dithioimidate) **128** giving access to an unusual N-3-substituted 2-methylthiopteridine-4-one **130** in moderate yield. A more substantial variation in this strategy has shown that the 1,3-dimethyllumazine system **132** can be prepared from methyl isocyanate and a 5-aminomethyl-6-cyanopyrazine **131** in high yield. Similar strategies have been used for the synthesis of potent anticancer agents (see Section 10.18.12.8 <2000JME1620>). Taylor's synthesis can also tolerate reactive substituents in the putative 6-position of the pteridine product. For example, in a search for anti-infective compounds, the 5-chloromethylpyrazine-*N*-oxide **133** was reacted firstly with substituted aromatic amines and then with guanidine to form the compounds for evaluation, **134**.



Scheme 26

Iminophosphoranes have also proved to be key intermediates because they react with carbonyl compounds, isocyanates, isothiocyanates, acid chlorides, carbon dioxide, and carbon disulfide to give a wide range of imines and heterocumulenes, which are intermediates to pteridines. The preparation of iminophosphoranes has been investigated

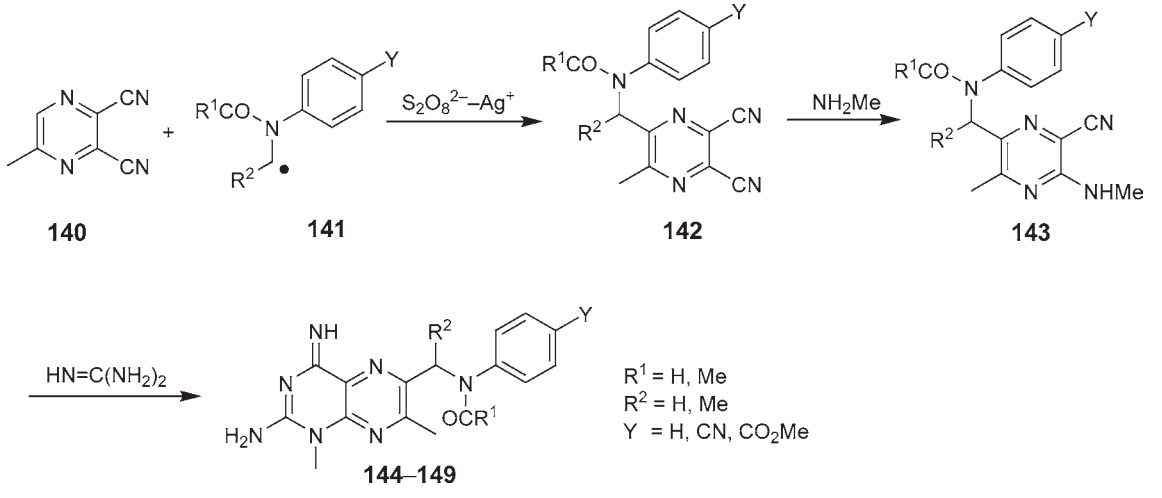
in detail <1996J(P1)247> (**Scheme 27**). Synthesis of 2,3-disubstituted pteridines from pyrazines using aza-Wittig reaction–heterocyclization methodology was reported <1998S1185, 1998J(P1)2277>. The iminophosphoranes **135** reacted with aryl isocyanates to give the corresponding pteridines **137** *via* the carbodiimide intermediate **136**.



Scheme 27

In some cases, side reactions were observed. When 4-chlorophenyl isocyanate reacted with iminophosphorane **135** (R = Pr^i), along with the corresponding pteridin-4(3*H*)-one (43%), the hydrolyzed compound, 3-isopropylpteridine-2,4-(1*H*,3*H*)-dione (26%), was also isolated. In cases with additional functional groups in the pteridine substrate such as esters, polycyclic compounds such as the imidazo[2,1-*b*]pteridine derivative **138** (37%) were obtained. Similarly, *N*-allyl and *N*-(1-methylprop-2-enyl) groups in **137** gave imidazo[2,1-*b*]pteridines **139** by iodoamination.

Analogues of folic acid and methanopterins were synthesized utilizing the radical alkylation chemistry from 5-methylpyrazine-2,3-carbonitrile **140** (**Scheme 28**) <1997JHC973>. The radical intermediates **141** were generated from corresponding carboxylic acids, for example *N*-acetyl-2-anilinoacetic acid, and reacted with pyrazine **140** to give the fully substituted pyrazine **142**. This on reaction with methylamine gave 2-substituted product **143** regioselectively. However, when ethylamine or butylamine reacted, a mixture of 2- and 3-substituted products was isolated in which the 2-isomer was the major product. Compound **143**, on reaction with guanidine, afforded the 6-anilinomethyl pteridine **144** and several variations were also described (**Table 8**).

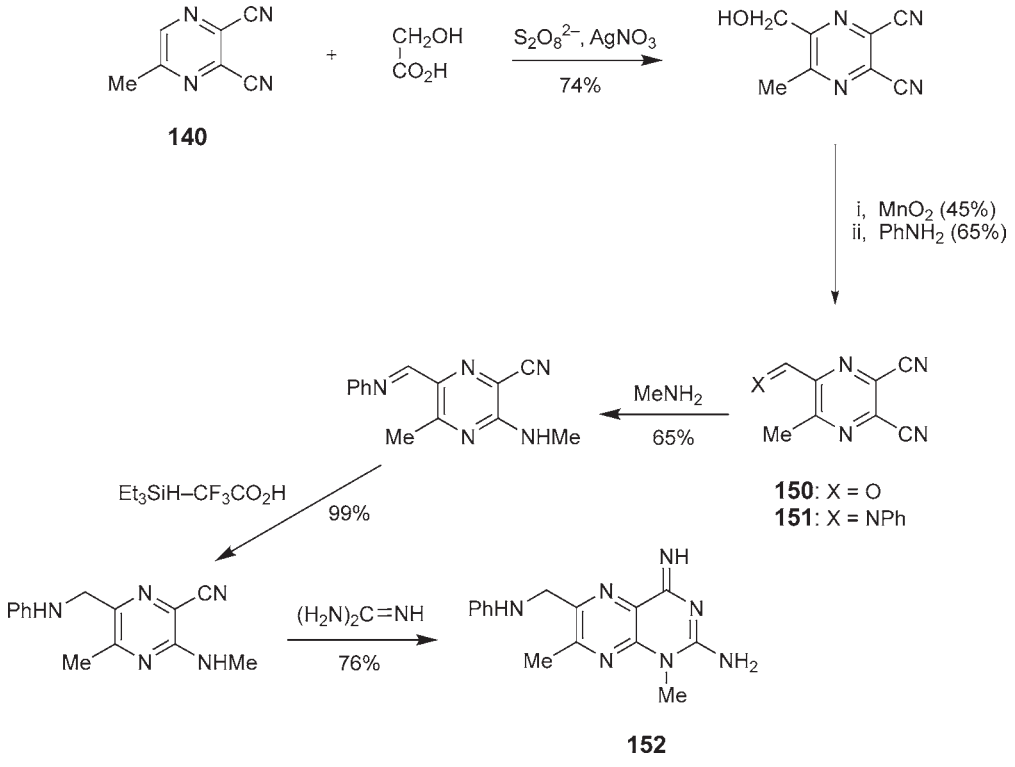


Scheme 28

Table 8 **Scheme 28** examples <1997JHC973>

Compound	R^1	R^2	*Y*	*Yield (%) in cyclization*
144	H	H	H	45
145	Me	H	H	57
146	H	Me	H	45
147	Me	Me	H	34
148	Me	H	CN	41
149	H	H	CO_2Me	76

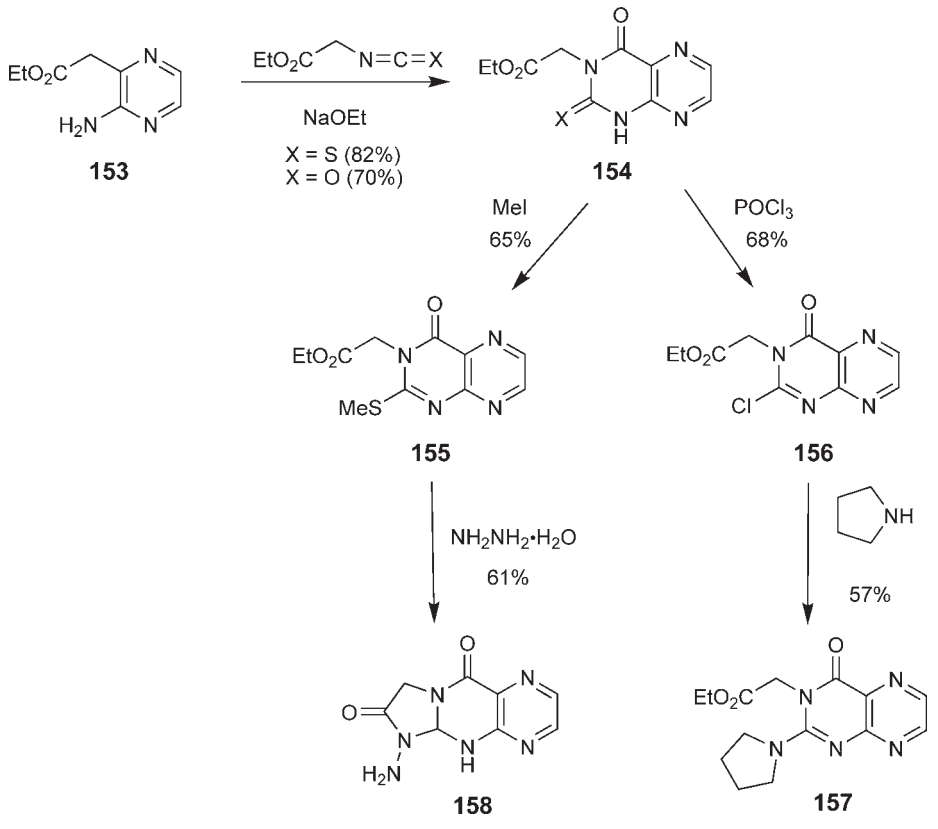
Another method for the synthesis of 6-anilinomethylpteridine derivatives has been reported in which the hydroxymethyl radical was generated from glycolic acid. A benefit of this synthetic approach is that polyfunctional substituents can be accommodated including ribose and dicarboxylic acids <1997JHC973>. Variations involving less complex substituents but with synthetic flexibility at C-6 were demonstrated using glycolic acid as the radical precursor (**Scheme 29**). From the aldehyde **150**, a range of 6-arylaminoalkyl substituents become accessible.



152

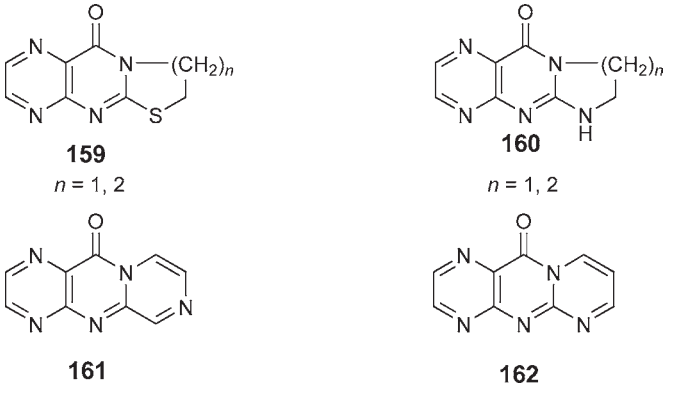
Scheme 29

The 2-aminopyrazine **153** also reacted with isothiocyanates, isocyanates, or dithioketals to afford the corresponding pteridines (**Scheme 30**) <2001JHC1173>. For example, with ethyl isothiocyanatoacetate, and ethyl isocyanatoacetate, the corresponding thioureidopyrazine and urethane derivatives, respectively, were obtained, which, on cyclization in the presence of sodium ethoxide, gave 2-thio and oxo-N-3-protected pteridines **154** in good yields. **154** (X = S), on reaction with methyl iodide, afforded a 2-methylthiopteridine **155**; **155** was also obtained directly from **153** by the condensation with ethyl *N*-[bis(methylthio)methylene]glycinate. **154** (X = S) also reacted with phosphorus oxychloride to give a 2-chloro derivative **156**, which was a substrate for nucleophilic displacement reactions with nitrogen nucleophiles such as pentylamine, morpholine and pyrrolidine, the latter giving **157**. Hydrazine hydrate reacted with 2-chloro- and 2-methylthioderivatives of **154** to give *N*-aminolactam derivatives **158**.

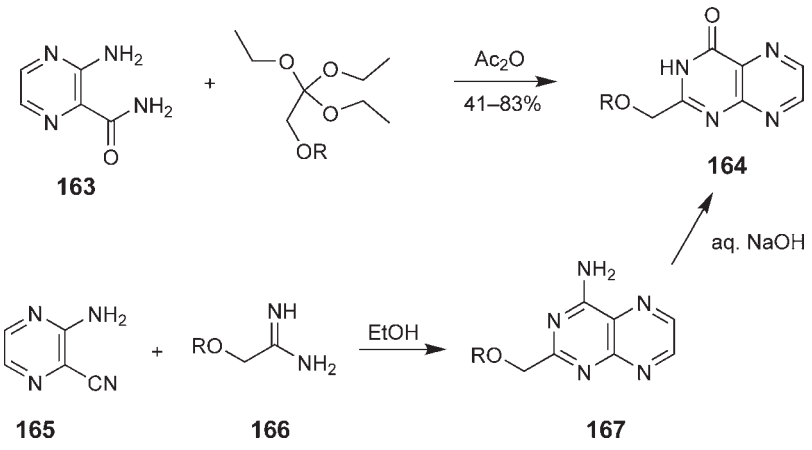


Scheme 30

The one-step synthesis of further tri- and tetracyclic pteridine derivatives from 2-aminopyrazine **153** has also been described <2001JHC1173>. Cyclic analogues of *N*-[bis(methylthio)methylene]amino reagents such as 2-(methylthio)-2-thiazoline, 5,6-dihydro-2-(methylthio)-4*H*-1,3-thiazine, 2-(methylthio)-2-imidazoline, 2-(methylthio)-1,4,5,6-tetrahydropyrimidine, 2-(methylthio)-2-pyrazine, and 2-chloropyrimidine reacted with aminopyrazine **153** to afford thiazolo/thiazino[2,3-*b*]- **159** ($n = 1$ (53%), $n = 2$ (42%)), imidazo/pyrimidino[2,1-*b*]- **160** ($n = 1$ (53%), $n = 2$ (57%)), pyrazino[2,1-*b*]- **161** (21%), and pyrimido[2,1-*b*]-pteridine **162** (42%) derivatives, respectively.



The synthesis of 2-alkoxymethylpteridines (antiallergic compounds) has also been achieved by the Taylor synthesis <1996EJM273> (**Scheme 31**). The 3-aminopyrazine-2-carboxamide **163** reacted with orthoesters to give 2-alkoxymethylpteridine derivative **164**. Alternatively, **164** was synthesized by condensing 3-aminopyrazine-2-carbonitrile **165** with the acetoxyamidine **166** followed by the base hydrolysis (**Table 9**).

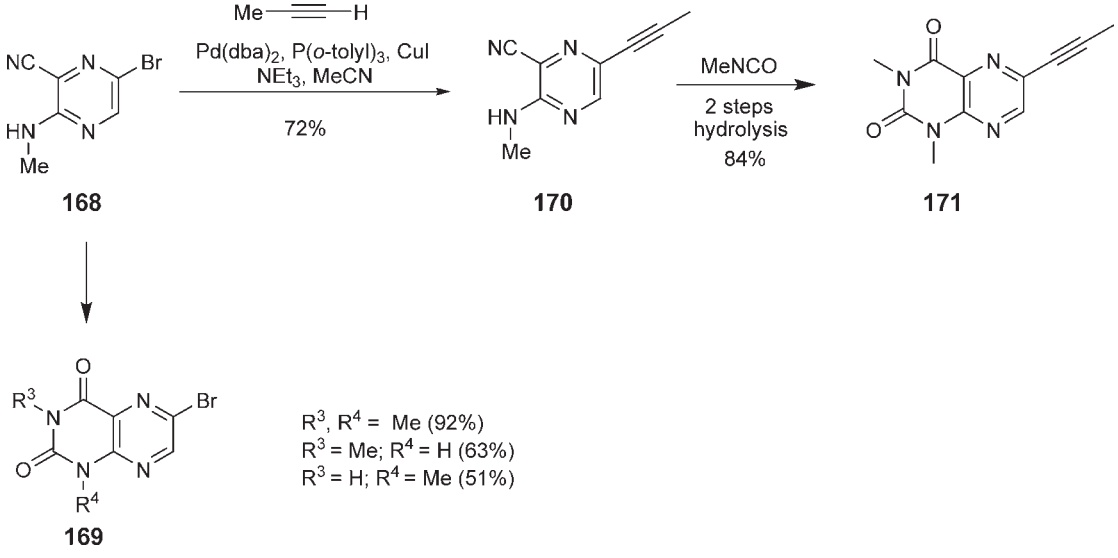


Scheme 31

Table 9 Alkyloxymethyl pteridine synthesis from pyrazines (**Scheme 31**) <1996EJM273>

Compound	*R*	*Yield (%)*
164 from **163**	Me	75
	Et	44
	Pr	36
	C_6H_5	70
164 from **167**	Et	65
	$(CH_3)_2CH$	66
	CF_3CH_2	50
	$C_6H_5CH_2$	83

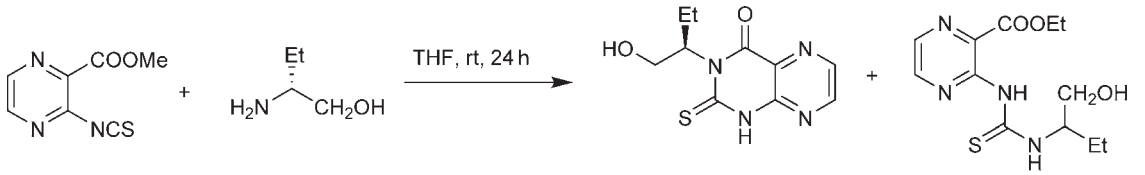
Palladium-mediated cross-coupling reactions in pteridine chemistry provide for variation at position 6 using halogenated pyrazines or pteridines as substrates (see Section 10.18.7.4). The 6-bromopyrazine **168** is a versatile intermediate leading to pteridine **169**; both compounds have been shown to be substrates for palladium-mediated cross-coupling reactions <2000J(P1)89> (**Scheme 32**).



Scheme 32

Pyrazine **168** underwent cross-coupling with propyne in the presence of bis(dibenzylidineacetone)palladium(0), tri-*o*-tolylphosphine, and copper(I) iodide to provide **170**. The pyrazines **168** and **170** were cyclized with methyl isocyanate or methyl chloroformate and sodium hydride to give corresponding pteridines **169** and **171**, respectively.

An isolated example of the synthesis of chiral pteridines from a chiral aliphatic precursor and a pyrazine has appeared (**Scheme 33**). 2-Isothiocyanatopyrazine-3-carboxylates have been converted into pteridines <1998JHC693>. Methyl 3-isothiocyanatopyrazine-2-carboxylate **172** reacted with (*R*)-(−)-2-amino-1-butanol in the absence of base, which provided the pteridine derivative **173** and uncyclized pyrazine derivative **174** in similar amounts. Similar reactions with pyridine precursors afforded pyrido[2,3-*d*]pyrimidines.



172 **173** 22% **174** 26%

Scheme 33

10.18.10 Ring Syntheses by Transformation of Other Rings

No significant examples of this type of synthesis appear to have been described during the period of this review; earlier examples can be found in CHEC-II(1996) <1996CHEC-II(7)679>.

10.18.11 Critical Comparisons of the Various Routes Available

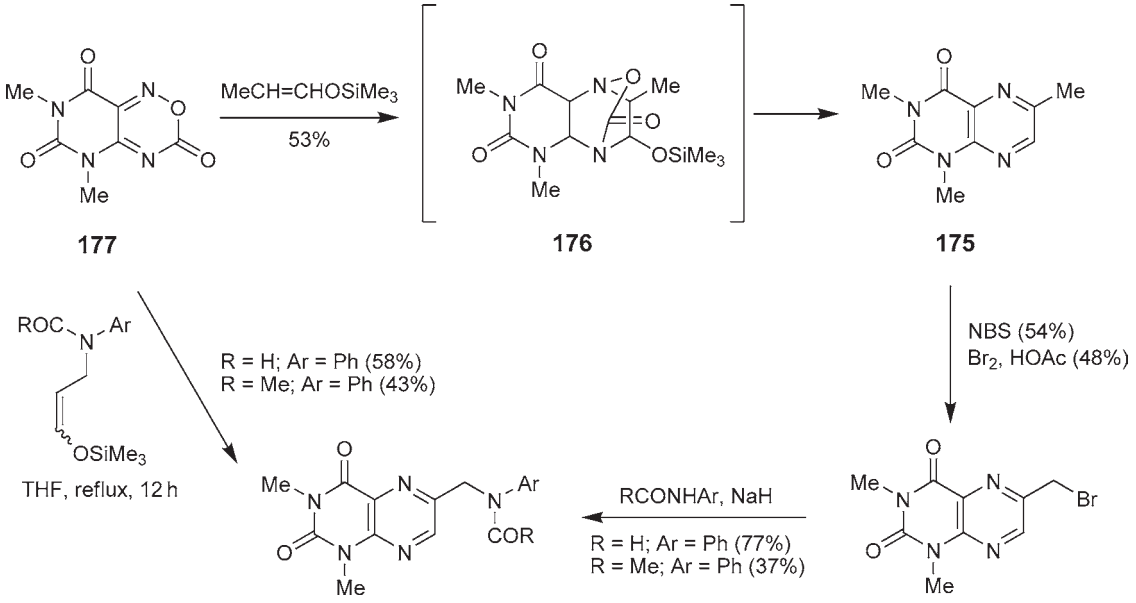
It could be argued that pteridine ring synthesis as such is well established both from pyrimidines and pyrazines. In the case of the former, a significant advance has been the improved ability to control the regioselectivity of cyclocondensation reactions by ensuring differential reactivity of the participating carbonyl groups in the aliphatic component <1997TL6835 1999JME4108, 1996RTC31, 1999JHC435, 1999JHC1317, 2001CHE755, 2003CCC965, 1996JOC8698, 1992S303, 2001JHC727, 2002ACT343, 2003OBC664>. These developments make the two approaches both complementary and comparable in terms of control of reactivity. A most important development from the strategic point of view has been the importance of creating diversity in the synthesis of polyazaheterocycles in general for applications in medicinal chemistry, for example. Once diversity is included in the requirements, the appropriateness of the pyrimidine-based or pyrazine-based routes becomes important. If a wide variety of substituents are required on positions 6 and 7, it is likely that a pyrimidine-based route will be preferred because diversity can be introduced from the aliphatic component. If diversity is required at position 2, both approaches are applicable because it has been shown that pteridines with good leaving groups, or with activatable groups, can be prepared by either route <1996PTR113, 2004T943, 2003OBC664, 2004PTR129, 2003OBC1909, 2003TL1267, 2000TL8177>. Similarly, halides suitable for organometallic coupling can be obtained by either route <2000J(P1)89, 2001BKC141, 1998T9559, 2001J(P1)3239, 2003RCB1403, 2000H(53)1259, 2004PTR129, 2003RCB1403>. Thus the synthetic approaches available have a great capacity for preparing pteridines of both variety and complexity. Ultimately a decision on the route to adopt may well depend on the availability of either the heterocyclic or the aliphatic precursor. Single stereoisomers can be accommodated by either pyrimidine- or pyrazine-based routes <2001JHC727, 2005PTR53O04/04, 1996JOC8698, 1992S303, 2002ACT343, 2003OBC664, 1998JHC693> and several steps may be necessary to prepare the required isomerically pure precursor <1996JOC8698>. For more complex substitution patterns involving fluorine or sulfur, significant effort may be required to obtain the necessary partner for condensation or for coupling <1998T9559, 1996T13017>. Additional examples that illustrate these general points can be found in the following description of the synthesis of special classes of pteridines (Section 10.18.12.1).

10.18.12 Important Compounds and Applications

A small number of applications do not readily fall within the following classification. Pteridines and other polyazaheterocycles have been considered for their use in high explosives in the form of nitro and *N*-oxide derivatives <2004MI81>.

10.18.12.1 Synthesis of Special Classes of Pteridines

Folate analogues continue to have importance in chemotherapy, especially heterocyclic analogues other than pteridines which are covered in Chapters 10.15–10.17 and 10.19. 1,3-Dimethyllumazine analogues of folates for use as model compounds have been prepared by side-chain elaboration of 6-bromomethyl-1,3-dimethyllumazine (**Scheme 34**) <1996JHC341>. More notable in this work, however, was the synthesis of the bromomethyl precursor itself; in addition to routine bromination of the 6-methyllumazine **175** prepared by condensation of dihydroxyacetone with 5,6-diamino-1,3-dimethyluracil, a cycloaddition reaction between trimethylsilyl enol ethers and the pyrimidyl bisimine **177**, via cycloadducts such as **176**, afforded substituted pteridines in moderate to good yields.

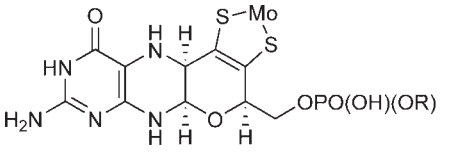


Scheme 34

The synthesis of molybdopterin <1996JBC7387> has attracted significant interest; pyrano[2,3-*g*]pteridines related to molybdopterin and metal complexes of their derivatives have been described <2001CC123>. A complete synthesis of the organic ligand in protected form has been described based upon careful choice of protecting groups (2-formino and 3-pivalyloxymethyl) and using building blocks described in Section 10.18.7.4 <2001J(P1)3239>.

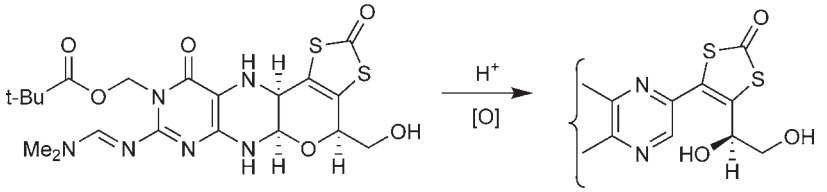
The metal is chelated by an ene-1,2-dithiolate (dithiolene) of the dihydropyran ring which is fused to a partially reduced pteridine **178**. The syntheses of these molybdopterin-related proligands were described as model compounds for verification of the stability *in vitro* <2001CC123>. The proligand **179** is a relatively stable compound; however, after several weeks, the pyran ring opened and oxidation to the diol derivatives **180** was observed (**Scheme 35**).

The organic ligand of the cofactor of the oxomolybdoenzymes has been synthesized in the protected form **181** (**Scheme 36**) <2001J(P1)3239>. Doubly protected 6-idodopterin **182** was coupled with the stannane **183** to afford **184**, which, on hydrolysis of the acetal to produce diol **185** and treatment with Fmoc chloride, yielded ring-closed *cis*- and *trans*- separable pyranopteridines **186** (Fmoc = 9-fluorenylmethyloxycarbonyl group). The *cis*-isomer **186**, the structure of which was confirmed by nuclear Overhauser effect (NOE) measurements, was reduced stereospecifically to give the corresponding tetrahydropterin which on reaction with Fmoc chloride gave the di-protected **187**. The phosphate unit was introduced by treating the alcohol with *N*,*N*-diisopropyl-bis[2-(methylsulfonyl)ethyl]phosphoramidite in the presence of tetrazole and, after oxidation with *tert*-butyl hydroperoxide, the protected proligand **181** was isolated.



178

R = H or nucleoside
(ligands on metal not shown)



179 **180**

Scheme 35

Limipterin **188** is a side-chain glycoside of biopterin <1996PTR110, 2006H(67)299>. In an example of the extensive manipulation of functional groups, biopterin was converted in five steps into the fully protected derivative **189** which featured the NPE group described Section 10.18.7.7. Unsurprisingly, glycosylation of this intermediate was problematic, there being so many potentially nucleophilic sites. After much experimentation, it was found that tin(IV) chloride activation of the 2-phthalimidoglucose tetraacetate **190** gave the required product **191**. Sequential cleavage of the phthalimide and peracetylation afforded a protected limipterin **192** from which limipterin itself was obtained by ammonolysis of the acetate esters and DBU cleavage of the NPE group (**Scheme 37**).

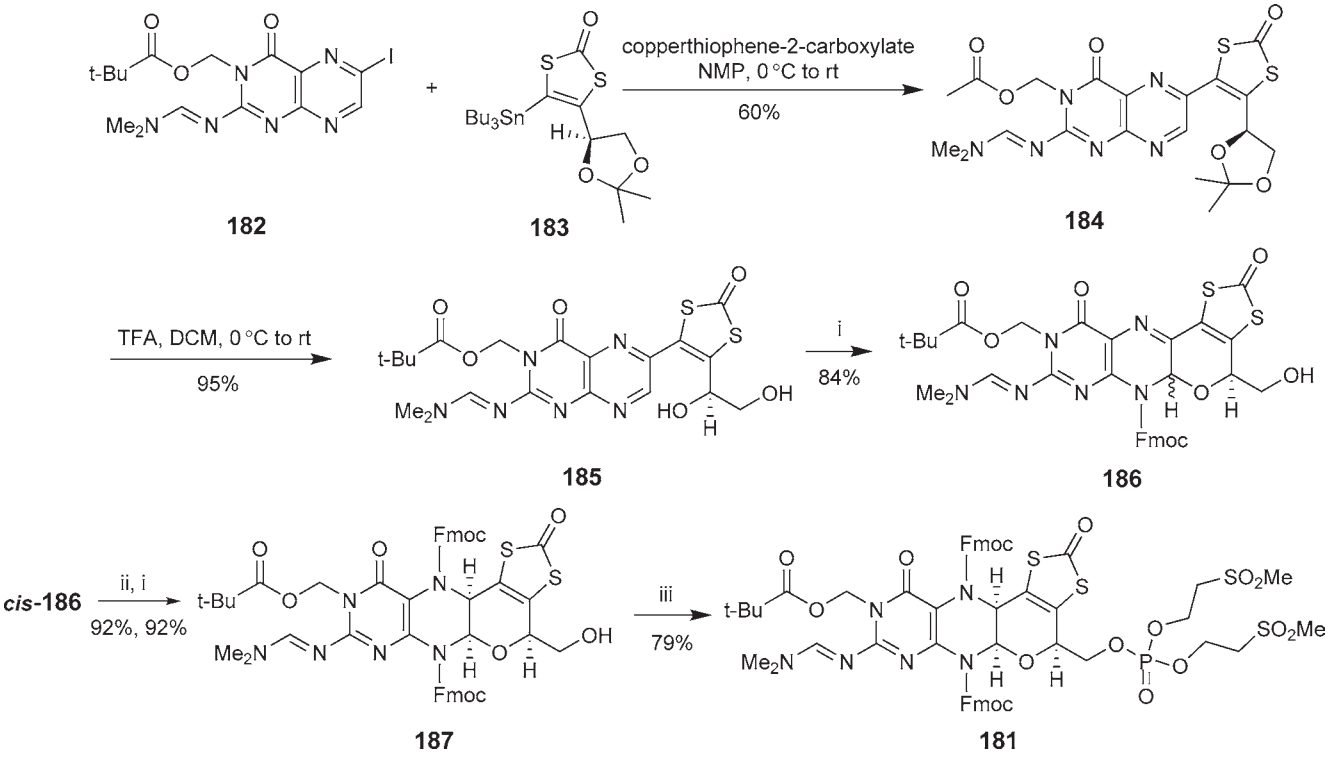
10.18.12.2 Photochemistry

Photolabile derivatives of pteridines have been prepared as photoaffinity probes for enzymes that use tetrahydrobiopterin as a cofactor <2000HCA2738>. Typically, these are derivatives of 6-phenylpterin and 6-hydroxymethylpterin, for example, 6-(4-azidophenyl)pterin. In general, the intense UV absorption of many pteridines, especially those bearing electron-donating substituents, renders them active in photochemistry. For example, methotrexate is known to be phototoxic; studies have shown that under irradiation, methotrexate caused damage to DNA at GG and GGG sites in double-stranded DNA (dsDNA) <2002JMM246>, leading to 8-oxodeoxyguanosine formation. Moreover, methotrexate underwent photohydrolysis to afford 2,4-diamino-6-hydroxymethylpterin which caused similar damage to DNA.

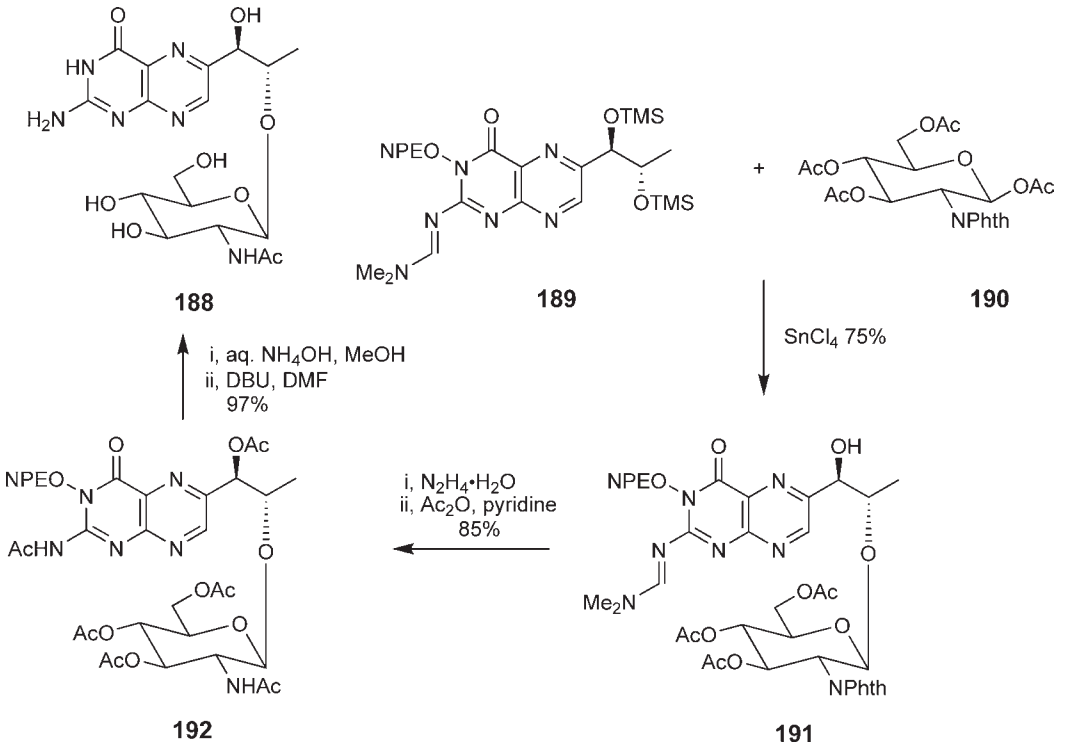
In nonbiological applications, mixed ruthenium complexes of bipyridyl ligands and substituted pteridine diones have been used as components of photovoltaic cells <2002JPH167>. When fabricated into sol–gel processed titanium oxide electrodes, these complexes achieved photocurrent conversion efficiency in the range 20–48%.

10.18.12.3 Metal Complexes

Several classes of enzyme involve metal–pterin cofactor interactions, notably the amino acid hydroxylases and xanthine oxidase. This fact has prompted extensive studies of the structures of complexes of pteridines with transition metals which have been reviewed in Section 10.18.3. To facilitate handling, 1,3-dimethyllumazine and other more highly substituted lumazines have been the common choices of ligand. Crystal structures reveal coordination geometries typical of the metals used. For example, a distorted octahedral geometry was observed for copper(II) complexes; the monomers were found to be hydrogen-bonded by noncoordinated water to form a complex network <1998ICA(268)77>. Lumazines typically act as bidentate ligands <1998ICA(277)103, 1999POL85> through N-5 and O-4 occupying the equatorial plane of octahedral complexes. Complexes with soft metal cations (cadmium(II) <1998ICA(277)103>, mercury(II)) have also been described <1998POL3409>, and the mercury complex had a trigonal bipyramidal configuration. Complexes with relevance specifically to molybdopterin with cobalt(III) and pteridinylethanethiolate model ligands have been prepared and their structures determined <1997J(P1)801>.


t-Bu
Me2N
Bu3Sn
copperthiophene-2-carboxylate
NMP, 0 °C to rt
60%
182
183
184
TFA, DCM, 0 °C to rt
95%
185
i
84%
186
Fmoc
cis-186
ii, i
92%, 92%
187
iii
79%
181
SO2Me
OH
HO

Scheme 36

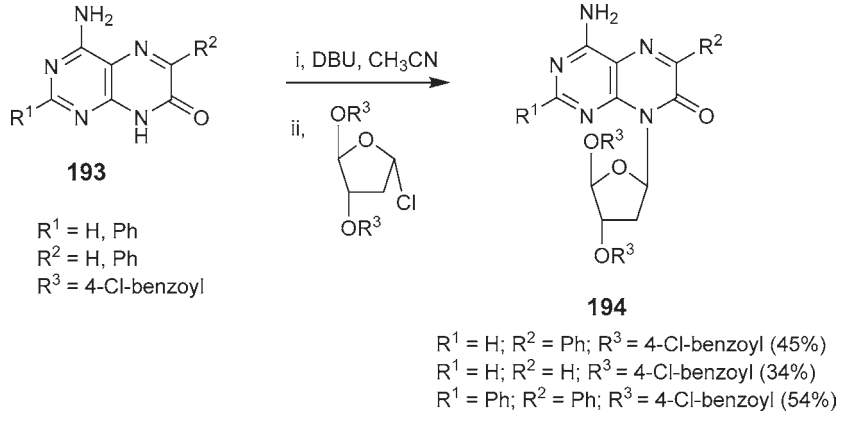


Scheme 37

10.18.12.4 Nucleoside and Nucleotide Analogues

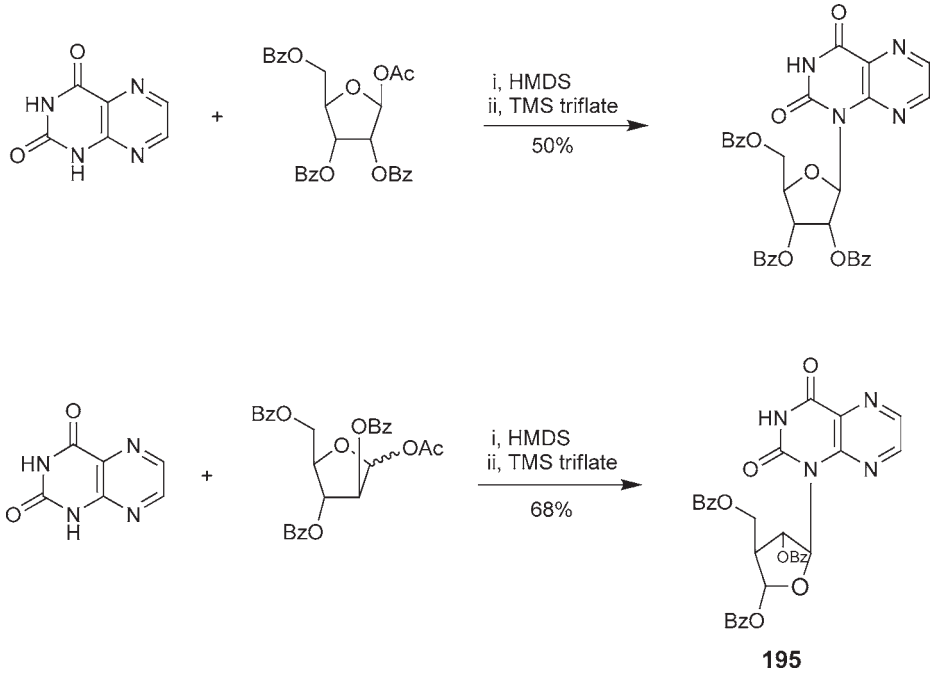
The obvious similarity between the purine bases of DNA and pteridines, especially between guanosine and pterins, has encouraged extensive studies of the synthesis and properties of pteridine-containing nucleoside and nucleotides. Synthetic methods have naturally built upon established methods of nucleic acid synthesis. The primary property of use in applications of these compounds to DNA chemistry is fluorescence, which is very much greater for pteridines than for purines.

Pteridine nucleosides can be synthesized by a variety of methods typical of the field. Thus a pteridine anion formed by deprotonation of **193** with a hindered base (DBU) coupled with an α-halodeoxyribofuranose to afford the corresponding nucleoside **194** with good stereoselectivity, a significant improvement upon previous methods using mercuric salts as promoters (**Scheme 38**) <1996TL8355>. Riboside analogues were also prepared.



Scheme 38

Other methods of coupling include trimethylsilyl (TMS)-triflate activation of 1-acetoxyribose and arabinose benzoates which were coupled in a one-pot reaction in which a silyl-protected pteridine was prepared using hexamethyl disilazane (**Scheme 39**). The arabinose derivatives were particularly of interest because of their α-configuration and the fact that the deprotected product showed significant anti-HIV activity (HIV = human immunodeficiency virus). Similar reactions were applied to the isomeric pyrimidino[4,3-*d*]pyrimidines. The deoxyribonucleosides were prepared using 1-chloro-3,5-diacetyl-2-deoxy-D-ribofuranose as the glycosyl donor <1997JHC1581>.

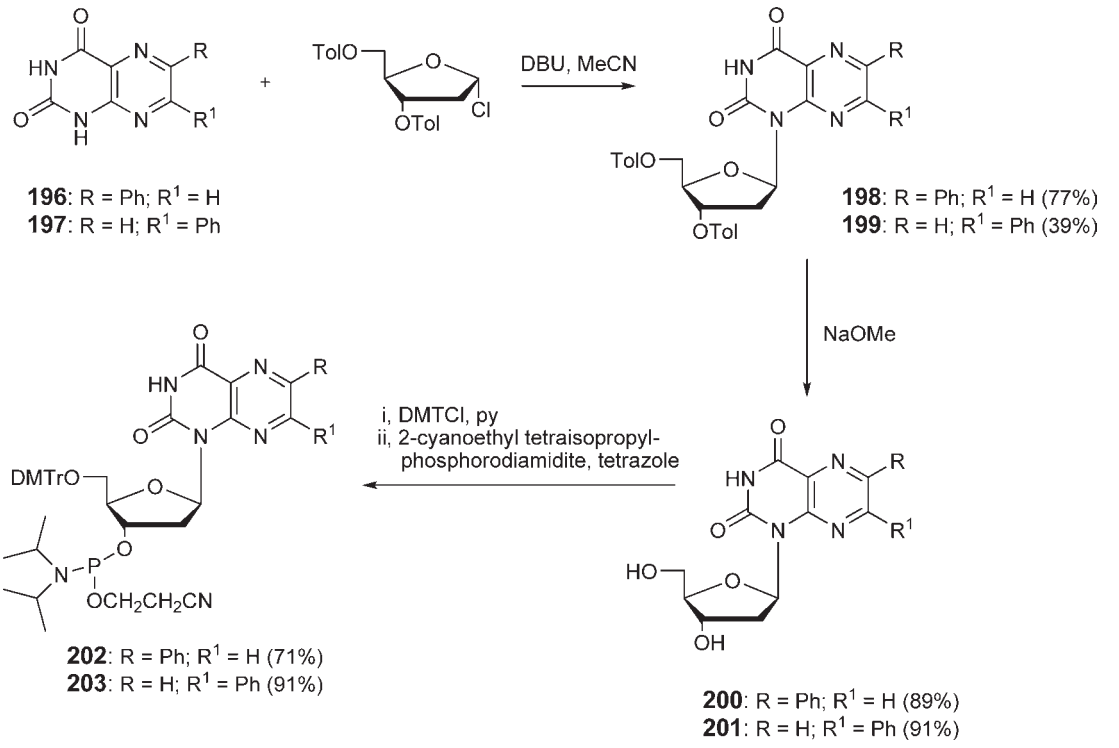


Scheme 39

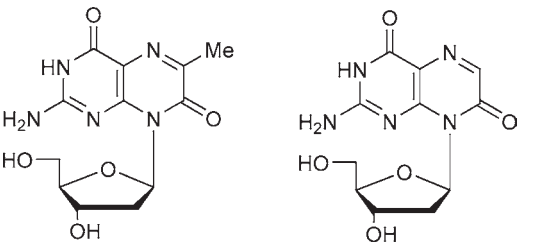
Pteridine nucleosides commonly contain phenyl substituents to enhance their fluorescent properties. Such compounds lend themselves to derivatization to provide compounds suitable for incorporation into polynucleotides by phosphoramidite coupling. 6- and 7-Aryllumazines were among the first pteridines to be converted into 5′-*O*-dimethoxytrityl-3′-*O*-(β-cyanoethyl)-*N*,*N*-diisopropylphosphoramidites and subsequently coupled into self-complementary oligonucleotides (**Scheme 40**) <1996NN431>. The 6- and 7-substituted lumazine nucleoside phosphoramidites **196** and **197** can be effectively incorporated into oligonucleotide sequences in different positions of the chain. Glycosylations of **196** and **197** were achieved using 2-deoxy-3,5-di-*O*-*p*-toluoyl-α-D-ribofuranosyl chloride as the glycoside donor to give the protected nucleosides **198** and **199**. Deacylation by sodium methoxide in methanol gave the free 6- and 7-substituted lumazines **200** and **201** in moderate yield. These were then converted into the corresponding 3′-*O*-(β-cyanoethyl-*N*,*N*-diisopropyl)phosphoramidites by the treatment with (β-cyanoethoxy)bis(diisopropylamino)phosphane to give **202** and **203** in good yield ready for incorporation into oligonucleotides.

This work has been extended with more detailed studies of the configuration and conformation of the pteridinyl DNA building blocks <1997NN863>. A recent study has used 4-amino-6-methylpteridin-7(8*H*)-one as a substitute for adenine to investigate the pre-melting transitions of short AT tracts <2006B5039>; the greater sensitivity of this fluorescent nucleoside compared with normal UV measurements allowed a greater insight into the subtle differences in the conformation of AT duplexes related to the width of the minor groove.

The practicality of using pteridine nucleotides with lumazines and isoxanthopterins as aglycones in solid-phase synthesis has been well demonstrated thereby making these compounds widely available for structural and mechanistic studies <1997NN1369>. For example, 6-methyl-8-ribosylated isoxanthopterin derivatives **204** and **205** can be considered as guanosine analogues and are highly fluorescent <1998NN175>.

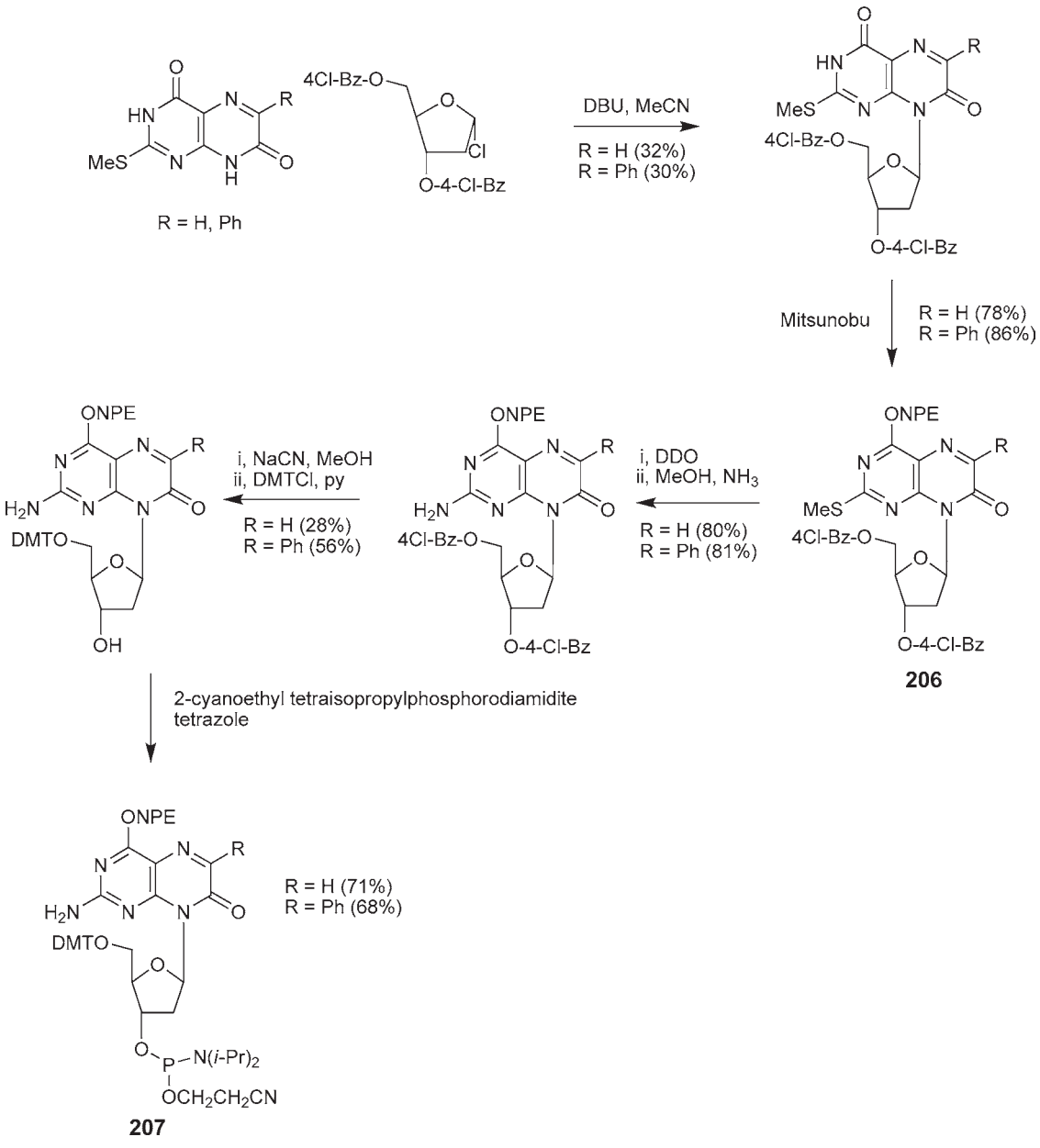


Scheme 40



The studies described above have been extended and refined. For isoxanthopterin and 6-phenylisoxanthopterin derivatives to be used as fluorescence markers in oligonucleotide synthesis, new building blocks (**207**, related to **202** and **203**) were prepared containing the 2-(4-nitrophenyl)ethyl (NPE) and [2-(4-nitrophenyl)ethoxy]carbonyl protecting groups for use in automated solid-phase synthesis (**Scheme 41**) <2001HCA2330>. Melting studies on oligonucleotides containing these pteridinyl nucleotides showed that they allowed the formation of stable duplexes with little structural interference as suggested by the small reduction in T_m (1–2 °C) in pteridine-containing oligonucleotides compared with the analogous purine-containing oligonucleotide. Synthesis through the methylthio intermediates **206** is to be preferred because additional amino group protection is not required. Oxidative cleavage (see Section 10.18.7.2) and the use of the NPE protecting group (see Section 10.18.7.7) have already been described.

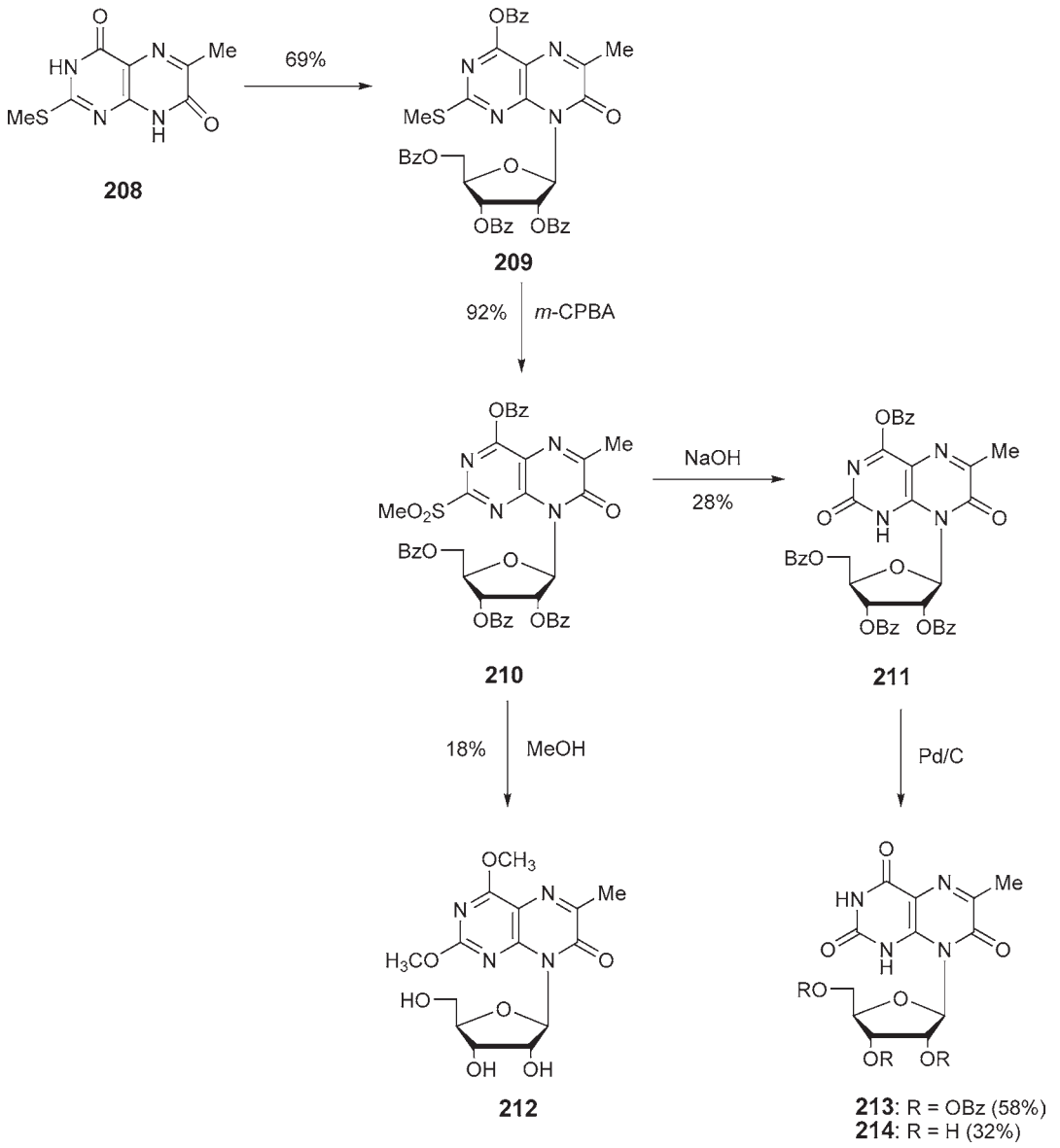
An alternative strategy illustrating the introduction of diversity through a 2-methylthio substituent used 4-*O*-benzyl protection; although many new compounds were prepared, yields in most steps were low <2004NN51>. Glycosylation of 6-methyl-2-methylthio-4(3*H*),7(8*H*)pteridinedione **208** with *O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose gave **209** in moderate yield. Compound **209** was then oxidized by *m*-chloroperbenzoic acid to the corresponding 2-methylsulfonyl derivative **210** in excellent yield. Hydrolysis of **210** by sodium hydroxide in THF afforded 4-benzyl-6-methyl-8-(2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranosyl)-2-(1*H*),7(8*H*)pteridinone **211**. Methanolysis of **210** afforded the bis-methyl ether **212**. Hydrogenolysis converted **211** to **213**, followed by debenzoylation to give 6-methyl-8-*β*-D-ribofuranosyl-2-(1*H*),4(3*H*),7(8*H*)-pteridinone **214** (**Scheme 42**).



Scheme 41

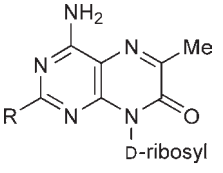
An extensive pioneering study of pteridine-containing nucleotides <1997ABI86> investigated 18 fluorescent examples and largely established their competence as intrinsic fluorescent probes within an oligonucleotide, in contrast to oligonucleotides conjugated to large fluorophores such as fluorescein. While fluorescence lifetimes and quantum yields varied substantially throughout the series, importantly it was found by T_m measurements that 3-methylisoxanthopterin-containing ds DNA oligonucleotides caused a destabilization of the duplex equivalent to 1 bp mismatch, as would be expected from the blocking of a hydrogen-bonding site, but that the 6-methyl isomer to which hydrogen bonding can occur in the pyrimidine ring caused no destabilization of the DNA duplex.

The detailed fluorescence characterization of pteridine analogues of adenosine nucleosides has been reported <2001ABI231>. The 4-aminopteridin-7-one 8-nucleosides **215** and **216** had absorption maxima at 310 and 330 nm, respectively, and both emit at 430 nm. The fluorescence was monoexponential with a lifetime of 3.8 and 4.3 ns,



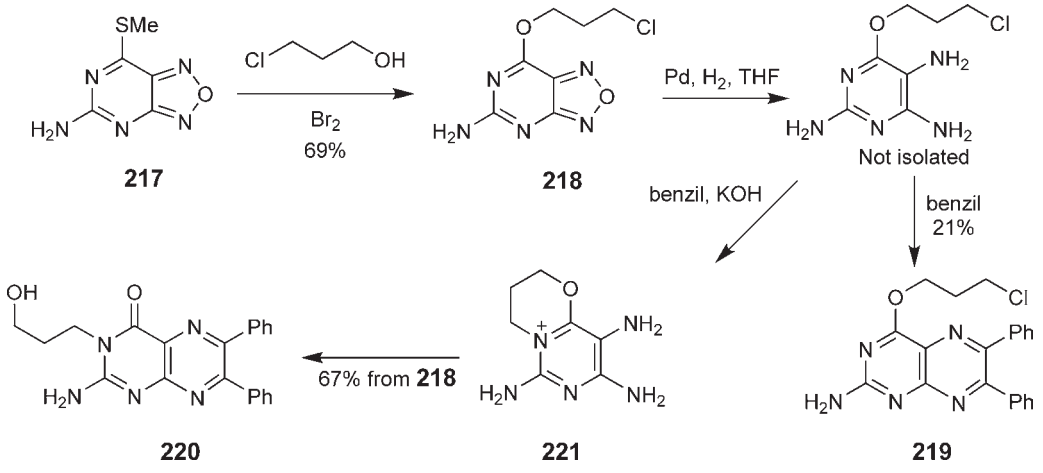
Scheme 42

resepectively. On incorporation into oligonucleotides, substantial quenching was observed but, as noted in other cases, melting studies suggested minimal disruption of the duplex structure. When an oligonucleotide containing **215** or **216** interacts with an enzyme to open up the duplex or upon denaturation, such compounds can act as reporters through restoration of fluorescence.



215: R = H
216: R = Me

6,7-Diphenylpterin conjugated to an oligonucleotide through a spacer on either N-2 or N-3 has been used as a probe of photooxidative damage to a complementary sequence of single-stranded DNA representing a gene (*bcr-abl*) that is implicated in the pathogenesis of chronic myeloid leukaemia <2004OBC3588>. The ultimate coupling of the pteridine to the oligonucleotide used phosphoramidite methodology, in the case of the 2-amino-linked compound *via* an additional *N*-hydroxysuccinimide coupling to a spacer. The synthesis of the 3-substituted compound with a short linking chain is of interest with respect to the manipulation of the functional groups on the pyrimidine through a complex series of aromatic and aliphatic nucleophilic substitution reactions. The furazanopyrimidine **217** was converted into the 3-chloropropyloxypyrimidine **218** which served as the precursor for cyclization. Hydrogenolysis followed by immediate cyclization with benzil gave **219** in low yield with the chloropropyl substituent intact but immediate cyclization with benzil in methanolic potassium hydroxide afforded the required 3-hydroxypropyl pyrimidine **220**. It was suggested that an intermediate was the pyrimido[6,1-*b*][1,3]oxazine salt **221** (**Scheme 43**). The interaction of ring heteroatoms with flexible alkyl chains bearing displaceable substituents is a relatively common occurrence in pteridine chemistry <2004T943>, and in this work, a number of novel transformations were discovered as has been described in Section 10.18.5.4.



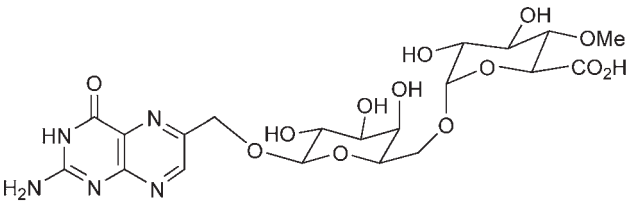
Scheme 43

The use of pteridine nucleosides as probes for the study of interactions of DNA with proteins has become sufficiently well established to attract the writing of a number of review articles <1996MITU466, 2001MI257, 2002COR775, B-2003MI(360)128>, of specific studies in the detection of polymerase chain reaction (PCR) products <2004NARe62>, and in the investigation of triplex formation <2004NAR432>. A recent review concentrates upon the possibility of recognizing single genetic events in the post-genomic era <2006COR491>.

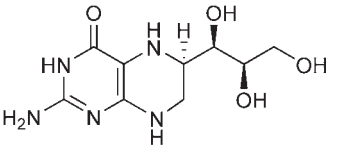
10.18.12.5 Natural Products

Despite the long history of pteridine chemistry, isolated examples of novel natural products and new derivatives of known compounds continue to occur. A novel pterin glycoside, called cyanopterin **222**, has been identified in *Syrnechocytis* spp. <1999BBA61>; it is a disaccharide derivative of 6-hydroxymethylpterin and thus a further example of a class of compounds widely found in prokaryotes including photosynthetic bacteria <1970MI91>. The available evidence suggested that the biologically active form is the 5,6,7,8-tetrahydro derivative, but the cellular function is unknown.

The identity of a glucosylated derivative of L-biopterin from *Synechococcus* sp. PCC 7942 has been confirmed as the 2′-*O*-α-glucosyl derivative by 2-D NMR spectroscopy <2001PTR121>. Tetrahydro-D-monapterin **223** has been identified as the native pteridine in *Tetrahymena pyriformis* <2001HCA918>; the configuration and structure were confirmed by comparison with synthetic samples of known configuration.

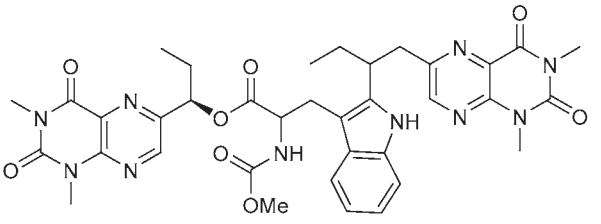


222

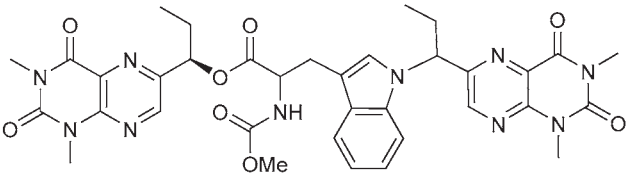


223

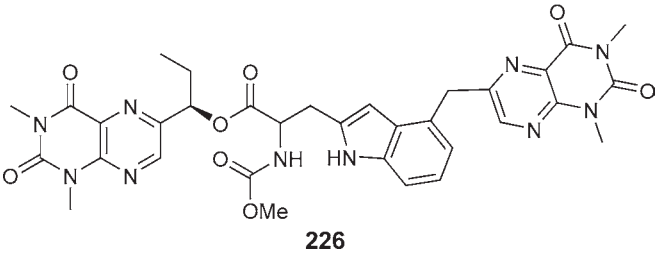
Unusual pteridine alkaloids including **224–226** have been identified from sponges (*Clathria* spp.) collected off Argentina <2002T4481>. The pteridines, which are 6(2′-hydroxypropyl) and 6-propyl derivatives of 1,3-dimethyllumazine, are linked to a core tryptophan through an ester and 1-, 2-, or 4-alkylation, respectively.



224



225



226

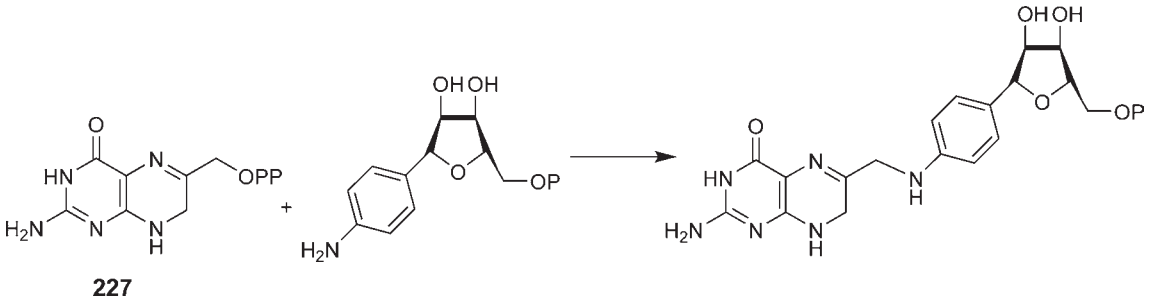
A wide range of known pteridines including pterin, biopterin, isoxanthopterin, and lumazine have been found in the pigments of the migratory locust <2003MI19>. In an unusual case of identification, the structure of a pteridine natural product has been revealed by X-ray crystallography of the pteridine bound to the ribosome inactivating protein from Himalayan mistletoe <2005JBC20712>. The pteridine, 2-amino-4-isopropyl-6-pteridine 6-carboxylic acid, apparently binds with its carboxylate group close to a key catalytic arginine residue.

10.18.12.6 Biosynthetic Pathways

The details of the biosynthesis of pteridine pigments continue to attract attention, especially because of the importance of aromatic acid hydroxylation in the early development of the nervous system. A valuable model experimental system is the zebra fish because both early neural development and later pigmentation can be studied. It has been found that the enzymes of tetrahydrobiopterin biosynthesis (GTP cyclohydrolase 1, 6-pyruvoyl-5,6,7,8-tetrahydropterin synthase, and sepiapterin reductase) are expressed within 24 h post fertilization consistent with a need for a supply of tetrahydrobiopterin. Later, 48 h post fertilization, the sepiapterin-forming pathway becomes established leading to oxopteridine pigments <2000JBC18926, 2000JBC23406>. There is evidence that the sepiapterin reductase in *Chloribium tepidum* affords L-*threo*-tetrahydrobiopterin whereas animal enzymes produce L-*erythro*-tetrahydrobiopterin, yet the architecture and folding of the two proteins are very similar. The basis for this stereochemical difference has been

attributed by X-ray crystallography to a differently located phenylalanine side chain in the *Chlorobium* enzyme that causes the substrate to present the opposite face for reduction compared with the animal enzyme <2006JBC2249>.

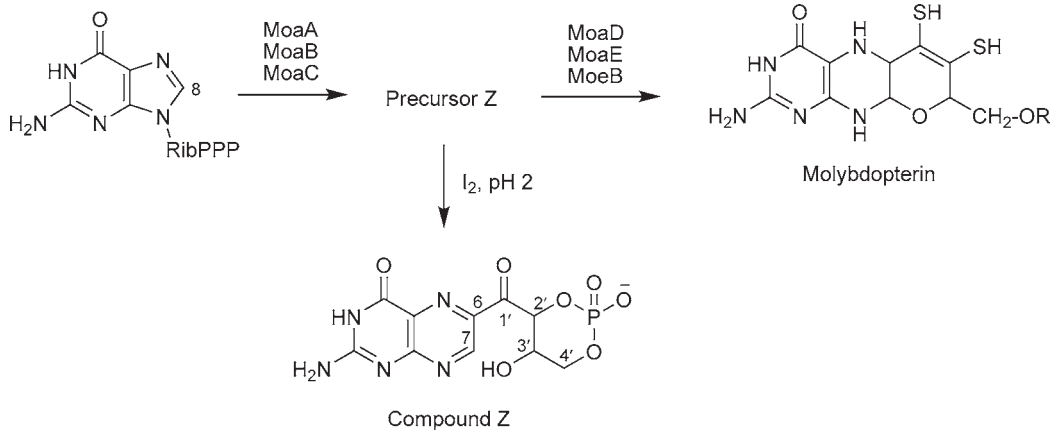
The enzymes in the zebra fish pathway are presumably very similar to those of other vertebrates. However a completely different type of GTP cyclohydrolase has been identified in the hyperthermophilic euryarchaeon, *Methanococcus jannashii* <2002B15074>. This enzyme, in purified recombinant form, produced as a stable end product 2-amino-5-formylamino-6-ribofuranosylamino-4(3*H*)-pyrimidinone monophosphate, a compound that is an intermediate in the action of normal GTP cyclohydrolases. The biosynthesis of the incorporation of the pterin into methanopterin in *Methanobacterium thermoautotrophicum* has been proposed to occur via substitution of 7,8-dihydro-6-hydroxymethylpterin diphosphate **227** (**Scheme 44**) <1998BBA257>.



Scheme 44

It has been known for some time that two molecules of 6,7-dimethyl-8-D-ribityllumazine dismute to form riboflavin. An intermediate pentacyclic compound has now been detected by pre-steady-state kinetic studies <2003JBC47700>.

The biosynthesis of molybdopterin has been investigated using $^{13}C/^{15}N$ double labeling experiments using labeled glucose, ribulose 5-phosphate, and guanine <1998MI24>. The stable product known as compound Z (**Scheme 45**), which is not on the pathway to molybdopterin, was shown to be derived from so-called precursor Z, which is on the pathway. Two complex mechanisms involving rearrangements of the pentose and purine carbon skeletons were proposed, both of which are in contrast to previously proposed mechanisms <1994JBC23981, 1995JBC1082>, but from the available data it was not possible to draw firm conclusions. The detailed labeling pattern of the compound Z, investigated by both 1-D and 2-D NMR spectroscopy, indicated that the carbon atoms of a pentose or pentulose are diverted to the ring atoms C-6 and C-7 and to the side-chain atoms C-2′, C-3′, and C-4′ of compound Z. Carbon atom C-1′ of compound Z is derived from carbon atom C-8 of a guanine derivative. The heavy isotope distribution was investigated by 1-D and 2-D NMR spectroscopy.



Scheme 45

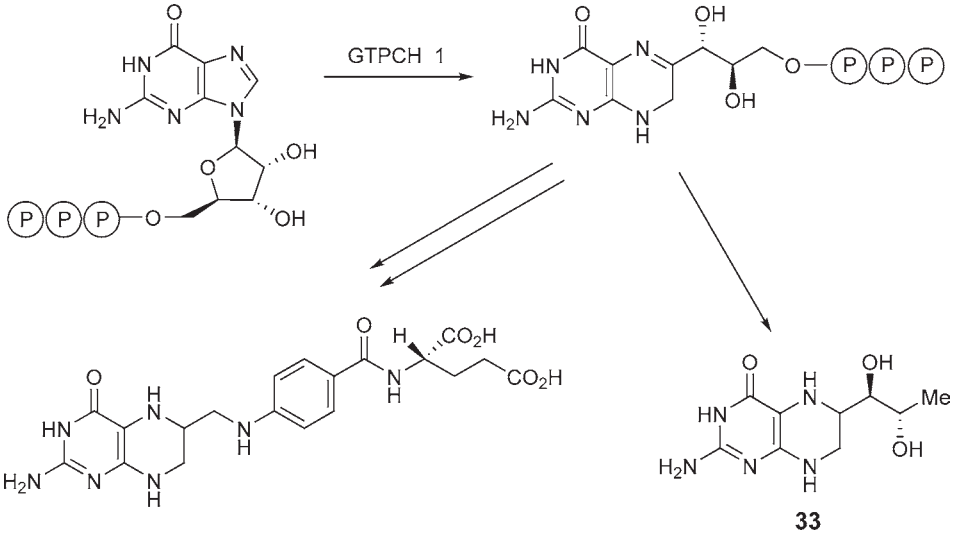
Folate biosynthesis has also been studied in plants and the dihydroneopterin aldolase from *Arabidopsis thaliana* has been crystallized and its structure determined; the construction of the active site has similarities with those of other

early enzymes in the folate pathway but the mechanism of action appears to be distinct from that of aldolases of primary metabolism <2004JMB967>. Consistent with the structural similarities of pterin-transforming enzymes, both structural and mechanistic similarities have been recognized between the dihydroneopterin triphosphate epimerase and dihydroneopterin aldolase of *E. coli* <1998JBC17418>.

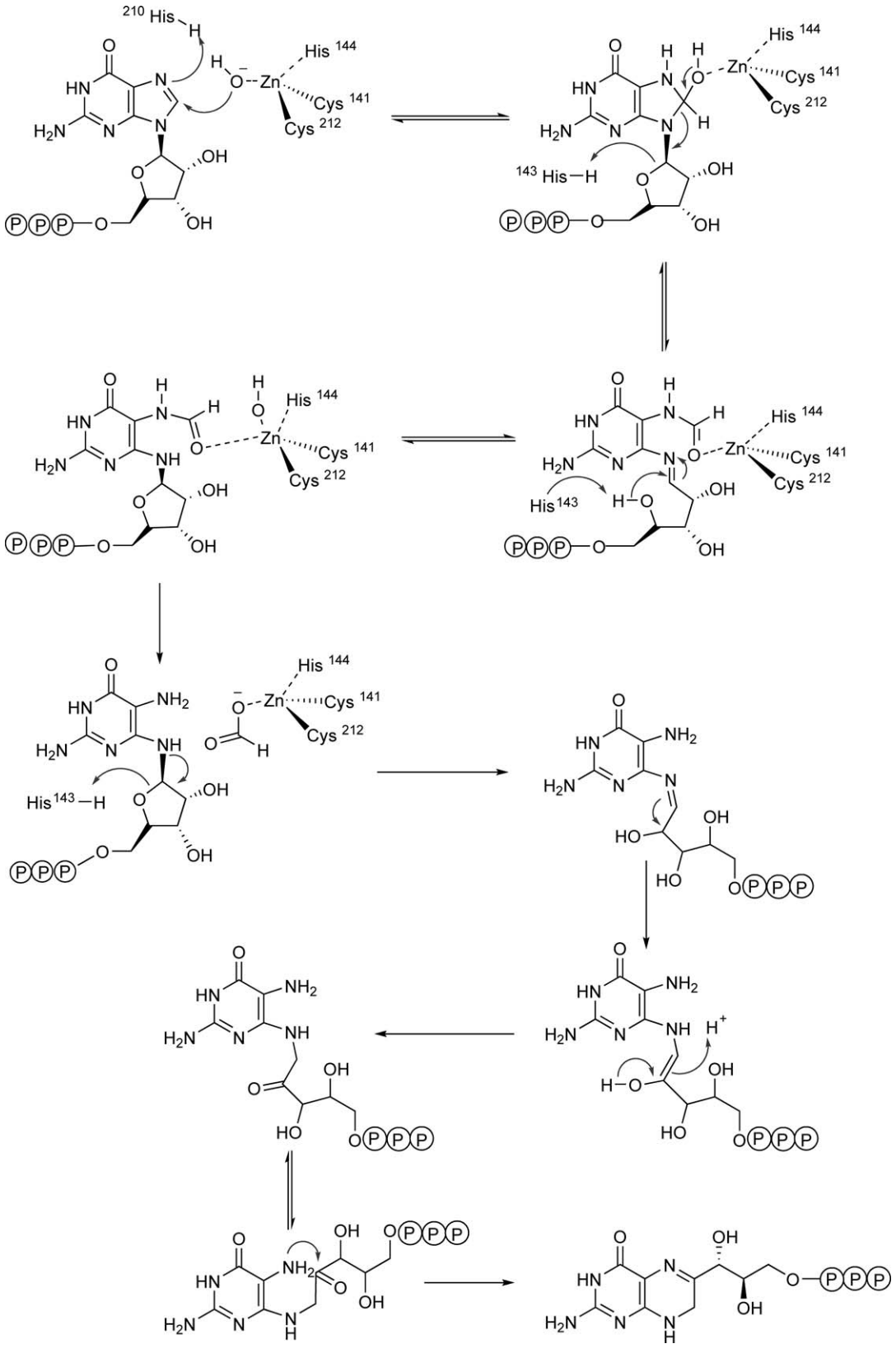
A range of studies have shown the importance of neopterin and biopterin as regulators of biological processes. Thus tetrahydobiopterin levels have been implicated in the regulation of both amino acid hydroxylases and NOS <1999MI79>. Neopterin and dihydroneopterin have been cited as modulators of oxidative stress and initiators of pro-apoptotic mechanisms <2002MI203>. Neopterin has been argued to be an important mediator of host-defense reactions in the immune system <2004PTR107>. Evidence has been presented to suggest that 7,8-dihydroneopterin in cells may inhibit the deleterious oxidation of low-density lipoprotein <2002MI509>. On the other hand, it has been argued that high concentrations of tetrahydropterins initiate apoptosis and contribute to the pathogenesis of neurodegeneration <2002MI71>. These differing points of view serve to emphasize the importance of chemical balance in complex biochemical systems.

10.18.12.7 Chemical Mechanism of Action of Pteridine-Synthesising or -Transforming Enzymes

GTP cyclohydrolases are the enzymes that catalyze the conversion of GTP into pteridines. GTPCH 1 is the enzyme that forms dihydroneopterin at the start of the folate and biopterin pathways (**Scheme 46**) and its mechanism of action has been the subject of detailed study by kinetic, isotopic labeling, site-directed mutagenesis, and crystallographic methods. There are two distinct phases to the reaction catalyzed by GTPCH 1, first the hydrolytic ring opening of the imidazole ring of GTP and second the Amadori rearrangement of the ribose and its recyclization to form the pteridine ring (**Scheme 47**). There has been much discussion of the chemical basis for these reactions and related transformations in the biosynthesis of the molybdenum cofactor (see Section 10.18.12.6) <1997BML779>, but a combination of precedent in enzyme chemistry and synthetic chemistry together with detailed studies of GTPCH 1 itself has led to a consensus. An apparently late rate-determining step in the complex sequence of reactions makes direct deductions of mechanism from reaction kinetics difficult <2001B7896>, but on the other hand the relative rates of reaction of mutant enzymes have been important in identifying critical catalytic residues <2003JMB503>. The critical discovery was of an active site zinc cation coordinated to essential cysteines (two) and a histidine residue. A mechanism for the first phase of the reaction (imidazole ring opening) involving zinc-coordinated water in a manner very similar to that of the metallopeptidases was proposed. The formamide product was argued to be hydrolyzed by the same catalytic apparatus, again analogous to the action of metallopeptidases. Strong evidence has been adduced to show that the first-phase hydrolytic reactions are rapid compared with the



Scheme 46



Scheme 47

following Amadori rearrangement and recyclization <2002JMB829>. The second-phase reaction, the Amadori rearrangement which precedes cyclization, is a mechanism supported by isotope incorporation from solvent <1998JBC28132>. The properties of some inhibitors of GTPCH 1 that also have weak substrate characteristics have been interpreted with the aid of model reactions consistently with the hydrolytic first phase of the reaction pathway of GTPCH 1 <2004T943>.

A group of enzymes of particular chemical and biological interest is that using tetrahydrobiopterin as cofactor. In particular, the NOSs have posed a challenge because of the need to define a role for tetrahydrobiopterin in the reaction mechanism. It is now thought that tetrahydrobiopterin has both a structural role in stabilizing the active dimer of NOSs <1999JBC24921> and a role in electron transfer during oxidation <2000B11763, 2002MI133>. The allosteric stabilization of NOS dimers has been associated with the suppression of uncoupling of arginine oxidation under which conditions NOSs produce toxic superoxide radicals <2000BJ767>. Simple pteridine analogues of tetrahydrobiopterin have featured in these studies, notably the 4-amino analogue, which is an inhibitor, and the 5-methyl derivative, which is capable of sustaining catalytic activity. The 4-amino analogue has been reported to show some preference for inhibiting the inducible isoform of NOS <1999MI25>. Surprisingly, in cells and tissues, a number of 7,7-dimethyldihydropterins have been found to support nitric oxide synthesis but the molecular mechanism is unknown <2005PTR112P56>. From a study of the behavior of the 4-amino analogue of tetrahydrobiopterin, it was suggested that this compound acts as an inhibitor because it cannot donate a proton to an activated oxygen–iron species at the heme, whereas this is possible for the weakly acidic tetrahydrobiopterin <2003JBC48602>. Studies of the mechanism of NOS under high pressure promise to reveal more of the details of the mechanism of action of tetrahydrobiopterin <2006BBA578>. While the primary application for the synthesis of inhibitors of NOSs has been in medicinal chemistry (see Section 10.18.12.8), pteridine-based photoaffinity labels have been synthesized and used to investigate the active site region of neuronal NOSs <2000HCA2738>.

The structural requirements for pteridine binding to tyrosine hydroxylase, which also uses tetrahydrobiopterin as its cofactor, have been investigated using kinetic measurements and molecular modeling based on a crystal structure <2000B13676>. Using the recombinant human enzyme, it was shown that substitutions at C-2, C-4, N-5, and N-8 abolish cofactor activity. Molecular modeling studies showed that several conformers could bind but defined the essential binding interactions for pterins with this enzyme, notably π-stacking with Phe-300 hydrogen bonds between N-2 and N-3 and Glu-332, and indicating that space is available for bulky substituents at C-6 and a separation of 4.2 Å between C-4a and the active site iron <1997MI7219>. From a study of tyrosine hydroxylase using both tetrahydrobiopterin and 6-methylpterin as a cofactor analogue, it was concluded that tetrahydrobiopterin is the natural reductant of the non-heme iron in the normal mechanism of action of the enzyme although no radical intermediates were detected <2006B2372>.

Sepiapterin reductase catalyzes the final steps in the biosynthesis of tetrahydrobiopterin. A high-resolution crystal structure has defined how a specific hydrogen bond cluster binds the pyrimidine ring of sepiapterin to the enzyme through interaction with an aspartate residue, thereby positioning the side-chain carbonyl group close to C4′ of NADPH for reduction. The fact that hydroxylated amino acid derivatives such as *N*-acetyl serotonin also bind suggested that there is a feedback mechanism integrating the formation of indoleamines and pteridines *in vivo*. The significance of pterins in biological control mechanisms has been referred to in Section 10.18.12.6. The structural relationship of sepiapterin reductase with other enzymes in the so-called short-chain dehydrogenase reductase family has been investigated <2001MI825>.

The stereochemical course of the reaction catalyzed by dihydroneopterin aldolase has been established <2002JBC28841>. By carrying out the reaction in deuterium oxide and using multinuclear NMR spectroscopy of folate derived from the reaction product, 6-hydroxymethylpterin, it was shown that the late-stage enol intermediate undergoes protonation to form 6-hydroxymethylpterin with deuterium predominantly in the *S*-configuration.

Riboflavin synthase catalyzes the dismutation of 8-D-ribityl-6,7-dimethyllumazine to form the flavin ring system and the general features of the mechanism of this reaction have been known for some time. Recent X-ray structural studies of the enzyme from archaeal organisms such as methanobacteria have shown that the chemical mechanism of action is similar to that of enzymes from eubacteria and eukaryotes although the structures of the enzymes differ greatly <2006JBC1224>.

The expansion in the power of computers and theoretical methods has made it possible to investigate the mechanism of action of enzymes by combinations of quantum-mechanical and molecular-mechanical calculations. A study of two possible mechanisms for dihydrofolate reductase catalysis was consistent with indirect proton transfer from aspartate to N-5 of the pterin as has been suggested for many years by crystallographic evidence <2003PCB14036>. This conclusion is also consistent with the outcome of a study that directly measured the pK_a of the active site aspartate in the *Lactobacillus casei* enzyme <1999B8038>. Observations of chemical shifts of

aspartate when dihydrofolate was bound suggested a strong polarization of the pterin ring that provided a driving force for protonation of O-4 of the substrate. The hydrogen-bonding network then facilitated proton transfer to N-5 as required for reduction of the C(6)–N(5) double bond. Further evidence for the indirect proton-transfer mechanism comes from studies of the binding of 5-formyltetrahydrofolate to dihydrofolate reductase as shown by crystallography; data were interpreted to indicate a keto–enol tautomersim involving the O-4 carbonyl group <1996B7012>.

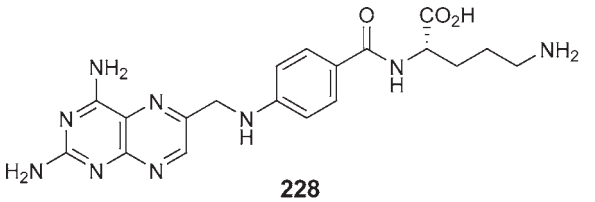
Another physical technique that has been applied to the study of the detailed mechanism of action of pteridine-reducing enzymes is isothermal calorimetry. It has been used to investigate the thermodynamics of the reaction catalyzed by the R67 dihydrofolate reductase <2004B7403>. The data argued for the formation of an enthalpy-driven tight enzyme substrate complex in which the cofactor's pyridine ring has a high degree of overlap with the pteridine ring of the substrate. The pteridine reductases of parasites such as leishmania and trypanosomes are also short-chain reductases. Crystal structures of enzymes from these sources complexed with inhibitors have defined the structural relationships that lead to strong binding and emphasize differences between these enzymes and bacterial and vertebrate dihydrofolate reductases <2005JMB105, 2005MI64>. For example, trimethoprim, a good antibacterial drug, is too bulky to bind to the active site of the *Leishmania* enzyme. It is also of interest that the trypanosomal enzyme was shown to be more active in reducing fully conjugated substrates such as biopterin and folic acid, unlike the bacterial and vertebrate enzymes. It is to be anticipated that such studies will form the basis of the design and synthesis of selective drugs for the treatment of tropical parasitic diseases. A further relevant enzyme for a drug target for tropical diseases is the quinonoid dihydropterin reductase from *Leishmania major* <2002JBC38245>, the crystal structure of which has been solved. It has been suggested that the bifunctional deaminase and reductase involved in riboflavin biosynthesis is a potential target for antibacterial drugs especially in view of the strong structural homology between the reductase domain of the bifunctional enzyme and dihydrofolate reductase as shown by X-ray crystallography <2006JBC7605>.

10.18.12.8 Medicinal Chemistry

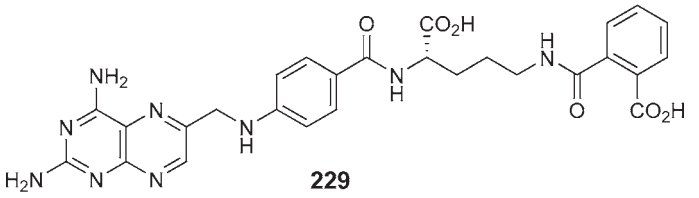
The medicinal chemistry of pteridines began with antifolates in the 1940s, originally as antibacterial and anticancer agents, and such compounds still attract attention today. Modifications have been made in all parts of the folate molecule. Approaches to developing selective antifolates, especially with regard to tropical parasitic diseases, have been reviewed <2006CME377>. Analogues with pyridine or thiophene rings in place of the benzene ring of 4-aminoglutamate have been synthesized by standard methods <1997JME370>. In the glutamate side chain, γ,γ-difluoromethotrexate has been prepared and investigated as a substrate and inhibitor of folate-dependent enzymes <1996JME66>. The precursor difluoroglutamic acid was a poor substrate for folylpoly-γ-glutamate synthetase but difluoromethotrexate was equipotent with methotrexate and is a dihydrofolate reductase inhibitor and an inhibitor of cell growth. Folylpoly-γ-glutamate synthetase has also been investigated with compounds containing ornithine as a side chain (**228**) <1996JHC1355>; such compounds were inhibitors in the 0.1 μM range (K_i) but were about 10-fold weaker in activity than the corresponding 5- or 8-deazapterin analogues. Phosphono analogues of methotrexate have been prepared and evaluated as prodrugs for methotrexate <2006JME770>.

In anticancer therapy, it has become recognized that non-polyglutamatable folate analogues have advantages because they can make effective use of the reduced folate carrier for influx into the target cells and are less effectively pumped out <1999CME329>. A lead compound in this field, PT523 **229**, which is 10–100 times more potent than MTX as a cell growth inhibitor, has been recognized to have especially strong binding to human dihydrofolate reductase <1997B13897>, and this has been associated with contacts between the phthaloyl group and the enzyme <1997B4399>. However the therapeutic efficacy of PT523 appears to be limited by hematological toxicity. Many second-generation compounds, especially 1-deaza analogues, have followed <2000JME1620> but with further modifications to both the phthaloyl ring and substitution of sulfur for methylene groups in the ornithine side chain. The potency of compounds in this class against human leukemia cell lines was in the nanomolar range. Synthetic approaches to these compounds included both Wittig reagents formed from 6-bromomethylpteridines and pyrazine precursors followed by hydrogenation of the alkenes so obtained. A group of compounds in this study also contained variations of the 4-aminobenzoate ring to include additional substituents and a naphthalene analogue. There are, however, limits to the size of modification that can be inserted in this region without loss of biological activity. The replacement of the benzene ring by a bicyclo[2.2.2]octane afforded compounds without measurable activity <2001EJM237>.

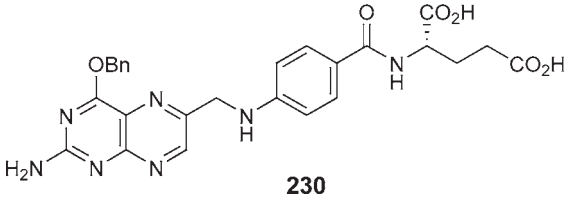
O^4-Benzylfolates, such as **230**, have been investigated as inhibitors of DNA allyltransferase with some promise <2004JME3887>; they can readily be prepared from 2,5,6-triamino-4-*O*-benzylpyrimidine by standard ring-forming condensation *via* the pteridine 6-aldehyde and reductive amination to insert the 4-aminobenzoyl glutamate.



228

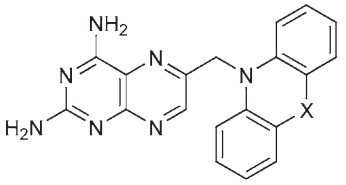


229

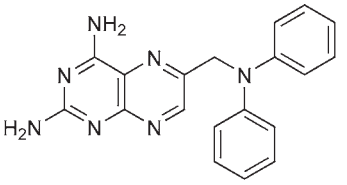


230

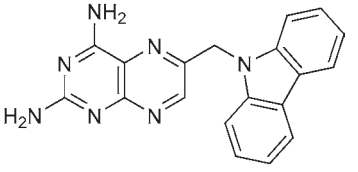
Anti-infective drugs remain a major application of pteridines with dihydrofolate reductases as common target enzymes. The emphasis of research is upon potency, selectivity, and obtaining new antifolates to which the target organisms do not show resistance. Also a wide range of infections including AIDS and parasitic infections are attracting attention. A recognized feature of antibacterial dihydrofolate reductase inhibitors as compared with vertebrate enzymes is the lack of a hydrophobic pocket in the latter group. Thus it is probable that new antifolates that also bear large hydrophobic groups will be selective for the enzyme of infectious agents compared with humans. Following this logic, a large number of bridged diarylamine derivatives **231–233** have been prepared by alkylation of 2,4-diamino-6-bromomethylpteridine <1999JME4853>. Whereas most of the compounds prepared were active against dihydrofolate reductases from a range of species (*Pneumocystis carinii*, *Toxoplasma gondii*, *Mycobacterium avium*, and rat liver), the dibenz[*b*,*f*]azepine derivative (**231**: X = CH_2CH_2) had high selectivity (20–500-fold); it was argued that its distinctive properties are associated with the puckered seven-membered ring compared with the planar six-membered rings found in other compounds. The synthesis of naphthalene-containing compounds based upon the same logic has been described in Section 10.18.9.2 <1997PTR173>.



231: X = CH=CH, CH_2CH_2, CH_2, O, or S



232

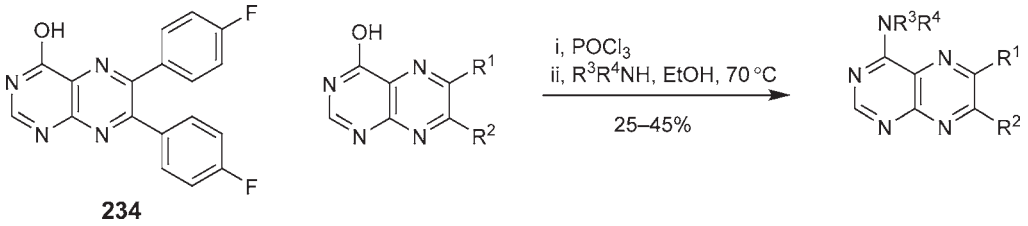


233

The lipophilicity strategy for obtaining dihydrofolate reductase inhibitors has been further exploited with the attachment of chloronaphthyl groups by substitution of 2,4-diamino-6-chloromethyl-7-methylpteridine prepared as noted above using Taylor's pyrazine method <1997PTR173>. The most active compounds had R^1 = Me, R^3 = Cl or R^1 = Me, R^3 and R^4 = Cl; against the rat liver and *T. gondii* enzyme, the IC_{50} was 0.26 μM and against *P. carinii*, 1.9 μM, a selectivity that was insufficient to encourage further study of this series as potential drugs.

A novel approach to the production of antimalarial drugs has been described taking advantage of the *in vivo* transformation of pteridines by resident enzymes <2005AAC3652>. It was shown that simple precursors such as 2,4-diamino-6-hydroxymethylpterin can be converted into aminopterin or methotrexate, depending upon the precursor chosen, and that the dihydrofolate reductase inhibitors so formed were active against *Plasmodium falciparum*.

Antiviral applications have not figured strongly in pteridine medicinal chemistry. However a report of screening a library of pteridines, variants of 6,7-diphenylpteridines, has identified significant activity against a hepatitis C virus RNA polymerase <2005BML675>. Such compounds lend themselves to library synthesis (**Scheme 48**). The most active compound **234** found had 6,7-di(4-fluorophenyl) substituents and a 4-hydroxyl group (IC_{50} 0.5 μM).

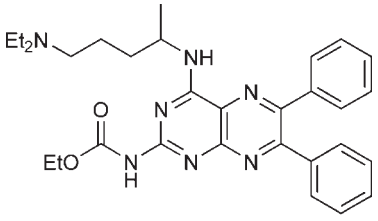


234

Scheme 48

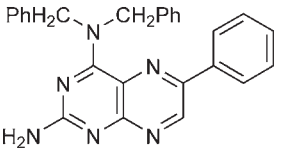
Pteridines have emerged as candidates for antiviral (herpes) screening in *in silico* virtual combinatorial syntheses <1999JME3308>. 6,7-Diphenylpteridines have also been investigated as nematocidal compounds and comparative molecular field analysis has been carried out <1997QSA372>.

In a further demonstration of the biological activity of 6,7-diaryl pteridines, activity has also been found against biological targets remote from folate or biopterin pathways. In a study seeking new targets against *Mycobacterium tuberculosis*, the novel highly substituted pteridine carbamate **235** was found to be active against the protein FTsZ, which has the characteristics of a GTPase and appears to be related to tubulin. Compound **235** was synthesized by adaptations of standard nucleophilic substitution and condensation chemistry from 2-amino-4,6-dichloropyrimidine <2004BML3161>.

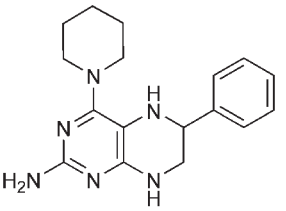


235

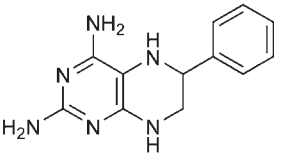
The multiple functions of nitric oxide make the NOSs significant targets for medicinal chemical intervention. Early studies did not have the benefit of recent structural and mechanistic information <1998JBC33142>. A systematic study of the neuronal isoform (nNOS) carried out before the full crystal structure became available showed that the enzyme could accept a 4-amino group or large and hydrophobic substituents at positions 4 and 6 as exemplified by **236–238** in addition to close analogues of the natural C-6 dihydroxypropyl side chain <1999JME4108>. This work also exploited a wide range of pyrimidine and side-chain modification-based synthetic methodologies. Unlike dihydrofolate reductases, where 2,4-diaminopyrimidines predominate, it has been established that 4-oxo compounds, including tetrahydro derivatives, are effective inhibitors of NOSs <2001JBC49133>; unsurprisingly, large substituents at O-4 and C-6 were also tolerated, for example, **239** and **240**. As the extent of knowledge of structure and activity increased, it was possible to develop a 3-D quantitative structure–activity relationship embodying the data and these analyses provide informative predictive power for the design of inhibitors of nNOS <2002JME2923>. Because of the different functions of nitric oxide produced in different tissues by the three isoforms, selectivity between isoforms is an important goal. There is little direct evidence with respect to pteridine-based inhibitors in this context but it has been shown that the 4-amino analogue of tetrahydrobiopterin selectively inhibits inducible nitric oxide synthase (iNOS) compared with endothelial nitric oxide synthase (eNOS) in a mouse cell model expressing both enzymes <2002PTR126). An extended modeling study has provided some design paradigms for isoform-selective inhibitors <2005JME4783>; a general feature recognizable in the compounds illustrated here was that hydrophobic substituents at N(O)-4 and C-6 increased affinity and selectivity for the neuronal isoform. Despite these developments, it is important to recognize that many of the NOS inhibitors of potential therapeutic interest are not pteridines and compete with the substrate, arginine, on binding to the enzyme. A novel series of compounds has hybridized the structure of methotrexate and **238** by placing the 4-aminobenzoylglutamate side chain as a substituent on N-4. These compounds both inhibited NOS and showed some antitumor activity <2006ACT249>. A review of the field of NOS inhibition has appeared <2004MI662>.



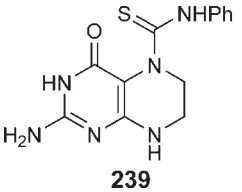
236



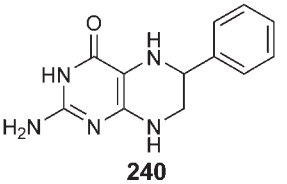
237



238



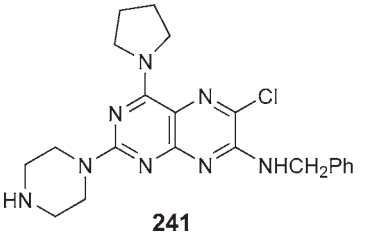
239



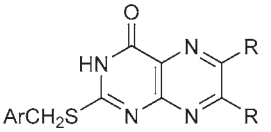
240

Cancer chemotherapy lends a number of additional targets beyond folate metabolism to pteridine-based inhibitors. 4-Arylaminopyridines have been noted as part of the pharmacophore for protein kinases that use ATP. It is interesting, therefore, that aminopteridines have been found to have significant activity as inhibitors of phosphodiesterases that hydrolyze cAMP. Such compounds, like the kinase inhibitors, are of interest in cancer therapy. The trialkylaminopteridine **241** is a potent inhibitor and arrests the division of cells with the induction of apoptosis <2002BP659>; the synthesis of this compound has been highlighted in (Section 10.18.7.2 <1998JME4733>. As noted above, 4-*O*-benzylpteridine derivatives, especially 4-*O*-benzylfolate, have been found to be potent inhibitors of the human DNA repair protein, alkyl DNA transferase, and significantly more so than a clinical lead compound, 6-*O*-benzylguanine <2004JME3887>. Screening cancer cell lines has identified a number of synthetically accessible pteridine templates for new lead discovery <2005BMC3513>; for example, 2-arylthioalkyl pteridines **242** and 4-hydroxyethylamino pteridines **243** all showed significant activity.

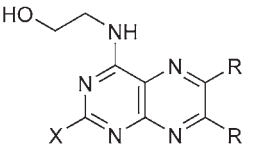
Inflammatory diseases are also targets for pteridines. Traditional antifolates and novel compounds find activity. For example, in rheumatoid arthritis, a wide range of methotrexate analogues, 10-deazaaminopterins, have been investigated for their ability to reduce inflammation <1997JME370>. These compounds were prepared by side-chain alkylation of 2,4-diamino-6-bromomethylpteridine; a thiophene-containing analogue **244** was found to be effective in this study. 7-Substituted pteridines such as **245** have been shown to have significant adenosine kinase-inhibiting activity <2004BML4165>; however, the activity (50–500 nM) was poorer than that of several competing related heterocyclic systems including pyrazolopyrimidines and alkynylpyrimidines, a phenomenon that had been observed before in related studies <2001JME2133>.



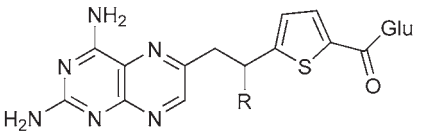
241



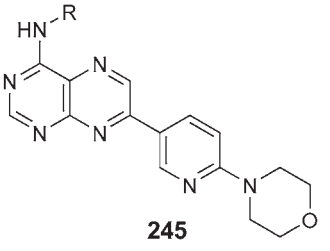
242
R = H, Me
Ar = substituted phenyl, quinolyl, benzimidazolyl, pyrrolidinyl



243
R = H, Me
X = OH, NH_2, SH



244
R = H, Et



245
R = H, $(CH_2)_nPh$ where n = 2–4, $(CH_2)_2$-3-indolyl

The similarity in the pyrimidine ring of pteridines and pterins, especially to the purines adenine and guanosine, undoubtedly makes them good templates for inhibitor design as these examples show. Another enzyme for which inhibition by pteridines has been established is xanthine oxidase <1999BBA387>. In this case, the limitation on structure for inhibitors in the pteridine series was that there should be no substituent on C-7 and that the pteridines should be fully conjugated. The best inhibitors ($IC_{50} \sim 0.1\ \mu M$) were 6-formylpterin and 6-hydroxylumazine.

10.18.12.9 Toxicology

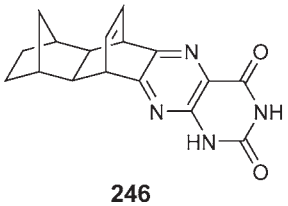
Although pteridines are valuable templates for drug design, many nevertheless show toxicity. The naturally occurring pterins, xanthopterin and isoxanthopterin, were found to inhibit the viability of MCF-7 (human mammary carcinoma) cells at concentrations in the 100 mM range <2005MI119>.There is evidence that some pteridines can inhibit cytochromes P450 evidently through coordination to the heme iron <1997PTR21>. Only fully conjugated pteridines with side-chain hydroxyl groups such as neopterin and biopterin showed significant activity (~60% inhibition under the conditions used). Neopterin accumulation has been found to be associated with a number of pathological indications including decreasing membrane fluidity, cell cycle inhibition, and apoptosis induction <1998PTR103>. On the other hand, tetrahydrobiopterin and its precursors were found to be beneficial by increasing membrane fluidity, stimulating the cell cycle, and reducing cholesterol precipitation. These results suggest that for healthy functioning, the cellular concentration of neopterin could be critical.

The putative *E. coli* gene of the 6-pyruvoyltetrahydropterin synthase (PTPS) was cloned and overexpressed in order to identify the enzymatic activity to synthesize 6-pyruvoyltetrahydropterin from dihydroneopterin triphosphate <2002MI234>. The protein was shown to have another new catalytic function to convert sepiapterin to 7,8-dihydroneopterin.

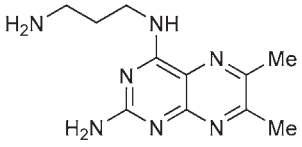
10.18.12.10 Nanochemistry

Nanostructures and nanochemistry are growth fields that have connections with the molecular scale and properties of DNA; it is not surprising, therefore, that pteridines have been brought into research. Various structural types have been considered, for example, **246**.

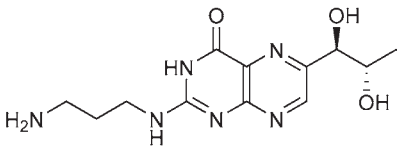
The folding of large DNA molecules in the presence of pteridine conjugates of amines and polyamines has been investigated <2005JA10910>. The structures selected were synthetically accessible analogues such as the naturally occurring pteridine, oncopterin **248**, which has been found in malignant lymphoma patients <1993MI1>. On the basis of information from denaturation, UV and fluorescence spectroscopy, and transmission electron microscopy, it was deduced that the folding of DNA was not a continuous process but took place in a series of separate steps. It was further shown that a 6,7-dimethyl analogue of oncopterin **247** and its spermine derivative also induce folding of DNA more effectively than polyamines alone <2005CEJ4835>. The mechanisms by which these processes occurred were not considered to be through a strong interaction of the pteridine component with the DNA duplex.



246



247



248

Another field of nanochemistry is molecular imprinting. Pteridines and many other compounds have been investigated in high-throughput and combinatorial studies of imprinted polymer synthesis <2004MAR59>. In a more specific study of folates and dihydrofolate reductase inhibitors, it was found possible to prepare polymers that were able to absorb folate derivatives and provide materials with the potential to act as chromatographic media <2001JA2146>. The most selective systems were found with 2-vinylpyridine as the functional monomer but methacrylic acid also was an effective building block.

10.18.13 Further Developments

10.18.13.1 Physicochemical Properties

A method has been described for he prediction of the pK_as of carbon–hydrogen bonds in aromatic heterocycles including pteridines, in DMSO solution <2007T1568>.

10.18.13.2 Reactivity of Conjugated Pteridines

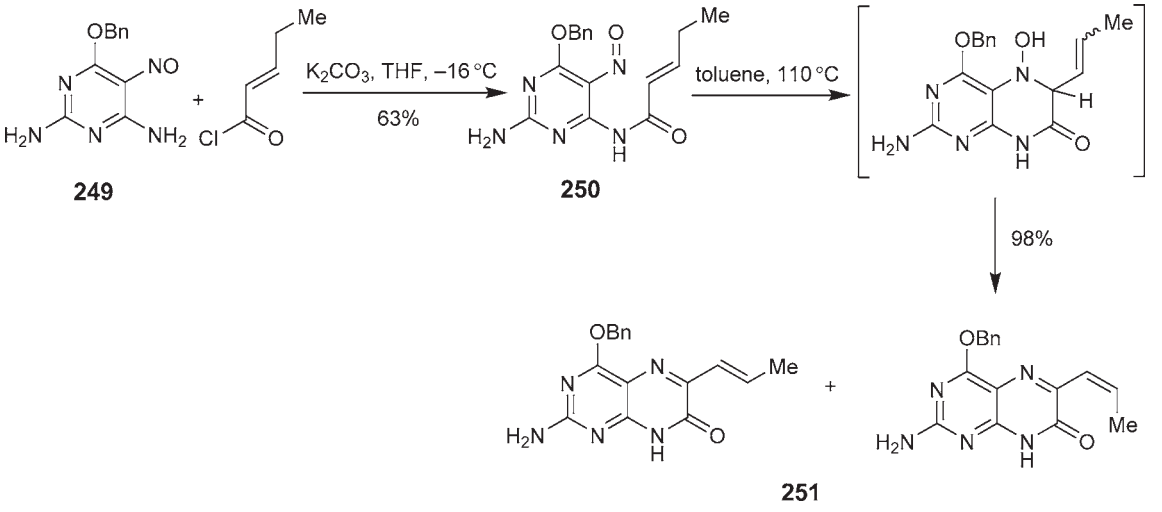
Further studies of the oxidation of 6-formylpterin, itself an oxidation product of more extended C6 substituted pterins including folic acid, in the dark but in the presence of NADH have confirmed the formation of reactive oxygen species <2007BBR1105>.

10.18.13.3 Reactions of Substituents

The reaction of 6-methylpteridines with *N*-chlorosuccinimide has been shown to be a mild and efficient route to 6-trichloromethylpteridines and other similarly substituted heterocycles in yields in excess of 70% avoiding the experimental problems associated with phosphorus-based reagents <2007CL552>.

10.18.13.4 Synthesis from Pyrimidines

Two papers describing the intramolecular ene cyclization for the preparation of C6 functionalized pteridines has appeared. Thus 4-amino-5-nitrosopyrimidines such as **249** reacted with α,β-unsaturated acid chlorides acylating at the 6-amino group group to afford nitrosoamides **250** which on thermolysis in toluene underwent the pericyclic cyclization and subsequent loss of water to afford a mixture of the *E*- and *Z*-isomers of the 6-oxopteridine **251** in good yield <2006HCA1140, 2007HCA521>.



249 **250** **251**

10.18.13.5 Synthesis from Pyrazines

A one-pot procedure for the synthesis of amino and phenyl substituted pteridines using *N*,*N*-dimethyldichloromethyleneiminium chloride has been described <2006H(68)933>.

10.18.13.6 Medicinal Chemistry

A computational study of the isoforms of nitric oxide synthases has concluded that because of the close similarities between the isoforms, the design of isoform selective inhibitors will be a difficult task <2006CMC1929>.

A further review of the mechanism of action of tetrahydrobiopterin in nitric oxide synthases has appeared with emphasis on studies of the enzyme under high pressures <2006BBA578>.

An important discovery is that procaryotes contain a different GTP cyclohydrolase 1 family distinct from the well studied canonical eukaryotic enzyme. Potentially, this enzyme is a target for new antibacterial drugs <2006JBC37586>.

Further compounds in the 6,7-diarylpteridine class with potential antiviral activity have been described. These compounds were rigidified by cyclizing the two benzene rings with methylene bridges. However this standard medicinal chemical modification did not improve the activity compared with compounds already described (see Section 10.18.12.8) <2007EJO2987>.

10.18.13.7 Enzyme Mechanisms

The structure of dihydroneopterin aldolase has been analyzed further with respect to the functional roles of conserved active site glutamate and lysine residues <2006B15232>. NMR studies have also suggested that the isomerization of dihydroneopterin to dihydromonapterin catalyzed by the same enzyme involves the action of the same functional groups <2007MI2240>.

Relevant Websites

http://www.bh4.org An academic website chiefly concerned with the tetrahydrobiopterin in disease.

http://www.nitricoxideresearch.com A commercial website that provides extensive retrospective bibliographies of relevant published research. While focusing on nitric oxide biology, it has clickable subsections dealing with pteridines and pterins.

References

1857LA117 F. Wöhler, *Liebigs Ann. Chem.*, 1857, 117.
1857LA200 H. Hlasiwetz, *Liebigs Ann. Chem.*, 1857, 200.
1889NAT335 F. G. Hopkins, *Nature*, 1889, **40**, 335.
1889PCS117 F. G. Hopkins, *Proc. Chem. Soc.*, 1889, **5**, 117.
1891NAT197 F. G. Hopkins, *Nature*, 1891, **45**, 197.
1892NAT581 F. G. Hopkins, *Nature*, 1892, **45**, 581.
1894CB2116 O. Kühling, *Chem. Ber.*, 1894, **27**, 2116.
1894PRS5 F. G. Hopkins, *Proc. R. Soc.*, 1894, **57**, 5.
1895CB1968 O. Kühling, *Chem. Ber.*, 1895, **28**, 1968.
1895MI661 F. G. Hopkins, *Philos. Trans. Royal Soc. London, Ser. B*, 1895, **186**, 661.
1901CB1234 S. Gabriel and J. Colman, *Chem. Ber.*, 1901, **34**, 1234.
1906CB250 O. Isay, *Chem. Ber.*, 1906, **39**, 250.
1908CB3957 F. Sachs and G. Meyerheim, *Chem. Ber.*, 1908, **41**, 3957.
1925CB2178 H. Wieland and C. Schöpf, *Chem. Ber.*, 1925, **58**, 2178.
1926CB2067 C. Schöpf and H. Wieland, *Chem. Ber.*, 1926, **59**, 2067.
1933LA226 H. Wieland, H. Metzger, C. Schöpf, and M. Bülow, *Liebigs Ann. Chem.*, 1933, *226*.
1936LA49 C. Schöpf and E. Becker, *Liebigs Ann. Chem.*, 1936, 49.
1940LA182 R. Purrmann, *Liebigs Ann. Chem.*, 1940, 182.
1940LA98 R. Purrmann, *Liebigs Ann. Chem.*, 1940, 98.
1941LA83 C. Schöpf and R. Reichert, *Liebigs Ann. Chem.*, 1941, 83.
1941LA284 R. Purrmann, *Liebigs Ann. Chem.*, 1941, 284.
1949JA1753 D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Am. Chem. Soc.*, 1949, **71**, 1753.
1959CB2468 W. Pfleiderer, *Chem. Ber.*, 1959, **92**, 2468.
1963AG993 W. Pfleiderer, *Angew. Chem.*, 1963, **75**, 993.
1970MI911 H. S. Forrest and C. Van Baalen, *Annu. Rev. Microbiol*, 1970, **24**, 91.
B-1976MI1 J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, Eds.; 'The Tautomerism of Heterocycles', Academic Press, New York, 1976.
B-1985MI1 R. L. Blakley and S. J. Benkovic, Eds.; 'Folates and Pterins', Wiley, New York, 1985, vol. 2.
B-1987MI1 W. Lovenberg and R. A. Levine, Eds.; 'Unconjugated Pterins in Neurobiology; Basic and Clinical Aspects', Taylor & Francis, London, 1987.
B-1988MI1 D. J. Brown, Ed.; 'Pteridines', Wiley, New York, 1988.
1990PTR129 J. Ferre, K. B. Jacobson, and W. Pfleiderer, *Pteridines*, 1990, **2**, 129.
B-1992MI1 H. Wachter, D. Fuchs, A. Hausen, G. Reibnegger, G. Weiss, E. R. Werner, and G. Werner-Felmayer, 'Neopterin Biochemistry – Methods and Clinical Application', W. de Gruyter, Berlin, 1992.
1992S303 S. Murata, T. Sugimoto, S. Ogiwara, K. Mogi, and H. Wasada, *Synthesis*, 1992, 303.

1993MI1 S. Ogiwara, H. Hidaka, T. Sugimoto, R. Teradaira, K. Fujita, and T. Nagatsu, *J. Biochem.*, 1993, **113**, 1.
1994JBC23981 R. B. Irby and W. L. Adair, Jr., *J. Biol. Chem.*, 1994, **269**, 23981.
1995JBC1082 M. M. Wuebbens and K. V. Rajagopalan, *J. Biol. Chem.*, 1995, **270**, 1082.
1996B7012 H. Lee, V. M. Reyes, and J. Kraut, *Biochemistry*, 1996, **35**, 7012.
1996CHEC-II(7)679 W. Pfleiderer; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, ch. 18, p. 679.
1996CPB1115 Y. Asahi, M. Tanaka, and N. Yamamoto, *Chem. Pharm. Bull.*, 1996, **44**, 1115.
1996EJM273 G. Ferrand, H. Dumas, J. C. Depin, and Y. Quentin, *Eur. J. Med. Chem.*, 1996, **31**, 273.
1996H(43)437 E. C. Taylor, M. Takahashi, and N. Kobayashi, *Heterocycles*, 1996, **43**, 437.
1996JBC7387 R. M. Garrett and K. V. Rajagopalan, *J. Biol. Chem.*, 1996, **271**, 7387.
1996J(P1)247 T. Okawa, S. Eguchi, and A. Kakehi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 247.
1996JHC341 M. Igarashi, T. Kambe, and M. Tada, *J. Heterocycl. Chem.*, 1996, **33**, 341.
1996JHC1355 A. Rosowsky, R. A. Forsch, and R. G. Moran, *J. Heterocycl. Chem.*, 1996, **33**, 1355.
1996JME66 T. Tsukamoto, T. Kitazume, J. J. McGuire, and J. K. Coward, *J. Med. Chem.*, 1996, **39**, 66.
1996JOC8698 A. M. Fernandez and L. Duhamel, *J. Org. Chem.*, 1996, **61**, 8698.
1996MI1 16th International Winter Workshop on Biochemical and Clinical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 24 Feb.–2 Mar., 1996 (*Pteridines*, 1996, **7**, 39).
1996MITU466 M. E. Hawkins, W. Pfleiderer, J. R. Knutson, D. Porter, and F. Balis, *Biophys. J.*, 1996, **70**, TU466.
1996NN431 Y. Maurinsh and W. Pfleiderer, *Nucleos. Nucleot.*, 1996, **15**, 431.
1996PTR110 H. Yamamoto, T. Hanaya, K. Harada, H. Kawamoto, and W. Pfleiderer, *Pteridines*, 1996, **7**, 110.
1996PTR113 K. Abou-Hadeed and W. Pfleiderer, *Pteridines*, 1996, **7**, 113.
1996RTC31 J. Bergman, C. Damberg, and H. Vallberg, *Recl. Trav. Chim. Pays-Bas*, 1996, **115**, 31.
1996T13017 C. Dunn, C. L. Gibson, and C. J. Suckling, *Tetrahedron*, 1996, **52**, 13017.
1996TL8355 O. Jungmann and W. Pfleiderer, *Tetrahedron Lett.*, 1996, **37**, 8355.
1997ABI86 M. E. Hawkins, W. Pfleiderer, F. M. Balis, D. Porter, and J. R. Knutson, *Anal. Biochem.*, 1997, **244**, 86.
1997AXC213 R. L. Beddoes, A. Dinsmore, M. Helliwell, C. D. Garner, and J. A. Joule, *Acta Crystallogr., Sect. C*, 1997, **53**, 213.
1997B4399 J. M. Johnson, E. M. Meiering, J. E. Wright, J. Pardo, A. Rosowsky, and G. Wagner, *Biochemistry*, 1997, **36**, 4399.
1997B13897 V. Cody, N. Galitsky, J. R. Luft, W. Pangborn, A. Rosowsky, and R. L. Blakley, *Biochemistry*, 1997, **36**, 13897.
1997BBR774 K. Oettl, S. Dikalov, H. J. Freisleben, W. Mlekusch, and G. Reibnegger, *Biochem. Biophys. Res. Commun.*, 1997, **234**, 774.
1997BML779 M. J. Dufton, C. L. Gibson, A. R. Pitt, S. Athmani, and C. J. Suckling, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 779.
1997H(45)765 T. Sugimoto and W. Pfleiderer, *Heterocycles*, 1997, **45**, 765.
1997IC3869 Y. Funahashi, Y. Hara, H. Masuda, and O. Yamauchi, *Inorg. Chem.*, 1997, **36**, 3869.
1997JCD3909 D. C. Rees, Y. L. Hu, C. Kisker, and H. Schindelin, *J. Chem. Soc., Dalton Trans.*, 1997, 3909.
1997JHC973 M. Tada, Y. Asawa, and M. Igarashi, *J. Heterocycl. Chem.*, 1997, **34**, 973.
1997JHC1581 A. Nagarajan, B. R. Meltsner, and T. J. Delia, *J. Heterocycl. Chem.*, 1997, **34**, 1581.
1997JIS773 H. Schindelin, C. Kisker, and D. C. Rees, *J. Biol. Inorg. Chem.*, 1997, **2**, 773.
1997JMB656 W. R. Cannon, B. J. Garrison, and S. J. Benkovic, *J. Mol. Biol.*, 1997, **271**, 656.
1997JME370 J. I. Degraw, W. T. Colwell, J. Crase, R. L. Smith, J. R. Piper, W. R. Waud, and F. M. Sirotnak, *J. Med. Chem.*, 1997, **40**, 370.
1997J(P1)801 A. Dinsmore, J. H. Birks, C. D. Garner, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1997, 801.
1997J(P2)1529 S. P. Greatbanks, I. H. Hillier, C. D. Garner, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1529.
1997JPH43 M. S. Kritsky, T. A. Lyudnikova, E. A. Mironov, and I. V. Moskaleva, *J. Photochem. Photobiol. B*, 1997, **39**, 43.
B-1997MI1 W. Pfleiderer and H. Rokos, Eds.; 'Chemistry and Biology of Pteridines and Folates – 1997 Proceedings of the 11th International Symposium on Pteridines and Folates', Blackwell Science, Berlin, 1997.
1997MI2 16th International Winter Workshop on Biochemical and Clinical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 16–22 Feb., 1997 (*Pteridines*, 1997, **8**, 27).
1997MI7219 G. Auerbach, A. Herrmann, M. Gütlich, M. Fischer, U. Jacob, A. Bacher, and R. Huber, *EMBO J.*, 1997, **16**, 7219.
1997NN863 O. Jungmann and W. Pfleiderer, *Nucleos. Nucleot.*, 1997, **16**, 863.
1997NN1369 R. Charubala, J. Maurinsh, A. Rösler, M. Melguizo, O. Jungmann, M. Gottlieb, J. Lehbauer, M. Hawkins, and W. Pfleiderer, *Nucleos. Nucleot.*, 1997, **16**, 1369.
1997POL607 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *Polyhedron*, 1997, **16**, 607.
1997PTR1 S. Murata, T. Sugimoto, and K. Murakami, *Pteridines*, 1997, **8**, 1.
1997PTR21 R. Horejsi, J. Daczki, R. Möller, K. Öttl, K. Vrecko, and G. Reibnegger, *Pteridines*, 1997, **8**, 21.
1997PTR173 A. Rosowsky, R. A. Forsch, S. F. Queener, and J. R. Bertino, *Pteridines*, 1997, **8**, 173.
1997PTR188 T. Sugimoto, C. Seo, S. Murata, and W. Pfleiderer, *Pteridines*, 1997, **8**, 188.
1997QSA372 A. Martinez, C. Ochoa, J. Rodriguez, M. Rodriguez, A. Castro, M. Gonzalez, and M. M. Martinez, *Quant. Struct. Act. Relat.*, 1997, **16**, 372.
1997TL6835 S. Taghavi-Moghadam and W. Pfleiderer, *Tetrahedron Lett.*, 1997, **38**, 6835.
1998BBA257 R. H. White, *Biochim. Biophys. Acta*, 1998, **1380**, 257.
1998H(48)1255 S. Murata, K. Kiguchi, and T. Sugimoto, *Heterocycles*, 1998, **48**, 1255.
1998ICA(268)77 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *Inorg. Chim. Acta*, 1998, **268**, 77.
1998ICA(277)103 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *Inorg. Chim. Acta*, 1998, **277**, 103.
1998JA3295 M. D. Erion and M. R. Reddy, *J. Am. Chem. Soc.*, 1998, **120**, 3295.
1998JBC17418 C. Haußmann, F. Rohdich, E. Schmidt, A. Bacher, and F. Richter, *J. Biol. Chem.*, 1998, **273**, 17418.
1998JBC28132 A. Bracher, W. Eisenreich, N. Schramek, H. Ritz, E. Götze, A. Herrmann, M. Gütlich, and A. Bacher, *J. Biol. Chem.*, 1998, **273**, 28132.

1998JBC33142 H. M. Bömmel, A. Reif, L. G. Fröhlich, A. Frey, H. Hofmann, D. M. Marecak, V. Groehn, P. Kotsonis, M. L. La, S. Köster, M. Meinecke, M. Bernhardt, M. Weeger, S. Ghisla, G. D. Prestwich, W. Pfleiderer, and H. H. W. Schmidt, *J. Biol. Chem.*, 1998, **273**, 33142.

1998JCX565 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *J. Chem. Crystallogr.*, 1998, **28**, 565.

1998JHC693 U. Urleb, *J. Heterocycl. Chem.*, 1998, **35**, 693.

1998JME4733 K.-H. Merz, D. Marko, T. Regiert, G. Reiss, W. Frank, and G. Eisenbrand, *J. Med. Chem.*, 1998, **41**, 4733.

1998J(P1)2277 T. Okawa, M. Kawase, S. Eguchi, A. Kakehi, and M. Shiro, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2277.

1998MI1 17th International Winter Workshop on Biochemical and Clinical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 14–21 Feb., 1998 (*Pteridines*, 1998, **9**, 145).

1998MI24 C. Rieder, W. Eisenreich, J. O'Brien, G. Richter, E. Götze, P. Boyle, S. Blanchard, A. Bacher, and H. Simon, *Eur. J. Biochem.*, 1998, **255**, 24.

1998MI119 J. Marelius, M. Graffner-Nordberg, T. Hansson, A. Hallberg, and J. Åqvist, *J. Comput.-Aided Mol. Des.*, 1998, **12**, 119.

1998NN175 M. Melguizo, M. Gottlieb, R. Charubala, and W. Pfleiderer, *Nucleos. Nucleot.*, 1998, **17**, 175.

1998POL3409 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *Polyhedron*, 1998, **17**, 3409.

1998PTR85 G. Reibnegger, R. Horejsi, K. Oettl, and W. Mlekusch, *Pteridines*, 1998, **9**, 85.

1998PTR103 V. Rudzite, E. Jurika, G. Baier-Bitterlich, B. Widner, G. Reibnegger, and D. Fuchs, *Pteridines*, 1998, **9**, 103.

1998PTR175 K. Abou-Hadeed and W. Pfleiderer, *Pteridines*, 1998, **9**, 175.

1998S1185 T. Okawa, M. Kawase, and S. Eguchi, *Synthesis*, 1998, 1185.

1998T9559 A. Dinsmore, C. D. Garner, and J. A. Joule, *Tetrahedron*, 1998, **54**, 9559.

1999AXC254 M. Helliwell, A. Dinsmore, C. D. Garner, and J. A. Joule, *Acta Crystallogr., Sect. C*, 1999, **55**, 254.

1999B8038 M. G. Casarotto, J. Basran, R. Badii, K. H. Sze, and G. C. K. Roberts, *Biochemistry*, 1999, **38**, 8038.

1999BBA61 H. W. Lee, C. H. Oh, A. Geyer, W. Pfleiderer, and Y. S. Park, *Biochim. Biophys. Acta*, 1999, **1410**, 61.

1999BBA387 K. Oettl and G. Reibnegger, *Biochim. Biophys. Acta*, 1999, **1430**, 387.

1999CCR323 W. Kaim, B. Schwederski, O. Heilmann, and F. M. Hornung, *Coord. Chem. Rev.*, 1999, **182**, 323.

1999CME329 A. Rosowsky, *Curr. Med. Chem.*, 1999, **6**, 329.

1999H(50)117 S. Murata, M. Kujime, T. Sugimoto, K. Murakami, and C. Seo, *Heterocycles*, 1999, **50**, 117.

1999IC2600 H. L. Kaufmann, P. J. Carroll, and S. J. N. Burgmayer, *Inorg. Chem.*, 1999, **38**, 2600.

1999IC2607 S. J. N. Burgmayer, H. L. Kaufmann, G. Fortunato, P. Hug, and B. Fischer, *Inorg. Chem.*, 1999, **38**, 2607.

1999JA12140 R. Castillo, J. Andrés, and V. Moliner, *J. Am. Chem. Soc.*, 1999, **121**, 12140.

1999JBC24921 A. Reif, L. G. Fröhlich, P. Kotsonis, A. Frey, H. M. Bömmel, D. A. Wink, W. Pfleiderer, and H. Schmidt, *J. Biol. Chem.*, 1999, **274**, 24921.

1999JCX571 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *J. Chem. Crystallogr.*, 1999, **29**, 571.

1999JHC435 S. Molina, J. Cobo, A. Sanchez, M. Nogueras, and E. De Clercq, *J. Heterocycl. Chem.*, 1999, **36**, 435.

1999JHC1317 Y. Yamada, H. Yasuda, Y. Yoshihara, and K. Yoshizawa, *J. Heterocycl. Chem.*, 1999, **36**, 1317.

1999JME3308 J. V. De Julián-Ortiz, J. Gálvez, C. Muñoz-Collado, R. García-Domenech, and C. Gimeno-Cardona, *J. Med. Chem.*, 1999, **42**, 3308.

1999JME4108 L. G. Fröhlich, P. Kotsonis, H. Traub, S. Taghavi-Moghadam, N. Al-Masoudi, H. Hofmann, H. Strobel, H. Matter, W. Pfleiderer, and H. Schmidt, *J. Med. Chem.*, 1999, **42**, 4108.

1999JME4853 A. Rosowsky, V. Cody, N. Galitsky, H. N. Fu, A. T. Papoulis, and S. F. Queener, *J. Med. Chem.*, 1999, **42**, 4853.

1999J(P1)163 C. L. Gibson, A. Lang, K. Ohta, and C. J. Suckling, *J. Chem. Soc., Perkin Trans. 1*, 1999, 163.

1999MI1 18th International Winter Workshop on Chemical, Biochemical and Clinical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 6–13 Mar., 1999 (*Pteridines*, 1999, **10**, 47).

1999MI25 K. Schmidt, G. Werner-Felmayer, B. Mayer, and E. R. Werner, *Eur. J. Biochem.*, 1999, **259**, 25.

1999MI77 Y. Q. Chen, M. Gulotta, H. T. A. Cheung, and R. Callender, *Photochem. Photobiol.*, 1999, **69**, 77.

1999MI79 T. Nagatsu and H. Ichinose, *Mol. Neurobiol.*, 1999, **19**, 79.

1999MI359 B. W. Williams, *Biophys. J.*, 1999, **76**, A359.

1999MI1117 S. Y. Egorov, A. A. Krasnovsky, M. Y. Bashtanov, E. A. Mironov, T. A. Ludnikova, and M. S. Kritsky, *Biochem.-Moscow*, 1999, **64**, 1117.

1999POL85 F. Hueso-Ureña, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, M. Quirós-Olozábal, and J. M. Salas-Peregrín, *Polyhedron*, 1999, **18**, 85.

1999PTR79 H. Traub and W. Pfleiderer, *Pteridines*, 1999, **10**, 79.

1999PTR91 G. Reibnegger, J. Pauschenwein, and E. R. Werner, *Pteridines*, 1999, **10**, 91.

2000B11763 A. C. F. Gorren, N. Bec, A. Schrammel, E. R. Werner, R. Lange, and B. Mayer, *Biochemistry*, 2000, **39**, 11763.

2000B13676 B. Almås, K. Toska, K. Teigen, V. Groehn, W. Pfleiderer, A. Martinez, T. Flatmark, and J. Haavik, *Biochemistry*, 2000, **39**, 13676.

2000BBR307 B. Widner, C. Mayr, B. Wirleitner, and D. Fuchs, *Biochem. Biophys. Res. Commun.*, 2000, **275**, 307.

2000BJ767 P. Kotsonis, L. G. Fröhlich, Z. V. Shutenko, R. Horejsi, W. Pfleiderer, and H. Schmidt, *Biochem. J.*, 2000, **346**, 767.

2000H(53)1259 S. Murata, C. Seo, M. Kujime, and T. Sugimoto, *Heterocycles*, 2000, **53**, 1259.

2000HCA954 K. Oettl, W. Pfleiderer, and G. Reibnegger, *Helv. Chim. Acta*, 2000, **83**, 954.

2000HCA2738 V. Groehn, L. Fröhlich, H. Schmidt, and W. Pfleiderer, *Helv. Chim. Acta*, 2000, **83**, 2738.

2000ICC231 T. R. Chen, Y. Y. Wu, C. P. Wu, J. D. Chen, C. W. Huang, T. C. Keng, and J. C. Wang, *Inorg. Chem. Commun.*, 2000, **3**, 231.

2000JBC18926 I. Ziegler, T. McDonaldo, C. Hesslinger, I. Pelletier, and P. Boyle, *J. Biol. Chem.*, 2000, **275**, 18926.

2000JBC23406 I. Ziegler, T. McDonaldo, C. Hesslinger, I. Pelletier, and P. Boyle, *J. Biol. Chem.*, 2000, **275**, 23406.

2000JME1620 A. Rosowsky, J. E. Wright, C. M. Vaidya, R. A. Forsch, and H. Bader, *J. Med. Chem.*, 2000, **43**, 1620.

2000JMM433 E. R. Acuña-Cueva, F. H. Hueso-Ureña, S. B. Jiménez-Pulido, and M. N. Moreno-Carretero, *J. Mol. Model.*, 2000, **6**, 433.

2000J(P1)89 N. Sato and S. Fukuya, *J. Chem. Soc., Perkin Trans. 1*, 2000, 89.

2000M1371 H. Brunner and S. Rosenboem, *Monatsh. Chem.*, 2000, **131**, 1371.

2000MI1 19th International Winter-Workshop on Biochemical and Clinical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 12–19 Feb., 2000 (*Pteridines*, 2000, **11**, 1).

2000PCA7386 J. K. Hurst, P. Wormell, G. B. Bacskay, and A. R. Lacey, *J. Phys. Chem. A*, 2000, **104**, 7386.

2000PTR32 A. Martinez, K. K. Dao, J. McKinney, K. Teigen, and N. A. Froystein, *Pteridines*, 2000, **11**, 32.

2000PTR60 K. Oettl, J. Greilberger, and C. Reibnegger, *Pteridines*, 2000, **11**, 60.

2000PTR90 K. Oettl, J. Greilberger, and G. Reibnegger, *Pteridines*, 2000, **11**, 90.

2000TL8177 A. D. Baxter, E. A. Boyd, P. B. Cox, V. Loh, C. Monteils, and A. Proud, *Tetrahedron Lett.*, 2000, **41**, 8177.

2001ABI231 M. E. Hawkins, W. Pfleiderer, O. Jungmann, and F. M. Balis, *Anal. Biochem.*, 2001, **298**, 231.

2001B7896 A. Bracher, N. Schramek, and A. Bacher, *Biochemistry*, 2001, **40**, 7896.

2001BKC141 Y. Kim, Y. Kang, and D. Baek, *Bull. Korean Chem. Soc.*, 2001, **22**, 141.

2001CC123 B. Bradshaw, D. Collison, C. D. Garner, and J. A. Joule, *J. Chem. Soc., Chem. Commun.*, 2001, 123.

2001CHE755 N. N. Kolos, V. A. Chebanov, V. D. Orlov, and Y. N. Surov, *Chem. Heterocycl. Compd.*, 2001, **37**, 755.

2001EJM237 R. C. Reynolds, C. A. Johnson, J. R. Piper, and F. M. Sirotnak, *Eur. J. Med. Chem.*, 2001, **36**, 237.

2001H(54)283 T. Sugimoto, K. Ikemoto, S. Murata, M. Tazawa, T. Nomura, Y. Hagino, H. Ichinose, T. Nagatsu, and A. Wada, *Heterocycles*, 2001, **54**, 283.

2001HCA918 T. Sugimoto, K. Ikemoto, S. Murata, M. Tazawa, T. Nomura, Y. Hagino, H. Ichinose, and T. Nagatsu, *Helv. Chim. Acta*, 2001, **84**, 918.

2001HCA2330 J. Lehbauer and W. Pfleiderer, *Helv. Chim. Acta*, 2001, **84**, 2330.

2001ICA(325)65 S. B. Jiménez-Pulido, M. Sieger, A. Knödler, O. Heilmann, M. Wanner, B. Schwederski, J. Fiedler, M. N. Moreno-Carretero, and W. Kaim, *Inorg. Chim. Acta*, 2001, **325**, 65.

2001JA2146 M. Quaglia, K. Chenon, A. J. Hall, E. De Lorenzi, and B. Sellergren, *J. Am. Chem. Soc.*, 2001, **123**, 2146.

2001JBC49133 P. Kotsonis, L. G. Fröhlich, C. S. Raman, H. Y. Li, M. Berg, R. Gerwig, V. Groehn, Y. H. Kang, N. Al-Masoudi, S. Taghavi-Moghadam, D. Mohr, U. Münch, J. Schnabel, P. Martásek, B. S. S. Masters, H. Strobel, T. Poulos, H. Matter, W. Pfleiderer, and H. Schmidt, *J. Biol. Chem.*, 2001, **276**, 49133.

2001JHC727 M. D. Lopez, M. L. Quijano, A. Sanchez, M. Nogueras, and J. N. Low, *J. Heterocycl. Chem.*, 2001, **38**, 727.

2001JHC1173 A. Chowdhury, Y. Shibata, M. Morita, K. Kaya, and K. Hiratani, *J. Heterocycl. Chem.*, 2001, **38**, 1173.

2001JME2133 C. H. Lee, M. Q. Jiang, M. Cowart, G. Gfesser, R. Perner, K. H. Kim, Y. G. Gu, M. Williams, M. F. Jarvis, E. A. Kowaluk, A. O. Stewart, and S. S. Bhagwat, *J. Med. Chem.*, 2001, **44**, 2133.

2001J(P1)3239 B. Bradshaw, A. Dinsmore, W. Ajana, D. Collison, C. D. Garner, and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3239.

B-2001MI1 S. Milstien, G. Kapatos, R. A. Levine, and B. Shane, Eds.; 'Chemistry and Biology of Pteridines and Folates – Proceedings of the 12th International Symposium on Pteridines and Folates', Kluwer Academic Publishers, Boston, 2001.

2001MI2 20th International Winter Workshop on Clinical, Chemical and Biochemical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 10–17 Feb., 2001 (*Pteridines*, 2001, **12**, 1).

2001MI176 A. C. F. Gorren, A. J. Kungl, K. Schmidt, E. R. Werner, and B. Mayer, *Nitric Oxide-Biol. Chem.*, 2001, **5**, 176.

2001MI825 K. Fujimoto, M. Hara, H. Yamada, M. Sakurai, A. Inaba, A. Tomomura, and S. Katoh, *Chem. Biol. Interact.*, 2001, **130**, 825.

2001MI257 M. E. Hawkins, *Cell Biochem. Biophys.*, 2001, **34**, 257.

2001MI975 J. Vásquez-Vivar, J. Whitsett, P. Martásek, N. Hogg, and B. Kalyanaraman, *Free Radic. Biol. Med.*, 2001, **31**, 975.

2001PTR121 Y. K. Choi, Y. K. Hwang, Y. H. Kang, and Y. S. Park, *Pteridines*, 2001, **12**, 121.

2001PTR147 U. Demel, Z. Földes-Papp, D. Fuchs, and G. P. Tilz, *Pteridines*, 2001, **12**, 147.

2002ACT343 Q. Z. Yao, Z. X. Zhang, and L. Xiao, *Acta Chim. Sin.*, 2002, **60**, 343.

2002B15074 D. E. Graham, H. M. Xu, and R. H. White, *Biochemistry*, 2002, **41**, 15074.

2002BBA124 R. Horejsi, C. Jung, R. Möller, E. Tafeit, and G. Reibnegger, *Biochim. Biophys. Acta*, 2002, **1571**, 124.

2002BP659 B. Wagner, S. Jakobs, M. Habermeyer, F. Hippe, Y. S. Cho-Chung, G. Eisenbrand, and D. Marko, *Biochem. Pharmacol.*, 2002, **63**, 659.

2002COR775 M. J. Rist and J. P. Marino, *Curr. Org. Chem.*, 2002, **6**, 775.

2002H(56)387 N. Chen, K. Ikemoto, T. Sugimoto, S. Murata, H. Ichinose, and T. Nagatsu, *Heterocycles*, 2002, **56**, 387.

2002H(57)1841 M. Kujime, K. Kudoh, and S. Murata, *Heterocycles*, 2002, **57**, 1841.

2002JBC28841 V. Illarionova, W. Eisenreich, M. Fischer, C. Hauβmann, W. Römisch, G. Richter, and A. Bacher, *J. Biol. Chem.*, 2002, **277**, 28841.

2002JBC38245 L. F. Lye, M. L. Cunningham, and S. M. Beverley, *J. Biol. Chem.*, 2002, **277**, 38245.

2002JMB829 N. Schramek, A. Bracher, M. Fischer, G. Auerbach, H. Nar, R. Huber, and A. Bacher, *J. Mol. Biol.*, 2002, **316**, 829.

2002JME2923 H. Matter, P. Kotsonis, O. Klingler, H. Strobel, L. G. Fröhlich, A. Frey, W. Pfleiderer, and H. Schmidt, *J. Med. Chem.*, 2002, **45**, 2923.

2002JMM246 E. R. Acuña-Cueva, S. B. Jiménez-Pulido, and M. N. Moreno-Carretero, *J. Mol. Model.*, 2002, **8**, 246.

2002JOC4526 B. Zaleska, T. Bazanek, R. Socha, M. Karelus, J. Grochowski, and P. Serda, *J. Org. Chem.*, 2002, **67**, 4526.

2002JPH167 S. Anandan, S. Latha, and P. Maruthamuthu, *J. Photochem. Photobiol.*, 2002, **150**, 167.

2002MI1 21st International Winter Workshop on Clinical, Chemical and Biochemical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 23 Feb.–2 Mar., 2002 (*Pteridines*, 2002, **13**, 39).

2002MI71 C. Enzinger, B. Wirleitner, N. Spöttl, G. Böck, D. Fuchs, and G. Baier-Bitterlich, *Neurochem. Int.*, 2002, **41**, 71.

2002MI133 A. C. F. Gorren and B. Mayer, *Curr. Drug Metab.*, 2002, **3**, 133.

2002MI203 K. Oettl and G. Reibnegger, *Curr. Drug Metab.*, 2002, **3**, 203.

2002MI234 H. J. Woo, Y. K. Hwang, Y. J. Kim, J. Y. Kang, Y. K. Choi, C. G. Kim, and Y. S. Park, *FEBS Lett.*, 2002, **523**, 234.

2002MI467 K. Hirakawa, M. Aoshima, Y. Hiraku, and S. Kawanishi, *Photochem. Photobiol.*, 2002, **76**, 467.

2002MI509 I. Herpfer, J. Greilberger, G. Ledinski, B. Widner, D. Fuchs, and G. Jürgens, *Free Radic. Res.*, 2002, **36**, 509.

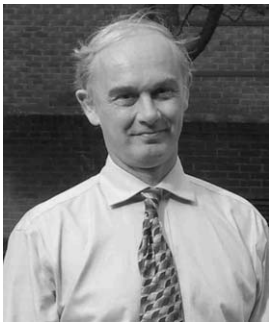
2002POL1961 E. R. Acuña-Cueva, R. Faure, N. A. Illán-Cabeza, S. B. Jiménez-Pulido, and M. N. Moreno-Carretero, *Polyhedron*, 2002, **21**, 1961.

2002PTR115 R. Horejsi, R. Möller, E. Tafeit, and G. Reibnegger, *Pteridines*, 2002, **13**, 115.

2002PTR126 N. J. Mueller, R. B. Walter, P. Linscheid, A. Schaffner, and G. Schoedon, *Pteridines*, 2002, **13**, 126.
2002T4481 I. A. Zuleta, M. L. Vitelli, R. Baggio, M. T. Garland, A. M. Seldes, and J. A. Palermo, *Tetrahedron*, 2002, **58**, 4481.
B-2003MI(360)128 C. R. Cremo; in 'Methods in Enzymology: Biophotonics, Pt A', G. Marriot and I. Parker, Eds.; Academic Press, San Diego, 2003, 360, p. 128.
2003CCC965 H. Wamhoff and M. Tzanova, *Collect. Czech. Chem. Commun.*, 2003, **68**, 965.
2003CRV2365 C. C. Wei, B. R. Crane, and D. J. Stuehr, *Chem. Rev.*, 2003, **103**, 2365.
2003HCA1 Q. H. Yao and W. Pfleiderer, *Helv. Chim. Acta*, 2003, **86**, 1.
2003ICA(342)209 E. R. Acuña-Cueva, R. Faure, N. A. Illán-Cabeza, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, and M. Quirós-Olozábal, *Inorg. Chim. Acta*, 2003, **342**, 209.
2003JBC47700 B. Illarionov, I. Haase, A. Bacher, M. Fischer, and N. Schramek, *J. Biol. Chem.*, 2003, **278**, 47700.
2003JBC48602 M. Sørlie, A. C. F. Gorren, S. Marchal, T. Shimizu, R. Lange, K. K. Andersson, and B. Mayer, *J. Biol. Chem.*, 2003, **278**, 48602.
2003JMB503 J. Rebelo, G. Auerbach, G. Bader, A. Bracher, H. Nar, C. Hösl, N. Schramek, J. Kaiser, A. Bacher, R. Huber, and M. Fischer, *J. Mol. Biol.*, 2003, **326**, 503.
2003MI1 22nd International Winter Workshop on Clinical, Chemical and Biochemical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 22 Feb.–1 Mar., 2003 (*Pteridines*, 2003, **14**, 41).
2003MI19 V. Nemec, M. Breuer, and A. De Loof, *Eur. J. Entomol.*, 2003, **100**, 19.
2003PCA178 E. Seibert, A. S. Chin, W. Pfleiderer, M. E. Hawkins, W. R. Laws, R. Osman, and J. B. A. Ross, *J. Phys. Chem. A*, 2003, **107**, 178.
2003PCB2139 C. Hemann, P. Ilich, and R. Hille, *J. Phys. Chem. B*, 2003, **107**, 2139.
2003PCB14036 S. Ferrer, E. Silla, I. Tunon, S. Marti, and V. Moliner, *J. Phys. Chem. B*, 2003, **107**, 14036.
2003OBC664 D. Guiney, C. L. Gibson, and C. J. Suckling, *Org. Biomol. Chem.*, 2003, **1**, 664.
2003OBC1909 C. L. Gibson, S. La Rosa, and C. J. Suckling, *Org. Biomol. Chem.*, 2003, **1**, 1909.
2003POL483 E. R. Acuña-Cueva, R. Faure, N. A. Illán-Cabeza, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, and M. Quirós-Olozábal, *Polyhedron*, 2003, **22**, 483.
2003RCB1403 A. V. Gulevskaya, D. Van Shee, and A. F. Pozharskii, *Russ. Chem. Bull.*, 2003, **52**, 1403.
2003TL1267 C. L. Gibson, S. La Rosa, and C. J. Suckling, *Tetrahedron Lett.*, 2003, **44**, 1267.
2004B7403 M. B. Strader, S. Chopra, M. Jackson, R. D. Smiley, L. Stinnett, J. Wu, and E. E. Howell, *Biochemistry*, 2004, **43**, 7403.
2004BBR379 K. Oettl, J. Greilberger, S. Dikalov, and G. Reibnegger, *Biochem. Biophys. Res. Commun.*, 2004, **321**, 379.
2004BML3161 R. C. Reynolds, S. Srivastava, L. J. Ross, W. J. Suling, and E. L. White, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3161.
2004BML4165 A. Gomtsyan, S. Didomenico, C.-H. Lee, A. O. Stewart, S. S. Bhagwat, E. A. Kowaluk, and M. F. Jarvis, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4165.
2004JMB967 S. Bauer, A.-K. Schott, V. Illarionova, A. Bacher, R. Huber, and M. Fischer, *J. Mol. Biol.*, 2004, **339**, 967.
2004JME3887 M. E. Nelson, N. A. Loktionova, A. E. Pegg, and R. C. Moschel, *J. Med. Chem.*, 2004, **47**, 3887.
2004MAR59 F. Lanza and B. Sellergren, *Macromol. Rapid Commun.*, 2004, **25**, 59.
2004MI1 23rd International Winter Workshop on Clinical, Chemical and Biochemical Aspects of Pteridines, St. Christoph/Arlberg, Austria, 28 Feb.–6 Mar., 2004 (*Pteridines*, 2004, **15**, 45).
2004MI81 R. W. Millar, S. P. Philbin, R. P. Claridge, and J. Hamid, *Propellants Explos. Pyrotech.*, 2004, **29**, 81.
2004MI662 H. Matter and P. Kotsonis, *Med. Res. Rev.*, 2004, **24**, 662.
2004NAR432 A. K. Shchyolkina, D. N. Kaluzhny, O. F. Borisova, M. E. Hawkins, R. L. Jernigan, T. M. Jovin, D. J. Arndt-Jovin, and V. B. Zhurkin, *Nucleic Acids Res.*, 2004, **32**, 432.
2004NARe62 M. E. Hawkins and F. M. Balis, *Nucleic Acids Res.*, 2004, **32**, e62.
2004NN51 S. Matysiak, B. Waldscheck, and W. Pfleiderer, *Nucleos. Nucleot. Nucleic Acids*, 2004, **23**, 51.
2004OBC3588 C. W. Crean, R. Camier, M. Lawler, C. Stevenson, R. J. H. Davies, P. H. Boyle, and J. M. Kelly, *Org. Biomol. Chem.*, 2004, **2**, 3588.
2004PTR10 S. Muranishi, R. Soyka, and W. Pfleiderer, *Pteridines*, 2004, **15**, 10.
2004PTR107 G. Hoffmann and W. Schobersberger, *Pteridines*, 2004, **15**, 107.
2004PTR129 T. Döring, R. C. Boruah, and W. Pfleiderer, *Pteridines*, 2004, **15**, 129.
2004STC159 E. R. Acuña-Cueva, S. B. Jiménez-Pulido, M. N. Moreno-Carretero, and M. Quirós-Olozábal, *Struct. Chem.*, 2004, **15**, 159.
2004T943 C. L. Gibson, S. La Rosa, K. Ohta, P. H. Boyle, F. Leurquin, A. Lemaçon, and C. J. Suckling, *Tetrahedron*, 2004, **60**, 943.
2004TL5643 V. Bavetsias, E. A. Henderson, and E. McDonald, *Tetrahedron Lett.*, 2004, **45**, 5643.
2005AAC3652 E. Nduati, S. Hunt, E. M. Kamau, and A. Nzila, *Antimicrob. Agents Chemother.*, 2005, **49**, 3652.
2005BMC3513 P. M. S. Chauhan, C. J. A. Martins, and D. C. Horwell, *Bioorg. Med. Chem.*, 2005, **13**, 3513.
2005BML675 Y. Ding, J. L. Girardet, K. L. Smith, G. Larson, B. Prigaro, V. C. H. Lai, W. D. Zhong, and J. Z. Wu, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 675.
2005CEJ4835 N. Chen, S. Murata, and K. Yoshikawa, *Chem. Eur. J.*, 2005, **11**, 4835.
2005CGD1597 A. Crispini, D. Pucci, A. Bellusci, G. Barberio, M. La Deda, A. Cataldi, and M. Ghedini, *Cryst. Growth Des.*, 2005, **5**, 1597.
2005H(65)2917 N. Chen, K. Ikemoto, S. Komatsu, and S. Murata, *Heterocycles*, 2005, **65**, 2917.
2005JA10910 N. Chen, A. A. Zinchenko, S. Murata, and K. Yoshikawa, *J. Am. Chem. Soc.*, 2005, **127**, 10910.
2005JBC20712 V. Mishra, S. Bilgrami, R. S. Sharma, P. Kaur, S. Yadav, R. Krauspenhaar, C. Betzel, W. Voelter, C. R. Babu, and T. P. Singh, *J. Biol. Chem.*, 2005, **280**, 20712.
2005JMB105 A. W. Schüttelkopf, L. W. Hardy, S. M. Beverley, and W. N. Hunter, *J. Mol. Biol.*, 2005, **352**, 105.
2005JME4783 H. Matter, H. S. A. Kumar, R. Fedorov, A. Frey, P. Kotsonis, E. Hartmann, L. G. Fröhlich, A. Reif, W. Pfleiderer, P. Scheurer, D. K. Ghosh, M. Schlichting, and H. Schmidt, *J. Med. Chem.*, 2005, **48**, 4783.
2005MI1 24th International Winter Workshop on Clinical, Chemical and Biochemical aspects of Pteridines, St. Christoph/Arlberg, Austria, 27 Feb.–6 Mar., 2005 (*Pteridines*, 2005, **16**, 125).
2005MI64 N. Schormann, B. Pal, O. Senkovich, M. Carson, A. Howard, C. Smith, L. DeLucas, and D. Chattopadhyay, *J. Struct. Biol.*, 2005, **152**, 64.
2005MI119 J. L. Lord, A. de Peyster, P. J. E. Quintana, and R. P. Metzger, *Cancer Lett.*, 2005, **222**, 119.

2005PTR53O04/04 C. J. Suckling, J. Huggan, R. M. Rao, L. Kiefer, and C. L. Gibson, *Pteridines*, 2005, **16**, 53O04/04.
2005PTR112P56 S. R. Kunuthur, C. J. Suckling, C. L. Gibson, and R. M. Wadsworth, *Pteridines*, 2005, **16**, 112P56.
2005PTR112P57 C. J. Suckling, J. Huggan, L. Berlouis, and C. L. Gibson, *Pteridines*, 2005, **16**, 112P57.
2006ACT249 F. Tang, G. H. Zheng, Q. Z. Yao, G. Lu, W. F. Zhou, and Q. J. Wang, *Acta Chim. Sin.*, 2006, **64**, 249.
2006B2372 P. A. Frantom, J. Seravalli, S. W. Ragsdale, and P. F. Fitzpatrick, *Biochemistry*, 2006, **45**, 2372.
2006B5039 K. E. Augustyn, K. Wojtuszewski, M. E. Hawkins, J. R. Knutson, and I. Mukerji, *Biochemistry*, 2006, **45**, 5039.
2006B15232 Y. Wang, Y. Li, and H. G. Yan, *Biochemistry*, 2006, **45**, 15232.
2006BBA578 A. C. F. Gorren, S. Marchal, M. Sørlie, K. K. Andersson, R. Lange, and B. Mayer, *Biochim. Biophys. Acta*, 2006, **1764**, 578.
2006CMC1929 A. Tafi, L. Angeli, G. Venturini, M. Travagli, F. Corelli, and M. Botta, *Curr. Med. Chem.*, 2006, **13**, 1929.
2006CME377 D. C. M. Chan and A. C. Anderson, *Curr. Med. Chem.*, 2006, **13**, 377.
2006COR491 U. Asseline, *Curr. Org. Chem.*, 2006, **10**, 491.
2006HCA1140 M. Xu and A. Vasella, *Helv. Chim. Acta*, 2006, **89**, 1140.
2006H(67)299 T. Hanaya, K. Soranaka, K. Harada, H. Yamaguchi, R. Suzuki, Y. Endo, H. Yamamoto, and W. Pfleiderer, *Heterocycles*, 2006, **67**, 299.
2006H(68)933 J. M. Quintela, C. Peinador, M. J. Moreira, R. Toba, and M. Chas, *Heterocycles*, 2006, **68**, 933.
2006JBC1224 A. Ramsperger, M. Augustin, A. K. Schott, S. Gerhardt, T. Krojer, W. Eisenreich, B. Illarionov, M. Cushman, A. Bacher, R. Huber, and M. Fischer, *J. Biol. Chem.*, 2006, **281**, 1224.
2006JBC2249 S. Supangat, K. H. Seo, Y. K. Choi, Y. S. Park, D. Son, C. D. Han, and K. H. Lee, *J. Biol. Chem.*, 2006, **281**, 2249.
2006JBC7605 S.-C. Chen, Y.-C. Chang, C.-H. Lin, and S.-H. Liaw, *J. Biol. Chem.*, 2006, **281**, 7605.
2006JBC37586 B. El Yacoubi, S. Bonnett, J. N. Anderson, M. A. Swairjo, D. Iwata-Reuyl, and V. De Crecy-Lagard, *J. Biol. Chem.*, 2006, **281**, 37586.
2006JME770 Y. Feng and J. K. Coward, *J. Med. Chem.*, 2006, **49**, 770.
2006OBC1811 M. Nonogawa, T. Arai, N. Endo, S. P. Pack, T. Kodaki, and K. Makino, *Org. Biomol. Chem.*, 2006, **4**, 1811.
2006RJO136 R. Singh and Geetanjali, *Russ. J. Org. Chem. (Engl. Transl.)*, 2006, **42**, 136.
2007BBR1105 M. Nonogawa, S. P. Pack, T. Arai, N. Endo, P. Sommani, T. Kodaki, and K. Makino, *Biochem. Biophys. Res. Commun.*, 2007, **353**, 1105.
2007CL552 S. Goswami, A. C. Maity, and H. K. Fun, *Chem. Lett.*, 2007, **36**, 552.
2007HCA521 F. L. Zhang, W. B. Schweizer, M. Xu, and A. Vasella, *Helv. Chim. Acta*, 2007, **90**, 521.
2007MI2240 Y. Wang, Y. Li, Y. Wu, and H. G. Yan, *FEBS J.*, 2007, **274**, 2240.
2007T1568 K. Shen, Y. Fu, J. N. Li, L. Liu, and Q. X. Guo, *Tetrahedron*, 2007, **63**, 1568.
2007EJO2987 M. Slusarczyk, W. M. De Borggraeve, S. Yoppet, and G. J. Hoornaert, *Eur. J. Org. Chem.*, 2007, 2987.

Biographical Sketch



Colin Suckling is Freeland Professor of Chemistry at the University of Strathclyde, Glasgow, Scotland. He studied at the University of Liverpool (B.Sc. 1967, Ph.D. 1970, D.Sc. 1989) and at the Eidgenössische Technische Hochschule, Zürich (1970–72). Appointed to the University of Strathclyde as a lecturer in organic chemistry in 1972 and professor in 1984, he has since held positions in senior academic management (1992–2002) before returning to full-time academic chemistry. Professor Suckling began working on the interfaces of chemistry and biology well before it became fashionable and has contributed to the literature of heterocyclic chemistry, biomimetic chemistry, enzymes applied to organic synthesis, catalytic antibodies, and DNA binding compounds. Currently, his research emphasis is on medicinal chemistry including applications of pteridines and related compounds for the treatment of cardiovascular and infectious diseases. In 2006, Professor Suckling was awarded the OBE for services to science and higher education in the United Kingdom.



Colin Gibson was born in the Scottish border town of Hawick before the family moved to southern England when he was 10 years old. He went to Southampton University for his B.Sc. studies and stayed there to carry out Ph.D research with Professor Ray Baker, FRS. After Southampton, Colin was awarded a University of Melbourne research fellowship in Australia working with Professor Don Cameron. On returning to the UK, he took up a postdoctoral research associateship with Professor Sir Alan Battersby, FRS, at Cambridge University. A senior research fellowship at Christ's College, Cambridge, followed this. The heady heights of Cambridge were succeeded by a short interlude at Surrey University (1988–1991) as a member of faculty. At Surrey, he started his interests in folate and pteridine chemistry. In 1991, he made the move back to Scotland and joined the Strathclyde Chemistry Department as a lecturer. Since then, he has collaborated extensively with Professor Colin Suckling on the synthesis and biochemistry of pteridines and deazaguanines. He also has an independent research program in asymmetric synthesis. In 1997, he was promoted to senior lecturer.



Judith Huggan carried out her B.Sc. studies at the University of Paisley under the supervision of Dr. Graham Patrick and was awarded her B.Sc. (Hons.) degree (1st Class) in medicinal chemistry. She then moved to the University of Strathclyde to undertake PhD research with Professor C. J. Suckling and Dr. C. L. Gibson in the area of pteridine chemistry. Upon completion of her studies she undertook postdoctoral research in the department, designing and synthesizing novel compounds for the potential treatment of inflammatory diseases.

10.20
Bicyclic 6-6 Systems: Five or More Heteroatoms

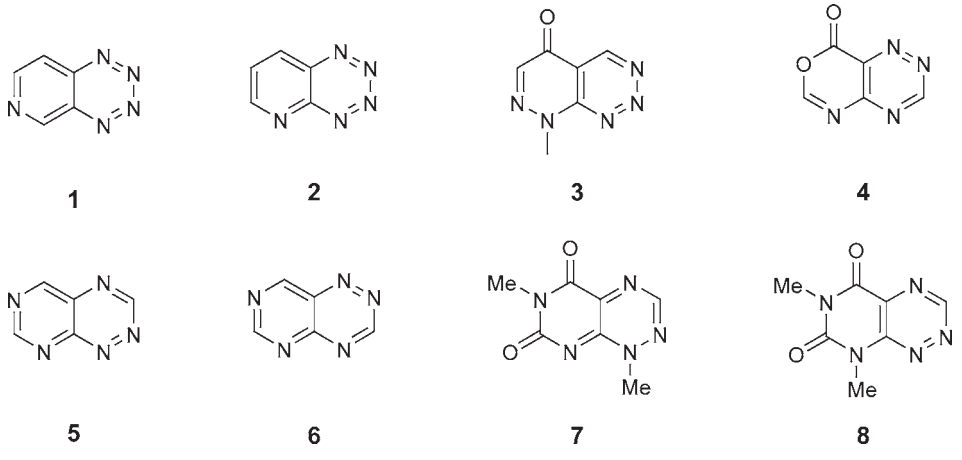
K. Hemming
University of Huddersfield, Huddersfield, UK
© 2008 Elsevier Ltd. All rights reserved.

10.20.1 Introduction 1094
10.20.2 Theoretical Methods 1094
10.20.3 Experimental Structural Methods 1095
10.20.3.1 Introduction 1095
10.20.3.2 X-Ray Diffraction 1095
10.20.3.3 NMR Spectroscopy 1095
10.20.3.4 Mass Spectrometry 1098
10.20.3.5 UV Spectroscopy 1099
10.20.3.6 Infrared Spectroscopy 1100
10.20.4 Thermodynamic Aspects 1101
10.20.5 Reactivity of Fully Conjugated Rings 1102
10.20.5.1 Introduction 1102
10.20.5.2 Thermal and Photochemical Reactions 1102
10.20.5.3 Electrophilic Attack 1102
10.20.5.4 Nucleophilic Attack and Reduction 1103
10.20.6 Reactivity of Nonconjugated Rings 1104
10.20.6.1 Introduction 1104
10.20.6.2 Reactivity of the Pyrimidotriazines (Azapteridines) 1104
10.20.6.3 Reactivity of Other Ring Systems 1108
10.20.7 Reactivity of Substituents Attached to Ring Carbon Atoms 1109
10.20.7.1 Rearrangement Reactions 1109
10.20.7.2 Reactions at the α-Carbon of Substituents Attached to Ring Carbons 1110
10.20.7.3 Reactions of Hetero Substituents 1110
10.20.7.4 Miscellaneous Reactions of Substituents Attached to Ring Carbons 1113
10.20.8 Reactivity of Substituents Attached to Ring Heteroatoms 1116
10.20.9 Syntheses of Bicyclic 6-6 Systems with Five or More Heteroatoms 1117
10.20.9.1 Introduction 1117
10.20.9.2 Syntheses Involving the Construction of a Second Heterocyclic Ring onto an Existing Heterocyclic Ring 1117
10.20.9.2.1 One heteroatom in the ring being formed 1117
10.20.9.2.2 Two heteroatoms in the ring being formed 1117
10.20.9.2.3 Three heteroatoms in the ring being formed 1121
10.20.9.2.4 Four heteroatoms in the ring being formed 1126
10.20.9.3 Syntheses from Acyclic Precursors 1128
10.20.9.4 Syntheses from Other Heterobicyclic and Related Systems 1128
10.20.10 Important Compounds and Applications 1128

10.20.10.1 Introduction 1128
10.20.10.2 The 6-Azapteridines 1129
10.20.10.3 The 7-Azapteridines 1129
10.20.10.4 The Pyrazinothiadiazines 1131
10.20.11 Further Developments 1131
References 1132

10.20.1 Introduction

Following the organization used in CHEC-II(1996) <1996CHEC-II(7)785>, this chapter deals with heterocycles with two six-membered heterocyclic rings which have five or more heteroatoms at positions other than the ring junction. In addition to the 44 ring systems that appeared in CHEC-II(1996), four new systems have appeared, including systems with five heteroatoms distributed 1:4 between the two rings. The new systems are pyrido[2,3-*e*]- and pyrido[3,4-*e*]-1,2,3,4-tetrazines **1** and **2**, the pyridazino[4,3-*e*]-1,2,3-triazine **3**, and the 1,3-oxazino[4,5-*e*]-1,2,4-triazine **4**. The pyrimido[5,4-*e*]-1,2,4-triazines **5** and pyrimido[4,5-*e*]-1,2,4-triazines **6**, the 7-azapteridines and 6-azapteridines respectively, still dominate the literature and hence the chapter, with the 7-azapteridine natural products toxoflavin **7** and fervenulin **8** particularly well represented. It is of note that several diazinothiadiazines have become increasingly important since the appearance of CHEC-II(1996). The material in this chapter follows the standard chapter arrangement for *Comprehensive Heterocyclic Chemistry* and is not arranged according to ring system.



10.20.2 Theoretical Methods

It was reported in CHEC-II(1996) <1996CHEC-II(7)785> that little theoretical work had been reported for the diverse heterocyclic systems covered in this chapter, and this lack of interest has continued. One exception is the azapteridines for which the relative hydration-free energy differences ($\Delta\Delta G_{hyd}$) have been calculated using a combined quantum mechanical and thermodynamic cycle perturbation approach. Good correlation was obtained with experimental data for hydration equilibrium constants. Thus, a $\Delta\Delta G_{hyd}$ of -6.1 kcal mol^{-1} for 7-azapteridine relative to pteridine correctly predicted that 7-azapteridine is completely hydrated under conditions that leave pteridine only 20% hydrated <1998JA3295>. The hydration of 7-azapteridines has been discussed elsewhere <2000JOC7391>, and its extent is important, for example, in drug design. *Ab initio* calculations have also appeared which deal with the tautomerism of the pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides (see Section 10.20.4) <1998J(P2)1889>.

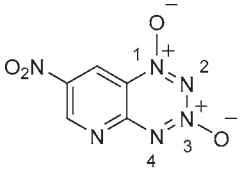
10.20.3 Experimental Structural Methods

10.20.3.1 Introduction

The very diverse nature of the compounds covered in this chapter renders the presentation of common spectroscopic characteristics an impossible task for many of the heterocyclic systems covered. Nonetheless, the dominance, and hence importance, in the literature of a small number of systems, particularly the 7-azapteridines and 6-azapteridines, means that some meaningful compilations can be presented. Important and nonroutine results are also presented. For data on specific individual compounds, many of which are routine and predictable, the reader is directed to the relevant references included elsewhere in this chapter, and to those references that appeared in CHEC-II(1996) <1996CHEC-II(7)785>.

10.20.3.2 X-Ray Diffraction

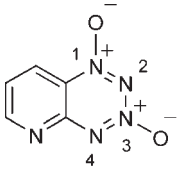
Only one study has been published involving an X-ray crystallographic structure since the nine systems that appeared in CHEC-II(1996) were discussed <1996CHEC-II(7)785>. Thus, 7-nitropyrido[2,3-*e*]-1,2,3,4-tetrazine 1,3-dioxide **9** <2004RCB2577> has been found to be virtually planar with an N(1)–N(2)–N(3)–N(4) torsion angle of 4.7°. The N-4 and N-2 endocyclic bond angles were 114.4° and 115°, respectively, whereas those for N-3 and N-1 were larger at 128.1° and 122.4°, respectively. The N–N and C–N bond lengths in the tetrazine ring differed only slightly from those in the corresponding benzotetrazine, with values of 1.391, 1.321, 1.382, 1.308, and 1.357 Å for C–N(1), N(1)–N(2), N(2)–N(3), N(3)–N(4), and N(5)–C, respectively.



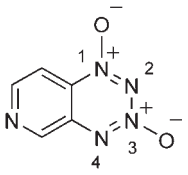
9

10.20.3.3 NMR Spectroscopy

The ^{14}N NMR spectra (acetone-d_6) of compounds **9–11** show two narrow signals corresponding to N-1 and N-3 of the tetrazine 1,3-dioxide ring, with N-1 appearing as a narrower signal and at lower field ($\delta = -39$ ppm, $\Delta\nu_{1/2} = 20$–30 Hz) than N-3 ($\delta = -45$ ppm, $\Delta\nu_{1/2} = 30$–45 Hz) <2004RCB2577>.



10

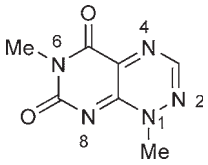
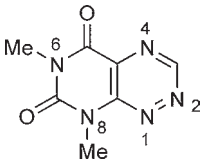


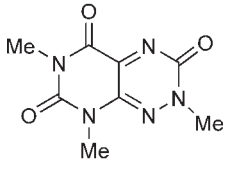
11

Complete ^{15}N NMR chemical shifts together with ^{1}H–^{15}N coupling constants (referenced externally to $^{15}NH_4Cl$ in DMSO-d_6: DMSO – dimethyl sulfoxide) have been determined for toxoflavin **7** and fervenulin **8** in $CDCl_3$ using pulsed field gradient heteronuclear multiple bond correlation (HMBC) techniques <2000H(52)811>, and are presented in **Table 1**.

