

11.01

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: No Extra Heteroatom

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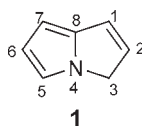
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11.01.1 Introduction

Bicyclic 5-5 systems with one ring junction nitrogen atom and no extra (endocyclic) heteroatoms were first covered by W. Flitsch in CHEC-II(1996) <1996CHEC-II(8)1>.

The parent compound **1** is usually named 3*H*-pyrrolyzine instead of 3*H*-pyrrolo[1,2-*a*]pyrrole, the systematic name; numbering is shown.



Pyrrolizines, partially reduced pyrrolizines, benzopyrrolizines, and pyrrolizinones are covered in this chapter; however, the chemistry of naturally occurring pyrrolizidines and analogous compounds is beyond the scope of this chapter.

11.01.2 Theoretical Methods

A theoretical (*ab initio* and density functional theory (DFT) calculation) and experimental (X-ray and gas-electron diffraction (GED)) study has been devoted to pyrrolizin-3-one **2** and 1,2-dihydropyrrolizin-3-one **3** <2001J(P2)2195>. This work provides definitive structural parameters for **2** (solid and gas phases) and **3**. Good agreement was reached between experimental data (X-ray and GED) and those calculated by *ab initio* methods. Force fields calculated at the B3LYP/6-31G* and B3LYP/6-311+G* level (B3LYP/6-31G* on H-atoms) confirmed the *C_s* symmetry of **2** and **3** (as free molecules) with pronounced distortion of the exocyclic bonds and angles at the bridgehead. As expected, partial hydrogenation on going from **2** to **3** has considerable effect on the bond lengths and angles in the semisaturated ring. A noteworthy effect which was predicted by calculation (in good agreement with X-ray data) concerns the amide group; among the three C–N bonds, the one involved in the amide moiety (N(4)–C(3)) changes the most, shortening by ca. 0.03 Å. The unusual N(4)–C(3) bond lengthening in **2** is consistent with its reluctance to create an antiaromatic 8π-electron system by delocalization (see **Tables 1** and **2**).

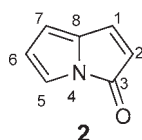


Table 1 Selected data comparing solid-state (XRD), experimental gas-phase (GED, *r*_{h1}) and calculated gas-phase (MP2, *r*_e) geometries for **2**; bond lengths in Å and angles in degrees

Parameter	XRD	GED	MP2
C(7)–C(8)	1.364(2)	1.395(5)	1.387 5
C(6)–C(7)	1.437(2)	1.439(4)	1.436 2
C(5)–C(6)	1.365(2)	1.394(2)	1.386 3
C(1)–C(8)	1.457(2)	1.461(3)	1.458 4
C(1)–C(2)	1.344(2)	1.363(10)	1.360 5
C(2)–C(3)	1.489(2)	1.498(3)	1.494 1
C(4)–C(5)	1.384(2)	1.389(7)	1.381 3
N(4)–C(8)	1.381(2)	1.380(7)	1.376 3
N(4)–C(3)	1.408(2)	1.437(4)	1.431 9
C(3)–O(3)	1.207(2)	1.215(4)	1.209 8
O(3)–C(3)–N(4)	125.22(12)	124.4(9)	125.4
C(5)–N(4)–C(8)	110.03(10)	108.7(7)	110.6
C(3)–N(4)–C(5)	138.68(11)	137.5(6)	138.2
C(3)–N(4)–C(8)	111.13(10)	111.17(10)	111.16
C(7)–C(8)–N(4)	107.85(11)	107.7(4)	107.8
C(1)–C(8)–N(4)	106.85(10)	107.6(4)	107.3
C(1)–C(8)–C(7)	145.23(13)	141.8(6)	144.9

<2001J(P2)2195>.

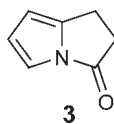
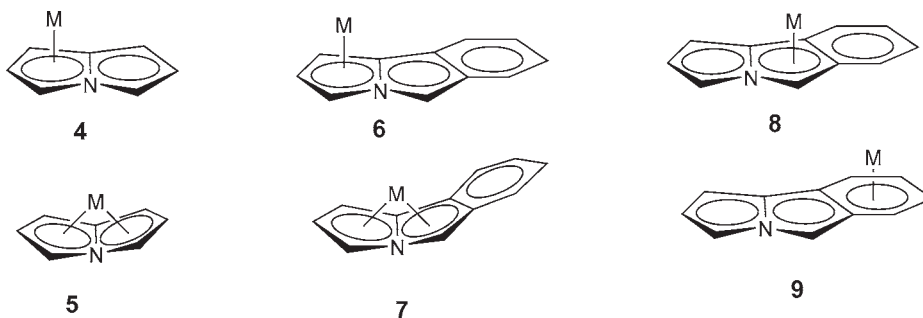


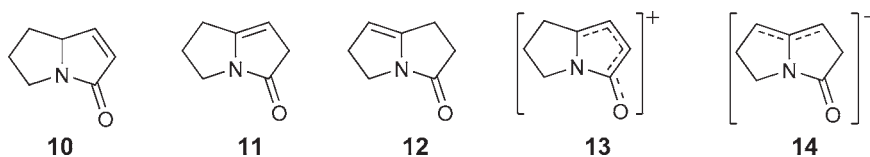
Table 2 Selected data comparing solid-state (XRD) and calculated gas-phase (MP2) for **3**; bond lengths in Å and angles in degrees

Parameter	XRD	MP2
C(7)–C(8)	1.358(2)	1.380 0
C(6)–C(7)	1.437(2)	1.436 7
C(5)–C(6)	1.363(2)	1.384 7
C(1)–C(8)	1.502(2)	1.503 3
C(1)–C(2)	1.545(2)	1.547 9
C(2)–C(3)	1.515(2)	1.526 8
C(4)–C(5)	1.387(2)	1.380 1
N(4)–C(8)	1.390(2)	1.384 6
N(4)–C(3)	1.392(2)	1.406 8
C(3)–O(3)	1.216(2)	1.209 5
O(3)–C(3)–N(4)	124.35(13)	125.4
C(5)–N(4)–C(8)	110.62(12)	111.0
C(3)–N(4)–C(5)	135.58(13)	135.4
C(3)–N(4)–C(8)	113.76(11)	113.7
C(7)–C(8)–N(4)	107.34(12)	107.4
C(1)–C(8)–N(4)	109.71(12)	110.3
C(1)–C(8)–C(7)	149.92(13)	142.3

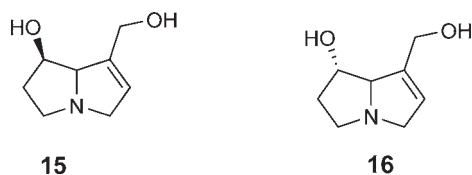
Recent studies (calculation at the B3LYP/6-311+G(d,p) level) on the hapticity of unsolvated monomeric complexes of two pyrrolizine anions with Li, Na, and K were described <2005JCD1157>. These calculations suggest two hapticities for 4-azapentalenyl complexes: η^5 -binding mode **4**, which prevails in the case of lithium complex, and folded structure **5**, which prevails in the case of Na and K analogues. Similar calculations on the benzannulated anion complexes were also undertaken. According to these calculations, η^5 -binding structures **6**, **8**, and η^6 -binding structure **9** are more stable (ca. 1.2 kcal mol⁻¹) than η^6 -binding folded structure **7** in the case of lithium complex. For sodium complex, structures **7** and **9** were the only minima located (**7** is 2.15 kcal mol⁻¹ below **9**). The folded structure **7** was the only minimum located in the case of potassium complex.



A series of calculations was performed in order to rationalize the easy isomerization of pyrrolam A **10** during its synthesis and/or isolation from plants and insects extracts <2004JOC6105>. A partial potential energy surface for the interconversion **11/10** through **13** and **11/12** through **14** was constructed using DFT geometry optimization and energy evaluation (MP2/6-311+G^{*}//B3LYP6-311+G^{*}). The relative stabilities calculated by molecular mechanics and semi-empirical methods could not predict the easy rearrangement of **10** to **11**; only the MP2 model comes close to the experimental data.



Giordan *et al.* <1996JCC156> have performed a theoretical study to compare the relative stability of *endo*- and *exo*-conformers of retronicine **15** and heliotridine **16** alkaloids. The *ab initio* calculations (HF/6-31G*) suggested a greater stability of *exo*-conformers for both diastereomers (retronicine (2.6 kcal mol⁻¹), heliotridine (3.1 kcal mol⁻¹)) in excellent agreement with the available experimental structural data (X-ray and ¹H nuclear magnetic resonance (NMR)). Semi-empirical and molecular mechanics methods appeared inappropriate for these conformational analyses. However, using MM3(92) with reoptimized H-bonding parameters, Giordan <1998JCC1853> has found a set of probable *exo*-puckered conformers for retronicine and *exo/endo*-puckered conformers for heliotridine **16**.

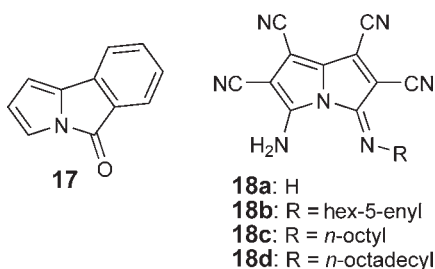


Schmitz *et al.* <2001JPO90> developed two group increment schemes for converting HF/6-31G(d) and B3LYP/6-31G(d) calculated energies of aliphatic amines to estimations of heats of formation. Application to the pyrrolizidine yielded calculated values of -1.09 (HF) and -1.02 (B3LYP) instead of -0.93 kcal mol⁻¹ (experimental).

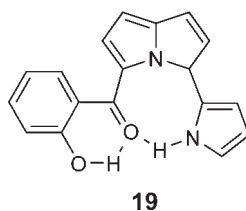
11.01.3 Experimental Structural Methods

11.01.3.1 X-Ray

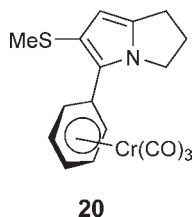
X-Ray investigation of pyrrolizinones **2** and **3** (see [Tables 1 and 2](#)) showed that both compounds are essentially planar with a butterfly angle (about the junction bond) of 3.06° for **2** and (surprisingly) only 1.14° for **3**. Moreover, these X-ray data clearly show that the amide C–N bond is shorter in **3** than in **2** (see discussion in [Section 11.01.2](#)). The same C–N bond elongation was noticed in the case of 5*H*-pyrrolo[2,1-*a*]isoindol-5-one **17** <1999J(P1)2047>. Flamini *et al.* <2001J(P1)3069> reported the X-ray and molecular structure of 5-amino-3-(hex-5-enylimino)-1,2,6,7-tetracyano-3*H*-pyrrolizine **18** which consists of highly planar 5-amino-3-iminopyrrolizine moiety: C(3)–N(14) (1.27 Å) and C(5)–N(9) (1.32 Å).



The X-ray structure analysis carried out for the 6-(2-hydroxybenzoyl)-5-(pyrrolo-2-yl)-3*H*-pyrrolizine **19** unambiguously showed the allylic double bond to be located between C-1 and C-2 <2003AXo321>.

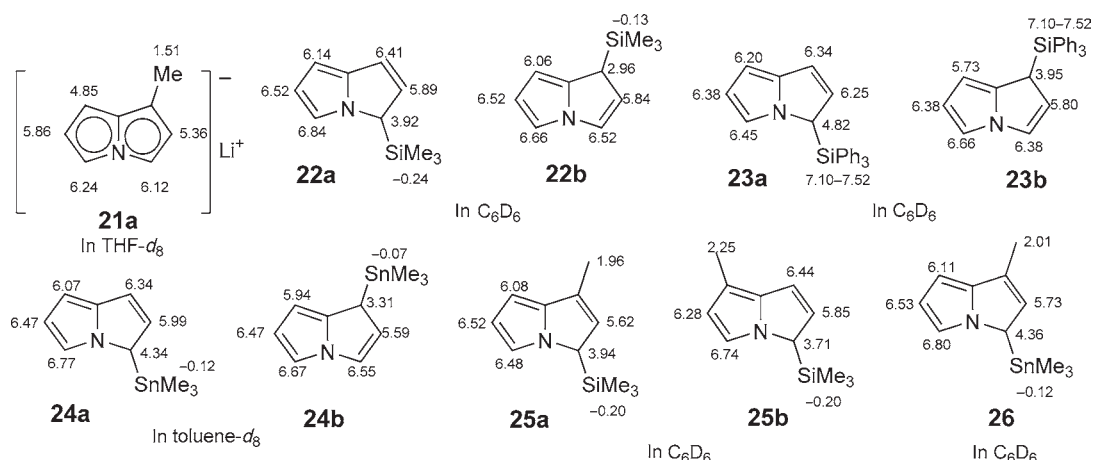


X-Ray data of tricarbonylchromium complex of 6-methylsulfanyl-5-phenyl-2,3-dihydro-1*H*-pyrrolizine **20** showed that the benzene ring is inclined at about 40° to that of the dihydropyrrolizine. Moreover, the tricarbonylchromium group is positioned *syn* to the nitrogen atom <1998J(P1)1175>.



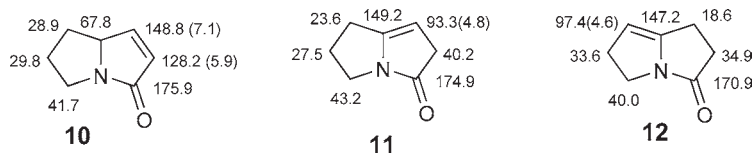
11.01.3.2 NMR Spectra

Typical NMR data were compiled in CHEC-II(1996) <1996CHEC-II(8)2> for 3*H*-pyrrolizine **1**, its lithium salt, the pyrrolizin-3-one **2**, and its regioisomer (pyrrolizin-2-one). More recently, Kissounko *et al.* <1998JOM(556)145> reported the ¹H chemical shifts of the parent pyrrolizine anion and anion **21a** as well as those of their silylated or stannylated derivatives **22–26**.



¹¹⁹Sn Chemical shifts were also reported for isomers **24a** (115.3 ppm) and **24b** (116.15 ppm). The reported ²*J*_{Sn–H} for **24** and **26** range between 42 and 54 Hz except ²*J*_{H(1)–Sn} for **24b** which is surprisingly high (95 Hz)!

By using ¹H and ¹³C NMR spectroscopy, Watson *et al.* <2004JOC6105> could assign the structure of each pyrrolam regioisomer **10–12**.



Owing to signal overlap, only partial assignment ¹H (6.55–7.99 ppm) and ¹³C resonances were possible for anions **6–9**. Of course, most of the compounds described in this chapter were well characterized mainly due to the NMR techniques.

11.01.3.3 UV and IR Spectroscopy

Ultraviolet (UV) data are seldom reported for new pyrrolizine derivatives. Flamini *et al.* <2001J(P1)3069> described the optical spectra of 5-amino-3-imino-1,2,6,7-tetracyano-3*H*-pyrrolizines **18**, which exhibit an intense broad absorption band centered at ca. 580 nm.

No characteristic IR data were reported for pyrrolizines or dihydropyrrolizines. An almost complete set of vibrational frequencies was deduced by combining an infrared (IR) and a Raman spectrum of pyrrolizinone **2** <2001J(P2)2195>. The experimental values thus obtained were used to scale the theoretical complete set of vibrational frequencies of **2**. Using the same scaling constant, the authors proposed a set of calculated vibrational frequencies for dihydropyrrolizinone **3**.

11.01.3.4 Mass Spectrometry

This subject was not covered in CHEC-II(1996) <1996CHEC-II(8)1>. This technique is frequently employed for identification of metabolites in extracts from leaving organisms. The parent ions of pyrrolizine derivatives are usually observed by mass spectrometry even in electronic impact mode. The mass spectrum of the thallium salt of 3*H*-pyrrolizine was described by Kissounko *et al.* <1998JOM(556)145> as follows: (electronic ionization (EI), 70 eV) *m/z*: 309 (23%, M^+ for ^{205}Tl); 307 (9.5%, M^+ for ^{203}Tl); 205 (100%, $^{205}\text{Tl}^+$); 203 (43%, $^{203}\text{Tl}^+$); 104 (76%, $\text{C}_7\text{H}_6\text{N}^+$); 66 (35%, $\text{C}_4\text{H}_4\text{N}^+$); 39 (38%, C_3H_3^+). The parent ions M^+ of pyrrolizinones are also detected <2005JOC6629> and, generally, a characteristic loss of carbon monoxide (-28) is observed <1981JOC2809>. Ji *et al.* <2000MI117> reported a rapid and accurate method for the pyrrolizinones' molecular weight determination by matrix-free laser desorption/ionization time-of-flight mass spectrometry (LDI-TOF-MS) technique.

11.01.4 Thermodynamic Aspects

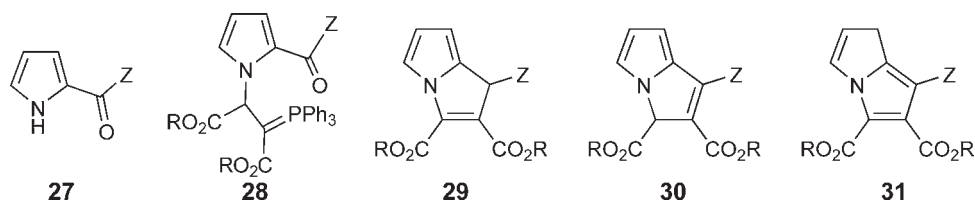
11.01.4.1 Aromaticity

The pK_a value (~ 29) attributed by Okamura and Katz <1967T2941> to pyrrolizine seems too high, as was pointed out by Flitsch <1996CHEC-II(8)3>. Kissounko *et al.* <1998JOM(556)145> reported the preparation of pyrrolizine anion by using thallium ethoxide (for deprotonation of 3*H*-pyrrolizine) which is indicative of a rather moderate pK_a value for the pyrrolizine anion. The benzannulated analogue of the latter was reported by Bermingham *et al.* <2005JCD1157>, who described its preparation by reacting its conjugate acid with potassium at low temperature. No data were given concerning the pK_a value of this *a priori* aromatic anion.

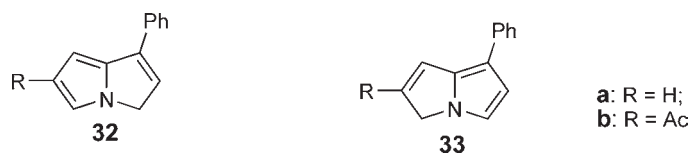
11.01.4.2 Tautomerism

As summarized in CHEC-II(1996) <1996CHEC-II(8)3>, 3*H*-pyrrolizinones are more stable than the corresponding 1*H*-pyrrolizinones. Moreover, for substituted ones, there is equilibrium between 3*H*- and '5*H*'-tautomer depending on the position and the electronic nature of the substituent(s) of the pyrrolizine framework. Thus, treatment of pyrrolizine anion **4** with group 14 electrophiles (R_3SiCl and R_3SnCl) gives a mixture of 1-substituted-1*H*- and 3-substituted-3*H*-pyrrolizines; the latter slightly predominate in the case of tin derivatives and the former predominate in the case of silylated ones. In the case of 1-methylpyrrolizine anion, only the 1-methyl-3-substituted-3*H*-pyrrolizine isomers were detected when the reaction was performed in tetrahydrofuran (THF). In 1,2-dimethoxyethane (DME), both 3- and 5-silylated regioisomers (**25a/25b** = 3/1) were obtained exclusively as their 3*H*- and '5*H*'-tautomer, respectively <1998JOM(556)145>.

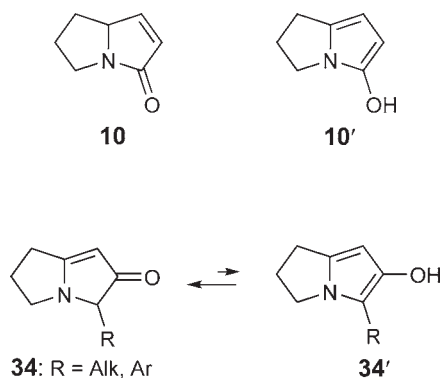
1*H*-Pyrrolizine **29** could be obtained from the corresponding stable phosphorus ylide **28** (with $Z = \text{H}$), which was prepared by reacting dialkyl acetylenedicarboxylate with triphenylphosphine and 2-acyl-1*H*-pyrrole **27** <1999JCM382>. Only 3*H*-tautomer **30** was obtained when $Z = \text{CF}_3$ <2006ARK55>, while 1*H*-tautomers **31** were exclusively isolated when starting from pyrrole **27** bearing $Z = \text{CO}_2\text{R}$ or CONHR <2001T5873>.



Previously, Llopart and Joule <2004ARK20> obtained a mixture of tautomers **32a** and **33a** when 2-benzoylpyrrole was reacted with vinyltriphenylphosphonium bromide and sodium hydride. Starting from 4-acetyl-2-benzoylpyrrole, the same reaction only resulted in the (somewhat unstable) tautomer **32b**. Surprisingly, no 1*H*-tautomers were observed in these cases. Similar tautomerization was observed in the case of 3*H*-pyrrolizines bearing 2(6)-diethylphosphonate substituent <1996PS275>.



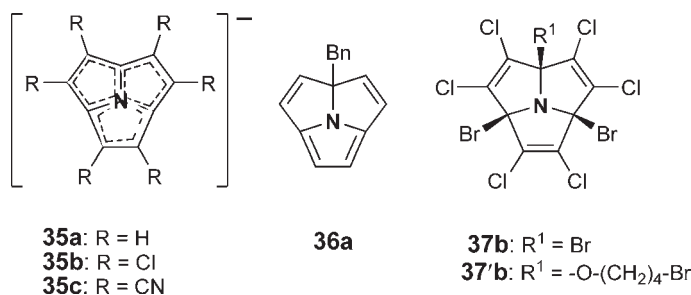
The enol form **10'** of pyrrolam **A 10** could not be detected despite its aromatic character [\[2004JOC6105\]](#). Also, its pyrrolinone analogues **34** exist mainly as β -enaminones [\[1985TL833\]](#); the tautomeric hydroxypyrrole **34'** was only observed when R = CO₂Et (**Scheme 1**) [\[1988JOC5680\]](#).



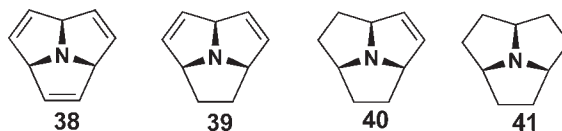
Scheme 1

11.01.4.3 Miscellaneous

Recently, Mascal and Cerón Bertran [\[2005JA1352\]](#) reported the preparation and characterization of **35** (aza-analogue anions of triquinacenes) which are stable enough in THF solution (in the absence of acid). Moreover, the hexachloro anion **35b** could be isolated as tetraethylammonium salt by column chromatography on alumina. As expected, anion **35a** was more nucleophilic than **35b**. Indeed, only the former could be benzylated leading to **36a**. However, **35b** reacts easily with molecular bromine at low temperature yielding the corresponding α,α,α -tribromide **37b** or dibrominated ether **37'b** when this bromination was conducted in THF.



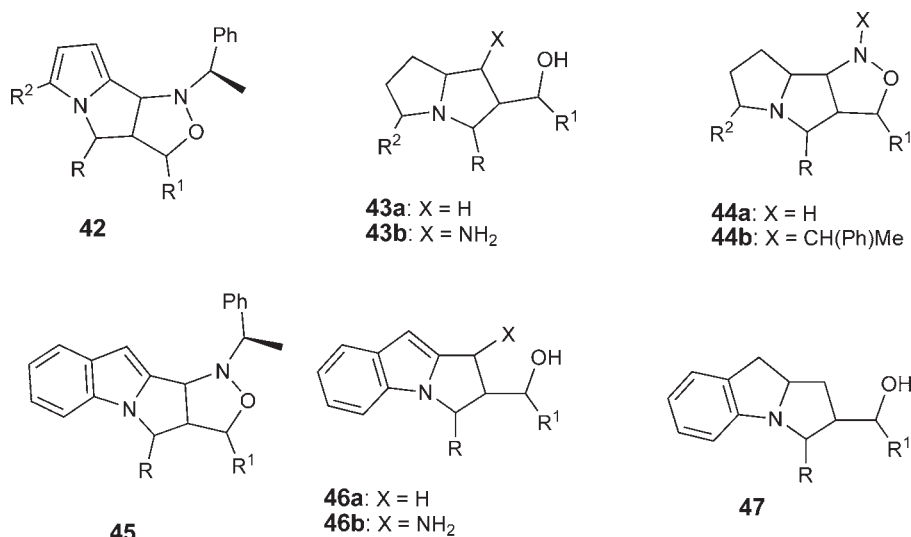
Vianello and Maksić [\[2005TL3711\]](#) reported a theoretical prediction (DFT calculations) of the acidity of the conjugate acid of azatriquinanes **35a** and its still unknown hexacyano analogue **35c**. These calculations predict a pK_a value of 10.7 (in dimethyl sulfoxide (DMSO)) for the couple involving anion **35a** and -26.5 for that involving anion **35c**. Earlier, Jiao *et al.* [\[2001JOC3902\]](#) described a DFT computation devoted to the enthalpies of formation and hydrogenation, ionization potential, proton affinities of the neutral aza-tricyclic compounds **38–41**, and the spin properties of their corresponding radical ammoniums.



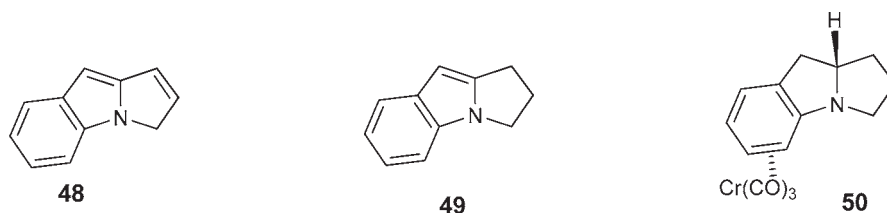
11.01.5 Reactivity of Fully Conjugated Rings

11.01.5.1 Reduction

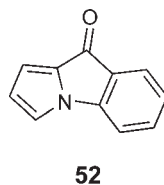
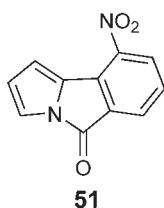
As expected, when using Pd/C in alcohols at room temperature, exclusively hydrogenation of the C(1)–C(2) double bond in **32b** takes place; the pyrrole ring remains unsaturated despite an overnight reaction period <2004ARK20>. Blockhuys *et al.* <2001J(P2)2195> described once more the selective enone C=C bond reduction of pyrrolizin-3-one **2** under mild conditions (1 atm H₂, Pd/C), as described earlier <1971CB2170>. Beccalli *et al.* <2002EJO2080, 2001T8323> studied the hydrogenation of substrate **42** using Pd(OH)₂ under atmospheric pressure of hydrogen in methanol, and found that the pyrrole ring saturation requires the presence of HCl. Using 1 equiv of HCl, a mixture of **43a** and **43b** was obtained. When a large amount of HCl is used (e.g., 20 equiv), the pyrrole nucleus saturation becomes faster than the cleavage of the isoxazolidine ring and hydrogenolysis of the benzylic and pseudobenzylic amino group, leading selectively to a mixture of compounds **44a** and **44b**. In the absence of hydrochloric acid, only hydrogenolysis of N–O and N–Bn bonds took place with no saturation of the pyrrole ring. A similar study was performed with the benzo-annulated analogues **45**. The use of Pd(OH)₂ in methanol, or Pd/C in acetic acid, resulted in the *N*-debenzylation and isoxazolidine ring cleavage leading to compounds **46**. Semireduction of the indole moiety, leading to **47**, requires the presence of hydrochloric acid <2000JOC8924>.



As expected, under a hydrogen atmosphere in the presence of Pd/C in ethanol, the benzannulated pyrrolizine **48** leads to the dihydropyrrolizine derivative **49**. However, semireduction of the pyrrole ring could be performed via the tricarbonyl chromium complex of **49** with various hydrides. Use of cyanoborohydride in trifluoroacetic acid (TFA) gave the best results for compound **50**, both in terms of chemical yield (92%) and diastereoselectivity (90% of the *trans*-isomer) <2000TL1123>.



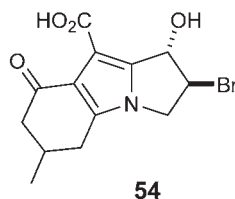
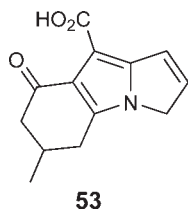
The pyrrole ring reduction in the benzannulated pyrrolizin-3-one **51** seems to take place easily in the presence of Pd/C in methanol under atmospheric pressure of hydrogen, at room temperature, and, noteworthy, under neutral conditions. The nitro group is also reduced under these mild conditions <2001JME4615>. Unlike **51**, under the same conditions, 1,2-diphenylpyrrolizin-3-one gave the 1,2-dihydro analogue with no pyrrole ring reduction. The pyrrole nucleus saturation of this pyrrolizinone required Adams catalyst <1996CHEC-II(8)4>. As expected, reduction of 1,2-dihydropyrrolizin-1-one takes place smoothly with sodium borohydride in methanol <2002T10407>. Deoxygenation of the benzannulated pyrrolizin-1-one **52** was performed under Wolff–Kishner conditions in 49% yield <2004JOC5476>.



The azatriquinane **36a** which may be regarded as an annulated bis-pyrrolizine readily undergoes stereoselective hydrogenation in presence of rhodium on alumina, leading to the fully saturated tricyclic compound with a *trans* relative orientation between the benzyl group and the two hydrogen atoms located on the two other junctions' carbon atoms <2005JA1352>.

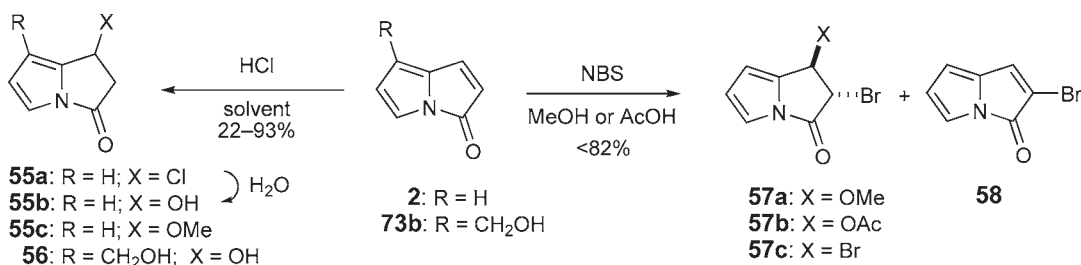
11.01.5.2 Electrophilic Attack

No significant examples of electrophilic attack on 3*H*-pyrrolizines were reported since CHEC-II(1996). Nevertheless, treatment of the tricyclic pyrrolizine **53** with aqueous bromine in THF afforded, as expected, the corresponding bromohydrin **54** <1997T4549>.



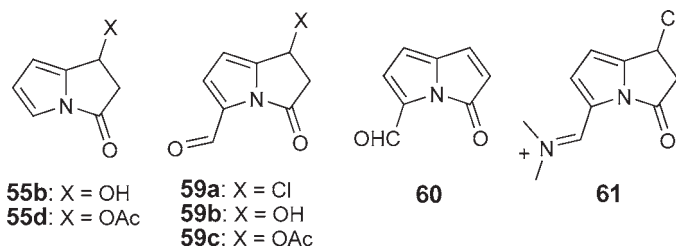
Electrophilic substitutions at the pyrrole nucleus were described only with 1,2-dihydropyrrolizines which react with the same regioselectivity as would do equivalently substituted monocyclic pyrroles.

McNab and Thornley reported a detailed study related to the reactivity of 3*H*-pyrrolizin-3-one **2** toward various electrophilic reagents <2000J(P1)3584>. In the presence of dry hydrochloric acid in dichloromethane, pyrrolizinone **2** gave in 93% yield the corresponding electrophilic addition compound **55a** which easily undergoes nucleophilic substitution when treated with water, thus leading to **55b**. The same sequence carried out with 7-hydroxymethyl-3*H*-pyrrolizin-3-one afforded in 63% yield, 1-hydroxy-7-hydroxymethylpyrrolizin-3-one **56**, which constitutes the base of a number of alkaloids isolated from various *Senecio* species <1991P2691>. Treatment of **2** with dry HCl in refluxing methanol gives only the methoxy compound **55c**; this reaction goes either through **55a** or directly by trapping of the transient pseudobenzylic cation intermediate. Also, pyrrolizinone **2** was allowed to react with *N*-bromosuccinimide (NBS), either in methanol or acetic acid leading to the corresponding oxobromination adducts **57** in up to 82% yield. These results were not reproducible; for instance, in some cases, **57b** was obtained along with the fully conjugated compound **58** and traces of the dibromo derivative **57c**. Under free radical conditions (NBS, PhCOO₂COPh) pyrrolizin-3-one **2** gives only traces of the expected derivative **57c**, and it probably undergoes spontaneous β -elimination leading to **58** which was isolated in 55% yield (Scheme 2).

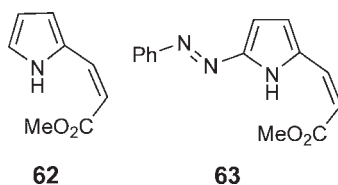


Scheme 2

Attempts to perform the formylation of **2** under Vilsmeier conditions (POCl_3 , dimethylformamide (DMF)) in refluxing dichloroethane (15 min) followed by work-up with an aqueous solution of sodium acetate afforded a mixture of recovered **2** and six other products: **55b**, **55d**, **59a-c**, and **60**. As outlined by the authors [<2000J\(P1\)3584>](#), formylation may not take place directly on **2**; they suggested a plausible mechanism, assuming that all products of this reaction, including recovered **2**, would arise from the hydrochlorination compound **55a** which may partially undergo formylation leading to **61**. After work-up, **55a** leads to **2**, **55b** and **55d**, whereas **61** leads to **59** and **60**.

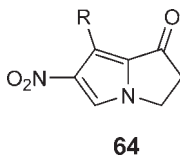


The same authors [<2000J\(P1\)3584>](#) studied the reactivity of **2** toward benzenediazonium (chloride or tetrafluoroborate) salts. No diazo coupling took place under neutral or slightly acidic conditions. However, under basic conditions (NaOH in $\text{H}_2\text{O}/\text{MeOH}$), a mixture of **62** and **63** was obtained. This result clearly indicates that the diazo coupling takes place through the anion of **62** which arises from the base-catalyzed methanolysis of amide **2** in which the pyrrole ring is obviously not nucleophilic enough.

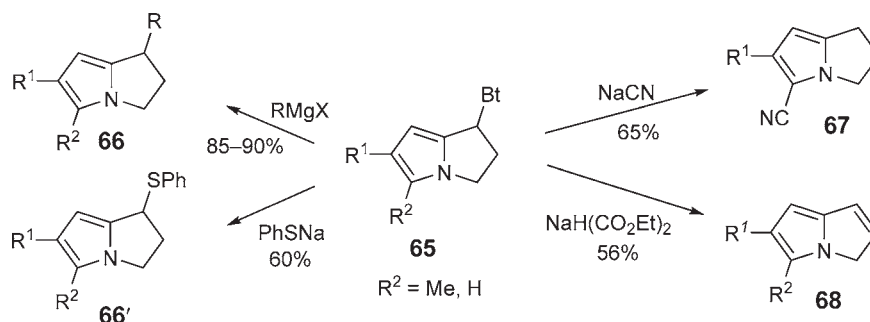


11.01.5.3 Nucleophilic Attack

Pyrrolizine itself is not prone to nucleophilic attack. Treatment of 3*H*-pyrrolizine as well as 1-methyl-3*H*-pyrrolizine with *n*-butyllithium gives the corresponding conjugated bases **4** and **21a**, respectively [<1998JOM\(556\)145>](#). As with the pyrrole nucleus, pyrrolizines show no electrophilic behavior. On the other hand, most of the additions described with pyrrolizin-3-one **2** were performed via electrophilic additions as seen above [<2000JCS\(P1\)3584>](#), except in the case of the soft reducing agent, sodium borohydride, which reacts with **2** in ethanol via a conjugate 1,4-addition to afford the corresponding 1,2-dihydro-3*H*-pyrrolizin-3-one **3** [<1999J\(P1\)2049>](#). As expected, treatment of 2,3-dihydro-1*H*-pyrrolizin-1-ones **64** with sodium borohydride leads to the corresponding pseudobenzylic alcohols [<2002T10407>](#).



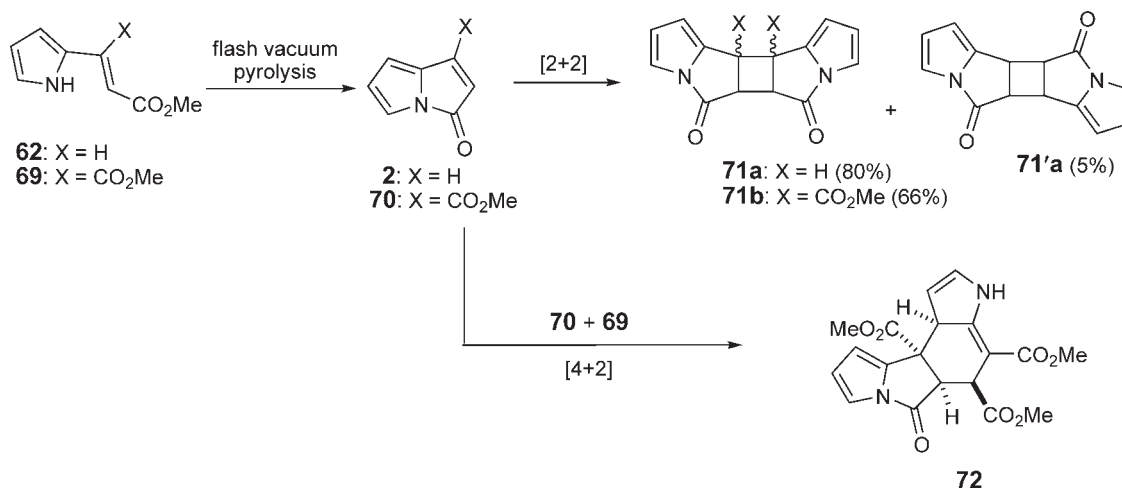
Katritzky *et al.* [<1997JOC4148>](#) achieved some transformations of 1-(benzotriazol-1-yl)-2,3-dihydro-1*H*-pyrrolizine **65** based on nucleophilic attacks either at 1- or 5-position. Indeed, reaction of **65** with Grignard reagents and thiophenolate gives smoothly the *ipso*-substitution of the benzotriazol-1-yl group leading to **66** and **66'**, respectively, while sodium cyanide in DMF leads to **67** via nucleophilic substitution of benzotriazol-1-yl group via a conjugated nucleophilic attack on the pyrrole nucleus and concerted or subsequent departure of benzotriazole anion, followed by rearomatization of the pyrrole nucleus. Treatment of **65** with the malonate anion resulted in an elimination of benzotriazole leading to the corresponding 3*H*-pyrrolizine **68** (Scheme 3).



Scheme 3

11.01.5.4 Cycloaddition and Cyclization

Since the examples compiled in CHEC-II(1996) <1996CHEC-II(8)7>, no new examples of cycloaddition involving pyrrolizines have been described. However, Comer *et al.* reported two types of cycloaddition involving the pyrrolizin-3-one moiety. Flash vacuum pyrolysis (FVP) of **69** leads to 1-carbomethoxy-3*H*-pyrrolizin-3-one **70**, which spontaneously dimerizes to give [2+2] cycloadduct **71b** as a mixture of *syn*- and *anti*- (head-to-head) stereoisomers, whose structures were secured by X-ray analysis <1996CCC1083>. Moreover, it was also found that **70** reacts with its precursor **69** leading to the cyclocondensation compound **72** via a formal [4+2] cycloaddition <1996AXC3064>. Unlike **70**, the parent pyrrolizin-3-one **2** needs photochemical activation to promote its dimerization leading to *syn*- and *anti*-**71a** and their (head-to-tail) regioisomer **71'a**, which was isolated as a single *syn*-stereomer <2000ARK252>. Assignment of structures and relative stereochemistry of dimers **71a** and **71'a** rely mainly on NMR data. The ratio of regioisomers **71a**/**71'a** is highly dependent on reaction conditions: in methanol an almost equimolar mixture of the three isomers was obtained; meanwhile in the presence of slight excess of benzophenone (triplet sensitizer) the photodimerization becomes faster and more selective in favor of the (head-to-head) regioisomer **71a** which was isolated in 80% yield along with 5% of the (head-to-tail) regioisomer **71'a**. As stated by the authors, these photochemical reactions involving **2** were initially performed in order to achieve a photochemically promoted regioselective conjugate 1,4-addition of alcohols by analogy with similar experiments performed with butenolides <1993J(P1)2141>. No nucleophilic 1,4-addition adducts were detected in the case of substrate **2** (Scheme 4).

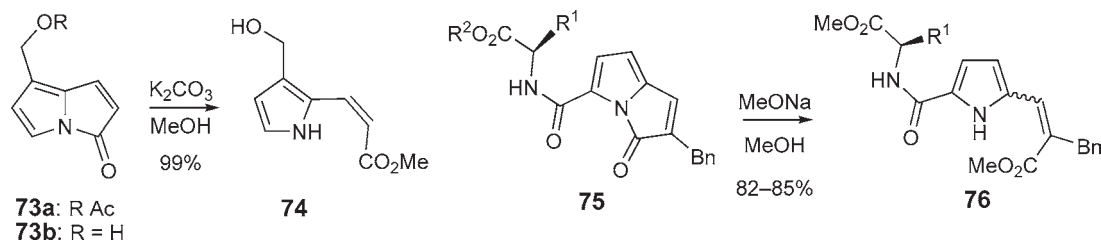


Scheme 4

11.01.5.5 Ring Openings

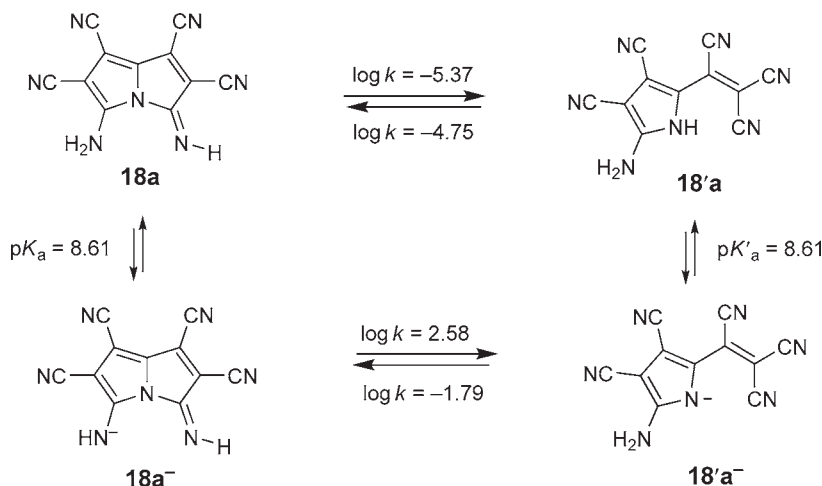
As seen in Section 11.01.5.2, pyrrolizinone **2** easily undergoes ring opening in the presence of aqueous sodium hydroxide during the base-catalyzed diazo coupling, leading to the corresponding *cis*-acrylate **62**. In order to get

7-hydroxymethyl-3*H*-pyrrolizin-3-one **73b** by selective methanolysis of the acetate moiety, compound **73a** was allowed to react with anhydrous potassium carbonate in methanol at room temperature, but even under such mild base-catalyzed conditions, **73b** undergoes quantitative methanolysis of the pyrrolizinone moiety to give exclusively the (*Z*)-methyl acrylate **74** <2000J(P1)3584>. Easy base-catalyzed methanolysis was also observed with pyrrolizinone derivatives **75** where the 2-benzyl-5-carbonyl-3*H*-pyrrolizin-3-one substructure acts as a characteristic red tag for various amino acids. The stereochemistry of the resulting acrylates **76** depends on the nature of the amino acid bearing this pyrrolizinone moiety; only (*Z*)-isomers were obtained in the case of leucine and phenylalanine whereas the glycine derivative affords a mixture of (*Z*)- and (*E*)-isomers (Scheme 5) <2002TL3673>.



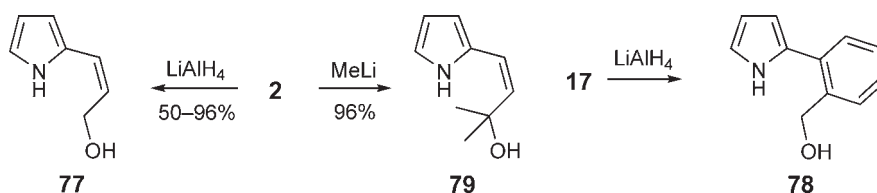
Scheme 5

Compound 5-amino-3-imino-1,2,6,7-tetracyano-3*H*-pyrrolizine **18a** was found to be stable only in the solid state or in anhydrous organic solvents. Addition of aqueous solutions at pH > 5 to such organic solutions of **18a** resulted in a rapid changes of its UV spectra indicating the absence of **18a** and the formation of other species <2002PCA200>. A kinetic study (stopped flow in the pH range from -0.5 to +13) of the isomerization between **18a** and **18'a⁻** has revealed the existence of the corresponding conjugate species, that is, **18a⁻** and **18'a**. This study also allowed the p*K*_a value determination for each couple as well as the forward and reverse isomerization rates between acid species **18a**/**18'a** and between basic ones **18a⁻**/**18'a⁻**. The monocyclic base **18'a⁻** is the only species observed at pH > 7. As expected, at pH < 2, an equilibrium is established between the acidic forms where the pyrrolizinone **18a** predominates: **18a**/**18'a** = ca. 79/21. However, at low pH, slow decomposition of **18a** takes place via its protonated form (Scheme 6).



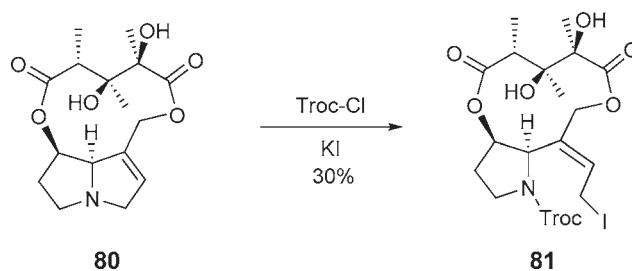
Scheme 6

Unlike with sodium borohydride (see Section 11.01.5.2), pyrrolizin-3-one **2** reacts with lithium aluminumhydride mainly as an amide. No conjugate addition occurs, and only the reductive lactam cleavage takes place to give stereoselectively the (*Z*)-allylic alcohol **77**. Similarly, benzo-annulated pyrrolizin-3-one **17** gives the corresponding benzylic alcohol **78**. The same reactivity was observed with organometallics such as methyllithium which gives exclusively the tertiary (*Z*)-allylic alcohol **79** (Scheme 7).



Scheme 7

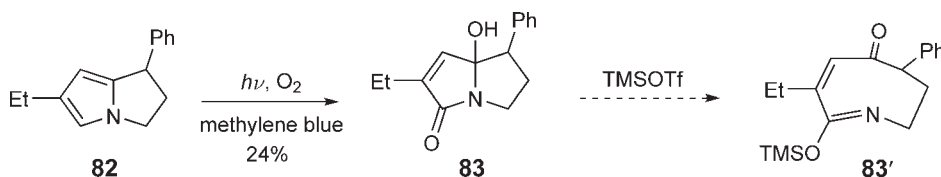
As with many $N(\text{sp}^3)$ -azaheterocycles, monocrotaline **80** undergoes regioselective ring opening leading to **81** when treated with 2,2,2-trichloroethylchloroformate (Troc-Cl) in presence of potassium iodide (Scheme 8) <1999JA2951>.



Scheme 8

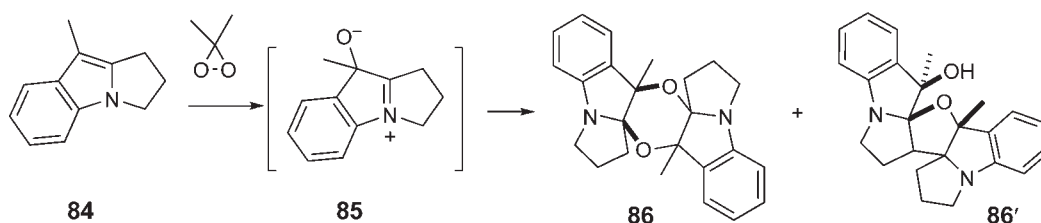
11.01.5.6 Miscellaneous

Under singlet oxygen conditions (O_2 , $h\nu$, methylene blue), the dihydropyrrolizine **82** gives the hydroxy-pyrrolidinone **83** in only 24% yield. The authors speculated that a possible ring opening promoted by a suitable silylating agent such as TMSOTf would lead to the azadiene **83'** (Scheme 9) <2004ARK20>.



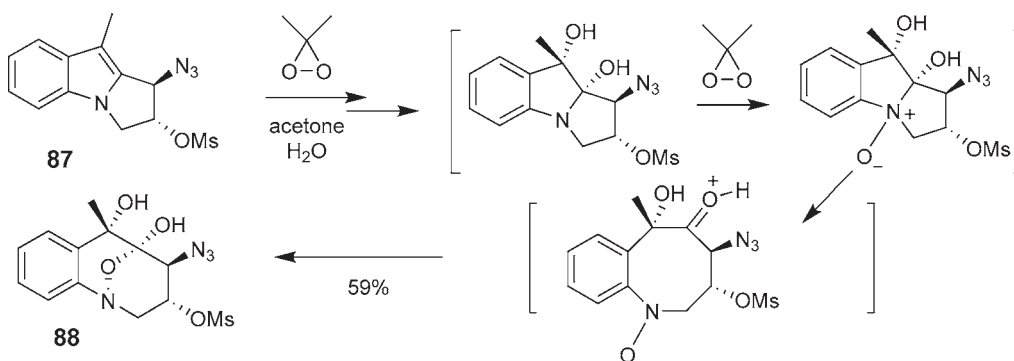
Scheme 9

Upon treatment with dimethyldioxirane (DMDO), benzannulated dihydropyrrolizine **84** afforded two dimers **86** and **86'**, each as a mixture of two diastereomers <1997JA1159>. The zwitterionic species **85** is postulated as intermediate in these dimerizations (Scheme 10).



Scheme 10

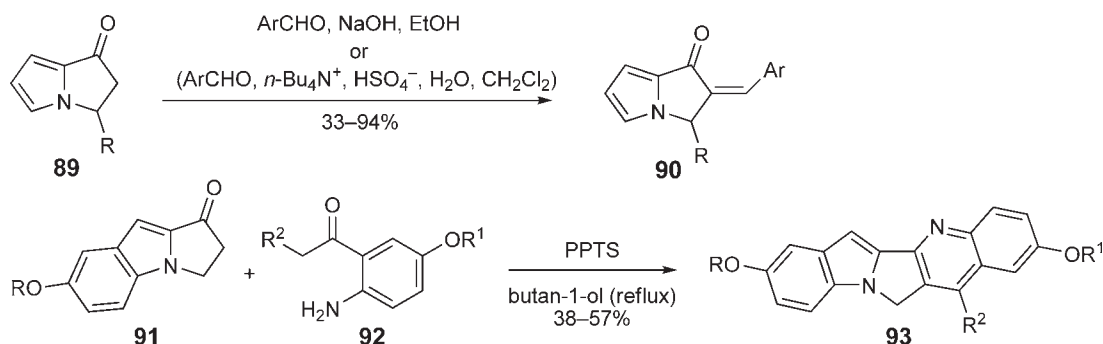
Reaction of dihydropyrrolizine **87** with DMDO in aqueous acetone gives the oxidative rearrangement compound **88** in 59% yield <2003OL785>. A plausible mechanism was proposed as shown in **Scheme 11**.



Scheme 11

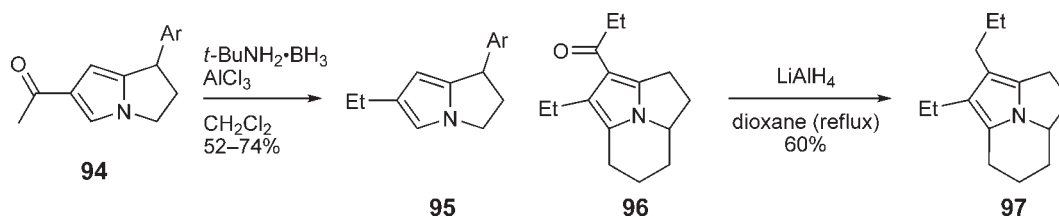
11.01.6 Reactivity of Substituents Attached to Ring Carbon Atoms

3-Aryldihydropyrrolizin-1-ones **89** were involved in aldolization reactions with a number of aromatic aldehydes, either in ethanolic solution of sodium hydroxide or using tetrabutylammonium hydrogenosulfate as catalyst in a heterogeneous system ($\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$). Whatever the conditions used, these aldolizations led selectively to the (*Z*)-stereoisomers **90** <2000BMC945>. Benzo-annulated analogues **91** were reacted with various 2-acylanilines **92** leading with low to moderate yields to **93** according to Friedländer reaction (**Scheme 12**) <2004BML2363>.



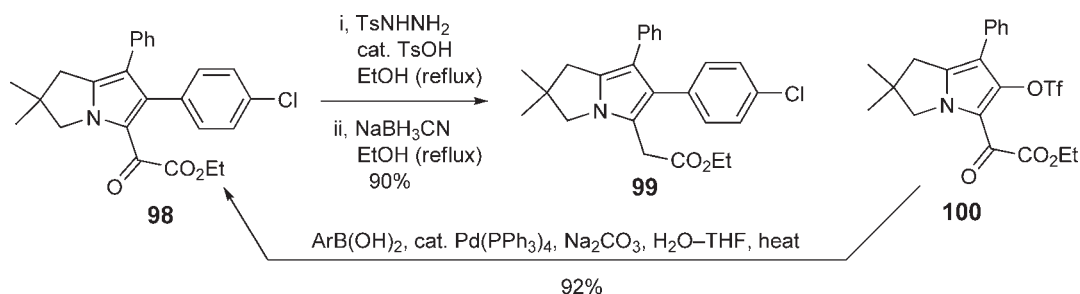
Scheme 12

Carbonyl groups positioned on the pyrrole nucleus of dihydropyrrolizines may undergo reduction to the corresponding pseudobenzyl methylene under various reductive conditions. Thus, treatment of 1-aryl-6-acetyl-1,2-dihydropyrrolizines **94** with *t*- $\text{BuNH}_2\cdot\text{BH}_3$ complex and AlCl_3 resulted in the reduction of the acetyl group into ethyl as shown in **95** <2004ARK20>. Similar reduction was observed when **96** was treated with LiAlH_4 thus leading to alkaloid (*R*)-(+)-myrmicarin 217 **97** (**Scheme 13**) <2000JOC2824>, which was discovered in the secretions of *Myrmecaria* ants <1996T13539>.



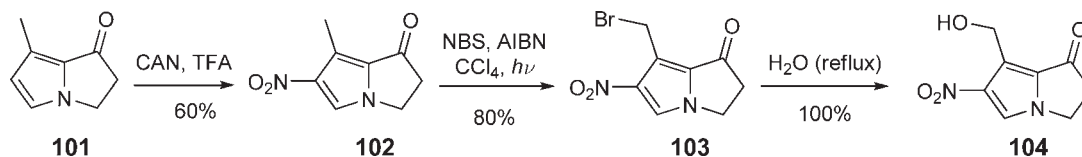
Scheme 13

Catalytic reduction (HCO_2NH_4 , Pd/C) of the ketoester moiety of dihydropyrrolizine **98** was nonselective, since the desired compound **99** was obtained along with the dechlorinated analogue. Chemoselective reduction of the keto group of **98** was performed by reduction of the corresponding tosylhydrazone with NaBH_3CN in 90% yield [<1999T5145>](#). Compound **98** was synthesized by Suzuki coupling of triflate **100** with (4-chlorophenyl)boronic acid in the presence of $\text{Pd}(\text{PPh}_3)_4$ and 5.4 M aqueous potassium hydroxide in refluxing THF (**Scheme 14**). Under the Suzuki or other cross-coupling reaction conditions, analogues of triflate **100** without the ketoester substituent, the expected coupling compounds, were obtained in less than 10% yield [<1999T5145>](#).



Scheme 14

In an attempt to oxidize the methyl group of danaidone **101** to the corresponding formyl group with ceric ammonium nitrate (CAN) in acetic or TFA, Rajaraman and Jimenez [2002T10407](#) obtained the nitration compound **102** as the major compound. However, scaling up under the same conditions gives a mixture of products. Even under refluxing reaction conditions, CAN could not give oxidation at the pseudobenzyl carbon atom of the deactivated dihydropyrrolizone **102**. Finally, the desired pseudobenzyl alcohol **104** was synthesized in two steps starting from **102**; bromination under free radical conditions (NBS, 2,2'-azobisisobutyronitrile (AIBN), CCl₄, *hν*) afforded **103** which undergoes quantitative nucleophilic substitution in refluxing water leading to **104** (Scheme 15). When applied to the danaidone **101**, this free radical bromination procedure resulted in the bromination of the pyrrole ring which is not deactivated as in **102**.



Scheme 15

11.01.7 Ring Synthesis Classified by Number of Ring Atoms in Each Component

In this section, whatever the saturation level of the aza-bicyclic compound considered, we will focus only on the bond-formation step which leads to the azabicyclic skeleton of pyrrolizines and their derivatives. The reported routes will be classified according to the number of atoms in the newly formed bond, as already done in CHEC-II(1996) <1996CHEC-II(8)12> and shown in **Figure 1**. Not all of these modes were equally employed; the most popular are 1,8-; 1,2-; 2,3-; 3,4-; 1,8,2,3-; 1,2,3,4-; and 1,8,3,4-bond formations. Each of these modes will be described in this section; all other bond-formation modes will be discussed in **Section 11.01.9**.

11.01.7.1 1,8-Bond Formation

Despite the development of some new methods for this strategy of bicyclic system formation, the intramolecular C-acylation of pyrrole is still frequently employed. This reaction may be performed starting from *N*- β -cyanoethylpyrroles as well as starting from their acid, ester, and even amide analogues.

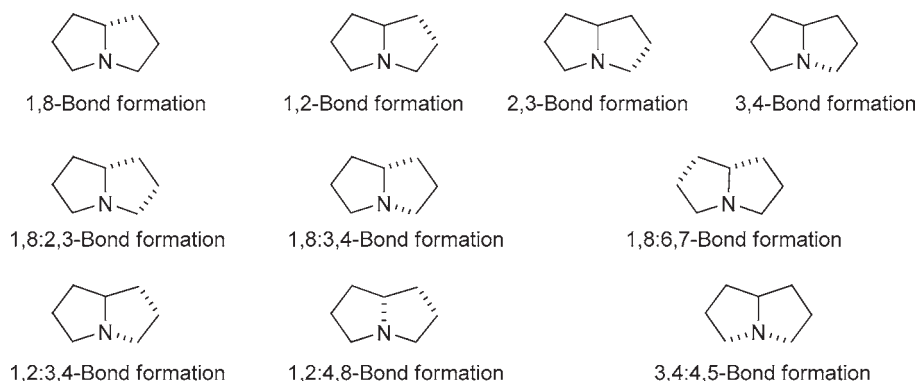
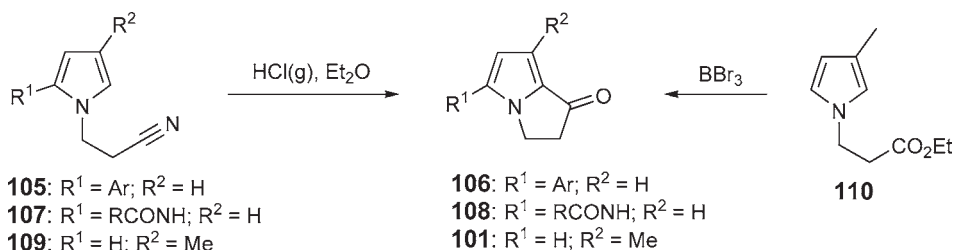


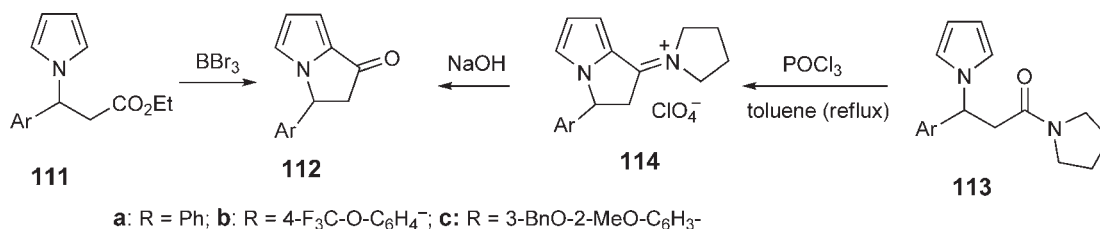
Figure 1 Various modes of bond formation.

When submitted to the Houben–Hoesch cyclization (dry HCl in Et₂O or THF), 2-aryl-1-β-cyanoethylpyrroles **105** have led to a series of 5-aryl-1,2-dihydropyrrolizin-1-ones **106**. Some of the latter showed remarkable anti-inflammatory and/or analgesic activities on mice <2003CCL565>. Analogues **108** were also obtained following the same method starting from pyrrole derivatives **107** <2003JIC851>. This cyclization was already described with substrate **109** as selectively leading to danaidone **101** in good yield <1966JA1305>. More recently, Rajaraman and Jeminez <2002T10407> described this cyclization with variable yields (0–25%) in danaidone **101**; pyrrole polymerization was suspected because of the difficulty in controlling the HCl concentration. For this reason, they employed the ester analogue **110** as substrate for this cyclization; thus, danaidone **101** was isolated in 75% yield using BBr₃ as catalyst, according to an earlier procedure described by Jefford *et al.* (Scheme 16) <1995HCA1511>.



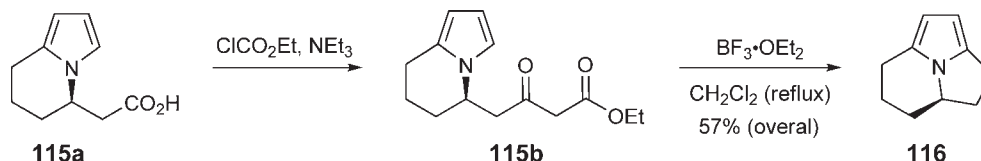
Scheme 16

Sonnet *et al.* <2000BMC945> had already used this ester cyclization catalyzed with BBr₃, for the synthesis of 3-arylpyrrolizin-1-ones **112**, which were evaluated as potential aromatase inhibitors. This method could not be applied to the substrate **111b**, due to the sensitivity of the trifluoromethoxy group to boron tribromide. The corresponding dihydropyrrolizinone **112b** could be synthesized via the Vilsmeier cyclization; treatment of amide **113b** with phosphorus oxychloride in refluxing toluene led to an iminium ion which was isolated as its perchlorate salt **114b**. Treatment of the latter with sodium hydroxide afforded the expected product **112b**. The same authors had previously employed this Vilsmeier method for the cyclization of **113a** <1993H(36)2129> and, recently, Lisowski *et al.* <2004JME1448> prepared **112c** in 53% yield via the same procedure (Scheme 17).



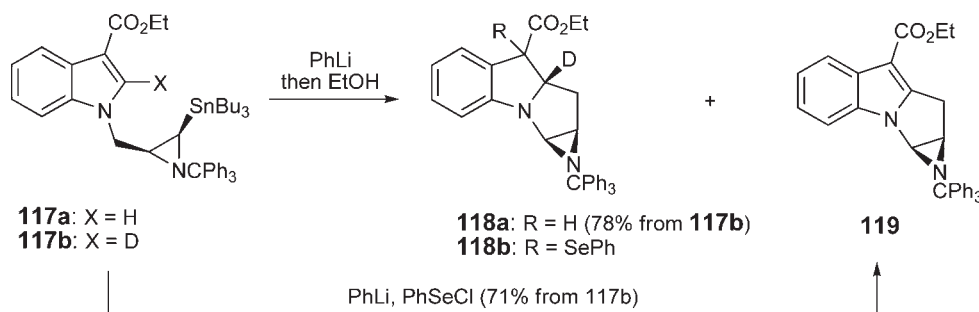
Scheme 17

Sayah *et al.* <2000JOC2824> attempted direct cyclization of acid **115a** with phosphorus pentaoxide and isolated the expected compound **116** in poor yield (20%). They could improve the yield (57%) of this ring closure via the mixed anhydride **115b** which was isolated prior to its cyclization in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 18).



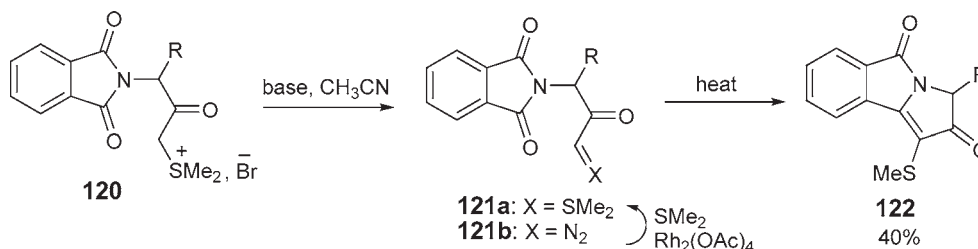
Scheme 18

Vedejs and Little <2002JA748> developed a new route to leucoaziridinomitosenes derivative **119** via intramolecular Michael addition using substrate **117b**. Preliminary attempts of tin–lithium exchange and subsequent intramolecular Michael addition from **117a** had led to a complex mixture due to the competition between indole C–H lithiation and tin–lithium exchange. Treatment of monodeuterated substrate **117b** with phenyllithium and quenching of the resulting Michael enolate with ethanol afforded **118a** in 78% yield along with 5% of **119** and 17% of the destannylated substrate. These results clearly show a great deuterium isotope effect that efficiently prevents the indole lithiation. A value of $k_{\text{H}}/k_{\text{D}} = ca. 35$ was found for the C-2 indole deprotonation. Achievement of this sequence starting from **117b** in the presence of phenylselenenyl chloride allowed direct isolation of product **119** in 71% yield (Scheme 19). The presumed selenide intermediate **118b** was not observed. In this synthesis, the deuterium atom serves as a protecting group for the indole C(2)–H bond during the tin–lithium exchange; moreover, this blocking group is removed during the final spontaneous *syn*-elimination sequence <2004JOC1794>. A similar route was earlier developed by Ziegler and Belema utilizing the cyclization of an aziridinyl radical instead of the anionic species derived from **117** <1997JOC1083>.



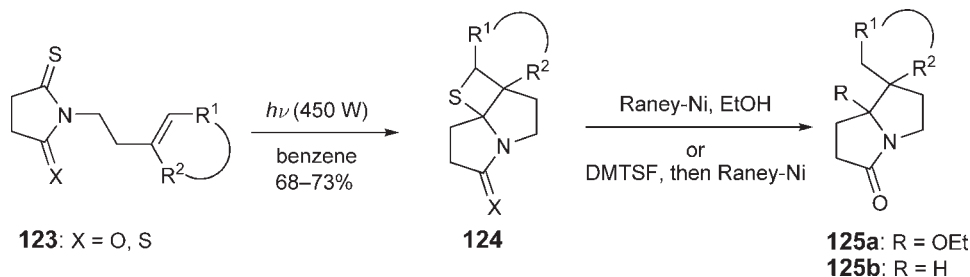
Scheme 19

Tolstikov *et al.* <1989IZV1209> have previously described the synthesis of the benzo-annulated pyrrolizindione **122** starting from sulfonium salt **120**, via the corresponding sulfur ylide **121a**. The same group described a modified procedure where ylide **121a** was generated *in situ* by reacting Me_2S with diazoketone **121b** in the presence of $\text{Rh}_2(\text{OAc})_4$ (Scheme 20) <2002IZV189>. Pyrrolam regioisomer **12** was synthesized in 87% yield via an intramolecular Wittig reaction of *N*-(3-iodopropyl)succinimide <2004JOC6105>.



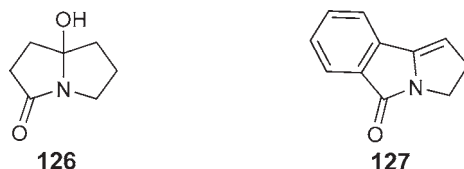
Scheme 20

Padwa *et al.* <2001OL1781, 2004JOC33> succeeded in constructing the saturated pyrrolizinones **125** by photochemical-promoted intramolecular cyclization of thiolactams **123** leading to **124**. Treatment of the latter with Raney-Ni in ethanol afforded compound **125a**, while treatment with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) followed by Raney-Ni leads to bicyclic hexahydropyrrolizin-3-ones **125b** (Scheme 21).

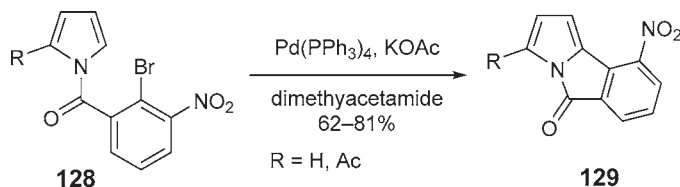


Scheme 21

N-(3-Iodopropyl)succinimide was subjected to intramolecular reductive cyclization with samarium iodide (3 equiv) in presence of Fe(DBM)₃ catalyst (where DBM = dibenzoylmethane enolate) to afford the corresponding hemiaminal **126** which smoothly undergoes partial dehydration leading to the pyrrolam A regioisomer **12**. When applied to *N*-(3-iodopropyl)phthalimide, a similar sequence afforded pyrrolizinone **127** <1996TL2577>.

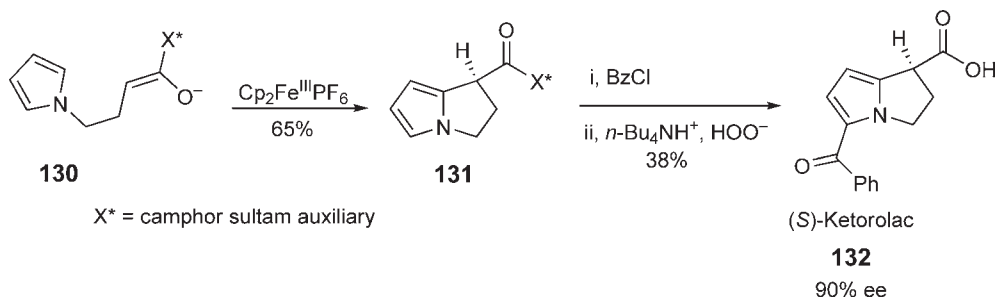


Benzo-annulated pyrrolizin-3-ones **129** were synthesized in good yields from *N*-*o*-benzoylated pyrroles **128** by an intramolecular Heck reaction (Scheme 22) <2001JME4615>.



Scheme 22

(*S*)-Ketorolac **132**, a nonsteroidal anti-inflammatory drug (NSAID), was synthesized in a two-step procedure based on an intramolecular oxidative coupling of pyrrole at the C-2 position with a chiral sultam enolate **130** leading to dihydropyrrolizine **131** as a 4.5:1 mixture of epimers (Scheme 23). Subsequent benzoylation, performed on the crude



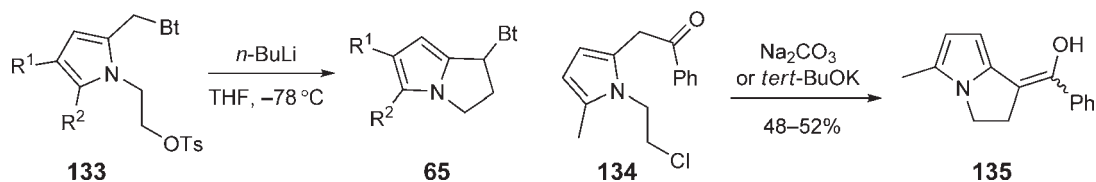
Scheme 23

reaction mixture of the coupling step, followed by hydrolysis afforded (*S*)-ketorolac in 38% overall yield and 90% ee <2005AGE609>. The best result was reached with ferrocenium hexafluorophosphate as oxidant, which is well known to convert enolates into radical species by single-electron transfer <2002EJO718>.

11.01.7.2 1,2-Bond Formation

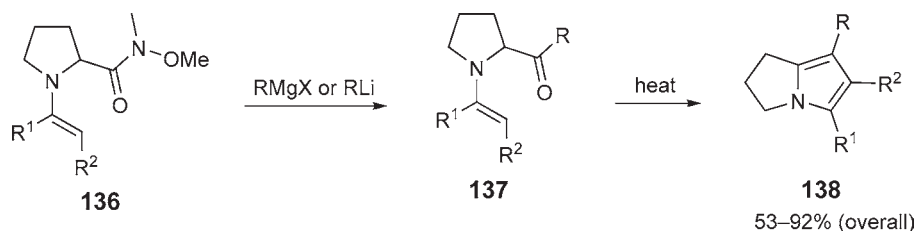
Katritzky *et al.* <1997JOC4148> described the cyclization of pyrrole derivatives **133** via lithiation at the benzotriazol-1-ylmethyl group and subsequent intramolecular nucleophilic displacement of tosylate to give in good yields dihydropyrrolizines **65**, which lead to 3*H*-dihydropyrrolizines **68** under treatment with malonate anion (see Section 11.01.5.3).

Reaction of compound **134**, either with sodium carbonate or potassium *tert*-butoxide, leads in moderate yields to the enolized bicyclic compound **135** along with a dimer resulting from the oxidative coupling of the initial enolate of substrate **134** (Scheme 24) <2005T1693>.



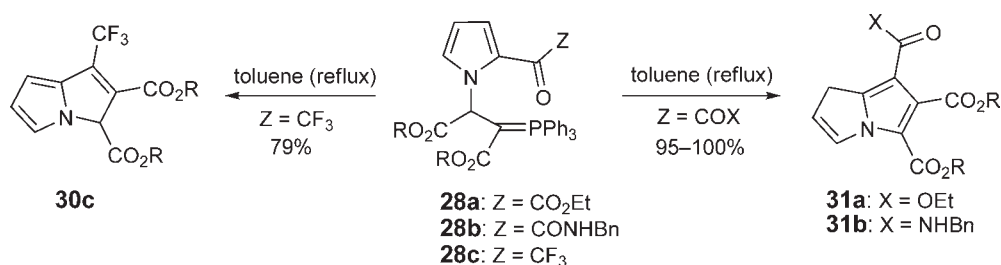
Scheme 24

Reaction of Weinreb *N*-vinylprolinamides **136** with organometallic reagents afforded ketoenamines **137** which were thermally cyclized to dihydropyrrolizines **138** in good yields (53–92%). The success of this cyclization requires an electron-withdrawing R² group (Scheme 25) <2002S2450>.



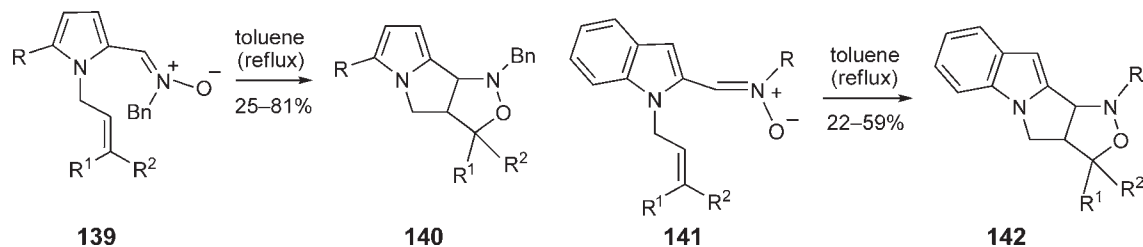
Scheme 25

Intramolecular Wittig reaction of keto-stabilized ylide **28** took place in refluxing toluene leading to the 1*H*-dihydropyrrolizines **31** in the case of α -ketocarboxylic derivatives <2001T5873>, while trifluoroacetyl ylide **28c** afforded exclusively the 3*H*-dihydropyrrolizine **30c** (Scheme 26) <2006ARK55>.



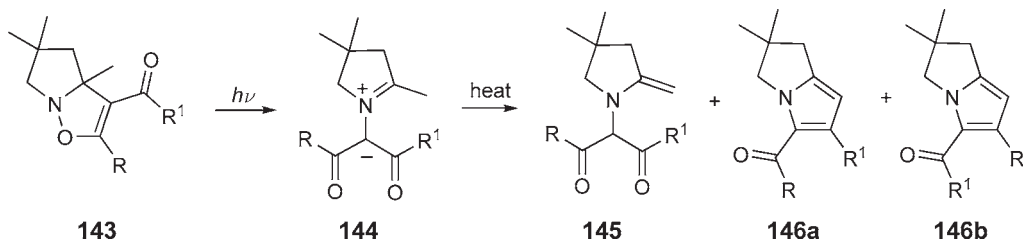
Scheme 26

Intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones **139** has been shown to lead selectively to the fused ring regioisomer **140** when R^1 and/or R^2 are alkyl or phenyl substituents, while substrates with a monosubstituted carbon–carbon double bond gave mainly the bridged regioisomer **141** (<2001T8323, 2002EJO2080>). These cycloadditions also were studied with unsaturated nitrones **141** derived from indole nucleus. Similar substituent effects were observed; the benzo-annulated dihydropyrrolizines **142** are preferred regioisomers when the $C=C$ is mono- or disubstituted (Scheme 27) (<2000JOC8924>).



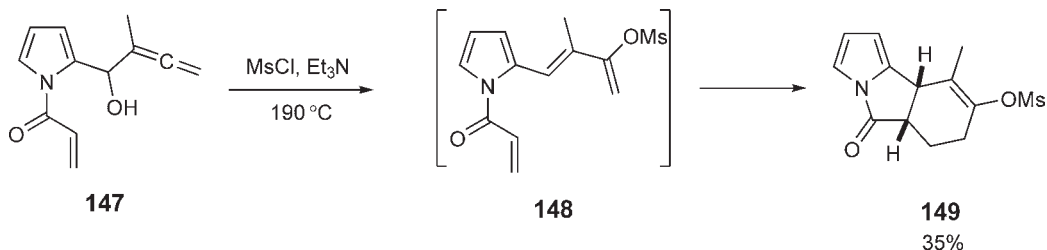
Scheme 27

Photochemically promoted rearrangement of 2,3-dihydroisoxazoles **143** resulted in the isolation of azomethines **144** which undergo thermal rearrangement and cyclization leading to a mixture containing its tautomer **145** and dihydropyrrolizines **146**. Regioisomer **146a** was obtained in 63% yield when $R = H$ and $R^1 = OMe$ (Scheme 28) (<2003EJO1438>).



Scheme 28

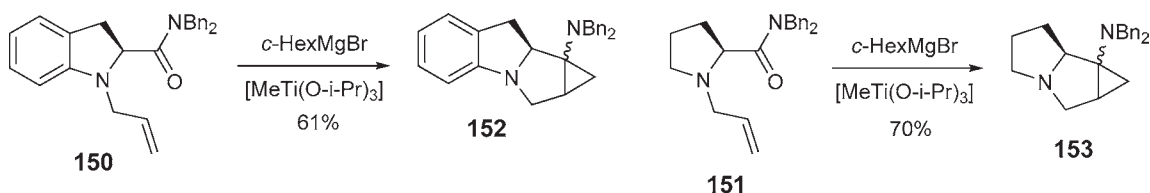
Reaction of α -allenyl alcohol **147** with methanesulfonyl chloride and triethylamine in toluene at 190 °C, in a sealed tube, led to the tricyclic dihydropyrrolizin-4-one **149** in 35% yield. This transformation involves a domino mesylation/ $\sigma[3,3]$ transposition/intramolecular Diels–Alder cycloaddition via diene **148** (Scheme 29) (<2002CC1472>).



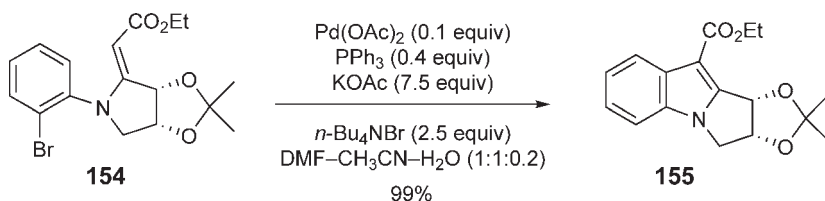
Scheme 29

Indoline and proline derivatives **150** and **151**, on treatment with ϵ -HexMgBr and $MeTi(O-i-Pr)_3$, underwent the intramolecular Kulinkovich cyclopropanation leading to annelated pyrrolizines **152** and **153**, respectively, as mixtures of *cis*- and *trans*-diastereomers (Scheme 30) (<2004CEJ785>).

Benzo-annulated dihydropyrrolizine **155** was quantitatively prepared via the Heck cyclization of **154** (Scheme 31) (<2001TL7513>).

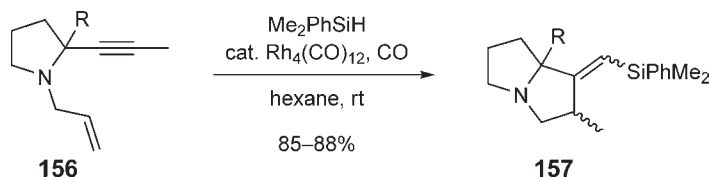


Scheme 30



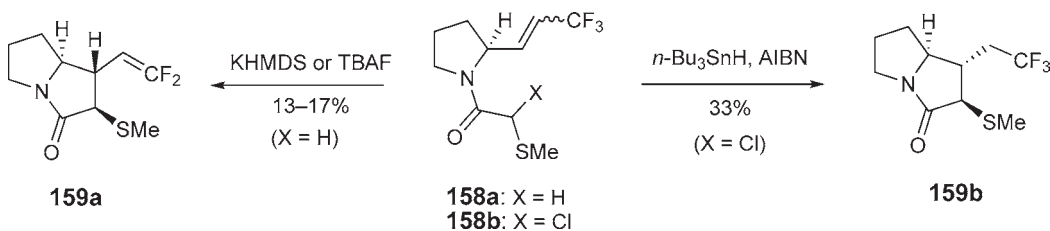
Scheme 31

When submitted to the silylcarbocyclization developed by Ojima *et al.* (Me₂PhSiH, Rh₂(CO)₁₂, CO) enynes **156** afforded a diastereomeric mixture of pyrrolizines **157** in good yield (Scheme 32) <2006TL6312>.



Scheme 32

Base-promoted (KHMDs or TBAF) cyclization of trifluoropropenyl derivative **158a** gave poor yields (13–17%) of fluorinated hexahydropyrrolizine **159a** (HMDS = hexamethyldisilazide; TBAF = tetrabutylammonium fluoride). Chlorination of **158a** with *N*-chlorosuccinimide (NCS) gave α -chlorosulfide **158b** which was reacted with Bu₃SnH in the presence of AIBN to afford pyrrolizinone **159b** in moderate yield (33%) (Scheme 33) <2004T8919>.

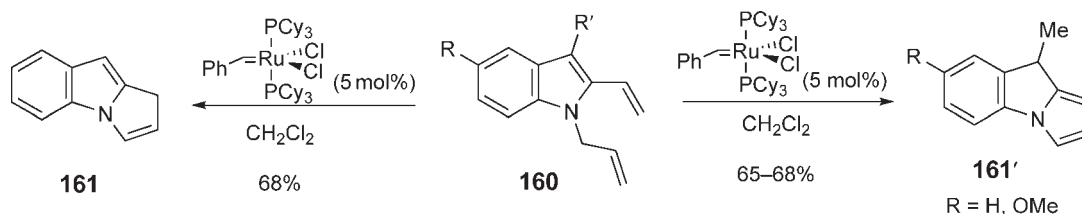


Scheme 33

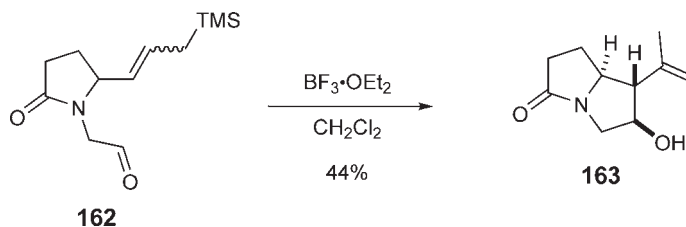
1*H*-Dihydropyrrolizines **161** were obtained from **160** by ring-closing metathesis using commercial first-generation Grubbs' catalyst <2002TL4765>; surprisingly, the resulting carbon–carbon double bond shifts toward the nitrogen atom. In the case of the substrate bearing a methyl group at the C-3 position, the indolic double bond also shifts leading to tautomer **161'** (Scheme 34).

11.01.7.3 2,3-Bond Formation

Hexahydropyrrolizin-4-one **163** was obtained as a major diastereomer, in moderate yield, via allylsilane–aldehyde ring closure of **162** upon exposure to BF₃·OEt₂ in methylene chloride (Scheme 35) <2005T1155>.

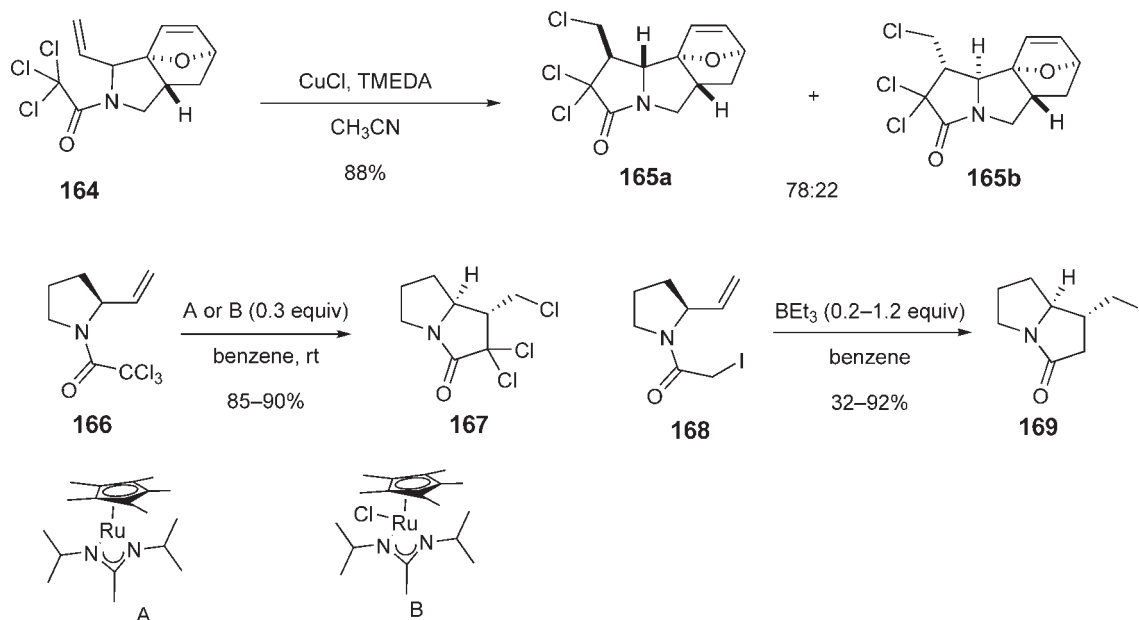


Scheme 34



Scheme 35

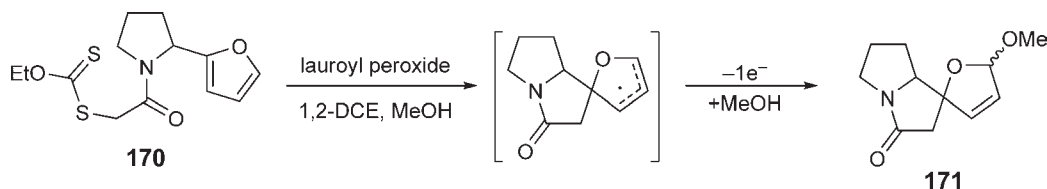
Treatment of trichloroacetamide **164** with CuCl/TMEDA in refluxing chloroform achieved a stereoselective halogen atom transfer radical cyclization, yielding tetracyclic pyrrolizinone **165** in 88% yield, with a diastereomeric ratio **165a**/**165b** = 78:22 (TMEDA = tetramethylethylenediamine) <2001EJO1845>. Nagashima *et al.* studied this Kharasch intramolecular reaction in the case of proline-derived substrate **166** by using Ru(II) catalysts which could promote this cyclization at room temperature leading smoothly to pyrrolizinone **167** in high yields <2003CC442, 2005T10216>. Similar BEt₃-promoted halogen atom-transfer cyclization was achieved with *N*-(2-iodoacetyl)-vinylpyrrolidine **168** to give selectively the 1-*exo*-isomer **169** (Scheme 36) <1997H(45)863, 1998J(P1)1691>.



Scheme 36

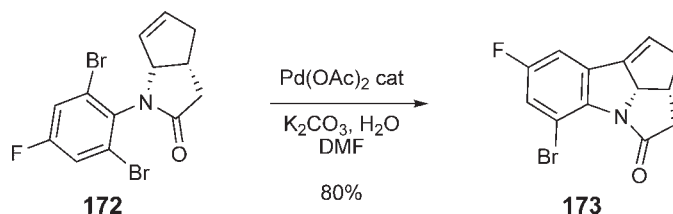
Spiro tricyclic pyrrolizinone **171** was obtained with 65% yield (and almost poor stereoselectivity) by intramolecular radical cyclization of the xanthate **170** upon exposure of the latter to 2 equiv of lauroyl peroxide, in a refluxing 3:1 mixture of methanol and 1,2-dichloromethane. The radical generated from the xanthate moiety cyclizes with the

furane ring via a 5-*exo*-mode and the resulting allylic radical is further oxidized with the lauroyl peroxide to conjugated oxonium which is finally trapped with methanol leading to **171** (Scheme 37) <2006CC665>.



Scheme 37

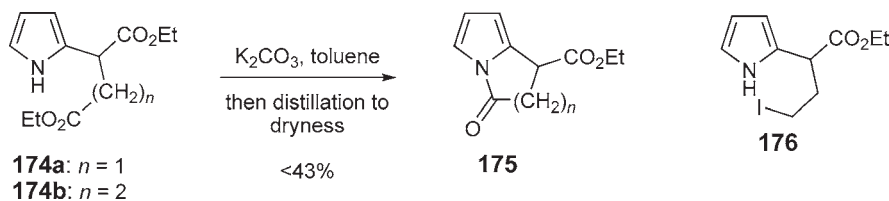
Conversion of **172** to the tetracyclic benzo-annulated pyrrolizinone **173** was achieved by using the Heck reaction in DMF/H₂O (Scheme 38); the best conversion and yield (80%) were observed in the absence of phosphine ligands <2005JOC268>.



Scheme 38

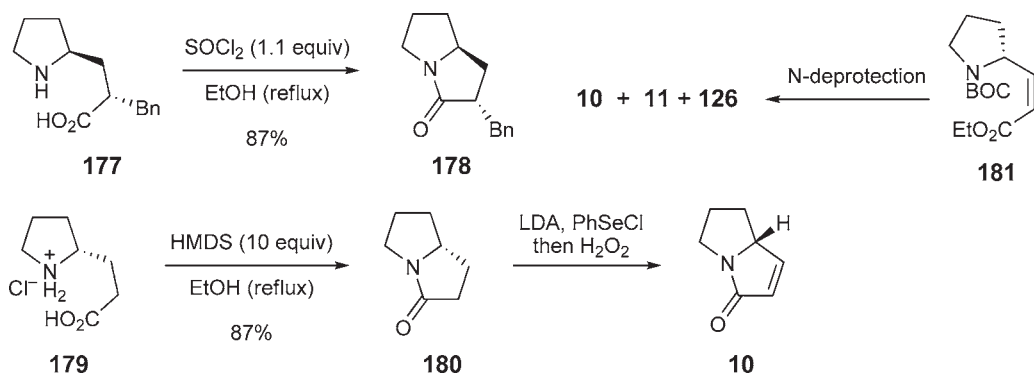
11.01.7.4 3,4-Bond Formation

Intramolecular *N*-acylation of pyrrole derivative **174a** under various basic conditions proved more difficult than expected; the best yield (43%) of dihydropyrrolizinone **175a** was obtained upon treatment with K₂CO₃ in toluene followed by distillation to dryness <2004TL6587>. This moderate yield may be attributed to the poor nucleophilicity of the pyrrole nitrogen atom, and also to the ring strain; indeed similar cyclization of homologue **174b** was less difficult. Moreover, attempted cyclization of **176** via intramolecular *N*-alkylation, either under basic or neutral conditions, failed. Only the enolate C-alkylation cyclopropane derivative was obtained (Scheme 39).



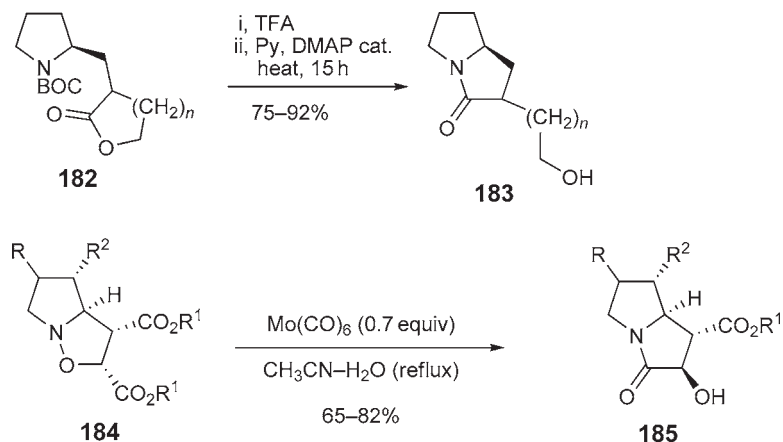
Scheme 39

Intramolecular *N*-acylation of saturated substrates is in general more efficient. Refluxing of the L-proline-derived γ -amino-acid **177** and thionyl chloride (1.1 equiv) in ethanol allowed the synthesis of pyrrolizin-3-one **178** in 87% yield <2004SC3191>. Lactamization of **179** was achieved by refluxing its hydrochloride in acetonitrile, in the presence of HMDS (10 equiv) and catalytic amount of TMSCl <1997TA515>. Phenyselenation of the resulting lactam **180**, followed by oxidative elimination, led to pyrrolam A **10** without isomerization of the carbon–carbon double bond (cf. Section 11.01.4.2), whereas one-pot deprotection and cyclization of carbamate **181** performed under various conditions led, in all cases, to variable ratios of pyrrolam A **10** and its tautomer **11** as well as hemiaminal **126** (Scheme 40) <2004JOC6105>.



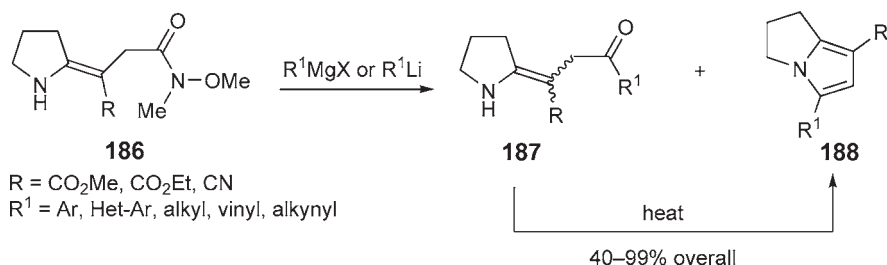
Scheme 40

A similar transformation was performed on lactones **182** which afforded the corresponding pyrrolizinones **183** in good to excellent yields [<2005HCA2250>](#). Treatment of pyrroloisoxazolines **184** with $\text{Mo}(\text{CO})_6$ in a refluxing $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ mixture allowed reductive cleavage of N–O bond and subsequent lactamization leading to highly functionalized pyrrolizinones **185** (Scheme 41) [<2000EJO3633>](#).



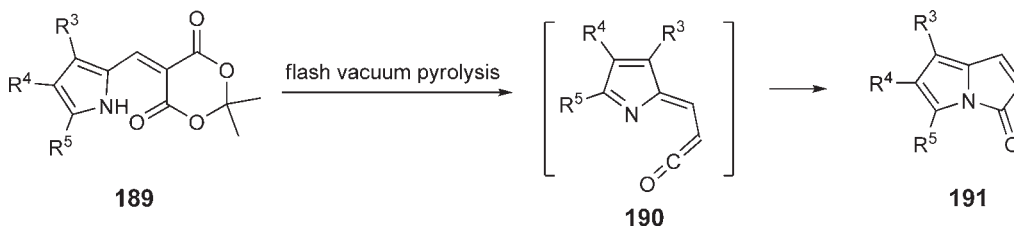
Scheme 41

In the presence of organometallic reagents (R^1MgX , R^1Li , diisobutylaluminium hydride (DIBAL-H)), the Weinreb amides **186** lead selectively to the corresponding carbonyl derivatives **187** as a mixture of *Z/E* isomers which spontaneously undergo partial cyclization to dihydropyrrolizines **188** (Scheme 42). This cyclization was completed by refluxing the crude mixture in chloroform in the presence of silica gel [<2002S2450>](#).



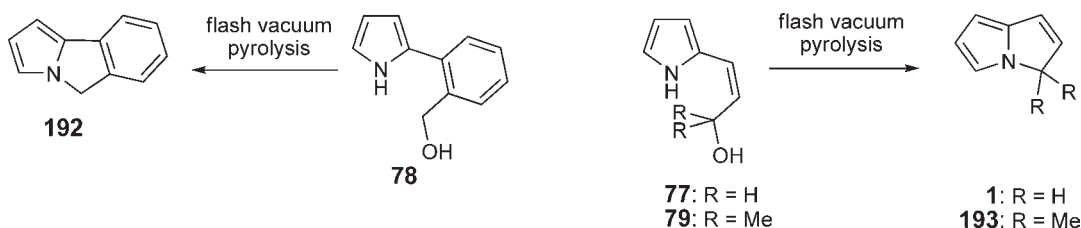
Scheme 42

As mentioned in CHEC-II(1996) <1996CHEC-II(8)16>, 3*H*-pyrrolizin-3-one **2** and many other substituted analogues were synthesized by FVP of Meldrum's acid derivatives **189** via the *in situ*-generated pyrrol-2-ylmethylidene ketenes **190** which cyclize by an intramolecular *N*-acylation (Scheme 43) <1997J(P1)2195, 2000J(P1)3584>.



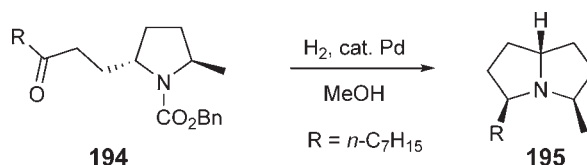
Scheme 43

Pyrrolizin-3-ones may also be obtained by FVP of 3-(pyrrol-2-yl)propenoate esters such as **62**, **69**, and **74**. Also, benzo-annulated pyrrolizinone **17** was obtained by FVP of 2-(*o*-methoxycarbonylphenyl)pyrrole <1999J(P1)2047>. FVP of alcohols **77**, **78**, and **79** led to 3*H*-pyrrolyzine derivatives **1**, **192**, and **193**, respectively, in good yields (66–95%). These transformations proceed by elimination of water and subsequent electrocyclization of the *in situ*-generated cumulene (Scheme 44) <1999J(P1)2049>.



Scheme 44

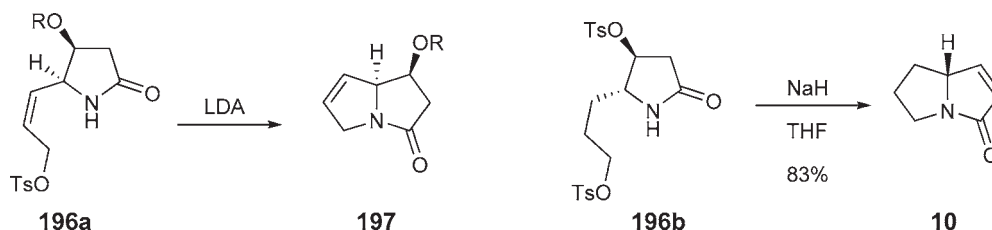
Xenovinine **195**, a natural alkaloid, was obtained by catalytic hydrogenolysis of carbamate **194** and subsequent intramolecular reductive amination of the *in situ*-generated *N*-deprotected ketopyrrolidine <1999T8915>. Enantiodivergent synthesis of **195** with the same reductive amination as final step was also reported (Scheme 45) <1998EJO1955>.



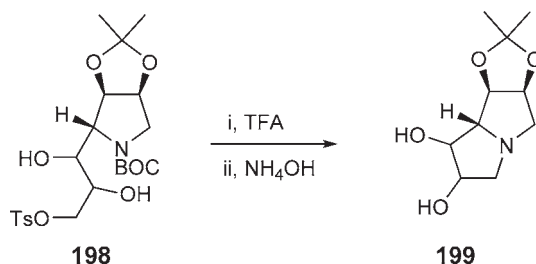
Scheme 45

Lactams **196** undergo easy ring closure by intramolecular *N*-alkylation under basic conditions, at low temperature. In presence of lithium diisopropylamide (LDA), **196a** gives the corresponding tetrahydropyrrolizin-3-one **197**, which was a key intermediate in the synthesis of (+)-loline, a pyrrolizine alkaloid from rye grass and tall fescue <2001J(P1)1831>. Substrate **196b** undergoes cyclization followed by E₁cb elimination leading to (*R*)-pyrrolam A **10** (Scheme 46) <1999TA3827>.

Treatment of derivatives **198** with TFA followed by neutralization with aqueous ammonia allowed the *t*-butoxycarbonyl (BOC) cleavage and subsequent *N*-alkylation leading to **199**, which after hydrolysis of the acetonide afforded the corresponding tetrahydroxypyrrolizidine that showed selective, but moderate, inhibition of amyloglucoside from *Rhizopus mold* (Scheme 47) <2004TA323>.

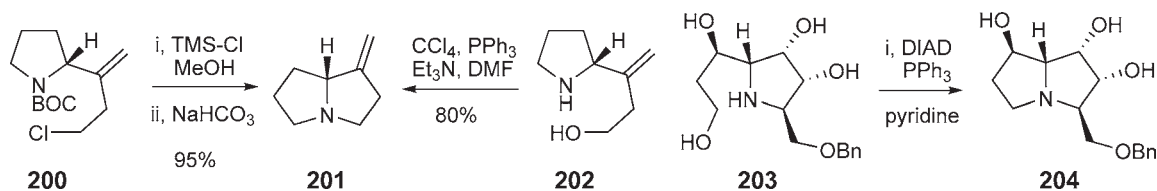


Scheme 46



Scheme 47

When submitted to the same sequence (TMS-Cl/MeOH, then NaHCO_3), compound **200** underwent deprotection and cyclization leading to saturated pyrrolizine **201** <2005T3221>. The latter was also obtained (80%) in a one-step intramolecular cyclization of amino alcohol **202** in the presence of carbon tetrachloride, triphenylphosphine, and triethylamine in DMF <2005RJOC70>. Albeit in low yield (20%), aminoalcohol **203** was selectively cyclized to pyrrolizine **204** using the Mitsunobu conditions (Scheme 48). Use of $\text{CBr}_4/\text{PPh}_3$ system did not improve yields of **204** <2003JOC7818>.

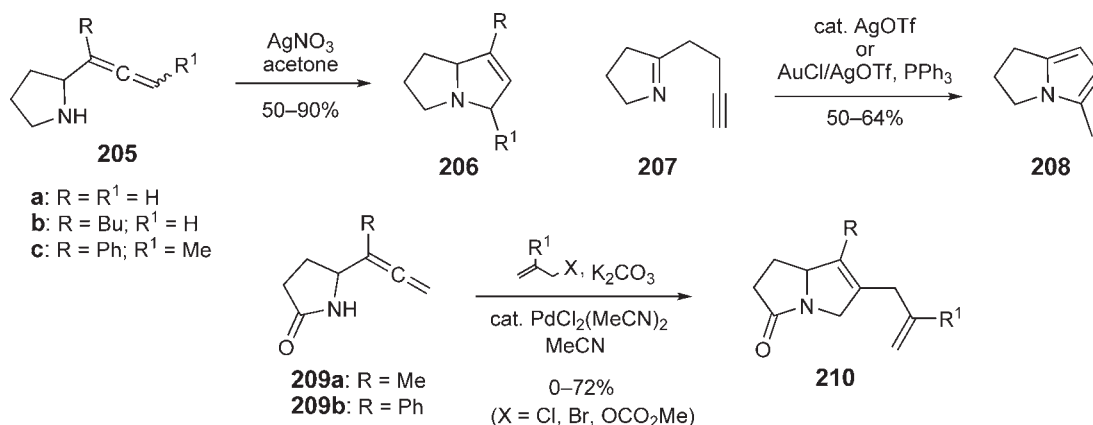


Scheme 48

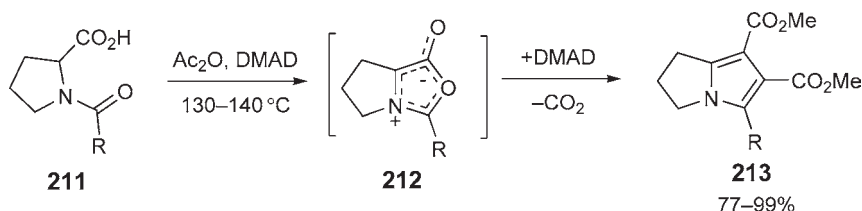
Tetrahydropyrrolizines **206** were synthesized by reacting amino allenes **205** with catalytic amount of silver nitrate in acetone at room temperature, in the dark <2001OL3855>. Treatment of the homopropargylic imine **207** with AgOTf (5 mol%) or AuCl/AgOTf and PPh_3 led to 3-methyl-1,2-dihydropyrrolizine **208** in 64% or 50% yield, respectively <2006JOC4525>. Tetrahydropyrrolizin-4-ones **210** were obtained via a Pd-catalyzed coupling-cyclization of homo-allenyl lactams **209** with allyl halides or allyl acetates, in presence of PdCl_2 (0.1 equiv) (Scheme 49) <2001T5123>.

11.01.7.5 1,8:2,3-Bond Formation

This route relies on 1,3-dipolar cycloaddition reactions; a series of dihydropyrrolizines **213** were synthesized by heating the proline derivatives **211** with dimethyl acetylenedicarboxylate (DMAD) at 130–140 °C in the presence of acetic anhydride. Reaction between **211** and Ac_2O provides the mesoionic oxazalone intermediate **212** which adds to dimethyl acetylenedicarboxylate, giving a cycloadduct, which undergoes spontaneous decarboxylation leading to **213** (Scheme 50) <1998JME4744, 1977JME812>.

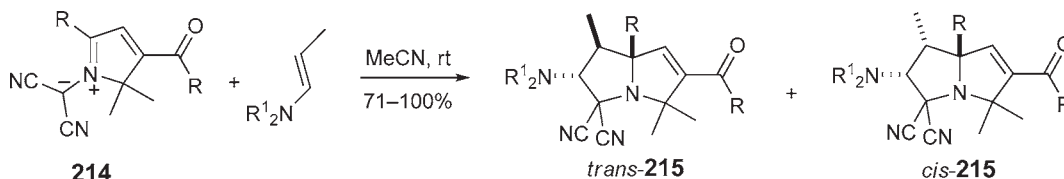


Scheme 49



Scheme 50

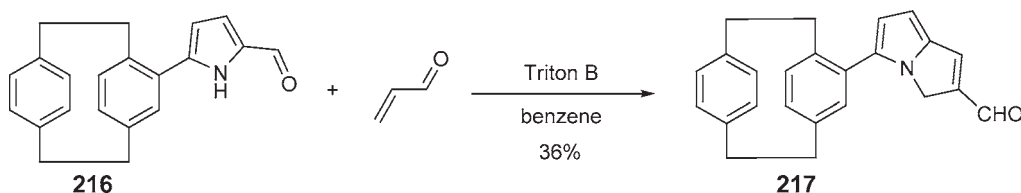
When reacted with electron-rich enamines (*E*)-R¹₂N-CH=CH-Me, stable azomethine ylides **214** <1999T9515> undergo regioselective 1,3-dipolar cycloadditions giving rise to tetrahydropyrrolizines **215** as mixtures of *cis*- and *trans*-isomers with poor diastereoselectivity, which is an argument in favor of a two-step instead of a concerted mechanism (Scheme 51) <1999T9535>.



Scheme 51

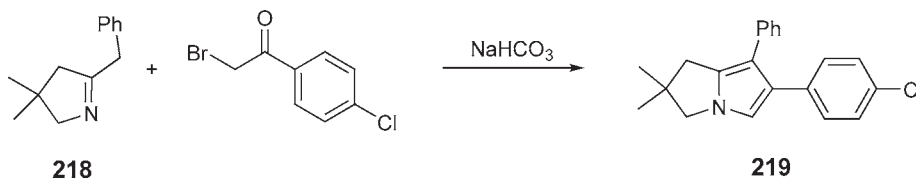
11.01.7.6 1,2:3,4-Bond Formation

Under basic conditions (Triton B), in the presence of acrolein, 2-formylpyrrole derivative **216** underwent *N*-alkylation by 1,4-addition followed by intramolecular aldolization–crotonization leading to 3*H*-pyrrolizine **217** (Scheme 52) <2004CHE166>.



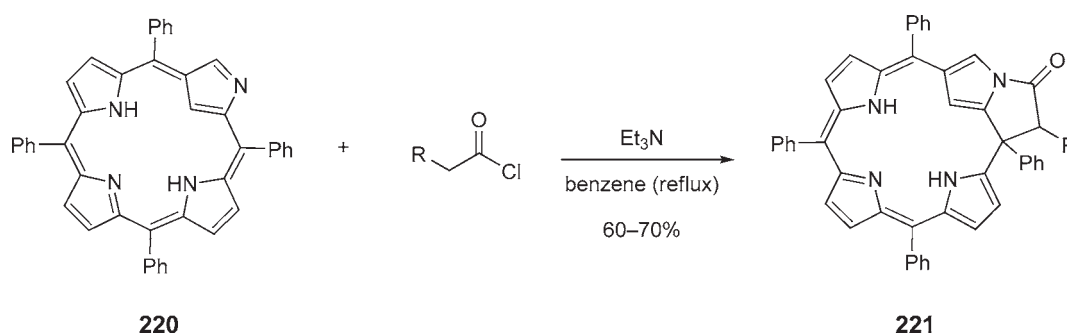
Scheme 52

Dihydropyrrolizine **219**, a precursor of ML 300, was efficiently obtained in a one-step cyclization between cyclic imine **218** and ω -bromo-4-chloroacetophenone in the presence of NaHCO_3 (Scheme 53) <2003WO018583>.



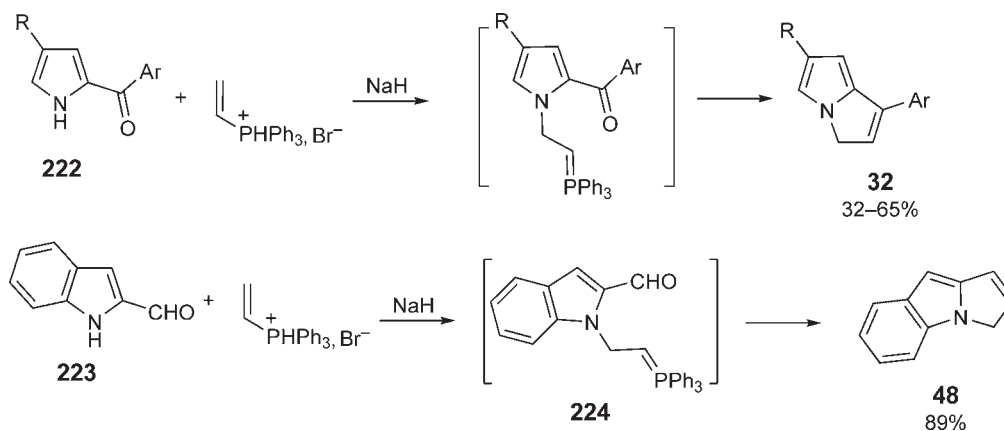
Scheme 53

Tetraphenyl-2-aza-21-carbaporphyrin **220** was reacted with various acyl chlorides and excess triethylamine in refluxing dry benzene, and unexpected pyrrolidin-2-one-fused N-confused calix[4]phyrins **221** were isolated in 60–70% yield (Scheme 54) <2006OL1137>.



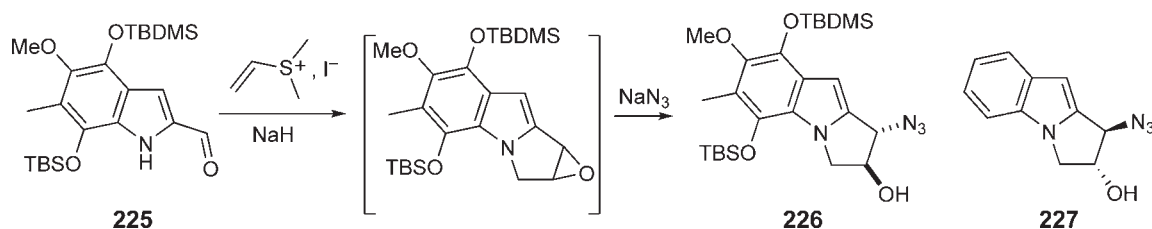
Scheme 54

Reaction of 2-arylpyrroles **222** with vinyltriphenylphosphonium bromide in presence of sodium hydride gives a nucleophilic addition, thus generating a phosphonium ylide which undergoes intramolecular Wittig olefination leading to 1-arylpyrrolizines **32**, which are, in some cases, in equilibrium with their tautomers **33** (cf. Section 11.01.4.2) <2004ARK20>. Similar procedures were employed for the preparation of the tricyclic mitosine **48** starting from indol-2-carbaldehyde **223** and vinyl triphenylphosphonium bromide, via ylide **224** (Scheme 55) <2000TL1123>.



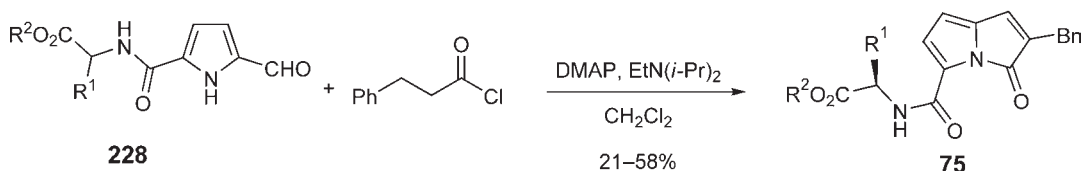
Scheme 55

Reaction of 2-formylindole derivative **225** with dimethylvinylsulfonium iodide in the presence of sodium hydride resulted in a tetracyclic epoxide which was submitted to ring opening by action of sodium azide to lead, regioselectively, to the benzo-annulated dihydropyrrolizine **226** <1996JOC816>. A similar sequence was performed starting from a chiral, nonracemic vinylsulfonium salt prepared from camphorquinone, and sodium salt of indole-2-carboxaldehyde and led to tricyclic azido alcohol **227** in 35% yield and only 43% ee (Scheme 56) <2001TA999>.



Scheme 56

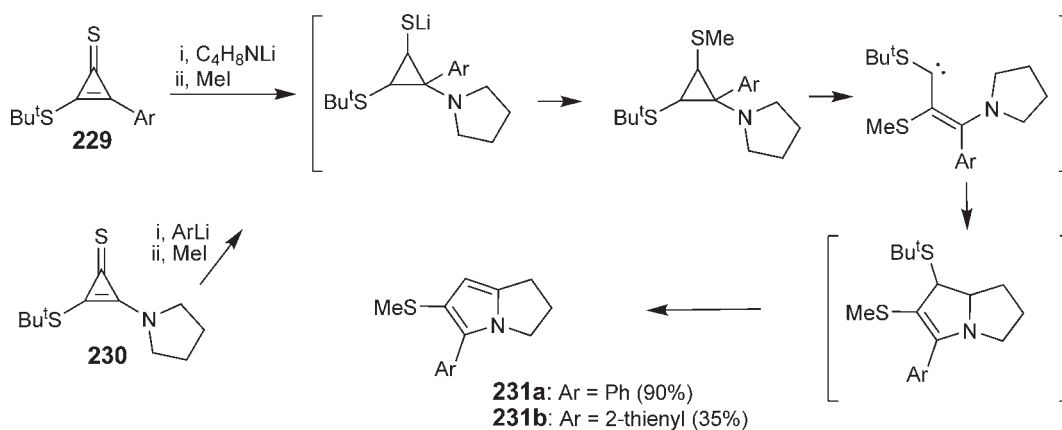
Pyrrolizin-3-ones **75** were synthesized in one step from 2-formylpyrrole derivatives **228** and hydrocinnamoyl chloride in the presence of 4-dimethylaminopyridine (DMAP) and *N,N*-diisopropylethylamine (DIPEA), in low to moderate yields (Scheme 57) <2002TL3673>.



Scheme 57

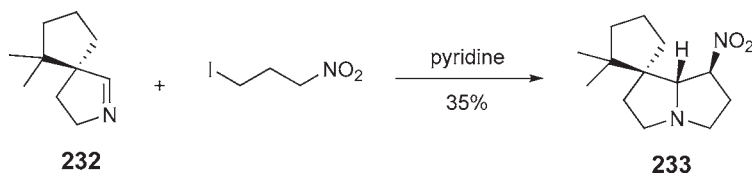
11.01.7.7 1,8:3,4-Bond Formation

Treatment, at low temperature, of either **229** with lithium pyrrolidinide, or **230** with aryllithium, and subsequent alkylation with methyl iodide allowed the isolation of 6-methylsulfanyl-5-aryl-2,3-dihydropyrrolizines **231** in moderate to good yields <2000JOC3341>. A possible mechanism was postulated as shown in Scheme 58.



Scheme 58

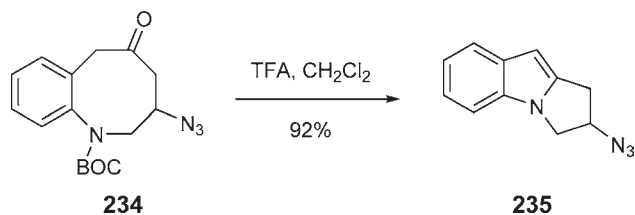
Reaction of (+)-polyozonimine **232** with 3-iodo-1-nitropropane in the presence of pyridine yielded (+)-nitro-polyozonimine **233** in 35% yield (Scheme 59) <2000TL6623>.



Scheme 59

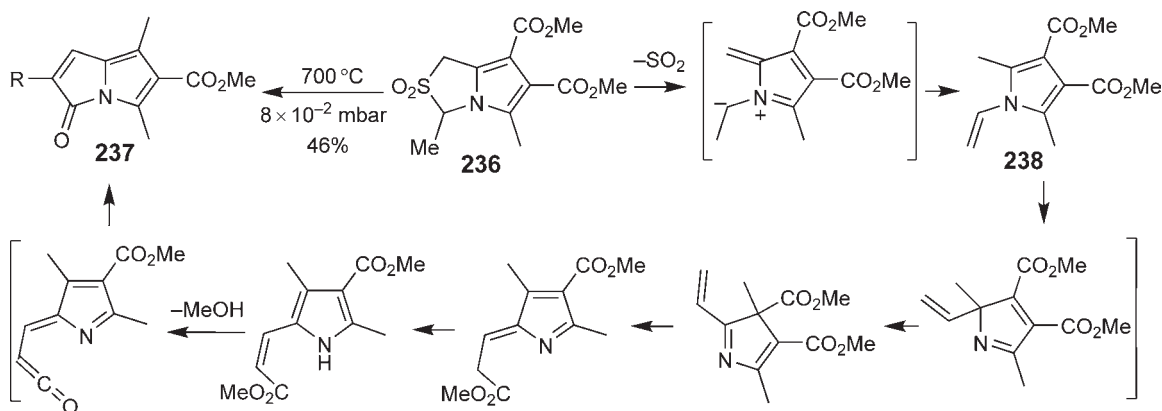
11.01.8 Ring Synthesis by Transformation of Another Ring

Aza-bicyclic compound **234**, in presence of TFA, undergoes *N*-BOC cleavage and subsequent intramolecular cyclization/dehydration leading to the benzo-annulated dihydropyrrolizine **235**, in 92% yield (Scheme 60) <2004T7367>.



Scheme 60

FVP of the aza-bicyclic sulfone **236** at 700°C and 8×10^{-2} mbar resulted in 3*H*-pyrrolizin-3-one **237** <2004TL3889>. At same temperature and 'lower' pressure, that is, 4×10^{-2} mbar, the same sulfone affords a mixture of **237** and vinyl pyrrole **238** in 44% and 27% yield, respectively. The latter was the only product obtained when the thermolysis of **236** was performed in a sealed tube in sulfolane. This result and others led Pinho e Melo *et al.* <2005JOC6629> to suggest the plausible eight-step mechanism shown in Scheme 61.

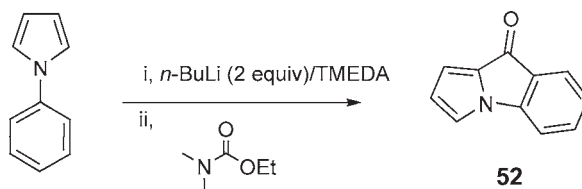


Scheme 61

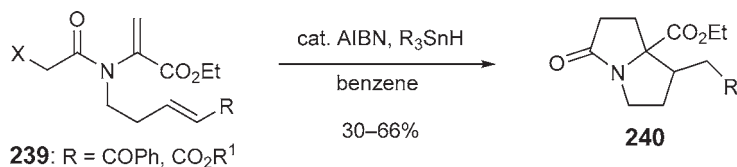
11.01.9 Miscellaneous Synthetic Methods

Double metalation of *N*-phenyl pyrrole by using 2 equiv of *n*-butyllithium in presence of TMEDA (2 equiv) and carbonylation with ethyl *N,N*-dimethylcarbamate afforded the benzo-annulated pyrrolizinone **52** in 84% yield (Scheme 62) <2004JOC5476>.

N-Homoallylic enamides **239** derived from pyruvate were subjected to free radical cyclization in presence of R_3SnH and AIBN. The radical species generated from the C-halogen bond homolytic cleavage underwent a 5-*endo*-cyclization followed either by a 5-*exo*- or 6-*endo*-cyclization and reduction of the final radical species (Scheme 63)



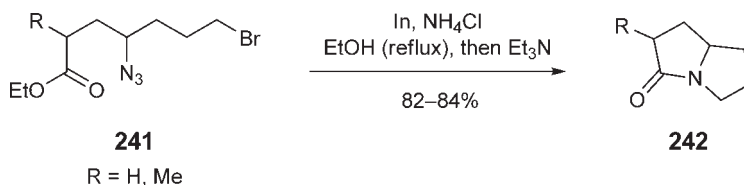
Scheme 62



Scheme 63

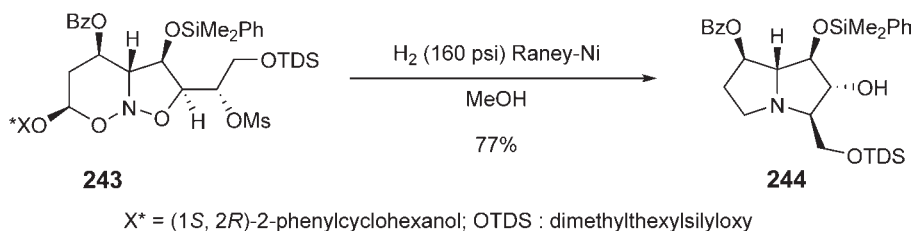
<1999J(P1)427>. The regioselectivity of the second radical cyclization depends on the electronic nature of the homoallylic double bond; pyrrolizines **240** which result from a final 5-*exo*-cyclization mode are preferred in the case of electron-poor carbon–carbon double bonds, such as enones or enoates; electron-rich double bonds lead to indolizines via a final 6-*endo*-cyclization. The best yields of pyrrolizines were observed with iodide precursors. The *cis*-isomers of **240** predominate in this 5-*endo*-5-*exo*-cyclization.

Renaud *et al.* <2002AGE3460> reported a two-step sequence for the preparation of hexahydropyrrolizines starting from 5-bromopent-1-ene and α -iodoesters: treatment of these substrates with $PhSO_2N_3$ and $(Bu_3Sn)_2$ in the presence of catalytic amount of the initiator $t-BuO-N=N-O-t-Bu$ results in a radical carboazidation leading to the corresponding 4-azido-7-bromoheptanoate **241**, which was then submitted to chemoselective reduction of the azido group with indium, and subsequent spontaneous double cyclization to afford pyrrolizines **242** (Scheme 64).



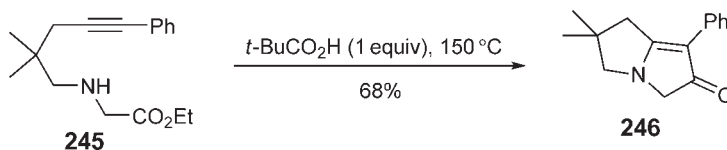
Scheme 64

Catalytic reduction (Raney-Ni, H_2) of the nitroso acetal-mesylate **243** resulted in reductive cleavage of both N–O bonds followed by intramolecular reductive amination and finally intramolecular *N*-alkylation providing the masked 7-epiaustraline alkaloid **244** (Scheme 65) <1998JA7357>.



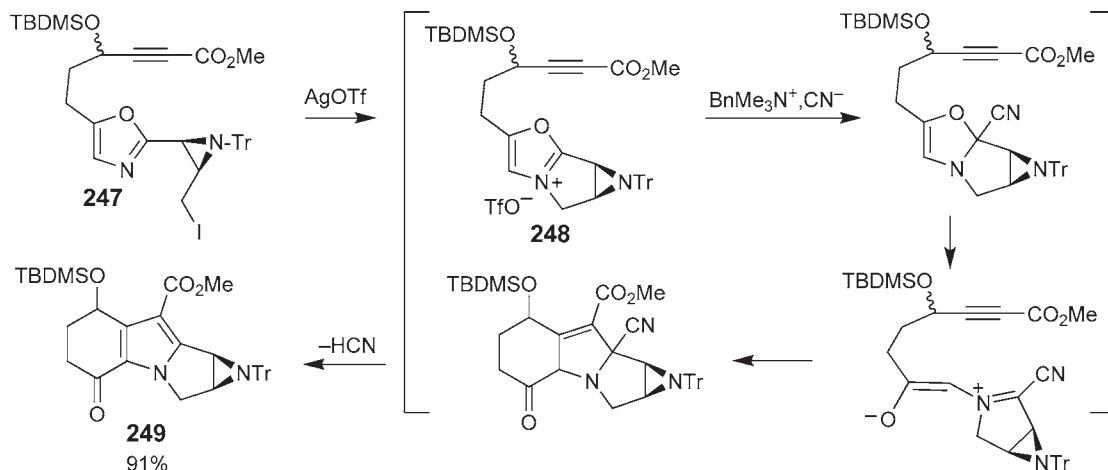
Scheme 65

Pyrrolizinone **246** is a key intermediate in the synthesis of the ML-3000 drug which was described by Cossy and Belotti <1997JOC7900>; this pyrrolizinone intermediate was constructed in one-step (68%), via a thermal acid-promoted intramolecular bicyclization of the ω -acetylenic amino ester **245** by heating at 150 °C in presence of pivalic acid (1 equiv) (Scheme 66).



Scheme 66

For an enantiocontrolled synthesis of aziridinomitosines, Vedejs *et al.* <2003JA15796> developed an elegant strategy which relies on an intramolecular cyano-promoted dipolar [2+3] cycloaddition. Treatment of substrate **247** with silver triflate in refluxing acetonitrile induces an intramolecular *N*-alkylation of the oxazole ring, thus providing salt **248**. Then, the latter was added to a solution of $\text{BnMe}_3\text{N}^+\text{CN}^-$ in acetonitrile to afford in 91% overall yield the tetracyclic 1*H*-dihydropyrrolizine **249** according to the mechanism described in Scheme 67.

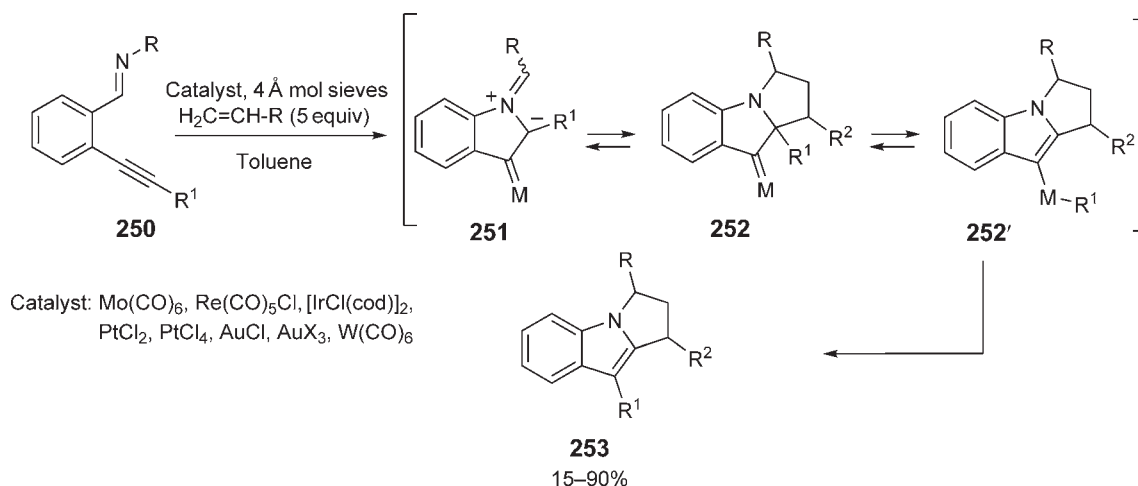


Scheme 67

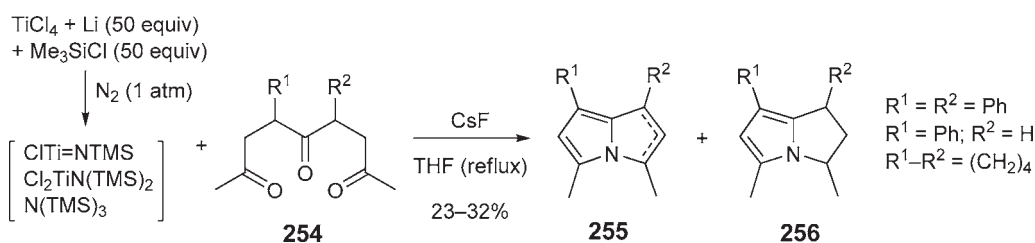
Kusama *et al.* <2002JA11592> reported the construction of mitosene derivatives **253** in a one-step procedure by reacting various electron-rich olefins in a [3+2] cycloaddition with tungsten-containing azomethine ylides **251**, which is generated *in situ* from *N*-(*o*-alkynylphenyl)imine derivatives **250** and tungsten hexacarbonyl, under photochemical activation. The resulting cycloadduct **252** probably undergoes R^1 -[1,3] shift giving rise to **252'**, which, after a final reductive elimination, leads to the mitosene skeleton **253** (Scheme 68). Recently, Kusama *et al.* <2006OL289> demonstrated the feasibility of the same reaction catalyzed with Re(I) , Ir(I) , Pd(II) , Pt(II) , and Au(III) .

Regioisomers of pyrrolizines **255** and their dihydroanalogues **256** were obtained as a mixture, in moderate yield, by reacting the 1,4,7-triketones **254** with titanium–nitrogen complexes ($\text{ClTi}=\text{NTMS}$, $\text{Cl}_2\text{TiN}(\text{TMS})_2$, and $\text{N}(\text{TMS})_3$) prepared by reduction of TiCl_4 with lithium under a nitrogen atmosphere (Scheme 69) <2004BCJ1655>.

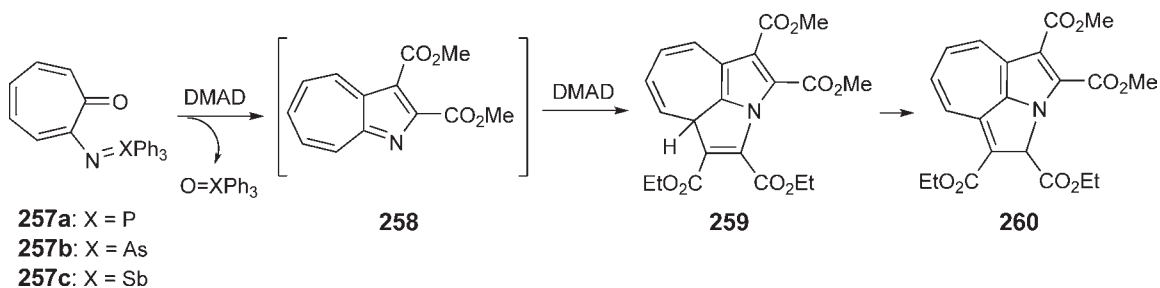
Reaction of (tropon-2-ylimino)pnictoranes **257** with DMAD was shown to give the cyclohepta-annulated pyrrolizine **260** <2001J(P1)1901>. The latter could not be obtained from the (tropon-2-ylimino)bismuthorane. 1-Azaazulene derivative **258** was postulated as intermediate resulting from cyclocondensation of **257** with DMAD followed by elimination of $\text{O}=\text{XPh}_3$. Compound **258** was previously shown to react with DMAD giving 1*H*-pyrrolizine **259**, which undergoes hydrogen atom migration resulting in the formation of 3*H*-pyrrolizine derivative **260** (Scheme 70) <1978J(P1)429>.



Scheme 68



Scheme 69



Scheme 70

11.01.10 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

The mitomycinoids, which were the focus of this part in the CHEC-II(1996) <1996CHEC-II(8)22>, are still attracting many synthetic efforts <1995SL475> due to their challenging architecture, unusual metabolic activation pathway <1997B9211>, and potent antitumor activities <1998CRV2723, 2002CRV2477>. Bioreductive activation of mitomycins A **261a** leads to the aminoleukoaziridinomitosenes **264**, which is believed to be the intermediate responsible for DNA cross-linking <1996MI1623>. Unlike mitomycins, aziridinomitosenes **265** do not require reductive activation for DNA alkylation (Figure 2).

Several approaches have been developed for the total synthesis of mitomycins, but only few of them were enantioselective. In Scheme 71 are summarized the main strategies described for the synthesis of more or less functionalized mitomycinoids.

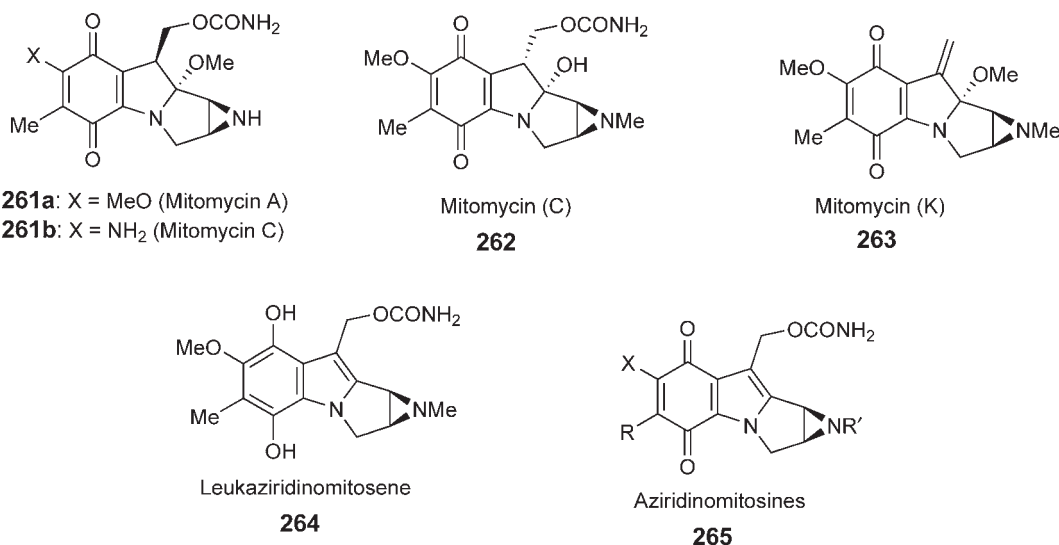
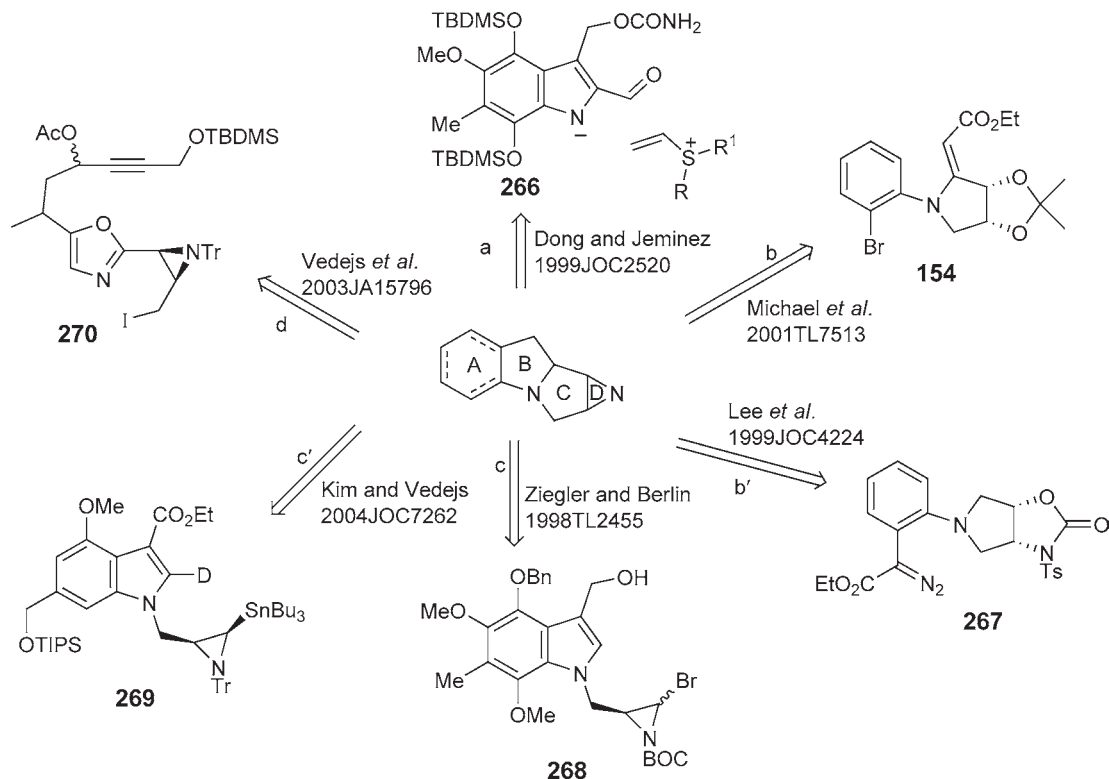


Figure 2



Scheme 71

The most functionalized mitomycin precursor was synthesized by Dong and Jimenez <1999JOC2520> in a racemic form, starting from indolic anion **266** and vinylsulfonium salts (route a); they also explored a diastereoselective version of this synthesis by using enantiopure vinylsulfonium salts, which gave low asymmetric induction <2001TA999>.

Michael *et al.* <2001TL7513> described a Heck cyclization of **154** to form functionalized mitosene **155** which was further transformed into tetracyclic compound (route b). Also Lee *et al.* <1999JOC4224> described a synthesis in

which they constructed ring B by a copper-catalyzed regioselective carbon–hydrogen insertion reaction starting from the diazoester **267** (route b'). Ziegler and Berlin <1998TL2455> reported a desmethoxymitomycin A total synthesis relying on the construction of ring C by a diastereoselective cyclization of an enantiopure aziridiny radical generated from **268** (route c). Similar ring C formation was developed by Kim and Vedejs <2004JOC7262>, who performed this cyclization by intramolecular Michael addition of the lithium aziridine anion generated *in situ* by Sn–Li exchange from deuterated substrate **269**. Vedejs *et al.* <2003JA15796> described another strategy in which they could construct rings A, B, and C (route d) in a one-pot procedure starting from oxazole **270**.

11.01.11 Important Compounds and Applications

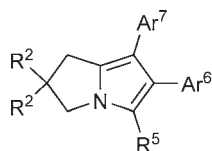
Several water-soluble polyhydroxylated pyrrolizidine alkaloids isolated from plants and microorganisms have been described; many of these are inhibitors of glycosidases or glycotransferases. These enzymes that catalyze the hydrolysis of the glycosidic linkage in biomolecules, such as carbohydrates and glycoconjugates, are involved in a large variety of biological functions making them essential for all living organisms <2001P265>. Therefore, these glycoprocessing enzymes are considered as potential therapeutic targets in many diseases <2001P265>. Because of their limited availability, only few natural polyhydroxylated pyrrolizidines have been studied for their therapeutic potential. Therefore, several hundred related pyrrolizidines were synthesized; Zou reported a general review on the various methodologies developed in these syntheses <2005MI1363>.

Dihydropyrrolizines and dihydropyrrolizinones are widely employed as scaffolds in medicinal chemistry, and many drugs or drug candidates are based on these skeletons.

Aryl-substituted pyrrolizinones **90** were examined for their potential as inhibitors of the cytochrome P450 aromatase <2000BMC945>. Some benzo-annulated tetrahydropyrrolizinones were evaluated as inhibitors of cyclin-dependent kinases (CDKS) <2001JME4615>.

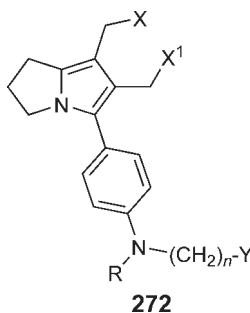
Ketorolac **132**, a nonsteroidal anti-inflammatory drug with cyclooxygenase (COX) inhibitory activity, was marketed as a racemic mixture. It is now well established that (*S*)-ketorolac is the active enantiomer <1999MI382>. Therefore, efforts were devoted to the selective synthesis of this active stereomer, either by enzymatic kinetic resolution <2001TA1865> or by enantioselective synthesis <2005AGE609>.

ML-3000 (**271a**), also a nonsteroidal anti-inflammatory which acts as an inhibitor of cyclooxygenases (COX-1, COX-2) and 5-lipoxygenase (5-LOX) enzymes, was intensively studied <1999T5145>. Several 6,7-diaryl-2,3-1*H*-dihydropyrrolizines were synthesized and evaluated as inhibitors of COX-1, COX-2, and 5-LOX. From this structure–activity relationship study, it was concluded that the balance of COX-1/COX-2 and 5-LOX inhibition can be modulated by modifying the aromatic substituents at the 6- and 7-position of the dihydropyrrolizine scaffold <2002EJM953, 2003WO018583>.



271a: $R^2 = \text{Me}$; $R^5 = \text{CH}_2\text{CO}_2\text{H}$; $\text{Ar}^6 = o\text{-ClC}_6\text{H}_4$; $\text{Ar}^7 = \text{Ph}$

Dihydropyrrolizines **272**, their salts and solvates, were prepared and evaluated as potential antitumor drugs or as site-specific DNA alkylating agents in the gene-relating technologies <1998WO9827095>.



11.01.12 Further Developments

11.01.12.1 Structural Aspects

Laihia *et al.* reported new spectroscopic (^1H , ^{13}C , ^{15}N NMR, ESI-MS) and X-ray data of three spiro[pyrrolizidine-3,3'-oxindoles] <2006MI1001-01>.

11.01.12.2 Syntheses

[1,8-bond formation]: Hoyes *et al.* described a new methodology for the formation of tetrahydro pyrrolizin-3-one derivatives by intramolecular trapping of *in situ* generated ketene acetal with imide <2006OL5191>. This cyclization takes place with high level of diastereoselectivity. Mechanistic details were deduced from spectroscopic data (MS and NMR). Recently, de Figueiredo *et al.* employed this methodology in the construction of pyrrolizin-3-one derivatives, which were involved in the total synthesis of the telomerase inhibitor UCS1025A <2007AGE2883>.

[1,2-bond formation]: Quiroz *et al.* performed in good yield, intramolecular cyclization of diethyl 2-(1-(2-bromoethyl)-5-oxopyrrolidin-2-yl)malonate into the corresponding hexahydro pyrrolizin-3-one <2007TL1571>.

[3,4-bond formation]: McNab *et al.* synthesized 5-phenyl-3*H*-pyrrolizin-3-one, in 38% yield by FVP of (*E*)-methyl 3-(1-phenyl-1*H*-pyrrol-2-yl)acrylate at 850 °C <2007ARK85>. Unlike intramolecular *N*-acylation of **174a** (Scheme 39) which was revealed to be rather difficult, when performed with dimethyl 2-(phenyl(1*H*-pyrrol-2-yl)methyl)malonate this reaction takes place smoothly at 0 °C in presence of sodium hydride <2007T5608>. Similar cyclization was performed on ethyl 3-(pyrrolidin-2-yl)propanoate in refluxing ethanolic solution of sodium ethylate, leading in 67% yield to hexahydro pyrrolizin-3-one **180**. This lactam was then transformed into (*S*)-pyrrolam A, enantiomer of **10**, as previously described (Scheme 40) <2007S663>.

[1,2,3,4-bond formation]: Mikolajczyk *et al.* described the synthesis of 6-(methylsulfinyl)-3*H*-pyrrolizine by reacting pyrrole-2-carbaldehyde with an α -phosphorylvinyl sulfoxide in presence of excess sodium hydride in refluxing benzene. This transformation involves a tandem Michael addition/Horner olefination leading to 2-(methylsulfinyl)-3*H*-pyrrolizine which finally undergoes base-catalyzed isomerization to the corresponding thermodynamic tautomer <2006JOC8818>. Schobert and Wicklein described a new synthesis of (*R*)-pyrrolam A **10**, which also relies on a domino addition/Wittig intramolecular olefination by reacting (*R*)-benzyl proline and an immobilized (on polystyrene) triarylphosphoranylidene ketene ($\text{Ar(Ph)}_2\text{P}=\text{C}=\text{C}=\text{O}$) <2007S1499>. Pilipecz *et al.* reported on an easy addition of 2-nitromethylene-pyrrolidine to α -di- and α,α' -tricarbonyl, and subsequent cyclization leading to substituted dihydro-1*H*-pyrrolizines <2007H(71)1919>.

Very recently, Vedejs and co-workers reported new results concerning their continuing investigations towards the synthesis of enantiopure aziridinomitosene A, by harnessing their methodology (see Section 11.01.9, Scheme 67) <2007JOC(ASAP)>.

Xia *et al.* reported on the metabolism of lasiocarpine (prototype heliotridine pyrrolizidine alkaloids) by F344 rat liver microsomes, and isolated 6,7-dihydro-7-hydroxy-1-hydroxymethyl-5*H*-pyrrolizine (DHP)-derived DNA adducts, thus showing the potential use of such DHP-derived DNA adducts as biomarkers of exposure and tumorigenicity for all pyrrolizidine alkaloids <2006MI1001-02>.

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Biographical Sketch



Hamid Dhimane was born (1957) and raised in Morocco. Since 1978, he attended Reims-Champagne-Ardennes University (France) from which he graduated with a master's (DEA) degree in chemistry in 1983. He carried out his Ph.D. thesis in the group of Professor Josselin Chucho at the same university, working on the formation and reactivity of aminomethyleneketenes by flash vacuum pyrolysis. From 1987 to 1989, he was a postdoctoral fellow at Okayama University (Japan) working with Professor Sigeru Torii on reductive and electroreductive carbon-carbon bond-forming reactions in Pb(0)/Pb(II) redox system. Then, he joined the group of Professor Jean-Marcel J. Tronchet at Geneva University (Department of Pharmaceutical Chemistry), where he has spent one year as postdoctoral fellow working on the synthesis of isoxazolidine analogues of nucleosides. In 1990, he was appointed as Maître de Conférences at P. & M. Curie – Paris 6 University, where he joined the group of Gérard Lhommet, working on the total synthesis of indolizidine and pyrrolizidine alkaloids. In 2001, he was appointed full professor of chemistry at Paris Descartes University (Biomedical Research Centre), where he is involved in the synthesis of natural and non-natural compounds of potential biological and/or therapeutic relevance. His current topics include the design and synthesis of peptidomimetics, methionine amino peptidase (MetAP) inhibitors, and 'caged' nucleotides.



Gérard Lhommet was born in 1945 in Paris (France). He obtained his M.Sc. from the University of Paris in 1969. He carried out his Ph.D. studies under the supervision of Profs Pierre Maitte and Henri Sliwa at UPMC (P. and M. Curie University), Paris between 1970 and 1975. After a postdoctoral position at the East Anglia University in Norwich, UK, with Prof A.R. Katritzky (1976–1977), he accepted a position as Assistant Professor at UPMC, Paris. In 1985, he became Full Professor at the same university. His research interests include the development of new strategies sparing chiral auxiliaries for use in asymmetric and natural product synthesis.

11.03

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 2:0

L. Micouin

CNRS, Paris, France

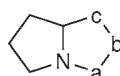
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11.03.1 Introduction

This chapter covers bicyclic systems containing two fused five-membered rings with one bridgehead nitrogen and two extra heteroatoms in the same ring. The chapter mainly concentrates on the literature which has appeared from 1995 onwards, since older work has been comprehensively reviewed in Chapter 8.03 of CHEC-II(1996) <1996CHEC-II(8)79>. No more recent review has been published dealing specifically with these ring systems, but the intrinsic chemistry of the corresponding monocyclic five-membered heterocycles is covered in Volume 5 and is therefore beyond the scope of this chapter. In spite of a wide variety of possible heteroatom combinations with these systems, only 18 have been reported in the literature and are represented in **Table 1** together with the names of the parent (fully unsaturated) heterocycles and recent selected references. Among them, some have received little attention (such as **4**, **6**, or **15**), or are found in the context of other research fields, reported as casual examples, whereas saturated systems such as **16** or **17** have been extensively studied, especially during the last decade. Tricyclic systems, derived from the general bicyclic structure by benz-ring fusion onto the pyrrole ring, are reported in **Table 2**. The chemistry of triazoloisindoles **28–30** has been reviewed <2002CHE1019>.

Table 1 Ring systems 1–18



Ring system (structure number)	Heteroatom location	Reference
Pyrrolo[1,2- <i>c</i>][1,2,3]triazole 1	a=b=N	1997JP12919, 2001JP11778, 2002JP2126
Pyrrolo[1,2- <i>b</i>][1,2,4]triazole 2	a=c=N	1993JAN1866
Pyrrolo[2,1- <i>c</i>][1,2,4]triazole 3	b=c=N	2004TL1877, 2006AGE1463
Pyrrolo[2,1- <i>b</i>][1,3,4]oxadiazole 4	a=N, c=O	1984JCM325
Pyrrolo[1,2- <i>d</i>][1,2,4]oxadiazole 5	b=N, c=O	2001T7391
Pyrrolo[1,2- <i>b</i>][1,2,5]oxadiazole 6	a=O, b=N	2002PPS960
Pyrrolo[1,2- <i>b</i>][1,2,4]oxadiazole 7	a=O, c=N	2001OL4165, 2003JCD2540, 2003MI253
Pyrrolo[2,1- <i>b</i>][1,3,4]thiadiazole 8	a=N, c=S	2001CC1950
Pyrrolo[1,2- <i>b</i>][1,2,5]thiadiazole 9	a=S, b=N	2001JP1662, 2005JA11250, 2005AGE1513
Pyrrolo[1,2- <i>b</i>][1,2,5]thiadiazole 10	a=S, c=N	1997BSB639
Pyrrolo[2,1- <i>c</i>][1,2,4]thiadiazole 11	b=S, c=N	1994T7019
Pyrrolo[1,2- <i>c</i>][1,3,2]diazaphosphole 12	a=P, b=N	2001JA9488, 2004CEJ6048
Pyrrolo[1,2- <i>c</i>][1,3,2]diazasilole 13	a=Si, b=N	1974CB2804
Pyrrolo[1,2- <i>c</i>][1,3,2]oxazasilole 14	a=Si, b=O	2005OM5566
Pyrrolo[1,2- <i>b</i>][1,4,2]dioxazole 15	a=c=O	1988T5209
Pyrrolo[1,2- <i>c</i>][1,3,2]oxazaborole 16	a=B, b=O	2005JA5384
Pyrrolo[1,2- <i>c</i>][1,3,2]oxazaphosphole 17	a=P, b=O	2002ASC868
Pyrrolo[1,2- <i>c</i>][1,2,3]oxathiazole 18	a=S, b=O	2004JA9558, 2003OL811, 2002TL1915

Several polycyclic structures, incorporating this 5-5 fused system, such as **35** <1996TL8351>, **36** <2004JA5984>, **37** <2006AG(E)1463>, or **38** <1999PS261> have also been reported. It is interesting to note that almost all the fused bicyclic 5-5 systems described in this chapter are synthetic compounds, and that only a few examples of natural products containing this framework are known <2001OL4165>.

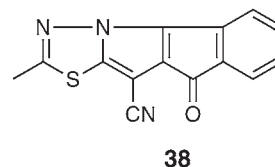
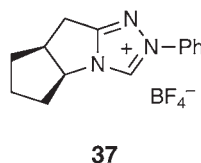
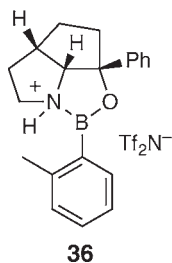
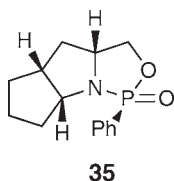
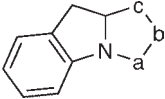
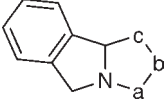


Table 2 Benz-fused ring systems 19–34

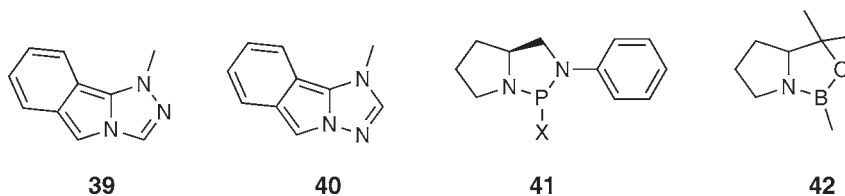
Ring system (structure number)	Heteroatom location	Reference
(a) <i>Indoles</i> 		
[1,2,3]Triazolo[1,5- <i>a</i>]indole 19	a=b=N	1999WO9902528
[1,2,4]Triazolo[4,3- <i>a</i>]indole 20	b=c=N	2005BMC1847
[1,3,4]Oxadiazolo[3,2- <i>a</i>]indole 21	a=N, c=O	
[1,2,4]Oxadiazolo[4,5- <i>a</i>]indole 22	b=N, c=O	1990JHC1185
[1,2,4]Oxadiazolo[2,3- <i>a</i>]indole 23	a=O, c=N	1975CB3483
[1,3,2]Oxazaborolo[3,4- <i>a</i>]indole 24	a=B, b=O	2000TA4329
[1,3,2]Diazaborolo[3,4- <i>a</i>]indole 25	a=B, b=N	1997TA3625
[1,2,5]Thiadiazaz[2,3- <i>a</i>]indole 26	a=S, b=N	2005JA11250
[1,3,4]Thiadiazaz[2,3- <i>a</i>]indole 27	a=N, c=S	2003PHA607
(b) <i>Isoindoles</i> 		
[1,2,3]Triazolo[5,1- <i>a</i>]isoindole 28	a=b=N	2005TL8531
[1,2,4]Triazolo[5,1- <i>a</i>]isoindole 29	a=c=N	2001EJO1407, 2000T377
[1,2,4]Triazolo[3,4- <i>a</i>]isoindole 30	b=c=N	2002CHE1019
[1,3,4]Oxadiazolo[2,3- <i>a</i>]isoindole 31	a=N, c=O	1987IJB1130
[1,3,4]Thiadiazolo[2,3- <i>a</i>]isoindole 32	a=N, c=S	2004H(63)2243
[1,2,4]Thiadiazolo[3,4- <i>a</i>]isoindole 33	b=S, c=N	1993JP127
[1,2,5]Thiadiazolo[2,3- <i>a</i>]isoindole 34	a=S, b=N	2005JA11250

11.03.2 Theoretical Methods

Only a few specific applications of theoretical methods to ring systems 1–34 have been described. Five-membered ring fusion can influence the properties of the corresponding monocyclic heterocycles, on which a number of calculations have been conducted (see Volume 5). Thus, the structures of triazoles **39** and **40** were calculated by PPP and CNDO/2 methods <2002CHE1019, 1989CHE281>. It was concluded on the basis of analysis of the canonical and localized MOs that they must be regarded as 10 π -electron 1,2-disubstituted isoindoles, and not 14 π -electron systems, as would be expected on the basis of their usual tautomeric structural representation. As a result, it is possible to propose a high diene activity of these compounds in Diels–Alder reactions. Compound **39** is predicted to be more reactive than **40** according to highest occupied molecular orbital (HOMO) energies calculations by the PPP/2 method.

Semi-empirical quantum mechanical AM1 techniques, with full optimization of geometrical parameters, have been conducted on a range of diamidophosphites **41** for the calculation of their Tolman's angles <2004EJO2214>. It appeared that the nature of X group can strongly influence the steric demand of these ligands, with values ranging from 122° to 168°.

Several *ab initio* calculations <1994JA8516> and semi-empirical methods <1993JOC799> have been used to investigate the asymmetric reductions catalyzed by oxazaborolidines of type **42** <1998AGE1986>.



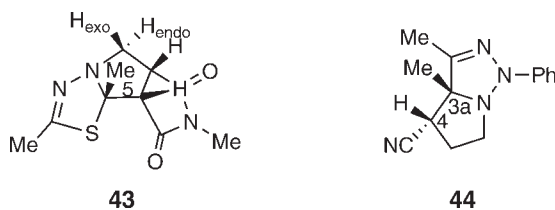
11.03.3 Experimental Structural Methods

Numerous 5-5 bicyclic systems described in this chapter have been investigated using spectroscopic methods, mainly proton or heteronuclear (¹³C, ¹¹B, ³¹P, or ¹⁵N) NMR. This technique has been particularly useful to determine

relative configurations in these fused bicycles, or predict their reactivity. Complementary methods, such as ^{29}Si <2001JP1706> nuclear magnetic resonance (NMR), infrared (IR) <1997TL1165>, or X-ray spectroscopy <1996AXC3213, 1999ZK367> can also provide additional information on configurational or chemical properties of this class of heterocycles.

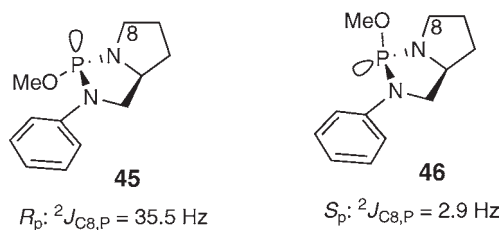
11.03.3.1 Proton NMR Spectroscopy

Proton NMR is a useful tool, not only for structure determination, but also for providing structural information on the configuration of fused systems. The bowl-shaped structure of **43** is evidenced by the strong deshielding of 5-*endo* proton (4.8 ppm) compared to its geminal partner 5-*exo* (3.6 ppm), confirming the analogy of this structure with the tripentagon bowl-unit present in the dodecahedron <2001CC1950>. Ring fusion configuration of compound **44** has been ascertained by NOE between H-4 and Me-3a <2001JP11778>. The 1,3-*cis* relationship between P=X group and protons in phosphorus-containing heterocycles results in their deshielding <1977JOC1022>.



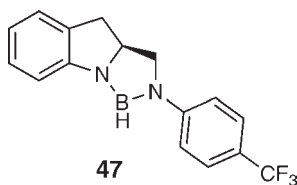
11.03.3.2 Carbon-13 NMR Spectroscopy

The analysis of the magnitude of $^2J_{\text{CP}}$ coupling constants in cyclic phosphines is a very convenient method for assigning the relative configuration of phosphorus in 5-5 bicyclic systems. Thus, the $^2J_{\text{CP}}$ value is maximum if the lone pair on phosphorus and the carbon atom in β -position are in a *syn* periplanar relationship, whereas minimum values are characteristic for anticlinal positions <2001MI591, 2005EJO2097, 2005TA3224>. For example, compound **45** exhibits a $^2J_{\text{CP}} = 35.5$ Hz while its diastereomer **46** is characterized by a coupling constant of $^2J_{\text{CP}} = 2.9$ Hz <2004EJO2214>.



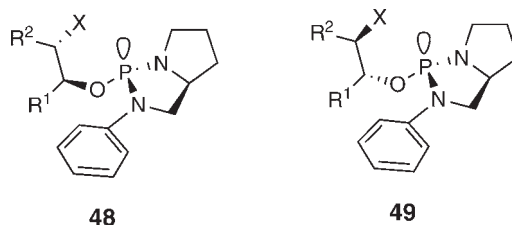
11.03.3.3 Boron-11 NMR Spectroscopy

Chiral diazaborolidines catalysts in asymmetric reductions have been less described than the corresponding oxazaborolidines. Although not isolated, the formation of compound **47** has been characterized by ^{11}B NMR spectroscopy with the detection of a signal at 24 ppm (from $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as an external standard) <2000TA4329>.



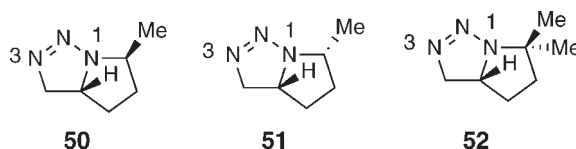
11.03.3.4 Phosphorus-31 NMR Spectroscopy

The use of diazaphospholidines as chiral derivatizing agents for the determination of the enantiomeric composition of choro- or bromohydrins has been reported. Thus, ^{31}P NMR spectra of a range of diastereomeric derivatives have been described to show a systematic deshielding from 0.2 to 12.9 ppm of isomers **48** compared to isomers **49** <2000TA1273>.



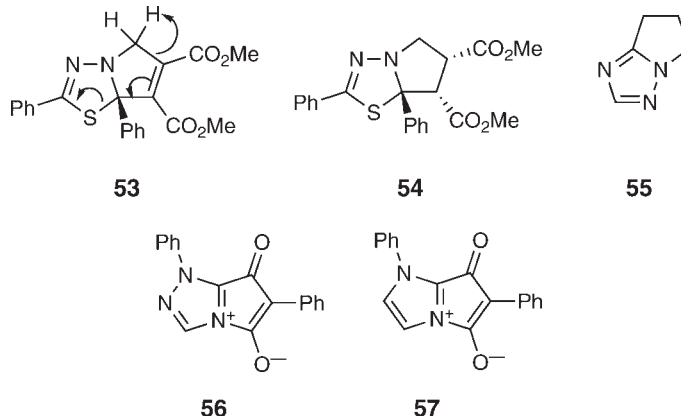
11.03.3.5 Nitrogen-15 NMR Spectroscopy

^{15}N NMR spectroscopy is still underexploited in structural analysis of nitrogen-containing heterocycles. It can however be a powerful tool, for instance in tautomerism studies <2002JP2126>. Some ^{15}N NMR investigations of lanthanide induced shift have been performed on bicycles **50–52**, showing that the complexing site of these 4,5-dihydro-1*H*-1,2,3-triazoles is located on N-3.



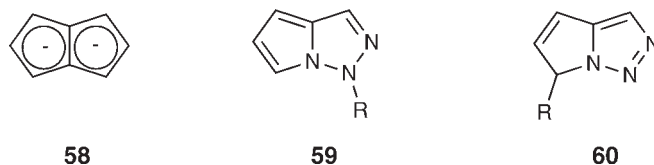
11.03.4 Thermodynamic Aspects

Very little is known on the thermodynamic aspects of ring systems **1–34**. Several 5-5 membered rings have been reported to be unstable, such as compound **53** <1998JP11998>. This stability is dependent on unsaturation level, since the corresponding dihydro-derivative **54** is a stable compound. Ring strain has also been evoked to explain the difficulty of forming simple bicyclic triazole **55** <2001TL7353>. The ease of decomposition of **56** compared to compound **57** illustrates the destabilization of the ring systems by addition of an extra nitrogen atom to the cationic fragment of sydnones <1988JOC2889>.

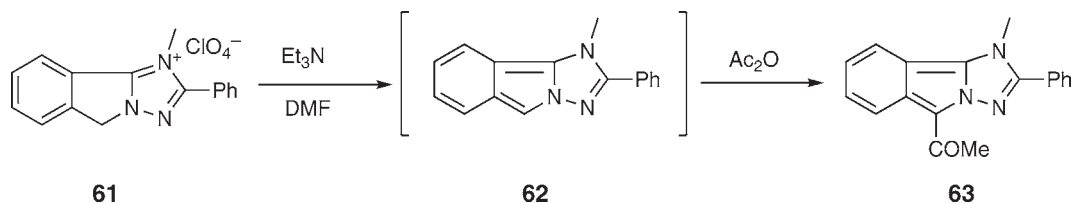


As outlined in CHEC-II <1996CHEC-II(8)79>, only a few ring systems **1–34** having a 10π -electron aromatic structure isoelectronic with the pentalene dianion **58** have been described. Triazoles **59**, having two adjacent

nitrogens each contributing to the π systems, have been reported to be energetically unfavorable compared with the isomeric triazoles **60**. Only a few *N*-carboxy derivatives of **59**, with some aromatic character, have been described <1990JOC571>.



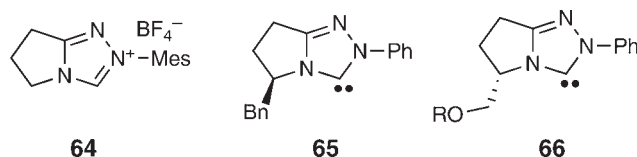
The aromatic character of triazoloindole **62** has been evidenced by its ability to enter into electrophilic substitution reactions, for instance with acetic anhydride, leading to the acetylated derivative **63** <2002CHE1019> (Scheme 1).



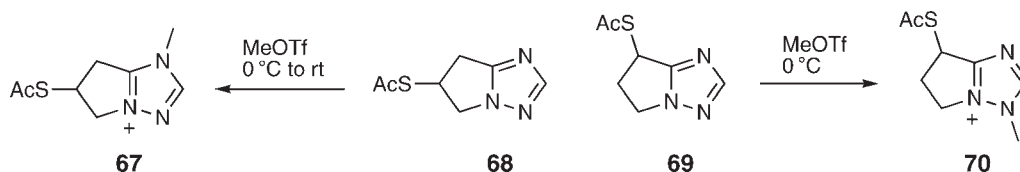
Scheme 1

11.03.5 Reactivity of Fully Conjugated Rings

Only a few reactions at the conjugated ring of bicyclic 5-5 fused systems have been reported. An important transformation is however the deprotonation of triazolium salts, leading to nucleophilic carbenes <2004ACR534>. The acidity of compound **64** has been highlighted by its ability to undergo a rapid exchange of the C-2 proton with deuterium in CD_3OD <2005OL3873>. The irreversible deprotonation by strong bases leads to useful catalysts **65**, **66** <2006AGE1463, 2005T6368, 2005JA6284, 2005JOC5725, 2004JA8876, 1998JP11891> for enantioselective transformations, or to metallic complexes <2005OM6301, 2005OM2411>.



Alkylation of dihydropyrrolotriazoles with triflates can lead to the corresponding triazolium salts in a regioselective manner (Scheme 2) <1993JAN1866>.



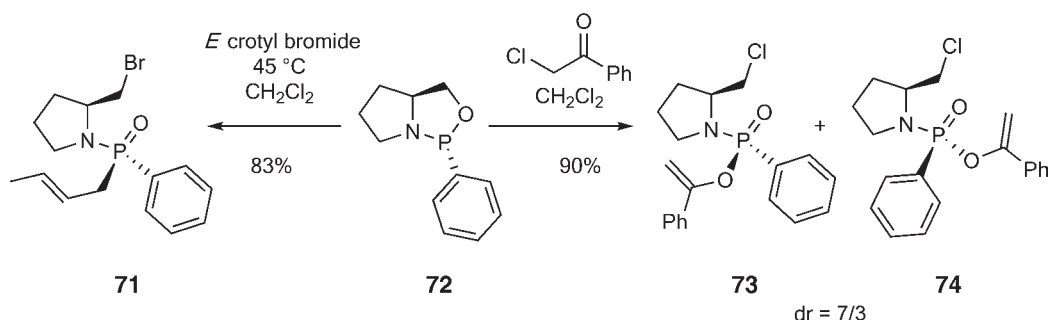
Scheme 2

11.03.6 Reactivity of Nonconjugated Rings

As in CHEC-II <1996CHEC-II(8)79>, reactions of nonconjugated rings have been classified according to the nature of the reactive center.

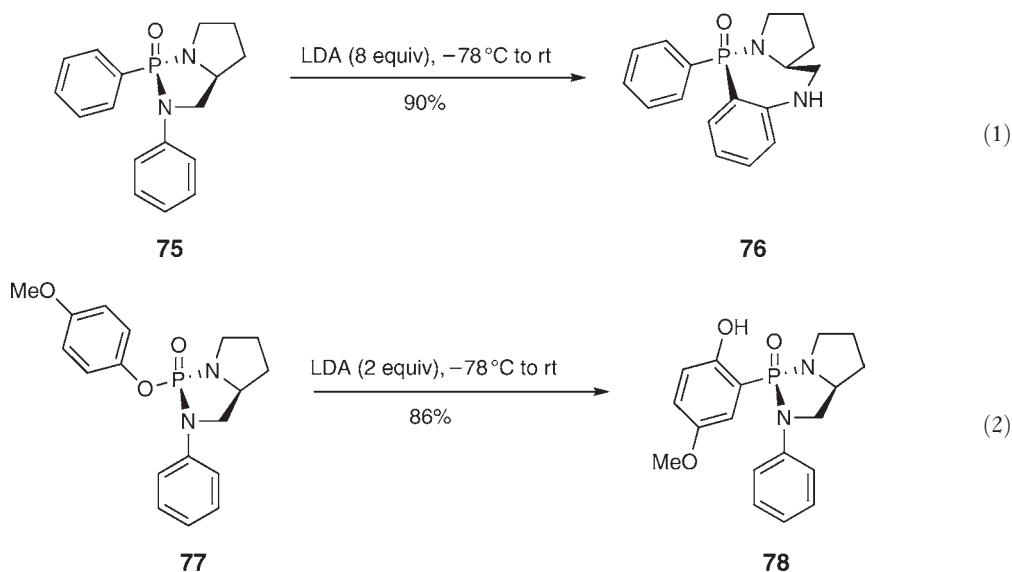
11.03.6.1 Reactions at Phosphorus

The oxazaphospholidine **72** can undergo an enantiospecific Michaelis–Arbuzov reaction with activated electrophiles, leading to phosphinamide **71** with complete retention of configuration at the phosphorus atom (**Scheme 3**) <1989CC805, 1997T11577>. Under the same reaction conditions, *E*-crotyl bromide led to the corresponding phosphinamide with retention of the double bond configuration. It is interesting to note that a Perkow reaction is observed with α -chloroacetophenone, leading to compounds **73** and **74** in a 7/3 diastereomeric ratio. The mechanism of this transformation has been discussed (**Scheme 3**).

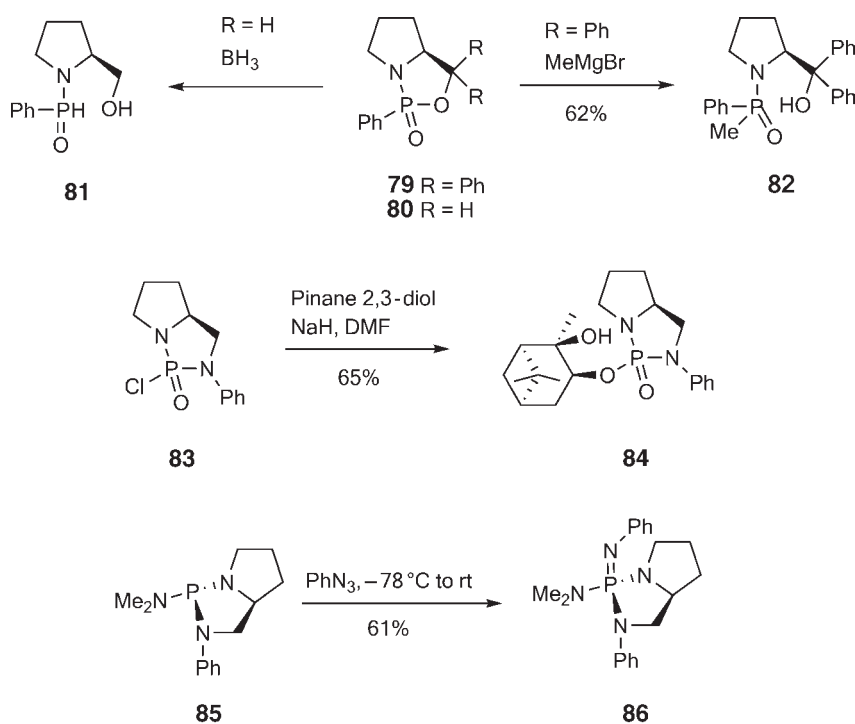


Scheme 3

The ring expansion of diazaphospholidine oxide **75** involves a stereospecific migration of phosphorus atom from N to a Csp² center (**Equation 1**). The overall retention of configuration at the phosphorus center has been explained by a sequential intramolecular apical addition, Berry pseudo-rotation and apical elimination pathway <1999AGE1479>. A P–O to P–C stereospecific rearrangement occurs when only 2 equiv of lithium diisopropylamide (LDA) are used for the deprotonation step, leading to diazaphospholidine oxide **78** from compound **77** (**Equation 2**) <1999EJO1099, 1998CEJ1061>.



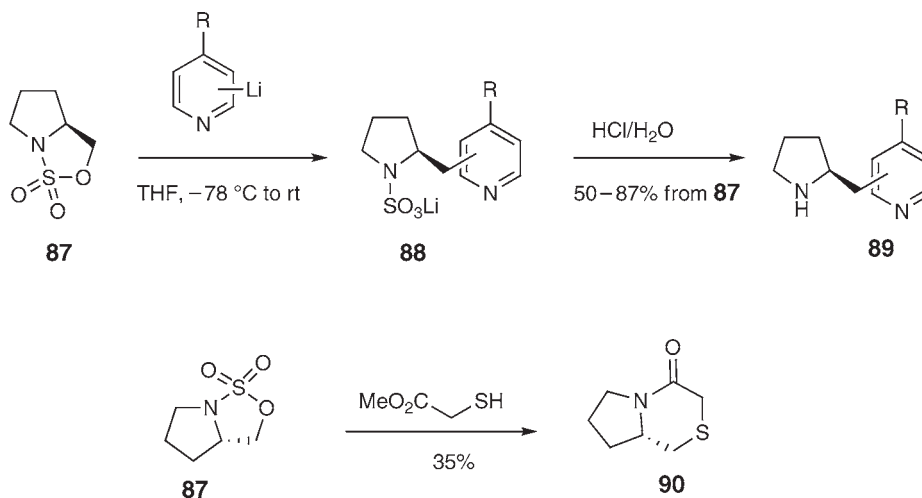
The ring opening of various phosphinamides occurs with inversion of the phosphorus configuration <1996TL39, 1996TL2853, 1998JP11027, 2005TL8677>, leading to interesting ligands such as **81** or **82** (**Scheme 4**). The chlorodiazaphosphole oxide **83** leads to phosphoramidate **84** when treated with pinane 2,3-diol in the presence of NaH <2004TA47>. The same reaction with diamines has been reported <2001TA685, 2004TA1881>. A similar reactivity is observed with chlorodiazaphospholidines <2005ASC61, 2002ASC868>. Among various oxidation reactions described at the phosphorus center of diazaphospholidines <2002TL4025>, the stereospecific reaction of compound **85** with phenylazide leading to iminophosphorane **86** is noteworthy <1999JA5807>.



Scheme 4

11.03.6.2 Reactions at Carbon

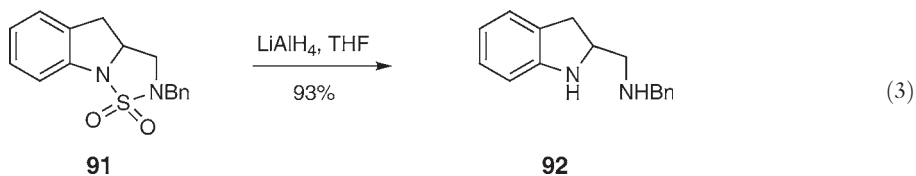
Cyclic sulfamates are excellent precursors for the synthesis of substituted pyrrolidines (Scheme 5). The reaction of compound **87** with a full range of lithiated pyridines leads to chiral pyrrolidine–pyridine conjugate base catalysts **89** for use in asymmetric Michael addition reactions <2004JA9558>. A similar strategy can be used for the preparation of bicyclic thiomorpholinones **90** <2003OL811>, diamines <1990TA877>, or pyrrolidine analogs of epibatidine <2005BML1637>. The regioselective alkylation or acylation reaction of pyrrolotriazoles has been studied <1990JOC571>.



Scheme 5

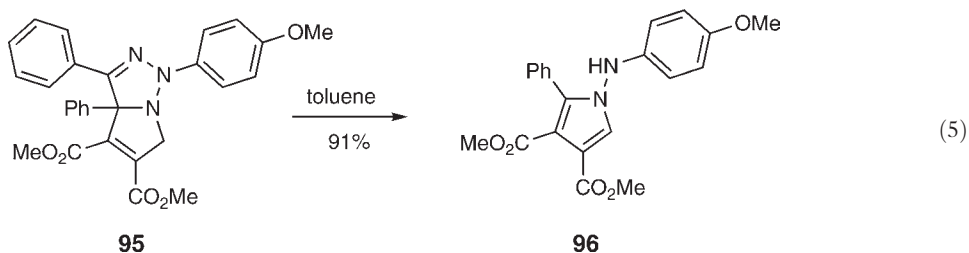
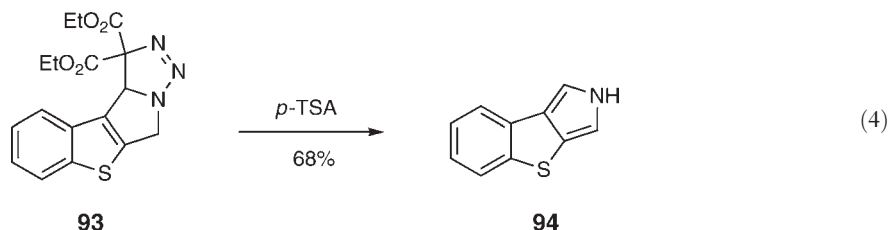
11.03.6.3 Reactions at Sulfur

The oxidation of sulfamidites to sulfamides is a way to prepare these heterocycles, although the direct reaction of amino-alcohols with sulfonyl chloride is generally more convenient [\(<1990TA885>\)](#). The reduction of sulfamides leads to the corresponding diamines ([Equation 3](#)) [\(<2005JA11250>\)](#).



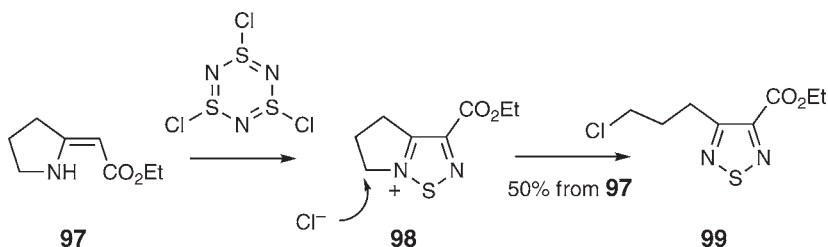
11.03.6.4 Reactions at Nitrogen

Triazolines can decompose under various conditions. Compound [93](#) leads to the corresponding pyrrole [94](#) under acidic conditions ([Equation 4](#)) [\(<2003TL1477>\)](#), whereas thermal treatment of bicycle [95](#) leads to [96](#) by a cycloreversion pathway ([Equation 5](#)) [\(<1996JP11617>\)](#).



11.03.6.5 Miscellaneous Reactions

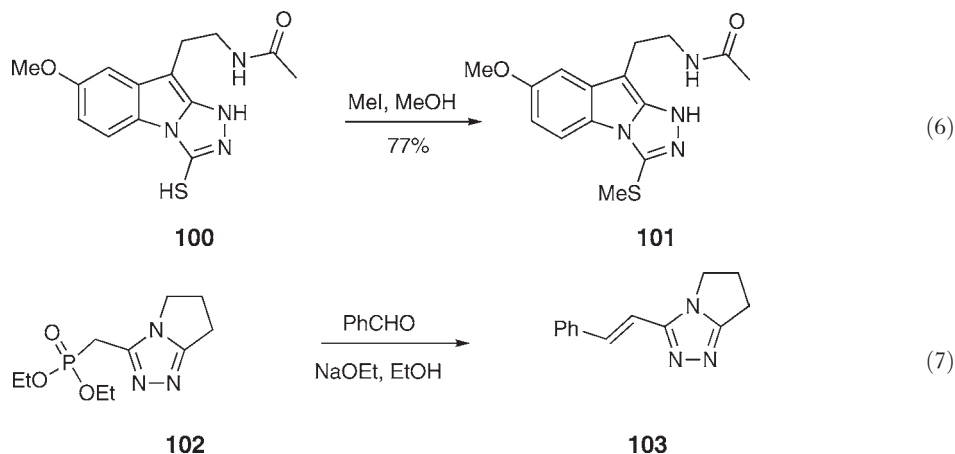
The *in situ* nucleophilic opening of thiadiazolium [98](#), prepared from compound [97](#), has been described ([Scheme 6](#)) [\(<2001JP1662>\)](#).



Scheme 6

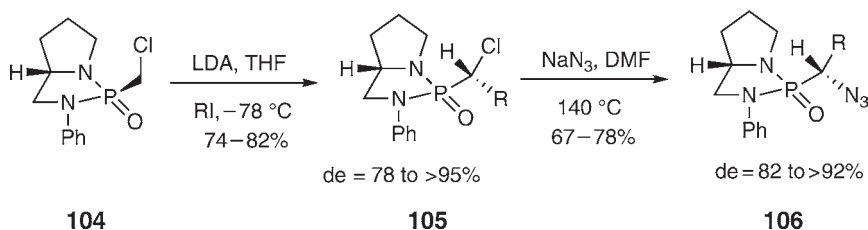
11.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Only a few reactions of the substituents attached to ring carbon atoms of bicyclic systems **1–34** have been reported. Methylation of compound **100** occurs at sulfur to give **101** (Equation 6) <2005BMC1847>. Horner–Emmons reaction of phosphonate **102** with benzaldehyde leads to triazole **103** as a single *E*-stereoisomer (Equation 7) <2004TL1877>.



11.03.8 Reactivity of Substituents Attached to Ring Heteroatoms

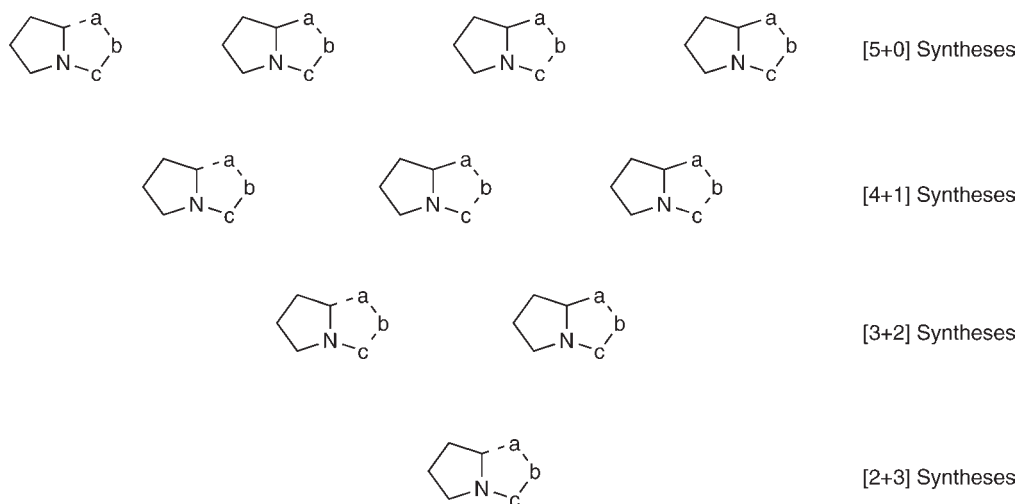
Chloromethylphosphonamide **104** has been alkylated with diastereoselectivities up to >95%. The corresponding azido compounds **106** were obtained by nucleophilic displacement, with partial to full stereospecificity <2000HA528>. This two-step process can lead to aminophosphonic acids after reduction of the azido group and hydrolysis of the chiral appendage (Scheme 7).



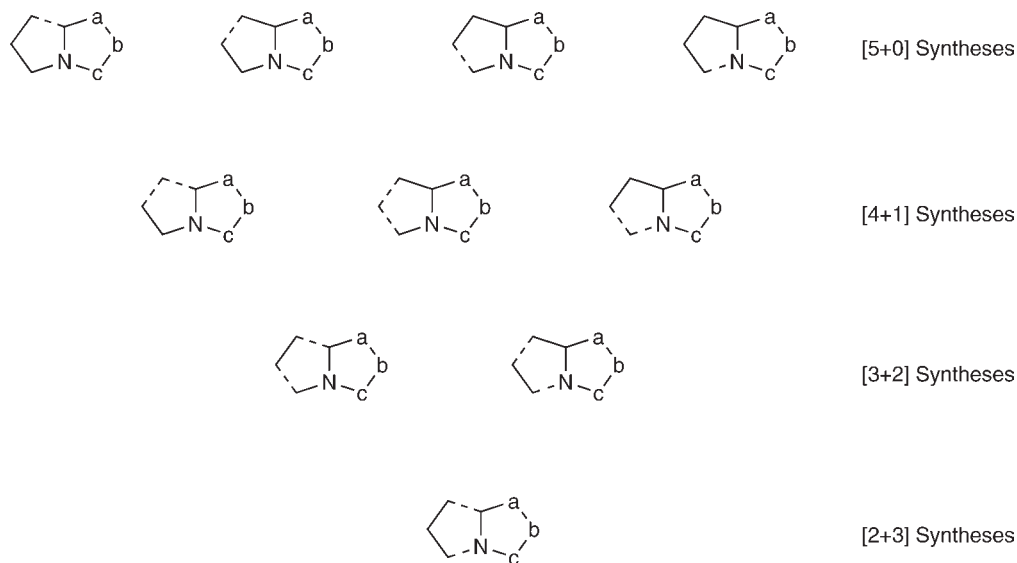
Scheme 7

11.03.9 Ring Syntheses from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The majority of syntheses of pyrrolo-fused bicyclic 5-5 systems starts from pyrrole derivatives and involves the formation of the ring containing the three heteroatoms. These syntheses can be classified according to the number of atoms in the pyrrole derivative and the number of additional atoms required for the formation of the second ring. This classification, used in CHEC-II(1996) <1996CHEC-II(8)79>, is summarized in Scheme 8. A second, less common, type of synthetic route involves the formation of the pyrrole ring, as depicted in Scheme 9. In addition, there are a number of syntheses with both rings formed simultaneously.



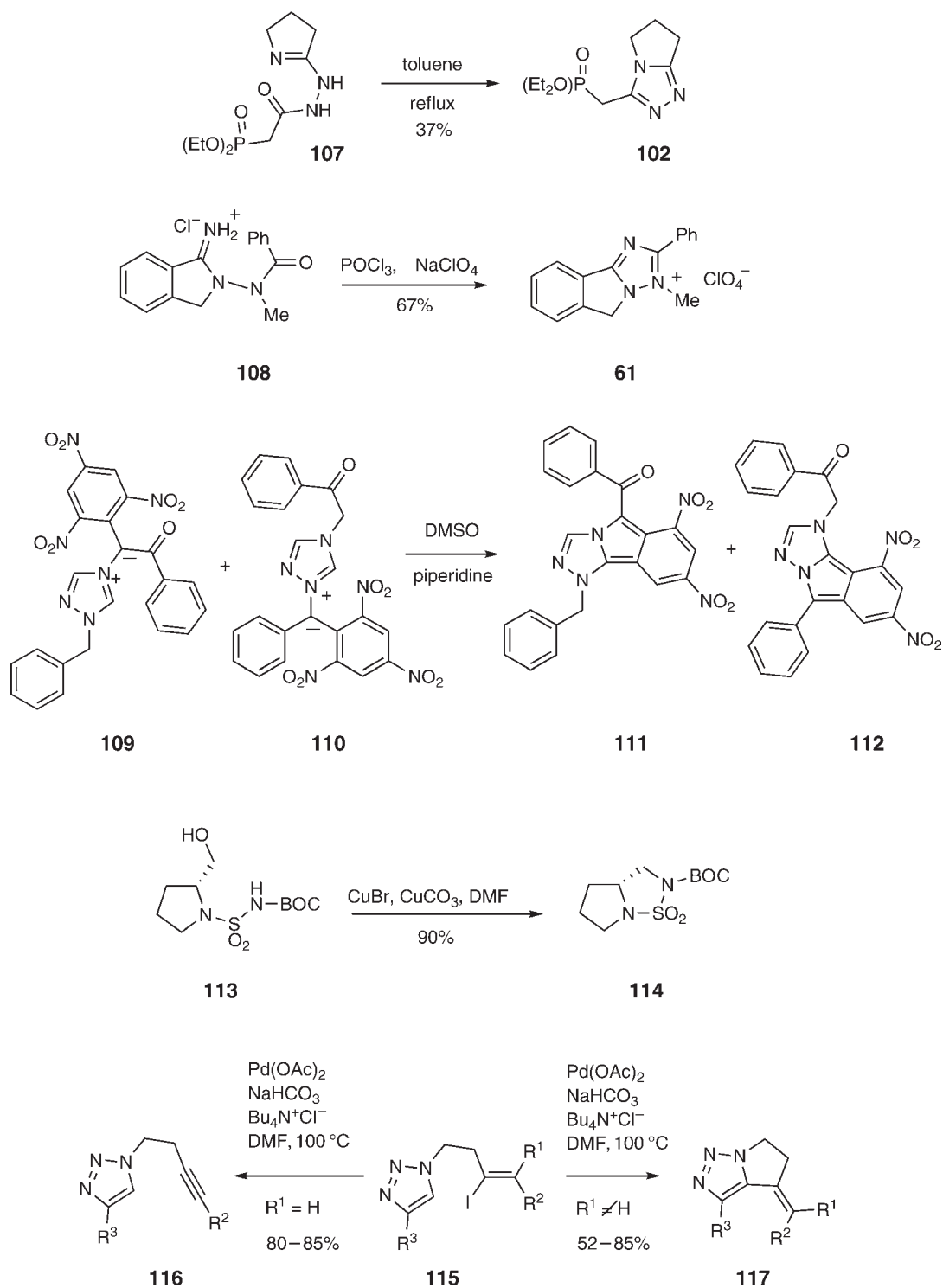
Scheme 8



Scheme 9

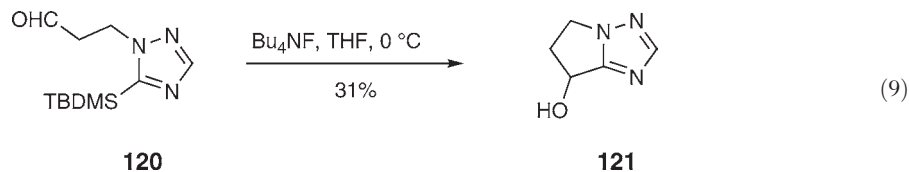
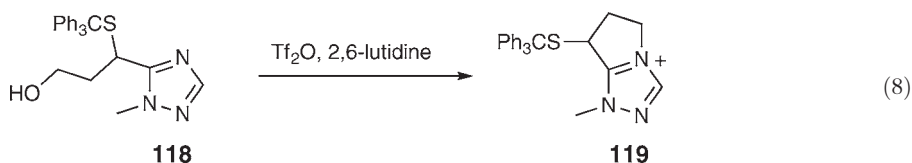
11.03.9.1 [5+0] Syntheses

The use of cyclodehydration reactions is a classical way for the formation of bicyclic triazoles. Precursors such as amidrazones [107](#) [<2004TL1877>](#) or [108](#) [<2002CHE1019>](#) are generally not isolated and spontaneously cyclize under reaction conditions [<2005BML4359>](#) ([Scheme 10](#)). Although less frequent, the pyrrole ring can also be elaborated by intramolecular condensations. Thus, a mixture of ylides [109](#) and [110](#) leads to the corresponding highly conjugated isomers [111](#) and [112](#) after cyclization and nitrous acid elimination [<2001EJO1407>](#). Examples of ring formation by intramolecular displacement using Goldberg's procedure have been reported [<2000T381>](#). Heck-type reactions [<2006SL1446>](#) or radical cyclizations [<2001JOC3717>](#) can also lead to bicyclic triazoles. In the former case, substrate containing a vinylic hydrogen led to homopropargyl compounds instead of the heterocycle, showing that the intramolecular elimination occurred more rapidly than the Heck reaction.



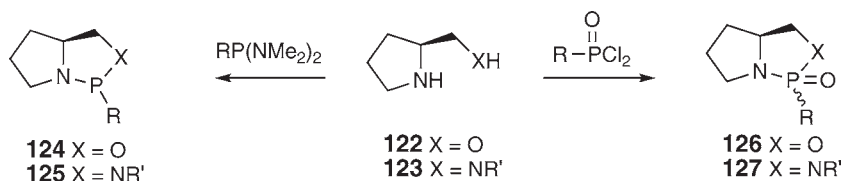
Scheme 10

The formation of azolium salt by intramolecular cyclization has been reported [\[1993JAN1866\]](#) as well as a similar cyclization under desilylating conditions (Equations 8 and 9).



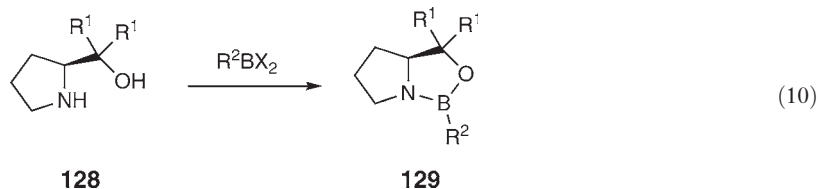
11.03.9.2 [4+1] Syntheses

Most of the syntheses in this category involve the condensation with electrophilic heteroatoms. The use of phosphorus(III) electrophiles generally leads to diastereomerically pure bicyclic systems [<2002ASC868, 2000CEJ2874, 2000TA1273, 1999JA5807, 2003T6473, 1999JOC8940>](#), whereas a diastereomeric mixture is obtained with phosphorus(V) reagents (**Scheme 11**) [<1999JOC1958, 1996TL8351>](#). In the latter case, diastereomers can generally be separated by column chromatography.

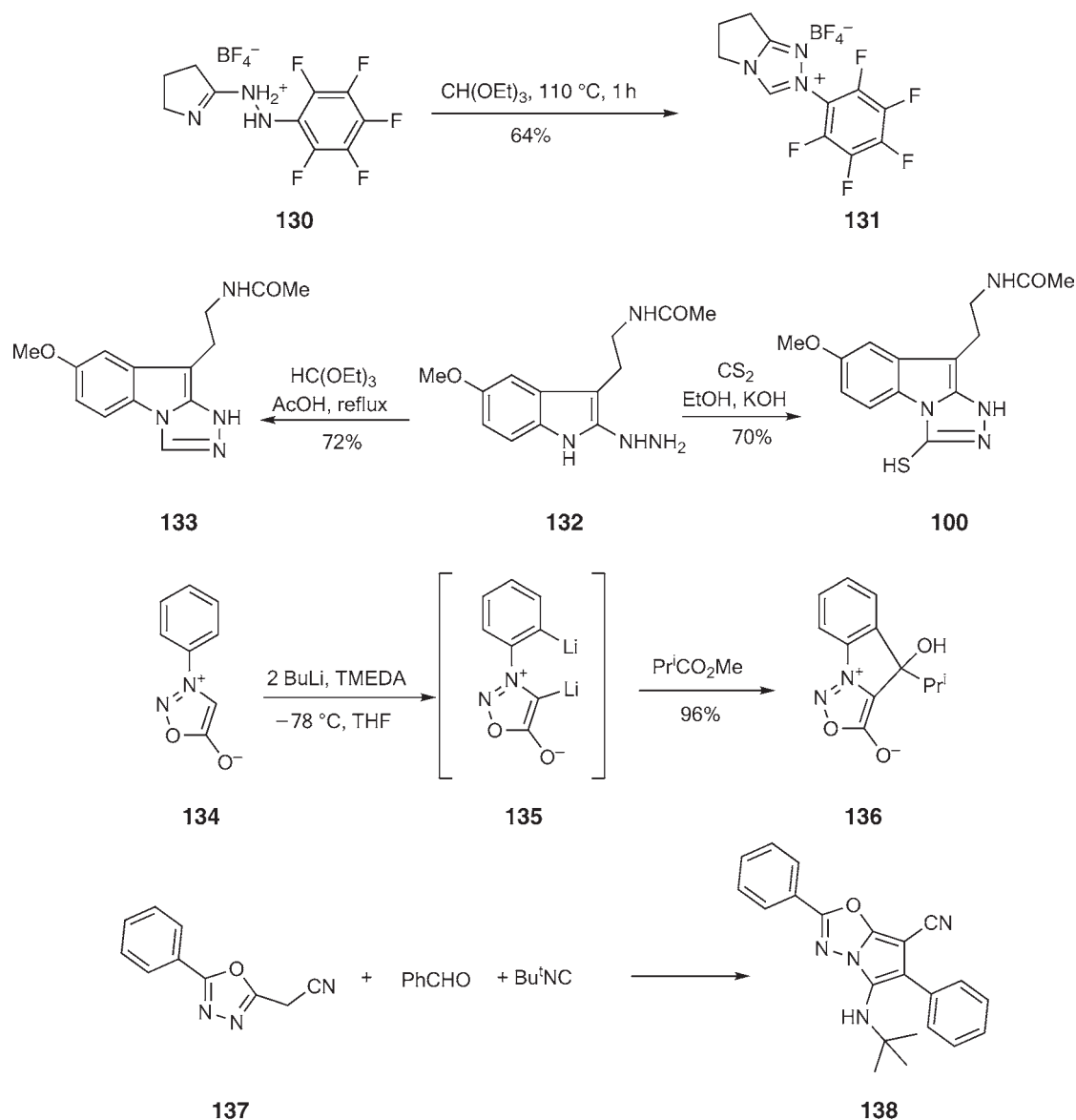


Scheme 11

Bicyclic oxazaborolidines are also prepared by condensation of pyrrolidino alcohols and electrophilic boranes such as $\text{BH}_3\text{-THF}$ or $\text{BH}_3\text{-Me}_2\text{S}$ complexes, trimethylboroxine, *n*-butylboronic acid, 4-*t*-butylphenylboronic acid, or trialkylborates (**Equation 10**) [<2006T7621>](#). Sulfamidates such as **87** have been prepared by a similar strategy, either directly by treatment of prolinol with sulfuryl chloride, or by a two-step process involving cyclization with thionyl chloride followed by oxidation of the transient sulfamidite [<2003OL811, 1990TA877, 2005BMCL1637, 1990TA885>](#).



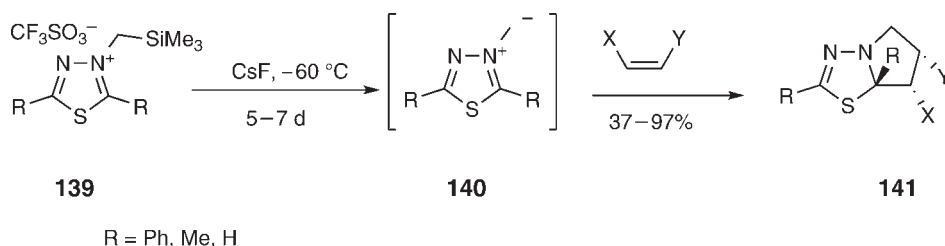
Bicyclic triazolium salts such as **131** are typically prepared by the condensation of amidrazone salts with trimethyl or triethyl orthoformate [<1998JP11891, 2005JOC5725, 2006AGE1463>](#). This practical route has been used for the preparation of several chiral bicyclic triazolium salts as bench stable precursors for *N*-heterocyclic carbenes (**Scheme 12**) [<2002JA10298, 2004JA8876, 2005JA6284, 2005T6368, 2005OL905>](#). A similar approach has been used for the synthesis of triazolindole derivatives **132** or **100** [<2005BMC1847>](#). Condensation of methyl 2-methylpropanoate with dilithiated sydnone **135** has been reported to give the corresponding mesoionic compound **136** in excellent yield [<1997TL1165, 1996S1183>](#). Condensation with an isonitrile enables the preparation of compound **136** by a three-component reaction [<2004WO2004108722>](#).



Scheme 12

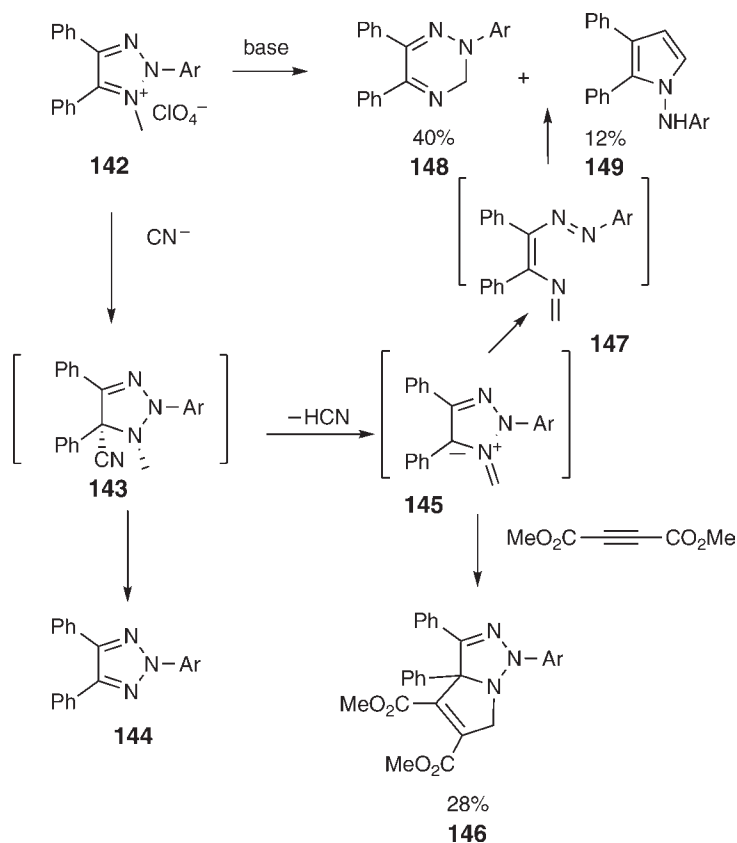
11.03.9.3 [3+2] Syntheses

1,3-Dipolar cycloadditions are powerful tools for the elaboration of five-membered heterocycles. It is therefore not surprising to find several examples of such a strategy for the preparation of 5-5 bicyclic systems starting from cyclic dipoles. In some cases, these reactive species have to be prepared at low temperature. The reaction of unstable 1,3,4-thiazolium-3-methanide dipoles **140** with a wide range of cyclic or acyclic alkenes has been investigated [\[2002JP12851, 2001CC1950\]](#). The regiochemistry was indicative of a dipole HOMO-controlled cycloaddition, with the ‘anionic’ terminus of the dipole bonding to the unsubstituted carbon of the alkene. The *endo*-cycloadduct was generally obtained as the major stereoisomer although some steric effect of the bridgehead substituent could be responsible for a lower selectivity with cyclic dipolarophiles such as maleimides. In most cases the reaction was stereospecific, leading respectively to *trans*-derivatives from *E*-alkenes and *cis*-isomers from *Z*-alkenes (Scheme 13). A similar study has been conducted on the corresponding 1,2,3-triazolium-1-methanide 1,3 dipoles, leading to adduct **44** [\[2001JP11778\]](#).



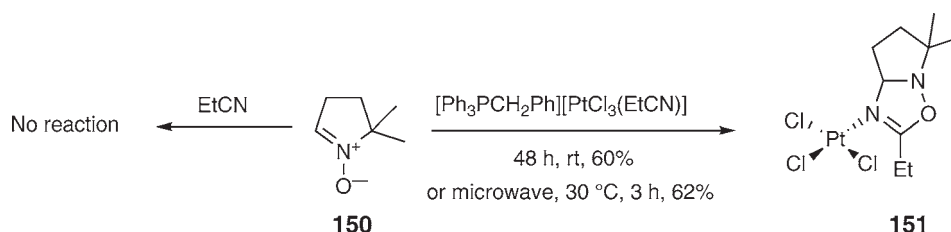
Scheme 13

Azolium systems with C–H bonds can be deprotonated to give rise to an internal azolium ylide or an isoelectronic stable azole carbene system, whereas fully substituted heterocycles such as **142** can evolve in a more complex manner under basic conditions or with nucleophiles. Thus, in the presence of cyanide ion, the formation of adduct **143** could be evidenced by NMR spectroscopy. This intermediate, when stirred at ambient temperature for 48 h in the presence of dimethylacetylene azodicarboxylate (DMAD), led to the adduct **146** (28%) along with products **148** (40%) and **149** (12%) (Scheme 14) <1997JP12919>.



Scheme 14

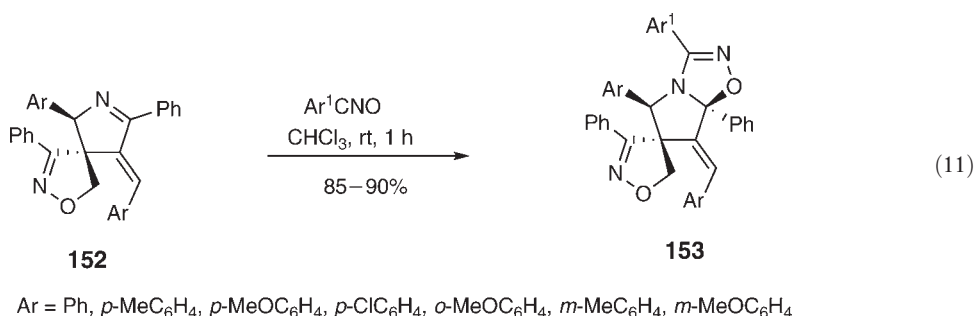
The reaction of cyclic nitrone with phenyl isothiocyanate <2003MI253>, isocyanate <1974JOC568>, or cyanoesters <1995JP11417> has been reported. The beneficial effect of activation of the dipolarophile by coordination on a platinum complex and focused microwave irradiation has been described (Scheme 15) <2003JCD2540>.



Scheme 15

11.03.9.4 [2+3] Syntheses

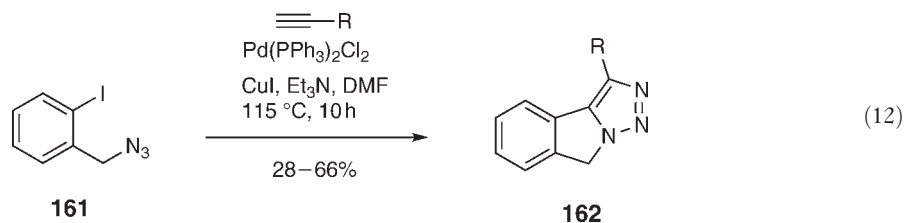
Five-membered heterocycles can behave as dipolarophiles in cycloaddition reactions. The reactions of cyclic imidates <1994T5159> or imines with nitrile oxides <1990T7865> or nitrilimines <1985AP556> have been described. An interesting chemoselective transformation has been reported with compound **152**. A completely diastereoselective cycloaddition of nitrile oxides with this rigid and sterically congested compound occurred on the less hindered double bond, leading to several spiro-pyrroline derivatives (Equation 11) <2001T7391>.

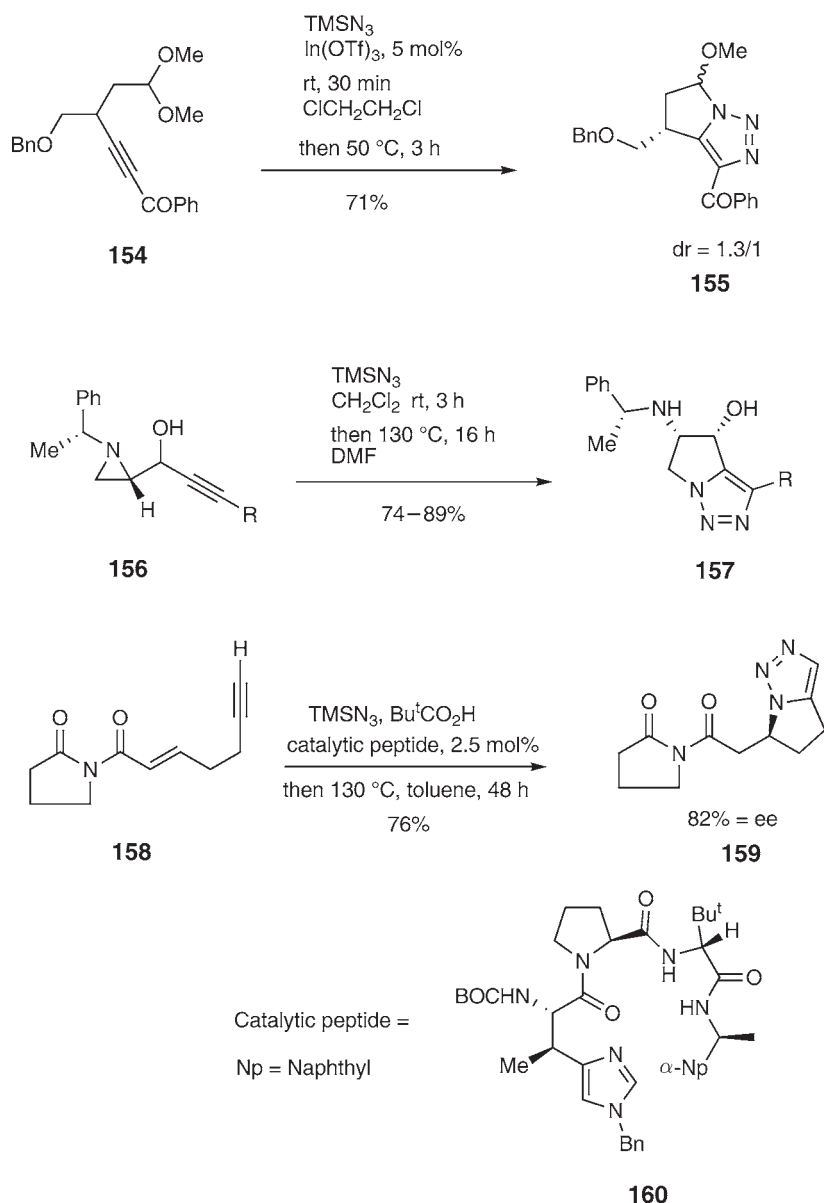


11.03.9.5 Simultaneous Formation of Both Rings

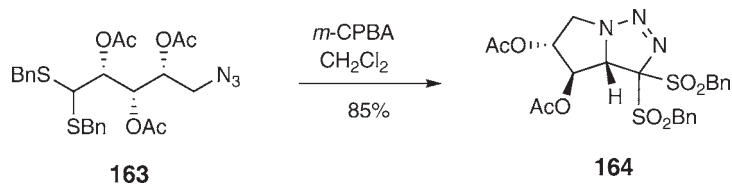
Since the first synthesis of pyrrolotriazoles by intramolecular 1,3-dipolar cycloaddition of azidoalkenes <1965JA749>, several examples of 5-5 bicyclic systems based on the simultaneous formation of both rings have been reported. In most of the cases, cyclization follows the azidation reaction in a sequential manner, without isolation of the intermediate <2003T1477>. Pyrrolotriazoles have been prepared from acetals <2005TL8639>, aziridines <2005SL2187>, or unsaturated imides <2002JA2134>. In the latter case, enantio-enriched material could be obtained using an asymmetric conjugate azide addition catalyzed by peptide **160** (Scheme 16).

Another route involves a palladium–copper-catalyzed tandem carbon–carbon formation/cycloaddition sequence (Equation 12) <2005TL8531>. Notably, cycloadditions of azide to the internal alkynes failed under click chemistry reaction conditions <2003DDT1128>. Cyclization under oxidative conditions has been reported from dithioacetal **163** (Equation 13) <1996TL3925>. The formation of **164** as a single diastereoisomer has been explained by stereoelectronic effects.



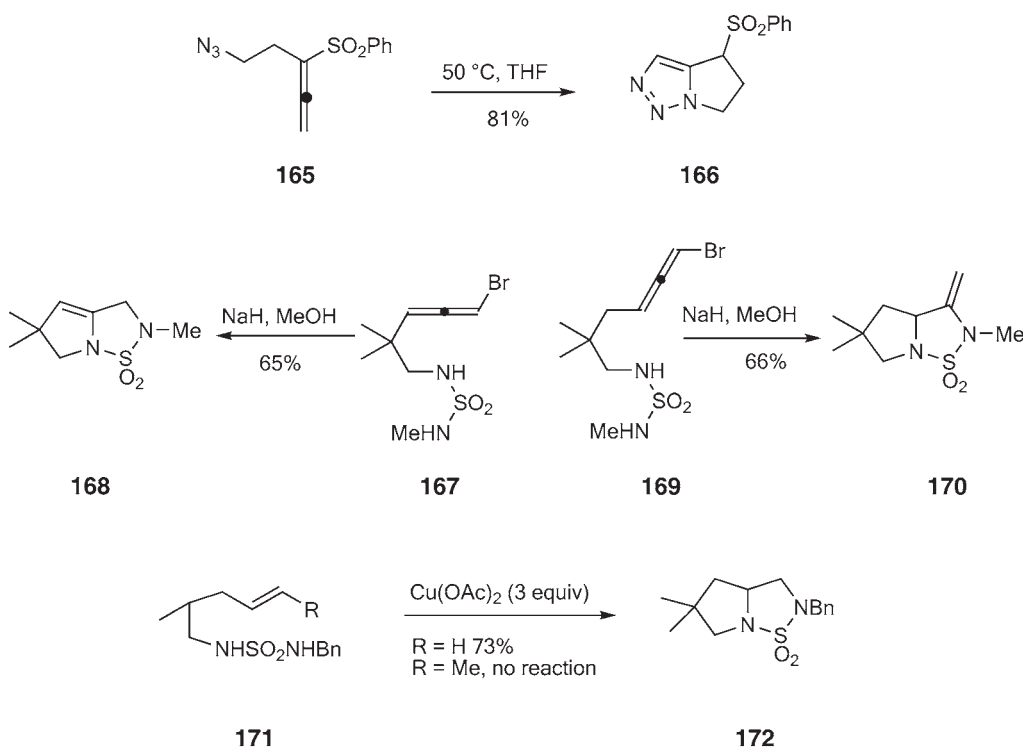


Scheme 16



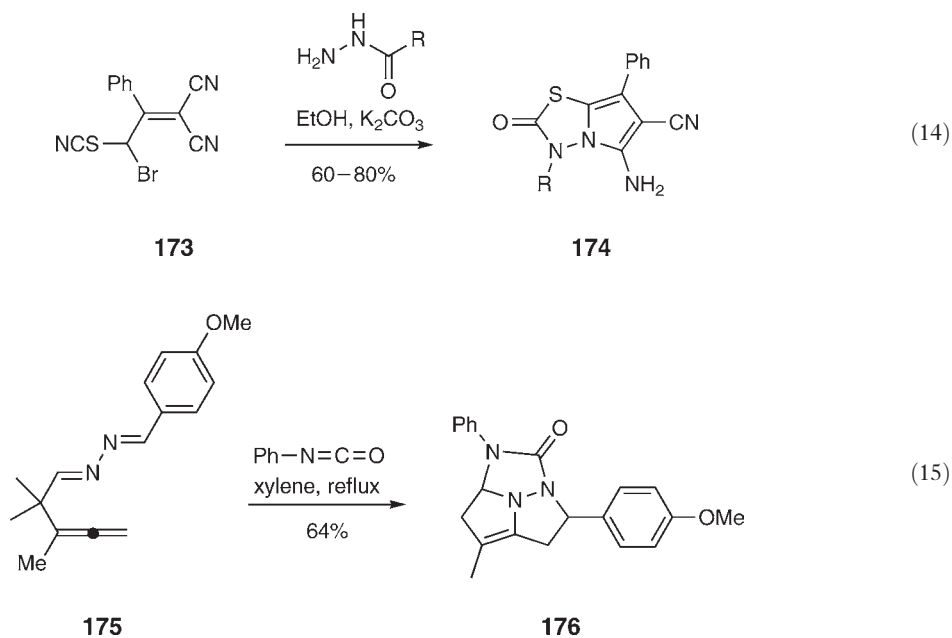
(13)

Allenes are useful precursors for fused 5-5 bicyclic systems. Cyclization of compound **165** under thermal conditions to the corresponding triazole has been reported [\[2004JOC2128\]](#). A similar route has been described for the preparation of bicyclic sulfamides [\[2005AGE1513\]](#). Interestingly, the regioselectivity of the cyclization varies with the length of the tether between the two reactive functions, leading to systems with endo- or exocyclic unsaturation. Sulfamides have also been prepared by a copper acetate-promoted intramolecular diamination of unactivated olefins [\[2005JA11250\]](#). It was shown that substitution at the terminal position of the olefin affects the reactivity of the substrate ([Scheme 17](#)).



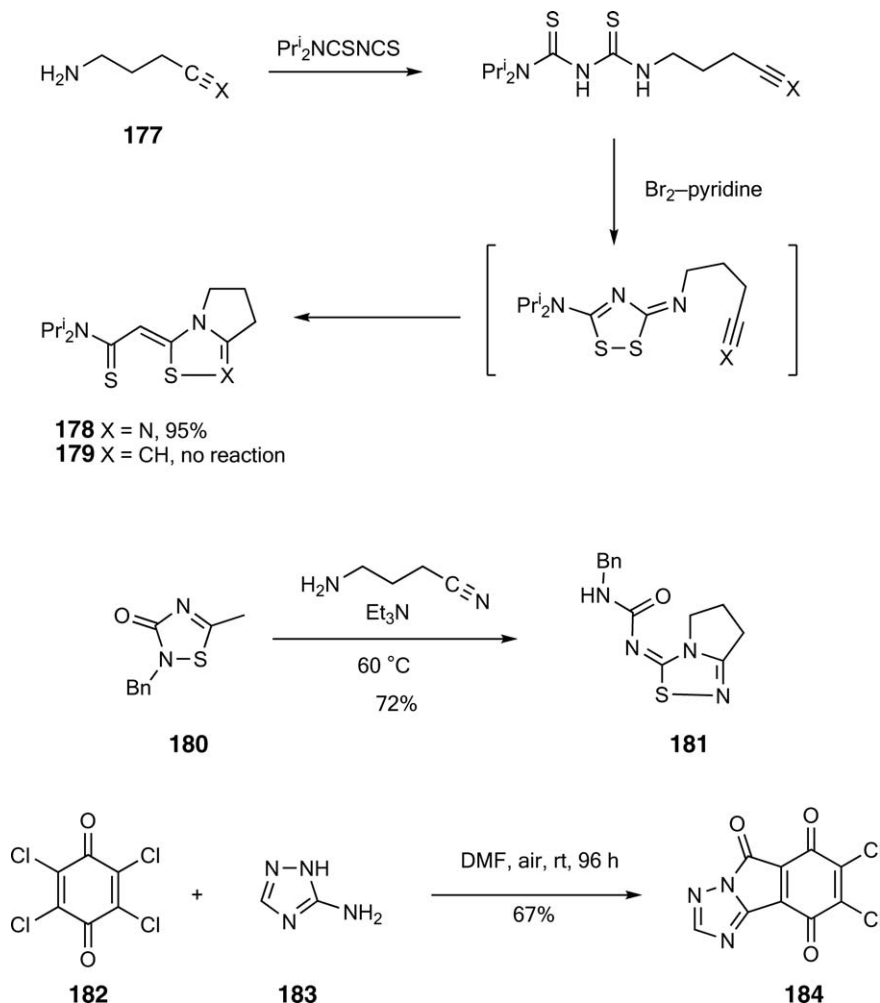
Scheme 17

A number of other ring systems have been prepared by intramolecular bis-annulation procedures. Pyrrolothiadiazolines **174** were prepared by condensation between hydrazides and compound **173** (Equation 14) <1998JPR676>. The thermally induced intra-intermolecular criss-cross cycloaddition of azine **175** in the presence of phenyl isocyanate leads to heterocyclic compound **176** containing three fused five-membered rings (Equation 15) <2002TL6431>.



11.03.10 Ring Syntheses by Transformation of Another Ring

Only a few examples of this type have been reported. In some cases, some heterocycles can act as masked 1,3-dipoles. Thus, the synthesis of fused 1,2,4-thiadiazoles based on this principle has been reported <1996JP1225>. It is interesting to note that in contrast to the easy formation of compound **178**, the fused thiazole **179** could not be obtained from the corresponding acetylenic amine. Closely related accesses to fused diazoles from chlorothiadiazolones <1994T7019> or 1,3,4-oxadiazoles <1984T2703> have been described. Aminotriazole **183** can condense with tetrachloroquinone **182** in the presence of DMF to give compound **184** (Scheme 18) <1997PHA23>.



Scheme 18

11.03.11 Synthesis of Particular Classes of Compounds

Several routes to the pyrrolo[1,2-*c*][1,2,3]triazole skeleton have been described. Intramolecular dipolar cycloaddition of azido-alkenes or alkynes seems to be the most convenient process, although the cyclization efficiency seems to be highly substrate dependent (Scheme 16) <2002JA2134, 2003T1477, 2005SL2187, 2005TL8639>. The formation of this bicyclic system by an intramolecular Heck reaction is an attractive alternative. The recent syntheses of sulfamides by intramolecular cyclization of alkenes or allenes offer a complementary route to the classical

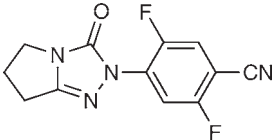
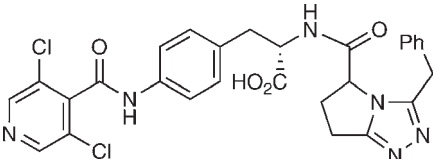
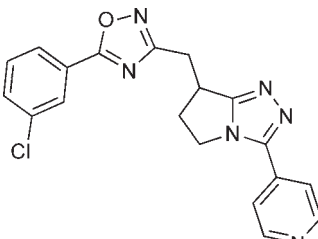
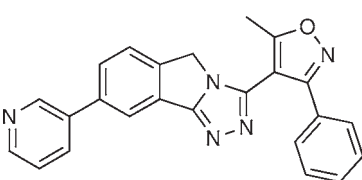
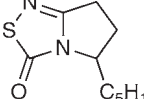
condensation approaches. Several preparations of pyrrolothiadiazoles of general formula **8** have been described <1998JPR676, 2001CC1950, 2002JP12851>, but none of these methods seems to be general.

11.03.12 Important Compounds and Applications

Oxazaborolidines **127** are very important catalysts for the enantioselective reduction of ketones, with a predictable absolute configuration and generally high enantiomeric excess. Recent examples of their use in the synthesis of compounds of interest have been reviewed <2006T7621>, and include the syntheses of natural products or bioactive compounds <1998AGE1986>. Protonated oxazaborolidines are also excellent catalysts for Diels–Alder reactions <2002JA9992, 2004JA4800, 2005OL1633> or cyanosilylation reactions <2005JA5384>, and have been recently used in several syntheses of bioactive compounds <2004JA13708, 2005JA11958, 2006JA6310, 2006JA740>. Other 5,5 bicyclic systems such as oxaza- or diaza-phospholidines have been used as ligands for asymmetric transformations such as hydroborations <2002ASC868>, allylations or aldol reactions <2003JA2208, 1999JOC1958>, and conjugate additions <2004CEJ6048>. The importance of bicyclic azolium salts as carbenes precursor is rapidly growing, since these species are recognized as catalysts in benzoin or Stetter reactions and analogous transformations <2004ACR534>.

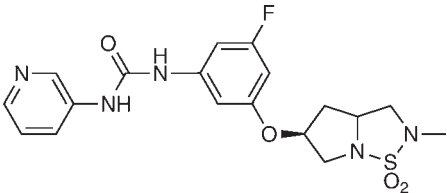
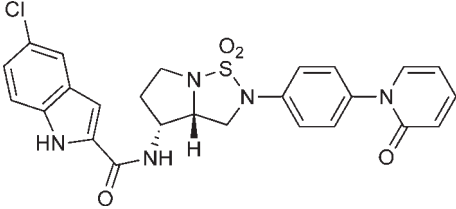
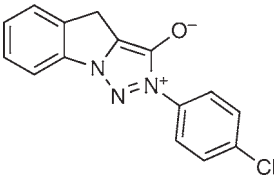
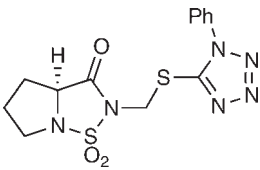
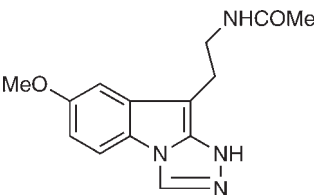
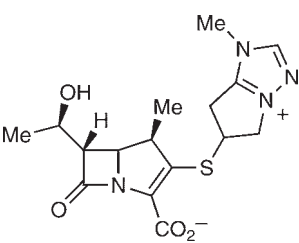
Several biological activities of 5-5 bicyclic systems have been reported, especially in patents, although the correlation between activities and this particular framework have not been clearly established (Table 3).

Table 3 Biologically active compounds

Structure	Activity	Reference
	Herbicide	1999DE19901846
	α 4-Integrin inhibitor	2006WO2006052961
	Metabotropic glutamate receptor antagonist	2005WO2005080397
	GABA-A α 5 receptor ligand	2004US2004058670
	Nitric oxide synthase inhibitor	1999WO9964426

(Continued)

Table 3 (Continued)

<i>Structure</i>	<i>Activity</i>	<i>Reference</i>
	Heart failure treatment	2005US2005159416
	Factor Xa inhibitor	2005WO2005032468
	Anti-inflammatory	1999WO9902528
	Elastase inhibitor	1996US5494925
	Antioxidant	2005BMC1847
	Antibiotic	1993JAN1866

11.03.13 Further Developments

Several reports on the use of bicyclic azolium salts as carbene precursors have recently appeared <2006JA8418, 2006OL3785, 2006AGE6021, 2006T11477, 2006SL2431> as well as the use of phosphoramides <2006AGE5000, 2006TL2721, 2006CC2292, 2006JOC1513, 2006JOC1523, 2007JOC707> or oxazaborolidines <2007JA1498> in enantioselective reactions. New syntheses of sulfamides <2007CEJ1692> and oxadiazoles <2006TL6961, 2006QSAR504> have been reported.

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Biographical Sketch



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11.02

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 1:0

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11.02.1 Introduction

This chapter covers the bicyclic 5-5 systems with one ring junction nitrogen atom and one extra heteroatom. There is a related chapter in CHEC-II(1996), entitled “Bicyclic 5-5 System with One Ring Junction Nitrogen Atom: One Extra Heteroatom 1:0,” that covers the knowledge on this type of compounds from 1982 to 1995 <1996CHEC-II(8)25>. No general review except this one exists, nor are there systematic studies on the subject.

There are nine possible parent structures (labeled A to I), in which the double bonds can be arranged in different ways to give 22 basic structures (structures 1–22 in Figure 1):

1. Pyrrolo[1,2-*b*]pyrazole (A). The different arrangement of the double bonds give four tautomeric systems: 1*H*-(A) **1**, 3*H*-(A) **2**, 4*H*-(A) **3**, 6*H*-(A) **4**.
2. Pyrrolo[1,2-*a*]imidazole (B) and pyrrolo[1,2-*c*]imidazole (C). Each of them exists as four tautomeric systems: 1*H*-(B) **5**, 3*H*-(B) **6**, 5*H*-(B) **7**, 7*H*-(B) **8**, 1*H*-(C) **9**, 3*H*-(C) **10**, 5*H*-(C) **11**, 7*I*-(C) **12**.
3. Pyrrolo[1,2-*b*]isoxazole (D) **13**.
4. Pyrrolo[2,1-*b*]oxazole (E) **14**.
5. Pyrrolo[1,2-*c*]oxazole (F). This parent structure must be partially saturated. There are three possible isomeric systems: 1*H*,3*H*-(F) **15**, 3*H*,5*H*-(F) **16**, 3*H*,7*H*-(F) **17**.
6. Pyrrolo[1,2-*b*]isothiazole (G) **18**.
7. Pyrrolo[2,1-*b*]thiazole (H) **19**.
8. Pyrrolo[1,2-*c*]thiazole (I). This system, like F, must be partially saturated, and again three isomers are possible: 1*H*,3*H*-(I) **20**, 3*H*,5*H*-(I) **21**, 3*H*,7*H*-(I) **22**.

Reduced derivatives of all these parent structures (dihydro, tetrahydro, and fully saturated systems) increase greatly the number of possible compounds. Oxo compounds are also possible, and each of the nine parent structures has five different positions where the carbonyl group could be located.