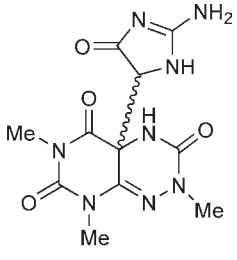
^{15}N NMR data for the naturally occurring 2-methyl-fervenulone **12** and its *4a*-substituted analogue **13** have also been reported <2000JNP1641>, and are listed in **Table 2**. This chapter also contains detailed ^{1}H and ^{13}C data for these compounds, including some very elegant HMBC and heteronuclear single quantum correlation (HSQC) structural assignments for the separated diastereomers of natural product **13**.

Table 1 ^{15}N NMR data for toxoflavin **7** and fervenulin **8**

Atom number (*J values in hertz*)	^{15}N *shift* (*ppm*) *for toxoflavin* **7** 	^{15}N *shift* (*ppm*) *for fervenulin* **8** 
N-1	187 $^{2}J = 3.0$, $^{3}J = 6.2$	365.2 $^{3}J = 2.0$, $^{4}J = 1.5$
N-2	304.5 $^{2}J = 317.6$, $^{3}J = 4.5$	374.7 $^{2}J = 13.7$
N-4	296.1 $^{2}J = 12.8$	273.8 $^{2}J = 13.2$
N-6	142.3 $^{2}J = 2.0$	136.1 $^{2}J = 2.0$
N-8	172.8 $^{4}J_{\text{N, N1-Me}} = 1.5$, $^{4}J_{\text{N, N6-Me}} = 1.0$	96.5 $^{2}J = 2.0$



12



13

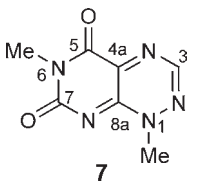
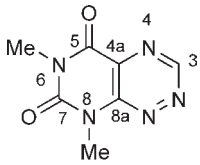
Table 2 ^{15}N NMR data (DMSO-d_6) for 2-methyl-fervenulones **12** and **13**

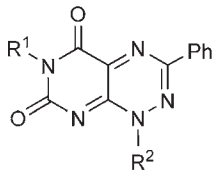
Atom	^{15}N *shift* (*ppm*) *compound* **12**	^{15}N *shift* (*ppm*) *compound* **13** (*two diastereomers*)
N-1	314.6	285.3 and 279.8
N-2	181.9	130.9 and 132.1
N-4	Not seen	81.3
N-6	152.6	143.9 and 142.0
N-8	110.5	108.7 and 111.0

A detailed and useful assignment of the ^{1}H and ^{13}C data for toxoflavin **7** and fervenulin **8** has appeared, and is summarized in **Table 3** <2000H(52)811>.

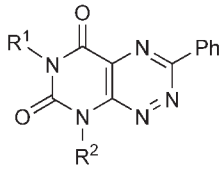
A comprehensive list of routine ^{1}H NMR shifts for a wide range of 3-phenyltoxoflavin and 3-phenylfervenulin derivatives **14** and **15** has appeared <2001J(P1)130>, together with a study of the ^{1}H NMR data of some of the corresponding 4-oxides <1999M819>. Other fervenulin and fervenulone derivatives have had detailed lists of ^{1}H NMR data presented <1996JHC949, 1995JOC7063>. The ^{13}C NMR spectrum of fervenulone **16** shows C-4a at 146 ppm, a signal that is shifted to 76 ppm in the C-4a ethoxy derivative **17**. The signal for C-8a in both compounds was identified by its coupling to the N(8)-Me in the HMBC spectrum, and remained almost unchanged at 135 and 138 ppm, respectively <1995JOC7063>.

Table 3 ^{1}H and ^{13}C NMR (ppm) data for toxoflavin **7** and fervenulin **8** ($CDCl_3$)

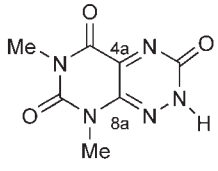
Atom	*Toxoflavin*  **7**	*Fervenulin*  **8**
H_3	8.92	9.84
N(1)–Me	4.16	
N(6)–Me	3.50	3.58
N(8)–Me		3.92
C-3	145.2	154.3
C-4a	145.5	130.8
C-5	158.5	159.3
C-7	154.3	149.3
C-8a	150.4	151.1
N(1)–Me	43.4	
N(6)–Me	29.2	29.5
N(8)–Me		29.8



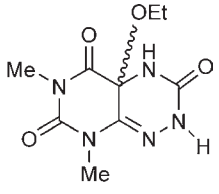
14



15



16

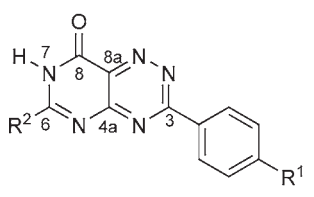


17

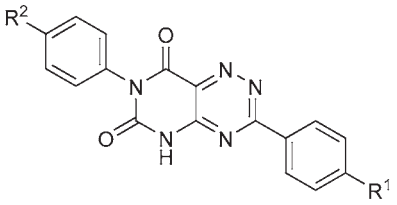
Compounds **12–17**, as discussed previously, are known as the 7-azapteridines. Several useful studies involving detailed ^{1}H and ^{13}C NMR analyses of the less studied 6-azapteridines have also appeared <2003CCC965, 2003ARK98, 2001JHC141>. Data for the 3-aryl-pyrimido[4,5-*e*]-1,2,4-triazines **18** (in $CDCl_3$) are given in **Table 4** <2003CCC965>. Compounds **19** show the extra carbonyl (at C-6) at 159.1–159.6 ppm, C-4a at 149.5–150.2 ppm, C-8a at 150.7–151.0 ppm and the N-5 proton at 12.8–13.1 ppm <2003ARK98>. The exocyclic amine in compound **20** ($R^1 = R^2 = H$) appears at 8.3 ppm ($CDCl_3$) in the ^{1}H NMR spectrum with the two methyl groups appearing at 3.27 and 3.38 ppm. In compound **20** ($R^1 = R^2 = Me$), the N-5 and N-7 methyl groups resonate at 3.59 and 3.66 ppm, whereas the exocyclic dimethylamine protons resonate as a singlet at 2.39 ppm <2001JHC141>, a feature that attracted some attention in CHEC-II(1996) <1996CHEC-II(7)785>.

Table 4 ^{1}H and ^{13}C NMR data (ppm) for the 6-azapteridines 18

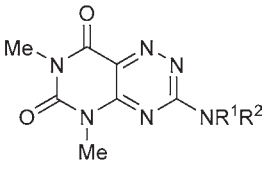
Atom	*$R^1 = Cl$, $R^2 = Ph$*	*$R^1 = OMe$, $R^2 = Ph$*	*$R^1 = H$, $R^2 = H$*	*$R^1 = OMe$, $R^2 = H$*
C-3	160.4	162.8	159.5	163.4
C-4a	140.0	139.2	156.5	159.7
C-6	161.4	161.2	155.5	156.5
C-8	163.7	164.4	164.3	164.7
C-8a	155.8	133.1	142.0	141.0
H-6			8.57	8.52
H-7	13.39	13.31	13.16	13.01



18



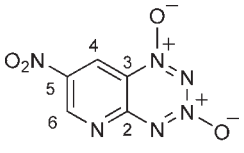
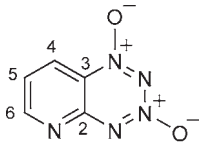
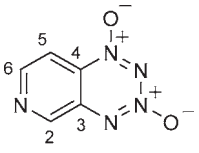
19



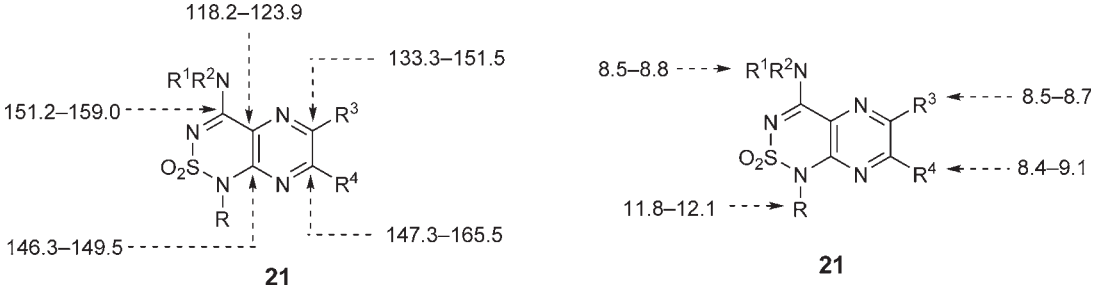
20

The pyrido[2,3-*e*]- and pyrido[3,4-*e*]-1,2,3,4-tetrazines **9–11** constitute a new class of heterocycle to add those reported in CHEC-II(1996) <1996CHEC-II(7)785> and their ^{1}H and ^{13}C NMR assignments are therefore worthy of inclusion here and are shown in **Table 5** <2004RCB2577>.

Table 5 ^{1}H and ^{13}C NMR signals (ppm) for pyridotetrazines **9–11** in acetone-d_6

Atom	 **9**	 **10**	 **11**
C-2	156.4	153.1	144.5
C-3	125.9	126.2	125.4
C-4	126.0	128.6	148.5
C-5	145.5	127.0	117.1
C-6	155.8	160.9	156.2
H-2			9.58
H-4	9.40	8.77	
H-5		7.93	7.83
H-6	9.94	9.31	9.08

The search for novel bronchodilators containing the pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxide ring **21** has resulted in the synthesis and full characterisation of over 35 compounds containing structure **21** <1999JME1698, 2000JME4219>. For these compounds, ^{13}C NMR spectroscopy is most instructive and the range of resonances (DMSO-d_6) is shown in **Figure 1**. In cases where ring protons are present, **Figure 1** also shows the relevant ^{1}H NMR data for those situations where $R^1 = R^2 = H$, $R = H$, $R^3 = H$ or $R^4 = H$.

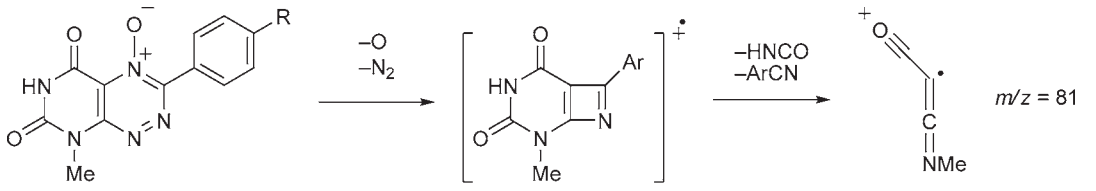


21

Figure 1 ^{13}C and ^{1}H data (ppm) for pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxides **21**.

10.20.3.4 Mass Spectrometry

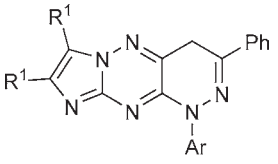
The fervenulin-4-oxides **22** show a stable parent ion together with loss of 16 mass units as prominent peaks in the electron impact mass spectra. Loss of dinitrogen is a further common process and other fragmentation by loss of HNCO and ArCN leads to the prominent *m*/*z* 81 fragment <1999M819>, as shown in **Scheme 1**.



22

Scheme 1

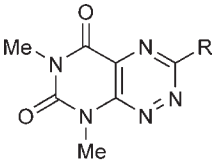
The prominence of the parent ion is a feature of the mass spectra of the heterocyclic systems covered in this chapter, and CHEC-II(1996) also reflects upon this feature <1996CHEC-II(7)785>. Recent fast atom bombardment (FAB) and electrospray ionization mass spectra of toxoflavin **7** shows the parent ion as the most intense peak together with significant peaks from the expected losses of MeNCO and N_2 <2003MI890, 1997MI33>, while the pyrimido[4,5-*e*]-1,2,4-triazines **19** show a prominent parent ion together with loss of ArCNO as the base peak <2003ARK98>. The pyridazino[6,5-*e*]-1,2,4-triazines **23** show the parent ion as the base peak and show further fragmentation by loss of H and loss of PhCN <1999CHE376, 1999KGS426>.



23

10.20.3.5 UV Spectroscopy

In keeping with other sections of this chapter, the pyrimido[5,4-*e*]-1,2,4-triazines (i.e., the 7-azapteridines) dominate the literature. Three very comprehensive listings of data have appeared <2001J(P1)130, 1997H(45)643, 1996JHC949> since those listed in CHEC-II(1996) <1996CHEC-II(7)785> and these concern analogues of fervenulin and toxoflavin. Thus, the 3-phenyltoxoflavins **14** show λ_{max} in the region 291–299 nm and 434–436 nm in 1,4-dioxane. The corresponding 3-phenylfervenulin systems **15** show λ_{max} in the region 277–282 nm and 372–377 nm in the same solvent <2001J(P1)130, 1997H(45)643>. The 3-phenylfervenulin 4-oxides **22** show an additional absorption at 203 nm <1999M819>. A wider range of 3-substituted fervenulins **24** has also been studied and a representative selection (neutral species in 1,4-doxane) is shown in **Table 6** <1996JHC949>. The only strong bathochromic shift occurred with the 3-styryl derivative (entry 4), as may be expected given the extended chromophore. Other less detailed studies of the UV spectra of 7-azapteridines have also appeared <2000JNP1641, 1997MI33>.



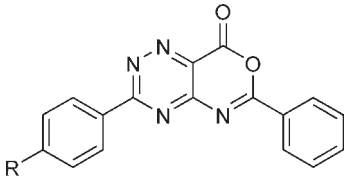
24

The 3,7-disubstituted pyrimido[4,5-*e*]-1,2,4-triazines (i.e., 6-azapteridines) **19** ($R^1 = R^2 = H$) show λ_{max} at 330 nm, which shifts to 354 nm when R^1 is methoxy <2003ARK98>. It is of note that the 3,6-disubstituted systems **18** ($R^2 = Ph$, $R^1 = H$ or OMe) show λ_{max} at 340 and 323 nm, respectively, whereas the 3-monosubstituted systems ($R^2 = H$, $R^1 = H$ or OMe) show λ_{max} constant at ~335 nm <2003CCC965>.

Only a few nonazapteridines have had their UV spectra reported since CHEC-II(1996). Thus, the imidazo-fused pyridazino[6,5-*e*]-1,2,4-triazines **23** show λ_{max} values (dioxane) at 325 and 410 nm <1999CHE376, 1999KGS426>, and the 1,3-oxazino[4,5-*e*]-1,2,4-triazines **25** show maximum absorption at 290 nm <2003ARK98>.

Table 6 Selected UV absorption data for 3-substituted fervenulins **24** <1996JHC949>

R	$\lambda_{max}(nm)$ {[*sh*] = *shoulder*}		
H	238	274	348
Me	238	270 [sh]	348
Bu^t	237	270 [sh]	345
–CH=CHPh	225	313	390
CH_2Br	248		348
–CH=NOH		267	368
–C(O)Ph		268	
–CHO	240	274 [sh]	344
–C(O)Me	262	281 [sh]	344
–COOH		258	343
$–CONH_2$		256	344



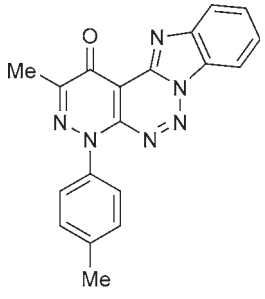
25

10.20.3.6 Infrared Spectroscopy

Among the 7-azapteridines, the 3-phenyltoxoflavin systems **14** show ν_{max} (KBr) at 1660–1680 cm^{-1} and 1700–1720 cm^{-1}, whereas the 3-phenylfervenulin systems **15** show ν_{max} (KBr) at 1675–1690 cm^{-1} and 1725–1735 cm^{-1} <2001J(P1)130>. The fervenulone-based pyrimido[5,4-*e*]-1,2,4-triazine triones **12** and **13** are of interest, with the simpler heterocycle **12** showing carbonyl stretches (KBr) at 1728, 1694, and 1666 cm^{-1} and the 4a-substituted compounds **13** (diastereoisomers) showing carbonyl stretches (KBr) at 1784, 1724, and 1676 cm^{-1} <2000JNP1641>.

With the 6-azapteridines, some useful information can be gained by comparing the 6-unsubstituted pyrimido[4,5-*e*]-1,2,4-triazin-8-ones **18** (R^2 = H) to the corresponding 6-aryl system **18** (R^2 = Ar) whereby the latter show the N–H stretch at 3432–3438 cm^{-1} and the C=O at 1697–1703 cm^{-1}, and the former show the N–H stretch at 3434–3438 cm^{-1}, the C=O at 1716–1719 cm^{-1} and the C=N additionally at 1593–1602 cm^{-1} <2003CCC965>. The 6,8-diones **19** and **20** show carbonyl stretching frequencies at 1680–1693 and 1740–1749 cm^{-1} <2003ARK98, 2001JHC141>.

The benzimidazo-fused pyridazino[4,3-*e*]-1,2,3-triazinone **26** shows some interesting infrared absorbances (KBr) with strong peaks for C=O, N=N, C=C, and C=N at 1635, 1610, 1570, and 1510 cm^{-1}, respectively <1997CHE749, 1997KGS853>.



26

The 1,3-oxazino[4,5-*e*]-1,2,4-triazines **25** show ν_{max} (KBr) at 1778 and 1719 cm^{-1} <2003ARK98>, although the rarity of this heterocyclic system in the literature prevents correlation with other data – the system was not listed as known at the time of CHEC-II(1996) <1996CHEC-II(7)785>.

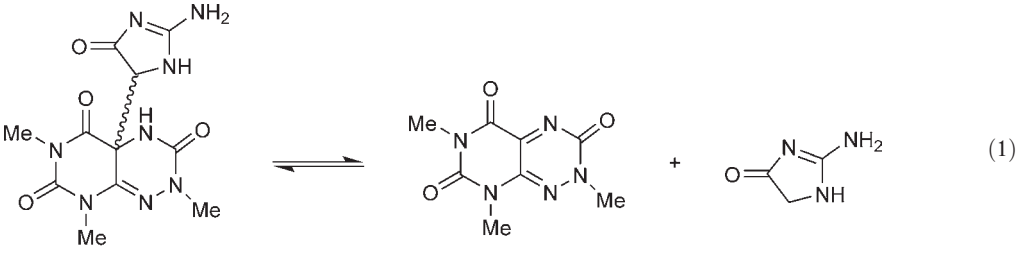
10.20.4 Thermodynamic Aspects

The tautomerism of the pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxide ring present in compound **21** has been studied in solution <1998J(P2)1889>, particularly with reference to the acidity (pK_a ~1–4) of the H–N(1) (**21**, R = H) proton. Further advances in the study of the tautomeric forms of the systems that appear in this chapter have not appeared since CHEC-II(1996), and the detailed and interesting discussion contained therein remains pertinent <1996CHEC-II(7)785>.

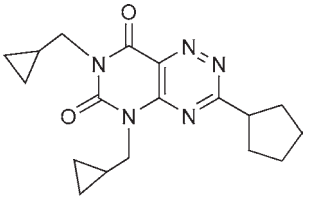
The fervenulin-4-oxides **22** show excellent thermal stability with melting points in excess of 240 and 320 °C (R = H and Cl, respectively) when recrystallized from methanol. The same compounds show good thermal stability in the presence of acid <1999M819>.

The wide range of 3-substituted fervenulin analogues **24** synthesized by Pfleiderer and Werner-Simon <1996JHC949> show melting points across the full range from 70 °C (R = –CHBrPh) to over 300 °C (R = $CONH_2$) with many of these showing decomposition over 200 °C. Solubility of these compounds is generally good in methanol, DMSO, and toluene/ethyl acetate, where the latter is also used as the chromatographic eluent, reflecting the stability of these compound to silica chromatography <1996JHC949>. pK_a's (in water) were determined in the same study and range from 2.04 for the 3-carboxylic acid derivative **24** (R = COOH) to −5 for the 3-(1,2-dibromo-2-phenyl)ethyl derivative **24** (R = –CHBrCHBrPh). Toxoflavin **7** also shows good chromatographic behavior in dichloromethane-methanol or ethyl acetate–chloroform–acetic acid as eluent with a silica gel stationary phase for thin-layer chromatography (TLC) or as an 80% aqueous methanol injection on a Shim-pack capillary liquid chromatography (CLC)-NH_2 column with UV detection at 260 nm <2003MI890, 1997MI33>.

Stability experiments conducted with the 4a-substituted fervenulone natural product **13** showed that the compounds were thermally unstable. Thus, as shown in Equation (1), >50% degradation to compounds **12** and **27** occurred upon heating to 52 °C in DMSO-d_6. Conversion to the trifluoroacetate salt gave increased thermal stability <2000JNP1641>. The isofervenulin analogue **28** is unstable at elevated temperature (60 °C), undergoing degradation to unspecified products <2004JHC637>.



13 **12** **27** (1)



28

As discussed in Section 10.20.2, theoretical and experimental parameters for the hydration of 7-azapteridine (pyrimido[5,4-*e*]-1,2,4-triazine) **5** show that the molecule undergoes essentially complete conversion into the neutral hydrate in aqueous solution <2000JOC7391, 1998JA3295>.

6-Azapteridines (pyrimido[4,5-*e*]-1,2,4-triazines) are stable solids with good thermal stability. Thus, the 3,6-diarylpyrimido[5,4-*e*]-1,2,4-triazines **18** (R^2 = Ar) show melting points in excess of 350 °C without decomposition after recrystallization from ethanol. The corresponding 6-unsubstituted system **18** (R^2 = H) shows decomposition at ~325 °C <2003CCC965>. These systems are soluble in chloroform.

The imidazo-fused pyridazino[6,5-*e*]-1,2,4-triazines **23** are stable to silica gel chromatography and also show high thermal stability, giving melting points in excess of 250 °C upon recrystallization from dimethylformamide (DMF) <1999CHE376, 1999KGS426>.

The pyrido[2,3-*e*]- and pyrido[3,4-*e*]-1,2,3,4-tetrazines **9–11** are new heterocyclic systems since the appearance of CHEC-II(1996) <1996CHEC-II(7)785> and are reported as stable yellow solids which recrystallize from ethanol and melt without decomposition in the range 180–230 °C. These three compounds are stable to chromatographic separation on silica with ethyl acetate–chloroform as eluent.

Pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxides **21** have attracted reasonable attention in recent years and are typically stable solids, which are isolated by recrystallization from methanol–water or ethanol–water <1999JME1698, 2000JME4219, 2003HCA139>, often with melting points in excess of 200/250 °C.

10.20.5 Reactivity of Fully Conjugated Rings

10.20.5.1 Introduction

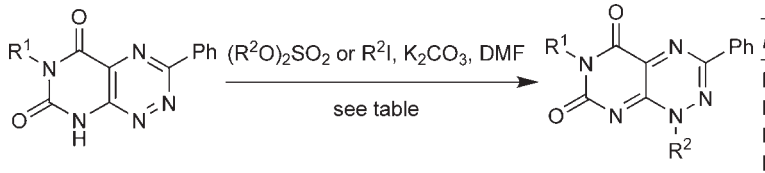
This section includes reactions where, although one of the rings in the bicyclic 6-6 system may not be fully conjugated, the ring at which reaction is occurring is fully conjugated. In line with the arrangement used in CHEC-II(1996) <1996CHEC-II(7)785>, for the purpose of this section, which deals with six-membered rings only, fully conjugated rings contain no sp^3 hybridized carbon or nitrogen. Lactams and similar ring systems will thus be dealt with as nonconjugated and hence appear in Section 10.20.6.

10.20.5.2 Thermal and Photochemical Reactions

Only two reactions appeared in this section in CHEC-II(1996) <1996CHEC-II(7)785> and no further examples have appeared since that time.

10.20.5.3 Electrophilic Attack

The 3-phenylpyrimido[5,4-*e*]-1,2,4-triazines **29** (also known as 3-phenylreumycins where $R^1 = Me$) can be transformed into the corresponding 1,6-disubstituted analogues **30** upon selective alkylation with dialkyl sulfates or alkyl halides in DMF in the presence of potassium carbonate as shown in Equation (2) <2001J(P1)130, 1997H(45)643>.

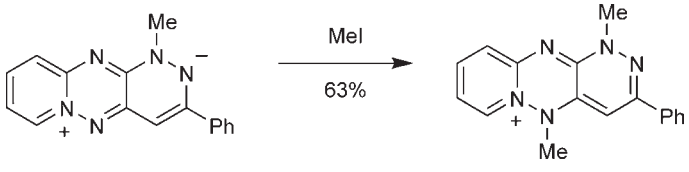


29 **30**

R^1	R^2	*Yield* **30** (%)
Me	Me	91
Me	Et	79
Me	Cyclopentyl	81
Me	Pr^i	85
Ph	Me	86
Ph	Bu	82
Ph	Cyclohexyl	81
Ph	Bu^t	85

(2)

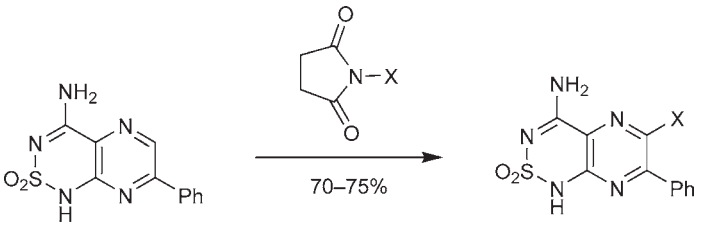
The reaction of the zwitterionic pyridazino[3,4-*e*]-1,2,4-triazine **31** with methyl iodide gave the corresponding *N*-methyl compound **32** via selective alkylation on the triazine N-1 (Equation 3) <2003ARK62>.



31 **32**

(3)

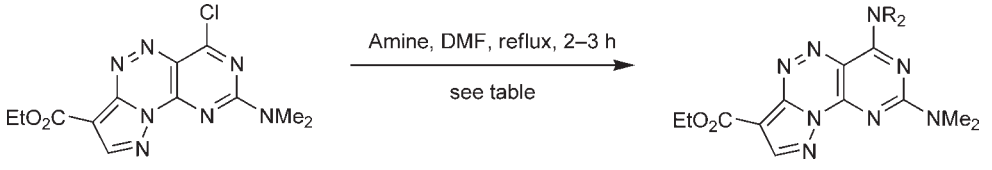
The pyrazino[2,3-*c*]-1,2,6-thiadiazine **33** (Equation 4) reacts readily with *N*-bromosuccinimide or *N*-chlorosuccinimide to the give 6-bromo and 6-chloropyrazinothiadiazines **34** <1999JME1698>.



33 **34**: X = Cl or Br (4)

10.20.5.4 Nucleophilic Attack and Reduction

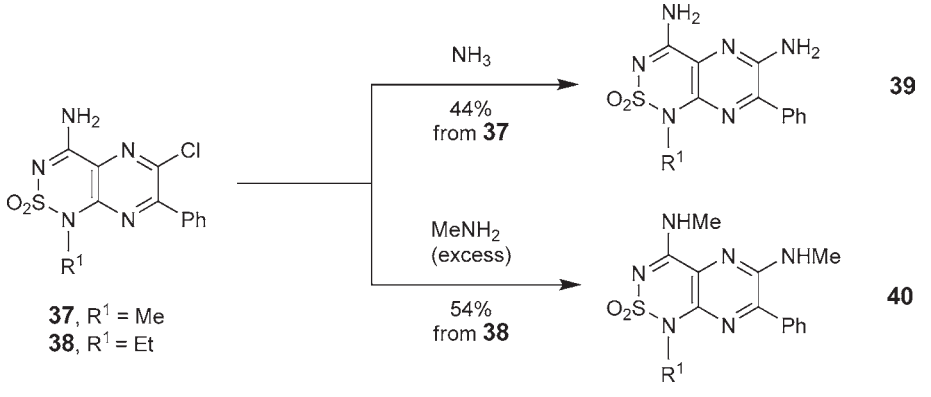
Nucleophilic attack on the chloro-substituted pyrimido[4,5-*e*]-1,2,4-triazines **35** by amines allows the synthesis of the corresponding amino-substituted systems **36** as shown in Equation (5) <1996T3037>.



35 **36** (5)

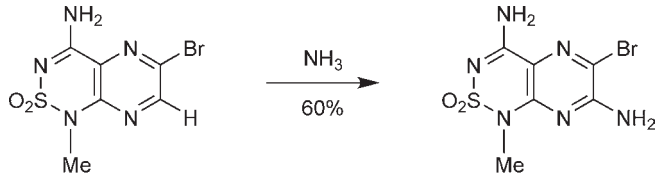
NR$_2$ (*see Equation* 5)	*Yield* (%) *of* **36** *from* **35**
4-Phenylpiperazino	86
4-Benzylpiperazino	50
N-4′-Acetylphenylpiperazino	67
4-Piperidinopiperidino	58
Piperazino	66

When the 6-chloropyrazino[2,3-*c*]-1,2,6-thiadiazine **37** was reacted with ammonia, the 6-amino derivative **39** was isolated, as shown in **Scheme 2**. The treatment of compound **38** with excess methylamine yielded the bis-methylamino compound **40**, the result of chlorine displacement by nucleophilic attack at the fully conjugated ring accompanied by transamination <2003HCA139>.



Scheme 2

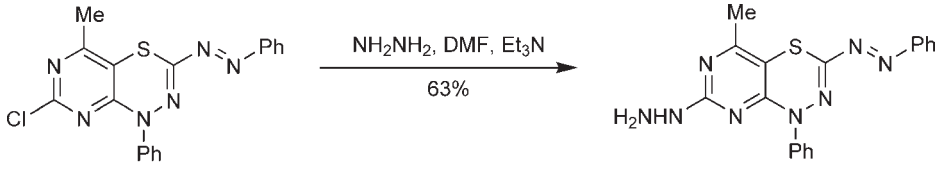
The 7-unsubstituted 6-bromopyrazino[2,3-*c*]-1,2,6-thiadiazine **41** behaved in a different manner, yielding the product **42** of Chichibabin amination at C-7 when reacted with ammonia, a process that is shown in Equation (6) <2003HCA139>.



(6)

41 **42**

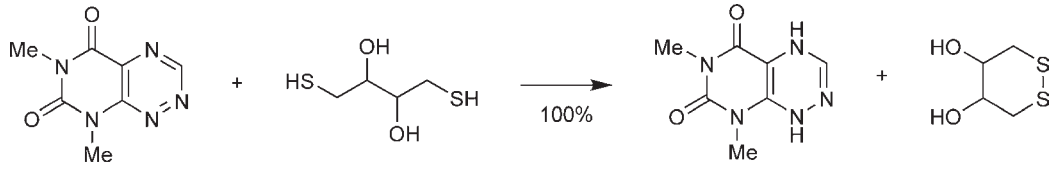
The substitution of the 6-chloro substituent of the 6-chloropyrimido[4,5-*e*]-1,3,4-thiadiazine **43** with hydrazine in DMF in the presence of a tertiary amine gave the 6-hydrazinopyrimido[4,5-*e*]-1,3,4-thiadiazine **44** (Equation 7) <2005PS2477>.



(7)

43 **44**

The natural product fervenulin **8** reacts with dithiothreitol (DTT) **45** in the absence of oxygen as shown in Equation (8) to give the dihydro derivative **46** in quantitative yield, a process that can be reversed in the presence of atmospheric oxygen. A clear 3 ppm upfield shift of the CH proton of the triazine ring in the ^{1}H NMR spectrum, together with characterization by mass spectrometry, confirmed that the reduction had occurred. It is of some note that this process is believed to be responsible for the biological activity (see Section 10.20.10) of several such triazine analogues via the oxidation of active site cysteine and through the *in vivo* involvement of reduced glutathione <2003BML2895>.



(8)

8 **45** **46**

10.20.6 Reactivity of Nonconjugated Rings

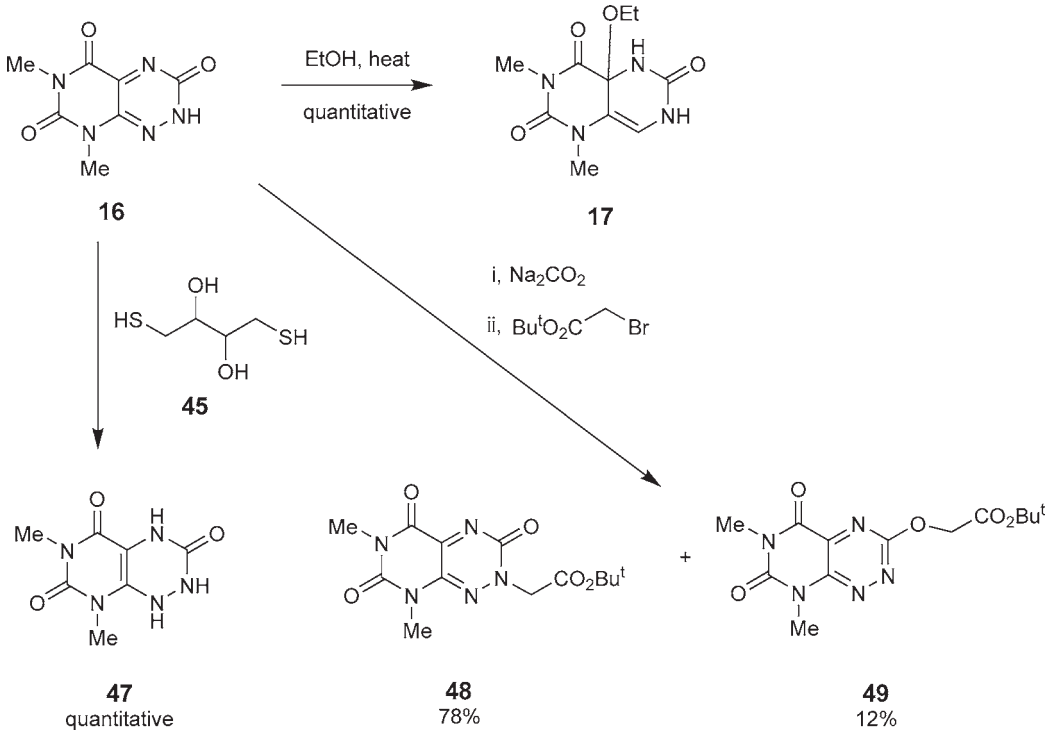
10.20.6.1 Introduction

This section includes reactions where, although one of the rings in the system may be fully conjugated, the ring at which reaction is occurring is nonconjugated. In keeping with the organization used in CHEC-II(1996) <1996CHEC-II(7)785>, lactams and similar ring systems will be dealt with as nonconjugated systems even if they are isomeric with a fully conjugated ring. Finally, the pyrimidotriazines (azapteridines) will be treated in a separate section.

10.20.6.2 Reactivity of the Pyrimidotriazines (Azapteridines)

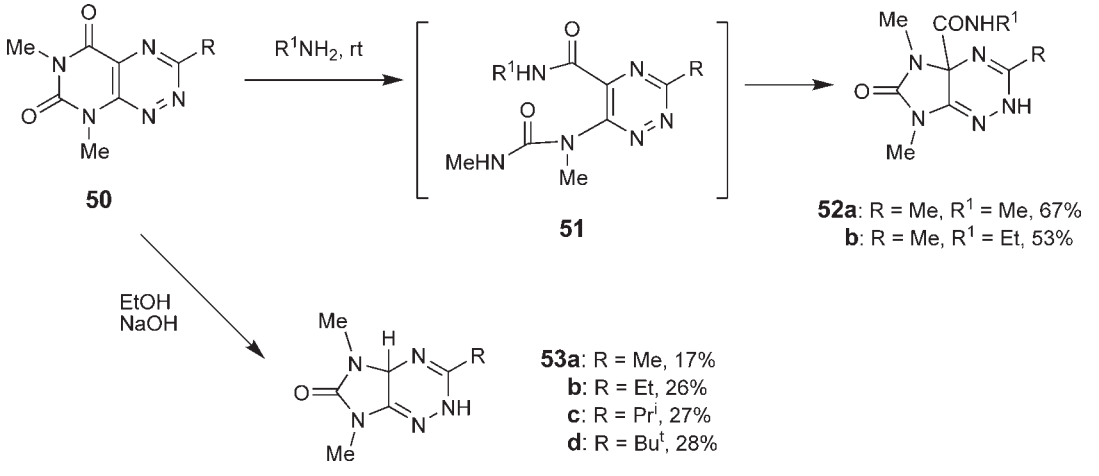
The reactivity of fervenulone **16** has been studied <1995JOC7063>, and is shown in **Scheme 3**. Thus, reaction with boiling ethanol gave the 4a-ethoxy-substituted system **17** as the only product, the structure of which was unambiguously assigned. On the basis of this process, the same study explored the reactivity of fervenulone **16** toward DTT **45** and found that DTT functioned not as a nucleophile, but rather in a manner analogous to that shown in Equation (8)

(Section 10.20.5.4), in order to furnish the reduction product **47**. In an additional reaction, it was found that treatment of the preformed sodium salt of fervenulone **16** with *tert*-butyl bromoacetate in DMF gave N-2-substituted analogue **48** together with a small amount of the O-alkylated adduct **49**.



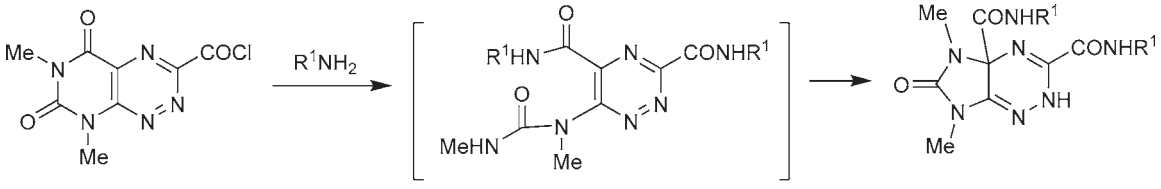
Scheme 3

In a study involving 3-methylfervenulin **50** (R = Me) <1996JHC949>, shown in **Scheme 4**, it was found that reaction with methanolic methylamine or ethylamine at room temperature gave the imidazo[4,5-*e*]-1,2,4-triazines **52a** and **52b**, respectively. This transformation is believed to proceed via the intermediate 1,2,4-triazin-6-yl urea derivatives **51**. The same investigation showed that the reaction of a range of 3-alkylfervenulins **50** with ethanolic sodium hydroxide gave the 3-alkyl imidazo[4,5-*e*]-1,2,4-triazines **53**.



Scheme 4

A similar process was found to occur with the fervenulin-3-carboxyl chloride **54**, which upon treatment with an amine gave the bis-adduct intermediate **55**, which ring-closed to the imidazo[4,5-*e*]-1,2,4-triazine bis-carboxamides **56** as shown in **Scheme 5** <1996JHC949>. The structure of the products **56** was confirmed by X-ray crystallographic analysis.

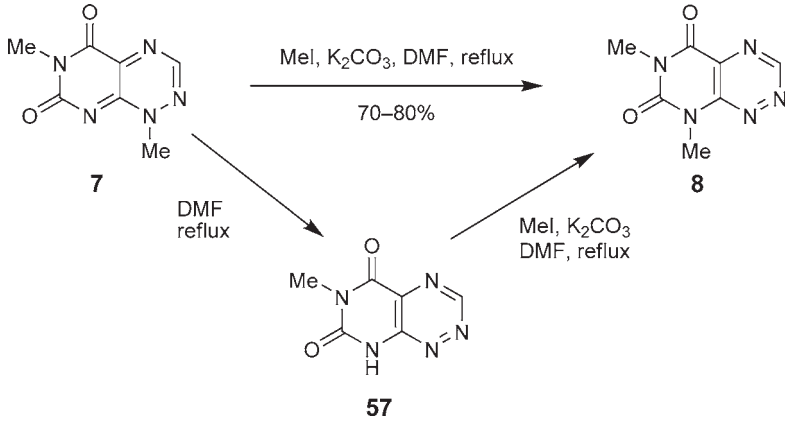


54 **55** **56**

R^1 = Pr^n, 73%; R^1 = Bu^t, 59%; R^1 = Et, 69%; R^1 = Me, 60%

Scheme 5

The dealkylation–alkylation of toxoflavin **7** with methyl iodide in DMF at reflux furnishes fervenulin **8**, as shown in **Scheme 6**. Interestingly, heating toxoflavin **7** at reflux in DMF results in demethylation to give the 1-demethylated species, reumycin **57**, which can be methylated to give fervenulin **8** <1997H(45)643>.

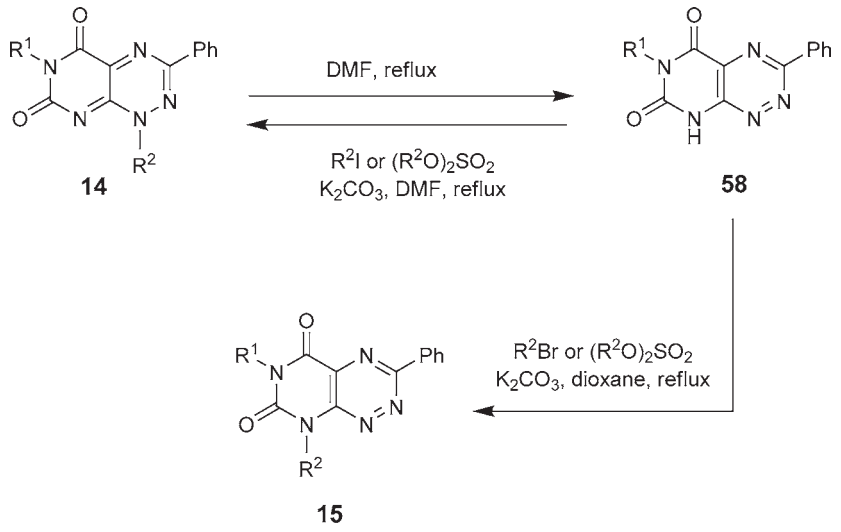


7 **8** **57**

Scheme 6

The 1,6-disubstituted 3-phenylpyrimido[5,4-*e*]-1,2,4-triazines **14** also undergo dealkylation to give the 6-monosubstituted 3-phenylpyrimido[5,4-*e*]-1,2,4-triazines **58** which in turn undergo alkylation in dioxane to give the 6,8-disubstituted 3-phenylpyrimido[5,4-*e*]-1,2,4-triazine derivatives **15**. Alternatively, alkylation of compounds **58** in DMF gives the 1,6-disubstituted 3-phenylpyrimido[5,4-*e*]-1,2,4-triazines **14** as shown in **Scheme 7** <2001J(P1)130, 1997H(45)643>.

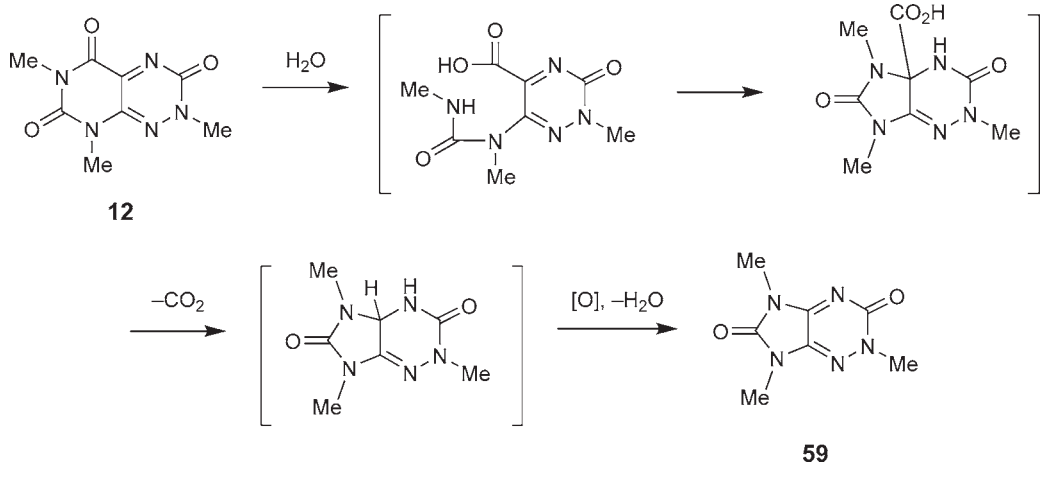
2-Methylfervenulone **12** is a natural product that undergoes nucleophilic attack of water at the nonconjugated ring to give the imidazo[4,5-*e*]-1,2,4-triazine **59** via the mechanistic pathway shown in **Scheme 8** <2000JNP1641>.



14 58 15

R^1	R^2	*Yield (%) of* **15** *from* **58**	*Yield (%) of* **14** *from* **58**
Me	Me	89	91
Me	Pr^n	78	80
Me	Bu^n	81	82
Ph	Pr^n	84	88
Me	Pr^i	67	85
Ph	Bu^t		85
Ph	Me	85	86
Ph	Bu^n	80	82

Scheme 7

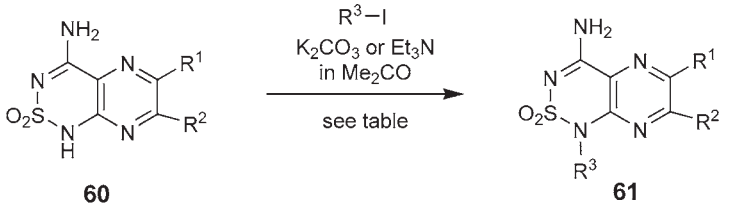


12 59

Scheme 8

10.20.6.3 Reactivity of Other Ring Systems

The pyrazino[2,3-*c*][1,2,6]thiadiazine-2,2-dioxides **60** have been the subject of detailed study, and are readily substituted at the thiadiazine ring sp^3 nitrogen as shown in Equation (9) to give the 1-substituted systems **61** in the yields shown in the accompanying table <2000JME4219, 1999JME1698>.



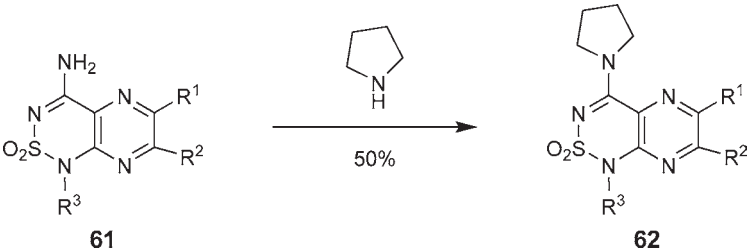
60 **61**

R^1	R^2	R^3	Yield (%) of **61** from **60** (*Equation 9*)	*Reference*
Ph	Ph	Et	78	1999JME1698
Ph	Ph	CH_2Ph	79	1999JME1698
Ph	Ph	CH_2CO_2Et	85	1999JME1698
Ph	Ph	$CH_2CO_2Bu^t$	58	1999JME1698
Et	H	Et	60	2000JME4219
Pr^i	H	Et	56	2000JME4219
H	Et	Et	56	2000JME4219
2-Thienyl	2-Thienyl	Et	69	1999JME1698
2-Furyl	2-Furyl	Me	72	1999JME1698
2-Pyridyl	2-Pyridyl	Me	20	1999JME1698
Ph	Me	Et	75	1999JME1698
CH_2–$(CH_2)_3$–CH_2		Me	63	2000JME4219
Cl	Ph	Et	74	1999JME1698
Bu^t	H	Et	61	2000JME4219
Br	Ph	CH_2CO_2Et	74	1999JME1698

(9)

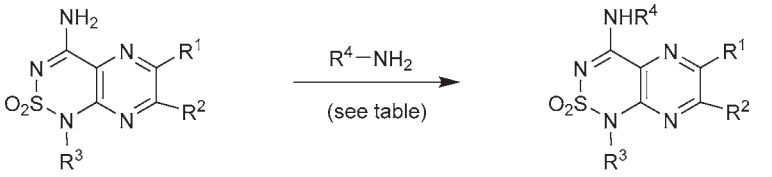
The reaction of pyrazino[2,3-*c*][1,2,6]thiadiazine-2,2-dioxides **61** with secondary amines proceeds very readily and allows access to, for example, the 4-pyrrolidinyl derivative **62** as shown in Equation (10). A similar reaction with primary amines allowed access to a range of 4-amino-pyrazino[2,3-*c*][1,2,6]thiadiazine-2,2-dioxides **63**, as shown in Equation (11) <2000JME4219>.

Nucleophilic displacement of the 4-amino group of pyrazino[2,3-*c*][1,2,6]thiadiazine-2,2-dioxides **61** with water gives the 4-oxo derivatives **64**, giving a very versatile entry to this system. The corresponding 4-thioxo analogues **65** were easily accessed by the treatment of compounds **64** with P_2S_5, as shown in **Scheme 9** <2003HCA139>.



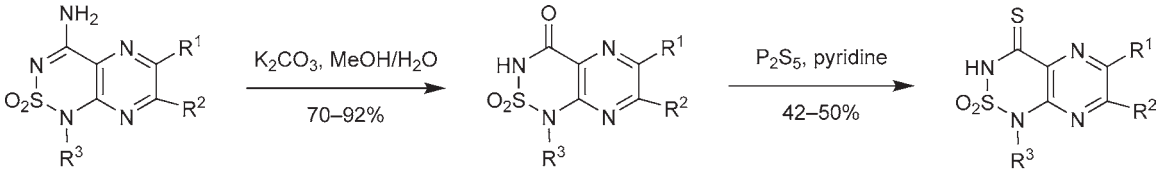
61 **62**

(10)



R^1	R^2	R^3	R^4	*Yield (%) of* **63** from **61** (*equation 11*)
H	Ph	Me	$CH_2CH_2NH_2$	56
H	Ph	Et	CH_2Ph	40
Me	H	Et	CH_2Ph	81
Me	Et	Et	CH_2CH_2OH	97
Me	Et	Et	NH_2	88
Me	Et	Et	$CH_2CH_2NMe_2$	84

(11)



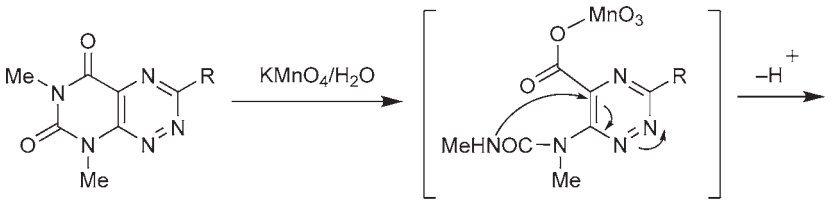
a: R^3 = Me, R^1 = R^2 = Ph; **b**: R^3 = Me, R^1 = R^2 = 4-$MeOC_6H_4$; **c**: R^3 = Me, R^1 = H; R^2 = Ph

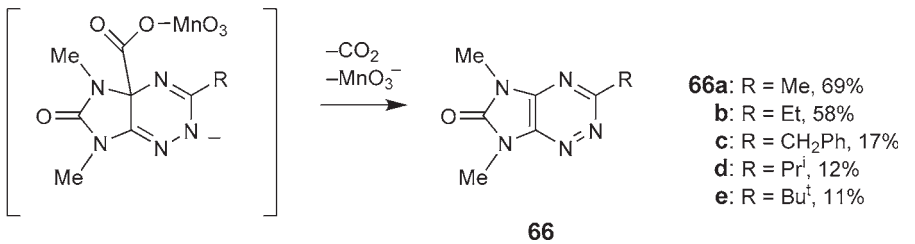
Scheme 9

10.20.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.20.7.1 Rearrangement Reactions

The 5-oxo substituent of the 3-alkylfervenulins **24** reacts with aqueous potassium permanganate to give the imidazo[4,5-*e*]-1,2,4-triazin-6-ones **66** via the ring-opening–ring-closure process suggested in **Scheme 10** <1996JHC949>.





Scheme 10

10.20.7.2 Reactions at the α-Carbon of Substituents Attached to Ring Carbons

The 3-alkylfervenulin derivatives **67a–c** undergo a wide range of reactions at the α-carbon as shown in **Scheme 11** <1996JHC949>. Thus, the reaction of 3-methylfervenulin **67a** with benzaldehyde in the presence of zinc chloride results in an aldol condensation to yield the 3-styrylfervenulin **68**. Mild oxidation of 3-styrylfervenulin **68** with permanganate in pyridine/water at ice to room temperature gave the fervenulin carboxylic acid **69**. It is noteworthy that this acid was prone to decarboxylation, giving fervenulin **8** upon boiling in water, but was converted quantitatively into the crude acid chloride **70** upon reaction with thionyl chloride. The acid chloride **70**, usually generated *in situ*, was easily converted into the fervenulin-3-carboxamides and carboxylates **71** after reaction with alcohols and amides as detailed in **Table 7**.

Brominations of 3-alkylfervenulin derivatives **67a–c** gave varied results depending upon the substrate that was used and the method of bromination <1996JHC949>. Thus, 3-methylfervenulin **67a** reacted with bromine in acetic acid to give the 3-dibromomethyl derivative **72**, whereas 3-ethylfervenulin **67b** gave only complex and inseparable mixtures. 3-Benzylfervenulin **67c** reacted in the expected manner with bromine in acetic acid to give a good yield of 3-(1-bromobenzyl)fervenulin **73**. Although the reaction with bromine in acetic acid failed to yield useful products, 3-ethylfervenulin could, however, be brominated with *N*-bromosuccinimide/azabisisobutyronitrile (NBS/AIBN) to give the 3-(1-bromoethyl) derivative **74a** in good yield together with the corresponding dibromo derivative **74b** in low yield. The 3-(bromomethyl)fervenulin **75** was formed in very low yield from the reaction of 3-methylfervenulin with NBS/AIBN, but was best accessed from the reduction of the dibromomethyl compound **72** with stannous bromide.

The reactivity of the dibromo compounds **72** and **74b** was also explored, and it was shown that reaction with ethylene glycol gave the corresponding cyclic acetals **76**, while reaction of compound **72** with hydroxylamine furnished the fervenulin-3-carbaldoxime **77**, which was found to be resistant to hydrolysis.

The reaction of the monobromo derivatives **74a** and **75** with silver acetate gave 3-(acetoxymethyl)fervenulin **80** and 3-acetylfervenulin **78**, respectively, in excellent yields (**Scheme 11**) <1996JHC949>. 3-Acetylfervenulin **78** and 3-(acetoxymethyl)fervenulin **80** gave the corresponding alcohols **79** and **81** after hydrolysis in methanolic ammonia.

It is of interest that the methyl alcohol **81** underwent oxidation with chromic acid to afford 3-acetylfervenulin **83** in good yield, whereas the same conditions resulted in the conversion of alcohol **79** into fervenulin **8**. The desired product of this latter transformation, that is, fervenulin-3-carboxaldehyde **82**, could, however, be obtained, albeit in low yield, by the oxidation of alcohol **79** with manganese dioxide. Fervenulin-3-carboxaldehyde **82** could be obtained in much better yield from the treatment of 3-styrylfervenulin **68** with periodate in the presence of osmium tetroxide, or by ozonolysis of the same substrate.

Aldehyde **82** was extremely reactive and was best isolated as the hydrate **84a**. Indeed, recrystallization of the aldehyde **82** from ethanol gave 3-(1-ethoxy-1-hydroxymethyl)fervenulin **84b**, while reaction with ethylene glycol gave the cyclic acetal **76a**. The reactivity of the aldehyde **82** was exploited by easy Schiff base formation upon reaction with *p*-aminobenzoylglutamic acid, a process that was followed by reduction to give the fervenulin-based folic acid analogue **85** <1996JHC949>.

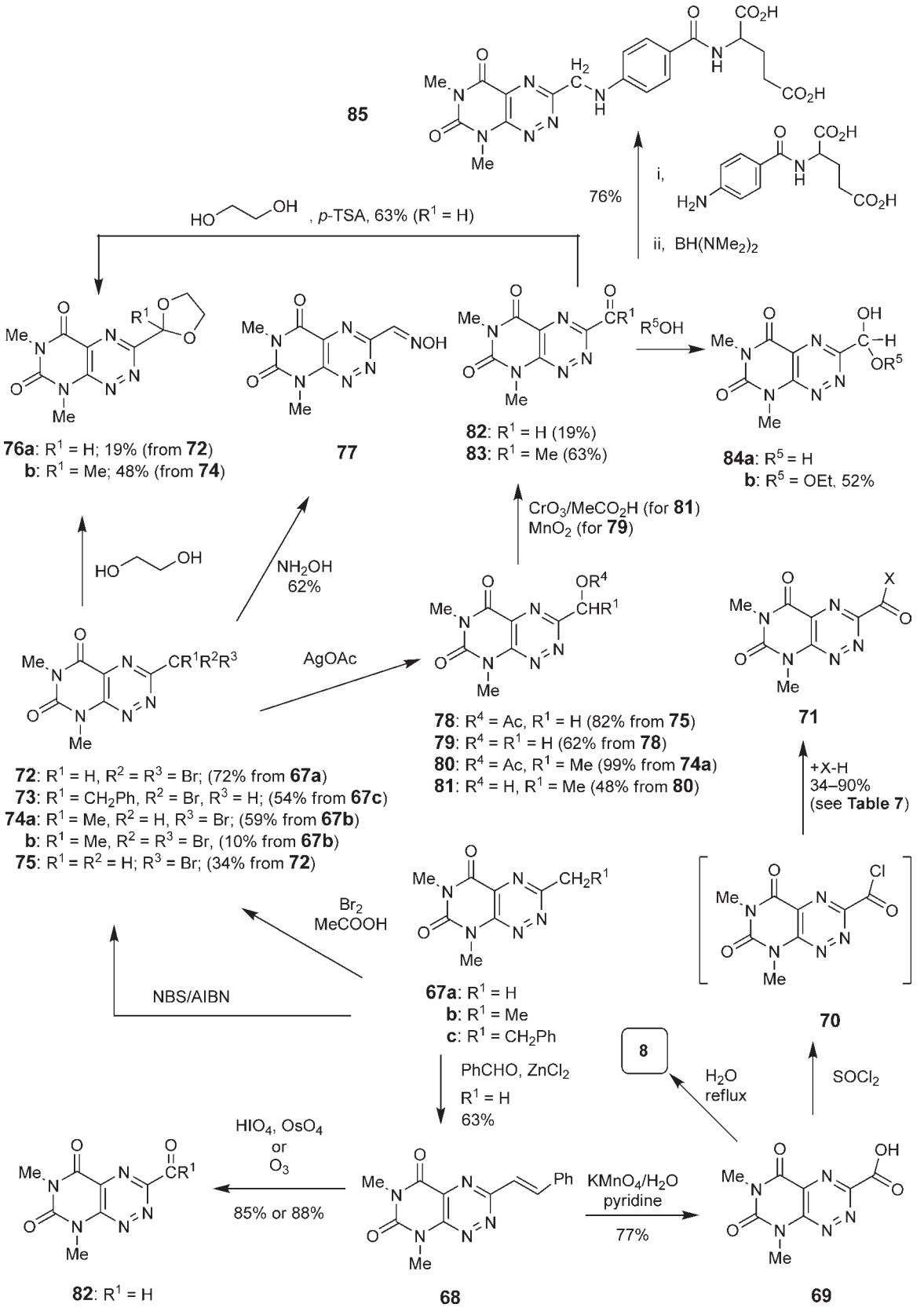
In the search for novel orally active hypoglycemic agents, a team from Hoffmann–LaRoche used the readily available (see Section 10.20.9.2.3) chloromethylpyrimido[4,3-*e*]-1,2,4-triazine **86** as a starting material for the synthesis of the protein tyrosine phosphatase inhibitors **87** (individual yields were not detailed), as shown in Equation (12) <2003BML2895>.

C-7 methyl substituents on the 7-methylpyrazino[2,3-*c*][1,2,6]thiadiazine **88** undergo aldol condensation reactions with aryl aldehydes to give the 7-styryl compounds **89** as shown in **Scheme 12**. It is interesting to note that the 6-methyl analogues **90** do not react, a consequence of the lower acidity of the 6-methyl group <2003HCA139>.

The 6-methylpyrazino[2,3-*c*][1,2,6]thiadiazine **90** underwent reaction with potassium permanganate at pH 8 to give the 6-carboxylic acids **91**, as shown in **Scheme 13**. The subsequent reaction of the carboxylic acid **91c** with thionyl chloride followed by coupling to benzylamine gave the amide **92**. It is again of interest to note that the 7-methyl analogues **88** were not reactive toward permanganate under the same conditions <2003HCA139>.

10.20.7.3 Reactions of Hetero Substituents

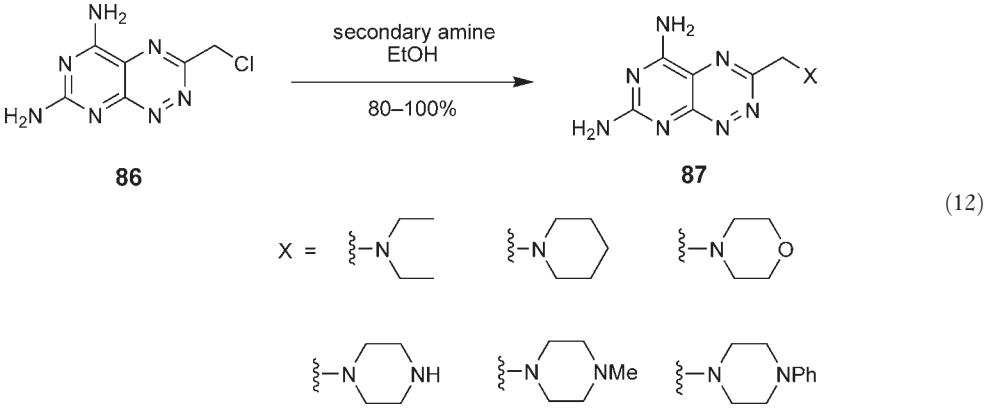
The 3-amino-5,7-dimethylpyrimido[4,5-*e*]-1,2,4-triazine **93** (Equation 13) undergoes acetylation with acetic anhydride in pyridine to give the mono-acetylated analogue **94** together with a small amount (9%) of the corresponding diacetylated derivative <2001JHC141>.


85
76%
i,
ii, BH(NMe2)2
HO OH , p-TSA, 63% (R1 = H)
76a: R1 = H; 19% (from 72)
b: R1 = Me; 48% (from 74)
77
82: R1 = H (19%)
83: R1 = Me (63%)
R5OH
84a: R5 = H
b: R5 = OEt, 52%
CrO3/MeCO2H (for 81)
MnO2 (for 79)
NH2OH
62%
AgOAc
78: R4 = Ac, R1 = H (82% from 75)
79: R4 = R1 = H (62% from 78)
80: R4 = Ac, R1 = Me (99% from 74a)
81: R4 = H, R1 = Me (48% from 80)
71
+X-H
34–90%
(see Table 7)
72: R1 = H, R2 = R3 = Br; (72% from 67a)
73: R1 = CH2Ph, R2 = Br, R3 = H; (54% from 67c)
74a: R1 = Me, R2 = H, R3 = Br; (59% from 67b)
b: R1 = Me, R2 = R3 = Br, (10% from 67b)
75: R1 = R2 = H; R3 = Br; (34% from 72)
Br2
MeCOOH
NBS/AIBN
67a: R1 = H
b: R1 = Me
c: R1 = CH2Ph
70
8
PhCHO, ZnCl2
R1 = H
63%
H2O
reflux
SOCl2
HIO4, OsO4
or
O3
85% or 88%
KMnO4/H2O
pyridine
77%
82: R1 = H
68
69

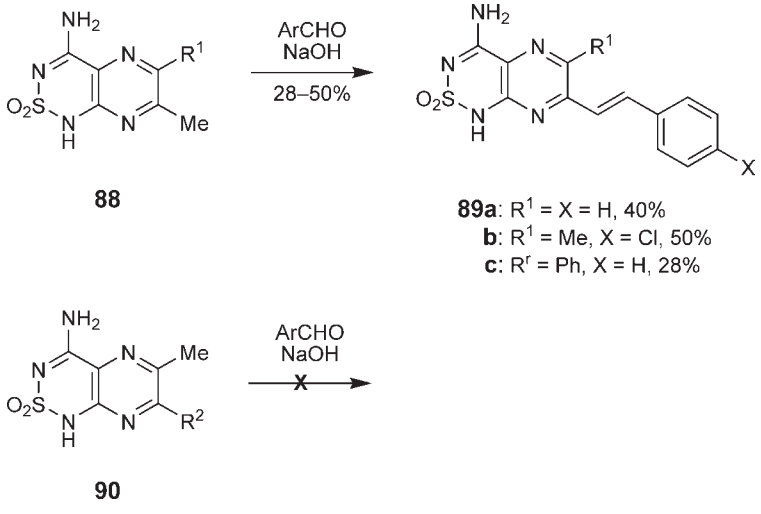
Scheme 11

Table 7 The synthesis of fervenulin-3-carboxamides and carboxylates **71** (see **Scheme 11**)

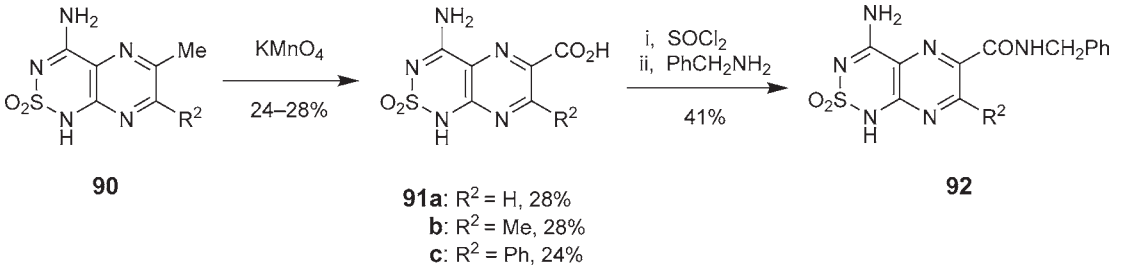
X	*Yield (%)*	*Reference*
OMe	34	1996JHC949
OEt	90	1996JHC949
NH_2	79	1996JHC949
$NHCH_2CHMe_2$	60	1996JHC949
$NHCH_2CH_2NEt_2$	39	1996JHC949
NEt_2	58	1996JHC949
	71	1996JHC949



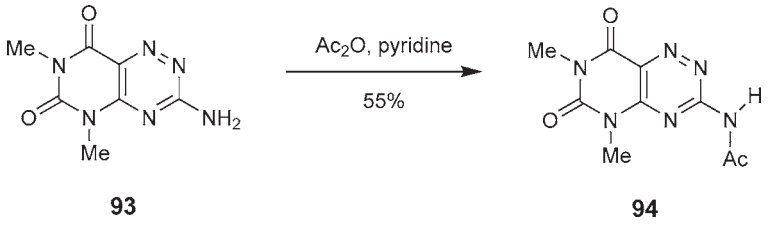
(12)



Scheme 12

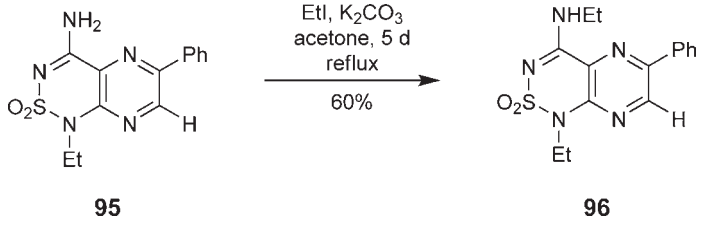


Scheme 13



(13)

Alkylation of the exocyclic amino group of the 4-amino-6-phenylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide **95**, shown in Equation (14), with ethyl iodide and potassium carbonate in acetone gave the corresponding 4-ethylamino derivative **96** in a clean and efficient manner, although the researchers noted that the procedure is not general due to competitive formation of dialkylated products <2000JME4219>. The procedure described in Section 10.20.6.3 (Equations 10 and 11) is, in fact, a more efficient entry to 4-alkylamino pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide.



(14)

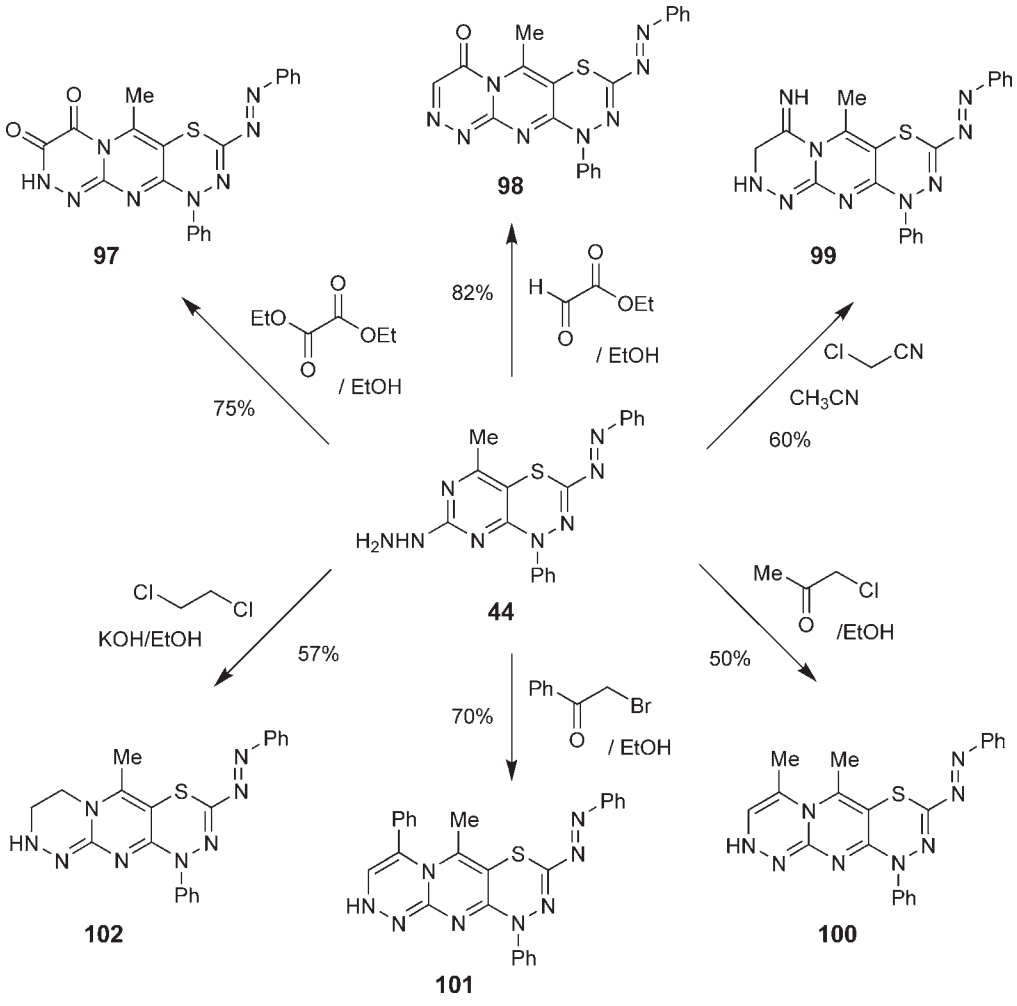
The 6-hydrazinopyrimido[4,5-*e*][1,3,4]thiadiazine **44** (see Section 10.20.5.4, Equation (7), for the synthesis of this compound) undergoes reaction with diethyl oxalate in ethanol at reflux to afford the triazino-fused system **97**, as shown in **Scheme 14**. Similarly, reaction with glyoxalic acid in ethanol gave compound **98**, reaction with chloroacetonitrile in acetonitrile gave compound **99**, reaction with chloroacetone in ethanol at reflux gave compound **100**, and reaction with phenacyl bromide in ethanol at reflux gave compound **101**. Finally, reaction with 1,2-dichloroethane in the presence of ethanolic potassium hydroxide gave the triazino-fused pyrimido[4,5-*e*][1,3,4]thiadiazine **102** <2005PS2477>.

10.20.7.4 Miscellaneous Reactions of Substituents Attached to Ring Carbons

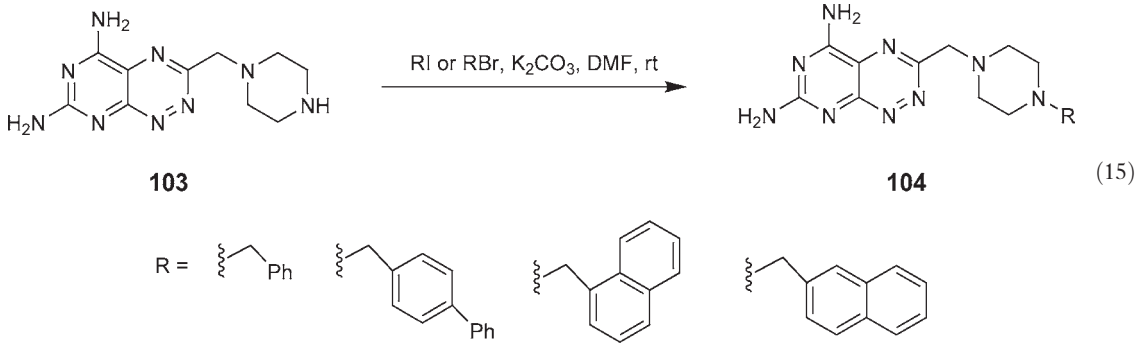
The piperazine-substituted pyrimido[5,4-*e*][1,2,4]triazine **103** undergoes selective reaction with benzylic halides to provide the benzylic piperazinyl analogues **104** <2003BML2895> as shown in Equation (15). The products are protein tyrosine phosphatase inhibitors.

The reaction of the pyrido-fused pyridazino[3,4-*e*][1,2,4]triazinium compound **105** with secondary amines results in the ring-opening of the pyridine moiety to yield dienyl-substituted pyridazino[3,4-*e*][1,2,4]triazines of which the pyrrolidine compound **106**, shown in **Scheme 15**, is typical <2003ARK62, 1998ACO285, 1995JOC4919>. Compound **106** has been the subject of a detailed study and has been shown to react as a diene in the presence of fumaronitrile and *N*-phenylmaleinimide to give the Diels–Alder adducts **107** and **108**, respectively <2003ARK62>,

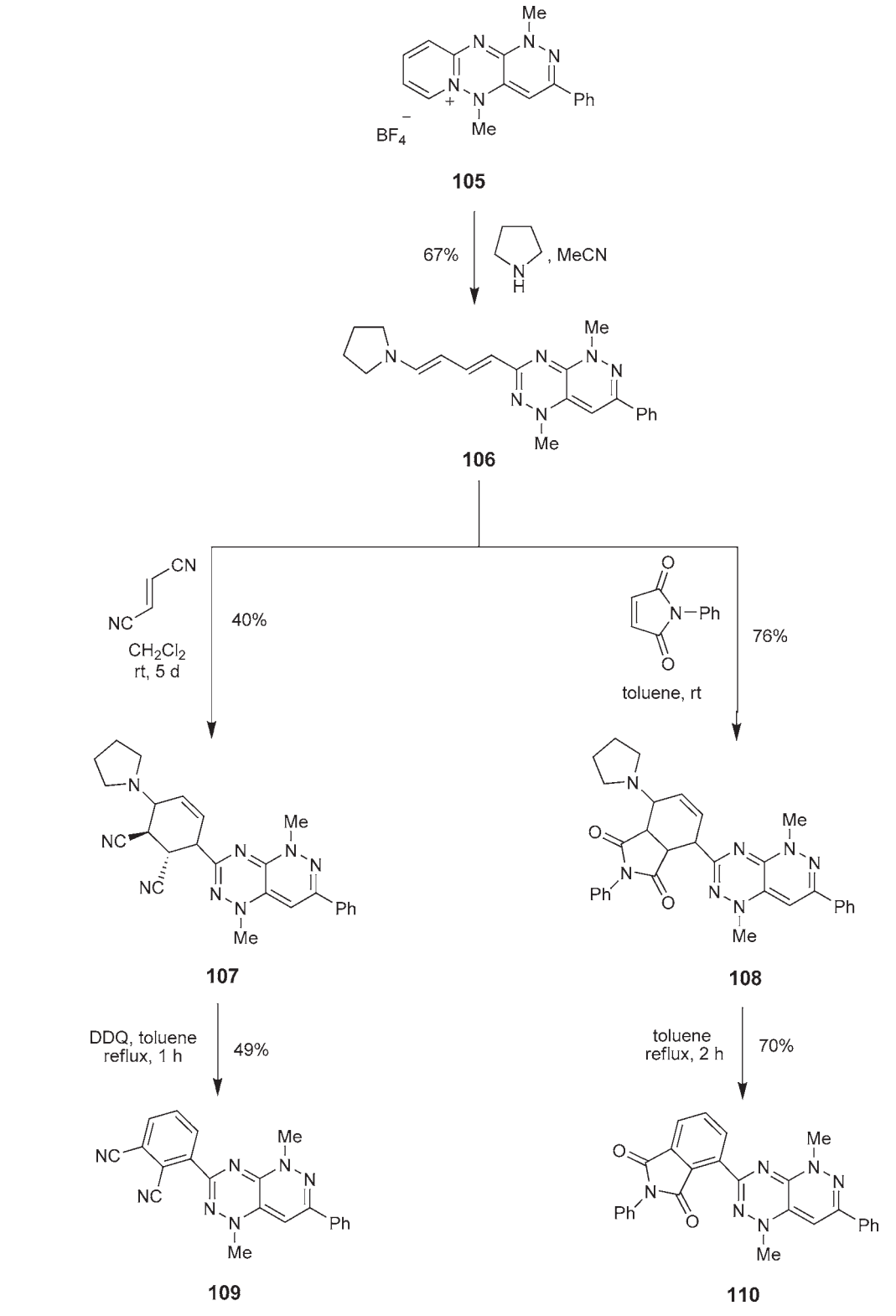
also shown in **Scheme 15**. Aromatization was facile in the case of compound **108**, whereby simple heating in toluene was sufficient to yield the isoindol-2,7-dione-substituted pyridazino[3,4-*e*][1,2,4]triazine **110**. Similar reaction of the fumaronitrile adduct **107** required oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the aromatized dicyanobenzene-substituted pyridazino[3,4-*e*][1,2,4]triazine derivative **109** <2003ARK62>.



Scheme 14



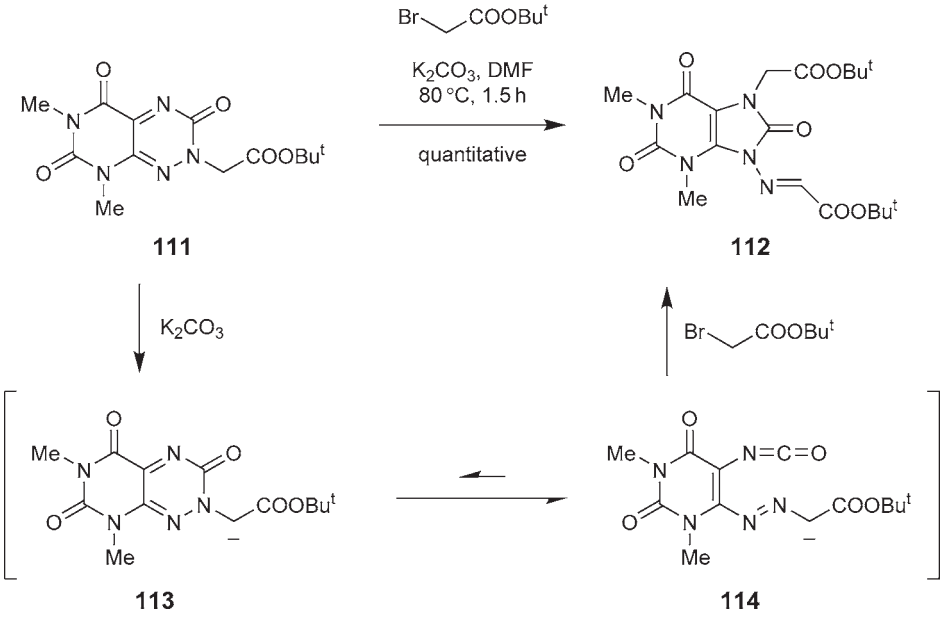
(15)


Me
N
N
N
N
N
Ph
Me
BF4
105
67%
, MeCN
N
H
Me
N
N
N
N
N
Ph
Me
106
CN
NC
CH2Cl2
rt, 5 d
40%
O
N–Ph
O
76%
toluene, rt
N
NC
NC
Me
N
N
N
N
Ph
Me
107
N
O
N
Ph
O
Me
N
N
N
N
Ph
Me
108
DDQ, toluene
reflux, 1 h
49%
NC
NC
Me
N
N
N
N
Ph
Me
109
toluene
reflux, 2 h
70%
O
N
Ph
O
Me
N
N
N
N
Ph
Me
110

Scheme 15

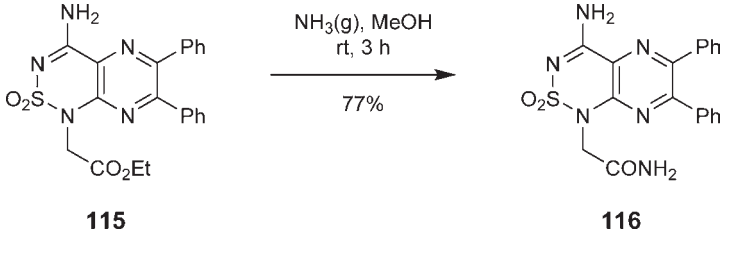
10.20.8 Reactivity of Substituents Attached to Ring Heteroatoms

The (*tert*-butoxycarbonyl)methylpyrimido[5,4-*e*]-1,2,4-triazine **111** underwent quantitative rearrangement to the purine analogue **112** in the presence of potassium carbonate and *tert*-butyl bromoacetate in DMF, as shown in **Scheme 16** <1995JOC7063>. This reaction is believed to proceed via an electrocyclic ring-opening of intermediate anion **113** that is analogous to the anion-accelerated aza-Cope rearrangement. The formation of the α-ester, α-diazo anion **114** from anion **113** is suggested as a thermodynamic driving force for the process, with anion **114** undergoing ring closure followed by reaction with *tert*-butyl bromoacetate in order to drive the reaction toward the formation of the purine derivative **112**.

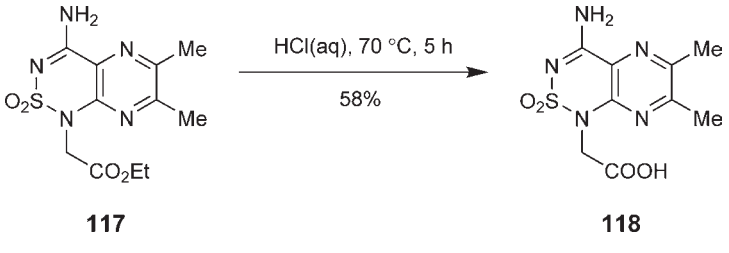


Scheme 16

The *N*-(ethoxycarbonyl)methylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides **115** and **117**, shown in Equations (16) and (17), undergo aminolysis and hydrolysis to yield the corresponding amide and carboxylic acid **116** and **118**, respectively <1999JME1698, 2000JME4219>.



(16)



(17)

10.20.9 Syntheses of Bicyclic 6-6 Systems with Five or More Heteroatoms

10.20.9.1 Introduction

The presentation of material in this section parallels that detailed in CHEC-II(1996) <1996CHEC-II(7)785>. Hence, syntheses in which a second heterocyclic ring is built onto a preexisting heterocyclic ring will be detailed first. These syntheses constitute by far the largest class and will be classified further by the number of heteroatoms present in the ring being formed, that is, one atom, two atoms, three atoms, or four atoms. Where the amount of material so dictates, the syntheses have been subdivided further according to how the heteroatoms in the new ring are disposed to the ring junction (e.g., either 1,2,3 or 1,2,4 for the three-heteroatom series). It is important to note, therefore, that this section is not arranged specifically according to particular ring systems and that some ring systems will hence appear in more than one subsection of this section.

10.20.9.2 Syntheses Involving the Construction of a Second Heterocyclic Ring onto an Existing Heterocyclic Ring

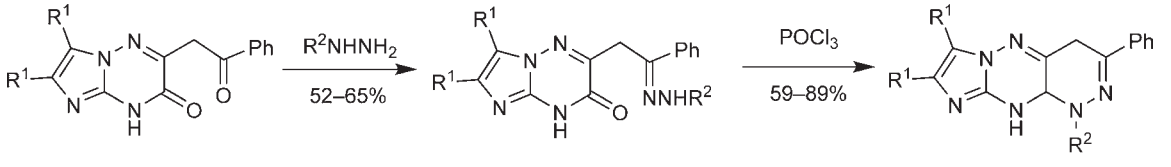
10.20.9.2.1 One heteroatom in the ring being formed

No methods in this category have appeared since 1995 as, indeed, was the case in CHEC-II(1996) <1996CHEC-II(7)785>.

10.20.9.2.2 Two heteroatoms in the ring being formed

10.20.9.2.2(i) Two heteroatoms disposed 1,2 to the ring junction

The benzoylmethyl-substituted condensed triazinones **118** undergo condensation with aryl hydrazines in boiling propan-2-ol or hexan-1-ol to produce the corresponding hydrazones **119** which are easily cyclized upon boiling in neat phosphorus oxychloride to give the novel condensed pyridazino[6,5-*e*]-1,2,4-triazines **120** shown in **Scheme 17** <1999CHE376, 1999KGS426>.



118 **119** **120**

R^1 = Ph, R^2 = Ph; 65% and 59%
R^1, R^1 = condensed benzene, R^2 = Ph; 57% and 62%
R^1, R^1 = condensed benzene, R^2 = 4-Tol; 52% and 89%

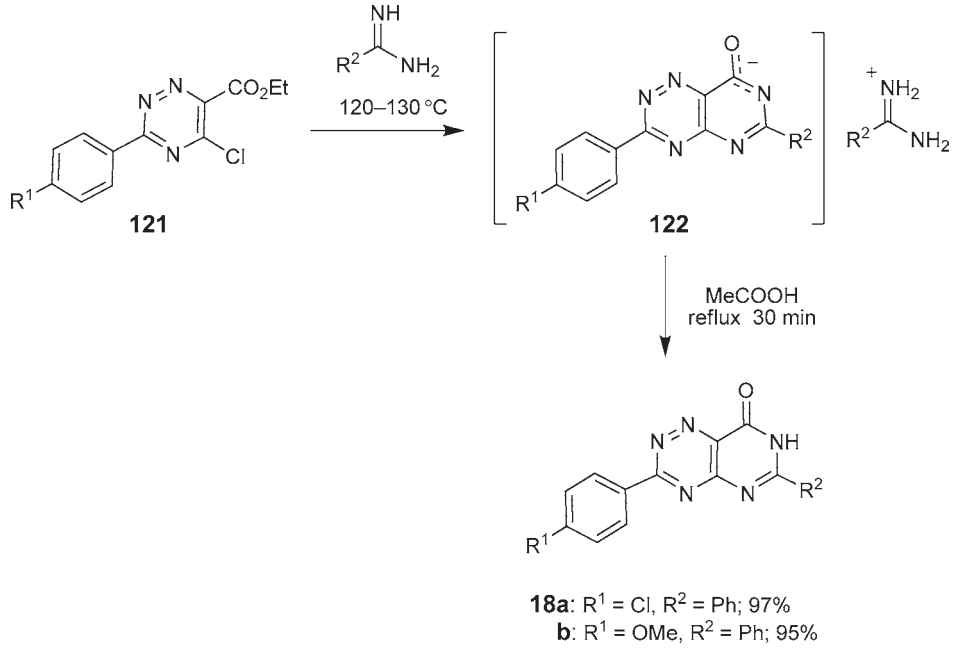
Scheme 17

10.20.9.2.2(ii) Two heteroatoms disposed 1,3 to the ring junction

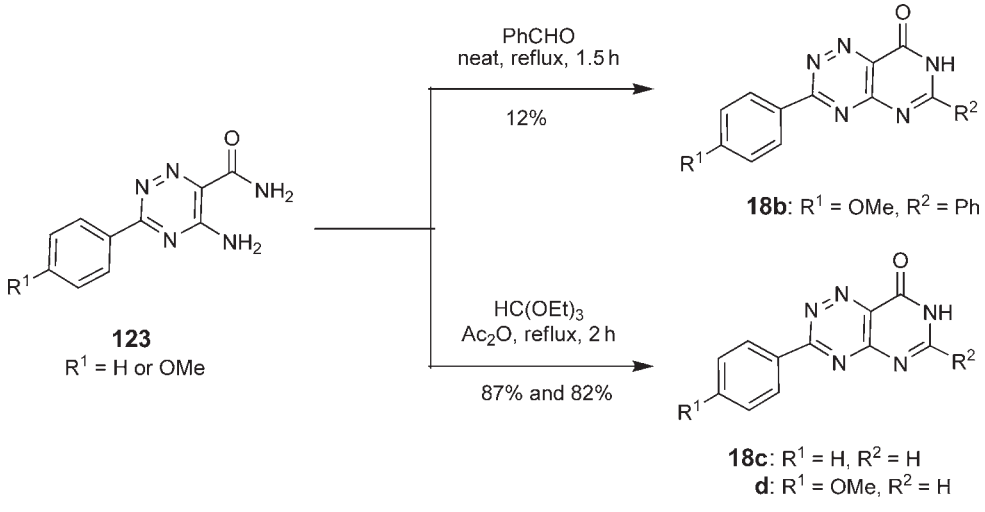
The pyrimido[4,5-*e*][1,2,4]triazines (6-azapteridines) **18a** and **18b**, shown in **Scheme 18**, were formed upon the reaction of the ethyl 1,2,4-triazine-6-carboxylates **121** with benzamidine, a reaction which proceeds via the action of boiling acetic acid upon the characterized intermediate salt **122** <2003CCC965>. The same researchers (**Scheme 19**) also showed that the 5-amino-1,2,4-triazine-6-carboxamide **123** (R^1 = OMe) can undergo reaction in neat benzaldehyde to furnish a low yield of the 6-azapteridine **18b**. More importantly, the 5-amino-1,2,4-triazine-6-carboxamides **123** were found to undergo reaction with triethyl orthoformate to yield the 6-unsubstituted-3-arylpyrimido[4,5-*e*][1,2,4]triazines **18c** and **18d**, also shown in **Scheme 19** (R^2 = H) <2003CCC965>, one of only a few entries to such compounds.

The pyrimido[4,5-*e*]-1,2,4-triazine **28** is an isofervenulin analogue and is a potential antianxiety agent that has attracted attention in the synthetic community. Attempts to prepare compound **28** from the reaction of

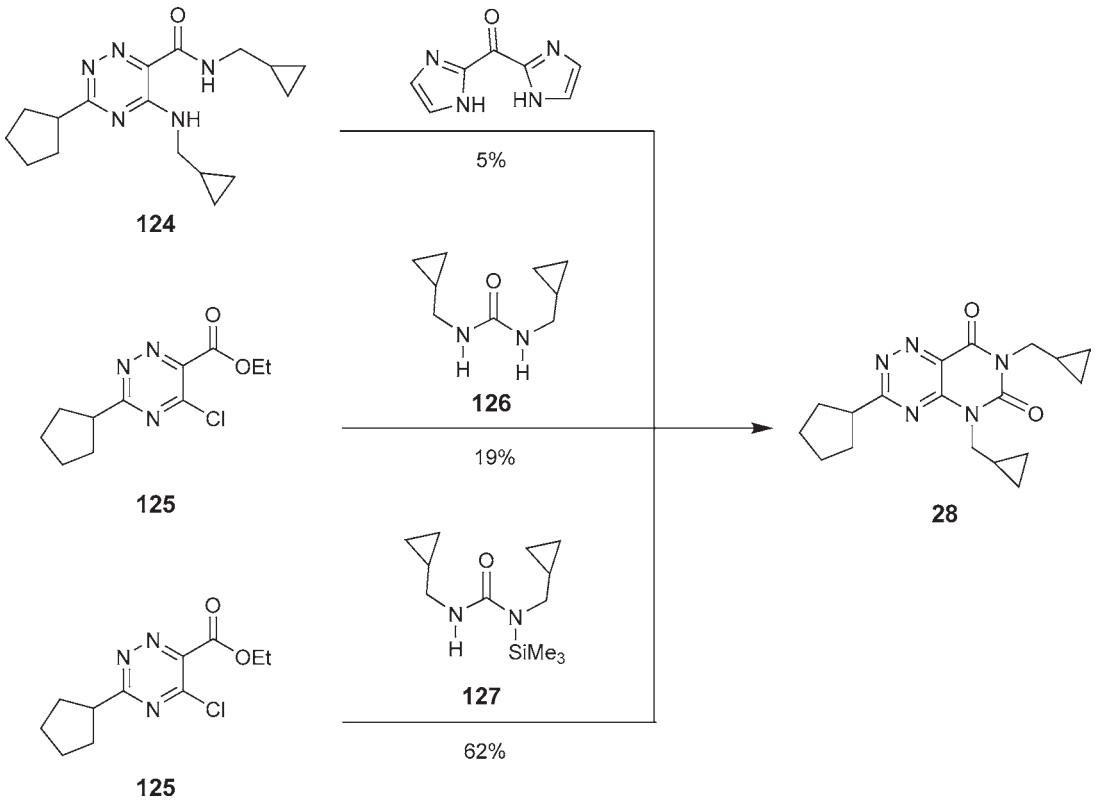
5-amino-1,2,4-triazine-6-carboxamide **124** with 1,1′-carbonyldiimidazole generated only trace amounts of the desired compound (**Scheme 20**). Reaction of the 5-chloro-1,2,4-triazine-6-carboxylate **125** with urea **126** was only slightly more successful. However, reaction of the urea **126** with trimethylsilyl chloride gave the silylurea **127** which reacted smoothly with compound **125** to afford the desired isofervenulin analogue **28**. It is of note that the latter reaction was N-selective and that no oxazine side products were formed. The deprotonation of silylurea **127** with *n*-BuLi followed by the addition of compound **125** resulted in improved yields of compound **28**, which was formed in 76% yield under these conditions <2004JHC637>.



Scheme 18

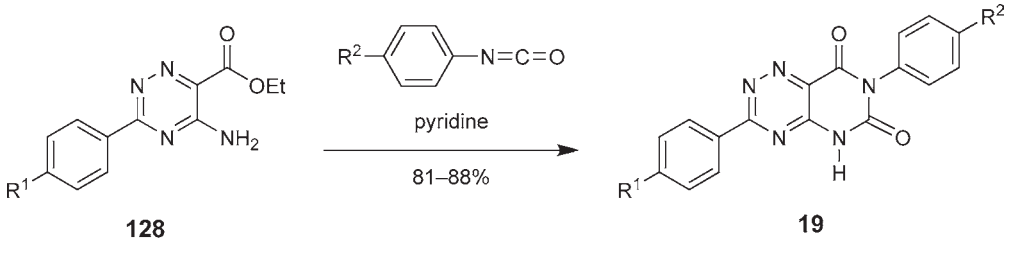


Scheme 19



Scheme 20

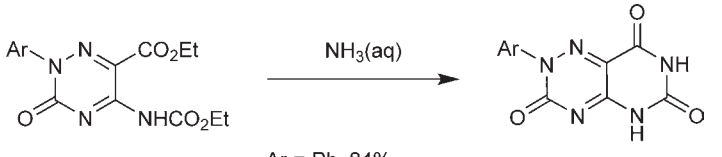
The pyrimido[4,5-*e*]-1,2,4-triazines **19** were synthesized from the 5-amino-1,2,4-triazine-6-carboxylate **128** upon reaction with an aryl isocyanate in the presence of pyridine, with the appropriate aryl isocyanate acting as a source of two of the ring atoms, as shown in Equation (18) <2003ARK98>.



(18)

R^1 = Cl, OMe; R^2 = H, Cl

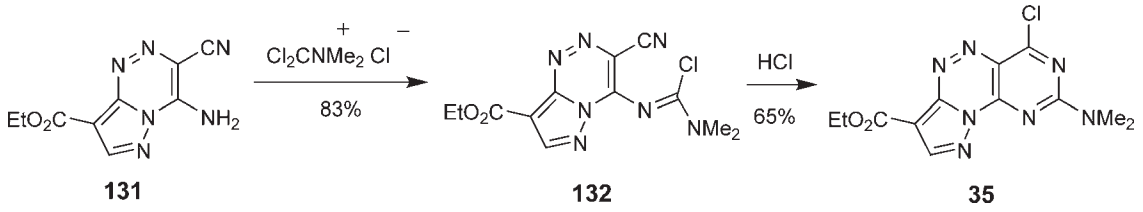
The ethoxycarbonylamino-1,2,4-carboxylates **129** react with aqueous ammonia to give a selection of 2-aryl pyrimido[4,5-*e*]-1,2,4-triazine triones **130** as shown in Equation (19) <2006ARK68>.



Ar = Ph, 84%
Ar = 4-$MeOC_6H_4$, 86%
Ar = 4-ClC_6H_4, 79%
Ar = 4-$O_2NC_6H_4$, 74%

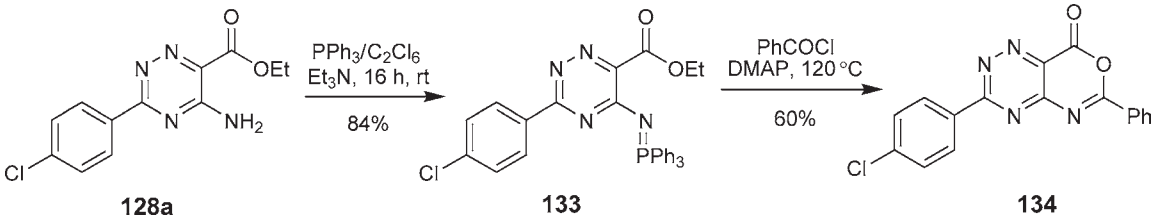
(19)

The pyrazolo-fused pyrimido[4,5-*e*]-1,2,4-triazine **35** was synthesized using the 5-amino-6-cyano triazine **131** (**Scheme 21**) as the precursor. Reaction with phosgeniminium chloride gave the amide halide intermediate **132** which in turn produced the pyrimido[4,5-*e*]-1,2,4-triazine **35** upon treatment with gaseous hydrogen chloride <1996T3037>.



Scheme 21

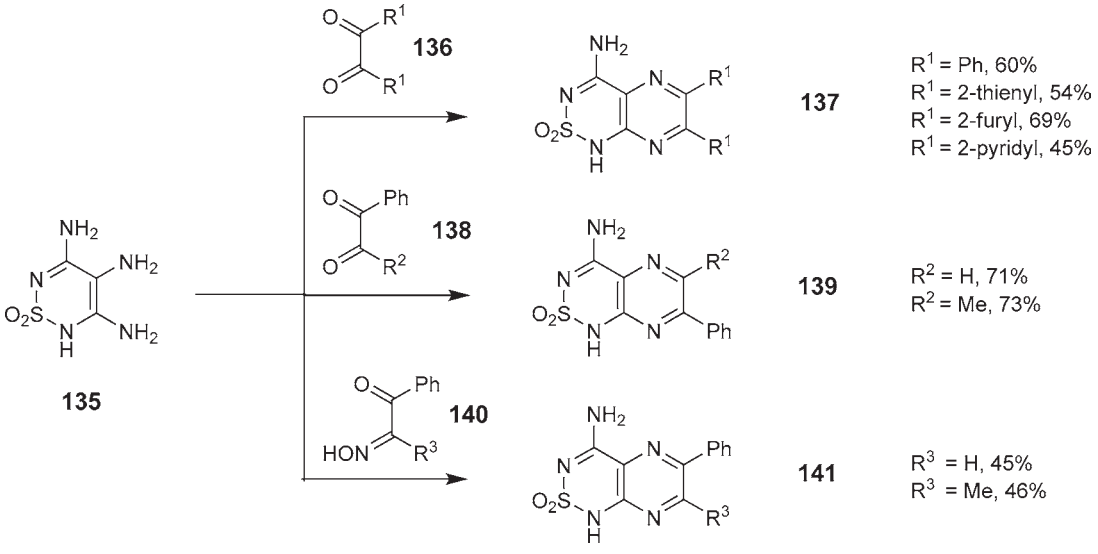
Only one nonazapteridine (pyrimido[4,5-*e*]-1,2,4-triazine) derivative has been synthesized by the methods covered in this section. Thus, the reaction of the 5-amino-1,2,4-triazine-6-carboxylate **128a** with triphenylphosphine/hexachloroethane produced the iminophosphorane **133** which underwent aza-Wittig reaction in hot benzoyl chloride in the presence of catalytic 4-dimethylaminopyridine (DMAP) to give the oxazino[6,5-*e*]-1,2,4-triazine **134** as shown in **Scheme 22** <2003ARK98>, which, as discussed in Section 10.20.1, constitutes an addition to the 44 ring systems covered by the remit of this chapter that were known at the time of CHEC-II(1996) <1996CHEC-II(7)785>.



Scheme 22

10.20.9.2.2(iii) Two heteroatoms disposed 1,4 to the ring junction

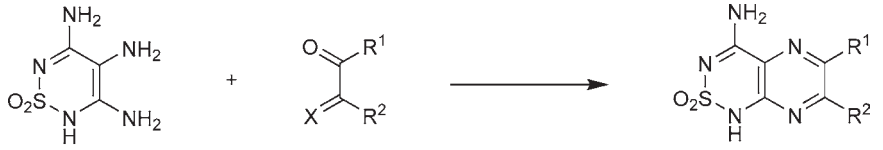
Condensation reaction between the 3,4,5-triamino-1,2,6-thiadiazine **135** and a symmetrical 1,2-diketone **136** (**Scheme 23**) gave the pyrazino[2,3-*e*][1,2,6]thiadiazines **137**. When the dicarbonyl used was the nonsymmetric



Scheme 23

1-phenyl-1,2-propanedione or phenylglyoxal **138** (R^2 = Me or H), the 7-phenyl isomers **139** were isolated. Interestingly, the corresponding 6-phenyl isomers **141** could be isolated from the reaction of the appropriate hydroxyiminoketones **140** with 3,4,5-triamino-1,2,6-thiadiazine **135** <1999JME1698>.

The same researchers later extended the scope of the process and Equation (20) and **Table 8** show a typical range of pyrazino[2,3-*c*][1,2,6]thiadiazines **142** that is available from thiadiazine **135** using these methods <2000JME4219>.

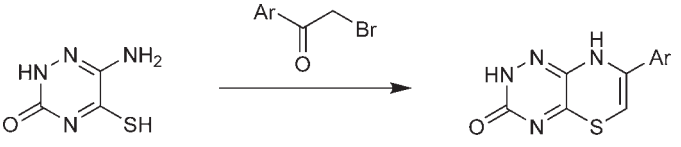


135 **142** (20)

Table 8 Pyrazino[2,3-*c*][1,2,6]thiadiazines **142** from thiadiazine **135** (see Equation 20)

R^1	R^2	X	*Yield* (%) *of* **142** *from* **135**
CH_2–$(CH_2)_3$–CH_2		O	57
Me	Pr^i	O	53
Me	Bu	O	73
Me	H	NOH	91
Et	H	NOH	42
Pr	H	NOH	80
Pr^i	H	NOH	71
Bu^t	H	NOH	75

The reaction of 5-mercapto-6-amino-1,2,4-triazin-3-one **143** with α-haloketones gives the thiazino[2,3-*e*]-1,2,4-triazines **144** shown in Equation (21), although the publication lacks further detail (yields, for example, are not given) and focuses upon the synthesis of other heterocyclic systems <2001PS205>.



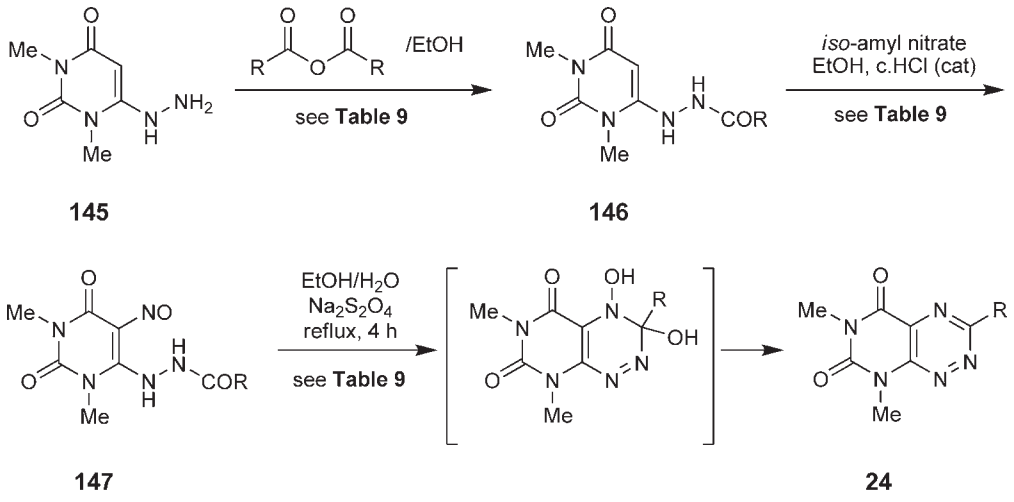
143 **144** (21)

10.20.9.2.3 Three heteroatoms in the ring being formed

10.20.9.2.3(i) Three heteroatoms disposed 1,2,4 to the ring junction

The classic nitrosative cyclization <1996CHEC-II(7)785> of 4-hydrazino uracil derivatives has continued to be the method of choice for the synthesis of the pyrimido[5,4-*e*]-1,2,4-triazine (7-azapteridine) nucleus that is present in the toxoflavin and fervenulin natural products and their analogues. Thus, Pfleiderer and co-workers have synthesized a range of 3-substituted fervenulin derivatives **24** starting from 4-hydrazino-1,3-dimethyluracil **145**, using the method shown in **Scheme 24**. The reaction of hydrazine **145** with anhydrides produced the acylated derivatives **146** which underwent nitrosation at the 5-position to give the 5-nitroso uracils **147**. Reductive cyclization and air oxidation produced the desired fervenulin analogues **24** in the yields shown in the accompanying **Table 9** <1996JHC949>.

The benzylidenehydrazino-substituted uracils **148** can act as starting materials for the synthesis of either the 3-phenyltoxoflavins **14** or the 8-demethyl 3-phenylfervenulin derivatives **29**, depending upon whether the hydrazino uracil starting material **148** has an R^2 substituent or not, as shown in Equations (22) and (23) <1997H(45)643, 2001J(P1)130>.



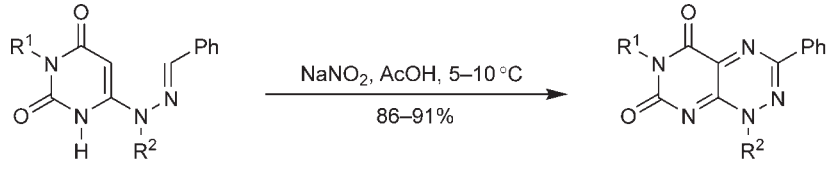
145 **146** **147** **24**

a: R = Et; **b**: R = CH_2Ph; **c**: R = Pr^i; **d**, R = Bu^t

Scheme 24

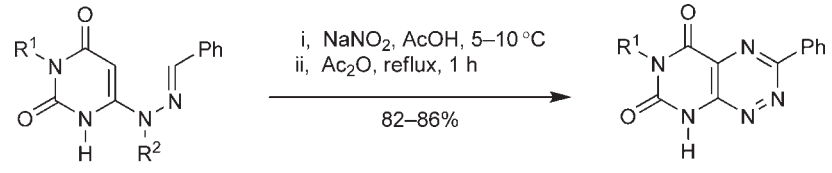
Table 9 3-Substituted fervenulin derivatives (**24**) from hydrazine (**145**) (**Scheme 24**)

R	*Yield* (%) **146**	*Yield* (%) **147**	*Yield* (%) **24**	*Reference*
Et	64	89	60	1996JHC949
CH_2Ph	77	92	40	1996JHC949
Pr^i	87	91	43	1996JHC949
Bu^t	75	99	25	1996JHC949



(22)

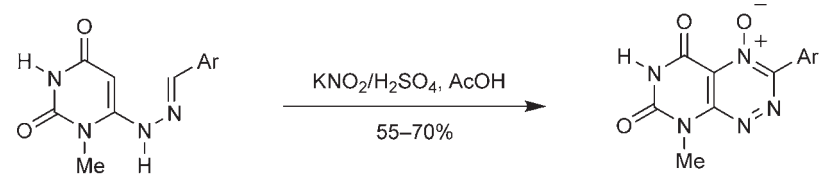
148 **14a**: $R^1 = R^2$ = Me
b: R^1 = Ph, R^2 = Me



(23)

148: R^2 = H **29**: R^1 = Me or Ph

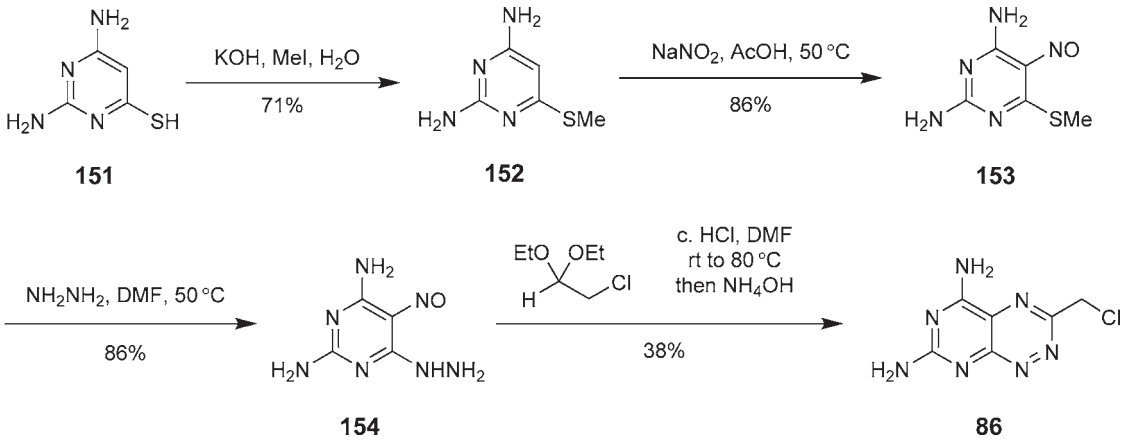
A slight variation on this theme, shown in Equation (24), has allowed access to the 6-demethylfervenulin-4-oxides **150** starting from benzylidenehydrazino uracils **149** <1999M819>.



(24)

149 **150**
Ar = C_6H_5 or 4-ClC_6H_4

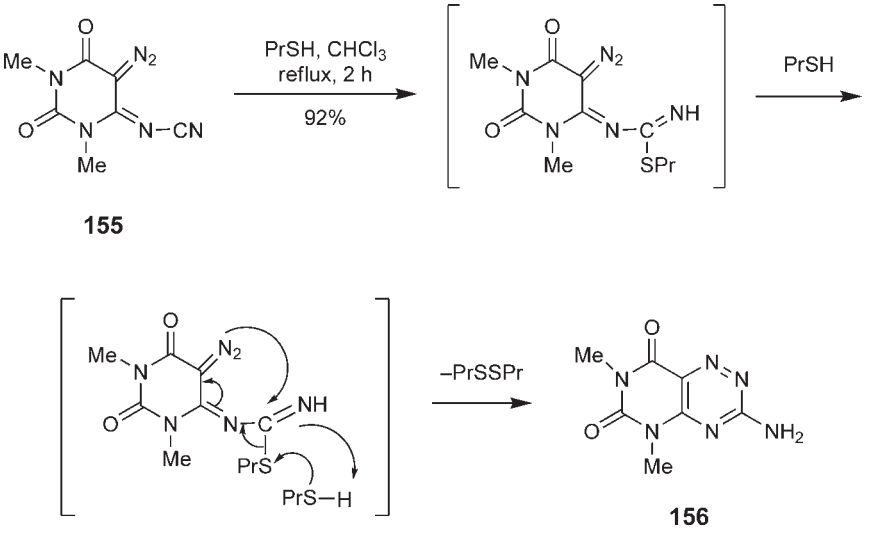
The chloromethylpyrimido[5,4-*e*]-1,2,4-triazine **86** is an extremely versatile starting material (see Section 10.20.7.2, Equation 12) and was synthesized from the commercially available thiol **151** as shown in **Scheme 25**. Thus, *S*-methylation of compound **151** gave the sulfide **152**, which was nitrosated to allow access to the nitroso-thiomethyl derivative **153**. Nucleophilic substitution of the thiomethyl group by hydrazine gave the cyclization precursor **154**, which underwent cyclization with chloroacetaldehyde diethyl acetal under acidic conditions to give the chloromethylpyrimido[5,4-*e*]-1,2,4-triazine **86** after workup with aqueous ammonia <2003BML2895>.



151 **152** **153** **154** **86**

Scheme 25

The reaction of the cyanoimino-5-diazopyrimidine 2,4-dione **155** with a large excess of propanethiol gave the 3-aminopyrimido[4,5-*e*]-1,2,4-triazine 6,8-dione (6-azapteridine) **156** as shown in **Scheme 26**. The mechanistic pathway is also shown in **Scheme 26** and relies upon the addition of propanethiol to the cyanoimino group followed by propanethiol-mediated cyclization and loss of a disulfide <2001JHC141>.

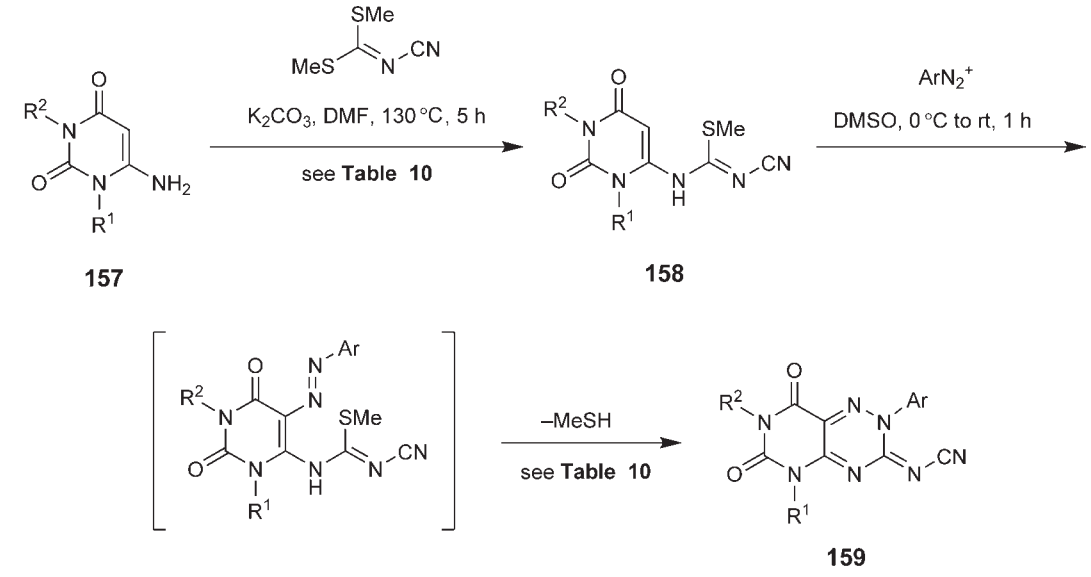


155 **156**

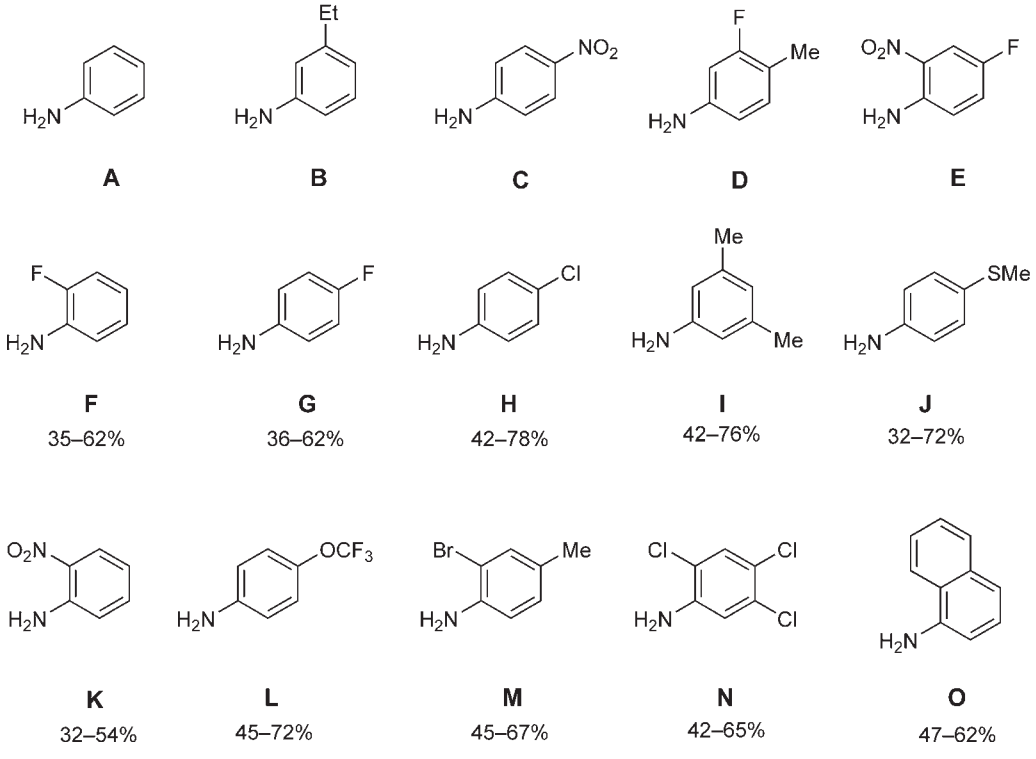
Scheme 26

The reaction of 6-aminouracils **157** with dimethyl *N*-cyanodithioimidocarbonate, shown in **Scheme 27**, gave the intermediates **158** which on coupling to phenyldiazonium salt, followed by elimination of methanethiol, gave the 5,7-disubstituted-2-phenylpyrimido[4,5-*e*]-1,2,4-triazines **159** (Ar = Ph) in the isolated yields shown in **Table 10** (entries

1–6). The authors also applied this procedure to a 90-member combinatorial library of 5,7-disubstituted-2-aryl-pyrimidotriazines **159** using the same set of 1-cyano-3-(pyrimidin-4-ylamino)-2-methylisothiourea intermediates **158** (see **Table 10**/**Scheme 27**) with aryldiazonium salts derived from the range of arylamines **A–O** that is shown in **Scheme 27**. Isolated yields are shown in **Table 10** for indicative amines **A–E**, and yield ranges are indicated in **Scheme 27** for amines **F–O** <2004TL9319>.



ArN_2^+ from:

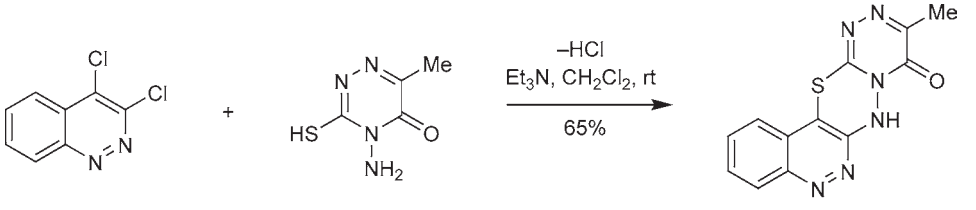


Scheme 27

Table 10 Pyrimido[4,5-*e*][1,2,4]triazines **159** from 6-aminouracils **157** (Scheme 27)

R^1	R^2	*Yield (%) of* **158**	*Yield (%) of* **159**	ArN_2^+ *from amine*
Me	Me	77	77	**A**
Bn	Bn	86	70	**A**
Ph	Me	72	65	**A**
Ph	4-$MeOC_6H_4CH_2$	73	45	**A**
Bn	Me	83	69	**A**
Me	H	92	61	**A**
Me	Me		72	**B**
Bn	Bn		68	**B**
Ph	Me		65	**B**
Ph	4-$MeOC_6H_4CH_2$		52	**B**
Bn	Me		61	**B**
Me	H		47	**B**
Me	Me		65	**C**
Bn	Bn		85	**C**
Ph	Me		52	**C**
Ph	4-$MeOC_6H_4CH_2$		48	**C**
Bn	Me		52	**C**
Me	H		46	**C**
Me	Me		42	**D**
Bn	Bn		50	**D**
Ph	Me		65	**D**
Ph	4-$MeOC_6H_4CH_2$		65	**D**
Bn	Me		42	**D**
Me	H		43	**D**
Me	Me		54	**E**
Bn	Bn		72	**E**
Ph	Me		65	**E**
Ph	4-$MeOC_6H_4CH_2$		62	**E**
Bn	Me		44	**E**
Me	H		42	**E**

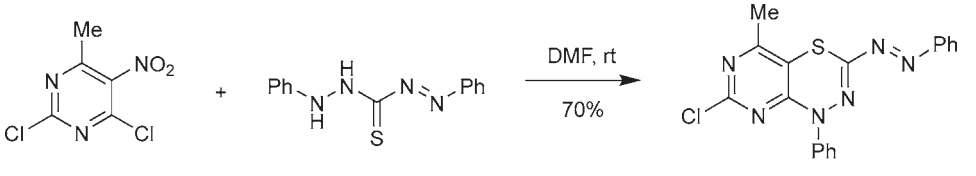
In common with most other sections in this chapter, progress in areas other than the azapteridines is limited to only a few publications. Thus, as shown in Equation (25), the amino-(thioxo)-triazine **161** acts as the 3-heteroatom component and undergoes a regiospecific cyclocondensation reaction with the dichlorocinnoline **160** to give the condensed pyridazino[3,4-*e*]-1,3,4-thiadiazine tetracycle **162** via loss of two units of HCl <2000PS315>.



(25)

160 **161** **162**

The reaction of 2,6-dichloro-3-methyl-5-nitropyrimidine **163** with dithizone **164** resulted in the formation of the 6-chloropyrimido[4,5-*e*]-1,3,4-thiadiazine **43** shown in Equation (26) which, as discussed in Section 10.20.5.4 (Equation 7), is a useful substrate for subsequent nucleophilic substitution <2005PS2477, 2004HCO335, 1997IJC223>.

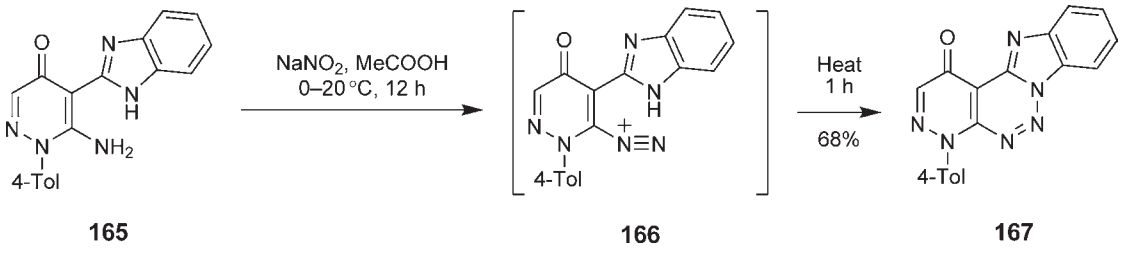


(26)

163 **164** **43**

10.20.9.2.3(ii) Three heteroatoms disposed 1,2,3 to the ring junction

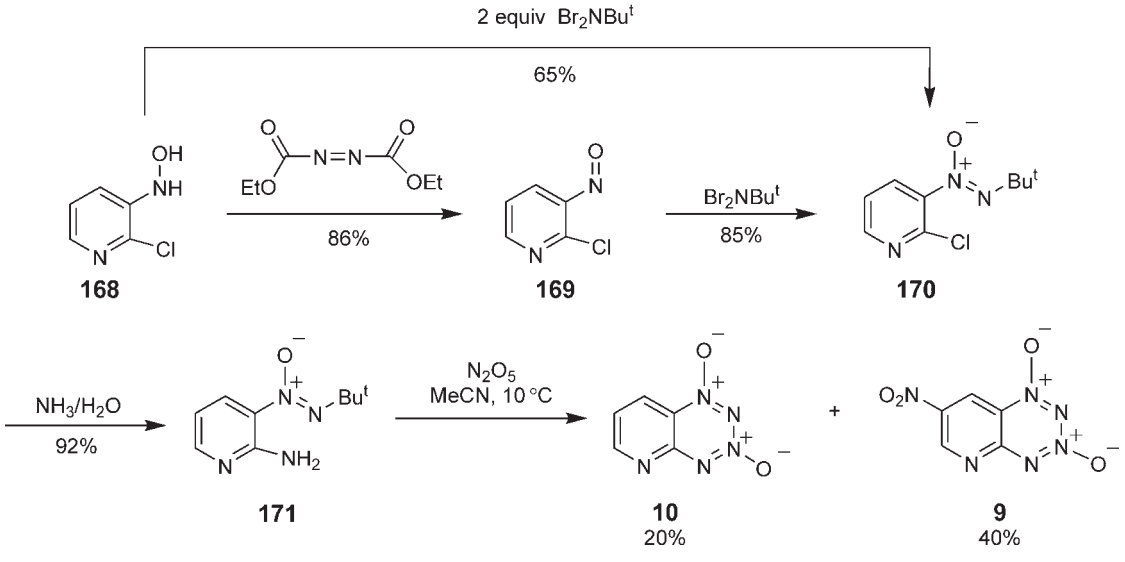
Only one new synthesis has appeared in this category since those reported in CHEC-II(1996) <1996CHEC-II(7)785>, and the reader is advised to consult this review of earlier work in order to gain an understanding of this subject from the early 1960s to 1995. One of the routes described therein is a [5+1] component synthesis in which nitrous acid provides the single heteroatom of a pyrimidotriazine. This type of approach has since been employed in the synthesis of the benzimidazo-fused pyridazino[4,3-*e*]-1,2,3-triazine **167**, which was accessed from the 6-amino-4-pyridazinone **165** via the intermediate diazonium salt **166** as shown in **Scheme 28** <1997CHE749, 1997KGS853>.



Scheme 28

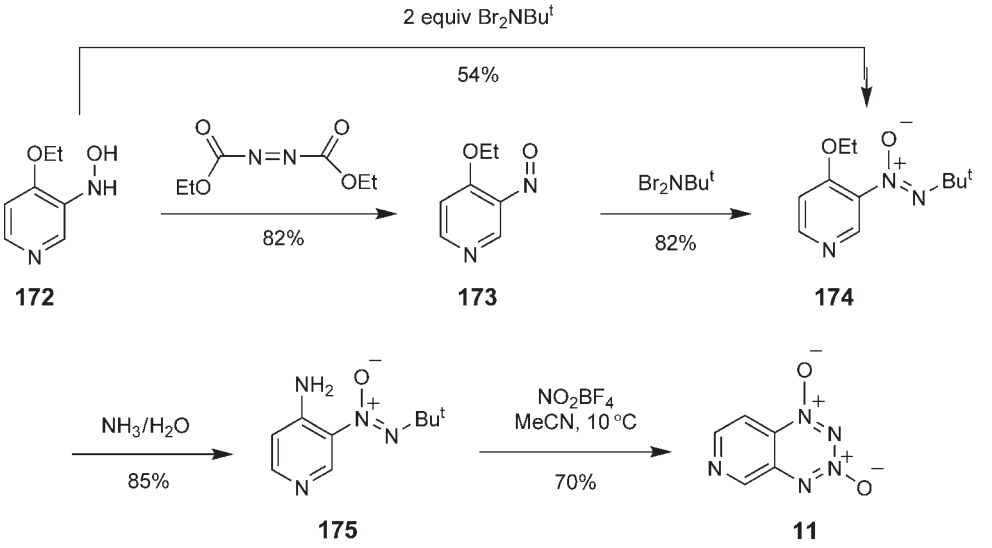
10.20.9.2.4 Four heteroatoms in the ring being formed

This type of heterocyclic system, and hence this type of synthesis, was unknown at the time of CHEC-II(1996) <1996CHEC-II(7)785>. Since then, two new closely related systems have been discovered. Thus, the pyrido[2,3-*e*]-1,2,3,4-tetrazine 1,3-dioxides **9** and **10** were synthesized by the route shown in **Scheme 29**. In this process, the hydroxylamine **168** was oxidized with ethyl azodicarboxylate to give the nitroso compound **169**. The reaction of this compound with *N*,*N*-dibromo(*tert*-butyl)amine allowed access to the 3-(*tert*-butyl-*NNO*-azoxy)-2-chloropyridine **170**, which underwent smooth chlorine atom displacement with aqueous ammonia (autoclave, 150–180 °C) to give the corresponding 2-amino compound **171**. Finally, treatment of the 2-amino compound **171** with nitric anhydride furnished the pyridotetrazines **9** and **10**, where the former is the result of over-nitration. It is of interest to note that the direct treatment of the hydroxylamine **168** with 2 equiv of *N*,*N*-dibromo(*tert*-butyl)amine gave compound **170** directly. Also of interest is the fact that the final nitration step is only successful with nitric anhydride, and that all attempts to use nitronium tetrafluoroborate failed <2004RCB2577>.



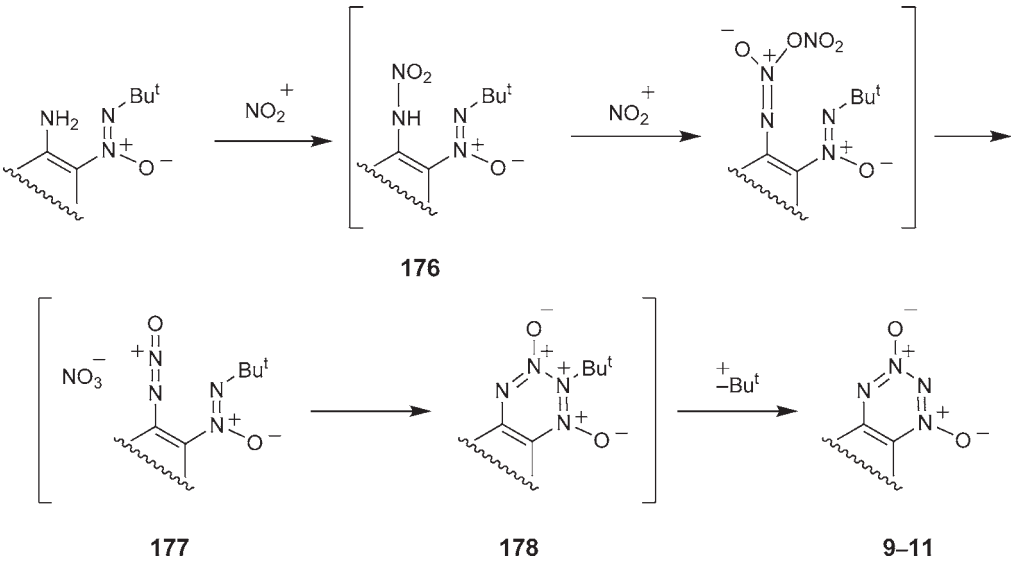
Scheme 29

The related pyrido[3,4-*e*]-1,2,3,4-tetrazine 2,4-dioxide **11** was accessed using a similar sequence of reactions, starting with the hydroxylamine **172** as shown in **Scheme 30**. The key differences are that the 4-amino derivative **175** was accessed through displacement of an ethoxy group from the intermediate **174** rather than by the chlorine displacement used above, and that ring closure this time could only be achieved with nitronium tetrafluoroborate. Nitric anhydride, in contrast to the reaction shown in **Scheme 29**, gave no product <2004RCB2577>.



Scheme 30

The mechanism of these processes is worthy of mention, and is summarized in **Scheme 31**. The amine is nitrated and is hence transformed into a *N*-nitroamine **176**, which then undergoes further nitration onto the *N*-nitroamine oxygen followed by dissociation into the oxodiazonium intermediate **177**. Intermediate **177** then behaves as the electrophile for the *tert*-butyl-*NNO*-azoxy group, resulting in the formation of the intermediate *tert*-butyltetrazine **178**. Loss of the *tert*-butyl cation then gives the isolated tetrazines **9–11** <2004RCB2577, 2004CRV2601, 2002EJO2342>.



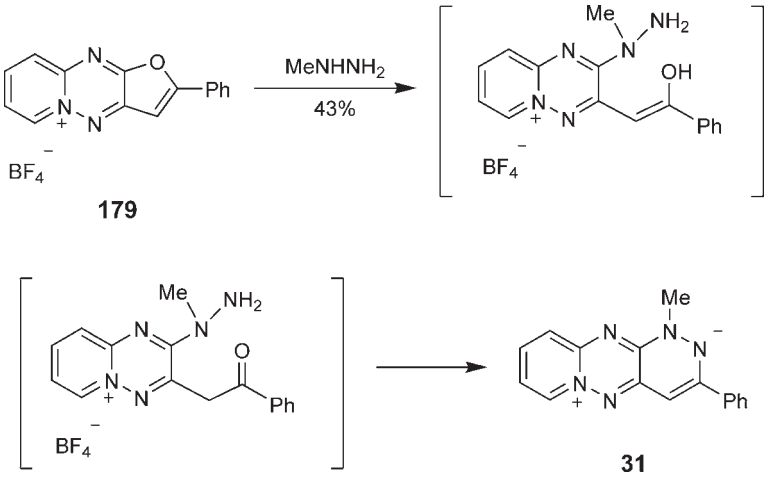
Scheme 31

10.20.9.3 Syntheses from Acyclic Precursors

There are no further examples of syntheses in this class, and the reader is again referred to the very few examples that are reported in CHEC-II(1996) <1996CHEC-II(7)785>.

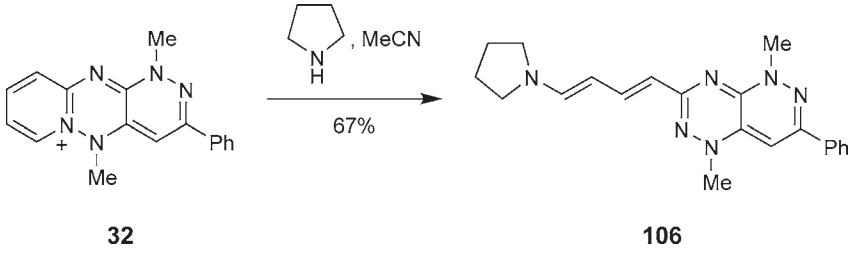
10.20.9.4 Syntheses from Other Heterobicyclic and Related Systems

The arylfuro-fused pyrido[1,2-*b*][1,2,4]triazinium salt **179** undergoes reaction with methyl hydrazine to give the zwitterionic pyrido-fused pyridazino[3,4-*e*][1,2,4]triazine **31** as shown in **Scheme 32** <2003ARK62, 1997CC757>. Nucleophilic attack of the hydrazine at the bridgehead results in the elimination of an enol that then allows ring closure via attack of the other hydrazine nitrogen onto the carbonyl of the keto tautomer.



Scheme 32

Methylation of compound **31** from **Scheme 32** gives the N-methylated analogue **32** (see Section 10.20.5.3), shown in Equation (27), which is then able to function as a fused heterocyclic precursor for the synthesis of the pyridazino[3,4-*e*][1,2,4]triazine **106** after reaction with pyrrolidine <2003ARK62>.



(27)

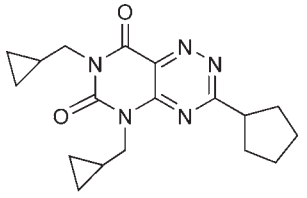
10.20.10 Important Compounds and Applications

10.20.10.1 Introduction

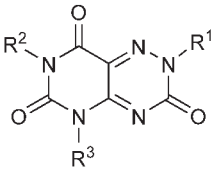
Three classes of compound dominate this section, namely the 6-azapteridines or pyrimido[4,5-*e*][1,2,4]triazines, the 7-azapteridines or pyrimido[5,4-*e*][1,2,4]triazines, and the pyrazinothiadiazines, particularly the pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides. None of the other systems that have appeared in this chapter show important applications.

10.20.10.2 The 6-Azapteridines

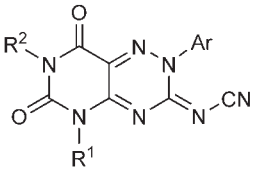
These are the pyrimido[4,5-*e*][1,2,4]triazines and have been of some interest as aza-analogues of the naturally occurring 7-azapteridines. During the studies that these compounds have consequentially attracted, it has been found that compound **28** is of interest as a potential anti-anxiety agent that is under clinical evaluation <2004JHC637>. The 6-azapteridines have also attracted attention because of antiviral activity <2004TL9319, 2006ARK68> and have attracted general interest due to their structural similarity to the biological active pteridines and purines <2006ARK68, 2004TL9319, 2003CCC965, 2003ARK98>. As part of one such study <2004TL9319>, the 'urea' functionality present in the generalized pyrimido[4,5-*e*][1,2,4]triazinone **180** was replaced with a cyanoguanidine, a common method for increasing biological activity <2004TL9319, 2002BML601, 2002JME4513>, giving the pyrimido[4,5-*e*][1,2,4]triazin-3-ylidenecyanamides **159**, which were prepared as a 90-member combinatorial library. In another study, the 2-aryl-substituted pyrimido[4,5-*e*][1,2,4]triazines **130** were tested for cytotoxicity against the human breast adenocarcinoma cell line *MCF7*, but showed activity (IC_{50}) only in the range 70–126 $\mu mol\,l^{-1}$ <2006ARK68>.



28

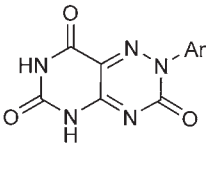


180



159

(see **Table 10** and **Scheme 27**)



130

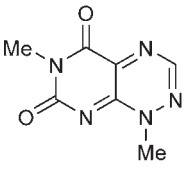
Ar = Ph
Ar = 4-$MeOC_6H_4$
Ar = 4-ClC_6H_4
Ar = 4-$O_2NC_6H_4$

10.20.10.3 The 7-Azapteridines

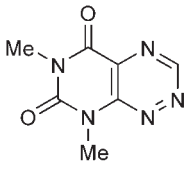
These are the pyrimido[5,4-*e*][1,2,4]triazines and have attracted great attention due to biological interest in the natural products toxoflavin **7** and fervenulin **8** and their analogues. Aspects of these systems were covered in CHEC-II(1996) <1996CHEC-II(7)785>. Since this time, toxoflavin has attracted further attention due to its occurrence as a toxic contaminant produced by several microorganisms responsible for fatal food poisonings in several fermented food types, including sour fermented corn flour in northeastern China <1995MI600>, the cultivated edible white fungus *Tremella fuciformis* <1995MI600, 1999MI63>, and fermented coconut food (bongkrek) in Indonesia <1999MI63, 1995MI600>. In these cases *Pseudomonas cocovenenans* was originally identified as the responsible bacterium, although this was later transferred to the genus *Burkholderia* on the basis of phenotypic and genetic studies <1995MI600>. Toxoflavin has been isolated from *Burkholderia cocovenenans* <1999MI63>, *Burkholderia glumae* <2003MI890, 2004MI921>, and *Burkholderia gladioli* <1997MI33>. Toxoflavin and fervenulin have been recognized as bacterial disease phytotoxins produced by *B. glumae* and *B. gladioli* causing inhibition of seedling elongation and chlorosis on rice leaves <1997MI33>. Toxoflavin produced by *B. glumae* has also been identified as a causative phytotoxic agent in rice grain rot and in bacterial wilt in several other species, whereby it was shown that toxoflavin-deficient mutants failed to cause wilt <2003MI890>. A later publication <2004MI921> detailed the fact that toxoflavin is able to act as an active electron carrier between nicotinamide adenosine dinucleotide (NADH) and oxygen and can produce hydrogen peroxide and bypass the cytochrome system, perhaps explaining not only the herbicidal activities previously attributed to toxoflavin <1996CHEC-II(7)785>, but also the attributed antibacterial and antifungal activities. The same paper proposed a working model for the regulation of toxoflavin biosynthesis and transport, and produced the first evidence that quorum sensing is involved in phytotoxin production <2004MI921>.

Given the interest detailed above, it is no surprise that pyrimido[5,4-*e*][1,2,4]triazines have attracted attention as lead substances for future investigation. Of particular interest are toxoflavin **7**, fervenulin **8**, 2-methylfervenulone (MSD 92) **181**, reumycin (demethylfervenulin) **182**, and pyrizinostatin **183** which display antibiotic activity <2000H(52)811, 1999M819, 1996JHC949>, although their relatively high toxicity has prevented clinical use. This toxicity has been ascribed to the Michael-type reactivity of the ring junction 4a-position <1995JOC7063, 2000JNP1641, 2004MI349>, and the ease of reduction of the conjugated system <2004MI349, 2003BML2895,

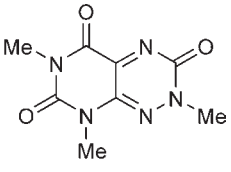
1995JOC7063>, among other factors. Toxoflavin and its 3- and 6-substituted derivatives have been shown to possess potent antiviral and potent oral or parenteral antitumor activities <2001J(P1)130, 1997H(45)643, 1997JPP09255681>, as well as interesting herbicidal properties <1998JPP1075807>. Interestingly, part of the same work claims that, within the 3-phenyl series, 1-alkyltoxoflavins **14** are more biologically active than the 8-alkylfervenulins **15** <2001J(P1)130, 1997H(45)643>. The reduced derivatives **184** have also been found to possess antitumor activity <1997JPP09255681>. In the context of cancer therapy, it is of interest to note that the 7-azapteridine ring system has been identified as a Polo-like kinase 1 (PLK1) inhibitory scaffold <2004MI349>. These investigations found that substituted toxoflavins were more potent PLK inhibitors than the fervenulins and showed potent (low micromolar) antiproliferative activity toward a human colon cancer cell line that correlated well with PLK1 inhibitory activity. A typical example is the toxoflavin analogue **185** with an IC_{50} for PLK1 of 1.6 nM and a GI_{50} against human colon cancer cell line SW620 of 0.91 μM <2004MI349>.



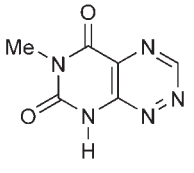
7



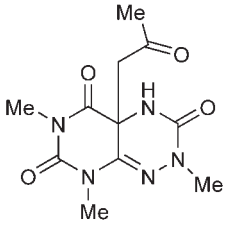
8



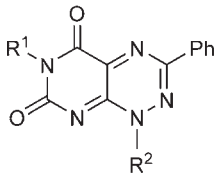
181



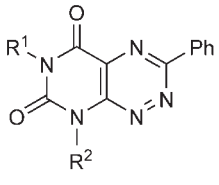
182



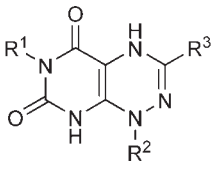
183



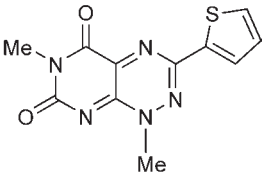
14



15



184

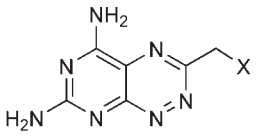


185

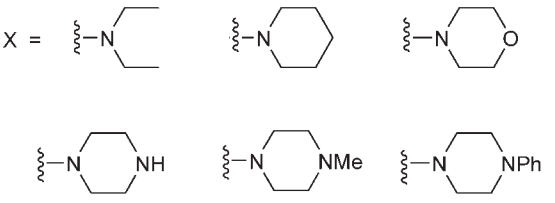
Toxoflavin **7** has been shown to contract blood vessels via its effect on Ca^{2+} channels, with the vasocontractor effect dependent upon extracellular Ca^{2+}. The effect was found to be dependent upon the contractile status of the vascular tissue. The possibility of using toxoflavin as an opener of calcium channels is suggested by this work <1996BJP293>.

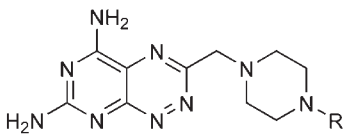
2-Methylfervenulone (MSD 92) **181** was identified as a lead in a high throughput screen for inhibitors of Src-homology 2 (SH2) domain mediated protein–protein interactions <1995JOC7063>.

Protein tyrosine phosphatases (PTPases) and kinases are responsible for the regulation of the phosphorylation/dephosphorylation of proteins involved in several human disease types and are hence targets for therapeutic intervention. It is of some interest to note, therefore, that 2-methylfervenulone (MSD 92) **181** has been identified as a novel protein tyrosine phosphatase inhibitor <2000JNP1641>. PTPases known as PTB1B and PTPα are believed to play a role in the regulation of the insulin receptor, possibly via dephosphorylation of its active form, and small molecule inhibitors of these PTPases are of some importance in the search for treatments for type 2 diabetes and obesity. It is significant that the pyrimido[5,4-*e*][1,2,4]triazine-5,7-diamines **87** and **104** constitute a new and novel class of orally active *in vitro* PTPase inhibitor with the ability, in the cases of compound **104a** and **104b**, to lower blood glucose levels upon oral administration, making them of great potential as hypoglycemic reagents and antidiabetic agents <2003BML2895>.

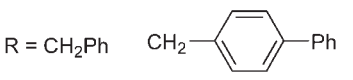


87



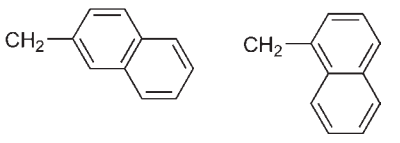


104



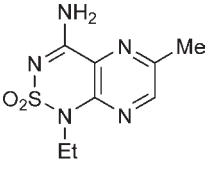
104a

104b



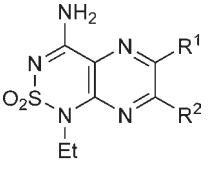
10.20.10.4 The Pyrazinothiadiazines

4-Amino-1-ethyl-6-methylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide **186**, known as PF-904, was found to inhibit bronchoconstriction caused by a number of spasmogens *in vivo* and to prevent airway hyperreactivity and reduce bronchospasm, eosinophil lung infiltration, and airway microvascular leakage. *In vitro* studies revealed compound **186** to be a relaxant of human bronchus and an inhibitor of human bronchial cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP) phosphodiesterase. These results suggest compound **186** as an antiasthma agent <1997EPH69>. A larger-scale study, including additional toxicological work, also identified compound **186** as the best bronchodilating agent from among a wide range of *N*1-substituted-4-amino pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides <2000JME4219>.



186

The 6- or 7-phenyl-substituted 1-ethyl-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides **187** were found to show significant platelet aggregation inhibition comparable to other antithrombotic agents. Strong evidence was found that this activity was due to interference with the platelet arachidonic acid pathway <1999JME1698>.



187: R^1 or R^2 = Ph

10.20.11 Further Developments

Recent work has demonstrated that the sodium nitrite mediated cyclization of a series of hydrazino uracil glycosides gives a range of toxoflavin glycosides together with their 4-oxide analogues, where the latter can be reduced to the former with hyposulfite. The method of cyclization is as discussed in Section 10.20.9.2.3(i) in Equations (22)–(24).

The toxoflavin glycosides that are so produced are potential prodrugs for antibody-directed enzyme tumor therapy <2007CAR1254>. A series of toxoflavin like compounds (azapteridines) have been identified as inhibitors of hepatitis C RNA-dependent RNA polymerase, a result of some interest given that the use of toxoflavins, as discussed in Section 10.20.10.3, has been limited by their toxicity <2007MI1>. Acyl homoserine lactone quorum sensing (see Section 10.20.10.3) and its implications in toxoflavin phytotoxin biosynthesis have been studied further, providing further information on the production and role of toxoflavin in diseased rice <2007MI4950>. Fervenulin, 2-methylfervenulin-3-one and their 4-*N*-oxides have been subject to a detailed study by X-ray diffraction, ^{1}H NMR and ^{13}C NMR spectroscopy, with the same workers undertaking an in depth study of their chemical reactivity to oxidation, chlorination, alkylation, and nucleophilic attack <2006KFZ49>. Later work established the outcome of the reaction of the same three species with indoles <2007KFZ49>.

References

1995JOC4919 A. Kotschy, G. Hajós, and A. Messmer, *J. Org. Chem.*, 1995, **60**, 4919.
1995JOC7063 M. M. Mehrotra, D. D. Sternbach, R. D. Rutkowske, and P. L. Feldman, *J. Org. Chem.*, 1995, **60**, 7063.
1995MI600 N. Zhao, C. Qu, E. Wang, and W. Chen, *Int. J. Syst. Bacteriol.*, 1995, **45**, 600.
1996CHECII(7)785 P. H. Doyle; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 785.
1996BJP293 Z. Wang, M. Ma, and R. Wang, *Br. J. Pharmacol.*, 1996, **117**, 293.
1996JHC949 S. Werner-Simon and W. Pfleiderer, *J. Heterocycl. Chem.*, 1996, **33**, 949.
1996T3037 J. M. Quintela, M. J. Moreira, and C. Peinador, *Tetrahedron*, 1996, **52**, 3037.
1997EPH69 J. Cortijo, M. Martí-Cabrera, L. Berto, F. Antón, E. Carrasco, M. Grau, and E. J. Morcillo, *Eur. J. Pharmacol.*, 1997, **333**, 69.
1997CC757 Z. Riedl, G. Hajós, A. Messmer, A. Rockenbauer, L. Korecz, G. Kollenz, W. M. F. Fabian, K. Peters, and E. M. Peters, *J. Chem. Soc., Chem. Commun.*, 1997, 757.
1997CHE749 Yu. M. Volovenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 749.
1997H(45)643 T. Nagamatsu and H. Yamasaki, *Heterocycles*, 1997, **45**, 643.
1997IJC223 M. Rahimzadeh, M. M. Heravi, and A. Malekan, *Indian J. Chem.*, 1997, **6**, 223.
1997JPP09255681 T. Nagamatsu, Y. Yamagishi, and F. Yoneda, *Jpn. Kokai Tokkyo Koho*, JP 09 255681/1997 (1997) (*Chem. Abstr.*, 1997, **127**, 336635w).
1997KGS853 Yu. M. Volovenko, *Khim. Geterotsikl. Soedin.*, 1997, **33**, 853.
1997MI33 N. Furuya, K. Iiyama, N. Shiozaki, and N. Matsuyama, *J. Fac. Agric., Kyushu Univ.*, 1997, **42**, 33.
1998ACO285 G. Hajós and A. Kotschy, *Acta Chim. Slov.*, 1998, **45**, 285.
1998JA3295 M. D. Erion and M. R. Reddy, *J. Am. Chem. Soc.*, 1998, **120**, 3295.
1998J(P2)1889 N. Campillo, I. Alkorta, J. A. Páez, and P. Goya, *J. Chem. Soc., Perkin Trans. 2*, 1998, 1889.
1998JPP10175807 M. Ozasa. T. Amakusa, and T. Nagamatsu, *Jpn. Kokai Tokkyo Koho*, JP 10 175807/1998 (1998) (*Chem. Abstr.*, 1998, **129**, 64309x).
1999CHE376 V. P. Kruglenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 376.
1999JME1698 N. Campillo, C. García, P. Goya, J. A. Páez, E. Carrasco, and M. Grau, *J. Med. Chem.*, 1999, **42**, 1698.
1999KGS426 V. P. Kruglenko, *Khim. Geterotsikl. Soedin.*, 1999, **35**, 426.
1999M819 S. Youssif, *Monatsh. Chem.*, 1999, **130**, 819.
1999MI63 R. A. Garcia, J. H. Hotchkiss, and K. H. Steinkraus, *Food Addit. Contam.*, 1999, **16**, 63.
2000H(52)811 H. Koshino, Y. Kono, K. Yoneyama, and J. Uzawa, *Heterocycles*, 2000, **52**, 811.
2000JME4219 N. Campillo, C. García, P. Goya, I. Alkorta, and J. A. Páez, *J. Med. Chem.*, 2000, **43**, 4219.
2000JNP1641 H. Wang, K. L. Lim, S. L. Yeo, X. Xu, M. M. Sim, A. E. Ting, Y. Wing, S. Yee, Y. H. Tan, and C. J. Pallen, *J. Nat. Prod.*, 2000, **63**, 1641.
2000JOC7391 F. Terrier, M. Sebban, R. Goumont, J. C. Hallé, G. Moutiers, I. Cangelosi, and E. Buncel, *J. Org. Chem.*, 2000, **65**, 7391.
2000PS315 R. M. Abdel-Rahman, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **166**, 315.
2001JHC141 T. Ueda, N. Yatsuzuka, S.-i. Nagai, K. Okada, E. Takeichi, H. Segi, and J. Sakakibara, *J. Heterocycl. Chem.*, 2001, **38**, 141.
2001J(P1)130 T. Nagamatsu and H. Yamasaki, *J. Chem. Soc., Perkin Trans. 1*, 2001, 130.
2001PS205 M. M. Heravi, G. Rajabzadeh, M. Rahimizadeh, M. Bakavoli, and M. Ghassemzadeh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **170**, 205.
2002BML601 A. B. Cooper, C. L. Strickland, J. Wang, J. Desai, P. Kirschmeier, R. Patton, W. R. Bishop, P. C. Weber, and V. Girijavallabhan, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 601.
2002EJO2342 A. M. Churakov, O. Yu. Smirnov, S. L. Ioffe, Yu. A. Strelenko, and V. A. Tartakovsky, *Eur. J. Org. Chem.*, 2002, 2342.
2002JME4513 K. Matsuno, T. Nakajima, M. Ichimura, N. A. Giese, J.-C. Yu, N. A. Lokker, J. Ushiki, S.-I. Ide, S. Oda, and Y. Nomoto, *J. Med. Chem.*, 2002, **45**, 4513.
2003ARK62 Z. Riedl, G. Hajós, P. Kövér, and G. Kollenz, *ARKIVOC*, 2003, **v**, 62.
2003ARK98 H. Wamhoff and M. Tzanova, *ARKIVOC*, 2003, **ii**, 98.
2003BML2895 K. R. Guertin, L. Setti, L. Qi, R. M. Dunsden, B. W. Dymock, P. S. Jones, H. Overton, M. Taylor, G. Williams, J. A. Sergi, K. Wang, Y. Peng, M. Renzetti, R. Boyce, F. Falcioni, R. Garippa, and A. R. Olivier, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2895.
2003CCC965 H. Wamhoff and M. Tzanova, *Collect. Czech. Chem. Commun.*, 2003, **68**, 965.
2003HCA139 N. Campillo, J. A. Páez, and P. Goya, *Helv. Chim. Acta*, 2003, **86**, 139.
2003MI890 Y. Jeong, J. Kim, S. Kim, Y. Kang, T. Nagamatsu, and I. Hwang, *Plant Dis.*, 2003, **87**, 890.
2004CRV2601 A. M. Churakov and V. A. Tartakovsky, *Chem. Rev.*, 2004, **104**, 2601.

2004HCO335 M. M. Heravi, M. Bakherad, M. Rahimzadeh, M. Bakavoli, and M. Ghassemzadeh, *Heterocycl. Commun.*, 2004, **10**, 335.

2004JHC637 A. Bach, X. Jiang, J. McKenna, K. Prasad, O. Repič, and W.-C. Shieh, *J. Heterocycl. Chem.*, 2004, **41**, 637.

2004MI349 K. C. Goh, H. Wang, N. Yu, Y. Zhou, Y. Zheng, Z.-Y. Lim, K. Sangthongpitag, L. Fang, M. Du, X. Wang, A. B. Jefferson, J. Rose, B. Shamoon, C. Reinhard, B. Carte, M. Entzeroth, B.-H. Ni, M. L. Taylor, and W. Stünkel, *Drug Dev. Res.*, 2004, **62**, 349.

2004MI921 J. Kim, J.-G. Kim, Y. Kang, J. Y. Jang, G. J. Jog, J. Y. Lim, S. Kim, H. Suga, T. Nagamatsu, and I. Hwang, *Mol. Microbiol.*, 2004, **54**, 921.

2004RCB2577 V. A. Tartakovsky, I. E. Filatov, A. M. Churakov, S. L. Ioffe, Yu. A. Strelenko, V. S. Kuz'min, G. L. Rusinov, and K. I. Pashkevich, *Russ. Chem. Bull.*, 2004, **53**, 2577.

2004TL9319 I. Y. Lee, S. Y. Kim, J. Y. Lee, C.-M. Yu, D. H. Lee, and Y.-D. Gong, *Tetrahedron Lett.*, 2004, **45**, 9319.

2005PS2477 M. M. Heravi, M. Bakherad, M. Rahimzadeh, M. Bakavoli, and M. Ghassemzadeh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2005, **180**, 2477.

2006ARK68 J. Stýskala, J. Slouka, and V. Švecová, *ARKIVOC*, 2006, **i**, 68.

2006KFZ49 Yu. A. Azev, D. Gabel′, E. Lork, P. Brakman, and P. A. Gorchakov, *Khim. Farm. Zh.*, 2006, **40**, 49 (English translation: *Pharmaceut. Chem. J.*, 2006, **40**, 398).

2007CAR1254 S. Wang, D. Liu, X. Zhang, S. Li, Y. Sun, J. Li, Y. Zhou, and L. Zhang, *Carbohydr. Res.*, 2007, **342**, 1254.

2007KFZ49 Yu. A. Azev, E. Lork, P. Brakman, and P. A. Gorchakov, *Khim. Farm. Zh.*, 2007, **41**, 49 (English translation: *Pharmaceut. Chem. J.*, 2007, **41**, 109).

2007MI1 T. Middleton, H. B. Lim, D. Montgomery, T. Rockway, D. Liu, L. Klein, W. Qin, J. E. Harlan, W. M. Kati, and A. Molla, *Letters in Drug Design and Discovery*, 2007, **4**(1), 1.

2007MI4950 G. Devescovi, J. Bigirimana, G. Degrassi, L. Cabrio, J. J. LiPuma, J. Kim, I. Hwang, and V. Venturi, *Appl. Environ. Microbiol.*, 2007, **73**, 4950.

Biographical Sketch



Karl Hemming is currently senior lecturer in organic chemistry at the University of Huddersfield, UK. He completed his first degree and PhD (1993) at the University of Salford, with a PhD thesis under the supervision of Dr. R. K. Smalley on the topic of the synthesis and reactions of small ring nitrogen heterocycles. Postdoctoral studies were carried out with Prof. R. J. K. Taylor at the Universities of East Anglia and York. Karl then lectured in organic chemistry at the Universities of Bath and Hertfordshire before moving to Huddersfield in the summer of 2001. His current research interests include the chemistry and applications of the β-lactams and β-sultams, the synthesis of seven-membered heterocyclic rings of biological interest, and the development of new methodologies for the synthesis of bicyclic alkaloids.

10.19
Bicyclic 6-6 Systems: Other Four Heteroatoms 2:2

J. M. Herbert
Sanofi–Aventis, Alnwick, UK
© 2008 Elsevier Ltd. All rights reserved.

10.19.1 Introduction **979**
10.19.2 Diazinodiazines **979**
10.19.2.1 Pyridazinopyridazines **979**
10.19.2.1.1 Theoretical and experimental structural methods 979
10.19.2.1.2 Reactivity 980
10.19.2.1.3 Ring synthesis 981
10.19.2.1.4 Important compounds and applications 985
10.19.2.2 Pyrimidopyridazines **985**
10.19.2.2.1 Theoretical and experimental structural methods 985
10.19.2.2.2 Reactivity 987
10.19.2.2.3 Ring synthesis 994
10.19.2.2.4 Important compounds and applications 999
10.19.2.3 Pyrazinopyridazines **1000**
10.19.2.3.1 Theoretical and experimental structural methods 1000
10.19.2.3.2 Reactivity 1000
10.19.2.3.3 Ring synthesis 1003
10.19.2.3.4 Important compounds and applications 1006
10.19.2.4 Pyrimidopyrimidines **1006**
10.19.2.4.1 Theoretical and experimental structural methods 1006
10.19.2.4.2 Reactivity 1008
10.19.2.4.3 Ring synthesis 1020
10.19.2.4.4 Important compounds and applications 1034
10.19.2.5 Pyrazinopyrazines **1035**
10.19.2.5.1 Theoretical and experimental structural methods 1035
10.19.2.5.2 Reactivity 1036
10.19.2.5.3 Ring synthesis 1043
10.19.2.5.4 Important compounds and applications 1048
10.19.3 Diazinooxazines **1048**
10.19.3.1 Pyridazinooxazines **1048**
10.19.3.1.1 Reactivity 1048
10.19.3.1.2 Ring synthesis 1048
10.19.3.2 Pyrimidooxazines **1051**
10.19.3.2.1 Reactivity 1051
10.19.3.2.2 Ring synthesis 1054
10.19.3.2.3 Important compounds and applications 1059
10.19.3.3 Pyrazinooxazines **1060**
10.19.3.3.1 Structural methods 1060
10.19.3.3.2 Reactivity 1060
10.19.3.3.3 Ring synthesis 1060
10.19.4 Diazinothiazines **1062**

10.19.4.1 Introduction 1062
10.19.4.2 Pyridazinothiazines 1062
10.19.4.2.1 Reactivity 1062
10.19.4.2.2 Ring synthesis 1063
10.19.4.3 Pyrimidothiazines 1063
10.19.4.3.1 Theoretical and experimental structural methods 1063
10.19.4.3.2 Reactivity 1064
10.19.4.3.3 Ring synthesis 1066
10.19.4.3.4 Important compounds and applications 1071
10.19.4.4 Pyrazinothiazines 1071
10.19.4.4.1 Reactivity 1071
10.19.4.4.2 Ring synthesis 1072
10.19.4.4.3 Important compounds and applications 1073
10.19.5 Oxazinooxazines 1073
10.19.5.1 Introduction 1073
10.19.5.2 Theoretical and Experimental Structural Methods 1073
10.19.5.2.1 1,3-Oxazino[5,4-*d*][1,3]oxazines 1073
10.19.5.2.2 1,3-Oxazino[6,5-*e*][1,3]oxazines 1074
10.19.5.2.3 1,4-Oxazino[3,2-*b*][1,4]oxazines 1074
10.19.5.3 Reactivity 1074
10.19.5.3.1 1,3-Oxazino[5,4-*d*][1,3]oxazines 1074
10.19.5.3.2 1,3-Oxazino[6,5-*e*][1,3]oxazines 1075
10.19.5.3.3 1,4-Oxazino[3,2-*b*][1,4]oxazines 1075
10.19.5.4 Ring Synthesis 1075
10.19.5.4.1 1,3-Oxazino[5,4-*d*][1,3]oxazines 1075
10.19.5.4.2 1,3-Oxazino[6,5-*e*][1,3]oxazines 1076
10.19.5.4.3 1,4-Oxazino[3,2-*b*][1,4]oxazines 1077
10.19.6 Oxazinothiazines 1078
10.19.6.1 Introduction 1078
10.19.6.2 Reactivity 1078
10.19.6.2.1 1,3-Oxazino[5,6-*c*][1,2]thiazines 1078
10.19.6.3 Ring Synthesis 1078
10.19.6.3.1 1,2-Oxazino[4,5-*b*][1,4]thiazines 1078
10.19.6.3.2 1,3-Oxazino[5,6-*c*][1,2]thiazines 1079
10.19.6.4 Important Compounds and Applications 1079
10.19.7 Thiazinothiazines 1079
10.19.7.1 Introduction 1079
10.19.7.2 Theoretical and Experimental Structural Methods 1079
10.19.7.3 Ring Synthesis 1079
10.19.8 Further Developments 1080
10.19.8.1 Pyridazino[4,5-*d*]pyrazines 1080
10.19.8.2 Pyrimido[4,5-*d*]pyrimidines 1080
10.19.8.3 Pyrimido[5,4-*d*]pyrimidines 1082
10.19.8.4 Pyrazino[2,3-*b*]pyrazines 1082
10.19.8.5 Pyridazino[3,4-*b*][1,4]thiazines 1082
10.19.8.6 Pyrimido[4,5-*b*][1,4]thiazines 1083
References 1083

10.19.1 Introduction

The present chapter builds on the review of diazinodiazine chemistry in CHEC(1984) <1984CHEC(3)329> and the expanded review of bicyclic 6-6 systems with two heteroatoms per ring, which appeared in CHEC-II(1996) <1996CHEC-II(7)737>. The scope of the present review is essentially that of the corresponding chapter in CHEC-II(1996).

10.19.2 Diazinodiazines

All of the 13 possible diazinodiazines without bridgehead heteroatoms are known, and are summarized in **Figure 1**. For all of these, published and patented results since 1994 are reviewed in the present chapter, with the exception of the pyrazino[2,3-*d*]pyrimidines (pteridines), which are reviewed in Chapter 10.18. A further review of the chemistry of diazinodiazines has also appeared recently <B-2004SOS(16)1337>.

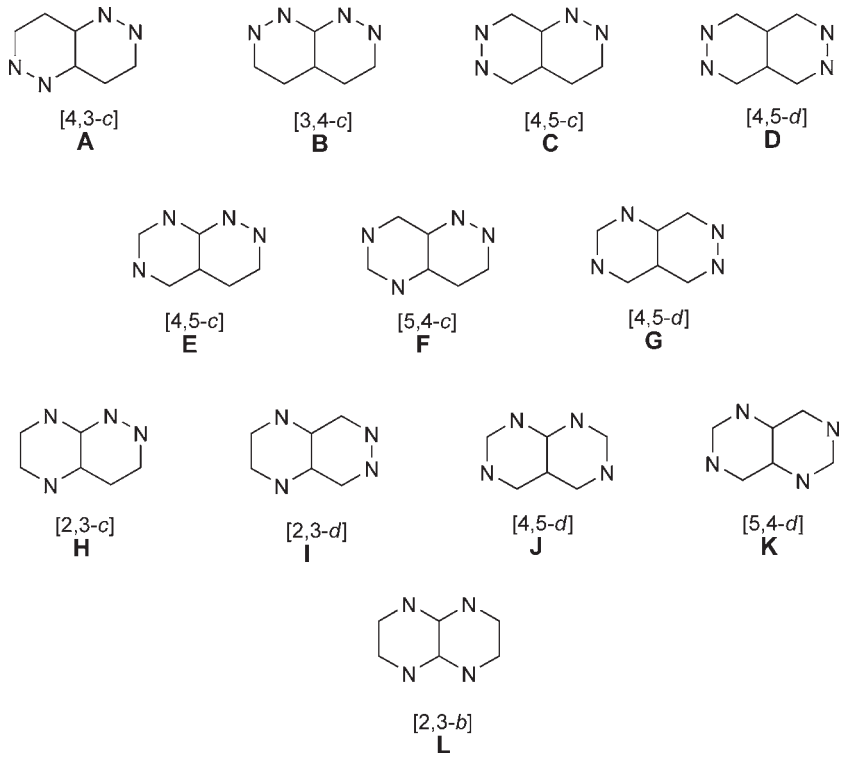
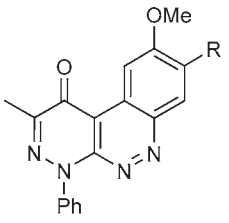


Figure 1

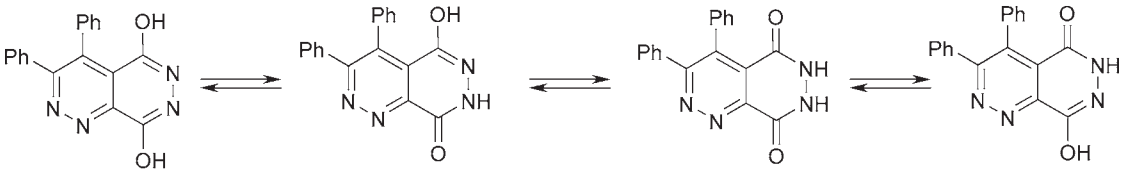
10.19.2.1 Pyridazinopyridazines

10.19.2.1.1 Theoretical and experimental structural methods

Structural studies of pyridazinopyridazines were discussed extensively in CHEC(1984) <1984CHEC(3)329>, and updated in CHEC-II(1996) <1996CHEC-II(7)737>, but relatively few new results have been reported since then. In the ^{1}H NMR spectra of benzo-fused pyridazino[3,4-*c*]pyridazines **1**, the proton at position 10 is strongly shielded by the adjacent carbonyl group, being observed at δ 9.04 (R = H) or 9.11 (R = OMe). Based on electronic spectra, recorded over a pH range from 2 to 11 <2002SC989>, it has been determined that pyridazino[4,5-*c*]pyridazine derivative **2** exists as a mixture of four tautomers (**Scheme 1**). Molecular orbital calculations have permitted the complete assignment of the infrared spectrum of pyridazino[4,5-*d*]pyridazine **3** <2000PCA7386>, and the description of the nonbonding orbitals on nitrogen in the same system as perturbed naphthalene σ-orbitals, with contributions from σ^*-orbitals <1999PCA3089>.



1



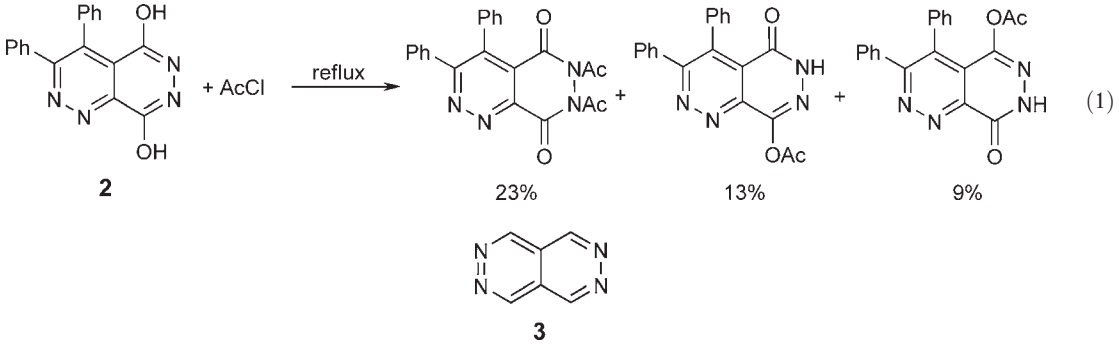
2

Scheme 1

10.19.2.1.2 Reactivity

10.19.2.1.2(i) Pyridazino[4,5-*c*]pyridazines

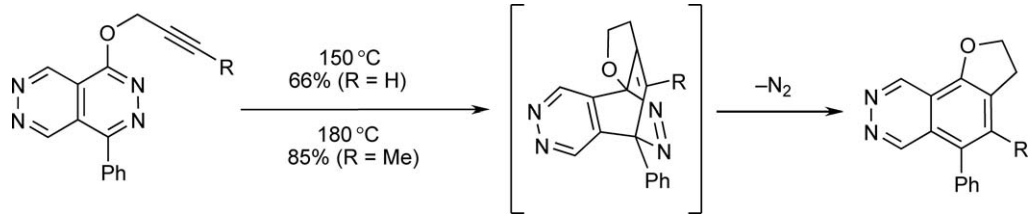
Shalaby and co-workers <2002SC989> have reported that acetylation of dihydroxypyridazino[4,5-*c*]pyridazine **2** gives a mixture of O- and N-acetylated species (Equation 1), although treatment of **2** with ethyl bromoacetate in the presence of potassium carbonate gave only the 6,7-dialkylated product (39% yield).



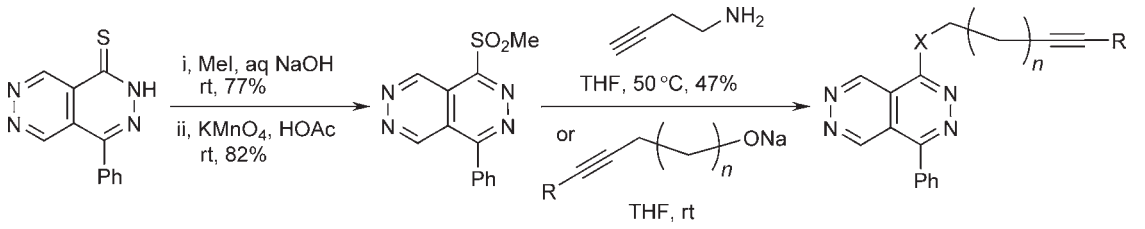
2 **3** (1)

10.19.2.1.2(ii) Pyridazino[4,5-*d*]pyridazines

The use of derivatives of pyridazino[4,5-*d*]pyridazine as dienophiles for the preparation of benzene ring-substituted phthalazines was reported in CHEC-II(1996) <1996CHEC-II(7)737>. Additional applications of the procedure have been published since <1995H(41)2519, 1999SC1577> and the methodology has been reviewed <B-2004SOS(16)315>. Notable examples include the use of these systems in intramolecular Diels–Alder reactions to give pyrazino[4,5-*b*]carbazoles <2004T6495> and furano[2,3-*f*]phthalazines <1994JHC357>. The latter process (**Scheme 2**) is sensitive to both steric and entropic effects: the process is very much slower with R = Me than where R = H, due to the steric



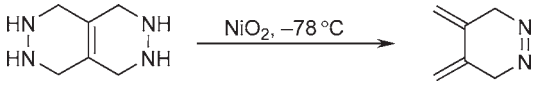
Scheme 2



Scheme 3

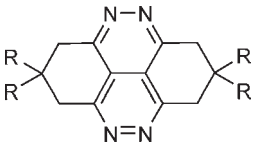
interaction between the methyl group and the phenyl substituent at C-4, while the homologous acetylene ($n = 2$) fails to react, probably as a result of the absence of entropic assistance to cyclization. The acetylenic intermediates were obtained by displacement of a sulfone group at C-1 of the heterocycle (**Scheme 3**).

The generation of a diene from an octahydro derivative of the same system has also been reported <1993JPC13408>. Presumably, this process occurs by cycloelimination of nitrogen from an initial oxidation product (Equation 2).



(2)

peri-Fused pyridazino[4,5-d]pyridazine derivatives **4** undergo self-assembly in the presence of copper(I) salts, forming lattices with a sodalite-like structure <2004JCD695> if the counterion is perchlorate or nitrate. In the presence of a halide, tubular and helical structures are observed <2004JCD1153>.

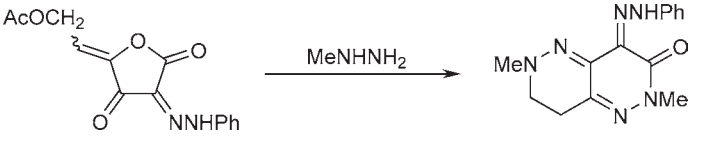


4

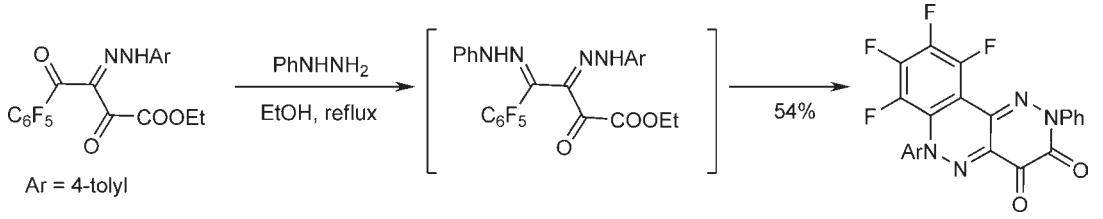
10.19.2.1.3 Ring synthesis

10.19.2.1.3(i) Pyridazino[4,3-*c*]pyridazines

Since the appearance of CHEC-II(1996), no entirely new approaches to pyridazino[4,3-*c*]pyridazines have been reported. However, the cyclization of furanylidene acetates described previously has been extended to permit the preparation of *ortho*-quinonoid systems, as illustrated in Equation (3) <1990JPS123>. A further variation on the bicyclization of a bis(hydrazone) has been reported more recently (**Scheme 4**), involving nucleophilic displacement of fluoride from a pentafluorophenyl group <2005MC252>.



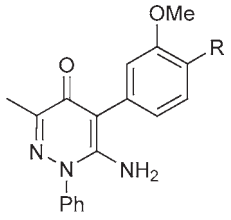
(3)



Scheme 4

10.19.2.1.3(ii) Pyridazino[3,4-*c*]pyridazines

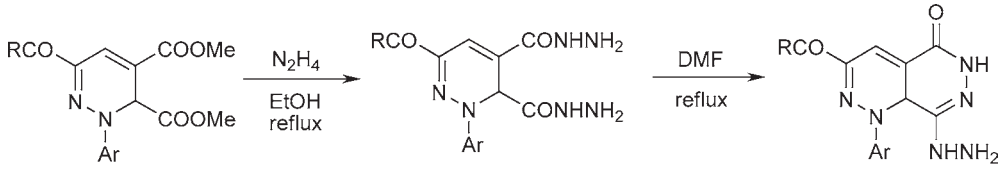
Although no new method for formation of simple pyridazino[3,4-*c*]pyridazines has appeared since the publication of CHEC-II(1996), a further method for the construction of benzo-fused derivatives has been described <1997CHE750>. Electrophilic attack of the diazonium salts formed from aromatic amines **5**, with sodium nitrite in acetic acid, upon the neighboring methoxyarene results in formation of pyridazino[3,4-*c*]cinnolines **1**.



5

10.19.2.1.3(iii) Pyridazino[4,5-*c*]pyridazines

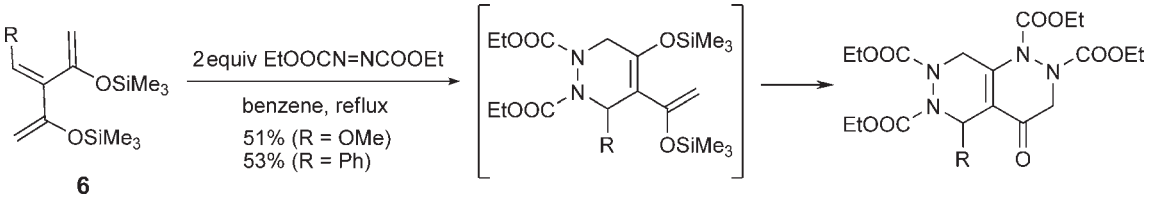
The condensation of a pyridazine-2,3-dicarboxylic acid derivative with hydrazine remains a favored method for the formation of pyridazino[4,5-*c*]pyridazines. In the examples generalized in **Scheme 5**, the presence of an excess of hydrazine hydrate results in formation of the bis(acylhydrazide), which undergoes cyclization in dimethylformamide (DMF) to give the 8-hydrazinopyridazino[4,5-*c*]pyridazine <2001S1861, 2004JHC647>.



R	*Ar*	*Yield* (*step* 1) (%)	*Yield* (*step* 2) (%)
2-Furyl	Ph	90	90
2-Thienyl	Ph	95	95
2-Furyl	4-$MeOC_6H_4$	90	88

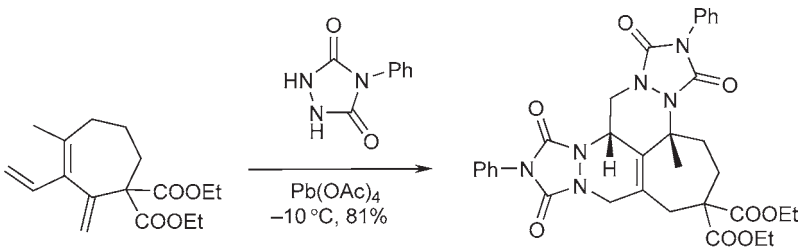
Scheme 5

Azodicarboxylates can serve as alternatives to hydrazine as a source of the N–N unit in pyridazinopyridazines. Such an approach has been used to construct the pyridazino[4,5-*c*]pyridazine system by using a 'diene-transmissive' Diels–Alder cycloaddition between silyl enol ether **6** and diethyl azodicarboxylate <1994CL1833>, in which the initial cycloadduct rapidly undergoes a second addition. Desilylation occurs upon workup and a moderate yield of the pyridazino[4,5-*c*]pyridazine product is obtained in a single step (**Scheme 6**). A similar principle is involved in tandem cycloadditions using *N*-phenyltriazoline-3,5-dione as the dienophile <2005EJO4167, 2006JHC1115>, as exemplified in the generation of fused derivative **7** (Equation 4).



6

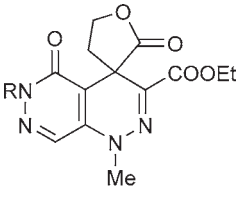
Scheme 6



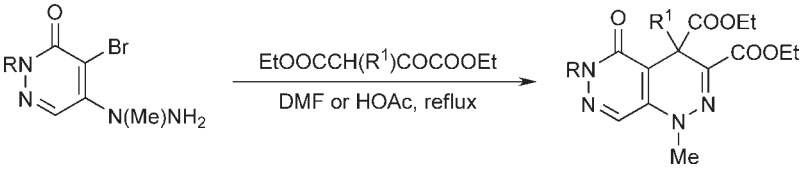
(4)

7

The formation of pyridazino[3,4-*c*]pyridazines by enehydrazine cyclization was described in CHEC-II(1996) <1996CHEC-II(7)737>. In its original form, the method suffers from competing Fischer indolization, but it has been used successfully for the preparation of *spiro*-fused systems such as **8** <1996H(43)1613>. A more generally useful approach to pyridazino[4,5-*c*]pyridazines <1992JHC1313> involves cyclization of the enehydrazines formed from ketosuccinates with brominated 4-hydrazinopyridazines in refluxing acetic acid (Equation 5). In this case, Fischer indolization accounts for less than 10% of the product. Similarly, whereas the cyclization of enehydrazines formed from 3-bromo-2-ketopropionates <1996H(43)1863> gives low yields of the pyridazine product in refluxing dioxane (**Scheme 7**), a variation using a Wurtz coupling to form the second ring provides more satisfactory results (**Scheme 8**).

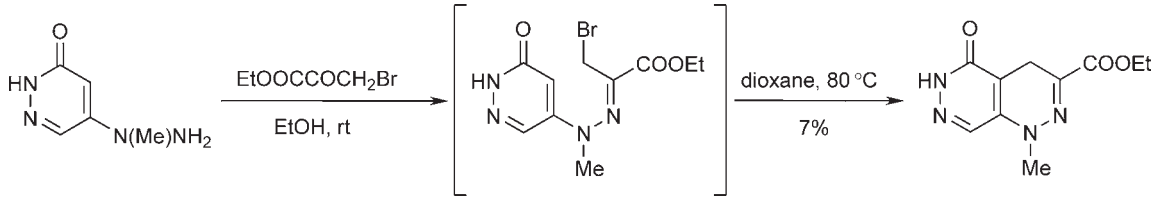


8

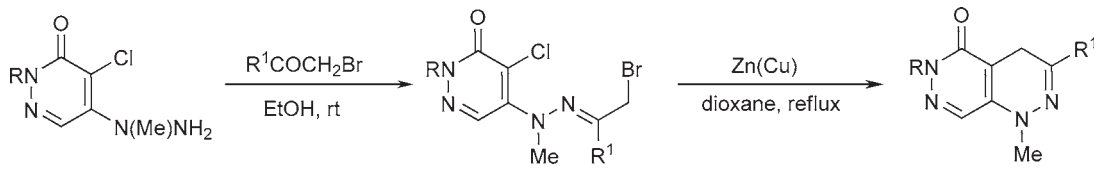


(5)

R	R^1	*Yield* (%)	*R*	R^1	*Yield* (%)
Ph	Me	84	Ph	H	73
Me	Me	61	Me	H	62
H	Me	72	H	H	68
CH_2Ph	Me	72			



Scheme 7

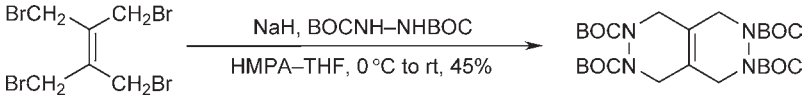


R	R^1	*Yield* (*step* 1) (%)	*Yield* (*step* 2) (%)
H	COOEt	92	82
Me	COOEt	44	68
Ph	COOEt	69	79
CH_2Ph	COOEt	53	54
H	Ph	89	10

Scheme 8

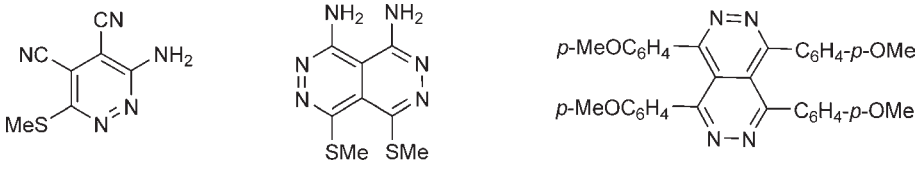
10.19.2.1.3(iv) Pyridazino[4,5-*d*]pyridazines

The reaction of a pyridazine-4,5-dicarboxylic acid derivative with hydrazine remains a favored approach for the preparation of pyridazino[4,5-*d*]pyridazines <2000TL2863, 2002JCCS217>, and di-*tert*-butyl hydrazodicarboxylate has been used as a hydrazine substitute in the presence of perhydro derivatives, as illustrated in Equation (6) <1993JPC13408>.



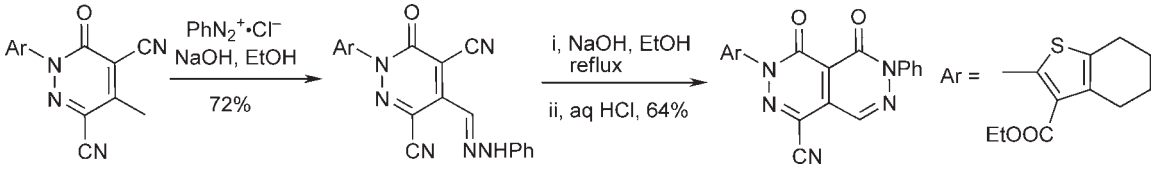
(6)

An alternative hydrazine derivative used is *S*-methyldithiocarbazate, which is reported to react with tetracyanoethylene via a charge-transfer complex, giving a mixture of polysubstituted pyridazine **9** and pyridazino[4,5-*d*]pyridazine **10** <1995PS(101)189>. 1,4,5,8-Tetrakis(4-methoxyphenyl)pyridazino[4,5-*d*]pyridazine **11** has also been prepared by cyclization of tetrakis(4-methoxyphenyl)ethane with hydrazine itself <2000RJO1157>.

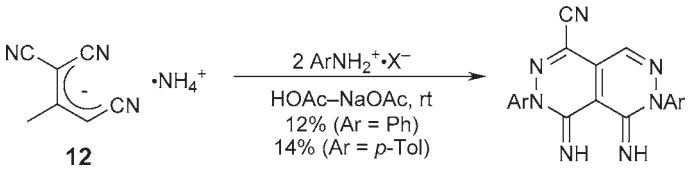


9 **10** **11**

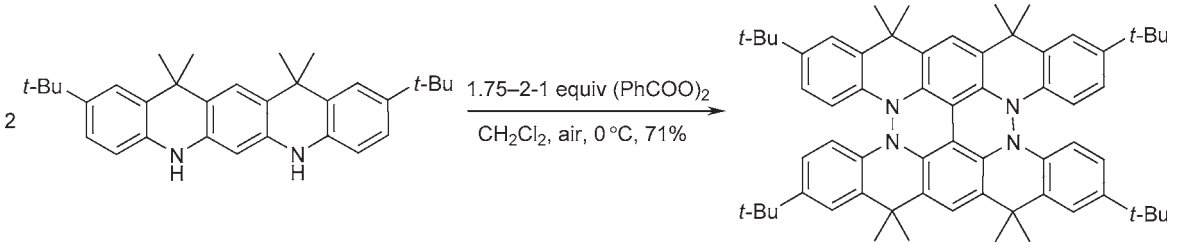
A different approach has been used to build a second pyridazine ring onto a 4-cyano-5-methylpyridazinone by reaction with benzenediazonium chloride, and subsequent base-promoted cyclization (**Scheme 9**). The imine formed initially is hydrolyzed on acidic workup to give the diketone product <2003PS1667>. Similarly, reaction of the malononitrile adduct **12** with 2 equiv of an arenediazonium chloride generates the pyridazino[4,5-*d*]pyridazine system in a single step (Equation 7) <1993JCM8>. More recently, an entirely different approach to this system has been reported (Equation 8), in which a highly fused system is formed by oxidative dimerization of a diamine precursor <2005JA9312>.



Scheme 9



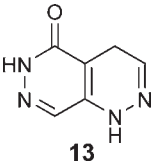
(7)



(8)

10.19.2.1.4 Important compounds and applications

No pyridazinopyridazine derivatives are presently marketed as pharmaceuticals or agrochemicals. However, the interleukin-1 antagonist CK-103A **13** is a lead compound of a series of analogues, which are proposed as protective agents against uveitis <1997MI427>, and derivatives of 1,4,5,6-tetrahydropyridazino[4,5-*c*]pyridazin-4-one have been reported as anti-inflammatory agents <1997CNP1147378>.

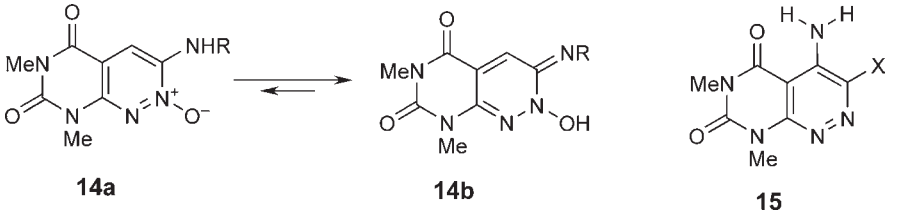


13

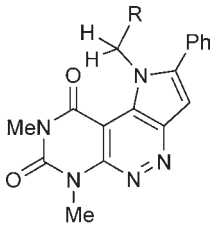
10.19.2.2 Pyrimidopyridazines

10.19.2.2.1 Theoretical and experimental structural methods

CHEC(1984) contains a detailed discussion of structural and spectrometric data for the isomeric pyrimidopyridazines <1984CHEC(3)329>, which was updated in CHEC-II(1996) <1996CHEC-II(7)737>. More recent work includes detailed theoretical and experimental studies of pyrimido[4,5-*c*]pyridazine-5,7-diones. Adjacent sites at C-3 and C-4 of this system are very electron deficient, the effective π-charges being +0.047 and +0.10, respectively, with the result that nucleophilic attack at these centers is strongly favored <1999RCB1150>. Among adducts formed by such nucleophilic attack, there is considerable evidence for certain tautomers being favored as a result of intramolecular hydrogen bonding. In *N*-oxides **14**, the NH signals appear at a lower field (by 3–4 ppm) in the ^{1}H NMR spectrum than those in the deoxygenated species, consistent with such hydrogen bonding <2000CHE1213>. The ultraviolet (UV) spectrum of **14** is also very different from those of analogues without a free NH, and the conclusion was drawn that the predominant tautomer is the *N*-hydroxy species **14b**, rather than the amine **14a**. Hydrogen bonding is also observable between the NH of 4-amino adducts and the carbonyl at position 5 <2001CHE1461>, to the extent that in **15**, the NH protons are magnetically nonequivalent, giving rise to discrete resonances at δ 5.79 and 8.86 in the ^{1}H NMR spectrum, which only coalesce at 60 °C <2004RCB846>.

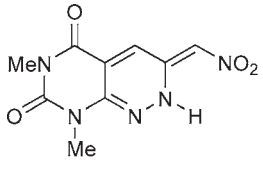


A related effect is observed in the ^{1}H NMR spectra of annulated species **16**. The protons α- to nitrogen are deshielded by the 5-carbonyl group and appear at δ 4.73–5.55 <2003RCB441>; on the other hand, the terminal methyl (R = Et, Pr) is shielded by the nearby benzene ring and protons are observed at δ 0.50–0.59.

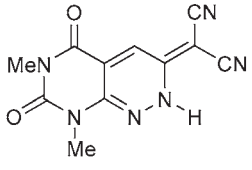


16

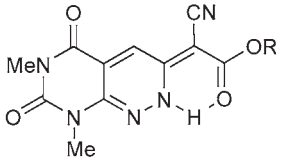
Tautomers analogous to **14b** are also favored in the products formed by addition of carbon nucleophiles at the same position. Tautomer **17** of the nitromethane adduct, and tautomers **18** and **19** of malononitrile and alkyl cyanoacetate adducts are favored due to a combination of conjugation with the electron-withdrawing groups and intramolecular hydrogen bonding <2000CHE975>. Evidence for this tautomeric preference includes infrared spectra, where the carbonyl and cyano bands appear at 1645 and 2150 cm^{-1} respectively, and nuclear magnetic resonance (NMR) spectroscopy, where no signal is evident due to a proton between CN and CO, and where H-4 appears as a doublet due to coupling to NH.



17

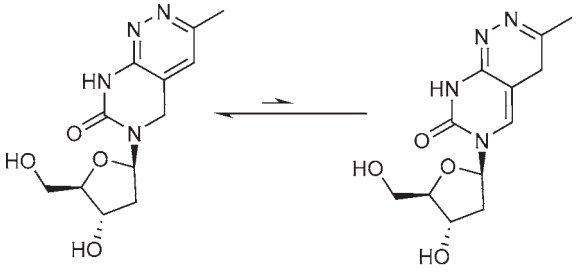


18



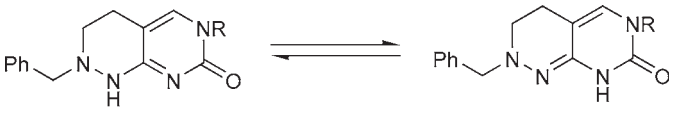
19

Tautomerism is also of interest in the case of the pyrimidine nucleoside analogue **20** <2003TL3387>, where the solid-state structure has been established crystallographically as the 5*H* tautomer **20a**, wherein the pyridazine ring is fully aromatic, rather than the 8*H* tautomer **20b**.



20a **20b**

Prototropic tautomerism of 2-alkylated tetrahydro species **21** is solvent dependent, tautomers **21a** and **21b** being identified as the major species present in DMSO-d_6 (DMSO – dimethyl sulfoxide) and deuterochloroform, respectively <2000HCA1693> by NOE experiments. Acetylated analogue **22** appears to behave similarly, although in this case the spectrum is complicated by the presence of amide rotamers. As judged from the N–H signals observed in ^{1}H NMR spectrum, the major species in deuterochloroform is **22a**, whereas, in DMSO-d_6, the tautomeric equilibrium constant approaches unity, and both tautomers are present.

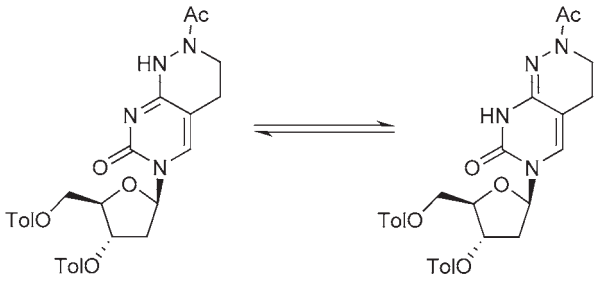


Predominant in $CDCl_3$

21a

Observed in DMSO

21b



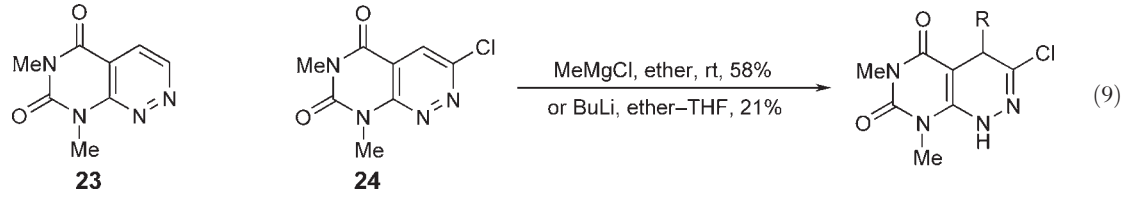
22a

10.19.2.2.2 Reactivity

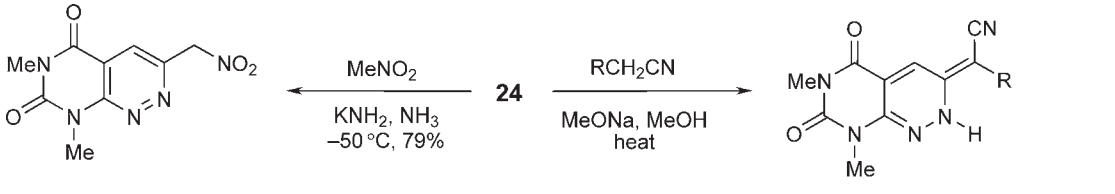
10.19.2.2.2(i) Pyrimido[4,5-*c*]pyridazines

The reactivity of pyrimido[4,5-*c*]pyridazines was discussed in detail in CHEC(1984) <1984CHEC(3)329> and a few additional results were reviewed in CHEC-II(1996) <1996CHEC-II(7)737>. A variety of results have been reported since the appearance of CHEC-II(1996), including the thermal extrusion of nitrogen from the parent to provide 1,3-diazabiphenylene <1993MI343>.

Much of the recently reported work on nucleophilic substitution at C-3 and C-4 of pyrimido[4,5-*c*]pyridazine-5,7-diones is included in a review of nucleophilic substitution in pyridazines <2001CHE1461>. 6,8-Dimethylpyrimido[4,5-*c*]pyridazine-5,7-dione **23** and its derivatives undergo attack at both C-3 and C-4. Under conditions of kinetic control, addition occurs preferentially at the more electron-deficient C-4, whereas thermodynamic control conditions, or the use of bulkier nucleophiles, favor addition at the less hindered position 3. This duality is illustrated by the addition of Grignard and organolithium reagents to C-4 of 3-chloro analogue **24** (Equation 9), whereas stabilized nucleophiles such as the anion of nitromethane add at C-3 (**Scheme 10**) <2000CHE975>. Displacement of the 3-chloride occurs also upon treatment of **24** with amines (Equation 10) <2000CHE1213>.

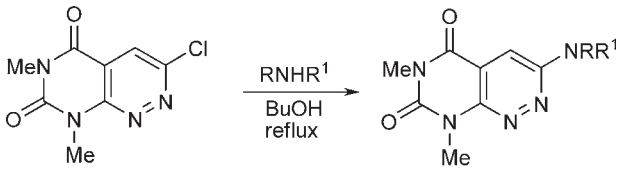


23 **24** (9)



82% (R = CN), 11% (R = COOMe), 32% (R = COOEt)

Scheme 10

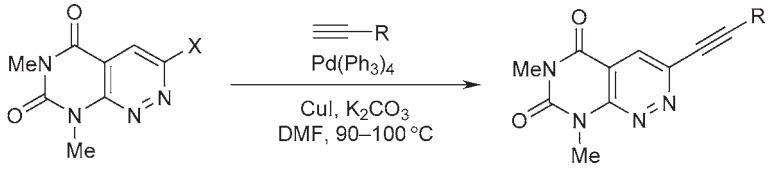


24

$RNHR^1$ = $MeNH_2$, Me_2NH, $PrNH_2$, $CyNH_2$
$BnNH_2$, piperidine, morpholine
(50–77%)

(10)

Sonogashira coupling of acetylenes with **24** and with the triflate **25** have also been reported (Equation 11) <2003RCB441>. The latter substrate is formed by treatment of the trione **26** with trifluoromethanesulfonic anhydride and pyridine; chloride and triflate are comparable in respect of cross-coupling yields.



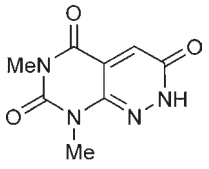
24 (X = Cl), **25** (X = OTf)

(11)

X	*R*	*Yield* (%)
Cl	$SiMe_3$[a,b]	71
OTf	Ph	80
Cl	Ph	74
Cl	p-C_6H_4Cl	22

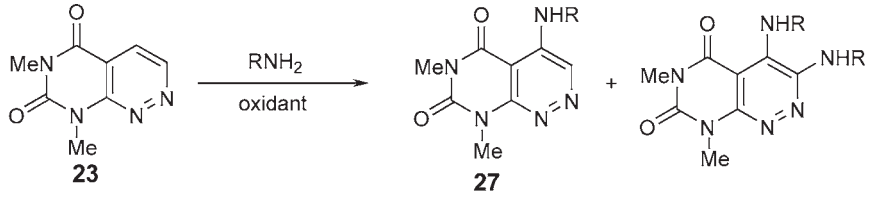
X	*R*	*Yield* (%)
Cl	CH_2OH	32
OTf	CH_2OH	38
Cl	CH_2OTHP	46[a]
Cl	n-C_6H_{13}	47[a]

[a]Pd_2dba_3–PPh_3 as catalyst system.
[b]Triethylamine as base and solvent.



26

Derivatives of **23** undergo Chichibabin amination under comparatively mild conditions in the presence of an oxidant (Equation 12); the major product results from amination at C-4, but is accompanied by up to 10% of the 3,4-diamine <2000MC150>.



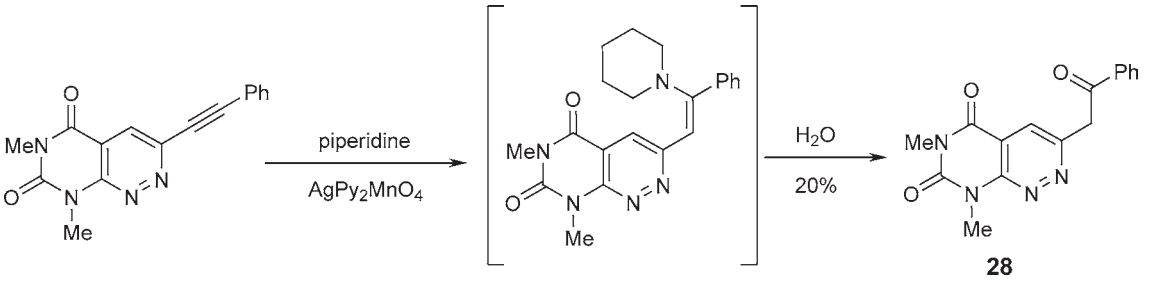
23 **27**

(12)

R	*Oxidant*	*Temp.*	*Yield* **27** (%)
H	$KMnO_4$	–78 °C	70
Me	$KMnO_4$	–20 °C	90
Et	Py_2AgMnO_4	–20 °C	85
Pr	Py_2AgMnO_4	rt	60

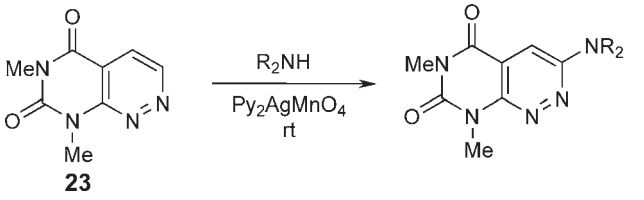
R	*Oxidant*	*Temp.*	*Yield* **27** (%)
t-Bu	Py_2AgMnO_4	rt	63
Cy	Py_2AgMnO_4	rt	53
CH_2Ph	Py_2AgMnO_4	rt	51

Alkynes, obtained as above, also undergo Chichibabin amination; in this case, cyclization occurs *in situ* to form a pyrrole <2003RCB441>. Although pyrrole formation is expected to involve attack at C-4 followed by cyclization onto the acetylene, the possibility of initial attack occurring at the acetylene cannot be excluded, in view of the isolation of ketone **28** (**Scheme 11**) <2005JHC413>.



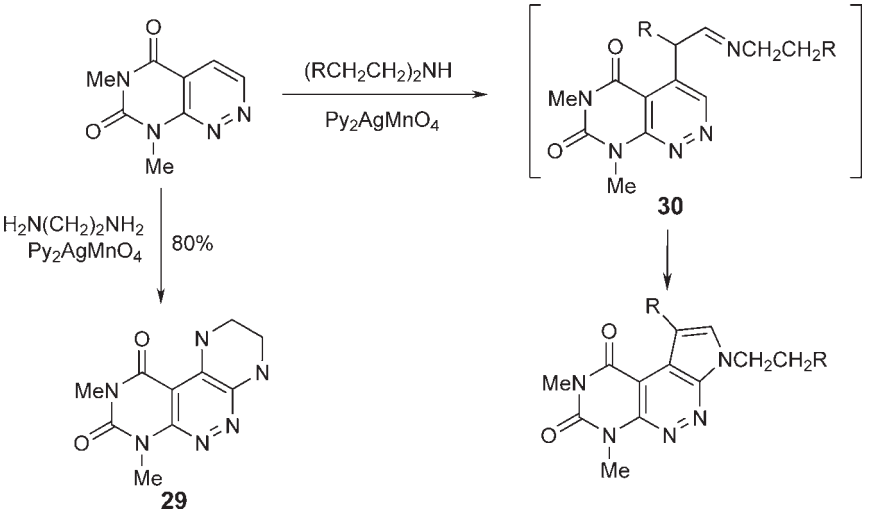
Scheme 11

The corresponding reaction of **23** with dimethylamine and with cyclic secondary amines (piperidine and morpholine) is less facile and gives the thermodynamically more favored C-3 addition product (Equation 13) <1999RCB1150>. Using ethylenediamine, the cyclization product **29** is obtained in 80% yield (**Scheme 12**), although with 1,3-propanediamine, 1,4-butanediamine, and 1,2-cyclohexanediamine the yields are reduced (70%, 25%, and 1%, respectively), consistent with the importance of entropy as a driving force for the second (intramolecular) amination.



R_2NH	*Yield (%)*
Me_2NH	13
piperidine	10
morpholine	5

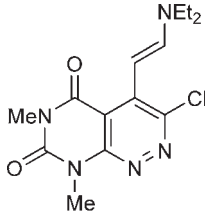
(13)



Scheme 12

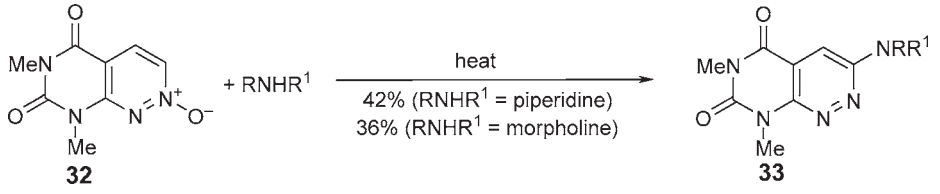
The course of the amination reaction is strongly dependent upon the nature of the amine used. With secondary amines, initial oxidation of the amine occurs to form an enamine; attack of this intermediate at C-4 leads to a species such as **30** (**Scheme 12**), which ring-closes to form a pyrrole isomeric with that already described <2001TL5981>.

The same products are also formed from the reaction of **24** with secondary amines <2004RCB846>. Support for the proposed mechanism is provided by the observation that the same products are obtained when **23** is treated with a pre-formed imine, and by the isolation of the stable enamine **31** in 15% yield as a side product from the reaction of triethylamine with **24**.

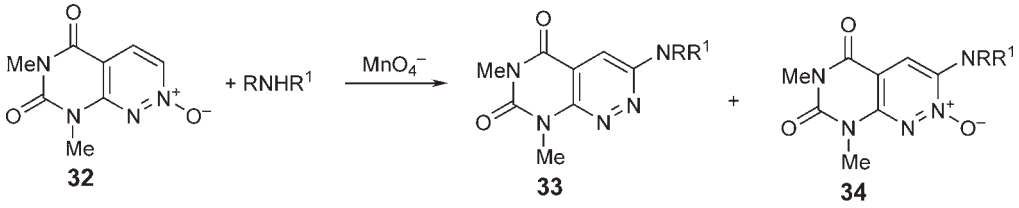


31

The 2-*N*-oxide **32** is formed in 90% yield by oxidation of **23** with peroxytrifluoroacetic acid <2000CHE1213>, and reacts with amines to give the product of attack at C-3 (**33**; Equation 14). In the presence of an oxidant, the same adduct is formed in low yield, accompanied by its *N*-oxide (**34**; Equation 15) <2000CHE1213, 2003T7669, 2005JHC375>. Using isopropylamine or cyclohexylamine, **34** is accompanied by an imidazole-fused product **35**, formed by further reaction with the imine formed *in situ* from the same amine, followed by cyclization (Equation 16) <2000CHE1213>. Amines **34** have been shown to be intermediates in the latter reaction <2002MC157>. Analogous products are formed upon treatment of 3-chloro species **24** with either of these amines in the presence of an oxidant.



32 **33** (14)

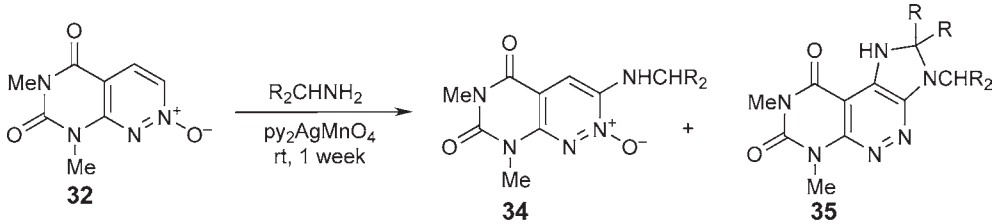


32 **33** **34** (15)

RNHR^1	*Ratio* **33**/**34**
NH_3	0:100
$MeNH_2$	61:39
$EtNH_2$	33:67

RNHR^1	*Ratio* **33**/**34**
Me_2NH	0:100
$PrNH_2$	13:87
$CyNH_2$	0:100

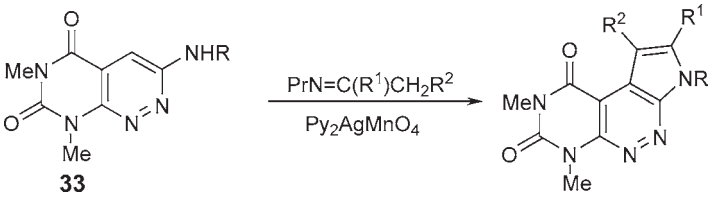
RNHR^1	*Ratio* **33**/**34**
$PhCH_2NH_2$	37:63
Piperidine	37:63
Morpholine	40:60



32 **34** **35** (16)

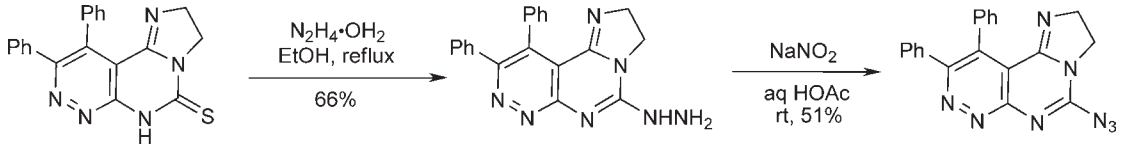
R_2CHNH_2	*Yield*, **34**	*Yield*, **35**
Pr^iNH_2	22%	4.5%
$CyNH_2$	Not stated	10%

In the absence of the *N*-oxide, the reaction of 3-aminopyridazino[3,4-*d*]pyrimidinediones **33** with imines takes a different course (Equation 17), and cyclization of the intermediate occurs to form a pyrrole ring <2005JHC375>. The reaction with cyclohexylamine in this instance results in the formation of highly fused dimeric products <2003T7669, 2006T652>.



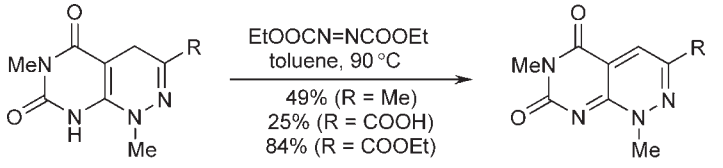
(17)

The direct nucleophilic displacement of a thione at position 7 has been reported (**Scheme 13**), together with the further conversion of the resulting hydrazine to an azide or to a triazole <1998FA113>. Similarly, 7-amination has been carried out by displacement of methanesulfinyl and methanesulfonyl groups <2006BMCL4257>.



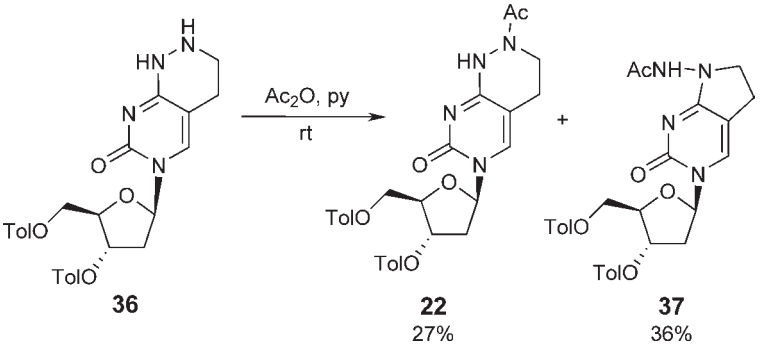
Scheme 13

Dehydrogenation of 1,4-dihydropyrimido[4,5-*c*]pyridazine-5,7-diones can be achieved using diethyl azodicarboxylate (Equation 18) <2004H(63)1393>.

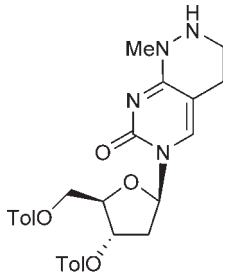


(18)

Acetylation of the nucleoside analogue **36** occurs at both positions 1 and 2. However, the 1-acetylated product undergoes spontaneous ring contraction to give a pyrrolo[2,3-*d*]pyrimidine **37** (Equation 19) <2000HCA1693>. Treatment of **22** with a catalytic quantity of sodium methoxide in methanol again gives **37** (85%) by an unusual acyl migration, the 1-acyl product undergoing spontaneous ring contraction. The same ring contraction is observed if either **36** or its 1-methyl derivative **38** are treated with a base <1999HCA2028>. Acylation of **36** using carboxylic acid *N*-hydroxysuccinimide esters has also been reported: the product is presumably analogous to **22**, but the regiochemistry was not confirmed <1997WO97/28177>.

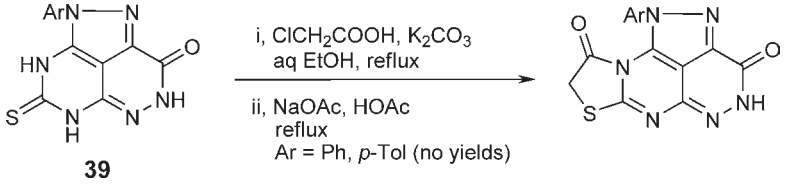


(19)

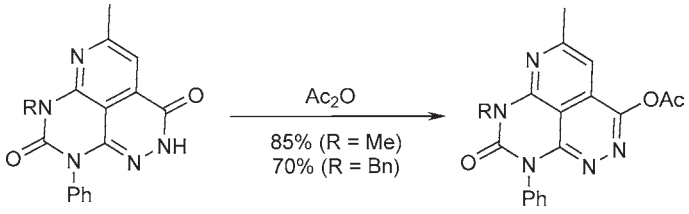


38

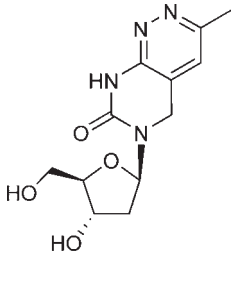
A range of selectivities are observed in the alkylation and acylation of pyrimido[4,5-*c*]pyridazinones and -thiones. As might be expected, alkylation of the fused system **39** occurs selectively at sulfur (Equation 20), and the product is subsequently cyclized by intramolecular acylation of the adjacent nitrogen <1993JCM208>. In contrast, diones **40** are acetylated selectively at the 3-oxygen (Equation 21) <1997FA657>. Nucleoside analogue **41** is phosphorylated and dimethoxytritylated at the primary alcohol of the sugar unit without any requirement to protect N8 <2002WO02/02584> but, in contrast, *N*-acetylation of the antiviral nucleoside tricribine **42** requires prior protection of the sugar hydroxyl groups <2000JME2457>.



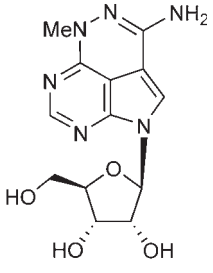
39 (20)



40 (21)



41

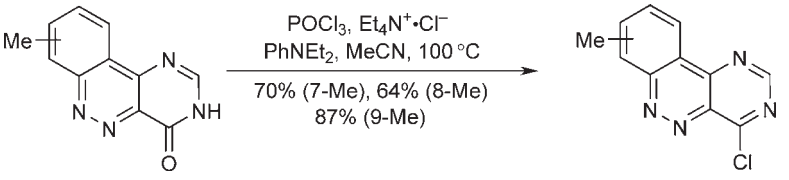


42

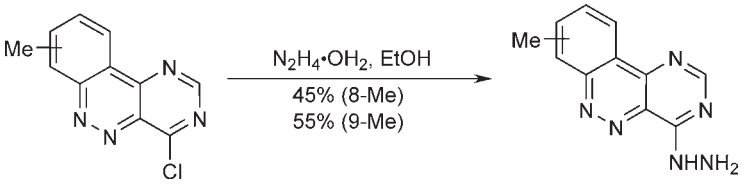
10.19.2.2.2(ii) Pyrimido[5,4-*c*]pyridazines

Few reactions of this system were reported in CHEC(1984) <1984CHEC(3)329> and none in CHEC-II(1996), but there has been progress since the appearance of the latter. Although chlorination of pyrimido[5,4-*c*]pyridazin-8-one is not achieved under conventional conditions <1984CHEC(3)329>, this conversion has been carried out on

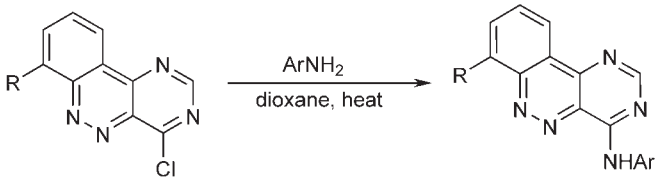
benzannulated derivatives (Equation 22) with the addition of *N*,*N*-diethylaniline and a tetraalkylammonium salt <1994AF156, 1994IJB764>, and more recently in the presence of pyridine <2005AP590>. The chlorine can be displaced successfully with hydrazine (Equation 23) and with amines (Equation 24) <1995AF1131, 2005AP590>. The products from the latter process undergo the expected acetylation at the amino substituent <2000PJC681>. Nucleophilic substitution of a dihydro analogue with alcohols has also been reported (Equation 25) <1994EJM245>. An alternative approach to nucleophilic substitution, as elsewhere, involves displacement of an alkylthio substituent. 8-Oxo-6-thiones **43** are alkylated selectively at sulfur <1993JIC533>, while alkylation of the 6,8-dithione proceeds to give the 6,8-bis(alkylthio)species <1996IJB1185>. In the case of the bis(methylthio) species, the thioether at C-8 undergoes nucleophilic displacement in preference to that at C-6 (**Scheme 14**).



(22)



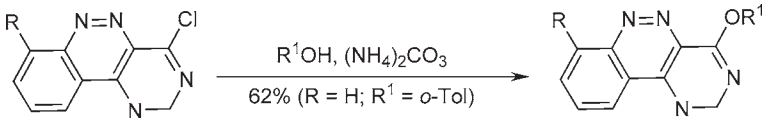
(23)



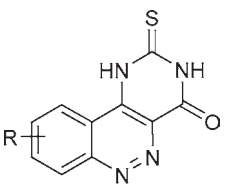
(24)

R	*Ar*	*Yield* (%)
H	3-ClC$_6$H$_4$	70
H	4-MeOC$_6$H$_4$	58
H	*o*-Tol	60
H	*p*-Tol	65

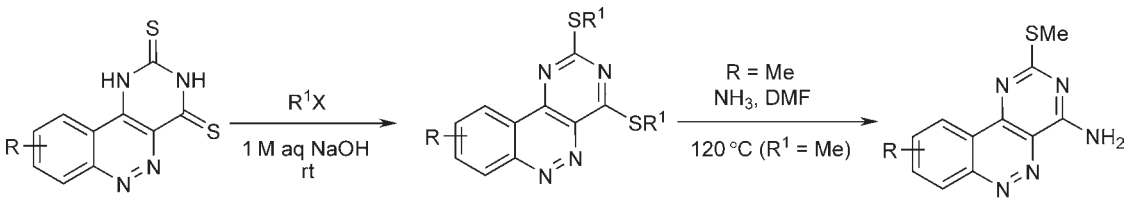
R	*Ar*	*Yield* (%)
Me	3-ClC$_6$H$_4$	72
Me	4-MeOC$_6$H$_4$	52
Me	*m*-Tol	62
Me	*p*-Tol	70



(25)



43



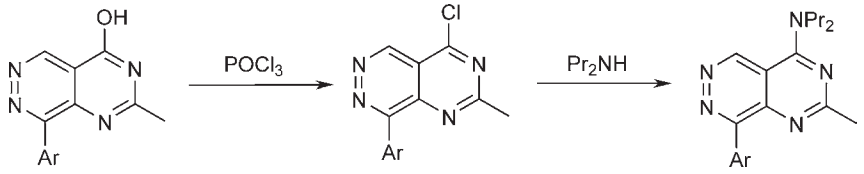
R	R^1	*Yield* (%) (*step* 1)	*Yield* (%) (*step* 2)
H	Me	68	68
7-Me	Me	63	65
8-Me	Me	66	63
9-Me	Me	61	65
H	Et	62	
7-Me	Et	58	

R	R^1	*Yield* (%) (*step* 1)
8-Me	Et	61
9-Me	Et	65
H	CH_2COOEt	54
7-Me	CH_2COOEt	52
8-Me	CH_2COOEt	51
9-Me	CH_2COOEt	54

Scheme 14

10.19.2.2.2(iii) Pyrimido[4,5-*d*]pyridazines

Nucleophilic reactivity at positions 5 and 8 of pyrimido[4,5-*d*]pyridazines was reviewed in CHEC(1984) <1984CHEC(3)329> and in CHEC-II(1996) <1996CHEC-II(7)737>. More recently, the preparation and amination of a 4-chloro species (**Scheme 15**) has been reported, although details given are limited <1998WO98/35967>.

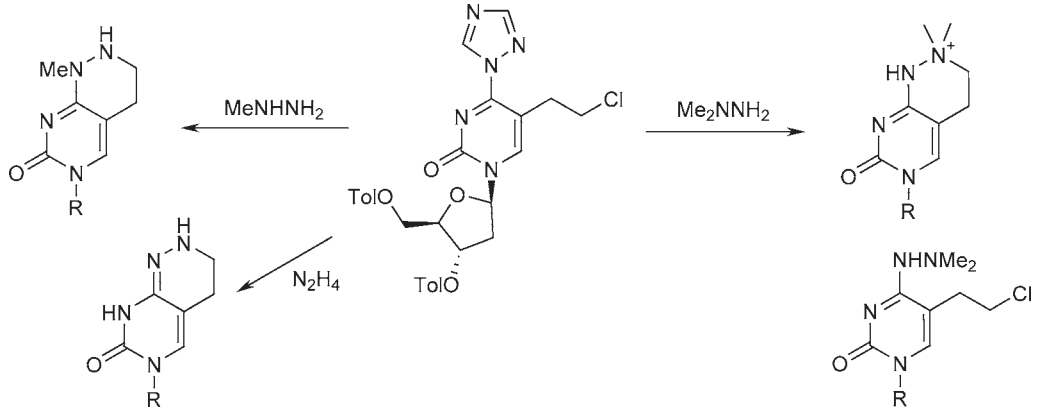


Scheme 15

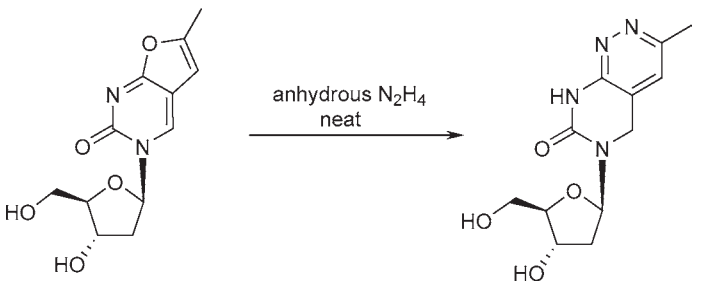
10.19.2.2.3 Ring synthesis

10.19.2.2.3(i) Pyrimido[4,5-*c*]pyridazines (E)

The principal means for construction of pyrimido[4,5-*c*]pyridazines described in CHEC(1984) is the ring closure by reaction of a pyrimidine bis-electrophile with a hydrazine <1984CHEC(3)329>. This approach has been used to prepare tricribine **42** <2004NN31> and a number of analogues <1999NN2475, 2000JME2438, 2001NN1823, 2003NN2171, 2004BML3517>, and variations on the theme have been developed for the preparation of nucleoside analogues from 3-(1,2,4-triazol-1-yl)-4-(2-chloroethyl)pyrimidin-2-ones (**Scheme 16**) <1999HCA2028, 1995HCA291, 2000HCA1693> and from furano[2,3-*d*]pyrimidine nucleosides (Equation 26) <2003TL3387>.

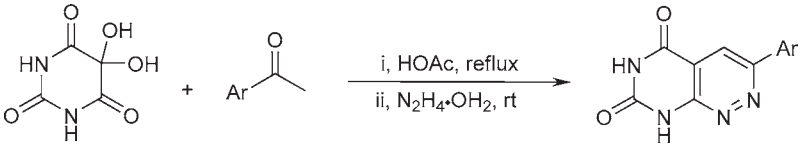


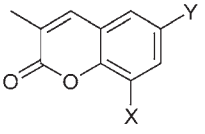
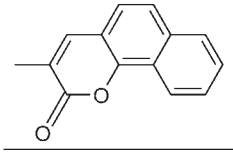
Scheme 16



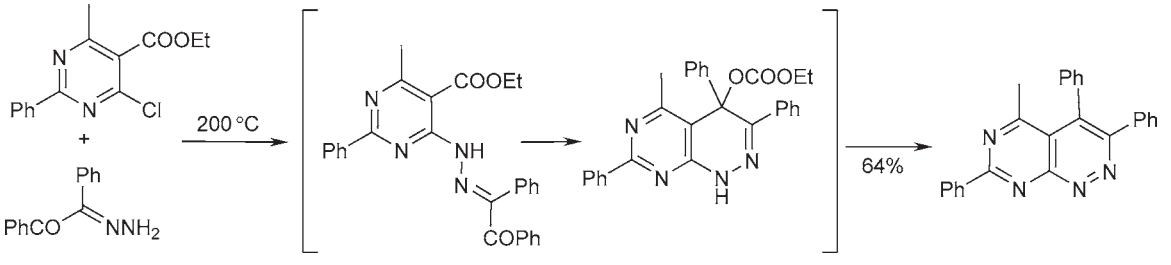
(26)

Further variations include the reaction of alloxan hydrate with a methyl ketone and hydrazine to form the pyridazine ring in a single pot (Equation 27) and the use of benzoin hydrazone for the same purpose (**Scheme 17**) <1996IJB598, 2001BKC311>. In the latter case, cyclization of the intermediate hydrazine is followed by migration of the ethoxycarbonyl group, and elimination of the resulting carbonate. The Michael acceptor **44** (**Scheme 18**) has also been treated with hydrazine, and the adduct treated with acid to give a pyrimido[4,5-*c*]-pyridazine <2001H(55)2413>.

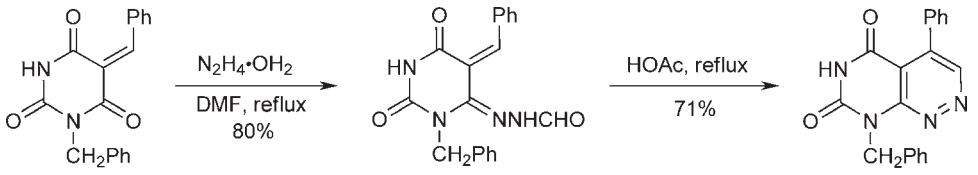


Ar		*Yield (%)*	*Reference*
Ph		76	1998JME3812
p-$C_6H_4CF_3$		85	1998JME3812
	X = Y = H	84	2005JHC1223
	X = H, Y = Cl	88	2005JHC1223
	X = H, Y = Br	89	2005JHC1223
	X = Y = Cl	87	2005JHC1223
	X = Y = Br	83	2005JHC1223
	X = Cl, Y = NO_2	86	2005JHC1223
		90	2005JHC1223

(27)



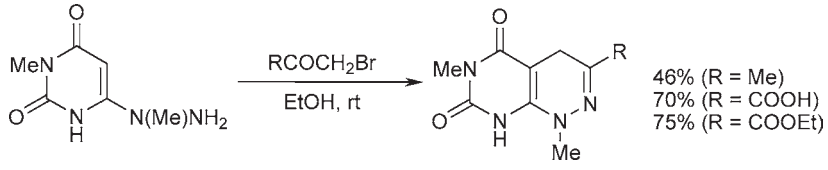
Scheme 17



44

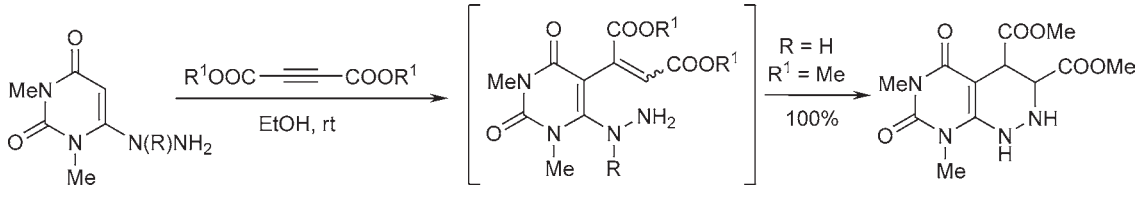
Scheme 18

A second approach described in CHEC(1984) <1984CHEC(3)329>, and used in a number of instances in recent work, involves the reaction of a bifunctional electrophile with a 4-hydrazinopyrimidine. Such electrophiles include α-diketones <2002M79, 2003RCB441, 1996JCM442, 2003BKC1429> and α-ketoesters <1996H(47)315>. In the second case, the six-membered ring is a minor product at best, and cyclization tends to favor the seven-membered ring. Reaction of an *N,N*-disubstituted hydrazine with an α-haloketone (Equation 28) gives a 5,8-dihydropyrimido[4,5-*c*]pyridazine <2004H(63)1393>.



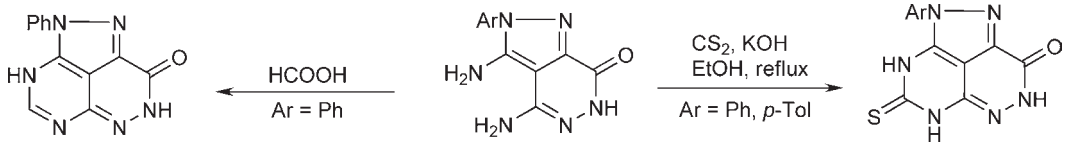
(28)

In the manner already described (*vide supra*) for pyridazinopyridazines, pyrimido[4,5-*c*]pyridazines can be formed by reaction of a 4-hydrazinopyrimidine with a dialkyl acetylenedicarboxylate (**Scheme 19**); in principle, an indazole side product is possible, but this is not observed in practice <1999TL1793>.



Scheme 19

A final approach to pyrimido[4,5-*c*]pyridazines involves construction of a pyrimidine ring from a 3-aminopyridazine-4-carboxylic acid derivative as described in both CHEC(1984) and CHEC-II(1996) <1984CHEC(3)329, 1996CHEC-II(7)737>. Further examples of this approach have appeared since the publication of CHEC-II(1996) <2000JCCS951, 2006JHC243> and the approach has been used to prepare *peri*-fused systems (**Scheme 20**) <1993JRM1239>.

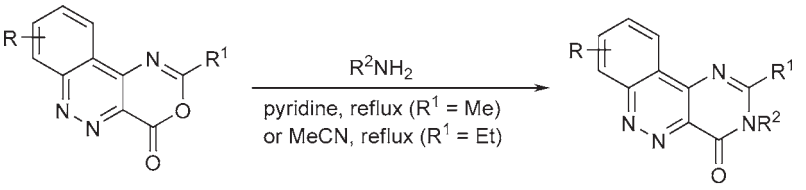


Scheme 20

10.19.2.2.3(ii) Pyrimido[5,4-*c*]pyridazines (F)

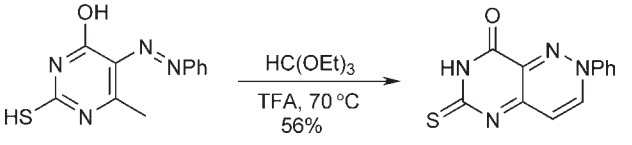
In CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>, the principal route to pyrimido[5,4-*c*]pyridazines involves formation of a pyrimidine ring from a 4-aminopyridazine-3-carboxylic acid. This remains the most common method <1996IJB1185, 1997PHA838, 1998PHA156, 1999M1409>. In a small variation of

the approach, benzannulated derivatives have also been prepared via oxazines (Equation 29). Cyclization of 6-methyl-5-phenylazopyrimidines was also reported in CHEC(1984), and a variation of this method has been described, using the same type of substrate with an orthoformate (Equation 30) <2002CPB364>. Starting from an alloxan hydrazone, it is also possible to form the pyridazine ring by means of a Wittig reaction as shown in **Scheme 21** <1997JCM1576>.

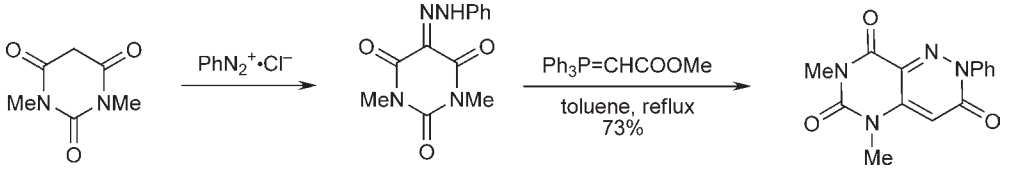


R	R^1	R^2	*Yield* (%)	*Reference*
H	Me	NH_2	86	1998PHA834
H	Me	NHMe	70	1997PHA838
H	Me	$NHCSNH_2$	88	1998PHA834
H	Me	NHAc	72	1998PHA834
H	H	NHPh	83	1998PHA834
H	Me	CH_2CH_2OMe	70	1997PHA91
H	Me	$CH_2CH_2NEt_2$	72	1997PHA838
H	Me	Ph	60	1997PHA838
H	Me	CH_2Ph	78	1997PHA838
8-F	Me	NH_2	79	1998PHA834
9-F	Me	$3,4,5\text{-}C_6H_2(OMe)_3$	76	1997PHA838
7-Cl	Me	$CH_2CH_2NEt_2$	71	1997PHA838
9-Cl	Me	NHAc	69	1998PHA834
$7,8\text{-}Cl_2$	Me	CH_2CH_2OMe	52	1997PHA838
8-Me	Me	Bu	63	1997PHA838
9-Me	Me	NHMe	74	1998PHA834
$8,9\text{-}Me_2$	Me	NH_2	75	1998PHA834

(29)

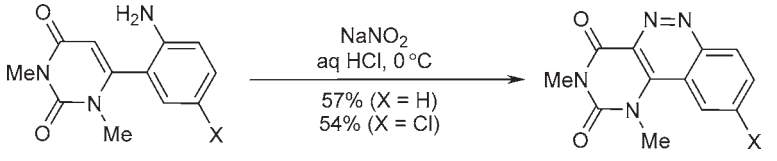


(30)



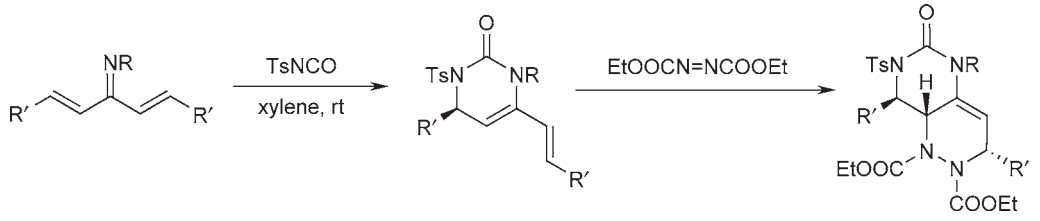
Scheme 21

A novel approach to benzannulated systems <2002T10137> involves diazotization of a 6-(2-aminophenyl)uracil, obtained by Suzuki coupling of the chlorouracil with a 2-pivaloylaminophenylboronic acid, and provides a relatively short route to pyrimido[5,4-*c*]cinnolines (Equation 31).

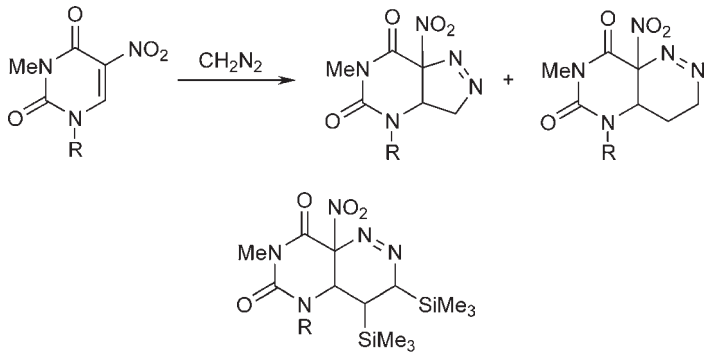


(31)

Two new methods for the construction of reduced forms of this system have also been reported since the publication of CHEC-II(1996). **Scheme 22** illustrates the preparation of an octahydropyrimido[5,4-*c*]pyridazine using sequential [4+2] cycloaddition reactions, the initial azatriene being treated sequentially with a reactive isocyanate and then diethyl azodicarboxylate to provide the cycloadduct <1997CC1013>. Cycloaddition of 5-nitrouracils with diazomethane gives a mixture of pyrazole and pyridazine-fused products (Equation 32) <1997T7045>; the same reaction is observed using $Me_3SiC(Li)N_2$, in which case the disilylated product **45** is isolated, consistent with the addition of two molecules of diazomethane followed by cyclization with the loss of nitrogen. However, the process is not general: in the absence of the electron-withdrawing nitro group, only the pyrazole product is obtained.



Scheme 22

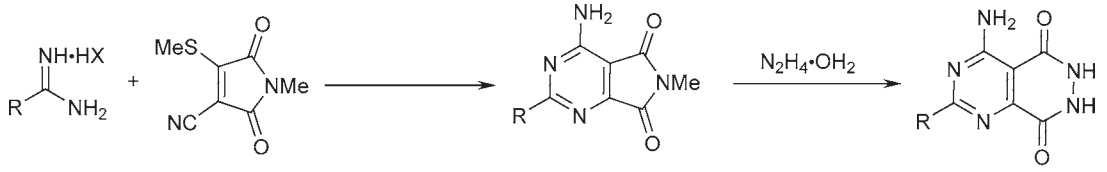


(32)

45

10.19.2.2.3(iii) Pyrimido[4,5-*d*]pyridazines

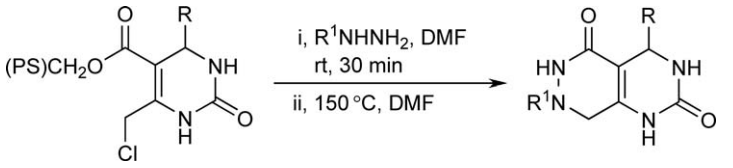
A variety of methods for the preparation of pyrimido[4,5-*d*]pyridazines are discussed in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>, and most of the work that has appeared since describes adaptations of the earlier methods. Notable examples include the use of imide hydrazinolysis in a two-step construction of the ring system (**Scheme 23**) <1996H(43)1597, 2002JHC571>. In addition, the reaction of 4-(halomethyl)pyrimidine-5-carboxylates with



R	X^-	*Yield, step* 1 (%)	*Yield, step* 2 (%)
NH_2	½ CO_3^{2-}	74	62
SCH_2Ph	Cl^-	75	79
Me	Cl^-	56	94
Ph	Cl^-	84	99

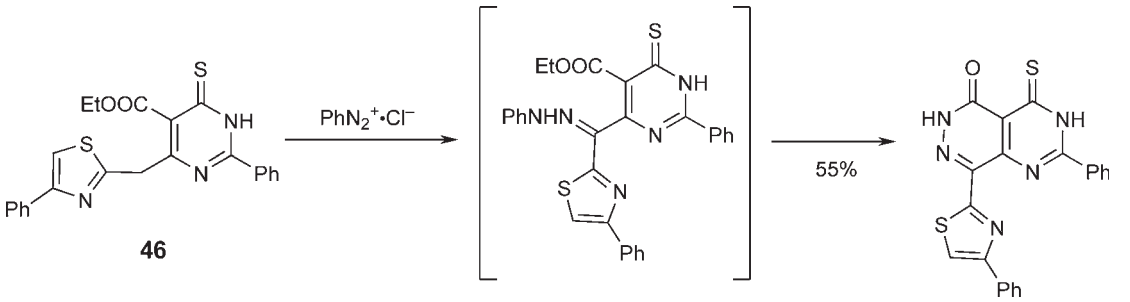
Scheme 23

hydrazines has been adapted to provide a traceless polymer-supported synthesis of pyridazinopyrimidine-2-ones (Equation 33), suitable for the preparation of compound libraries <2002JCO501>.

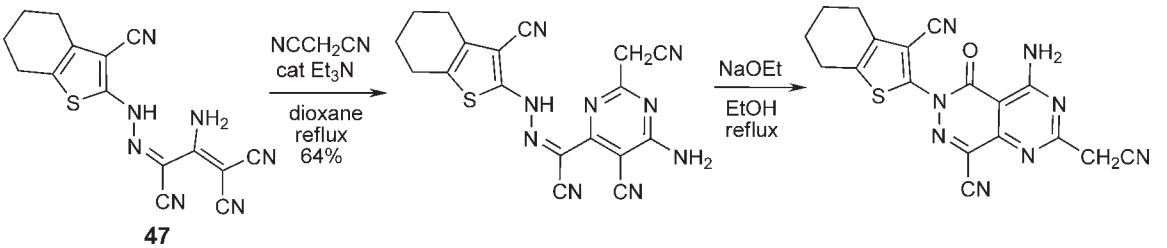


(33)

8-(2-Thiazolyl)pyrimido[4,5-*d*]pyridazines have been prepared by utilizing the reaction of the active methylene compound **46** with benzenediazonium chloride (**Scheme 24**) to give a hydrazone, which cyclizes spontaneously <1999JPR147>. A further approach described recently <2002HAC108> involves reaction of the malononitrile derivative **47** with a further equivalent of malononitrile, forming a pyrimidine with a suitably disposed hydrazine, which cyclizes on exposure to strong base (**Scheme 25**).



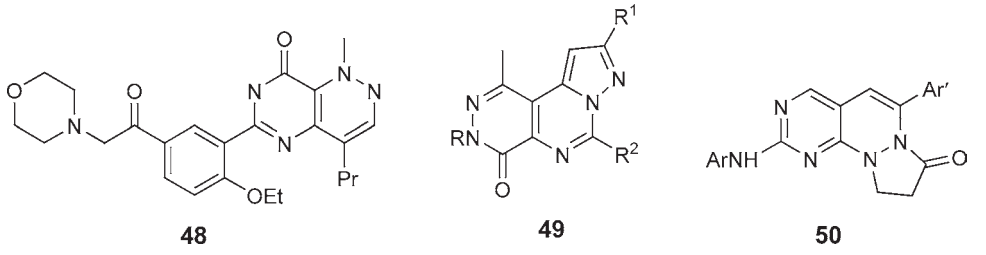
Scheme 24



Scheme 25

10.19.2.2.4 Important compounds and applications

No pyrimidopyridazine derivatives have been marketed since the appearance of CHEC-II(1996). However, the cGMP inhibitor **48** is reported as a backup to sildenafil for the treatment of erectile dysfunction <2001EP1090644> and for the stabilization of blood pressure during hemodialysis <2001USP6271228>, by inhibition of PDE-5 (PDE = phosphodiesterase). Two series of annulated structures **49** and **50** have been described as selective inhibitors of PDE-5 <2005BML2381, 2006JME5363> and lymphocyte specific kinase <2006BML4257, 2006H(68)2037>, respectively. Finally, contrary to earlier reports, it has recently been determined that tricribine **42** is of value in anticancer therapy <2005WO2005/094322>.

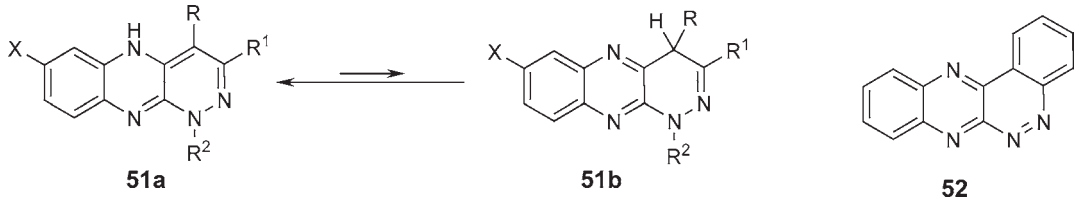


10.19.2.3 Pyrazinopyridazines

The syntheses and reactions of pyridazino[3,4-*b*]quinoxalines, benzo derivatives of the pyrazino[2,3-*c*]pyridazines, have been reviewed <1998JHC1101, 2005JHC387>.

10.19.2.3.1 Theoretical and experimental structural methods

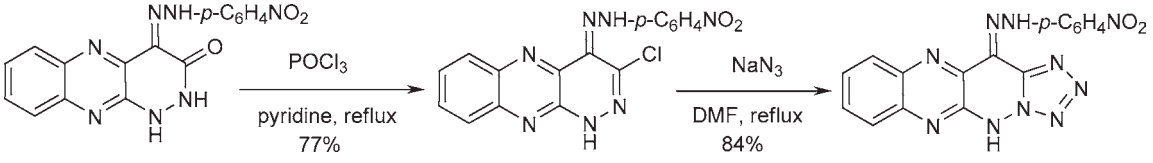
Structural data are available in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737> for the pyrazinopyridazines. Since the publication of the latter, some additional data have been reported for a number of pyridazino[3,4-*b*]quinoxalines. 4-Substituted derivatives **51** (R = COOR, COR, CN), are reported to exist predominantly as the 5*H* tautomer **51a** from NMR data, an NOE being observed between the NH and H-6. <1993JHC1659, 2002JKC581, 2002H(56)291>. Modified neglect of diatomic overlap (MNDO) calculations have been reported for quinoxalinocinnoline **52**: these indicate that the quinoxaline and benzo subunits act as independent aromatic systems, with little interaction between them, so that halide substitutents in the benzo subunit are not particularly susceptible to nucleophilic displacement <1994J(P1)2751, 1996J(P1)1699> while N-5 and N-6 are essentially nonbasic.



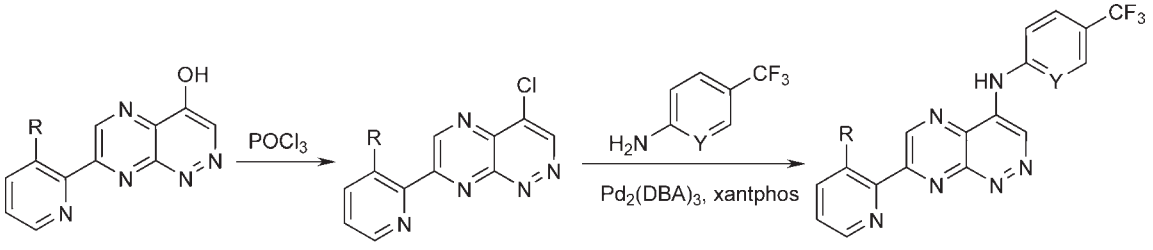
10.19.2.3.2 Reactivity

10.19.2.3.2(i) Pyrazino[2,3-*c*]pyridazines

Little information concerning the reactivity of this system was included in either CHEC(1984) or CHEC-II(1996). However, a variety of results have been appeared in the past decade. Pyrazino[2,3-*c*]pyridazines undergo nucleophilic substitution at C-3 (**Scheme 26**) <1997JHC39> and at C-4 (**Scheme 27**) <2005WO2005/099710>. In the presence of acid, a protonated dibenzannulated species is susceptible to nucleophilic addition (**Scheme 28**); the quinonoid adduct is air stable as a salt, but aromatizes in the presence of base <1996J(P1)1699>. The process is unaffected by

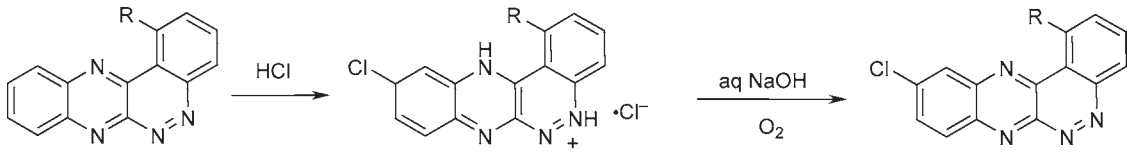


Scheme 26

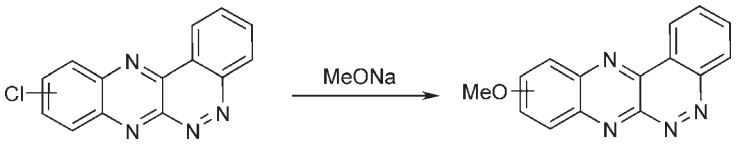


Scheme 27

the presence of a chloro substituent at position 1 (R = Cl vs. H) but is rather less efficient where R = Me, possibly as a result of steric hindrance to protonation. The chlorine substituent thus introduced is itself susceptible to nucleophilic displacement (Equation 34) <1994J(P1)2751>.

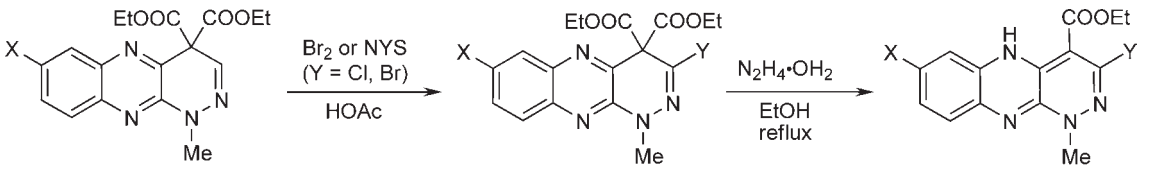


Scheme 28



(34)

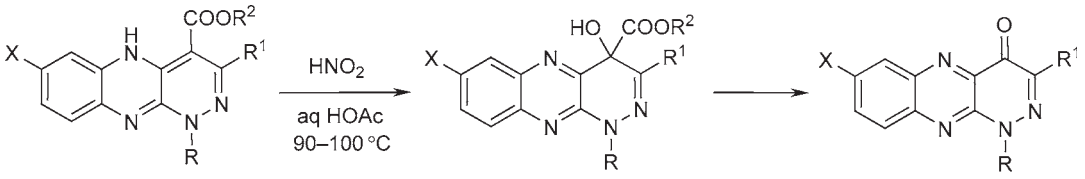
Reports of electrophilic substitution are scarce, but pyridazino[2,3-*b*]quinoxaline-4,4-dicarboxylates reportedly undergo bromination and chlorination at C-3 with *N*-halosuccinimides in acetic acid (**Scheme 29**). Treatment of the product with hydrazine hydrate results in hydrolysis and mono-decarboxylation <2003JHC837>.



X	*Y*	*Step* 1 *conditions* (*yield*)	*Step* 2 *yield* (%)
H	Br	Br_2, HOAc, rt (49%)	78
Cl	Br	NBS, HOAc, reflux (60%); Br_2, HOAc, rt (75%)	92
H	Cl	NCS, HOAc, reflux (29%)	79
Cl	Cl	NCS, HOAc, reflux (61%)	95

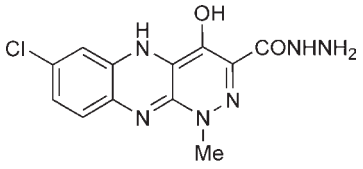
Scheme 29

Several methods have been described for the introduction of a carbonyl substituent at C-4, among which nitrous acid oxidation of a 3,4-dicarboxylate (**Scheme 30**) followed by treatment with base is most commonly used. It is suggested that the active oxidant is nascent oxygen <2000JHC791>; this can abstract the NH proton, and the resulting radical can either couple with a hydroxyl radical to form the alcohol directly, or suffer further oxidation to the pyridazinoquinoxalinium cation, which would be expected to undergo attack of water at C-4. A third proposed mechanism involves epoxidation of the C(4)–C(4a) double bond, followed by ring opening. Although the 4-hydroxy species eliminates methyl formate upon exposure to base, it is stable to acid and to treatment with oxidants. Treatment of the oxidation product (**Scheme 30**: R^1 = COOMe) with hydrazine hydrate to form an acyl hydrazide also results in reduction of the carbonyl to form a 1,5-dihydro product such as **53** <2005JHC551>. This is converted into the acyl azide on treatment with sodium nitrite in acetic acid, and the latter undergoes a Curtius rearrangement to give 3-amino derivatives or their carbamates, depending upon the reaction conditions.



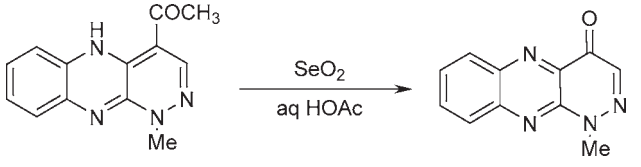
R	R^1	R^2	*X*	*Step* 1 *yield* (%)	*Step* 2 *conditions* (*yield*) (%)	*Reference*
Me	H	Et	Cl	43	KOH, aq EtOH, reflux (74%)	2002H(58)359
Me	Cl	Et	Cl	94	$N_2H_4{\cdot}OH_2{\cdot}OH_2$, EtOH (97%) then NBS, aq HOAc (87%)	2003JHC837
Me	Cl	Et	H	92	$N_2H_4{\cdot}OH_2{\cdot}OH_2$, EtOH (94%) then NBS, aq HOAc (97%)	2003JHC837
Me	Br	Et	Cl	93	$N_2H_4{\cdot}OH_2{\cdot}OH_2$, EtOH (86%) then NBS, aq HOAc (82%)	2003JHC837
Me	Br	Et	H	80	$N_2H_4{\cdot}OH_2{\cdot}OH_2$, EtOH (89%) then NBS, aq HOAc (93%)	2003JHC837
Me	COOMe	Me	H	59	DBU, EtOH, reflux (55%)	2000JHC791
Me	COOMe	Me	Cl	70	DBU, EtOH, reflux (83%)	2000JHC791
Et	COOMe	Me	H	57	DBU, EtOH, reflux (54%)	2000JHC791
Et	COOMe	Me	Cl	84	DBU, EtOH, reflux (84%)	2000JHC791
Me	CF_3	Et	H	92	DBU, EtOH, reflux (81%)	2002H(56)291
Me	CF_3	Et	Cl	96	DBU, EtOH (71%) then $NaBrO_3$, aq HOAc (84%)	2002H(56)291

Scheme 30

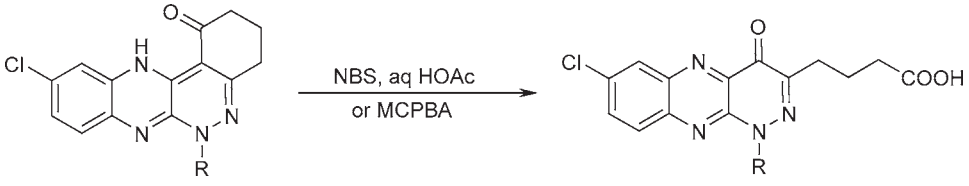


53

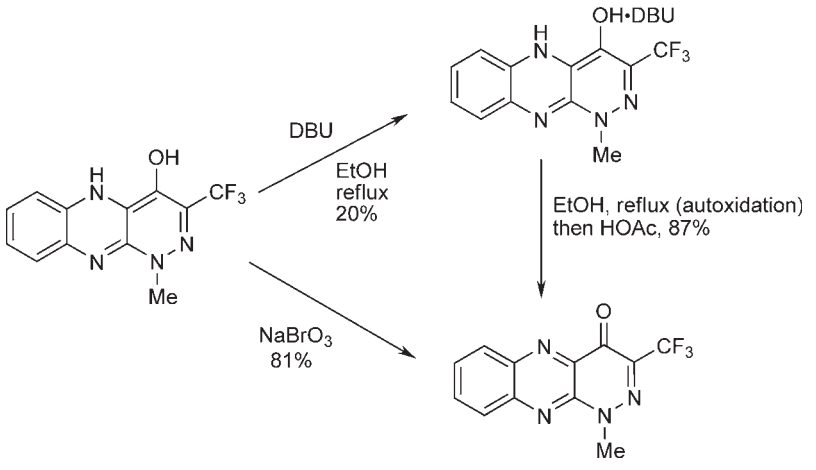
Other means for the introduction of a 4-oxo substituent include the Baeyer–Villiger oxidation of 4-acetylpyridazino[3,4-*b*]quinoxalines using selenium dioxide (Equation 35), NBS, or sodium bromate <2002H(56)291, 2002H(58)359, 2002JHC551>. Baeyer–Villiger oxidation has also been used to prepare 4-oxopyridazino[3,4-*b*]quinoxaline-3-butanoic acids as shown in Equation 36 <2000JHC1257>. 1,5-Dihydro derivatives of the same system are also oxidized to the 4-oxo species (**Scheme 31**), either by treatment with sodium bromate or by autoxidation of their 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) complexes <2002H(56)291>.



(35)



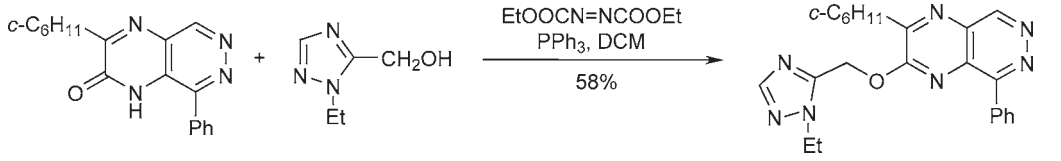
(36)



Scheme 31

10.19.2.3.2(ii) Pyrazino[2,3-*d*]pyridazines

The reactivity of this system was discussed in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>, and few additional results have appeared since. Of some interest is the reported 7-O-alkylation using Mitsunobu conditions (Equation 37) <2001WO2001/051492, 2006TL2257>.

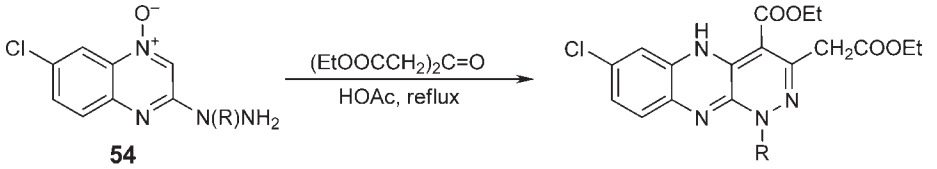


(37)

10.19.2.3.3 Ring synthesis

10.19.2.3.3(i) Pyrazino[2,3-*c*]pyridazines

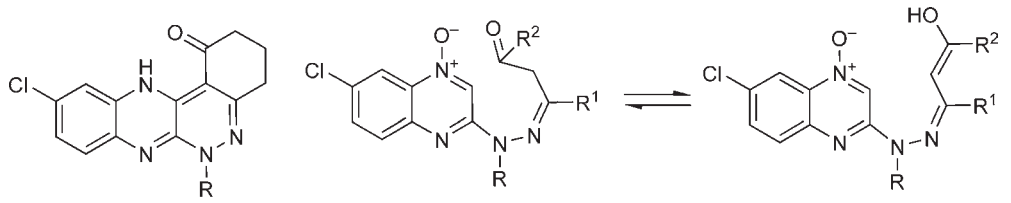
A number of approaches to pyrazino[2,3-*c*]pyridazines were disussed in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>. The formation of pyridazino[3,4-*b*]quinoxalines by reaction of a 2-hydrazinoquinoxaline-4-oxide **54** with dimethyl acetylenedicarboxylate (DMAD) was described in CHEC-II(1996), and has been reviewed on several occasions since <1995JHC1085, 2002JHC551, 2005JHC387>. An alternative to this method involves the reaction of **54** with a 1,3-dicarbonyl species such as an acetonedicarboxylate (Equation 38). The corresponding reaction with 1,3-cyclohexanedione has been used to prepare the annellated species **55** <2000JHC1257>. 2-(1-Pyrazolyl)quinoxaline-4-oxides are commonly obtained as side products in these processes, and it is probable that the process proceeds via a tautomeric species such as **56**, where the keto form **56a** can collapse to form a pyrazole, while the enol form **56b** attacks at C-3 of the quinoxaline to form the tricyclic product <1996JHC757, 2000JHC103>.



54

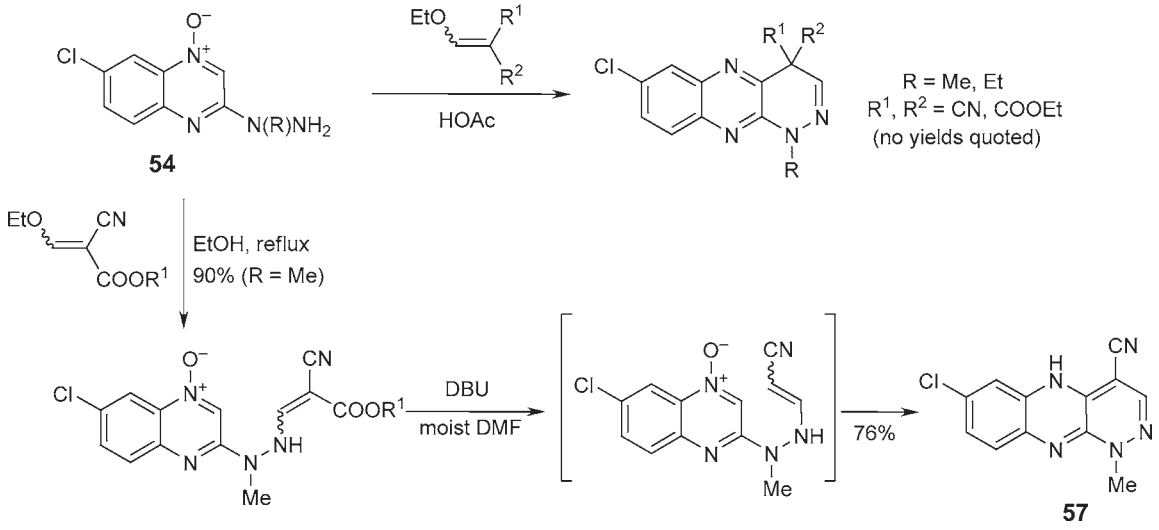
(38)

Conditions	*Yield, R = Me* (%)	*Yield, R = Et* (%)
HOAc, H_2SO_4	76	80
HOAc alone	64	96



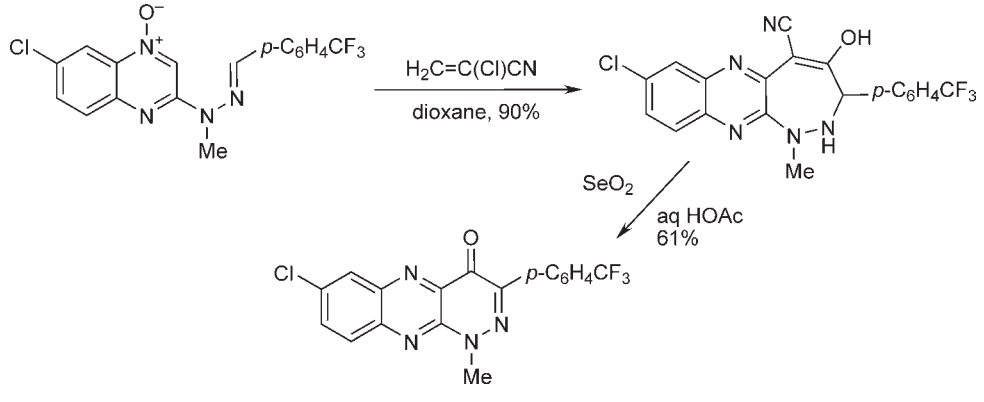
55 **56a** **56b**

Further variations on the same principle involve reaction of **54** with ethoxymethylenecyanoacetates and related species <2002JHC551> in acetic acid to form a product bearing two ester or nitrile groups at C-4 (**Scheme 32**). Alternatively, treatment of the intermediate enehydrazine with base results in decarboxylation, which is followed by cyclization to the 1,5-dihydro species **57** <1993JHC1659>. The corresponding reactions with ethoxymethylenemalonates and with 1,3-diketone derivatives <2002H(58)359, 2002H(56)291> have also been reported, and provide analogues of **57** bearing ester or acyl groups in place of the nitrile at C-4. A stepwise process to the same system has been described also <2001H(54)359, 2002JHC551>, wherein a hydrazone undergoes cyclization in the presence of chloroacrylonitrile; the intermediate diazepine undergoes a ring contraction on treatment with *N*-bromosuccinimide (NBS) in water <1996CHEC-II(7)737> or selenium dioxide <1999JKC302> to form the pyridazine ring (**Scheme 33**). This method has also been used to prepare analogues bearing a furanyl or thienyl substituent at C-3 <2005JHC249>.



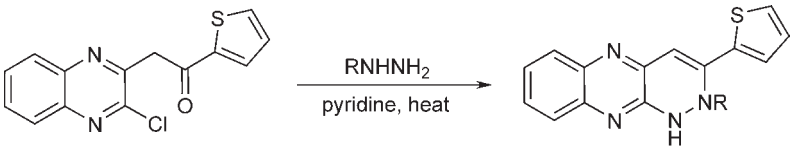
54 **57**

Scheme 32



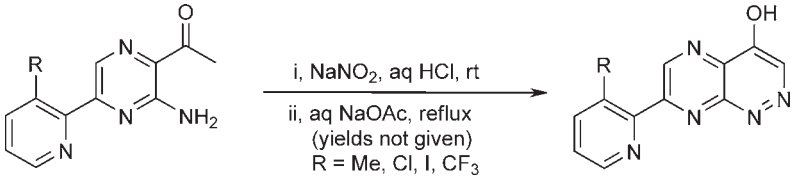
Scheme 33

Further examples of annulation of a pyridazine ring onto an existing pyrazine have been reported, which involve the reaction of a hydrazine with a pyrazine bis-electrophile, as illustrated in Equation (39) <2000PS(165)205>.

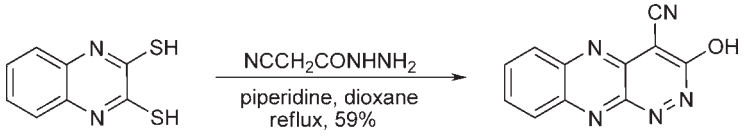


(39)

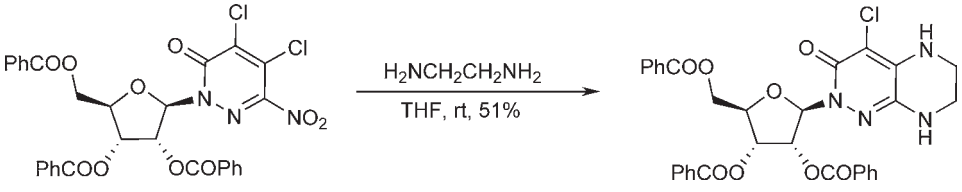
Diazotization of a 3-acetyl-2-aminopyrazine <2005WO2005/099710> provides an alternative approach to the pyrazino[2,3-*c*]pyridazine (Equation 40). The formation of either the pyrazine or a pyridazine ring by addition of the four ring atoms onto its counterpart in a single step has also been reported; Equation (41) illustrates the reaction of a pyrazine 2,3-bis-electrophile with cyanoacetic acid hydrazide to form a pyridazine ring in a single step <2000PS(164)259>, while Equation (42) illustrates an equivalent process, using ethylenediamine to form a pyrazine ring by displacement of chloride and nitrite <1992JHC1409>.



(40)



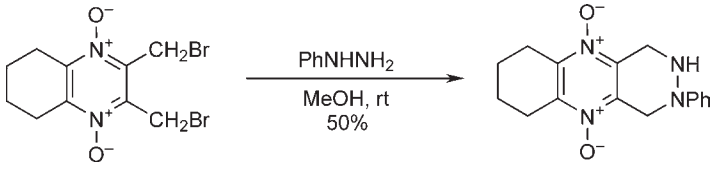
(41)



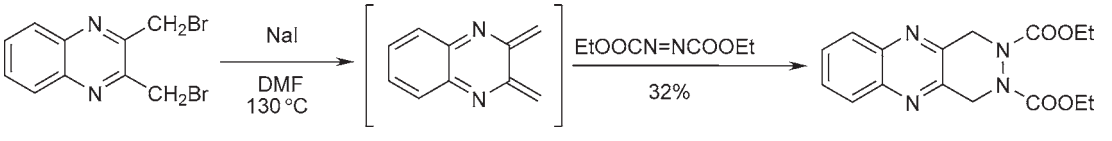
(42)

10.19.2.3.3(ii) Pyrazino[2,3-*d*]pyridazines

As described in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>, the reaction of a pyrazine-2,3-dicarboxylic acid derivative with a hydrazine remains a major means for preparation of pyrazino[2,3-*d*]pyridazines <1994JHC1135, 2000JIC494, 2002IJB1486, 2002CHE336>, and the corresponding reaction of 2,3-bis(bromomethyl)pyrazine-*N*-oxides (Equation 43) has been reported <1993CHE437>. An equivalent conversion <1995TL6777> is achieved by cycloaddition of diethyl azodicarboxylate (DEAD) with a diene formed from a 2,3-bis(bromomethyl)pyrazine (**Scheme 34**).

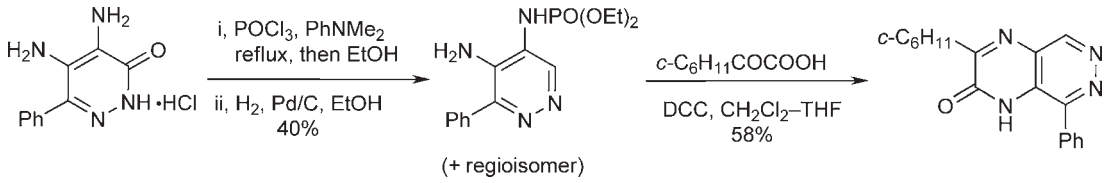


(43)



Scheme 34

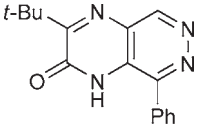
Cyclocondensation of 4,5-diaminopyridazinones with 1,2-diketones was described in both CHEC(1984) and CHEC-II(1996); a further example of this process has been reported, using glyoxal <1992JHC87>, along with a variation <2001WO2001/051492, 2006TL2257>, wherein an N-phosphorylated diamine undergoes an aza-Wadsworth Emmons reaction with an α-ketocarboxylic acid under comparatively mild conditions (**Scheme 35**).



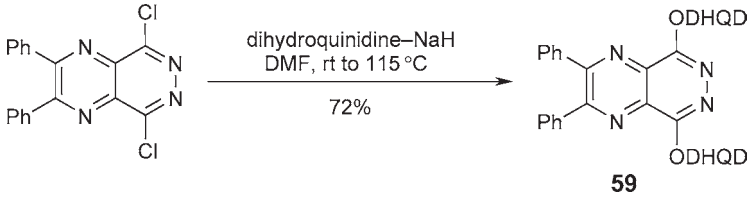
Scheme 35

10.19.2.3.4 Important compounds and applications

No new pyrazinopyridazine derivatives have been marketed as pharmaceuticals or agrochemicals, although the simple derivative **58** is reported as a high-affinity gamma-aminobutyric acid (GABA) antagonist <2006TL2257>. The dihydroquinidine derivative **59**, whose preparation is shown in Equation (44), is of interest as a chiral ligand in the Sharpless asymmetric dihydroxylation reaction <1993TA133>.



58



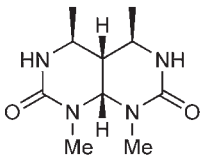
59 (44)

10.19.2.4 Pyrimidopyrimidines

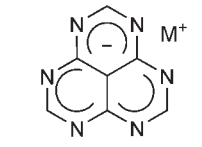
10.19.2.4.1 Theoretical and experimental structural methods

10.19.2.4.1(i) Pyrimido[4,5-*d*]pyrimidines

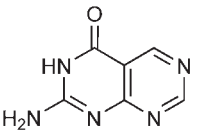
Spectrometric data for pyrimido[4,5-*d*]pyrimidines were discussed in detail in CHEC(1984) <1984CHEC(3)329>, and additional structural data are referenced in CHEC-II(1996) <1996CHEC-II(7)737>. Limited new data have been published regarding tautomerism <2000PS(158)9>. Crystal structure data have been reported for 2,7-dione derivative **60** <1995RCB131>, confirming the all-*cis* stereochemistry shown, and for the hexaazaphenalenyl anion **61**, whose structure is characterized by strong π-stacking and hydrogen bonding <2005IC8197>. 2-Aminopyrimido[4,5-*d*]pyrimidin-4-one **62** has been studied in the context of its N-alkylation <2003EJM719>. Based on similarities between the UV spectra of neutral and protonated forms of **62**, it is concluded that protonation occurs principally at N-1 (pK_a 2.8), the resulting cation being stabilized by delocalization between the three nitrogen atoms of the same ring. Molecular orbital (MO) calculations have been reported for the 2,4-dione **63**, which show that the effective π-charge at C-7 (+0.198) is greater than that at C-5 (+0.183), thereby favoring nucleophilic attack at C-7 <1994CHE1083>.



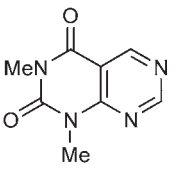
60



61



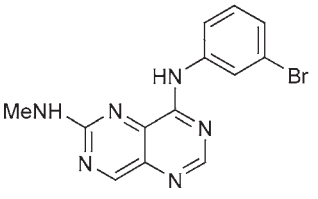
62



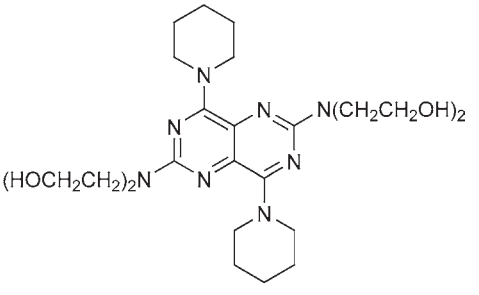
63

10.19.2.4.1(ii) Pyrimido[5,4-*d*]pyrimidines

Some spectrometric and structural data for pyrimido[5,4-*d*]pyrimidines were reported in CHEC(1984) and CHEC-II(1996) <1984CHEC(3)329,1996CHEC-II(7)737>; some additional data have been reported since. The X-ray crystal structure of **64**, when compared to pyrido[3,2-*d*]- and pyrido[3,4-*d*]pyrimidines with an analogous substitution pattern, illustrates that a nitrogen atom at the 5-position leads to rather less deformation of the molecule than a carbon <1997JMC1820>, as it avoids the need to relieve steric interactions between the C-5 and N-9 protons. MO calculations have been used to determine the first and second ionization potentials of the anticoagulant dipyridamole **65** as 239.04 and 554.85 kcal mol^{-1}, respectively, the first electron being removed from a ring nitrogen atom <2001CPL(349)146>. N-1(5) is calculated as the favored site of protonation (ΔH_f −13.95 kcal mol^{-1}), diprotonation being unfavorable due to the high energy required (197.94 kcal mol^{-1}). The mass spectrometric behavior of **65** has also been described <2003JMP540>.

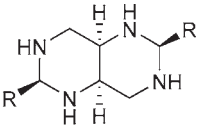


64

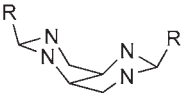


65

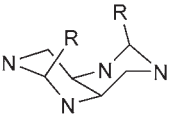
Both theoretical and experimental studies have been reported for *cis*- and *trans*-1,3,5,7-tetraazadecalin systems **66** and **67** <1996AJC285, 1998JOC8850>. The former is reportedly more stable as the *N*-inside form **66a** (calc. ΔH_f 29.6 kJ mol^{-1}) than as the *N*-outside form **66b** (calc. ΔH_f 56.3 kJ mol^{-1}), although the two forms exist in equilibrium. The more crystalline *trans*-form **67** again exists in two all-chair conformations, **67a** and **67b**, of which the former (calc. ΔH_f 37.8 vs. 46.1 kJ mol^{-1} for R = H) is more stable <1996AJC285>. The conformational effect of changing the 2- and 6-substituents is reportedly small.



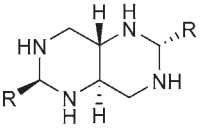
66



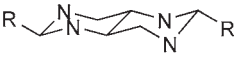
66a



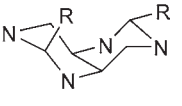
66b



67



67a



67b

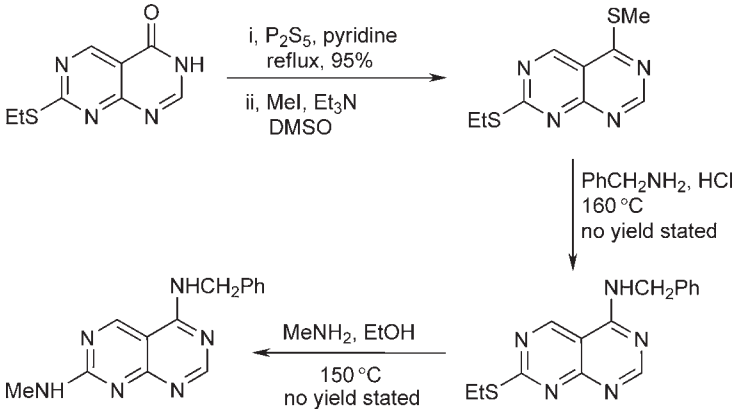
Unlike many saturated 1,3-diaza heterocycles, NMR data of **66** and **67** show no evidence of ring-chain tautomerism <1998JOC8850>; the NMR spectra have been assigned fully, the small vicinal coupling constants observed for H-4

and H-8 being consistent with a *gauche* relationship between groups at the bridgehead, as in **66a**. The NMR spectrum of **67** (R = H) contains only four resonances as a result of its high symmetry, but the signals are complex, and its structure was confirmed independently by X-ray diffraction; **67** is the first reported example of a 1,3-diazine with all of the N–H bonds axial. Detailed theoretical calculations have been reported for **66** and **67**, and the stereochemistries of both are strongly influenced a double anomeric effect.

10.19.2.4.2 Reactivity

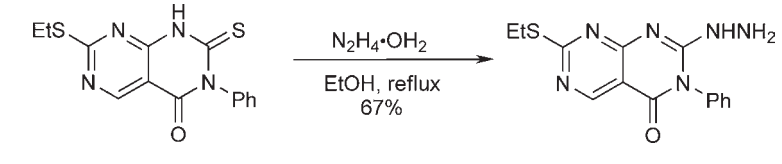
10.19.2.4.2(i) Pyrimido[4,5-*d*]pyrimidines

The nucleophilic reactivity of pyrimido[4,5-*d*]pyrimidines was reviewed in CHEC(1984) <1984CHEC(3)329>, most of the examples cited involving displacement of a chlorine or alkylthio substituent by a nitrogen nucleophile. Additional examples have appeared more recently of the displacement by amines of chloro <2004WO041821>, methylthio <2005WO2005/121142>, benzylthio <2003WO03/082871>, benzylsulfinyl and -sulfonyl <2001WO01/29041>, methanesulfonyl <2000WO00/24744, 2004WO065378, 2005WO2005/011597>, and benzenesulfonyl <2000USP6060477, 2001WO01/29041> groups at C-2(6) of the pyrimido<4,5-*d*]pyrimidine system. Useful selectivity in nucleophilic displacement has been reported also: the displacement of a C-4 alkylthio group in the presence of a similar group at C-7 has been reported <1995WO95/19774, 1997USP5654307>; the latter group is then displaced with an excess of a second amine (**Scheme 36**).

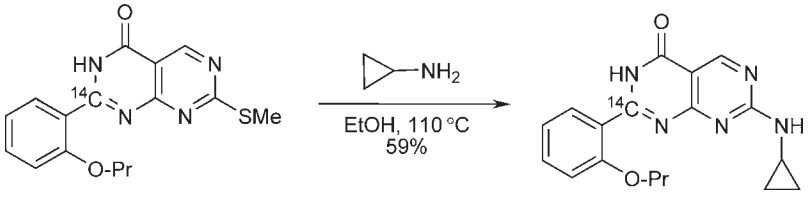


Scheme 36

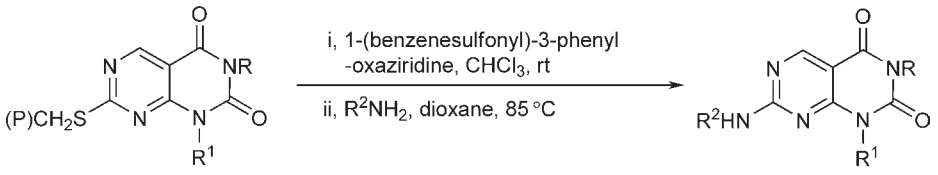
The selective displacement of a 2-thione in the presence of 4-oxo and 7-ethylthio substituents (Equation 45) has also been reported <2000PS(158)9>. The displacement of a 2-methylthio group using cyclopropylamine (Equation 46) has also been used in the synthesis of radiolabeled phosphodiesterase inhibitor SKF 97992 <1995JLR891> and as a means of cleaving an alkylthio linker used in the solid-phase synthesis of a compound library (Equation (47); (P) indicates a polymer support)<2003S1739>. The selective displacement of a 7-benzylsulfonyl group in the presence of a primary methanesulfonyl group has also been reported (Equation 48)<2001WO01/29041>.



(45)

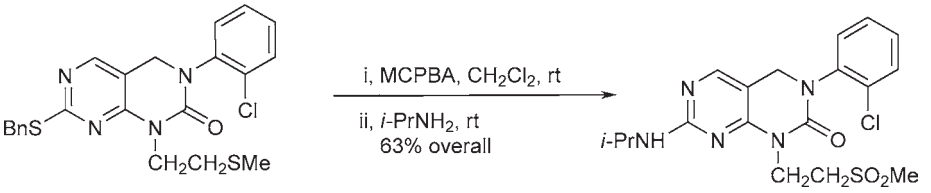


(46)



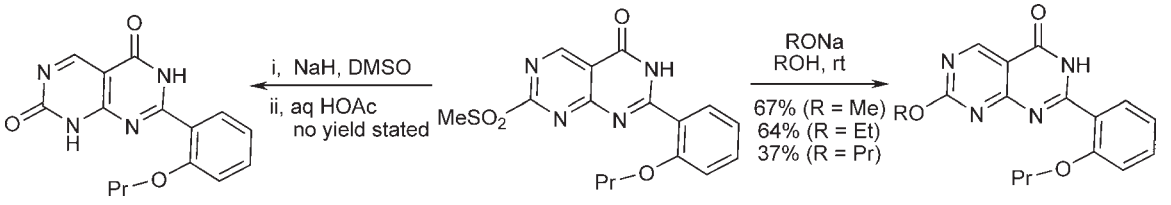
R	R^1	R^2NH_2	*Yield* (%)
Ph	H	Pyrrolidine	68
Ph	4-NCC_6H_4	Pyrrolidine	61
Ph	cyclohexyl	Pyrrolidine	65
Ph	cyclopentyl	Pyrrolidine	48
Ph	CH_2CH_2CN	Pyrrolidine	70
2-FC_6H_4	H	Pyrrolidine	42
2-FC_6H_4	4-NCC_6H_4	Pyrrolidine	72
2-FC_6H_4	CH_2CH_2CN	Pyrrolidine	69
2-FC_6H_4	cyclopropyl	3-Morpholin-4-yl-propylamino	45
Pr	H	Pyrrolidine	67
3-$EtOOCC_6H_4$	CH_2CH_2CN	3-Morpholin-4-yl-propylamino	59
3-$EtOOCC_6H_4$	3-FC_6H_4	3-Morpholin-4-yl-propylamino	52
3-$EtOOCC_6H_4$	4-NCC_6H_4	3-Morpholin-4-yl-propylamino	55
Ph-AlaOMe	4-NCC_6H_4	Pyrrolidine	59
Ph-AlaOEt	H	3-Morpholin-4-yl-propylamino	65
Ph-AlaOMe	4-NCC_6H_4	Pyrrolidine	75
Ph-AlaOEt	4-NCC_6H_4	3-Morpholin-4-yl-propylamino	61
Ph-AlaOEt	H	2-Pyridin-2-ylethylamino	70
Ph-AlaOEt	CH_2COOEt	3-Morpholin-4-yl-propylamino	72

(47)



(48)

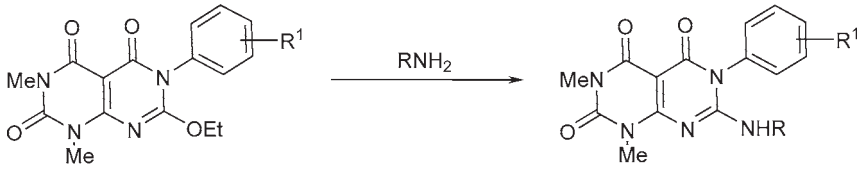
Extensions of the nucleophilic reactivity of pyrimido[4,5-*d*]pyrimidines have been reported since the appearance of CHEC-II(1996), and include the displacement of a methanesulfonyl group by oxygen nucleophiles (**Scheme 37**) <2000USP6060477> and the displacement of an ethoxy group by a range of nitrogen nucleophiles, as exemplified in Equation (49) <1999HCO365>. Oxidative amination of pyrimido[4,5-*d*]pyrimidine-2,4-diones proceeds in the presence of potassium permanganate <1994CHE1083>, generally forming the 7-amino product (Equation 50) as a result both of the greater electron deficiency at C-7 than at C-5, and of the greater steric hindrance to attack at C-5.



Scheme 37

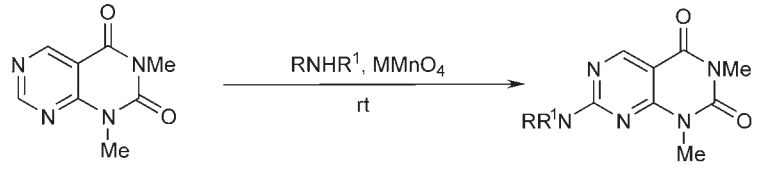
Recently, palladium-catalyzed carbonylation of chloropyrimido[4,5-d]pyrimidines has been reported (Equation 51) <2006WO065703>. Raney nickel-mediated desulfurization of alkylthiopyrimido[4,5-*d*]pyrimidines was described in CHEC(1984), and has been applied recently both in the desulfurization of reduced species (Equation 52) <2001WO64679> and for cleavage of sulfur linkages in traceless solid-phase synthesis <1999BMCL965,

1999MI33>. Covalent hydration of pyrimido[4,5-*d*]pyrimidines was reported in CHEC-II(1996) <1996CHEC-II(7)737>; covalent hydration across the 7–8 bond of 6- and 8-methylated species **68** and **69** has been investigated in detail <2003EJM719>.



R	R^1	*Conditions*	*Yield* (%)
H	4-Me	$CHCl_3$–EtOH, reflux	73
H	2-COOMe	$CHCl_3$–EtOH, reflux	84 (as R = COOH)
NH_2	H	Hydrazine, reflux	75
NH_2	4-Me	Hydrazine, reflux	88
NH_2	3-CF_3	Hydrazine, reflux	71
CH_2COOEt	4-Me	$CHCl_3$, rt	57
CH(Me)COOEt	4-Me	DMSO, 150 °C	22 (as R = COOH)
CH(Me)COOEt	3-CF_3	DMSO, 150 °C	17 (as R = COOH)
CH(Me)Ph	4-Me	90 °C	69

(49)

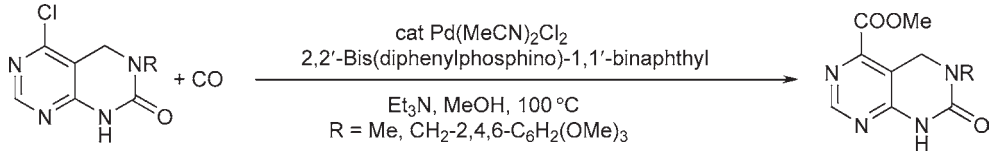


RNHR^1	*Oxidant*	*Yield* (%)
NH_3	$KMnO_4$	79
$MeNH_2$	$KMnO_4$	90[a]
$EtNH_2$	$KMnO_4$	78

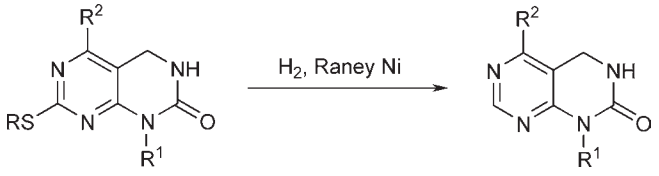
RNHR^1	*Oxidant*	*Yield* (%)
t-$BuNH_2$	$AgPy_2MnO_4$	51
Piperidine	$AgPy_2MnO_4$	75
Morpholine	$AgPy_2MnO_4$	83

[a]Inseparable 2.6:1 mixture of 7-and 5-adducts.

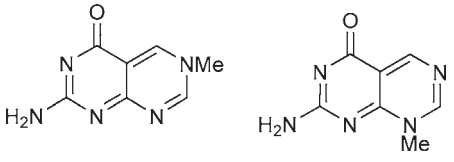
(50)



(51)

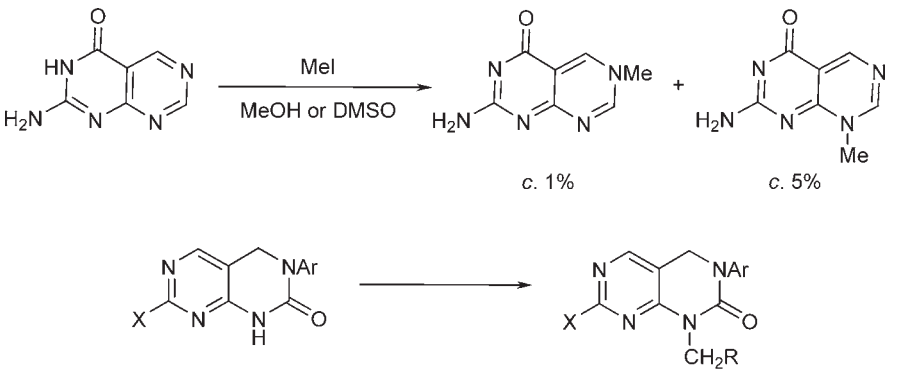


(52)

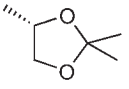
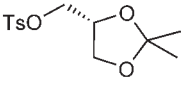
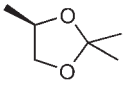
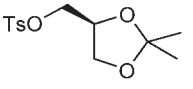
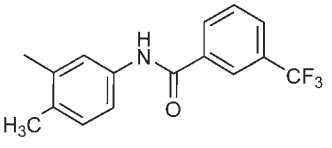
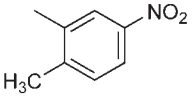


68 **69**

Methylation of 2-aminopyrimido<4,5-*d*]pyrimidin-4-ones under conventional conditions proceeds to give only small quantities of 6- and 8-methylated derivatives (Equation 53), accompanied by ring-cleavage products <2003EJM719>, but alkylation of 4,5-dihydropyrimido<4,5-*d*]pyrimidin-2-ones is considerably more efficient under a variety of conditions (Equation 54).

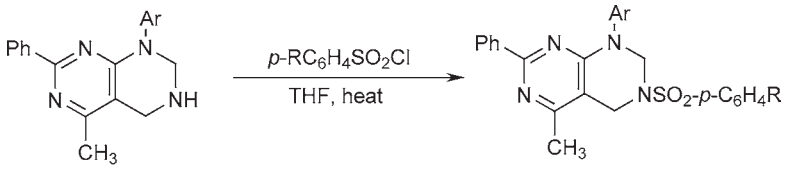


(53)

X	Ar	R	Conditions	Yield (%)	Reference
NH-*i*-Pr	2-ClC$_6$H$_4$	CH_2OMe	$MeOCH_2CH_2OH$ *i*-PrOOCN=NCOO-*i*-Pr PPh_3, THF, 55–60 °C	28	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$	$CH_2NPhthal$	$PhthalNCH_2CH_2OH$, EtOOCN=NCOOEt, PPh_3, dioxane	90	2003WO03/082871
SCH_2Ph	2-ClC$_6$H$_4$	CH_2OTIPS	$TIPSOCH_2CH_2I$, NaH, DMF, 0–30 °C	56	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$	CH_2SMe	$MeSCH_2CH_2OH$, PrOOCN=NCOO-*i*-Pr PPh_3, THF, rt	88	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$	CH_2-1-piperidinyl	Piperidine-1-ethanol PrOOCN=NCOO-*i*-Pr PPh_3, THF, rt	57	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$	COOEt	NaH, DMF, rt then $BrCH_2COOEt$	74	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$			90	2001WO01/29041
SCH_2Ph	2-ClC$_6$H$_4$		K_2CO_3, DMF, 80 °C 	98	2001WO01/29041
SMe		H	K_2CO_3, DMF, 80 °C NaH, DMF, 0 °C then MeI, rt	82	2005WO2005/011597
SO_2Me		H	NaH, DMF, 0 °C then MeI, rt	70	2005WO2005/011597

(54)

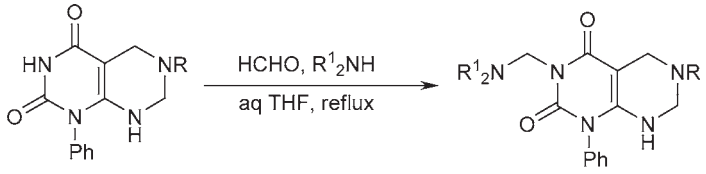
Further examples of N-substitution have been reported, including the sulfonylation of tetrahydro systems (Equation 55) <2004MI321>, and the reaction of tetrahydropyrimido[4,5-*d*]pyrimidine-2,4-diones with methylenimines formed *in situ* (Equation 56), which occurs selectively at the amide nitrogen <1996APH39>. Pyrimido[4,5-*d*]pyrimidine-2,4-dione can also be converted into nucleoside analogues by means of a modified Hilbert–Johnson reaction (Equation 57), the 1,3-bis-alkylation product being formed as a minor contaminant <1997JHC1581>.



(55)

R	*Ar*	*Yield* (%)
Me	3,4-$Cl_2C_6H_3$	74
Me	3,4-$Cl_2C_6H_3$	77
Me	4-FC_6H_4	73
Me	4-HOC_6H_4	70

R	*Ar*	*Yield* (%)
NHAc	3,4-$Cl_2C_6H_3$	73
NHAc	3,5-$Cl_2C_6H_3$	69
NHAc	4-FC_6H_4	78
NHAc	4-ClC_6H_4	82

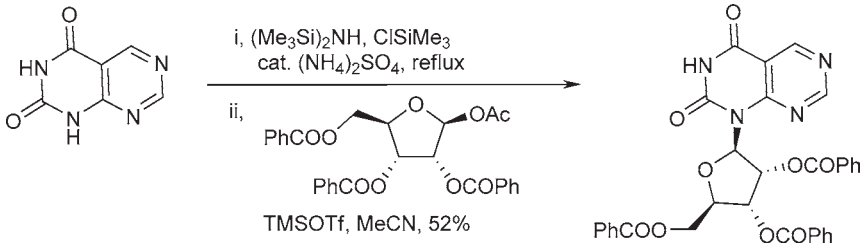


(56)

R	*R^1_2NH*	*Yield* (%)
CH_2Ph	Piperidine	50
CH_2CH_2OH	Piperidine	70

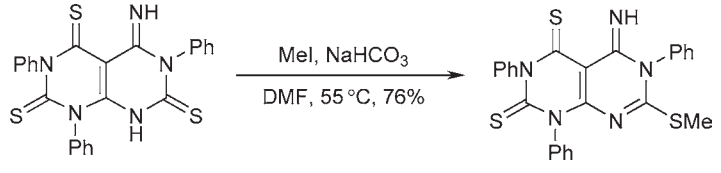
R	*R^1_2NH*	*Yield* (%)
CH_2Ph	1-Phenylpiperazine	72
Cy[a]	1-Phenylpiperazine	35

[a]Reaction in dioxane.

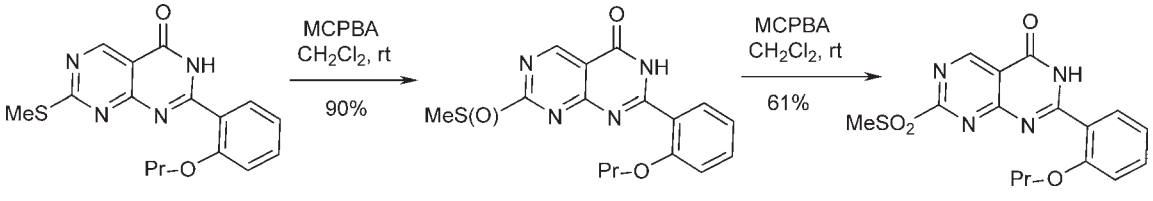


(57)

The reactivity of thione and alkylthio substituents toward nucleophilic displacement has been described above. *S*-Alkylation of pyrimido[4,5-*d*]pyrimidinethiones is a reasonably efficient process <1998BCJ2387, 2000PS(158)9> and it is possible to carry out the alkylation of one thione in the presence of two others (Equation 58) <2003BMC2575>. Oxidation of alkylthio substituents to the corresponding sulfoxides and sulfones has been reported on a number of occasions, usually with *m*-chloroperbenzoic acid (MCPBA) as the oxidant <1995WO95/19774, 1997USP5654307, 2001WO01/29041>, although magnesium monperoxyphthalate <2006BMCL4400>, oxaziridines <1999WO99/61444, 2006WO038112>, and dimethyldioxirane <1995WO95/19774, 1997USP5654307> have been used with comparable efficiency. Such oxidation generally gives either the sulfone or a mixture of the sulfone and sulfoxide (both of which are susceptible to nucleophilic displacement), but an example of a stepwise oxidation sequence has been reported (**Scheme 38**) <2000USP6060477>.

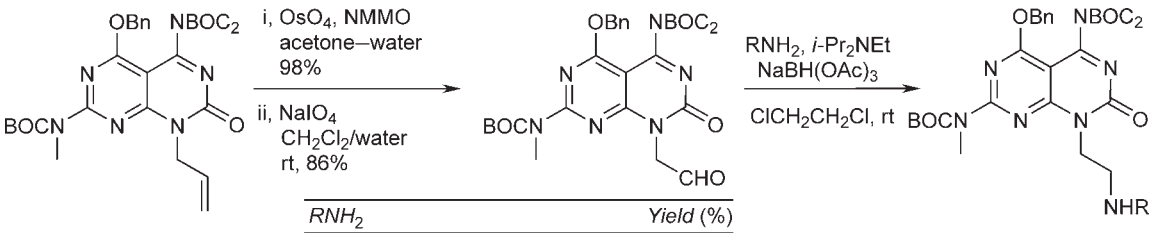


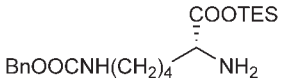
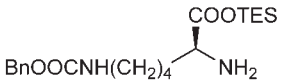
(58)



Scheme 38

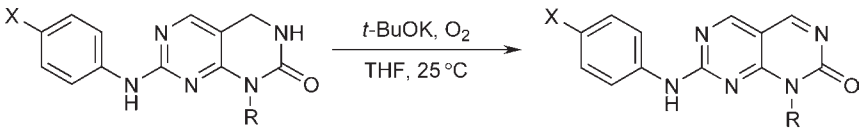
The stability of the pyrimido[4,5-*d*]pyrimidin-2(1*H*)-one core to oxidative and reducing conditions is illustrated further in the preparation of a range of 1-(2-aminoethyl) derivatives by oxidative cleavage of a 1-allyl species and reductive amination of the resulting aldehyde (**Scheme 39**) <2002WO02/066482>.

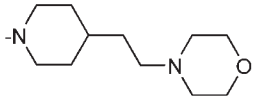


RNH$_2$	*Yield* (%)
	70
	72
$BOCNH(CH_2)_5NH_2$	55

Scheme 39

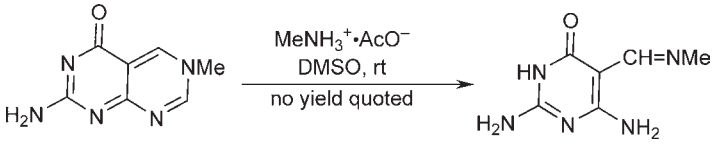
In contrast to the observations above, oxidation of the partially hydrogenated core proceeds in air upon treatment with strong base (Equation 59) <1999WO99/61444>.



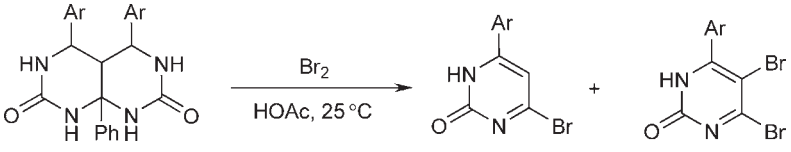
R	*X*	*Yield* (%)
Me	1-Pyrazolyl	65
Me	4-Methyl-1-piperazinyl	61
Me	4-(Dimethylamino)-1-piperidinyl	60
i-Pr	1-Pyrazolyl	73
i-Pr	4-Methyl-1-piperazinyl	78
i-Pr	4-(Dimethylamino)-1-piperidinyl	18
i-Pr		85
Cyclopentyl	OMe	Not stated
Cyclopentyl	$OCH_2CH_2NEt_2$	24
Cyclopentyl	1-Pyrazolyl	40
Cyclopentyl	4-Methyl-1-piperazinyl	67
Cyclopentyl	1-Piperidinyl	Not stated
Cyclopentyl	3-Hydroxy-1-piperidinyl	45
Cyclopentyl	4-Hydroxy-1-piperidinyl	30
Cyclopentyl		32
Bicyclo[2.2.1]heptan-1-yl	4-Methyl-1-piperazinyl	70

(59)

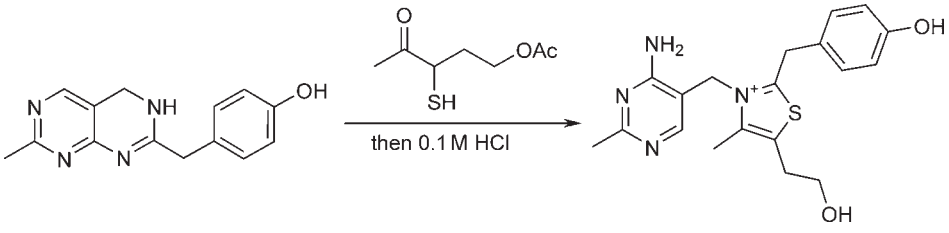
Some additional examples of the reactivity of pyrimido[4,5-*d*]pyrimidines are worth mentioning in conclusion. Ring cleavage of 6-methylated derivatives (Equation 60) has been reported, and a related process is probably responsible for the poor yields obtained upon methylation of this system <2003EJM719>. Ring cleavage also occurs upon treatment of 1,3,6,8-tetraazadecalins with bromine <2004CHE194> and, in this case, is accompanied by aromatization of the remaining ring (Equation 61). Ring cleavage also occurs upon treatment of a dihydropyrimido[4,5-*d*]-pyrimidine with thiol nucleophiles <1995JA2351>; the example shown in Equation (62) is the reverse of the thiochrome method (see Section 10.19.2.4.2). In contrast, alkaline cleavage of 2,4-dione **70** proceeds only with difficulty <1994CHE1083>. The lysine conjugate **71** has been reported to undergo self-assembly into helical nanotubes <2001JA3584, 2005JA8307>. By way of comparison, **72** contains the same core as **71**, and undergoes self-assembly to form hydrogen-bonded cyclic hexamers <1996CC1527>. Semicarbazone **73** and thiosemicarbazide **74** have been reported as tridentate chelating agents, forming octahedral complexes with Co(II), Cu(II), and Ni(II) <2002ASJ312>.



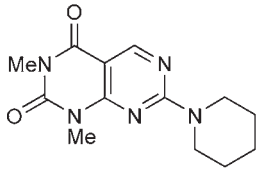
(60)



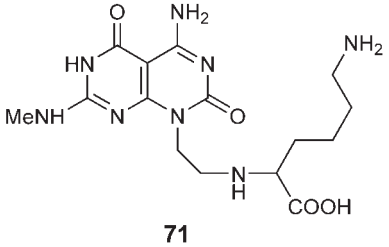
(61)



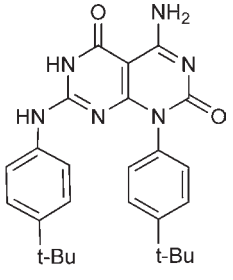
(62)



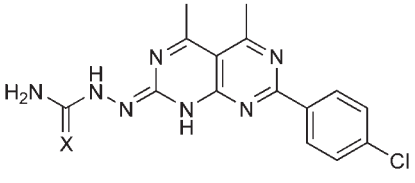
70



71



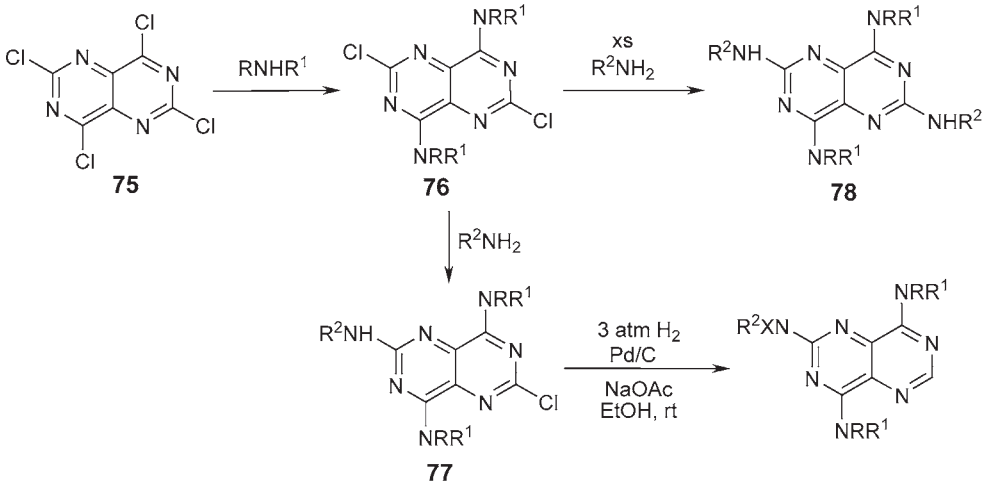
72



73 (X = O), **74** (X = S)

10.19.2.4.2(ii) Pyrimido[5,4-*d*]pyrimidines

The nucleophilic reactivity of the readily available 2,4,6,8-tetrachloropyrimido[5,4-*d*]pyrimidine **75** was outlined in CHEC(1984) <1984CHEC(3)329>; little was added in CHEC-II(1996), but a variety of results have been reported since. Much effort has been expended in the preparation of analogues of the anticoagulant dipyridamole **65**, all involving nucleophilic substitution of **75**. Although much of the published work simply describes sequential displacement of the 4- and 8-chlorides followed by the 2- and 6-chlorides <2000BML585, 2003JPP261569, 2004JME4905>, some groups have made efforts to carry out substitution in a sequential fashion. Thus, an initial disubstitution product **76** can be converted either to a triamine **77** or to a tetramine **78** (**Scheme 40**), the former being subjected to reductive dechlorination. The sequential displacement of chlorines from positions 4 and 8 has also been achieved <2002J(P1)108>. Nevertheless, subsequent displacement of the 2- and 6-halides is unselective where the groups at C-4 and C-8 are different (**Scheme 41**), and the methodology is best suited to the preparation of 2,4,6,8-tetrasubstituted species, where the groups at C-2 and C-6 are identical. Reactions of **75** with resin-bound amines provide around 15–20% of disubstitution product in addition to the desired monoadduct <2004CCT413>, limiting the usefulness of these methods in solid-phase synthesis.



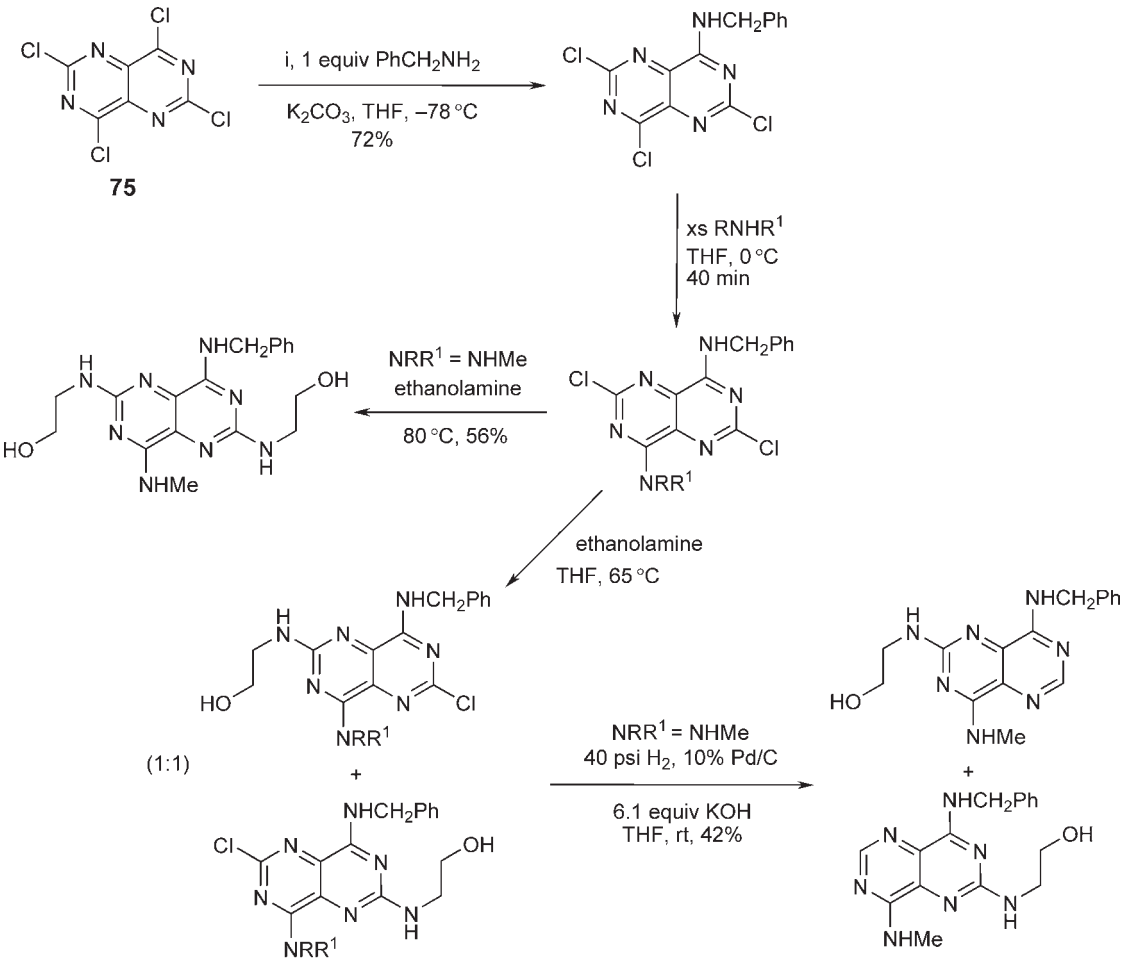
RNHR[1]	**76** *Yield* (%)	*R*[2]*NH*$_2$	**77** *Yield* (%)	*Hydrog' Yield* (%)	**78** *Yield* (%)	*Reference*
MeNHOSiMe$_2$-*t*-Bu	ns[a]		89			1990USP4963541
$H_2NCH_2CH_2OH$	ns[a]	*n*-$C_8H_{17}NH_2$	ns[a]	98		1996MCR61
Piperidine	ns[a]	$MeNHCH_2CH_2OH$			84	1990USP4963541
	51	$MeNHCH_2CH_2OH$			76	1996MCR61
Hexamethylenimine						
p-$MeOC_6H_4NH_2$	62	$H_2NCH_2CH_2OH$	91	45		2002J(P1)108
$PhCH_2NH_2$	69	$H_2NCH_2CH_2OH$	61	46	73	2002J(P1)108

[a]Yield not stated; this reference contains further examples without yields.

Scheme 40

An alternative approach to selective functionalisation of **75** <2002DEP10115921> involves a first nucleophilic substitution step, followed by reduction of the 7-8 double bond and concomitant removal of the 8-chloride. The reduced species is N-acetylated, and the key intermediate **79** can be functionalized at either of C-2 or of C-6 (**Scheme 42**). Phosphorus(III) reduction is then used to remove the remaining chlorine, and the second aromatic ring is reinstated by peroxide oxidation.

Selectivity is more readily achieved in nucleophilic substitution of 2,4,8-trichloropyrimido[5,4-*c*]pyrimidine **80**: amination at C-4 deactivates C-2 to further nucleophilic attack, so that the second displacement occurs at C-8, as exemplified in **Scheme 43** <1995DEP4325900, 1996DEP19502179>. Nucleophilic amination of **80** followed by two



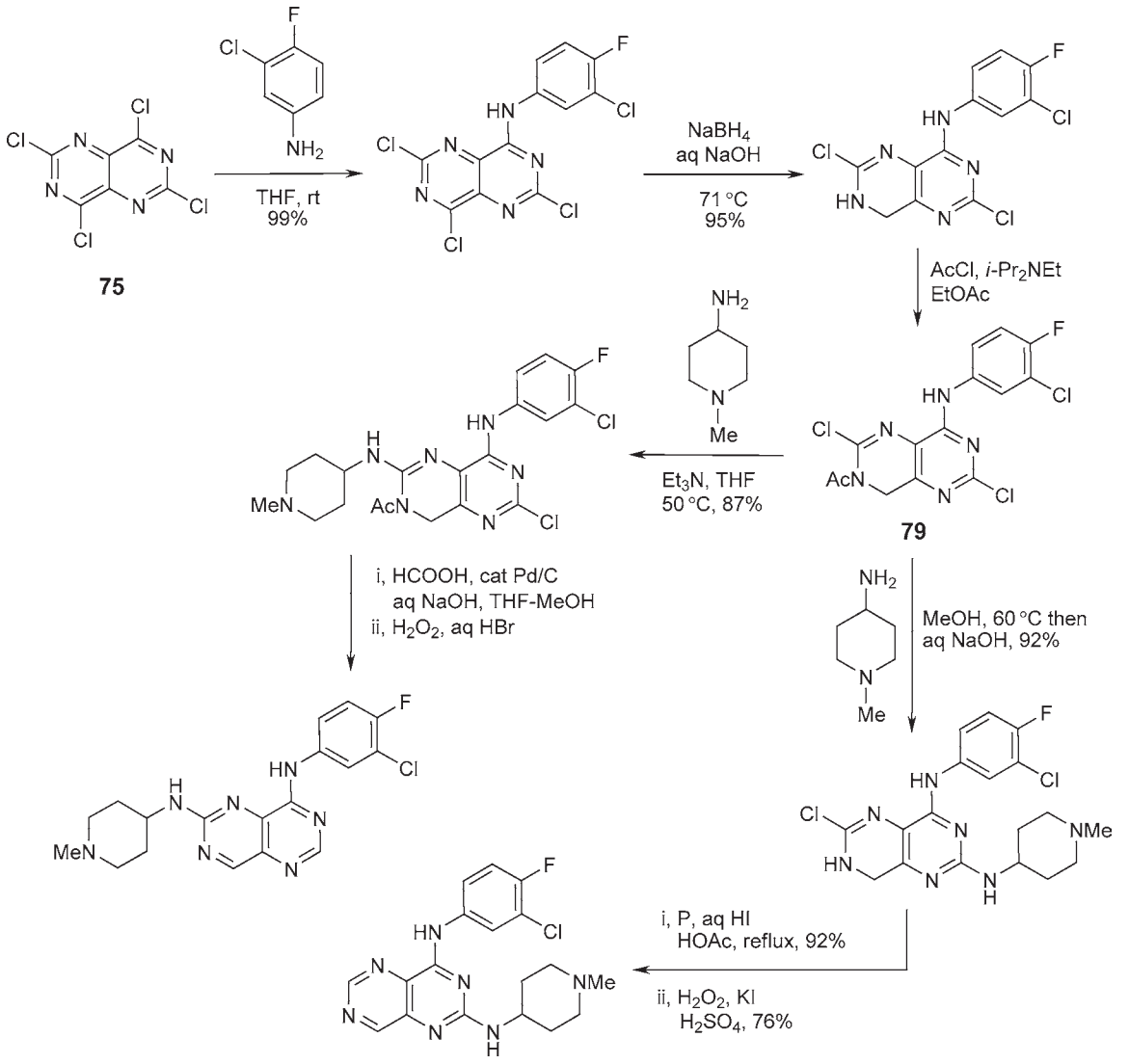
RNHR^1	*Yield step 2* (%)	*Yield step 3* (1:1) (%)
NH_3	46	47
$MeNH_2$	41	65

RNHR^1	*Yield step 2* (%)	*Yield step 3* (1:1) (%)
Me_2NH	67	25
Piperidine	63	56

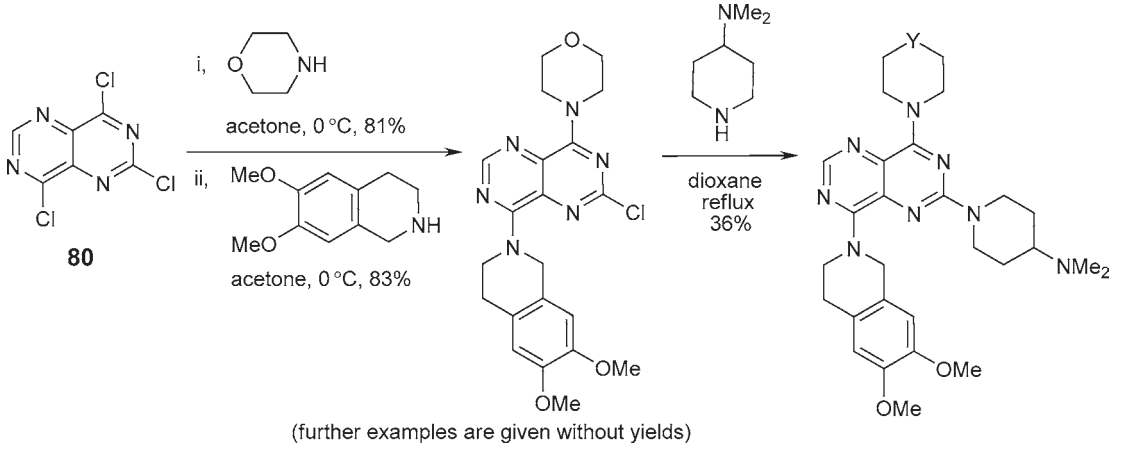
Scheme 41

reduction steps has also been used to generate pyrimido[5,4-*d*]pyrimidin-4-amines (**Scheme 44**) <1996DEP4431867, 1996WO07657>. This approach has since been used in the solid-phase synthesis of a 16 000-member compound library <2004CCT413>. In a logical extension of the chemistry already described for the tetra- and trichloro systems, 4,6-dichloropyrimido[5,4-*d*]pyrimidine is readily prepared from the 4-oxo precursor (**Scheme 45**), and undergoes amination at C-4, followed by nucleophilic substitution at C-6 as expected <1997JMC1820>.

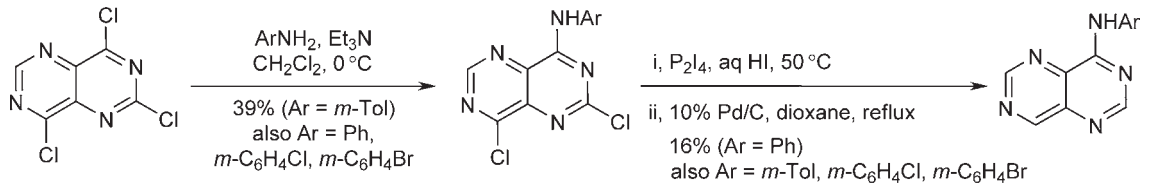
In a further approach to disubstituted pyrimido[5,4-*d*]pyrimidines, 4-amination is carried out in the presence of a 6-(methylthio) group <2000WO00/55162>, whose oxidation provides a second nucleofugic group (**Scheme 46**). Selectivity can also be achieved using 4-hydroxy-6-methylthiopyrimido[5,4-*c*]pyrimidine, which undergoes nucleophilic amination at C-4 in the presence of hexamethyldisilazane (**Scheme 47**), presumably *via* a 4-silyloxy intermediate <1997WO97/32880, 1997WO97/32882> or, following oxidation at sulfur, at C-6 (**Scheme 48**; in both cases, further examples are given without yields) <1997WO97/32882>. Subsequent chlorination and amination provides a 4,6-diamine.



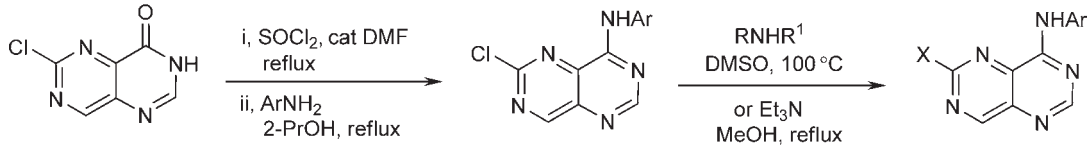
Scheme 42



Scheme 43

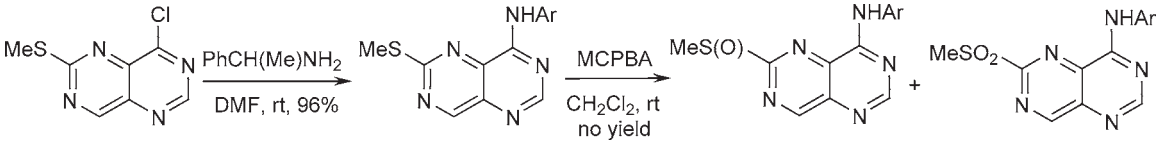


Scheme 44



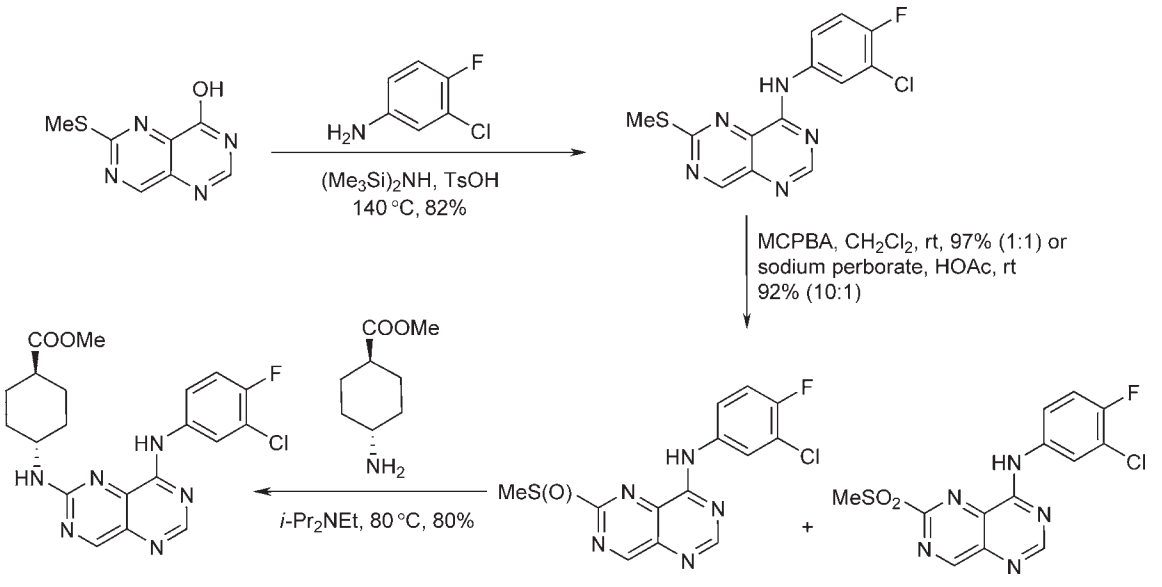
Ar	*Step* 1 *yield* (%)	*RNHR*^{1}*/MeOH*	*Yield* (%)
Ph	79	$MeNH_2$	82
3-MeC_6H_4	71	NH_3	54
		$MeNH_2$	61
		Me_2NH	92
		Morpholine-4-ethylamine	78
		Histamine	75
3-BrC_6H_4	80	NH_3	72
		$MeNH_2$	68
		Me_2NH	70
		$Me_2NCH_2CH_2NH_2$	64
		Morpholine-4-ethylamine	51
		Morpholine-4-propylamine	92
		Histamine	59
		Imidazole-1-propylamine	93
		MeOH (+Et_3N)	100

Scheme 45

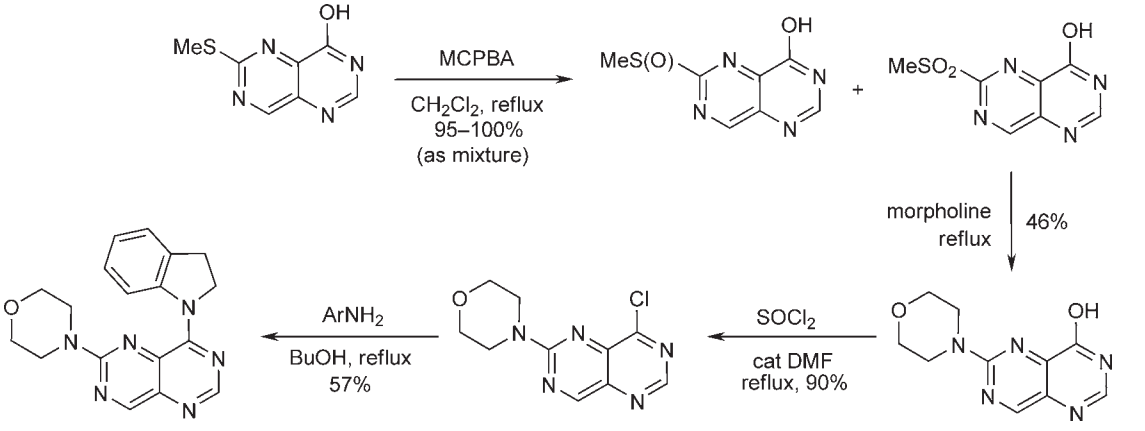


Scheme 46

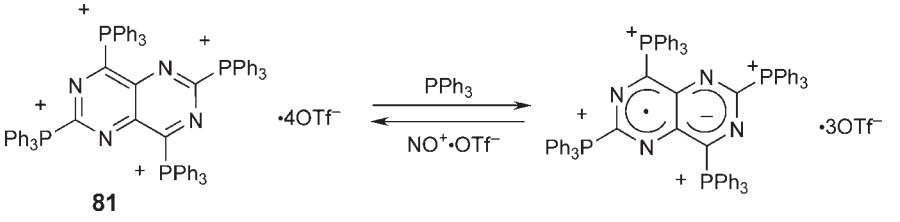
Products formed by diamination of **75** have also been reported to undergo reductive polymerization in the presence of a nickel catalyst <1998CL1163, 2002MM2993>, while the substitution of all chlorides in **75** by triphenylphosphine has been reported to give the highly oxidizing tetracation **81** <1996AGE1232>. The latter is the oxidized form of a reversible two-step redox system, with at least the oxidizing power of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Excess triphenylphosphine in the system is sufficient to reduce the tetracation to a stable radical cation (Equation 63).



Scheme 47

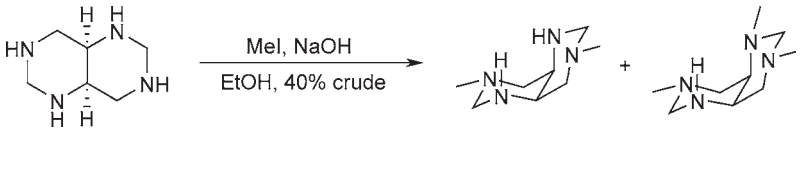


Scheme 48

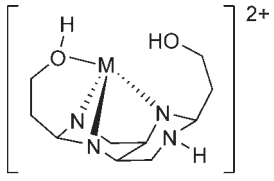


81 (63)

The perhydro system **66** (R = H) undergoes alkylation in the presence of iodo- or bromomethane <1998JOC8850> to give a mixture of di- and trimethyl derivatives (Equation 64), the former being somewhat unstable. Neither mono- nor tetraalkylation products could be isolated, and attempts to carry out sequential reductive methylation were unsuccessful. The use of the 2,6-bis(hydroxymethyl) derivative (**66**, R = CH_2OH) as a ligand for cadmium(II) and lead(II) has also been reported <1997TL8073>, the metal being coordinated to three of the four nitrogen centers and one oxygen, as in structure **82**.



(64)



82

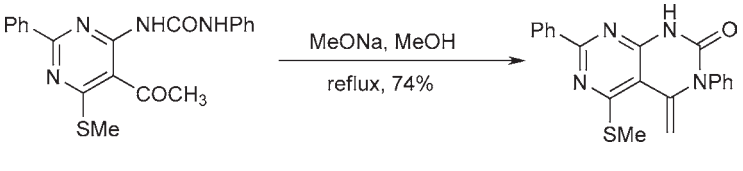
10.19.2.4.3 Ring synthesis

10.19.2.4.3(i) Pyrimido[4,5-*d*]pyrimidines

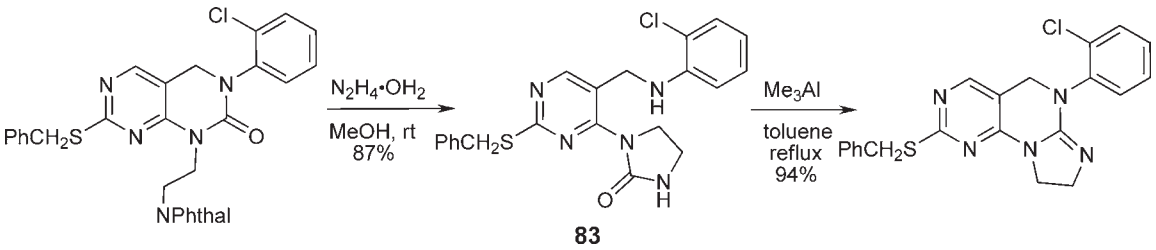
A number of methods for preparation of pyrimido[4,5-*d*]pyrimidines are described in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>. Further examples of all of these, and a number of novel approaches, are described in this section, in increasing order of the number of carbon atoms added to an existing substituted pyrimidine.

10.19.2.4.3(i)(a) Pyrimido[4,5-*d*]pyrimidines by cyclization

The most direct recent examples of the formation of pyrimido[4,5-*d*]pyrimidines <1995RCB1278, 2001WO01/29042> involve dehydrative cyclization of an *N*-(5-acylpyrimidin-4-yl)urea (Equation 65) or of an *N*-(5-alkoxycarbonylpyrimidin-4-yl)urea <2004BML4185>. Dehydrative cyclization of imidazolidinone **83** (**Scheme 49**), itself obtained by ring opening of a pyrimido[4,5-*d*]pyrimidin-2-one, requires treatment with trimethylaluminium <2003WO03/082871>, while related ring-closure processes occur upon treatment of *tert*-butyl carbamate **84** with sodium hydride (Equation 66) <2006WO065703> and treatment of *N*-ethoxycarbonylamide **85** with triethylamine (Equation 67) <2005WO121142>. Cyclization also occurs by elimination of hydrogen bromide from an *N*-(5-bromomethyl)pyrimidin-4-yl)urea (**Scheme 50**) <2001WO01/29042> and, in very poor yield, by intramolecular attack via an amine upon the presumed chloroiminium intermediate formed upon activation of an amide with phosphoryl chloride <1999H(51)255> (Equation 68). In a further approach, urea **86** undergoes intramolecular nucleophilic displacement of chloride (Equation 69) to give a 1-substituted pyrimido[4,5-*d*]pyrimidin-2-one <2006BMCL4400>.

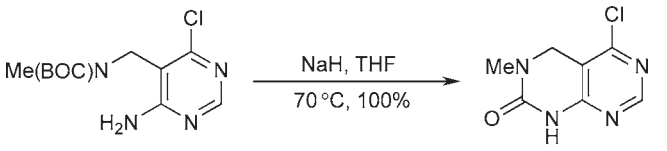


(65)

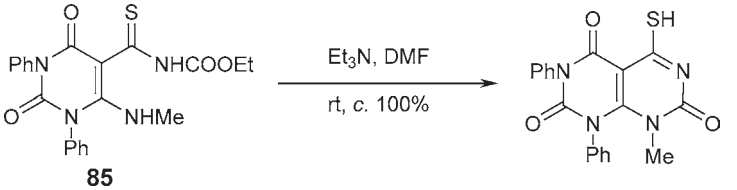


83

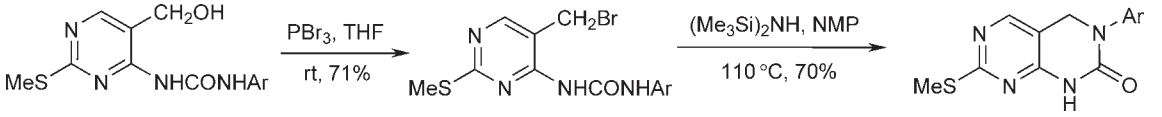
Scheme 49



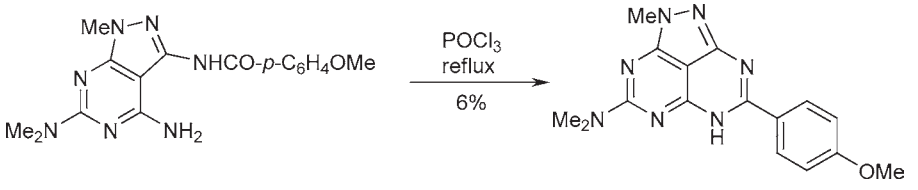
84 (66)



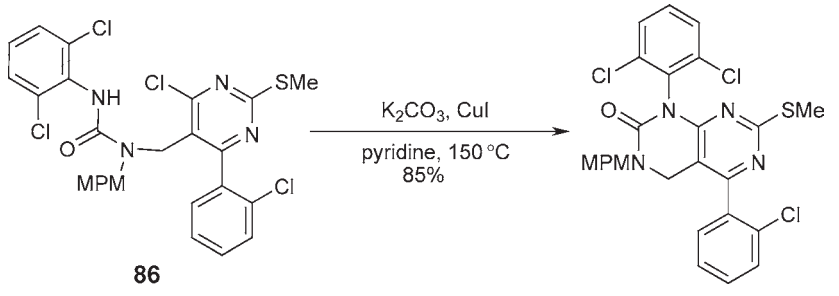
85 (67)



Scheme 50



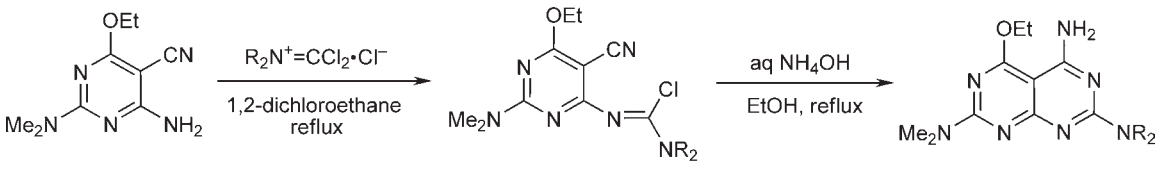
(68)



86 (69)

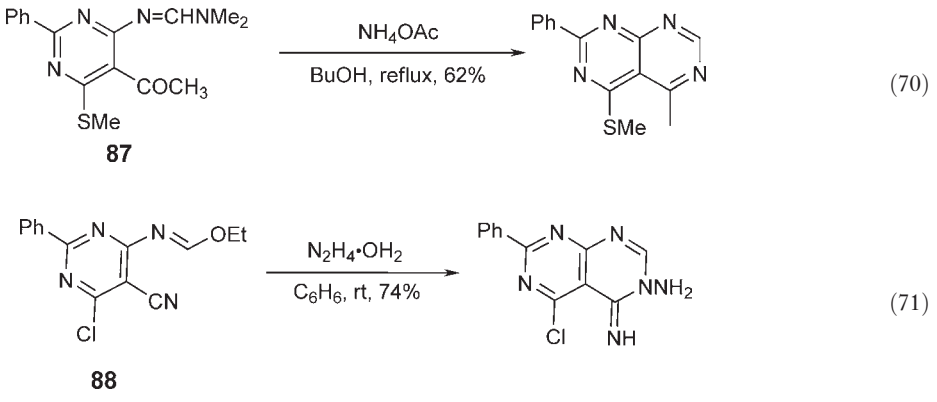
10.19.2.4.3(i)(b) Pyrimido[4,5-*d*]pyrimidines from a substituted pyrimidine and an amine

Reaction of a 5-cyano-4-pyrimidinylamine with a dichloroiminium salt (**Scheme 51**) gives a chloroamidine; ammonolysis of this intermediate provides pyrimido[4,5-*d*]pyridines <1998H(48)1923, 1998T9903>. Two further methods have been published in which a second pyrimidine ring is annulated to an existing one by ammonolysis, the key intermediates being *N*,*N*-dimethylamidine **87** (Equation 70) <1995RCB1278> and imidate **88** (Equation 71) <2004CPA209>.