Several of those structures that were not present in CHEC-II(1996) in the corresponding chapter are now described in the literature. Of the 22 basic structures, today, only 13 are described in the literature: 3*H*-pyrrolo[1,2-*b*]pyrazole <2000SL955, 1998JOC9131>, 6*H*-pyrrolo[1,2-*b*]pyrazole <1995JFC203>, 1*H*-pyrrolo[1,2-*a*]imidazole <2000S1439>, 5*H*-pyrrolo[1,2-*b*]imidazole <1999J(P1)2049, 1999J(P1)2047, 1997J(P1)2203>, 7*H*-pyrrolo[1,2-*a*]imidazole <1990J(P1)1821, 1992CB1939>, 1*H*-pyrrolo[1,2-*c*]imidazole <1989H(29)1137>, 3*H*-pyrrolo[1,2-*c*]imidazole <1983CL763>, 5*H*-pyrrolo[1,2-*c*]imidazole <2003TL1379, 2000TL4991, 1999J(P1)2049>, pyrrolo[1,2-*b*]oxazole, 1*H*,3*H*-pyrrolo[1,2-*c*]oxazole <2004JOC7558, 2002TL463, 2000H(53)1011, 1999TL2525, 1998H(48)635, 1997SL390>, pyrrolo[2,1-*b*]thiazole <2002H(57)1697,

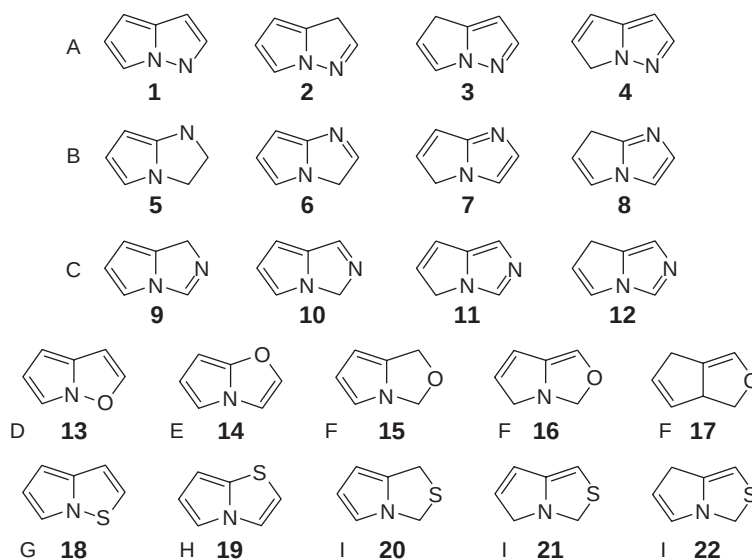


Figure 1 The 22 basic structures.

2001JA2074, 1998PS251, 1998T3913>, 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole <2005JOC6629, 2005SL239, 2004JHC493, 2002SUL87, 2002T5093, 2002CHE86, 2002JOC4045, 2002BML341, 2001H(55)1843, 2001J(P1)1795, 2001HCA972, 2000JME2149, 2000T10011, 2000T7267, 2000T3419, 2000CC675, 1998JME74, 1997SC2125, 1995BML2913, 1995BML2909, 1995BML2903, 1995BCJ1969>.

Below are listed all the other compounds that include the basic framework structure of the parent derivatives.

Seventeen examples of the pyrrolo[1,2-*b*]pyrazole nucleus are described: 2,3-dihydro-1*H*- <2000SL955>, 5,6-dihydro-4*H*- <2002TL4191, 2004BML3581, 2005JBC19298, 2005TL2387, 2005B2293, 2004BML3585, 2004JME3674, 2002TL6431, 1998JAN599, 1997TL1095, 1997SL1013>, 2-oxoperhydro- <1999JOC1347, 1999TL395, 2002T1433, 2005T1155>, 3*a*,4,5,6-tetrahydro-3*H*- <2002AGE4456>.

Several derivatives of the pyrrolo[1,2-*a*]imidazole system are known including the dihydro, -2,3-dihydro-1*H*- <2000S1439>, 6,7-dihydro-5*H*- <2004TA3181, 2003BMC3559, 2003SL780, 2002T4445>, -perhydro- <2000JOC3683, 2002JOC8224, 1998J(P1)2061, 1997TL1647, 1996TL1707, 1996TL1711>, 2-oxoperhydro- <2005OL3601, 2004EJO2883, 2002JOC4951>, 3-oxoperhydro- <2002OL1547, 2002J(P2)2078>, and 5-oxodihydro- derivatives <2002JCS(P1)2078>.

Dihydro-1*H*-pyrrolo[1,2-*c*]imidazoles are also known, particularly in the dioxo series <1998JME63, 2004JOC9313> and 5,6,7,7*a*-tetrahydropyrrolo- <2005JOC2368>. One example of the 5,6,7,7*a*-tetrahydropyrrolo[1,2-*c*]imidazolidinium salt is described <2005CEJ1833>.

Perhydropyrrolo[1,2-*c*]imidazoles are reported <1996TA3431, 1996TL3051, 1996TL7465, 1999AG(E)2556, 2004T4399, 2005TL1263>. Different oxo derivatives have been reported: 1-oxoperhydro- <1990JOC2254, 1997M395, 1997JA6153, 1997TA1855, 2000BMC135, 2001JA2919, 2001JFC275, 2001TL407, 2001TL410>, 3-oxoperhydro- <2002AGE4556, 2002CEJ2464, 2002TA1769, 2005JA14586>, 1-oxo-3-thioxoperhydro- <2000TL135>, 1,3-dioxoperhydro- <1996JME4439, 1997JME2653, 1999BML1679, 2000CC785, 2000T3245, 2001JME186, 2001JME198, 2003BML1429, 2003TA1323, 2005BML1161, 2005JME2548, 2005TL3131>, 1,5-dioxoperhydro- <2005TL143>.

Only two examples of the pyrrolo[1,2-*b*]isoxazole system have been found from 1996 – 3*a*,4,5,6-tetrahydropyrrolo- <1997J(P1)155, 1997T2979, 1997TA1031, 2001HCA3822, 2001T4349, 2001TA3297, 2002TA437, 2003TL523, 2005JOC3157> and the synthetic routes to a large number of perhydropyrrolo[1,2-*b*] are available <1996T4225, 1996TA2793, 1997JOC3119, 1997T2979, 1997T7057, 1997T11869, 1997T14763, 1997T16803, 1997TA109, 1997TA293, 1997TA1031, 1998EJO419, 1998J(P1)1, 1998T6947, 1998T9429, 1998T10857, 1998T15691, 1999AGE1116, 1999TL2853, 2000CRC793, 2000EJO3633, 2000OL2475, 2000T187, 2000TL1583, 2001CC1590, 2001J(P1)3409, 2001OL1367, 2001T8959, 2001TL4155, 2001TL5937, 2002BML677, 2002EJO1941, 2002JA4968, 2002OL177, 2002OL2921, 2002TL5711, 2002TL6383, 2003HCA3066, 2003TL523, 2003TL2315, 2004AGE1559, 2004BML3967, 2004TL4097, 2005BML545, 2005CEJ6878, 2005JA13386, 2005JOC856, 2005JOC3157, 2005T8836, 2005T10886>.

There is no pyrrolo[2,1-*b*]oxazole described in the literature in contrast to perhydropyrrolo[2,1-*b*]oxazoles which have been often reported <1996JA7429, 1996JA9876, 1996JOC2586, 1996JOC3362, 1996JOC4949, 1996JOC5712, 1996T9035, 1996T10761, 1997JNP755, 1997JOC6704, 1996T15127, 1997TL4075, 1997T7011, 1998JME4556, 1998LS2243, 1998TL1697, 1999CC1371, 1999CSR383, 1999JA2762, 1999JA5334, 1999J(P1)2605, 1999JOC1979, 1999T8931, 1999TL3673, 1999TL4639, 1999TL8071, 2000EJO1719, 2002EJO1484, 2004TL5175, 2005JOC10368, 2005OL4657, 2005T7774, 2005TL3407, 2006TL69> as well as 3-oxo <2003T6291, 2003CC440> and many 5-oxoperhydro derivatives <2000TL8193, 2000TL9377, 2001J(P1)3029, 2001JOC4939, 2003T241, 2004BML5537, 2004BML3885, 2004BML5537, 2004JOC2773, 2004T1235, 2004T1247, 2004TL5047, 2004T17731, 2005JOC10368>. Two examples of dihydro derivatives are also known <2003EJO1438, 1999JMO297>.

Pyrrolo[1,2-*c*]oxazoles are reported <1997SL390, 1999JMO297, 2002TL463, 2004JOC7558, 2004JOC9313, 2006TA53>. The dihydropyrrolo derivatives are described in several references <1996TL4573, 1997T11731, 1998CC461, 1998EJO509, 1998J(P1)223, 1998TL1193, 1999TL2525, 1999CC2333, 1999JOC547, 1999OL717, 2000T2437, 2000TL8285, 2001J(P1)2997, 2001T5123, 2001TA1353, 2001TL5705, 2001JOC6483, 2001JOC7555, 2002EJO3543, 2002J(P1)80, 2002TL463, 2002TL6609, 2002TL3919, 2002OL119, 2003AGE5987, 2003OL1717, 2003OBC3749, 2003TL5033, 2004AJC669, 2004T5759, 2004T8031, 2004TA1239, 2005JA8298, 2005OBC2872, 2006TA53>. Since 1996, an important number of references concern the preparation, reactivity, uses, and biological activities of the perhydropyrrolo[1,2-*c*]oxazoles <2000TA1193, 2002CC1146, 2003HAC42, 2003TL6605, 2003RCM1651, 2004JOC7092, 2004TA603, 2005CEJ939, 2005TA2133, 2005TL303> and their corresponding oxoperhydro derivatives: 1-oxo <1997TA2001, 1997TL4203, 1998AGE1414, 1998J(P1)3777, 1999JME628, 2000JOC914, 2000OL1987, 2002AGE4556, 2002TL857, 2002TL861, 2004JA11770, 2004JA16312, 2004PNA5839, 2005JOC7432, 2005OL35, 2005T2481, 2005T10018, 2005TA2075, 2006JOC97, 2006OL383>, 3-oxo <1996JOC125, 1996JOC5418, 1996T869, 1996TL5095, 1996TL7717, 1997TA149, 1997TL607, 1997TL1415, 1997TL3879, 1997TL4179, 1998AGE3144, 1998EJO509, 1998EJO1955, 1998J(P1)3577, 1998JOC5680, 1998TL6787, 1999JA6098, 1999JA11139, 1999JOC5280, 1999JOC498, 1999T3495, 2000BMC135, 2000BML2015, 2000CJC776, 2000JA6950, 2000TA2033, 2000TL5915, 2001AGE3361, 2001BML2691, 2001CPB492, 2001CPB1487, 2001EJO517, 2001JA315, 2001JA9706, 2001JME3563, 2001JOM244, 2001OPD241, 2002JOC5517, 2002TL7777, 2003JA7596, 2003JOC7818, 2003JOC9747, 2003OL3771, 2003T3307, 2003TL1095, 2003TL7997, 2004AJC669, 2004JOC3578, 2004JOC7157, 2004OL2481, 2004T4173, 2004T5759, 2004TL1445, 2005CEJ945, 2005OL3243, 2005OL4419, 2005TA3887, 2005TL5309>, 5-oxo <1996JA9073, 1996JOC6153, 1996T3719, 1996TL4573, 1997BML2973, 1997T11731, 1997TA2421, 1997TL5891, 1997TL8037, 1998CC461, 1998JA2330, 1998JA3894, 1998JA6629, 1998JA7429, 1998T10295, 1998TL857, 1998TL7475, 1999CC2333, 1999JA5334, 1999JA10478, 1999JOC547, 1999OL2015, 1999TA3887, 1999T3305, 1999TL2525, 1999TL2707, 1999TL7787, 2000T2437, 2000TL8285, 2001J(P1)2997, 2001J(P1)3007, 2001JOC6483, 2001JOC7555, 2001JOC8831, 2001TA1353, 2001TL5705, 2002EJO3543, 2002JOC6582, 2002JOC8688, 2002T9737, 2002TA647, 2002TL463, 2002TL3919, 2002TL9531, 2003JME4196, 2003JOC9723, 2003OBC2364, 2004JOC7558, 2004T8031, 2004TA1239, 2005JA8998, 2005OBC2872, 2005OL4165, 2005TL143, 2006TA53, 2006TL1461>, 1,5-dioxo <2002TA2229, 2004M853>, 3,5-dioxo <1996JA3063, 1997JOC6754>, 3,7-dioxo <1996JME56, 1996JOC2624>, 5,7-dioxo <1998J(P1)223, 2002J(P1)80>.

No pyrrolo[1,2-*b*]isothiazoles are reported in the literature and only tetrahydro and perhydro derivatives are known <2003T7047>.

Pyrrolo[2,1-*b*]thiazoles are reported <1998T3913, 2001JA2074> as well as 2,3-dihydro <2004S2317, 1998JME3763>, 2,3,7,7a-tetrahydro <2002J(P1)548>, and perhydro <1997JME3594, 1998JME4556, 1998T3913, 1998TL8579, 1999JME2977, 2001JA2074, 2001TL145, 2004OL3285, 2004TL4139, 2005OL3601, 2006TL2233>. Pyrrolo[1,2-*c*]thiazoles are reported in several articles <1999EJP309, 2000JME2149, 2000T3419, 2000T7267, 2000T10011, 2002BML341, 2002J(P1), 2002T5093, 2004TL3889, 2005JOC6629> and some of their derivatives are also known, such as 1-oxopyrrolo <2001HCA972>, dihydro <2000T3419>, and tetrahydro <1998CC299, 2002TL3919>.

11.02.2 Pyrrolo[1,2-*b*]pyrazole

11.02.2.1 Introduction

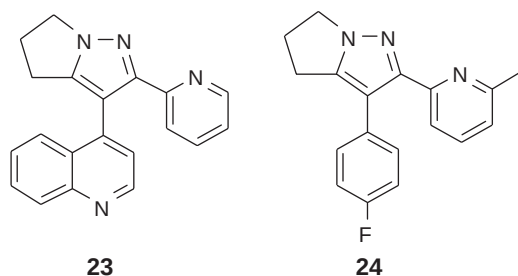
There are only few examples of this type of compound that have been published since 1996 in the literature. In CHEC-II(1996), there are only seven examples <1983TL1067, 1985T811, 85TL5739, 1987J(P1)653, 1987J(P1)657, 1990MI802-01>. Some derivatives, such as dihydro or perhydro, are known.

11.02.2.2 Theoretical and Experimental Structural Methods

Theoretical calculations on this type of compound have not been described nor have any thermodynamic discussions.

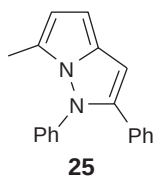
11.02.2.2.1 X-Ray

The structure of dihydro-4,5-6*H*-pyrrolo[1,2-*b*]pyrazoles **23** and **24** have been determined by X-ray crystallography <2004BML3581>.



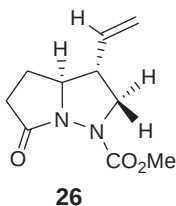
11.02.2.2.2 NMR spectroscopy

No detailed description of ^1H or ^{13}C nuclear magnetic resonance (NMR) spectroscopy has been reported on this class of compound. A general description of the NMR spectra of compound **25** is given in the synthesis of a pyrrole <1998JOC9131>.



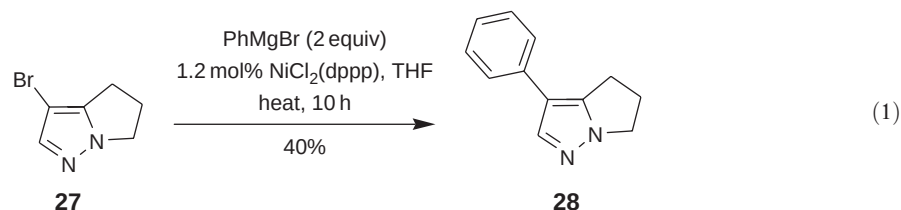
11.02.2.2.3 IR and UV spectroscopy

The carbonyl stretching frequency in the infrared (IR) spectrum for the two carbonyl groups in the perhydro-6-oxopyrrolo[1,2-*b*]pyrazole **26** are 1772 and 1737 cm^{-1} .



11.02.2.3 Reactivity

No reactions involving this type of compound nor any derivatives have been reported so far. One reaction on the 3-bromopyrrolo[1,2-*b*]pyrazole is described. 4,5-Dihydro-6*H*-3-bromopyrrolo[1,2-*b*]pyrazole **27** reacted in the presence of $\text{NiCl}_2(\text{dppp})$ (1.2 mol%) and 2 equiv of PhMgBr to produce the natural product whitasomnine **28** (dppp = 1,3-bis(diphenylphosphino)propane; (Equation 1) <1996TL1095>).

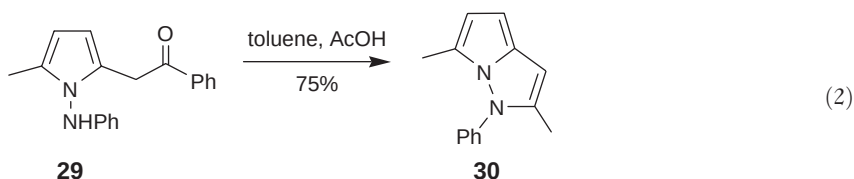


11.02.2.4 Synthesis

11.02.2.4.1 Ring synthesis from acyclic compounds classified by number of ring atoms contributed by each component

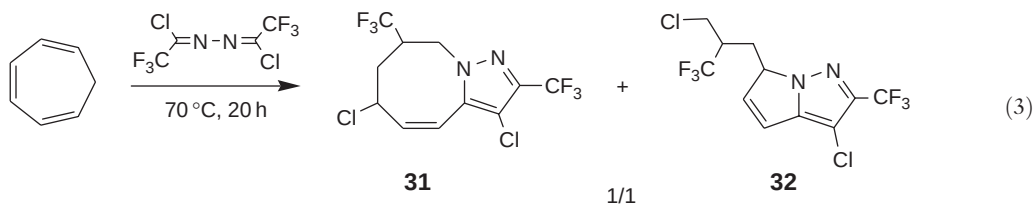
11.02.2.4.1(i) Synthesis of 3*H*-pyrrolo[1,2-*b*]pyrazole

The amino pyrrole **29** derived from the reaction with phenylhydrazine [<1998JOC9131>](#) was found to undergo an acid-catalyzed intramolecular condensation with the carbonyl present to give the 3*H*-pyrrolo[1,2-*b*]pyrazole **30** ring system in a good yield (75%) ([Equation 2](#)).



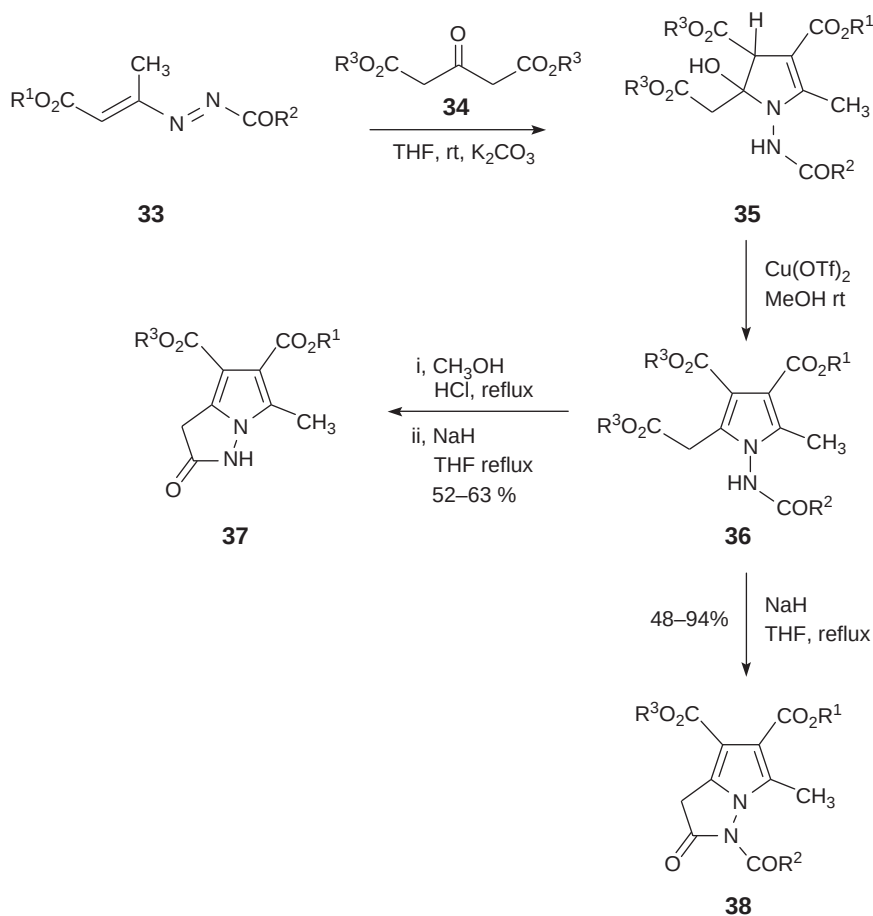
11.02.2.4.1(ii) Synthesis of 6*H*-pyrrolo[1,2-*b*]pyrazole

This kind of compound was obtained in the reaction of cycloheptatriene with dichloroazine $\text{CF}_3\text{CCl}=\text{N}=\text{N}=\text{CClCF}_3$ when heated at 70 °C. A 1:1 mixture of rearranged adducts **31** and **32** was isolated and this latter compound was obtained as a mixture of two diastereomers in the ratio 77:23 (NMR spectroscopy, yield not given). The formation of these two compounds requires considerable skeletal rearrangement of any initial [3+2] or [3+6] cycloadduct and a satisfactory mechanism cannot be proposed. It was not possible to differentiate between structures **31** and **32** on the basis of the spectral data obtained ([Equation 3](#)) [<1995JFC203>](#).



11.02.2.4.1(iii) Synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole

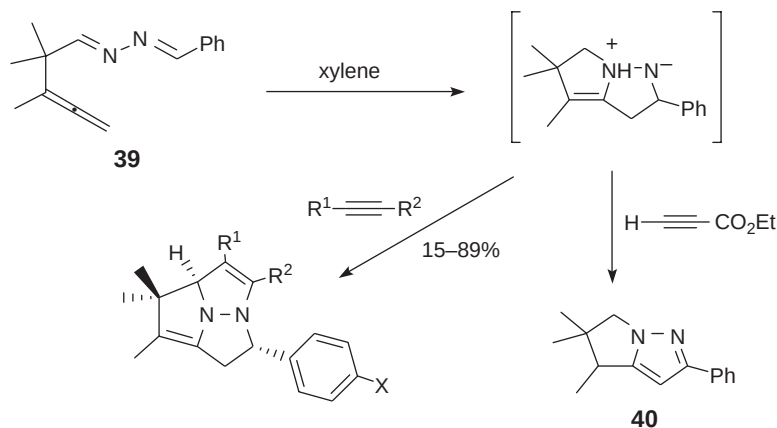
An easy synthesis of the 2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole system can be performed by reaction of 1,2-diaza-1,3-butadienes **33** with dialkyl 1,3-acetonedicarboxylate **34** in the presence of potassium carbonate. At first, 1-aminopyrroles **36** was produced by dehydration in the presence of copper(II) trifluoromethanesulfonate. Treatment of these compounds with sodium hydride led to *NH*-substituted 2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole **38**. Under the same reaction conditions, and after acidic treatment, *NH*-BOC-protected 1-aminopyrrole was transformed to *NH*-unsubstituted 2-oxo-2,3-dihydro-1*H*-pyrrolo[1,2-*b*]pyrazole **37** (BOC = *t*-butylcarbonyl) ([Scheme 1](#)).



Scheme 1

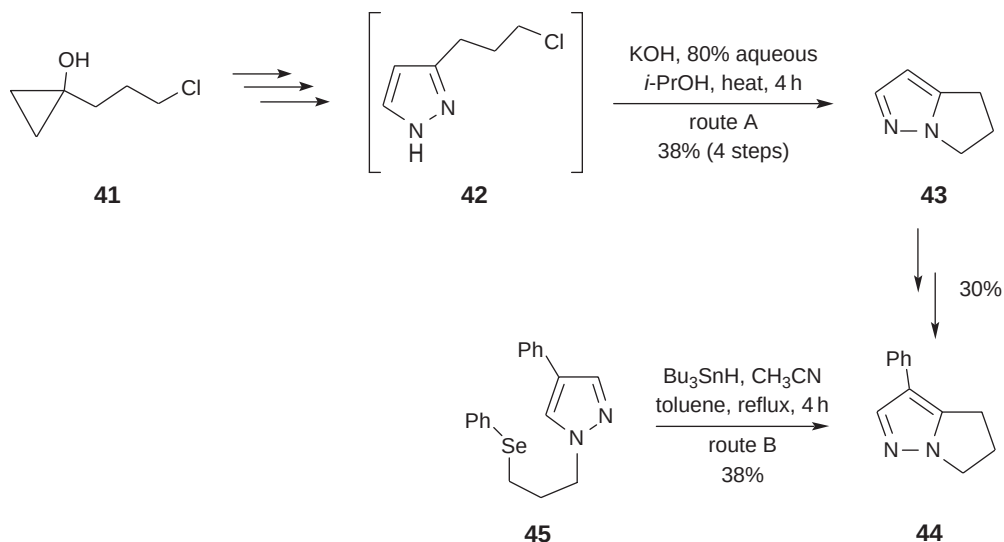
11.02.2.4.1(iv) Synthesis of 5,6-dihydro-4*H*-pyrrolo[1,2-*b*]pyrazole

A side product **40** was isolated in the reaction of allenylazine **39** with alkynes, because of the low reactivity of the alkyne when $\text{R}^1 = \text{H}$ and $\text{R}^2 = \text{CO}_2\text{Et}$ (Scheme 2) <2005T2387>.



Scheme 2

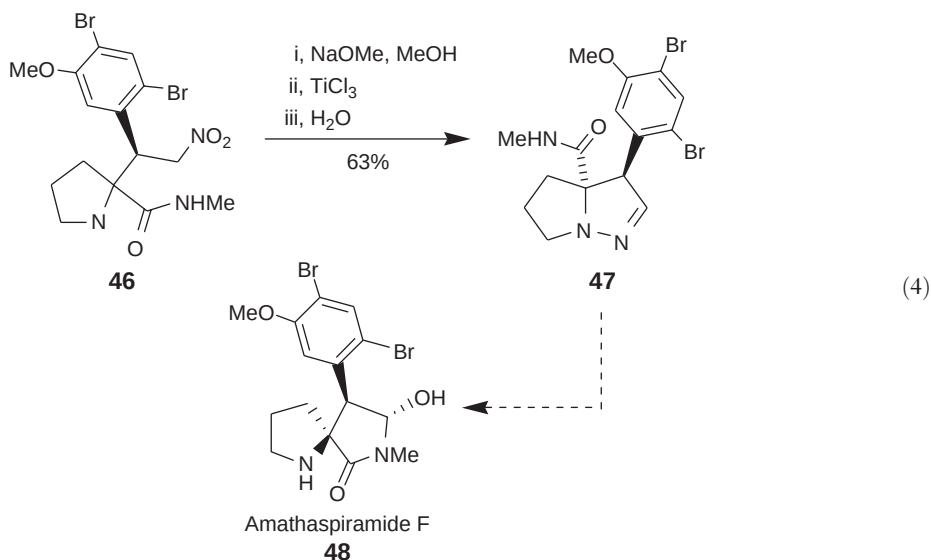
The alkaloid whitasomnine **44** was prepared according two different routes. The first approach (route A) was based on the cyclization of the 1-(3-chloropropyl)cyclopropanol **41** (**Scheme 3**). The final cyclization involved the reaction of 3-(3-chloropropyl)pyrazole **42** to form the final pyrazole **43** in 40% yield, which is then transformed to the natural product <1996TL1095>. The second approach (route B) is based on the radical cyclization of the substituted pyrazole **45** in the presence of Bu_3SnH in acetonitrile under refluxing toluene. Whitasomnine **44** was isolated in 38% yield <2002TL4191>.



Scheme 3

11.02.2.4.1(v) Synthesis of tetrahydro and perhydro derivatives

The tetrahydro derivative **47** was obtained from an unexpected cyclization of the nitro compound **46** by deprotonation with NaOMe in methanol followed by a treatment with TiCl_4 , then with H_2O . This side product was observed in the approach of amathaspiramide F **48** (**Equation 4**) <2002AGE4556>.



11.02.3 Pyrrolo[1,2-*a*]imidazoles

11.02.3.1 Introduction

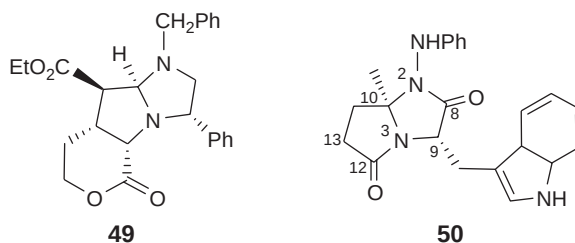
Pyrrolo[1,2-*a*]imidazoles are mainly present in the literature as perhydro derivatives. Some of these substituted compounds present interesting biological activity. The aromatic unsaturated system is rare and was prepared in one case by flash vacuum pyrolysis [<1999J\(P1\)2047>](#).

11.02.3.2 Theoretical and Experimental Structural Methods

There are no theoretical methods that have been described in the literature on this class of products.

11.02.3.2.1 X-Ray

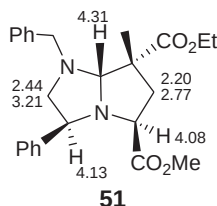
Some structures, related to pyrrolo[1,2-*a*]imidazoles, have been reported. The tricyclic perhydro derivative [49](#) [<1997TL1647>](#) as well as the 3-(1*H*-indol-3-ylmethyl)-7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*) dione [50](#) have been determined and some interesting aspects on compound [50](#) have been highlighted.



The bicyclic skeleton of [50](#) is distorted, with the N(2)–C(8)–C(9) and N(3)–C(12)–C(13) bond angles particularly small (105.6° and 104.8°, respectively) for an sp²-hybridized carbon atom; the imidazolidinone moiety, which is almost planar with small distortions due to the steric requirements of the substituents, has an N(2)–C(10)–N(3) bond angle of 98.1°, which is much smaller than expected for an sp³-hybridized carbon atom.

11.02.3.2.2 Proton NMR spectroscopy

There are several reported spectra for this type of compounds, but they were used only for structural confirmation and there are no systematic studies. For example, chemical shifts were reported for the hexahydropyrrolo[1,2-*a*]imidazole [51](#) [<1996TL1707>](#).



11.02.3.2.3 Carbon-13 NMR spectroscopy

The information is usually reported to confirm the structure of the molecules [<1996TL1707, 1997TL1647, 1998J\(P1\)2061, 2002JOC4951, 2002JOC8224>](#).

11.02.3.2.4 IR and UV spectroscopy

No significant IR data and electronic absorption spectroscopy have been reported.

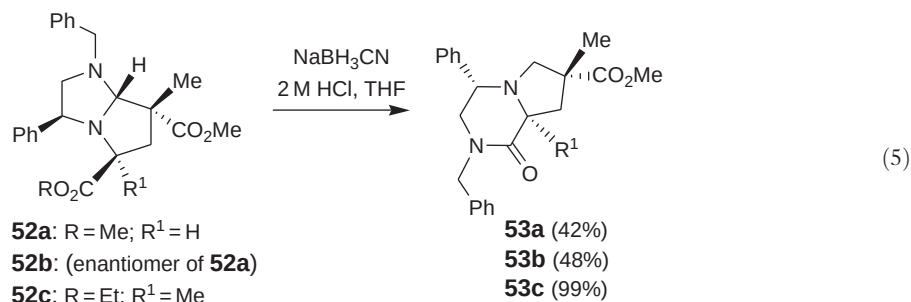
11.02.3.3 Reactivity

11.02.3.3.1 Reactivity of fully conjugated rings

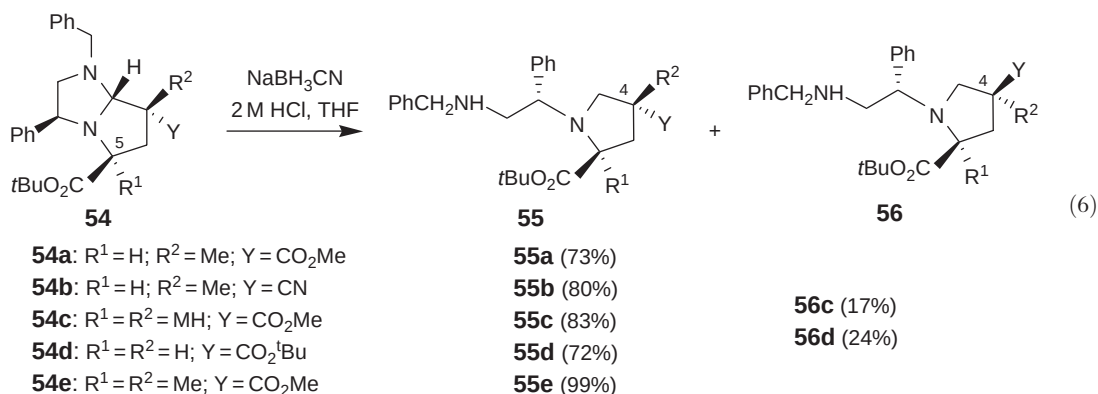
No data on any system have been reported.

11.02.3.3.2 Reactivity of nonconjugated rings

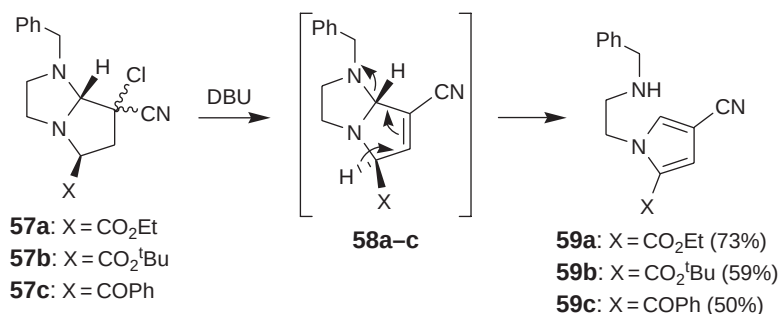
Aminal reduction (NaBH_3CN , 2 M HCl, EtOH) of the C-5-methoxycarbonyl pyrroloimidazole **52a** or its enantiomer **52b** resulted solely in lactamization to pyrrolopyrazines **53a** and **53b**, respectively; the C-5-ethoxycarbonyl pyrroloimidazole **52c** similarly cyclized to **53c** (Equation 5) <1996TL1711, 1997TL1647>.



Increasing the steric hindrance of the ester was found to suppress completely the undesired lactamization. Thus, C-5-*t*-butoxycarbonyl cycloadducts **54a–e** were reduced in near quantitative yield (NaBH_3CN , 2 M HCl, THF) to the *N*-substituted pyrrolidines **55a–e** with, in some cases, the formation of the C-4 epimers **56c** and **56d** in low yield (Equation 6) <1996TL1711>.



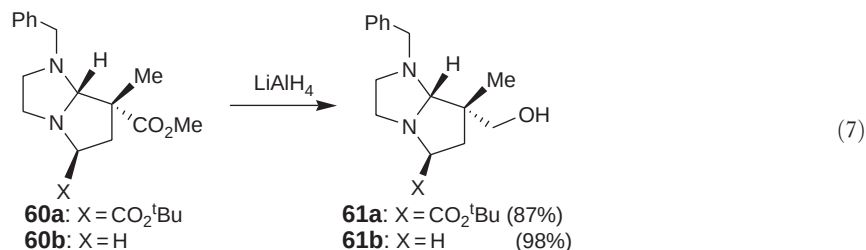
The hexahydropyrrolo[1,2-*a*]imidazole chloro cycloadducts **57a–c**, as a 1/1 mixture of stereoisomers, underwent an elimination on treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) at 100 °C. It was not possible to isolate the desired dihydropyrroles **58a–c** and a second elimination occurred to form the *N*-substituted pyrroles **59a–c** respectively (Scheme 4) <1998J(P1)2061>.



Scheme 4

11.02.3.3.3 Reactivity of the substituents attached to ring carbon atom

Treatment of methylhexahydro-1*H*-pyrrolo[1,2-*a*]imidazole **60a** with LiAlH_4 in Et_2O afforded a diol **61a** in 87% yield, whereas similar treatment of **60b** gave alcohol **61b** in 98% yield. During the reduction, no ring opening was observed (Equation 7) <1998J(P1)2061>.

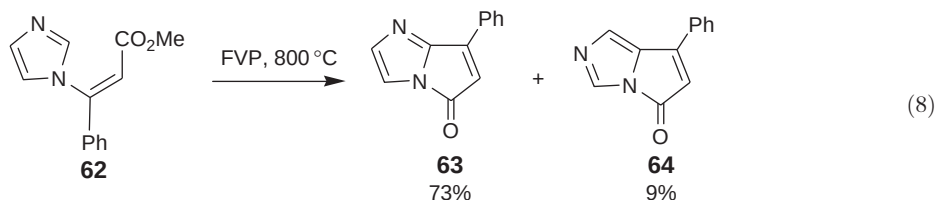


11.02.3.4 Synthesis

11.02.3.4.1 Ring synthesis from acyclic compounds classified by number of ring atoms contributed by each component

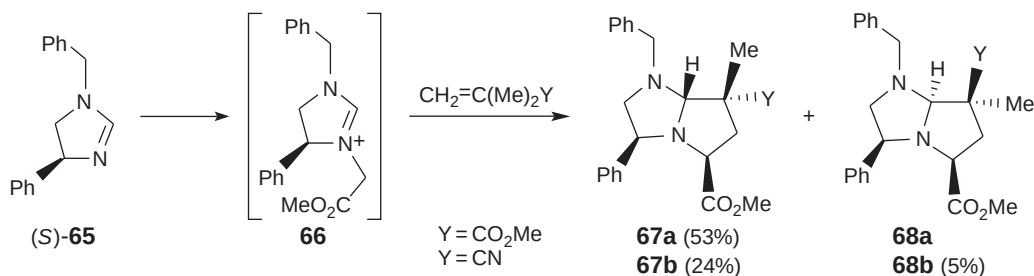
11.02.3.4.1(i) Synthesis of 3*H*-pyrrolo[1,2-*a*]imidazolone

Pyrolysis of the known 1-vinylimidazole **62** at 800°C (0.01 Torr) gave the expected pyrrolo[1,2-*a*]imidazolone **63** in 73% yield (identified by comparison of its NMR spectra with those of other examples related to this ring system), and only a trace (ca. 9%) of the isomeric product **64** was obtained <1999J(P1)2047>. It is noteworthy that the conditions required for sigmatropic migration of the vinyl substituent are significantly milder than for migration of the aryl group (Equation 8).



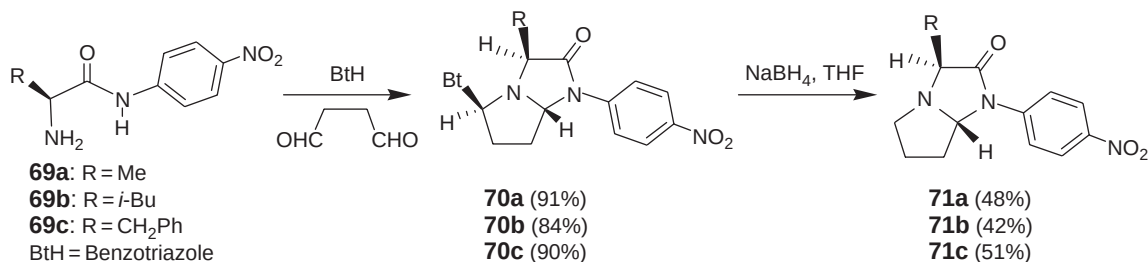
11.02.3.4.1(ii) Synthesis of dihydro and perhydro derivatives

The 1,3-dipolar cycloaddition of azomethine ylides to alkene dipolarophiles has been shown to be a rapid way to assemble pyrrolidine rings. The stereodefined transition states of such pericyclic processes are also ideally suited to the asymmetric synthesis of such systems, as required for many natural product targets containing pyrrolidine rings or fused pyrrolidines <1996TL1707, 1996TL1711, 1997TL1647, 1998J(P1)2061, 2000JHC481>. This method represents a 'one-pot' enantioselective 1,3-dipolar cycloaddition of dipolarophile alkenes to homochiral azomethine ylides generated from imidazolines **65** through imidazolium salt **66**. Optically active hexahydropyrroloimidazole adducts of type **67a** and **67b** were obtained as major products. Compound **67b** is contaminated with 5% of **68b** when the azomethine ylide is substituted by a cyano group (Scheme 5).



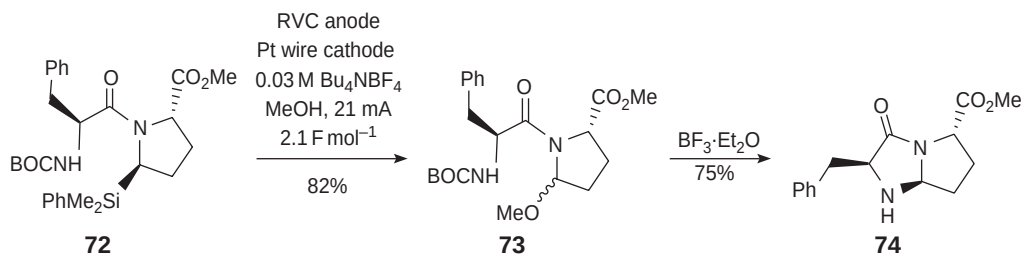
Scheme 5

Substituted tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazol-2-ones **70a–c** can also be prepared from optically pure amino-amides **69a–c** by reaction with succindialdehyde and benzotriazole in CH₂Cl₂ at room temperature for 24 h. After recrystallization of these compounds to give the single diastereomers, they were reduced with sodium borohydride in tetrahydrofuran (THF) to give the corresponding perhydro derivatives **71a–c** in moderate yields (Scheme 6). It was found that this reaction was most efficient by using 4 equiv of NaBH₄ in THF at 40 °C for 36 h <2002JOC4951>.



Scheme 6

Anodic oxidation of silylated amino acids afforded compound **67** that is directly used to prepare the corresponding perhydro pyrrolo[1,2-*a*]imidazolidine. The oxidation of **72** was performed in an undivided cell using a reticulated vitreous carbon anode, a 0.03 M Et₄NOTs in MeOH electrolyte solution, and constant current conditions. Current was passed until 2.0 F mol^{−1} of charge had been consumed. The reaction led to the formation of the methoxylated product **73** in 82% yield along with 4.4% of the recovered starting material (Scheme 7). The intramolecular cyclization was then completed with the use of BF₃·Et₂O and the stereochemistry of the bicyclic product **74** assigned with the use of a nuclear Overhauser enhancement spectroscopy (NOESY) experiment <2002OL1547>.



Scheme 7

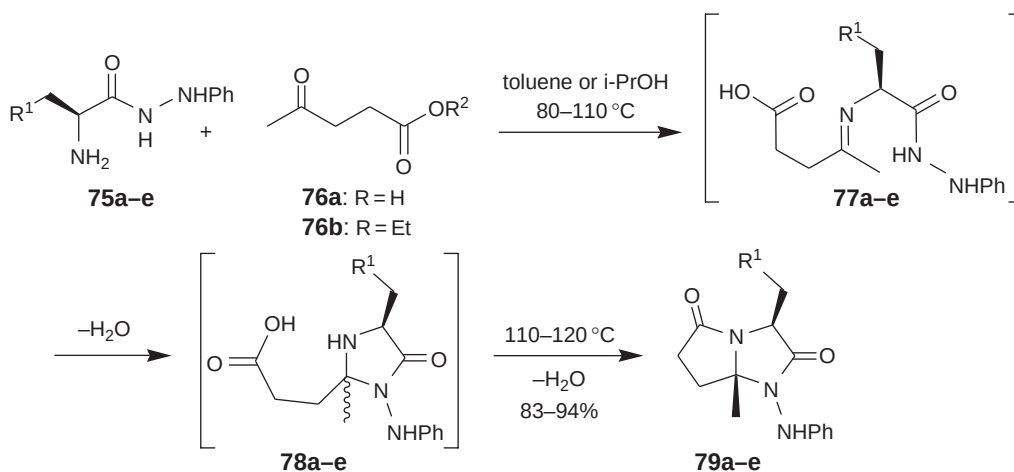
α -Amino acid phenylhydrazides **75a–e** readily react with levulinic acid to produce the imidazolidin-4-one intermediates **78a–e**, which undergo a second ring closure to afford the dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione derivatives **79a–e** (Scheme 8; Table 1). It has been established that the solvent polarity has a great influence on the rate of the second condensation reaction, but not on the first <2004EJO2883>.

A diastereoselective dipolar cycloaddition of chiral nitrone **80** with alkene dipolarophiles afforded imidazo[1,2-*b*]-isoxazole (Scheme 9). The conversion via N–O reduction of this ring system with Raney-Ni in methanol gave the corresponding pyrrolo[1,2-*b*]imidazole in 66% yield. The structure has been confirmed by X-ray diffraction crystal structure analysis <2000SL967>.

11.02.4 Pyrrolo[1,2-*c*]imidazoles

11.02.4.1 Introduction

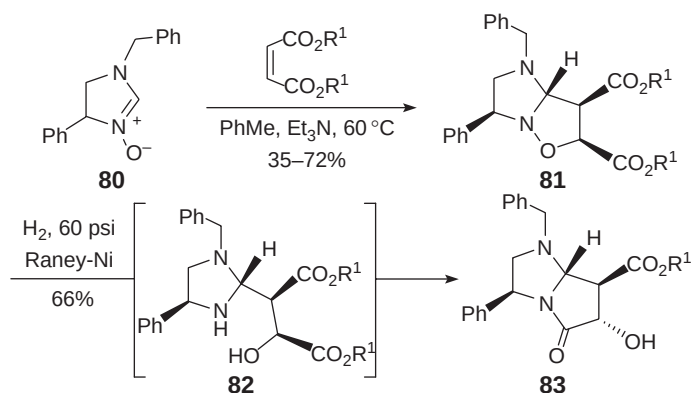
Several pyrrolo[1,2-*c*]imidazoles have been studied for their physiological activities. Most of these compounds demonstrated a high affinity for the 5-HT_{1A} receptor. Pyrrolo[1,2-*c*]imidazoles are present in the literature as tetrahydro, perhydro, 1-oxoperhydro, 3-oxoperhydro, 7-oxoperhydro, 1,3-dioxoperhydro, 1,5-dioxoperhydro, 2,7-dioxoperhydro, and 1-thio-3-oxoperhydro derivatives.



Scheme 8

Table 1 Preparation of various dihydro-1H-pyrrolo[1,2-a]imidazole-2,5-diones

Entry	Starting material	R	Product	Yield (%)
1	75a	H	79a	94 ^a
2	75b	Ph	79b	84 ^a
3	75c	Me ₂ CH	79c	83 ^a
4	75d	CH ₃ SCH ₂	79d	90 ^a
5	75e	Indoyl	79e	87 ^b
6	75f	Imidazolyl	79f	90 ^b

^aToluene, 110 °C, 54 h.^bi-PrOH, 80 °C, 2 h, then toluene, 120 °C, 6 h.

Scheme 9

11.02.4.2 Theoretical and Experimental Structural Methods

No theoretical data have been reported for this type of system.

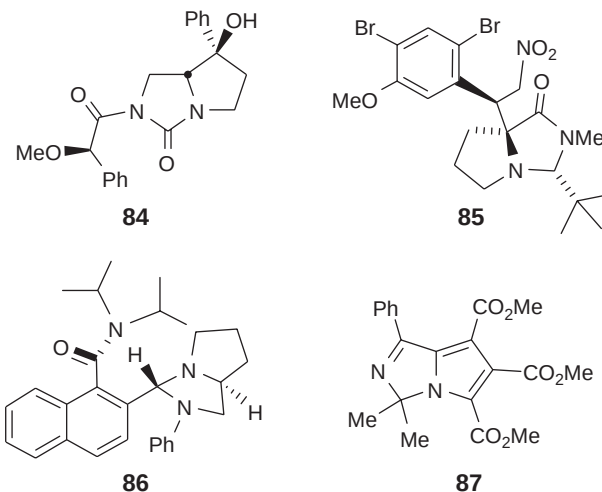
11.02.4.2.1 X-Ray

Some structures of this type of compound were established by X-ray diffraction analysis. For example, the structure of compound **84** resulting from the enantioselective Norrish–Yang cyclization of prochiral imidazolidinone was

determined <2001CC607>, as was structure **85** which has been used as an intermediate in the total synthesis of amathaspiramide F <2002AGE4556>; the structures of the optically active atropisomeric amides **86** obtained by dynamic resolution <1999AGE2556> were also elucidated by X-ray diffraction.

11.02.4.2.2 Proton and carbon-13 NMR spectroscopy

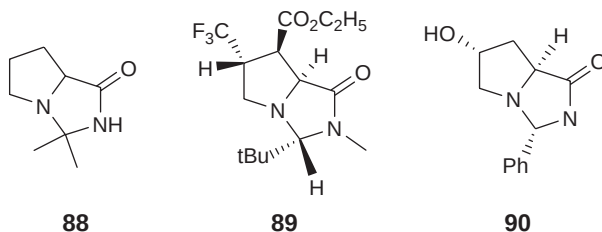
One can find a great number of recorded spectra for this type of compound. In general, the spectra were recorded to establish and confirm the structure of the compounds. There are no systematic NMR studies. The most interesting data are described for trimethyl-3,3-dimethyl-1-phenyl-3*H*-pyrrolo[1,2-*c*]imidazole-5,6,7-tricarboxylate **87**. The ¹H NMR spectrum of this compound exhibits signals for the three methoxycarbonyl groups; the region of the ¹³C NMR spectrum typical of the olefins or aromatic groups (δ 100–140 ppm) contains, in addition to the signals of the phenyl group, four signals for the carbon atoms at 107.2, 121.5, 131.4, and 139.2 ppm.



¹³C NMR spectra were reported for the structural determination of many perhydro derivatives. In some cases, the stereochemistry has been established by spectroscopic analysis <2005JA14586, 2001JFC275>.

11.02.4.2.3 IR and UV spectroscopy

No particular studies have been published on the IR or ultraviolet (UV) spectroscopic properties of this type of compound. No abnormal IR frequencies have been reported and, for example, classical IR frequencies for the CO bond at respectively 1700, 1709, and 1685 cm⁻¹ have been observed for compounds **88**, **89**, and **90** <1997M395, 2001JFC275, 2001TL407>.

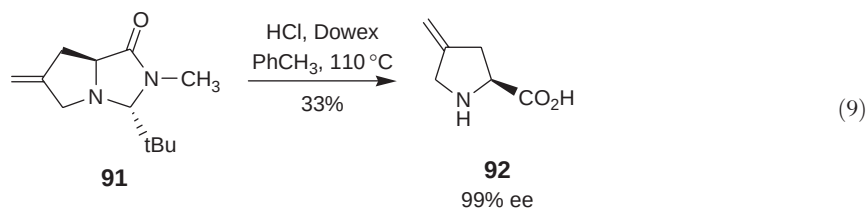


11.02.4.2.4 Mass spectrometric methods

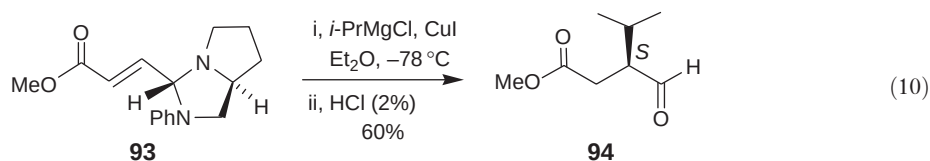
Other than descriptions of the mass spectrometric spectra of several compounds for structure confirmation, there are no detailed studies reported.

11.02.4.3 Reactivity

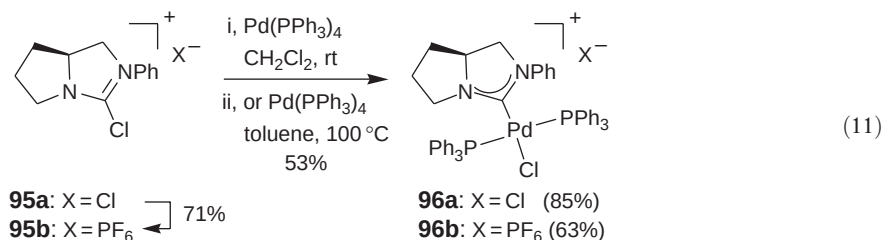
Aminals can be hydrolyzed easily. The hydrolysis of the amina **91** provides the amino acid **92** in optically pure form (Equation 9) <1997TA1855>.



In the asymmetric total synthesis of the marine natural product, methyl sarcoate, the key step for the introduction of the chirality, was achieved by using an asymmetric Michael addition. Asymmetric addition of *i*-PrMgCl to aminal ester **93** in the presence of a catalytic amount of CuI, followed by acidic hydrolysis of the aminal function, afforded the chiral aldehyde **94** in 60% yield (Equation 10) <2005TL1263>.



A final use of pyrrolo[1,2-*c*]imidazoline was applied in the field of organic catalysis. The reaction of a 2-chloroimidazolinium salt of type **95a** or **95b** with Pd(PPh₃)₄ in CH₂Cl₂ at room temperature gave efficiently the corresponding metal carbene complexes **96a** and **96b** that can be used in catalytic cross-coupling reactions. These new Fischer carbene complexes showed appreciable catalytic activity in Suzuki, Heck, and Kumada–Corriu cross-coupling reactions as well as Buchwald–Hartwig aminations (Equation 11) <2005CEJ1833>.

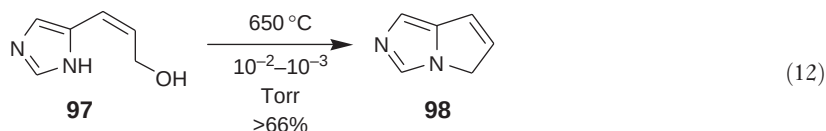


11.02.4.4 Synthesis

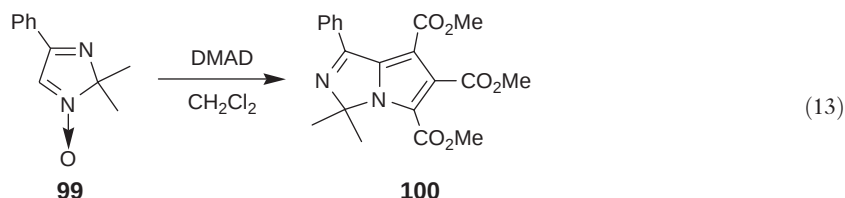
11.02.4.4.1 Ring synthesis from acyclic compounds classified by number of ring atoms contributed by each component

11.02.4.4.1(i) 3*H*- and 5*H*-Pyrrolo[1,2-*c*]imidazole

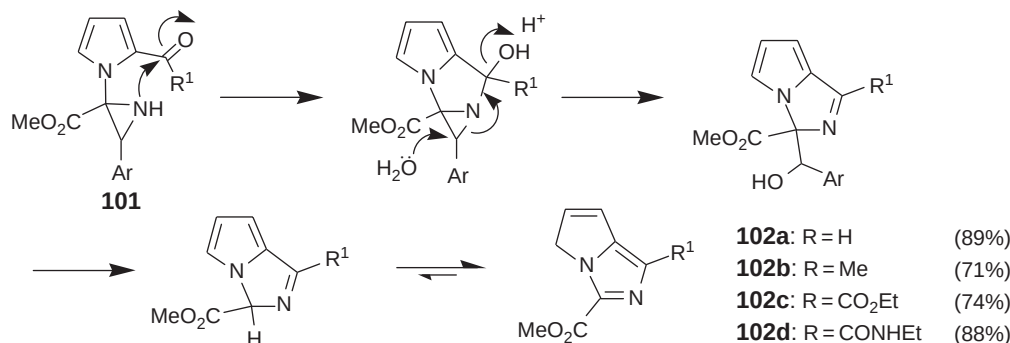
The 3*H*-pyrrolo derivative **98** can be obtained by flash vacuum pyrolysis of allylic alcohol **97** at 650 °C at 10^{−2}–10^{−3} Torr. The method is not general, and only one example on unsubstituted starting material was presented (Equation 12) <1999J(P1)2049>.



The reaction of nitrene **99** with dimethyl acetylenedicarboxylate (DMAD) at room temperature in CH₂Cl₂ gave a colorless crystalline product that has been identified as trimethyl 3,3-dimethyl-1-phenyl-3*H*-pyrrolo[1,2-*c*]imidazole-5,6,7-tricarboxylate **100**. A mechanism explaining this transformation has been reported (Equation 13) <2001RCB882>.

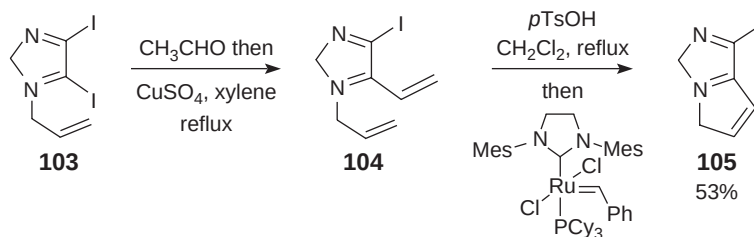


The aziridine **101** derived from pyrrole-2-carboxaldehyde was found to undergo a further unusual transformation when treated with trifluoroacetic acid (TFA) at room temperature, giving the 5*H*-pyrrolo[1,2-*c*]imidazole **102** in good yield. The cyclization is initiated by protonation of the carbonyl group (Scheme 10) <2000TL4991>.



Scheme 10

A synthesis of 5*H*-pyrrolo[1,2-*c*]imidazole **105** has been developed via a chemoselective addition/dehydration of acetaldehyde on diiodo imidazole **103** giving the vinylic imidazole **104**. This compound, treated under the metathesis condition in the presence of the second-generation Grubbs catalyst, gave the final product **105** (Scheme 11) <2003TL1379>.



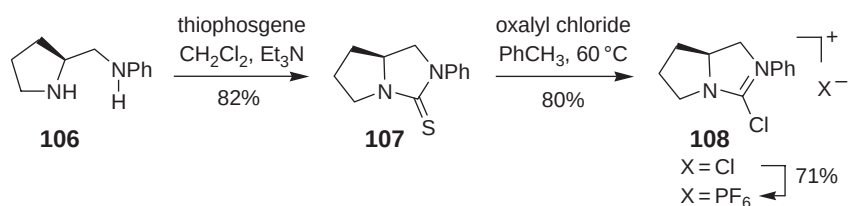
Scheme 11

11.02.4.4.1(ii) Tetrahydropyrrolo[1,2-*c*]imidazolinium salt

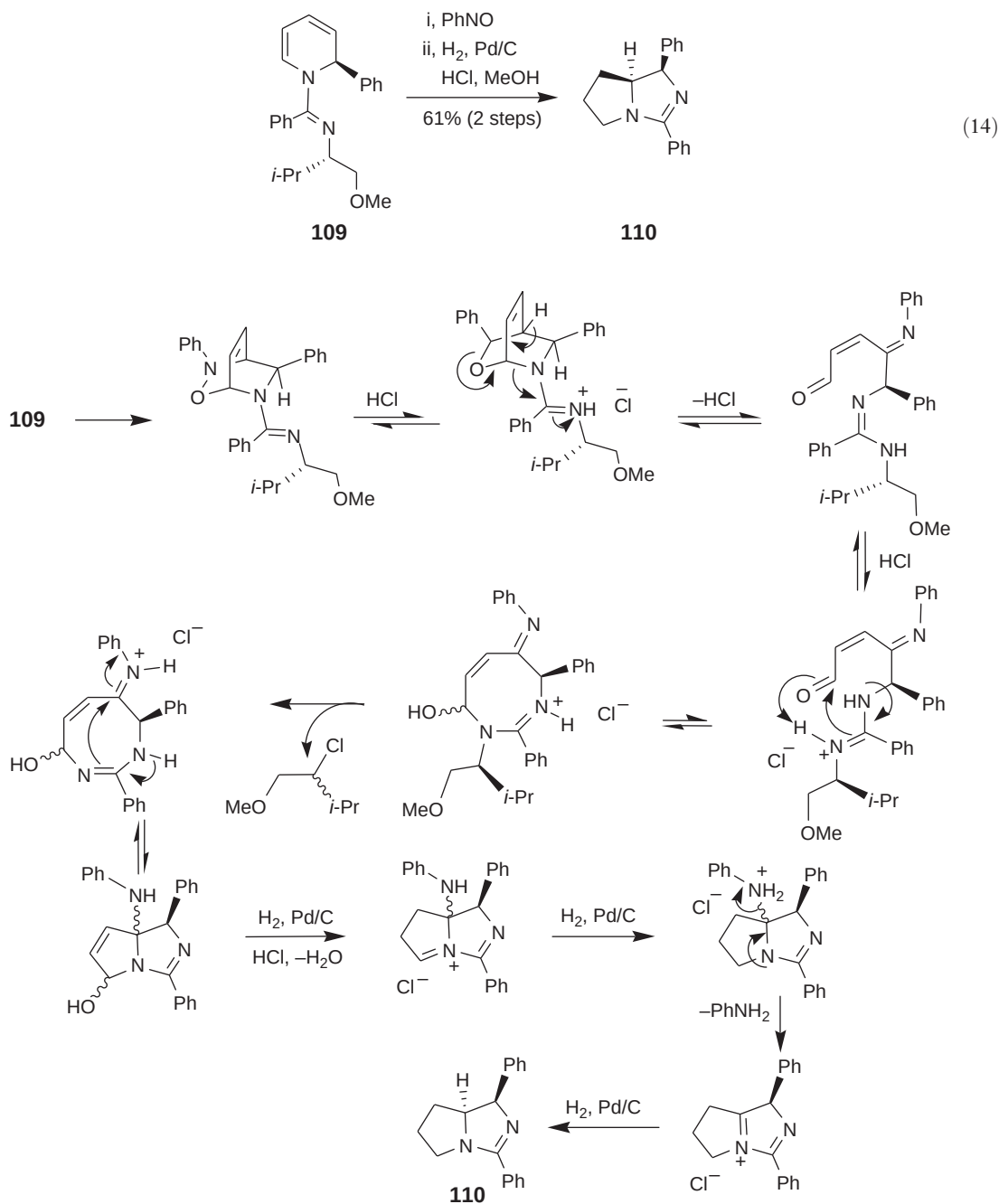
The synthesis of this salt started with the enantiomerically pure 1,2-diamine **106**, that was converted into the corresponding thiourea derivative **107** (Scheme 12). Exposure of the thiourea **107** to oxalyl chloride in toluene at 60 °C cleanly afforded the desired imidazolinium chloride **108**. These two salts were used to produce new palladium and nickel carbene complexes. The structure of both palladium carbene complexes **96a** and **96b** has been elucidated by X-ray diffraction <2005CEJ1833>.

11.02.4.4.1(iii) Tetrahydropyrrolo[1,2-*c*]imidazole

The hydrogenation of **109** over palladium on charcoal in acidic methanol produced (1*R*,7*aS*)-1,3-diphenyl-5,6,7,7*a*-tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole **110** in 61% isolated yield (Equation 14). This reaction was totally unexpected and the authors proposed a mechanism that explains this transformation <2005JOC2368>. The mechanism is shown in Scheme 13. Many of the steps are interchangeable, but the end product is the same. The partial racemization observed could occur by epimerization of the phenyl-substituted carbon adjacent to the imine produced after the cleavage of the bicyclo-adduct.



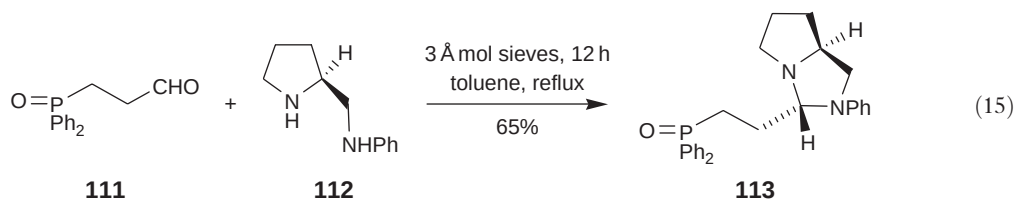
Scheme 12



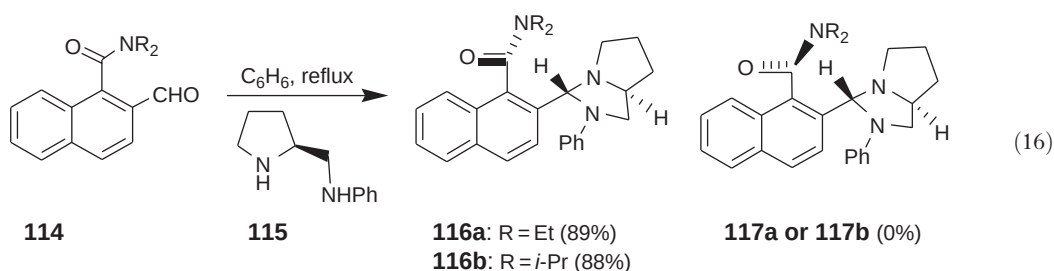
Scheme 13

11.02.4.4.1(iv) Perhydropyrrolo[1,2-*c*]imidazoles

A synthesis of novel chiral phosphine oxide aminoral **113** has been developed by reacting phosphine oxide aldehyde **111** with diamine **112**. The condensation gave a single diastereomer of the phosphine oxide aminoral in 65% yield. This compound can be used as chiral auxiliary in asymmetric synthesis (Equation 15) <1996TA3431, 1996TL3051, 1996TL7465>.



In the same manner, the enantiopure atropoisomer amides **116a** and **116b** were obtained through dynamic resolution by formation of an optically enriched chiral aminoral. Refluxing **114** with **115** in benzene or toluene for 24 h gave the aminorals **116** in excellent yield with greater than 90:10 diastereoselectivity <1999AGE2556, 2000TL3279, 2004T4399> (Equation 16).

11.02.4.4.1(v) Oxo and dioxo pyrrolo[1,2-*c*]imidazoles

1-Oxo-perhydropyrrolo[1,2-*c*]imidazole has been obtained by reaction of α -aminocarboxamides **118**, with carbonyl compounds **119**, in refluxing methanol in the presence of *p*-toluenesulfonic acid as catalyst (Equation 17; Table 2) <1997M395>.

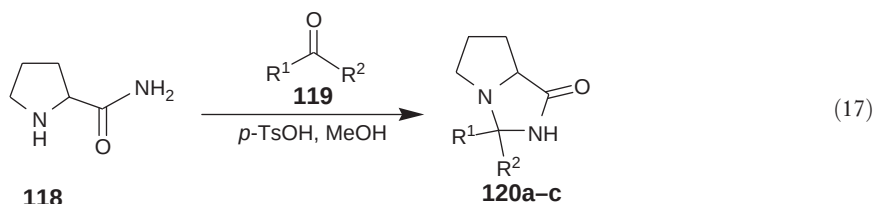
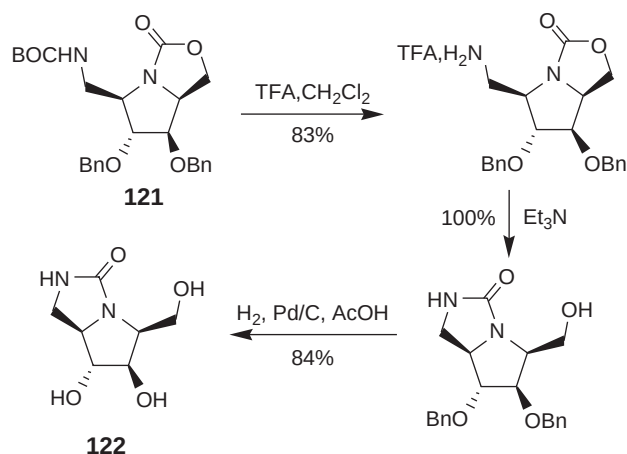


Table 2

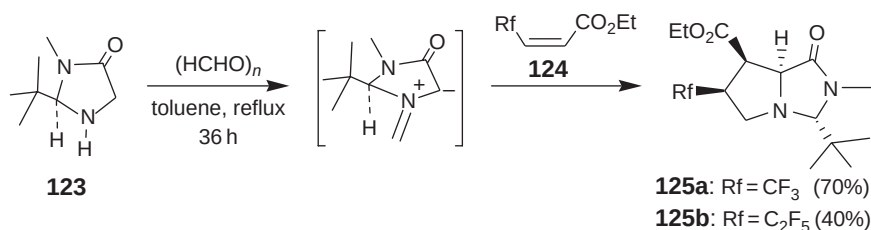
120	R^1	R^2	Yield (%)
a	$-(\text{CH}_2)_4-$		53
b	$-(\text{CH}_2)_4-$		70
c	CH_3		40
	C_2H_5		

The synthesis of the imidazoline **122** was achieved from **121** by cleavage of the BOC group with TFA in dichloromethane followed by treatment of the salt with Et_3N and eventually under hydrogen in the presence of Pd/C (Scheme 13). This compound showed poor biological activity on α -glucosidase (Scheme 14) <2000BMC135>.



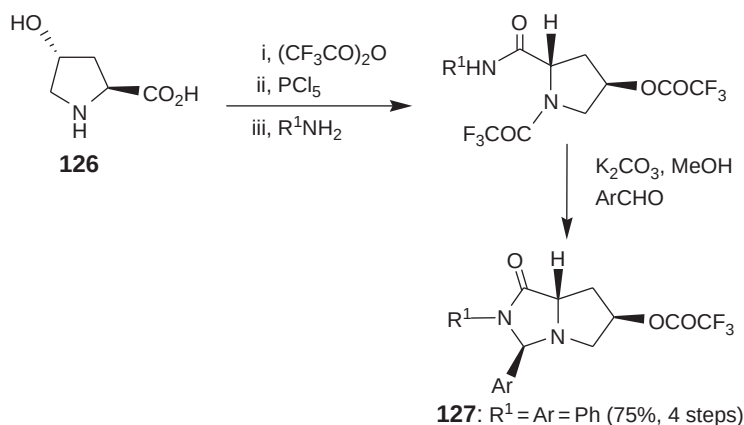
Scheme 14

The 1,3-dipolar cycloaddition of imidazolinone **123** with ethyl *cis*-4,4,4-trifluorocrotonate **124** provided, after 36 h at reflux, the regio- and stereoisomer **125** (90%), accompanied with traces of three other unidentified cycloadducts (10%) <2001JFC275>. Compound **125** was isolated in 70% yield (Scheme 15). The structures of the final product were elucidated by nuclear Overhauser effect (NOE) experiments. This high selectivity is the result of a preferred *endo*-orientation of both ester and CF₃ groups in the transition state and of an impeded *endo*-approach of the CF₃-substituted terminus of the alkene to the sterically hindered α -site of **123**.



Scheme 15

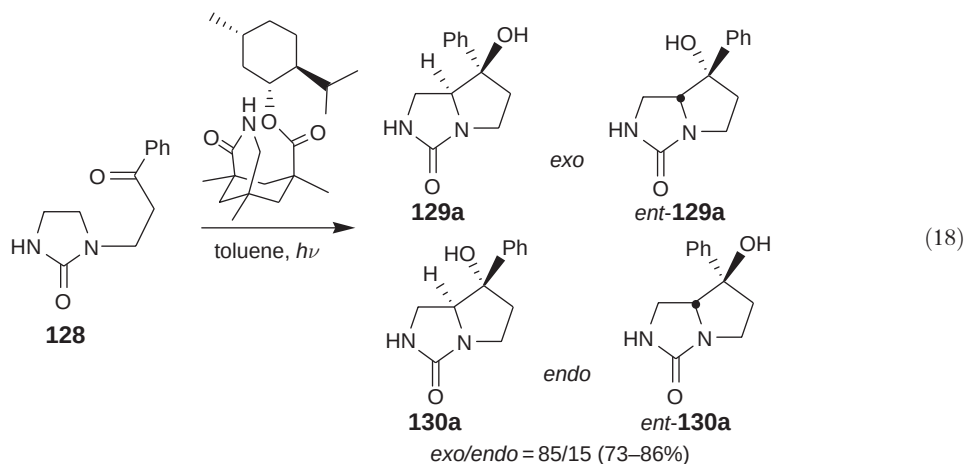
A parallel library of optically active bicyclic tertiary amines **127** bearing N-chiral bridgehead nitrogen atoms was readily prepared by condensation of primary amines, cyclic amino acids **126**, and aldehydes. This method gives access to a large variety of substituted hexahydro-1*H*-pyrrolo[1,2-*c*]imidazol-1-ones of type **127** (Scheme 16). These



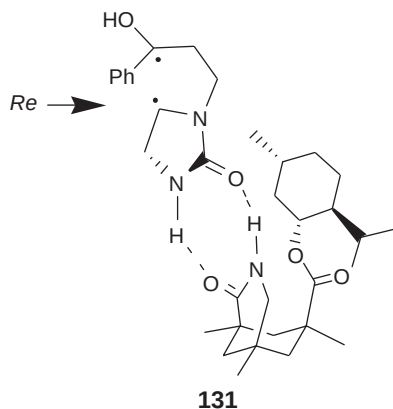
Scheme 16

compounds were studied as chiral inducers to the addition of diethylzinc on benzaldehyde (Scheme 16) <2001TL407, 2001TL411, 2002TA1769>.

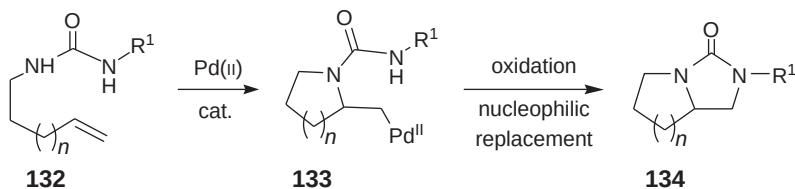
Optically active 3-oxo-perhydropyrrolo[1,2-*c*]imidazoles were prepared by enantioselective radical-type cyclizations using a chiral host. Of the four possible diastereomers formed from prochiral imidazolidin-2-one **128**, the *exo*-isomers **129a** and *ent*-**129a** are the preferred diastereomers in toluene solution whereas the *endo*-isomers **130a** and *ent*-**130a** are favored in the polar protic solvent *tert*-BuOH. *Endo*-Isomers **130a** and *ent*-**130a** are formed in small quantity, the average *exo/endo* ratio being around 85/15 (Equation 18) <2001CC607, 2002CEJ2464>.



The C-C bond-formation step which is decisive for the absolute configuration of products occurs from the C-5 *Re*-face of a 1,4-biradical intermediate **131** as depicted below.

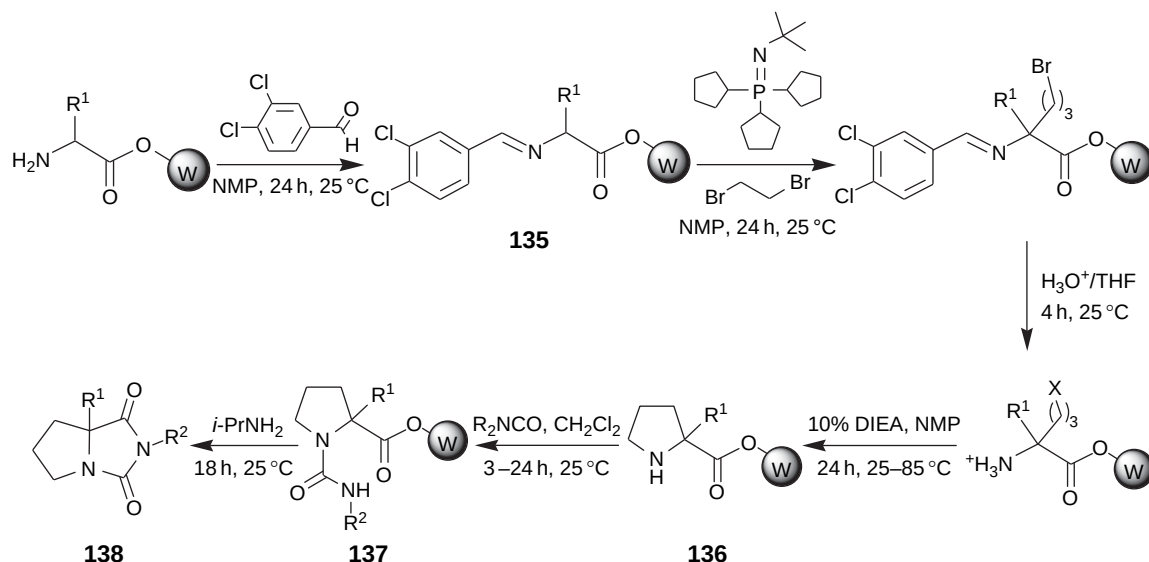


ω -Alkenyl-substituted ureas **133** underwent cyclization in the presence of an electrophilic palladium(II) catalyst, leading to an intermediate amino pallada-compound of type **134**. Palladium replacement through the second amino group of the urea under oxidative conditions regenerated the palladium(II) catalyst and released the diamination product as a cyclic urea **135** (Scheme 17). All reactions reached high to full conversion, and no compounds other than the diamination products were produced <2005JA14586>.



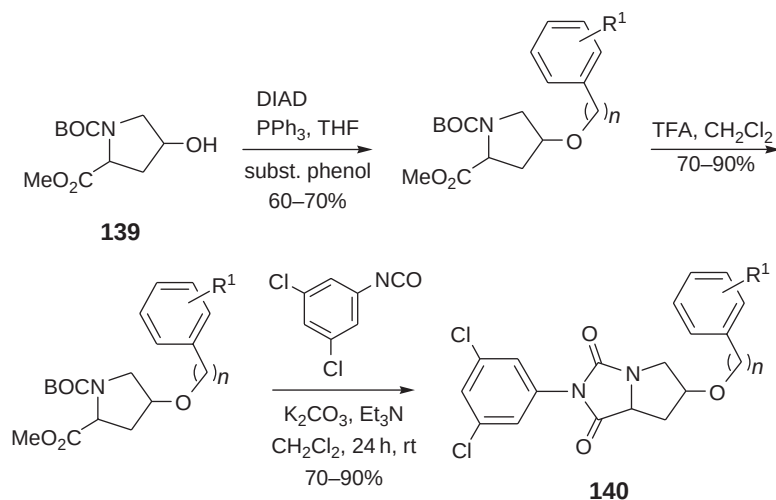
Scheme 17

Several syntheses of 1,3-dioxoperhydropyrrolo[1,2-*c*]imidazoles have been developed using different strategies. α -Substituted bicyclic proline hydantoin were prepared by alkylation of aldimines **135** of resin-bound amino acids with α,ω -dihaloalkanes and intramolecular displacement of the halide to generate α -substituted prolines **136** and homologs (Scheme 18). After formation of resin-bound ureas **137** by reaction of these sterically hindered secondary amines with isocyanates, base-catalyzed cyclization/cleavage yielded the desired hydantoin products <2005TL3131>.

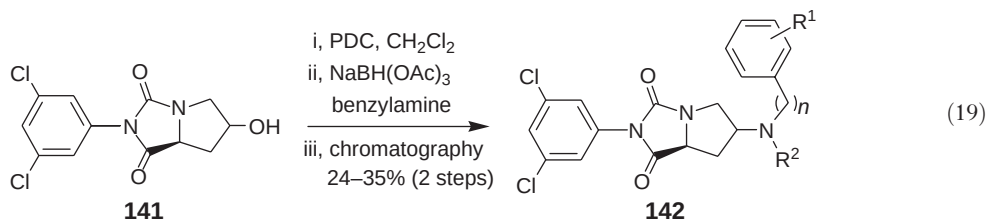


Scheme 18

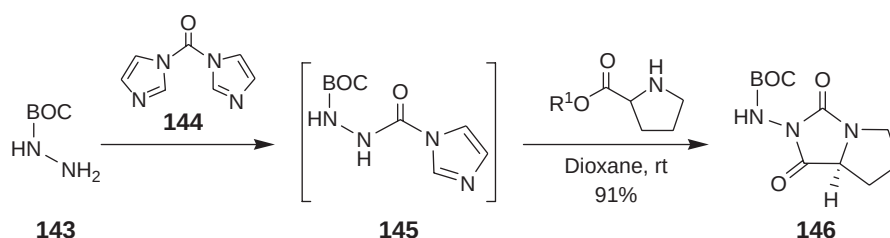
Homochiral hydroxyproline **139** served as the starting material for the synthesis of various bicyclic[5.5]hydantoin **140** (Scheme 19). The corresponding amino derivatives **142** were also available by oxidation of the alcohol **141** and reductive amination of the ketone followed by separation of diastereomers by silica gel column chromatography (Equation 19) <2005BML1161>.



Scheme 19

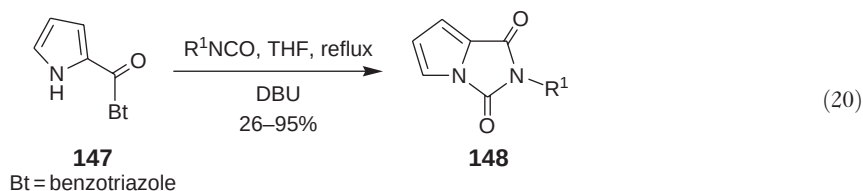


Another possibility to produce 1,3-dioxoperhydropyrrolo[1,2-*c*]imidazoles started with the reaction of *tert*-butyl carbamate **143** with carbonyldiimidazole **144**. The intermediate **145** was treated with L-proline in dioxane at room temperature to give the 3-aminohydantoin **146** in good yield (91%) (Scheme 20) <2000TL135>.

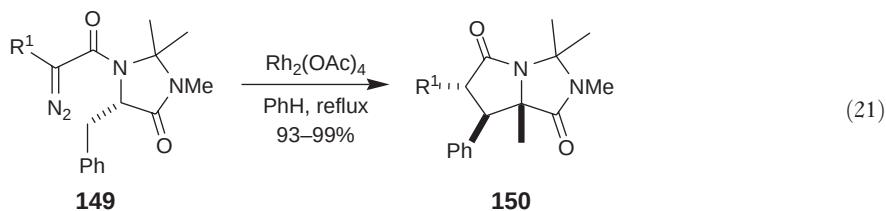


Scheme 20

A synthesis of 1,3-pyrrolo[1,2-*c*]imidazoles **148** has been obtained by reacting **147** with isocyanates in THF under reflux for 4 h in the presence of DBU. This reaction gave high yields of 1,3-dioxo-1,2,3,4-tetrahydropyrrolo[1,2-*c*]imidazoles (Equation 20) <2004JOC9313>.



1,5-Dioxo-derivatives **150** can be efficiently synthesized via Rh(II)-catalyzed intramolecular C–H insertion from various α -diazoamides. For example, intramolecular C–H insertion occurred readily in **149** under refluxing benzene conditions and produced the corresponding γ -lactams **150** with improved yields and excellent stereoselectivity (Equation 21) <2004JOC9313>.



11.02.5 Pyrrolo[1,2-*b*]isoxazoles

11.02.5.1 Introduction

In CHEC-II(1996) <1996CHEC-II(8)48>, it was reported that pyrrolo[1,2-*b*]isoxazoles are not known, but many examples of 3a,4,5,6-tetrahydro and perhydro pyrrolo[1,2-*b*]isoxazoles have been described.

11.02.5.2 Theoretical and Experimental Structural Methods

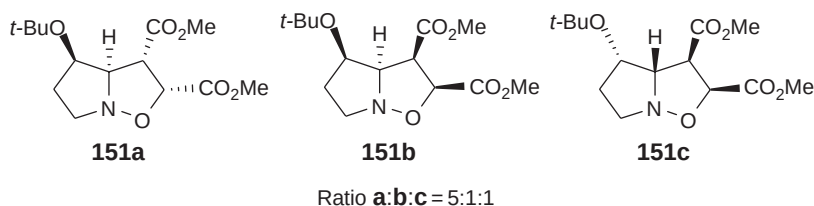
There are no theoretical calculations on this type of compound.

11.02.5.2.1 X-Ray

The X-ray structures of some perhydropyrrolo[1,2-*b*]isoxazoles have been established in order to determine the stereochemistry of the cycloadducts obtained by addition of nitrones to activated double bonds <1997T2979, 2005T8836, 2005JOC856>.

11.02.5.2.2 Proton NMR spectroscopy

No general studies have been carried out for these compounds, but there are several reports in which the stereochemistry of the final product has been elucidated by NOESY, correlation spectroscopy (COSY), or heteronuclear single quantum correlation (HSQC) experiments. For example, intensive NOESY experiments were used to establish the exact nature of each of the three cycloadducts **151a–c** generated by the cycloaddition of a substituted nitrone to dimethyl (*Z*)-diethylenedicarboxylate <2000EJO3633>.

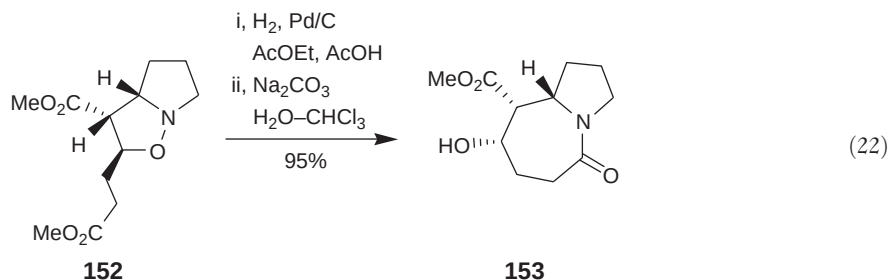


11.02.5.3 Reactivity

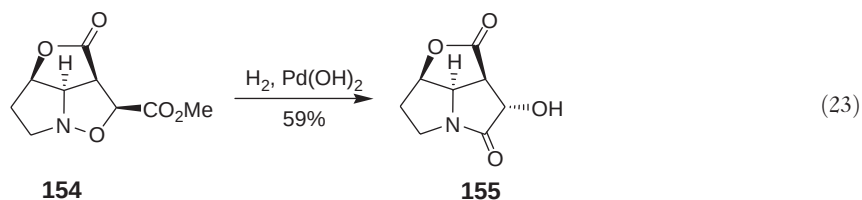
11.02.5.3.1 Ring Opening and N–O bond cleavage

11.02.5.3.1(i) Hydrogenolysis

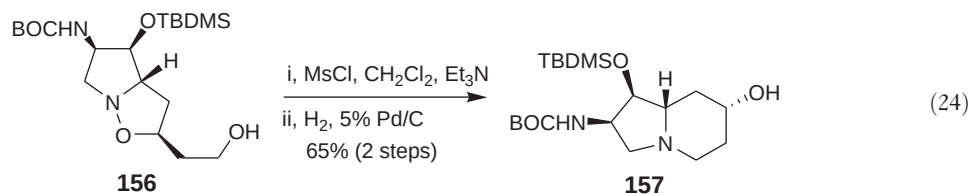
In the synthesis of the azabicyclic core of the *Stemona* alkaloids, methyl (2*RS*,3*SR*,3a*RS*)-2-(2-ethoxycarbonyl)ethyl)-hexahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate was hydrogenolyzed over 10% Pd–C in EtOAc and acetic acid at room temperature to give after cyclization the bicyclic lactam **153** <2005JOC3157> (Equation 22). This route was also used to produce pyrrolozolidinone-based dipeptide isosteres <2005T8836>.



In the same manner, compound **154**, treated by hydrogen in the presence of Pd(OH)₂/C in methanol, was transformed to the α-hydroxylactam **155** (Equation 23) <2001OL1367>.

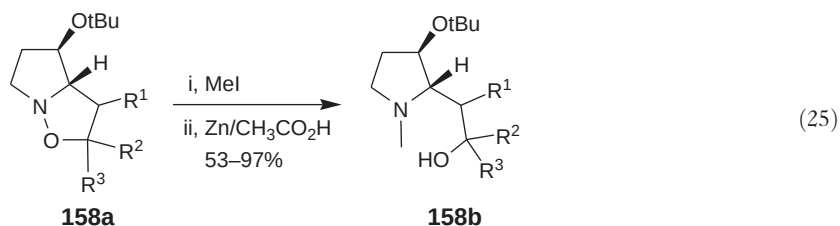


An interesting route to indolizidine **157** is based on N–O bond cleavage in perhydro[1,2-*b*]isoxazole **156** by hydrogenolysis of the mesylated intermediate (Equation 24) <2000TL1583>.

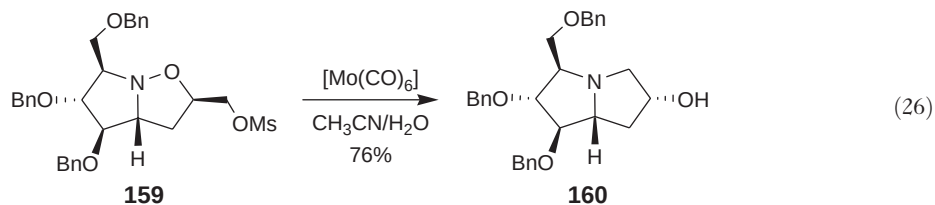


11.02.5.3.1(ii) Reductive cleavage

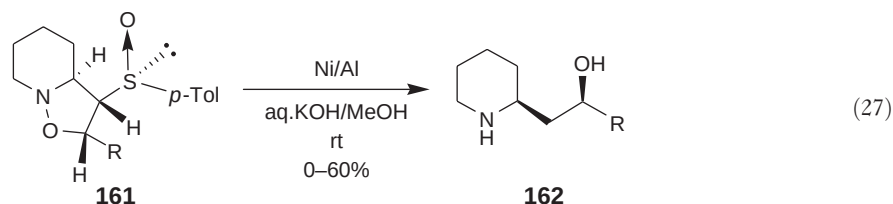
Conversion of isoxazolidines to the corresponding *N*-methyl γ -aminoalcohols was achieved by methylation with MeI followed by reduction with Zn in acetic acid or hydrogenation over Pd/C (Equation 25) <1997TA293>.



The reductive cleavage of the N–O bond in **159** can also be achieved with $[\text{Mo}(\text{CO})_6]$ in aqueous MeCN, yielding the pyrrolizidine derivative **160** (Equation 26) <2003HCA3066>.

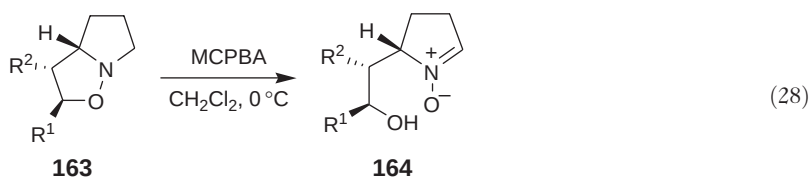


The reductive cleavage of the N–O bond in the isoxazolidine **162** unmasks the 1,3-amino alcohol moiety. Thus, isoxazolidines can be viewed as direct precursors of γ -amino alcohols. The reductive cleavage of the cycloadduct proved difficult. W2 Raney-Ni and nickel boride were both ineffective. In contrast, nickel–aluminium alloy in an alkaline medium efficiently reduced the N–O bond at room temperature in the presence of a base (Equation 27) <1997TA109>.



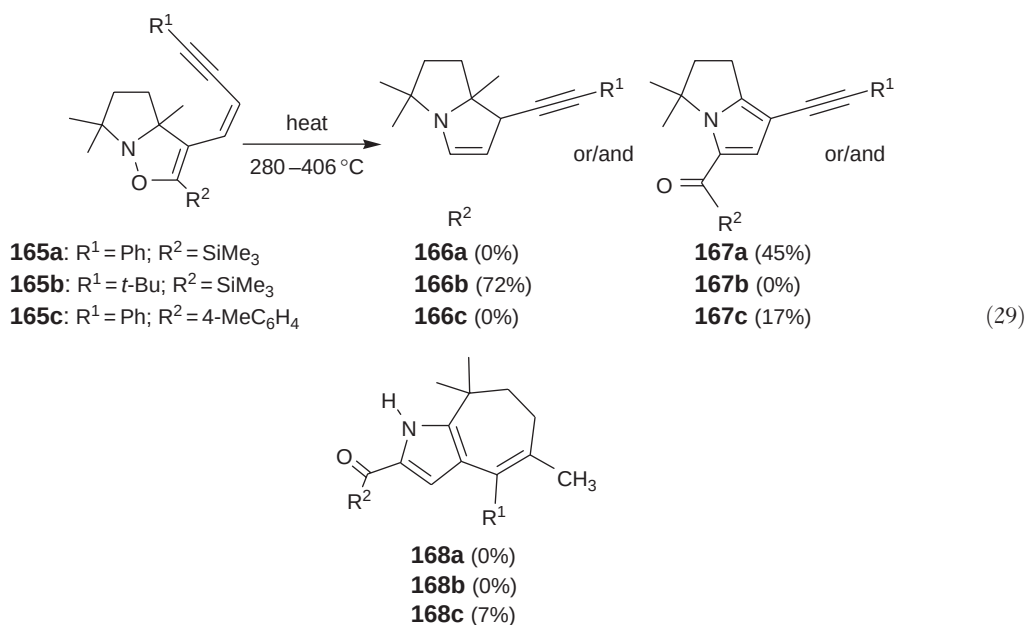
11.02.5.3.1(iii) Oxidative cleavage

The oxidation of the perhydropyrrolo[1,2-*b*]isoxazole **163** with *m*-chloroperbenzoic acid (MCPBA) led to the regio-selective ring cleavage to give nitrone **164**. This reaction has been applied with success in the total synthesis of several types of polycyclic guanidine alkaloids (Equation 28) <2001TL4155, 2002OL177, 2002OL2921, 2002TL6383, 2005CEJ6878>.

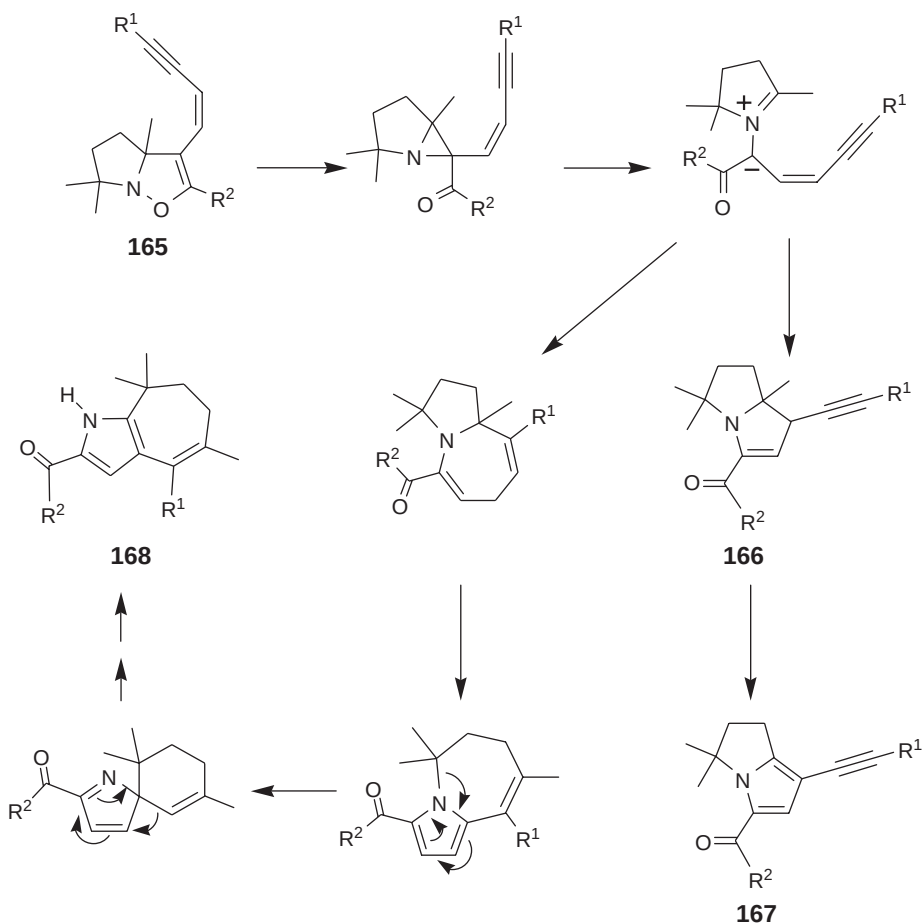


11.02.5.3.2 Thermal and photochemical rearrangements

The thermal reactions of the butenynyl-substituted tetrahydropyrrolo[1,2-*c*]isoxazole **165a** and **165b** were performed in benzene using short-time thermolysis conditions at 280–406 °C with a contact time of ca. 10 s. When compound **165a** was reacted in these conditions, **167a** was isolated as a sole product in contrast to **165b** which only produced **166b** in 72% yield. If the SiMe₃ group (R¹) is replaced by an aromatic moiety, such as in **165c**, the thermolysis of this latter compound gave **167c** and **168c** in 17% and 7% yield, respectively (Equation 29).

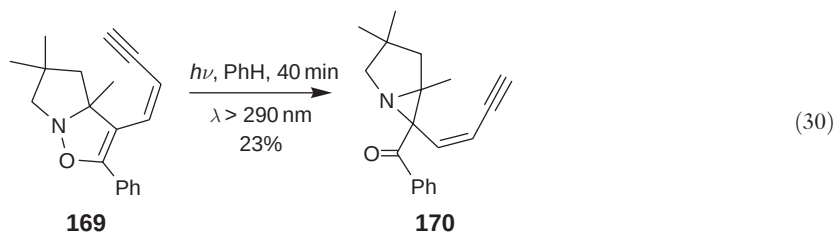


These results can be explained according to mechanistic considerations shown in Scheme 21 <2001HCA3822>.



Scheme 21

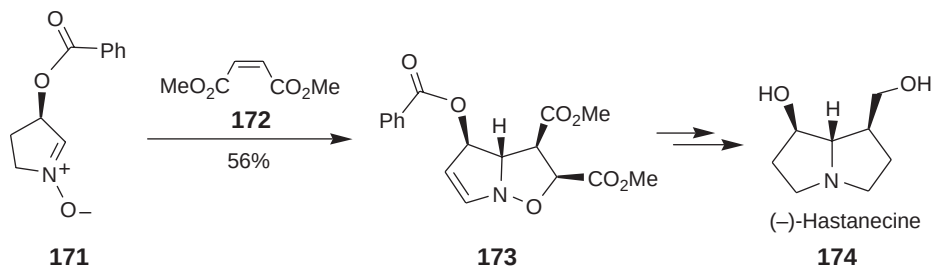
In addition, annulated aziridine **170** was obtained in pure form by photochemical transformation of **169** (Equation 30) <2001HCA3822>.



11.02.5.4 Synthesis

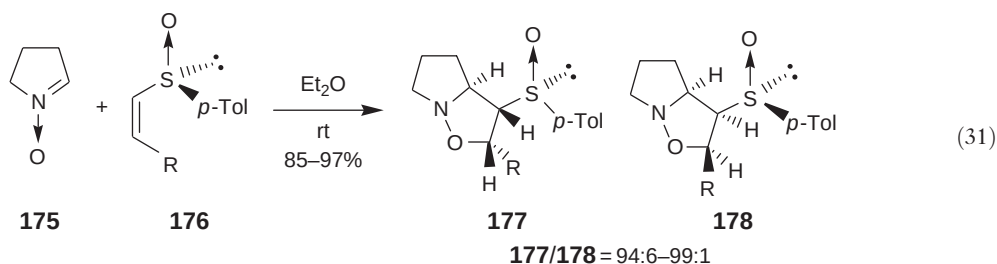
The general method, that has been widely used for the synthesis of perhydropyrrolo[1,2-*b*]isoxazoles, is based on a cycloaddition reaction of cyclic nitrones with dipolarophiles. The nitron is easily available by oxidation of the corresponding hydroxylamine with mercuric chloride. The cycloaddition of nitron to dipolarophiles is highly regioselective and stereoselective and have been often applied in the total synthesis of natural products <2001OL1367, 2004BML3967, 2005JOC3157>. As one representative example of dipolar cycloaddition, reaction

of substituted pyrrolidine *N*-oxide **171** and dimethyl ethylenedicarboxylate **172** in benzene at room temperature gave the perhydropyrrolo[1,2-*b*]isoxazole **173** that was eventually transformed to (–)-hastanecine **174** in a few steps (Scheme 22) <2000EJO3633>.



Scheme 22

Many type of alkenes have been used as dipolarophiles for the synthesis of perhydropyrrolo[1,2-*c*]isoxazolines through dipolar cycloaddition with nitrones. The most common dipolarophiles involved in this reaction are alkenes <1997TA293, 1999T187, 2001TL4155, 2002OL177>, substituted unsaturated esters <1996TA2793, 1996JOC8578, 1997T16080, 1997T7057, 1997TA1031, 1998T6947, 1999TL2853, 2000EJO3633, 2001TL5937, 2002TL5711, 2003TL523, 2004AGE1559, 2005JOC3157, 2005CEJ6878>, aldehydes <2002JA4968>, amides <2001CC1359, 2005JOC856, 2005T8836, 2005JOC3157>, allylic alcohols <1997JOC3119, 2003HCA3066, 2003T5231>, allenes <2004TL4097>, vinyl boranes <2005T10886>, vinyl ethers <1998T15691>, ketoesters <1998T10857>, unsaturated lactones <2004BML3967, 2005JOC3157>, diiron acyl complexes <1999AC(E)1116>, etc., giving a great number of perhydropyrroloisoxazoles. A highly stereoselective cycloaddition of substituted (*Z*)-vinyl sulfoxides **176** with cyclic nitrone **175** gave useful perhydro intermediates **177** and **178** that have been used for the total synthesis of (–)-hygroline (Equation 31) <1997TA109>.



Several tetrahydro derivatives were synthesized by reaction of nitrones with DMAD <1997T2979, 1997TA1031, 2002TA437, 2003TL523> methyl propiolate <1997J(P1)155> or *t*-butyl propynal <2001HCA3822, 2001T4349, 2001TA3297>.

11.02.6 Pyrrolo[2,1-*b*]oxazole

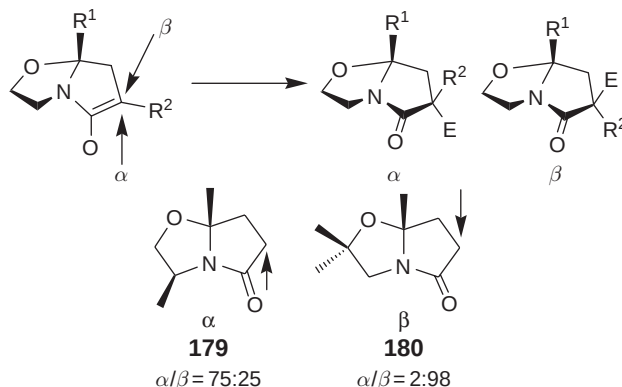
11.02.6.1 Introduction

There has been no report on this kind of compound in the literature for the period concerned. The perhydro derivatives were, on the contrary, well-studied for several years and applied in a variety of routes for the total synthesis of natural products or to produce optically active derivatives, mainly following the Meyers protocol <1984JA1146>. Only two examples of dihydropyrrolo[2,1-*b*]oxazoles are available and one example of a tetrahydro derivative is described.

11.02.6.2 Theoretical and Experimental Structural Methods

There is one report that showed how torsional, involving allylic CH bonds and steric effects but not orbital distortions, provide an explanation for the stereoselectivity of pyrrolidinone enolate alkylations. A prediction was

made and verified experimentally. The calculated energy activation differences described <1999JA5334> correspond to product ratio of 75:25 for **179**, and 2:98 for **180** at -78°C , and are in good agreement with experimental results (Scheme 23) <1997JA4565, 1998JA7429>.



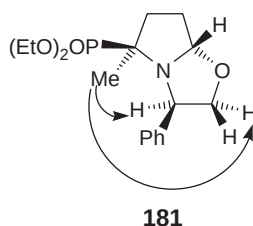
Scheme 23

11.02.6.2.1 X-Ray

Two structures have been determined by X-ray diffraction for stereochemical determination. The structure of one enolate derived from Meyers oxazolidinone was reported <1996JA7429> as well as structure of (3*S*,5*R*,7*aR*)-5-(benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine which was obtained as only one diastereomer <1998TL1697, 1999JOC1979>.

11.02.6.2.2 NMR Spectroscopy

The ^1H and ^{13}C NMR descriptions of a great number of perhydro-pyrrolo-oxazoles have appeared since the important contribution in the field by Meyers *et al.* They are mainly used for structural determination and to prove the stereochemistry of the substitution of these compounds. Some NOESY experiments were performed for the structural elucidation of diethyl (3*R*,5*S*,7*aS*)-5-methyl-3-phenylhexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-yl-phosphonate **181** <2004TL5175>.



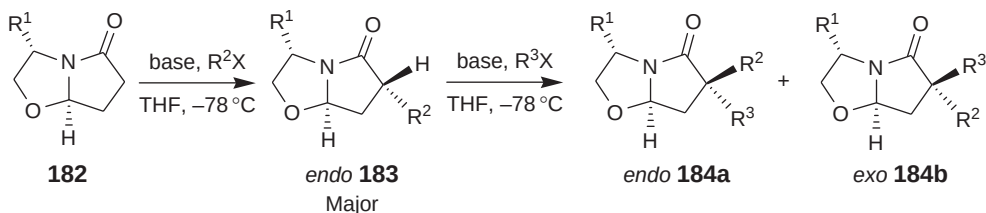
11.02.6.3 Reactivity

The studies of the reactivity of saturated pyrrolo[2,1-*b*]oxazoles are in general associated with the reactivity of Meyers chiral bicyclic lactams and their applications in asymmetric synthesis.

11.02.6.3.1 Reaction with electrophiles

Meyers lactams are widely used in synthesis of substituted synthons of interest and their functionalization is carried out under strong base conditions giving C-alkyl derivatives. Alkylation of bicyclic lactam **182** with electrophiles (alkyl, allyl, benzyl halides, chlorophosphonate), and a strong base (*s*-BuLi, LiHMDS, or KHMDS; HMDS=hexamethyldisilazide) in THF at -78°C gave an *endo-exo* mixture of products where the major one is the *endo*-compound **183** in good yields. The ratios were determined by ^1H NMR spectroscopy and are usually up to

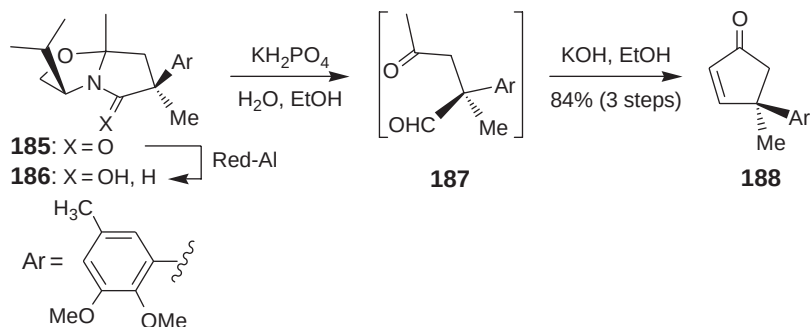
80/20 in favor of the *endo*-product. After separation of the two diastereomers, the monosubstituted chiral lactam obtained could be again alkylated in the presence of a strong base and gave the disubstituted compounds **184a** and **184b** with excellent diastereoselectivity in favor of the *endo*-product (Scheme 24) <1996JA7429, 1996JA9876, 1996JOC5712, 1999CC1371, 2000TL8193>.



Scheme 24

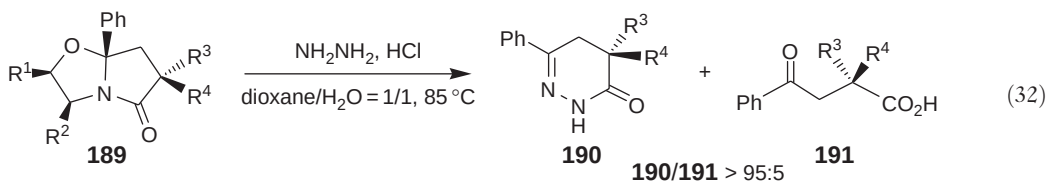
11.02.6.3.2 Ring-opening

The substituted chiral bicyclic lactam **185** prepared according to Scheme 24 were reduced with Red-Al to give **186** and easily hydrolyzed in the presence of KH_2PO_4 to give the ketoaldehyde **187**, which under basic conditions (KOH in ethanol) cyclized to afford cyclic ketone **188** (Scheme 25) <1999JA2762>. Other reagents such as $\text{Bu}_4\text{NH}_2\text{PO}_4$ were used for the same type transformation <2004BML3885, 1999CC1371>.

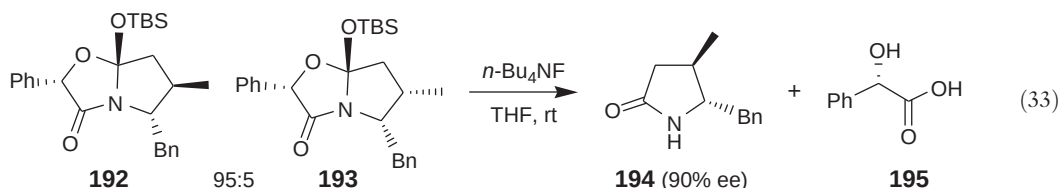


Scheme 25

Bicyclic lactams **189** are uniquely suited as precursors for the synthesis of chiral substituted 4,5-dihydro-2*H*-pyridazinones **190** by hydrolysis with NH_2NH_2 and HCl in dioxane at 85°C . The reaction gave, as a side product, the ketoacid **191** in some cases (Equation 32) <2003TL7997>.

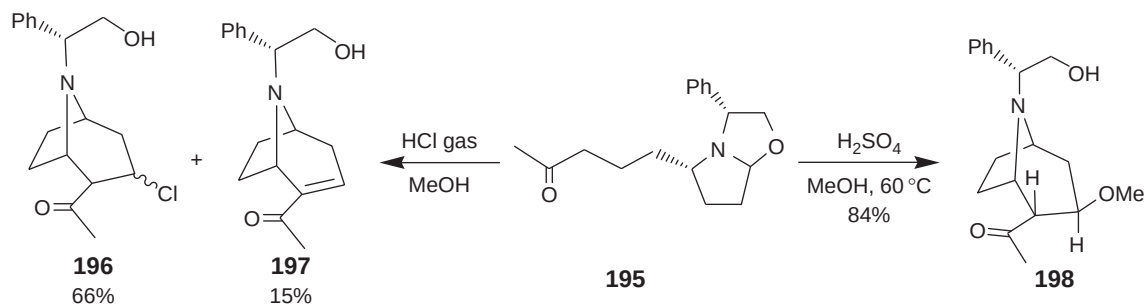


Optically active *N*-unprotected-2-pyrrolidinones **194** were obtained from selenocarboxylate or allylamine via radical cyclization and subsequent one-step cleavage of the C–O and C–N bond of the inseparable mixture of the two bicyclic oxyxazolidinones **192** and **193** with *n*- Bu_4NF . The initial radical reaction is highly stereoselective. Products were obtained with ee up to 90%. The mandelic acid **195**, which served as the chiral auxiliary in this method, was recovered with no loss of optical activity (Equation 33) <2003T6291>.



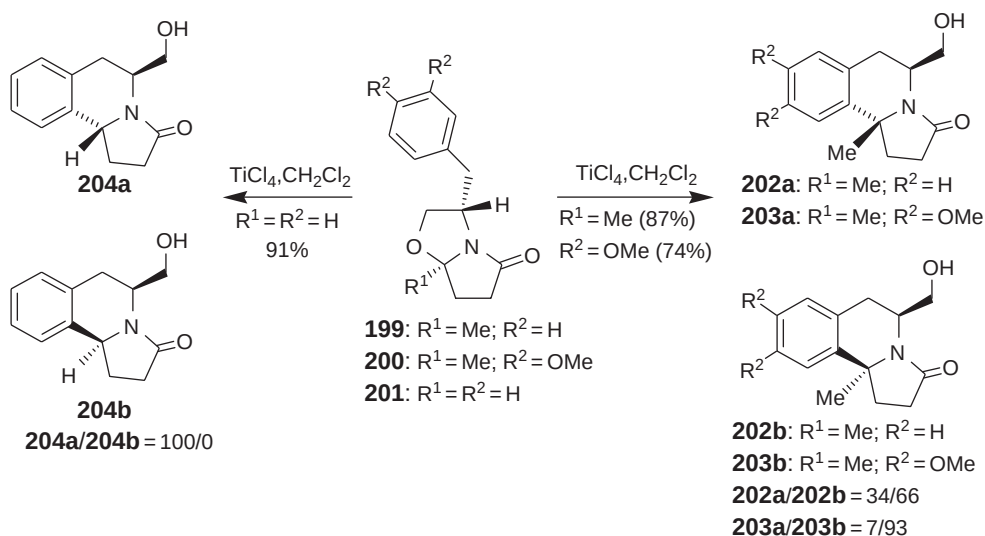
11.02.6.3.3 Ring-opening/cyclization

Cleavage of 5-(3-phenyl-hexahydro-pyrrolo[2,1-*b*]oxazol-5-yl)-pent-3-en-2-one **195**, when conducted in methanol with HCl gas, produced compounds **196** and **197** in an 80/20 ratio, or after treatment with sulfuric acid in methanol at 60 °C afforded **198** as a single isomer (Scheme 26). Compound **198** was used for the total synthesis of the potent neurotoxic (+)-ferruginine <1997JOC6704>.



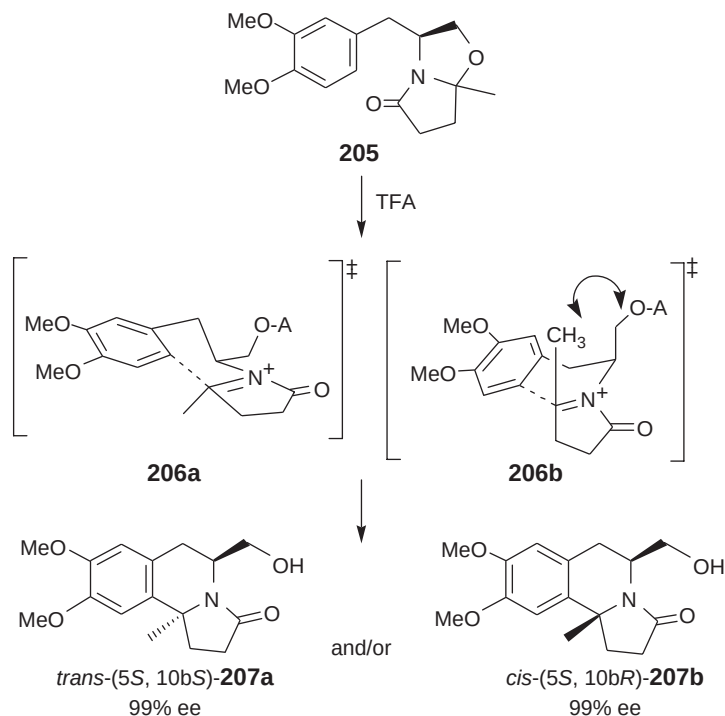
Scheme 26

The stereoselective synthesis of pyrrozoisoquinoline ring system has been achieved by the reaction of perhydro derivatives **199** and **200** with TiCl_4 as Lewis acid, at low temperature, in dichloromethane. The reaction furnished a 2:1 mixture of two diastereomers **202a** and **202b** for **199** and was highly stereoselective for **200** giving **203a** and **203b** as a 93/7 mixture. If $\text{R}^1 = \text{R}^2 = \text{H}$ for **201**, the reaction was totally stereoselective and product **204a** was isolated without trace of **204b** (Scheme 27) <2001J(P1)3029>.



Scheme 27

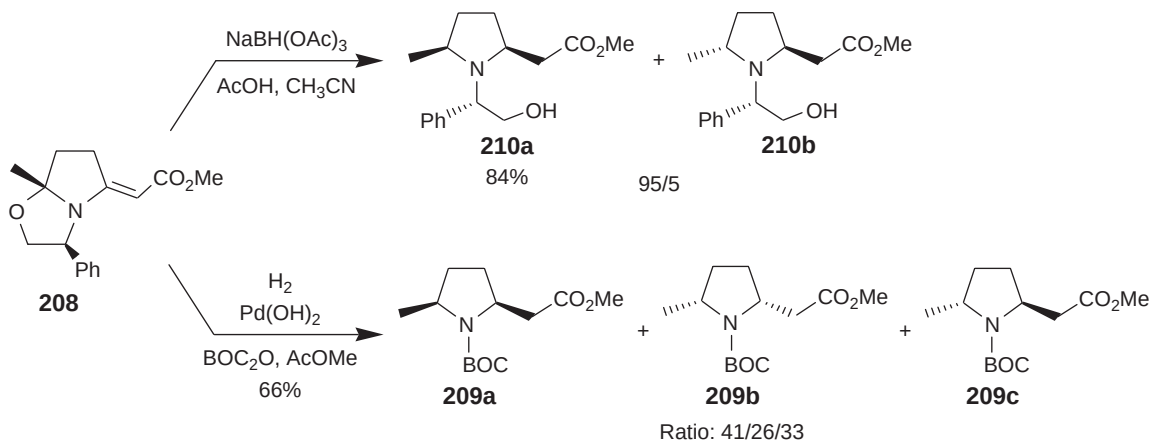
The ring-opening of **205** in presence of TFA followed by cyclization of the two possible conformations of the *N*-acyliminium ions **206a** or **206b** gave the pyrrolo[2,1-*a*]isoquinolones **207a** and **207b** in high yield (88%) with moderate stereoselectivity (2/1) (Scheme 28) <2005JOC10368>.



Scheme 28

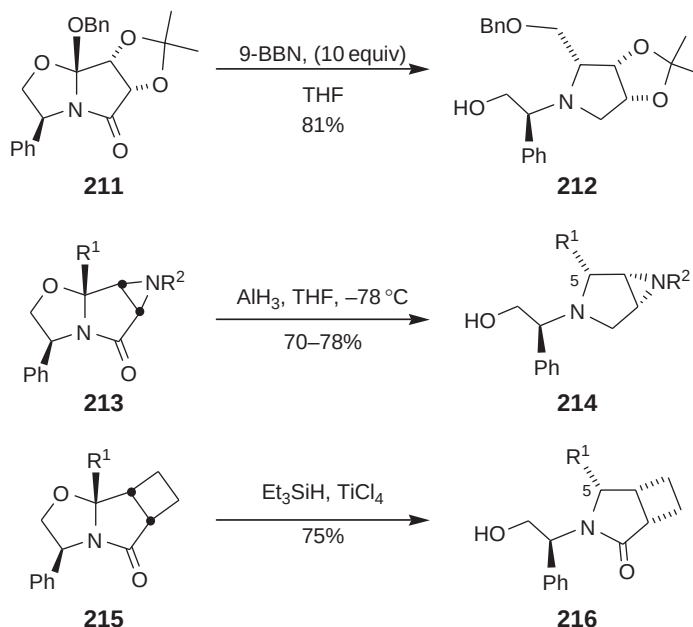
11.02.6.3.4 Ring-opening by reduction

The reduction of pyrrolo[2,1-*b*]oxazoles was achieved with different reducing agents. Catalytic hydrogenation of **208** in the presence of Pd(OH)₂ and BOC₂O gave under these conditions, in 66% yield, a mixture of three isomers consisting in a mixture of the *cis*-isomers (2*S*,5*S*)-**209a** and (2*R*,5*R*)-*ent*-**209b** (ratio 61:39) and of the *trans*-isomer (2*S*,5*R*)-**209c** in a ratio of 41/26/33. Treatment of **208** with sodium triacetoxyborohydride led to the reduction of the C–C double bond along with the cleavage of the oxazolidine ring to give compounds **210a** (84%) and **210b** in a ratio 95:5 (Scheme 29) <2005T7774>.



Scheme 29

Treatment of **211** with 9-borabicyclo[3.3.1]nonane (9-BBN; 10 equiv) in THF afforded **212** in 81% yield as a single diastereomer <1999T8931>. The reduction of the aziridine lactam derivative **213** with AlH_3 and of the cyclobutane **215** with Et_3SiH in the presence of TiCl_4 led respectively to **214** and **216** with a high degree of inversion of configuration at C-5 (Scheme 30) <1995TL3491, 1995JOC4359, 1996JOC2586>.



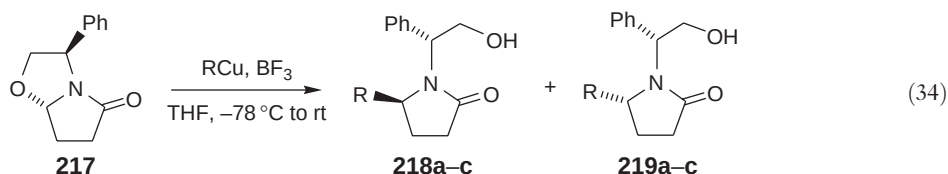
Scheme 30

11.02.6.3.5 Nucleophilic addition

Alkyl chains may be introduced on acyliminium derivatives using lower-order cuprates complexed with $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 31). The best results were obtained in THF with cuprates generated from $\text{CuBr} \cdot \text{Me}_2\text{S}$, at room temperature. Simple alkyl groups (Me, Bu) were easily introduced in good yield and selectivity (Table 3) through cuprate addition in THF at -78°C followed by stirring at rt for 12 h. The phenyl group was added with good stereoselectivity but in poor yield using this method (Equation 34) <2001TA1219>.

Table 3 Addition of organocuprate to **217** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$

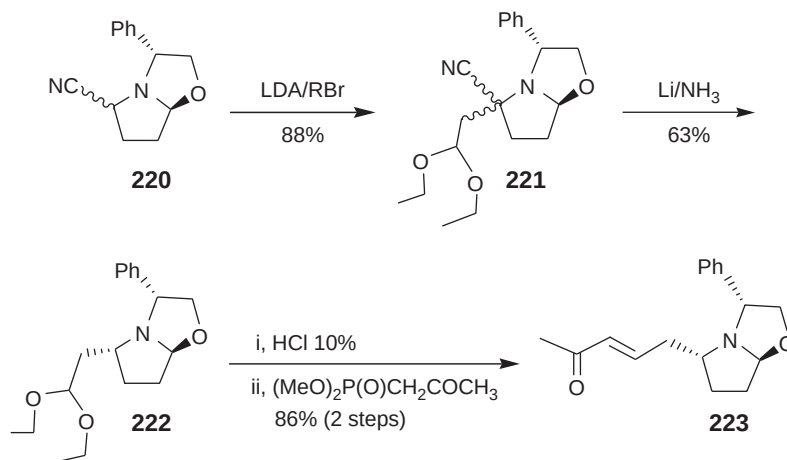
Nucleophile	Solvent	Products 218 and 219	Yield (%)	de (%)
MeCu	THF	a (R = Me)	85	76
<i>n</i> -BuCu	THF	b (R = Bu)	95	74
<i>n</i> -BuCu	Et_2O	b (R = Bu)	38	
PhCu	THF	c (R = Ph)	32	75



11.02.6.3.6 Reactivity of the substituent attached to ring carbon atom

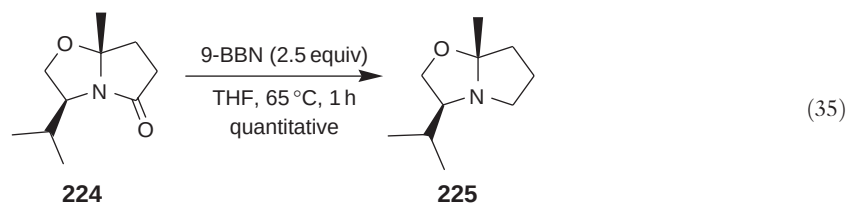
Alkylation of **220** was achieved by treatment with lithium diisopropylamide (LDA) followed by addition of an appropriate alkyl halide. Decyanation of compound **221** was achieved using Li/NH_3 , to give compound **222** in 66%

yield as a single stereomer. This reaction has been shown to be completely stereoselective and furnish pyrrolidine **222** with the *2R*-configuration. Careful cleavage of the acetal function with dilute HCl was effected without opening of the oxazolidine ring and furnished the aldehyde which was not isolated but immediately converted into the *trans*-enone **223** by treatment with dimethyl(2-oxopropyl)phosphonate under Horner–Wadsworth–Emmons conditions (Scheme 31) <2002EJO1484, 1997JOC6704, 1999CSR383>.



Scheme 31

(3*S*-*cis*)-(+)-Tetrahydro-3-isopropyl-7a-methylpyrrolo[2,1-*b*]oxazol-5(6*H*)-one **224** was reduced using 2.5 equiv of 9-BBN to give the corresponding amine **225** in quantitative yield (Equation 35) <1999TL3673>.



11.02.6.4 Synthesis

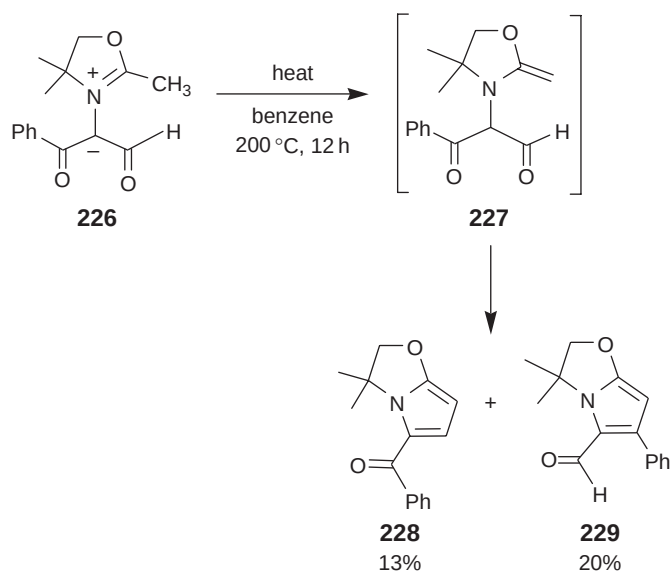
11.02.6.4.1 Dihydropyrrolo[2,1-*b*]oxazole

Aromatic pyrrolo[2,1-*b*]oxazoles are unknown compounds. Dihydro derivatives **228** and **229** have been obtained from the thermal rearrangement of dihydrooxazole **226** through intermediate **227** (Scheme 32) <2003EJO1438>.

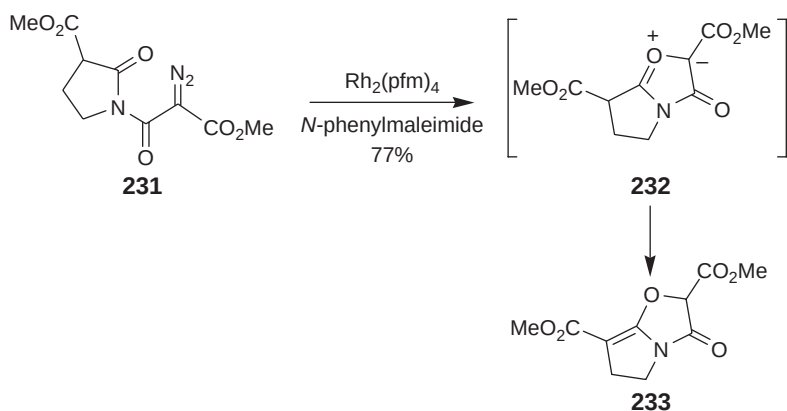
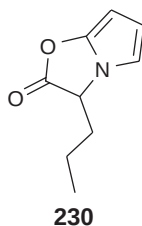
In one example, carbonylation of allylamine catalyzed by rhodium phosphine (1,4-diphos) gave a dihydropyrrolo[2,1-*b*]oxazole **230** <1999JMO297>.

11.02.6.4.2 Tetrahydro derivatives

When 1-[diazo(methoxycarbonyl)acetyl]-2-oxopyrrolidine derivative **231** was treated with Rh₂(pfm)₄ (pfm = perfluorobutyro amidate) in the presence of *N*-phenylmaleimide, none of the desired dipolar cycloadduct was formed but instead the acidic proton at C-3 in the isomünchnone intermediate **232** was transferred, and the fused oxazolidinone 3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*b*]oxazole-2,7-dicarboxylic acid dimethyl ester **233** was isolated in 77% yield (Scheme 33) <1997JOC6842>.



Scheme 32

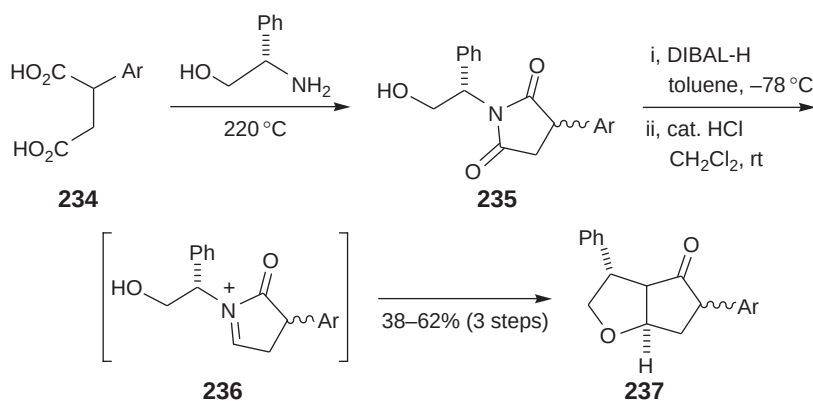


Scheme 33

11.02.6.4.3 Perhydro derivatives

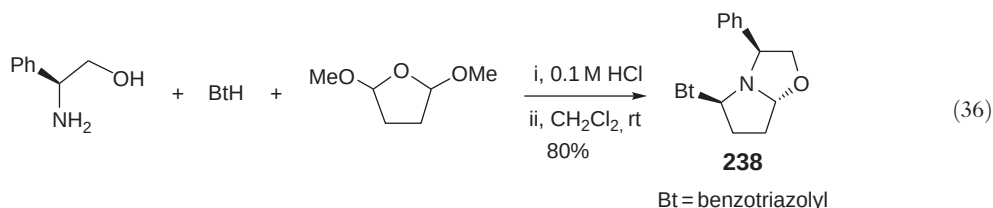
11.02.6.4.3(i) Cyclizations under acidic conditions and cyclocondensations

There are many reports on the preparation of this type of compound under acidic conditions <1998TL1697, 1999T8931, 1999TL4639, 2000TL8193, 2001JOC4939, 2001TA1219, 2001TL145, 2003TL2315, 2004T1235, 2004T1247, 2004TL5175, 2005JOC10368, 2005OL4657>. Condensation of (*S*)-phenylglycinol with **234** furnished the succinimide derivatives **235**, which were regioselectively reduced and cyclized via the intermediate *N*-acyliminium species **236** to afford the bicyclic lactams **237** (Scheme 34) <2000TL8193>.

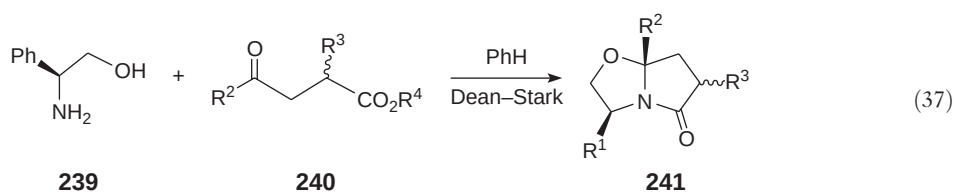


Scheme 34

Another representative example is the preparation of (3*S*,5*R*,7*aR*)-5-(benzotriazol-1-yl)-3-phenyl[2,1-*b*]oxazopyrrolidine **238** that was synthesized from benzotriazole, (*S*)-phenylglycinol, and 2,5-dimethoxy-tetrahydrofuran at room temperature. This reaction entailed the formation of two heterocyclic rings and two new chiral centers in one step (Equation 33) by double Robinson–Schöpf condensation of the dialdehyde with the amino group and benzotriazole intercepting the initially formed iminium ion (Equation 36) <1999JOC1979>.



A number of 5-oxo-perhydropyrrolo[2,1-*b*]oxazoles **241** were obtained by condensation of the corresponding oxoacid **239** or oxoester with α -amino alcohol **240** (Equation 37) <1996JOC3362, 1998JME4556, 2004TL7731, 2004TL5047, 2004JOC2773, 2004BML5537, 2004BML3073, 2005TL8385, 2006TL69>. This method has been applied for the preparation of Meyers bicyclic lactams that were used in asymmetric synthesis of many natural compounds <1996JA9876, 1996JOC2586, 1999CC1371, 1999JA2762, 1999T8931>.

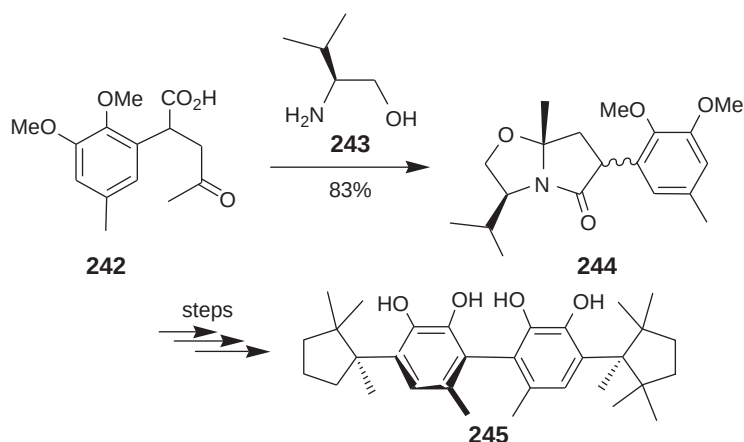


For example, 3-isopropyl-7*a*-methyl-5-oxo-perhydropyrrolo[2,1-*b*]oxazole **244** formed by condensation of (*S*)-valinol **243** and 2-(2,3-dimethoxy-5-methylphenyl)-4-oxopentanoic acid **242** in toluene was the key intermediate in the total synthesis of (–)-mastigophorene B **245** (Scheme 35) <1999JA2762>.

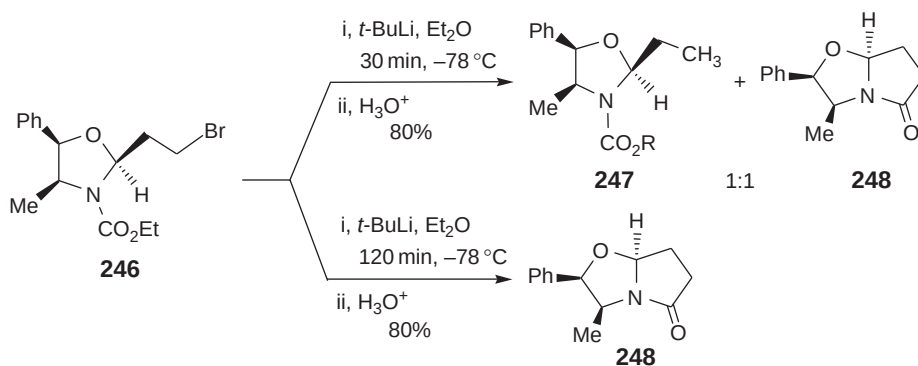
11.02.6.4.3(ii) Cyclizations under basic conditions

In the preparation of (2*R*,3*S*,7*aS*)-2-phenyl-3-methyl-5-oxo-2,3,5,6,7,7*a*-hexahydropyrrolo-[2,1-*b*]oxazole **248**, the reaction time is the most important parameter in the *trans*-halometallation. For instance, by stirring **246** with 1 or 2 equiv of *tert*-butyllithium in Et₂O at –78 °C for 30 min, **247** and the bicyclic lactam **248** were obtained as an equimolar mixture. The latter substance was isolated as a single product when the reaction time was increased to 120 min for the reactions of 2-(2'-bromoethyl)oxazolidine **246** with *tert*-butyllithium (Scheme 36) <1996T10761>.

Perhydropyrrolo[2,1-*b*]oxazoles were also produced in good yields (60–92%) in the presence of Et₃N in CHCl₃ by condensation of γ -chloroketones with β -aminoalcohols <2000EJO1719>.



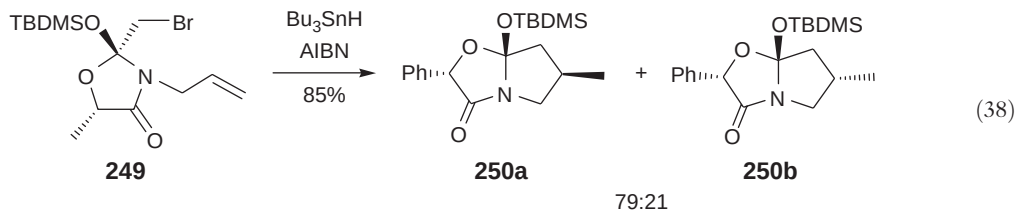
Scheme 35



Scheme 36

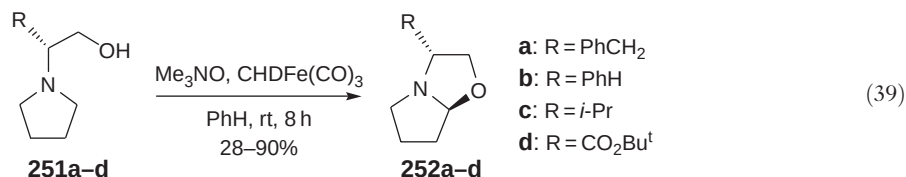
11.02.6.4.3(iii) Cyclization under radical conditions

Exposure of **249** to Bu_3SnH at 110°C resulted in the clean formation of the desired bicyclic lactam **250** in 85% yield. The product contained two diastereomers **250a** and **250b**, whose ratio was revealed to be 79:21 (Equation 38) <2003T6291>.



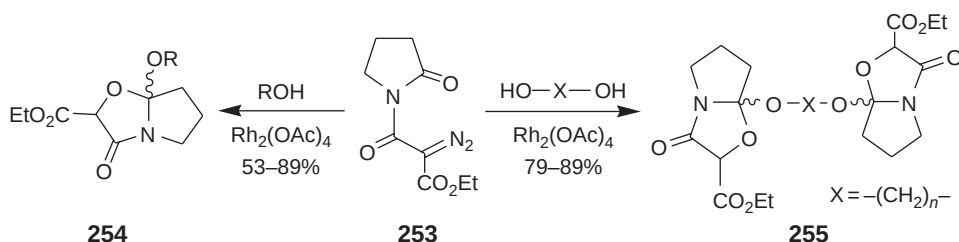
11.02.6.4.3(iv) Oxidative cyclization method

The oxidative cyclization of chiral 2-pyrrolidino-1-ethanol derivatives is shown in the reaction of **251** with trimethylamine N -oxide and a substoichiometric amount of cyclohexadiene iron tricarbonyl to produce the corresponding oxazolopyrrolidine ring **252**. The mechanism of this reaction is unknown. Both amine oxide and iron complex are essential for the reaction (Equation 39) <2005TL3407>.



11.02.6.4.3(v) Carbenoid cyclization

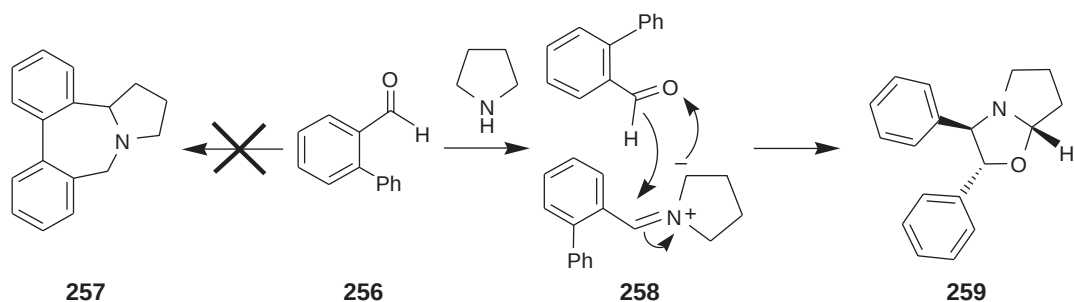
When the diazoimides **253** are subjected to $\text{Rh}_2(\text{OAc})_4$ at 80°C in presence of an alkyl alcohol, perhydropyrrolo[2,1-*b*]-oxazol-4-ones **254** were isolated in good yields as a diastereomeric mixture. If the alcohol is replaced by terminal alkyl diols, the corresponding bis(2,3-fused perhydropyrrolo[2,1-*b*]-oxazol-4-one) systems **255** were obtained (Scheme 37) <2003CC440>.



Scheme 37

11.02.6.4.3(vi) 1,3-Dipolar cycloaddition

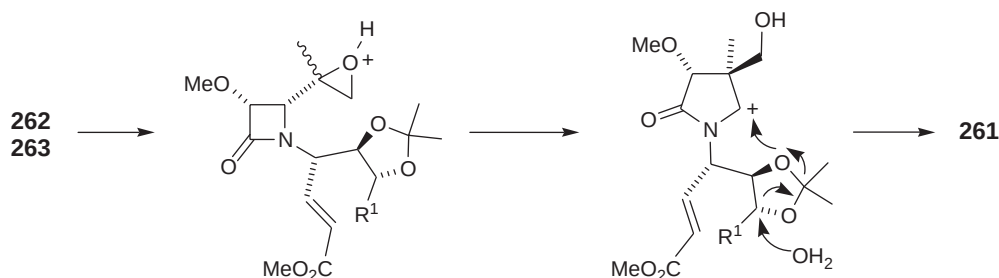
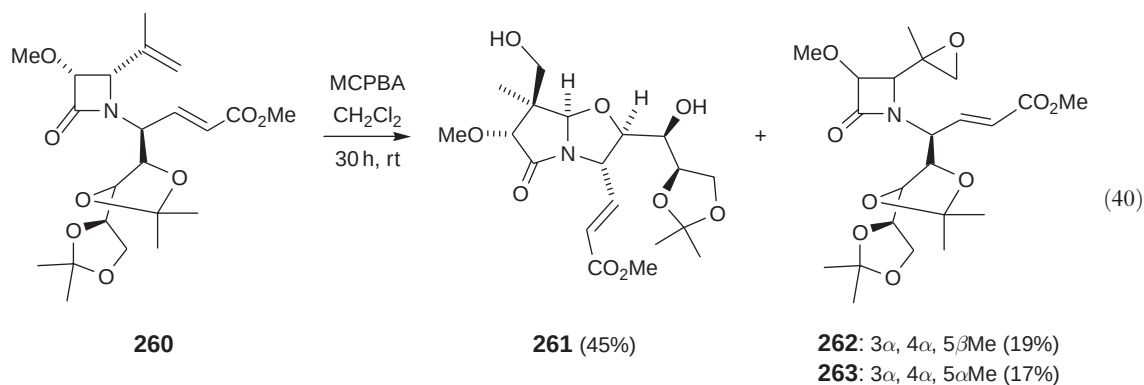
The reaction of the aldehyde **256** with proline gave a product which was not the expected dihydrodibenz[*c,e*]azepine **257**. Spectroscopic analysis revealed that this new product was an oxazolidine **259** (obtained as a single isomer) resulting from the 1,3-cycloaddition of the azomethine ylide **258** to the precursor aldehyde **256** (Scheme 38) <1999J(P1)2605>.



Scheme 38

11.02.6.4.3(vii) Ring expansion

An unusual rearrangement has been observed when *trans*- α,β -unsaturated ester **260** on treatment with MCPBA gave a mixture of three products in 80% yield. The most abundant product was identified as the bicyclic γ -lactam **261** (45%) and the minor constituents were identified as the epoxides **262** (19%) and **263** (17%) (Equation 40) <2003T241>. A mechanism has been postulated to explain this transformation (Scheme 39).



Scheme 39

11.02.7 Pyrrolo[1,2-*c*]oxazoles

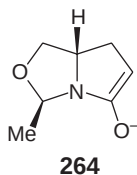
11.02.7.1 Introduction

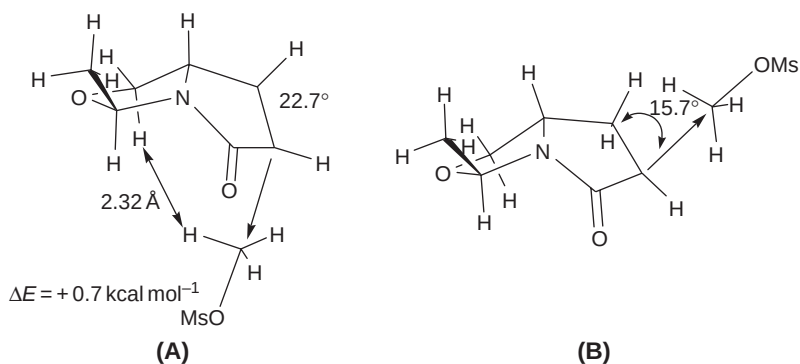
Aromatic pyrrolo[1,2-*c*]oxazoles cannot be drawn, and the only structure that one can find in the literature is the 1*H*,3*H*-derivatives. The derivatives 3*H*,5*H* and 3*H*,7*H* are unknown. All compounds described are dihydro and mainly oxo perhydro derivatives.

11.02.7.2 Theoretical and Experimental Structural Methods

11.02.7.2.1 Theoretical methods

A study on the torsional and steric effects controlling the stereoselectivities of alkylation of pyrrolidinone enolates has been performed in order to explain the high degree of stereoselectivity observed by Meyers and others <1988JOC4094, 1990H191, 1991T9503, 1996AC(E)2708, 1996JOC5710, 1997JOC5712>. The enolates of bicyclic pyrrolidinones react with electrophiles to give products of α - or β -attack, depending on the nature of R and the second ring. For the α -transition state of **264** (**A**), there is a repulsive interaction between the hydrogens which are separated by only 2.32 Å, which is less than the sum of their van der Waals radii (2.4 Å). The β -attack (**B**) has slightly larger torsional strain, and the total energy difference is 0.7 kcal mol⁻¹, favoring α -attack <1999JA5334>. The calculated activation energy differences described here correspond to a ratio of 15:85 for **264** at -78 °C (calculated by $k_1/k_2 = e^{-\Delta E/RT}$), and are in good agreement with experimental results <1997JA4565, 1998JA7429>.

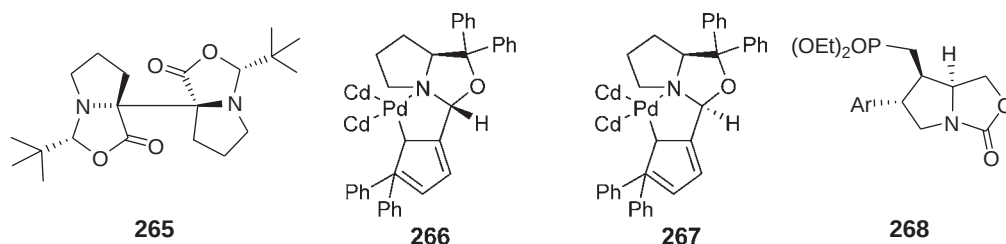




11.02.7.2.2 X-Ray

Few structures have been solved for this kind of compound. A crystal structure of (2*R*,5*R*,2′*R*,5′*R*)-bi(2,2′-*tert*-butyl-1,1′-aza-3,3′-oxabicyclo[3.3.0] octan-4,4′-one prepared from the diastereoselective dimerization of the pivaloyl oxazolidin-5-one derivative of proline has been obtained for the determination of the absolute stereochemistry of the C- α atoms of compound **265**.

The two palladium derivatives **266** and **267** showed a unique structure of the PdCl₂-phosphinooxazolidine complexes. Both complexes adopt a square planar geometry with the palladium being coordinated to the nitrogen and phosphorus atoms of phosphinooxazolidine; however, the coordination of **266** is considerably distorted from planarity, as shown by the dihedral angle of 10.2° between plane N–Pd–C(12) and plane P–Pd–C(11), whereas complex **267** adopts a coplanar coordination. Collectively, these results indicate that **267** is more thermodynamically stable than **265**. These complexes are efficient catalysts in the enantioselective Diels–Alder reactions of cyclopentadiene with dienophiles and enantioselectivity up to 98% ee for all the dienophiles could be obtained [<2002CC1146>](#). The stereostructure of product **268** was established by X-ray crystallography analysis [<1998J\(P1\)3577>](#).



11.02.7.2.3 NMR spectroscopy

The structures of most of the compounds described have been established by ¹H and ¹³C NMR spectroscopy and in some cases the stereostructures of other compounds have been elucidated by NOESY experiments [<1996TL4573, 1998J\(P1\)3577, 2001J\(P1\)2997>](#).

11.02.7.2.4 IR spectroscopy

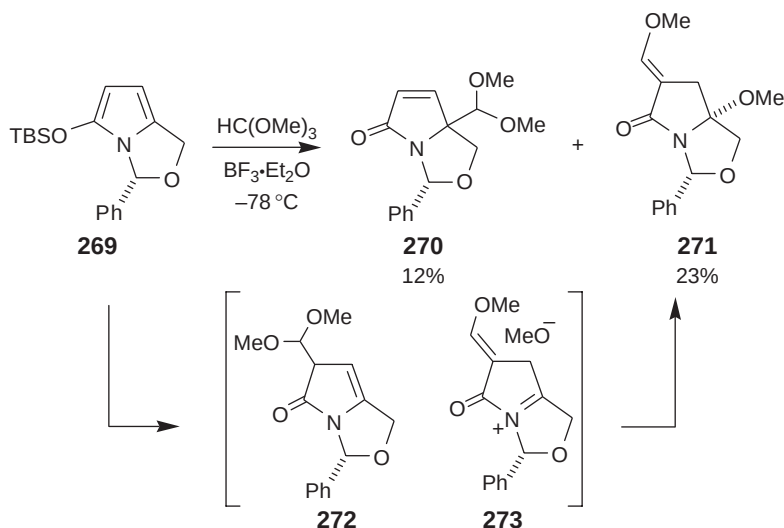
No particular behavior other than classical stretching frequency has been reported. IR spectra have been published for structural determination.

11.02.7.3 Reactivity

Pyrrolo[1,2-*c*]oxazole itself was used for further elaboration of more complex molecules. The main members of this family that are used as intermediates in organic synthesis are the 3-oxo and 5-oxo perhydropyrrolo[1,2-*c*]oxazoles. One can find also a number of 1,3-dioxo, 3,5-dioxo, 3,7-dioxo, and 5,7-dioxo perhydropyrrolo[1,2-*c*]oxazoles that were prepared and/or converted into another valuable compounds.

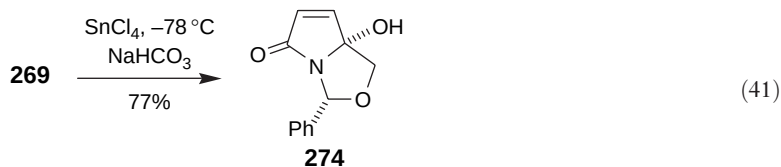
11.02.7.3.1 Reaction with electrophiles

When the pyrrolo[1,2-*c*]oxazole **269** was treated with trimethyl orthoformate in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$, in dichloromethane at -78°C , a mixture of compounds was obtained from which the expected 5-dimethoxymethyl derivative, **270**, was isolated in poor yield (12%) with another dimethoxylated compound **271** (23%). The formation of **271** could be explained by the addition of the formyl cation equivalent at C-7, followed by the protonation at C-6 of the resulting enamide **272** leading to the electrophilic *N*-acyliminium ion **273** (Scheme 40). The regioselectivity of this electrophilic addition of trimethylorthoformate to the silyloxypyrrole **269** at C-7, in a 'non-vinylogous' manner, is unusual <1999TL2525>.

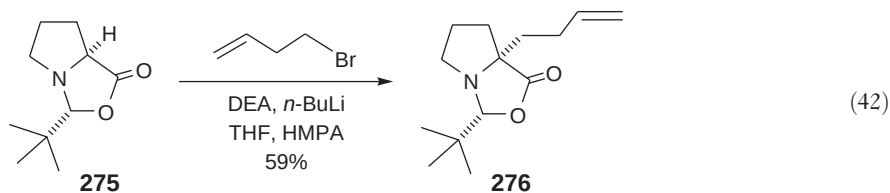


Scheme 40

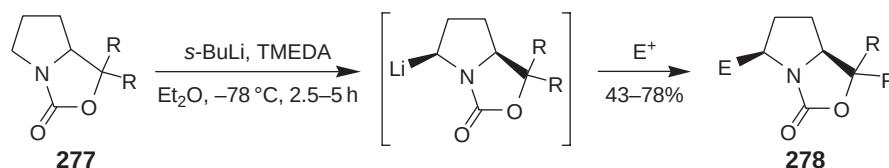
When **269** was treated with SnCl_4 in presence of sodium bicarbonate at -78°C , (2*R*,5*R*)-5-hydroxy-2-phenyl-3-oxa-1-azabicyclo[3.3.0]octan-8-one **274** was formed (Equation 41) <2006TA53>.



The perhydro oxopyrrolo[1,2-*c*]oxazoles are alkylated after metallation in presence of a strong base with alkyl, benzyl, allyl halides, triflates, ketones, aldehydes, esters, or other electrophiles to give chiral monosubstituted lactams <1997TL4203, 1999JME628, 2000JOC914, 2000OL1987, 2002TL857, 2002TL861, 2005OL35, 2005T2481, 2005TL0018, 2006JOC97>. These compounds can be further alkylated a second time and give disubstituted derivatives in high yield and good stereoselectivity <2003JOC9723>. 1-Oxo perhydropyrrolo[1,2-*c*]oxazole **275** under deprotonation conditions with lithium diethylamide (LiDEA) in THF/HPMA and subsequent quenching of the formed enolate with 4-bromo but-1-ene afforded **276** (HPMA=hexamethylphosphoramide; Equation 42) <1999JME628>. The reaction gave the same type of alkylated product if the corresponding silyloxy enolate of the starting compound was used <2002AGE4556>.

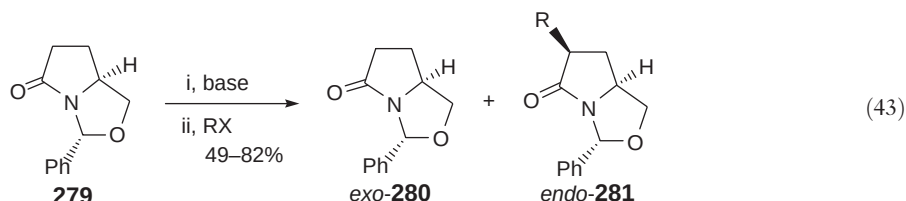


Interestingly, deprotonation of the 3-oxo-pyrrolo[1,2-*c*]oxazole **277** with *s*-BuLi at -78°C took place at the C-5 position. Addition of an electrophile provided the substituted products **278** in good yields. Stannyl and silyl chlorides, dimethyl sulfate, ketones, and benzaldehyde were successfully used as electrophiles. A significant feature of this lithiation–substitution reaction is the generally high *cis*-diastereoselectivity; only single diastereomers of products were isolated (Scheme 41) <2001JA315>.

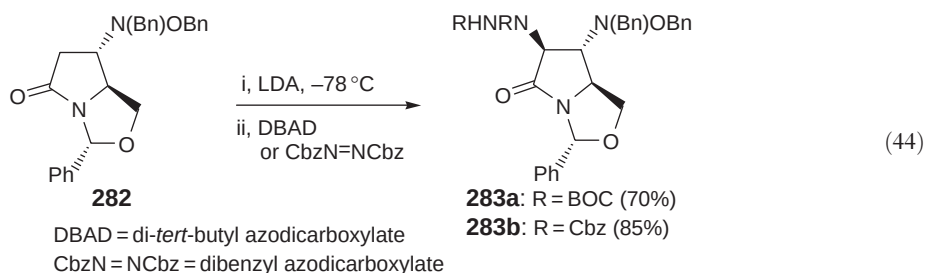


Scheme 41

Alkylation of 5-oxo-pyrrolo[1,2-*c*]oxazole **279** proceeded selectively from the *exo*-face of the corresponding enolate when treated with a base and an electrophile such as RX. Depending on the reaction conditions and the base used, the ratio *exo/endo* **280/281** varied from 63/37 to 98/2 (Equation 43) <1999TL2707>.



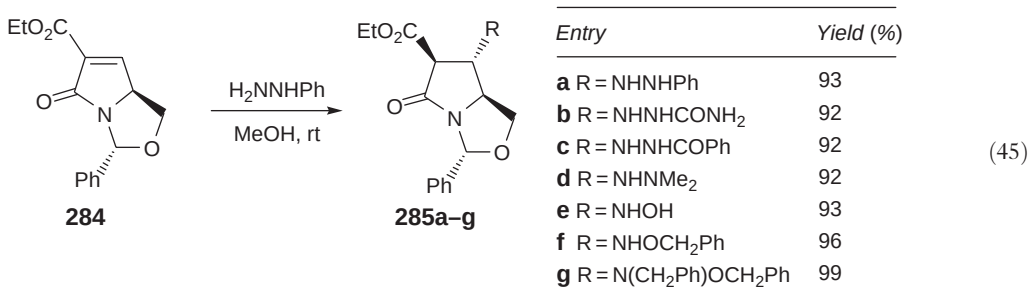
L-4,4-Difluoroglutamic acid was prepared via the electrophilic difluorination of a lactam under two sequential identical fluorinations <1999OL2015>. Diamino-substituted pyrrolidinones **283** were accessible through deprotonation of bicyclic lactam **282** with LDA followed by quenching of the resultant enolate with either di-*tert*-butyl azodicarboxylate or dibenzyl azodicarboxylate. The corresponding diamino lactams **283a** and **283b** were obtained in excellent yields and as single diastereomers (Equation 44) <1999TA3887>.



11.02.7.3.2 Reaction with nucleophiles

1,4-Nucleophilic addition has been realized on 1-oxo-pyrrolo[1,2-*c*]oxazole and the 5-oxo-derivative as well. Malonates, hydrazines, hydroxylamine, LiCH_2CN , $\text{Zn}[\text{CH}_2\text{CN}]_2$, Me_2CuLi , amines, and vinylmagnesium bromide/CuI have been used as nucleophiles <1996TL4573, 1997TL5891, 1997TL8037, 2001J(P1)2997, 2001JOC6483, 2001TA1353, 2002TL9531, 2005JA8298, 2005OBC2872>.

The conjugate addition of activated nitrogen nucleophiles, such as hydroxylamine and hydrazine derivatives, to α,β -unsaturated bicyclic lactam **284** gave the corresponding β -amino product **285** in good yield and excellent diastereoselectivity. These products can be manipulated to afford enantiopure β -aminopyrrolidinones of potential application as conformationally constrained, substituted glutamate templates (Equation 45) <2001J(P1)2997>.

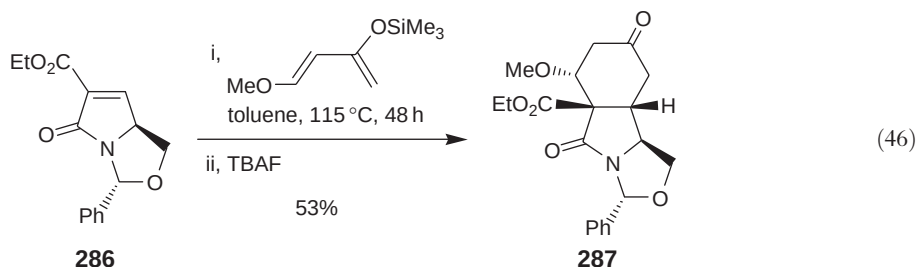


A hydroxy group can be introduced on this bicyclic system as a nucleophile. The pyrrolo[1,2-*c*]oxazole system can be hydroxylated at the 7a-position to produce in good yield the corresponding 7a-hydroxypyrrolo[1,2-*c*]oxazole. The diastereoselectivity of this nucleophilic addition is total, with attack at the iminium ion on the face hindered by the phenyl group at C-3. <2002TL463, 2004JOC7558, 2006TA53>.

11.02.7.3.3 Cycloaddition reactions

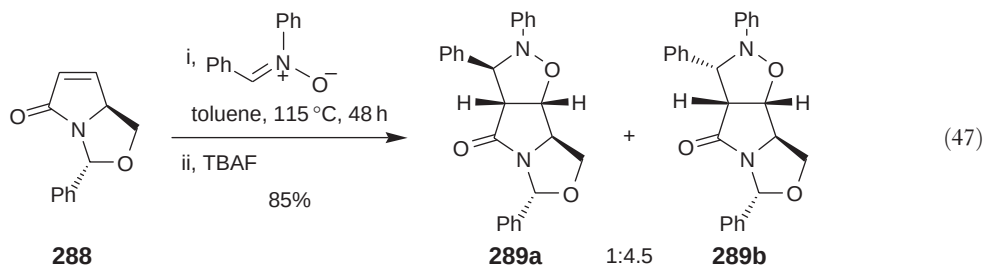
11.02.7.3.3(i) Diels-Alder reaction

The reaction of 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene with enone **286** in refluxing toluene for 48 h, followed by treatment with tetrabutylammonium fluoride (TBAF), gave the adduct **287** as a single diastereomer (Equation 46) <1997T11731>.



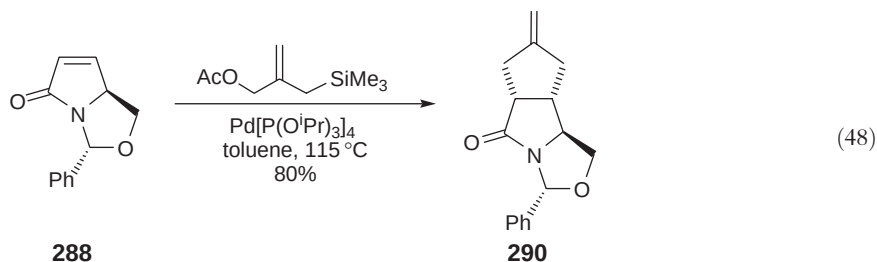
11.02.7.3.3(ii) 1,3-Dipolar cycloaddition

The dipole *N*-α-diphenylnitrone, upon reaction with enone **288** in refluxing toluene for 24 h, gave the diastereomeric products **289a** and **289b** in a ratio of 1:4.5. The regiochemistry of the addition was given by ¹H and ¹³C NMR experiments (NOESY and COSY) (Equation 47) <1997T11731>.



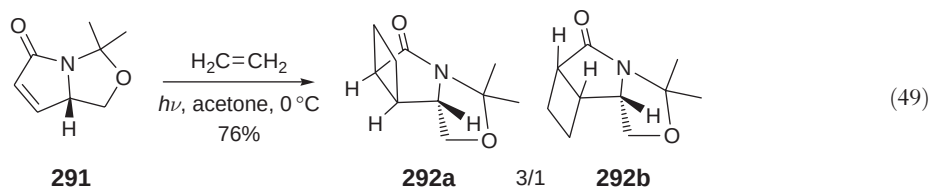
11.02.7.3.3(iii) [3+2] Cycloaddition reaction

The [3+2] cycloaddition of trimethylenemethane (TMM) on the unsaturated lactam **288** worked efficiently with the use of Pd[P(O^{*i*}Pr)₃]₄ (generated *in situ* from palladium(II) acetate (20 mol%) and triisopropyl phosphite (160 mol%)). The reaction proceeded cleanly in refluxing toluene to afford exclusively the desired cycloadduct **290** in 80% isolated yield (Equation 48) <2003TL5033>.



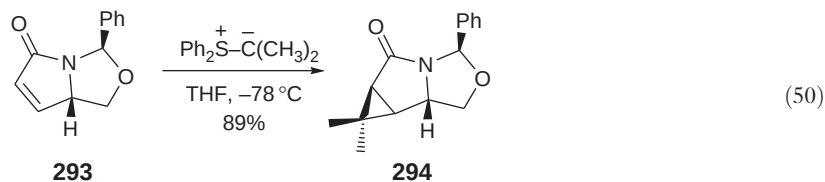
11.02.7.3.3(iv) [2+2] Photocycloaddition reaction

The cycloaddition of γ -lactam **291** possessing a fused bicyclo[3.3.0]octane system has been examined. The reaction proceeded smoothly under irradiation (450 W high-pressure mercury lamp, Pyrex filter) in the presence of ethylene in acetone to give a mixture of cycloadducts **292a** and **292b**, albeit with somewhat low stereoselectivity (**292a**/**292b** = 3/1). These results suggest that the cycloaddition of ethylene occurred from the sterically less hindered β -face. The poor stereoselectivity observed in **291** could be attributed to the presence of a planar amide bond which increased the degree of the attack of ethylene from the sterically more hindered concave face (Equation 49) <1998TL1193>.



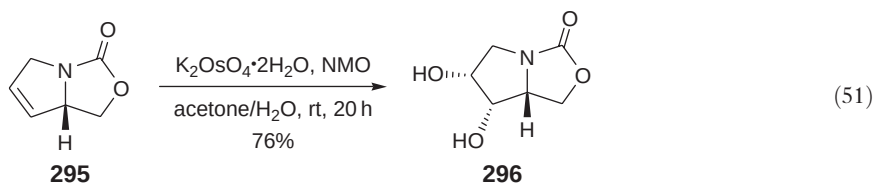
11.02.7.3.3(v) Cyclopropanation

Cyclopropanation of (5*R*,7*S*)-5-phenyl-5,6,7,7a-tetrahydro-6-oxapyrrolizin-3-one **293** with diphenylsulfonium isopropylide in THF at -78°C smoothly afforded the products **294**. The products **294** arise from the cyclopropanation of the less hindered '*exo*'-face (Equation 50) <1999JOC547>. The stereochemical assignments were confirmed by single crystal X-ray diffraction.

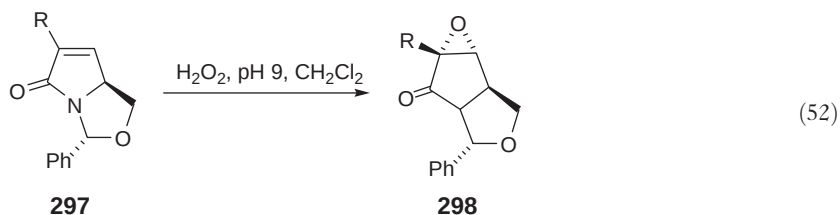


11.02.7.3.4 Oxidation reactions

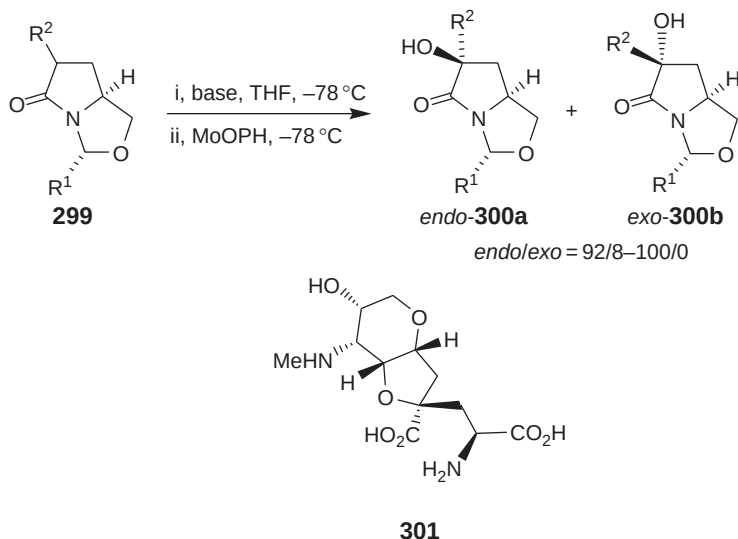
The unsubstituted pyrrolo[1,2-*c*]oxazol-3-one **295** underwent a dihydroxylation with catalytic osmium tetroxide to exclusively give diol **296**. This diol resulted from attack of the oxidizing agent from the concave face of the molecule due to the pseudoaxial protons that sterically hinder the β -face to be attacked by the osmium reagent (Equation 51) <2004AJC669>.



In some cases, the pyrrolo[1,2-*c*]oxazoles were epoxidized with hydrogen peroxide in dichloromethane affording the epoxide with control of stereoselectivity (Equation 52) <1997TA2421, 2000T2437, 2004TA1239>.



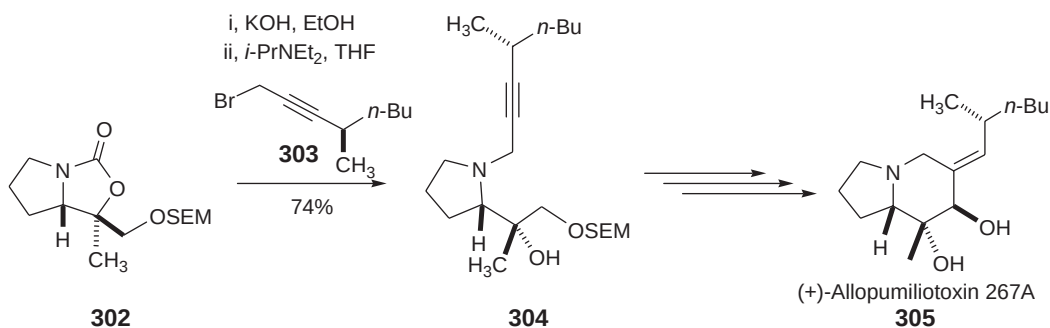
Generation of the lithium enolate of the lactam **299** by treatment with LDA at -78°C followed by addition of MoOPH gave a 92:8 mixture of α -hydroxylated lactams **300a** and **300b**. The oxidant approaches the enolate from the sterically hindered concave face to afford the *endo*-product. These synthons are valuable intermediates in the total synthesis of dysiherbaine **301**, a selective agonist of non-NMDA-type glutamate receptors (NMDA = *N*-methyl-D-aspartate; Scheme 42) <1999TL7787, 2002T9737>.



Scheme 42

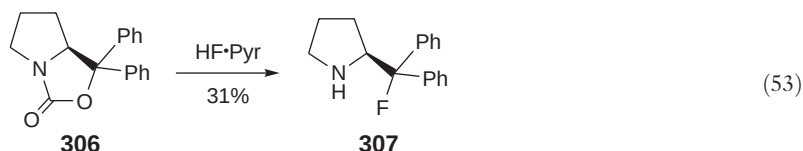
11.02.7.3.5 Ring-opening reactions

The basic hydrolysis of the 3-oxoperhydropyrrolo[1,2-*c*]oxazole **302** with KOH in ethanol followed by reaction with propargyl bromide **303** in presence of Hünig's base in THF produced the derivative **304**. This compound was further converted in a few steps to the natural product allopumiliotoxin 267A, **305** (Scheme 43) <1999JA6098, 2000JA6950>.



Scheme 43

When the diphenyloxazolidinone **306** was treated with HF in pyridine, the fluorinated amine **307** was produced efficiently. This method has been applied for the synthesis of optically active (*S*)- α -(fluorodiphenylmethyl)alkylamines that can be used for combinatorial libraries (Equation 53) <2000TA2033>.

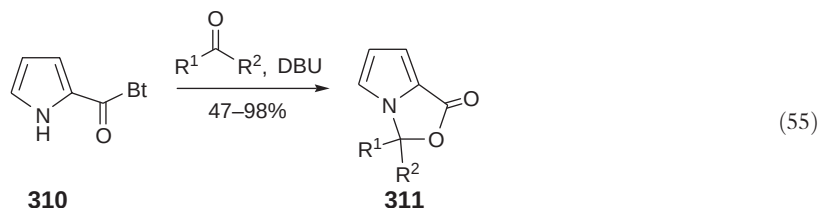
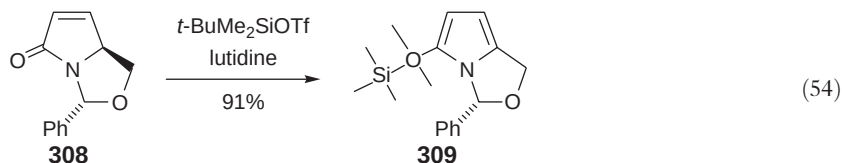


Some derivatives of 5-oxoperhydropyrrolo[1,2-*c*]oxazoles were hydrolyzed using trifluoroacetic acid in a mixture of THF/H₂O to produce substituted 5-hydroxymethylpyrrolidin-2-ones <1998TL857, 2000TL8285>.

11.02.7.4 Synthesis

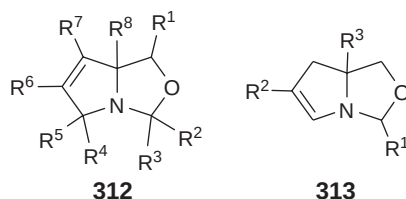
11.02.7.4.1 Pyrrolo[1,2-*c*]oxazoles

The silyloxypyrrole **309** was prepared in 91% yield from the α,β -unsaturated lactam **308** with TBDMSOTf and 2,6-lutidine (Equation 54) <1999TL2525>. Alternatively, the pyrrolo[1,2-*c*]oxazoles derivatives **311** were prepared by reaction between the stable benzotriazol-1-yl(1*H*-pyrrol-2-yl)methanone **310** and various ketones (Equation 55) <2004JOC9313>. These two examples are the rare representatives of the pyrrolo[1,2-*c*]oxazole ring system described in the literature to date.

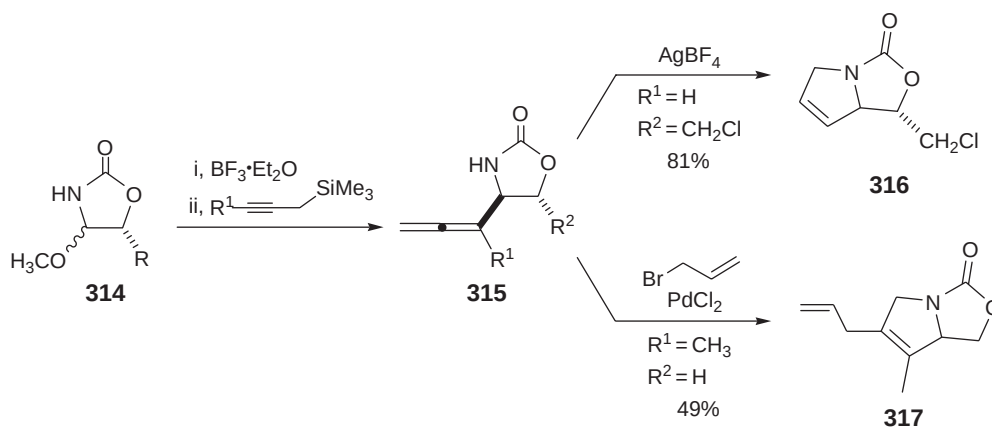


11.02.7.4.2 Dihydropyrrolo[1,2-*c*]oxazoles

This system is represented by the formulae **312** and **313** exclusively and was described in only six reports.

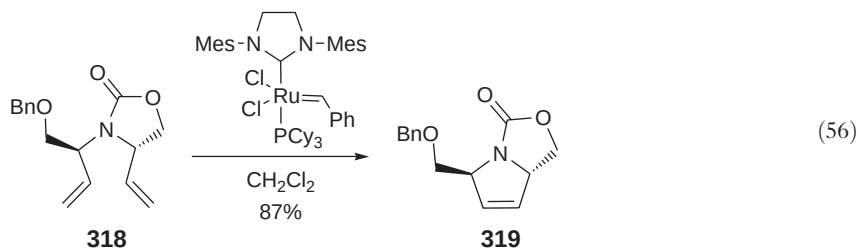


The methoxy group of (4*RS*,5*S*)-5-chloromethyl-4-methoxy-2-oxazolidinone **314** was substituted by an allene function through the use of propargyl trimethylsilane as a nucleophile and BF₃·OEt₂ as a Lewis acid, via the intermediate *N*-acyliminium ion. The reaction proceeded with excellent diastereoselectivity (>98% de) to furnish compound **315**. Cyclisation with 0.5 equiv of silver tetrafluoroborate led to the enantiomerically pure compound **316**. If compound **315** was treated with PdCl₂(MeCN)₂ in presence of allyl bromide, it cyclized to furnish **317** (Scheme 44) <1998EJO509, 2001T5123>. A slightly different approach using the palladium-catalyzed cyclization of a β -amino acid allene derivative has been proposed in one case <1999OL717>.

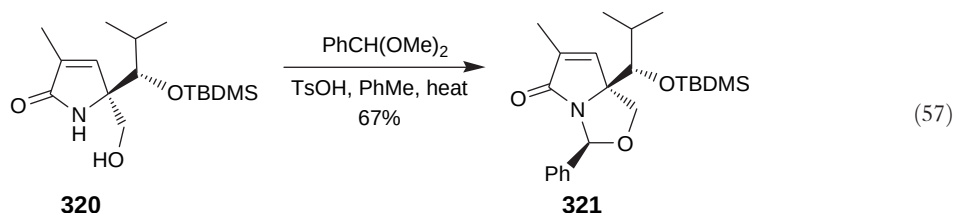


Scheme 44

Ring-closing metathesis of diene **318** with a Grubbs second-generation catalyst gave 2,5-dihydropyrrole **319** (Equation 56). The absolute stereochemistry was assigned based on single crystal X-ray diffraction analysis <2003AGE5987>.



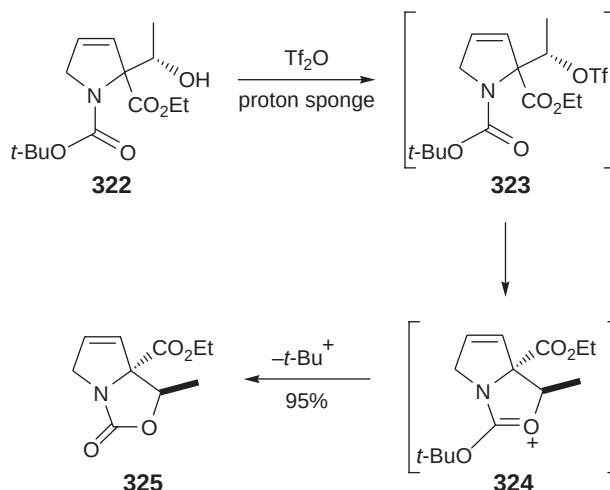
The amide alcohol **320** submitted to the reaction of benzaldehyde and TsOH in benzene afforded the aminal function of the bicyclic lactam **321** as a single diastereomer (Equation 57) <2002TL6609>. This type of reaction has been often used for the preparation of perhydro derivatives as well.



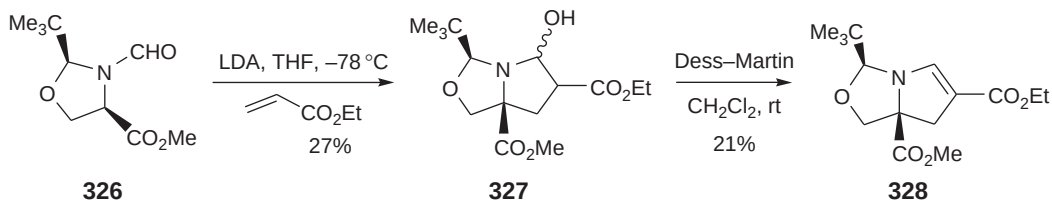
The reactive triflate **323** prepared from the aldol adduct **322** promoted an intramolecular attack by the BOC carbonyl group (expecting subsequent loss of a *tert*-butyl cation) to afford the dihydro derivative **325** through the oxonium **324** (Scheme 45) <2003OBC3749>.

The Michael addition reaction of the serine-derived oxazolidine **326** with ethyl acrylate gave two products. The major product of the reaction was found to be the bicyclic compound **327**, which was formed in 27% yield, accompanied by the unsaturated ester **328**. The Dess–Martin oxidation of **327** resulted only in formation of the elimination product, the 7,7a-dihydro-1*H*, 3*H*-pyrrolo[1,2-*c*]oxazole **328** (Scheme 46) <2001JOC7555>.

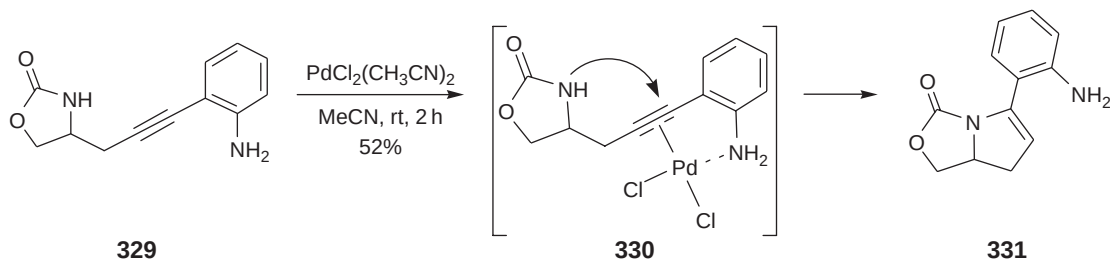
The cyclic carbamate **329** under Pd-catalyst treatment in refluxing acetonitrile led to the formation of the corresponding bicyclic product **331**. A plausible mechanism involves complexation of the $\text{Pd}(\text{II})$ catalyst to the triple bond, possibly helped by coordination to the aniline nitrogen, giving rise to the π -complex **330** (Scheme 47) <2003OL1717>.



Scheme 45



Scheme 46

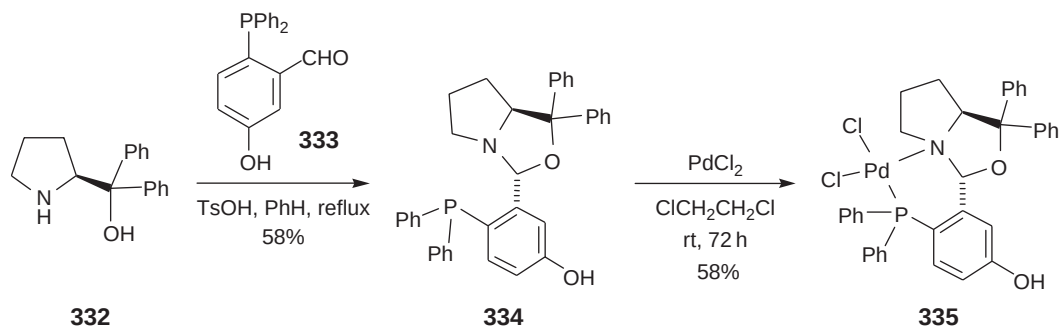


Scheme 47

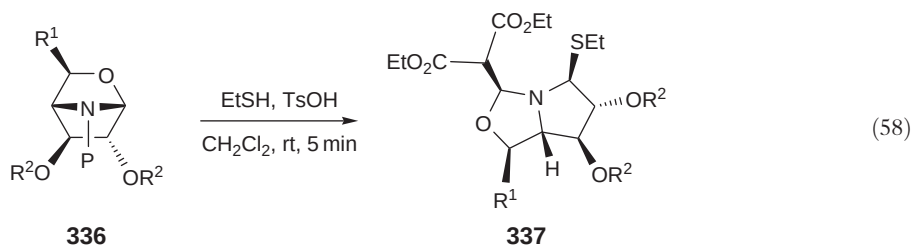
11.02.7.4.3 Perhydropyrrolo[1,2-*c*]oxazoles

These systems are reported as cyclopentaoxazolidines and are usually obtained from azeotropic dehydration of aldehydes with amino alcohols [\[2003HAC42\]](#). Particularly, several phosphorus ligands have been obtained in good yields, for example, **334** (by condensation of *ortho*-2-(diphenylphosphino)-5-hydroxy-benzaldehyde **333** with the commercially available (*R*)-pyrrolidinylmethanol **332**). A palladium complex was easily prepared by reaction of **334** with PdCl_2 , giving **335**. These chiral oxazolines have proved to be extremely efficient ligands in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Enantiomeric excesses up to 96% have been obtained ([Scheme 48](#)) [\[2000TA1193, 2004JOC7092, 2005TA2133\]](#).

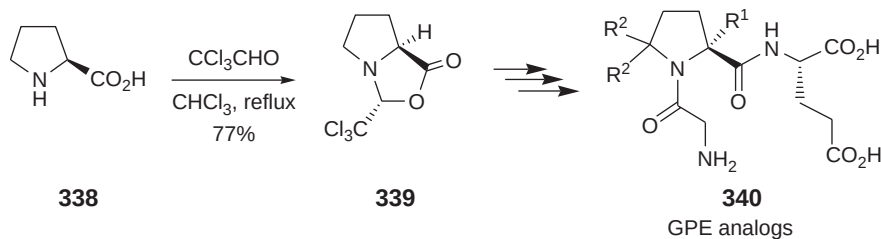
Some more substituted perhydro derivatives were synthesized by skeletal rearrangement of anhydro azasugars **336** under acidic conditions in the presence of EtSH producing ethyl thioglycosides of azasugars **337** ([Equation 58](#)) [\[2003TL6605, 2004TA603\]](#).



Scheme 48

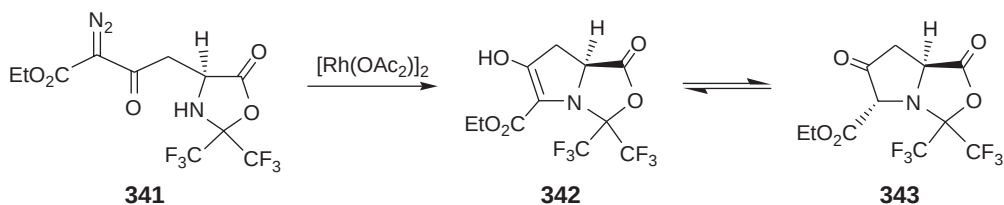
11.02.7.4.4 1-Oxoperhydropyrrolo[1,2-*c*]oxazoles

Proline has been often used in reactions with aldehydes to form 1-oxo perhydropyrrolo[1,2-*c*]oxazole structures [<1998J\(P1\)3777, 2004PNA5839>](#). These compounds were used for the asymmetric synthesis of proline derivatives which are present in natural products or analogs (Scheme 49) [<2005T10018, 2005TA2075, 2006JOC97>](#).



Scheme 49

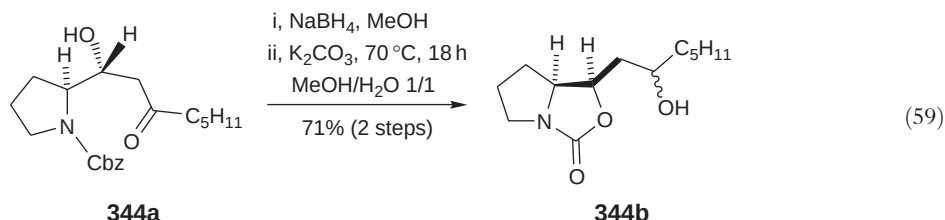
Transition metal-catalyzed reactions of α -diazocarbonyl compounds proceed via electrophilic Fischer-type carbene complexes. Consequently, when α -diazoketone **341** was treated, at room temperature, with catalytic amounts of $[\text{Rh}(\text{OAc})_2]_2$, it gave the formation of a single NH insertion product, which was assigned to the enol structure **342**. At room temperature, in both solid state and in solution, **342** tautomerizes to give the expected 1-oxoperhydropyrrolo[1,2-*c*]oxazole derivative **343** (Scheme 50) [<1997TA2001>](#).



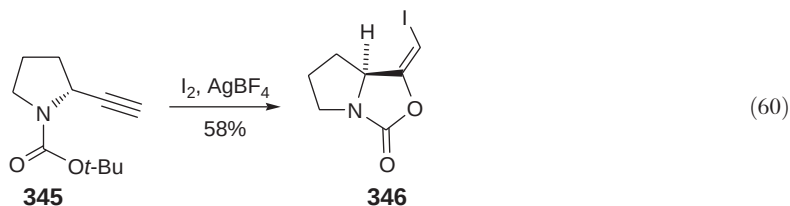
Scheme 50

11.02.7.4.5 3-Oxoperhydropyrrolo[1,2-*c*]oxazoles

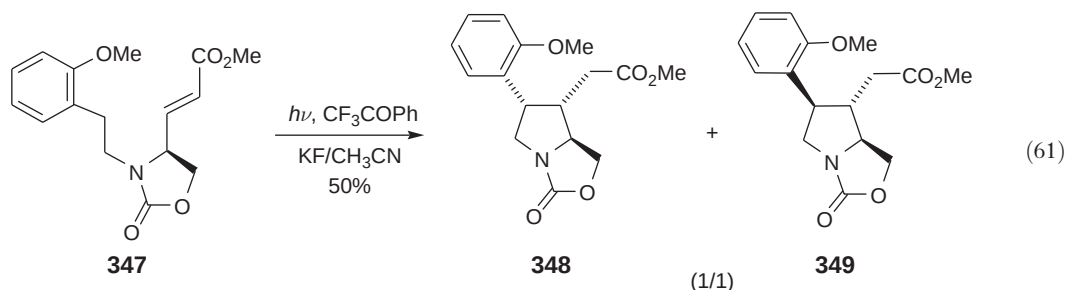
In most of the reports found on these types of compounds, they were prepared by condensation of an amino alcohol derived from proline with phosgene <1997TL4179>, triphosgene <2001BML2691, 2004JOC3578, 2005TL5309>, phenylchlorocarbonate <2001CPB492, 2001CPB1487>, carbonyldiimidazole <2001EJO517>, or from the *N*-protected proline carbamates in presence of a base (NaH, NaOH, or LiHMDS) <1996JOC125, 1997TA149, 1997TL1415, 1998TL6787, 2000CJC776, 2001JA9706, 2002JOC5517, 2003JOC9747, 2004OL2481, 2005CEJ945, 2005OL3243>, or with diethylaminosulfur trifluoride (DAST) <2003T3307>. A typical example is represented in Equation (59). (1*R*)-1-[(*S*)-*N*-Benzyloxycarbonylpyrrolidin-2-yl]-1-hydroxy-3-octanone **344a**, after reduction with NaBH₄ in methanol, reacted with K₂CO₃ in a mixture methanol/water (1/1) to give the (1*R*,7*aS*)-tetrahydro-1-(2-oxoheptyl)-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-ol **344b** <2005OL4419>.



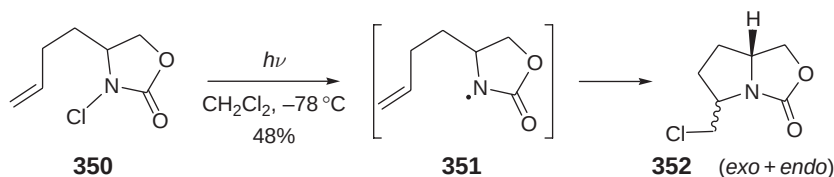
Other protocols, such as iodocyclization of alkene or alkyne **345** affording **346** (Equation 60) <1996JA9073, 2000BML2015>, cyclization of allyl chloride derivative <1998EJO509>, or of mesylate <1998JOC5680> were used in order to access this class of products.



Several radical approaches have been also used for the synthesis of 3-oxo-perhydo derivatives based on the use of trimethylstannyl chloride or tributylstannyl chloride activation in presence of 2,2'-azobisisobutyronitrile (AIBN) <1996JOC5418, 2000TL5915>. Photochemical strategies were applied to the formation of 3-oxo perhydo intermediates <1998J(P1)3577>. Compounds **348** and **349** were isolated as a 1:1 mixture after photolysis of **347** using a high-pressure mercury lamp in quartz tubes at room temperature in the presence of α -trifluoro-acetophenone and KF (Equation 61) <2002TL7777>.

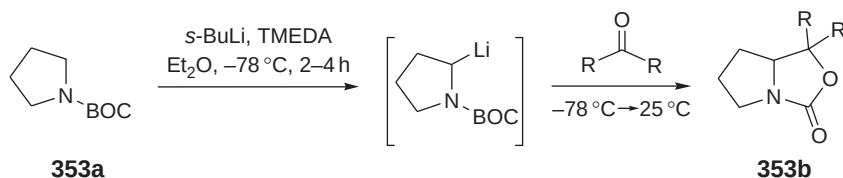


By photolysis of *N*-chloro-4-butenyloxazolidin-2-one **350** at 300 nm in CH₂Cl₂ at -78 °C, the intermediate carbamyl radical **351** underwent 5-*exo*-cyclization and gave a 2:1 diastereomeric mixture of bicyclo[3.3.0]azaoctanes **352** (Scheme 51) <1999T3495>.



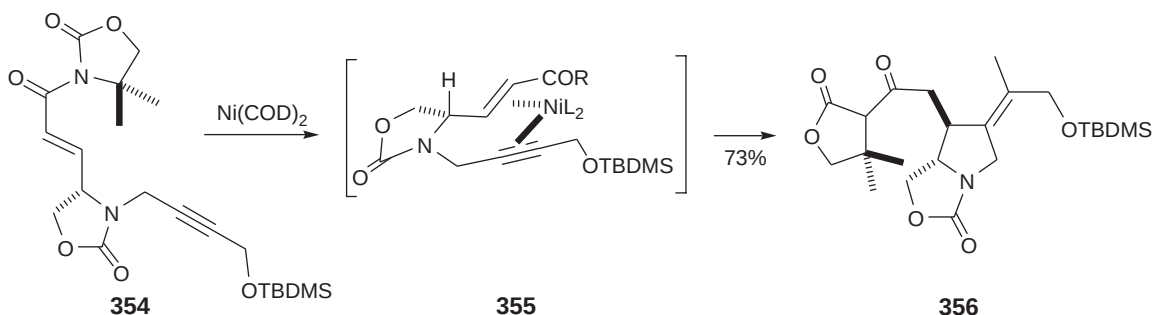
Scheme 51

The direct metallation of *N*-BOC piperidine **353a** with *sec*-BuLi in presence of TMEDA in THF at low temperature and reaction with a symmetrical ketone directly afforded the five-membered oxazolidinone **353b** (Scheme 52) <2001JA315>.



Scheme 52

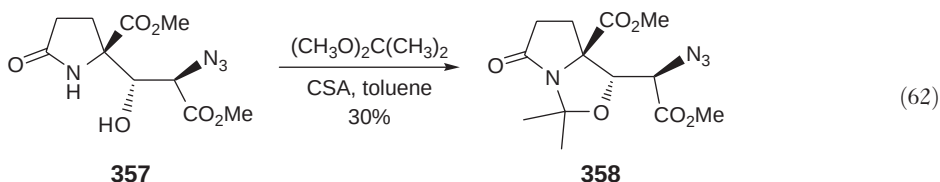
Some other catalytic routes to 3-oxoperhydropyrrolo[1,2-*c*]oxazole have been described in the literature using nickel(0) or palladium(0) as catalysts <1999JA1139, 2001JOM244, 2003OL3771, 2004JOC7157>. As a typical example, cyclization of **354** with commercial trimethylaluminium and [Ni(COD)₂] (10 mol%) in THF afforded a 73% yield in **356** with a diastereomeric ratio (d.r.) of >97:3 in favor of the desired *trans*-isomer (COD = cyclooctadiene). Commercial dimethylzinc, under identical conditions, afforded a 67% yield in **356**, also with a >97:3 diastereomeric ratio. The parallel orientation of the two reactive π components in chelated structure **355** is responsible for the *trans*-relationship of the two substituents in product **356** (Scheme 53) <1998AGE3144>.



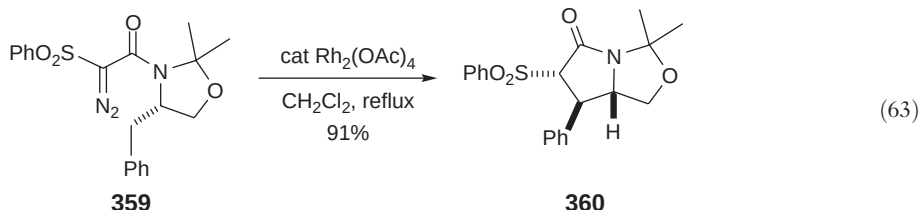
Scheme 53

11.02.7.4.6 5-Oxoperhydropyrrolo[1,2-*c*]oxazoles

This motif is easily accessible from the condensation under acidic conditions of substituted hydroxymethyl pyrrolidone with a ketone, an aldehyde, or a masked ketone or aldehyde. Benzaldehyde <1996T3719, 1999JA10478, 2002JOC8688>, methoxypropene <1998T10295>, and dimethoxypropane <2001JOV8831, 2002TA647, 2005OL4165> have been used for this cyclization often catalyzed by TsOH or camphorsulfonic acid (CSA). Compound **358**, used as an intermediate in the total synthesis of (–)-kaitocephalin, was prepared from **357** following this procedure shown in Equation (62) <2005OL4165>.

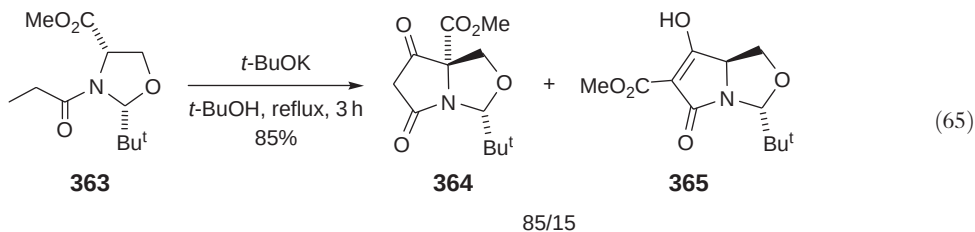
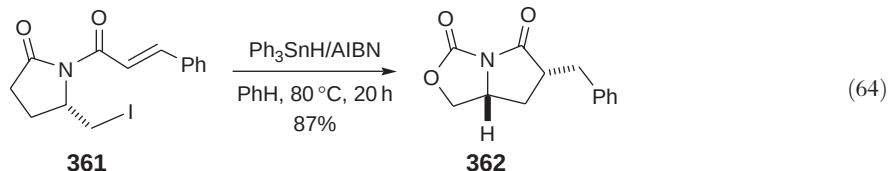


The rhodium acetate complex catalyzed the intramolecular C–H insertion of (*R*)-diazo-(*R*)-(phenylsulfonyl)acetamides **359** derived from (*R*)-amino acids to afford in high yield the 6-benzenesulfonyl-3,3-dimethyl-7-phenyl-tetrahydro-pyrrolo[1,2-*c*]oxazol-5-one **360** (Equation 63) <2002JOC6582, 2005TL143>.



11.02.7.4.7 1,5-, 3,5-, and 5,7-Dioxoperhydropyrrolo[1,2-*c*]oxazoles

Several dioxo compounds have been synthesized following different procedures. 1,5-Dioxo derivatives were prepared by intermolecular cyclization of (*S*)-proline with chloral (CCl₃CHO) in refluxing chloroform <2002TA2229> or by direct intramolecular cyclization of protected glutamic acid after treatment with thionyl chloride <2004M853, 2004TL1445>. 3,5-Dioxo derivative **362** has been obtained in one case by radical 5-*exo-trig*-cyclization of halogeno compound **361** under Bu₃SnH/AIBN treatment in refluxing benzene (Equation 64) <1996JA3063>. 5,7-Dioxo derivatives were synthesized using an intramolecular Dieckmann condensation of **363** induced by potassium *tert*-butoxide in 2-methylpropan-2-ol at reflux. Two products **364** and **365** were isolated in a ratio 85/15 (Equation 65) <1998J(P1)223>.



11.02.8 Pyrrolo[1,2-*b*]isothiazoles

11.02.8.1 Introduction

Aromatic pyrrolo[1,2-*b*]isothiazoles are not known and only a sulfone analog of tetrahydro and one perhydro derivative have been prepared.

11.02.8.2 Theoretical and Experimental Structural Methods

11.02.8.2.1 Theoretical methods

No molecular calculations are available for this systems.

11.02.8.2.2 Experimental structural methods

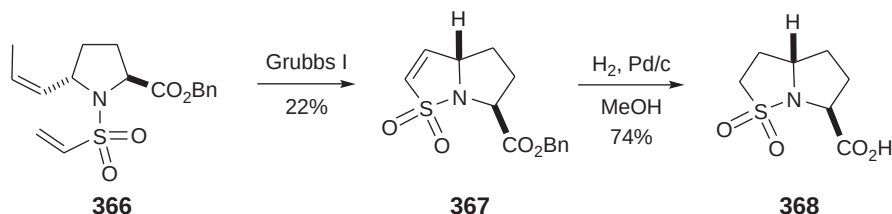
Other than classical ^1H and ^{13}C NMR spectra which have been reported for these compounds, no detailed studies have appeared in the literature. One X-ray crystal analysis of the TBDMS-protected alcohol analog of acid **368** has been carried out for structural proof.

11.02.8.3 Reactivity

No reactivity has been reported for these compounds.

11.02.8.4 Synthesis

The tetrahydro- and perhydropyrrolo[1,2-*b*]isothiazoles **367** and **368** were synthesized as sulfone derivatives from an olefin metathesis of the diene **366** with the first-generation Grubbs catalyst followed by hydrogenation under palladium on charcoal (Scheme 54) <2003T7047>.



Scheme 54

11.02.9 Pyrrolo[2,1-*b*]thiazoles

11.02.9.1 Introduction

Pyrrolo[1,2-*b*]thiazoles are aromatic compounds but only one fully conjugated derivative has been described. A few dihydro and tetrahydro derivatives have been prepared, mainly in connection with search for biologically active drugs. Saturated compounds are also known.

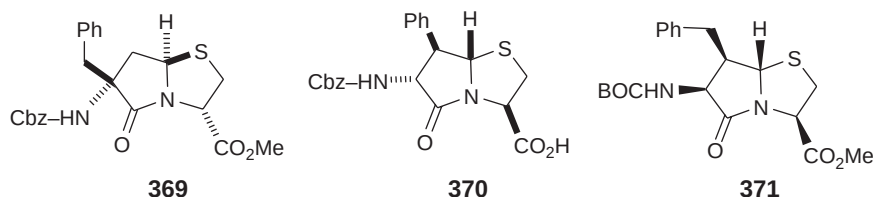
11.02.9.2 Theoretical and Experimental Structural Methods

11.02.9.2.1 Theoretical methods

Theoretical calculations on this type of compound have not been reported.

11.02.9.2.2 Experimental structural methods

X-Ray structures of several perhydro derivatives such as **369–371** have been reported <1999JME2977, 2001TL145, 2004TL4139>. A comparison of the ϕ, ψ dihedrals defining the turn region of **369** with those of the classical type II β -turn compounds reveals that the two torsion angles constrained by the heterocycle ($\psi_2 = 123^\circ$ and $\phi_3 = 113^\circ$) as well as the nonconstrained angles ($\phi_2 = -53^\circ$ and $\psi_3 = -26^\circ$) fall within the acceptable range of an ideal type II β -turn compound. No further information can be found on the two other structures in these reports.



Some extensive nOe difference experiments were performed to establish the relative configuration of several polysubstituted perhydropyrrolo[2,1-*b*]thiazoles [<1999JME2977, 2004TL4139>](#). The other recorded spectra for this type of compounds were used only to confirm the structures. There are no systematic studies.

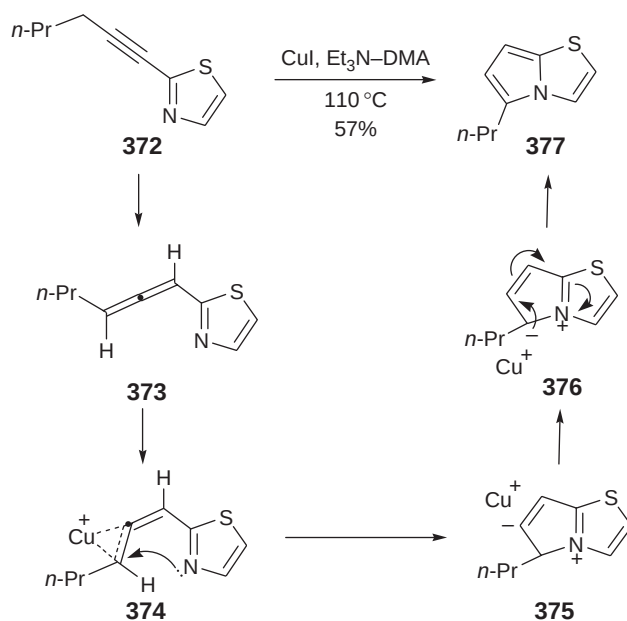
11.02.9.3 Reactivity

There has been no study on the aromatic pyrrolo system or on the perhydro derivative.

11.02.9.4 Synthesis

11.02.9.4.1 Pyrrolo[2,1-*b*]thiazoles

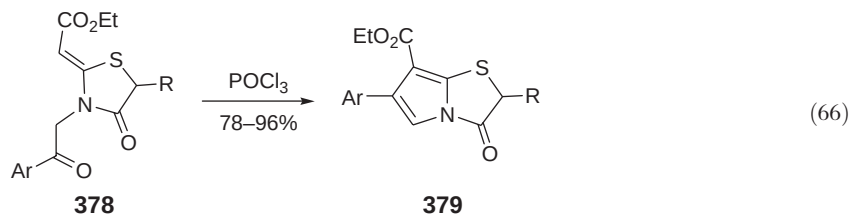
This system was described in one report and has been synthesized by a copper-assisted cycloisomerization of alkynyl imines. The authors proposed the following mechanism: at first, **372** could undergo a base-induced propargyl–allenyl isomerization to form **373**; next, coordination of copper to the terminal double bond of the allene (intermediate **374**) would make it subjected to intramolecular nucleophilic attack to produce a zwitterion **375**. The latter would isomerize into the more stable zwitterionic intermediate **376**, which would be transformed to the thiazole **377** (Scheme 55) [<2001JA2074>](#).



Scheme 55

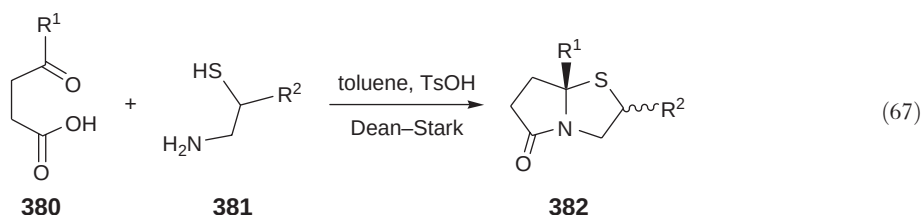
11.02.9.4.2 Dihydropyrrolo[2,1-*b*]thiazoles

Only 2,3-dihydropyrrolo[2,1-*b*]thiazoles have been described. When refluxing in POCl_3 , compounds **378** were found to give pyrrolo[2,1-*b*]thiazole derivatives **379** in good yields. Formally, this reaction is like a Chichibabin pyrrolothiazole synthesis; however, in contrast with the basic conditions used in the typical procedure, acidic conditions were employed in the present case (Equation 66) [<2004S2317>](#).



11.02.9.4.3 Perhydropyrrolo[2,1-*b*]thiazoles

The tetrahydropyrrolo[2,1-*b*]thiazol-5(6*H*)-ones **382** were readily synthesized from the appropriate amino thiols **381** and keto acids **380** in one step via a condensation, as shown in Equation (67) <1998JME4556>.



11.02.9.5 Important Compounds and Applications

Some of these compounds are able to modulate dopamine receptor activity and may be possible therapeutic agents for the treatment of Parkinsonian symptoms as well as tardive dyskinesia <1996BR287, 1997JME3594, 1999JME2977>. (+)-*trans*-2-[(4-Chlorophenoxy)methyl]-7 α -(3,4-dichlorophenyl) tetrahydropyrrolo [2,1-*b*]oxazol-5(6*H*)-one has been found to possess interesting hypoglycemic properties <1998JME4556>.

11.02.10 Pyrrolo[1,2-*c*]thiazoles

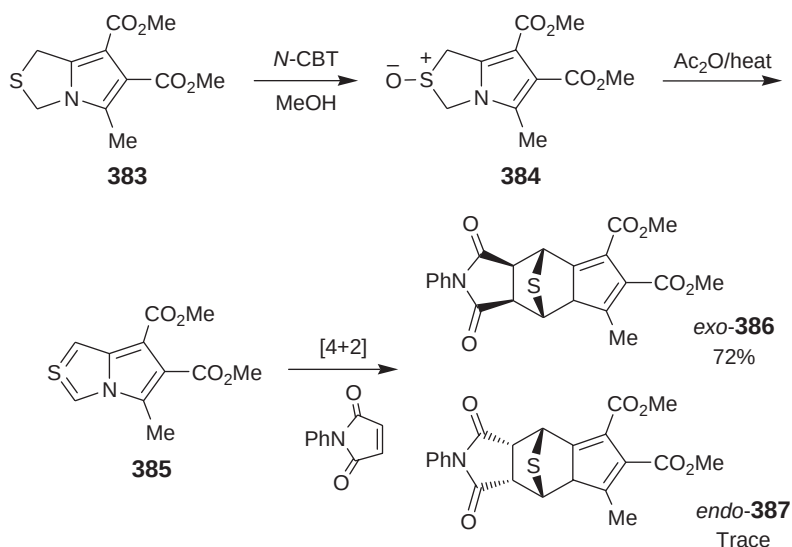
11.02.10.1 Introduction

There are only few publications on this type of compound and some on dihydro and tetrahydrothiazole derivatives. There have been no theoretical calculations reported, and NMR, IR, and other structural data were reported to only confirm the structures of the synthesized products.

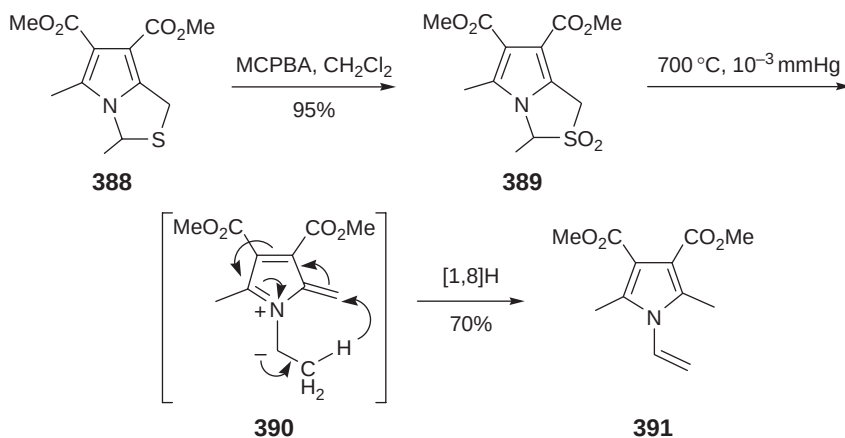
11.02.10.2 Reactivity

After treatment of sulfide **383** with *N*-chlorobenzotriazole (*N*-CBT) in methanol to give sulfoxide **384**, followed by reaction with Ac₂O, the 'nonclassical' thiazole **385** was obtained. This highly reactive compound reacted with *N*-phenylmaleimide to give a mixture of the corresponding [4+2] cycloadducts **386** (major) and **387** (minor) in good yield. The reaction worked also with activated double bond or triple bonds (Scheme 56) <2000T10011>.

When dimethyl-2,2-dioxo-5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3]thiazole-6,7-dicarboxylate was heated under flash vacuum pyrolysis at 700 °C/10⁻³ mmHg, sulfur dioxide was eliminated and the vinylpyrrole **391** was obtained, which can be explained by allowed suprafacial [1,8]H shifts in the 8 π 1,7-dipolar system **390**. Concerted sigmatropic shifts can only occur when the methyl groups adopt an inward (*Z*)-conformation (Scheme 57) <2002J(P1)1795, 2004TL3889, 2005JOC6629>.



Scheme 56



Scheme 57

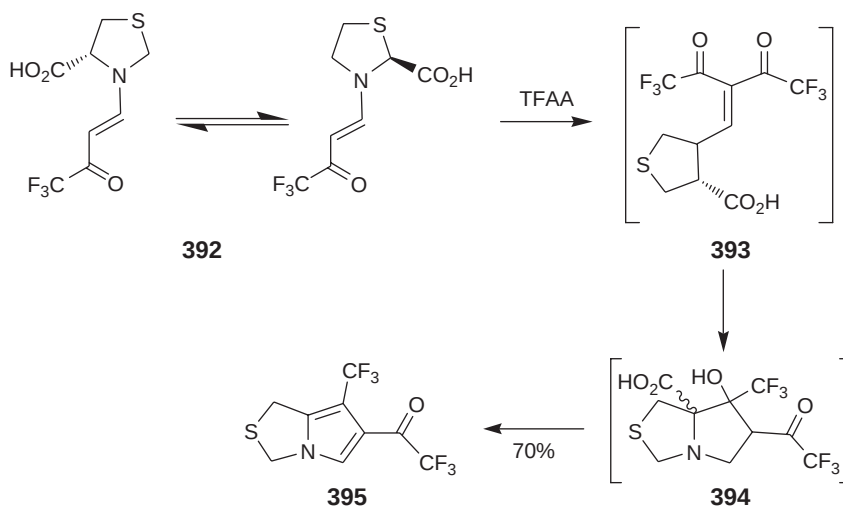
11.02.10.3 Synthesis

11.02.10.3.1 Pyrrolo[1,2-*c*]thiazole

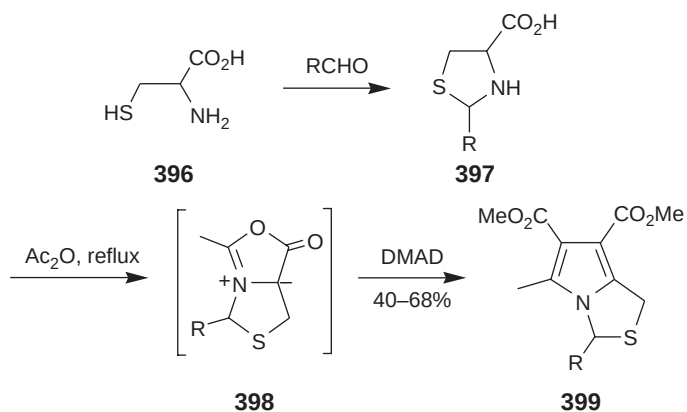
Reaction of the thia-amino acid **392** with trifluoroacetic anhydride gave the 2,2,2-trifluoro-1-[7-(trifluoromethyl)-1*H*-pyrrolo[1,2-*c*]-[1,3]thiazol-6-yl] ethanone pyrrole **395**. The formation of the pyrrole can be rationalized by a sequence involving trifluoroacetylation of the enamine **392** affording dione **393** followed by loss of water and carbon dioxide to give the aromatic product **395**. These decarboxylations afford fluorinated derivatives of heterocyclic skeletons known to exhibit interesting biological activity (Scheme 58) <2000T7267>.

Dimethyl-3,5-dimethyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3]thiazole-6,7-dicarboxylate **399** (R = H) was prepared from cysteine **396** using the method developed of Padwa *et al.* <1989JOC644>. The thiazolidine carboxylic acid **397** (R = H), obtained by reaction of the cysteine with formaldehyde, was heated in the presence of acetic anhydride and DMAD to give the sulfide **399** by dipolar cycloaddition of the acetylene to the intermediate dipole **398** (Scheme 59) <2002J(P1)1795>.

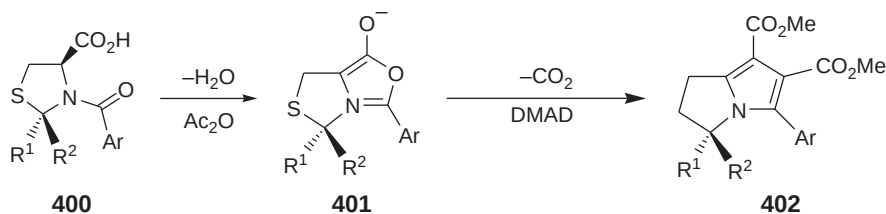
In the same manner, several 1*H*,5*H*-pyrrolo[1,2-*c*]thiazoles **402** have been prepared from the cycloaddition of diene **401** with DMAD (Scheme 60) <2002T5093, 2005JOC6629>.



Scheme 58



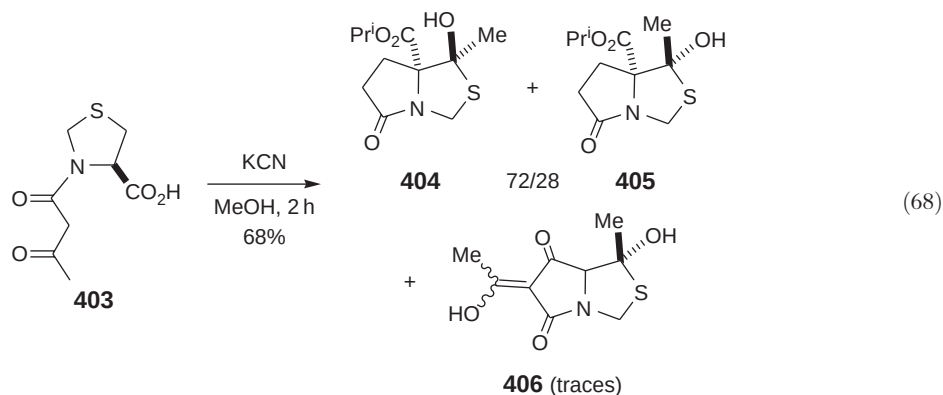
Scheme 59



Scheme 60

11.02.10.3.2 Tetrahydropyrrolo[1,2-*c*]thiazole

Only two articles report on the synthesis of tetrahydropyrrolo[1,2-*c*]thiazoles. The L-thiaproline **403** was converted (KCN (150 mol%), MeOH, 2 h) into a 72:28 mixture of the aldol products **404** and **405** (68% yield, 99% ee). In this reaction, a small amount of the acylation product **406** was also formed (Equation 68) <1998CC299, 2002TL3919>.



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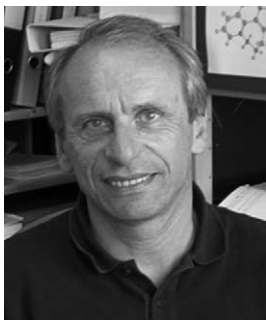
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Biographical Sketch



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11.04

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 1:1

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Université Paul Cezanne-CNRS, Marseille, France

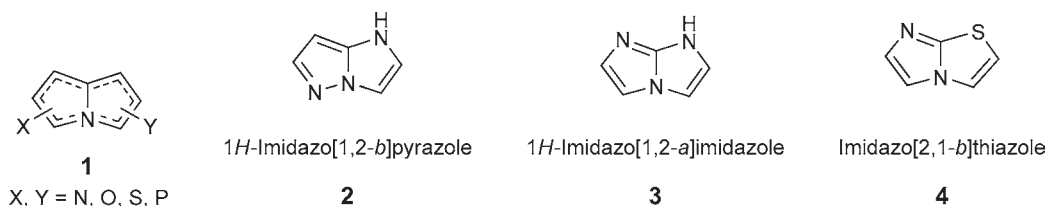
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11.04.1 Introduction and Scope

As already mentioned in CHEC-II(1996) <1996CHEC-II(8)95>, a large number of isomeric ring systems in which both fused heterocyclic five-membered rings contain one bridgehead nitrogen atom and one further heteroatom in each ring such as in compounds of type **1** are possible, depending upon the type and the relative position of both heteroatoms and the degrees of unsaturation. Some of these 5-5 fused bicyclic systems are well-known and have received considerable attention all over the past few years (more than 250 references cited here). Several heterocycles containing fully conjugated or nonconjugated rings have been reported in the literature and will be examined here, with an emphasis on those systems which contain nitrogen, oxygen, sulfur, and phosphorus as heteroatoms. Among them, much of the chemistry has been focused on imidazo[1,2-*b*]pyrazoles **2**, imidazo[1,2-*a*]imidazoles **3**, and imidazo[2,1-*b*]thiazoles **4**, listed in **Scheme 1**, as well as their partially hydrogenated, carbonylated, and benz-fused analogs, which will dominate this chapter even if the other categories, cited in the previous edition, should also be carefully treated and not discarded.



Scheme 1

This chapter is an update to Chapter 8.04 of CHEC-II(1996) <1996CHEC-II(8)95>; it covers the literature from 1995 to 2007. More specifically, it contains major informations on the preparation and reactivity of these bicyclic 5-5 systems. Furthermore, a variety of biological activities and important applications in the chemical, medical, and agrochemical field beyond the scope of this chapter. Considering the little information obtained in few areas, coverage of sections dealing with structural, theoretical and thermodynamic data has been kept to a minimum since only imidazo[1,2-*a*]imidazole and imidazo[1,2-*b*]pyrazole systems have been the subject of recent studies. The most important structural data have already been summarized in CHEC-II(1996), Chapter 8.04.

The reactivity and the synthesis of the fully unsaturated heterocycles compared to their partially or fully saturated members have been examined and developed in detail. The literature is mostly associated with ring synthesis, and a great deal of effort has been devoted over the last decade to develop various strategies and tactics for the preparation of these systems. Reactions in [Section 11.04.9](#) are classified strictly according to the number of atoms in the

heterocyclic fragment and the number of additional atoms that participate in the elaboration of the second ring. Within each section, all methods are divided into specific type of bond formation, whereas in Section 11.04.10, ring synthesis is based on the transformation of another ring.

These diverse classes of compounds, frequently encountered as biologically active compounds, have received more attention because of their increasing usefulness both as synthetic intermediates and therapeutic agents.

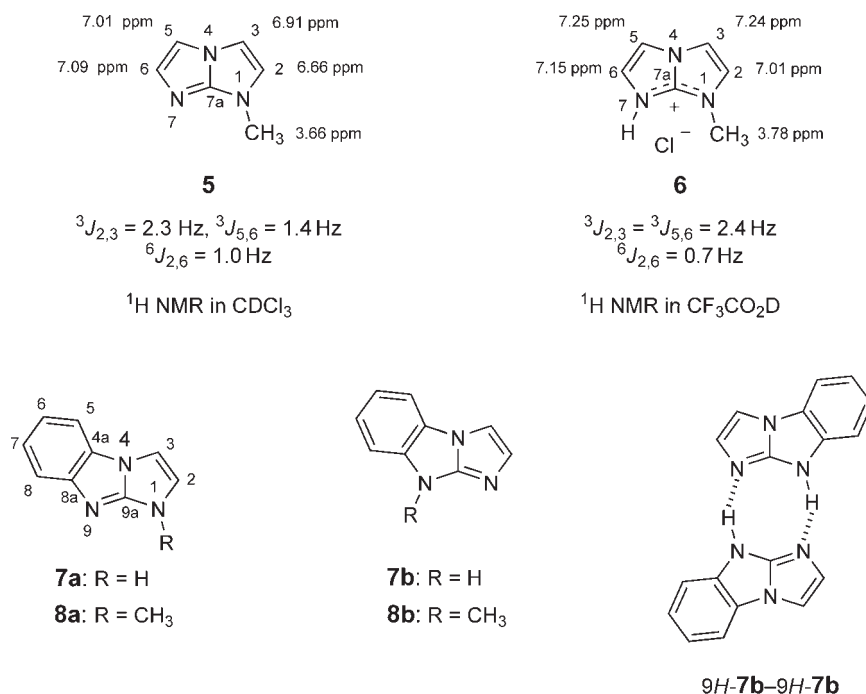
11.04.2 Theoretical Methods

No specific studies have been reported on the application of theoretical methods to these ring systems since CHEC-II(1996) <1996CHEC-II(8)95>.

11.04.3 Experimental Structural Methods

A full range of spectral data was routinely reported for each of the new compounds isolated. Nuclear magnetic resonance (NMR) spectroscopy and X-ray crystallography have essentially only been used as methods of structure determination/confirmation and the results are unexceptional. The use of mass spectrometry in these series of compounds has been mainly confined to molecular ion determination. Ultraviolet (UV), infrared (IR), and Raman techniques have been used for confirmation of structures, but no special report has been published. The major data in this field are well documented in CHEC-II(1996) and will not be reproduced in this chapter. Over the last decade, all these methods played a major role in establishing the structure, but did not provide new interesting structural information on these bicyclic systems. In consequence, these methods are not considered worthy of mention in detail here.

Beside routine structure determination, several investigations have been devoted to imidazo[1,2-*a*]imidazoles and imidazo[1,2-*a*]benzimidazoles (Scheme 2). In the imidazo [1,2-*a*]imidazole series, the most significant results are the presence of a ${}^6J_{2,6}$ coupling useful for assignments and the increase of the ${}^3J$ constant on protonation. Similar comments hold for the imidazo[1,2-*a*]benzimidazole series concerning now the ${}^3J_{2,3}$ coupling values. The solid-state cross-polarization magic angle spinning (CPMAS) NMR chemical shifts are remarkably like those found in solution except for the imidazo[1,2-*a*]benzimidazole **7**, where the nitrogen signals are shifted 17 ppm in opposite directions. This behavior supported a 9*H*-**7b**–9*H*-**7b** dimeric structure of the crystal already proposed by McNab and

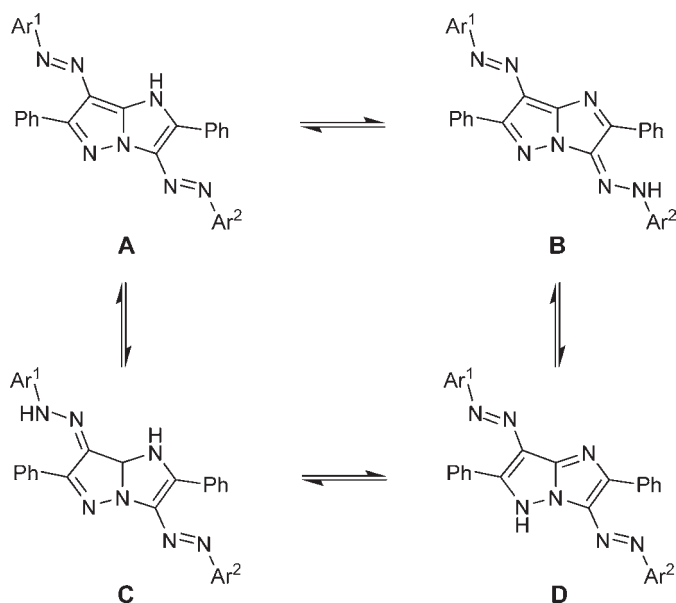


Scheme 2

co-workers. Tautomerism in the case of imidazo[1,2-*a*]benzimidazole **7** was determined by NMR comparison with compounds **8a** and **8b** and *ab initio* calculations (HF/6-311G**) confirmed the greater stability of 9*H*-over 1*H*-imidazo[1,2-*a*]benzimidazole tautomer with an energy difference of 9.98 kJ mol⁻¹ <1997J(P1)1605, 2002ARK48>.

11.04.4 Thermodynamic Aspects

The proton dissociation constants, of two series of 3,7-bis(aryloxy)-2,6-diphenyl-1*H*-imidazo[1,2-*b*]pyrazoles, in the ground state and the excited state were determined by the spectrophotometric method and utilizing the Forster energy cycle, respectively. These constants were correlated by the Hammett equation and the results of such correlations with spectral data indicated that both series of compounds exist in solution almost exclusively in the 1*H*-bis-(aryloxy) tautomeric form **A** <2002T2875> (Scheme 3).

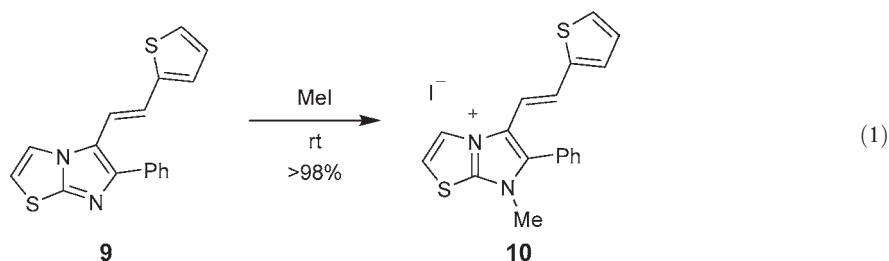


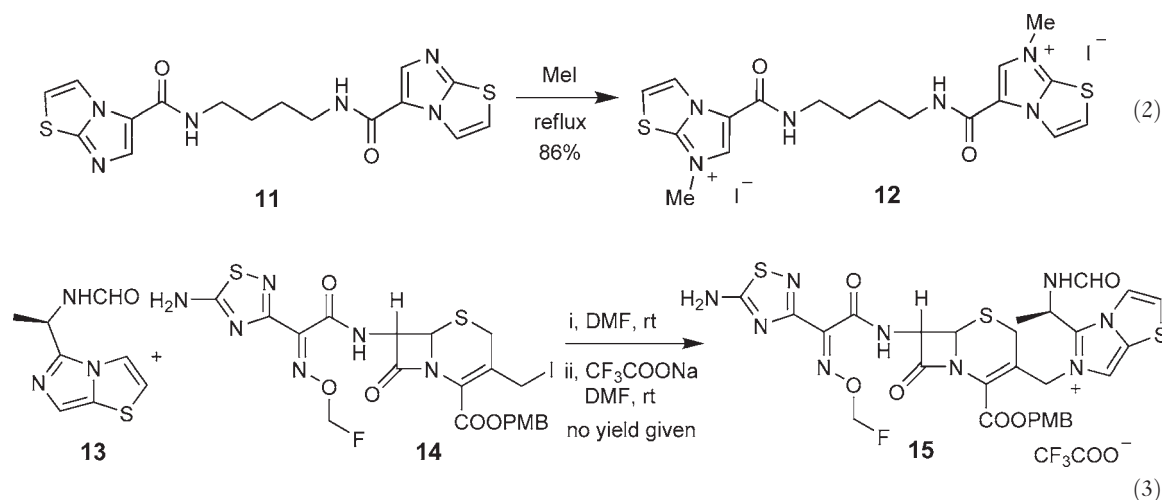
Scheme 3

11.04.5 Reactivity of Fully Conjugated Rings

11.04.5.1 Electrophilic Attack at Nitrogen

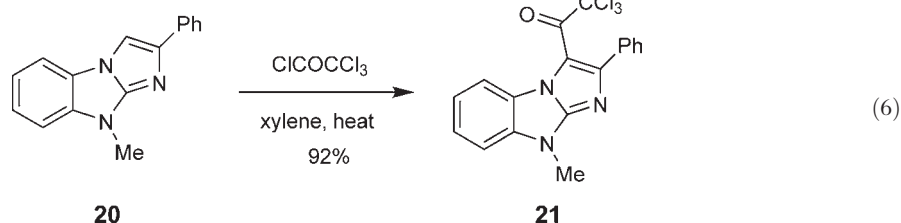
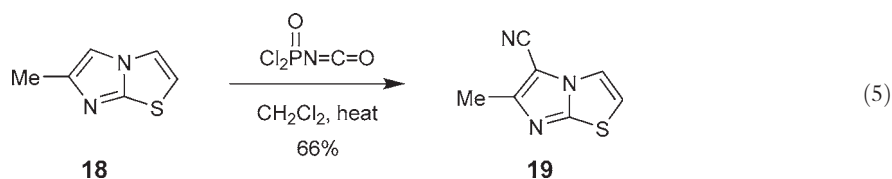
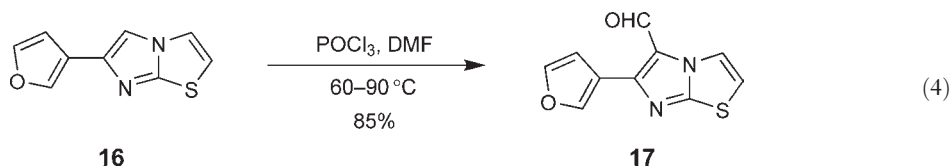
Alkylations of 5,5-fused ring systems with alkyl halides have been reported for substituted imidazo[2,1-*b*]thiazoles and imidazo[5,1-*b*]thiazoles to occur at the N-7 and N-6 positions, respectively. The monomethyl ammonium imidazo[2,1-*b*]thiazole salt **10** was obtained by quaternization of the tertiary base in **9** with a large excess of iodomethane and methylation of the bisamide **11** gave the symmetrical bisammonium salt **12** (Equations 1 and 2). A series of cephalosporins bearing a 5-substituted imidazo[5,1-*b*]thiazole group **15** was synthesized by allylation of **13** with compound **14** (Equation 3) <1995JME1090, 1996EJM741, 2000BMC2781>.



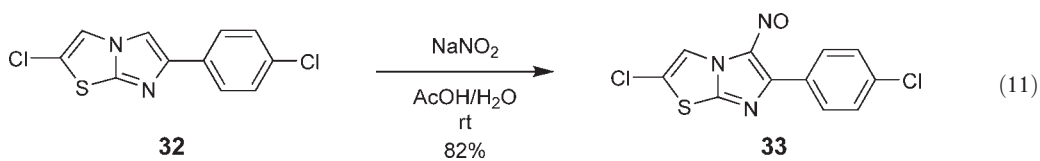
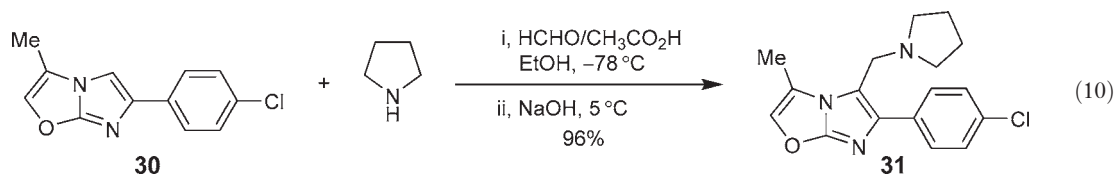
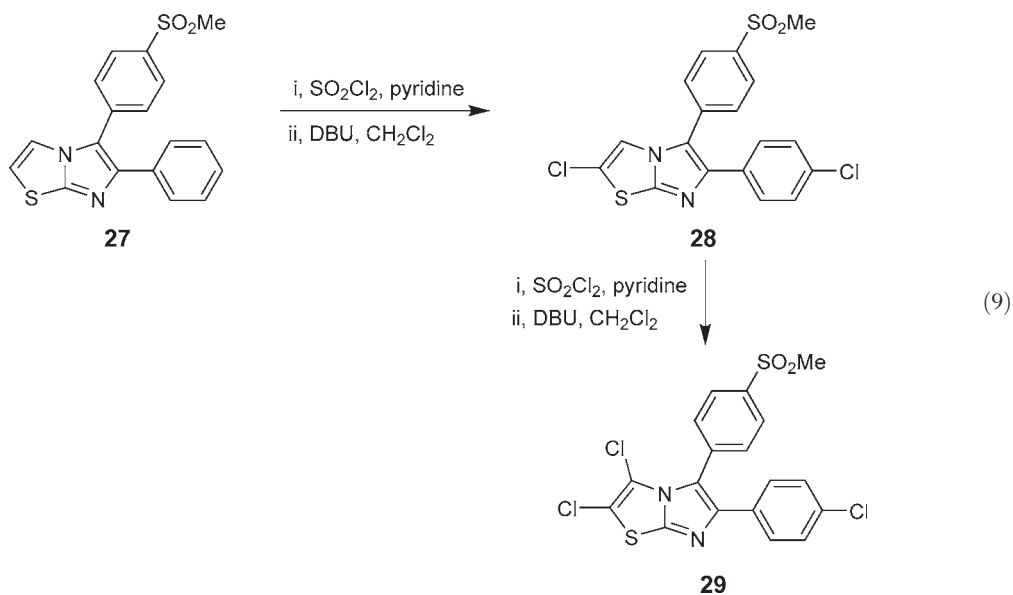
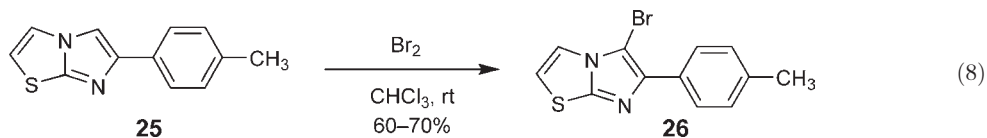
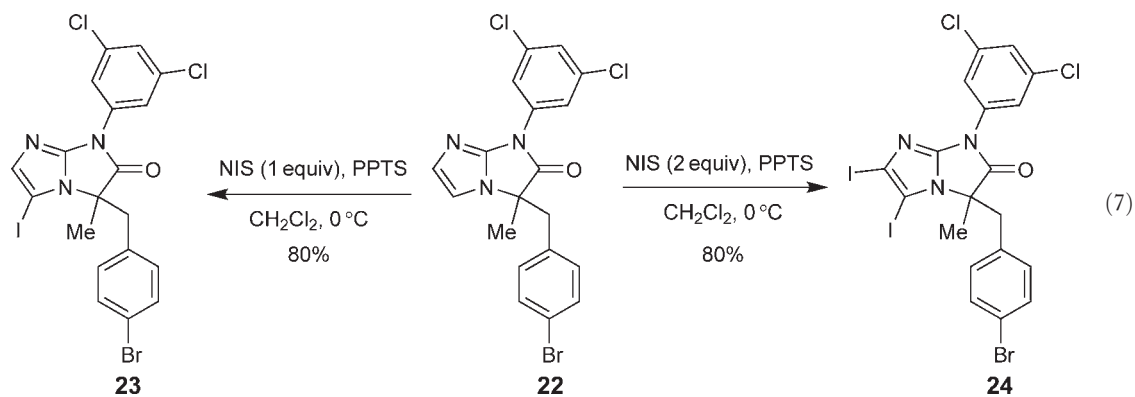


11.04.5.2 Electrophilic Attack at Carbon

Vilsmeier–Haack formylation reaction of the 6-substituted imidazo[2,1-*b*]thiazole derivative **16** took place at the C-5 position and provided the corresponding aldehyde **17** (Equation 4) <1996MI247, 1997JHC1763, 2001CHE1021>. Introduction of a cyano group into the electron-rich heterocyclic system **18** by treatment with isocyanatophosphoric acid dichloride showed a similar selectivity (Equation 5) <2002S2416>. Acylation of the 2-phenyl-benzimidazo[1,2-*a*]-imidazole **20** was reported with trichloroacetyl chloride to yield the 3-acylated product **21** (Equation 6) <1999PCJ361>.



The imidazole-based 5-5 bicyclic compound, the 1,3,3-trisubstituted imidazo [1,2-*a*]imidazol-2-one **22**, treated with 1 equiv of *N*-iodosuccinimide (NIS) underwent a regioselective iodination at the C-5 position giving **23** whereas 2 equiv of NIS led to the diiodide **24** (Equation 7) <2004JME5356>. The bromination and chlorination of the imidazo[2,1-*b*]thiazole derivatives **25** and **27** were also studied and examples are reported in Equations (8) and (9) <1996MI247, 1997BML47>. Imidazo[2,1-*b*]oxazoles **30** participated in a Mannich reaction, with formaldehyde and secondary amines, to give the amino-methylated products **31** (Equation 10) <1997T6959>. Nitrosation of the 6-aryl-imidazo[2,1-*b*]thiazole system **32** was successful and occurred at the C-6 position, leading to compound **33** (Equation 11) <2000JHC875, 2001EJM743>.



11.04.5.3 Nucleophilic Attack at Carbon

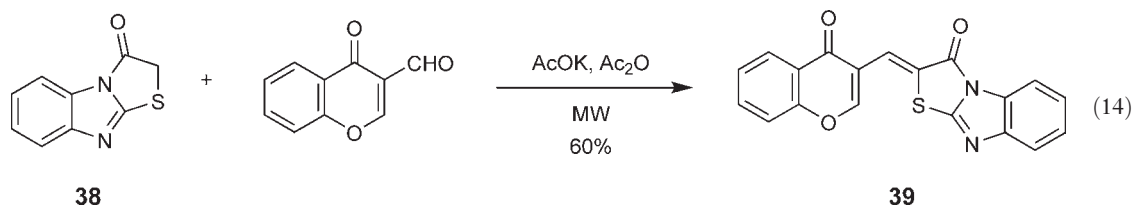
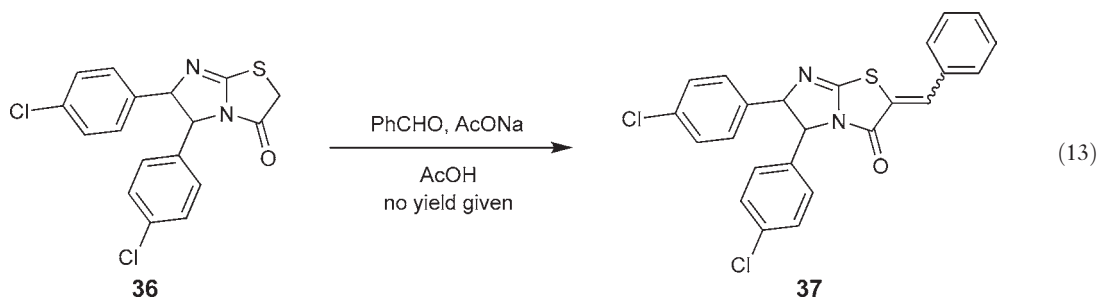
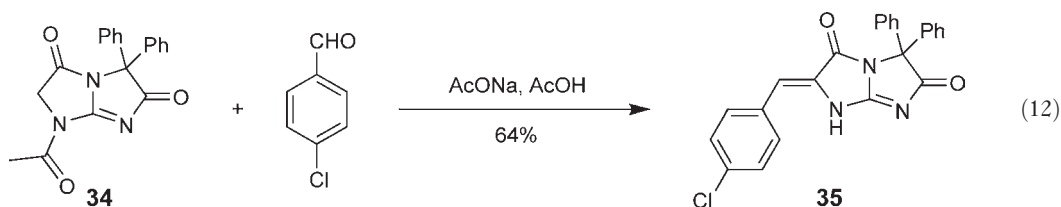
No significant advance has been performed in this area since publication of CHEC-II(1996), which covers the topic in detail <1996CHEC-II(8)95>.

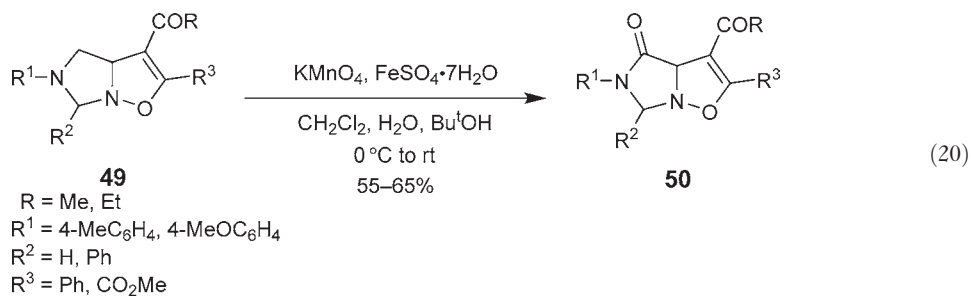
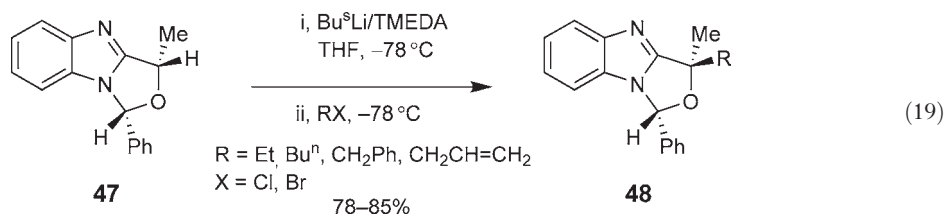
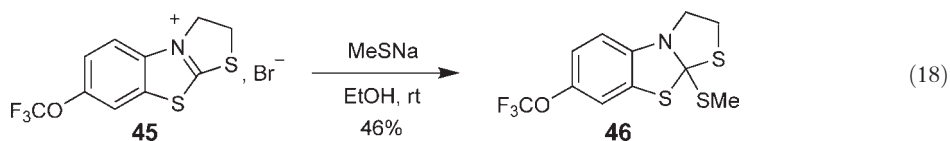
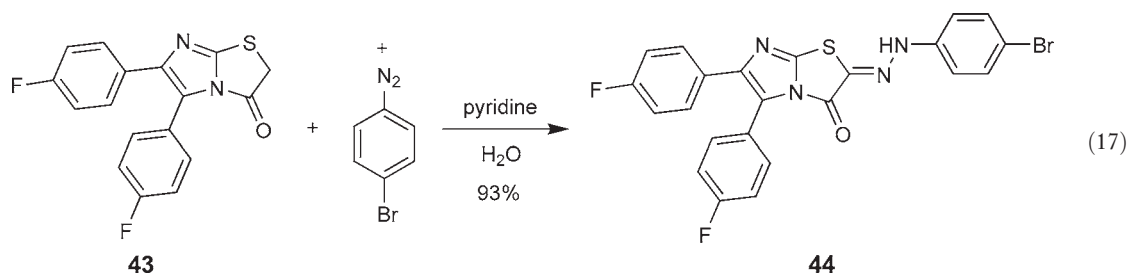
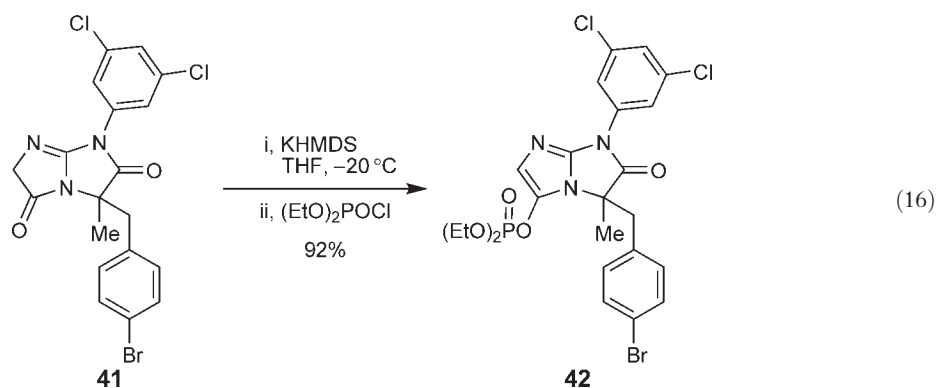
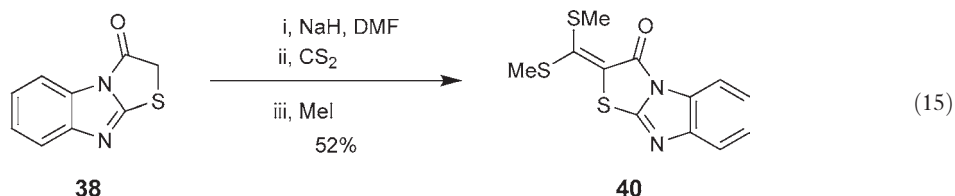
11.04.6 Reactivity of Nonconjugated Rings

11.04.6.1 Reactions Where the Ring System Is Preserved

11.04.6.1.1 Functionalization of ring carbon atoms

The Knoevenagel reaction between aldehydes and a range of imidazo-fused bicyclic 5-5 systems has been extensively reported for the preparation of arylidene derivatives. For instance, the 6,7-dihydro-imidazo[1,2-*a*]imidazole-2,5-dione **34** and the 5,6-dihydro-imidazo[2,1-*b*]thiazol-3-one **36** placed in AcONa/AcOH solution afforded the condensation products **35** and **37**, respectively (Equations 12 and 13) <2002JHC243, 1996JRM1817, 2004PS305>. Microwave (MW)-assisted Knoevenagel condensation was investigated for the functionalization of benzo[4,5]imidazo[2,1-*b*]thiazol-3-one **38** with 4-oxo-4*H*-chromene-3-carbaldehyde (Equation 14) <1995CCC1178>. Alternatively, reaction of **38** with tetravalent electrophiles such as carbon disulfide followed by methylation yielded the bis-(methylthio)methylene thiazolobenzimidazolone **40** (Equation 15) <1989ZC206>. Conversion of the bicyclic guanidine **41** to the imidazo[1,2-*a*]imidazol-2-one derivative **42** was performed by transformation of the amide moiety into a vinyl phosphonate (Equation 16) <2003TL6509>. Hydrazone formation with aryldiazonium intermediates could be used to functionalize imidazo[2,1-*b*]thiazol-3-ones **43** at the C-2 position selectively (Equation 17) <2004PS305>. When the tricyclic thiazolium salt **45** was reacted with sodium methyl sulfide, it stopped at a stable tricyclic benzothiazole derivative **46** which contains a rarely observed four-heteroatom-substituted carbon atom (Equation 18) <1999JME2828>. Direct lithiation of the substituted oxazolo[3,4-*a*]benzimidazole **47** with Bu^sLi and tetramethylethylenediamine (TMEDA) occurred at the C-5 of the oxazole ring. Attack of the transient lithiated species with alkyl halides proceeded with retention of configuration and yielded compounds **48** (Equation 19) <1998TA2245>. Oxidation of tetrahydro-imidazo[1,5-*b*]isoxazoles **49** with an excess of KMnO₄/FeSO₄ led to the 4-oxo analogs **50** (Equation 20) <2004SC1617>.

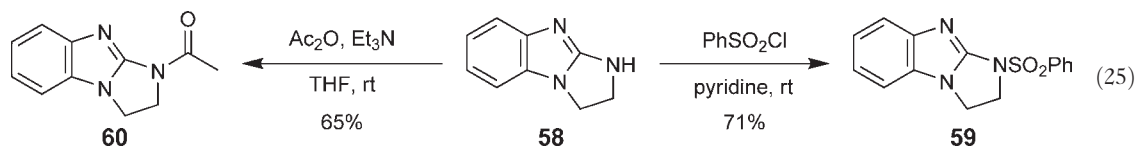
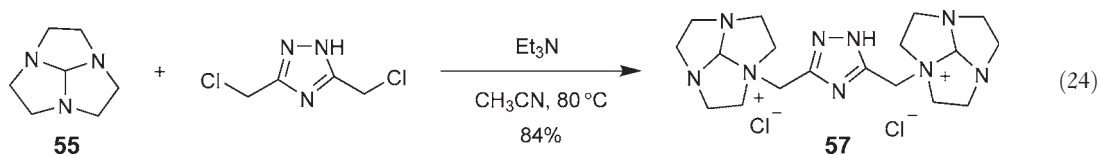
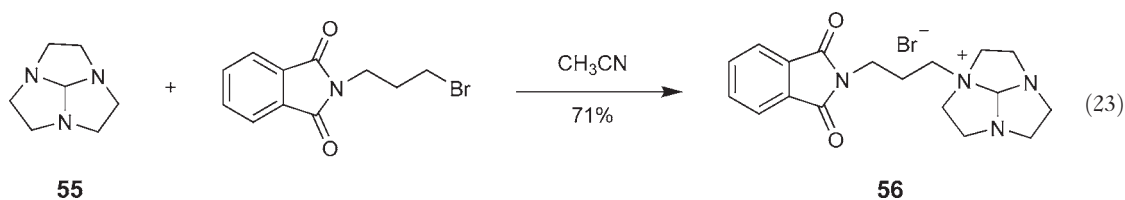
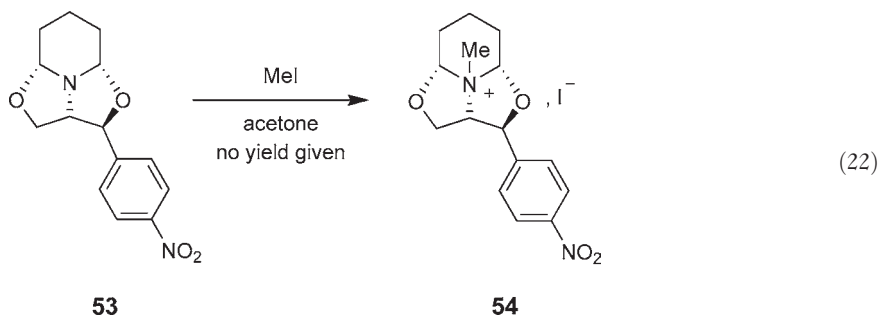
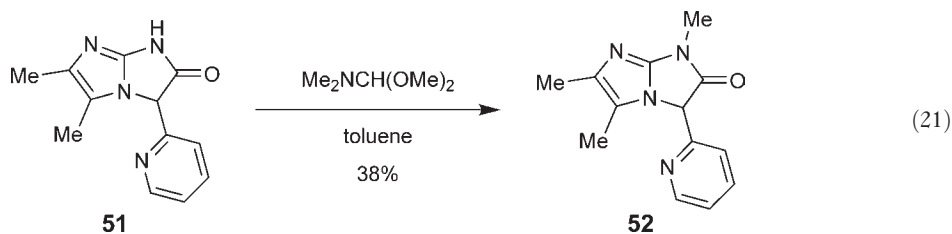


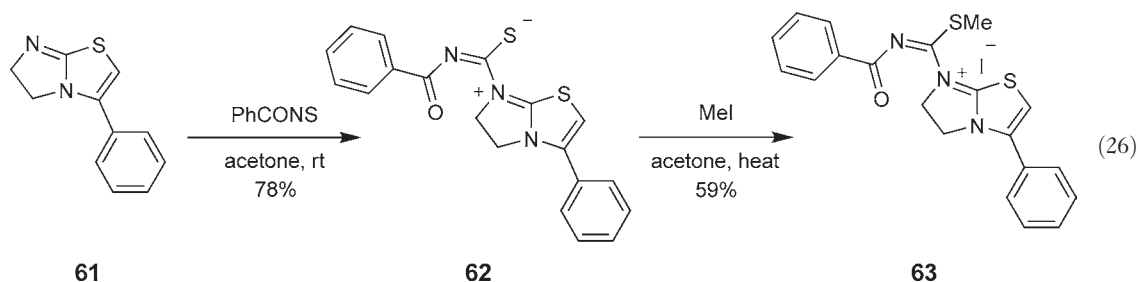


11.04.6.1.2 Functionalization of ring heteroatoms

11.04.6.1.2(i) Reaction at nitrogen

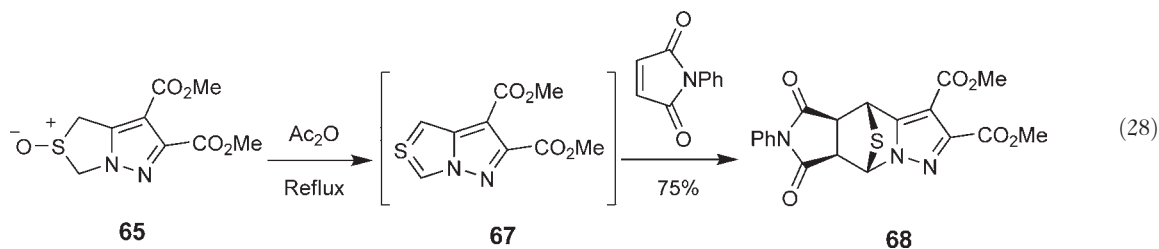
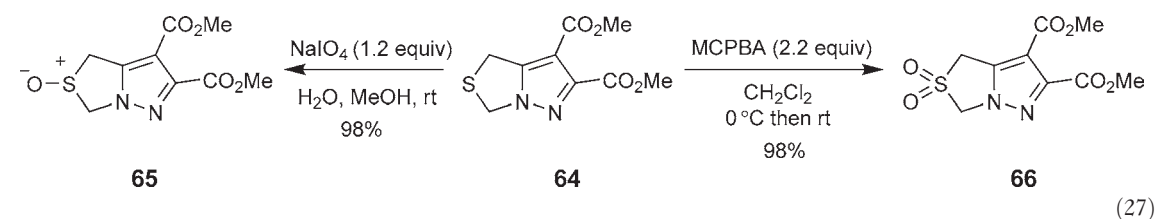
Treatment of the imidazo[1,2-*a*]imidazol-2-one **51** and the hexahydro-1,4-dioxo-2a-aza-cyclopenta[*cd*]indene **53** with dimethoxymethyl-dimethylamine or methyl iodide led to the formation of the corresponding *N*-acylated compounds **52** and **54**, respectively (Equations 21 and 22) <1995JHC141, 2001CHE898>. The alkylation and benzylation of 1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane **55** have been also studied. For example, reaction of **55** with *N*-(3-bromopropyl)phthalimide gave the insoluble monoamiminium bromide salt **56** and with 3,5-bis(chloromethyl)-1*H*-pyrazole hydrochloride, as bifunctional alkylating reagent, generated the bis-macrocycle **57** having a pyrazole bridging unit (Equations 23 and 24) <2001OL2855, 1997HCA2315, 2001JCD2232>. The dihydro-imidazole[1,2-*a*]benzimidazole **58** easily underwent reaction with benzenesulfonyl chloride and acylation with acetic acid anhydride at N-1 forming **59** and **60**, respectively (Equation 25) <1998PJC2541>. In the case of 3-phenyl-5,6-dihydro-imidazo[2,1-*b*]thiazole **61**, electrophilic attack of benzoyl isothiocyanate at N-7 and subsequent alkylation with methyl iodide yielded the imidazo[2,1-*b*]thiazolium salt **63** (Equation 26) <1995JHC1581>.





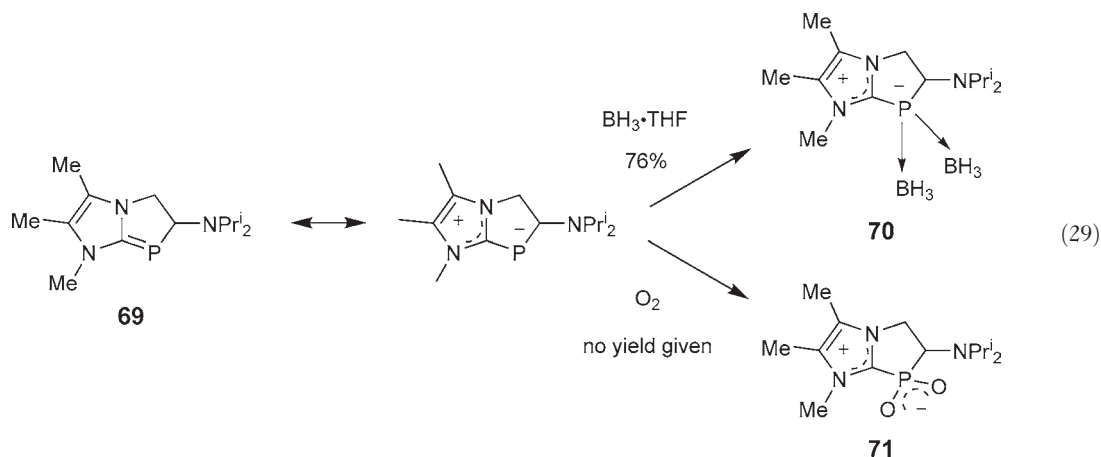
11.04.6.1.2(ii) Reaction at sulfur

Oxidation of sulfur atom of pyrazolo[1,5-*c*]thiazole **64** into sulfoxide **65** followed by Pummerer-type dehydration furnished the transient ‘nonclassical’ pyrazolo[1,5-*c*]thiazole, the thiocarbonyl ylide **67**, which could react with various dipolarophiles such as *N*-phenylmaleimide (Equations 27 and 28) <2000T10011>. In an excess of oxidizing agent, pyrazolo[1,5-*c*]thiazole **64** was readily converted to sulfone **66** (Equation 27) <2001J(P1)1795>.



11.04.6.1.2(iii) Reaction at phosphorus

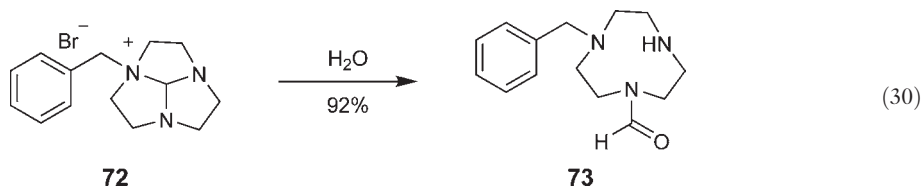
A small amount of compound **71** with two oxygen atoms on the phosphorus atoms was obtained by oxidation of the azaphospholene **69** phosphorus atom and the complex **70** containing two BH₃ groups by derivatization of **69** with the Lewis acid BH₃·THF (Equation 29) [<2001AGE3144>](#).



11.04.6.2 Ring Cleavage Reactions

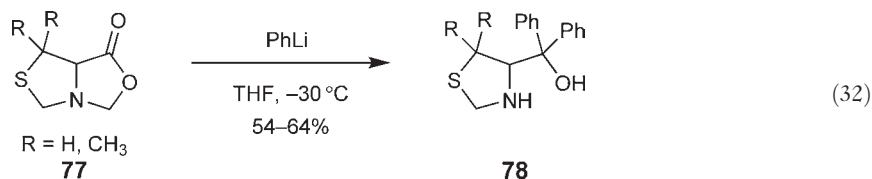
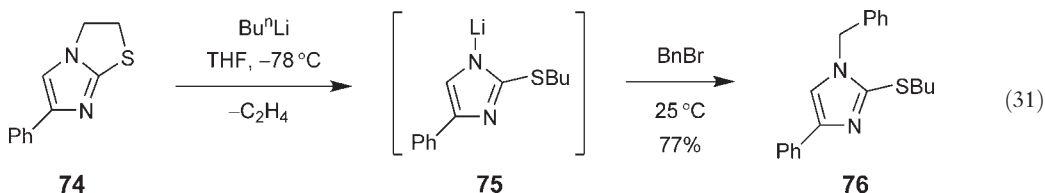
11.04.6.2.1 Ring opening through hydrolysis

The monoammonium salt of 1,4,7-triazatricyclo[5.2.1.0^{4,10}]decane **72** when treated with water led to the desired substituted 1,4,7-triazacyclononane **73** in 92% yield (Equation 30) <2001OL2855>.



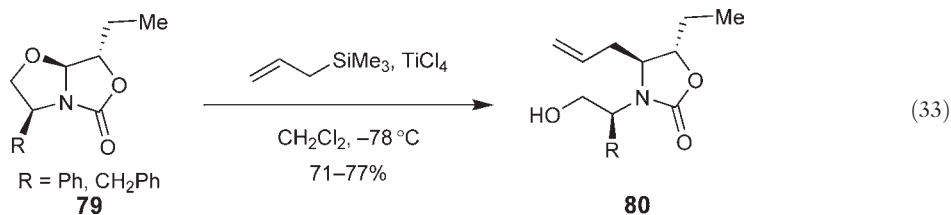
11.04.6.2.2 Nucleophilic attack of organometallic derivatives

Thiophilic addition of organolithium reagents such as BuⁿLi to imidazo[2,1-*b*]thiazoline **74** occurred at low temperature with extrusion of ethylene. Thus, the transient lithiated species **75** could be trapped with benzyl bromide liberating the 2-thioalkylimidazole **76** (Equation 31) <2000OL2877>. On treatment with phenyllithium, bicyclic dihydro-thiazolo[3,4-*c*]oxazol-1-ones **77** underwent ring opening to afford the sulfur-containing β-amino alcohol ligands **78** (Equation 32) <1997TA2033>.



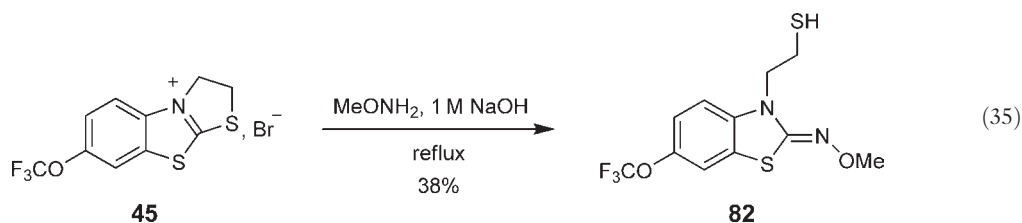
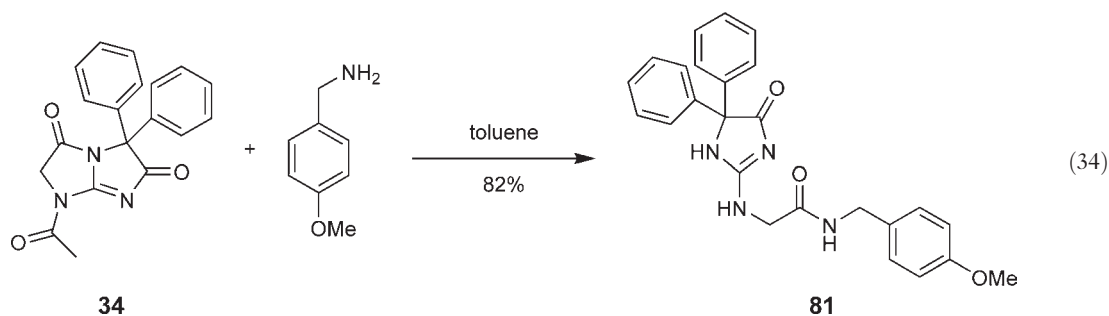
11.04.6.2.3 S_E2' electrophilic substitution

In the presence of allyltrimethylsilane, titanium tetrachloride catalyzed the ring cleavage of the tetrahydro-1,5-dioxo-3a-aza-pentalen-4-ones **79** giving the oxazolidinones **80** (Equation 33) <2001T5393>.



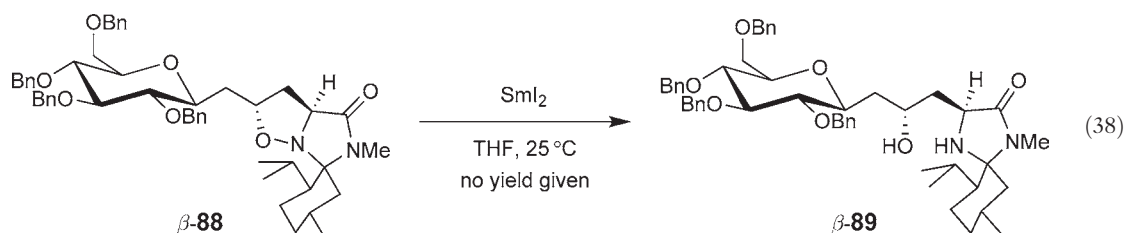
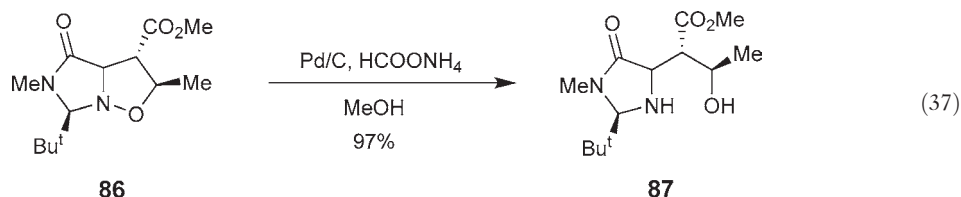
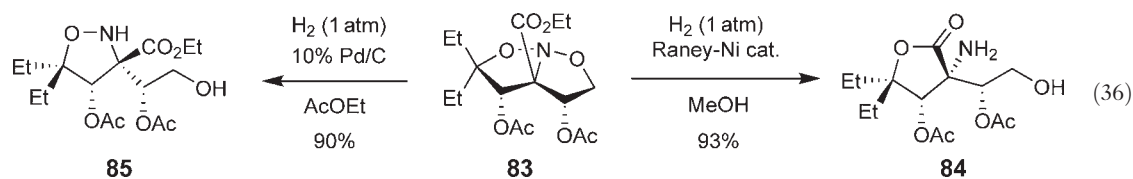
11.04.6.2.4 Amine-induced ring opening

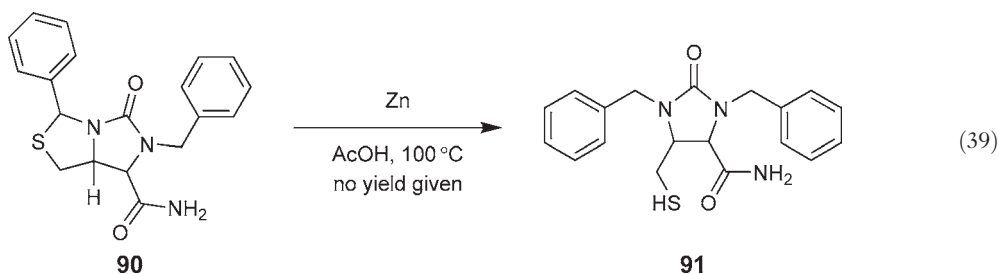
Nucleophilic attack of substituted alkylamines including benzylamines to 6,7-dihydro-imidazo[1,2-*a*]imidazole-2,5-diones **34**, cleaved the imidazolidinone ring to generate the acetamide derivatives **81** (Equation 34) <1998APH389, 2001JST73>. Reaction of the tricyclic thiazolium salt **45** with methoxyamine gave the oxime **82** (Equation 35) <1999JME2828>.



11.04.6.2.5 Ring opening through reduction of NO and CS bond

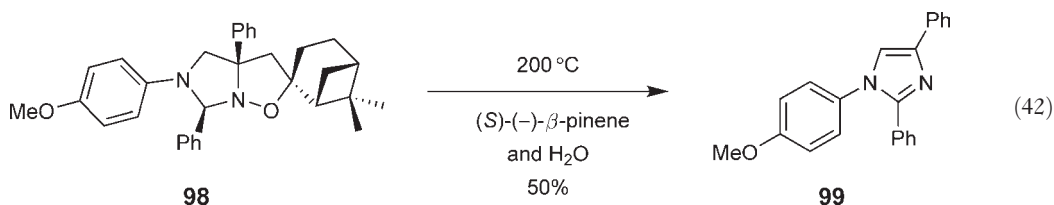
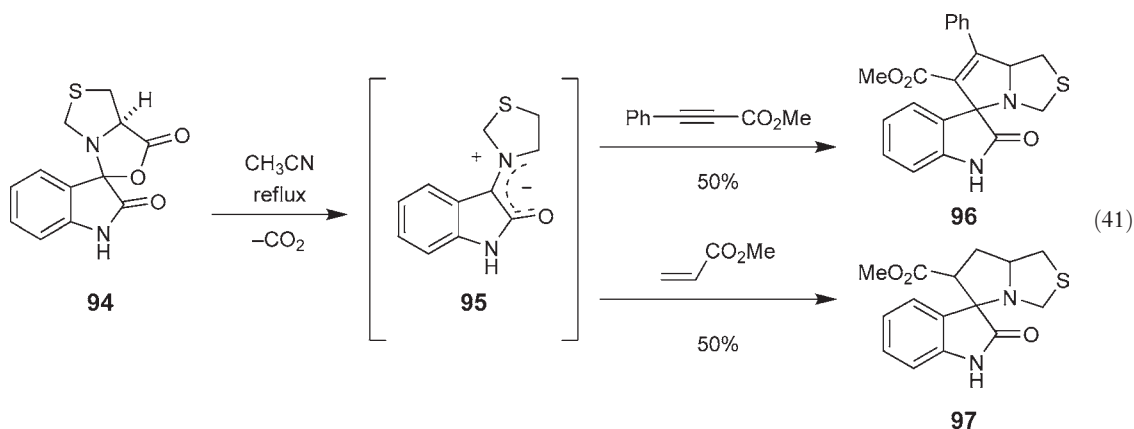
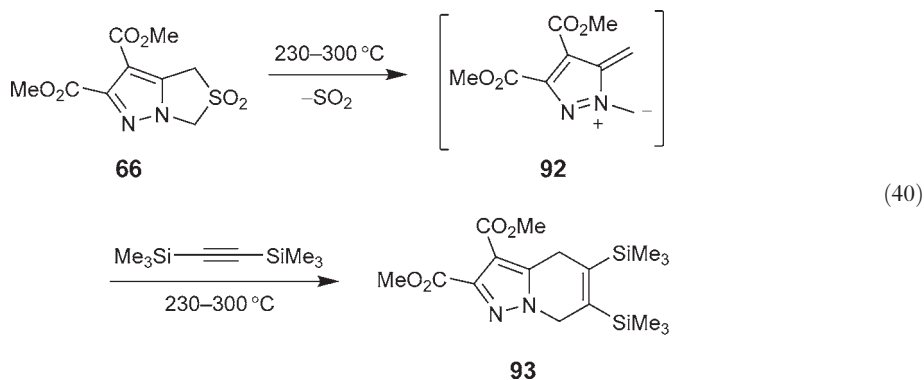
Raney Ni-catalyzed hydrogenolysis of the nitroso acetal **83** opened the bicyclic compound to give lactone **84** resulting from two N–O bond cleavages and lactonization, whereas the same reaction with palladium gave rise to the selective cleavage of the less-hindered N–O bond leading to the isoxazolidine **85** (Equation 36) <1998CEJ2501>. The tetrahydro-imidazo[1,5-*b*]isoxazol-4-one **86** was converted to the free amino alcohol **87** under transfer hydrogenolysis conditions using ammonium formate in the presence of palladium (Equation 37) <2004OL1653>. As an alternative, samarium(II)-mediated cleavage of the N–O bond in the tetrahydro-imidazo[1,5-*b*]isoxazol-4-one **88** liberated the γ -hydroxy- α -amino acid derivative **89** (Equation 38) <2001OL1375>. Benzylic C–S bond cleavage of 2-oxo-2-phenyl-imidazo[1,5-*c*]thiazole **90** was initiated by zinc in acetic acid at 100 °C and gave rise to the imidazolidinone **91** (Equation 39) <2003S2311>.





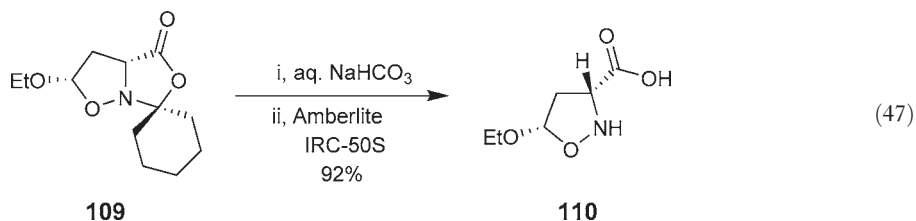
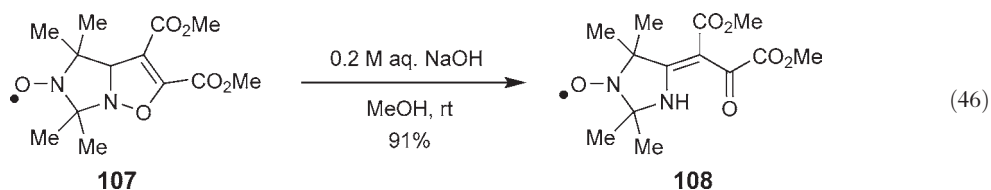
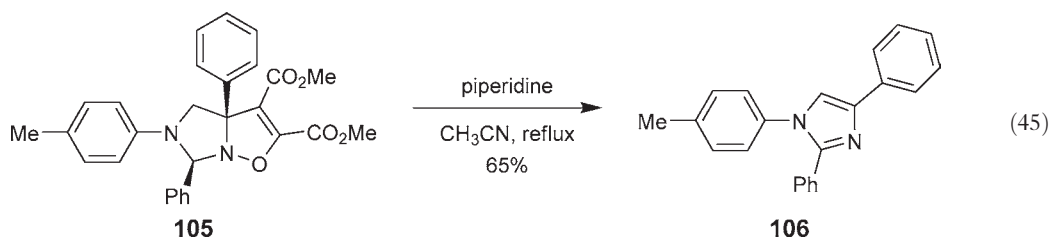
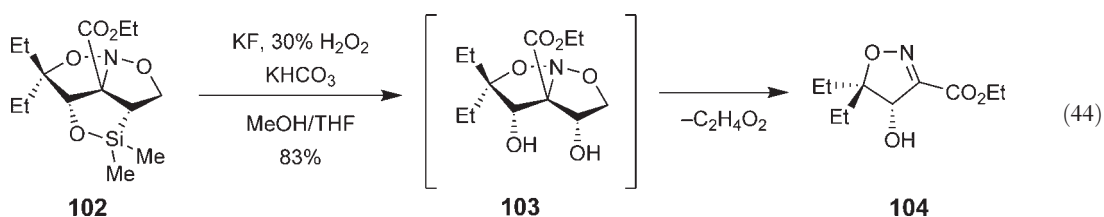
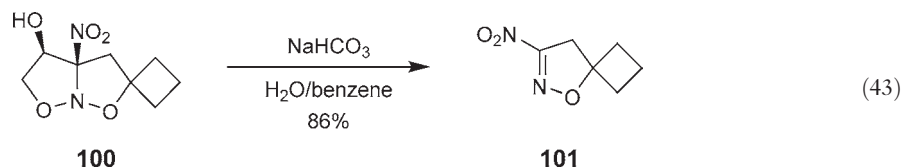
11.04.6.2.6 Ring opening through thermolysis

Thermal sulfur dioxide extrusion from the 5-thia-1,6 α -diazapentalene 5,5-dioxide **66** generated the diazafulvenium methide intermediate **92** which could undergo a $[8\pi+2\pi]$ cycloaddition with the electron-rich dipolarophile bis(trimethylsilyl)acetylene (Equation 40) <2001J(P1)1795>. In another example, azomethine ylide **95** formation involved decarboxylation of thiazolo-oxazolidinones **94** in refluxing acetonitrile and subsequent 1,3-dipolar cycloaddition with methyl phenylpropiolate or methyl acrylate to afford the novel spiro compounds **96** and **97**, respectively (Equation 41) <2002SC435>. The retro-1,3-dipolar cycloaddition of the perhydroimidazoisoxazole derivative **98** led to the corresponding imidazole adduct **99** (Equation 42) <2001TA1463>.



11.04.6.2.7 Base-promoted ring opening

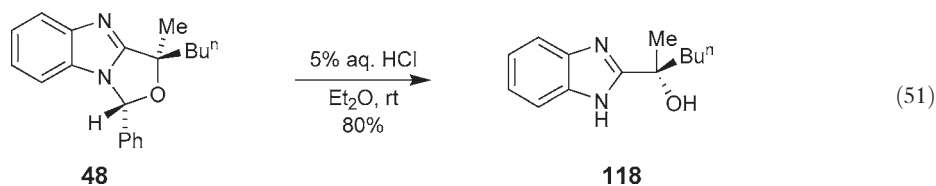
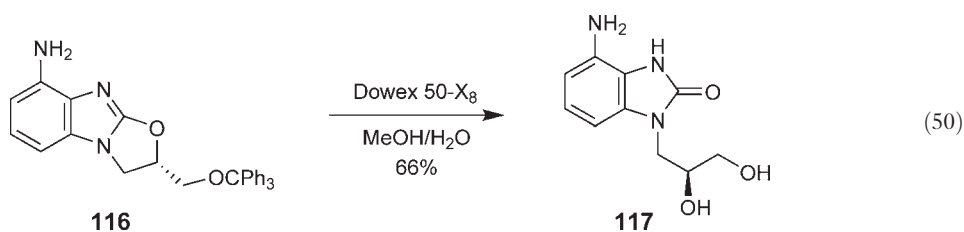
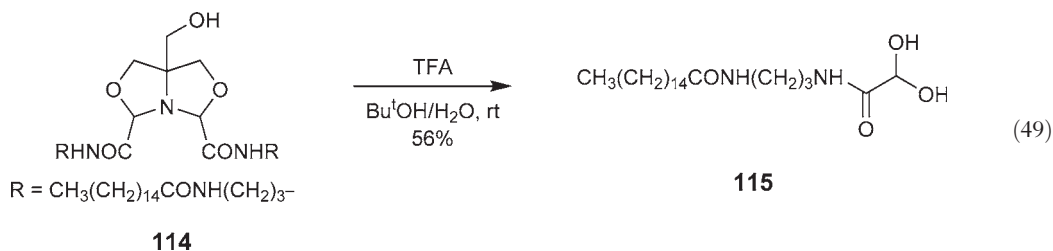
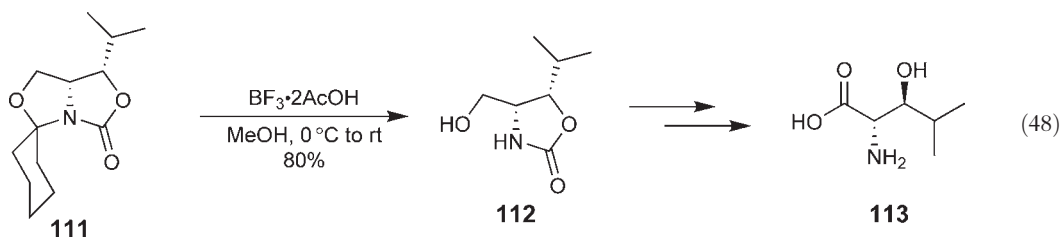
Grob-type fragmentation of the bicyclic nitroso acetal **100** was utilized for the synthesis of the isoxazoline **101** (Equation 43) <2002DOC21>. This type of compound was also made via a tandem Tamao hydroxy desilylation-fragmentation, as depicted Equation (44) <1998CEJ2501>. The 3*a*,4,5,6-tetrahydro-imidazo[1,5-*b*]isoxazole **105** was converted to the corresponding imidazole **106** in the presence of piperidine via a double concerted *cis*-elimination mechanism (Equation 45) <2001T3413>. Base-catalyzed ring cleavage of 5,6(4*H*)-dihydro-imidazo[1,5-*b*]isoxazole-5-oxyls **107** leads to imidazolidine-1-oxyls **108** (Equation 46) <2000RCB116>. Saponification of the dihydro-1,5-dioxo-6*a*-aza-pentalen-4-one **109** liberated the isoxazolidine carboxylic acid **110** (Equation 47) <1994JOC8101>.



11.04.6.2.8 Acid-promoted ring opening

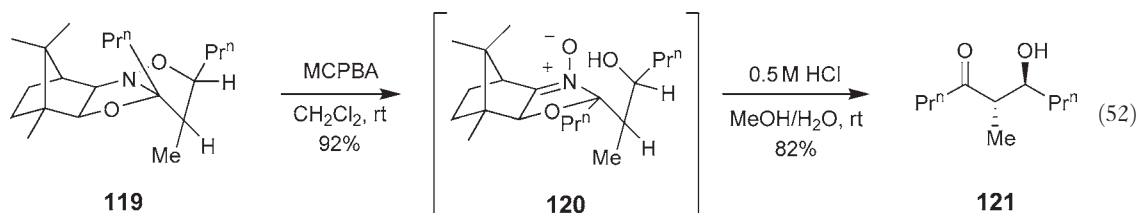
Ring cleavage of the bicyclic dihydro-oxazolo [3,4-*c*]oxazol-3-one **111** derived from D-serine was realized by action of boron trifluoride–acetic acid complex leading to the oxazolidinone **112**, a useful building block for the synthesis of

α -amino β -hydroxy acids **113** (Equation 48) <1995TL7031, 1996T11673>. Under trifluoroacetic acid (TFA) conditions, fission of the dihydro-oxazolo[3,4-*c*]oxazole **114** occurred to give the hydrated α -oxo-aldehyde **115** (Equation 49) <2001TL1875>. Acid-catalyzed hydrolysis of 7,8-dihydro[1,3]oxazolo[3,2-*c*]purin-4-amine **116** and 3*H*-benzo[4,5]imidazo[1,2-*c*]oxazole **48** gave the corresponding ring-opened products **117** and **118**, respectively (Equations 50 and 51) <2000CCC1126, 1998TA2245>.



11.04.6.2.9 Oxidative ring opening

Oxidation of the tetrahydro-oxazolo[3,2-*b*]isoxazole **119** followed by a spontaneous fragmentation of the transient *N*-oxide resulted in the nitron intermediate **120**. Acidic methanolysis of this latter liberated the β -hydroxy ketone **121** (Equation 52) <1995JOC1720>.

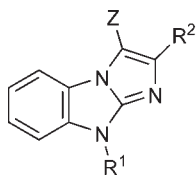


11.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

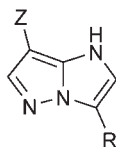
A wide variety of standard reactions for the transformation of substituents attached to ring carbon atoms have been reported in the literature. A selection of routine functional group transformations is summarized in [Table 1](#) and in the few lines that follow. The selected examples can be classified according to the nature of the transformation, the reagents implicated, and the type of ring system [E–M](#) whose substituents underwent the modification.

Table 1 A selection of functional group transformations of substituents (Z) attached to ring carbon atoms

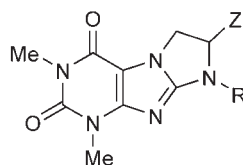
<i>Transformation of Z</i>	<i>Type ring system</i>	<i>Reagents</i>	<i>Reference</i>
$\text{COCH}_2\text{X} \rightarrow \text{COCH}_2\text{NR}_2$	E	HNR_2 , benzene	2002PJC377
$\rightarrow \text{COCH}_2\text{PPh}_3+$	E	PPh_3 , benzene	2002PJC377
$\text{COOH} \rightarrow \text{H}$	F	H_2SO_4 , EtOH	1999SC311
$\text{COOH} \rightarrow \text{COCl}$	J	$(\text{COCl})_2$, DMF, DCM	2000JHC95
$\text{COOR} \rightarrow \text{CH}_3$	F	LAH, THF	1999SC311
$\text{COOR} \rightarrow \text{CHO}$	J	LAH, THF then MnO_2 , CHCl_3	2004JME6556
$\text{COOR} \rightarrow \text{COOH}$	F	NaOH , H_2O , EtOH	1999SC311
$\text{COOR} \rightarrow \text{COOH}$	E	NaOH , H_2O , EtOH	1999PCJ361
$\text{COOR} \rightarrow \text{COOH}$	J	NaOH , H_2O , EtOH	1995EJM901
$\text{COOR} \rightarrow \text{COOH}$	H	NaOMe , MeOH	2000JOC7779
$\text{COOR} \rightarrow \text{CH}_2\text{OH}$	L	NaBH_4 , MeOH	2003BMC3475
$\text{COOR} \rightarrow \text{CONHR}$	G	$\text{H}_2\text{N}(\text{CH}_2)_n\text{R}$, EtOH	2002FA697
$\text{COOR} \rightarrow \text{CONHNH}_2$	J	$\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH	2002HCO433
$\text{COOR} \rightarrow \text{CONHNH}_2$	F	$\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH	1999SC311
$\text{CONHNH}_2 \rightarrow \text{CON}_3$	F	HNO_3 , H_2O	1999SC311
$\text{CONHNH}_2 \rightarrow \text{CON}_3$	J	NaNO_2 , HCl	2002HCO433
$\text{CON}_3 \rightarrow \text{NHCOOR}$	F	ROH, toluene	1999SC311
	J		2002HCO433
$\text{NH}_2 \rightarrow \text{NHCOR}$	F	$(\text{RCOO})_2\text{O}$, TEA, DCM	1999SC311
$\text{COCCl}_3 \rightarrow \text{COOR}$	E	NaOEt , EtOH	1999PCJ361
$\text{COCCl}_3 \rightarrow \text{COOR}$	E	$\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, PhH	
$\text{CH}=\text{O} \rightarrow \text{CH}_2\text{OH}$	J	NaBH_4 , MeOH	1997JHC1763
$\text{CH}=\text{O} \rightarrow \text{CH}=\text{CHCO}_2\text{R}$	J	NaH , $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$, THF	1997JHC1763
$\text{CH}=\text{O} \rightarrow \text{CH}(\text{OH})\text{Me}$	J	MeMgBr , THF	1997JHC1763
$\text{CH}=\text{NO} \rightarrow \text{CH}_2\text{CN}$	J	Ac_2O	1997JHC1763
$\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{OR}$	J	MeI , DMF	1997JHC1763
$\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{NH}_2$	L	i, phthalimide, PPh_3 , DEAD, THF ii, NH_2NH_2 , EtOH	2003BMC3475
$\text{CH}_2\text{OH} \rightarrow \text{CH}_2\text{Cl}$	J	PCl_5 , toluene	2000AF550
$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{SAr}$	M	HSAr , K_2CO_3 , DMF	2004JHC51
$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{NR}_2$	J	HNR_2 , EtOH	1998PCJ139
$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{CN}$	J	KCN , H_2O , acetone	2000AF550
$\text{CH}_2\text{CO}_2\text{H} \rightarrow \text{CH}_2\text{CONR}_2$	K	i, $(\text{Imid.})_2\text{CO}$, THF ii, 2-MeS-CysOMe·HCl, DMF	1999T10283
$\text{OPO}(\text{OEt})_2 \rightarrow \text{I}$	I	NaI , TMSCl , H_2O	2003TL6509
$\text{I} \rightarrow \text{R}_2\text{NSO}_2$	I	Pentyl ¹⁶ MgCl , SO_2 , NCS, R_2NH	2003TL6509
$\text{I} \rightarrow \text{Ar}$	I	$\text{ArB}(\text{OH})_2$, $(\text{dppf})\text{PdCl}_2$	2003TL6509



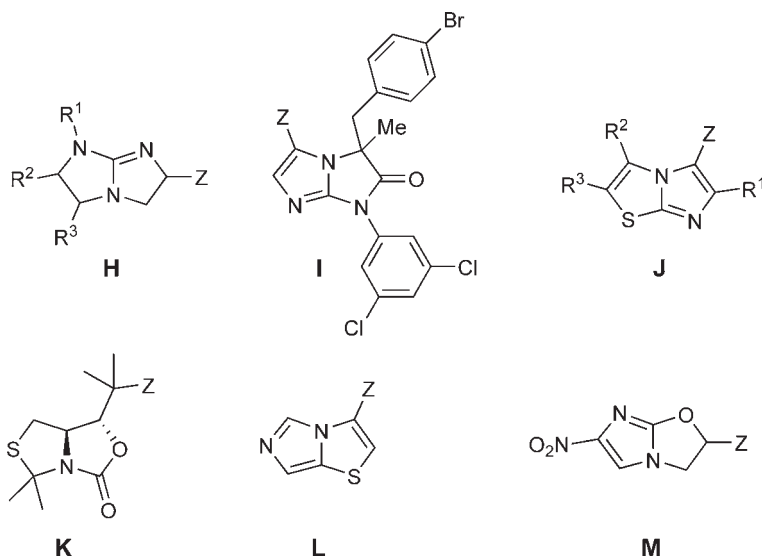
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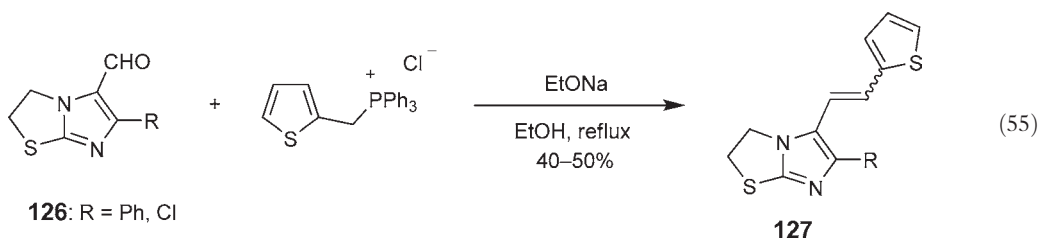
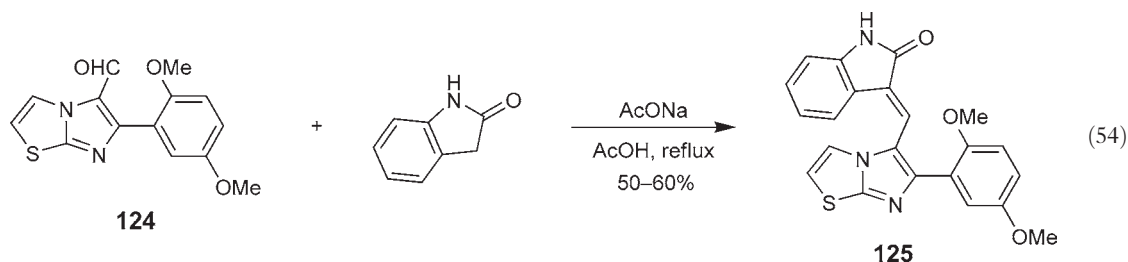
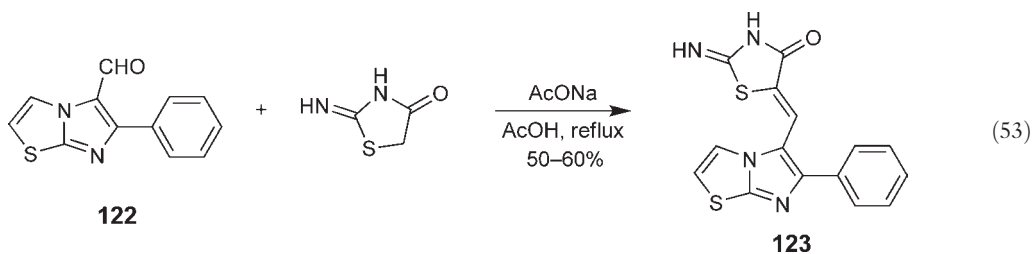
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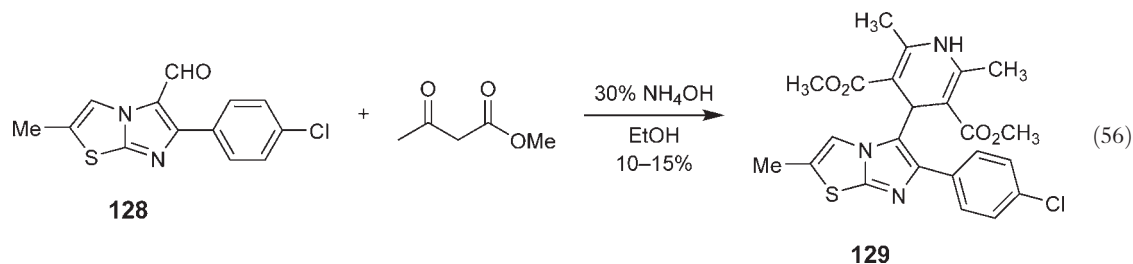


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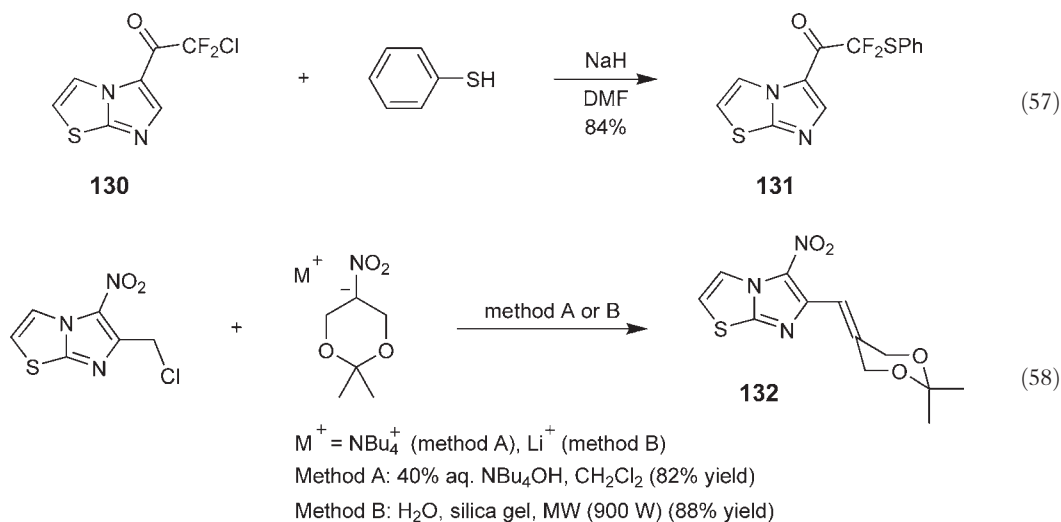


The Knoevenagel adducts **123** and **125** were conveniently prepared by treating the 6-substituted imidazo[2,1-*b*]-thiazole-5-carbaldehydes **122** and **124** with 2-iminothiazolidine-4-one and indolinone in sodium acetate/acetic acid, respectively (Equations 53 and 54) <1996EJM383, 1997EJM919>. The Wittig reaction applied to aldehyde **126** using (2-thienylmethyl)triphenylphosphonium chloride gave a mixture of (*E*)- and (*Z*)-isomers of partially hydrogenated 5-(2-thienylvinyl) imidazo[2,1-*b*]thiazoles **127** (Equation 55) <1995JME1090>. Imidazo[2,1-*b*]thiazole systems bearing a dihydropyridine ring **129** were synthesized by means of the Hantzsch reaction (Equation 56) <1997EJM151>.





The chlorodifluoromethylated ketone **130** proved to be a valuable substrate for promoting $S_{RN}1$ substitution reaction with sodium phenylthiolate and to generate a new α -(phenylthio)- α,α -difluoroacetophenone derivative **131** (Equation 57) <2001TL3459>. Upon treatment with nitronate anions under classical $S_{RN}1$ reaction conditions or MW irradiation, 6-chloromethyl-5-nitro-imidazo[2,1-*b*]thiazole **132** yielded 5-nitroimidazothiazoles bearing a trisubstituted ethylenic double bond at the 6-position (Equation 58) <2001SC1257>.

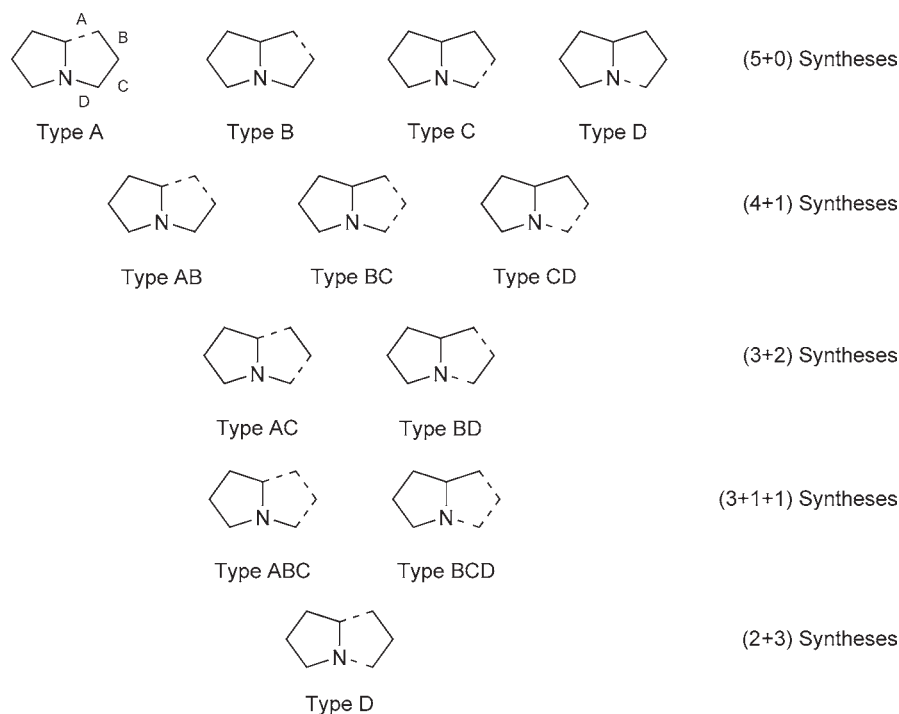


11.04.8 Reactivity of Substituents Attached to Ring Heteroatoms

No significant advances have been performed in this area since the publication of CHEC-II(1996), and the reader should refer for information on this topic to <1996CHEC-II(8)95>.

11.04.9 Ring Syntheses Classified by Number of Ring Atoms in Each Component

The search for new and efficient methods for the synthesis of fused bicyclic 5-5 systems containing a bridgehead nitrogen atom and two extra heteroatoms in each ring has been an active area of research in organic synthesis all over the last decade. The numerous preparative routes reported in the literature are highlighted in the following sections. As outlined in the corresponding chapter of the CHEC-II(1996) <1996CHEC-II(8)95>, the different approaches are classified in terms of the number of atoms in the heterocyclic fragment and the number of additional atoms that participate to the elaboration of the second ring. Within each section, all methods are divided into specific types of bond formation. Scheme 4 summarizes all the possible ring closure routes as already illustrated in CHEC-II(1996) <1996CHEC-II(8)107>. Such a classification system will be followed throughout this section. By contrast, the final section deals with syntheses where both rings are formed simultaneously, usually from an acyclic precursor.



Scheme 4

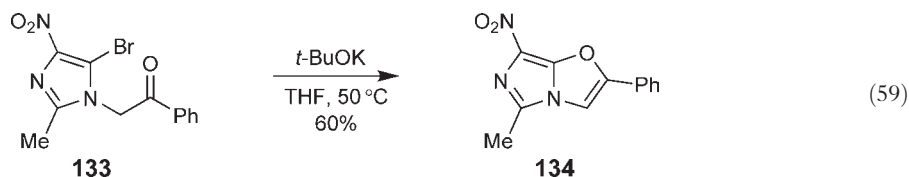
11.04.9.1 (5+0) Syntheses

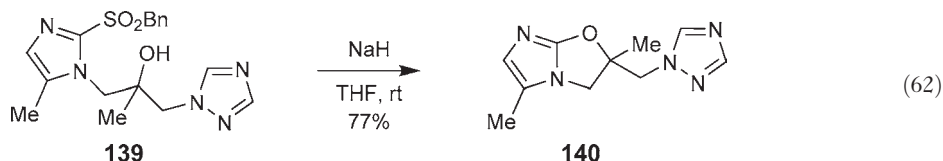
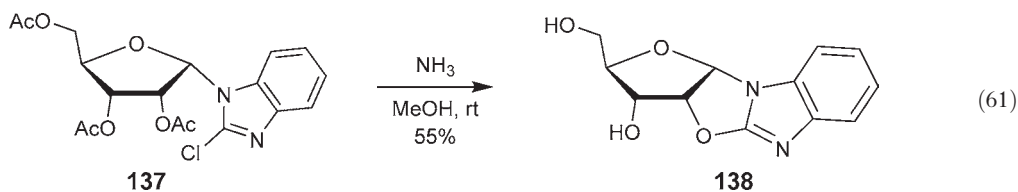
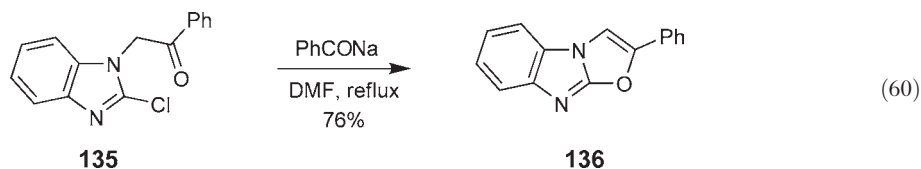
11.04.9.1.1 Type A syntheses

11.04.9.1.1(i) Intramolecular nucleophilic *ipso*-substitutions

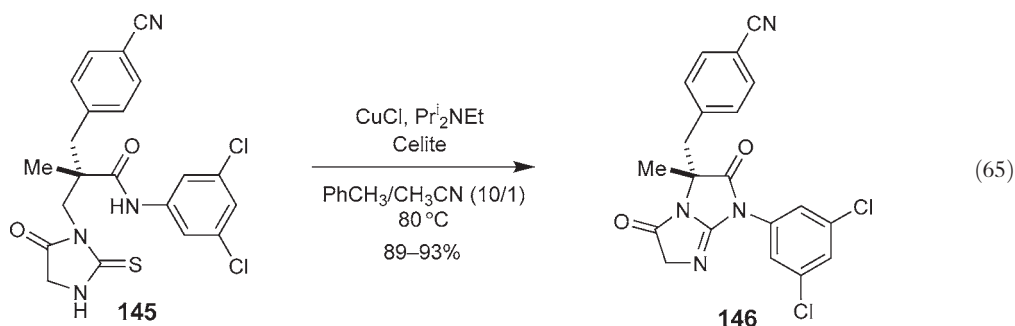
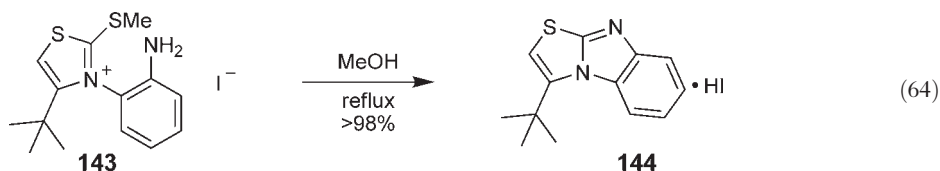
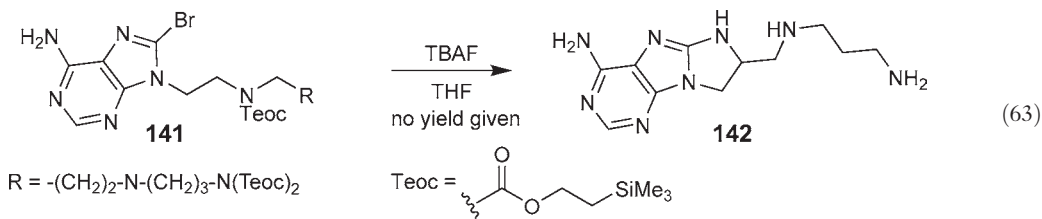
Intramolecular nucleophilic *ipso*-substitution reactions on aromatic compounds have been successfully employed in synthesis for the preparation of 5-5 fused heterobicyclic systems. A range of nucleophiles, including hydroxy, amino, thiol groups, the enolic form of ketones, and their respective anions, were tested and proved to be particularly efficient. Moreover, it turned out that the commonly used halogenides, alkylsulfanyl, and alkylsulfonyl groups are good leaving groups for this transformation. This section is organized according to the nature of the nucleophile.

Oxygen atom as internal nucleophile. Construction of the bicyclic imidazo [2,1-*b*]oxazole **134** can be effected through a two-step procedure involving first reaction of 5-bromo-2-methyl-4-nitroimidazole **133** with phenylacetyl bromide followed by nucleophilic intramolecular displacement of bromine atom by the enolate generated by action of potassium *tert*-butoxide (Equation 59) <1999H(50)1081>. The same methodology was applied with success to the synthesis of oxazolo[3,2-*a*]benzimidazole **136** by heating 2-chloro-1-phenacylbenzimidazole **135** with sodium benzoate in dimethylformamide (DMF) at reflux (Equation 60) <2001CHE1179>. Deprotection of **137** liberates the corresponding free α -nucleoside which undergoes a concomitant cyclization to give the 2,2'-*O*-cyclonucleoside **138** (Equation 61) <1997JME811>. In another case, alkylsulfonyl (SO₂R) groups of 2-alkylsulfonylimidazoles such as **139** showed a great susceptibility to nucleophilic displacement by an alkoxide generating 2,3-dihydro-imidazo[2,1-*b*]oxazoles **140** (Equation 62) <1999S1613, 2002S2691>.

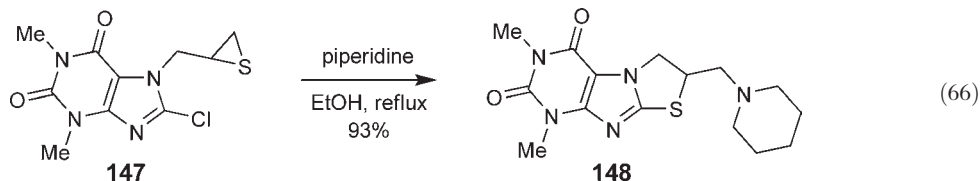




Nitrogen atom as internal nucleophile. In order to extend the scope of this reaction, substrates in which substituted aliphatic and aromatic amines act as nucleophiles were also tested for the preparation of different heteroaromatic nitrogen compounds. Simultaneous deprotection of all the nitrogen atoms of the 8-bromo purine derivative **141** in the presence of tetrabutylammonium fluoride (TBAF) gave rise to cyclization of a transient amide by intramolecular substitution of bromine at C-8 leading to the substituted 2,3-dihydro-1*H*-imidazo[1,2-*e*]purine **142** (Equation 63) <1999BML233>. In another example, preformed thiazolium salts such as **143** easily undergo intramolecular *ipso*-attack of a thiomethyl group in position 2, resulting in free thiazolo[3,2-*a*]benzimidazoles **144** after a subsequent basic treatment (Equation 64) <2005MOL327>. More recently, copper(I) chloride-promoted intramolecular cyclization of thiohydantoin **145** has been described to give bicyclic guanidine derivatives **146** in high yield (Equation 65) <2005TL273>.

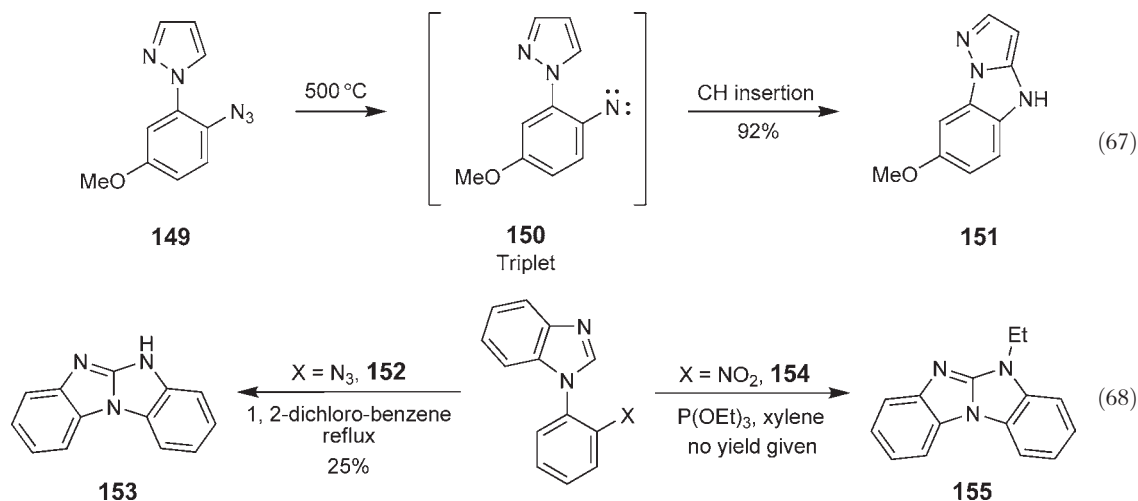


Sulfur atom as internal nucleophile. In this area, it has been shown that the reaction of 8-bromo-1,3-dimethyl-7-(2,3-epithiopropyl)xanthine **147** with a range of aliphatic and aromatic amines generates efficiently 2-amino-substituted 2,3-dihydro-thiazolo[2,3-*f*]xanthine derivatives **148**. The process involves a sequential amine-induced thiirane ring opening followed by thiolate *ipso*-substitution of chlorine atom (Equation 66) <1994PCJ647>.



11.04.9.1.1(ii) Intramolecular CH nitrene insertion

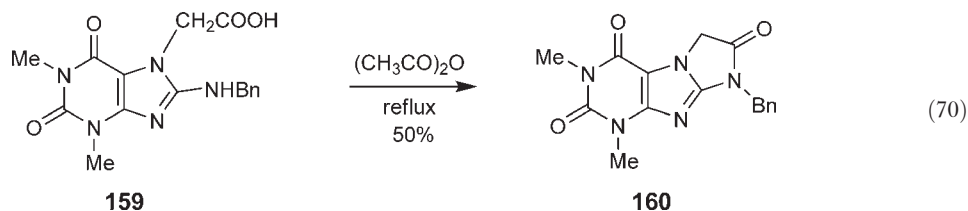
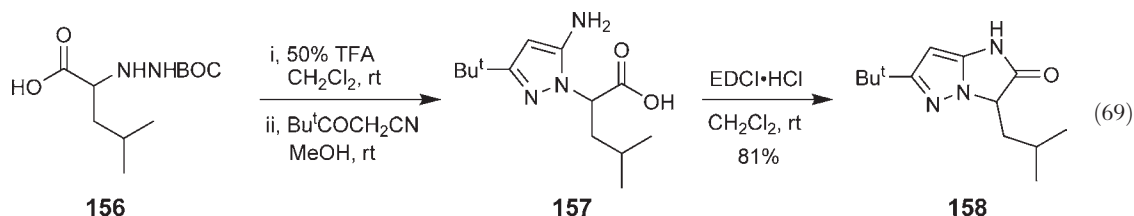
Nitrenes are highly reactive nitrogen intermediates that were usually generated either by thermolysis of azides or phosphorus(III)-mediated deoxygenation of nitro compounds. Their use in synthesis has been already reported for the preparation of nitrogen heterocyclic compounds <B-1984MI95>. As carbenes, they are known to undergo facile intramolecular insertion into C–H bonds. A typical example is the cyclization of 1-(2-azido-5-methoxyphenyl)-pyrazole **149** to 7-methoxypyrazolo [1,5-*a*]benzimidazole **151** in the gas phase using flash vacuum pyrolysis (FVP). Under these conditions, the azide **149** generates a transient triplet nitrene **150** which inserts into the pyrazole 5-CH bond even better since the incipient nitrene is substituted in the *para*-position by an electron-donating group (Equation 67) <1996CC1211>. In the same way, thermolysis of the 1-(2-azidophenyl)imidazole gave the 9*H*-imidazo[1,2-*a*]benzimidazole in 12% yield <1997J(P1)1605>. Tetracyclic benzimidazo[1,2-*a*]benzimidazoles **155** and **153** were prepared by deoxygenation of 1-(2-nitrophenyl)benzoimidazole **154** with triethyl phosphite and thermal decomposition of 1-(2-azidophenyl) benzoimidazole **152**, respectively (Equation 68) <2000PJS168>.



11.04.9.1.2 Type B syntheses

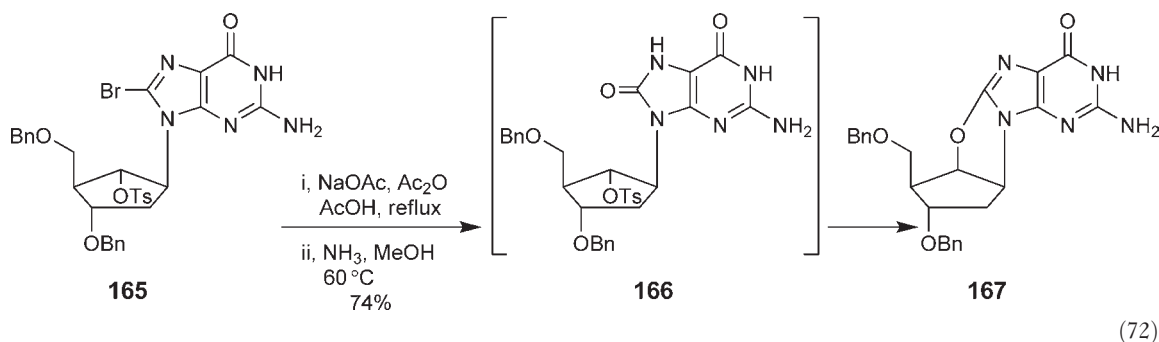
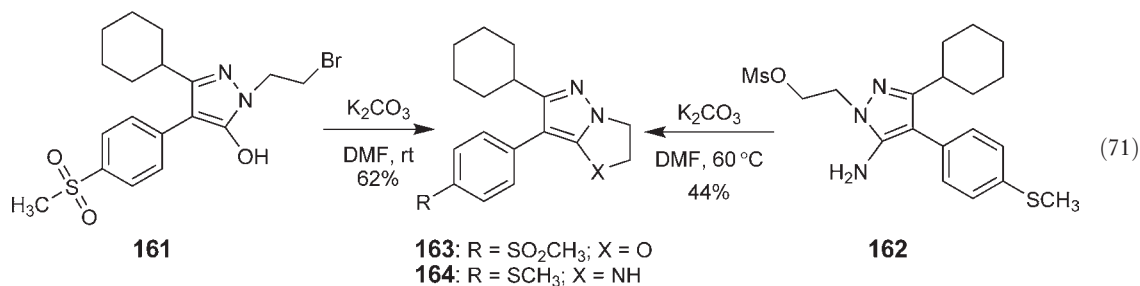
11.04.9.1.2(i) Lactamization involving EDCI- or mixed anhydride-mediated coupling reactions of carboxylic acid derivatives

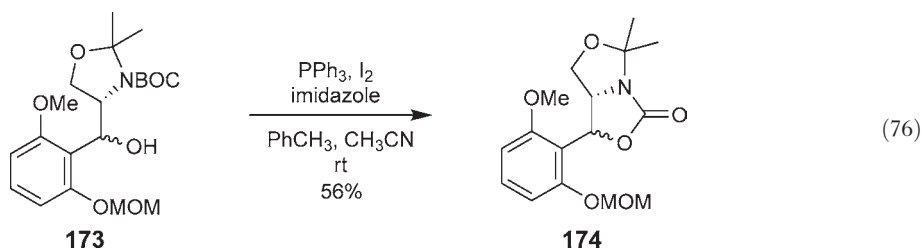
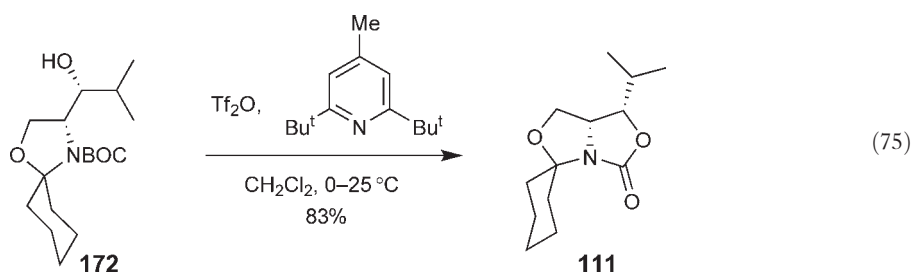
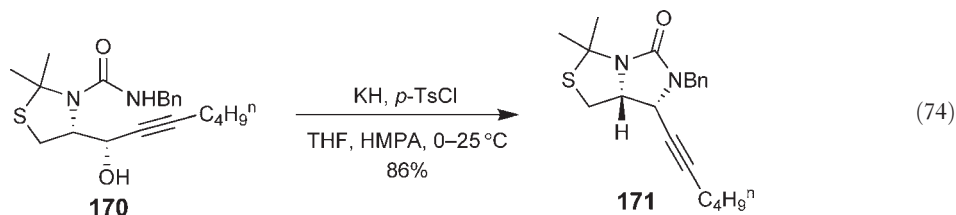
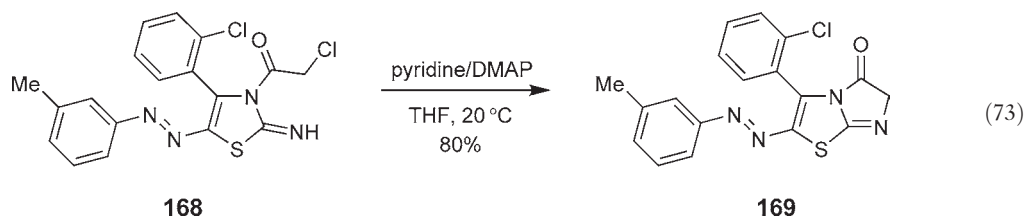
1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI)-assisted intramolecular cyclodehydration of the amino pyrazole **157**, easily prepared from the corresponding *t*-butoxycarbonyl (BOC)-protected α -hydrazino acid **156**, resulted in the formation of imidazo[1,2-*b*]pyrazol-2-one **158** (Equation 69) <2004TL619>. A solid-phase synthesis of the latter involved formation of the requisite 5-aminopyrazole on solid support followed by a tandem cyclization–cleavage of the resin under acidic conditions <2004TL1275>. *N*-8-Benzyl-1,3,6,8-tetrahydro-imidazol-7-on[2,1-*f*]-theophylline **160** was synthesized via cyclization of 8-benzyl-aminotheophylline-7-acetic acid **159** in boiling acetic anhydride (Equation 70) <1999EJM1085, 2002FA697>.



11.04.9.1.2(ii) Intramolecular alkylation of oxygen, nitrogen, or sulfur heteroatom by a suitable alkyl chain substituted with an appropriately leaving group

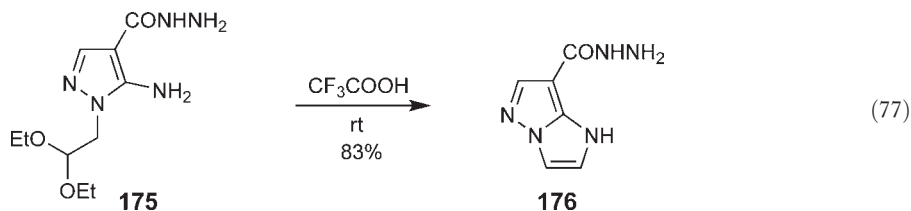
A series of 2,3-dihydro-pyrazolo[5,1-*b*]oxazoles **163** and 2,3-dihydro-imidazo[1,2-*b*]pyrazoles **164** were obtained by cyclization of the corresponding 5-hydroxy- and 5-amino-2,4,5-substituted pyrazoles **161** and **162** through internal nucleophilic displacement of the labile bromide ion or mesylate group by the hydroxyl oxygen or amine nitrogen, respectively (Equation 71) <2004BMC1357>. Conversion of the 8-bromo-6'-*O*-tosyl-2'-deoxyadenosine derivative **165** into the carbocyclic 8,6'-dihydroxyadenosine **167** was achieved by sequential acetolysis and intramolecular substitution of the tosylate group by the transient 8-keto intermediate **166** (Equation 72) <1999J(P1)1833, 2004OBC183>. Base-induced heterocyclization of the 2-chloro-1-(2-imino-thiazol-3-yl)-ethanone-type compound **168** with 4-dimethylaminopyridine (DMAP)/pyridine furnished the related imidazo[2,1-*b*]thiazole **169** (Equation 73) <2002JHC1133>. Selective intramolecular nucleophilic attack of the nitrogen present in **170** on the propargylic tosylate gave rise to the tetrahydro-imidazo[1,5-*c*]thiazol-5-one **171** (Equation 74) <1994JOC5865>, whereas participation of *N*-BOC carbonyl oxygen to cyclization of the alcohols **172** and **173**, converted into transient triflate or iodide, led to the dihydro-oxazolo[3,4-*c*]oxazol-3-ones **111** and **174**, respectively (Equations 75 and 76) <1995TL7031, 1996T11673, 2001TA1689>.

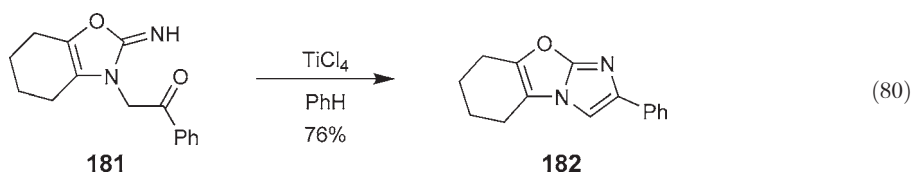
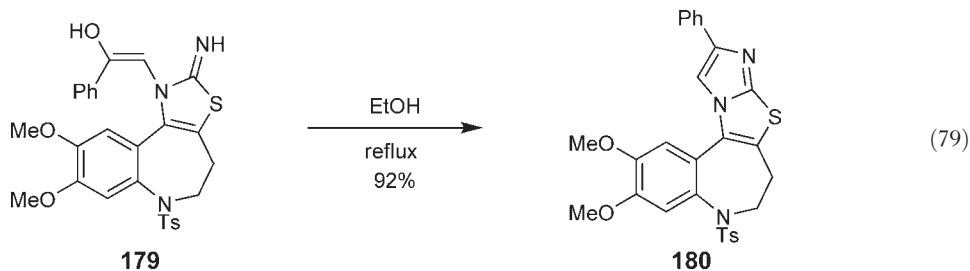
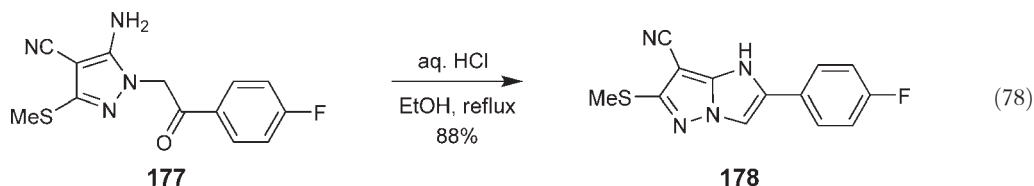




11.04.9.1.2(iii) Intramolecular Mannich-type condensation

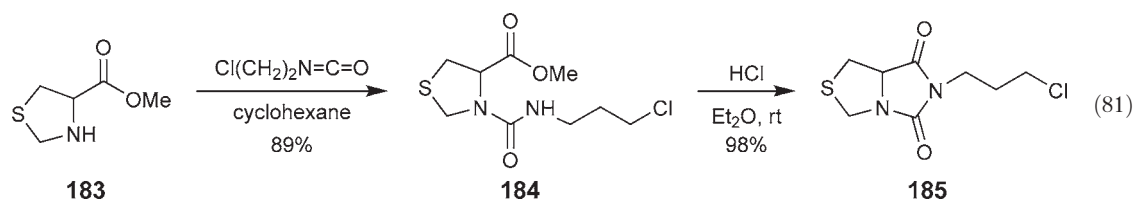
Syntheses in this category involve acid-catalyzed cyclization of heterocyclic amines with carbonyl or acetal side chains followed by dehydration or alcohol elimination, respectively. Classical monosubstituted imidazo [1,2-*b*]-pyrazoles **176** were prepared by ring closure of 1-alkyl-5-aminopyrazole precursors **175** (Equation 77) <1999SC311>, and 3-methylthio-5-amino-4-cyano-1-(aroylmethyl)pyrazoles **177** afforded new trisubstituted adducts **178** (Equation 78) <2005JHC209, 2005SC493>. In a similar type of reaction, *N*-substituted 2-iminothiazole derivatives **179** can be transformed into imidazo[2,1-*b*]-thiazoles **180** (Equation 79) <2001HCO33, 2001HCO535, 2003CHE965, 2004HCO25, 2005BML1561> and can also be associated with intermolecular Mannich reactions in multicomponent versions <1997JHC1763>. Titanium(IV) chloride-assisted cyclization of suitable substrates derived from 2-aminooxazoles **181** provided a variety of imidazo[2,1-*b*]oxazoles **182** (Equation 80) <1997JHC589>.





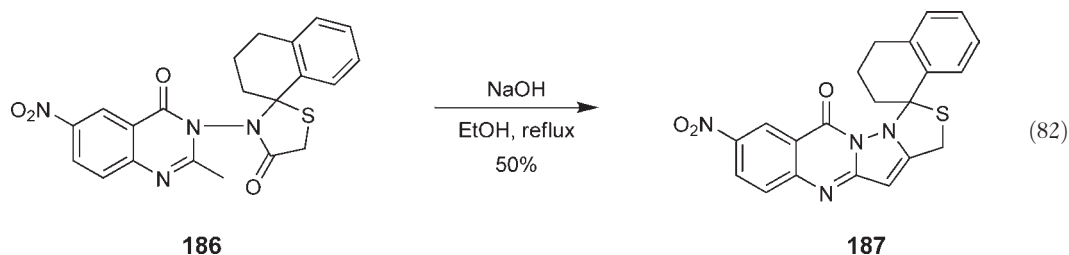
11.04.9.1.2(iv) Maleimidation via acid-catalyzed amide cyclization

An access to *N*-substituted 4,6-dioxo-imidazo[3,4-*c*]thiazoles **185** was developed considering first the reaction of 2-chloroethylisocyanate with methyl thiazolidine 4-carboxylate **183** that generated the ureide **184**. Cyclization of the imidazole ring occurred in acidic medium via an addition–elimination mechanism and delivered the imidazothiazole **185** (Equation 81) <2001MI117>.



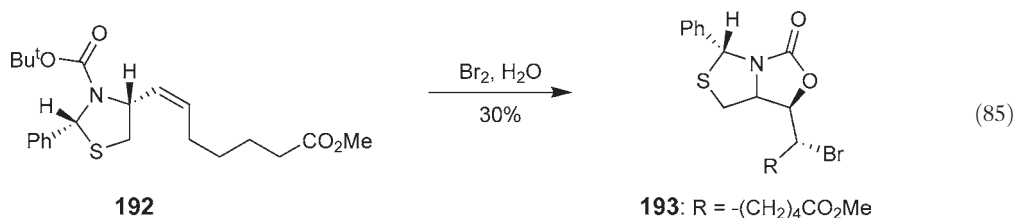
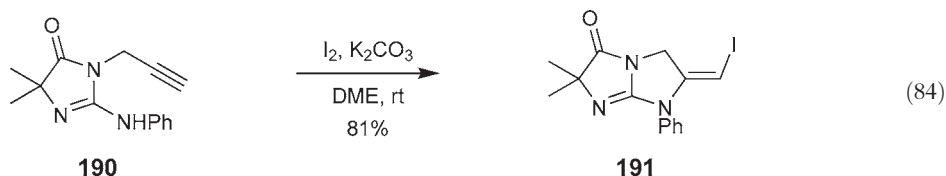
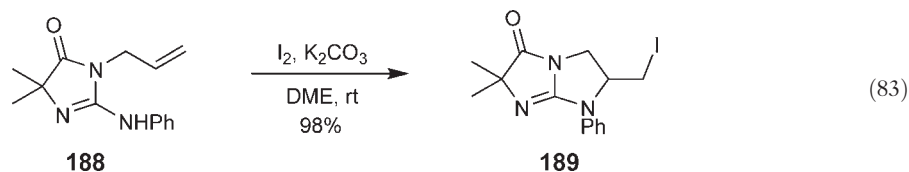
11.04.9.1.2(v) Base-catalyzed annulation

In another approach, the 3-[3'-(2'-spirothiazolidin-4'-one)]quinazolin-4-one derivative **186** in the presence of sodium hydroxide in ethanol undergoes intramolecular cyclocondensation with the formation of the spirothiazolopyrazoloquinazolinone **187** in moderate yield (Equation 82) <2001PS1>.



11.04.9.1.2(vi) Iodo- or bromocyclization

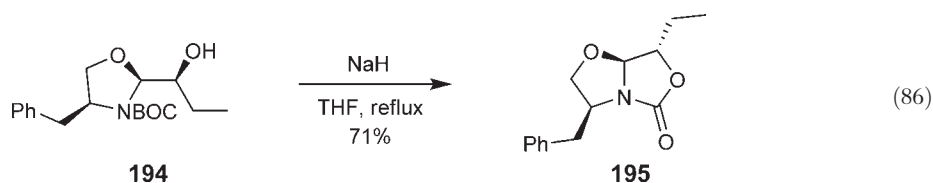
Methodologies based on the electrophilic halocyclization of unsaturated substrates were also used for the construction of these bicyclic 5-5 systems. As an example, regio- and stereoselective alkene and alkyne iodocyclizations of the respective 3-(alk-2-enyl)- and 3-alkynyl-2-(substituted amino)-1-imidazolin-4-ones **188** and **190** gave the corresponding imidazo[1,2-*a*]imidazol-3-one units **189** and **191** (Equations 83 and 84) <1996T2827, 1996T6581>. In a similar way, bromination of the thiazoline **192** resulted in the formation of the cyclic urethane **193** although the yield was considerably lower (Equation 85) <1995JOC321>.

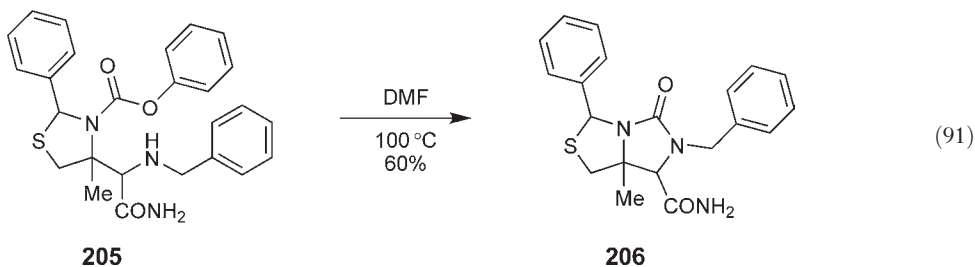
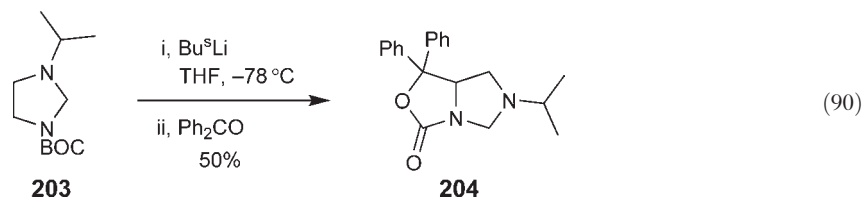
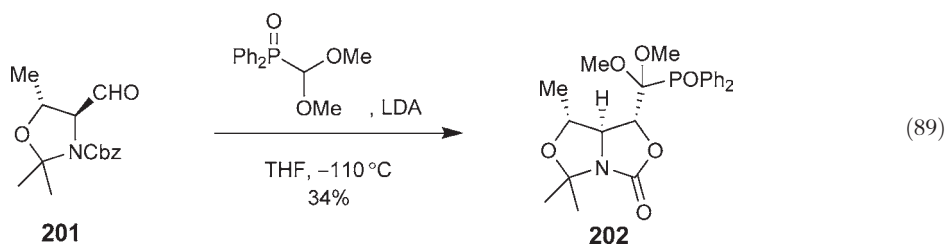
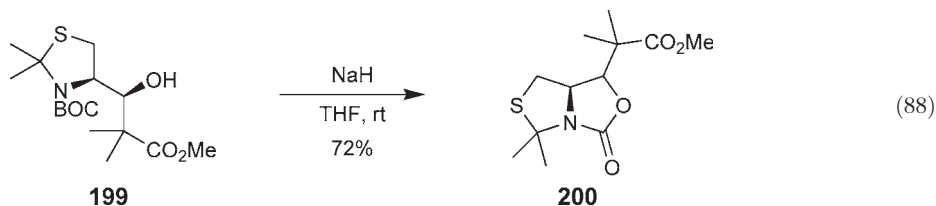
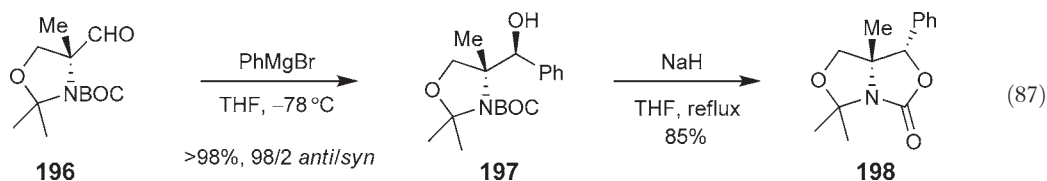


11.04.9.1.3 Type C syntheses

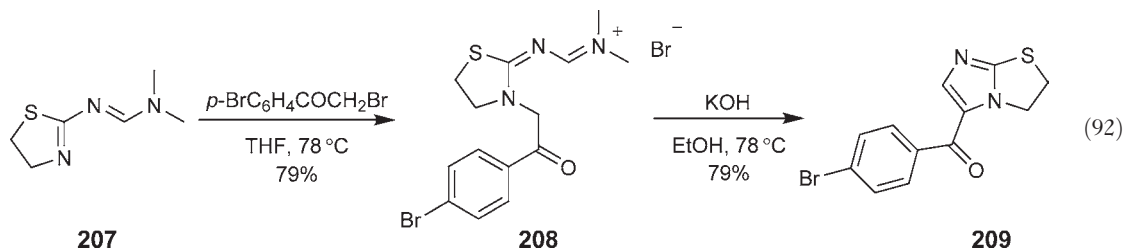
11.04.9.1.3(i) Reactivity of BOC and related protecting groups

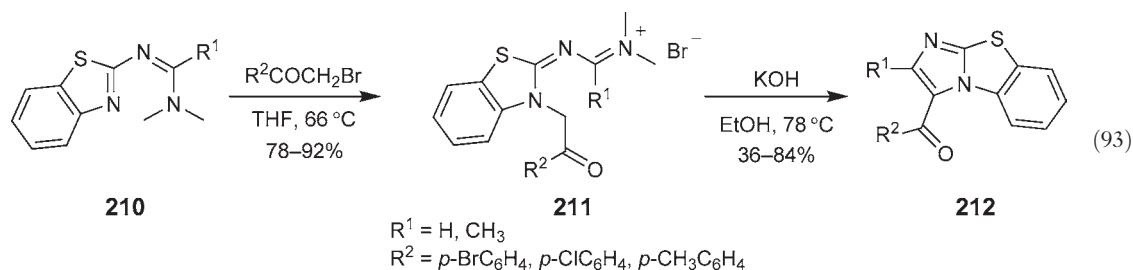
As reported in a recent review, one of the important properties of the *N*-BOC group is its capacity to react intramolecularly with nucleophiles such as hydroxy and amino groups generating 2-oxazolidinone and 2-imidazolidinone fragments, respectively <2002T2701>. To illustrate, treatment of the *N*-BOC α -hydroxy oxazolidine **194** and the α -methylated Garner's aldehyde addition adduct **197**, with sodium hydride as the base, liberated the tetrahydro-1,5-dioxo-3a-aza-pentalen-4-one **195** (Equation 86) <2001T5393> and the dihydro-oxazolo[3,4-*c*]oxazol-3-one **198** (Equation 87) <2000TA2195, 2003TA399, 2004TA719>. In a similar type of reaction, the dihydro-thiazolo[3,4-*c*]oxazol-3-one **200** was obtained from the β -hydroxy-carboxylate precursor **199** (Equation 88) <1999T10283>. A one-step process involving diastereoselective addition of lithiated phosphane oxide to threonine-derived aldehyde **201** gave the transient alkoxy anion that cyclized to the bicyclic oxazolidinone **202** (Equation 89) <2004EJO1149>. α -Lithiation of the imidazoline **203** with Bu^sLi followed by alkylation with benzophenone afforded the tetrahydro-imidazo[1,5-*c*]oxazol-3-one derivative **204** (Equation 90) <2003OBC1532>. A synthesis of the tetrahydro-imidazo[1,5-*c*]thiazol-5-one-type compound **206** from the β -amino-thiazolidine **205**, based on the intramolecular displacement of the phenoxide anion by the amino group, was also reported (Equation 91) <2003S2311>.



11.04.9.1.3(ii) Annulation of *N*-alkyl amidiniums

1,3-Diazadienes have been used in organic synthesis for the preparation of various heterocyclic compounds. Alkylation of 1,3-diazadienes **207** and the benz-fused analog **210** at the nitrogen atom by aryl acyl bromides provided the *N*-alkyl amidinium bromides **208** and **211**, which underwent annulation to the 2,3-dihydro-imidazo[2,1-*b*]thiazole **209** and imidazo[2,1-*b*]benzothiazoles **212**, respectively (Equations 92 and 93) <2001S741, 2002J(P1)741>.

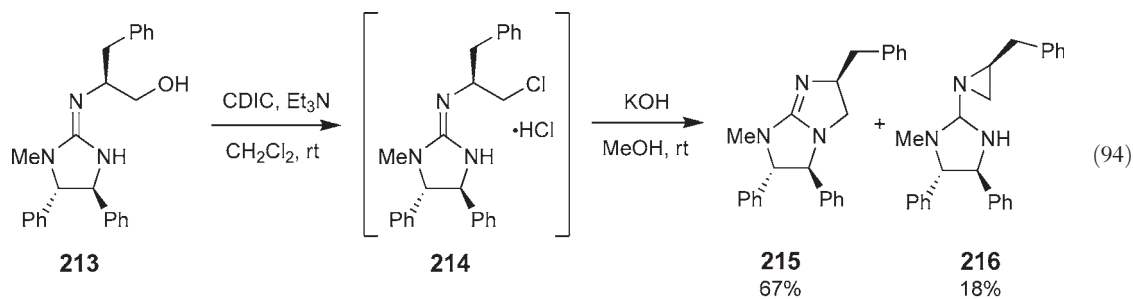




11.04.9.1.4 Type D syntheses

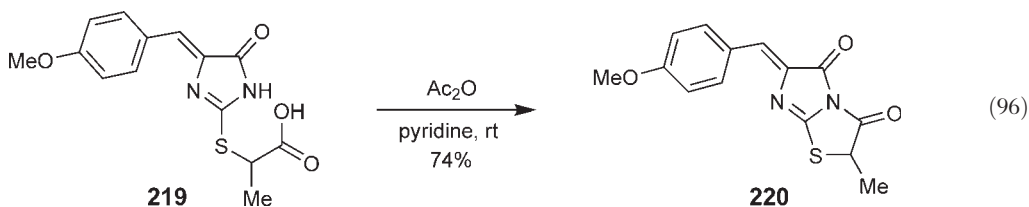
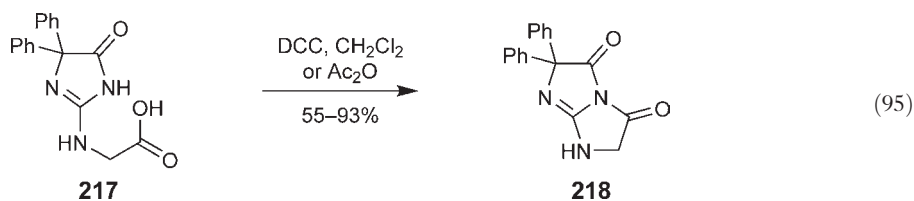
11.04.9.1.4(i) Intramolecular alkylation of the nitrogen bridgehead atom by an alkyl chloride

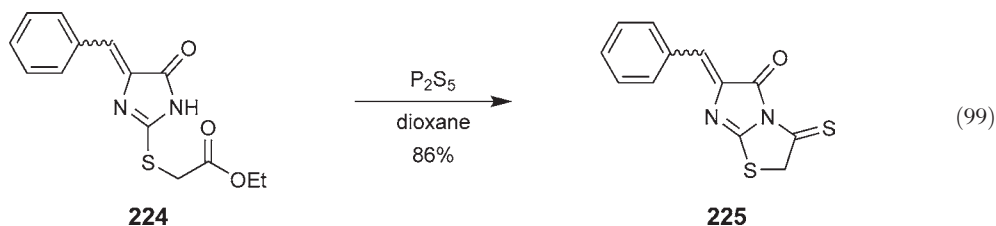
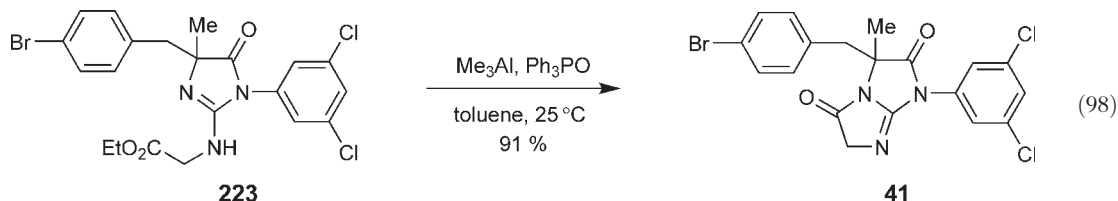
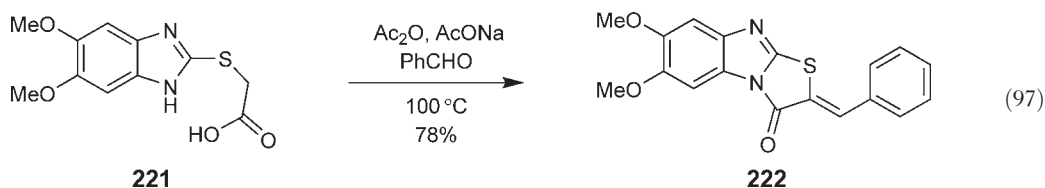
The 2,3,5,6-tetrahydro-imidazo[1,2-*a*]imidazole system **215**, a bicyclic guanidine, was prepared by treatment of the 2-(2-hydroxyethylimino)imidazolidine **213** with 2-chloro-1,3-dimethylimidazolium chloride (CDIC). The resulting chlorine-substituted product **214** evolved to the desired bicyclic guanidine **215** together with the aziridine intermediate **216** via a smooth cyclization reaction under basic conditions (Equation 94) <2000JOC7779>.



11.04.9.1.4(ii) Lactamization induced by DCC, mixed anhydride coupling reactions, or a modified Weinreb's procedure

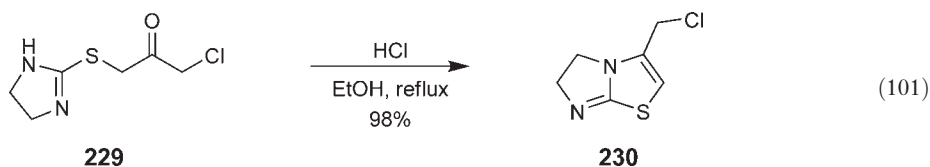
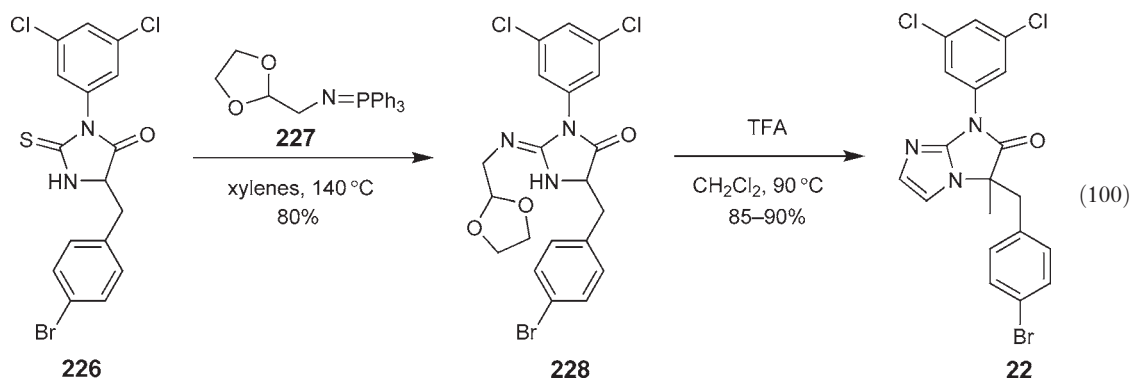
Ring closure of the *N*-(5,5-diphenyl-4-oxo-2-imidazolyl)glycine **217** to the 6,6-diphenyl-1,6-dihydro-imidazo[1,2-*a*]imidazole-3,5-dione **218** (Equation 95) and conversion of the 2-thiolacetic acid open chain compounds **219** and **221** into the respective imidazo[2,1-*b*]thiazole-3,5-dione **220** and benzo[4,5]imidazo[2,1-*b*]thiazol-3-one **222** was carried out by activation of their acid functions with *N,N'*-dicyclohexylcarbodiimide (DCC) or acetic anhydride (Equations 96 and 97) <1995AP517, 2001JST73, 1997AP85, 2000PHA429>. From ester derivatives, a direct cyclization of **223** to the amide **41** could be achieved by action of AlMe₃ and Ph₃PO using a modified Weinreb's procedure (Equation 98) <2003TL6509>. Cyclization of the 5-benzylidene-2-carbomethoxythiohydantoin **224** in the presence of P₂S₅ afforded the 4-benzylidene-imidazo[2,1-*b*]thiazole-2-thione-5-one **225** (Equation 99) <2004PS185>.

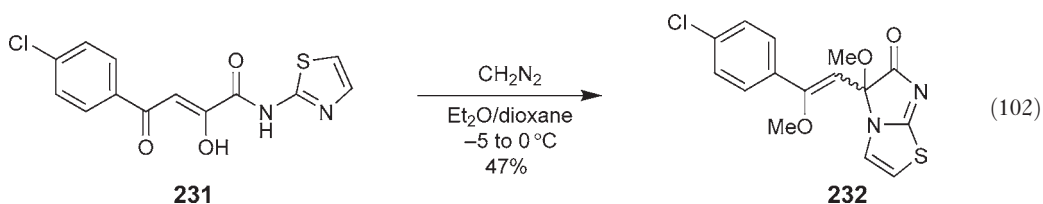




11.04.9.1.4(iii) Intramolecular Mannich-type condensation

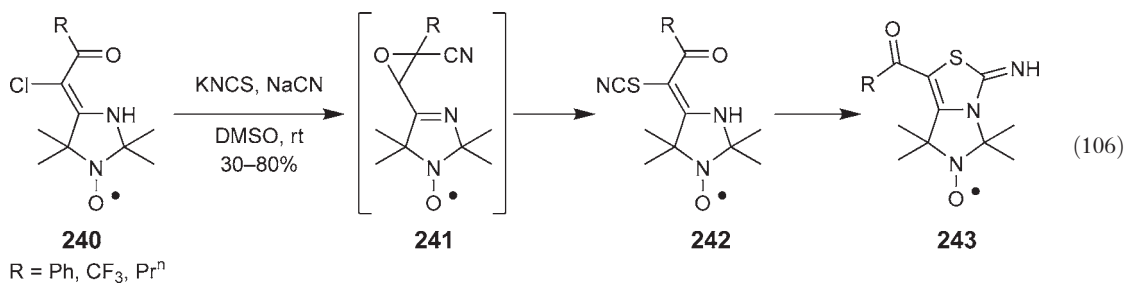
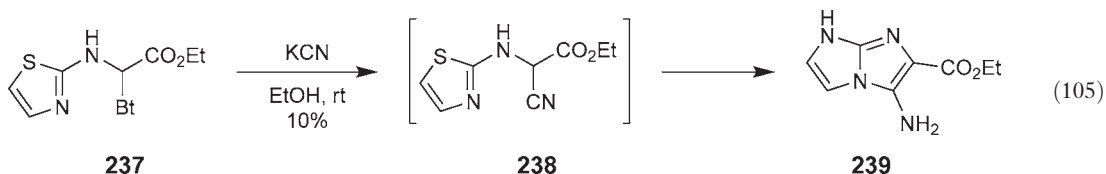
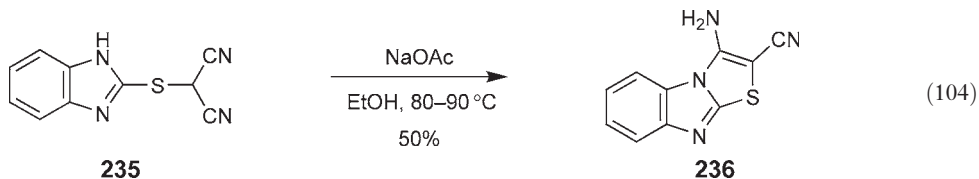
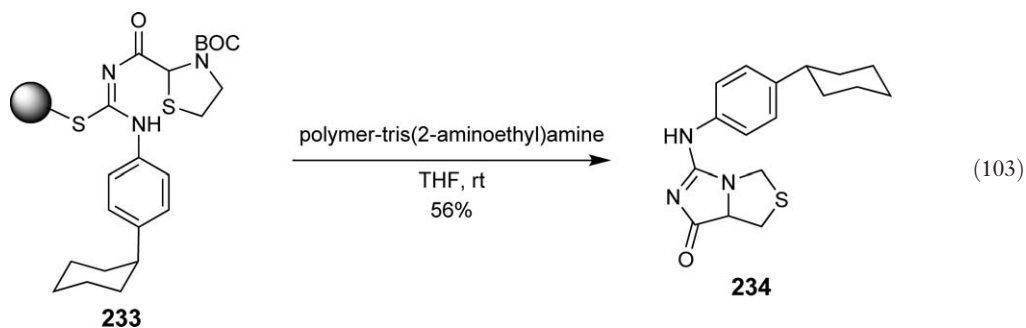
Syntheses of different bicyclic compounds using a Mannich-type condensation are summarized here. Reaction of the thiohydantoin **226** with the aza-phosphonium ylide **227** produced the guanidine derivative **228**. This latter compound was cyclized to the 1,3,3-trisubstituted 1*H*-imidazo [1,2-*a*]imidazol-2-one **22** by treatment with TFA (Equation 100) <2004JME5356>. For the synthesis of 5,6-dihydro-imidazo[2,1-*b*]thiazoles such as compound **230**, heterocyclization of the intermediate 1-chloro-3-(4,5-dihydro-1*H*-imidazol-2-ylsulfanyl)-2-propanone **229** in refluxing EtOH with a catalytic amount of HCl provided a suitable approach (Equation 101) <1995APF261, 2005RJO152>. Intramolecular cyclization of 2-thiazolylamides of 2-aryl-2-hydroxy-2-oxo-2-butenic acids **231** in the presence of diazomethane afforded bicyclic 5-(2-aryl-2-methoxyethenyl)-5-methoxy-6-oxo-5,6-dihydro-imidazole[2,1-*b*]thiazoles **232** in moderate yields (Equation 102) <2002CHE757>.





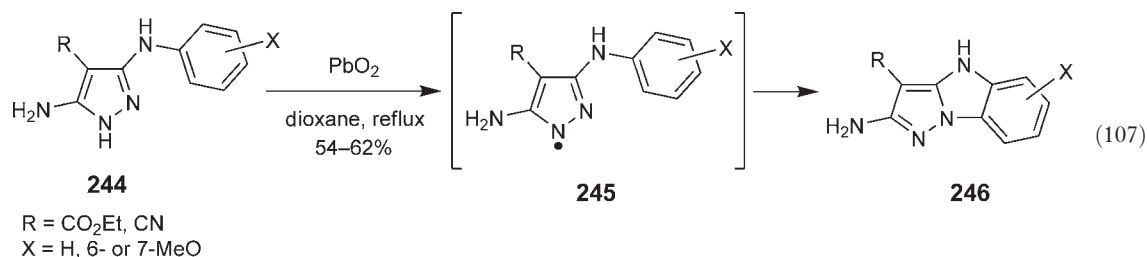
11.04.9.1.4(iv) Nucleophilic attack of amino groups to electrophilic tetravalent functions

A method for solid-phase synthesis of the 5-amino-1,7*a*-dihydro-imidazo[1,5-*c*]thiazol-7-one **234** was developed. Upon treatment with polymer-supported polyamine, the BOC group was easily deprotected and the free amine of **233** attacked the isothiourea moiety and liberated **234** from the solid support (Equation 103) <2002TL4463>. A new thiazolo[3,2-*a*]benzimidazole derivative **236** was synthesized by intramolecular addition of benzoimidazole to malonitrile (Equation 104), and in the same way, the α -benzotriazolyl- α -amidino ester **237** placed in the presence of potassium cyanide in the presence of sodium cyanate yielded the corresponding amino imidazo[2,1-*b*]thiazole **239** (Equation 105) <1996JRM116, 1999PS101, 1996TL1787>. Chloro-substituted enaminones **240** derived from imidazolidine nitroxides when treated with potassium isothiocyanate gave the substitution adducts **242**, which cyclized to 6,7-dihydro-imidazo[1,5-*c*]thiazole compounds **243** (Equation 106) <2003EJO3599>.



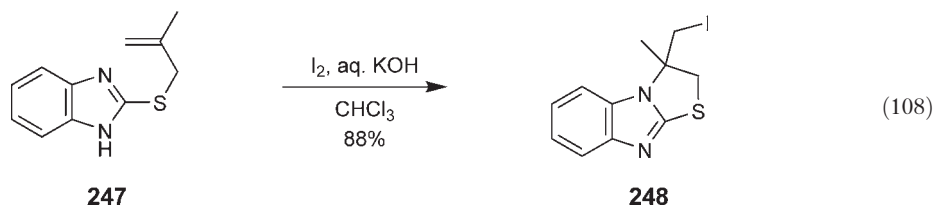
11.04.9.1.4(v) Oxidative cyclization

Substituted anilinopyrazoles **244** were oxidized by lead(IV) to give intermediate pyrazolyl radicals **245**, which underwent cyclization reaction with the formation of pyrazolo[1,5-*a*]benzimidazoles **246** (Equation 107) <1994CB1729>.



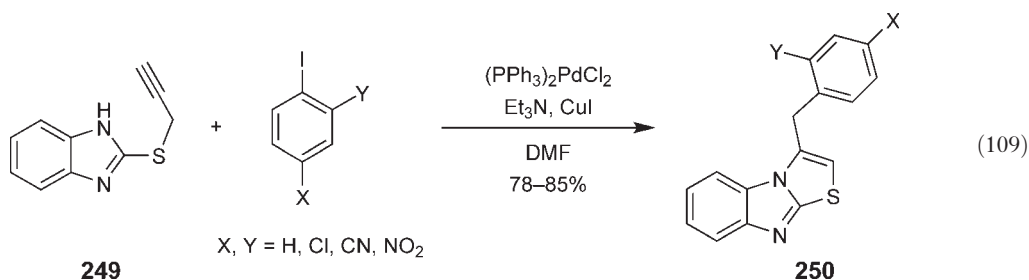
11.04.9.1.4(vi) Halocyclization

The iodocyclization of 2-methallylmercapto benzimidazole **247** proceeded in a regioselective manner by treatment with iodine and aqueous KOH in chloroform to give the dihydro-thiazolo[3,2-*a*]benzimidazole **248** (Equation 108) <1999RJ0730>.



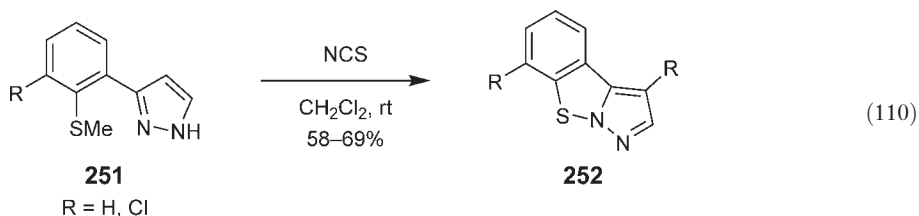
11.04.9.1.4(vii) Palladium-copper-catalyzed heterocyclization

A methodology for the synthesis of substituted thiazolo[3,2-*a*]benzimidazoles **250** from 2-propargylmercapto benzimidazole **249** was developed based on a tandem Sonogashira cross-coupling with iodoaryls and a subsequent exocyclic heterocyclization (Equation 109) <2004TL5747>.



11.04.9.1.4(viii) Cyclization induced by the intermediate formation of a sulfonium ion

Pyrazolo[1,5-*b*]benzothiazoles **252** were prepared from 3(5)-[2'-methyl-thiophenyl]pyrazoles **251** and *N*-chlorosuccinimide. The ring closure may involve a sequential nucleophilic heteroaromatic nitrogen displacement of a sulfonium chlorine atom followed by dealkylation of the resulting sulfonium salt to form the sulfenylimine moiety (Equation 110) <1996H(43)221>.

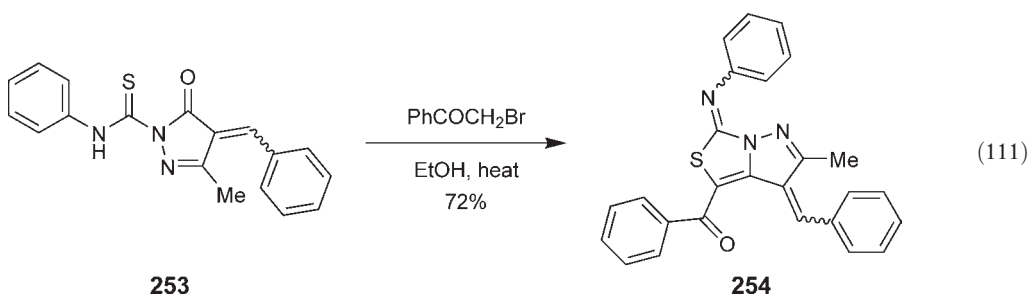


11.04.9.2 (4+1) Syntheses

11.04.9.2.1 Type AB syntheses

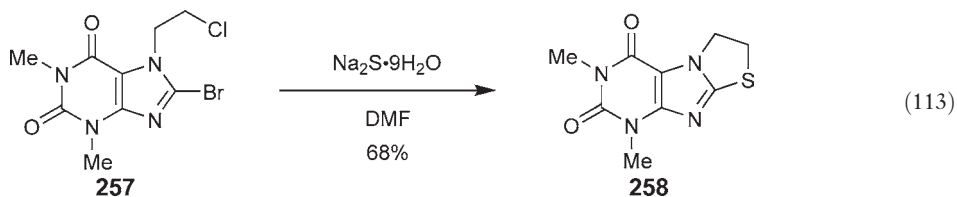
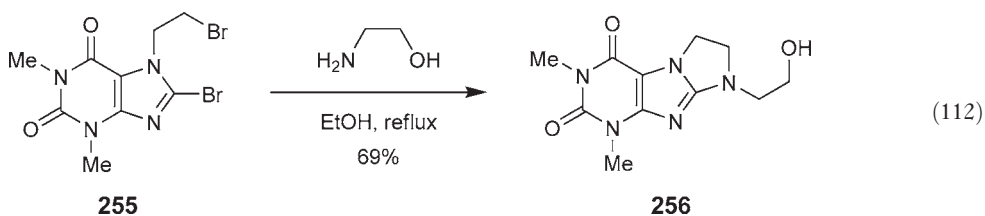
11.04.9.2.1(i) Cyclization with α -haloketones

Syntheses in this category consist of intermolecular thioalkylation of 5-oxo-4,5-dihydro-pyrazole-1-carbothioic acid phenyl amides **253** followed by intramolecular aldol condensation to give substituted pyrazolothiazole-type compounds **254** (Equation 111) <1998PS119>.



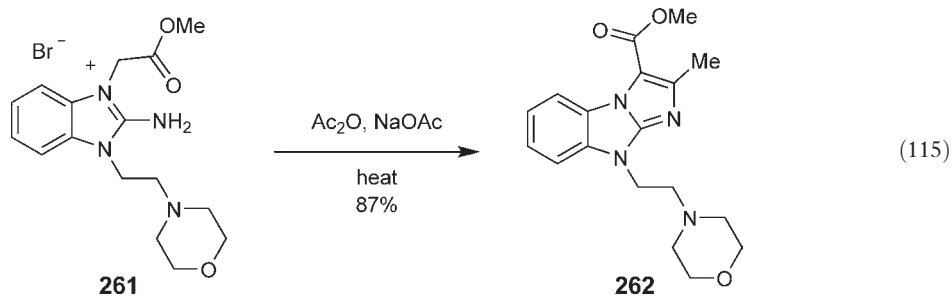
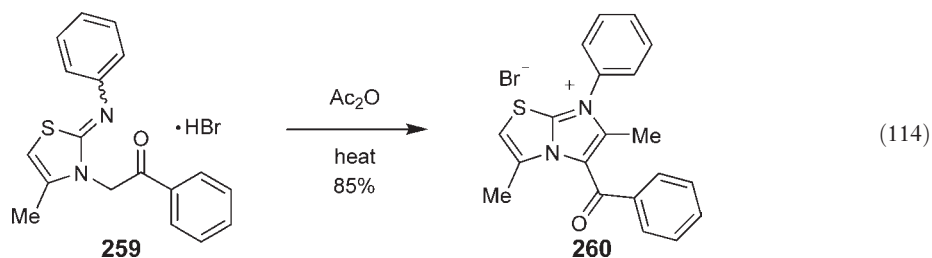
11.04.9.2.1(ii) Double substitution reaction by a primary amine or a sulfide

8 β -Hydroxyethyl-1,3,6,7-tetrahydro-(8*H*)-imidazo[2,1-*f*]theophylline **256** was prepared by condensation of 7 β -bromoethyl-8-bromotheophylline **255** with 2-aminoethanol (Equation 112) <1999EJM1085>. Based on this strategy, a rapid access to 6,7-dihydro-1*H*-thiazolo [2,3-*f*]purine-2,4-diones **258** was also described as in Equation (113) <1996PCJ194>.



11.04.9.2.2 Type BC syntheses

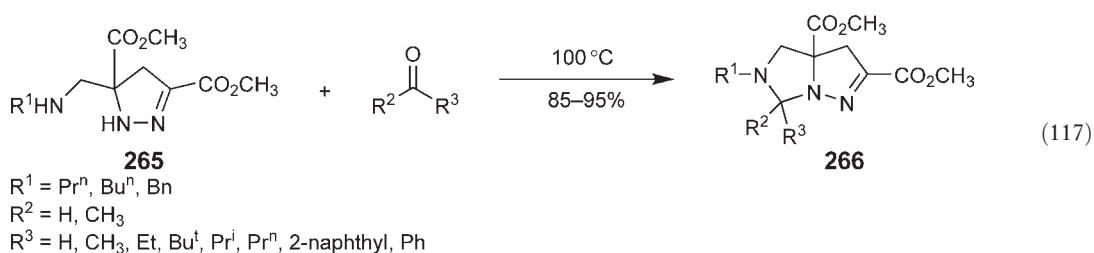
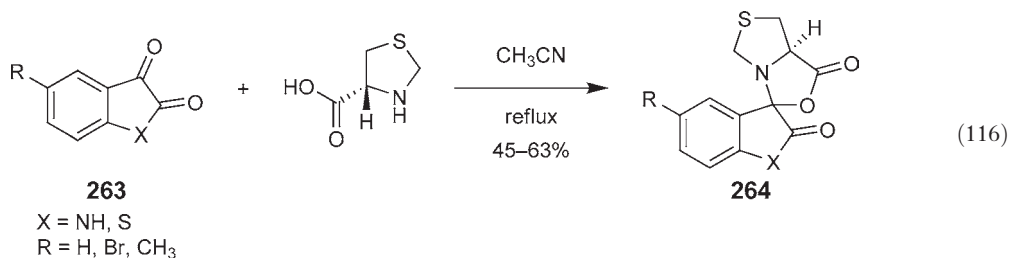
Acetic anhydride-promoted ring-closure reaction of 2-phenylimino-thiazoles **259** and 2-amino-benzoimidazolium salts **261** give the corresponding imidazo[2,1-*b*]thiazolium **260** and imidazo[1,2-*a*]benzimidazole **262** compounds (Equations 114 and 115) <1997CHE728, 1999PCJ361>. A similar cyclocondensation was reported for the elaboration of pyrazolo [1,5-*a*]benzimidazoles <2004RJO221>.



11.04.9.2.3 Type CD syntheses

11.04.9.2.3(i) Mannich condensation with ketones and aldehydes

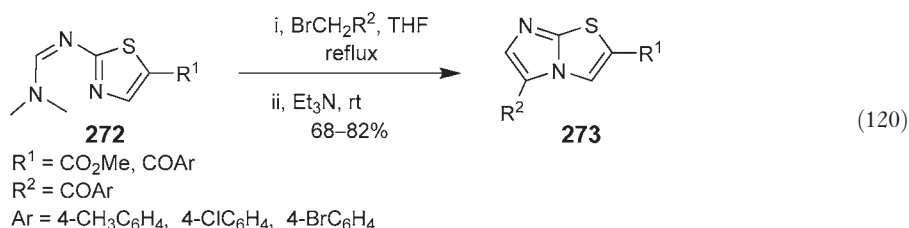
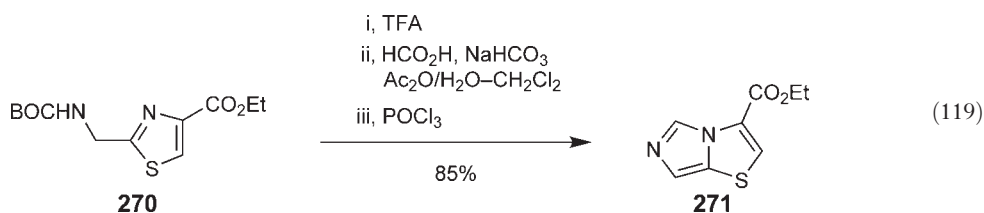
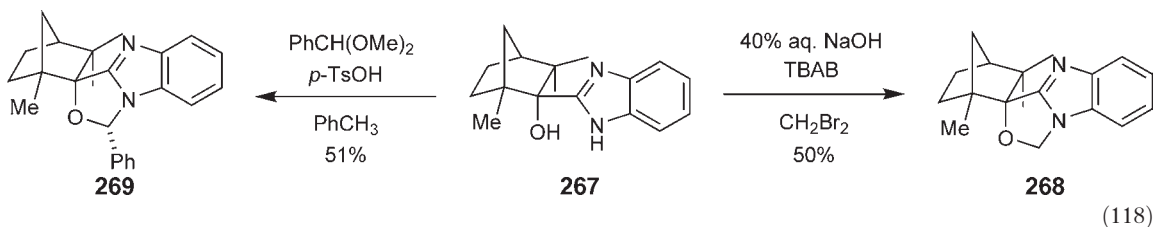
Reaction of isatin or thioisatin **263** with (*R*)-(-)-thiaproline afforded thiazolo-oxazolidinones **264** as precursor of azomethine ylides, obtained by decarboxylation, for 1,3-dipolar cycloadditions (Equation 116) <2002SC435, 2004PS2549>. Condensation of 5-(alkylamino)methyl-2-pyrazolines **265** with ketones or aldehydes led to tetrahydro-imidazo[1,5-*b*]pyrazoles **266** (Equation 117) <1998JCCS375>.



11.04.9.2.3(ii) Condensation with methylene and others CH equivalents

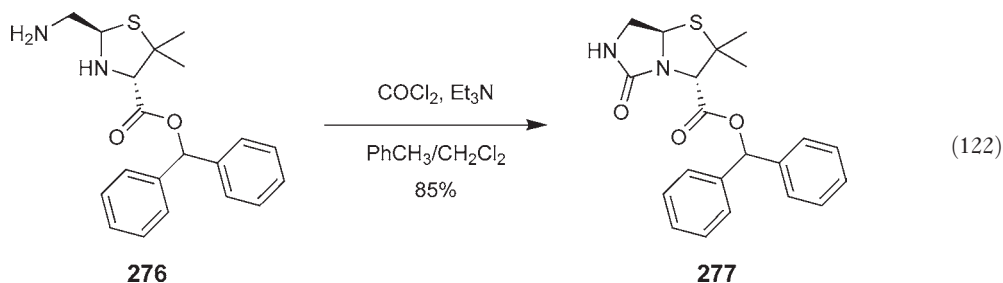
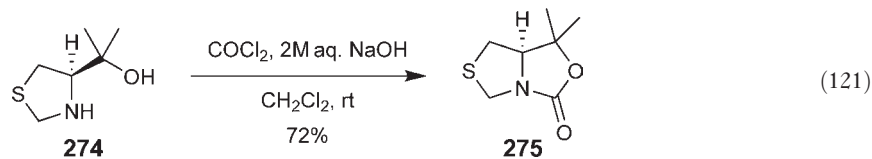
Chiral hydroxy benzimidazole **267** was dialkylated with dibromomethane or benzaldehyde dimethyl acetal to form benzo[4,5]imidazo[1,2-*c*]oxazoles **268** and **269** (Equation 118) <1997TA1491, 1998TA2245>. After removal of the BOC group and formylation of the liberated amine, formylaminomethylthiazole cyclized in phosphoryl chloride to

afford ethyl imidazo[5,1-*b*]thiazole **271** (Equation 119) <2003BMC3475>. Also, reaction of amidines **272** with α -carbonylated bromides followed by treatment with triethylamine gave imidazo[2,1-*b*]thiazoles **273** (Equation 120) <2003JOC4912>.



11.04.9.2.3(iii) Condensation with phosgene

(*R*)-Cysteine-derived thiazolidine alcohols **274** and penicillin-derived thiazolidine amines **276** reacted with phosgene to liberate dihydro-thiazolo[3,4-*c*]oxazol-3-ones **275** and tetrahydro-imidazo[5,1-*b*]thiazol-5-ones **277**, respectively (Equations 121 and 122) <1995T3015, 1995AP81>. An example with (*R*)-valine was also reported <2000TA2093>.

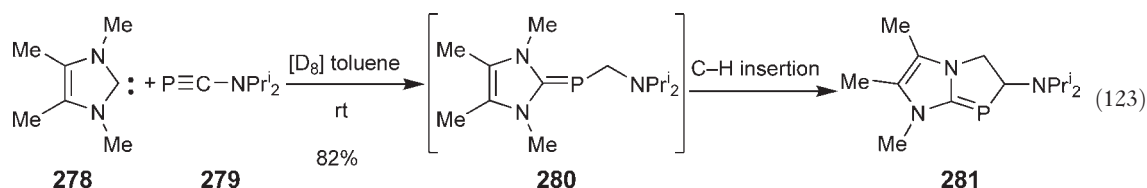


11.04.9.3 (3+2) Syntheses

11.04.9.3.1 Type AC syntheses

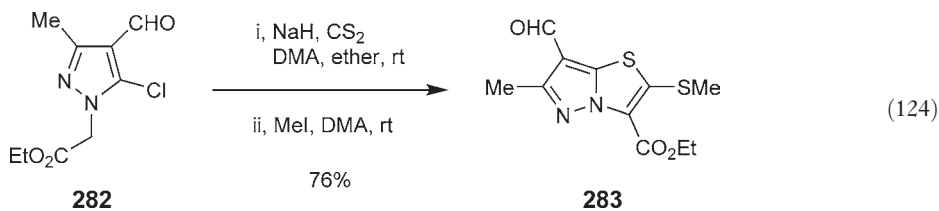
11.04.9.3.1(i) Annelation via carbene insertion

By treating the soft *N*-heterocyclic carbene 1,3,4,5-tetramethylimidazol-2-ylidene **278** with an electron-rich di(isopropyl)amino-phosphaalkyne **279**, the bicyclic azaphospholene **281** was formed in almost quantitative yield via a P–C_{carbene} bond formation **280** and C–H insertion (Equation 123) <2001AGE3144>.



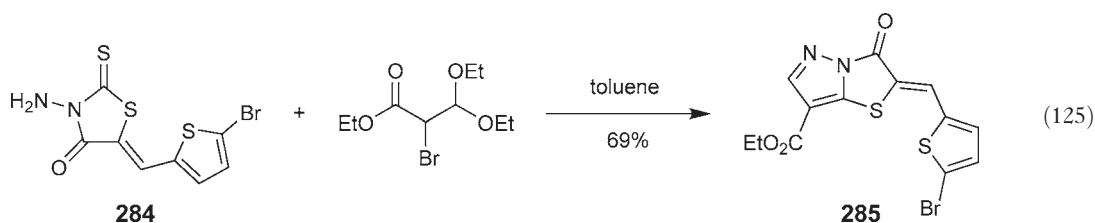
11.04.9.3.1(ii) Condensation to carbon disulfide

A tandem reaction between ethyl 1-pyrazolacetate **282**, carbon sulfide, and iodomethane was developed for the preparation of pyrazolo[5,1-*b*]thiazole derivatives **283** (Equation 124) <2000SC763>.



11.04.9.3.1(iii) Tandem condensation–sulfur extrusion reaction

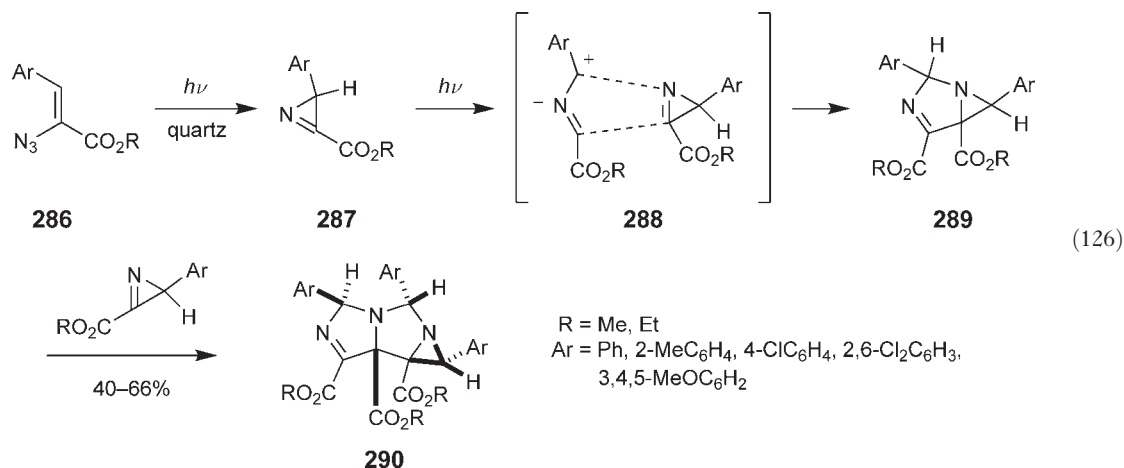
3-Aminorhodanines **284** reacted with ethyl 2-bromo-3,3-diethoxypropionate to provide 2,3-dihydro-pyrazolo[5,1-*b*]thiazoles **285**. The mechanism proposed for the cyclization involved via a sequential condensation–sulfur extrusion reaction (Equation 125) <1994JHC1719>.



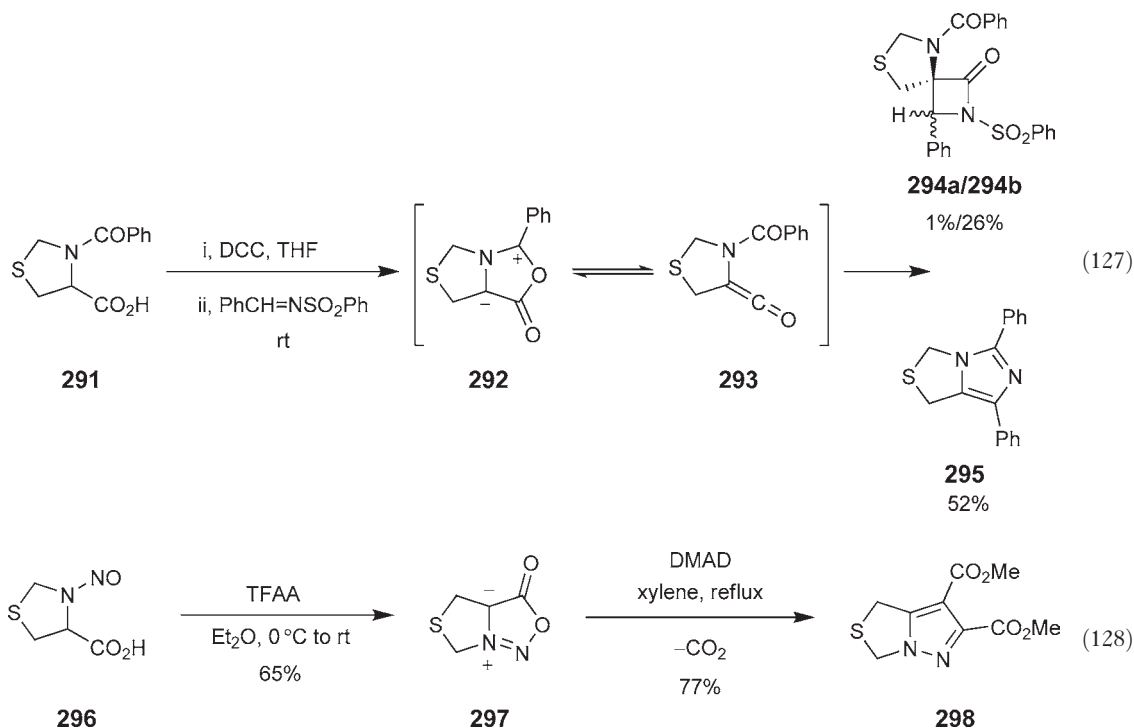
11.04.9.3.1(iv) 1,3-Dipolar cycloadditions

Other approaches including 1,3-dipolar cycloadditions of azomethine ylides or nitroxides to alkene or alkyne dipolarophiles have been applied to the synthesis of these ring systems.

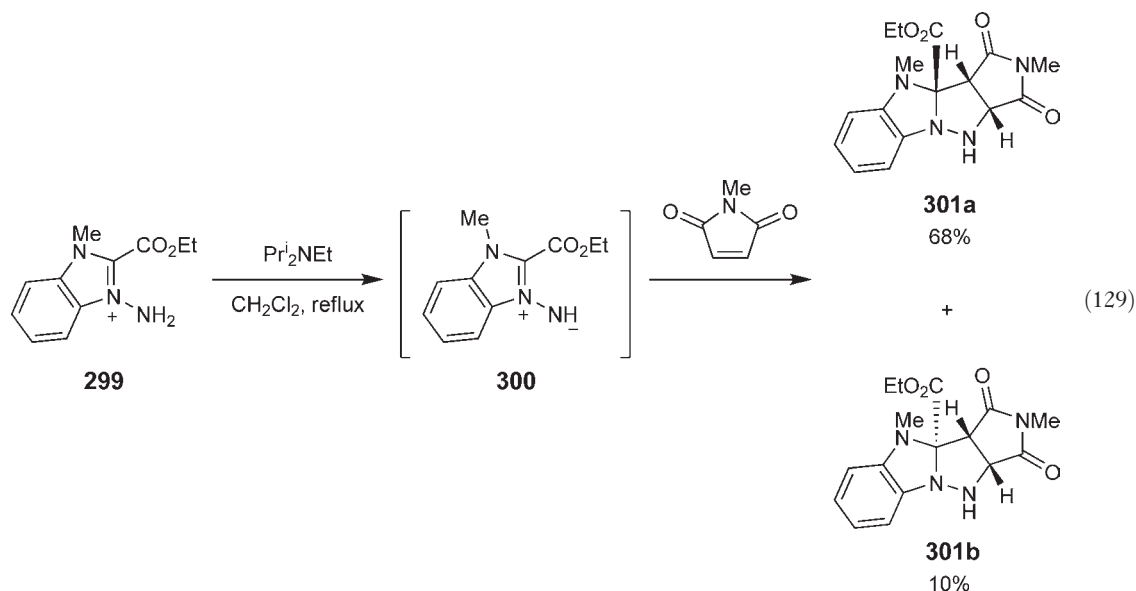
Intermolecular 1,3-dipolar cycloaddition of azomethine ylide, münchnones, and azolium N-aminide intermediates. Azide **286** undergoes conversion into azirine **287** and photoactivated azirine ring opening by C–C bond cleavage to give azomethine ylide **288** via a well-documented transformation. [3+2] cyclization of this 1,3-dipole to another molecule of azirine generated the nonisolated dimers **289**, which underwent a photo-ring-opening and cycloaddition to a second molecule of **290** to yield the trimer 2,3,5,7a-tetrahydro-imidazo [1,5-*c*]imidazoles **287** (Equation 126) <1986J(P1)1119>. A reinvestigation of this reaction was more recently reported <1998T9837>.



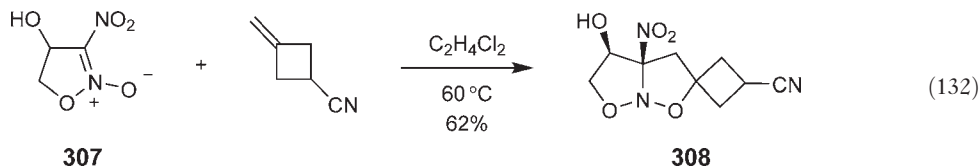
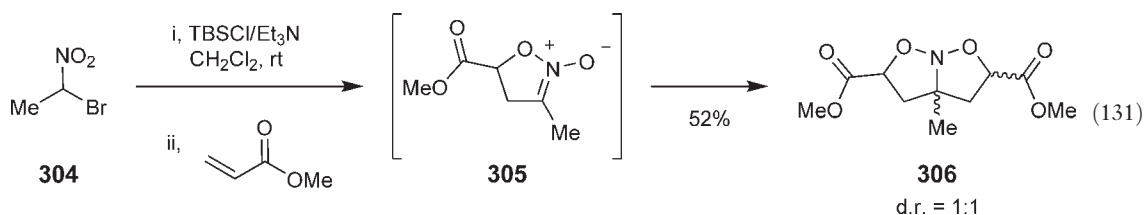
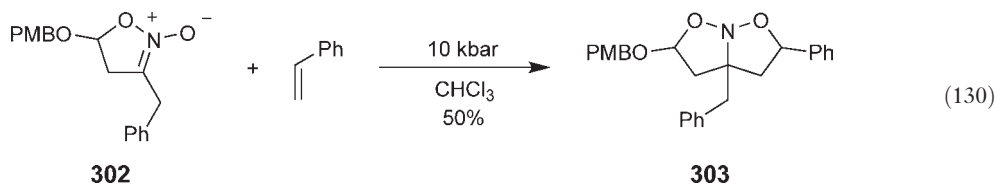
5*H*,7*H*-Thiazolo[3,4-*c*]oxazolium-1-oxide bicyclic mesoionic compounds **292** (or münchnone intermediates) in equilibrium with their ketene valence tautomers **293** were prepared from *N*-acyl-(*R*)-thiazolidine-4-carboxylic acids **291** and DCC as dehydrating agent, and underwent cycloaddition reactions with imines to afford mixtures of 1*H*,3*H*-imidazo[1,5-*c*]thiazole **295** and diastereomeric spiro- β -lactam derivatives **294a** and **294b** (Equation 127) <1995T9385, 1999T201>. Treatment of *N*-nitroso-thiazolidine-4-carboxylic acid **296** with trifluoroacetic anhydride (TFAA) provided the azomethine ylide sydnone **297** which participated in cycloaddition with dimethyl acetylenedicarboxylate (DMAD) followed by extrusion of carbon dioxide to give the 4,6-dihydro-pyrazolo[1,5-*c*]thiazole **298** (Equation 128) <2000T10011>.

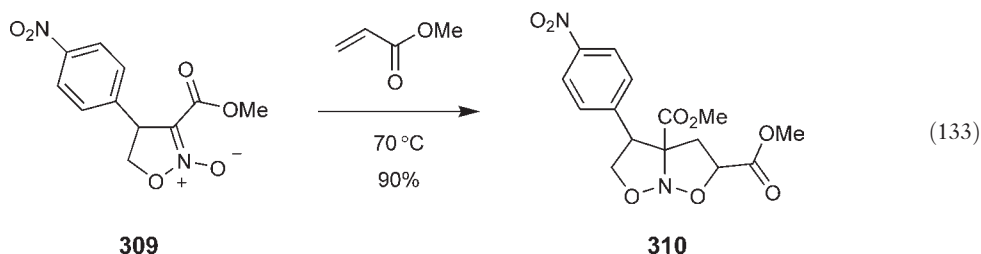


Azolium *N*-aminide intermediate **300**, readily generated from the corresponding salt **299** in the presence of Hünig's base, behaved as 1,3-dipole equivalents with *N*-methylmaleimide producing a mixture of *endo/exo*-tetrahydro-pyrazolo [1,5-*a*]benzimidazole cycloadducts **301a** and **301b** in 78% yield (Equation 129) <2001JOC8528>.

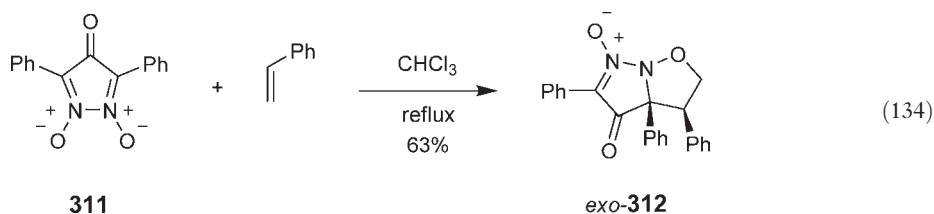


Intermolecular 1,3-dipolar cycloaddition of N-oxides. Although 1,3-dipoles such as 3-alkylated isoxazoline *N*-oxides (or cyclic nitronates) **302** were not highly reactive, they could undergo cycloaddition with a slight excess of electron-deficient alkene under reflux toluene or using high pressure (10 kbar) for the preparation of two five-membered bicyclic nitroso acetal-type tetrahydro-isoxazolo[2,3-*b*]isoxazoles **303** (Equation 130) <1998TL8869, 2001EJO553>. These types of compounds were also obtained by treatment of the 1-bromonitroalkane **304** with *tert*-butyldimethylchlorosilane, triethylamine, and 50 equiv of methyl acrylate via a double cycloaddition process under milder conditions (Equation 131) <2003OL4907>. Reaction of activated 3-nitroisoxazoline *N*-oxides **307** and 3-carboxylic acid methyl ester isoxazoline *N*-oxides **309** with methyl acrylate and small-ring alkenes at 60–70 °C gave rise to the corresponding 3a-nitro-tetrahydro-isoxazolo[2,3-*b*]isoxazole **308** and tetrahydro-isoxazolo[2,3-*b*]isoxazole-3a-carboxylic acid methyl ester **310**, respectively (Equations 132 and 133) <2002DOC21, 1995BSB449>.

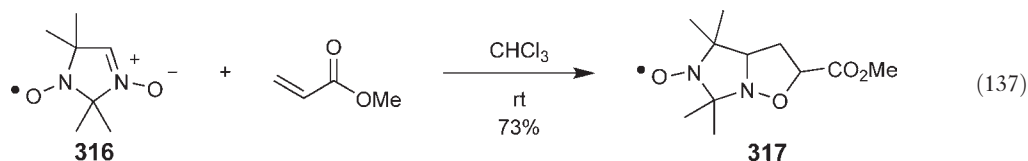
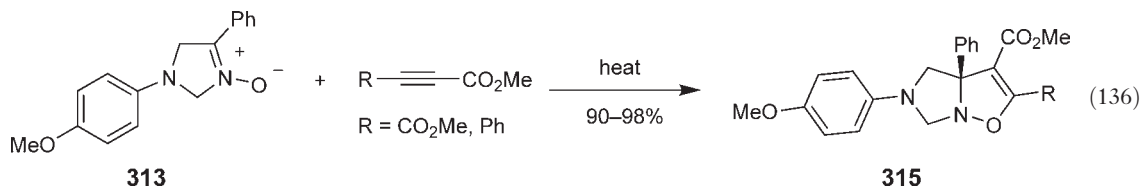
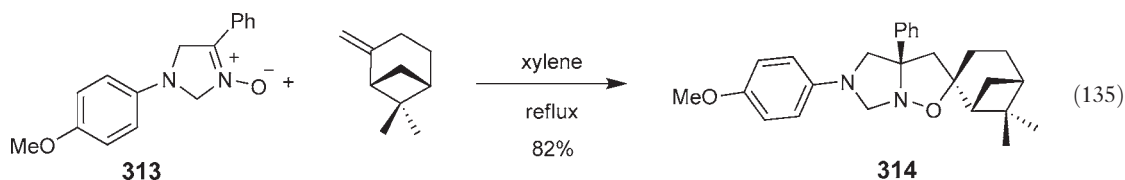


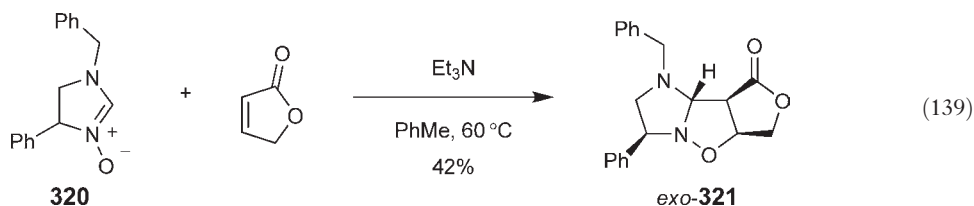
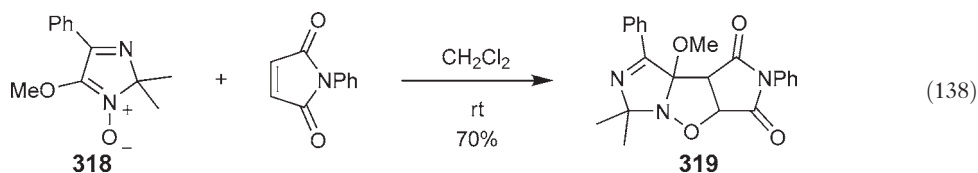


Pyrazolone-1,2-dioxides **311** were subjected to cycloaddition with a wide range of olefinic compounds leading to the *exo*-2,3,3*a*,4-tetrahydro-pyrazolo[1,5-*b*]isoxazole cycloadducts **312**. The behavior of these reactive species **311** toward unsaturated compounds, stereochemical and mechanistic aspects, were discussed in details (Equation 134) <1994J(P2)1337>.

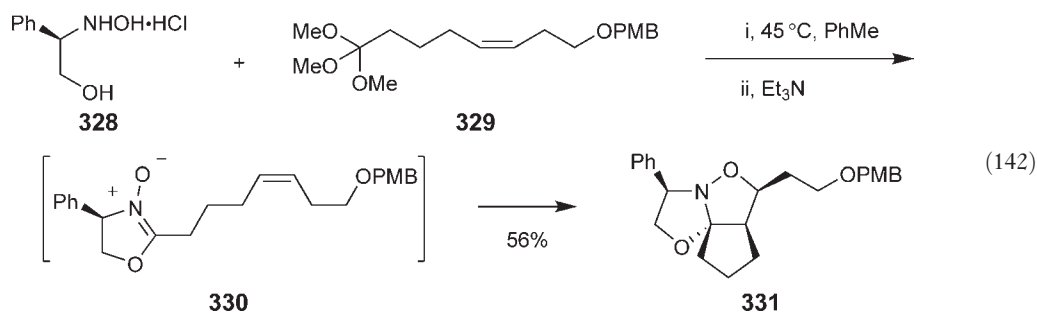
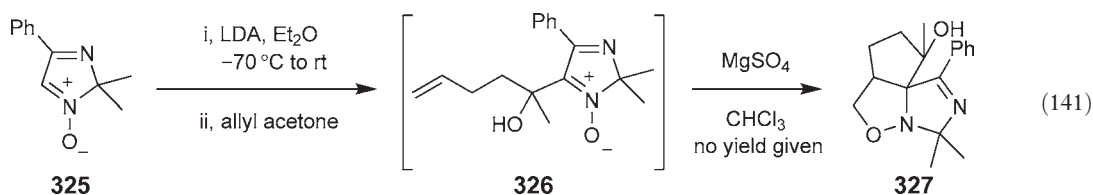
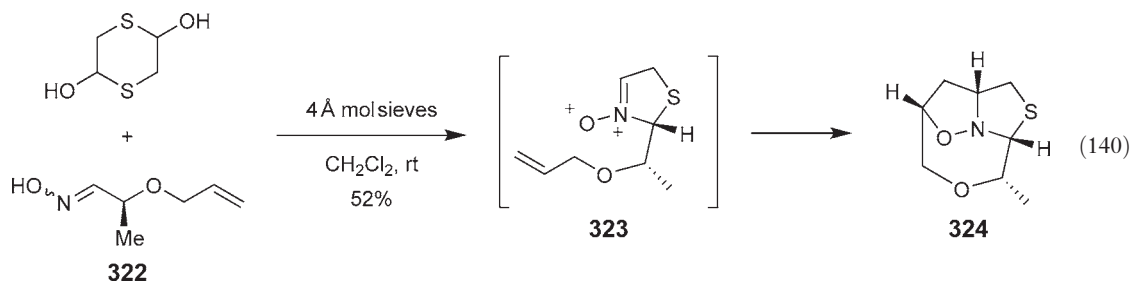


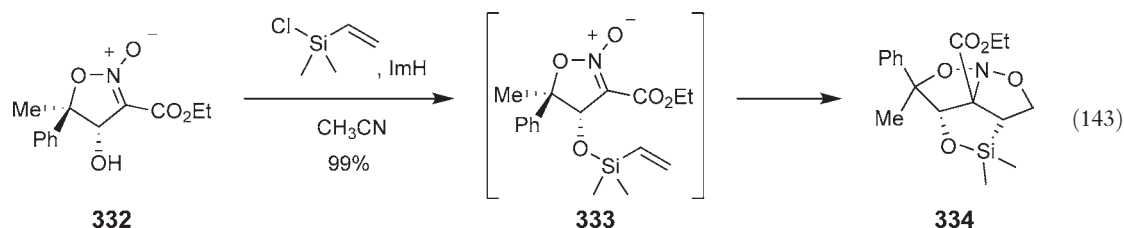
Regio- and diastereoselective 1,3-dipolar cycloaddition of Δ^3 -imidazoline 3-oxides **313** with styrene, methyl acrylate, or the (1*S*)-(-)- β -pinene resulted in the formation of perhydroimidazo[1,5-*b*]isoxazoles **314** (Equation 135), whereas the cycloaddition performed with the activated alkynes (DMAD and alkyl phenylpropionates) gave 3*a*,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles **315** (Equation 136) <1985TL4801, 1998H(48)537, 2001TA1463, 2001T3413, 2004SC1617>. In the same way, 5-oxyl imidazo[1,5-*b*]isoxazoles derivatives **317** were prepared from 2,2,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl **316** (Equation 137) <1985TL4801, 1988BAU1677, 1994RCB838, 2000RCB116>, and imidazole oxide-derived cyclic α -methoxynitrones **318** reacted with *N*-phenylmaleimide and DMAD to form the corresponding 2,3,3*a*,6-tetrahydro-imidazo[1,5-*b*]isoxazoles **319** and 3*a*,6-dihydroimidazo[1,5-*b*]isoxazoles (Equation 138) <2001RCB882>. Similarly, imidazoline nitrones (or imidazolium-3-oxides) **320** were involved in diastereoselective cycloaddition with alkene dipolarophiles substituted by electron-withdrawing groups to afford hexahydro-imidazo[1,2-*b*]isoxazoles **321** (Equation 139) <2000SL967>.



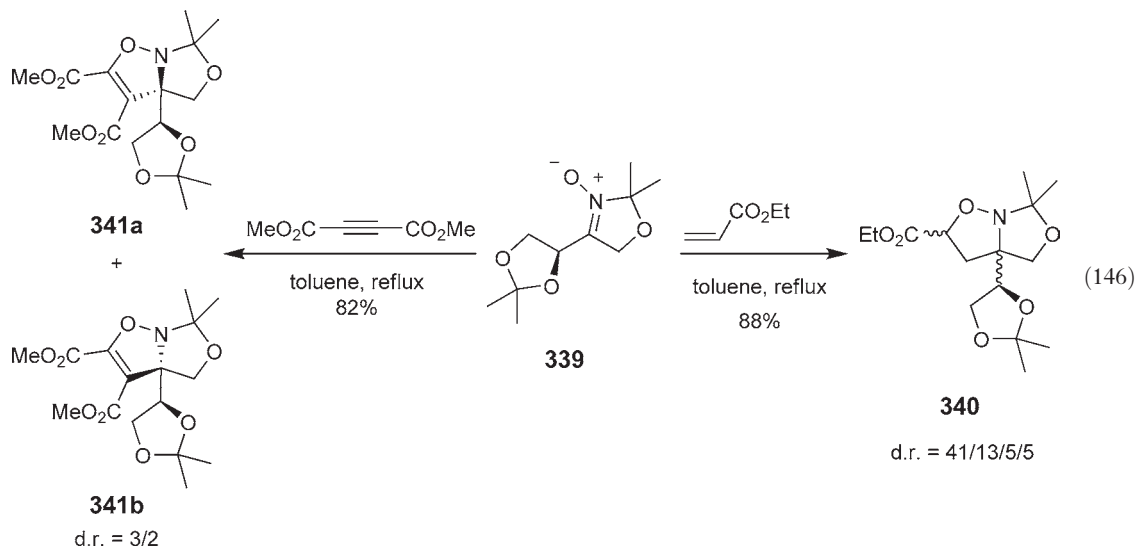
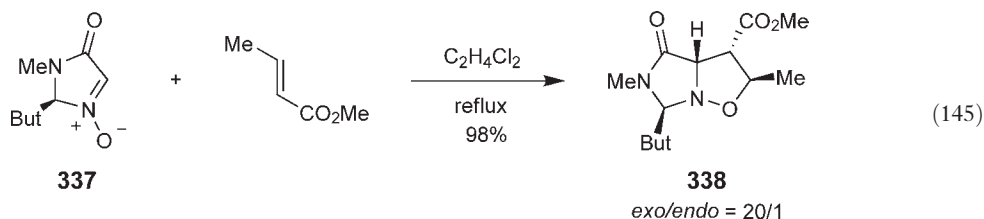
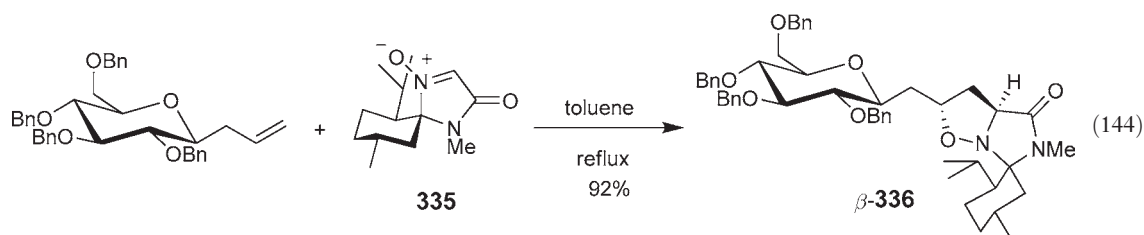


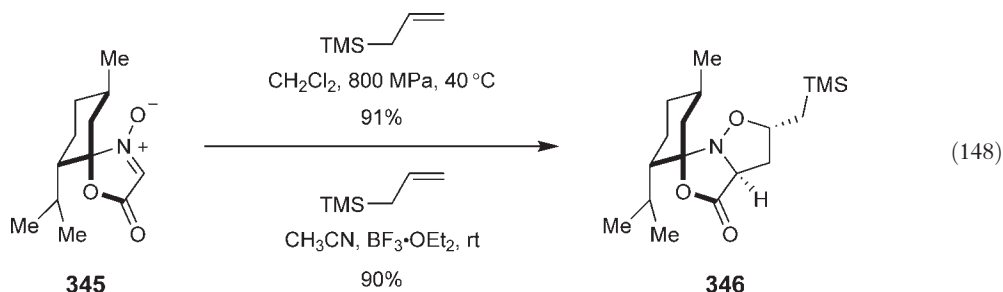
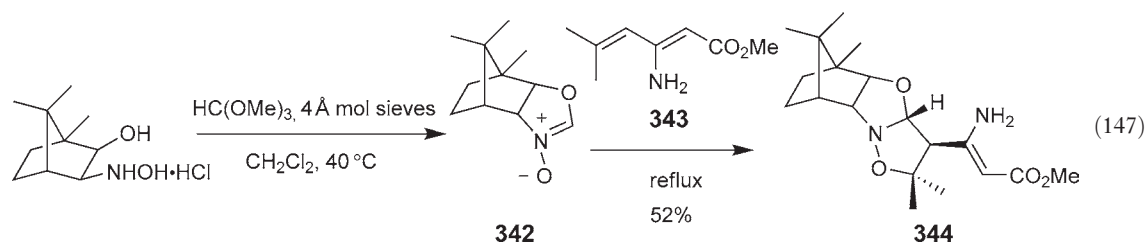
Intramolecular 1,3-dipolar cycloaddition. A domino reaction of the optically pure 5-alkenal oxime **322** with 2,5-dihydroxy-1,4-dithiane in the presence of molecular sieves led to the cyclic nitrone **323** as intermediate. These later spontaneously underwent an intramolecular 1,3-dipolar cycloaddition furnishing only one diastereomer of the tricyclic compound **324** (Equation 140) <1995MI1649>. Ring closure of the 2*H*-imidazole-1-oxide **326** obtained from α -hydroxymethyl nitrone **325** yielded the 2,3,3*a*,6-tetrahydro-imidazo [1,5-*b*]isoxazole-based derivative **327** (Equation 141) <2000T4071>. Condensation of the orthoester **329** with the hydroxyaminoalcohol hydrochloride derived from (*R*)-phenylglycinol **328** gave the intermediate oxazoline *N*-oxide **330**. After treatment with triethylamine and increasing the temperature, the intermediate **330** cyclized to the tricyclic adduct **331** resulting from an *exo*-transition state (Equation 142) <2005S103>. Silicon-tethered 1,3-dipolar cycloaddition of 4-hydroxy-2-isoxazoline-2-oxides **332** allowed the regio- and stereospecific formation of tetrahydro-isoxazolo[2,3-*b*]isoxazole units **334** under very mild conditions (Equation 143) <1996JA9446, 1998TL1041, 1998JOC8235, 1998CEJ2501>.





Asymmetric intermolecular 1,3-dipolar cycloaddition of chiral nitrones. Homochiral imidazole-derived nitrones **335** and **337**, prepared from (–)-menthone and glycine methyl amide and from Seebach's *tert*-butyl-substituted imidazolidinones, respectively, reacted regio- and stereoselectively with a range of alkenes to give the tetrahydro-imidazo[1,5-*b*]-isoxazol-4-ones **336** and **338** (Equations 144 and 145) <2001OL1375, 2004OL1653>. Some experiments have also been carried out using chiral cyclic nitrones derived from L-erythrose **339** for the formation of tetrahydro- or dihydro-isoxazolo[2,3-*c*]oxazole **340** and **341** (Equation 146) <2000JOC7000>. Enantiomerically pure camphor-derived oxazoline *N*-oxides **342**, obtained by condensation of 3-hydroxylaminoborneol with orthoesters, have proved to be versatile 1,3-dipoles for asymmetric [2+3] cycloadditions with various types of alkenes, such as γ,δ -unsaturated β -enamino ester **343** (Equation 147) <1995JOC1720, 2000OL1053>. Finally, asymmetric 1,3-dipolar cycloadditions employing cyclic chiral nitrones of the spiro 3-oxazolin-5-one 3-oxide type such as **345** were also reported (Equation 148) <1997T5725>.

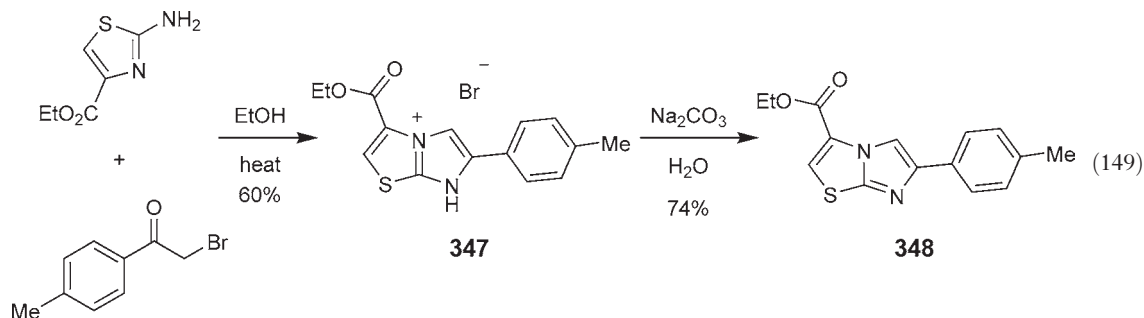


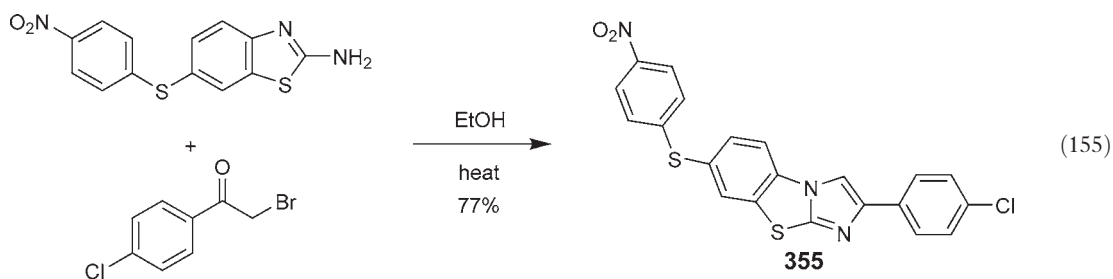
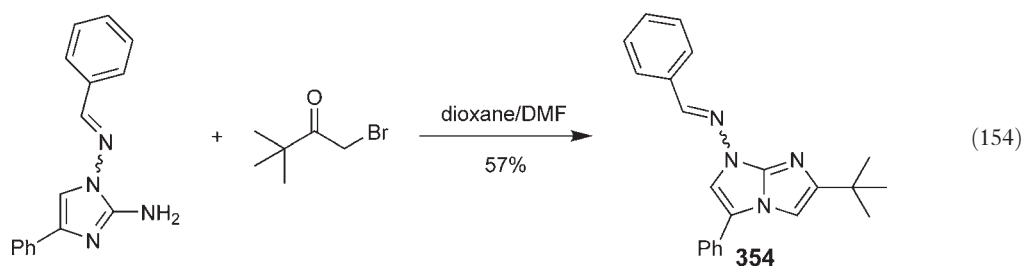
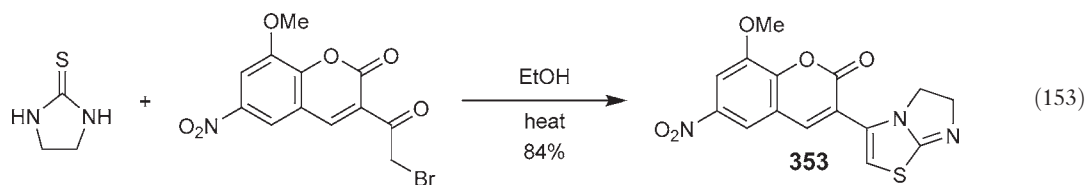
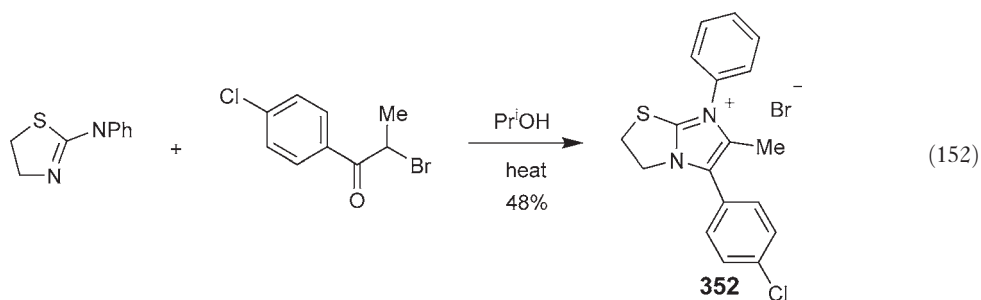
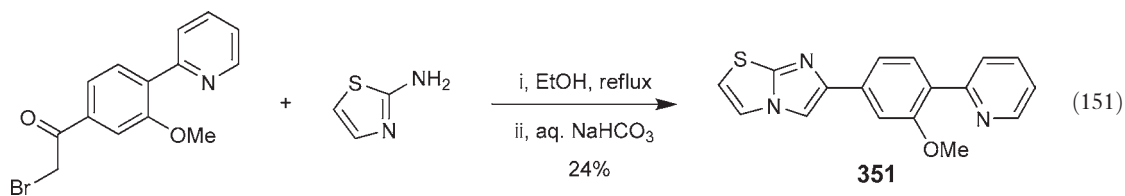
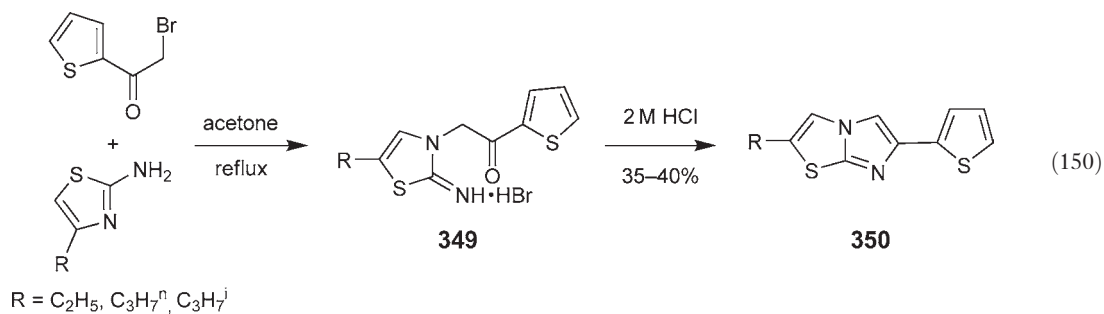


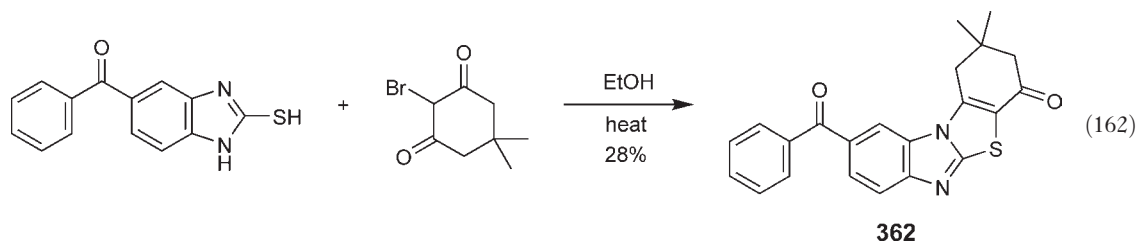
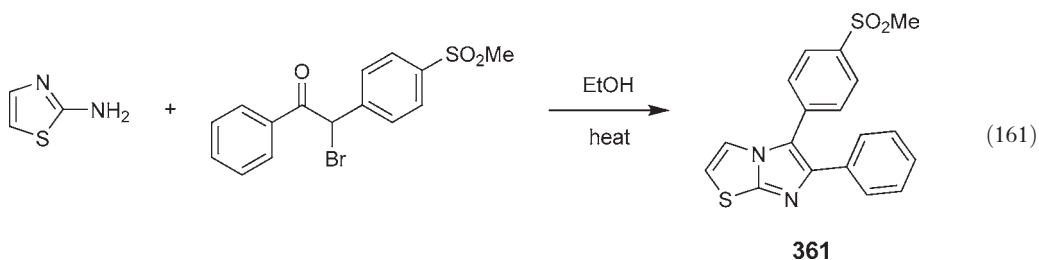
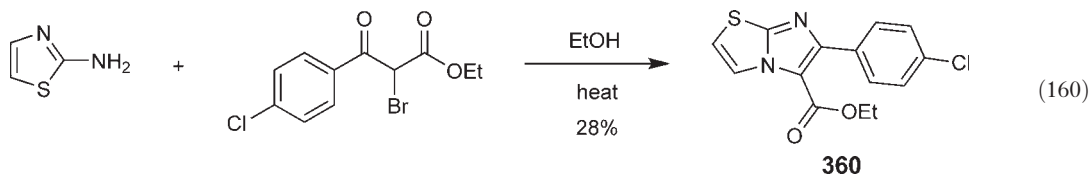
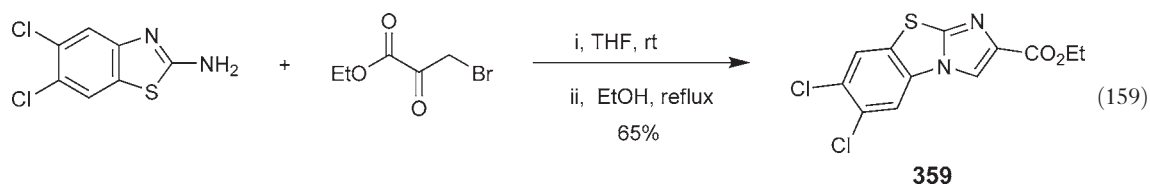
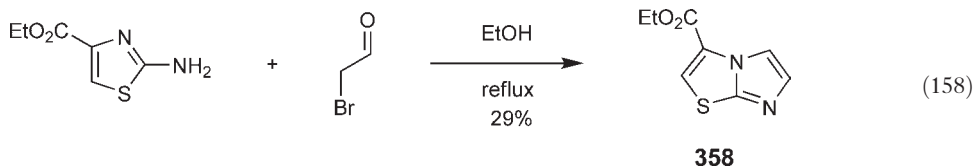
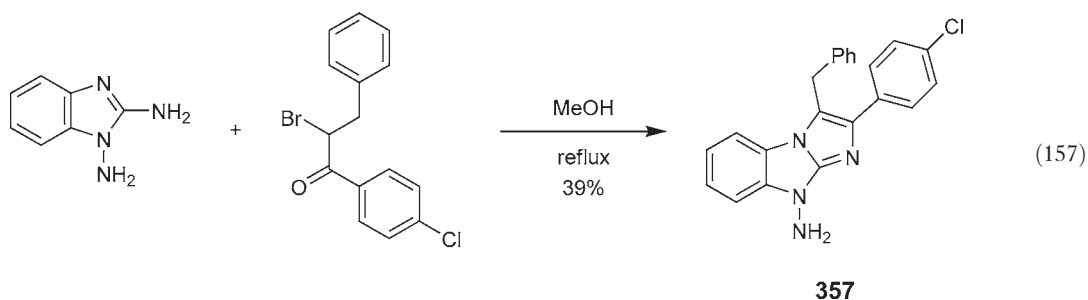
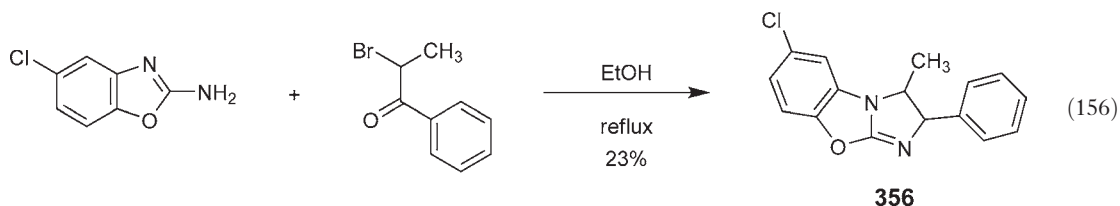
11.04.9.3.2 Type BD syntheses

11.04.9.3.2(i) Sequential X (X = N, O, S)-alkylation/Mannich cyclocondensation

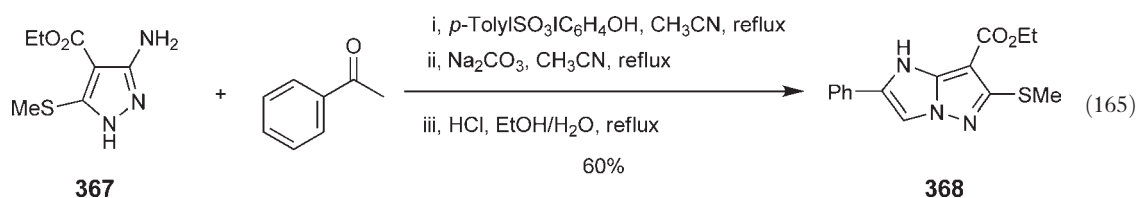
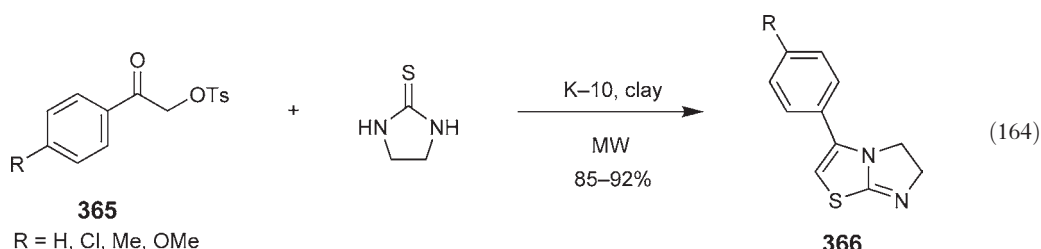
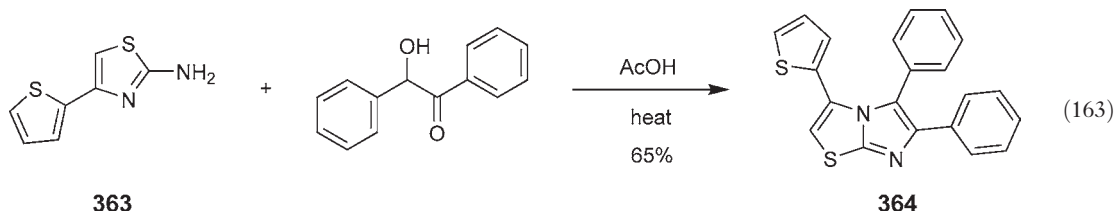
With α -halocarbonyl reagents. Most of syntheses in this category were performed by alkylation of heterocyclic heteroatoms with α -halocarbonyl compounds and subsequent annulation which involved intramolecular Mannich cyclocondensation. Considering this strategy, the use of α -bromoketones allowed the conversion of 2-aminothiazoles to imidazo[2,1-*b*]thiazol-4-ylum salts **347** and imidazo[2,1-*b*]thiazoles **348**, **350**, and **351** (Equations 149–151) <1999EJM883, 2001EJM743, 2002SC481, 2003JCCS1085, 2004BMC17, 2004IJB393>, of 2-amino-2-thiazolines to 2,3-dihydro-imidazo[2,1-*b*]thiazol-7-ium salts **352** (Equation 152) <1997CHE724>, of imidazolidine-2-thione to 5,6-dihydro-imidazo[2,1-*b*]thiazoles **353** (Equation 153) 2002AF388>, of 2-aminoimidazoles to imidazo[1,2-*a*]imidazoles **354** (Equation 154) <1996CHE1035>, of substituted 2-aminobenzothiazoles leading to imidazo[2,1-*b*]benzothiazoles **355** (Equation 155) <1997H(45)2239, 2001MI53, 2002AF388, 2002PAS309, 2005SC901>, of 2-aminobenzoxazoles to imidazo[2,1-*b*]benzoxazoles (Equation 156) <1997H(45)2239>, of 2-aminobenzoimidazoles to imidazo[1,3-*a*]benzimidazoles **357** (Equation 157) <2002HCO151>. With bromoacetaldehyde, it was possible to prepare imidazo[2,1-*b*]thiazoles **358** from 2-aminothiazoles (Equation 158) <1995EJM901>. α -Bromoketoesters were employed in the elaboration of imidazo[2,1-*b*]benzothiazoles **359** from 2-aminobenzothiazoles (Equation 159) <1996EJM575, 2001MI53, 2001EJP209> and imidazo[2,1-*b*]benzoxazoles from 2-aminobenzoxazoles <1997EJM83> with moderate success. α -Halo- β -ketoesters and α -bromodiarylethanones were also tested in the preparation of imidazo[2,1-*b*]thiazoles **360** and **361** from 2-aminothiazoles and the corresponding benz-analogs, but poor yields were frequently encountered in these transformations (Equations 160 and 161) <1995EJM901, 2002HCO433, 1997BML47, 2004H(62)815, 1997H(45)2239>. Finally, condensation of α -bromo cyclic diketones with 2-mercaptobenzothiazole derivative gave the compound **362** comprising the thiazolo[3,2-*a*]benzimidazole unit (Equation 162) <1999PS101>.



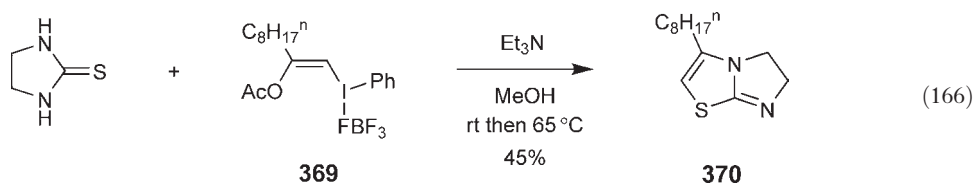




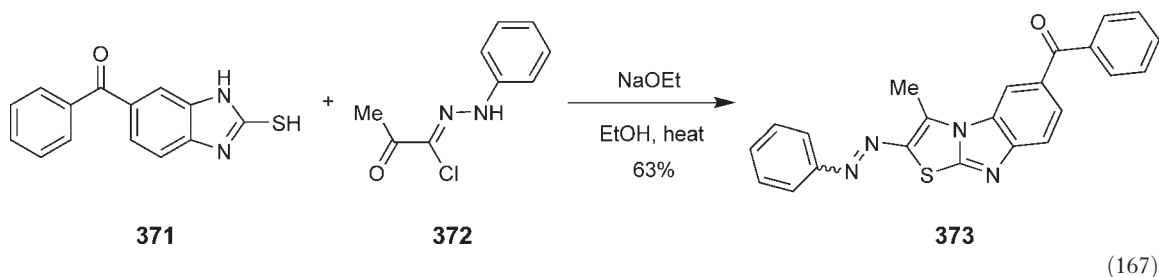
With α -hydroxy ketones and their related tosyloxy derivatives. The imidazo [2,1-*b*]thiazole **364** was prepared by acetic acid-catalyzed cyclocondensation of 2-hydroxy-1,2-diphenyl-ethanone with thiophenyl-substituted 2-aminothiazole **363** (Equation 163) <2002MI110>. Under MW irradiation and in the presence of montmorillonite K-10 clay, a mixture of α -tosyloxyketones **365** and 2-imidazolidinethione led to the substituted 5,6-dihydro-imidazo[2,1-*b*]thiazoles **366** (Equation 164) <1998J(P1)4093>. When using α -tosyloxyacetophenone, prepared by reaction of acetophenone with [hydroxyl(tosyloxy)iido]benzene (HTIB), 5-aminopyrazole **367** could be converted to imidazo[1,2-*b*]pyrazole **368** in basic medium (Equation 165) <2005JHC209>.



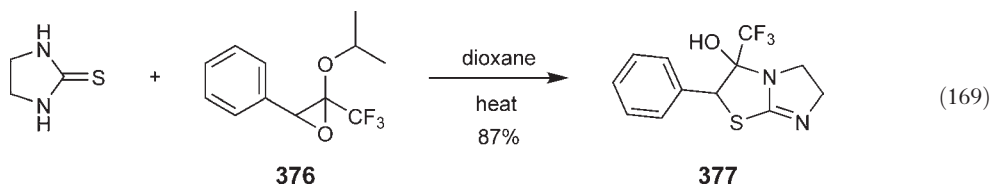
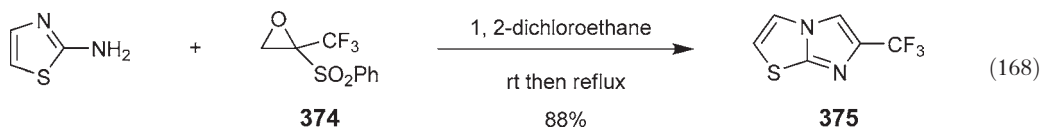
With α - λ^3 -iodanyl ketone precursors. Exposure of (2-acetoxyvinyl)phenyl- λ^3 -iodanes **369** to 2-imidazolidinethione and triethylamine in methanol produced the bridgehead heterocycle **370** of type 5,6-dihydro-imidazo[2,1-*b*]thiazoles (Equation 166) <2003JOC7887>.



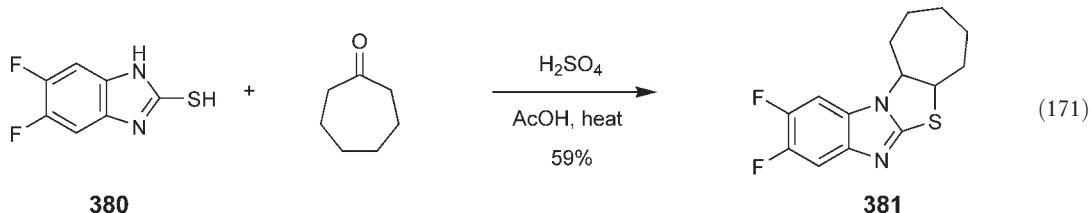
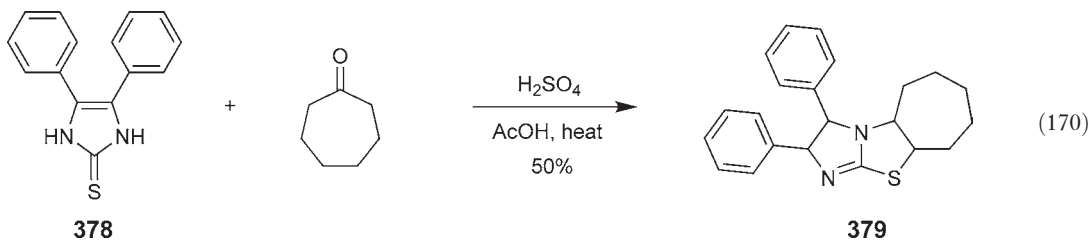
With α -keto-N-arylhydrazidoyl chlorides. The thiazolo[3,2-*a*]benzimidazole **373** was obtained by treating the 2-mercaptopbenzimidazole **371** with α -acetyl-N-arylhydrazidoyl chloride **372** and NaOEt in refluxing ethanol (Equation 167) <1999PS101>.



With α -trifluoromethyl oxiranes. α -Opening oxirane ring of the 2-benzenesulfonyl-2-trifluoromethyl-oxirane **374** by nucleophilic attack with 2-aminothiazole followed by Mannich cyclocondensation of the intermediate trifluoroketone gave the 6-trifluoromethyl-imidazo[2,1-*b*]thiazole **375** (Equation 168) <1995JFC83>. The same transformation was conducted with 2-isopropoxy-2-trifluoromethyl-3-phenyloxirane **376** and 2-imidazolidinethione and furnished the 2,3,5,6-tetrahydro-imidazo[2,1-*b*]thiazole **377** in good yield (Equation 169) <1999RJO741>.

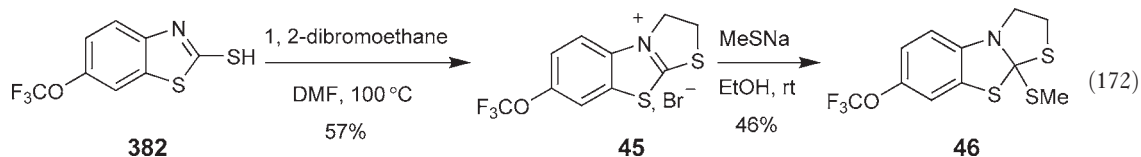


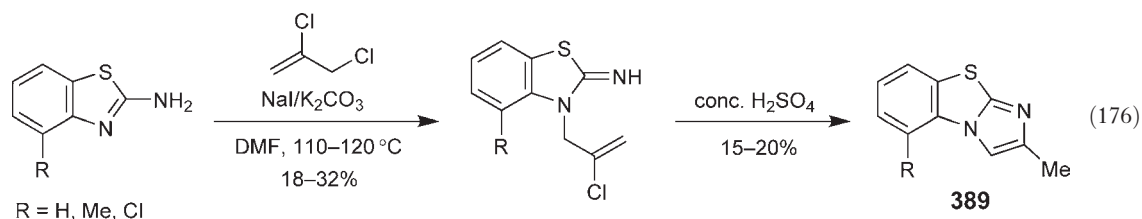
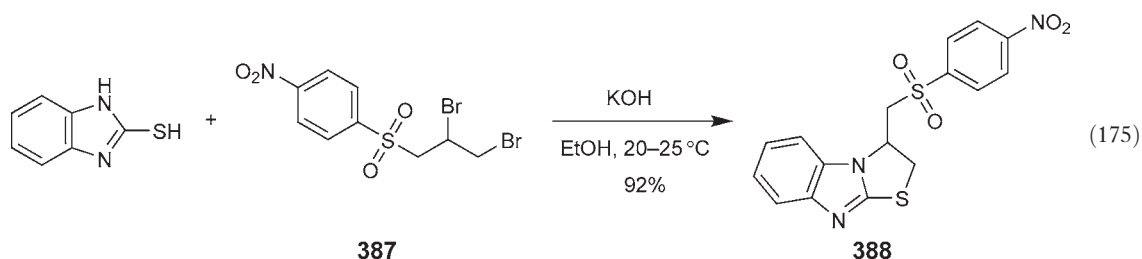
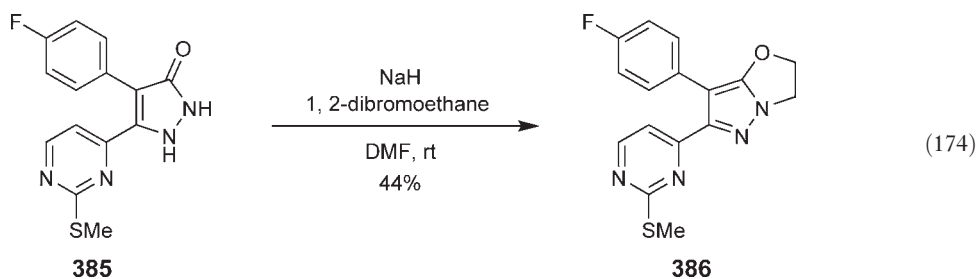
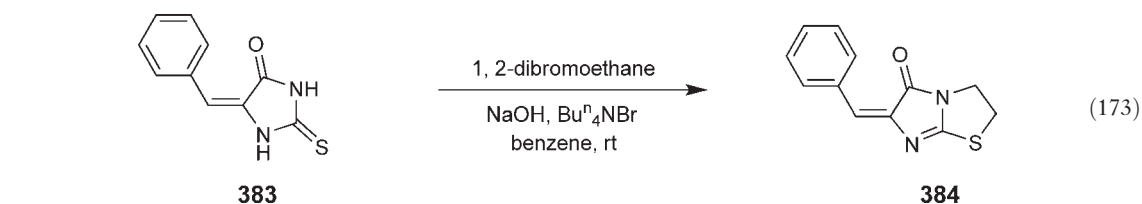
With ketones. The 1*H*-imidazole-2(3*H*)-thione **378** and 2-mercaptobenzimidazole **380** reacted separately with cycloheptanone to form the tetrahydro-imidazo[2,1-*b*]thiazole **379** and the dihydro-thiazolo[3,2-*a*]benzimidazole **381**, respectively (Equations 170 and 171) <2000JHC943, 2001RJO564>.



11.04.9.3.2(ii) N,X (X = N, O, S)-Dialkylolation with 1,2-dihaloalkanes and 2,3-dichloropropene

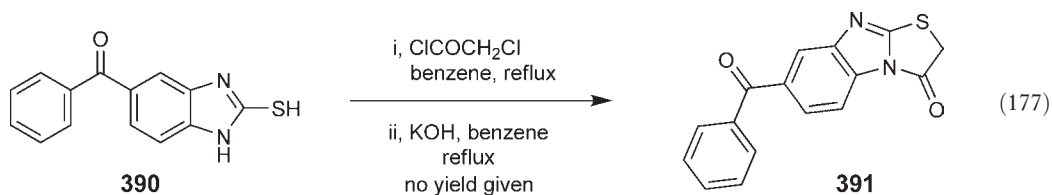
An approach to the synthesis of bicyclic 5-5 systems such as the tricyclic thiazolium salt **45**, 2,3-dihydro-imidazo[2,1-*b*]thiazol-5-one **384**, and 2,3-dihydro-pyrazolo[5,1-*b*]oxazole **386** was proposed and involved heterocyclization reactions of 2-mercaptobenzothiazole **382**, thiohydantoin **383**, and 2*H*-pyrazol-3-ol **385** with 1,2-dibromoethane, respectively (Equations 172–174) <1999JME2828, 2002EJC777, 1996MI383, 2004BML4945>. Examples using substituted dibromo analogs **387** and 2,3-dichloropropene were also reported allowing the preparation of thiazolobenzimidazoles **388** and imidazobenzothiazoles **389** (Equations 175 and 176) <2004RJO591, 1995CHE500, 1997H(45)1579>.





11.04.9.3.2(iii) Sequential *N*-acylation/*X*-alkylation

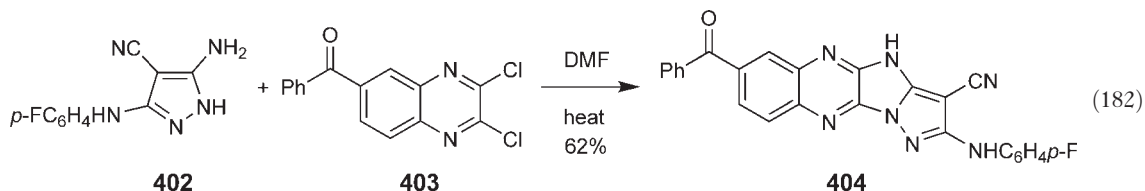
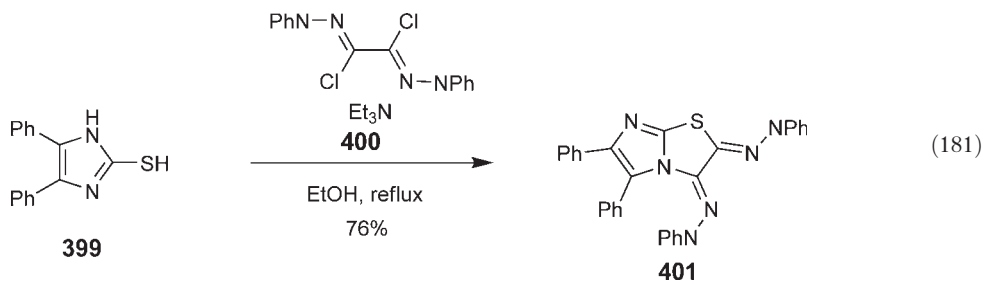
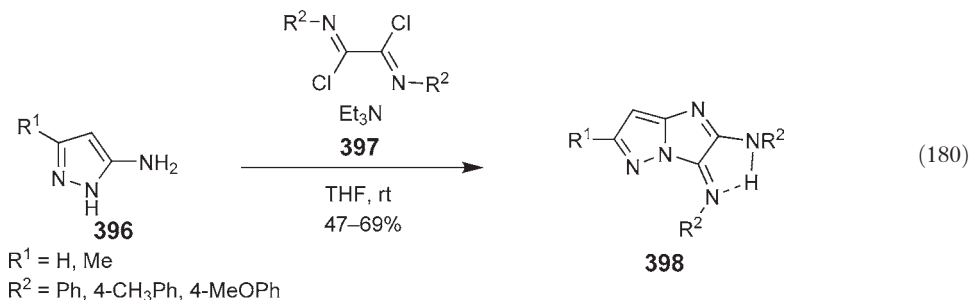
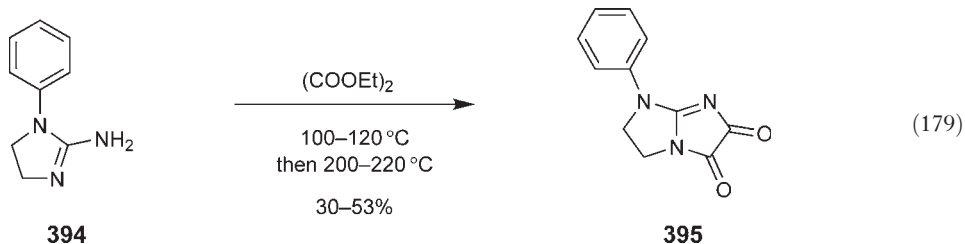
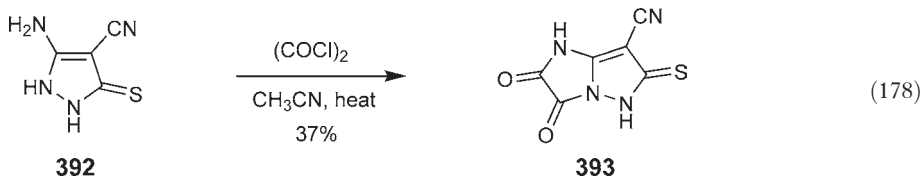
A useful and simple preparation of the thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one **391** is the reaction of 2-mercapto-benzimidazole **390** with chloroacetyl chloride (Equation 177) <1996MI442>.



11.04.9.3.2(iv) *N,N'*-Diacylative reactions with oxalic acid derivatives

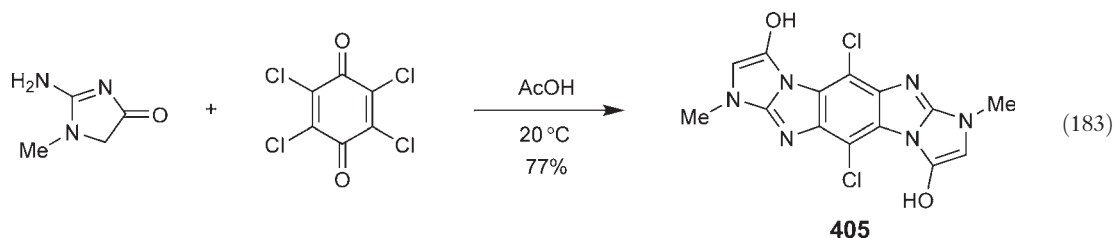
The 2,3-dioxo-6-thioxo-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*b*]pyrazole **393** and 5,6-dioxo-2,3-dihydro-1*H*-imidazo[1,2-*a*]-imidazole **395** were synthesized by condensation of the respective 5-amino-3-thioxo-2,3-dihydro-pyrazole **392** and 2-aminoimidazoline **394** compounds with either oxalyl dichloride or diethyl oxalate in moderate to poor yields (Equations 178 and 179) <1995JPR472, 2002EJM845>. These cyclizations can suffer from various side reactions such as expulsion of CO, polymerization, or formation of open-chain products. To solve these problems, reagents such as oxalic acid bis-imidoyl- and bis-hydrazoylchlorides **397** and **400** as well as 2,3-dichloroquinoxalines **403**

were used with a series of dinucleophiles comprising 3-aminopyrazoles **396**, 2-aminoimidazole **399**, and 2-mercaptoimidazole **402** as depicted in Equations (180–182) <1999SL468, 2001EJO2245, 2002JCCS1035, 2004JCM264, 2001IJB195, 2000PS1>.

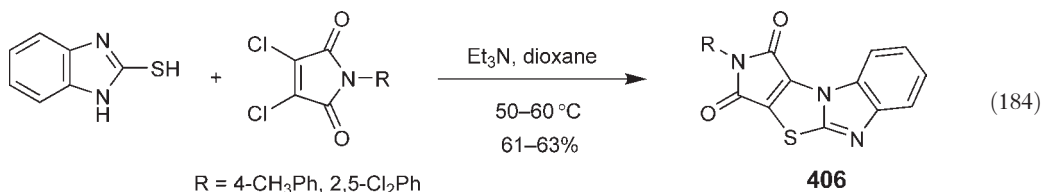


11.04.9.3.2(v) Bis-substitution reactions via charge-transfer complexes

With chlorinated quinones. New heterocycles containing 1,2-dihydro-imidazo [1,2-*a*]imidazol-3-one **405** or 1*H*-imidazo[1,2-*b*]pyrazole moieties were obtained via charge-transfer interaction of creatinine or 3-aminopyrazole with some π -deficient compounds such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 2,3,5,6-tetrachloro-1,4-benzoquinone, 2,3-dichloro- or 2,3-dicyano-1,4-naphthoquinone, and 3,4,5,6-tetrachloro-1,2-benzoquinone (Equation 183) <1996BSB159, 2001HCO541, 2000PS1>.

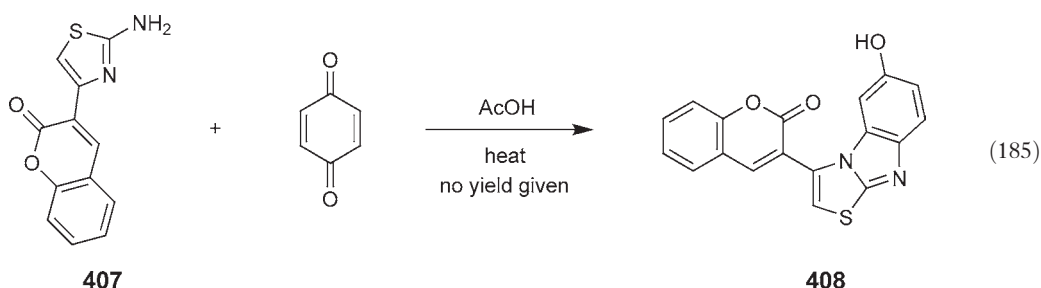


With *dichloromaleimides*. A similar cyclization of 2-mercaptobenzimidazole with an appropriate dichloromaleimide as key reagent gave thiazolo[3,2-*a*]benzimidazole derivatives **406** (Equation 184) <2001H(55)2189>.



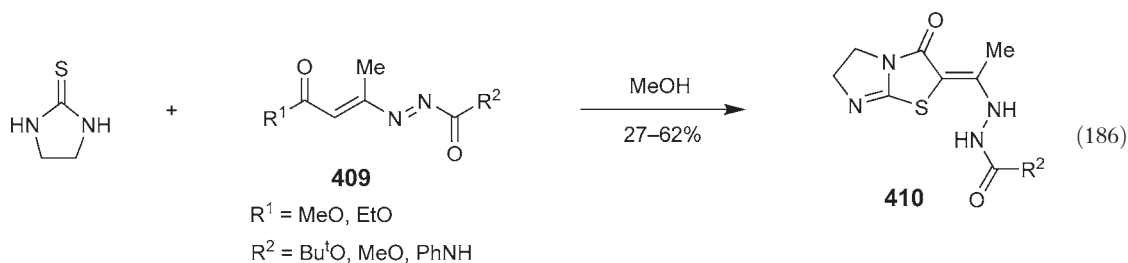
11.04.9.3.2(vi) Tandem 1,4-conjugate addition/Mannich condensation

The only case of this type reported in the literature concerns the preparation of the substituted hydroxy-thiazolo [3,2-*a*]-benzimidazole **408** from 2-aminothiazole **407** and 1,4-benzoquinone in glacial acetic acid (Equation 185) <1997PS185>.



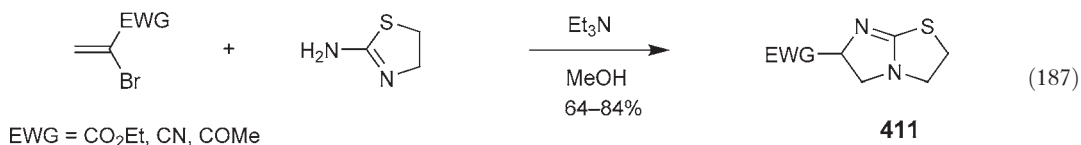
11.04.9.3.2(vii) Tandem 1,4-conjugate addition/lactamization

Some work was carried out to investigate the reaction of 1,2-diaza-1,3-butadienes **409** with 2-imidazolidinethione in methanol at room temperature. 5,6-Dihydro-imidazo[2,1-*b*]thiazol-3-ones **410** were formed in 27–62% yield (Equation 186) <1999T13423>.

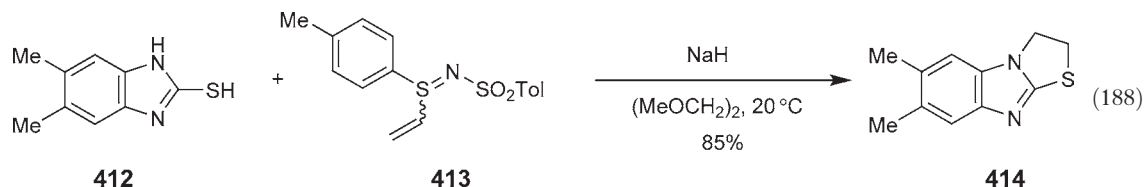


11.04.9.3.2(viii) Tandem 1,4-conjugate addition/alkylation

With *α*-bromo Michael acceptors. Condensation reaction of 2-aminothiazoline with *α*-bromo-*α*,*β*-unsaturated compounds, commercially available or generated *in situ*, provided a route to functionalized 2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazoles **411** (Equation 187) <1994H(38)2593>.

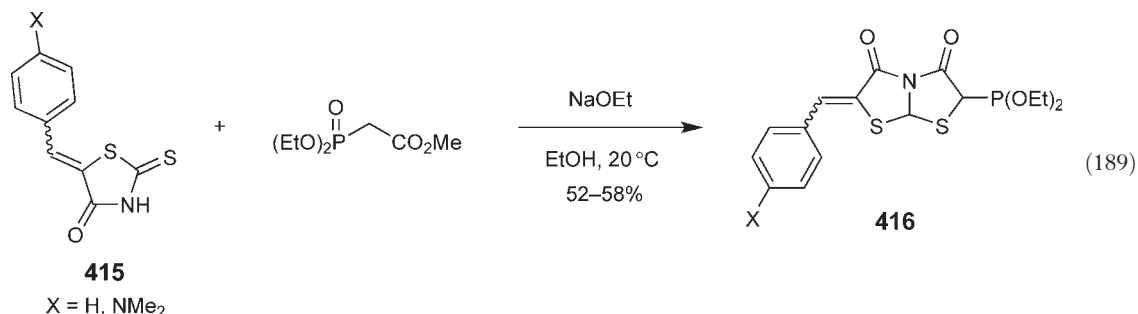


With *S*-vinylsulfilimines. A novel synthesis of the dihydro-thiazolo [3,2-*a*]benzimidazole **414** was achieved by the ring closure of 2-mercaptobenzimidazole **412** using *S*-ethenylsulfilimine **413** and basic conditions (Equation 188) <2000OPP401>.



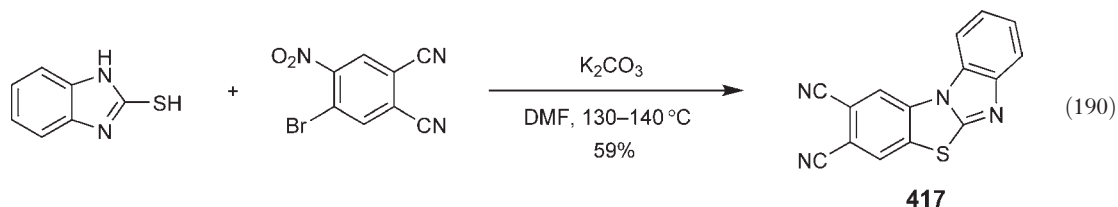
11.04.9.3.2(ix) Nucleophilic attack at a carbon–heteroatom double bond/lactamization

More recently, 2-thioxo-4-thiazolidinones **415** were reported to undergo facile thiophilic addition of α -phosphonyl carbanions and subsequent lactamization to generate bicyclic thiazolo [2,3-*b*]thiazole-3,5-diones **416** (Equation 189) <2004PS1307>.



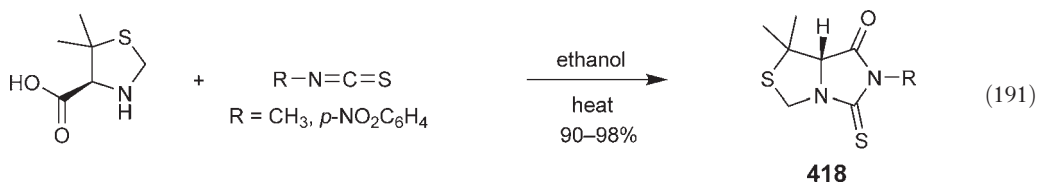
11.04.9.3.2(x) Nucleophilic *ipso*-substitution

Ring closure of 2-mercaptobenzimidazole can also be achieved through *ipso*-substitution of 4-bromo-5-nitro-phthalonitrile leading to the tetracyclic compound **417**. An example is given in Equation (190) <2000CHE1065>.



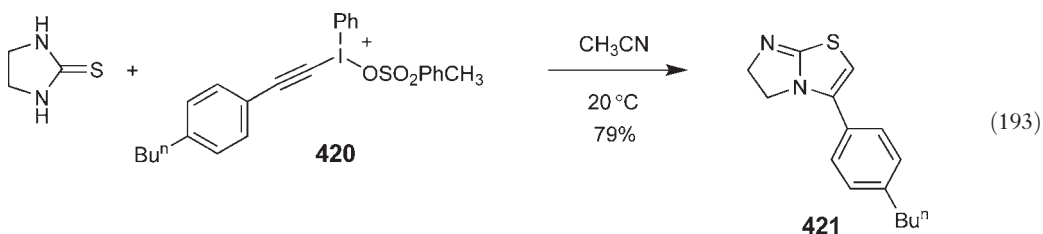
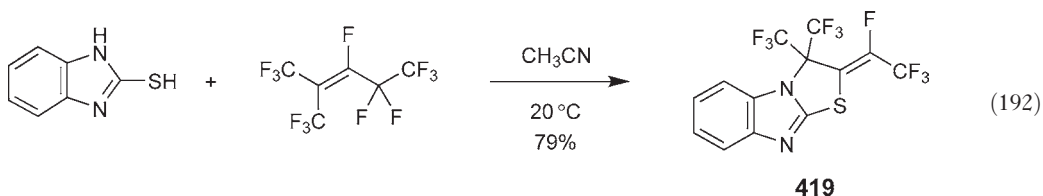
11.04.9.3.2(xi) Other cyclocondensations with isothiocyanate or isocyanate

(*S*)-5,5-Dimethyl-thiazoline-4-carboxylic acid reacted efficiently with alkyl and aryl isothiocyanates to give bicyclic thiohydantoins **418**. A similar diastereo- and regioselective cyclization of chiral 1,3-thiazolidine-2,4-dicarboxylic acids was also reported (Equation 191) <1996JHC1099, 1998HCA744>.



11.04.9.3.2(xii) Miscellaneous transformations

Two approaches have been applied for the synthesis of imidazo[2,1-*b*]thiazole ring systems. Reaction of 2-mercapto-benzimidazole with perfluoro-2-methylpent-2-ene in the presence of triethylamine gave compound **419** (Equation 192), and cyclocondensation of 2-imidazolidinethione with the alkynyl(phenyl)iodonium salt **420** afforded product **421** (Equation 193) <2001RCB1446, 2003JCM715>.

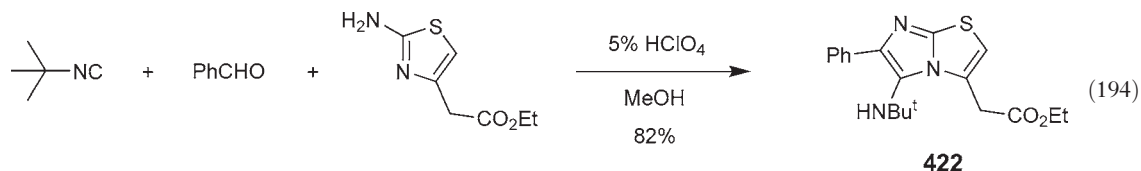


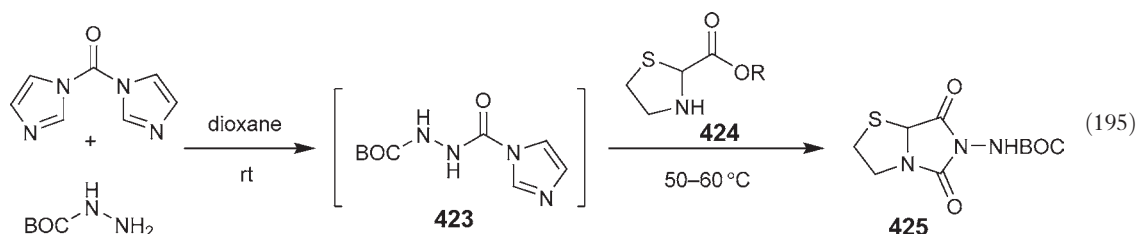
11.04.9.4 (3+1+1) Syntheses

11.04.9.4.1 Type BCD syntheses

11.04.9.4.1(i) Multicomponent one-pot reactions

Multicomponent reactions allow the development of rapid and efficient library synthesis of a range of fused heterocycles. For instance, it was found that electron-poor and electron-rich amidines, such as 2-aminothiazoles, 2-aminooxazoles, and 3-aminopyrazoles, reacted with benzaldehyde and *tert*-butylisocyanide in the presence of perchloric acid in methanol to produce high to low amounts of corresponding adducts. Using this methodology, the trisubstituted imidazo[2,1-*b*]thiazole **422** was prepared in 82% yield (Equation 194) <1998AGE2234>. More recently, this fused heterocycle has been synthesized via an MW-assisted Ugi three-component coupling reaction catalyzed by scandium triflate <2003TL4369>, and alternative aldehydes such as glyoxylic acid and macroporous polystyrene glyoxylate have been used <2004OL4989>. Finally, the 6-amino-dihydro-imidazo[5,1-*b*]thiazole-5,7-dione **425** was prepared in a simple pseudo-one-pot reaction sequence from carbonyldiimidazole, *tert*-butyl carbazate, and thiazolidine ester **424**. The reaction involved conversion of *tert*-butyl carbazate to the intermediate **423**, displacement of the imidazolyl moiety by **424**, and the succeeding cyclization (Equation 195) <2000TL1159>.



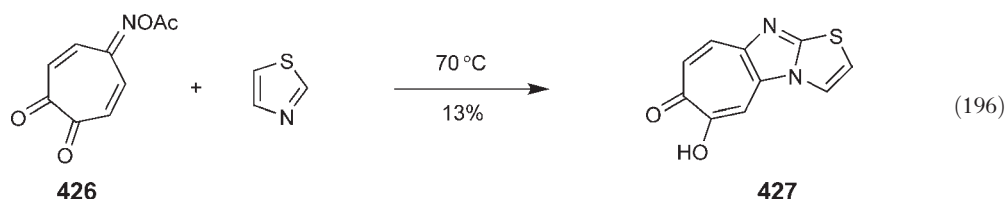


11.04.9.5 (2+3) Syntheses

11.04.9.5.1 Type AD syntheses

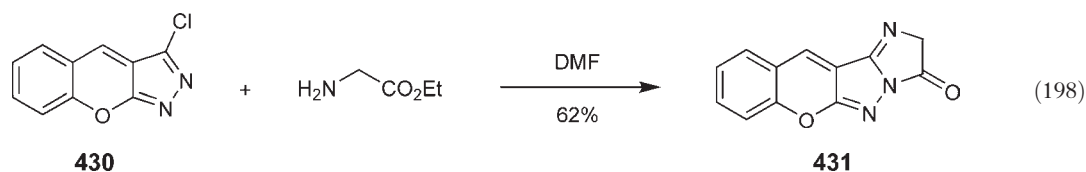
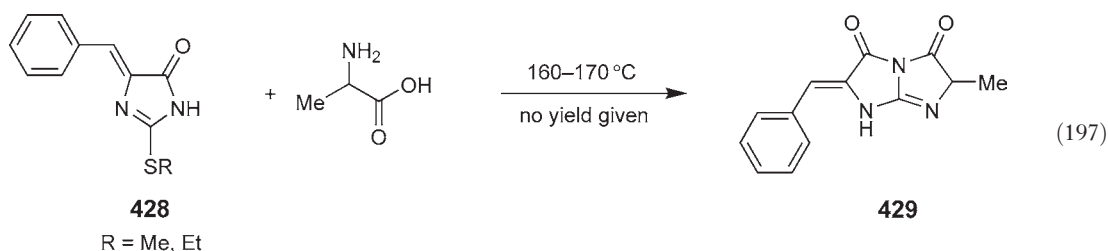
11.04.9.5.1(i) Sequential 1,4-conjugate addition/Mannich addition

The synthesis of novel heterocycle-fused troponoids was performed by reaction of the nitrosotropolone acetate **426** in neat thiazole at 70 °C giving the thiazole-condensed heterocycle **427** but in only 13% yield (Equation 196) <2004H(62)535>.



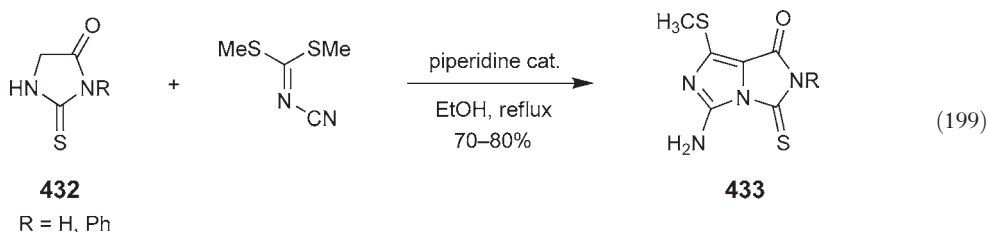
11.04.9.5.1(ii) Sequential *ipso*-substitution/lactamization

The behavior of 2-alkylthiohydantoins **428** and 3-chlorobenzopyrano[2,3-*c*]pyrazole **430** toward α -amino acid derivatives was studied. 2-Alkylthiohydantoins **428** condensed with alanine at high temperature, and the reaction of 3-chlorobenzopyrano[2,3-*c*]pyrazole **430** with ethyl glycinate was carried out in DMF at reflux to give the cycloadduct **431** in 62% yield (Equations 197 and 198) <2000PS77, 2000FA641>.