R^2	*Yield, step* 1 (%)	*Yield, step* 2 (%)
Me_2	43	57
$(CH_2)_5$	20	34

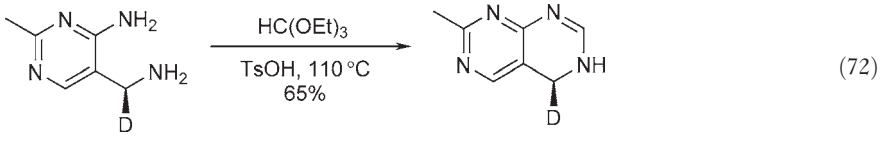
Scheme 51

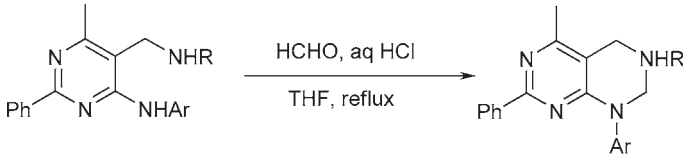


10.19.2.4.3(i)(c) Pyrimido[4,5-*d*]pyrimidines from a substituted pyrimidine and a C_1 unit

Recent examples of the methods described in CHEC(1984) and CHEC-II(1996), and involving condensation of a substituted pyrimidine with a C_1 unit, include the condensation of 3-amino-4-cyanopyrimidines with orthoformates <1995WO95/19774> and a variety of carboxylic acid derivatives <1995EJM525, 1996JIC698, 1998JRM2880, 2002EJC995>.

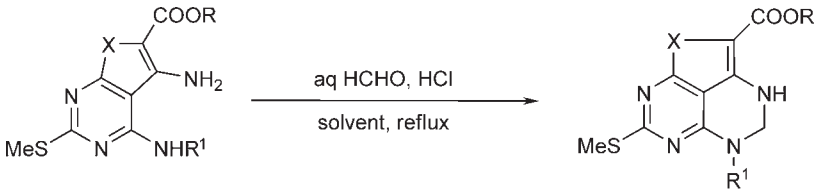
3,4-Dihydropyrimido[4,5-*d*]pyrimidines are formed by reaction of a 4-amino-5-(aminomethyl)pyrimidine with a C_1 electrophile. Thus, cyclization using phosgene <2001WO64679>, triphosgene <2005BMC4385>, or *N*,*N*′-carbonyldiimidazole <1994JHC1503, 2006OL1545> gives a 2-oxo product. The reaction with triethyl orthoformate (Equation 72) has been used to prepare a selectively deuterium-labeled 2-unsubstituted product <1996JOC4172>, while 2-aryl-3,4-dihydropyrimido[4,5-*d*]pyrimidines have been prepared by cyclization with orthobenzoates <1995JA2351>. Cyclization reactions have also been reported using cyanogen bromide to provide a 3,4-dihydropyrimido[4,5-*d*]pyrimidin-2-amine <1999WO99/61444> and using formaldehyde to give a 1,2,3,4-tetrahydropyrimido[4,5-*d*]pyrimidine (Equation 73). The same approach has also been used to prepare a range of *peri*-heterocyclic fused systems using formaldehyde (Equation 74), triethyl orthoformate (Equations 75 and 76) <2003S1377>, or ethyl chloroformate (Equation 77) <1999H(51)255> as the electrophile. Similarly, cyclization reactions of 4,5-quinazolinediamines have been used to prepare a range of pyrimido[4,5-*de*]quinazolines (Equations 78 and 79) <2004USP0254205>. A related approach to 2-iminopyrimido[4,5-*d*]pyrimidines involves the reaction of an *N*-(5-iminomethyl-4-pyrimidinyl)phosphinimine with an isocyanate (Equation 80) <1996OPP694>.





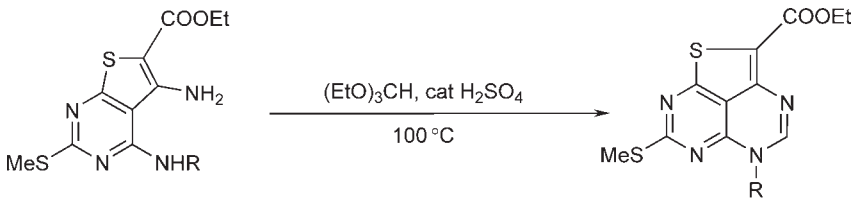
R	*Ar*	*Yield* (%)	*Reference*
H	Ph	84	2003MI105
H	4-HOC_6H_4	69	2002SPH245
H	4-$MeOC_6H_4$	82	2002SPH245
H	4-ClC_6H_4	73	2002SPH245
Et	Ph	84	2003MI105
Et	4-HOC_6H_4	74	2003APH487
Et	4-ClC_6H_4	82	2003APH487
Et	3,4-$Cl_2C_6H_3$	77	2003APH487
allyl	3,4-$Cl_2C_6H_3$	83	2003APH487
allyl	3,5-$Cl_2C_6H_3$	75	2003APH487
Bu	4-$EtOC_6H_4$	77	2003APH487
Bu	3,4-$Cl_2C_6H_3$	82	2003APH487
Bu	3,5-$Cl_2C_6H_3$	79	2003APH487
Ph	Ph	82	2003MI105
4-ClC_6H_4	Ph	72	2004MI321
4-ClC_6H_4	4-HOC_6H_4	78	2004MI321
4-ClC_6H_4	4-ClC_6H_4	83	2004MI321
4-$EtOC_6H_4$	4-ClC_6H_4	86	2004MI321
4-$EtOC_6H_4$	3,4-$Cl_2C_6H_3$	73	2004MI321
3,4-$Cl_2C_6H_3$	4-$EtOC_6H_4$	76	2004MI321
3,4-$Cl_2C_6H_3$	3,4-$Cl_2C_6H_3$	77	2004MI321
3,5-$Cl_2C_6H_3$	4-$EtOC_6H_4$	88	2004MI321
3,5-$Cl_2C_6H_3$	3,5-$Cl_2C_6H_3$	74	2004MI321

(73)



X	*R*	R^1		*Yield* (%)	*Reference*
NMe	Me	Bu	MeOH	48	1999CHE1381
NMe	Me	CH_2CH_2OH	MeOH	83	2003PJC1275
NMe	Me	CH_2COOEt	EtOH	78	2003S1377
S	Et	CH_2COOEt	EtOH	77	2003S1377
S	Me	CH_2CH_2OH	MeOH	81	2003PJC1275
S	Et	Me	EtOH	96	1996CHE93
S	Et	i-Pr	EtOH	77	1996CHE93
S	Et	c-Pr	EtOH	64	1996CHE93
S	Et	Bu	EtOH	58	1996CHE93
S	Et	4-BrC_6H_4	EtOH	88	1996CHE93
S	Et	2-ClC_6H_4	EtOH	71	1996CHE93

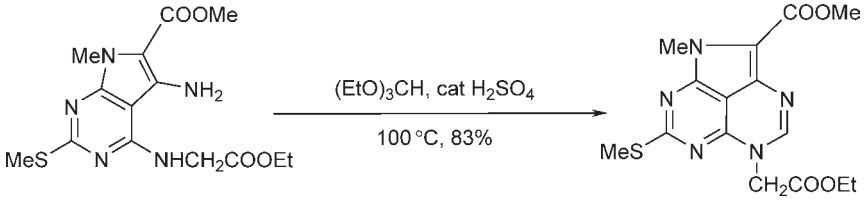
(74)



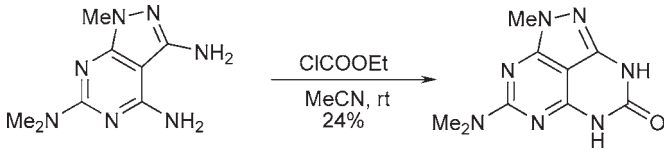
(75)

R	*Yield* (%)	*Reference*
Me	96	1995LA1703
i-Pr	60	1995LA1703
Cyclopropyl	90	1995LA1703
Bu	97	1995LA1703

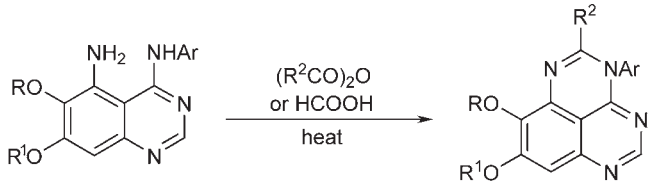
R	*Yield* (%)	*Reference*
2-ClC_6H_4	77	1995LA1703
2-BrC_6H_4	63	1995LA1703
CH_2CH_2OH	79	2003PJC1275
CH_2COOEt	68	2003S1377



(76)

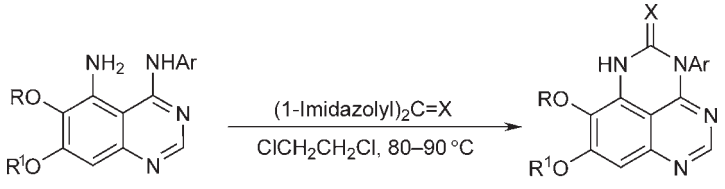


(77)



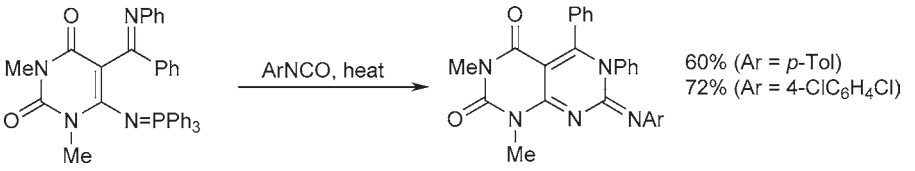
R	R^1	*Ar*	R^2	*Reaction temp.* (°C)	*Yield* (%)
Me	Me	Ph	H	110	54
Me	Me	Ph	Me	150	62
Me	Me	Ph	Et	170	14
Me	Me	3-BrC_6H_4	H	110	83
Me	Me	3-BrC_6H_4	Me	150	47
Me	Me	3-BrC_6H_4	Et	170	38
Me	Me	3-ClC_6H_4	Me	150	42
Me	Me	4-ClC_6H_4	H	110	59

(78)



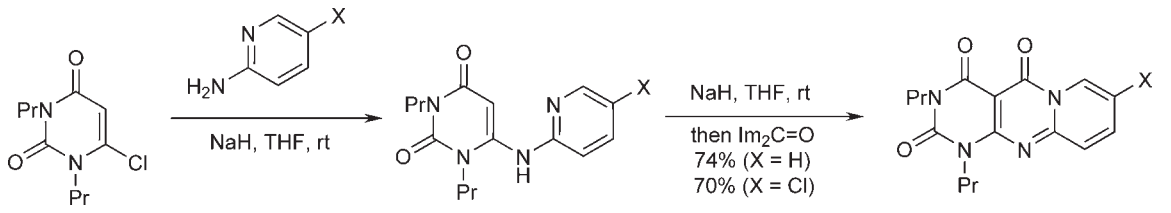
R	R^1	*Ar*	*X*	*Yield* (%)
Me	Me	Ph	O	59
Me	Me	Ph	S	55
Me	Me	3-BrC_6H_4	O	75
Me	Me	3-BrC_6H_4	S	91
Me	Me	3-ClC_6H_4	O	58
Me	Me	4-ClC_6H_4	S	82

(79)



(80)

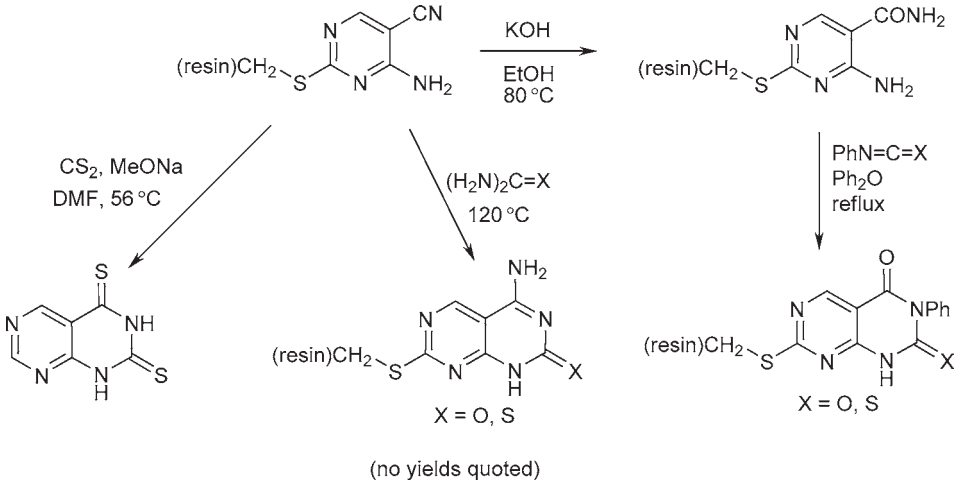
An alternative [5+1] cyclization process in which, formally, an *N*-(4-pyrimidinyl)amidine reacts with carbonyldiimidazole (CDI) to form a second pyrimidine ring, has been described also (**Scheme 52**) <1994JHC81>.



Scheme 52

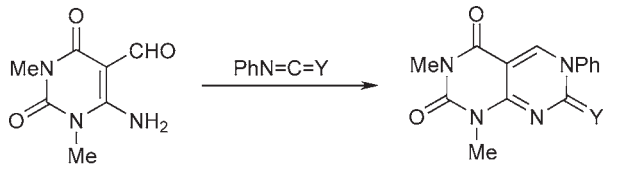
10.19.2.4.3(i)(d) Pyrimido[4,5-*d*]pyrimidines from substituted pyrimidines and a CN unit

The formation of pyrimido[4,5-*d*]pyrimidines by condensation of 3-aminopyrimidine-4-carboxylic acid derivatives with isocyanates and isothiocyanates was described in CHEC(1984) <1984CHEC(3)329>, and CHEC-II(1996) <1996CHEC-II(7)737>. Further examples of these reactions have appeared <1996CC1527, 1998HCA646, 2002WO02/066482, 2000PS(158)9, 2004CPA209>, while cyclizations of ethyl 4-aminopyrimidine-4-carboxylates <2003S1739> and -carbonitriles <1999BMCL965> with urea have been adapted for use with polymer-bound substrates. Cyclization reactions of a resin-bound 3-amino-4-cyanopyrimidine, and of the corresponding amide, with a variety of C_1 electrophiles are used in the solid-phase synthesis of a series of pyrimido[4,5-*d*]pyrimidin-2-ones and -thiones (**Scheme 53**), the unbound heterocycle eventually being liberated in most cases by aminolysis or by Raney Nickel-mediated hydrogenolysis of the sulfide linker.



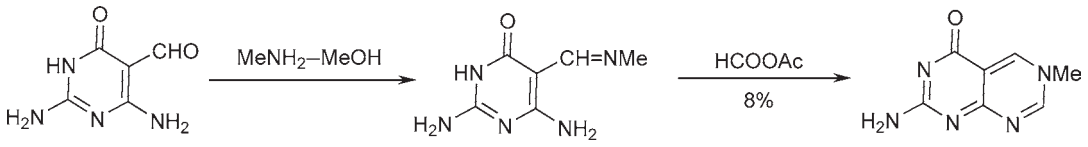
Scheme 53

4-Amino-5-formyluracils undergo an analogous cyclization on treatment with an isocyanate or an isothiocyanate <2004TL2405> in the solid state (Equation 81), while 4-amino-1,3-dimethyl-5-formyluracil undergoes the same overall conversion in a low-yielding two-step process (**Scheme 54**) <2003EJM719>. Alternatively, urea formation from 4-chloro-5-(methylamino)pyrimidines and an isocyanate <2004WO2004/041822, 2004USP0204427> and subsequent cyclization provides a useful route to 3,4-dihydropyrimido[4,5-*d*]pyrimidines (**Scheme 55**). A novel use of formamide to provide a CN unit for the annulation of two pyrimidine rings onto an existing quinoline nucleus (Equation 82) has been described, and also uses piperidine as a leaving group at C-4 of the starting material <1994BSF279>.

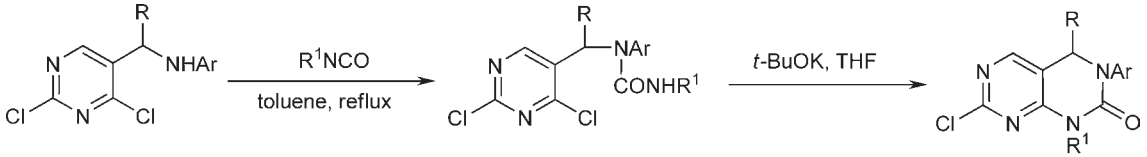


Y	*MW*, *100 °C*, 6 *min*	*$CHCl_3$*, *reflux* 6*h*
O	84	57
S	80	54

(81)



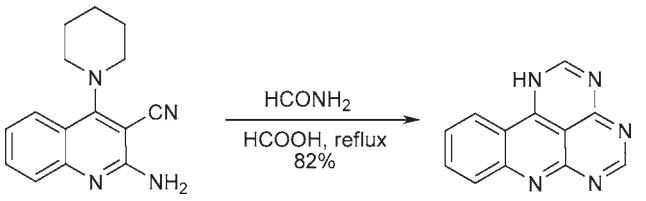
Scheme 54



R^a	Ar^a	R^{1a}	*Yield*[a] (%)
H	4-$MeOC_6H_4$	COPh (isolated as H)	29
H	4-$MeOC_6H_4$	(*S*)-$CH_2CH(Me)OSiPh_2$-*t*-Bu	59
H	4-$MeOC_6H_4$	cyclopentyl	9[b]
H	4-$MeOC_6H_4$	*trans*-3-TBDMSO-cyclopentyl	8[b]
H	4-$MeOC_6H_4$	cyclohexyl	26[b]
H	4-$MeOC_6H_4$	*trans*-4-TBDMSO-cyclohexyl	21[b]
H	4-$MeOC_6H_4$	*cis*-3,5-(t-$BuPh_2SiO)_2$cyclohexyl	44
H	4-$MeOC_6H_4$	3-sulfolanyl	23[b]
H	4-$MeOC_6H_4$	1-BOC-3-pyrrolidinyl	2[b]
H	4-$MeOC_6H_4$	1-BOC-3-piperidinyl	10[b]
H	4-$MeOC_6H_4$	1-BOC-4-piperidinyl	13*[b]
H	4-$MeOC_6H_4$	tetrahydropyran-4-yl	2[b]
Me	4-$MeOC_6H_4$	Ph	78
Me	4-$MeOC_6H_4$	3-NCC_6H_4	86
Me	4-$MeOC_6H_4$	(*R*)-$CH_2CH(Me)OSiPh_2$-*t*-Bu	73,78[c]
Me	4-$MeOC_6H_4$	(*S*)-$CH_2CH(Me)OSiPh_2$-*t*-Bu	46[d]
Me	4-$MeOC_6H_4$	(*S*)-CH(Me)Ph	*c.* 48[d]
Me	4-$MeOC_6H_4$	*trans*-4-TBDMSO-cyclohexyl	9[e]
H	2-Cl-5-$MeOC_6H_3$	*cis*-3,5-(t-$BuPh_2SiO)_2$cyclohexyl	29
Me	2-Cl-5-$MeOC_6H_3$	Ph	40
Me	2-F-4-$MeOC_6H_3$	Ph	38
Me	2-F-4-$MeOC_6H_3$	3-NCC_6H_4	68
Et	4-$MeOC_6H_4$	Ph	60
i-Pr	4-$MeOC_6H_4$	Ph	49

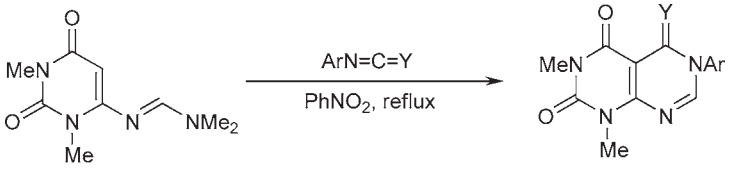
[a] Further examples are given, but without yields.
[b] Yields after subsequent reaction with aniline.
[c] Yields of *R,S* and *R,R*-diastereomers respectively.
[d] Mixture of diastereomers.
[e] Yield after deprotection.

Scheme 55



(82)

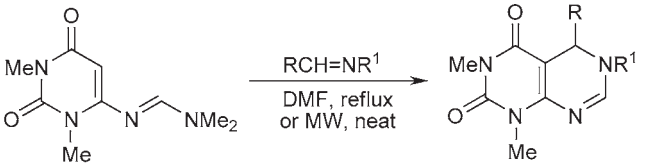
Amidines formed by condensation of 4-aminouracils with dimethylformamide dimethyl acetal are effective dienophiles, and form pyrimido[4,5-*d*]pyrimidines by [4+2] cycloaddition with isocyanates, isothiocyanates (Equation 83) <2005TL1433> and imines (Equation 84). A similar process has also been reported, using a nitrone as the dienophile (Equation 85) <2006BMCL3537>.



Ar	*X*	*Yield* (%)
Ph	O	86
4-BrC_6H_4	O	82
4-ClC_6H_4	O	83
Ts	O	80

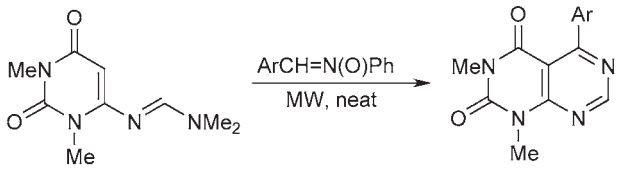
Ar	*X*	*Yield* (%)
Ph	S	85
4-BrC_6H_4	S	80
4-ClC_6H_4	S	81
4-FC_6H_4	S	85
CH_2Ph	S	84

(83)



Reference	*R*	R^1	*Thermal*		*MW*	
			Time (*h*)	*Yield* (%)	*Time* (*min*)	*Yield* (%)
2001S1299	Ph	Ph	5	95		
2001S1299	4-ClC_6H_4	Ph	8	87		
2001S1299	4-$O_2NC_6H_4$	4-ClC_6H_4	7.5	90		
2001S1299	4-$MeOC_6H_4$	Ph	8	88		
2001S1299	4-ClC_6H_4	4-$EtOC_6H_4$	3.6	70		
2001S1299	4-ClC_6H_4	3-ClC_6H_4	12	90		
2004SL1179	Ph	Ts	3.5	72	5	97
2004SL1179	*p*-Tol	Ts	3	75	5	94
2004SL1179	*p*-Tol	4-$ClC_6H_4SO_2$	4	70	5	95
2004SL1179	4-ClC_6H_4	Ts	4	70	4.5	98
2004SL1179	4-$O_2NC_6H_4$	Ts	3.5	72	4.5	90
2004SL1179	*p*-Tol	SO_2Ph	4	75	4.5	95
2004SL1179	4-$MeOC_6H_4$	Ts	3.5	73	5	96
2004SL1179	4-ClC_6H_4	Ts	4	75	5	95
2006BMCL3537	COOEt	Ph			3.5	95
2006BMCL3537	COOEt	4-ClC_6H_4			4.0	85
2006BMCL3537	COOEt	*p*-Tol			3.5	86
2006BMCL3537	COOEt	4-$MeOC_6H_4$			3.0	95
2006BMCL3537	COOEt	4-$O_2NC_6H_4$			4.5	84
2006BMCL3537	COOEt	4-BrC_6H_4			4.0	83

(84)

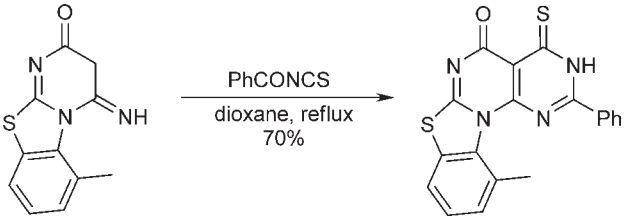


(85)

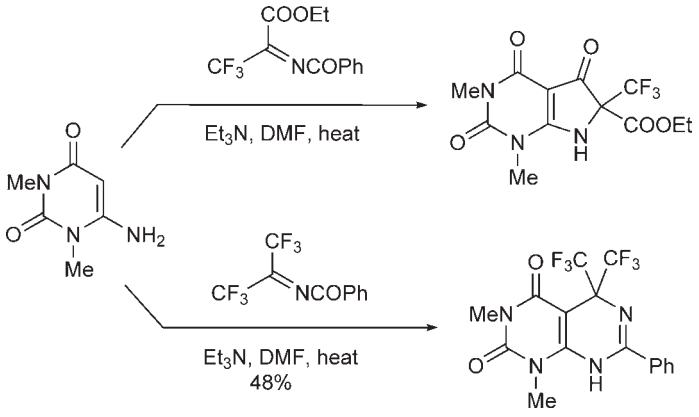
Ar	*Time* (*min*)	*Yield* (%)	*Ar*	*Time* (*min*)	*Yield* (%)
Ph	3.5	90	4-$MeOC_6H_4$	3.0	87
4-ClC_6H_4	3.0	88	4-$O_2NC_6H_4$	3.5	85
p-Tol	3.5	82	4-BrC_6H_4	3.5	80

10.19.2.4.3(i)(e) Pyrimido[4,5-*d*]pyrimidines from substituted pyrimidines and a CNC or NCN unit

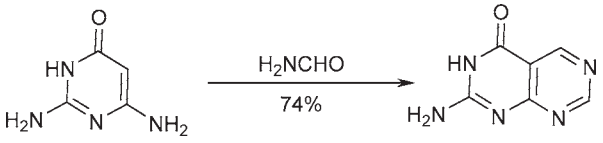
Annulation based on a 4-aminopyrimidine, which serves as a bis-nucleophile at nitrogen and at C-5, was described in CHEC(1984) <1984CHEC(3)329>. More recently, benzoyl isothiocyanate <1997JIC818> (Equation 86) and *N*-benzoylimines <2001RCB1113> have been reported as CNC reagents; in the latter case, the course of the reaction of 5-amino-1,3-dimethyluracil with substituted *N*-benzoylimines has been found to depend upon the exact nature of the acylimine, and either a 1,4-dihydropyrimido[4,5-*d*]pyrimidine derivative or a 3-indolone can be formed (**Scheme 56**). Variations on the same concept involve the use of excess formamide to provide all additional atoms of the product (Equation 87) <2003EJM719> and the use of Mannich-type conditions to form a tetrahydropyrimido[4,5-*d*]pyrimidine (Equation 88). This last approach has also been used to prepare tetrahydropyrimido[4,5-*d*]pyrimidine analogues of folic acid <1993H(35)1397>. A process wherein lithiation at C5 of a 4-aminopyrimidine and quenching of the intermediate anion with chlorocarbonyl isocyanate results in formation of a second pyrimidine ring in a single step (**Scheme 57**) <1996CC1527>.



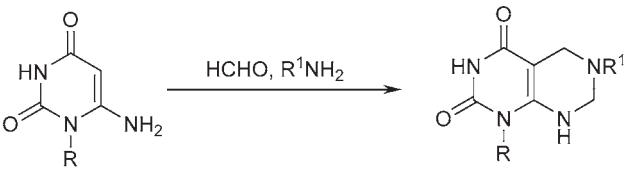
(86)



Scheme 56

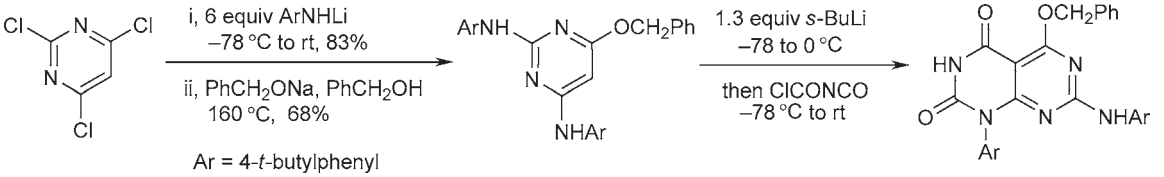


(87)



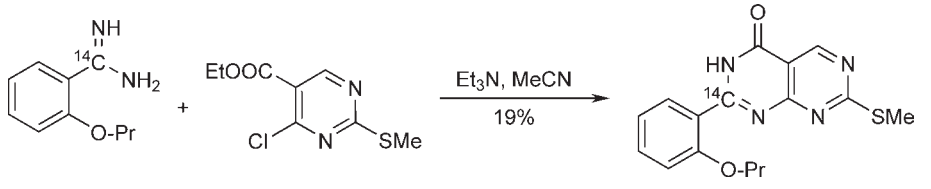
R	R^1	*Conditions*	*Yield (%)*	*Reference*
Me	Ph	aq EtOH, 20 °C	73	2000ZNB443
Me	4-$MeOC_6H_4$	aq EtOH, 20 °C	80	2000ZNB443
Ph	cyclohexyl	aq EtOH, reflux	70	1996APH39
Ph	CH_2Ph	aq EtOH, reflux	80	1996APH39
Ph	CH_2CH_2OH	aq EtOH, reflux	60	1996APH39
Ph	$CH_2CH{=}CH_2$	aq EtOH, reflux	40	1996APH39
2-$C_6H_4ClCH_2$	cyclohexyl	HOAc, MeOH, 40 °C	38	2004JCM341
2-$C_6H_4ClCH_2$	Ph	HOAc, MeOH, 40 °C	34	2004JCM341
2-$C_6H_4ClCH_2$	*p*-Tol	HOAc, MeOH, 40 °C	63	2004JCM341
2-$C_6H_4ClCH_2$	*p*-C_6H_4OH	HOAc, MeOH, 40 °C	49	2004JCM341

(88)

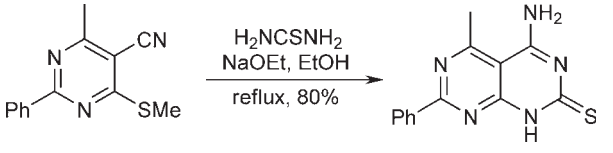


Scheme 57

The reaction of a 4-chloro-5-acylpyrimidine with an amidine to form a pyrimido[4,5-*d*]pyrimidine was described in CHEC(1984), and a number of examples of this type of process have appeared since <1996H(43)2153, 2000USP6060477, 2003EJC11>, including the preparation of the key intermediate in the synthesis of a [^{14}C]-labeled drug development candidate (Equation 89) <1995JLR891>. Variations on this process have also been published, wherein the leaving group at C-4 of the starting material is a methylthio <1996FA781, 2004IJC1561, 2005WO2005/091711, 2005IJB834> or azido <1998JRM2880> group, rather than a chloride ion. A further process related to that illustrated in Equation (90) involves cyclization of a 4-chloro-5-cyanopyrimidine with thiourea <1998BCJ2387>. An analogous cyclization of a 4-(methylthio)-5-cyanopyrimidine with cyanoguanidine to form an *N*-(pyrimido[4,5-*d*]-pyrimidin-2-yl)cyanamide has also been reported <2003JIC311>.

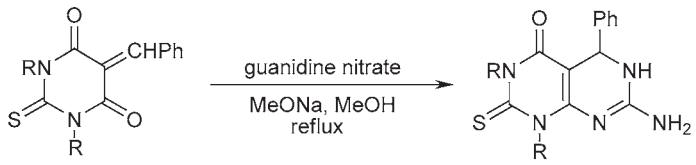


(89)



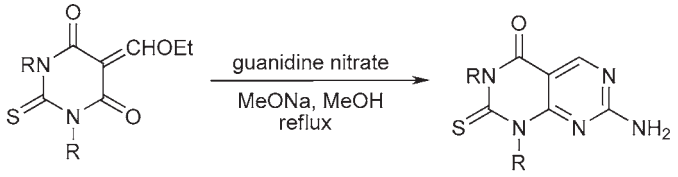
(90)

5-Methylene derivatives formed from alloxan can serve as bis-electrophiles and react with species such as guanidine to give pyrimido[4,5-*d*]pyrimidines directly (Equations 91 and 92). Formation of the Michael acceptor and the corresponding cyclization with thiourea can be carried out either in a single step (Equation 93) <2003RCB2457> or with isolation of the intermediate (**Scheme 58**) <2003SC3747>; in either case, the process is reported to proceed most efficiently in the solid state under microwave irradiation.



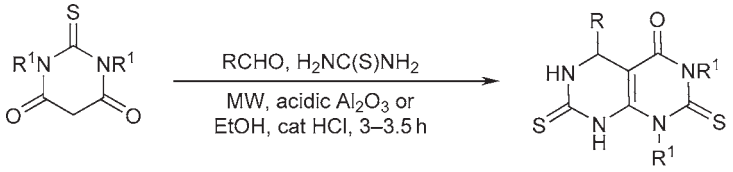
(91)

R	*Yield (%)*	*Reference*	*R*	*Yield (%)*	*Reference*
Ph	60	1998IJH193	2-$MeOC_6H_4$	70	1998IJH193
Ph	62	2005CJC1056	3-$MeOC_6H_4$	72	2005CJC1056
o-Tol	65	2005CJC1056	4-ClC_6H_4	70	1998IJH193
m-Tol	75	1998IJH193	3-$MeOC_6H_4$	60	1998IJH193



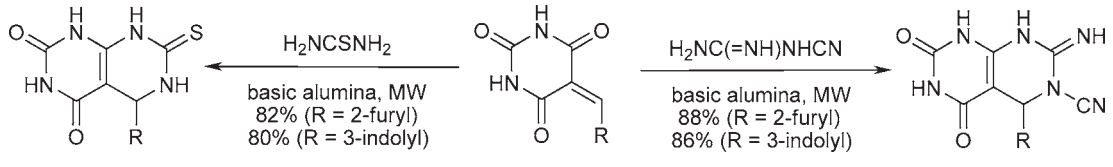
(92)

R	*Yield (%)*	*Reference*	*R*	*Yield (%)*	*Reference*
Ph	70	1998IJH193	2-$MeOC_6H_4$	75	1998IJH193
Ph	72	2005CJC1056	3-$MeOC_6H_4$	75	2005CJC1056
o-Tol	59	2005CJC1056	4-ClC_6H_4	60	1998IJH193
m-Tol	75	1998IJH193	3-$MeOC_6H_4$	55	1998IJH193



(93)

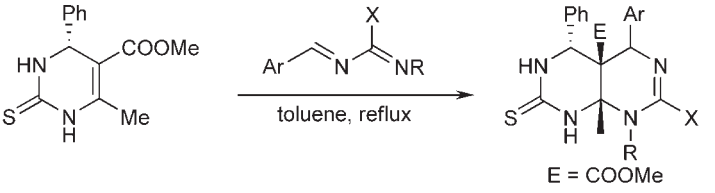
R	R^1	*Thermal yield (%)*	*MW yield (%)*
Ph	Ph	64	80
Ph	H	65	82
2-Furyl	H	63	84
2-Furyl	Ph	62	83
Benzo-1,3-dioxolan-5-yl	H	68	86
Benzo-1,3-dioxolan-5-yl	H	67	87



Scheme 58

10.19.2.4.3(i)(f) Pyrimido[4,5-*d*]pyrimidines from substituted pyrimidines and a CNCN unit

A 4-ethoxycarbonylpyrimidine-2-thione can serve as the dienophile component in which the pyrimido[4,5-*d*]pyrimidine system is formed by a hetero-Diels–Alder process (Equation 94); PM3 calculations predict a preference for the *endo*, rather than the *exo*-pathway, and in practice the *endo*-adduct is the sole product <2005T4237>.

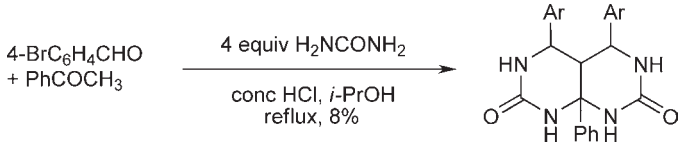


(94)

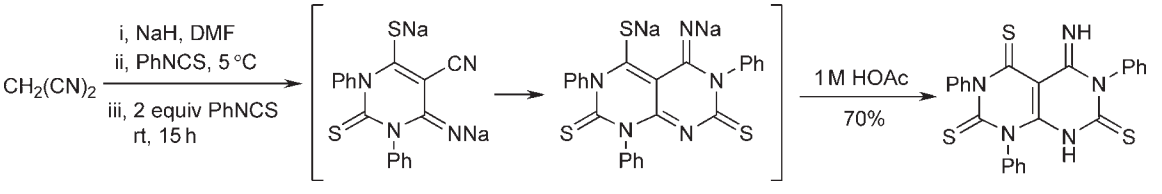
Ar	X = NH_2, R = H yield (%)	X = H, R = Me yield (%)	Ar	X = NH_2, R = H yield (%)	X = H, R = Me yield (%)
Ph	70	72	4-$MeOC_6H_4$	80	82
4-ClC_6H_4	74	76	4-EtC_6H_4	71	73
4-HOC_6H_4	77	79	*p*-Tol	78	80

10.19.2.4.3(i)(g) Pyrimido[4,5-*d*]pyrimidines from acyclic precursors

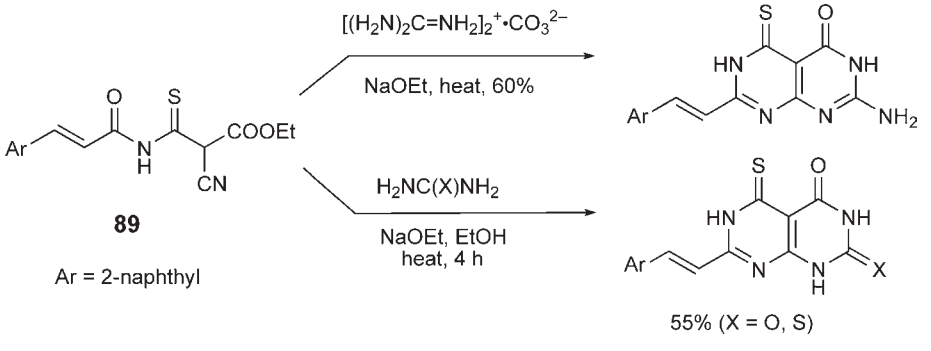
A number of examples have been published in which the pyrimido[4,5-*d*]pyrimidine system is constructed in a single step from acyclic precursors. In the simplest case, the reaction of a urea and an aldehyde (or mixture of aldehydes) gives an octahydropyrimido[4,5-*d*]pyrimidine-2,7-dione in a single step, as illustrated in Equation (95) <1995RCB131, 2004CHE194>. Malononitrile reacts with phenyl isothiocyanate in the presence of base <2003BMC2575> to form a pyrimido[4,5-*d*]pyrimidine directly (**Scheme 59**). The thioimide **89** (**Scheme 60**) undergoes bicyclization when treated with a single equivalent of guanidine carbonate, urea, or thiourea <1995PJC1018, 1996IJB144>.



(95)



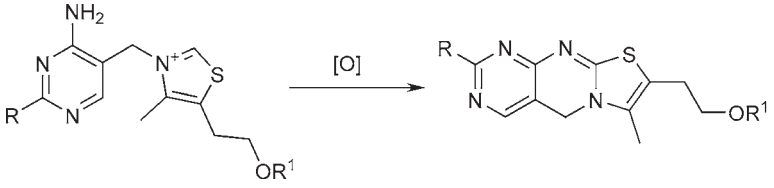
Scheme 59



Scheme 60

10.19.2.4.3(i)(h) Pyrimido[4,5-*d*]pyrimidines from other ring systems

Few methods have been described for preparation of pyrimido[4,5-*d*]pyrimidines from other ring systems, although the amination of a pyrimido[5,4-*f*]-1,3-oxazinium salt was reported in CHEC-II(1996) <1996CHEC-II(7)737>. Worthy of note is the 'thiochrome' method, generalized in Equation (96), which is principally of interest as an assay for thiamine phosphate synthase activity. This involves oxidation of thiamine or a derivative using an enzyme-based system <2002RJC1808>, or using ferricyanide, either alone <2004OBC2538> or with hydrogen peroxide <2001B10095>.

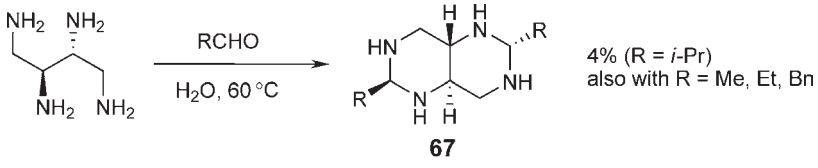


(96)

10.19.2.4.3(ii) Pyrimido[5,4-*d*]pyrimidines

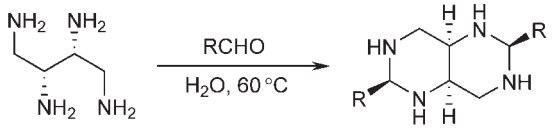
The preparation of pyrimido[5,4-*d*]pyrimidines by condensation of 5-aminopyrimidine-4-carboxylic acid derivatives with a C-1 unit, analogous to the method used for pyrimido[4,5-*d*]pyrimidines, was discussed in outline in CHEC(1984) <1984CHEC(3)329>. A number of additional reports have appeared of this type of reaction, using formamide <1996DEP4431867>, amidines <1997WO97/32882>, orthoesters <1997JMC1820>, guanidine <2003WO03/001887> and carbon disulfide <1997JIC624>. Analogous reactions of 4-amino-5-(aminomethyl)pyrimidines with phosgene <2004WO2004/041822> and phosgene substitutes <2005WO2005/011597> lead to tetrahydro- or 3,4-dihydropyrimido[4,5-*d*]pyrimidines.

Two groups have reported single step preparations of 1,3,5,7-tetraazadecalins **66** and **67**, albeit in modest yields, from 1,2,3,4-tetraaminobutanes and aldehydes. With the *rac*-tetramine the *trans*-disubstituted product **67** is formed (Equation 97) <1996AJC285>. The equivalent process with the *meso*-tetramine reportedly gives only the *cis*-disubstituted product **66** in all cases (Equation 98).



67

(97)



66

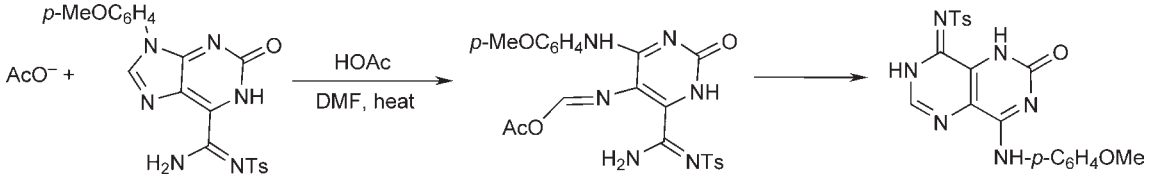
R	*Yield (%)*	*Reference*	*R*	*Yield (%)*	*Reference*
H	100[a]	1998JOC8850	Et	ns[b]	1996AJC285
Me	9	1996AJC285	*i*-Pr	ns[b]	1996AJC285
CH_2OH	ns[b]	1997TL8073	CH_2Ph	ns[b]	1996AJC285

[a]Reaction at room temperature in *i*-PrOH.
[b]not stated.

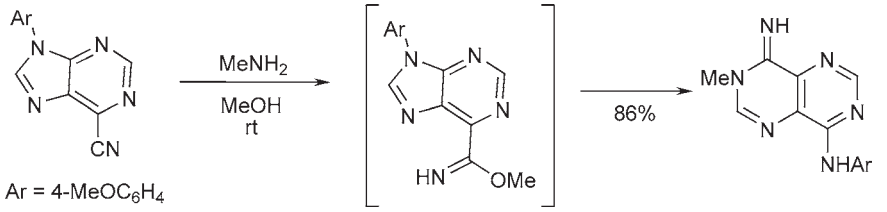
(98)

Pyrimido[5,4-*d*]pyrimidines are formed by ring expansion of 4-purinylamidines and related species in the presence of a nucleophile. The process appears to proceed by an ANRORC process, as outlined in **Scheme 61** <2001J(P1)1241, 2001J(P1)2532>. Variations on the same reaction have been reported, in which the group at C-4 of the purine is an amidine <2001J(P1)1241, 2001J(P1)2532>, an imidate (**Scheme 62**) <2004OBC1019>, or an

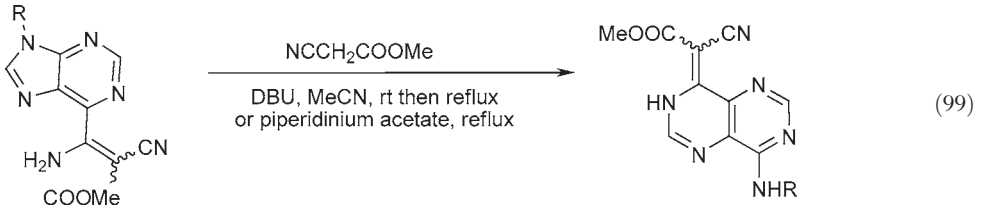
aminomethylenemalonate unit (Equation 99) <2004OBC2340>. Further examples involve the formation of the amidine unit *in situ* (Equation 100) <1995NN1601>; this methodology has been used to prepare pyrimido[5,4-*d*]pyrimidine nucleoside analogues (Equation 101) <1994NN1125>.



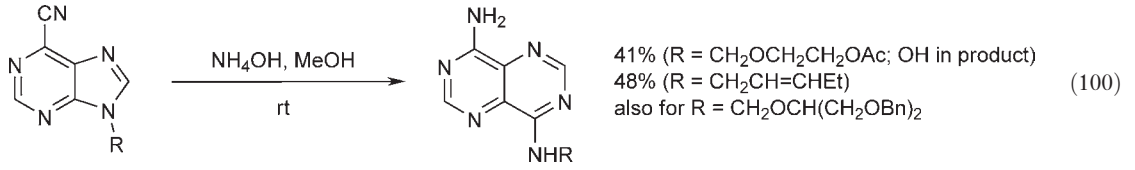
Scheme 61



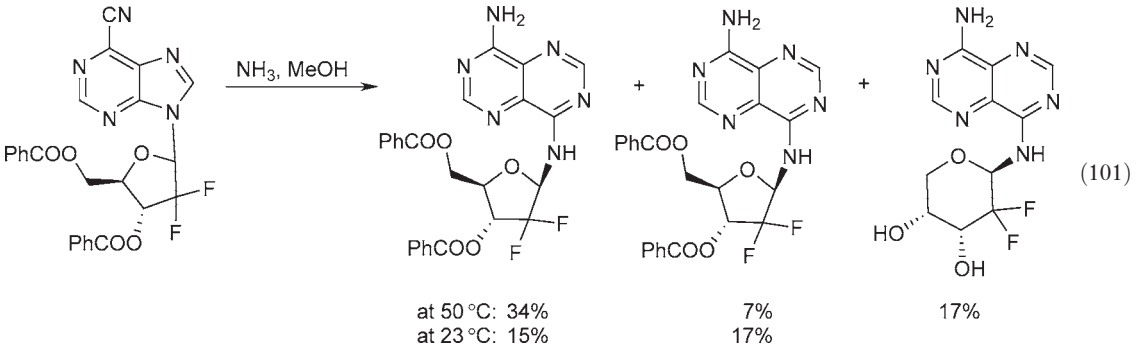
Scheme 62



(99)

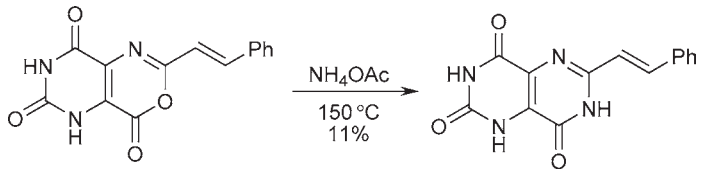


(100)



(101)

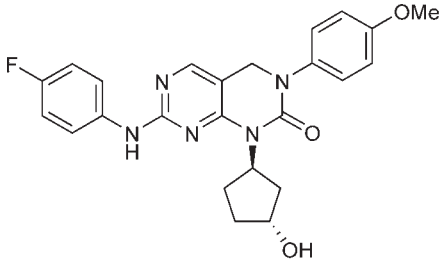
Pyrimido[5,4-*d*]pyrimidines have also been prepared by the reaction of pyrimido[5,4-*d*][1,3]oxazines with amines (Equation 102) <1990JME1721>, although amination of the alternate pyrimido[4,5-*e*][1,3]oxazines has not been reported.



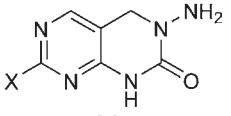
(102)

10.19.2.4.4 Important compounds and applications

No new pyrimido[4,5-*d*]pyrimidines have been marketed since the appearance of CHEC-II(1996), although a number have been claimed as potential medicinal agents <2005WO121142, 2006WO038112>. Of these, RO4396686 **90** has been studied in some detail as an inhibitor of tumor angiogenesis <2006BMCL1950>, while 3-amino derivatives **91** are claimed as pesticides.

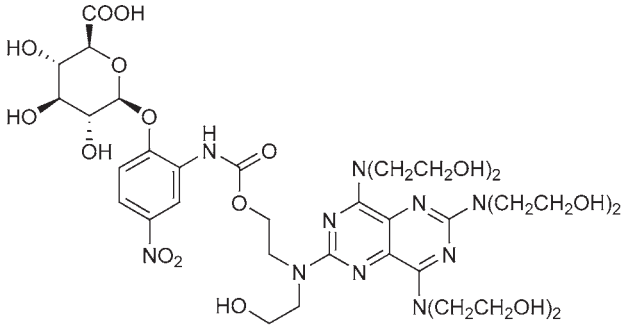


90

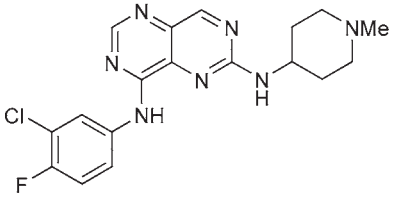


91
X = H, Me, SMe

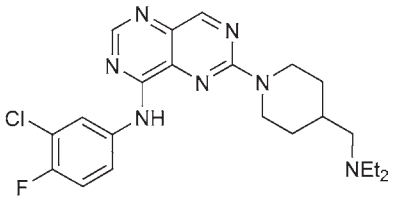
Dipyridamole (*Persantin*; **65**) remains the major notable pyrimido[5,4-*d*]pyrimidine derivative in clinical use; **65** is used clinically as an anticoagulant, but has also been found to possess useful antineoplastic <1999MI93> and antioxidant <2000BBA(1474)177> activity. A variety of derivatives and analogues of **65** have been developed, including polyurethane-bound forms <1997MI167, 1997MI296> and a number of conjugates, of which **92** is active against L1210 only in the presence of *β*-glucuronidase <1998CRC421>. Compound **65** has also been used to potentiate the cyctotoxicity of certain antifolate antineoplastic agents, and analogues have been examined in an effort to optimize this activity <2004JME4905>. Activity against human solid tumors is also reported for **93** and **94** <2004JEP502>, which are designed as selective inhibitors of human epidermal growth factor kinase.



92



93



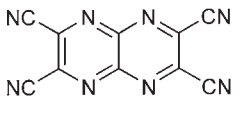
94

10.19.2.5 Pyrazinopyrazines

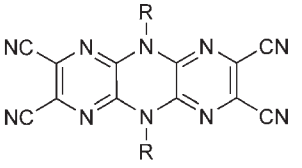
10.19.2.5.1 Theoretical and experimental structural methods

Structural and spectroscopic studies of pyrazino[2,3-*b*]pyrazine derivates were discussed in CHEC(1984) <1984CHEC(3)329>, and more recent data were reported in CHEC-II(1996) <1996CHEC-II(7)737>. Theoretical studies of the parent molecule, as for pyridazino[4,5-*d*]pyridazine, lead to the description of the nonbonding orbitals on nitrogen as perturbed naphthalene σ-orbitals, with contributions from σ^*-orbitals <1999PCA3089>. Infrared and Raman data for the parent have been reviewed and reassigned based on theoretical calculations <2000PCA7386>.

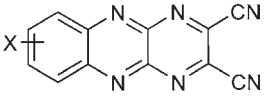
The electronic properties of tetracyanopyrazino[2,3-*b*]pyrazine **95** and related species are of considerable interest, given the potential usefulness of such materials in electronic devices. Compound **95** can act as an *n*-type carrier <2005MI620>, being easily and reversibly reduced to a relatively stable radical anion. With donors such as tetrathiafulvalene, **95** forms charge-transfer adducts, which are semiconductive in the solid state. The pyrazine-fused derivatives **96** possess strong intramolecular charge-transfer chromophores, wherein the nitrogen atoms of the central ring act as electron donors, and the dicyanopyrazines as acceptors <1997JHC653>. Reduction potentials of these compounds vary from −1.30 to −1.34 eV, and they are of interest for use in emitters for electroluminescence devices. Vapor-phase deposition of **96** (R = $C_{12}H_{23}$) on PTFE reportedly results in formation of a uniaxial film, with the alkyl chains perpendicular to the substrate surface <2003MCL157>. Dicyanopyrazinoquinoxalines **97** have also been reported as n-type transistor materials <2004OL2007>. From PM3 calculations, the lowest unoccupied molecular orbital (LUMO) in **97** is localized on the pyrazinopyrazine ring, and the highest occupied molecular orbital (HOMO) on the benzene ring, so that the size of the HOMO–LUMO gap can be controlled by the nature of substituents on the benzo ring.



95

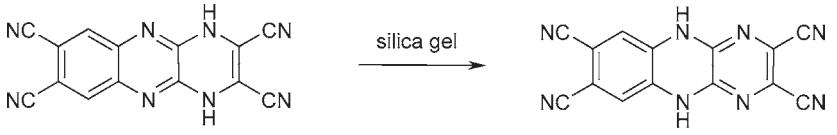


96



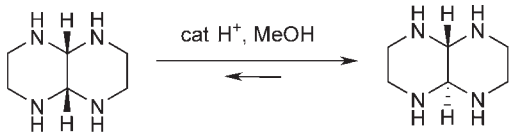
97

In partially hydrogenated pyridazino[2,3-*b*]quinoxalines, the 5,10-dihydro tautomer is expected to be more stable. In practice, the initial product, **98a**, from condensation of 2,3-dichloro-6,7-dicyanoquinoxaline with diaminomaleonitrile, isomerizes to the more stable tautomer **98b** on standing <1997JHC653>.

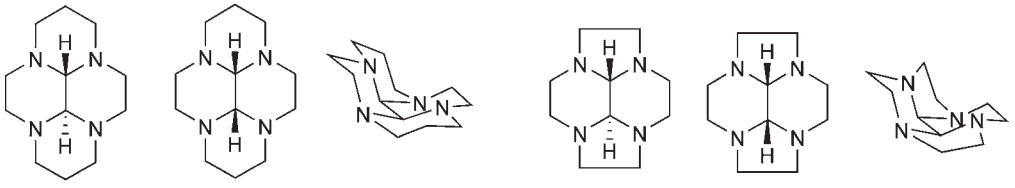


98a **98b**

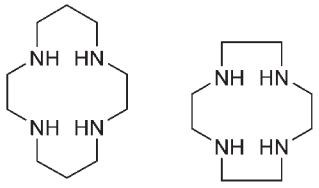
A variety of studies of 1,4,5,8-tetraazadecalins have been reported. The simplest representative of this series **99** is reported to undergo acid-catalyzed equilibration in methanol solution to give a 34:66 mixture of *cis*- and *trans*-**99**. <2002J(P2)552>. A low-temperature crystal structure of **99** has been reported <2004AXE1847>. The fused derivatives **100** and **101** are of interest as intermediates in the preparation of substituted derivatives of cyclam **102** and cyclen **103** (see Section 10.19.2.5.3), and have been the subject of theoretical studies <1995H(41)1023>. For *trans*-**100**, ΔH_f is calculated as 44.17 and 39.17 kcal mol^{-1} for the *trans–trans* and *cis–trans* fused forms, respectively. For *cis*-**100**, ΔH_f is calculated to be 35.82 kcal mol^{-1}. The ^{1}H NMR spectra of *trans*- and *cis*-**100** have methine signals at 2.14 and 3.00 ppm, respectively <1995H(41)1023>, consistent with a downfield shift for protons proximal to the lone pair of nitrogen. The *trans*-forms of **100** and **101** are rigid, while their *cis*-forms exhibit fluxional behavior involving the sequential inversion of nitrogen centers. The *cis*-forms possess conformations in which the four nitrogen atoms are nonequivalent. As a result, two opposing nitrogen lone pairs are directed toward the concave face of the molecule, while the other two are directed toward the convex face; the latter exhibit far greater nucleophilic reactivity <2001NJC1168>.



cis-**99** *trans*-**99**

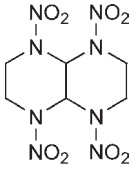


trans-**100** *cis*-**100** *trans*-**101** *cis*-**101**



102 **103**

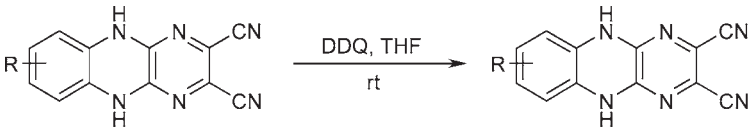
Extensive theoretical and experimental thermodynamic studies have been carried out on the explosive 1,4,5,8-tetranitro-1,4,5,8-tetraazadecalin (TNAD; **104**). Much of the data are summarized in a 2005 publication <2005IJQ(102)398> in which detailed decomposition profiles are proposed, although additional theoretical studies have been reported since <2006PCB10651>. The first step activation energy is lower for *trans*-**104** than for the *cis*-form (18.5 vs. 33.3 kJ mol^{-1}).



104

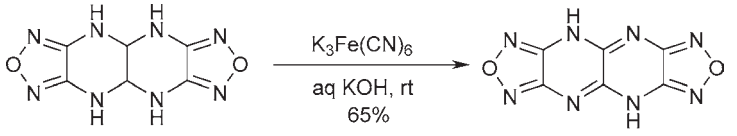
10.19.2.5.2 Reactivity

The reactivity of aromatic pyrazino[2,3-*b*]pyrazines remains largely unexplored; in CHEC(1984) and CHEC-II(1996), only covalent hydration <1984CHEC(3)329> and oxidation <1996CHEC-II(7)737> are described, and little chemistry of the fully aromatic system or of benzo-fused derivatives has been reported since. Additional examples of the dehydrogenation of reduced derivatives of this system using DDQ (Equation 103) <2004OL2007> and ferricyanide (Equation 104) <1997CHE216> have been reported since the appearance of CHEC-II(1996). Further reactivity of the dehydrogenated product **105** has also been reported <1997CHE216>: treatment with nitric acid results in the abstraction of the elements of hydrogen to give, in effect, a stable diradical in 87% yield. On the other hand, treatment of **105** with formaldehyde gives a bis(hydroxymethyl) derivative (**Scheme 63**), which undergoes O-nitration on treatment with nitric acid. The reversible hydrogenation of the parent heterocycle has been reported in the context of its possible use in hydrogen storage <2005USP002857>, and the ΔH° of hydrogenation has been calculated as -12.5 kcal mol^{-1} H_2.



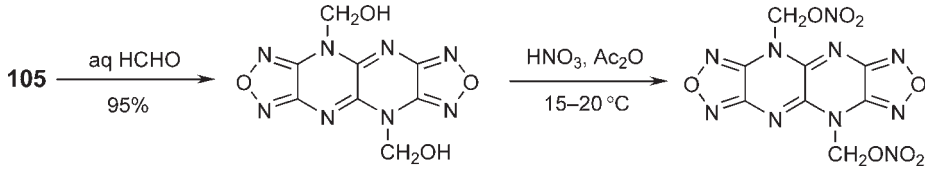
R	*Yield* (%)
H	95
6,7-Me_2	93
5,8-$(OMe)_2$	79
6,7-$(OMe)_2$	80
6,7-Benzo	84

(103)



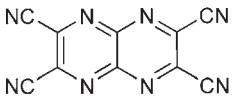
105

(104)

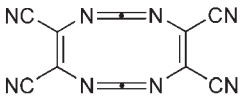


Scheme 63

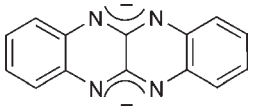
Irradiation of 2,3,6,7-tetracyano-1,4,5,8-tetraazanaphthalene **106** at low temperature results in isomerization to a product identified as **107**. The latter is reconverted into **106** upon exposure to visible light <2003CPL(375)605>. By comparison, attempts to prepare all-carbon analogues of **107** result only in the formation of naphthalenes. The dianion **108** has been used as a ligand to link two bis(molybdenum) units <2006IC767>.



106



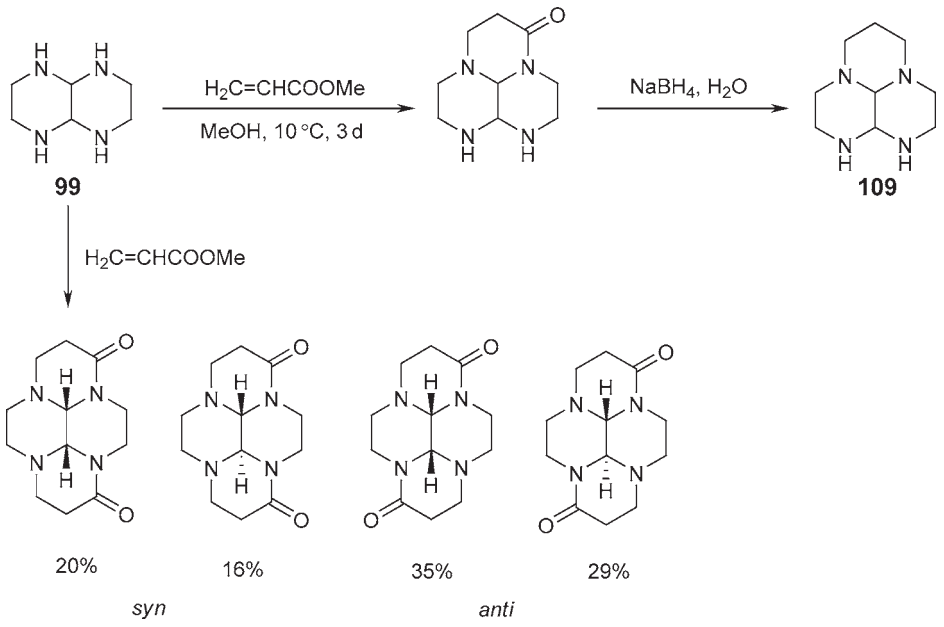
107



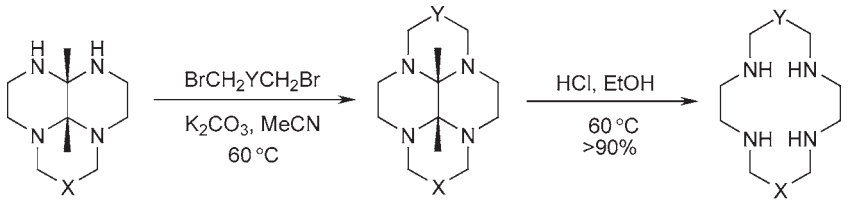
108

A considerable number of reports of the reactivity of the fully hydrogenated system **99** and its derivatives have appeared in the last decade. The nitration of **99**, using either nitric acid in acetic anhydride (in 83% yield) <1997MI110> or dinitrogen pentoxide <2004DE19501377>, produces the tetranitro derivative **104**. More reports have appeared describing the N-alkylation of **99** and its derivatives as a means for the selective preparation of cyclams. As exemplified in **Scheme 64**, *cis*- or *trans*-**99** reacts with methyl acrylate to give, following ring closure, an amide whose reduction with borohydride provides the annulated species **109** <2002WO02/06209>. In the presence of excess methyl acrylate, a mixture of adducts is obtained <2002J(P2)552> due to isomerization of the starting material during the reaction. Borane reduction of this mixture results in quantitative conversion into a mixture of *cis*- and *trans*-**100**, whose stereochemistries were assigned by NMR correlation experiments.

The further conversion of **109** into a number of annulated products has been reported, along with the acid-promoted cleavage of the adducts to give cyclens, cyclams, and their analogues (**Scheme 65**). Oxygenated cyclen derivatives can be obtained by the same sequence, using diethyl oxalate in place of the alkylating agent in the same sequence <2006T6855>. In addition to acidic hydrolysis, these tetracyclic species can be cleaved by an exchange reaction with ethylenediamine, which returns **99** in addition to the desired cyclen (Equation 105) <1998WO98/49151>. Hydrolysis of the ethylene bridge can also be achieved by oxidation to a bis(amidinium) salt **110** using bromine, followed by basic hydrolysis <1999USP5886174, 2000USP6114521, 2000WO00/53588>, but the overall yield in this process is comparatively poor.

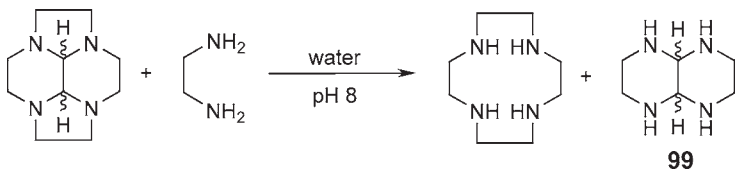


Scheme 64

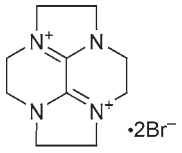


X	*Y*	*Yield step* 1 (%)	*Yield step* 2 (%)	*Reference*
Bond	Bond	60	>90	1998TL6861
Bond	CH_2	74	>90	1998TL6861
Bond	1,6-C_6H_4			2000CCC99
CH_2	Bond	90	>90	1998TL6861
CH_2	CH_2	90	>90	1998TL6861
CH_2	1,6-C_6H_4			2000CCC99
CH_2	CH($CH_2C_6H_6$-4-NO_2)	74	90	2004TL3059
CH_2	CH(CH_2-9-anthracenyl)	51		2003JCD3704

Scheme 65

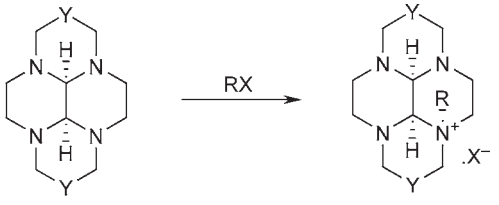


(105)



110

However, the tetracyclic amines can undergo further alkylation at those nitrogen centers with *exo*-lone pairs to give either quaternary salts **111** (Equation 106) or *cis*-bis-quaternary salts **112** (Equation 107), depending on the reaction conditions. The second alkylation is slower than the first, and solvent choice is important in determining the course of the reaction, with mono-quaternization generally favored in toluene (presumably as a result of precipitation of the adduct), and dialkylation being favored by more polar solvents. Trialkylation is not observed, even after extended periods with an excess of alkylating agent <2000TL1249>. Singly quaternized species **111** can also react with a different, alkylating agent to form differentially bis-quaternized products (Equation 108). The reactions of **102** and **103** with bis(bromomethyl)benzenes have also been reported: in this case, a dimeric structure of general form **113** is obtained <2003EJO3047>.

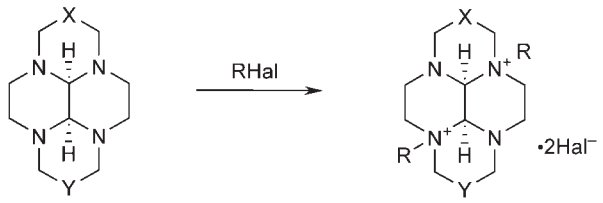


111

Y	*RX*	*Conditions*	*Yield (%)*	*Reference*
bond	MeI	Toluene, rt	98	2000TL1249
bond	EtI	MeCN, rt	94	2000TL1249
bond	PrI	MeCN, rt	90	2000TL1249
bond	$PhCH_2Br$	Toluene, rt	95	2000TL1249
bond	$4\text{-}O_2NC_6H_4CH_2Br$	MeCN	94	2000TL1249
bond	$BrCH_2COOEt$	Toluene, rt	88	2000TL1249
bond	ICH_2CONH_2	Toluene, rt	79	2000TL1249
bond	$ClCH_2CONH_2$	Toluene or MeCN, rt	0	2000TL1249
bond	$Br(CH_2)_2Br$	Toluene or MeCN, rt	74	2000TL1249
bond	$Br(CH_2)_3Br$	Toluene or MeCN, rt	69	2000TL1249
CH_2	MeI	Toluene, rt	62	2000JO10591
CH_2	$PhCH_2Br$	MeCN, rt	95	2000CCC243
CH_2	$PhCH_2Br$	Acetone, rt	62	1995PJC1039

(106)

This alkylation chemistry has also been applied to systems bearing substituents at the bridgehead <2002CC312, 2004CC588> and in the upper and lower rings <2004CC2212>. In this case, only the product of alkylation adjacent to the bridgehead substituent is observed; steric repulsion between the bridgehead methyl and the *N*-substituent is minimized in this way, and bis-quaternization does not occur. Similarly, **114**, where both bridgehead centers are substituted, does not undergo N-quaternization <2002CC312>. The steric effect of a bridgehead methyl group can facilitate the subsequent hydrolysis so that, in the examples shown in **Scheme 66**, hydrolysis proceeds at room temperature where the methyl group is located on a five-membered ring (X = bond), but requires reflux where it is located on a six-membered ring ($X = CH_2$) <2002CC312, 2005JOC7042>.

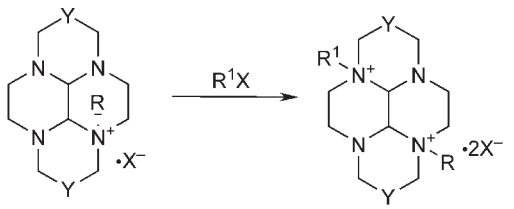


112

X	*Y*	*RX*	*Conditions*	*Yield (%)*	*Reference*
Bond	Bond	MeI	$CHCl_3$, 60 °C	60	2000T6427
Bond	Bond	MeI	MeCN, rt	98	2000TL1249
Bond	Bond	EtI	MeCN, rt	94	2000TL1249
Bond	Bond	EtI	Toluene, 60 °C	92	1999JO2683
Bond	Bond	PrI	MeCN, rt	95	2000TL1249
Bond	Bond	PrI	Toluene, 60 °C	91	1999JO2683
Bond	Bond	BuI	Toluene, 60 °C	84	1999JO2683
Bond	Bond	AmI	Toluene, 60 °C	76	1999JO2683
Bond	Bond	n-C_6H_{13}I	Toluene, 60 °C	79	1999JO2683
Bond	Bond	n-C_8H_{17}I	Toluene, 60 °C	77	1999JO2683
Bond	Bond	n-$C_{10}H_{21}$I	Toluene, 60 °C	72	1999JO2683
Bond	Bond	n-$C_{12}H_{25}$I	Toluene, 60 °C	85	1999JO2683
Bond	Bond	n-$C_{14}H_{29}$I	Toluene, 60 °C	94	1999JO2683
Bond	Bond	n-$C_{16}H_{33}$I	Toluene, 60 °C	74	1999JO2683
Bond	Bond	n-$C_{18}H_{37}$I	Toluene, 60 °C	77	1999JO2683
Bond	Bond	$HCCCH_2$I	Toluene, 60 °C	94	1999JO2683
Bond	Bond	$PhCH_2Br$	MeCN, rt	79	1996CC947
Bond	Bond	4-$O_2NC_6H_4CH_2Br$	MeCN-MeOH, rt	95	2000TL1249
Bond	Bond	$BrCH_2COOEt$	MeCN, rt	88	2000TL1249
Bond	Bond	ICH_2CONH_2	MeCN, rt	84	2000TL1249
Bond	Bond	$ICH_2CH_2NPhthal$	MeCN, 50 °C	40	2005EJI2044
Bond	Bond	$I(CH_2)_4NPhthal$	MeCN, 50 °C	93	2005EJI2044
Bond	CH_2	$PhCH_2Br$	MeCN, rt	56	1996CC947
CH_2	CH_2	MeI	$CHCl_3$, rt	67	1995H(41)1023
CH_2	CH_2	MeI	MeCN, rt	72	2000JO10591
CH_2	CH_2	$PhCH_2Br$	MeCN, rt	93	1996CC947

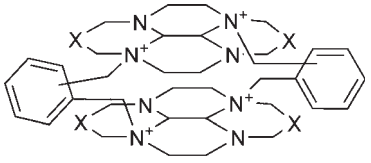
(107)

Ammonolysis or alkaline hydrolysis of **111** or **112** provides access to cyclams containing one or two tertiary amine centers (Equation 109). In a further use of this methodology, **109** and its lower homologue are quaternized with an alkyl bromide <2004EJO5027> and then ring-cleaved to produce an *N*-alkyltetramine (Equation 110). The same approach can be used for the preparation of linear octamines (Equation 111). Borohydride reduction of either **111** or **112**, however, results in only partial cleavage to form a piperazine derivative (**Scheme 67**) <1995PJC1039> in the former case, or a cross-bridged product in the latter, as exemplified in Equation (112). Cleavage to give a 1,4-bridged piperazine is also observed on aqueous hydrolysis of the cyclam/phenylglyoxal cyclocondensation product (Equation 113) <2003T4579>.



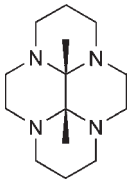
Y	*R*	R^1X	*Conditions*	*Yield (%)*	*Reference*
bond	$PhCH_2Br$	MeI	MeCN, rt	0	2000TL1249
bond	$PhCH_2Br$	MeI	MeCN-MeOH, rt	90	2000TL1249
bond	CH_2-4-$C_6H_4NO_2$	MeI	MeCN-MeOH, rt	84	2000TL1249
bond	CH_2COOEt	MeI	MeCN, rt	89	2000TL1249
bond	CH_2COOEt	EtI	MeCN, rt	77	2000TL1249
bond	CH_2COOEt	$PhCH_2Br$	MeCN, rt	81	2000TL1249
bond	CH_2COOEt	4-$O_2NC_6H_4CH_2Br$	MeCN, rt	83	2000TL1249
CH_2	CH_2Ph	MeI	Acetonitrile, rt	82	2000CCC243
CH_2	CH_2Ph	$PhCH_2Br$	Acetonitrile, rt		2000CCC243
CH_2	CH_2-4-$C_6H_4NO_2$	MeI	Acetonitrile, rt		2000CCC243
CH_2	CH_2-4-$C_6H_4NO_2$	EtI	Acetonitrile, rt		2000CCC243
CH_2	CH_2COOEt	MeI	Acetonitrile, rt		2000CCC243
CH_2	CH_2COOEt	EtI	Acetonitrile, rt		2000CCC243

(108)

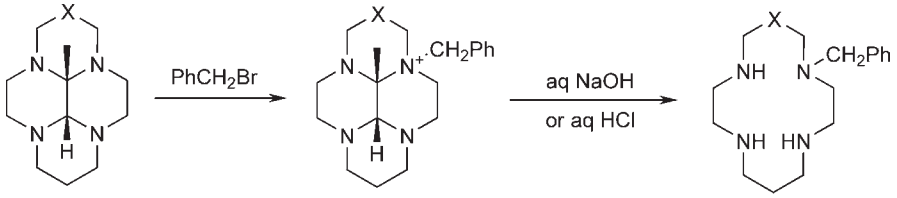


113

X = bond, CH_2

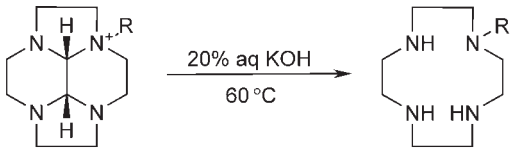


114



X	*Step* 1	*Step* 1 *yield (%)*	*Step* 2	*Step* 2 *yield (%)*
bond	MeCN, rt	53	aq NaOH, rt	80
CH_2	MeCN, rt	53	aq NaOH, reflux	80

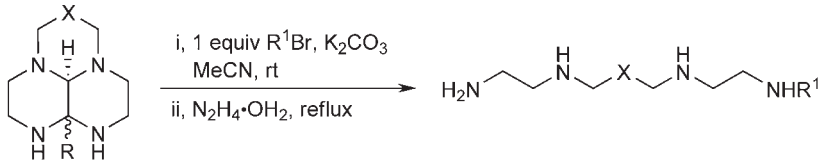
Scheme 66



R	*Yield* (%)	*Reference*
Et	92	1999JO2683
Pr	95	1999JO2683
Bu	100	1999JO2683
Am	100	1999JO2683
n-C_6H_{13}	84	1999JO2683

R	*Yield* (%)	*Reference*
n-C_8H_{17}	79	1999JO2683
n-$C_{10}H_{21}$	75	1999JO2683
n-$C_{12}H_{25}$	82	1999JO2683
n-$C_{14}H_{29}$	85	1999JO2683
n-$C_{16}H_{33}$	84	1999JO2683
n-$C_{18}H_{37}$	78	1999JO2683

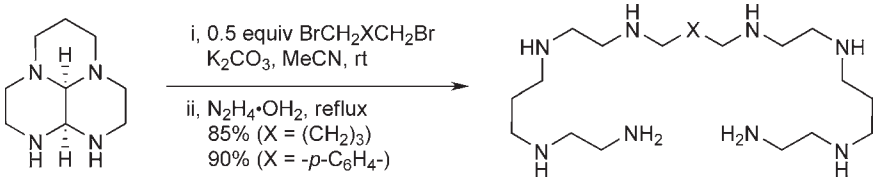
(109)



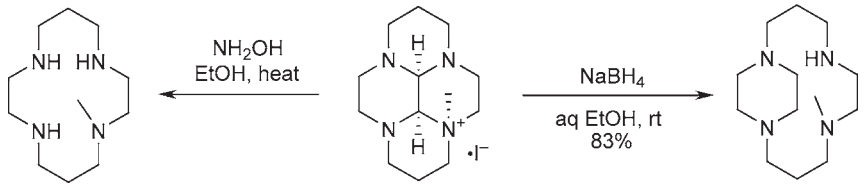
X	*R*	R^1	*Yield* (%)
Bond	H (*cis*)	CH_2Ph	60
Bond	H (*cis*)	Pr	62
Bond	Me	CH_2Ph	63
Bond	Me	Pr	65
CH_2	H (*cis*)	CH_2Ph	76

X	*R*	R^1	*Yield* (%)
CH_2	H (*cis*)	Pr	74
CH_2	H (*trans*)	CH_2Ph	86
CH_2	H (*trans*)	Pr	74
CH_2	Me (*cis*)	CH_2Ph	76
CH_2	Me (*cis*)	Pr	72

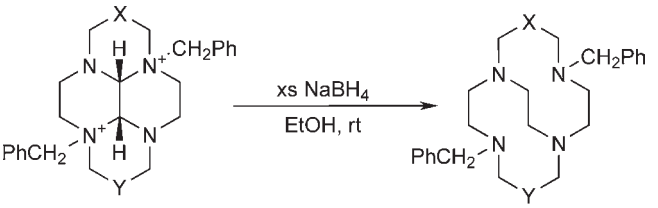
(110)



(111)

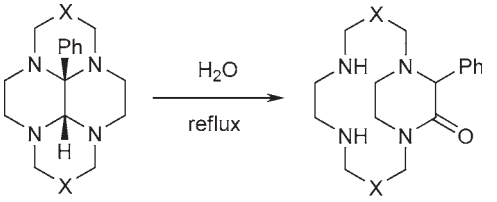


Scheme 67



(112)

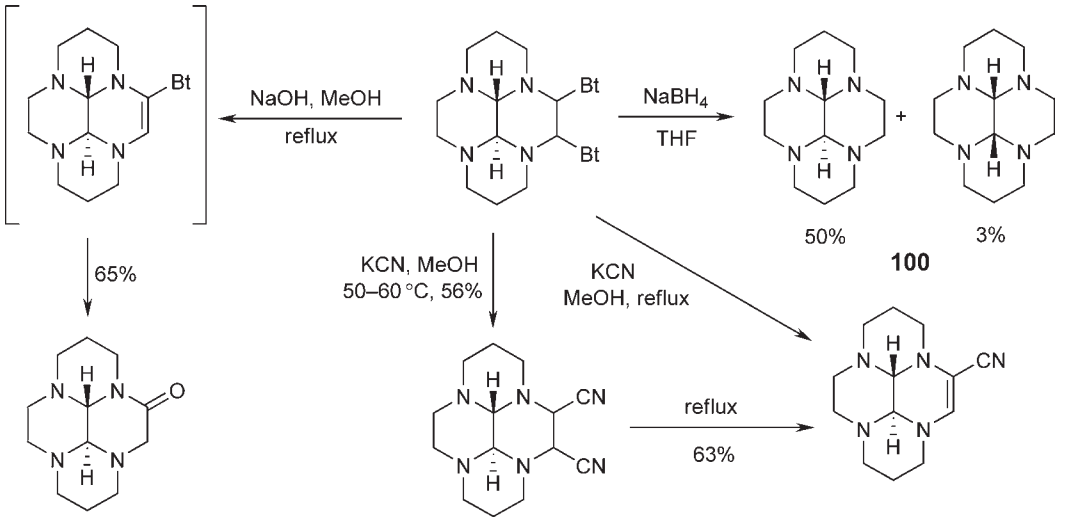
X	*Y*	*Yield (%)*	*Reference*
Bond	Bond	87–99	1996CC947
Bond	CH_2	64–98	1996CC947
CH_2	CH_2	83–96	1996CC947
$CH(CH_2C_6H_4\text{-}4\text{-}NO_2)$	CH_2	78	2004CC2212



(113)

60% (X = bond), 100% (X = CH_2)

The benzotriazole adducts formed by an alternative approach to derivatives of **100** undergo a variety of reactions (**Scheme 68**), including elimination to give, after hydrolysis, a 2-oxo species. The benzotriazole group is also readily replaced by nucleophilic substitution or upon treatment with borohydride to provide **100** <1995H(41)1023>.

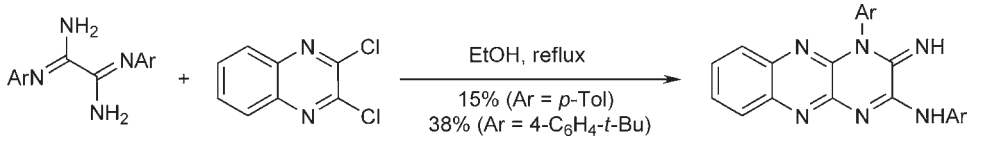


Scheme 68

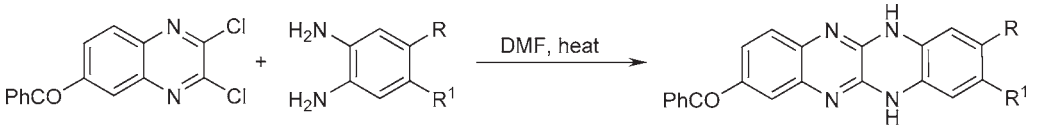
10.19.2.5.3 Ring synthesis

The principal means for preparation of unreduced pyrazino[2,3-*b*]pyrazines and their fused and quaternized analogues involve the reaction of a 1,2-diamine with a 1,2-bis-electrophile, as reported in CHEC(1984) <1984CHEC(3)329> and CHEC-II(1996) <1996CHEC-II(7)737>. Additional examples of the condensation of dichloropyrazines with diamines have been reported since the appearance of CHEC-II(1996) <1997CHE1352,

1997JHC653, 2002EJO1368, 2003H(60)2457, 2004OL2007>, along with some variations such as the condensation of 2,3-dichloroquinoxaline with an oxalamidine (Equation 114) <2002ZNB946>. 7-Benzoylation of 2,3-dichloroquinoxaline <2001IJB195> results in a completely regioselective reaction with a 4-substituted *o*-phenylenediamine (Equation 115).



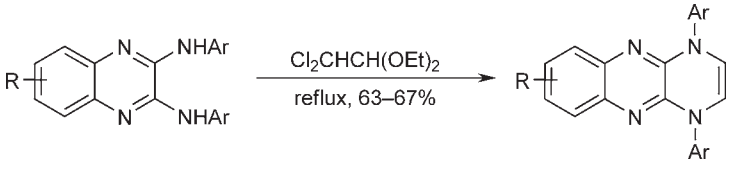
(114)



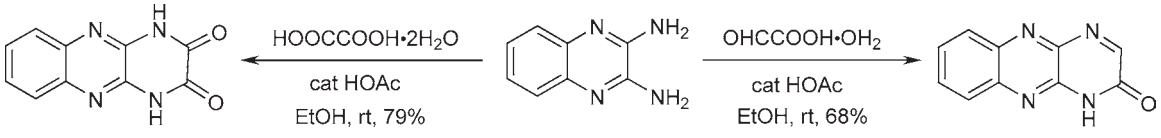
(115)

R	R^1	*Yield* (%)
H	H	74
Me	Me	80
H	COPh	76

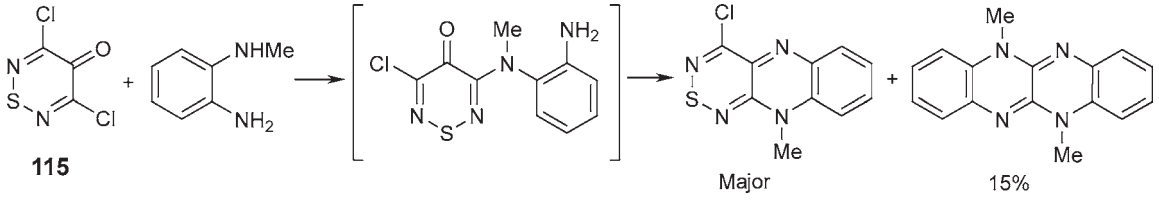
The condensation of *o*-pyrazinediamine with glyoxal was reported in CHEC(1984), and the process has been extended to include a range of diketones <1997CHE1473, 2004OL2007, 2005BML3241>. Reported variations include the condensation of 2,3-diaminoquinoxalines with dichloroacetaldehyde diethyl acetal (Equation 116) <2000S1679> and with glyoxylic and oxalic acids (**Scheme 69**) <2002DEP10111728>. In an interesting variation on the same principle (**Scheme 70**), the thiadiazine derivative **115** serves as a three-carbon electrophile, coupling with two molecules of *N*-methyl-*o*-phenylenediamine <2000J(P1)2601>, although this is not the major reaction pathway.



(116)



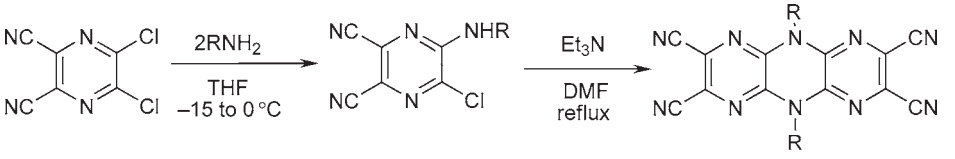
Scheme 69



115

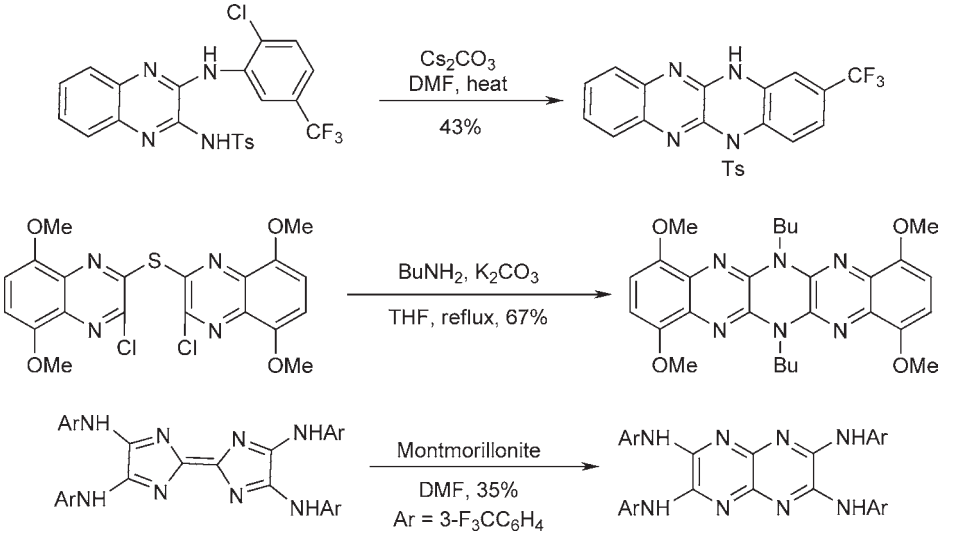
Scheme 70

Further variations on the amine/electrophile coupling principle have appeared in the past decade, including the intermolecular coupling of 3-chloro-2-aminopyrazines to give 5,10-dihydrodipyrazino[2,3-*b*:2′,3′-*e*]pyrazines, as exemplified in **Scheme 71** <2000MI71, 1997JHC653>. The formation of a quinoxalino[2,3-*b*]quinoxaline by dehydrochlorination, following diamination of a dichloroquinoxaline (Equation 117), has also been described <1994CHE340>, as has the cyclization illustrated in Equation (118) <1996J(P1)2443>. This must proceed by nucleophilic displacement of hydrogen sulfide, and succeeded where coupling of a diamine with a dichloropyrazine failed. An entirely different approach to the pyrimido[2,3-*b*]pyrimidine nucleus has appeared recently <2005S643> and involves the isomerization of a bis(imidazolylidene) in the presence of montmorillonite clay (Equation 119).



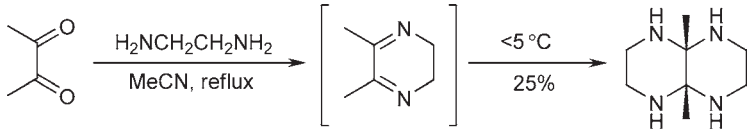
R	*Yield* (%)	*R*	*Yield* (%)	*R*	*Yield* (%)
Me	43	Ph	38	4-$BuOC_6H_4$	36
Bu	37	*p*-Tol	49	4-$AcNHC_6H_4$	45
CH_2Ph	46	4-BuC_6H_4	61	CH_2COOMe	30

Scheme 71



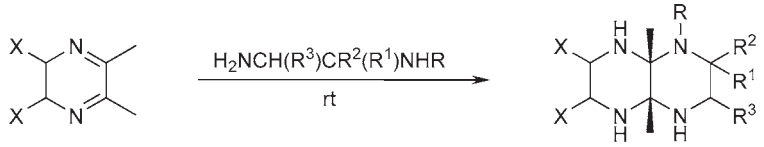
The condensation of ethylenediamine with glyoxal to give 1,4,5,8-tetraazadecalin **99** was described in CHEC(1984); this approach has been used extensively as a result of interest in the use of **99** as a scaffold for the construction of selectively functionalized cyclams. Compound **99** is also obtained from oxalic acid and ethylenediamine in the presence of hydrogen over a zeolite catalyst <2002CL236>. The reaction is less efficient when diketones are used; angularly substituted tetraazadecalins are reported to be isolable in comparatively few cases <1999H(51)2305>, where a mixture of α-diketone with excess ethylenediamine is heated at reflux in order to form dihydropyrazine **116**, then kept for a period at low temperature to permit the second ring formation (**Scheme 72**). The tetraazadecalins readily dissociate to **116** at room temperature in acetonitrile or chloroform. Nevertheless, a number of examples have been reported of the successful formation of 4*a*,8*a*-disubstituted *cis*-1,4,5,8-tetraazadecalins by condensation of 1,2-diamines with **116** and analogues (Equation 120). The yields are typically better when the reaction is carried out in the absence of solvent, most notably for the condensation of **116** with

1,2-cyclohexanediamine where, in acetonitrile, the tricyclic product is accompanied by tetracycle **117**, formed in 42% yield by dissociation of ethylenediamine from the tricycle and reaction of the resulting hexahydroquinoxaline with a second molecule of cyclohexanediamine. A further variation of Equation (120) involves the formation of **100** in a 77% yield by condensation of 2,3-dihydroxypiperazine with ethylenediamine <1998MI236>.



116

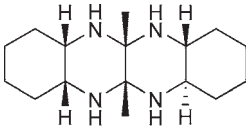
Scheme 72



X,X	*R*	R^1	R^2	R^3	*Solvent*	*Yield (%)*	*Reference*
H,H	H	H	H	H	none	78	1999H(51)2305
H,H	H	H	Me	H	none	41	1999H(51)2305
H,H	H	Me	Me	H	none	35	1999H(51)2305
H,H	Me	H	H	H	none	53	1999H(51)2305
H,H	H	H	$-(CH_2)_4-$		None	82	2000H(53)1677
H,H	H	H	$-(CH_2)_4-$		MeCN	8[a]	2000H(53)1677
$-(CH_2)_4-$ (*trans*)	H	H	H	H	MeCN	32	1999H(51)2305
$-(CH_2)_4-$ (*trans*)	H	H	$-(CH_2)_4-$ (*trans*)		MeCN	61	1999H(51)2305
$-(CH_2)_4-$ (*trans*)	H	H	$-(CH_2)_4-$ (*cis*)		MeCN	62	1999H(51)2305

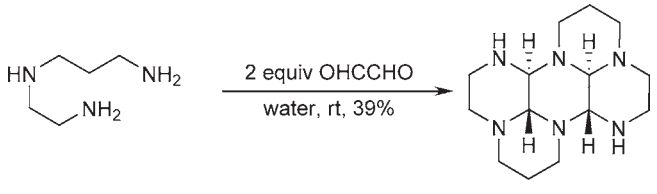
(120)

[a]Major product is **117**.

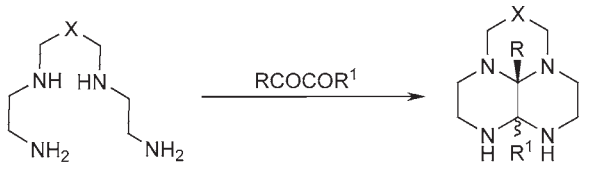


117

The formation of fused 1,4,5,8-tetraazadecalins by condensation of 1,2-diketones with linear or cyclic tetramines has been the subject of considerable study. The reaction of cyclam **102** and cyclen **103** with glyoxal has been known for some years (see <1996CC947, 1995H(41)1023> and references therein), and gives the thermodynamically favoured *cis*-product with the maximum number of six-membered rings in chair conformations. More recently, condensations have been reported of 1,2-diketones with linear triamines (Equation 121) <1996H(43)1391> and tetramines (Equation 122), and of sarcophagine with dimethyl oxalate (**Scheme 73**)<1996CC1175>.

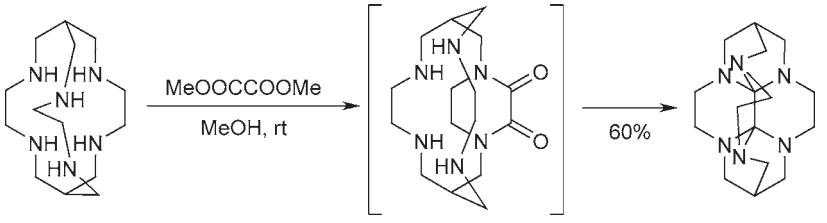


(121)



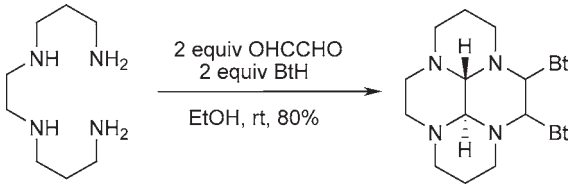
X	*R*	R^1	*Conditions*	*Yield* (*isomer*)	*Reference*
Bond	H	H	EtOH, –10 °C	0	2003EJO1050
Bond	H	H	EtOH, 80 °C	71% (*cis*), 11% (*trans*)	2003EJO1050
CH_2	H	H	EtOH, –10 °C	95% (*trans*)	2003EJO1050
CH_2	H	H	EtOH, 80 °C	95% (*cis*)	2003EJO1050
Bond	Me	Me	MeCN, <5 °C	90% (*cis*)	1998TL6861
CH_2	Me	H	Water, 4 °C	Not cited (80:20 *cis*/*trans*)	2005JOC7042
CH_2	Me	H	MeCN, <5 °C	69% (*cis*) after alkylation	2002CC312
CH_2	Me	Me	MeCN, <5 °C	95% (*cis*)	1998TL6861

(122)

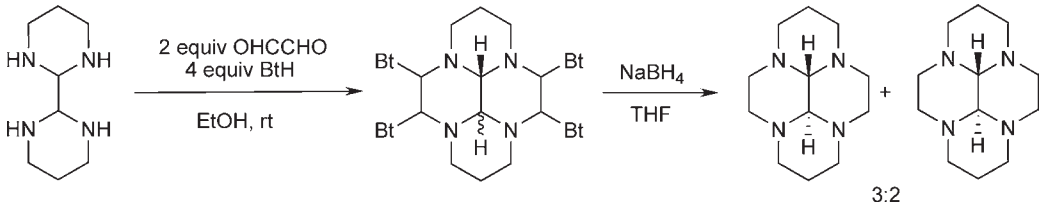


Scheme 73

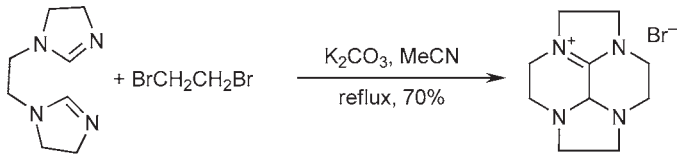
In an alternative approach, *trans*-fused derivatives of **99** are formed under kinetic control by a benzotriazole-mediated process (Equation 123) <1995H(41)1023>. Subsequent reductive removal of the benzotriazole (Bt) substituents is accompanied by partial (reversible) ring opening, leading to the more favored *cis*-isomer. A similar sequence can be carried out using 2,2′-bis(hexahydropyrimidine) as the tetramine component (**Scheme 74**). Finally, treatment of bis(imidazole) **118** with 1,2-dibromoethane results in formation of cationic species **119** (Equation 124). At a higher temperature, this is oxidized to the dicationic product **110**, which can also be obtained by oxidation of **119** with aqueous hydrogen peroxide <2002JOC4081>.



(123)



Scheme 74



(124)

118 **119**

10.19.2.5.4 Important compounds and applications

Tetracyanopyrazino[2,3-*b*]pyrazines such as **95** and **96** are of interest for use in electronic devices. However, apart from species of synthetic importance as described above, the most notable compound from the viewpoint of utility is the explosive TNAD **104** <1997THE199, 2005IJQ(102)398>.

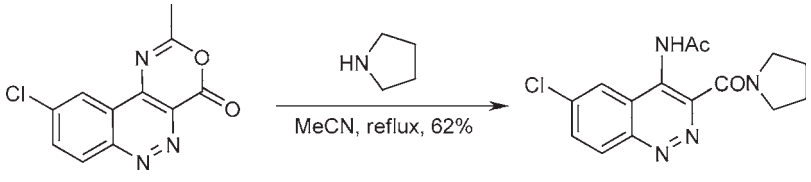
10.19.3 Diazinooxazines

Diazinooxazines were not discussed in CHEC(1984), and since its publication the only review of importance is that in CHEC-II(1996) <1996CHEC-II(7)737>. Representatives of a number of systems have now been reported, but the range of information published is somewhat limited and, for most systems, no new information is available on structural methods or on commercially important compounds.

10.19.3.1 Pyridazinooxazines

10.19.3.1.1 Reactivity

Available data on the reactivity of these systems were discussed in CHEC-II(1996) <1996CHEC-II(7)737> and little has been published since, the most notable report being of nucleophilic ring-opening reactions to form 4-aminocinnoline-3-carboxamides (Equation 125) <1997PHA838>.

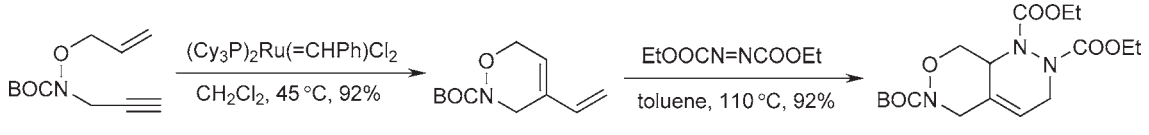


(125)

10.19.3.1.2 Ring synthesis

10.19.3.1.2(i) Pyridazino[4,3-*d*][1,2]-oxazines

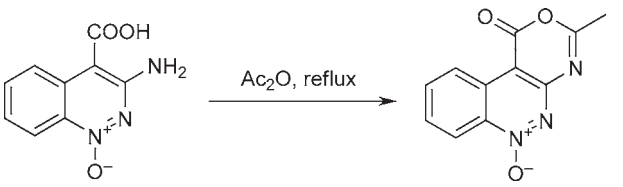
Hydrogenated derivatives of this system have been prepared from acyclic enyne precursors (**Scheme 75**) by ring-closing metathesis, followed by [4+2] cycloaddition of the resulting diene with diethyl azodicarboxylate <2003S2017>.



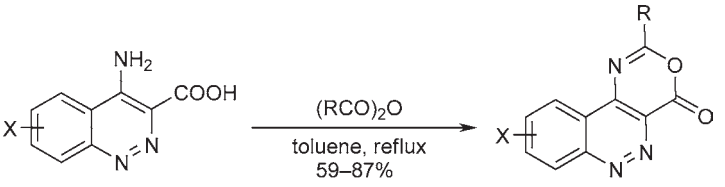
Scheme 75

10.19.3.1.2(ii) Pyridazino[3,4-*d*][1,3]oxazines and pyridazino[4,3-*d*][1,3]oxazines

Preparations of pyridazino[3,4-*d*][1,3]oxazines by ozonolysis of pyrrolo[2,3-b]pyridazine-3-carboxylates and from the reaction of *N*-(4-ethoxycarbonylpyridazin-3-yl)phosphinimines with acyl halides were described in CHEC-II(1996) <1996CHEC-II(7)737>. A simpler form of the latter approach has now been reported <1994CC2451>, wherein the 1-*N*-oxide of 3-aminocinnoline-4-carboxylic acid undergoes cyclization with acetic anhydride (Equation 126). The isomeric pyridazino[4,3-*d*][1,3]oxazines have been prepared in a similar manner (Equation 127) <1997PHA838>.



(126)



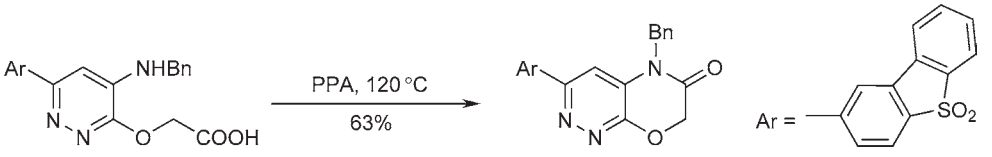
R	*X*	*Yield* (%)	*R*	*X*	*Yield* (%)
Me	H	70[a]	Me	7-Me	78
Me	7-F	75	Me	8-Me	87
Me	9-F	71	Et	H	68
Me	8-Cl	72	Et	7-Cl	72
Me	9-Cl	81	Et	7-Me	75
			Ph	H	59[a]

[a]Reaction carried out by heating without solvent.

(127)

10.19.3.1.2(iii) Pyridazino[3,4-*b*][1,4]oxazines

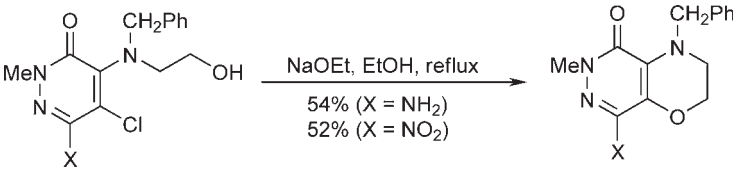
Two approaches to pyridazino[3,4-*b*][1,4]-oxazines by nucleophilic displacement of 3,4-disubstituted pyridazines were reported in CHEC-II(1996) <1996CHEC-II(7)737>, and two further reports of the use of this approach have appeared since <2001JMT(545)75, 2003JMT(666)625>. A further approach has also appeared, involving cyclization of a 2-[4-aminopyridazin-3-yloxy]acetic acid, as exemplified in Equation 128 <2002ZN(B)668, 2003JMT(666)625>.



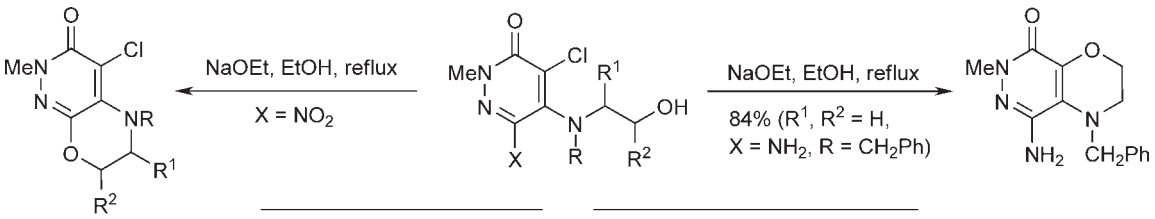
(128)

10.19.3.1.2(iv) Pyridazino[4,5-*b*][1,4]oxazines

The formation of pyridazino[4,5-*b*][1,4]oxazines from ethanolamines and 3,4-dichloropyridazines was discussed in CHEC-II(1996) <1996CHEC-II(7)737>, and is included in a more recent review of 3(2*H*)-pyridazinone chemistry <1998JHC1075>. Further examples of this approach have been reported <2004T3763>, along with variants in which an *N*-(chloropyridazinyl)ethanolamine undergoes intramolecular displacement of chloride (Equation 129 and **Scheme 76**) <2001JMT(545)75>. In the case illustrated in **Scheme 76**, cyclization can also occur with displacement of nitrite to give an isomeric pyridazino[3,4-*b*][1,4]-oxazine. A more novel approach is from 4-chloro-5-hydroxypyridazin-3(2*H*)-ones (**Scheme 77**) <2004SC1399, 2003TL8995>. In this case, cyclization follows a Smiles rearrangement via an intermediate such as **120**.



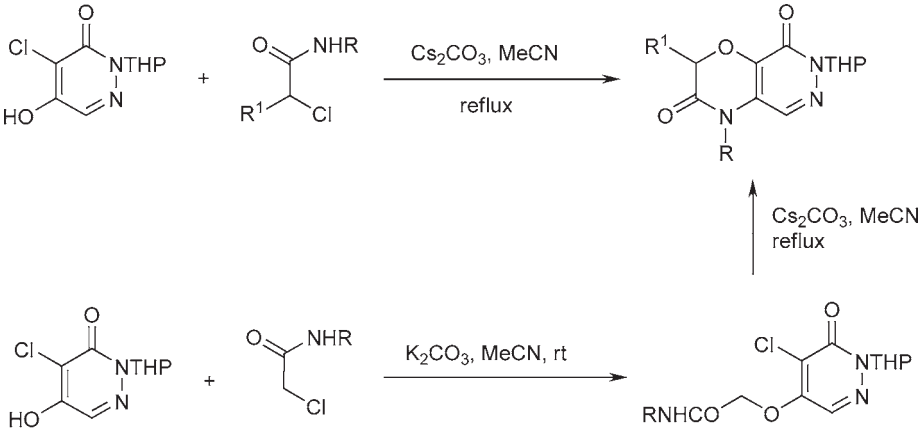
(129)

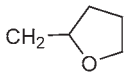
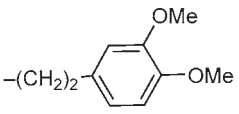
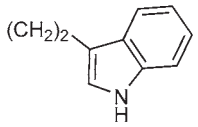


R	R^1, R^2	*Yield* (%)
H	H, H	52
H	*cis*-$(CH_2)_3$	60

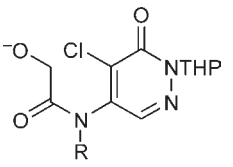
R	R^1, R^2	*Yield* (%)
H	*cis*-$(CH_2)_4$	59
CH_2Ph	H, H	73

Scheme 76



R	*Yield*, R^1 = *H* (*one step*) (%)	*Yield*, R^1 = *H* (*two steps*) (%)	*Yield*, *R* = *Me* (*one step*) (%)
Pr	65	92	21
Cy	53	93	33
CH_2Cy	62	94	40
	68	92	36
CH_2Ph	55	94	46
CH_2CH_2Ph	67	94	45
(R)-CH(Me)Ph	61	92	
(S)-CH(Me)Ph	61		33
	59	91	40
	83	10	

Scheme 77



120

10.19.3.2 Pyrimidooxazines

10.19.3.2.1 Reactivity

10.19.3.2.1(i) Pyrimido[4,5-*c*][1,2]oxazines

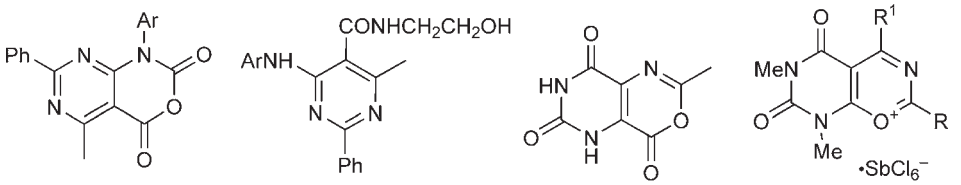
Partially reduced pyrimido[4,5-*c*][1,2]oxazines prove to be robust to catalytic hydrogenation conditions, in the preparation of a tritiated nucleoside analogue (Equation 130) <1997WO97/28177>.



(130)

10.19.3.2.1(ii) Pyrimido[1,3]oxazines

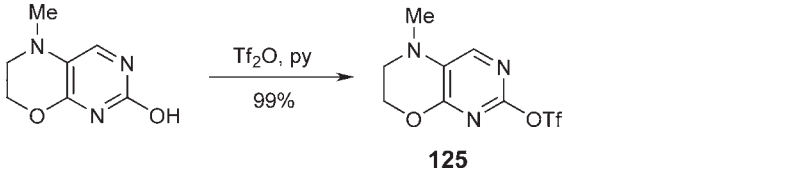
Pyrimido[1,3]oxazines are reactive toward amines; anhydride **121** undergoes ring opening and decarboxylation on treatment with ethanolamine to give the amide **122** <1996MI459>. The reactions of amide **123** <2002MI10> with amines to form pyrimido[5,4-*d*]pyrimidines have already been mentioned, while the equivalent process with pyrimido[5,4-*e*]oxazinium salt **124** is discussed in CHEC-II(1996) <1996CHEC-II(7)737>.



121 **122** **123** **124**

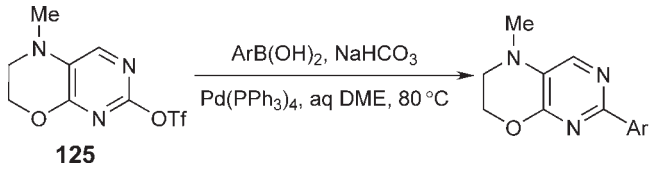
10.19.3.2.1(iii) Pyrimido[4,5-*b*][1,4]oxazines

The triflate **125** is formed from the hydroxy precursor (Equation 131) and undergoes a variety of nucleophilic substitution processes <2006TL4437>, including Suzuki and Stille couplings (Equations 132 and 133, respectively). Amination of **125** with aliphatic amines occurs under thermal conditions, using either conventional or microwave heating (Equation 134), but the reactions of **125** with less reactive amines require palladium catalysis (Equation 135).

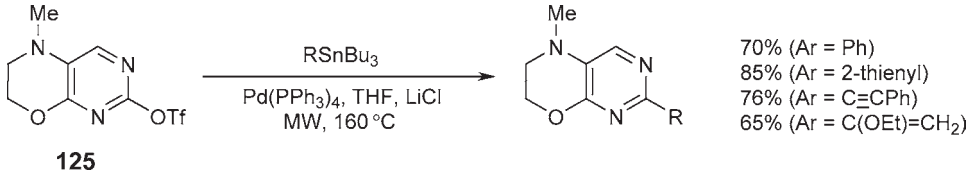


(131)

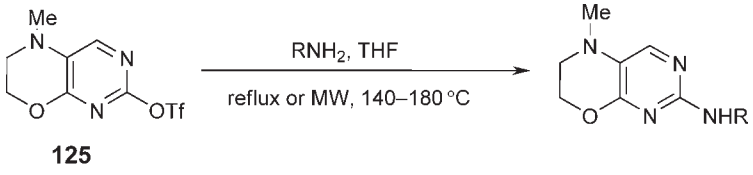
125



(132)

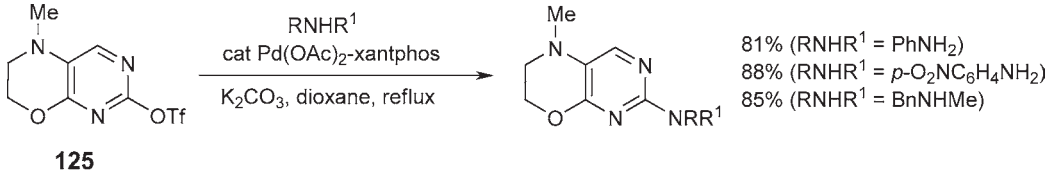


(133)



(134)

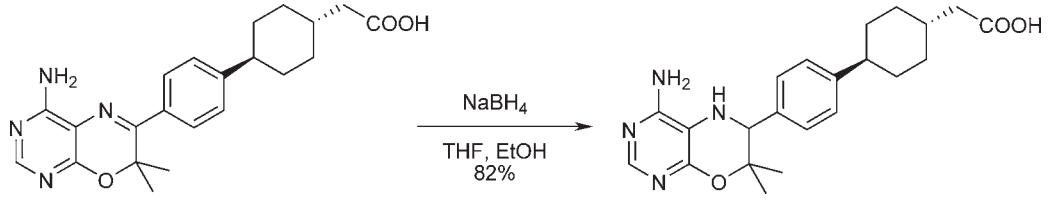
	Reflux conditions		*MW conditions*	
R	*Time (h)*	*Yield (%)*	*Time (min)*	*Yield (%)*
Bu	24	80	5	88
CH_2Ph	48	88	5	92
cyclohexyl	92	85	15	85
Pr			12	86
$(CH_2)_2$-*p*-Tol			5	80



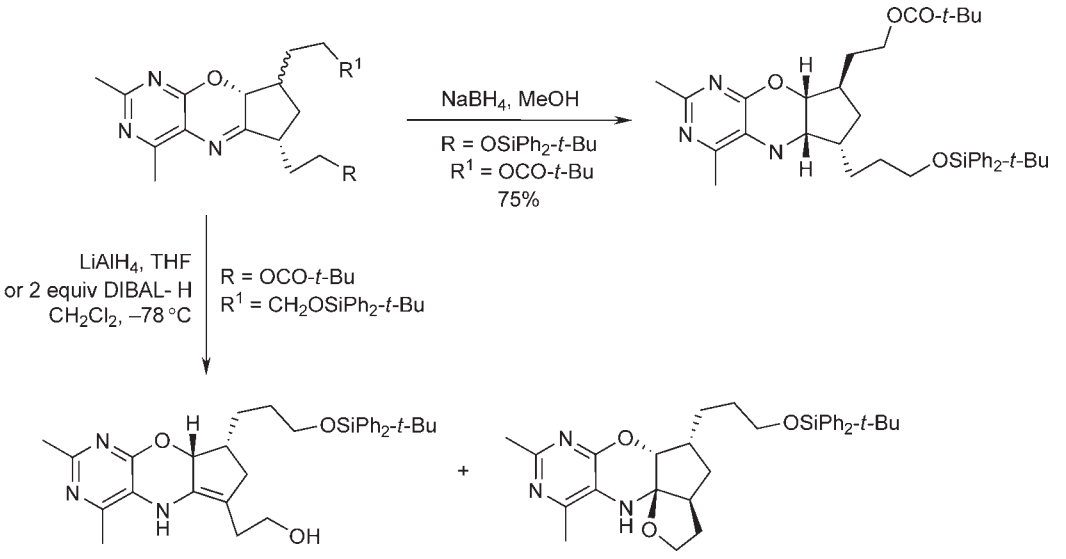
(135)

xantphos = 1,8-Bis(diphenylphosphinyl)-9,9-dimethylxanthene

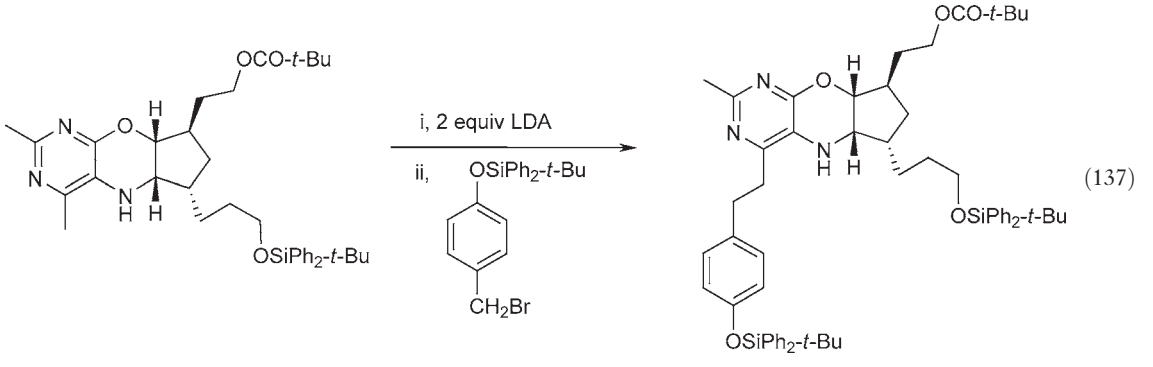
1,2-Dihydropyrimido[4,5-*b*][1,4]oxazines are reduced upon treatment with metal hydrides, as exemplified in Equation (136) <2004WO2004/047755>. In studies toward an unusual subunit of the polypeptide laminin <2003USP0199531>, it was found that the exact course of this reaction depends upon the substitution pattern at adjacent positions (**Scheme 78**), so that aminal formation competes with double bond reduction. NMR spectroscopy confirmed the presence of a *cis*-ring junction in the product. In the same work, alkylation of the dianion derived by treatment of a 5,7-dimethyl-1,2,3,4-tetrahydropyrimido[4,5-*b*][1,4]oxazine with strong base occurred selectively at the 5-methyl group (Equation 137).



(136)



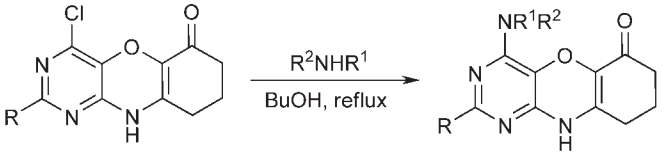
Scheme 78



(137)

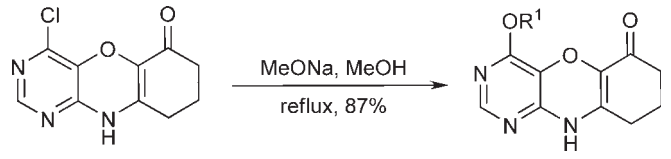
10.19.3.2.1(iv) Pyrimido[5,4-*b*][1,4]oxazines

O-Alkylation and annulation of pyrimido[5,4-*b*][1,4]oxazines was described in CHEC-II(1996) <1996CHEC-II(7)737>. More recently, nucleophilic substitution at C-4 of a benzo derivative has been reported <1998CHE1201>; a chlorine atom at this position is readily displaced by an amine (Equation 138), alkoxide (Equation 139), and sulfur nucleophiles (Equation 140). The piperazine adducts **126** (R = H, Me) were prepared by this approach and are of interest as selective PDE-V inhibitors <2005BML1829>. One example of side-chain substitution has been reported, in which the nucleoside analogue **127** undergoes dimethoxytritylation at the primary alcohol in the presence of the unprotected ring nitrogen <1998TL8385>.

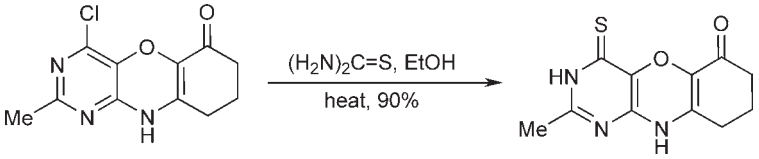


R	*R*^{1}*NHR*^{2}	*Yield* (%)
H	Piperidine	86
H	Morpholine	96
H	*N*-Methylpiperazine	77
Me	$PhCH_2NH_2$	62
Me	Piperidine	86
Me	Morpholine	96
Me	*N*-Methylpiperazine	77

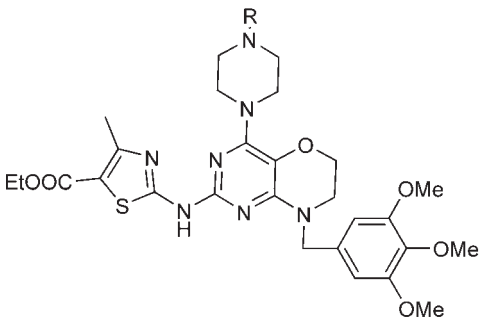
(138)



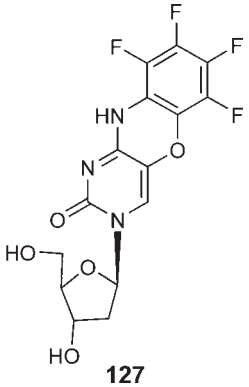
(139)



(140)



126



127

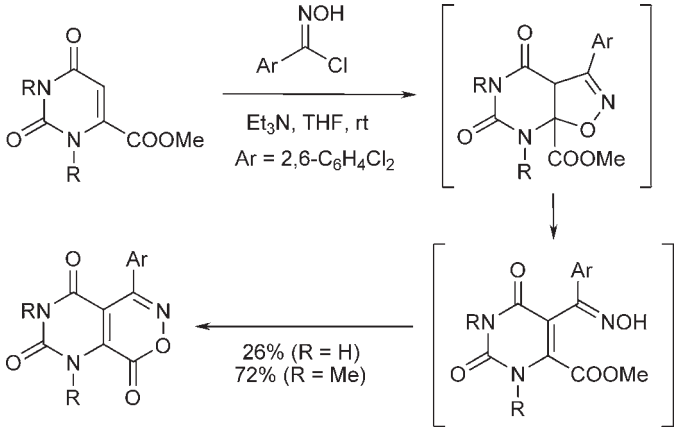
10.19.3.2.2 Ring synthesis

10.19.3.2.2(i) Pyrimido[4,5-*c*][1,2]oxazines

The preparation of pyrimido[4,5-*c*][1,2]oxazines by intramolecular displacement of a triazole from position 4 of a 2-pyrimidinone was described in CHEC-II(1996) <1996CHEC-II(7)768>. This approach has since been used for the preparation of a number of nucleoside analogues containing this ring system <1997WO97/28177, 2001NN1049>.

10.19.3.2.2(ii) Pyrimido[5,4-*d*][1,2]oxazines

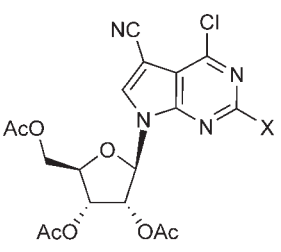
Cycloaddition of methyl orotate or its 1,3-dimethyl derivative with 2,6-dichlorobenzonitrile oxide (generated *in situ*; **Scheme 79**), or with the corresponding isocyanate, gives an oxazolo[4,5-d]pyrimidine. This intermediate undergoes ring opening under the reaction conditions, and recyclization occurs to provide a pyrimido[5,4-*d*][1,2]oxazine <1992H(34)1423>.



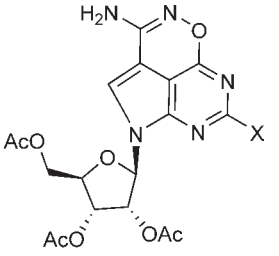
Scheme 79

10.19.3.2.2(iii) Pyrimido[5,4-*e*][1,2]oxazines

One example of the generation of this system has appeared, in which the treatment of a pyrrolo[2,3-*d*]pyrimidine **128** with hydroxylamine gives the *peri*-fused nucleoside analogue **129** <2003WO03/061385>.



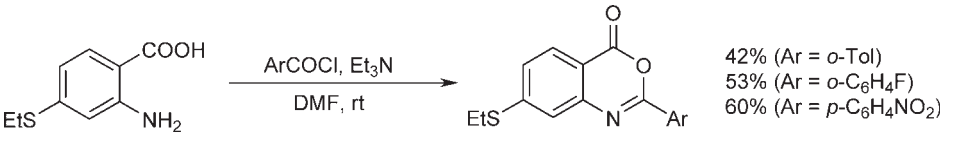
128



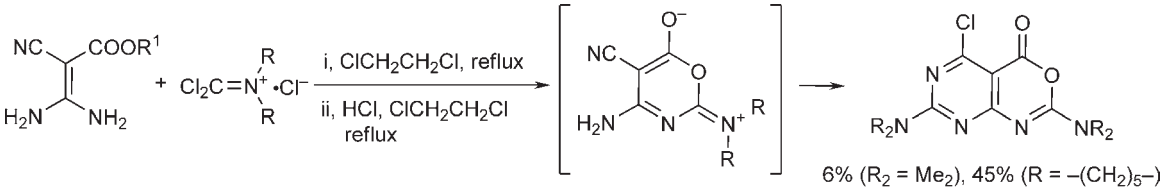
129

10.19.3.2.2(iv) Pyrimido[4,5-*d*][1,3]oxazines

The routes to pyrimido[4,5-*d*][1,3]oxazines described in CHEC-II(1996) <1996CHEC-II(7)737> involve the reaction of 4-aminopyrimidine-5-carboxylic acids with ethyl chloroformate, and the cyclization of 4-aminopyrimidin-2-one with 2 equiv of hexafluoroacetone. Two further examples of the former method have appeared more recently <1996MI459, 2004WO041818>, and the related cyclization using aromatic acid chlorides (Equation 141) has also been reported <2000BMC2803>. In a more direct approach, modest yields of pyrimido[4,5-*d*][1,3]oxazin-4-ones are obtained by treatment of 3,3-diaminocyanoacrylates with an excess of dichloromethylenedimethylimmonium chloride (**Scheme 80**). The intermediate betaine **130** can be isolated (R = Me) and converted into the pyrimidooxazine in a stepwise process <1999HCO203>.



(141)

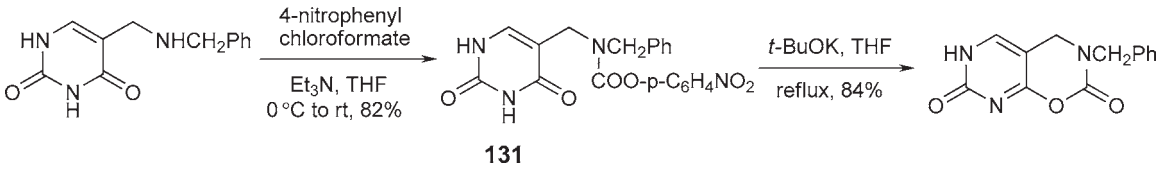


130

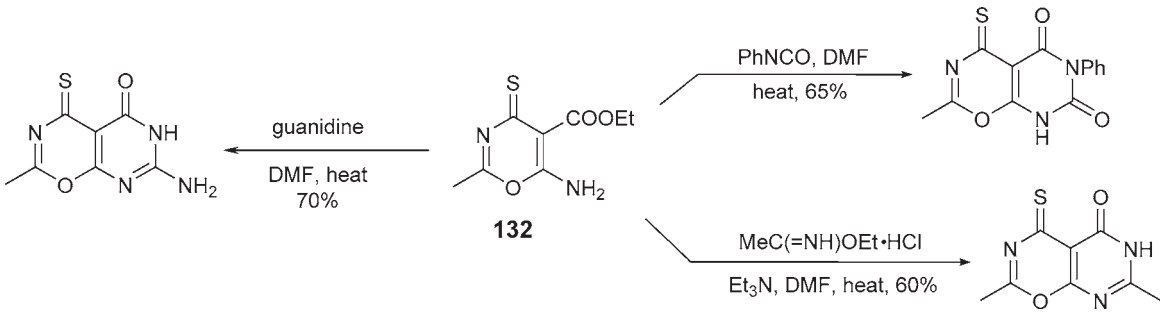
Scheme 80

10.19.3.2.2(v) Pyrimido[5,4-*e*][1,3]oxazines

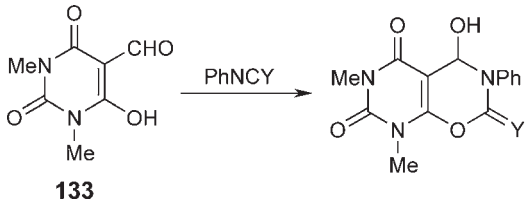
Direct ring closure of the carbamate **131** has recently been reported as a means to access the pyrimido[5,4-*e*]-[1,3]oxazine system (**Scheme 81**) <2006SL1519>. The annulation of a pyrimidine ring onto oxazine **132**, using guanidine, isocyanates, or imidates, provides access to pyrimido[5,4-*e*][1,3]oxazines with different substituents at C-7 (**Scheme 82**) <1996PS15>. Alternatively, the solid-state reaction of pyrimidine derivative **133** with phenyl isocyanate or isothiocyanate results in formation of an oxazine ring (Equation 142) <2004TL2405>; this reaction is reported to be more efficient when microwave heating is used.



Scheme 81



Scheme 82

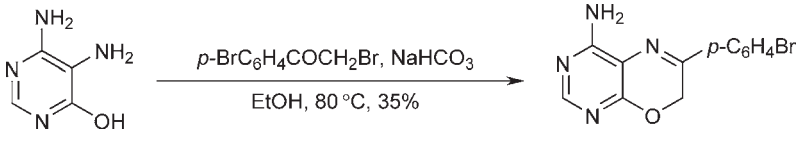


	MW, 6 min		*$CHCl_3$, reflux 5–6 h*
Y	*Temp (°C)*	*Yield (%)*	*Yield (%)*
O	60–65	87	65
S	80–90	85	60

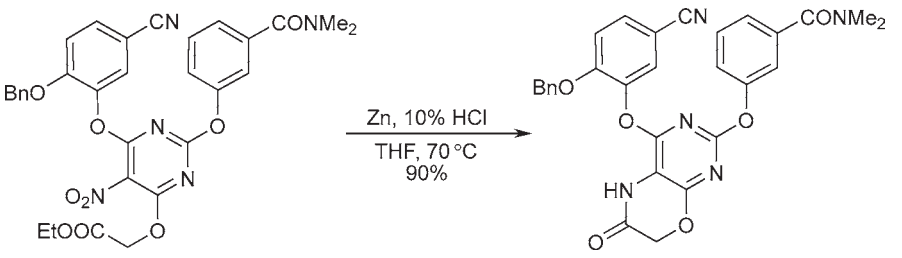
(142)

10.19.3.2.2(vi) Pyrimido[4,5-*b*][1,4]oxazines

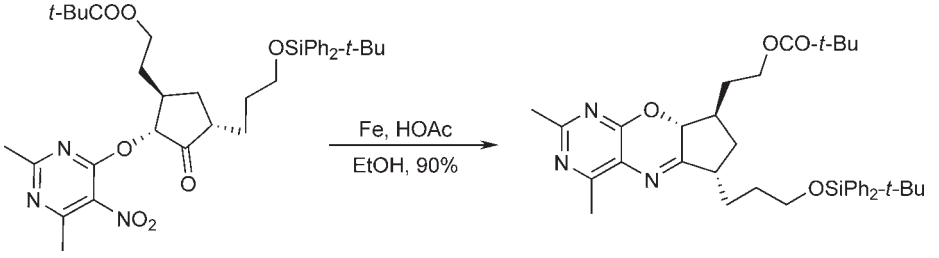
The formation of pyrimido[4,5-*b*][1,4]oxazines by condensation of a 4-aminopyrimidin-3-one with ethyl pyruvate was included in CHEC-II(1996). The same type of cyclization, using an α-bromoketone as the bis-electrophile as exemplified in Equation (143), has been used to prepare a number of 1,2-dihydropyrimido[4,5-*b*][1,4]oxazines <2004WO2004/047755>. Two related processes have also been reported; in one, the reduction of a 5-nitropyrimidin-3-yloxyacetic acid ester results in cyclization to form a pyrimido[4,5-*b*][1,4]oxazine-3-one (Equation 144) <1998BML2235>. In the other, reduction of a nitro group by iron, Raney nickel, or by hydrogenation over a palladium catalyst is followed by intramolecular imine formation (Equation 145) to give a substructure of the polypeptide laminin <2002JOC6097, 2003USP0199531>. An alternative approach involved intramolecular reaction of an amine as above with the mesylate, formed after reduction of the ketone. However, in this case cyclization failed under a variety of conditions. Intramolecular attack by azide as a nucleophile in a Schmidt-type process has also been reported (Equation 146) <1996IJB595>.



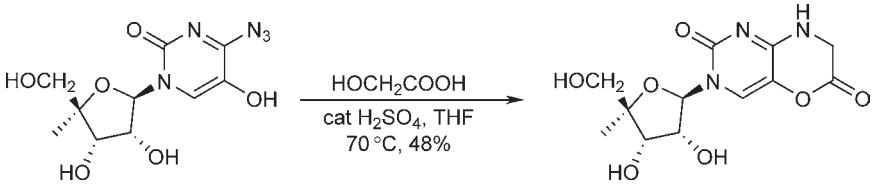
(143)



(144)

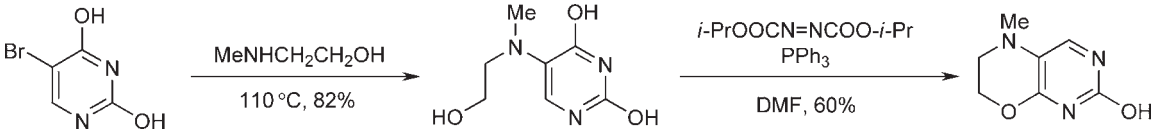


(145)

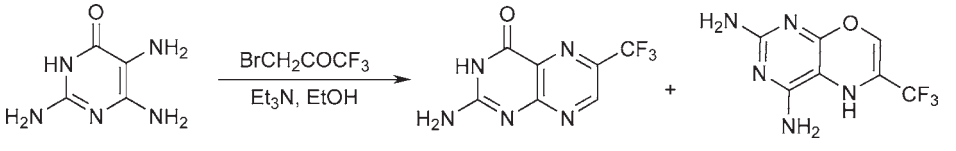


(146)

Other approaches to pyrimido[4,5-*b*][1,4]oxazines include the reaction of an ethanolamine derivative with a halopyrimidin-4-ol (**Scheme 83**), followed by ring closure <2006TL4437>. Formation of a pyrimido[4,5-*b*][1,4]-oxazine is also a competing reaction in a reported approach to pteridines (Equation 147) <1996T13017>.



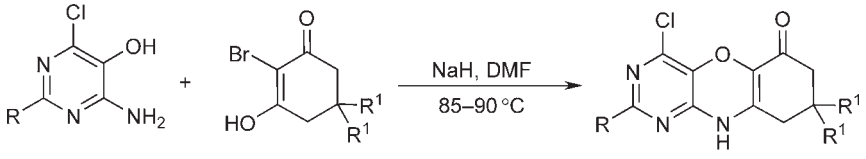
Scheme 83



(147)

10.19.3.2.2(vii) Pyrimido[5,4-*b*][1,4]oxazines

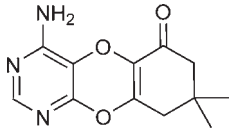
In CHEC-II(1996), the preparation of pyrimido[5,4-*b*][1,4]oxazines by reaction of a 4-amino-5-hydroxypyrimidine with ethyl chloroacetoacetate was described <1996CHEC-II(7)737>. A similar method has since been used to prepare benzannulated derivatives of this system (Equation 148); where R and R^1 are both hydrogen, the product is accompanied by the pyrimidodioxin **134** <1998CHE1201>. A further variant involving nucleophilic displacement of fluoride from perfluorobenzene provides a tetrafluorinated analogue (Equation 149) <1998TL8385>. The formation of a partially reduced pyrimido[5,4-*b*][1,4]oxazine by condensation of a 4-azido-5-hydroxypyrimidin-2-one with glycine has also been reported (Equation 150) <1996IJB595>.



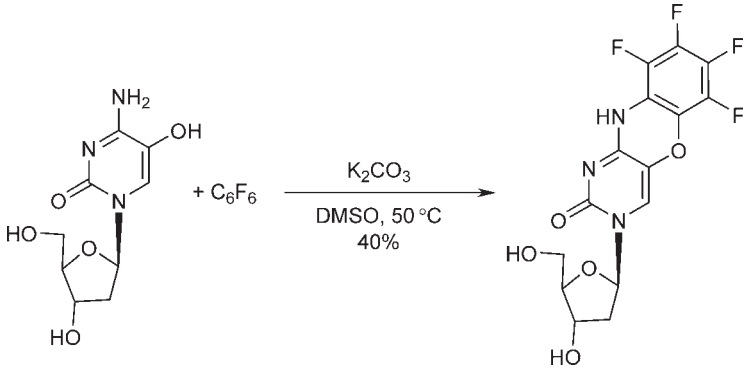
R	R^1	*Yield* (%)
H	H	59
H	Me	39

R	R^1	*Yield* (%)
Me	H	67
Me	Me	59

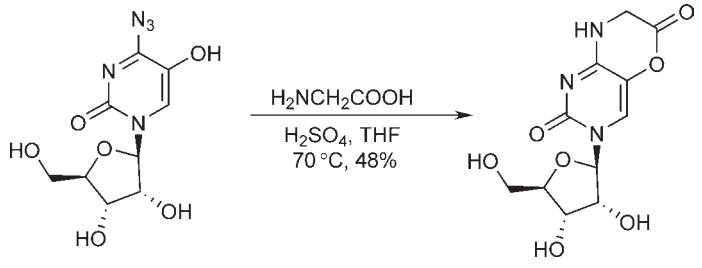
(148)



134

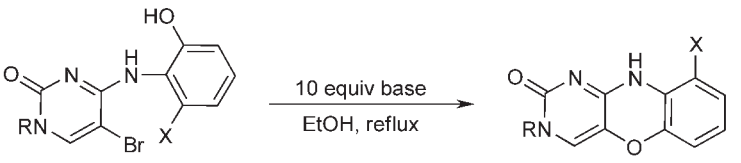


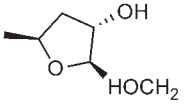
(149)



(150)

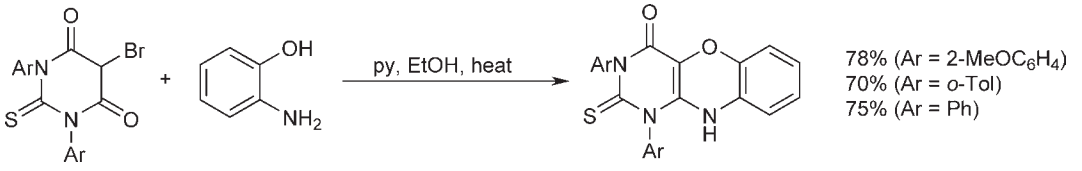
Several reports have appeared of the formation of benzo-fused systems by cyclization of a 5-bromo-4-(2-hydroxyphenylamino)pyrimidine (Equation 151). It is worth noting that, although cyclization of the bromo precursor is commonly successful, the iodinated analogue simply undergoes dehalogenation under the same conditions <1995JA3873>. Further approaches involve the reaction of a pyrimidine bis-electrophile with 2-aminophenol <2000IJB65> (Equation 152) and the cyclization of a 4-chloropyrimidin-5-yloxyacetaldehyde with a substituted benzylamine (Equation 153) <2005BML1829>.



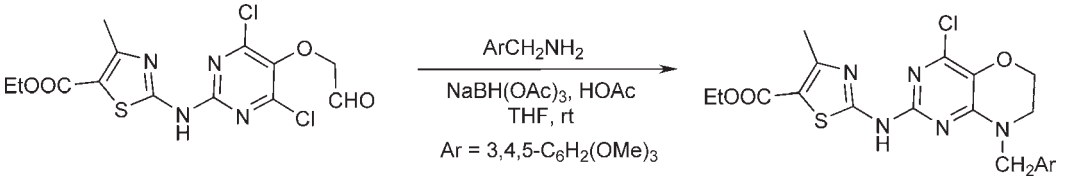
R	*X*	*Base*	*Yield (%)*	*Reference*
CH_2COOEt	H	CsF, Cs_2CO_3	n.s.	2002OL4395
CH_2COOEt	OCH_2CH_2NHCbz	CsF, Cs_2CO_3	83	2002OL4395
CH_2COOEt	$O(CH_2)_3NHCbz$	CsF, Cs_2CO_3	83	2002OL4395
CH_2COO-t-Bu	OH	KF	73	2002OL4073
	H	KF	50[a]	1995JA3873

[a] After subsequent protection.

(151)

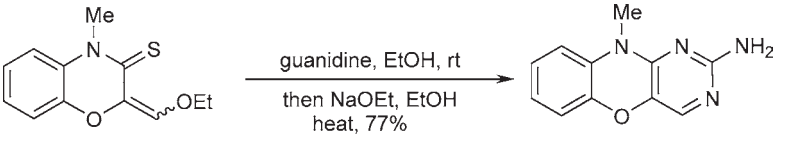


(152)



(153)

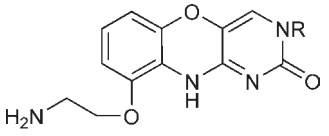
A number of methods have been published for the annulation of a pyrimidine ring onto an existing 1,4-oxazine. All involve the reaction of guanidine with an oxazine-based three-carbon system, as in Equation (154) <2001PS(175)129>. In more elaborate examples, the guanidine derivative is a heterocyclic amine <2004HCO163, 2004ZNB424>.



(154)

10.19.3.2.3 Important compounds and applications

'G-clamp' nucleoside analogues **135** are of interest for the generation of artificial nucleotide sequences, as a result of their ability to bind tightly to guanine. Incorporation of these into antisense nucleotides is reported to confer enhanced potency <1999PNA3513>.

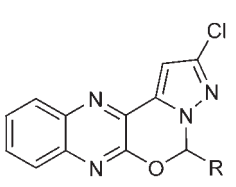


135

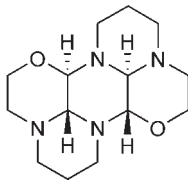
10.19.3.3 Pyrazinooxazines

10.19.3.3.1 Structural methods

Crystallographic studies show that pyrazole-fused derivative **136** forms staircase-like π-stacked rods <2003TL9161>. AM1 calculations have been reported for the pentacyclic system **137** <1996H(43)1991>.



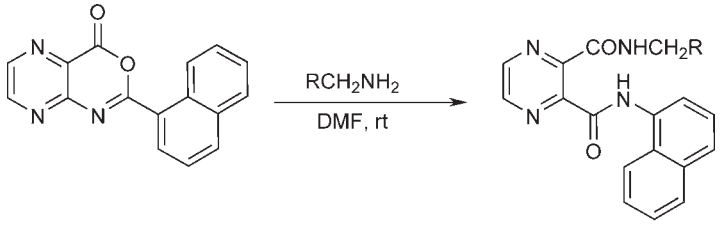
136



137

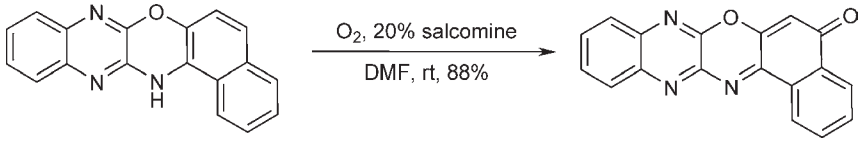
10.19.3.3.2 Reactivity

Little information on the reactivity of pyrazinooxazines was available for inclusion in CHEC-II(1996) <1996CHEC-II(7)737> and little has been published since. Ring opening of pyrazino[2,3-*d*][1,3]oxazines by amines to form amides (Equation 155) has been reported, but is rather inefficient <2005WO2005/115986>. As shown in Equation (156), oxidation of a benzannulated pyrazino[2,3-*b*][1,4]oxazine, catalyzed by *N*,*N*′-bis(salicyliden)ethylenediiminecobalt(II) (salcomine), gives a quinonoid product, of interest for its antineoplastic activity <2001H(54)619>.



(155)

R	*Yield* (%)	*R*	*Yield* (%)
Cyclobutyl	7	4-Tetrahydropyranyl	10
1-Cyclopentenyl	8	Cyclohexylmethyl	31
Cycohexyl	5		

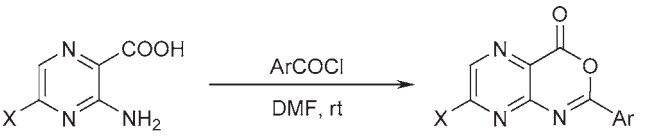


(156)

10.19.3.3.3 Ring synthesis

10.19.3.3.3(i) Pyrazino[2,3-*d*][1,3]oxazines

The principal method for preparation of pyrazino[2,3-*d*][1,3]oxazines, as reported in CHEC-II(1996) <1996CHEC-II(7)737> involves cyclization of a 2-aminopyrazine-3-carboxylic acid ester with an aromatic acid chloride. Further applications of this three-step approach have been reported <1994S405, 2000BMC2803>, but a one-pot approach has also been developed (Equation 157). This cyclization has also been carried out using acetic anhydride in place of an acid chloride <2005JMT(741)67>.



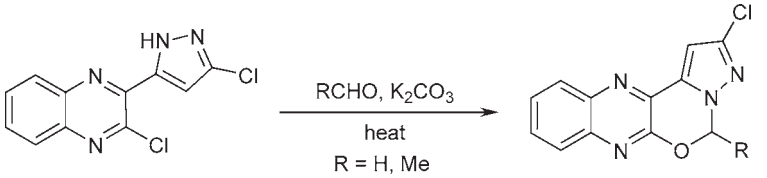
X	Ar	Base	Yield (%)	Reference
H	Ph	Et_3N	30	2005JMT(741)67
H	2-FC_6H_4	Et_3N	21	2000WO00/30646
H	2,6-$F_2C_6H_4$	Et_3N	21	2000WO00/30646
H	1-naphthyl	i-Pr_2NEt, HATU	a	2005WO2005/115986
SEt	2-FC_6H_4	Et_3N	53	2000WO00/30646
SEt	2-ClC_6H_4	Et_3N	42	2000WO00/30646
SEt	2-$O_2NC_6H_4$	Et_3N	60	2000WO00/30646
SEt	*o*-Tol	Et_3N	33	2000WO00/30646

[a]Yield not given.

(157)

10.19.3.3.3(ii) Pyrazino[2,3-*e*][1,3]oxazines

One example of the preparation of this system has been reported <2003TL9161>, wherein a 2-(5-pyrazolyl)quinoxaline reacts with formaldehyde or acetaldehyde (Equation 158) to give fused derivative **138**.

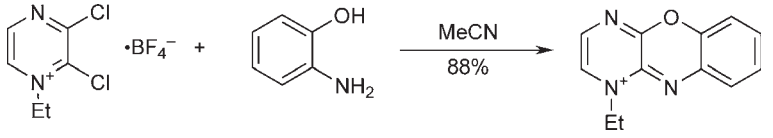


138

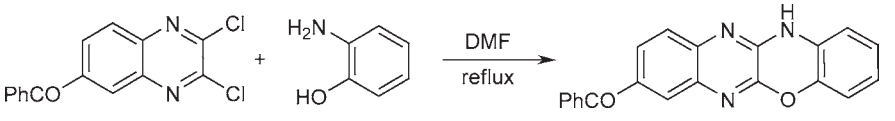
(158)

10.19.3.3.3(iii) Pyrazino[2,3-*b*][1,4]oxazines

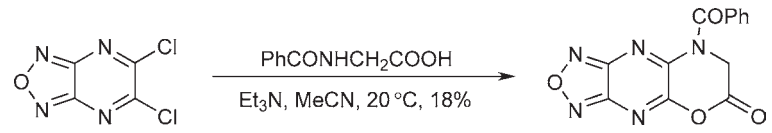
The preparation of reduced pyrazino[2,3-*b*][1,4]oxazines by reaction of a 2,3-dichloropyrazine with ethanolamine was described in CHEC-II(1996) <1996CHEC-II(7)737>. The related reaction with 2-aminophenols has since been used for the preparation of benzo-fused systems <1994CHE340, 1997CHE1352, 2001H(54)619>. The regioselectivity of cyclization is governed by electronic effects where one nitrogen center of the pyrazine is quaternized (Equation 159) <2001MC78> or where the electrophilic component is 6-benzoyl-2,3-dichloroquinoxaline (Equation 160) <2001IJB195>. In a further variation of this process, hippuric acid is used to form the oxazine ring (Equation 161) <1997CHE1352>. The pentacyclic system **139** is formed in a single step by condensation of *N*-(2-hydroxyethyl)-propane-1,3-diamine with glyoxal (Equation 162); the bicyclic intermediate can be elaborated to **139** upon heating with catalytic acetic acid in 36% yield, but the equivalent process using pyruvaldehyde does not proceed beyond the bicyclic stage <1996H(43)1991>.



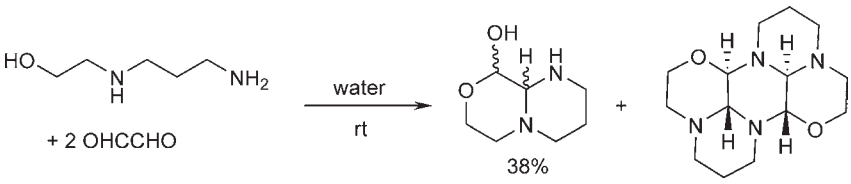
(159)



(160)



(161)



(162)

10.19.4 Diazinothiazines

10.19.4.1 Introduction

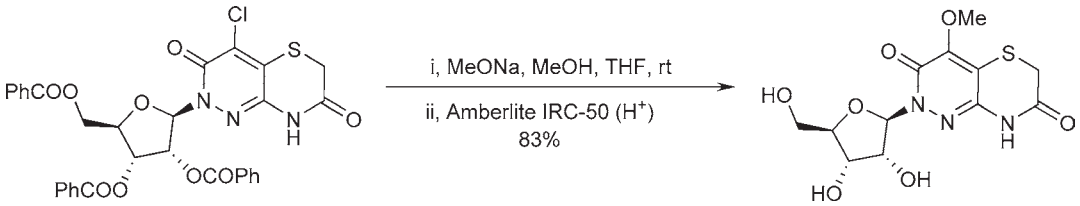
Diazinothiazines were not discussed in CHEC(1984), but the chemistry of five known diazinothiazine systems was reviewed in CHEC-II(1996) <1996CHEC-II(7)737>. Some older syntheses of diazinothiazines are also included in a recent review <B-2004SOS(17)55>. Generally, the only structural data available for diazinothiazines are those acquired in the course of confirming the identity of products, and so structural studies will not be discussed separately.

10.19.4.2 Pyridazinothiazines

10.19.4.2.1 Reactivity

10.19.4.2.1(i) Pyridazino[3,4-*b*][1,4]thiazines

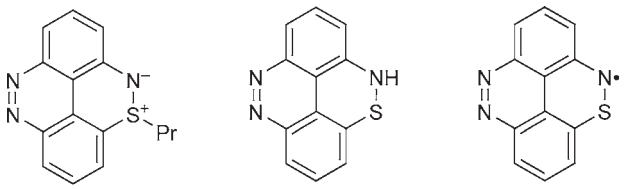
The displacement of chloride from C-8 of this system by methoxide has been reported (Equation 163). It is worth noting that the equivalent reaction is not observed if the sulfur is replaced by nitrogen <1992JHC1409>.



(163)

10.19.4.2.1(ii) Pyridazino[4,5-*d*][1,2]thiazines

The ylide **140** <2000JOC8068> is stable to attempted reduction using sodium borohydride, diisobutylaluminium hydride (DIBAL-H), or lithium aluminium hydride <2000JOC6388>, but eliminates propene on heating to form the annulated parent **141**. Oxidation of the latter with lead(IV) oxide and potassium carbonate forms a radical, **142**, which is stable to chromatography and can be stored in air for several days.

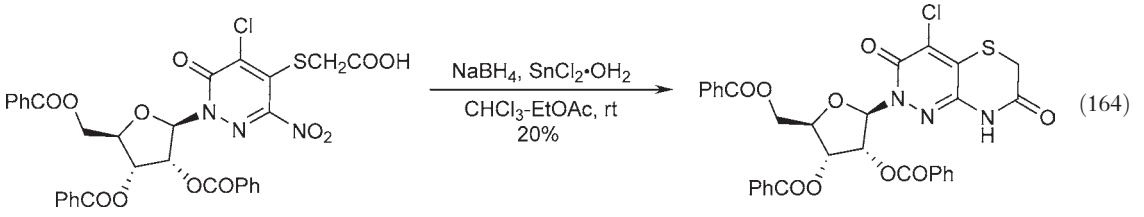


140 **141** **142**

10.19.4.2.2 Ring synthesis

10.19.4.2.2(i) Pyridazino[3,4-*b*][1,4]thiazines

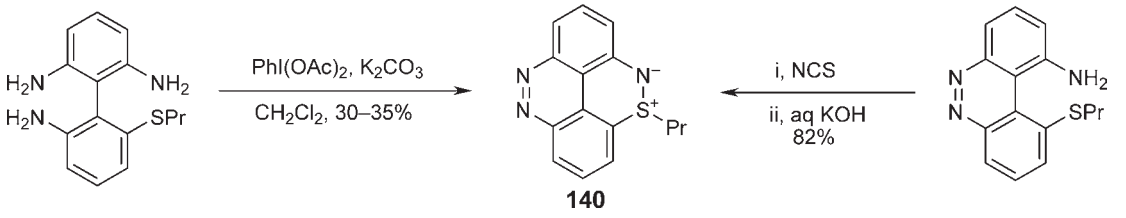
In the only report of the generation of a pyridazino[3,4-*b*][1,4]thiazine <1992JHC1409>, reduction of a 2-(3-nitropyridazin-4-yl)thioacetic acid derivative is accompanied by cyclization (Equation 164).



(164)

10.19.4.2.2(ii) Pyridazino[4,5-*d*][1,2]thiazines

The ylide **140** is formed by two oxidation processes (**Scheme 84**). The most direct route, from 6′-isopropylthiobiphenyl-2,6,2′-triamine gives only traces of **140** in the absence of base <2000JOC6388>.

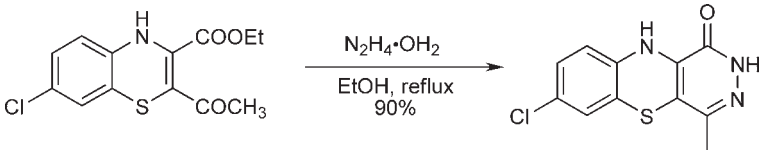


140

Scheme 84

10.19.4.2.2(iii) Pyridazino[4,5-*b*][1,4]thiazines

Methods for the preparation of pyridazino[4,5-*b*][1,4]thiazines were reviewed in CHEC-II(1996) <1996CHEC-II(7)737>. The system has also been prepared by cyclization of a ketoacid with hydrazine (Equation 165) <1988DEP3701737>, but no further chemistry of this system has been reported.

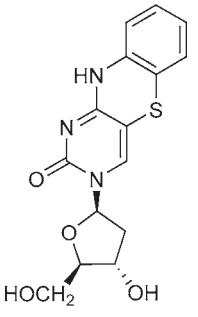


(165)

10.19.4.3 Pyrimidothiazines

10.19.4.3.1 Theoretical and experimental structural methods

MO calculations, CD, absorption, and fluorescence data have been reported for the cytosine analogue **143** <2003PCB9094>.

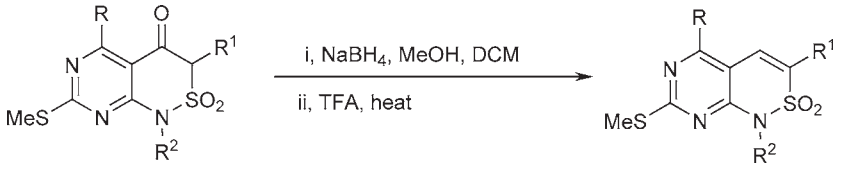


143

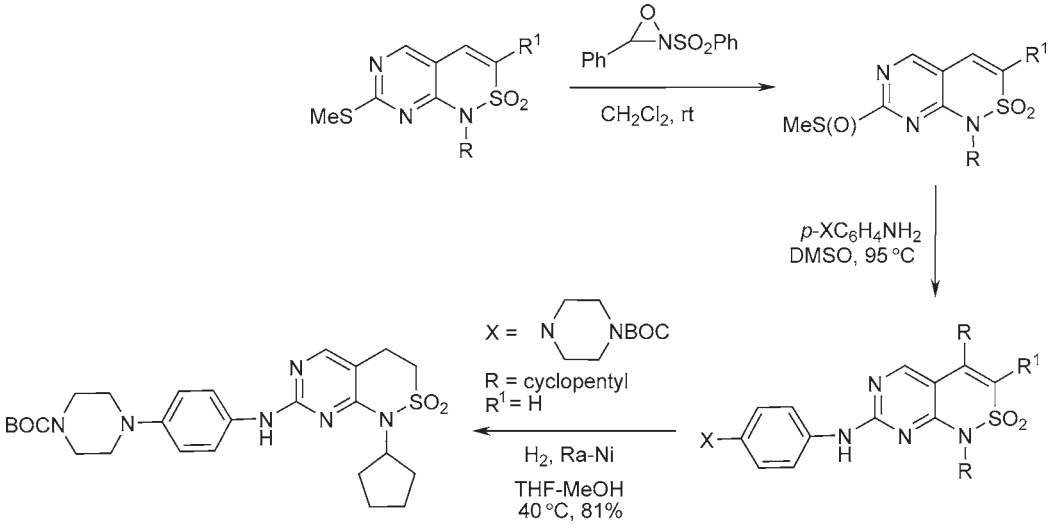
10.19.4.3.2 Reactivity

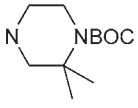
10.19.4.3.2(i) Pyrimido[4,5-*c*][1,2]thiazines

The removal of a ketone at C-4 of a pyrimido[4,5-*c*][1,2]thiazine has been carried out by borohydride reduction followed by acid-catalyzed dehydration (**Scheme 85**) <2002WO076463>. A methylthio group at C-7 of the product is oxidized using oxone <2002WO076463> or, as in **Scheme 86**, by an oxaziridine. The resulting sulfoxide undergoes nucleophilic displacement by an amine <2003WO03/062246>; hydrogenation of the product over Raney nickel results in reduction of the 3,4-double bond.



Scheme 85



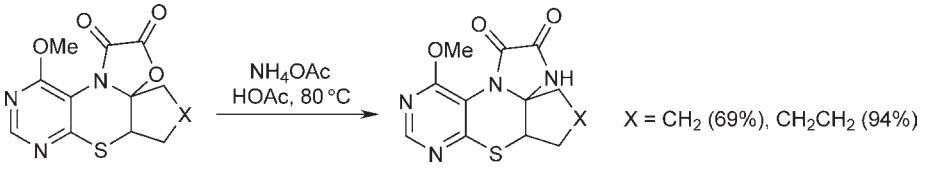
R	R^1	*Yield, step* 1 (%)	*X*	*Yield, step* 2 (%)
Et	Me	57	4-BOC-1-piperazinyl	45
Cp	H	83	4-BOC-1-piperazinyl	52
Cp	H	83		58
Cp	Me	70	4-BOC-1-piperazinyl	62
Cp	Et	74	4-BOC-1-piperazinyl	70

Scheme 86

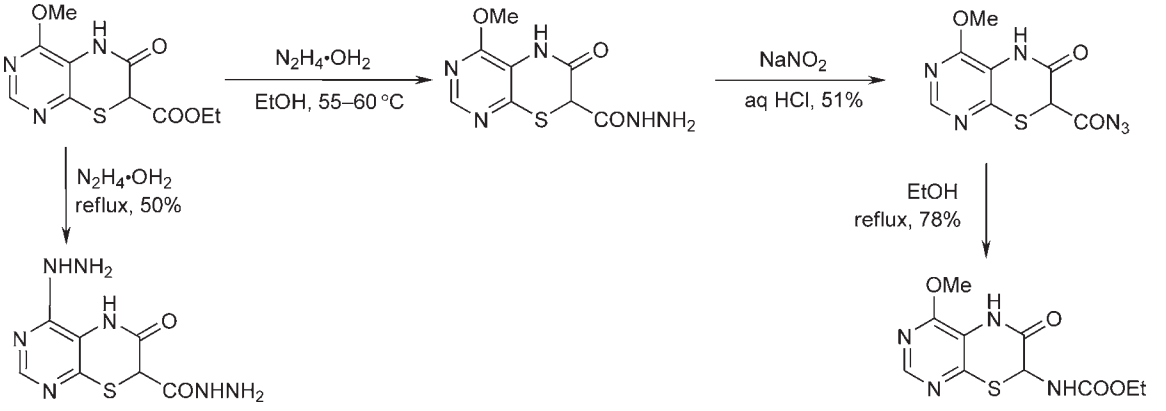
10.19.4.3.2(ii) Pyrimido[4,5-*b*][1,4]thiazines

Reactions of pyrimido[4,5-*b*][1,4]thiazines were discussed in CHEC-II(1996) <1996CHEC-II(7)737>; more recently, reported reactions of this system involve nucleophilic substitution in a number of guises. Hemiaminals at C-3 react with ammonium acetate to form aminals (Equation 166) <1999CHE97>. The formation of acyl hydrazides from pyrimido[4,5-*b*][1,4]thiazine-2-carboxylic acids, along with their subsequent conversion to acyl azides and Curtius

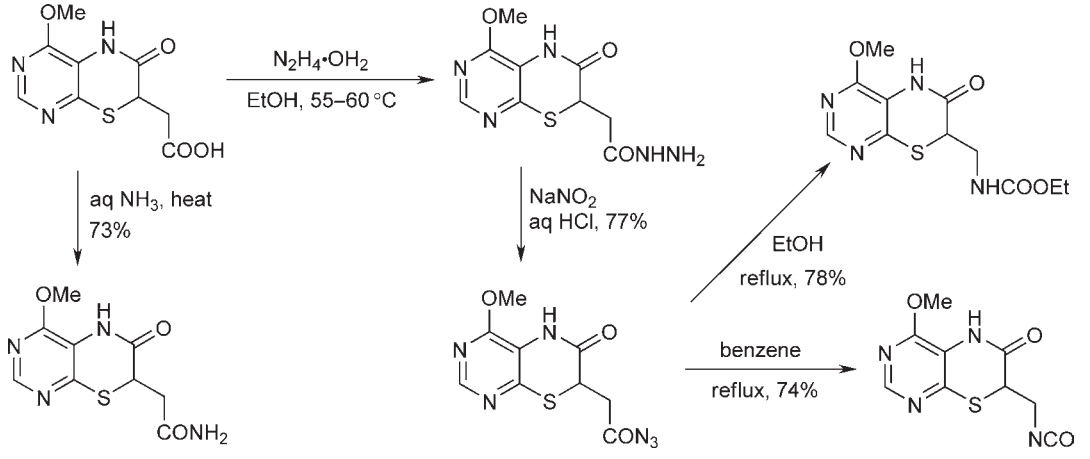
rearrangement to give the corresponding amines, has been reported (**Scheme 87**) <1999CHE733>. Under more forcing conditions, however, the reaction with hydrazine can also result in displacement of a methoxy group at C-5 (**Scheme 87**). The formation of amides and hydrazides from pyrimido[4,5-*b*][1,4]thiazine-2-acetic acids has also been reported (**Scheme 88**) <1999PCJ4>, along with the replacement of a 3-oxo substituent by sulfur using diphosphorus pentasulfide (Equation 167) <1999CHE733>.



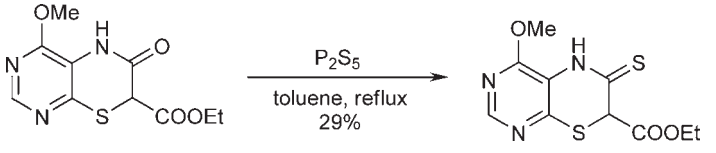
(166)



Scheme 87



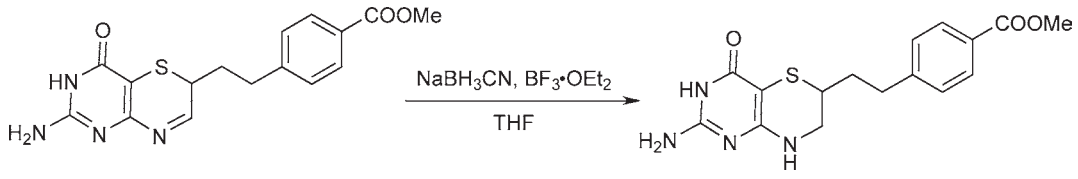
Scheme 88



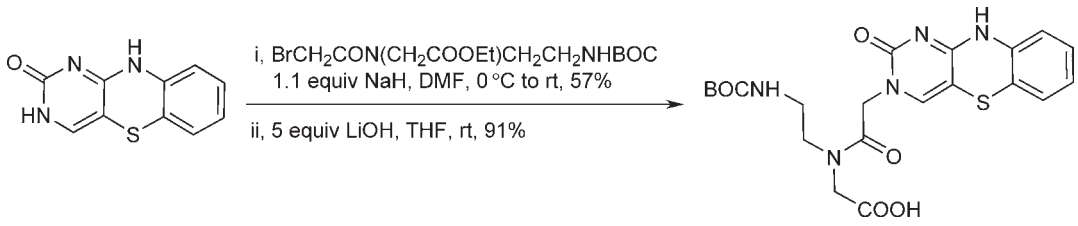
(167)

10.19.4.3.2(iii) Pyrimido[5,4-*b*][1,4]thiazines

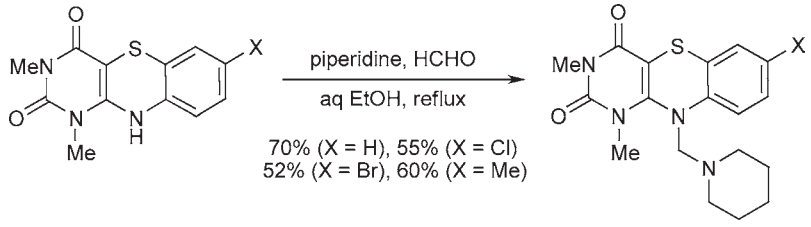
Reports have now appeared of the reactivity of benzo derivatives of this system. Reduction of a C═N double bond in the thiazine ring is reported as difficult <1997JME2502>, but can be carried out using sodium cyanoborohydride in the presence of boron trifluoride etherate (Equation 168). Some reactions of ring nitrogen atoms have also been reported, including direct alkylation (Equation 169) <2001EJO1781> and a Mannich reaction to form 5-(aminomethyl) derivatives (Equation 170) <1994IJB65>.