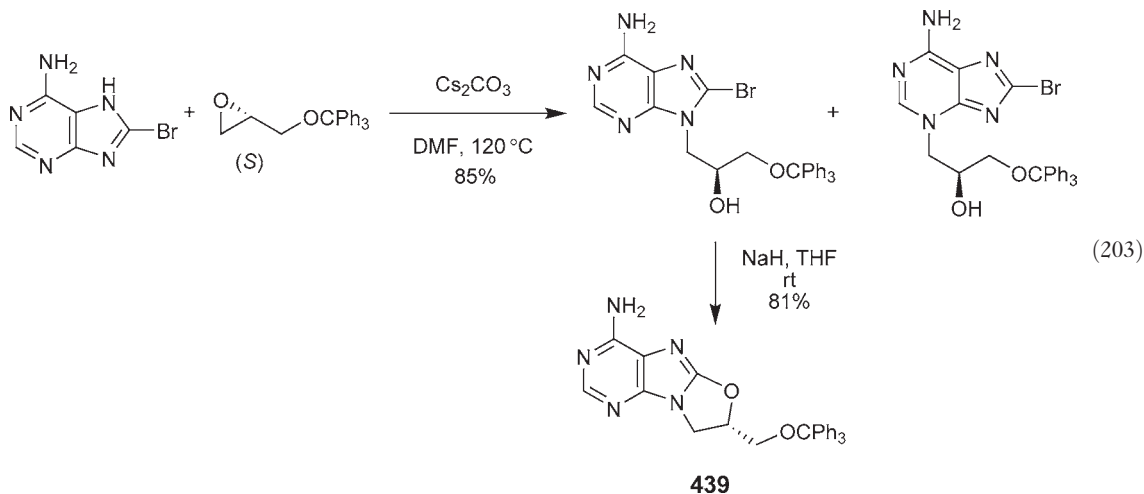
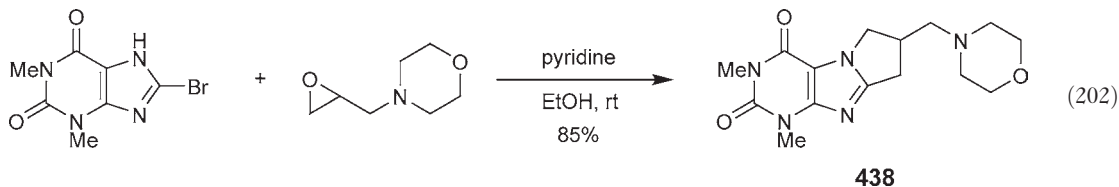
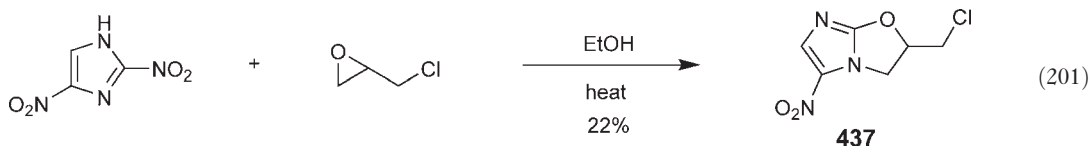
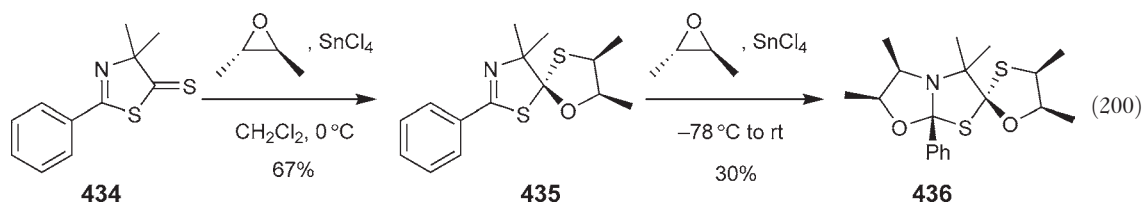
11.04.9.5.1(iii) Annellation with *N*-cyanodithioiminocarbonate

Imidazo[1,5-*c*]imidazoles **433** were formed by action of dimethyl *N*-cyanodithioiminocarbonate on the 2-thioxohydantoin derivatives **432**, as shown in Equation (199) <2004SC805>.



11.04.9.5.1(iv) Condensation with methyloxirane-type reagents

Lewis acid SnCl_4 -assisted reaction between the 1,3-thiazole-5-thione **434** and *trans*-2,3-dimethyloxirane led to the *cis*-4,5-dimethyl-1,3-oxathiolane **435**. The same Lewis acid enabled a second addition of *trans*-2,3-dimethyloxirane onto the $\text{C}=\text{N}$ bond of the 1,3-thiazole ring of **434**, leading to the formation of the tetrahydro-2*H*-thiazolo[2,3-*b*]-oxazole adduct **436** (Equation 200) <2000HCA3163>. Condensation of 2,4-dinitroimidazole, 8-bromothecophylline, and 8-bromoadenine with substituted methyloxiranes involved sequential *N*-alkylation-*ipso*-substitution and furnished a series of 2,3-dihydro-imidazo[2,1-*b*]oxazole derivatives **437**, **438**, and **439** (Equations 201–203) <2000CCC1126, 2000EJO3489, 2005TL3561, 2004JHC51>.

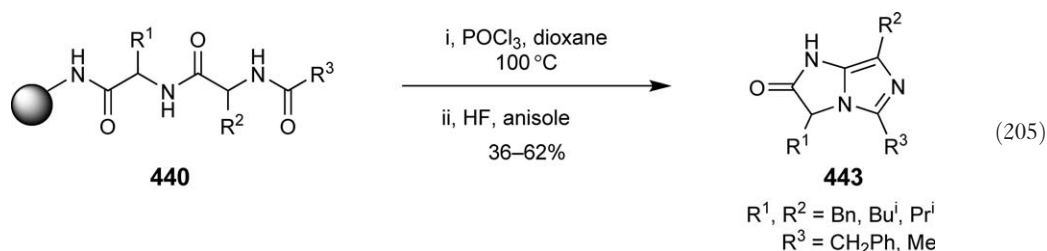
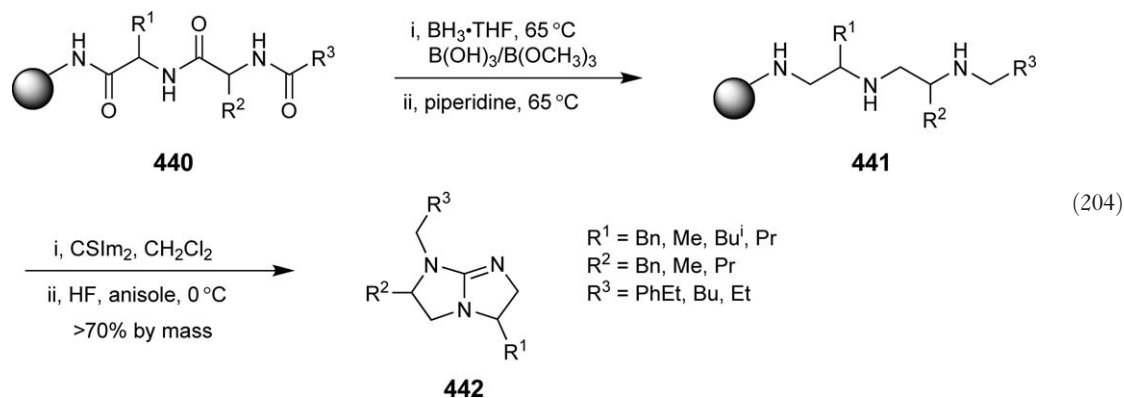


11.04.9.6 Simultaneous Formation of Both Rings

A different strategy was proposed to reach the formation of these fused bicyclic 5-5 systems that involved the elaboration of both rings simultaneously from an acyclic chain precursor.

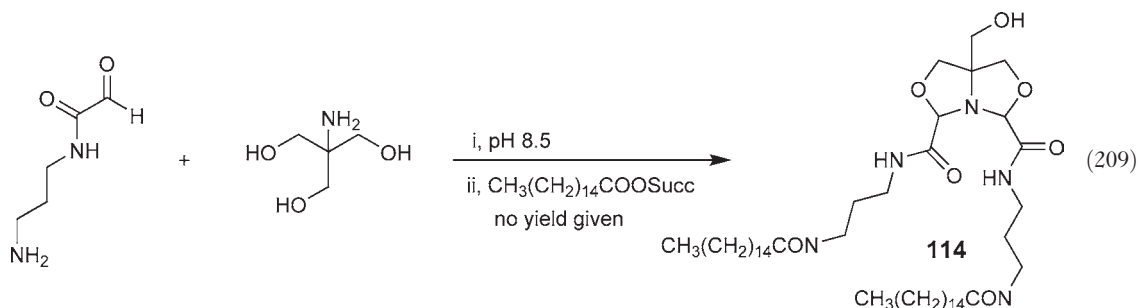
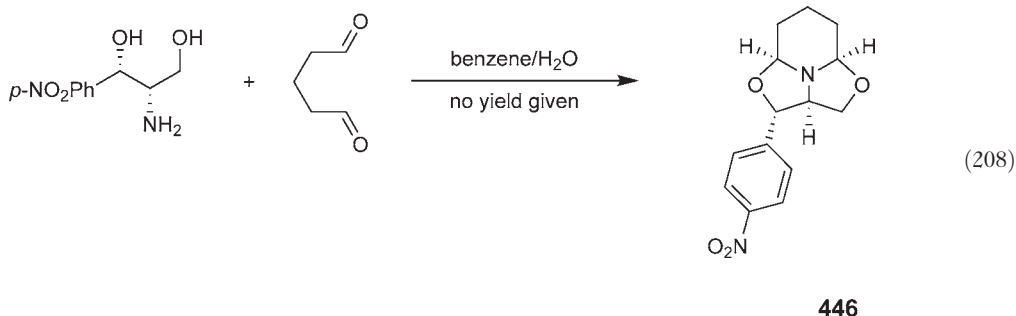
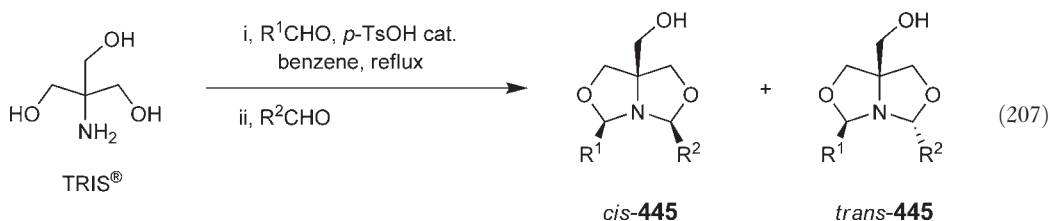
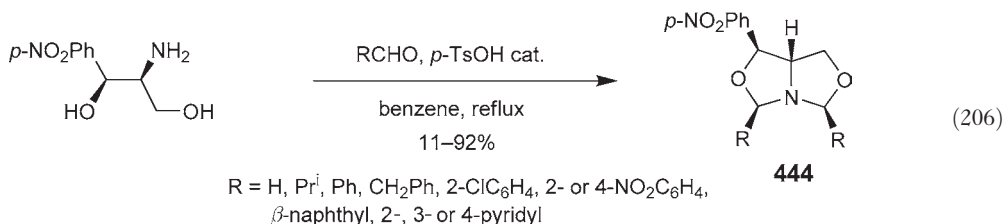
11.04.9.6.1 Cyclization of *N*-acylated dipeptides

Two examples of solid-phase synthesis of substituted 2,3,5,6-tetrahydro-imidazo[1,2-*a*]imidazoles **442** and 1*H*-imidazo[1,5-*a*]imidazol-2-ones **443** illustrate this new approach. In one case, carbonyl reduction of the resin-bound *N*-acylated dipeptides **440** followed by cyclization of the resulting triamines **441** gave the trisubstituted bicyclic guanidines **442** after cleavage from the resin (Equation 204) <1998JOC8622>, whereas the starting *N*-acylated dipeptides **440** placed under Bischler–Napieralski conditions generated the bicyclic 1*H*-imidazo[1,5-*a*]imidazol-2-ones **443** (Equation 205) <2001TL623>.



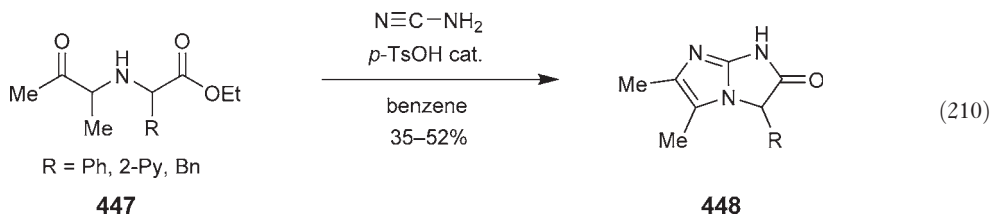
11.04.9.6.2 Cyclocondensation between substituted β -amino alcohols and carbonyl derivatives

Under thermodynamic control, acid-catalyzed ring closures of *L*-*p*-nitrophenylserinol with paraformaldehyde, aliphatic and aromatic aldehydes provided a large series of 1-aza-4-(4-nitrophenyl)-2,8-(un)substituted-3,7-dioxabicyclo[3.3.0]octane derivatives **444** as a unique diastereoisomer (Equation 206) <1997T1891>. Direct cyclocondensation between tris(hydroxymethyl)aminomethane (the so-called TRIS[®]) and two identical or different carbonyl compounds furnished a mixture of diastereomeric fused structures *cis*-**445** and *trans*-**445** that ratios strongly in favor of the *trans*-products, depending on the nature of R^1 and R^2 substituents (Equation 207) <2000T3799>. Investigations on the origin of the stereochemistry observed were realized. The results were presented in terms of conformational analysis, anomeric effects, chelating properties, and aggregation phenomena <2000CAR127, 2004EJO2644>. In addition, spontaneous condensation of (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol with glutaraldehyde <2001CHE898> and reaction of a lipophilic glyoxylic amide derivative with the TRIS[®] compound <2001TL1875> were reported to generate quite similar bicyclic adducts **446** and **114** (Equations 208 and 209).



11.04.9.6.3 Acid-promoted cyclization with cyanamide

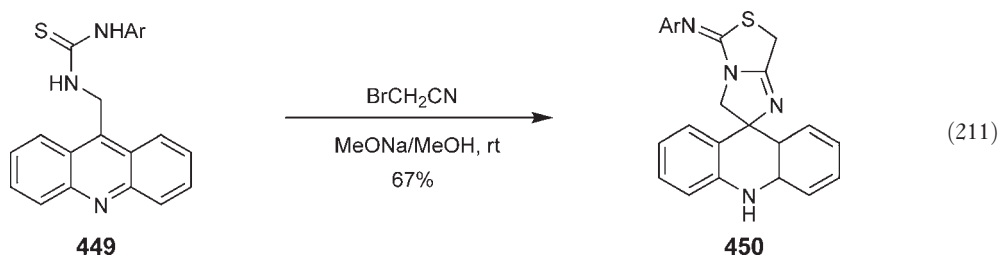
A synthesis of variously substituted imidazo[1,2-*a*]imidazol-2-ones **448** was described. These compounds were prepared by cyclocondensation of α -amino acid derivatives **447** with cyanamide (Equation 210) <1995JHC141>.



11.04.9.6.4 Reaction of thiourea with bromoacetonitrile

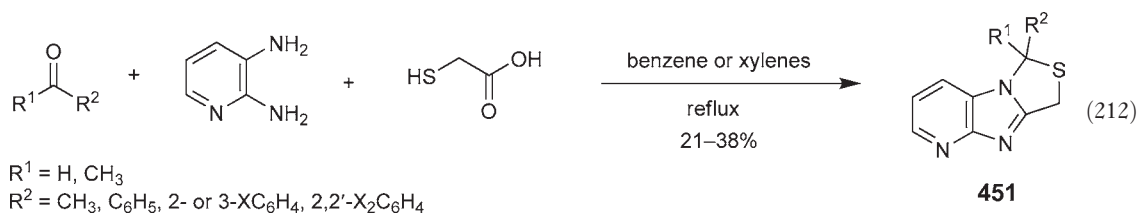
Under basic conditions, *N*-acridinylmethyl-substituted thiourea **449** placed in the presence of bromoacetonitrile gave rise to the unexpected formation of the spiro[dihydro-acridine-9(10*H*),2'-(2',7'-dihydro-3'*H*-imidazo[1,2-*c*]thiazol-5'-ylidene-*p*-nitrophenyl)amine] **450** in 67% yield. The reaction involved displacement of the bromine atom of

bromoacetonitrile by the sulfur anion followed by intramolecular attack of the thiourea nitrogen to the nitrile and subsequent addition of the imino anion to the acridinyl moiety (Equation 211) <2001JOC4416>.



11.04.9.6.5 One-pot three-component synthesis

2-Mercaptoacetic acid could be used as a versatile synthon for the synthesis of 1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole-type compounds <1996FA279, 1997FA673>. For instance, 2,3-diaminopyridine and 2-mercaptoacetic acid were reacted in a three-component reaction with a suitable carbonyl compound and provided the 1*H*,3*H*-thiazolo[3,4-*a*]-imidazo[4,5-*b*]pyridines **451** (Equation 212) <1994FA345>.

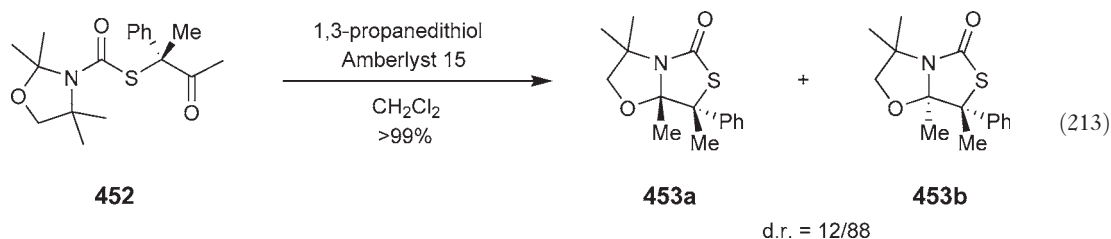


11.04.10 Ring Synthesis by Transformation of Another Ring

In contrast to the previous section, the desired bicyclic systems were prepared by modification of ring-containing precursors using very similar methods of synthesis. Various examples are depicted in this section.

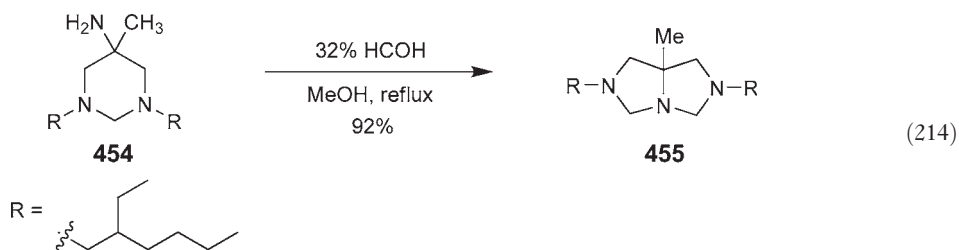
11.04.10.1 Acid-Promoted Intramolecular Condensation

Formation of enantio- and diastereoenriched 1-aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-ones **453a** and **453b** was accomplished by ring closure of acyl-substituted *S*-benzyl thiocarbamates **452** in presence of Amberlyst 15 and 1,3-propanedithiol via a rearrangement of the oxazolidine ring (Equation 213) <2000JPR828>.



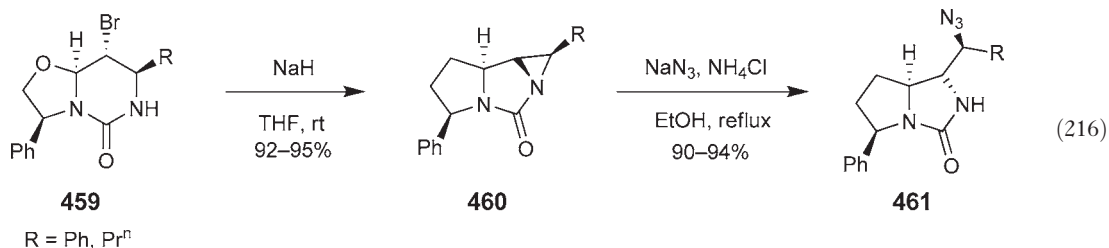
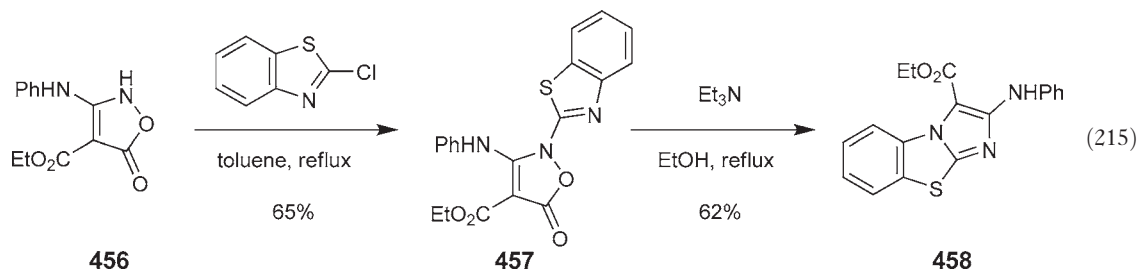
11.04.10.2 Mannich Condensation

Hexetidin **454** could be converted to hexedin **455** by action of paraformaldehyde under neutral conditions in refluxing methanol (Equation 214) <1997PHA195>.



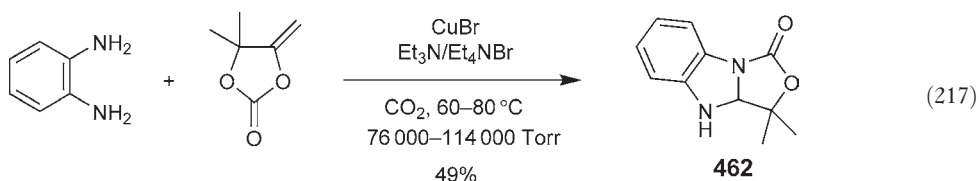
11.04.10.3 Base-Catalyzed Rearrangement

A convenient access to the imidazobenzothiazole **458** proceeded through *N*-arylation of isoxazolone **456** with 2-chlorobenzothiazole to give the 2-benzothiazol-2-yl isoxazolone **457** and its subsequent rearrangement in refluxing ethanol in the presence of triethylamine (Equation 215) <2004JCCS1347>. Ring contraction of ureides **459** involving deprotonation of the urea by sodium hydride and intramolecular alkylation generated the aziridines **460**, which could be opened regioselectively by different nucleophiles such as sodium azide. The corresponding enantiopure 7-substituted tetrahydro-imidazo [5,1-*b*]oxazol-5-ones **461** were isolated (Equation 216) <1998TL5373>.



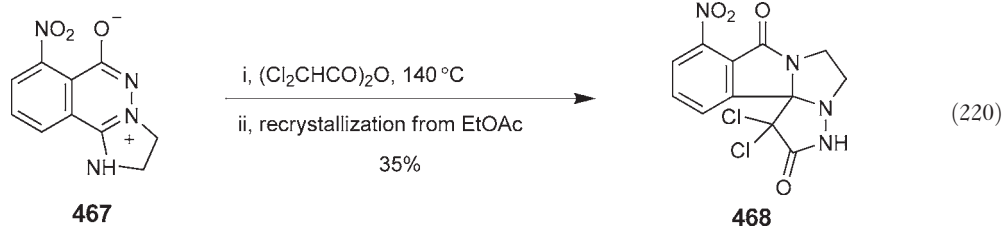
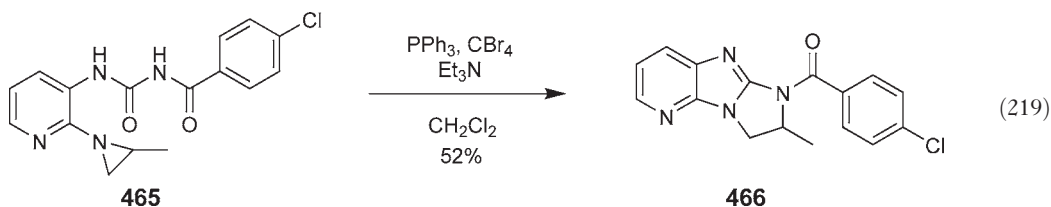
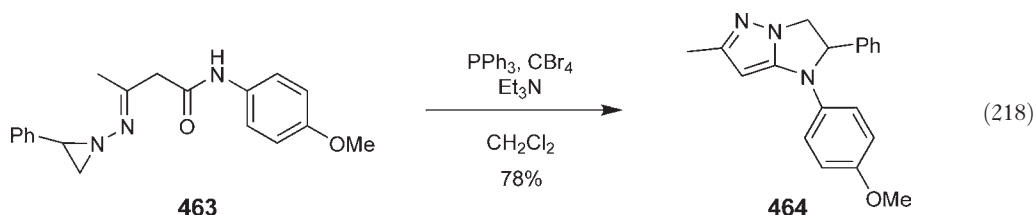
11.04.10.4 Copper-Catalyzed Condensation

A new heterocyclic system, 3*a*,4-dihydro-3*H*-benzo[4,5]imidazo[1,2-*c*]oxazol-1-one **462**, was synthesized by reaction of 4,4-dimethyl-5-methylene-1,3-dioxolan-2-one with *o*-phenylenediamine in the presence of copper bromide as catalyst in carbonyl dioxide at 60–80 °C under high pressure (Equation 217) <1999CHC216>.



11.04.10.5 Thermal Rearrangement

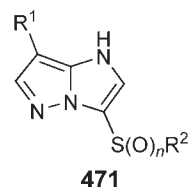
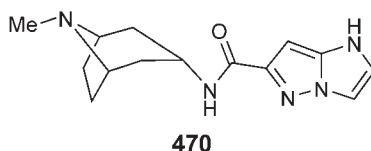
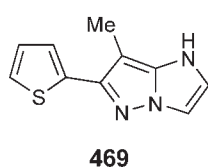
The thermal rearrangement of *N*-aziridinylimino ketenimines **463** to bicyclic 5-5 fused heterocycles such as 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazoles **464** occurred under Apple's conditions (Equation 218) <2003JHC363>. Application of these conditions to the heterocyclization reaction of 2-(2-methylaziridin-1-yl)-3-ureidopyridines **465** allowed the synthesis of the pyridine-fused heterocycles, 2,3-dihydro-1*H*-imidazo[2',3':2,3]imidazo[4,5-*b*]pyridines **466** (Equation 219) <2002JHC975>. The ring transformation of 2,3-dihydro-7-nitro-1*H*-imidazo[2,1-*a*]-phthalazin-4-ium-6-olate **467** to triazapentalenoindene **468** involved thermal rearrangement by action of dichloroacetic anhydride (Equation 220) <1994H(38)1453, 1997T7021>.



11.04.11 Important Compounds and Applications

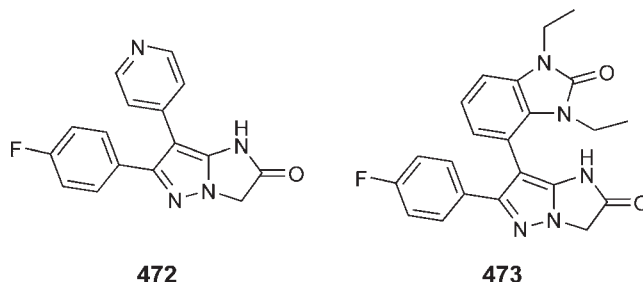
Several of the fused heterocyclic systems discussed in this chapter have useful biological activities and little has been reported concerning other applications, such as their use as additives for motor fuels or as starting materials for color photographic couplers and dyes. The most significant applications found in the literature are summarized here.

Different kinds of 1*H*-imidazole[1,2-*b*]pyrazole derivatives, already patented, have demonstrated remarkable anti-inflammatory, antiulcer, and antiallergy activity. To illustrate, compound **469** at a dose of 50 mg/kg p.o. exhibited a significant 44.2% inhibition of inflammation in a carrageenin test in Wister rats <1995JPP07278148>. Some, such as *N*-(tropanyl)imidazo[1,2-*b*]pyrazolocarboxamide **470**, were described to have potential as central nervous system (CNS) agents <1994JHC737>. Others with a similar type of nucleus, for example, **471**, have proved to be useful as starting materials for color photographic couplers and dyes <1995JPP07278455>.

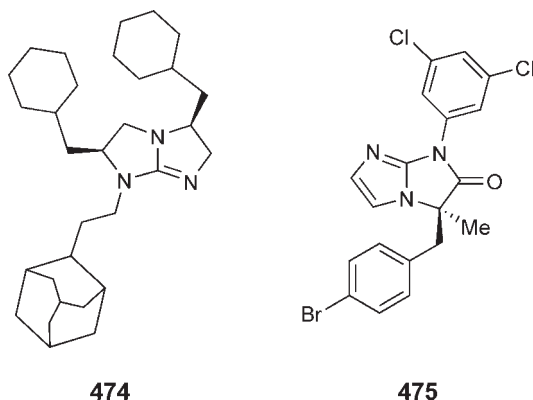


$\text{R}^1 = \text{H, halo, alkoxy, etc.}$
 $\text{R}^2 = \text{alkyl, aryl}$
 $n = 0-2$

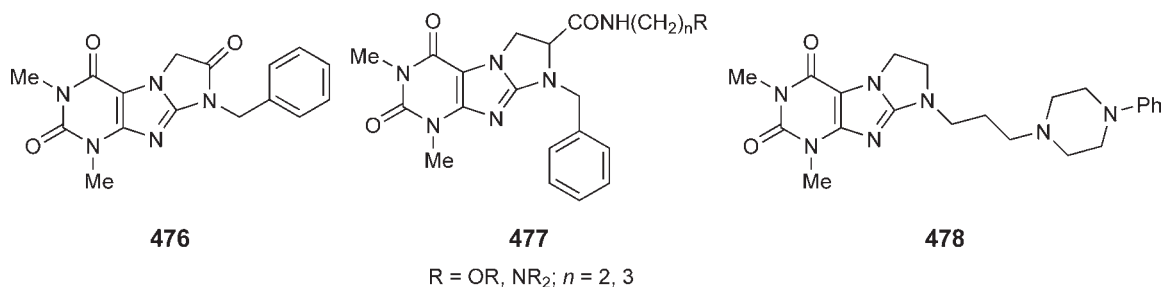
Analogs of the interesting imidazo[1,2-*b*]pyrazol-2-one 5-5-bicyclic systems were synthesized and evaluated for their possible ability to act as CNS agents <1994JHC737>. The pyridine-substituted analog **472** has been reported to cause inhibition of both interleukin-1 and tumor necrosis factor <1993EPP531901>, whereas its benzimidazolone-substituted counterpart **473** behaved like a mitogen-activated protein (MAP) kinase inhibitor with anti-inflammatory activity <2002WO2002072576>.



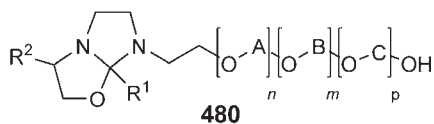
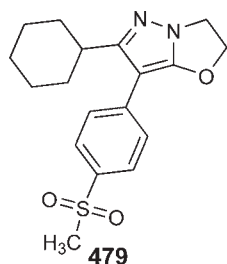
Some bicyclic guanidines, partially hydrogenated imidazo[1,2-*a*]imidazole bicyclic systems such as **474**, have been reported to have potent antifungal activities against *Candida albicans* and *Cryptococcus neoformans* <1999AAC106>. A series of structurally related imidazo[1,2-*a*]imidazol-2-ones were found to be a new class of nonpeptidic lymphocyte function-related antigen LFA-1 inhibitors that should have therapeutic potential for the treatment or prevention of inflammatory and immune cell-mediated diseases. For instance, **475** inhibited binding of leukointegrins to cell adhesion molecules (CAMs) <2001WO2001007440, 2004WO2004041827>.



Several derivatives of imidazo[2,1-*f*]theophyllines were synthesized and tested for their CNS activity. Compounds **476** showed significant antiserotonin and long-lasting hypothermic effects, and both **477** and **478** possess anti-convulsant properties <1999EJM1085, 2002FA697>.

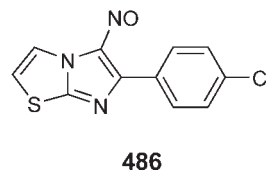
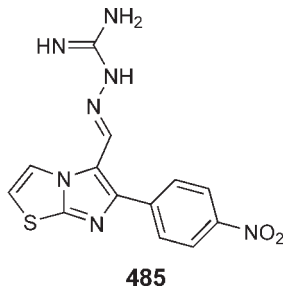
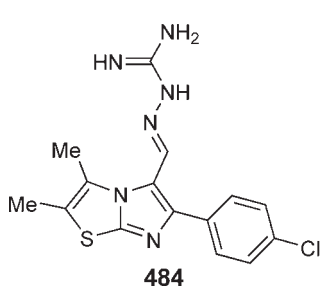
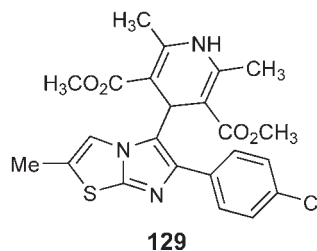
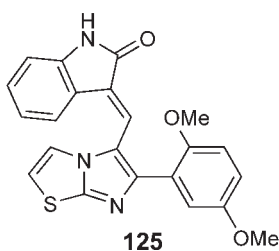
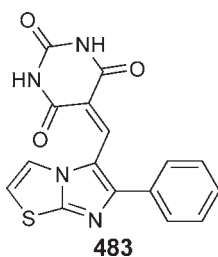
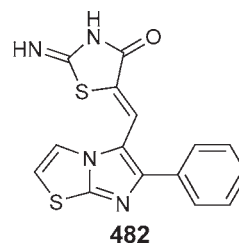
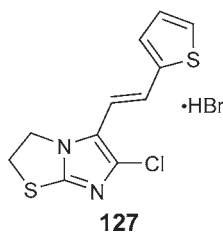
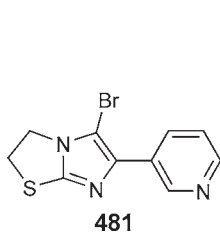


Nonsteroidal anti-inflammatory drugs are widely used to treat acute or chronic inflammation acting by inhibition of cyclooxygenase (COX) enzymes which catalyze the formation of prostaglandins. The pyrazolo[5,1-*b*]oxazolidine **479** was considered the most potent and selective COX-2 inhibitor with an IC₅₀ of 1.3 μM <2004BMC1357>. In another field, alkoxyated imidazo-oxazole compounds of general formula **480** are used as additives formulated for motor fuels <1994EPP627583>.

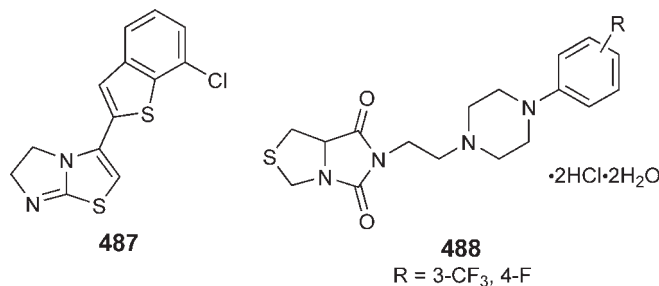


In addition to fundamental chemical interest, imidazo[2,1-*b*]thiazoles and its partially hydrogenated counterparts have a broad spectrum of biological properties. Some of them are:

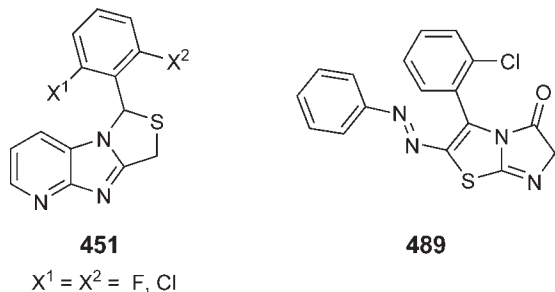
1. 5-Bromo-6-(3-pyridyl)-2,3-dihydro-imidazo[2,1-*b*]thiazole **481** was reported to be herbicidally active against *Setaria*, *Sinapis*, and *Stellaria* <1996MI247>.
2. The hydrobromide of (*E*)-6-chloro-5-(2-thienylvinyl)-2,3-dihydro-imidazo[2,1-*b*]thiazole **127** was found to be potent as an inhibitor of mitochondrial NADH dehydrogenase becoming a preferred target of commercial pesticides, especially insecticides and acaricides <1995JME1090, 1999EJM883>.
3. 6-Substituted imidazo[2,1-*b*]thiazoles with a lactam ring derived from 2-iminothiazolidine-4-one **482** and from pyrimidine-2,4,6-trione **483** and 6-substituted-2,3-dihydro-imidazo[2,1-*b*]thiazole with a bicyclic 2-indolinone system **125** were discovered as new cardotonic agents and showed a positive inotropic activity <1996EJM383, 1997EJM919>.
4. By contrast, an interesting antiarrhythmic activity was observed for compound **129** <1997EJM151>.
5. Imidazo[2,1-*b*]thiazole guanylhya zones bearing a chlorophenyl group, for example, **484**, or 3- or 4-nitrophenyl group, for example, **485**, showed mainly antitumor activity but the simultaneous presence of both antitumor and borderline positive inotropic activity was confirmed in compound **484** <1996JME2852, 2000BMC2359>, and 5-nitroso-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole **486** demonstrated significant antitubercular activity <2001EJM743>.



Recently, dihydro-imidazo[2,1-*b*]thiazole heterocycles have been evaluated as antidepressant agents. These compounds are 5-HT1A receptor agonists which inhibit neuronal reuptake of 5-hydroxytryptamine and/or noradrenaline. Thus, the 4-chlorobenzo[*b*]thiophene-substituted analog **487** displaced 5-HT1A by 60% and inhibited 5-HT and noradrenaline uptake by 97% and 103% <2001WO2001068653>. To that end, N-substituted 4,6-dioxo-imidazo[3,4-*c*]thiazoles **488** revealed an efficient analgesic activity enhanced by their lack of toxicity at high dose <2001MI1117>.



The thiazoloimidazopyridine derivatives **451** were tested for their effect on human immunodeficiency virus (HIV)-induced cytopathogenicity in a human T₄-lymphocyte cell line and showed a reproducible anti-HIV activity that caused a 50% or greater reduction of viral cytopathic effect <1994FA345>. Finally, imidazo[2,1-*b*]thiazolone **489** was found to have an antitumor activity and proved to be effective against brain tumor cell lines <2002JHC1133>.



Acknowledgments

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Biographical Sketch



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11.06

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 3:0

S. Saba and J. A. Ciaccio

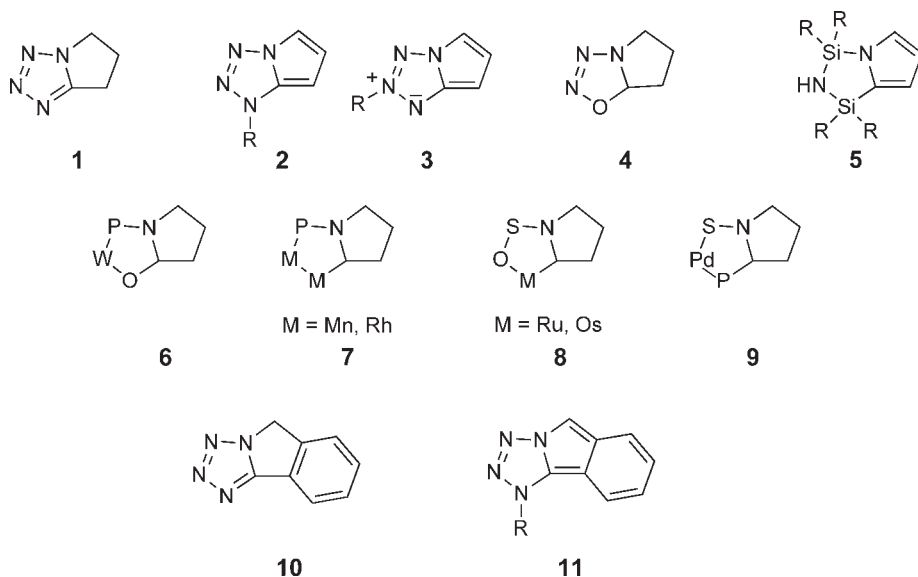
Fordham University, Bronx, NY, USA

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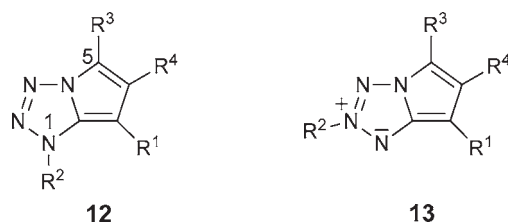
11.06.1 Introduction

This chapter expands on the review presented in CHEC-II(1996) (Chapter 8.06) covering fused 5-5 ring systems with one bridgehead nitrogen and three other heteroatoms all in the same ring <1996CHEC-II(8)191>. Since the publication of CHEC-II(1996), additional entries into such systems have appeared in the literature. The ring systems covered by this chapter are shown. These include the pyrrolo[1,2-*d*]tetrazoles **1–3**, pyrrolo[1,2-*d*]oxatriazole **4**, 2,3a-diaza-1,3-disilapentalene **5**, transition metal-containing bicyclic structures **6–9**, and tetrazolo[5,1-*a*]isoindoles **10 and 11**. No major reviews have been published that are exclusively devoted to fused bicyclic heterocycles described in this chapter; however, various aspects of tetrazoloisoindoles **10 and 11** appearing in the literature until September 2001 have been reviewed <2002CHE1019>.

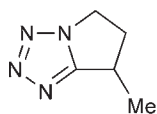
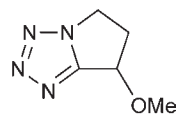


11.06.2 Theoretical Methods

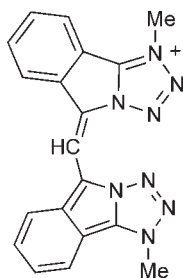
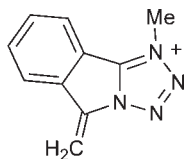
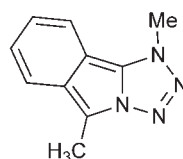
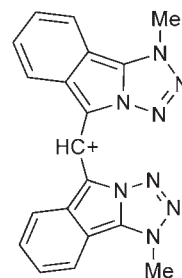
A few theoretical methods applied to ring systems discussed in this chapter have been reported. In connection with studies of the reactivity and site of electrophilic substitution in a series of substituted 1*H*-pyrrolotetrazoles **12** and (mesoionic) 2*H*-pyrrolotetrazoles **13** (Section 11.06.5.1), semi-empirical AM1 computations of atomic charges have been shown to be consistent with observation of slightly higher reactivity of isomer **13** over isomer **12** ($R^1 = H$, $R^2 = Me$, $R^3 = H$, $R^4 = H$) with C-5 as the preferred site of substitution <2001J(P1)729>.



Density functional theory methods using the hybrid B3LYP functionals have been performed to study geometries and energetics of several intramolecular [2+3] dipolar cycloadditions of azides to nitriles (Section 11.06.6.1) toward fused tetrazole formation, including tetrazoles **14 and 15** <2003JOC9076>.

**14****15**

Nonempirical quantum-chemical calculations using density functional theory were performed on cation **16** (only one resonance structure shown) and model compounds **17** (only one resonance structure shown) and **18** in order to appraise the contribution of different resonance structures to the total structure of cation **16**. Application of natural bonding orbital theory reveals significant contribution by three resonance forms in which the positive charge is either on a tetrazole ring nitrogen or delocalized on the benzene ring. A small but non-negligible contribution is also made by the carbocationic resonance structure **19** <2004JST193>.

**16****17****18****19**

11.06.3 Experimental Structural Methods

11.06.3.1 X-Ray

Crystallographic data for the bridged cluster $\text{Rh}_6(\text{CO})_{14}(\mu_2\text{-P}(\text{NC}_4\text{H}_4)_3)$ formed from the reaction of tripyrrolylphosphine and $\text{Rh}_6(\text{CO})_{15}(\text{NCMe})$ shows inclusion of the ring system **20** with bond lengths and bond angles shown in **Table 1**. The numbering of the atoms corresponds to the numbering in the original reference <2002JA8922>.

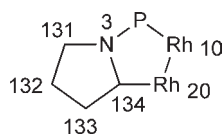
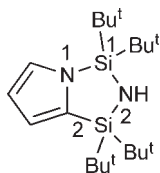
**20**

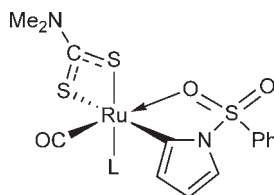
Table 1 Bond lengths (Å) and angles (°) <2002JA8922>

Bond lengths (Å)		Bond angles (deg)	
Rh(10)–Rh(20)	2.7270(9)	N(3)–P–Rh(10)	110.8(3)
Rh(10)–P	2.223(2)	P–Rh(10)–Rh(20)	89.55(6)
P–N(3)	1.735(7)	Rh(20)–C(134)–N(3)	108.2(5)
N(3)–C(131)	1.362(11)	C(134)–N(3)–P	120.6(6)
C(131)–C(132)	1.382(12)	N(3)–C(131)–C(132)	109.8(8)
C(132)–C(133)	1.385(13)	C(131)–C(132)–C(133)	107.2(8)
C(133)–C(134)	1.407(12)	N(3)–C(134)–C(133)	105.5(8)

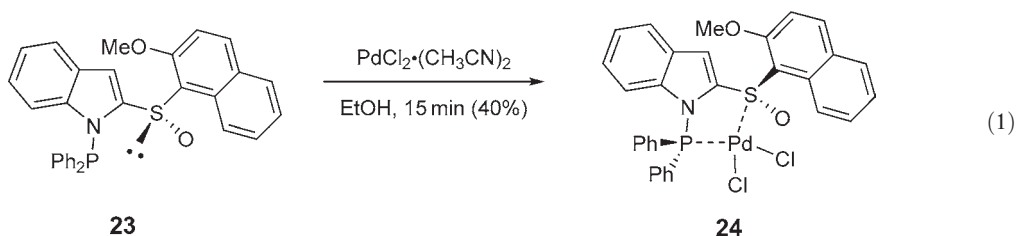
As part of the structural characterization of bicyclic heterocycle **21**, single crystal diffraction measurements have revealed the following selected bond lengths (pm) and angles (deg): Si(1)–N(2) 172.7(2), N(2)–Si(2) 173.1(2); Si(1)–N(2)–Si(2) 118.4(1) <1996JOM203>.

**21**

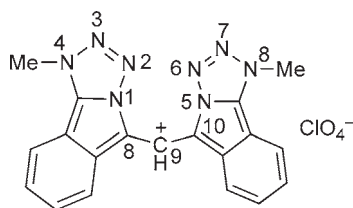
Single crystal X-ray structure determination of the neutral monophosphine complex Ru(2-C₄H₃NSO[O]Ph)(η^2 -S₂CNMe₂)(CO)(PPh₃) **22**, prepared by sequential treatment of Ru(2-C₄H₃NSO[O]Ph)Cl(CO)(PPh₃)₂ with Ag⁺ and Me₂NCS₂[−], has revealed a structure that can be described as a distorted tetrahedron, and both the dimethylthiocarbamate and *N*-phenylsulfonylpyrrolyl ligands adopt bidentate binding modes. Tables of bond lengths and bond angles for complex **22** can be found in the original reference <1995JOM219>.

**22:** L = PPh₃

N-Diphenylphosphano nitrogen-containing five-membered aromatic compounds bearing chiral sulfinyl groups have been developed as new chiral ligands in asymmetric palladium-catalyzed allylic alkylation reactions <2004T2155>. The molecular structure of the complex formed between chiral sulfoxide ligand **23** and [PdCl₂•(CH₃CN)₂] was determined by X-ray analysis to be five-membered chelate **24**, formed by coordination of the sulfinyl sulfur atom and the phosphano group to the palladium catalyst (Equation 1). Selected crystallographic data are presented in the original paper.

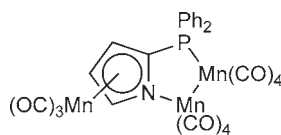
**23****24**

Voitenko *et al.* have investigated the structure of bis-(1-methyltetrazolo[5,1-*a*]isoindole-5)monomethyne cyanide perchlorate **25** by X-ray crystallography. According to the X-ray diffraction data, the organic cation in this compound possesses a twisted shape. The tricyclic segments are turned relative to each other due to repulsion between N-2 and N-6 of the tetrazole rings; the angle between mean square planes of the tricyclic fragments being 139.4°. The repulsion between the tricyclic templates also leads to significant expansion of the C-10–C-9–C-8 bond angle up to 132.7(3)°. The data also indicate very close values for respective bond lengths and bond angles in the two halves of the cation. Tables of bond lengths and bond angles can be found in the original reference <2004JST193>.



25

Single crystal structure analysis of the trinuclear complex **26** revealed the bidentate ligand 2-diphenylphosphinoazacyclopentadienylmanganese tricarbonyl bridging across an $\text{Mn}_2(\text{CO})_8$ unit as a novel four-electron donating chiral N,P-ligand <1999JOM235>. This complex is said to represent the first example of an anionic nitrogen center in a phosphine ligand <2004JCD3383>.

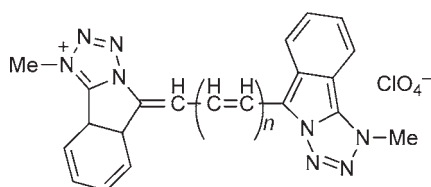


26

11.06.3.2 Electronic Spectra

The ultraviolet-visible (UV-Vis) spectra of several isomeric pyrrolotetrazoles **12** and **13** in methanol have been compared. The spectra of 2*H*-pyrrolotetrazoles **13** are characterized by pronounced bathochromic shifts of the longest wavelength compared to those of **12**; they also display green or blue fluorescence. The largest bathochromic shift for the 2*H*-pyrrolotetrazole **13** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{Ph}$) is ascribed to unhindered conjugative interaction of the phenyl group and the heterocycle, which is not possible to that extent for **12** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{Ph}$) <2001J(P1)720>.

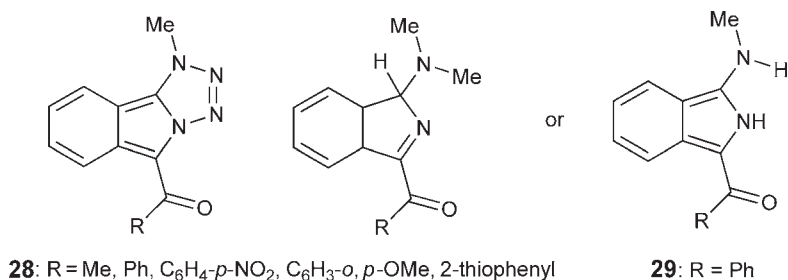
Electronic absorption spectra of complexes formed between cyanine dyes **27** with $\text{K}_3[\text{Fe}(\text{CN})_6]$ and $\text{K}_2[\text{Ni}(\text{CN})_4]$ in acetonitrile were reported <2002MI557>. The overlap of bands produced by electronic transitions of the metals with the bands due to transition with the dyes did not allow for an unambiguous conclusion regarding the coordination polyhedra of iron and nickel in these complexes.



27

11.06.3.3 IR Spectra

An explanation of the unusual stability of 5-acyl tetrazoloisindoles **28** was provided by an infrared (IR) study of their solvent-sensitive bands that permitted assignment of the bands associated to the valence mode of the $\text{C}=\text{O}$ bond in the $1700\text{--}1500\text{ cm}^{-1}$ range <2003JST171>. The position of these bands is unexpectedly low, confirming a large polarization of the $\text{C}=\text{O}$ bond, a result that was in accord with the chemical deactivation of this group. A mechanism for the formation of degradation products from air-exposed solutions of **29** in CDCl_3 was proposed with the aid of IR spectroscopy.



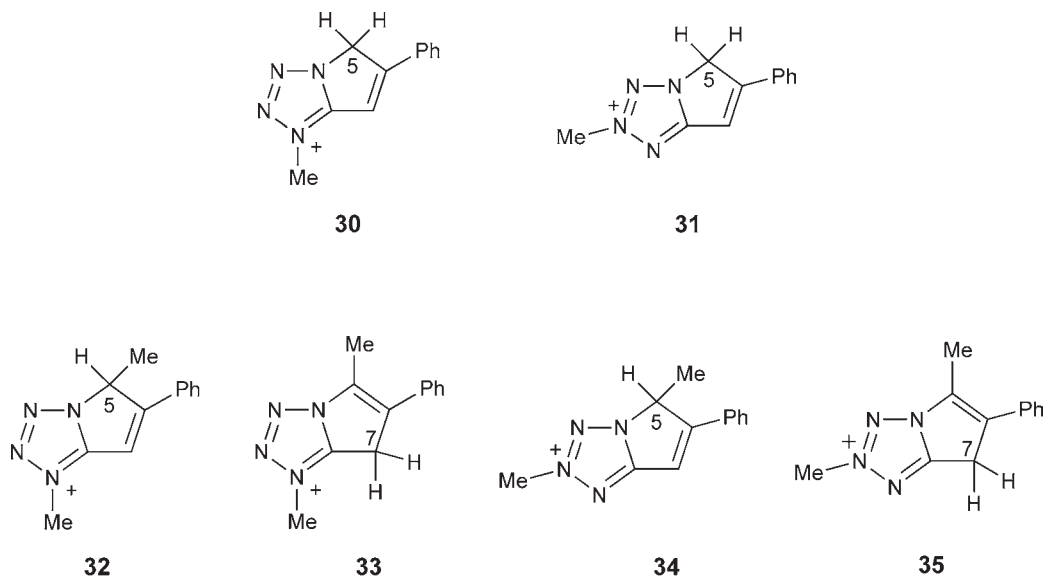
11.06.4 Thermodynamic Aspects

No significant data have been reported since 1995 on thermodynamic aspects of systems described in this chapter <1996CHEC-II(8)191>.

11.06.5 Reactivity

11.06.5.1 Reaction with Electrophiles

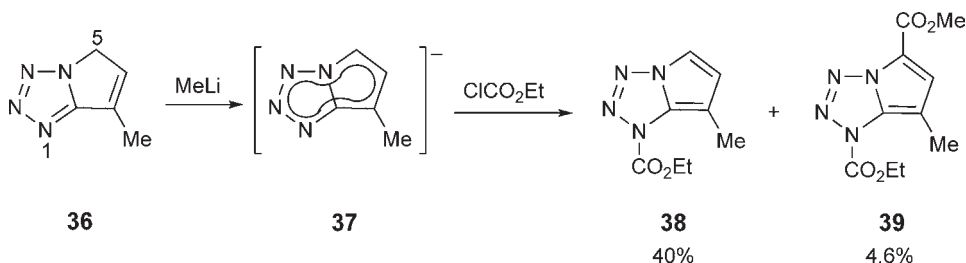
Pyrrolotetrazoles **12** and **13** produce stable salts with strong acids. This is exemplified by the formation of a picrate of **12** (R¹ = H, R² = Me, R³ = H, R⁴ = Me) and perchlorates of **12** and **13** (R¹ = H, R² = Me, R³ = H, R⁴ = Ph). Nuclear magnetic resonance (NMR) experiments have demonstrated that protonation occurs exclusively at C-5, as shown by structures **30** and **31** for the latter compounds. In contrast, protonation occurs at C-5 and C-7 for 5-substituted derivatives **12** and **13** (R¹ = H, R² = Me, R³ = Me, R⁴ = Ph) leading to cations **32–35**.



As substrates, pyrrolotetrazoles **12** and **13** have been used in a variety of electrophilic substitutions. It has been observed that with the exception of bromination, monosubstitution (acetylation, benzoylation, carbamoylation, formylation, azo coupling, nitrosation, and reaction with dimethyl acetylenedicarboxylate (DMAD)) occurs preferentially at C-5, if the 5- and 7-positions are both available. Upon bromination, double substitution occurs at C-5 and C-7 with the same substrates. It has further been observed that substitution at C-7 occurs only if C-5 is occupied <2001J(P1)729>.

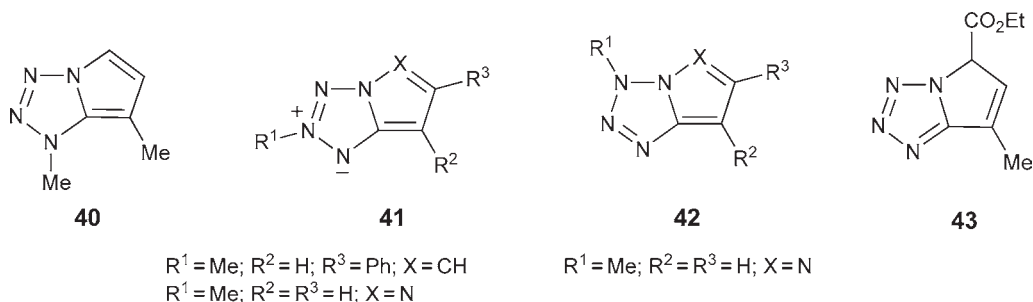
11.06.5.2 Nucleophilic Acyl Substitution of 7-Methyl-5*H*-pyrrolotetrazole Monoanion

Moderhack and Decker reexamined the ethoxycarbonylation of the anion **37** derived from 7-methyl-5*H*-pyrrolotetrazole **36** with ethyl chloroformate (Scheme 1) <1996JOC5646>.



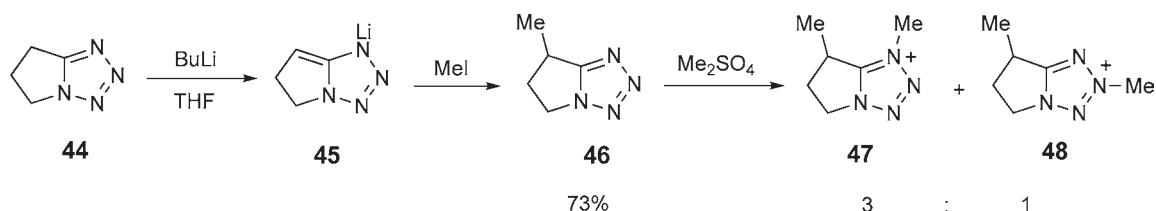
Scheme 1

Their studies revealed that acylation occurs preferentially at N(1) leading to a 40% yield of 1-(ethoxycarbonyl)-7-methyl-1*H*-pyrrolotetrazole **38** along with traces (4.6% yield) of 1,5-bis(ethoxycarbonyl)-7-methyl-1*H*-pyrrolotetrazole **39**. The 1*H*-pyrrolotetrazole structures of **38** and **39** were established by comparison of their ^{13}C NMR spectra with a model 1*H*-isomeric system **40**. Additional support for the 1*H*-isomeric system came from ^{13}C NMR spectral comparisons with pyrrolotetrazoles **41** and **42** that are representatives of the 2*H*- and 3*H*-systems. These studies showed that the ^{13}C NMR spectral data presented earlier by Dulcere and co-workers <1990JOC571> in a previous acylation study of the monoanion **37** was not compatible with what was believed to be the 5*H*-pyrrolotetrazole **43**.



11.06.5.3 Lithiation/Alkylation of Pyrrolotetrazoles

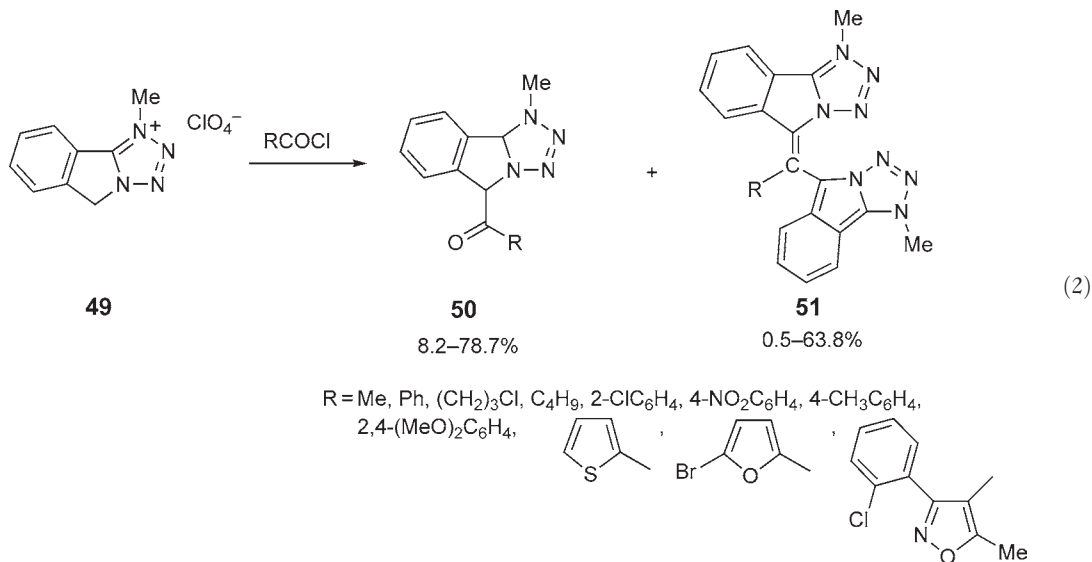
Treatment of a THF solution of trimethylenetetrazole **44** with a solution of BuLi in hexane affords a yellow to orange solution of the lithiated tetrazole **45** (structure tentatively assigned). Alkylation with MeI gives 7-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*e*]tetrazole **46** in 73% yield. Quaternization of **46** with dimethyl sulfate affords a mixture (3:1) of tetrazolium salts **47** and **48** from which PF_6^- salts were obtained by crystallization (Scheme 2) <1997MI671>.



Scheme 2

11.06.5.4 Acylation of 1-Methyltetrazolo[5,1-*a*]isoindolium Perchlorate

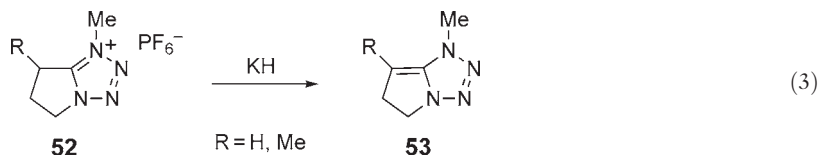
Treatment of 1-methyltetrazolo[5,1-*a*]isoindolium perchlorate **49** with acyl chlorides and triethylamine in dioxane as solvent affords a mixture of the 5-acyl-1-methyltetrazolo[5,1-*a*]isoindoles **50** and the monomethine cyanine dye **51** (Equation 2) <2004T195>.



The yields and relative amounts of products greatly depend on proportions of requisite starting compounds. Optimal yields of the acylated products are obtained using a 1:1:1 ratio of the reactants, whereas best yields of cyanine dyes are afforded when 1:1:2 molar ratios are used. Using the latter ratio, the yields of acylation products **50** are in the range 8.2–78.7% while those for the cyanines **51** are 0.5–63.8%. This acylation offers a route to cyanine dyes of the tetrazoloisoindole series with varying R groups.

11.06.5.5 Photoextrusion of Molecular Nitrogen from Annulated 5-Alkylidene-4,5-dihydro-1*H*-tetrazoles

Quast *et al.* investigated the deprotonation followed by irradiation of a series of annulated tetrazolium salts <1998EJO317>. Attempts at deprotonation of trimethylenetetrazolium hexafluorophosphates **52** and isolation of 5-alkylidene-4,5-dihydro-1*H*-tetrazoles **53** proved to be unsuccessful (Equation 3). Deprotonation of tetrazolium salt **52** (R = H) in THF-*d*₈ occurred at low temperature (−50 °C); however, slow decomposition of the product occurred, which precluded its isolation but permitted its characterization by NMR spectroscopy. Photoirradiation of the product at −60 °C (λ ≥ 320 nm) led to a complex mixture of unidentified products. Deprotonation of **52** (R = Me) also occurred at −45 °C in THF-*d*₈ but led to unidentified products upon irradiation.

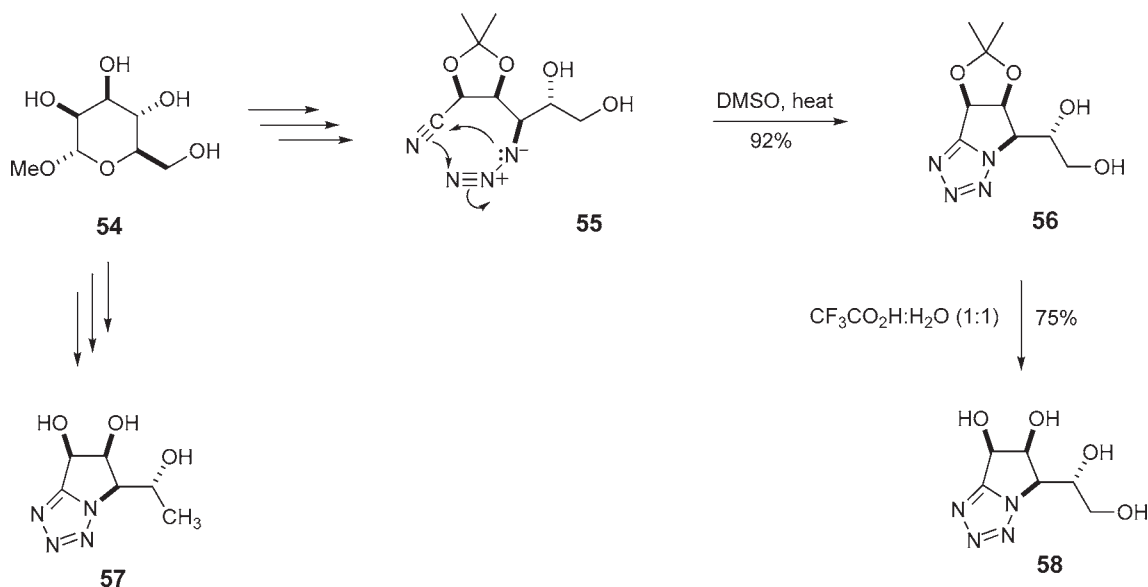


11.06.6 Synthesis

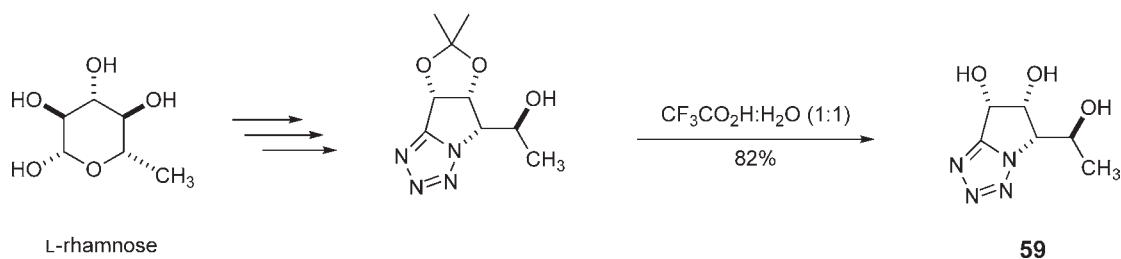
11.06.6.1 Intramolecular [2+3] Cycloaddition of Azides and Nitriles

The synthesis of D-mannotetrazole **58** and D-rhamnotetrazole **57** from mannopyranoside **54** (Scheme 3), and L-rhamnotetrazole **59** from L-rhamnose (Scheme 4), provides the first examples of tetrazole analogs of carbohydrates

in the furanose form <1999T4501, 1995TL7507>. All three novel sugar mimics were prepared by a key, intramolecular [1,3] dipolar cycloaddition of 4-azidonitriles (e.g., **55**, Scheme 3). These workers observed that the intramolecular cycloaddition leading to formation of furanose-derived [3.3.0] bicyclic tetrazoles occurs efficiently (with ca. 90% isolated yields for cyclized products) but was notably slower than that leading to pyranose-derived [4.3.0] bicyclic tetrazoles <1999T4501, 1995TL7507>.



Scheme 3



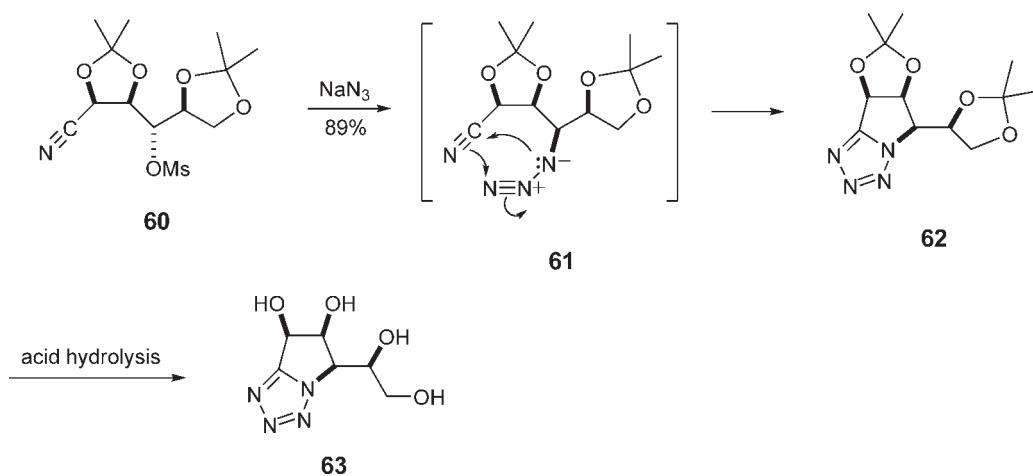
Scheme 4

A subsequent report outlined the synthesis of a diastereomer of tetrazole **58** that used similar methodology <1997TL4655>. Treatment of nitrile mesylate **60** with sodium azide affords D-talonotetrazole **62**, presumably by intramolecular [1,3] dipolar cycloaddition of a 4-azido-4-deoxy-D-talonitrile intermediate **61**. Acid hydrolysis affords the deprotected tetrazole **63** (Scheme 5).

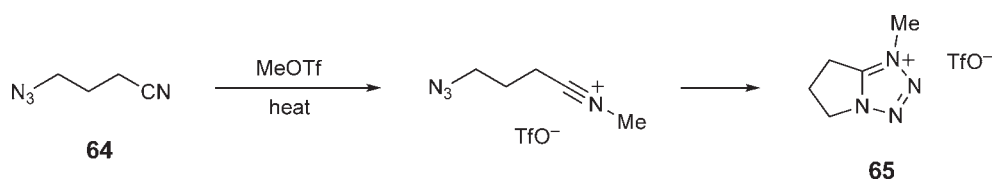
The intramolecular [2+3] cycloaddition of *in situ* generated azides to *N*-methylnitrilium ions has also been used for the preparation of tetrazolium salts. With exclusion of moisture, treatment of 4-azidobutanenitrile **64** with methyl triflate in boiling 1,2-dichloroethane affords 1-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*e*]tetrazolium trifluoromethane sulfonate **65** in 68% yield (Scheme 6) <1997MI671>.

11.06.6.2 Synthesis of 1*H*- and (Mesoionic) 2*H*-Pyrrolotetrazoles

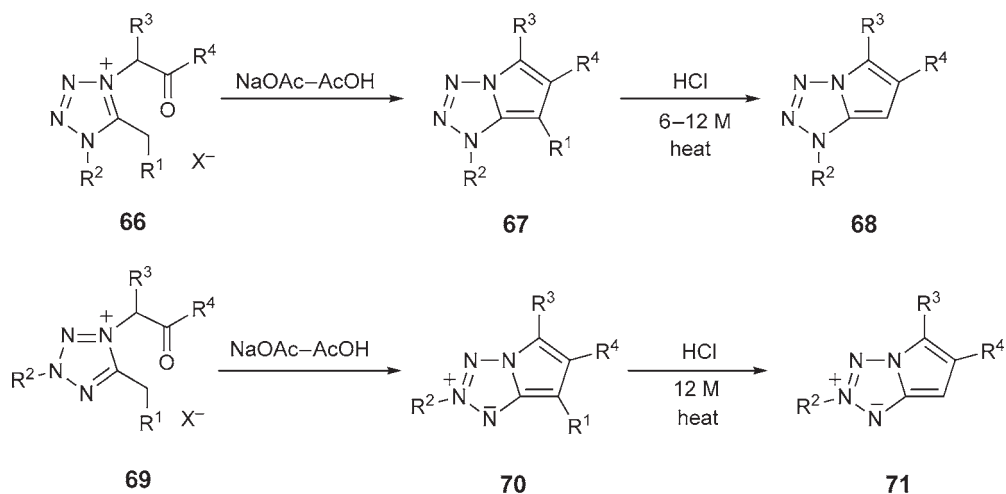
A series of substituted 1*H*- and (mesoionic) 2*H*-pyrrolotetrazoles were prepared by Moderhack *et al.* by cyclization of tetrazolium salts **66** and **69** bearing acylmethyl functions both at the ring carbon and the adjacent nitrogen (Scheme 7)



Scheme 5



Scheme 6

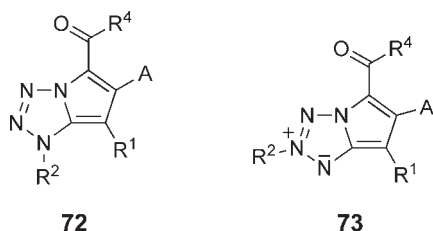


- a: $\text{R}^1 = \text{Ac}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Ph}$
 b: $\text{R}^1 = \text{CO}_2\text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Ph}$
 c: $\text{R}^1 = \text{CO}_2\text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{Ph}$
 d: $\text{R}^1 = \text{CO}_2\text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = 4\text{-BrC}_6\text{H}_4$
 e: $\text{R}^1 = \text{Ac}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$
 f: $\text{R}^1 = \text{CO}_2\text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$
 g: $\text{R}^1 = \text{Ac}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Ph}$
 h: $\text{R}^1 = \text{Ac}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$

Scheme 7

<2001J(P1)720>. These cyclizations were mediated with sodium acetate–acetic acid buffers affording moderate to good yields (52–86%) and low to moderate yields (10–60%) of 7-acyl-substituted 1*H*- and (mesoionic) 2*H*-pyrrolotetrazole derivatives **67a–g**, and **70a–d** and **70f–h**, respectively. In most cases, deacylation of pyrrolotetrazoles **67** and **70** could be effected easily by heating with HCl affording moderate to excellent yields of **68a–e** and **71a–e**.

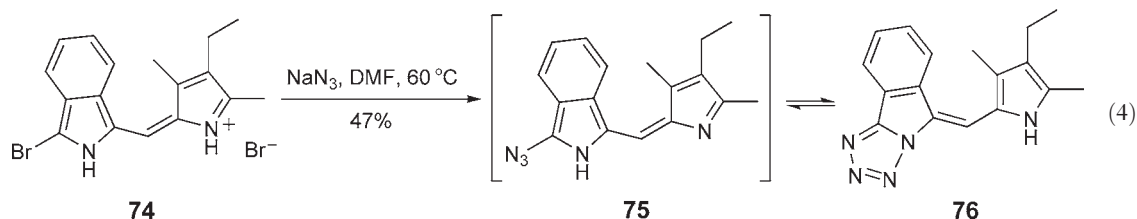
Cyclization of tetrazole derivatives **66a**, **66e**, and **69e–h** was also achieved by heating in the presence of anhydrides and base, which gave 5,7-diacyl pyrrolotetrazoles **72a–c**, and **73a** and **73d–i**, respectively, in moderate to excellent yields.



- a: R¹ = Ac; R² = Me; R⁴ = Me; A = H
 b: R¹ = Ac; R² = Me; R⁴ = Ph; A = Me
 c: R¹ = Ac; R² = Me; R⁴ = Me; A = Me
 d: R¹ = CO₂Me; R² = Me; R⁴ = Me; A = H
 e: R¹ = Ac; R² = Ph; R⁴ = Ph; A = H
 f: R¹ = Ac; R² = Ph; R⁴ = Me; A = H
 g: R¹ = CO₂Me; R² = Me; R⁴ = Me; A = Me
 h: R¹ = Ac; R² = Ph; R⁴ = Ph; A = Me
 i: R¹ = Ac; R² = Ph; R⁴ = Me; A = Me

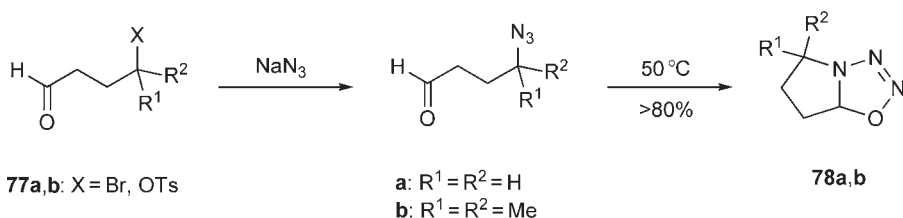
11.06.6.3 Synthesis of 8-Ethyl-7,9-dimethyltetrazolo[1,5-*i*]benzopyrromethene

The reaction of the C(Hal)=N -function with azide ion or hydrazoic acid is known to give the tetrazole system. As part of a mechanistic study of the one-pot synthesis of an azadibenzoporphyrine in 84% isolated yield from reaction of a 1-bromobenzopyrromethene hydrobromide **74** with sodium azide at 140 °C, **74** was treated with azide at lower temperature (60 °C) in an attempt to isolate the proposed azide mechanistic intermediate **75**; however, the fused tetrazole **76** was isolated in 47% yield (identified by X-ray analysis) (Equation 4) <1999MI530>. Upon heating a dimethyl formamide (DMF) solution of tetrazole **76** to 140 °C for 1 h, the desired porphyrin was indeed obtained in 14% yield, consistent with the temperature-dependent equilibrium between tetrazole and azide that has been observed with some fused tetrazoles.



11.06.6.4 Synthesis of 5,6,7,7a-Tetrahydro-pyrrolo[1,2-*d*]-[1.2.3.4]oxatriazoles

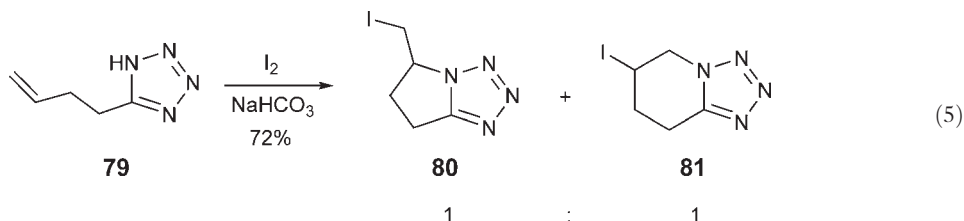
Tandem nucleophilic substitution–[2+3] cycloaddition reaction of 4-bromo- and 4-toluenesulfonyloxy aldehydes **77** with sodium azide in DMF at 50 °C affords excellent yields (>80%) of substituted pyrrolo[1,2-*d*][1.2.3.4]oxatriazoles **78** (Scheme 8) <2002HAC307>.



Scheme 8

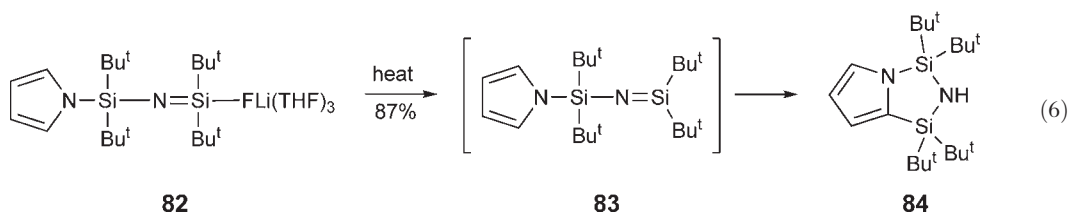
11.06.6.5 Synthesis of 5-Iodomethyl-6,7-dihydro-tetrazolo[1,5-*a*]pyrrole

Iodocyclization of the olefinic tetrazole 5-but-3-enyl-1*H*-tetrazole **79** using NaHCO₃ and I₂ in anhydrous acetonitrile at 0 °C under argon atmosphere in the dark affords a 72% isolated yield of a 1:1 mixture of 5-iodomethyl-6,7-dihydro-tetrazolo[1,5-*a*]pyrrole **80** and 6-iodo-5,6,7,8-tetrahydro-tetrazolo[1,5-*a*]pyridine **81** (Equation 5) <2003T6759>.



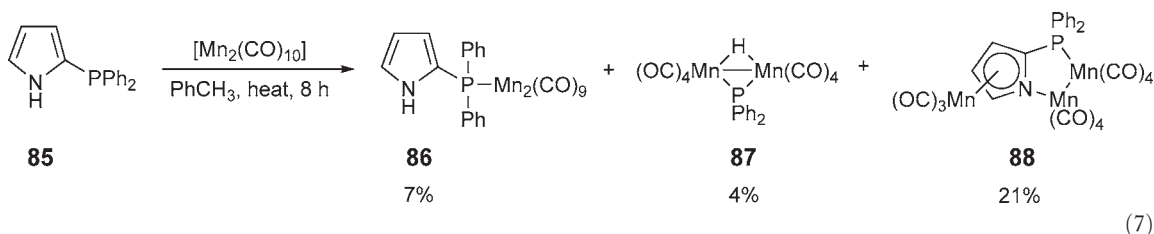
11.06.6.6 Synthesis of 2,2,4,4-Tetra-*tert*-butyl-1,3-diaza-2,4-disilabicyclo[3.3.0]octane

Under drastic thermal conditions, the iminosilane–LiF adduct **82** eliminates LiF and the iminosilane intermediate **83** rearranges intramolecularly by C–H bond insertion affording 2,2,4,4-tetra-*tert*-butyl-1,3-diaza-2,4-disilabicyclo[3.3.0]octane **84** in 87% yield (Equation 6) <1996JOM203>.



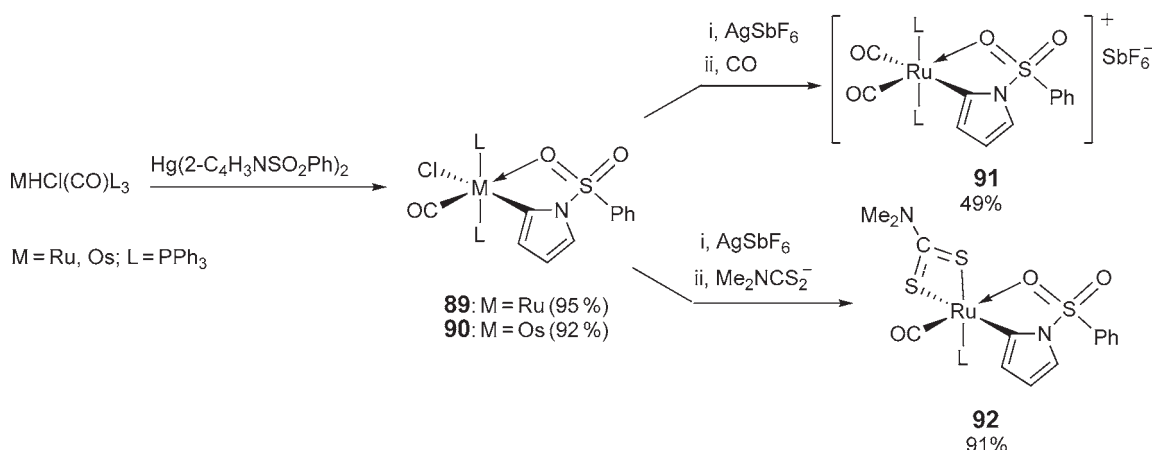
11.06.6.7 Synthesis of a Trinuclear Manganese Complex from the Bidentate Ligand 2-Diphenylphosphinoazacyclopentadienyl Tricarbonyl

Diphenyl(2-thienyl)phosphine reacts with [Mn₂(CO)₁₀] to afford μ -thienyl complexes via P–C bond cleavage. In order to establish whether or not the ligand diphenyl(2-pyrrolyl)phosphine **85** behaves like the analogous thienylphosphine, it was treated with [Mn₂(CO)₁₀] for 8 h in refluxing toluene. This led to a mixture containing low isolated yields of a simple substitution product **86** (7%) and a complex obtained by P–C bond cleavage (**87**, 4%), along with a more significant amount (21% yield) of the trinuclear complex **88** as a red, microcrystalline solid (Equation 7) <1999JOM235>. Treatment of **85** with [Mn₂(CO)₁₀] at room temperature in toluene with UV irradiation for 20 h affords only two P–C cleavage products in moderate yields.



11.06.6.8 Monomercurated *N*-Protected Pyrroles as Pyrrolyl Group Transfer Reagents to Ruthenium and Osmium

Transition metal 2-pyrrolyl *N*-phenylsulfonyl derivatives **89** and **90** are afforded in 95% and 92% yields, respectively, by treatment of $\text{MHCl}(\text{CO})(\text{PPh}_3)_3$ ($\text{M} = \text{Ru}, \text{Os}$) with $(2\text{-C}_4\text{H}_3\text{NSO}[\text{O}]\text{Ph})_2\text{Hg}$ (Scheme 9) <1995JOM219>.

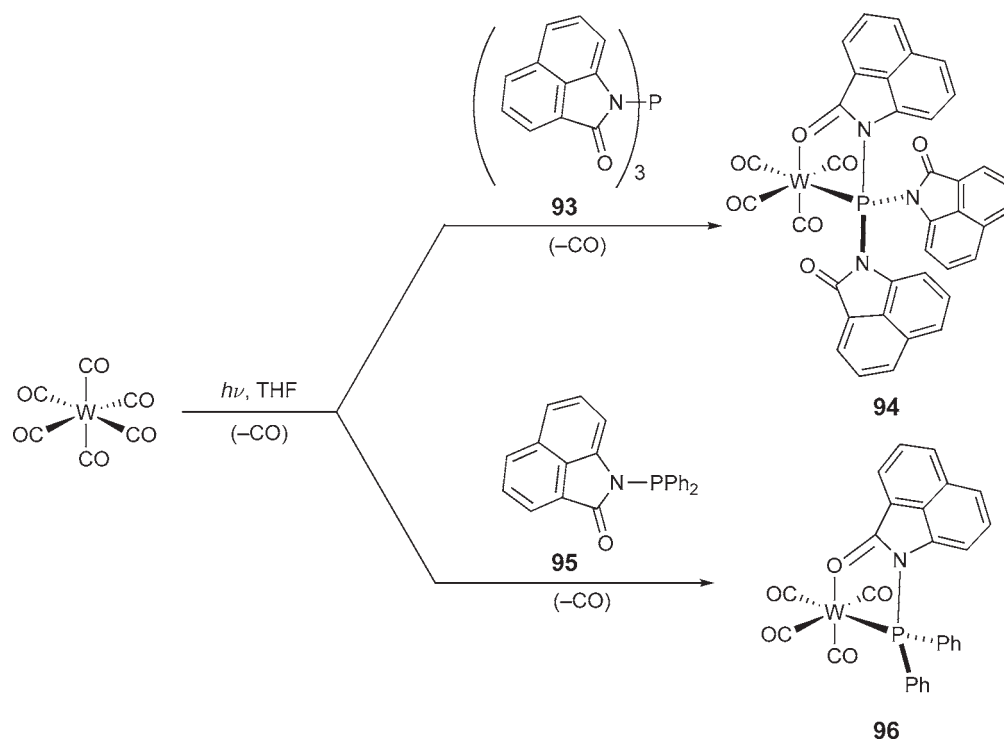


Scheme 9

The presence of a chelate ring in **89** and **90** was indicated by the very low $\nu(\text{SO})$ IR spectral values, suggesting coordination of the phenyl sulfonate group in both complexes; however, two doublets in the ^{31}P NMR spectra of both **89** and **90** indicated a mutually *trans* arrangement of ligands, consistent with the *N*-phenylsulfonylpyrrolyl group forming a five-membered chelate ring in which the sulfur-bound phenyl group is directed toward one PPh_3 ligand while the terminal oxo group is directed toward the other. Sequential treatment of **89** with Ag^+ and $\text{Me}_2\text{NCS}_2^-$ affords a complex (**92**; 91% yield) with a chelate ligand of a similar type. The dicarbonyl cationic complex **91** is afforded in 49% yield upon sequential treatment of **89** with Ag^+ followed by CO .

11.06.6.9 Preparation of Tungsten Tetracarbonyl Complexes with Bidentate P,O-Bound Naphtholactamatophosphane Ligands

Photocatalytic activation of $\text{W}(\text{CO})_6$ in THF and subsequent addition of **93** and **95** leads to the tetracarbonyl complexes **94** and **96**, respectively; both exhibit a bidentate, P,O-bound naphtholactamatophosphane ligand (Scheme 10) <2003ZFA223>.



Scheme 10

11.06.7 Important Compounds and Applications

11.06.7.1 Sugar-Based Furanotetrazoles as Glycosidase Inhibitors

A number of naturally occurring polyhydroxylated nitrogen heterocycles behave as sugar mimics toward glycosidases and other sugar-processing enzymes (e.g., **97**, Table 2). Bicyclic aromatic analogs that have the aromatic ring linking the pseudo-anomeric center to the ring nitrogen often display a higher level of inhibition, perhaps due to the polyhydroxylated moiety being effectively locked by the rigid aromatic ring in a conformation favorable to inhibition <1999T4489, 1995TL7511>. Polyhydroxylated pyrrolidines are often more potent inhibitors of glycosidases that process six-membered pyranoside substrates than their piperidine, six-membered, equivalents <1999T4501>; however, it has been shown that, while D-pyranotetrazoles **98** and **99** are potent mannosidase inhibitors, the D-furanotetrazoles **57** and **58** are not (Table 2) <1999T4489, 1995TL7511>. In contrast, the tetrazole of L-rhamnofuranose **59** is a much more potent inhibitor of mannosidases than the pyranose equivalent **100** (Table 3) <1999T4489, 1996TL8565>. Although azamannofuranose analogs are usually more potent inhibitors of α -mannosidase than are azamannopyranoses, it appears from these workers' results that this may not be true for analogs with an sp^2 carbon at the pseudo-anomeric position <1999T4489>.

11.06.7.2 Structural Identification of a Palladium Complex with a Chiral Sulfoxide Ligand Used in Asymmetric Palladium-Catalyzed Allylic Alkylations

A mechanism for the asymmetric induction for Pd-catalyzed allylic alkylations using chiral ligands such as **23** was proposed on the basis of stereochemical results and the X-ray structure of the intermediate Pd complex **24** <2004T2155>. The enantioselectivity of the alkylations, an example of which is shown in Equation (8), was rationalized by a conformational equilibrium that favored one of two possible π -allylpalladium complexes due to steric interference between the aryl substituent on the sulfinyl group of **24** and the phenyl of the π -allyl system.

Table 2 Some pyranose and furanose tetrazoles as glycosidases; percentage inhibition at ~1 mM <1999T4489>

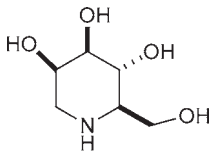
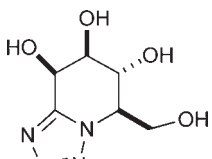
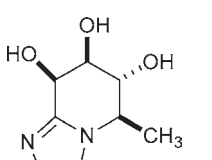
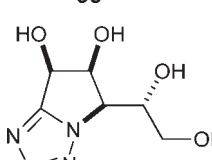
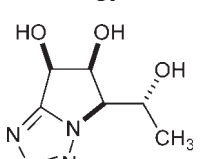
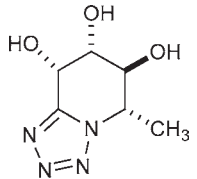
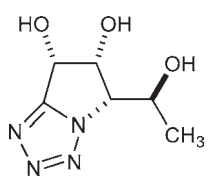
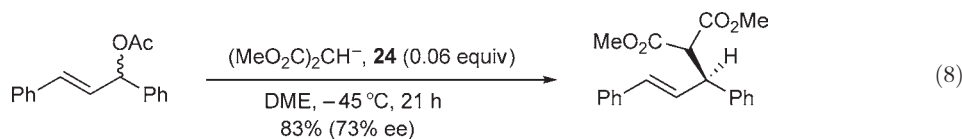
Substrate	α -Mannosidase (human liver)	β -Mannosidase (human liver)
 97	58	4
 98	56	28
 99	92	2
 57	0	4
 56	0	4

Table 3 Comparison of an L-rhamnopyranose and L-rhamnofuranose as glycosidases; percentage inhibition at ~1 mM <1999T4489, 1996TL8565>

Enzyme	 100	 59
α -Mannosidase (jack bean)	0	0
α -Rhamnosidase (<i>P. decumbens</i>)	25	100 (K_i 5.6×10^{-5} M)



11.06.8 Further Developments

The molecular structure of a complex formed between cyanine dye **27** ($n = 1$) with $K_2[Ni(CN)_4]$ has been shown by X-ray diffraction to consist of two organic cations and a centrosymmetric inorganic dianion $[Ni(CN)_4]^{2-}$, and it is apparently only the second cyanine molecular complex whose structure has been reported to date <2006MIIm103>.

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11.05

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 2:1

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11.05.1 Introduction

The [5,5]-fused bicyclic ring system with one fusion nitrogen atom and three additional heteroatoms in a 2:1 distribution over both five-membered rings (2N1) is the origin of a great number of structures. The additional heteroatoms are mainly nitrogen, oxygen, or sulfur, and less commonly phosphorus or silicon atoms.

The various types of [5,5] (2N1)-ring systems are shown in (Table 1). The first column refers to the position of the heteroatoms; the position of the fusion nitrogen atom is given in parentheses. In the second column, the heteroatoms are quoted in the order of their position, the slash indicating the position of the fusion nitrogen atom at 4- or 7-position. The last two columns survey the [5,5] (2N1)-ring systems covered in CHEC-II and CHEC-III.

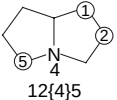
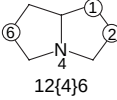
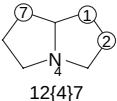
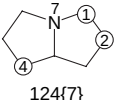
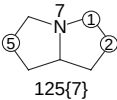
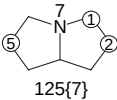
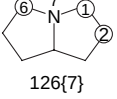
Review reports on the synthesis of bicyclic 5-5 systems with one ring junction nitrogen atom featuring three extra heteroatoms (2:1) have been previously published in this series <1996CHEC-II(8)123> and in a periodic series of volumes dedicated to heterocyclic chemistry <1998AHC271>.

11.05.2 Theoretical Methods

Two kinds of pyrazolotriazole magenta dyes are used in color photographic materials. One is the 1*H*-pyrazolo[5,1-*c*]-[1,2,4]triazole skeleton, and the other is the 1*H*-pyrazolo[1,5-*b*][1,2,4]triazole skeleton as shown in the representative azomethine dye **1** (Figure 1) <1994J(P2)531>.

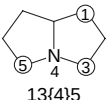
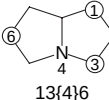
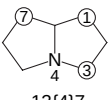
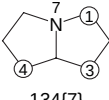
Extensive *ab initio* modeling of the excited states of pyrazolotriazole dyes such as (Z)-*N*¹-(3,6-dimethyl-7*H*-pyrazolo[5,1-*c*][1,2,4]triazol-7-ylidene)-*N*⁴,*N*⁴-dimethylbenzene-1,4-diamine **2** and (Z)-*N*¹-(2,6-dimethyl-7*H*-pyrazolo[1,5-*b*][1,2,4]triazol-7-ylidene)-*N*⁴,*N*⁴-dimethylbenzene-1,4-diamine **3** (Figure 1) have been carried out, highlighting the value of the computational models in predicting actual chemical behavior, even in a relatively difficult case such as that of the chemistry of excited states <2001J(P2)953>.

Table 1 [5,5] Fused ring systems (2N1): one fusion nitrogen atom, two heteroatom in one fused ring, and one in the other ring

<i>Topology of heteroatom positions</i>	<i>Heteroatoms in positional order</i>	<i>Name of (5,5) (2N1) system</i>	<i>CHEC-II</i>	<i>CHEC-III</i>
 12{4}5	ON/O	Isoxazolo[2,3- <i>d</i>][1,2,4]oxadiazole		
	ON/N	Pyrazolo[1,5- <i>d</i>][1,2,4]oxadiazole		
	NS/O	Isoxazolo[3,2- <i>c</i>][1,2,4]thiadiazole		
	NN/N	Pyrazolo[5,1- <i>c</i>][1,2,4]triazole	+	+
	PS/N	Pyrazolo[1,5- <i>c</i>][1,3,4]thiazaphosphole	—	
 12{4}6	NN/S	Thiazolo[3,4- <i>c</i>][1,2,4]triazole	+	+
	NN/N	Imidazo[5,1- <i>c</i>][1,2,4]triazole		+
 12{4}7	ON/O	Oxazolo[3,2- <i>d</i>][1,2,4]oxadiazole	+	
	ON/S	Thiazolo[3,2- <i>d</i>][1,2,4]oxadiazole	+	
	ON/N	Imidazo[1,2- <i>d</i>][1,2,4]oxadiazole	+	+
	SSi/N	Imidazo[1,2- <i>d</i>][1,4,2]thiazasilole		
	SS/N	Imidazo[2,1- <i>c</i>][1,2,4]dithiazole	+	+
		[1,2,4]Dithiazolo[4,3- <i>a</i>]benzimidazole		+
	SN/N	Imidazo[1,2- <i>d</i>][1,2,4]thiadiazole	—	+
		[1,2,4]Thiadiazolo[4,3- <i>a</i>]benzimidazole	+	+
	NO/O	Oxazolo[2,3- <i>c</i>][1,2,4]oxadiazole	—	
		[1,2,4]Oxadiazolo[3,4- <i>b</i>]benzoxazole	+	
	NO/S	Thiazolo[2,3- <i>c</i>][1,2,4]oxadiazole	—	
		[1,2,4]Oxadiazolo[3,4- <i>b</i>]benzothiazole	+	
		Imidazo[2,1- <i>c</i>][1,2,4]oxadiazole	+	
	NS/O	Oxazolo[2,3- <i>c</i>][1,2,4]thiadiazole	+	
		[1,2,4]Thiadiazolo[3,4- <i>b</i>]benzoxazole		
	NS/S	Thiazolo[2,3- <i>c</i>][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[3,4- <i>b</i>]benzothiazole	+	+
		Imidazo[2,1- <i>c</i>][1,2,4]thiadiazole	+	
		[1,2,4]Thiadiazolo[4,3- <i>a</i>]benzimidazole	+	
	NN/O	Oxazolo[2,3- <i>c</i>][1,2,4]triazole	—	+
		[1,2,4]Triazolo[3,4- <i>b</i>]benzoxazole	+	+
	NN/S	Thiazolo[2,3- <i>c</i>][1,2,4]triazole	+	+
		[1,2,4]Triazolo[3,4- <i>b</i>]benzothiazole	+	+
	NN/Se	Selenazolo[2,3- <i>c</i>][1,2,4]triazole	+	
	NN/N	Imidazo[2,1- <i>c</i>][1,2,4]triazole	+	+
		[1,2,4]Triazolo[4,3- <i>a</i>]benzimidazole	+	+
	NP/S	Thiazolo[3,2- <i>d</i>][1,4,2]diazaphosphole	+	+
		[1,4,2]Diazaphospholo[5,1- <i>b</i>]indazole	+	+
 124{7}	SOS/	Thiazolo[3,2- <i>c</i>][1,2,3]oxathiazole	+	
	NNS/	Thiazolo[3,2- <i>c</i>][1,2,3]triazole	+	+
	NNN/	[1,2,3]Triazolo[1,5- <i>a</i>]benzothiazole	+	+
		Imidazo[1,2- <i>c</i>][1,2,3]triazole	+	+
	PSN/	Imidazo[1,2- <i>c</i>][1,2,3]thiazaphosphole	+	
 125{7}		[1,2,4]Diazaphospholo[5,4- <i>b</i>]benzothiazole	+	
 125{7}	NNO/	Oxazolo[3,4- <i>c</i>][1,2,3]triazole	+	
	NNN/	Imidazo[1,5- <i>c</i>][1,2,3]triazole		
 126{7}	ONO/	Isoxazolo[2,3- <i>b</i>][1,2,5]oxadiazole		
	NNN/	Pyrazolo[1,5- <i>c</i>][1,2,3]triazole		

(Continued)

Table 1 (Continued)

Topology of heteroatom positions	Heteroatoms in positional order	Name of (5,5) (2N1) system	CHEC-II	CHEC-III
	NN/N	Pyrazolo[1,5- <i>b</i>][1,2,4]triazole [1,2,4]Triazolo[1,5- <i>b</i>]indazole	+	+
	ON/S	Thiazolo[4,3- <i>b</i>][1,3,4]oxadiazole	+	+
	SN/S	Thiazolo[4,3- <i>b</i>][1,3,4]thiadiazole	+	+
	SN/N	Imidazo[5,1- <i>b</i>][1,3,4]thiadiazole	+	
	NO/N	Imidazo[5,1- <i>b</i>][1,3,4]oxadiazole	+	+
	NN/S	Thiazolo[3,4- <i>b</i>][1,2,4]triazole	+	+
	NN/N	Imidazo[1,5- <i>b</i>][1,2,4]triazole	+	+
	ON/S	Thiazolo[4,3- <i>b</i>][1,3,4]oxadiazole	+	+
	ON/N	Imidazo[2,1- <i>b</i>][1,3,4]oxadiazole	+	+
	SN/S	Thiazolo[2,3- <i>b</i>][1,3,4]thiadiazole	+	+
	SN/N	Imidazo[2,1- <i>b</i>][1,3,4]thiadiazole	+	+
		[1,3,4]Thiadiazolo[3,2- <i>a</i>]benzimidazole	+	
	SSi/O	[1,3,4]Thiazasilo[2,3- <i>b</i>]benzoxazole	+	
	SSi/S	[1,3,4]Thiazasilo[2,3- <i>b</i>]benzothiazole	+	
	SeN/N	Imidazo[2,1- <i>b</i>][1,3,4]selenadiazole		
	NP/S	Thiazolo[2,3- <i>b</i>][1,3,4]diazaphosphole	+	
	NN/N	Imidazo[1,2- <i>b</i>][1,2,4]triazole		+
	NN/S	[1,2,4]Triazolo[5,1- <i>b</i>]benzothiazole		+
	ONO/	Oxazolo[3,2- <i>b</i>][1,2,4]oxadiazole	+	
	ONN/	Imidazo[1,2- <i>b</i>][1,2,4]oxadiazole	+	+
	SSN/	Imidazo[1,2- <i>b</i>][1,2,4]dithiazole		
	SNS/	Thiazolo[3,2- <i>b</i>][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[3,2- <i>b</i>]benzothiazole	+	+
	SNN/	Imidazo[1,2- <i>b</i>][1,2,4]thiadiazole	+	+
		[1,2,4]Thiadiazolo[2,3- <i>a</i>]benzimidazole	+	+
	NNO/	Oxazolo[3,2- <i>b</i>][1,2,4]triazole	+	+
		[1,2,4]Triazolo[5,1- <i>b</i>]benzoxazole	+	
	NNS/	Thiazolo[3,2- <i>b</i>][1,2,4]triazole	+	+
		[1,2,4]Triazolo[3,2- <i>b</i>]benzothiazole	+	+
	NNN/	Imidazo[1,2- <i>b</i>][1,2,4]triazole	+	+
		[1,2,4]Triazolo[1,5- <i>a</i>]benzimidazole	+	+

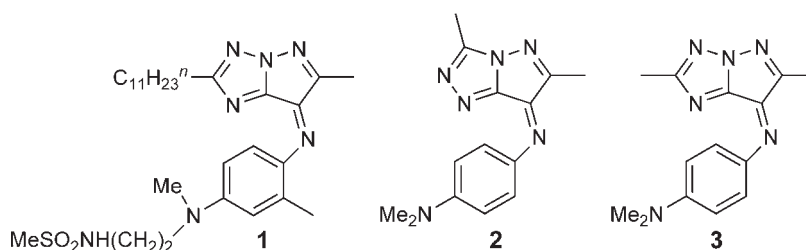


Figure 1

11.05.3 Experimental Structural Methods

11.05.3.1 X-Ray

The following structures have been assigned or confirmed by X-ray analysis.

12{4}7: *NN/S* 3-Phenyl-[1,2,4]-triazolo[3,4-*b*]benzothiazole **4** <2002AX(E)380>, 7-methyl-(4'-methylphenyl)-[1,2,4]triazolo[3,4-*b*]benzothiazole **5** <1999AX(C)948>, 3-cyclopropyl-[1,2,4]triazolo[3,4-*b*]benzothiazole **6**

<1999AX(C)1119>, 3-(2'-phenyl-quinolin-4'-yl)-[1,2,4]triazolo[3,4-*b*]benzothiazole **7** <2002JST41, 2001MI2>, (4*R*,4*aR*)-4,4a-bis-ethoxycarbonyl-4,4a-dihydro-1,2,5,10c-tetraaza-3-thiabenz[6,7]cyclohepta[1,2,3-*cd*]-pentalene-6(5*H*)-one **8** <2001T7191> (Figure 2); *NN/N* 1-methyl-2,3,6,7-tetrahydro-8*H*-cyclopenta[*d*]-imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidin-9(1*H*)-one **9** <2002JHC319>, 6-bromomethyl-7-ethoxycarbonyl-2,6-dimethyl-2,3,5,6-tetrahydro-7*H*-imidazo[2,1-*c*][1,2,4]triazole-3-thione **10** <1996T791> (Figure 2).

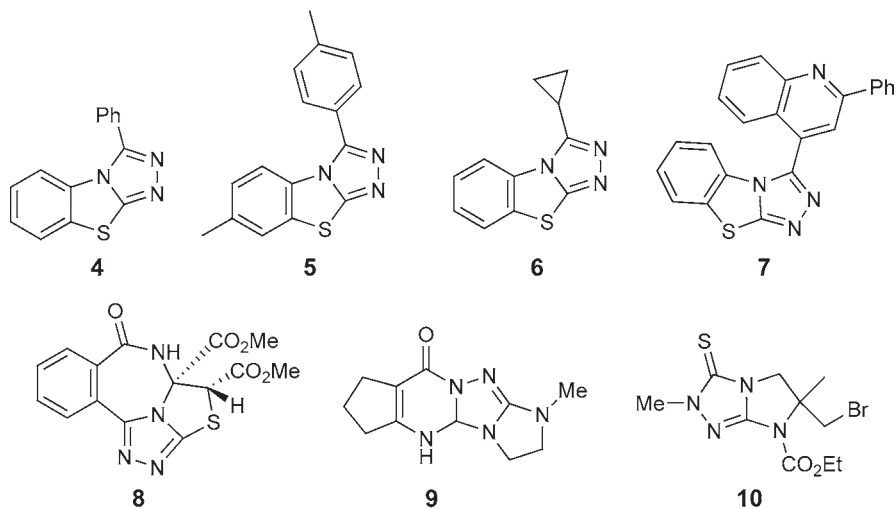


Figure 2

13{4}5: *NN/N* 5-[(2'-(1*H*-Tetrazol-5-yl)biphenyl-4-yl)methyl-2,7-diethyl-5*H*-pyrazolo[1,5-*b*][1,2,4]triazole **11** <1998CPB69>, 5-[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl-2,7-diethyl-5*H*-pyrazolo[1,5-*b*][1,2,4]triazol-6-yl)methanol **12** <1998CPB287> (Figure 3).

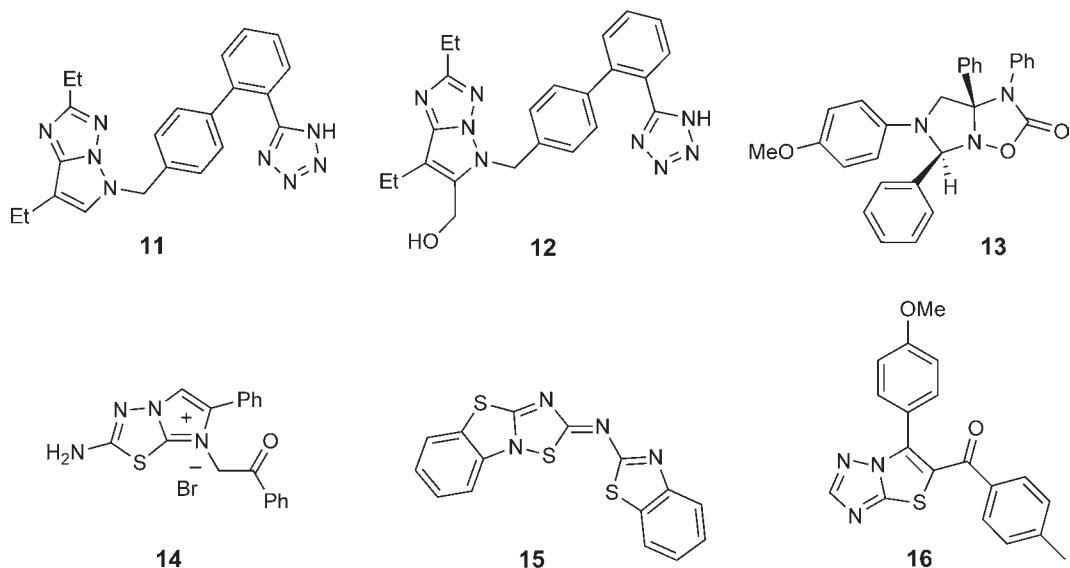


Figure 3

13{4}6: *NO/N* (5*S*,7*aR*)-6-(4'-Methoxyphenyl)-1,5,7a-triphenyltetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-one **13** <2004SPL553> (Figure 3).

13{4}7: *SN/N* 2-Amino-7-(2'-oxo-2'-phenylethyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazolium bromide **14** <2002ARK32> (Figure 3).

134{7}: *SNS*/ (Dibenzothiazol-2-yl)tetraazathiapentalene **15** <2004EJO4203>; *NNS*/ {6-(4'-methoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazol-5-yl}(*p*-tolyl)methanone **16** <2000OL429> (Figure 3), 6-(4-nitrobenzyl)-2-phenylthiazolo[3,2-*b*][1,2,4]triazole **17** <2005TL1607>, 5-benzylidene-2-(2'-chlorophenyl)thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one **18** <1999AX(C)1939>, 5-(2'-fluorobenzylidene)-2-[1'-(2''-fluoro-4''-biphenyl)ethyl]-thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-one **19** <2004AX(C)356>, 1'-methyl-4'-*p*-tolyl-1*H*-indole-3-spiro-2'-pyrrolidine-3'-spiro-5''-(thiazolo[3,2-*b*][1,2,4]triazole)-2,6-(3''*H*,5''*H*)-dione **20** <2003AX(E)1796>; *NNN*/ 1,3,3a,9-tetraazacyclopent[*a*]azulene **21** <1999J(P1)1339>, 4-(4'-chlorophenyl)-2-methyl-5,6-diphenyl-7*H*-imidazo[1,2-*b*][1,2,4]triazole **22** <1996JHC1877, 1997JHC71> (Figure 4).

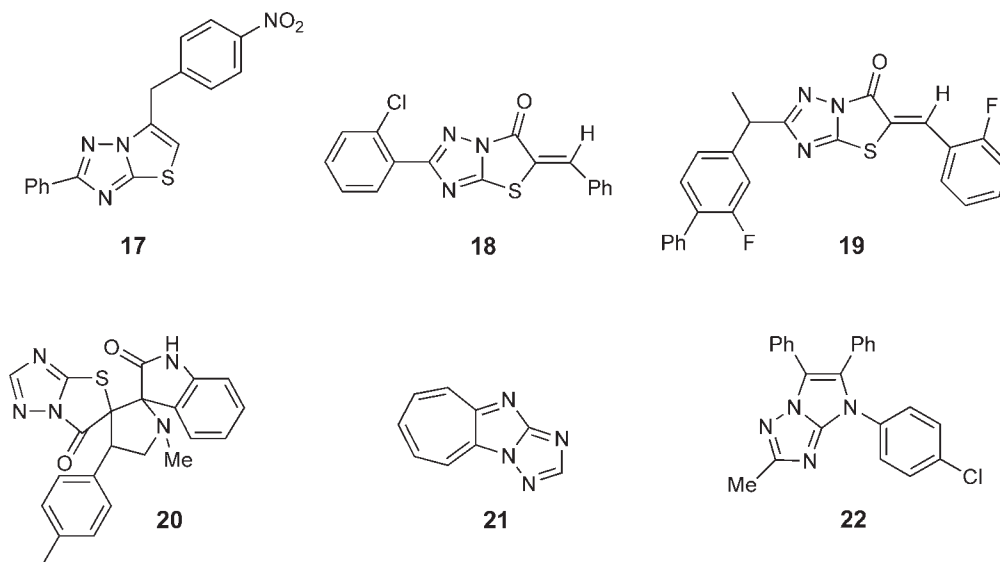


Figure 4

11.05.3.2 NMR Data

11.05.3.2.1 Proton NMR

The [5,5] (2*N*1)-fused heterocyclic system contains four ring-carbon atoms, the fusion carbon atom and two and one carbon atom in the respective five-membered rings.

11.05.3.2.1(i) Saturated rings with CH₂ and CH groups

The ¹H NMR data refer to at least one saturated five-membered ring moiety. The following compounds have been subjected to detailed study by ¹H NMR spectroscopy.

12{4}7: *NNS*/ 4*H*-Thiazolo[2,3-*c*][1,2,4]triazole derivative **23** <1998IJH23>, 3-amino-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **24** <2003JHC821> (Figure 5); 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles **25** (Table 2) <1997AJC911, 2001SC2841>; (4*R*,4*aR*)-4,4a-dihydro-bis-methoxycarbonyl-1,2,5,10c-tetraaza **8** and pentaaza-3-thiabenz[6,7]cyclohepta[1,2,3-*cd*]-pentalene-6(5*H*)-ones **26** and **27** (Table 3) <2001T7191>; 6-bromomethyl-3-(4'-nitrophenyl)-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazolium bromides **28** (Table 4) <2000RJOC1033>; 5,6-dihydro-1,6,6-trimethyl-thiazolo[2,3-*c*][1,2,4]triazolium-aminides **29** (Table 5) <1996T791>, 6-bromomethyl-5,6-dihydro-1,6-dimethyl-thiazolo[2,3-*c*][1,2,4]triazolium bromides **30** (Table 6) <1996T791>.

6-Iodomethyl-3-phenyl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **31** <2004CHE1077>; 5-iodomethyl-3-phenyl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **32** <2004CHE1207>; 5,6-dihydro-3-pyrazinyl-thiazolo[3,2-*b*][1,2,4]triazole **33** <2004PS(179)2519>; 5,6-bis-phenylhydrazono-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **34** <2004JCR(S)264> (Figure 5); *NNN*/ 7-benzoyl-6-bromomethyl-2,6-dimethyl-2,3,5,6-tetrahydro-7*H*-imidazo[2,1-*c*][1,2,4]triazole-3-thione **35** (Table 7) <1996T791>, imidazo[2',1':3,4][1,2,4]triazolo[1,5-*a*]pyrimidines **36** (Table 8) <2002JHC319>; *NP/S* compounds **37** (Table 9) <2005ZN(B)7>.

124{7}: *NNS*/ 3-Methyl-5,6-dihydrothiazolo[3,2-*c*][1,2,3]triazole **38** <2000SC417> (Figure 6); *NNN*/ 5,6-dihydro-4*H*-imidazo[1,2-*c*][1,2,4]triazoles **39** (Table 10) <2000HAC387>.

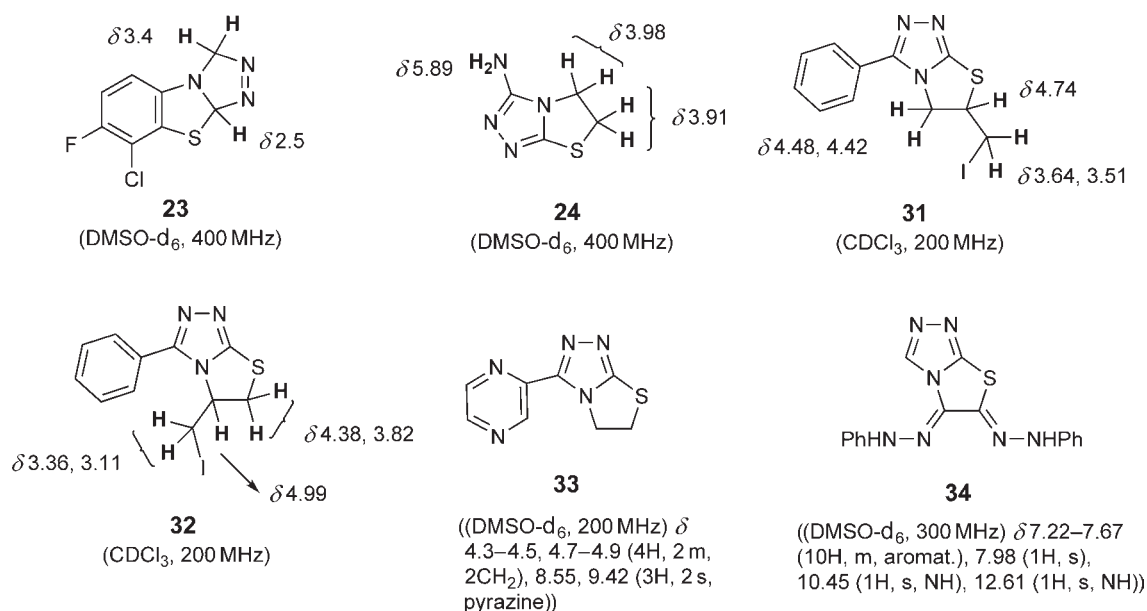


Figure 5

Table 2 Proton NMR data for compounds **25** ((CDCl₃, 200 MHz), *J* (Hz))

	<i>R</i>		References
 25	Cl	δ 7.71 (1H, s), 7.57–7.61 (1H, m), 7.36–7.40 (2H, m), 4.39 (2H, t, <i>J</i> = 7.1), 4.05 (2H, t, <i>J</i> = 7.1)	1997AJC911
	CF ₃	δ 8.00 (1H, s), 7.95 (1H, d, <i>J</i> = 7.8), 7.72 (1H, d, <i>J</i> = 7.8), 7.61 (1H, t, <i>J</i> = 7.8), 4.43 (2H, t, <i>J</i> = 7.2), 4.09 (2H, t, <i>J</i> = 7.2)	1997AJC911

Table 3 Proton NMR data for compounds **8**, **26**, and **27** ((DMSO- d_3 , 500 MHz), *J* (Hz))

	<i>Y</i>	<i>Z</i>	
 8 : <i>Y</i> , <i>Z</i> = CH 26 : <i>Y</i> = N; <i>Z</i> = CH 27 : <i>Y</i> = CH; <i>Z</i> = N	CH	CH	δ 9.89 (1H, s, NH), 8.09 (1H, d, <i>J</i> = 7.4, H7), 7.99 (1H, d, <i>J</i> = 7.4, H8), 7.71 (1H, t, <i>J</i> = 7.4, H10), 7.65 (1H, d, <i>J</i> = 7.4, H9), 6.38 (1H, s, H4), 3.77 (3H, s, 4-CO ₂ CH ₃), 3.50 (3H, s, 4a-CO ₂ CH ₃)
	N	CH	δ 10.04 (1H, s, NH), 9.18 (1H, s, H10), 8.82 (1H, d, <i>J</i> = 5.8, H8), 7.95 (1H, d, <i>J</i> = 5.8, H7), 6.40 (1H, s, H4), 3.79 (3H, s, 4-CO ₂ CH ₃), 3.53 (3H, s, 4a-CO ₂ CH ₃)
	CH	N	δ 10.06 (1H, s, NH), 9.38 (1H, s, H7), 8.84 (1H, d, <i>J</i> = 5.8, H9), 7.98 (1H, d, <i>J</i> = 5.8, H10), 3.77 (3H, s, 4-CO ₂ CH ₃), 3.52 (3H, s, 4a-CO ₂ CH ₃)

13{4}6: *NO/N* Tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-ones **40** (Table 11) <1997T13873, 1999SC3889> and similar thiones <2003PS(178)881, 2004M17>; *NN/N* imidazo[1,5-*b*][1,2,4]triazole-2,5-dithiones **41** (Table 12) <1998SL786>.

13{4}7: *NN/S* 2-Amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **42** <2003JHC821>; 2-(3'-chlorophenyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **43** <1997AJC911>; 5-iodomethyl-2-phenyl-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **44** <2004CHE1207, 1999RJOC730>; 6,7-dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-

Table 4 Proton NMR signals for compounds **28** ((CD₃OD, 300 MHz), *J* (Hz))

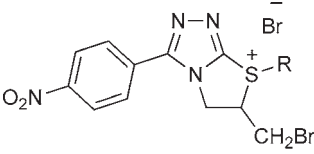
 28	<i>R</i>	
	Me	δ 2.92 (3H, s, CH ₃), 3.77–3.85 (1H, m, CH), 3.95 (1H, dd, <i>J</i> = 13.6, 3.8, CH), 4.45–4.54 (1H, m, CH), 4.65 (1H, m, CH), 4.80 (1H, dd, <i>J</i> = 19.8, 4.4), 8.11, 8.49 (4H, d, d, <i>J</i> = 9.8, arom.)
	Et	δ 1.52 (3H, t, <i>J</i> = 7.4, CH ₃), 3.46 (2H, q, <i>J</i> = 7.4, CH ₂), 3.78–3.85 (1H, m, CH), 3.95 (1H, dd, <i>J</i> = 13.2, 3.8), 4.44–4.53 (1H, m, CH), 4.64 (1H, m, CH), 4.79 (1H, d, <i>J</i> = 19.2, 4.4), 8.10, 8.48 (4H, d, d, <i>J</i> = 9.8, arom.)
	CH ₂ COPh	δ 1.29 (3H, t, <i>J</i> = 7.4, CH ₃), 3.79–3.87 (1H, m, CH), 3.97 (1H, dd, <i>J</i> = 14.0, 3.8, CH), 4.23 (2H, q, <i>J</i> = 7.4, CH ₂), 4.32 (2H, d, <i>J</i> = 9.2, CH ₂), 4.50–4.61 (1H, m, CH), 4.72 (1H, m, CH), 4.97 (1H, d, d, <i>J</i> = 19.8, 4.4), 8.12, 8.45 (4H, d, d, <i>J</i> = 9.8, arom.)

Table 5 Proton NMR data for compounds **29** (CDCl₃, *J* (Hz))

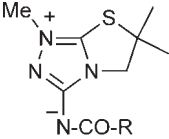
 29	<i>R</i>	
	OEt	δ 1.25 (3H, t, <i>J</i> = 7.0, CH ₂ CH ₃), 1.74 (6H, s, C(CH ₃) ₂), 3.66 (3H, s, NCH ₃), 4.05 (2H, s, CH ₂), 4.09 (2H, q, <i>J</i> = 7.3, CH ₂ CH ₃)
	Ph	δ 1.70 (6H, s, C(CH ₃) ₂), 3.62 (3H, s, NCH ₃), 4.22 (2H, s, CH ₂), 7.30–8.18 (5H, m, arom.)

Table 6 Proton NMR data for compound **30** ((DMSO-*d*₆, 200 MHz), *J* (Hz))

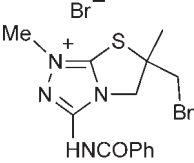
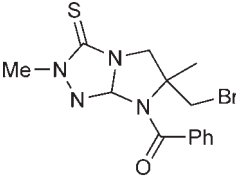
 30		
		δ 1.93 (3H, s, CCH ₃), 3.91 (3H, s, NCH ₃), 4.25 (1H, d, <i>J</i> = 10.5, CH ₂), 4.32 (1H, d, <i>J</i> = 10.5, CH ₂), 4.52 (1H, d, <i>J</i> = 12.4, CH ₂), 4.72 (1H, d, <i>J</i> = 12.4, CH ₂), 7.61 (2H, t, <i>J</i> = 7.3, arom.), 7.73 (1H, t, <i>J</i> = 7.3, arom.), 8.05 (2H, d, <i>J</i> = 6.9, arom.)

Table 7 Proton NMR shifts for compound **35** ((CDCl₃, 200 MHz), *J* (Hz))

 35		
		δ 1.99 (3H, s, CCH ₃), 3.49 (3H, s, NCH ₃), 3.73 (1H, d, <i>J</i> = 11.2, CH ₂), 4.28 (1H, d, <i>J</i> = 11.1, CH ₂), 4.50 (1H, d, <i>J</i> = 11.2, CH ₂), 7.43 (2H, t, <i>J</i> = 7.2, arom.), 7.57 (1H, t, <i>J</i> = 7.4, arom.), 7.62 (2H, d, <i>J</i> = 8.3, arom.)

b[[1,2,4]triazol-2'-yl]isoquinolinium bromide **45** <2003JHC1041>; 2-aryl-5-arylidene-thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-ones **46** <1999AF1006, 2001AF470, 2001PHA613, 2000EJM743, 1998PHA94, 1999IJC(B)867, 2001IJH75, 1998IJH297, 2002IJH261, 1999IJH237, 2001IJH313> (**Figure 6**), 5,6-bis-(phenylhydrazono)-2-phenylthiazolo[3,2-*b*][1,2,4]triazole **47** <2002MI7>; 2-(2',4'-dinitrophenyl)-3-(*p*-methoxyphenyl)-6-(*m*-tolyl)-*cis*-3,3a-dihydropyrazolo[3,4-

Table 8 NMR data for compounds **36** (CDCl₃, 400 MHz)

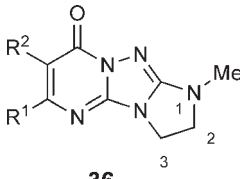
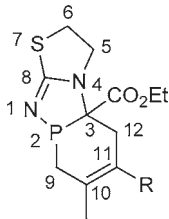
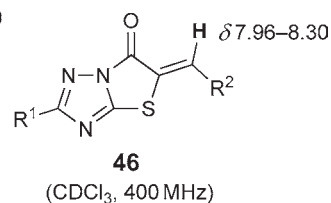
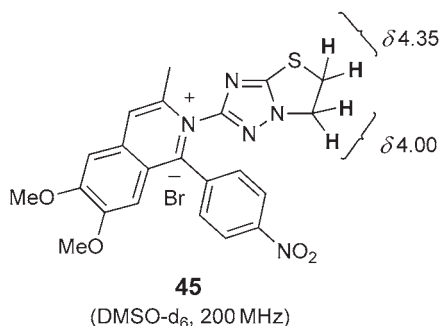
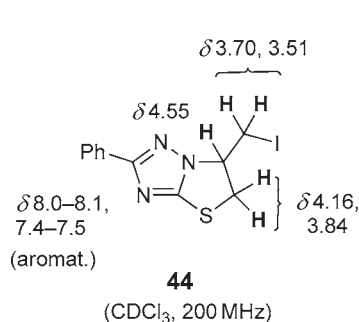
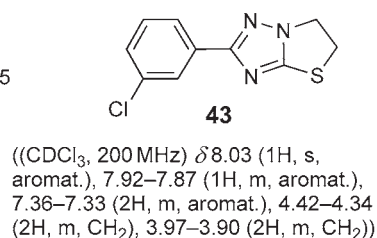
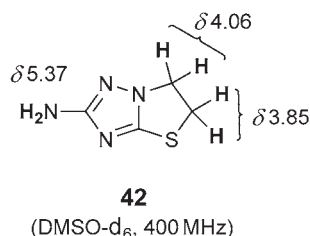
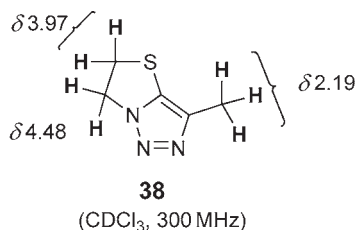
	R^1	R^2	δ <i>N</i> -Me (s)	δ 2-CH ₂ (m)	δ 3-CH ₂ (m)	δ $R^1 + R^2$
 36	Me	H	3.05	4.06	4.23	2.28 (s)
	(CH ₂) ₄		3.04	4.03	4.19	2.60 (t), 1.75 (4H, m), 2.60 (t)

Table 9 Proton NMR data for compounds **37** ((CDCl₃, 400 MHz), *J* (Hz))

<i>R</i>	
 37	Me δ 1.27 (3H, t, <i>J</i> = 7.1, OCH₂CH₃), 1.70 (3H, s, 11-CH₃), 1.80 (3H, s, 10-CH₃), 2.82, 2.25 (2H, H-12), 2.60, 2.47 (2H, H-9), 3.36–4.08 (4H, m, H-5, H-6), 4.29–4.26 (2H, OCH₂CH₃) H δ 1.28 (3H, t, <i>J</i> = 7.1, OCH₂CH₃), 1.73 (3H, s, 10-CH₃), 2.83, 2.61 (2H, H-12), 2.75, 2.72 (2H, H-9), 3.39–3.96 (4H, m, H-5, H-6), 4.30 (2H, q, <i>J</i> = 7.1, OCH₂CH₃), 5.37 (1H, m, H-11)

**Figure 6**

δ [1,2,4]triazolo[3,2-*b*]thiazole **48** <1999IJC(B)867, 2001IJH75, 1998IJH297, 2002IJH261, 2003IJH97, 1999IJH55, 1999IJH237, 2003IJH375>, 2-alkyl-5a-hydroxy-6,6-dimethyl-8-oxo-5a,5,6,7,8,8a-hexahydro-[1,2,4]triazolo[3,2-*b*]benzothiazoles **49** <1999IJH127> (Figure 7).

134{7}: *NNO*/ Oxazolo[3,2-*b*][1,2,4]triazole **50** <2002TL607> (Figure 7).

Table 10 Proton NMR data for compounds **39** ((DMSO- d_6 , 200 MHz), J (Hz))

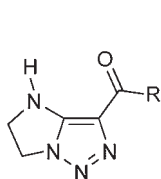
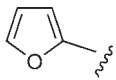
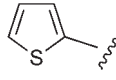
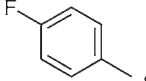
		R
 39		δ 7.92–8.02 (2H, m), 7.42 (1H, s, NH), 6.72–6.75 (1H, m), 4.43–4.23 (4H, $J = 9.2$)
		δ 8.49–8.52 (1 H, m), 7.97–8.00 (1 H, m), 7.44 (1H, s, NH), 7.27 (1H, t), 4.44–4.24 (4 H, $J = 9.2$)
		δ 8.40–8.47 (2H, m), 7.49 (1H, s, NH), 7.32–7.41 (2H, m), 4.46, 4.24 (4H, $J = 9.2$)

Table 11 Proton NMR shifts for compounds **40** ((CDCl₃, 200 MHz), J (Hz))

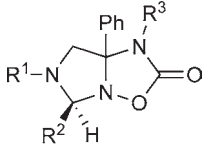
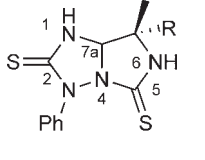
	R^1	R^2	R^3	
 40	4-Me-C ₆ H ₄	H	Ph	δ 2.28 (3H, s), 3.48 (1H, d, $J = 10.8$), 4.18 (1H, d, $J = 10.8$), 4.38 (1H, d, $J = 10.2$), 5.04 (1H, d, $J = 10.2$), 6.68 (2H, d, $J = 8.5$), 6.88 (2H, m), 7.10 (2H, d, $J = 8.5$), 7.30 (3H, m), 7.40 (5H, s)
	4-Me-C ₆ H ₄	H	4-MeO-C ₆ H ₄	δ 2.30 (3H, s), 3.35 (1H, d, $J = 10.8$), 3.78 (3H, s), 4.20 (1H, d, $J = 10.8$), 4.36 (1H, d, $J = 10.3$), 5.08 (1H, d, $J = 10.3$), 6.15–6.32 (6H, m), 7.12 (2H, d, $J = 8.3$), 7.42 (5H, s)
	Ph	2,3-(MeO) ₂ -C ₆ H ₃	Ph	δ 3.85 (3H, s), 4.00 (3H, s), 4.40 (2H, $J = 11.3$), 6.40 (1H, s), 6.60–6.90 (9H, m), 7.10–7.40 (9H, m)
	Ph	2,3-(MeO) ₂ -C ₆ H ₃	2-Me-C ₆ H ₄	δ 3.78 (3H, s), 3.85 (3H, s), 4.00 (3H, s), 4.35 (2H, $J = 11.1$), 6.50 (1H, s), 6.60–6.90 (10H, m), 7.15–7.25 (2H, m), 7.40 (5H, s)

Table 12 Proton NMR data for compounds **41** ((DMSO- d_6 , 300 MHz), J (Hz))

	R
 41	Me δ 1.30 (s, 7-CH ₃), 1.36 (s, 7-CH ₃), 5.48 (s, 7a-H), 7.15 (t, $J = 7.5$, 4-H, 3-Ph), 7.34 (dd, $J = 7.5$, 3,5-H, 3-Ph), 7.86 (d, $J = 7.5$, 2,6-H, 3-Ph), 9.87 (s, 1-H), 10.36 (s, 6-H)
	Ph δ 1.66 (s, 7-CH ₃), 5.73 (s, 7a-H), 7.13 (t, $J = 7.5$, 4-H, 3-Ph), 7.27–7.47 (m, 3,5-H, 3-Ph, 7-Ph), 7.79 (d, $J = 7.5$, 2,6-H, 3-Ph), 9.93 (s, 1-H), 11.01 (s, 6-H)

11.05.3.2.1(ii) CH groups in unsaturated rings

12{4}5: *NN*/*N* 5-[(1,4-Dihydro-1,4-dioxo-3-(phenylamino)-2-(naphthalenyl)sulfonyl]-3-methyl-6-phenyl-5*H*-pyrazolo[5,1-*c*][1,2,4]triazole **51** <2004PS(179)1907>; 3-[(1-methylbenzimidazol-2-yl)carbonyl]-6-phenylpyrazolo[5,1-*c*][1,2,4]triazole **52** <2004HAC432>; 3-aryloxymethyl-6-methylpyrazolo[5,1-*c*][1,2,4]triazoles **53** and **54** <2003IJC(B)2054>; 3-aryl-7-ethoxycarbonyl-6-methyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **55** <2004RRC1018>; and 6-methyl-3-phenyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **56** <2002ARK133> (Figure 8).

3-Aryl-7-(4'-diethylamino-2'-methylphenyl)imino-6-methyl-pyrazolo[5,1-*c*][1,2,4]triazoles **57** <2002ARK133>; 7-benzylidene-6-methyl-3-phenylimino-2*H*-pyrazolo[5,1-*c*][1,2,4]triazole **58** and 6-benzylidene-6-methyl-2-phenyl-3-phenyliminopyrazolo[5,1-*c*][1,2,4]triazole **59** <1998PS(134/135)119>; 3-phenylamino(1*H*)pyrazolo[5,1-*c*][1,2,4]triazol-6-ol **60** and 1-phenyl-3-phenylamino(1*H*)pyrazolo[5,1-*c*][1,2,4]triazol-6-ol **61** <1999EJC175>; 6-amino-7-cyano-3-phenylpyrazolo[5,1-*c*][1,2,4]triazole **62** <1996SC3827> (Figure 9); pyrazolo[5,1-*c*][1,2,4]triazoles **63** (Table 13) <2000H(53)917>.

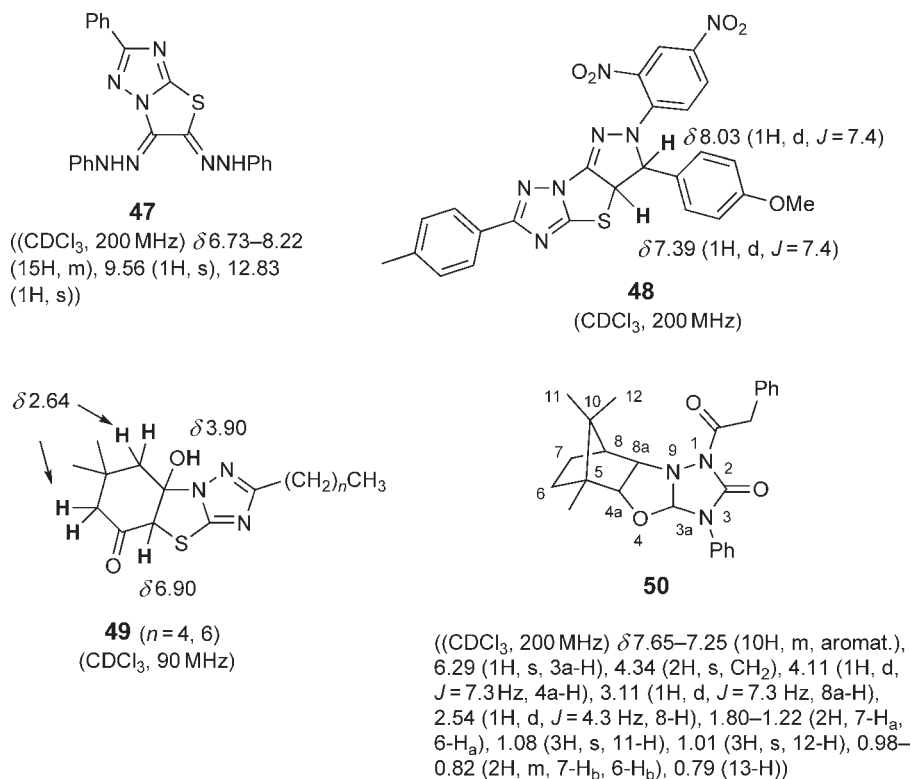


Figure 7

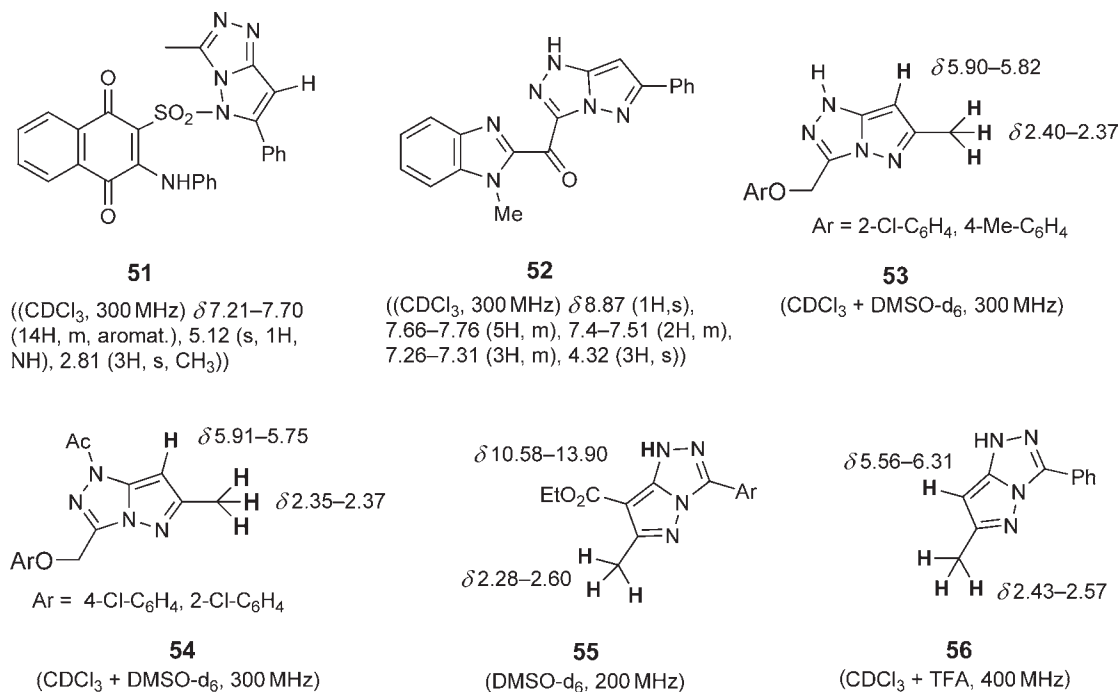


Figure 8

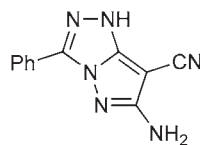
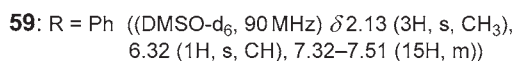
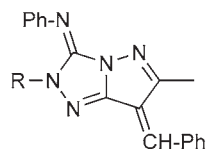
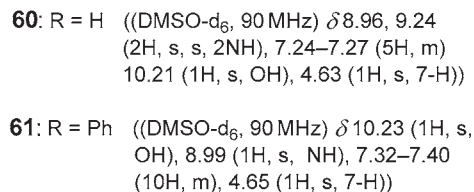
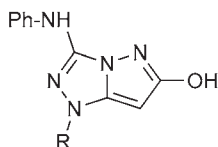
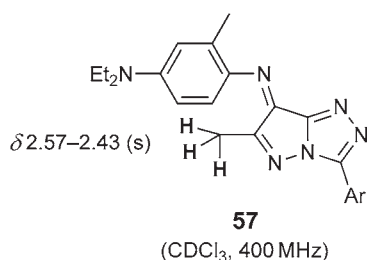


Figure 9

Table 13 Proton NMR signals for compounds **63** ((CDCl₃, 300 MHz), *J* (Hz))

<i>R</i>	
63	Me δ 2.24 (3H, s), 4.37 (1H, d, <i>J</i> = 10.6), 4.48 (1H, d, <i>J</i> = 10.6), 5.28 (1H, d, <i>J</i> = 12.1), 5.37 (1H, d, <i>J</i> = 12.1), 5.54 (1H, dd, <i>J</i> = 2.3, 1.7), 5.61 (1H, dd, <i>J</i> = 6.0, 2.3), 6.12 (1H, dd, <i>J</i> = 6.0, 1.7), 7.00–7.45 (14H, m)
	NO ₂ δ 4.40 (1H, d, <i>J</i> = 10.5), 4.56 (1H, d, <i>J</i> = 10.5), 5.32 (1H, d, <i>J</i> = 12.5), 5.40 (1H, d, <i>J</i> = 12.5), 5.65–6.22 (3H, m), 7.00–8.35 (14H, m)

12[4]6: *NN/V* 3-Ethoxycarbonylimidazo[5,1-*c*][1,2,4]triazoles **64** <1999CHE1349> (Figure 10).

12[4]7: *ON/V* (1-Methyl-1*H*-benzimidazol-2-yl)-[1,2,4]oxadiazolo-[4,5-*a*]-benzimidazol-3-yl-methanone **65** (Figure 10) <2004HAC432>; *SN/V* imidazo [1,2-*d*][1,2,4]thiadiazoles **66** (Table 14) <2005JOC6230>; 3-*p*-tolylsulfonfyl-imidazo[1,2-*d*][1,2,4]thiadiazole **67** <2005JOC6230> (Figure 10); *NS/S* [1,2,4]thiadiazolo[3,4-*b*]benzothiazol-3(3*H*)-ones **68** (Table 15) <1997H(45)1579>; *NN/O* oxazolo[2,3-*c*][1,2,4]triazoles **69** and **70** (Table 16) <2000SC3423, 1997IJC(B)711>; 3-mercaptomethylbenzoxazolo[3,4-*b*][1,2,4]triazole **71** <1996M549> (Figure 10).

NN/S [1,2,4]Triazolo[3,4-*b*]benzothiazole-3-thione derivatives **72** (Figure 10), [1,2, 4]triazolo[3,4-*b*]benzothiazole-3-thiones **73** and **74** (Figure 11) <2002MI3>; [1,2,4]triazolo[3,4-*b*]benzothiazole derivatives **75–78** (Table 17) <2002JST41, 2001MI2>; 5,6-bis-methoxycarbonyl-thiazolo[2,3-*c*][1,2,4]triazoles **79–82** (Table 18) <2001T7191>; 3-(3-phenyl-1*H*-pyrazol-5-yl)thiazolo[2,3-*c*]-s-triazol-5(6*H*)-one **83** <2001IJC(B)636> (Figure 12); pyrano[2',3':4,5]thiazolo[2,3-*c*][1,2,4]triazoles **84** (Table 19) <1999ZN(B)1589>; triazolo[1,2,4]thiazolo[5,4-*a*]acridin-12(7*H*)-ones **85–88** (Table 20) <1999MRC86>.

5-Methyl[1,2,4]triazolo[3,4-*b*]benzothiazole **89** and 5-methyl-2-phenylpyrrolo[1',2';1,5][1,2,4]triazolo[3,4-*b*]benzothiazole **90** <1998IJC(B)921> (Figure 12); [1,2,4]triazolo[2,1-*b*]benzothiazole **91** and 3-phenyl-[1,2,4]triazolo[3,4-*b*]benzothiazole **4** (Table 21) <1996EJM575>.

3,5-Disubstituted thiazolo[2,3-*c*][1,2,4]triazoles **92** and **93** (Table 22) <1996IJH21, 2005SC1753, 2002IJC(B)403>.

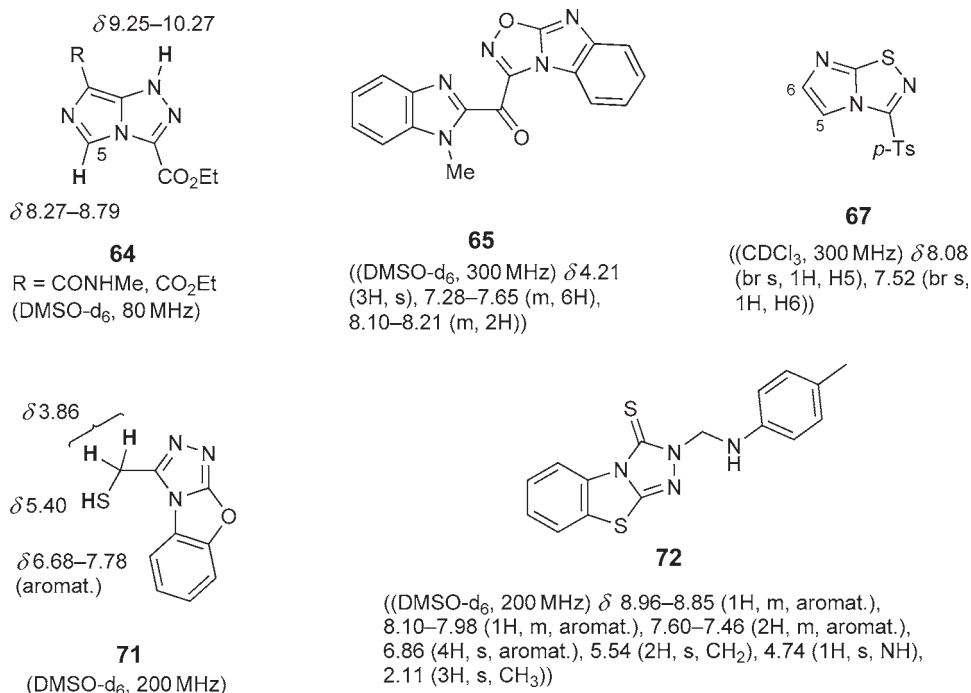
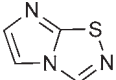


Figure 10

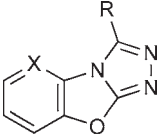
Table 14 Proton NMR signals for compounds **66** (300 MHz, *J* (Hz))

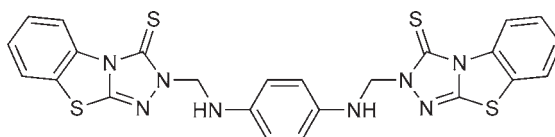
	<i>Ar</i>		<i>Solv.</i>
 66 (<i>n</i> = 4, 6)	2-NH ₂ -C ₆ H ₄	δ 7.83–7.86 (2H, m), 7.44–7.46 (2H, m), 7.21–7.28 (2H, m), 6.77–6.79 (1H, m), 6.57–6.59 (1H, m)	D
	3-CO ₂ H-C ₆ H ₄	δ 8.57 (1H, t, <i>J</i> = 6.9, NH), 8.10 (1H, s), 7.94 (1H, t, <i>J</i> = 7.1, NH), 7.87 (1H, s), 7.71–7.78 (2H, m), 7.40 (1H, t, <i>J</i> = 7.7), 7.30 (1H, s)	D
	2-CN-C ₆ H ₄	δ 7.92 (1H, br s, NH), 7.70–7.74 (1H, m), 7.60–7.65 (2H, m), 7.56 (1H, s), 7.10 (1H, s), 7.00 (1H, br s, NH)	C + D
	2,4-Di-Br-C ₆ H ₃	δ 8.12 (1H, s), 7.81–7.94 (5H, m, aromat., 2NH), 7.30 (1H, s)	D
	1-Naphthyl	δ 8.67 (1H, d, <i>J</i> = 7.7), 8.22 (1H, t, <i>J</i> = 6.9), 8.05 (1H, d, <i>J</i> = 7.8), 7.92 (1H, d, <i>J</i> = 7.2), 7.50–7.62 (m, 4H), 7.24–7.28 (m, 1H), 5.61–5.80 (1H, br s, NH), 5.18–5.32 (1H, Br s, NH), 3.37 (2H, br q, <i>J</i> = 6.4, NHCH ₂ CH ₂), 2.88 (2H, br q, <i>J</i> = 6.3, NHCH ₂ CH ₂), 1.50 (2H, br quint, NHCH ₂ CH ₂ CH ₂), 1.36 (2H, br quint, NHCH ₂ CH ₂ CH ₂), 1.15–1.25 (m, 4H, 2CH ₂)	D

C = CDCl₃; D = DMSO-d₆.**Table 15** Proton NMR shifts for compounds **68** (CDCl₃, 400 MHz)

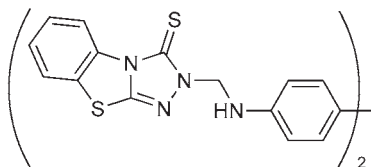
<i>R</i>	
68	H δ 7.36–7.46 (2H, m), 7.50–7.52 (1H, m), 8.21–8.23 (1H, m)
	Cl δ 7.40–7.43 (1H, m), 7.48–7.52 (1H, m), 8.13–8.16 (1H, m)
	MeO δ 3.86 (3H, s), 6.93–6.96 (1H, m), 7.01–7.02 (1H, m), 8.08–8.11 (1H, m)

Table 16 Proton NMR signals for compound **69** and **70** (DMSO- d_6 , 360 MHz)

	<i>R</i>	<i>X</i>		<i>Reference</i>
	Ph	N	δ 8.3–7.1 (8H, m, aromat.)	2000SC3423
	NH ₂	N	δ 8.3–7.2 (3H, m, aromat.), 5.1–4.9 (2H, br s, NH ₂)	2000SC3423
	4-OH-C ₆ H ₄	CH	δ 8.5 (1H, br s, OH), 6.8–7.1 (8H, m, aromat.)	1997IJC(B)711
	PhCH ₂	CH	δ 6.7–7.8 (9H, m, aromat.), 4.4 (2H, s, CH ₂)	1997IJC(B)711
69: X = N 70: X = CH				



73: ((DMSO- d_6 , 200 MHz) δ 8.90–8.66 (2H, m, aromat.), 7.97–7.78 (2H, m, aromat.), 7.57–7.30 (4H, m, aromat.), 6.76 (4H, s, aromat.), 5.49 (4H, s, CH₂), 4.61 (2H, br s, NH))



74: ((DMSO- d_6 , 200 MHz) δ 8.97–8.85 (2H, m, aromat.), 8.10–7.98 (2H, m, aromat.), 7.58–7.49 (4H, m, aromat.), 7.31 (4H, d, J = 8.2 Hz, aromat.), 6.94 (4H, d, J = 8.2 Hz, aromat.), 5.60 (4H, s, CH₂), 4.91 (2H, br s, NH))

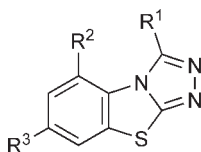
Figure 11

5,7-Dimethyl-pyrazolo[3',4':4,5]thiazolo[2,3-*c*][1,2,4]triazole **94** <1999H(51)829>; 5-*p*-bromophenyl-3-(2-thienyl)-thiazolo[2,3-*c*][1,2,4]triazole **95** <2003IJC(B)401>; 3-methyl-5-coumaryl-thiazolo[2,3-*c*][1,2,4]triazole **96** <1999IJC(B)18>; 5-(*p*-chlorophenyl)-3-(*p*-*t*-butylphenyl)thiazolo[2,3-*c*][1,2,4]triazole **97** <2001IJC(B)54>; 3-hydrazino[1,2,4]triazolo[3,4-*b*]benzothiazole **98** and 3-hydroxy[1,2,4]triazolo[4',5':1,5][1,2,4]triazolo[3,4-*b*]benzothiazole **99** (Figure 13) <2005IJC(B)625>; *NN*/*N* compound **100** <1997CHE1352>; 5,6-bis-(4-tolylimino)-6*H*-imidazo[2,1-*c*][1,2,4]triazole **101** <2001EJO2257>; 6,7-dihydro-5-oxo-imidazo[2,1-*c*][1,2,4]triazoline-3-thione **102** <1998MI1> (Figure 13); *NP*/*S* compounds **103** and **104** (Table 23) <2005ZN(B)7>.

124{7}: *NNS*/ 3-Methylthiazolo[3,2-*c*][1,2,3]triazole **105** <2004TL6129>; *NNN*/ 1-(4-bromophenyl)-3-phenyl-1,2,3-triazolo[1,5-*a*]benzimidazole **106** <1997JOC1136> (Figure 14).

13{4}5: *NN*/*N* 2,7-Diethyl-1*H*-pyrazolo[1,5-*b*][1,2,4]triazoles **107** (Table 24) <1998CPB287>; 6-*tert*-butyl-2-methylthiopyrazolo[1,5-*b*][1,2,4]triazole **108** <2003OBC4268> (Figure 14).

13{4}6: *ON*/*S* *N*-Aryl-spiro[cyclohexane-1,5-thiazolo[4,3-*b*][1,3,4]oxadiazol]-2-amine **109** <2004IJC(B)901>; 2-(arylamino)-5-(*D*-glycosyl)-5-*H*-thiazolo[4,3-*b*][1,3,4]oxadiazole **110** <2001IJC(B)440>; 2-(2-phenyl-1,8-naphthylidene-3-yl)spiro[3-*H*-indole-3,5'-[1,3,4]oxadiazolo[3,2-*c*]thiazole]-2(1*H*)-one **111** <1999IJC(B)1203> (Figure 14); *SN*/*S* *N*-phenylspiro[cyclohexane-1,5-thiazolo[4,3-*b*][1,3,4]thiadiazol]-2-amine **112** <2004IJC(B)901>; 2-(arylamino)-5-(*D*-glycosyl)-5-*H*-thiazolo[4,3-*b*][1,3,4]thiadiazole **113** (Figure 14) <2001IJC(B)440>; *NN*/*S* 1-amino-2-(arylamino)-5-(*D*-glycosyl)-5-*H*-thiazolo[3,4-*b*][1,3,4]thiadiazole **114** (Figure 14) <2001IJC(B)440>; 5-aryl-1-(2',4'-dimethylphenyl)-2-sulfanyl-1,5-dihydrothiazolo[3,4-*b*][1,2,4]triazoles **115** (Table 25) <1996JCR(S)388>; *NN*/*N* 2,5-dimethylmercaptoimidazo[1,5-*b*][1,2,4]triazole **116** <1998SL786> (Figure 15).



75: R¹ = 5-methyl-1-(4-chlorophenyl)-1,2,3-triazol-4-yl; R² = Me; R³ = H

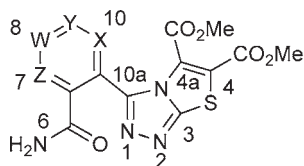
76: R¹ = 2-phenylquinoline-4-yl; R² = Me; R³ = H

77: R¹ = 2-furyl; R² = H; R³ = Me

78: R¹ = 3-bromopyridyl; R² = H; R³ = Me

Table 17 Proton NMR shifts for compounds **75–78** ((CDCl₃, 400 MHz), *J* (Hz))

Compound		Reference
75	δ 7.14–7.72 (3H, m, benzothiazole), 7.14–7.47 (4H, q or 2d, <i>J</i> = 8.5, aromat.), 2.45 (3H, s, Me-benzothiazole), 2.75 (3H, s, Me-triazole)	2002MI5
76	δ 8.35–8.33 (1H, d, <i>J</i> = 8.4, 8'H), 8.25–8.26 (1H, m, benzothiazole), 8.23 (1H, s, 5'H), 8.22 (1H, s, 7'H), 7.79–7.83 (1H, m, benzothiazole), 7.48–7.58 (5H, m, aromat.), 7.31 (1H, s, 3'H), 7.26–7.27 (1H, d, <i>J</i> = 1.48, benzothiazole), 6.99–7.01 (1H, d, <i>J</i> = 7.63, 6'H), 1.51 (3H, s, Me-benzothiazole)	2002MI5
77	δ 8.06–8.10 (1H, d, <i>J</i> = 8.4, benzothiazole), 7.49–7.50 (1H, d, <i>J</i> = 1.0, benzothiazole), 7.24–7.29 (q or 2d, <i>J</i> = 8.4, benzothiazole), 7.75–7.76 (1H, 2d, <i>J</i> = 1.8, 0.8, H5), 7.22–7.24 (1H, 2d, <i>J</i> = 3.5, 0.8, H3), 6.68–6.71 (1H, 2d, <i>J</i> = 1.8, 0.8, H4), 2.50 (3H, s, Me), 2.49 (3H, s, CH ₃ -Ph)	2001MI2
78	δ 9.00–8.92 (1H, t, <i>J</i> = 8.4, benzothiazole), 7.38–7.42 (1H, d, benzothiazole), 7.19–7.22 (2H, m, benzothiazole), 9.00 (1H, s, H2), 8.33–8.35 (1H, t, <i>J</i> = 2, H4), 7.55 (1H, s, H6), 2.48 (3H, s, CH ₃ -Ph)	2001MI2



79: X = N; Y, W, Z = CH

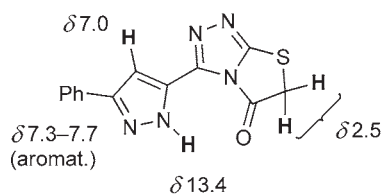
80: Y = N; X, W, Z = CH

81: W = N; X, Y, Z = CH

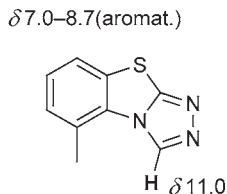
82: Z = N; X, W, Y = CH

Table 18 Proton NMR data for compounds **79–82** ((DMSO-*d*₆, 500 MHz), *J* (Hz))

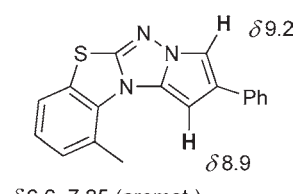
Compound	
79	δ 8.71 (1H, d, <i>J</i> = 7.8, H-9), 8.08 (2H, s, <i>NHH</i> ; d, <i>J</i> = 4.2, H-7), 7.64 (1H, dd, <i>J</i> = 7.8, 4.2, H-8), 7.60 (1H, s, <i>NHH</i>), 3.91 (3H, s, 4-CO ₂ CH ₃), 3.68 (3H, s, 4a-CO ₂ CH ₃)
80	δ 8.93 (1H, d, <i>J</i> = 5.8, H-8), 8.79 (1H, s, H-10), 8.37 (1H, s, <i>NHH</i>), 7.84 (1H, d, <i>J</i> = 5.8, H-7), 7.75 (1H, s, <i>NHH</i>), 3.89 (3H, s, 4-CO ₂ CH ₃), 3.44 (3H, s, 4a-CO ₂ CH ₃)
81	δ 9.10 (1H, s, H-7), 8.91 (1H, d, <i>J</i> = 5.8, H-9), 8.32 (1H, s, <i>NHH</i>), 7.67 (1H, d, <i>J</i> = 5.8, H-10), 7.62 (1H, s, <i>NHH</i>), 3.92 (3H, s, 4-CO ₂ CH ₃), 3.45 (3H, s, 4a-CO ₂ CH ₃)
82	δ 8.86 (1H, d, <i>J</i> = 4.8, H-8), 8.34 (1H, s, <i>NHH</i>), 8.11 (1H, d, <i>J</i> = 7.8, H-10), 7.82 (1H, dd, <i>J</i> = 7.8, 4.8, H-9), 7.71 (1H, s, <i>NHH</i>), 3.89 (3H, s, 4-CO ₂ CH ₃), 3.47 (3H, s, 4a-CO ₂ CH ₃)



83
(DMSO-*d*₆, 300 MHz)



89
(CCl₄, 60 MHz)



90
(CDCl₃, 60 MHz)

Figure 12

Table 19 Proton NMR data for compounds **84** (CDCl₃, 80 MHz)

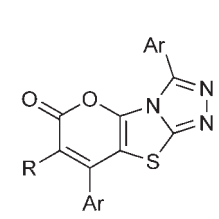
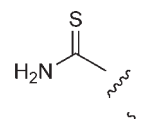
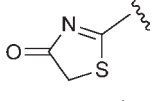
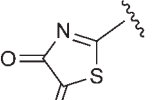
<i>R</i>	
 84 Ar = 4-MeO-C₆H₄	 δ 3.2 (6H, 2 MeO), 7.2–8.0 (8H, m, aromat.), 9.8 (2H, br s, NH₂)
	 δ 3.1 (6H, 2 MeO), 5.8 (2H, s, thiazolinone-CH₂), 7.0–7.9 (8H, m, aromat.)
	 δ 3.2 (9H, 3 MeO), 7.0–7.8 (m, 12H, aromat.), 8.4 (1H, s, Ar-CH=)

Table 20 Proton NMR values for compounds **85–88** (CF₃CO₂D, 400 MHz)

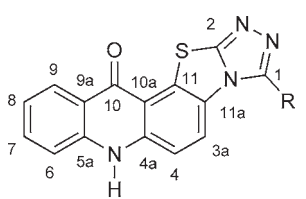
	85	86	87	88	
 85: R = H 86: R = Me 87: R = Et 88: R = Ph	H-1	9.96			
	H-3a	8.77	8.72	8.63	8.67
	H-4	8.21	8.33	8.25	8.22
	H-6	7.90	8.01	7.93	7.87
	H-7	8.10	8.22	8.13	8.08
	H-8	7.71	7.84	7.74	7.69
	H-9	8.47	8.67	8.53	8.51

Table 21 Proton NMR data for compounds **91** and **4** (CDCl₃, 300 MHz)

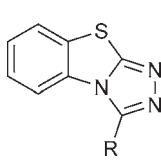
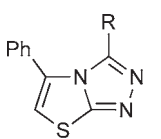
<i>Compound</i>	<i>R</i>	
	91	H δ 7.40–7.60 (2H, m, aromat.), 7.76–7.83 (2H, m, aromat.), 9.03 (1H, s, H-3)
	4	Ph δ 7.26–7.86 (9H, m, aromat.)

Table 22 Proton NMR data for compounds **92** and **93** ((CDCl₃, 300 MHz), *J* (Hz))

<i>R</i>		<i>Reference</i>
	4-Cl-C ₆ H ₄	δ 7.54 (5H, m), 7.93 (2H, d, <i>J</i> = 8.2), 8.49 (2H, d, <i>J</i> = 8.8), 8.76 (1H, s) 2005SC1753
	4-Me-C ₆ H ₄	δ 2.47 (3H, s), 7.29–7.37 (2H, m), 7.50–7.56 (3H, m), 7.91–7.94 (2H, m), 8.43 (2H, d, <i>J</i> = 8.3), 8.75 (1H, s) 2005SC1753
92: R = 4-Cl-C₆H₄ 93: R = 4-Me-C₆H₄		

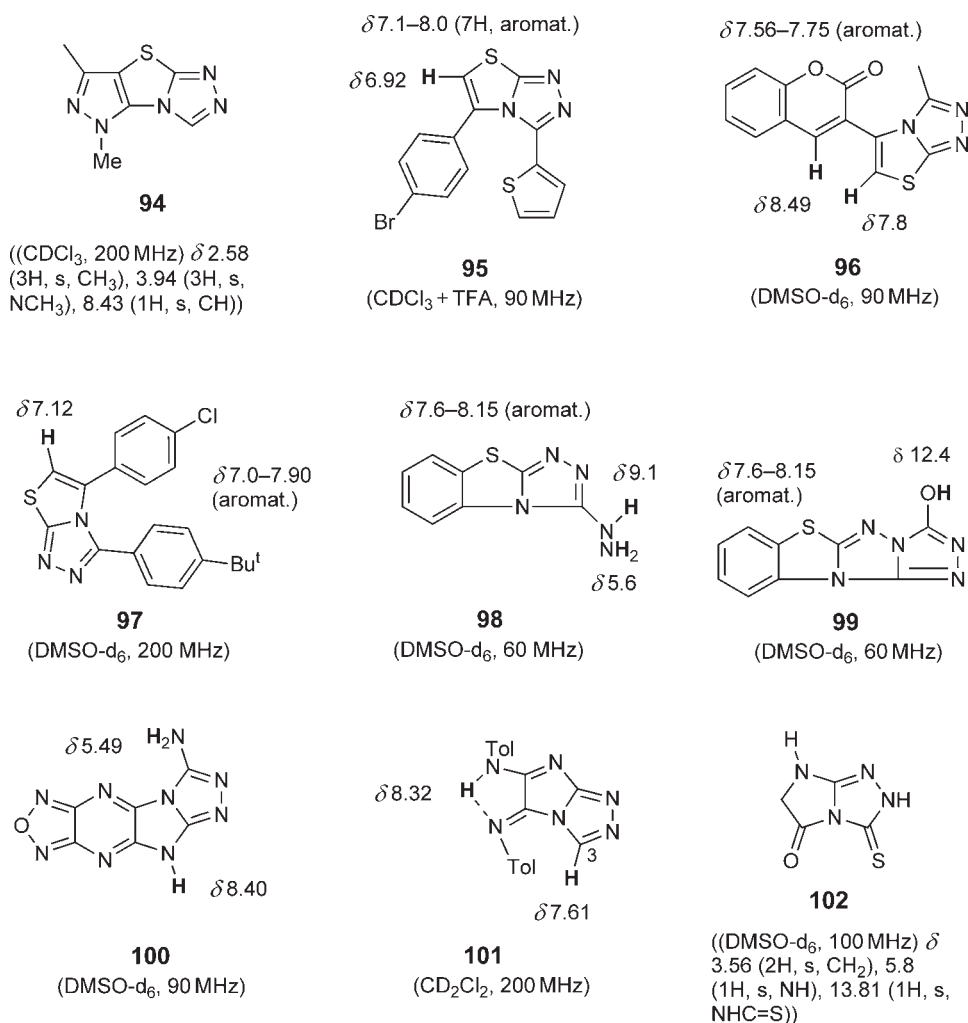
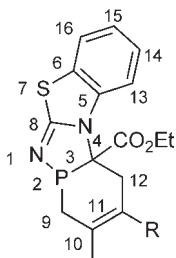


Figure 13

Table 23 Proton NMR data for compounds **103** and **104** ((CDCl₃, 400 MHz), *J* (Hz))

Compound	
	103 δ 1.18 (3H, t, <i>J</i> = 7.1, OCH ₂ CH ₃), 1.34 (3H, d, <i>J</i> _{PH} = 4.4, 11-CH ₃), 1.70 (3H, s, 10-CH ₃), 2.72, 3.48 (2H, H-12), 2.96 (3H, d, <i>J</i> _{PH} = 26, H-9), 4.21–4.36 (2H, m, OCH ₂), 6.86 (1H, dd, <i>J</i> = 7.7, 1.1, H-16), 7.16 (1H, ddd, <i>J</i> = 7.7, 8.6, 1.1, H-14), 7.30 (1H, td, <i>J</i> = 7.7, 1.3, H-15), 7.46 (1H, dd, <i>J</i> = 8.6, 1.3, H-13)
	104 δ 1.18 (3H, t, <i>J</i> = 7.1, OCH ₂ CH ₃), 1.75 (3H, s, 10-CH ₃), 2.72, 3.36 (4H, m, H-9, H-12), 4.11–4.35 (2H, m, OCH ₂), 5.26 (1H, br s, H-11), 6.81 (1H, dd, <i>J</i> = 7.8, 1.0, H-16), 7.16 (1H, td, <i>J</i> = 7.7, 1.3, H-14), 7.29 (1H, td, <i>J</i> = 7.8, 1.4, H-15), 7.47 (1H, dd, <i>J</i> = 7.7, 1.3, H-13)

103: R = Me
104: R = H

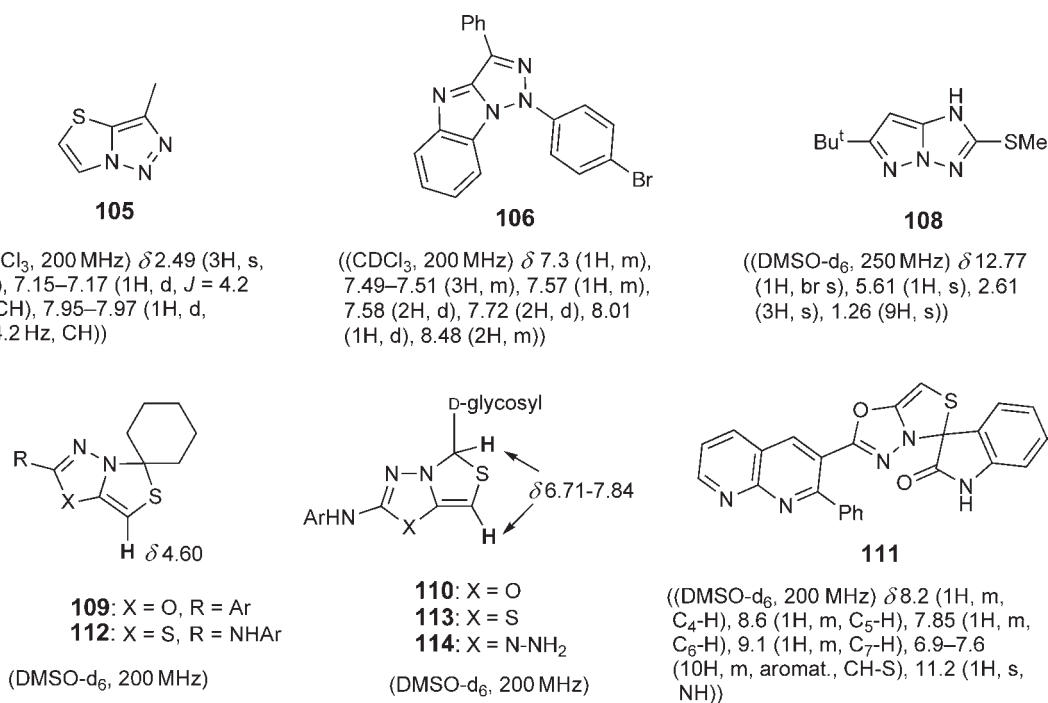


Figure 14

Table 24 Proton NMR signals for compounds **107** ((DMSO-d₆, 300 MHz), J (Hz))

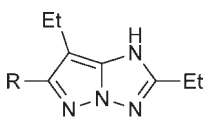
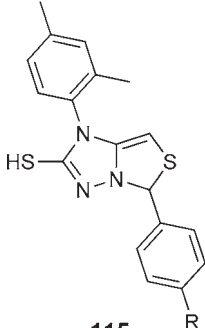
<i>R</i>	
 107	CH ₂ OCH ₃ δ 1.18 (3H, t, J = 7.6), 1.28 (3H, t, J = 7.9), 2.51 (2H, q, J = 7.6), 2.74 (2H, q, J = 7.9), 3.21 (3H, s), 4.34 (2H, s), 12.33 (1H, br s)
	CHO δ 1.22 (3H, t, J = 7.5), 1.32 (3H, t, J = 7.5), 2.82 (4H, q, J = 7.5), 9.89 (1H, s), 12.86 (1H, br s)
	CH ₂ OH δ 1.18 (3H, t, J = 7.6), 1.27 (3H, t, J = 7.6), 2.41–2.86 (4H, m), 4.39 (2H, br d), 4.75 (1H, br t), 12.20 (1H, br s)

Table 25 Proton NMR signals for compounds **115** (CDCl₃ + DMSO-d₆, 360 MHz)

<i>R</i>	
 115	H δ 6.72–8.00 (10H, m, aromat. and H-5, H-7), 2.21 (3H, s, CH ₃), 2.19 (3H, s, CH ₃)
	4-Cl δ 6.67–7.93 (9H, m, aromat., H-5, H-7), 2.12 (3H, s, CH ₃), 2.00 (3H, s, CH ₃)
	4-Me δ 6.64–7.94 (9H, m, aromat., H-5, H-7), 2.28 (3H, s, CH ₃), 2.22 (3H, s, CH ₃), 2.10 (3H, s, CH ₃)
	4-MeO δ 6.71–8.02 (9H, m, aromat., H-5, H-7), 3.78 (3H, s, CH ₃), 2.21 (3H, s, CH ₃), 2.10 (3H, s, CH ₃)

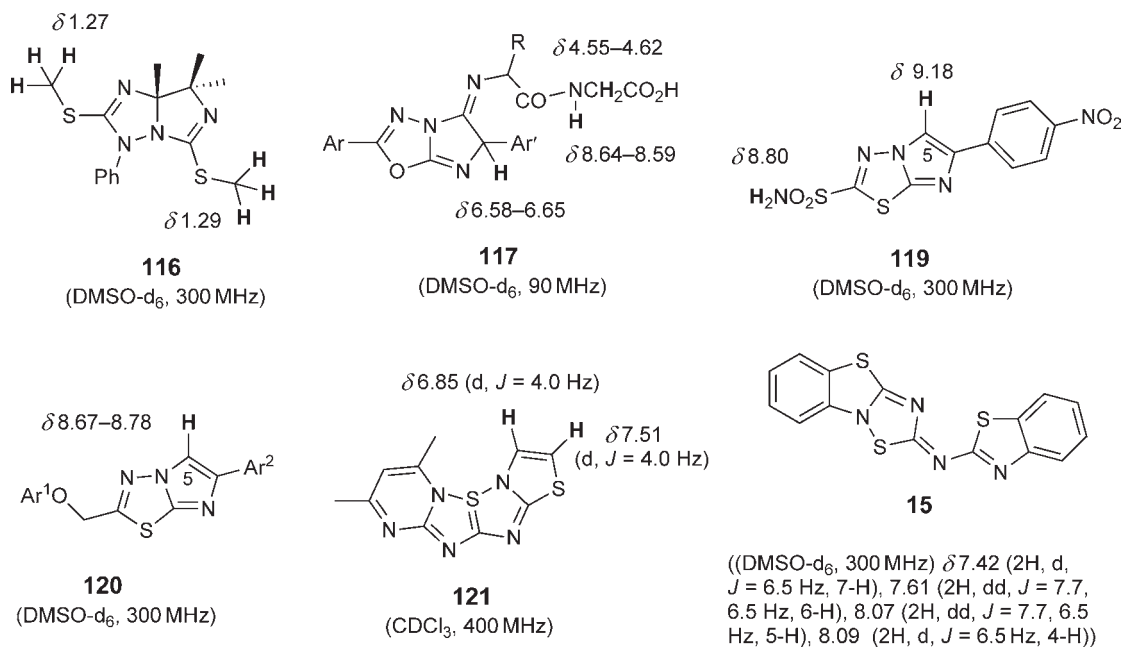


Figure 15

13{4}7: *ON/N* Imidazo[2,1-*b*][1,3,4]oxadiazoles **117** <1996MI4> (Figure 15); 2,6-diaryl-5,6-dihydroimidazo[2,1-*b*][1,3,4]oxadiazoles **118** (Table 26) <2003S1079>; *SN/N* 6-(4'-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide **119** <1996AF949>; 6-aryl-2-aryloxymethylimidazo[2,1-*b*][1,3,4]thiadiazole **120** <2005SC2881> (Figure 15).

Table 26 Proton NMR data for compounds **118** (DMSO- d_6 , 400 MHz)

	<i>R</i>	δ 5-CH ₂	δ 6-CH
 118	Ph	4.13, 4.20	5.21
	4-Cl-C ₆ H ₄	4.15, 4.23	5.24

13{4}7: *SN/S*/ 2,4-Dimethyl-6 λ^4 -thiadiazolo[3'',2'':2',3' [1,2,4]thiadiazolo[1',5':1,5][1,2,4]thiadiazolo[2,3-*a*]pyrimidine **121** <1996JA6355>; (dibenzothiazol-2-yl)tetraazathiapentalene **15** <2004EJO4203> (Figure 15); *NNS*/ 6-*p*-bromophenylthiazolo[3,2-*b*]-2-(2'-thienyl)[1,2,4]triazole **122** <2003IJC(B)401>; 3-ethylthiazolo[2,3-*b*][1,2,4]triazole **123** <1999IJC(B)18>; 6-arylthiazolo[3,2-*b*]-2-(*p*-*tert*-butylphenyl)[1,2,4]triazole **124** <2001IJC(B)54> (Figure 16);

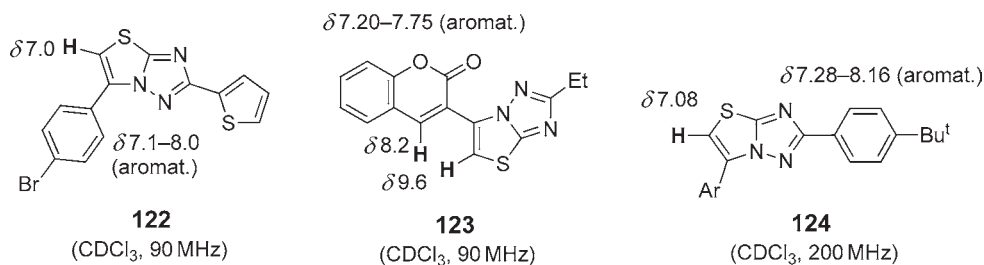
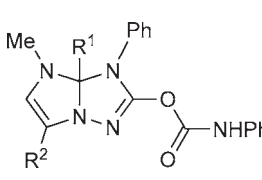


Figure 16

NNN/ 4-methyl-3-phenyl-2-phenylcarbamoyloxy-3*H*,4*H*-imidazo[1,2-*b*][1,2,4]triazole-3*a*-carboxylic acid ethyl ester **125** and 4,3*a*-dimethyl-3-phenyl-2-phenylcarbamoyloxy-3*H*,4*H*-imidazo[1,2-*b*][1,2,4]triazole-6-carboxylic acid methyl ester **126** (Table 27) <2001JOC8528>.

Table 27 Proton NMR data for compounds **125** and **126** ((CDCl₃, 500 MHz), *J* (Hz))

	Compound	<i>R</i> ¹	<i>R</i> ²	
	125	CO ₂ Et	H	δ 12.23 (1H, s), 7.53 (2H, dd, <i>J</i> = 8.0, 1.8), 7.40 (2H, ddd, <i>J</i> = 8.0, 7.2, 1.8), 7.32 (2H, dd, <i>J</i> = 7.9, 1.4), 7.29 (1H, ddd, <i>J</i> = 8.0, 7.2, 1.8), 7.22 (2H, dd, <i>J</i> = 7.9, 7.3), 7.19 (1H, d, <i>J</i> = 1.8), 7.01 (1H, d, <i>J</i> = 1.8), 6.97 (1H, dd, <i>J</i> = 7.3, 1.4), 4.46 (2H, q), 1.43 (3H, t)
	126	Me	CO ₂ Me	δ 10.40 (1H, s), 7.62–7.24 (9H, m), 7.16–7.06 (1H, m), 6.04 (1H, s), 3.70 (3H, s), 3.19 (3H, s), 2.04 (3H, s)

11.05.3.2.2 Carbon-13 NMR

For compounds of the following systems, ¹³C NMR data have been reported.

11.05.3.2.2(i) Saturated rings with CH₂ and CH groups

12{4}7: *NN*/*S* 3-Amino-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazole **24** <2003JHC821> (Figure 17); 3-aryl-5,6-dihydrothiazolo[2,3-*c*][1,2,4]triazoles **25** (Table 28) <1997AJC911>; (4*R*,4*aR*)-4,4*a*-dihydro-bis-methoxycarbonyl-1,2,5,10*c*-tetraaza **8** or pentaaza-3-thiabenz[6,7]cyclohepta[1,2,3-*cd*]-pentalene-6(5*H*)-ones **26** and **27** (Table 29) <2001T7191>; 5,6-dihydro-1,6,6-trimethyl-thiazolo[2,3-*c*][1,2,4]triazolium aminides **29** (Table 30) and 6-bromomethyl-5,6-dihydro-1,6-dimethyl-thiazolo[2,3-*c*][1,2,4]triazolium bromides **30** (Table 31) <1996T791>; *NN*/*N* 7-benzoyl-6-bromomethyl-2,6-dimethyl-2,3,5,6-tetrahydro-7*H*-imidazol[2,1-*c*][1,2,4]triazole-3-thione **35** (Table 32) <1996T791>.

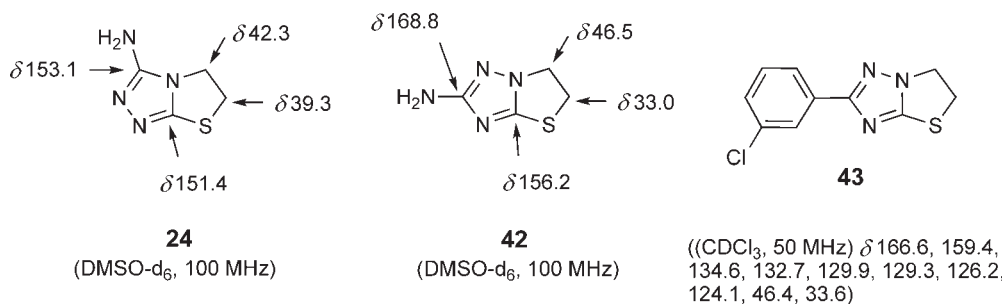
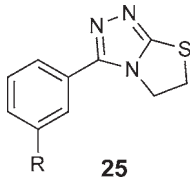


Figure 17

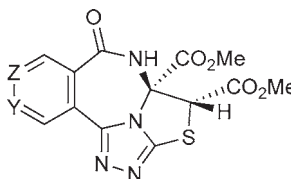
Table 28 Carbon NMR data for compounds **25** ((CDCl₃, 50 MHz), *J*(Hz))

	<i>R</i>	
	Cl	δ 156.0, 150.6, 135.0, 130.4, 130.0, 128.2, 126.4, 124.4, 45.3, 37.9
	CF ₃	δ 160.5, 150.4, 131.6 (q, <i>J</i> = 33.4 Hz), 129.8, 129.6, 127.7, 126.7 (q, <i>J</i> = 3.7 Hz), 123.6 (q, <i>J</i> = 27.5 Hz), 123.3 (q, <i>J</i> = 3.7 Hz), 45.3, 37.9

NP/*S* Compounds **127** and **128** (Table 33) <2005ZN(B)7>.

13{4}6: *NO*/*N* 6-*N*-Aryl-1-*N*-methyl-7*a*-phenyl-5,6,7,7*a*-tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-thiones **129** (Table 34) <2003PS(178)881>; *NN*/*N* imidazo[1,5-*b*][1,2,4]triazole-2,5-dithiones **41** (Table 35) <1998SL786>.

Table 29 Carbon NMR data for compounds **8**, **26**, and **27** (DMSO- d_6 , 125 MHz)

	Compound	
	8	δ 167.8, 166.5, 166.2, 155.6, 149.8, 133.7, 133.4, 132.1, 132.0, 127.4, 122.2, 72.6, 63.8, 55.1, 54.8
	26	δ 166.5, 166.2, 166.0, 156.2, 153.0, 148.4, 147.9, 138.5, 119.0, 117.1, 72.8, 63.8, 55.3, 54.9
	27	δ 166.5, 165.9, 165.4, 156.8, 154.2, 153.0, 148.1, 129.0, 125.6, 119.6, 72.8, 63.2, 54.7, 54.3

8: Y, Z = CH
26: Y = N; Z = CH
27: Y = CH; Z = N

Table 30 Carbon NMR data for compounds **29** (CDCl₃, 50 MHz)

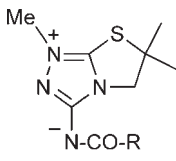
	<i>R</i>	
	OE _t	δ 14.2 (CH ₂ CH ₃), 28.6 (C(CH ₃) ₂), 37.1 (NCH ₃), 56.7 (C(CH ₃) ₂), 59.3 (CH ₂ CH ₃) 69.6 (CH ₂), 147.9, 156.3, 160.2 (CO)
	Ph	δ 29.8 (C(CH ₃) ₂), 38.2 (NCH ₃), 60.3 (C(CH ₃) ₂), 70.8 (CH ₂), 128.0, 129.4, 130.6 (<i>para</i>), 139.3 (<i>ipso</i>), 150.4, 157.7, 172.7 (CO)
	29	

Table 31 Carbon NMR data for compounds **30** (DMSO- d_6 , 50 MHz)

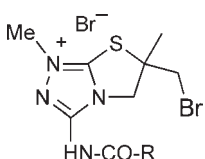
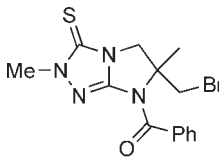
	<i>R</i>	
	OE _t	δ 14.5 (CH ₂ CH ₃), 25.5 (C(CH ₃ CH ₂ Br)), 38.9 (NCH ₃), 41.0 (CH ₂ Br), 56.8 (NCH ₂) 62.7 (CH ₂ CH ₃), 72.9 (C(CH ₃ CH ₂ Br)), 145.5, 152.2 (CO), 155.3
	Ph	δ 25.6 (C(CH ₃ CH ₂ Br)), 38.5 (NCH ₃), 41.1 (CH ₂ Br), 57.6 (NCH ₂), 73.1 (C(CH ₃ CH ₂ Br)), 128.9, 129.0, 131.5 (<i>ipso</i>), 133.7 (<i>para</i>), 145.9, 155.8, 166.3 (CO)
	30	

Table 32 Carbon NMR data for compound **35** (CDCl₃, 50 MHz)

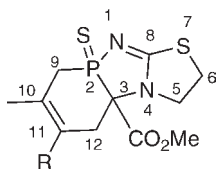
	
35	δ 24.1 (C(CH ₃ CH ₂ Br)), 36.8 (NCH ₃), 37.4 (CH ₂ Br), 52.4 (NCH ₂), 74.0 (C(CH ₃ CH ₂ Br)), 128.7, 128.9, 133.0 (<i>para</i>), 133.6 (<i>ipso</i>), 150.1 (CN), 162.4 (CS), 167.8 (CO)

13{4}7: *NN/S* 2-Amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **42** <2003JHC821> and 3-(4-chlorophenyl)-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **43** <1997AJC911> (Figure 17).

11.05.3.2.2(ii) CH groups in unsaturated rings

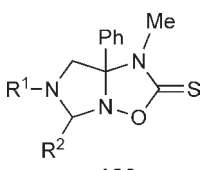
12{4}5: *NN/N* 3-Aryl-7-arylidene-6-methyl-pyrazolo[5,1-*c*][1,2,4] triazole **57** <2002ARK133> (Figure 18); 3-aryl-7-ethoxycarbonyl-6-methyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **55** (Table 36) <2002ARK133>.

Table 33 Carbon NMR signals for compounds **127** and **128** (CDCl₃, 50 MHz)

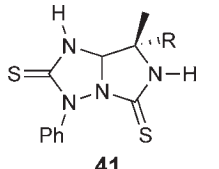
Compound	C-3	C-5	C-6	C-8	C-9	C-10	C-11	C-12
	68.9	45.1	30.4	168.0	41.4	125.8	126.0	36.3
128 (R = H)	68.5	45.0	30.2	168.3	40.4	135.7	118.5	28.6

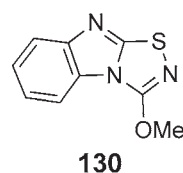
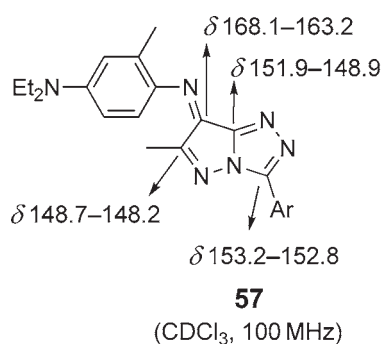
127: R = Me
128: R = H

Table 34 Carbon NMR shifts for compounds **129** (50 MHz)

	R ¹	R ²		Solv.
	4-Me-C ₆ H ₄	H	δ 20.1, 31.0, 53.9, 75.5, 93.5, 115.0, 126.4, 128.6, 129.2, 129.4, 129.5, 135.5, 142.7, 182.4	D + C
	4-MeO-C ₆ H ₄	Ph	δ 31.9, 55.7, 55.9, 87.2, 92.6, 115.2, 116.9, 126.9, 127.9, 128.9, 129.0, 129.4, 130.0, 136.2, 137.0, 139.6, 154.1, 183.6	C

C = CDCl₃; D = DMSO-d₆.**Table 35** Carbon NMR data for compounds **41** (DMSO-d₆, 75 MHz)

R	
	Me δ 25.3 (7-CH ₃), 26.4 (7-CH ₃), 60.8 (7-C), 83.9 (7a-C), 123.1–141.2 (2,6-, 4-, 3,5-, 1-C, 3-Ph), 179.5 (2-C), 188.1 (5-C)
Ph	δ 23.4 (7-CH ₃), 66.6 (7-C), 85.1 (7a-C), 124.8–142.4 (2,3,4,5,6-C, 3-Ph, 7-Ph), 141.0 (1-C, 3-Ph), 179.4 (2-C), 189.3 (5-C)

((CDCl₃, 100 MHz) δ 163.2, 150.3, 148.1, 128.2, 124.9, 121.8, 119.2, 111.7, 57.5)**Figure 18**

12[4]7: *NN*/N Imidazo[1,2-*d*][1,2,4]thiadiazoles **66** (Table 37) (signals not assigned) and [1,2,4]thiadiazolo[4,3-*a*]benzimidazoles **130** (Figure 18) (signals not assigned) <2005JOC6230>; *NS*/S [1,2,4]thiadiazolo[3,4-*b*]benzothiazol-3(3*H*)-ones **68** (Table 38) <1997H(45)1579>; *NN*/S triazolo[1,2,4]thiazolo[5,4-*a*]acridin-12(7*H*)-ones **85–88** (Table 39) <1999MRC86>; 5,7-dimethyl-pyrazolo[3',4':4,5]thiazolo[2,3-*c*][1,2,4]triazole **94** <1999H(51)829> (Figure 19); 3,5-disubstituted thiazolo[2,3-*c*][1,2,4]triazoles **93** (Table 40) <2005SC1753>; 3-substituted-5,6-bis-methoxy-carbonylthiazolo[2,3-*c*][1,2,4]triazoles **79–82** (Table 41) <2001T7191>; *NP*/S compound **131** <2005ZN(B)7> (Figure 19), and **103** and **104** (Table 42) <2005ZN(B)7>.

Table 36 Carbon NMR signals for compounds **55** (DMSO- d_6 , 100 MHz)

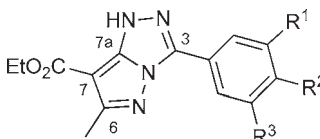
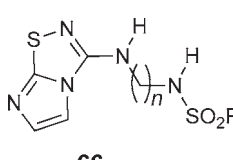
	R^1	R^2	R^3	δ C-3	δ C-6	δ C-7	δ C-7a
 55	Br	OH	Br	151.0	137.0	82.5	159.0
	Br	OMe	H	147.8	137.0	86.6	156.8
	Bu ^t	OH	Bu ^t	156.0	139.4	86.4	158.8

Table 37 Carbon NMR signals for compounds **66** (100 MHz)

	<i>R</i>	<i>Solv.</i>	
 66	1-Naphthyl	δ 161.3, 158.8, 143.7, 137.2, 134.7, 134.3, 129.5, 129.1, 128.4, 128.1, 126.9, 124.4, 124.1, 109.5	C
	2-NH ₂ -Ph	δ 142.2, 136.7, 133.3, 129.0, 120.0, 116.8, 115.0, 111.3	C
	3-CO ₂ H-Ph	δ 165.8, 156.8, 148.1, 144.3, 136.8, 134.4, 128.0, 127.8, 127.4, 124.5, 111.4	D
	Me	δ 156.8, 144.2, 136.8, 111.2	D

C = CDCl₃; D = DMSO- d_6 .**Table 38** Carbon NMR signals for compounds **68** (CDCl₃, 100 MHz)

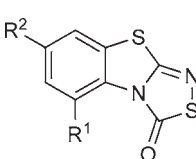
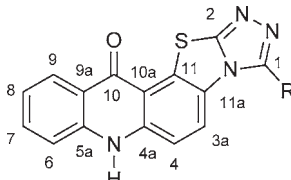
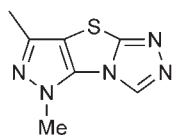
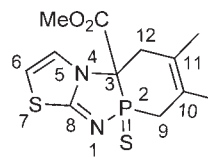
	R^1	R^2	
 68	H	H	δ 114.5, 123.3, 126.7, 127.1, 127.8, 130.9, 154.2, 172.8
	Me	H	δ 23.3, 121.0, 127.0, 127.1, 128.5, 130.9, 131.1, 155.2, 173.0
	H	Cl	δ 115.2, 123.2, 127.5, 129.4, 132.3, 153.5, 172.6
	H	MeO	δ 55.9, 108.5, 113.0, 115.2, 124.7, 129.2, 154.2, 158.2, 172.6

Table 39 Carbon NMR data for compounds **85–88** (CF₃CO₂D, 100 MHz)

	Carbon	85	86	87	88
 85 : R = H 86 : R = Me 87 : R = Et 88 : R = Ph	C-1	137.0	149.3	153.5	150.5
	C-2	160.2	161.2	160.8	161.4
	C-3a	123.3	122.8	122.7	123.3
	C-4	121.4	121.8	121.3	121.1
	C-4a	143.0	143.0	142.6	142.7
	C-5a	143.2	143.6	143.3	143.2
	C-6	120.5	120.8	120.5	120.9
	C-7	139.0	139.4	139.1	139.4
	C-8	127.4	127.8	127.4	127.8
	C-9	127.5	127.9	127.6	127.9
	C-9a	121.3	121.7	121.4	121.8
	C-10	179.2	179.7	179.5	179.8
	C-10a	116.6	117.2	116.8	116.7
	C-11	133.5	134.2	133.8	134.0
	C-11a	125.4	126.4	126.0	126.5

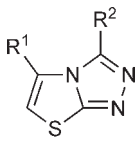
**94**

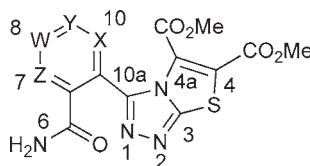
((DMSO- d_6 , 50 MHz) δ 12.3 (CH₃), 34.4 (NCH₃), 115.1 (C-4a), 126.2 (C-5), 146.1 (C-1), 152.0 (C-7a), 154.4 (C-3a))

**131**

((CDCl₃, 100 MHz) δ 20.4 (CH₃-10), 20.6 (CH₃-11), 38.8 (C-12), 41.6 (C-9), 53.5 (OCH₃), 69.0 (C-3), 103.5 (C-6), 122.2 (C-5), 125.6 (C-10), 126.2 (C-11), 167.8 (C-8), 175.0 (CO))

Figure 19**Table 40** Carbon NMR data for compounds **93** (CDCl₃, 75 MHz)

	R^1	R^2	
	4-Cl-C ₆ H ₄	Ph	δ 127.0, 129.0, 129.5, 129.6, 132.2, 133.2, 137.1, 140.2, 165.2, 167.9, 168.0, 190.1
	Ph	4-Me-C ₆ H ₄	δ 21.9, 126.4, 128.9, 129.5, 129.9, 131.1, 132.6, 133.3, 145.3, 164.7, 167.7, 168.8, 190.1

93

79: X = N; Y, W, Z = CH

80: Y = N; X, W, Z = CH

81: W = N; X, Y, Z = CH

82: Z = N; X, W, Y = CH

Table 41 Carbon NMR data for compounds **79–82** (DMSO- d_6 , 125 MHz)

Compound	
79	δ 168.6, 160.4, 158.9, 155.4, 150.1, 149.6, 142.7, 137.7, 134.0, 127.7, 126.3, 125.5, 54.8, 54.4
80	δ 167.0, 160.4, 157.9, 155.2, 153.0, 152.5, 146.4, 142.6, 126.9, 126.3, 122.2, 122.0, 54.8, 54.2
81	δ 167.0, 160.7, 158.2, 156.0, 152.6, 149.4, 148.5, 143.0, 127.2, 126.6, 126.5, 121.0, 54.8, 53.9
82	δ 166.4, 160.5, 158.2, 154.8, 151.2, 149.2, 147.9, 141.9, 127.0, 126.6, 126.4, 123.4, 54.7, 54.3

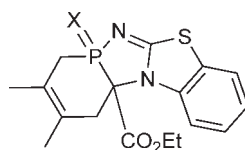
124{7}: *NNS*/ Ylides **132** (Table 43) <1998T3913>.

13{4}5: *NN*/ *N*-6-*tert*-Butyl-2-methylthiopyrazolo[1,5-*b*][1,2,4]triazole **108** <2003OBC4268> (Figure 20).

13{4}6: *NO*/ *N* Imidazo[1,5-*b*][1,2,4]oxadiazole **133** <2001RCB882> (Figure 20); *NN*/ *S* thiazolo[3,4-*b*][1,2,4]triazole **134** <2003PS(178)1175>; *NN*/ *N* 2,5-dimethylmercaptoimidazo[1,5-*b*][1,2,4]triazole **116** <1998SL786> (Figure 20).

13{4}7: *SN*/ *N* Imidazo[2,1-*b*][1,3,4]thiadiazole **135** <2004S1067> (Figure 20), **136** and **137** (Table 44) <2004BMC5651>; 6-aryl-2-aryloxymethylimidazo[2,1-*b*][1,3,4]thiadiazoles **120** (Table 45) <2005SC2881>; *NN*/ *N* 4-methyl-3-phenyl-2-phenylcarbamoyloxy-3*H*,4*H*-imidazo[1,2-*b*][1,2,4]triazole-3*a*-carboxylic acid ethyl ester **125** and 4,3*a*-dimethyl-3-phenyl-2-phenylcarbamoyloxy-3*H*,4*H*-imidazo[1,2-*b*][1,2,4]triazole-6-carboxylic acid methyl ester **126** (Table 46) <2001JOC8528>.

134{7}: *ONN*/ Imidazo[1,2-*b*][1,2,4]oxadiazoles **138** <2001RCB882> (Figure 20); *SNS*/ [1,2,4]thiazolo[3,2-*b*]-benzothiazole **15** <2004EJO4203>; *SNN*/ 2-ethylamino[1,2,4]thiadiazolo[2,3-*a*]benzimidazole **139**



103: X = S

104: X = Se

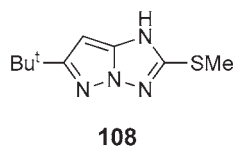
Table 42 Carbon NMR data for compounds **103** and **104** (CDCl₃, 100 MHz)

Compound	C-3	C-5	C-6	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16
103	67.3	135.1	123.5	166.5	41.5	126.5	125.3	35.4	123.4	127.0	123.4	110.0
104	68.5	134.9	123.8	166.9	43.3	126.8	125.8	35.4	123.5	127.1	123.5	110.1

Table 43 Carbon NMR data for compounds **132** (DMSO-d₆, 62.5 MHz)

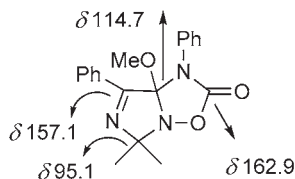
<i>R</i>		
	CHCOPh	δ 190.1, 138.7, 135.1, 134.5, 133.3, 130.9, 129.2, 128.9, 121.0, 58.5, 9.4
	C(CN) ₂	δ 137.6, 130.5, 126.5, 120.3, 119.9, 45.0, 9.7

132



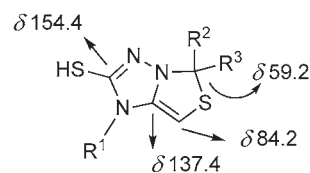
108

((DMSO-d₆, 50 MHz) δ 161.4, 147.6, 138.0, 74.8, 32.5, 30.5, 14.8)



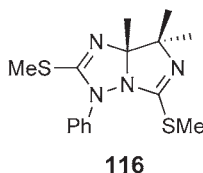
133

(CD₃OD, 50 MHz)



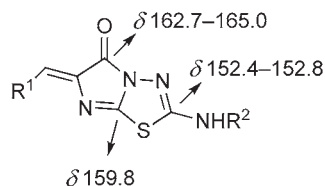
134

(DMSO-d₆, 100 MHz)



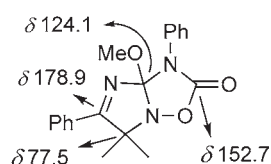
116

((DMSO-d₆, 75 MHz) δ 13.7 (5-SCH₃), 15.7 (2-SCH₃), 21.8 (7a-CH₃), 25.8, 26.8 (7-CH₃), 72.7 (5-C), 100.9 (6-C), 121.6–143.7 (2-, 6-, 4-, 3, 5-, 1-C, 3-C₆H₅), 158.2 (2-C), 167.3 (5-C))



135: R¹, R² = Ar

(DMSO-d₆, 100 MHz)



138

(CDCl₃, 50 MHz)

Figure 20

Table 44 Carbon NMR data for compounds **136** and **137** (75 MHz)

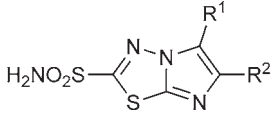
	Compound	Solv.
	136	δ 164.3, 159.9, 147.6, 145.7, 127.1, 126.7, 115.0, 110.6, 56.0 D
	137	δ 166.6, 152.0, 148.7, 139.6, 130.0, 129.5, 127.9, 110.9, 102.4, 21.4 C
136: R ¹ = H; R ² = 4-MeO-C ₆ H ₄ 137: R ¹ = SCN; R ² = 4-Me-C ₆ H ₄		
C = CDCl ₃ ; D = DMSO-d ₆ .		

Table 45 Carbon NMR data for compounds **120** (DMSO-d₆, 100 MHz)

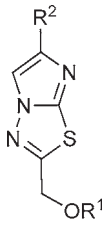
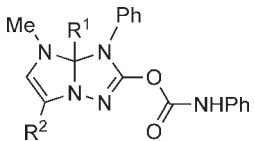
	R ¹	R ²	
	Ph	Ph	δ 65.1, 110.7, 115.2, 121.9, 124.3, 129.0, 129.1, 130.5, 130.7, 143.7, 144.1, 145.7, 153.5, 161.7
	2-Me-C ₆ H ₄	4-Br-C ₆ H ₄	δ 21.0, 65.1, 110.5, 112.7, 115.7, 121.1, 123.0, 126.5, 128.9, 130.8, 131.0, 132.4, 133.6, 139.0, 144.9, 145.1, 157.6, 162.7
	2,4-Cl ₂ -C ₆ H ₃	4-Br-C ₆ H ₄	δ 67.0, 110.5, 114.3, 117.6, 128.1, 129.4, 130.4, 130.7, 132.4, 133.1, 145.7, 151.7, 154.1, 160.4
	4-Cl-C ₆ H ₄	4-Me-C ₆ H ₄	δ 20.5, 65.4, 110.8, 116.4, 117.9, 122.4, 124.6, 127.4, 129.1, 130.4, 130.8, 131.4, 142.3, 144.6, 145.0, 153.6, 160.6
120			

Table 46 Carbon NMR data for compounds **125** and **126** (CDCl₃, 100 MHz)

	Compound	R ¹	R ²	
	125	CO ₂ Et	H	δ 164.3, 154.6, 154.3, 139.9, 139.2, 131.2, 129.6, 128.6, 127.1, 124.6, 122.5, 121.8, 119.5, 119.4, 63.5, 38.1, 14.1
	126	Me	CO ₂ Me	δ 168.6, 154.6, 150.5, 137.3, 135.0, 129.3, 129.1, 129.0, 127.6, 126.3, 124.5, 124.2, 121.6, 120.0, 53.3, 32.7, 14.8

<1999JHC991>; *NNO*/ 5,5,6,6-tetracyclopropyl-3-methyl-5,6-dihydro-3*H*-oxazolo[3,2-*b*][1,2,4]triazol-7-ium-2-olate **140** <2004JA700> (Figure 21).

11.05.3.2.3 Phosphorus-31 NMR

The following compounds have been studied by P-31 NMR spectroscopy.

11.05.3.2.3(i) Saturated rings with CH₂ and CH groups

12{4}7: *NP/S* Thiazolo[3,2-*d*][1,4,2]diazaphospholes **141–143**, **127**, and **128** (Table 47) <2005ZN(B)7>.

11.05.3.2.3(ii) CH groups in unsaturated rings

12{4}7: *NP/S* Thiazolo[3,2-*d*][1,4,2]diazaphospholes **131**, **144**, and **145** (Table 48) <2005ZN(B)7>; compounds **146–149**, **103**, and **104** (Table 49) <2005ZN(B)7>.

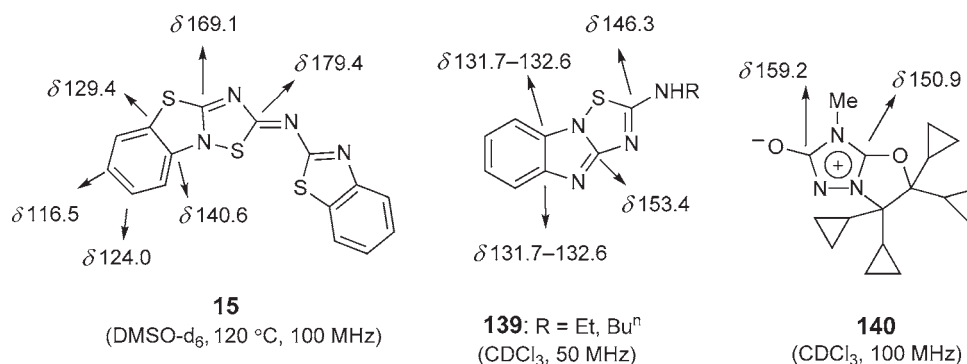


Figure 21

Table 47 Phosphorus-31 NMR data for compounds **141–143**, **127**, **128** (CDCl₃, 36.23 MHz)

			Compound
141 : R = Me 142 : R = H	127 : R = Me; X = S 128 : R = H; X = S	143	141 : δ 83.9 142 : δ 83.1 127 : δ 120.6 128 : δ 119.8 143 : δ 113.4

Table 48 Phosphorus-31 NMR data for compounds **131**, **144**, and **145** (CDCl₃, 36.23 MHz)

	Compound	
131 : R = Me 145 : R = H	144	131 : δ 118.5 145 : δ 114.3 144 : δ 118.2

11.05.3.3 Mass Spectra

For numerous [5,5] (2N1)-compounds, mass spectra data have been included in their spectral characterization. Mostly the molecular ion has been given, and in some cases fragments have also been assigned. Only few reports contain a complete analysis; these include the following ring systems:

12{4}5: ON/N <1997T17461>; NN/N <2004PS(179)1907, 2004RRC1018, 2004HAC432, 2003IJC(B)2054, 2002ARK133, 2001PS(173)223, 2001MI1, 1997T17461, 2000H(53)917>.

12{4}7: ON/N <2004HAC432>; SN/N <2005JOC6230, 2001IJH315, 1997IJH255, 2004BMC5651, 2003EJM781, 2005SC2881>; NV/S <2001IJH315, 2004IJH241, 1997AJC911, 2001SC2841, 2002JST41, 2001MI2, 2000BKC425, 1998IJC(B)921, 1997JOC5766, 1996IJC(B)842, 1996T791, 2004PS(179)2519, 1996EJM575, 2005SC1753, 1999IJC(B)18, 2004PS(179)1019, 2005IJC(B)625>; NN/N <1998MI1, 2000HAC387, 2002JHC319>.

124{7}: NNS/ <2000SC417, 2004TL6129, 1998T3913>; NVN/ <2000HAC387>.

13{4}5: NN/N <1998CPB287, 1998CPB69, 2003OBC4268, 2000SL1411>.

Table 49 Phosphorus-31 NMR data for compounds **146–149**, **103**, **104** (CDCl₃, 36.23 MHz)

		Compound
		146: δ 84.0 147: δ 82.5 103: δ 119.6 148: δ 118.4 104: δ 112.5 149: δ 111.8
146: R = Me 147: R = H	103: R = Me; X = S 148: R = H; X = S 104: R = Me; X = Se 149: R = H; X = Se	

13{4}6: *NN/S* <2003PS(178)1175>; *ON/S* <1999IJC(B)1203>; *NO/N* <1997T13873>.

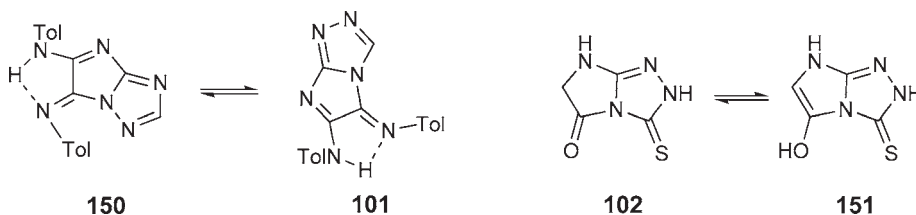
13{4}7: *ON/N* <2003S1079>; *SN/S* <1997JHC367>; *SN/N* <2003S1079, 2004S1067, 2003IJC(B)1463, 2001IJC(B)303, 1997IJC(B)394, 1996IJC(B)238>; *NN/S* <1997AJC911, 2000EJM743, 1999SC4417, 1999IJC(B)867, 2001JCS(P1)424, 1998IJH231, 2000IJH275, 1999IJH341, 1998IJH309, 1999IJH247>.

134{7}: *SNS/* <2004EJO4203>; *NNN/* <2001JOC8528>.

11.05.4 Thermodynamic Aspects

11.05.4.1 N–H Tautomerism

The energy difference in compounds **150** and **101** has been investigated <2001EJO2257> (Figure 22). The thermochemistry favors compound **101** by 3.3 kcal mol^{−1}, probably most often due to the absence of the long-range quadrupole C–H— π interaction found in **101** <2000JA3746> (Figure 22).

**Figure 22**

Compound 5-hydroxy-4-thioimidazo[1,2-*c*][1,2,4]triazole is present as a mixture of tautomers **102** and **151**, as detected in the ¹H NMR spectrum <1998MI1> (Figure 22).

11.05.4.2 Photochemical Properties

Azomethine is used in conventional three-color photographic dyes (yellow, magenta, and cyan). These dyes are used because all three-color images can be created by a single coupling reaction with oxidized developer during the development process, dye hue can be well controlled by choice of coupler structure and substituent pattern, high dye extinction coefficients give high silver to image density conversion, and the images thus created are remarkably photostable <1999J(P2)2147>. This photostability arises primarily as a consequence of molecular flexion about the azomethine bond in the singlet and triplet excited states <2001JCS(P2)953>. Despite the good light stability of these compounds, they show photodegradation upon prolonged exposure to light, and determining the mechanism by which

photodegradation occurs is an important technical goal. Accordingly, the determination of azomethine dye triplet energies with respect to that of singlet oxygen has been the matter of a series of recent studies <1999JPH29, 2001JPC(A)1214>.

The aggregation and light stability of two pyrazolotriazole dyes **152** and **153** (Figure 23) on hydrated glass surfaces <2002PCP1766> or at oil/aqueous interfaces <2005PCP1815> has been investigated using steady-state and time-resolved fluorescence spectroscopy as well as wave-induced fluorescence spectroscopy.

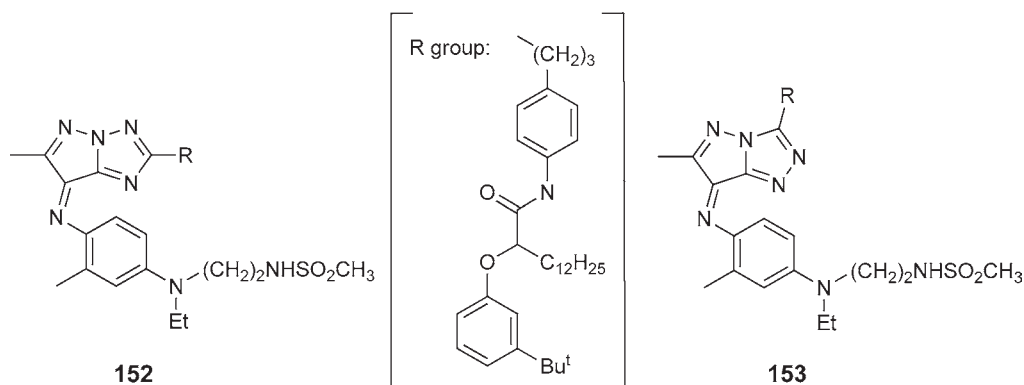


Figure 23

Characterization of the excited states of pyrazolotriazole azomethine dyes is of considerable importance in view of their extensive image-forming magenta dyes. The 7*H*-pyrazolo[5,1-*c*][1,2,4]triazole skeleton is introduced by taking advantage of the excellent color reproduction properties of the respective dyes in a subtractive color system <1977J(P1)2047>. The isomeric skeleton 7*H*-pyrazolo[1,5-*c*][1,2,4]triazole was also reported to bring forth comparable magenta dyes <1994J(P2)531>. In a recent study, the theoretical prediction and direct observation of the excited states of pyrazolotriazole azomethine dyes **2** and **3** (Figure 1) have been investigated by steady-state fluorescence <2001J(P2)953>. It was concluded that the fluorescent transient is, in fact, a non-Boltzmann population of the ‘hot’ molecules in the S_1 electronic state. The non-Boltzmann nature of the fluorescent transient is a consequence of the existence of a barrier-less relaxation path leading toward an S_1 - S_0 crossing, which corresponds to the twisted geometry.

Triplet energy transfer measurements from porphyrin and phthalocyanine sensitizers give the triplet energies of six {(*Z*)-*N*⁴,*N*⁴-diethyl-2-(alkyl, aryl)-*N*¹-(3-phenyl-7*H*-pyrazolo[5,1-*c*][1,2,4]triazol-7-ylidene)benzene-1,4-diamine} azomethine dyes **154** with adsorption maxima in ethanol at 546–633 nm to lie in the range of 115–88 kJ mol⁻¹ <2003PPS563> (Figure 24).

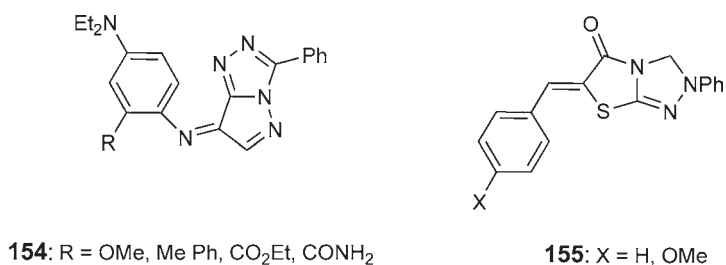


Figure 24

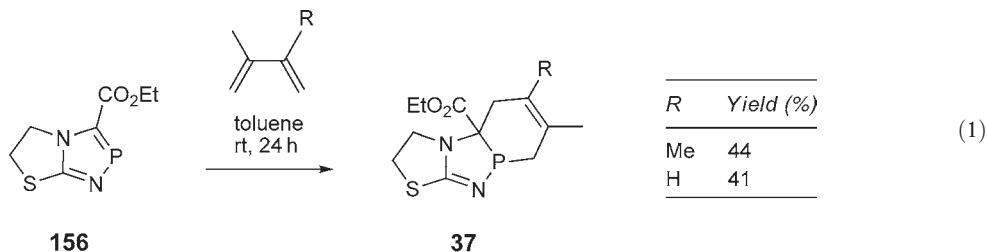
11.05.4.3 Electrochemical Properties

The redox characteristics, using linear sweep and cyclic voltammetry, of a series of (*Z*)-6-arylidene-2-phenyl-2,3-dihydrothiazolo[2,3-*c*][1,2,4]triazol-5(6*H*)-ones **155** (Figure 24) have been investigated in different dry solvents (acetonitrile, 1,2-dichloroethane, tetrahydrofuran (THF), dimethyl sulfoxide (DMSO)) at platinum and gold electrodes. It was concluded that these compounds lose one electron forming the radical cation, which loses a proton to form the radical. The radical dimerizes to yield the bis-compound which is still electroactive and undergoes further oxidation in one irreversible two-electron process to form the diradical dication on the newly formed C–C bond <2001MI3>.

11.05.5 Reactivity of Fully Conjugated Rings

11.05.5.1 Diels–Alder Reaction

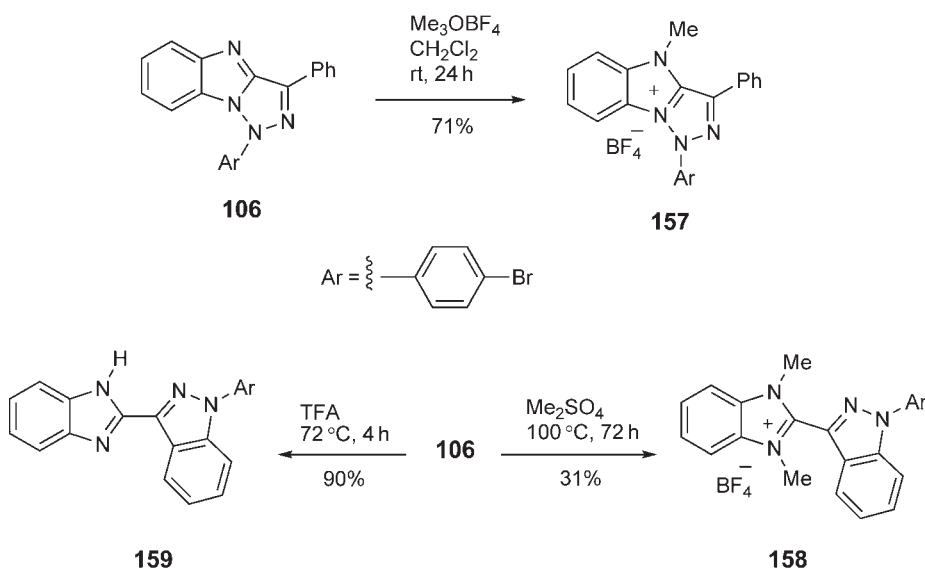
The Diels–Alder (DA) reaction of several heterocyclic fused heterophospholes including annelated azaphospholes and phosphinines <1996CHEC-II(3)709, 1995S361, 2001CRV3549, 2004HAC271>, such as thiazolo[3,2-*d*][1,4,2]diazaphospholes, with 2,3-dimethylbutadiene and isoprene has been investigated <2005ZN(B)7>. A density functional theory (DFT) analysis for the investigation of the origin of the stereo- and regioselectivities in the DA reactions of azaphospholes has been published <2006T1548>. 3-Ethoxycarbonyl-5,6-dihydrothiazolo[3,2-*d*][1,4,2]diazaphosphole **156** <1992S267> (similar reactivity has been observed for 3-alkoxycarbonylthiazolo[3,2-*d*][1,4,2]diazaphospholes and 1,4,2-diazaphospholo[5,4-*b*]benzothiazoles) reacts with 2,3-dimethylbutadiene and with isoprene to form [2 + 4]-cycloadducts **37** (Equation 1) <2005ZN(B)7>.



11.05.5.2 Electrophilic Attack at Ring Nitrogen

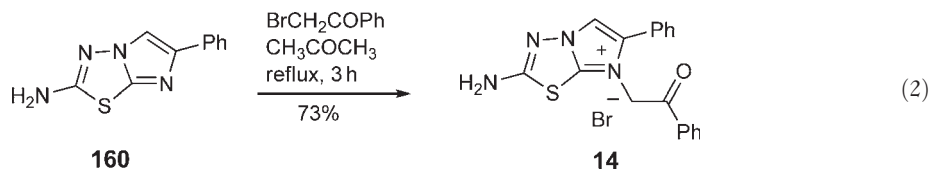
11.05.5.2.1 *N*-alkylation

1-(4'-Bromophenyl)-3-phenyl-[1,2,3]triazolo[1,5-*a*]benzimidazole **106** reacts with trimethyloxonium fluoroborate, at room temperature, to afford one single product whose structure proved to be **157** (Scheme 1) <1997JOC1136>. However, when the same tricyclic compound **106** was alkylated with dimethyl sulfate at 100 °C, a totally different product was isolated, which proved to be 1,3-dimethyl-2-[1-(4-bromophenyl)indazol-3-yl]benzimidazolium salt **158** (Scheme 1) <1997JOC1136>. A similar type of ring opening is observed when compound **106**, treated with trifluoroacetic acid (TFA), leads to product **159** (Scheme 1) <1997JOC1136>.



Scheme 1

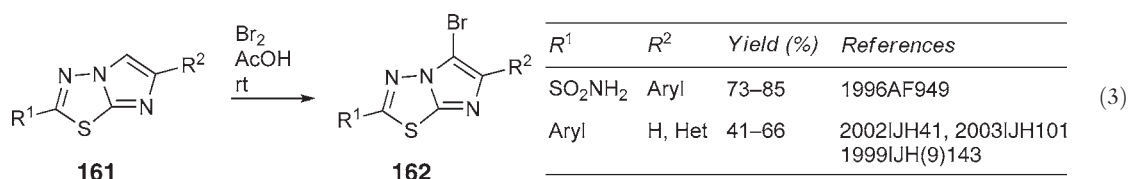
The reaction of 2-amino-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole **160** <1967ZC341> with 2-bromoacetophenone gives the corresponding salt **14** (Equation 2) <2002ARK32>.



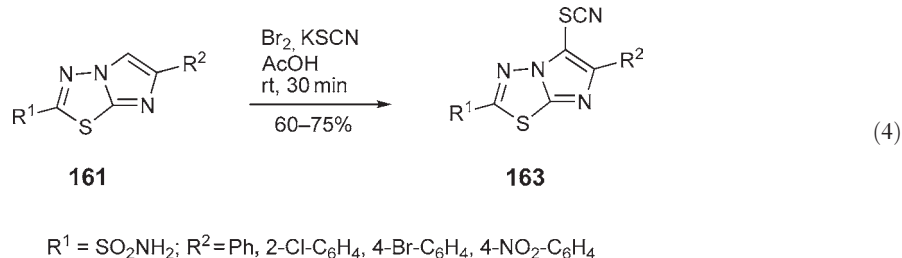
11.05.5.3 Electrophilic Attack at Ring Carbon

11.05.5.3.1 Bromination and sulfonation

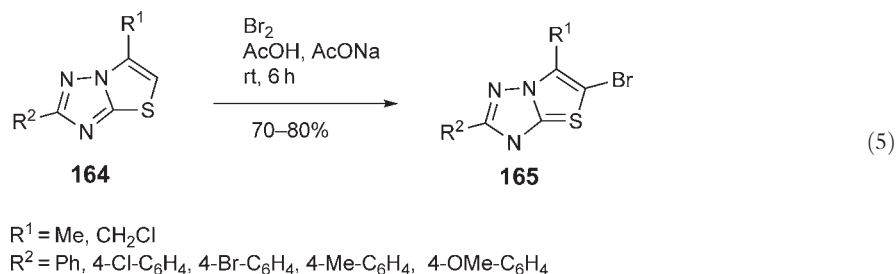
Bromination of the free base **161** provides the corresponding 6-substituted 5-bromoimidazo[2,1-*b*][1,3,4]thiadiazoles **162** (Equation 3) <1996AF949, 1999IJH(9)143, 2002IJH41, 2003IJH101>.



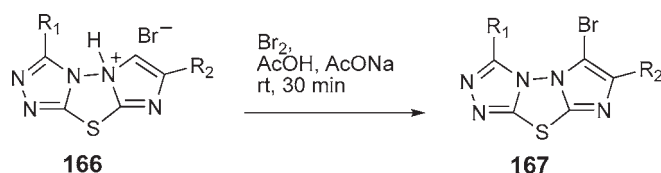
The reaction of compounds **161** with bromine followed by treatment with potassium thiocyanate affords 5-thiocyanato-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **163** (Equation 4) <2000EJM853>.



Bromination of 2-aryl-thiazolo[3,2-*b*][1,2,4]triazoles **164** gives the corresponding 5-substituted 6-bromo thiazolo[3,2-*b*][1,2,4]triazoles **165** (Equation 5) <2000FAR71>.



Highly functionalized imidazo[2,1-*b*][1,3,4]thiadiazoles **166** react with bromine in acetic acid to give the corresponding monobrominated derivatives **167** (Equation 6) <2003IJC(B)1463, 2001IJC(B)303, 2003IJH33, 2002IJH125>.

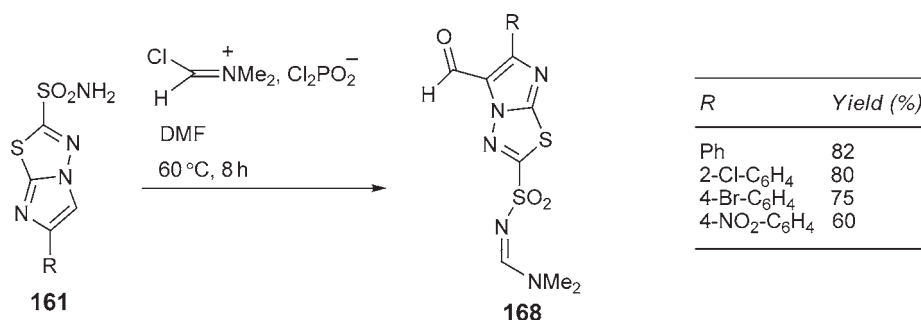


R_1	R_2	Yield (%)	Reference
3-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	50	2003JC(B)1463
4- <i>t</i> -Bu-C ₆ H ₄	4-Br-C ₆ H ₄	41	2003JC(B)303
2-Me-C ₆ H ₄	4-C ₆ H ₅ -C ₆ H ₄	61	2002IJH125
4-MeO-C ₆ H ₄	4-Cl-C ₆ H ₄	47	2003IJH33

(6)

11.05.5.3.2 C-alkylation

The reaction of compounds **161** with the Vilsmeier reagent affords 5-formyl-6-substituted imidazo[2,1-*b*][1,3,4]thiadiazole-2-*N*-(dimethylaminomethino)sulfonamides **168** (Equation 7) <1999AF858>.

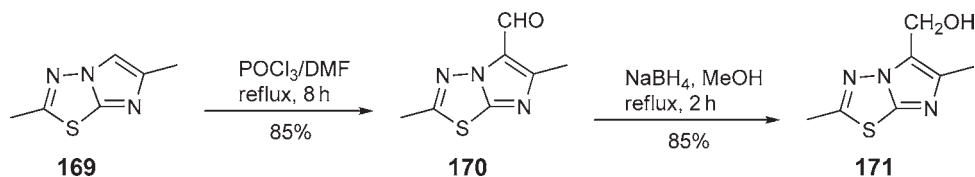


R	Yield (%)
Ph	82
2-Cl-C ₆ H ₄	80
4-Br-C ₆ H ₄	75
4-NO ₂ -C ₆ H ₄	60

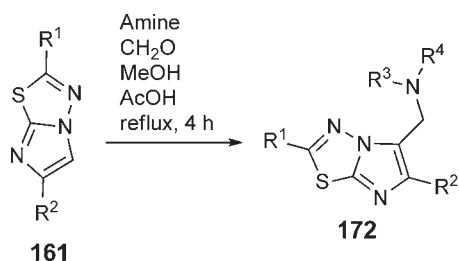
(7)

The Vilsmeier–Haack reaction of 2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole **169** gives aldehyde **170**, which after reduction with sodium borohydride affords 2,6-dimethyl-5-hydroxymethylimidazo[2,1-*b*][1,3,4]thiadiazole **171** (Scheme 2) <2000AF550, 2006BMC3069, 2006TL2811>.

Mannich reaction of 2-cyloalkyl(heteroaryl)-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **161** with formaldehyde in the presence of cyclic bases (piperidine and pyrrolidine), in methanol with a catalytic amount of acetic acid, gives the corresponding *C*-alkylated derivatives **172** (Equation 8) <2006BMC3069>.



Scheme 2



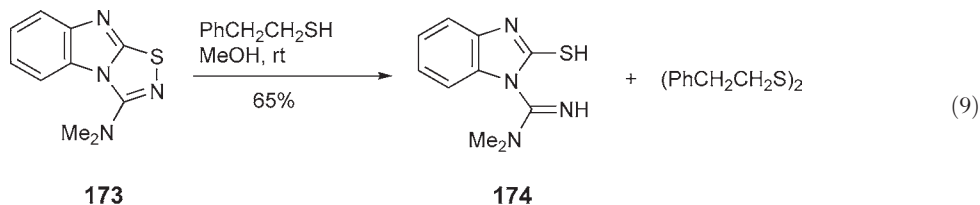
R^1	R^2	Amine	R^3R^4	Yield (%)
<i>n</i> -C ₆ H ₁₁	4-Br-C ₆ H ₄	Piperidine	C ₅ H ₁₀	58
<i>n</i> -C ₆ H ₁₁	Ph	Pyrrolidine	C ₄ H ₈	59
2-Furyl	4-Br-C ₆ H ₄	Piperidine	C ₅ H ₁₀	47
2-Furyl	Ph	Pyrrolidine	C ₄ H ₈	60

(8)

11.05.5.4 Reaction with Nucleophiles

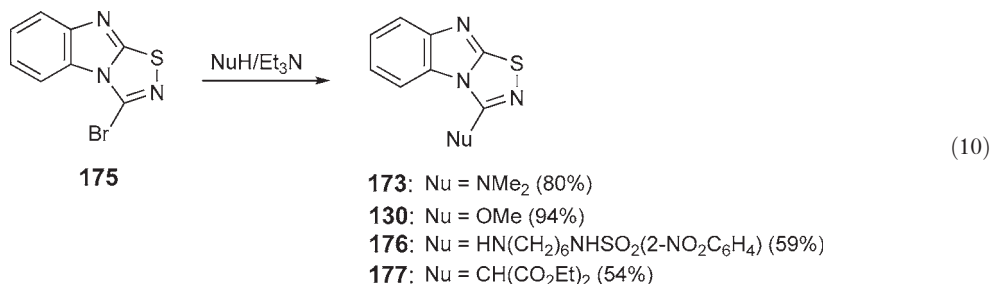
11.05.5.4.1 Ring opening induced by nucleophiles

Thiadiazoles (THDs) react with an excess of phenylethyl mercaptan at room temperature to produce the ring opening of the tricyclic derivatives <2005JOC6230, 2005JMC2266>, for THD **173** to give compound **174** in 65% yield (Equation 9).

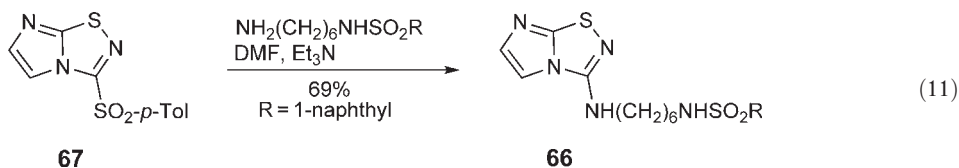


11.05.5.4.2 Nucleophilic displacement of bromide

The tricyclic bromo THD **175** undergoes uneventfully nucleophilic substitution with aqueous dimethylamine or with sodium methoxide in methanol, under mild conditions, affording the corresponding 3-substituted THDs **173** and **130** in good yields (Equation 10) <2005JOC6230, 2005JMC2266>. Similarly, other nucleophiles such as *N*-(6-aminohexyl)-2-nitrobenzene sulfonamide and diethyl malonate, in the presence of triethylamine, also give substituted THDs **176** and **177**, respectively, in moderate yields (Equation 10).



Analogously, the derivatization of bicyclic THD **67** with diamines, in dimethylformamide (DMF) with triethylamine as the base, via an S_NAr mechanism, is possible as shown for the synthesis of compound **66** (Equation 11) <2005JOC6230, 2005JMC2266>.



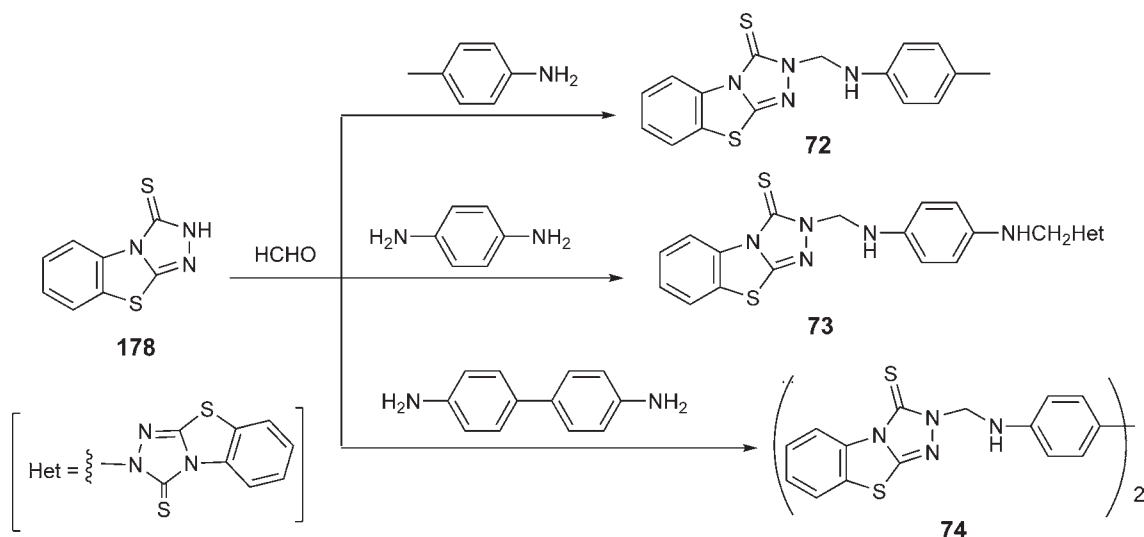
11.05.6 Reactivity of Nonconjugated Rings

11.05.6.1 Electrophilic Attack at Ring Nitrogen

11.05.6.1.1 *N*-alkylation

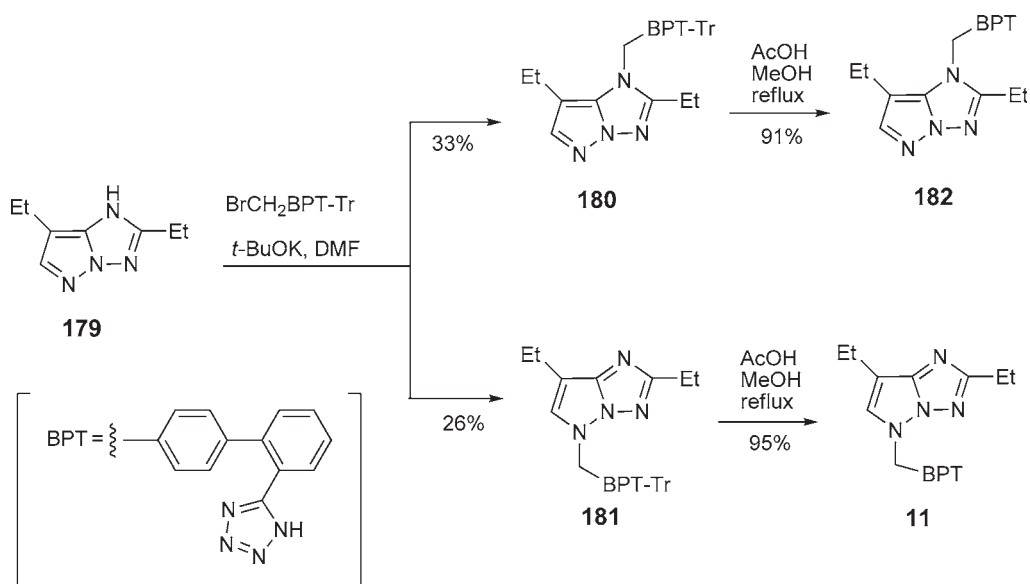
Mannich and double-Mannich reaction with [1,2,4]triazolo[3,4-*b*]benzothiazole-3-thione **178** and *p*-toluidine, phenylenediamine, and benzidine, in the presence of formaldehyde, gave compounds **72–74** (unreported yields) (Scheme 3) <2002MI3, 2002MI4>.

The *N*-alkylation of 2,7-diethyl-pyrazolo[1,5-*b*][1,2,4]triazole **179** has been extensively investigated <1998CPB69, 1998CPB287>. As shown, reaction of *N*-triphenylmethyl-5-[5-[4'-(bromomethyl)biphenyl-2-yl]tetrazole with



Scheme 3

compound **179** gives a mixture of alkylated *N*1 and *N*5 derivatives, **180** and **181**, respectively, which are separated and subsequently treated with acetic acid to give the deprotected compounds **182** and **11**, respectively (Scheme 4).

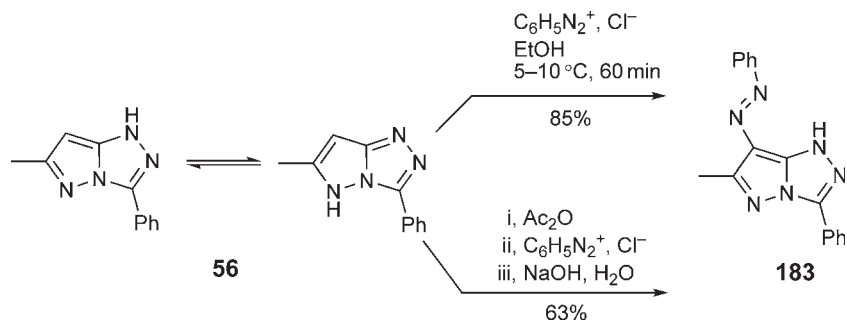


Scheme 4

11.05.6.2 Electrophilic Attack at Ring Carbon

11.05.6.2.1 Azo coupling

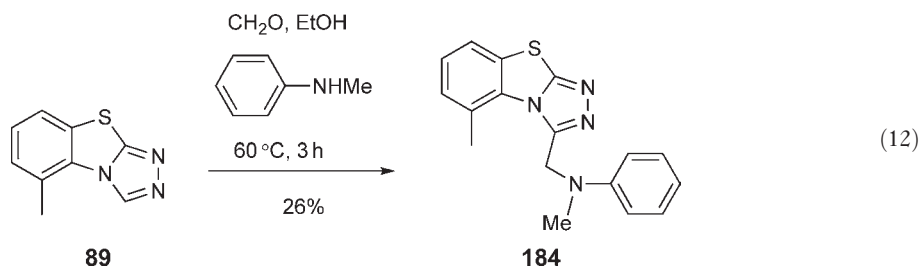
The reaction of 6-methyl-3-phenyl-(1*H*)pyrazolo[5,1-*c*][1,2,4]triazole **56** with phenyldiazonium chloride affords 1*H*-6-methyl-3-phenyl-7-phenylazo-pyrazolo[3,2-*c*][1,2,4]triazole **183**; the structure of this compound was unequivocally assigned when compared with an identical product prepared in the reaction of compound **56** with acetic anhydride followed by azo coupling and basic hydrolysis (Scheme 5) <2003RRC533>.



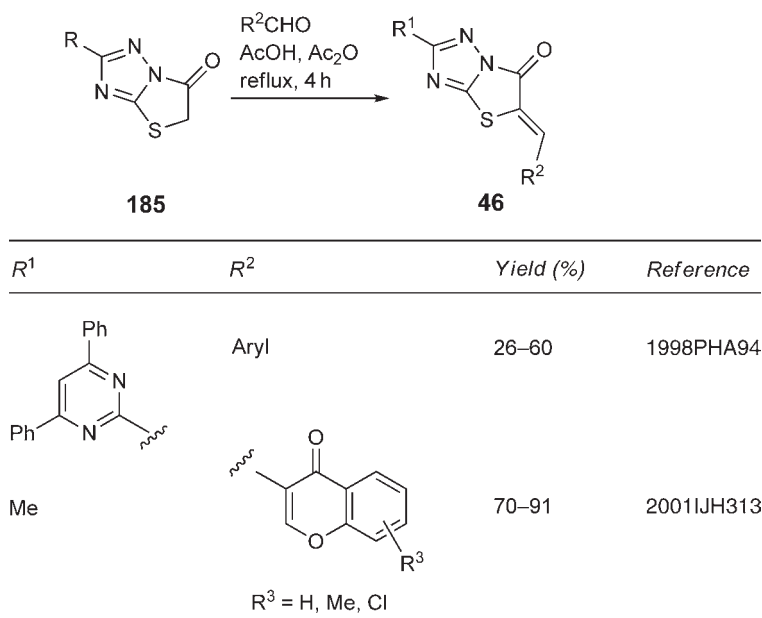
Scheme 5

11.05.6.2.2 Condensation with aldehydes

When compound **89** was treated with formaldehyde and *N*-methylaniline, the Mannich base 3-(*N*-methylanilino-methyl)-5-methyl[1,2,4]triazolo[3,4-*b*]benzothiazole **184** was formed (Equation 12) <1998IJC(B)921>.



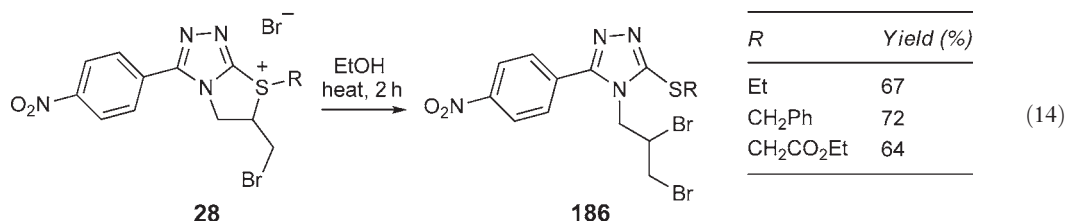
Condensation of compound **185** with different functionalized aromatic aldehydes yields 6-substituted thiazolo[3,2-*b*][1,2,4]-triazol-5(6*H*)-ones **46** (Equation 13) <1998PHA94, 2001IJH313>.



11.05.6.3 Nucleophilic Attack at Ring Carbon with Concomitant Ring Opening

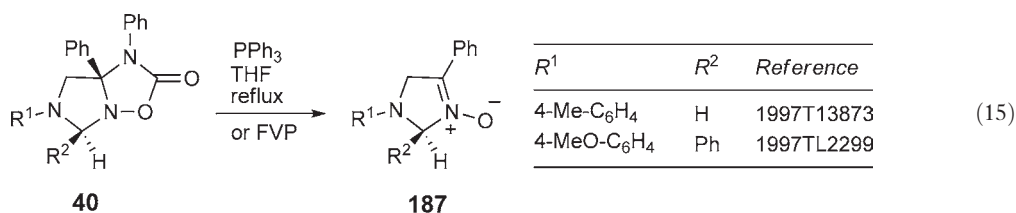
11.05.6.3.1 X-nucleophiles

When salts **28** are heated in boiling ethanol, dibromo derivatives **186** are obtained as a result of the ring cleavage of the thiazole ring (Equation 14) <2000RJOC1033>.

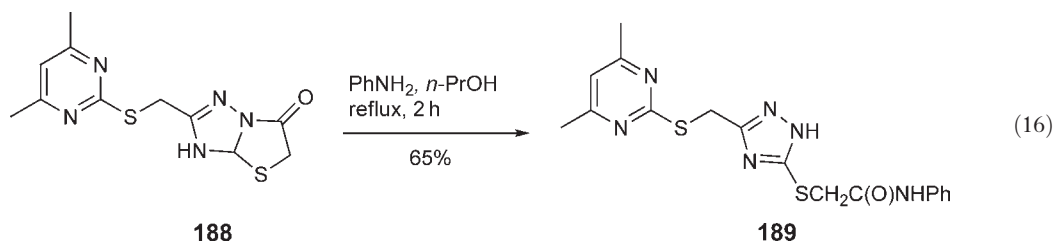


11.05.6.3.2 Ring opening induced by nucleophilic attack with P- and N-nucleophiles

The retro-1,3-dipolar cycloaddition of imidazo[1,5-*b*][1,2,4]oxadiazoles **40**, promoted by reaction with triphenylphosphine at reflux in THF, gives the cyclic nitrones **187** (unreported yields) (Equation 15) <1997T13873>. The ring opening of compounds **40** leading to heterocycles **187** (Equation 15) can also be achieved thermally in the condensed phase under vacuum <1997TL2299>.

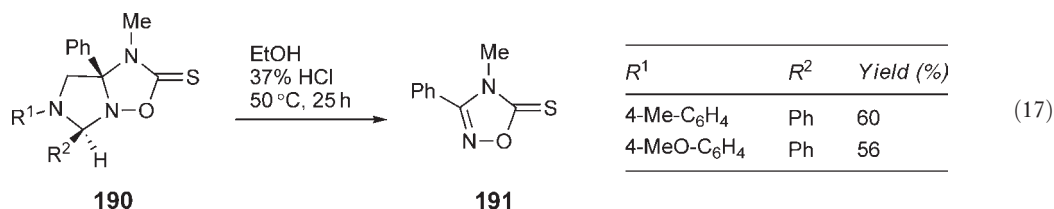


The thiazolotriazolone ring in **188** is easily opened to give anilide **189** after treatment with an excess of aniline (Equation 16) <2003PS(178)2431>.



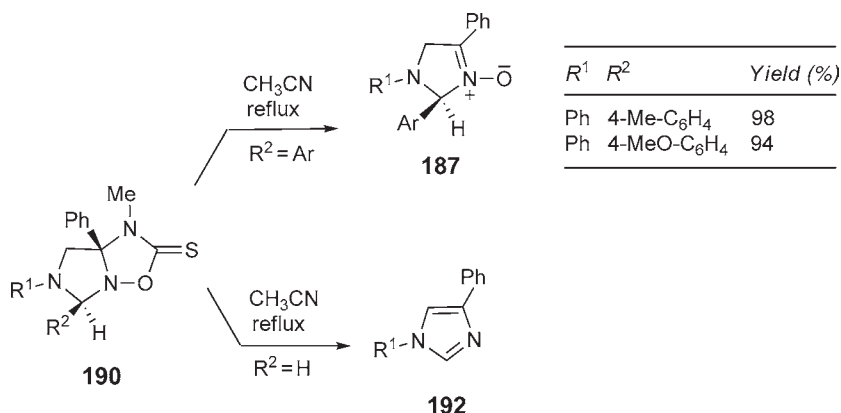
11.05.6.3.3 Ring opening induced by acids

Compounds **190** on heating with ethanol/HCl convert to 4*H*[1,2,4]oxadiazole-5-thiones **191** (Equation 17) as a result of the ring opening in acid media <2003PS(178)881>.



11.05.6.3.4 Thermal ring opening

Heating compounds **190** in acetonitrile, at reflux, gives the cyclic nitrones **187** (R¹ = Ph) (unreported yields), but imidazoles **192** are produced when R¹ = H (Scheme 6) <2004SPL553>.

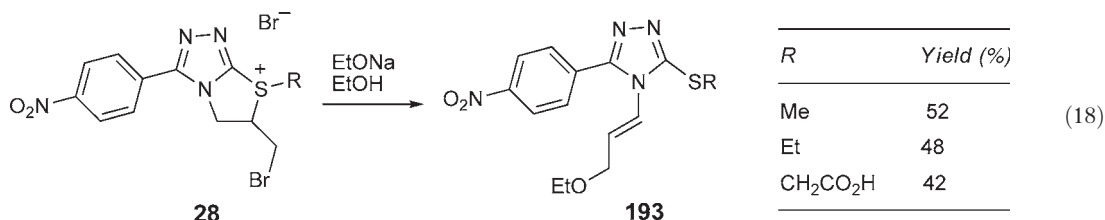


Scheme 6

11.05.6.4 Elimination

11.05.6.4.1 Elimination of one ring

Treatment of salts **28** with sodium ethoxide results in nucleophilic displacement of the primary bromide atom, capture of the hydrogen atom attached to the carbon contiguous to the nitrogen ring atom, followed by cleavage of the thiazole ring with formation of triazoles **193** (Equation 18) <2000RJOC1033>.



(18)

11.05.7 Reactivity of Substituents Attached to Ring Carbon

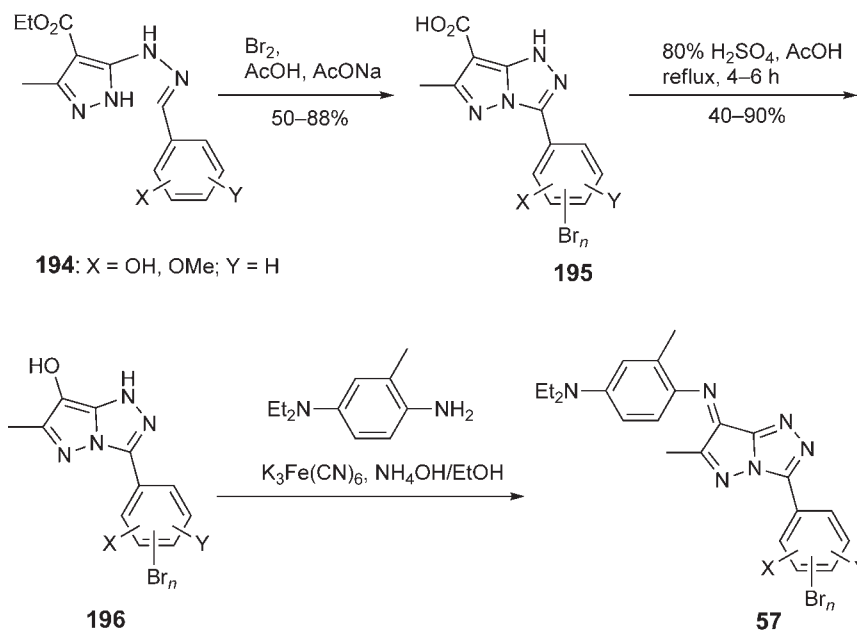
11.05.7.1 Straightforward Conversions

A number of straightforward reactions typical of heteroaromatic substituents have been reported:

- CHO → CH₂OH <2006BMC3069>;
- CHO → C=NOH → CN <2006BMC3069, 1999FAR51>;
- CO₂R → CO₂H <2002ARK133, 2000FAR71>;
- CO₂H → OH <2002ARK133>;
- CO₂H → COCl <2001FAR15>;
- CH₂Cl → CH₂I <2000FAR71>;
- CH₂X (X = Br, Cl) → CH₂OH <2000FAR71, 1999FAR51>;
- CH₂I → CH₂B⁺I⁻ (B = pyridine, quinoline, urea, semicarbazide) <1997MI3, 1999FAR51>;
- CH₂OH → CH₂OAc <2000FAR71, 1999FAR51>;
- CH₃ → CH₂Br <2000FAR71>;
- CH₂Br → CH₃ <2000FAR71>; and
- SH → H <1998IJC(B)921>.

11.05.7.2 Decarboxylation

The reaction of differently substituted 5-arylidenehydrazono-4-ethoxycarbonyl-3-methyl-(1*H*)pyrazoles **194** ($X = 2\text{-NO}_2$, 4-NO_2 , 2-Cl , 4-Me , 4-NMe_2 , 2-OMe) with bromine in acetic acid in the presence of sodium acetate leads mainly to 3-aryl-7-ethoxycarbonyl-6-methyl-(1*H*)pyrazolo[5,1-*c*][1,2,4]triazoles **195** (Scheme 7) <1977J(P1)2047>.



Scheme 7

However, it has been found that for the same reaction, for similar substrates **194**, substituted with electron-donating groups, such as OH, OCH₃, using an excess of bromine, in the presence of calculated excess of sodium acetate, polybrominated compounds **195** at the aromatic ring are obtained (Scheme 7) <2002ARK133>. The formation and the structure of compounds **195** are confirmed by acid hydrolysis (80% H₂SO₄) followed by decarboxylation to provide 3-aryl-6-methyl-(1*H*)pyrazolo[5,1-*c*][1,2,4]triazoles **196**, which are easily converted into the azomethine dyes **57** (unreported yields) by coupling with 4-*N,N*-diethylamino-2-methylaniline in aqueous alkaline K₃Fe(CN)₆ solution (Scheme 7) <2002ARK133>.

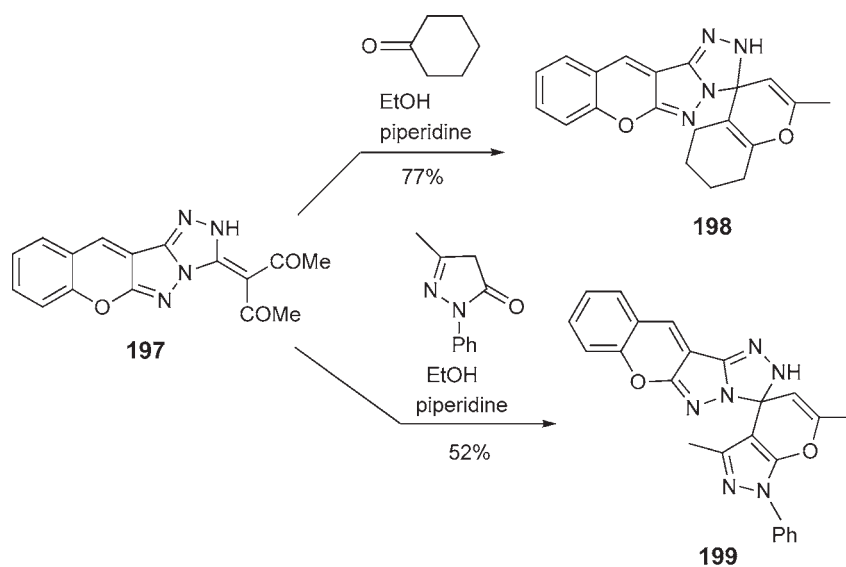
11.05.7.3 Michael Additions

Compound **197** has been treated with carbonyl-containing derivatives such as cyclohexanone and 3-methyl-1-phenylpyrazol-5-one, in refluxing ethanol containing some drops of piperidine as catalyst, in order to promote Michael additions leading to spiro derivatives **198** and **199**, where an acetyl group has been eliminated during the process (Scheme 8) <2000FES641>.

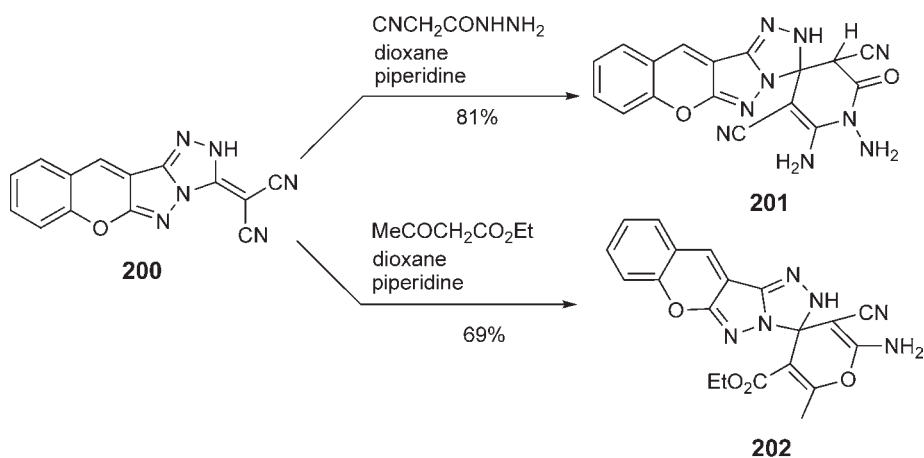
Conversely, but following a similar mechanism, compound **200** reacts with active methylenic compounds such as cyanoaceto-hydrazide and ethyl acetoacetate, in refluxing dioxane in the presence of piperidine, leading to the spiro-2-pyridone **201** and 6-aminopyran **202** (Scheme 9) <2000FES641>.

The reaction of compound **98** with Michael acceptors such as acrylonitrile in the presence of pyridine gives a product which reveals to be the β -(3-hydroazino-1,2,4-triazolo[3,4-*b*]benzothiazole)propanenitrile **203**, which on reflux with hydrochloric acid underwent hydrolysis, followed by simultaneous cyclization, forming 3-(pyrazol-5-one-1-yl)-[1,2,4]triazolo[3,4-*b*]benzothiazole **204** (Scheme 10) <2004IJH241>.

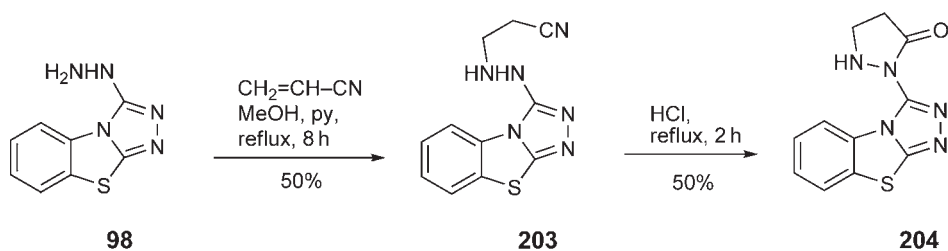
The Michael addition of ylide **132** with dimethyl acetylenedicarboxylate (DMAD) has been investigated <1998T3913>. Depending on the solvent, different adducts are isolated. Using acetonitrile, 3-methylthiazolo[3,2-*c*][1,2,3]triazole **105**



Scheme 8

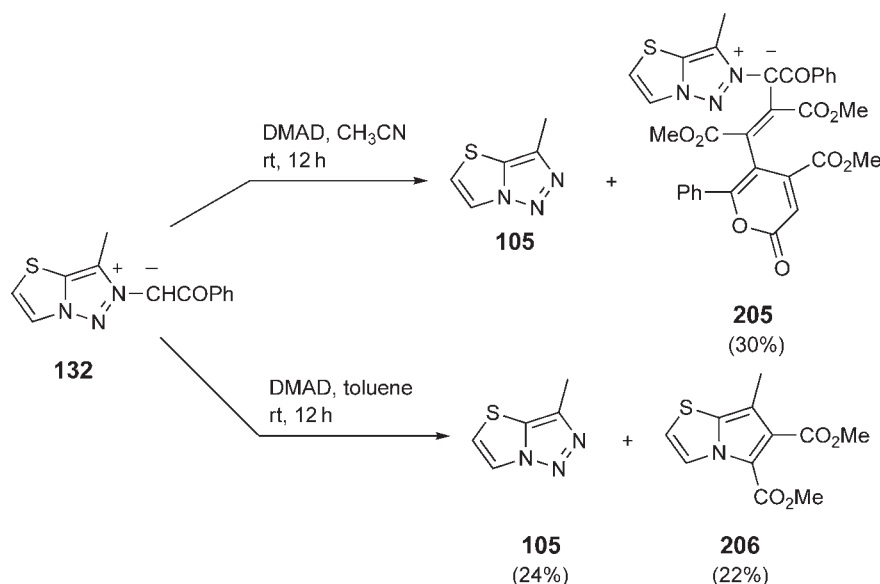


Scheme 9



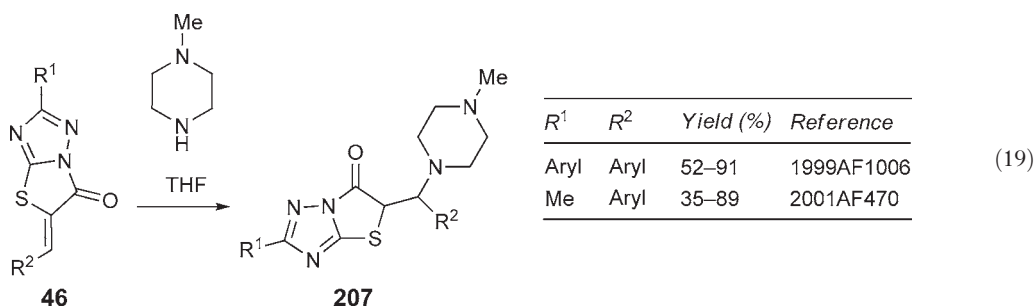
Scheme 10

(unreported yield) and compound **205** (30%) are isolated, while when the solvent used is toluene, the detected products are **105** and **206** (Scheme 11).

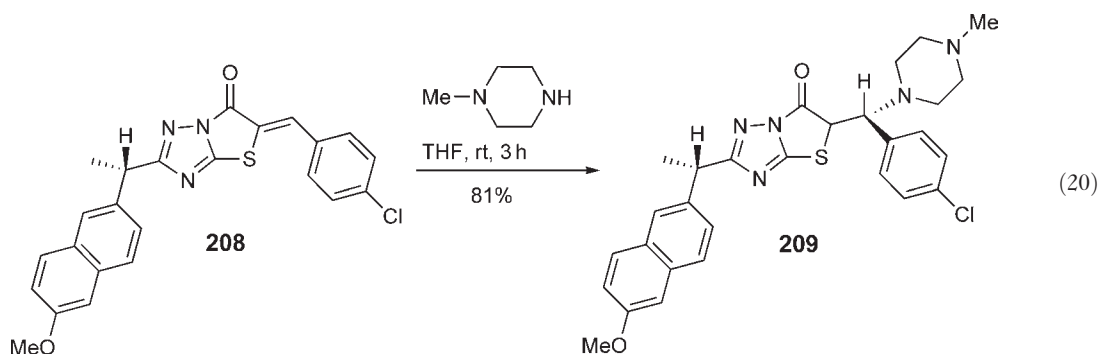


Scheme 11

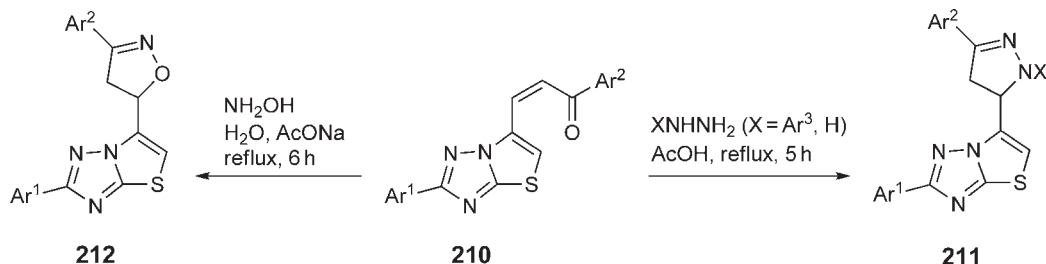
Michael-type addition of cyclic amines (piperidine, *N*-methylpiperazine) to thiazolo[3,2-*b*][1,2,4]triazole-5(6*H*)-ones **46** provides an easy entry to 2-aryl(alkyl)-6-(α -aminoaryl)methylthiazolo[3,2-*b*][1,2,4]triazol-6(5*H*)-ones **207** (Equation 19) <1999AF1006, 2001AF470>.



Enantiomerically pure compounds of type **208** have been synthesized and submitted to asymmetric Michael addition with secondary cyclic amines such as *N*-methylpiperazine to give enantiomerically pure derivatives **209** (Equation 20) <2004AF35>.



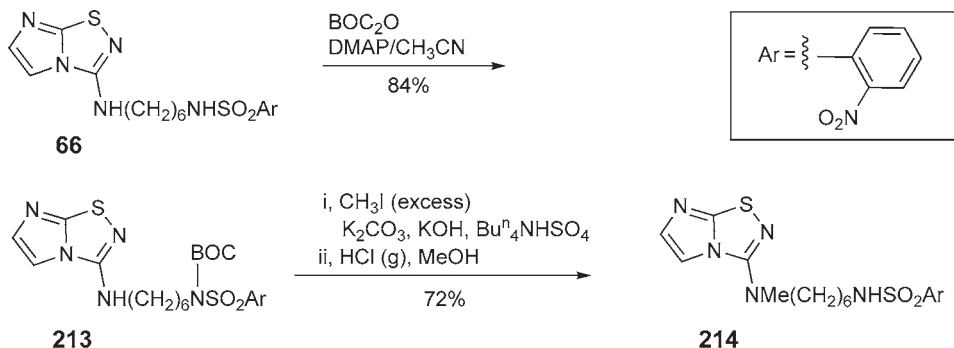
The reaction of different substituted hydrazines (or hydroxylamines) with the α,β -unsaturated ketones **210** gives pyrazolines **211** (or isoxazolines **212**), as the result of a Michael addition reaction followed by an intramolecular Mannich reaction (Scheme 12) <2001FAR32>.



Scheme 12

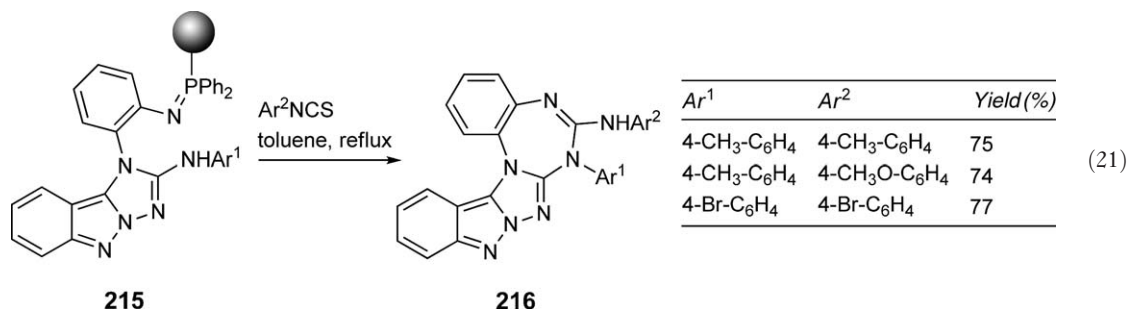
11.05.7.4 N-Alkylation

N-methylation of the 3-amino-substituted THD **66** has been reported <2005JOC6230, 2005JMC2266>. Due to the calculated pK_a 's of the two nitrogens, selective methylation of the nitrogen attached to the THD nucleus is only possible for the synthesis of compound **214** via intermediate **213** in a two-step protocol (Scheme 13).

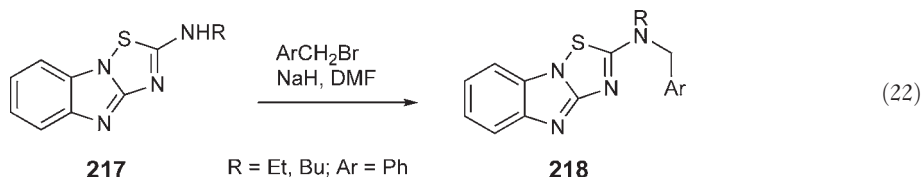


Scheme 13

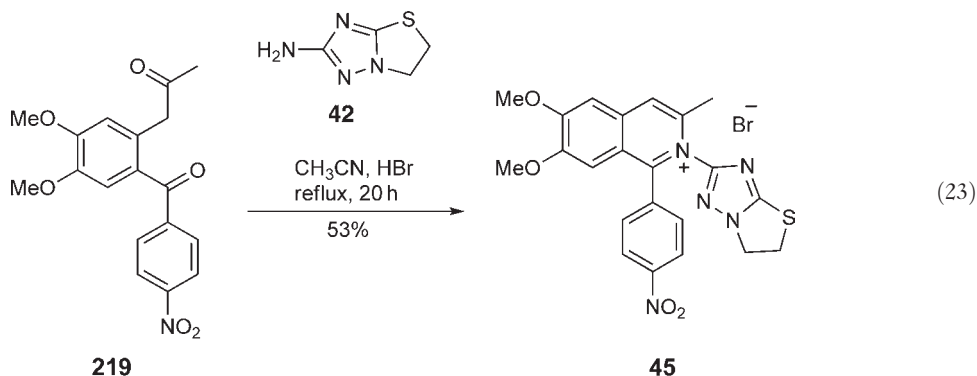
Iminophosphoranes **215** react with an excess of aromatic isocyanates to produce the pentacyclic compounds **216** in good yields (Equation 21) <2000SL1411>.



The reaction of *N*-alkylamino[1,2,4]thiadiazolo[2,3-*a*]benzimidazoles **217** with arylmethyl bromides gives the *N*-alkylated derivatives **218** (unreported yields) (Equation 22) <1998BMCL505>.

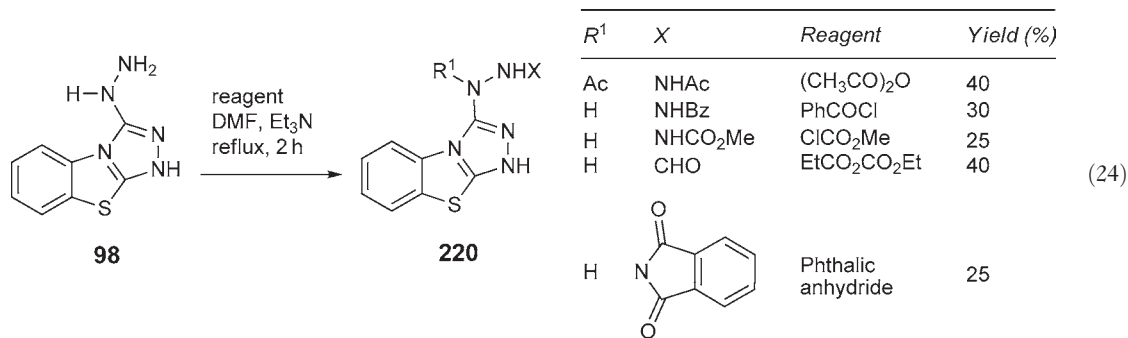


6,7-Dimethoxy-3-methyl-1-(4-nitrophenyl)-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium bromide **45** is also prepared by reacting 4,5-dimethoxy-2-(4-nitrobenzoyl)phenylacetone **219** with 2-amino-5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazole **42** <2003JHC821, 2003JHC1041> (Equation 23).

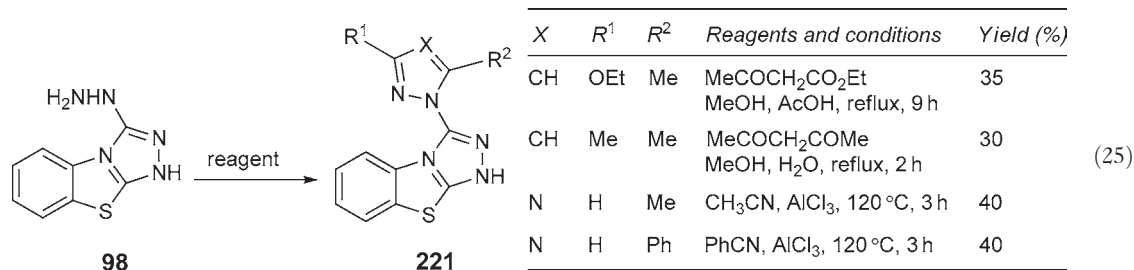


11.05.7.5 *N*-Acylation

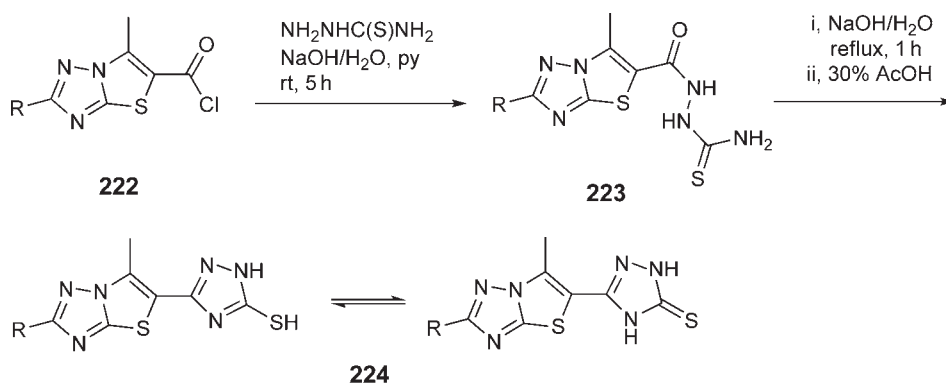
The *N*-acylation reaction of a series of 3-hydrazino-[1,2,4]triazolo[3,4-*b*]benzothiazoles has been reported <1996IJC(B)842>. Refluxing compound **98** with methyl chloroformate, acetic anhydride, and benzoyl chloride, in the presence of pyridine, affords differently 3-substituted hydrazino-[1,2,4]triazolo[3,4-*b*]benzothiazoles **220** (Equation 24) <2004IJH241>. The reaction of compound **98** with a series of acylating reagents in refluxing DMF has been investigated, affording an array of different substituted [1,2,4]triazolo[3,4-*b*]benzothiazoles **220** (Equation 24) <2004IJH241>.



The reaction of compound **98** with 1,3-dicarbonyl compounds such as ethyl acetoacetate and acetylacetone provides an easy entry to differently substituted 1,2,4-triazole derivatives **221** (Equation 25) <2004IJH241>. Analogously, the reaction of compound **98** with different nitriles such as acetonitrile, benzonitrile, and *p*-toluenenitrile, in 1:2 ratio in the presence of anhydrous aluminium chloride at 160–170°C, affords the corresponding compounds **221** (Equation 25) <2004IJH241>.



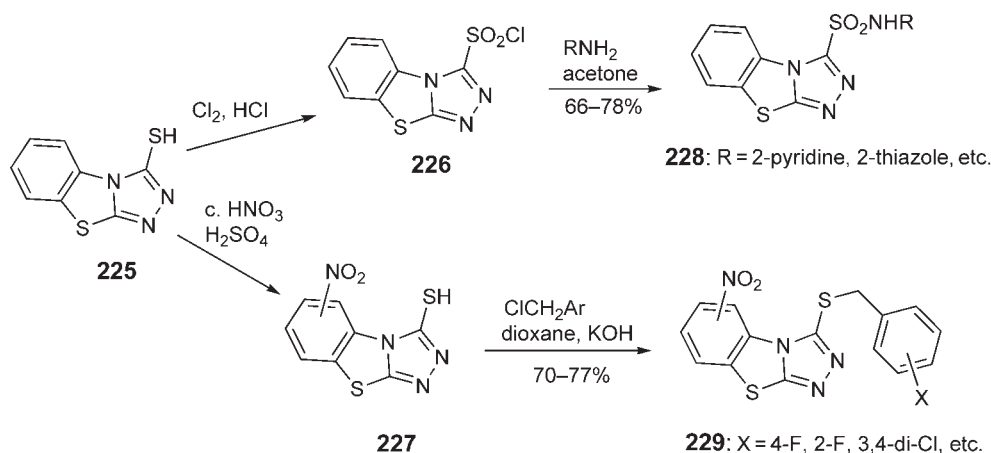
Acylation of thiosemicarbazides with acyl chloride **222**, under standard basic conditions, gives 2-aryl-5-methyl-thiazolo[3,2-*b*][1,2,4]triazole-6-carbothiosemicarbazides **223**, that on sodium hydroxide-promoted cyclization affords 2-aryl-5-methyl-thiazolo[3,2-*b*][1,2,4]triazol-6-yl)-1*H*-1,2,4-triazole-3-thiones **224** (unreported yields) (Scheme 14) <2001FAR15>.



Scheme 14

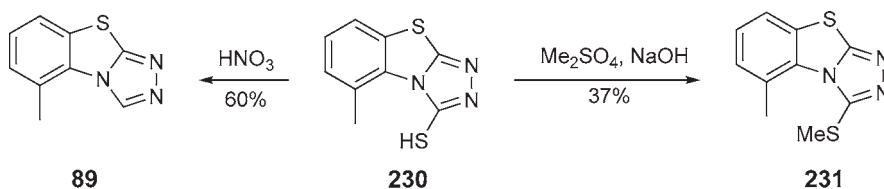
11.05.7.6 S-Alkylation

[1,2,4]Triazolo[3,4-*b*]benzothiazole-3-thiol **225** has been transformed, via intermediates **226** and **227**, into sulfonamides **228** and *S*-benzyl derivatives **229**, respectively (Scheme 15) <2001AF916>.



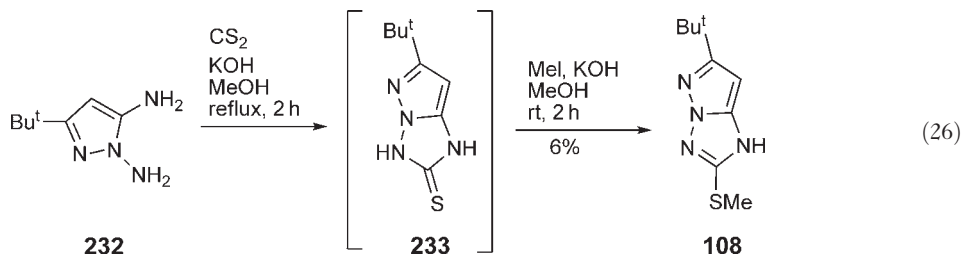
Scheme 15

Methylation of **230** using dimethyl sulfate and sodium hydroxide gave exclusively the corresponding 3-*S*-Me derivative **231** (Scheme 16) <1998IJC(B)921>.

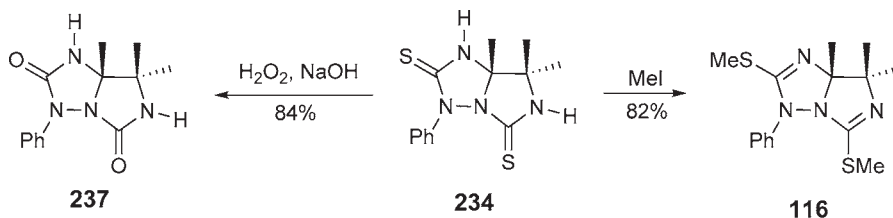


Scheme 16

The reaction of pyrazole **232** with carbon disulfide provides thione **233** that is methylated to give 6-*tert*-butyl-2-methylthiopyrazolo[1,5-*b*][1,2,4]triazole **108** (Equation 26) <2003OBC4268>.

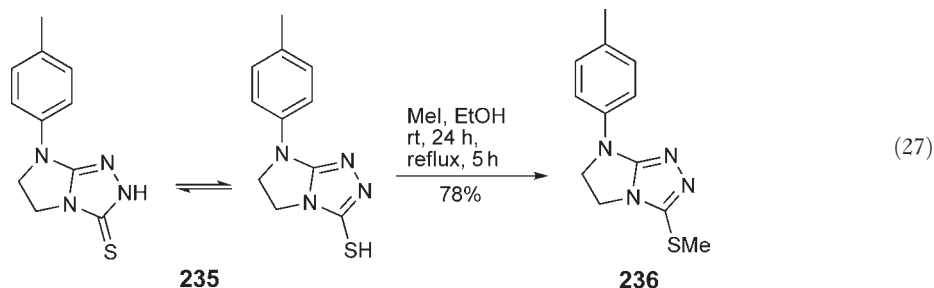


Imidazo[1,5-*b*][triazole]-2,5-dithione **234** reacts with methyl iodide to give the di-*S*-methyl derivative **116** (Scheme 17) <1998SL786>.



Scheme 17

By alkylation with methyl iodide, 7-(4-methylphenyl)-2,5,6,7-tetrahydroimidazo[2,1-*c*][1,2,4]triazol-3*H*-thione **235** <1995MI1> affords 7-(4-methylphenyl)-3-methylthio-5*H*-6,7-dihydroimidazo[2,1-*c*][1,2,4]triazole **236** in 78% yield (Equation 27) <2006BMC3635>.



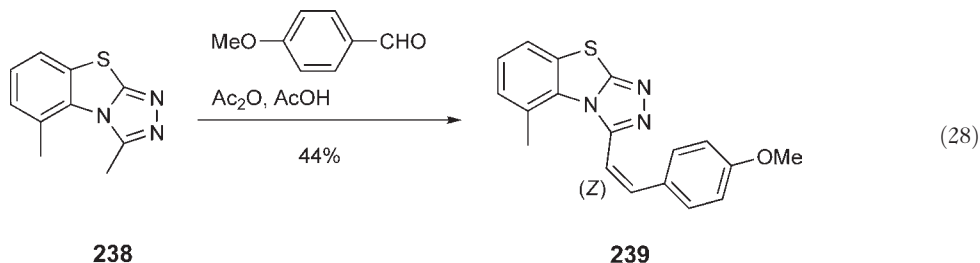
11.05.7.7 Desulfuration

Compound **230** is subjected to desulfuration with dilute nitric acid to give product **89** in 60% yield (Scheme 16); the same product is obtained when compound is treated with Raney-nickel <1998IJC(B)921>.

Dithione **234** is converted to the imidazolidinone **237** on treatment with hydrogen peroxide in the presence of sodium hydroxide (Scheme 17) <1998SL786>.

11.05.7.8 Aldol-Type Reaction

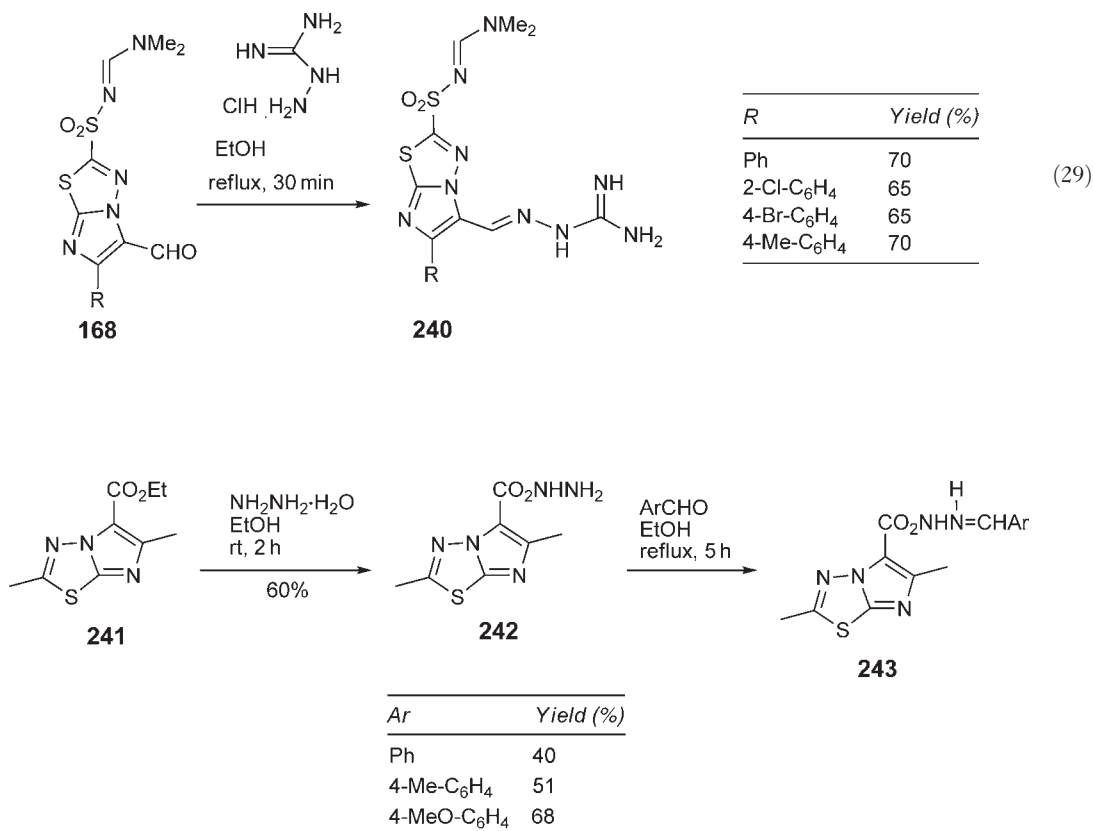
Condensation of compound **238** with *p*-anisaldehyde in the presence of acetic anhydride/acetic acid affords compound **239** as the only (*Z*)-isomer isolated (Equation 28) <1998IJC(B)921>.



11.05.7.9 Imine Formation and Related Reactions

Reaction of compounds **168** with aminoguanidine hydrochloride produces (*E*)-5-guanidylhydrazones **240** (Equation 29) <2000EJM853>.

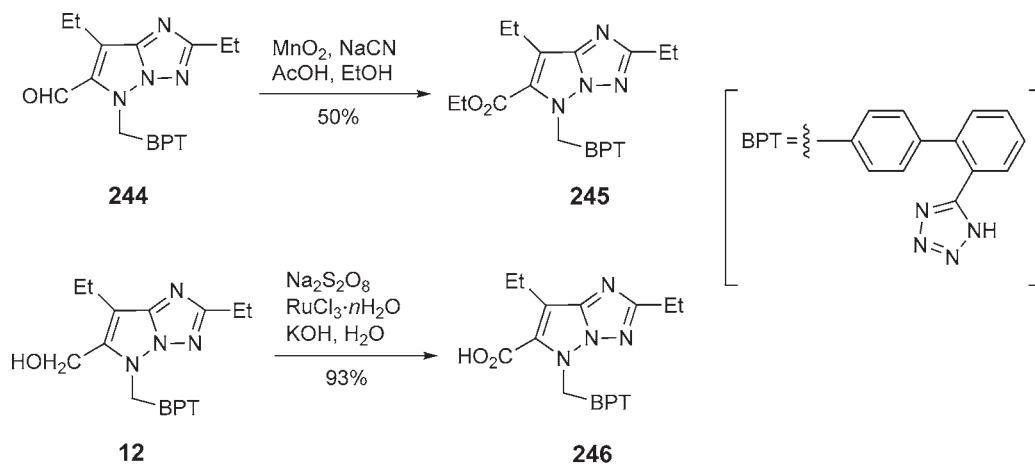
When compound **241** is refluxed with hydrazine hydrate, 2,6-dimethyl-imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazide **242** was isolated. This product, after reaction with the appropriate aldehydes, yields the corresponding hydrazones **243** (Scheme 18) <2003EJM781>.



Scheme 18

11.05.7.10 Oxidation

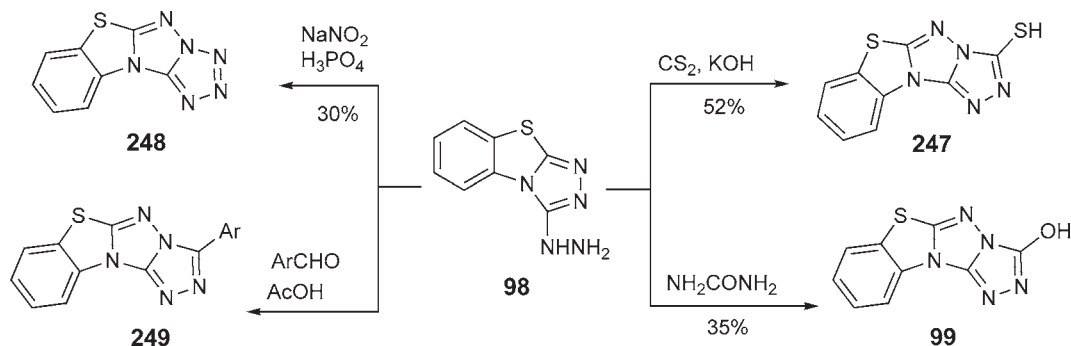
Aldehyde **244** reacts with manganese dioxide and sodium cyanide in ethanol to give ethyl ester **245** (Scheme 19), while oxidation of alcohol **12** with sodium peroxodisulfate in the presence of a catalytic amount of ruthenium chloride furnishes the carboxylic acid **246** (Scheme 19) <1998CPB287>.



Scheme 19

11.05.7.11 Condensation Forming an Additional Fused Ring

Compound **98** reacts with carbon disulfide in the presence of an alkali solution to give 3'-mercapto-1,2,4-triazolo[4',5':1,5]-[1,2,4]triazolo[3,4-*b*]benzothiazole **247**. Treatment of product **98** with urea at 200°C for 4 h affords 3'-hydroxy-1,2,4-triazolo[4',5':1,5]-1,2,4-triazolo[3,4-*b*]benzothiazole **99** (Scheme 20). Finally, the addition of concentrated phosphoric acid in the presence of sodium nitrite to compound **98** produces 1,2,3,4-tetra-zolo[1',5':1,5]-1,2,4-triazolo[3,4-*b*]benzothiazole **248**, and refluxing substituted benzaldehydes in acetic acid provides an easy access to 3'-aryl-1,2,4-triazolo[4',5':1,5]-1,2,4-triazolo[3,4-*b*]benzothiazoles **249** (Scheme 20) (Table 50) <2005IJCB625>.



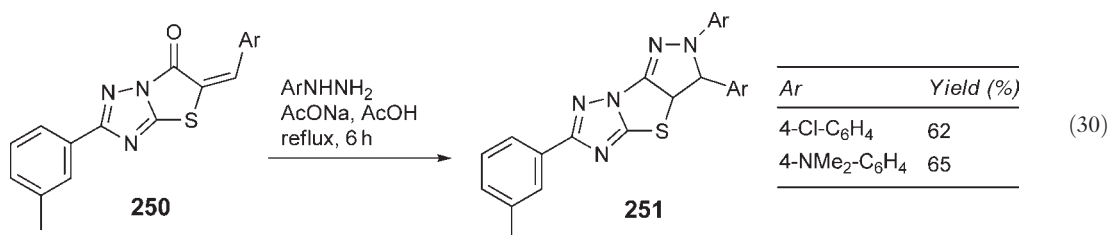
Scheme 20

It is reported that a number of 2-aryl-6-arylidene-thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-ones react with hydrazine <2003IJH97> or aryl hydrazines to produce biological active pyrazolo[3',4':4,5]thiazolo[3,2-*b*][1,2,4]triazoles <2001IJH75, 1998IJH297, 2002IJH261, 1999IJH55, 1999IJH237, 2003IJH375>. Accordingly, condensation of

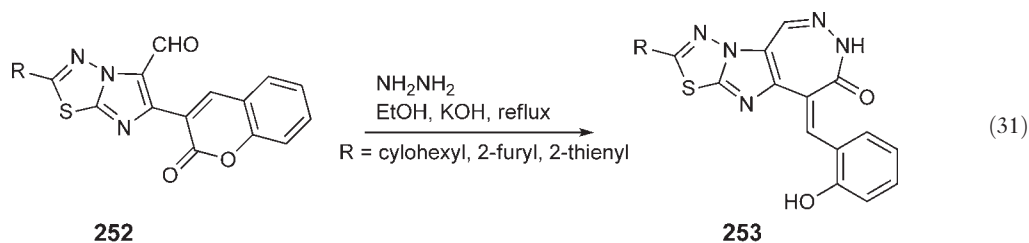
Table 50 3'-Aryl-1,2,4-triazolo[4',5':1,5]-1,2,4-triazolo[3,4-*b*]benzothiazoles **249**

<i>Ar</i>	Yield (%)
Ph	55
4-MeO-C ₆ H ₄	50
2-HO-C ₆ H ₄	52
2-NO ₂ -C ₆ H ₄	58

5-arylidene-2-(*m*-tolyl)- [3,2-*b*]thiazol[1,2,4]triazolo-6(5*H*)-ones **250** with arylhydrazines gives the corresponding 2,3-diaryl-6-(*m*-tolyl)-3,3-dihydropyrazolo[3,4-*d*][1,2,4]triazolo[3,2-*b*]thiazoles **251** (Equation 30) <1999IJC(B)867>.



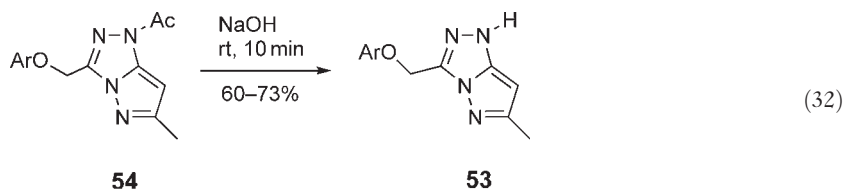
Treatment of carboxyaldehydes **252** with hydrazine hydrate in ethanolic KOH under refluxing conditions provides an easy entry to the novel imidazo[2,1-*b*][1,3]thiazole fused diazepinones **253** via lactone ring opening by intramolecular nucleophilic attack of the amino group of the intermediate hydrazone which could not be isolated (Equation 31) <2006TL2811>.



11.05.8 Reactivity of Substituents Attached to a Ring Heteroatom

11.05.8.1 Detachment of a Substituent

Deacetylation of 1-acetyl-3-aryloxymethyl-6-methyl-pyrazolo [5,1-*c*][1,2,4]triazoles **54** is achieved with sodium hydroxide to give 3-aryloxymethyl-6-methyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **53** (Equation 32) <2003IJC(B)2054>.



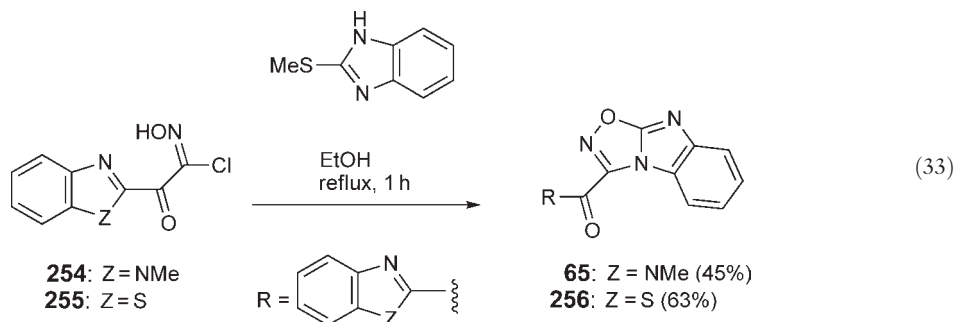
11.05.9 Ring Syntheses Classified by the Number of Ring Atoms in Each Component

11.05.9.1 Ring Closure of a Substituent Providing Three Ring Atoms of the Second Ring: (5)3 → (5,5)

11.05.9.1.1 (5)O1N2C3 → 12{4}7

11.05.9.1.1(i) ON/N Imidazo[1,2-*d*][1,2,4]oxadiazole

Compound **254** reacts with 2-methylthio-1*H*-benzimidazole in refluxing ethanol/triethylamine to give (1-methyl-1*H*-benzimidazol-2-yl)-1,2,4-oxadiazolo[4,5-*a*]benzimidazol-3-yl-methanone **65** (Equation 33) <2004HAC432>. Similarly, benzothiazol-2-ylcarbonylhydroximoyl chloride **255** reacts with 2-methylthiobenzimidazole in refluxing ethanol to give an intermediate that cyclizes to 3-(benzothiazol-2-yl)carbonylbenzimidazo[1,2-*d*][1,2,4]oxadiazole **256** (Equation 33) <1997T17461>.

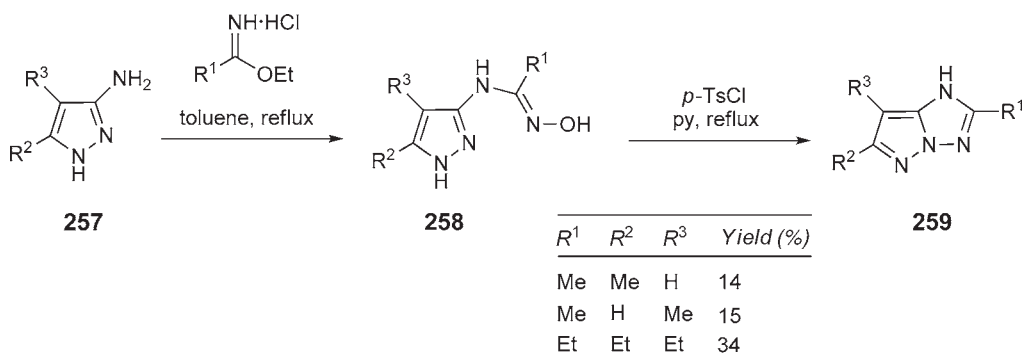


11.05.9.1.2 (5)N1C2N3

11.05.9.1.2(i) (5)N1C2N3 → 13{4}5

11.05.9.1.2(i)(a) NN/N Pyrazolo[1,5-*b*][1,2,4]triazole

3-Aminopyrazoles **257** substituted at the C-4 and C-5 positions react with a variety of imidate hydrochlorides giving *N*-hydroxyamidines **258**, that after tosylation and intramolecular cyclization afford the corresponding pyrazolo[1,5-*b*]-[1,2,4]triazole derivatives **259** (Scheme 21) <1998CPB287, 1998CPB69>.

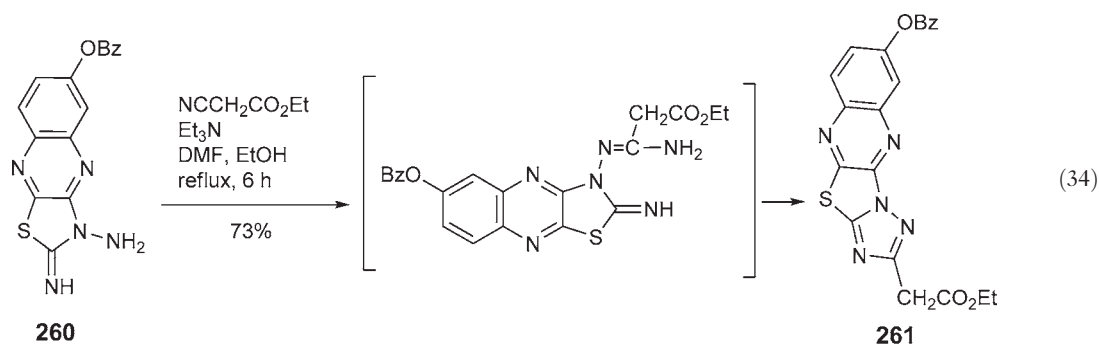


Scheme 21

11.05.9.1.2(ii) (5)N1C2N3 → 134{7}

11.05.9.1.2(ii)(a) NNS/Thiazolo[3,2-*b*][1,2,4]triazole

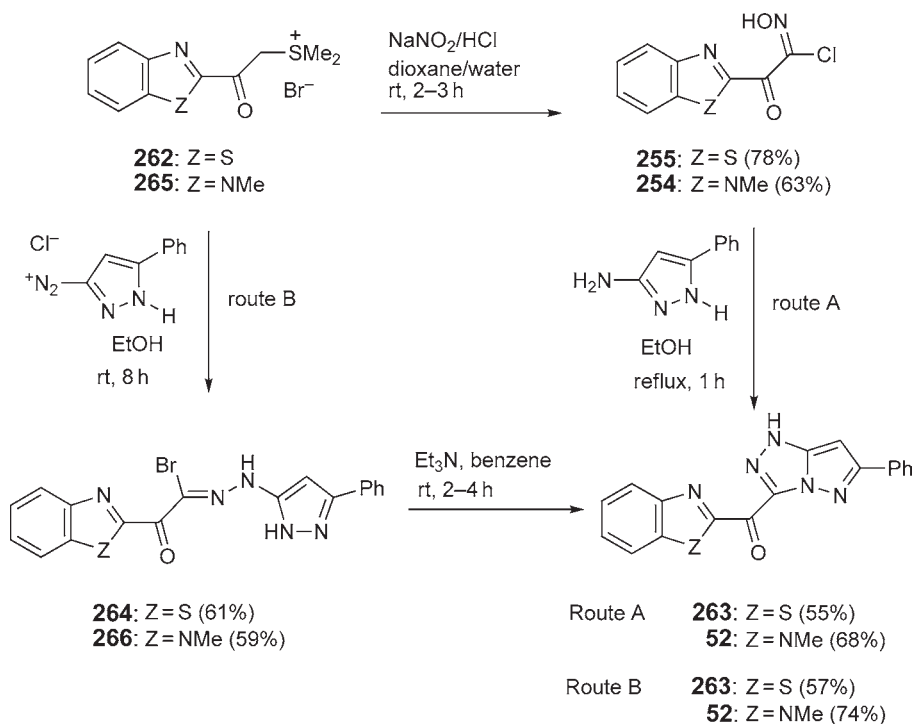
Cyclization of 6-benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-*b*]quinoxaline **260** was achieved upon treatment with ethyl cyanoacetate in DMF/Et₃N to yield [1,2,4]triazolo[3',2':3,2]thiazolo[4,5-*b*]quinoxaline derivative **261** (Equation 34) <2000PS(157)87>.



11.05.9.1.3 (5)N1N2C3

11.05.9.1.3(i) (5)N1N2C3 $\rightarrow$ 12{4}511.05.9.1.3(i)(a) NN/N Pyrazolo[5,1-*c*][1,2,4]triazole

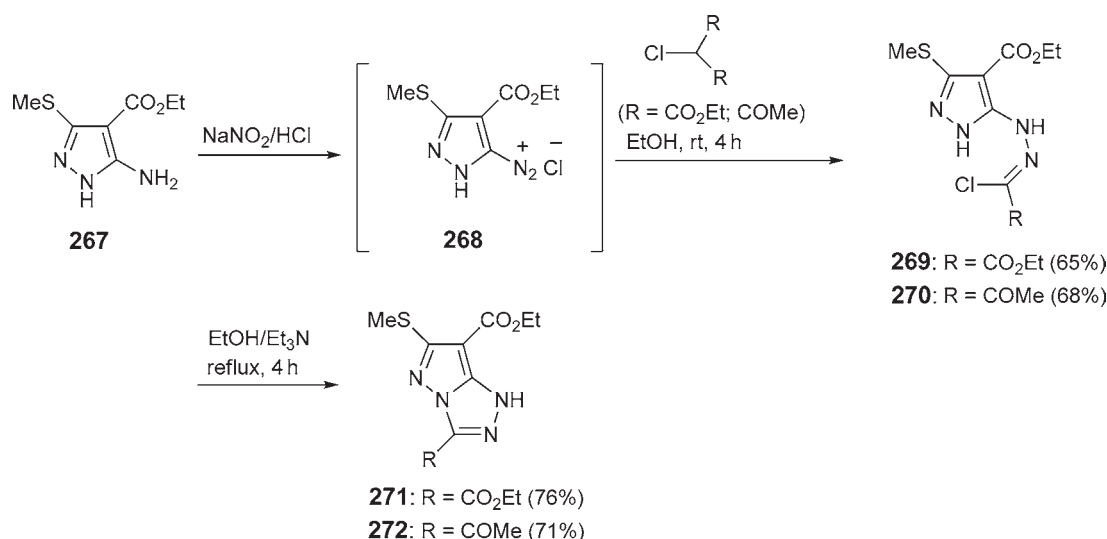
Treatment of benzothiazol-2-yl-1-ethanonedimethylsulfonium bromide **262** with sodium nitrite in a mixture of dioxane and water, in the presence of hydrochloric acid, at room temperature, gives benzothiazol-2-ylcarbonylhydroximoyl chloride **255**. The reaction of compound **255** with 5-amino-3-phenyl-1*H*-pyrazole in refluxing ethanol gives 3-(benzothiazol-2'-yl)carbonyl-6-phenyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole **263** (route A) (Scheme 22) <1997T17461>. Compound **263** has also been synthesized in two steps (route B) from benzothiazol-2-yl-1-ethanonedimethylsulfonium bromide **262** and reaction with 3-phenylpyrazole-5-diazonium chloride to afford intermediate α -oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-2-benzothiazolethanehydrozonoyl bromide **264**. Compound **264** undergoes intramolecular cyclization when treated with triethylamine, in benzene, at room temperature to give product **263** <2001SC1647>.



Scheme 22

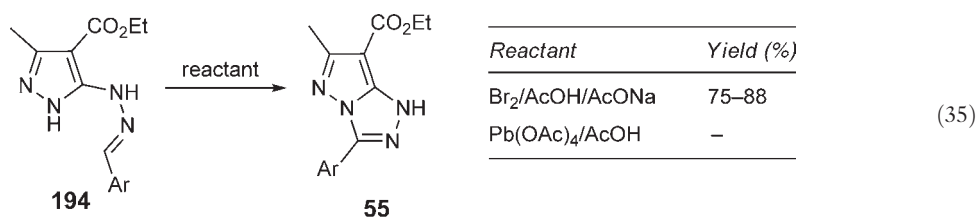
Similarly, the *N*-methylbenzimidazole derivative **52** is synthesized as shown in Scheme 22. Treatment of 1-(1-methylbenzimidazol-2-yl)-1-ethanone-2-dimethylsulfonium bromide **265** with sodium nitrite in an acid mixture of water/dioxane affords a good yield of a product identified as 2-(1-methylbenzimidazol-2-yl) carbonylhydroximoyl chloride **254** which, by reacting with 5-amino-3-phenyl-1*H*-pyrazole in refluxing ethanol, was transformed to product **52** (route A). This latter compound **52** has also been prepared by an alternative pathway (route B), starting from 1-(1-methylbenzimidazol-2-yl)-1-ethanone-2-dimethylsulfonium bromide **265** and reaction with 3-phenylpyrazole-5-diazonium chloride; intermediate α -oxo-*N*-(3-phenyl-1*H*-pyrazol-5-yl)-2-(1-methylbenzimidazole)ethane-hydrazono-yl bromide **266** is obtained. Subsequent treatment of this compound with triethylamine in refluxing ethanol affords a product identical to compound **52** <2004HAC432>.

Reaction of ethyl 5-amino-3-methylthio-1*H*-pyrazol-4-carboxylate **267** with sodium nitrite in the presence of hydrochloric acid gives the diazo intermediate **268**, which on treatment with active methylenic compounds such as ethyl α -chloroacetate or α -chloroacetylacetone affords the hydrazonyl chlorides **269** and **270**, respectively, whose reaction with triethylamine in refluxing ethanol convert them into ethyl 4-hydro-2-methylthiopyrazolo[5,1-*c*]-[1,2,4]triazole-3,6-dicarboxylate **271** and ethyl 6-acetyl-4-hydro-2-methylthiopyrazolo[5,1-*c*][1,2,4]triazole-3-carboxylate **272** (Scheme 23) <2001MI1>.



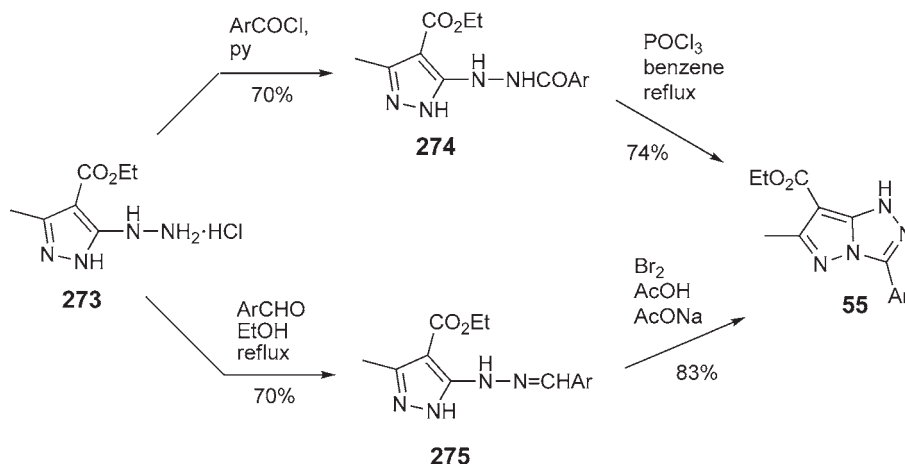
Scheme 23

Treatment of 3-methyl-4-ethoxycarbonyl-5-arylidenehydrazono-1*H*-pyrazoles **194** with bromine, in the presence of sodium acetate, in acetic acid gives substituted ethyl 3-aryl-7-ethoxycarbonyl-6-methyl-1*H*-pyrazolo[5,1-*c*]-[1,2,4]triazoles **55** (Equation 35) <2002ARK133>. Analogously, the reaction of compounds **194** with lead tetracetate [Pb(OAc)₄] in acetic acid also gives 1*H*-pyrazolo[5,1-*c*][1,2,4]triazoles **55** (unreported yield) (Equation 35) <2002ARK133>.



3-Methyl-4-ethoxycarbonyl-5-benzoyl-hydrazino-1*H*-pyrazole **274**, prepared by reacting benzoyl chloride and 3-methyl-4-ethoxycarbonyl-5-benzoyl-hydrazino-1*H*-pyrazole hydrochloride **273**, in the presence of pyridine in acetonitrile, has been cyclized with phosphoryl chloride in benzene or toluene to give 7-ethoxycarbonyl-6-methyl-3-phenyl-1*H*-pyrazolo[5,1-*c*][1,2,4]triazole **55**. This compound has been also synthesized through cyclization of

3-methyl-4-ethoxycarbonyl-5-benzylidene-hydrazino-1*H*-pyrazole **275** with bromine in acetic acid in the presence of anhydrous sodium acetate <2004RRC1018> (Scheme 24).

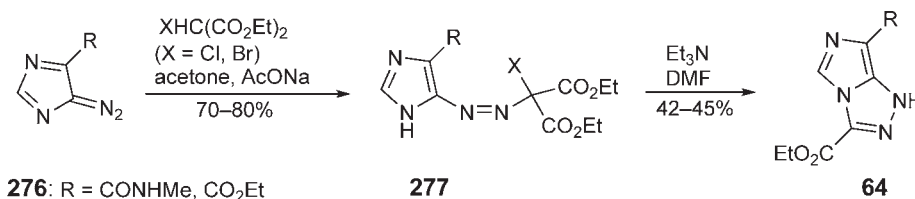


Scheme 24

11.05.9.1.3(ii) (5)N1N2C3 $\rightarrow$ 12{4}6

11.05.9.1.3(ii)(a) NN/N Imidazo[5,1-*c*][1,2,4]triazole

The synthesis of ethyl ester derivatives of imidazo[5,1-*c*][1,2,4]triazole-3-carboxylic acid **64** has been reported (Scheme 25) <1999CHE1349>. Starting from the known substituted 5-diazoimidazoles **276**, their coupling with malonic acid derivatives afforded the azo compounds **277**, which on treatment with triethylamine in DMF, upon prolonged heating time, gave products **64** in moderate yield.



Scheme 25

11.05.9.1.3(iii) (5)N1N2C3 $\rightarrow$ 12{4}7

11.05.9.1.3(iii)(a) NN/N Imidazo[2,1-*c*][1,2,4]triazole

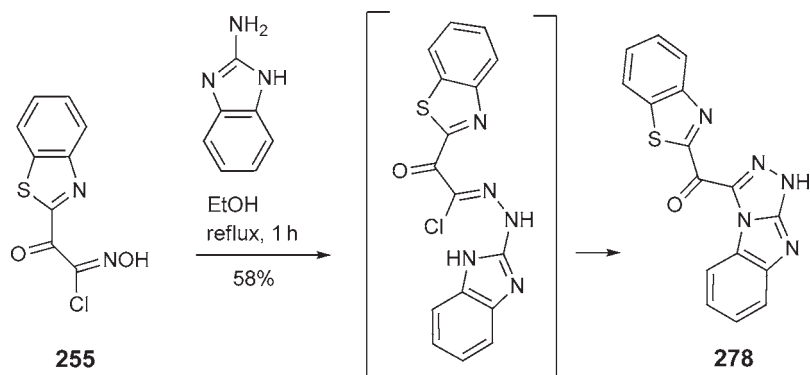
Benzothiazol-2-ylcarbonylhydroximoyl chloride **255** reacts with 2-aminobenzimidazole in refluxing ethanol to give (2-benzothiazolyl)-2-oxoacetic-(2-benzimidazolyl)hydrazonyl chloride as the presumed intermediate that cyclizes *in situ* to 3-(benzothiazol-2-yl)carbonyl-1*H*-[1,2,4]triazolo[4,3-*a*]benzimidazole **278** (Scheme 26) <1997T17461>.

11.05.9.1.3(iii)(b) NN/O Oxazolo[2,3-*c*][1,2,4]triazole

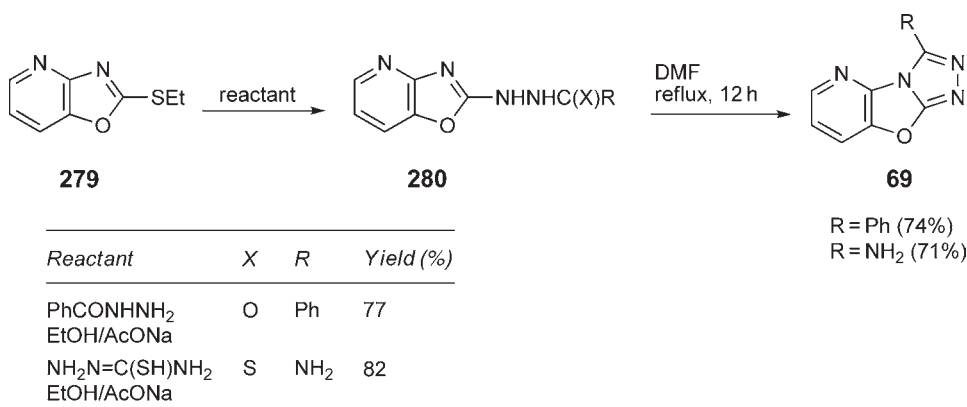
The reaction of 2-ethylthioxazolo[4,5-*b*]pyridine **279** with phenyl hydrazide and thiosemicarbazide gives compounds **280** which, after refluxing in DMF, afford the oxazolotriazoles **69** in good overall yields <2000SC3423> (Scheme 27).

11.05.9.1.3(iii)(c) NN/S Thiazolo[2,3-*c*][1,2,4]triazole

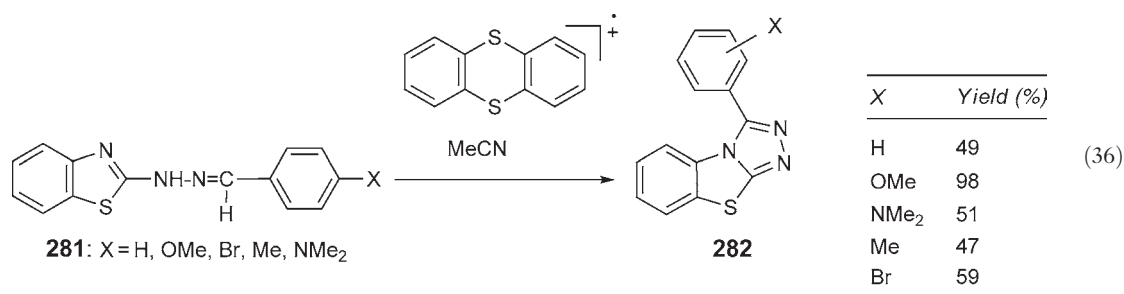
2-Benzothiazolylhydrazones **281** react with the thianthrene cation radical to give [1,2,4]triazolo[3,4-*b*]benzothiazoles **282** in an oxidative intramolecular cyclization reaction (Equation 36) <2000BKC425>.



Scheme 26



Scheme 27

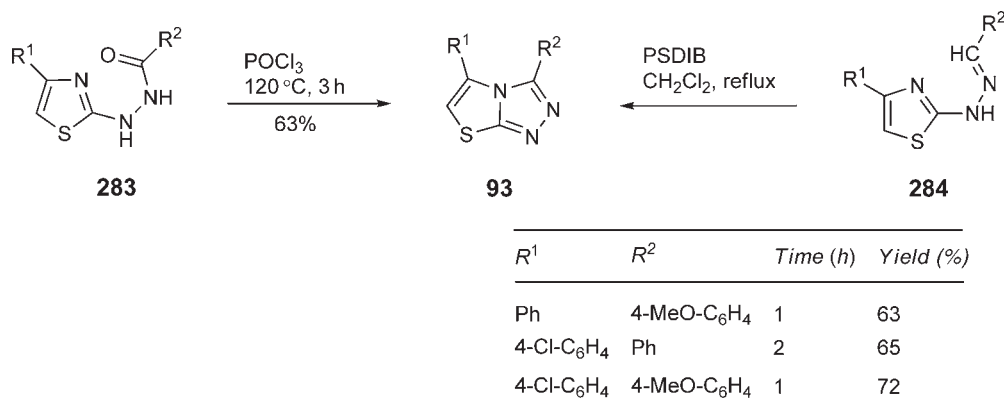


Treatment of arylthiosemicarbazides with α -haloketones provide thiazole derivatives **283**, which after POCl₃-promoted cyclization give thiazolo[2,3-*c*][1,2,4]triazoles **93** (Scheme 28) <1996IJH21, 2002IJC(B)403, 2003IJC(B)401, 2001IJC(B)54, 2001FAR54, 2001FAR24>. The reaction of arenecarbaldehyde-4-arylthiazol-2-ylhydrazones **284** with poly[(4-diacetoxyiodo)styrene] (PSDIB) in refluxing methylene chloride results in the formation of 3,5-diarylthiazolo[2,3-*c*][1,2,4]triazoles **93** (Scheme 28) <2005SC1753>.

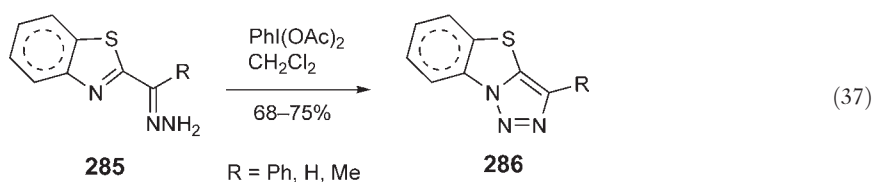
11.05.9.1.4 (5)C3N2N1 $\rightarrow$ 124{7}

11.05.9.1.4(i) NNS/ Thiazolo[3,2-*c*][1,2,3]triazole

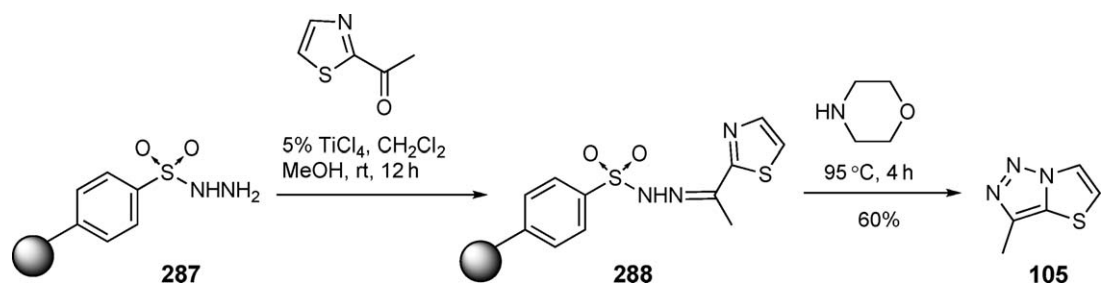
Free or benzo-fused 1,2,3-triazoles **286** have been prepared by iodobenzene diacetate-mediated oxidation of hydrazones **285** (Equation 37) <2000SC417>.



Scheme 28



A regioselective solid-phase synthesis of 3-methylthiazolo[3,2-*c*][1,2,3]triazole **105** has been achieved using polystyrene-sulfonyl hydrazide resin (PS-Ts-NHNH₂) **287**. The reaction of resin **287** with 1-thiazol-2-yl-ethanone in 5% TiCl₄/MeOH provides hydrazone **288** and subsequent treatment of this latter compound with morpholine at 95 °C gave fused triazole **105** in 60% yield (Scheme 29) <2004TL6129>.

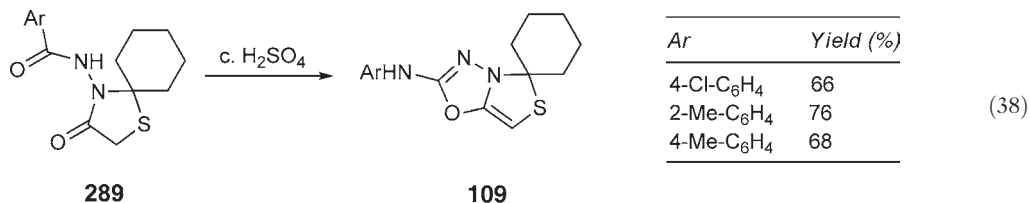


Scheme 29

11.05.9.1.5 (5)N3C2O1 → 13{4}6

11.05.9.1.5(i) ON/S Thiazolo[4,3-*b*][1,3,4]oxadiazole

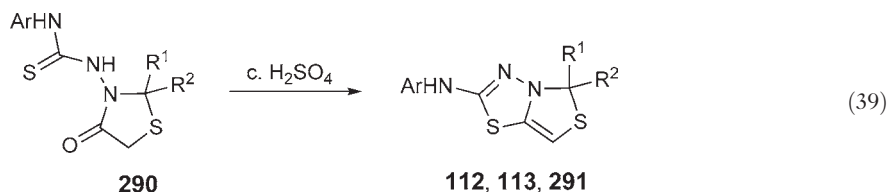
Arylamino-spiro(cyclohexane)-(1',2)-4-thiazolidinones **289**, on treatment with concentrated sulfuric acid, give thiazolo[4,3-*b*][1,3,4]oxadiazoles **109** (Equation 38) <2004IJC(B)901, 1999IJC(B)1203>.



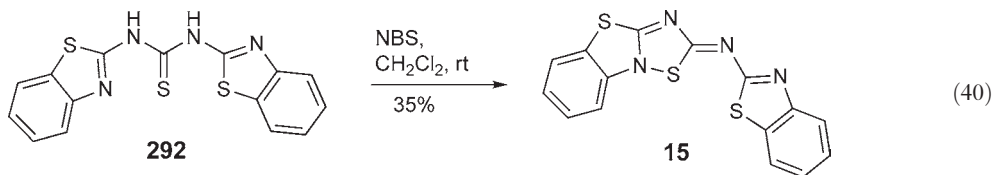
11.05.9.1.6 (5)N3C2S1

11.05.9.1.6(i) (5)N3C2S1 $\rightarrow$ 13{4}611.05.9.1.6(ii)(a) SN/S Thiazolo[4,3-*b*][1,3,4]thiadiazole

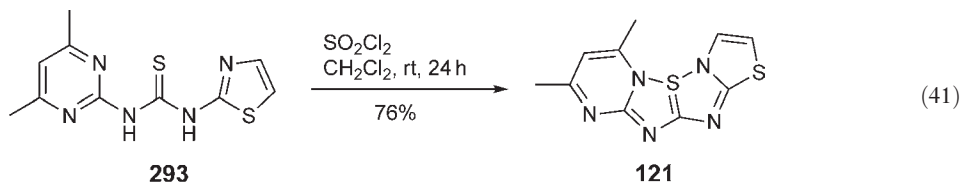
4-Thiazolidinones **290** give substituted thiazolo[4,3-*b*][1,3,4]thiadiazoles **112**, **113**, and **291** after intramolecular cyclization mediated by concentrated sulfuric acid (Equation 39) (Table 51) <2001IJC(B)440, 2004IJC(B)901, 1996JCR(S)388>.

11.05.9.1.6(ii) (5)N3C2S1 $\rightarrow$ 134{7}11.05.9.1.6(ii)(a) SNS/ Thiazolo[3,2-*b*][1,2,4]thiadiazole

Oxidation of *N,N'*-bis(benzothiazol-2-yl)thiourea **292** with *N*-bromosuccinimide (NBS) affords the crystalline tetraazathiapentalene **15** (Equation 40) <2004EJO4203>.

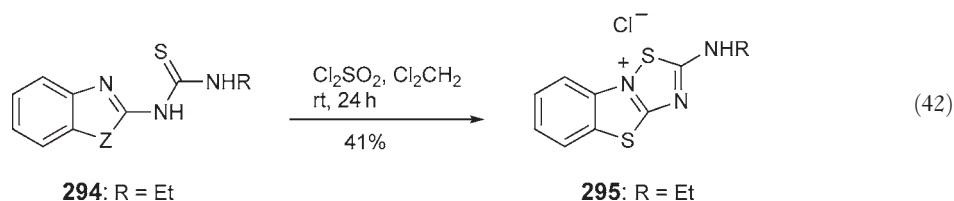


The oxidation of thiourea **293** with sulfuryl chloride gives 2,4-dimethyl-6 λ^4 -thiadiazolo[3'',2'':2',3']-[1,2,4]-thiadiazolo[1',5':1,5][1,2,4]thiadiazolo[2,3-*a*]pyrimidine **121** (Equation 41) <1996JA6355>.

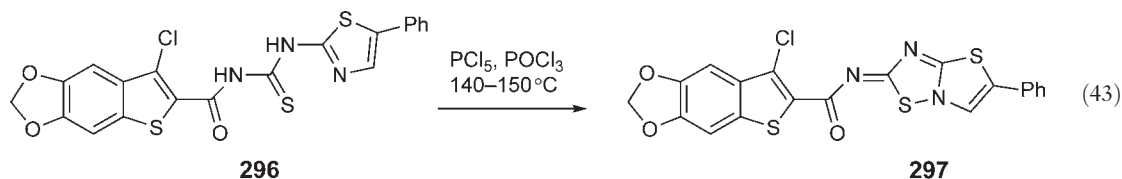
**Table 51** Thiazolo[4,3-*b*][1,3,4]thiadiazoles **112**, **113**, **291**

Compound	Ar	R ¹	R ²	Yield (%)	Reference
113	4-MeO-C ₆ H ₄	D-xylobutyl	H	72	2001IJC(B)440
	2-Me-C ₆ H ₄	D-glucopentyl	H	77	2001IJC(B)440
	2-Me-C ₆ H ₄	D-xylobutyl	H	78	2001IJC(B)440
112	4-MeO-C ₆ H ₄	-(CH ₂) ₅ -		71	2004IJC(B)901
	2-Me-C ₆ H ₄	-(CH ₂) ₅ -		60	2004IJC(B)901
	4-Me-C ₆ H ₄	-(CH ₂) ₅ -		64	2004IJC(B)901
291	2,4-di-Me-C ₆ H ₄	Ph	H	72	1996JCR(S)388
	2,4-di-Me-C ₆ H ₄	4-MeO-C ₆ H ₄	H	71	1996JCR(S)388
	2,4-di-Me-C ₆ H ₄	4-Me-C ₆ H ₄	H	68	1996JCR(S)388
	2,4-di-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	H	76	1996JCR(S)388

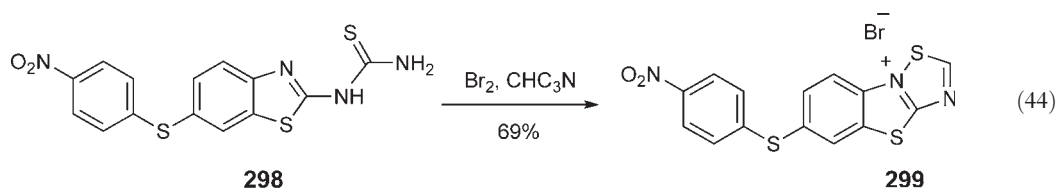
Treatment of *N*-alkyl-*N'*-(2-benzothiazolyl)thioureas **294** with sulfonyl chloride, at room temperature, affords 2-aminoethyl[1,2,4]thiadiazolo[3,2-*b*]benzothiazolium chloride **295** (Equation 42) <1999JHC991>.



Compound **296** undergoes a ring-closure reaction on treatment with PCl_5 in POCl_3 , leading to thiazolo[3,2-*b*]-[1,2,4]thiazolidine derivative **297** (unreported yield) (Equation 43) <1999PHA491>.

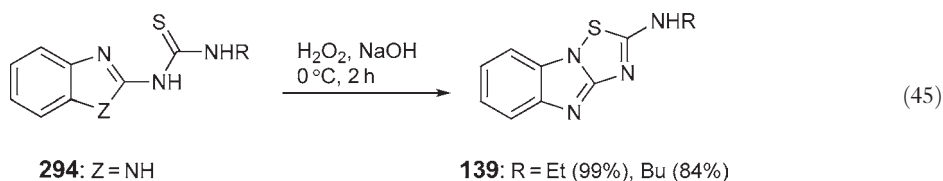


Treatment of 1-[6-[(*p*-nitrophenyl)thio]-benzothiazol-2-yl]thiourea **298** with bromine in chloroform yields 2-amino-7-[(*p*-nitrophenyl)thio][1,2,4]thiadiazolo[3,2-*b*]benzothiazolium bromide **299** (Equation 44) <2002MI15>.



11.05.9.1.6(ii)(b) SNN/ Imidazo[1,2-*b*][1,2,4]thiadiazole

Oxidation of *N*-alkyl-*N'*-(2-benzimidazolyl)thioureas **294** with hydrogen peroxide, in the presence of sodium hydroxide, gives 2-alkylamino[1,2,4]thiadiazolo[2,3-*a*]benzimidazoles **139** (Equation 45) <1999JHC991>.

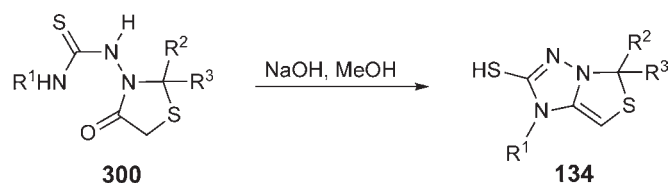


11.05.9.1.7 (5)N3C2N1

11.05.9.1.7(i) (5)N3C2N1 → 13{4}6

11.05.9.1.7(i)(a) NN/S Thiazolo[3,4-*b*][1,2,4]triazole

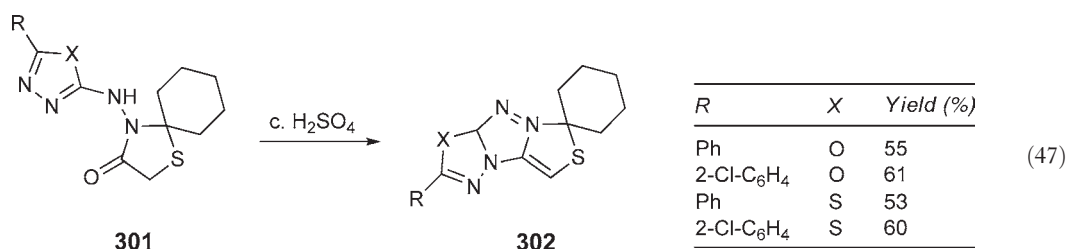
Very interestingly, similar 1,2-thiazolidin-4-ones **300** behave differently in a basic medium, reacting with sodium hydroxide to give thiazolo[3,4-*b*][1,2,4]triazoles **134** (Equation 46) <1996JCR(S)388, 2003PS(178)1175>.



(46)

R^1	R^2	R^3	Yield (%)	Reference
2,4-di-Me-C ₆ H ₃	H	Aryl	69–72	1996JCR(S)388
Het	-(CH ₂) _n -		60–64	2003PS(178)1175

However, the cyclodehydration of 3-[2-aryloxymethyl-1,3,4-oxa(thia)diazol-5-yl]imino-spiro(cyclohexane)1,2-thiazolidin-4-ones **301** with concentrated sulfuric acid at 0 °C furnishes tricyclic derivatives **302** (Equation 47) <2002IJC(B)1314>.

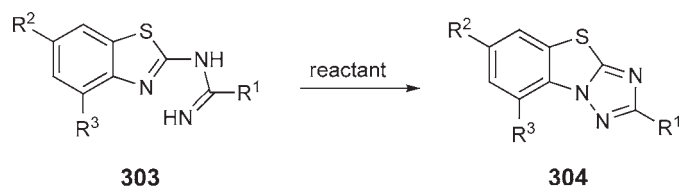


(47)

11.05.9.1.7(ii) (5)N3C2N1 → 134{7}

11.05.9.1.7(ii)(a) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole

Oxidative cyclization, promoted by manganese dioxide or phenyliodo(III) diacetate (PIDA), amidinobenzothiazoles **303** afford [1,2,4]triazolo[3,2-*b*]benzothiazoles **304** (Equation 48) (Table 52) <2001IJH315, 1996OPP362>.



(48)

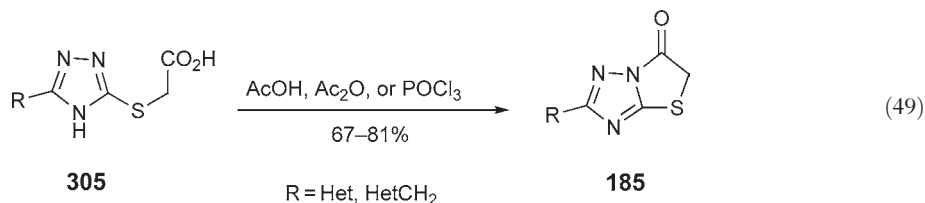
Table 52 [1,2,4]Triazolo[3,2-*b*]benzothiazoles **304**

Reactant	R^1	R^2	R^3	Yield	Reference
MnO ₂ , benzene, reflux, 4 h	Me	Me	H	59	2001IJH315
	Me	H	Me	78	2001IJH315
	Me	Me	Me	39	2001IJH315
PIDA, CF ₃ CH ₂ OH, rt, 1 h	Ph	H	H	78	1996OPP362
	4-Me-C ₆ H ₄	H	H	73	1996OPP362
	4-Cl-C ₆ H ₄	H	H	71	1996OPP362

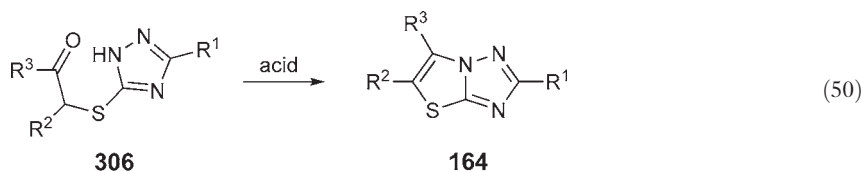
11.05.9.1.8 (5)S4C5C6 → 134{7}

11.05.9.1.8(i) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole

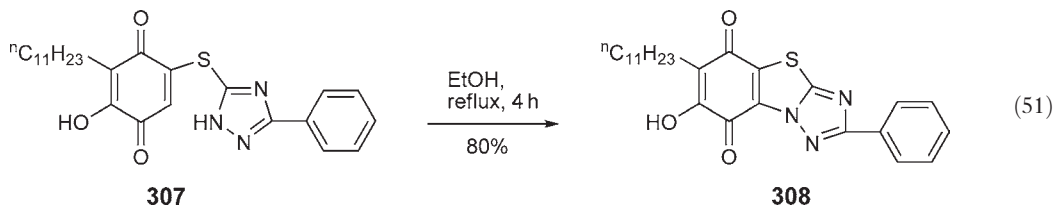
Cyclodehydration of 3-carboxymethylsulfanyl-1,2,4-triazoles **305** (R = Het, HetCH₂) with a mixture of acetic acid/ acetic anhydride, or phosphorus oxytrichloride, yields 5,6-dihydrothiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-ones **185** (Equation 49) <1998PHA94, 1998IJH231, 2003PS(178)2431>.



2-(2-Oxoalkylsulfanyl)-1,2,4-triazoles **306** are cyclized through dehydration with acids such as polyphosphoric acid (PPA) or POCl₃ to give thiazolo[3,2-*b*][1,2,4]triazoles **164** (Equation 50) (Table 53) <1996IJH21, 2002IJC(B)403, 2003IJC(B)401, 2001IJC(B)54, 1999IJC(B)18, 1997BMCL57, 1999FAR51, 2002FAR38, 2001FAR15, 2001FAR54, 2001FAR24>.



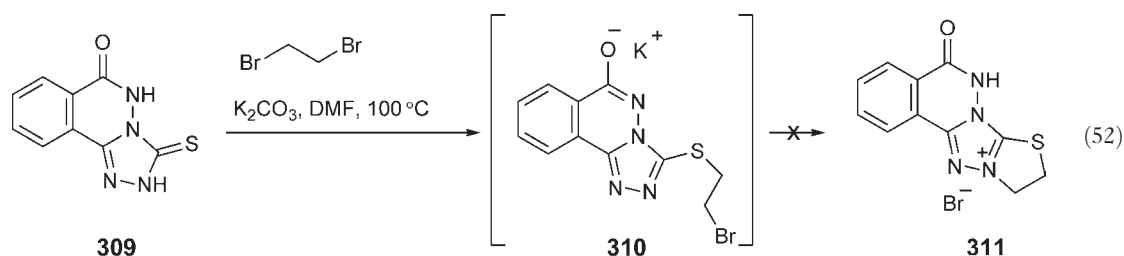
Intermediate quinones **307** spontaneously cyclize in refluxing ethanol to give the corresponding [1,2,4]triazolo[3,2-*b*]-benzothiazoles **308** (Equation 51) <1997IJH255>.



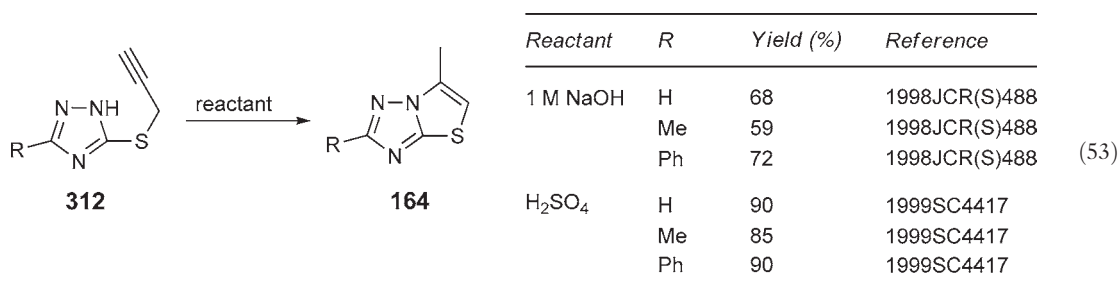
The intramolecular cyclization of intermediate **310** obtained by alkylation of precursor **309** has been reported to fail; consequently, compounds **311** could not be isolated (Equation 52) <2002T8963>.

Table 53 Thiazolo[3,2-*b*][1,2,4]triazoles **164**

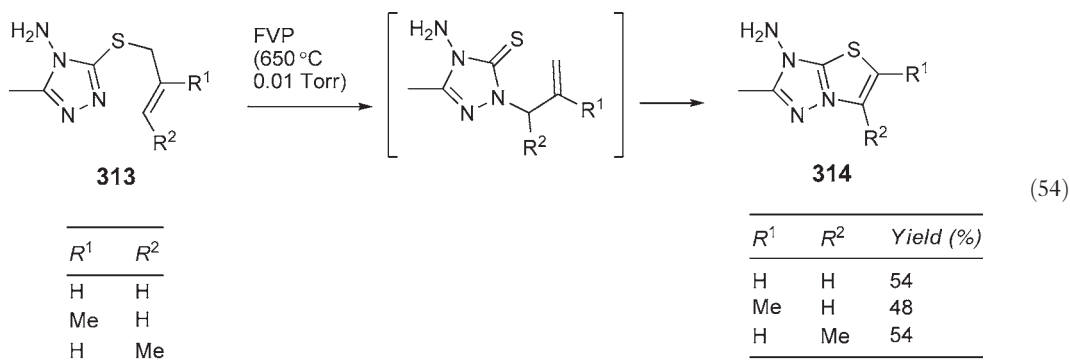
Reagent	R ¹	R ²	R ³	Yield (%)	Reference
PPA, 150 °C	Aryl	H	Aryl	48–53	1996IJH21, 2002IJC(B)403, 2003IJC(B)401
PPA	Me	H	Het	73	1999IJC(B)18
POCl ₃	Me	H	Het	79	1999IJC(B)18
PPA, xylene, 140 °C	H	Aryl	Aryl		1997BMCL57
H ₂ SO ₄ , 0 °C	CH ₂ Het	H	Aryl	75	2003PS(178)2431
	Aryl	H	CH ₂ Cl		1999FAR51
	Het	H	Alkyl		2002FAR38
	Het	H	C ₆ H ₅		2002FAR38
	Het	CO ₂ Et	Alkyl		2001FAR15, 2001FAR54
	Aryl	H	Aryl		2001FAR24



3-Mercaptoalkynyl-1,2,4-triazoles **312** are cyclized to the corresponding thiazolo[3,2-*b*][1,2,4]triazoles **164** by using different catalytic systems, such as basic conditions: 1 M aqueous sodium hydroxide <1998JCR(S)488>; sodium methoxide in methanol <1999IJH341>; sulfuric acid <1999SC4417>; sulfuric acid adsorbed on silica gel <1998IJH309>; HZSM-5 zeolite <1999IJH247>; sulfuric acid adsorbed on silica gel under microwave irradiation <2000JCR(S)464>; Pd(II) salts <2005TL1607> (Equation 53).

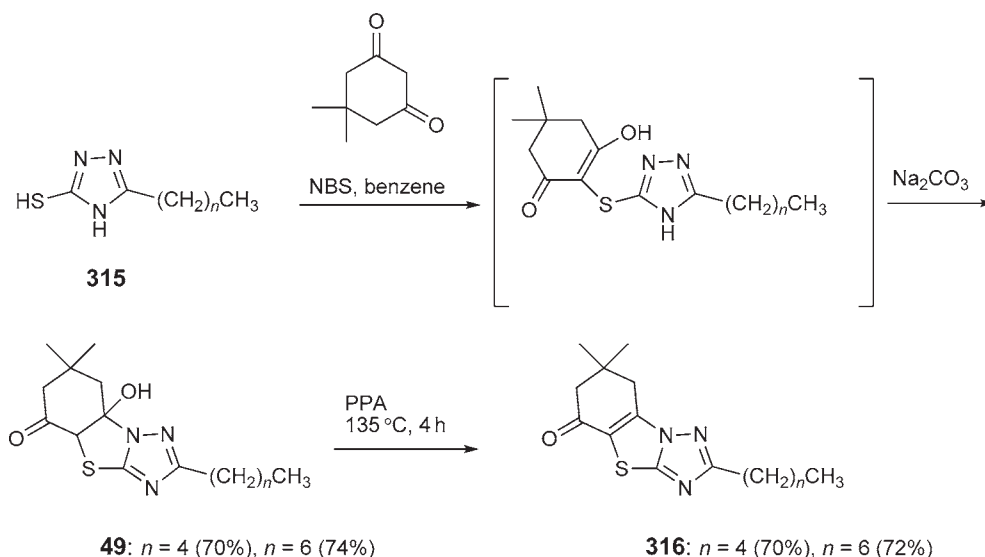


Flash vacuum pyrolysis (FVP) of 4-amino-3-allylthio-4*H*-1,2,4-triazoles **313** furnishes thiazolo[3,2-*b*][1,2,4]triazoles **314** (Equation 54) <2001J(P1)424>. The mechanism is thought to involve initial [3,3] sigmatropic shift of the allyl group, followed by cleavage of the N–N bond to give a thiaza-allyl radical, which then undergoes cyclization, rearrangement, and alkyl group extrusion <2001J(P1)424>.

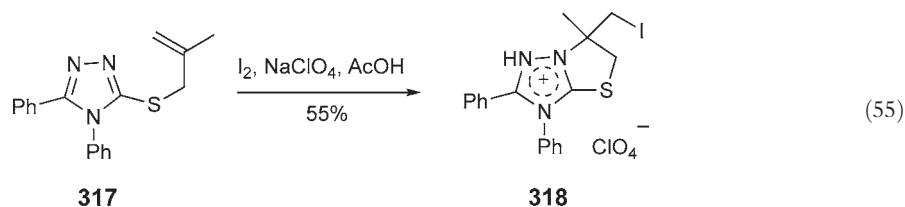


The reaction of dimedone with 3-alkyl-5-ercapto-1,2,4-triazoles **315** in the presence of NBS gives intermediates, which after reaction with a solution of aqueous sodium carbonate afford 2-alkyl-5a-hydroxy-6,6-dimethyl-8-oxo-5a,6,7,8,8a-hexahydro[1,2,4]triazolo[3,2-*b*]benzothiazoles **49**. Finally, reaction with PPA provides the dehydrated heterocyclic derivatives **316** (Scheme 30) <1999IJH127>.

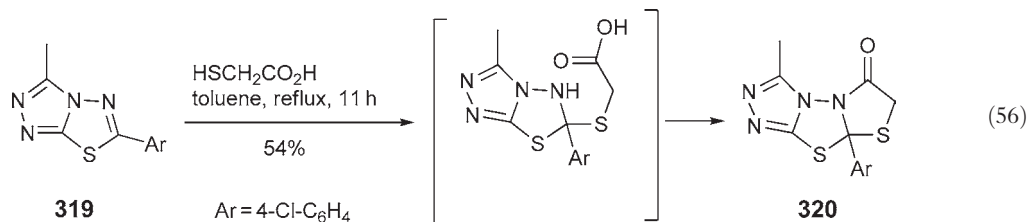
The intramolecular iodine-promoted cyclization of 2-(2-methyl-2-propenylthio)-1,2,4-triazoles **317** exclusively afford the corresponding thiazolo[3,2-*b*][1,2,4]triazolium perchlorates **318** (Equation 55) <1999RJOC730>.



Scheme 30

11.05.9.1.8(ii) SN/S Thiazolo[2,3-*b*][1,3,4]thiadiazole

The reaction of 3-methyl-6-(4-chlorophenyl)[1,2,4]triazolo[3,4-*b*]-1,3,4-thiadiazole **319** with thioglycolic acid gives thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,2,3]thiadiazol-6(7*H*)-one **320** (Equation 56) <2002IJH167>.



11.05.9.1.9 (5)C5C6O7 $\rightarrow$ 12{4}7

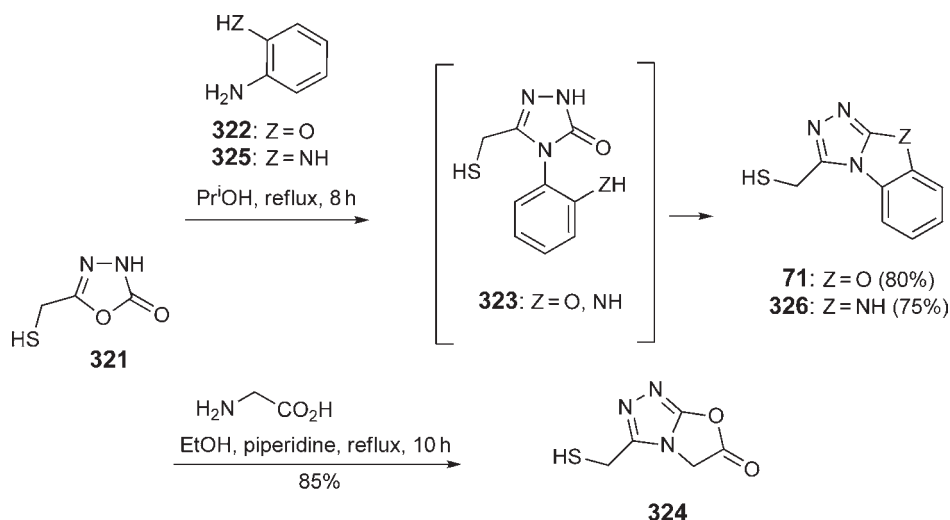
11.05.9.1.9(i) NN/O Oxazolo[2,3-c][1,2,4]triazole

Reaction of 2-mercaptomethyl-1,3,4-oxadiazolin-5-one **321** with *o*-aminophenol **322** and glycine, in refluxing isopropanol, gives 3-mercaptomethyl-[1,2,4]triazole[3,4-*b*]benzoxazole **71**, via intermediate **323** (Scheme 31), and 3-mercaptomethyl-6-oxo-oxazolo[2,3-*c*][1,2,4]triazole **324**, respectively <1996M549>.

11.05.9.1.10 (5)C5C6N7 $\rightarrow$ 12{4}7

11.05.9.1.10(i) NN/N Imidazo[2,1-c][1,2,4]triazole

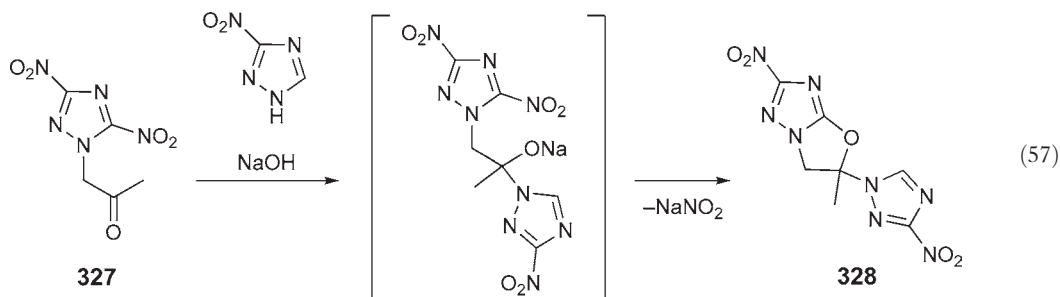
Treatment of 2-mercaptomethyl-1,3,4-oxadiazolin-5-one **321** with *o*-phenylenediamine **325**, in refluxing isopropanol, affords 3-mercaptomethyl-[1,2,4]triazolo[4,3-*a*]benzimidazole **326** (Scheme 31) <1996M549>.



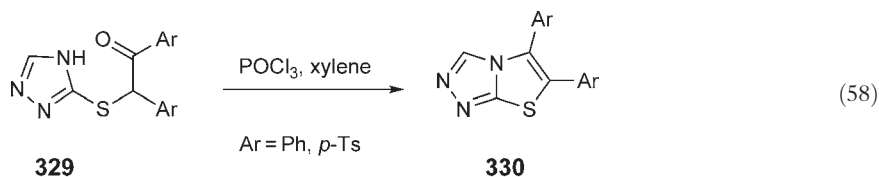
Scheme 31

11.05.9.1.11 (5)C6C5O4 $\rightarrow$ 134{7}11.05.9.1.11(i) NNO/ Oxazolo[3,2-*b*][1,2,4]triazole

The reaction of 3-nitro-1,2,4-triazole with propanone **327** results in a complex reaction mixture, where oxazolo[3,2-*b*][1,2,4]triazole **328** is detected and isolated (unreported yield) (Equation 57) <2001RJOC1217>.

11.05.9.1.12 (5)S7C6C5 $\rightarrow$ 12{4}711.05.9.1.12(i) NN/S Thiazolo[2,3-*c*][1,2,4]triazole

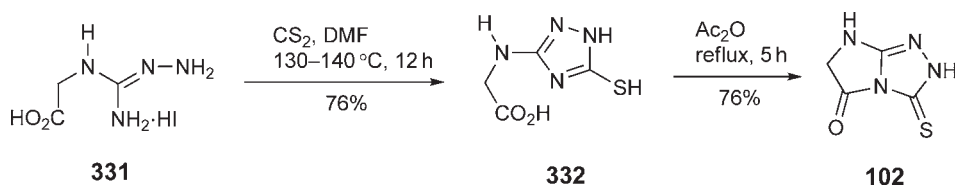
2-Mercaptoalkyl-substituted 1,2,4-triazoles **329** are cyclized with phosphorus(III) oxychloride in xylene to provide 5,6-diarylthiazolo[2,3-*c*][1,2,4]triazoles **330** (unreported yields) (Equation 58) <1997BMCL57>.



11.05.9.1.13 (5)N7C6C5

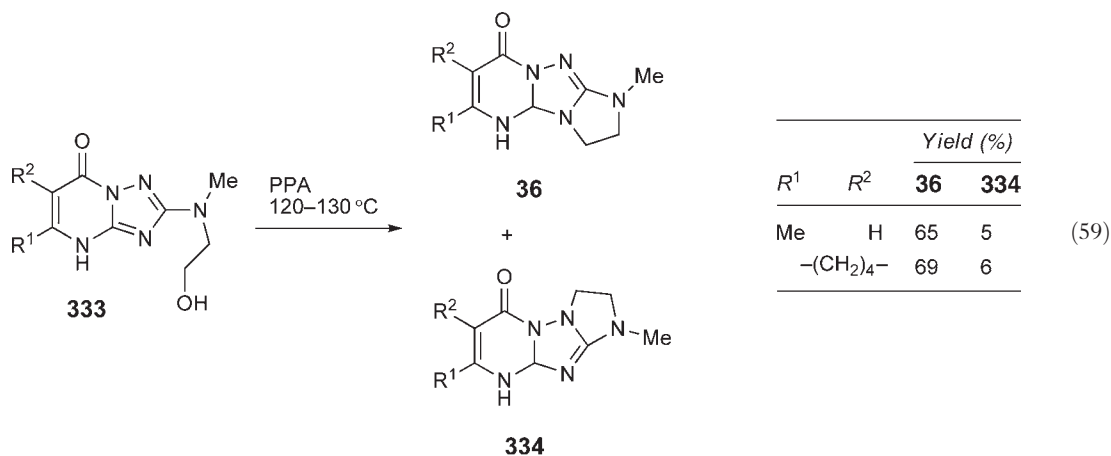
11.05.9.1.13(i) (5)N7C6C5 $\rightarrow$ 12{4}711.05.9.1.13(i)(a) NN/N Imidazo[2,1-*c*][1,2,4]triazole

The reaction of 2-amino-guanidine-1-acetic acid hydroiodide **331** with carbon disulfide, heating the substrates in DMF at 130–140 °C for 12 h, produces compound **332** in 76% yield. This compound was subjected to cyclization reaction with acetic anhydride to give 6,7-dihydro-5-oxo-imidazo[2,1-*c*][1,2,4]triazole **102** in 76% yield (Scheme 32) <1998MI1>.

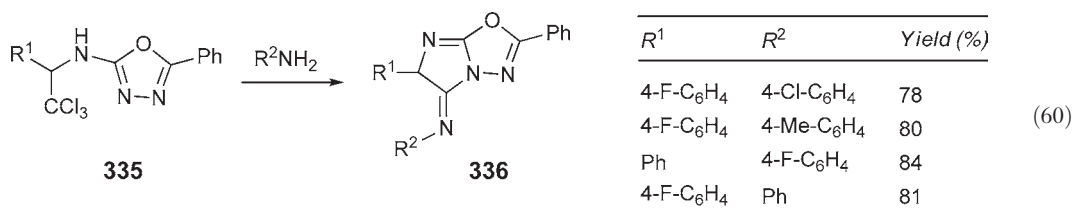


Scheme 32

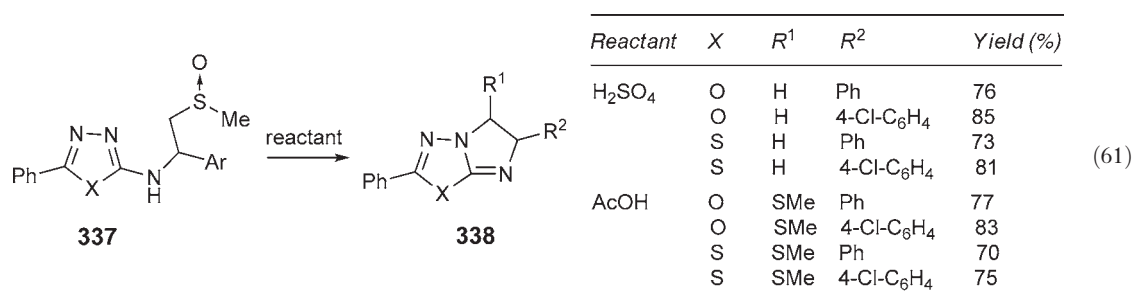
The ring closure of 2-[*N*-(2-hydroxyethyl)-*N*-methyl]amino[1,2,4]triazolo[1,5-*a*] pyrimidin-5-ones **333**, promoted by PPA, gives the major compounds **36** and minor amounts of the isomeric derivatives **334** (Equation 59) <2002JHC319>.

11.05.9.1.13(ii) (5)N7C6C5 $\rightarrow$ 13{4}711.05.9.1.13(ii)(a) ON/N Imidazo[2,1-*b*][1,3,4]oxadiazole, SN/N Imidazo[2,1-*b*][1,3,4]thiadiazole

Compounds **335** on treatment with arylamines undergo cyclocondensation to yield compounds **336** (Equation 60) <1996IJC(B)385, 1996MI4>.

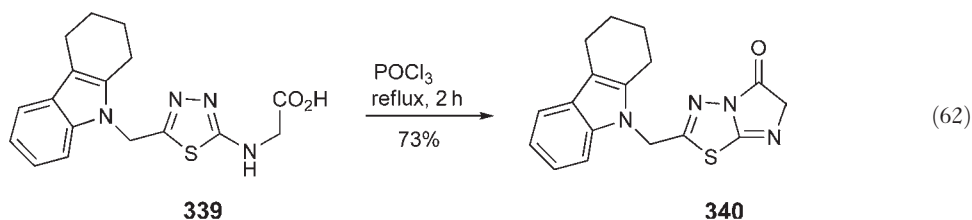


Oxa(thia)diazole precursors **337** are annulated in acid conditions to furnish imidazo[2,1-*b*][1,3,4]oxa(thia)diazoles **338** (Equation 61) <2003S1079>.



(61)

Condensation of 3-amino-5-(1,2,3,4-tetrahydrocarbazol-9-ylmethyl)-1,3,4-thiadiazole with chloroacetic acid affords compound **339** that on treatment with phosphoryl chloride cyclizes to 2-(1,2,3,4-tetrahydrocarbazol-9-ylmethyl)-imidazo[2,1-*b*][1,3,4]thiadiazole-5-(6*H*)-one **340** (Equation 62) <1998IJH231>.



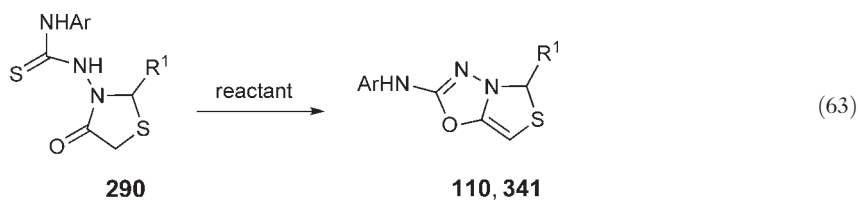
(62)

11.05.9.2 Ring Closure of Two Adjacent Substituents Providing Two and One Ring Atoms: (5)2,1 → (5,5)

11.05.9.2.1 (5)N3C2,O1 → 13{4}6

11.05.9.2.1(i) ON/S Thiazolo[4,3-*b*][1,3,4]oxadiazole

The intramolecular cyclization reaction of 4-thiazolidinones **290**, promoted by iodine in the presence of potassium iodide (or by reaction with methyl iodide in methanol), gives thiazolo[4,3-*b*][1,3,4]oxadiazoles **110** and **341** (Equation 63) (Table 54) <2001IJC(B)440, 1996JCR(S)388>.



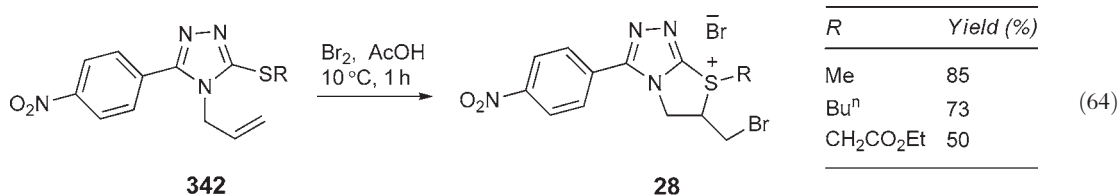
(63)

Table 54 Thiazolo[4,3-*b*][1,3,4]oxadiazoles **110** and **341**

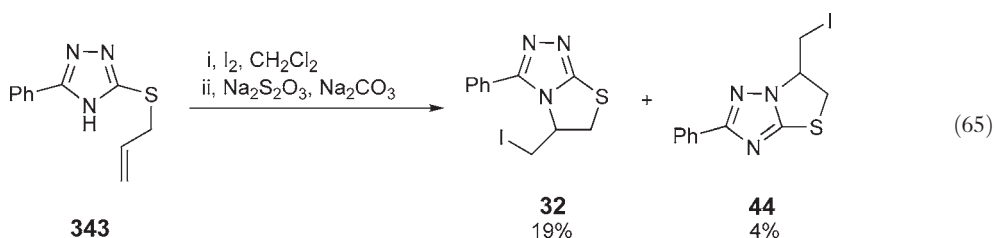
Reactant	Compound	Ar	R ¹	Yield (%)	Reference
KI/I ₂ NaOH, EtOH reflux, 2 h	110	4-MeO-C ₆ H ₄	D-xylobutyl	75	2001IJC(B)440
		2-Me-C ₆ H ₄	D-glucopentyl	70	2001IJC(B)440
		2-Me-C ₆ H ₄	D-xylobutyl	72	2001IJC(B)440
MeI, MeOH	341	2,4-Di-Me-C ₆ H ₄	Ph	64	1996JCR(S)388
		2,4-Di-Me-C ₆ H ₄	4-MeO-C ₆ H ₄	68	1996JCR(S)388
		2,4-Di-Me-C ₆ H ₄	4-Me-C ₆ H ₄	62	1996JCR(S)388
		2,4-Di-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	63	1996JCR(S)388

11.05.9.2.2 (5)C5C6,S7 $\rightarrow$ 12{4}711.05.9.2.2(i) NN/S Thiazolo[2,3-*c*][1,2,4]triazole

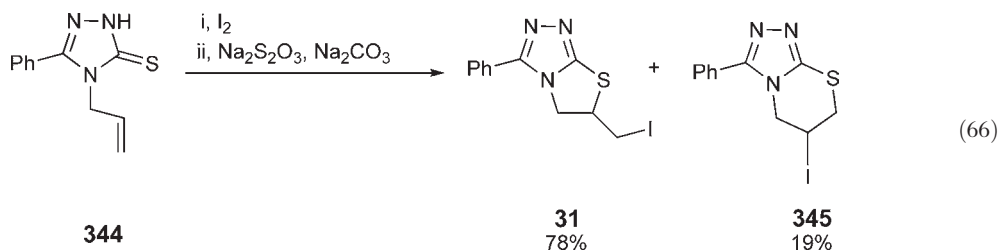
Fused heterocyclic systems derived from 3-mercapto-1,2,4-triazole can be obtained by heterocyclization of 4-allyl-1,2,4-triazole-3-thione derivatives by treatment with halogens or mineral acids <1996T791>. Compounds **342** react with bromine yielding thiazolium halides **28** in good yield (Equation 64) <2000RJOC1033>.



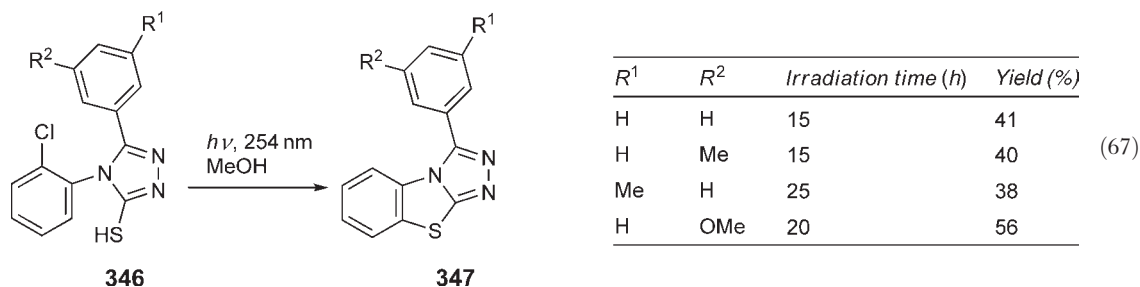
A related iodo-promoted cyclization of the analogous triazole derivative **343** has been reported to give a more complex reaction mixture, where compounds **32** and **44** have been characterized (Equation 65) <2004CHE1207>.



The iodo-promoted cyclization reaction of 4-allyl-5-phenyl-1,2,4-triazole-3(4*H*)-thione **344** gives a mixture of compounds **31** and **345** (Equation 66) <2004CHE1077>.

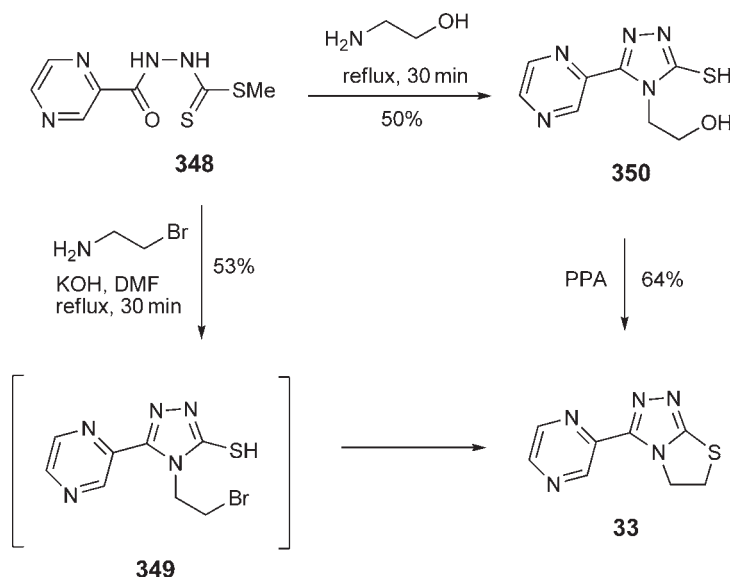


A general photochemical-based synthesis of [1,2,4]triazolo[3,4-*b*]benzothiazoles **347** from 4,5-disubstituted 1,2,4-triazole-3-thione **346** has been described (Equation 67) <1997JOC5766>.



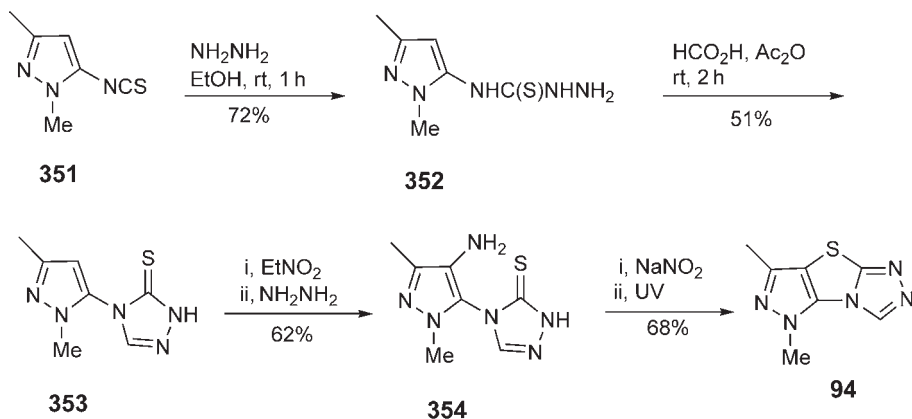
The synthesis of a series of thiazolo[2,3-*c*][1,2,4]triazole derivative **33** has been approached by base-mediated intramolecular cyclization of bromide **349** or acid-promoted ring closure of alcohol **350**, obtained from pyrazinoyl-dithiocarbamate **348** (Scheme 33) <2004PS(179)2519>.

Starting from the known isothiocyanate **351** <1998JHC29>, the cyclization of the semicarbazide **352**, obtained from compound **351**, by condensation with hydrazine hydrate, gives thione **353**, whose nitrosation and reduction



Scheme 33

provides aminopyrazole **354**, which after diazotation and UV irradiation leads to 5,7-dimethyl-pyrazolo[3',4':4:5]thiazolo[2,3-*c*][1,2,4]triazole **94** (Scheme 34) <1999H(51)829>.



Scheme 34

11.05.9.2.3 (5)C5C6,N4 → 134{7}

11.05.9.2.3(i) NNN/ Imidazo[1,2-*b*][1,2,4]triazole

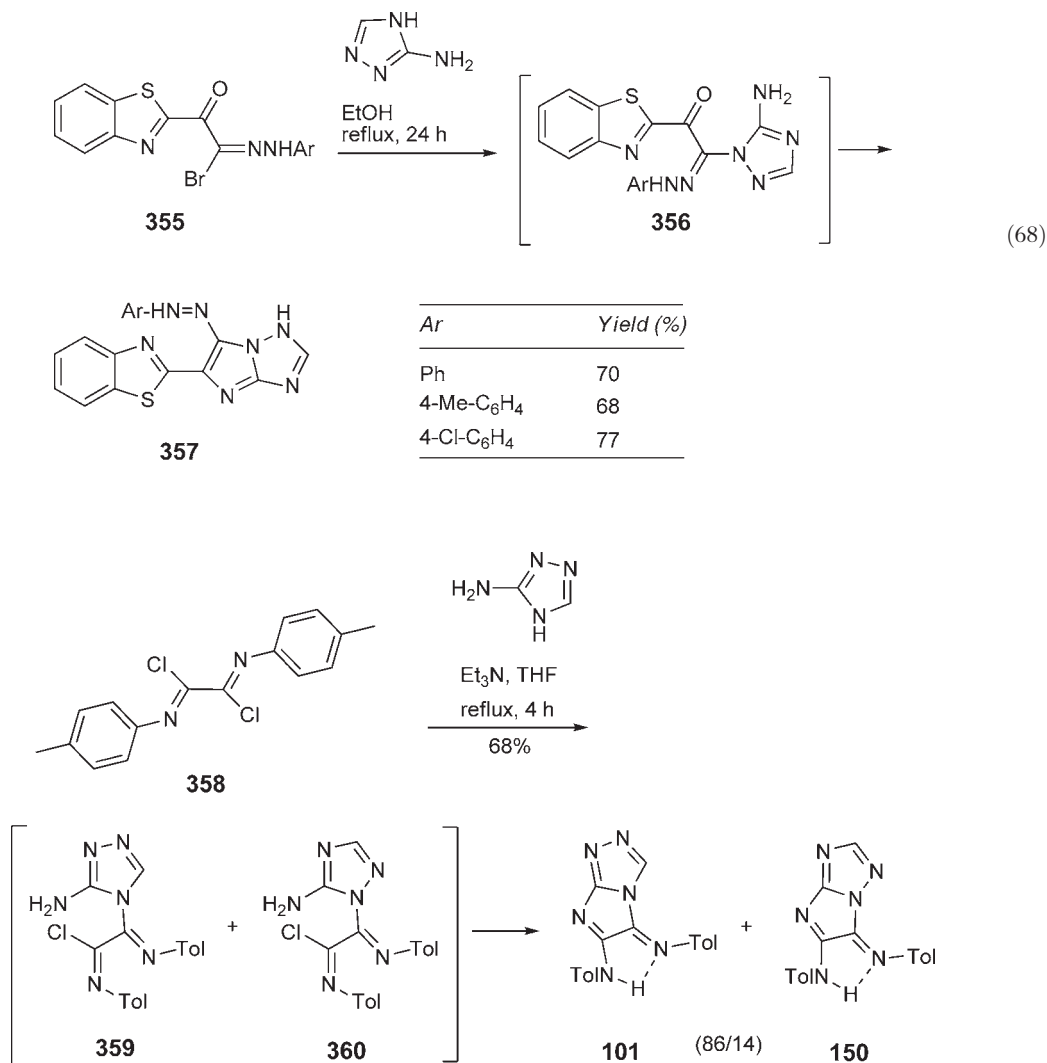
Treatment of hydrazonoyl bromide **355** with 5-amino-1*H*-1,2,4-triazole furnishes imidazo[1,2-*b*][1,2,4]triazole derivative **357**, via intermediate **356** (Equation 68) <1997HAC129>.

11.05.9.2.4 (5)C5C6,N7 → 12{4}7

11.05.9.2.4(i) NN/N Imidazo[2,1-*c*][1,2,4]triazole

Treatment of bis(tolylimido)l dichloride **358** with 3-aminotriazole (that can exist as two tautomeric structures) affords, after refluxing in THF in the presence of triethylamine, a separable mixture of 5,6-bis-(4-tolylimino)-5*H*-

imidazo[2,1-*c*][1,2,4]triazole **101** and 5,6-bis-(4-tolylimino)-6*H*-imidazo[1,2-*b*][1,2,4]triazole **150** in a 5 : 1 ratio, via the tautomeric intermediates **359** and **360** (Scheme 35) <2001EJO2257, 1999SL468>.



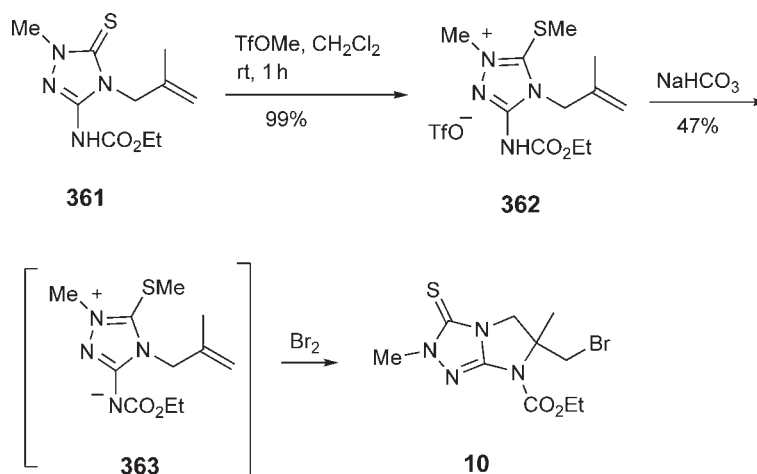
Scheme 35

The synthesis of imidazo[2,1-*c*][1,2,4]triazolo-3-thiones has been investigated. For instance, the reaction of 1,2,4-triazoline-3-thione **361** <1995JHC275> with methyl trifluoromethanesulfonate affords the stable 3-methylmercapto-1,2,4-triazolium trifluoromethanesulfonate **362** in quantitative yield, which after treatment with sodium bicarbonate and bromine provides 6-bromomethyl-2,6-dimethyl-7-ethoxycarbonyl-2,3,5,6-tetrahydro-7*H*-imidazo[2,1-*c*][1,2,4]triazolo-3-thione **10** in 47% yield, via intermediate **363** (Scheme 36) <1996T791>.

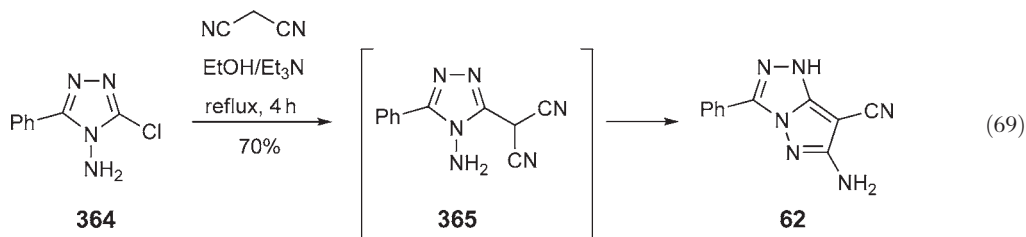
11.05.9.2.5 (5)C7C6,N5 → 12{4}5

11.05.9.2.5(i) NN/N Pyrazolo[5,1-*c*][1,2,4]triazole

The reaction of *N*-amino-2-chloro-5-phenyl[1,2,4]triazole **364** with malonodinitrile, in the presence of triethylamine, in refluxing ethanol gives intermediate **365** that spontaneously cyclized to give 6-amino-7-cyano-3-phenylpyrazolo[5,1-*c*][1,2,4]triazole **62** in 70% yield (Equation 69) <1996SC3827>.



Scheme 36

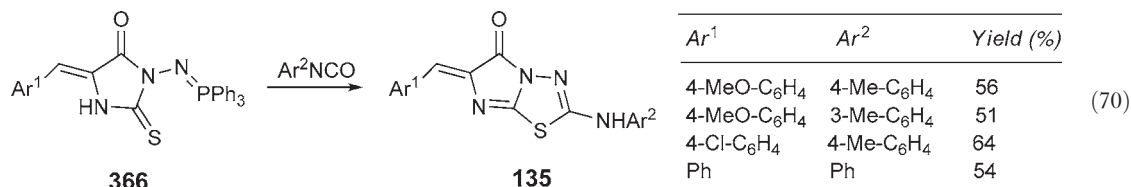


11.05.9.3 Formation of the Second Ring by Insertion of One-Atom Ring Member between Two Adjacent Substituents at the First Ring, Each Providing One Atom for the Second Ring: (5)1,1 + 1 $\rightarrow$ (5,5)

11.05.9.3.1 (5)S1,N3 + C2 $\rightarrow$ 13{4}7

11.05.9.3.1(i) SN/N Imidazo[2,1-*b*][1,3,4]thiadiazole

When solutions of iminophosphorane **366** in anhydrous DMF are treated with an aromatic isocyanate at room temperature, 2-arylamino-imidazo[2,1-*b*][1,3,4]thiadiazol-5(6*H*)-ones **135** are isolated (Equation 70) <2004S1067>.

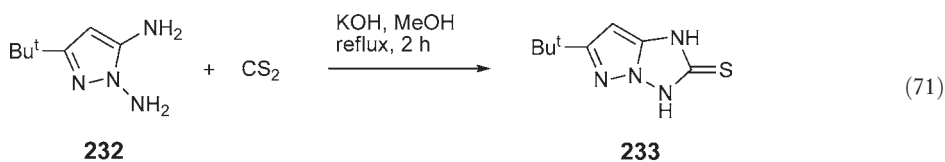


11.05.9.3.2 (5)N1,N3 + C2

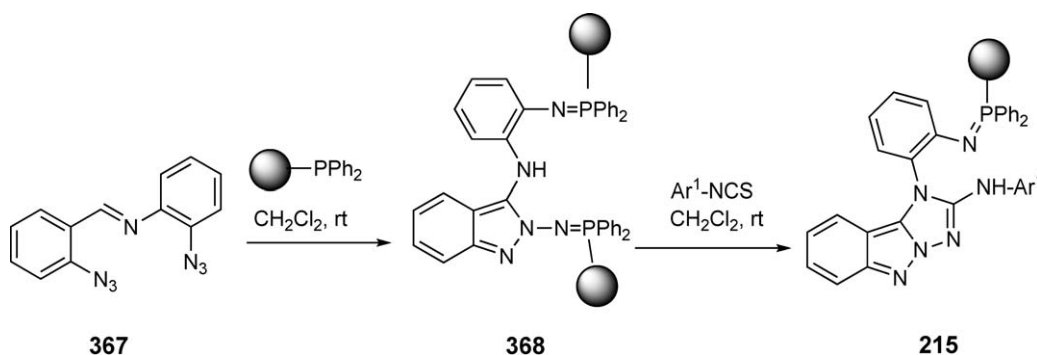
11.05.9.3.2(i) (5)N1,N3 + C2 $\rightarrow$ 13{4}5

11.05.9.3.2(i)(a) NN/N Pyrazolo[1,5-*b*][1,2,4]triazole

The reaction of 1,5-diamino-3-*tert*-butylpyrazole **232** with carbon disulfide affords 6-*tert*-butylpyrazolo[1,5-*b*]-[1,2,4]triazole-2-thione **233** (unreported yield) (Equation 71) <2003OBC4268>.



An efficient solid-phase synthesis of [1,2,4]triazolo[1,5-*b*]indazoles has been described starting from bis(azide) **367**. The coupling of this compound with polymer-bound triphenylphosphine gives compound **368**. This unprecedented bis(iminophosphorane) reacts with various isothiocyanates to give the corresponding iminophosphoranes **215** (unreported yields) attached to the resin (**Scheme 37**) <2000SL1411>.

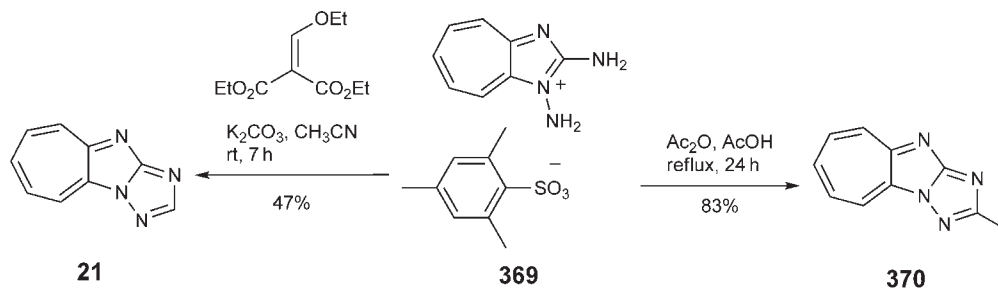


Scheme 37

11.05.9.3.2(ii) (5)N1,N3 + C2 $\rightarrow$ 134{7}

11.05.9.3.2(ii)(a) NNN/ Imidazo[1,2-*b*][1,2,4]triazole

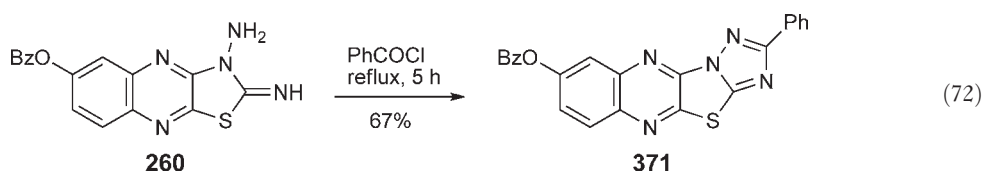
The reaction of salt **369** with acetic anhydride affords a cyclized product characterized as 2-methyl-1,3,3a,9-tetrazaacyclopentant[*a*]azulene **370** (**Scheme 38**) <1999J(P1)1339>. The reaction of 1,2-diamino-1,3-diazaazulenium compound **369** with diethyl ethoxymethylenedicarboxylate (DEEM) provides a complex reaction mixture, one of the isolated products being compound **21**, which is isolated in 29% yield when the reaction is carried out in ethanol, but in 47% yield, when acetonitrile is used as solvent (**Scheme 38**) <1999J(P1)1339>.



Scheme 38

11.05.9.3.2(ii)(b) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole

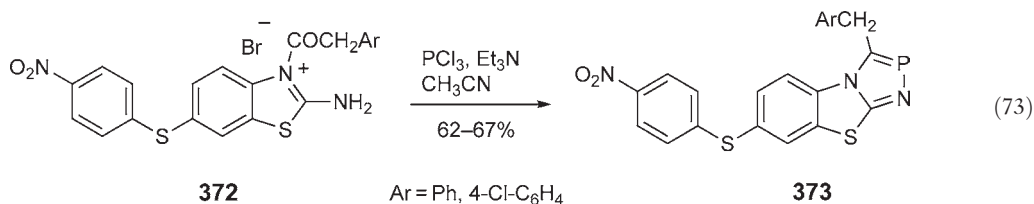
The reaction of 6-benzoyl-3-amino-2-imino-2,3-dihydrothiazolo[4,5-*b*]quinoxaline **260** with benzoyl chloride cleanly affords the expected compound **371** in moderate yield (**Equation 72**) <2000PS(157)87>.



11.05.9.3.3 (5)N1,C3 + P2

11.05.9.3.3(i) (5)N1,C3 + P2 $\rightarrow$ 12{4}711.05.9.3.3(i)(a) NP/S Thiazolo[3,2-*d*][1,4,2]diazaphosphole

The 2-amino-3-phenacylbenzothiazolium bromides **372** react with phosphorus trichloride and triethylamine in acetonitrile to form 3-aryl-7-[(*p*-nitrophenyl)thio]benzothiazolo[3,2-*d*][1,2,4]diazaphospholes **373** (Equation 73) <2002MI15>.

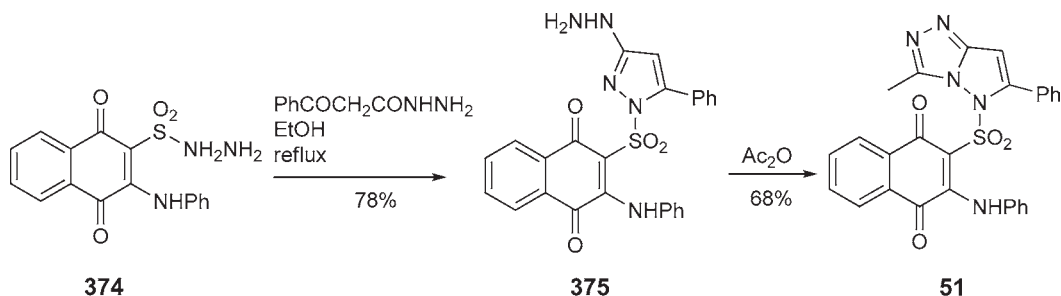


11.05.9.4 Formation of the Second Ring by Insertion of One-Atom Ring Member between a Substituent at the First Ring Providing Two Ring Atoms, and the Adjacent Ring Atom: (5)2 + 1 $\rightarrow$ (5,5)

11.05.9.4.1 (5)N1N2 + C3

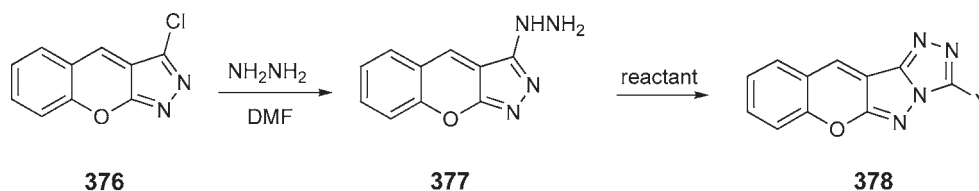
11.05.9.4.1(i) (5)N1N2 + C3 $\rightarrow$ 12{4}511.05.9.4.1(i)(a) NN/N Pyrazolo[5,1-*c*][1,2,4]triazole

The reaction of 2-anilino-1,4-naphthoquinone **374** with benzoylacetic acid hydrazide gives 3-hydrazino-pyrazolyl derivative **375**, that is acetylated to produce 5-[[1,4-dihydro-1,4-dioxo-3-(phenylamino)-2-naphthalenyl]sulfonyl]-3-methyl-6-phenyl-5*H*-pyrazolo[5,1-*c*][1,2,4]triazole **51**. This latter derivative is also obtained in 51% yield from reaction of **374** with benzoylacetic acid hydrazide in the presence of a mixture of acetic acid–sodium acetate <2004PS(179)1907> (Scheme 39).



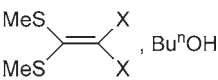
Scheme 39

The reaction of compound **376** with hydrazine gives product **377** that has been transformed into similar triazoles **378**, after reaction with carbon disulfide in the presence of alcoholic potassium hydroxide, benzoic acid in the presence of phosphorus oxychloride, or 3-[bis-(methylthiomethylene)]pentan-2,4-dione and 1,1-dicyano-2,2-dimethylthioethylene, in refluxing *n*-butanol (Scheme 40) (Table 55) <2000FES641>.



Scheme 40

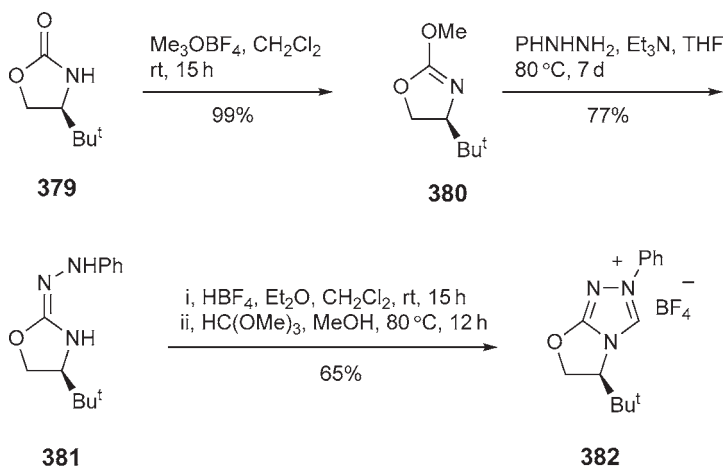
Table 55 Pyrazolo[5,1-*c*][1,2,4]triazole **378**

<i>Reactant</i>	<i>Y</i>	<i>Yield (%)</i>
CS ₂ /KOH	SH	79
 , Bu ⁿ OH	CH(COMe) ₂	79
	CH(CN) ₂	82
(X = COMe, CN)		

11.05.9.4.1(ii) (5)N1N2 + C3 → 12{4}7

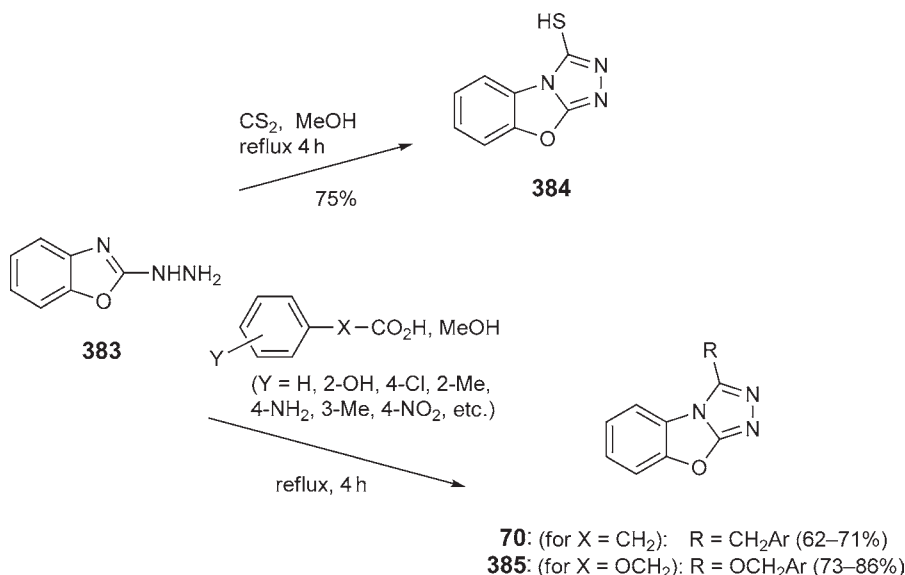
11.05.9.4.1(ii)(a) NN/O Oxazolo[2,3-*c*][1,2,4]triazole

Bicyclic chiral triazolium salt **382** has been used as a precatalyst in the asymmetric benzoin condensation affording benzoin products in high yields with enantiomeric excesses higher than 95% [<2002AG\(E\)1743>](#). The synthesis of this robust triazolium catalyst **382** [<2002AG\(E\)1743>](#) starts from compound **379**, via intermediates **380** and **381**, and is achieved according to a previously modified protocol ([Scheme 41](#)) [<1998J\(P1\)1891>](#). A rationale and predictions of the stereochemistry in these reactions, based on computational chemistry, have been proposed [<2004PNA5770>](#).



Scheme 41

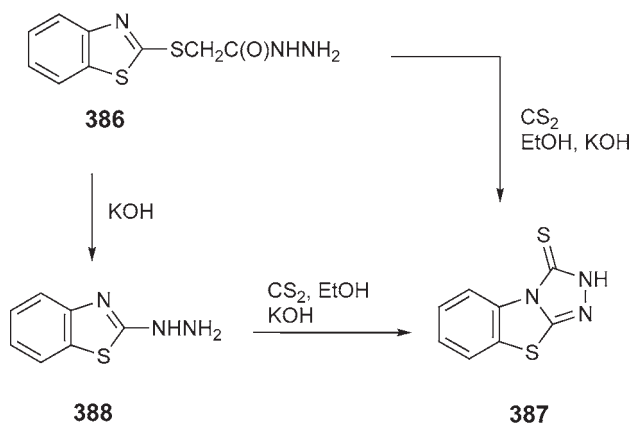
A series of benzoxazolo[3,2-*c*][1,2,4]triazoles **384**, **70**, and **385** have been synthesized from 2-hydrazinobenzoxazole **383**, using standard reactions ([Scheme 42](#)) [<1997IJC\(B\)711>](#).



Scheme 42

11.05.9.4.1(ii)(b) NN/S Thiazolo[2,3-*c*][1,2,4]triazole

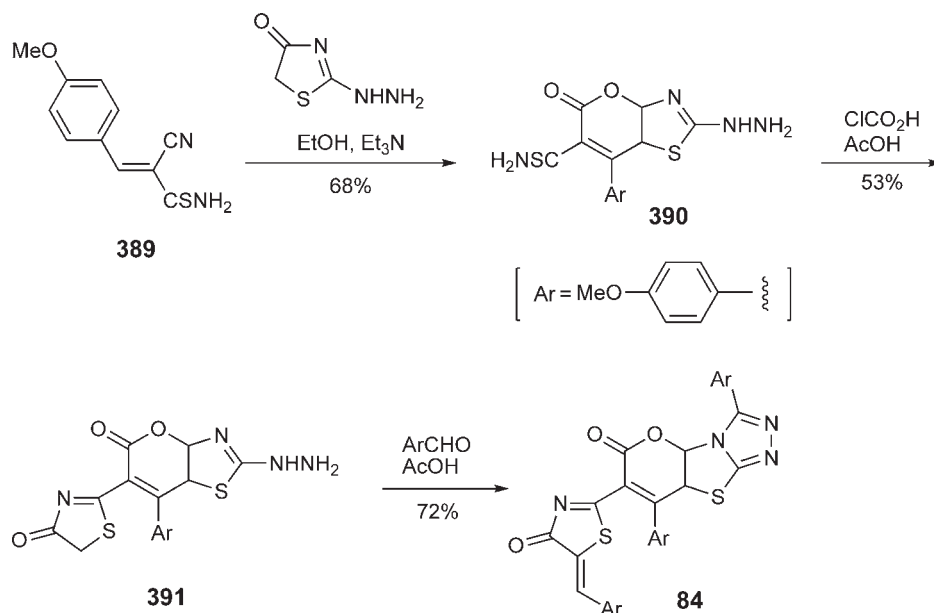
Treatment of a solution of 2-benzothiazolylthioacetyl hydrazide **386** in ethanol with carbon disulfide in the presence of potassium hydroxide gives the rearrangement product [1,2,4]triazolo[3,4-*b*]benzothiazole-3-thiol **387** (unreported yield) (Scheme 43). The structure of this compound was confirmed by its analytical and spectroscopic data, and confirmed by unequivocal synthesis from 2-benzothiazolhydrazine **388** under the same experimental conditions <2002MI3, 2002MI4>.



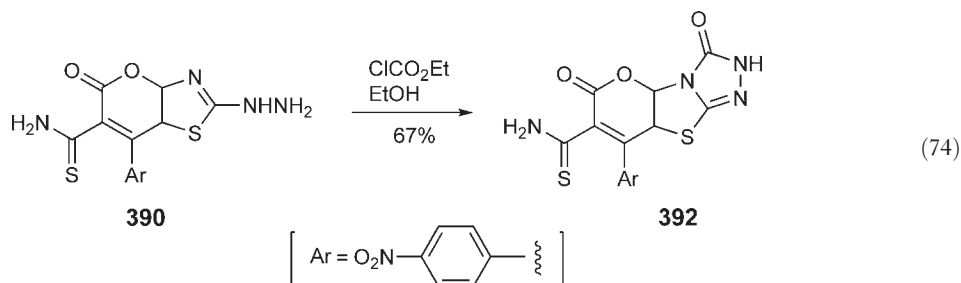
Scheme 43

The reaction of thiocarboxamidocinnamionitrile derivative **389** with 2-hydrazinothiazol-4(5*H*)-one in absolute ethanol containing a catalytic amount of triethylamine affords 5-oxopyrano[2,3-*d*]thiazole **390**. It has been found that the reaction of compound **390** with chloroacetic acid gives the 5-oxopyrano[2,3-*d*]thiazole **391**. The structure of this compound has been confirmed by its reaction with 4-methoxybenzaldehyde in acetic acid to give the 6-oxopyrano[2',3':4,5]thiazolo[2,3-*c*][1,2,4]triazole derivative **84** (Scheme 44) <1999ZN(B)1589>.

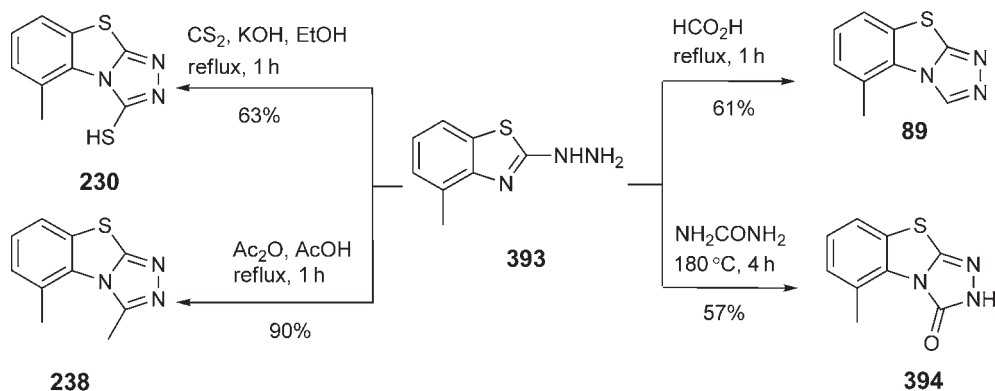
The reaction of compound **390** with ethyl chloroformate has also been investigated and gives 8-(4-nitrophenyl)-3,6-dioxo-7-thiocarboxamidopyrano[2',3':4,5]thiazolo[2,3-*c*][1,2,4]triazole **392** (Equation 74) <1999ZN(B)1589>.



Scheme 44

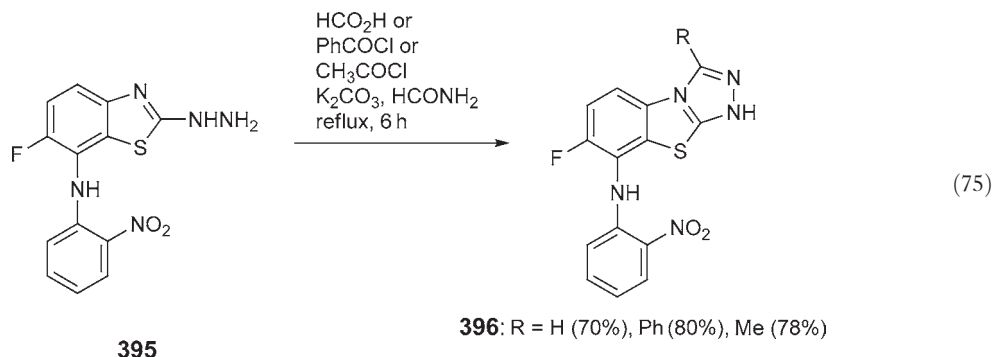


Trying to prepare precursors for the synthesis of 3-substituted [1,2,4]triazolo[5,1-*b*]benzothiazoles, 2-hydrazino-4-methylbenzothiazole **393** was submitted to reaction with formic acid, urea, carbon disulfide, and acetic anhydride to give compounds **230**, **238**, **89**, and **394** (Scheme 45) <1998IJC(B)921>.

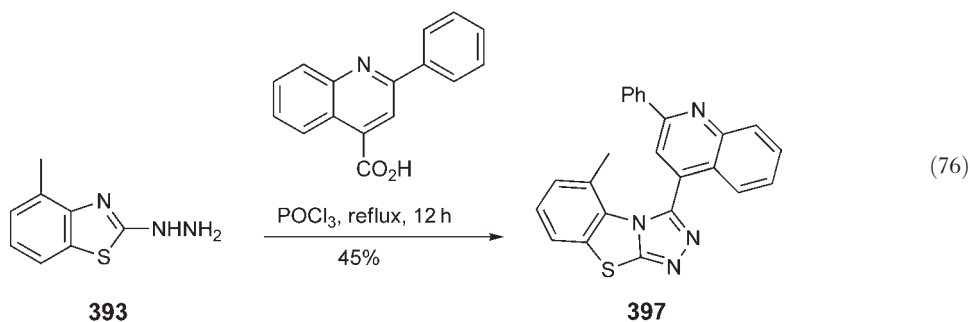


Scheme 45

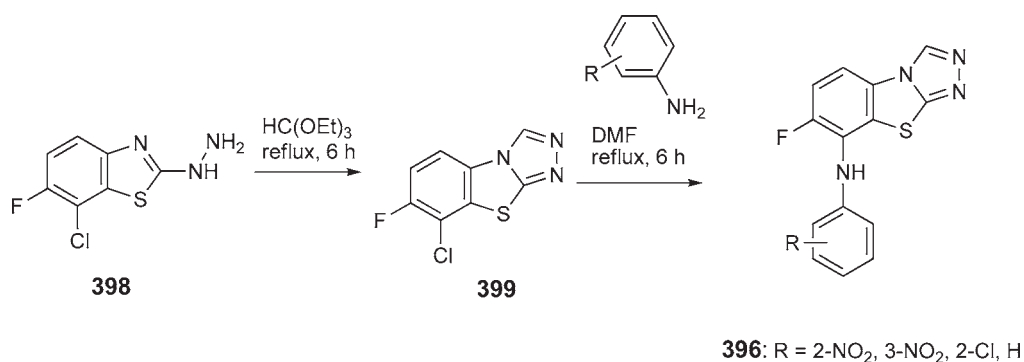
The reaction of a solution 2-hydrazinobenzothiazoles in DMF with formic acid, benzoyl chloride, or acetyl chloride, in the presence of potassium carbonate, gave the 8-fluoro-9-substituted-[1,3]-benzothiazolo[5,1-*b*]-3-substituted-1,2,4-triazoles in good yield, as shown for 6-fluoro-7-(2'-nitrophenylamino)-2-hydrazinobenzothiazole **395** yielding compound **396** (Equation 75) <2004IJH89>.



Novel 5-methyl-substituted [1,2,4]triazolo[3,4-*b*]benzothiazoles **397** have been prepared from 2-hydrazino-4-methylbenzothiazole **393** and several aromatic acids (Equation 76) <2002JST41, 2001MI2>.



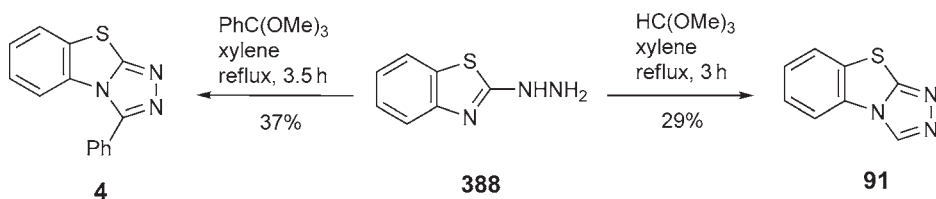
The reaction of 7-chloro-6-fluoro-2-hydrazinobenzothiazole **398** with triethyl orthoformate at reflux leads to the 4*H*-thiazolo[2,3-*c*][1,2,4]triazole derivative **399** (unreported yield), that has been further reacted with different substituted anilines to afford compounds **396** (unreported yields) (Scheme 46) <1998IJH23>.



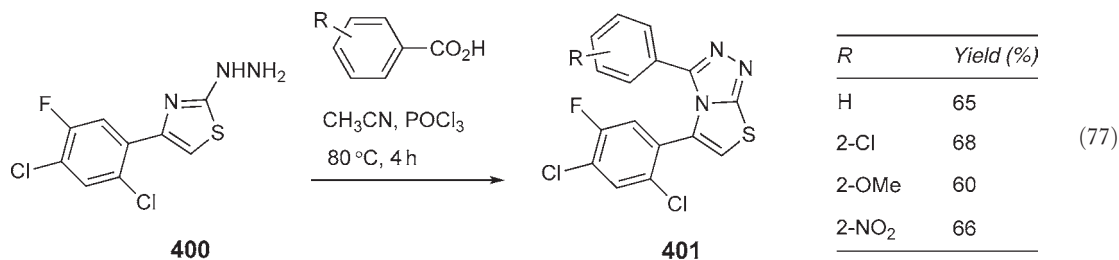
Scheme 46

The reaction of 2-hydroazinobenzothiazole **388** with trimethyl orthoformate or trimethyl orthobenzoate allows to prepare compounds **91** and **4** respectively, in poor yield (Scheme 47) <1996EJM575>.

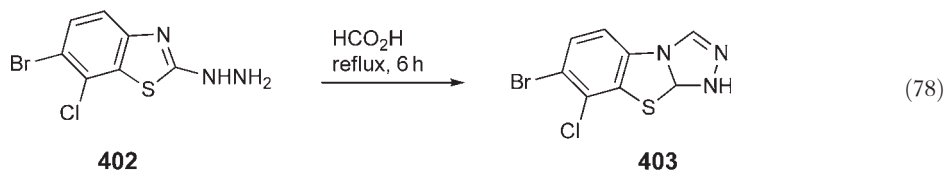
2-Hydrazinobenzothiazole derivative **400** reacted with substituted benzoic acids to provide compounds **401** in good yields (Equation 77) <2004PS(179)1019>.



Scheme 47



The reaction of 6-bromo-7-chloro-2-hydrazinobenzothiazole **402** with formic acid gives the corresponding [1,2,4]triazolo[3,2-*b*]benzothiazole derivative **403** (unreported yield) (Equation 78) <2000IJH275>, a particular and surprising reactivity that has some precedents <1971JOC10, 1985JHC831>.

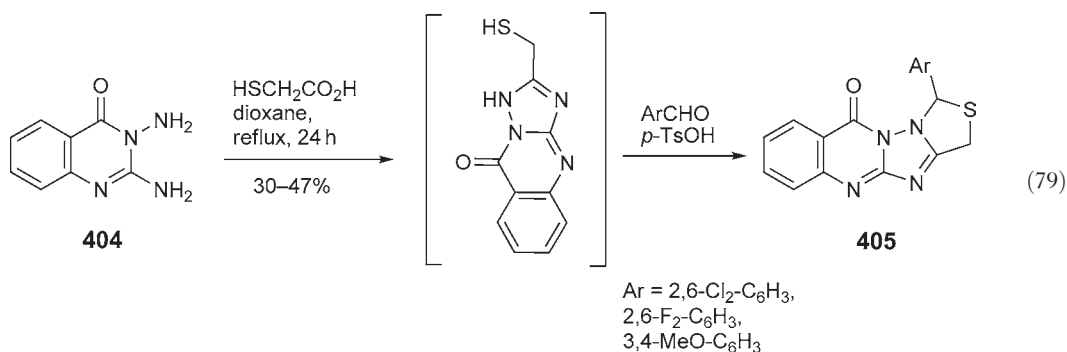


11.05.9.4.2 (5)C7S6 + C5

11.05.9.4.2(i) (5)N1N2 + C3 $\rightarrow$ 13{4}6

11.05.9.4.2(i)(a) NN/S Thiazolo[3,4-*b*][1,2,4]triazole

The reaction of 2,3-diaminoquinazolin-4-one **404** with aryl aldehydes and thioglycolic acid gives 2-substituted 1,3-dihydro-thiazolo[3',4':2,3][1,2,4]triazolo[5,1-*b*]quinazolin-5-ones **405** (Equation 79) <2004MI10>.



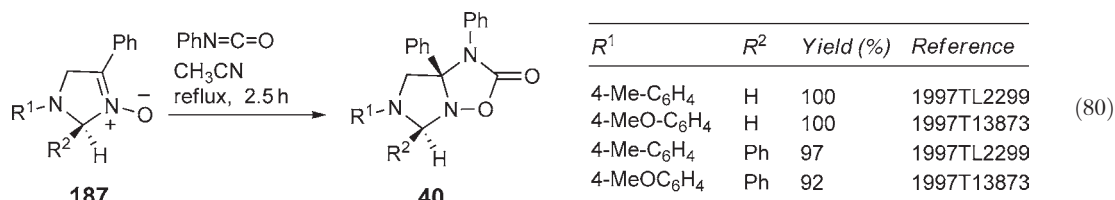
11.05.9.5 Formation of the Second Ring by Insertion of a Two-Atom Ring Member between a Substituent at the First Ring Providing One Atom and the Adjacent Ring Atom: (5)1 + 2 → (5,5)

11.05.9.5.1 (5)O1 + C2N3

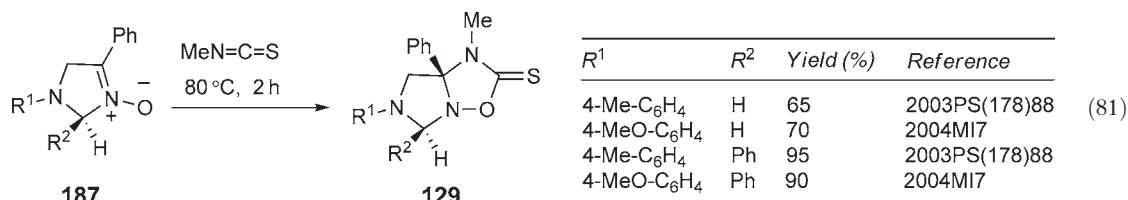
11.05.9.5.1(i) (5)O1 + C2N3 → 13{4}6

11.05.9.5.1(i)(a) NO/N Imidazo[1,5-*b*][1,2,4]oxadiazole

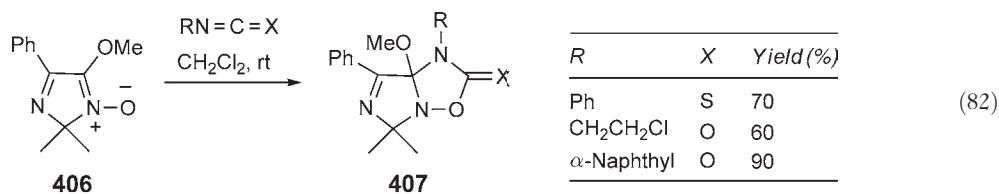
Imidazoline 3-oxides **187** undergo regio- and diastereoselective 1,3-dipolar cycloaddition with aryl isocyanates to give *cis*-5,6,7,7a-tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazoles **40** in good yields (Equation 80) <1997TL2299, 1997T13873>.



Similarly, the reaction of cyclic nitrones **187** with methyl isothiocyanate gives tetrahydroimidazo[1,5-*b*][1,2,4]oxadiazol-2(1*H*)-thiones **129** (Equation 81) <2003PS(178)881, 2004MI7>.



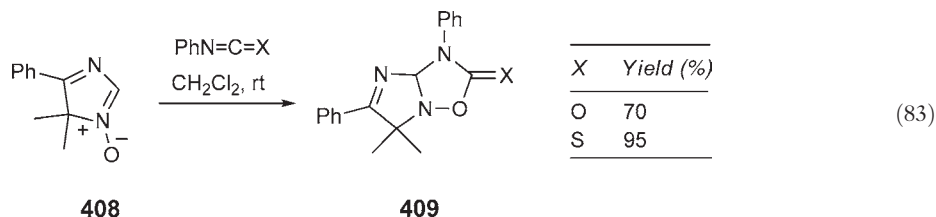
Cyclic α -methoxynitrones **406** react with isocyanates and isothiocyanates at 25 °C giving rise to 1,3-dipolar addition products **407** (Equation 82) <2001RCB882>.



11.05.9.5.1(ii) (5)O1 + C2N3 → 13{4}7

11.05.9.5.1(ii)(a) ONN/Imidazo[1,2-*b*][1,2,4]oxadiazole

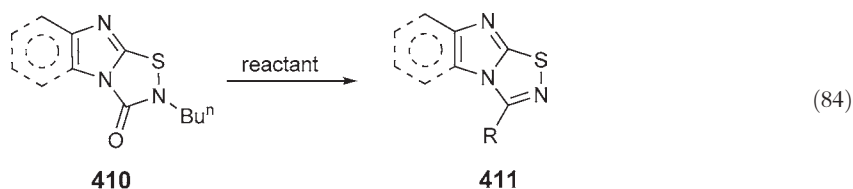
Cyclic α -methoxynitrones **408** react with isocyanates and isothiocyanates at room temperature to furnish 1,3-dipolar addition products **409** (Equation 83) <2001RCB882>.



11.05.9.5.2 (5)S1 + N2C3 → 12{4}7

11.05.9.5.2(i) SN/N Imidazo[1,2-*d*][1,2,4]thiadiazoles

Conveniently functionalized bicyclic or tricyclic imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-ones **410**, prepared by using the standard procedure <1983T2311>, react with cyanogen bromide or *p*-toluenesulfonyl cyanide, in methylene chloride at room temperature, to provide 3-substituted THDs **411** (Equation 84) such as **67** (Figure 10) or **175** (Equation 10) in good yield (Table 56) <2005JOC6230, 2005JMC2266>. The exchange reaction could be extended to a variety of substituted nitriles (bromoacetonitrile, cyanamide, etc.) giving fused THDs.

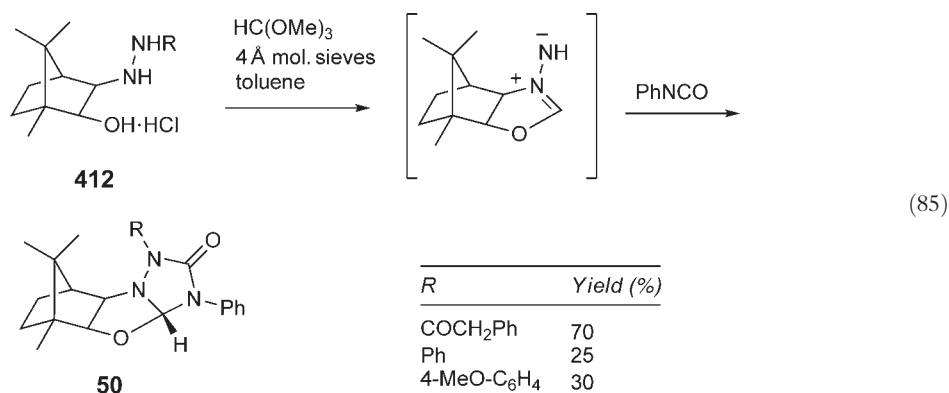
**Table 56** Imidazo[1,2-*d*][1,2,4]thiadiazoles **67** and **175**

Reactant	Compound	R	Yield (%)	Reference
BrCN, CH ₂ Cl ₂ , rt, 12–48 h	175	Br	81	2005JOC6230 2005JMC2266
<i>p</i> -TsCN, CH ₂ Cl ₂ , rt, 12–48 h	67	<i>p</i> -Ts	75	2005JOC6230 2005JMC2266

11.05.9.5.3 (5)N1 + C2N3 → 134{7}

11.05.9.5.3(i) NNO/ Oxazolo[3,2-*b*][1,2,4]triazole

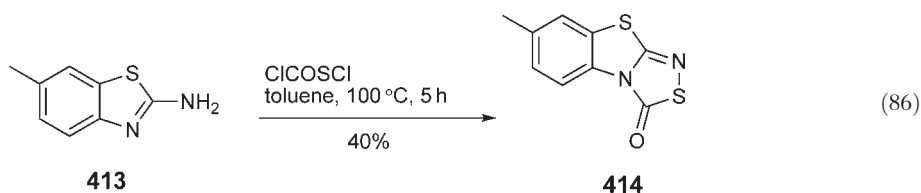
After treatment with an excess of trimethyl orthoformate, the hydrazino-isborneol derivatives **412**, via the corresponding dipoles, and reaction with phenylisocyanate, furnish stereoselectively oxazolo[3,2-*b*][1,2,4]triazoles **50** (Equation 85) <2002TL607, 2000PAC1721, 1995JOC1720>.



11.05.9.5.4 (5)N1 + S2C3 → 12{4}7

11.05.9.5.4(i) NS/S Thiazolo[2,3-*c*][1,2,4]thiadiazole

The reaction of 2-aminobenzothiazoles and chlorocarbonylsulfonyl chloride, with or without amines as catalyst, provides a new entry to the synthesis of [1,2,4]thiadiazolo[3,4-*b*]benzothiazol-3(3*H*)-ones <1997H(45)1579> in modest yields. In the best example, 6-methyl-2-aminobenzothiazole **413** gives the target molecule **414** in 40% yield without adding any base (Equation 86).

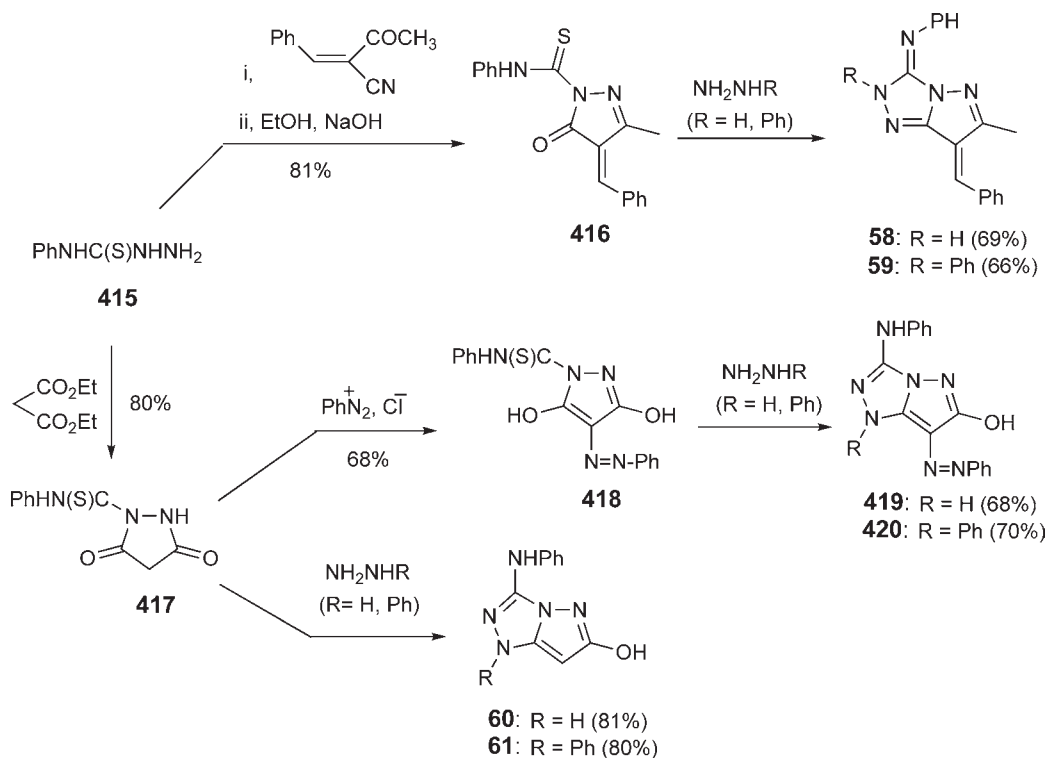


11.05.9.5.5 (5)C3 + N1N2

11.05.9.5.5(i) (5)C3 + N1N2 $\rightarrow$ 12{4}5

11.05.9.5.5(i)(a) NN/N Pyrazolo[5,1-*c*][1,2,4]triazole

The reaction of 4-phenyl-3-thiosemicarbazide **415** with different reactants has been investigated (Scheme 48). Treatment with α -acetyl-cinnamionitrile in refluxing ethanol gives a pyrazole intermediate, that after boiling in an ethanol solution containing sodium hydroxide affords the pyrazolo-5-one **416**, whose reaction with hydrazine hydrate or with phenylhydrazine gives the pyrazolo[5,1-*c*][1,2,4]triazole derivatives **58** and **59** respectively, in a process that occurs through the loss of hydrogen sulfide and ammonia (Scheme 48) <1998PS(134/135)119>. Analogously, the reaction of 4-phenyl-3-thiosemicarbazide **415** with diethyl malonate, in refluxing ethanolic piperidine, is documented to give 3,4-dihydroxy-1-thiocarbanilido-pyrazole **417** in 80% yield (Scheme 48). The structure of pyrazole **417** has been established on the basis of its analytical and spectral data. Further confirmation of this structure is obtained through its reactivity toward some chemical reagents. Thus, coupling with benzene diazonium chloride in an alcoholic sodium acetate solution gives 2,5-dihydroxy-4-phenylazo-1-thiocarbanilido-pyrazole **418** in 68% yield. The structure of this compound is supported by its reactivity with hydrazine hydrate and phenylhydrazine to give compounds **419** and **420** in 68% and 70% yield respectively <1999EJC175>. Similarly, pyrazole **417** reacts with hydrazine hydrate and phenylhydrazine to give products **60** and **61**, in 81% and 80% yield respectively <1999EJC175> (Scheme 48).

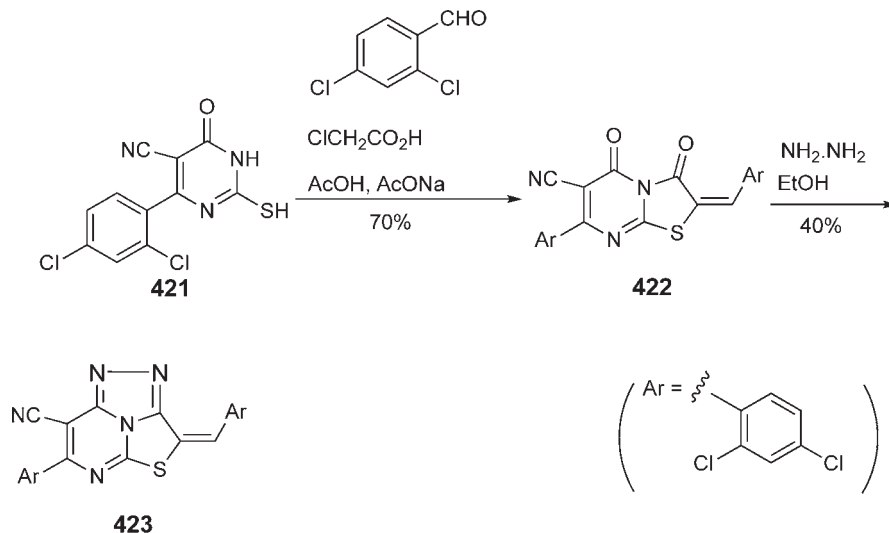


Scheme 48

11.05.9.5.5(ii) (5)C3 + N1N2 → 12{4}6

11.05.9.5.5(ii)(a) NN/S Thiazolo[4,3-*c*][1,2,4]triazole

The reaction of 2-mercapto-4-(2',4'-dichlorophenyl)-5-cyanopyrimidin-6(1*H*)one **421** (obtained by stirring ethyl cyanoacetate and thiourea with 2,4-dichlorobenzaldehyde in sodium ethylate at room temperature, in 70% yield), with a solution of monochloroacetic acid and *p*-chlorobenzaldehyde in glacial acetic acid, in the presence of sodium acetate, affords 2-[(*p*-chlorophenyl)methylene]-6-cyano-7-(2',4'-dichlorophenyl)thiazolo[3,2-*a*]pyrimidin-3,5-dione **422**. Finally, the reaction of compound **422** with hydrazine hydrate converts it into product **423** (Scheme 49) <1996PS(116)39>.



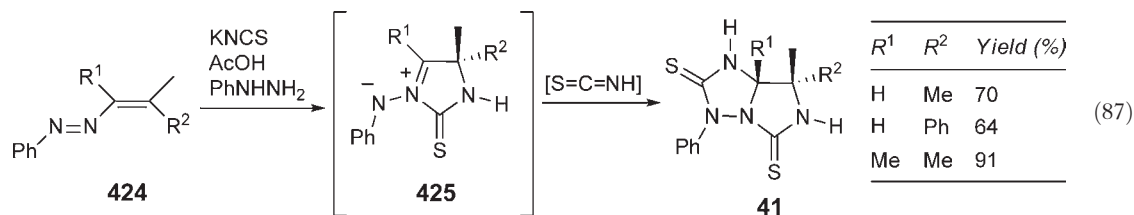
Scheme 49

11.05.9.5.6 (5)N3 + N1C2

11.05.9.5.6(i) (5)N3 + N1C2 → 13{4}6

11.05.9.5.6(i)(a) NN/N Imidazo[1,5-*b*][1,2,4] triazole

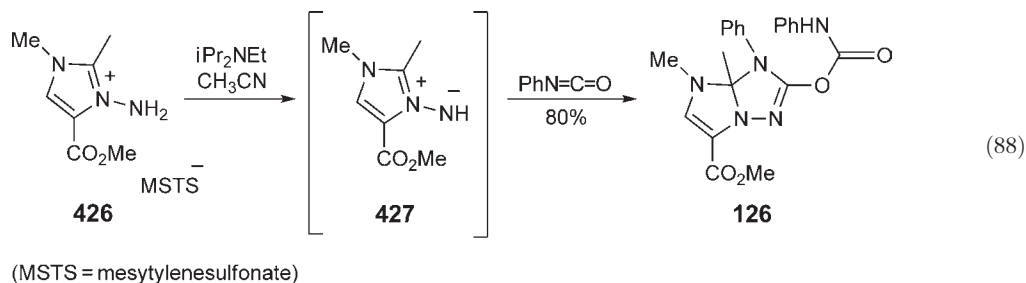
The reaction of phenylazoalkenes **424** with an excess of potassium thiocyanate in acetic acid produces the cycloadducts **425** that undergo further [3+2]-cycloaddition reaction with thiocyanic acid at the azomethine imine function giving rise to the bicyclic product imidazo[1,5-*b*][triazole]-2,5-dithiones **41** (Equation 87) <1998SL786>.



11.05.9.5.6(ii) (5)N3 + N1C2 → 13{4}7

11.05.9.5.6(ii)(a) NN/N Imidazo[1,2-*b*][1,2,4]triazole

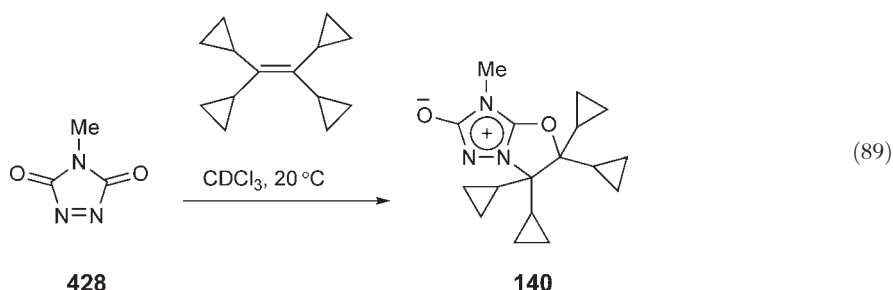
Azolium *N*-amidine **426**, readily prepared from salt **426** in the presence of *N*-ethyl-diisopropylamine, reacts with phenylisocyanate to afford the corresponding imidazo[1,3-*b*][1,2,4]triazole **126** in a formal [4+2] cyclocondensation process (Equation 88) <2001JOC8528>.



11.05.9.5.7 (5)O4 + C5C6 → 134{7}

11.05.9.5.7(i) NNO/ Oxazolo[3,2-*b*][1,2,4]triazole

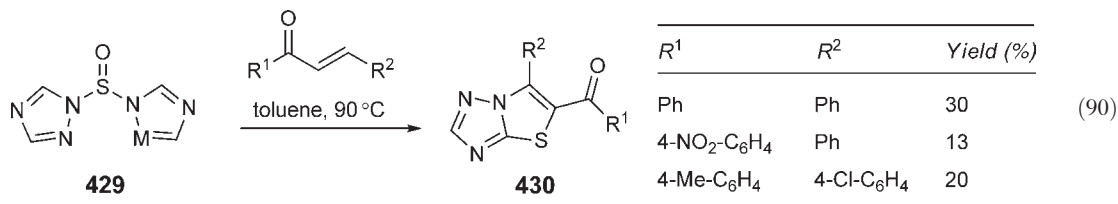
The reaction of 4-methyl-1,2,4-triazoline-3,5-dione **428** with tetracyclopropylethylene gives 5,5,6,6-tetracyclopropyl-3-methyl-5,6-dihydro-oxazolo[3,2-*b*][1,2,4]triazolium-2-olate **140** (unreported yield) (Equation 89) <2004JA700>.



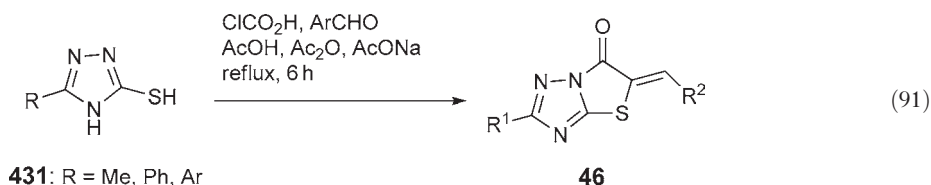
11.05.9.5.8 (5)S4 + C5C6 → 134{7}

11.05.9.5.8(i) NNS/ Thiazolo[3,2-*b*][1,2,4]triazole

The reaction of chalcones with 1,1-bis(1,2,4-triazolyl) derivative **429** is a new method for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles **430** (Equation 90) <2000OL429>.

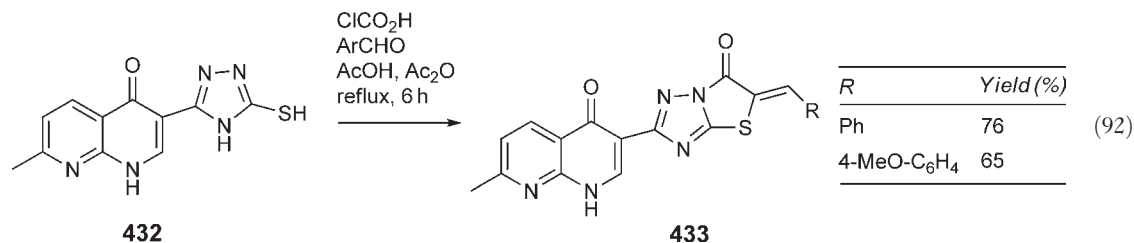


The 'one-pot' reaction of 3-(alkyl)aryl-5-mercapto-1,2,4-triazoles **431** with chloroacetic acid, in the presence of an appropriate aromatic aldehyde, gives thiazolo[3,2-*b*][1,2,4]triazol-5(6*H*)-ones **46** (Equation 91) (Table 57) <1999AF1006, 2001AF470, 2000EJM743, 2001IJH75, 1998IJH297, 2002IJH261, 2003IJH97, 1999IJH55, 1999IJH237, 2003IJH375, 1999IJC(B)867, 1998IJC(B)953, 2003PS(178)2431>.

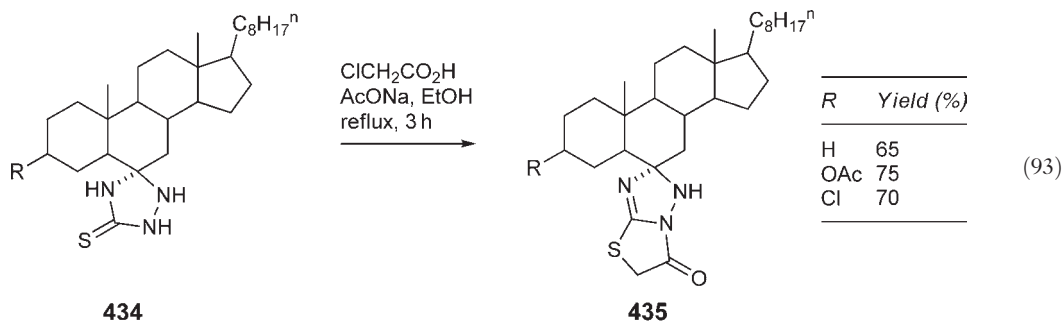
**Table 57** 2-Aryl-5-arylidene-1,2,4-triazolo[3,2-*b*]thiazol-6(5*H*)-ones **46**

<i>R</i> ¹	<i>R</i> ²	Yield (%)	Reference
Me	4-Cl-C ₆ H ₄	89	1999AF1006
Ph	Ph	29	2001AF470
4-Bu ^t -C ₆ H ₄	4-NMe ₂ -C ₆ H ₄	50	2000EJM743
2-Cl-C ₆ H ₄	4-NO ₂ -C ₆ H ₄	78	2001IJH75
4-NO ₂ -C ₆ H ₄	4-Cl-C ₆ H ₄	62	1998IJH297
3-Me-C ₆ H ₄	4-MeO-C ₆ H ₄	50	1999IJC(B)867
3-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	52	1999IJC(B)867
3-Me-C ₆ H ₄	4-NMe ₂ -C ₆ H ₄	65	1999IJC(B)867
4-Me-C ₆ H ₄	4-Cl-C ₆ H ₄	60	1998IJC(B)953
4-Me-C ₆ H ₄	4-NO ₂ -C ₆ H ₄	70	1998IJC(B)953
4-Me-C ₆ H ₄	3-NO ₂ -C ₆ H ₄	70	1998IJC(B)953
4-Me-C ₆ H ₄	4-NMe ₂ -C ₆ H ₄	75	1998IJC(B)953

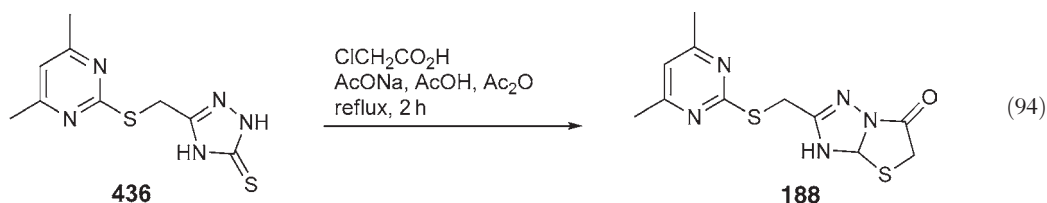
Similarly, 3-(5-mercapto-1,2,4-triazol-3-yl)-7-methyl-1,4-dihydro-4-oxo-1,8-naphthyridines **432**, after reaction with substituted benzaldehydes, chloroacetic acid in the presence of the mixture of acetic anhydride and acetic acid, gives the corresponding 3-(6-arylidene-5-oxo-5,6-dihydro-thiazolo[3,2-*b*]-1,2,4-triazol-2-yl)-7-methyl-1,4-dihydro-4-oxo-1,8-naphthyridines **433** (Equation 92) <2002EJC323>.



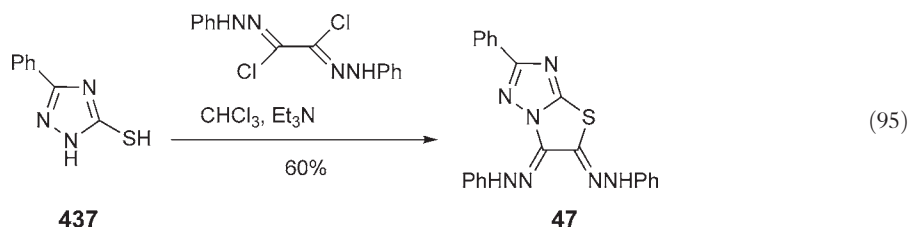
Steroidal 1',2',4'-triazolidine-3'-thiones **434** react with chloroacetic acid and fused sodium acetate to give steroidal oxospirothiazolotriazines **435** in good yield (Equation 93) <1999IJC(B)1218>.



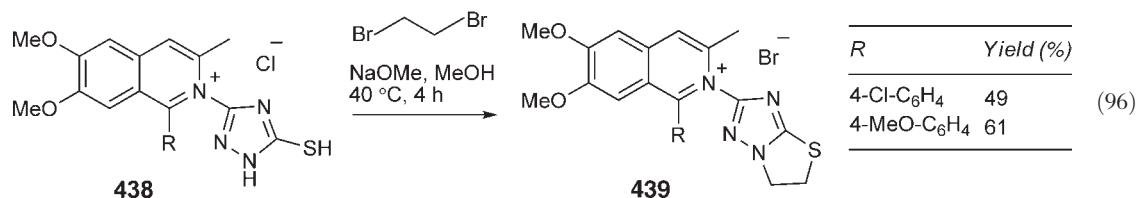
Analogously, 5-(pyrimidylsulfanyl)methyl-1,2,4-triazolidine-3-thione **436** reacts with chloroacetic acid, sodium acetate in acetic acid, to give **188** in 77% yield (Equation 94) <2003PS(178)2431>.



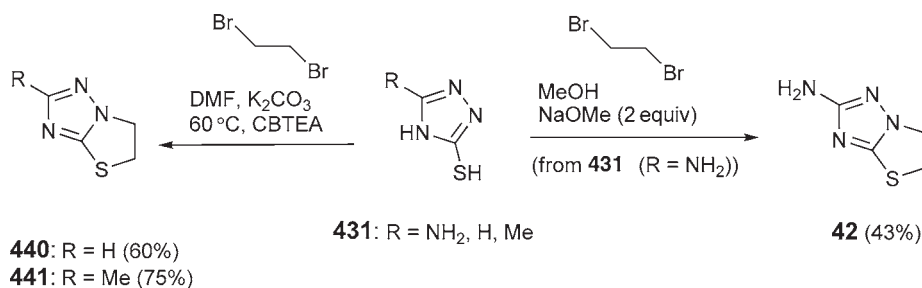
When 5-phenyl-1,2,4-triazole-3-thiol **437** reacts with bis-hydrazonoyl chloride, in ethanol in the presence of sodium ethoxide (or in refluxing chloroform in the presence of triethylamine), compound **47** is obtained (Equation 95) <2002MI7>.



5'-Mercapto-1'*H*-1,2,4-triazol-3'-yl-isoquinolinium chlorides **438** react with 1,2-dibromoethane to produce a variety of substituted 6,7-dimethoxy-3-methyl-*N*-(5',6'-dihydrothiazolo[3,2-*b*][1,2,4]triazol-2'-yl)isoquinolinium bromides **439** (Equation 96) <2003JHC1041>.

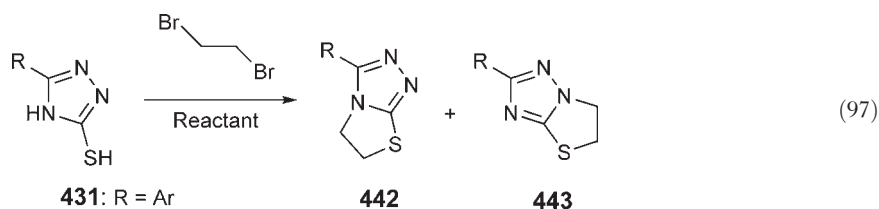


In the ring closure of 5-amino-2,3-dihydro-1*H*-1,2,4-triazolo-3-thione **431** (*R* = NH₂) with 1,2-dibromoethane in the presence of sodium methoxide (2 equiv), compound **42** was formed as the main product (Scheme 50) <2003JHC821>. Similarly, the same type of functionalized thiazolo[3,2-*b*][1,2,4]triazoles **440** and **441** were isolated in the reaction of 1,2-dibromoethane with 2,3-dihydro-1*H*-1,2,4-triazolo-3-thione (**431**, *R* = H) or 2,3-dihydro-5-methyl-1*H*-1,2,4-triazolo-3-thione (**431**, *R* = Me), using DMF as the solvent in the presence of potassium carbonate and benzyltriethylammonium chloride (CBTEA) (Scheme 50) <2004PS(179)1799>.



Scheme 50

Similar results have been reported starting from 2-aryl-substituted precursors **431**, leading to compounds **442** and **443** (Equation 97) (Table 58) <1997AJC911, 2001SC2841>.

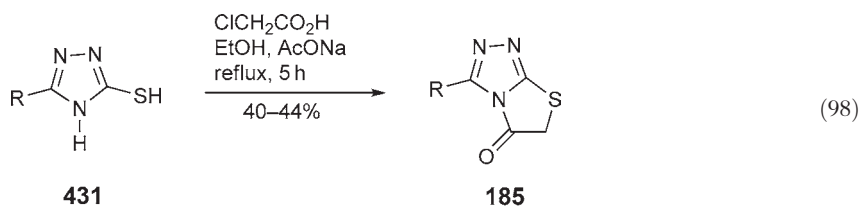
**Table 58** Thiazolo[3,2-*b*][1,2,4]triazoles **442** and **443**

<i>R</i>	<i>Reactant</i>	<i>Yield (%)</i>		<i>Reference</i>
		442	443	
2-MeO-C ₆ H ₄	KOH, NaHCO ₃ , reflux	31		2001SC2841
3-Cl-C ₆ H ₄	EtOH, EtONa (1 mol)	5	10	1997AJC911

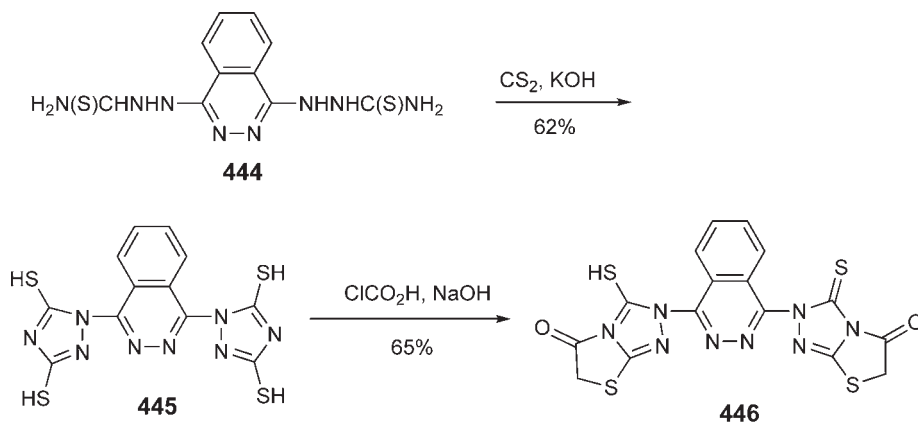
11.05.9.5.9 (5)S7 + C6C5 → 12{4}7

11.05.9.5.9(i) NN/S Thiazolo[2,3-*c*][1,2,4]triazole

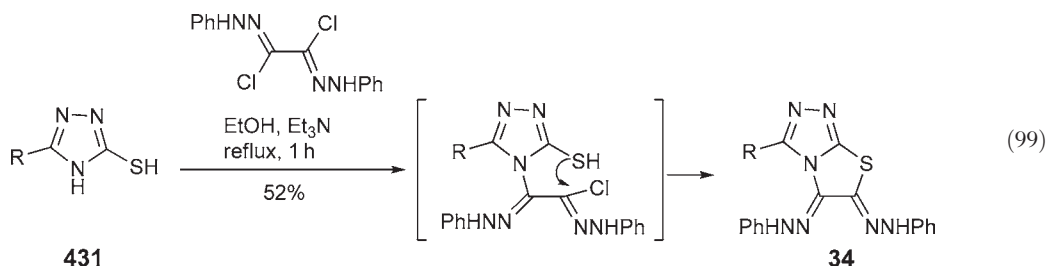
1,2,4-Triazoles **431** react with chloroacetic acid to furnish 3-heteroaryl-thiazolo[2,3-*c*][1,2,4]triazole-5-(6*H*)-ones **185** (R = Het) (Equation 98) <2001IJC(B)636>.



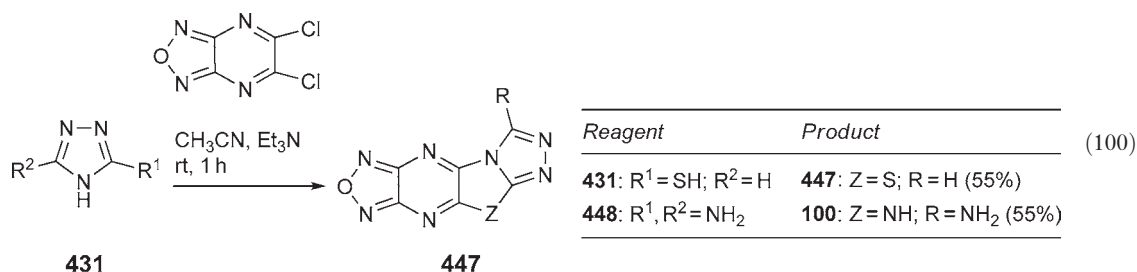
1,4-Dichlorophthalazine on condensation with thiosemicarbazide in DMF afforded 1,4-bis(thiosemicarbazido)phthalazine **444**, that undergoes cyclization with carbon disulfide in the presence of potassium hydroxide to give 1,4-bis(3',5'-dithioxy-[1,2,4]triazol-1-yl)phthalazine **445**. Compound **445** reacts with monochloric acid in the presence of NaOH to give 1,4-bis-(1'-thioxy-6'-oxo-[1,2,4]triazolo[3,4-*b*]-1,3-thiazol-2'-yl)phthalazine **446** (Scheme 51) <2001IJC(B)500>.

**Scheme 51**

When bis-hydrazonoyl chloride is treated with 3-mercapto-1,2,4-triazole **431** ($R = H$) in ethanol in the presence of triethylamine at reflux, compound **34** is isolated in 52% yield (Equation 99) <2004JCR(S)264>.



5,6-Dichlorofurazano[3,4-*b*]pyrazine readily reacts with 2-mercapto-1,3,4-triazole **431** ($R^1 = SH$, $R^2 = H$) to give compound **447** ($Z = S$, $R = H$) (Equation 100) <1997CHE1352>.



11.05.9.5.10 (5)N7 + C5C6

11.05.9.5.10(i) (5)N7 + C5C6 $\rightarrow$ 12{4}7

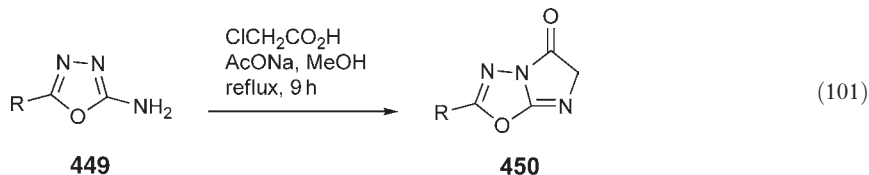
11.05.9.5.10(i)(a) NN/N Imidazo[2,1-*c*][1,2,4]triazole

5,6-Dichlorofurazano[3,4-*b*]pyrazine reacts with 2,5-diamino-1,3,4-triazole **448** ($R^1, R^2 = NH_2$) to give compound **100** ($Z = NH$, $R^1 = NH_2$) (Equation 100) <1997CHE1352>.

11.05.9.5.10(ii) (5)N7 + C5C6 $\rightarrow$ 13{4}7

11.05.9.5.10(ii)(a) ON/N Imidazo[2,1-*b*][1,3,4]oxadiazole

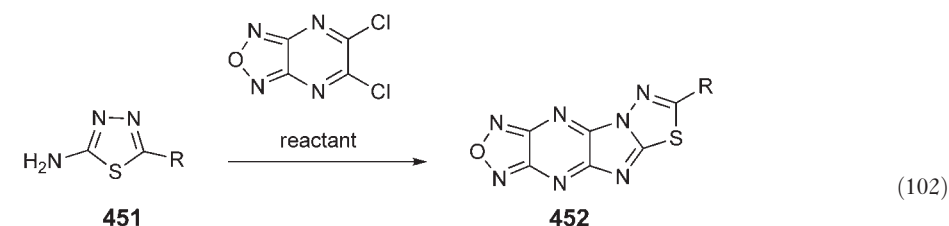
The reaction of 2-amino-5-aryl-1,3,4-oxadiazoles **449** with chloroacetic acid afford imidazo[2,1-*b*][1,3,4]oxadiazoles **450** (unreported yield) (Equation 101) <1996JIC702>.



11.05.9.5.10(iii) (5)N7 + C5C6 $\rightarrow$ 13{4}7

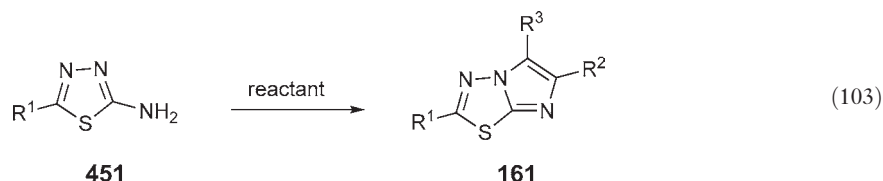
11.05.9.5.10(iii)(a) SN/N Imidazo[2,1-*b*][1,3,4]thiadiazole

5,6-Dichlorofurazano[3,4-*b*]pyrazine reacts with 2-amino-5-methyl-1,3,4-thiadiazole **451** ($R = Me$) to give compound **452** (Equation 102) <1997CHE1352, 1999IJH(9)143>.



Reactant	R	Yield (%)	Reference
MeCN, Et ₃ N, rt, 1 h	Me	62	1997CHE1352
AcONa, EtOH, reflux, 5 h	2,4-Di-Cl-C ₆ H ₃	40	1999IJH(9)143

2-Amino-1,3,4-thiadiazole-5-sulfonamide **451** ($R^1 = \text{SO}_2\text{NH}_2$) on condensation with a 2-bromoketones in ethanol gave the hydrobromide salts of imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **161** (Equation 103) (Table 59) <1996AF949>. Analogously, 5-substituted 2-amino-1,3,4-thiadiazoles **451** ($R^1 = \beta\text{-indolyl}$; $R^1 = \text{SH}$; $R^1 = \text{imidazolin-2-ylidene}$), under the same conditions and using the same reactants, afford various functionalized imidazo[2,1-*b*][1,3,4]thiadiazoles **161** ($R^1 = \beta\text{-indolyl}$, $R^2 = 4\text{-Cl-C}_6\text{H}_4$, $R^3 = \text{H}$; $R^1, R^2 = 4\text{-Cl-C}_6\text{H}_4$, $R^3 = \text{H}$; $R^1 = \text{imidazolin-2-ylidene}$, $R^2 = \text{aryl}$, $R^3 = \text{H}$) <1997IJC(B)394, 1996IJC(B)238, 1997BMCL651> (Equation 103) (Table 59).



5-Substituted (ethyl, *n*-propyl, benzyl), cyclohexyl, 2-furyl, and 2-thienyl) 2-amino-1,3,4-thiadiazoles **451** react with α -bromoarylketones to give imidazo[2,1-*b*][1,3,4]thiadiazoles **161** in good yields (Equation 103) (Table 59) <2006BMC3069, 2006TL2811>.

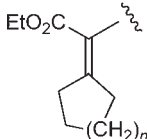
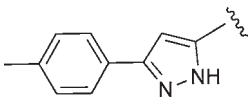
Compound **451** ($R^1 = \text{aryl}$) in refluxing chloroacetic acid and in the presence of anhydrous sodium acetate gives 2-substituted aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **161** (unreported yields) (Equation 103) (Table 59) <1997JIC125>. Under the same experimental conditions, compound **451** ($R^1 = 4\text{-Bu}^t$) is transformed to the corresponding derivative **161** in 68% yield (Equation 103) (Table 59) <2000IJH255>.

The reaction of commercially available 2-amino-5-methyl-1,3,4-thiadiazole **451** ($R^1 = \text{Me}$) with chloroacetone followed by treatment with 1 M HBr provides 2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole **161** (Equation 103) (Table 59) <2000AF550>.

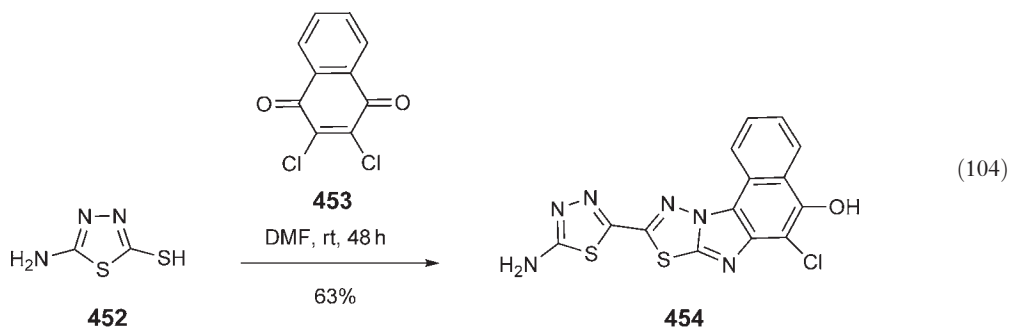
The reaction of 5-cycloalkyl- or 5-alkyl-substituted 2-amino-5-methyl-1,3,4-thiadiazoles with α -haloketones is reported. This is the case of 2-amino-5-(1-adamantyl)-1,3,4-thiadiazole <2000IJH65> or 2-amino-5-methyl-1,3,4-thiadiazole **451** ($R^1 = \text{Me}$) (Equation 103) and ethyl 2-chloroacetate leading to 5-ethoxycarbonyl-2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole **161** (Equation 103) (Table 59) <2003EJM781>. The reaction of α -haloketones with 2-amino-5-methyl-1,3,4-thiadiazoles substituted at C-5 with complex heterocyclic ring system, such as 7-methyl-1,4-dihydro-1,8-naphthyridin-4-one (DMF, anhydrous Na_2CO_3) <2003EJC135>, or 1-aryl-5-methyl-1,2,3-triazole (EtOH, reflux) is reported <2002MI11>.

The reaction of 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles **451** ($R^1 = \text{ArOCH}_2$) with α -bromoacetophenone, under microwave irradiation in ethanol as the solvent <2005SC2881>, or in water <2005JCR744>, affords 2,6-disubstituted imidazo[2,1-*b*][1,3,4]thiadiazoles **161** ($R^1 = \text{ArOCH}_2$, $R^2 = \text{Ph}$, $R^3 = \text{H}$) in very fast reactions, with no added catalyst or dehydrating agents (Equation 103) (Table 59). When the same reactions are carried out heating in oil baths at 80–90 °C, even after 15 h, the reactions are not completed and the yields are poorer. The reaction of 2-amino-5-[3-(4-methylphenyl)-1*H*-pyrazol-5-ylmethyl]-1,3,4-thiadiazole **451** with α -bromo-4-chloroacetophenone gives 6-(4-chlorophenyl)-2-[3-(4-methylphenyl)-1*H*-pyrazol-5-yl-methyl]imidazo[2,1-*b*][1,3,4]thiadiazole **161** (Equation 103) (Table 59) <1996IJC(B)273>. A number of substituted 2-amino-5-aryl-1,3,4-thiadiazoles **451** ($X = \text{H}$ <1999IJH33>; $X = \text{Bu}^t$ <2000IJH255>; $X = 2,4\text{-di-Cl}$ <1999IJH(9)143>; $X = 2,4\text{-di-NO}_2$ <2002IJH41>; $X = 2\text{-pyridyl}$ <2003IJH101>) react with α -halogeno ketones (or methyl aryl ketones in the presence of NBS) to give the expected imidazo[2,1-*b*][1,3,4]thiadiazoles **161** (Equation 103) (Table 59).

Table 59 Imidazo[2,1-*b*][1,3,4]thiadiazoles **161**

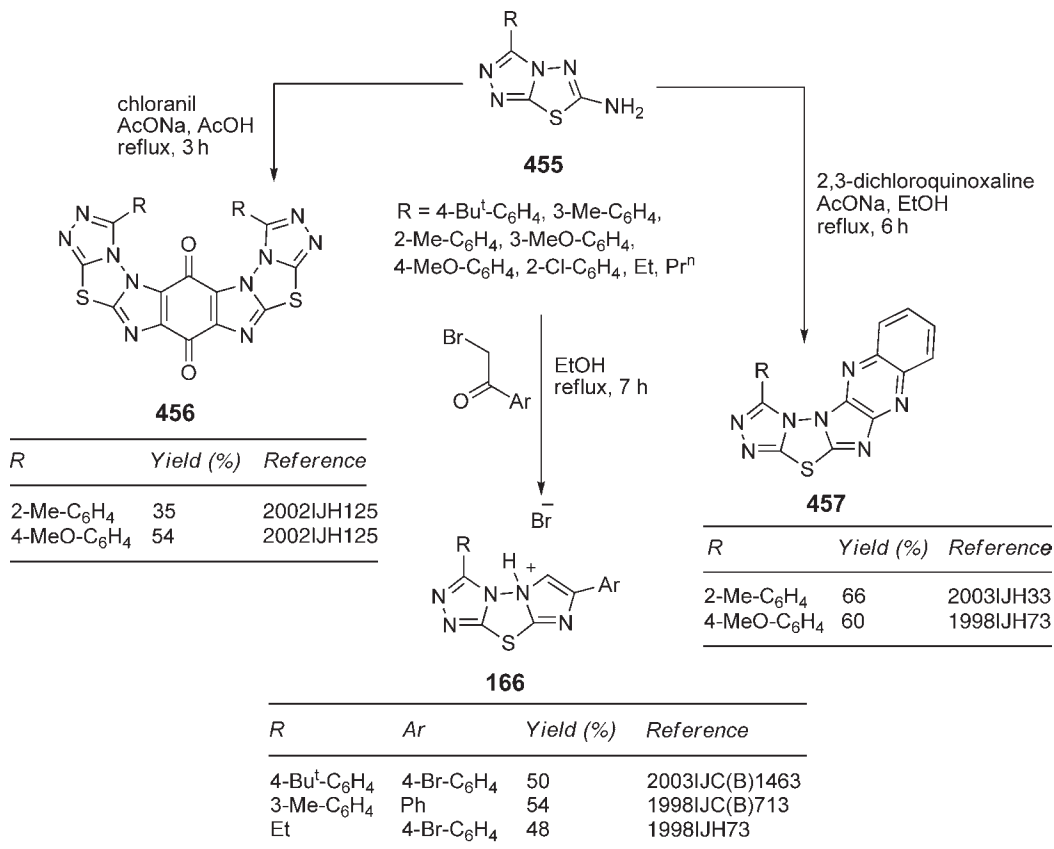
Reactant	R^1	R^2	R^3	Yield (%)	References
$R^2\text{COCH}_2\text{Br}$, EtOH, heat, 12 h, Na_2CO_3	SO_2NH_2	Ph	H	54	1996AF949
		2-Cl- C_6H_4	H	51	
		4-Br- C_6H_4	H	50	
	β -Indolyl	4-Cl- C_6H_4	H	84	1997IJC(B)394
	$\text{SCH}_2(4\text{-Cl-}\text{C}_6\text{H}_4)$	4-Cl- C_6H_4	H	51	1996IJC(B)238
	Cyclohexyl	4-Br- C_6H_4	H	75	2006BMC3069
	2-Furyl	4-Br- C_6H_4	H	42	2006TL2811
	2-Thienyl	4-Br- C_6H_4	H	70	
ClCO_2H , MeOH, AcONa, reflux, 9 h	Aryl	H	OH		1997IJC125
	Bu ^t	H	OH	68	200MI2
ClCH_2COMe , CH_3CN , reflux, 8 h; HBr, reflux, 1 h	Me	Me	H		2000AF550
Ethyl 2-chloroacetoacetate, EtOH, py, rt, 5 h	Me	Me	CO_2Et		2003EJM781
PhCOCH_2Br , MW, 16 min	PhCH_2O	Ph	H	78	2005SC2881
	2-Me- $\text{C}_6\text{H}_4\text{-CH}_2\text{O}$	Ph	H	75	
	4-Cl- $\text{C}_6\text{H}_4\text{-CH}_2\text{O}$	Ph	H	80	
$R^2\text{COCH}_2\text{Br}$, EtOH, reflux		4-Cl- C_6H_4	H		1997BMCL651
		4-Br- C_6H_4	H		1997BMCL651
		4-Cl- C_6H_4	H	62	1996IJC(B)273
	Aryl	Aryl	H	43–56	1999IJH33, 2000IJH255, 1999IJH(9)143, 2002IJH41, 2003IJH101
ArCOCH_3 , NBS, benzene, reflux	2,4-Cl- C_6H_3	Aryl	H	43–66	1999IJH(9)143

The reaction of 5-amino-3*H*-1,3,4-thiadiazole-2-thione **452** with 2,3-dichloro-1,4-naphthoquinone **453** in DMF, at room temperature (rt) for 48 h, gave the complex naphthoquinoimidazolothiadiazole **454** (Equation 104) <1996PS(116)261>.



A series of substituted triazolo[3,4-*b*][1,3,4]thiadiazoles **455** have been submitted to reaction with different two-carbon activated reagents such as chloranil or 2,3-dichloroquinoxaline, to give the complex linear heterocycles **456**

and **457** (Scheme 52) <2002IJH125, 2003IJH33>, or with α -halogenoketones to give highly complex and functionalized imidazo[2,1-*b*][13,4]thiadiazoles **166** (Scheme 52) <2003IJC(B)1463, 2001IJC(B)303, 1998IJC(B)713, 2003IJH189, 1998IJH73>.