(168)



(169)

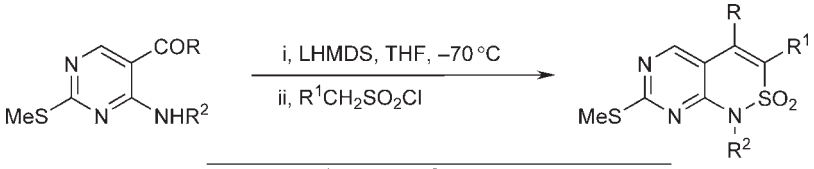


(170)

10.19.4.3.3 Ring synthesis

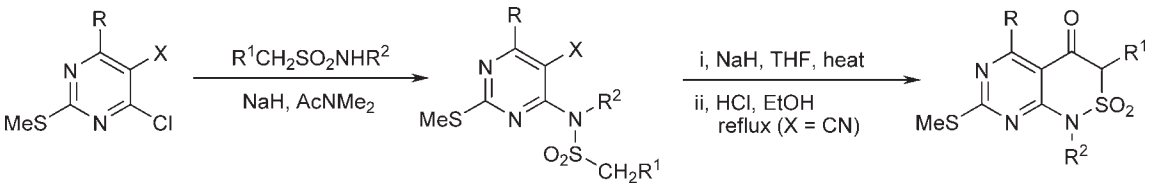
10.19.4.3.3(i) Pyrimido[4,5-*c*][1,2]thiazines

Pyrimido[4,5-*c*][1,2]thiazines have been synthesized by formation of 4-(alkanesulfonamido)pyrimidine bearing an electrophilic substitutent at C-5, and cyclization of an anion generated adjacent to the sulfonamide. The 5-substituent can be a ketone (Equation 171) <2003WO03/062246>, or a carboxylate or nitrile, in which case the product contains a carbonyl group at C-4 (**Scheme 89**) <2002WO02/076463>.



R	R^1	R^2	*Yield* (%)
H	Me	Et	5
H	Me	Cyclopentyl	19
H	Et	Cyclopentyl	9
H	Pr	Cyclopentyl	8

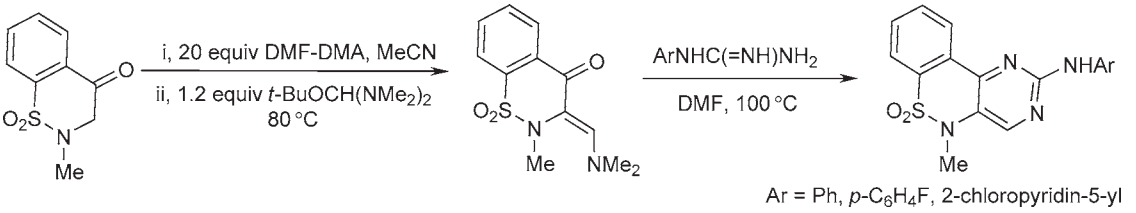
(171)



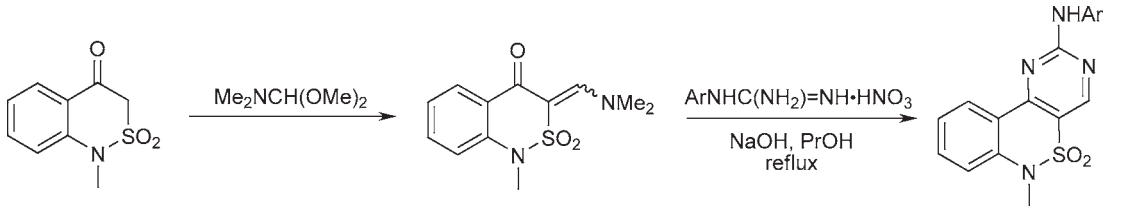
Scheme 89

10.19.4.3.3(ii) Pyrimido[5,4-*c*][1,2]thiazines and Pyrimido[4,5-*e*][1,2]thiazines

The formation of a pyrimido[5,4-*c*][1,2]thiazine by annulation of a pyrimidine ring onto a benzo[*e*][1,2]thiazin-4-one has been reported, involving condensation with dimethylformamide dimethyl acetal followed by Bredereck's reagent (**Scheme 90**), and reaction of the resultant vinylogous amide with guanidine <2005WO2005/037843>. Essentially, the same approach has been used to prepare annulated forms of the isomeric pyrimido[4,5-*e*][1,2]thiazines, as outlined in **Scheme 91** <1998WO98/28281>.



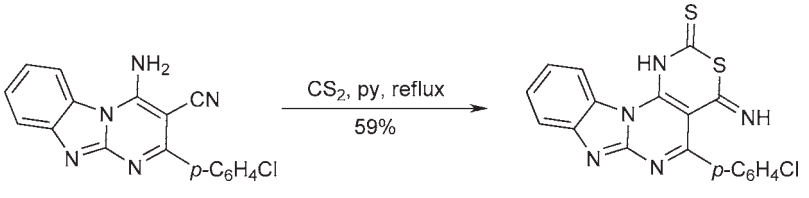
Scheme 90



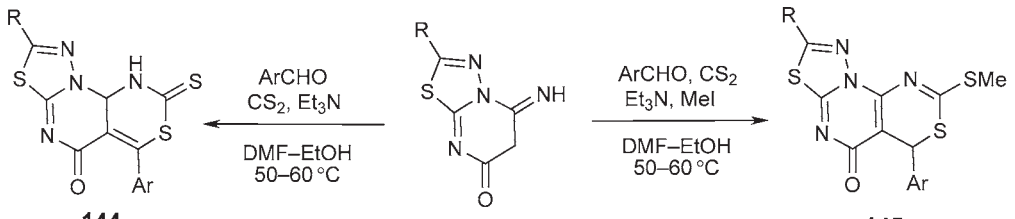
Scheme 91

10.19.4.3.3(iii) Pyrimido[4,5-*d*][1,3]thiazines

Two distinct approaches to the pyrimido[4,5-*d*][1,3]thiazine system have been reported. In one, a 5-cyanopyrimidin-4-amine is condensed with carbon disulfide to give an iminodiazinothiazine product (Equation 172) <2002EJC995>. In a variation of this approach, a 4-iminopyrimidine-6-thione is coupled with an aromatic aldehyde (**Scheme 92**), and the intermediate undergoes an analogous cyclization with carbon disulfide to give either the 2-thione **144** or 2-methylthio substituted product **145** <1999RCB364>. The second reported approach involves the cyclization of an allantoin-derived enone with thiourea (Equation 173) <2003SC3747>; the analogous reaction using thiosemicarbazide has also been described <2001H(55)2413>.



(172)



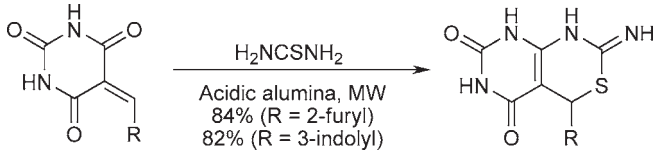
144

R	Ar	Yield (%) 144	145
H	Ph	63	66
Me	Ph	72	70
H	2-furyl	63	

145

R	Ar	Yield (%) 144	145
H	*p*-C_6H_4F	60	93
Me	*p*-C_6H_4F	71	85
Me	2-furyl		87

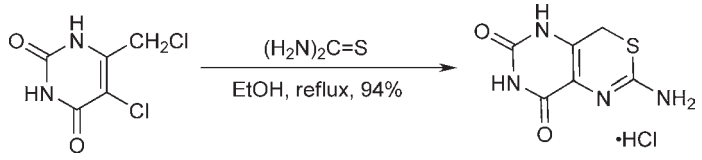
Scheme 92



(173)

10.19.4.3.3(iv) Pyrimido[5,4-*d*][1,3]thiazines

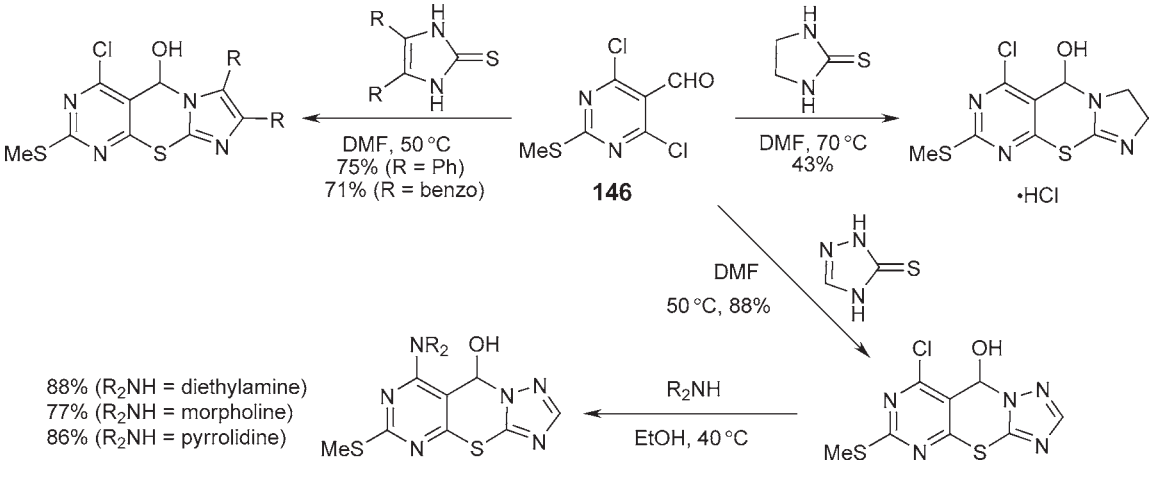
A representative of this series has been prepared as shown in Equation (174), by condensation of thiourea with a 5-halo-4-(halomethyl)uracil <2004FA987>.



(174)

10.19.4.3.3(v) Pyrimido[5,4-*e*][1,3]thiazines

The preparation of pyrido[5,4-*e*][1,3]thiazines by coupling of 4-halopyrimidine-5-pyrimidinecarboxylates with N-substituted thioureas was recorded in CHEC-II(1996) <1996CHEC-II(7)780>. A related approach has since been used to prepare a series of heteroannulated derivatives from the aldehyde **146**, as summarized in **Scheme 93** <2000CHE751>.

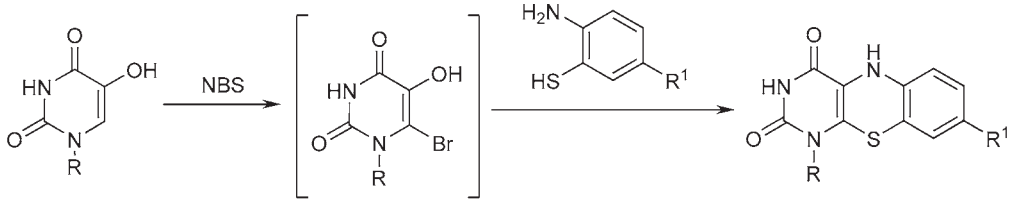


146

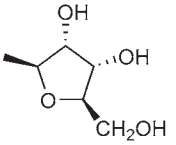
Scheme 93

10.19.4.3.3(vi) Pyrimido[4,5-*b*][1,4]thiazines

The preparation of pyrimido[4,5-*b*][1,4]thiazines by two different approaches was described in CHEC-II(1996) <1996CHEC-II(7)737>. The reaction of a 1,2-biselectrophile with a 3-mercaptopyrimidin-5-amine has since been used to prepare a variety of fused systems <1999CHE97, 2002MC120, 2004RJO1067>. The inverse process, wherein a 4-bromo-5-hydroxyuracil or similar species is coupled with a 2-aminothiol, has been used to prepare benzannulated species (**Scheme 94**) <2003CPB630>. Fused derivatives of this system have also been prepared by coupling of a 2-(dimethylaminomethylene)-3-chlorothiazine with a 3-aminopyrazole (Equation 175) <2005HCO317>.

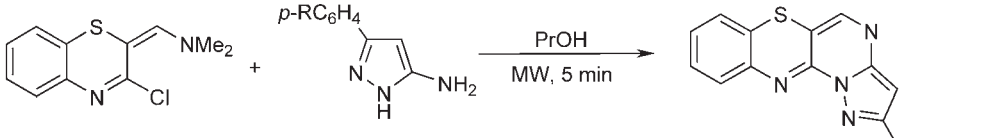


R	R^1	*Conditions*	*Yield* (%)
H	H	EtOH, reflux	75
CH_2OEt	H	EtOH, reflux	62
CH_2OEt	H	THF, rt	79
CH_2OEt	Me	THF, rt	64
CH_2OEt	Cl	THF, rt	70

R	R^1	*Conditions*	*Yield* (%)
CH_2OCH_2OAc	H	EtOH, reflux	69
CH_2OCH_2Ph	H	THF, rt	70[a]
CH_2OCH_2Ph	Me	THF, rt	63[a]
CH_2OCH_2Ph	Me	THF, rt	65[a]
	H	EtOH, reflux	59

[a]Use of ethanol results in replacement of OBn by OEt.

Scheme 94

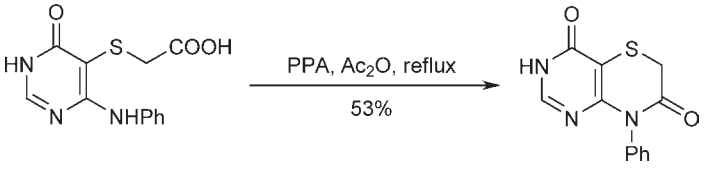


76% (R = H), 82% (R = F), 81% (R = Cl)
79% (R = Br), 80% (R = OMe), 76% (R = Me)

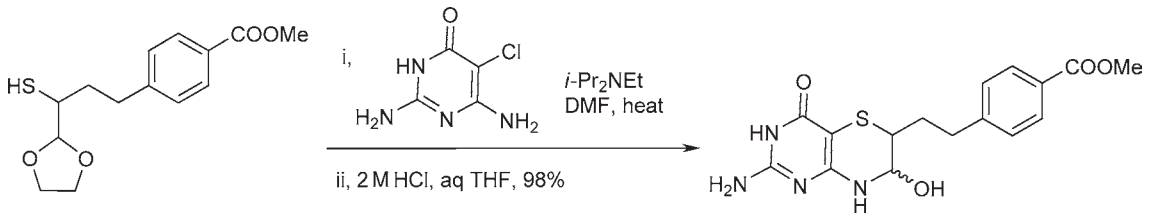
(175)

10.19.4.3.3(vii) Pyrimido[5,4-*b*][1,4]thiazines

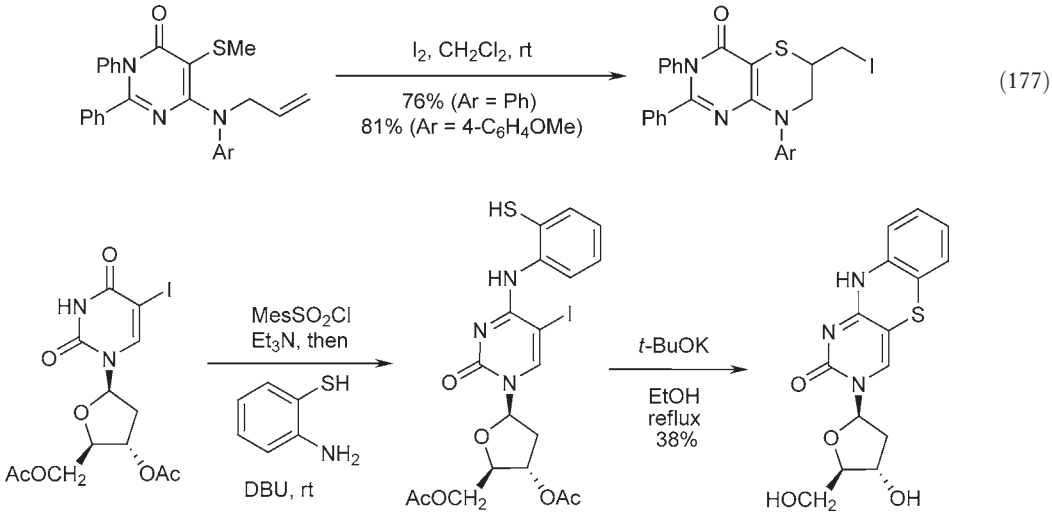
Methods for the formation of pyrimido[5,4-*b*][1,4]thiazines were reviewed in CHEC-II(1996) <1996CHEC-II(7)776>, and a number of additional methods have been reported since. Methods for annulation of a thiazine onto an existing pyrimidine include the dehydrative cyclization shown in Equation (176) <1994M1129> and the coupling of an aminopyrimidine with a 2-mercaptoaldehyde (**Scheme 95**) <1997JME2502>. The second heterocyclic ring can also be constructed by iodocyclization of an allylamine precursor (Equation 177); the *S*-methyl group is presumably lost as methyl iodide <1997T13841>. Benzannulated products have been prepared by condensation of 2-aminothiophenols with 5-halopyrimidin-4-yl mesitylenesulfonates (**Scheme 96**; Mes = mesityl), via biarylamine intermediates <1995JA3873>. The same regiochemistry is obtained from symmetrical 4-bromoallantoin derivatives (Equation 178) <2000IJB65>.



(176)

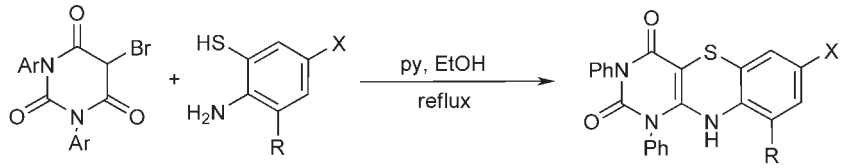


Scheme 95



(177)

Scheme 96

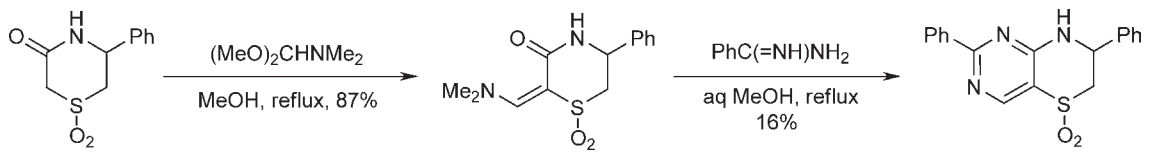


Ar	*R*	*X*	*Yield* (%)
Ph	H	H	78
Ph	H	Cl	72
Ph	H	OMe	68
Ph	H	Me	70
2-MeOC$_6$H$_4$	H	H	72

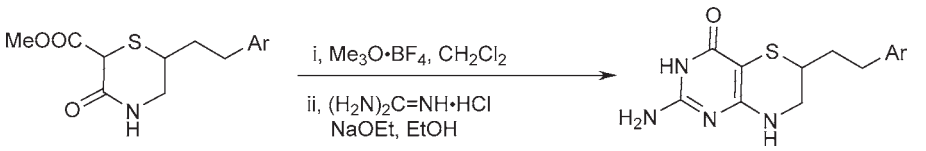
Ar	*R*	*X*	*Yield* (%)
2-MeOC$_6$H$_4$	Cl	H	72
o-Tol	H	H	65
o-Tol	Cl	H	65
o-Tol	OMe	H	73
o-Tol	Me	H	78

(178)

The bicyclic system has also been prepared by annulation of a pyrimidine ring onto an existing thiazine (**Scheme 97**); the cyclization fails with acetamidine or *S*-methylthiourea <1996JHC235>. Alternatively, a pyrimidine ring is formed by reaction of guanidine with the lactim ether formed by *O*-methylation of a 2-methoxycarbonyl-1,4-thiazin-2-one (**Scheme 98**)<1997JME2502>.



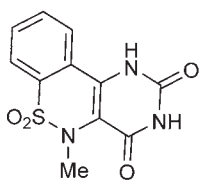
Scheme 97



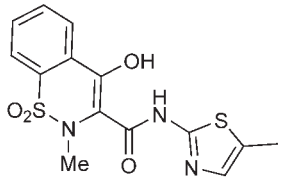
Scheme 98

10.19.4.3.4 Important compounds and applications

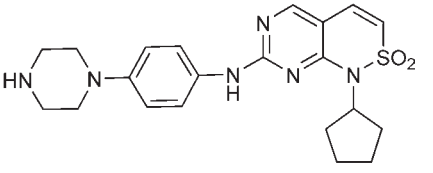
No pyrimidothiazines have been marketed in their own right. However, the pyrimido[5,4-*c*][1,2]thiazine **147** is reported as a metabolite of meloxicam **148** <1995MI1219>. Pyrimido[4,5-*c*][1,2]thiazine **149** and related compounds are claimed as inhibitors of cyclin-dependent kinases <2003WO03/062246>, while **150** is reported to be in clinical evaluation as an antineoplastic agent <1997JME2502>.



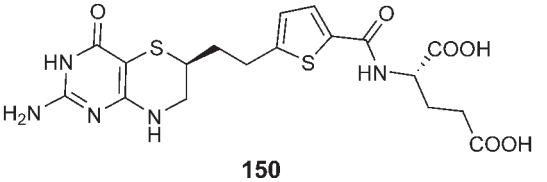
147



148



149



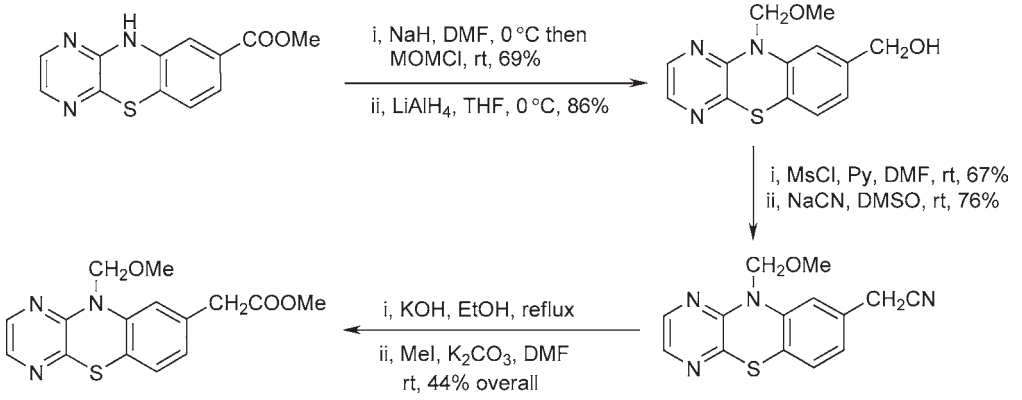
150

10.19.4.4 Pyrazinothiazines

10.19.4.4.1 Reactivity

10.19.4.4.1(i) Pyrazino[2,3-*b*][1,4]thiazines

Reactivity of pyrazino[2,3-*b*][1,3]thiazines was described in CHEC-II(1996) <1996CHEC-II(7)737>. The only recent report of reactions of this system, as summarized in **Scheme 99** <2004CPB675>, describes N-protection followed by an ester reduction/homologation sequence. After further elaboration of the side chain, the ring nitrogen is deprotected by treatment with hydrochloric acid.

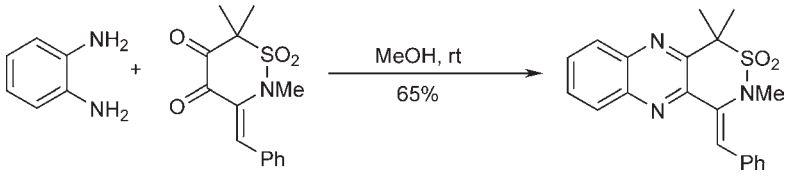


Scheme 99

10.19.4.4.2 Ring synthesis

10.19.4.4.2(i) Pyrazino[2,3-*d*][1,2]thiazines

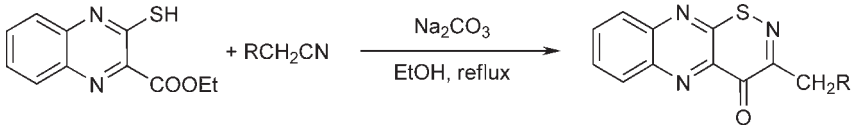
A benzannulated pyrazino[2,3-*d*][1,2]thiazine has been prepared by coupling of *o*-phenylenediamine with a thiazine-4,5-dione (Equation 179) <1992AP461>.



(179)

10.19.4.4.2(ii) Pyrazino[2,3-*e*][1,2]thiazines

Benzannulated pyrazino[2,3-*e*][1,2]thiazines have been prepared by the reaction of 3-ethoxycarbonyl-2-mercaptoquinoxaline with active nitriles (Equation 180) <2001AFF335>.

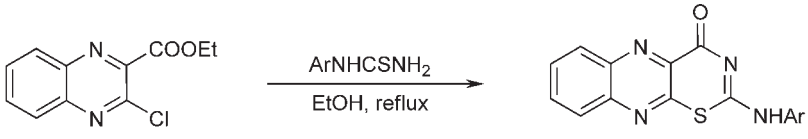


74% (R = CN)
77% (R = $CONH_2$)
73% (R = COOEt)

(180)

10.19.4.4.2(iii) Pyrazino[2,3-*e*][1,3]thiazines

1,3-Thiazino[5,6-b]quinoxalines have been prepared, as shown in Equation (181), by condensation of ethyl 2-chloroquinoxaline-3-carboxylate with thiourea <1993IJB901>.

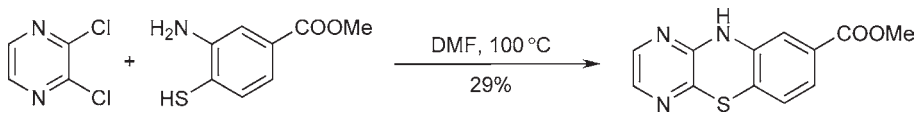


Ar	*Yield* (%)	*Ar*	*Yield* (%)	*Ar*	*Yield* (%)
Ph	85	3-ClC_6H_4	76	4-EtC_6H_4	66
2-$MeOC_6H_4$	53	4-ClC_6H_4	64	2,4-$Me_2C_6H_3$	54
4-$MeOC_6H_4$	65	4-BrC_6H_4	62	4-*i*-PrC_6H_4	46
2-FC_6H_4	67	3-Cl-4-FC_6H_4	67	2,4,6-$Me_3C_6H_2$	51
4-FC_6H_4	77	*p*-Tol	81		

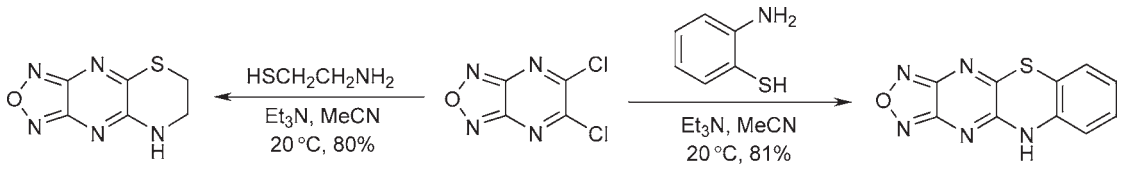
(181)

10.19.4.4.2(iv) Pyrazino[2,3-*b*][1,4]thiazines

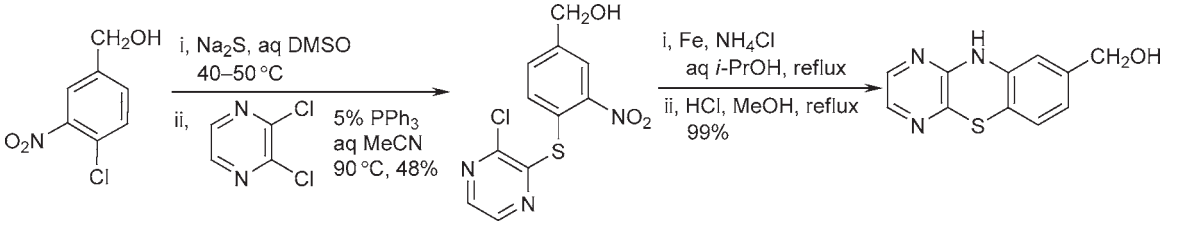
Published routes to pyrazino[2,3-*b*][1,4]thiazines, as reviewed in CHEC-II(1996) <1996CHEC-II(7)737>, involved the reaction of a 3-aminopyrazine-2-thiol with a biselectrophile and of a 3-chloropyrazin-2-amine with thioglycolate. In more recent work, the system is formed by condensation of a dichloropyrazine with a 2-aminothiophenol (Equation 182) <2002CPB922>. The same approach, using either 2-aminothiophenol or 2-aminoethanethiol, has been used to form oxadiazole-fused systems (**Scheme 100**) <1997CHE1352>. In studies toward the synthesis of ER-49890 **151**, benzannulated pyrazino[2,3-*b*][1,4]thiazines have also been accessed by an indirect sequence (**Scheme 101**)<2005H(65)403>.



(182)



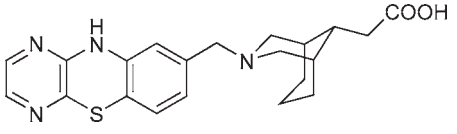
Scheme 100



Scheme 101

10.19.4.4.3 Important compounds and applications

No pyrazinothiazine derivatives have been marketed to date. However, the adhesion molecule inhibitor ER-49890 **151** is of interest for the treatment of autoimmune conditions <2004CPB675>.



151

10.19.5 Oxazinooxazines

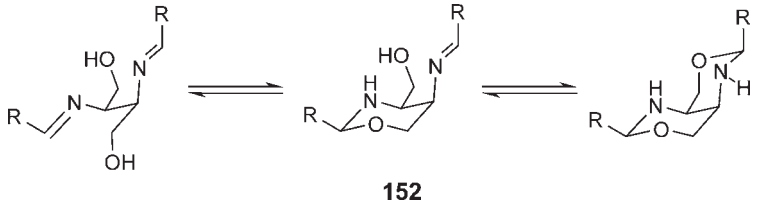
10.19.5.1 Introduction

Relatively, few of the possible oxazinooxazines have been described. Available information on the known oxazinooxazines was reviewed in CHEC-II(1996) <1996CHEC-II(7)737>, and this section merely expands on the earlier review.

10.19.5.2 Theoretical and Experimental Structural Methods

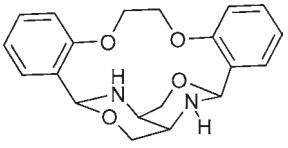
10.19.5.2.1 1,3-Oxazino[5,4-*d*][1,3]oxazines

Detailed crystallographic, NMR spectroscopic, and theoretical studies have been reported on perhydro-1,3-oxazino[5,4-*d*][1,3]oxazines. System **152** can exist in three tautomeric forms whose ratio, where R is an aryl substituent, correlates with the Hammett σ value for R; with electron withdrawing group-substituted aryl substituents, the oxazinooxazine tautomer is observed almost exclusively. The principal tautomer also has the most thermodynamically stable conformation, with the 2- and 6-substituents equatorial, heteroatoms in an '*N*,*O*-inside' arrangement, and the N–H bond axial <1997TL3573>. The last feature is clear from NOE experiments, and is stereoelectronic in origin: the most stable conformers have the nitrogen lone pair *anti*-periplanar to oxygen. MO calculations also indicate an energetic preference for this conformation.



152

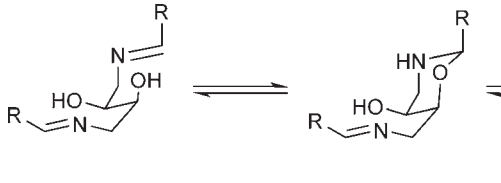
The 2,6-bis(2-hydroxyphenyl) species (**152**, R = 2-HOC_6H_4) exists almost exclusively as acyclic and monocyclic tautomers at room temperature, although the bicyclic species is observed by VT-NMR at −50 °C in $CDCl_3$ <2001JOM(630)67>. In contrast, bridged analogue **153** exists exclusively as the oxazinooxazine form in $CDCl_3$, even on heating; this tautomer is stabilized by strong O···HN hydrogen bonding, which is observable by NMR spectrometry and by X-ray diffraction.



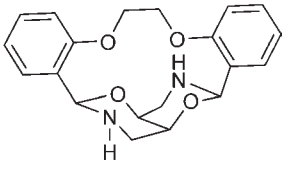
153

10.19.5.2.2 1,3-Oxazino[6,5-*e*][1,3]oxazines

Tautomerism in *cis*-perhydro-1,3-oxazino[6,5-*e*][1,3]oxazines **154** parallels that described for the isomeric system **151** <1999EJO2033, 1999JOC1166, 2001JOM(630)67>, and has been the subject of crystallographic, NMR, and theoretical studies. 2,7-Bis(hydroxyaryl) derivatives exhibit a preference for open chain tautomers but bridging the hydroxy groups, as in **155**, again results in a species that exists in the oxazinoxazine form.



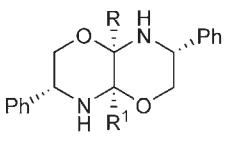
154



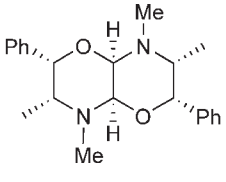
155

10.19.5.2.3 1,4-Oxazino[3,2-*b*][1,4]oxazines

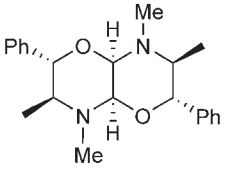
Structural data have been reported for **156** <2000SC2721>; these provide evidence of a stabilizing *exo*-anomeric effect. Nitrogen centers in **156** are *anti*-periplanar and oxygens are gauche due to a preference for the best donor (N) to be *anti*-periplanar to the best acceptor (C–O). Enthalpies of formation have been determined for **157** and **158**, from which is derived a destabilization energy of 12 kJ mol^{-1} for C-3 in relation to C-2, due to the extra steric repulsion of the *cis*-substituents in C-3 <1995MI779>. Thermodynamic data have also been reported for **159** <1997MI565>.



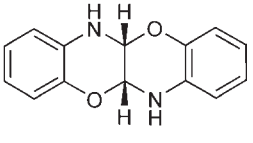
156



157



158

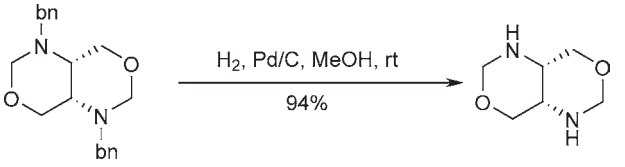


159

10.19.5.3 Reactivity

10.19.5.3.1 1,3-Oxazino[5,4-*d*][1,3]oxazines

Bridged oxazinooxazine **153** forms a complex with Ni(II) <2001JOM(630)67>. Complexes are also observed with Pb(II), wherein the ligand is isomerized to the dihydroxydiimine form, and with Cd(II), in which case a mixture is formed, with the ligand present in all three tautomers. The formation of **152** by catalytic hydrogenolysis of its 1,5-dibenzyl derivative has been reported (Equation 183) <2006S1093>.



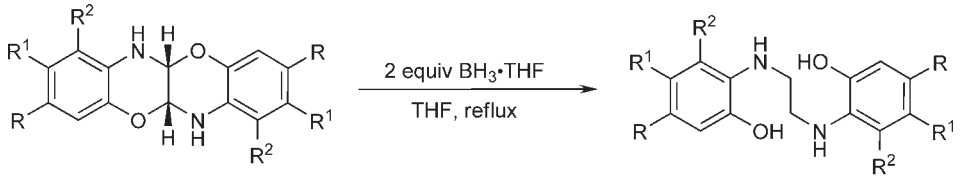
(183)

10.19.5.3.2 1,3-Oxazino[6,5-*e*][1,3]oxazines

Bridged ligand **155** forms complexes with Ni(II), but not with Pb(II), the latter being too large for the available cavity <2001JOM(630)67>. 1,3-Oxazino[6,5-*e*][1,3]oxazines undergo facile hydrolysis in aqueous solution and transacetalization in alcohols <1999EJO2033>. Alkylation of **154** is inefficient, with only the 3,7-dibenzyl derivative being isolated in low yield. However, **154** successfully undergoes acetylation and N-nitrosation <1999EJO2033>.

10.19.5.3.3 1,4-Oxazino[3,2-*b*][1,4]oxazines

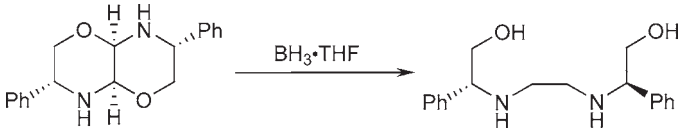
As yet, few reports have appeared on the reactivity of 1,4-oxazino[3,2-*b*][1,4]oxazines other than reductive ring-opening: this reaction has been used for the preparation of *N*,*N*′-diarylethylenediamines (Equation 184) <2001T55> and homochiral diaminodiols (Equation 185) <2001TA247>.



(184)

R	R^1	R^2	*Yield* (%)
H	H	H	94
H	H	Me	52
H	NO_2	H	77
H	Cl	H	99

R	R^1	R^2	*Yield* (%)
H	Me	H	93
H	*t*-Bu	H	68
Me	H	H	79

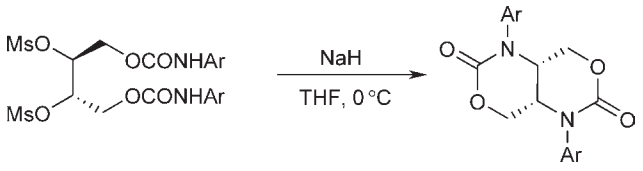


(185)

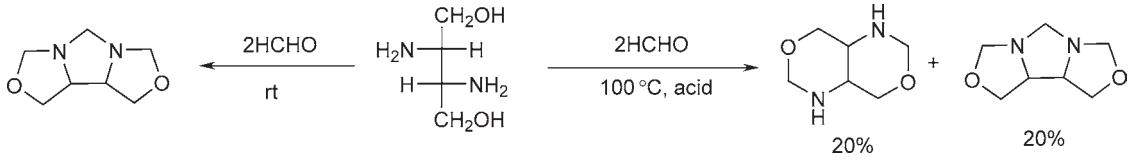
10.19.5.4 Ring Synthesis

10.19.5.4.1 1,3-Oxazino[5,4-*d*][1,3]oxazines

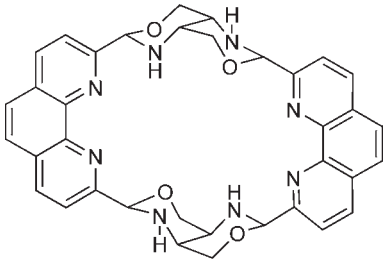
The bicyclization of diethyl 2,3-bis(benzamido)succinate with thionyl chloride was described in CHEC-II(1996) <1996CHEC-II(7)737>. An alternative cyclization approach (Equation 186) involves double intramolecular displacement of mesylate by carbamate anions <2000TA4709>. A number of reports have also appeared wherein systems **152** and their *trans*-fused analogues are formed by reaction of *threo*- or *meso*-2,3-diamino-1,4-butanediol, respectively, with aldehydes <1997TL3573>. In this case, the oxazinooxazine is formed only under conditions of thermodynamic control, along with the tricyclic kinetic product (**Scheme 102**). This approach has been used to prepare a series of compounds **152** with aryl substituents <1999JOC1166, 1999EJO2033>, bridged structures such as **153** and the macrocycle **160** <2000AGE2685>. A more recent report describes formation of *trans*-perhydro-1,3-oxazino[5,4-*d*][1,3]oxazine via an imidazolidine intermediate in two steps (**Scheme 103**) <2006S1093>. However, in this case, yields from this process and using the methodology above were modest, and better results were obtained by condensation of homochiral *N*,*N*′-disubstituted dihydroxybutanediamines with formaldehydes (Equation 187), followed by deprotection as in Section 10.19.5.3.1 <2006S1093>.



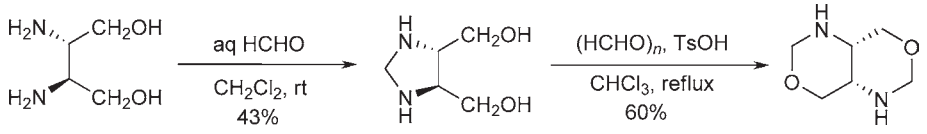
(186)



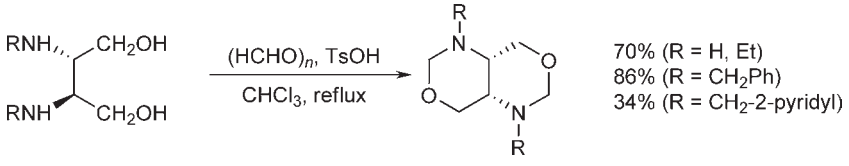
Scheme 102



160



Scheme 103

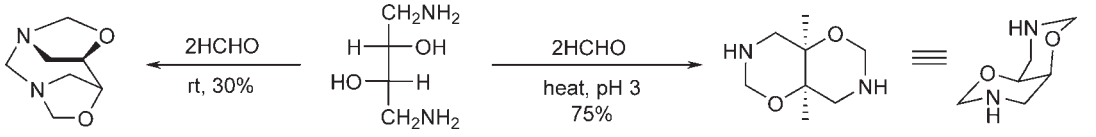


(187)

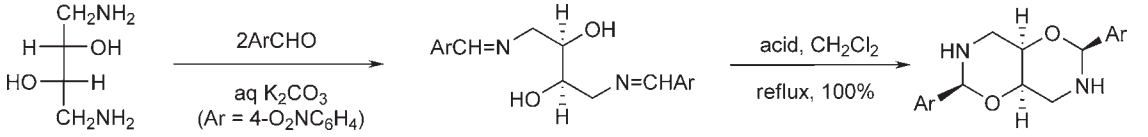
10.19.5.4.2 1,3-Oxazino[6,5-*e*][1,3]oxazines

The synthesis of perhydro-1,3-oxazino[6,5-*e*][1,3]oxazines **154** proceeds in a manner analogous to the preparation of the corresponding 1,3-oxazino[5,4-*d*][1,3]oxazines (Section 10.19.5.4.1). In the condensation of *threo*-2,3-dihydroxy-1,4-butanediamines with formaldehyde, the *cis*-oxazinooxazine is the thermodynamic product, with a bridged bis(oxazolidine) being formed under conditions of kinetic control as exemplified in **Scheme 104** <1997TL3573, 1999EJO2033>. The *trans*-fused systems are obtained from the *meso*-dihydroxydiamines, although in the *trans*-series, the second cyclization is hindered by strain in the transition state. In both cases, condensation with an aldehyde other than formaldehyde gives a 2,6-diequatorially substituted product <1999JOC1166>. The process can also be carried

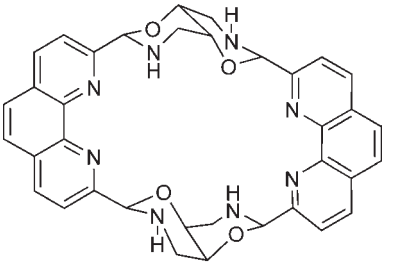
out with isolation of an intermediate Schiff base, which undergoes cyclization on treatment with acid (**Scheme 105**) <1997TL3573> or on extended storage in the solid state <1999JOC1166>. This methodology has been used to prepare bridged derivatives such as **155** <1999EJO2033, 1999JOC1166>, a variety of 4,8-disubstituted species <1999EJO2033, 2001EJO729> and the macrocycle **161** <2000AGE2685>. A further route to perhydro-1,3-oxazino[6,5-*e*][1,3]oxazines has been described, in which the trichloroacetimidate derived from diol **162** cyclizes upon treatment with iodine monochloride (Equation 188) <1996CC355>.



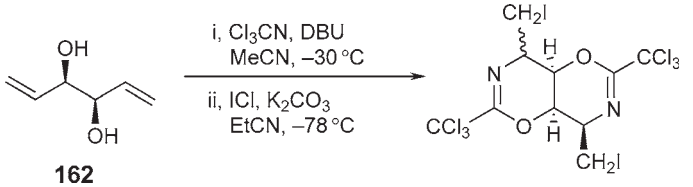
Scheme 104



Scheme 105



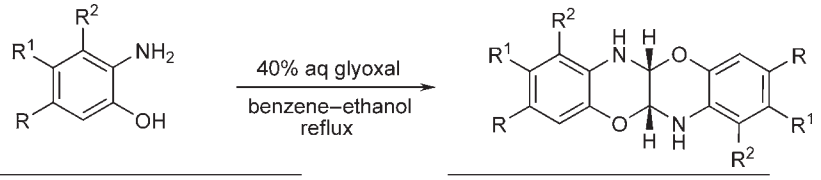
161



162 (188)

10.19.5.4.3 1,4-Oxazino[3,2-*b*][1,4]oxazines

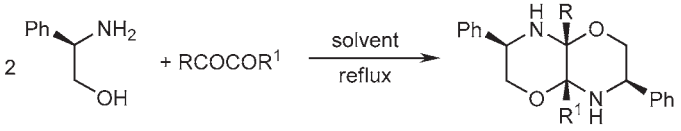
Preparations of perhydro-1,4-oxazino[3,2-*b*][1,4]oxazines by reaction of a substituted ethanolamine with a 1,2-bis-(electrophile) or with a propargylic alcohol were described in CHEC-II(1996) <1996CHEC-II(7)737>. A number of additional examples of the condensation of substituted ethanolamines with 1,2-diketones have appeared since <2001TA247, 2003STC295>, including the preparation of a number of benzannulated (Equation 189) <2001T55> and homochiral products (Equation 190) <2000SC2721>. The latter process is a simplification of a less selective earlier method <1992CJC2764>.



(189)

R	R^1	R^2	*Yield* (%)
H	H	Me	74
H	NO_2	H	86
H	Cl	H	76

R	R^1	R^2	*Yield* (%)
H	Me	H	78
H	*t*-Bu	H	43
Me	H	H	83



(190)

R	R^1	*Solvent*	*Yield* (%)
Me	Me	Benzene	85
Et	Et	Benzene	86
Me	Et	Toluene	62
Me	Pr	Toluene	61

10.19.6 Oxazinothiazines

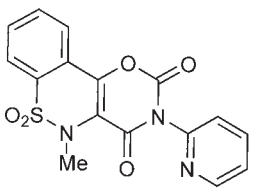
10.19.6.1 Introduction

Only one example of an oxazinothiazine was included in CHEC-II(1996) (*vide infra*), and few have been described since, the most notable example of this system being the anti-inflammatory agent droxicam **162** <1982FRP10409>.

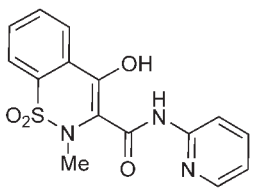
10.19.6.2 Reactivity

10.19.6.2.1 1,3-Oxazino[5,6-*c*][1,2]thiazines

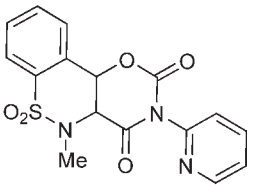
The sole reported reaction of an oxazinothiazine is the pH-dependent polarographic reduction of droxicam (**162**, a prodrug of piroxicam, **163**), which is reported to give the corresponding dihydro derivative **164** <2004JPB157>.



162



163

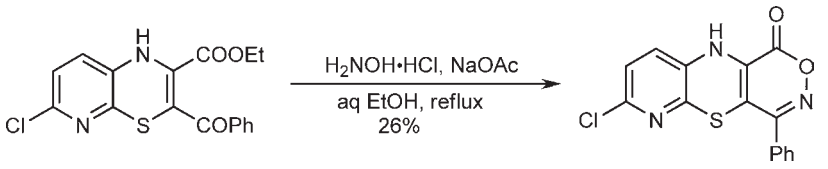


164

10.19.6.3 Ring Synthesis

10.19.6.3.1 1,2-Oxazino[4,5-*b*][1,4]thiazines

Annulated forms of this system have been prepared by ring-closure of an annulated 2-acyl-1,4-thiazine-3-carboxylate with hydroxylamine; one example is shown in Equation (191) <1988DEP3701737>, and another is included in CHEC-II(1996) <1996CHEC-II(7)737>.



(191)

10.19.6.3.2 1,3-Oxazino[5,6-*c*][1,2]thiazines

The formation of droxicam **162** by ring-closure of **163** with triphosgene in the presence of triethylamine has been reported <1997JPC477>.

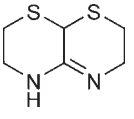
10.19.6.4 Important Compounds and Applications

The pharmacological profile of droxicam (Ombolam, **162**) is similar to that of piroxicam **163**; the prodrug shows improved gastrointestinal tolerance although adverse hepatic effects have been reported <2004JPB157>.

10.19.7 Thiazinothiazines

10.19.7.1 Introduction

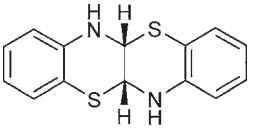
Only derivatives of the 1,4-thiazino[3,2-*b*][1,4]thiazine system have been prepared, although the 1,4-thiazino[2,3-*b*][1,4]thiazine **165** has been identified among the oxidation products of *S*-aminoethylcysteine ketimine <1995MI315>.



165

10.19.7.2 Theoretical and Experimental Structural Methods

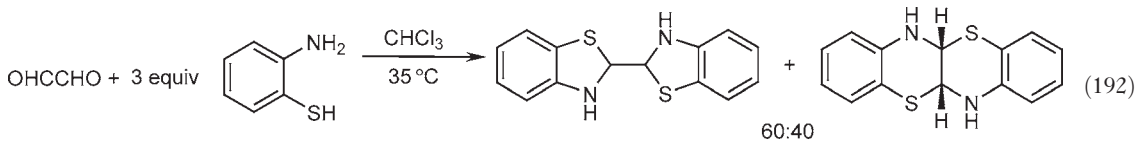
Experimental thermodynamic data have been reported for dibenzo-1,4-thiazino[3,2-*b*][1,4]thiazine **166** <1997MI565>; compared to the corresponding oxazinooxazine, replacement of oxygen by sulfur increases ring strain. Crystallographic data show that the nitrogen centres in **166** are *anti*-periplanar <1994JCM458>.



166

10.19.7.3 Ring Synthesis

The condensation of 2-aminoethanethiol with a 1,2-bis(electrophile) to give a mixture of perhydro-1,4-thiazino[3,2-*b*][1,4]thiazine and 2,2′-bis(thiazolidine) was included in CHEC-II(1996) <1996CHEC-II(7)737>. The direct preparation of this target from glyoxal was not achieved, but this method has been used successfully for the preparation of **166** (Equation 192).



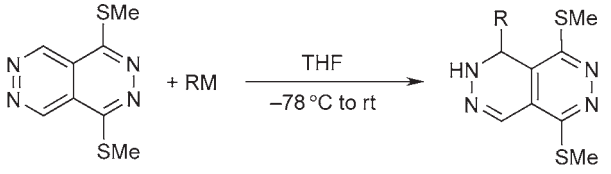
(192)

166

10.19.8 Further Developments

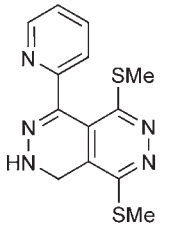
10.19.8.1 Pyridazino[4,5-*d*]pyrazines

1,4-Bis(methylthio)pyridazine[4,5-*d*]pyridiazine undergoes nucleophilic addition by organometallic reagents at C-5 to give 5,6-dihydro derivatives (Equation 193) although, using 2-lithiopyridine, the 7,8-dihydro product **167** is isolated <2007H(71)141>. An equivalent reaction observed where one of the methylthio groups is replaced by 3,5-dimethyl-1-pyrazolyl.

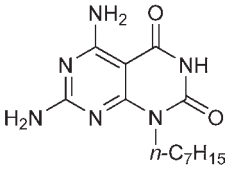


(193)

RM	*Yield (%)*	*RM*	*Yield (%)*	*RM*	*Yield (%)*
PhLi	91	4-$MeOC_6H_4Li$	43	1-Naphthyl-MgBr	90
PhMgCl	40	4-$MeOC_6H_4MgBr$	88	2-Naphthyl-Li	33
BuLi	65	2-$MeOC_6H_4Li$	51	2-Thienyl-Li	90
BuCu.LiI	61	1-Naphthyl-Li	52	2-Pyridinyl-Li	18



167



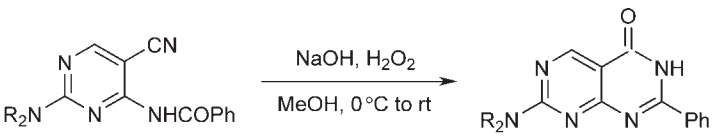
168

10.19.8.2 Pyrimido[4,5-*d*]pyrimidines

Recently-reported pyrimido[4,5-*d*]pyrimidine **168**, prepared as in Equation (90), has been reported as a 'Janus-AT' heterocycle, where the molecule is designed to have the hydrogen-bonding characteristics of both a diaminopurine and uracil/thymine <2007JOC466>. Crystallographic studies show that **168** forms a linear formate-bridged supramolecular array.

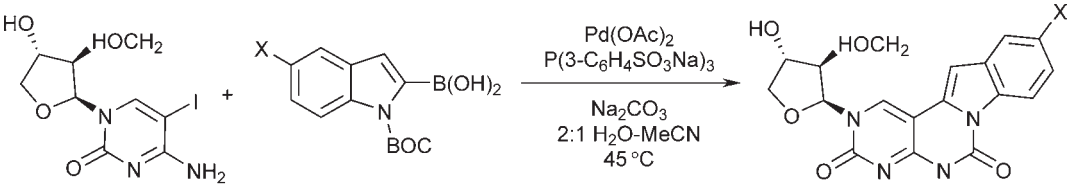
A method related to that of **Scheme 51** has been used for the oxidative cyclization of 4-benzamido-5-cyanopyrimidines (Equation 194) <2006SC2693> while, as exemplified in Equation (195), pyrrole and indole-fused systems have been prepared by Suzuki coupling of a 5-iodocytidine derivative with a 1-BOC-2-pyrrolyl or indolylboronic acid and concomitant cyclization <2007JOC102, 2007JOC5046>, the products being of interest as fluorescent nucleoside analogues. Two forms of three-component coupling to form pyrimido[4,5-*d*]pyrimidines have also been reported recently, of which the first (**Scheme 106**) involves non-concerted cycloaddition of an *N*-(4-pyrimidinyl)amidine with an imine formed *in situ*. Loss of the elements of dimethylamine from the intermediate gives the observed product <2007SL595>. In a further three-component condensation <2007T1770, 2007JHC1009>, 6-amino-1,3-dimethyluracil is converted into a series of pyrimido[4,5-*d*]pyrimidines by heating with an aldehyde and urea in a domestic microwave oven (**Scheme 107**). After a brief period of heating, using benzaldehyde it was found that the

intermediate **169** could be isolated; subsequent exposure of the intermediate to the same reaction conditions generated the pyrimidopyrimidine product. A further example of the process in Equation (91) has also been reported, using potassium carbonate as the base in refluxing water <2007JHC1253>.



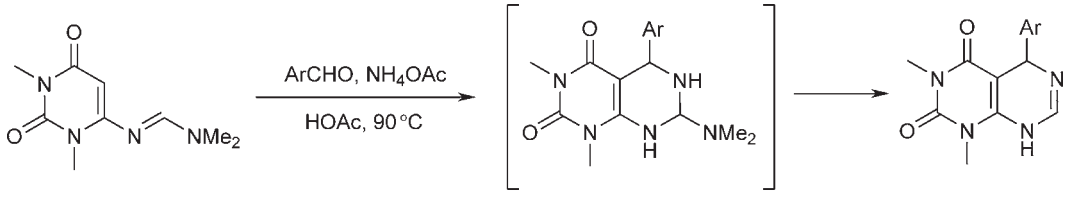
R_2N	Yield (%)	R_2N	Yield (%)
4-Morpholinyl	59	4-Methylpiperazin-1-yl	68
1-Piperidinyl	60	4-Phenylpiperazin-1-yl	61
4-Benzyl-1-piperazinyl	76	NHBu	55
4-(2-Methoxyphenyl)piperazin-1-yl	55	NH-*n*-C_7H_{15}	58
1,2,3,4-Tetrahydroquinolin-1-yl	50	NH-*c*-C_6H_{11}	52

(194)



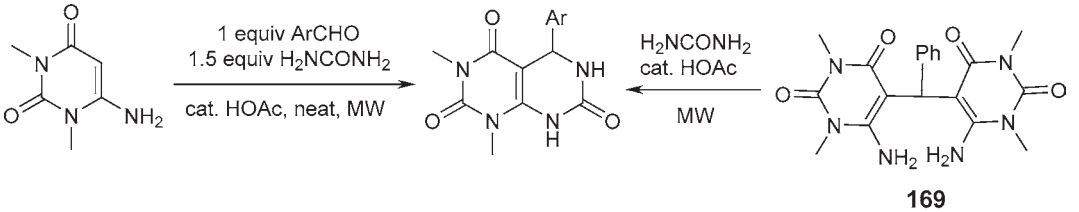
(195)

X	Yield (%)	X	Yield (%)	X	Yield (%)
H	75	SMe	79	CN	46
OMe	72	F	82	NMe_2	84



Ar	Yield (%)	Ar	Yield (%)	Ar	Yield (%)
Ph	88	4-$MeOC_6H_4$	91	2-Thienyl	85
4-Tol	90	4-ClC_6H_4	93	*n*-Bu	75
4-$O_2NC_6H_4$	84	4-BrC_6H_4	80	PhCH=CH–	70

Scheme 106

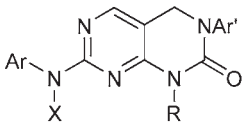


169

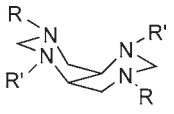
Ar	Yield (%)	Ar	Yield (%)	Ar	Yield (%)
Ph	87	4-$MeOC_6H_4$	75	4-ClC_6H_4	80
4-Tol	86	4-FC_6H_4	76	4-BrC_6H_4	80

Scheme 107

A number of development candidates of general formula **170** have been patented as potential antineoplastic agents <2006USP7094270, 2006USP7115740> and as agents for maintaining self-renewal in embryonic stem cell cultures <2006WO135824>.



170



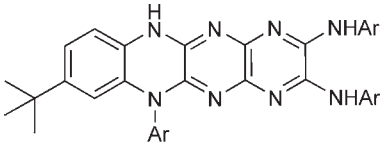
171

10.19.8.3 Pyrimido[5,4-*d*]pyrimidines

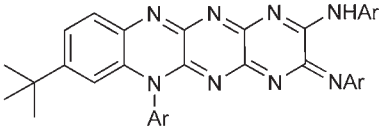
The proton affinities derived from DFT calculations for *cis*-1,3,5,7-tetraazadecalins **171** (R = H, R′ = Me; R = Me, R′ = H; R = R′ = Me) are higher than that of the 'proton sponge', 1,8-bis(dimethylamine)naphthalene <2006EJOC4938>. It is proposed that the basicity of the nitrogen centers in **171** is enhanced by anomeric effects, and that the protonated forms are further stabilized by cooperative binding by neighboring nitrogen centers. The method shown in **Scheme 62** for the generation of pyrimido[5,4-*d*]pyrimidines from purines has been extended <2007EJO1324>, and the use of dipyridamole **65** in conjunction with aspirin and an angiotensin II antagonist for stroke prevention has been described <2006EP1733729>.

10.19.8.4 Pyrazino[2,3-*b*]pyrazines

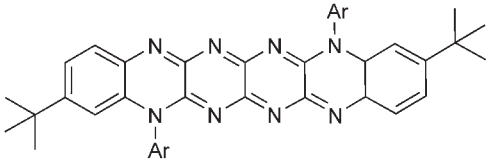
The approach to pyrazino[2,3-*b*]quinoxalines shown in Equation (114) has now been used to prepare pyrazino[2,3-*b*]pyrazines <2007EJO1237>, whose nickel complexes have also been prepared. The same publication also describes the formation of **172** by treatment of conjugated system **173** with sodium thiosulfate. The former is reconverted to the latter on exposure to air and, on further aerial oxidation at 130 °C, **173** eventually forms the highly condensed system **174**. Detailed studies of the formation of the tetrahydropyrazinopyrazine **101** have been reported, along with theoretical studies, and structural data for the *trans* isomer <2007T6915>.



172



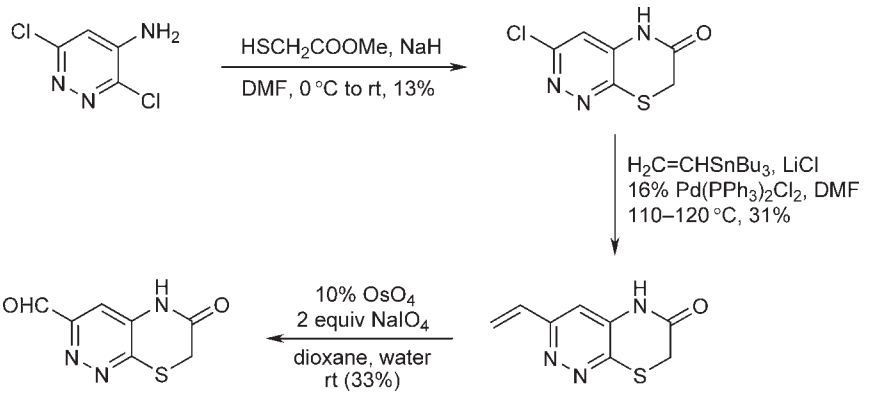
173



174

10.19.8.5 Pyridazino[3,4-*b*][1,4]thiazines

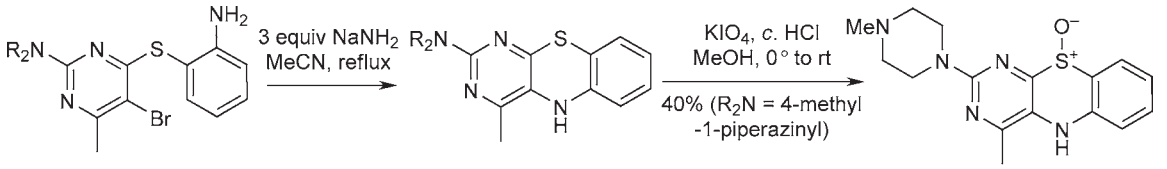
A report of the generation of pyridazino[3,4-*b*][1,4]thiazines has appeared <2006USP7141564> in which the ring system is formed in modest yield by the reaction of 4-amino-3,6-dichloropyridazine with methyl mercaptoacetate in the presence of base (**Scheme 108**). A Stille coupling is then used to introduce a vinyl group, whose oxidative cleavage gives the aldehyde. Reductive amination of this intermediate gave a series of compounds of interest as antibacterial agents.



Scheme 108

10.19.8.6 Pyrimido[4,5-*b*][1,4]thiazines

A recent report describes the formation of benzo derivatives of the pyrimido[4,5-*b*][1,4]thiazine system by cyclization (**Scheme 109**) <2007BMC2120>. The compounds prepared have some 5-lipoxygenase inhibitory activity, the active inhibitor being the corresponding sulfoxide, which has been prepared by oxidation of the parent (**Scheme 109**).



R_2N	Yield (%)
Pyrrolidin-1-yl	60
4-Methyl-1-piperidinyl	55
4-Methylpiperazin-1-yl	55
4-Phenyl-1-piperazinyl	85

R_2N	Yield (%)
Piperidin-1-yl	75
4-Hydroxy-1-piperidinyl	55
4-Ethylpiperazin-1-yl	65
Morpholin-4-yl	80

Scheme 109

References

1982FRP10409 J. E. Soler (Provesan s. a.), *Fr. Pat.* 10409 (1982).

1984CHEC(3)329 R. N. Castle and S. D. Phillips; in 'Comprehensive Heterocyclic Chemistry', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 3, p. 329.

1988DEP3701737 G. Fengler, A. Klausener, H. J. Buysch, M. Mardin, and K. B. Pelster (Bayer AG), *Ger. Pat.* 3701737 (1988).

1990JME1721 J. B. Jiang, D. P. Hesson, B. A. Dusak, D. L. Dexter, G. J. Kang, and E. Hamel, *J. Med. Chem.*, 1990, **33**, 1721.

1990JPS123 A. G. El-Kourashy, A. Mousaad, and E. S. H. El Ashry, *Alexandria J. Pharm. Sci.*, 1990, **4**, 123 (*Chem. Abstr.*, 1991, **114**, 163245).

1990USP4963541 D. W. Brooks and A. A. Basha (Abbott), *US Pat.* 4963541 (1990).

1992AP461 H.-D. Stachel, H. Poschenrieder, and V. Lomitzky, *Arch. Pharm. (Weinheim, Ger.)*, 1992, **325**, 461.

1992CJC2764 N. Farfán, R. L. Santillan, D. Castillo, R. Cruz, P. Joseph-Nathan, and J.-C. Daran, *Can. J. Chem.*, 1992, **70**, 2764.

1992H(34)1423 J. N. Kim and E. K. Ryu, *Heterocycles*, 1992, **34**, 1423.

1992JHC87 S. Mataka, O. Misumi, W. H. Lin, M. Tashiro, K. Takahashi, and A. Tori-i, *J. Heterocycl. Chem.*, 1992, **29**, 87.

1992JHC1313 T. Okawara and M. Furukawa, *J. Heterocycl. Chem.*, 1992, **29**, 1313.

1992JHC1409 S.-G. Lee, S.-Y. Choi, and Y.-J. Yoon, *J. Heterocycl. Chem.*, 1992, **29**, 1409.

1992S591 A. Hamed, *Synthesis*, 1992, 591.

1993CHE437 D. G. Mazhukin, A. Ya. Tikhonov, L. B. Volodarskii, and E. P. Konovalova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1993, **29**, 437.

1993H(35)1397 T. J. Delia, M. Baumann, and A. Bunker, *Heterocycles*, 1993, **35**, 1397.

1993IJB901 O. P. Bansal, J. S. Srinivas, P. P. Singh, and A. Y. Junnarkar, *Indian J. Chem., Sect. B*, 1993, **32**, 901.

1993JCM8 A. W. Erian, *J. Chem. Res. (S)*, 1993, 8, *J. Chem. Res. (M)*, 1993, 0155.

1993JCM208 A. O. Abdelhamid, *J. Chem. Res. (S)*, 1993, 208.

1993JHC1659 Y. Kurasawa, A. Takada, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 1993, **30**, 1659.

1993JIC533 R. G. Menon and E. Purushothaman, *J. Indian Chem. Soc.*, 1993, **70**, 533.
1993JPC13408 P. Dowd, W. Chang, C. J. Partian, and W. Zhang, *J. Phys. Chem.*, 1993, **97**, 13408.
1993JRM1239 A. O. Abdelhamid, *J. Chem. Res. (M)*, 1993, 1239.
1993MI343 O. S. Abou-Teim, *Al-Azhar Bull. Sci.*, 1993, **4**, 343 (*Chem. Abstr.*, 1995, **122**, 133097).
1993TA133 H. C. Kolb, Y. L. Bennani, and K. B. Sharpless, *Tetrahedron Asymmetry*, 1993, **4**, 133.
1994AF156 L. V. G. Nargund, R. Jose, and Y. S. R. Reddy, *Arzneim.-Forsch.*, 1994, **44**, 156.
1994BSF279 R. Mekheimer, *Bull. Soc. Chim. Fr.*, 1994, **131**, 279.
1994CC2451 M. Scobie and G. Tennant, *J. Chem. Soc., Chem. Commun.*, 1994, 2451.
1994CHE340 S. V. Litvinenko, V. I. Savich, and L. D. Bobrovnovik, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1994, **30**, 340.
1994CHE1083 A. V. Gulevskaya, A. F. Pozharskii, S. V. Shorshnev, and E. A. Zheltushkina, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1994, **30**, 1083.
1994CL1833 O. Tsuge, T. Hatta, K. Yakata, and H. Haeda, *Chem. Lett.*, 1994, 1833.
1994EJM245 L. V. G. Nargund, V. V. Badiger, and S. M. Yarnal, *Eur. J. Med. Chem.*, 1994, **29**, 245.
1994IJB65 V. K. Ahluwalia, R. Aggarwal, and R. Kumar, *Indian J. Chem., Sect. B*, 1994, **33**, 65.
1994IJB764 L. V. G. Nargund, V. V. Badiger, and S. M. Yarnal, *Indian J. Chem., Sect. B*, 1994, **33**, 764.
1994JCM458 N. Farfan, R. Santillan, B. Castillo, P. Carretero, M. de Jesus Rosales, E. Garcia-Baez, A. Flores-Vela, J.-C. Daran, and S. Halut, *J. Chem. Res. (S)*, 1994, 458.
1994JHC81 F. Gatta, M. R. Del Giudice, A. Borioni, and C. Mustazza, *J. Heterocycl. Chem.*, 1994, **31**, 81.
1994JHC357 N. Haider and C. Loll, *J. Heterocycl. Chem.*, 1994, **31**, 357.
1994JHC1135 A. Monge, J. A. Palop, A. Piñol, F. J. Martínez-Crespo, S. Narro, M. González, Y. Sáinz, A. López de Ceráin, E. Hamilton, and A. J. Barker, *J. Heterocycl. Chem.*, 1994, **31**, 1135.
1994JHC1503 M. R. Del Giudice, A. Borioni, C. Mustazza, and F. Gatta, *J. Heterocycl. Chem.*, 1994, **31**, 1503.
1994J(P1)2751 A. Ahmad, L. J. Dunbar, I. G. Green, I. W. Harvey, T. Shepherd, D. M. Smith, and R. K. C. Wong, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2751.
1994JRM2521 N. Farfan, R. Santillan, B. Castillo, P. Carretero, M. de Jesus Rosales, E. Garcia-Baez, A. Flores-Vela, J.-C. Daran, and S. Halut, *J. Chem. Res (M)*, 1994, 2521.
1994M1129 U. Hain, K. Gewald, R. Schindler, and M. Gruner, *Monatsh.*, 1994, **125**, 1129.
1994NN1125 T. E. Mabry, C. D. Jones, T. S. Chou, J. M. Colacino, G. B. Grindey, J. F. Worzalla, and H. L. Pearce, *Nucleos. Nucleot.*, 1994, **13**, 1125.
1995AF1131 L. V. G. Nargund and K. S. Nargund, *Arzneim.-Forsch.*, 1995, **45**, 1131.
1995DEP4325900 A. Heckel, U. Bamberger, and A. Mauz (Thomae GmbH), *Ger. Pat.* 4325900 (1995).
1995EJM525 H. H. Hassanein, H. M. El Nahal, and F. R. Gerges, *Eur. J. Med. Chem.*, 1995, **30**, 525.
1995H(41)1023 T. Okawara, H. Takaishi, Y. Okamoto, T. Yamasaki, and M. Furukawa, *Heterocycles*, 1995, **41**, 1023.
1995H(41)2519 N. Haider, *Heterocycles*, 1995, **41**, 2519.
1995HCA291 D. Loakes and D. M. Brown, *Nucleosides Nucleotides*, 1995, **14**, 291.
1995JA2351 A. D. Backstrom, R. A. S. McMordie, and T. P. Begley, *J. Am. Chem. Soc.*, 1995, **117**, 2351.
1995JA3873 K.-Y. Lin, R. J. Jones, and M. Matteucci, *J. Am. Chem. Soc.*, 1995, **117**, 3873.
1995JHC1085 Y. Kurasawa, A. Takada, and H. S. Kim, *J. Heterocycl. Chem.*, 1995, **32**, 1085.
1995JLR891 K. W. M. Lawrie, C. E. A. Novelli, D. Saunders, and W. J. Coates, *J. Labelled Compd. Radiopharm.*, 1995, **36**, 891.
1995LA1703 S. Tumkevicius, *Liebigs Ann.*, 1995, **9**, 1703.
1995MI315 L. Pecci, F. Pinnen, A. Antonucci, and D. Cavallini, *Amino Acids*, 1995, **8**, 315.
1995MI779 L. A. Torres, R. Gudino, I. Hernandez-Contreras, M. E. Ochoa, N. Farfan, and R. L. Santillan, *J. Chem. Thermodyn.*, 1995, **27**, 779.
1995MI1219 J. Schmid, U. Busch, G. Trummlitz, A. Prox, S. Kaschke, and H. Wachsmuth, *Xenobiotica*, 1995, **25**, 1219.
1995NN1601 T. S. Rao and G. Revankar, *Nucleos. Nucleot.*, 1995, **14**, 1601.
1995PJC1018 M. G. Assy, A. A. Hataba, and H. Y. Moustafa, *Polish J. Chem.*, 1995, **69**, 1018.
1995PJC1039 R. A. Kolinski, *Pol. J. Chem.*, 1995, **69**, 1039.
1995PS(101)189 A. A. Hassan, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1995, **101**, 189.
1995RCB131 M. O. Dekaprilevich, A. N. Kravchenko, L. I. Khmel'nitskii, O. V. Lebedev, Yu. T. Struchkov, and Yu. A. Strelenko, *Russ. Chem. Bull.*, 1995, **44**, 131.
1995RCB1278 A. V. Komkov, A. M. Sakharov, V. S. Bogdanov, and V. A. Dorokhov, *Russ. Chem. Bull.*, 1995, **44**, 1278.
1995TL6777 N. E. Alexandrou, G. A. Mertzanos, J. Stephanidou-Stephanatou, C. A. Tsoleridis, and P. Zachariou, *Tetrahedron Lett.*, 1995, **36**, 6777.
1995WO95/19774 A. J. Bridges, W. A. Denny, D. Fry, A. Kraker, R. Meyer, G. W. Rewcastle, and A. M. Thompson (Warner Lambert), *PCT* WO 95/19774 (1995).
1996AGE1232 R. Weiss, R. May, and B. Pomrehn, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1232.
1996AJC285 T. K. O'Leary and R. W. Read, *Aust. J. Chem.*, 1996, **49**, 285.
1996APH39 H. Sladowska, M. Sieklucka-Dziuba, G. Rajtar, R. Wydro, and Z. Kleinrok, *Acta Polon. Pharm.*, 1996, **53**, 39.
1996CC355 S. H. Kang and D. H. Ryu, *Chem. Commun.*, 1996, 355.
1996CC947 G. R. Weisman, E. H. Wong, D. C. Hill, M. E. Rogers, D. P. Reed, and J. C. Calabrese, *Chem. Comm.*, 1996, 947.
1996CC1175 B. Korybut-Daszkiewicz and J. Klimkiewicz, *Chem. Comm.*, 1996, 1175.
1996CC1527 A. Marsh, M. Silvestri, and J.-M. Lehn, *Chem. Commun.*, 1996, 1527.
1996CHE93 S. Tumkevicius, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1996, **32**, 93.
1996CHEC-II(7)737 H. Wamhoff, C. Sattler, and E. Kroth; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 737.
1996CHEC-II(7)768 H. Wamhoff, C. Sattler, and E. Kroth; in 'Comprehensive Heterocyclic Chemistry II', Pergamon, 1996, vol. 7, p. 768.
1996CHEC-II(7)776 H. Wamhoff, C. Sattler, and E. Kroth; in 'Comprehensive Heterocyclic Chemistry II', Pergamon, 1996, vol. 7, p. 776.
1997CHEC-II(7)780 H. Wamhoff, C. Sattler, and E. Kroth; in 'Comprehensive Heterocyclic Chemistry II', Pergamon, 1996, vol. 7, p. 780.
1996FA781 J. Dominguez, J. Charris, L. Iarrusso, S. Lopez, G. Lobo, and F. Riggione, *Farmaco*, 1996, **51**, 781.

1996DEP19502179 A. Heckel and U. Bamberger (Thomae GmbH), *Ger. Pat.* 19502179 (1996).
1996DEP4431867 F. Himmelsbach and T. von Rüden (Thomae GmbH), *Ger. Pat.* 4431867 (1996).
1996H(43)1391 T. Okawara, Y. Okamoto, S. Ehara, T. Yamasaki, and M. Furukawa, *Heterocycles*, 1996, **43**, 1991.
1996H(43)1597 Y. Tominaga, N. Yoshioka, and S. Kataoka, *Heterocycles*, 1996, **43**, 1597.
1996H(43)1613 T. Yamasaki, Y. Yoshihara, Y. Okamoto, and M. Furukawa, *Heterocycles*, 1996, **43**, 1613.
1996H(43)1863 T. Yamasaki, M. Oda, Y. Okamoto, T. Okawara, and M. Furukawa, *Heterocycles*, 1996, **43**, 1863.
1996H(43)1991 T. Okawara, Y. Okamoto, S. Ehara, T. Yamasaki, and M. Furukawa, *Heterocycles*, 1996, **43**, 1991.
1996H(43)2153 A. Schmidt, A. Hetzheim, and D. Albrecht, *Heterocycles*, 1996, **43**, 2153.
1996H(47)315 T. Yamasaki, K. Nishida, Y. Okamoto, T. Okawara, and M. Furukawa, *Heterocycles*, 1996, **47**, 315.
1996IJB144 A. A. Hataba, M. G. Assy, and R. M. Fikry, *Indian J. Chem., Sect. B*, 1996, **35**, 144.
1996IJB595 A. F. Sayed Ahmed, *Indian J. Chem., Sect. B*, 1996, **35**, 595.
1996IJB598 M. G. Assy, S. El-Bahaie, M. R. Ibrahim, and Y. A. Ibrahim, *Indian J. Chem., Sect. B*, 1996, **35**, 598.
1996IJB1185 R. G. Menon and E. Purushothaman, *Indian J. Chem., Sect. B*, 1996, **35**, 1185.
1996JCM442 S. Youssif and M. Assy, *J. Chem. Res. (S)*, 1996, 442.
1996JHC235 M. Takahashi and J. Yuda, *J. Heterocycl. Chem.*, 1996, **33**, 235.
1996JHC757 Y. Kurasawa, A. Takano, K. Kato, A. Takada, H. S. Kim, and Y. Okamoto, *J. Heterocycl. Chem.*, 1996, **33**, 757.
1996JIC698 R. M. Fikry, *J. Indian Chem. Soc.*, 1996, **73**, 698.
1996JOC4172 R. Nicewonger, C. A. Costello, and T. P. Begley, *J. Org. Chem.*, 1996, **61**, 4172.
1996J(P1)1699 I. W. Harvey, D. M. Smith, and C. R. White, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1699.
1996J(P1)2443 A. R. Ahmad, L. K. Mehta, and J. Parrick, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2443.
1996MCR61 A. Basha, J. D. Ratajczyk, R. D. Dyer, P. Young, G. W. Carter, and C. D. W. Brooks, *Med. Chem. Res.*, 1996, **6**, 61.
1996MI459 J. Pluta, M. Flendrich, and J. Cieplik, *Boll. Chim. Farm.*, 1996, **135**, 459.
1996OPP694 A. Hamed and M. Al-Talib, *Org. Prep. Proced. Int.*, 1996, **28**, 694.
1996PS15 M. G. Assy, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **108**, 15.
1996T13017 C. Dunn, C. L. Gibson, and C. J. Suckling, *Tetrahedron*, 1996, **52**, 13017.
1996WO07657 F. Himmelsbach, T. von Rüden, G. Dahmann, and T. Metz (Thomae GmbH), *PCT* WO 1996007657.
1997BCC296 Y. B. J. Aldenhoff, A. P. Pijpers, and L. H. Koole, *Bioconjugate Chem.*, 1997, **8**, 296.
1997CC1013 T. Saito, H. Kimura, T. Chonan, T. Soda, and T. Karakasa, *Chem. Commun.*, 1997, 1013.
1997CHE216 I. B. Starchenko, V. G. Andrianov, and A. F. Mishnev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 216.
1997CHE750 Yu. M. Volovenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 750.
1997CHE1352 I. B. Starchenkov and V. G. Andrianov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 1352.
1997CHE1473 S. V. Pirigov, S. F. Mel'nikova, and I. V. Tselinskii, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1997, **33**, 1473.
1997CNP1147378 C. Qiu, *Chin. Pat.* 1147378 (1997) (*Chem. Abstr.*, 1999, 131, 314189).
1997FA657 H. Sladowska, M. Bodetko, M. Sieklucka-Dziuba, G. Rajtar, D. Zolkowska, and Z. Kleinrok, *Farmaco*, 1997, **52**, 657.
1997JCM1576 A. A. Nada, A. W. Erian, N. R. Mohamed, and A. M. Mahran, *J. Chem. Res. (M)*, 1997, 1576.
1997JHC653 J.-y. Jaung, M. Matsuoka, and F. Fukunishi, *J. Heterocycl. Chem.*, 1997, **34**, 653.
1997JHC39 H. S. Kim, E. K. Kim, S. S. Kim, Y. T. Park, Y. S. Hong, and Y. Kurasawa, *J. Heterocycl. Chem.*, 1997, **34**, 39.
1997JHC1581 A. Nagarajan, B. R. Meltsner, and T. J. Delia, *J. Heterocycl. Chem.*, 1997, **34**, 1581.
1997JIC624 G. A. Ahmed, *J. Indian Chem. Soc.*, 1997, **74**, 624.
1997JIC818 A. A. Hataba, R. M. Fikry, and H. Y. Moustafa, *J. Indian Chem. Soc.*, 1997, **74**, 818.
1997JME2502 M. D. Varney, C. L. Palmer, W. H. Romines, III, T. Boritzki, S. A. Margosiak, R. Almassy, C. A. Janson, C. Bartlett, E. J. Howland, and R. Ferre, *J. Med. Chem.*, 1997, **40**, 2502.
1997JME1820 G. W. Rewcastle, A. J. Bridges, D. W. Fry, J. R. Rubin, and W. A. Denny, *J. Med. Chem.*, 1997, **40**, 1820.
1997JPR477 F. Bracher and C. Berns, *J. Prakt. Chem.*, 1997, **339**, 477.
1997MI110 M. Lu, C. Lu, Y. Wei, and Z. Li, *Nanjing Ligong Daxue Xuebao*, 1997, **21**, 110 (*Chem. Abstr.*, 1997, **127**, 6766).
1997MI167 Y. B. J. Aldenhoff, R. Blezer, T. Lindhout, and L. H. Koole, *Biomaterials*, 1997, **18**, 167.
1997MI427 G. C. Y. Chiou, Z. Chen, B. Xuan, T. Yamasaki, and T. Okawara, *J. Ocul. Pharmacol. Ther.*, 1997, **13**, 427 (*Chem. Abstr.*, 1997, **127**, 326164).
1997MI565 R. Gudino, L. A. Torres, M. Campos, R. L. Santillan, and N. Farfán, *J. Chem. Thermodynamics*, 1997, **29**, 565.
1997PHA91 A. Stanczak, W. Lewgowd, Z. Ochocki, W. Pakulska, and A. Szadowska, *Pharmazie*, 1997, **52**, 91.
1997PHA838 A. Stanczak and W. Pakulska, *Pharmazie*, 1997, **52**, 838.
1997T7045 R. Saladino, L. Stasi, C. Crestini, R. Nicoletti, and M. Botta, *Tetrahedron*, 1997, **53**, 7045.
1997T13841 A. K. Sharma and M. P. Mahajan, *Tetrahedron*, 1997, **53**, 13841.
1997THE199 S. Zeman, *Thermochim. Acta*, 1997, **290**, 199.
1997TL3573 A. Star, N. G. Lemcoff, I. Goldberg, and B. Fuchs, *Tetrahedron Lett.*, 1997, **38**, 3573.
1997TL8073 O. Reaney, M. Grabarnik, I. Goldberg, S. Abramson, A. Star, and B. L. Fuchs, *Tetrahedron Lett.*, 1997, **38**, 8073.
1997USP5654307 A. J. Bridges, W. A. Denny, D. Fry, A. Kraker, R. Meyer, G. W. Rewcastle, and A. M. Thompson (Warner Lambert), *US Pat.* 5654307 (1997).
1997WO97/28177 D. Brown, A. Hamilton, D. Loakes, A. Simmonds, and C. Smith (Amersham International), *PCT* WO 97/28177.
1997WO97/32880 F. Himmelsbach, G. Dahmann, T. von Rüden, and T. Metz (Thomae GmbH), *PCT* WO 97/32880 (1997).
1997WO97/32882 F. Himmelsbach, G. Dahmann, T. von Rüden, and T. Metz (Thomae GmbH), *PCT* WO 97/32882 (1997).
1998BCJ2387 A. W. Erian and F. A. Abu-Shanab, *Bull. Chem. Soc. Jpn*, 1998, **71**, 2387.
1998BML2235 B. O. Buckman, R. Mohan, S. Koovakkat, A. Liang, L. Trinh, and M. M. Morrissey, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2235.
1998CHE1201 N. V. Sazonov, I. E. Mamaeva, and T. S. Safonova, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1998, **34**, 1201.
1998CL1163 T. Yamamoto and B.-L. Lee, *Chem. Lett.*, 1998, 1163.
1998CRC421 F. Schmidt, J.-C. Florent, and C. Monneret, *C. R. Hebd. Seances Acad. Sci., Ser. C*, 1998, **1**, 421.
1998FA113 Sh. M. Radwan and H. S. El-Kashef, *Farmaco*, 1998, **53**, 113.
1998HCA646 T. Masquelin, D. Sprenger, R. Baer, F. Gerber, and Y. Mercadel, *Helv. Chim. Acta*, 1998, **81**, 646.
1998H(48)1923 Z. Wang and R. Neidlein, *Heterocycles*, 1998, **48**, 1923.

1998IJH193 N. A. Devi, Ch. K. Khuman, R. K. T. Singh, and L. W. Singh, *Indian J. Heterocycl. Chem.*, 1998, **7**, 193.
1998JCM675 A. F. Sayed Ahmed, *J. Chem. Res. (S)*, 1998, 675.
1998JHC1075 P. Mátyus, *J. Heterocycl. Chem.*, 1998, **35**, 1075.
1998JHC1101 Y. Kurasawa and H. S. Kim, *J. Heterocycl. Chem.*, 1998, **35**, 1101.
1998JME3812 C. Altomare, S. Cellamare, L. Summo, M. Catto, A. Carotti, U. Thull, P.-A. Carrupt, B. Testa, and H. Stoeckli-Evans, *J. Med. Chem.*, 1998, **41**, 3812.
1998JOC8850 O. Reany, I. Goldberg, S. Abramson, L. Golender, B. Ganguly, and B. Fuchs, *J. Org. Chem.*, 1998, **63**, 8850.
1998JRM2880 A. F. Sayed Ahmed, *J. Chem. Res. (M)*, 1998, 2880.
1998MI236 M. Lu, C. Lu, Y. Wei, and Z. Li, *Nanjing Ligong Daxue Xuebao*, 1998, **22**, 236 (*Chem. Abstr.*, 1998, **129**, 177582).
1998PHA156 A. Stanczak, W. Lewgowd, and W. Pakulska, *Pharmazie*, 1998, **53**, 156.
1998PHA834 A. Stanzcak, Z. Ochocki, and W. Pakulska, *Pharmazie*, 1998, **53**, 834.
1998T9903 Z. Wang and R. Neidlein, *Tetrahedron*, 1998, **54**, 9903.
1998TL6861 G. Hervé, H. Bernard, N. Le Bris, J.-J. Youane, H. Handel, and L. Toupet, *Tetrahedron Lett.*, 1998, **39**, 6861.
1998TL8385 J. Wang, K.-Y. Lin, and M. D. Matteuci, *Tetrahedron Lett.*, 1998, **39**, 8385.
1998WO98/28281 J. M. Davis, P. D. Davis, D. F. C. Moffatt, and M. J. Batchelor (Celltech), *PCT* WO 98/28281 (1998).
1998WO98/35967 J. R. McCarthy (Neurocrine Biosci.), *PCT* WO 98/35967 (1998).
1998WO98/49151 G. Ripa and M. Argese (Dibra SPA), *PCT* WO 98/49151 (1998).
1999BML965 S. K. Srivastava, W. Haq, and P. M. S. Chauhan, *Bioog. Med. Chem. Lett.*, 1999, **9**, 965.
1999CCT35 S. K. Srivastava, W. Haq, and P. M. S. Chauhan, *Comb. Chem. High Throughput Screening*, 1999, **2**, 33.
1999CHE97 T. S. Safonova and I. E. Mamaeva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 97.
1999CHE733 T. S. Safonova and A. F. Keremov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 733.
1999CHE1381 S. Tumkevicius and V. Masyavicius, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1999, **35**, 1381.
1999EJO2033 A. Star, I. Goldberg, N. G. Lemcoff, and B. Fuchs, *Eur. J. Org. Chem.*, 1999, 2033.
1999H(51)255 Z. Wang and R. Neidlein, *Heterocycles*, 1999, **51**, 255.
1999H(51)2305 T. Yamaguchi, S. Ito, Y. Iwase, K. Watanabe, and K. Harano, *Heterocycles*, 1999, **51**, 2305.
1999HCA2028 D. Loakes, R. Bazzanini, and D. M. Brown, *Helv. Chim. Acta*, 1999, **82**, 2028.
1999HCO203 Z. Wang, R. Neidlein, and C. Krieger, *Heterocycl. Commun.*, 1999, **5**, 203.
1999HCO365 H. Wamhoff, J. Muhr, M. Horn, P. Sohar, and A. Csampai, *Heterocycl. Commun.*, 1999, **5**, 365.
1999JKC302 H. S. Kim and G. Jeong, *J. Korean Chem. Soc.*, 1999, **43**, 302.
1999JO2683 W. C. Baker, M. J. Choi, D. C. Hill, J. L. Thompson, and P. A. Petillo, *J. Org. Chem.*, 1999, **64**, 2683.
1999JOC1166 A. Star and B. Fuchs, *J. Org. Chem.*, 1999, **64**, 1166.
1999JPP158180 U. Masahiro, S. Kazuyuki, and S. Akira (Nippon Nohyaku Co.), *Jpn. Pat.* 11-158180 (1999).
1999JPR147 A. W. Erian, *J. Prakt. Chem.*, 1999, **341**, 147.
1999M1409 A. M. Amer, M. A. El-Bermaui, A. F. S. Ahmed, and S. M. Soliman, *Monatsh. Chem.*, 1999, **130**, 1409.
1999PCJ4 T. S. Safonova, A. F. Keremov, and Yu. A. Ershova, *Pharm. Chem. J.*, 1999, **33**, 4.
1999MI93 S. Desbene, H. D.-T. Van, S. Michel, F. Tillequin, M. Koch, F. Schmidt, J.-C. Florent, C. Monneret, R. Straub, J. Czech, M. Gerken, and K. Bosslet, *Anti-Cancer Drug Design*, 1999, **14**, 93.
1999NN2475 A. R. Porcari, K. Z. Borysko, R. G. Ptak, J. M. Breitenbach, L. L. Wotring, J. C. Drach, and L. B. Townsend, *Nucleos. Nucleot.*, 1999, **18**, 2475.
1999PCA3089 J. K. Hurst, P. Wormell, J. R. Reimers, and A. R. Lacey, *J. Phys. Chem. (A)*, 1999, **103**, 3089.
1999PNA3513 W. M. Flanagan, J. J. Wolf, P. Olson, D. Grant, K.-Y. Lin, P. W. Wagner, and M. D. Matteucci, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 3513.
1999RCB364 M. A. Kulnikov, S. Sh. Shukurov, U. Nurov, and Yu. Khadzhiboev, *Russ. Chem. Bull.*, 1999, **48**, 364.
1999RCB1150 A. V. Gulevskaya, D. V. Besedin, and A. F. Pozharskii, *Russ. Chem. Bull.*, 1999, **48**, 1150.
1999SC1577 N. Haider, E. Mavrokordatou, and A. Steinwender, *Synth. Commun.*, 1999, **29**, 1577.
1999TL1793 P. J. Bhuyan, K. C. Lekhok, and J. S. Sandhu, *Tetrahedron Lett.*, 1999, **40**, 1793.
1999USP5886174 M. Argese, G. Ripa, A. Scala, and V. Valle, *US Pat.* 5886174 (1999).
1999WO99/61444 E. M. Dobrusin, J. M. Hamby, J. B. Kramer, M. C. Schroeder, H. D. H. Showalter, P. Toogood, and S. A. Trumpp-Kallmeyer (Warner-Lambert), *PCT* WO 99/61444 (1999).
2000AGE2685 A. Star, I. Goldberg, and B. Fuchs, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 2685.
2000BBA(1474)177 L. Iuliano, C. Piccheri, I. Coppola, D. Pratico, F. Micheletta, and F. Violi, *Biochim. Biophys. Acta, General Subjects*, 2000, **1474**, 177.
2000BMC2803 P. Jakobsen, A. M. Horneman, and E. Persson, *Bioorg. Med. Chem.*, 2000, **8**, 2803.
2000BML585 H. C. Barlow, K. J. Bowman, N. J. Curtin, A. H. Calvert, B. T. Golding, B. Huang, P. J. Loughlin, D. R. Newell, P. G. Smith, and R. J. Griffin, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 585.
2000CCC99 M. Chadim, M. Budesinsky, J. Hodacova, and J. Zavada, *Coll. Czech. Chem. Commun.*, 2000, **65**, 99.
2000CCC243 J. Kotek, P. Hermann, P. Vojtisek, J. Rohovec, and I. Lukes, *Coll. Czech. Chem. Comm.*, 2000, **65**, 243.
2000CHE751 A. Brukshtus and S. Tumkevicius, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2000, **36**, 751.
2000CHE975 A. V. Gulevskaya, V. V. Goryunenko, and A. F. Pozharskii, *Chem. Heterocycl. Compd.*, 2000, **36**, 975.
2000CHE1213 D. V. Besedin, A. V. Gulevskaya, and A. F. Pozharskii, *Chem. Heterocycl. Compd.*, 2000, **36**, 1213.
2000H(53)1677 T. Yamaguchi, S. Ito, Y. Iwase, K. Watanabe, and K. Harano, *Heterocycles*, 2000, **53**, 1677.
2000HCA1693 D. Loakes, M.-J. Guo, J.-C. Yang, and D. M. Brown, *Helv. Chim. Acta*, 2000, **83**, 1693.
2000IJB65 M. S. Chande and V. V. Sugdare, *Indian J. Chem., Sect. B*, 2000, **39**, 65.
2000JCCS951 M. A. Barsy, *J. Chinese Chem. Soc.*, 2000, **47**, 951.
2000JHC103 H. S. Kim, S. T. Kwag, K. O. Choi, and Y. Okamoto, *J. Heterocycl. Chem.*, 2000, **37**, 103.
2005JHC375 A. F. Pozharskii and A. V. Gulevskaya, *J. Heterocycl. Chem.*, 2005, **42**, 375.
2000JHC791 Y. Kurasawa, A. Tsuruoka, N. Rikiishi, and N. Fujiwara, *J. Heterocycl. Chem.*, 2000, **37**, 791.
2000JHC1257 Y. Kurasawa, K. Sakurai, S. Kajiwara, K. Harada, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2000, **37**, 1257.
2000JIC494 M. A. Zahran, *J. Indian Chem. Soc.*, 2000, **77**, 494.

2000JME2438 A. R. Porcari, R. G. Ptak, K. Z. Borysko, J. M. Breitenbach, S. Vittori, L. L. Wotring, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 2000, **43**, 2438.

2000JME2457 A. R. Porcari, R. G. Ptak, K. Z. Borysko, J. M. Breitenbach, J. C. Drach, and L. B. Townsend, *J. Med. Chem.*, 2000, **43**, 2457.

2000JA10561 E. H. Wong, G. R. Weisman, D. C. Hill, D. P. Reed, M. E. Rogers, J. S. Condon, M. A. Fagan, J. C. Calabrese, K.-C. Lam, I. A. Guzci, and A. L. Rheingold, *J. Am. Chem. Soc.*, 2000, **122**, 10561.

2000JOC6388 V. Benin, P. Kaszynski, M. Pink, and V. G. Young, Jr., *J. Org. Chem.*, 2000, **65**, 6388.

2000JOC8068 V. Benin and P. Kaszynski, *J. Org. Chem.*, 2000, **65**, 8068.

2000J(P1)2601 P. A. Koutentis and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2601.

2000PCA7386 J. K. Hurst, P. Wormell, G. B. Bacskay, and A. R. Lacey, *J. Phys. Chem. A*, 2000, **104**, 7386.

2000MC150 D. V. Besedin, A. V. Gulewskaya, and A. F. Pozharskii, *Mendeleev Commun.*, 2000, 150.

2000MI71 J.-Y. Jaung and S. D. Kim, *Fiber. Polym.*, 2000, **1**, 71 (*Chem. Abstr.*, 2001, *136*, 168959).

2000PJC681 A. M. Amer, I. A. G. Attia, M. El-Mobayad, and S. Asker, *Pol. J. Chem.*, 2000, **74**, 681.

2000PS(158)9 R. M. Shaker, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **158**, 9.

2000PS(164)259 H. Abdel-Ghany, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **164**, 259.

2000PS(165)205 I. M. El-Deen and F. F. Mahmoud, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2000, **165**, 205.

2000RJO1157 A. V. Vasil'ev, A. P. Rudenko, and E. V. Grinenko, *Russ. J. Org. Chem. (Engl. Transl.)*, 2000, **36**, 1157.

2000S1679 C. Käpplinger and R. Beckert, *Synthesis*, 2000, 1679.

2000SC2721 V. Santes, E. Gómez, G. Jiminéz, R. Santillan, A. Guitiérrez, and N. Farfán, *Synth. Commun.*, 2000, **30**, 2721.

2000T6427 S. Rojas-Lima, N. Farfán, R. Santillan, D. Castillo, M. E. Sosa-Torres, and H. Höpfl, *Tetrahedron*, 2000, **56**, 6427.

2000TA4709 S. Lee, C. W. Lim, J. K. Lee, O.-S. Jung, and Y.-A. Lee, *Tetrahedron Asymmetry*, 2000, **11**, 4709.

2000TL1249 J. Rohovec, R. Gyepes, I. Císa¡rová, J. Rudovský, and I. Lukeš, *Tetrahedron Lett.*, 2000, **41**, 1249.

2000TL2863 E. Sotelo, B. Pita, and E. Raviña, *Tetrahedron Lett.*, 2000, **41**, 2863.

2000USP6060477 G. A. Piazza and R. Pamukcu (Cell Pathways), *US Pat.* 6060477 (2000).

2000USP6114521 M. Argese, G. Ripa, A. Scala, and V. Valle, *US Pat.* 6114521 (2000).

2000WO00/24744 W. Harris, C. H. Hill, and I. E. D. Smith (Hoffmann LaRoche), *PCT* WO 00/24744 (2000).

2000WO00/30646 P. Jakobsen, A. Hornemann, and E. Persson (Novo Nordisk), *PCT* WO 00/30646 (2000).

2000WO00/53588 M. Argedi, G. Manfredi, F. Rebasti, and G. Ripa, *PCT* WO 53588 (2000).

2000WO00/55162 F. Himmelsbach, E. Langkopf, S. Blech, B. Jung, T. Metz, and F. Solca (Boehringer-Ingelheim), *PCT* WO 00/55162 (2000).

2000ZNB443 W. S. Hamama, *Z. Naturforsch., Teil B*, 2000, **55**, 443.

2001AFF335 O. S. Moustafa and M. S. Abbady, *Afinidad*, 2001, **58**, 335.

2001B10095 J. J. Reddick, R. Nicewonger, and T. P. Begley, *Biochemistry*, 2001, **40**, 10095.

2001BKC311 H. A. Saad, H. Y. Moustafa, M. G. Assy, and M. A. Sayed, *Bull. Korean Chem. Soc.*, 2001, **22**, 311.

2001CHE1461 A. F. Pozharskii and A. V. Gulevskaya, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 1461.

2001CPL(349)146 C. Alves, M. Castilho, L. H. Mazo, M. Tabak, and A. B. F. da Silva, *Chem. Phys. Lett.*, 2001, **349**, 146.

2001EJO729 A. Star, I. Goldberg, and B. Fuchs, *Eur. J. Org. Chem.*, 2001, 729.

2001EJO1781 A. B. Eldrup, B. B. Nielsen, G. Haaima, H. Rasmussen, J. S. Kastrup, C. Christensen, and P. E. Nielsen, *Eur. J. Org. Chem.*, 2001, 1781.

2001EP1090644 C. M. Murray (Pfizer), *Eur. Pat.* 1090644 (2001).

2001H(54)359 Y. Kurasawa, S. Ohshima, Y. Kishimoto, M. Ogura, Y. Okamoto, and H. S. Kim, *Heterocycles*, 2001, **54**, 359.

2001H(54)619 F. Miyata, S. Yoshida, T. Yamori, and T. Katoh, *Heterocycles*, 2001, **54**, 619.

2001H(55)2413 E. Abdelghani, *Heterocycles*, 2001, **55**, 2413.

2001IJB195 M. S. A. El-Gaby, A. M. Sh. El-Sharief, Y. A. Ammar, Y. A. Mohamed, and A. A. El-Salam, *Indian J. Chem., Sect. B*, 2001, **40**, 195.

2001JA3584 H. Fenniri, P. Mathivanan, K. L. Vidale, D. M. Sherman, K. Hallenga, K. V. Wood, and J. G. Stowell, *J. Am. Chem. Soc.*, 2001, **123**, 3584.

2001JOM(630)67 A. Star, I. Goldberg, and B. Fuchs, *J. Organomet. Chem.*, 2001, **630**, 67.

2001J(P1)1241 B. L. Booth, I. M. Cabral, A. M. Dias, A. P. Freitas, A. M. Matos Beja, M. F. Proença, and M. Ramos Silva, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1241.

2001J(P1)2532 A. Al-Azmi, B. L. Booth, R. A. Carpenter, A. Carvalho, E. Marrelec, R. G. Pritchard, and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2532.

2001JMT(545)75 O. Eliás, L. Károlyházy, G. Stájer, F. Fülöp, K. Czakó, V. Harmath, O. Barabás, K. Keseru, and P. Mátyus, *J. Mol. Struct. Theochem*, 2001, **545**, 75.

2001MC78 G. L. Rusinov, P. A. Slepukhin, V. N. Charushin, and O. N. Chupakhin, *Mendeleev Commun.*, 2001, 78.

2001NJC1168 M. Le Baccon, F. Chuburu, L. Toupet, H. Handel, M. Soibinet, I. Deschamps-Olivier, J.-P. Barbier, and M. Aplincourt, *New J. Chem.*, 2001, **25**, 1168.

2001NN1049 W. J. Cummins, A. L. Hamilton, C. L. Smith, and M. S. J. Briggs, *Nucleos., Nucleot. Nucleic Acids*, 2001, **20**, 1049.

2001NN1823 K. S. Gudmundsson, Z. Wang, S. M. Daluge, and P. L. Feldman, *Nucleos., Nucleot. Nucleic Acids*, 2001, **20**, 1823.

2001PS(175)129 H. M. Moustafa, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2001, **175**, 129.

2001RCB1113 V. B. Sokolov, A. Yu. Aksinenko, and I. V. Martynov, *Russ. Chem. Bull.*, 2001, **50**, 1113.

2001S1299 M. Gohain, D. Prajapati, B. J. Gogoi, and J. S. Sandhu, *Synlett*, 2004, 1179.

2001S1861 M. M. Abdel-Khalik, S. M. Agamy, and M. H. Elnagdi, *Synthesis*, 2001, 1861.

2001T55 M. E. Ochoa, S. Rojas-Lima, H. Höpfl, P. Rodriguez, D. Castillo, N. Farfan, and R. Santillan, *Tetrahedron*, 2001, **57**, 55.

2001TA247 V. Santes, E. Gómez, V. Zárate, R. Santillan, N. Farfána, and S. Rojas-Limab, *Tetrahedron Asymmetry*, 2001, **12**, 247.

2001TL5981 A. V. Gulevskaya, D. V. Besedin, A. F. Pozharskii, and Z. A. Starikova, *Tetrahedron Lett.*, 2001, **42**, 5981.

2001USP6271228 E. B. Grossman (Pfizer), *US Pat.* 6271228 (2001).

2001WO01/29041 J. P. Dunn, D. M. Goldstein, W. Harris, I. E. D. Smith, and T. R. Welch (Hoffmann LaRoche), *PCT* WO 01/29041 (2001).

2001WO01/29042 L. P. Dunn, L. E. Fisher, D. M. Goldstein, W. Harris, C. H. Will, I. E. D. Smith, and T. R. Welch (Hoffmann LaRoche), *PCT* WO 01/29042 (2001).

2001WO2001/051492 W. P. Blackaby, R. T. Lewis, and L. J. Street (MSD), *PCT* WO 2001 051492 (2001).

2001WO64679 J. L. Adams, J. C. Boehm, R. F. Hall, and J. J. Taggart (Smithkline Beecham), *PCT* WO 01/64679 (2001).
2002ASJ312 B. K. Rai and P. Choudhary, *Asian J. Chem.*, 2002, **14**, 312 (*Chem. Abstr.*, 2002, **136**, 288193).
2002CC312 F. Boschetti, F. Denat, E. Espinosa, and R. Guilard, *Chem. Commun.*, 2002, 312.
2002CHE336 Yu. M. Volovenko and G. G. Dubinina, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2002, **38**, 336.
2002CL236 K. V. Subba Rao, B. Srinivas, A. R. Prasad, and M. Subrahmanyam, *Chem. Lett.*, 2002, 236.
2002CPB364 H. Shih, H. B. Cottam, and D. A. Carson, *Chem. Pharm. Bull.*, 2002, **50**, 364.
2002CPB922 T. Kaneko, R. S. J. Clark, N. Ohi, T. Kawahara, H. Akamatsu, F. Ozaki, A. Kamada, K. Okano, H. Yokohama, K. Muramoto, M. Ohkuro, O. Takenaka, and S. Kobayashi, *Chem. Pharm. Bull.*, 2002, **50**, 922.
2002DEP10111728 F. Pflücker, M. Schwarz, V. Scholz, and H. Neunhoeffer (Merck), *Ger. Pat.* 101 11728 (2002).
2002DEP10115921 R. Lock, W. Belzer, and W. Rall (Boehringer–Ingelheim), *Ger. Pat.* 101 15921 (2002).
2002EJC995 A. B. A. El-Gazzar, *Egypt. J. Chem.*, 2002, **45**, 995.
2002EJO1368 G. Kaupp and M. R. Naimi-Jamal, *Eur. J. Org. Chem.*, 2002, 1368.
2002H(56)291 Y. Kurasawa, I. Matsuzaki, W. Satoh, Y. Okamoto, and H. S. Kim, *Heterocycles*, 2002, **56**, 291.
2002H(58)359 Y. Kurasawa, J. Takizawa, Y. Maesaki, A. Kawase, Y. Okamoto, and H. S. Kim, *Heterocycles*, 2002, **58**, 359.
2002HAC108 W. W. Wardakhan and D. H. Fleita, *Heteroatom Chem.*, 2002, **13**, 108.
2002IJB1486 Y. A. Ammar, M. M. F. Ismail, M. S. A. El-Gaby, and M. A. Zahran, *Indian J. Chem., Sect. B*, 2002, **41**, 1486.
2002JCO501 R. Pérez, T. Beryozkina, O. I. Zbruyev, W. Haas, and C. O. Kappe, *J. Comb. Chem.*, 2002, **4**, 501.
2002J(P1)108 J. S. Northen, F. T. Boyle, W. Clegg, N. J. Curtin, A. J. Edwards, R. J. Griffin, and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 2002, 108.
2002J(P2)552 M. Antoine, H. Bernard, N. Kervarec, and H. Handel, *J. Chem. Soc., Perkin Trans. 2*, 2002, 552.
2002H(58)359 Y. Kurasawa, J. Takizawa, Y. Maesaki, A. Kawase, Y. Okamoto, and H. S. Kim, *Heterocycles*, 2002, **58**, 359.
2002JCCS217 H. A. A. Medien, *J. Chin. Chem. Soc.*, 2002, **49**, 217.
2002JHC551 Y. Kurasawa, A. Kawase, J. Takizawa, Y. Maesaki, E. Kaji, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2002, **42**, 551.
2002JHC571 Y. Tominaga, Y. Shigemitsu, and K. Sasaki, *J. Heterocycl. Chem.*, 2002, **39**, 571.
2002JOC4081 P. S. Athey and G. E. Kiefer, *J. Org. Chem.*, 2002, **67**, 4081.
2002JOC6097 F. Busqué, S. A. Hopkins, and J. P. Konopelski, *J. Org. Chem.*, 2002, **67**, 6097.
2002JKC581 S. U. Lee, J. H. Hur, H. S. Jung, H. S. Kim, and Y. Kurasawa, *J. Korean Chem. Soc.*, 2002, **46**, 581.
2002M79 A. M. Amer, M. El-Mobayed, A. M. Ateya, and T. S. Muhdi, *Monatsh. Chem.*, 2002, **133**, 79.
2002MC120 I. G. Abramov, V. V. Zhanderev, A. V. Smirnov, L. S. Kalandadze, M. E. Gashin, and V. V. Plakhtinskii, *Mendeleev Commun.*, 2002, 120.
2002MC157 A. V. Gulevskaya, A. F. Pozharskii, D. V. Besedin, and Z. A. Starikova, *Mendeleev Comm.*, 2002, 157.
2002MI10 O. V. Kolesnikov, V. P. Chernikh, and L. A. Shemchuk, *Ukraine. Visnik Farmatsii*, 2002, 10 (*Chem. Abstr.*, 2002, **138**, 187723).
2002MM2993 T. Yamamoto and B.-L. Lee, *Macromolecules*, 2002, **35**, 2993.
2002OL4073 C. Ausín, J.-A. Ortega, J. Robles, A. Grandas, and E. Pedroso, *Org. Lett.*, 2002, **4**, 4073.
2002OL4395 K. G. Rajeev, M. A. Maier, E. A. Lesnik, and M. Manoharan, *Org. Lett.*, 2002, **4**, 4395.
2002RJC1808 A. I. Vovk, L. V. Babii, and I. V. Murav'eva, *Russ. J. Gen. Chem. (Engl. Transl.)*, 2002, **72**, 1808.
2002SC989 A. A. Shalaby, M. M. El-Shahawi, N. A. Shams, and S. Batterjee, *Synth. Commun.*, 2002, **32**, 989.
2002SPH245 J. Cieplik, J. Pluta, and O. Gubrynowicz, *Sci. Pharm.*, 2002, **70**, 245.
2002T10137 P. Tapolcsányi, G. Krajsovszky, R. Andó, P. Lipcsey, G. Horváth, P. Mátyus, Z. Riedl, G. Hajós, B. U. W. Maes, and G. L. F. Lemière, *Tetrahedron*, 2002, **58**, 10137.
2002WO02/02584 S. Kumar, M. McDougall, S. Nampalli, and C. Neagu (Amersham Pharmacia Biotech), *PCT* WO 02/02584.
2002WO02/06209 H. Handel, H. Bernard, and M. Antoine, *PCT* WO 02/06209 (2002).
2002WO02/066482 H. Fenniri, *PCT* WO 02/066482 (2002).
2002WO02/076463 W. E. Bondinell, D. A. Holt, M. Lago, M. J. Neeb, and M. A. Semones (SmithKline Beecham), *PCT* WO 02/076463 (2002).
2002ZN(B)668 A. A. F. Wasfy, M. M. H. Arief, M. S. Amine, S. G. Donia, and A. A. Aly, *Z. Naturforsch., Teil B*, 2002, **57b**, 668.
2002ZNB946 O. Hampel, C. Rode, D. Walther, R. Beckert, and H. Goerls, *Z. Naturforsch., Teil B*, 2002, **57**, 946.
2003APH487 J. Cieplik, J. Pluta, and O. Gubrynowicz, *Acta Pol. Pharm.*, 2003, **60**, 487.
2003BKC1429 S. Youssif, S. El-Bahaie, and E. Nabih, *Bull. Korean Chem. Soc.*, 2003, **24**, 1429.
2003BMC2575 A. Ranise, A. Spallarossa, S. Schenone, O. Bruno, F. Bondavalli, A. Pani, M. E. Marongiu, V. Mascia, P. La Colla, and R. Loddo, *Bioorg. Med. Chem.*, 2003, **11**, 2575.
2003CPB630 T. Miyashita, M. Baba, S. Shigeta, K. Mori, and K. Shinozuka, *Chem. Pharm. Bull.*, 2003, **51**, 630.
2003CPL(375)605 N. Akai, S. Kudoh, and M. Nakata, *Chem. Phys. Lett.*, 2003, **375**, 605.
2003EJC11 G. A. Ahmed, H. Y. Mostafa, M. G. Assy, and N. S. Mansor, *Egypt. J. Chem.*, 2003, **46**, 11.
2003EJM719 M. G. Gebauer, C. McKinlay, and J. E. Gready, *Eur. J. Med. Chem.*, 2003, **38**, 719.
2003EJO1050 F. Chuburu, R. Tripier, M. Le Baccon, and H. Handel, *Eur. J. Org. Chem.*, 2003, 1050.
2003EJO3047 S. Develay, R. Tripier, F. Chuburu, M. Le Baccon, and H. Handel, *Eur. J. Org. Chem.*, 2003, 3047.
2003H(60)2457 C. Käpplinger, R. Beckert, J. Koci, G. Braunerova, K. Weisser, and H. Görls, *Heterocycles*, 2003, **60**, 2457.
2003JCD3704 A. M. Funston, K. P. Ghiggino, M. J. Grannas, W. D. McFadyen, and P. A. Tregloan, *J. Chem. Soc., Dalton Trans.*, 2003, 3704.
2003JHC837 Y. Kurasawa, W. Satoh, I. Matsuzaki, Y. Maesaki, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2003, **40**, 837.
2003JIC311 A. S. Saxena, A. Goel, and V. J. Ram, *J. Indian Chem. Soc.*, 2003, **80**, 311.
2003JMP540 E. R. Filho, A. M. Paixao Almeida, and M. Tabak, *J. Mass Spectrom.*, 2003, **38**, 540.
2003JMT(666)625 O. Elias, L. Karolyhazy, G. Horvath, V. Harmat, and P. Matyus, *J. Mol. Struct. Theochem*, 2003, **666–667**, 625–636.
2003JPP261569 K. Taguchi and S. Higuchi, *Jpn Pat.* 2003-261569 (2003).
2003MCL157 J. T. Saito, Y. Ueda, K. Harada, and K. Fukunishi, *Mol. Cryst. Liq. Cryst. (A)*, 2003, **407**, 157.
2003MI105 J. Cieplik, *Annales Universitatis Mariae Curie-Sklodowska, Sectio AA: Chemia*, 2003, **58**, 105.
2003NN2171 A. R. Porcari, R. G. Ptak, K. Z. Borysko, J. M. Breitenbach, J. C. Drach, and L. B. Townsend, *Nucleos., Nucleot. Nucleic Acids*, 2003, **22**, 2171.
2003PCB9094 L. M. Wilhelmsson, P. Sandin, A. Holmen, B. Albinsson, P. Lincoln, and B. Norden, *J. Phys. Chem. (B)*, 2003, **107**, 9094.

2003PJC1275 S. Tumkevicius and Z. Sarakauskaite, *Pol. J. Chem*., 2003, **77**, 1275.

2003PS(178)1667 K. M. H. Hilmy, R. M. Mohareb, A. El-Torgman, and Y. M. Sharawy, *Phosphorus, Sulfur Silicon Relat. Elem*., 2003, **178**, 1667.

2003RCB441 V. V. Gorunenko, A. V. Gulevsjkaya, and A. F. Pozharskii, *Russ. Chem. Bull*., 2003, **52**, 441.

2003RCB2457 M. Kidwai, R. Mohan, and S. Saxena, *Russ. Chem. Bull*., 2003, **52**, 2457.

2003S1377 S. Tumkevicius, Z. Sarakauskaite, and V. Masevicius, *Synthesis*, 2003, 1377.

2003S1739 N. Graveleau and T. Masquelin, *Synthesis*, 2003, 1739.

2003S2017 Y.-K. Yang and J. Tae, *Synthesis*, 2003, 2017.

2003SC3747 M. Kidwai, R. Mohan, and S. Rastogi, *Synth. Commun*., 2003, **33**, 3747.

2003STC295 Y. Xie, H. Jiang, C. Du, Y. Zhu, X. Xu, and Q. Liu, *Struct. Chem*., 2003, **14**, 295.

2003T4573 R. Tripier, F. Chuburu, M. Le Baccon, and H. Handel, *Tetrahedron*, 2003, **59**, 4573.

2003T7669 A. V. Gulevskaya, O. V. Serduke, A. F. Pozharskii, and D. V. Besedin, *Tetrahedron*, 2003, **59**, 7669.

2003TL3387 D. Loakes, D. M. Brown, S. A. Salisbury, M. G. McDougall, C. Neagu, S. Nampallic, and S. Kumarc, *Tetrahedron Lett*., 2003, **44**, 3387.

2003TL8995 S.-D. Cho, S.-Y. Song, Y.-D. Park, J.-J. Kim, W.-H. Joo, M. Shiro, J. R. Falck, D.-S. Shina, and Y.-Ji. Yoonc, *Tetrahedron Lett*., 2003, **44**, 8995.

2003TL9161 C. Banekovich, K. Mereiter, and B. Matuszczak, *Tetrahedron Lett*., 2003, **44**, 9161.

2003USP0199531 T. Wippke, J. Arnold, J Lawton, J. Starkey, J. P. Konopelski, S. Hopkins, and F. N. Sanchez, *US Pat.* 2003/0199531.

2003WO03/001887 S. T. Moe, P. J. Ala, E. Perola, C. H. Faerman, J. J. Clement, J. A. Ali, P. M. Will, S. A. Marchese, A. S. Magee, J. V. Gazzaniga, C. Farady, M. A. Navia, and P. R. Connelly (Essential Therapeutics), *PCT* WO 03/001887.

2003WO03/061385 H. An, H. Zhi, K. Smith, Y. Ding, and J.-L. Girardet (Ribapharm), *PCT* WO 03/061385.

2003WO03/062246 J. T. Repine (Warner-Lambert), *PCT* WO 03/062246 (2003).

2003WO03/082871 D. M. Goldstein, R. C. Hawley, A. S.-T. Lui, and E. B. Sjogren (Hoffmann La Roche), *PCT* WO 03/082871.

2004AXE1847 I. Saenger, H. W. Lerner, and M. Bolte, *Acta Crystallogr., Sect. E*, 2004, **60**, 1847.

2004BML3517 K. L. Smith, V. C. H. Lai, B. J. Prigaro, Y. Ding, E. Gunic, J.-L. Girardet, W. Zhong, Z. Hong, S. Lang, and H. An, *Bioorg. Med. Chem. Lett*., 2004, **14**, 3517.

2004BML4185 P. Sharma, N. Rane, and V. K. Gurram, *Bioorg. Med. Chem. Lett*., 2004, **14**, 4185.

2004CC588 F. Boschetti, F. Denat, E. Espinosa, J.-M. Lagrange, and R. Guilard, *Chem. Commun*., 2004, 588.

2004CCT413 M. El-Araby, R. S. Pottorf, and M. R. Player, *Comb. Chem. High Throughput Screening*, 2004, **7**, 413.

2004CC2212 E. A. Lewis, R. W. Boyle, and S. J. Archibald, *Chem. Commun*., 2004, 2212.

2004CHE194 V. F. Sedova and O. P. Shkurko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2004, **40**, 194.

2004CPA209 H. H. Abdel-Razik and S. B. Said, *Chem. Pap*., 2004, **58**, 209.

2004CPB675 T. Kaneko, R. S. J. Clark, N. Ohi, F. Ozaki, T. Kawahara, A. Kamada, K. Okano, H. Yokohama, M. Ohkuro, K. Muramoto, O. Takenaka, and S. Kobayashi, *Chem. Pharm. Bull*., 2004, **52**, 675.

2004DEP19501377 H. Ritter, D. E. H.-H. Licht, and P. Michaud (Deutsch-Französich Forschungsinstitut), *Ger. Pat.* 195 01377 (2004).

2004EJO5027 G. Claudon, N. Le Bris, H. Bernard, and H. Handel, *Eur. J. Org. Chem*., 2004, 5027.

2004FA987 F. Corelli, M. Botta, A. Lossani, S. Pasquini, S. Spaderi, and F. Focher, *Farmaco*, 2004, **59**, 987.

2004H(63)1393 S. Naya, K. Shibayama, and M. Nitta, *Heterocycles*, 2004, **63**, 1393.

2004HCO163 P. S. N. Reddy, P. Reddy, G. J. Reddy, and K. S. Rao, *Heterocycl. Commun*., 2004, **10**, 163.

2004IJB1561 O. M. Singh and F. Ahmed, *Indian J. Chem., Sect. B*, 2004, **43**, 1561.

2004JCD695 P. V. Solntsev, J. Sieler, A. N. Chernega, J. A. Howard, T. Gelbrich, and K. V. Domasevitch, *J. Chem. Soc., Dalton Trans*., 2004, 695.

2004JCD1153 P. V. Solntsev, J. Sieler, H. Krautscheid, and K. V. Domasevitch, *J. Chem. Soc., Dalton Trans*., 2004, 1153.

2004JCM341 S. Youssif, *J. Chem. Res*., 2004, 341.

2004JEP502 F. F. Solca, A. Baum, E. Langkopf, G. Dahmann, K.-H. Heider, F. Himmelsbach, and J. C. A. van Meel, *J. Pharmacol. Exp. Ther*., 2004, **311**, 502.

2004JHC647 M. A. Al-Shiekh, A. M. S. El-Din, E. A. Hafez, and M. H. Elnagdi, *J. Heterocycl. Chem*., 2004, **41**, 647.

2004JME4905 N. J. Curtin, H. C. Barlow, K. J. Bowman, A. H. Calvert, R. Davidson, B. T. Golding, B. Huang, P. J. Loughlin, D. R. Newell, P. G. Smith, and R. J. Griffin, *J. Med. Chem*., 2004, **47**, 4905.

2004JPB157 J. A. Acuña, M. D. Vázquez, M. L. Tascón, and P. Sánchez-Batanero, *J. Pharm. Biomed. Anal*., 2004, **36**, 157.

2004MI321 J. Cieplik, J. Pluta, and O. Gubrynowicz, *Boll. Chim. Pharm*., 2004, **243**, 321.

2004NN31 A. R. Porcari and L. B. Townsend, *Nucleos., Nucleot. Nucleic Acids*, 2004, **23**, 31.

2004OBC1019 M. A. Carvalho, T. M. Esteves, M. F. Proença, and B. L. Booth, *Org. Biomol. Chem*., 2004, **2**, 1019.

2004OBC2340 M. A. Carvalho, M. E. A. Zaki, Y. Álvares, M. F. Proença, and B. L. Booth, *Org. Biomol. Chem*., 2004, **2**, 2340.

2004OBC2538 B. G. Lawhorn, R. A. Mehl, and T. P. Begley, *Org. Biomol. Chem*., 2004, **2**, 2538.

2004OL2007 J. Nishida, Naraso, S. Murai, E. Fujiwara, H. Tada, M. Tomura, and Y. Yamashita, *Org. Lett*., 2004, **6**, 2007.

2004RCB846 V. V. Goryunenko, A. V. Gulevskaya, and A. F. Pozharskii, *Russ. Chem. Bull*., 2004, **53**, 846.

2004RJO1067 A. A. Shklyarenko, V. V. Yakovlev, and V. N. Chistokletov, *Russ. J. Org. Chem. (Engl. Transl.)*, 2004, **40**, 1067.

2004SC1399 C. Ma, S.-D. Cho, J. R. Falck, and D.-S. Shin, *Synth. Commun*., 2004, **34**, 1399.

2004SL1179 A. J. Thakur, P. Saikia, D. Prajapati, and J. S. Sandhu, *Synthesis*, 2001, 1299.

B-2004SOS(16)315 N. Haider and W. Holzer; in 'Science of Synthesis', Y. Yamamoto, Ed.; Georg Thieme Verlag, Stuttgart, 2004, vol 16, p. 315.

B-2004SOS(16)1337 T. Ishikawa; in 'Science of Synthesis', Y. Yamamoto, Ed.; Georg Thieme Verlag, Stuttgart, 2004, vol. 16, p. 1337.

B-2004SOS(17)55 H. Ulrich; in 'Science of Synthesis', S. M. Weinreb, Ed.; Georg Thieme Verlag, Stuttgart, 2004, vol. 17, p. 55.

2004T3763 S.-D. Cho, Y.-D. Park, J.-J. Kim, W.-H. Joo, M. Shiro, L. Esser, J. R. Falck, C. Ahn, D.-S. Shinb, and Y.-J. Yoon, *Tetrahedron*, 2004, **60**, 3763.

2004T6495 N. Haider and J. Käferbock, *Tetrahedron*, 2004, **60**, 6495.

2004TL2405 I. Devi, H. N. Borah, and P. J. Bhuyan, *Tetrahedron Lett*., 2004, **45**, 2405.

2004TL3059 E. A. Lewis, C. C. Allan, R. W. Boyle, and S. J. Archibald, *Tetrahedron Lett*., 2004, **45**, 3059.

2004USP0254205 K.-C. Luk and Z. Zhang (Hoffmann LaRoche), *US Pat.* 2004/0254205.

2004USP0204427 Y. Chen, A. Dermatakis, J.-J. Liu, K.-C. Luk, C. Michoud, and P. L. Rossman (Hoffmann LaRoche), *US Pat.* 2004/0204427.

2004WO041818 J. K. Pratt, D. A. Betebenner, P. L. Donner, B. E. Green, D. J. Kempf, K. F. McDaniel, and C. J. Maring (Abbott), *PCT* WO 2004/041818 (2004).

2004WO2004/041821 K.-C. Luk, P. L. Rossman, S. Scheiblich, and S.-S. So (Hoffmann LaRoche), *PCT* WO 2004/041821 (2004).

2004WO2004/041822 A. Dermatikis, M. M. Kabat, P. L. Rossman, and S.-S. So (Hoffmann LaRoche), *PCT* WO 2004/041822 (2004).

2004WO2004/047755 B. M. Fox, N. Furukawa, X. Hao, K. Iio,T. Inaba, S. M. Jackson, F. Kayser, M. Labelle, K. Li, T. Matsui, D. L. McMinn, M. Ogawa, S. M. Rubinstein, S. Sagawa, K. Sugimoto, M. Suzuki, M. Tanaka, G. Ye, A. Yoshida, and G. Zhang (Japan Tobacco), *PCT* WO 2004/047755 (2004).

2004WO065378 C. M. Biwersi, D. J. McNamara, J. T. Repine, P. L. Toogood, S. N. Vanderwel, and J. S. Warmus (Warner-Lambert), *PCT* WO 2004/065378.

2004ZNB424 U. Girreser, D. Heber, M. Rostaie-Gerylow, and M. Schuett, *Z. Naturforsch. Teil B*, 2004, **59**, 424.

2005AP590 K. Rehse and H. Gonska, *Arch. Pharm. (Weinheim, Ger.)*, 2005, **338**, 590.

2005BMC4385 L. A. McDermott, M. Simcox, B. Higgins, T. Nevins, K. Kolinsky, M. Smith, H. Yang, J. K. Li, Y. Chen, J. Ke, N. Mallalieu, T. Egan, S. Kolis, A. Railkar, L. Gerber, and K.-C. Luk, *Bioorg. Med. Chem.*, 2005, **13**, 4385.

2005BML1829 J. Kempson, W. J. Pitts, J. Barbosa, J. Guo, O. Omotoso, A. Watson, K. Stebbins, G. C. Starling, J. H. Dodd, J. C. Barrish, R. Felix, and K. Fischer, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1829.

2005BML2381 J. Feixas, M. P. Giovannoni, C. Vergelli, A. Gavaldà, N. Cesari, A. Graziano, and V. Dal Piaz, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2381.

2005BML3241 Z. Székelyhidi, J. Pató, F. Wáczek, P. Bánhegyi, B. Hegymegi-Barakonyi, D. Erös, G. Mészáros, Ferenc Hollósy, D. Hafenbradl, S. Obert, B. Klebl, G. Kéri, and L. Örfi, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3241.

2005CJC1056 H. S. Thokchom, A. D. Nongmeikapam, and W. S. Laitonjam, *Can. J. Chem.*, 2005, **83**, 1056.

2005EJI2044 C. Anda, A. Bencini, E. Berni, S. Ciattini, F. Chuburu, A. Danesi, C. Giorgi, H. Handel, M. Le Baccon, P. Paoletti, R. Tripier, V. Turcry, and B. Valtancoli, *Eur. J. Inorg. Chem.*, 2005, 2044.

2005EJO4167 S. Bräse, H. Wertal, D. Frank, D. Vidovic, and A. de Meijere, *Eur. J. Org. Chem.*, 2005, 4167.

2005H(65)403 T. Kaneko, F. Ozaki, R. S. J. Clark, Y. Komatsu, and K. Okano, *Heterocycles*, 2005, **65**, 403.

2005HCO317 K. N. Jayaveera, S. Sailaja, J. J. Reddy, and K. S. Rao, *Heterocycl. Commun.*, 2005, **11**, 317.

2005IC8197 S. Suzuki, Y. Morita, K. Fukui, K. Sato, D. Shiomi, T. Takui, and K. Nakasuji, *Inorg. Chem.*, 2005, **44**, 8197.

2005IJB834 K. G. Baheti, J. S. Jadhav, A. T. Suryavanshi, and S. V. Kuberkar, *Indian J. Chem., Sect. B*, 2005, **44**, 834.

2005IJQ(102)398 M. H. Liu, C. Chen, and Y.-S. Hong, *Int. J. Quantum Chem.*, 2005, **102**, 398.

2005JA8307 J. G. Moralez, J. Raez, T. Yamazaki, R. K. Motkuri, A. Kovalenko, and H. Fenniri, *J. Am. Chem. Soc.*, 2005, **127**, 8307.

2005JA9312 K. Shiraishi, A. Rajca, M. Pink, and S. Rajca, *J. Am. Chem. Soc.*, 2005, **127**, 9312.

2005JHC249 Y. Kurasawa, E. Kaji, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2005, **42**, 249.

2005JHC387 Y. Kurasawa and H. S. Kim, *J. Heterocycl. Chem.*, 2005, **42**, 387.

2005JHC413 A. V. Gulevskaya, S. V. Dang, and A. F. Pozharskii, *J. Heterocycl. Chem.*, 2005, **42**, 413.

2005JHC551 Y. Kurasawa, A. Kawase, J. Takizawa, Y. Maesaki, E. Kaji, Y. Okamoto, and H. S. Kim, *J. Heterocycl. Chem.*, 2005, **42**, 551.

2005JHC1223 V. R. Rao and M. M. Mohan Reddy, *J. Heterocycl. Chem.*, 2005, **42**, 1223.

2005JOC7042 F. Boschetti, F. Denat, E. Espinosa, A. Tabard, Y. Dory, and R. Guilard, *J. Org. Chem.*, 2005, **70**, 7042.

2005JMT(741)67 M. A. Farran, R. M. Claramunt, C. Lopez, E. Pinilla, M. R. Torres, and J. Elguero, *J. Mol. Struct. Theochem*, 2005, **741**, 67.

2005MC252 A. S. Fokin, Y. V. Burgart, V. I. Saloutin, and O. N. Chupakhin, *Mendeleev Commun.*, 2005, 252.

2005MI620 W. W. Lai, A. R. Millward, A. H. Francis, and P. G. Rasmussen, *PMSE Prepr.*, 2005, **92**, 620 (*Chem. Abstr.*, 2005, **142**, 420516).

2005S643 F. Stöckner, C. Käpplinger, R. Beckert, and H. Görls, *Synthesis*, 2005, 643.

2005T4237 P. Sharma, A. Kumar, N. Rane, and V. Gurram, *Tetrahedron*, 2005, **61**, 4237.

2005TL1433 D. Prajapati and A. J. Thakur, *Tetrahedron Lett.*, 2005, **46**, 1433.

2005USP002857 G. P. Pez, A. R. Scott, A. C. Cooper, and H. Cheng (Air Products), *US Pat.* 2005/002857 (2005).

2005WO2005/011597 T. Sim, H-S. Lee, R. Ren, Q. Ding, X. Wang, T. Uno, G. Zhang, Y. Liu, B. Li, L. Li, N. Gray, and S. You (IRM), *PCT* WO 2005/011597 (2005).

2005WO2005/037843 J. M. Jiminez, J. Green, H. Gao, Y.-C. Moon, G. Brenchley, R. Knegtel, and F. Pierard (Vertex Pharmaceuticals), *PCT* WO 2005/037843 (2005).

2005WO2005/085210 K. Ohmoto, K. Hisaichi, M. Okuma, and M. Tanaka (Ono), *PCT* WO 2005085210 (2005).

2005WO2005/091711 S. K. Agarwal, R. K. Tadiparthi, P. Aggarwal, and S. Shivkumar (Orchid Chem.), *PCT* WO 2005/091711.

2005WO2005094322 J. Q. Cheng and S. M. Sebti, *PCT* WO 2005094322 (2005).

2005WO2005099710 K. J. Hodgetts (Neurogen), *PCT* WO 2005/099710 (2005).

2005WO2005/115986 K. Amin, J. Broddefalk, H. Desfosses, E. Evertsson, Z. Liu, C. Milburn, K. Nilsson, M. Tremblay, C. Walpole, Z. Wei, and H. Yang, *PCT* WO 2005/115986.

2005WO2005/121142 T. Sakai, H. Kawasaki, H. Abe, K. Hayakawa, T. Iida, S. Kikuchi, T. Yamaguchi, T. Nanayama, H. Kurachi, M. Tamaru, Y. Hori, M. Takahashi, and T. Yoshida (Japan Tobacco), *PCT* WO 2005/121142.

2006BML1950 L. A. McDermott, B. Higgins, M. Simcox, K.-C. Luk, T. Nevins, K. Kolinsky, M. Smith, H. Yang, J. K. Li, Y. Chen, J. Ke, N. Mallalieu, T. Egan, S. Kolis, A. Railkar, L. Gerber, J.-J. Liu, F. Konzelmann, Z. Zhang, T. Flynn, O. Morales, and Y. Chen, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1950.

2006BML3537 D. Prajapati, M. Gohain, and A. J. Thakur, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3537.

2006BML4257 M. Sabat, J. C. VanRens, T. A. Brugel, J. Maier, M. J. Laufersweiler, A. Golebiowski, B. De, V. Easwaran, L. C. Hsieh, J. Rosegen, S. Berberich, E. Suchanek, and M. J. Janusz, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4257.

2006BML4400 S. R. Natarajan, D. D. Wisnoski, J. E. Thompson, E. A. O'Neill, and S. J. O'Keefe, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4400.

2006EJO4938 A. Singh, S. Chakraborty, and B. Ganguly, *Eur. J. Org. Chem.*, 2006, 4938.

2006EP1733729 L. Hilbrich, J. C. Gilbert, D. M. Humphreys, and A. Riedel, *Eur. Pat.*, 2006, 1733729.

2006H(68)2037 J. C. Van Rens, M. Sabat, T. A. Brugel, J. Maier, M. J. Laufersweiler, A. Golbiowski, S. Berberich, and B. De, *Heterocycles*, 2006, **68**, 2037.

2006IC767 F. A. Cotton, Z. Li, C. Y. Liu, C. A. Murillo, and D. Villagrán, *Inorg. Chem.*, 2006, **45**, 767.

2006JHC243 E. A. El Rady and M. A. Barsy, *J. Heterocycl. Chem.*, 2006, **43**, 243.
2006JHC1115 J. M. M. Mendoza, E. A. V. Lopez, R. M. Esparza, M. F. Alamo, and E. I. Klimova, *J. Heterocycl. Chem.*, 2006, **43**, 1115.
2006JME5363 M. P. Giovannoni, C. Vergelli, C. Biancalani, N. Cesari, A. Graziano, P. Biagini, J. Gracia, A. Gavalda, and V. Dal Piaz, *J. Med. Chem.*, 2006, **59**, 5363.
2006OL1545 K. Miyata, R. Tamamushi, A. Ohkubo, H. Taguchi, K. Seio, T. Santa, and M. Sekine, *Org. Lett.*, 2006, **8**, 1545.
2006PCB10651 L. Qiu, H.-M. Xiao, W.-H. Zhu, J.-J. Xiao, and W. Zhu, *J. Phys. Chem. B*, 2006, **110**, 10651.
2006S1093 J.-L. Gras and E. Taulier, *Synthesis*, 2006, 1093.
2006SC2693 S. B. Katiyar, A. Kumar, and P. M. S. Chauhan, *Synth. Commun.*, 2006, **36**, 2693.
2006SL1519 H. P. Dijkstra, C. Gaulon, D. Niculescu-Duvaz, and C. J. Springer, *Synlett*, 2006, 1519.
2006T652 O. V. Serduke, A. V. Gulevskaya, A. F. Pozharskii, Z. A. Starikova, and I. A. Profatilova, *Tetrahedron*, 2006, **62**, 652.
2006T6855 M. Argese, M. Brocchetta, M. De Miranda, P. Paoli, F. Perego, and P. Rossi, *Tetrahedron*, 2006, **62**, 6855.
2006TL2257 A. Mitchinson, W. P. Blackaby, S. Bourrain, R. W. Carling, and R. T. Lewis, *Tetrahedron Lett.*, 2006, **47**, 2257.
2006TL4437 S. El-Kazzouli, G. Lavecchia, S. Berteina-Raboin, and G. Guillaumet, *Tetrahedron Lett.*, 2006, **47**, 4437.
2006USP7094270 A. Chen, A. R. Daniewski, W. Harris, M. M. Kabat, E. A. Liu, J. J. Liu, K.-C. Luk, and C. Michoud, *US Pat.*, 2006, 7094270.
2006USP7115740 Y. Chen, A. Dermatakis, J.-J. Liu, K.-C. Luk, C. Michoud, and P. L. Rossoman, *US Pat.*, 2006, 7115740.
2006USP7141564 G. Brooks, D. T. Davies, G. E. Jones, R. E. Markwell, and N. D. Pearson, *US Pat.*, 2006, 7141564.
2006WO038112 V. M. Baragi, D. W. Brammer, C. L. Courtney, B. C. Korniski, and C. A. Lesch (Warner-Lambert), *PCT* WO 2006/038112 (2006).
2006WO065703 J. D. Oslob, J. Zhu, K. Barr, J. Crossrow, B. Raimundo, and H. Tanaka (Sunesis Pharmaceuticals), *PCT* WO 2006/065703 (2006).
2006WO135824 S. Chen, S. Ding, F. Yan, and P. G. Schultz, *PCT Int. Appl. WO*, 2006 2006/135824.
2007BMC2120 M. Bakavoli, M. Nikpour, M. Rahimizadeh, M. R. Saberi, and H. Sadeghian, *Bioorg. Med. Chem.*, 2007, **15**, 2120.
2007EJO1237 F. Stöckner, R. Beckert, D. Gleich, E. Birckner, W. Günther, H. Görls, and G. Vaughan, *Eur. J. Org. Chem.*, 2007, 1237.
2007EJO1324 M. A. Carvalho, S. Esperanca, T. Esteves, and M. F. Proenca, *Eur. J. Org. Chem.*, 2007, 1324.
2007H(71)141 T. Zs. Nagy, K. Lörincz, A. Csámpai, and A. Kotschy, *Heterocycles*, 2007, **71**, 141.
2007JHC1009 M. Dabiri, H. Arvin-Nezhad, H. R. Khavasi, and A. Bazgir, *J. Heterocycl. Chem.*, 2007, **44**, 1009.
2007JHC1253 M. Kidwai and K. Singhal, *J. Heterocycl. Chem.*, 2007, **44**, 1253.
2007JOC102 K. Miyata, R. Mineo, R. Tamamushi, M. Mizuta, A. Ohkubo, H. Taguchi, K. Seio, T. Santa, and M. Sekine, *J. Org. Chem.*, 2007, **72**, 102.
2007JOC466 A. Asadi, B. O. Patrick, and D. M. Perrin, *J. Org. Chem.*, 2007, **72**, 466.
2007JOC5046 M. Mizuta, K. Seio, K. Miyata, and M. Sekine, *J. Org. Chem.*, 2007, **72**, 5046.
2007SL595 D. Prajapati, K. J. Borah, and M. Gohain, *Synlett*, 2007, 595.
2007T1770 M. Dabiri, H. Arvin-Nezhad, H. R. Khavasi, and A. Bazgir, *Tetrahedron*, 2007, **63**, 1770.
2007T6915 M. Argese, M. Brocchetta, M. De Miranda, A. Ferraris, P. Dapporto, P. Paoli, and P. Rossi, *Tetrahedron*, 2007, **63**, 6915.

Biographical Sketch



J. M. Herbert carried out his PhD research with associate professor P.D. Woodgate and Dr. W.A. Denny at the University of Auckland, into the synthesis and reactions of perimidine derivatives. He then carried out postdoctoral research with Dr. R.J.K. Taylor at the University of East Anglia on the reactions of pyrylium salts, before moving into Industry. He is presently a team leader in the Isotope Chemistry and Metabolite Synthesis Department of sanofi-aventis in Alnwick, UK.

10.21
Tricyclic Systems: Central Carbocyclic Ring with Fused Five-membered Rings

A. Graham and M. Robinson
University of Wales Swansea, Swansea, UK
© 2008 Elsevier Ltd. All rights reserved.

10.21.1 Introduction **1136**
10.21.2 Theoretical Methods **1137**
10.21.3 Experimental Structural Methods **1139**
10.21.3.1 X-Ray, Neutron, and Electron Diffraction **1139**
10.21.3.2 Photoelectron Spectroscopy **1140**
10.21.3.3 IR Spectroscopy **1140**
10.21.3.4 UV and Visible Spectroscopy **1140**
10.21.3.5 ESR Spectroscopy **1141**
10.21.3.6 Mass Spectrometry **1141**
10.21.3.7 NMR Spectroscopy **1141**
10.21.3.7.1 Proton NMR spectroscopy 1141
10.21.3.7.2 Carbon-13 NMR spectroscopy 1142
10.21.4 Thermodynamic Aspects **1142**
10.21.5 Reactivity of Fully Conjugated Rings **1143**
10.21.5.1 Reactions of the Carbocyclic Ring **1143**
10.21.5.1.1 Unimolecular thermal and photochemical reactions 1143
10.21.5.1.2 Electrophilic attack 1143
10.21.5.1.3 Nucleophilic attack 1144
10.21.5.1.4 Reactions with a cyclic transition state 1145
10.21.5.2 Reactions of the Heterocyclic Ring **1145**
10.21.5.2.1 Thermal and photochemical reactions 1145
10.21.5.2.2 Electrophilic attack at nitrogen 1145
10.21.5.2.3 Electrophilic attack at carbon 1146
10.21.5.2.4 Nucleophilic attack at carbon 1148
10.21.5.2.5 Nucleophilic attack at sulfur 1148
10.21.5.2.6 Deprotonation 1148
10.21.5.2.7 Reduction 1148
10.21.5.2.8 Oxidation 1149
10.21.5.2.9 Reactions with cyclic transition states 1149
10.21.6 Reactivity of Nonconjugated Rings **1149**
10.21.6.1 Reactions of the Carbocyclic Ring **1149**
10.21.6.1.1 Thermal and photochemical reactions 1149
10.21.6.1.2 Reactions with carbenes 1150
10.21.6.1.3 Nucleophilic attack at carbon 1150
10.21.6.1.4 Dehydrogenation 1151
10.21.6.2 Reactions of the Heterocyclic Ring **1151**
10.21.6.2.1 Thermal and photochemical reactions 1151
10.21.6.2.2 Electrophilic attack at carbon 1152
10.21.6.2.3 Electrophilic attack at nitrogen 1152

10.21.6.2.4 Electrophilic attack at sulfur 1153
10.21.6.2.5 Nucleophilic attack at carbon 1154
10.21.6.2.6 Oxidation 1154
10.21.7 Reactivity of Substituents Attached to Ring Carbon Atoms 1155
10.21.7.1 In Conjugated Systems 1155
10.21.7.1.1 On the carbocyclic ring 1155
10.21.7.1.2 On the heterocyclic ring 1156
10.21.7.2 In Nonconjugated Systems 1158
10.21.8 Reactivity of Substituents Attached to Ring Heteroatoms 1158
10.21.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component 1159
10.21.9.1 Synthesis of Compounds with a Central Four-Membered Ring 1159
10.21.9.1.1 Compounds with one heteroatom in each heterocyclic ring 1159
10.21.9.1.2 Compounds with two heteroatoms in one heterocyclic ring and one in another 1160
10.21.9.1.3 Compounds with two heteroatoms in both heterocyclic rings 1161
10.21.9.1.4 Compounds with more than two heteroatoms in either ring 1162
10.21.9.2 Synthesis of Compounds with a Central Five-Membered Ring 1162
10.21.9.2.1 Compounds with one heteroatom in each heterocyclic ring 1162
10.21.9.2.2 Compounds with two heteroatoms in one heterocyclic ring and one in another 1163
10.21.9.2.3 Compounds with two heteroatoms in both heterocyclic rings 1165
10.21.9.2.4 Compounds with two or more heteroatoms in either heterocyclic ring 1166
10.21.9.3 Synthesis of Compounds with a Central Six-Membered Ring 1166
10.21.9.3.1 Compounds with one heteroatom in each heterocyclic ring 1166
10.21.9.3.2 Compounds with two heteroatoms in one heterocyclic ring and one in another 1181
10.21.9.3.3 Compounds with two heteroatoms in both heterocyclic rings 1185
10.21.9.3.4 Compounds with more than two heteroatoms in either ring 1187
10.21.9.4 Synthesis of Compounds with a Central Seven- or Larger-Membered Ring 1188
10.21.9.4.1 Compounds with one heteroatom in each heterocyclic ring 1188
10.21.9.4.2 Compounds with two heteroatoms in one heterocyclic ring and one in another 1190
10.21.9.4.3 Compounds with two heteroatoms in both heterocyclic rings 1190
10.21.9.4.4 Compounds with more than two heteroatoms in either ring 1190
10.21.10 Ring Syntheses by Transformations of Another Ring 1190
10.21.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available 1191
10.21.12 Important Compounds and Applications 1191
10.21.13 Further Developments 1193
References 1193

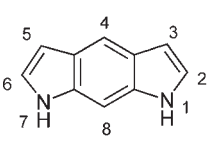
10.21.1 Introduction

This chapter reviews the systems where account is taken of the size of the central carbocyclic ring, the relative orientation of the fused five-membered heterocyclic rings, the types of heteroatoms, their number, and, in rings with more than one heteroatom, their relative situations.

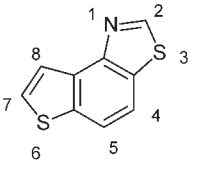
Since this area was last reviewed <1996CHEC-II(7)841>, a number of general reviews concerned with members of this class of compounds have appeared <1996CRV49, 1999CRV1863, 2000CRV3755, 2004CRV4891, 2004CRV5085> and some reviews are concerned with specific systems, such as benzodithiazolyls <1999CCR135>. Developments in the synthesis of the benzodipyrrole-containing antitumor agents CC-1065 and the related duocarmycins <1997CRV787, 2001CRV3893> and carbazole alkaloids such as staurosporine, furostifoline, arcyriaflavins A–D, and rebeccamycin <2001AHC1, 2002CRV4303> have been reviewed and detail recent strategies for the synthesis of both the carbocyclic and heterocyclic ring systems. Developments in the synthesis of

low-band-gap polymers based on cyclopentadithiophenes <1997CRV173> and the chemistry and applications of photochromic diarylethenes, which undergo reversible cyclization under ultraviolet (UV) irradiation to form benzodithiophenes, have also been reviewed <2000CRV1789, 2000CRV1685>. Electronic materials based on bistetrathiafulvalene (bis-TTFs) and the cyclopentadithiophene nucleus have also been reviewed <2004CRV4891, 2004CRV5085, 2005JMC1123>.

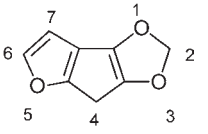
The nomenclature used here corresponds to that used in *Chemical Abstracts* which utilizes the style: cyclobuta-, penta-, benzo-, etc., di(heterocycle) if the fused rings are similar. Otherwise the form of 'heterocycle [cyclopenta-etc.] heterocycle' is used. Compound **1** is described as a benzodipyrrole rather than a pyrroloindole, the correct name being benzo[1,2-*b*:5,4-*b*′]dipyrrole. Compound **2** is named as a thieno[3,2-*e*′]benzothiazole and compound **3** is named as a furo[3′,2′]cyclopenta[1,2-*d*]-1,3-dioxole.



1



2

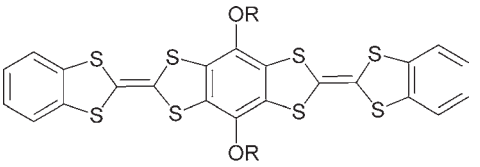


3

10.21.2 Theoretical Methods

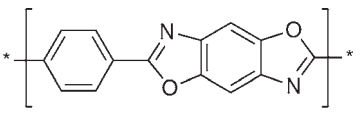
An *ab initio* study using the 6-31G* basis set was used to investigate the vibrational and electronic structures of a benzodithiophene and benzodifuran quinone as potential redox switches. The calculated and experimental data were found to be in good agreement <2000JEC24>.

Ab initio and PM3 semi-empirical methods have been used to optimize the geometry of the benzo[1,5-*c*:2,4-*c*′]-dithiolane **4** (R = H or Et). Electron density calculations predicted desymmetrization in the radical cation <1997PCB3665, 1997SM(86)1999>.



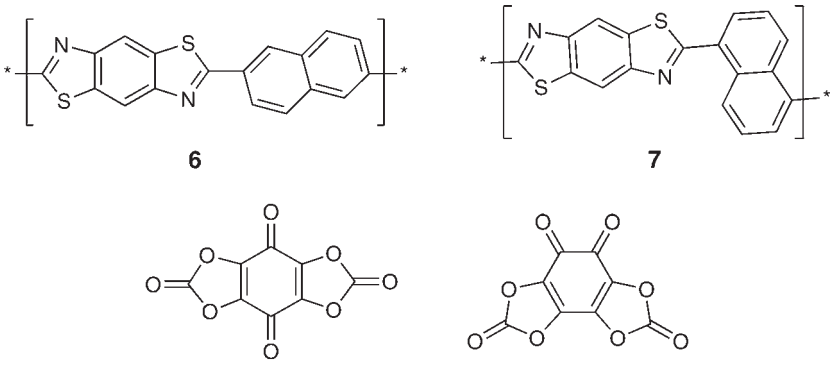
4

An AM1/ZINDO-CI approach was used to predict the optical adsorption spectra for a series of polybenzobisoxazoles such as **5**. The calculations indicated that the adsorption peaks should become blue-shifted as the torsion angle increases <2004PLM8871>.



5

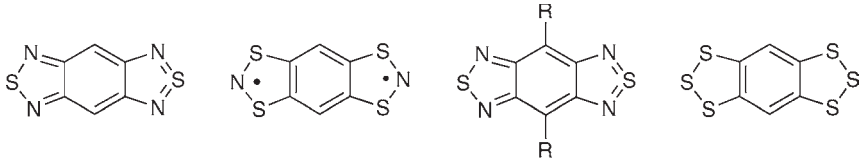
The torsion angle between the monomer units of poly(1,5-naphthalenebenzobisthiazole) **6** and poly(2,6-naphthalenebenzobisthiazole) **7** has been investigated using *ab initio* methods and was calculated to be 138° and 23°, respectively <2005PLM5630, 2005MM1711>. The dissociation enthalpies for polycyclic oxocarbons **8** and **9** have been calculated using DFT and the B3LYP/6-31+G* basis set. They were found to be stable with respect to dissociation to carbon monoxide <2003JOC1475>.



6 **7**

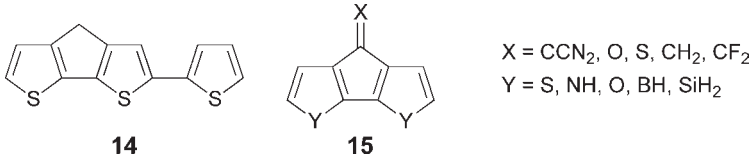
8 **9**

Ab initio calculations at the B3LYP level predicted that the electronic structure of benzo[1,2-*c*:4,5-*c*′]bis[1,2,5-thiadiazole] **10** adopts a less ylidic resonance than the linear sulfur diimide <1997JPO33>, and contains a hypervalent sulfur atom <1997T10169>. The electronic structure of the dithiazole diradical **11** has been calculated <1997JA12136>. A modified neglect of diatomic overlap (MNDO)-PM3 method was used to calculate the highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) gap of a series of benzo[1,2-*c*:3,4-*c*′]-bis[1,2,5]thiadiazoles **12** (R = Me, SPh, or *N*-methylpyrrole) <1996CM570>. The structures of radical cations and dications derived from benzo[1,2-*d*:4,5-*d*″]bis[1,2,3]trithiole **13** have been optimized using density functional theory (DFT) at the B3LYP/6-31G* level and the energies of the singlet and triplet states calculated <2003EJO4902>. The high-resolution vibronic structures of benzodithiophenes have been calculated at the B3LYP/6G** level and the calculated first ionization energies were found to correlate well with experimental data (see Section 10.21.3.2).



10 **11** **12** **13**

The interest in low-band-gap polymers which allow electrical conduction has stimulated investigations into conjugated polymeric systems based on cyclopentadiheterocycles. *Ab initio* calculations, using the B3P86/6-31G* basis set, on the electronic properties of sp^3-bridged oligothiophenes, such as **14**, have shown that the nature of the bridging atom has no effect on band gap energies other than that associated with the planarization of the system and that the rigidification improves electron-donating abilities <1999SM(101)602>. The electronic structures of dipyrroles, difurans, diboroles, and disiloles such as **15** have been calculated using semi-empirical methods <1999JOC7419, 2004MI335>.



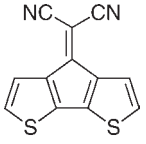
14 **15**

Ab initio MNDO-AM1 calculations on the electronic and geometric structures of a series of 4-substituted cyclopentadisiloles have been reported and the lowest HOMO–LUMO gaps were calculated for the most electron-withdrawing substituents <1996SM(79)115, 1997MI347, 2003MI467>. An *ab initio* Hartree–Fock (HF) and MNDO-AM1 calculation on the electronic structures of polycyclopentadisiloles gave similar results <2004MI335>.

A DFT calculation at the B3LYP level optimized the geometries of 4-substituted [2,1-*b*:3,4-*b*′]dithiophenes, dipyrroles, difurans, and diboroles **15**. The electronic structures were analyzed by the natural bond orbital (NBO) method with respect to their suitability as building blocks for conducting polymers, and it was calculated that materials with the most electron-withdrawing substituents had the lowest HOMO–LUMO gaps <1999JOC7419>.

The geometries of a series of 4-substituted cyclopentadithiophenes were optimized by DFT using the B3LYP/LANL2DZ basis set. The HOMO–LUMO gap was found to be dependent on the chalcogen substituent and the LUMO is stabilized by the larger chalcogens, resulting in smaller bandwidths <2004SM(140)127>.

A DFT calculation at the B3LYP level on a 4-substituted cyclopentadithiophene **16** predicted adsorption maxima 1 eV larger than experimental values <2002PCB9221>.

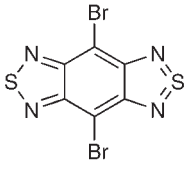


16

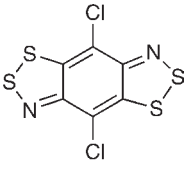
10.21.3 Experimental Structural Methods

10.21.3.1 X-Ray, Neutron, and Electron Diffraction

Early studies on benzo[1,2-*c*:3,4-*c*′]bisthiadiazoles found S–N bond distances to be of the order of 1.620 Å <1996CHEC-II(7)841>, and subsequent analysis has revealed that benzobisthiadiazoles adopt planar conformations <1996CM570>. Additional studies have shown that benzo[1,2-*c*:4,5-*c*′]bisthiadiazole **17** has S–N bond lengths of approximately 1.601 Å <1997T10169> and benzo [1,2-*d*:4,5-*d*″]bisthiadiazole **18** has S–N bond lengths of 1.638 Å <1997JA12136>.



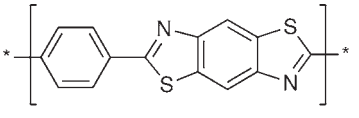
17



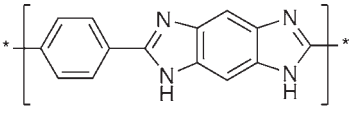
18

X-Ray methods have been used to determine the crystal structures of benzobisdithiazoles. These materials adopt a face-to-face dimer configuration with intermolecular S–S distances in the range 3.49–3.56 Å <2002CPL(357)385, 2002CPL(362)97, 2003SM(137)1263>.

The structures of polymers containing benzobisthiazoles **19**, benzobisoxazoles **5**, and benzobisimidazoles **20** are rigid-like materials with high specific strength, and have applications as organic light-emitting diodes (LEDs) <2001PSB559, 2002PSB1760, 2005PLM5630, 2000PLM9003>. For polybenzobisthiazoles, it was found that the torsion angles varied. Thus, the angle between the benzobisthiazole and phenyl rings in **19** was found to be 20.5° <2000PSB376>, while in poly(1,5-naphthalenebenzobisthiazole) **6** the torsion angle was found to be 115° <2005MM1711>. The torsion angle between the naphthyl and benzobisthiazole rings in poly(2,6-naphthalenebenzobisthiazole) **7** was found to be 23.2° <2005PLM5630>. The structures of polymers containing cyclopentadithiophenes have also been determined <1999CM2743, 2001CM1665>.



19



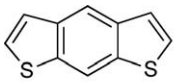
20

The crystal structures of the tricyclic ABC-ring fragments of the duocarmycin family of antitumor agents have been reported <1997JA4977>, as has the crystal structure of a diindocarbazole derivative <2000J(P2)2337>.

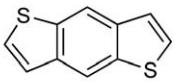
Few neutron or electron diffraction studies have been reported, although the neutron structure analysis of substituted poly(benzobisthiazole) and poly(benzobisoxazole) derivatives of **19** and **5** has been reported and the torsion angle between the benzobisthiazole and phenyl rings was shown to be 7.2° larger than that determined from X-ray methods <1999MM4010, 2001MM2012>.

10.21.3.2 Photoelectron Spectroscopy

Gas-phase photoelectron spectroscopy (PES) has been used in conjunction with theoretical calculations to investigate the hole-vibrational and electron-vibrational couplings in fused benzodithiophenes. The first ionization energies of benzo[1,2-*b*:5,4-*b*′]dithiophene **21** and benzo[1,2-*b*:4,5-*b*′]dithiophene **22** were found to be to be 7.585 and 7.573 eV, respectively <2006CEJ2073>.



21

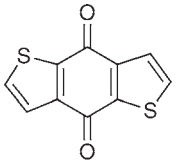


22

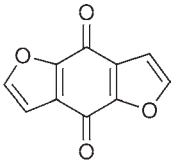
10.21.3.3 IR Spectroscopy

Infrared (IR) methods have been little used, other than for routine structural confirmation. IR spectroscopy has been employed to distinguish between linearly and angularly fused systems since adjacent hydrogens on angularly fused systems exhibit an out-of-plane deformation band at approximately 810 cm^{-1} <1998SM(92)25>. Fourier transform infrared (FTIR) methods have been used to examine the electronic adsorption bands of polymers based on 4-substitued cyclopentadithiophenes during doping processes <1998SM(92)25, 1999SM(101)123, 2001CM1665, 2002OL4535>. Hydrogen bonding in solid-state polybenzobisoxalozes leading to improved stability has been determined from FTIR methods <2001PSB559>.

Raman and near-visible IR spectroscopy has been used to characterize the radical cation of the bis-TTF **4** <1997PCB3665, 1997SM(86)1999>. FTIR has been used to confirm *ab initio* calculations for the radical cation of benzodithiophene **23** and benzodifuran **24**. The bisthiophene was found to adsorb at lower wavelengths than the bisfuran <2000JEC24>.



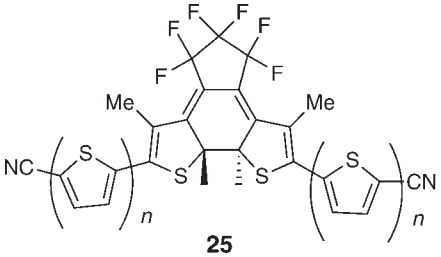
23



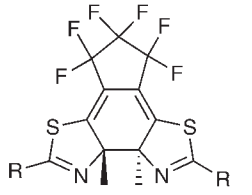
24

10.21.3.4 UV and Visible Spectroscopy

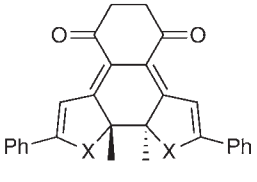
Few studies have been concerned only with UV spectra, although they have been used to study the photochromism of diarylethenes. Dithienylperfluorocyclopentenes cyclize to the closed-ring forms **25** with adsorption maxima between 588 and 653 nm <1997T12263>. Metal-complexed dithienylperfluorocyclopentenes have lower closed-form adsorption maxima of 604–630 nm <1999CEJ3285>. This is also seen with polymer-supported dithienylperfluorocyclopentenes which have closed-form adsorption maxima between 529 and 542 nm <2002MI279>. Dithiazolylperfluorocyclopentenes cyclize to give ring-closed forms **26** which have adsorption maxima in the range of 391–406 nm <1998T6627>. 2,3-Bis(thienyl)quinones and 2,3-bis(pyrrolyl)quinones **27** also display reversible photochromism and have adsorption maxima around 580 nm. 2,3-Bis(furanyl)quinones have lower adsorption maxima of 532 nm <2001JA7703>.



25
n = 0–2



26
R = Me, Ph, or 4-$MeOC_6H_4$



27
X = S, O, NMe

Cyclopentadithiophenes have adsorption maxima in the range 217–255 nm with more conjugated systems adsorbing at higher values. Thus, polymeric cyclopenta[1,2-*b*:3,4-*b*′]dithiophenes have adsorption maxima between 500 and 640 nm depending upon substituents and polymer length <1999SM(101)123, 2001SM(119)99, 2001CM1665, 2003MM2705>. The increase in adsorption maximum compared to the monomer is attributed to increased conjugation in the polymeric material <2003JOC9813, 2003SM(135)85>. Benzo[1,2-*c*:4,5-*c*′]bis[1,2,5-thiadiazole] **10** has an adsorption maximum at 523 nm and substituents on the benzene ring shift this to higher wavelengths <1997T10169>. Benzodithiophene **23** and benzodifuran **24** adsorb at 339 and 313 nm, respectively <2000PLM9003>. Data for a series of poly-*p*-phenylbenzobisthiazoles derivatives of **19** and diazoles have also been reported <2001PSB559, 2002PSB1760, 2004PLM459>. The interconversion of the oxidized and reduced forms of diindolocarbazoles have also been studied using UV spectroscopy <2000J(P2)2337>.

10.21.3.5 ESR Spectroscopy

Electron spin resonance (ESR) methods have been used to observe the formation of the radical cations and dications of benzo[1,2-*d*:4,5-*d*′]bis[1,2,3]trithiole **13** and benzo[1,2-*d*:4,5-*d*′]bis[1,2,3]dithiazole **17**, and the experimental results confirm the *ab initio* calculations performed <2003EJO4902, 1997JA12136>. ESR has also been used to confirm the formation of superoxides upon photolysis of aryl benzobisthiazoles and aryl benzobisoxazoles in the presence of molecular oxygen <2003MM4699>.

10.21.3.6 Mass Spectrometry

In the great majority of examples, mass spectral data have been used only to establish the molecular ions or for elemental analysis. Extended cyclopentadithiophene, benzobisoxazole, and benzobisthiazole systems have been shown to exhibit doubly charged parent ions <2002OL4535, 2003MM2705, 2003MM4699>.

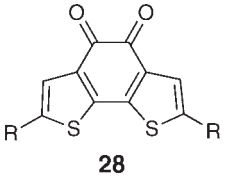
Gas chromatography–mass spectrometry (GC–MS) has been used to identify the fragments formed upon photolysis of aryl benzobisthiazoles and aryl benzobisoxazoles. It was shown that both compounds undergo different chemical reactions when photolyzed in the solid state with the aryl benzobisthiazole having greater photostability <2003MM4699>.

10.21.3.7 NMR Spectroscopy

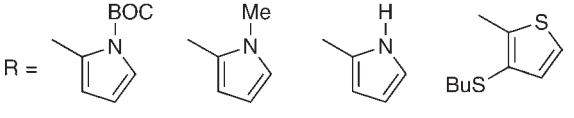
Nuclear magnetic resonance (NMR) methods are routinely used for structural confirmation and a number of the papers referred to in this chapter contain ^{1}H NMR data in addition to ^{13}C NMR data.

10.21.3.7.1 Proton NMR spectroscopy

The methylene protons in cyclopentadithiophenes absorb at $\delta = 6.36$–6.52 ppm <1996CHEC-II(7)841>, and subsequent studies have shown that the methylene protons in 4-substituted cyclopentadithiophenes absorb at slightly higher δ values <1999SM(102)1000, 2002OL4535>. In α-substituted benzo[2,1-*b*:3,4-*b*′]dithiophene-4,5-diones **28**, the methylene protons absorb around $\delta = 7.32$–7.68 ppm <2003SM(135)85>.

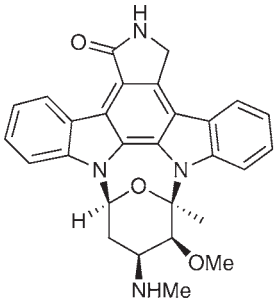


28

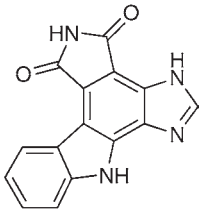


The chemical shifts and coupling constants have been determined for the antifungal agent tjipanazole A (see Section 10.21.12) and a derivative <1998MI723>. NMR methods have been used to verify the formation of the radical cation in a benzo[1,2-*d*:4,5-*d*′]bis-1,2,3-trithiole **13** which is supported by theoretical calculations

<2003EJO4902>. The proton shifts and coupling constants for several benzodiindole alkaloids such as staurosporine **29** have been tabulated <2004JNP783, 1999JNP959>. ^{1}H NMR data for the indolobenzopyrrole antitumor agent granulatamide **30** have also been reported (see Section 10.21.12) <1998JOC9850>.



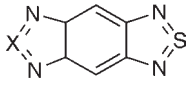
Staurosporine
29



Granulatamide
30

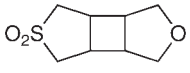
10.21.3.7.2 Carbon-13 NMR spectroscopy

^{13}C NMR spectroscopy is used in conjunction with proton NMR methods for routine structural analysis. The ^{13}C spectra of benzobisdithiazoles **31** have been reported, and when X = Se the adjacent carbon atoms appear at slightly higher chemical shift values than for the sulfur analogue <1997T10169>.