Scheme 52

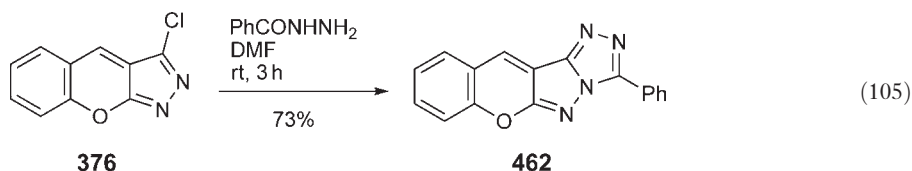
11.05.9.6 Formation of the Second Ring by Addition of a Three-Atom Ring Member to Two Ring Adjacent Positions of the First Ring: (5)1 + 3 → (5,5)

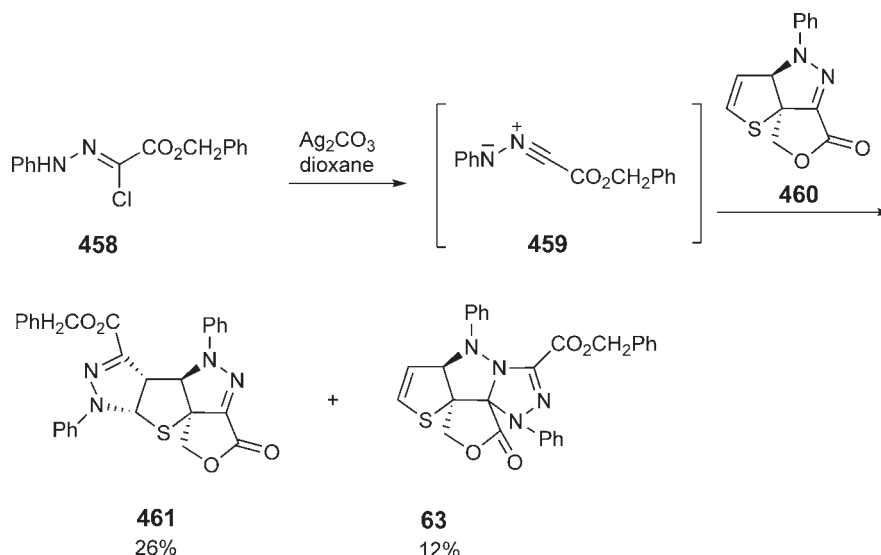
11.05.9.6.1 (5)[N4C7a] + N1N2C3 → 12{4}5

11.05.9.6.1(i) NN/N Pyrazolo[5,1-*c*][1,2,4]triazole

The cycloaddition of nitrilimines toward furo[3,4-*c*]thieno[2,3-*d*]pyrazoles has been investigated as a function of the electron-withdrawing or electron-donating character of the substituents attached to the aromatic rings <2000H(53)917>. For instance, nitrilimine **459**, obtained *in situ* from hydrazonoyl chloride **458**, by base treatment with silver carbonate in dioxane, when reacted with **460**, gives a mixture of compounds **461** and **63** (Scheme 53) <2000H(53)917>.

Similarly, chlorobenzopyrano[2,3-*c*]pyrazole **376** on treatment with benzoic acid hydrazide gives benzopyranodiazolotriazole derivative **462** (Equation 105) <2000FES641>.



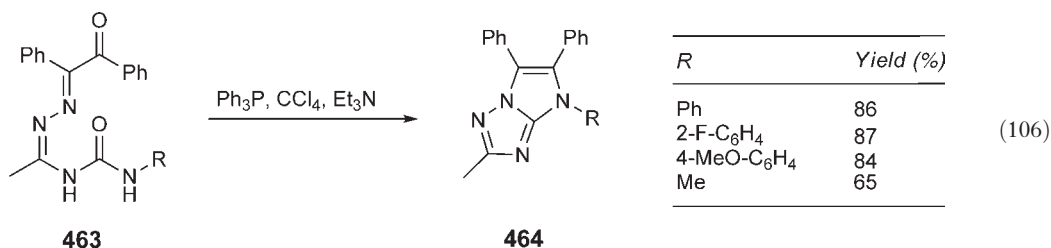


Scheme 53

11.05.9.7 Formation of the [5,5]-Fused Rings from Chain Fragments

11.05.9.7.1 One fragment: $8 \rightarrow (5,5)$

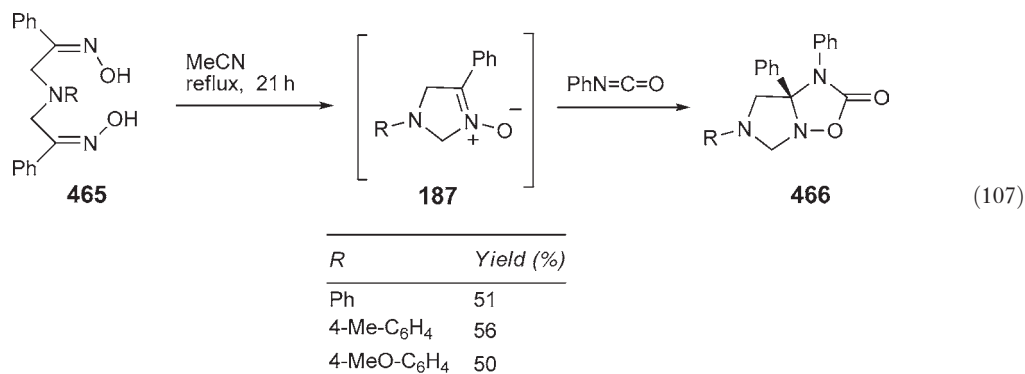
When benzyl 1-ureidoethylidene hydrazones **463** are treated with triphenylphosphine, the obtained products are 7*H*-imidazo[1,2-*b*][1,2,4]triazoles **464** (Equation 106) <1996JHC1877, 1997JHC71>.



11.05.9.7.2 Two fragments providing 6 + 2 ring atoms: $6 + 2 \rightarrow (5,5)$

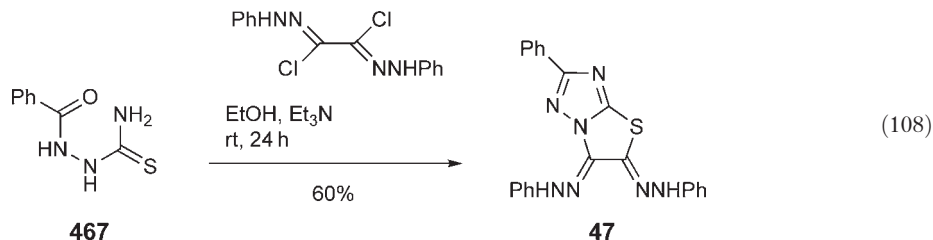
11.05.9.7.2(i) $\text{N1C2} + \text{O3}\{\text{N4}\}\text{C5C6C7C7a} \rightarrow 13\{4\}6$

The reaction of compounds **465** with an excess of aryl isocyanate in acetonitrile at reflux leads to the formation of imidazooxadiazolones **466**, via a Beckmann fragmentation that affords a presumed cyclic nitrone intermediate **187** (Equation 107) <1999SC3889>.



11.05.9.7.2(ii) $C5C6C\{7a\} + N1N2C3N4N5 \rightarrow 134\{7\}$

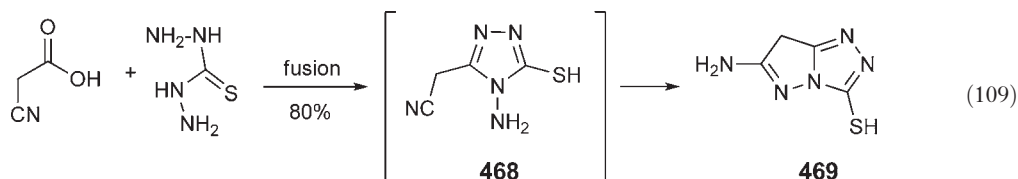
2,3-Bis-phenylhydrazono derivative of thiazolo[3,2-*b*][1,2,4]triazole **47** is obtained (Equation 108) by reacting bis-hydrazonoyl chloride with 1-benzoylthiosemicarbazide **467** <2002MI7>.



11.05.9.7.3 Two fragments providing 5 + 3 ring atoms: $5 + 3 \rightarrow (5,5)$

11.05.9.7.3(i) $C6C7 + C2N1\{N7\}C3a(N3)S4 \rightarrow 12\{4\}5$

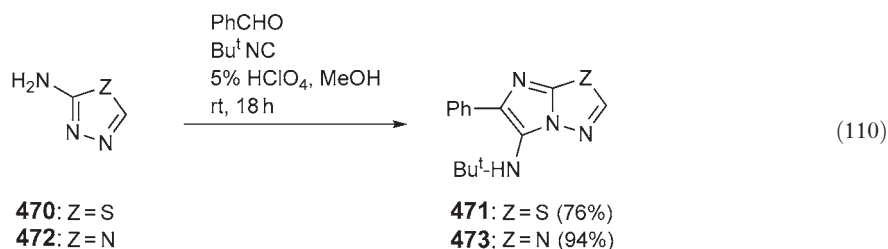
The reaction of cyanoacetic acid with thiocarbonylhydrazide in solid state at 180 °C for 15 min gives intermediate **468**, that spontaneously cyclizes to 6-amino-3-thiol-7*H*-pyrazolo[5,1-*c*][1,2,4]triazole **469** in 80% yield <2001PS(173)223> (Equation 109).



11.05.9.7.4 Three fragments: $2 + 2 + 3 \rightarrow (5,5)$

11.05.9.7.4(i) $C5 + C6 + N\{4\}N7C7a \rightarrow 13\{4\}7$

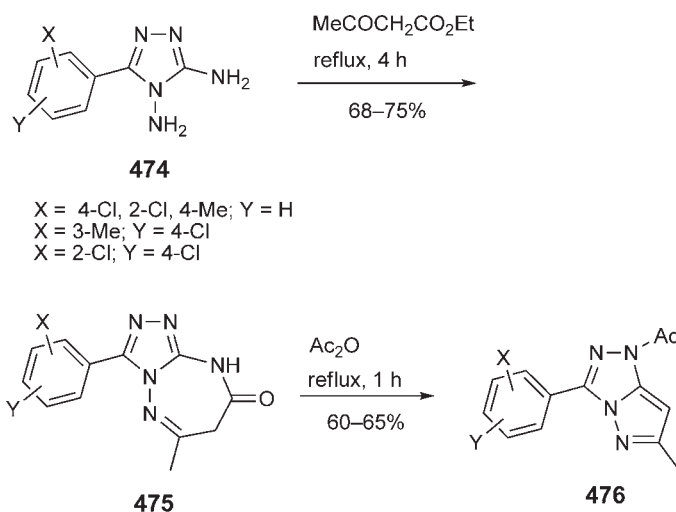
The reaction of 2-amino-1,3,4-thiadiazole **470** and 3-amino-1,2,4-triazole **472** with benzaldehyde and *tert*-butylisocyanide gives imidazo[2,1-*b*][1,3,4]thiadiazoles **471** and imidazo[1,2-*b*][1,2,4]triazoles **473**, respectively, in a one-pot process (Equation 110) <1998AG(E)2234>.



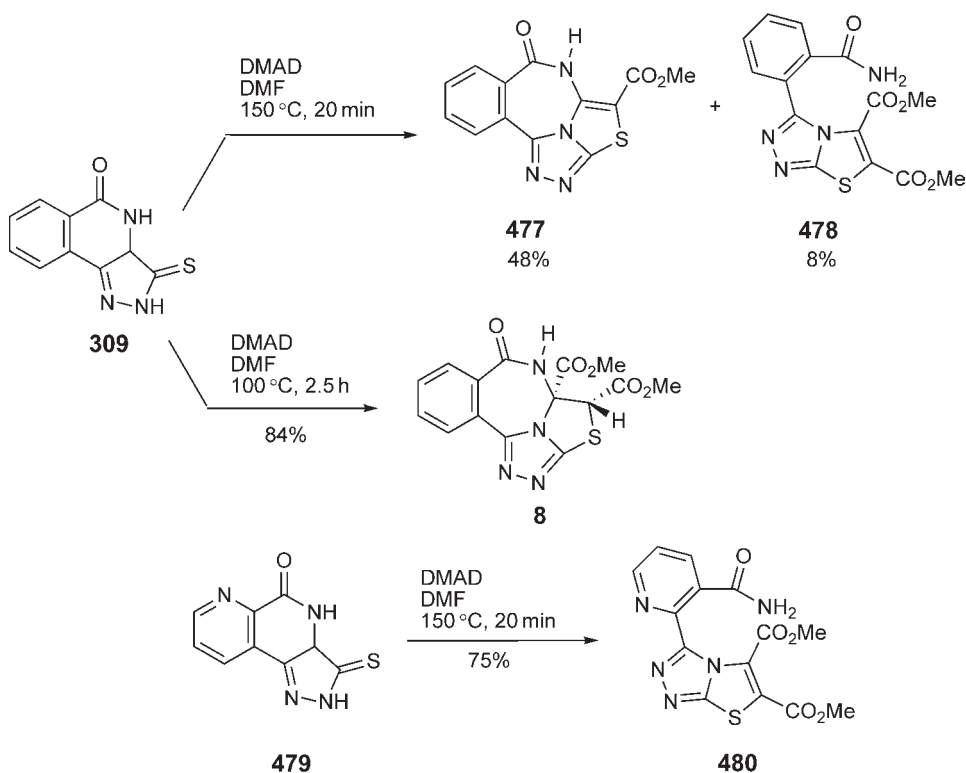
11.05.10 Ring Syntheses by Transformation of Another Ring

Triazolotriazepinones **475**, obtained by reaction of 4,5-diamino-3-aryloxymethyl-1,2,4-triazoles **474**, on heating with acetic anhydride undergo ring contraction reaction to yield 1-acetyl-3-aryloxymethyl-6-methyl-pyrazolo[5,1-*c*][1,2,4]triazoles **476** (Scheme 54) <2003IJC(B)2054>. This type of transformation has been previously documented by other authors <1974JHC751>.

[1,2,4]Triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3(2*H*)-thiones **309** undergo an unprecedented ring transformation on treatment with dimethyl acetylenedicarboxylate in DMF, resulting in a new method for the synthesis of thiazolo[2,3-*c*][1,2,4]triazole derivatives, which is strongly dependent on the reaction temperature and the



Scheme 54

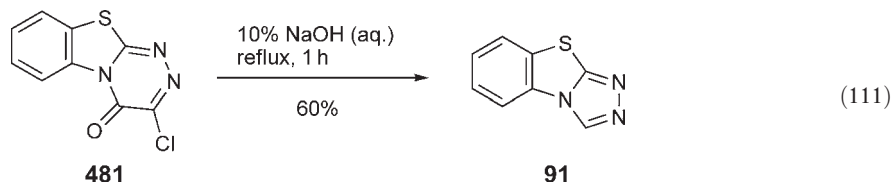


Scheme 55

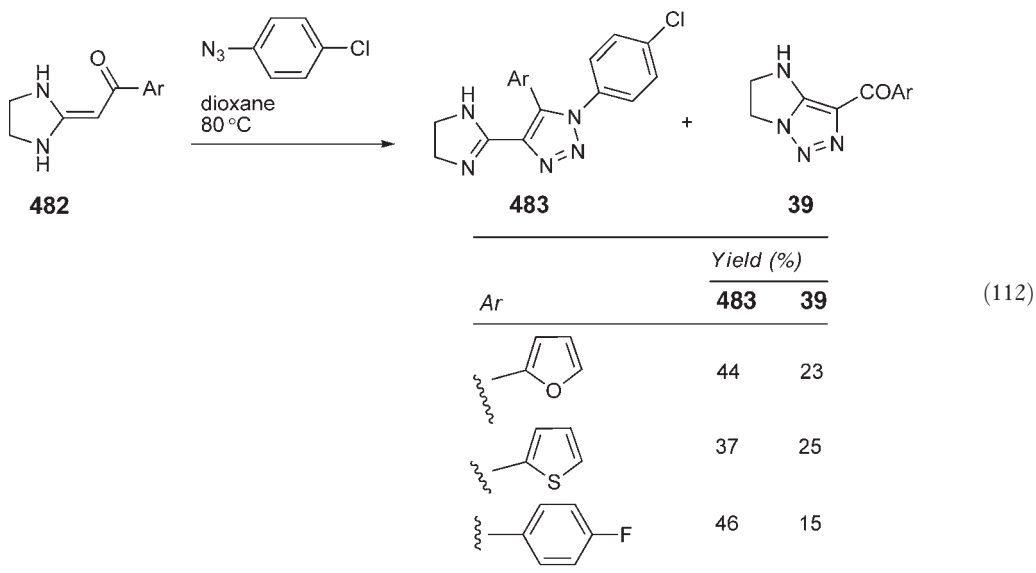
structure of the starting material (Scheme 55) <2001T7191>. For compound **309**, when the reaction is carried out at 150 °C for 20 min, products **477** and **478** are detected and isolated; however, when the reaction is performed at 100 °C for 2.5 h, compound **8** is isolated. Products **477** and **8** are the first representatives of a novel ring system. Moreover, the incorporated functionalities (alkoxycarbonyl and related groups) make the

subsequent couplings possible to produce new compounds with potential biological activities. Very interestingly, the azo derivative **479**, under the former experimental conditions, gives only compound **480** (Scheme 55) <2001T7191>.

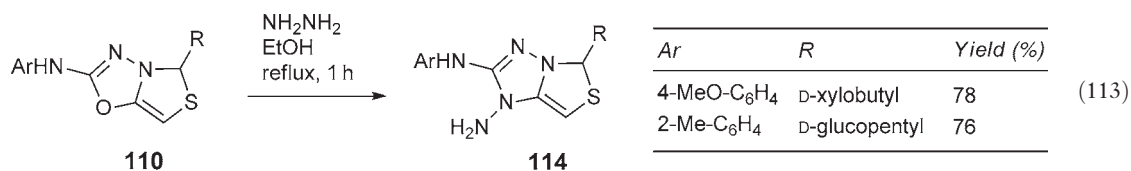
3-Chloro-1,2,4-triazino[3,4-*b*]benzothiazol-4*H*-one **481** gives the rearranged compound **91**, with a thiazolo[2,3-*c*][1,2,4]triazole nucleus, after refluxing with a 10% aqueous solution of NaOH (Equation 111) <1996IJC(B)842>.



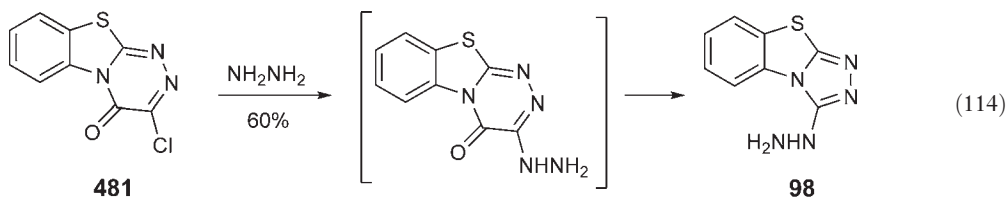
The aryl-substituted heterocyclic ketene aminals **482** react with 4-chlorophenyl azide to give polysubstituted 1,2,3-triazoles **483** and imidazo[1,2-*c*][1,2,4]triazoles **39** (Equation 112) <2000HAC387>. Polysubstituted 1,2,4-triazoles are formed by the nucleophilic attack of the α -carbon of the azide. Then, through the cyclocondensation and aromatization sequences, the fused heterocycles resulted by a 1,3-dipolar addition at first, and then through a Dimroth rearrangement and deamination of chloroaniline <1992JOC184>.



Thiazolo[4,3-*b*][1,2,4]oxadiazoles **110** react with hydrazine hydrate to give thiazolo[3,4-*b*][1,2,4]triazoles **114** (Equation 113) <2001IJC(B)440>.



3-Hydrazino-1,2,4-triazolo[3,4-*b*]benzothiazole **98** is obtained by heating 3-chloro-1,2,4-triazino[3,4-*b*]benzothiazole 4(*H*)-one **481** (Equation 114) <2005IJC(B)625>.



11.05.11 Important Compounds and Applications

11.05.11.1 Agrobiological Activity

11.05.11.1.1 Herbicidal activity

11.05.11.1.1(i) 12{4}7: NN/S

Bicyclic triazolone derivatives **484** and **485** <2002WO038562> (Figure 25) exhibit excellent, long-lasting, and selective herbicidal activity against a broad range of weeds at low dosage, and low toxicity against mammals and fish.

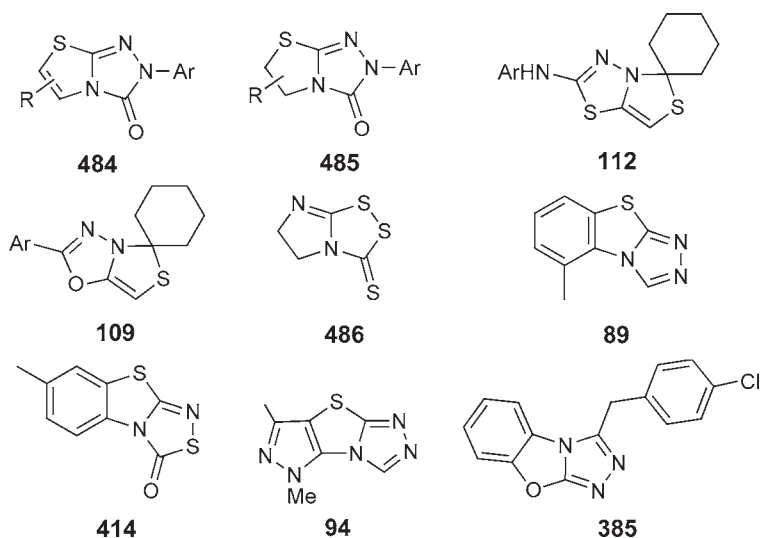


Figure 25

11.05.11.1.1(ii) 13{4}7: ON/N, SN/N

The molluscicidal activity of imidazo[2,1-*b*][1,3,4]thiadiazoles and imidazo[2,1-*b*][1,3,4]oxadiazoles, such as compounds **112** and **109** (Figure 25), have been evaluated against the snail *Lymnaea acumiata*, which is a vector of the giant liver flukes, *Fasciola gigantica* and *Fasciola hepatica* <2004IJC(B)901>.

11.05.11.1.1(iii) 134{7}: NNS/

2,6-Substituted-thiazolo[3,2-*b*][1,2,4]triazoles have been investigated showing high herbicidal activity against diseases of rice <2004JAP182623, 2002WO102809>.

11.05.11.1.2 Antifungal activity

11.05.11.1.2(i) 12{4}7: SS/N, NN/S, NS/S

Maneb **486** (Figure 25) is an ethylene bis-dithiocarbamate (EBDC) fungicide used in agriculture for the control of early and late blights in potatoes and tomatoes, as well as many other diseases in fruits, vegetables, field crops, and

ornamental plants. The toxic effects of EBDCs are usually associated with ethylenethiourea (ETU) and ethylenebis(isocyanate)sulfide (EBIS), the main metabolites of their hydrolysis and photolysis. EBIS is known to cause peripheral paralysis and thyroid dysfunction in rats. Liquid chromatography (LC) with diode array ultraviolet absorbance detection has been used for the analytical simultaneous determination of the fungicide Maneb **486** <2004JC(A) (1043)225> (Figure 25).

Compound **414** <1997H(45)1579> is structurally related to **89** (tricyclazole) (Figure 25), a well-known fungicide, which inhibits the biosynthetic pathway for melanin, because of its potent activity against rice blast disease caused by *Pyricularia oryzae*. Analogs of tricyclazole, such as **94** (Figure 25), poorly inhibit the growth and pigmentation of fungi tested and are less efficient than the parent compound <2004MI4>. Formulations containing tricyclazole have been described exhibiting bactericidal effects in preventing and treating rice blast and other fungal diseases of rice, vegetables, and tree fruits <2004CNP1478394>.

A series of benzoxazolo[3,2-*c*][1,2,4]triazoles have been synthesized and submitted to herbicidal and fungicidal testing <1997IJC(B)711>, the most active being compound **385** (Figure 25) in both analyses.

11.05.11.1.2(ii) 134{7} NNS/ system

Analogs of strobilurine, such as substituted thiazolo[3,2-*b*][1,2,4]triazoles at C-2, -5, and -6 positions of the heterocyclic skeleton, have been investigated as agrochemical fungicides <1999EUP909760>.

11.05.11.2 Pharmacological Activity

11.05.11.2.1 Antibacterial activity

Derivatives of several ring systems have been evaluated with respect to their antibacterial activity (Table 60).

Table 60 Antibacterials

<i>Ring system</i>	<i>References</i>
13{4}7: ON/N	1999IJC(B)1203
SN/N	2000EJM853, 2002MI11
12{4}7: NN/N	2006BMC3635, 2004MI9

Compounds **137** and **240** (Figure 26) showed a high degree of antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* comparable to that of sulfamethoxazole. However, they were found to show moderate activity against *Salmonella typhi*, *Pseudomonas aeruginosa*, and *Pneumococci* <2000EJM853>. These compounds were also evaluated for their preliminary *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* H37Rv strain using broth dilution assay methods; the results show that these compounds exhibited moderate to good antitubercular activity <2004BMC5651>. The antibacterial activity of compounds **111** (Figure 26) was determined against the following bacteria: *E. coli*, *P. aeruginosa*, *Bacillus subtilis*, and *Bacillus mycoides*. This evaluation showed that these compounds are moderately to highly active in the bacteria test at 600 µg/disc concentration <1999IJC(B)1203>.

11.05.11.2.2 Antifungal activity

Derivatives of several ring systems have been tested to be active as antifungals (Table 61).

Compounds **487** and **488** (Figure 26) showed activity against *Candida albicans* <2002IJC(B)403>. Products **489** (Figure 26) have been screened for antifungal activities against *Helicobacter oxyzae* and *Aspergillus flavus* <1997IJC125>.

Compounds **490** <2001IJC(B)500> (Figure 27) show good activity against *E. coli*, and **392** <2001IJC(B)500> (Figure 27) proved to be moderately active against *Aspergillus niger* <1999ZN(B)1589>. Compounds **491** <1998IJH23> (Figure 27) have been screened for antibacterial and antifungal activities against *S. aureus*, *E. coli*, and *C. albicans*; the nitro derivatives are considerable active against all species tested, while the chloro derivatives show mainly activity against *C. albicans*. Thiazolo[3,2-*b*][1,2,4]triazole derivatives such as **492** (Figure 27) have been found to be active against *P. aeruginosa* and *C. albicans* <1996IJH21>.

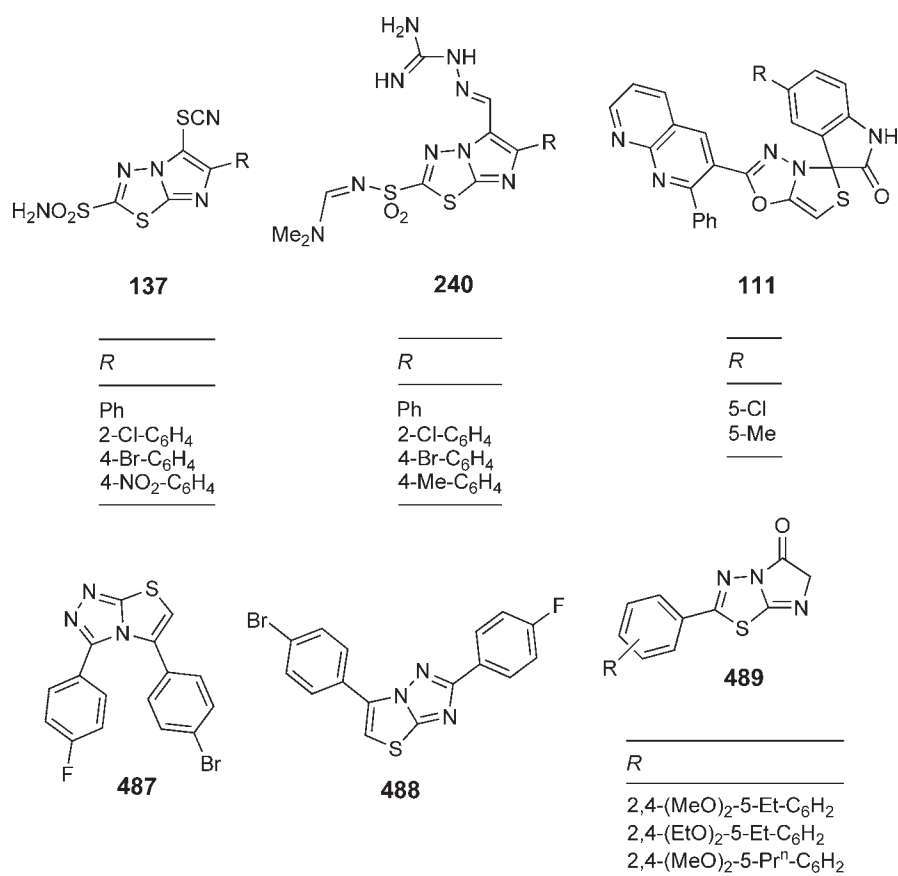


Figure 26

Table 61 Antifungals

Ring system	References
12{4}6: NN/N	2001PS(173)223
12{4}7: NN/S	2002IJC(B)403, 2001IJC(B)500, 1999ZN(B)1589, 1998IJH23, 2004PS(179)1019
13{4}6: NN/S	2002IJC(B)1314
13{4}7: SN/N	1997JIC125, 2003IJC(B)1463, 2001IJC(B)303, 2002WO072621
ON/N	1996IJC(B)385
134{7}: NNS/	2002IJC(B)403, 1996IJH21, 2005FAR14

Products **401** (Figure 28) are active against *C. albicans* and *C. albicans* ATCC <2004PS(179)1019>. Molecules **302** (Figure 28) have been evaluated for their fungicidal activity against *Pyricularia oryzae*, *Pseudoperonospora cubensis*, *Sphaerotheca fulginea*, *Phytophthora infestans*, and *Puccinia coronata*, and show moderate to strong activity <2002IJC(B)1314>. *In vitro* fungicidal activity of compounds **336** (Figure 28) has been tested against *Alternaria solani* and *Fusarium oxysporum* <1996IJC(B)385>. Compounds **166** (Figure 28) have been found active against *E. coli*, *S. aureus*, and *P. aeruginosa* <2003IJC(B)1463, 2001IJC(B)303>. 6-Amino-3-thiol-7H-pyrazolo[5,1-*c*][1,2,4]-triazole **469** <2001PS(173)223> (Figure 28) is highly antifungal active against *Aspergillus ochraceus*, *Penicillium chrysogenum*, and *A. flavus* (MIC values were 50–75 µg ml⁻¹); this result indicates that this compound is nearly as active as the standard fungicide mycostatine (MIC 30 µg ml⁻¹).

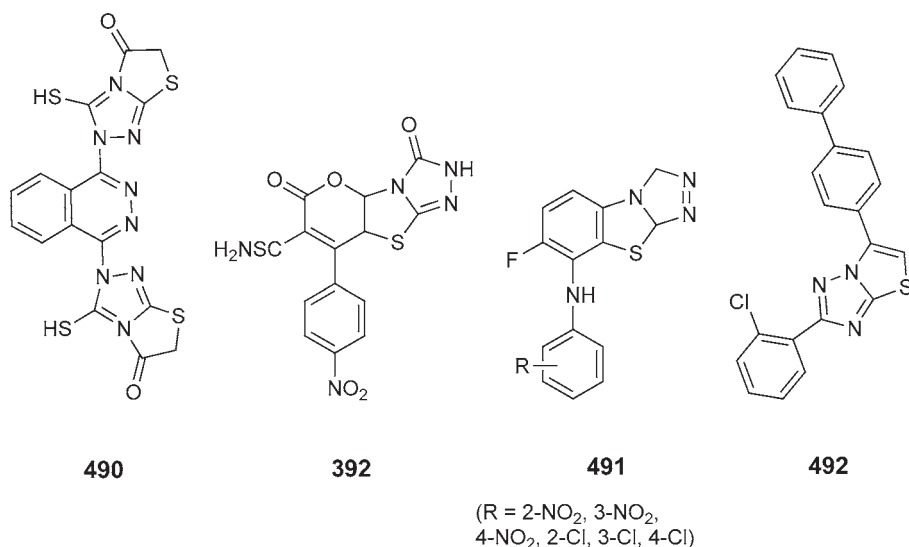


Figure 27

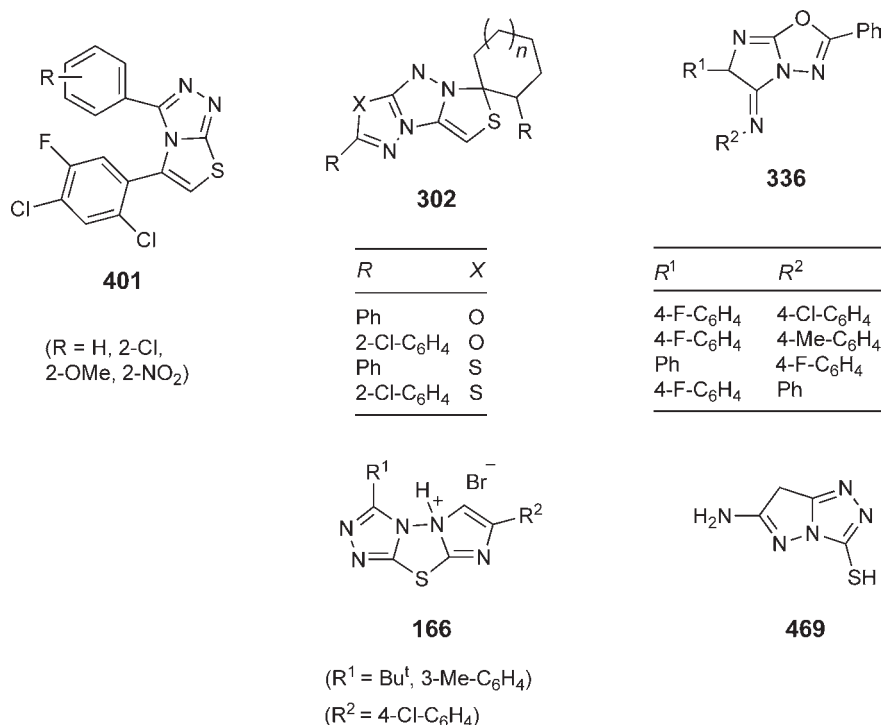


Figure 28

11.05.11.2.3 Various pharmacological activities

Compounds with [5,5] (2N1)-fused systems have been found to be pharmacologically active (Tables 62 and 63).

Compound 493 (Figure 29) has been investigated as a potential human immunodeficiency virus (HIV) integrase inhibitor <1997JMC920>. The antiviral activity of products 114 (Figure 29) has been tested against the viral species *Chenopodium amaranticolor*; the most active compounds (Ar=4-MeOC₆H₄, 4-MeC₆H₄; R=xylobutyl) exhibited antiviral activity equivalent to virazole at 1000 ppm <2001IJC(B)440>. Compound

243 (Figure 29) was tested in several cell lines in a one-dose *in vitro* primary cytotoxicity assay, and passed the criteria for activity (20–29% growth percentages); next, it was scheduled for evaluation against the full panel of 60 human tumor cell lines at minimum of five concentrations at 10-fold dilution, showing very favorable cytotoxicity <2003EJM781>.

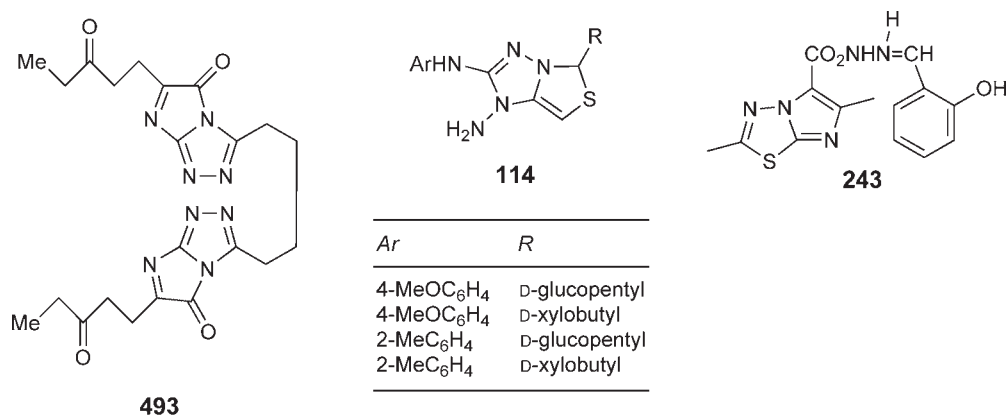


Figure 29

Benzothiazolotriazoles play a vital role in the field of medicinal chemistry. Some of the benzothiazolotriazoles **396** (Figure 30) are reported to possess antimicrobial and antitubercular biological activities <2004IJH89, 2004MI2>. Compounds **228** and **229** <2001AF916> (Figure 30) have been evaluated for antitubercular activity against the H₃₇Rv strain of *M. tuberculosis* with promising compounds for further development.

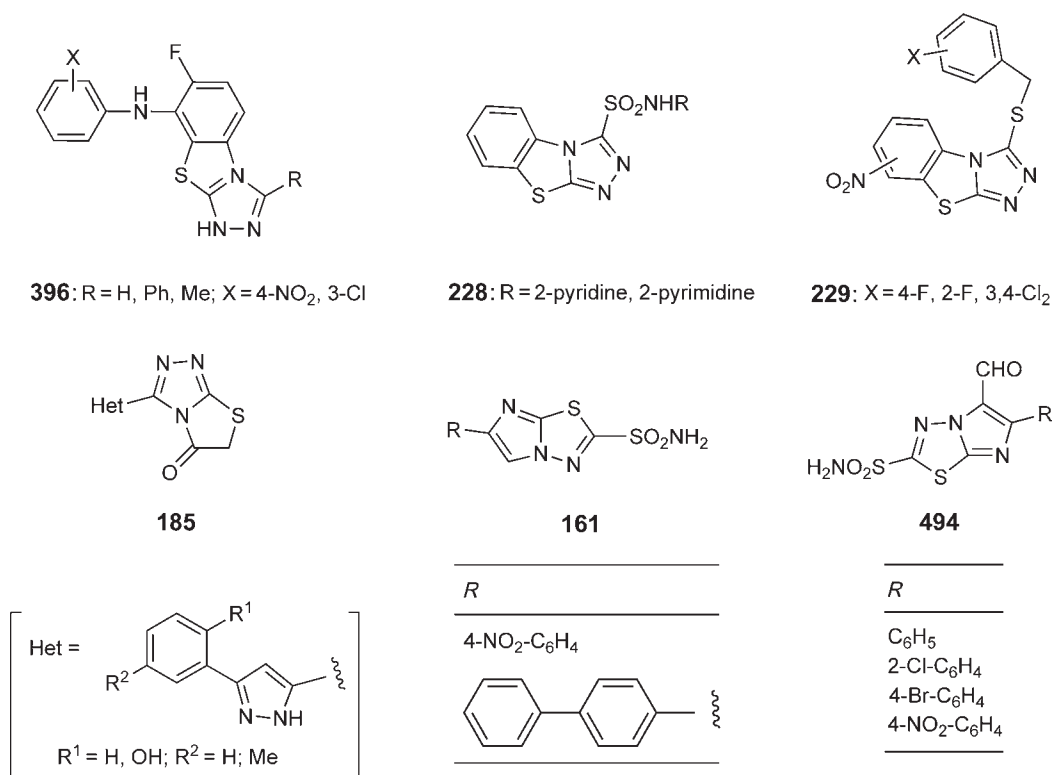


Figure 30

Compounds **185** and **161** (Figure 30) have been also evaluated in antimicrobial activity tests <2001AF916>. Compound **185** (Figure 30) showed maximum activity against *Klebsiella pneumoniae*, and was highly active against *Proteus vulgaris* and moderately active against *E. coli* <2001JC(B)636>. Imidazo[2,1-*b*][1,3,4]thiadiazoles **161** (Figure 30) have been investigated for their anticonvulsant and analgesic properties <1996AF949>. The cytotoxic properties of compounds **494** (Figure 30) against several human tumor cell lines have been analyzed <1999AF858>.

Compound **330** (Figure 31) is a potent and very selective cyclooxygenase-2 (COX-2) inhibitor <1997BMCL57>. Three-dimensional quantity–structure activity relationship (3-D QSAR) analysis of this compound and other members of a series of 5,6-diarylthiazolo[3,2-*b*][1,2,4]triazoles has been carried out <2004MI5>.

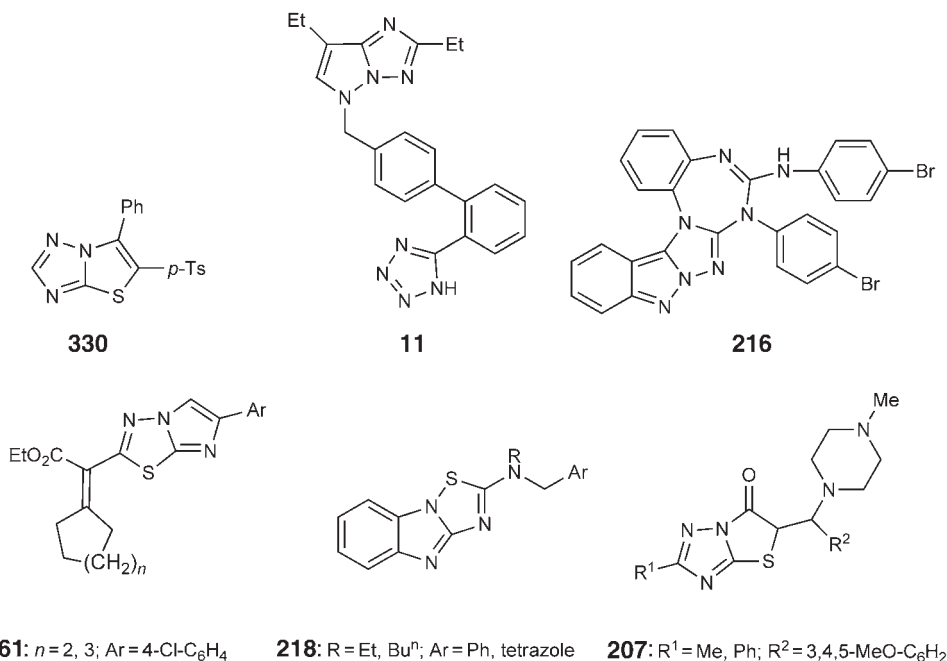


Figure 31

6-(4-Bromophenyl)amino-7-(4-chlorophenyl)indazolo[2',3':1,5][1,2,4]triazolo[4,3-*a*]-1,3,5-benzotriazepine **216** (Figure 31) is as a novel inhibitor of COX-2 with anti-inflammatory activity in animal models <2000SL1411, 2004MI6>. YM358 **11** (Figure 31) has been identified as a potent nonpeptide angiotensin II receptor antagonist, and promising lead compound for the treatment of cardiovascular diseases <1997MI2>. Compounds **161** (Figure 31) have been investigated as potential leishmanicides <1997BMCL651>. Heterocycles **139** (Figure 21) have been prepared as analogs of losartan, and the biological evaluation has shown that they are moderate PDE 4 inhibitors <1998BMCL505>. Compounds **207** (Figure 31) have been tested for their anti-inflammatory activity and ulcerogenic potential in mice <1999AF1006>; particularly, product **495** (Figure 32) showed higher anti-inflammatory activity than its analog derivatives and indomethacin <2001AF470>.

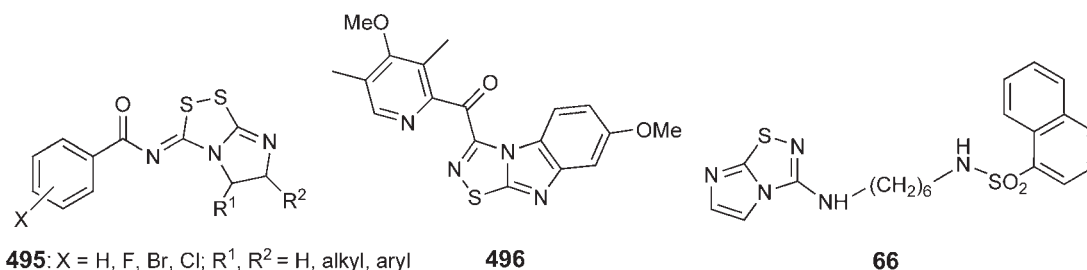


Figure 32

A family of arylimidazodithiazoles **495** (Figure 32) incorporating various substituents at 5- and 6-positions in the heterocyclic system have been prepared as inverse agonists of G protein-coupled receptor 6 (GPR6) <2001USP062765>. 3-Substituted [1,2,4]thiadiazolo[4,5-*a*]benzimidazoles and analogs have been reported as proton pump inhibitors; concretely, **496** (Figure 32) can be used in the treatment of peptic ulcers by inhibition of the proton pump enzyme H^+/K^+ -ATPase <1997WO9731923, 2000USP6093738>. Sulfonamide derivatives of imidazo[1,2-*d*][1,2,4]thiadiazoles and [1,2,4]thiadiazolo[4,5-*a*]benzimidazoles have been investigated as inhibitors of fibrin cross-linking and transglutaminases. Compound **66** (Figure 32) inhibits the factor XIIIa ($IC_{50} = 0.52 \mu M$) <2005MI2, 2003EUP1348710>.

11.05.11.3 Materials

Several polyheterocyclic compounds containing a condensed 1,2,4-triazole nucleus, such as 3,5-disubstituted thiazolo[2,3-*c*][1,2,4]triazoles, are thermostabilizers for polypropylene and polycapromide <2003MI2>. Triazolo[3,4-*b*][1,3]benzothiazolidicarbonitrile derivatives are used to prepare hexazocyclanes-fluorophores as active media for liquid and solid lasers, scintillators, and for transformation of short-wave radiation to long-wave radiation <2004RUP2238276>.

11.05.11.3.1 Polymer Langmuir–Blodgett films

A polymer film containing a strong colored compound, such as a cyanide dye, has attracted much attention as a key material for digital recording systems such as CD-R (compact disk recording). The introduction of a large dyestuff, such as 3-(2'-aminomethyl)-6-*tert*-butyl-7-[4'-[*N*-ethyl-*N*-(2-methylsulfonylaminoethyl)amino]-2'-methylphenylimino]pyrazolo[3,2-*c*][1,2,4]triazole **497** (Figure 33), in a polymeric Langmuir–Blodgett film was successful <1998L5555>.

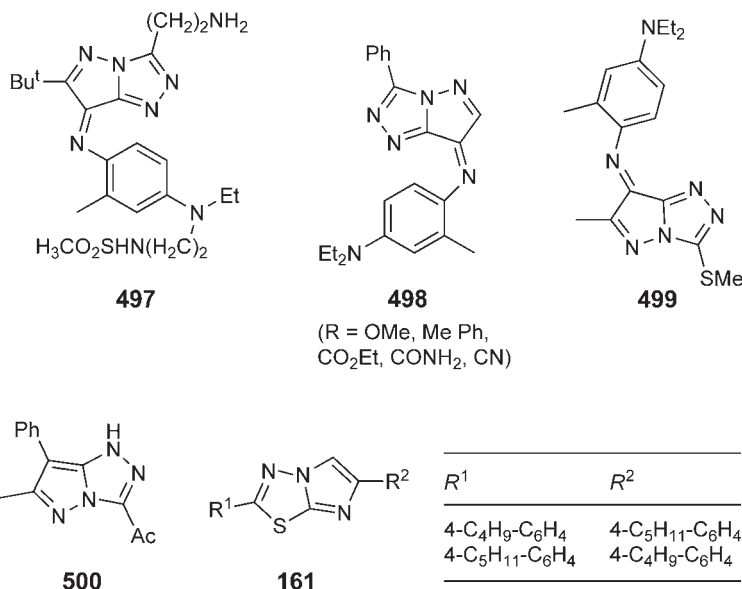


Figure 33

11.05.11.3.2 Photographic materials

[5,5] (2N1)-Fused heterocycles have been found of major application as photographic materials. Azomethine dyes are used in conventional three-color (yellow, magenta, and cyan) photographic imaging <1998JAP10264541, 2003PPS563>.

11.05.11.3.2(i) Magenta coupler

Various dyes obtained by oxidative coupling of the appropriate pyrazolotriazoles such as **498** (Figure 33) <2003PPS563, 1999JPC(B)9867> are used as magenta dye-forming couplers for color photography <2003JAP149775>.

12{4}7: NN/S <1999JAP11052530>.

124{7}: NNN/ <1997JAP09269573>.

13{4}5: NN/N <2005JAP170974>.

11.05.11.3.2(ii) Free radical photoinitiators

A new class of free radical photoinitiators such as **499** (Figure 33) <1998CM3555> have been developed based on pyrazolone azomethine dyes.

11.05.11.3.2(iii) Colorant dispersion compositions

Various imidazotriazoles are used as colorant compositions showing good particle dispersion stability and color picture light resistance <2003JAP192978>.

11.05.11.3.2(iv) Inkjet printing

Imidazotriazoles are employed as heterocyclic components in inkjet printing inks with good image formation <2000JAP103996>.

Pyrazolo[1,5-*b*][1,2,4]triazole azomethines were investigated and used for manufacturing of inks, optical filters, thermal transfer printing materials, and toners. Some of them were prepared and formulated into a water-thinned jet printing ink <2002JAP256164, 2000EUP1035172>.

11.05.11.3.2(v) Inhibitors for corrosion of metals

Corrosion of steel in acid solution has practical importance; hence, efforts to develop more efficient and environmentally compliant methods to prevent corrosion have been ongoing <1996SM(78)103>. Compounds with functional groups containing heteroatoms such as alkylimidazole <1996MI1> and triazole <1996MI2> compounds, which can donate lone pair electrons, are found to be particularly useful as inhibitors for corrosion of metals and have been used as effective inhibitors for steel in acidic media.

Related pyrazole-containing compounds such as **500** and **161** (Figure 33) have shown similar properties in 1 M H₂SO₄ using electrochemical methods; the choice of these molecules is based on the presence of an electron cloud on the aromatic rings, the presence of π electrons of N=N, C=N, C=O, and C=S is expected to affect the corrosion of carbon steel <2003MI1>.

11.05.11.3.3 Hair dyes

Some [5,5] (2N1)-fused heterocycles have found major applications as hair-dyeing compositions <2004EUP1428510, 1997WO35552>.

11.05.11.3.3(i) 126{7}: NNN/ system

Preparations containing 1*H*-7-amino-3,6-dimethylpyrazolo[1,5-*c*][1,2,3]triazoles <1999EUP923929> are oxidative hair dyes.

11.05.11.3.4 Liquid crystals

Imidazo[2,1-*b*][1,3,4]thiadiazoles **161** (Figure 33), containing practically planar and rigid heteroaromatic systems with two condensed heterocycles, which have different π -conjugation, have been identified as useful fragments for liquid crystal molecules <2002MI6>.

11.05.11.4 Analytical Applications

LC is currently used extensively in the photographic industry. One application is to quantify some of the components of photographic paper. As demands to reduce analysis time increase, an analytical method that can give improved productivity is required. One possible alternative to LC is capillary electrochromatography (CEC). In a recent paper, this analytical protocol was applied to separate some color photographic paper components <2002MI1>.

11.05.12 Further Developments

Bakavoli *et al.* have synthesized new 3-substituted [1,2,4]triazolo[3',4';2,3][1,3]triazolo[4,5-*b*]quinoxalines by the cyclocondensation of [1,3]thiazolo[4,5-*b*]quinoxaline-2(3*H*)-one hydrazone with aroyl chlorides, trimethylorthoformate, or triethylorthoacetate; ¹H NMR data are provided <2006PS(111)99>.

Starting from 1-substituted-16-(12*H*-11-oxa-17-thia-15-aza-cyclopenta[*a*]phenathrene-16-yl)-hydrazines, the reaction with formic acid or acetic anhydride gave novel 1-substituted-6*H*-5-oxa-7-thia-8,9,10a-triaza-pentaleno[4,5-*a*]-phenathrenes, and 1-substituted-10-methyl-6*H*-5-oxa-7-thia-8,9,10a-triaza-pentaleno[4,5-*a*]phenathrenes, whose *in vitro* antibacterial activity has been also evaluated; ¹H NMR and MS data are described <2006EJM891>.

Bicyclic chiral triazolium salt **382** <2002AG(E)1743> has been used in new catalytic enantioselective crossed aldehyde-ketone benzoin cyclizations <2006SL2431, 2006AG(E)3492>.

The Groebke-type multi-component reaction between 3-amino-1,2,4-triazole, aromatic aldehydes and benzylic isonitriles afforded *N*-alkylidene-4*H*-imidazo[1,2-*b*][1,2,4]triazol-6-amines in moderate to good yields <2006TL6891>.

The synthesis and the antifungal, anti-inflammatory and analgesic effects <2006MI4>, or antimicrobial activity <2006MI5> of novel 1-alkyl-2-alkylthio-1,2,4-triazolobenzimidazole derivatives have been communicated.

Heravi and co-workers have reported the solvent-free regioselective cyclization of 3-allylmercapto-1,2,4-triazoles to thiazolo[3,2-*b*][1,2,4]triazoles over sulfuric acid adsorbed in silica gel <2006PS(181)377>, or over HZSM-5 zeolite using microwave irradiation <2006MI6, 2006IJH411>.

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Biographical Sketch



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His present interests include the development of new synthetic methodologies in carbohydrates, free radical chemistry, organometallic chemistry (Pauson–Khand reaction, transition metal (PtCl_2 , AuCl)-mediated cycloisomerization of polyunsaturated precursors), and synthesis/biological evaluation of heterocyclic systems (CSIC reaction, tacrine analogs).



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In addition, she is Scientific Consulting of the Pharmaceutical Company (Laboratorios Farmacéuticos Rovi S.A.) and involving in common research R&D projects.

11.07

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 2:2

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11.07.1 Introduction

This chapter reviews bicyclic systems containing two fused five-membered rings with one bridgehead nitrogen and two other heteroatoms (nitrogen, oxygen, and sulfur) in each ring. Among the possible structural backbones, 16 have been so far found in the literature and are listed in **Figure 1**. All these fused-ring systems have been previously reviewed in CHEC-II(1996) <1996CHEC-II(8)199>, and no additional fused-ring system has been substantiated since then. Except for scarce examples, all the literature published since 1995 dealt with [1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazole including one review <1998H(48)561> summarizing the syntheses, reactivities, spectroscopic properties, and biological activities of these compounds.

Because little, in terms of chemical reactivity or synthesis, has appeared since the last edition, most of the information gathered in this chapter has been described in CHEC-II(1996) <1996CHEC-II(8)199>.

11.07.2 Theoretical Methods

There are little data on theoretical chemistry associated with such ring systems. In a series of 5,5-fused heterocycles, the inner salt **1** displays a substantial aromatic character as indicated by the aromaticity index *I*(5,5) with a value of 82 <1987T4725>.

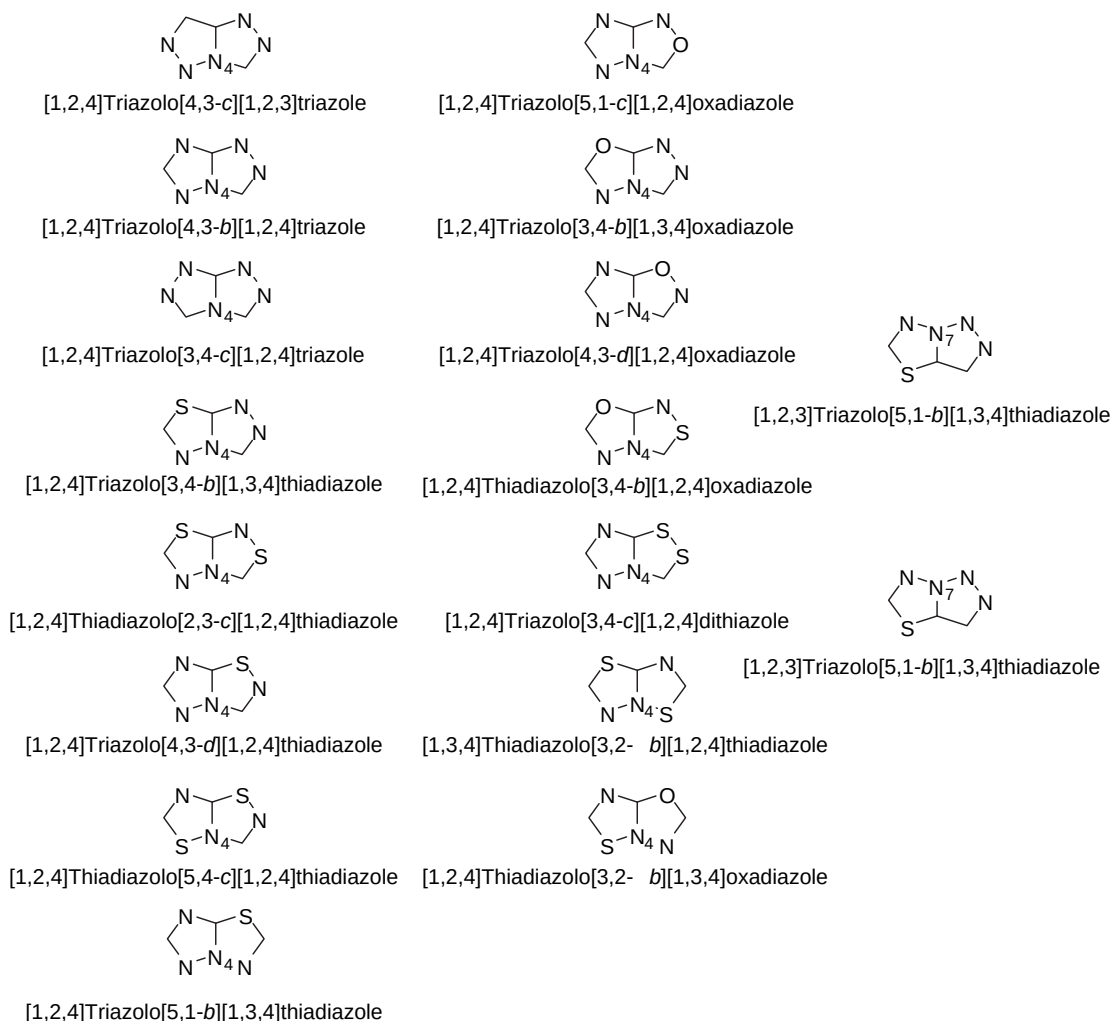
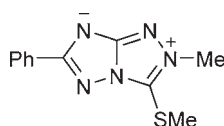


Figure 1



1

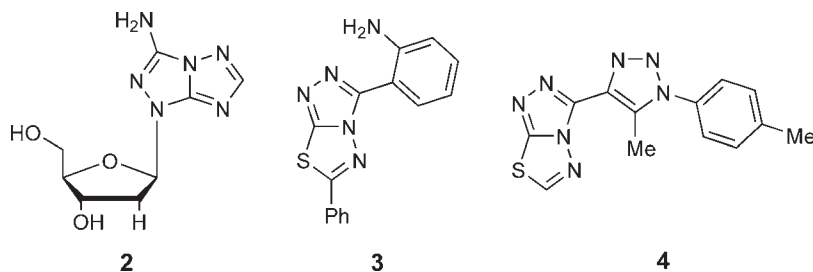
11.07.3 Experimental Structural Methods

11.07.3.1 X-Ray

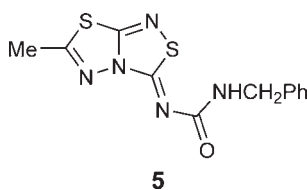
The first single-crystal structure was reported for 6-methyl-3-phenyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole in which the nucleus of the triazolothiadiazole system was planar confirming the aromatic character of the 10 π -electron system <1974CSC7>. This is generally the case for the entire series of 5,5-fused heterocycles.

X-Ray analyses of azapentalenes have been used to determine the structure of products from reactions with ambiguous reaction sites or with concomitant rearrangements. Thus, the X-ray structure of the β -D-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole **2** establishes that glycosylation has occurred at the N-1 position; furthermore, it also shows that the compound is the β -anomer. In addition to intermolecular hydrogen bonds in the crystal structure an intramolecular hydrogen bond is extended from OH-5 to N-7 <1984NN187>. The X-ray structure of the inner salt of compound **1** has been determined

and its mesoionic form has been characterized <1985BCJ735>. The structure of 3-(2-aminophenyl)-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **3** is based on X-ray crystallography; it indicates that in the course of its formation (cf. Section 11.07.3.1) a thioaroyl group has migrated and has been incorporated into the thiadiazole ring of the product <1989LAI055>. The structure of 3-[5-methyl-1-(4-methylphenyl)-2,3-dihydro-1*H*-1,2,3-triazol-4-yl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **4** has been solved <2002JST1>. As in analogous compounds, the substituents did not conjugate with the fused central core <2005JCS61>.



The unexpected structure of the 3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole **5** has been established from its X-ray analysis <1994T7019>. The X-ray analyses of crystal structures also reveal the interplanar angle of the fused heterocycles, which varies only slightly. In keeping with its aromatic character, the mesoionic system **1** is planar <1985BCJ735>. As in other fully conjugated azapentalene systems, the dihedral angle of the fused five-membered rings does not strongly deviate from coplanarity; the dihedral angle in **3** is 1.9° <1989LAI055>, which is close to the angle found in other fused five-membered rings <1978AHC(22)183> (cf. literature cited in <1984NN187,1985BCJ735>). Only in **2**, the dihedral angle between the planes of the two fused triazole rings is significantly larger as the value is 3.6° <1984NN187>.



11.07.3.2 NMR Data

The (5,5) (2N2)-fused heterocyclic system contains three ring carbon atoms, one fusion carbon atom, and one additional nonfusion carbon atom in each five-membered ring. Only scattered ¹H and ¹³C nuclear magnetic resonance (NMR) data are available for these systems.

11.07.3.2.1 ¹H NMR data

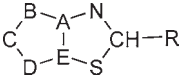
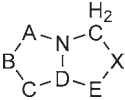
Most of the (5,5) (2N2)-fused heterocyclic systems are fully substituted aromatic systems and therefore they do not have any hydrogens attached to the ring. Very little is reported on C-unsubstituted compounds. Methine groups are generally part of a ring azomethine moiety and are either linked to a fusion atom C or N or to a nonfusion atom N or S (Table 1).

Table 1 ¹H NMR data for ring methine groups in (5,5) (2N2) systems

<i>X-CH=N</i>	<i>Solvent</i>	δ (range)(ppm)	<i>Reference</i>
X-(fusion atom): C	DMSO- <i>d</i> ₆	7.86	1992JHC713
X-(fusion atom): N	DMSO- <i>d</i> ₆	7.2–7.9 (under arom. H)	1993IJH135, 2002EJM511
	DMSO- <i>d</i> ₆	5.5	1992IJB467
	CDCl ₃	7.86	1987CB965
X-(nonfusion atom): N	DMSO- <i>d</i> ₆	8.02	1984NN187, 1993JHC1289
X-(nonfusion atom): S	DMSO- <i>d</i> ₆	6.2	1992IJB714
	DMSO- <i>d</i> ₆	7.7–8.14 (under arom. H)	1990IJB135, 2002JST1

The resonance range of protons attached to a saturated ring carbon atom is at lower field, as it would be expected for aminal-, hemiaminal-, or thioaminal-type protons. On the other hand, there are two publications <1990IJB176, 1990H(31)2147> that report signals at high field ($\delta = 1.3\text{--}1.6$ ppm) which do not conform with this assignment but which may be mistaken (Table 2).

Table 2 ^1H NMR data for hydrogen attached to saturated ring carbon atoms in (5,5) (2N2) systems

Structural unit	Solvent	δ (range)(ppm)	Reference
	DMSO- d_6	7.86	1993IJH135
	DMSO- d_6	1.3–1.6	1990IJB176, 1990H(31)2147
	DMSO	7.04–6.65	1998SC3974
	CDCl_3	6.3	1990IJB135, 1996IJB718
	X = N	5.55–5.9	1992PS99
	X = O	5.82–5.89	1992PS99

11.07.3.2.2 ^{13}C NMR data

Most ^{13}C NMR data on ring carbon atoms are reported for [1,2,4]triazolo[4,3-*c*][1,2,4]triazoles and scarce data are available for other (5,5) (2N2)-systems. Systematic correlation is difficult and is mostly influenced by the substituents attached to the ring. Chemical shift for the carbons can range from 120 to 170 ppm, the fused one being usually between 150 to 160 ppm <1993JHC1289, 1977OMR508, 1985BCJ735, 1985H(23)2613, 1984TL5427, 1986T2121, 1987CB965, 1992JHC713, 1994T7019, 1991IJB435, 1999CPA215, 2000MRC210, 2001MRC411, 2005JCS61>.

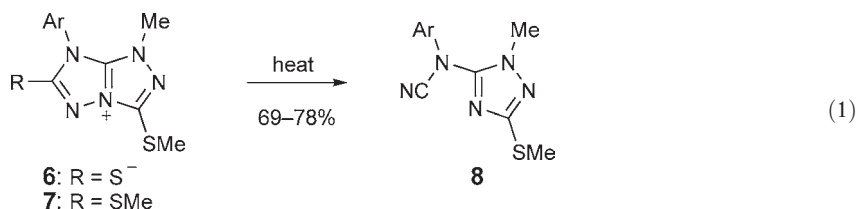
11.07.4 Thermodynamic Aspects

The ring-chain equilibrium position of substituted diazoalkylthiadiazoles is influenced by substituents and solvents and has been determined by NMR spectroscopy <1992JHC713> (cf. Section 11.07.8.1.3).

11.07.5 Reactivity of Fully Conjugated Rings

11.07.5.1 Thermally Induced Ring Opening

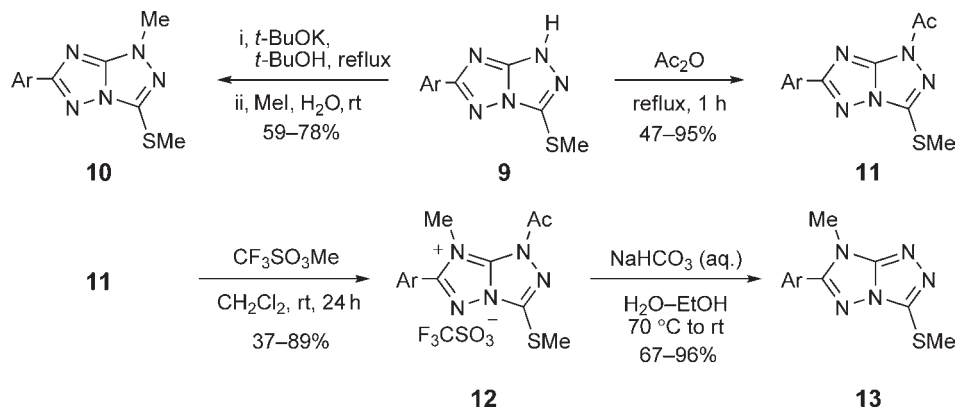
Both the inner salts **6** of anhydro 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium hydroxides and their methylation products **7**, when heated above the melting points, suffer loss of sulfur or of methyl iodide and sulfur, respectively, and concomitant ring opening into 1-methyl-3-methylthio-5 (arylcyanamino)[1,2,4]triazoles **8** takes place (Equation 1) <1984TL5427, 1986T2121>.



11.07.5.2 Electrophilic Attack at Ring Nitrogen

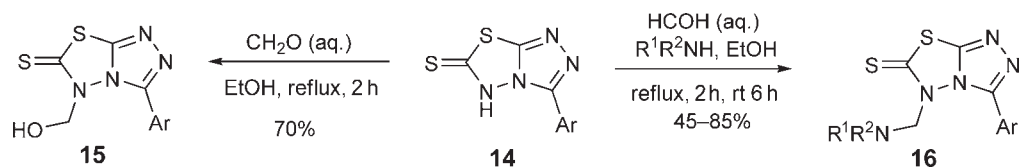
11.07.5.2.1 *N*-Methylation and *N*-acetylation

Alkylation or acylation takes place at the nitrogen in position 1 when 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole **9** is treated with methyl iodide or acetyl chloride, furnishing compound **10** or **11**, respectively <1983S415>. The 7-methyl isomers **13** are obtained after conversion of compounds **9** into the 1-acetyl derivatives **11** followed by methylation with methyl trifluoromethanesulfonate to give the 1-acetyl-6-aryl-7-methyl-3-methylthio-1*H*-[1,2,4]triazolo[4,3-*b*]-[1,2,4]triazol-7-ium-trifluoromethanesulfonates **12**, which upon treatment with aqueous sodium carbonate afford the 7-methyl derivatives **13** <1985BCJ735>.

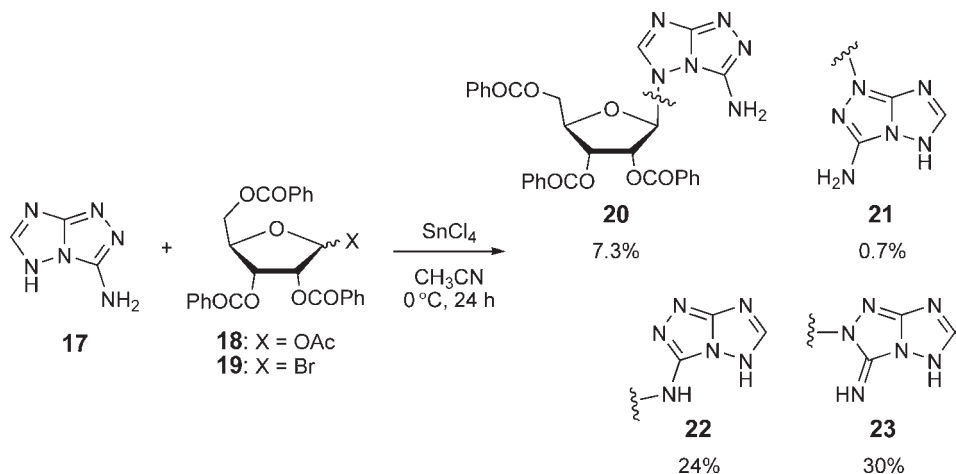


11.07.5.2.2 *N*-Hydroxymethylation and *N*-glycosylation

The reaction of 3-(2-benzofuranyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione **14** with formaldehyde in ethanol gives the 5-(hydroxymethyl) derivative **15**. The same reaction in the presence of a primary or secondary amine in ethanol affords the corresponding Mannich base **16** <1992IJB167>.



Glycosylation of 3-amino-5(7)*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole **17** with 1-*O*-acetyl- 2,3,5-tri-*O*-benzoyl-D-ribofuranose **18** or 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide **19** can be selective or nonselective, depending on the reaction conditions (Scheme 1). In the presence of trimethylsilyl triflate or boron trifluoride etherate, the

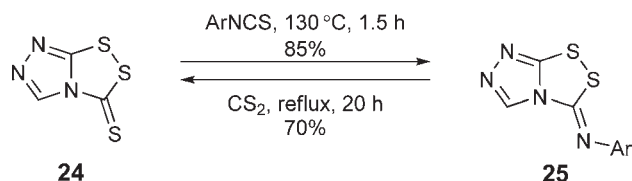


Scheme 1

1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl) derivative **20** is obtained in low yield as sole product. However, the same reaction using stannic chloride as Lewis acid furnished a mixture of four products **20–23** (Scheme 1) <1993JHC1289>.

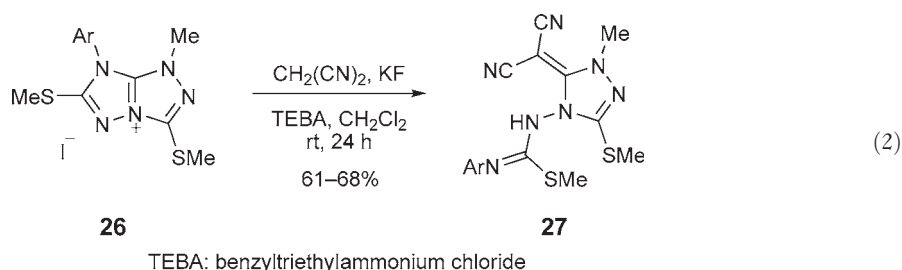
11.07.5.2.3 Exchange of a functionalized ring carbon with carbonic acid derivatives

The 3-arylimino and 3-thione functions of the 5-aryl-3*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazoles **24** and **25** are formally interchanged upon heating **25** with carbon disulfide and **24** with arylisothiocyanates, respectively <1983ABC1017>.

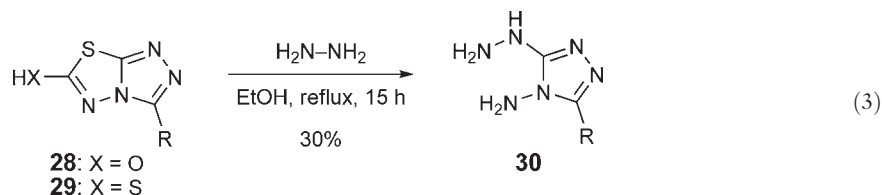


11.07.5.3 Nucleophilic Attack at Carbon

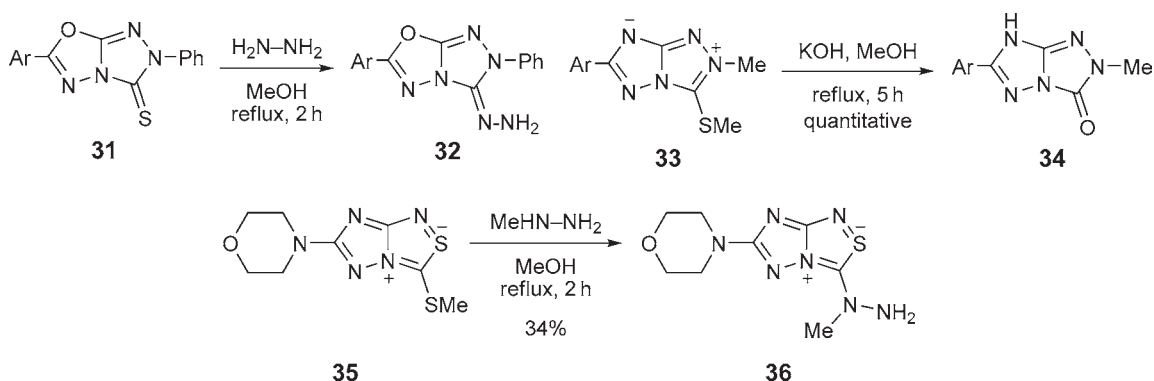
The nucleophilic attack on the bridging carbon results in two different reactivities. Usually ring opening occurs. Malononitrile under hydrolytic solid–liquid phase-transfer conditions attacks the methiodides **26** at the fusion carbon atom, thereby inducing ring opening and the formation of 4-(*N*-aryl-*S*-methylisothioureido)-5-(dicyanomethylene)-1-methyl-3-methylthio-4,5-dihydro-1*H*-[1,2,4]triazoles **27** (Equation 2) <1986T2121>.



The 3-hetaryl-substituted 6-hydroxy- and 6-thiol[1,2,4]triazolo[3,4-*b*][1,2,4]thiadiazoles **28** and **29** on treatment with hydrazine hydrate gave the 3-hetaryl-substituted 4-amino-5-hydrazino-[1,2,4]triazoles **30** (Equation 3) <1990IJB135>.



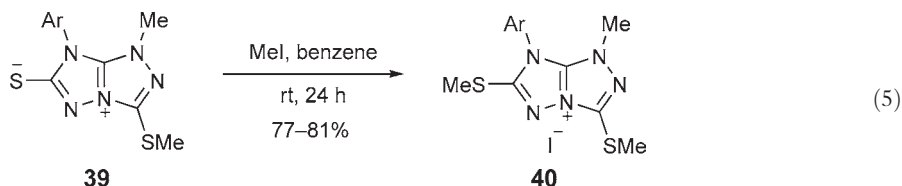
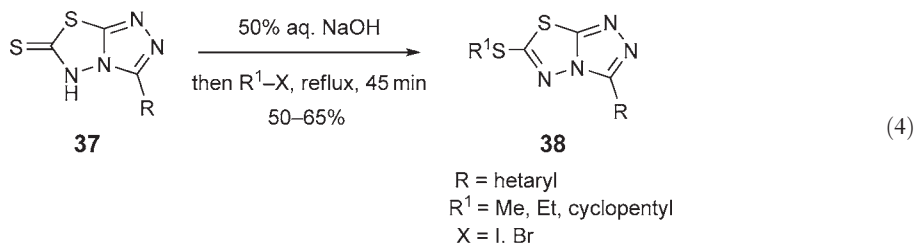
In some cases, however, a formal external heteroatom exchange takes place. The thione **31** was converted into the corresponding hydrazone **32** with hydrazine <1984JCCS315>. Alkaline hydrolysis of the inner salts **33** results in the displacement of the methylthio group and the formation of the 7*H*-[1,2,4]triazolo[4,3-*b*] [1,2,4]triazol-3(2*H*)-ones **34** <1985BCJ735>. By analogy, displacement of methylthio group of 3-methylthio-6-morpholino-1,2,4-triazolo[5,1-*c*]-[1,2,4]thiadiazole **35** with methylhydrazine gave compound **36** <2000JHC261>.



11.07.6 Reactivity of Substituents Attached to Ring C-Atoms

11.07.6.1 S-Alkylation

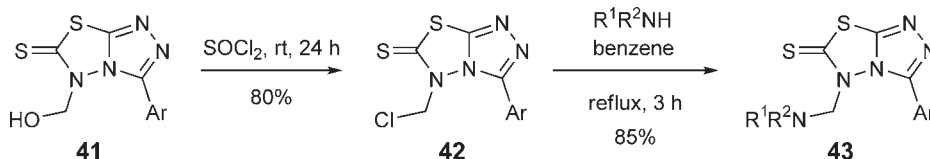
When thioxo (or thiol) derivatives (as part of a thiourea function incorporated into the heterocyclic system) are present, effective *S*-alkylation is observed. Thus, the 3-heteroaryl-substituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thiones **37** dissolved in sodium hydroxide solution react with alkyl halides to afford the corresponding 6-alkylthio derivatives **38** (Equation 4) <1992IJB167>. The mesoionic compounds **39**, inner salts of anhydro-7-aryl-1-methyl-3-methylthio-6-sulfonyl-[1,2,4]triazolo[4,3-*b*][1,2,4]triazolium hydroxides, are methylated with methyl iodide to give the corresponding quaternary salts **40** (Equation 5) <1984TL5427, 1986T2121>.



11.07.7 Reactivity of Substituents Attached to Ring Heteroatoms

11.07.7.1 Conversion of *N*-Hydroxymethyl Groups

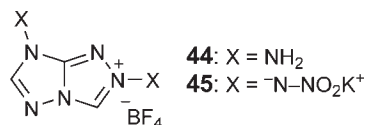
The hydroxymethyl side chain of 3-(2-benzofuranyl)-5-(hydroxymethyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thione **41** can be converted to chloromethyl derivative upon treatment with thionyl chloride; amines can displace this chloride to provide the corresponding aminal **43** (Scheme 2) <1992IJB167>.



Scheme 2

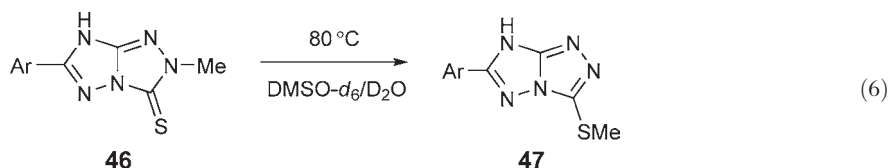
11.07.7.2 Nitration of *N*-Amino Groups

The nitration of the 2,7-diamino-7*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]triazolium ion **44** with nitronium tetrafluoroborate affords after workup with base the corresponding potassium bis(*N*-nitro imides) **45** <1991IZV1239>.



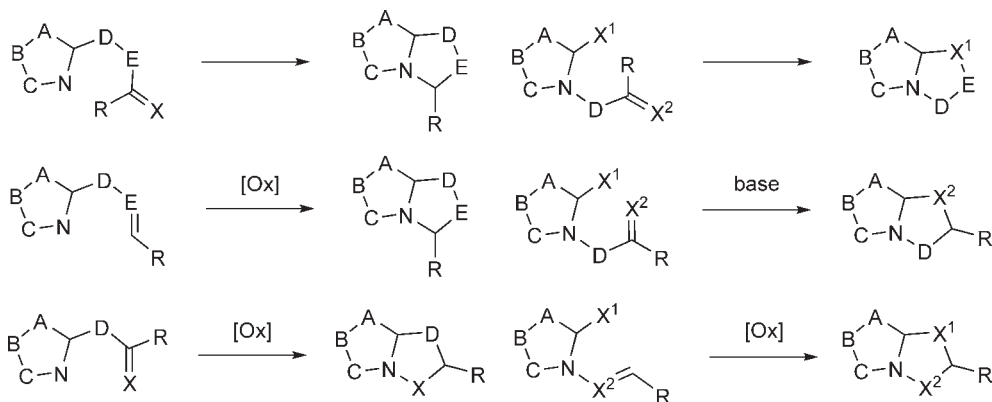
11.07.7.3 *N*- to *S*-Methyl Migration

On heating, 6-aryl-2-methyl-7/*f*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole-3(2*H*)-thiones **46** undergo *N*-to-*S* migration of the methyl group, yielding the rearranged products **47** (Equation 6) <1985BCJ735>.



11.07.8 Ring Syntheses Classified by the Number of Ring Atoms in Each Component

The number of methods available for the synthesis of bicyclic systems containing two fused five-membered rings with one bridgehead nitrogen can be summarized in a few general reactions: dehydrative ring closure, oxidative Schiff base cyclization, and base-induced closure (Scheme 3). One-pot reactions involving precursor synthesis followed by cyclization are also known.

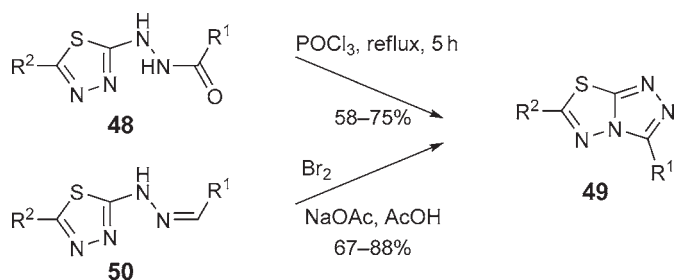


Scheme 3

11.07.8.1 Ring Closure of a Substituent Providing Three Ring Atoms: (5)3 → (5,5)

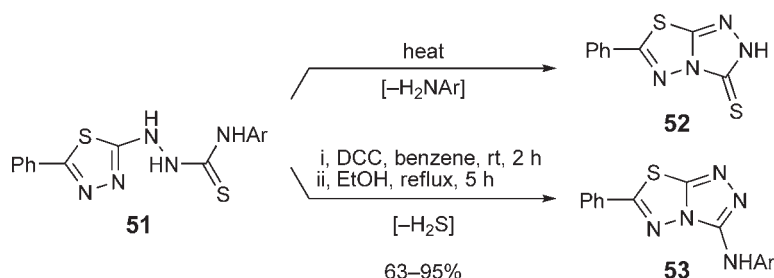
11.07.8.1.1 *NN*/*NS*: [1,2,4] Triazolo[3,4-*b*][1,3,4]thiadiazole

The 5-substituted 2-acylhydrazino[1,3,4]thiadiazoles **48** are cyclized with POC1₃ to give the corresponding 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **49**. The same compound **49** is also obtained from 5-substituted 2-benzylidenethydrazino[1,3,4]thiadiazoles **50** upon oxidative cyclization with bromine (Scheme 4) <1990IJB135>.



Scheme 4

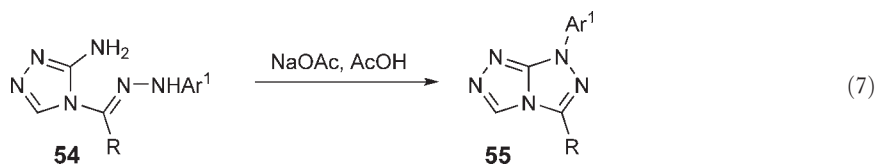
The 2-[4-aryl(thiocarbamoylhydrazino)]-5-phenyl[1,3,4]thiadiazoles **51** can react in two ways. Upon heating, reaction leads to cyclized 6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole-3(2*H*)thiones **52** and, on the other hand, the thiosemicarbazides **51** undergo cyclodesulfurization affording [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **53** when treated with dicyclohexylcarbodiimide (Scheme 5) <1986JHC1339>.



Scheme 5

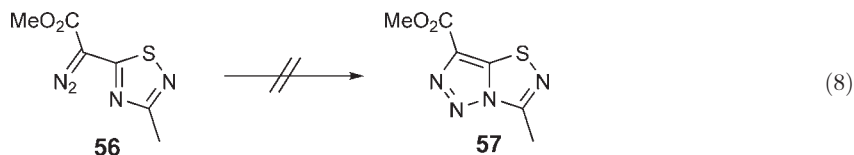
11.07.8.1.2 NN/NN: [1,2,4]Triazolo[3,4-*c*][1,2,4]triazole

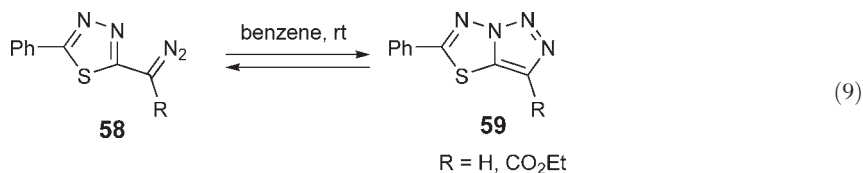
In the presence of sodium acetate in acetic acid, the arylhydrazones **54** (available from the reaction of ω -halogen- ω -(arylhydrazono)acetophenones with 3-amino[1,2,4]triazole) undergo cyclization to yield 3-aryl-1-aryl-1*H*-[1,2,4]-triazolo[3,4-*c*][1,2,4]triazoles **55** (Equation 7) <1987CB965>.



11.07.8.1.3 NN/NS: [1,2,3]Triazolo[5,1-*b*][1,3,4]thiadiazole

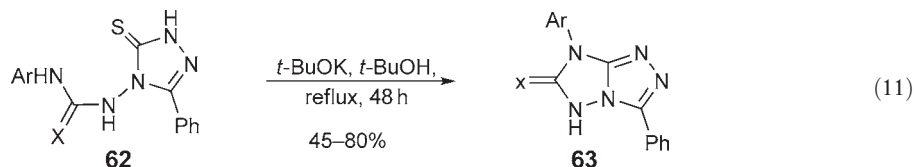
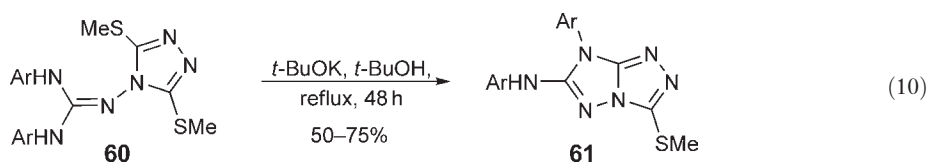
Whereas methyl 5-(3-methyl[1,2,4]thiadiazolyl)diazoacetate **56** shows no tendency to cyclize to 7-methoxycarbonyl-3-methyl[1,2,3]triazolo[3,4-*b*][1,2,4]thiadiazole **57**, the 5-(1-diazoalkyl)substituted [1,3,4]thiadiazoles **58** are in equilibrium with the fused bicyclic form, the [1,2,3]triazolo[5,1-*b*][1,3,4]thiadiazoles **59** <1988BSB795, 1992JHC713>. The latter ring-closed form **59** prevails in the solid state as indicated by infrared (IR; KBr disk). The chain/ring equilibrium of the diazoimine/triazole forms is shifted toward the open-chain diazo form **58** by raising the temperature and by using less polar solvents (Equations 8 and 9).



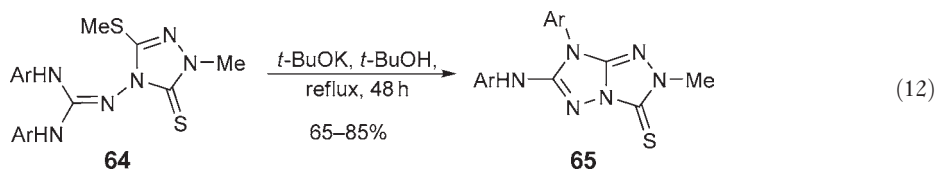


11.07.8.1.4 NN/NN: [1,2,4]Triazolo[4,3-*b*][1,2,4]triazole

4-(*N,N'*-Diarylguanidino)-3,5-bis(methylthio)[1,2,4]triazoles **60** undergo base-induced cyclization to give 7-aryl-6-arylamino-3-methylthio-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles **61** (Equation 10) <1988H(27)161>. Similarly, the cyclization of the *N*-substituted 4-ureido and 4-thioureido derivatives of 3-phenyl-4,5-dihydro-1*H*-[1,2,4]triazole-5-thiones **62** affords 7-substituted 5*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-6(7*H*)-one and -triazole-6(7*H*)-thiones **63**, respectively (Equation 11) <1991RRC619>.

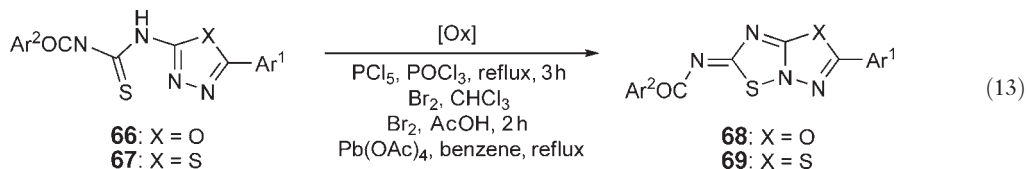


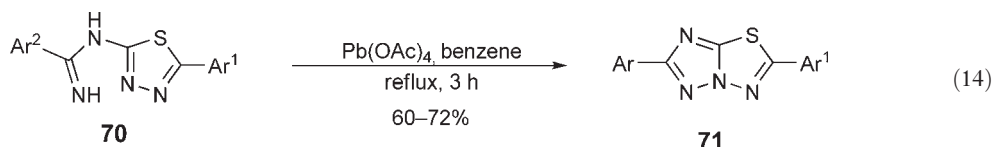
In the case of 4-(*N,N'*-diaryl)guanidines **64**, base-induced cyclization occurs at carbon bearing the methylthio to give the corresponding 7-aryl-6-arylamino-2-methyl-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-3(2*H*)-thiones **65** (Equation 12) <1986H(24)3363, 1987JP(1)2667>.



11.07.8.1.5 ON/SN: [1,2,4]Thiadiazolo[3,2-*b*][1,2,4]oxadiazole; SN/SN: [1,2,4]Thiadiazolo[3,2-*b*][1,2,4]-thiadiazole; SN/NN: [1,2,4]Triazolo[5,1-*b*][1,3,4]thiadiazole

Oxidative (dehydrogenative) cyclization of 2-(*N*-aroylthioureido)-5-aryl[1,3,4]oxadiazoles **66** and -thiadiazoles **67** affords 6-(aroylimino)-2-aryl-6*H*-[1,2,4]thiadiazolo[3,2-*b*][1,3,4]oxadiazoles **68** and -[1,3,4]thiadiazolo[3,2-*b*][1,2,4]thiadiazoles **69**, respectively (Equation 13). Phosphorus pentachloride, bromine and lead tetraacetate have been used to accomplish these cyclizations <1988IJB185, 1988IJB997>. The same cyclization of 2-aryl-5-(arylamidino)[1,3,4]thiadiazoles **70** gives 2,6-diaryl[1,2,4]-triazolo[5,1-*b*][1,3,4]thiadiazoles **71** (Equation 14) <1991IJB435>.

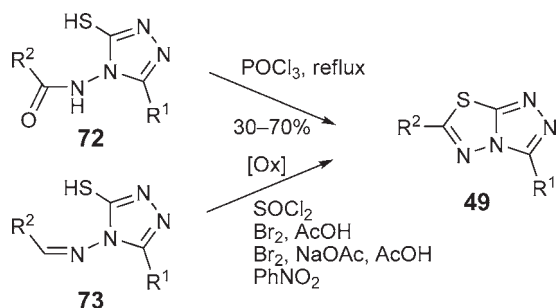




11.07.8.2 Ring-Closure of Two Adjacent Substituents Providing Two and One Ring Atoms: (5)2,1 $\rightarrow$ (5,5)

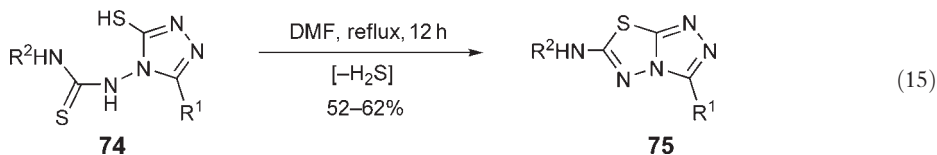
11.07.8.2.1 NN/NS: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole

Treatment of 4-arylamino-5-thiol[1,2,4]triazoles **72** with POCl_3 induces a dehydrative cyclization to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **49** (Scheme 6) <1990IJB135, 1984JHC1689, 1988JCCS393, 1993PS171>. The same fused heterocycles **49** can be obtained from the cyclization of 5-substituted-2-acylhydrazino[1,3,4]thiadiazoles **48** (cf. Section 11.07.8.1.1). Compound **49** can also be obtained under oxidative conditions using hydrazone **73** as starting material. The following oxidants have been used: bromine, thionyl chloride, or phosphorus pentachloride (Scheme 6) <1986LA1540, 1990IJB135, 1990M221, 1991JIC341, 1992FA305, 2003IJB2010>.

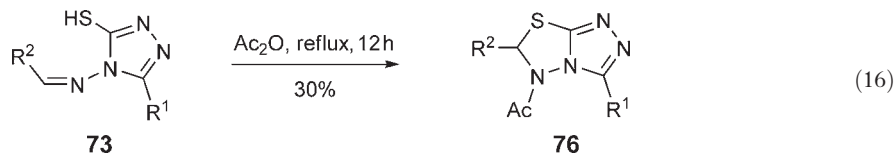


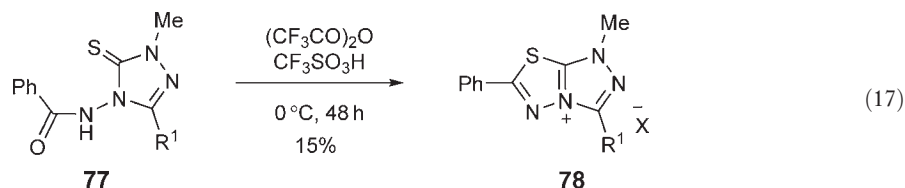
Scheme 6

Upon heating in dimethylformamide (DMF) at reflux temperature, the 4-thioureido-5-sulfonyl[1,2,4]triazoles **74** undergo cyclization to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **75** (Equation 15) <1983S411, 1988IJB576, 1988ABC1229>.



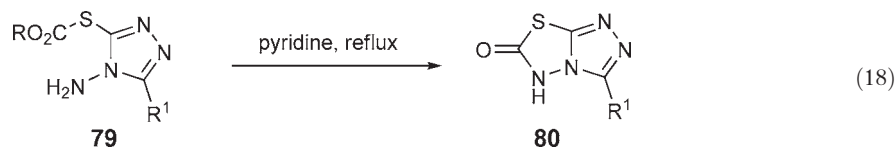
The Schiff base derivatives **73** of the 3-hetaryl-substituted 4-amino-3-thiol-1,2,4-triazoles, on treatment with acetic anhydride, undergo cyclization to give the corresponding 3-substituted-5-acetyl-5,6-dihydro-6-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **76** (Equation 16) <1990IJB135>. Similar treatment of 4-(*N*-benzoylamino)-4,5-dihydro-1-methyl-3-methylthio-1*H*-[1,2,4]triazole-5-thione **77** leads to the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazolium trifluoromethanesulfonate **78** (Equation 17) <1986LA1540>.



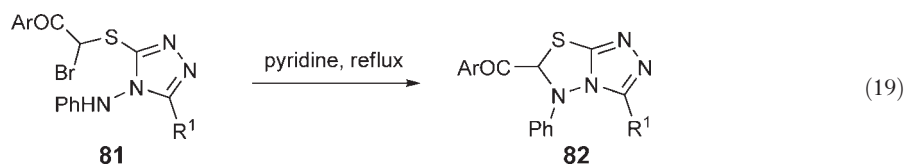


11.07.8.2.2 NN/NS: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole

Refluxing the 4-amino-3-ethoxycarbonylthio-5-phenyl-4*H*-[1,2,4]triazole **79** in pyridine induces cyclization to 3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6(5*H*)-one **80** (Equation 18) <1991RRC619>.

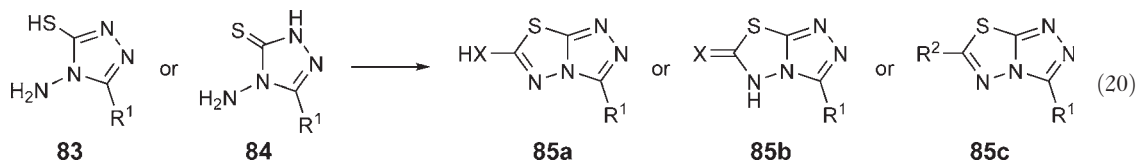


Heating to reflux a pyridine solution of 3-substituted-5-(1-aryl-1-bromo)methylthio-4-phenylamino-4*H*-[1,2,4]triazoles **81** (available from the corresponding 1,2,4-triazoles with phenacyl bromides and subsequent ultraviolet (UV) light-induced bromination) affords 3-substituted-6-aryl-5,6-dihydro-5-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **82** (Equation 19) <1993IJH135>.



11.07.8.3 Formation of the Second Ring by Insertion of a One-Atom Ring Member between Two Adjacent Substituents at the First Ring, Each Providing One Atom for the Second Ring: (5)1,1 + 1 → (5,5) NN/NS: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole

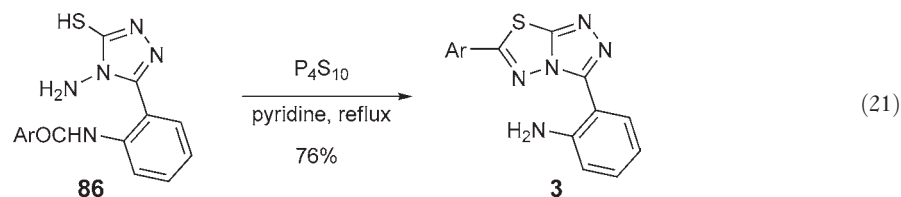
The most widely used method for the preparation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **85** employs 4-amino-5-thio-4*H*-[1,2,4]triazoles **83** or 4-amino-1,2,4-triazole-5(4*H*)-thiones **84** as starting materials. The reaction of the triazoles **83** or **84** with carbonic acid derivatives furnishes [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles with a heteroatom substituent (N, O, S) at position 6; the O- and S-functions are formulated as 6-hydroxy and 6-thio derivatives **85a** or as thiadiazol-(5*H*)6-ones and -thiadiazol-(5*H*)6-thiones **85b**, respectively; reaction with carboxylic acid derivatives provides the 6-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **85c** (Equation 20; Table 3).



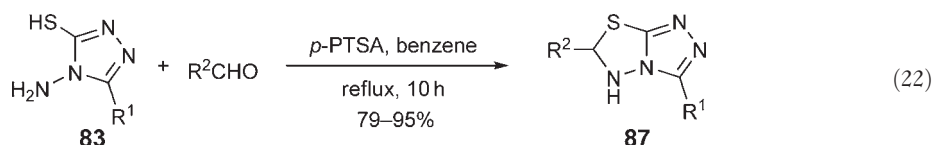
On treatment with phosphorus pentasulfide, 4-amino-5-thio-4*H*-[1,2,4]triazoles **86** are converted into 6-aryl-3-(2-aminophenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **3**. This transformation is presumed to involve three steps: first, the transformation of the amide into the thioamide; second, transfer of the thioaroyl group from the phenylamino side chain to the *N*-amino group of the triazole ring; and, finally, cyclodehydrosulfurization leading to **3** (Equation 21) <1989LAI055>.

Table 3 Formation of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **85** from carbonic acid derivatives

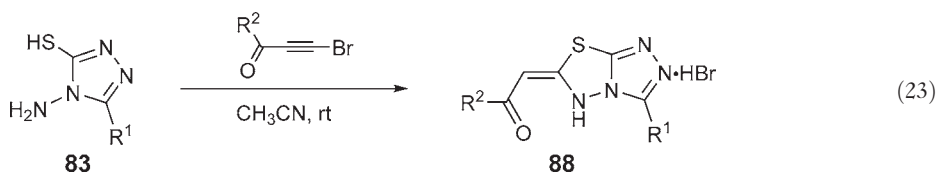
Reagent	Structure	X	Reference
CS ₂ , base	85a	N	1988MI102, 1988IJB128, 1989JIC330, 1989FA703, 1990SUL239, 1991PJC1297, 1992IJB714
	85b	S	1987JHC1173, 1988JIC49, 1991JIC474, 1992IJB167, 1992IJH211, 1993MI127, 1996IJB745, 1996SC3827, 2001SC2447, 2002EJM511
BrCN	85a	N H	1986JHC1339, 1986MI607, 1987JHC1173, 1991IJH61, 1991H(32)1897
RN=C=S	85a	R N	1983S411, 1986MI607, 1987JHC1173, 1991IJH61, 1991H(32)1897, 1992IJB714
RCO-N=C=S	85a	RC O N	1988JIC49, 1991IJH61, 1991SUL167, 1991H(32)1897, 1992CHJ59, 1994MI220
ClCO ₂ Et, base	85a	O	1990IJB135
	85b	O	1991SUL167
R ² CO ₂ H, POCl ₃	85c		1983IJB712, 1984IJB793, 1986IJB566, 1986MI607, 1987JHC1173, 1988JCCS393, 1989JHC177, 1989FA703, 1989JCCS353, 1989MI1028, 1989MI35, 1990H(31)2147, 1990IJB135, 1990IJB176, 1990MI49, 1990SUL239, 1991JIC250, 1991JIC341, 1991JIC474, 1991MI129, 1991CCL277, 1991FA1489, 1991RRC619, 1991SUL167, 1992IJB467, 1992IJB673, 1992IJB714, 1992FA305, 1992IJH211, 1992CHJ59, 1992MI193, 1993MI127, 1993MI115, 1993MI512, 1993MI56, 1993MI397, 1993IJH19, 1993MI101, 1993PS171, 1994MI74, 1998JIC465, 1998JCCS535, 1999PJC1203, 2001SC2447, 2002EJM511
R ² CO ₂ Cl	85c		1987MI395, 1992IJB167, 1988JCCS393, 1991PJC1297, 1997JHC1255
R ² CO ₂ COR ³	85c		1987MI395, 1989MI35, 1991PJC1297, 1993PS171
R ² CN	85c		1994KGS137, 2001SC2447
HCONMe ₂	85c		1990IJB135



The condensation of 4-amino-5-thiol-4*H*-[1,2,4]triazoles **83** with aldehydes (or ketone) in the presence of an acid catalyst affords 3,6-disubstituted-5,6-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **87** (Equation 22) <1988MI102, 1990IJB176, 1990H(31)2147, 1991RRC619, 1992IJB167, 1998PS41, 1998IJB498>.

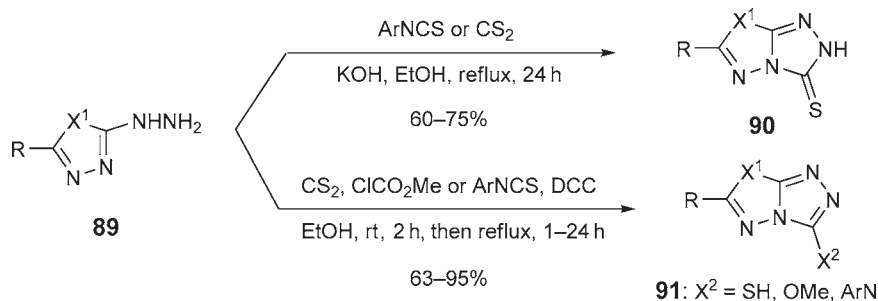


Treatment of 4-amino-3-phenyl-5-thio-4*H*-[1,2,4]triazole **83** with bromoacylacetylenes gives the corresponding 6-(acylmethylene)-5,6-dihydro-3-phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazohydrobromides **88** (Equation 23) <1988ZOR2151>.



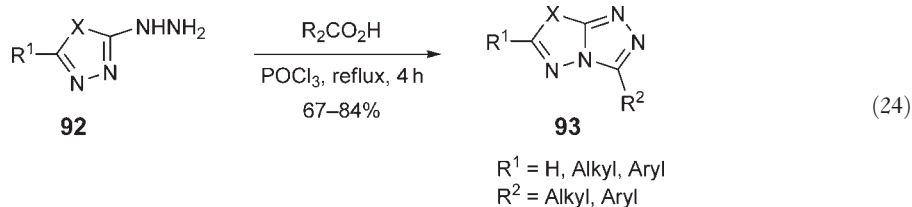
11.07.8.4 Formation of the Second Ring by Insertion of a One-Atom Ring Member between a Substituent at the First Ring, Providing Two Atoms and the Adjacent Ring Atom: (5)2 + 1 → (5,5)

11.07.8.4.1 *NN/NO*: [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazole; *NN/NS*: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole
Hydrazines of type **89** react with various carbonic acid derivatives to furnish cyclized product. Under basic conditions (KOH), in the presence of carbon disulfide or arylisothiocyanates, the cyclized thione **90** is obtained (**Scheme 7**) <1966JOC3528, 1984JCCS315>. Analogous reactions performed in the absence of base gave **91** as a 3-thiol when performed with carbon disulfide, as a 3-hydroxyl with methyl chloroformate, or as a 3-arylamino with arylisothiocyanates in the presence of dicyclohexylcarbodiimide (**Scheme 7**) <1986JHC1339, 1992IJB467>.

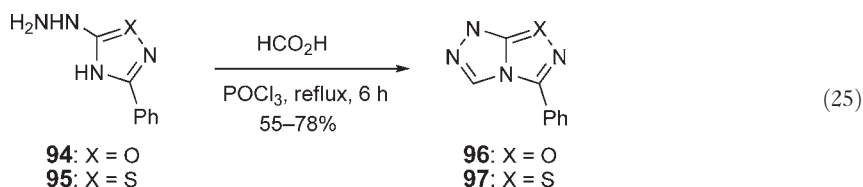


Scheme 7

The reaction of the hydrazine **92** and carboxylic acids affords 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **93**; with formic acid, the corresponding 3-unsubstituted products are formed (**Equation 24**) <1992IJB467, 2004JCCS351>.



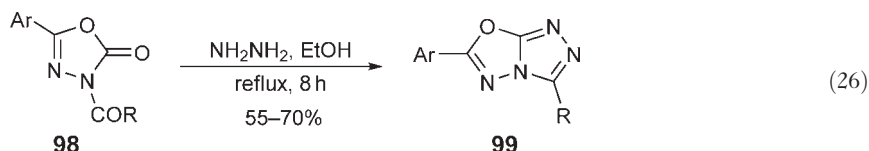
11.07.8.4.2 *ON/NN*: [1,2,4]Triazolo[4,3-*b*][1,2,4]oxadiazole; *SN/NN*: [1,2,4]Triazolo[4,3-*b*][1,2,4]thiadiazole
5-Hydrazino-3-phenyl[1,2,4]oxadiazole **94** and -thiadiazole **95** react with formic acid to give 3-phenyl[1,2,4]triazolo[4,3-*b*][1,2,4]oxadiazole **96** and -thiadiazole **97**, respectively (**Equation 25**) <1991EJC597>.



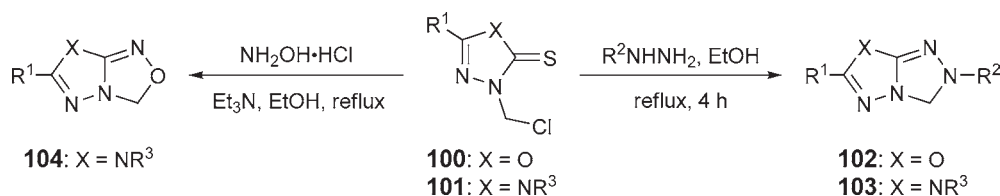
11.07.8.5 Formation of the Second Ring by Insertion of a Two-Atom Ring Member between a Substituent at the First Ring, Providing One Atom and the Adjacent Ring Atom: (5)1 + 2 → (5,5)

11.07.8.5.1 *NN/NO*: [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazole; *NO/NN*: [1,2,4]Triazolo[3,2-*c*][1,2,4]-oxadiazole; *NN/NN*: [1,2,4]Triazolo[4,3-*b*][1,2,4]triazole

The cyclocondensation of 3-acyl/3-aryl-5-aryl[1,3,4]oxadiazol-2(3*H*)-ones **98** with hydrazine hydrate gives the corresponding 3,6-disubstituted-[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles **99** (Equation 26) <1991H(32)237>.

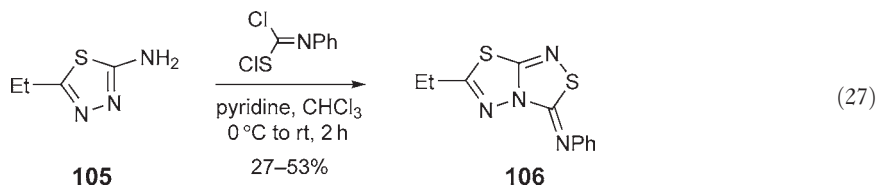


The reaction of 5-aryl-3-(chloromethyl)[1,3,4]oxadiazole-2(3*H*)-thiones **100** with hydrazine or methylhydrazine yields the corresponding 2,3-dihydro[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole derivatives **102** <1984JCED477>. By analogy, hydrazine and phenylhydrazine convert the [1,2,4]triazole-2(3*H*)-thiones **101** into 3,7-dihydro-2*H*-[1,2,4]triazolo[4,3-*c*][1,2,4]triazoles **103** <1992PS99, 2002JCCS1035>. Finally, the azole-2(3*H*)-thiones **101** react with hydroxylamine to form the 3,7-dihydro[1,2,4]triazolo[5,1-*c*][1,2,4]oxadiazoles **104** (Scheme 8) <1992PS99>.



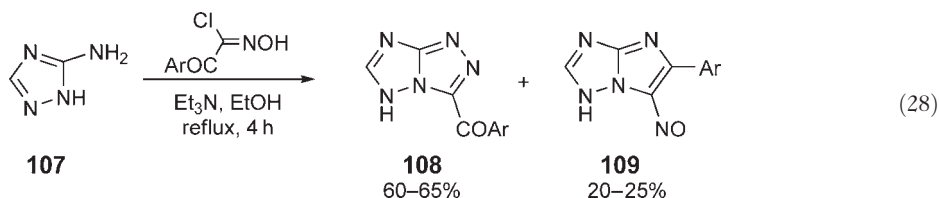
11.07.8.5.2 *NS/NS*: [1,3,4]Thiadiazolo[2,3-*c*][1,2,4]thiadiazole

2-Amino-5-ethyl[1,3,4]thiadiazole **105** upon reaction with 1-chloro-1-phenyliminomethanesulfonyl chloride yields 6-ethyl-3-phenylimino-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole **106** (Equation 27) <1986S1027>. For another synthesis of a compound related to compound **106**, see Section 11.07.9.2 <1994T7019>.



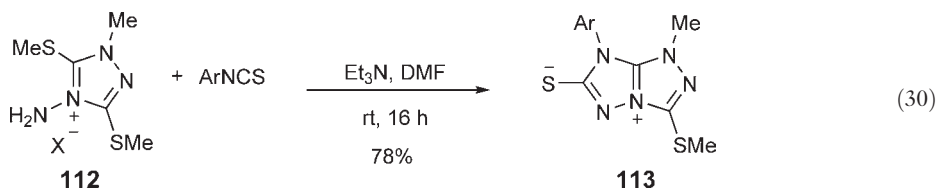
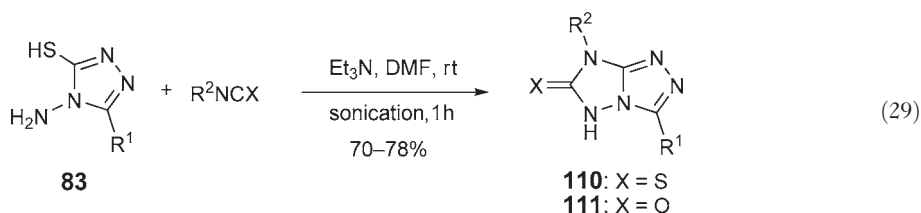
11.07.8.5.3 *NN/NN*: [1,2,4]Triazolo[4,3-*b*][1,2,4]triazole

The treatment of arylglyoxylhydroximoyl chlorides with 2 equiv of 3-amino-2*H*-[1,2,4]-triazole **107** in the presence of triethylamine produces a mixture of 3-aryl-[1,2,4]triazolo[4,3-6][1,2,4]triazole **108** and 5-aryl-6-nitroso-1*H*-imidazo[1,5-*c*][1,2,4]triazole **109** (Equation 28) <1984JHC1029>.

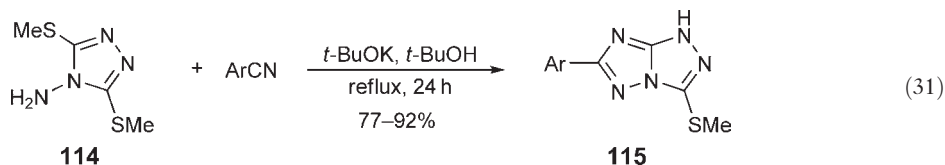


11.07.8.5.4 NN/NN: [1,2,4]Triazolo[4,3-*c*][1,2,4]triazole

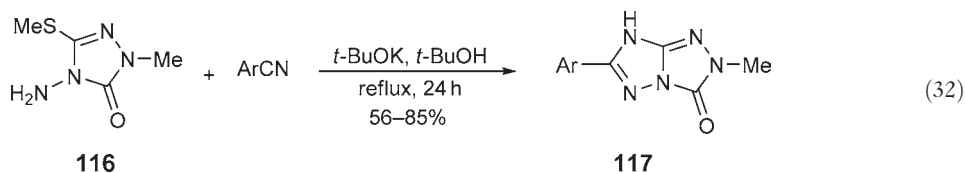
Contrasting with the reported formation of fused [1,3,4]thiadiazole rings in the course of the reaction of 3-substituted-4-amino-5-thio-4*H*-[1,2,4]triazoles **83** with various isothiocyanates (cf. Section 11.07.8.3, Table 3), the reactions with methyl isothiocyanate and with phenylisocyanate afford 3,7-disubstituted-6,7-dihydro-5*H*-[1,2,4]triazolo[4,3-*c*][1,2,4]triazole-6-thiones **110** and -triazole-6-ones **111**, respectively (Equation 29) <1986MI607, 1992IJB167>. The same reaction of 4-amino-1-methyl-3,5-bis(methylthio)[1,2,4]triazolium iodide **112** with aryl isothiocyanates yields the mesoionic compounds **113** (Equation 30) <1984TL5427, 1986T2121>.

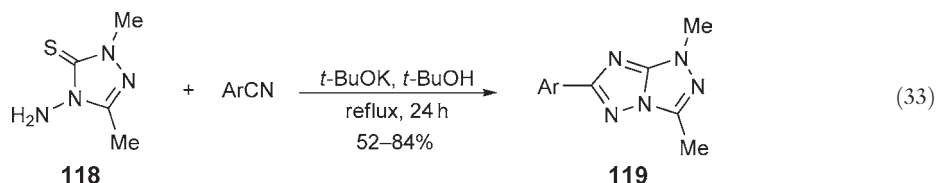


4-Amino-3,5-bis(methylthio)[1,2,4]triazole **114** reacts with aromatic nitriles under basic conditions furnishing the 1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles **115** (Equation 31) <1983S415, 1985BCJ735>.



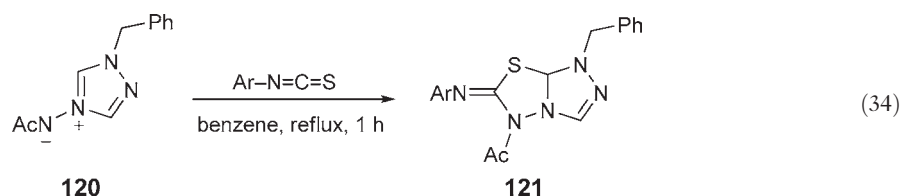
Similarly, the reaction of 4-amino-1-methyl-3-methylthio-1*H*-[1,2,4]triazol-5(4*H*)-one **116** furnishes 6-aryl-2-methyl-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazol-3(2*H*)-ones **117** (Equation 32) <1985BCJ735> and the 4-amino[1,2,4]triazole-5(4*H*)-thione **118** furnishes 6-aryl-1,3-dimethyl-1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles **119** (Equation 33) <1985H(23)2613>.





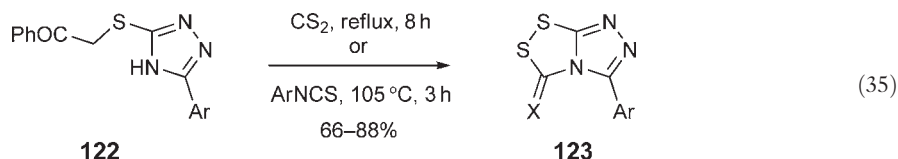
11.07.8.5.5 NN/NS: [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazole

The reaction of 1-benzyl-4-(acetylimido)-1*H*-[1,2,4]triazolium inner salt **120** (an azomethine imine) with aromatic isothiocyanates yields among other products 5-acetyl-6-(arylimino)-1,5,6,7-anhydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **121** (Equation 34) <1984CCC1713>.



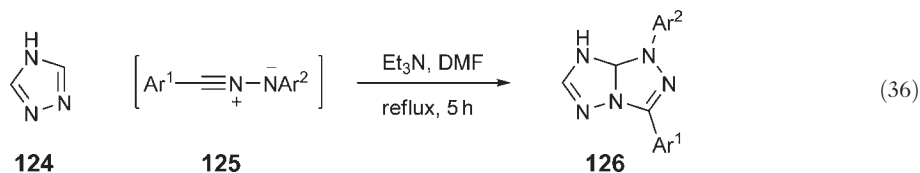
11.07.8.5.6 SS/NN: [1,2,4]Triazo[3,4-*c*][1,2,4]dithiazole

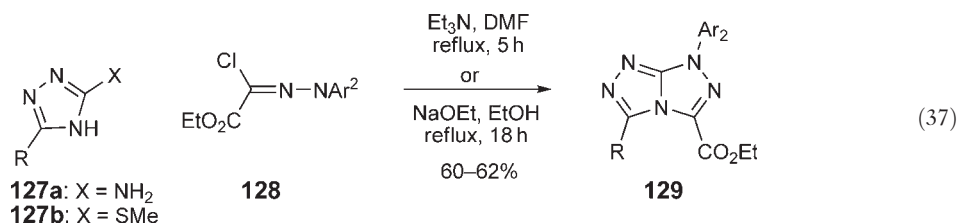
5-Aryl-3-phenacylthio-1,2,4-triazoles **122** react with carbon disulfide and aryl isothiocyanates to give 5-aryl-3*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazole-3-thiones and the 3-arylimino derivatives **123** (Equation 35) <1983ABC1017>.



11.07.8.6 Formation of the Second Ring by Addition of a Three-Atom Ring Member to Two Adjacent Ring Positions of the First Ring: (5) + 3 → (5,5), NN/NN: [1,2,4]Triazolo[4,3-*b*][1,3,4]triazole and NN/NN: [1,2,4]Triazolo[3,4-*c*]-[1,2,4]triazole

The electrolysis of the 4-nitrophenylhydrazone of 4-dimethylaminobenzaldehyde generates the corresponding diarylnitrilimine intermediate **125**, which in the presence of [1,2,4]triazole **124** undergoes 1,3-dipolar cycloaddition to give the 7,7a-dihydro-1*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazole **126** (Equation 36) <1985ZC443>. A similar cycloaddition takes place between 3-amino[1,2,4]triazole **127a** and the 4-tolylhydrazone of ethyl chloroglyoxalate **128** in the presence of triethylamine. Presumably, the [3+2] cycloaddition of the 1,3-dipolar nitrilimine intermediate is followed by the elimination of ammonia to furnish ethyl 1-(4-methylphenyl)-1*H*-[1,2,4]triazolo[3,4-*c*][1,2,4]triazole-3-carboxylate **129** (Equation 37) <1988JIC194>.

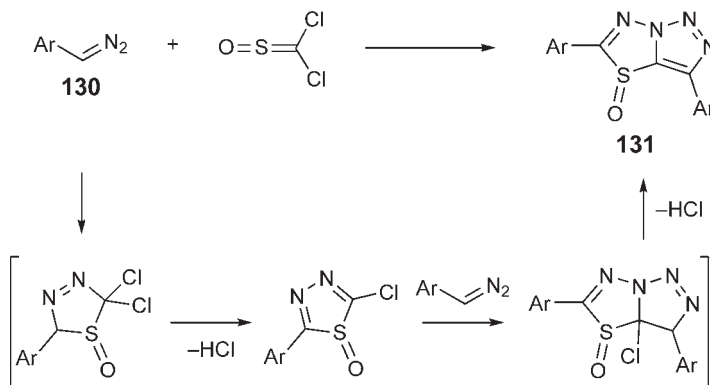




In the case of 3-methylthio[1,2,4]triazole **127b**, the same compound **129** is obtained; however, the mechanism is probably stepwise <2004JCCS351, 2002IJB821>.

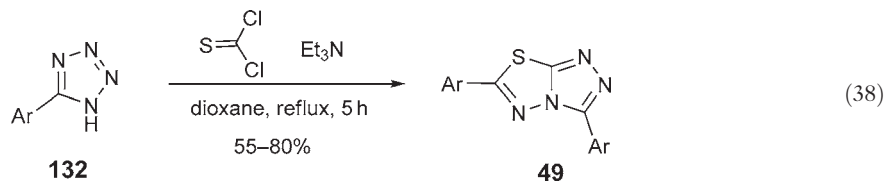
11.07.8.7 Formation of the 5,5-Fused Rings from Three Fragments, Providing Two, Three, and Three Ring Atoms: 2+3+3 → (5,5) NNSN: [1,2,3]Triazolo[5,1-*b*]-[1,3,4]thiadiazole

The reaction of a fourfold excess of aryldiazomethanes **130** with dichlorosulfine leads to 3,5-diaryl[1,2,4]triazolo[5,1-*b*]-[1,3,4]thiadiazole-4-oxides **131**. The formation of the fused heterocycles **131** is rationalized on the basis of two consecutive cycloaddition steps, each followed by elimination of hydrogen chloride promoted by the excess of aryldiazomethane (Scheme 9) <1984JCM175>.



Scheme 9

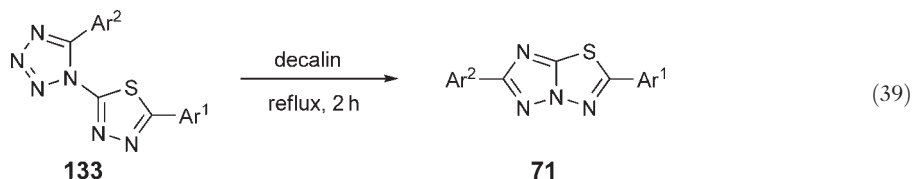
The reaction of tetrazole **132** with thiophosgene leads to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **49**. The reaction involves the *in situ* generation of aryldiazomethanes by decomposition of the tetrazole, followed by two cycloadditions (Equation 38) <1999CPA215>.



11.07.9 Ring Synthesis by Transformation of Another Ring

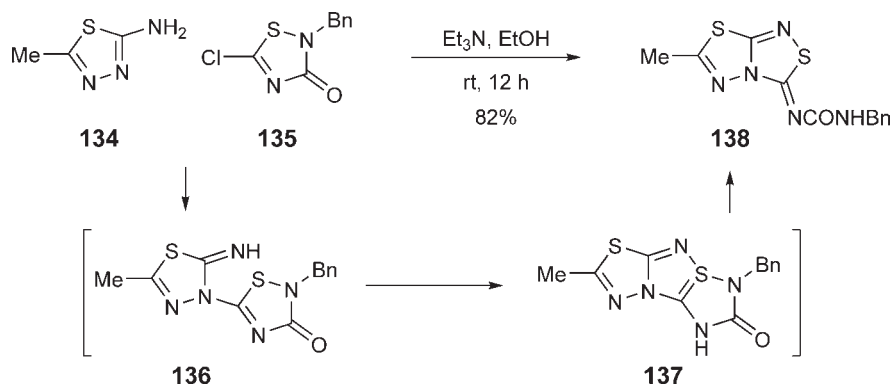
11.07.9.1 Thermolysis with Extrusion of Dinitrogen

The thermolysis of 1-([1,3,4]thiadiazol-2-yl)tetrazoles **133** gives rise to the loss of dinitrogen from the tetrazole ring and the formation of 2,6-diaryl[1,2,4]triazolo[5,1-*b*][1,3,4]thiadiazoles **71** (Equation 39) <1985IJB908, 1990FA953>. (For another synthesis of compounds **71**, see Section 11.07.8.1.5.)

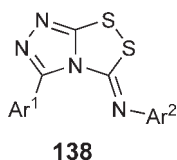


11.07.9.2 Ring Closure and Ring Opening

In the presence of triethylamine, the reaction of 2-amino-5-methyl[1,3,4]thiadiazole **134** with 2-benzyl-5-chloro-[1,2,4]thiadiazol-2-one **135** gives 3-(benzylcarbamoylimino)-6-methyl-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazole **138**. Presumably, the first-formed intermediate **136** rearranges through the thiapentalene intermediate **137** to the fused thiadiazole product **138** (Scheme 10) <1994T7019>.



Scheme 10



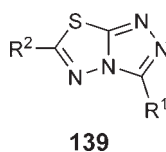
11.07.10 Important Compounds and Applications

In many cases, fused heterocycles have been synthesized with the primary goal of investigating their biological properties. Although a large number of these fused systems have been found to exhibit different activities, no specific compound has emerged as potentially useful in any pharmaceutical or agrochemical field.

11.07.10.1 Agrobiological Activity

5-Aryl-3-arylimino[1,2,4]triazolo[3,4-*c*][1,2,4]dithiazoles **138** have been compared with dithane M-45 for their fungitoxicity against *Helminthosporium oryzae* and *Fusarium oxysporium* <1983ABC1017>.

A number of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **139** with a wide variety of substituents have been screened and tested for their activity against fungi (e.g., *Helminthosporium oryzae* and others) <1983JJB712, 1988ABC1229, 1992JJB467, 1993PS171, 1999JIC461>. For many [1,2,4]triazolo[3,4-*c*][1,3,4]thiadiazoles, both fungicidal and herbicidal activities have been found <1993MI512, 1993MI56, 1993MI397, 1994MI74, 1994MI127>.



11.07.10.2 Pharmacological Activity

A large number of fused heterocycles have been found to exhibit antimicrobial activities, but apparently none of them shows any outstanding activities.

11.07.10.2.1 Bactericidal activity

The evaluation of the fused cyclic systems as antibacterial compound is by far the most abundant studied biological activity.

Mainly [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **139** have been tested for their activity against various bacteria like *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Bacillus subtilis* (**Table 4**).

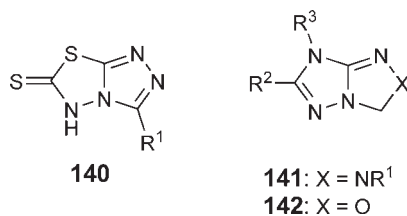
Table 4 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles **139** with bactericidal activity

<i>R</i> ¹	<i>R</i> ²	Reference
H	Aryl	1991RRC619, 1999IJB998
Aryl	Aryl	1989MI1028, 1992IJH211, 1996IJB745, 1996FA659, 1999MI151
Hetaryl	Hetaryl	1998FA574, 1999PJC1203, 2000JCCS535, 2000IJB847, 2001IJB828, 2002IJH2, 2002IJH2, 2003IJB401
Aryl	SH	1990IJB135
Aryl	NHPh	1987JHC1173, 2001IJB828, 2003IJH189
Hetaryl	Alkyl	1991MI129, 1991CCL277, 2000JIC302, 2002IJH255, 2002MI1882, 2003IJB2010
4-Pyridyl	Aryl	1991CCL277, 1991MI513
4-Pyridyl	H, hetaryl	1991CCL277
4-Pyridyl	ArCONH	1992CHJ59

Other systems of this type including 5,6-dihydro derivatives <1990IJB135, 1991RRC619, 1997FA259, 1997IJH317, 2003IJB1756> and 6(5*H*)-thiones <1987JHC1173, 1988IJB576, 1989JIC330, 1991JIC474> have been screened.

11.07.10.2.2 Fungicidal activity

[1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazoles **139** have been evaluated against fungi (*Aspergillus*) <1999IJB998, 2002IJH255>. Some other fused heterocyclic systems such as 3-aryl[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazole-6(5*H*)-thiones **140** <1988IJB128, 1989JIC330>, 2,7-dihydro-3*H*-[1,2,4]triazolo[4,3-*b*][1,2,4]triazoles **141**, and 3*H*,7*H*-[1,2,4]triazolo[5,1-*c*]-[1,2,4]oxadiazoles **142** <1992PS99> have been found to be active against pathogenic fungi (e.g., *C. albicans*).



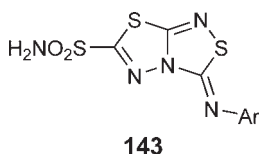
11.07.10.2.3 Various pharmacological activities

Numerous 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **139** have been found to possess various activities (**Table 5**).

Table 5 Pharmacological activities of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **139**

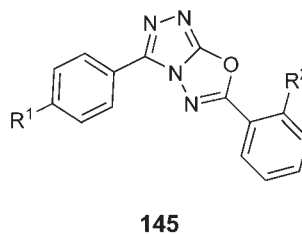
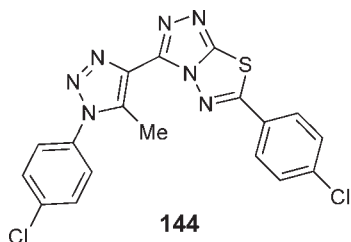
Activity	Reference
Anti-inflammatory	1984IJB793, 1998FA399, 2000JIC302, 2002IJH255, 2002IJH303
CNS depressant	1984IJB793
Analgesic/anti-inflammatory	1986IJB566, 1998FA399, 2004IJH2333
Antihypertensive	1987MI395
Anthelmintic/larvicidal	1989FA703, 1992IJB673, 1998FA399, 2003IJH257, 2004IJH131
Antiviral	1996FA659, 1997FA259, 2002FA253, 2004PS1497
Diuretic	2003IJB401

A series of 3-arylimino-6-sulfamoyl-3*H*-[1,3,4]thiadiazolo[2,3-*c*][1,2,4]thiadiazoles **143** due to their corneal permeability and ocular hypotensive effect were suggested to be active against glaucoma <1993MI97, 1993MI109>.



6-(*p*-Chlorophenyl)-3-[1-(*p*-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole **144** has been found to inhibit the proliferation of tumors *in vitro* and *in vivo* by possibly inducing a redifferentiation. <2005PHA378>.

Other 3,6-disubstituted-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **139** or [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles **145** were also evaluated for anticancer properties but showed little, if any, activity <2004PS1595, 2004JCCS1343>.



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11.08

Bicyclic 5-5 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 3:1

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11.08.1 Introduction

There has been no specific review published in this particular field of 5-5 bicyclic ring systems, so that attention has to be drawn to the earlier contributions produced in CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)227>.

Reviews concerning tetrazoles <1976RCR183> and the chemistry of tetrazoles <1977AHC323, 2004SOS861> as well as imidazoles <2002SOS325, 2003PHC206> also incorporating some fused 5-5 bicyclic ring systems have been produced. **Figure 1** surveys the structural variations governed within this review. Among these compounds, tricyclic and also in some cases polycyclic derivatives exhibiting a fused 5–5 system were considered for a brief review outline. Therefore, this review includes partially saturated and unsaturated derivatives of the pyrazolo[1,5-*d*]tetrazole series **1–5**; oxazolo[3,2-*d*]tetrazole derivatives **6**; isoxazolo[2,3-*d*]tetrazole derivatives **7**; thiazolo[3,2-*d*]tetrazole derivatives **8**; isothiazolo [2,3-*d*]tetrazole derivatives **9** and imidazo[1,5-*d*]tetrazoles **10**.

In the case of azolo-fused tetrazoles care should be exercised when consulting the literature on the possible valence bond tautomerism of the bicyclic systems to the monocyclic azido-tetrazoles <1973CI371, 1973S123, 1975RCR481, 1979CRV181, 1988JOC2354, 1998JA4723>. As additional heteroatoms, the first row elements, and sulfur were considered while other elements of the second or higher rows such as phosphorus, silicon, or selenium as well as metal containing 5-5 bicyclic ring systems were disregarded.

11.08.2 Theoretical Methods

There are only a few new theoretical studies of new 5-5 bicyclic ring systems. In one study azido-tetrazole isomerization was investigated (**Scheme 1**) <1998JOC2354, 1998JA4723>. The model systems chosen were fully conjugated (10 π -electrons) thiazolo[3,2-*d*]tetrazole in its unsubstituted form as well as substituted derivatives.

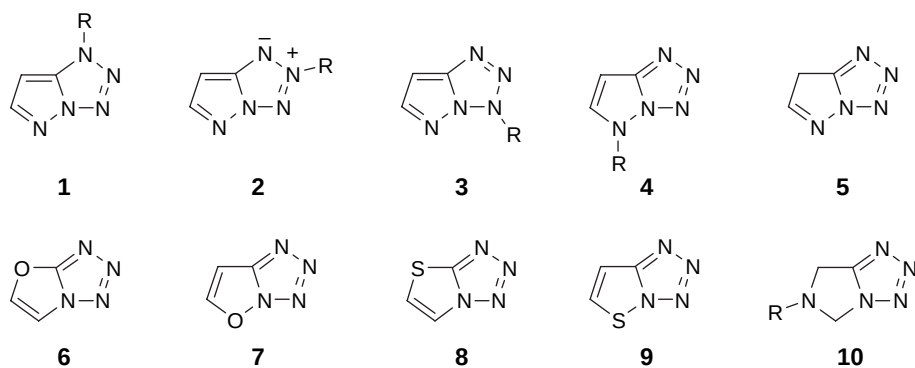
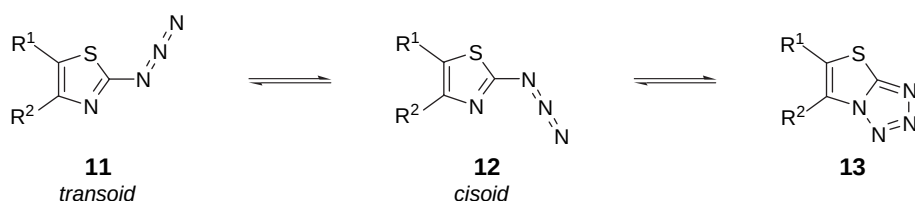


Figure 1 Overview of title compounds.



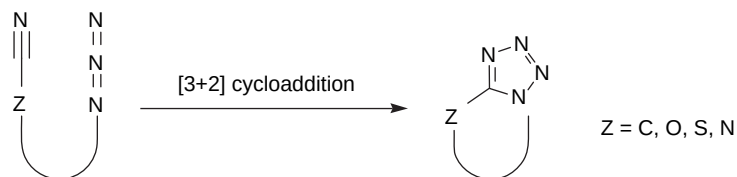
Scheme 1

The isomerization reaction was studied considering the *cisoid*/*transoid*-azido forms **11** and **12** and the cyclized tetrazole form **13** both in gas-phase and in solution. The mechanism as well as the transition state structure were localized. The effect of electron-donating (methyl) and electron-withdrawing (chloro) substituents at the azathiazole ring were also investigated <1998JA4723>. In addition, the effects of temperature on the equilibrium of the isomerization reaction were examined by the determination of the enthalpy and entropy changes in solution <1988JOC2354>.

Upon cyclization in the gas phase, there is a large electron density redistribution, which makes it necessary to use extended basis and high-order electron correlation terms to describe the thermodynamics. This indicates the gas-phase preference of the azido forms **11/12**. The analysis of the electron density in the azide, tetrazole, and transition state reaction pathway reveals the complexity and asynchronism in the electron redistribution which permits to differentiate different chemical events along the cyclization. First, the linearity of the azide is lost, which approaches the nitrogen of the azathiazole. Then the lone pair attacks the azido group leading to the desired cyclization. The electron density change associated by these events gives rise to a large free energy barrier in the gas phase. While in the gas phase the azido forms **11/12** are preferred, in solution the conversion to the tetrazole **13** is exergonic. The stability of the latter one is increased by the polarity of the solvent. This can be explained by the larger polarity of the tetrazole and the larger solvent-induced polarization.

Substituents have a great influence on the equilibrium of the azido–tetrazole isomerization. It is shifted to the cyclization product of type **13** by electron-donating substituents and to the azido forms of type **11/12** by electron-withdrawing groups.

Another theoretical investigation deals with the intramolecular [3+2] dipolar cycloaddition (Huisgen reaction) of azides and nitriles (Scheme 2) to form tetrazoles <2003JOC9076>.



Scheme 2

The following aspects were examined:

- (i) There is no correlation between barriers and the free energy of the reaction. In addition, the structure of the transition state of the reaction is always quite similar. It is noteworthy that the reaction pathway is asynchronous probably due to a charge effect.
- (ii) The tetrazole has a higher dipole moment than the reactants so it is better stabilized by solvation.
- (iii) In contrast to the intermolecular reaction, the electron-withdrawing power of the substituents on the nitrile or azide is not the dominant factor governing the intramolecular reaction. Effects such as strain, tether length, and preorganization of the reactants are equally important.

In addition, the mechanism of the zinc-catalyzed [3+2] dipolar cycloaddition of azides and nitriles to form tetrazoles was examined [\[2003JA9983\]](#). The energy barrier of the reaction is lowered by 5–6 kcal mol⁻¹ which corresponds to an acceleration of 3–4 orders of magnitude. The source of the catalytic activity seems to be the coordination of the Lewis acidic zinc halide to the nitrile, which is supported by model calculations. Also AlCl₃ was examined as another Lewis acid which catalyzes the reaction to a greater extent than ZnBr₂.

11.08.3 Experimental Structural Methods

The newly synthesized 5-5 bicyclic ring systems are mostly completely characterized using standard analytical techniques. Nevertheless, some 5-5 bicyclic ring systems are only sparsely characterized. Accordingly, ¹³C and ¹H NMR chemical shifts are reported for most of these new compounds. **Figure 2** shows the structures of the new compounds which are especially characterized by ¹³C NMR spectroscopy and other analytical methods.

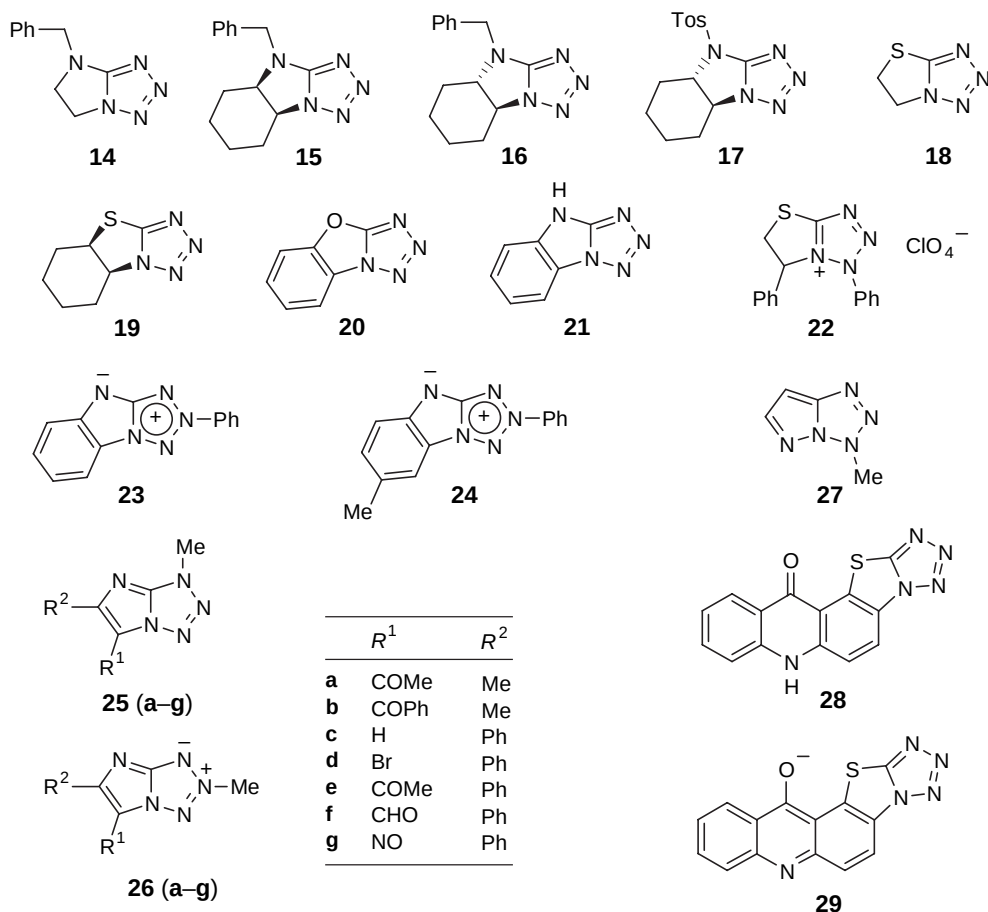


Figure 2 Substances with reported ¹³C NMR data.

In **Table 1** the ^{13}C NMR data are presented for the bridgehead carbon because this atom resembles the only constant feature of the structures described. In the Table are also given IR spectroscopic data and UV absorption maxima as far as they were reported. ^{15}N NMR data were not reported for these compounds. The reported ^1H NMR data are not characteristic for the 5-5 bicyclic ring systems since the new compounds are to a great extent highly unsaturated. Only the two carbons at one of the five-membered rings could have characteristic protons. Nevertheless, mostly these positions are substituted. Therefore, the ^1H NMR signals derive from protons which are located in the vicinity of the molecule and are not characteristic for the 5-5 bicyclic ring systems and therefore not listed.

Table 1 Compiled ^{13}C NMR, IR and UV data

Compound	^{13}C NMR ^a (ppm)	IR ν (cm^{-1})	UV λ_{max} (nm)	Reference
14	165.5			2001OL4091 ^d
15	165.9			2001OL4091 ^d
16	166.2			2001OL4091 ^d
17	160.4			2001OL4091 ^d
18	161.9			2001OL4091 ^d
19	160.5			2001OL4091 ^d
20	129.4 ^b			2001OL4091 ^d
21	149.9 ^b			2001OL4091 ^d
22	160.1			2001CHE702 ^d
23	159.5	1640, 1580, 1558, 1500	393, 320, 254, 212, 204	1999JHC863 ^d
24	159.6	1554, 1490, 1482, 1426	395, 329, 256, 218	1999JHC863 ^d
25a	157.7	1657	279, 222	2000JPR(342)591 ^d
25c	150.4	3109	289, 252, 224	2000JPR(342)591 ^d
25d	146.8		296, 248	2000JPR(342)591 ^d
25e	157.5	1656	289, 249, 223	2000JPR(342)591 ^d
25f	161.3	1650	298, 254, 227	2000JPR(342)591 ^d
25g	161.5		357, 273, 237	2000JPR(342)591 ^d
26a	159.4 ^b	1631	279, 240, 231	2000JPR(342)591 ^d
26b	159.8 ^b	1663		2000JPR(342)591 ^d
26c	156.3	3135	328, 271, 224	2000JPR(342)591 ^d
26d	155.0		334, 267, 225	2000JPR(342)591 ^d
26e	159.8 ^b	1663	280, 254, 222	2000JPR(342)591 ^d
26f	160.6 ^b	1642	294, 259, 220	2000JPR(342)591 ^d
27	152.0			1996JOC5646
28	159.5	2121 ^c		1996JHC747 ^d
29	158.8	2125 ^c		1996JHC747 ^d

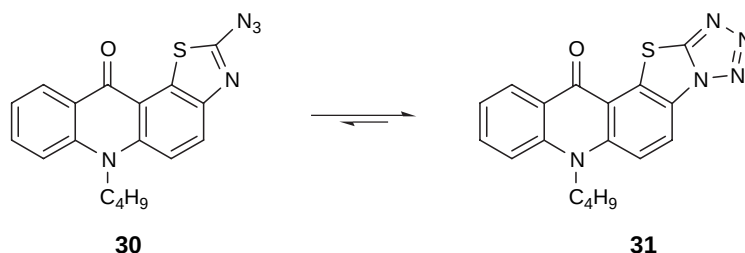
^aSignal for the bridgehead carbon atom.

^bTentative assignment because other aromatic signals are nearby.

^cIR band corresponds to the azide functionality in the tetracyclic derivative; compare to **30** in **Scheme 3**.

^d ^1H NMR data are also reported.

For some compounds NMR data were collected to determine the equilibrium constants for the tautomerism between the azide form such as for **30** and the tetrazole derivative **31** (**Scheme 3**). Similar investigations were conducted for the compounds **28** and **29** and the solvent effects and substituent effects are discussed <1996JHC747>.



Scheme 3

For the example shown in (Scheme 3), the ^1H NMR signals in $\text{DMSO}-d_6$ revealed that the equilibrium lies to 75% in favor of the tetrazole form **31**.

Mass spectra have been reported for most of the compounds and based on modern milder ionization methods the molecular ions were observed in most cases.

Literature data on bond lengths and bond angles were mostly reported in the previous volume concerning to a great extent planar aromatic 5-5 bicyclic ring systems <1996CHEC-II(8)227>. Similar data derived from X-ray analysis are available only for the new compound *trans*-2-methyl-3,7-diphenyl-2,3-dihydrothiazolo[3,2-*d*]tetrazolium perchlorate **32** (Figure 3) <2001CHE702> within the review period.

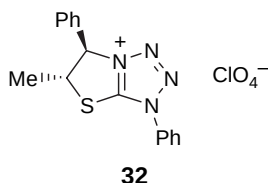


Figure 3 Structure of **32**.

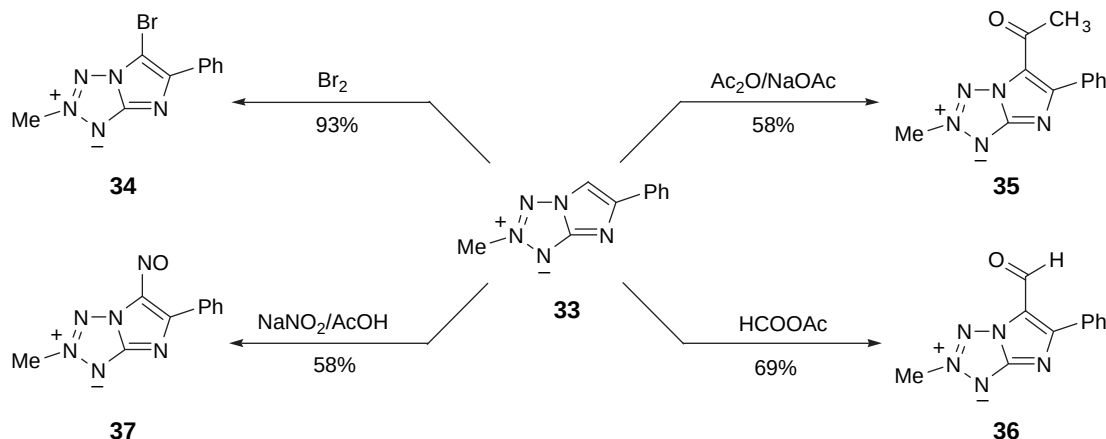
11.08.4 Thermodynamic Aspects

In the past the equilibrium constant between the ring-opened azide form and the tetrazole form (Scheme 1) was investigated using NMR techniques. The dependency for the equilibrium constant in different solvents, the physical state of the samples, the temperature, and the number and the type of substituents were determined. For typical references of such investigations, see CHEC-II (1996) <1996CHEC-II(8)227> as well as some selected references <1984CS195, 1986CC959, 1988JOC5371, 1988CC1144, 1992JCS(PI)239>. Only a limited number of new contributions can be added, such as the equilibrium constants determined for **30/31** (Scheme 3) <1996JHC747>. Some recent references mention this behavior but do not determine equilibrium constants.

11.08.5 Reactivity of Fully Conjugated Systems

The main focus on the reactions of 5-5 bicyclic ring systems within the review period was the electrophilic substitution at a carbon atom. For earlier reports and electrophilic modifications on the carbon as well as on the nitrogen atoms of 5-5 bicyclic ring systems, the previous volumes should be consulted <1996CHEC-II(8)227>. For characteristic contributions concerning the attack on nitrogen see <1978OMR(11)507, 1983JHC1629>, <1985T4621>, and for the attack on carbon see <1973UKZ60, 1976UKZ1298>.

The electrophilic modification at the carbon atom of the fully conjugated 5-5 bicyclic ring system **33** was accomplished by standard methods. The bromination of the 5-5 bicyclic ring system **33** can be realized in the reaction with bromine (Scheme 4) to afford **34**, whereas the introduction of an acetyl group to give **35** or a formyl



Scheme 4

group to form **36** is realized with the appropriate reagents. Nitroization can be easily realized in the reaction with sodium nitrite/acetic acid to form the nitroso derivative **37**.

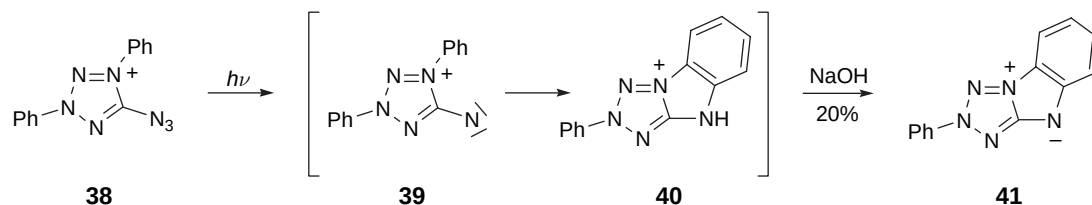
11.08.6 Reactivity of Nonconjugated Systems

The main focus of the chemistry concerning 5-5 bicyclic ring system has been directed toward the synthesis of these materials. New follow-up chemistry of nonconjugated partially hydrogenated compounds was not reported within the period. Sparsely, the unsuccessful synthesis of nonconjugated systems was assigned to an azide–tetrazole equilibrium and the instability of the ring-opened azide form leading to decomposition products which were neither isolated nor characterized <2001OL4091>. Similar contributions have been reported earlier for the decomposition of nonconjugated 5-5 bicyclic ring systems under acidic, basic, or thermal conditions <1984CS195, 1993CB129, 1996CHEC-II(8)227>.

11.08.7 Synthesis of 5-5 Bicyclic Ring Systems

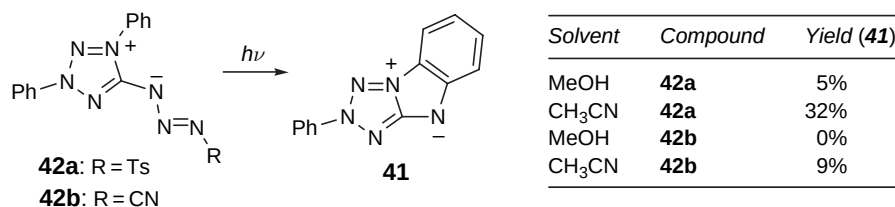
11.08.7.1 Photochemical Synthesis

The photochemical reaction of azide-functionalized tetrazole derivatives such as **38** leads to the formation of the 5-5 bicyclic ring system **40** (Scheme 5) in very moderate yields <1999JHC863>. This reaction is believed to proceed via the singlet nitrene intermediate **39**. Attack at the aromatic substituent in *ortho* position leads to product **40** <1974JOC2546> by subsequent cyclization. This intermediate is deprotonated during the workup conditions to the mesoionic tricyclic derivative **41**.



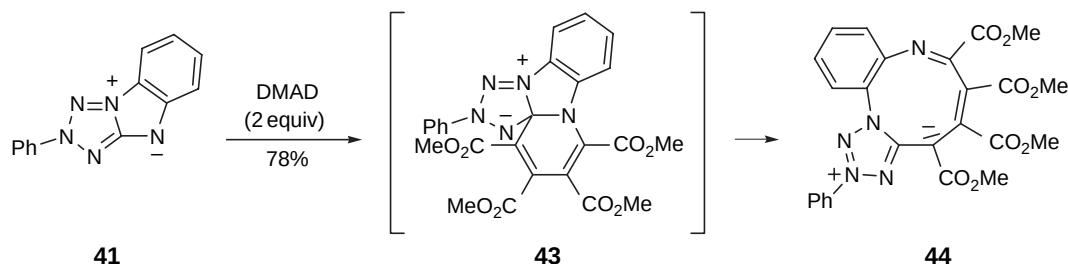
Scheme 5

The photochemical reaction can also proceed via the triplet state and in this case no cyclization is observed. Especially when acetophenone is added as a triplet sensitizer, **41** is not formed. Remarkable is the observation that in the presence of anthracene or pyrene as triplet quencher, the yield of the cyclization product **41** was not enhanced and that nitrene insertion into CH bonds of anthracene or pyrene was observed. When the photochemical cyclization reaction was performed with the tosyl azide derivative **42a** or the azido nitrile derivative **42b** (Scheme 6), only low yields of the tricyclic amide **41** (32% from **42a**, 9% from **42b**, respectively) were obtained <2001JCS(PI)2476>.



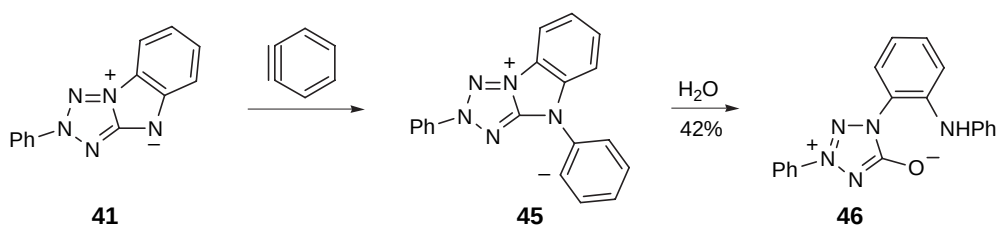
Scheme 6

The mesoionic compound **41** was further used in a reaction with dimethyl acetylene dicarboxylate (DMAD) to produce a nine-membered cycloadduct **44** which is formed by a reaction cascade of double addition of the alkyne and transannular ring opening of the intermediate **43** (Scheme 7) <2003OBC978>.



Scheme 7

The nucleophilic addition of the mesoionic compound **41** was further investigated upon addition to arynes <2003OBC978> (Scheme 8). In this case the process stops at a single addition of the anion to the arynes to form **45** and workup under aqueous conditions led to the formation of the tetrazolium-5-olate **46**.

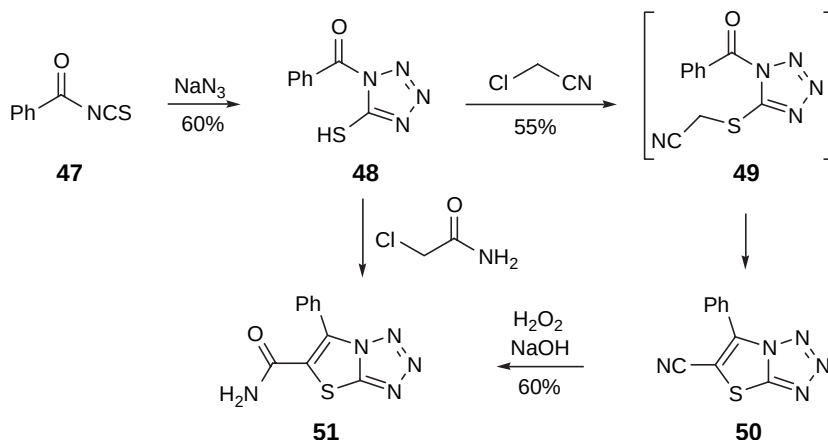


Scheme 8

When other acceptor systems such as tetracyanoethylene, ethyl propiolate, dibenzoylacetylene, or dimethyl azodicarboxylate were reacted with **41**, no additional products were formed. Accordingly, the scope of the reaction for the nucleophilic addition of **41** to electron-poor alkenes, alkynes, and diazo compounds is quite narrow.

11.08.7.2 Synthesis via Condensation

The conversion of acyl isothiocyanates **47** with sodium azide leads to thiol-functionalized tetrazole derivatives such as **48** (Scheme 9) <1995PJC1022>. The reaction of **48** with chloro acetonitrile leads to an intermediate **49** that reacts in

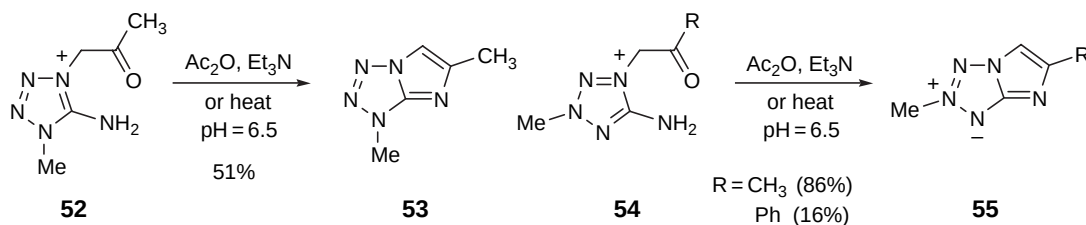


Scheme 9

a spontaneous intramolecular condensation to the 5-5 bicyclic ring system **50**. Hydrolysis of the product **50** with hydrogen peroxide under basic conditions led to the amide-functionalized bicyclic compound **51**.

The hydrolysis product **51** can alternatively be accessed directly from the reaction of the thiol derivative **48** with chloro acetamide. Other electrophiles for the reaction with the thiol derivative were also described which lead to functionalized tetrazole or 5-6 fused bicyclic ring systems.

An alternative approach to 5-5 bicyclic fused ring systems utilizing a condensation reaction was described by Moderhack *et al.* <2000JPC591> (Scheme 10). The amino-substituted tetrazole derivatives **52** and **54** gave the neutral **53** as well as the mesoionic derivatives **55** in moderate to excellent yields (16–86%; R = CH₃ or Ph).

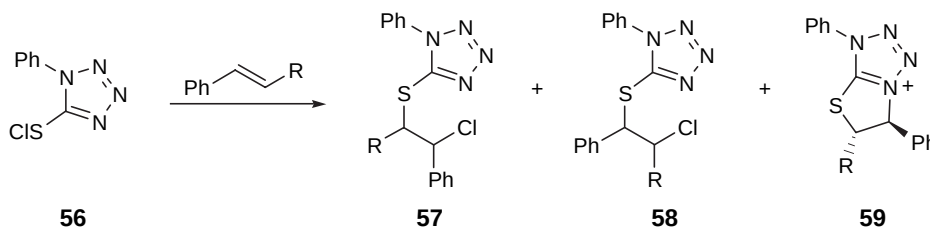


Scheme 10

The further modifications of these cyclization products have been described above (Scheme 4).

11.08.7.3 Synthesis via Sulfenyl Chlorides

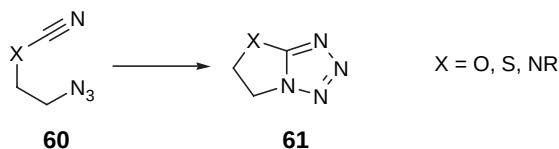
When the thiole derivatives are converted into the corresponding sulfenyl chloride such as **56**, an addition reaction to styrene or β -methylstyrene in nitromethane gives regioisomeric mixtures of adducts **57** and **58** (Scheme 11) <2001CHE702> as well as the cyclization products **59** which are generated in 47% (R = H) and 52% (R = CH₃) yield, respectively.



Scheme 11

11.08.7.4 Synthesis via [3+2] Cycloadditions

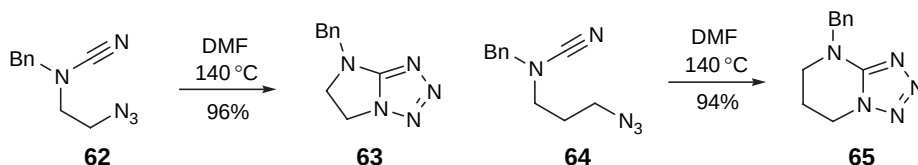
The [3+2] cycloaddition of azides to double and triple bond systems has found considerable interest over the last couple of years. The reaction can either be performed under thermal conditions or by copper(I) catalysis <2001AG(E)2004, 2002AG(E)2596>. In an attempt to broaden the chemistry of such cycloaddition processes, Sharpless *et al.* reported the generation of tetrazole derivatives **61** by an intramolecular process (Scheme 12). In



Scheme 12

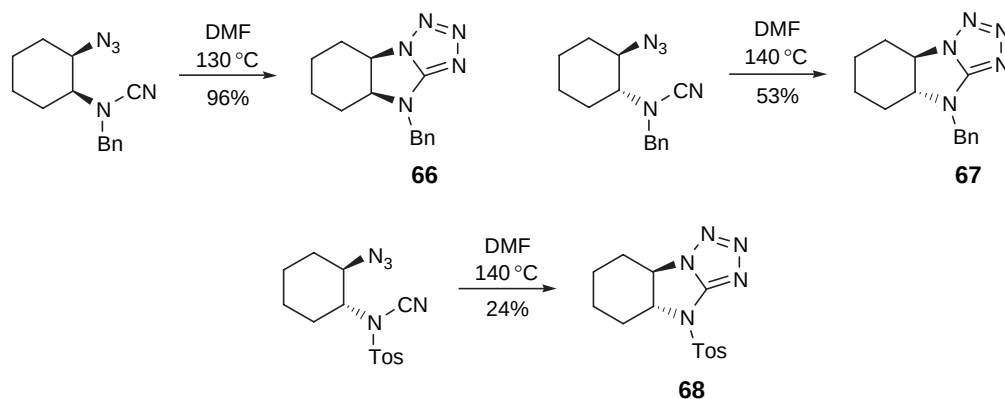
this case a heteroatom-bonded nitrile functionality and an azide functionality are incorporated in the [3+2] cycloaddition reaction as in **60** <2001OL4091>. If the nitrile functionality is bonded to another heteroatom as in the case of cyanates (X=O), thiocyanates (X=S), or cyanamides (X=NR), the reactivity of the intramolecular cyclization reaction is enhanced. It seems to be similar to other intermolecular [3+2] cycloadditions where only activated nitriles give reasonable results. The intramolecular reaction of azides with cyanates, thiocyanates, or cyanamides provides access to a broad class of fused heterocyclic compounds **61** with one nitrogen atom in the ring junction position.

The thermal cyclization of 2- or 3-azide functionalized cyanamides **62** and **64** allows the synthesis of a range of 5-5 and 5-6 fused bicyclic ring systems such as **63** and **65** <2001OL4091> (Scheme 13). Earlier approaches to such ring systems were based on the cyclization of imidoil azides <1997JHC1375> which were generated from azides and imidoil chlorides by nucleophilic attack or by nitroization of imidoil hydrazines <1976JOC2860, 1964CB2185>.



Scheme 13

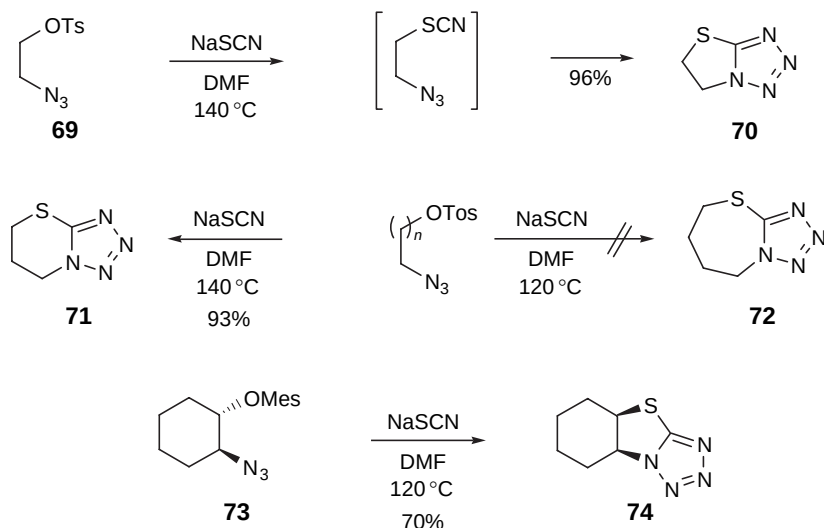
Also, the intramolecular [3+2] cycloaddition approach can be used to generate several tricyclic ring systems **66–68** when the azide and the cyanamide functionalities are bonded to a carbocyclic ring <2001OL4091> (Scheme 14). The relative stereochemistry of the starting materials is preserved in the products. While the yield of the *cis*-fused 5-5-6 tricyclic ring system **66** is very high, the yield of the *trans*-fused products **67** and **68** is considerably lower as expected based on the unfavorable conformation for the cycloaddition process. The even lower yield for the tosylated and therefore activated derivative **68** was rationalized by its decreased thermal stability.



Scheme 14

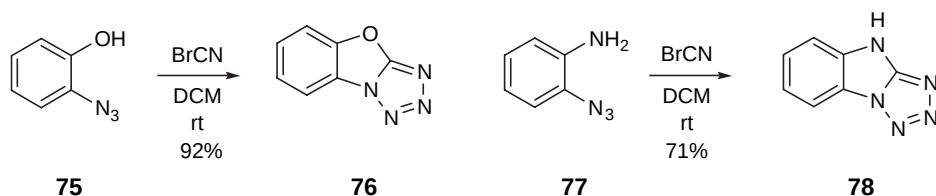
The synthetic approach can also be used for the incorporation of oxygen and sulfur in the bicyclic ring systems when cyanates and thiocyanates are used as starting materials <2001OL4091>. The reaction starts from azido tosylates **69** which are treated with sodium thiocyanate, and the nucleophilic substitution as well as the cyclization reaction are performed in a one-pot process (Scheme 15). Interestingly, the intramolecular cyclization of aliphatic azido thiocyanates gave the desired 5-5 bicyclic system **70** and 5-6 bicyclic system **71** in excellent yields, whereas the 5-7 bicyclic system **72** was not formed at all. This is most likely based on the fact that for the cycloaddition the geometry in the seven-membered ring prohibits a favorable overlap of the involved orbitals. Also, 5-5-6 tricyclic ring systems **74** were accessible by this method incorporating a *trans*-configured azido mesylate **73**. According to the reaction mechanism, the nucleophilic displacement of the mesylate by the thiocyanate group leads to a *cis*-fused 5-5-6 tricyclic ring system.

One can easily envisage the formation of stereochemically enriched materials by an asymmetric version if the methodology developed by Jacobsen *et al.* <2000ACR421> of epoxide ring-opening reactions with azides is applied in the reaction sequence.



Scheme 15

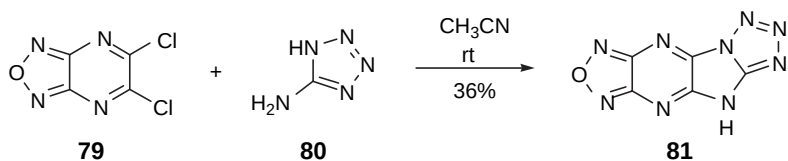
When phenol derivatives are used as linkers between the azido and the cyanate functionality, a one-pot process leads to the desired 5-5-6 tricyclic ring systems such as **76** in good to excellent yields by simple stirring of the starting material **75** in the presence of bromocyanide and triethylamine as a base at room temperature (Scheme 16). The azido cyanate intermediates are cyclized under these mild conditions and the 5-oxotetrazole adducts can be isolated in excellent yields. In a similar fashion, if azido aniline derivatives such as **77** are applied, the corresponding tricyclic amino tetrazole ring systems **78** are obtained in good yields.



Scheme 16

11.08.7.5 Synthesis via Nucleophilic Aromatic Substitution

The synthesis of the polycyclic 5-5-6-5 derivative **81** was realized by nucleophilic substitution of the 5,6-dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine **79** with 5-aminotetrazole **80** (Scheme 17). This conversion took place at room temperature and the product **81** was isolated in moderate 36% yield. Many other heterocyclizations with *N,N*-, *N,O*-, *N,S*-bidentate nucleophiles gave the corresponding reaction in up to 93% yield <1997CHE1352>.



Scheme 17

One has to realize that the cycloaddition products, namely the tetrazoles, are in equilibrium with the open chain azido form. The aromatic moiety of the phenol and aniline derivatives not only favors the formation of the cyclic

tetrazole derivatives but also increases their stability by their σ -withdrawing ability. Consequently, aliphatic azido alcohols gave no stable cyclization products and decomposition was observed.

11.08.8 Medicinal Applications

Compounds **82** and **83** (Figure 4) were tested *in vitro* against a variety of bacteria in a 0.2 g l^{-1} concentration and the diameters of inhibition zones were reported in millimeters <1995PJC1022>. Among the tested bacteria and tetrazole compounds, the 5-5 bicyclic ring system **82** showed activity against *Salmonella* spp. (5 mm inhibition zone diameter), whereas the 5-5 bicyclic ring system **83** exhibits activity against *Staphylococcus albus* (6 mm) and *Bacillus subtilis* (5 mm). These activities were comparable to the reference compound penicillin G procaine under the test conditions.

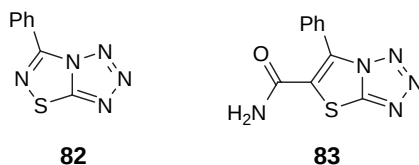


Figure 4 5-5 Bicyclic ring systems tested for biological activity.

In a test series for finding lymphocyte function-associated antigen-1 (LFA-1) inhibitors, several bicyclic analogs of compound **84** were investigated <2004JMC5356> and compared to this known hydantoin-based LFA-1 inhibitor **84**. Among the candidates was also a 5-5 bicyclic ring tetrazole derivative **87** (Figure 5). As the binding constants K_d (μM) revealed, the compound **85** was much less effective than the inhibitor **84** or derivatives with lower nitrogen content **85** and **86**. In addition, the stability of **87** in aqueous solution was not very high and decomposition was encountered.

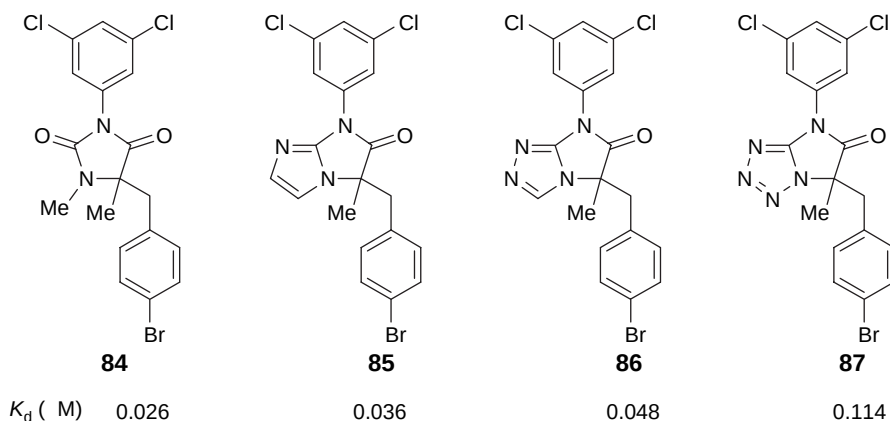


Figure 5 Structure of some new lymphocyte function-associated antigen-1 inhibitors.

In a test series of new coumarin derivatives also obtaining a 5-5 bicyclic subunit, the compound **88** (Figure 6) was found to have good biological activity against *S. albus*, *Pseudomonas aeruginosa*, and *Escherichia coli* bacteria while the desired activity against *Artemia salina*, the brine shrimp larva, was only moderate <2000FES641>.

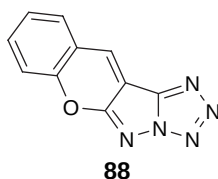


Figure 6 Structure of the biologically active 5-5-6-6 coumarin derivative **88**.

11.08.9 Industrial Applications

According to patent literature, some 5-5 bicyclic ring systems are used as photographic couplers and imaging materials (89–92, (Figure 7)). They act as an emulsion layer and a photo-insensitive hydrophobic colloid layer containing solid powder dispersion. These materials show good safe-light characteristics and provide low-fog images with less color stains. Furthermore, they are used as brightening agents, dye-forming couplers, dyeing agents for brightening, and color-developing reducing agents. As photosensitive decoloring elements these systems provide fewer stains during storage and color fastness, prevention of background staining, improved storage stability, and color reproduction <1998JAP(K)09160163, 1998JAP(K)10055049, 1998JAP(K)10264517, 1995JAP(K)07175182, 2001JAP(K)2001281820>.

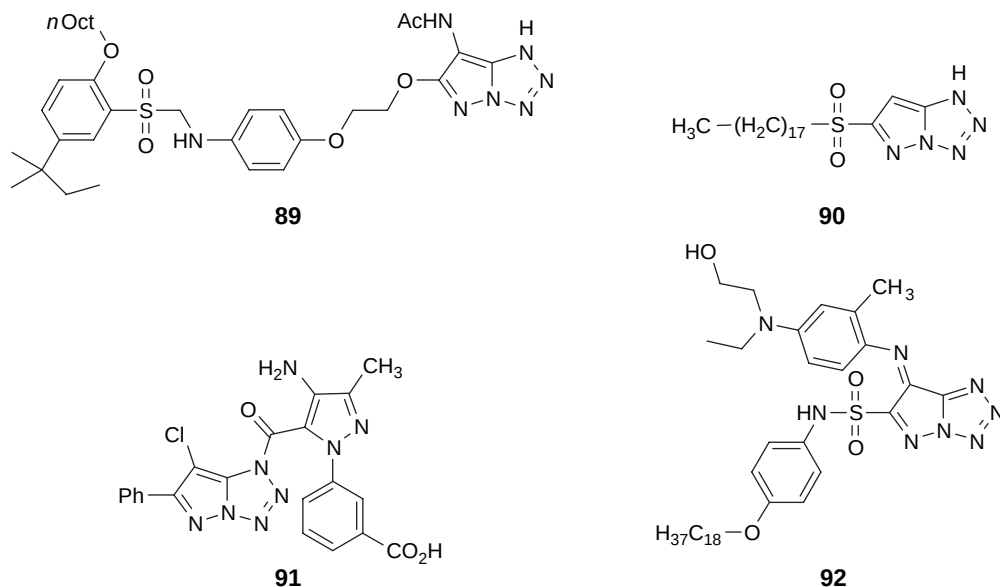


Figure 7 Patented 5-5 bicyclic ring compounds for photographic applications.

Applications in the area of solar cells are semiconductors containing dyes with a 5-5 bicyclic ring system such as **93** (Figure 8) which show high photoelectrical conversion efficiency <2005JAP(K)2005209682>.

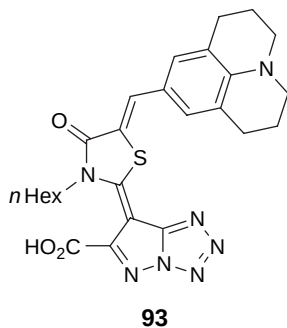


Figure 8 Patented 5-5 bicyclic ring compounds for solar cell applications.

In patented hair dyes the mentioned 5-5 bicyclic ring systems such as **94** and **95** (Figure 9) are used as oxidative couplers <1999EUP923929, 1997WO9735551, 2003FRP2830192, 2004EUP1428510>.

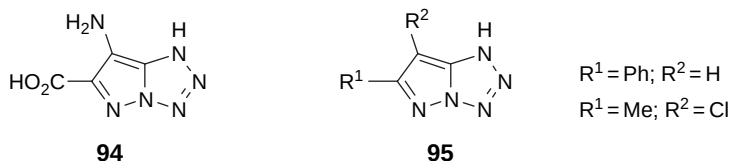


Figure 9 Patented 5-5 bicyclic ring compounds for cosmetic applications.

In inkjet-technology materials of type **96** and **97** act as colorants (**Figure 10**). The application can be either using an ink-containing core-/shell-type colored resin particle dispersion comprising core of colorant-containing particle coated with shell of colorant-free resin or using a printing sheet comprising a support coated with a porous ink-receiving layer. These materials show superior properties concerning abrasion resistance, good color reproducibility, improved light fastness, and gas resistance. The printing results are light resistant images having high saturation with high dots and without roughness.

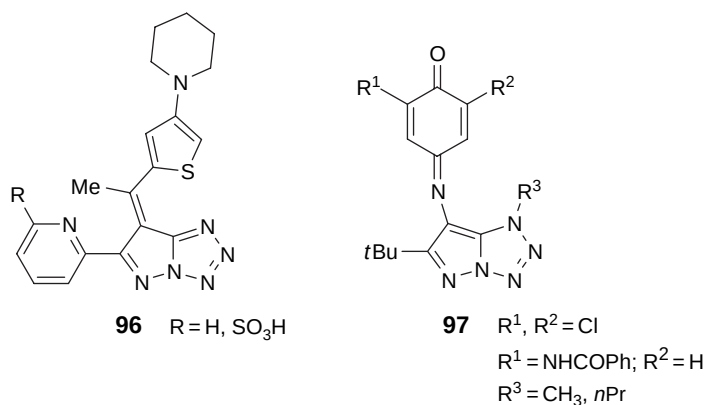


Figure 10 Patented 5-5 bicyclic ring compounds for inkjet applications.

The principle of this method is an image-forming method using the colored particles, consisting of a colorant-containing core and a colorant-free shell which are part of an aqueous dispersion used with a porous ink-receiving layer <1999JAP(K)11188965, 2000JAP(K)2000075553, 2002USP2002156154, 2002EUP1258511, 2002EUP1264867, 2003JAP(K)2003064285, 2005JAP(K)2005014293, 2005JAP(K)2005088334, 2005JAP(K)2005007700, 2003JAP(K)2003213152>.

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11.09

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: No Extra Heteroatom O:O

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11.09.1 Introduction

Indolizine, whose numbering system is shown in formula **1**, is a ring system present in many families of natural alkaloids, mainly in the fully saturated form named indolizidine (**Figure 1**).

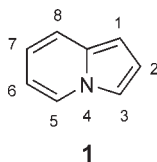


Figure 1

A complete review on the synthesis of indolizines has appeared <2000HOU(10)745>. This chapter is an extension of the reviews in CHEC(1984) <1984CHEC-I(4)443> and CHEC-II(1996) <1996CHEC-II(8)237>, mainly focusing on the development of synthetic methods aimed at the synthesis of natural alkaloids and important bioactive compounds containing the indolizidine nucleus.

11.09.2 Theoretical Methods

Indolizine possesses a delocalized 10π -electron system resulting from the combination of a π -excessive (pyrrole-like) and a π -deficient (pyridine-like) ring. The features are reflected by the reactivity: the five-membered ring undergoes electrophilic substitutions while the six-membered ring resembles the reactivity of a pyridine ring. Recent density functional theory (DFT) calculations (B3LYP/6-31G^{*}) showed that the pyrrole-like ring has an extended highest occupied molecular orbital (HOMO), whereas the lowest unoccupied molecular orbital (LUMO) mostly resides at the pyridine ring, a distribution that is not appreciably varied by the introduction of an electron-withdrawing group at the C-6 position <2004OL1159>. Moreover, another study performed on substituted indolizines (DFT, B3LYP/6-31G) indicated that the C-3 is always the carbon atom with the highest electron density and with the largest atomic coefficient in the HOMO, and is therefore the preferential site of attack by an electrophile <2004JOC2332>.

The aromaticity of indolizine was examined using the nucleus-independent chemical shift values at several different levels of theory confirming the trend indole > isoindole > indolizine <2003JMT157>.

11.09.3 Experimental Structural Methods

The X-ray analysis of compound **2** (**Figure 2**) was used to confirm its structure and revealed that only the carbomethoxy group at C-1 lies on the plane of indolizine nucleus as already evidenced for other 1,2,3-trisubstituted indolizidines <2000CHE1192>.

The NMR spectra of indolizidine derivatives have already been described accurately <1984CHEC(4)443; 1996CHEC-II(8)237>; more recently, the extensive use of mono- and bidimensional ¹H and ¹³C NMR spectra allowed the structural assignment of natural compounds such as grandisine A possessing an indolizidine nucleus (**Figure 3**) <2005JOC1889>.

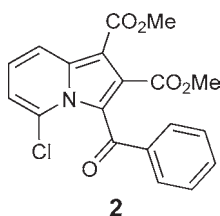


Figure 2

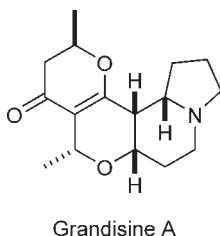


Figure 3

11.09.4 Thermodynamic Aspects

It is worth while to describe briefly the conformational behavior of the fully saturated bicyclic system, previously analyzed <1984CHEC-I(4)443>. The *trans*-fused conformation, shown in compound **3**, is significantly more stable in respect to the *cis*-isomer by 10 kJ mol^{-1} (Figure 4). As a general rule, the pseudoequatorial position for the five-membered ring and the equatorial position of the six-membered ring are favored. Infrared (IR) spectroscopy is a useful tool for determining the *trans*-fusion and they are present in several indolizidine derivatives. The presence of substituents can influence the stereochemistry of the fusion as demonstrated by the two compounds **3** and **4** whose structures were obtained by X-ray diffraction analysis of their salts <2003JOC9214>.

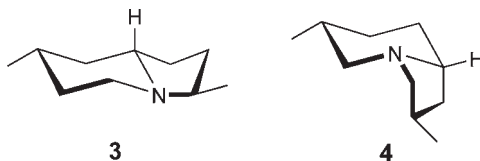


Figure 4

Several pyridyl-substituted indolizines are fluorescent and their photophysics have been studied <1999MI155, 2002MI279>. This property has found application in the synthesis of indolizine-substituted β -cyclodextrins <2005T3939> used as fluorescent chemosensors for organic guest molecules <2005CAR1706, 2005JFC385>.

11.09.5 Reactivity of Fully Conjugated Rings

The reactivity of the fully conjugated rings has already been described in details in the preceding editions of CHEC(1984) and CHEC-II(1996), and no significant advances have been reported <1984CHEC(4)443, 1996CHEC-II(8)237>. The most general features of this reactivity can be summarized as follows.

Indolizine is an electron-rich system and its reactions involve mainly electrophilic substitutions, which occur about as readily as for indole and go preferentially at the C-3 position, but may also take place at the C-1. Consistent with their similarity with pyrroles rather than pyridines, indolizines are not attacked by nucleophiles nor are there examples of nucleophilic displacement of halide-substituted systems.

Indolizine is much more basic than indole ($pK_a = 3.9$ vs. -3.5), and the stability of the cation makes it less reactive and resistant to acid-catalyzed polymerization. Protonation occurs at C-3, although 3-methylindolizine protonates also at C-1. Introduction of methyl groups raises the basicity of indolizines. Electrophilic substitutions such as acylation, Vilsmeier formylation, and diazo-coupling all take place at C-3. Nitration of 2-methylindolizine under mild conditions results in substitution at C-3, but under strongly acidic conditions it takes place at C-1, presumably via attack on the indolizinium cation. However, the nitration of indolizines often can provoke oxidation processes.

Catalytic reduction in acidic solution gives a pyridinium salt. Complete saturation, affording indolizidines, results from reduction over platinum.

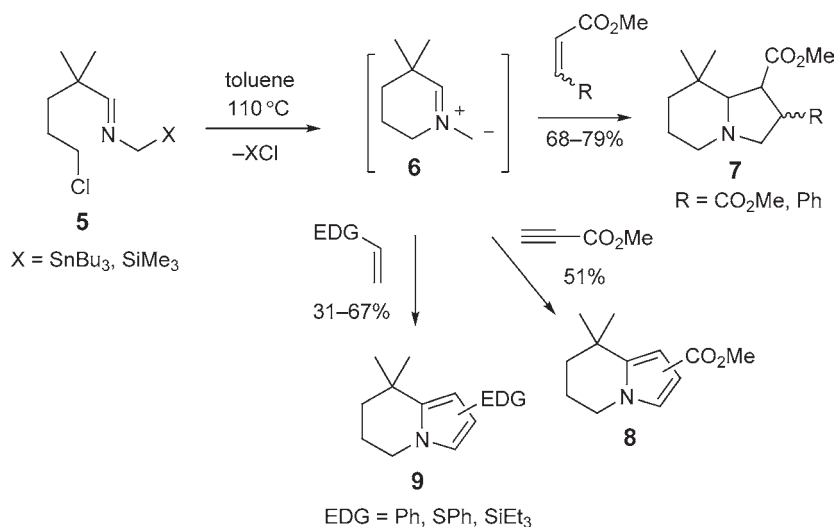
Despite its 10-electron aromatic π -system, indolizine apparently participates as an eight-electron system in its reaction with acetylene dicarboxylate, although the process may be stepwise and not concerted. By carrying out the reaction in the presence of a noble metal as catalyst, the initial adduct is converted into an aromatic cyclazine.

11.09.6 Ring Synthesis from Acyclic Compounds

11.09.6.1 Simultaneous Formation of More than One Bond

11.09.6.1.1 Cycloadditions

A 1,3-dipolar cycloaddition of the nonstabilized azomethine ylide **6** is the key step in a three-component reaction. The azomethine ylides were generated from (2-azaallyl)stannanes or (2-azaallyl)silanes **5** through an intramolecular *N*-alkylation/demetallation cascade. The ylides underwent cycloaddition reactions with dipolarophiles yielding indolizidine derivatives **7–9** <2004JOC1919> (Scheme 1).



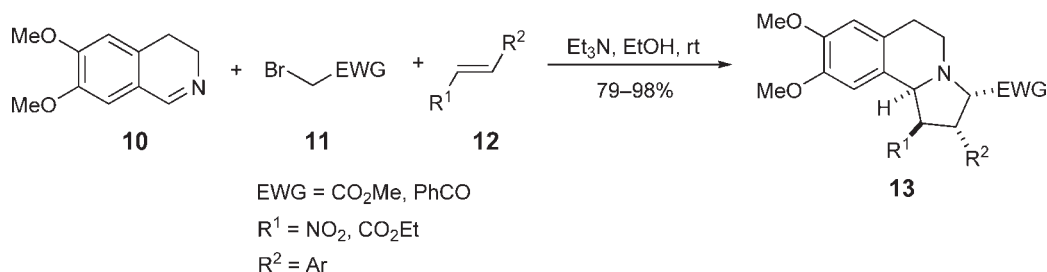
Scheme 1

An azomethyne ylide is also invoked as an intermediate in the three-component reaction between the dihydroisoquinoline **10**, an alkylating reagent **11**, and the dipolarophile **12**, which, in a one-pot process, afforded the indolizidine derivatives **13** <2005S2039> (Scheme 2).

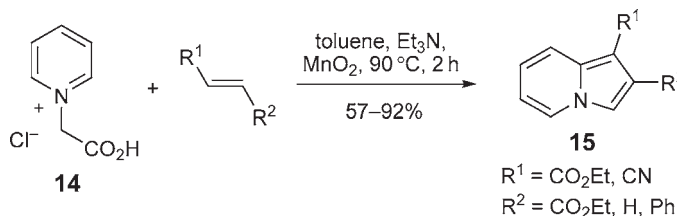
The 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient alkenes and alkynes has been used for a long time. More recently, this reaction was applied to the synthesis of 3-unsubstituted indolizines using *N*-(carboxymethyl)pyridinium halides which underwent decarboxylation upon cycloaddition <2000S1733>. The reaction was performed using electron-deficient alkenes together with a mild oxidant such as MnO_2 to obtain the fully conjugated product (Scheme 3).

Using benzotriazole methodology, it was possible to obtain indolizine compounds by cycloaddition of benzotriazole-substituted *N*-ylides to bromoalkenes and acetylene derivatives <1999JOC7618>.

This cycloaddition has found application in the combinatorial synthesis of indolizines on solid support <1999TL8741; 2005BML453> and on soluble support as poly(ethyleneglycol) <2004SL1231>.

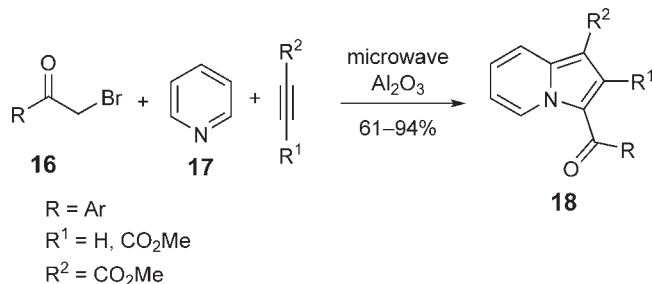


Scheme 2



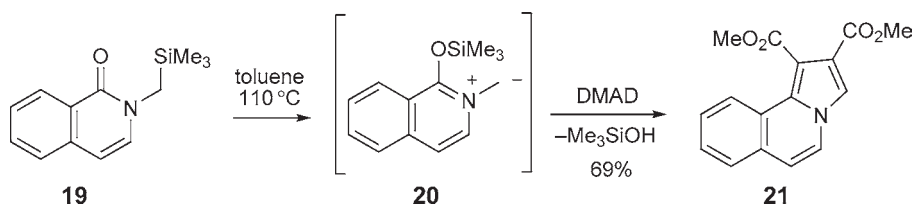
Scheme 3

A recent method for the synthesis of the indolizine skeleton is represented by a three-component reaction between α -bromo ketones **16**, pyridine **17**, and ethyl propiolate or diethyl acetylenedicarboxylate. These three reagents, under microwave irradiation and catalysis by basic alumina, afforded a good variety of 3-aryl indolizines **18** <2003OL435> (Scheme 4).



Scheme 4

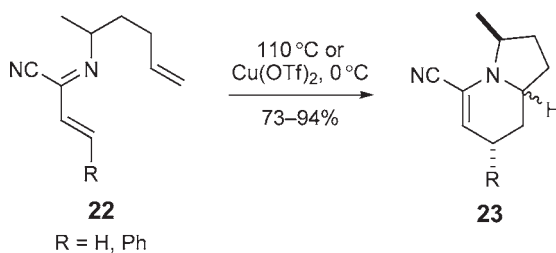
Another variation of this procedure is provided by the use of *N*-(silylmethyl)pyridine analogues **19**, which through 1,4-silatropy and subsequent 1,3-dipolar cycloaddition afforded the corresponding indolizines **21** <2003S1398> (Scheme 5).



Scheme 5

Also, tetrahydroquinolizinium ylides have found application in 1,3-dipolar cycloadditions with acetylenic esters <2001JOC1638>.

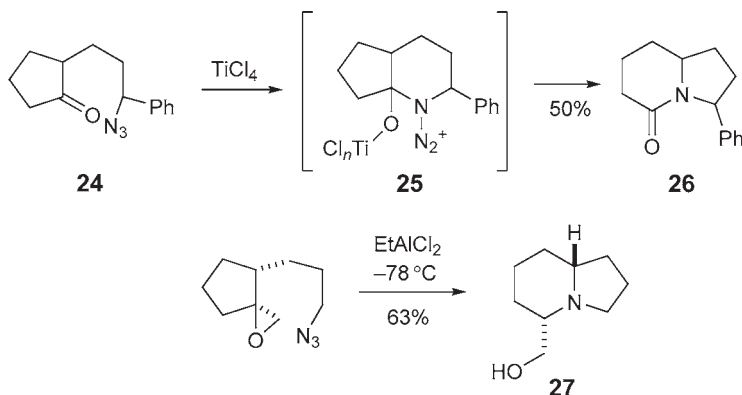
Finally, intramolecular Diels–Alder reactions, catalyzed by Lewis acids [<1999TL7215>](#) or thermally induced [<1997JOC2093>](#), were used to obtain cyano-substituted indolizidine derivatives (**Scheme 6**).



Scheme 6

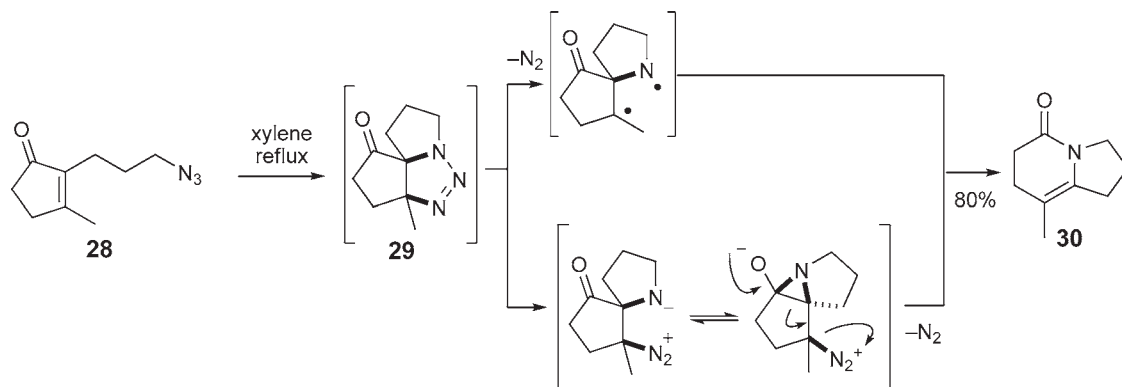
11.09.6.1.2 Other reactions

Alkyl azides have been involved in the synthesis of indolizidinone derivatives in several ways. One example (**Scheme 7**) is the intramolecular Schmidt reaction between alkyl azides and ketones which can be used to transform azidoketone **24** into the corresponding indolizidinones **26** through intermediate **25** [<2001JOC886>](#) or with epoxides to obtain the indolizidine **27** [<2004JOC3093>](#).



Scheme 7

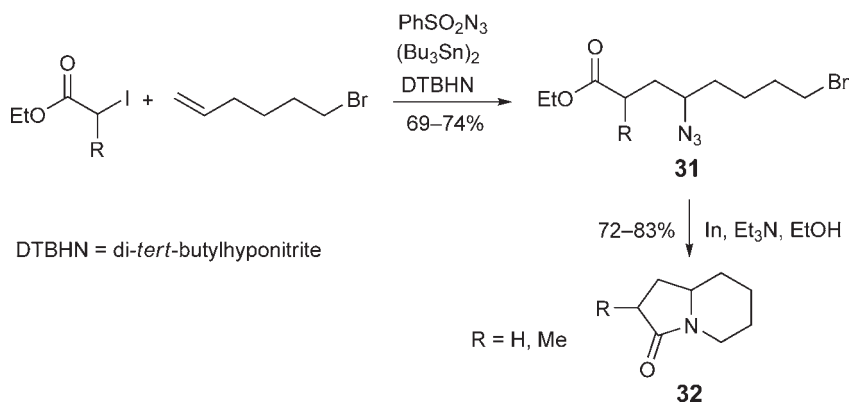
In another example (**Scheme 8**), the intramolecular cycloaddition of an azido functionality onto an enone group afforded bicyclic derivatives with bridgehead *N* atoms. The cyclopentenone derivative **28** afforded the indolizidinone **30** through the proposed compound **29** which might react through a diradical intermediate or through a betaine intermediate [<2002TL5385>](#).



Scheme 8

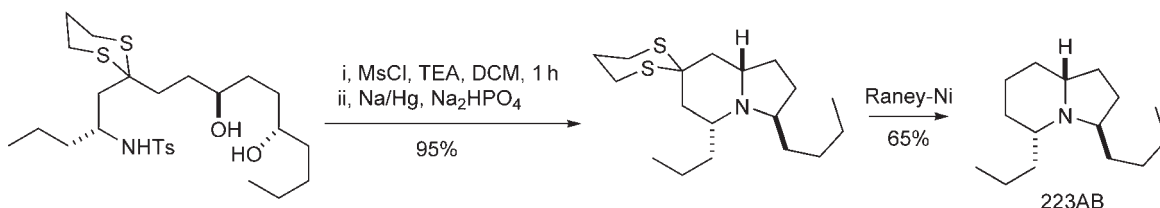
11.09.6.2 Sequential Formation of Bonds

Azides are also involved in other procedures in order to obtain the indolizidinone skeleton where the azido group acts only as a precursor of a primary amine group. The radical carboazidation process described in [Scheme 9](#) allowed the easy assembly of the precursor **31** which upon reduction of the azido group afforded the indolizidinones **32** in good overall yield [<2004JOC2755>](#).



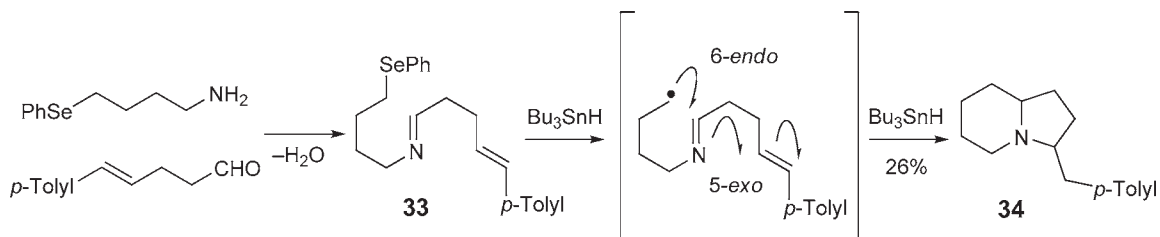
Scheme 9

Reactions where the reduction of a functionalized nitrogen, or the deprotection of an amine group, start a domino process with the sequential formation of the two rings of the indolizidine system, find many examples in the literature. A recent one is provided by the synthesis of (–)-indolizidine 223AB [<2004OL1493>](#) ([Scheme 10](#)).



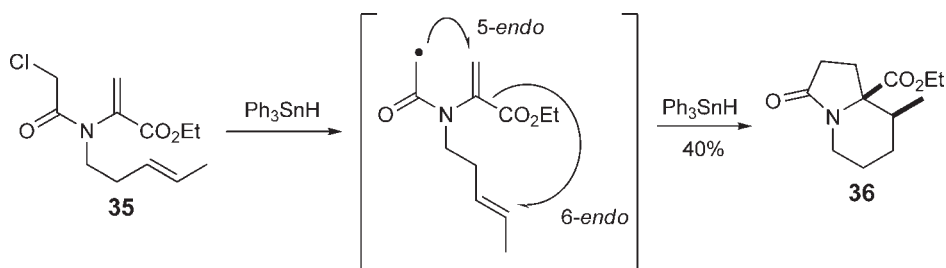
Scheme 10

Several methods based on radical cyclizations have been developed and applied to the synthesis of the fully saturated system. An example ([Scheme 11](#)) is provided by the tandem radical cyclization of properly substituted imines **33** obtained from ω -benzeneselenylamines and aldehydes [<1995TL5623>](#).



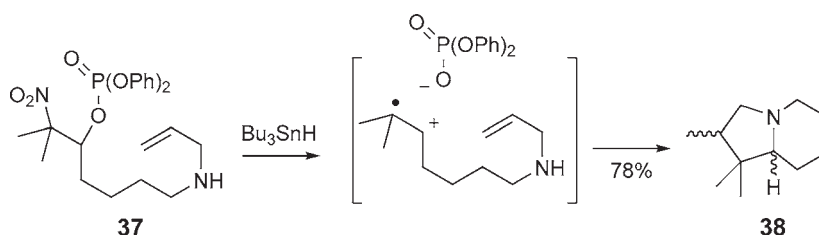
Scheme 11

The same approach ([Scheme 12](#)) was used with the amide **35** involving a 5-*endo*/6-*endo*-trig-tandem cyclization, which afforded exclusively indolizidinone **36** [<1998TL7197>](#).



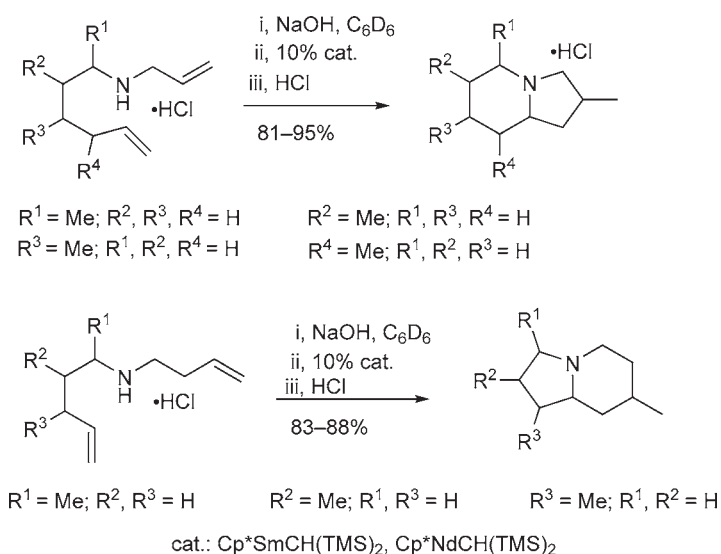
Scheme 12

Phosphorylated derivatives of β -nitroalcohols, upon exposure to Bu_3SnH and AIBN, afford β -(phosphatoxy)alkyl radicals. These radicals undergo heterolytic cleavage of the phosphate group to afford an alkene radical cation which is trapped intramolecularly in a tandem polar/radical crossover sequence. Derivative **37** (Scheme 13), through a 6-*exo*/5-*exo* overall cyclization, afforded the indolizidine derivative **38** as an equimolecular mixture of two diastereoisomers <2003JA7942, 2002OL2573>.



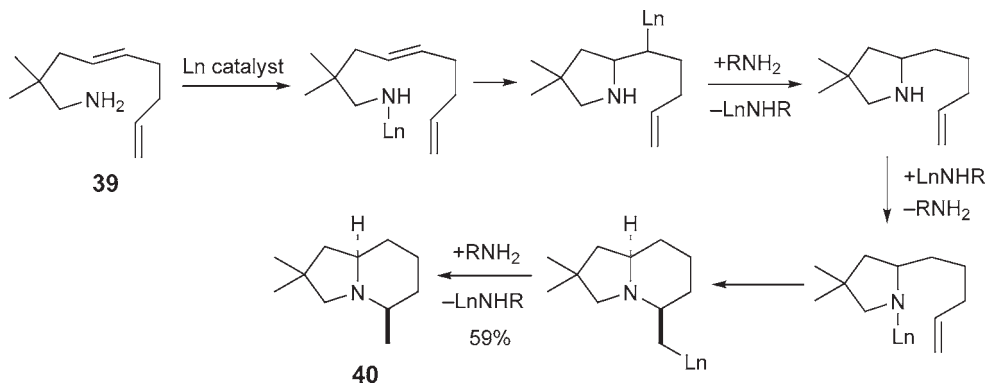
Scheme 13

The organolanthanide-catalyzed intramolecular amination/cyclization reaction revealed to be a useful tool for the synthesis of the fully saturated system and has been studied in detail by several authors. In this process, C–N and C–C bond-forming steps can be coupled to assemble the indolizidine skeleton, as well as other nitrogen-containing heterocycles. Using different catalysts such as $\text{Cp}^*\text{SmCH}(\text{TMS})_2$ and $\text{Cp}^*\text{NdCH}(\text{TMS})_2$, a large number of the possible regioisomers of dimethyl-substituted indolizidine (Scheme 14) were obtained <2003JOC9214, 1998JA1757>.



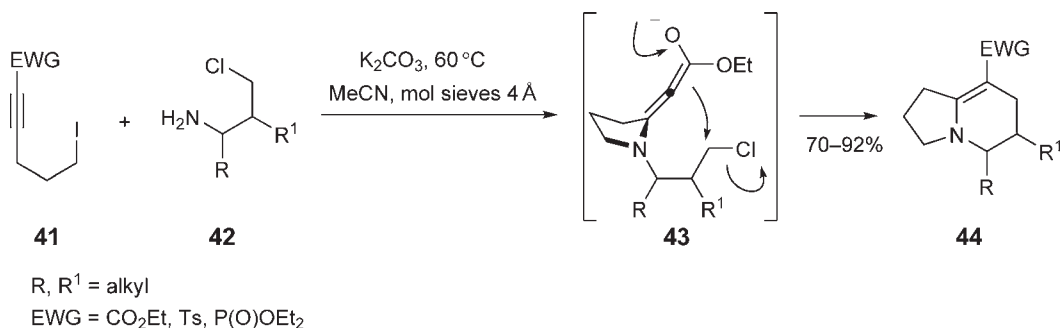
Scheme 14

Recently the primary amine **39** was transformed into indolizidine **40** using an ytterbium catalyst. After a regio-specific C=C bond insertion of the internal olefin into the Ln–N bond, a second insertion is accomplished as illustrated in the proposed mechanism <2004JOC1038> (Scheme 15).



Scheme 15

An efficient sequential reaction process was developed from γ -amino chlorides **42** with propargylate **41** (Scheme 16). In the proposed mechanism, after the alkylation of the nitrogen atom, a subsequent cyclization by the same nucleophilic center induced the formation of intermediate **43**, which cyclized to afford the indolizidine **44** <2001OL3927, 2005OL705>. This synthetic approach found application in the synthesis of indolizidine 223A.



Scheme 16

11.09.7 Ring Syntheses by Transformation of Another Ring

The literature reported in the chapter is organized according to the following criteria:

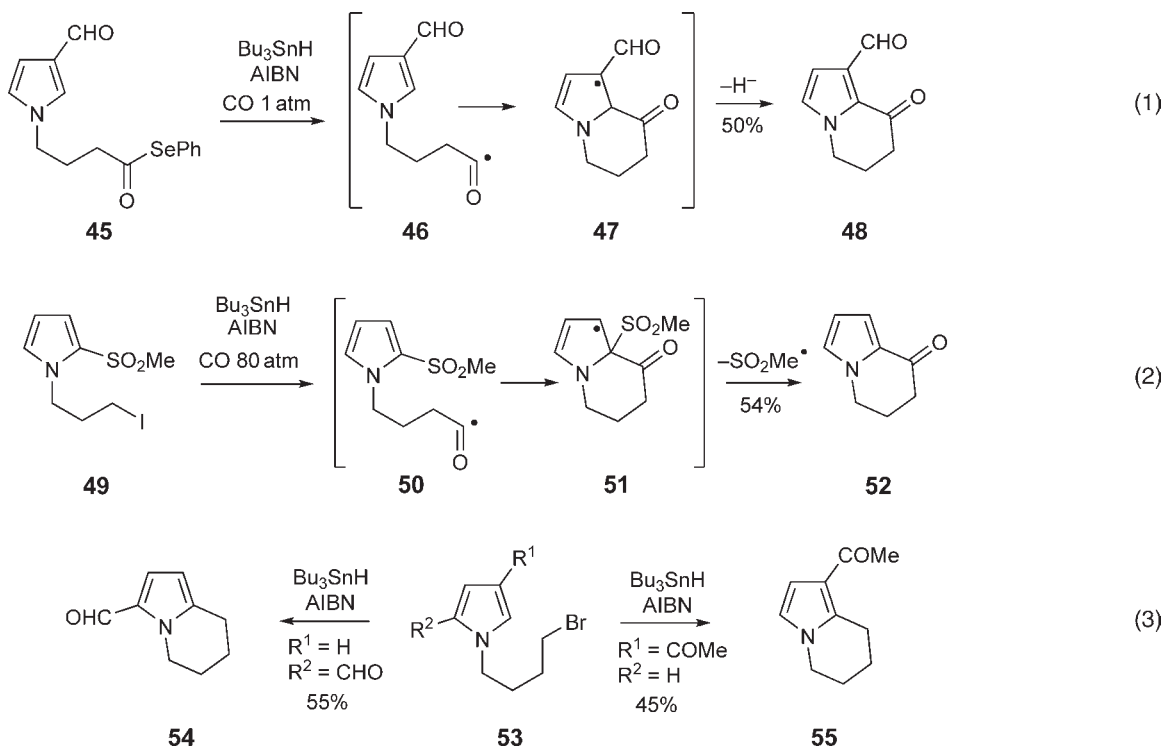
- (1) the size of the azaheterocyclic ring (five-membered or six-membered) preexisting in the starting material; and
- (2) the number of carbon atoms of the fragment present on the heterocyclic nitrogen atom which is involved in the cyclization step (when the fragment present on the starting material is able to form a ring (four atoms for a five-membered ring, three atoms for a six-membered ring), it is treated independently from the point of attachment of the fragment on the ring).

11.09.7.1 Starting Materials Containing One Five-Membered Aza Heterocyclic Ring

11.09.7.1.1 Reagents contributing four carbon atom fragments

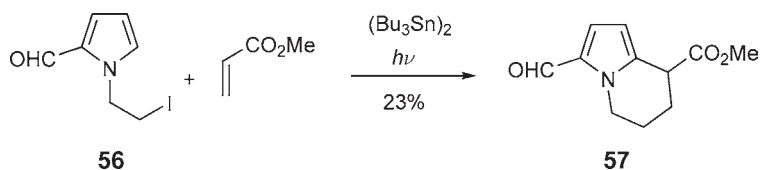
Several radical reactions were used for the synthesis of indolizine derivatives via a ring closure involving the substituent present on the nitrogen atom of a pyrrole ring. Starting from acylselenide precursors **45**, it was possible to obtain indolizidinone derivative **48** with good yields (Scheme 17, Equation 1) <2001TL7887>. To avoid the loss of carbon monoxide it was necessary to maintain a CO atmosphere in the reaction, although at ambient pressure.

The use of a higher CO pressure allowed the same intramolecular reaction starting with alkyl iodide derivatives **49** <2000TL3035> (Scheme 17, Equation 2). Without the presence of the CO atmosphere, the same reaction affords the expected indolizine derivatives **54** and **55** <1997TL7937> (Scheme 17, Equation 3).



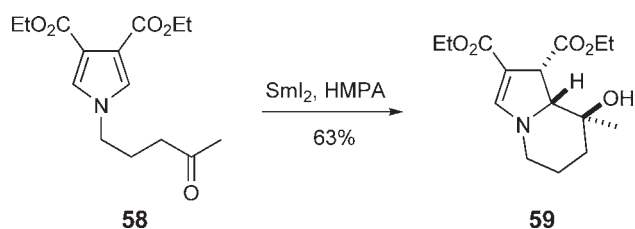
Scheme 17

The radical cyclization can also involve an acrylate to obtain CO₂Me-substituted indolizine derivatives **57** (Scheme 18) <2000TL10181>.



Scheme 18

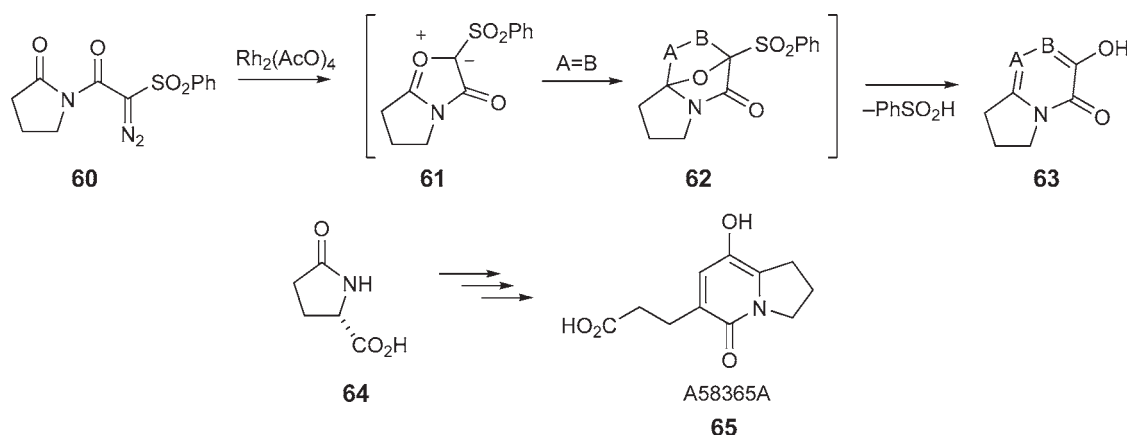
A radical anion is involved in the samarium iodide-induced cyclization of the pyrrole derivative **58** (Scheme 19) <2003OL4305>.



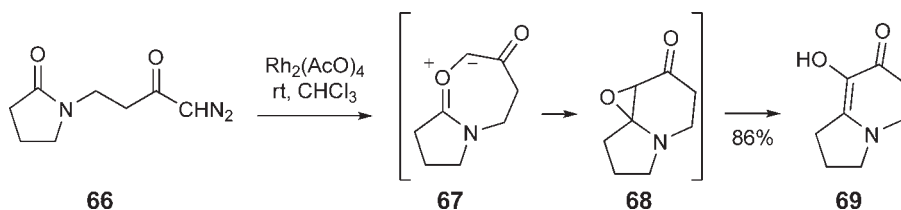
Scheme 19

The isomunchnone-based 1,3-dipolar cycloaddition approach proved to be very useful for the synthesis of several different compounds possessing the indolizine skeleton. This synthetic procedure starts from the diazoimide **60**, which, under the catalysis of $\text{Rh}_2(\text{AcO})_4$, gives a rhodium carbenoid species that undergoes an intramolecular cyclization onto the neighboring carbonyl oxygen to form the mesoionic 1,3-dipole **61**. This 1,3-dipole can be trapped with several dipolarophiles, such as phenyl vinyl sulfone, methyl acrylate, methyl vinyl ketone, and isobutyl vinyl ether to form the unstable adduct **62** that, by elimination of PhSO_2H , affords the corresponding indolizine **63** (Scheme 20) <1999JOC8648, 2003OL4195>.

The possibility to vary the regiochemistry of the 1,3-dipolar cycloaddition, using electron-rich or electron-poor alkenes as dipolarophiles, and the further elaboration of the final adducts make this approach extremely versatile as demonstrated by the synthesis of the ACE inhibitor A58365A **65** starting from L-pyrroglutamic acid **64** (Scheme 20) <1999JOC8648>. In a similar process, the diazoketoamide **66** underwent a Rh-catalyzed transformation into derivative **69** through the formation of the dipole **67** which rearranged to the epoxide **68** (Scheme 21) <2000JOC7124>.



Scheme 20

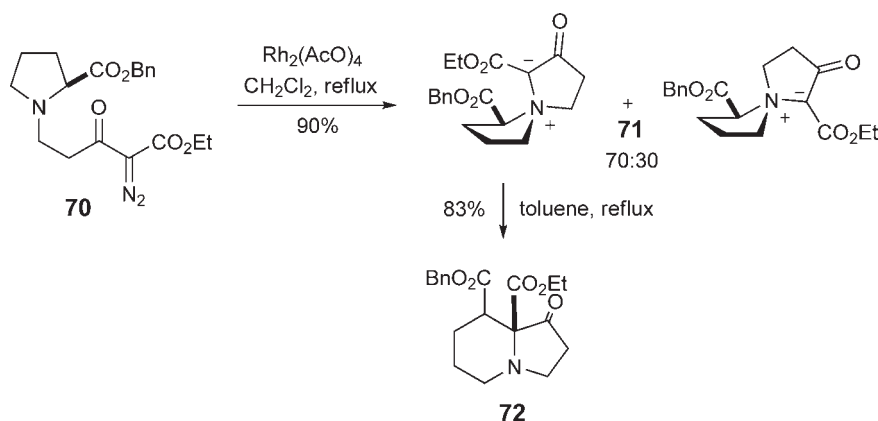


Scheme 21

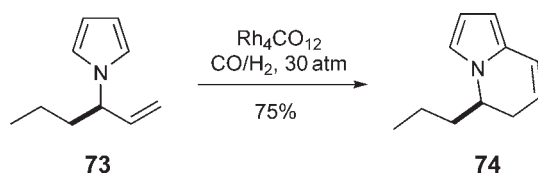
Coupling the metal carbene reactivity with the [1,2]-Stevens rearrangement was demonstrated to be useful for obtaining indolizidine skeleton (Scheme 22) <2004TA2609>. The diazo compound **70**, obtained from proline, using $\text{Rh}_2(\text{OAc})_4$ or $\text{Cu}(\text{acac})_2$ as catalyst, afforded the corresponding ammonium ylide **71** as a mixture of two diastereoisomers. Each of the two ylides underwent stereospecific [1,2]-Stevens rearrangement in refluxing toluene. The major diastereoisomer afforded indolizidinone **72**.

Again, rhodium-complexes, although in a completely different process, catalyzed the formation of indolizidine derivatives through the hydroformylation of pyrroles bearing a terminal double bond. The intermediate aldehyde reacted to afford the final product **74** (Scheme 23) <2004TA1821>.

The extension of the Kulinkovich reaction to succinimide **75** gave a new entry into substituted indolizidines. Initially, it was demonstrated that reacting **75** under the Kulinkovich conditions, with terminal alkenes and



Scheme 22



Scheme 23

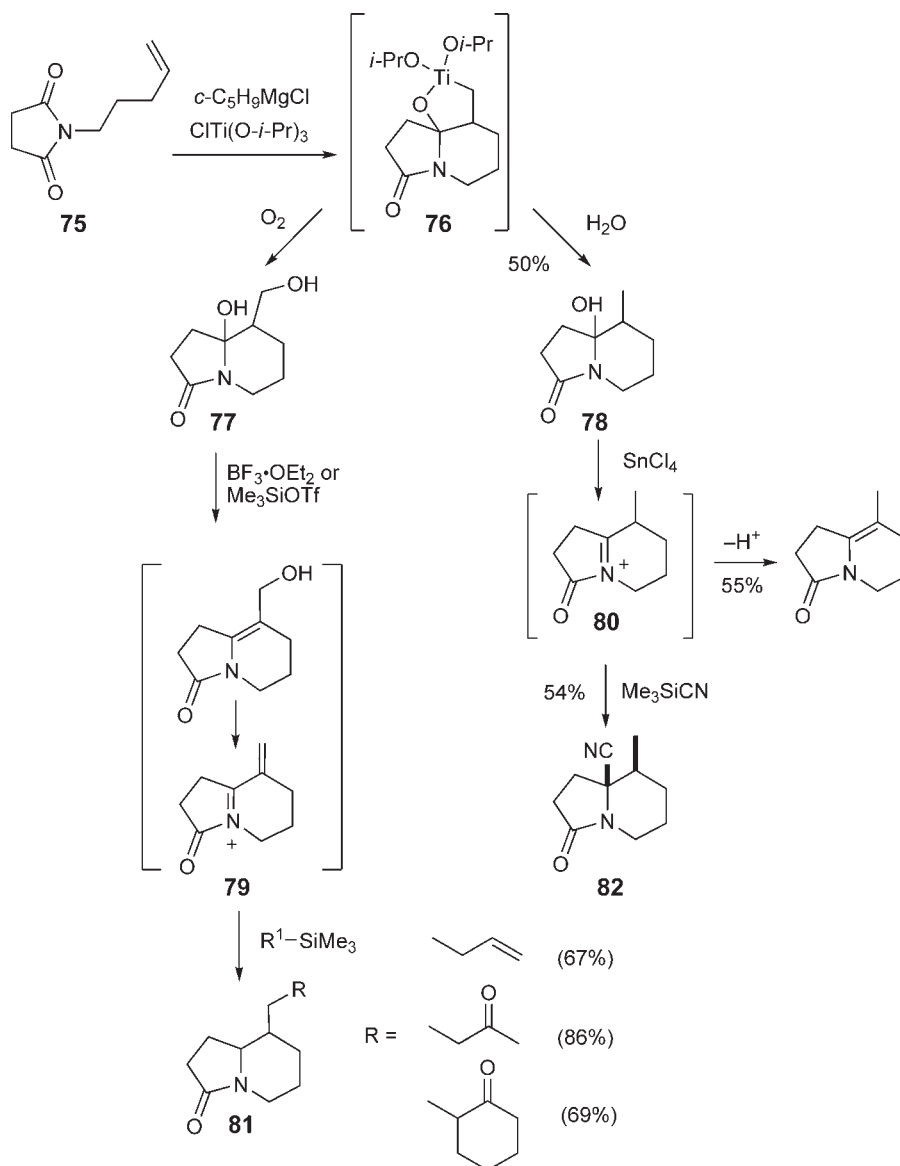
cyclopentylmagnesium chloride, afforded intermediate **76**, which was hydrolyzed to afford compounds **77** and **78** (Scheme 24) <1997JA8127>. Later on, it was demonstrated that compounds **77** and **78** represented useful precursors to tertiary *N*-acyliminium ions which reacted with a wide variety of nucleophiles affording several new indolizidinone derivatives <1999OL1331>.

Indolizidinone compounds can also be obtained through secondary *N*-acyliminium ions as outlined in the next three examples (Scheme 25), differing in the nature of the nucleophilic moiety. In the first example (Scheme 25, Equation 4) it is a furan ring (compound **83**) which acted intramolecularly as a nucleophile. By varying the substitution pattern on the furan ring, as in **83** and **86**, it is possible to obtain a variety of derivatives <1998JOC6914>. The intermolecular reaction of the acyliminium ion with a furanone precursor **90** easily affords indolizidinones (Scheme 25 Equation 5) <2000TL9709; 2000TL2899>. A similar intramolecular approach was also used with *N*-acyliminium ions derived from sulfur-substituted lactams <1998TL8585>. In the third example (Scheme 25, Equation 6), an alkynyltungsten moiety **94** acted as a nucleophile affording carbobenzyloxy-substituted indolizidinones **95** <2001JOC6193>.

The 1,3-dipolar cycloadditions of five-membered cyclic nitrone **96** with alkylidenecyclopropane derivatives **97** proved to be very efficient, considering both the number of structures obtained and the straightforward procedure. The key step in this procedure is the thermal rearrangement of the intermediate isoxazolidine **98**, whose reactivity is largely influenced by the nature of the substituents both on the starting alkylidenecyclopropane and on the nitrone. The several possible transformations are depicted in Scheme 26 <2003CRV1213, 2005JOC5636, 2006JOC2417>. This procedure has found application in the synthesis of several natural products (see Section 11.09.8.2). More recently, the reduction of isoxazolidine N–O bond using SmI₂ <2004TL8375> afforded the corresponding aminoalcohols **101**, which, by treatment with Pd(OAc)₂, were transformed into the corresponding dihydropyridones **102**.

11.09.7.1.2 Reagents contributing three carbon atom fragments

The ring-closing metathesis (RCM) approach is useful for the synthesis of indolizidinone derivatives. The procedures published are based on the use of compound **103**, an amide of a pyrrolidine derivative bearing on C-1 the second unsaturated branch ready for the cyclization. The reaction proceeded smoothly with high yields in both examples (Scheme 27) <2001JOC9056, 2004JOC3968>.



Scheme 24

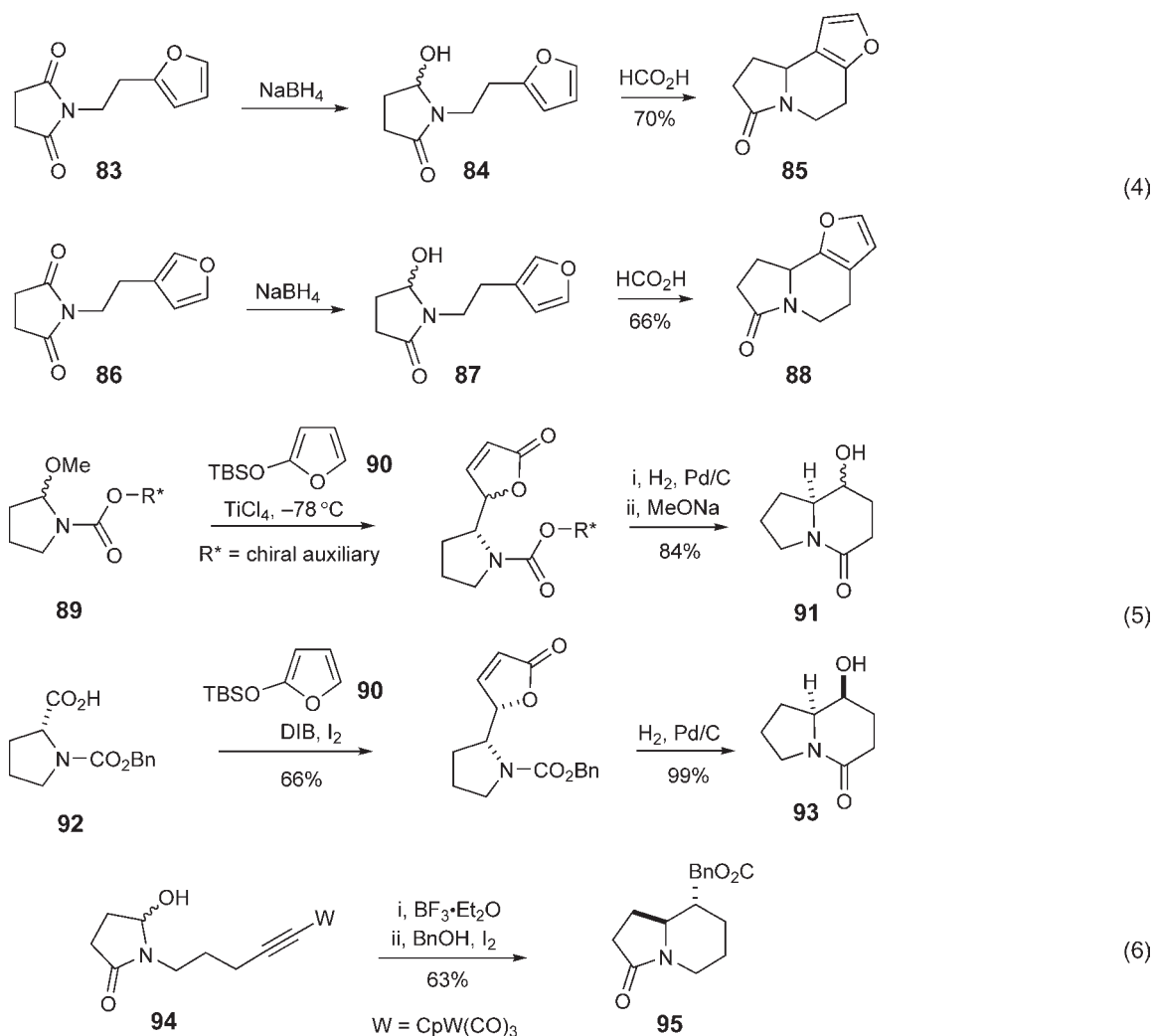
Another significant application of the metathesis reaction was obtained in the transformation of the bicyclic lactam **105** into the corresponding indolizidinone **107**. The overall transformation is obtained through a cross-metathesis (CM) with ethylene followed by a ring-opening metathesis (ROM) and an RCM process (Scheme 28) <2004TL565>.

Alkenyl and alkynyl Fischer carbene complexes reacted with pyrrole imine **108** to give, through a 1,2- and 1,3-metal migration, respectively, indolizine derivatives at a different level of unsaturation (Scheme 29) <1999JA3065>.

The addition of a titanium homoenolate **115** to a proline derivative **114** proved to be a feasible approach for the formal synthesis of pumiliotoxin 251D. The addition proceeded with high stereoselectivity (Scheme 30) <1999JOC1410>.

The same synthesis was also performed using a radical reaction for the transformation of compound **117**, again derived from proline <1996SL909>.

A Dieckmann cyclization was a key step in the synthesis of a renin inhibitor. In this case, the indolizidinone product was an useful intermediate toward the stereoselective synthesis of the open-chain product <2002JOC4261>.



Scheme 25

Finally, the enamine **119** easily cyclized to the corresponding indolizidine **120** in refluxing ethanol (Scheme 31) <2003JOC3281>.

11.09.7.1.3 Reagents contributing two carbon atom fragments

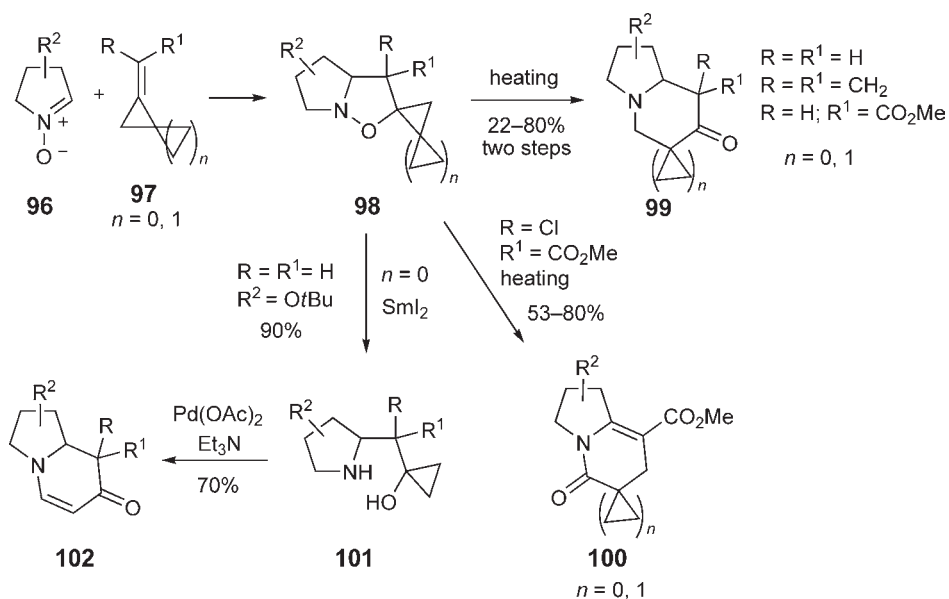
Also, in this case, the RCM approach has been employed with success. Most of the examples present in the literature concerned the use of γ -lactam derivatives (Scheme 32) <2002OL3497, 2000TA753, 2000SL319, 2004TL1559>.

Analogous substrates were used for an intramolecular Heck reaction to obtain indolizidinone derivatives (Scheme 33) <2000SL319, 2002S87>.

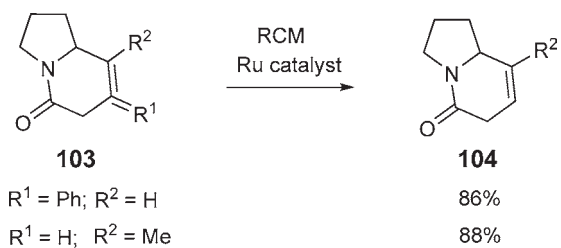
Some congeners of indolizidine 223A (compounds **135–138**) were obtained, using, as the key step, the silylstannylation/cyclization of allenic aldehydes as described in Scheme 34 <2004JOC9151>.

11.09.7.1.4 Reagents contributing one carbon atom fragment

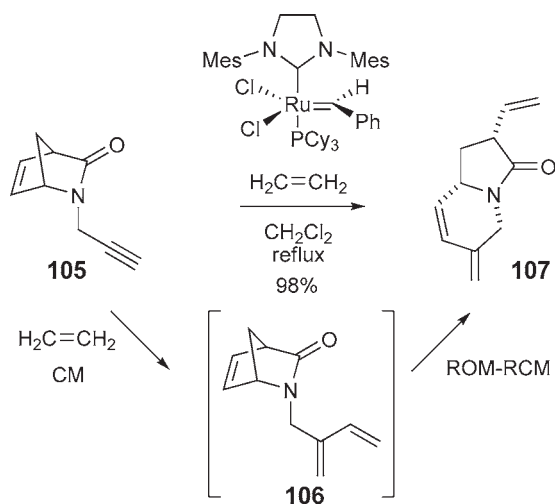
An oxidative Mannich cyclization methodology allowed the synthesis of indolizidine skeletons. The oxidation of the α -silylamide **140** with ceric ammonium nitrate (CAN) formed *in situ* an *N*-acylaminium cation, which cyclized to afford the bicyclic compound **141** (Scheme 35) <1998JOC841>.



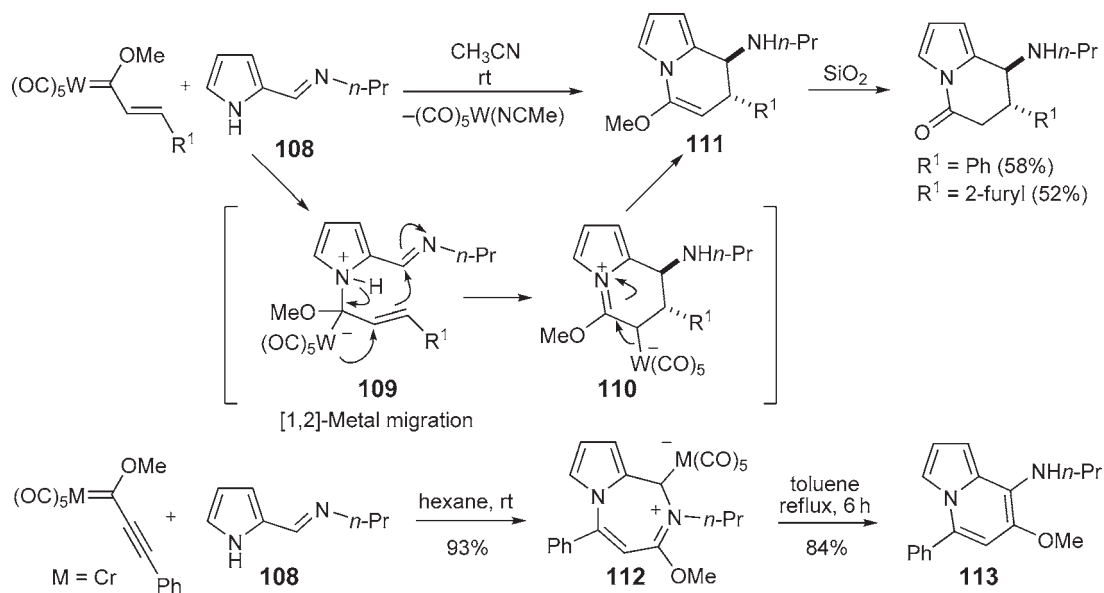
Scheme 26



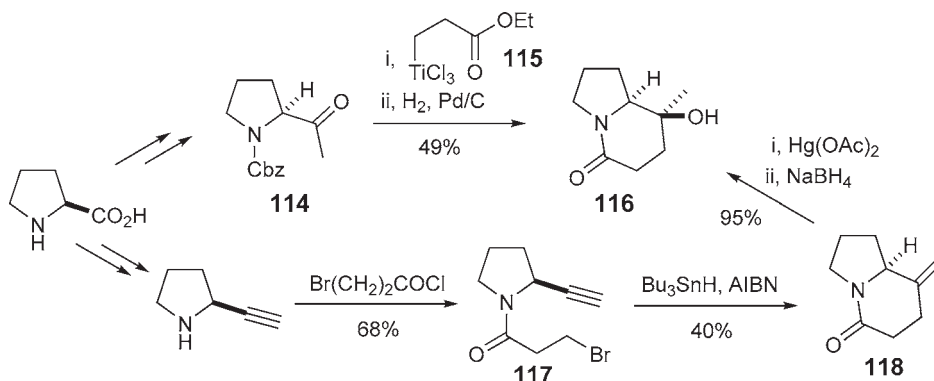
Scheme 27



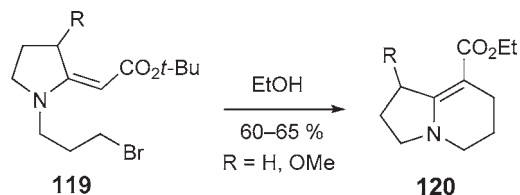
Scheme 28



Scheme 29



Scheme 30

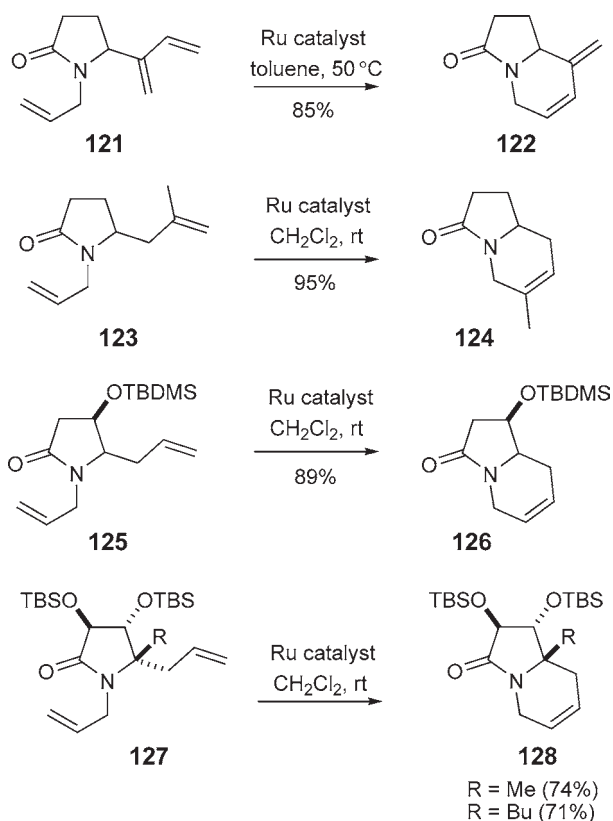


Scheme 31

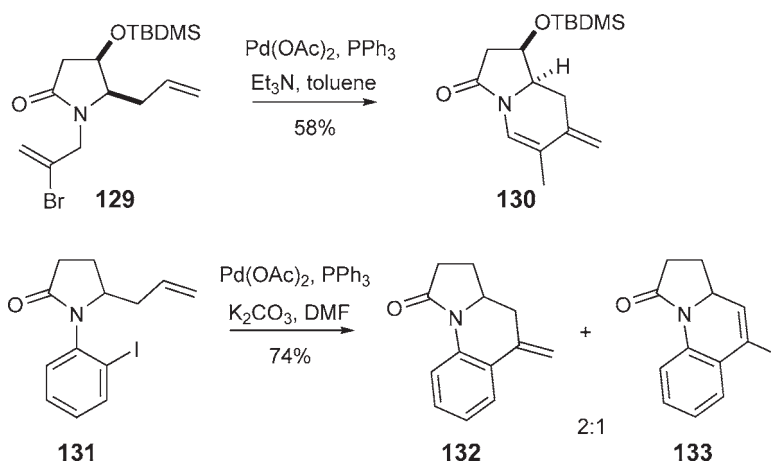
11.09.7.2 Starting Materials Containing One Six-Membered Aza Heterocyclic Ring

11.09.7.2.1 Reagents contributing three carbon atom fragments

Particularly straightforward is the synthesis of the indolizine skeleton by reacting the potassium salt of piperidine with 2-*tert*-butylthio-3-phenylcyclopropenethione **143** and methyl iodide (Scheme 36) <2000JOC3341>.



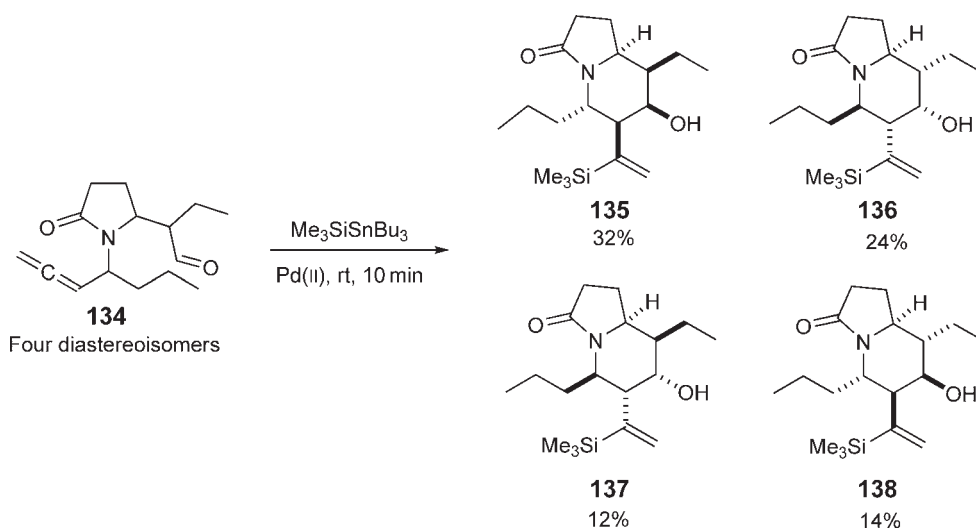
Scheme 32



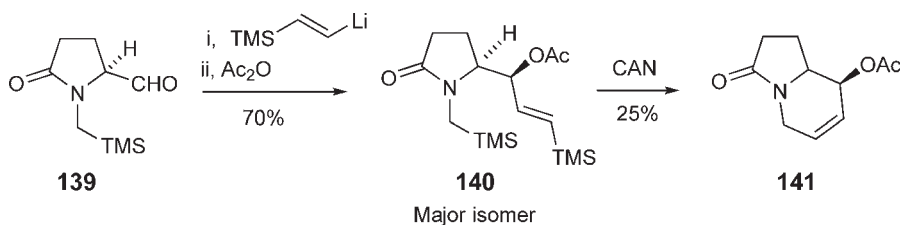
Scheme 33

Allene-substituted lactams or cyclic imines are useful intermediates in the synthesis of indolizine derivatives. While the former are stable and need a Pd(0) catalyst and the presence of phenyl iodide to react [<1997TL6275>](#), the latter are produced *in situ* and react immediately ([Scheme 37](#)) [<2001JA2074>](#).

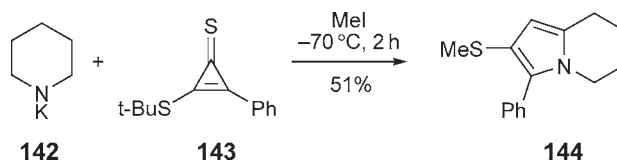
The lactam **145**, bearing a terminal triple bond, is transformed into the corresponding allene derivative **146** through a Crabbé reaction ([Equation 7](#)). Using Pd(PPh₃)₄ as the catalyst and in the presence of phenyl iodide, the corresponding indolizine is obtained. The lactam nitrogen atom is added to the central carbon atom of the allene



Scheme 34



Scheme 35



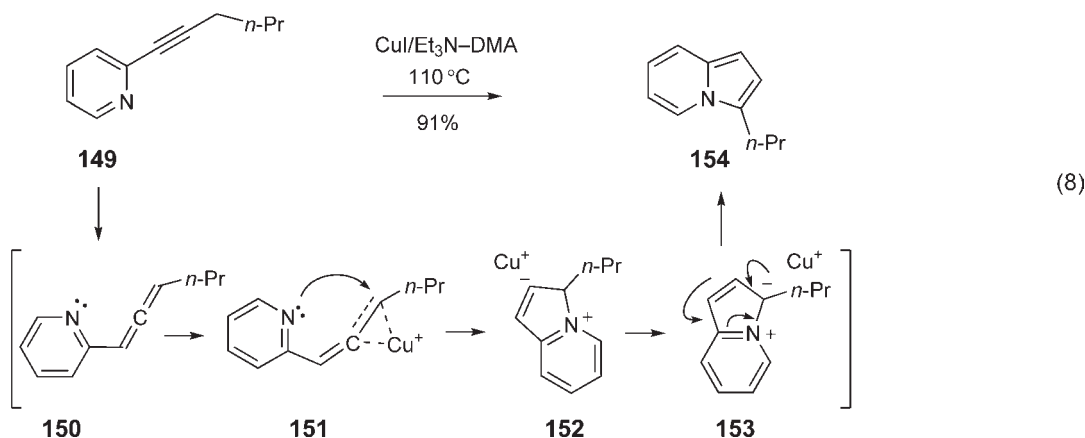
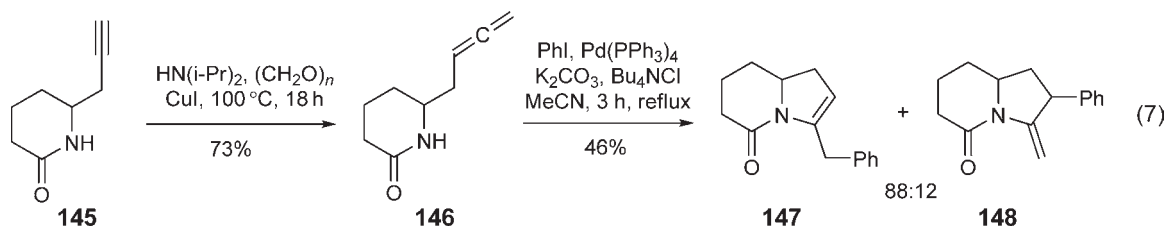
Scheme 36

group to afford a mixture of compounds **147** and **148** <1997TL6275>. On the other hand, the substituted pyridine **149** was proposed to undergo a base-induced propargyl allenyl isomerization. The allene **150** underwent the transformation to **154** through the mechanism proposed in Scheme 37 (Equation 8) <2001JA2074>.

Other approaches to enantiopure indolizidines using radical cyclization are reported (Scheme 38). The first example, Equation (9) <1996TL1599>, is based on the synthesis of the 1,4-dihydropyridine **157** starting from amina **155** and on the final radical cyclization, which afforded a mixture of compounds **158** and **159**. The second example, Equation (10), which essentially differs in the synthesis of the pyridine derivative, allowed the synthesis of indolizidinone **162** bearing a trifluoromethyl group on the bridgehead position <2002OL1571>. A similar procedure was used for the synthesis of 8*a*-*epi*-dendroprimine <2002JOC5044>. In the third example (Scheme 38, Equation 11) the approach is reversed, since the radical is formed on the pyridine ring <1997TL5383>.

An intramolecular Michael reaction affording indolizidinones **166** was initiated by addition of tetrabutylammonium triphenyldifluorosilicate (TBAT) on allylsilanes **165** (Scheme 39) <2003TL6629>.

Several other examples are reported in the literature on the synthesis of indolizidine skeleton through the intramolecular nucleophilic attack of the six-membered ring nitrogen atom onto an electrophilic center such as an alkyl halide <2000OL3861, 1997S95>, triflate <2001OL711>, and esters <1998TL5693>.



Scheme 37

11.09.7.2.2 Reagents contributing two carbon atom fragments

The Chichibabin reaction for the synthesis of indolizines has been revisited and some variations have been proposed. The modified benzotriazole **168** reacted with substituted pyridines **167** in refluxing dimethylformamide (DMF). The indolizine **169** bears a triazole moiety that proved useful for the construction of benzo-annulated indolizines [<2000JOC8059>](#). Also, cyclic iminium ylides like **170** can be used in the Chichibabin reaction. Their solvolysis produced the corresponding indolizinones **171** (Scheme 40).

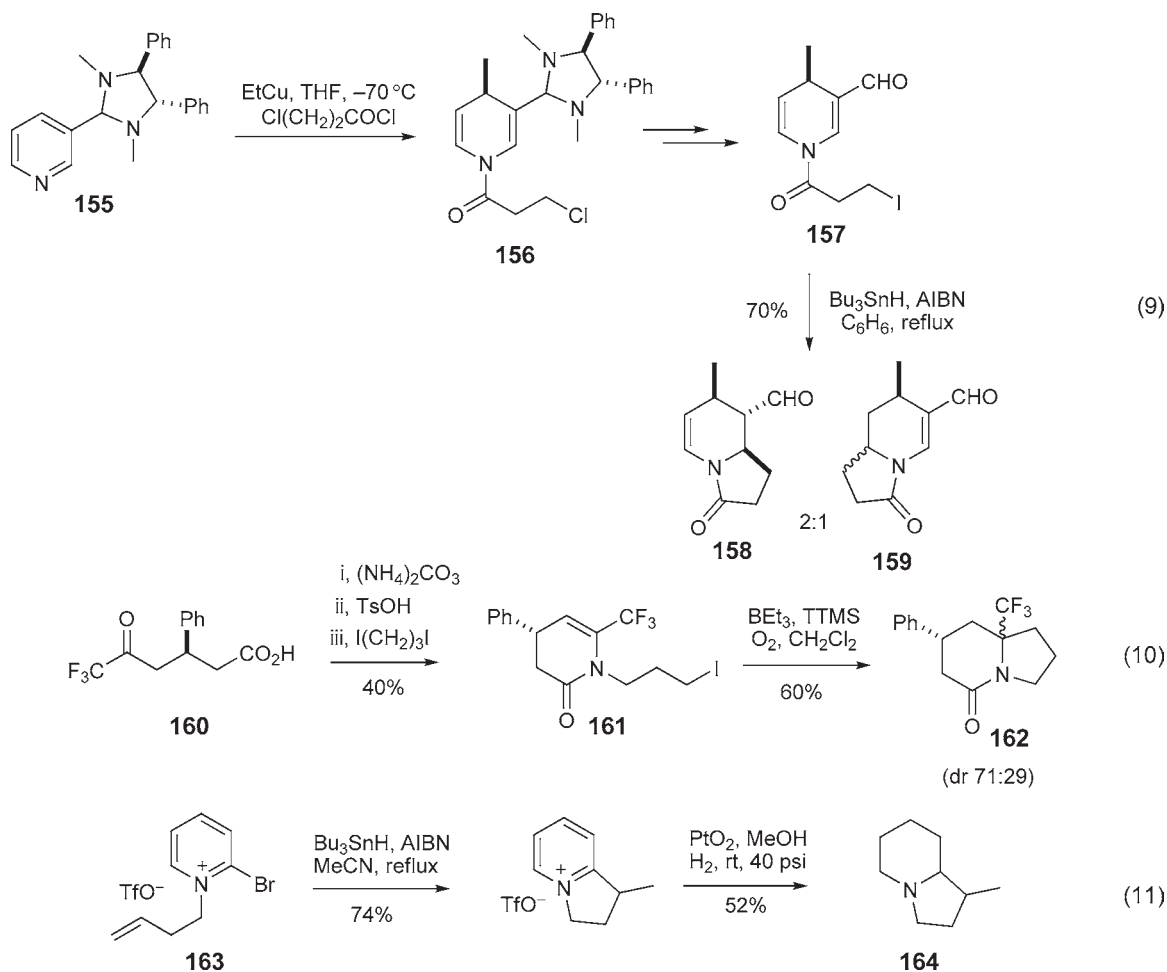
RCM chemistry has also been used to synthesize indolizinones (Scheme 41) [<2002OL1971>](#). The starting piperidine derivative, bearing the necessary unsaturated chains, was obtained through a diastereoselective aza-Diels–Alder reaction. After some elaboration, compound **173** was cyclized to afford the bicyclic derivative which proved unstable and was immediately reduced to indolizidinone **174**. An efficient synthetic approach is provided by a ‘one-pot’ procedure starting from the cyclic imine **175**, which, upon treatment with LDA, a nitrile and propargyl bromide, afforded the indolizine derivatives **179** in good overall yield (Scheme 42). The nucleophilic attack of the carbanion on the nitrile formed anion **177** which was alkylated with propargyl bromide. The obtained azadiene **178** obtained cyclized at room temperature to afford the bicyclic compounds **179** [<1996JOC2185>](#).

11.09.7.2.3 Reagents contributing one carbon atom fragment

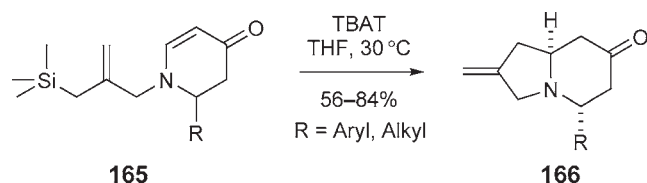
A useful method for the synthesis of 1-unsubstituted 2-arylindolizines is provided by the 1,5-dipolar cyclization of pyridinium ylides derived from **181**, in the presence of the oxidant tetrakis(pyridine)cobalt(II) dichromate (TPCD), which oxidizes the intermediate dihydroindolizine **182** (Scheme 43). The study demonstrated that the presence of an aryl group on the double bond was necessary for the reaction to occur.

11.09.7.3 Starting Materials Already Containing the Indolizidine Ring

Due to the widespread presence of the indolizidine skeleton in many natural products, both the procedures aimed at the functionalization and elaboration of the ring are also of interest. A clear example of this is represented by the elaboration of indolizidinone **184** that was transformed into several different polyhydroxy or alkylated products (Scheme 44) [<1995JOC398>](#).



Scheme 38

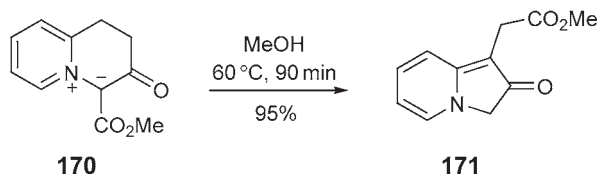
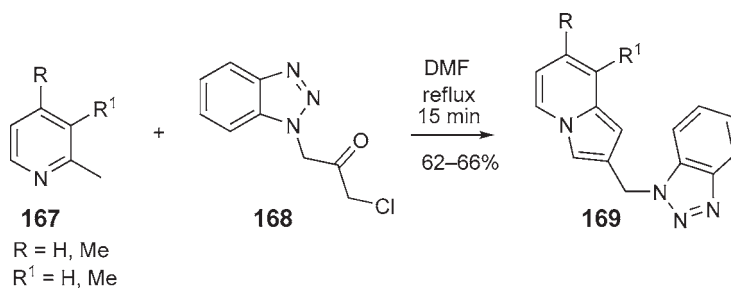


Scheme 39

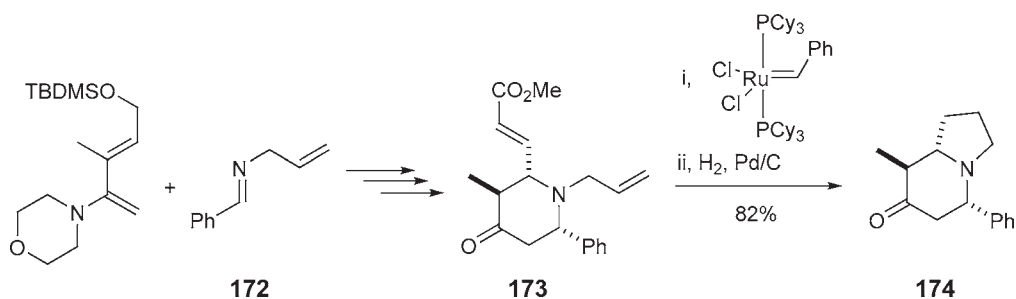
In the same research line is the decarboxylation procedure developed for the transformation of indolizidinones bearing a carboxylic group in the 8a-position <1996TL5581>. Of practical interest is the possibility to selectively reduce the double bond of unsaturated indolizindiones <2001JOC2181>.

Often, in the synthesis of natural products containing the indolizidine substructure, it is necessary to modify a preformed indolizidine ring. This is the case in the synthesis of (+)-myrmicarins **217** **191** where the key step is the closure of the third ring through an electrophilic substitution on the pyrrole nucleus (Scheme 45) <2000JOC2824>.

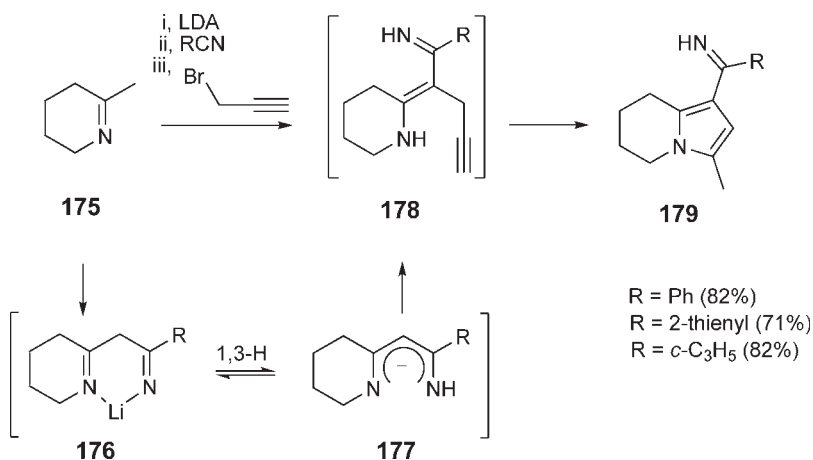
Finally, the Nazarov reaction was used to build a quaternary center in a study aimed at the synthesis of a potential precursor of cephalotaxine <2000S2113>.



Scheme 40



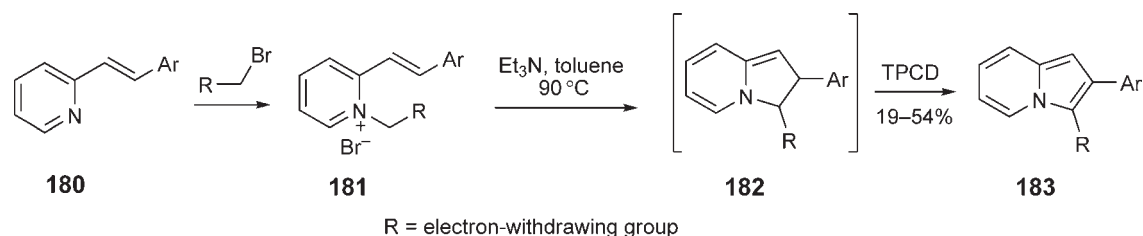
Scheme 41



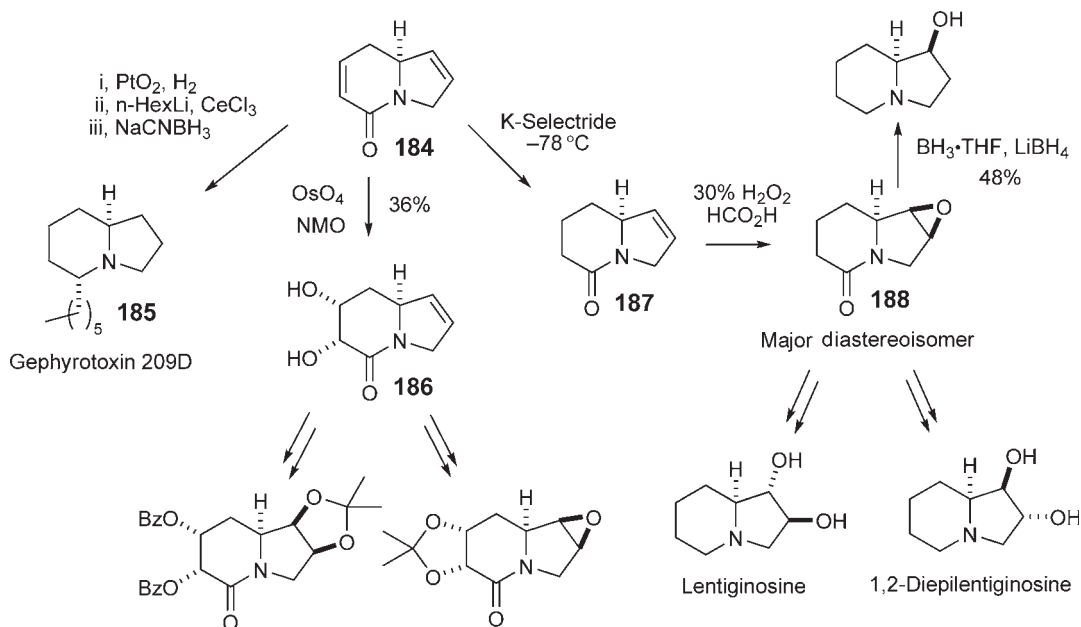
Scheme 42

11.09.8 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

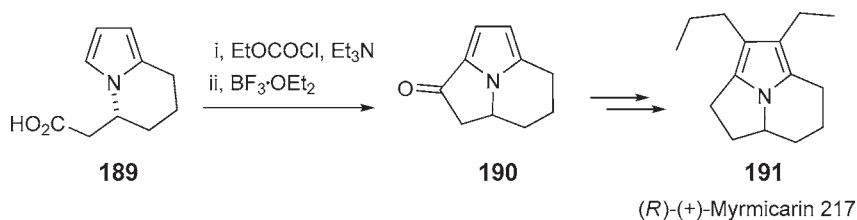
An impressive number of alkaloids and bioactive compounds containing the indolizidine skeleton have been synthesized. These belong principally to three classes which will be separately analyzed. Other natural products not belonging to these classes will be collected in section 11.09.8.3.



Scheme 43



Scheme 44

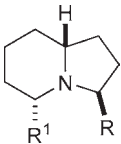
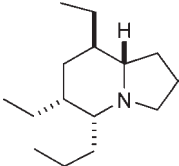
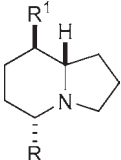


Scheme 45

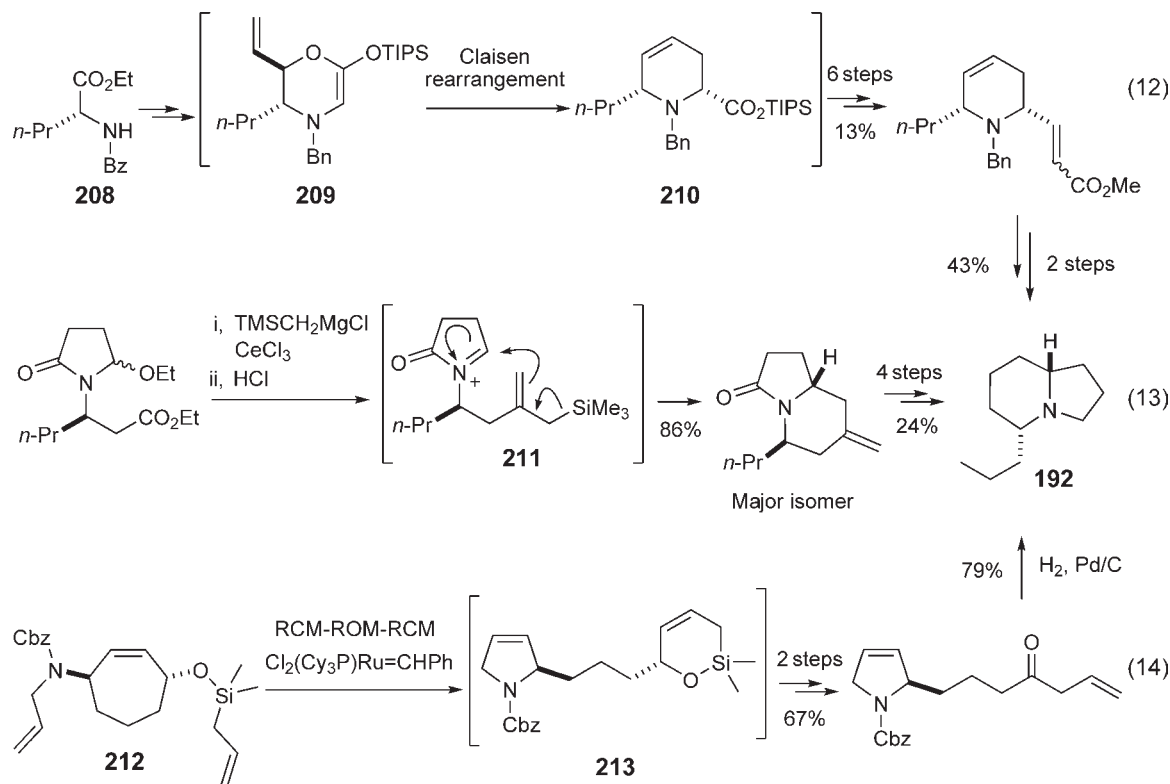
11.09.8.1 Amphibian Alkaloids

These alkaloids belong to a large class of compounds (more than 200), most of them containing the indolizidine skeleton, which are isolated from the skin of neotropical brightly colored frogs. These compounds have stimulated great interest in recent years for their numerous biological properties, including neurotoxicity, potentiation of muscle contraction, immunomodulatory activity <1998JNP162, 2003JME445, 2005WO2005070415, 2005WO2005070418>. This interest has resulted in numerous total syntheses of these alkaloids that have been accomplished in these years. Several reviews have been also published on the subject <2000COR205, 2001MI91, 2001PAC573, 2002MI611, 2002PAC1339, 2005NPR603>. Most of the compounds that contain the perhydroindolizidine ring with substituents scattered in positions 3, 5, 6, and 8 belong to the class of gephyrotoxins. The structures of the compounds synthesized are reported in [Table 1](#).

Table 1 Structure of indolizidine alkaloids (bicyclic gephyrotoxins) synthesized since 1995

				
	<i>R</i>	<i>R</i> ¹	<i>Name</i>	<i>Reference</i>
192	H	<i>n</i> -C ₃ H ₇	(–)-Indolizidine 167B	1995H(41)1797, 1996TL1445, 1997JOC8549, 1997PAC583, 1997S1151, 1999H(51)593, 1999TL1661, 2000JOC4543, 2000OL465, 2001TA2073, 2002TL455, 2002TL6739, 2003OL583, 2004JOC3093, 2005TL4559
193	H	<i>n</i> -C ₆ H ₁₃	(–)-Indolizidine 209D	1995HCA1511, 1995JOC398, 1995T9747, 1995TL303, 1996TL1445, 1998TA3289, 2000JOC4543, 2000OL465, 2001OL2985, 2001TA2073, 2003OL583, 2005TL2101, 2005TL4559
194	<i>n</i> -C ₄ H ₈ OH	<i>n</i> -C ₃ H ₇	(–)-Indolizidine 239 CD	1999OL349
195	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₄ H ₈ OH	(–)-Indolizidine 239 AB	1996TA2211, 1998T10457
196	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₃ H ₇	(–)-Indolizidine 223AB	1995JOC717, 1997J(Pi)1315, 1998T10457, 2000OL2169, 2002T9621, 2004OL1493
197	<i>n</i> -C ₄ H ₉	CH ₃	(–)-Indolizidine 195B	1996TA1585, 1998JOC4832, 1998T10457
198	<i>n</i> -C ₄ H ₉	CO ₂ Et	(–)-Indolizidine 237A	1995LA965, 1999TL3713
				
199			(–)-Indolizidine 223A	2002OL1715, 2003JOC4400, 2004T6197, 2005JA8398, 2005OL705
				
200	<i>n</i> -C ₅ H ₁₁	CH ₃	(–)-Indolizidine 209B	1995HCA1511, 1995T9747, 1996SL981, 1997PAC583, 1997T9553, 1998TL5189, 2000J(Pi)1919, 2000JOC4543, 2001JA12477, 2002TA2257, 2002TL8635, 2003OL5011
201	<i>n</i> -C ₇ H ₁₅	CH ₃	(–)-Indolizidine 237D	2005H(65)5
202	4-Pentenyl	CH ₃	(–)-Indolizidine 207A	1995JOC529, 1997JOC8182, 1997T9553, 2000JOC4543,
203	6-Heptenyl	CH ₃	(–)-Indolizidine 235B'	1997T9553
204	4-Heptenyl	CH ₃	(–)-Indolizidine 235B	1997JOC8182
205	4-Pentynyl	CH ₃	(–)-Indolizidine 205A	1997JOC8182
206	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	(–)-Indolizidine 209I	2000JOC8908, 2000SL1745, 2005JOC7364
207	<i>n</i> -C ₄ H ₉	<i>n</i> -C ₃ H ₇	(–)-Indolizidine 223J	2000JOC8908, 2000SL1745

The structures of these compounds have been a challenge for many different research groups in the application of new synthetic methodologies (see Sections 11.09.09 and 11.09.10). Among the strategies adopted, the three reported in **Scheme 46** for the synthesis of alkaloid **192** are noticeable for the selectivity and the elegance of the ring construction. Starting from the α -amino acid **208**, Angle and Henry <1997JOC8549> generated the silyl ketene acetal **209**, *in situ* in four steps, which underwent a Claisen rearrangement affording the pipecolic ester derivative **210**. Subsequent transformations gave **192** (**Scheme 46**, Equation 12). An intramolecular cyclization of the *N*-acyliminium ion **211** was the key step for the synthesis of **192** proposed by the Remuson's group <1999TL1661> (**Scheme 46**, Equation 13). A very efficient domino process (ring rearrangement metathesis, RRM) was used for the synthesis of **192** by the Blechert's group <2002TL6739>. The starting carbocycle **212** underwent, under the catalysis of an Ru-carbene, a cascade ring-closing, ring-opening, ring-closing metathesis to afford intermediate **213**, which was desilylated *in situ* and finally transformed into **192** (**Scheme 46**, Equation 14).



Scheme 46

Another class of these amphibian alkaloids, the pumiliotoxins, contain an alkylidene side chain on C-6 of the indolizidine ring (**Table 2**). Due to their myotonic and cardiotonic activity, and challenging structure, they also have been the object of synthetic interest. A review points out the state of the art at the beginning of the decade <1996CRV505>.

Overman *et al.* <1996JA9062> and Kibayashi *et al.* <2002JOC5517> have utilized the same alkynyl intermediate **222** as a substrate in their chemistry (**Scheme 47**). While the first group uses a nucleophilic attack of the triple bond on the iminium cation **223**, the second group performs a regioselective hydrostannylation, followed by Pd-catalyzed carbonylation, to provide the precursor **224** to the cyclization step.

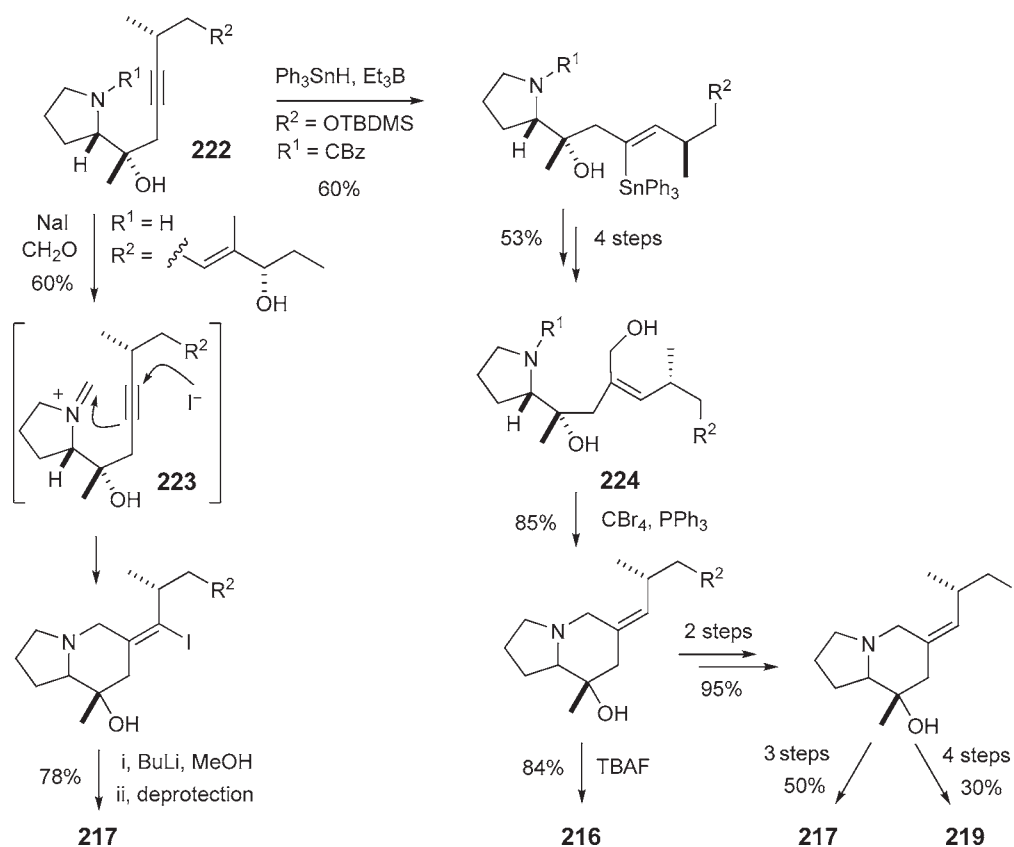
Sato *et al.* <1997JA6984> (**Scheme 48**, Equation 15) and Tang and Montgomery <2000JA6950> (**Scheme 48**, Equation 16) attached the alkynyl substituent on nitrogen inducing the cyclization of the intermediate **225** by a Ti- or Ni-catalyzed reaction, respectively.

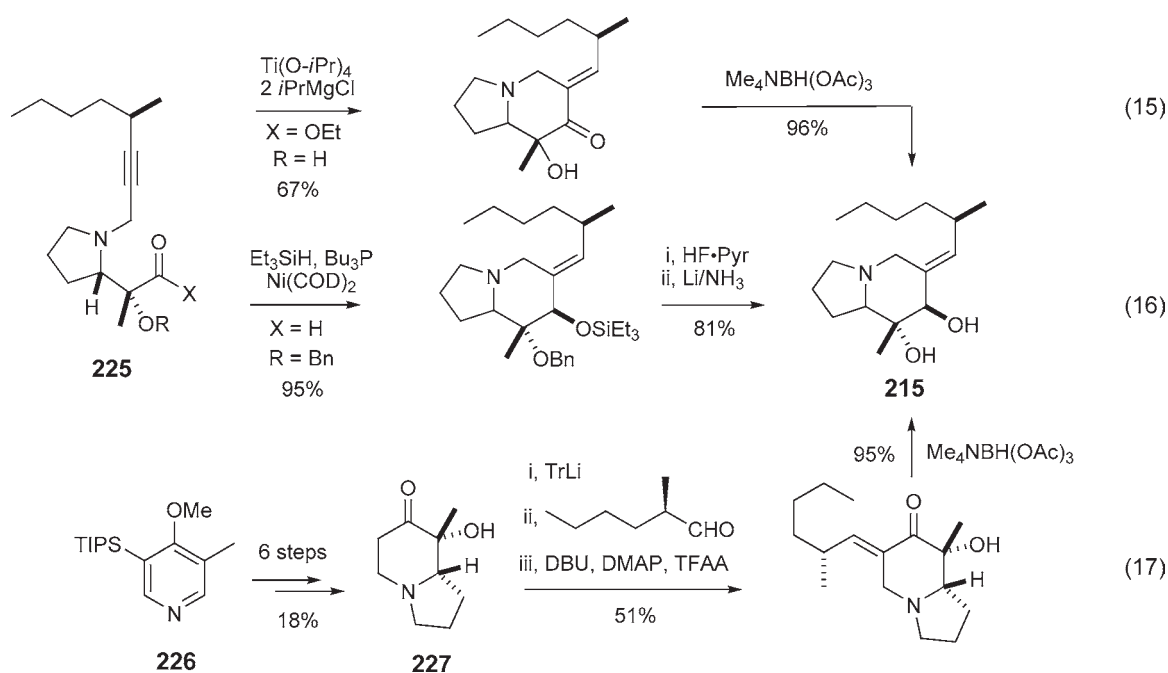
Comins *et al.* <2001OL469> achieved the synthesis of the same allopumiliotoxin 267A **215** by a stereoselective alkylation of the appropriately substituted 4-MeO-pyridine **226**. The C-6 side chain is introduced by an aldol condensation between an aldehyde and indolizidinone **227** (Equation 17).

Table 2 Structure of pumilio- and allopumiliotoxins synthesized since 1995

	<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>Name</i>	<i>Reference</i>
214	H	<i>n</i> -C ₃ H ₇		(+)-Pumiliotoxin 251D	2002EJO3315
215	OH	<i>n</i> -C ₃ H ₇		Allopumiliotoxin 267A	1997JA6984, 1996JA9073, 2000JA6950, 2001OL469
216	H	CH ₂ OH		(+)-Pumiliotoxin 225F	2002JOC5517

	<i>R</i>	<i>R</i> ¹	<i>R</i> ²	<i>Name</i>	<i>Reference</i>
217	H	H	H	(+)-15-(<i>S</i>)-Pumiliotoxin A	1996JA9062, 2002JOC5517
218	H	OH	H	(+)-Allopumiliotoxin 323B'	1996JA9073, 2001CEJ1845
219	H	H	OH	(+)-Pumiliotoxin B	1996JA9062, 2002JOC5517
220	H	OH	OH	(+)-Allopumiliotoxin 339A	1996JA9073, 2000JA6950
221	OH	H	OH	(+)-Allopumiliotoxin 339B	2000JA6950

**Scheme 47**



Scheme 48

11.09.8.2 Sugar Mimetics

The polyhydroxyindolizidine alkaloids, whose most important examples are castanospermine, swainsonine, and lentiginosine, are noted for their potent glycosidase inhibitory activity [<2000TA1645, 1998CC1161, 1996CRV683>](#). Their activity is believed to be a result of their ability to mimic the transition state involved in polysaccharide hydrolysis. Many important biological processes where glycosidases play a crucial role are being uncovered, opening the possibility for these compounds and their analogues to behave as biochemical tools and therapeutic targets for the treatment of diseases like diabetes, cancer, and viral diseases. Therefore, the interest for the synthesis of natural compounds of this class has exploded in the recent years. Their simple, but intensely functionalized, structure has been the challenge for many research groups in searching stereodivergent approaches not only to obtain natural products, but also to synthesize their analogues. Only the syntheses of natural products are mentioned and analyzed in this chapter ([Figure 5](#)).

RCM, followed by dihydroxylation of the double bond, is one of the most used methods for the synthesis of these compounds. For two syntheses of (–)-swainsonine [230](#), the five-membered ring is formed by RCM, followed by *cis*-dihydroxylation. Blechert *et al.* [<2002JOC4325>](#) prepared the precursor 2,5-dihydropyrroline [234](#) by domino ring-opening/ring-closing metathesis of an amino cyclopentene derivative [233](#) ([Scheme 49](#)).

Lindsay and Pyne [<2002JOC7774>](#) cyclized the diallylamine [236](#) obtained by stereoselective opening of the epoxide [235](#) ([Scheme 50](#)).

Pericàs *et al.* [<2005JOC2325>](#) chose for the synthesis of the same alkaloid the six-membered carbamate [239](#) obtained by RCM of simple precursors ([Scheme 51](#)).

Klitzke and Pilli [<2001TL5605>](#) and Singh *et al.* [<2002JOC4630>](#) used metathesis to form the six-membered ring in two syntheses of lentiginosine [231](#).

1,3-Dipolar cycloaddition chemistry of five-membered hydroxylated nitrones [241](#) has been used by the Brandi group [<1995JOC6806, 1996SL761>](#) for efficient syntheses of lentiginosine and bioactive analogues ([Scheme 52](#)). The synthesis of both enantiomers, and the measurement of their inhibitory activity, served to establish the absolute configuration of this recently discovered natural product, which is the most potent and selective inhibitor of amyloglucosidase having an indolizidine structure known up to now.

The same nitrone [241](#) was employed in a stereoselective alkylation with a Grignard reagent by Petrini *et al.* [<1995JOC5706>](#) for another synthesis of lentiginosine.

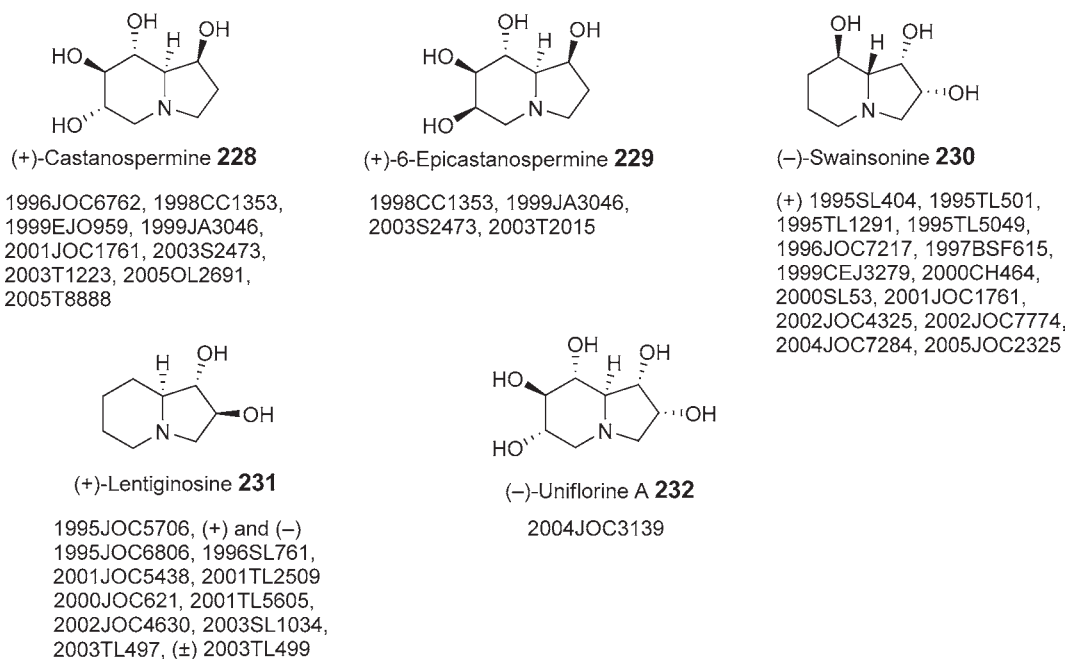
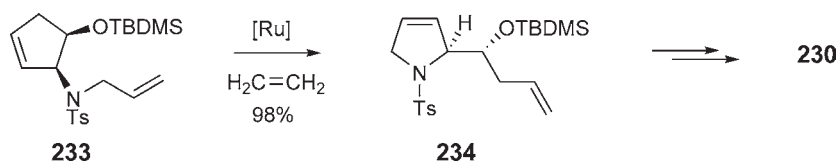
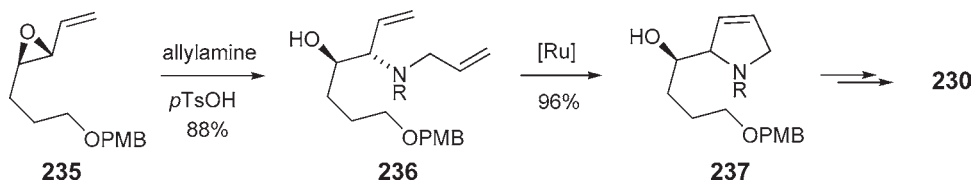


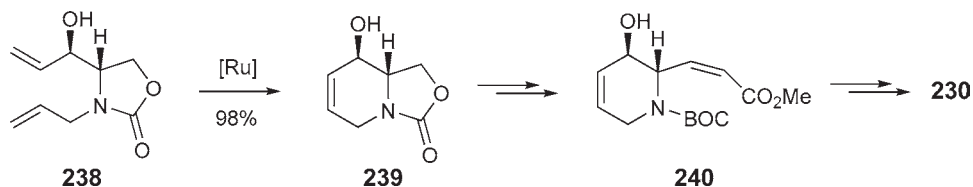
Figure 5



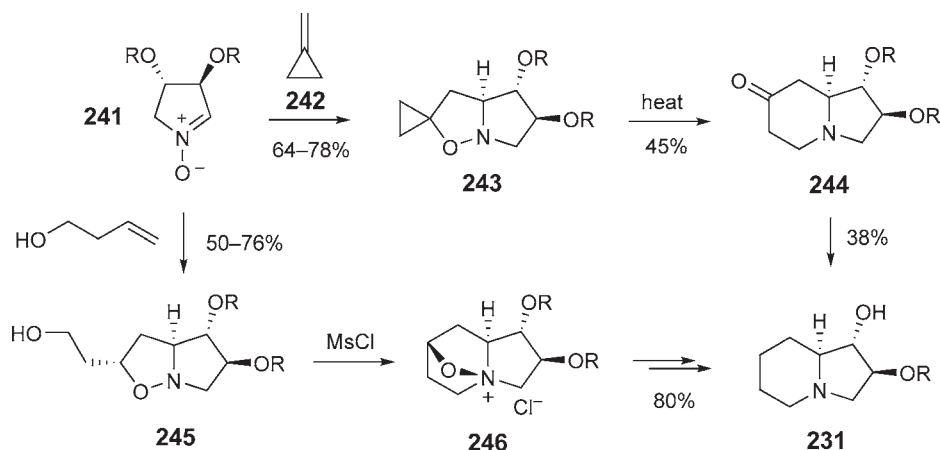
Scheme 49



Scheme 50

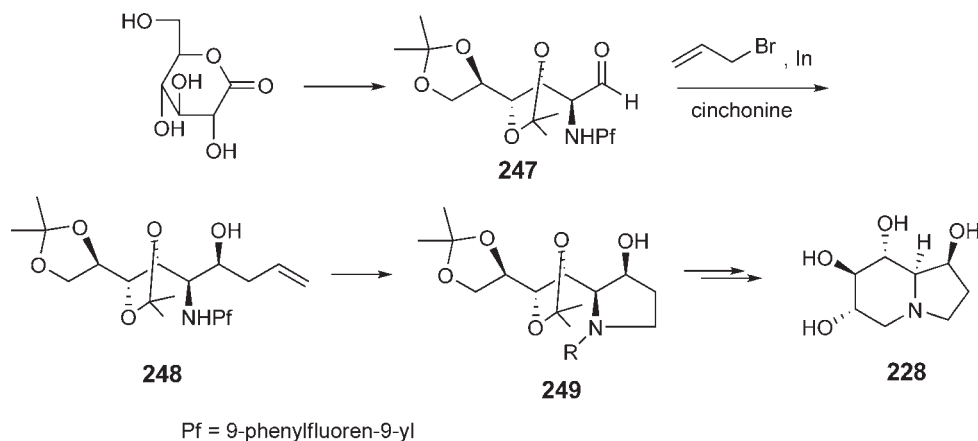


Scheme 51



Scheme 52

Stereoselective allylation of aldehydes is another preferred strategy for the synthesis of appropriate intermediates for the total synthesis and introduction of hydroxy functionalities. Park and co-workers [<2003S2473>](#) proposed a synthesis of castanospermine **228** through a key indium-mediated allylation in the presence of (+)-cinchonine of an α -amino aldehyde **247** derived from D-glucono- δ -lactone ([Scheme 53](#)).

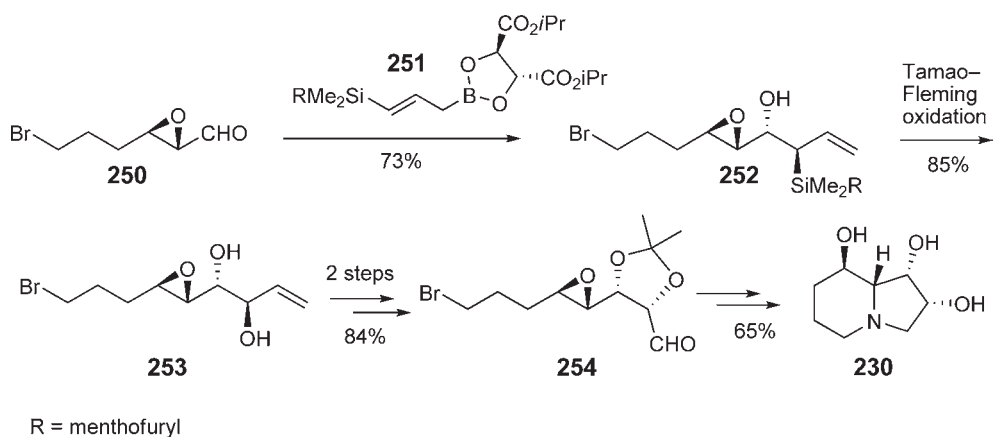


Scheme 53

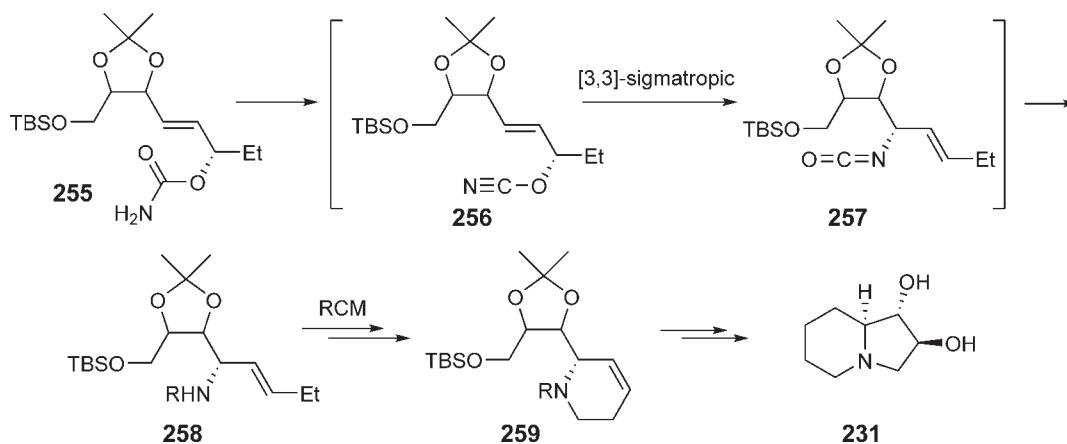
Hunt and Roush [<1995TL501>](#) achieved a synthesis of swansonine **230** via a stereoselective allylation of a silyl allylboronate derived from tartaric acid followed by a Tamao–Fleming oxidation to introduce the C-2 hydroxy functionality ([Scheme 54](#)).

An interesting allylamine synthesis by using a [3,3]-sigmatropic allylcyanate-to-isocyanate rearrangement has been used to synthesize lentiginosine **231** [<2003SL1034>](#) ([Scheme 55](#)). The synthesis commences with an RCM for the synthesis of the six-membered heterocyclic ring.

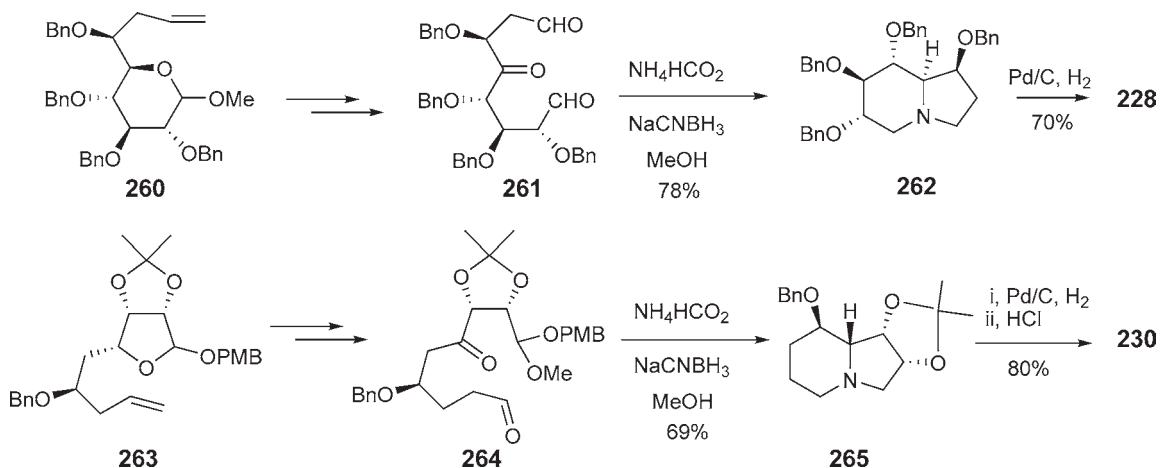
Reductive amination is used in most of the syntheses as the method for the formation of a five- or six-membered aza heterocyclic ring. A triple reductive amination approach to castanospermine and swainsonine has been reported by Mootoo *et al.* [<2001JOC1761>](#) ([Scheme 56](#)).



Scheme 54



Scheme 55



Scheme 56

11.09.8.3 Miscellaneous Natural Products

The numerous syntheses of the alkaloids reported in [Figure 6](#) indicate the wide interest in these compounds and the richness of synthetic methodologies devoted to their synthesis.

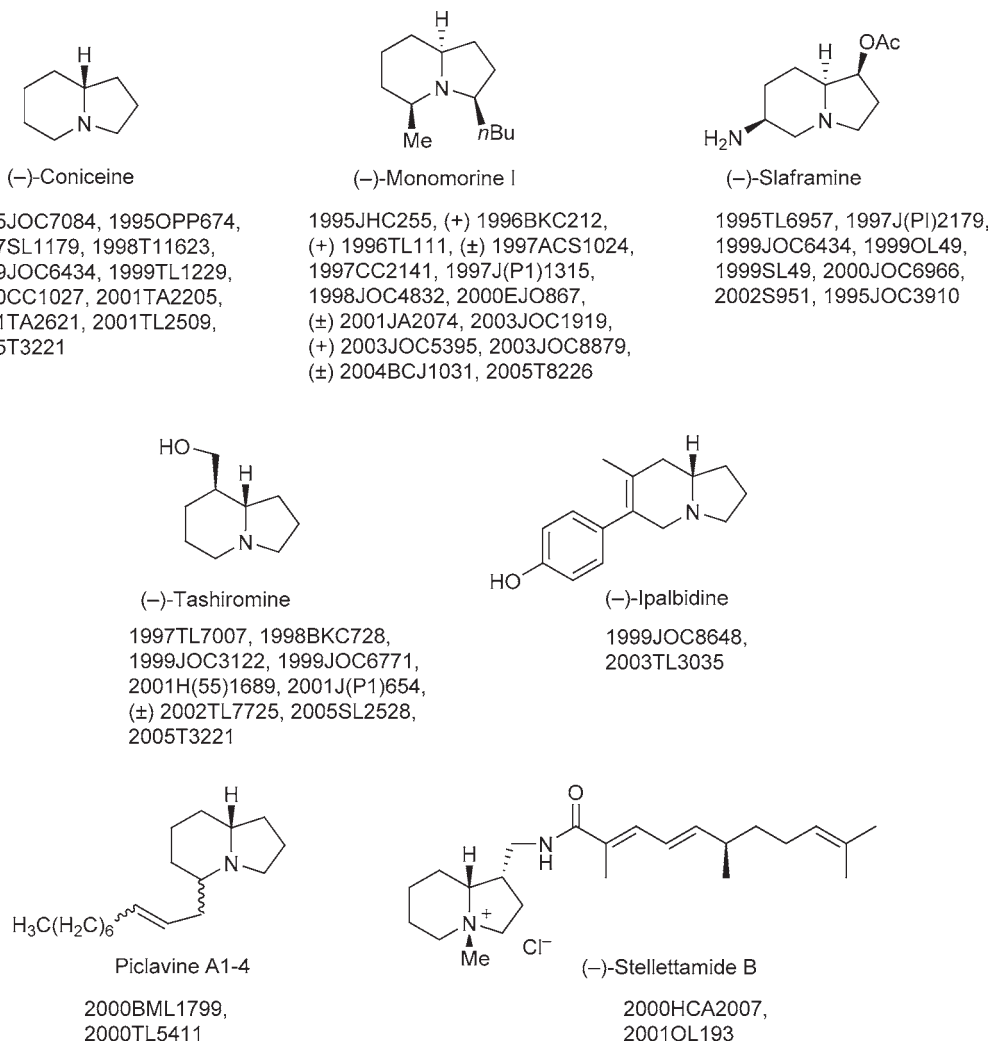
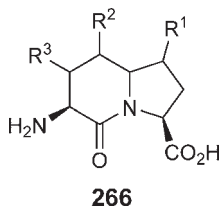


Figure 6

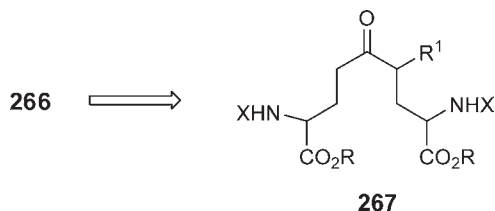
11.09.8.4 Dipeptide Isosteres

Indolizidin-5-ones, whose general formula is [266](#), have been the object of many studies as constrained mimetics of dipeptides able to induce β -turns [<1997T12789>](#).



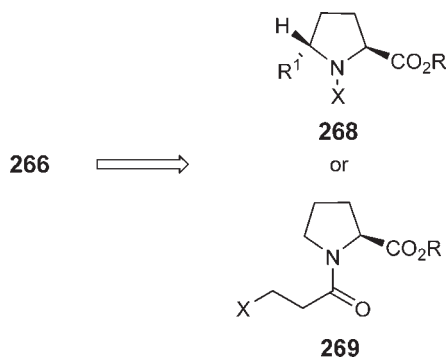
The numerous synthetic approaches relied principally on the formation of a 5-substituted proline ester by reductive amination followed by cyclization of the lactam ring.

A δ -keto-bis- α -amino acid derivative **267** is a common precursor in these syntheses (**Scheme 57**), obtained by asymmetric Schöllkopf alkylation <1994TL4091>, by Claisen condensation of glutamic acid precursors <1997TL6483, 1998JOC5937>, or by hydrogenation of bis- α,β -unsaturated amino acid derivatives <2001TL3159>.

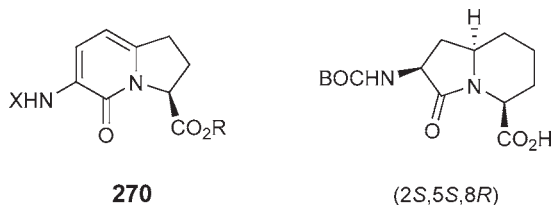


Scheme 57

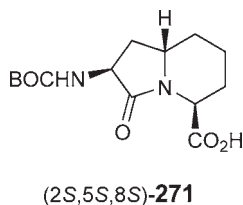
Other approaches started directly from diversely functionalized pyrrolutamic acid derivatives **268**, substituted on C-5 <2000T4289, 2000BML243, 1996BML1567, 2002TL5087, 2005JOC4124>, or **269** substituted on nitrogen <1999TL7939, 1999TL5987>, differing by the method of formation of the lactam ring. In two cases, the cyclization of the six-membered ring is achieved by an RCM <2003JOC7219, 2004TL2623>. Unsaturated analogues **270** having the pyridone structure were synthesized again from pyrrolutamic acid <2002TL9663> or 3-aminopyridine derivatives <2002JOC741>.



Scheme 58



The dipeptide isosteres with indolizin-3-one structure **271** were also synthesized using similar strategies <1998JOC7463>.



11.09.9 Important Compounds and Applications

Indolizine **272** exhibited good activity as a histamine H3 antagonist <2003BML1767>. A-289099 (**273**) is a potent and orally active antimitotic agent against various cancer cell lines. The anticancer activity is exerted through inhibition of tubulin polymerization by binding at the colchicine site <2002BML465>.

A series of indolizidinones **274–278** were designed and synthesized to evaluate their inhibitory effect on Factor VIIA (FVIIa) in comparison to thrombin (Factor IIa (FIIa)), plasmin, and FXIa <2002BML2907>.

The bicyclic 2-pyridone-containing 3CP (human rhinovirus 3C protease) inhibitor **279** displayed improved inhibition properties and exhibited potent antirhinoviral activity in cell culture when tested against a number of different human rhinovirus (HRV) serotypes <2002BML733>.

Synthesis, cytotoxicity *in vitro* and *in vivo*, and structure–activity relationships of septicine **280** and its analogues were reported (Figure 7) <2003BML1679>.

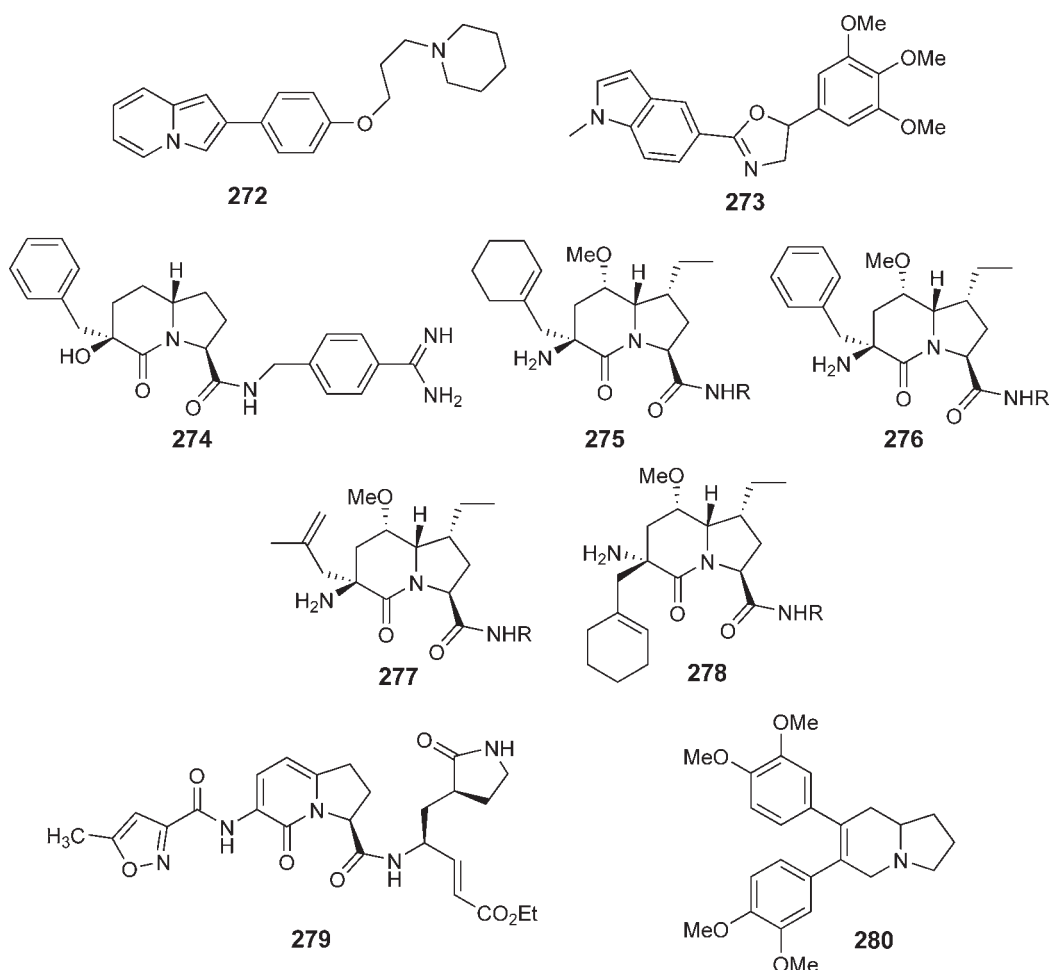


Figure 7

A series of indolizines **281** and azaindolizines **282** were screened as possible inhibitors of 15-lipoxygenase (15-LO) from soybeans and rabbit reticulocytes. Most compounds studied were significantly more active than quercetin (IC_{50} 51 μ M) <2003BML5409>. The indolizine and azaindolizine sulfonates were particularly studied and showed high activity <2005BMC5409>.

Novel macrocyclic and open-chain ‘taxoid mimicking’ compounds were synthesized. Two of these, compounds **283** and **284**, were found to possess cytotoxicity with micromolar level IC_{50} values against human breast cancer cell lines <2004BML3491>.

Compound (–)-A58365A **285**, whose new synthesis was reported, is an angiotensin-converting enzyme (ACE) inhibitor, active at nanomolar concentrations <1999OL83>.

3-Formyl-substituted aminindolizine (*S*)-**286** displayed a K_i value of 6.0 nM for the high-affinity dopamine D3 binding site. In contrast, D3 affinity of the enantiomer (*R*)-**286** was 300-fold lower <2001BML2863>.

The indolizidine ring seemed to be an interesting template in the construction of dual NK_1/NK_2 antagonists (Figure 8) <2002BMC2905>.

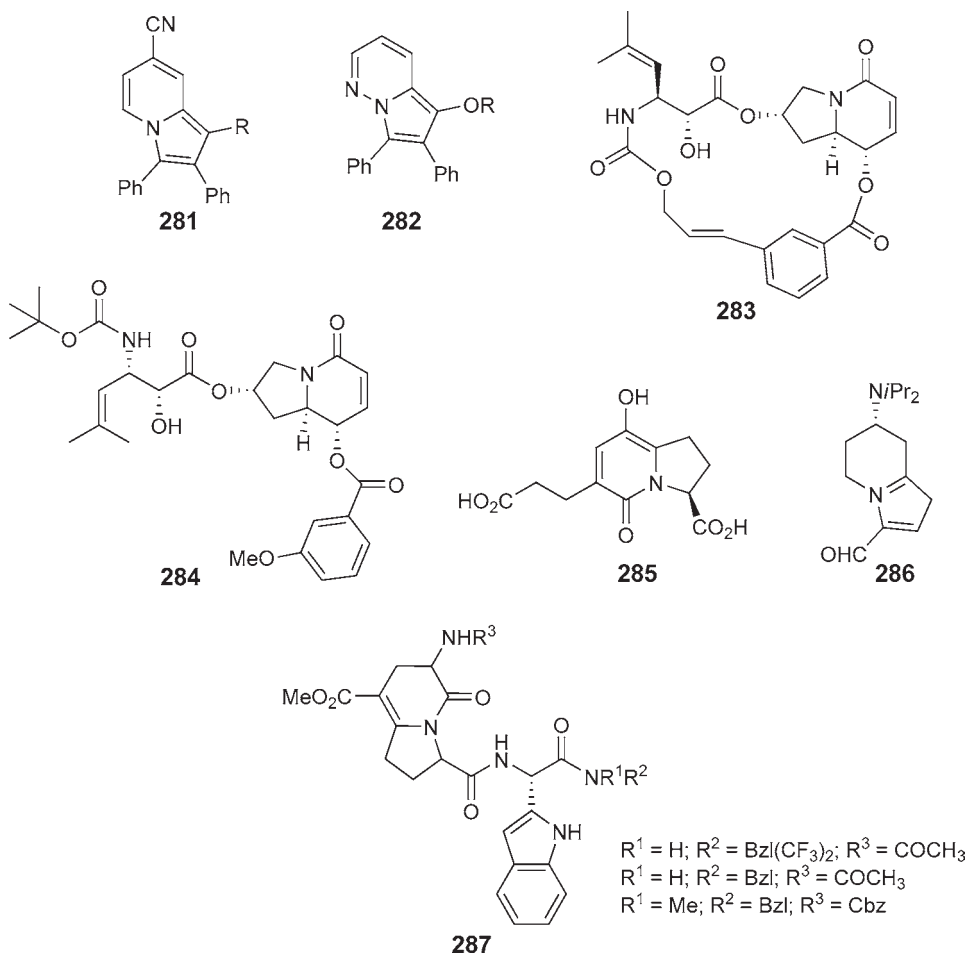


Figure 8

11.09.10 Further Developments

11.09.10.1 Thermodynamic Aspects

Three new fluorescent indolizine modified β -cyclodextrins have been investigated as molecular chemosensors for the detection of volatile organic compounds <2007MI312>.

The crystal structure of dimethyl indolizine-1,6-dicarboxylate shows that the indolizine unit is almost planar. The two carboxylate groups are coplanar with the indolizine moiety <2006AX(E)4080>.

11.09.10.2 Ring Synthesis from Acyclic Compounds

11.09.10.2.1 Simultaneous formation of more than one bond

A highly efficient access to diversely substituted indolizines using a new three-component condensation of activated methylene compounds, aldehydes, and isonitriles is described [<2006QSAR504>](#).

11.09.10.2.2 Sequential formation of bonds

Azabicyclononencarboxylate acylated with unsaturated carboxylic acids is converted via tandem olefin metathesis in indolizidine scaffolds [<2006OL5553>](#).

Adducts of 2-chloro-2-cyclopropylideneacetates with enantiopure five-membered cyclic nitrones undergo cascade ring enlargements to yield indolizin-5-ones. The ring enlargement process is triggered by the abstraction of a bridgehead proton induced by a base [<2006JOC2417>](#).

A trihydroxyindolizidine lactone is obtained by elaboration of an isoxazolidine synthesized by a domino stereo-selective retrocycloaddition/intramolecular cycloaddition process of an enantiopure pyrroline-*N*-oxide [<2006TA292>](#).

11.09.10.3 Ring Syntheses by Transformation of Another Ring

11.09.10.3.1 Starting materials containing one five-membered azaheterocyclic ring

Novel synthetic procedures for indolizidine alkaloids were developed via a samarium diiodide-promoted carbon–nitrogen bond cleavage as a key step. Application of the procedure led to the total synthesis of (+)-(8R, 8aR)-perhydro-8-indolizidinol [<2006H193>](#).

Bicyclic silyloxypyrrole, via the selective formation of a quaternary stereogenic center and a ring-closing metathesis as the main steps, was converted into new polyhydroxyindolizidines [<2006TA53>](#).

A diastereoselective synthesis of 3,5-disubstituted indolizidines based on an intermol. addition of an allylsilane on an acyliminium ion derived from (*S*)-pyroglutamic acid, is described [<2006TA1253>](#).

The synthesis of 8-homocastanospermine via the 1,3-dipolar cycloaddition of five-membered cyclic nitrone derived from malic acid and unsaturated D-threo-hexaldonolactone is reported [<2006CJC534>](#).

11.09.10.3.2 Starting materials containing one six-membered azaheterocyclic ring

A library of 1,2,3,7-tetrasubstituted indolizines was synthesized using poly(ethylene glycol) (PEG) bound pyridinium salts reacting with alkenes or alkynes in the presence of Et₃N [<2006JHC781>](#).

An efficient method for the synthesis of IV Group metals substituted indolizines from diverse propargyl-substituted pyridines in the presence of Au-catalyst, has been developed [<2006JA12050>](#).

11.09.10.3.3 Starting materials already containing the indolizidine ring

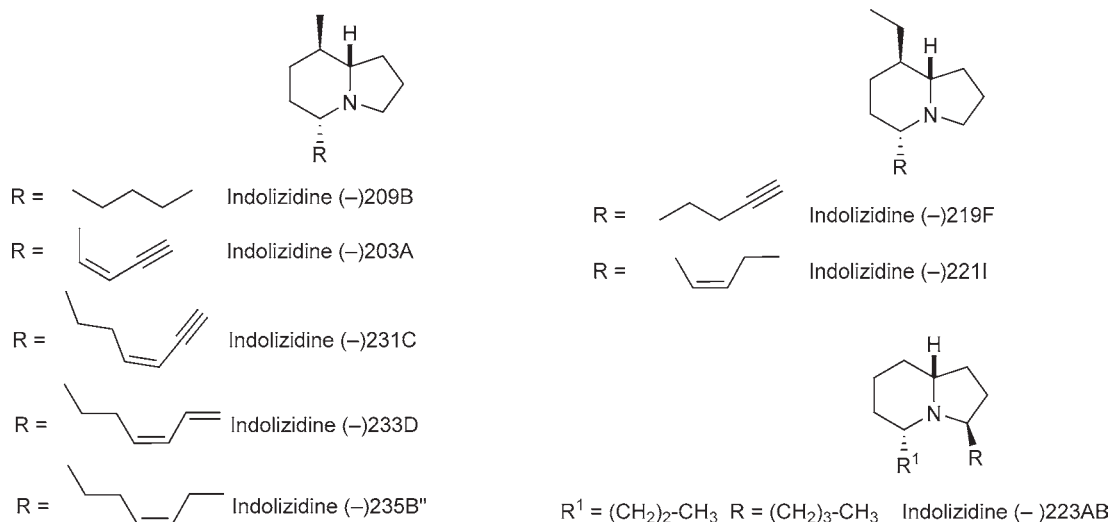
Stereoselective Michael additions of carbon-, nitrogen-, oxygen-, and sulfur-centered nucleophiles to 6,7-dehydro-5-oxoindolizidine have been reported [<2006JOC6630>](#).

11.09.10.4 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

11.09.10.4.1 Amphibian alkaloids

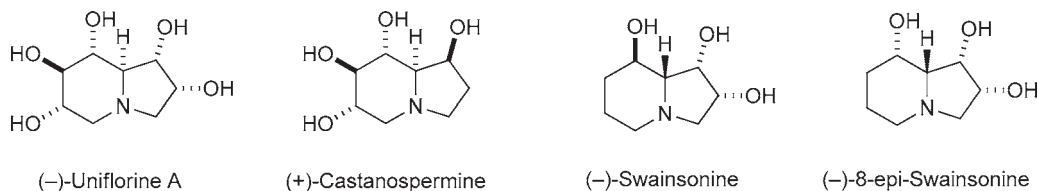
The first asymmetric syntheses of amphibian alkaloids (–)-203A, (–)-219F and (–)-221I were reported, together with new asymmetric syntheses of poison frog-indolizidines (–)-209B, (–)-231C, (–)-233D, and (–)-235B [<2006TL577, 2006TL581>](#). The syntheses allowed the confirmation of the absolute stereochemistry of both indolizidines 203A and 233D to be 5S,8R,9S.

A new synthesis of indolizidine (–)-223AB was also reported [<2006JOC2547>](#).



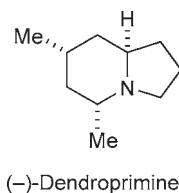
11.09.10.4.2 Sugar mimetics

A new synthesis of Uniflorine A and its analogues has been achieved using ring closing metathesis to form sugar-substituted pyrrolines <2006JOC6273>. Similar substrates were applied for the synthesis of (+)-castanospermine and analogues <2006JOC4667>. The enantioselective syntheses of both enantiomers of swainsonine have been achieved starting from furan <2006OL1609>. A novel and efficient synthesis of (–)-8-epi-swainsonine is also reported <2006SL1443>.



11.09.10.4.3 Miscellaneous natural products

The synthesis of the alkaloid (–)-dendroprimine is obtained via a piperidine derivative obtained through a one-pot azaelectrocyclization protocol <2006OL3813>. A new synthesis of (±)-tashiromine is also reported <2006JOC704>.



11.09.10.5 Important Compounds and Applications

1-Substituted, particularly hydroxyphenylmethyl- or hydroxyalkyl substituted, indolizines have shown activity against *Mycobacterium tuberculosis* <2006MI26>. 3-Substituted indolizine-1-carbonitrile derivatives displayed activity against MPTpA/MPTpB phosphatases which are involved in infectious diseases <2006BMCL59>.

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11.10

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 1:0

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11.10.1 Introduction

The organization of this chapter can easily be visualized by considering the series of molecules shown in [Figure 1](#), all of them being shown in their fully conjugated aromatic form. The next section will deal with pyrazolo[1,5-*a*]pyridines, for which most of new synthetic work was devoted to the aromatic system. Then, the cationic isoxazolo- and isothiazolo[2,3-*a*]pyridines will be covered together; for these compounds, and in contrast with their nitrogen equivalents, the quasi-exclusive amount of work is now devoted to partially reduced systems. The same type of organization will be used for imidazo[1,5-*a*]pyridines and their oxygen and sulfur analogues, the latter being reviewed

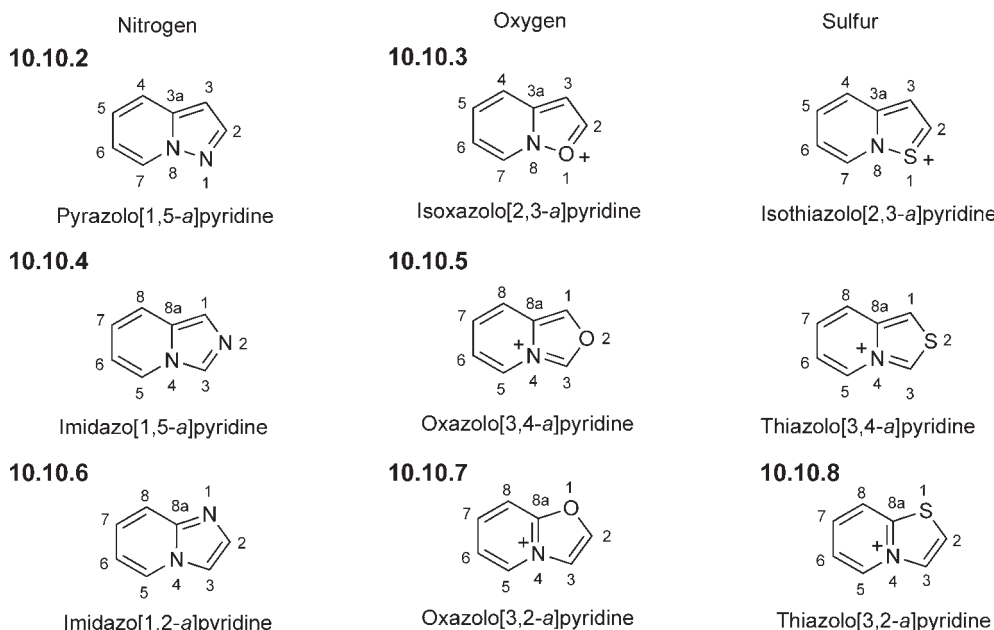


Figure 1

together. Finally, imidazo[1,2-*a*]pyridines and their oxygen and sulfur analogues will be presented independently since the important synthetic work devoted to partially or totally reduced oxazolo[3,2-*a*] systems clearly merits an independent section. This chapter concludes with a brief description of ring systems containing a less common heteroatom than nitrogen, oxygen, or sulfur in the five-membered ring.

11.10.2 Pyrazolo[1,5-*a*]pyridine

11.10.2.1 Introduction

Pyrazolo[1,5-*a*]pyridines can be viewed as 8-aza analogues of indoles <2000S1727>. Considering the metabolic instability of these latter and their high biological relevance, it is not surprising that these indole isosteres have been the subject of considerable work in the field of medicinal chemistry. This class of heterocycles was covered with other fused diazines and triazines in volume 5 (Chapter 4.05) in CHEC(1984) <1984CHEC-I(5)613> and in an independent section in CHEC-II(1996) (volume 8, Chapter 9.10.2) <1996CHEC-II(8)249>. The organization of this section roughly follows the one used in CHEC-II(1996) but focuses on new synthetic methodologies available for this heterocyclic system.

11.10.2.2 Theoretical Methods

No new calculations were specifically devoted to this heterocyclic system since CHEC-II(1996) <1996CHEC-II(8)249>. However, modeling of bioactive compounds containing this heterocycle have been published as exemplified by the use of the highly potent dopamine D4 receptor ligand FAUC113 as template for comparative molecular field analysis (CoMFA) of dopamine D4 receptor antagonists <2001JME1151>.

11.10.2.3 Experimental Structural Methods

Similarly to the above section, no additional specific nuclear magnetic resonance (NMR) data have been published since CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>: NMR data for new substituted compounds are routinely reported. Several X-ray structures of bioactive molecules possessing this heterocyclic core have been reported <1999BML1979, 1999JME779>.

11.10.2.4 Thermodynamic Aspects

Similarly to the above section, no additional specific studies have been published since CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>.

11.10.2.5 Reactivity of Fully Conjugated Rings

As specified in CHEC-II(1996) <1996CHEC-II(8)249>, pyrazolo[1,5-*a*]pyridines are aromatic systems in which the bridgehead nitrogen N-8 contributes to the aromaticity with its lone pair. Therefore, this is a 'pyrrole-like' nitrogen of low pK_a and nucleophilicity. On the other hand, the N-1 is a 'pyridine-like' nitrogen and is indeed the site of protonation. An important amount of synthetic work has been devoted to electrophilic substitution, reactions that occur with high regioselectivity at the C-3 position and additional examples will be presented. Figure 2 summarizes these main characteristics. Functionalizations through metal-catalyzed coupling reactions have gained importance since the previous issue and will be especially highlighted in the following paragraphs.

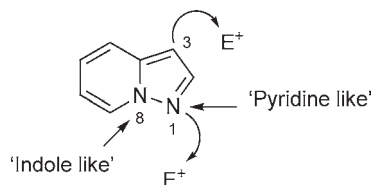
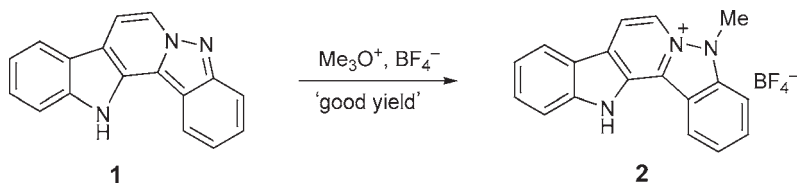


Figure 2

11.10.2.5.1 Electrophilic attack at nitrogen

Alkylation of the 'pyridine-like' nitrogen in **1** with the Meerwein's salt allowed the preparation of a derivative **2** of this ring system suitable for the evaluation of intercalating properties (**Scheme 1**) <2000BML1767, 1996BML2831>.



Scheme 1

11.10.2.5.2 Electrophilic attack at carbon

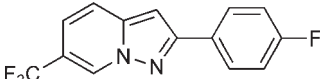
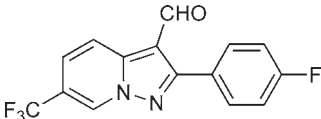
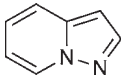
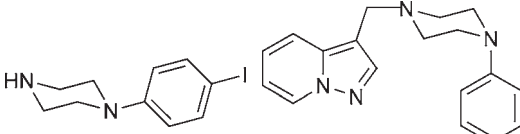
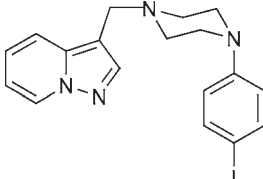
Electrophilic attack at carbon is a well-documented reaction which occurs regioselectively at the C-3 position. It was illustrated by numerous examples, including nitrations, halogenations, acylations, and Mannich reactions in CHEC(1984) and CHEC-II(1996) <1996CHEC-II(8)249>. **Table 1** reports some additional recent examples. It should be noted that all these synthetic transformations were carried out in the field of medicinal chemistry.

Table 1 Electrophilic attack at C-3

Substrate	Conditions	Product	Yield (%)	Reference
	BrCOCHBrMe AlCl_3		77	2003TA529
	ClCO_2Et , pyridine Then <i>t</i> -BuOK, air		34	1999JME779
	ClCO_2Et Pyridazine		53	1999JME779
	 CH_2O , Et_2NMe AcOH		82	2002TA2303

(Continued)

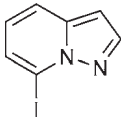
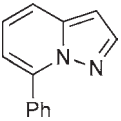
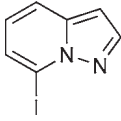
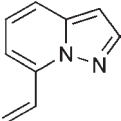
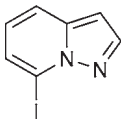
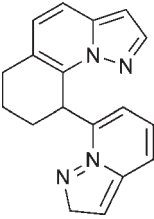
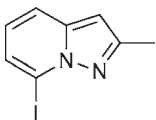
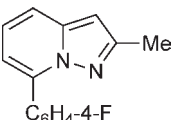
Table 1 (Continued)

Substrate	Conditions	Product	Yield (%)	Reference
	POCl ₃ DMF		94	2006BMC944
	 CH ₂ O, AcOH		42	1999BML97

11.10.2.5.3 Nucleophilic attack at carbon

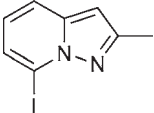
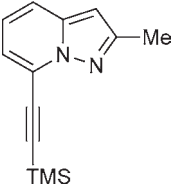
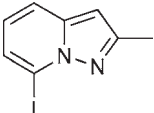
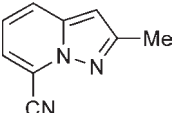
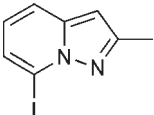
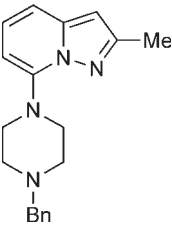
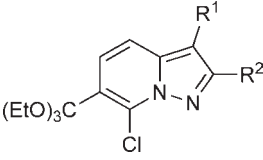
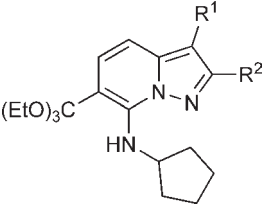
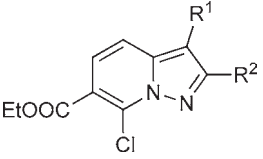
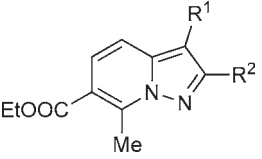
As mentioned in CHEC(1984) and CHEC-II(1996), nucleophilic substitution of hydrogen atoms has not been reported, but substitution of halogens either through direct S_NAr or using metal-catalyzed coupling reactions have been explored. This field was investigated in detail quite recently by Gmeiner and co-workers in the case of easily available 7-iodo derivatives <2000S1727>, and some representative examples are reported in [Table 2](#).

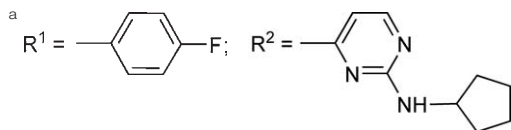
Table 2 Functionalization of 7-halo derivatives

Substrate	Conditions	Product	Yield (%)	Reference
	PhSnBu ₃ Pd(PPh ₃) ₄ Toluene, reflux		82	2000S1727
	CH ₂ =CHSnBu ₃ Pd(PPh ₃) ₄ Toluene, reflux		62	2000S1727
	CH ₂ =CHSnBu ₃ PdCl ₂ (PPh ₃) ₂ NMP, 120 °C		83	2000S1727
	4-FC ₆ H ₅ -B(OH) ₂ Pd(PPh ₃) ₄ Toluene, H ₂ O NaHCO ₃ , reflux		80	2000S1727

(Continued)

Table 2 (Continued)

Substrate	Conditions	Product	Yield (%)	Reference
	TMSC≡CH Pd(PPh ₃) ₄ CuI, Et ₃ NMe ₂ , rt		66	2000S1727
	CuCN, Pd ₂ (dba) ₃ DPPF, dioxane Reflux		95	2000S1727
	4-Bn-piperazine Pd ₂ (dba) ₃ , P(<i>t</i> -Bu) ₃ <i>t</i> -BuONa, toluene 120 °C		50	2000S1727
	Cyclopentylamine 80 °C		96 ^a	2006BMC944
	Me ₂ Zn, Pd(PPh ₃) ₄ THF, 60 °C		45 ^a	2006BMC944

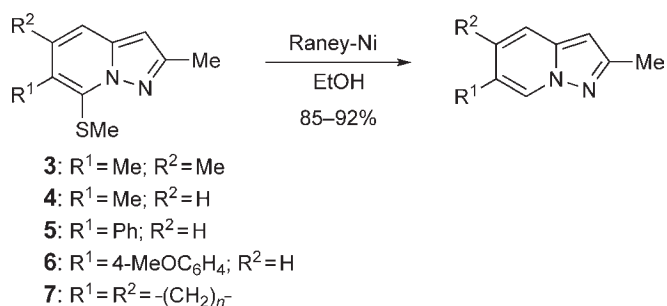


11.10.2.5.4 Nucleophilic attack at hydrogen

Deprotonation readily occurs at C-7, and the resulting anion can further react with various electrophiles. Thus, treatment with BuLi at −78 °C followed by reaction with diiodoethane was used to prepare the 7-iodo derivatives depicted in [Table 2](#), while the 7-chloro derivatives were prepared by lithiation with lithium diisopropylamide (LDA), followed by reaction with CCl₄. The 7-formyl derivative of the parent pyrazolo[1,5-*a*]pyridine has been prepared in 82% yield by reaction of the BuLi-generated anion with ethyl formate [\[2001JME2691\]](#).

11.10.2.5.5 Reaction at surfaces

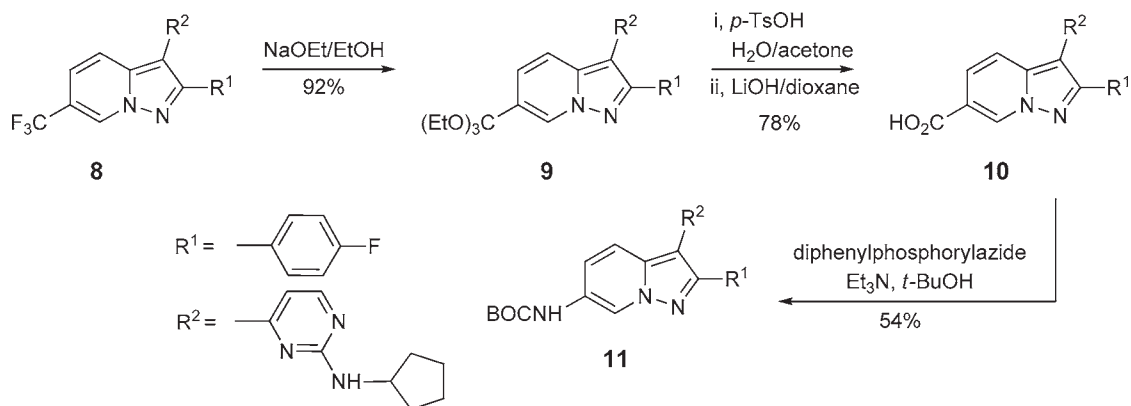
As previously reported in CHEC-II(1996) [\[1996CHEC-II\(8\)249\]](#), this ring system is fairly resistant to reduction, and, under more forcing conditions, the six-membered ring is reduced preferably. Desulfurization with Raney-Ni of 7-SMe derivatives was reported [\[1999T7645\]](#) to occur efficiently, as shown in [Scheme 2](#).



Scheme 2

11.10.2.6 Reactivity of Substituents Attached to Ring Carbon Atoms

Apart from classical functional group interconversions that have already been discussed in previous issues, several interesting synthetic transformations of substituents attached to the ring need to be mentioned. First, carboxylic acids at C-2 or C-3 can be conveniently transformed into their acyl chloride derivatives by reaction with oxalyl chloride [<2002JME4594>](#). Further reaction of the acyl chlorides with amines gives the corresponding amides in good yields. Interesting functional group interconversions have been recently reported by Allen *et al.* [<2006BMC944>](#), some of them involving the overall transformation of a trifluoromethyl group at C-8 into an *N*-protected amine. This synthesis is depicted in [Scheme 3](#).



Scheme 3

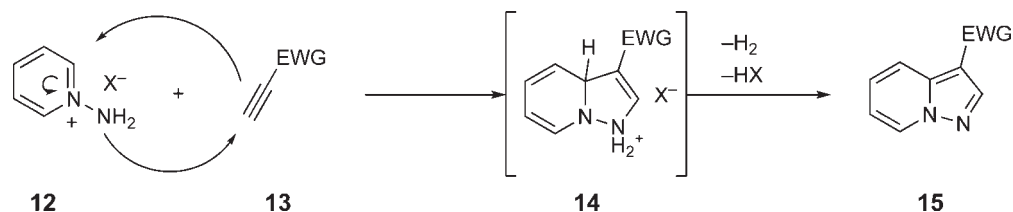
O-Alkylation of 4-hydroxylated [<1996H\(43\)2249>](#) or 5-hydroxylated [<1996T8471>](#) derivatives was reported to occur without competitive *N*-alkylation.

11.10.2.7 Synthesis

11.10.2.7.1 Fully conjugated ring

The most widely used approach to synthesize this heterocycle continues to be the condensation of *N*-aminopyridinium derivatives **12** with 1,2-ambident synthons such as **13** bringing two carbons and resulting in the ring closure of the five-membered ring. As outlined in [Scheme 4](#), this ring closure requires further dehydrogenation of intermediate **14** for the production of **15**. This process most often occurs spontaneously, but sometimes is facilitated by bubbling air or oxygen into the reaction medium.

Many different ambident synthons have been used in this synthesis, and recent examples collected in [Table 3](#) complete the array of substrates that can be used for this ring closure mentioned in previous issues.



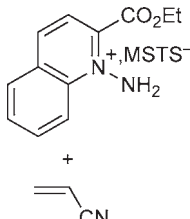
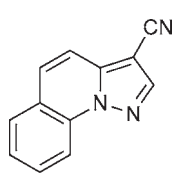
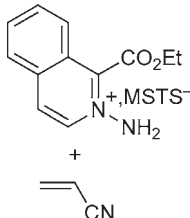
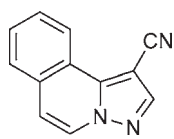
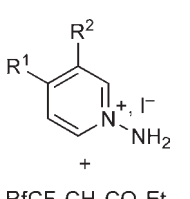
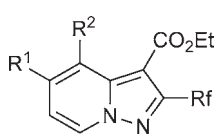
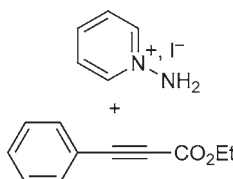
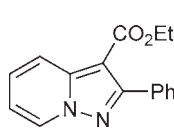
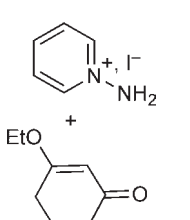
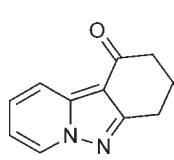
Scheme 4

Table 3 Synthesis through ring closure of *N*-aminopyridinium derivatives

Substrate	Conditions	Product	Yield (%)	Reference
	Et ₃ N, EtOH Reflux, 5 h		72–80	1999BML97
	Et ₃ N, EtOH Reflux, 5 h		72–80	1999BML97
	K ₂ CO ₃ , air–O ₂ DMF, rt, 2 h		45	2001JME2691
	K ₂ CO ₃ , air–O ₂ DMF, rt, 1.5 h		72	2001JME2691
	(<i>i</i> -Pr) ₂ EtN DCM, reflux 6 h		36 ^a	1999JOC9001

(Continued)

Table 3 (Continued)

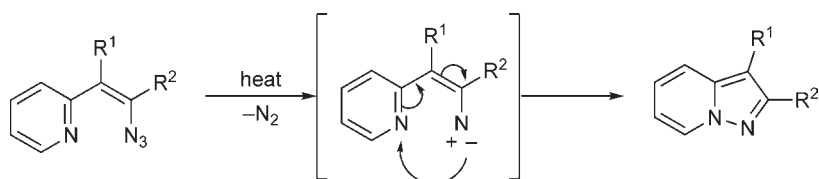
Substrate	Conditions	Product	Yield (%)	Reference
	<i>i</i> -(Pr) ₂ EtN MeCN, reflux 20 h		61 ^a	1999JOC9001
	<i>i</i> -(Pr) ₂ EtN MeCN, reflux 48 h		23 ^a	1999JOC9001
	K ₂ CO ₃ /NEt ₃ DMF, 50 °C, 5–6 h		54–95	1998JFC57
	KOH, DMF		32	1996BML2059
	K ₂ CO ₃ , Ethylene glycol 130 °C, 16 h		38	2002BML2377

^aMSTS[−] = mesitylenesulfonate.

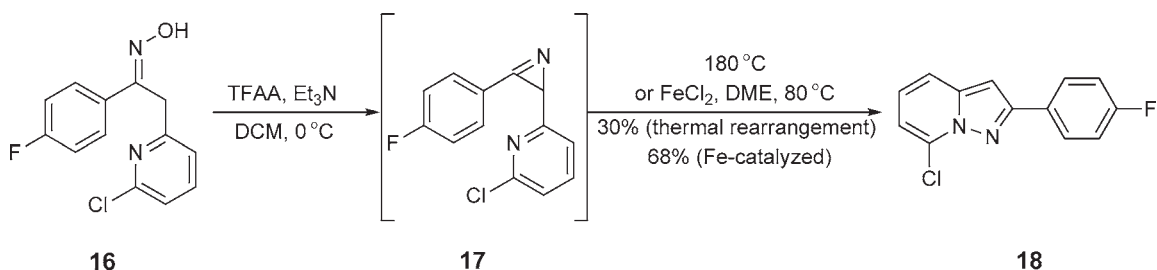
Examples reported in **Table 3** merit additional comments: the high regioselectivity observed with nonsymmetric aminopyridiniums is clearly an advantage of this synthetic route; however, most yields are quite low.

Another synthetic methodology of growing importance is based on the rearrangement of a transient nitrene, most often generated by thermolysis of an azido group as depicted in **Scheme 5**.

In this case, the efficiency of the synthetic route of course clearly depends on the availability of the azido substrate, but the key ring closure is quite efficient in most cases <2000BML1767, 2004JHC531, 1996BML2831>. Interestingly, the transient nitrene can also be generated from the rearrangement of an intermediate azirine **17**, generated from an oxime **16** (**Scheme 6**) <2003T9001>.

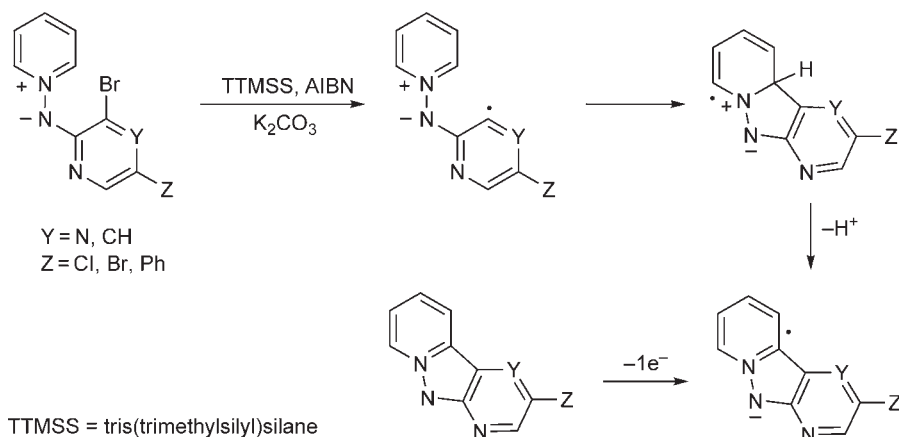


Scheme 5



Scheme 6

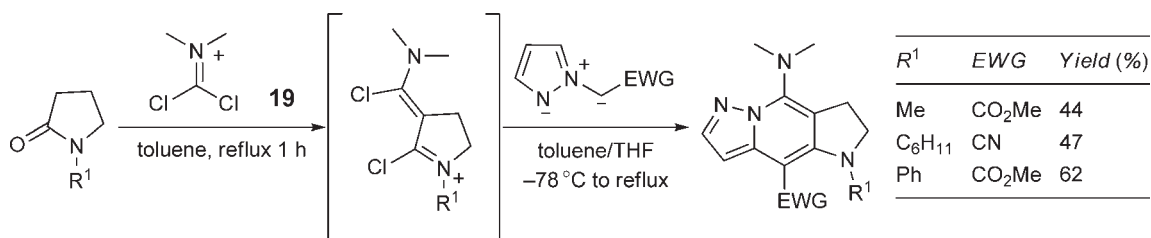
Apart from these important synthetic methodologies, other new approaches have appeared, and they can be classified depending on the size (five- or six-membered ring) of the heterocyclic ring formed in the process. A ring closure involving the formation of the five-membered ring was reported to proceed through a radical cyclization as depicted in [Scheme 7](#). However, this methodology suffers from low yields (2–56%) due to competitive reduction of the starting material yielding 2-aminopyridines [<2002SL1093>](#).



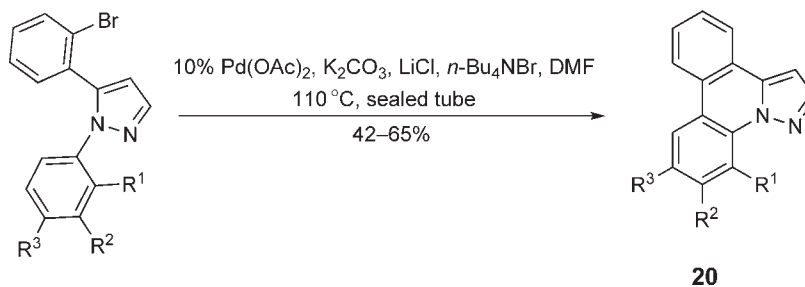
Scheme 7

A new and general entry to azolo[1,5-*a*]pyridines possessing a dimethylamino moiety at C-7 was recently devised from Viehe's salt **19** [<2006TL1395>](#). This reaction gives access to a large array of substituted heterocycles in good yields (44–69%) and efficient reaction sequences. As depicted in [Scheme 8](#), this new synthetic methodology involves the construction of the six-membered ring as shown by selected examples.

Another contribution involving formation of the six-membered ring was reported by Dominguez [<2003OL1095>](#). In this case, the key step involves a biaryl Mizoroki–Heck-type coupling. Fair yields (42–65%) of pyrazolophenanthridines **20** can be obtained from easily available starting materials prepared from acetophenones and hydrazines ([Scheme 9](#)).

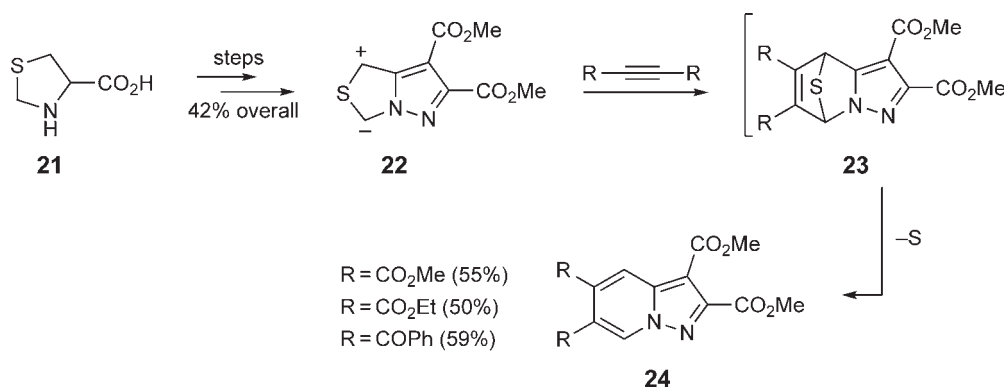


Scheme 8



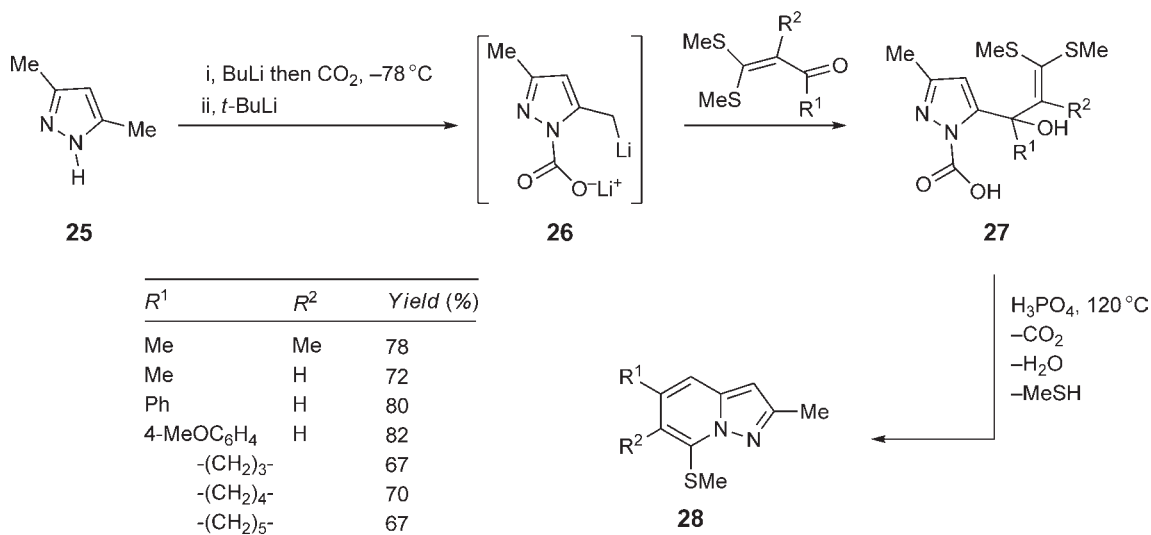
Scheme 9

A cycloaddition process involving dipole **22**, readily prepared from thiazolidine **21**, was reported to produce adducts such as **23** in the presence of sufficiently reactive dipolarophiles [<2000T10011>](#). These adducts furnished substituted pyrazolo[1,5-*a*]pyridines **24** in fair yields upon further heating and extrusion of sulfur. However, diphenylacetylene did not react with dipole **22** (Scheme 10).



Scheme 10

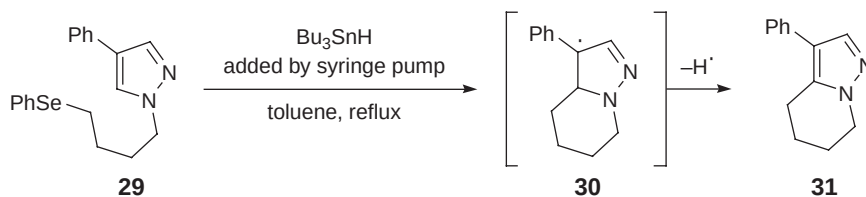
Finally, another interesting new procedure [<1999T7645>](#) involving construction of the six-membered ring should be mentioned in this section. Dianion **26** resulting from the successive treatment of 3,5-dimethylpyrazole with organolithium reagents and carbon dioxide was reacted with an α -oxoketene dithioacetal. Treatment of the resulting adduct **27** with phosphoric acid induced the ring closure to form the six-membered ring present in **28** (Scheme 11). The latter could be conveniently desulfurized upon reaction with Raney-Ni.



Scheme 11

11.10.2.7.2 Partially saturated rings

Tetrahydropyrazolo[1,5-*a*]pyridine derivatives possessing a fully reduced six-membered ring can be prepared by partial reduction of the aromatic ring <1999BML97, 1999BML1979>. Numerous other strategies have appeared for this synthetic purpose. The saturated six-membered ring can be formed by radical cyclization <2002TL4191> starting from selenide **29**: the success of this ring closure depends on the ability of the substituent attached on the pyrazole ring (a phenyl is shown in Scheme 12) to stabilize the intermediate radical **30**. In case of an ester instead of a phenyl substituent, the yield drops to 36% (versus 66% with a phenyl) while no cyclized product is produced when a dimethyl acetal group is attached to the starting pyrazole.



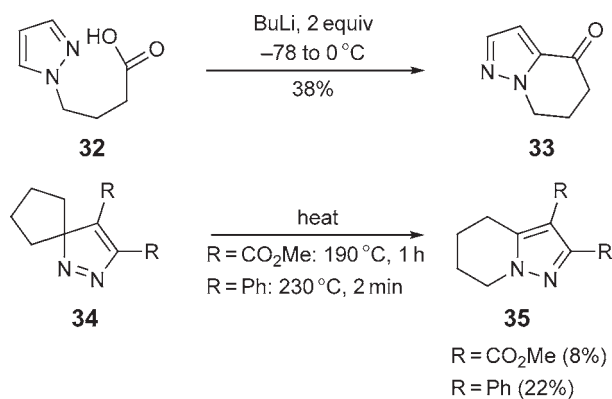
Scheme 12

Anionic ring closure of *N*-substituted pyrazole **32** can be carried out by its treatment with BuLi <1997SL1013>. Although the yield is modest, this is a quite straightforward approach to these heterocycles. Thermal rearrangement of 3,3-spiro-pyrazoles **34** was also found to give (besides other products) the tetrahydro derivatives **35** (Scheme 13) <2001H(55)1859>.

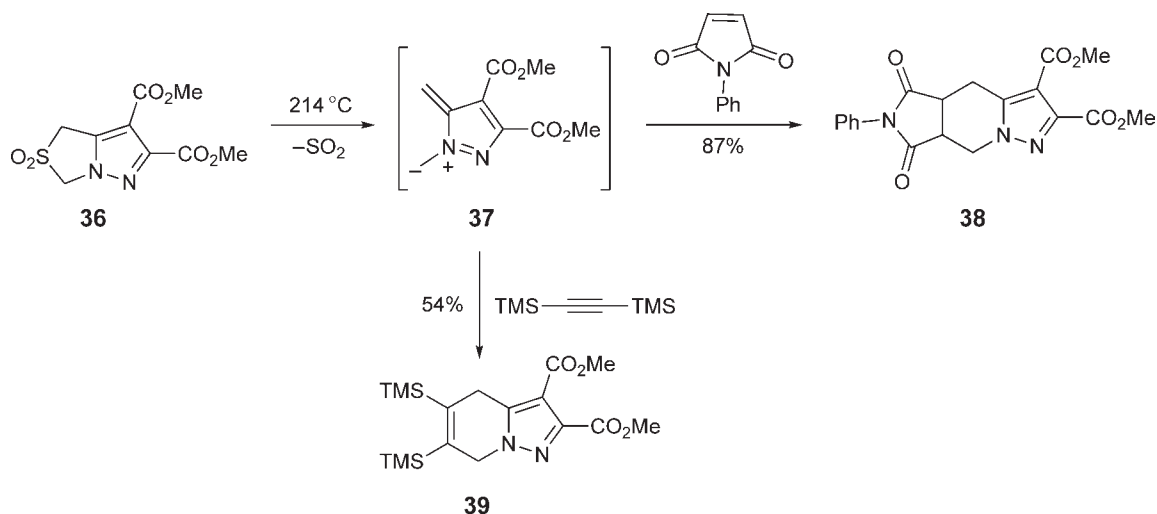
An elegant strategy to pyrazolo[1,5-*a*]pyridines derivatives in which the six-membered ring is partially or totally reduced relies on the cycloaddition of diazafulvenium methide **37**, generated through SO_2 extrusion from pyrazolo sulfone **38** in refluxing 1,2,4-trichlorobenzene, with various dipolarophiles <2006TL791> (Scheme 14).

The preparation of partially reduced derivatives in which the five-membered ring is reduced is less well documented. In a series of papers, Huisgen reported the 1,3-dipolar reactivity of isoquinolinium imide **41** in which loss of aromaticity occurs during cycloaddition <1998EJO379, 1998EJO387, 1998T9848>. Cycloaddition of this compound with dimethyl fumarate or maleate gives **42** and **43** as mixture of diastereoisomers (Scheme 15).

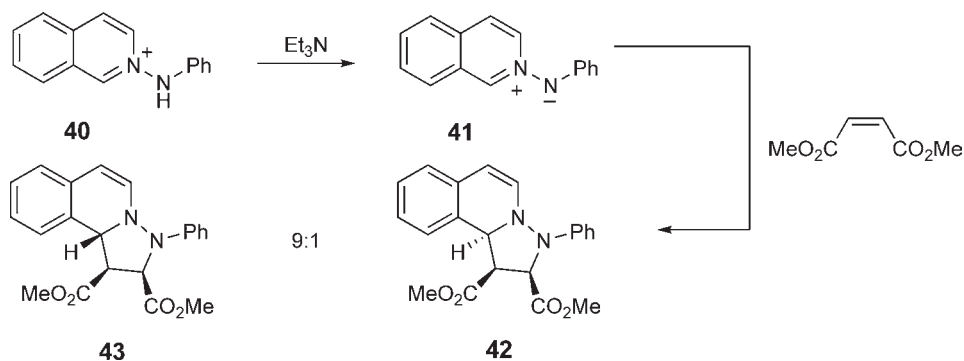
Finally, fully reduced heterocycles have been prepared either from a sequential azomethine imine cycloaddition–palladium-mediated cyclization process <2003T4451>, or from the reaction of *N*-(1-benzotriazolylalkyl)-*N,N*-disubstituted hydrazine with methylvinyl ether <1997JOC8210>.



Scheme 13



Scheme 14

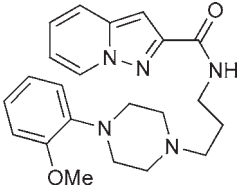
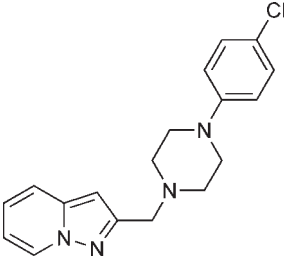
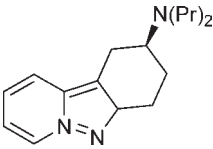
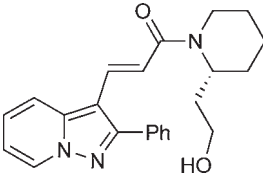
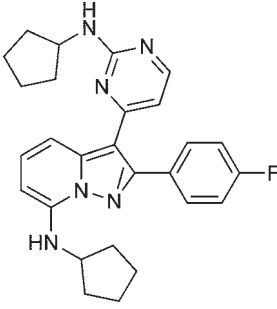


Scheme 15

11.10.2.8 Important Compounds and Applications

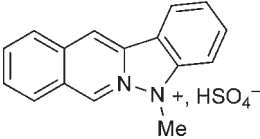
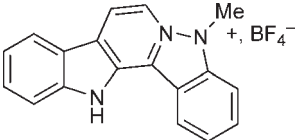
As mentioned in the introduction of this section, an important amount of synthetic work was devoted to this heterocyclic system and was mostly conducted by medicinal chemists. Aiming at developing selective ligands for the dopamine D4 receptor subtypes, the group of Gmeiner has published a series of papers reporting the use of this heterocyclic system as a scaffold for such molecules. Considering that dopamine receptors D4 are associated with neuropathologies such as schizophrenia, attention-deficit disorder, mood disorders, and Parkinson's disease, the potential of new selective ligands as drug candidates is quite high. Important compounds, together with their various biological activities issued from the Gmeiner's group and others, are collected in [Table 4](#).

Table 4 Biologically active compounds including the pyrazolo[1,5-a]pyridine core

<i>Compound</i>	<i>Biological activity</i>	<i>Reference</i>
	Dopamine D3 antagonist (FAUC 329)	2002JME4594
	Dopamine D4 antagonist (FAUC 213)	2001JME2691
	Dopamine D3 agonist (FAUC 725)	2002BML2377
	Diuretic Adenosine A1 antagonist (FK453)	1996BML2059
	Antiherpetic (GW3733)	2006BMC944

(Continued)

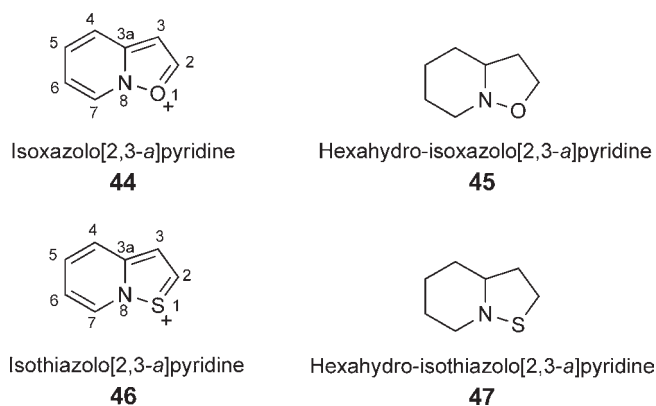
Table 4 (Continued)

Compound	Biological activity	Reference
	Inhibitor of reverse transcriptase (Ellipticin analogue)	1996BML2831
	Intercalating agent	2000BML1767

11.10.3 Isoxazolo[2,3-*a*]pyridine and Isothiazolo[2,3-*a*]pyridine

11.10.3.1 Introduction

Isoxazolo[2,3-*a*]pyridines **44**, isothiazolo[2,3-*a*]pyridines **46**, and their fully saturated derivatives **45** and **47** (Scheme 16) were discussed in CHEC(1984) <1984CHEC(6)613> and CHEC-II(1996) <1996CHEC-II(8)249>. Very little information was available on the isothiazolo[2,3-*a*]pyridine ring system while most of the informations given on the oxygenated parent, isoxazolo[2,3-*a*]pyridines, concerned the fully saturated system. Careful examination of the literature clearly shows that the situation did not change much: almost no references have been reported on isothiazolo[2,3-*a*]pyridines and most of the work done in the last decade concerns the synthesis and reactivity of hexahydro-isoxazolo[2,3-*a*]pyridines **45**. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will focus on the partially/completely saturated derivatives.



Scheme 16

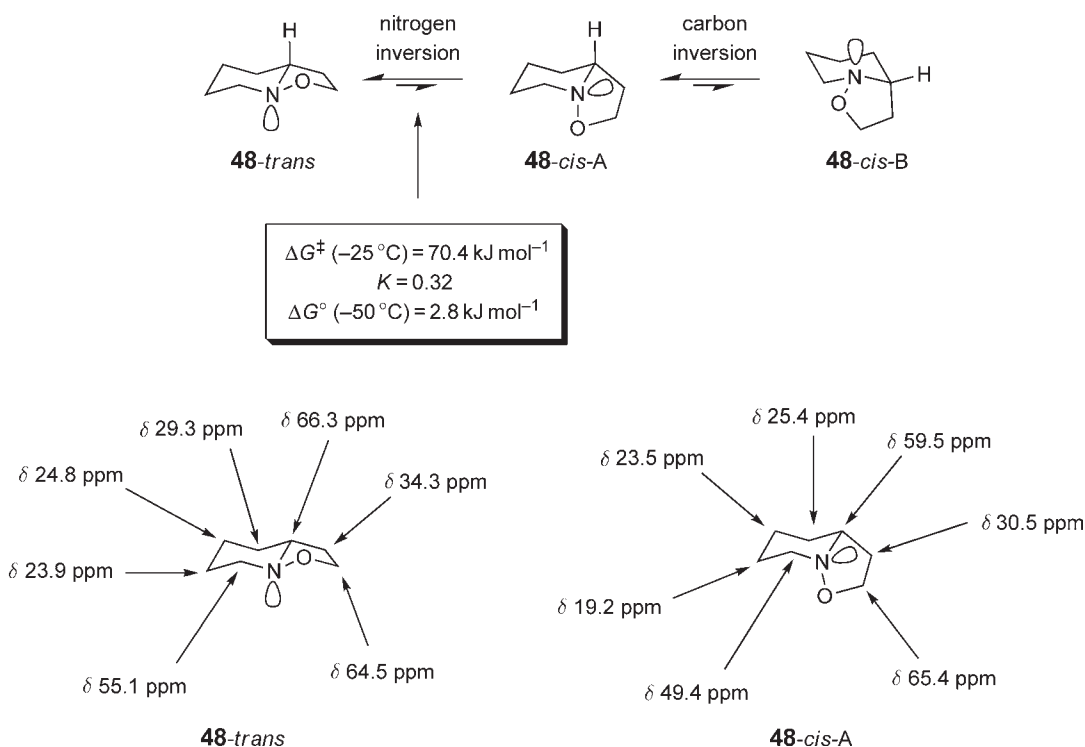
11.10.3.2 Theoretical Methods

No new calculations were specifically devoted to this ring system.

11.10.3.3 Experimental Structural Methods

NMR data for new compounds are routinely reported. The hexahydro-isoxazolo[2,3-*a*]pyridine ring system **48** can exist as a mixture of three conformers **48-trans**, **48-cis-A**, and **48-cis-B** (Scheme 17). While the two conformers possessing a *cis* ring junction **48-cis-A** and **48-cis-B** are interconverted by chair inversion, conversion of the *cis*-conformer **48-cis-A** to **48-trans** requires inversion of the nitrogen. The presence of the adjacent oxygen slows down

the lone-pair inversion in the nitrogen to such an extent that the presence of two interconverting isomers could be identified by ^{13}C NMR spectroscopy which offers a convenient way to measure the nitrogen inversion barrier as well as the relative stability of the *cis*- and *trans*-isomers <1997T11869>: typical data can be found in **Scheme 17** and show the higher stability of the *trans*-isomer. Concerning the *cis*-pair, the equilibrium is in favor of conformer A, which is in accordance with the fact that an oxygen substituent is better tolerated than an alkyl substituent in axial position.



Scheme 17

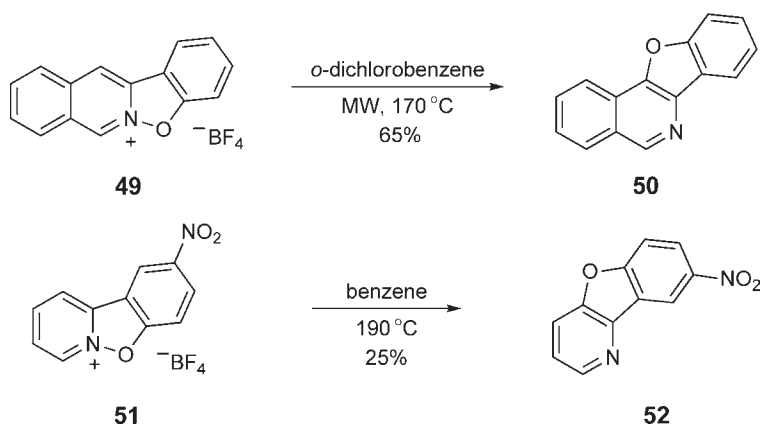
NMR data depicted in **Scheme 17** deserve some additional comments since they can be especially useful to indicate which conformer is the major one. In the minor *cis*-isomer, all carbon atoms, except C-2, are more shielded than the corresponding carbon in the *trans*-isomer. This can be easily explained by considering that the axial oxygen in **48-cis-A** or the axial CH_2 in **48-cis-B** respectively causes shielding of C-4, C-6 and C-5, C-7 due to their γ -*gauche*-interactions.

11.10.3.4 Thermodynamic Aspects

The NMR studies described in the precedent section allowed to determine the thermodynamic parameters of the equilibrium depicted in **Scheme 17**.

11.10.3.5 Reactivity of Fully Conjugated Rings

Apart from isolated reports summarized in **Scheme 18**, the chemistry of the fully conjugated ring systems has not been especially developed since CHEC-II(1996). In 2002, Timári *et al.* reported the generation of aryloxonium ions from thermolysis of isoxazolo[2,3-*a*]pyridinium tetrafluoroborates **49** and **51** and their subsequent cyclization, respectively, to benzofuro[3,2-*b*]pyridine **50** and **52** <2002TL6035>. In addition, it was shown that isoxazolo[2,3-*a*]pyridinium acetate could be attacked by alcohols in the presence of Na_2CO_3 to afford 6-alkoxy-substituted 2-phenacylpyridines in moderate yields <1996H(43)1179>.



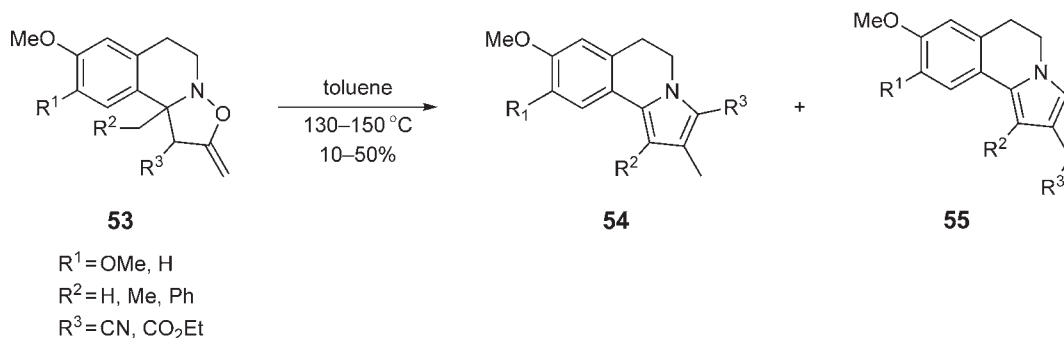
Scheme 18

11.10.3.6 Reactivity of Nonconjugated Rings

In contrast to the conjugated system, the reactivity of hexahydro-isoxazolo[2,3-*a*] pyridines has been the subject of considerably more attention, which can most certainly be attributed to its greater synthetic potential, as demonstrated by the synthesis of many complex natural products. However, most of the reactions reported since 1996 have been known for many years and the last decade was in fact characterized by their use in syntheses or optimization. After a brief survey of the thermal reactions, procedures involving the reductive cleavage of the N–O bond will be detailed.

11.10.3.6.1 Unimolecular thermal reactions

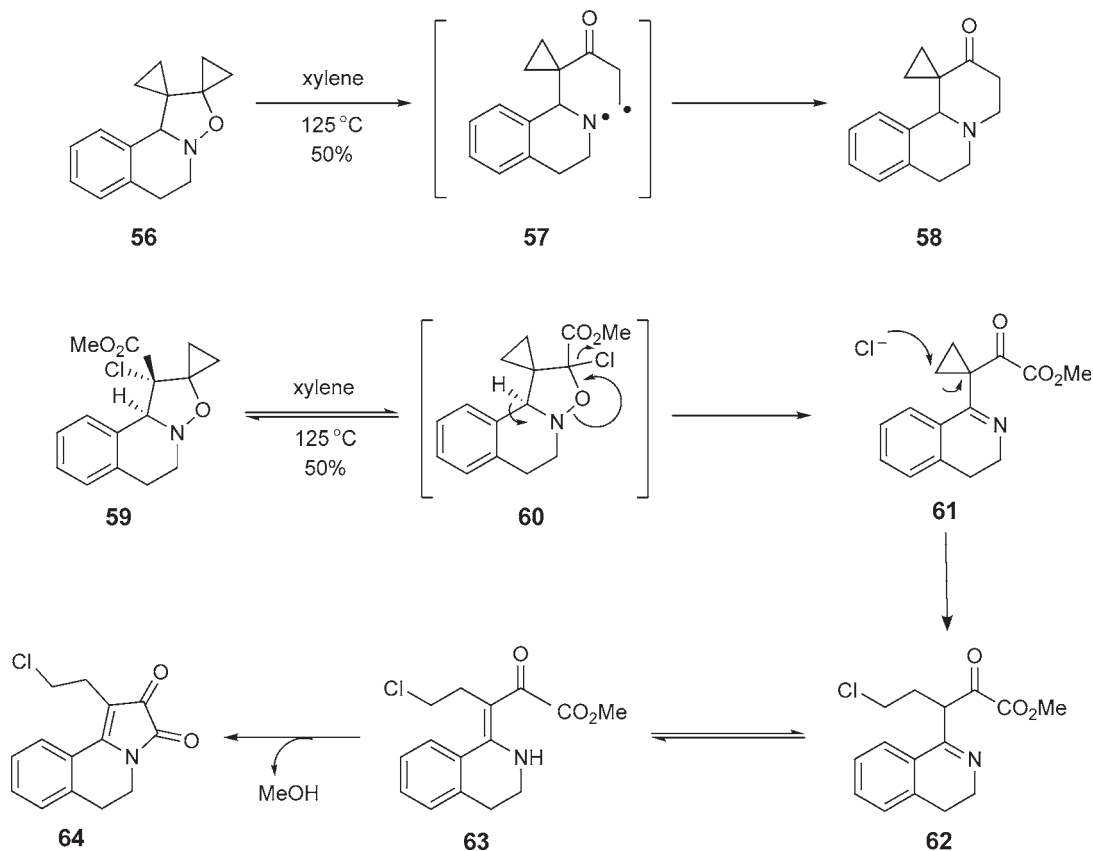
In 1997, Zhao and Eguchi demonstrated that 2-methylene-1,5,6,10b-tetrahydro-2*H*-isoxazolo[3,2-*a*]isoquinolines **53**, obtained by 1,3-dipolar cycloaddition of isoquinoline *N*-oxides with electron-deficient allenes, undergo thermal rearrangement when heated at 130–150 °C in toluene to afford two isomers, **54** and **55**, of 5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline derivatives (Scheme 19). The formation of these fused-ring pyrroles can be rationalized on the basis of occurrence of two competitive consecutive rearrangements, one of which, as the minor route, involves an initial 1,3-hydrogen shift to give 4-isoxazolines followed by known rearrangement via acylaziridine intermediates, while the other, the major one, involves transient formation of pyrrolidin-3-ones followed by a novel rearrangement via bond scission and cyclocondensation <1997J(P1)2973>.



Scheme 19

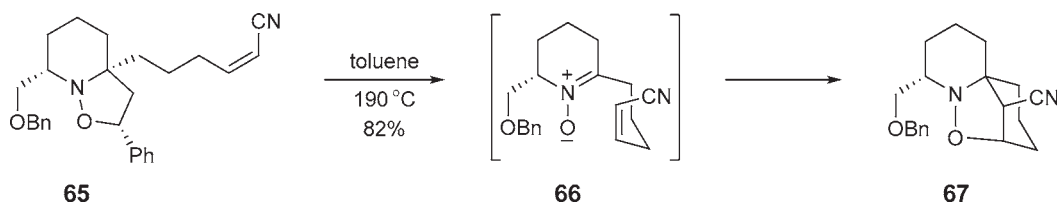
An interesting thermally induced rearrangement concerns strained bis-spirocyclopropanated hexahydro-isoxazolo[2,3-*a*]pyridines such as **56** which easily rearrange upon heating with selective opening of one of the two spiro-fused cyclopropane rings. This process produces 4-pyridones such as **58** in good yield <1999JOC1665> (Scheme 20). In contrast, replacing the second cyclopropyl group by a chloroester **59** dramatically reverses the

reactivity since **64** is now produced. The formation of compound **64** can be rationalized only assuming that the primary cycloadducts **59** undergo a cycloreversion–recycloaddition sequence finally leading to the thermodynamically more stable cycloadducts **60**. Once the cycloaddition–cycloreversion equilibrium is established, a mixture of cycloadducts based on their relative thermodynamic stability is formed. The 4-spirocyclopropaneisoxazolidine **60**, which must form in this process, can undergo a sequential ring opening followed by nucleophilic attack of chloride on the bisacceptor-substituted cyclopropane ring in **61** to form the α -ketoester **62** (Scheme 20). The enamine tautomer **63** then cyclizes with loss of methanol to produce **64** <1999JOC755>.



Scheme 20

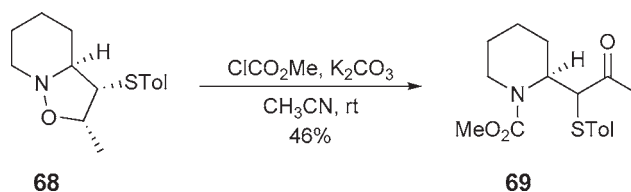
Finally, the reversibility of the nitrone/alkene [3+2] cycloaddition, mainly used to access the hexahydro-isoxazolo[2,3-*a*]pyridine ring system (see Section 11.10.3.7), can be used to functionalize these heterocycles. Accordingly, Holmes *et al.* found that a cycloreversion–cycloaddition reaction could be performed from **65** by simple heating in toluene at 190 °C. Under these conditions, the product of the reaction was found to be the *exo*-adduct **67** (Scheme 21) <2002J(P1)1494>.



Scheme 21

11.10.3.6.2 Electrophilic attack at nitrogen

In addition to the hydrogenolytic cleavage exploited in most cases for the cleavage of the N–O bond (see [Section 11.10.3.6.3](#)), hexahydro-isoxazolo[2,3-*a*]pyridines are excellent substrates for heterolytic ring-opening reactions. In particular, activation of **68** through quaternization of the nitrogen atom by reaction with methyl chloroformate, followed by a Hofmann-like elimination process, leads to β -amino ketone **69** in correct yield ([Scheme 22](#)) <1997TA109>.



Scheme 22

11.10.3.6.3 N–O Bond reduction

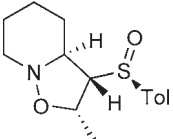
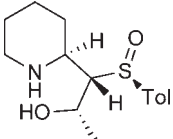
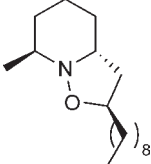
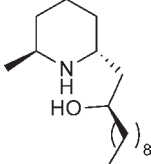
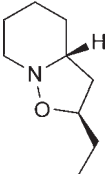
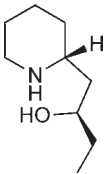
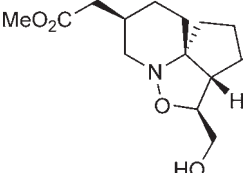
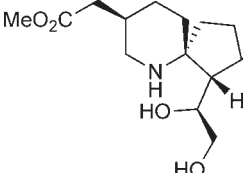
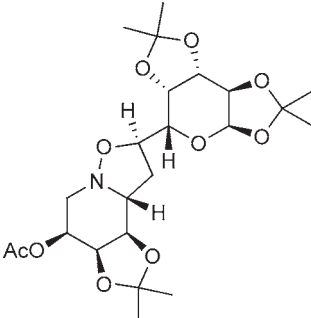
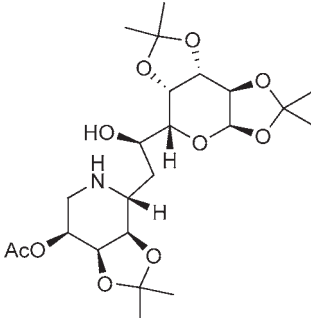
Most of the reactions of interest involve the opening of the isoxazole ring. This reductive opening has been known for years and was reported in CHEC(1984) and CHEC-II(1996). Over the years, many different reagents have been used and/or developed for this ring-opening process: examples of the most useful ones are collected in [Table 5](#) and give an overview of the protocols available for N–O bond reduction.

Table 5 N–O bond reduction

Substrate	Reducing agent, conditions	Product	Yield (%)	Reference
	H ₂ , PdCl ₂ MeOH, 6.5 atm, rt		91	1996JOC1023
	H ₂ , Pd/C EtOH, 5 atm, rt		100	2000TL929
	H ₂ , Pd(OH) ₂ MeOH, rt		91	2002SL1344
	H ₂ , Raney-Ni MeOH, rt		84	1997TA109

(Continued)

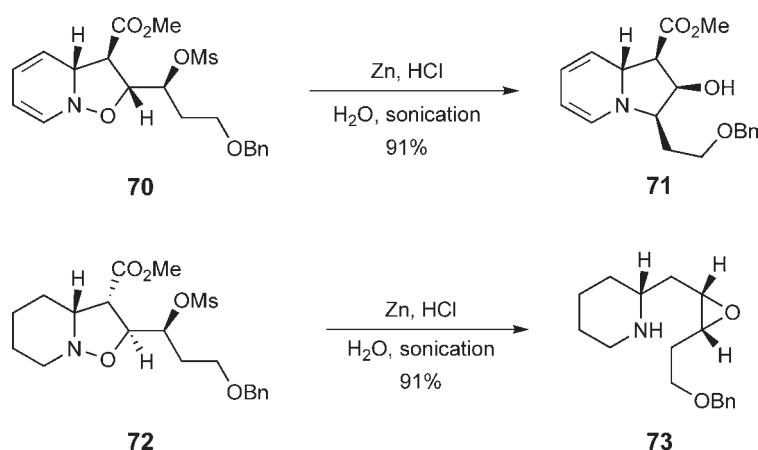
Table 5 (Continued)

Substrate	Reducing agent, conditions	Product	Yield (%)	Reference
	Ni/Al, KOH MeOH, rt		92	1997TA109
	Zn, AcOH 70 °C		86	1997T11203
	LiAlH ₄ THF, reflux		86	1996LA2083
	SmI ₂ THF, rt		64	2001OL413
	Mo(CO) ₆ H ₂ O/CH ₃ CN, reflux		67	2000CC2127

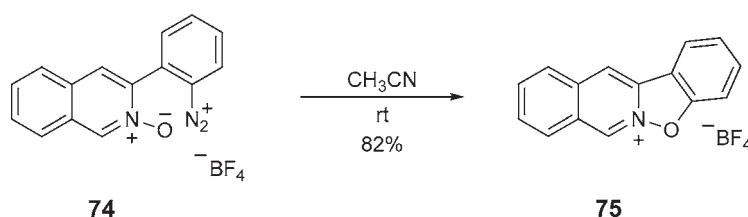
Interestingly, both the amino and the hydroxy groups can participate in another reaction with a suitable reacting group present in the molecule as shown with the two examples in [Scheme 23](#) <1998T11581>. Finally, it should be mentioned that this N–O bond reduction is also efficient starting from quaternary ammonium derivatives of hexahydro-isoxazolo[2,3-*a*]pyridines <1999JOC1932>.

11.10.3.7 Ring Syntheses from Acyclic Compounds

As was the case for their reactivity, fully conjugated ring systems have received only little attention since CHEC-II(1996). In 2002, Timári *et al.* reported the synthesis of isoxazolo[2,3-*a*]pyridinium tetrafluoroborate **75** from pyridinium *N*-oxide **74** ([Scheme 24](#)) <2002TL6035>. Formation of the new ring system can be interpreted by a nucleophilic attack of the *N*-oxide at the electrophilic carbon atom bearing the diazonium group, followed by nitrogen elimination, a reaction that was earlier observed by Abramovitch and Inbasekaran <1978CC149>.



Scheme 23



Scheme 24

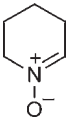
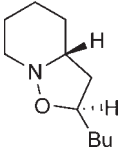
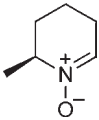
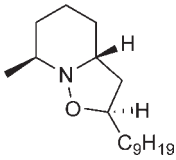
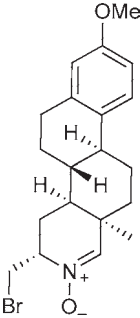
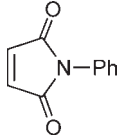
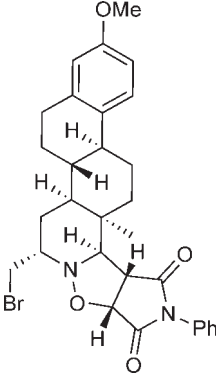
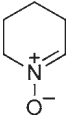
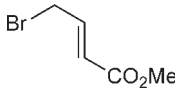
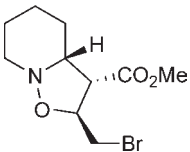
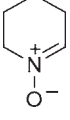
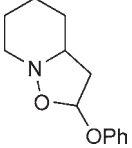
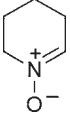
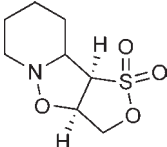
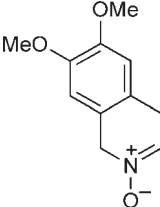
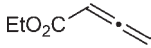
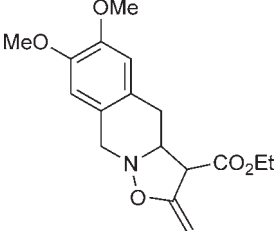
11.10.3.8 Ring Syntheses of Saturated Rings from Acyclic Compounds

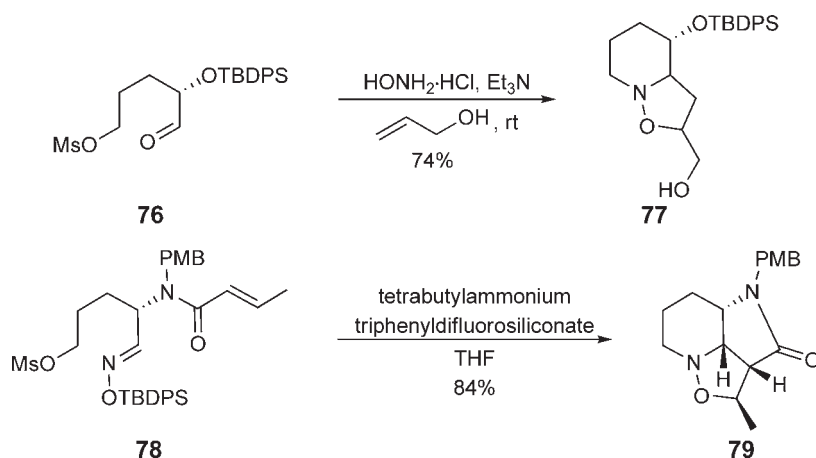
The importance of hexahydro-isoxazolo[2,3-*a*]pyridines as intermediates for the asymmetric synthesis of complex molecules and alkaloids has led to a continued interest in their preparation. A close look at the literature clearly reveals that the method of choice for their preparation remains the 1,3-dipolar cycloaddition between a tetrahydropiperidine *N*-oxide and an alkene [<B-2003MI1>](#). A condition for such a reaction to take place is a good overlap between the interacting highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) orbitals, which depends on the relative orbital energies of both the dipolarophile and the dipole. Electron-withdrawing groups on the dipolarophile normally favor an interaction of the LUMO of the dipolarophile with the HOMO of the dipole that leads to the formation of the new bonds, whereas electron-donating groups on the dipolarophile normally favor the inverse of this interaction. Concerning the regioselectivity of the reaction, simple, alkyl-monosubstituted alkenes usually produce hexahydro-isoxazolo[2,3-*a*]pyridines possessing the substituent at C-2 while electron-deficient olefins usually lead to hexahydro-isoxazolo[2,3-*a*]pyridine adducts with the electron-withdrawing group attached to position 3, in agreement with the frontier molecular orbital (FMO) theory. Finally, concerning the stereoselectivity of the reaction, the *exo*-mode is usually favored. It is worth noting that this 1,3-dipolar cycloaddition is commonly referred as a [3+2] cycloaddition, which is not the correct symbolism. According to IUPAC recommendations, this cycloaddition is either a [4+2] (number of electrons involved in the process) or a [3+2] cycloaddition (number of atoms participating in the reaction).

Representative examples illustrating these concepts and 'general rules' as well as giving an overview of all different dipolarophiles engaged in the formation of hexahydro-isoxazolo[2,3-*a*]pyridines are collected in [Table 6](#).

Interestingly, the nitrone can be formed *in situ* by direct condensation of an aldehyde possessing a suitable leaving group and hydroxylamine hydrochloride, as in the synthesis of **77** from **76** [<2001OL953>](#) ([Scheme 25](#)) or by deprotection of a silyl-protected oxime as exemplified by the synthesis of cycloadduct **79** [<2002SL1344>](#). Epoxides [<1997T13165>](#) or double bonds together with activating agents (*N*-bromosuccinimide (NBS), iodine) [<2001T1119>](#) can also be used in place of the internal leaving groups.

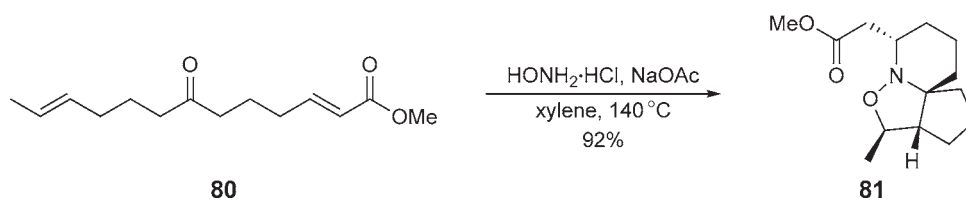
Table 6 [3+2] cycloaddition to hexahydro-isoxazolo[2,3-a]pyridines

<i>Dipole</i>	<i>Dipolarophile</i>	<i>Conditions</i>	<i>Product</i>	<i>Yield (%)</i>	<i>Reference</i>
		CHCl ₃ /MeOH 60 °C, 2.5 d		93	1996CJC2434
		Neat 145 °C 45 min		81	1997T11203
		Benzene 50 °C, 2 h		81	2005SL637
		CHCl ₃ 60 °C, 13 h		51	1998T6947
		C ₂ H ₂ Cl ₄ 50 °C, 16 h		58	2003S1221
		Toluene 40 °C, 12 h		86	2003S1329
		CH ₂ Cl ₂ rt		80	1997T9575



Scheme 25

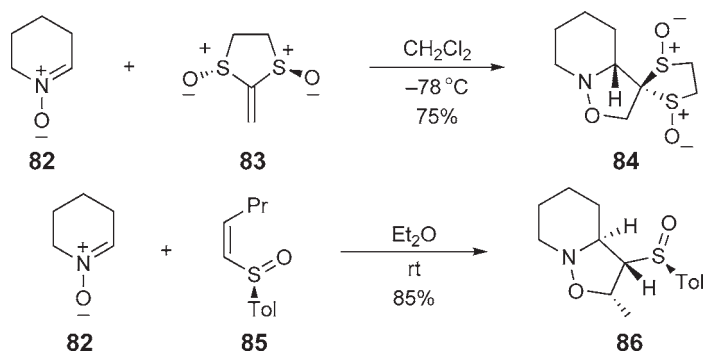
High levels of convergence and efficiency can be reached starting from fully acyclic substrates possessing an oxime (or a ketone precursor) and two alkenes: tandem intramolecular Michael addition/cycloaddition reactions yield fused hexahydro-isoxazolo[2,3-*a*]pyridines in good yields and excellent selectivities as exemplified by the cycloaddition to **81**, en route to halichlorine and pinnaic acid (Scheme 26) <1999TL7921>. When the use of high temperatures is prohibited, an alternative protocol relying on the use of a catalytic palladium(II)-mediated cyclization–intermolecular cycloaddition cascade can be used in place of the thermal reaction <1997T15051>.



Scheme 26

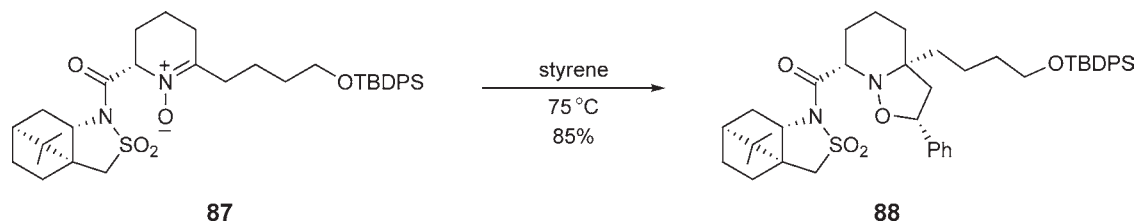
The development of this 1,3-dipolar cycloaddition reaction has entered a new stage in recent years as control of the stereochemistry in the addition step is now the major challenge. The selectivity challenge is to control the regio-, diastereo-, and enantioselectivity of the 1,3-dipolar reaction <1998CRV863>. The stereochemistry can be controlled by either choosing the appropriate substrates or controlling the reaction by a metal complex acting as a catalyst, strategies that have all been applied to the synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines.

Various chiral dipolarophiles have been used in the asymmetric synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines. Examples include *trans*-2-methylene-1,3-dithiolane 1,3-dioxide **83** <1998JOC3481>, chiral vinyl sulfoxide **85** <1997TA109>, or chiral dioxolanes <2001TA1747> (Scheme 27).



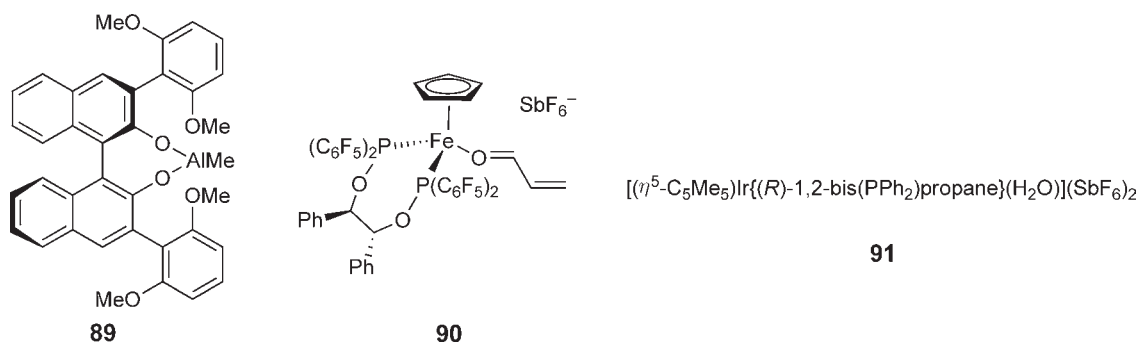
Scheme 27

On the nitron side, high levels of selectivities have been reached using camphorsultam-derived nitron **87** since hexahydro-isoxazolo[2,3-*a*]pyridine **88** en route to (–)-histrionicotoxin was obtained as a single regio- and diastereoisomer <1999JA4900> (Scheme 28). A polyhydroxylated hexahydro-isoxazolo[2,3-*a*]pyridine could also be obtained starting from a nitron derived from a *C*₂-symmetric piperidine <2002TL9357>.



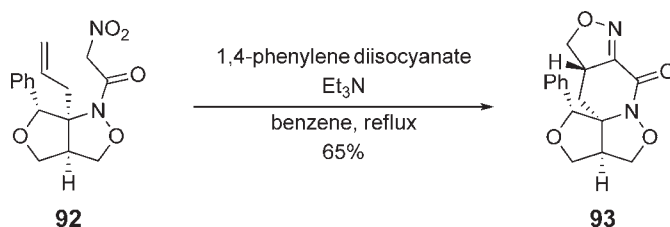
Scheme 28

Finally, the catalytic enantioselective 1,3-dipolar cycloaddition reaction has recently been developed to be a highly selective reaction of nitrones with electron-deficient alkenes activated by chiral Lewis acids. High levels of regio-, diastereo-, and enantioselectivities can now be reached using catalysts **89** <2000JOC9080>, **90** <2002JA4968>, or **91** <2005JA13386> (Scheme 29).



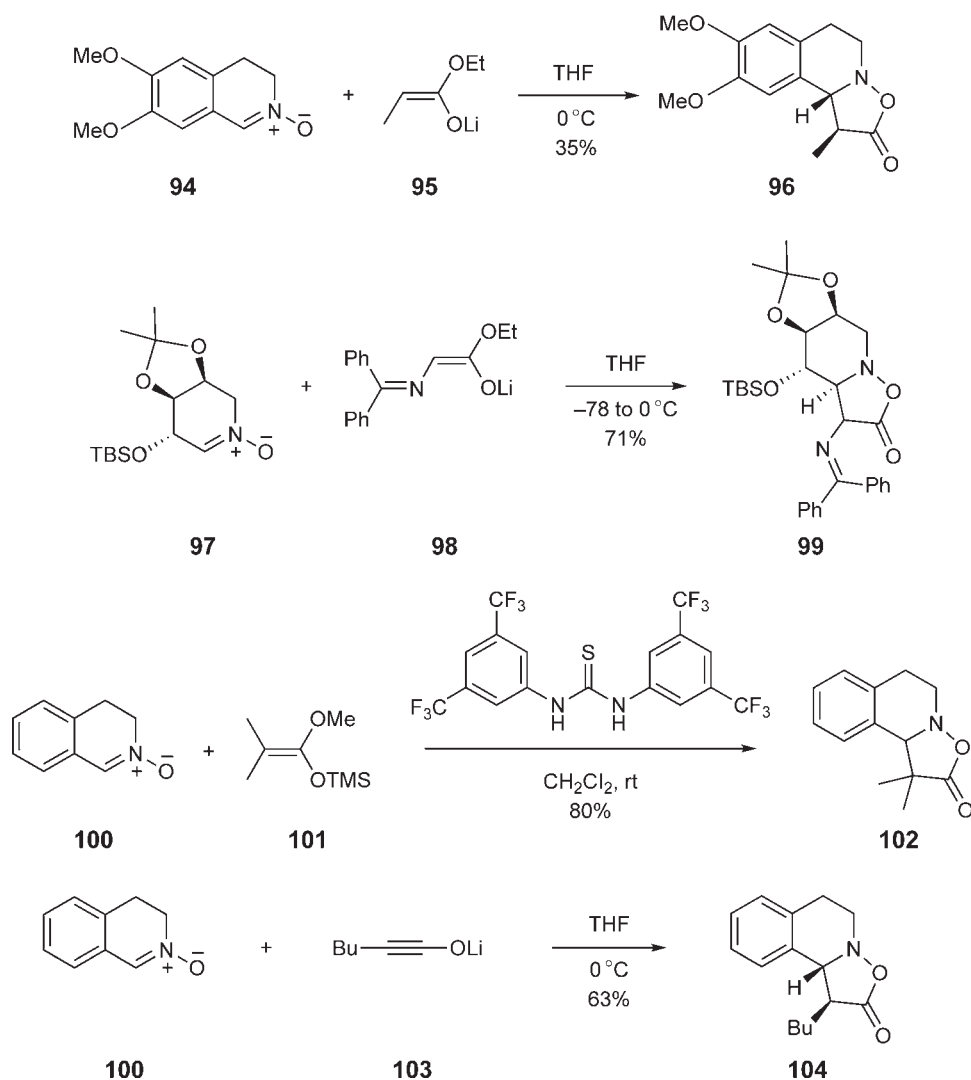
Scheme 29

If nitrones have been widely used as 1,3-dipoles in the synthesis of hexahydro-isoxazolo[2,3-*a*]pyridines, the use of nitroacetates such as **92** in the cycloaddition sequence allows for an efficient access to hexahydro-isoxazolo[2,3-*a*]pyridin-7-ones such as **93** after spontaneous dehydration (Scheme 30) <2000JOC499>.



Scheme 30

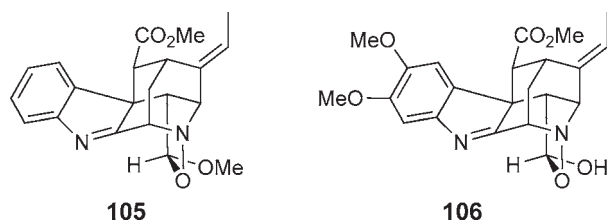
An efficient preparation of hexahydro-isoxazolo[2,3-*a*]pyridin-2-ones relies on the anionic addition of nucleophiles at the electrophilic carbon of the nitron followed by cyclization of the resulting *N*-oxide. As shown by results collected in Scheme 31, various nucleophiles can be engaged in the reaction and include enolates **95** <2002OL3119> or **98** <2000BML1811>, silyl acetals **101** <2003TL2817>, or ynolates **103** <2002OL3119> (Scheme 31).



Scheme 31

11.10.3.9 Important Compounds and Applications

Few isoxazolo[2,3-*a*]pyridines have found important applications in the field of chemistry and/or medicinal chemistry. Natural products of the nareline family such as nareline methyl ester **105** <1997P1303> or 10,11-dimethoxy-nareline **106** <2004JNP547> have been isolated (Scheme 32).



Scheme 32

11.10.4 Imidazo[1,5-*a*]pyridine

11.10.4.1 Introduction

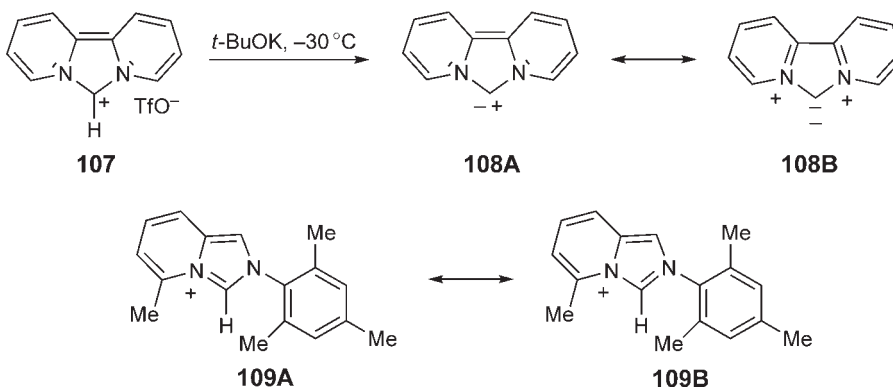
Imidazo[1,5-*a*]pyridines can be viewed as imidazoles fused to a benzene ring. This class of heterocycles was briefly covered in CHEC(1984) <1984CHEC(6)613> along with other imidazoles fused to six-membered rings and it was covered together with imidazo[1,2-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)249>. Chemistry published on this heterocycle is less abundant in comparison to their isomers covered in Sections 11.10.2 and 11.10.6. Quite recently, a growing interest for this heterocycle has appeared due to the development of N-heterocyclic carbene (NHC) ligands: special focus will be put on this specific topic in this chapter.

11.10.4.2 Theoretical Methods

No new calculations were specifically devoted to this heterocyclic system since CHEC-II(1996). Redox properties of chalcogeno-ureas possessing this heterocyclic skeleton and resulting from the reaction of Arduengo carbenes such as **108** with sulfur or selenium was investigated through semi-empirical calculations <2000EJI1935>.

11.10.4.3 Experimental Structural Methods

As for the previous section, no additional specific NMR data has been published since CHEC(1984) and CHEC-II(1996): NMR data for new substituted compounds are routinely reported. Several X-ray structures including new substituted compounds <2002AG3104>, imidazopyridinium derivatives <2002EJO375, 1999H(50)887>, fused derivatives <1995JA3278>, and carbene ligands <2005T6207, 1998AGE344, 2005JA3290> have been reported. Carbenes, such as **108** generated by deprotonation of cationic salt **107**, were thoroughly investigated by Weiss <1998AGE344>. On the basis of *ab initio* calculations (3-21G*), they were shown to be better represented by canonical form **108A** (Scheme 33). Similarly, on the basis of X-ray studies, the most important canonical forms **109A** and **109B** of imidazolium salts **109** were determined <2005T6207>.



Scheme 33

11.10.4.4 Thermodynamic Aspects

No specific studies on this topic were published in the last decade.

11.10.4.5 Reactivity of Fully Conjugated Rings

Imidazo[1,5-*a*]pyridines are aromatic systems in which the bridgehead nitrogen N-4 contributes to the aromaticity with its lone pair. Therefore, this nitrogen atom is not nucleophilic and electrophilic attacks occur at the N-2 position. S_EAr occurs at C-1, but also sometimes at C-3, depending on the conditions used (Figure 3).

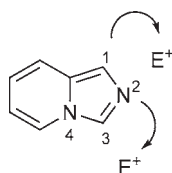
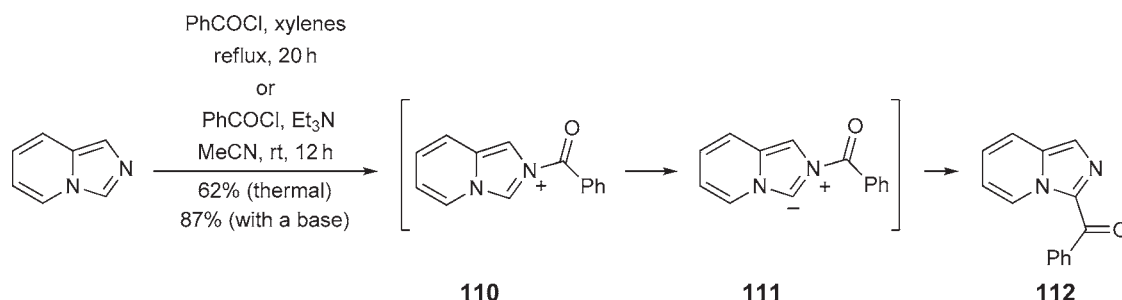


Figure 3

11.10.4.5.1 Electrophilic attack at nitrogen

Alkylation at N-2 readily occurs with alkyl iodides or benzyl bromide [<2003BML3475, 2005JA3290>](#). In case of acyl chlorides, such as benzoyl chloride, *N*-acylation gives an intermediate imidazo[1,5-*a*]pyridinium ion **110** which reacts further in the presence of triethylamine, or under thermal conditions, to give an intermediate ylide **111**. A subsequent 1,2-rearrangement exclusively gives the C-3-substituted product (**Scheme 34**). Sterically hindered aryl chlorides only gave recovered starting material under these conditions [<1998H\(48\)1015>](#).



Scheme 34

11.10.4.5.2 Electrophilic attack at carbon

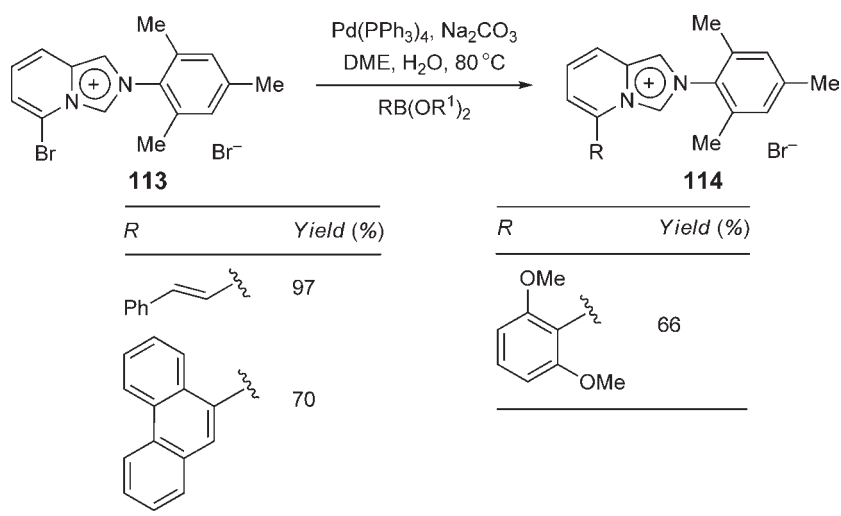
Electrophilic attack at carbon occurs regioselectively at the C-1 position, although the reaction shown in **Scheme 34** might interfere to give small amounts of C-3-substituted product. This was illustrated by some examples in CHEC(1984). Additional recent examples include acylations under Friedel–Crafts conditions [<1998H\(48\)1015, 2001CPB799>](#).

11.10.4.5.3 Nucleophilic attack at carbon

No examples of such reactions have been disclosed. Displacement of halogens on the parent heterocycle through metal-catalyzed processes have surprisingly not been reported to our knowledge on the neutral heterocycle. Recently, Suzuki–Miyaura cross-coupling reactions of imidazolium bromide **113** with various boronic acids or esters were reported [<2005T6207>](#) to proceed in good yield, without deprotonation at the C-3 position (**Scheme 35**).

11.10.4.5.4 Nucleophilic attack at hydrogen

Deprotonation of imidazo[1,5-*a*]pyridines occurs at C-3. This was illustrated by some examples in CHEC(1984). A more recent report describes lithiation at C-3 position with *n*-BuLi, followed by reaction of the resulting anion with TsCN, thus affording the corresponding 3-cyano derivative [<1997H\(46\)443>](#). When imidazolinium ions are treated with a base, deprotonation then occurs at C-3 to give carbenes. These compounds were found to be excellent C-ligands for transition metals. **Table 7** summarizes some carbenes possessing this heterocyclic skeleton that have been prepared through this manner, and, in some cases, directly used for the preparation of various complexes.



Scheme 35

Table 7 Generation of NHC from imidazo[1,5-a]pyridinium ions

Substrate	Conditions	Product	Yield (%)	Reference
	Pd(OAc) ₂ NaI, <i>t</i> -BuOK, THF		52	2005T6207
	[Ir(COD)Cl] ₂ <i>t</i> -BuOK, THF		77	2005T6207
	NaH, <i>t</i> -BuOK (cat.)		n.r. ^a	2005JA3290
	NaH, <i>t</i> -BuOK (cat.) Then [Rh(COD)Cl] ₂		91	2005JA3290
	<i>t</i> -BuOK, THF −30 °C		n.r. ^a	1998AGE344

^an.r. = not reported.

11.10.4.5.5 Reactions at surfaces

The six-membered ring was reported to be selectively reduced over the five-membered ring in CHEC(1984) and CHEC-II(1996). More recent examples confirm this reactivity <1998H(48)1015, 1996CPB991>.

11.10.4.6 Reactivity of Substituents Attached to the Ring

Among the rare reports of chemical transformation of substituents attached to the ring, the total reduction of an aromatic ketone linked at C-1 (lithium aluminium hydride (LAH)), then Et₃SiH/trifluoroacetic acid (TFA), overall yield 20%) is of interest <1998H(48)1015>. One example related to Wittig olefination of the 1-formyl derivative of the parent heterocycle was reported to occur in low yield <2001CPB799>.

11.10.4.7 Synthesis

11.10.4.7.1 Fully conjugated ring

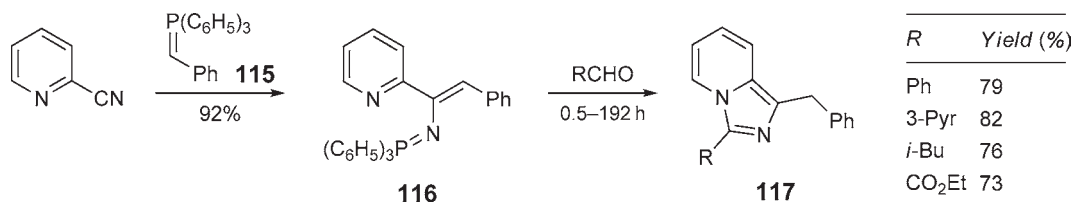
Most of the synthetic methods available for the synthesis of this heterocyclic core rely on the construction of the five-membered ring. The most 'classical' method involves the cyclocondensation of 2-aminomethylpyridine amide derivatives under various dehydrating conditions. This was exemplified by numerous examples in CHEC(1984) and CHEC-II(1996). Additional and more recent examples, together with their yields and conditions, are gathered in Table 8.

Table 8 Synthesis of imidazo[1,5-a]pyridines through cyclocondensation of 2-aminomethylpyridine amide derivatives

Substrate	Conditions	Product	Yield (%)	Reference
	POCl ₃		94	2001CPB799
	POCl ₃ Toluene, 110 °C		77	2004H(63)2355
	PPA 120 °C, 18 h		n.r. ^a	2005BML2129
	POCl ₃ DCM, reflux, 3 h		93	2002BML465

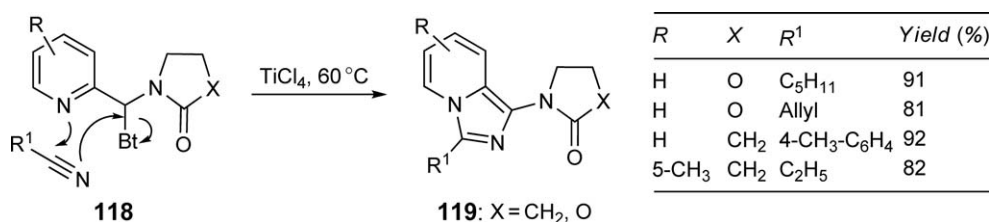
^an.r. = not reported.

New strategies have appeared for the formation of the five-membered ring. The first one relies on a tandem aza-Wittig/electrocyclic ring closure of N-vinyl phosphazenes <1995T3683>. Thus, azaphosphazane **116**, resulting from the reaction of 2-cyanopyridine and ylide **115**, was reacted with different aldehydes to afford the C-3 substituted derivatives **117**. Although the reported yields were satisfactory, protracted reaction times were most often needed (Scheme 36).



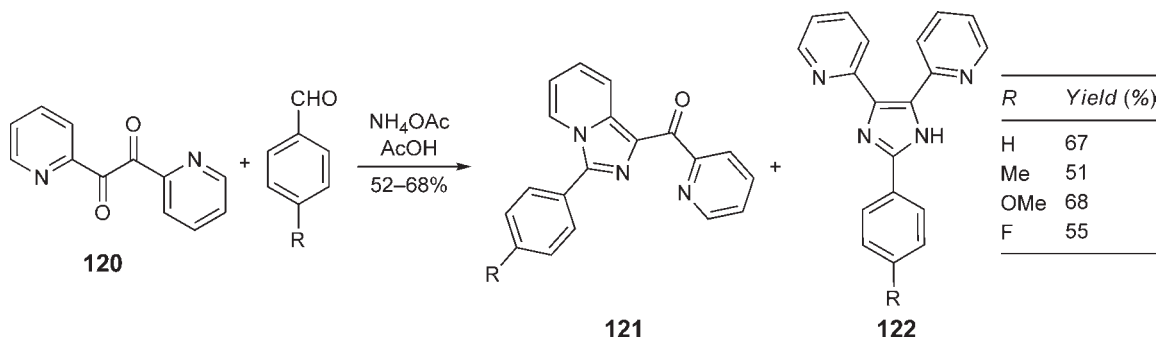
Scheme 36

Katritzky *et al.* reported a straightforward access to 1-amido-3-alkylamino[1,5-*a*]pyridines **119** involving the ring closure of the five-membered ring by reaction of nitriles and benzotriazole derivatives **118** induced by TiCl₄ <2001JOC2862, 1999TA255>. Compounds **118** are in turn obtained in high yields by a condensation reaction between the 2-formyl pyridine, the required amide, and benzotriazole. Yields are good to excellent, and the reaction tolerates various substituents at C-3 (Scheme 37).



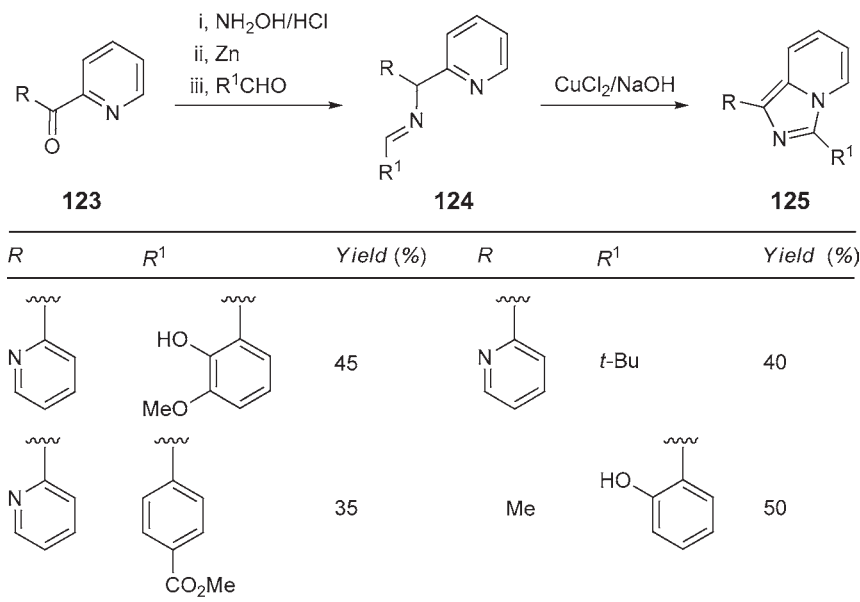
Scheme 37

More recently, a new and straightforward one-pot approach was reported by Bu *et al.* <2003JOC5415>. This reaction involves the cyclocondensation of 1,2-dipyridin-2-yl-ethane-1,2-dione **120** and arylaldehydes, in the presence of ammonium acetate. Imidazo[1,5-*a*]pyridines **121** were obtained in reasonable yields, but competitive formation of imidazoles **122** was observed. The amount of ammonium acetate used in this reaction was also shown to strongly influence the yield of the cyclization (Scheme 38).



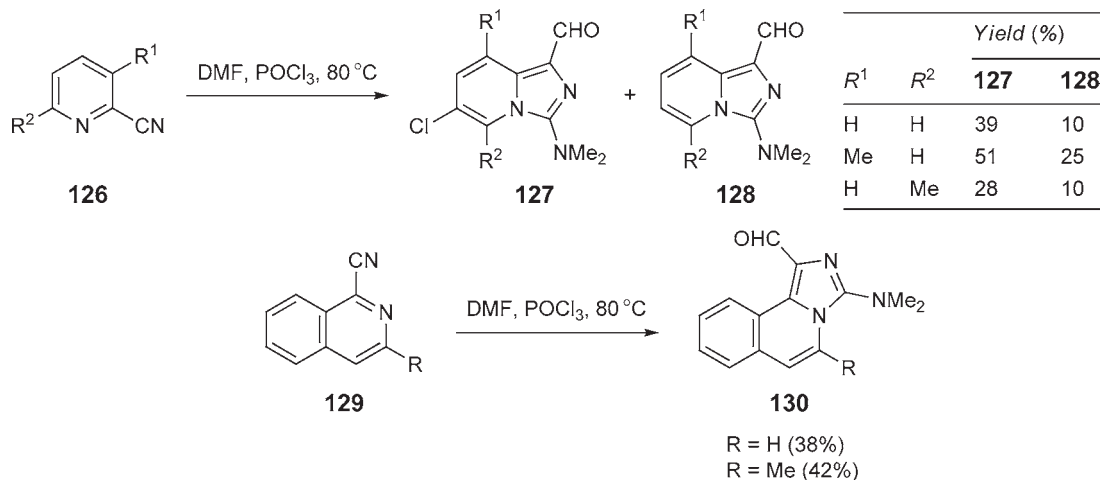
Scheme 38

This methodology was recently extended to the use of 2,2'-dipyridyl ketones and aromatic (or heteroaromatic) aldehydes <2005JOC2353>. In these cases, imidazoles were indeed not produced and the isolated yields of 1-(2-pyridyl)-3-aryl-imidazo[1,5-*a*]pyridines were very good (70–90%). Related cyclizations (Scheme 39) leading to **125** can also be promoted by copper(II) chloride, starting from Schiff bases **124**, themselves synthesized from 2-pyridyl ketones **123**: the proposed mechanism involves an oxidative cyclization of **124**, resulting in a reduction of copper(II) to copper(I), which is then reoxidized to copper(II) by oxygen. However, the yields are quite low <2002AG3104>.



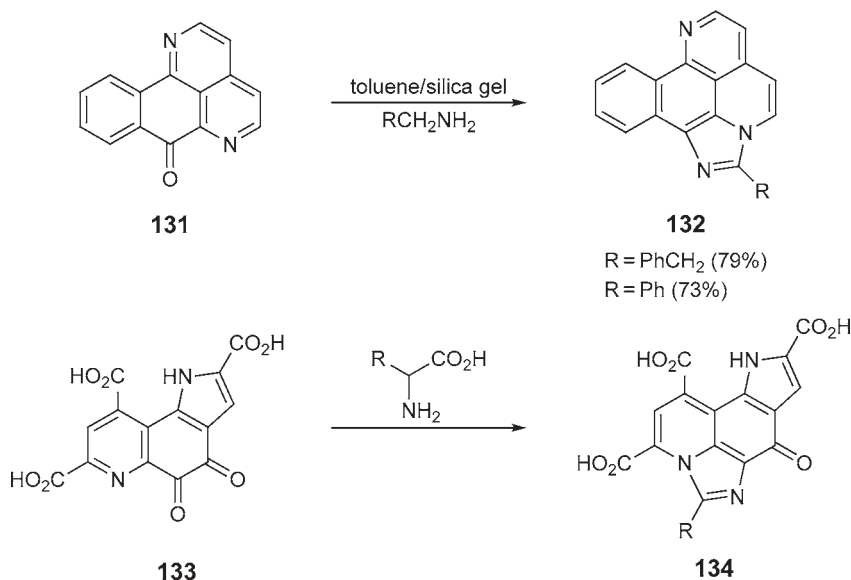
Scheme 39

A Vilsmeier reaction of pyridine-2-carbonitriles **126** was found to produce mixtures of 1-formyl-2-dimethyl-amino[1,5-*a*]pyridines with a chlorine atom **127** or a hydrogen **128** at the C-7 position <1998J(P1)3851>. When extended to isoquinoline-1-carbonitriles such as **129**, this reaction gave in modest yield compounds **130** (Scheme 40). Later on, it was demonstrated that this reaction leads to imidazo[1,5-*a*]pyridinium chlorides when *N,N*-dimethylbenzamides were used instead of dimethylformamide (DMF) <1999H(50)887>.



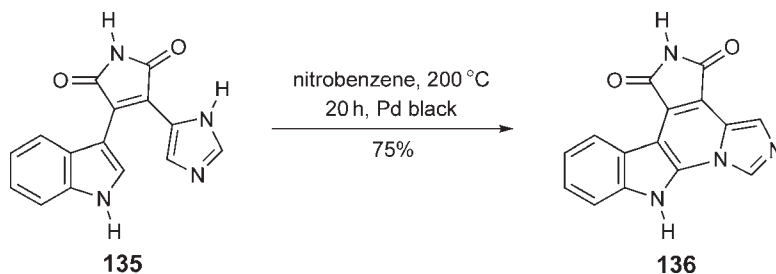
Scheme 40

Reaction of pyridines in neat isocyanides, in the presence of triflic acid, gives good yields of imidazo[1,5-*a*]pyridinium derivatives <2002EJO375>. Other examples of ring closure of the five-membered ring that appear to be restricted to specific substrates are depicted in **Scheme 41**: reaction of sampangine **131**, a natural antifungal alkaloid, with amines in the presence of silica gel gave fused heterocycles **132** possessing an imidazo[1,5-*a*]pyridine core in good yield <2001H(54)721>. Similarly, pyrroloquinoline quinone (PQQ) **133**, identified as a cofactor of methanol dehydrogenase, was found to react with amino acids to give imidazopyrroloquinolines (IPQs) **134** <1996CPB1493, 1995JA3278, 1996J(P2)1331>.



Scheme 41

A single example of strategy involving the synthesis of the parent heterocyclic core via six-membered ring formation could be found (**Scheme 42**). This synthesis was developed in the field of natural product synthesis, aiming at prepare isogranulatimide **136** from didemnidide A **135**, both isolated from the Brazilian ascidian *Didemnum granulatum*. Compound **136** belongs to an important class of natural bioactive substances: it was shown to be a G2 checkpoint inhibitor <1998JOC9850, 1998T1745, 2000JOC530>.

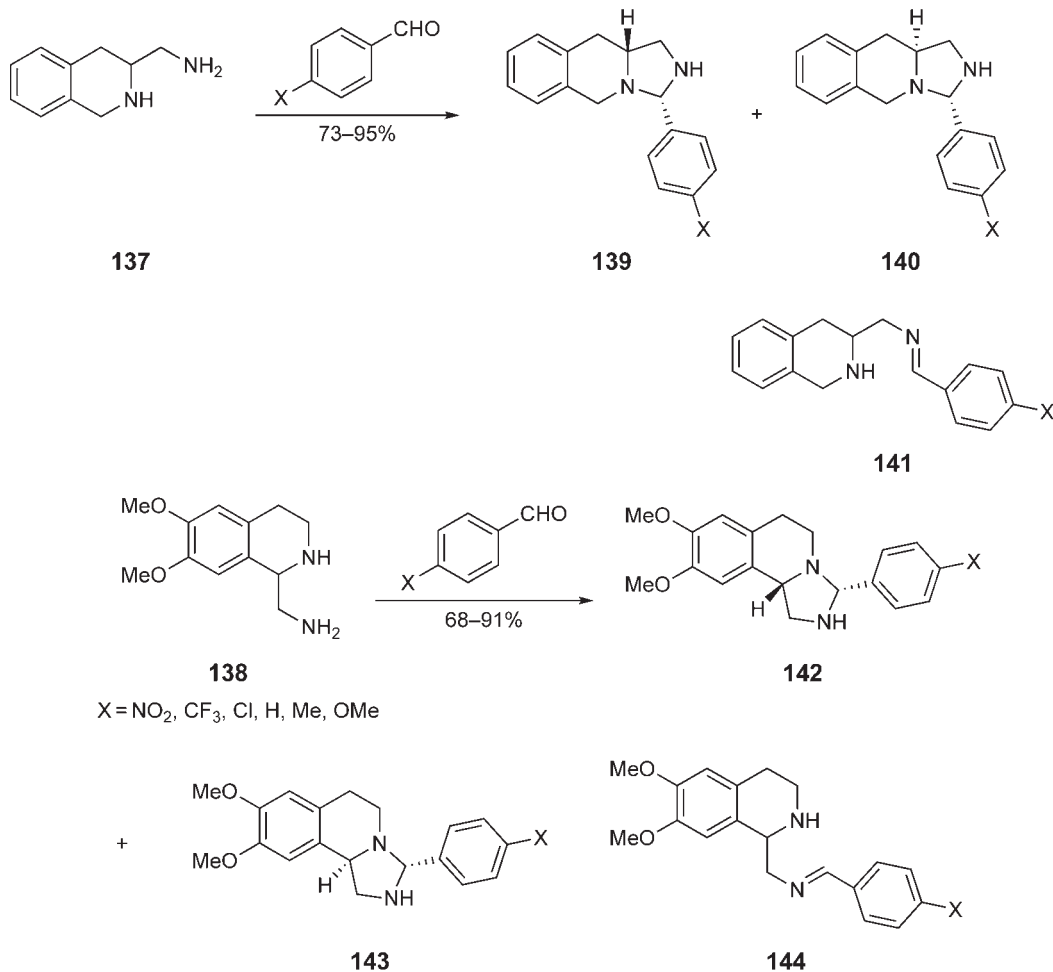


Scheme 42

11.10.4.7.2 Partially saturated rings

Synthesis of the heterocyclic core possessing a fully saturated six-membered ring can be achieved using a catalytic hydrogenation (see [Section 11.10.4.5.5](#)). The six-membered ring can also be formed starting from the appropriate

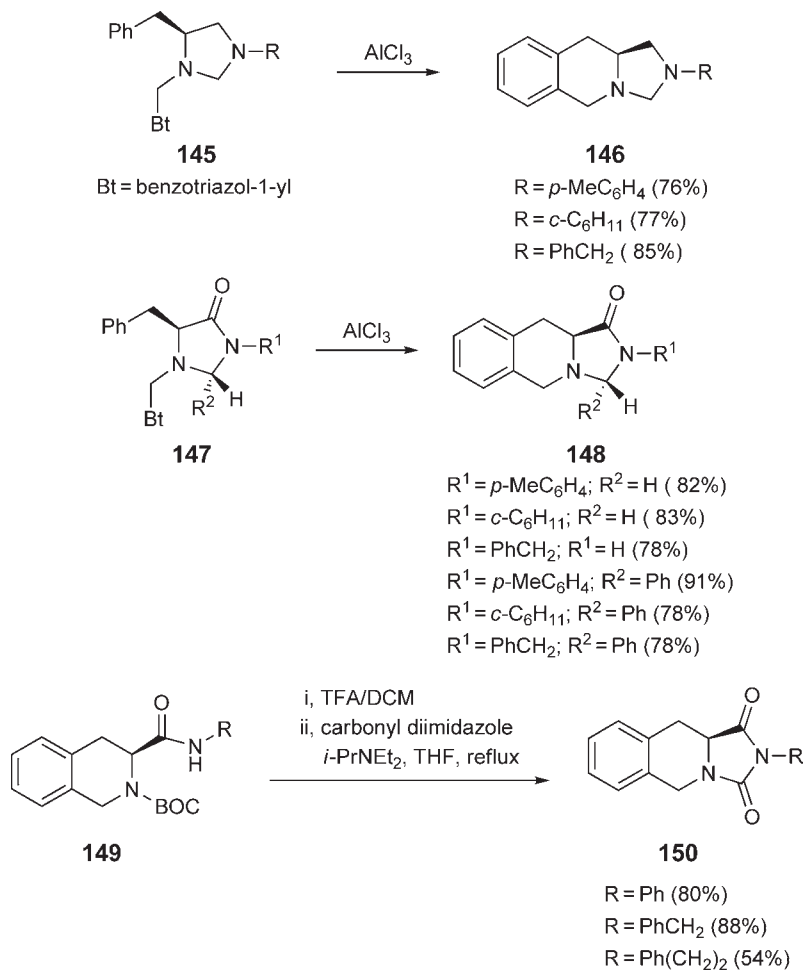
1,2-disubstituted imidazole using conventional chemistry <1996CPB991>. Fully saturated compounds can be prepared through condensation of 3-aminomethyl-1,2,3,4-tetrahydroisoquinoline **137** or 1-aminomethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **138** with aldehydes <2003JOC5705>. This condensation affords mixtures of stereoisomers at the newly created stereocenter that were shown to be in equilibrium with the intermediate imines **141** or **144**. In case of diamine **137**, the stereoisomer **140** was the major component (almost 90%) of the mixture, while in case of **138**, compound **142** predominated to a maximum amount of 70% (Scheme 43).



Scheme 43

Enantiomerically pure hexahydroimidazo[1,5-*b*]isoquinolines **146** can be generated by treating benzotriazolyl intermediates **145** with aluminium chloride. Similarly, their 1-oxo derivatives **148** were produced in good yields from **147** (Scheme 44) <2002JOC8224>. Compounds **145** and **147** are easily prepared from L-phenylalanine. An optimized synthesis of tetrahydroisoquinoline hydantoins **150** has recently appeared <2004TL7081> with the aim of combining bulky pharmacophore moieties with hydantoins, the latter appearing frequently in combinatorial libraries prepared in medicinal chemistry <1996TL937>. Thus, the best overall yield was obtained using the strategy depicted in Scheme 44.

Several fully saturated derivatives that can be viewed as aza analogues of polyhydroxylated indolizidine alkaloids have also been prepared for their biological evaluation <2000JOC136, 2000T1005>.



Scheme 44

11.10.4.8 Important Compounds and Applications

Quite few natural products including the imidazo[1,5-*a*]pyridine skeleton have been reported. Apart from isogranulatamide **136**, already mentioned in Section 11.10.4.7.1, compounds of general structure **151** have been isolated from the marine sponge *Xestospongia* sp. <2003T6539>, cribrosatatin 6 **152** has been isolated from the marine sponge *Chribrochalina* sp. and shows interesting biological activity as growth inhibitor of cancer cells and a number of pathogenic bacteria as well as fungi <2003JNP544>. It has been synthesized by the group of Nakahara (Figure 4) <2004H2355>.

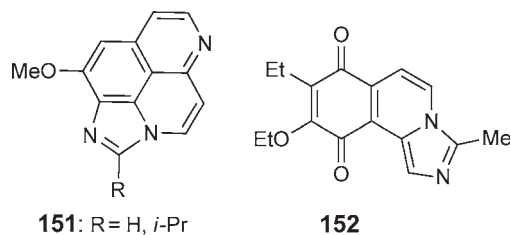
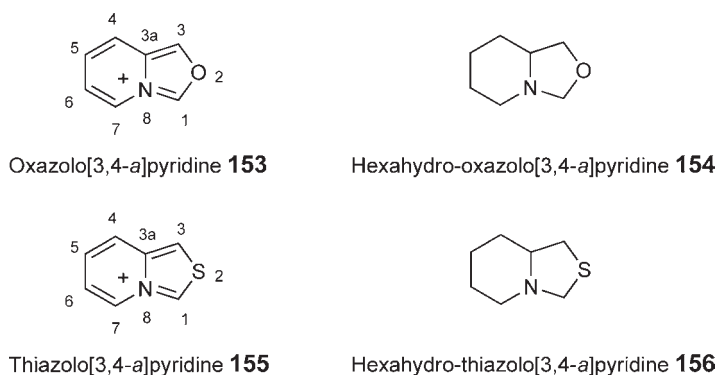


Figure 4

11.10.5 Oxazolo[3,4-*a*]pyridine and Thiazolo[3,4-*a*]pyridine

11.10.5.1 Introduction

Oxazolo[3,4-*a*]pyridines **153**, thiazolo[3,4-*a*]pyridines **155**, and their fully saturated derivatives **154** and **156** were discussed in CHEC(1984) <1984CHEC(6)613> and CHEC-II(1996) <1996CHEC-II(8)249>: very little information was available on the thiazolo[3,4-*a*]pyridine ring system while most of the information concerned the fully saturated oxygenated parent, oxazolo[3,4-*a*]pyridines. Careful examination of the literature clearly indicated that the situation has not changed much: almost no references were reported on thiazolo[3,4-*a*]pyridines and most of the work done in the last decade concerns the synthesis and reactivity of hexahydro-oxazolo[2,3-*a*]pyridines **154**. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will focus on the partially/completely saturated derivatives (Scheme 45).



Scheme 45

11.10.5.2 Theoretical Methods

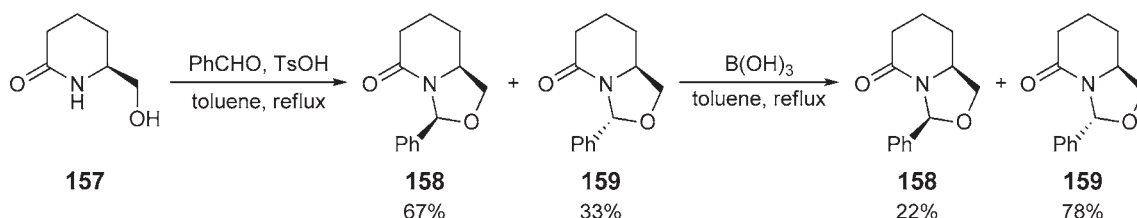
No new calculations were specifically devoted to this ring system.

11.10.5.3 Experimental Structural Methods

NMR data for new compounds are routinely reported. The conformational preference of the hexahydro-oxazolo[3,4-*a*]pyridine ring system **154** for the *trans*-conformer was discussed in detail in CHEC(1984) and CHEC-II(1996) and will therefore not be detailed here. Note should be made that the major conformer observed in solution is not necessarily the major one in the solid state <2002TA47>. As for other ring systems, careful analysis of coupling constants can permit the structure determination of the major isomer in solution <2002TA47, 2000EJO645, 1996T10609>.

11.10.5.4 Thermodynamic Aspects

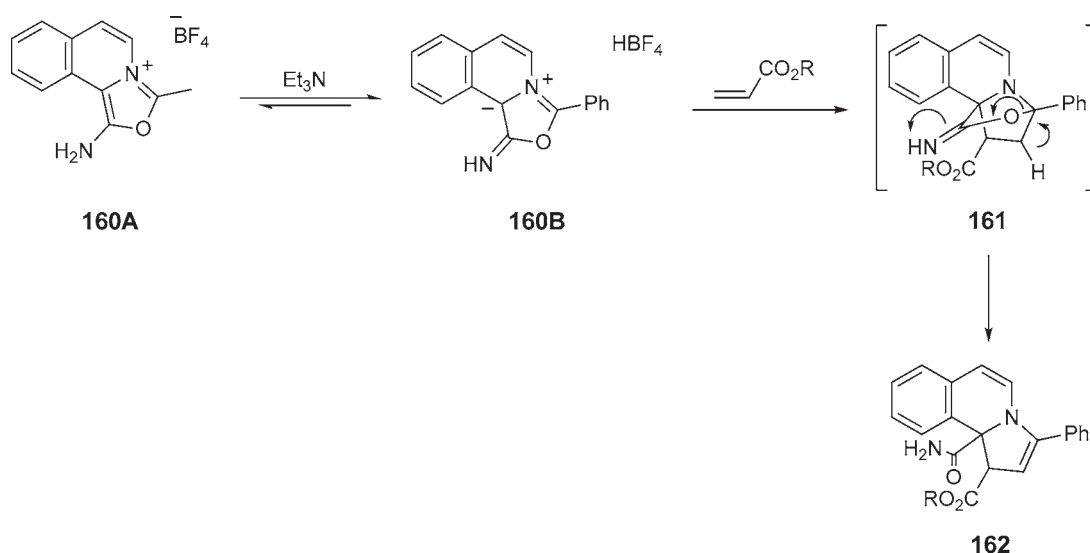
An important feature of saturated oxazolo[3,4-*a*]pyridines is their easy epimerization at the a-minal C-1 stereocenter. A quite explicit example has been reported by Moloney *et al.* and is depicted in Scheme 46. The reaction between lactam **157** and benzaldehyde produces a mixture of hexahydro-oxazolo[3,4-*a*]pyridines, the kinetic product **158** being the major one. Equilibration of the mixture with boric acid allows the ratio of diastereoisomers to be reversed since *trans*-oxazolidine **159** is now the major product <1998TL1025>; the equilibration of epimeric oxazolidines via ring-chain tautomerism has been investigated in detail and explains the epimerization observed for some hexahydro-oxazolo[3,4-*a*]pyridines <1993JOC1967>.



Scheme 46

11.10.5.5 Reactivity of Fully Conjugated Rings

Apart from isolated reports summarized in [Scheme 47](#), the chemistry of the fully conjugated ring systems has not been especially developed since CHEC-II(1996). In 1999, Monnier *et al.* reported the 1,3-dipolar cycloaddition of Reissert compound **160** with acrylates. Addition of triethylamine traps hydrofluoroboric acid and increases the proportion of münchnone imine **160B**; the reaction therefore predominantly yields 1,3-adduct **161** which rearranges to **162** ([Scheme 47](#)) <1996BSB777, 1999EJO297>.



Scheme 47

11.10.5.6 Reactivity of Nonconjugated Rings

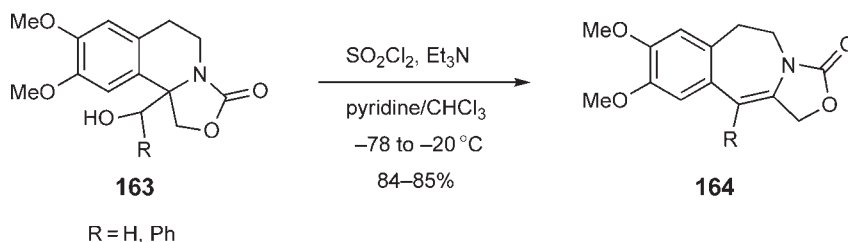
In contrast with the conjugated system, the reactivity of hexahydro-oxazolo[3,4-*a*]pyridines has been the subject of considerably more attention, which can most certainly be attributed to their greater synthetic potential, as demonstrated with the synthesis of many complex natural products. However, most of the reactions reported since 1996 have been known for many years, and the last decade was in fact characterized by their use in syntheses or optimization. After a brief survey of the thermal reactions, procedures involving the opening of the five-membered ring will be surveyed and the last part of this section will be devoted to the functionalization of the C-6 and C-7 positions.

11.10.5.6.1 Unimolecular reactions

The ring rearrangement of 8a-(1-hydroxy-alkyl)-hexahydro-oxazolo[3,4-*a*]pyridin-3-ones **163** upon treatment with sulfuryl chloride was reported in 2004: activation of the alcohol and ring extension produces 5,6-dihydro-1*H*-oxazolo[3,4-*a*]azepin-3-ones **164** in excellent yields ([Scheme 48](#)) <2004H(63)17>.

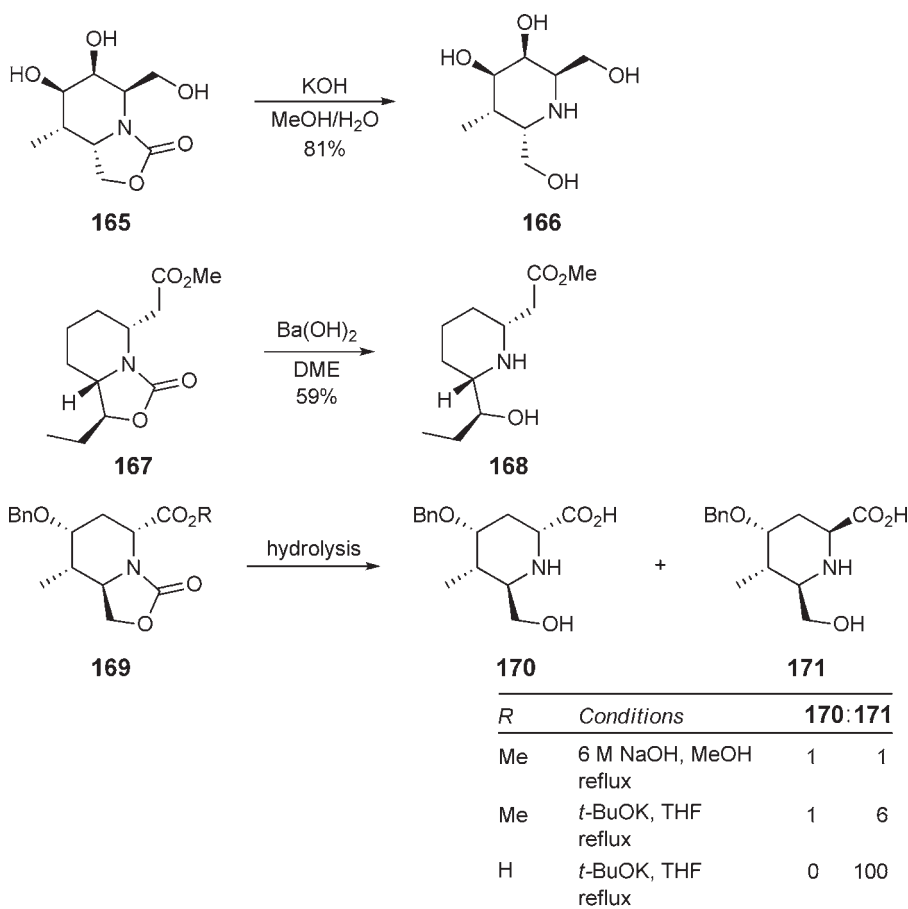
11.10.5.6.2 Nucleophilic attack at carbon

Most of the reactions involving nucleophilic attack at a carbon atom of the ring result in cleavage of the five-membered ring system (which is in most cases either an oxazolidine or an oxazolidinone). Basic hydrolysis of



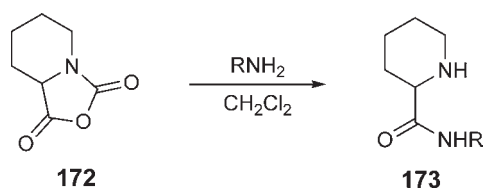
Scheme 48

hexahydro-oxazolo[3,4-*a*]pyridin-3-ones is probably the most common of these reactions since it has been used in a lot of syntheses of natural products. Some examples are collected in [Scheme 49](#) and show that polysubstituted 2-hydroxymethyl-piperidines are usually produced in high yields [<2001BMC1269, 2004AGE2001>](#). Care should, however, be taken during the hydrolysis of base-sensitive substrates since epimerization might occur and the choice of the base can therefore be crucial, as exemplified for the hydrolysis of **169** ([Scheme 49](#)) [<1998JOC3918>](#).



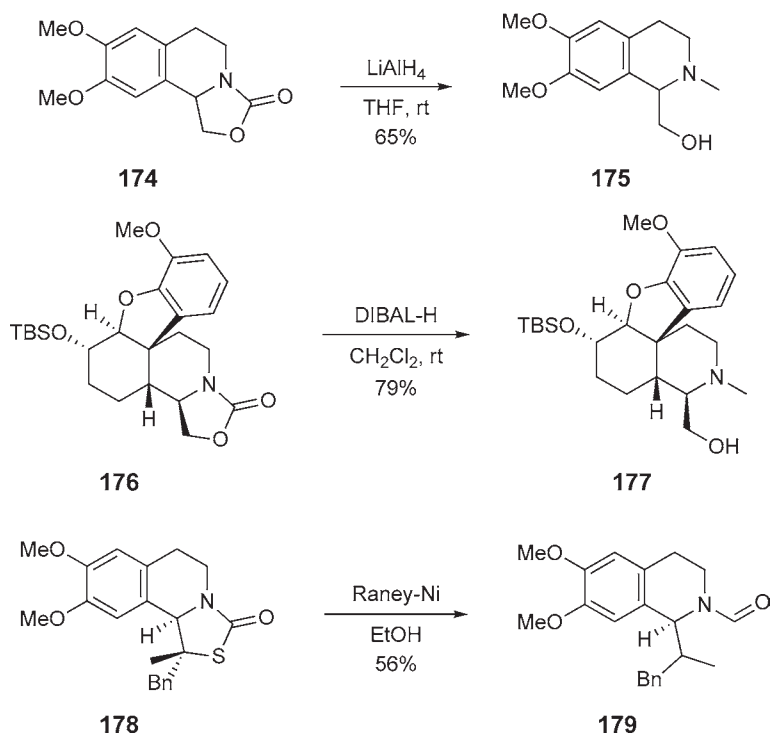
Scheme 49

Instead of water (or hydroxide ion), amines can be used to cleave the five-membered ring of tetrahydro-oxazolo[3,4-*a*]pyridine-1,3-dione **172**: pipelicolic acid amides **173** are usually obtained in good yields (36–93%, [Scheme 50](#)) [<1998EJM23>](#).



Scheme 50

Finally, the nucleophile involved in this ring-opening process can also be a hydride or other reducing agent. In this case, polysubstituted *N*-methyl-2-hydroxymethyl-piperidines are obtained starting from hexahydro-oxazolo[3,4-*a*]pyridin-3-ones such as **174** <1996H(43)545> or **176** <1998S665>. Importantly, reduction of hexahydro-thiazolo[3,4-*a*]pyridin-3-one **178** with Raney-Ni in ethanol results in concomitant desulfurization, producing *N*-formyl piperidine **179** in good yield (Scheme 51) <2001EJO1267>.



Scheme 51

Another quite common reaction involving nucleophilic attack at a carbon atom of the ring is the hydrolysis of hexahydro-oxazolo[3,4-*a*]pyridines and tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones. This reaction has been known for years and is best performed under acidic conditions, respectively, producing 2-hydroxymethyl-piperidines or pipercolic acid derivatives in good yields; representative examples are collected in Table 9. Ammoniolysis of tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones with amino acid derivatives has also been reported and produces substituted pipercolic acid amides in good yields <2003H(61)259>.

Ring opening of the oxazolidine ring is an efficient method to functionalize the hexahydro-oxazolo[3,4-*a*]pyridine skeleton. Many nucleophiles can be used in this reaction and the most common one is hydride, producing an amino alcohol such as **181**; different hydride sources can be used and a combination of sodium borohydride and chlorotrimethylsilane has been recently reported as an especially efficient reagent for this transformation <2000SL104>. Carbon nucleophiles have also been successfully used but require activation of the oxazolidine with a Lewis acid to form the intermediate iminium ion. High yields of addition products are however usually reached using this functionalization method as shown by the reaction of **182** with trimethylsilyl cyanide (TMSCN) and $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 52) <2005JOC4397>.

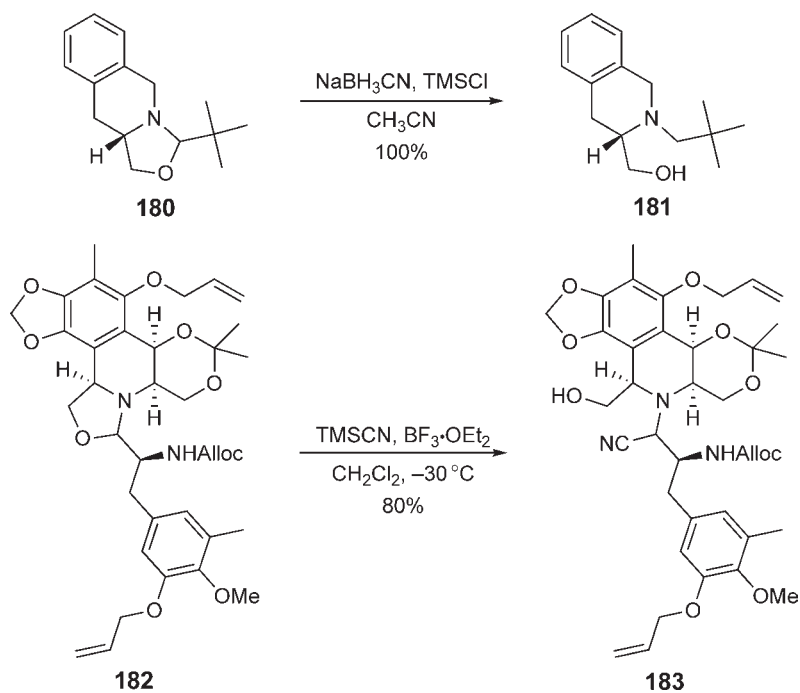
Table 9 Hydrolysis of hexahydro-oxazolo[3,4-*a*]pyridines and tetrahydro-oxazolo[3,4-*a*]pyridin-1-ones

Substrate	Conditions	Product	Yield (%)	Reference
	AcOH, H ₂ O		98	2001TA3173
	Dowex 50Wx4 MeOH, rt		87	1998H(49)73
	TFA, H ₂ O/CH ₂ Cl ₂ rt		73	2004OBC1031
	HSCH ₂ CH ₂ SH, HCl CF ₃ CH ₂ OH, rt		75	1996J(P1)227
	H ₂ O, <i>i</i> -PrOH CF ₃ CH ₂ OH, rt		77	1996T14757
	HCl, H ₂ O/MeOH Reflux		98	1996TL7163

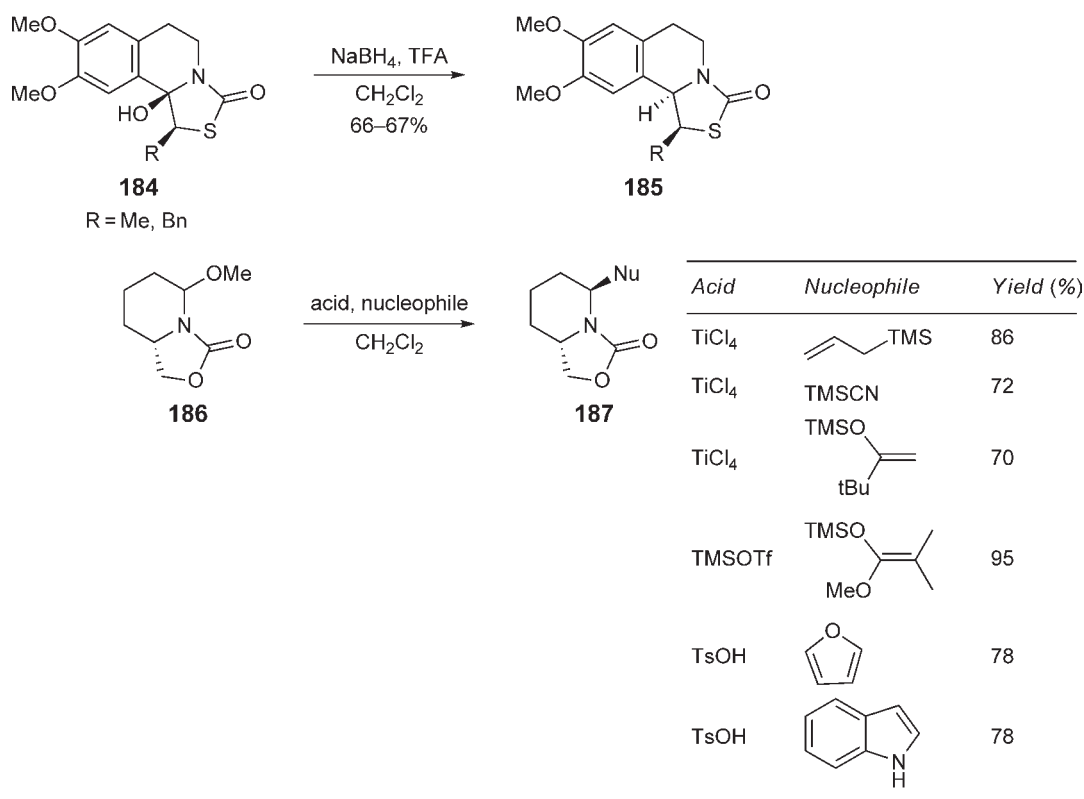
Treatment of α -hydroxy- or α -alkoxy-substituted hexahydro-oxazolo[3,4-*a*]pyridin-3-ones with an acid allows for the generation of bicyclic *N*-acyliminium ions which can then smoothly react with nucleophiles, usually with high diastereoselectivities (**Scheme 53**) <2001EJO1267, 1998SL206>.

11.10.5.6.3 Nucleophilic attack at hydrogen (deprotonation) – Alkylation

A deprotonation–alkylation sequence from tetrahydro-oxazolo[3,4-*a*]pyridin-5-ones or hexahydro-oxazolo[3,4-*a*]pyridin-3-ones is an especially efficient method for diastereoselective functionalization, respectively, via the lactam enolate or

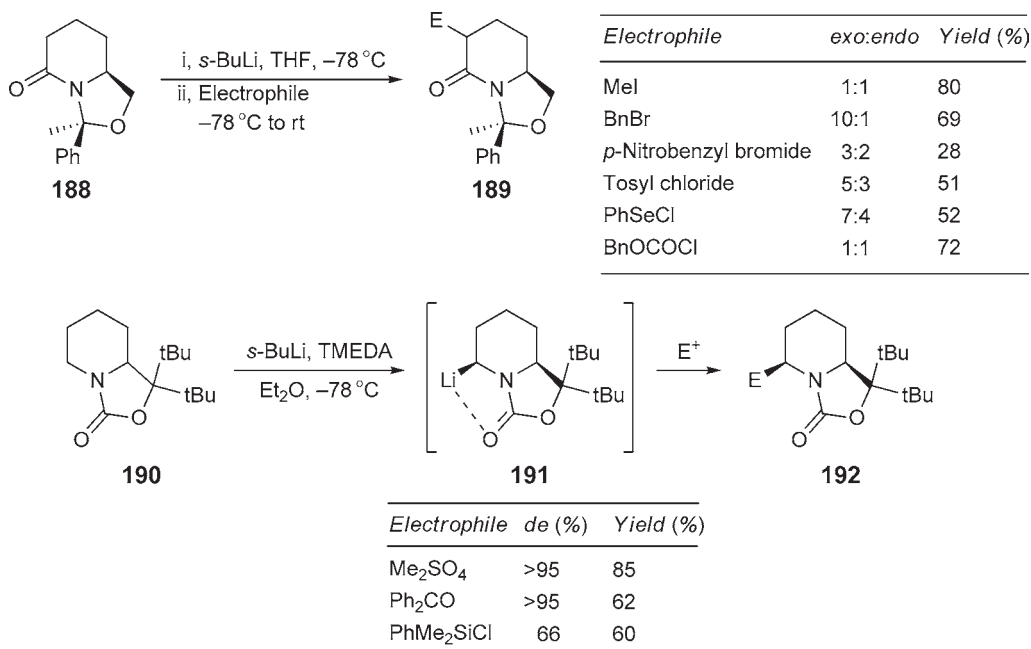


Scheme 52



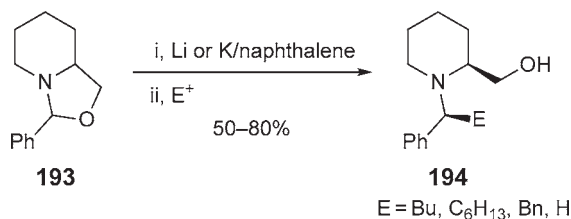
Scheme 53

α -lithio-amine, and is a strategy that has proved to be very successful, permitting ring manipulations in a highly diastereocontrolled sense. In 2001, Moloney *et al.* demonstrated that alkylation of lactam **188** with a wide range of electrophiles proceeds with predominantly *exo*-diastereoselectivity, but the efficiency of this process depends on the substitution at the hemiaminal ether system and the stereoselectivity remains low with some electrophiles. Products obtained can be readily deprotected to give substituted hydroxymethyl lactams in good yield (Scheme 54) <2004OBC1031>. An especially interesting and useful procedure was reported by Gross and Beak, who investigated lithiation substitutions of **190**: treatment with *s*-BuLi and tetramethylethylenediamine (TMEDA) followed by dimethyl sulfate provided diastereomerically pure **192** in 85% yield. The reaction of **190** with benzophenone was also highly stereoselective, while the substitution of the intermediate organolithium derivative **191** with chlorodimethylphenylsilane was not completely selective. The origin of the diastereoselectivity was attributed to the intermediacy of the configurationally stable organolithium derivative **191** due to the chelation with the carbamate (Scheme 54) <2001JA315>.



Scheme 54

Finally, Azzena reported on the reductive functionalization of hexahydro-oxazolo[3,4-*a*]pyridine **193**: its reaction with potassium or lithium and naphthalene followed by trapping of the intermediate organolithium derivative allowed for the isolation of piperidine **194** with useful levels of selectivities (Scheme 55) <2002J(P1)360>.



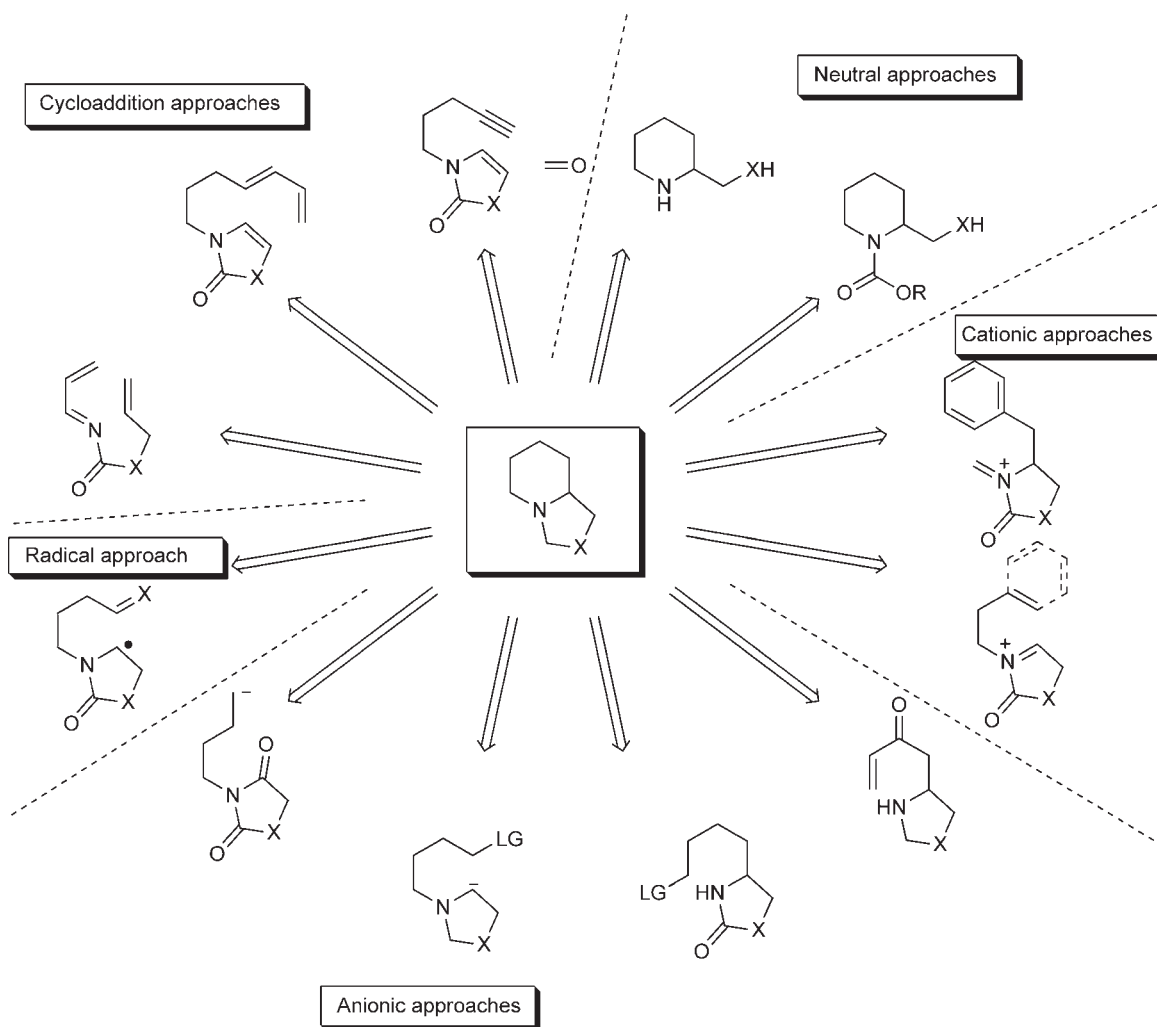
Scheme 55

11.10.5.7 Ring Syntheses from Acyclic Compounds

No new or original methods for the preparation of oxazolo[3,4-*a*]pyridines or thiazolo[3,4-*a*]pyridines have been reported since CHEC-II(1996). Emphasis will therefore be put on the synthesis of their fully saturated derivatives.

11.10.5.8 Ring Syntheses of Saturated Rings from Acyclic Compounds

If little was done since CHEC-II(1996) for the synthesis of unsaturated compounds, an amazing amount of work has been devoted to the synthesis of their saturated counterparts, as it can be judged by the increasing number of publications dealing with this matter. A lot of different options are available to access the saturated oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine ring systems, and [Scheme 56](#) gives an overview of the possibilities or disconnections that can be envisioned. The most logical way of organizing those syntheses is to classify them depending on the nature (anionic, cationic, radical, etc.) of the key step involved in the process; reactions discussed in this section will be classified accordingly.

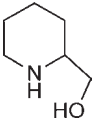
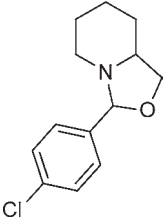
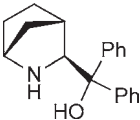
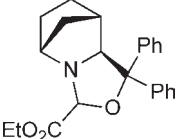
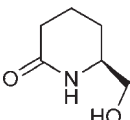
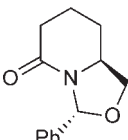
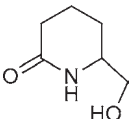
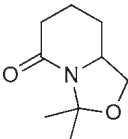
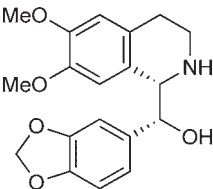
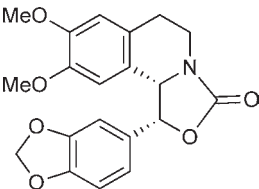
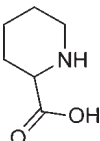
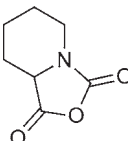
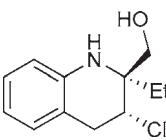
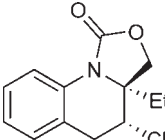
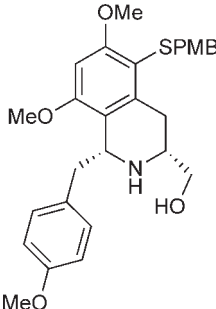
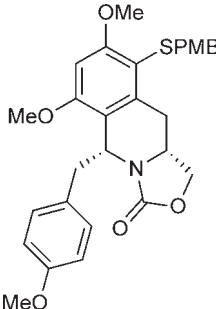


Scheme 56

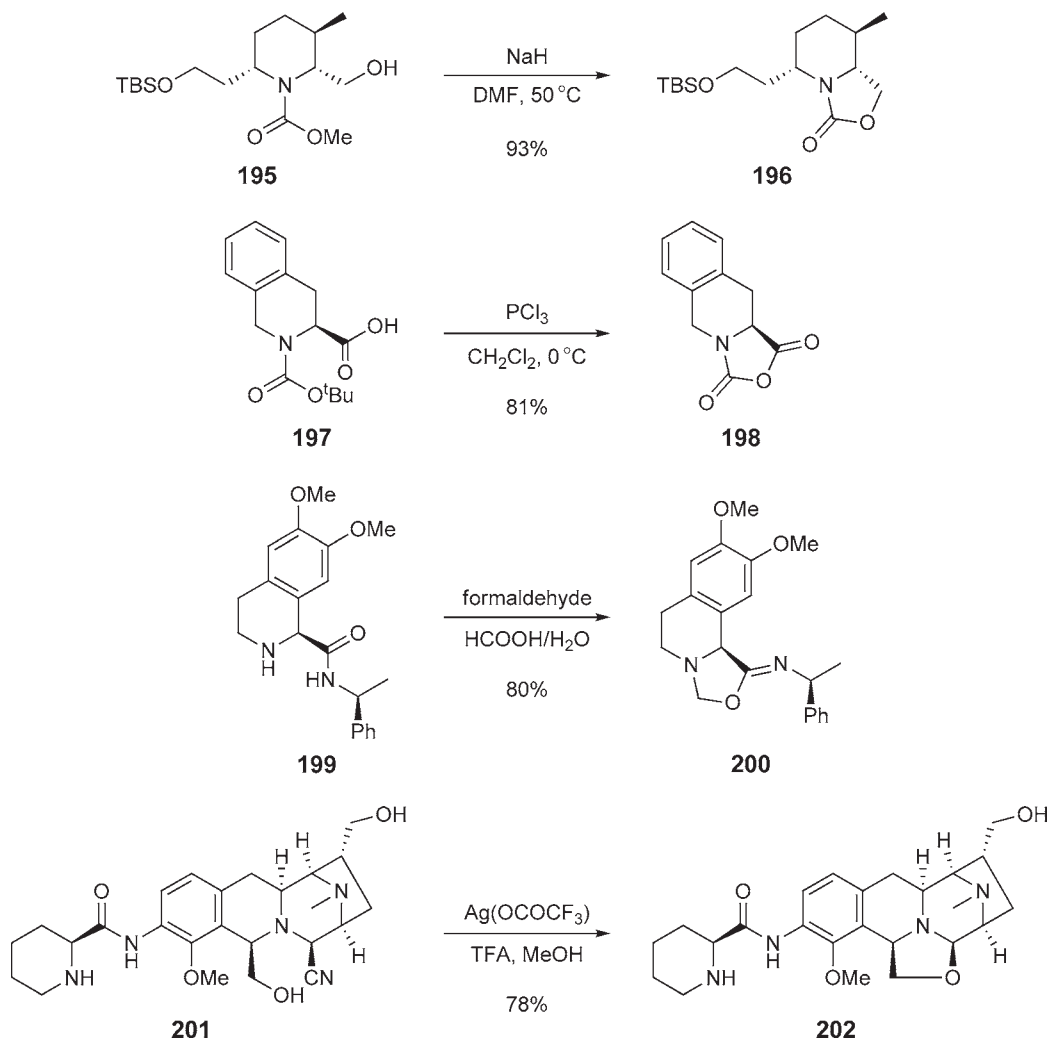
11.10.5.8.1 Neutral approaches: Formation of the five-membered ring

A quite simple way to form the oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine ring system is to build the five-membered ring, respectively, starting from a 2-hydroxymethyl-piperidine or 2-thiomethyl-piperidine. The reaction of the latter compounds with aldehydes, acetals, phosgene, carbonates, or synthetic equivalents have been known for years and will therefore not be detailed here. Representative and typical examples are summarized in [Table 10](#).