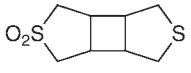


X = Se, S
31

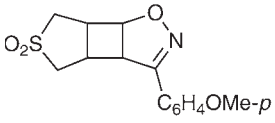
The ^{13}C NMR data for a series of tricyclic sulfolanes **32–36** have been reported, and it was found that carbons α and β to the sulfur are generally unaffected by nature of the adjacent fused ring and resonate at 53–55 ppm and 33–36 ppm respectively <1999J(P1)605>. The ^{13}C NMR data for staurosporine **29** and related alkaloids <1999JNP959, 2004JNP783>, and the granulatamide alkaloids such as **30** have been reported <1998JOC9850>.



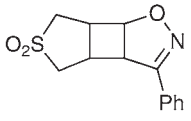
32



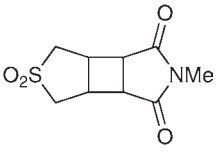
33



34



35

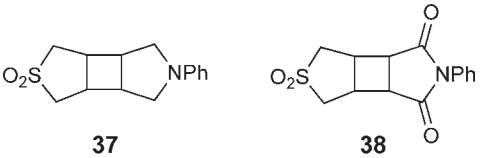


36

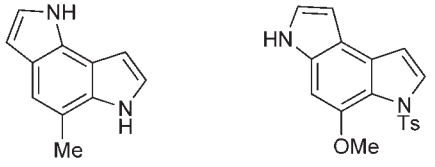
10.21.4 Thermodynamic Aspects

Given the great diversity of systems, trends are difficult to correlate. Generally, melting points increase with increasing ring sizes. Thus, benzodiheterocycles melt at higher temperatures than cyclopentadiheterocycles and cyclobutadiheterocycles. Substitution on either the fused or central rings affects the melting point. The temperature at which a compound melts is dependent upon the substituent, the type of heteroatoms present, their number, and, in compounds with more than one heteroatom, their relative situations. The greater the opportunity for intramolecular attractions and π-stacking, the greater the associated stability and hence an increase in melting points. For example, the tricyclic sulfolane **37** has an m.p. of 132–135 °C, whereas the corresponding imide **38** has an m.p. of 310–315 °C <1999J(P1)605>. This trend is

also seen with benzodipyrroles where 5-methyl-1,6-dihydrobenzo[1,2-*b*:3,4-*b*′]dipyrrole **39** has an m.p. of 149–151 °C and 4-methoxy-3-tosyl-3,6-dihydrobenzo[1,2-*b*;4,3-*b*′]dipyrrole **40** has an m.p. of 73–74 °C <1996JOC5804>.

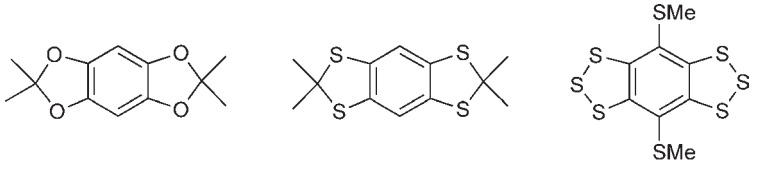


37 **38**



39 **40**

Cyclopentadithiophene systems melt between 74 and 115 °C, dependent upon the relative position of the sulfur atoms <1996CHEC-II(7)841>. Benzo[1,2-*b*:4,5-*b*′]dithiophene **22** has an m.p. of 196–197 °C <1996T13227>, which is much higher than that reported for the analogous angularly fused system <1996CHEC-II(7)841>. The benzobisdioxole **41** has an m.p. of 119–122 °C, and the dithiole analogue **42** has a higher m.p. of 145–147 °C <2002JOC4635>. The more substituted benzobistrithiole **43** has an m.p. of 208–210 °C <1995T2533>.



41 **42** **43**

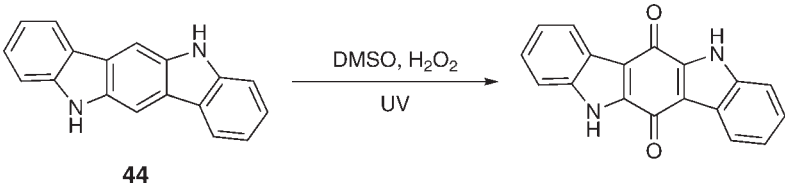
Many of the naturally occurring tricyclic systems such as the indolocarbazole alkaloids, viz. the arcyriaflavins, rebeccamycins, and staurosporines, tend to decompose around 300 °C <1999JOC4697, 2000JOC7541>. Systems that contain a large number of heteroatoms also decompose at high temperatures. For example, benzobisthiadiazloes **31** decompose around 280 °C, but when the sulfur atom is exchanged for selenium the decomposition temperature rises to about 300 °C <1996CM570, 1997T10169>.

10.21.5 Reactivity of Fully Conjugated Rings

10.21.5.1 Reactions of the Carbocyclic Ring

10.21.5.1.1 Unimolecular thermal and photochemical reactions

Indolo[3,2-*b*]carbazole **44** undergoes a photochemically induced oxidation in the presence of hydrogen peroxide and moderate heat to give the corresponding quinone which is also produced by oxidation with chromium trioxide (Equation 1) <2002T1443>.



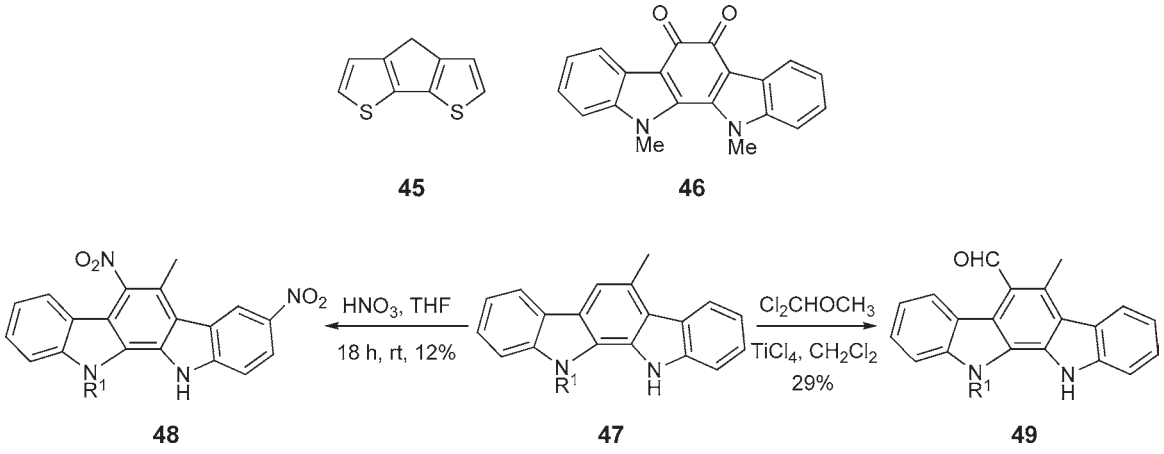
44

(1)

10.21.5.1.2 Electrophilic attack

Various ring systems, such as **45**, undergo metallation on reaction with organolithium bases and the resulting anions can be trapped with a range of electrophiles to give substituted products <1998JA13453, 2001RJC1751,

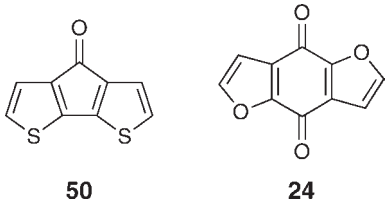
2002JMC2597>. *N,N*-Dimethylindolocarbazole is oxidized to the corresponding dione **46** in 48% yield on stirring in dichloromethane in the presence of catalytic quantities of vanadyl acetylacetonate ($VO(acac)_2$) and *tert*-butyl hydroperoxide <1996JOC413>. A related indolocarbazole derivative also gives the dione in 32% yield on reaction with 85% *m*-chloroperbenzoic acid (MCPBA). Indolocarbazole **47** (R^1 = 4-*O*-methyl-β-D-glucopyranosyl) is nitrated under standard conditions to produce the dinitro compound **48** as the major product, and is formylated using dichloromethyl methyl ether in the presence of titanium(IV) chloride as the Lewis acid to give **49** <2004BMC1955> (**Scheme 1**).



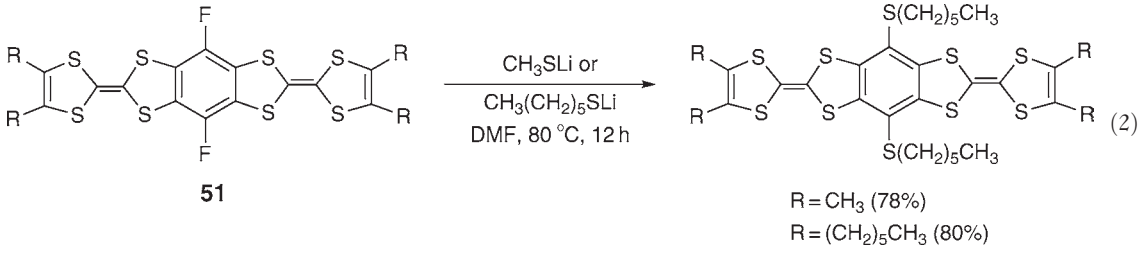
Scheme 1

10.21.5.1.3 Nucleophilic attack

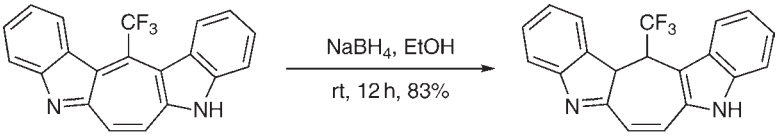
4*H*-Cyclopenta[2,1-*b*:3,4-*b*′]dithiophen-4-one **50** and benzo[1,2-*b*:4,5-*b*′]difuran-4,8-dione **24** have typical carbonyl reactivity and undergo the expected nucleophilic addition chemistry to produce functionalized materials <2000JOC2577, 2001J(P1)740, 2003CC2548, 2003MM2705, 2004CL156>.



Fluorinated bis(tetrathiafulvalenes), such as **51** (R = CH_3 or $(CH_2)_5CH_3$), undergo double *ipso*-substitution on reaction with thiolate anions in oxygen-free dimethylformamide (DMF) to produce the substitution products (Equation 2) <1995JA9995>.



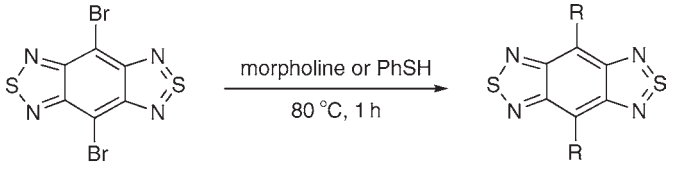
Cycloheptindole derivative **52** (Section 10.21.9.4.1(iv)) is reduced with sodium borohydride to give **53**, and also adds deuterium oxide at the activated double bond (Equation 3) <2000T1911>.



(3)

52 **53**

The nonclassical hererocycle **17** undergoes nucleophilic substitution reactions with morpholine and thiophenol at elevated temperatures to produce the corresponding disubstituted heterocycles (Equation 4) <1997T10169>.



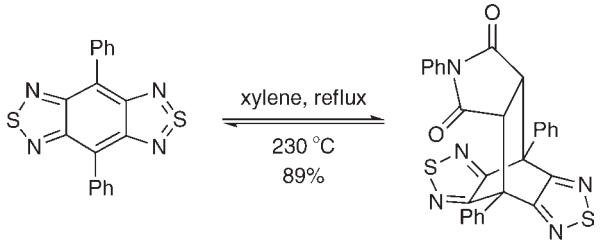
(4)

17

R = $N(CH_2)_4O$ (10%)
R = SPh (11%)

10.21.5.1.4 Reactions with a cyclic transition state

The nonclassical benzobis(thiadiazole) **54** undergoes Diels–Alder reaction when heated with *N*-phenylmaleimide in refluxing xylene to produce the 1:1 cycloadduct **55** in 89% yield (Equation 5) <1997T10169>. The cycloadduct reverts to starting materials by a retro-Diels–Alder reaction at its decomposition point (>230 °C).



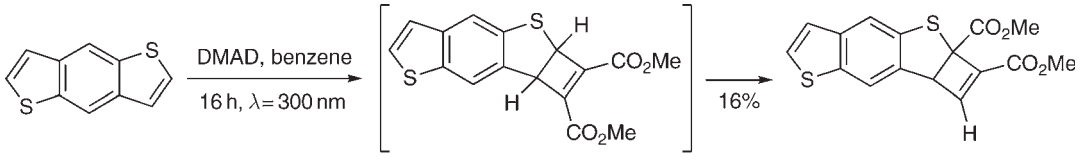
(5)

54 **55**

10.21.5.2 Reactions of the Heterocyclic Ring

10.21.5.2.1 Thermal and photochemical reactions

Benzo[1,2-*b*:4,5-*b*′]dithiophene **22** undergoes photochemical [2π+2π] cycloaddition with electron-deficient butadiynes on irradiation at 300 nm to produce photoadducts in low yields. The reaction with dimethyl acetylenedicarboxylate proceeds directly to produce the secondary photoadduct **56** (Equation 6) <2003JOC8258>.



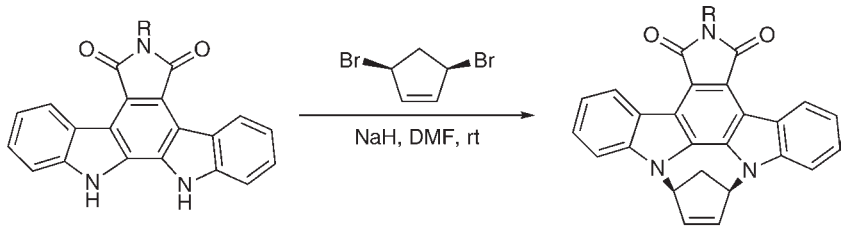
(6)

22 **56**

10.21.5.2.2 Electrophilic attack at nitrogen

The conformation of the rebeccamycin class of indolocarbazoles, which contain flexible glycoside substituents, has been investigated using a range of analogues such as **57** (where R = glycoside) <1999JOC5670, 2000JOC7541>.

Analogues related to K-252a, which contain a carbocyclic substituent, have been synthesized by the reaction of the indolocarbazole unit with *cis*-dibromocyclopentene (Equation 7) <2005OBC2953>.

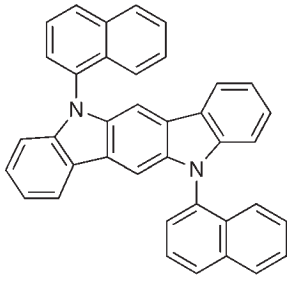


57

R = Bn (89%)
R = H (23%)
R = 4-MeOC$_6$H$_4$CH$_2$ (73%)

(7)

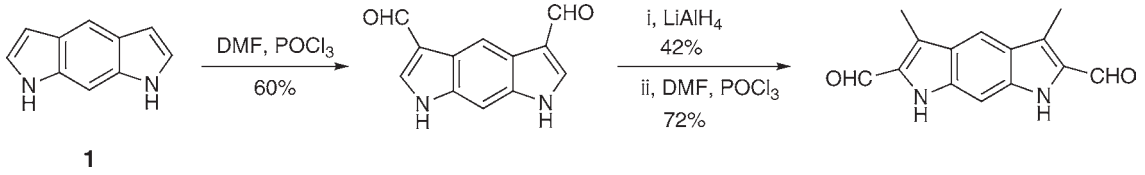
The novel indolo[3,2-*b*]carbazole compound **58** has been prepared in good yield by an Ullmann condensation reaction of 5,11-dihydroindolo[3,2-*b*]carbazole with 1-iodonaphthalene. The product was found to exist in two isomeric forms, *cis* and *trans*, attributable to the hindered rotation of the bonds binding the naphthyl groups <1999JA5097>.



58

10.21.5.2.3 Electrophilic attack at carbon

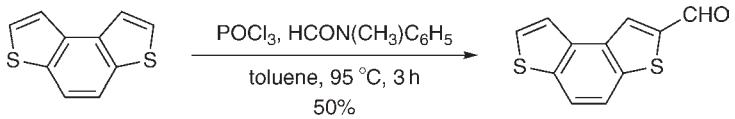
Benzodipyrrole **1** is selectively formylated at the 3- and 6-positions by a Vilsmeier–Haack reaction to produce 3,6-diformylbenzodipyrrole which is reduced by lithium aluminium hydride to give 3,6-dimethylbenzodipyrrole. This can also undergo subsequent Vilsmeier–Haack formylation to afford the 2,5-dialdehyde (**Scheme 2**) <2005AGE4053>.



1

Scheme 2

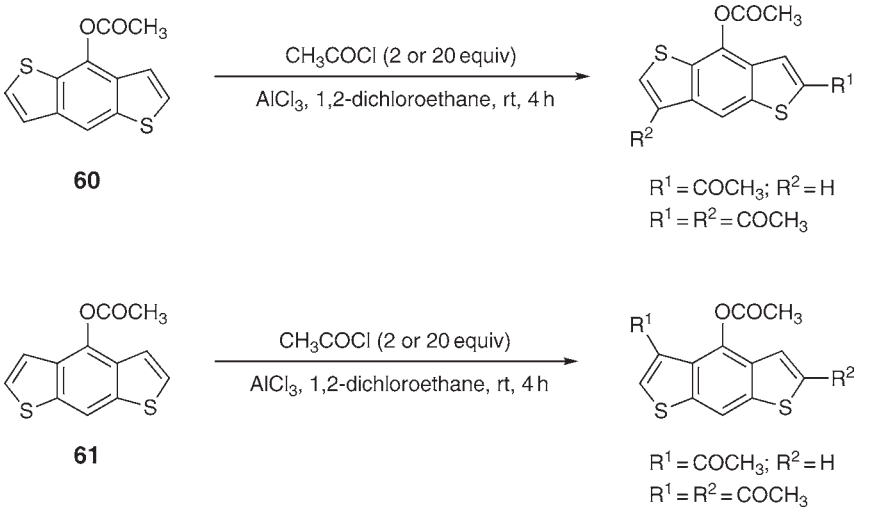
Benzo[1,2-*b*;4,3-*b*′]dithiophene **59** undergoes monoformylation using the Vilsmeier reagent in toluene (Equation 8) <2000CC1139, 2001CM3906>.



59

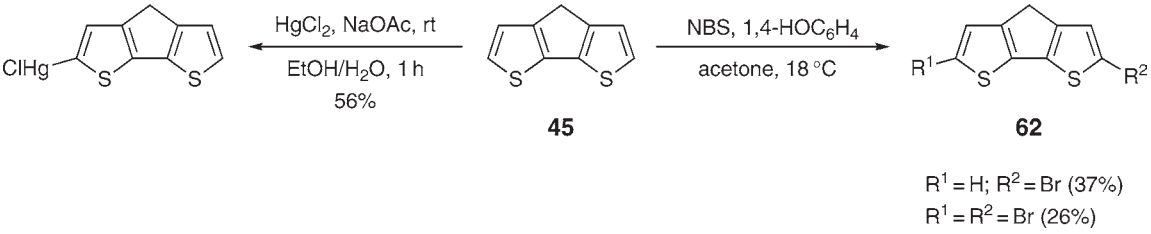
(8)

4-Acetoxybenzo[1,2-*b*:4,5-*b*′]dithiophene **60** and the isomeric 4-acetoxybenzo-[1,2-*b*:5,4-*b*′]dithiophene **61** are acylated using 2 equiv of acetyl chloride under typical Friedel–Crafts conditions to give the 2-acetyl derivatives (Equation 9). The diacetyl derivatives from each dithiophene series are prepared by Friedel–Crafts acetylation using a large excess of acetyl chloride to produce the unsymmetrical disubstituted compounds. Acetylation is thought to occur initially at C-2 and then at the carbon β to the second sulfur atom <1998JME4658>.



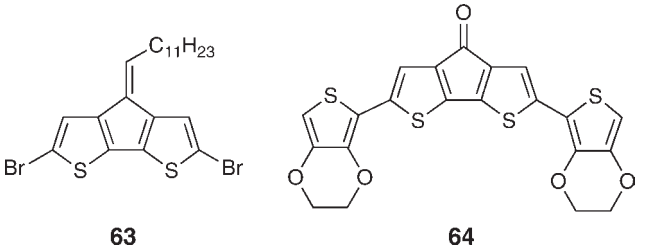
(9)

The unsubstituted cyclopenta[2,1-*b*:3,4-*b*′]dithiophene, **45**, undergoes both mono- and dibromination on reaction with *N*-bromosuccinimide (NBS) in the absence of light to give a mixture of brominated products, such as **62**, or 2-chloromercuration on reaction with mercuric chloride (**Scheme 3**) <1999T14985>. Alkyl-substituted cyclopenta[2,1-*b*:3,4-*b*′]dithiophene derivatives of **45** undergo efficient bromination under similar conditions to give the dibrominated compounds in high yield <2003MM2705>.



Scheme 3

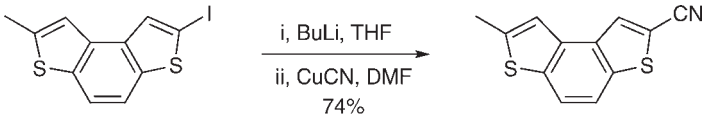
Transition metal-catalyzed polymerizations have been reported to give high-purity, regioregular poly-3-alkylthiophenes suitable for use in electronic devices. Thus, the Negishi protocol using a nickel catalyst and Rieke zinc was employed for the polymerization of **63** to produce the product as a low molecular weight polymer <2003CC2548>.



The related polythiophene **64** has been produced in 63% yield by a Stille coupling from 2-(tributylstannyl)-3,4-(ethylenedioxy)thiophene and 2,6-dibromo-4*H*-cyclopenta[2,1-*b*:3,4-*b*′]dithiophen-4-one catalyzed by $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ in refluxing toluene <2004CM3667>.

10.21.5.2.4 Nucleophilic attack at carbon

2-Iodo-7-methylbenzo[1,2-*b*:4,3-*b*′]dithiophene **65** undergoes nucleophilic substitution on reaction with copper cyanide in DMF to produce the nitrile derivative **66** (Equation 10) <1997TL457>.



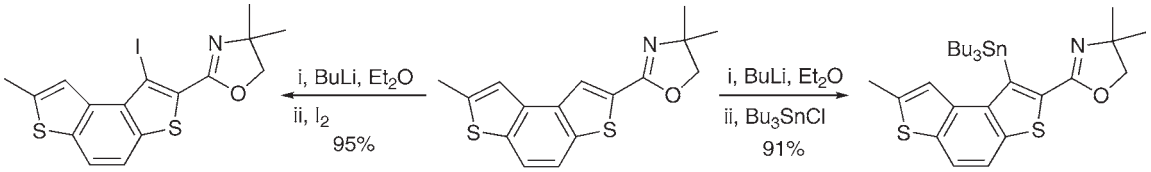
65 **66** (10)

10.21.5.2.5 Nucleophilic attack at sulfur

No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

10.21.5.2.6 Deprotonation

Various heterocyclic nuclei undergo metallation on exposure to organolithium bases to produce lithiated intermediates which have been trapped with a range of electrophiles such as iodine, alkyl disulfides, or aldehydes <1998CC1233, 2003SM(135)107, 2003T6481, 2005JA11620>. The strong *ortho*-directing nature of the oxazoline moiety has been used to generate the organolithium species of 2-methylbenzo[1,2-*b*:4,3-*b*′]dithiophene **67** which is subsequently trapped to generate the iodo- or tributylstannyl derivatives **68** and **69** (**Scheme 4**) <1997JOC4465, 1997TL457>. Organolithium species are commonly transmetallated and used in transition metal-mediated coupling reactions <1998AGE2484, 2001SM(119)99, 2002OL4535, 2005JMC1123>.

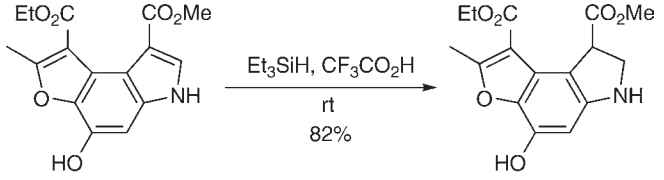


68 **67** **69**

Scheme 4

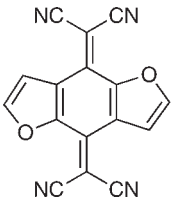
10.21.5.2.7 Reduction

The furoindole **70** is selectively reduced in high yield to the corresponding unstable, air-sensitive furoindoline **71** by ionic hydrogenation with triethylsilane in trifluoroacetic acid (TFA) (Equation 11) <2001OL1343>.

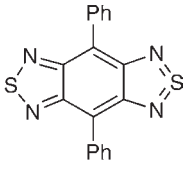


70 **71** (11)

The electrochemical properties of 4,8-bis(dicyanomethylene)-4,8-dihydrobenzo[1,2-*b*:4,5-*b*′]difuran **72** have been investigated by cyclic voltammetry in the search for new materials with enhanced conducting properties <2000JOC2577>. Upon single-electron reduction the central quinonoid ring gains the aromatic stability of benzene, whereas the fused heterocyclic part loses the aromaticity of the furan nucleus.



72

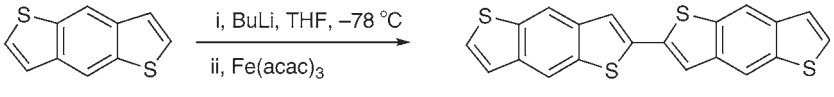


54

Cyclic voltammetry of nonclassical heterocycles, such as **54**, shows two reversible, one-electron reduction waves <1997T10169, 1996CM570>. The first reduction potentials of these heterocycles are comparable to those of *para*-benzoquinone indicating their high electron affinity. The high electron affinity of **54** is attributable to the 14π electron ring system containing a hypervalent sulfur atom, which is thought to generate a more stable Kekulé-type thiadiazole upon accepting an electron. The selenadiazole analogue shows higher reduction potentials than **54** due to the lower LUMO level.

10.21.5.2.8 Oxidation

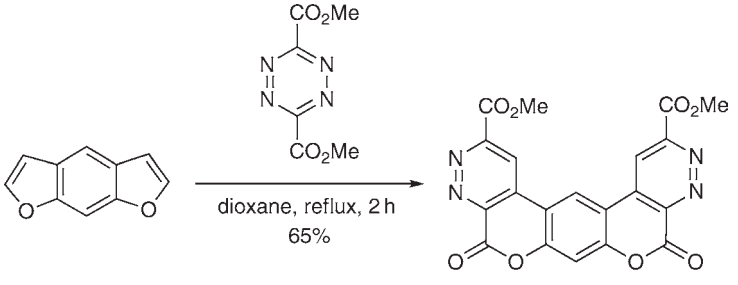
Various thiophene-containing heterocycles, such as benzodithiophenes **21** and **22**, undergo oxidative coupling to produce the dimeric compound on exposure to lithium bases and metal salts (Equation 12) <2001ACR359, 2003SM(135)107, 2005JMC1123>. The dimer has been shown to undergo highly reversible oxidation in cyclic voltammetry experiments. Various other related heterocyclic nuclei have been shown to undergo reversible electrochemical oxidation <2001J(P1)740, 2004CL156, 2004CM3667, 2005JA614, 2005JOC10569>.



22 (12)

10.21.5.2.9 Reactions with cyclic transition states

The benzodifuran **73** undergoes Diels–Alder cycloaddition with 3,6-dimethoxycarbonyl-1,2,4,5-tetrazine to afford the pyridazino-psoralen derivative **74** in good yield (Equation 13). It is proposed that the product arises through a two-step process in which the cycloaddition is accompanied by opening of the furan ring with concomitant expansion to a pyrone ring upon intramolecular transesterification <2000JHC907, 2005T4805>.



73 74 (13)

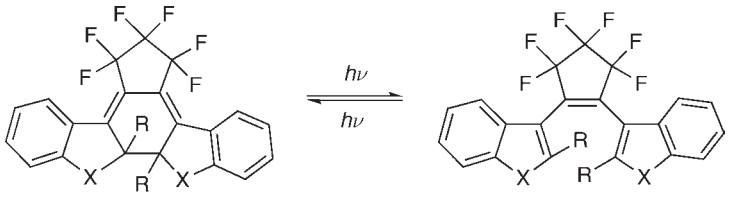
10.21.6 Reactivity of Nonconjugated Rings

10.21.6.1 Reactions of the Carbocyclic Ring

10.21.6.1.1 Thermal and photochemical reactions

The cyclization and cycloreversion of 1,2-bis(heteroaryl)ethene systems under photochemical conditions has received considerable attention due to the ability of these compounds to function as molecular switches, and the

photochemistry of compounds containing thienyl, furanyl, and indolyl groups has been reported <2000CRV1685, 2001JA7703, 2001T4559, 2004CSR85>. For example, ring-closed compounds such as **75** undergo a thermally irreversible photochromic reaction to the ring-opened isomers (Equation 14) <2005JOC10323>.

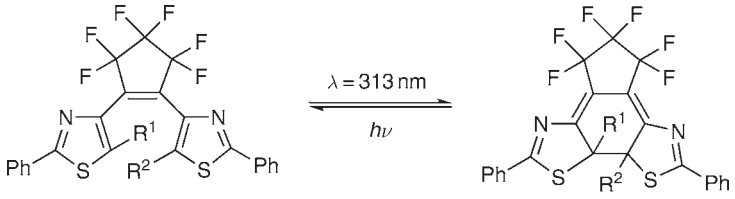


(14)

75

R = CH_3 or C_4H_9
X = O or S

The photochromic dithiazolylethenes **76** undergo photocyclization reactions from the open-ring forms to the closed-ring forms **77** upon irradiation ($\lambda = 313$ nm) <1998T6627, 2002EJO3796>. The open-ring forms are restored on exposure to visible light (Equation 15).



(15)

76

$R^1 = R^2 = OCH_3$
$R^1 = OCH_3$; $R^2 = CH_3$
$R^1 = R^2 = CH_3$

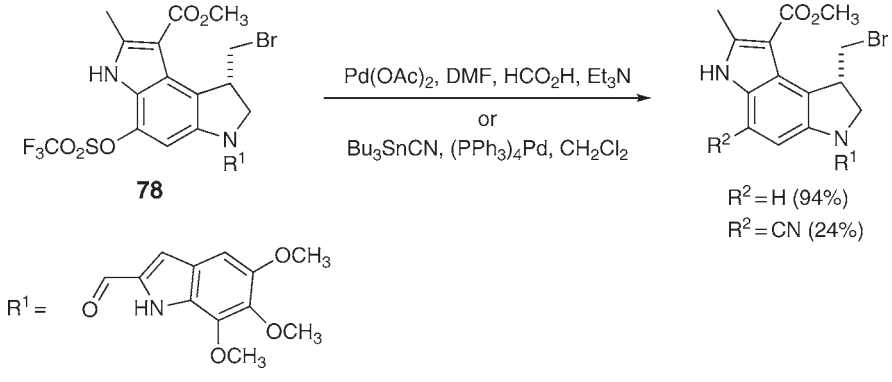
77

10.21.6.1.2 Reactions with carbenes

No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

10.21.6.1.3 Nucleophilic attack at carbon

The 8-*O*-trifluoromethanesulfonate substituent on the aromatic B-ring of the duocarmycin derivative DU-86 **78** can be replaced in acceptable yields using either palladium(0)-catalyzed reduction or cyanation with tributyltin cyanide (Equation 16) <1996BMC1379>.



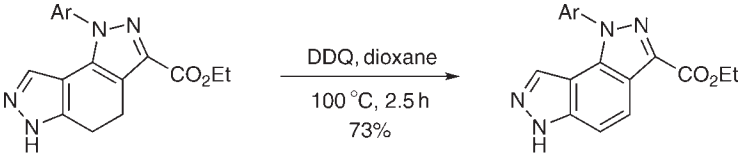
(16)

78

R^2 = H (94%)
R^2 = CN (24%)

10.21.6.1.4 Dehydrogenation

A number of saturated systems are oxidized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to produce the corresponding fully conjugated derivatives. Thus, the aromatization of the central ring of tetrahydrobenzodipyrazole **79** to give the dihydrobenzodipyrazole is accomplished using DDQ in refluxing dioxane (Equation 17) <2005BML1315>. Similarly, the indolocarbazole nucleus is prepared by Mannich cyclization of 1,2-bis(3-indolyl)-ethane followed by oxidative aromatization with DDQ (see Section 10.21.9.3.3(i)(a)) <1999JOC5670>.

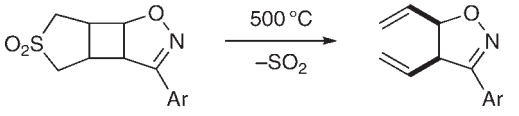


79 (17)

10.21.6.2 Reactions of the Heterocyclic Ring

10.21.6.2.1 Thermal and photochemical reactions

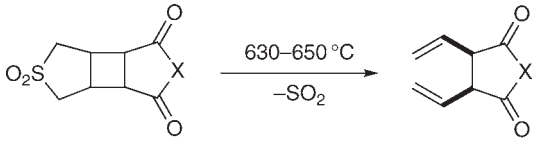
The sulfone **80** undergoes clean extrusion of sulfur dioxide on exposure to flash vacuum pyrolysis conditions to produce divinyl compound **81** (Equation 18) <1999J(P1)605>.



80 **81** (18)

Ar = Ph (19%)
Ar = 4-MeOC$_6$H$_4$ (33%)

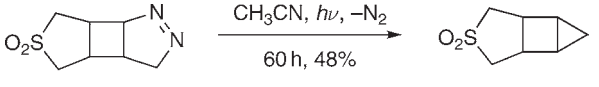
The related sulfone **82** also undergoes pyrolysis under similar conditions to produce 1,2-divinyl compound **83** (Equation 19) <1999J(P1)605>.



82 **83** (19)

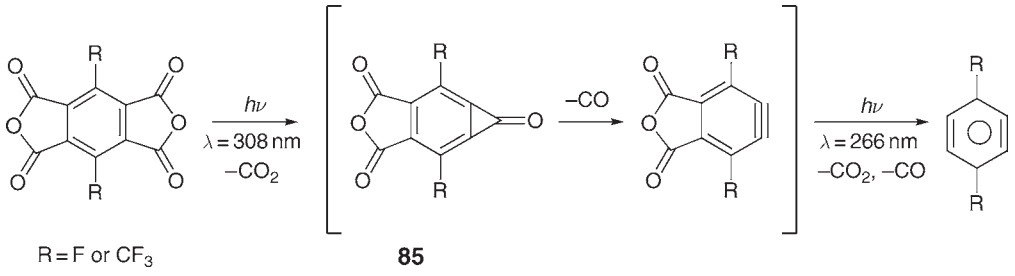
X = O (80%)
X = NH (63%)
X = NMe (58%)
X = NPh (52%)

The diazomethane adduct **84** extrudes nitrogen to give the cyclopropane derivative on photolysis in acetonitrile <1999J(P1)605> (Equation 20).



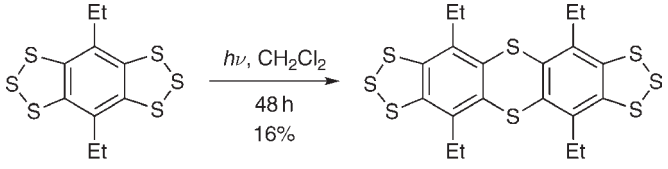
84 (20)

Benzenetetracarboxylic dianhydride derivatives undergo photolysis in a nitrogen matrix at 13 K to produce benzdiynes by a stepwise process which is dependent on the ring substituents <2002JA4512>. Upon irradiation at 308 nm, the dianhydrides are initially converted into cyclopropanone intermediate **85** by loss of carbon dioxide and subsequently decompose by loss of carbon monoxide to produce the benzyne (**Scheme 5**).



Scheme 5

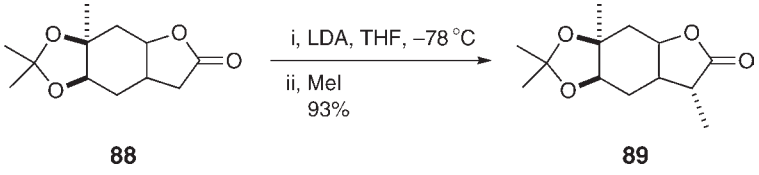
Photolysis of these benzynes at 266 nm leads to production of 3,6-difluoro- and 3,6-bis(trifluoromethyl)-1,4-benzdiyne which are converted into the corresponding hexatriynes upon further irradiation at 266 nm. 4,8-Diethylbenzo[1,2-*d*;4,5-*d*′]bis[1,2,3]trithiole **86** undergoes photolytic degradation on irradiation with a high-pressure mercury lamp, without the requirement for an additional desulfurization reagent, to produce thianthrene **87** in low yield (Equation 21) <2000TL1801>.



(21)

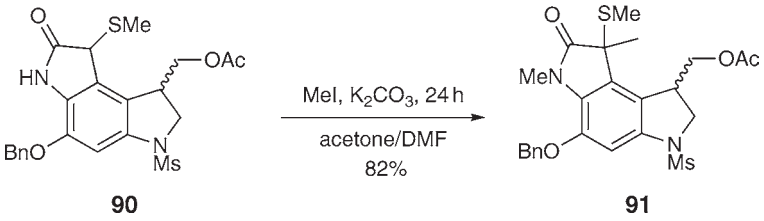
10.21.6.2.2 Electrophilic attack at carbon

The enolate generated by reaction of lactone **88** with lithium diisopropylamide (LDA) is quenched with an excess of methyl iodide to give methyl lactone **89** in excellent yield. As expected, the electrophilic attack is stereoselective for the less sterically hindered convex face of the lactone enolate, giving the product with the desired 7*R*-stereochemistry with greater than 95:5 selectivity (Equation 22) <1997TL3817>.



(22)

The oxindole **90** is exhaustively methylated to give the bismethylated derivative **91** in good yield on reaction with potassium carbonate and methyl iodide in acetone and DMF (Equation 23) <1997JA6214>.

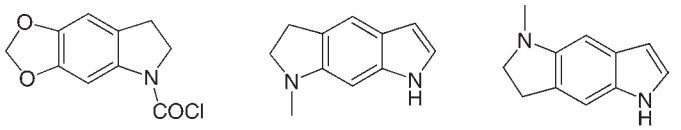


(23)

10.21.6.2.3 Electrophilic attack at nitrogen

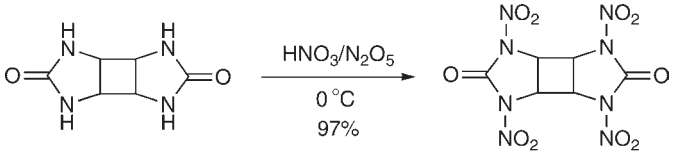
Nitrogen substituents undergo the expected range of reactions in a manner analogous to simpler nitrogen-containing heterocycles. Thus, the introduction of *t*-butoxycarbonyl (BOC), acetyl, trifluoroacetyl, benzoyl, trifluoromethansulfonyl, and benzyl groups has been reported for various systems <2000BMC381, 2003OBC2111, 2003T8233, 2005JOC9798>. The carbonyl chloride derivative **92** is produced on reaction of the corresponding amine with

phosgene <1998EJM839>. A number of studies have manipulated the N-substituent in order to modulate either biological or physicochemical properties. Thus, anions generated from tetrahydroindolopyrroles, such as **93** and **94**, are alkylated using alkyl halides or acylated <1996JME4966>.



92 **93** **94**

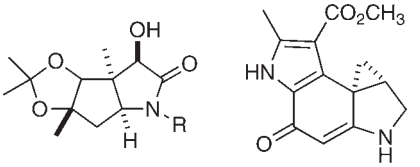
The cleavage of isoxazolidine rings has been reported to occur under either hydrogenation conditions <1997J(P1)1805>, or by reaction with methyl iodide <1997T16897>. Nitration and formylation at ring nitrogen substituents have also been reported. Thus, nitration of photodimer **95** by either dinitrogen pentoxide/nitric acid solution or 100% nitric acid yields nitramine **96** (Equation 24) <1996JOC9340>.



95 **96** (24)

Reaction of hydroxy lactam **97** with acetic formic anhydride gives the formyl derivative **98** in high yield <2000OL99>.

Duocarmycin derivative **99** does not undergo formylation under Vilsmeier conditions at the expected position in the A-ring, but instead is formylated at the amine group of the C-ring although no yields are reported for this transformation <2000BMC1195>.

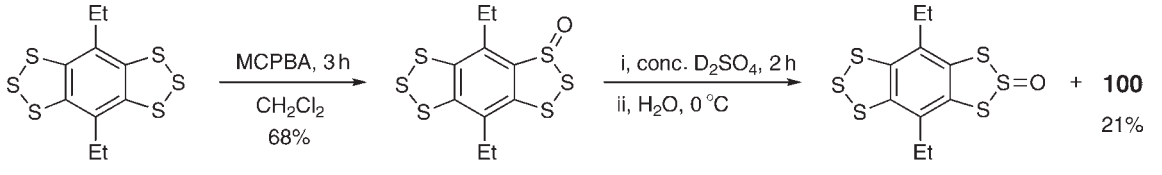


97: R = H
98: R = CHO

99

10.21.6.2.4 Electrophilic attack at sulfur

4,8-Diethylbenzo[1,2-*d*:4,5-*d*′]bis[1,2,3]trithiole **86** can be oxidized with MCPBA to produce the 1-sulfoxide **100** which undergoes further oxidation on reaction with deuterated sulfuric acid to produce a dication (**Scheme 6**) <2003EJO4902>. On quenching with water this dication gave a mixture of the 1- and 2-sulfoxides **100** and **101**.



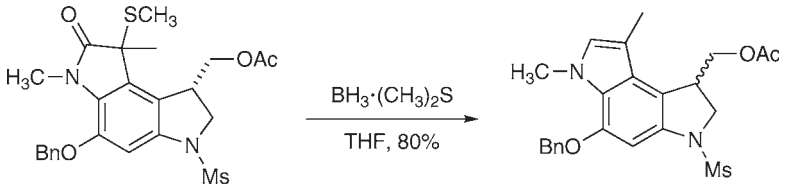
86 **100** **101** 41%

100 21%

Scheme 6

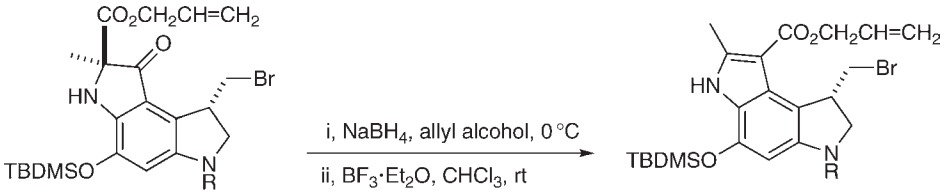
10.21.6.2.5 Nucleophilic attack at carbon

Carbonyl groups that are part of the heterocyclic ring undergo the expected ring-opening processes on reaction with a range of nucleophiles <1995JOC5224, 1997JME2123, 1998TL6963, 2000CL450, 2001T4999, 2002MM2277, 2005JOC9798, 2005OBC448>. Oxindole **91** undergoes reduction on reaction with borane–dimethyl sulfide to give the dihydrodipyrrole **102** in good yield (Equation 25) <1997JA6214>.



91 **102** (25)

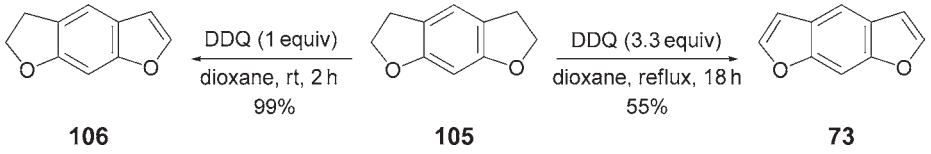
The related derivative **103** gives the 2-methyl isomer **104** on reduction with sodium borohydride and subsequent Wagner–Meerwein rearrangement (Equation 26) <1999JME2946>.



103 **104** (26)

10.21.6.2.6 Oxidation

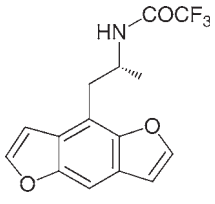
The radical cation derived from **86** is generated on reaction with either antimony(v) chloride ($SbCl_5$) or the nitrosonium salt $NOPF_6$ <2003EJO4902>. Selective monooxidation of 2,3,5,6-tetrahydrobenzo[1,2-*b*;5,4-*b*′]difuran **105** is accomplished using 1 equiv of DDQ in dioxane at room temperature to afford the oxidized product **106** in almost quantitative yield (**Scheme 7**). Oxidation of both tetrahydrofuran rings of **105** is achieved using an excess of DDQ in refluxing dioxane to give **73** <2005T4805>.



106 **105** **73**

Scheme 7

The isomeric 2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b*′]difuran is also oxidized using an excess of DDQ to produce the fully conjugated benzo[1,2-*b*;4,5-*b*′]difuran **107** in 64% yield <2001JME1003>.



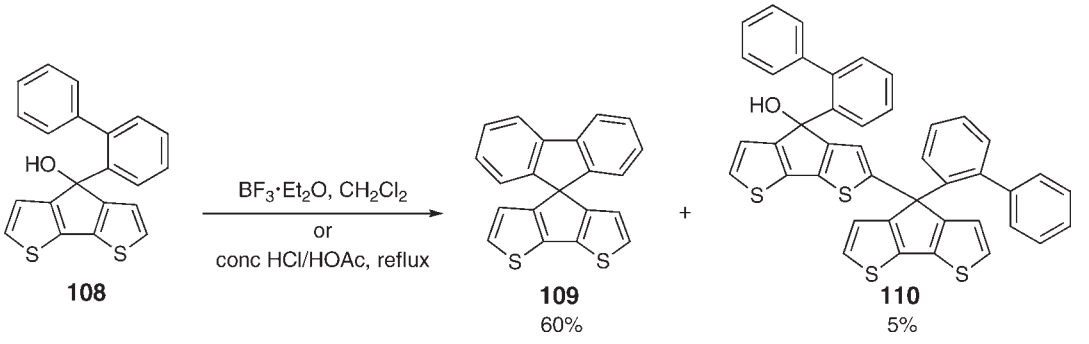
107

10.21.7 Reactivity of Substituents Attached to Ring Carbon Atoms

10.21.7.1 In Conjugated Systems

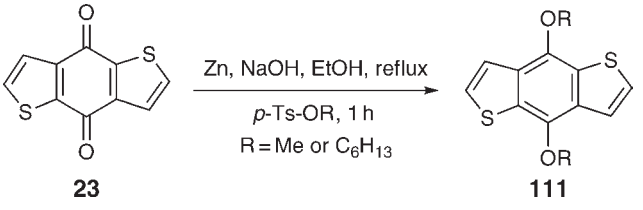
10.21.7.1.1 On the carbocyclic ring

Treatment of the tertiary alcohol **108** with either boron trifluoride–diethyl etherate in dichloromethane or concentrated hydrochloric acid in acetic acid leads to the formation of the spiro compond **109** by an intramolecular condensation reaction (Equation 27) <2001J(P1)740>. Both reagents generate a triarylmethyl cation which undergoes intramolecular electrophilic attack at the *ortho*-position of the terminal phenyl unit. Due to the stabilizing aryl units, the lifetime of the cation is sufficiently long for it to react intermolecularly at the α-thienyl position. Thus, independent of which dehydrating reagent is used, a dimeric material **110** is also produced, the yield of which is strongly dependent on the dilution of the reaction mixture. Thus, reactions utilizing boron trifluoride–diethyl etherate in dilute dichloromethane gave **109** with only trace amounts of the dimeric material.



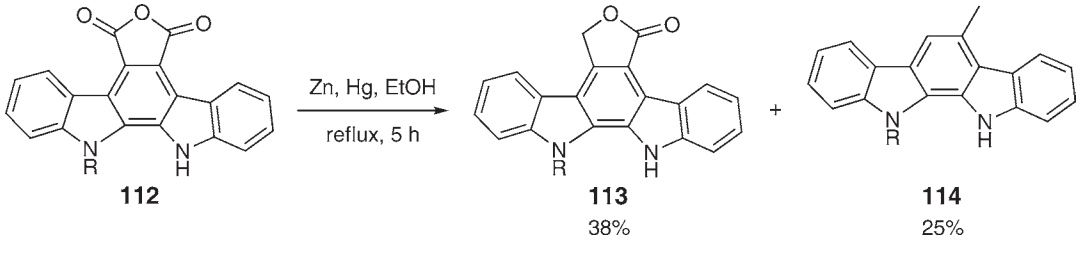
(27)

Thiophene-fused benzoquinones, such as **23**, can be easily alkylated to produce dialkoxybenzodithiophene compounds **111** on reaction with tosyl esters (Equation 28) <2002SM(130)139>.



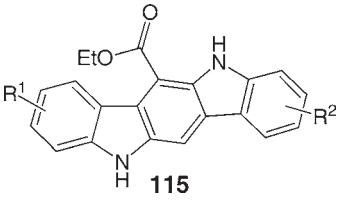
(28)

The anhydride moiety of a rebeccamycin analogue **112** (where R = glycoside) is partially or totally reduced by reaction with a zinc–mercury amalgam to give lactones **113** and indolocarbazoles **114** as a mixture of regioisomers (Equation 29) <2004BMC1955>.



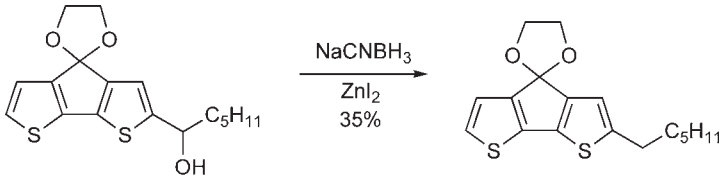
(29)

The carbonyl function of indolocarbazole **115** undergoes the expected range of reactions <2004EJO2593>.



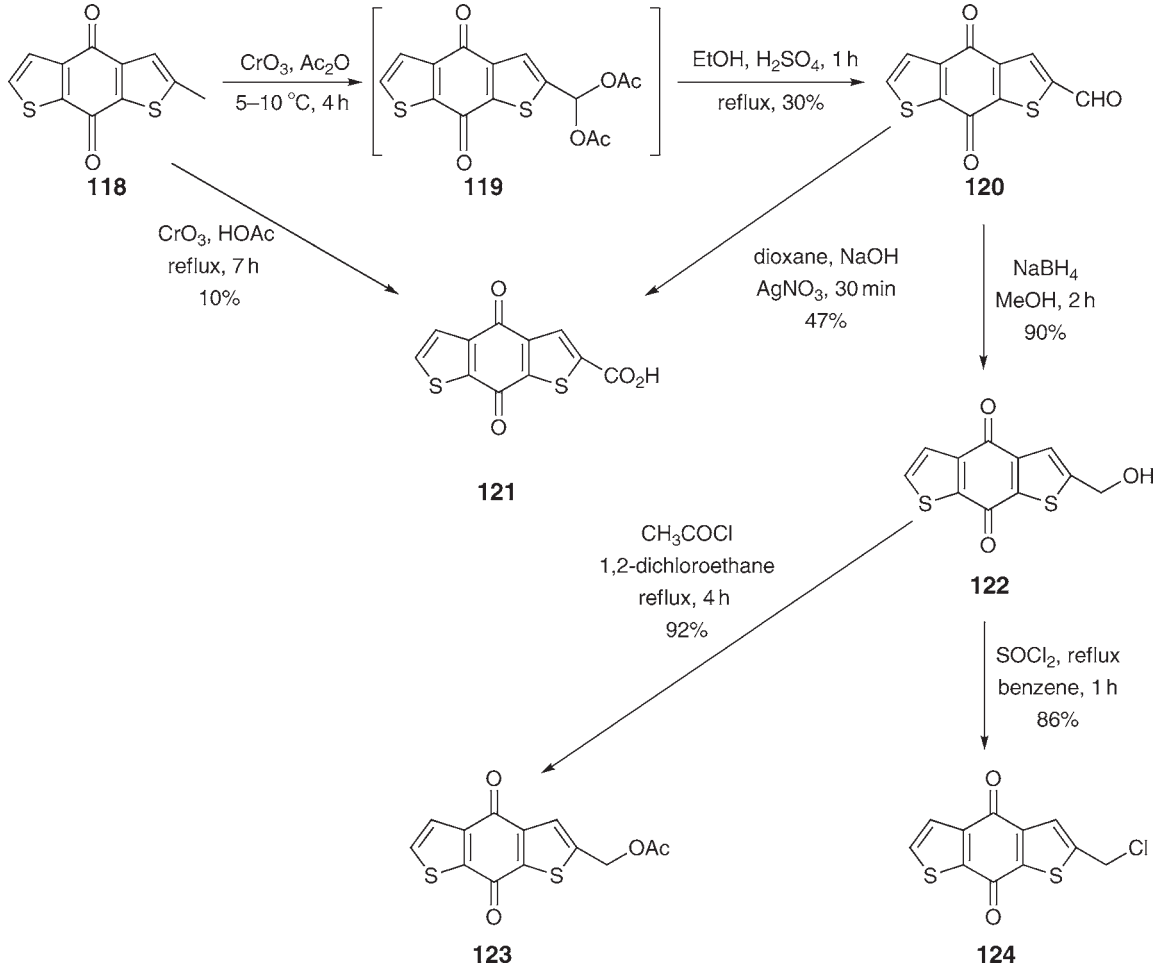
10.21.7.1.2 On the heterocyclic ring

Reduction of the unstable alcohol **116** is achieved using sodium cyanoborohydride in the presence of zinc iodide to produce the saturated compound **117** <2001SM(119)99> (Equation 30).



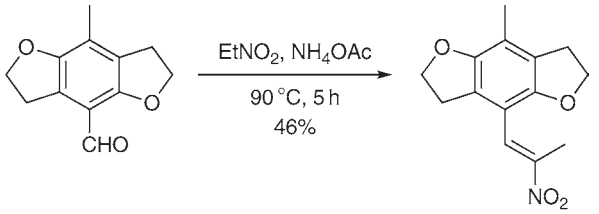
116 **117** (30)

The methyl substituent of 2-methyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]dithiophene-4,8-dione **118** undergoes a number of synthetic transformations (**Scheme 8**), and is therefore a key intermediate for the preparation of a range of anthraquinone derivatives <1999BMC1025>. Thus, oxidation of **118** with chromium trioxide in acetic anhydride at low temperatures affords the diacetate intermediate **119** which is hydrolyzed with dilute sulfuric acid to yield the aldehyde **120**. Direct oxidation of **118** to the carboxylic acid **121** proceeded in very low yield; however, it can be produced efficiently by oxidation of aldehyde **120** using silver nitrate in dioxane. Reduction of aldehyde **120** with sodium borohydride in methanol gives a 90% yield of 2-hydroxymethyl derivative **122** which reacts with acetyl chloride or thionyl chloride to produce the 2-acetoxymethyl- and 2-chloromethyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b*′]-dithiophene-4,8-diones **123** and **124**, respectively.



Scheme 8

4-Formyl-8-methyl-2,3,6,7-tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran **125** undergoes condensation with nitroethane to give the nitropropene product **126** which undergoes reduction with lithium aluminium hydride to afford the saturated amine (Equation 31) <1996JME2953>.



(31)

125 **126**

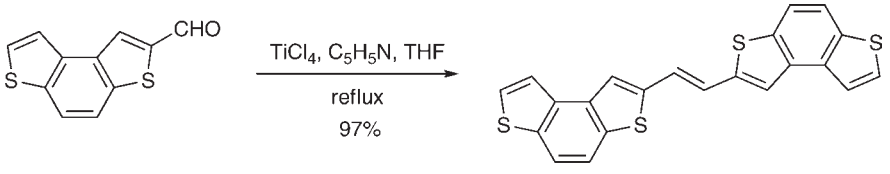
The homochiral oxazoline **127** is produced in good yield by reaction of nitrile **66** with (*S*)-valinol and zinc chloride (Equation 32) <1997JOC4465>.



(32)

66 **127**

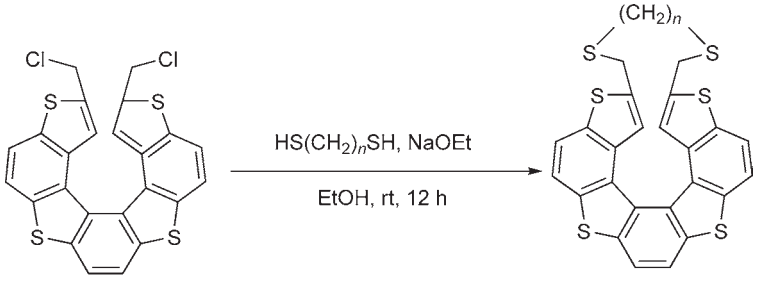
The carbonyl moiety of 2-formylbenzo[1,2-*b*;4,3-*b*′]dithiophene **128** undergoes a range of expected Wittig reactions <2000CC1139, 1998J(P1)935> or McMurry coupling to produce the corresponding unsaturated product **129** (Equation 33) <2003T6481>.



(33)

128 **129**

A series of bridged [7]thiaheterohelicenes **131** with a variety of helical pitches have been prepared from 2,13-bis(chloromethyl)thiaheterohelicene **130** with alkyl dithiols (Equation 34) <2002JOC1795>.



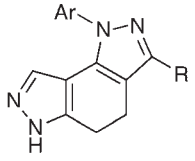
(34)

130 **131**

n = 2 58%
n = 3 18%
n = 4 4%

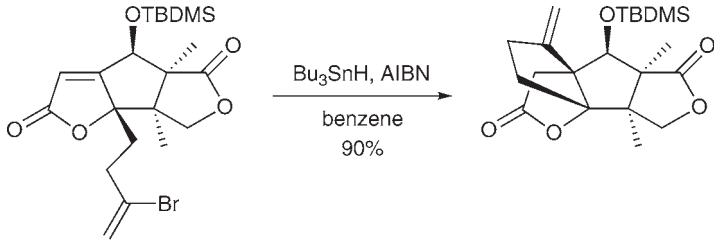
10.21.7.2 In Nonconjugated Systems

The ester and amide derivatives of dihydrobenzodipyrazole **132** undergo the expected reactions to produce a wide range of derivatives <2005BML1315>.



132
R = CO_2Et or $CONH_2$

Treatment of the tricyclic compound **133** with tributyltin hydride and 2,2′-azobisisobutyronitrile (AIBN) produces a radical which cyclizes to give **134** creating a new quaternary center (Equation 35) <2002JA2080>.

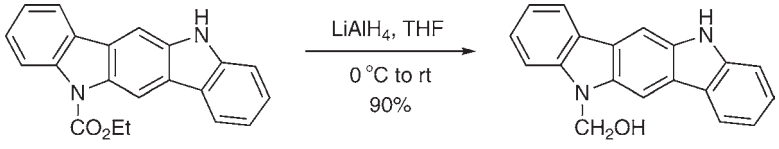


(35)

133 **134**

10.21.8 Reactivity of Substituents Attached to Ring Heteroatoms

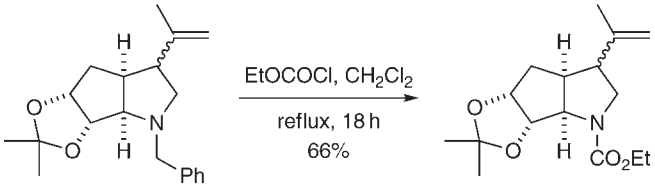
A number of nitrogen protecting groups have been employed during the synthesis and manipulation of a wide range of tricyclic systems. Thus, the removal of acetyl, trifluoroacetyl, benzenesulfonyl, toluenesulfonyl, benzyloxycarbonyl (Cbz), benzyl, and BOC have been described <1996JME4966, 1998CEJ1554, 1998H(48)31, 2000OL3181, 2002T1443, 2003T1265>. The carbamate group of indolocarbazole derivative **135** can be reduced to give the unstable hydroxymethyl compound **136** (Equation 36) <2003T1265>.



(36)

135 **136**

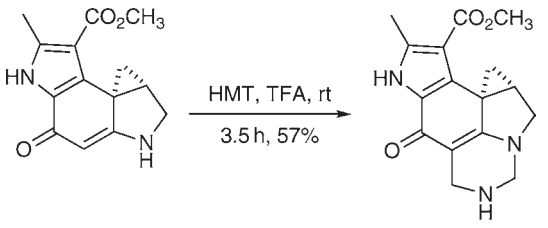
The *N*-benzyl group of the pyrrolidine **137** is cleaved with ethyl chloroformate to give the carbamate product **138** (Equation 37) <2003OBC2111>.



(37)

137 **138**

Treatment of duocarmycin segment A derivative **99** with hexamethylenetetramine (HMT) in TFA gives the novel ring structure **139** (Equation 38) <2000BMC1195>.



99 139 (38)

10.21.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The syntheses of the systems below are classified according to the size of the central carbocyclic ring, as well as by the number and nature of bonds formed. Where the only bond formed is that at the fusion of the carbocyclic ring, it is covered under the synthesis of the carbocyclic ring, rather than of the heterocyclic ring. This chapter will only deal with syntheses where the two heterocyclic rings are constructed virtually simultaneously, or where a second heterocyclic ring is constructed on an initially formed cycloalka-heterocycle. For the synthesis of the first heterocyclic ring, the appropriate chapter elsewhere in this work should be consulted. A number of the heterocyclic syntheses are analogous to those for simple or benzo-fused monocyclic heterocycles.

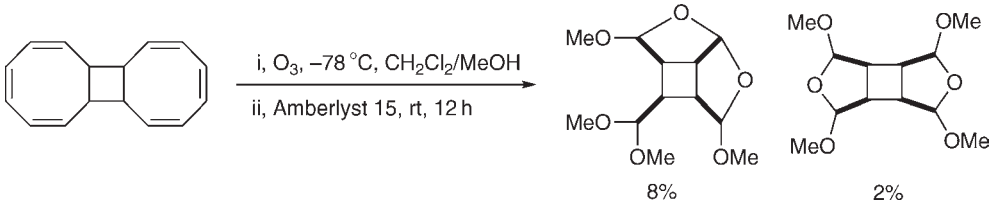
10.21.9.1 Synthesis of Compounds with a Central Four-Membered Ring

10.21.9.1.1 Compounds with one heteroatom in each heterocyclic ring

10.21.9.1.1(i) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.1.1(i)(a) Two C–O bonds

Trace amounts of cyclic acetals are produced from the [2+2] dimer of cyclooctatetraene on ozonolysis in a 2:1 mixture of dichloromethane and methanol followed by stirring with Amberlyst 15 resin (Equation 39) <2003TL9313>.



(39)

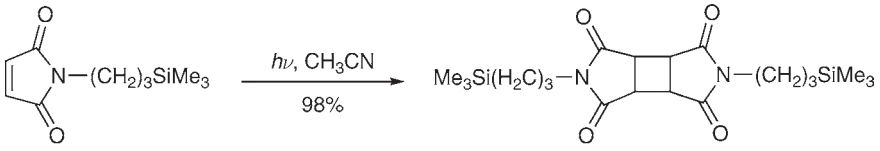
10.21.9.1.1(ii) Synthesis of the carbocyclic ring by formation of two bonds

The synthetic methods developed for the formation of tricyclic compounds containing a central cyclobutane ring systems continue to be dominated by photochemical approaches <1996CHEC-II(7)841>. In particular, photodimerization reactions of maleimides (Equation 40) have attracted significant recent attention in the field of copolymerizable photoinitiators <1995JOC2353, 2002CEJ4199>.



(40)

The influence of solvent on the nature and efficiencies of imide photoreactions has been demonstrated <1999JOC4411>. While irradiation of an acetonitrile solution of silylpropyl imide **140** results in quantitative conversion to the [2+2] photodimer (Equation 41), similar treatment of the imide in H_2O–CH_3CN mixtures produces only the functionalized pyrrolizidine.



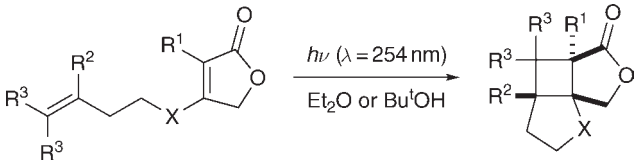
(41)

140

An intramolecular photocyclization approach has been developed for the synthesis of strained tetrahydrofuran and tetrahydropyrrole derivatives from tetronates (**Table 1**) <2004EJO4582, 2005JOC9798>. The cycloaddition reaction is not sensitive toward the degree of substitution on either reactive center and produces a single diastereoisomer in all cases (Equation 42).

Table 1 Intramolecular photocyclization of tetronates

X	R^1	R^2	R^3	*Yield* (%)
O	H	Me	H	61
O	H	H	Me	52
O	H	Me	Me	61
O	Me	H	H	76
NBOC	H	H	H	76



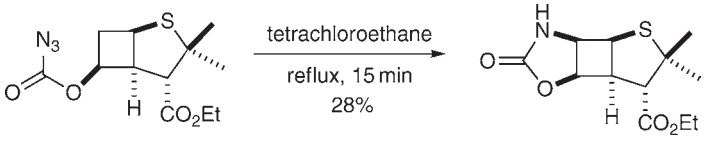
(42)

10.21.9.1.2 Compounds with two heteroatoms in one heterocyclic ring and one in another

10.21.9.1.2(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.1.2(i)(a) A C–N bond

Baldwin has utilized an intramolecular nitrene insertion reaction in an approach to hydrolytically stable analogues of penicillin <2001T4999, 2003T8233>. Although the reaction proceeded in only moderate yields, the product is formed with excellent facial selectivity (Equation 43).

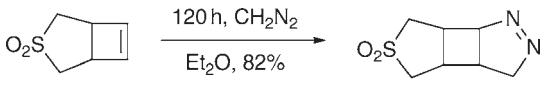


(43)

10.21.9.1.2(ii) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.1.2(ii)(a) A C–C and a C–N bond

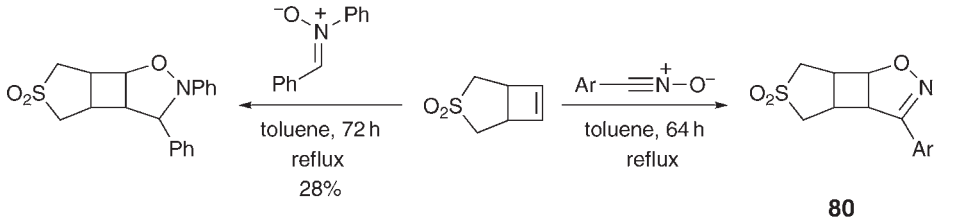
Cyclobut[*c*]thiophene is a poor dipolarophile and requires prolonged reaction times to produce the 1,3-dipolar cycloaddition product **84** on reaction with diazomethane (Equation 44) <1999J(P1)605>. Reactions with nitrile imines or azomethine imines fail to provide cycloadducts.



84 (44)

10.21.9.1.2(ii)(b) A C–C and a C–O bond

Cyclobut[*c*]thiophene also undergoes 1,3-dipolar cycloaddition reactions with nitrones and nitrile oxides to produce cycloadducts, such as **80**, albeit in moderate yields (**Scheme 9**) <1999J(P1)605>.



80

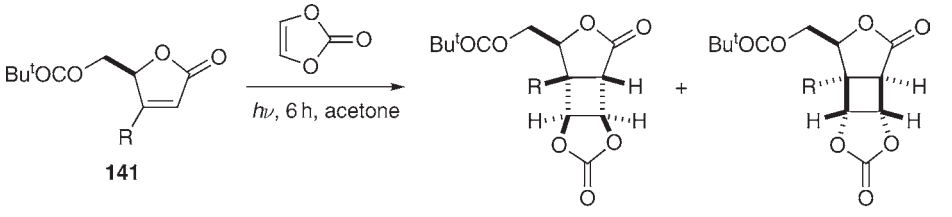
Ar = Ph (19%)

Ar = 4-$MeOC_6H_4$ (45%)

Scheme 9

10.21.9.1.2(iii) Synthesis of the carbocyclic ring by formation of two bonds

The homochiral 2(*5H*)-furanone **141** undergoes photochemical cycloaddition to vinylene carbonate <1996T1267, 1998TL6961> to generate cycloadducts derived from an *exo*-approach (Equation 45).



141

R = H	43%	6%
$R = CH_3$	48%	7%

(45)

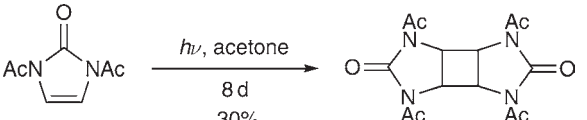
10.21.9.1.3 Compounds with two heteroatoms in both heterocyclic rings

10.21.9.1.3(i) Synthesis of the heterocyclic ring

No examples have been reported during this period.

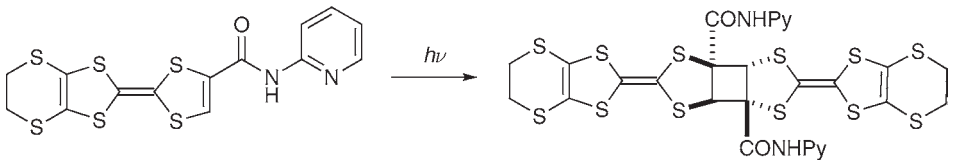
10.21.9.1.3(ii) Synthesis of the carbocyclic ring

The bisacetamide **142** undergoes photo-cyclodimerization to produce the tetramine in moderate yield (Equation 46) <1996JOC9340>. The efficiency of the reaction is severely reduced by a competing polymerization process.



142 (46)

Redox-active tetrathiofulvalenes undergo a [2+2] cycloaddition in the solid state to provide the corresponding dimeric photoadduct (Equation 47) <2004CC1538>.



(47)

10.21.9.1.4 Compounds with more than two heteroatoms in either ring

No examples have been reported during this period.

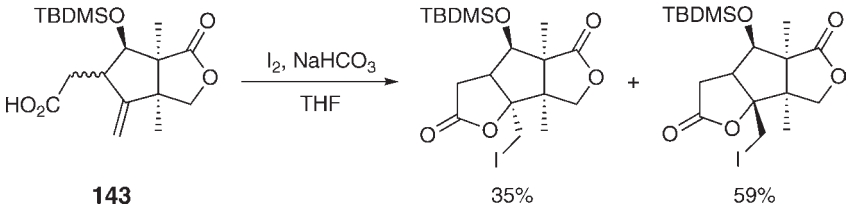
10.21.9.2 Synthesis of Compounds with a Central Five-Membered Ring

10.21.9.2.1 Compounds with one heteroatom in each heterocyclic ring

10.21.9.2.1(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.2.1(i)(a) A C–O bond

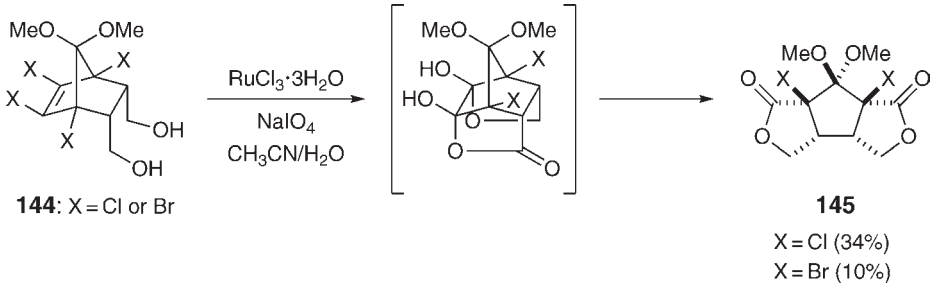
The iodolactonization of bicyclic lactone **143** provides a mixture of iodolactones (Equation 48) in excellent overall yield <2002JA2080>.



143 35% 59%

(48)

Exposure of **144** to catalytic quantities of ruthenium tetroxide, generated *in situ* from ruthenium trichloride and sodium periodate, produces the symmetrical lactones **145** <2000JA9558>. It is proposed that the products form as a result of the ruthenium-catalyzed oxidative cleavage of the α-diketones to produce intermediate glycols (Equation 49).



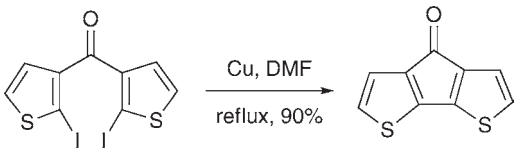
144: X = Cl or Br

145
X = Cl (34%)
X = Br (10%)

(49)

10.21.9.2.1(ii) Synthesis of the carbocyclic ring by formation of one bond

4*H*-Cyclopenta[2,1-*b*:3,4-*b*′]dithiophen-4-one **50** is of considerable interest since it serves as a precursor for the preparation of numerous polycyclopentadithiophenone derivatives which are important as low-band-gap materials <1997CRV173, 2005JMC1123>. A number of minor modifications have been reported that have improved the overall efficiency of the original synthesis <1995SM(72)147, 1998SM(92)25, 2000S1253>. Recently, a very effective three-step synthesis has been developed, the key step being a one-pot, double lithiation–iodination sequence which proceeds with total regioselectivity <2002S1053>. The final ring closure and oxidation is achieved using copper in DMF (Equation 50).



(50)

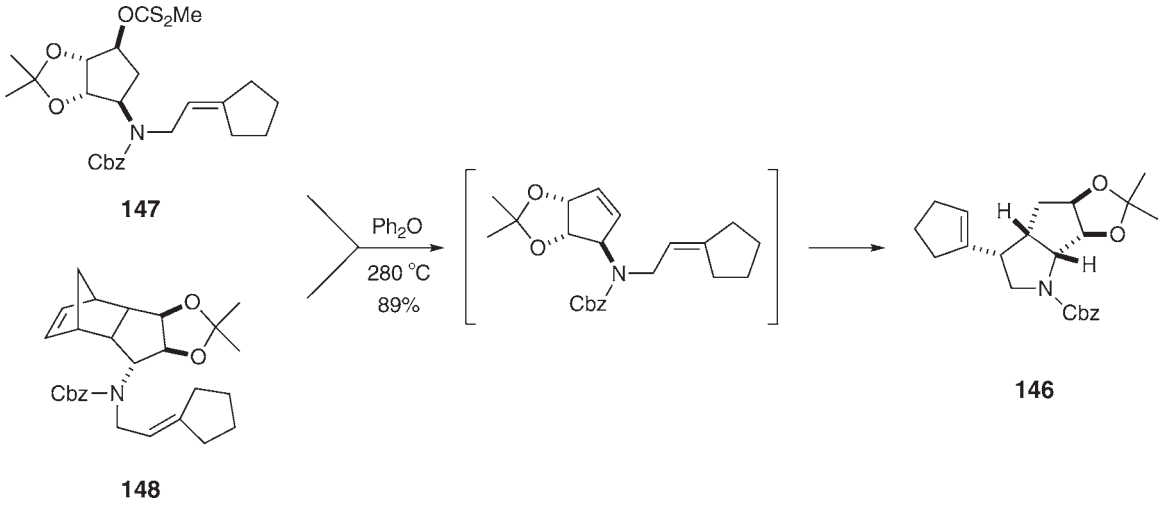
50

10.21.9.2.2 Compounds with two heteroatoms in one heterocyclic ring and one in another

10.21.9.2.2(i) Synthesis of the heterocyclic ring by formation of one bond

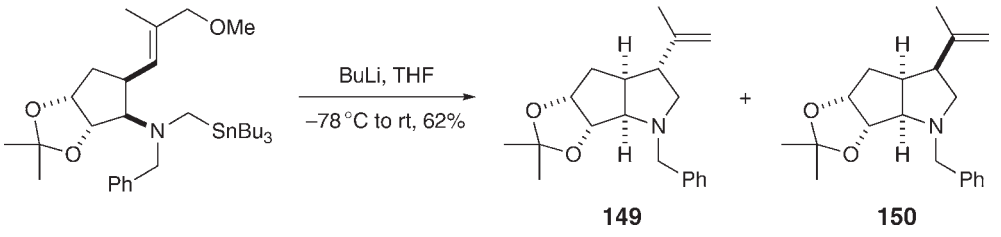
10.21.9.2.2(i)(a) A C–C bond

A stereocontrolled route to the trisubstituted pyrrolidine **146** is achieved using either a concurrent Chugaev-ene reaction or a retro-Diels–Alder-ene reaction <2000OL3181, 2001TL4523>, both approaches giving the pyrrolidine in good yields and with complete stereoselectivity. Thus, the thermolysis of either **147** or **148** produces a common intermediate which subsequently undergoes intramolecular ene reaction under the reaction conditions (**Scheme 10**).



Scheme 10

Related pyrrolidines **149** and **150** are produced from organolithium species which readily undergo cyclization onto suitably positioned alkenes <2003OBC2111>. The amino-stannane starting material undergoes tin–lithium exchange at low temperatures followed by cyclization on warming to produce two stereoisomers in a 4:1 ratio (Equation 51). The major product formed was found to be the stereoisomer **149**, contrary to expectation from model studies.

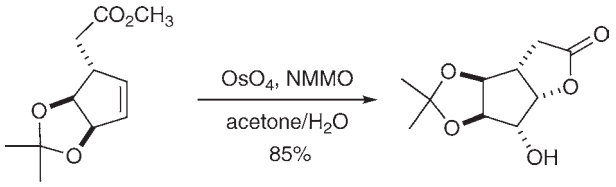


(51)

149 **150**

10.21.9.2.2(i)(b) A C–O bond

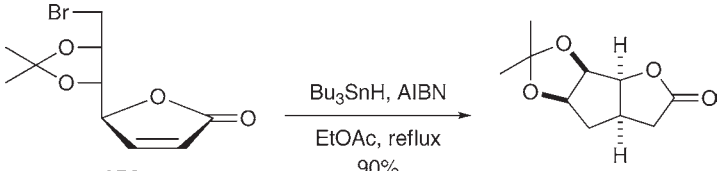
Osmylation of the olefinic ester **151** in an acetone–water mixture proceeds with high diastereoselectivity to produce the lactone **152** in a one-pot procedure (Equation 52) <1999TL5791>.



151 **152** (52)

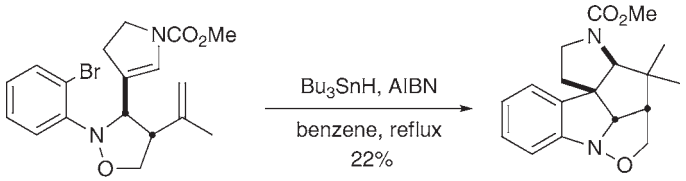
10.21.9.2.2(ii) Synthesis of the carbocyclic ring by formation of one bond

Highly functionalized cyclopentanes are produced by the intramolecular radical cyclization of homochiral bromolactones, such as **153**, with a high degree of both regio- and stereoselectivity, and in excellent yields (Equation 53) <1997T6879>. Introduction of a substituent onto the double bond has no effect on the stereoselectivity of the cyclization, allowing two stereogenic centers to be constructed simultaneously <1998JOC1919>.



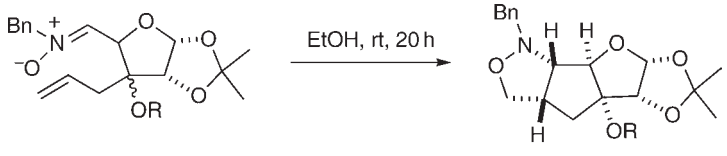
153 (53)

Radical-mediated intramolecular tandem cyclization of the precursor **154** gives the cycloadduct in low yield but does provide a concise route to the indole alkaloid skeleton of pseudocopsinine (Equation 54) <1996T647>.



154 (54)

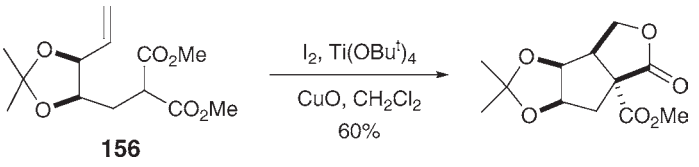
An intramolecular nitrone cycloaddition reaction has been used for the construction of isoxazolidinocarbocycle derivatives **155** from homochiral nitrone precursors in moderate yields (Equation 55) <1996T11265, 1997JOC8948>. Interestingly, the 3-oxy substituent was found to be critical in controlling the mode of cyclization. Thus, precursors containing alkoxy-bearing substituents cyclized to give exclusively five-membered ring products, whereas the precursor containing a hydroxyl substituent (R = H) provides a mixture of the five- and six-membered ring products (see also Section 10.21.9.3.2(ii)).



155 (55)

R = Me (50%)
R = Bn (60%)
R = allyl (57%)

The iodocarbocyclization of the homochiral unsaturated malonate derivative **156** proceeds with excellent asymmetric induction and in good yield in the presence of titanium *tert*-butoxide and copper oxide <1996JOC8256>. The stereoselectivity arises from a combination of allylic and homoallylic chiral induction (Equation 56).



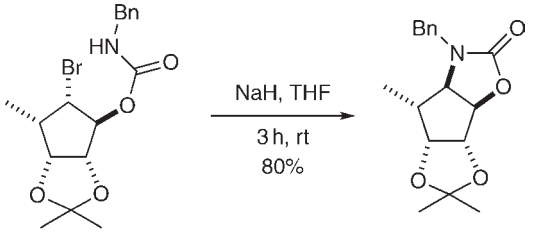
156 (56)

10.21.9.2.3 Compounds with two heteroatoms in both heterocyclic rings

10.21.9.2.3(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.2.3(i)(a) A C–N bond

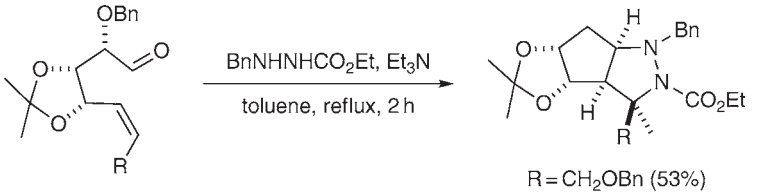
The protected aminocyclopentitol is produced on treatment of **157** with sodium hydride by the intramolecular nucleophilic displacement of the bromide in good yield (Equation 57) <2001HCA2119>.



157 (57)

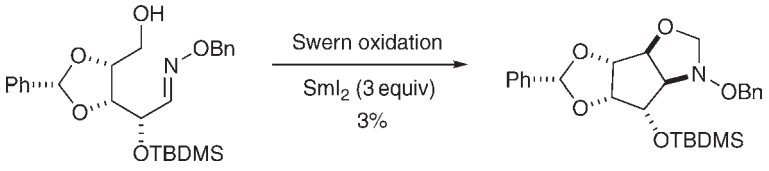
10.21.9.2.3(ii) Synthesis of the carbocyclic ring by formation of one bond

The application of 1,3-dipolar cycloaddition methodology has proven to be extremely useful in the synthesis of a number of functionalized cyclopentane derivatives. Intramolecular nitrone cycloaddition reactions of homochiral nitrones provide isoxazolidines with high levels of diastereoselectivity <1997T16897, 2000OL99, 2001JOC3834>, as do the intramolecular cycloaddition reactions of nitrile oxides <1999T15167, 2001JOC3834>. Similarly, the cycloaddition reactions of homochiral azomethine imines <1997J(P1)2457>, produced from the corresponding aldehydes and hydrazine derivatives, proceed in moderate yields and with good stereoselectivity (Equation 58).



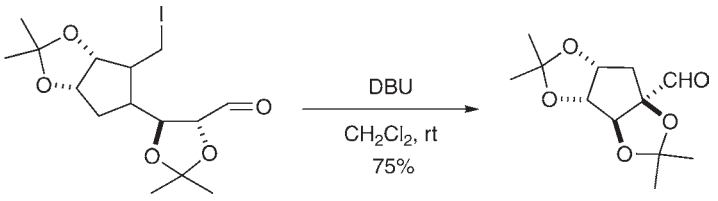
(58)

The samarium diiodide-mediated reductive cyclization of a sugar-derived oxime ether provides a trace amount of an unexpected cyclized product <1997JOC7397>. It is thought that its formation probably arises from an intermediate (methylthio)methyl ether formed with the excess of Swern reagent used to generate the aldehyde *in situ* after cyclization (Equation 59).



(59)

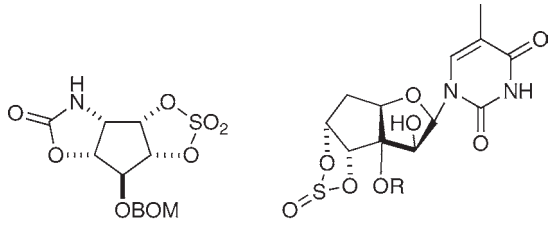
The base-mediated intramolecular alkylation of glucose derivatives provides highly functionalized cyclopentanes in good yield and without any of the expected side reactions (Equation 60) <2000TL5507, 2001T4729>.



(60)

10.21.9.2.4 Compounds with two or more heteroatoms in either heterocyclic ring

Few examples of this class of compound have been reported, although the cyclic sulfate **158** and the cyclic sulfite **159** have been reported as intermediates in carbohydrate and nucleoside synthesis, repectively <1996JOC480, 2001J(P1)1855>.

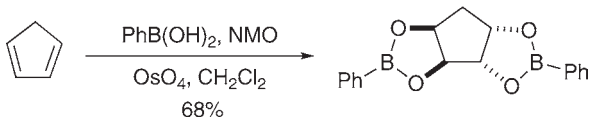


158 **159**

10.21.9.2.4(i) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.2.4(i)(a) Two C–O bonds

Cyclopentadiene undergoes catalytic osmylation to produce the bis(cyclic) boronate in good yield and with excellent selectivity for the *anti*-product (Equation 61) <1998JOC7322>. The reaction was found to be effective for a range of dienes (see also Sections 10.21.9.3.4(iii)(b) and 10.21.9.4.4).



(61)

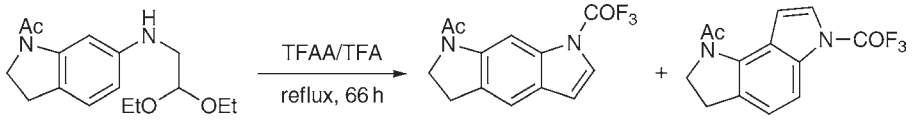
10.21.9.3 Synthesis of Compounds with a Central Six-Membered Ring

10.21.9.3.1 Compounds with one heteroatom in each heterocyclic ring

10.21.9.3.1(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.3.1(i)(a) A C–C bond

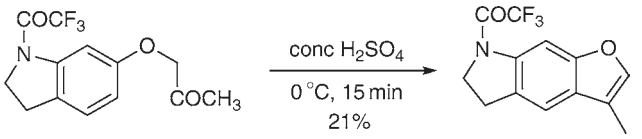
1-Acetyl-6-aminoindole is alkylated with bromoacetaldehyde diethyl acetal and the product cyclizes in refluxing trifluoroacetic anhydride (TFAA)/TFA to give a 4:1 mixture of 1,2,3,7-tetrahydropyrroloindoles **160** and **161** (Equation 62) <1996JME4966>.



160 71% **161** 19%

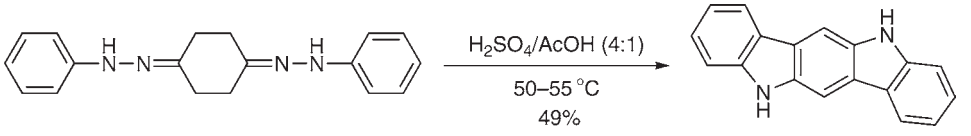
(62)

5,6-Dihydro-3-methylfuro[3,2-*f*]indole is prepared in a similar manner from the protected aminoindole by acid-catalyzed cyclization (Equation 63) <1996JME4966>.



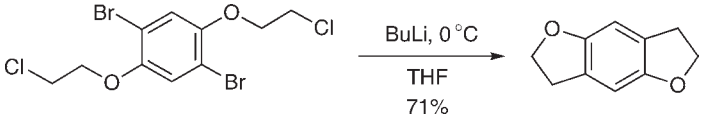
(63)

Indolo[3,2-*b*]carbazoles are prepared *via* a double Fischer cyclization of diarylhydrazones <2003T1265, 2005JA614>. Thus, treatment of the hydrazone with a mixture of sulfuric acid and acetic acid gives the linearly cyclized isomer in moderate yield (Equation 64). The use of alternative acid catalysts such as polyphosphoric acid trimethylsilylester (PPSE), polyphosphoric acid, or phosphorus trichloride gives small quantities of the isomeric angular compound in addition to the linear isomer. The reactions involving hydrazones with substituents in the aromatic rings gave variable quantities of coproducts which include the angular dihydroindolocarbazole isomer.



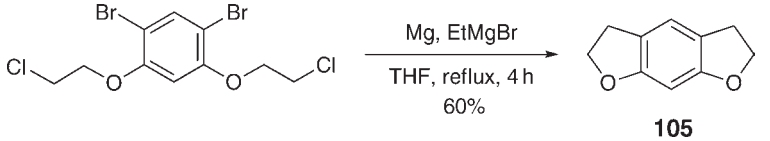
(64)

2,3,6,7-Tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran is efficiently synthesized using an intramolecular cyclization approach from the hydroquinone derivative using *n*-butyllithium (Equation 65) <1996JME2953, 1997JME2997>.



(65)

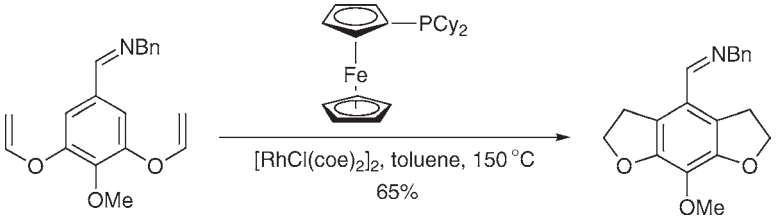
In a similar fashion, the isomeric tetrahydrobenzofuran **105** is produced from a resorcinol derivative on exposure to Grignard conditions (Equation 66) <2005T4805>.



105

(66)

Tetrahydrobis(benzofuran) is produced by a tandem cyclization reaction from the bis-vinyl ether on reaction with catalytic quantities of rhodium(I) salts in the presence of electron-rich phosphine ligands <2003OL1301>. Thus, employing 10 mol% of $[RhCl(coe)_2]_2$ with 20 mol% of a dicyclohexyl ferrocenyl phosphine ligand produces the bis-cyclized product (coe = cyclooctene; Equation 67).

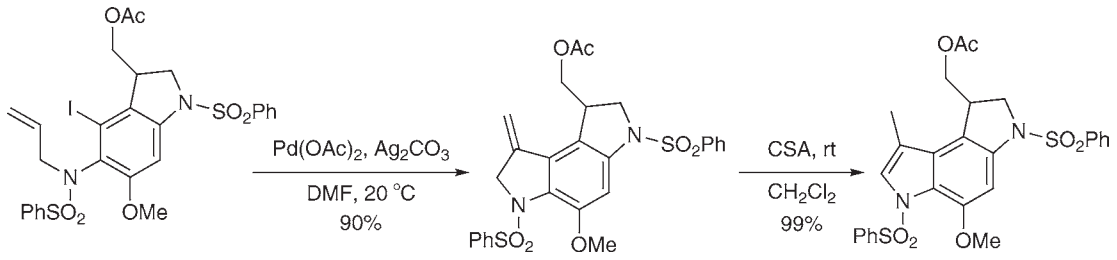


(67)

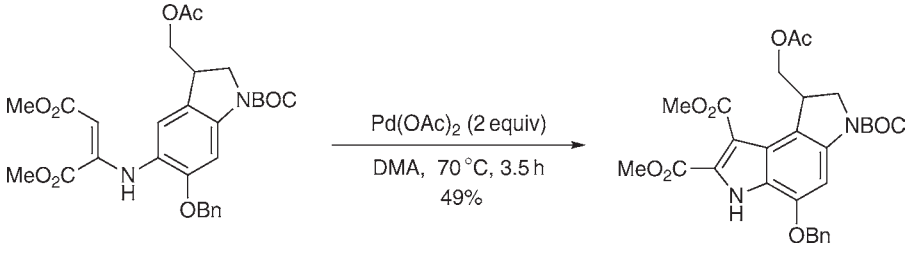
The Heck reaction of dihydroindoles produces a mixture of cyclized products, the ratio of which can be controlled by varying the reaction conditions <1998CEJ1554>. Hence, the *exo*-product is produced exclusively using palladium acetate as catalyst in the presence of silver carbonate and is isomerized to the *endo*-isomer on exposure to camphorsulfonic acid (CSA) at room temperature (**Scheme 11**).

The cyclization of a number of structurally related precursors has been reported to occur under radical conditions <1999JOC5946, 2000JOC4101>.

Palladium acetate has also been used to catalyze oxidative cyclizations to produce the related dihydroindole in dimethylacetamide (DMA) in moderate yields <1997BMEL749> (Equation 68). Similar cyclizations have been reported to occur in the presence of manganese dioxide and nitrobenzoic acid <1997TL7207>.

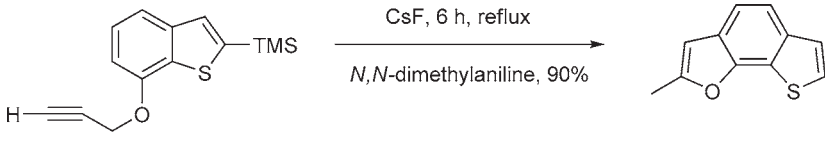


Scheme 11



(68)

Propargyl ether **162** undergoes an efficient Claisen rearrangement to produce either the five- or six-membered ring products depending on the reaction conditions <1999J(P1)3705>. Thus, heating the ether in the presence of cesium fluoride gives the five-membered ring product exclusively in excellent yield (Equation 69).

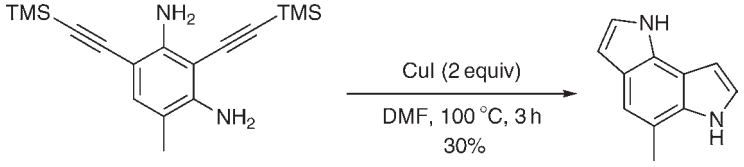


(69)

162

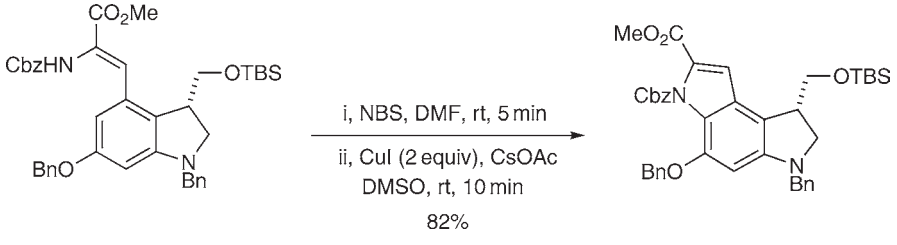
10.21.9.3.1(i)(b) A C–N bond

Benzodipyrroles are prepared by the copper iodide-mediated nitrogen cyclization onto silylalkynes with concurrent elimination of the silyl substituent <1996JOC5804>. Thus, dialkynyldiamines undergo bisannulation to afford benzodipyrroles in moderate yields (Equation 70).



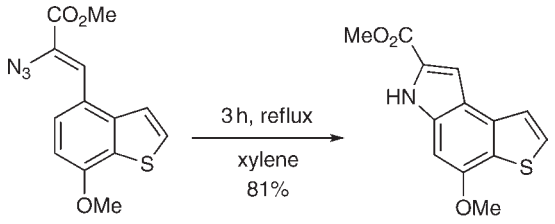
(70)

The tricyclic core of duocarmycin has been produced by a novel copper-mediated aryl amination reaction, which cleanly gives the cyclized product under exceptionally mild conditions <2003JA6630>. Selective *para*-bromination of indoline with *N*-bromosuccinimide (NBS) in DMF followed by aryl amination using 2 equiv of copper iodide quantitatively provides the indolinone (Equation 71).



(71)

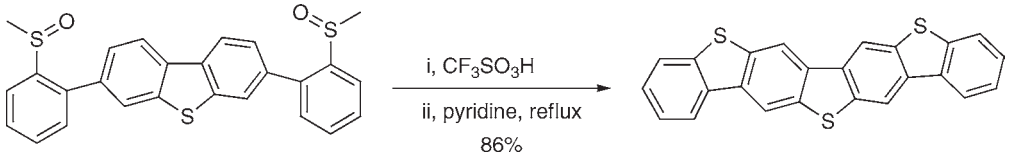
Vinyl azides have been shown to undergo efficient annulation to produce thienoindoles on heating <1997J(P1)3673>. Thus, the azide **163** provides the thienoindole in good yield on refluxing in xylene (Equation 72).



163 (72)

10.21.9.3.1(i)(c) A C–S bond

Dibenzothienobisbenzothiophene has been synthesized by the intramolecular cyclization of aromatic methyl sulfoxides under acid conditions followed by demethylation <1999JMC2095>. Thus, treatment of the corresponding sulfoxide with trifluoromethanesulfonic acid gives the cyclized product which is demethylated in refluxing pyridine (Equation 73).

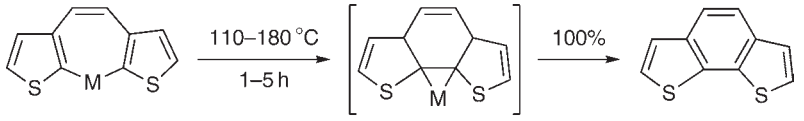


(73)

A related approach has been used for the synthesis of poly(thiaacene)s, which are novel helical aromatic polymers comprised of fused benzothiophene rings, poly(thiaheterohelicene) <2005OL755>.

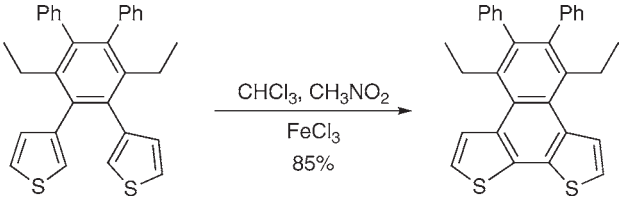
10.21.9.3.1(ii) Synthesis of the carbocyclic ring by formation of one bond

Dithienoheteroepines are readily synthesized from bis(2-bromo-3-thienyl)ethene on treatment with *tert*-butyllithium followed by the corresponding metal reagent, and readily undergo thermal decomposition to furnish benzodithiophenes <1997H(45)1899>. Interestingly, the isomeric thienoheteroepines proved remarkably stable to thermal decomposition, presumably due to the inability to produce the required intermediate (Equation 74).



M = Se,Te (74)

Iron(III) chloride has been used as an oxidant to catalyze the cyclization of acyclic precursors to highly derivatized benzodithiophenes <2006TL1551>. Thus, thiophene-based polycyclic aromatics have been produced in high yield (Equation 75).

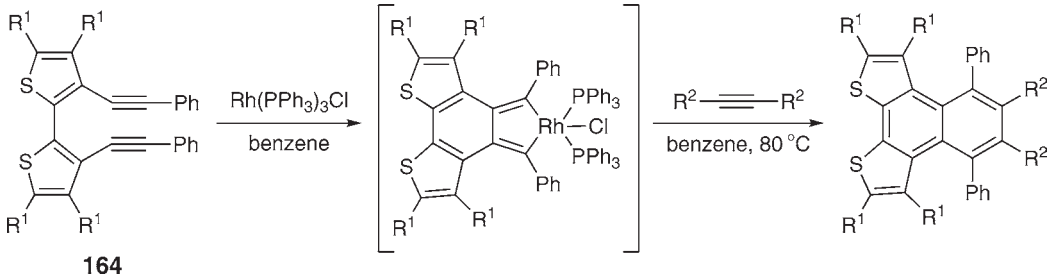


(75)

An interesting approach for the synthesis of enantiopure thiophene-based[7]helicene has been described which utilizes an intramolecular McMurry coupling using low-valent titanium as the key step <2004CEJ6531>. It was found that yields of the product varied widely due to the formation of varying quantities of the intermediate diol and desilylated starting material.

3,3′-Bis(phenylethynyl)-2,2′-bithiophene derivatives function as 1,6-diyne synthons for benzodithiophenes <1997HCA111>. Hence, treatment of **164** with chlorotris(triphenylphosphine)rhodium(I) provides an unstable

rhodium complex which undergoes metal displacement with a range of acetylenes to produce naphthodithiophenes (Equation 76). The intermediate rhodium complex also reacts with sulfur or oxygen under similar conditions to give the corresponding benzotrithiophenes or dibenzoyl-substituted benzodithiophenes in moderate yields (**Table 2**).



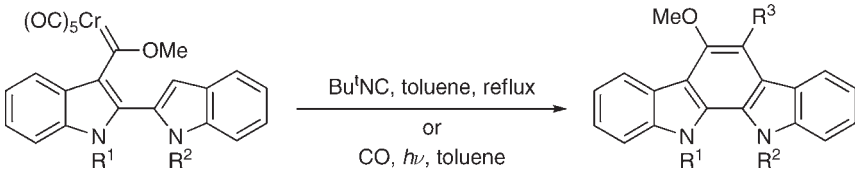
164 (76)

Table 2 Rhodium-mediated synthesis of naphthodithiophenes

R^1	R^2	*Yield* (%)
H	H	87
Benzo-fused	H	85
H	Ph	56
Benzo-fused	Ph	62
H	CO_2Me	81
Benzo-fused	CO_2Me	75

The structurally related diindolocarbazoles are produced as a mixture of isomers in moderate yields by the ammonium persulfate-mediated oxidation of 5,6-dihydroxyindoles in aqueous acidic media <1998JOC7002>.

Carbene complexes undergo benzannulation under photochemical conditions with carbon monoxide to give the indolocarbazoles *via* a ketene intermediate, or aminobenzannulation with *tert*-butyl isonitrile under thermal conditions *via* a ketenimine (Equation (77); **Table 3**) <1997TL6787, 2001T5199>.

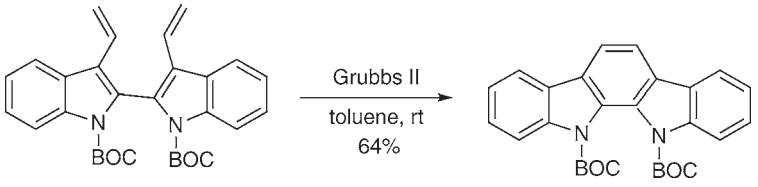


(77)

Table 3 Benzannulation reactions of carbene complexes

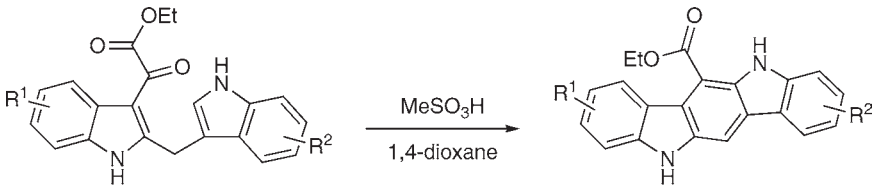
R^1	R^2	R^3	*Yield* (%)
Me	Me	Bu^tNH	89
Me	Allyl	Bu^tNH	58
MOM	Allyl	Bu^tNH	74
MOM	BOC	Bu^tNH	68
Me	Me	OH	51
Me	Allyl	OH	58
MOM	Allyl	OH	63
MOM	BOC	OH	71

A metathesis approach has been developed for the construction of the indolocarbazole nucleus of rebeccamycin and the unnatural sulfur analogue of furostifoline, although attempts to apply this strategy to the synthesis of furostifoline (see Section 10.21.12) proved unsuccessful <2005JOC10474>. Thus, exposure of the metathesis precursors to the Grubbs' second-generation catalyst gave the desired fused carbazoles in good yield (Equation 78).



(78)

Indolo[3,2-*b*]carbazoles bearing a carbonyl substituent at the 6-position have been synthesized directly by an intramolecular cyclization approach from dichloroacetyl substituted precursors <2004EJO2593>. However, due to a facile decarbonylation under the reaction conditions it was found to be more expedient to employ esters, such as **165**, produced by acylation with oxalyl chloride (Equation (79); **Table 4**).



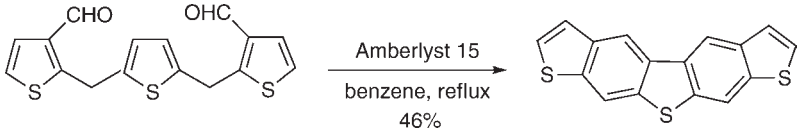
165

(79)

Table 4 Indolo[3,2-*b*]carbazoles synthesis by intramolecular cyclization

R^1	R^2	*Yield* (%)
H	H	92
H	2-OMe	90
8-OMe	H	88
H	3-OMe	89
8-OMe	2-OMe	95
8-OMe	4-OMe	86
10-OMe	2-OMe	82

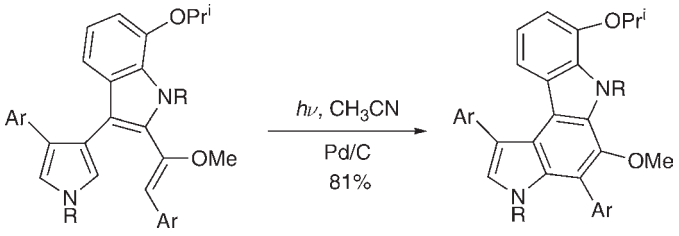
Thieno[3,2-*f*:4,5-*f*′]bis[1]benzothiophene has been prepared by an intramolecular cyclization reaction of dialdehydes utilizing Amberlyst 15 as the acid catalyst <2004JOC2197> (Equation 80).



(80)

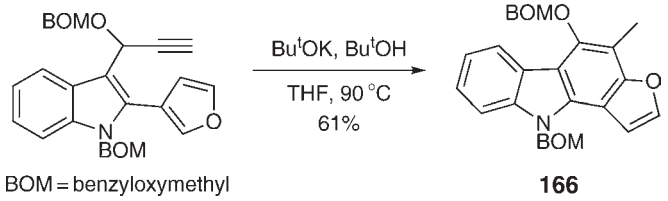
An intramolecular Friedel–Crafts approach has also been employed to synthesize 1,3,5,7-tetramethyl-4,8-dihydrobenzo[1,2-*c*:4,5-*c*′]dithiophene-4,8-dione <2003OL1883>.

A photochemical approach has been used for the formation of the pyrrolocarbazole core of the telomerase inhibitor dictyodendrin B (Equation 81) <2005JA11620>, for the central core of furostifoline <2002CPB143> and for the synthesis of 7-azaindolocarbazoles <2002T6621>.



(81)

Furostifoline itself has also been synthesized from 3-propargylindole using a novel allene-mediated electrocyclic reaction to produce the central core **166** in the presence of potassium *tert*-butoxide at elevated temperatures in good yield (Equation 82) <2001CPB881>.

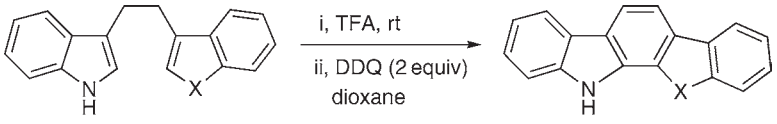


BOM = benzyloxymethyl

166

(82)

Indolocarbazole is prepared from 1,2-bis(3-indolyl)ethane upon treatment with TFA followed by DDQ oxidation (Equation 83). The related indolobenzofuran derivative has been synthesized in a similar fashion <1999JOC5670, 2004BMC1955>.

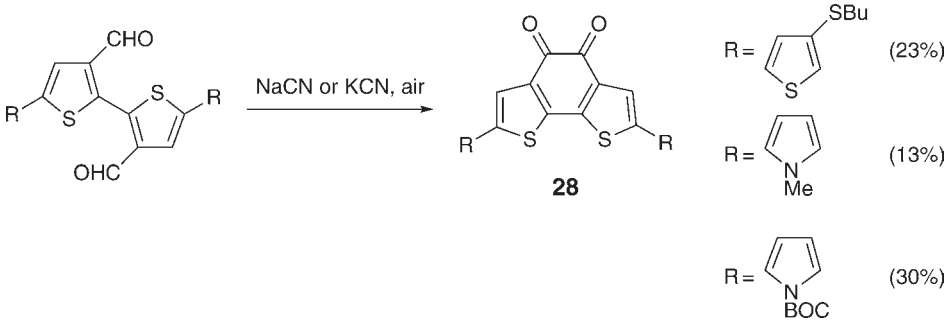


X = NH (74%)
X = O (68%)

(83)

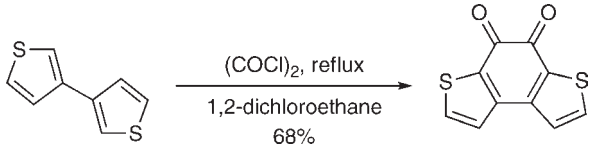
A number of routes to structurally diverse indolocarbazoles rely on a related cyclization approach and a number of catalysts have been used for this purpose <1999BMC1067, 1999JOC4697, 2000J(P1)2609, 2002T1443, 2004BML3925, 2004T2147>.

Novel tetrameric π-conjugated oligomers are produced by an intramolecular benzoin condensation from the dimeric thiophene, followed by air oxidation to give **28** <2003SM(135)85> in low yields (Equation 84).



(84)

The isomeric benzo[1,2-*b*:4,3-*b*′]dithiophene-4,5-quinone is prepared in reasonable yields by a one-step Friedel–Crafts reaction of 3,3′-bithienyl with oxalyl chloride in refluxing 1,2-dichloroethane over 7–10 days (Equation 85) <2001JA11899>.

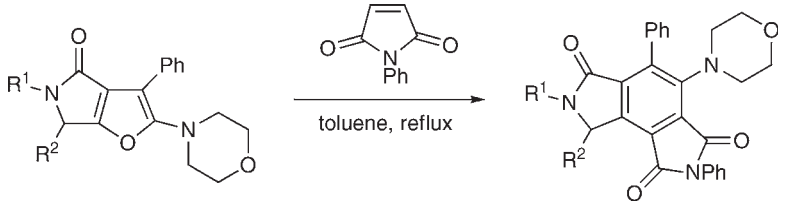


(85)

10.21.9.3.1(iii) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.3.1(iii)(a) Two C–C bonds

An interesting one-pot, five-component domino process using an intermolecular Diels–Alder reaction of furans with *N*-phenylmaleimide as its final step has been used to construct the central core of indolo[2,3-*a*]carbazoles (Equation 86) <2002AGE4291>. Thus, aminooxazoles produced from an Ugi three-component reaction undergo acylation/intramolecular Diels–Alder/retro-Diels–Alder cycloreversion with pentafluorophenyl arylprop-2-ynoates to give furan derivatives. Subsequent Diels–Alder cycloaddition at elevated temperatures with *N*-phenylmaleimide produces carbazoles in good yields (**Table 5**).

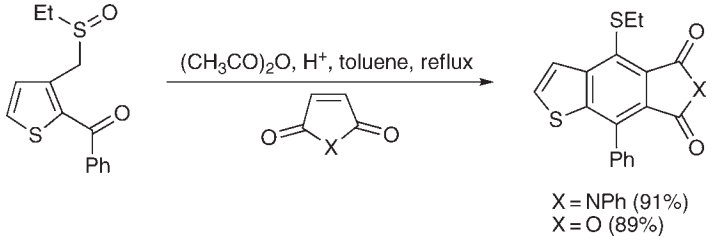


(86)

Table 5 Indolo[2,3-*a*]carbazole synthesis by multicomponent domino reactions

R^1	R^2	*Yield* (%)
C_4H_9	C_6H_{13}	67
3,4-$(MeO)_2C_6H_3$	$C_6H_5CH_2CH_2$	32
$MeO_2C(CH_2)_5$	C_6H_{13}	54
C_4H_9	4-FC_6H_4	45

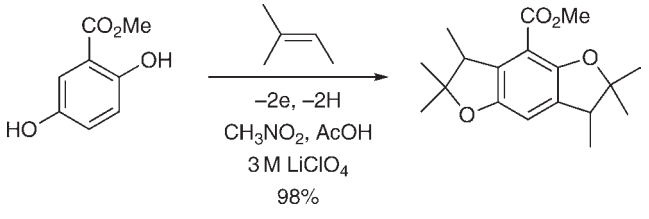
Substituted benzo[*b*]thiophene derivatives have been prepared in excellent yields by a tandem Pummer rearrangement/Diels–Alder reaction of the intermediate furan with maleic anhydride or *N*-phenylmaleimide (Equation 87) <1996JOC6166>.



(87)

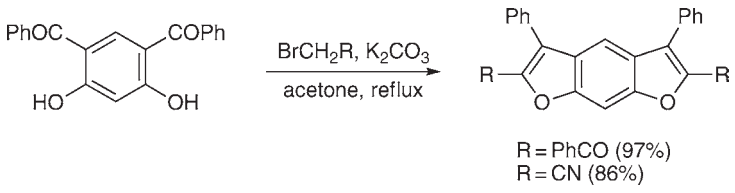
10.21.9.3.1(iii)(b) A C–C and a C–O bond

The direct electrochemical oxidation of phenols generates phenoxonium cations which are able to undergo [3+2] cycloaddition in the presence of unactivated alkenes to produce benzofurans <1999JOC7654>. Thus, electrolysis of methyl 2,5-dihydroxybenzoate in a solution of lithium perchlorate in nitromethane in the presence of acetic acid and 2-methyl-2-butene produces the dihydrobenzofuran in excellent yield (Equation 88).



(88)

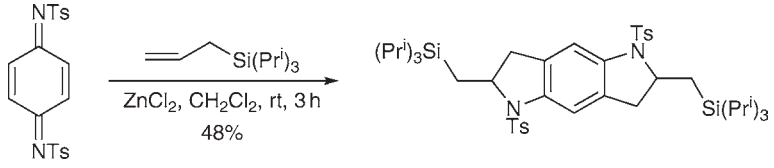
A series of the regioisomeric benzofuran derivatives are produced from a base-catalyzed cyclization/dehydration sequence of dihydroxydibenzoylbenzenes (Equation 89) <2002HCO179, 2005T545>. The cyclization of the related derivatives containing benzyl or bromoalkyl substituents (R = benzyl or $Br(CH_2)_{n-1}$, where $n = 8$ or 12) has been reported to occur in benzene under photochemical conditions <1995JOC1303, 2002J(P1)310>.



(89)

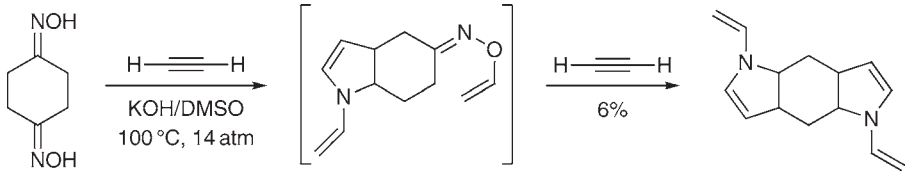
10.21.9.3.1(iii)(c) A C–C and a C–N bond

Exposure of *para*-quinone diimine and allylsilane to $ZnCl_2$ in dichloromethane leads to a slow bis-annulation reaction to give the pyrroloindole derivative in which the two silyl groups are *trans* to each other <2002OL953>. The results of optimization studies revealed that the amount and nature of the Lewis acid used and the temperature employed play an important role in determining the course of the reaction (Equation 90).



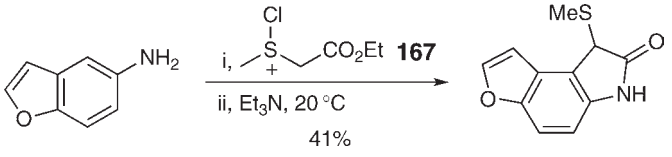
(90)

The dioxime of cyclohexane-1,4-dione reacts with acetylene in an autoclave in the presence of KOH/dimethyl sulfoxide (DMSO) (Trofimov reaction) to give 1,5-divinyl-4,8-dihydropyrrolo[2,3-*f*]indole by sequential [1,3]- and [3,3]-rearrangements in poor yield (Equation 91) <2004TL3789>.



(91)

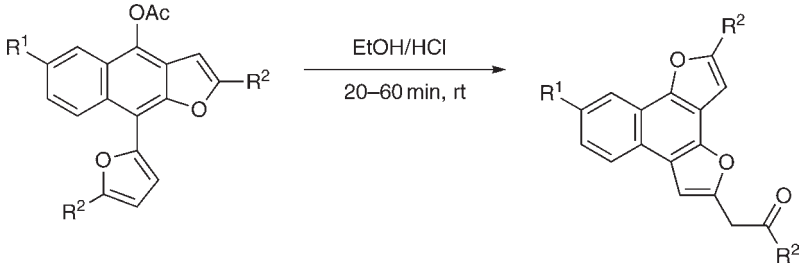
Oxyindoles are prepared using a modified Gassman synthesis from the chlorosulfonium salt **167** on reaction with substituted anilines <1996TL4631> (Equation 92).



(92)

10.21.9.3.1(iii)(d) Two C–O bonds

The cascade rearrangement of 4-acetoxy-9-furylnaphtho[2,3-*b*]furans in ethanol saturated with hydrogen chloride gas gives the tetracyclic naphthodifuran derivatives in moderate yields (Equation 93) <2006TL4117>. The reaction is thought to proceed *via* double recyclization of both furan rings of the initial molecule (**Table 6**).



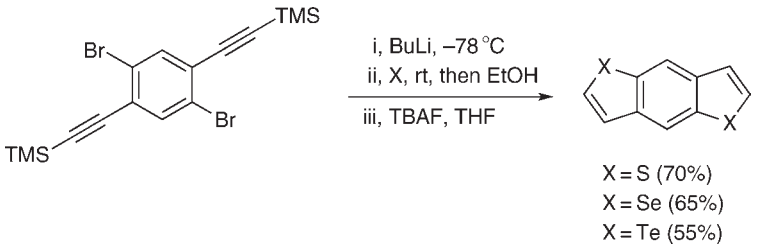
(93)

Table 6 Cascade rearrangement of 4-acetoxy-9-furylnaphtho[2,3-*b*]furans

R^1	R^2	*Yield* (%)
H	Me	40
Cl	Me	42
Br	Me	42
Br	Et	37

10.21.9.3.1(iii)(e) Two C–S bonds

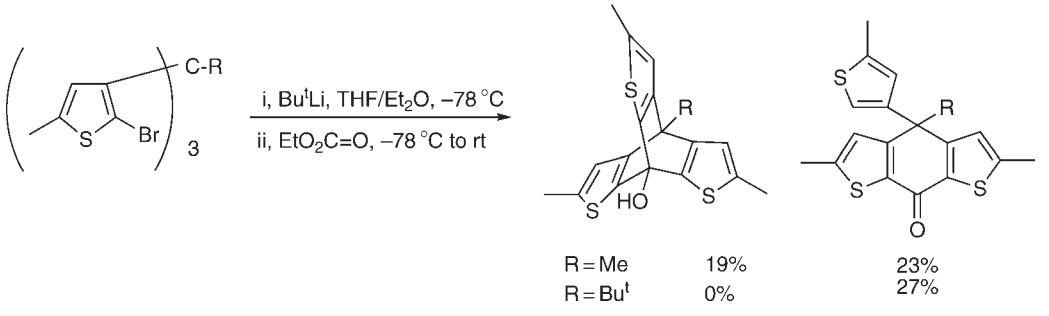
A series of benzo[1,2-*b*:4,5-*b*′]dichalcogenophenes (X = S, Se, Te) have been synthesized from 1,4-dibromo-2,5-bis(2-trimethylsilylethynyl)benzene using a cyclization reaction between the acetylene substituents and the chalcogenate anion in good yield (Equation 94) <2005JOC10569>.



(94)

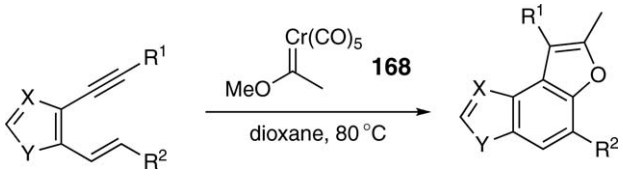
10.21.9.3.1(iv) Synthesis of the carbocyclic ring by formation of two bonds

8-Hydroxy-4-methylthiophenetriptycene is produced in addition to small amounts of the tricyclic ketone on generation of the trilithium salt derived from the bromide, followed by reaction with diethyl carbonate (Equation 95). Attempts to produce the corresponding 8-hydroxy-4-*tert*-butylthiophenetriptycene proved unsuccessful, giving the ketone along with the debrominated starting material <1996J(P1)1277>.



(95)

Benzannulation reactions of Fischer carbene complexes have proved a useful route for the synthesis of benzene rings fused to one furan ring and one additional heteroaromatic ring (Equation 96) <2005TL2211>. Thus, reaction of chromium carbene complex **168** with the conjugated dienyne systems produces benzofuran derivatives (**Table 7**).

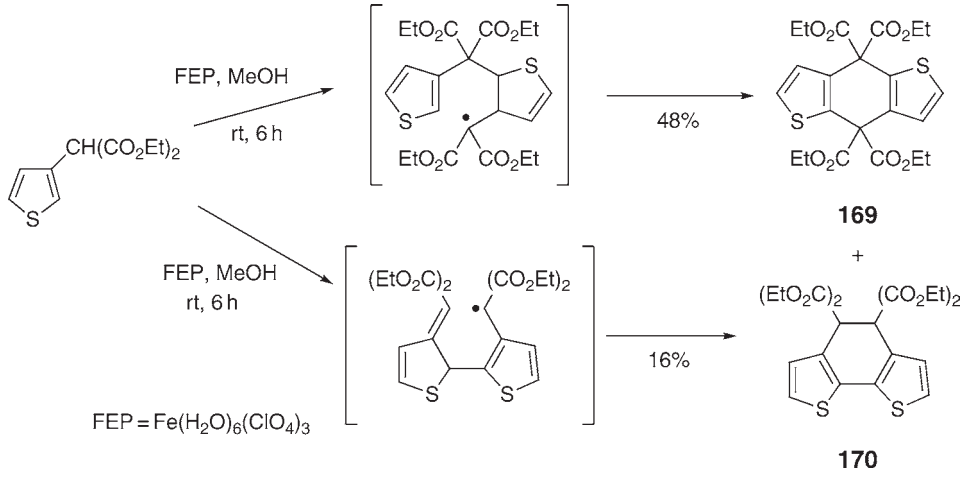


(96)

Table 7 Benzannulation reactions of Fischer carbene complexes

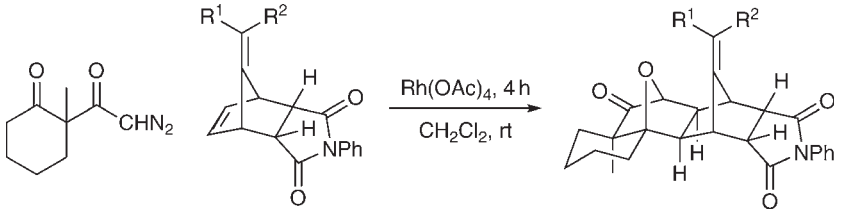
X	*Y*	R^1	R^2	*Yield* (%)
S	CH_2	TMS	CO_2Me	79
O	CH_2	TMS	CO_2Me	89
S	CH_2	TMS	H	56
S	CH_2	TMS	Me	64
S	CH_2	TMS	Ph	85
S	CH_2	TMS	CN	74
S	CH_2	Ph	CO_2Me	51
CH_2	S	TMS	CO_2Me	84
CH_2	O	TMS	CO_2Me	87

The oxidation of diethyl 3-thienylmalonate by metal oxidants such as $Fe(ClO_4)_3$, $Mn(OAc)_3$, and MnO_2 in a range of solvents affords the cyclized materials **169** and **170** in varying quantities <1996T13227>. In experiments involving $Fe(H_2O)_6(ClO_4)_3$ (FEP) and MnO_2, **169** is thought to arise from a 1,6-intramolecular homolytic aromatic substitution of the malonyl radical generated by oxidation of a head-to-tail dimer. Similarly, the formation of the dithiophene derivative **170** can be interpreted as arising from the oxidation of a tail-to-tail dimer (**Scheme 12**).



Scheme 12

Substituted norbornane derivatives have been synthesized by the reaction of norbornenes with carbonyl ylides derived from α-diazoketones by a 1,3-dipolar cycloaddition route (Equation 97) <2002TL5981>. These reactions occur in high yields and with excellent *exo*-selectivity (**Table 8**).

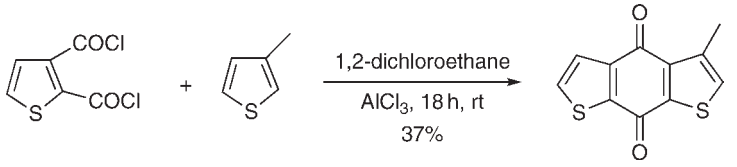


(97)

Table 8 1,3-Dipolar cycloaddition reactions of carbonyl ylides

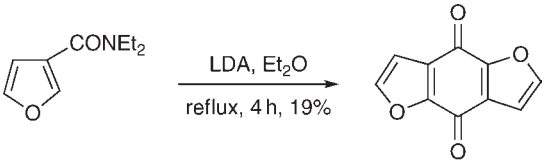
R^1	R^2	*Yield* (%)
H	4-MeC_6H_4	82
H	4-ClC_6H_4	79
-CH_2-CH_2-CH_2-CH_2-		84

Dithiophene-4,8-diones are produced by the cyclic diacylation of methylthiophenes using thiophene-2,3-dicarbonyl chloride and aluminium trichloride to afford the corresponding diones in low yields (Equation 98) <1999BMC1025>.



(98)

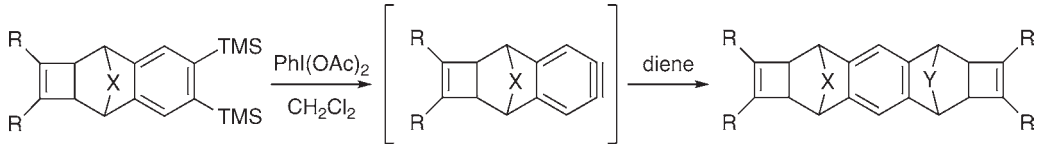
The related furan-fused quinone **24** is produced using a similar approach from the furan 3-carboxamide using a strong base, such as LDA, in low yield (Equation 99) <1995MM9, 2000JOC2577>.



(99)

24

Unsymmetrical cycloadducts are produced as a mixture of *syn*- and *anti*-isomers in good yield by the addition of dienes to monobenzynes generated sequentially from 1,2,4,5-tetrakis(trimethylsilyl) benzene by treatment with iodobenzene diacetate (Equation (100); **Table 9**) <1998J(P1)3921>.

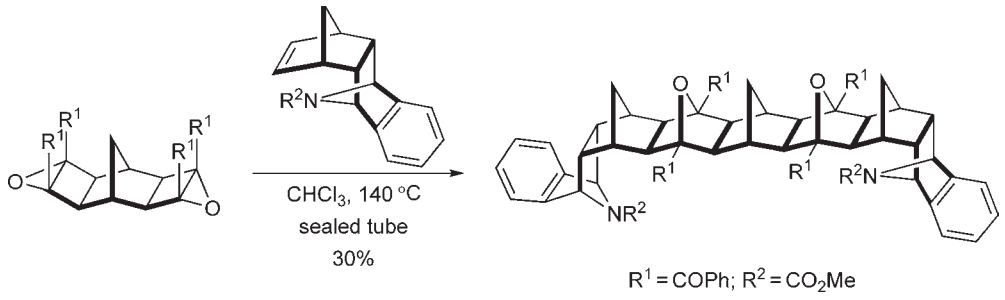


(100)

Table 9 Cycloaddition reactions of dienes to monobenzynes

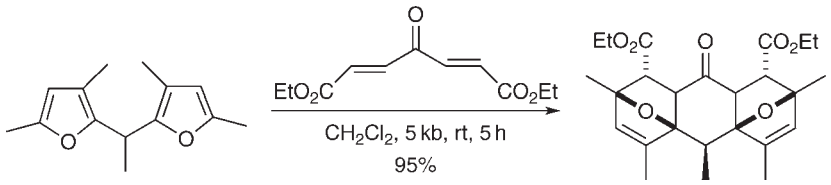
R	*X*	*Y*	*Yield* (%)
CO_2Me	O	O	96
CO_2Me	NCBZ	O	77
CO_2Me	NCBZ	NCBZ	84

A related series of cycloadducts has been produced employing a 1,3-dipolar cycloaddition approach <2000EJO3363, 2001TL465>. Thus, the 1,3-dipole formed from bis-epoxides on heating at high temperatures in a sealed tube undergoes cycloaddition to benzonorbornadienes to produce cycloadducts in a highly stereoselective *exo*,*exo*-fashion (Equation 101).



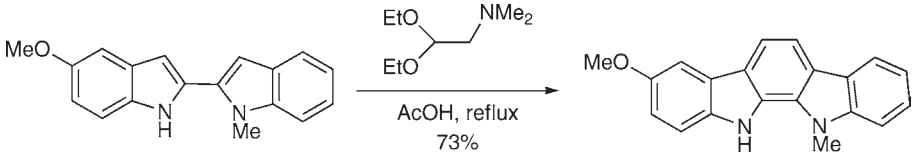
(101)

A double cycloaddition approach has also been used to construct cycloadducts which are converted into homochiral polypropanoates <1996TL4149, 2001HCA431>. Thus, 2,2′-ethylidenebis[3,5-dimethylfuran] undergoes a double cycloaddition with diethyl (2*E*,5*E*)-4-oxohepta-2,5-dienoate under high pressure to give the adduct in high yield as the only product (Equation 102).



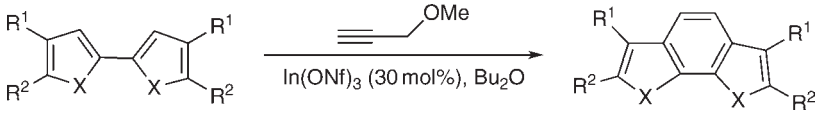
(102)

A number of procedures have been reported for the synthesis of indolocarbazoles by the addition of a two-carbon unit to biindolyl precursors. Thus, reaction of dimethylaminoacetaldehyde dimethyl or diethyl acetal with biindolyl in refluxing acetic acid provides a convenient route for the construction of the indolocarbazole ring system (Equation 103) <1999T2371, 2003OL3721, 2004TL7273>.



(103)

The indium nonaflate ($In(ONf)_3$)-catalyzed annulation of 2-thienyl- and 2-furylindoles, bithiophenes, and bifurans with methyl propargyl ether also provides tetracyclic heteroaryl annulated [*a*]carbazoles in moderate to good yields <2005AGE1336> (Equation (104); **Table 10**).

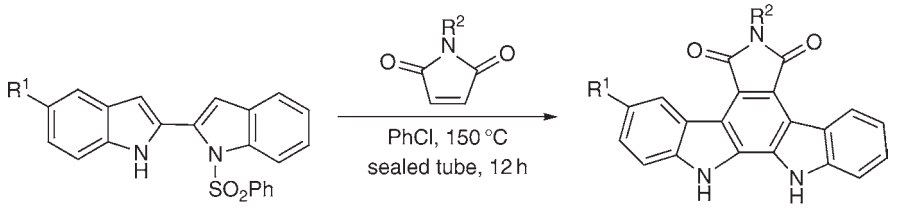


(104)

Table 10 Indium-catalyzed annulation of bithiophenes and bifurans

X	R^1	R^2	*Yield* (%)
S	Me	Me	40
S	H	Et	40
O	Me	Me	43

N-Sulfonyl-2,2′-biindoles undergo a formal [4+2] cycloaddition with various dienophiles to produce indolocarbazoles <2004TL4009>. Thus, reaction of **171** with *N*-benzylmaleimide in chlorobenzene in a sealed tube produces the cycloadduct in moderate yield (Equation 105) as the only observable product (**Table 11**). It is proposed that the reaction proceeds by an initial Michael addition, followed by a rapid cyclization and loss of the phenylsulfonyl group during the aromatization process. Similar cyclization reactions are observed with *N*-methylmaleimide, dimethylacetylene dicarboxylate, and 1,4-naphthoquinone.

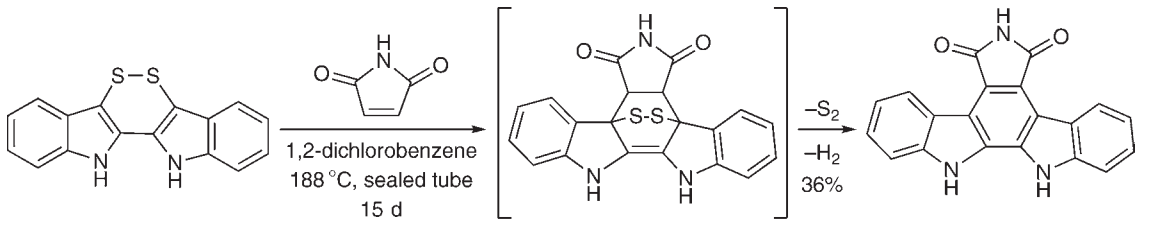


171 (105)

Table 11 Cycloaddition reactions of *N*-sulfonyl-2,2′-biindoles

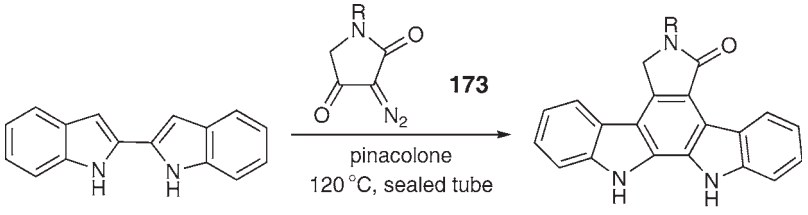
R^1	R^2	*Yield* (%)
Cl	Bn	50
Cl	Me	47
Me	Ph	42

Related indolocarbazoles have been synthesized using a Diels–Alder/retro-Diels–Alder approach. The rigid dithiete intermediate **172** produced in the initial cycloadduct reaction undergoes sulfur extrusion and dehydrogenation under the reaction conditions to produce the fully aromatized product (Equation 106) <1999TL3795>.



172 (106)

The total synthesis of the antifungal alkaloid K252a has been reported in which the indolocarbazole nucleus is constructed using novel rhodium carbenoid chemistry <1995JA10413, 1997JA9641>. Thus, reaction of 2,2′-biindole with diazolactam **173** in the presence of rhodium acetate in degassed pinacolone produces indolocarbazoles in moderate yields (Equation 107).

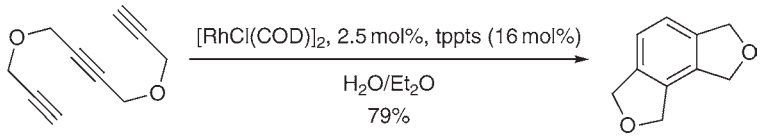


(107)

R = H (25%)
R = Bu^t (40%)
R = 4-MeC_6H_4 (55%)
R = 3,4-$Me_2C_6H_3$ (62%)
R = $C_6H_5CH_2$ (58%)

10.21.9.3.1(v) Synthesis of the carbocyclic ring by formation of three bonds

The [2+2+2] cyclotrimerization of triynes has been reported using rhodium catalysts <2003JA12143> under biphasic conditions. Thus, the cyclization of triyne **174** proceeds rapidly in a biphasic system to produce the tricyclic compound in good yield using an *in situ*-generated water-soluble rhodium catalyst (Equation 108) <2003JA7784>.

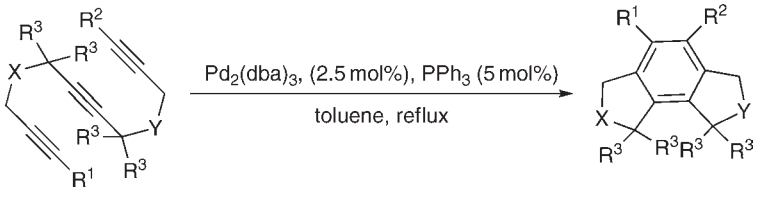


(108)

174

tppts = tris(*m*-sulfonatophenyl)phosphine

The [2+2+2] cyclotrimerization of triynes has also been reported to proceed in high yields using palladium catalysts in refluxing toluene (Equation (109); **Table 12**) <2003CEJ2469>.

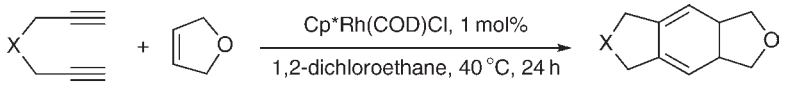


(109)

Table 12 [2+2+2] Cyclotrimerizations of triynes

X	*Y*	R^1	R^2	R^3	*Yield* (%)
O	O	CO_2Me	CO_2Me	H	95
O	O	CO_2Me	Me	H	61
O	O	Me	Me	H	35
O	O	CO_2Me	CO_2Me	Me	61
O	NBn	CO_2Me	CO_2Me	H	91
NBn	NBn	CO_2Me	CO_2Me	H	98

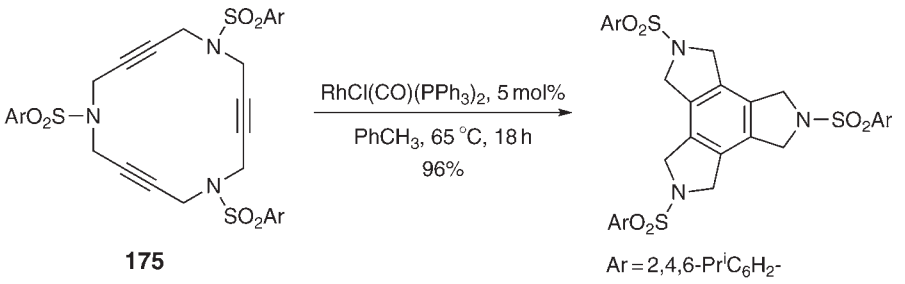
The catalytic cyclocarbonylations of diynes proceed efficiently to afford fused cyclohexadienes *via* trapping of the ruthenacyclopentadiene intermediate by an alkene component <2000JA4310>. Thus, the ruthenium-catalyzed cyclo-co-trimerization of 1,6-heptadiyne derivatives possessing a heteroatom at the 4-position affords heterotricycles in good yields (Equation 110).



(110)

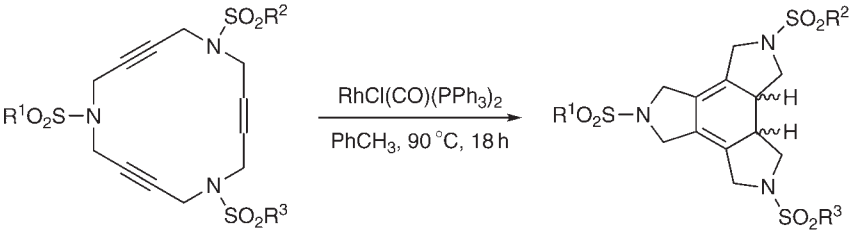
X = O (74%)
X = NTs (70%)

The nitrogen-containing 15-membered triacetylenic macrocycles 1,6,11-tris(arylsulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-triynes **175** and enediynic macrocycles 1,6,11-tris(arylsulfonyl)-1,6,11-triazacyclopentadeca-3-ene-8,13-diynes **176** undergo [2+2+2] cycloisomerization processes catalyzed by transition metals to give cycloadducts in high yields (Equation 111) <2005JOC2033>. Reactions of **176** with catalytic quantities of the rhodium salt $RhCl(CO)(PPh_3)_2$ produce the corresponding cycloadducts in excellent yields (**Table 13**).



175

(111)



176

cis or *trans*

Table 13 Rhodium-mediated [2+2+2] cycloisomerization reactions

176	R^1	R^2	R^3	*Yield* (%)
trans	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	98
trans	2,4,6-$Pr^iC_6H_2$	2,4,6-$Pr^iC_6H_2$	2,4,6-$Pr^iC_6H_2$	80
cis	4-MeC_6H_4	4-MeC_6H_4	4-MeC_6H_4	79
cis	2,4,6-$Pr^iC_6H_2$	2,4,6-$Pr^iC_6H_2$	2,4,6-$Pr^iC_6H_2$	68

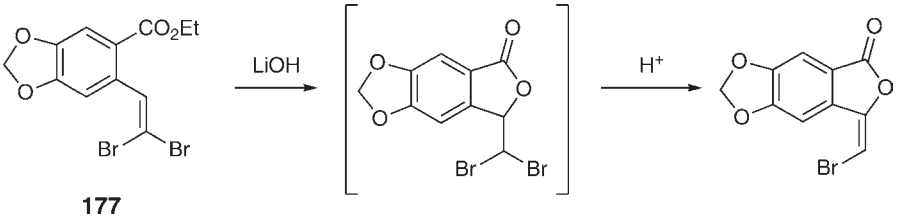
Diindolocarbazoles are produced as a mixture of isomers in moderate yields by the ammonium persulfate-mediated oxidation of 5,6-dihydroxyindoles in acidic aqueous media <1998JOC7002> or by the reaction of indole with nitrosobenzene under acid conditions <2000J(P2)2337>.

10.21.9.3.2 Compounds with two heteroatoms in one heterocyclic ring and one in another

10.21.9.3.2(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.3.2(i)(a) A C–O bond

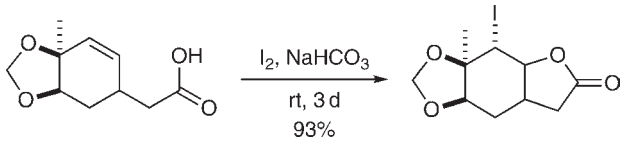
Treatment of a vinyl dibromide **177** with lithium hydroxide produces the corresponding lactone *via* hydrolysis to the acid and subsequent cyclization on protic workup (Equation 112) <2000JOC9120>.



177

(112)

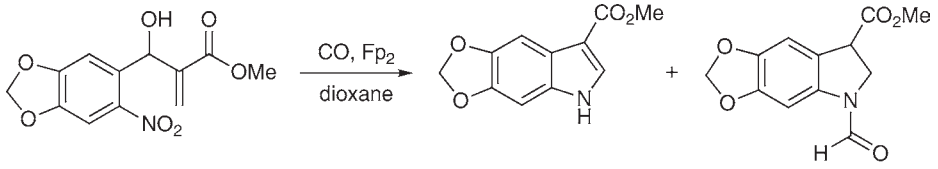
Homochiral lactones are also generated by iodolactonization reactions of cyclic alkenes in the presence of iodine in good yield (Equation 113) <1997TL3817>.



(113)

10.21.9.3.2(i)(b) A C–N bond

Exposure of the Baylis–Hillman adduct **178** to a high-pressure carbon monoxide atmosphere in the presence of a cyclopentadienyliron dicarbonyl dimer (Fp_2) catalyst unexpectedly gives small quantities of the *N*-formylindoline and indolecarboxylate (Equation 114) <2003T747>.

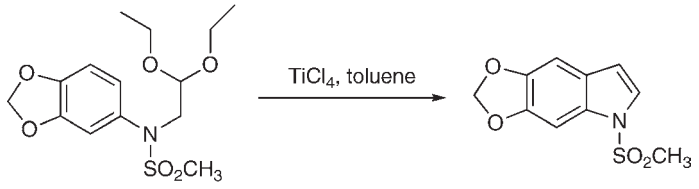


178 8% 7%

(114)

10.21.9.3.2(i)(c) A C–C bond

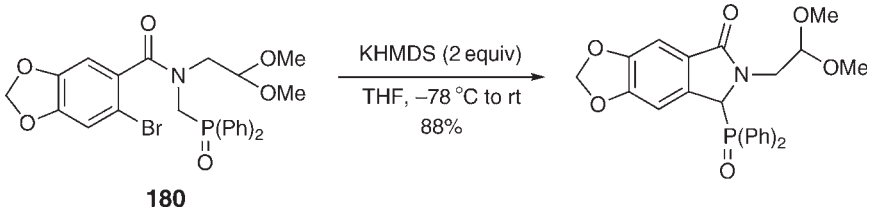
The protected aniline **179** undergoes titanium tetrachloride-mediated cyclization to give the protected indole (Equation 115) <1998EJM839>.



179

(115)

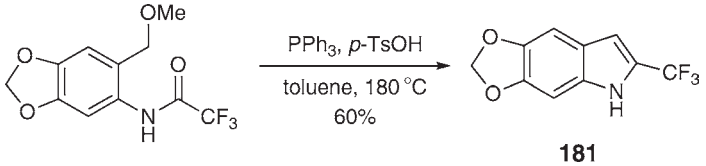
The phosphorylated bromobenzamide derivative **180** cyclizes to produce the phosphorylated isoindolinone on exposure to an excess of potassium hexamethyldisilazide (KHMDS) (Equation 116) <2000T1491>.



180

(116)

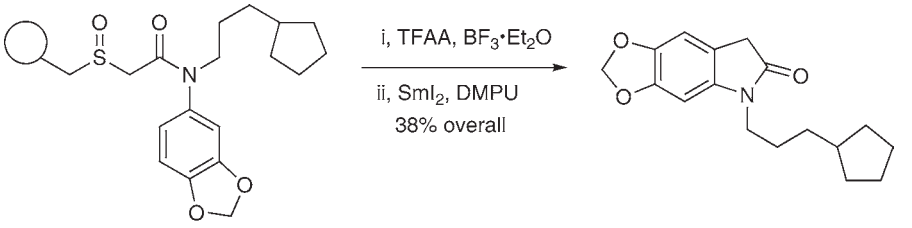
2-Trifluoromethylindole **181** is produced on heating 2-(*N*-trifluoroacetylamino)benzyl methyl ether in a sealed tube in the presence of triphenylphosphine and a catalytic quantity of *para*-toluenesulfonic acid (Equation 117) <1996J(P1)1261>.



181

(117)

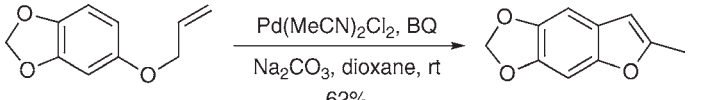
Oxindoles are prepared using a solid-phase Pummerer reaction. Thus, the immobilized amide **182** undergoes the Pummerer rearrangement on treatment with TFAA and boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) (Equation 118). Cleavage of the oxindole from the linker is achieved using samarium iodide and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) <2003CC2380>.



(118)

182

The allyl aryl ether **183** is converted into the 2-methylbenzofuran in a one-pot procedure *via* sequential Pd-catalyzed Claisen rearrangement and oxidative cyclization mediated by stoichiometric quantities of 1,4-benzoquinone (BQ) (Equation 119) <2005OL3355>.

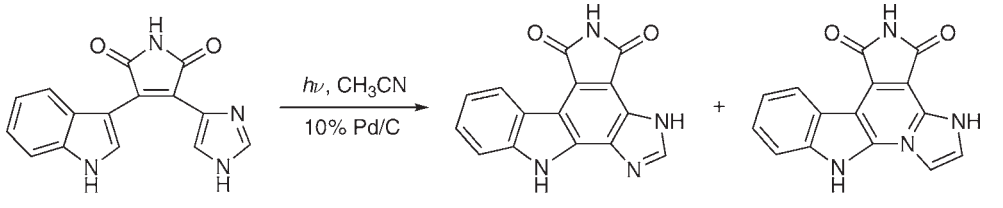


(119)

183

10.21.9.3.2(ii) Synthesis of the carbocyclic ring by formation of one bond

The alkaloids granulatamide **30** and isogranulatimide, isolated from marine invertebrates, have been synthesized from didemnimide A by a facile photochemical cyclization (Equation 120). It is unclear whether this is a biomimetic cyclization <1998JOC9850>.

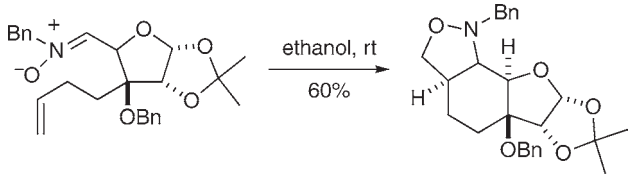


(120)

30
91%

8%

The intramolecular nitrone cyclization approach has been used to produce cycloadducts containing a central six-membered ring in a manner analogous to that described in Section 10.21.9.2.2(ii). Thus, the nitrone **184** bearing an alkoxy substituent at the 3-position gives the six-membered ring product **185** (Equation 121), whereas the hydroxyl-containing precursor gives the seven-membered ring cycloadduct exclusively <1997JOC8948> (see Section 10.21.9.4.2(ii)).

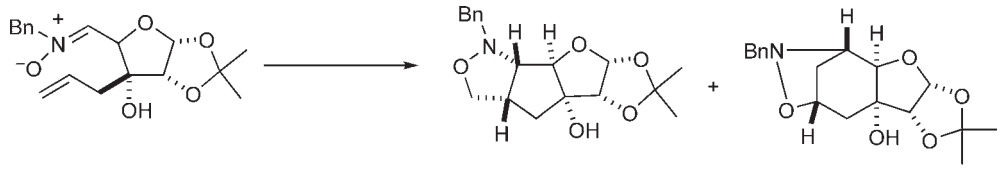


(121)

184 **185**

Furthermore, it was noted that the product ratio was also dependent on the nature of the solvent employed. Thus, the nitrone **186** (Equation 122) undergoes cyclization in nonpolar aprotic solvents such as benzene or toluene and polar aprotic solvents such as DMSO, DMF, or acetonitrile to afford the five-membered ring cycloadduct **155** as the

major product. The product ratio is reversed in cycloadditions carried out in alcohol solvents, such as methanol or ethanol <1996T11265>, which produce the six-membered ring cycloadduct as the major product.



186 155

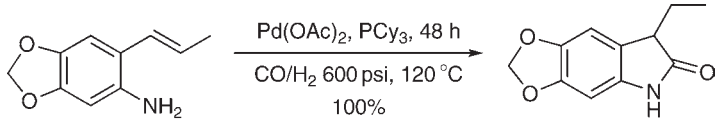
benzene	1.6 : 1	(85%)
DMF	4 : 1	(80%)
EtOH	1 : 1.6	(86%)

(122)

10.21.9.3.2(iii) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.3.2(iii)(a) A C–N and a C–C bond

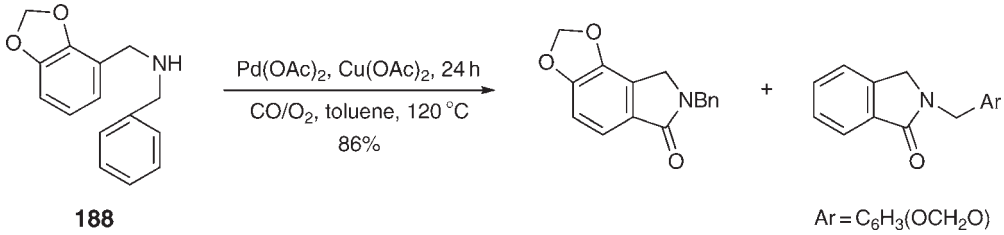
The carbonylation of the 2-aminostyrene **187** in dichloromethane under a carbon monoxide and hydrogen atmosphere produces the lactam in the presence of a palladium acetate/tricyclohexylphosphine catalyst in excellent yield and selectivity (Equation 123) <1996JA4264>.



187

(123)

The arylalkylamine **188** undergoes palladium(II)-catalyzed carbonylation with $Pd(OAc)_2$ and $Cu(OAc)_2$ in the presence of carbon monoxide gas containing oxygen to produce equal quantities of the isomeric benzolactams (Equation 124) <2004JA14342>.

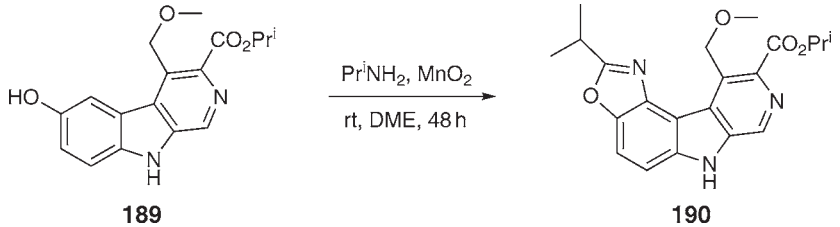


188 Ar = $C_6H_3(OCH_2O)$

(124)

10.21.9.3.2(iii)(b) A C–N and a C–O bond

Treatment of isopropyl 6-hydroxy-4-methoxymethyl-β-carboline-3-carboxylate **189** with a primary amine in the presence of an excess of manganese dioxide produces the oxazolo[4,5-*g*]-β-carboline **190** in moderate yield (Equation 125) <1998H(48)31>. The efficiency of the reaction is limited by the formation of by-products.

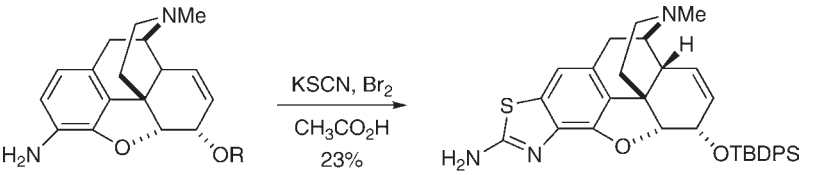


189 190

(125)

10.21.9.3.2(iii)(c) A C–N and a C–S bond

The aminothiazole ring of the novel opioid derivative **191** is produced on reaction of the corresponding amine with potassium thiocyanate and bromine in acetic acid (Equation 126) <2004JME1886>.



(126)

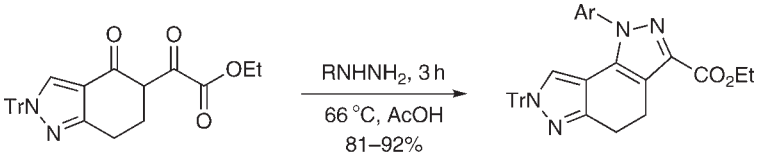
191

10.21.9.3.3 Compounds with two heteroatoms in both heterocyclic rings

10.21.9.3.3(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.3.3(i)(a) A C–N bond

The diketoester **192** reacts with substituted hydrazines to produce tetrahydrobenzodipyrazoles in high yields which are converted into dihydrobenzodipyrazoles on reaction with DDQ in refluxing dioxane (Equation 127) <2005BML1315>.

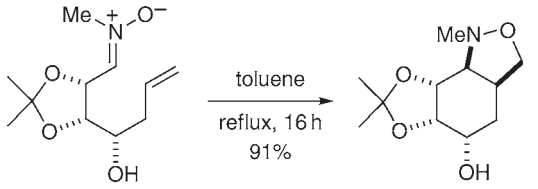


(127)

192

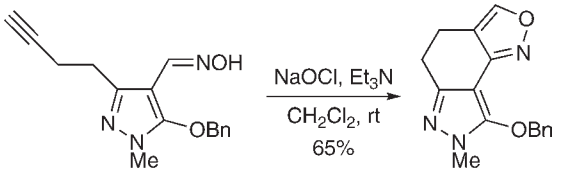
10.21.9.3.3(ii) Synthesis of the carbocyclic ring by formation of one bond

Further examples of intramolecular 1,3-dipolar cycloadditions (cf. Section 10.21.9.2.2(ii)) include the synthesis of an isoxazolidine from nitrone **193** (Equation 128) <1997J(P1)1805>, and a pyrazolo heterocycle from the nitrile oxide generated *in situ* from the oxime **194** (Equation 129) <1999TL3535>.



(128)

193



(129)

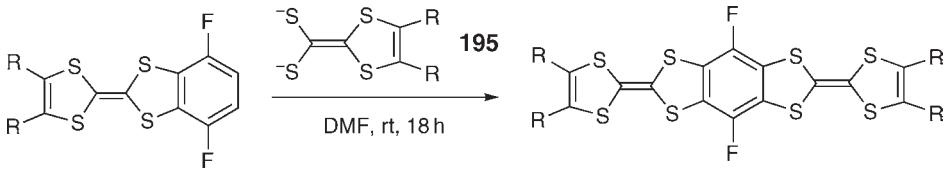
194

The synthesis of tetrahydroisoxazoloindazoles by an intramolecular [3+2] cycloaddition from an *in situ*-generated nitrile oxide that proceeds in good yields has also been reported <2004TL4934>.

10.21.9.3.3(iii) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.3.3(iii)(a) Two C–S bonds

Tetrathiafulvalene derivatives undergo reaction with nucleophiles, such as **195**, to produce the linearly-fused TTF compounds such as **51** in reasonable yields (Equation 130). A small amount of the angularly substituted regioisomer is also produced <1995JA9995>.

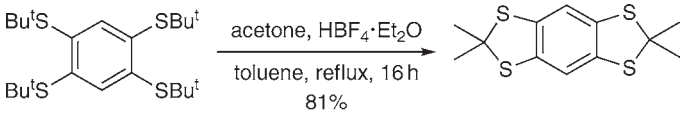


51

R = CH_3 (40%)
R = $CH_3(CH_2)_5$ (31%)

(130)

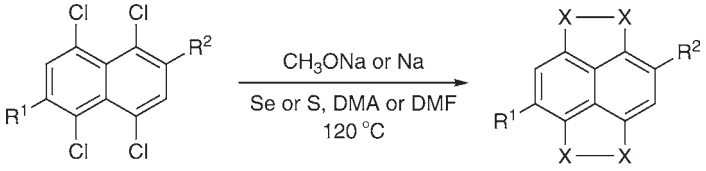
Acid-mediated hydrolysis of tetra-*tert*-butylthiobenzene **196** in the presence of acetone produces the thioacetonide **42** in good yield, thus avoiding the requirement to isolate the highly air-sensitive benzene-1,2,4,5-tetrathiol intermediate, and the use of highly toxic phosgene employed in previous syntheses (Equation 131) <2002JOC4635>.



196 **42**

(131)

Tetrathionaphthalenes and their corresponding selenium analogues are synthesized by reaction of tetrachloronaphthalenes **197** with *in situ*-generated sodium disulfide or with sodium diselenide (Equation 132). The yields of the sulfur analogues were found to be dependent on the method of disulfide generation (**Table 14**) <2001HAC287>.



197

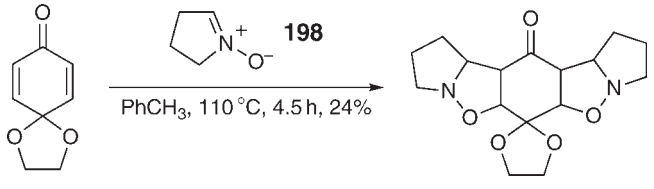
(132)

Table 14 Tetrathionaphthalene synthesis

R^1	R^2	X	*Yield* (%)
H	Me	S	10
H	Me	Se	52
Me	Me	S	23
Me	Me	Se	41

10.21.9.3.3(iii)(b) One C–C and one C–O bonds

para-Benzoquinone monoketal undergoes 1,3-dipolar cycloaddition with the cyclic nitrone **198** to produce a 2:1 cycloadduct as the major product even in the presence of an excess of the benzoquinone (Equation 133) <1997JOC7781>. The structure was assigned as the doubly *exo*-product due to the symmetry of the carbons of the dioxolane ring.



(133)

10.21.9.3.3(iv) Synthesis of the carbocyclic ring by formation of two bonds

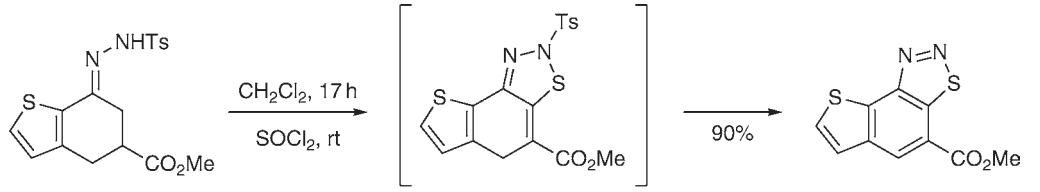
No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

10.21.9.3.4 Compounds with more than two heteroatoms in either ring

10.21.9.3.4(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.3.4(i)(a) A C–N bond

The *N*-tosylhydrazone **199** undergoes cyclization upon treatment with a large excess of thionyl chloride (20 equiv) to produce the fully aromatic thiadiazole **200** without any of the expected dihydrothiadiazole <1996H(33)1759>. It is envisaged that the ester substituent is the controlling factor in the formation of the fully aromatic product *via* formation of the intermediate illustrated (Equation 134).



199 **200** (134)

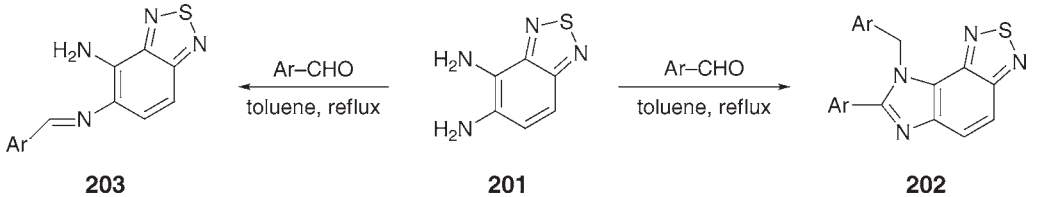
10.21.9.3.4(ii) Synthesis of the carbocyclic ring by formation of one bond

No examples have been reported during this period.

10.21.9.3.4(iii) Synthesis of the heterocyclic ring by formation of two bonds

10.21.9.3.4(iii)(a) Two C–N bonds

4,5-Diamino-2,1,3-benzothiadiazole **201** undergoes cyclization on reaction with selected aromatic aldehydes <2004T2953>. Thus, reactions with pyrene-1-carboxaldehyde or naphthalene-1-carboxaldehyde in refluxing toluene produce the corresponding imidazoles **202** in moderate yields, whereas reactions with *p*-(*N*,*N*-dimethylamino)benzaldehyde and *p*-[*N*,*N*-di(4-methylphenyl)amino]benzaldehyde under similar conditions gave the corresponding 5-imino derivatives **203** (**Scheme 13**).



203 **201** **202**

Ar = *p*-(*N*,*N*-dimethylamino)phenyl
Ar = *p*-[*N*,*N*-di(4-methyphenyl)amino]phenyl

Ar = 1-pyrenyl (15%)
Ar = 1-naphthyl (20%)

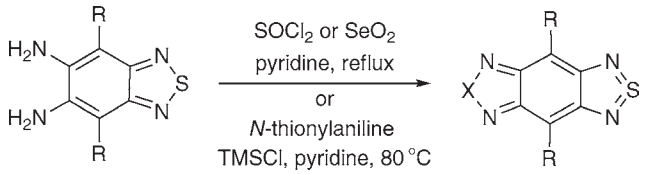
Scheme 13

10.21.9.3.4(iii)(b) Two C–O bonds

Bis(cyclic) boronates derived from cyclohexadienes are produced in good yields in a manner similar to that described in Section 10.21.9.2.4(i)(a) <1998JOC7322>.

10.21.9.3.4(iii)(c) Two N–S bonds

The nonclassical heterocycles **17** and **54** are prepared in high yields by the reaction of diamine **204** with thionyl chloride or *N*-thionylaniline and trimethysilyl chloride in pyridine (Equation 135). The corresponding selenium analogues were prepared by reaction of **193** with selenium dioxide (**Table 15**) <1995JA6791, 1997T10169>.



204 (135)

Table 15 Synthesis of nonclassical heterocycles

R	*X*	*Yield* (%)
Br	S	74
Ph	S	95
Br	Se	40
Ph	Se	82

10.21.9.3.4(iv) Synthesis of the carbocyclic ring by formation of two bonds

No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

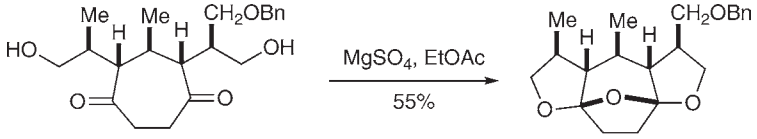
10.21.9.4 Synthesis of Compounds with a Central Seven- or Larger-Membered Ring

10.21.9.4.1 Compounds with one heteroatom in each heterocyclic ring

10.21.9.4.1(i) Synthesis of the heterocyclic ring by formation of one bond

10.21.9.4.1(i)(a) A C–O bond

The homochiral dione **205** undergoes magnesium sulfate-mediated acetalization to give the bisacetal **206** as a single enantiomer in reasonable yield from a multistep sequence (Equation 136) <1998TL5717>.



205 206 (136)

10.21.9.4.1(ii) Synthesis of the carbocyclic ring by formation of one bond

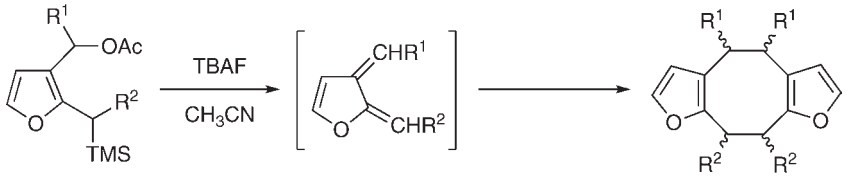
No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

10.21.9.4.1(iii) Synthesis of the heterocyclic ring by formation of two bonds

No examples have been reported since this area was last reviewed <1996CHEC-II(7)841>.

10.21.9.4.1(iv) Synthesis of the carbocyclic ring by formation of two bonds

2,3-Dimethylene-2,3-dihydrofuran derivatives, which are produced by fluoride-induced 1,4-conjugative elimination of trimethylsilyl acetate from the [(trimethylsilyl)methyl]-3-furan precursor **207**, undergo subsequent [4+4] dimerization reactions to produce cycloocta[1,2-*b*:6,5-*b*′]difuran derivatives as a mixture of isomers (Equation 137) <1995JA841>. A methyl substituent at the 3-methylene position was found to retard the rate of dimerization, an observation which is consistent with the proposed two-step mechanism involving the initial formation of a diradical intermediate in the rate-determining step (**Table 16**).

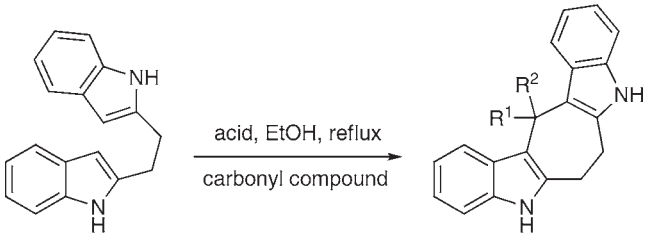


207 (137)

Table 16 2,3-Dihydrofuran synthesis by [4+4] dimerization reactions

R^1	R^2	*Yield* (%)
Me	H	42
H	Me	30
Me	Me	8

A series of cyclohept[1,2-*b*:5,4-*b*′]bisindole derivatives have been obtained by the reaction of 1,2-bis(1*H*-indol-2-yl)-ethane **208** with carboxylic acids, orthoesters, aldehydes, or ketones under acid conditions (Equation 138; **Table 17**) <2000T1911>. In the case of the reaction with TFA, the major product is the fully conjugated derivative (Section 10.21.5.1.3).

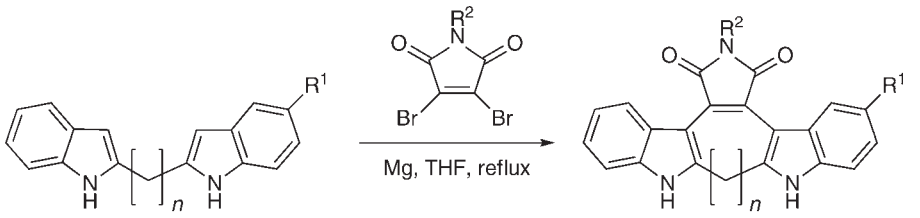


208 (138)

Table 17 Cyclohept[1,2-*b*:5,4-*b*′]bisindole synthesis

Carbonyl compound	R^1	R^2	*Yield* (%)
CF_3CO_2H/CoF_3	H	CF_3	12
$4\text{-}O_2NC_6H_4CHO$	H	$4\text{-}O_2NC_6H_4$	86
$3,4\text{-}(OCH_2O)C_6H_3CHO$	H	$3,4\text{-}(OCH_2O)C_6H_3$	65
CH_3COCH_3	CH_3	CH_3	80

The related cyclohepta-, cycloocta-, and cyclonona[*b*]indole-1,3-diones **209** have been produced in moderate to poor yields under Grignard conditions by reaction with dibromomaleimide (Equation 139; **Table 18**) <1999JOC8130>.

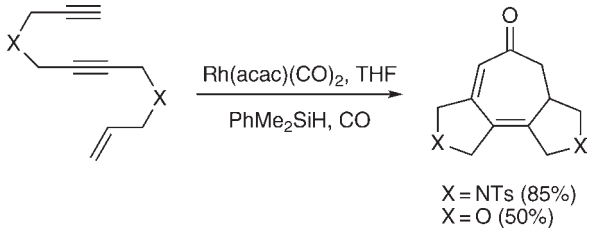


209 (139)

Table 18 Synthesis of cyclohepta-, cycloocta-, and cyclonona[*b*]-indole-1,3-diones

n	R^1	R^2	*Yield* (%)
1	H	H	17
1	OCH_3	H	8
1	H	CH_2OCH_2Ph	31
1	H	CH_3	49
2	H	CH_3	24
3	H	H	2

Heteroatom-containing enediynes undergo a carbotricyclization process on exposure to catalytic quantities of rhodium salts and phenyldimethylsilane under a carbon monoxide atmosphere to produce the corresponding fused tricyclic compounds (Equation 140) <2000JA2385>.



(140)

10.21.9.4.2 Compounds with two heteroatoms in one heterocyclic ring and one in another

10.21.9.4.2(i) Synthesis of the heterocyclic ring

No examples have been reported during this period.

10.21.9.4.2(ii) Synthesis of the carbocyclic ring by formation of one bond

The intramolecular nitrone cyclization approach has been used to produce cycloadducts containing a central seven-membered ring in a manner analogous to that described in Section 10.21.9.3.2(ii) <1996T11265>.

10.21.9.4.3 Compounds with two heteroatoms in both heterocyclic rings

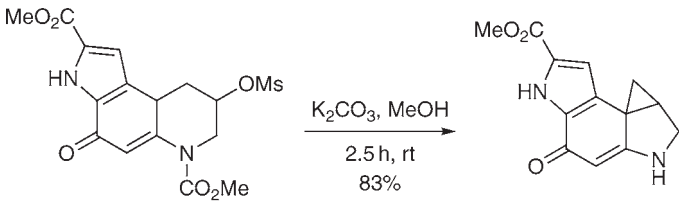
No examples have been reported during this period.

10.21.9.4.4 Compounds with more than two heteroatoms in either ring

Bis(cyclic) boronates derived from cycloheptadiene and cyclooctadiene are produced in good yields in a manner similar to that described in Section 10.21.9.2.4(i)(a) <1998JOC7322>.

10.21.10 Ring Syntheses by Transformations of Another Ring

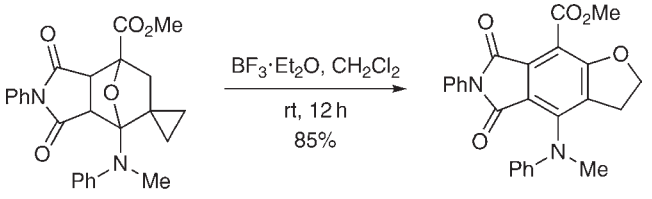
A novel approach to the construction of the duocarmycin core has involved the formation of the cyclopropane ring and the five-membered C-ring by an intramolecular ring contraction <1998CPB400, 2004OL2953>. Thus, treatment of the dihydroquinoline **210** with potassium carbonate in methanol gives the tetracyclic product **211** (Equation 141).



(141)

210 **211**

Cycloadduct **212** is converted into the dihydrobenzofuran **213** when treated with boron trifluoride diethyl etherate in good yield <2000JA8155>. The formation of the dihydrobenzofuran proceeds by an initial ring opening followed by a subsequent dehydration and acid-catalyzed cyclopropyl ketone rearrangement (Equation 142).



(142)

212 **213**

10.21.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The great diversity of systems in this chapter makes a comparison of synthetic approaches difficult and most of the best synthetic approaches have counterparts in the syntheses of simpler heterocycles. Since the area was last reviewed <1996CHEC-II(7)841>, established methods have continued to be of synthetic utility; in particular, the photocyclization chemistry of 1,2-bis(heteroaryl)ethene systems and the chemistry of bis-TTFs have been further explored. The focus, however, of these research efforts has tended to concentrate on the applications of these materials in electronic devices with less emphasis on novel synthetic approaches. A noticeable trend has been the increasing use of metal-mediated chemistry, in particular, chemistry involving transition metals. The diverse range of metals employed and the number of tricyclic systems synthesized admirably demonstrates the importance of this area.

Significant interest in the formation of the indolocarbazole and related ring systems has seen a number of approaches for the generation of this important nucleus. In particular, the addition of a two-carbon unit to biindoyls to construct the central carbon ring has attracted attention, and a number of diverse approaches involving acid-catalyzed addition, transition metal-mediated annulation, carbene insertion, metathesis, and cycloaddition have all proved successful. The intramolecular addition of 1,3-dipoles such as nitrones and nitrile oxides is an especially attractive approach for the synthesis of highly functionalized cyclopentane and cyclohexane derivatives, allowing the construction of two rings simultaneously and with the added attraction that these transformations proceed with high levels of diastereoselectivity. Recent studies have begun to elucidate the subtleties of this approach and have highlighted the importance of substituents and reaction conditions in controlling the outcome of the cycloaddition. Synthetic approaches for the synthesis of CC-1065 and its related family of antitumor agents have continued to attract considerable interest.

10.21.12 Important Compounds and Applications

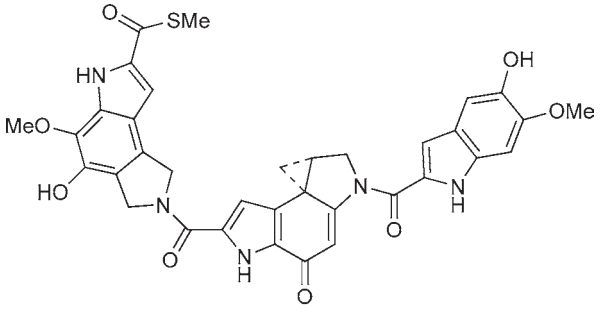
The wide structural diversity in the tricyclic compounds considered in this chapter ensures that they have found an equally diverse range of applications. The applications previously outlined <1996CHEC-II(7)841> have continued to be important and have been further developed. Carbocyclic anhydrides and imides continue to find application for the synthesis of polymeric materials which are used extensively in microelectronics due to their excellent thermal and electrical properties <2001PPO3>. Similarly, polymers containing benzobisthiazoles, benzobisoxazoles, and

benzobisimidazoles are rigid-like materials which display high specific strength due to hydrogen bonding and π-stacking and have found applications as organic LEDs <2001PSB559, 2001PPO3, 2002PSB1760, 2005PLM5630, 2000PLM9003>. The oxidation potential of all of these polymers has been determined by cyclic voltammetric (CV) methods and they show high potential for oxidation <2003SM(135)107, 2004PLM459>. The resulting cations are stabilized by resonance across the conjugated polymer giving rise to both inter- and intramolecular electron transport. Recent reports have suggested that macromolecular triazatruxenes which contain a diindolocarbazole core act as promising electroluminescence materials that are potentially useful for the production of pure-blue LEDs <2006MM3707>.

Polymers which have small HOMO–LUMO gaps have inherent conductive properties. The recent advent of molecular electronics has stimulated research into polycyclopentadiheterocycles and polybenzobisdiheterocycles <1997SM(84)973, 1998SM(92)25, 1999JOC7419, 2004PLM8871>. Both theoretical calculations and experimental data show that these materials possess the desired electrochemical properties for such applications. For example, bis-TTFs, which show long-range electron-transfer processes, offer possible applications as molecular wires <1997PCB3665, 1997SM(86)1999, 2001SM(119)99>. Polycyclopentadithiophenes also exhibit conductive properties <1999SM(102)1000>. Substitution on the cyclopentane moiety as well as substitution of sulfur for other elements results in a subsequent decrease in the HOMO–LUMO gap <1996SM(79)115, 1999SM(101)602, 2004SM(140)127, 2004MI335, 2003MI467>.

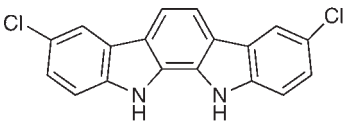
The photochromism displayed by diarylethenes gives them the potential to act as luminescent markers and much research has been undertaken to control the emission properties of derivative compounds/complexes. Altering the functionality associated with the diarylethene ultimately results in a shift of the adsorption wavelength, sometimes into the visible range, giving rise to different energy transitions <1995TL3453, 1997T12263, 1998T6627>.

Natural products containing benzodipyrrole moieties include the antitumor agents CC-1065, the duocarmycins, and yatakemycin **214**, and there is continuing interest in understanding further their mode of action in order to produce compounds with reduced toxicity <2004JA8396, 2003JA10971, 2005JOC7098>. Their activity is thought to derive from their ability to promote DNA alkylation reactions and *ab initio* calculations on the alkylation reaction have been reported <2004JOC6202>.

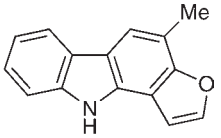


(+)-Yatakemycin
214

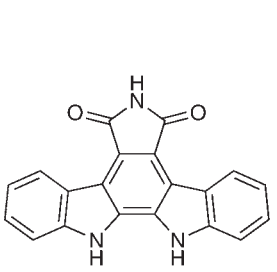
Similarly, there has been continued interest in the synthesis of naturally occurring carbazole alkaloids which display a range of biological activity such as the tjipanazoles **215**, staurosporine **29**, furostifoline **216**, arcyriaflavins A–D **217**, ZHD-0501 **218**, bictyodendrin B, and rebeccamycin <2001AHC(80)1, 2002CRV4303, 2005JA11620>. Indolobenzopyrrole-based alkaloids, such as granulatamide **30** <1998JOC9850>, have also attracted attention as important targets for the pharmaceutical industry. Improvements in analytical methods have led to the reassignment of many stereogenic centers, and advances in synthetic methodologies have been applied to the synthesis of these alkaloids to reduce the total number of steps and improve the overall yields.



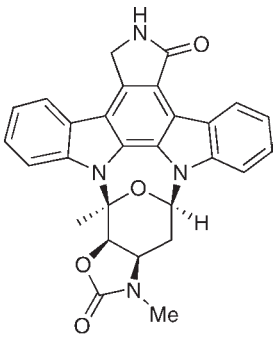
Tjipanazole D
215



Furostifoline
216



Arcyriaflavin A
217



ZHD-0501
218

A number of tricyclic nuclei are of interest to medicinal chemists and have been incorporated into a range of potential pharmaceutical lead compounds since they can be used as conformationally restricted bioisosteres of common cellular components. Thus, recent applications have included the use of tetrahydrobenzodifuran functionalities as conformationally restricted bioisosteres of the aromatic methoxy groups in prototypical hallucinogenic phenylalkylamines <1996JME4966>, the evaluation of benzodithiophenediones as potential cytotoxic agents <2005BML1315>, and investigation of benzodipyrazoles as potent CDK2 inhibitors <1999BMC1025>.

10.21.13 Further Developments

Recent developments in tricyclic systems can be found in the following articles <2006ACR935, 2006CC2750, 2006JA7136, 2007JOC574, 2007JOC2008, 2007OBC2046, 2007OL1883>.

References

1995JA841 M.-K. Leung and W. S. Trahanovsky, *J. Am. Chem. Soc.*, 1995, **117**, 841.
1995JA6791 M. Karikomi, C. Kitamura, S. Tanaka, and Y. Yamashita, *J. Am. Chem. Soc.*, 1995, **117**, 6791.
1995JA9995 K. Lahlil, A. Moradpour, C. Bowlas, F. Menou, P. Cassoux, J. Bonvoisin, J.-P. Launay, G. Dive, and D. Dehareng, *J. Am. Chem. Soc.*, 1995, **117**, 9995.
1995JA10413 J. L. Wood, B. M. Stoltz, and H.-J. Dietrich, *J. Am. Chem. Soc.*, 1995, **117**, 10413.
1995JOC1303 M. Abdul-Aziz, J. V. Auping, and M. A. Meador, *J. Org. Chem.*, 1995, **60**, 1303.
1995JOC2353 U. C. Yoon and S. J. Cho, *J. Org. Chem.*, 1995, **60**, 2353.
1995JOC5224 C. Marschner, J. Baumgartner, and H. Griengl, *J. Org. Chem.*, 1995, **60**, 5224.
1995MM9 H. K. Hall, Jr., A. B. Padias, I. Yahagi, P. A. Williams, M. A. Bruck, and X. Drujon, *Macromolecules*, 1995, **28**, 9.
1995SM(72)147 J. P. Ferraris, C. Henderson, D. Torres, and D. Meeker, *Synth. Met.*, 1995, **72**, 147.
1995T2533 E. Fanghänel, R. Herrmann, and H. Naarmann, *Tetrahedron*, 1995, **51**(9), 1995, 2533.
1995TL3453 Z. Sun, R. S. Hosmane, and M. Tadros, *Tetrahedron Lett.*, 1995, **36**, 3453.
1996CHEC-II(7)841 D. M. McKinnon; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Elsevier, Oxford, 1995, vol. 7, p. 841.
1996BMC1379 S. Nagamura, E. Kobayashi, K. Gomi, and H. Saito, *Bioorg. Med. Chem.*, 1996, **4**, 1379.
1996CM570 C. Kitamura, S. Tanaka, and Y. Yamashita, *Chem. Mater.*, 1996, **8**, 570.
1996CRV49 M. Lautens, W. Klute, and W. Tam, *Chem. Rev.*, 1996, **96**, 49.
1996H(33)1759 P. Stanetty, M. Kremslehner, and M. Müller, *Heterocycles*, 1996, **33**, 1759.
1996JA4264 B. El Ali, K. Okuro, G. Vasapollo, and H. Alper, *J. Am. Chem. Soc.*, 1996, **118**, 4264.
1996JME2953 A. P. Monte, D. Marona-Lewicka, M. A. Parker, D. B. Wainscott, D. L. Nelson, and D. E. Nichols, *J. Med. Chem.*, 1996, **39**, 2953.
1996JME4966 I. T. Forbes, S. Dabbs, D. M. Duckworth, P. Ham, G. E. Jones, F. D. King, D. V. Saunders, F. E. Blaney, C. B. Naylor, and G. S. Baxter, *J. Med. Chem.*, 1996, **39**, 4966.
1996JOC413 S. W. McCombie and S. F. Vice, *J. Org. Chem.*, 1996, **61**, 413.
1996JOC480 Y. Nishimura, Y. Umezawa, H. Adachi, S. Kondo, and T. Takeuchi, *J. Org. Chem.*, 1996, **61**, 480.
1996JOC5804 J. Ezquerra, C. Pedregal, C. Lamas, J. Barluenga, M. Pérez, M. A. García-Martín, and J. M. González, *J. Org. Chem.*, 1996, **61**, 5804.
1996JOC6166 C. O. Kappe and A. Padwa, *J. Org. Chem.*, 1996, **61**, 6166.
1996JOC8256 T. Inoue, O. Kitagawa, Y. Oda, and T. Taguchi, *J. Org. Chem.*, 1996, **61**, 8256.
1996JOC9340 J. W. Fischer, R. A. Hollins, C. K. Lowe-Ma, R. A. Nissan, and R. D. Chapman, *J. Org. Chem.*, 1996, **61**, 9340.
1996J(P1)1261 K. Miyashita, K. Kondoh, K. Tsuchiya, H. Miyabe, and T. Imanishi, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1261.
1996J(P1)1277 A. Ishii, K. Maeda, M. Kodachi, N. Aoyagi, K. Kato, T. Maruta, M. Hoshino, and J. Nakayama, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1277.
1996SM(79)115 A. K. Bakhshi, Y. Yamaguchi, H. Ago, and T. Yamabe, *Synth. Met.*, 1996, **79**, 115.

1996T647 P. J. Parsons, C. S. Penkett, M. C. Cramp, R. I. West, and E. S. Warren, *Tetrahedron*, 1996, **52**, 647.
1996T1267 R. Alibés, J. L. Bourdelande, J. Font, A. Gregori, and T. Parella, *Tetrahedron*, 1996, **52**, 1267.
1996T11265 R. Patra, N. C. Bar, A. Roy, B. Achari, N. Ghoshal, and S. B. Manda, *Tetrahedron*, 1996, **52**, 11265.
1996T13227 A. Citterio, R. Sebastiano, A. Maronati, F. Viola, and A. Farina, *Tetrahedron*, 1996, **52**, 13227.
1996TL4149 C. Marchionni, P. Vogel, and P. Roversi, *Tetrahedron Lett.*, 1996, **37**, 4149.
1996TL4631 S. W. Wright, L. D. McClure, and D. L. Hageman, *Tetrahedron Lett.*, 1996, **37**, 4631.
1997BML749 Y. Fukuda, Y. Oomori, and Y. Kusama, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 749.
1997CRV173 J. Roncali, *Chem. Rev.*, 1997, **97**, 173.
1997CRV787 D. L. Boger, C. W. Boyce, R. M. Garbaccio, and J. A. Goldberg, *Chem. Rev.*, 1997, **97**, 787.
1997H(45)1899 S. Yasuike, F. Nakashima, J. Kurita, and T. Tsuchiya, *Heterocycles*, 1997, **45**, 1899.
1997HCA111 U. Dahlmann and R. Neidlein, *Helv. Chim. Acta*, 1997, **80**, 111.
1997JA4977 D. L. Boger, D. L. Hertzog, B. Bollinger, D. S. Johnson, H. Cai, J. Goldberg, and P. Turnbull, *J. Am. Chem. Soc.*, 1997, **119**, 4977.
1997JA6214 E. A. Lukhtanov, I. V. Kutyavin, V. V. Gorn, M. W. Reed, A. D. Adams, D. D. Lucas, and R. B. Meyer, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 6214.
1997JA9641 J. L. Wood, B. M. Stoltz, H.-J. Dietrich, D. A. Pflum, and D. T. Petsch, *J. Am. Chem. Soc.*, 1997, **119**, 9641.
1997JA12136 T. M. Barclay, A. W. Cordes, J. D. Goddard, R. C. Mawhinney, R. T. Oakley, K. E. Preuss, and R. W. Reed, *J. Am. Chem. Soc.*, 1997, **119**, 12136.
1997JME2123 A. K. L. Fung, W. R. Baker, S. Fakhoury, H. H. Stein, J. Cohen, B. G. Donner, D. S. Garvey, K. P. Spina, and S. H. Rosenberg, *J. Med. Chem.*, 1997, **40**, 2123.
1997JME2997 A. P. Monte, S. R. Waldmann, D. Marona-Lewicka, M. A. Parker, D. B. Wainscott, D. L. Nelson, E. Saunders-Bush, and D. E. Nichols, *J. Med. Chem.*, 1997, **40**, 2997.
1997JOC4465 K. Tanaka, H. Suzuki, and H. Osuga, *J. Org. Chem.*, 1997, **62**, 4465.
1997JOC7397 J. Marco-Contelles, P. Gallego, M. Rodríguez-Fernández, N. Khiar, C. Destabel, M. Bernabé, A. Martínez-Grau, and J.-L. Chiara, *J. Org. Chem.*, 1997, **62**, 7397.
1997JOC7781 P. de March, M. Escoda, M. Figueredo, J. Font, A. Alvarez-Larena, and J. F. Piniella, *J. Org. Chem.*, 1997, **62**, 7781.
1997JOC8948 N. C. Bar, A. Roy, B. Achari, and S. B. Mandal, *J. Org. Chem.*, 1997, **62**, 8948.
1997J(P1)1805 S. Jiang, K. J. McCullough, B. Mekki, G. Singh, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1805.
1997J(P1)2457 J. K. Gallos, A. E. Koumbis, and N. E. Apostolakis, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2457.
1997J(P1)3673 S. S. Samanta, S. Chandra, and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3673.
1997JPO33 T. Strassner and J. Fabian, *J. Phys. Org. Chem.*, 1997, **10**, 33.
1997MI347 A. K. Bakhshi, D. Ladik, and J. Ladik, *Solid State Commun.*, 1997, **101**, 347.
1997PCB3665 K. Pokhodnia, P. Cassoux, J. Bonvoisin, A. Mlayah, S. Freznel, and K. Mullen, *J. Phys. Chem. B*, 1997, **101**, 3665.
1997SM(84)973 S. R. Gunatunga, G. W. Jones, M. Kalaji, P. J. Murphy, D. M. Taylor, and G. O. Williams, *Synth. Met.*, 1997, **84**, 973.
1997SM(86)1999 K. Pokhodnia, P. Cassoux, J. Bonvoisin, A. Mlayah, L. Brossard, S. Frenzel, and K. Mullen, *Synth. Met.*, 1997, **86**, 1999.
1997T6879 A. M. Horneman and I. Lundt, *Tetrahedron*, 1997, **53**, 6879.
1997T10169 Y. Yamashita, K. One, M. Tomura, and S. Tanaka, *Tetrahedron*, 1997, **53**, 10169.
1997T12263 M. Irie, T. Eriguchi, T. Takada, and K. Uchida, *Tetrahedron*, 1997, **53**, 12263.
1997T16897 M. P. van Boggelen, B. F. G. A. van Dommelen, S. Jiang, and G. Singh, *Tetrahedron*, 1997, **53**, 16897.
1997TL457 K. Tanaka, H. Suzuki, and H. Osuga, *Tetrahedron Lett.*, 1997, **38**, 457.
1997TL3817 D. P. Richardson, P. W. Cart, J. N. Cumming, W. G. Harbison, N. D. Raoof, M. S. Sanders, E. Shin, T. E. Smith, and T. H. Wintner, *Tetrahedron Lett.*, 1997, **38**, 3817.
1997TL6787 C. A. Merlic, D. M. McInnes, and Y. You, *Tetrahedron Lett.*, 1997, **38**, 6787.
1997TL7207 Y. Fukada, *Tetrahedron Lett.*, 1997, **38**, 7207.
1998AGE2484 K. Takahashi, S. Fujita, K. Akiyama, M. Miki, and K. Yanagi, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 2484.
1998CC1233 K. Takahashi and S. Tarutani, *J. Chem. Soc., Chem. Commun.*, 1998, 1233.
1998CEJ1554 L. F. Tietze, W. Buhr, J. Looft, and T. Grote, *Chem. Eur. J.*, 1998, **4**, 1554.
1998CPB400 H. Muratake, M. Tonegawa, and M. Natsume, *Chem. Pharm. Bull.*, 1998, **46**, 400.
1998EJM839 J. B. Hansen, A. Fink-Jensen, B. V. Christensen, F. C. Grtnvald, L. Jeppesen, J. P. Mogensen, E. B. Nielsen, M. A. Scheideler, F. J. White, and X.-F. Zhang, *Eur. J. Med. Chem.*, 1998, **33**, 839.
1998H(48)31 P. H. Oleson, D. Seidelmann, and J. B. Hansen, *Heterocycles*, 1998, **48**, 31.
1998JA13453 A. Berlin, G. Zotti, G. Schiavon, and S. Zecchin, *J. Am. Chem. Soc.*, 1998, **120**, 13453.
1998JME4658 Y.-H. Chao, S.-C. Kuo, C.-H. Wu, C.-Y. Lee, A. Mauger, I.-C. Sun, S. L. Morris-Natschke, and K.-H. Lee, *J. Med. Chem.*, 1998, **41**, 4658.
1998JOC1919 A. M. Horneman and I. Lundt, *J. Org. Chem.*, 1998, **63**, 1919.
1998JOC7002 P. Manini, M. d'Ischia, M. Milosa, and G. Prota, *J. Org. Chem.*, 1998, **63**, 7002.
1998JOC7322 A. Gypser, D. Michel, D. S. Nirschl, and K. B. Sharpless, *J. Org. Chem.*, 1998, **63**, 7322.
1998JOC9850 R. G. S. Berlinck, R. Britton, E. Piers, L. Lim, M. Roberge, R. Moreira da Rocha, and R. J. Andersen, *J. Org. Chem.*, 1998, **63**, 9850.
1998J(P1)935 K. Tanaka, H. Osuga, H. Suzuki, Y. Shogase, and Y. Kitahara, *J. Chem. Soc., Perkin Trans. 1*, 1998, 935.
1998J(P1)3921 A. Winling and R. A. Russell, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3921.
1998MI723 T. Mavromoustakous, I. K. Stamos, C. Kamoutsis, E. Theodoropoulou, M. Zervou, and E. Humpfer, *J. Pharm. Biomed. Anal.*, 1998, **16**, 723.
1998SM(92)25 R. Beyer, M. Kalaji, G. Kingscote-Burton, P. J. Murphy, V. M. S. C. Pereira, D. M. Taylor, and G. O. Williams, *Synth. Met.*, 1998, **92**, 25.
1998T6627 K. Uchida, T. Ishikawa, M. Takeshita, and M. Irie, *Tetrahedron*, 1998, **54**, 6627.
1998TL5717 J. H. Rigby and K. R. Fales, *Tetrahedron Lett.*, 1998, **39**, 5717.
1998TL6961 A. Gregori, R. Alibés, J. L. Bourdelande, and J. Font, *Tetrahedron Lett.*, 1998, **39**, 6961.
1998TL6963 A. Gregori, R. Alibés, J. L. Bourdelande, and J. Font, *Tetrahedron Lett.*, 1998, **39**, 6963.
1999BMC1025 Y.-H. Chao, S.-C. Kuo, K. Ku, I.-P. Chiu, C.-H. Wu, A. Mauger, H.-K. Wanga, and K.-H. Lee, *Bioorg. Med. Chem.*, 1999, **7**, 1025.

1999BMC1067 M. J. Slater, S. Cockerill, R. Baxter, R. W. Bonser, K. Gohil, C. Gowrie, J. E. Robinson, E. Littler, N. Parry, R. Randall, *et al.*, *Bioorg. Med. Chem.*, 1999, **7**, 1067.
1999CCR135 J. M. Rawson and G. D. McManus, *Coord. Chem. Rev.*, 1999, **189**, 135.
1999CEJ3285 A. Fernández-Acebes and J.-M. Lehn, *Chem. Eur. J.*, 1999, **5**, 3285.
1999CM2743 F. Fusalba, E. Mehdi, L. Breau, and D. Belanger, *Chem. Mater.*, 1999, **11**, 2743.
1999CRV1863 P. F. H. Schwa, M. D. Levim, and J. Michl, *Chem. Rev.*, 1999, **99**, 1863.
1999JA5097 N.-X. Hu, S. Xie, Z. Popovic, B. Ong, A.-M. Hor, and S. Wang, *J. Am. Chem. Soc.*, 1999, **121**, 5097.
1999JMC2095 H. Sirringhaus, R. H. Friend, C. Wang, J. Leuningerb, and K. Müllen, *J. Mater. Chem.*, 1999, **9**, 2095.
1999JME2946 N. Amishiro, A. Okamoto, C. Murakata, T. Tamaoki, M. Okabe, and H. Saito, *J. Med. Chem.*, 1999, **42**, 2946.
1999JNP959 P. Schupp, C. Eder, P. Proksch, V. Wray, B. Schneider, M. Herderich, and V. Paul, *J. Nat. Prod.*, 1999, **62**, 959.
1999JOC4411 U. C. Yoon, S. W. Oh, S. M. Lee, S. J. Cho, J. Gamlin, and P. S. Mariano, *J. Org. Chem.*, 1999, **64**, 4411.
1999JOC4697 S. Mahboobi, E. Eibler, M. Koller, S. Kumar, and A. Popp, *J. Org. Chem.*, 1999, **64**, 4697.
1999JOC5670 E. J. Gilbert, J. D. Chisholm, and D. L. Van Vranken, *J. Org. Chem.*, 1999, **64**, 5670.
1999JOC5946 M. Tercel, M. A. Gieseg, W. A. Denny, and W. R. Wilson, *J. Org. Chem.*, 1999, **64**, 5946.
1999JOC7419 U. Salzner, J. B. Lagowski, P. G. Pickup, and R. A. Poirier, *J. Org. Chem.*, 1999, **64**, 7419.
1999JOC7654 K. Chilba, M. Fukada, S. Kim, Y. Kitano, and M. Tada, *J. Org. Chem.*, 1999, **64**, 7654.
1999JOC8130 S. Mahboobi, T. Burgemeister, S. Dove, S. Kuhr, and A. Popp, *J. Org. Chem.*, 1999, **64**, 8130.
1999J(P1)605 R. A. Aitken, J. I. G. Cadogan, I. Gosney, C. M. Humphries (née Buchan), L. M. McLaughlin, and S. J. Wyse, *J. Chem. Soc., Perkin Trans. 1*, 1999, 605.
1999J(P1)3705 S. Chandra and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3705.
1999MM4010 Y. Takahashi, *Macromolecules*, 1999, **32**, 4010.
1999SM(101)123 M. Kalaji, P. J. Murphy, and G. O. Williams, *Synth. Met.*, 1999, **101**, 123.
1999SM(101)602 E. Orti, M. J. Sanchís, P. M. Viruela, and R. Viruela, *Synth. Met.*, 1999, **101**, 602.
1999SM(102)1000 C. A. Mills, D. M. Taylor, P. J. Murphy, G. W. Dalton, L. M. Jones, and A. V. Huges, *Synth. Met.*, 1999, **102**, 1000.
1999T2371 T. Janosik and J. Bergman, *Tetrahedron*, 1999, **55**, 2371.
1999T14985 M. Pasini, S. Destri, C. Botta, and W. Porzio, *Tetrahedron*, 1999, **55**, 14985.
1999T15167 J. K. Gallos, A. E. Koumbis, V. P. Xinpbaki, C. C. Dellios, and E. Coutoul-Argyropoulou, *Tetrahedron*, 1999, **55**, 15167.
1999TL3535 D. E. Kizer, R. B. Miller, and M. J. Kurth, *Tetrahedron Lett.*, 1999, **40**, 3535.
1999TL3795 M. M. Marques, A. M. Lobo, S. Prabhakar, and P. S. Branco, *Tetrahedron Lett.*, 1999, **40**, 3795.
1999TL5791 G. Mehta and N. Mohal, *Tetrahedron Lett.*, 1999, **40**, 5791.
2000BMC381 N. Amishiro, S. Nagamura, C. Murakata, A. Okamoto, E. Kobayashi, M. Asada, K. Gomi, T. Tamaoki, M. Okabe, N. Yamaguchi, *et al.*, *Bioorg. Med. Chem.*, 2000, **8**, 381.
2000BMC1195 N. Amishiro, A. Okamoto, M. Okabe, and H. Saito, *Bioorg. Med. Chem.*, 2000, **8**, 1195.
2000CC1139 T. Caronna, R. Sinisi, M. Catellani, L. Malpezzi, S. V. Meille, and A. Mele, *J. Chem. Soc., Chem. Commun.*, 2000, 1139.
2000CL450 Y. Watanabe, Y. Sakai, M. Ueda, Y. Oishi, and K. Mori, *Chem. Lett.*, 2000, 450.
2000CRV1685 M. Irie, *Chem. Rev.*, 2000, **100**, 1685.
2000CRV1789 B. L. Feringa, R. A. van Delden, N. Koumura, and E. M. Geertsema, *Chem. Rev.*, 2000, **100**, 1789.
2000CRV3755 E. E. Nifantiev, M. K. Grachev, and S. Y. Burmistrov, *Chem Rev.*, 2000, **100**, 3755.
2000EJO3363 R. N. Warrener, *Eur. J. Org. Chem.*, 2000, 3363.
2000JA2385 I. Ojima and S.-Y. Lee, *J. Am. Chem. Soc.*, 2000, **122**, 2385.
2000JA4310 Y. Yamamoto, H. Kitahara, R. Ogawa, H. Kawaguchi, K. Tatsumi, and K. Itoh, *J. Am. Chem. Soc.*, 2000, **122**, 4310.
2000JA8155 A. Padwa, J. P. Snyder, E. A. Curtis, S. M. Sheehan, K. J. Worsencroft, and C. O. Kappe, *J. Am. Chem. Soc.*, 2000, **122**, 8155.
2000JA9558 F. A. Kahn, B. Prabludas, J. Dash, and N. Sahu, *J. Am. Chem. Soc.*, 2000, **122**, 9558.
2000JEC24 M. Büschel, C. Stadler, C. Lambert, M. Beck, and J. Daub, *J. Elecroanal. Chem.*, 2000, **484**, 24.
2000JHC907 J. C. González-Gómez, T. Dedola, L. Santana, E. Uriarte, M. Begala, D. Copez, and G. Podda, *J. Heterocycl. Chem.*, 2000, **37**, 907.
2000JOC2577 K. Takahashi and K. Kobayashi, *J. Org. Chem.*, 2000, **65**, 2577.
2000JOC4101 D. L. Boger, A. Santillán, Jr., M. Searcey, S. R. Brunette, S. E. Wolkenberg, M. P. Hedrick, and Q. Jin, *J. Org. Chem.*, 2000, **65**, 4101.
2000JOC7541 J. D. Chisholm and D. L. Van Vranken, *J. Org. Chem.*, 2000, **65**, 7541.
2000JOC9120 D. L. Boger and S. E. Wolkenberg, *J. Org. Chem.*, 2000, **65**, 9120.
2000J(P1)2609 J. Bergman, E. Koch, and B. Pelcman, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2609.
2000J(P2)2337 L. Greci, G. Tommasi, R. Petrucci, G. Marrosu, A. Trazza, P. Sgarabotto, L. Righi, and A. Alberti, *J. Chem. Soc., Perkin Trans. 2*, 2000, 2337.
2000OL99 S. W. Baldwin and J. S. Debenham, *Org. Lett.*, 2000, **2**, 99.
2000OL3181 H. Nakagawa, T. Sugahara, and K. Ogasawara, *Org. Lett.*, 2000, **2**, 3181.
2000PLM9003 D. W. Tomlin, A. V. Fratini, M. Hunsaker, and W. W. Adams, *Polymer*, 2000, **41**, 9003.
2000PSB376 Y. Takahashi and H. Sul, *J. Polym. Sci., Part B*, 2000, **38**, 376.
2000S1253 P. Lucas, N. El Mehdi, H. A. Ho, D. Belanger, and L. Breau, *Synthesis*, 2000, 1253.
2000T1491 A. Couture, E. Deniau, P. Grandclaudon, and C. Hoarau, *Tetrahedron*, 2000, **56**, 1491.
2000T1911 J. Bergman, T. Janosik, L. Yudina, E. Desarbre, G. Lidgren, and L. Venemalma, *Tetrahedron*, 2000, **56**, 1911.
2000TL1801 T. Kimura, K. Tsujimura, S. Mizusawa, S. Ito, Y. Kawai, S. Ogawa, and R. Sato, *Tetrahedron Lett.*, 2000, **41**, 1801.
2000TL5507 J. Marco-Contelles and E. de Opazo, *Tetrahedron Lett.*, 2000, **41**, 5507.
2001ACR359 H. E. Katz, Z. Bao, and S. L. Gilat, *Acc. Chem. Res.*, 2001, **34**, 359.
2001AHC1 J. Bergman, T. Janosik, and N. Wahlström, *Adv. Heterocycl. Chem.*, 2001, **80**, 1.
2001CM1665 T. Benincori, V. Consonni, P. Gramatica, T. Pilati, S. Rizzo, F. Sannicolo, R. Todeschini, and G. Zotti, *Chem. Mater.*, 2001, **13**, 1665.
2001CM3906 T. Caronna, M. Catellani, S. Luzzati, L. Malpezzi, S. V. Meille, A. Mele, C. Richter, and R. Sinisi, *Chem. Mater.*, 2001, **13**, 3906.
2001CPB881 H. Hagiwara, T. Choshi, J. Nobuhiro, H. Fujimoto, and S. Hibino, *Chem. Pharm. Bull.*, 2001, **49**, 881.
2001CRV3893 D. J. Hill, M. J. Mio, R. B. Prince, T. S. Huges, and J. S. Moore, *Chem Rev.*, 2001, **101**, 3893.

2001HAC287 T. Kodama, M. Kodani, K. Takimiya, Y. Aso, and T. Otsubo, *Heteroatom Chem.*, 2001, **15**, 287.
2001HCA431 C. Marchionni, Pierre Vogel, and P. Roversi, *Helv. Chim. Acta*, 2001, **84**, 431.
2001HCA2119 A. Blaser and J.-L. Reymond, *Helv. Chim. Acta*, 2001, **84**, 2119.
2001JA7703 X. Deng and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2001, **123**, 7703.
2001JA11899 K. E. S. Phillips, T. J. Katz, S. Jockusch, A. J. Lovinger, and N. J. Turro, *J. Am. Chem. Soc.*, 2001, **123**, 11899.
2001JME1003 J. J. Chambers, D. M. Kurrasch-Orbaugh, M. A. Parker, and D. E. Nichols, *J. Med. Chem.*, 2001, **44**, 1003.
2001JOC3834 T. Ishikawa, K. Shimizu, H. Ishii, S. Ikeda, and S. Saito, *J. Org. Chem.*, 2001, **66**, 3834.
2001J(P1)740 U. Mitschke and P. Bauerle, *J. Chem. Soc., Perkin Trans. 1*, 2001, 740.
2001J(P1)1855 J. Ravn, N. Thorup, and P. Nielsen, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1855.
2001MM2012 Y. Takahasi, *Macromolecules*, 2001, **34**, 2012.
2001OL1343 J. Enjo, L. Castedo, and G. Tojo, *Org. Lett.*, 2001, **3**, 1343.
2001PSB559 H. H. Song, T. Cho, D. P. Heberer, T. D. Dang, F. E. Arnold, and L.-S. Tan, *J. Polym. Sci., Part B*, 2001, **39**, 559.
2001PPO3 G. Maier, *Prog. Polym. Sci.*, 2001, **26**, 3.
2001RJC1751 D. A. Kisun'ko, M. V. Zabalov, E. M. Myshakin, Y. F. Oprunenko, and D. A. Lemenovskii, *Russ. J. Gen. Chem.*, 2001, **71**, 1751.
2001SM(119)99 Y. Yonezawa, M. Kozaki, and K. Okada, *Synth. Met.*, 2001, **119**, 99.
2001T4559 K. Uchida, T. Matsuoka, S. Kobatake, T. Yamaguchi, and M. Irie, *Tetrahedron*, 2001, **57**, 4559.
2001T4729 J. Marco-Contelles, E. de Opazo, and N. Arroyo, *Tetrahedron*, 2001, **57**, 4729.
2001T4999 D. H. Martyres, J. E. Baldwin, R. M. Adlington, V. Lee, M. R. Probert, and D. J. Walkin, *Tetrahedron*, 2001, **57**, 4999.
2001T5199 C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller, and Q. Deng, *Tetrahedron*, 2001, **57**, 5199.
2001TL465 R. N. Warrener and G. Sun, *Tetrahedron Lett.*, 2001, **42**, 465.
2001TL4523 H. Nakagawa, T. Sugahara, and K. Ogasawara, *Tetrahedron Lett.*, 2001, **42**, 4523.
2002AGE4291 P. Janvier, H. Bienaymé, and J. Zhu, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 4291.
2002CEJ4199 J. von Sonntag, W. Knolle, S. Naumov, and R. Mehnert, *Chem. Eur. J.*, 2002, **8**, 4199.
2002CPB143 A. Yasuhara, N. Suzuki, and T. Sakamoto, *Chem. Pharm. Bull.*, 2002, **50**, 143.
2002CPL(357)385 W. Fujita and K. Awaga, *Chem. Phys. Lett.*, 2002, **357**, 385.
2002CPL(362)97 W. Fujita, K. Awaga, M. Takahashi, M. Takeda, and T. Yamazaki, *Chem. Phys. Lett.*, 2002, **362**, 97.
2002CRV4303 H. J. Knölker and K. R. Reddy, *Chem Rev.*, 2002, **102**, 4303.
2002EJO3796 S. Takami, T. Kawai, and Masahiro Irie, *Eur. J. Org. Chem.*, 2002, 3796.
2002HCO179 K. S. K. Murthy, B. Rajitha, M. K. Rao, T. R. Komuraiah, and S. M. Reddy, *Heterocycl. Commun.*, 2002, **8**, 179.
2002JA2080 V. B. Birman and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2002, **124**, 2080.
2002JA4512 T. Sato, S. Arulmozhiraja, H. Niino, S. Sasaki, T. Matsuura, and A. Yabe, *J. Am. Chem. Soc.*, 2002, **124**, 4512.
2002J(P1)310 K. K. Park, H. Lim, S.-H. Kim, and D. H. Bae, *J. Chem. Soc., Perkin Trans. 1*, 2002, 310.
2002JMC2597 P. Coppo, D. C. Cupertino, S. G. Yeates, and M. L. Turner, *J. Mater. Chem.*, 2002, **12**, 2597.
2002JOC1795 K. Tanaka, H. Osuga, and Y. Kitahara, *J. Org. Chem.*, 2002, **67**, 1795.
2002JOC4635 T. J. Reddy, T. Iwama, H. J. Halpern, and V. H. Rawal, *J. Org. Chem.*, 2002, **67**, 4635.
2002MI279 S. Y. Cho, M. Yoo, H.-W. Shin, K.-H. Ahn, Y.-R. Kim, and E. Kim, *Optical Mater.*, 2002, **21**, 279.
2002MM2277 Y. Watanabe, Y. Sakai, Y. Shibasaki, S. Ando, M. Ueda, Y. Oishi, and K. Mori, *Macromolecules*, 2002, **35**, 2277.
2002OL953 V. Nair, C. Rajesh, and N. P. Rath, *Org. Lett.*, 2002, **4**, 953.
2002OL4535 M. Kozaki, Y. Yonezawa, and K. Okada, *Org. Lett.*, 2002, **4**, 4535.
2002PCB9221 U. Salzner and M. E. Kose, *J. Phys. Chem. B*, 2002, **106**, 9221.
2002PSB1760 S. J. Bai, C. C. Wu, L. W. Tu, and K. H. Lee, *J. Polym. Sci. B*, 2002, **40**, 1760.
2002S1053 J. Z. Brezezinski and J. R. Reynolds, *Synthesis*, 2002, 1053.
2002SM(130)139 K. Shiraishi and T. Yamamoto, *Synth. Met.*, 2002, **130**, 139.
2002T1443 J. Bergman, N. Wahlström, L. N. Yudina, J. Tholander, and G. Lidgren, *Tetrahedron*, 2002, **58**, 1443.
2002T6621 S. Routier, N. Ayerbe, J.-Y. Mérour, G. Coudert, C. Bailly, A. Pierré, B. Pfeiffer, D.-H. Caignard, and P. Renard, *Tetrahedron*, 2002, **58**, 6621.
2002TL5981 S. Muthusamy, S. A. Babu, and C. Gunanathan, *Tetrahedron Lett.*, 2002, **43**, 5981.
2003CC2380 L. A. McAllister, S. Brand, R. de Gentile, and D. J. Procter, *J. Chem. Soc., Chem. Commun.*, 2003, 2380.
2003CC2548 P. Coppo, H. Adams, D. C. Cupertino, S. G. Yeates, and M. L. Turner, *J. Chem. Soc., Chem. Commun.*, 2003, 2548.
2003CEJ2469 Y. Yamamoto, A. Nagata, H. Nagata, Y. Ando, Y. Arikawa, K. Tatsumi, and K. Itoh, *Chem. Eur. J.*, 2003, **10**, 2469.
2003EJO4902 T. Kimura, T. Sasaki, H. Yamaki, E. Suzuki, and S. Niizuma, *Eur. J. Org. Chem.*, 2003, **24**, 4902.
2003JA6630 K. Yamada, T. Kurokawa, H. Tokuyama, and T. Fukuyama, *J. Am. Chem. Soc.*, 2003, **125**, 6630.
2003JA7784 H. Kinoshita, H. Shinokubu, and K. Oshima, *J. Am. Chem. Soc.*, 2003, **125**, 7784.
2003JA10971 J. P. Parrish, D. B. Kastrinsky, S. E. Wolkenberg, Y. Igarashi, and D. L. Boger, *J. Am. Chem. Soc.*, 2003, **125**, 10971.
2003JA12143 Y. Yamamoto, T. Arakawa, R. Ogawa, and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143.
2003JOC1475 H. Jiao and H.-S. Wu, *J. Org. Chem.*, 2003, **68**, 1475.
2003JOC8258 B. Wex, B. R. Kaafarani, A. G. Oliver, J. A. Krause Bauer, and D. C. Neckers, *J. Org. Chem.*, 2003, **68**, 8258.
2003JOC9813 X. Zhang and A. J. Matzger, *J. Org. Chem.*, 2003, **68**, 9813.
2003MI467 G. Gandhi and A. K. Bakhshi, *Solid State Commun.*, 2003, **128**, 467.
2003MM2705 P. Coppo, D. C. Cupertino, S. G. Yeates, and M. L. Turner, *Macromolecules*, 2003, **36**, 2705.
2003MM4699 Y.-H. So, S. J. Martin, B. Bell, C. D. Pfeiffer, R. M. Van Effen, B. L. Romain, and S. M. Lefkowitz, *Macromolecules*, 2003, **36**, 4699.
2003OBC2111 I. Coldham, K. N. Price, and R. E. Rathmell, *Org. Biomol. Chem.*, 2003, **1**, 2111.
2003OL1301 K. A. Ahrendt, R. G. Bergmann, and J. A. Ellman, *Org. Lett.*, 2003, **5**, 1301.
2003OL1883 Y. A. Jackson, D. Rajagopal, J. Bendolph, M. Guillory, M. V. Lakshmikantham, J. Yang, and M. P. Cava, *Org. Lett.*, 2003, **5**, 1883.
2003OL3721 J. T. Kuethe, A. Wong, and I. W. Davies, *Org. Lett.*, 2003, **5**, 3721.
2003SM(135)85 H. Ohnishi and K. K. Okada, *Synth. Met.*, 2003, **135–136**, 85.
2003SM(135)107 M. Kozaki, Y. Yonezawa, H. Igarashi, and K. Okada, *Synth. Met.*, 2003, **135–136**, 107.
2003SM(137)1263 W. Fujita and K. Awaga, *Synth. Met.*, 2003, **137**, 1263.
2003T747 D. K. O'Dell and K. M. Nicholas, *Tetrahedron*, 2003, **59**, 747.

2003T1265 L. N. Yudina and J. Bergman, *Tetrahedron*, 2003, **59**, 1265.
2003T6481 S. Maiorana, A. Papagni, E. Licandro, R. Annunziata, P. Paravidino, D. Perdicchia, C. Giannini, M. Bencini, K. Clays, and A. Persoons, *Tetrahedron*, 2003, **59**, 6481.
2003T8233 A. C. Ferguson, R. M. Adlington, D. H. Martyres, P. J. Rutledge, A. Cowley, and J. E. Baldwin, *Tetrahedron*, 2003, **59**, 8233.
2003TL9313 G. Mehta, V. Gagliardini, C. Schaeferb, and R. Gleiterb, *Tetrahedron Lett.*, 2003, **44**, 9313.
2004BMC1955 A. Voldoire, P. Moreau, M. Sancelme, M. Matulova, S. Léonce, A. Pierré, J. Hickman, B. Pfeiffer, P. Renard, N. Dias, *et al.*, *Bioorg. Med. Chem.*, 2004, **12**, 1955.
2004BML3925 R. S. Al-awar, J. E. Ray, K. A. Hecker, S. Joseph, J. Huang, C. Shih, H. B. Brooks, C. D. Spencer, S. A. Watkins, R. M. Schultz, *et al.*, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3925.
2004CC1538 T. Devic, P. Batail, and N. Avarvari, *J. Chem. Soc., Chem. Commun.*, 2004, 1538.
2004CL156 M. Kozaki, H. Igarashi, and K. Okada, *Chem. Lett.*, 2004, **33**, 156.
2004CM3667 A. Berlin, G. Zotti, S. Zecchin, G. Schiavon, B. Vercelli, and A. Zanelli, *Chem. Mater.*, 2004, **16**, 3667.
2004CEJ6531 M. Miyasaka, A. Rajca, M. Pink, and S. Rajca, *Chem. Eur. J.*, 2002, **10**, 6531.
2004CRV4891 F. Wudi and M. Bendikov, *Chem. Rev.*, 2004, **104**, 4891.
2004CRV5085 M. Iyoda, M. Hasegawa, and Y. Miyake, *Chem. Rev.*, 2004, **104**, 5085.
2004CSR85 H. Tian and S. J. Yang, *Chem. Soc. Rev.*, 2004, **33**, 85.
2004EJO2593 N. Wahlström, I. Romero, and J. Bergman, *Eur. J. Org. Chem.*, 2004, 2593.
2004EJO4582 M. Kemmler, E. Herdtweck, and T. Bach, *Eur. J. Org. Chem.*, 2004, 4582.
2004JA8396 M. S. Tichenor, D. B. Kastrinsky, and D. L. Boger, *J. Am. Chem. Soc.*, 2004, **126**, 8396.
2004JA14342 K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, and M. Tokuda, *J. Am. Chem. Soc.*, 2004, **126**, 14342.
2004JME1886 A. Zhang, W. Xiong, J. E. Hilbert, E. K. DeVita, J. M. Bidlack, and J. L. Neumeyer, *J. Med. Chem.*, 2004, **47**, 1886.
2004JNP783 N. L. Segraves, S. J. Robinson, D. Garcia, S. A. Said, F. J. Schmitz, H. Pietraszkiewitz, F. A. Valeriote, and P. Crews, *J. Nat. Prod.*, 2004, **67**, 783.
2004JOC2197 B. Wex, B. R. Kaafarani, and D. C. Neckers, *J. Org. Chem.*, 2004, **69**, 2197.
2004JOC6202 M. Freccero and R. Gandolfi, *J. Org. Chem.*, 2004, **69**, 6202.
2004MI335 A. K. Bakhshi and G. Gandhi, *Solid State Commun.*, 2004, **129**, 335.
2004OL2953 K. Hiroya, S. Matsumoto, and T. Sakamoto, *Org. Lett.*, 2004, **6**, 2953.
2004PLM459 Y.-H. Tang, M.-H. Tsai, C. C. Wu, and S. J. Bai, *Polymer*, 2004, **45**, 459.
2004PLM8871 D. Feng, S. Wang, Q. Zhaung, P. Wu, and Z. Han, *Polymer*, 2004, **45**, 8871.
2004SM(140)127 H. A. Aouchiche, S. Djennane, and A. Boucekkine, *Synth. Met.*, 2004, **140**, 127.
2004T2147 N. Wahlström, B. Stensland, and J. Bergman, *Tetrahedron*, 2004, **60**, 2147.
2004T2953 A. Saitoh, K. Okinaka, K. Suzuki, A. Seno, M. Kasahara, K. Ueno, T. Matsumoto, and S. Mataka, *Tetrahedron*, 2004, **60**, 2953.
2004TL3789 B. A. Trofimov, A. B. Zaitsev, E. Yu. Schmidt, A. M. Vasil'tsov, A. I. Mikhaleva, I. A. Ushakov, A. V. Vashchenko, and N. V. Zorina, *Tetrahedron Lett.*, 2004, **45**, 3789.
2004TL4009 J. T. Kuethe and I. W. Davies, *Tetrahedron Lett.*, 2004, **45**, 4009.
2004TL4934 K.-H. Park and W. J. Marshall, *Tetrahedron Lett.*, 2004, **45**, 4934.
2004TL7273 N. Wahlström and J. Bergman, *Tetrahedron Lett.*, 2004, **45**, 7273.
2005AGE1336 T. Tsuchimoto, H. Matsubayashi, M. Kaneko, E. Shirakawa, and Yusuke Kawakami, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 1336.
2005AGE4053 P. K. Panda, Y.-J. Kang, and C.-H. Lee, *Angew. Chem., Int. Ed. Engl.*, 2005, **44**, 4053.
2005BML1315 R. D. Alessio, A. Bargiotti, S. Metz, M. G. Brasca, A. Cameron, A. Ermoli, A. Marsiglio, P. Polucci, F. Roletto, M. Tibolla, *et al.*, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1315.
2005JA614 Y. Wu, Y. Li, S. Gardener, and B. S. Ong, *J. Am. Chem. Soc.*, 2005, **127**, 614.
2005JA11620 A. Fürstner, M. Domostoj, and B. Scheiper, *J. Am. Chem. Soc.*, 2005, **127**, 11620.
2005JMC1123 P. Coppo and M. L. Turner, *J. Mater. Chem.*, 2005, **15**, 1123.
2005JOC2033 A. Torrent, I. González, A. Pla-Quintana, A. Roglans, M. Moreno-Mañas, T. Parella, and J. Benet-Buchholz, *J. Org. Chem.*, 2005, **70**, 2033.
2005JOC7098 M. Freccero and R. Gandolfi, *J. Org. Chem.*, 2005, **70**, 7098.
2005JOC9798 B. Basler, O. Schuster, and T. Bach, *J. Org. Chem.*, 2005, **70**, 9798.
2005JOC10323 T. Yamaguchi and M. Irie, *J. Org. Chem.*, 2005, **70**, 10323.
2005JOC10474 S. C. Pelly, C. J. Parkinson, W. A. L. van Otterlo, and C. B. de Koning, *J. Org. Chem.*, 2005, **70**, 10474.
2005JOC10569 K. Takimiya, Y. Konda, H. Ebata, N. Niihara, and T. Otsubo, *J. Org. Chem.*, 2005, **70**, 10569.
2005MM1711 S. Y. Park, S. C. Moon, T. D. Dang, N. Venkatasubramanian, J. Lee, and B. L. Farmer, *Macromolecules*, 2005, **38**, 1711.
2005OBC448 H. Uno, H. Watanabe, Y. Yamashita, and N. Ono, *Org. Biomol. Chem.*, 2005, **3**, 448.
2005OBC2953 D. Moffat, C. J. Nichols, D. A. Riley, and N. S. Simpkins, *Org. Biomol. Chem.*, 2005, **3**, 2953.
2005OL755 T. Iwasaki, Y. Kohinata, and H. Nishide, *Org. Lett.*, 2005, **7**, 755.
2005OL3355 S. W. Youn and J. I. Eom, *Org. Lett.*, 2005, **7**, 3355.
2005PLM5630 S. Y. Park, S. C. Moon, T. D. Dang, N. Venkatasubramanian, J. Lee, and B. L. Farmer, *Polymer*, 2005, **46**, 5630.
2005T545 K. K. Park and J. Jeong, *Tetrahedron*, 2005, **61**, 545.
2005T4805 J. C. González-Gómez, L. Santana, and E. Uriarte, *Tetrahedron*, 2005, **61**, 4805.
2005TL2211 Y. Zhang, D. Candelaria, and J. W. Herndon, *Tetrahedron Lett.*, 2005, **46**, 2211.
2006ACR935 T. Bando and H. Sugiyama, *Acc. Chem. Res.*, 2006, **29**, 935.
2006CC2750 X. Gao, W. Wu, Y. Lin, W. Qui, X. Sun, G. Yu, and D. Zhu, *Chem. Commun.*, 2006, 2750.
2006CEJ2073 V. Coropceanu, O. Kwon, B. Wex, B. R. Kaafarani, N. E. Gruhn, J. C. Durivage, D. C. Neckers, and J.-L. Brédas, *Chem. Eur. J.*, 2006, **12**, 2073.
2006JA7136 K. Okano, H. Tokuyama, and T. Fukuyama, *J. Am. Chem. Soc.*, 2006, **128**, 7136.
2006MM3707 W.-Y. Lai, R. Zhu, Q.-L. Fan, L.-T. Hou, Y. Cao, and W. Huang, *Macromolecules*, 2006, **39**, 3707.
2006TL1551 J. Pei, W.-Y. Zhang, J. Mao, and X.-H. Zhou, *Tetrahedron Lett.*, 2006, **47**, 1551.
2006TL4117 V. V. Mel'chin and A. V. Butli, *Tetrahedron Lett.*, 2006, **47**, 4117.

2007JOC574 M. D. Ganton and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 574.
2007JOC2008 Y. Wada, H. Nagasaki, M. Tokuda, and K. Orito, *J. Org. Chem.*, 2007, **72**, 2008.
2007OBC2046 Y. Kagawa, I. Imae, and Y. Harima, *Org. Biomol. Chem.*, 2007, **5**, 2046–2054.
2007OL1883 T. P. Lebold and M. A. Kerr, *Org. Lett.*, 2007, **9**, 1883.

Biographical Sketch



Andy Graham was born in Liverpool; he graduated from the University of Liverpool in 1989, where he also obtained his Ph.D. in 1993 under the direction of Professor Phillip Page and Professor Kevin Park. Following a Royal Society Fellowship at the EHICS Strasbourg, with Professor Guy Solladié, he returned to the UK to complete postdoctoral positions at the University of York with Professor Richard Taylor and at the University of Liverpool with Professor Stan Roberts, before moving to Ireland to take up a lectureship at University College Cork. He moved to the University of Wales Swansea in 2001. His research interests include the development of novel supported catalysts, cycloaddition and rearrangement reactions in natural product synthesis, and the synthesis of novel biologically active peptidomimetics.



Mat Robinson was born in Malvern; he graduated from the University of Wales Swansea with a first class M.Chem. degree in 2004. He is also currently studying there for his Ph.D. under the supervision of Dr. Andy Graham. His research interests include the development of novel solid Lewis and Brönsted acids, nanomaterials, and rearrangement reactions in natural product synthesis.

10.22
Tricyclic Systems: Central Carbocyclic Ring with Fused Five- and Six-membered Rings

M. P. Groziak
California State University, East Bay, Hayward, CA, USA
© 2008 Elsevier Ltd. All rights reserved.

10.22.1 Introduction **1201**
10.22.2 Theoretical Methods **1202**
10.22.2.1 Molecular Orbital Methods 1202
10.22.2.2 Molecular Mechanics and Related Methods 1202
10.22.2.3 Other Methods 1202
10.22.3 Experimental Structural Methods **1203**
10.22.3.1 X-Ray Methods 1203
10.22.3.2 UV–Vis and Fluorescence Spectroscopy 1204
10.22.3.3 NMR Spectroscopy 1205
10.22.4 Thermodynamic Aspects **1205**
10.22.4.1 Solubilities and Chromatographic Behavior 1205
10.22.5 Synthesis of Particular Classes of Compounds **1206**
10.22.5.1 Benzo-Separated Purines 1206
10.22.5.2 Furocoumarins and Furochromones 1207
10.22.5.3 Ellipticines 1212
10.22.5.4 PQQ and Related Compounds 1215
10.22.5.5 Imidazo- and Triazoloquinolines 1217
10.22.6 Important Compounds and Applications **1222**
10.22.6.1 Benzo-Separated Purines 1222
10.22.6.2 Furocoumarins and Furochromones 1223
10.22.6.3 Ellipticines 1223
10.22.6.4 PQQ and Related Compounds 1224
10.22.7 Further Developments **1225**
References **1226**

10.22.1 Introduction

The corresponding chapter in CHEC-II(1996) that relates to the material presented herein is 7.22 <1996CHEC-II(7)875>. Although many 6-4-5, 6-5-5, 6-6-5, and 6-7-5 fused compounds have been reported since then, a majority of tricyclic ring systems with a central carbocyclic ring and fused five- and six-membered heterocyclic rings are contained within a handful of specialized classes of compounds. Thus, we focus here on the imidazo[4,5-*g*]quinazoline-based benzo-separated purines (Section 10.22.6.1), the furocoumarins and furochromones (Section 10.22.6.2), the pyrrolo[3,2-*g*]isoquinoline-based tetracyclic ellipticines (Section 10.22.6.3), and the pyrrolo[2,3-*f*]quinoline-based PQQ and related compounds (Section 10.22.6.4), each as an important class of compounds with special applications, and representative of the broader class of tricyclic heterocycles with a central carbocyclic ring and fused five and six rings. Other separate sections cover the synthetic work related to these compounds, the benzo-separated purines (Section 10.22.5.1), the furocoumarins and furochromones (Section 10.22.5.2), the ellipticines (Section 10.22.5.3), and PQQ and related compounds (Section 10.22.5.4). In addition, the synthesis of imidazo- and triazoloquinolines (Section 10.22.5.5) is covered, as these tricyclics were unfortunately not included in CHEC-II(1996). Structural formulas, equations, and schemes are presented fully in the synthetic sections, but only when there is a compelling reason to do so in the nonsynthetic ones.

10.22.2 Theoretical Methods

10.22.2.1 Molecular Orbital Methods

The stacking interactions of ellipticine and other DNA intercalators like ethidium, daunomycin, and 4,6′-diaminide-2-phenylindole with adenine/thymine (AT) and guanine/cytosine (GC) nucleic acid base pairs were investigated by means of a nonempirical correlated *ab initio* method <2002JA3366>. The investigators concluded that the London dispersion energy predominantly contributes to the stability of the intercalator/DNA base pair complex, despite the fact that the intercalators are cationic or at the least very polar. Thus, only methods which cover this dispersion energy are suitable for studying the intercalation process.

Oxidation by direct H^- transfer from the α-carbon of alcohols to the pyrroloquinoline quinone (PQQ) cofactor of alcohol dehydrogenases was studied using *ab initio* quantum mechanical methods <2001JCC1732>. Energies and geometries were calculated at the 6-31G(d,p) level of theory, results were compared to available structural and spectroscopic data, and the role of calcium in the enzymatic reaction was explored. Transition state searches at the semi-empirical and STO-3G(d) level of theory provided evidence that direct H^- transfer from the alcohol to C-5 of PQQ is energetically feasible.

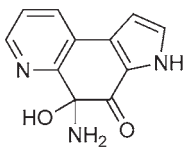
10.22.2.2 Molecular Mechanics and Related Methods

The intercalative binding of 9-hydroxyellipticine to the DNA segment $d(ATATATATATAT)_2$ was explored with four independent and extensive molecular dynamics (MD) simulations <1996BPM309>. All four converged in placing the pyridine ring of the ellipticine chromophore in the major groove, and the drug was found capable of adopting several distinct orientations, each stable over a period of hundreds of picoseconds.

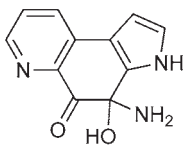
Using a bacterial methanol dehydrogenase crystal structure, molecular dynamic simulations of five enzyme-PQQ-$HOCH_3$ complexes in aqueous solution were conducted to probe the enzyme mechanism <2003JA8141>. Reasonable structures were obtained only when both Asp297 and Glu171 were ionized, and the results suggested that the latter plays the role of general base catalyst in PQQ reduction rather than the former, as had been previously suggested. In addition, the channel for allowing substrate and water into the active site entrance was mapped.

10.22.2.3 Other Methods

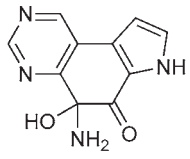
In a density functional theory (DFT) computational investigation of the regiochemical aspects of the redox cofactor tryptophan tryptophylquinone (TTQ), model tricyclic carbinolamines **1–6** related to PQQ were included for comparison <2003JOC3626>. These tricyclic models represented more regioselectivity in contrast to simpler bicyclic systems, and the fused electron-donating pyrrole and fused electron-withdrawing pyridine or pyrimidine showed a synergistic effect on each other. The barrier of the condensation reaction in the PQQ models (*c.* 22 kcal mol^{-1}) was found to be as much as 10 kcal mol^{-1} lower than that in the TQQ models, explaining the larger catalytic effect of PQQ relative to TTQ.



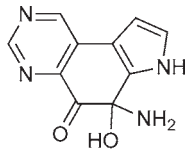
1



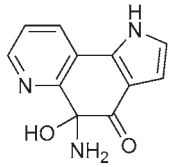
2



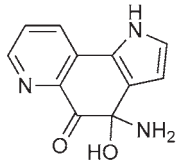
3



4



5



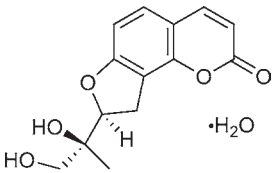
6

The reaction between furocoumarins and O_2 was explored using DFT, using a time-dependent formalism for excited states (TD-DFT) and a continuum model to take into account the effects of bulk solvation <2003MI235>. The generation of superoxide anions and singlet oxygen were both found feasible, but under certain conditions the generated superoxide anions could reduce the triplet psoralens, thereby scavenging the generation of reactive oxygen species.

10.22.3 Experimental Structural Methods

10.22.3.1 X-Ray Methods

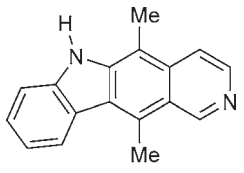
1,2-Dihydro-2-(1,2-dihydroxyprop-2-yl)-8*H*-furo[2,3-*h*]benzopyran-8-one **7**, a furocoumarin isolated from the roots of *Angelica* species, crystallized from aqueous MeOH as the monohydrate <2000AXCe136>. By X-ray crystallography, both chiral centers have the *S* configuration, and both OH groups hydrogen bond to the water molecule.



7

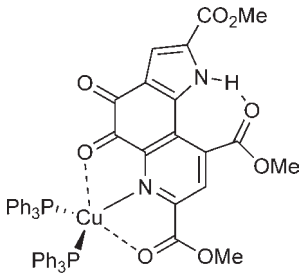
The X-ray crystal structure and thermal properties of a 1:1 inclusion complex between the phytoalexin psoralen (7*H*-furo[3,2-*g*][1]benzopyran-7-one) and permethylated β-cyclodextrin (TRIMEB) were reported <2004SME389>. The crystal structure data revealed the elongated guest molecule inducing an elliptical distortion in the host, and interacting *via* C–H···O hydrogen bonding and hydrophobic interactions. The thermal properties determined by hot stage microscopy, differential scanning calorimetry (DSC), and thermogravimetry indicated dehydration in the range 40–100 °C followed by melting at 137.1 °C.

The 1.5 Å resolution X-ray crystal structure of ellipticine **8** complexed to the 6 bp oligonucleotide d(CGATCG)$_2$ revealed the self-complementary hexamer adopting a double helical B-DNA conformation with an ellipticine molecule intercalated between the CpG steps at both ends of the duplex <2005AXD1009>. The intercalated molecules of **8** were aligned with their major axis parallel to the Watson–Crick hydrogen bonds of the base pairs. In addition, the DNA segment was found to be unwound and lengthened.



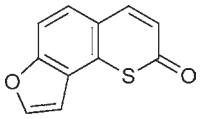
8

The first experimental structure determination of a 1:1 metal complex with a PQQ derivative outside the protein environment was reported <1999IC2753>, together with its cyclic voltammetry, infrared, UV–Vis absorption and electron paramagnetic resonance (EPR) spectral characterization. The molecular structure of [(**9**)Cu(PPh$_3$)$_2$](BF$_4$)·0.5EtOAc in the crystal showed a coordination of the [Cu(PPh$_3$)$_2$]$^+$ to **9** similar to that of Ca^{2+} to PQQ in the enzymes. Because they are isoambitalterdentate ligands, PQQ and its derivates tend to form oligonuclear metal compounds with complicated coordination patterns. Although the direct Cu-PQQ interaction and Ph$_3$P coordination are not immediately relevant, the formation of a five coordinate Cu(I) species could be useful in future studies of PQQ.



9

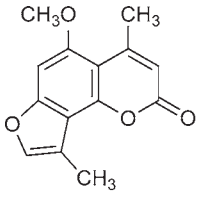
The X-ray crystal structure of 4*H*-thiopyrano[2,3-*e*]benzofuran-4-one **10**, the furocoumarin known as 1-thioangelicin, was reported, together with a study of its interaction with DNA, both in the dark and by UVA irradiation, using linear flow dichroism, chromatography, and ^{1}H NMR spectroscopy <2004FA125>. Theoretical calculations including molecular mechanics (MM) optimization, docking studies, and frontier molecular orbital (FMO) investigations provided further insight into the steric and electronic features of **10**, which was found able to intercalate in a DNA double helix and generate a *cis–syn* photoadduct upon irradiation, in agreement with the theoretical calculations.



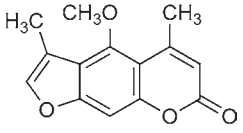
10

10.22.3.2 UV–Vis and Fluorescence Spectroscopy

4,4′-Dimethyl-5-methoxyangelicin **11** and 4,4′-dimethyl-5-methoxypsoralen **12** were added separately to 12 synthetic oligonucleotides, and their interaction and subsequent photoaddition reaction on UVA irradiation was studied <2000PCB4992>. The kinetics constant of the overall photoaddition process was determined accurately, the different intercalation sites were identified, and the value of the kinetics constant relative to each type of site was determined.

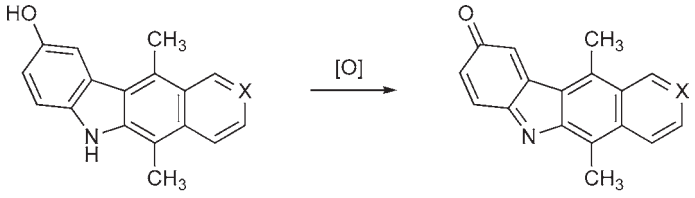


11



12

Based partly on UV–vis absorption but mostly on surface-enhanced Raman scattering (SERS) data, the electrochemical oxidation product from 9-hydroxyellipticine (9-OH-E) **13a** at Pt and Ag electrodes and that from N^2-methyl-9-hydroxyellipticinium cation (NMHE) **13b** at those electrodes and also by horseradish peroxidase-H_2O_2 were studied and their structures identified <1996JRS539>. The products, 9-oxoellipticine (9-oxo-E) **14a** from 9-OH-E and N^2-methyl-9-oxoellipticinium cation (NMOE) **14b** from NMHE both have quinone–imine structures readily identified from the vibrational analysis of their SERS spectra.



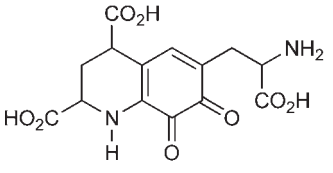
13a: X = N
b: X = N^+CH_3

14a: X = N
b: X = N^+CH_3

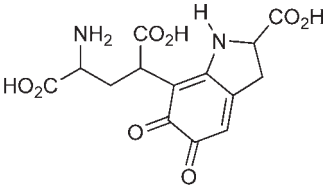
The characterization of the semiquinone radical anion species of PQQ in aprotic solvents was undertaken to provide information about the electrochemistry of coenzyme PQQ and to give valuable insight into the redox function of this coenzyme in living systems <1998JA7271>. The trimethyl ester of PQQ and its 1-methylated derivative were examined in aprotic organic solvents by cyclic voltammetry, electron spin resonance (ESR), and thin-layer UV–Vis techniques. The polar solvent CH_3CN was found to effectively solvate the radical anion species at the quinone moiety, where the spin is more localized, whereas the spin is delocalized into the whole molecule in the nonpolar solvent CH_2Cl_2.

10.22.3.3 NMR Spectroscopy

By 2D TOCSY NMR spectroscopy (TOCSY – total correlated spectroscopy), the structure of a biosynthetic intermediate of PQQ was shown to be 3a-(2-amino-2-carboxyethyl)-4,5-dioxo-4,5,6,7,8,9-hexahydroquinoline-7,9-dicarboxylic acid **15**, not its constitutional isomer **16** <2004JA3452>. This result shows that the last enzyme on the biosynthetic pathway of PQQ facilitates a pyrrole ring closure and an unprecedented eight-electron oxidation of **15**.



15



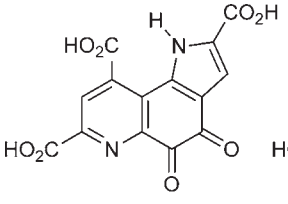
16

10.22.4 Thermodynamic Aspects

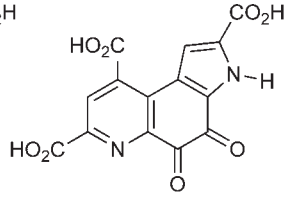
10.22.4.1 Solubilities and Chromatographic Behavior

The enantioselective separation of racemic synthetic dihydrofurocoumarins in which the stereogenic center is located in the furan ring was accomplished by cyclodextrin-based LC <2003JCH(1011)37>. Hydroxypropyl-β-cyclodextrin was the most effective chiral stationary phase, showing some enantioselectivity for 22 of the 28 dihydrofurocoumarins, and baseline resolving 16 of them in reversed-phase mode.

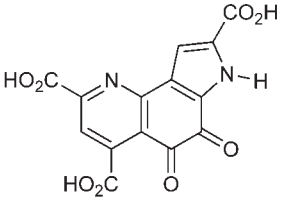
PQQ was successfully separated from three closely related isomers by capillary electrophoresis with UV detection <2000JCH(876)193>. Rapid and efficient separation of all four compounds **17–20** as their negatively charged carboxylate ions with baseline resolution was achieved by the addition of 1–5 mM R_4N^+ salts to the capillary buffer. Detection limits of PQQ and its three isomers were in the range of 7–15 μM with mass detection limits of 98–210 fmol.



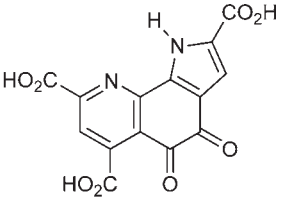
17



18



19



20

A determination of PQQ by capillary zone electrophoresis was also developed <2000JCH(739)101>. The optimal separation conditions were a 50 mM β-alanine·HCl pH 3.0 buffer, an applied voltage of 25 kV (negative polarity), and a temperature of 25 °C. The linear detection range for concentration versus peak area is that this assay is from 5 to 500 mM with a detection limit of 0.1–0.2 mM.

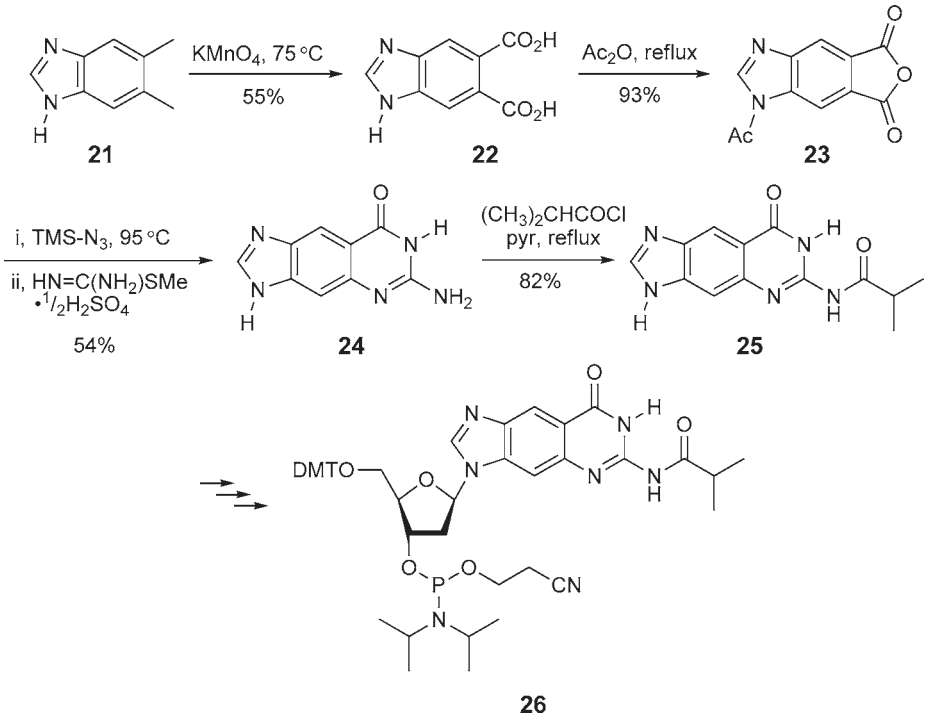
Using reverse-phase high-performance liquid chromatography (HPLC), the partition coefficient (log *P*) of 82 furocoumarins and analogs like psoralens, angelicins, allopsoralens, 8-azapsoralens, angular furoquinolin-2-ones, and sulfur and selenium isosteres of psoralen and angelicin has been determined <2001JPS732>. The chromatographic behavior was found to correlate well with the compounds' *in vitro* affinity toward DNA.

10.22.5 Synthesis of Particular Classes of Compounds

10.22.5.1 Benzo-Separated Purines

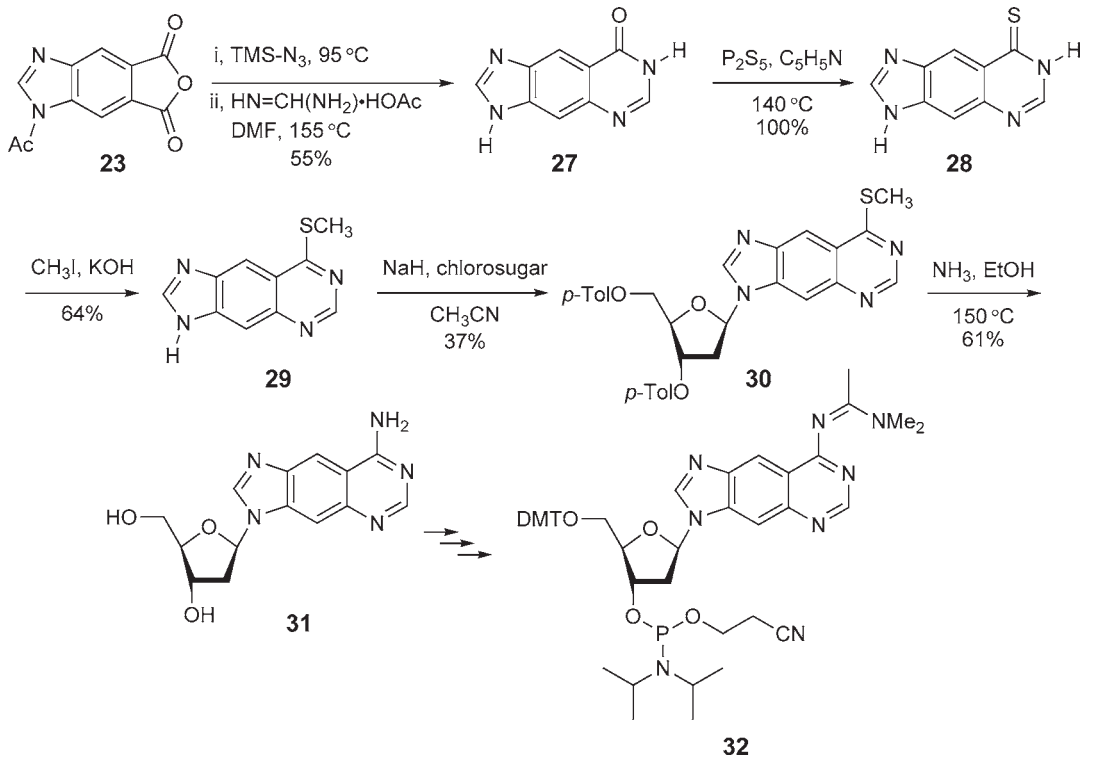
The development of compounds in which the pyrimidine ring and the imidazole ring of the purine system are separated by a benzene ring to form an extended or 'stretched-out' purine model was undertaken in the mid-1970s by Leonard and co-workers. The literature through 1995 relating synthetic and other aspects of these compounds appeared in CHEC-II(1996), Sections 7.22.11.1 and 7.22.12.1 <1996CHEC-II(7)875>. A general description of these structurally unique purine analogs appears in Section 10.22.6.1, while the highlights of the more recent synthetic developments in this field are summarized next.

A modified synthesis (**Scheme 1**) of *lin*-benzoguanine and its nucleoside phosphoramidite was developed <2005JOC639>. 5,6-Dimethylbenzimidazole **21** was oxidized by $KMnO_4$ to benzimidazole-5,6-dicarboxylic anhydride **22**, and conversion into 1-acetylbenzimidazole-5,6-dicarboxylic anhydride **23** was effected by heating **22** with Ac_2O. The five-membered cyclic anhydride was then enlarged to a six-membered oxazinedione ring by treatment with TMS-N_3, and direct condensation of this with *S*-methylisothiourea hemisulfate gave 6-aminoimidazo[4,5-*g*]quinazolin-8(7*H*)-one, also known as *lin*-benzoguanine, **24** in a 54% yield from **23**. Heterocycle **24** was isobutyrylated to **25**, and this was then processed in a series of routine steps to phosphoramidite **26**, ready for incorporation into oligodeoxynucleotides by standard automated protocols.



Scheme 1

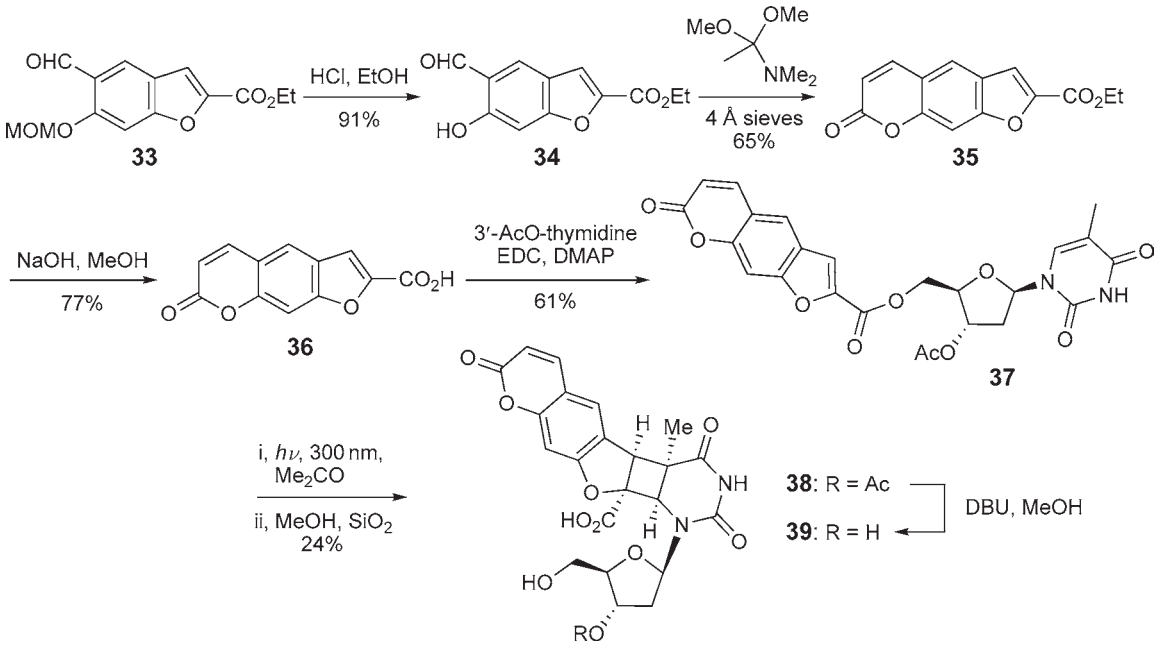
A new synthesis (**Scheme 2**) of *lin*-benzoadenosine and its phosphoramidite was also developed <2004JA1102>. The same 1-acetylbenzimidazole-5,6-dicarboxylic anhydride **23** used above was treated with TMS-N_3 followed by formamidinium acetate to give 8-aminoimidazo[4,5-*g*]quinazoline, also known as *lin*-benzohypoxanthine, **27** in a 55% yield from **23**. Heterocycle **27** was converted to the corresponding thiolactam **28** in quantitative yield, and **28** was then S-methylated with methyl iodide and base to give **29** in 64% yield. An anion-based condensation of **29** with the appropriate chlorodeoxyribose gave the protected nucleoside **30**, which was subjected to ammonolysis to give *lin*-benzoadenosine **31**. A series of routine steps led to phosphoramidite **32**, ready for incorporation into oligodeoxynucleotides by standard automated protocols.



Scheme 2

10.22.5.2 Furocoumarins and Furochromones

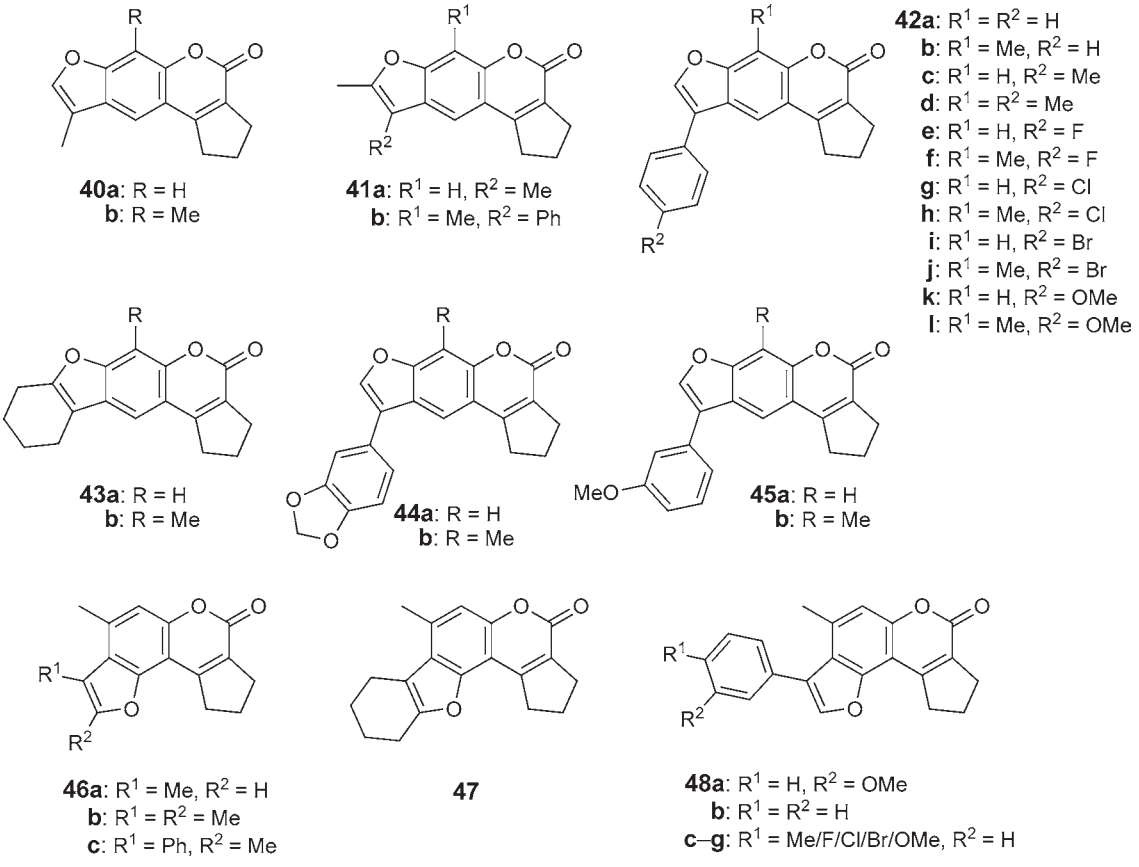
A straightforward synthesis (**Scheme 3**) of a furocoumarin-thymidine furan-side adduct was developed <1997JOC2630>. The methoxymethyl (MOM)-protecting group in **33** was removed in 91% yield with ethanolic HCl, and the resulting phenol **34** was condensed with dimethylacetamide dimethyl acetal in the presence of 4 Å



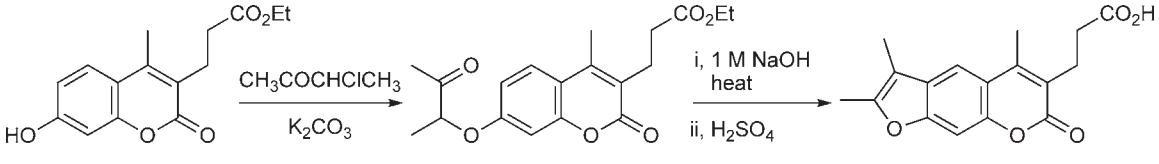
Scheme 3

molecular sieves to give 2′-(ethoxycarbonyl)psoralen **35**. Saponification of **35** afforded the 2-carboxypsoralen **36**. Acid **36** was then used to acylate the 5′-OH group of 3′-*O*-acetylthymidine, and the resulting ester **37** produced one photoproduct when irradiated with 300 nm light in the presence of Me_2CO as a photosensitizer. Transesterification of photoproduct with CH_3OH and SiO_2 gave **38**. The target nucleoside **39** was then obtained by deacetylation of **38**.

A large number of psoralen and allopsoralen (7*H*-furo[2,3-*f*]chromen-7-one) analogs **40–48** equipped with an annelated cyclopentane ring were synthesized from 7- and 9-hydroxy-1,2,3,4-tetrahydrocyclopenta[*c*]chromen-4-ones <2002MI230, 2002MI539>. Versions of many of these equipped with a 5-(4-methoxyphenyl) substituent instead of the cyclopenta[*c*] annelation were also prepared <2002MI539>. Of these, 9-phenyl-1,2,3,4-tetrahydrocyclopenta[*c*]furo[3,2-*g*]chromen-4-one **42a** was found to act as a central nervous system (CNS) stimulant as well as exhibiting cardiotropic activity and low toxicity.

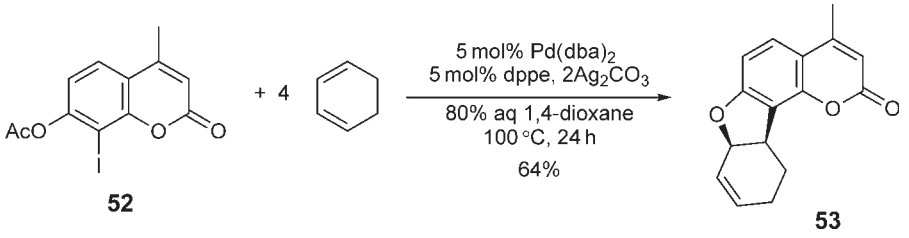


Amino acid-modified furocoumarins were prepared by condensation of the *N*-hydroxysuccinimide ester of 3-(2,3,5-trimethyl-7-oxofuro[3,2-*g*]chromen-6-yl)propanoic acid **51** with amino acids <2003JPH177>. Ethyl 3-(7-hydroxy-4-methyl-2-oxo-2*H*-3-chromenyl)propanoate **49**, prepared in 56% yield by Pechmann condensation of resorcinol and diethyl 2-acetylglutarate in the presence of HCl, was condensed with 3-chlorobutan-2-one in the presence of base to give propanoate **50** (**Scheme 4**). The MacLeod method was then used to fuse a furan ring to the benzopyran-2-one system. Heating **50** with NaOH solution (1 M) readily cyclized it into the corresponding psoralen furocoumarin **51** with simultaneous hydrolysis of the ester.



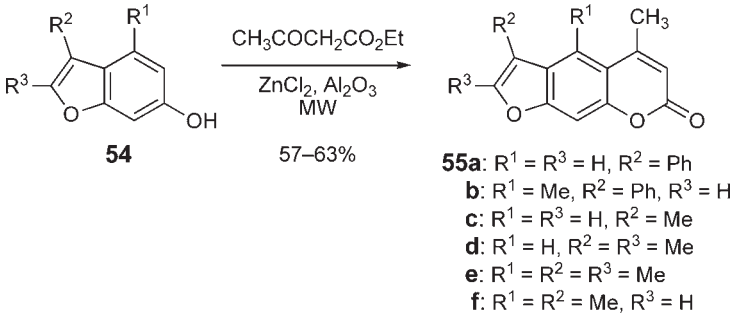
Scheme 4

An 'optimal' procedure (**Scheme 5**) for the annulation of 1,3-dienes by *o*-acetoxycoumarins leading to biologically interesting dihydrofurocoumarins like **53** was developed <2003OL797, 2003JOC6314>. In this Pd-catalyzed reaction, illustrated by the annulation of 1,3-cyclohexadiene by iodoacetoxycoumarin **52**, the presence of the acetylated phenolic oxygen and the use of Ag_2CO_3 were found to be crucial. A wide variety of terminal, cyclic, and internal 1,3-dienes can be utilized, and the reaction is very general and both regio- and stereoselective.



Scheme 5

Furocoumarins **55a–f** were conveniently prepared by the solventless Pechmann condensation of 6-hydroxybenzofurans **54** with ethyl acetoacetate catalyzed by $ZnCl_2/Al_2O_3$ and accelerated by microwave irradiation, as shown in **Scheme 6** <2003PS(178)143>.

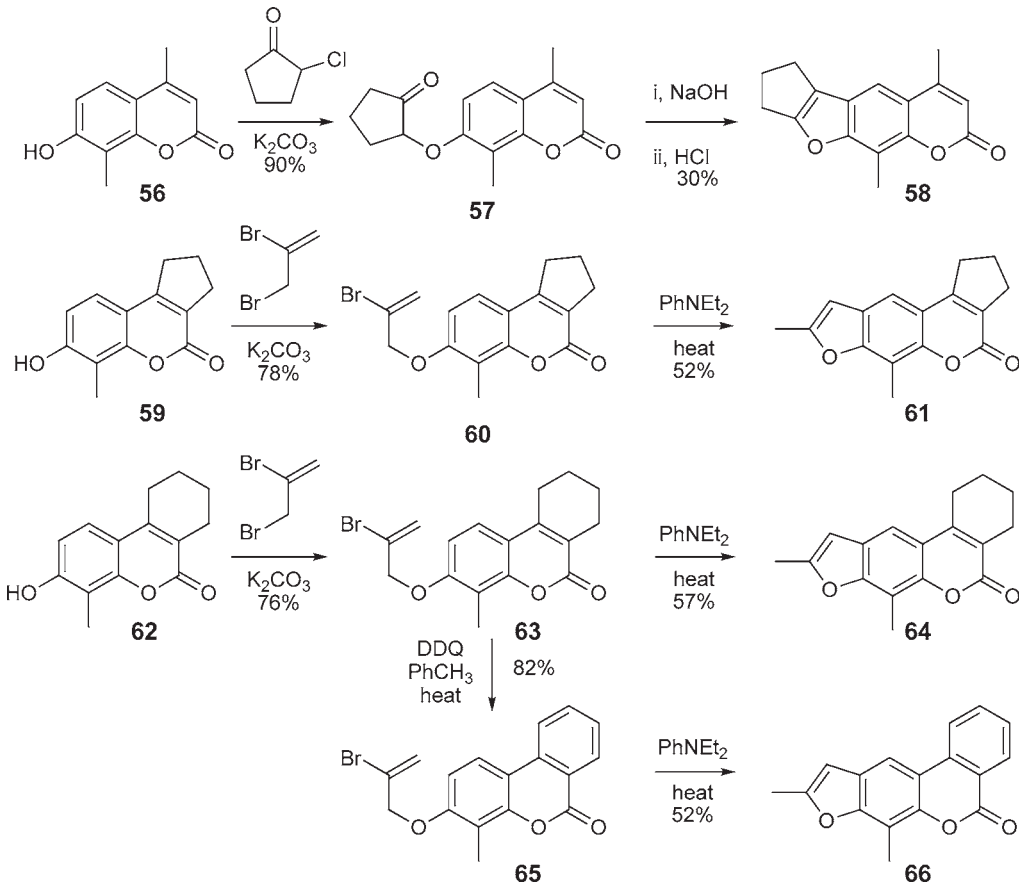


Scheme 6

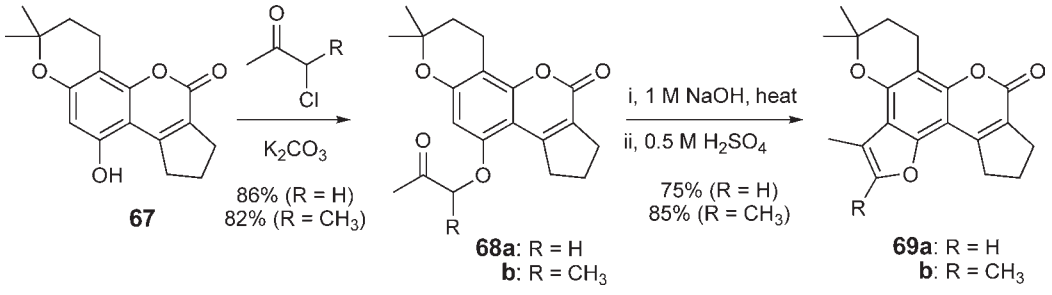
New tetracyclic psoralen derivatives were synthesized (**Scheme 7**) for their DNA interstrand cross-linking photoantiproliferative activity <2004ARK131>. Condensation of coumarin **56** with 2-chlorocyclopentanone gave intermediate **57**, and intramolecular cyclization under basic conditions converted **57** to the cyclopentane annulated psoralen **58**. Condensation of the cyclohexane annulated coumarin **59** with 2,3-dibromopropene gave intermediate **60**. Thermal intramolecular cyclization of **60** in $PhNEt_2$ gave target **61**, a constitutional isomer of **58**. Analogous to the sequence **59** → **50** → **61**, coumarin **62** was alkylated with 2,3-dibromopropene to give intermediate **63**, and **63** was cyclized to the cyclohexane annulated psoralen **64**. Intermediate **63** was also dehydrogenated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give benzocoumarin **65**, and **65** was thermally cyclized to the benzo annulated psoralen **66**. The photoantiproliferative activity of all compounds, tested on two human tumor cell lines, was higher than that of the well-known photochemotherapeutic drug 8-methoxypsoralen (8-MOP).

Modified pyranocoumarins containing a condensed cyclopentane fragment have been synthesized <2004MI427>. Using the MacLeod method for furan ring fusion (**Scheme 8**), hydroxydihydropyranocoumarin **67** was alkylated under Williamson conditions using chloroacetone and 3-chlorobutan-2-one to give **68a** and **68b**, respectively, in high yield. Heating these in 1 M NaOH followed by acid treatment cyclized them to 5,5-dimethyl-6,7,11,12-tetrahydrocyclopenta[*c*]furo[2,3-*f*]pyrano[2,3-*h*]chromen-9-ones **69a** and **69b**, respectively.

New synthetic routes (**Scheme 9**) to photosensitive linear and angular furocoumarins, furoquinolones, furoquinolines, and their analogs were the subject of a review <2004MOL50>. It focuses on the Fries rearrangement of acyloxyheteroarenes, like **70** → **71**, the condensation of acylhydroxyheteroarenes with α-carbonyl compounds, like **72** → **73**, and the transformations of dihydrofuroheteroarenes, like **74** → **75**.

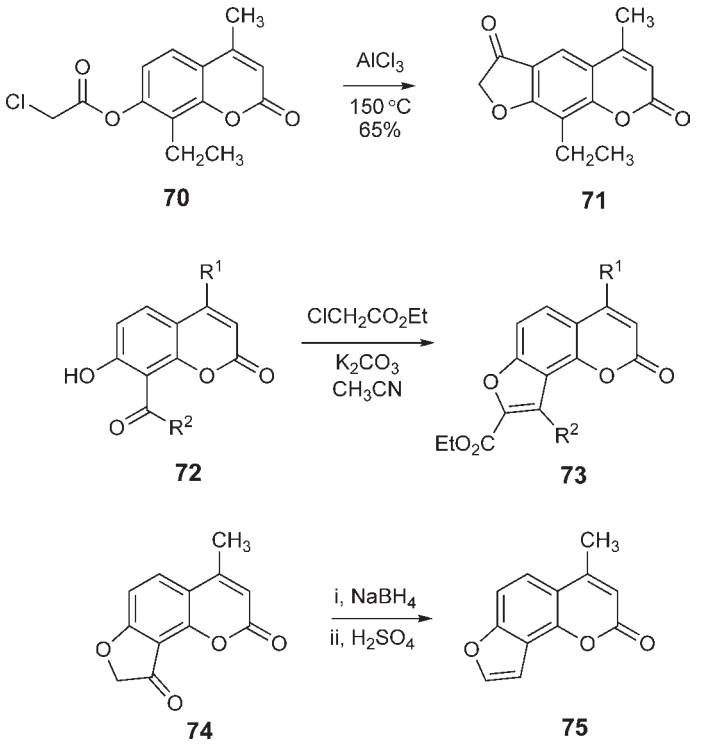


Scheme 7

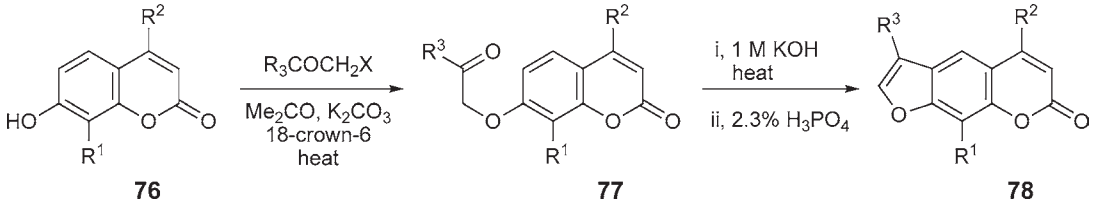


Scheme 8

A series of 3-alkyl- and 3-aryl-7*H*-furo[3,2-*g*]-1-benzopyran-7-ones **78** (linear furocoumarins) was synthesized and evaluated for their photochemical and nonphotochemical crosslink formation with DNA as well as for their spectrophotometric and fluorescent properties, lipophilicity, and ability to photobleach *N*,*N*-dimethyl-*p*-nitrosoaniline (RNO) after irradiation with UVA light <2002AP187>. The synthesis of the linear furocoumarins (**Scheme 10**) was a modification of a previously published method in which 7-hydroxy-2*H*-1-benzopyran-2-ones **76** were converted into *β*-ketoethers **77** by alkylation with haloketones under phase-transfer catalysis conditions. Base-catalyzed intramolecular condensation and subsequent acidification gave the corresponding **78**. A molecular complex between each one of these fluorescent furocoumarins and DNA was observed, but only compounds with a 3-Me or 3-Ph group showed UVA irradiation-induced crosslink formation.



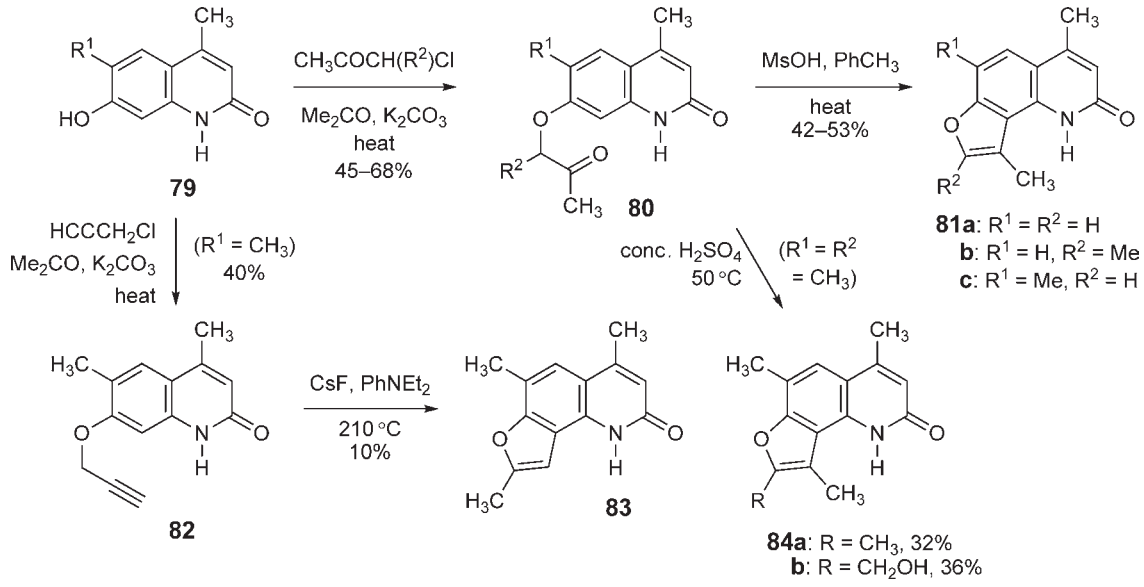
Scheme 9



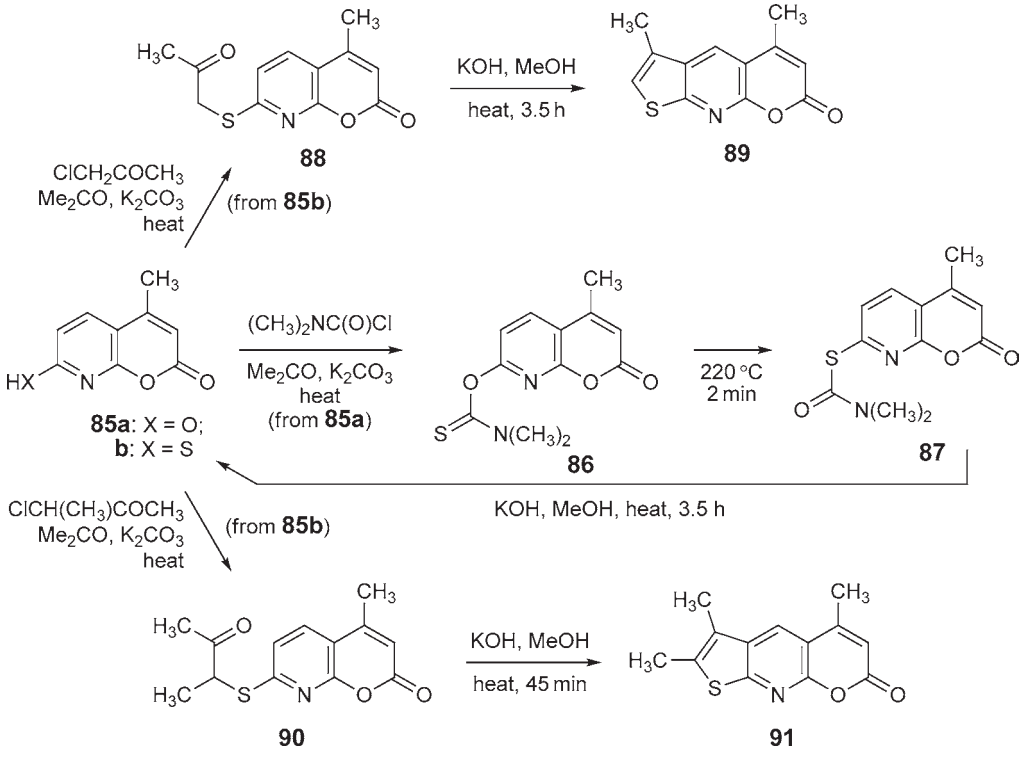
Scheme 10

A set of N1-unsubstituted furo[2,3-*h*]quinolin-2(1*H*)-ones including **81a–c**, **83**, and **84a** and **84b** were prepared by the route shown in **Scheme 11**, and their photobiological activities were compared with those of the photochemotherapeutic drugs 4,6,8,9-tetramethylfuro[2,3-*h*]quinolin-2(1*H*)-one (HFQ) and 8-methoxypsoralen 8-MOP <2002BMC2835>. The anti-proliferative activity of these furoquinolinones was tested upon UVA irradiation in mammalian cells, and almost all were found more active than 8-MOP, and free of any mutagenic activity and skin phototoxicity.

The tricyclics 4,4′-dimethyl-thieno-8-azacoumarin **89** and 4,4′,5′-trimethyl-thieno-8-azacoumarin **91** (**Scheme 12**) were prepared for photobiological activity testing on human tumor cell lines <2002BML1253>. 4-Methyl-7-hydroxypyrano[2,3-*b*]pyridin-2-one **85a** was condensed (no yields given) with *N*,*N*-dimethylthiocarbamoyl chloride under basic conditions to give thiocarbamate **86**, which was thermally isomerized under rapid conditions to isomer **87**. Hydrolysis of **87** gave the pyridin-2-thione **85b**, which was condensed with chloroacetone or 3-chloro-2-butanone to give **88** or **90**, respectively. Cyclization of **88** and **90** gave targets **89** and **91**, respectively. Target **89** was found to have a photocytotoxic ability higher than the well-known drug 8-MOP in one assay, and experiments revealed that a covalent photoaddition to DNA like that for furocoumarins was occurring. Notably, no skin phototoxicity was found.



Scheme 11

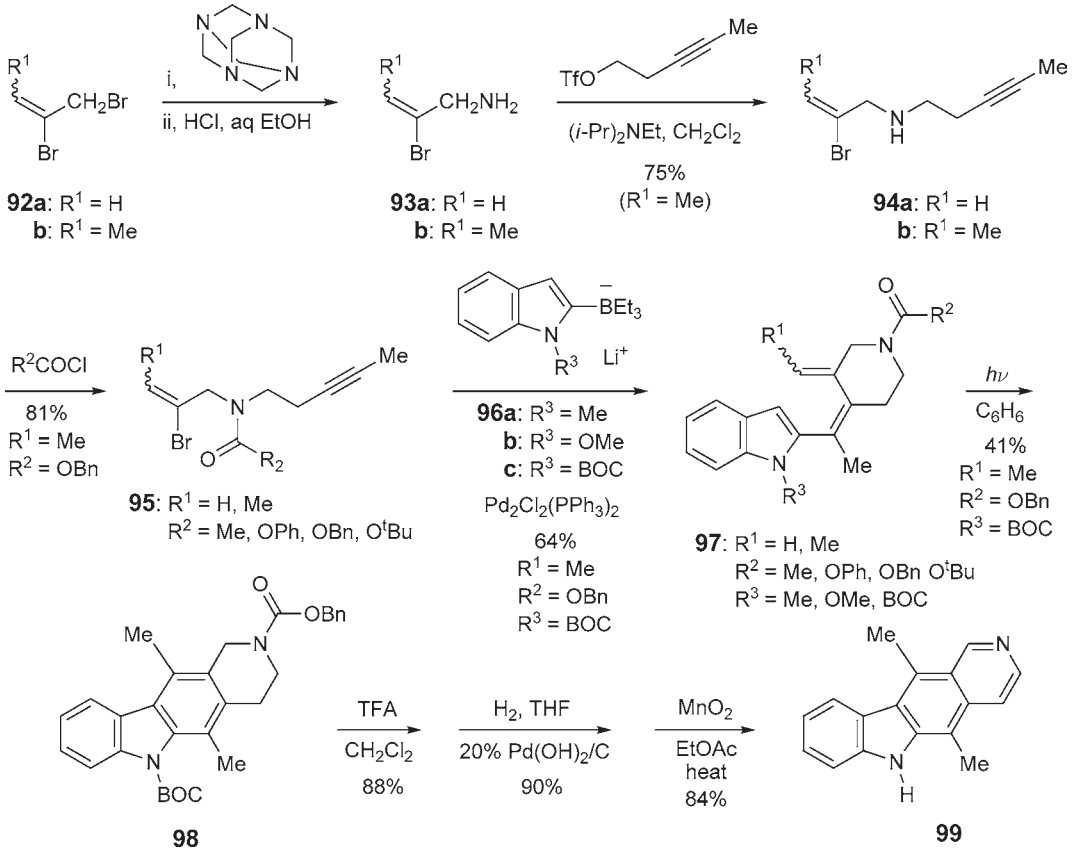


Scheme 12

10.22.5.3 Ellipticines

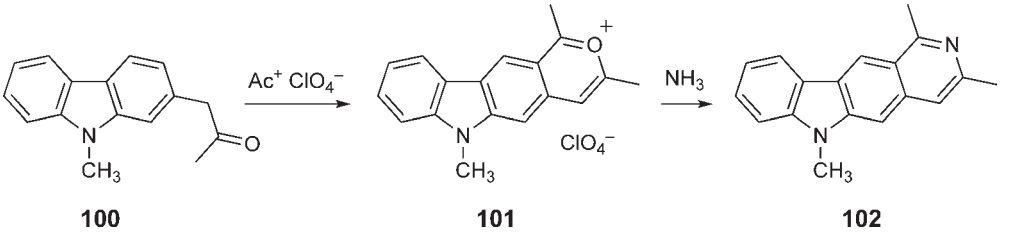
Recent developments in the total syntheses and structural modifications of the natural carbazole-containing ellipticine alkaloids and related indolocarbazoles were the subject of a review <2001COR507>. Modifications designed to effect changes in biological activities were emphasized.

A novel route (**Scheme 13**) to pyrido[4,3-*b*]carbazoles including ellipticine was developed, based on a Pd-catalyzed tandem cyclization/cross-coupling reaction of an indolylborate <1999T193>. The 2,3-dibromopropenes **92a** and **92b** were treated with hexamethylenetetramine according to a literature procedure to give allylamines **93a** and **93b**, which in turn were condensed with pent-3-ynyl triflate to give the secondary amines **94a** and **94b** in good yield. After N-acylation to **95**, these were condensed with indolylborates **96a–c**. This tandem cyclization/cross-coupling reaction provided hexatrienes **97** for subsequent photochemical ring closure to pyrido[4,3-*b*]carbazoles. One variant of **97** ($R^1 = Me$; $R^2 = OBn$; $R^3 = BOC$) underwent this ring closure in 41% yield to give pyrido[4,3-*b*]carbazole **98**. The protecting groups were removed, and the heterocycle was dehydrogenated with MnO_2 to give ellipticine **99**.



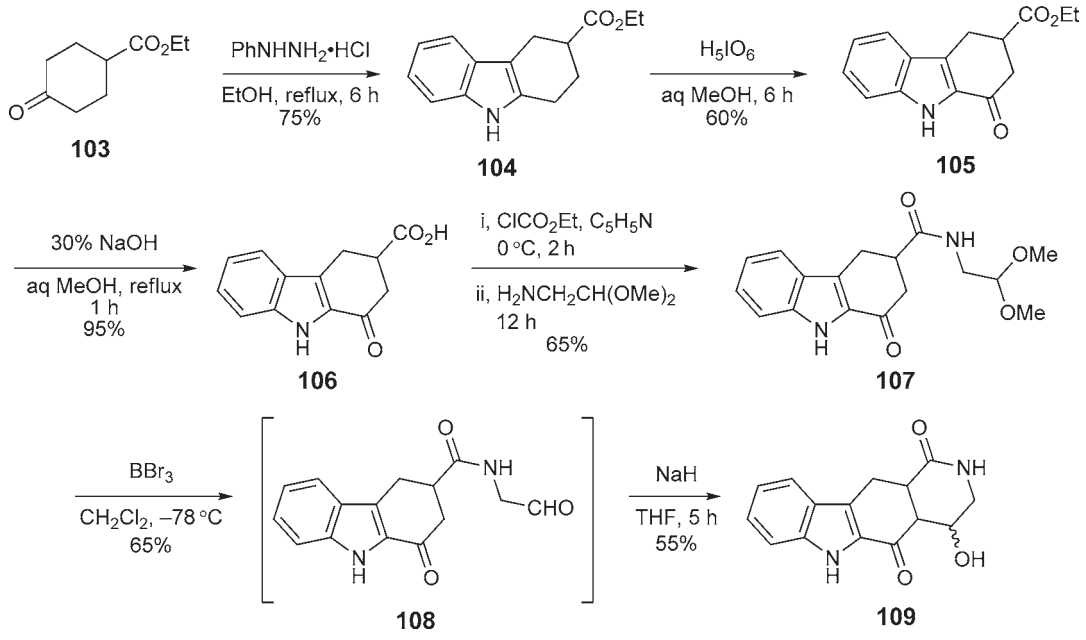
Scheme 13

The acid-catalyzed *ortho*-acylation of *β*-oxoalkyl derivatives of π-excess aromatic heterocycles known as the Dorofeenko–Dulenko–Krivun reaction affords condensed pyrylium derivatives which are convenient precursors of the corresponding pyridines <2001CHE1310>. By this approach (**Scheme 14**), carbazole **100** is converted into carbazolo[3,2-*c*]pyrylium **101**, a new 18π-electron heteroaromatic system, and **101** is readily transformed into isomer **102** of 6-methylellipticine via an S_N(ANRORC) reaction using ammonia. The yields for these transformations were not reported.



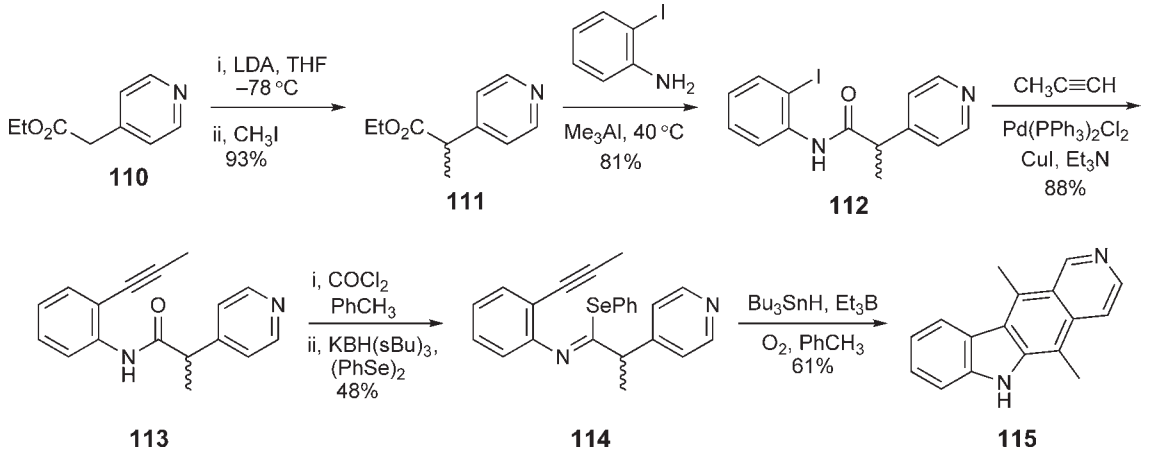
Scheme 14

The D ring of a precursor to ellipticine derivatives was constructed (**Scheme 15**) via an intramolecular aldol condensation <2004SC435>. Ethyl 4-oxocyclohexanecarboxylate **103** was condensed with $PhNHNH_2$ in a Fisher indole synthesis to give indole **104**, which was selectively oxidized with periodic acid to give the oxotetrahydrocarbazole **105**. Ester **105** was saponified to **106**, and this acid was converted into amide **107**. The dimethyl acetal group of **107** was cleaved with BBr_3, and the unstable aldehyde **108** obtained was directly treated with NaH to promote the intramolecular aldol reaction, giving **109** as a 1:1 mixture of epimeric alcohols.



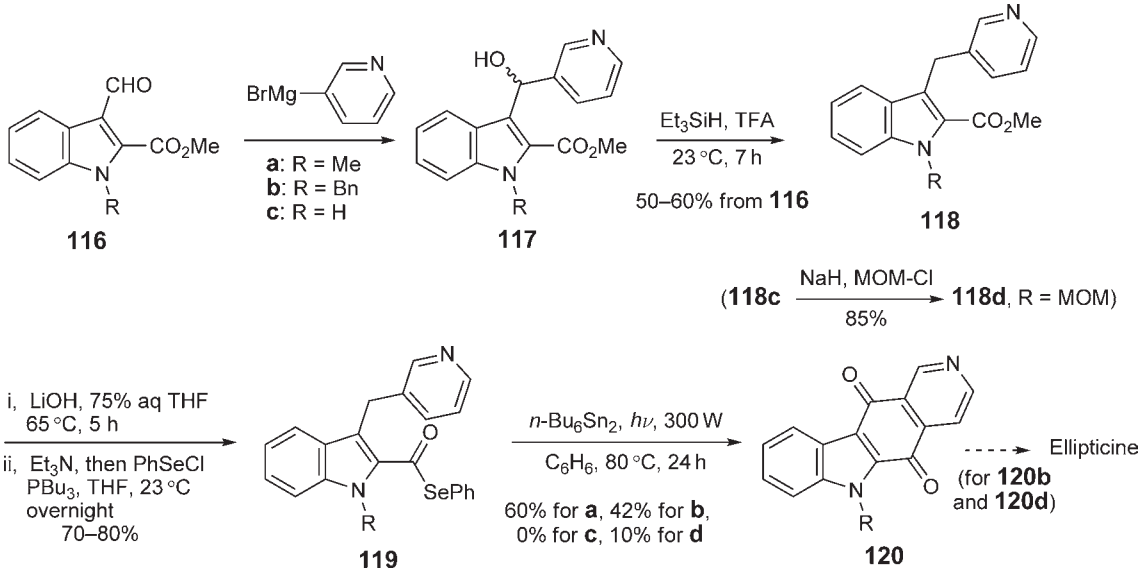
Scheme 15

A high-yielding total synthesis of ellipticine was developed using an imidoyl selenide as a precursor of an imidoyl radical in a cascade reaction <2005JOC10615>. As shown in **Scheme 16**, ethyl 2-(4-pyridyl)acetate **110** was alkylated to ester **111**, which was then condensed with 2-iodoaniline to give amide **112**. Palladium-catalyzed alkynylation of **112** then gave amide **113**, which was converted into imidoyl selenide **114**. An X-ray crystal structure determination of **114** revealed the *Z*-configuration about the C=N bond needed for the subsequent radical cyclization, which was mediated by Bu_3SnH and initiated with Et_3B to give ellipticine **115** in five steps with an overall yield of 19%.



Scheme 16

A formal total synthesis of ellipticine via known ellipticine *p*-quinones was accomplished along a route (**Scheme 17**) involving 2-indolylacyl radicals generated photochemically using *n*-Bu_6Sn_2 <2005JOC9077>. The 2,3-disubstituted indoles **116a–c** were condensed with 3-pyridylmagnesium bromide to give, after Et_3SiH deoxygenation of the intermediate alcohols **117**, methyl esters **118a–c**. At this point, **118c** was *N*-MOM protected to give **118d**. Hydrolysis of **118a–d** followed by phenylselenation gave selenoesters **119a–d** in good yield. Only **119a** and **119b** efficiently underwent regioselective cyclization upon treatment with *n*-Bu_6Sn_2 to give, after *in situ* oxidation at the interannular methylene group, ellipticine quinones **120a** and **120b**. The MOM-protected indole **119d** gave **120d** only in very low yield, and **119c** gave none of the target **120c**. Since **120b** and **120d** have been previously transformed into ellipticine, this route constitutes a formal synthesis of this natural product.



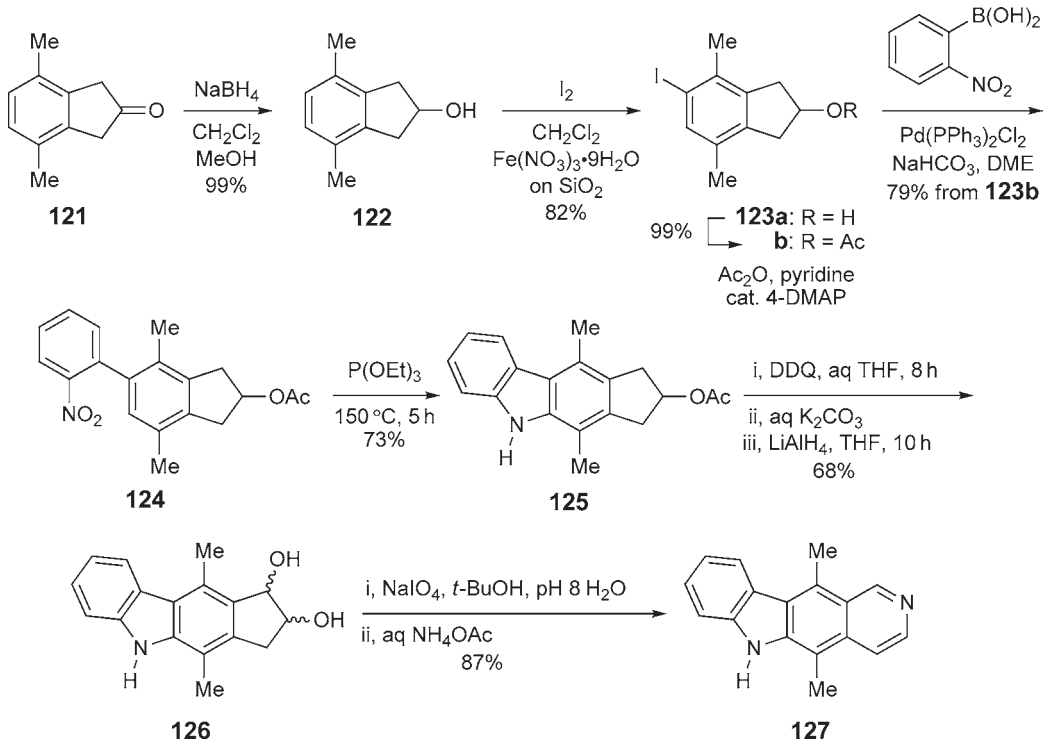
Scheme 17

A short synthesis (**Scheme 18**) of the tetracyclic pyridocarbazole alkaloid ellipticine **127** (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) starting from 4,7-dimethyl-1*H*-indene was developed, proceeding in a 13% overall yield <2006HCA111>. 4,7-Dimethylindan-2-one **121**, obtained via oxidation of the corresponding indene, was reduced to alcohol **122**, which was iodinated to **123a**. Alcohol **123a** was protected as the acetate **123b** before a Suzuki coupling using 2-nitrobenzeneboronic acid gave the nitrobiaryl **124**. Reductive cyclization of **124** with $P(OEt)_3$ gave the tetracyclic acetate **125**, and DDQ oxidation of **125** gave a keto acetate which was reduced directly to diols **126**. The mixture of alcohols **126** was treated with $NaIO_4$, and the crude product was worked up with NH_4OAc to give ellipticine **127** via dehydrative heterocyclization.

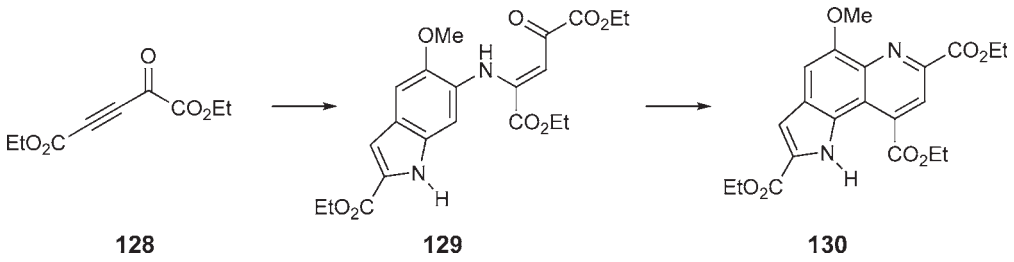
10.22.5.4 PQQ and Related Compounds

An alternative approach to the PQQ-triester **130**, a precursor to the cofactor PQQ, was developed starting with diethyl 4-oxopent-2-ynedioate **128** <1996HCA658>. Diastereoselective formation of diethyl (*Z*)-2-(2-(ethoxycarbonyl)-5-methoxy-1*H*-indol-6-ylamino)-4-oxopent-2-enedioate **129** followed by acid-catalyzed cyclocondensation gave the target **130** (**Scheme 19**).

Parallel syntheses of 2-methoxycarbonyl-, 2-methyl-, and 2-hydro-imidazo-7,9-dimethoxycarbonyl analogs **131a–c** of PQQ were developed <2004JOC2626>. The routes are typified by that developed for **131b** shown in **Scheme 20**, in which the diaminonitroanisole **132** was condensed with HOAc to give the nitrobenzimidazole **133**, which was reduced to the amine **134** and condensed with dimethyl *trans*-2-ketoglutaconate under Doebner–von Miller conditions to give imidazoquinoline **135** in good yield. Subsequent demethylation of **135** gave phenol **136**, which was treated with Fremy's salt to give **131b**.

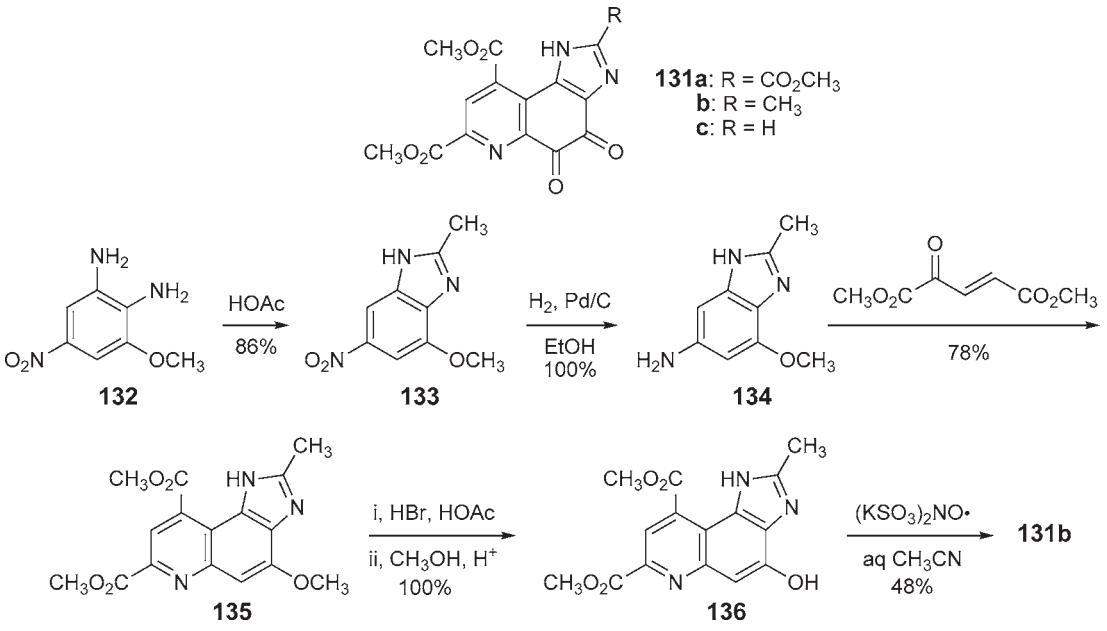


Scheme 18



Scheme 19

Optimization of the reaction conditions for the Pd-catalyzed cyclization of 2-(2-carbomethoxyethynyl)anilines led to a formal synthesis (**Scheme 21**) of PQQ and some of its analogs <2005T12330>. 2-Amino-5-nitrophenol **137** was protected as the cyclic carbamate **138a** by treatment with carbonyldiimidazole, and then **138a** was regioselectively nitrated to give **138b**. Alkaline hydrolysis gave amino alcohol **139a**, which was O-benzylated to **139b**. The amino group of **139b** was then converted to an iodo substituent under Sandmeyer conditions, providing **140**. After a condition variation study designed to find a regioselective reduction for the 6-nitro group in **140**, it was found that treatment with Fe(s) in 1:1 HOAc/EtOH at 100 °C generated the desired aniline **141a** as the major product. Mesylation of **141a** gave the bis-mesylamide **141b**, from which the mono-mesylamide **142** was obtained by methanolysis. The sequential coupling-cyclization reaction of **142** in the presence of methyl propiolate, $Pd(PPh_3)_4$, $ZnBr_2$, and *i*-Pr_2NEt in tetrahydrofuran (THF) gave the indole **143a**. Methanolysis of the remaining mesyl group on **143a** followed by nitro group reduction using Adams' catalyst produced the aniline **144**. Pyridine ring construction



Scheme 20

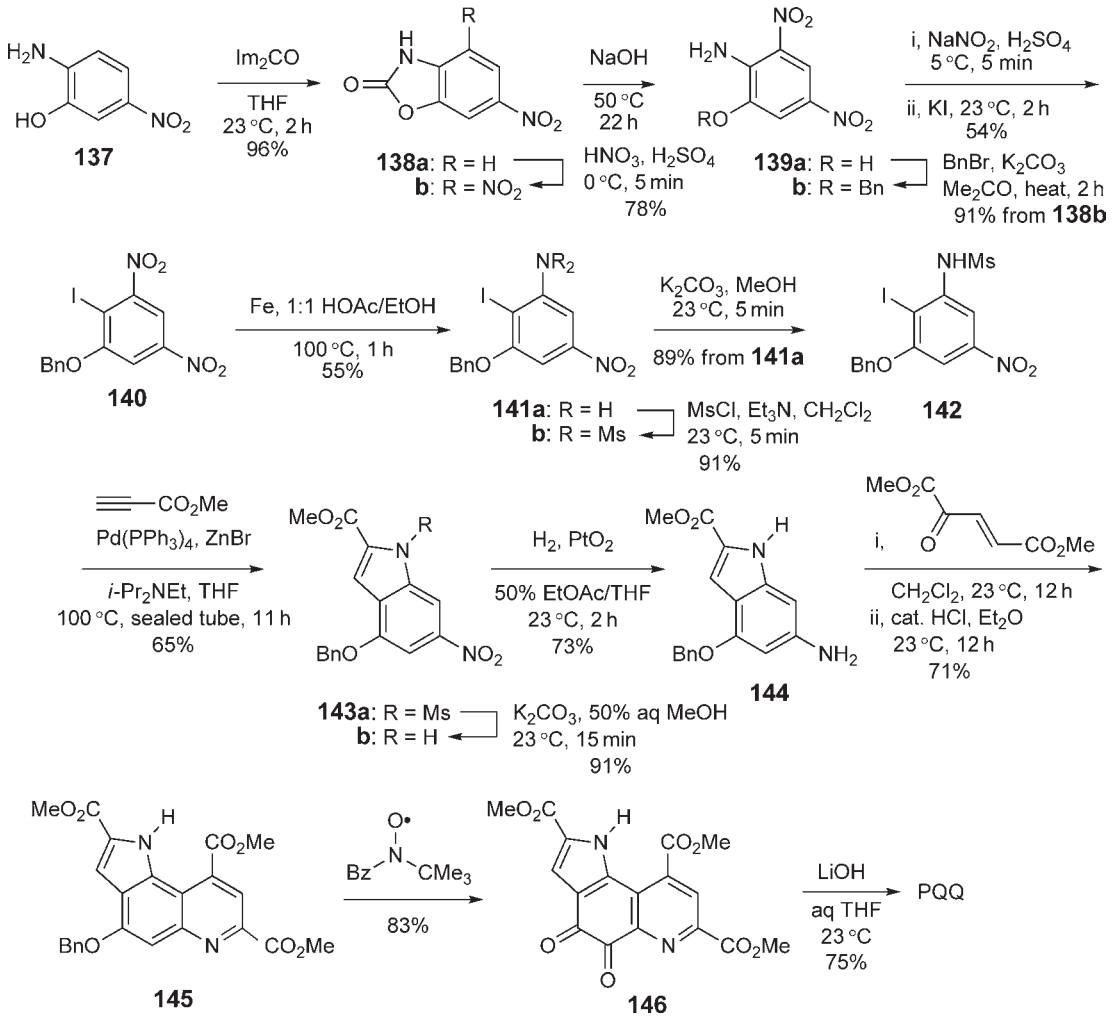
with dimethyl (*E*)-2-oxoglutaconate according to another group's procedure gave access to the tricyclic ring system of PQQ by generating triester **145**. Compound **145** was characterized by infrared (IR) and ^{1}H NMR spectroscopy and mass spectrometry, and since it had previously been converted into to PQQ via the orthoquinone **146** by others, this completed a formal synthesis of PQQ.

In a photochemical approach to pyridopyrroloquinolines (**Scheme 22**), 11-hydroxy-7-methyl-pyrido[3′,4′-4,5]pyrrolo[3,2-*f*]quinoline **151** was synthesized as an ellipticine analog and potential anticancer agent <2004CPB659>. When the 2-iodo version of enaminone **147a** failed to cyclize under photochemical conditions, **147a** was N-methylated to **147b**, which was subjected to irradiation under different conditions to afford oxocyclopentano[4,5]-pyrrolo[3,2-*f*]quinoline **148** in a best yield of 50%. When condensed with NH_2OH, ketone **148** afforded the (*Z*)-oxime **149**. Oxime **149** underwent a Beckmann rearrangement in polyphosphoric acid to give lactam **150**. Dehydrogenation of **150** gave the target hydroxypyrido-pyrroloquinoline **151**. Target heterocycle **151** and others, and their precursors synthesized in this effort were all found to be less effective than doxorubicin in the tumor cell lines studied.

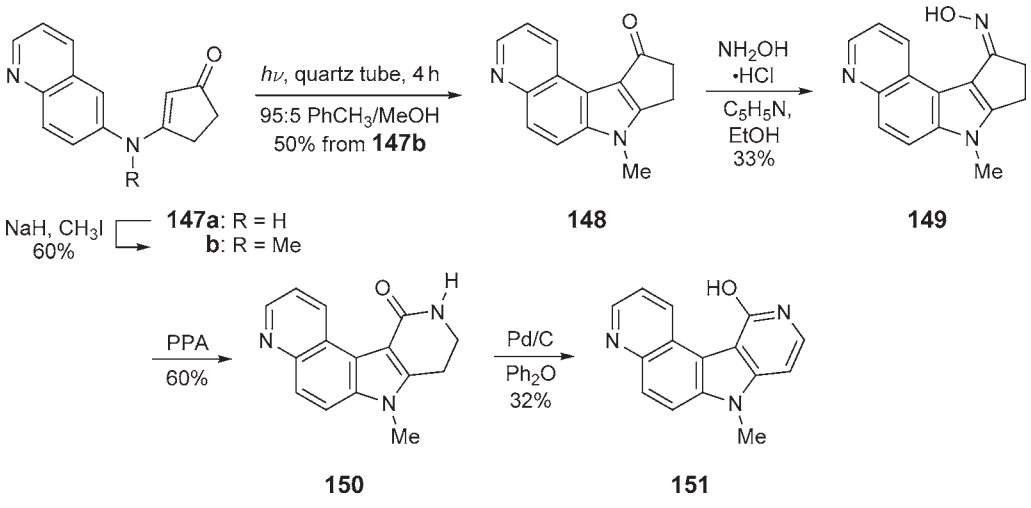
10.22.5.5 Imidazo- and Triazoloquinolines

Synthesis of imidazo- and triazolo[4,5-*f*] quinolines and imidazo- and triazolo[4,5-*h*]quinolines by the Gould–Jacobs reaction boiling at 250 °C in the inert medium of Dowtherm has been described (**Schemes 23** and **24**) <1988CCC1068>. The starting materials for these syntheses were the quinolone carboxylic acids **153** and **158** obtained by the base-catalyzed hydrolysis of esters **152** and **157**. The decarboxylation of acids **153** and **158** gave compounds **154** and **159** which, upon chlorination and subsequent hydrogenation, afforded the target compounds **156** and **161**, respectively. The structures of the latter were verified by detailed NMR, IR, UV, and mass spectroscopy which supported the presence/absence of functional groups and aromatization at the appropriate steps of the synthesis.

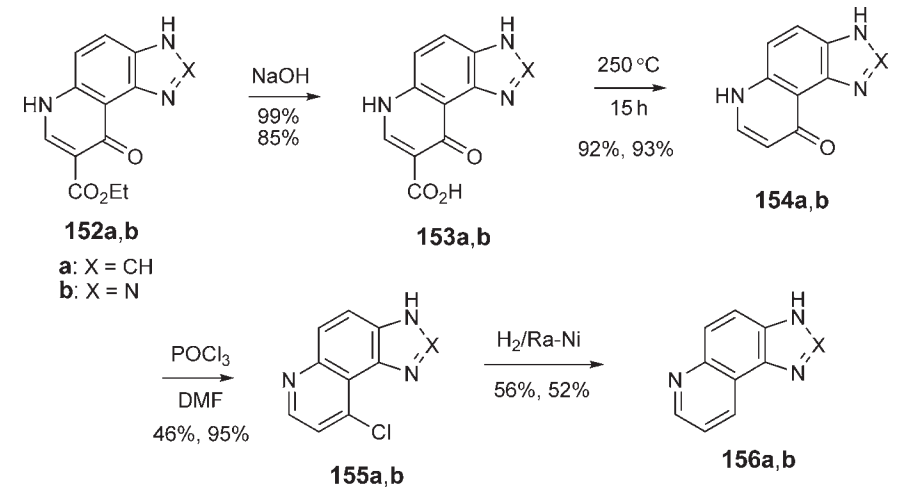
3-*N*-4- and 5-Benzimidazolyl and benzotriazolylamino derivatives of 2-propenoic acid **162–165** were also cyclized under the Gould–Jacobs reaction conditions to afford ring-fused substituted imidazo or triazolo[3,5-*f*]-**152**, **166–167** and -[4,5-*h*]quinolines **157**, **168–169** <1987CCC2918>. Cyclizations were effectively carried out in an inert medium of Dowtherm mixture of Ph_2O and PhPh at 250 °C. The optimum conditions (77–96% for **152a**,**152b**, **166–167**, 43–98% for **157a** and **157b**, **168–169**) were ~15–20 min and at a dilution of either 1 g/20 ml or 1 g/80 ml of Dowtherm. Lower concentrations did not give a clean separation of products, and higher concentrations led to carbonization.



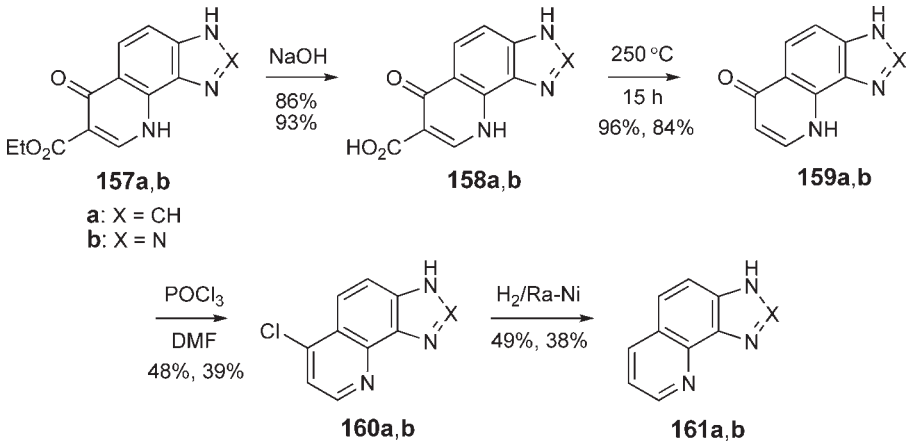
Scheme 21



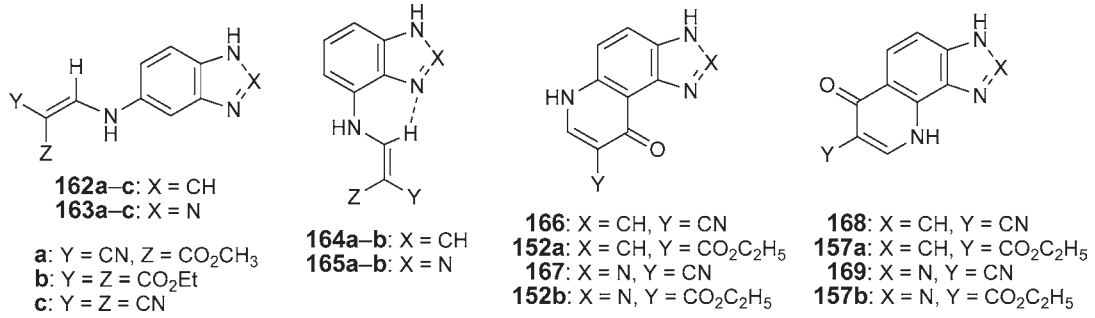
Scheme 22



Scheme 23



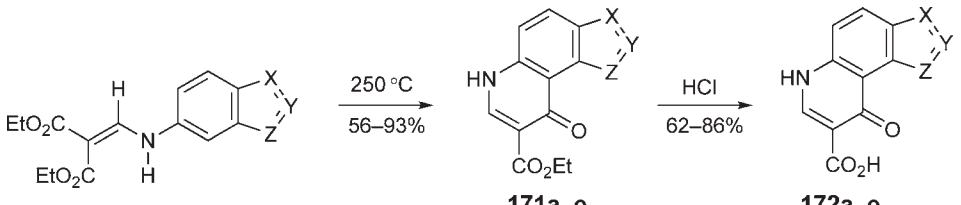
Scheme 24



The structures of the compounds were verified by ^{1}H NMR spectroscopy. Two doublets of benzene ring protons ($J = 9$ Hz) characteristic of mutual *ortho*-positions indicated angularly ring-fused structures. The shifts of ^{13}C NMR peaks and the features of the IR spectra (containing deformed out-of-plane vibrations at ~800 cm^{-1}) were characteristic of 1,2,3,4-tetrasubstitution and so also confirmed the angular ring fusion.

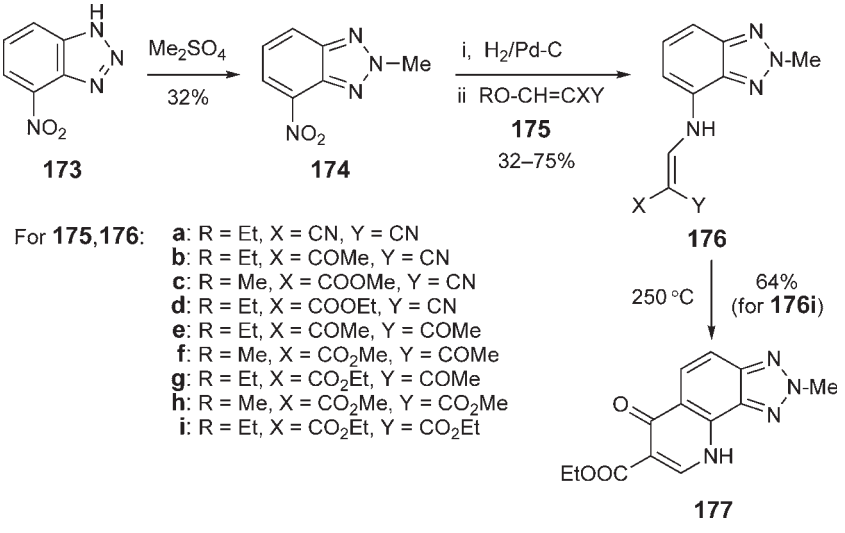
In addition, the malononitrile adducts **162c** and **163c** were cyclized using $AlCl_3$ in PhCl to the amino derivatives of **166** and **167**, respectively, in 93% and 72% yield <1987CCC2918>, and heterocycles **152a** and **152b** and **157a** and **157b** were converted with $POCl_3$/DMF into their corresponding chloro derivatives in 36–76% and 53–90% yields, respectively. These and many of the other reactions described above were summarized in a review article <2001AHC(78)189>.

Similar conditions as above also led to the thermal cyclization of all N-methylated derivatives of 5(6)-aminobenzimidazolyl and triazolyl 2-ethoxycarbonyl-2-propenoic acid derivatives <1988CHE424, 1994CCC1145>. As shown in **Scheme 25**, thermal cyclocondensation reactions of **170a–e** gave the angularly annelated **171a–e** as sole products. Acid hydrolysis of esters **171** gave the corresponding acids **172**. Basic hydrolysis did not afford the desired products apparently due to poor solubility of the esters. The steric position of the Me group had no effect on the ring closure. The mode of annelation was confirmed by ^{1}H NMR spectroscopy. Thus, the application of the Gould–Jacobs reaction to all *N*-methyl derivatives of benzimidazolyl and benzotriazolyl derivatives was found to proceed smoothly.



Scheme 25

The preparation of 2-methylbenzotriazole derivatives having an 4-aminoethylene substituent and two electron-accepting groups (i.e., CN, Ac, RO_2C, or a combination thereof) was also accomplished with relative ease <1984MI65, 1990CCC1038>. Cyclization to 7-ethoxycarbonyl-6,9-dihydro-6-oxo-2-methyl-2*H*-triazolo[4,5-*h*]quinoline **177** was achieved in good yield (**Scheme 26**).

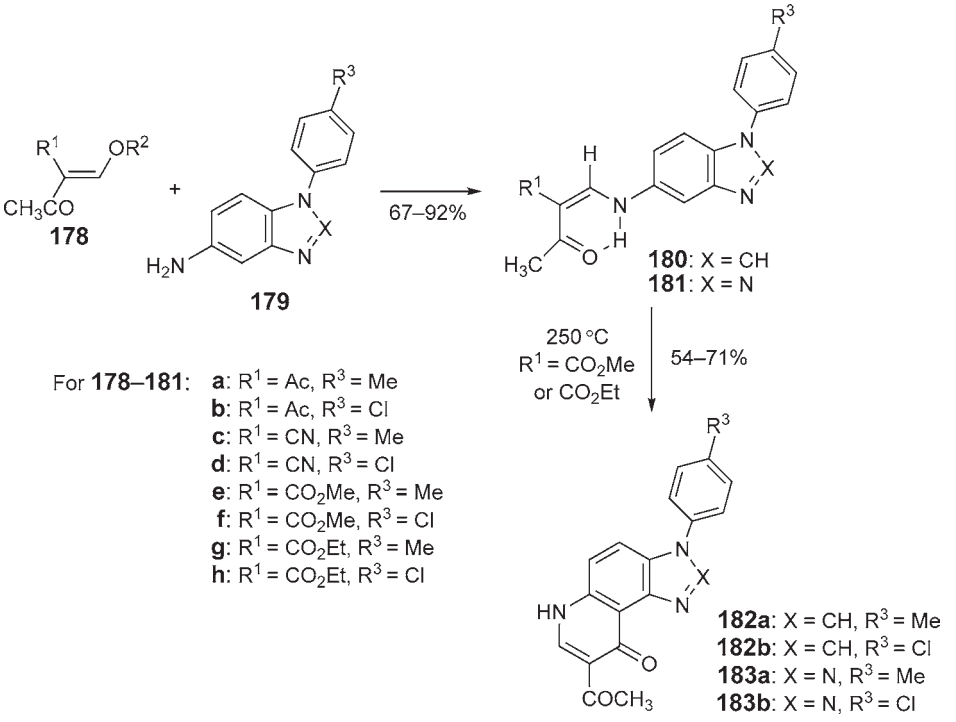


Scheme 26

The starting material for the synthesis of the 4-substituted derivatives **176** was the tautomeric 4(7)-nitrobenzotriazole **173**, which upon methylation with dimethyl sulfate in aq NaOH afforded the 4-nitro-2-methylbenzotriazole **174**. The ^{1}H NMR spectrum of the purified reaction mixture after methylation showed the existence of all three triazole ring *N*-methylated isomers in equal amounts. Compound **174** was isolated by virtue of its insolubility in conc HCl. Purity of products was confirmed by gas liquid chromatography (GLC).

Catalytic reduction followed by condensation with alkoxymethylene derivatives **175** afforded **176**. Compound **176i** was cyclized to 7-ethoxycarbonyl-6,9-dihydro-6-oxo-2-methyl-2*H*-triazolo[4,5-*h*]quinoline **177**. The IR spectra of compounds **176** revealed CN group stretching vibrations at 2200 cm^{-1} and NH stretching bands at 2950–3160 and 3445 cm^{-1}. The UV spectra of **176** showed absorption bands at 280 and 290 nm – very similar to those previously reported for 2-methylbenzotriazole.

As shown in **Scheme 27**, nucleophilic substitution reactions of alkoxymethylene derivatives **178** of 2,4-pentanedione and nitrile and ester derivatives of 3-oxobutanoic acid with substituted 1-phenyl-5-aminobenzimidazoles and benzotriazoles **179** gave adducts **180** and **181** which easily cyclized under thermal conditions to give the corresponding 8-acetyl-3-phenyl-6,9-dihydroazolo[4,5-*f*]quinolin-9(3*H*)-ones **182** and **183** <1992CCC397>. The nucleophilic substitution reactions of **178** and **179** were carried out simply by boiling for a short time in MeOH, affording **180** and **181** in high yields. The alkoxy derivatives **178** were prepared by the condensation of an alkyl orthoformate with an active methylene compound. The amino derivatives **179** were prepared by the catalytic reduction of the corresponding nitro derivatives.



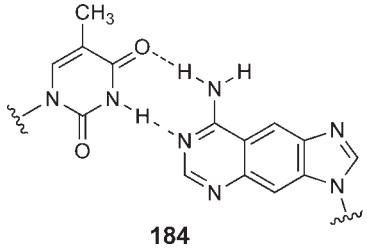
Scheme 27

The cyclization yield greatly depended on the amount of Dowtherm used. A low ratio of solvent to heterocycle led to partial carbonization and a high ratio generated a gel-like product which was difficult to separate. The IR spectra of **180** and **181** revealed acetyl group vibrational shifts to lower wavelength due to strong conjugation. The UV spectra of the substitution products showed a bathochromic shift due to a strong intramolecular hydrogen bonding between the acetyl CO group and the NH proton. The angular annelation of products **182** and **183** was deduced by the *ortho*-positions of the benzene ring protons evident from large coupling constants ($J > 9$ Hz) observed in the ^{1}H NMR spectra.

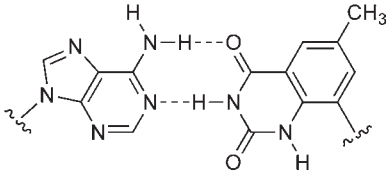
10.22.6 Important Compounds and Applications

10.22.6.1 Benzo-Separated Purines

In 2002, Kool and co-workers described a new genetic-pairing system that has a native DNA backbone but has all 4 bp replaced by new, larger pairs. Analogs of adenine and thymine were used in base pairs **184** and **185**, respectively, both extended in width by a benzene ring (2.4 Å) <2002SCI868, 2005PP133>. These were termed xA and xT, respectively. The adenine analog **184** came from phosphoramidite **32** (**Scheme 2**, Section 10.22.5.1), built upon Leonard's 2′-deoxy-*lin*-benzoadenosine heterocyclic framework. Kool found the expanded-diameter double helices to be more thermodynamically stable than the normal Watson–Crick helix, likely because of enhanced base stacking. Structural analysis of the new helices by 2D NMR spectroscopy showed a right-handed, double-stranded, and base-paired helical form, permitting the investigators to conclude that there was no structural or thermodynamic prohibition against this genetic system having a size different from the natural one. All pairs in this new helical system were fluorescent, suggesting practical applications in detection of natural DNA and RNA.



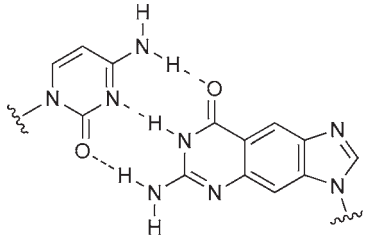
184



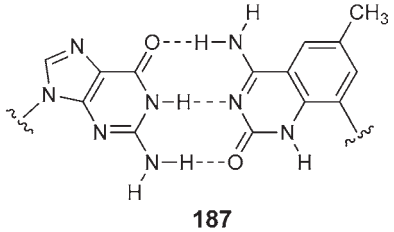
185

Base stacking studies <2004JA11826> showed that the two stretched analogs stack much more strongly than do their natural counterparts, but single substitutions were found to destabilize the natural helix unless multiple adjacent substitutions were used. Despite the local backbone strain estimated to be *ca.* +1 to 2 kcal mol^{-1}, the size-expanded bases were selective in their recognition of complementary partners. In a follow-up investigation of the properties of this new genetic complex <2005JA1396>, several sequences were found to form double-stranded helices while a pyrimidine-rich strand formed a triple helix as well. A preference was found for antiparallel orientation, and mismatch and size selectivity were substantial. The fluorescence and CD spectral characteristics of the new helices differed markedly from those of natural DNA, a result not unexpected given the extended pi electronic character of the expanded systems.

Very recently, Kool and co-workers added the expanded analogs of guanine and cytidine as shown in base pairs **186** and **187**, respectively, to their construction of new helices <2006JA14704>. These analogs were termed xG and xC, respectively. The guanine analog in **186** came from phosphoramidite **26** (**Scheme 1**, Section 10.22.5.1).



186



187

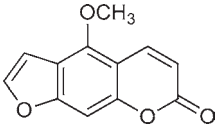
Using the four expanded bases xA, xT, xC, and xG, and the four naturally occurring bases A, T, C, and G, Kool and co-workers were able to construct an xDNA decamer duplex with eight component bases. The structure of the helix was solved in aqueous buffer solution using 1D and 2D NMR spectroscopic methods combined with restrained molecular dynamics, and it revealed the helix to be right-handed and antiparallel, and hydrogen-bonded like Watson–Crick DNA. The major and minor grooves were found to be much wider and more shallow than those of B-DNA, and the helix turn had only *ca.* 12 bp per 360° turn. The extensive intra- and interstrand base stacking surface area is thought to be responsible for the greater stability of this xDNA relative to natural DNA, and the paired self-assembly and other properties of the new designed xDNA system might well be functional in encoding information and transferring it to new complementary strands.

10.22.6.2 Furocoumarins and Furochromones

Recent developments in the synthesis, medicinal chemistry, and biological activity of furocoumarins were the subject of an extensive review <2004CME3239>. In it, the three main synthetic approaches of annelating a furan ring onto a coumarin, annelating a pyrone ring onto a benzofuran, and simultaneously forming both oxygenated rings onto a benzene are discussed separately. Discussions of the biological importance of furocoumarins focus mainly on their photochemotherapeutic potential.

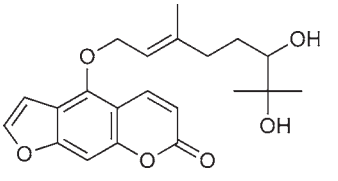
The photophysics, photochemistry, photobiology, and structural analysis of furocoumarins was reviewed <2005JPH168>. They absorb UVA light and act as photosensitizers, and thus have found use as molecular probes and as skin disease drugs. Photoexcited furocoumarins undergo [2+2] photocycloaddition reactions with thymidine and cytidine bases in DNA, forming mono- and di-adducts. Factors which control the photoreaction by influencing the degree of photobinding like the DNA base sequences, the UVA light dose, the excitation wavelengths, temperatures, and solvents were summarized.

5-Methoxypsoralen **188** is a naturally occurring linear furocoumarin found in citrus fruit rind and celery and parsley leaves. The use of oral or topical 5-methoxypsoralen plus UVA irradiation in the management of the skin disorders psoriasis and vitiligo was the subject of a medically oriented review <1998MI667>.

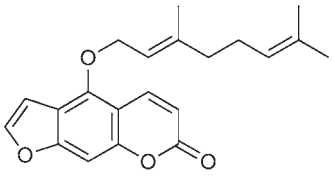


188

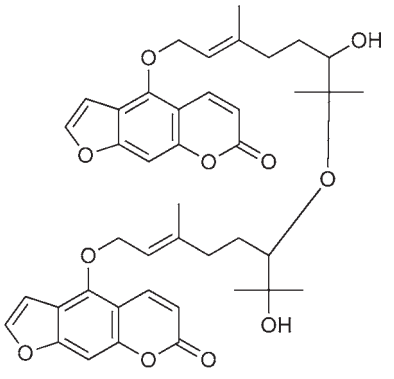
Three biologically active furocoumarins 6′,7′-dihydroxybergamottin **189**, bergamottin **190**, and paradisin-A **191** in grapefruit juice were isolated, purified, and characterized, and their inhibitory effects on hydroxylase and O-dealkylase activities of human cytochrome P450 isoenzymes CYP 3A4 and CYP 1B1 were investigated <2006BMC2606>. The purity of the compounds was analyzed by HPLC and their structures were determined in part by heteronuclear multiple bond correlation (HMBC) 2D NMR spectroscopy. Paradisin-A was found to be the most potent CYP 3A4 inhibitor, with all compounds showing a substantial inhibitory effect below 10 μM. Inhibitory effects on CYP 1B1 exhibited a greater variation. The inhibition of these enzymes may explain why there is an increase in bioavailability of certain orally administered drugs when taken with grapefruit juice.



189



190



191

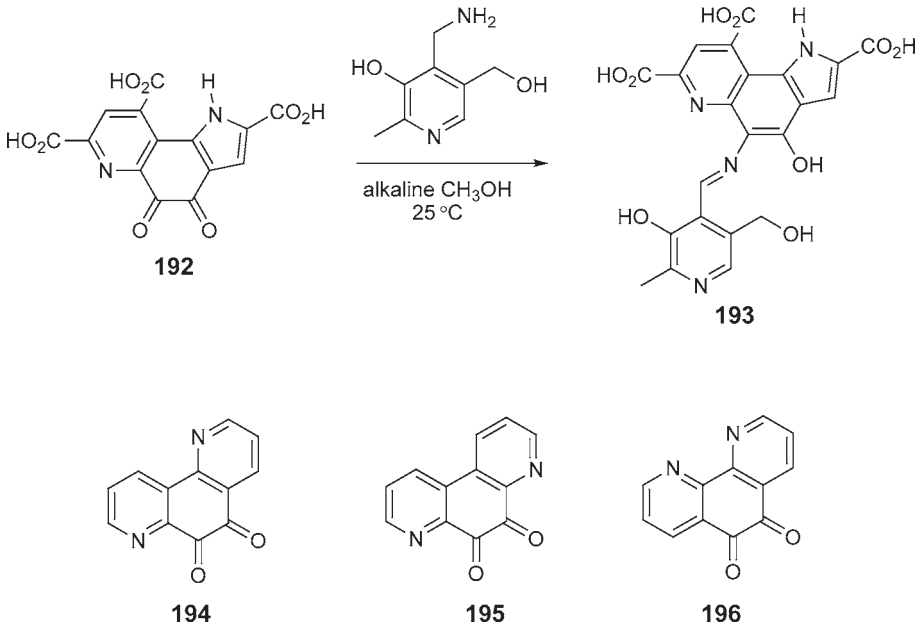
10.22.6.3 Ellipticines

Based on the observation that ellipticine binds preferentially to the RNA:DNA hybrid poly rA:poly dT, an assay was developed to rapidly screen large numbers of potential lead compounds for this property <2001JA6742>. The 3D structures of the compounds that preferentially bind to the RNA:DNA hybrid (ellipticine, ethidium, coralyne,

propidium, and TAS103) share a common structural motif consisting of a planar aromatic ring system with a 'bay' region. This potential pharmacophore could aid in the development of therapeutics which target transient, unique DNA or RNA structures in gene replication and expression.

10.22.6.4 PQQ and Related Compounds

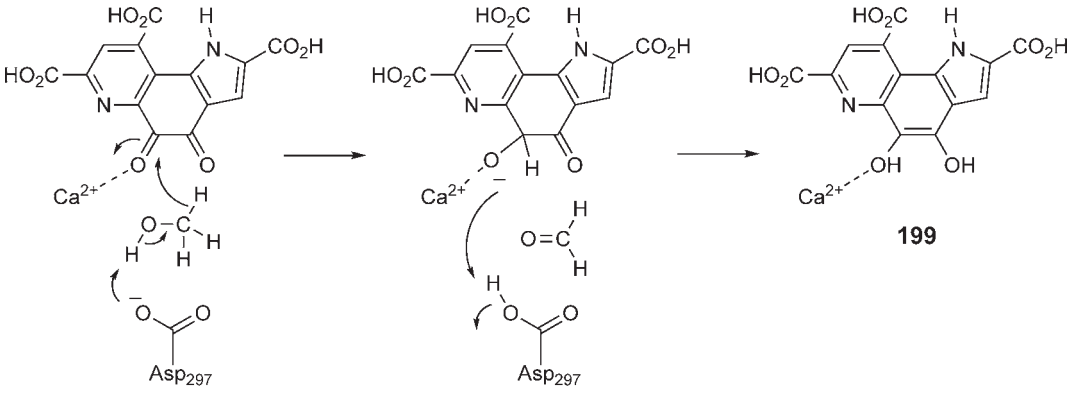
To model the intermediates formed by pyridoxal phosphate-dependent enzymes, the redox cofactor PQQ **192** was treated (**Scheme 28**) with pyridoxamine in basic CH_3OH at 25 °C <1999CPB1774>. A UV–Vis absorption band at *ca.* 500 nm gradually intensified, reached a maximum at 6 h, and then gradually decreased and disappeared. Suspecting the formation of ketimine adduct **193**, 1,7-phenanthroline-5,6-quinone **194**, 4,7-phenanthroline-5,6-quinone **195**, and 1,10-phenanthroline-5,6-quinone **196** were subjected to similar conditions. Only **196** failed to react with primary amines, implicating the requirement of a pyridine N-atom *peri* to the *o*-quinone carbonyl groups of **192**. Adduct **193** was obtained in crystalline form, its UV–Vis absorption spectra in CH_3OH and water were recorded, and its fast atom bombardment (FAB) mass spectrum obtained. The latter was consistent with the structure of **193**.



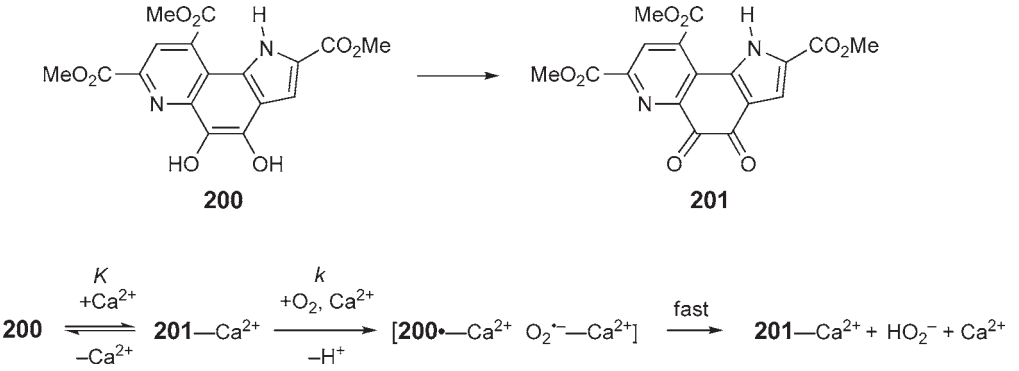
Scheme 28

Evidence for a hydride transfer mechanism (**Scheme 29**) for the PQQ-dependent enzyme methanol dehydrogenase (MDH) was obtained by a theoretical analysis combined with an improved refinement of a 1.9 Å resolution crystal structure of MDH from *Methylophilus methylotrophus* in the presence of CH_3OH <2001PNA432>. The alternative mechanism proceeding via a hemiketal intermediate was discounted when the observed tetrahedral configuration of the C-5 atom of PQQ in that crystal structure was shown to be the C-5-reduced form of the cofactor **198**, a precursor to the more common reduced form of PQQ **199**.

Other aspects of the MDH X-ray crystal structure have enabled other researchers to provide a deeper understanding of the reaction mechanism as well. For example, the reoxidation of a reduced PQQ to the quinone by O_2 was shown to be dramatically enhanced by the same Ca^{2+} revealed at the active site of the protein by the MDH crystal structure determination <1997CC29>. Using the trimethyl ester **200**, a preequilibrium between this diol and Ca^{2+} is followed by the donation of an electron from this complex to O_2, catalyzed by Ca^{2+} via the complex formation of $O_2^{\cdot-}$ and Ca^{2+} (**Scheme 30**). A rapid second electron transfer then completes the oxidation of **200** to **201**. Some kinetic evidence obtained in this model study indicated that the coordination of Ca^{2+} may occur to the 5-OH group and the pyridine nitrogen, facilitating the deprotonation of the former and thereby producing a strong electron donor.



Scheme 29



Scheme 30

Biosensors constructed for ethanol and D-glucose measurements in beverages were built using ferrocene compounds as electron transfer mediators between the coenzyme PQQ of immobilized enzymes glucose (GDH) and alcohol (ADH) dehydrogenases and a carbon electrode surface <2003JOM(668)83>.

10.22.7 Further Developments

The synthesis and properties of size-expanded DNAs, including those containing the benzo-separated purines, have been summarized in a review articles <2007ACR141>. These large bases destabilize DNA when they are singly substituted into it, but give highly stable modified duplexes when all base pairs are of the expanded type. A new synthesis of ellipticine and its 9-methoxy derivative, and of isoellipticine and its 7-carbethoxy derivative, was developed <2007JOC7106>. The key reaction in this approach is the preparation of polyfunctional aryl azides from the corresponding aryl triazenes using NaN_3 in the presence of $KNSO_4$ or $BF_3{\cdot}OEt_2/CF_3CO_2H$, conditions which tolerate a variety of functional groups like halides, esters, ketones, nitriles, aldehydes, and boronic esters. Finally, a simple and sensitive method for analyzing PQQ in various foods was developed, using LC/ESI tandem mass spectrometry <2007JAF7258>. Samples were treated with ^{15}N-labeled PQQ as an internal standard, and quantitative analyses of PQQ were performed by multiple reaction monitoring with LC/MS/MS. Free PQQ was detected in nearly all food samples at the 0.19–7.02 ng/g or ng/mL level.

References

1984MI65 D. Ilavsky, V. Bobosik, and V. Milata, *Nucleic Acids Res., Symp. Ser.*, 1984, **14**, 65.
1987CCC2918 V. Milata and D. Ilavsky, *Collect. Czech. Chem. Commun.*, 1987, **52**, 2918.
1988CCC1068 V. Milata, D. Ilavsky, and J. Lesko, *Collect. Czech. Chem. Commun.*, 1988, **53**, 1068.
1988CHE424 V. Milata and D. Ilavsky, *Chem. Heterocycl. Compd.*, 1988, **35**, 424.
1990CCC1038 V. Milata, D. Ilavsky, I. Goljer, J. Lesko, M. Chahinian, and E. Henry-Basch, *Collect. Czech. Chem. Commun.*, 1990, **55**, 1038.
1992CCC397 V. Bobosik, V. Milata, D. Ilavsky, and I. Goljer, *Collect. Czech. Chem. Commun.*, 1992, **57**, 397.
1994CCC1145 V. Milata, D. Ilavsky, I. Goljer, and Z. Lubomir, *Collect. Czech. Chem. Commun.*, 1994, **59**, 1145.
1996BPM309 A. H. Elcock, A. Rodger, and W. G. Richards, *Biopolymers*, 1996, **39**, 309.
1996CHEC-II(7)875 M. P. Groziak and F. G. Jacobs; in 'Comprehensive Heterocyclic Chemistry II', A. R. Katrizky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 875.
1996HCA658 D. Sicker, E. Stehfest, H. Wilde, and P. Martin, *Helv. Chim. Acta*, 1996, **79**, 658.
1996JRS539 S. Bernard, M. A. Schwaller, J. Moiroux, E. A. Bazzaoui, G. Levi, and J. Aubard, *J. Raman Spectrosc.*, 1996, **27**, 539.
1997CC29 S. Itoh, H. Kawakami, and S. Fukuzumi, *J. Chem. Soc., Chem. Commun.*, 1997, 29.
1997JOC2630 W. R. Kobertz and J. M. Essigmann, *J. Org. Chem.*, 1997, **62**, 2630.
1998JA7271 S. Itoh, H. Kawakami, and S. Fukuzumi, *J. Am. Chem. Soc.*, 1998, **120**, 7271.
1998MI667 W. McNeely and K. L. Goa, *Drugs*, 1998, **56**, 667.
1999CPB1774 Y. Nagata, Y. Matsushima, N. Fujii, S. Fukuda, H. Kanazawa, R. Yoda, and S. Matsumoto, *Chem. Pharm. Bull.*, 1999, **47**, 1774.
1999IC2753 M. Wanner, T. Sixt, K.-W. Klinkhammer, and W. Kaim, *Inorg. Chem.*, 1999, **38**, 2753.
1999T193 M. Ishikura, A. Hino, T. Yaginuma, I. Agata, and N. Katagiri, *Tetrahedron*, 1999, **56**, 193.
2000AXCe136 F. H. Billiot, D. R. Billodeaux, S. F. Watkins, and F. R. Fronczek, *Acta Crystallogr., Sect. C*, 2000, **4**, e136.
2000JCH(876)193 A. R. Smith, J. R. Kirchhoff, Z. Zhang, L. M. V. Tillekeratne, and R. A. Hudson, *J. Chromatogr., A*, 2000, **876**, 193.
2000JCH(739)101 Z. Glatz, M. Moravcova, and O. Janiczek, *J. Chromatogr., B*, 2000, **739**, 101.
2000PCB4992 V. Di Noto, L. Dalla Via, O. Gia, A. M. Onori, L. Cellai, and S. M. Magno, *J. Phys. Chem. B*, 2000, **104**, 4992.
2001AHC(78)189 V. Milata; in 'Advances in Heterocyclic Chemistry', A. R. Katritzky, Ed.; Elsevier, Amsterdam, 2001, vol. 18, p. 189.
2001CHE1310 A. V. Kibal'nyi, O. I. Kharaneko, and V. I. Dulenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2001, **37**, 1310.
2001COR507 G. H. Kirsch, *Curr. Org. Chem.*, 2001, **5**, 507.
2001JA6742 J. Ren, X. Qu, N. Dattagupta, and J. B. Chaires, *J. Am. Chem. Soc.*, 2001, **123**, 6742.
2001JCC1732 A. Jongejan, J. A. Jongejan, and W. R. Hagen, *J. Comput. Chem.*, 2001, **22**, 1732.
2001JPS732 S. Caffieri, *J. Pharm. Sci.*, 2001, **90**, 732.
2001PNA432 Y.-J. Zheng, Z.-X. Xia, Z.-W. Chen, F. S. Mathews, and T. C. Bruice, *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 432.
2002AP187 P. Körner, *Arch. Pharm (Weinheim, Ger.)*, 2002, **335**, 187.
2002BMC2835 C. Marzano, A. Chilin, F. Bordin, F. Baccichetti, and A. Guiotto, *Bioorg. Med. Chem.*, 2002, **10**, 2835.
2002BML1253 L. Dalla Via, S. M. Magno, P. Rodighiero, and O. Gia, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1253.
2002JA3366 D. Reha, M. Kabelac, F. Ryjacek, J. Sponer, J. E. Sponer, M. Elstner, S. Suhai, and P. Hobza, *J. Am. Chem. Soc.*, 2002, **124**, 3366.
2002MI230 M. M. Garazd, Y. L. Garazd, S. V. Shilin, T. N. Panteleimonova, and V. P. Khilya, *Chem. Nat. Compds.*, 2002, **38**, 230.
2002MI539 M. M. Garazd, Y. L. Garazd, A. S. Ogorodniichuk, and V. P. Khilya, *Chem. Nat. Compds.*, 2002, **38**, 539.
2002SCI868 H. Liu, J. Gao, S. R. Lynch, Y. D. Saito, L. Maynard, and E. T. Kool, *Science*, 2002, **302**, 868.
2003JA8141 S. Y. Reddy and T. C. Bruice, *J. Am. Chem. Soc.*, 2003, **125**, 8141.
2003JCH(1011)37 D. D. Schumacher, C. R. Mitchell, T. L. Xiao, R. V. Rozhkov, R. C. Larock, and D. W. Armstrong, *J. Chromatogr., A*, 2003, **1011**, 37.
2003JOC3626 J.-W. Zou, J.-M. Liang, and C.-H. Yu, *J. Org. Chem.*, 2003, **68**, 3626.
2003JOC6314 R. V. Rozhkov and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 6314.
2003JOM(668)83 J. Razumiene, A. Vilkanauskyte, V. Gureviciene, V. Laurinavicius, N. V. Roznyatovskaya, Y. V. Ageeva, M. D. Reshetova, and A. D. Ryabov, *J. Organomet. Chem.*, 2003, **668**, 83.
2003JPH235 J. Llano, J. Raber, and L. A. Eriksson, *J. Photochem. Photobiol., A*, 2003, **154**, 235.
2003MI177 M. V. Veselovskaya, S. V. Shilin, M. M. Garazd, and V. P. Khilya, *Chem. Nat. Compds.*, 2003, **39**, 177.
2003OL797 R. V. Rozhkov and R. C. Larock, *Org. Lett.*, 2003, **5**, 797.
2003PS(178)143 A. Shockravi, M. M. Heravi, and H. Valizadeh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2003, **178**, 143.
2004ARK131 L. Dalla Via, E. Uriarte, L. Santana, S. M. Magno, and O. Gia, *ARKIVOC*, 2004, **v**, 131.
2004CME3239 L. Santana, E. Uriarte, F. Roleira, N. Milhazes, and F. Borges, *Curr. Med. Chem.*, 2004, **11**, 3239.
2004CPB659 P.-J. Aragon, A.-D. Yapi, F. Pinguet, J.-M. Chezal, J.-C. Teulade, J.-P. Chapat, and Y. Blache, *Chem. Pharm. Bull.*, 2004, **52**, 659.
2004FA125 D. Vedaldi, A. Dolmella, S. Moro, G. Miolo, G. Viola, S. Caffieri, and F. Dall'Acqua, *Farmaco*, 2004, **59**, 125.
2004JA1102 H. Liu, J. Gao, L. Maynard, Y. D. Saito, and E. T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 1102.
2004JA11826 J. Gao, H. Liu, and E. T. Kool, *J. Am. Chem. Soc.*, 2004, **126**, 11826.
2004JA3452 O. T. Magnusson, H. Toyama, M. Saeki, R. Schwarzenbacher, and J. P. Klinman, *J. Am. Chem. Soc.*, 2004, **126**, 3452.
2004JOC2626 D. M. D. Fouchard, L. M. V. Tillekeratne, and R. A. Hudson, *J. Org. Chem.*, 2004, **69**, 2626.
2004MI427 Y. L. Garazd, M. M. Garazd, and V. P. Khilya, *Chem. Nat. Compds.*, 2004, **40**, 427.
2004MOL50 V. F. Traven, *Molecules*, 2004, **9**, 50.
2004SC435 Y. Erguen, S. Patir, and G. Okay, *Synth. Commun.*, 2004, **34**, 435.
2004SMC389 M. R. Caira, F. Giordano, and S. L. Vilakazi, *Supramol. Chem.*, 2004, **16**, 389.
2005AXD1009 A. Canals, M. Purciolas, J. Aymami, and M. Coll, *Acta Crystallogr., Sect. D*, 2005, **61**, 1009.
2005JA1396 J. Gao, H. Liu, and E. T. Kool, *J. Am. Chem. Soc.*, 2005, **127**, 1396.
2005JOC639 H. Liu, J. Gao, and E. T. Kool, *J. Org. Chem.*, 2005, **70**, 639.
2005JOC9077 M. L. Bennasar, T. Roca, and F. Ferrando, *J. Org. Chem.*, 2005, **70**, 9077.

2005JOC10615 J. M. Pedersen, W. R. Bowman, M. R. J. Elsegood, A. J. Fletcher, and P. J. Lovell, *J. Org. Chem.*, 2005, **70**, 10615.
2005JPH168 N. Kitamura, S. Kohtani, and R. Nakagaki, *J. Photochem. Photobiol., C*, 2005, **6**, 168.
2005PP133 E. T. Kool, *Polym. Prep.*, 2005, **46**, 133.
2005T12330 K. Hiroya, S. Matsumoto, M. Ashikawa, H. Kida, and T. Sakamoto, *Tetrahedron*, 2005, **61**, 12330.
2006BMC2606 B. Girennavar, S. M. Poulose, G. K. Jayaprakasha, N. G. Bhat, and B. S. Patil, *Bioorg. Med. Chem.*, 2006, **14**, 2606.
2006HCA111 T.-L. Ho and S.-Y. Hsieh, *Helv. Chim. Acta*, 2006, **89**, 111.
2006JA14704 S. R. Lynch, H. Liu, J. Gao, and E. T. Kool, *J. Am. Chem. Soc.*, 2006, **128**, 14704.
2007ACR141 A. T. Krueger, H. Lu, A. H. F. Lee, and E. T. Kool, *Acc. Chem. Res.*, 2007, **40**, 141.
2007JAF7258 N. Noji, T. Nakamura, N. Kitahata, K. Taguchi, T. Kudo, S. Yoshida, M. Tsujimoto, T. Sugiyama, and T. Asami, *J. Agric. Food Chem.*, 2007, **55**, 7258.
2007JOC7106 C.-Y. Liu and P. Knochel, *J. Org. Chem.*, 2007, **72**, 7106.

Biographical Sketch



Michael P. Groziak, PhD, specializes in the organic, inorganic, biochemistry, and medicinal chemistry of heterocycles and nucleosides, developing new classes of these compounds as biochemical tools, enzyme probes, and as potential antiviral, antitumor, and biocidal medicinal agents. His lab has developed new methodologies for the functionalization of heterocycles and for the synthesis of nucleosides. The majority of his research efforts are focused on practicing the art of heterocycle and nucleoside analog design, synthesis, and characterization.

A co-author of 52 publications/patents and 51 scientific meeting abstracts, Dr. Groziak has received funding for his research efforts from the ACS-PRF, CSUPERB, the NIGMS, the NSF, and the US Army. He chairs sessions of contributed papers in Heterocyclic Chemistry for the Organic Division at National ACS meetings and contributes review chapters to Progress in Heterocyclic Chemistry. He has served as an *ad hoc* member of the BNP (Bioorganic and Natural Products) and ADDT (Aids Drug Discovery and Development) Study Sections of the CSR/NIH and reviews proposals for the NIH, NSF, ACS-PRF, and the U.S. Army.

Dr. Groziak is a graduate of the University of Illinois, Urbana, with a BS in Chemistry (1977), and of Northwestern University, with an MS and PhD in organic chemistry (1978 and 1983). He did postdoctoral work in medicinal chemistry at the University of Michigan with Leroy B. Townsend and then in organic chemistry at the University of Illinois with Nelson J. Leonard. He joined the chemistry and biochemistry faculty at Southern Illinois University in Carbondale in 1989 and rose to the rank of tenured associate professor before moving to SRI International in the fall of 1996. In the spring of 2002, he left SRI and became affiliated with the Department of Chemistry at San José State University. In 2003, he joined the faculty of the Department of Chemistry and Biochemistry at California State University, East Bay, where he is now a tenured associate professor.

10.23
Tricyclic Systems: Central Carbocyclic Ring with Fused Six-membered Rings

B. R. Buckley
Loughborough University, Loughborough, UK
© 2008 Elsevier Ltd. All rights reserved.

10.23.1 Introduction **1230**
10.23.2 Theoretical Methods **1230**
10.23.3 Experimental Structural Methods **1232**
10.23.3.1 X-Ray Methods 1232
10.23.3.2 IR Spectroscopy 1233
10.23.3.3 UV and Visible Spectroscopy 1233
10.23.3.4 Mass Spectrometry 1234
10.23.3.5 NMR Spectroscopy 1234
10.23.4 Thermodynamic Aspects **1236**
10.23.5 Reactivities of Fully Conjugated Rings **1238**
10.23.5.1 General Chemical Reactions 1238
10.23.5.2 Complexes with Metal Ions 1239
10.23.6 Reactivities of Nonconjugated Rings **1241**
10.23.7 Reactivities of Substituents Attached to Ring Carbon Atoms **1242**
10.23.8 Reactivities of Substituents Attached to Ring Heteroatoms **1244**
10.23.9 Ring Synthesis **1244**
10.23.9.1 Compounds with a Central Four-Membered Ring 1244
10.23.9.1.1 Compounds with one heteroatom in each heterocyclic ring 1244
10.23.9.1.2 Compounds with two heteroatoms in each heterocyclic ring 1246
10.23.9.2 Compounds with a Central Five-Membered Ring 1247
10.23.9.2.1 Compounds with one heteroatom in each heterocyclic ring 1247
10.23.9.3 Compounds with a Central Six-Membered Ring 1248
10.23.9.3.1 Compounds with one heteroatom in each heterocyclic ring 1248
10.23.9.3.2 Compounds with two heteroatoms in one ring and one in another 1255
10.23.9.3.3 Compounds with two heteroatoms in each heterocyclic ring 1257
10.23.9.3.4 Compounds with more than two heteroatoms in either ring 1259
10.23.9.4 Compounds with a Central Seven-Membered or Larger Ring 1259
10.23.9.4.1 Synthesis of the heterocyclic ring 1259
10.23.9.4.2 Synthesis of the carbocyclic ring 1260
10.23.10 Ring Synthesis by Transformation of Another Ring **1260**
10.23.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available **1261**
10.23.11.1 Compounds with a Central Four-Membered Ring 1261
10.23.11.2 Compounds with a Central Five-Membered Ring 1261

10.23.11.3 Compounds with a Central Six-Membered Ring 1261
10.23.11.3.1 Pyridoquinolines 1261
10.23.11.3.2 Compounds with two heteroatoms in one ring and one in another 1261
10.23.11.3.3 Quinoxazolines 1262
10.23.11.4 Compounds with a Central Seven-Membered or Larger Ring 1262
10.23.12 Important Compounds and Applications 1262
10.23.13 Further Developments 1264
10.23.13.1 [1,10]-Phenanthroline 1264
10.23.13.2 Pyrazino[*f*]quinoxaline 1264
10.23.13.3 Pyrazino[2,3-*g*]quinoxaline 1264
10.23.13.4 4*H*,6*H*-Pyrano[3,2-*g*]chromene 1265
10.23.13.5 Pyrido[3,2-*g*]quinoline 1265
10.23.13.6 1*H*-Cyclopenta[1,2-*b*;4,3-*b*′]dipyridine 1265
10.23.13.7 Diazafluorenes 1265
References 1265

10.23.1 Introduction

The first review of this category of compounds as a group was in Chapter 7.23 of CHEC-II(1996) <1996CHEC-II(7)921>. This chapter will serve as an update to the original chapter and endeavors to inform the reader of the various syntheses available and the most recent theoretical and experimental techniques used for structure elucidation. General review articles can be found in <1996CHEC-II(7)921, 1998AHC291, 1999AHC295, B-2000MI1, 2001AHC199, 2004AHC1> and uses of 1,10-phenanthroline as a ligand have been reviewed in <2002CRV3129>.

Compounds with central four, five, six, seven, and eight carbocyclic rings have been reported and although many structural combinations are theoretically possible no larger central ring sizes have been found. The reactions reviewed here are by no means exhaustive but offer an overview of the area and highlight significant examples. The compounds presented in this chapter have a wide variety of applications; this includes analogues of perhaps the most well documented bidentate ligand, 2,2′-bipyridyl. Many of these substances exhibit significant biological activity or are themselves intermediates for biologically active compounds. The synthesis section is split in order of increasing carbocyclic ring size and by the number of heteroatoms in each ring. These sections are then further divided according to the number of bonds required to form the tricyclic system. A critical review of these methods is presented in Section 10.23.11.

Some of the interesting structural architectures to be reviewed and their names are presented in **Figure 1**.

10.23.2 Theoretical Methods

Conformational analysis of 3,3′-bridged 2,2′-bipyridyls, ionization potentials, and predicted electronic spectra were reported in <1996CHEC-II(7)921>. Compound **1** has been shown to have two independent molecules present in the asymmetric unit, and these geometric parameters were compared with those calculated using the TRIPOS molecular modeling optimization procedure of the SYBYL package (Tripos Associates Inc., 1992) using default parameters <1996AXC2097>. Differences were observed for bond distances in the isopropyl and methyl groups, bond angles at the junction of the isopropyl substituent, and torsion angles involving atoms of the central ring and the isopropyl group. Further studies using ROTENER (Nardelli, 1991) for difference potential energy profiles showed that rotation about the C–OEt bonds is not restricted by intramolecular hindrance, and, therefore, the orientation of these groups must be determined by van der Waals forces. ROTENER also indicated small energy barriers (ca. 7–8 kJ mol^{-1}) for the rotation of the ethyl groups; it also showed that the orientation of the isopropyl group is mainly determined by intramolecular steric effects.

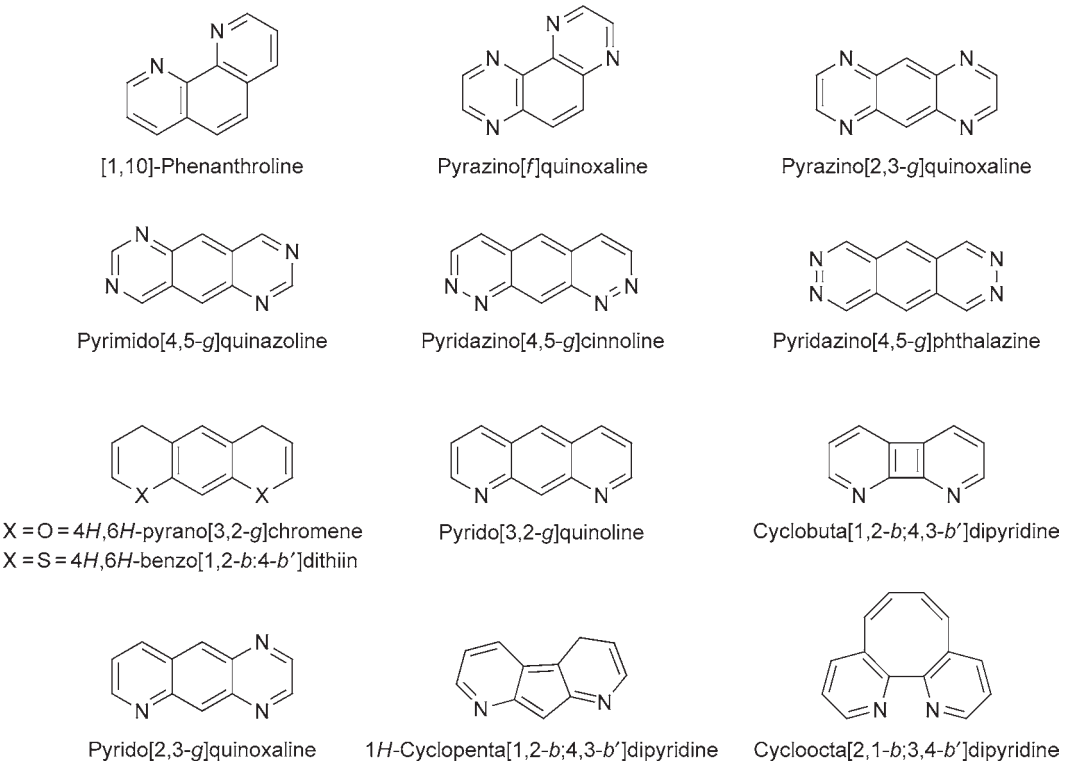
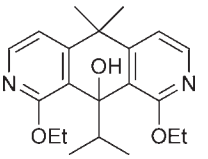
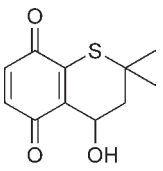


Figure 1



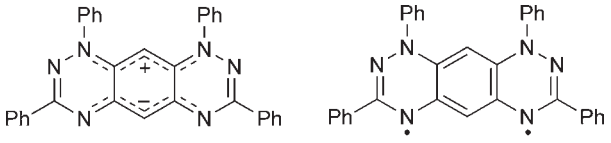
1

One of the most common methods for the synthesis of six-membered heterocycles fused to a six-membered carbocyclic ring appears to be through the use of the heteroatom Diels–Alder reaction (see Section 10.23.9.3.1). Density functional theory (DFT) has been reported to explain the orientation of the cycloaddition reaction of quinone **2** with several dienes <2000H(53)585>. Optimized geometry was calculated at the PM3 level, and *ab initio* 6-31G* restricted Hartree–Fock (RHF) molecular orbital calculations were performed to compare energies and frontier properties with those of the PM3 results. Activation energies were obtained from the *ab initio* methods and all calculations and surface maps were performed using the Spartan package. Zuloaga *et al.*, in the formation of pyranobenzoquinones, have also reported theoretical molecular modeling studies on the regioselectivity of the heteroatom Diels–Alder reaction using the AMPAC package <1995J(P2)939> and Bolognese *et al.* have used PBE0 hybrid DFT in their study toward antiproliferative quinolinediones <2004T8189>.



2

In the structural determination of tetraphenylhexaazanthracene (TPHA), both structures **3** and **4** had been proposed <1998JA2989>. The calculated charge distribution of TPHA agrees with the zwitterionic ground-state structure **3** (later confirmed by X-ray crystallography; see Section 10.23.3.1). Geometry optimizations were performed with DFT using Gaussian '94, employing the B3LYP functional and split valence 6-31G* basis set. The Mulliken charges are +0.33 for the positively charged portion of the zwitterion and −0.33 for the negatively charged portion, the calculated dipole moment being 5.1 D.

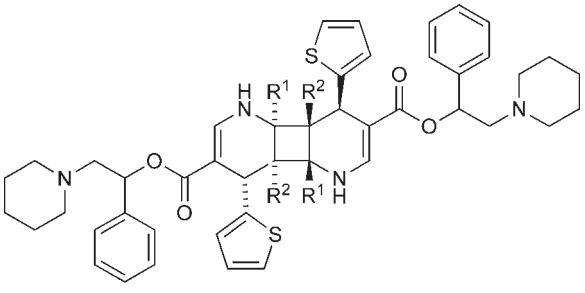


3 **4**

10.23.3 Experimental Structural Methods

10.23.3.1 X-Ray Methods

A range of X-ray structures having the diazabiphenylene core were reported in <1996CHEC-II(7)921>. The X-ray analysis of the perchlorate salt of **5** shows a crystallographic center of inversion <1997J(P2)1309, 1998BCJ321>. The diazatricyclododecadiene moiety adopts the *syn–syn*-conformation, and the tetrahydropyridine ring adopts a slightly twisted boat conformation with the 4-thienyl ring in a pseudoaxial orientation. The bond distance of the cyclobutane ring is long (1.609(5) Å), which is believed to be attributable to the bulky substituents attached to the cyclobutane ring.



5

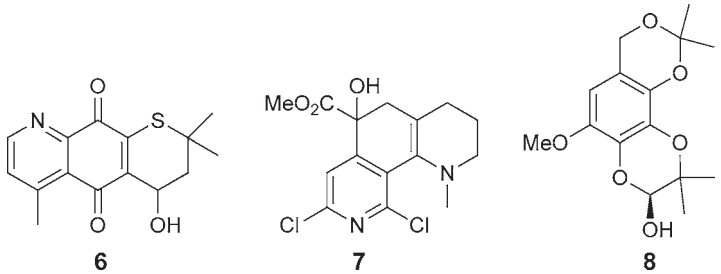
$R^1 = CH_3$

$R^2 = CO_2CH_3$

The crystal structure of **1** has been reported with 50% probability displacement ellipsoids indicating that the tricyclic structure is not rigid and deformations are produced by both intramolecular and packing interactions <1996AXC2097>.

The structure of tetraphenylhexaazanthracene was confirmed as **3** by X-ray crystallography and revealed a monoclinic unit cell, with the zwitterionic molecules arranged in stacks along the shortest crystallographic *c* axis. The charges are delocalized as depicted in **3** <1998JA2989>.

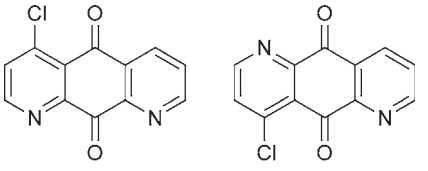
In many cases, X-ray crystallography has been used as a invaluable tool for structural elucidation, for example, in the synthesis of **6** <2000H(53)585>, **7** <2004JA5493>, and **8** <2003JOC4206>.



6 **7** **8**

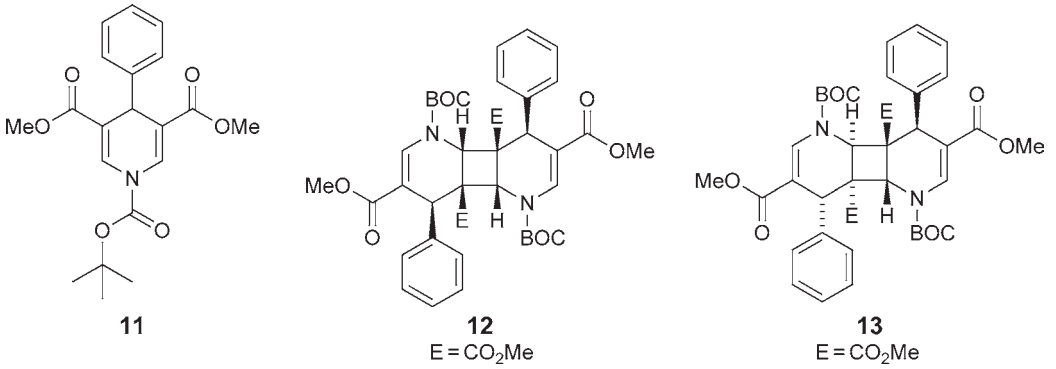
10.23.3.2 IR Spectroscopy

No definitive studies on infrared (IR) spectroscopy in this group have been found since the publication of Chapter 7.23 in CHEC-II(1996) <1996CHEC-II(7)921>. IR structural observations have only been found as supporting evidence for structure elucidation. For example, the ^{1}H nuclear magnetic resonance (NMR) spectra of the regioisomers **9** and **10** are very similar, therefore their structures were assigned using IR spectroscopy <1996H(43)447>. Considering the known effect of the nitrogen atom of the pyridine ring, which increases the wave number of the adjacent carbonyl group, it was proposed that the 1,8-diazaanthraquinone has the structure **9** because of the two C═O stretching vibrations at 1690 and 1670 cm^{-1}, whereas the 1,5- diazaanthraquinone exhibits one carbonyl band at 1690 cm^{-1} <1996H(43)447>.



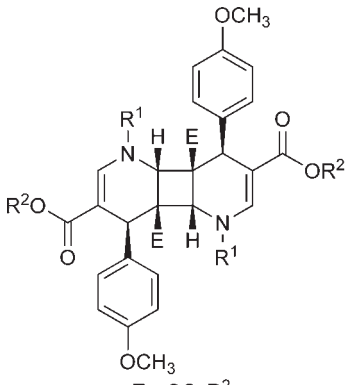
10.23.3.3 UV and Visible Spectroscopy

Ultraviolet (UV) data for several structural types were reported in <1996CHEC-II(7)921>. Solid-state dimerization (see Section 10.23.9.1.1) of **11** at an excitation of λ_{max} 308 nm gives caged dimers *via syn*-dimers **12**; however, the corresponding *anti*-dimer **13**, with λ_{max} 282 nm, is photostable <1999H(51)2367>.



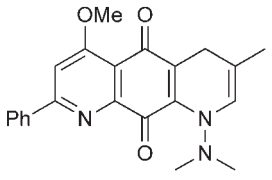
The fluorescence of TPHA **3** is not a mirror image of its absorption spectrum and the emission intensity is sensitive to concentrations greater than 10^{-5} M. The excitation profile of **3** also varies with concentration, believed to be due to aggregation of TPHA in solution and only emulates the ultraviolet–visible (UV–Vis) spectrum at concentrations less than 10^{-5} M. The λ_{em} decreased from 633 nm in toluene to 619 nm in dimethyl sulfoxide (DMSO), and this is thought to be indicative of a polar ground state and nonpolar excited state <1998JA2989>.

UV structural observations have generally only been found as supporting evidence for structure elucidation. Included here are several examples of λ_{max} observed for certain structural types: compound **5** has a λ_{max} 300 nm <1997J(P2)1309, 1998BCJ321>, compounds **14–18** all show λ_{max} of between 240–242 nm <1998EJO1213>, **19** has a λ_{max} of 289 nm <2000H(53)315>, **20** has a λ_{max} of 324 nm <2000M293>, **21** also has a λ_{max} of 324 nm <1997T14655>, and **22** has a λ_{max} of 406 nm <2000H(52)423>.

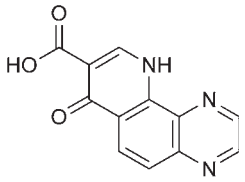


E = CO_2R^2

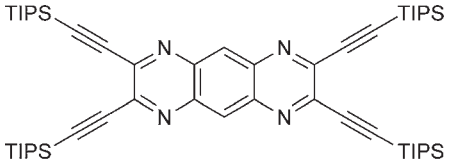
14: R^1 = H; R^2 = Et
15: R^1 = H; R^2 = Me
16: R^1 = Bn; R^2 = Et
17: R^1 = Me; R^2 = Et
18: R^1 = Me; R^2 = Me



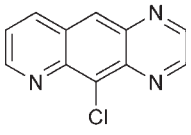
19



20



21



22

10.23.3.4 Mass Spectrometry

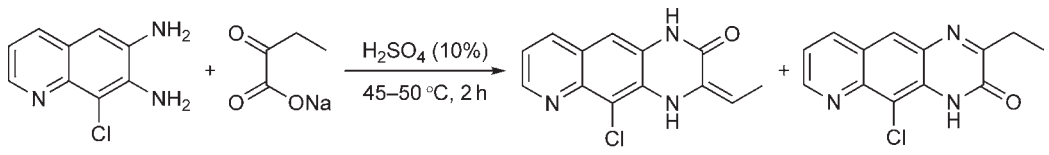
As reported in CHEC-II(1996) <1996CHEC-II(7)921>, no specific study on the mass spectra of these classes of compounds has been reported, although again this analytical method has only been used as a tool for structure elucidation or reference without critical analysis. Further information on the mass spectrometry of heterocycles can be found in a Russian review <2001MI1>.

10.23.3.5 NMR Spectroscopy

The chemical shifts in the ^{1}H NMR spectra of 1,6-, 1,8-, and 2,7-diazabiphenylenes are given in <1996CHEC-II(7)921> and reference to the ^{1}H NMR spectra of the 1,5-, 1,6-, 1,8-, 2,5-, 3,5-, and 4,5-diazafluoren-9-ones is also reported.

The ^{1}H and ^{13}C NMR spectra of the compounds **14–18** are consistent with a dimer structure as only one set of signals for both 1,4-dihydropyridines is observed <1997CL1269>. The ^{1}H and ^{13}C NMR spectra of the *t*-butoxycarbonyl (BOC)-protected *anti*-dimer **13** show just one set of signals, which is in contrast to the corresponding *syn*-dimer **12** that exhibits rotameric mixtures about the C–N bond. Compound **13** is believed to have a centrosymmetric structure resulting from its preparation in a topochemically controlled dimerization reaction <1999H(51)2367> (see Section 10.23.9.1.1).

The compounds **23** and **24**, prepared from **25**, were obtained as ethylidene and ethyl derivatives, but not as a tautomeric mixture, and this was evident from their ^{1}H NMR spectra (Equation 1) <2001FA933>.



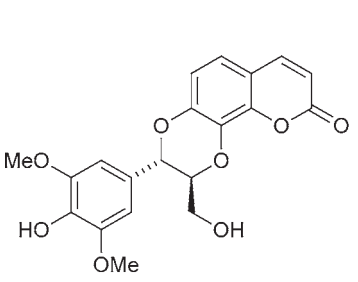
24%
23

12%
24

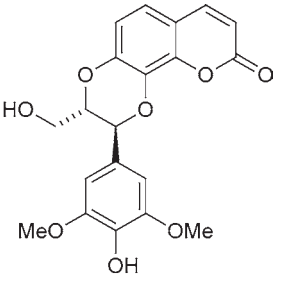
25

(1)

Enantiomerically pure daphneticin **26** and its regioisomer **27** have been synthesized by Pan and co-workers <2002TA1799>. The ^{1}H NMR spectra of **26** shows H-2 resonating as a doublet at 5.11 p.p.m. with a coupling constant of 9.2 Hz which is consistent of a *trans*-isomer and indicates the *threo*-configuration.

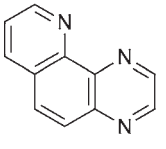


26

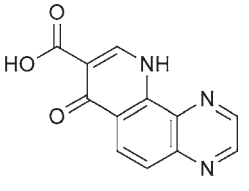


27

The angular annelation of the pyridine and pyrazine rings in **28** have been confirmed by a large coupling constant (9 Hz), and this is believed to be attributable to *ortho*-interaction of the protons. The same configurations on the 4-pyridone and pyrazine analogue **20** shows $^{3}J_{8,9} = 6$ Hz and $^{3}J_{2,3} = 1.8$ Hz, respectively <2000M293>.

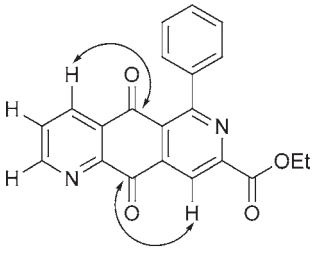


28

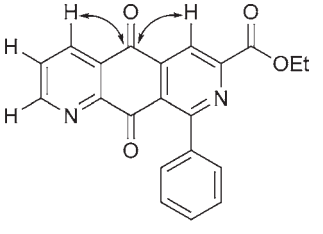


20

The structural assignment of both **29** and **30** was accomplished through extensive two-dimensional (2-D) NMR heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) spectroscopic studies <2004T8189>. In the HMBC spectrum of **29**, the proton at 8.64 p.p.m. shows a strong correlation $^{3}J_{\mathrm{C-H}}$ with the carbonyl carbon (C-10) at 180.9 ppm and the proton at 8.82 p.p.m. with the carbonyl carbon (C-5) at 181.7 ppm. The HMBC spectrum of **30** shows a significant strong correlation $^{3}J_{\mathrm{C-H}}$ of the C-5 carbonyl carbon with the H-6 proton at 8.52 ppm and the H-4 proton at 8.52 p.p.m.

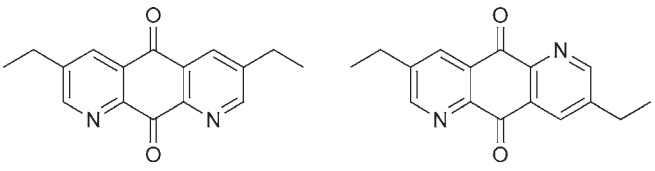


29



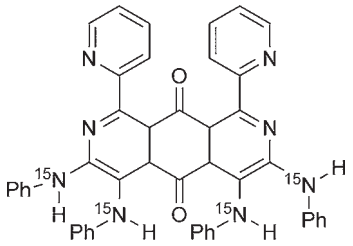
30

The structural assignment of the 1,5- and 1,8-diazaanthraquinones **31** and **32** was based on the different symmetry of both systems; the carbonyl carbon atoms of the 1,5-diaza system are equivalent and only a single ^{13}C NMR signal was observed (181.7 p.p.m.). However, the 1,8-diaza system is unsymmetrical and two ^{13}C NMR signals were observed (180.3 and 182.7 p.p.m.) <2000T1561>.



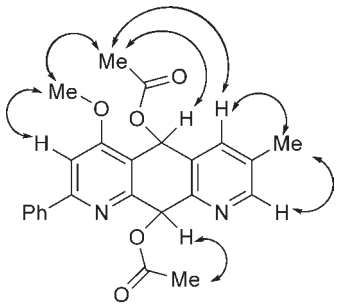
31 32

The ^{15}N NMR spectrum of the ^{15}N enriched compound **33** showed two signals at −265.12 (d, $^{1}J_{NH} = 90.4$ Hz) and −299.28 p.p.m. (d, $^{1}J_{NH} = 87.18$ Hz) <1997T5455>.



33

The 2-D nuclear Overhauser enhancement spectroscopy (NOESY) of **34** showed a correlation between the 3-aromatic proton (7.21 p.p.m.) and the 7-Me (2.58 ppm), through the signals 4-OMe (4.14 p.p.m.), 5-OAc (2.56 ppm), and the 6-aromatic proton (8.07 p.p.m.), establishing the location of 7-Me. Another correlation was observed between the 7-Me and 8-aromatic proton (8.93 p.p.m.) indicating the structure shown.



34

A range of ^{1}H and ^{13}C NMR spectra on the 1,8-diazaanthracene-2,9,10-triones <1995T6573, 1996T5933> and 4-phenylquinoline-5,8-quinones <1999S1335> have been reported in tabular form by Avendaño and co-workers.

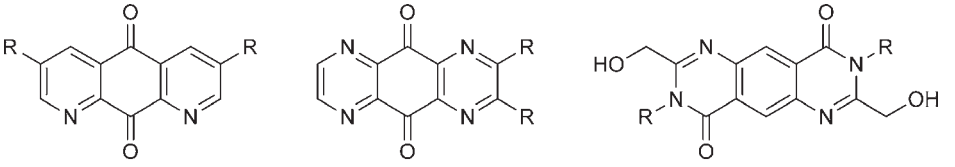
In the majority of cases, NMR spectroscopy has been used as a invaluable tool for structural elucidation; for example, in the synthesis of **7**, ^{1}H and ^{13}C NMR spectra were in accordance with the desired structure, which was confirmed by X-ray crystallography <2004JA5493>. Also, in the structural elucidation of **3**, sharp line ^{1}H and ^{13}C NMR spectra were observed but the compound was ESR silent, therefore indicating a closed-shell species (ESR = electron spin resonance).

10.23.4 Thermodynamic Aspects

Stability. The four-membered ring in the diazabiphenylene series of compounds is strained due to bond angle deformation <B-2000MI1>. The conventional ring strain energy for cyclobutane is 111 kJ mol^{-1}; alkyl substituents stabilize the ring by only a few kilojoules per mole.

Melting points. The majority of compounds reviewed in this chapter are solids. Some general trends are observed; for example, increasing the chain length of substituents attached to carbon atoms as shown in **35** decreases the melting point from >300 °C (where R = H) to 263–264 °C (where R = Me). Further increase in chain length to *n*-butyl decreases the melting point to 132–134 °C <2000T1561>. This is also true for the substituents on compound **36**;

where R = H, a melting point of 280 °C is observed; substitution to methyl groups lowers the melting point to 245–246 °C <1998JME4716>. For substituents attached to nitrogen the same general trend has been seen, for example, in **37**, where the melting point decreases from >250 to >230 to 205–215 °C as the substitution is increased from hydrogen to methyl to *n*-propyl <2002JME5543>.

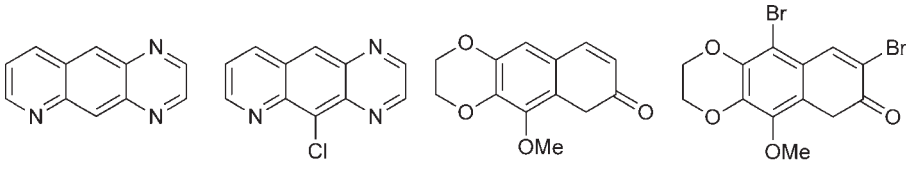


35 **36** **37**

Contrary to the above, for the diazabiphenylene series of compounds, substitution on the heteroatom significantly reduces the melting point (273–276 °C where R = H, **14**, 197–199 °C where R = Me, **17**) <1998EJO1213>.

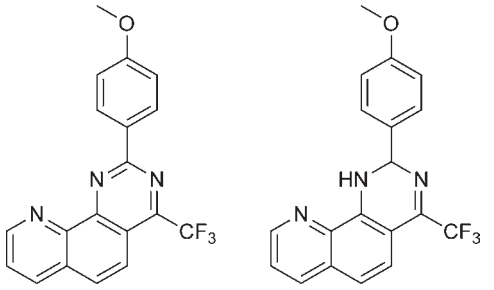
Some regioisomers have been found to have quite significantly different melting points. For example, compound **9** has a melting point of 254–255 °C, whereas **10** has a melting point of 220 °C (dec.) <1996H(43)477>.

Substitution at C-10 on pyrido[2,3-*g*]quinoxaline **38** with a chlorine atom **22** reduces the melting point from 219–221 to 175–177 °C <2000H(52)423>. However, bromination of **39** increases the observed melting point compared to **40** <1995T3197>.



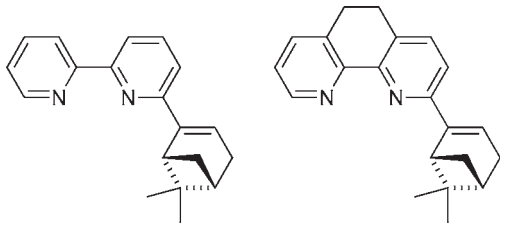
38 **22** **39** **40**

The fully aromatized compound **41** has a melting point (190–191 °C), some 30 °C higher than that of the corresponding partially conjugated compound **42** (160–161 °C) <1999H(51)2471>.



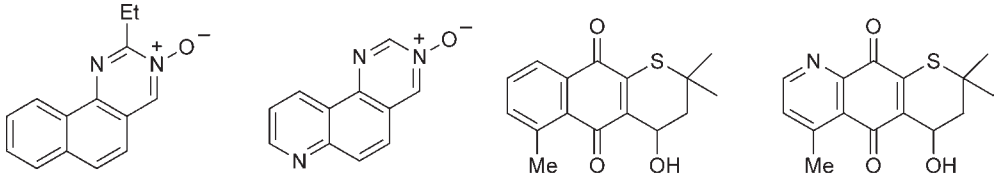
41 **42**

Moving from a bipyridyl **43** (m.p. 40 °C) to a phenanthroline **44** (m.p. 138 °C), the structural difference has been shown to drastically change the melting point observed <2000T8489>.



43 **44**

Changing the carbocyclic A ring in **45** to a pyridyl ring **46** increases the melting point from 204–205 to 260–265 °C <1996H(43)389>. However, replacement of the carbocyclic A ring **47** with a pyridyl unit **6** has the opposite effect, the melting point decreasing from 190 °C (dec.) to 168–169 °C <2000H(53)585>.



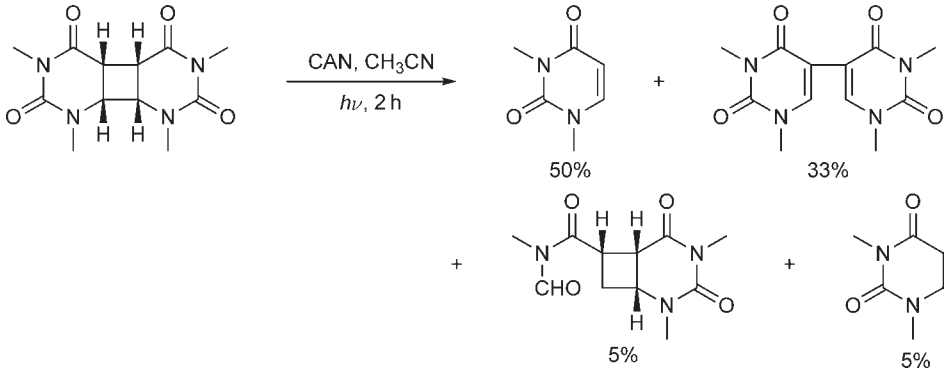
45 **46** **47** **6**

Chromatography. The majority of compounds in this review have been isolated using standard chromatographic techniques. The ee for daphneticin **26** and its regioisomer **27** were determined using chiral high-performance liquid chromatography (HPLC), with a chiralcel CDMPC column. Eluting with *n*-hexane/isopropyl alcohol (20:1) affords daphneticin (2*S*,3*S*) **26** with a retention time of 27.6 min and its regioisomer (2*S*,3*S*) **27** with a retention time of 30.7 min.

10.23.5 Reactivities of Fully Conjugated Rings

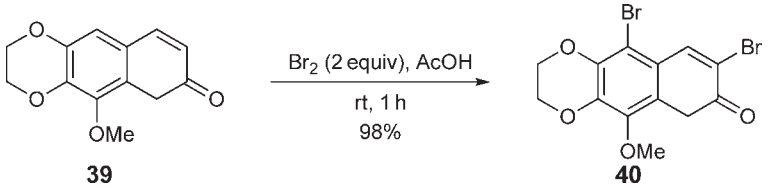
10.23.5.1 General Chemical Reactions

There is, obviously, not enough space here to allow the listing of all of the types of possible reactions for these classes of heterocycles, and therefore only illustrative examples are shown. A wide range of reactions for these types of heterocycles can be found in the original chapter <1996CHEC-II(7)921>, and general reactions on related heterocycles can be found in <B-2000MI1>. Several examples of fission of one of the rings in the diazabiphenylene series of compounds were reported in <1996CHEC-II(7)921>. A recent example is shown in Equation (2) <2001OL1455>.



(2)

Bromination of compounds such as **39** can be achieved with 2 equiv of bromine (Equation 3) <1995T3197>.

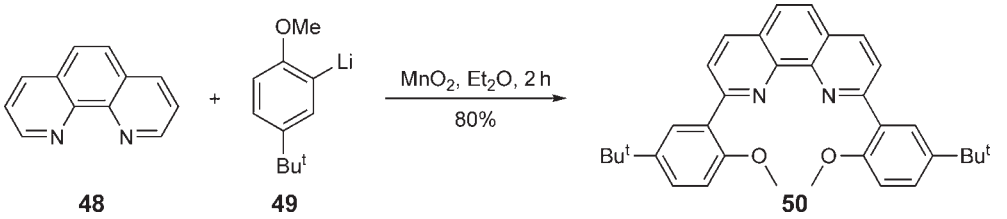


39 **40**

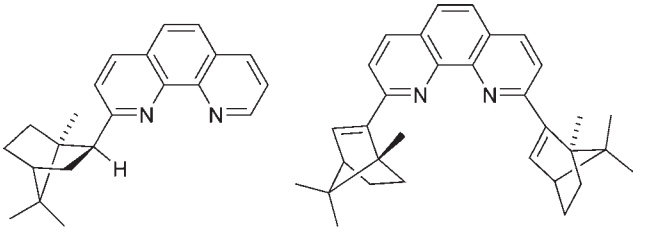
(3)

There are a wide number of reports regarding nucleophilic aromatic substitution α to nitrogen in 1,10-phenanthroline **48**. For example, the aryllithium reagent **49** adds to 1,10-phenanthroline **48** and on oxidative workup yields

product **50** (Equation 4) <1999T8377>. A similar procedure has also been used in the synthesis of both **51** and **52** from camphor <1996JA4299>.

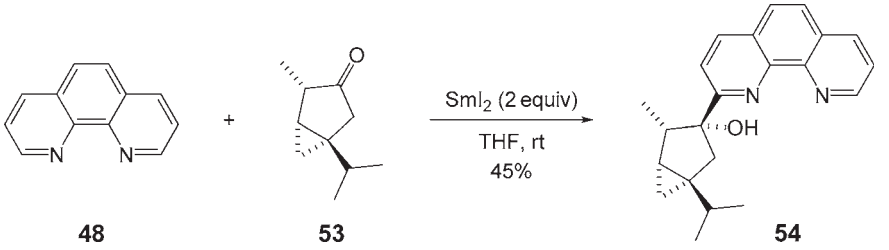


48 **49** **50** (4)



51 **52**

O'Neill and Helquist have also discovered that 1,10-phenanthroline **48** undergoes samarium iodide-promoted coupling with ketones and this process has been applied to the chiral ketone (−)-thujone **53** to give the corresponding phenanthroline **54** as a single stereoisomer (Equation 5) <1999OL1659>.



48 **53** **54** (5)

10.23.5.2 Complexes with Metal Ions

There are several hundred reports regarding metal complexes of ligands based upon the tricyclic 1,10-phenanthroline structure **48**. Overlap between the d orbitals of the metal and the σ-orbitals of the phenanthroline is believed to increase the stability of these types of complexes. Hence, there are many review articles in this area, dealing with, for example, subjects such as metal-organic molecular architectures <2005CCR545>, self-assembled structural motifs <2000CRV3483>, chemical sensors <2000CRV2537>, and molecular switches <2004ACR827>.

The versatility of the structural types possible for 1,10-phenanthroline ligands is exemplified in a review article on metal-to-ligand charge-transfer (MLCT) excited states of copper(II) bis-phenanthroline coordination compounds, where 14 different 1,10-phenanthroline-based ligands were discussed (**Figure 2**) <2000CCR243>.

With the ever-increasing demand for enantiomerically pure compounds, coupled with the success of 1,10-phenanthroline as a ligand for metals, it is not surprising that many groups have synthesized enantiomerically pure ligands with this structural motif for use in asymmetric catalysis <2002CRV3129>. For example, the ligand **51** gives excellent ee's for some palladium-catalyzed allylation reactions <1996JA4299> and cyclopropanation reactions <1995JMO(A)L7>. The interesting dinucleating ligand **55** has also been studied <1999T8377>.

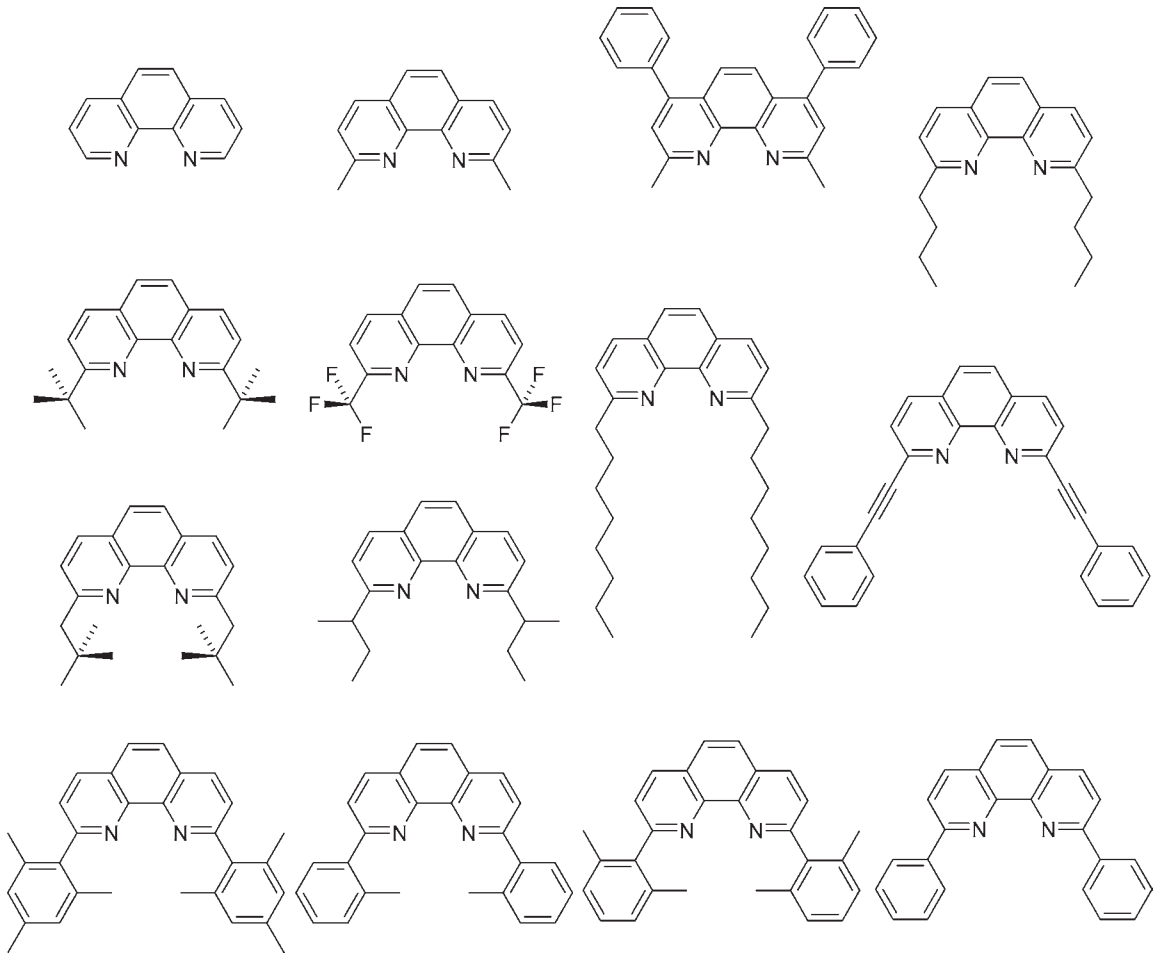
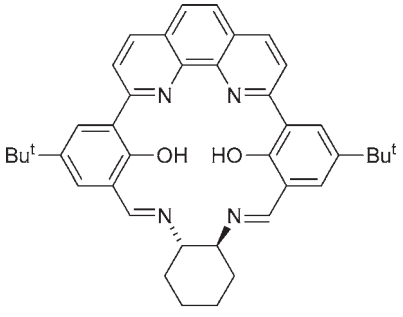


Figure 2

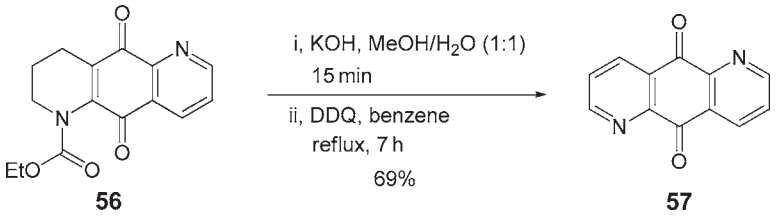


55

Other important ligands include those based upon the diazafluorene structure <2000JST91>. It has been shown that the coordination behavior of complexes containing the diazafluorene ring system is quite different to that of the parent 2,2′-bipyridyl or 1,10-phenanthroline systems, and evidence for unsymmetrical chelation has been observed <1998POL2463, 1996IC2253>.

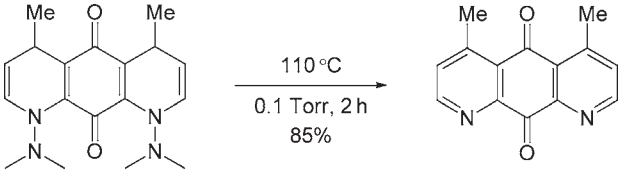
10.23.6 Reactivities of Nonconjugated Rings

Several examples of the reactivity of nonconjugated rings were reported in <1996CHEC-II(7)921>. The main reactivity appears to be by conversion into the aromatized product. For example, removal of the carbamate group in **56** and subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affords the aromatized product **57** (Equation 6) <1996H(43)447>.



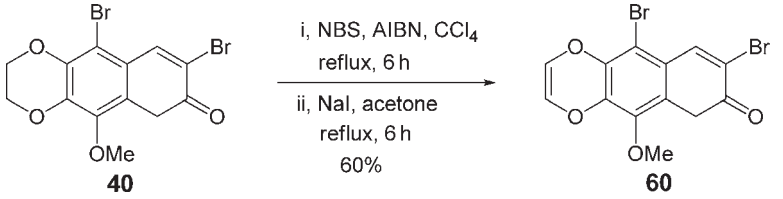
56 **57** (6)

Heating compounds such as **58**, neat at 110 °C under vacuum, afforded the corresponding aromatized product **59** through the double loss of dimethylamine (Equation 7) <2000T1561>. Other methods for aromatization include standing in air <1996T5933>, the use of MnO_2 <2000T4575>, and heating under reflux in xylenes <1995T6573> or ethanol <2000H(53)315>.



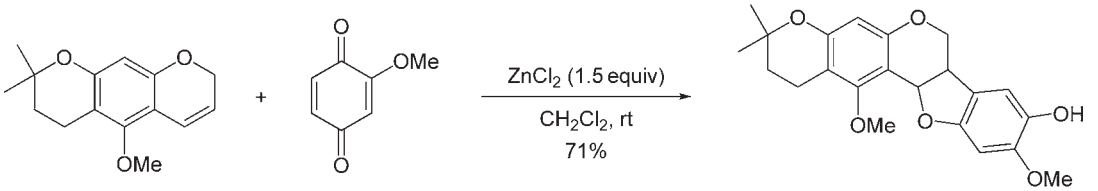
58 **59** (7)

Treatment of compound **40** with NBS/AIBN and NaI in acetone affords the fully conjugated product **60** (NBS = *N*-bromosuccinimide; AIBN = 2,2′-azobisisobutyronitrile; Equation 8) <1995T3197>.



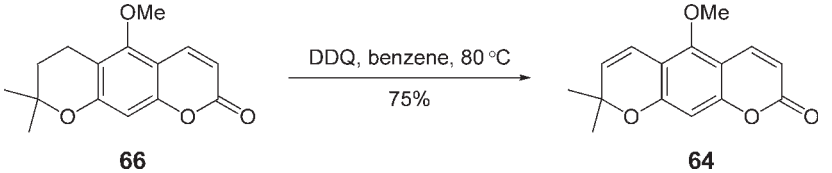
40 **60** (8)

The 2*H*-chromenes, such as **61**, can undergo $ZnCl_2$-mediated condensation with **62** to afford the corresponding pterocarpan **63** (Equation 9) <1997J(P1)1875>.

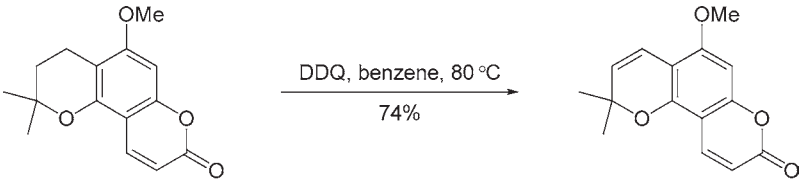


61 **62** **63** (9)

The natural products xanthoxyletin **64** and alloxanthoxyletin **65** have been prepared by DDQ oxidation of intermediates **66** and **67** (Equations 10 and 11) <2003JA4518>.

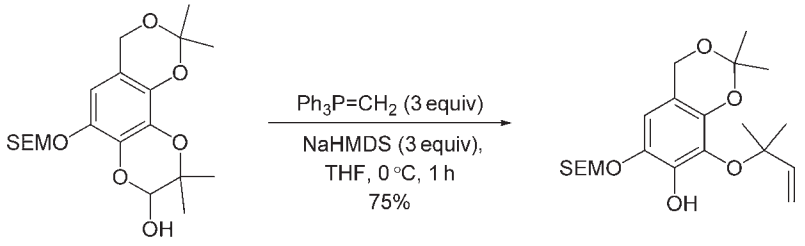


66 **64** (10)



67 65 (11)

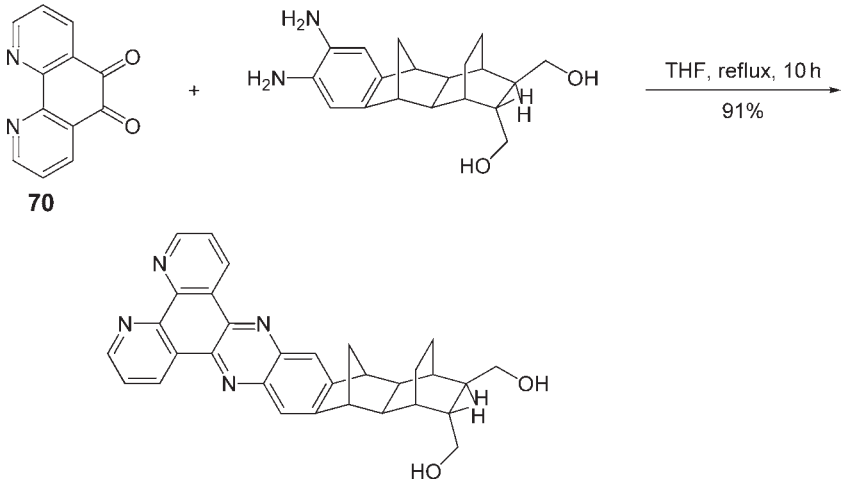
The lactol **68** undergoes ring opening via a Wittig olefination reaction to afford the product **69** (Equation 12) <2004JA5493>.



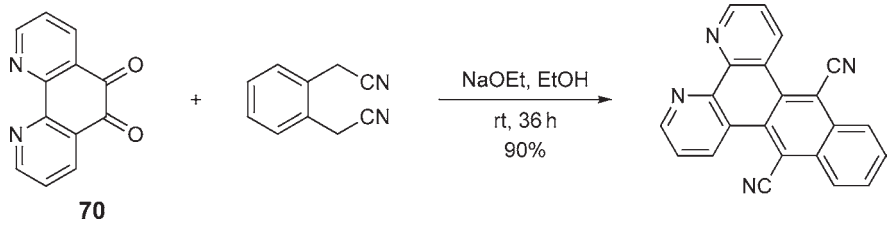
68 69 (12)

10.23.7 Reactivities of Substituents Attached to Ring Carbon Atoms

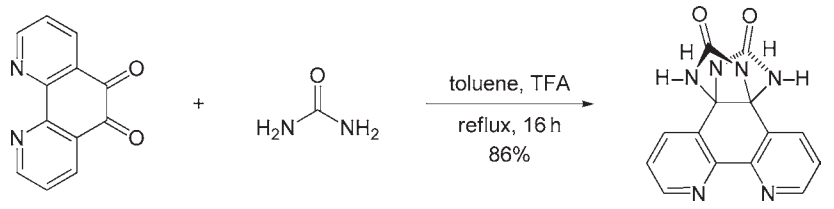
1,10-Phenanthroline-5,6-dione **70** can be condensed with a range of amines, for example, in the synthesis of bichromophoric systems based on buckminsterfullerene (Equation 13) <1996JA5032>; in the synthesis of luminescent complexes (Equation 14) <1999CC1171>; in the synthesis of molecular clips <1997JOC2234>, as well as other metal complexes <1999JCD1423>; and in the synthesis of phthalocyanine <2002CC2236> and nanostructures (Equation 15) <2002JA1532>.



70 (13)

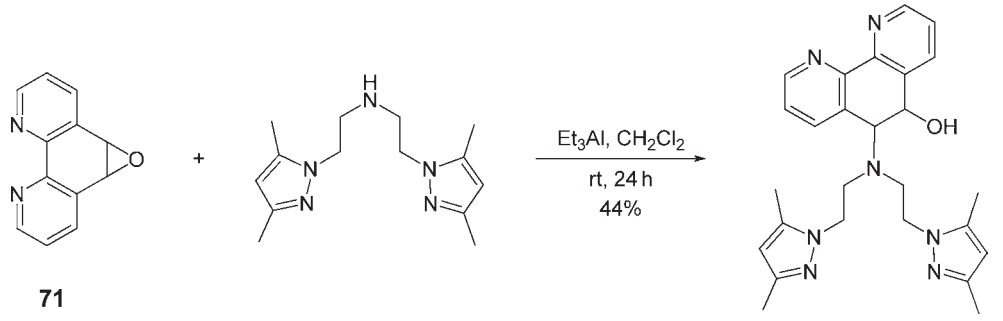


70 (14)



(15)

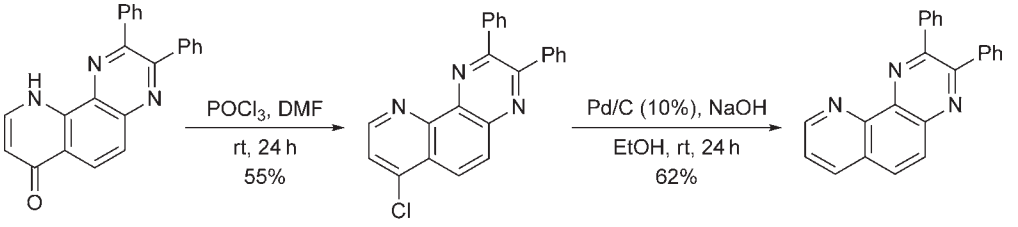
Ring opening of epoxide **71** can be achieved using triethylaluminium and the appropriate nucleophile (Equation 16) <2001JCD1813>.



71

(16)

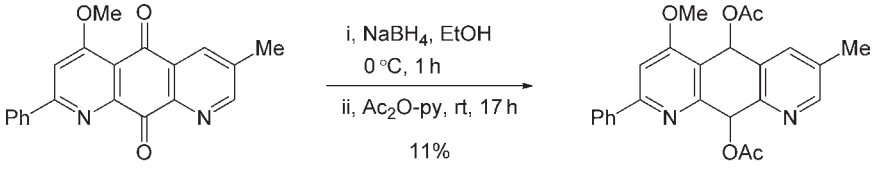
The most common method for achieving aromatization of compounds such as **72** is with phosphorus oxytrichloride and the addition of dimethylformamide (DMF; **Scheme 1**) (see, for example, <1996CHEC-II(7)921>, and more recently, <2004M283, 1997S567>). Reductive dechlorination of **73** with palladium on carbon in the presence of sodium hydroxide affords the corresponding heterocycle **74** (**Scheme 1**) <2004M283>.



72 **73** **74**

Scheme 1

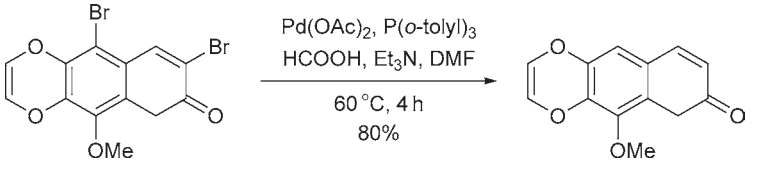
The dione functionality in compound **75** can be reduced with sodium borohydride, and subsequent acetyl protection affords **76** (Equation 17) <2000H(53)315>.



75 **76**

(17)

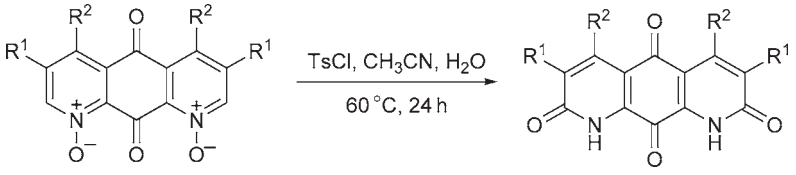
Dehalogenation is possible using a modified Heck procedure (Equation 18) <1995T3197>.



(18)

10.23.8 Reactivities of Substituents Attached to Ring Heteroatoms

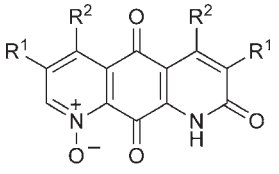
As reported in CHEC-II(1996) <1996CHEC-II(7)921>, the only examples of reactions in this category relate to the reaction of *N*-oxides of ring heteroatoms. Treatment of an *N*-oxide with $POCl_3$ or $POBr_3$ affords the corresponding α-halo compound <1996CHEC-II(7)921>. More recently, *N*-oxides have been converted *via* rearrangement into the corresponding 1,8-diazaanthracene-2,7,9,10-tetralones as shown in Equation (19) and **Table 1** <2000T4575>. This process can even be controlled to yield the monolactam *N*-oxide such as **77**.



(19)

Table 1 Reaction of *N*-oxides to form 1,8-diazaanthracene-2,7,9,10-tetralones (Equation 19)

R^1	R^2	*Yield* (%)
CH_3	H	33
C_2H_5	H	25
H	CH_3	35
C_2H_5	CH_3	40
C_2H_5	CH_3	30



77

10.23.9 Ring Synthesis

10.23.9.1 Compounds with a Central Four-Membered Ring

Compounds in this group are named as an 'aza' analogue of biphenylene; for example, cyclobuta[1,2-*b*:3,4-*b*′]dipyridine is referred to as 1,8-diazabiphenylene.

10.23.9.1.1 Compounds with one heteroatom in each heterocyclic ring

10.23.9.1.1(i) Synthesis of the heterocyclic ring

No examples of this approach were reported in CHEC-II(1996) <1996CHEC-II(7)921> and no further reports using this method have been found.

10.23.9.1.1(ii) Synthesis of the carbocyclic ring

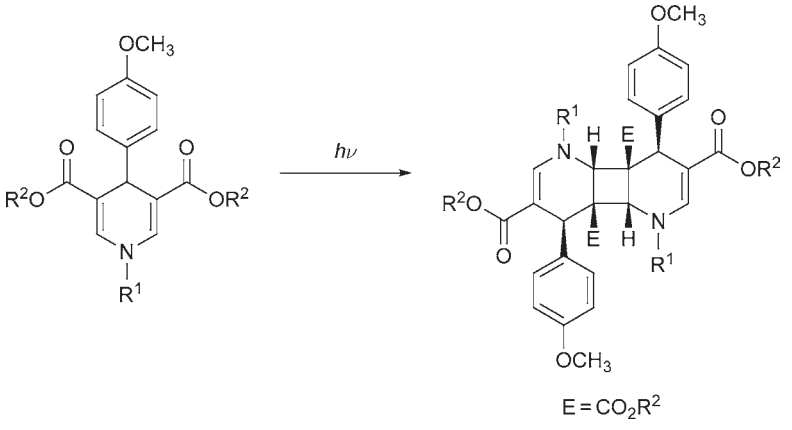
10.23.9.1.1(ii)(a) By formation of one bond

Nitrogen extrusion from tetraazaphenanthrolines is a well-known and useful route to diazabiphenylenes, and several methods were reported in <1996CHEC-II(7)921>. This route has, however, only been reported for the diazabiphenylenes and not the tri- or tetraaza analogues. Extrusion of SO_2 from dipyridothiophene dioxides is also possible <1996CHEC-II(7)921>. The 1,5- and 1,7- diazabiphenylenes are unknown.

No further advances have been reported since the publication of Chapter 7.23.8.1.1 in CHEC-II(1996) <1996CHEC-II(7)921>.

10.23.9.1.1(ii)(b) By formation of two bonds

Dimerization of compounds containing carbon–carbon double bonds has been used in the synthesis of cyclobutanes and this approach has been adopted by several groups. Solid-state synthesis has been reported by Hilgeroth and co-workers <1997CL1269, 1998EJO1213, 1999H(51)2367, 2000AGE576, 2002AGE3623>. On irradiation with an Ultra-Vitalux® lamp (300 W), which produces a light spectrum corresponding to sunlight, the crystalline 1,4-dihydropyridines **78–82** form the corresponding products in good yields (Equation 20; **Table 2**).

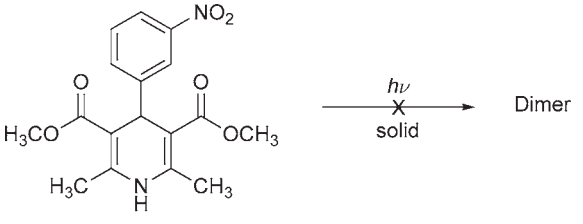


(20)

Table 2 Reaction of several 1,4-dihydropyridines in the solid state (Equation 20)

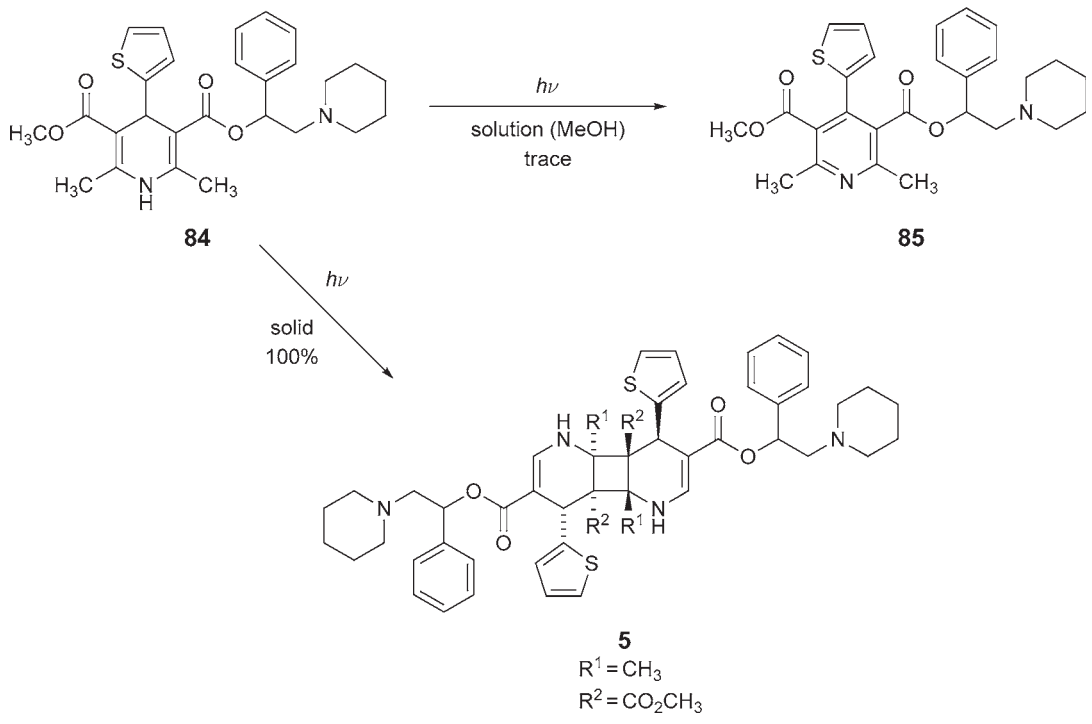
1,4-Dihydropyridine	R^1	R^2	*Yield* (%)
78	H	CH_3	65
79	H	C_2H_5	40
80	CH_2Ph	C_2H_5	60
81	CH_3	C_2H_5	60
82	CH_3	C_2H_5	52

Marubayashi *et al.* <1997J(P2)1309> have also shown that solid-state dimerization is possible and propose that there is a 'buffer zone' in the crystal structure of 1,4-dihydropyridines that governs the solid-state photodimerization process. This is exemplified by the fact that dimethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate **83** cannot undergo solid-state photodimerization (Equation 21), whereas the structurally related (4*RS*,1′*RS*)-methyl-1-phenyl-2-piperidinoethyl-1,4-dihydro-2,6-dimethyl-4-(2-thienyl)pyridine-3,5-dicarboxylate **84** affords a single product **5** (**Scheme 2**). Interestingly, when the photodimerization conditions are applied to the corresponding solution-phase reaction, the sole product is that of aromatization giving product **85**.



83

(21)



Scheme 2

Detailed inspection of the crystal structure of **84** revealed that there is a certain space between reacting molecules in the crystal to allow initiation of photodimerization. The space, designated as a 'buffer zone', buffers the steric hindrance from which the reacting molecules suffer when they approach each other. The buffer zone is formed by the disordered piperidine rings in **84**, but there is no extra space in the crystal structure of **83**, and therefore photodimerization does not occur. Further evidence of this 'buffer zone' was later reported by the same group, whereby polymorphic crystal forms had different reactivities toward photodimerization <1998BCJ321>.

In the above examples, only 'head-to-tail' dimers are observed, although it is possible to form the 'head-to-head' products and several methods were reported in CHEC-II(1996) <1996CHEC-II(7)921>.

10.23.9.1.2 Compounds with two heteroatoms in each heterocyclic ring

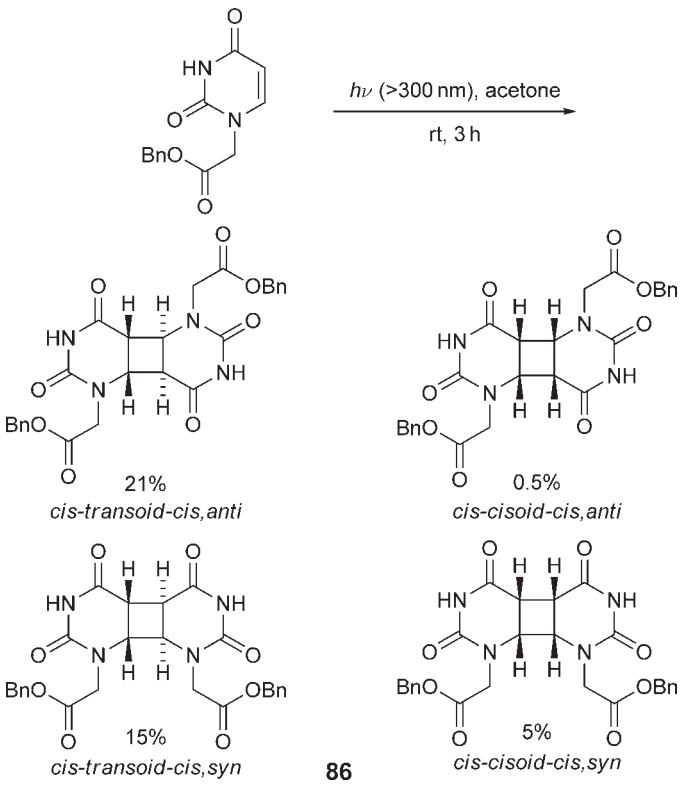
Compounds of this type are extremely important as they can be used for the preparation of catalytic antibodies, synthetic receptors, and model compounds for the investigation of the DNA lesion and recognition steps and DNA repair mechanisms (see Section 10.23.12).

10.23.9.1.2(i) Synthesis of the heterocyclic ring

No examples of this approach were reported in CHEC-II(1996) <1996CHEC-II(7)921> and no further reports using this method have been found.

10.23.9.1.2(ii) Synthesis of the carbocyclic ring

Dimers are obtained by short wave (>290 nm) irradiation of the substrate, and several publications and reviews were reported in CHEC-II(1996) <1996CHEC-II(7)921>; since this time, synthetic efforts have been focused on the preparation of *cis-cisoid-cis,syn*-dimers as they are biologically more abundant than the corresponding *cis-transoid-cis,syn*-dimers <1997HCA2191>. Several attempts to prepare the *cis-cisoid-cis,syn*-dimers were unsuccessful <1995JA5453>, although Carell *et al.* were able to prepare **86** as a mixture of all four possible uracil dimers <1997HCA2191> (Equation 22).



86 (22)

10.23.9.2 Compounds with a Central Five-Membered Ring

Compounds with a central five-membered ring are heterocyclic analogues of the hydrocarbon fluorene which have heteroatoms in both six-membered rings. The 'aza' nomenclature is used in this section. A comprehensive list of references for the known unsubstituted diazafluorene and diazafluoren-9-ones was presented in CHEC-II(1996) <1996CHEC-II(7)921>.

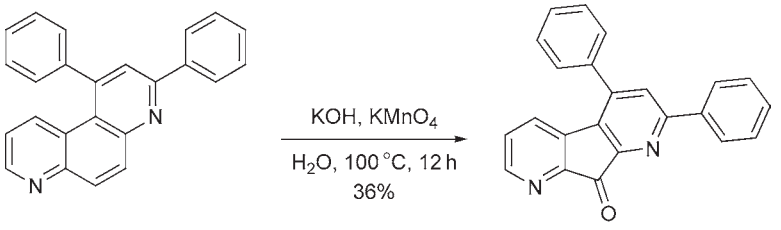
10.23.9.2.1 Compounds with one heteroatom in each heterocyclic ring

10.23.9.2.1(i) Synthesis of the heterocyclic ring

The only report concerning the construction of the heterocyclic ring of diazafluorenes was described in CHEC-II(1996) <1996CHEC-II(7)921> using a variant of the Hantzsch pyridine synthesis. Somewhat surprisingly, no further reports using this method have been found.

10.23.9.2.1(ii) Synthesis of the carbocyclic ring

The most common method used to synthesize the diazafluorenes is by alkaline oxidation of phenanthrolines <1996CHEC-II(7)921>. For example, Gusak *et al.* have shown that compounds such as **87** can be converted into the corresponding diazafluorenones using potassium hydroxide and potassium permanganate (Equation 23) <2004RJO1322>.



87 (23)

10.23.9.3 Compounds with a Central Six-Membered Ring

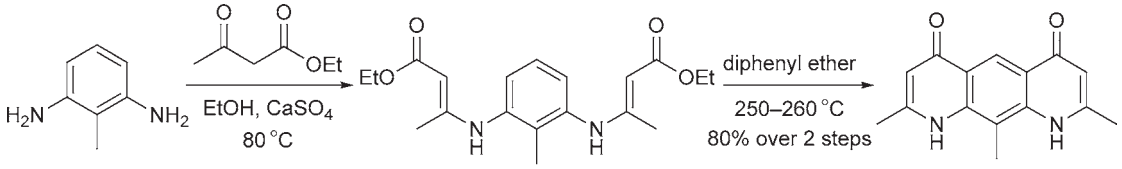
10.23.9.3.1 Compounds with one heteroatom in each heterocyclic ring

The preparation of compounds with a six-membered heterocycle fused to a six-membered carbocyclic ring is one of the most researched areas in organic chemistry. However, there are few examples for the construction of the carbocyclic ring. There are several review articles in this area <1984CHEC(2)395, 1984CHEC(3)599, 1996CHEC-II(7)921>.

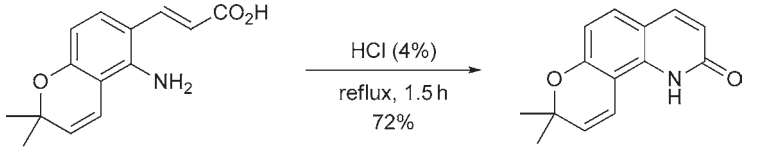
10.23.9.3.1(i) Synthesis of the heterocyclic ring

10.23.9.3.1(i)(a) By formation of one bond

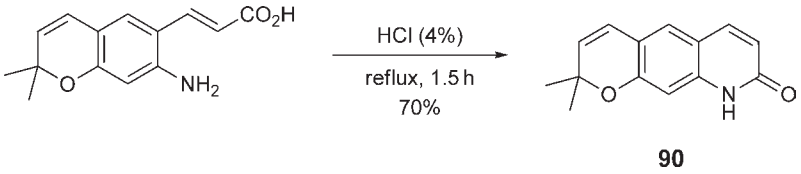
The general method for the synthesis of heterorings is by cyclization of a side chain attached to a heteroatom on the carbocyclic ring. For example, compounds of the type **88** can be easily synthesized in two steps from 2,6-diaminoaryl compounds (**Scheme 3**) <1996H(43)1621>. The regiospecific synthesis of **89** and **90** has been reported using a efficient amide formation as the ring-closing step (Equations 24 and 25) <1997S1249>.



Scheme 3

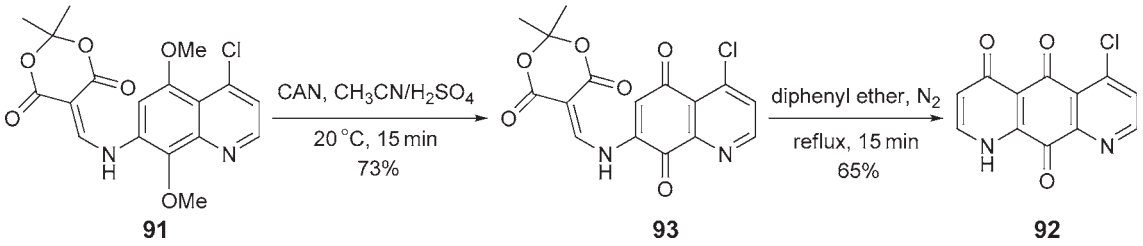


(24)



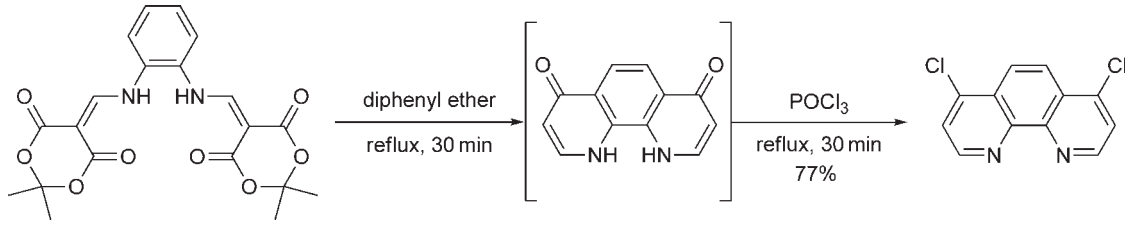
(25)

In Delfourne and co-workers' study toward the total synthesis of meridine, the Meldrum's acid derivative **91** was prepared. After several unsuccessful attempts to cyclize this material to the desired tricyclic compound **92**, it was found that conversion into the quinone **93** was necessary for cyclization to occur (**Scheme 4**) <1997T1743>. Another approach to compounds with a central six-membered carbocyclic ring using Meldrum's acid derivatives has been

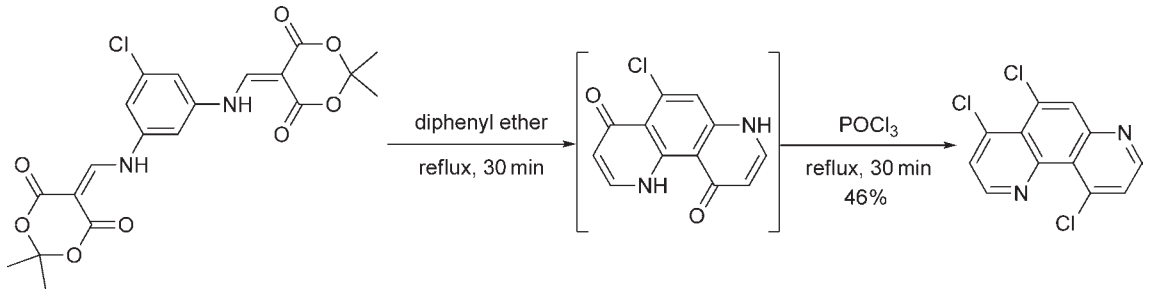


Scheme 4

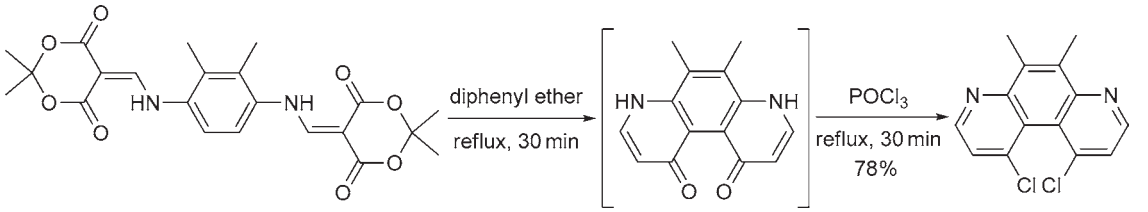
reported by Graf *et al.* <2002T9095>. They have shown that several structural types can be prepared by varying the substitution pattern of the phenylenediamine starting material (Equations 26–28). Azabenzisochromanoquinones can also be prepared using this methodology (Equation 29) <1997S567>.



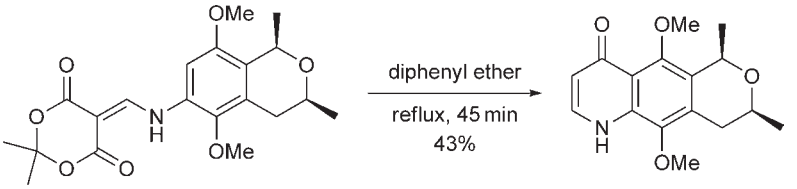
(26)



(27)

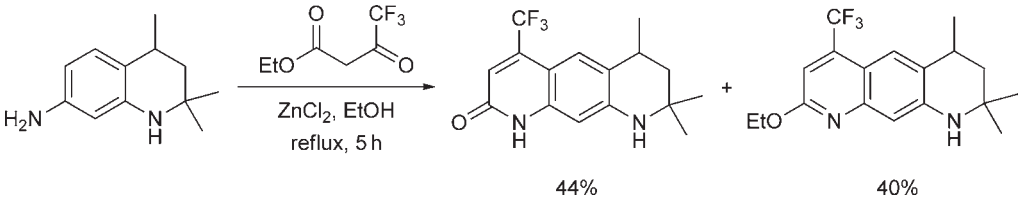


(28)



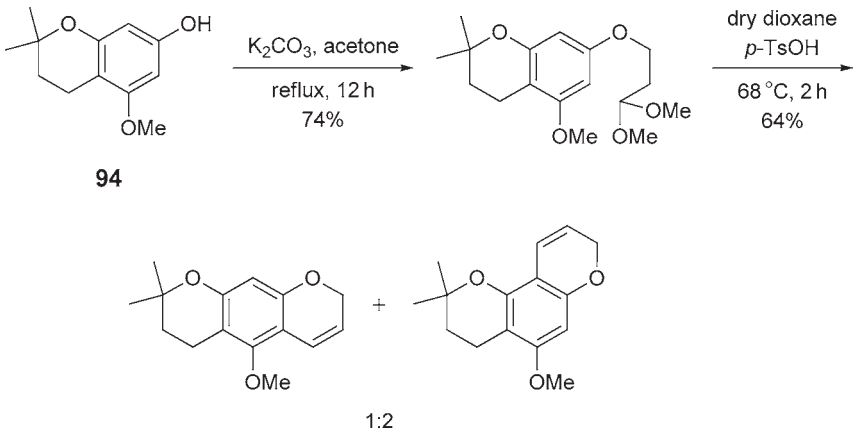
(29)

A modified Knorr cyclization has also been reported using ethyl 4,4,4-trifluoroacetoacetate in the synthesis of potent nonsteroidal androgen receptor agonists (Equation 30) <1998JME623, 1999BML1335, 1999BML1009>.

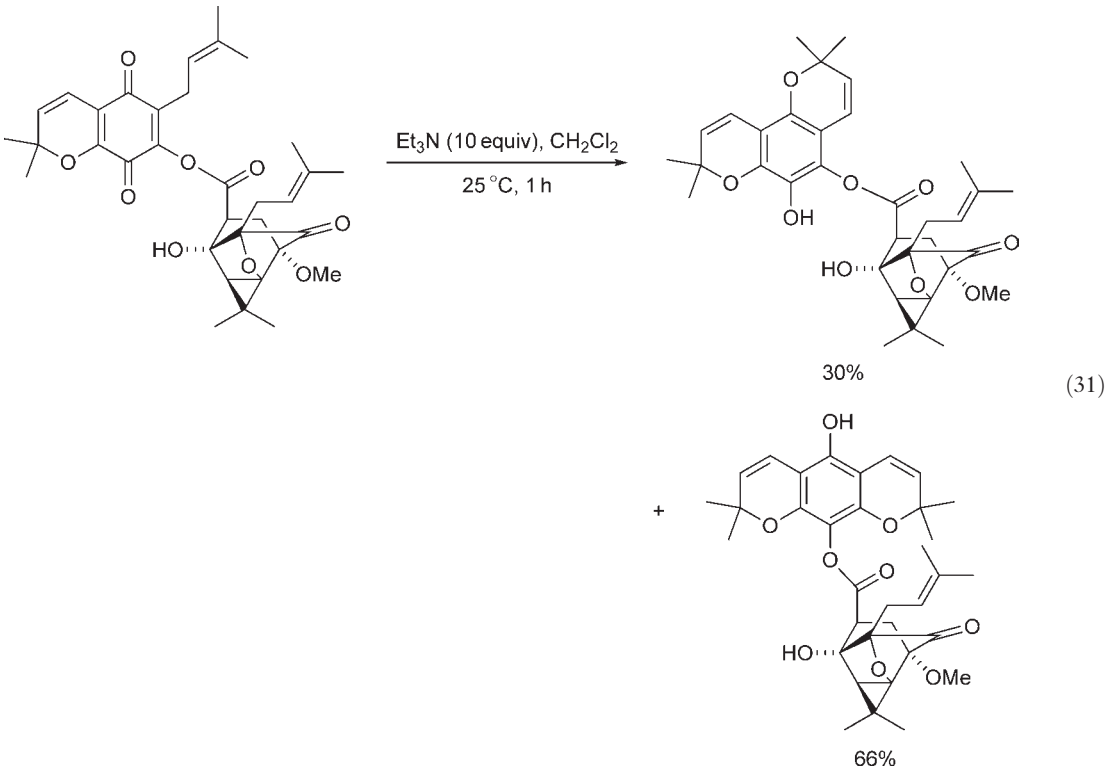


(30)

In the regioselective total synthesis of edulane and its analogues, the acid-catalyzed reaction of the chroman **93** was studied, giving rise to a mixture of chromenes (**Scheme 5**) <1997J(P1)1875>. Nicolaou *et al.* showed that it is possible to construct benzopyrans *via* an intramolectular 6π-electrocyclization, although a mixture of products was observed (Equation 31) <2004JA5493>.



Scheme 5



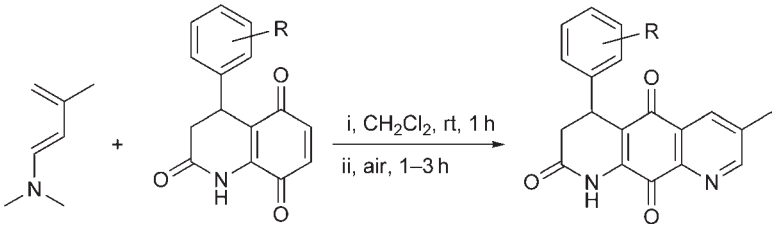
(31)

10.23.9.3.1(i)(b) By formation of two bonds

All possible isomers of the phenanthrolines are known and can be prepared by Skraup-type reactions, with the exception of the 2,8- and 3,8-phenanthrolines (which are structurally related to isoquinolines). Some of these compounds are commercially available. There have been no major advances in the synthesis of these compounds since CHEC-II(1996) <1996CHEC-II(7)921>.

The most common method for the synthesis of the heterocyclic ring by two bonds appears to be through the use of the heteroatom Diels–Alder reaction. For example, Avendaño and co-workers have prepared analogues of the antitumor agent diazaquinomycin A using this methodology (Equation 32; **Table 3**) <1997T3231>. Cystodamine has been prepared through a similar route (Equation 33) <1997TL4441>. Avendaño and co-workers have also reported a wide range of substrates for these reactions <1995T6573, 1995T7547, 1996T5933, 1999S1335, 2000T4575, 2000T1561> and improvements, by addition of an electrophilic scavenger resin which helps to suppress

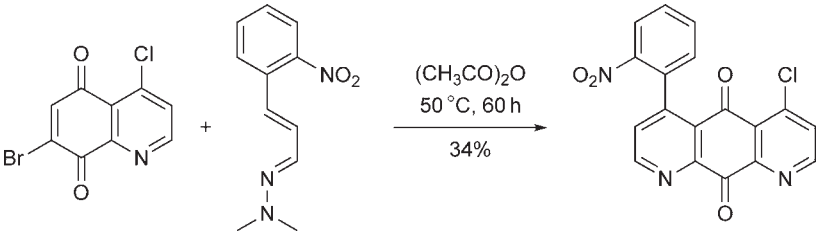
side-product formation (Equation 34; **Table 4**) <2000SL205>. This group has also shown that these reactions can be carried out by absorption of the substrate onto silica gel <1996TL6955>. Sano and co-workers have used the Diels–Alder approach to prepare 1,5-diazaanthraquinones with excellent regioselectivity (**Scheme 6**) <2000H(53)315> as have Tapia *et al.* <1996H(43)447>.



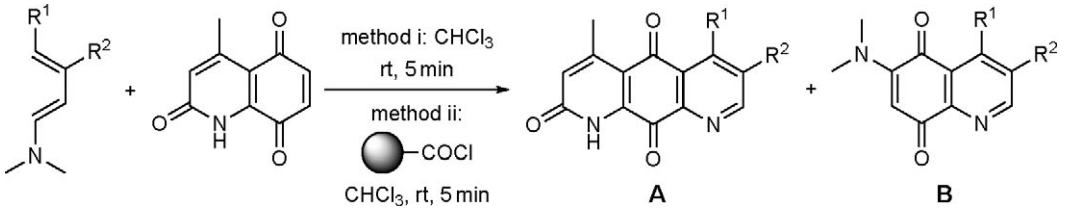
(32)

Table 3 Synthesis of several diazaquinomycin A analogues (Equation 32)

R	*Yield* (%)
H	48
o-OMe	59
m-OMe	52
p-OMe	58



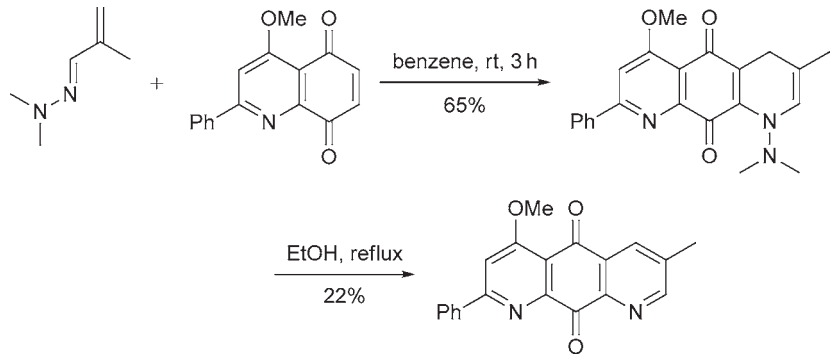
(33)



(34)

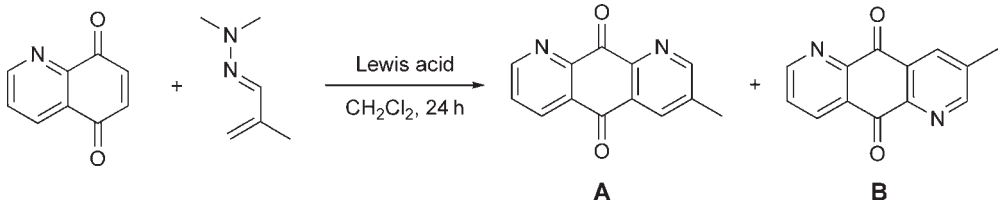
Table 4 Use of a electrophilic scavenger resin to improve yields in the heteroatom Diels–Alder reaction (Equation 34)

		Yield (%)			
		Method i		*Method ii*	
R^1	R^2	***A***	***B***	***A***	***B***
Me	H	51	35	53	15
Et	H	28	25	70	8
Pr^n	H	27	65	62	8
Bu^n	H	30	50	65	8
Et	Me	47	45	67	16



Scheme 6

The regioselectivity of the heteroatom Diels–Alder reaction has been studied using a variety of Lewis acids (Equation 35; **Table 5**) <1998BML2991>. The optimum conditions were found to be 1.2 equiv of both $ZnBr_2$ and the diene; with lower loadings of the $ZnBr_2$, only trace amounts of product were observed (this is believed to be due to the formation of a stable complex between the $ZnBr_2$ and the diene). A transition state (**Figure 3**) has been proposed for this transformation. The regioselectivity of the heteroatom Diels–Alder reaction of pyranobenzoquinones has also been studied <1995J(P2)939>.



(35)

Table 5 The regioselectivity of the heteroatom Diels–Alder reaction (Equation 35)

		Yield (%)	
Diene	*Lewis acid*	***A***	***B***
2.0 equiv		50	27
1.2 equiv	$ZnBr_2$ (1.2 equiv)	73	0
1.2 equiv	$ZnCl_2$ (1.2 equiv)	74	0
1.2 equiv	$AlCl_3$ (1.2 equiv)	No reaction	

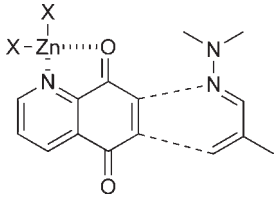
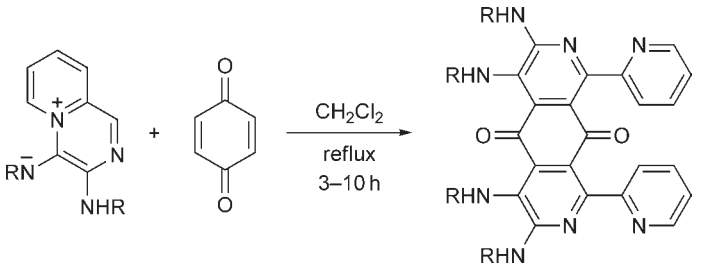


Figure 3

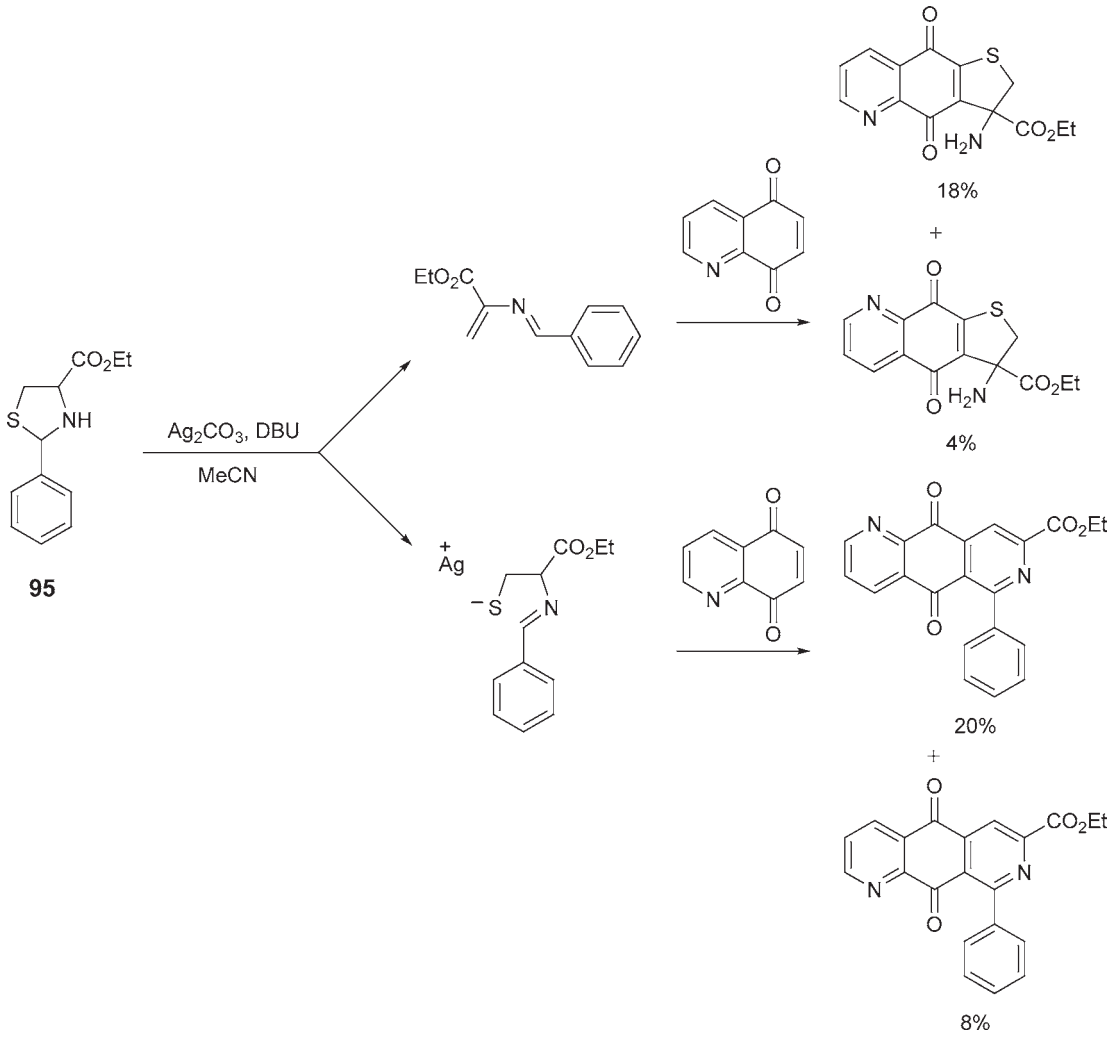
Döring has reported a novel regioselective double cycloaddition of pyrido[1,2-*a*]pyrazines to afford good yields of the corresponding azaquinones (Equation 36; **Table 6**) <1997T5455>. Another variant of the heteroatom Diels–Alder reaction has been reported by Bolognese *et al.* by reacting the thiazolidine **95** derived from cysteine and benzaldehyde with quinoline-5,8-dione <2004T8189>. The reaction follows two different pathways giving rise to several interesting products (**Scheme 7**). Six-membered nitrogen heterocycles can also be prepared by a silane-mediated direct condensation of nitroarenes with allylic carbanions (Equation 37) <1997TL4913, 1998T2607>.



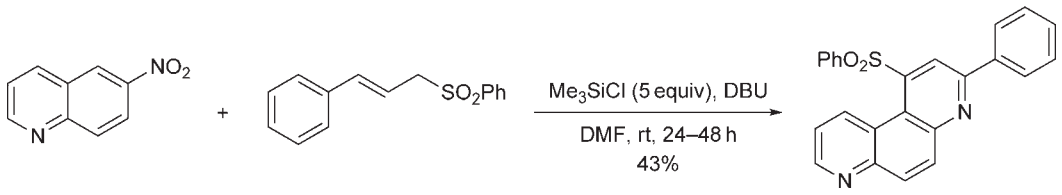
(36)

Table 6 Yields for the double cycloaddition reaction using pyrido[1,2-*a*]pyrazines (Equation 36)

R	*Yield* (%)
4-$CH_3C_6H_4$	92
3-$CF_3C_6H_4$	84
4-$EtOOCC_6H_4$	90
C_6H_5	88
^{15}N-Aza-C_6H_4	85

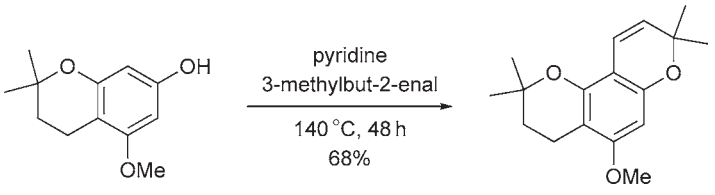


Scheme 7

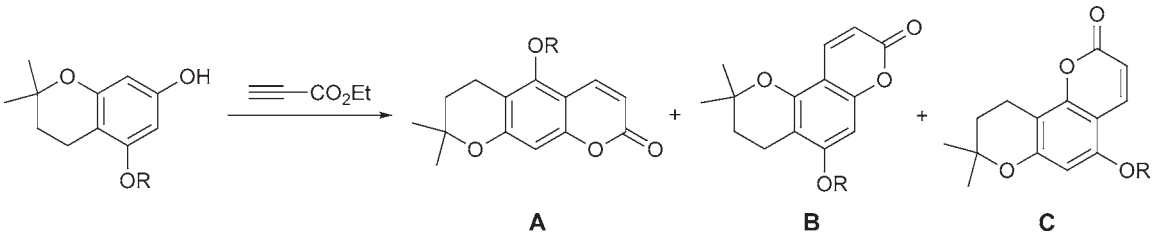


(37)

An effective method for the regioselective formation of chromenes has been reported by Subburaj *et al.* using base-catalyzed conditions (Equation 38) <1997J(P1)1875>. Trost *et al.* have shown that pyranocoumarins can be synthesized using palladium catalysis, although regioselectivity problems are encountered (Equation 39; **Table 7**) <2003JA4518>.



(38)

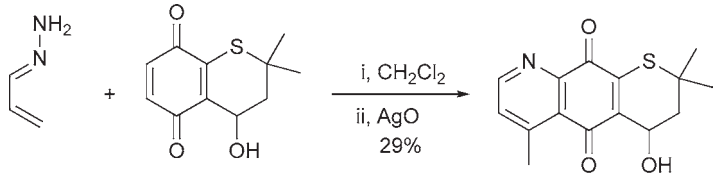


(39)

Table 7 Regioselectivity of pyranocoumarin formation (Equation 39)

R	*Conditions*	*Yield* (%)	*Ratio of products A:B:C*
Me	10% $Pd(OAc)_2$, 20% NaOAc, HCOOH, 25 °C	63	1.0:3.3:0
Me	1.0 (equiv) $AgBF_4$, THF, 25 °C	54	1.0:4.3:0
H	2.5% $Pd_2(dba)_3$, HCOOH, 30 °C then CH_3I, K_2CO_3, acetone	56	1.0:6.6:1.3
H	2.5% $Pd_2(dba)_3$, HCOOH, 10% NaOAc, HCOOH, 25 °C then CH_3I, K_2CO_3, acetone	68	1.0:2.8:0

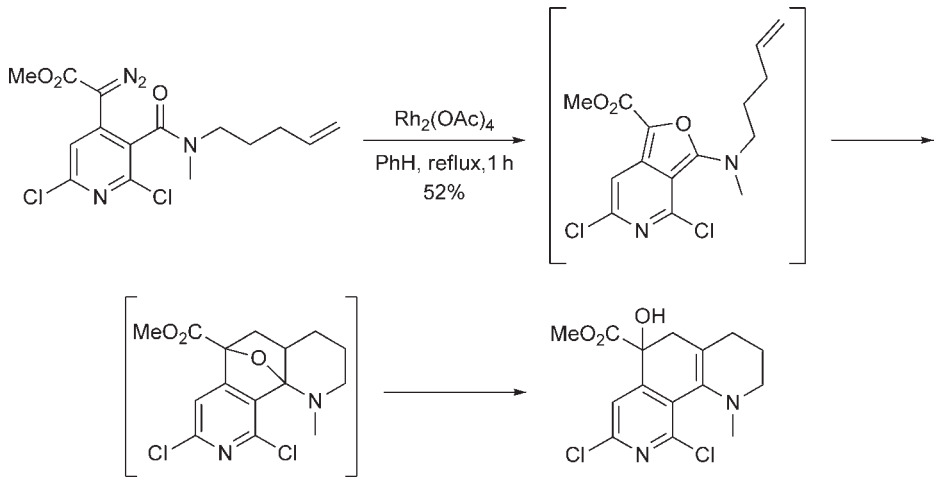
Reaction of quinone **2** with 1-dimethylamino-aza-1,3-pentadiene **96** in dichloromethane affords a rare example of a thiopyranoquinone **6** (Equation 40) <2000H(53)585>.



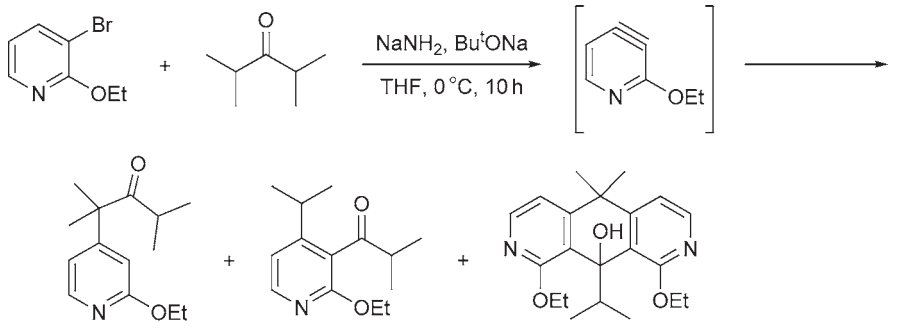
(40)

10.23.9.3.1(ii) Synthesis of the carbocyclic ring

There are few examples for reactions of this type, although Sarkar *et al.* have shown that both the carbocyclic and one of the heterocyclic rings can be prepared in a single operation when employing a metal-catalyzed domino reaction (**Scheme 8**) <2000TL759, 2003JOC4206>. An unusual hetarynic condensation has also been reported, although no yield for **97** was given (Equation 41) <1996AXC2097>.



Scheme 8



(41)

97

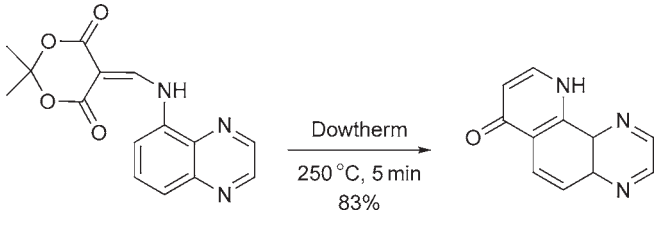
10.23.9.3.2 Compounds with two heteroatoms in one ring and one in another

10.23.9.3.2(i) Synthesis of the heterocyclic ring

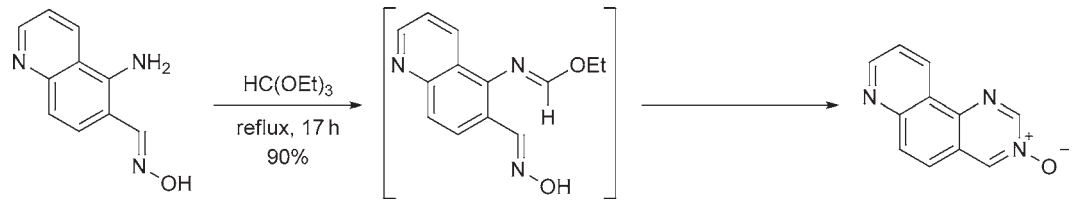
There are a wide number of reactions for the synthesis of these types of compounds; the examples shown are illustrative of the routes available.

10.23.9.3.2(i)(a) By formation of one bond

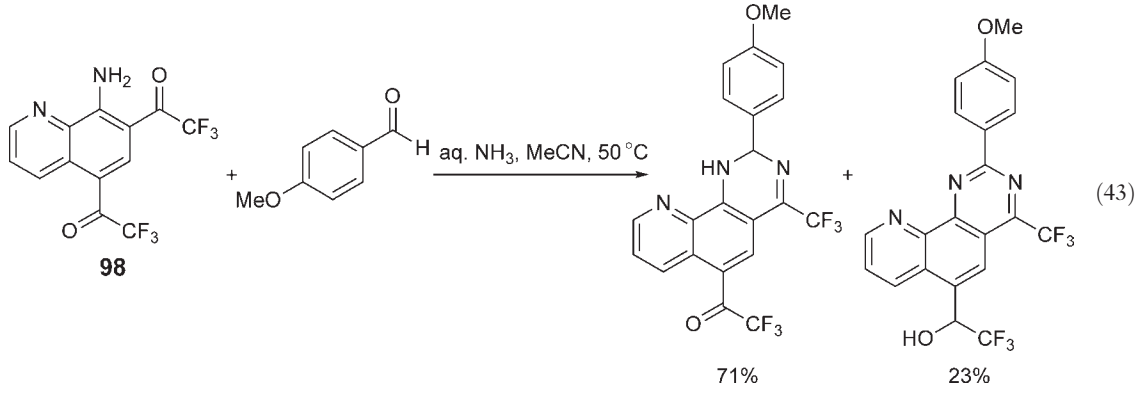
The Skraup quinoline synthesis and its variants are commonly used to prepare these types of systems from the appropriate aniline; further details can be found in CHEC-II(1996) <1996CHEC-II(7)921>. One such variant, the Gould–Jacobs reaction <1939JA2890>, has been exploited to prepare a range of pyrido[2,3-*f*]quinoxalines in good to excellent yields (Equation 42) <2000M293, 2004M283>. Fused pyrimidine mono-*N*-oxides have been reported using a cyclocondensation approach (**Scheme 9**) <1996H(43)389>. Fluorine-containing 1,2-dihydropyrido[3,2-*h*]quinazoline and pyrido[3,2-*h*]quinazolines have been prepared by treatment of compounds such as **98** with an appropriate aldehyde and ammonia (Equation 43) <1999H(51)2471>.



(42)

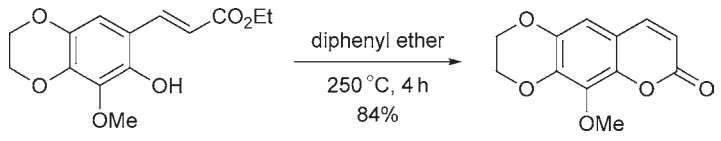


Scheme 9

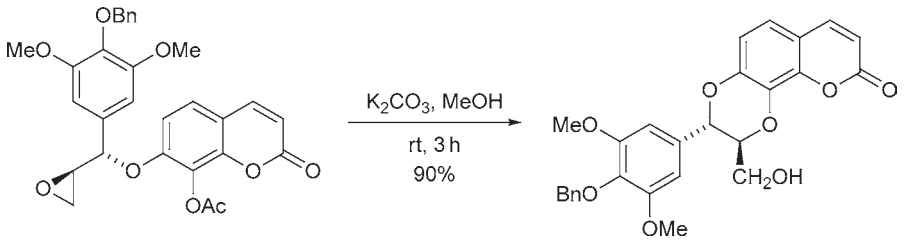


(43)

Several reports for the synthesis of coumarins have used lactone formation to erect the tricyclic core (Equation 44) <1995T3197, 1999SC929>. Other approaches to similar coumarins include the ring opening of an epoxide (Equation 45) <2002TA1799>.



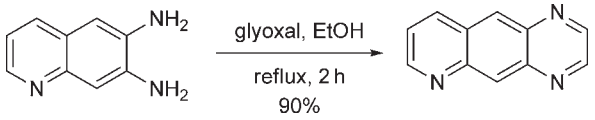
(44)



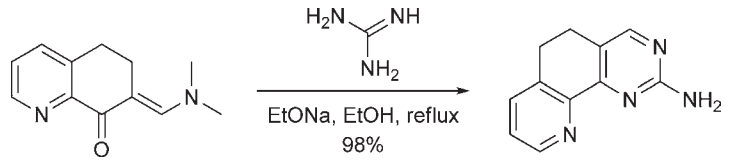
(45)

10.23.9.3.2(i)(b) By formation of two bonds

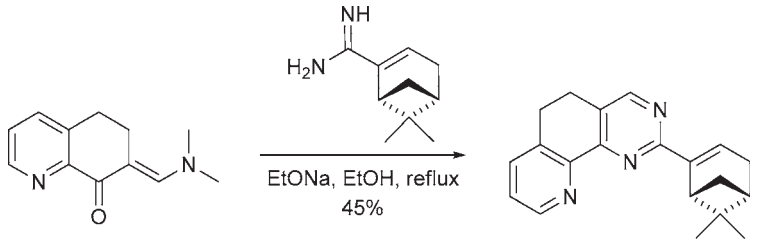
The majority of reactions required to form these types of heterocycles involve the condensation of a 1,2-diamine and a 1,2-dicarbonyl compound, as shown in Equation (46) <2000H(52)423>. Other examples include the reaction of enaminones with carboxamides (Equations 47 and 48) <1996S1012, 2000T8489> and the cyclocondensation of α-ketoesters (Equation 49) <2001FA933>. Nicolaou and Li have prepared **99** and **100** by reaction of the diol **101** with α-bromoisobutyraldehyde (Equation 50) <2001AGE4264>.



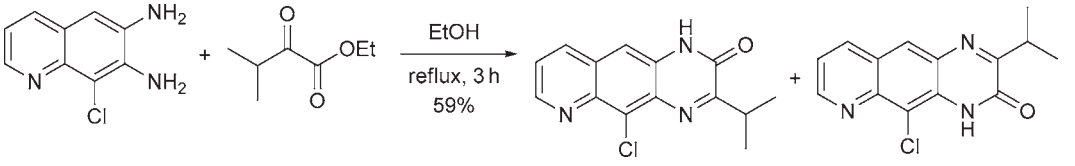
(46)



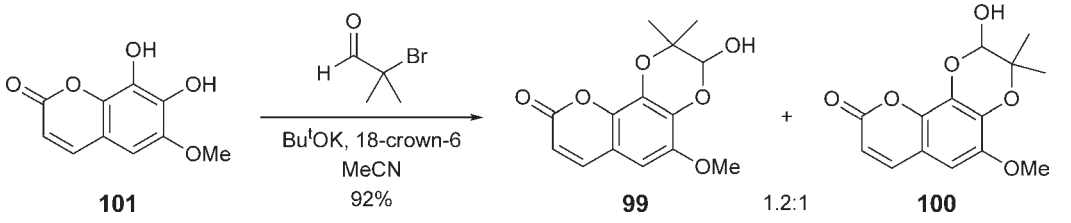
(47)



(48)



(49)



(50)

10.23.9.3.2(ii) Synthesis of the carbocyclic ring

10.23.9.3.2(ii)(a) By formation of one bond

No advances in this area have been found since the publication of CHEC-II(1996) <1996CHEC-II(7)921>.

10.23.9.3.2(ii)(b) By formation of two bonds

No advances in this area have been found since the publication of CHEC-II(1996) <1996CHEC-II(7)921>.

10.23.9.3.3 Compounds with two heteroatoms in each heterocyclic ring

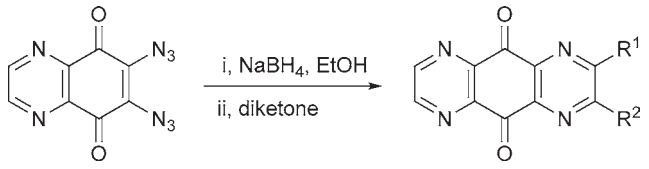
10.23.9.3.3(i) Synthesis of the heterocyclic ring

10.23.9.3.3(i)(a) By formation of one bond

As in CHEC-II(1996) <1996CHEC-II(7)921>, no examples of synthesis by formation of one bond have been found.

10.23.9.3.3(i)(b) By formation of two bonds

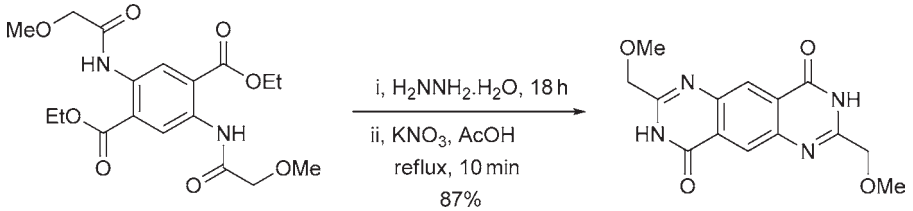
The majority of reports for this structural type concern the evaluation of compounds for biological activity. The synthesis of several pyrimidines has been reported <2002AHC189>. For example, simple condensation of 6,7-diamino-5,8-quinoxalinedione with a range of diketones forms several biologically active compounds (Equation 51; **Table 8**) <1998JME4716>. Reaction of **102** with a primary amine also gives biologically active quinazolines (Equation 52) <2002JME5543>.



(51)

Table 8 Formation of biologically active compounds from diketones (Equation 51)

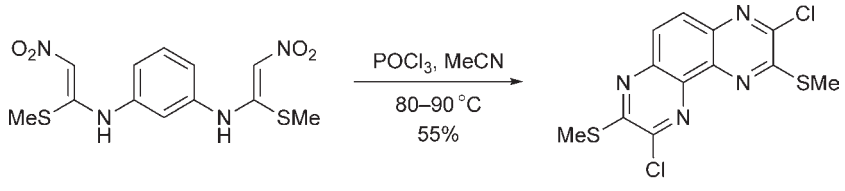
R^1	R^2	*Yield* (%)
H	H	48
CH_3	CH_3	91
CH_3	C_2H_5	81
C_2H_5	C_2H_5	84
Ph	Ph	65



102

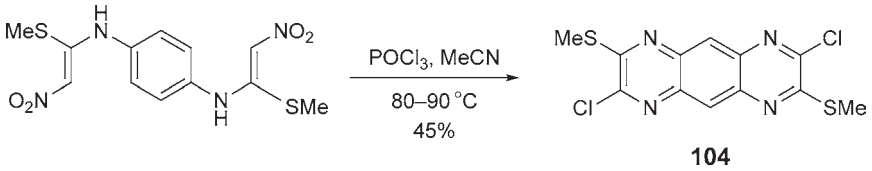
(52)

The pyrazinoquinoxazolines **103** and **104** have been prepared by heteroannulation of nitroketenes using $POCl_3$ (Equations 53 and 54) <2005OL2169>. Treatment of 1,2,3,4-tetraaminobenzene with a dialkynyl-1,2-dione affords the corresponding quinazoline (Equation 55) <1997T14655>.



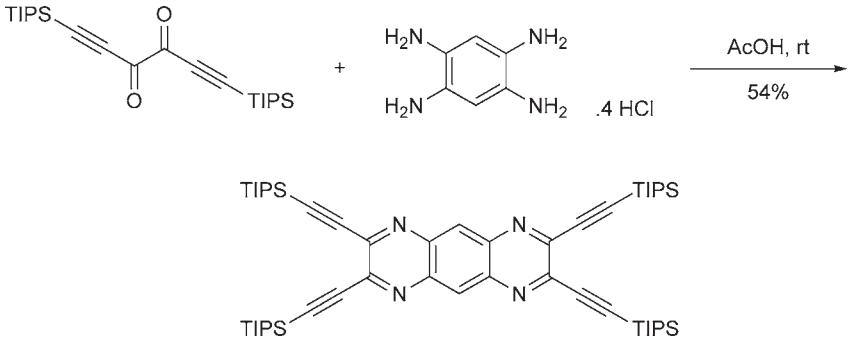
103

(53)



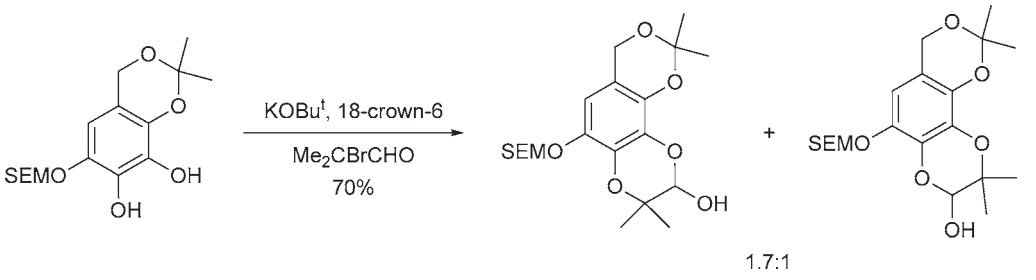
104

(54)



(55)

Nicolaou *et al.* have again used bromoisobutyraldehyde to prepare the regioisomeric lactols (Equation 56) <2004JA5493>.



(56)

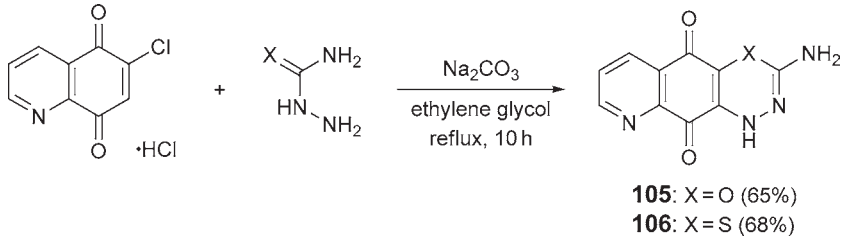
10.23.9.3.3(ii) Synthesis of the carbocyclic ring

As in CHEC-II(1996) <1996CHEC-II(7)921>, no examples for the synthesis of the carbocyclic ring have been found.

10.23.9.3.4 Compounds with more than two heteroatoms in either ring

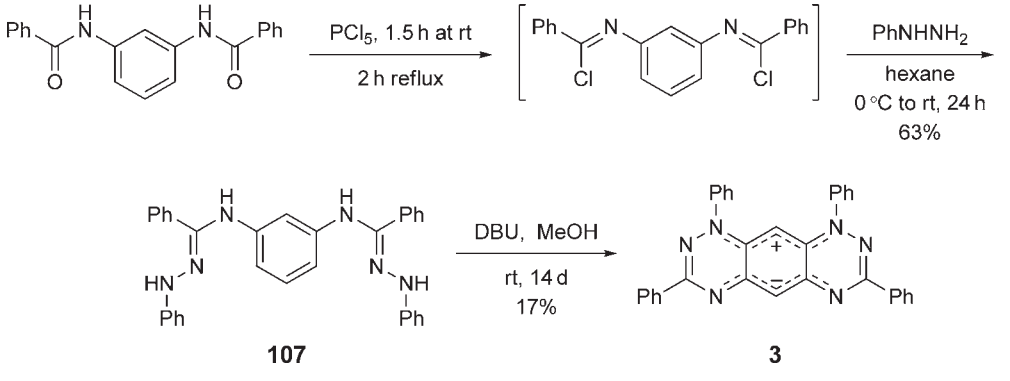
10.23.9.3.4(i) Synthesis of the heterocyclic ring

A review on the synthesis of 1,3,4-thiadiazines and 1,3,4-oxadiazines shows the formation of the diones **105** and **106** (Equation 57) <1998H(49)557>. TPHA **3** was prepared by treatment of **107** with DBU in air (**Scheme 10**) <1998JA2989, 1999PAC295>.



105: X = O (65%)
106: X = S (68%)

(57)



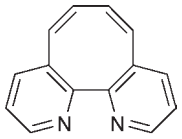
107 **3**

Scheme 10

10.23.9.4 Compounds with a Central Seven-Membered or Larger Ring

10.23.9.4.1 Synthesis of the heterocyclic ring

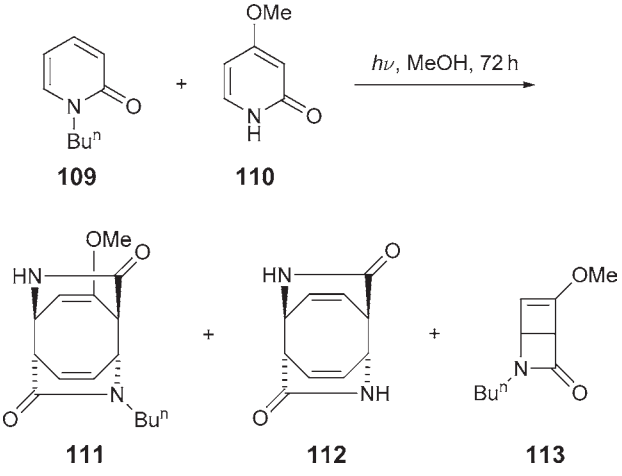
As reported in CHEC-II(1996) <1996CHEC-II(7)921>, compounds with a central seven- or eight-membered ring can be prepared by cyclization of an *O*-allyl oxime. However, only one report in this area could be found, the full paper by Wang and Wong on their previously described synthesis of **108** <1995T6941>.



108

10.23.9.4.2 Synthesis of the carbocyclic ring

Irradiation of **109** in the presence of **110** results in the [4+4] cycloaddition to give the cyclooctadienes **111** and **112** with the side product **113**; product formation is highly dependent on the reaction stoichiometry (Equation 58; **Table 9**) <1996TL1141, 2001TL5155>.



109 **110** **111** **112** **113**

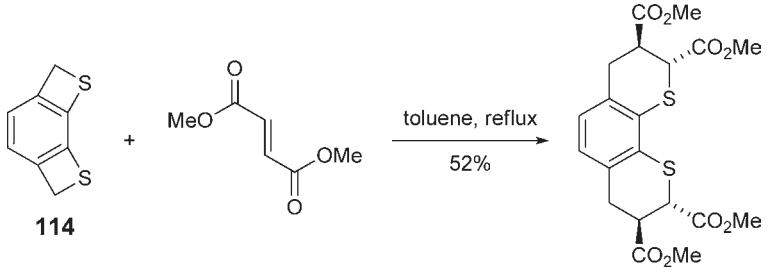
(58)

Table 9 Product distribution for the irradiation of **108** (Equation 58)

Ratio **109**:**110**	*Yield* **111** (%)	*Yield* **112** (%)	*Yield* **113** (%)
1:1	6	22	2
1:4	42	12	1

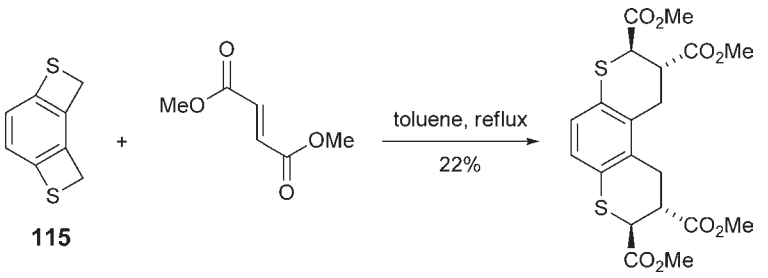
10.23.10 Ring Synthesis by Transformation of Another Ring

Several examples of ring transformation can be found in CHEC-II(1996) <1996CHEC-II(7)921> and some are referred to earlier in this chapter (see Sections 10.23.9.1.1 and 10.23.9.2.1). The benzobisthietes **114** and **115** can be ring-expanded by Diels–Alder reactions with dimethyl fumarate to afford the corresponding thiopyrans in moderate yield, due to competing oligomerization (Equations 59 and 60) <1998TL9639>.



114

(59)



(60)

10.23.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

This section of the chapter, as the title suggests, is devoted to the synthesis of tricyclic systems and offers comparison not only of the methods presented in this chapter but also those reported in the earlier review <1996CHEC-II(7)921>.

10.23.11.1 Compounds with a Central Four-Membered Ring

Nitrogen extrusion from tetraazaphenanthridines appears to be the most effective route for the synthesis of diazabiphenylenes (by the formation of one bond) as the corresponding reaction through extrusion of SO_2 from dipyridothiophene dioxides is low yielding (see Chapter 7.23.8.1.1 in CHEC-II(1996) <1996CHEC-II(7)921>). Undoubtedly, the most well-studied method for the synthesis of diaza- and tetraazabiphenylenes by formation of two bonds is by photodimerization, and excellent yields of highly functionalized products can be achieved (see, for example, **Scheme 2** <1998BCJ321>).

10.23.11.2 Compounds with a Central Five-Membered Ring

There are few reports regarding the synthesis of the carbocyclic ring and the main synthetic approach appears to be through alkaline oxidation of the corresponding phenanthroline. However, this method is often low yielding, and although optimization studies have been carried out, further work in this area would be of some value (see Chapter 7.23.8.2.1 in CHEC-II(1996) <1996CHEC-II(7)921>).

10.23.11.3 Compounds with a Central Six-Membered Ring

10.23.11.3.1 Pyridoquinolines

The synthesis of pyridoquinolines by the formation of one bond often requires harsh reaction conditions (heating under reflux in diphenyl ether, *ca.* 250–260 °C) but the product yield is generally good (70–80%). However, the heteroatom Diels–Alder reaction provides perhaps the most practical method, with a wide range of substrate types tested. Because of the large number of reports in this area, optimized conditions can now be applied which offer excellent regioselectivity and yields (see, for example, Equation (35) and **Table 6**).

10.23.11.3.2 Compounds with two heteroatoms in one ring and one in another

The Skraup and related quinoline syntheses are the method of choice for the cyclization of an appropriate aniline in generally good yield (see, for example, Chapter 7.23.8.3.2 in CHEC-II(1996) <1996CHEC-II(7)921>). Formation of this class of compounds by formation of two bonds is generally achieved by condensation of a 1,2-diketone and a 1,2-diamine in excellent yield (see, for example, Equation 52).

10.23.11.3.3 Quinoxazolines

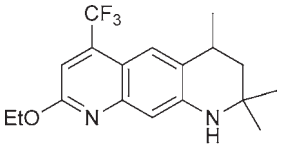
Excellent yields for the synthesis of quinoxazolines can again be achieved by condensation of a 1,2-diketone and a 1,2-diamine (see, for example, Equation 51 and **Table 9**).

10.23.11.4 Compounds with a Central Seven-Membered or Larger Ring

Only one method for the synthesis of these types of compounds has been reported through the thermal cyclization of *O*-allyl oximes in moderate to good yield (see, for example, <1995TL6941>).

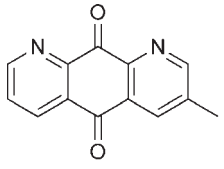
10.23.12 Important Compounds and Applications

Not surprisingly, many of the structural architectures presented in this chapter are either key intermediates for compounds with significant and useful biological activities or are themselves biologically active. 1,4-Dihydropyridine dimers have been used to synthesize anti-human immunodeficiency virus (anti-HIV) agents <1997CL1269, 1997EJO1214, 1999H(51)2367>. The natural products xanthoxyletin and alloxanthoxyletin **64** and **65** have been prepared using key chroman intermediates **66** and **67** (Equations 10 and 11) <2003JA4518>. Conformationally restricted analogues of nicotine and anabasine have been prepared using the intermediate **7** <2003JOC4206>. A series of 1,2-dihydropyridono[5,6-*g*]quinolines have been reported to be effective androgen receptor antagonists, compound **116** being just one example <1998JME623>.

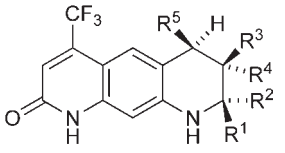


116

1,5-Diazaanthraquinones have been found to be interesting antitumor compounds <2004BML3929>. Some pyrido[2,3-*g*]isoquinolindiones are effective antiproliferative compounds <2004JME849, 2004T8189>. Several selective and potent human androgen receptor agonists were prepared from a known antagonist pharmacophore **117** <1999BML1009, 1999BML1335>. Analogues based on the 1,8-diazaanthraquinone core **118** exhibit cytotoxic activity comparable to that of doxorubicin in HOP62, SK-OV-3, and SF295 cells <1998BML2991>.

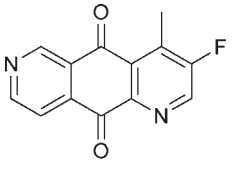


117

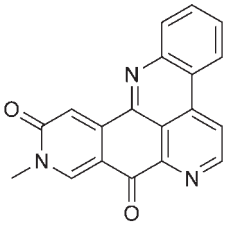


118

Some 1,7- and 1,8-diazaanthracenediones (e.g., **119**) have been used as key intermediates for the synthesis of cytotoxic analogues of the marine pyridoacridine amphimedine **120** <2002BMC2845>. They have also been used in the synthesis of meridine **121** and cystodamine **122** <1998T8421>.

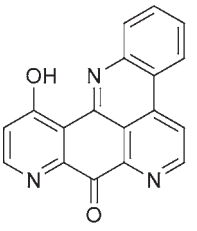


119

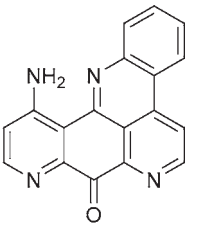


Pyridoacridine amphimedine

120

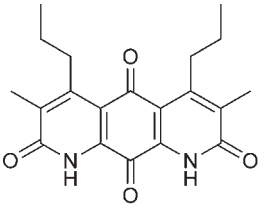


Meridine
121

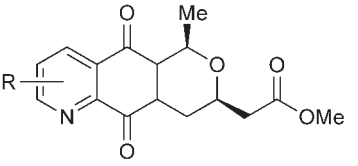


Cystodamine
122

Diazaquinomycin A **123** is a natural antibacterial agent isolated from a *Streptomyces* strain and has been synthesized by Avendaño and co-workers <1998TL673> (for previous syntheses, see <1996CHEC-II(7)921>). 6-Azapinanaomycin A methyl ester **124** and 6-azaeleutherin **125** have been shown to be effective antibiotics <1997S567>.

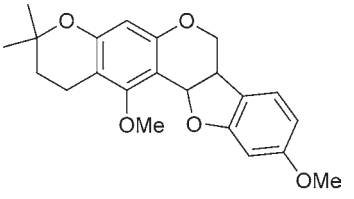


Diazaquinomycin A
123



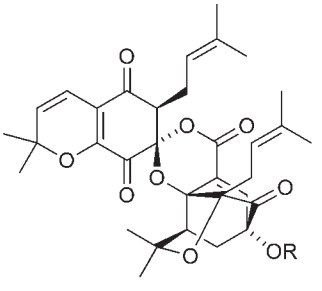
6-Azapinanaomycin A methyl ester **124**: R = 9-OH
6-Azaeleutherin **125**: R = 9-OMe, 3-Me

The total synthesis of edulane **126** has been achieved using the chromene **61** as a key intermediate in the synthesis <1997J(P1)1875>.



Edulane
126

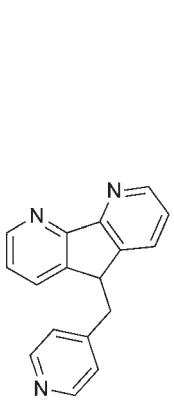
The total syntheses of 1-*O*-methyllateriflorine **127** and lateriflorone **128** have been described <2004JA5493>. It is believed that findings on the construction of **68** may give an insight on the biosynthetic pathway by which nature forms lateriflorone **128**.



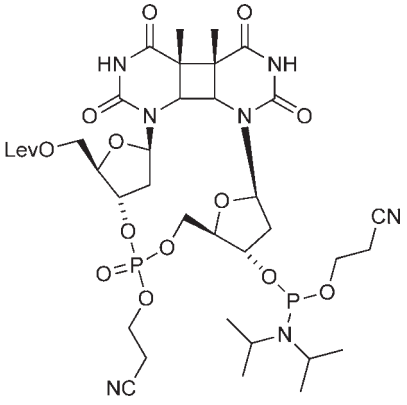
1-*O*-Methyllateriflorone **127**: R = Me
Lateriflorone **128**: R = H

Applications for the 1,10-phenanthroline nucleus are widespread; for example, they have been used as chelating agents (see Section 10.23.5.2), ligands for catalysis (see Section 10.23.5.2), as cytotoxic drugs <2002T9095>, and, when complexed with molybdenum, as cancer therapeutics <2005WO087783>.

Diazafluorenes such as **129** have found use as cognition enhancers <1995USP5424430> and biologically active cyclobutane oligodeoxyribonucleotides such as **130** have been prepared using a photochemical cycloaddition reaction <2003WO070741>.

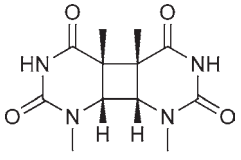


129



130

The *cis-syn*-pyrimidine dimers such as **131** are responsible for cell death and the degeneration of cells into tumor cells. They are formed by the UV irradiation of cells, inducing DNA damage by a [2π+2π] cycloaddition of pyrimidines located above each other in the DNA double strand (see, for example, <1996MI764, 1996JPC19714, 1997JA7440, 1997PCA4332, 1998AGE938, 1998MI192, 1999JA7318, 2001OL1455, 2004OBC2742>.



131

10.23.13 Further Developments

Since the preparation of this review several publications have been reported, a summary is shown below.

10.23.13.1 [1,10]-Phenanthroline

A search of the literature from 2006–7 reveals over 2000 hits, many using [1,10]-phenanthroline as a ligand for metal catalyzed reactions, for example <2007EJO508, 2006EJO4717>. A recent report using [2,11]-phenanthroline has also been described <2007JOC2769>.

10.23.13.2 Pyrazino[*f*]quinoxaline

Self-assembled fluorescent hexaazatriphenylenes that act as a light-harvesting antenna has been reported <2006JOC5752>. The design and synthesis of bismacrocyclic hexaazatriphenylene derivatives was recently reported in <2006OL1311>.

10.23.13.3 Pyrazino[2,3-*g*]quinoxaline

A range of pyrazino[2,3-*g*]quinoxalines were prepared using scaffold-directed small molecular heterocycle synthesis <2007JCC70>. A range of peralkynylated pyrazino[2,3-*g*]quinoxalines has also been reported <2006OL757>.

10.23.13.4 4*H*,6*H*-Pyrano[3,2-*g*]chromene

4*H*,6*H*-Pyrano[3,2-*g*]chromenes have been synthesized *via* intramolecular double ring-closing enyne metathesis <2007T977>. The synthesis and biological evaluation against *Mycobacterium tuberculosis* has been carried out using a 4*H*,6*H*-pyrano[3,2-*g*]chromene <2006BMC4610>.

10.23.13.5 Pyrido[3,2-*g*]quinoline

A search of the literature from 2006–7 reveals a large number of reports regarding the biological activities of this type of system, for example the synthesis and antiproliferative evaluation of certain pyrido[3,2-*g*]quinoline derivatives has been reported <2006BMC7370>.

10.23.13.6 1*H*-Cyclopenta[1,2-*b*;4,3-*b*′]dipyridine

1*H*-Cyclopenta[1,2-*b*;4,3-*b*′]dipyridines have been reported <2006JHC481>.

10.23.13.7 Diazafluorenes

The crystal structure and photochemical behavior in solution of the 3′-N-sulfamate analogue of thymidylyl(3′-5′)thymidine was reported <2007JOC43>. The [2+2] photocycloaddition of uracil derivatives with ethylene as a general route to *cis*-cyclobutane β-amino acids has been reported <2006SL1394>. Reversible photochemical conversion of helicity in self-assembled nanofibers from a 1,ω-thymidylic acid appended bolaamphiphile <2006AG(E)4601>. Efficient photosensitized splitting of the thymine dimer/oxetane unit on its modifying β-cyclodextrin by a binding electron donor <2006OBC2575>.

No further reports were found for pyrimido[4,5-*g*]quinazolines, pyridazino[4,5-*g*]cinnolines, pyridazino[4,5-*g*]phthalazines, pyrido[2,3-*g*]quinoxalines, cyclobuta[1,2-*b*;3,4-*b*′]dipyridines, cycloocta[2,1-*b*;3,4-*b*′]dipyridines.

References

1939JA2890 R. G. Gould and W. A. Jacobs, *J. Am. Chem. Soc.*, 1939, **61**, 2890.
1984CHEC(2)395 G. Jones, in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 2, p. 395.
1984CHEC(3)599 M. V. Sargent and F. M. Dean, in 'Comprehensive Heterocyclic Chemistry I', A. R. Katritzky and C. W. Rees, Eds.; Pergamon, Oxford, 1984, vol. 3, p. 599.
1995JA5453 J. R. Jacobsen, A. G. Cochran, J. C. Stephans, D. S. King, and P. G. Schultz, *J. Am. Chem. Soc.*, 1995, **117**, 5453.
1995JMO(A)L7 G. Chelucci, M. A. Cabras, and A. Saba, *J. Mol. Catal. A*, 1995, **95**, L7.
1995J(P2)939 F. Zuloaga, R. Tapia, and C. Quintanar, *J. Chem. Soc., Perkin Trans. 2*, 1995, 939.
1995T3197 T. Besson, N. Ruiz, G. Coudert, and G. Guillaumet, *Tetrahedron*, 1995, **51**, 3197.
1995T6573 J. M. Péres, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 1995, **51**, 6573.
1995T6941 X. C. Wang and H. N. C. Wong, *Tetrahedron*, 1995, **51**, 6941.
1995T7547 O. Martin, E. de la Cuesta, and C. Avendaño, *Tetrahedron*, 1995, **51**, 7547.
1995USP5424430 J. H. Jensen, T. D. Costello, L. De Brabander, Jr., and M. E. Voss, *US Pat.*, 5 424 430 (1995).
1996AXC2097 S. Ianelli, M. Nardelli, D. Belletti, K. Pasquier, and P. Caubére, *Acta Crystallogr., Sect. C*, 1996, **52**, 2097.
1996CHEC-II(7)921 K. J. Nichol, in 'Comprehensive Heterocyclic Chemistry II', A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Eds.; Pergamon, Oxford, 1996, vol. 7, p. 921.
1996H(43)389 S. Ostrowski, *Heterocycles*, 1996, **43**, 389.
1996H(43)447 R. A. Tapia, C. Quintanar, and J. A. Valderrama, *Heterocycles*, 1996, **43**, 447.
1996H(43)1621 C. Matias, A. Mahamoud, and J. Barbe, *Heterocycles*, 1996, **43**, 1621.
1996IC2253 Z. Lu, C. Duan, Y. Tian, and X. You, *Inorg. Chem.*, 1996, **35**, 2253.
1996JA4299 E. Peña-Cabrera, P.-O. Norrby, M. Sjören, A. Vitagliano, V. De Felice, J. Oslob, S. Ishii, D. O'Neill, B. Åkermark, and P. Helquist, *J. Am. Chem. Soc.*, 1996, **118**, 4299.
1996JA5032 J. M. Lawson, A. M. Oliver, D. F. Rothenfluh, Y.-Z. An, G. A. Ellis, M. G. Ranasinghe, S. I. Kahn, A. G. Franz, P. S. Ganapathi, M. J. Shephard, *et al.*, *J. Am. Chem. Soc.*, 1996, **118**, 5032.
1996JPC19714 A. Pezeshk, I. D. Podmore, P. F. Heelis, and M. C. R. Symons, *J. Phys. Chem.*, 1996, **100**, 19714.
1996MI764 M. P. Scannell, S.-R. Yeh, and D. E. Falvey, *Photochem., Photobiol.*, 1996, **64**, 764.
1996S1012 E. Bejan, H. A. Haddou, J. C. Daran, and G. G. A. Balavoine, *Synthesis*, 1996, 1012.
1996T5933 M. del Mar Blanco, M. Á.Alonso, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 1995, **52**, 5933.
1996TL1141 S. McN. Sieburth and C.-H. Lin, *Tetrahedron Lett.*, 1996, **37**, 1141.
1996TL6955 J. M. Péres, P. López-Alvarado, M. Á.Alonso, C. Avendaño, and J. C. Menéndez, *Tetrahedron Lett.*, 1996, **37**, 6955.
1997CL1269 A. Hilgeroth, *Chem. Lett.*, 1997, 1269.

1997HCA2191 T. Carell, R. Epple, and V. Gramlich, *Helv. Chim. Acta*, 1997, **101**, 2191.
1997JA7440 R. Epple, E.-U. Wallenborn, and T. Carell, *J. Am. Chem. Soc.*, 1997, **119**, 7440.
1997JOC2234 J. N. H. Reek, J. A. A. W. Elemans, and R. J. M. Nolte, *J. Org. Chem.*, 1997, **62**, 2234.
1997J(P2)1309 N. Marubayashi, T. Ogawa, T. Hamasaki, and N. Hirayama, *J. Chem. Soc., Perkin Trans. 2*, 1997, 1309.
1997J(P1)1875 K. Subburaj, M. G. Murugesh, and G. K. Trivedi, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1875.
1997PCA4332 M. P. Scannell, G. Prakash, and D. E. Falvey, *J. Phys. Chem. A.*, 1997, **101**, 4332.
1997S567 C. Tödter and H. Lackner, *Synthesis*, 1997, 567.
1997S1249 H.-B. Sun, F.-L. Qing, and X. Chen, *Synthesis*, 1997, 1249.
1997T1743 N. Bontemps, E. Delfourne, J. Bastide, C. Francisco, and F. Bracher, *Tetrahedron*, 1997, **53**, 1743.
1997T3231 P. Ferrer, C. Avendaño, and M. Söllhuber, *Tetrahedron*, 1997, **53**, 3231.
1997T5455 T. Billert, R. Beckert, P. Fehling, M. Döhring, and H. Görls, *Tetrahedron*, 1997, **53**, 5455.
1997T14655 R. Faust, C. Weber, V. Fiandanese, G. Marchese, and A. Punzi, *Tetrahedron*, 1997, **53**, 14655.
1997TL4441 Y. Kitahara, F. Tamura, and Akinori Kubo, *Tetrahedron Lett.*, 1997, **38**, 4441.
1997TL4913 Z. Wröbel, *Tetrahedron Lett.*, 1997, **38**, 4913.
1998AGE938 R. Epple and T. Carell, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 938.
1998AHC291 L. I. Belen'kii and N. D. Kruchkovskaya, *Adv. Hetrocycl. Chem.*, 1998, **71**, 291.
1998BCJ321 N. Marubayashi, T. Ogawa, and N. Hirayama, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 321.
1998BML2991 H. Lee, S. Lee, and S. Yang, *Bioorg. Med. Chem. Lett.*, 1999, **8**, 2991.
1998EJO1213 A. Hilgeroth, U. Baumeister, and F. W. Heinemann, *Eur. J. Org. Chem.*, 1998, 1213.
1998H(49)557 H. S. Kim and Y. Kurasawa, *Heterocycles*, 1998, **49**, 557.
1998JA2989 K. Hutchinson, G. Srdanov, R. Hicks, H. Yu, F. Wudl, T. Strassner, M. Nendel, and K. N. Houk, *J. Am. Chem. Soc.*, 1998, **120**, 2989.
1998JME623 L. G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X.-N. Wang, K. B. Marschke, J. W. Kong, L. J. Farmer, and T. K. Jones, *J. Med. Chem.*, 1998, **41**, 623.
1998JME4716 H.-W. Yoo, M.-E. Suh, and S. W. Park, *J. Med. Chem.*, 1998, **41**, 4716.
1998MI192 M. Yasuda, Y. Nishinaka, T. Nakazono, T. Hamasaki, N. Nakamura, T. Shiragami, C. Pac, and K. Shima, *Photochem., Photobiol.*, 1998, **67**, 192.
1998POL2463 S. Menon and M. V. Rajasekharan, *Polyhedron*, 1998, **17**, 2463.
1998T2607 Z. Wröbel, *Tetrahedron*, 1998, **54**, 2607.
1998T8421 Y. Kitahara, F. Tamura, M. Nishimura, and A. Kubo, *Tetrahedron*, 1998, **54**, 8421.
1998TL673 J. M. Péres, P. López-Alvarado, C. Avendaño, and J. C. Menéndez, *Tetrahedron Lett.*, 1998, **39**, 673.
1998TL9639 H. Meier and N. Rumpf, *Tetrahedron Lett.*, 1998, **39**, 9639.
1999AHC295 L. I. Belen'kii, N. D. Kruchkovskaya, and V. N. Gramenitskaya, *Adv. Heterocycl. Chem.*, 1999, **73**, 295.
1999BML1009 L. Zhi, C. M. Tegley, K. B. Marschke, and T. K. Jones, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1009.
1999BML1335 R. I. Higuchi, J. P. Edwards, T. R. Caferro, J. D. Ringgenberg, J. W. Kong, L. G. Hamann, K. L. Arienti, K. B. Marschke, R. L. Davis, L. J. Farmer, *et al.*, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1335.
1999CC1171 G. Albano, P. Belser, L. De Cola, and M. T. Gandolfi, *J. Chem. Soc., Chem. Commun.*, 1999, 1171.
1999H(51)2367 A. Hilgeroth, U. Baumeister, and F. W. Heinemann, *Heterocycles*, 1999, **51**, 2367.
1999H(51)2471 E. Okada and N. Tsukushi, *Heterocycles*, 1999, **51**, 2471.
1999JA7318 R. Epple and T. Carell, *J. Am. Chem. Soc.*, 1999, **121**, 7318.
1999JCD1423 X.-H. Zou, B.-H. Ye, H. Li, J.-G. Liu, Y. Xiong, and L.-N. Ji, *J. Chem. Soc., Dalton Trans.*, 1999, 1423.
1999OL1659 D. O'Neill and P. Helquist, *Org. Lett.*, 1999, **1**, 1659.
1999PAC295 F. Wudl, P. A. Koutentis, A. Weitz, B. Ma, T. Strassner, K. N. Houk, and S. I. Kahn, *Pure Appl. Chem.*, 1999, **71**, 295.
1999S1335 J. I. Úbeda, M. Villacampa, and C. Avendaño, *Synthesis*, 1999, 1335.
1999SC929 T. Dubuffet, A. Loutz, and G. Lavielle, *Synth. Commun.*, 1999, **26**, 929.
1999T8377 F. Lam, M. Feng, and K. S. Chan, *Tetrahedron*, 1999, **55**, 8377.
2000AGE576 A. Hilgeroth and U. Baumeister, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 576.
2000CCR243 D. V. Scaltrito, D. W. Thompson, J. A. O'Callaghan, and G. J. Meyer, *Coord. Chem. Rev.*, 2000, **208**, 243.
2000CRV2537 D. T. McQuade, A. E. Pullen, and T. M. Swager, *Chem. Rev.*, 2000, **100**, 2537.
2000CRV3483 G. F. Swiegers and T. J. Malefetse, *Chem. Rev.*, 2000, **100**, 3483.
2000H(52)423 P. Sanna, A. Carta, and G. Paglietti, *Heterocycles*, 2000, **52**, 423.
2000H(53)315 Y. Horiguchi, A. Toeda, K. Tomoda, and T. Sano, *Heterocycles*, 2000, **53**, 315.
2000H(53)585 R. A. Tapia, M. C. Garate, J. A. Valderrama, F. Zuloaga, P. R. Jenkins, J. Fawcett, and D. R. Russell, *Heterocycles*, 2000, **53**, 585.
2000JST91 W. Xiao, Z.-L. Lu, C.-Y. Su, K.-B. Yu, L.-R. Deng, H.-Q. Liu, and B.-S. Kang, *J. Mol. Struct.*, 2000, **553**, 91.
2000M293 J. Saloň, V. Milata, N. Prónayová, and J. Lesko, *Monatsh. Chem.*, 2000, **131**, 293.
B-2000MI1 A. R. Katritzky and A. F. Pozharskii; 'Handbook of Heterocyclic Chemistry', 2nd edn., Pergamon, Oxford, 2000.
2000SL205 E. Pascual-Alfonso, C. Avendaño, and J. C. Menéndez, *Synlett*, 2000, 205.
2000T1561 J. M. Péres, P. López-Alvarado, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 2000, **56**, 1561.
2000T4575 J. M. Péres, P. López-Alvarado, E. Pascual-Alfonso, C. Avendaño, and J. C. Menéndez, *Tetrahedron*, 2000, **56**, 4575.
2000T8489 F. Pezet, L. Routaboul, J.-C. Daran, I. Sasaki, H. A-Haddou, and G. G. A. Balavoine, *Tetrahedron*, 2000, **56**, 8489.
2000TL759 T. K. Sarkar, S. Basak, and S. K. Ghosh, *Tetrahedron Lett.*, 2000, **41**, 759.
2001AGE4264 K. C. Nicolaou and J. Li, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 4264.
2001AHC199 L. I. Belen'kii, N. D. Kruchkovskaya, and V. N. Gramenitskaya, *Adv. Hetrocycl. Chem.*, 2001, **79**, 199.
2001FA933 A. Carta, P. Sanna, L. Gherardini, D. Usai, and S. Zanetti, *Farmaco*, 2001, **56**, 933.
2001JCD1813 M. Riklin, D. Tran, X. Bu, L. E. Laverman, and P. C. Ford, *J. Chem. Soc., Dalton Trans.*, 2001, 1813.
2001MI1 V. G. Zaikin, A. V. Valamov, A. I. Mikaya, and N. S. Prostakov, '*Osnovy mass-spectrometrii organicheskikh soedinenii* (in Russian)', MAIK in '*Nauka-Interperiodika*', Moscow (2001).
2001OL1455 O. Krüger and U. Wille, *Org. Lett.*, 2001, **3**, 1455.

2001TL5155 S. McN. Sieburth, C. B. Masden-Duggan, and F. Zhang, *Tetrahedron Lett.*, 2001, **42**, 5155.
2002AGE3623 A. Hilgeroth, J. Molnár, and E. De Clercq, *Angew. Chem., Int. Ed. Engl.*, 2002, **41**, 3623.
2002AHC189 S. Radi, *Adv. Heterocycl. Chem.*, 2002, **83**, 189.
2002BMC2845 C. Brahic, F. Darro, M. Belloir, J. Bastide, R. Kiss, and E. Delforne, *Bioorg. Med. Chem.*, 2002, **10**, 2845.
2002CC2236 J. Rusanova, M. Pilkington, and S. Decurtins, *J. Chem. Soc., Chem. Commun.*, 2002, 2236.
2002CRV3129 G. Chelucci and R. P. Thummel, *Chem. Rev.*, 2002, **102**, 3129.
2002JA1532 J. A. A. W. Elemans, A. E. Rowen, and R. J. M. Nolte, *J. Am. Chem. Soc.*, 2002, **124**, 1532.
2002JME5543 E. B. Skibo, X. Huang, R. Martinez, R. H. Lemus, and W. A. Craigo, *J. Med. Chem.*, 2002, **45**, 5543.
2002T9095 G. I. Graf, D. Hastreiter, L. E. da Silva, R. A. Rebelo, A. G. Montalban, and A. McKillop, *Tetrahedron*, 2002, **58**, 9095.
2002TA1799 X. Ren, X. Chen, K. Peng, X. Xie, Y. Xia, and X. Pan, *Tetrahedron Asymmetry*, 2002, **13**, 1799.
2003JA4518 B. M. Trost, F. D. Toste, and K. Greenman, *J. Am. Chem. Soc.*, 2003, **125**, 4518.
2003JOC4206 T. K. Sarkar, S. Basak, Z. Slanina, and T. J. Chow, *J. Org. Chem.*, 2003, **68**, 4206.
2003WO070741 P. Clivio, M. Thomas, M. Ortiz, and U. Javier, *PCT Int. Appl. WO* 0 707 41 (2003).
2004ACR827 A. Del, D. Gatteschi, C. Sangregorio, and L. Sorace, *Acc. Chem. Res.*, 2004, **37**, 827.
2004AHC1 L. I. Belen'kii and V. N. Gramenitskaya, *Adv. Heterocycl. Chem.*, 2004, **87**, 1.
2004BML3929 C. Avendaño, J. M. Péres, M. del Mar Blanco, J. A. de la Fuente, S. Manzanaro, M. J. Vincent, M. J. Martín, N. Salvador-Tormo, and J. C. Menéndez, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3929.
2004JA5493 K. C. Nicolaou, P. K. Sasmal, and H. Xu, *J. Am. Chem. Soc.*, 2004, **126**, 5493.
2004JME849 A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, O. Mazzoni, E. Novellino, P. La Colla, G. Sanna, and R. Loddo, *J. Med. Chem.*, 2004, **47**, 849.
2004M283 J. Saloň, V. Milata, M. Chudík, N. Prónayová, J. Lesko, M. Seman, and A. Belicova, *Monatsh. Chem.*, 2004, **135**, 283.
2004OBC2742 F. Boussicault, O. Krüger, M. Robert, and U. Wille, *Org. Biomol. Chem.*, 2004, **2**, 2742.
2004RJO1322 K. N. Gusak, N. G. Kozlov, and A. B. Tereshko, *Russ. J. Org. Chem.*, 2004, **40**, 1322.
2004T8189 A. Bolognese, G. Correale, M. Manfra, A. Lavecchia, E. Novellino, and V. Barone, *Tetrahedron*, 2004, **60**, 8189.
2005CCR545 B.-H. Ye, M.-L. Tong, and X.-M. Chen, *Coord. Chem. Rev.*, 2005, **249**, 545.
2005OL2169 C. Venkatesh, B. Singh, P. K. Mahata, H. Ila, and H. Junjappa, *Org. Lett.*, 2005, **7**, 2169.
2005WO087783 M. Norton, R. P. Marta, C. C. Carlos, P. Lage, C. Claudia, S. S. Rodrigues, S. Sandra, M. Mora, M. J. P. Silva, P. M. Alves, *et al.*, *PCT Int. Appl. WO* 0 877 73 (2005).
2006AG(E)4601 R. Iwaura and T. Shimizu, *Angew. Chem. Int. Ed.*, 2006, **45**, 4601.
2006BMC4610 Z.-Q. Xu, K. Pupek, W. J. Suling, L. Enache, and M. T. Flavin, *Bioorg. Med. Chem.*, 2006, **14**, 4610.
2006BMC7370 S.-Y. Li, Y.-L. Chen, C. Wang, and C.-C. Tzenga, *Bioorg. Med. Chem.*, 2006, **14**, 7370.
2006EJO4717 S. Konrad, M. Bolte, C. Näther, and U. Lüning, *Eur. J. Org. Chem.*, 2006, 4717.
2006JHC481 M. T. Maghsoodlou, N. Hazeri, S. M. H. Khorassani, G. Marandi, and M. Nassiri, *J. Heterocycl. Chem.*, 2006, **43**, 481.
2006JOC5752 T. Ishi-i, K. Murakami, Y. Imai, and S. Mataka, *J. Org. Chem.*, 2007, **71**, 5752.
2006OBC2575 W.-J. Tang, Q.-H. Song, H.-B. Wang, J.-Y. Yu, and Q.-X. Guo, *Org. Biomol. Chem.*, 2006, **4**, 2575.
2006OL1311 P. Secondo and F. Fages, *Org. Lett.*, 2006, **8**, 1311.
2006OL757 S. Miao, M. D. Smith, and U. H. F. Bunz, *Org. Lett.*, 2006, **8**, 757.
2006SL1394 C. Gauzy, B. Saby, E. Pereira, S. Faure, and D. J. Aitken, *Synlett*, 2006, 1394.
2007EJO508 B.-L. Li, Z.-T. Liu, G.-J. Deng, and Q.-H. Fan, *Eur. J. Org. Chem.*, 2007, 508.
2007JCC70 G. Liu, L. Li, B. Kou, S. Zhang, L. Zhang, Y. Yuan, T. Ma, Y. Shang, and Y. Li, *J. Comb. Chem.*, 2007, **9**, 70.
2007JOC43 C. Moriou, M. Thomas, M.-T. Adeline, M.-T. Martin, A. Chiaroni, S. Pochet, J.-L. Fourrey, A. Favre, and P. Clivio, *J. Org. Chem.*, 2007, **72**, 43.
2007JOC2769 Y. Zhang, B. Illarionov, A. Bacher, M. Fischer, G. I. Georg, Q.-Z. Ye, D. V. Velde, P. E. Fanwick, Y. Song, and M. Cushman, *J. Org. Chem.*, 2007, **72**, 2769.
2007T977 Z. Liang, S. Ma, J. Yu, and R. Xu, *Tetrahedron*, 2007, **63**, 977.

Biographical Sketch



Benjamin R. Buckley was born in Nottingham; he studied at Manchester Metropolitan University, where he obtained a B.Sc. in 1999, and Loughborough University, where he obtained his Ph.D. in 2003 under the supervision of Professor Philip C. Bulman Page. Following this, he worked as postdoctoral research associate with Professor Philip C. Bulman Page for a further year and took up his present position as a research fellow at Loughborough University in January 2004. His scientific interests include all aspects of asymmetric synthesis, in particular asymmetric organocatalysis.