Table 10 Formation of saturated oxazolo[3,4-*a*]pyridines or thiazolo[3,4-*a*]pyridines from 2-hydroxymethyl-piperidines or 2-thiomethyl-piperidines

Substrate	Conditions	Product	Yield (%)	Reference
	4-Cl-C ₆ H ₄ -CHO		82	2005TL5451
	Ethyl glyoxylate Benzene, reflux		100	2002H(56)457
	PhCH(OMe) ₂ TsOH, B(OH) ₃ Toluene, reflux		82	1998TL1025
	2-Methoxy-propene TsOH, toluene Reflux		54	2004OBC1031
	Phosgene, Et ₃ N THF, rt		73	1996JOC8103
	Triphosgene THF, 40 °C		84	1996JME2781
	(Im) ₂ CO Toluene, 35 °C		76	1996TL10609
	(EtO) ₂ CO NaOEt, EtOH		98	1999T4999

The five-membered ring can also be formed by intramolecular nucleophilic attack of an alkoxide on a carbamate such as for the formation of **196** from **195** <1997T9553>, by dehydration of *N*-carbamate-pipecolic acid derivatives <2002EJO3936>, by treatment of amino-amides under Eschweiler–Clarke conditions <1999TA3371>, or by treatment of hydroxyl aminonitriles with silver trifluoroacetate <2002JA2951> (Scheme 57).



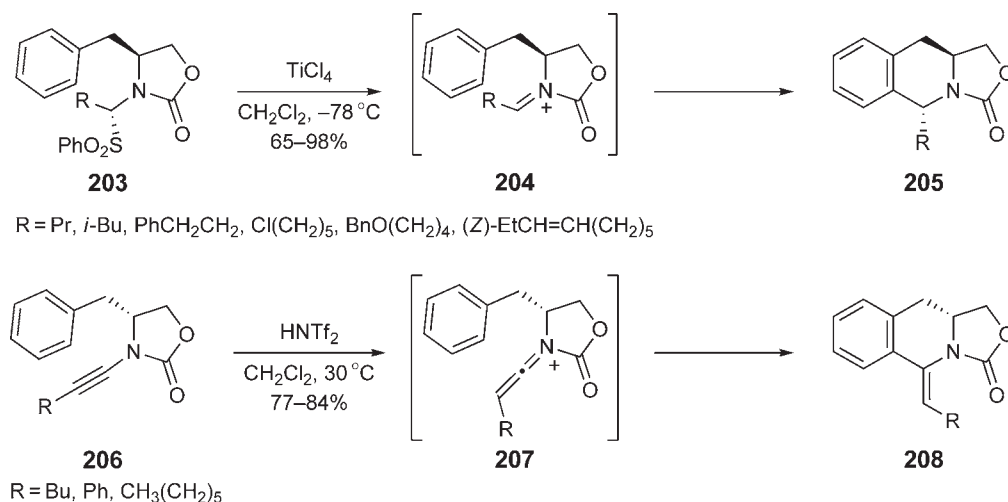
Scheme 57

11.10.5.8.2 Cationic approaches: Formation of the six-membered ring

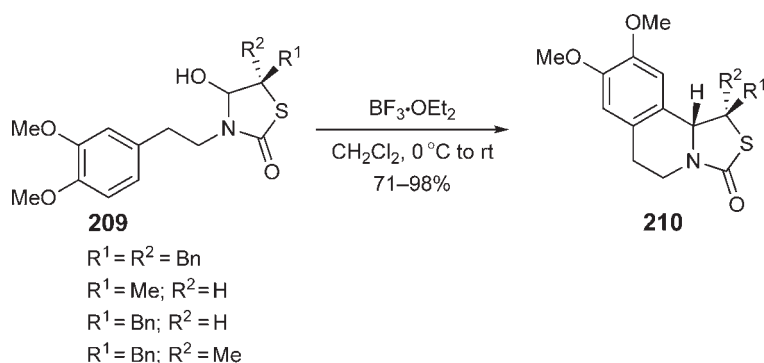
The Pictet–Spengler reaction provides useful routes to the saturated oxazolo[3,4-*a*]pyridine ring system. In a series of publications, Petrini *et al.* have shown that chiral *N*-acyliminium ions **204** obtained by treatment of optically active *N*-[1-(phenylsulfonyl)alkyl]oxazolidin-2-ones **203** with titanium tetrachloride react with electron-rich aromatic compounds to afford the corresponding adducts **205** in good yields and variable diastereoselectivities. The utilization of 4-benzyloxazolidin-2-one as a chiral auxiliary leads to intramolecular cyclization with exclusive formation of one diastereomer (Scheme 58) <2003TA1171, 2004TL2133>. The use of benzotriazole instead of the phenylsulfone has also been reported for the generation of the intermediate iminium ion <1999TA255> and treatment of *N*-alkynyl-oxazolidinones **206** with catalytic amount of HNTf₂ allows for the generation of intermediate keteniminium ions **207** which stereoselectively cyclize to **208** (Scheme 58) <2005OL1047>.

A related approach consists in the generation of endocyclic iminium ions from *N*-acylaminals **209**. As in the previous case, their treatment with boron trifluoride induces a diastereoselective cyclization, and thiazolo[3,4-*a*]pyridines **210** are isolated in good yields (Scheme 59) <2001EJO1267>. Alkenes can also participate and react well with the intermediate

iminium ions; in this case, a chloride atom from TiCl_4 is incorporated in the resulting cyclic product [<1997TL8833>](#), or an additional hydroxyl group when $\text{BF}_3 \cdot \text{OEt}_2$ is used to form the iminium ion [<1999CCC203>](#).



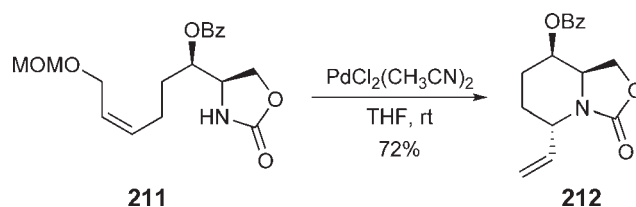
Scheme 58



Scheme 59

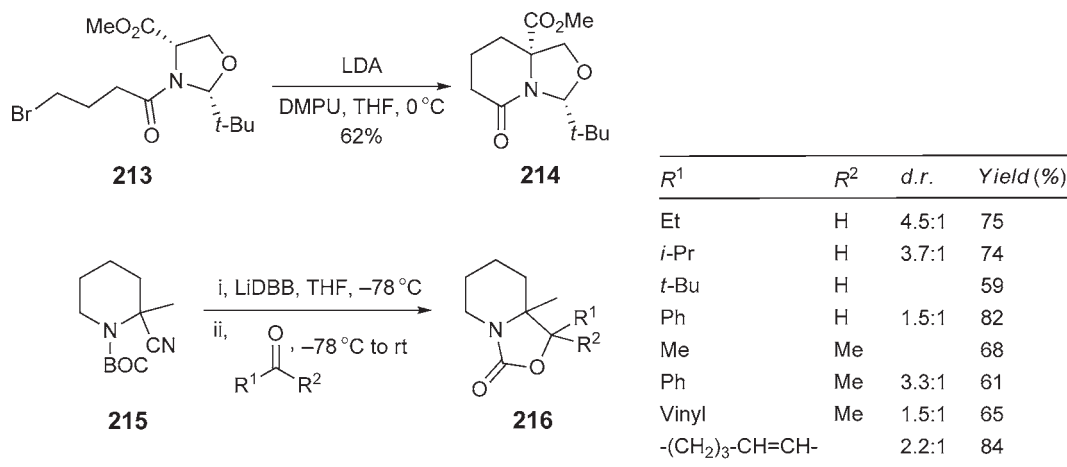
11.10.5.8.3 Anionic approaches

Different synthetic routes based on an anionic or related cyclization to form the six-membered ring have been developed. Therefore, cyclization of 4-(4-chloro-butyl)-oxazolidin-2-ones [<1996TL5723>](#) and 4-(3-carboxy-propyl)-oxazolidin-2-ones [<2004S3065>](#) have been reported. π -Allylpalladium complexes can also act as nucleophiles: treatment of protected allylic alcohol **211** with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ generates a π -allyl intermediate which is trapped by the oxazolidine to form the six-membered ring **212** in good yield (Scheme 60) [<1997JOC776>](#). The use of unprotected allylic alcohol has also been reported [<2001H\(54\)871>](#).



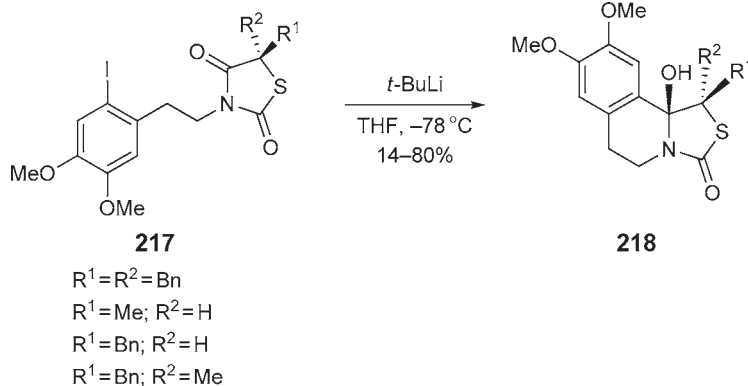
Scheme 60

Generation of an enolate from **213** and intramolecular diastereoselective cyclization was reported in 1996 and allowed the synthesis of **214** in good yield <1996J(P1)227>. Interestingly, reductive lithiation of aminonitrile **215** and further reaction with a wide range of aldehydes generates intermediate alkoxides, which finally react with the carbamate to afford bicyclic compounds **216** upon warming up of the reaction mixture (Scheme 61) <2004OL2745>.



Scheme 61

Parham cyclization performed on thiazolidinediones **217** (Scheme 62) proceeds regioselectively at the more electrophilic amide carbonyl and gives the unstable 10 β -hydroxy thiazoloisoquinolinones **218** in good yields. In all cases, attack of the organolithium intermediate occurs from the less-hindered face of the amide carbonyl group, affording the *cis*-compound with good stereoselectivity <2001EJO1267>.

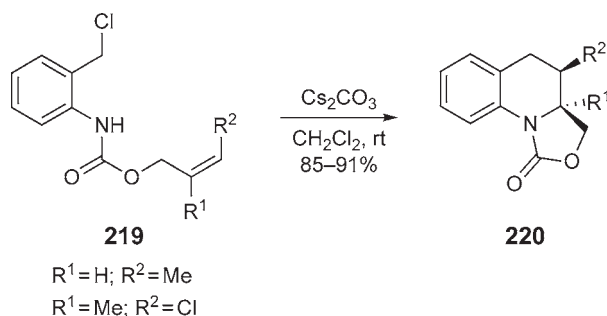


Scheme 62

Finally, intramolecular Michael addition from a 3-(2-oxo-but-3-enyl)-oxazolidin-5-one was reported to be catalyzed by boron trifluoride and afforded the cyclized product in fair yields. However, substitution at the enone group resulted in a less efficient cyclization <1996TL14757>.

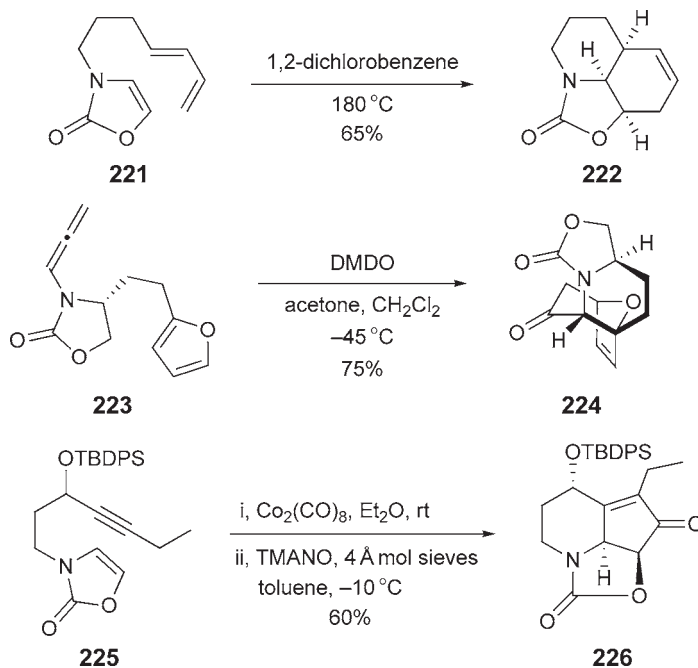
11.10.5.8.4 Cycloaddition approaches

In 1999, Steinhagen and Corey reported on the generation of *o*-azaxylylene by base-induced elimination of hydrogen chloride from *o*-chloromethylanilines **219**. This process was found to be highly effective and the intermediate *o*-azaxylylenes readily undergo intramolecular aza-Diels–Alder reactions under mild conditions to provide hydroquinolines **220** stereospecifically by a suprafacial cycloaddition (Scheme 63) <1999AGE1928>.



Scheme 63

Two other cycloaddition routes to the saturated oxazolo[3,4-*a*]pyridine ring systems have been reported: while intramolecular Diels–Alder cycloaddition from **221** generated tricyclic oxazolidinone **222** in good yield [\(<2002CC438>](#)), stereoselective intramolecular [4+3] cycloaddition of a nitrogen-stabilized chiral oxyallyl cation generated via epoxidation of *N*-tethered allenamide **223** afforded **224** in 75% yield and as a single diastereoisomer ([Scheme 64](#)) [\(<2003JA12694>](#)). Finally, an intramolecular Pauson–Khand approach to the tricyclic core of streptazolin and related natural products was reported and afforded **226** in good yield and selectivity ([Scheme 64](#)) [\(<2004JOC1803>](#)).



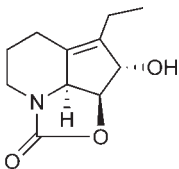
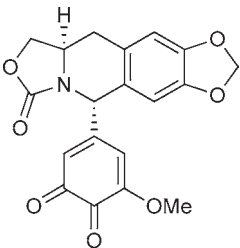
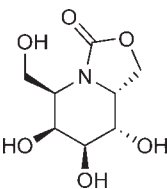
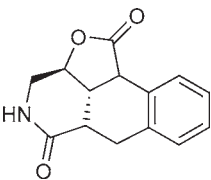
Scheme 64

To complete this paragraph dealing with the synthesis of saturated oxazolo[3,4-*a*]pyridines and thiazolo[3,4-*a*]pyridines, it is worth mentioning that other routes relying on carbenoid insertion [\(<2005TL143>](#) or radical-induced cyclization [\(<1996J\(P\)1793, 1998S665>](#) have also been developed since CHEC-II(1996).

11.10.5.9 Important Compounds and Applications

Many natural and/or biologically active products possessing an oxazolo[3,4-*a*]pyridine or thiazolo[3,4-*a*]pyridine core have been reported. Selected examples are collected in [Table 11](#) and show the high potential of molecules possessing these ring systems.

Table 11 Important compounds and applications

<i>Compound</i>	<i>Application</i>	<i>Reference</i>
 Dihydrostreptazolin	Antimicrobial	1981HCA1752
	DNA topoisomerase II inhibitor	1997BML2565
	Galactosidase inhibitor	2001BMC1269
	Antibacterial	1998BML1231

11.10.6 Imidazo[1,2-*a*]pyridine

11.10.6.1 Introduction

Imidazo[1,2-*a*]pyridines were covered in CHEC(1984) <1984CHEC(6)613> along with others imidazoles fused to six-membered rings and they were reviewed together with imidazo[1,5-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)249>. The chemical literature on this heterocycle is very abundant, due to its easy synthesis (most of the preparations use readily available 2-aminopyridines) and to the very broad spectrum of bioactivities displayed by many derivatives. A simple Beilstein search on the fully conjugated heterocycle (free sites everywhere) disclosed ca. 3000 hits for the past decade. Therefore, this chapter cannot be exhaustive in view of space limitations, but will mainly focus on the original synthetic methods that have appeared in the last decade.

11.10.6.2 Theoretical Methods

To our knowledge, no new calculations were specifically devoted to this heterocyclic system since CHEC-II(1996). AM1 calculations of the electron density in the HOMO of 3-carboethoxy-5-methyl derivative allowed for the rationalization of the regioselectivity of its chlorination <2000T7915>.

11.10.6.3 Experimental Structural Methods

As for the previous section, no additional specific NMR data have been published since CHEC(1984) and CHEC-II(1996): NMR data for new substituted compounds are routinely reported. Fluorescent properties of a series of

derivatives have been investigated <1999BCJ1327>. X-Ray structures of new substituted compounds appear regularly. Some examples are given in **Figure 5**, such as the tetrafluoroborate salt **227** <2000EJO1433>, the 5-thia derivative **228** <2000TL3447>, or the substituted derivative **229** <2002BML941>. In compound **230**, the alkenyl side chain does not lie in the plane of the heterocycle <2005AXE4037>. Other examples include **231** (crystallized into the active site of cyclin-dependent kinase 2 (CDK2)) <2003BML3021>, the 8-acetoxy derivative **232** <2002T8145>, the 3-imino derivative **233** <2006TL2989>, and the tricyclic compound **234** <2002T295>.

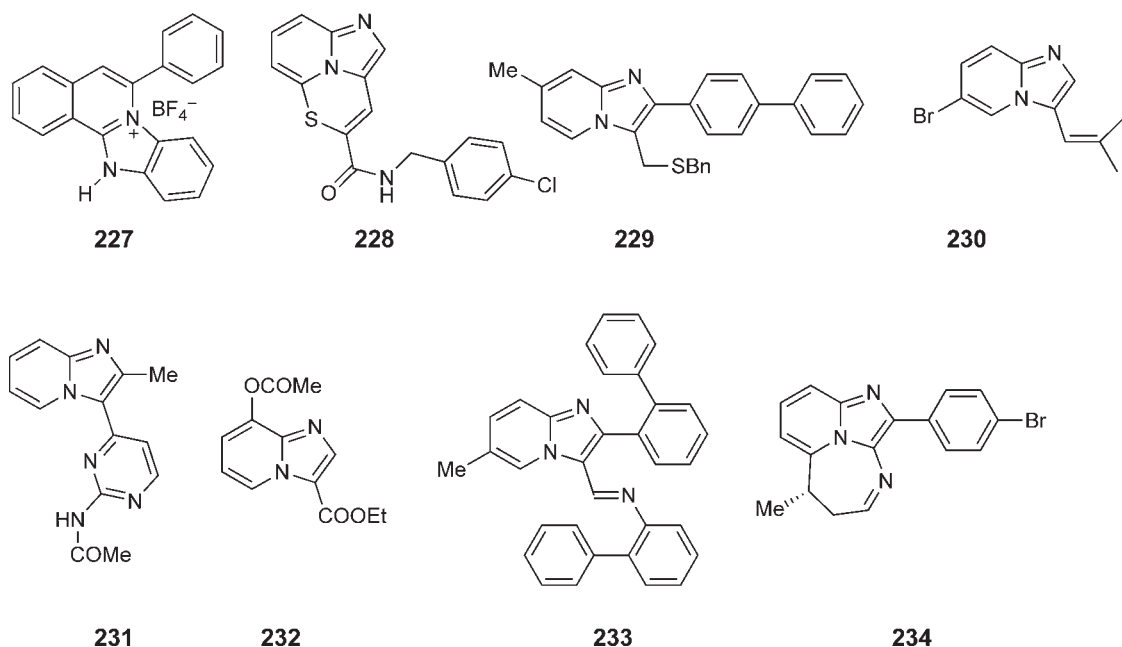
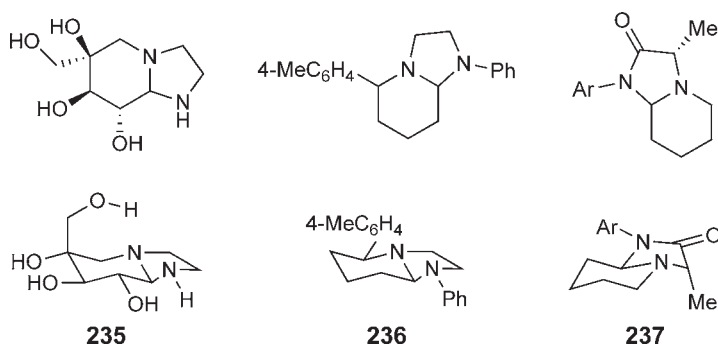


Figure 5

Conformational analysis of some octahydroimidazo[1,2-*a*]pyridine derivatives have been investigated by NMR studies <2000JOC3683, 2002JOC4951, 2000JOC7208>. For example, compounds **235–237** are depicted in **Scheme 65** in their preferred conformations. The anomeric carbon in such compounds is prone to epimerization, favoring a *trans* ring junction.



Scheme 65

11.10.6.4 Thermodynamic Aspects

No specific studies on this subject were published in the last decade.

11.10.6.5 Reactivity of Fully Conjugated Rings

Imidazo[1,2-*a*]pyridines are aromatic systems in which the bridgehead nitrogen N-4 contributes to the aromaticity with its lone pair. Therefore, this nitrogen atom is not nucleophilic and electrophilic attack occurs at the N-1 position. S_EAr occurs at C-3 (Figure 6).

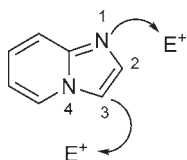
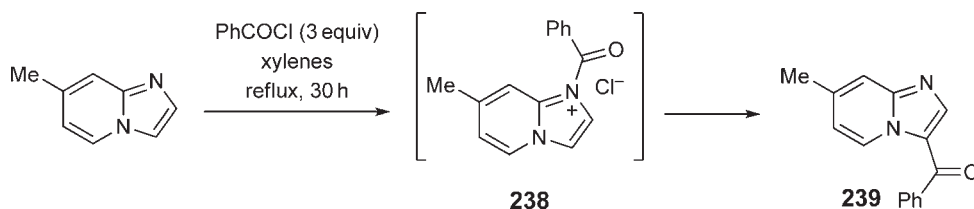


Figure 6

11.10.6.5.1 Electrophilic attack at nitrogen

Alkylation at N-1 readily occurs with alkyl halides or sulfonate esters <2002CHE675, 1997BML2753, 1992JME1650>. In case of reaction with an acyl chloride such as benzoyl chloride, *N*-acylation gives an intermediate imidazo[1,2-*a*]pyridinium ion **238** which, upon heating, gives the 3-acylated **239** compound in a single operation (Scheme 66) <1998TL9685>.



Scheme 66

11.10.6.5.2 Electrophilic attack at carbon

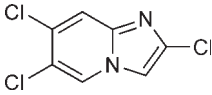
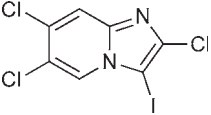
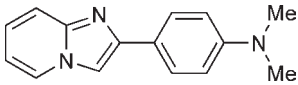
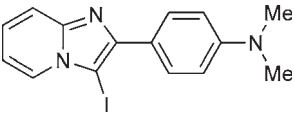
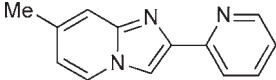
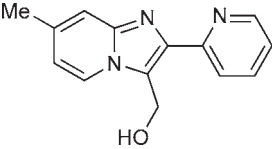
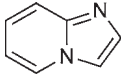
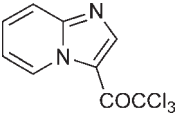
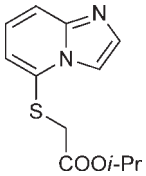
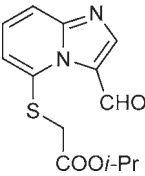
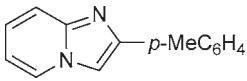
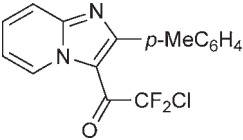
Electrophilic attack at carbon occurs regioselectively at the C-3 position. This was illustrated by numerous examples in CHEC(1984) and CHEC-II(1996). Additional more recent examples are summarized in Table 12.

Table 12 Aromatic electrophilic substitution at C-3 in imidazo[1,2-*a*]pyridines

Substrate	Conditions	Product	Yield (%)	Reference
	IP _{yr} BF ₄ /CH ₂ Cl ₂ 23°C, 3 h		95	1999T541
	I ₂ , Pyr		91	2005JOC4897
	NBS, MeCN Reflux 3 h		91	2003T5869

(Continued)

Table 12 (Continued)

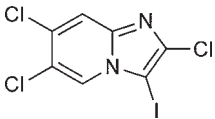
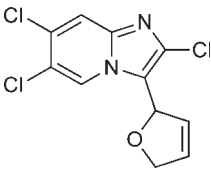
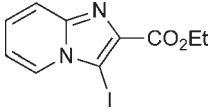
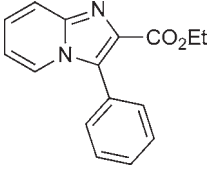
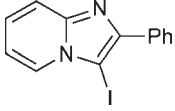
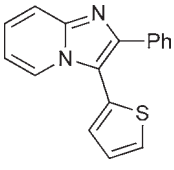
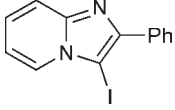
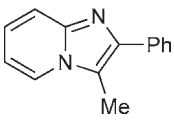
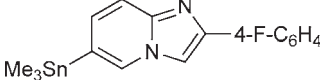
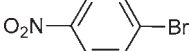
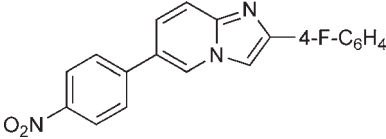
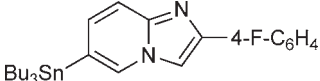
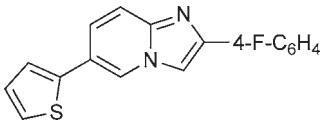
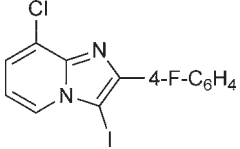
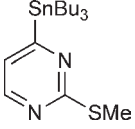
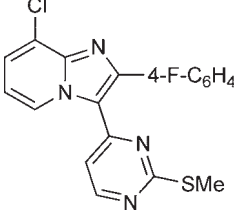
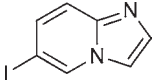
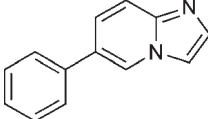
Substrate	Conditions	Product	Yield (%)	Reference
	NIS, MeCN rt, 1 h		82	2003JME1449
	I ₂ , CHCl ₃		52	2003JME237
	CH ₂ O AcOH/AcONa Reflux, 3 h		90	2002BML941
	CCl ₃ COCl DMAP, THF Reflux, 12 h		93	2000TL3447
	(CH ₂) ₆ N ₄ , AcOH 100 °C, 7 h		81	2002T489
	(ClCF ₂ CO) ₂ O Dichloroethane Reflux, 24 h		n.r. ^a	2001TL3077

^an.r. = not reported.

11.10.6.5.3 Nucleophilic attack at carbon

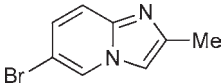
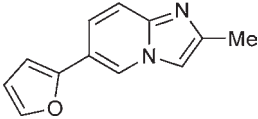
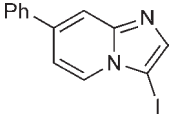
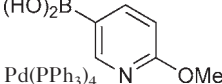
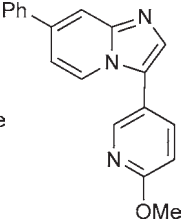
To our knowledge, direct substitution of hydrogen has not been reported. Displacements of halides at C-3 or C-5 are well-documented reactions that have been overviewed in CHEC(1984) and CHEC-II(1996). More recent examples include a copper-catalyzed coupling of an α,α -difluoro Reformatsky reagent with a 3-iodo derivative <2005JOC4897>, substitution of a 3-iodo derivative by a sulfide under Ullmann's conditions <1999T541>, substitution of a 5-chloro or bromo derivative by ethyl thioglycolate <2002T489, 2002H(57)21>, substitution of a 6-iodo derivative by cyanide anion under Pd(0)-catalyzed procedure <1998JME4317>, substitution of 5-chloro derivatives by anilines <1999PHA341>, and Buchwald aminations of 6-halo derivatives <2003JOC5614, 2003JOC4367>. Some of these examples demonstrate that the presence of an electron-withdrawing group attached on the heterocycle is not necessary for the success of the aromatic substitution. As regards to carbon-carbon bond formation, palladium-catalyzed cross-coupling reactions with various halides have been studied. Thus, examples of Negishi, Suzuki, Heck, and Stille reactions are collected in Table 13.

Table 13 Palladium-catalyzed C–C bond formation from halo derivatives of imidazo[1,2-a]pyridines

Substrate	Conditions	Product	Yield (%)	Reference
	 Pd(OAc) ₂ Ph ₃ As, AgCO ₃ DMF, 45 °C		98	2003JME1449
	C ₆ H ₅ B(OH) ₂ Pd(PPh ₃) ₄ Na ₂ CO ₃ , toluene 75 °C		73	2000JOC6572
	2-ThienylB(OH) ₂ Pd(PPh ₃) ₄ Ba(OH) ₂ , DME 75 °C		70	2000JOC6572
	MeB(OH) ₂ Pd(PPh ₃) ₄ NaOH, DME 75 °C		85	2000JOC6572
	 Pd(PPh ₃) ₄ Toluene, reflux		77	2003HCA3461
	 Pd(PPh ₃) ₄ Toluene, reflux		82	2003HCA3661
	 PdCl ₂ (PPh ₃) ₂ Toluene, 100 °C		45–50	2003OL1369
	PhB(OH) ₂ [PdCl ₂ (DPPF)] Ba(OH) ₂ DME, reflux		58	2001HCA3610

(Continued)

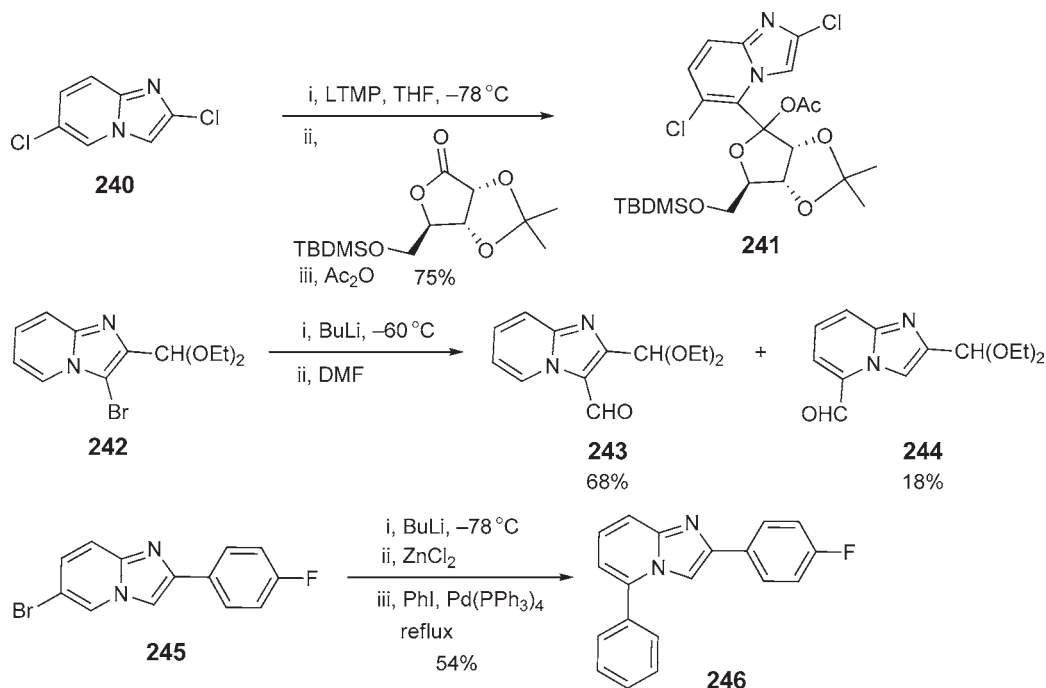
Table 13 (Continued)

Substrate	Conditions	Product	Yield (%)	Reference
	Furan-2-yl-B(OH) ₂ Pd(PPh ₃) ₄ NaOH DME, reflux		88	2001HCA3610
	(HO) ₂ B-  Pd(PPh ₃) ₄ Na ₂ CO ₃ Dioxane, reflux		n.r. ^a	2004BML909

^an.r. = not reported.

11.10.6.5.4 Nucleophilic attack at hydrogen

Deprotonation occurs at C-3 as illustrated by some examples in CHEC(1984) and CHEC-II(1996). It has been shown that the nature of the substituents on the ring can greatly influence the regioselectivity of this deprotonation. For example, compound **240** is selectively deprotonated at C-5 (and not at C-3) with LDA, PhLi, or lithium 2,2,6,6-tetramethylpiperidide (LTMP) <1997JOC3453>, which was most unexpected considering previous reports in this field. In a similar way, when 3-bromo derivative **242** is lithiated by lithium/halogen exchange, formylation with DMF gives both 3- and 5-formyl derivatives **243** and **244** <2003T5869>. This suggests a competitive lithiation at C-5 followed by a 'halogen dance' (bromine–lithium isomerization) at C-3 and C-5. Finally, when heterocycle **245** is lithiated at C-6 through bromine/lithium exchange, a subsequent Negishi coupling gives the 5-phenyl derivative **246** <2003HCA3661>: this also suggests an isomerization of the kinetically formed aryllithium (Scheme 67).



Scheme 67

11.10.6.5.5 Reactions at surfaces

The six-membered ring was reported to be selectively reduced in CHEC-II(1996). More recent examples using Pd/C or Raney-Ni confirm this reactivity <2003JOC3498, 2004JME3658>. Desulfurization of methylthio substituents attached to the six-membered ring has been reported, but, depending on the nature of the other substituents on this ring, it can lead to also to a concomitant reduction of the six-membered ring <2003JOC3498>. A pyridine ring attached to this heterocycle was selectively reduced with PtO₂ <2002FA825>.

11.10.6.6 Reactivity of Substituents Attached to the Ring

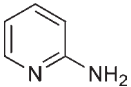
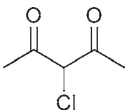
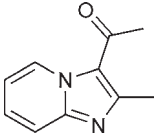
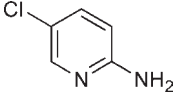
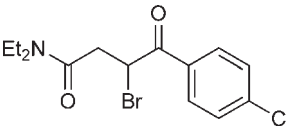
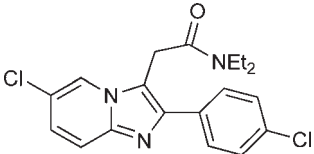
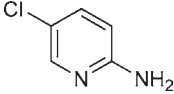
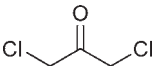
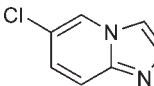
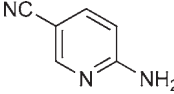
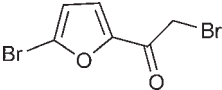
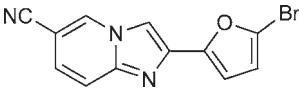
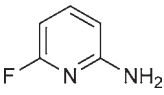
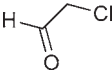
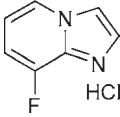
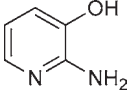
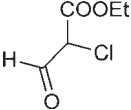
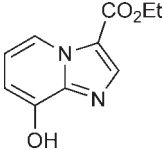
Reactivity of the substituents attached to the ring is quite classical and such transformations are routinely reported. However, some recent and more 'exotic' transformations are reported in this section. Examples include [3+2] cycloaddition of a nitrile oxide, generated at the C-3 position <1998TL8191>, condensation of a methyl ketone at C-3 with *N,N*-dimethylamine-formamide dimethyl acetal <2004BML2245>, reduction of an ester at C-3 <1997JME3109>, nucleophilic substitutions at a chloromethyl substituent linked at C-2 <2003ARK273>, the generation of a difluoroacetyl anion linked at C-3 <2001TL3077>, and the oxidation of sulfides linked at C-3 <1999T541>.

11.10.6.7 Synthesis

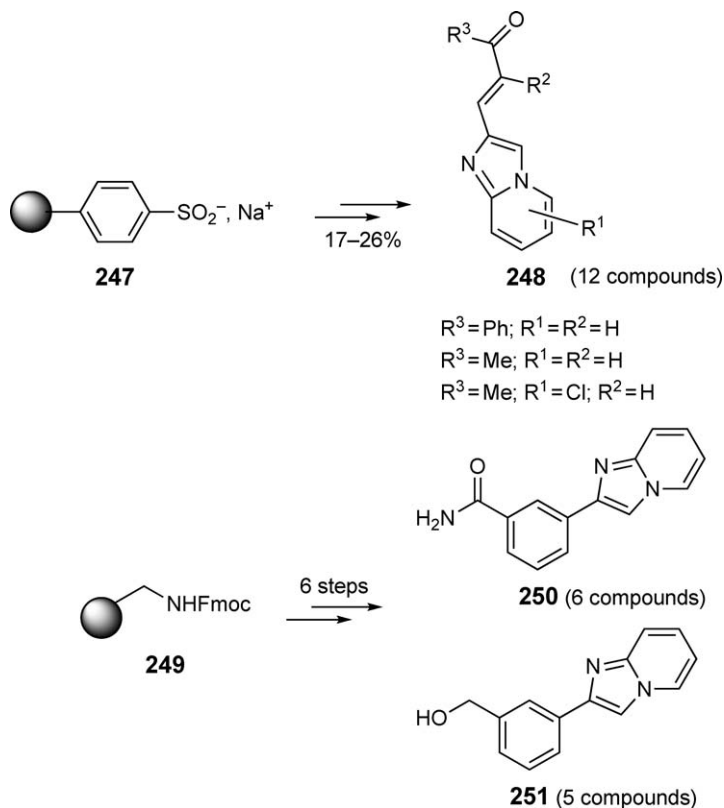
11.10.6.7.1 Fully conjugated ring

A lot of methods are available for the synthesis of this heterocycle, and most of them rely on the formation of the five-membered ring. In this section, only the methodologies of reasonable scope will be reported. The most 'classical' method involves the cyclocondensation of 2-aminopyridine with an α -halo carbonyl compound. Due to the broad availability of the required substrates and the efficiency of this cyclocondensation, it continues to be the method of choice to prepare this heterocycle. New examples highlighting the generality of this reaction are collected in Table 14.

Table 14 Synthesis of imidazo[1,2-*a*]pyridines through cyclocondensation of 2-aminopyridine and α -halo carbonyls

2-Aminopyridine	α -Halo carbonyl	Conditions	Product	Yield (%)	Reference
		EtOH/ THF Reflux, 12 h		44	2004BML2245
		<i>n</i> -BuOH Reflux		67	1997JME3109
		EtOH Reflux, 6 h		62	2003ARK273
		EtOH Reflux, 24 h		74	2004JME3658
		Water 60 °C, 2 h	 HCl	54	2002T489
		EtOH Reflux, 24 h		51	2002T8145

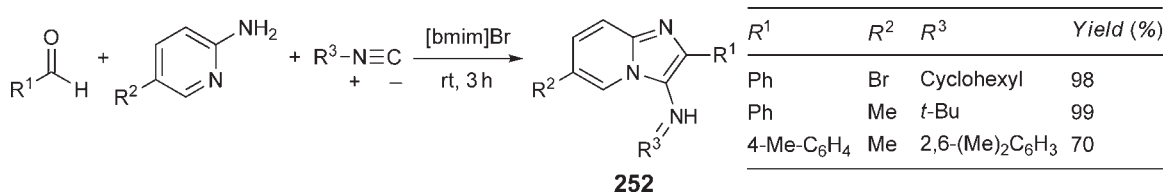
Due to the importance of this heterocycle in medicinal chemistry, solid-phase synthesis of derivatives based on this condensation reaction have been investigated. The first report in this area uses a sodium benzenesulfonate resin **247** and gives access in five steps and good overall yields to a library of imidazo[1,2-*a*]pyridines **248** functionalized at C-2 with an enone moiety <2002OL3935>. Later on, the preparation of libraries of compounds related to **250** or **251** from Rink amide resin **249** have been published (Scheme 68) <2003TL6265>.



Scheme 68

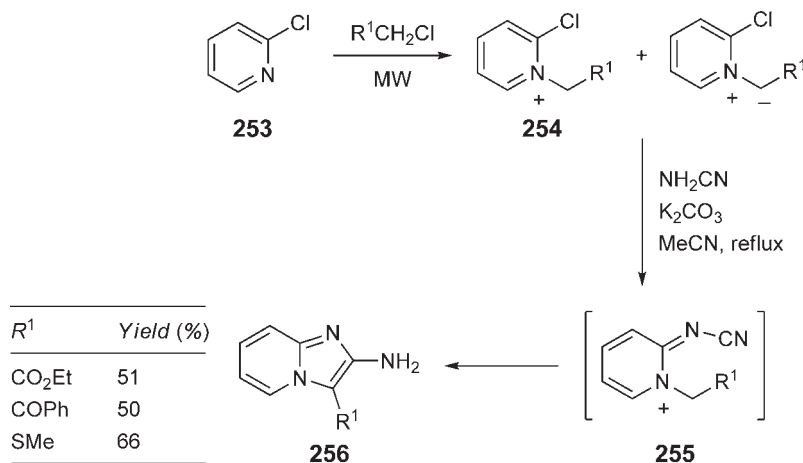
An operationally simple procedure involving a variation of this reaction and relying on the use of a polymer-supported [hydroxy(sulfonyloxy)iodo]benzene with aromatic ketones or alcohols has also been published <2004S2673>.

A multiple-component reaction especially suitable for combinatorial synthesis gives a straightforward access to 2-amino derivatives: when a solution of 2-aminopyridine is reacted with an aldehyde (aromatic or aliphatic) and an isonitrile under Lewis acid catalysis ($\text{Sc}(\text{OTf})_3$), the corresponding 2-amino imidazo[1,2-*a*]pyridines **252** are produced in good yields (70–95%) <1998TL3635>. Due to the efficiency of this Ugi three-component coupling, improvements in reaction time have been reported by using microwaves <2003TL4369> or ionic liquids (Scheme 69) <2006TL3031>.



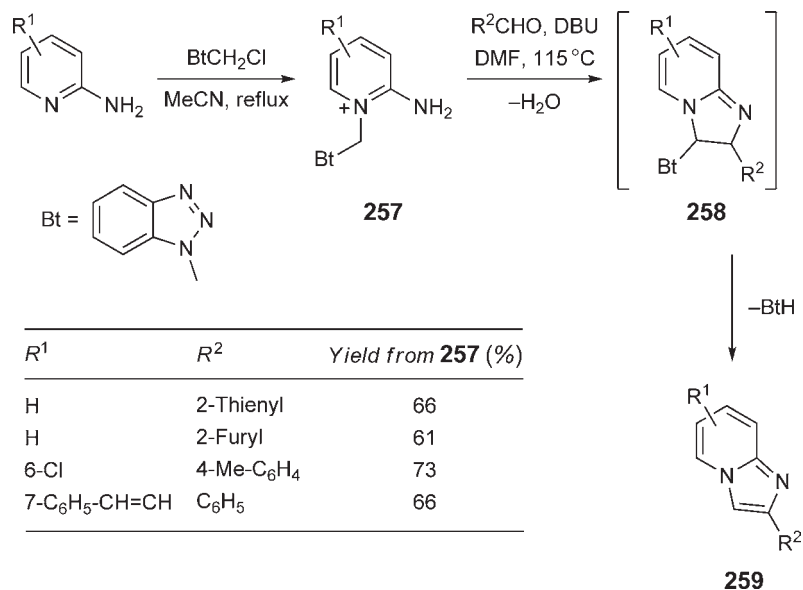
Scheme 69

An efficient synthesis of 2-amino derivatives **256** is depicted in **Scheme 70**: 2-halopyridines are first *N*-alkylated with various halides under microwave activation and next reacted with cyanamide under basic conditions [<1999T2317>](#). A rapid parallel synthesis of derivatives bearing a benzoyl substituent at C-3 based on this reaction has been described [<2002SL1544>](#).



Scheme 70

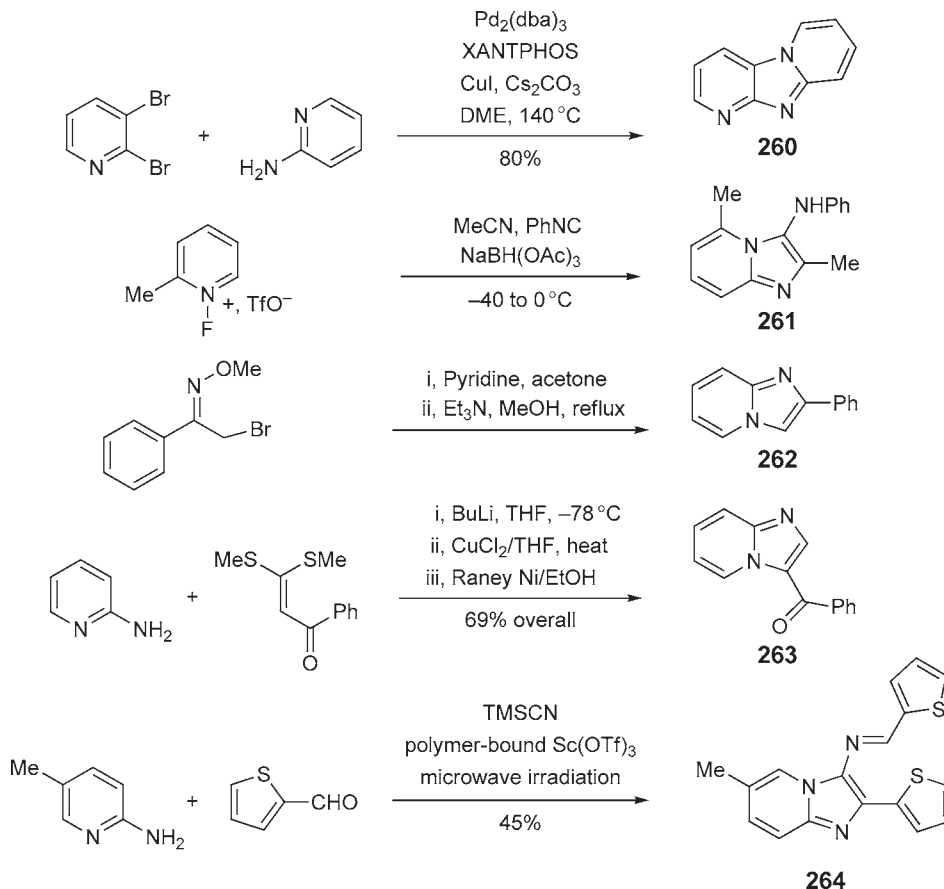
Katritzky *et al.* [<2000JOC9201>](#) reported an efficient synthesis of derivatives **259** based on the reaction of 2-amino-1-[α -benzotriazol-1-ylmethyl]pyridinium chlorides **257** with aldehydes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base. This method is, however, limited to the use of aromatic aldehydes (**Scheme 71**).



Scheme 71

Others interesting syntheses based on the formation of the five-membered ring include (1) the orthogonal tandem Pd- and Cu-catalyzed amination of 2,3-dibromopyridine with aminoazines to give **260** [<2006JOC260>](#), (2) the reaction of *N*-fluoropyridinium salts with nitriles and isocyanides under reducing conditions to give **261** [<2005TL4487>](#), (3) the cyclocondensation between pyridine and bromophenacyl bromide *O*-methyloxime, to give **262** [<1996S927>](#), (4) the

reaction of 2-aminopyridines with an-oxoketene *S,S*-acetal followed by CuCl_2 oxidative ring closure and desulfurization to give **263** <2000JOC1583>, (5) the microwave-assisted three-component reaction involving 2-aminopyridines, an aldehyde, and TMSCN to give **264** <2006TL2989>. All these syntheses are illustrated by one example in **Scheme 72**.



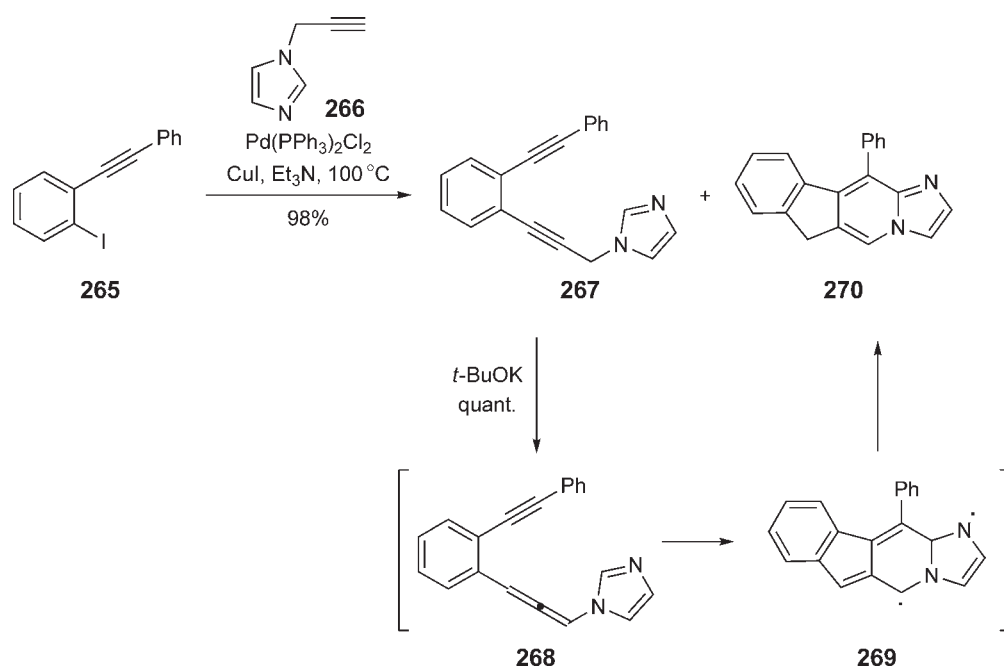
Scheme 72

Syntheses of imidazo[1,2-*a*]pyridines involving ring closure of the six-membered ring are less documented. An elegant route applied to the preparation of various heterocycles involves the reaction of iodide **265** with *N*-propargyl imidazole **266** under Sonogashira coupling conditions. The intermediate enediyne **267** gives enyne-allene **268** and then undergoes a Schmitt cyclization to give intermediate diradical **269** that finally gives **270**, as depicted in **Scheme 73** <2005JOC6647>.

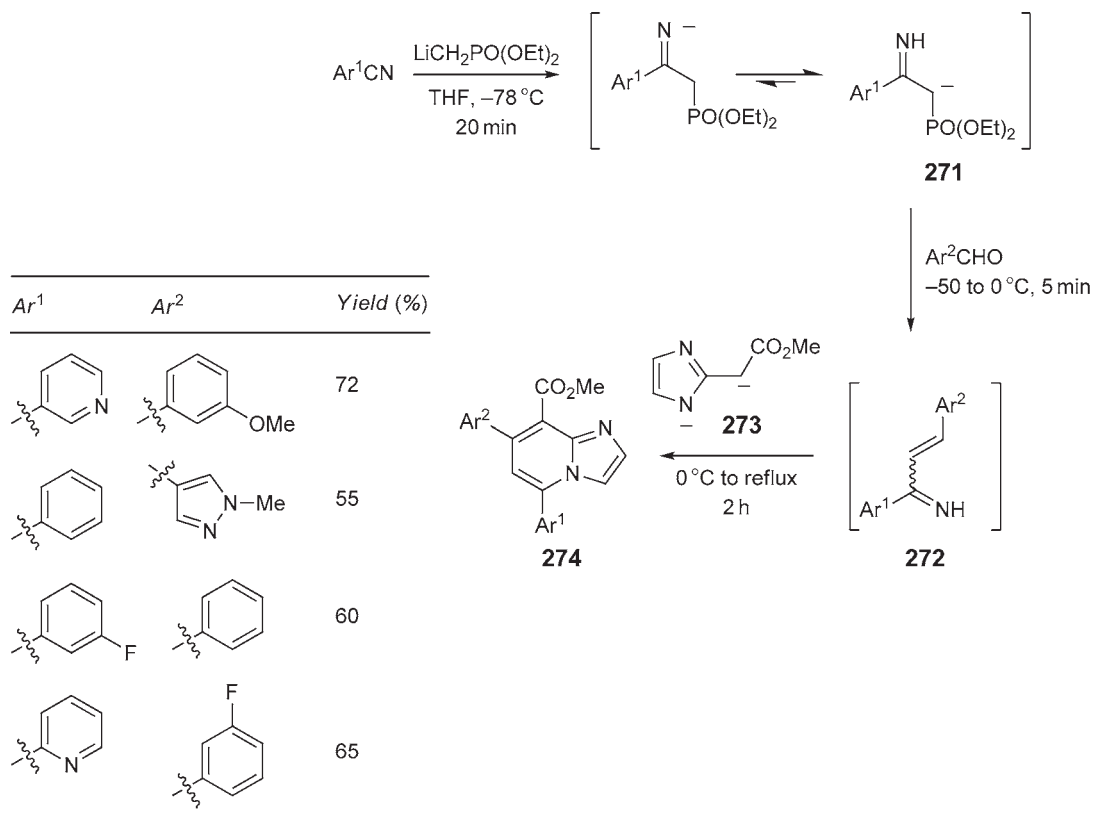
A series of aryl-substituted derivatives **274** have been recently prepared by an original ring-closure reaction <2006TL2941>. In these syntheses, aromatic nitriles react with lithiophosphonate to give **271**. Further reaction with aromatic aldehydes gives conjugated imines **272** and reaction of the latter with dianion **273** finally produces **274** in fair yields. This one-pot procedure is especially convenient to prepare derivatives possessing a substituted six-membered ring (**Scheme 74**).

Following a quite similar chemical transformation, the dianion of imidazole derivative **275** reacts with a variety of α -oxoketene dithioacetals **276** to give the adduct resulting from a conjugate addition. This compound spontaneously cyclodehydrates to give **277**. The SMe group may then be reduced using Raney-Ni <2003JOC3498>. Alternatively, the dianion of imidazole **278** adds in a 1,2-fashion to give **279**. Cyclodehydration of this intermediate needs further heating in the presence of phosphoric acid to give **280** (**Scheme 75**).

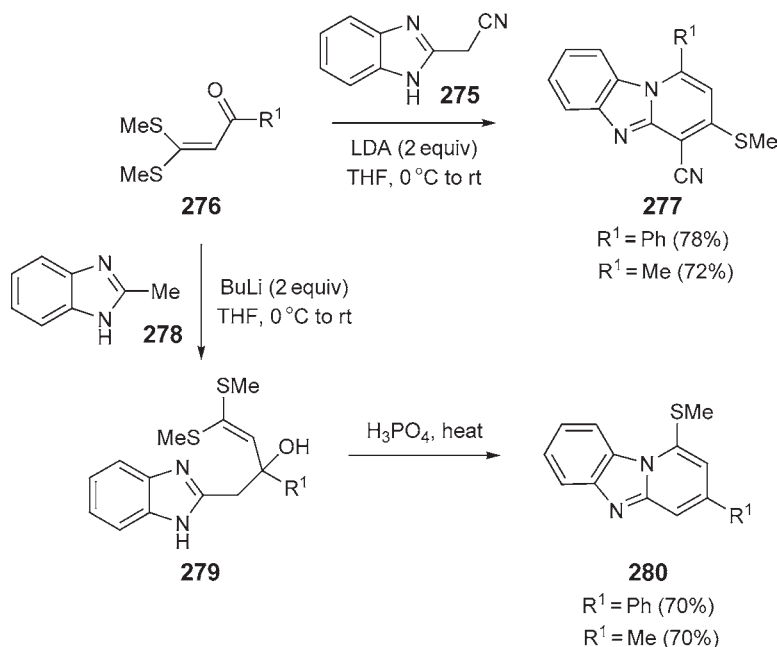
An elegant synthesis involving simultaneous closure of both five- and six-membered rings ought to be mentioned <2000EJO1433>. Oxidative cyclizations of functionalized aldehydes **281** with *ortho*-phenylene diamine in nitrobenzene directly give fused derivatives **282** in fair yields. In case of furyl derivatives (R^1), this reaction surprisingly gave an isomer of the expected heterocycle (**Scheme 76**).



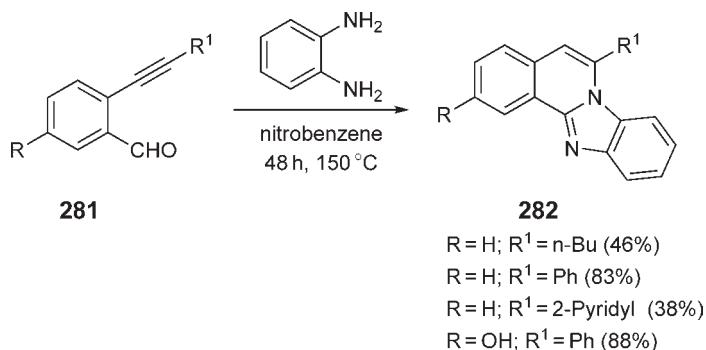
Scheme 73



Scheme 74



Scheme 75

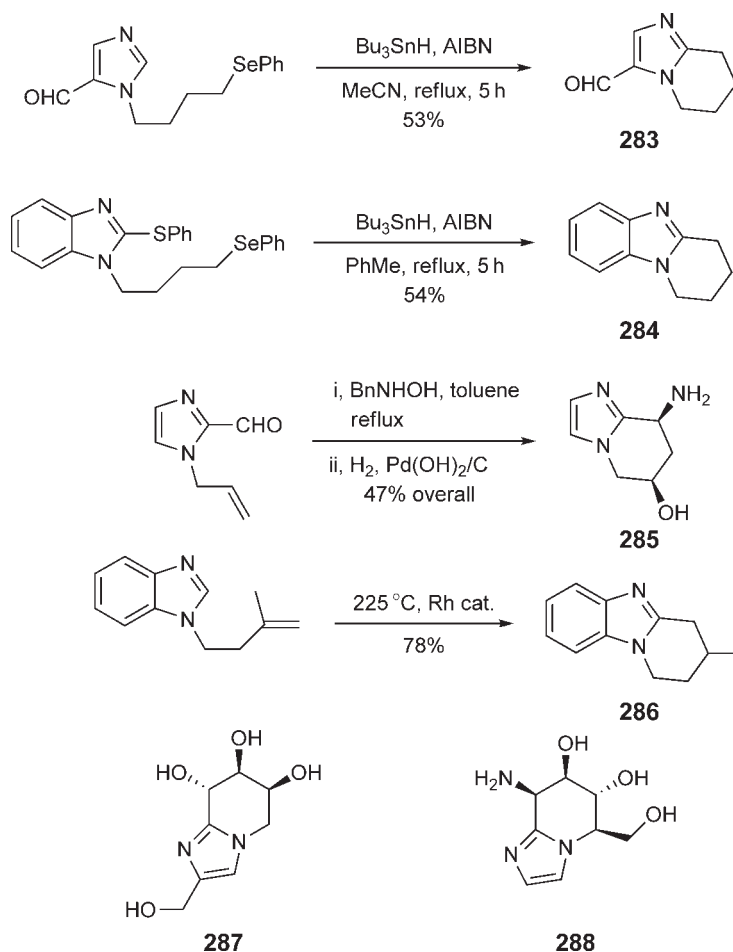


Scheme 76

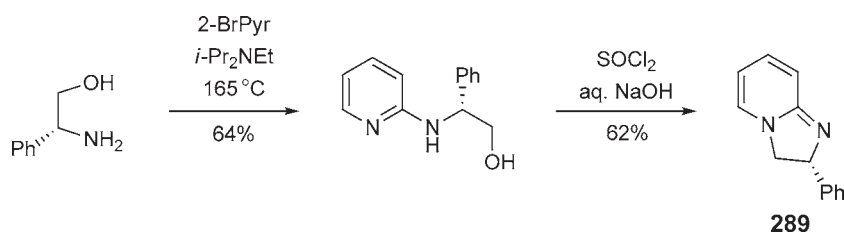
11.10.6.7.2 Partially saturated rings

Synthesis of this heterocyclic core with a fully saturated six-membered ring can be achieved by catalytic hydrogenation (see Section 11.10.6.5.5). The six-membered ring can also be formed starting from the appropriate imidazole using radical ring closure to give **283** <1999T8111> or **284** <1997TL3793>, through intramolecular nitronc cycloaddition <2002T4445> to give **285**, through rhodium-catalyzed CH activation to give **286** <2003OL2131> (Scheme 77). The simultaneous closure of both five- and six-membered rings leading to a saturated six-membered ring can be achieved through a [4+2] intramolecular cycloaddition of ketenimine-imine <1999TL6127>. A number of polyhydroxylated derivatives such as **287** or **288** have been synthesized through conventional carbohydrate chemistry <2004BML4039, 2005TA449, 2003TL3667>; these compounds were prepared because of their properties as selective and potent glycosidase inhibitors.

Partially saturated compounds can be prepared through annelation of heterocyclic 2-ketene amins with various bis-1,3-electrophiles <1998T6191, 1998TL9237>. Natural products (catharsitoxins A–C) have been prepared through imidazole ring closure <2001TL7079>. Partially saturated compounds such as **289**, prepared as outlined in Scheme 78, were found to be very efficient catalysts for enantioselective acylation of secondary alcohols <2004JA12226>.

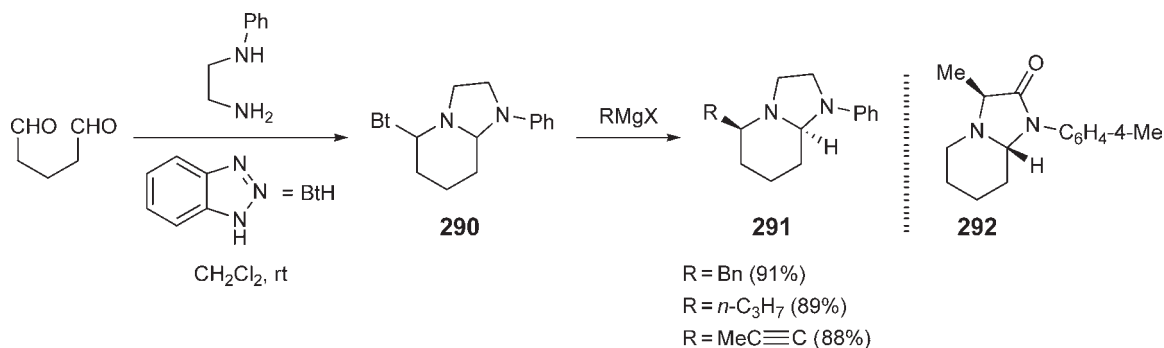


Scheme 77



Scheme 78

The synthesis and reactivity of imidazopyridinium halides, in which the five-membered ring is totally saturated, have also been investigated [\[2002JOC2382, 2003JOC10123\]](#). A synthesis of such derivatives has been described by Katritzky *et al.* [\[2000JOC3683\]](#) and relies on the condensation of glutaraldehyde and *N*-phenylethylene diamine in the presence of benzotriazole: bicyclic compound **290** is obtained in nearly quantitative yield. Treatment of the latter with Grignard reagents then furnishes derivatives **291** in very good yields. Careful examination of the NMR data of these compounds revealed that they were produced as single *cis*-stereoisomers as depicted in [Scheme 79](#). Compound **292** (major isomer shown) could be prepared following a similar strategy [\[2002JOC4951\]](#).



Scheme 79

11.10.6.8 Important Compounds and Applications

Imidazo[1,2-*a*]pyridines show an impressively large range of biological activities as illustrated with numerous examples in CHEC(1984) and CHEC-II(1996). This heterocycle continues to be a very popular scaffold for the development of new bioactive molecules, which is probably due to its easy preparation together with the success of some drugs possessing this skeleton. The best example continues to be Sanofi-Synthelabo zolpidem **293** (Stilnox[®], Ambien[®], Myslec[®]), a blockbuster for the treatment of sleeping disorders (Figure 7). It is most certainly impossible to be exhaustive when dealing with the biological activities of such derivatives considering the enormous literature on this subject. The following references will give an idea of activities reported for some derivatives: antiviral <2003OL1369>, anticancer <2004BML909, 2004BML2249, 2003BML3021>, anxiolytic <2004BML6559>, anti-malarial <2002FA825>, hypnotic <1997JME3109>, antiprotozoal <2004JME3658>, anti-inflammatory <1998JME4053>, activity against gastrointestinal diseases <2004WO2004101566>. This heterocycle continues to be one of the favorite scaffolds in medicinal chemistry.

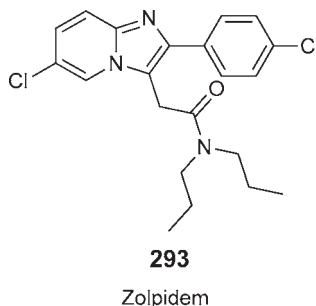
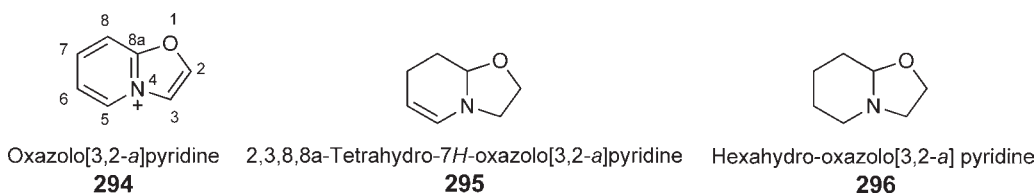


Figure 7

11.10.7 Oxazolo[3,2-*a*]pyridine

11.10.7.1 Introduction

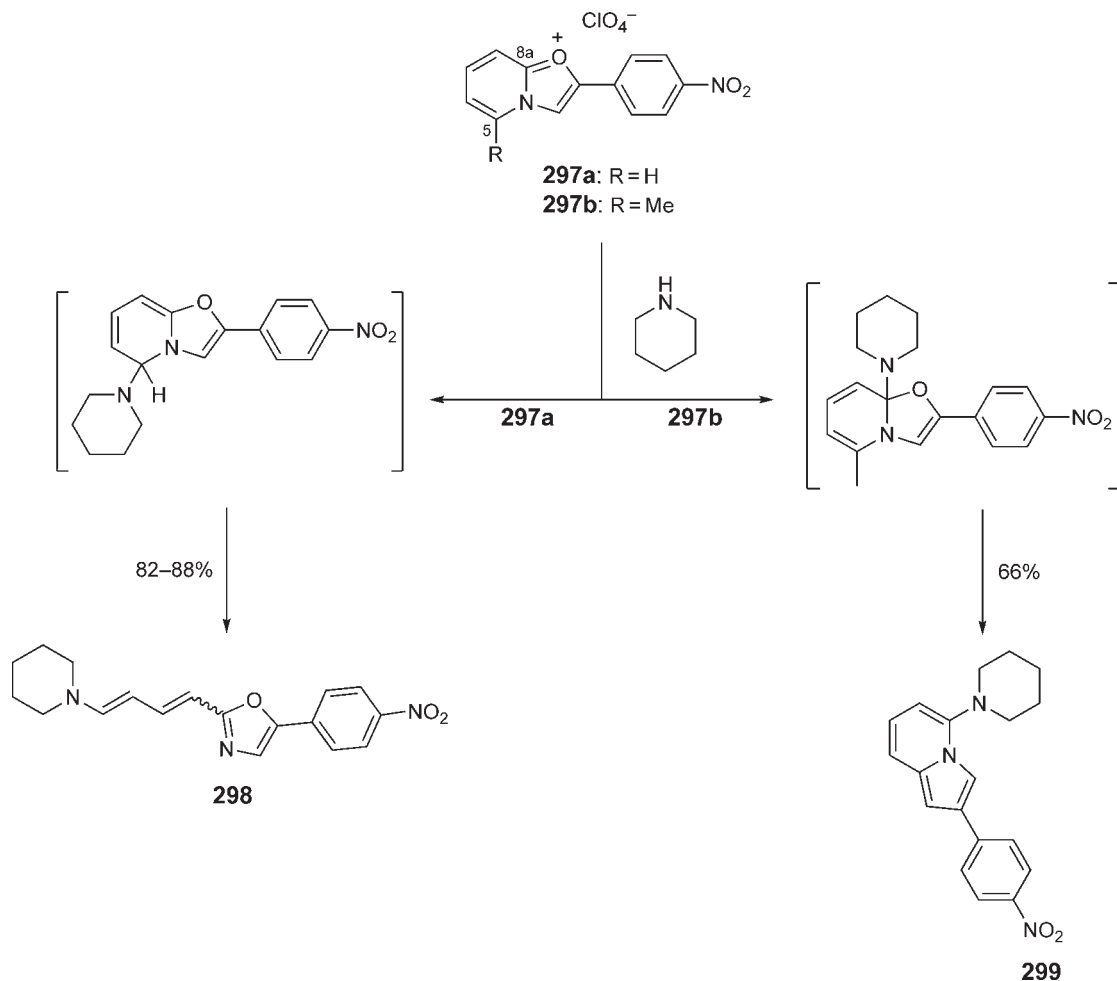
Oxazolo[3,2-*a*]pyridines **294**, first reported by Bradsher and Zinn <1967JHC66> and Pauls and Kröhnke <1976CB3653>, and especially their partially **295** or completely **296** saturated derivatives (Scheme 80) clearly emerged as important building blocks since CHEC-II(1996). Specific entries were devoted to this particular heterocycles in CHEC(1984) <1984CHEC(6)613> and CHEC-II(1996) <1996CHEC-II(8)249>. While the literature dealing with the fully conjugated rings is really not abundant (publications reporting on their synthesis or reactivity can be counted on one's fingers), there has been a growing number of publications on the syntheses and uses of saturated derivatives. Therefore, this chapter will briefly describe the new reactions of fully conjugated systems and will then focus on the partially/completely saturated derivatives.



Scheme 80

11.10.7.2 Theoretical Methods

To our knowledge, no new calculations were specifically devoted to this ring system. Semi-empirical SINDO1 calculations were however used to explain the unusual ambident behavior of oxazolo[3,2-*a*]pyridinium salts **297a** and **297b** toward piperidine (Scheme 81). Results obtained with these calculations demonstrate that the C-8a-adduct systematically possesses the lowest energy but in the case of an adduct between **297a** ($R = H$) and an amine, the difference of energy between addition at C-8a adduct or C-5 is negligible and the energy released during the ring cleavage yielding to **298** becomes the driving force, therefore explaining the difference in reactivity between salts **297a** and **297b** <1998EJO193>.

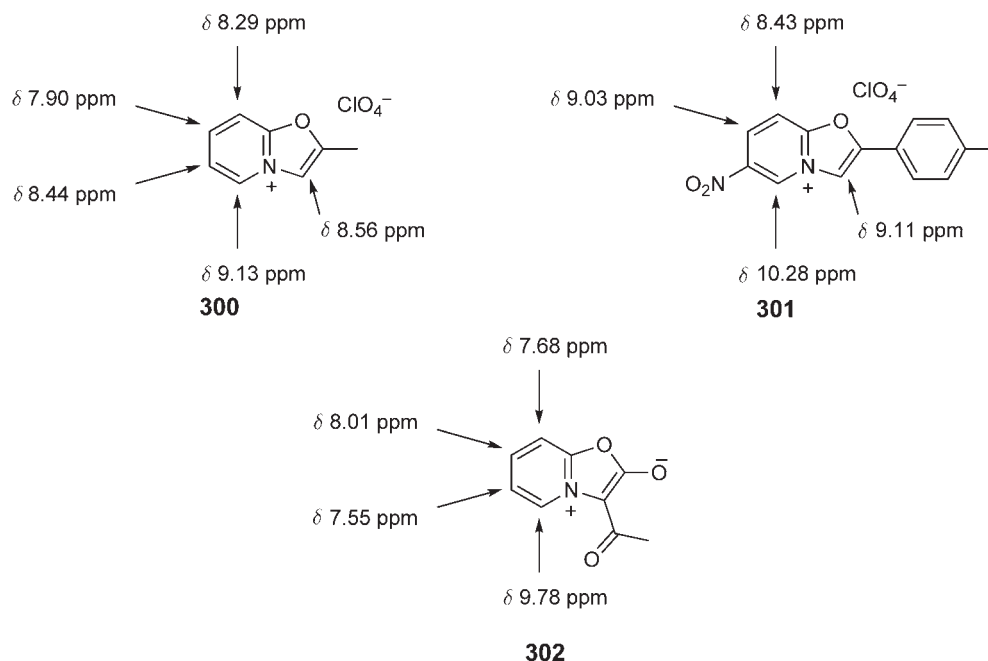


Scheme 81

11.10.7.3 Experimental Structural Methods

11.10.7.3.1 Fully conjugated systems

NMR data for new compounds are routinely reported: examples of ^1H NMR chemical shifts for a representative set oxazolo[3,2-*a*]pyridinium salts **300** <2005MOL1109>, **301** <2003MOL460>, as well as mesoionic compound **302** <2005MOL1109> are given in **Scheme 82**.



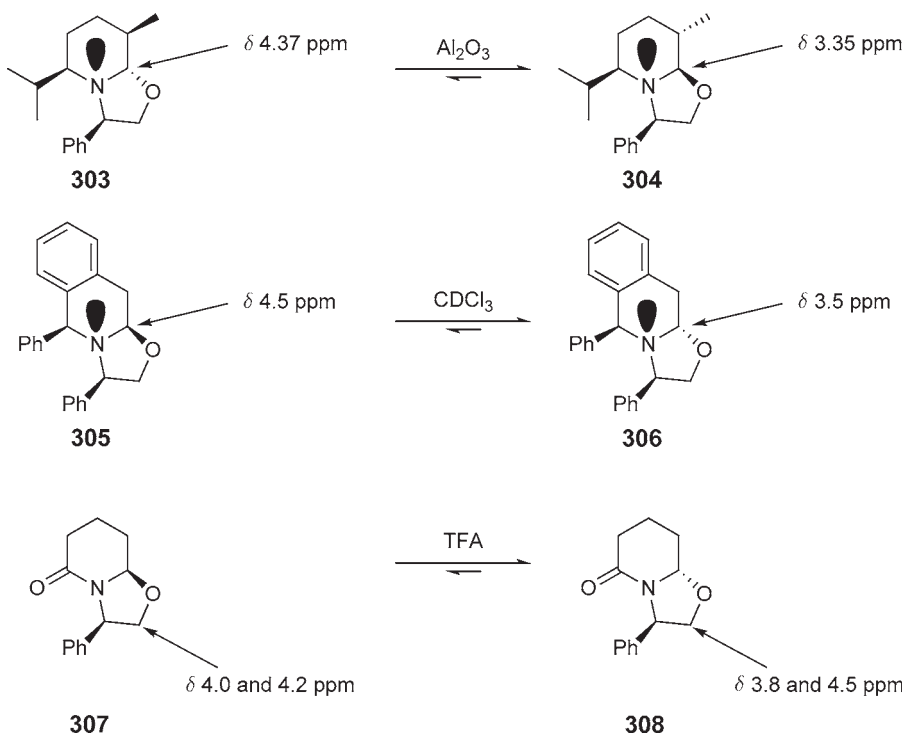
Scheme 82

11.10.7.3.2 Saturated systems

An important feature of polysubstituted perhydrooxazolo[3,2-*a*]pyridines is their high tendency for epimerization under acidic conditions at the C-8a anomeric stereocenter via an open iminium intermediate. This epimerization has been studied by NMR spectroscopy, which is a useful tool for assigning the stereochemistry of the perhydrooxazolo[3,2-*a*]pyridine ring system (**Scheme 83**). An interesting and meaningful example was reported by Marazano and Das who observed a huge difference in chemical shifts (ca. 1 ppm) for diastereoisomers **303/304** and **305/306**, a difference that was attributed to a deshielding effect due to the *syn*-relationship between the nitrogen doublet and the C-8a proton in **303** and **305** compared to the *anti*-arrangement in compounds **304** and **306** <1998JOC1767, 1998T9357>. Moreover, the predominance of **304** or **306** over **303** or **305** can be explained by destabilizing steric interactions between the phenyl groups of the oxazolidine ring and the substituent (isopropyl or phenyl) at C-5. Interestingly, this phenomenon seems to be quite general since Amat *et al.* reported a similar equilibration of 3-phenyl-hexahydro-oxazolo[3,2-*a*]pyridine-5-one **307** to its more stable isomer **308** under stronger acidic conditions <2003TA293>. Here again, typical chemical shifts allow for assignment of stereochemistry (**Scheme 83**).

11.10.7.3.3 Saturated systems: X-Ray

Structures of a wide number of hexahydro-oxazolo[3,2-*a*]pyridines have been determined using X-ray analysis. In most cases, the objective was structural confirmation and results usually were unexceptional. It should just be mentioned here that the crystal structure of *trans*-(3*R*,2*aS*)-(-)-3-phenyl-2,3,5,6,7,8-hexahydro-oxazolo[3,2-*a*]pyridine-5-thione revealed a significant participation of the tautomeric thio-enolic form as reflected by the short N-C(=S) bond length of 1.328 Å <2003AXE0519>.



Scheme 83

11.10.7.4 Thermodynamic Aspects

As seen from the NMR data in the previous section, an important feature of polysubstituted perhydrooxazolo[3,2-*a*]pyridines is their high tendency for epimerization under acidic conditions at the C-8a anomeric carbon.

11.10.7.5 Reactivity of Fully Conjugated Rings

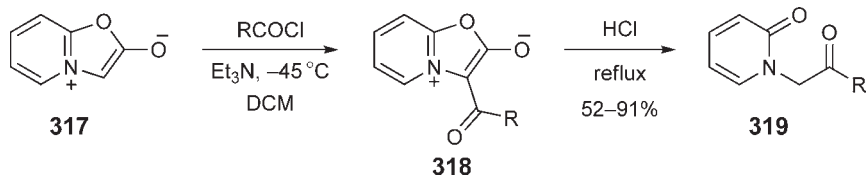
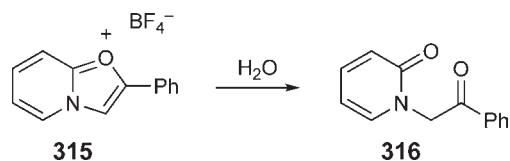
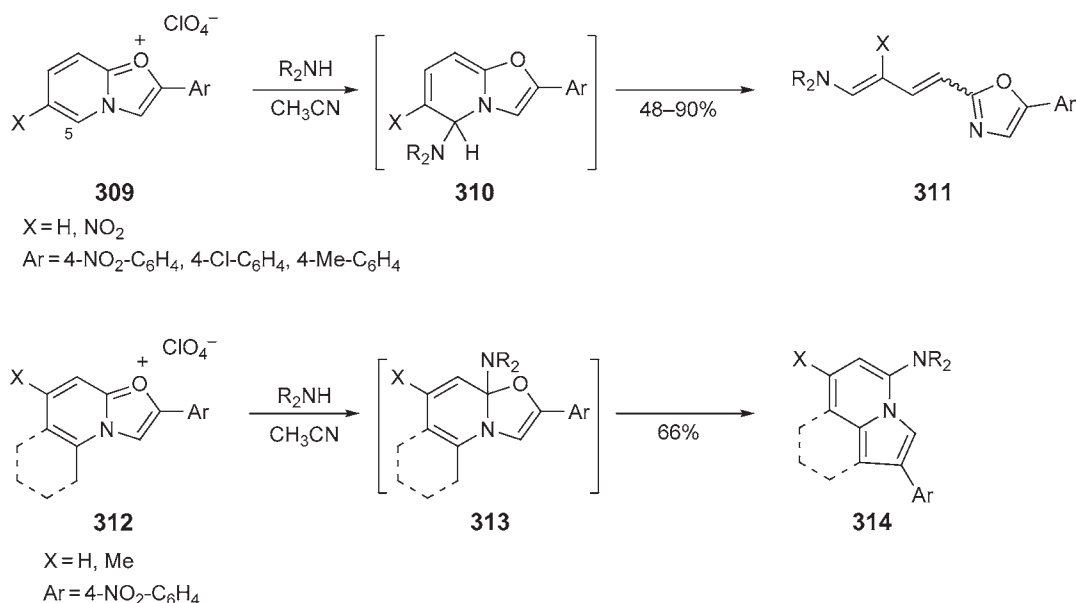
Not much work has been devoted to the reactivity of the oxazolo[3,2-*a*]pyridine ring system in the 1996–2006 time period. Babaev *et al.* however extensively studied the ambident reactivity and novel transformations of oxazolo[3,2-*a*]pyridinium salts which were shown to strongly depend both on the nature of the nucleophile and the salt (**Scheme 84**). When the oxazolo[3,2-*a*]pyridinium salt engaged in the reaction with an amine does not have any substituent at the C-5 position, adducts **310** are formed which gave dienes **311** in good yields <1998EJO193, 2003MOL460>. In contrast, substitution at C-5 by an alkyl group blocks the formation of the adduct at this position: the amine now adds to C-8a and indolizines **314** are now exclusively formed <1998EJO193, 2005IZV253>. Note that a similar behavior was observed when sodium methoxide was used in place of the amine.

While the reaction with amines gave dienes or indolizines depending on the substitution pattern of the starting oxazolo[3,2-*a*]pyridinium salts, their reaction with water exclusively gives *N*-phenacetylpyridones resulting from hydrolysis of the starting material as exemplified by the reaction of **315** with water (**Scheme 85**) <1997AXC1909, 1998EJO193>.

Finally, mesoionic oxazolo[3,2-*a*]pyridines such as **318**, obtained by reaction of **317** with acyl chlorides, are readily hydrolyzed to pyridones **319** by treatment with diluted hydrochloric acid (**Scheme 86**) <2005MOL1109>.

11.10.7.6 Reactivity of Nonconjugated Rings

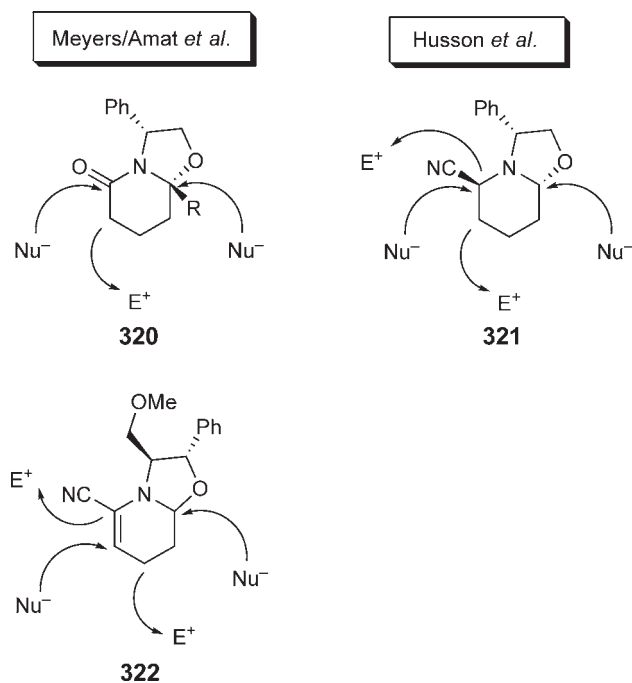
Considerably boosted by the work of Meyers and Brengel <1997CC1, 1998JOC1619, 2000JOC7240, 2000T9843>, Husson *et al.* <1983JA7754, 1986JOC4475, 1999CSR383>, and Amat *et al.* <2002AGE335, 2003TA1679, 2005OL2817, 2005OL3653>, the reactivity of fully saturated oxazolo[3,2-*a*]pyridines have been extensively studied



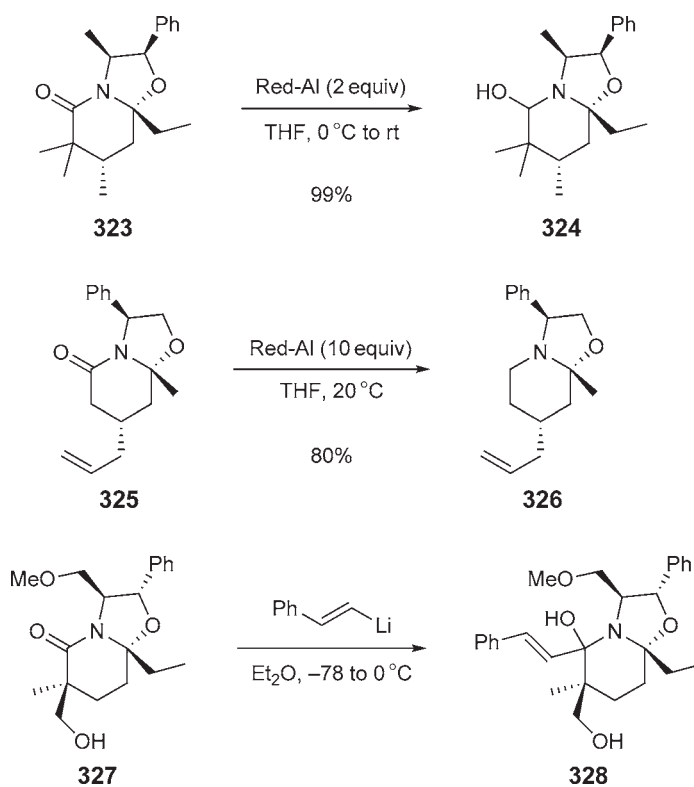
and used in many syntheses of natural products. Depending on the substitution pattern of the chiral perhydrooxazolo[3,2-*a*]pyridine used as molecular scaffold, various chemical transformations have been used to introduce functionalities at different positions of the bicyclic starting materials. [Scheme 87](#) summarizes the three templates mainly used as well as the strategies employed for their functionalizations. All the possible transformations will not be exhaustively reviewed in this section (excellent reviews have appeared on this topic [<1999CSR383, 2000T9843>](#)): instead, an overview of the possibilities and strategies will be discussed, trying to survey all different modes of reactivity of the perhydrooxazolo[3,2-*a*]pyridine ring system. The corresponding reactions will be classified according to the position of the ring transformed in the process.

11.10.7.6.1 Nucleophilic attack at C-5

The presence of an amide on perhydrooxazolo[3,2-*a*]pyridine skeleton allows for a substituent modification at the C-5 position. Among the possibilities are partial or full reduction of the amide as well as addition of organolithium reagents, respectively, starting from **323** [<1998JOC1732>](#), **325** [<1999TL8965>](#), or **327** ([Scheme 88](#)).

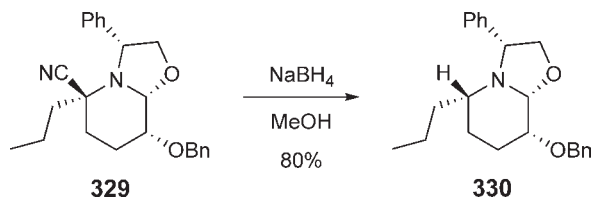


Scheme 87



Scheme 88

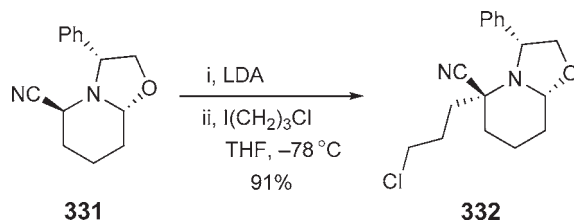
If the perhydrooxazolo[3,2-*a*]pyridine now possesses a nitrile at C-5, the aminonitrile can be reduced with sodium borohydride as exemplified in [Scheme 89](#) <1998T8783>. Another option is to generate an intermediate iminium ion and to further reduce it with zinc borohydride <1998T8783>.



Scheme 89

11.10.7.6.2 Electrophilic attack at C-5

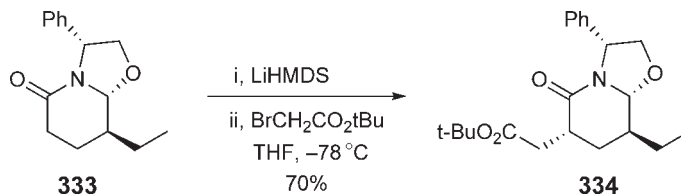
Here again, the presence of a nitrile group at C-5 allow for a great versatility: generation of an anion followed by its trapping with electrophiles allows for the introduction of an additional substituent in this position as exemplified by the diastereoselective alkylation of **331** ([Scheme 90](#)) <2005JOC4474>.



Scheme 90

11.10.7.6.3 Electrophilic attack at C-6

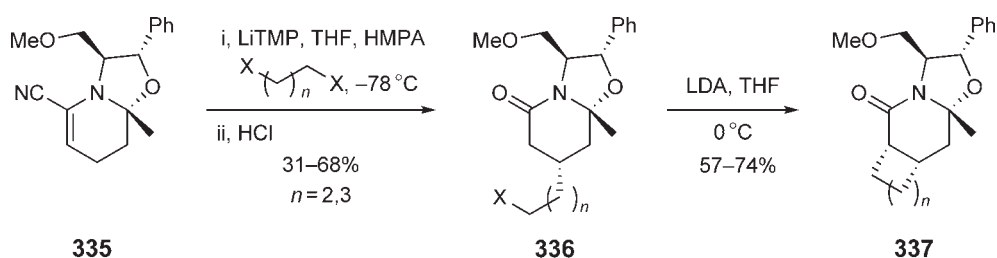
The presence of the amide group in hexahydro-oxazolo[3,2-*a*]pyridin-5-one **333** allows for a diastereoselective introduction of a substituent after generation of an enolate and its quenching with *tert*-butyl bromoacetate ([Scheme 91](#)) <2003OL3139>. Functionalization at C-6 via transient iminium/enamines starting from simple hexahydro-oxazolo[3,2-*a*]pyridines has also been recently reported <2000AGE1493>.



Scheme 91

11.10.7.6.4 Electrophilic attack at C-7

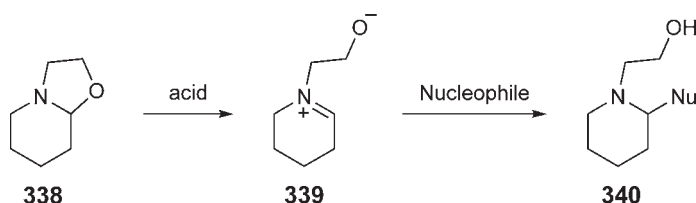
Only few general methods allow for the introduction of a substituent at the C-7 position. However, treatment of cyano-enamide **335** with LiTMP followed by reaction with electrophiles has been successfully used to introduce an alkyl chain at C-7. It is worth noting that the amide obtained by acidic hydrolysis of the cyano-enamide group can be further alkylated to form tricyclic hexahydro-oxazolo[3,2-*a*]pyridin-5-ones **337** ([Scheme 92](#)) <1998JOC1619>.



Scheme 92

11.10.7.6.5 Nucleophilic attack at C-8a

Perhydrooxazolo[3,2-*a*]pyridines **338** are excellent precursors of iminium ions **339** obtained after treatment of the oxazolidine with either a Brönsted or Lewis acid. Trapping of these intermediate iminium ions with nucleophiles then allows for substitution at the C-8a position together with ring opening, yielding functionalized piperidines **340** (Scheme 93).



Scheme 93

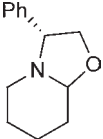
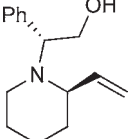
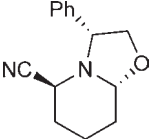
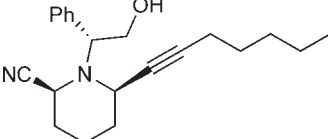
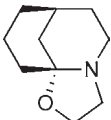
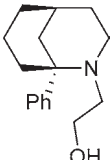
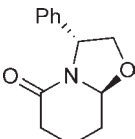
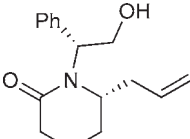
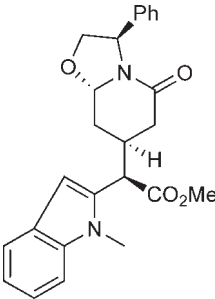
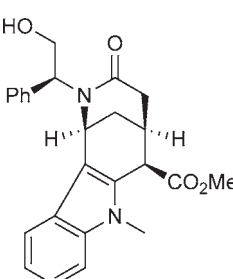
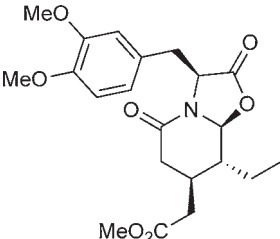
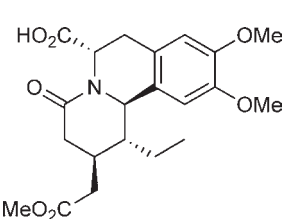
This reaction has been extensively used for the synthesis of polyfunctionalized piperidines with a wide range of nucleophiles: selected and representative examples are collected in Table 15. From these results, hydrides, Grignard reagents, aluminium derivatives, allylsilane, as well as aromatics can be used as nucleophiles to give the corresponding C-8a functionalized compounds in good yields and, in most cases, excellent selectivities.

Table 15 Nucleophilic attack at C-8a

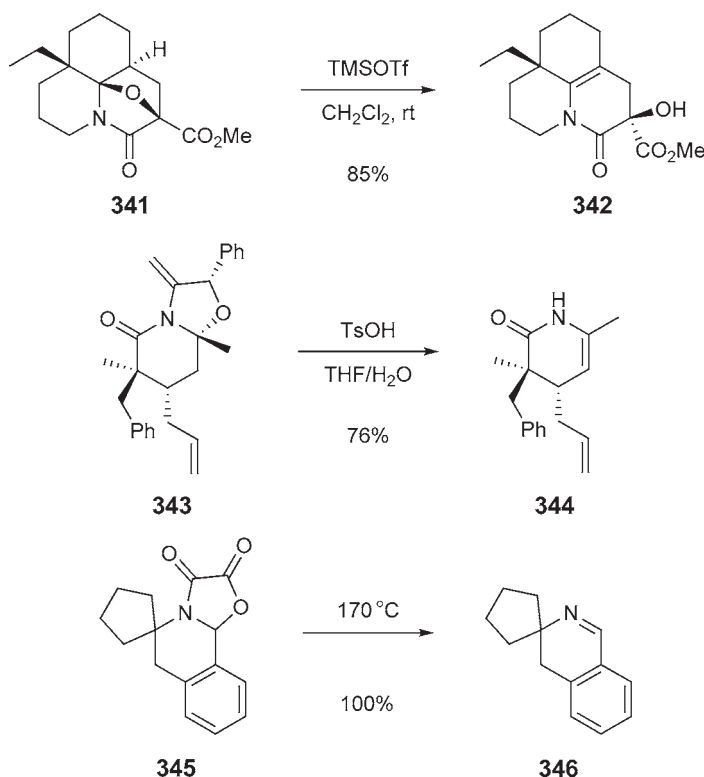
Substrate	Nucleophile, conditions	Product	Yield (%)	Reference
	NaBH ₄ MeOH, rt		62	1997JNP684
	NaBD ₃ CN BF ₃ ·OEt ₂ , THF		75–80	1997JA6446
	MeMgBr THF, rt		89	2003EJO2062

(Continued)

Table 15 (Continued)

Substrate	Nucleophile, conditions	Product	Yield (%)	Reference
	VinylMgBr THF, rt		95	2004OL1139
	C ₅ H ₁₁ C≡CH AlMe ₃ , Et ₃ N Toluene, rt		82	2004OL2333
	Ph ₃ Al Et ₂ O, rt		89	2001TL3013
	Allylsilane TiCl ₄ , DCM, rt		91	2003JOC1919
	TiCl ₄ , DCM, rt		50	2004CC1602
	BF ₃ ·OEt ₂ , DCM Reflux		82	2005OL2817

Interestingly, enamides or imines are produced in the absence of external or internal nucleophiles as shown by the formation of **342**, **344**, and **346**, respectively, obtained from **341** <1998JOC44>, **343** <1998JOC1619>, and **345** <1996SC3471> in good to excellent yields (Scheme 94).



Scheme 94

11.10.7.7 Ring Syntheses from Acyclic Compounds

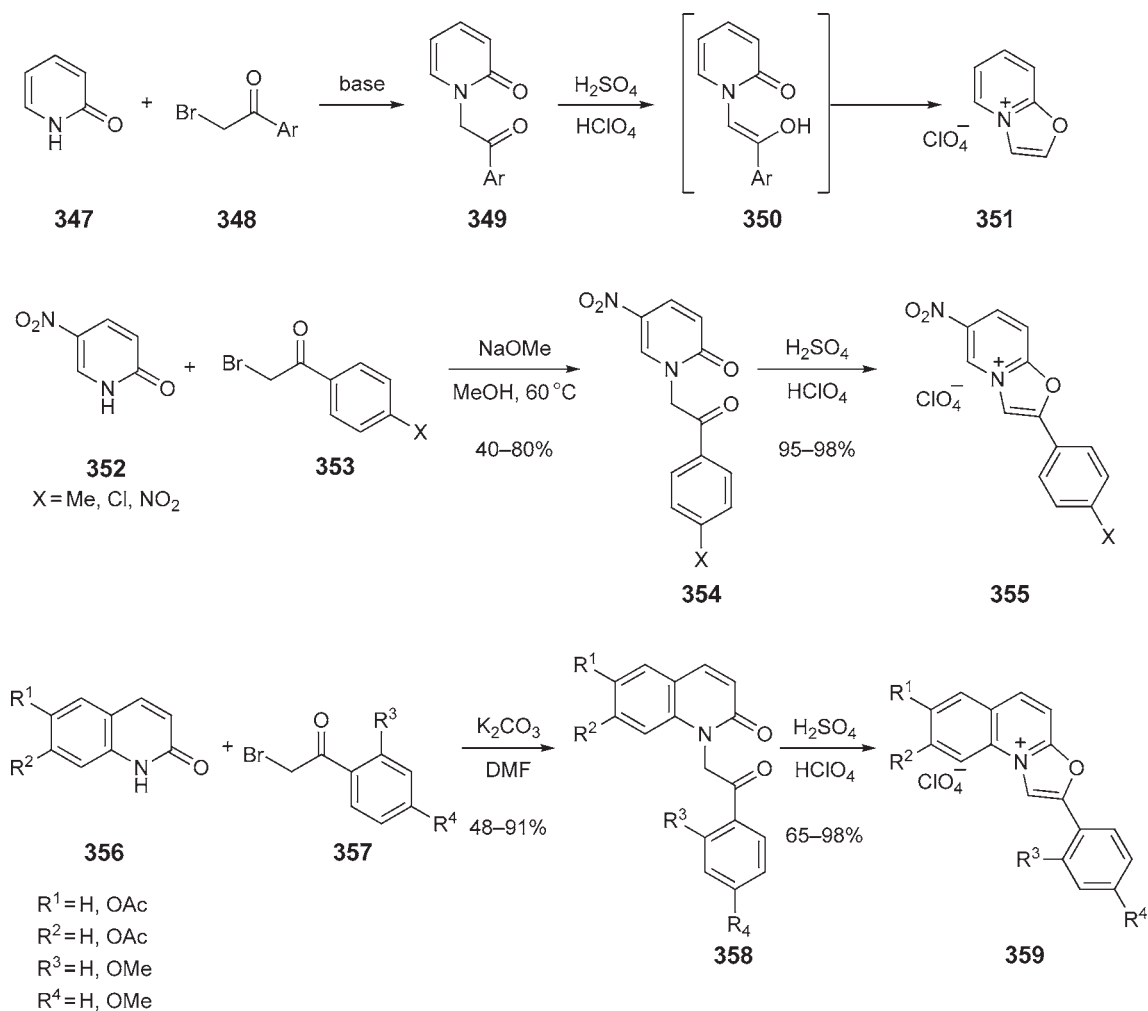
The most efficient routes to the cationic oxazolo[3,2-*a*]pyridine ring system **351** rely on the method of Bradsher and Zinn <1967JHC66> involving the cyclocondensation of *N*-phenacyl-2-pyridones **349** obtained by alkylation of readily available 2-pyridones **347** (Scheme 95). This method has been used by Babaev *et al.* to prepare a series of 6-nitro-oxazolo[3,2-*a*]pyridines **355** from 5-nitro-2-pyridone **352** in excellent yields <2003MOL460>. Similarly, tricyclic oxazolo[3,2-*a*]pyridines **359** have been prepared from the corresponding quinolin-2(1*H*)-ones **356** <2003H(60)131>.

11.10.7.8 Ring Syntheses of Saturated or Partially Saturated Rings from Acyclic Compounds

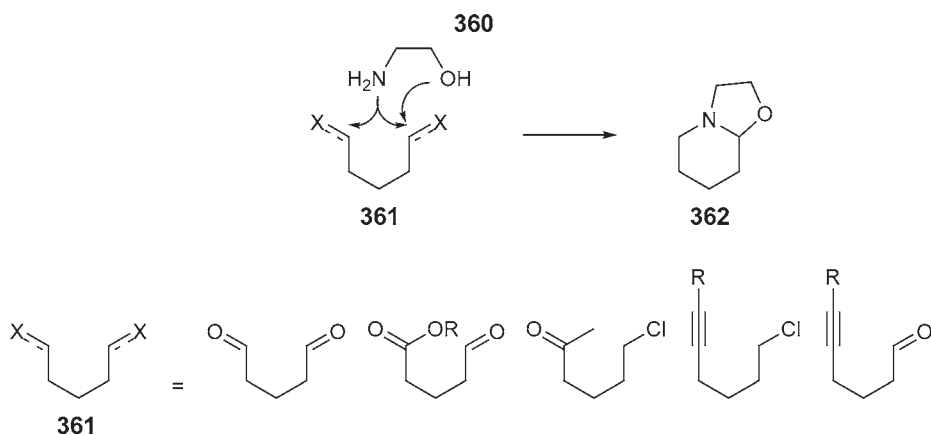
Many synthetic routes have been developed to access the saturated oxazolo[3,2-*a*]pyridine ring system. Among those, the most efficient ones rely on a similar strategy starting from an amino alcohol **360** and a bis-electrophile **361**, the latter being either a bis-aldehyde, a keto-ester, a chloro-ketone, or a chloroalkyne (Scheme 96). Among these electrophiles, the first two have demonstrated their utility and generality over the years and have been used for the preparation of many saturated oxazolo[3,2-*a*]pyridines **362**.

Examples of each of the methods are reported in Table 16 and show the different products obtained from the variation of the bis-electrophile and, when needed or suitable, additional nucleophile.

Another option to build the saturated oxazolo[3,2-*a*]pyridine skeleton relies on commencing from substrates **363** or **366** in which the six-membered ring is already formed. By reacting lactam **363** with sodium hydride and a Grignard reagent <1996TL849> or reducing amino acid-derived piperidine-2,6-dione **366** <1996SC1605>, perhydrooxazolo[3,2-*a*]pyridines **365** and **368** are obtained, respectively (Scheme 97).



Scheme 95



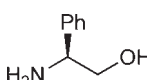
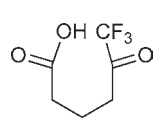
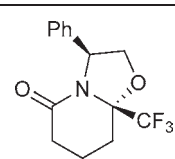
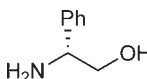
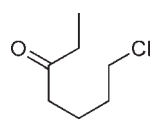
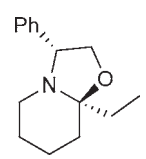
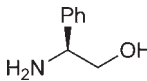
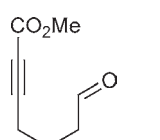
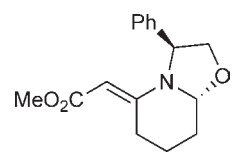
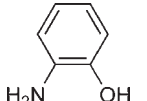
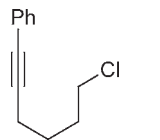
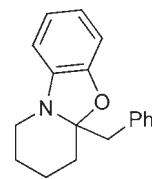
Scheme 96

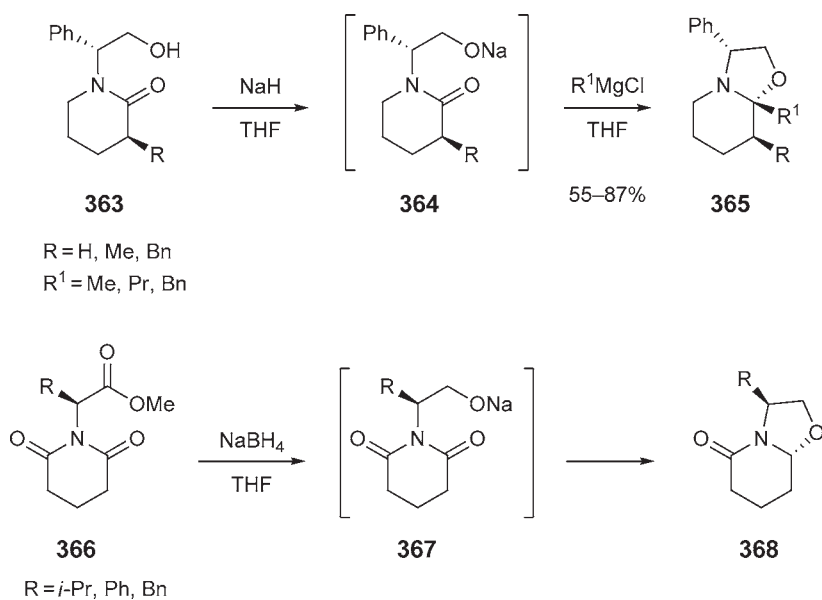
Table 16 Reaction of amino alcohols with bis-electrophiles

<i>Amino alcohol</i>	<i>Bis-electrophile</i>	<i>Additional nucleophile, conditions</i>	<i>Product</i>	<i>Yield (%)</i>	<i>Reference</i>
		NaBH ₄ MeOH		50	2000AGE1493
		KCN pH 3, H ₂ O		69	2001H(55)2273
		i, KCN, citric buffer, H ₂ O ii, ZnBr ₂ , MeOH		45	2000JOC7208
		P(OEt) ₃ MeOH/H ₂ O		58	1997T3627
		Benzotriazole CH ₂ Cl ₂ /H ₂ O		95	1998JOC6699
		Toluene Reflux		90	1996JOC4607
		Na ₂ SO ₄ , Et ₂ O		71	2005OL3653

(Continued)

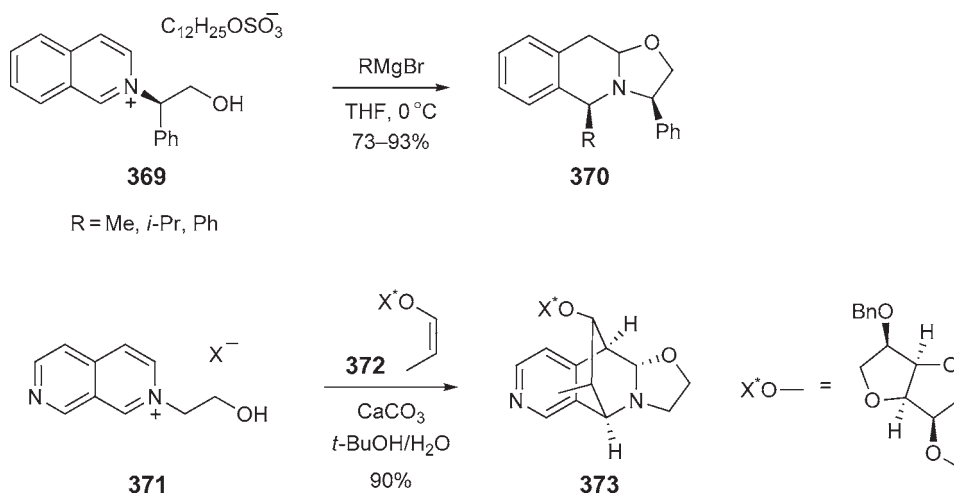
Table 16 (Continued)

<i>Amino alcohol</i>	<i>Bis-electrophile</i>	<i>Additional nucleophile, conditions</i>	<i>Product</i>	<i>Yield (%)</i>	<i>Reference</i>
		TsOH, Toluene Reflux		70	1999JA593
		Et ₃ N, Toluene Reflux		72	2000EJO1719
		4 Å mol sieves THF		88	2004JOC2888
		Pd(NO ₃) ₂ Dioxane, 120 °C		50	2002JA12670



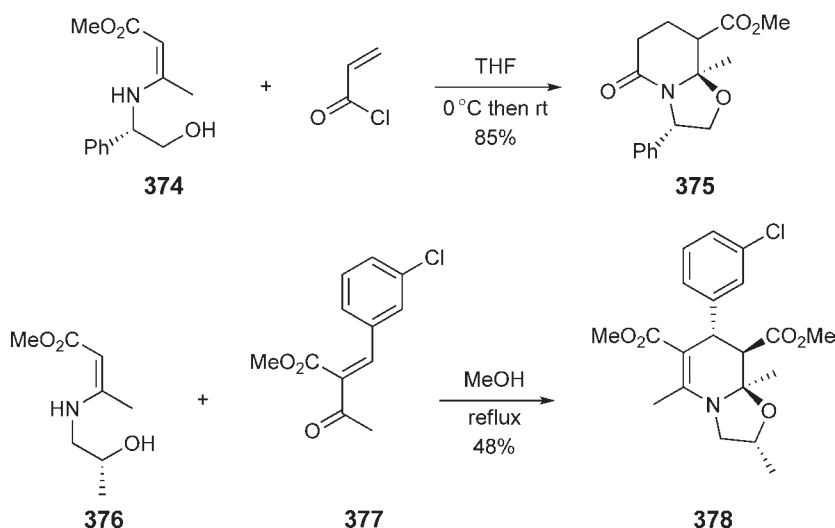
Scheme 97

Isoquinolinium **369** and [2,7]naphthyridin-2-ium **371** salts have also been used for the preparation of 2,3,8,8a-tetrahydro-5*H*-oxazolo[3,2-*a*]pyridine derivatives (**Scheme 98**): addition of Grignard reagents to **369** is followed by a spontaneous cyclization to **370** <1998JOC1767> while an asymmetric version of the Bradsher cycloaddition between **371** and chiral enol ether **372** gives **373** in good yield and selectivities <1996TL7019>.



Scheme 98

As shown by the two examples represented in **Scheme 99**, chiral enaminoesters are good candidates for the synthesis of saturated or partially saturated oxazolo[3,2-*a*]pyridine derivatives (**Scheme 99**): acylation of **374** with acryloyl chloride or conjugate addition of **376** to **377** afford in both cases substrates that readily undergo cyclization, respectively to **375** <2002TL2521> and **378** <1996JOC1890>.



Scheme 99

The intramolecular reaction between carbenoids and amides is clearly emerging as a powerful tool for the synthesis of saturated oxazolo[3,2-*a*]pyridine derivatives as shown by the cyclization of simple to extremely functionalized substrates **379** <2003CC440> and **381** <2005OL47> (**Scheme 100**): trapping the intermediate isomünchnone 1,3-dipoles by external (MeOH) or internal (indole) nucleophiles results in new heterocyclic fused systems with especially high efficiency.



11.10.7.9 Important Compounds and Applications

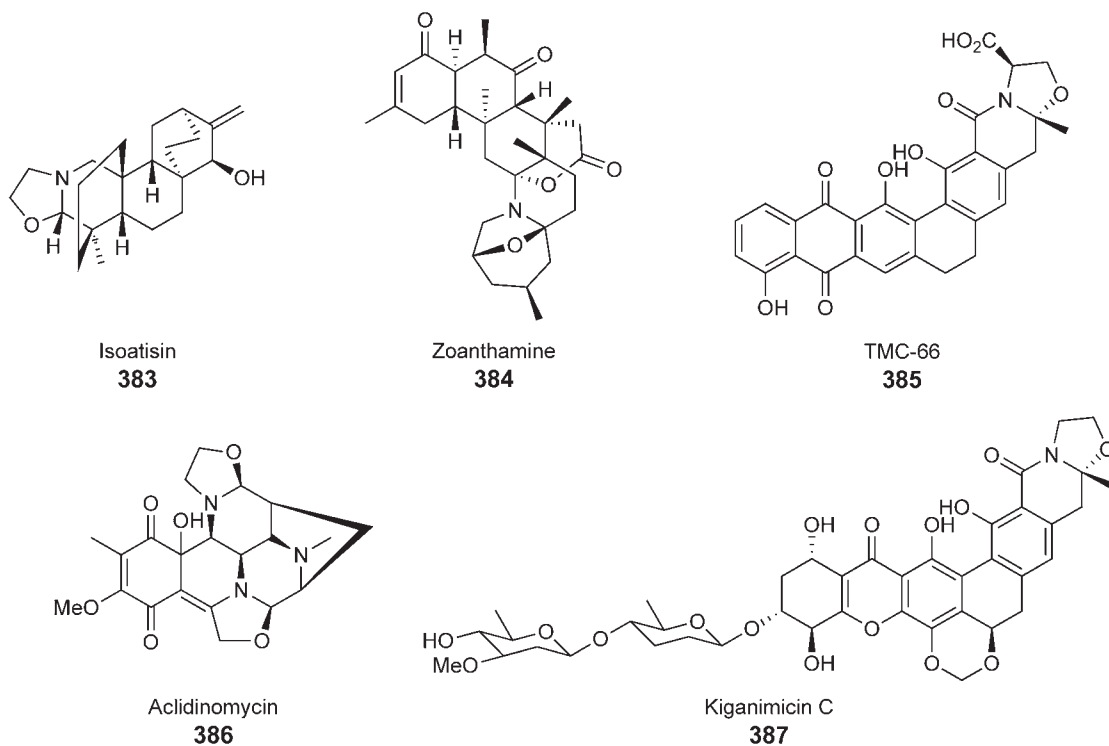
11.10.8 Thiazolo[3,2-a]pyridine

11.10.8.1 Introduction

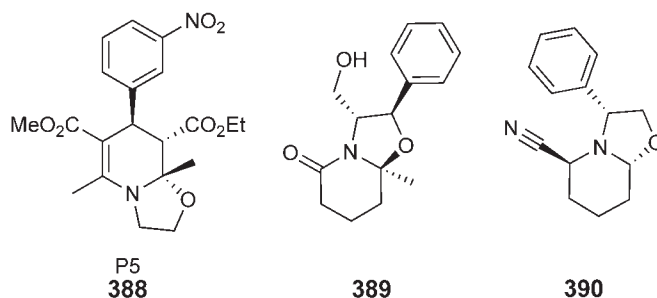
This class of heterocycle was covered in detail in CHEC(1984) <1984CHEC(6)613> along with others systems and it was reviewed together with thiazolo[3,4-*a*]pyridines in CHEC-II(1996) <1996CHEC-II(8)249>. The literature within the past 10 years for the fully conjugated system is not abundant: only 25 hits were found in the Beilstein

database for the past decade. Therefore, focus will be made on partially or fully saturated systems. Concerning the fully conjugated rings, mesoionic systems **393** <1997TL2435> and **394** <2004IZV176> have been synthesized respectively from **391** and **392** (Scheme 102). The structure of **394** ($X = \text{NO}_2$) was determined by X-ray crystallography. NMR spectroscopic studies of a couple of fused thiazoloazinium ring systems such as **395** have been conducted in detail. Basic molecular parameters like anionic charges and bond orders have been determined by *ab initio* and density functional theory (DFT) calculations in order to rationalize the site of reaction of these salts with secondary amines <2003JST295>. Several hitherto unknown thiazolo[3,2-*a*]quinolinium salts have been prepared and thoroughly characterized by NMR spectroscopy <1999JHC937>. The electrochemical behavior of some derivatives has also been investigated <1999JHC943>.

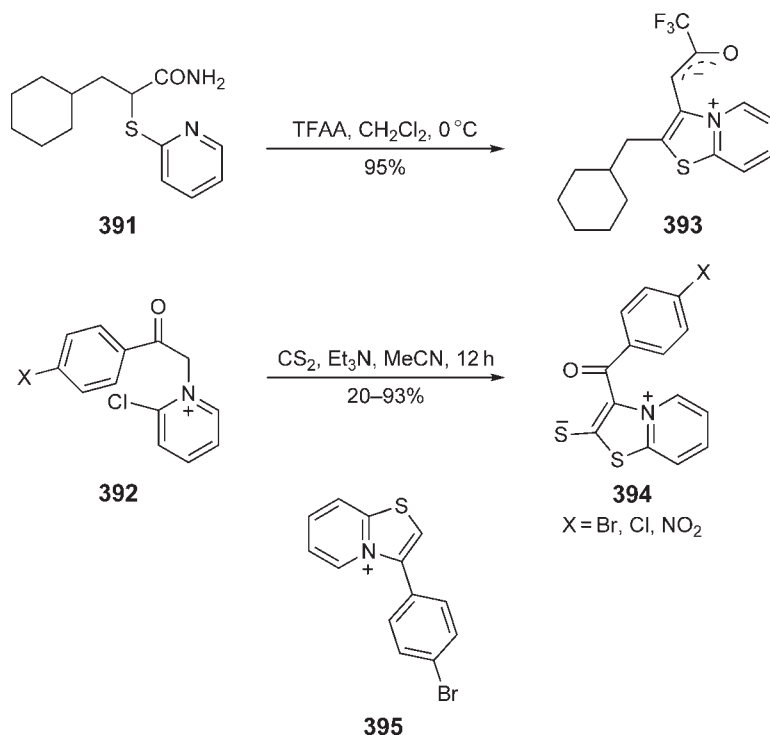
Natural compounds



Synthetic compounds



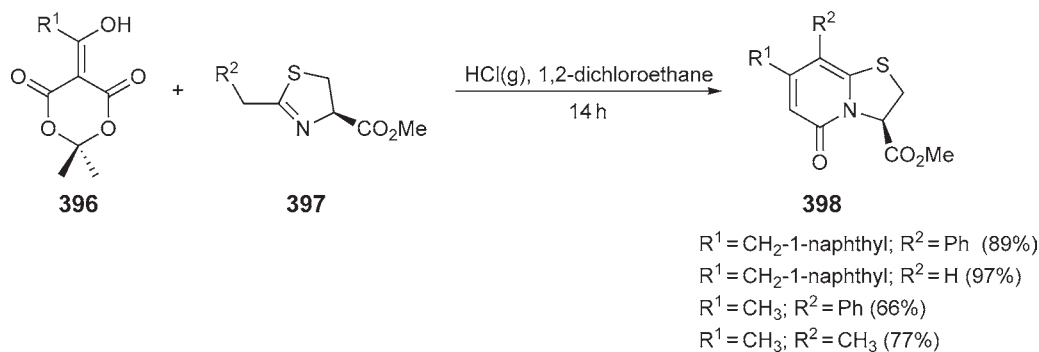
Scheme 101



Scheme 102

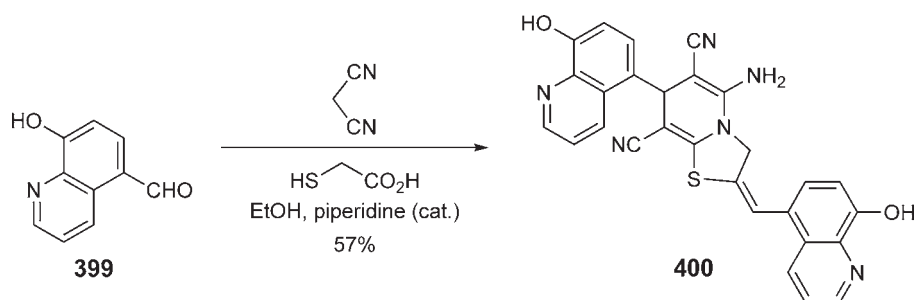
11.10.8.2 Ring Syntheses of Fully or Partially Saturated Rings from Acyclic Compounds

An enantioselective synthesis of 2-pyrimidones **398**, resulting from the condensation of a Δ^2 -thiazoline **396** and Meldrum's acid derivative **397**, was reported to occur without (or minimal) racemization, provided that the reaction is run in 1,2-dichloroethane [<2001JOC6756>](#). Its mechanism has been investigated in detail [<2004JA13002>](#). This reaction was improved later on by using microwaves [<2003MOD165>](#), and these compounds were shown to undergo Mannich reaction under microwave irradiation without severe erosion of the optical purity [<2004JOC7830>](#) ([Scheme 103](#)).



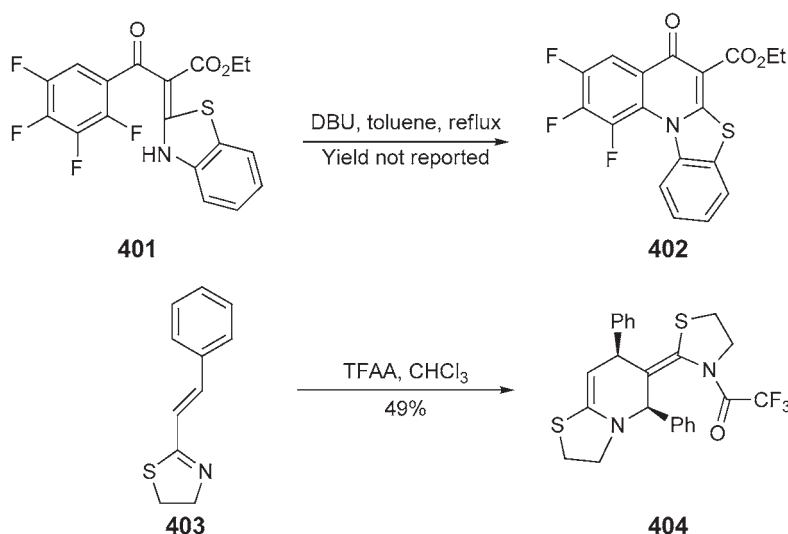
Scheme 103

The reaction of malononitrile, thioglycolic acid, and aldehyde **399** was found to produce compound **400** in fair yield when treated with a catalytic amount of piperidine ([Scheme 104](#)) [<2000FA109>](#).



Scheme 104

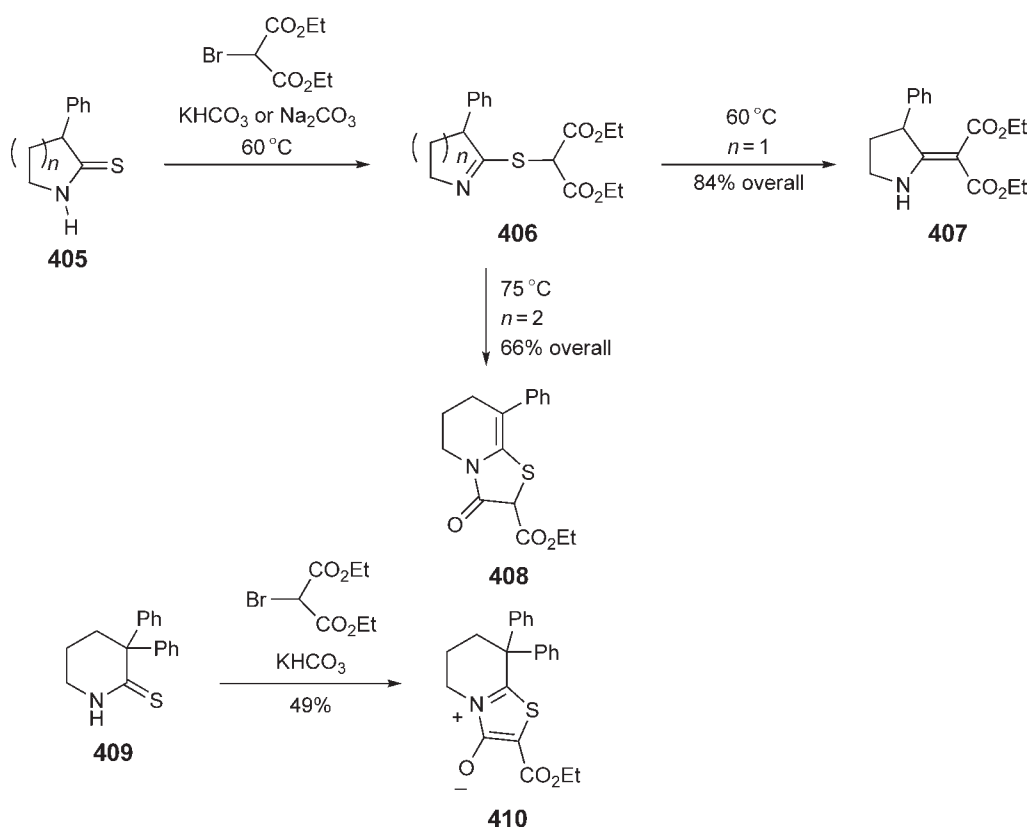
Compound **402** has been prepared in the course of a structure-activity study of new antibacterials <1999BML1339>. The key step for its synthesis relies on an intramolecular S_NAr reaction from **401**, to close the six-membered ring. The yield of this reaction is, however, not mentioned. Dimerization of 2-alkenylthiazolines such as **403** in the presence of trifluoroacetic anhydride provides a straightforward access to **404** <2001TL4937> (Scheme 105).



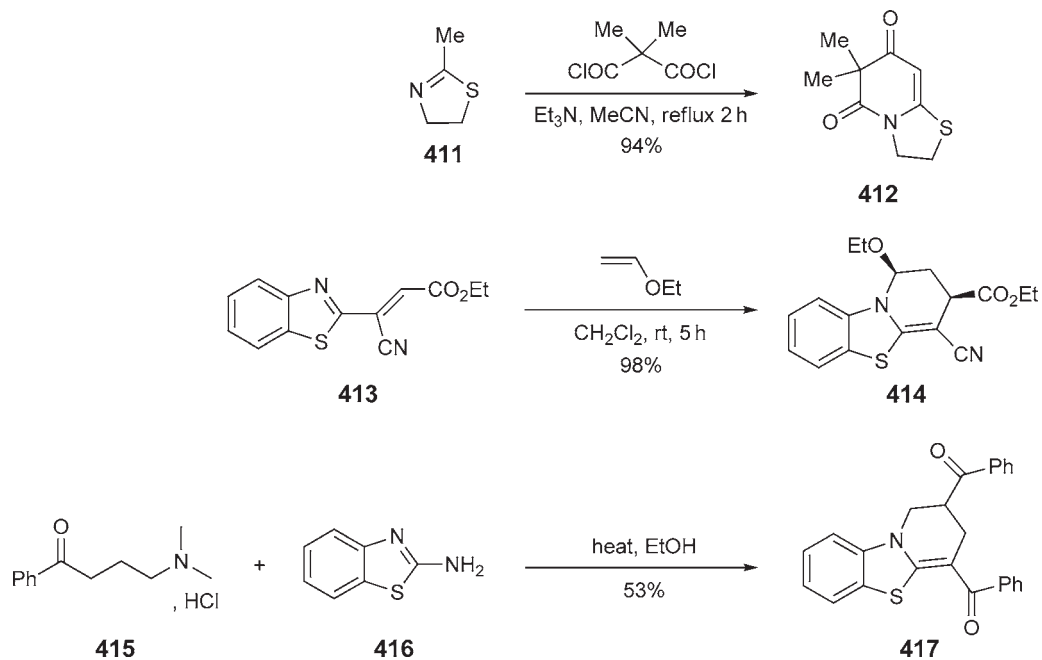
Scheme 105

The extrusion of sulfur from organic sulfides is a useful reaction best exemplified by the Eschenmoser sulfide contraction and has found many applications in synthesis of nitrogen heterocycles. In this reaction, thioamides are treated with enolisable α -halocarbonyl compounds, to form α -thioiminium salts. Recently, it was demonstrated that the size of the thiolactam is a very important parameter for the success of this reaction. As a matter of fact, six-membered ring thiolactams produce bicyclic ketene acetals **408**, whereas the expected β -amino ester **407** is produced from **406** ($n = 1$) <2001J(P1)2055>. Starting from **409**, the thioisomünchone **410** was isolated (Scheme 106). More recently, it was found that the nature of the base used in this reaction is also an important parameter and that important amounts of bicyclic thiazolidinone can be produced by using DBU <2004TL1437>.

Some partially saturated derivatives of this heterocycle can be prepared following a strategy involving the closure of the six-membered ring. Following this strategy, a straightforward preparation of *N*-acyl- β -keto cyclic ketene-*N,S*-acetals **412** from 2-alkylthiazolines **411** was recently disclosed <2005TL2045>. Similar derivatives **414** can be prepared from the highly reactive 1-aza-1,3-butadiene **413** through a Diels–Alder reaction <1996T733>, or from the reaction of Mannich base **415** with 2-aminobenzothiazole **416** <2002J(P1)555>. Only a single example is shown for clarity in Scheme 107; but all these syntheses are of reasonable scope.

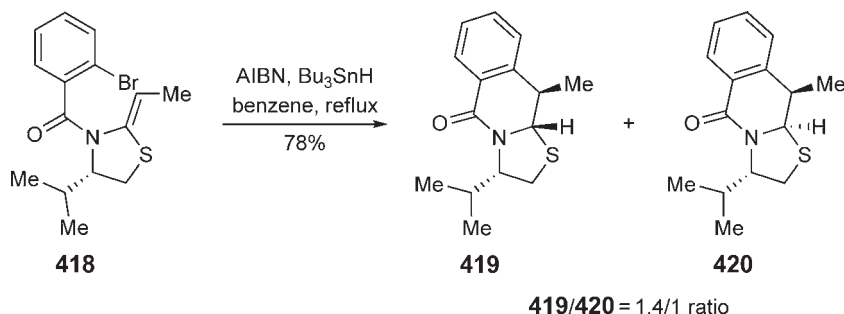


Scheme 106



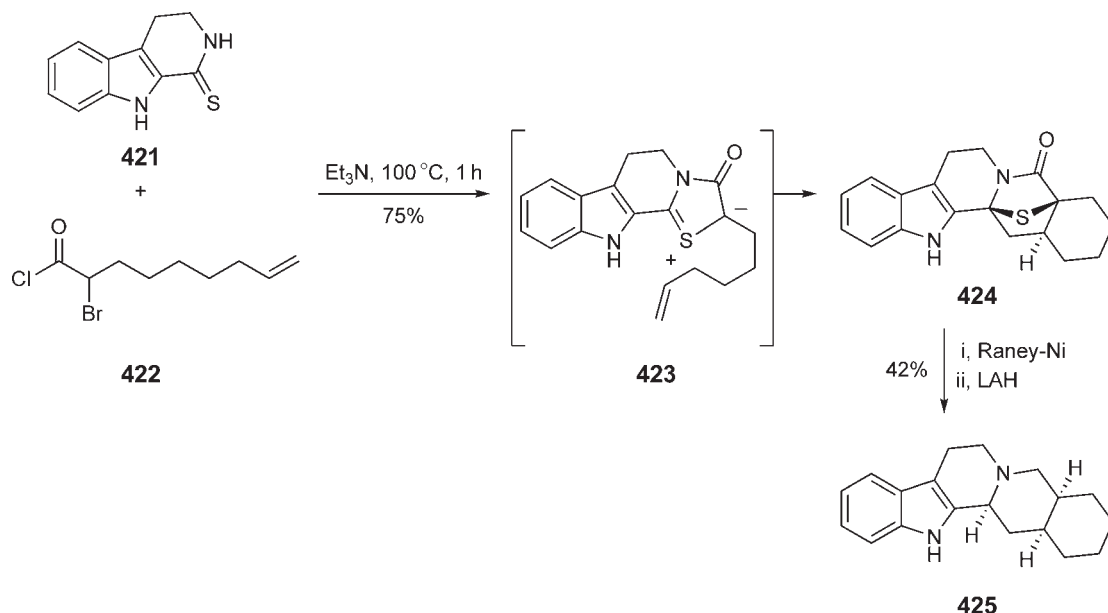
Scheme 107

Partially saturated derivatives can also be prepared through aryl radical cyclization of *N*-2-halobenzoyl cyclic ketene-*N,S*-acetals [<2005TL3801>](#). In this event, treatment of ketene-acetal **418** with Bu₃SnH afforded good yield of cyclized products **419** and **420**, as a mixture of two diastereoisomers, but with a total regioselectivity ([Scheme 108](#)).



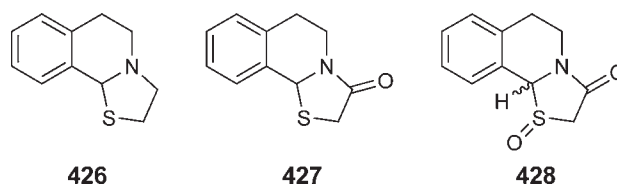
Scheme 108

An elegant one-pot bicycloannulation method for the synthesis of tetrahydroisoquinoline systems has been disclosed by Pawda *et al.* [<1998TL4757, 2000JOC2684>](#). This method generates a transient thioisomünchnone **423** that undergoes an intramolecular dipolar cycloaddition. The thus obtained cycloadduct **424** is next reduced with Raney-Ni, followed by LAH to furnish (±)-alloyohimbane **425** in 31% overall yield from **421** ([Scheme 109](#)).



Scheme 109

A series of thiazolo[2,3-*a*]isoquinolines **426**, 3-one derivatives **427**, and *S*-oxide derivatives **428** have been studied in detail as regard to their spectroscopic properties [<2001T3499, 2002TA2329, 2003T1173>](#). These compounds have been prepared using previously reported chemistry. One of the 3-one derivatives **427** was prepared in enantiomerically pure form and therefore gave access to optically enriched **428**. Isolated diastereoisomers of this *S*-oxide were however found to be unstable and to epimerize to give a thermodynamic mixture of *syn*- and *anti*-diastereoisomers. This epimerization was accompanied by a racemization ([Scheme 110](#)).



Scheme 110

11.10.8.3 Important Compounds and Applications

The addition of a covalent link between C5 of proline ring and the adjacent amino acid locks the amide bond into the *trans* configuration. This strategy has been thoroughly used for the modification of bioactive peptides, and the bicyclic thiolactam **429** has proved to be a very good tool for this purpose (Scheme 111). This compound is stable towards epimerization under physiological conditions, and is furthermore commercially available from Neosystem company (SNPE North America LLC): Fmoc-BTD, catalog number FB02601. Therefore, an important amount of work has been devoted for the preparation of modified peptides derived from this scaffold <1997BML331, 1998JME3664, 2002BML733, 2004BML6129>.



Scheme 111

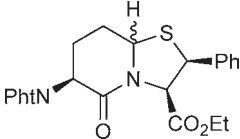
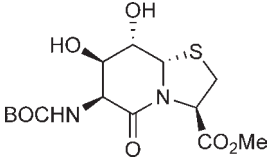
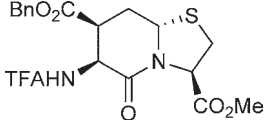
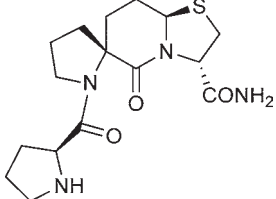
A number of compounds derived from the basic peptidomimetic **429** have been prepared for different purposes in medicinal chemistry. In most cases, the source of the sulfur atom is cysteine. Some examples of structures and targeted applications are reported in Table 17.

Table 17 Structure of some peptidomimetics based on fully saturated thiazolo[3,2-*a*]pyridine skeleton

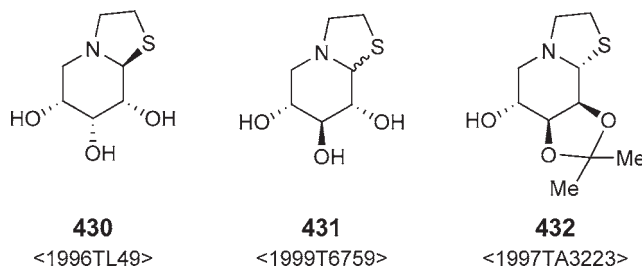
Structure	Application	Reference
	Substrate for the design of thrombin inhibitors	1999BML913, 1997TL8807
	Hypoglycemic agent	1998JME4556

(Continued)

Table 17 (Continued)

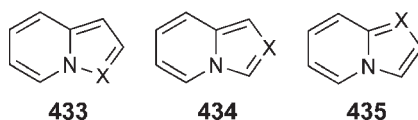
Structure	Application	Reference
	Leu-enkephalin analogues	2003CC1598
	Carbohydrate-derived peptidomimetic	2003EJO878
	Asp-Gly dipeptide mimetic	2004TL3245
	Peptidomimetic of L-propyl-L-leucyl-glycinamide	1999JME628

Polyhydroxylated indolizidines have attracted considerable interest due to their potent activity as glycosidase inhibitors. Some analogues of these molecules bearing a sulfur instead of a carbon atom at the anomeric position such as **430–432** have been prepared (**Scheme 112**). Compound **431** was shown to give a 3/7 mixture of epimers at the anomeric position in D₂O.

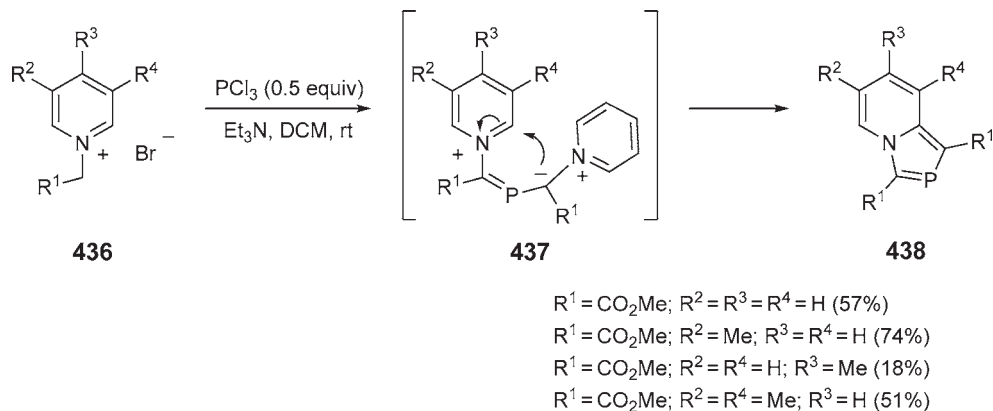
**Scheme 112**

11.10.9 Systems Containing a Less Common Heteroatom

Fully conjugated systems of general formula **433**, **434**, or **435** depicted in **Figure 8**, in which X = P, As, or Se⁺ have not been reported to our knowledge in literature in the past decade (1996–2006), though some examples have been reported in CHEC-II(1996) <1996CHEC-II(8)249>.

**Figure 8**

In fact, a single series of phosphorus-based heterocyclic compounds, 1,3-azaphospholo[5,1-*a*]isoquinolines (**435**; X = P), was reported together with their preparation through 1,5-electrocyclization of bis-(*N*-pyridinium ylidyl)phosphenium chlorides **437**, as shown in [Scheme 113](#) <1999TL1565>.

**Scheme 113**

Later on, it was demonstrated that these heterocycles can undergo Diels–Alder reactions in the presence of an electrophile (S_8 or MeI) and dienophiles <2002T1573, 2003HAC560>. These phosphorus-containing heterocycles were found to produce, upon reaction with tricarbonyl(cycloheptatriene)molybdenum(0) or tricarbonyl(mesitylene)tungsten(0), σ -complexes of the type $L_2M(\text{CO})_4$ or $L_3M(\text{CO})_3$ instead of π -complexes <1998EJI1079>. Some derivatives of this heterocycle were also found to display remarkable antibacterial activity <2005BML937>.

11.10.10 Further Developments

Since the writing of this chapter the following articles have been published with regard to the synthesis of imidazo[1,5-*a*]pyridines: <2007MI390, 2006TL3225, 2007TL4553>.

The following articles have also been published for the synthesis of imidazo[1,2-*a*]pyridines: <2006BMCL5598, 2007BMCL3558, 2007BMCL403, 2007TL3217, 2007JCO267, 2007TL4079>.

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1986JOC4475	D. S. Grierson, J. Royer, L. Guerrier, and H.-P. Husson, <i>J. Org. Chem.</i> , 1986, 51 , 4475.
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Biographical Sketch



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11.11

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: One Extra Heteroatom 0:1

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11.11.1 Introduction

The heterocycles covered in this chapter are shown in [Figure 1](#). In most of the cases the correct names are given. In the case of biologically relevant compounds as natural products the term indolizine or indolizidine preceded by the name of the other heteroatom is used (e.g., azaindoline). The trivial name diketopiperazine is also used for structure [11](#), especially when derived from dipeptides. In [Figure 1](#), the fully conjugated rings are reported, although nonconjugated and fully saturated products will also be covered in this chapter. In some cases, only one of the *H*-isomers is shown; when known, other isomers will appear in the chapter.

CHEC-II(1996) covers more than 100 examples of this kind of heterocyclic compound [<1996CHEC-II\(8\)287>](#). There are no specific reviews dealing directly with these heterocyclic systems. On the other hand, the saturated systems have been included in several review articles, [<2004CRV2667, 2005CRV2765, 2002NPR223, 2000NPR7>](#). The use of some of these heterocycles in medicinal chemistry has also been reviewed [<2000BMC1213>](#).

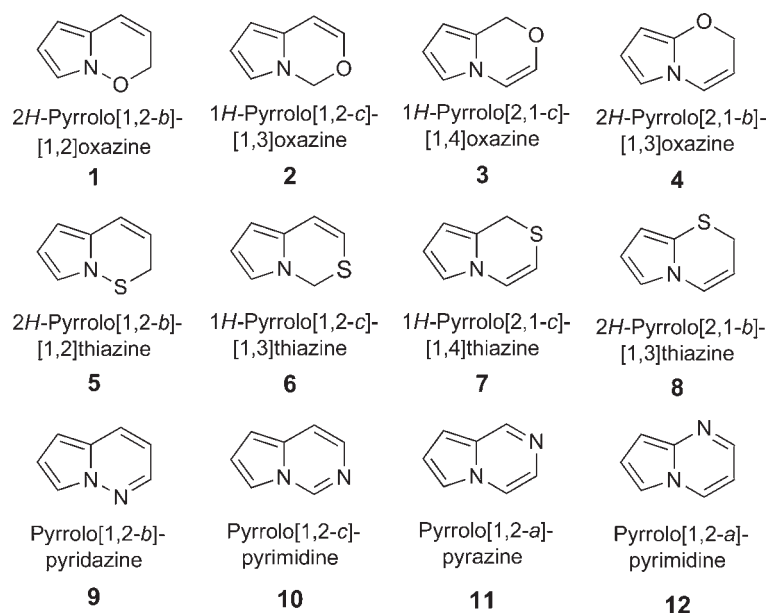
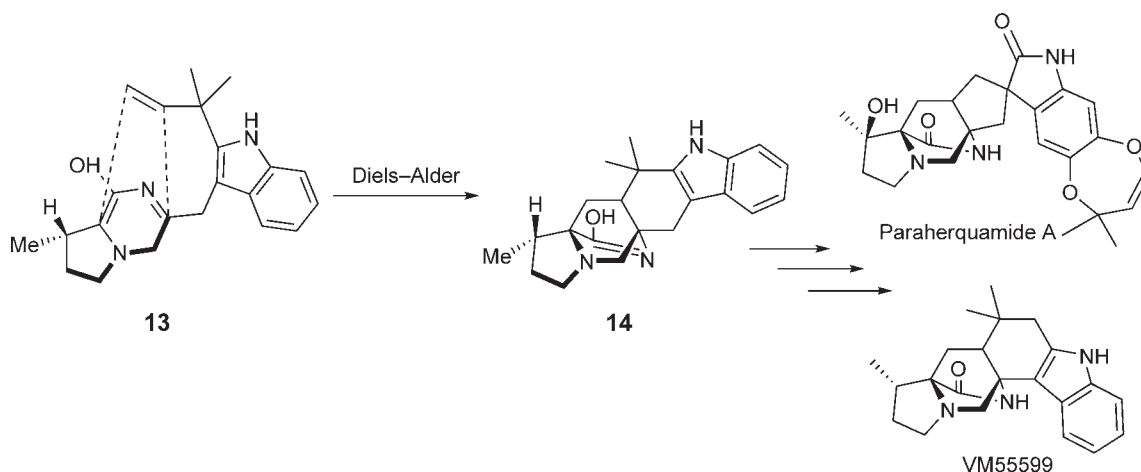


Figure 1

11.11.2 Theoretical Methods

A theoretical model derived from crystal structure data has been described for cyclic dipeptides (piperazin-2,5-diones) such as cyclo(L-Pro-Gly), cyclo(L-Pro-L-Leu), and cyclo(L-Pro-L-Ala). Conformations resulting from minimization of energy calculated using molecular mechanics were compared with traditional *ab initio* and density functional theory (DFT) geometric optimizations for each dipeptide. In all computational cases, the gas phase was assumed. The transition feature of the ultraviolet (UV) circular dichroism (CD) spectra was predicted for each peptide structure via the classical dipole interaction model. By coupling MP2 or DFT geometric optimizations with the classical physics method of the dipole interaction model, significantly better CD spectra were calculated than those using geometries obtained by molecular mechanics <2005PCA5463>.

DFT calculations have been used to study the mechanistic pathway of the intramolecular Diels–Alder cycloaddition involved in the biosynthesis of natural products paraherquamide A and VM55599. The cycloaddition involves a dihydropyrrolo[1,2-*a*]pyrazine as the azadiene and a standard alkene as the dienophile (Scheme 1). Analysis of the results reveals that these cycloadditions take place through concerted transition structures associated with [4+2]



Scheme 1

processes. Taken as a whole, these results show a reasonable agreement with the available experimental data <2003JOC2895>. The analysis of the activation parameters for synthetic models of the inter- and intramolecular cycloadditions furnishes a rationalization for a spontaneous cyclization process in the biosynthesis of the paraherquamide and VM55599.

The electronic structures of the unsaturated pyrrolo[1,2-*c*]pyrimidine **15** and the corresponding *N*-protonated species **16** in Figure 2 were studied using *ab initio* molecular orbital (MO) techniques. Molecular structures were obtained by geometric optimization using the Schlegel's algorithm. All theoretical calculations were performed at the closed-shell self-consistent field level (restricted Hartree–Fock, RHF), and the electron correlation effect was introduced through the second-order Möller–Plesset (MP2) theory, using the frozen-core approach <1999JOC7788>.

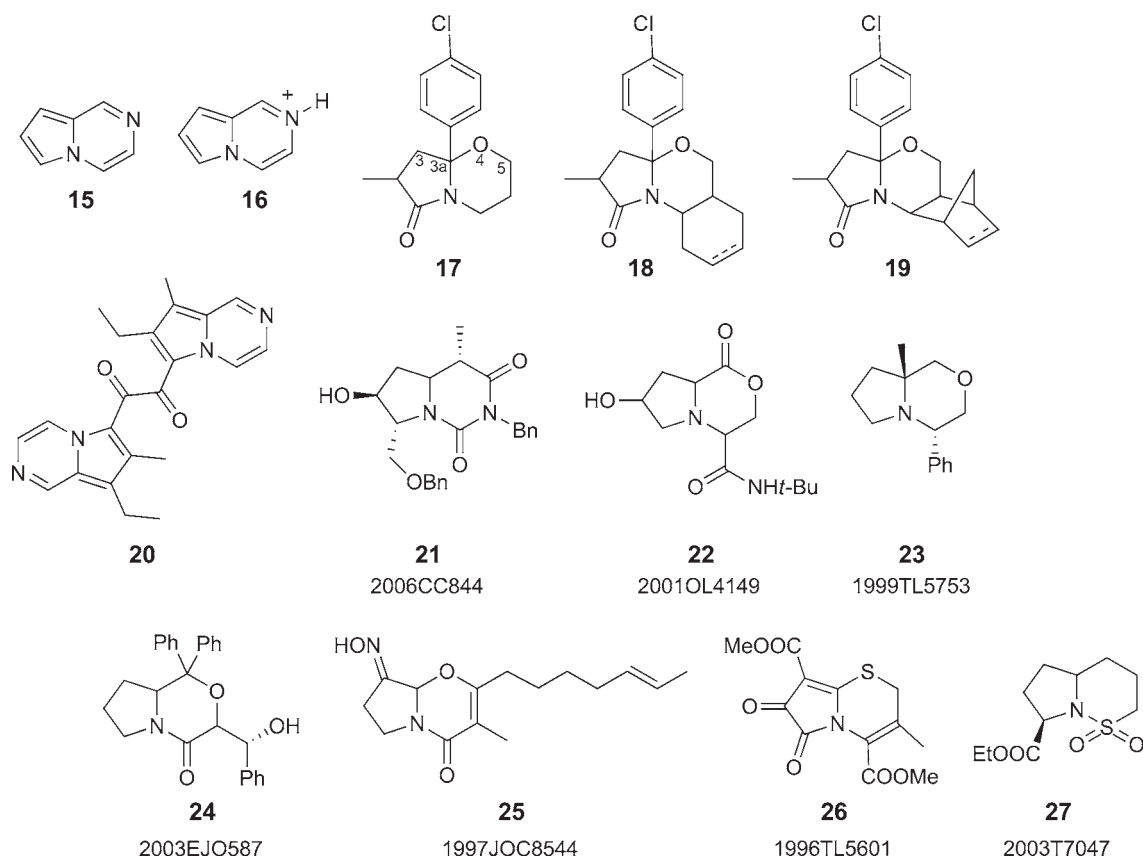


Figure 2

11.11.3 Experimental Structural Methods

A complete structure determination of the bicyclic hypoglycemic oxazines **17–19** has been described by ^1H , ^{13}C , nuclear Overhauser effect (NOE) difference, correlation spectroscopy (COSY) and heteronuclear multiple quantum correlation (HMQC) nuclear magnetic resonance (NMR) <1999J(P2)2011>, and electron ionization-induced fragmentations <1999JAM393>. The stereochemical arrangement was also determined by X-ray diffraction. From this study, it was shown that the oxazine ring has a very regular chair conformation and the five-membered ring has a conformation which is somewhere between a flat half-chair and an envelope with the carbon in position C-3 as the flap atom. Also the *trans*-fused oxazine shows a rather regular chair conformation with some puckering around the carbon in position 5. On the other hand, in the *cis*-fused compounds, the oxazine ring is more puckered at the O(4)–C(5) region around the oxygen and flattened in the pyrrole fusion region. The five-membered rings have in all cases a conformation which is somewhere between a flat half-chair and an envelope with the carbon in position C-3 as

the flap-atom. The characterization has been improved by the fragmentation patterns where a series of striking differences were observed due to highly stereospecific retro-Diels–Alder (RDA) fragmentation <1999JAM393>.

Most of the reported X-ray studies have been carried out to establish structures or conformations of different compounds. The X-ray of fully conjugated diene compound **20** has been reported showing supramolecular assemblies resulting in a π -stacking interaction between two adjacent molecules <2004TL7363>. The other structures reported in Figure 2 have been determined and parameters described in the corresponding papers.

Several structure determinations of hexahydropyrrolo[1,2-*a*]pyrazine-1,4-diones (diketopiperazines) via NMR spectroscopy and mass spectrometry (MS) have been described. The corrected structure of the major diketopiperazine produced by the sponge *Geodia baretii* previously named as berrettin **28** has been reported in a paper that contains all the NMR data of the heterocyclic system <2002TL3385>. Another series of diketopiperazines (**29–34**, Figure 3), have been isolated from the marine-derived fungus *Chromocleista* sp. and their structures determined on the basis of MS, NMR experiments, and derivatization methods <2006JNP580>. The structures of diketopiperazines contained in a library **35** of synthetic origin have been accurately determined using spectroscopic methods in solution <2000JOC2179> and even on the molecules directly linked to the insoluble supports where they have been prepared from **36**, using high-resolution magic angle spinning (HRMAS) NMR spectroscopy <2000JCO681>. The adduct of hexahydropyrrolo[1,2-*a*]pyrimidine with tetrahaloborate anions have been prepared and isolated by reaction of the simple heterocyclic amidine with a previously formed amidine-mixed boron trihalide salt. The resulting stable adduct **37** was isolated and fully characterized via ^1H and ^{13}C NMR spectroscopy <1996CJC2131>.

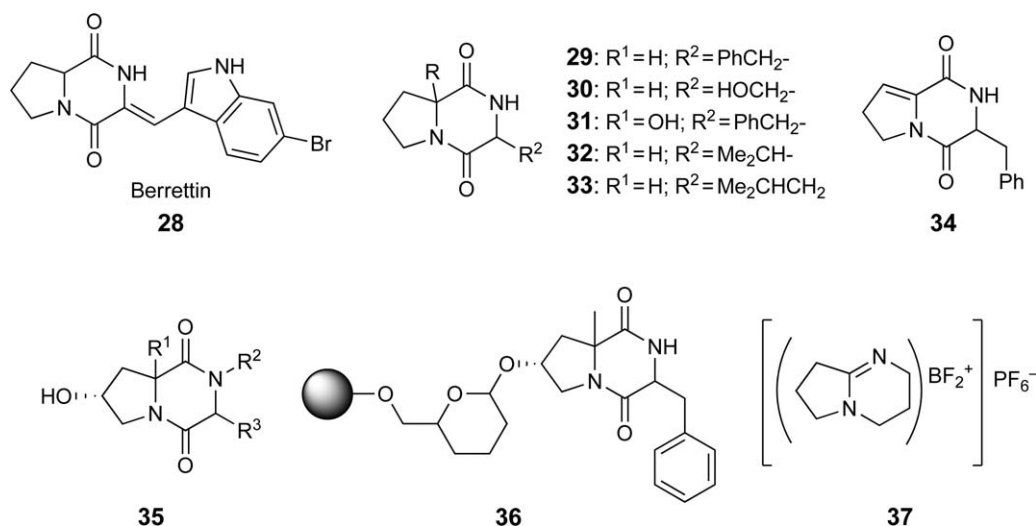


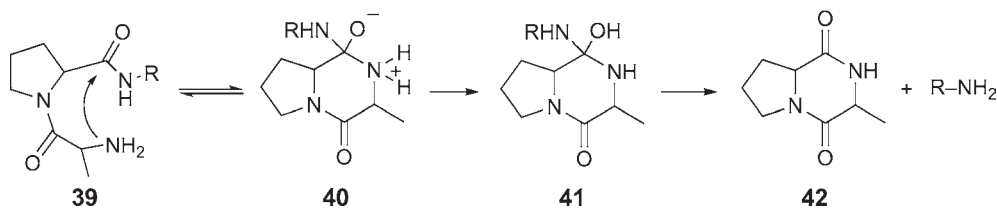
Figure 3

The first study of the energy of small cyclic peptide cation fragmentation has been reported for the cyclo(Pro-Gly) **38** system. The major primary decomposition reactions of the radical cation at low energy were found to be HNC loss and CO elimination. The heat of formation and vibrational frequencies of the reactant were calculated by DFT <1998JMP25>. Compound **38** has also been the object of a study related to the parent and fragment ion kinetic energy distributions by the peptide ions scattered on a hexanethiolate monolayer on Au^{111} <1999JMP217>. Most of the heterocycles covered in this chapter have been fully characterized by classical spectroscopic methods but they are cited in the parts related to their synthesis or reactivity.

11.11.4 Thermodynamic Aspects

The kinetics of the transformation of the peptide H-Ala-Pro-NH_2 into the corresponding diketopiperazine has been investigated in a large number of solvents, including aprotic and hydroxylic solvents. The study revealed that the first-order rate constant is considerably affected by the nature of the solvent and that the alkylammonium carboxylate

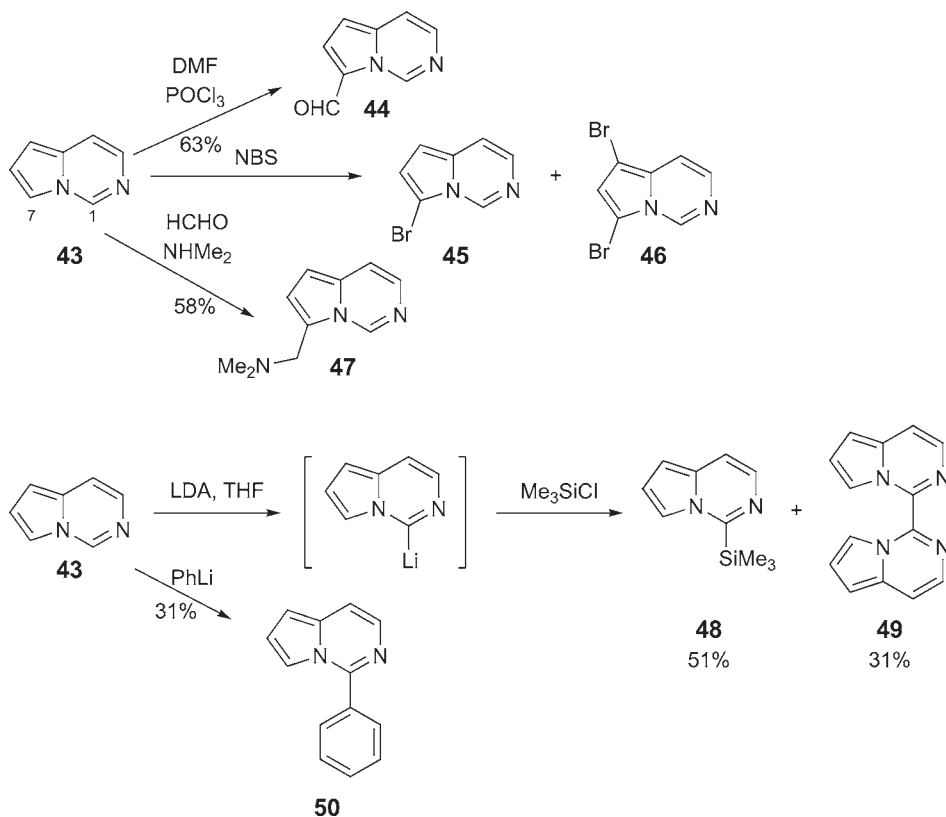
salt is an efficient catalyst of the reaction [<1999J\(P2\)329>](#). The reaction rate is retarded by solvents with a high capacity to stabilize solutes that are charged or dipolar, and that are hydrogen donors and/or acceptors. Moreover solvents with high cohesive energy density values significantly increase the reaction rate. The reaction of formation of the diketopiperazine involves the pre-equilibrium attack of the *N*-terminal amino group on the carbonyl carbon of the second residue, giving the zwitterionic cyclic intermediate **40** in an acid–base equilibrium with species **41** ([Scheme 2](#)). The step from the neutral form is prevalent and rate determining from acidic to moderately basic pH.



Scheme 2

11.11.5 Reactivity of the Fully Conjugated Rings

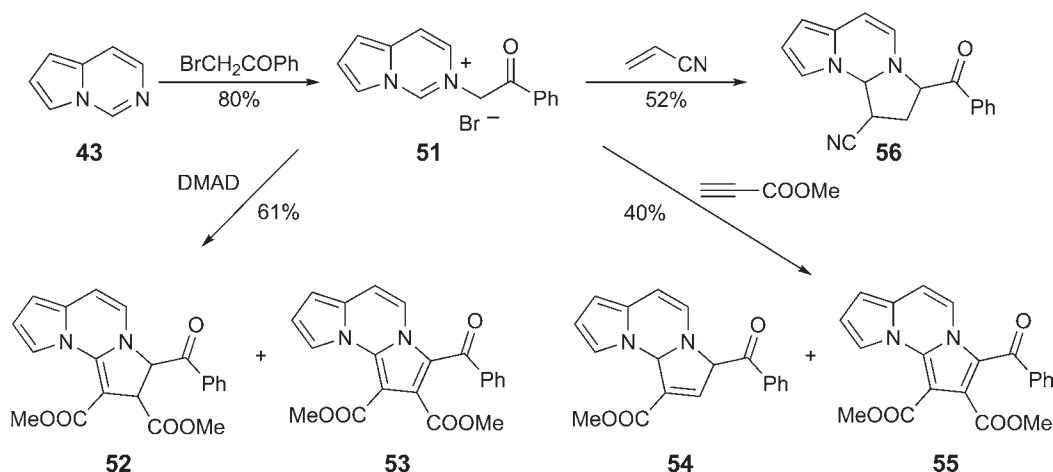
Due to the nature of the systems covered in this chapter, there are very few reports regarding the synthesis and the reactivity of the fully conjugated rings. Pyrrolo diazine **43** is a potentially useful intermediate in the synthesis of novel 2,2-bis-azole derivatives and in the preparation of heteroaromatic polycyclic cations with quaternary nitrogen, which are potential antitumor DNA intercalating agents. Compound **43** undergoes classical electrophilic aromatic substitution such as the Vilsmeier–Haack reaction with dimethylformamide (DMF) and phosphorus oxychloride that gave compound **44** formylated at position C-7 in moderate yield ([Scheme 3](#)), as predicted by theoretical calculations [<1999JOC7788>](#). Similarly, bromination of **43** with 1 equiv of *N*-bromosuccinimide (NBS) in CH_2Cl_2 occurred at



Scheme 3

C-7, giving the bromo derivative **45** together with the 5,7-dibromo compound **46** in 42% yield. However, the use of an excess of NBS gave exclusively the dibromo compound **46** in good yield (77%). The Mannich reaction on substrate **43** occurred at position C-7, giving the 7-dimethylaminomethyl derivative **47** (Scheme 3). Treatment of **43** with 1.1 equiv of the non-nucleophilic base, lithium diisopropylamide (LDA), at -78°C , followed by the addition of different electrophiles (such as Me_3SiCl) gave the 1-substituted derivatives **48** together dimeric compound **49** (Scheme 3). Even nucleophilic addition occurred at the C-1 position, as it was shown in the reaction of **43** with phenyllithium that generated 1-phenyl-1,2-dihydropyrrolo[1,2-*c*]pyrimidine **50**.

Quaternarization of **43** with phenacyl bromide produced the corresponding salt **51** that was reacted with several triple-bond-containing dipolarophiles (Scheme 4), such as dimethyl acetylenedicarboxylate (DMAD) or alkyl propiolates to give tricyclic compounds **52**, **53** and **54**, **55**. Compound **51** reacted also with acrylonitrile as dipolarophile in $\text{MeCN}/\text{K}_2\text{CO}_3$ to give the cycloadduct **56** as a mixture of diastereoisomers.

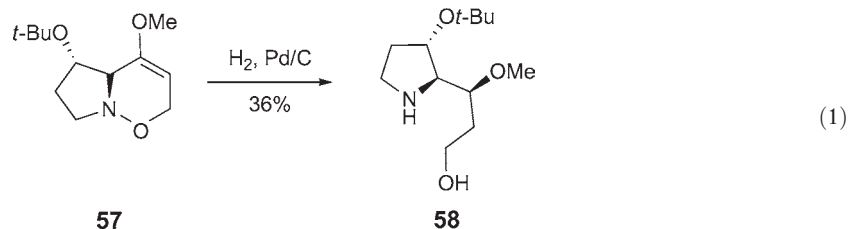


Scheme 4

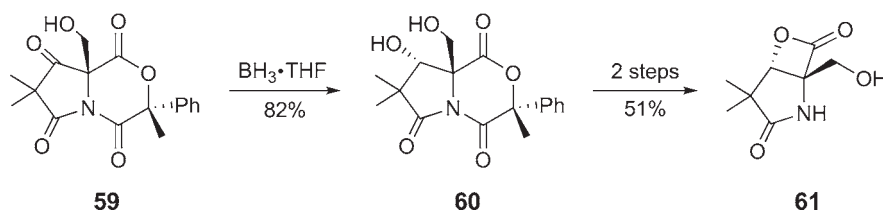
11.11.6 Reactivity of the Nonconjugated Rings

11.11.6.1 Reduction and Oxidation

1,2-Oxazines are prone to hydrogenolysis since the relatively weak N–O bond is easily cleaved. This reaction has often been employed for the transformation of this cycle (generally obtained from nitrones) into amino alcohols in a stereocontrolled manner. For example, reaction of **57** with hydrogen and palladium on charcoal as catalyst (Equation 1) furnished the expected substituted pyrrolidine **58** in moderate yields <2003EJO1153>.

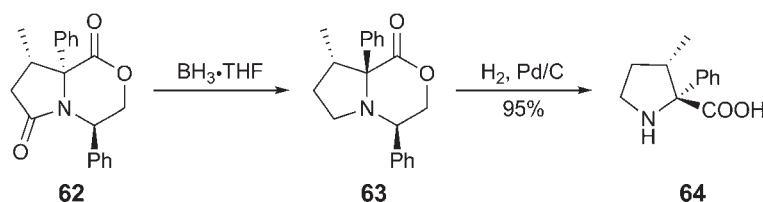


Compound **59** was prepared in six steps starting from *N*-(*p*-methoxybenzyl)glycine ethyl ester and (*R*)-*O*-acetyl-lactolactic chloride, as reported in Section 11.11.7.3. Stereoselective reduction of **59** with BH_3 at the carbonyl in position 8 (the only ketone among the other carbonyls) gave compound **60** in high diastereomeric purity (>95%). This diol was further opened in basic conditions and lactonized (Scheme 5) to produce an omuralide analogue **61** which can be potentially selective for proteasome inhibition <2001OL1395>.



Scheme 5

In the search of new methodologies for the asymmetric synthesis of nonproteinogenic amino acids, 8-methyl-4,8a-diphenyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6(7*H*)-dione **62**, obtained as described in [Scheme 24](#) ([Section 11.11.7.3](#)), was selectively reduced at the lactam carbonyl with BH_3 and further opened by hydrogenolysis to give *syn*-disubstituted proline derivative **64** in 95% yield [<1997SL935>](#) ([Scheme 6](#)). It is noteworthy that hydrogenolysis did not affect the benzylic position of bicyclic compound **63**.



Scheme 6

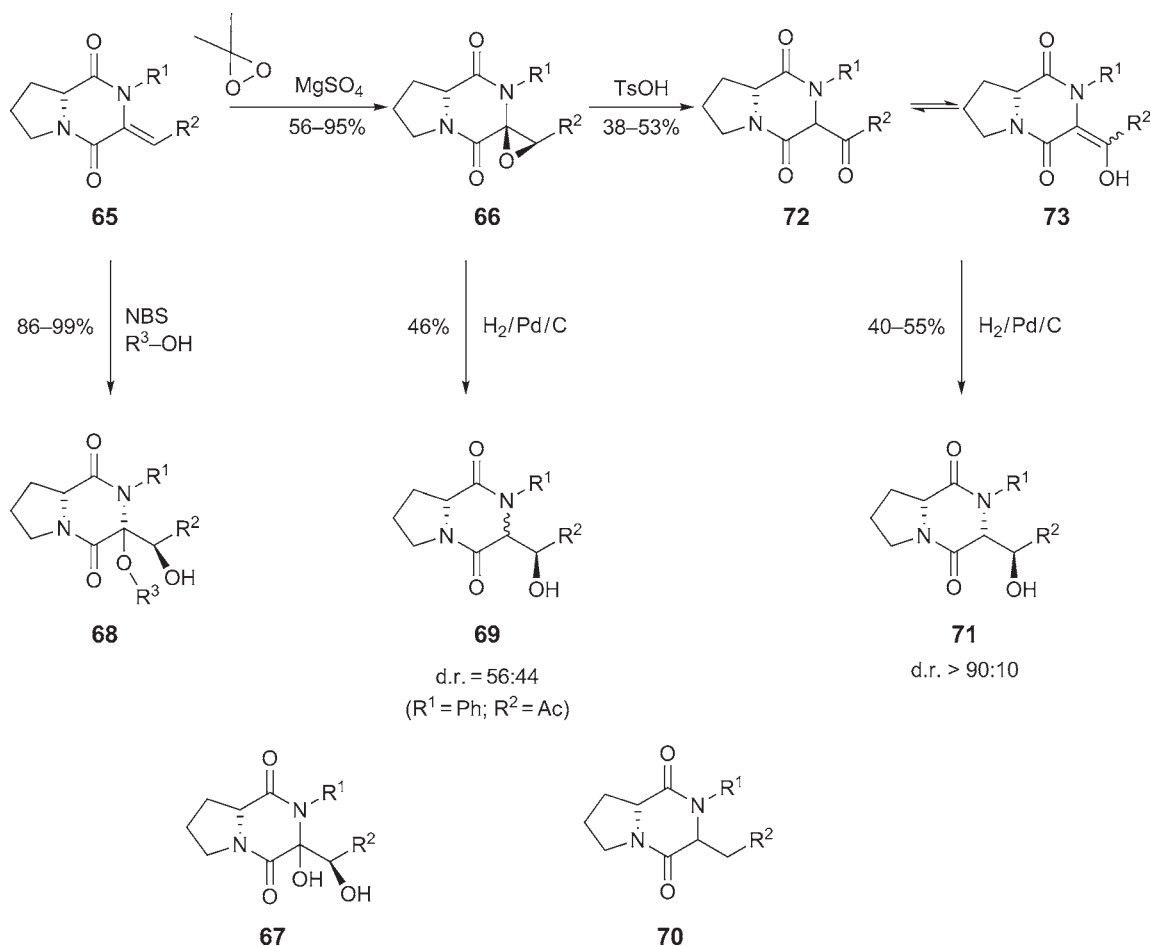
Alkylidene hexahydropyrrolo[1,2-*a*]pyrazine-1,4-diones (such as compound **65**, [Scheme 7](#)) have been submitted to different selective oxidations of the double bond. Epoxidation with dimethyldioxirane gave access to spirooxiranes **66** together with diols **67** when R^2 was H or Me. Bromohydroxylation and bromoalkoxylation of the same substrate gave high yields of enantiomerically pure 3-(1-bromoalkyl)pyrazine-2,5-dione **68**. On the other hand, direct hydrogenation of the intermediate epoxide **66** afforded epimeric mixtures of 3-(1-hydroxyalkyl)pyrazine-2,5-diones **69** and, in some cases, the completely deoxygenated derivative **70** was obtained. The stereoselective transformation of **66** into **71** (>80% de) was possible by primary acid cleavage of the oxirane ring to give the ketone **72** in tautomeric equilibrium with the enol form **73**. During further hydrogenation, conditions must be controlled since extended reaction times gave rise to the formation of 3-alkylpyrazine-2,5-diones **70**, which are probably formed by elimination of water from **71** with regeneration of product **66** that is further hydrogenated ([Scheme 7](#)) [<2003S67>](#).

11.11.6.2 Substitutions

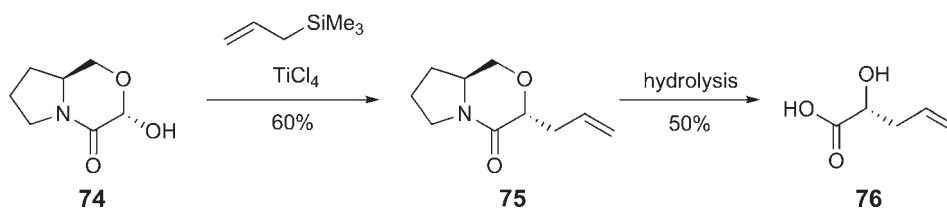
Tetrahydropyrrolo[1,4]oxazine **74**, obtained by photoinduced electron-transfer (PET) oxidative activation of substituted prolinol, undergoes nucleophilic substitution of the OH at position C-3 with allyltrimethylsilane in the presence of TiCl_4 ([Scheme 8](#)). The reaction was highly stereoselective and produced, after hydrolysis of the resultant amide **75**, optically active α -hydroxy acid **76** together with the auxiliary (*S*)-prolinol that can be effectively recycled [<1998TL7153>](#).

11.11.6.3 Ring-Opening Reactions

There are several reports dealing with the use of tetrahydropyrrolo[1,4]oxazinones derived from natural proline or prolinol as chiral auxiliaries for the synthesis of enantiomerically pure compounds. The preparation of the heterocycle is described in [Scheme 33](#) ([Section 11.11.7.4](#)). The presence of a rigid bicyclic skeleton allows stereoselective introduction of different substituents. The final ring opening of the system (generally by hydrolysis) provides enantiomerically pure compounds with the possibility of recycling the starting chiral auxiliary.



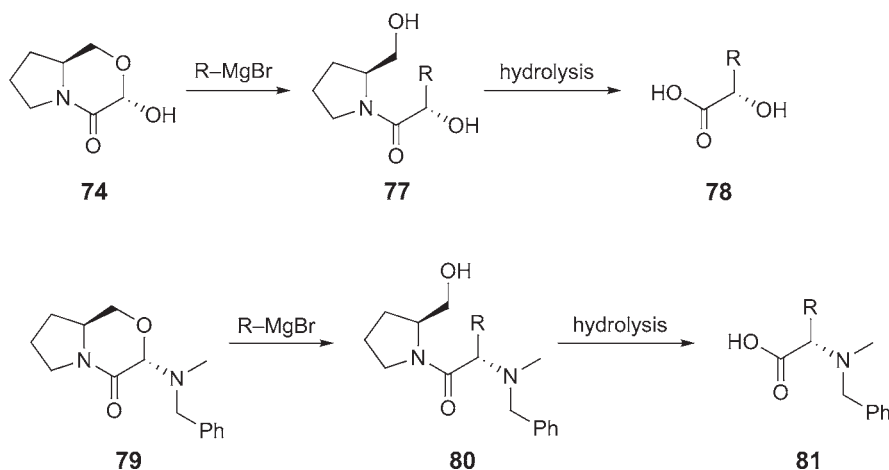
Scheme 7



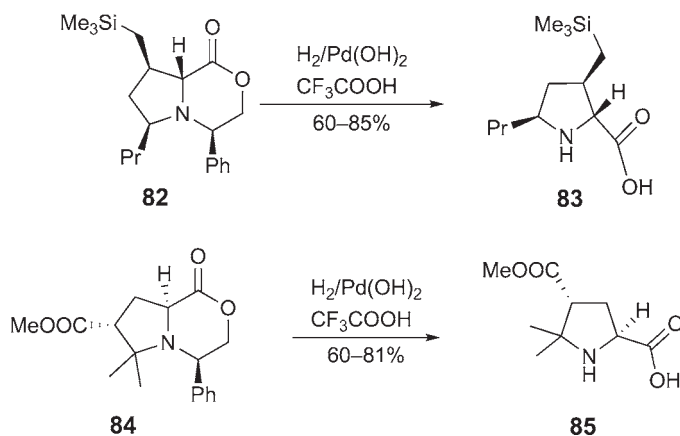
Scheme 8

The oxazinone **74** undergoes ring opening with Grignard reagents and, after hydrolysis of the prolinol amide, it was transformed into the hydroxy acids **78** (Scheme 9) <2000EJO657>. An analogous glycine-based template **79** was used for the preparation of chiral α -amino acids (doubly alkylated on the α -nitrogen, **81**) after ring opening with Grignard reagents followed by hydrolysis <1996TL3175>.

The hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one **82** (obtained by radical cyclization; see Section 11.11.7.3) was transformed into the proline derivative **83** by hydrogenation in the presence of the Pearlman's catalyst and a stoichiometric amount of trifluoroacetic acid (TFA) (Scheme 10). This reaction led with high yield to the disubstituted proline **83** in an enantiomerically pure form <2003SL1058>. In an analogous approach, the chiral (4*R*,7*R*,8*aS*)-methyl 6,6-dimethyl-1-oxo-4-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate **84** was hydrogenated on Pd(OH)₂ in the presence of TFA to give enantiomerically pure 5,5-dimethylproline derivatives **85** <2001SL1836> (Scheme 10).



Scheme 9

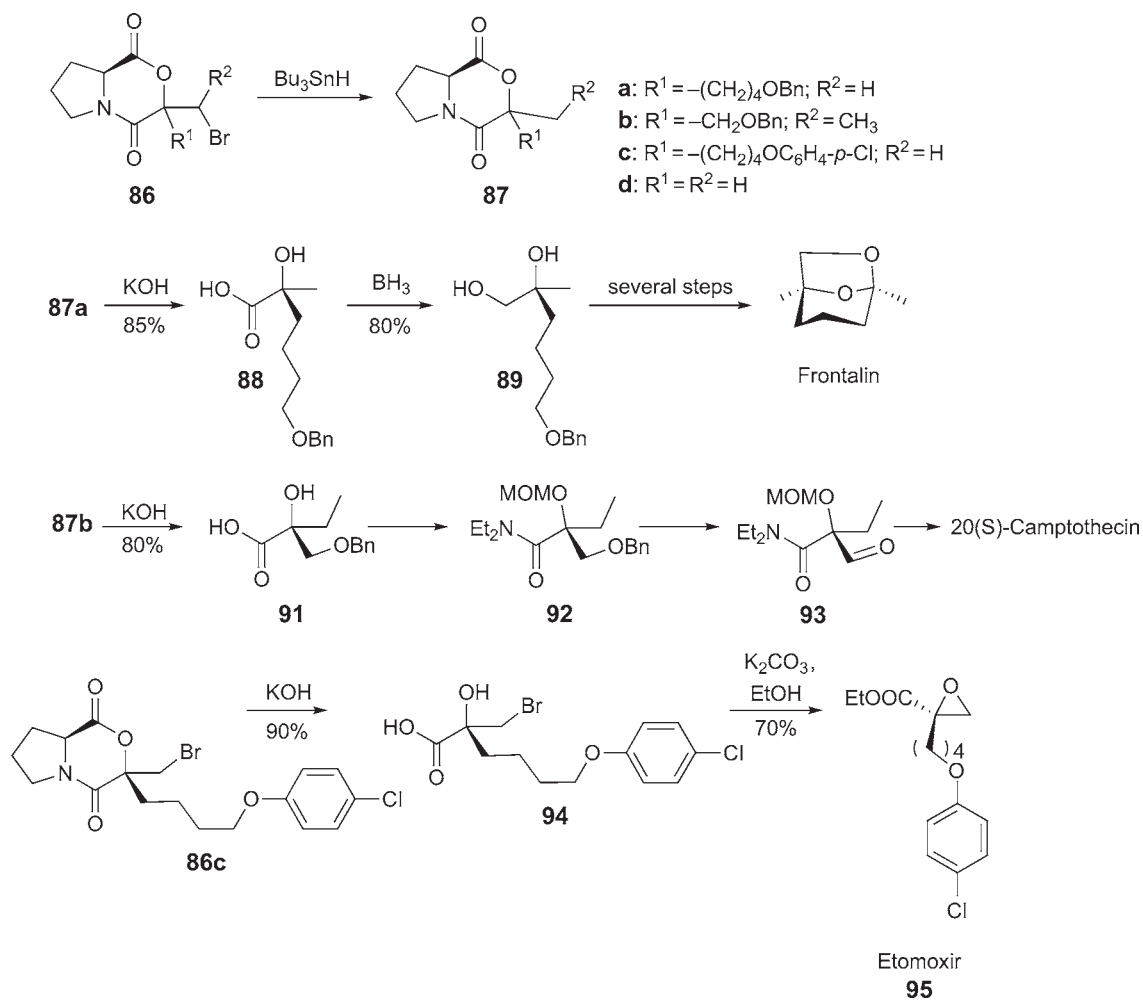


Scheme 10

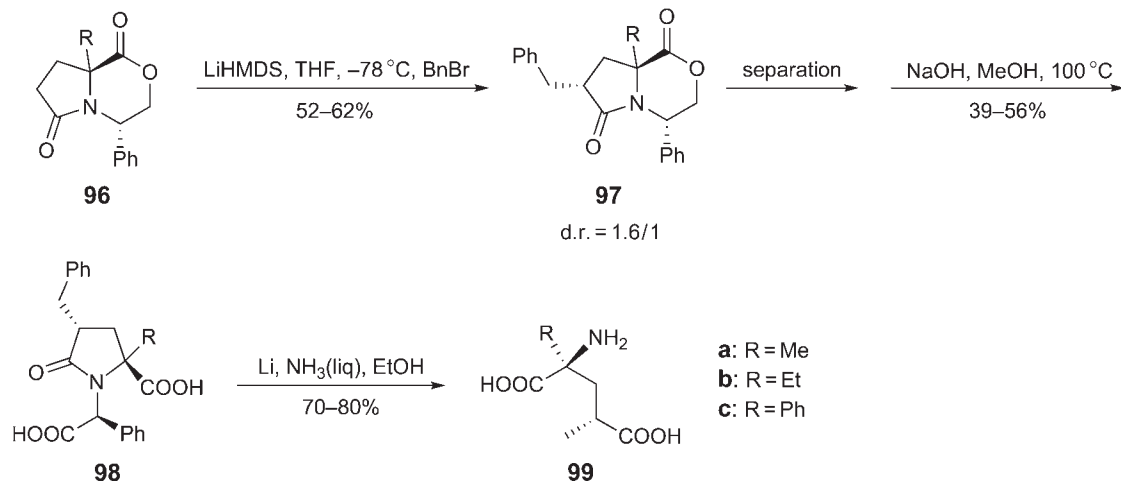
Enantiomerically pure tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,4(3*H*)-diones **86a–c**, obtained by stereoselective bromolactonization of the acrylamides derived from proline (see [Section 11.11.7.4](#)), are versatile intermediates for the synthesis of natural products or drugs. Compound **86a** was submitted to debromination with Bu_3SnH followed by ring opening in KOH and further reduction with BH_3 to give diol **89** that was then easily transformed into (*S*)-4-(2,2,4-trimethyl-1,3-dioxolan-4-yl)-1-butanol **90**, a key intermediate for (1*S*,5*R*)-(–)-frontalin, [<2002TA155>](#), one of the aggregation pheromones secreted from different species of pine beetles. The disubstituted compound **87b** was hydrolyzed and then rapidly transformed into enantiomerically pure (*S*)-*N,N*-diethyl-2-formyl-2-(*O*-MOM)-butyramide **93**, a versatile key intermediate for the synthesis of 20(*S*)-camptothecin analogues [<2000TA3985>](#). On the other hand, the brominated derivative **86c** was hydrolyzed to hydroxyacid **94** and finally cyclized to epoxide **95**, the powerful hypoglycemic agent etomoxir ([Scheme 11](#)) [<1997TA1187>](#).

A series of 8-substituted-4-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6-diones **96a–c** were alkylated by treatment with $LiHMDS$ followed by trapping with benzyl bromide to give compounds **97a–c** with a modest de in favor of the isomer reported in [Scheme 12](#) ($HMDS$ = hexamethyldisilazide) [<1999TL5753>](#). After separation of the major isomer, the ring opening with aqueous $NaOH$ in hot $MeOH$ gave the intermediate disubstituted pyroglutamic acids **98a–c**, suitable precursors of potential modulators of glutamate receptors **99a–c** [<2004T10547>](#).

Hydrolysis of the monolactim ethers **100a** and **100b** (derived from the Schöllkopf chiral auxiliary) with 3 *M* hydrochloric acid at rt gave opening of the six-membered ring furnishing the hydrochlorides **101a** and **101b**, which were further treated with triethylamine and BOC_2O to give the protected dipeptides **102a** and **102b**, formally derived from a 2-alkyl proline (BOC = *t*-butoxycarbonyl) [<2004TA1301>](#). 3-Hydroxy-3-phenyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-4(3*H*)-one **104**,

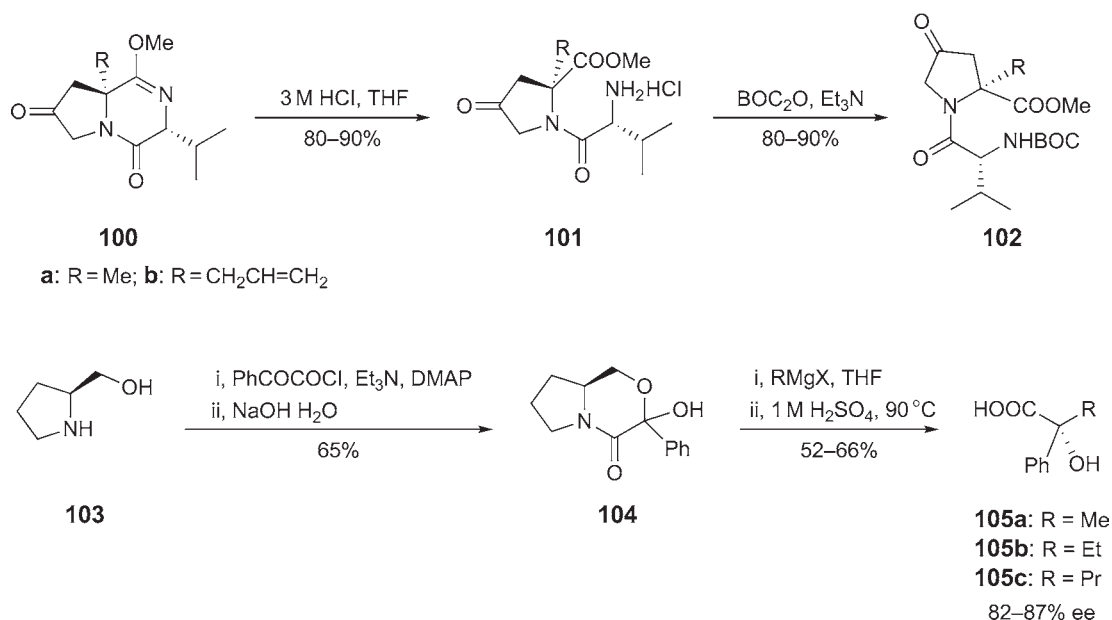


Scheme 11



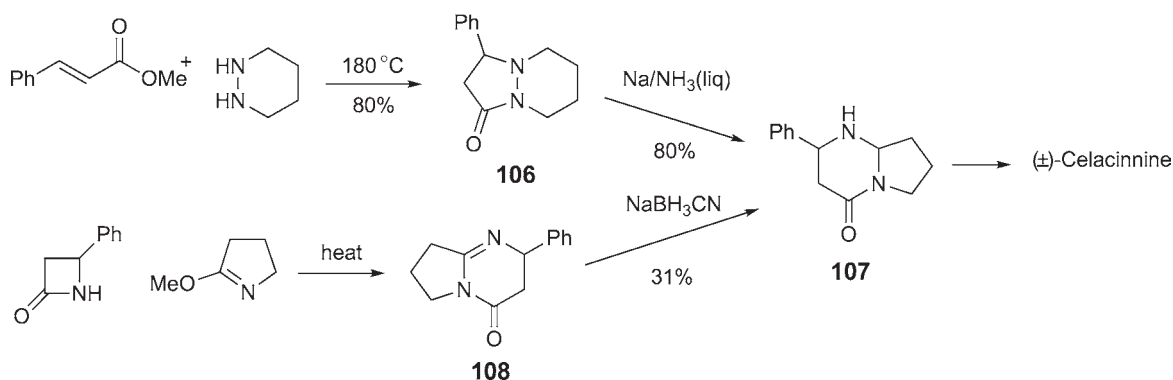
Scheme 12

obtained by reaction of prolinol and α -ketoacid chlorides, undergoes stereoselective ring opening with Grignard reagents (Scheme 13), forming α -alkyl mandelic acid **105a–c** with high ee <1998T14549>.



Scheme 13

An interesting ring opening with expansion of the ring has been reported starting from different bicyclic heterocycles. 3-Phenylhexahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-one **106** (prepared as reported in Scheme 14) was treated with Na in liquid ammonia to give the nine-membered lactam **107**. The same compound was prepared by reduction of 2-phenyl-2,3,7,8-tetrahydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one **108** with NaBH₃CN (Scheme 14). This compound was then elaborated to give the alkaloid (±)-celacinnine in acceptable yields <2002T7177>.

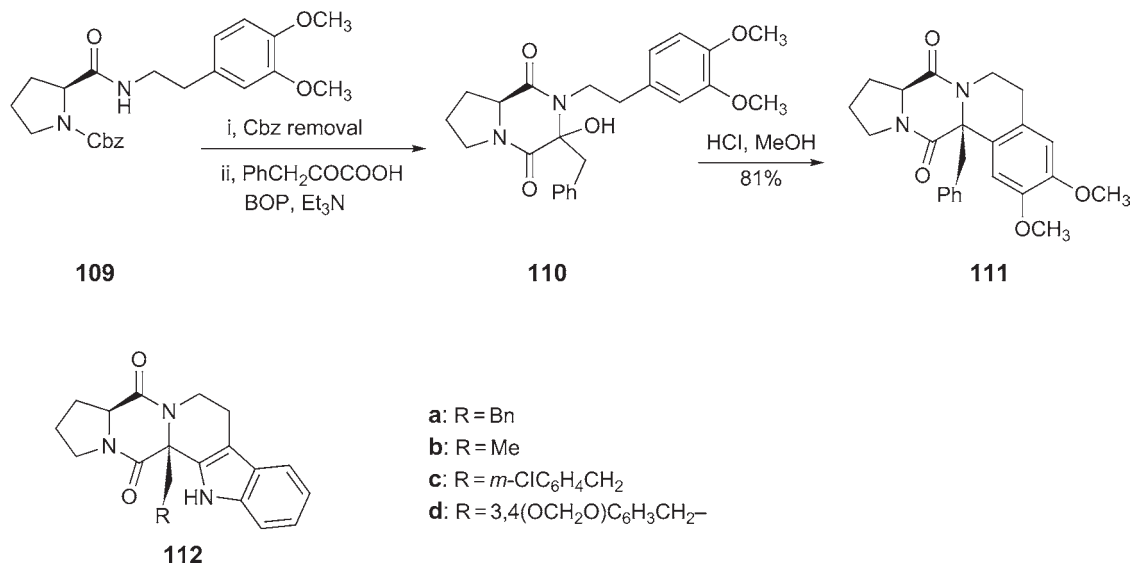


Scheme 14

11.11.6.4 Construction of Additional Rings

Intermediate diketopiperazine derivatives have been employed in the diastereoselective synthesis of benzyltetrahydroisoquinoline by 1,4-chirality transfer. *N*-Cbz-Proline was coupled with 2-(3,4-dimethoxyphenyl)ethylamine and the resulting amide **109**, after deprotection, was reacted with phenylpyruvic acid (Cbz = carbobenzyloxy group). Compound **110** underwent acid-catalyzed Pictet–Spengler condensation to yield final tetracyclic

diketopiperazine **111** with 90% de <2003EJO2443> (Scheme 15). The same behavior was observed with the amide derived from tryptamine and different substituted pyruvic acids leading to compounds **112a-d** <2005TA975> (Scheme 15).



Scheme 15

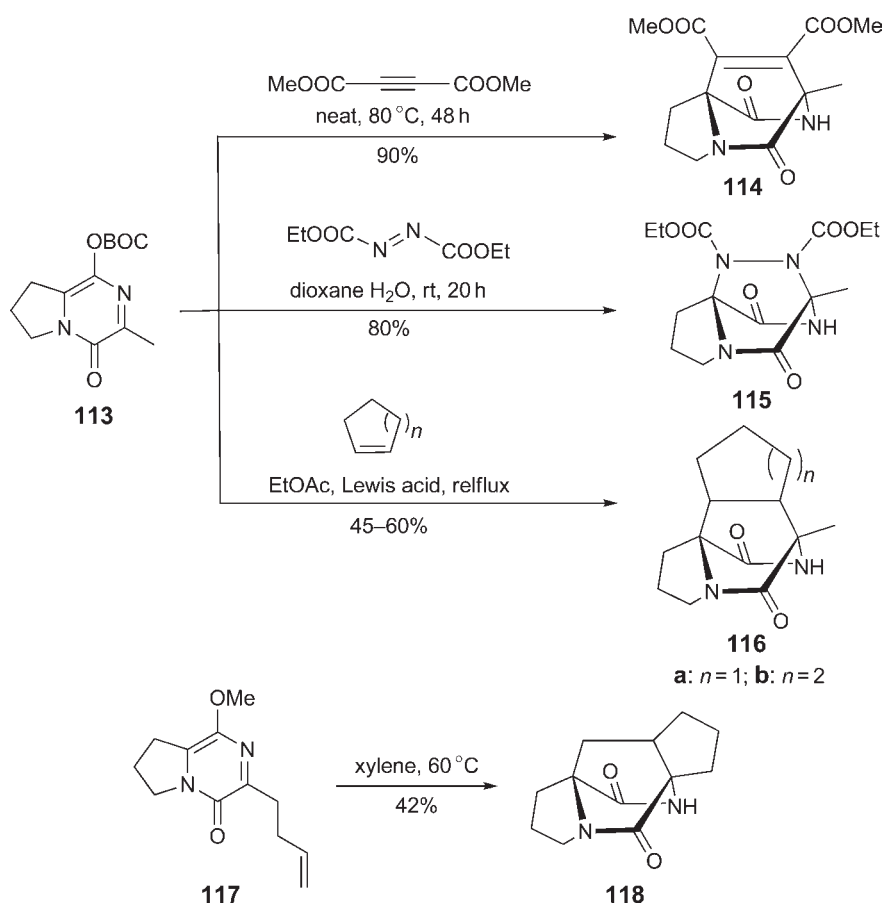
The reactivity of compound **113** toward reactive linear and cyclic dienophiles was reported in a study directed to find a model systems for the proposed [4+2] cycloaddition in the biosynthesis of the natural products brevianamides, paraherquamides, and marcfortines. With DMAD and diethyl azodicarboxylate the formation of **114** and **115** was almost quantitative after 48 h at 80 °C (Cbz = Carbobenzyloxygroup). When relatively unreactive dienophiles such as cyclopentene and cyclohexene were used, harsh reaction conditions and/or a Lewis acid catalyst are necessary for the formation of **116a** and **116b** (Scheme 16). In contrast, the analogous intramolecular reaction carried out on compound **117** takes place within a few hours at room temperature, even in the absence of a Lewis acid catalyst, to give **118** in 42% yield (Scheme 16) <2000T6345>.

Starting from diketopiperazine **119a**, obtained from proline, possessing exocyclic double bond, the bicyclo[2.2.2]-diazalactone core structure of important fungal metabolites isolated from *Aspergillus japonicus* JV 23 and *Aspergillus* sp. IMI 337664 was prepared. Azadiene **121** can be formed by BOC-mediated enolisation of **119a**. This product rapidly cyclized when treated with a solution of 4 M HCl in dioxane to give **120** as a single diastereoisomer via the free enol **122** generated by acid cleavage of the BOC group. The structure of the tetracyclic compound **120**, also obtained directly from **119** in acid medium, indicates that the starting mixture contains also noncyclized enol-amide **119b**, whose peptide bond is cleaved in acid conditions (Scheme 17) <2004TL4489>.

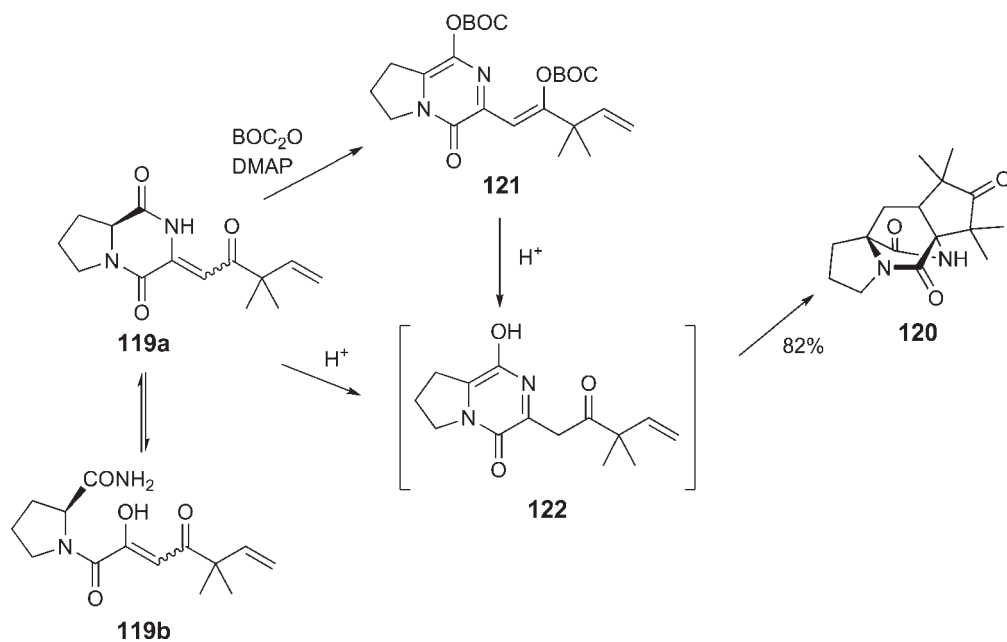
An intramolecular cycloaddition also occurred with 3-ylidenepiperazine-2,5-diones such as **124** or **125**, obtained by Wittig–Horner–Emmons reaction from phosphonate **121** and aldehydes **122** or **123**, respectively. The products of the Diels–Alder reaction are the bridged bicyclo[2.2.2]diazaoctane rings 126 and 127 that have been found in biologically active secondary metabolite such as VM55599 and brevianamide A. The different type of structures employed in this case requires a chemoselective reaction in order to produce the expected products as single diastereoisomers after 20 days (Scheme 18) <2001JOC3984>.

The synthesis of fluorobrevianamide E **129a**, the metabolically stable analogue of brevianamide E, was performed starting from substituted diketopiperazine **128** by treatment with *N*-fluoro-2,4,6-trimethylpyridinium triflate. The reaction carried out in tetrahydrofuran (THF) at 65 °C gave complete conversion into fluorobrevianamide E as a 1:1.6 mixture with the epimer **129b**, from which it could be separated by column chromatography on silica gel (Scheme 18) <2001AGE4461>.

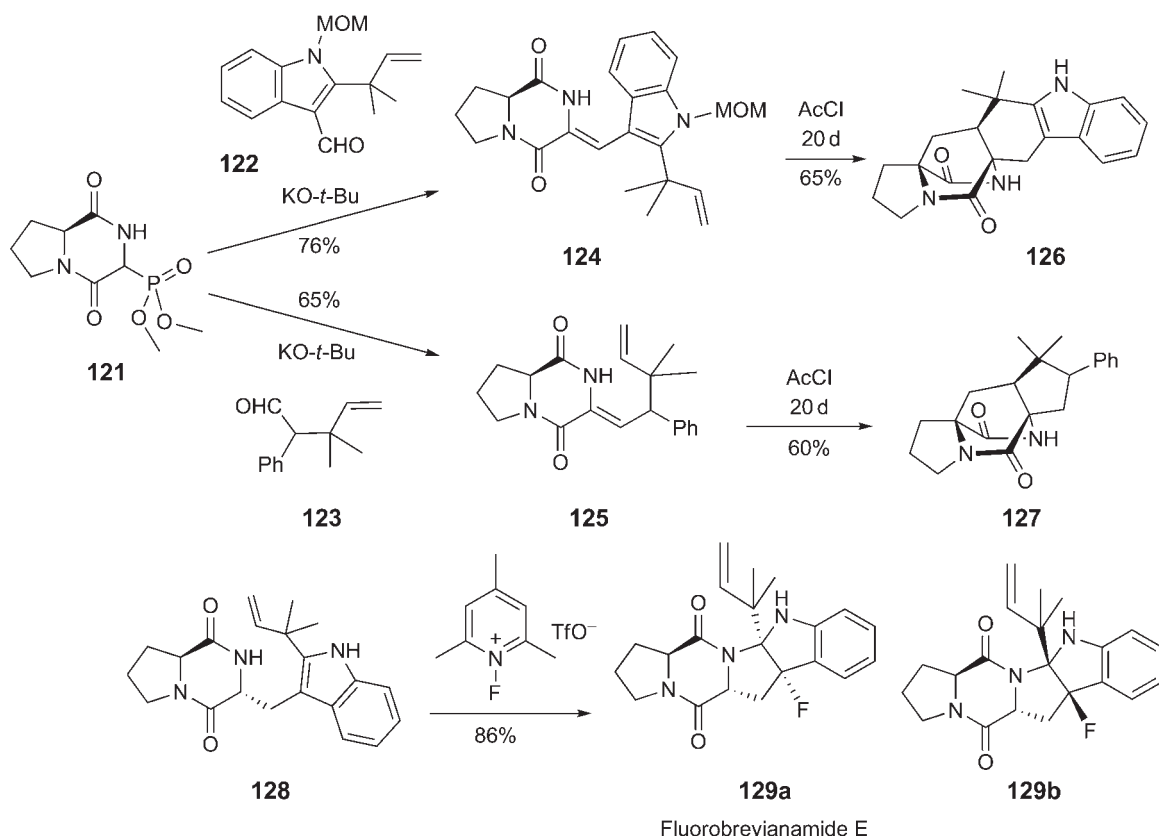
Spiro-lactam **131** was formed by reaction of *N,N'*-bis(aryl)tetrahydropyrrolo[2,1-*c*][1,4]oxazine-3,4-diylidenamines **130** with CO and ethylene in the presence of catalytic amounts of Ru₃(CO)₁₂. The reaction (Equation 2), a formal [2+2+1] cycloaddition, <2001CC593>, is highly stereoselective and the conditions have been studied in detail <2003JMO15>.



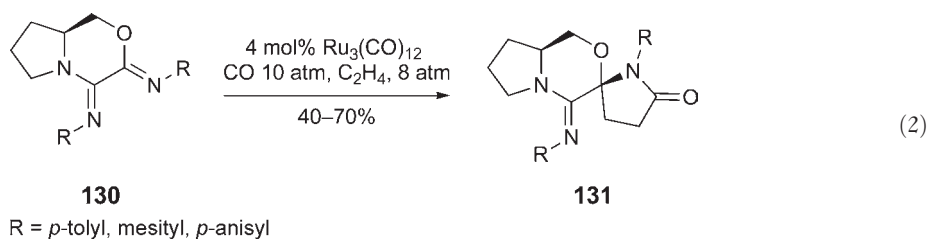
Scheme 16



Scheme 17



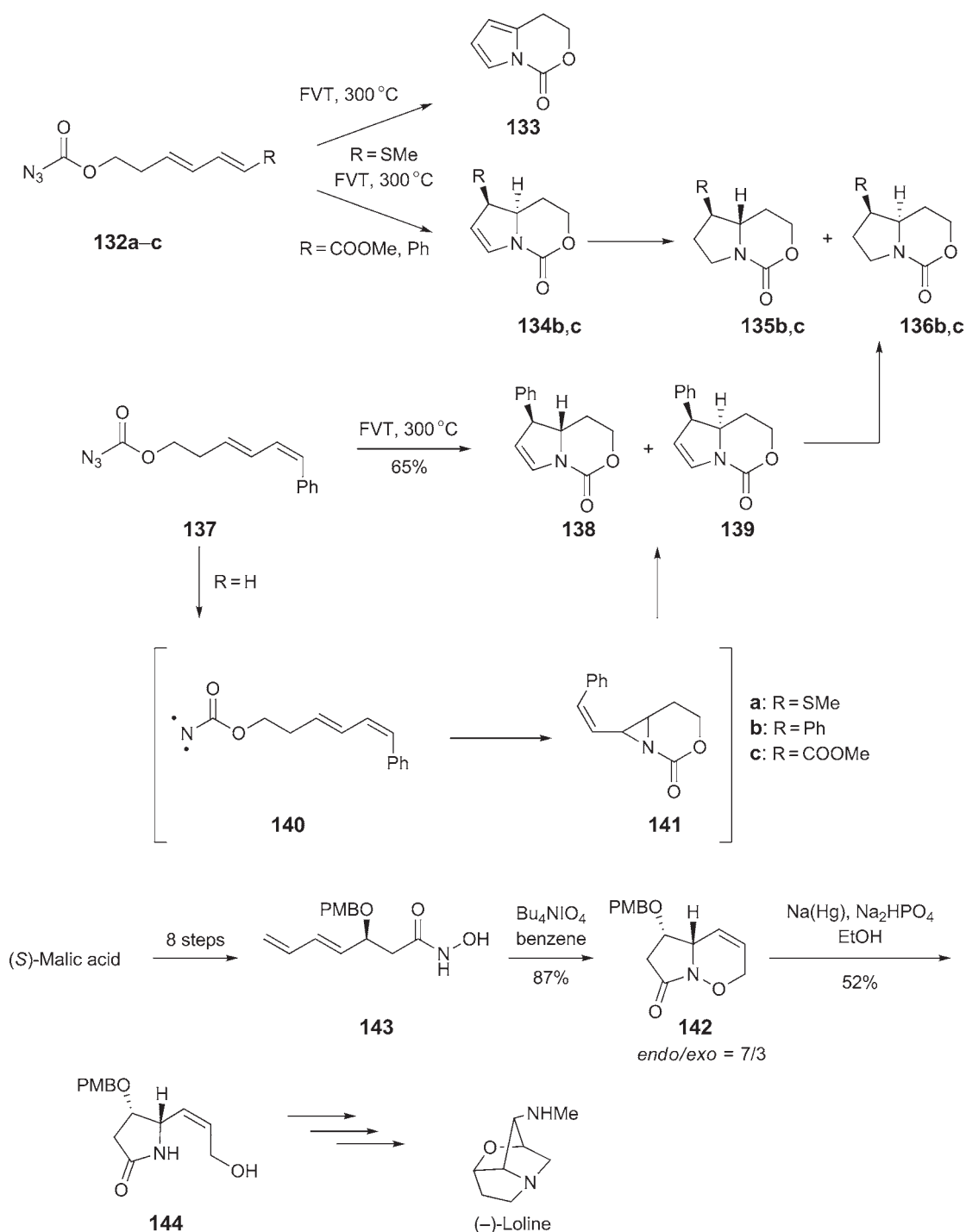
Scheme 18



11.11.7 Ring Synthesis

11.11.7.1 Synthesis from Single Acyclic Precursors

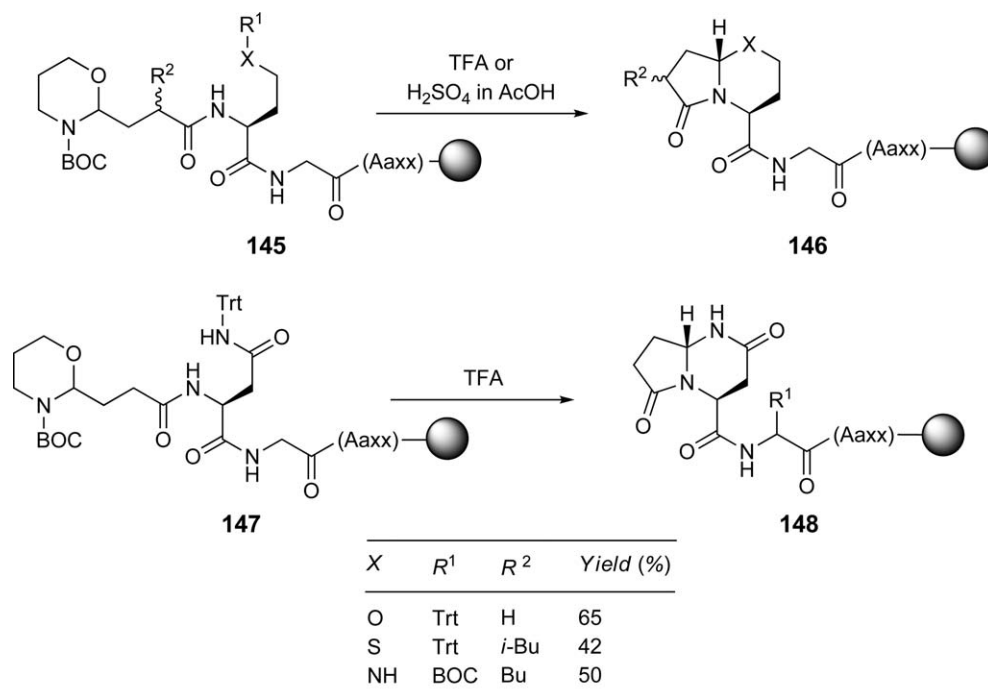
A series of dihydro-, tetrahydro-, and hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-ones have been obtained by flash vacuum thermolysis (FVT) of 3,5-hexadienyl azidoformates **132a-c** depending on the nature of the substituent and the stereochemistry at position C-6. With methylthio-dienylazidoformates **132a** the FVT gave the fused pyrrole **133** as the sole product. The corresponding azidoformates, containing a phenyl **132** or a carboxyethyl group **132c**, generated the tetrahydro derivatives **134b** and **134c** with *trans*-stereochemistry with respect to the ring junction. These products could be further reduced to give the hexahydro derivatives **135b,c** or **136b,c**. When an (*E,Z*)-diene was employed in the place of the (*E,E*)-diene, a mixture of the *cis*- and *trans*-isomers **138** and **139** was obtained with a small preference for the *cis*-isomer. A possible mechanism of this useful transformation has been proposed via loss of nitrogen to generate the acylnitrene **140** that may proceed with a double-bond insertion to produce the intermediate aziridine **141**. The further cleavage of one of the aziridine C-C bonds produced a vinyl-azomethine ylide that finally cyclized to the fused bicyclic compounds (Scheme 19) <2001JOC6585>.



Scheme 19

An intermediate 5-hydroxy-5,6-dihydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazin-7(4*aH*)-one **142** has been described in the total synthesis of (-)-loline, a pyrrolizidine alkaloid extracted from rye grass *Lolium cuneatum*. The key step of the synthesis was an intramolecular cycloaddition of acylnitrosodienes (obtained by *in situ* oxidation of the corresponding hydroxamic acids **143**). This reaction generated predominantly the *endo*-stereoisomer that was further cleaved at the N–O bond with Na(Hg) and further elaborated in several steps to reach the target compound (Scheme 19) <2001J(P1)1831>.

Bicyclic amino acids based on the skeleton of different perhydropyrrolo-azines have been often described as useful conformationally constrained dipeptide mimetics. With the aim of obtaining peptide analogues imitating the conformation of β -turn, a solid-phase synthesis of an array of bicyclic oxazines, thiazines, or pyrimidines has been described. The key reaction was the cyclization of an oligopeptide terminating with a precursor of an iminium ion intermediate **145** (Scheme 20). The ring closing was initiated by a nucleophile situated on the side chain of the last amino acid (such as homoserine, homocysteine, ornithine, or asparagine) that attacked the cyclic *N*-acyliminium ion generated in the presence of a strong acid such as TFA. The acid environment allowed the deprotection of the nucleophile and the contemporary generation of the iminium ion. The reaction was stereoselective regarding the mode of formation of the bicyclic compound with values close to 90–95% (Scheme 20), whereas a poor stereoselectivity was observed with different substituents at C-6. It is also worth of note that the cyclization also occurred when the terminal group of the asparagine was used as the nucleophile leading to lactam **148**. After the cyclization, the array of conformationally constrained peptides was removed from the resin using standard procedures <2005OL3601>.



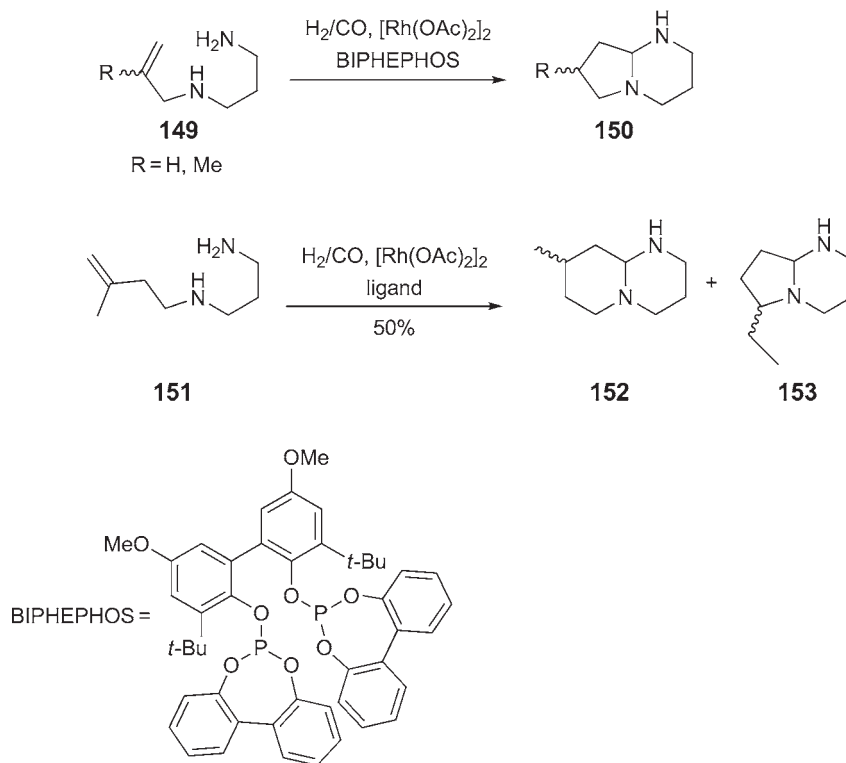
Scheme 20

An example of tandem hydroformylation/reductive amination was reported starting from allylamine **149**. The use of BIPHEPHOS as the ligand for the Rh-intermediate allowed a chemoselective formation of the octahydropyrrolo[1,2-*a*]pyrimidine **150** in good yields <1997TL4315>. Starting from the isomeric allylamine **151**, compound **152** was obtained as the minor isomer together with the corresponding octahydro-1*H*-pyrido[1,2-*a*]pyrimidine **153** (Scheme 21) <1997T17449>.

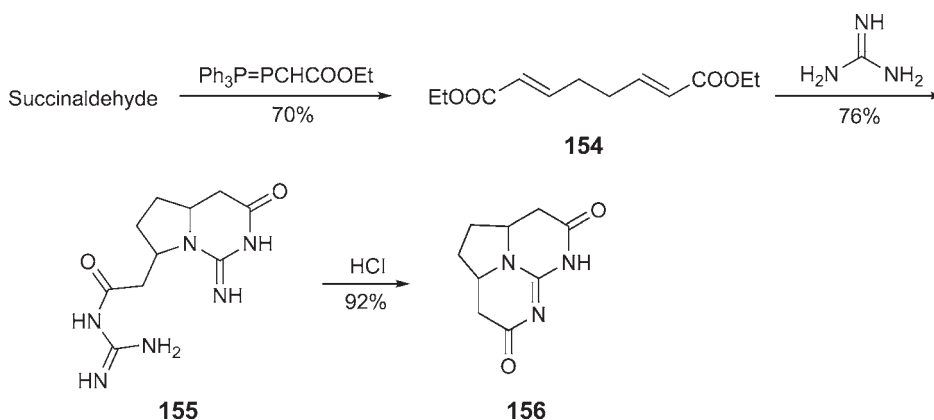
11.11.7.2 Synthesis from Two Acyclic Precursors

The synthesis of bicyclic molecules containing guanidinium subunits, such as **156** (Scheme 22), are of considerable interest due to the wide range of biological activities presented by this family of natural products (see Section 11.11.9). In one of the first biomimetic studies toward pylomycalin A, a series of polycyclic compounds have been prepared through an intermediate 1-imino-hexahydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one such as **155**. Succinaldehyde

was reacted with an excess of carboethoxymethylene-triphenylphosphorane to give the unsaturated dicarboxylic ester **154** that reacted with guanidine in DMF to form the bicyclic product **155**. This product was then transformed into polycyclic guanidine **156** that shows a ring system similar to that of ptilomycalin A <1996T8315>.



Scheme 21

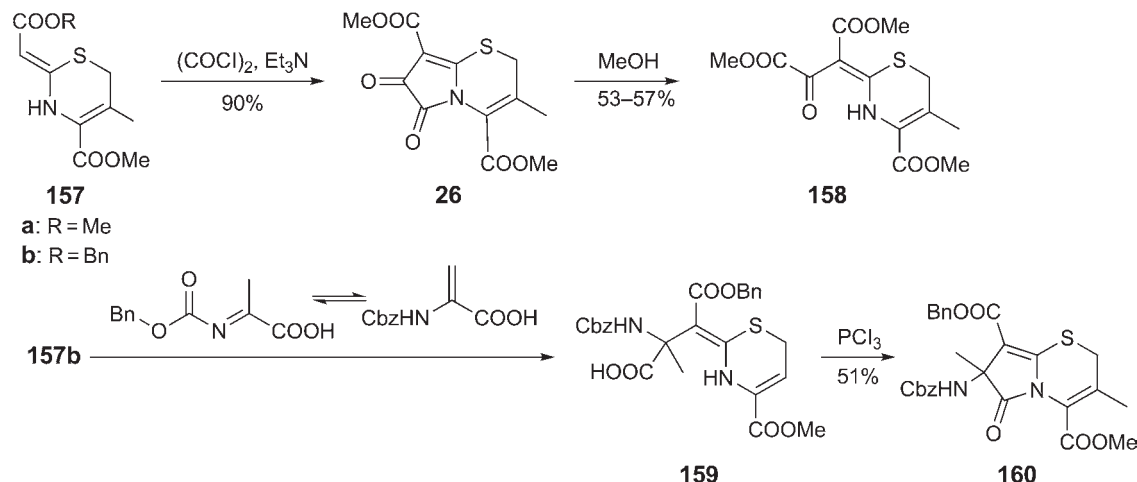


Scheme 22

11.11.7.3 Synthesis from a Preformed Six-Membered Ring

In the search for new β -lactam-type antibiotics, Young and co-workers described the synthesis of the bicyclic lactam **26** that was obtained starting from thiazines **157a** and **157b**. Treatment with oxalyl chloride in CH_2Cl_2 containing triethylamine as the base gave product **26** as a solid. However, this compound was extremely labile as it was opened in warm methanol to give thiazine **158** <1996TL5601>. An analogous behaviour was observed when the same kind

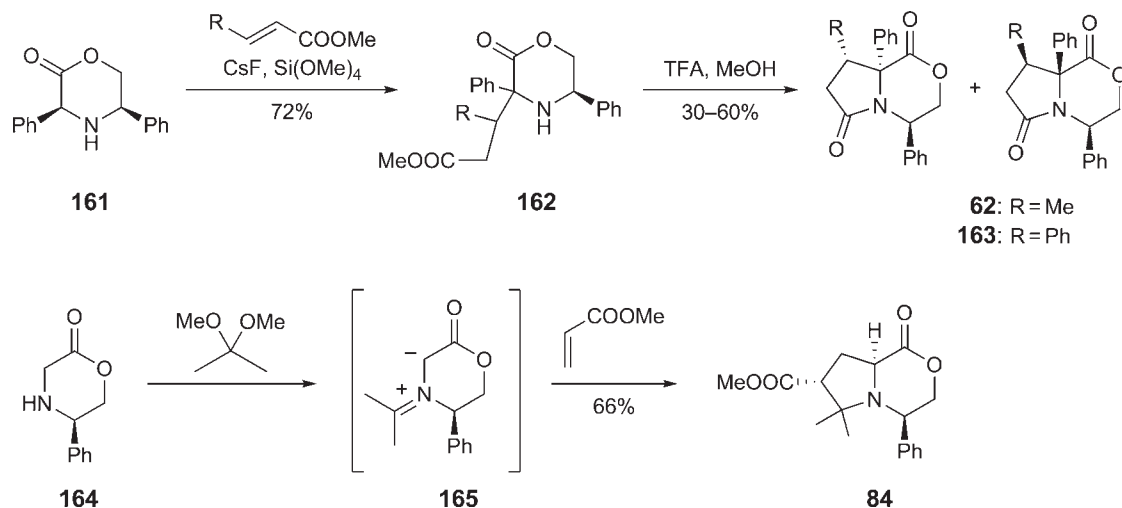
of thiazine **157b** was reacted with *N*-Cbz dehydroalanine. The reaction proceeded through a nucleophilic attack of the enamine on the imine tautomer of dehydroalanine and further cyclization mediated by PCl_3 to give compound **160** (Scheme 23) <2005T287>.



Scheme 23

The 3,5-diphenylmorpholine-2-one **161** was used to prepare bicyclic lactams **162** by reaction with the cesium fluoride/tetramethoxysilane system and different Michael acceptors. The adducts were rapidly obtained as a mixture of diastereoisomers that could be separated by column chromatography just after TFA-mediated cyclization to the 8-substituted-4,8a-diphenyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6(7*H*)-diones **62** and **163** <1997SL935>. These compounds were then reduced to give substituted prolines as described in Section 11.11.6.1.

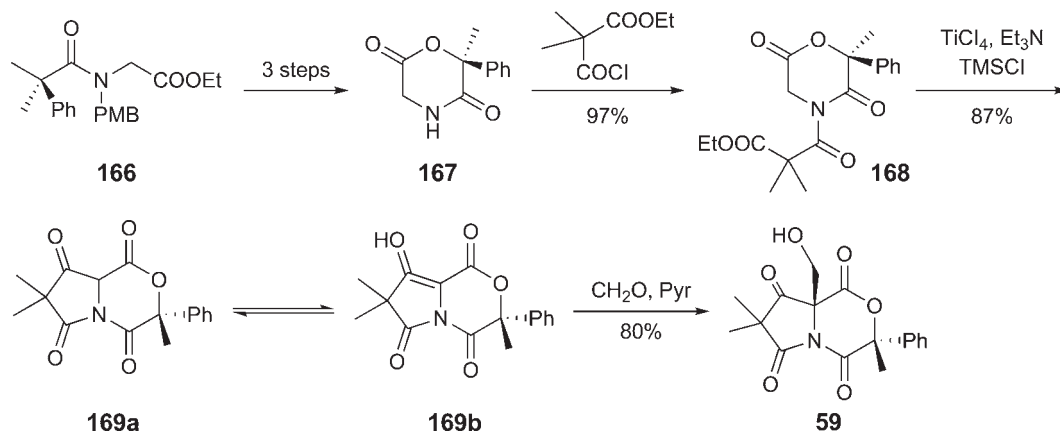
In an analogous approach, the chiral stabilized azomethine ylide **165**, generated *in situ* via Lewis acid-catalyzed condensation of (5*S*)-5-phenylmorpholin-2-one **164** with 2,2-dimethoxypropane, was trapped diastereoselectively with singly and doubly activated dipolarophiles such as the acrylate (Scheme 24). The cycloadduct **84** was then employed to furnish enantiomerically pure 5,5-dimethylproline derivatives (see Section 11.11.6.3), <2001SL1836>.



Scheme 24

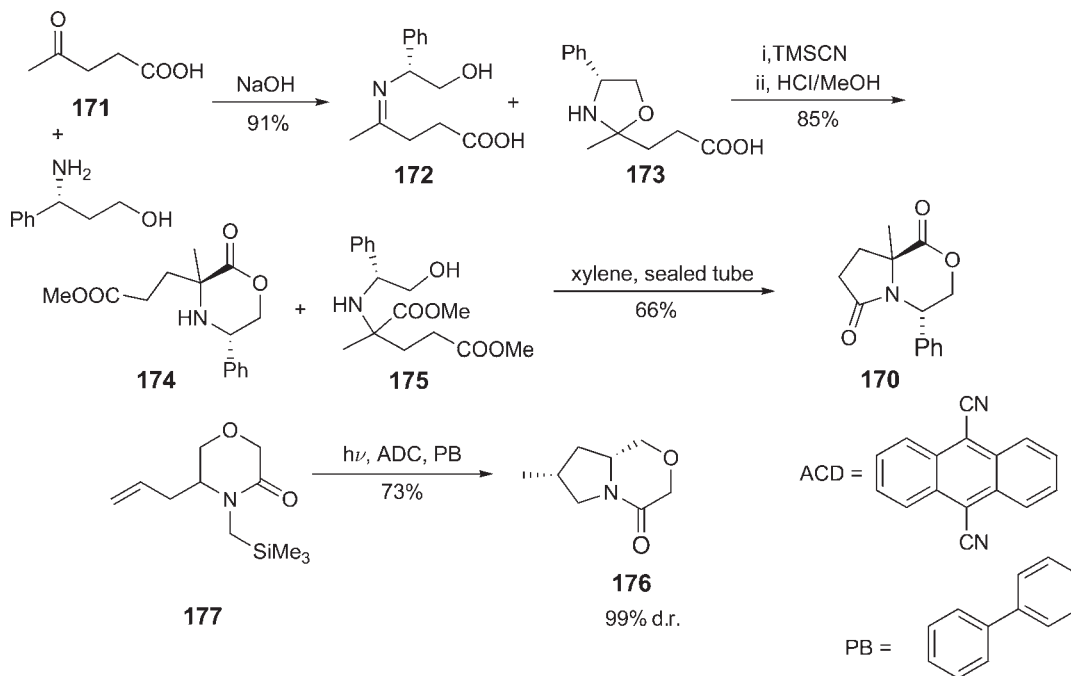
Crane and Corey prepared 8a-(hydroxymethyl)-3,7,7-trimethyl-3-phenyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,4,6,8(3*H*,7*H*,8*aH*)-tetraone **59** as the key intermediate in the synthesis of omuralide analogues (see Section 11.11.6.3). The synthesis started from compound **166**, the amide derived from *N*-*p*-methoxybenzylglycine ethyl

ester and (*R*)-*O*-acetylalrolactic acid. In three steps, the morpholinone **167** was obtained and further acylated at N-1 to give compound **168**, which underwent Dieckmann cyclization at C-6 in very good yields. The product **169a** exists in a tautomeric equilibrium in solution with its enolic form **169b** that underwent smoothly hydroxymethylation by reaction with aqueous formaldehyde in methanol and in the presence of pyridine, forming **59** stereoselectively and in good yield (Scheme 25). The face selectivity of the hydroxymethylation was controlled by the difference in steric hindrance derived by the atrolactic stereocenter <2001OL1395>.



Scheme 25

Starting from levulinic acid, it was possible to obtain 8a-substituted-4-phenyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,6(7*H*)-diones **170** (Scheme 26) via Strecker reaction. Compound **171** was treated with 1 equiv of sodium hydroxide and the salt reacted with (*R*)-phenylglycinol to give a mixture of the Schiff's base **172** and the 1,3-oxazolidine **173** that was reacted with trimethylsilyl cyanide. Further treatment with HCl-saturated methanol afforded a mixture of **174** and **175**. Heating at 200°C in a sealed tube provided **170** as two separable isomers in 73% and 10% yields, respectively <1999TL5753>.

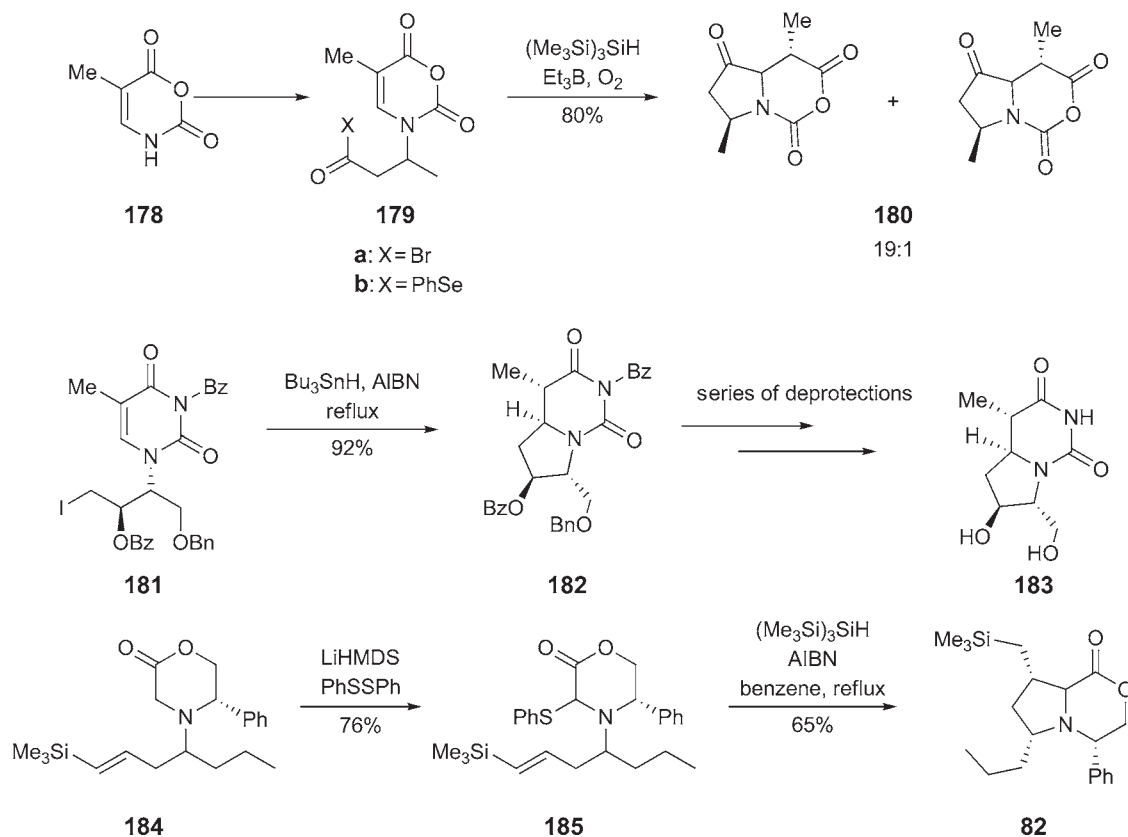


Scheme 26

Whereas the previous methods for the synthesis of pyrrolo-oxazines were based on traditional ionic cyclization, the preparation of 7-methyltetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-4(3*H*)-one **176** was reported using a new radical cyclization induced by photoelectronic transfer catalysis. This reaction is proceeding under very mild conditions and in neutral medium (Scheme 26).

Morpholinone **177**, derived from allyl glycine, cyclized stereoselectively under UV irradiation ($\lambda > 342$ nm) in the presence of 9,10-anthracene dicarbonitrile (ADC) and biphenyl (PB) to give compound **176** as a single diastereoisomer <2001JOC6896> (Scheme 26).

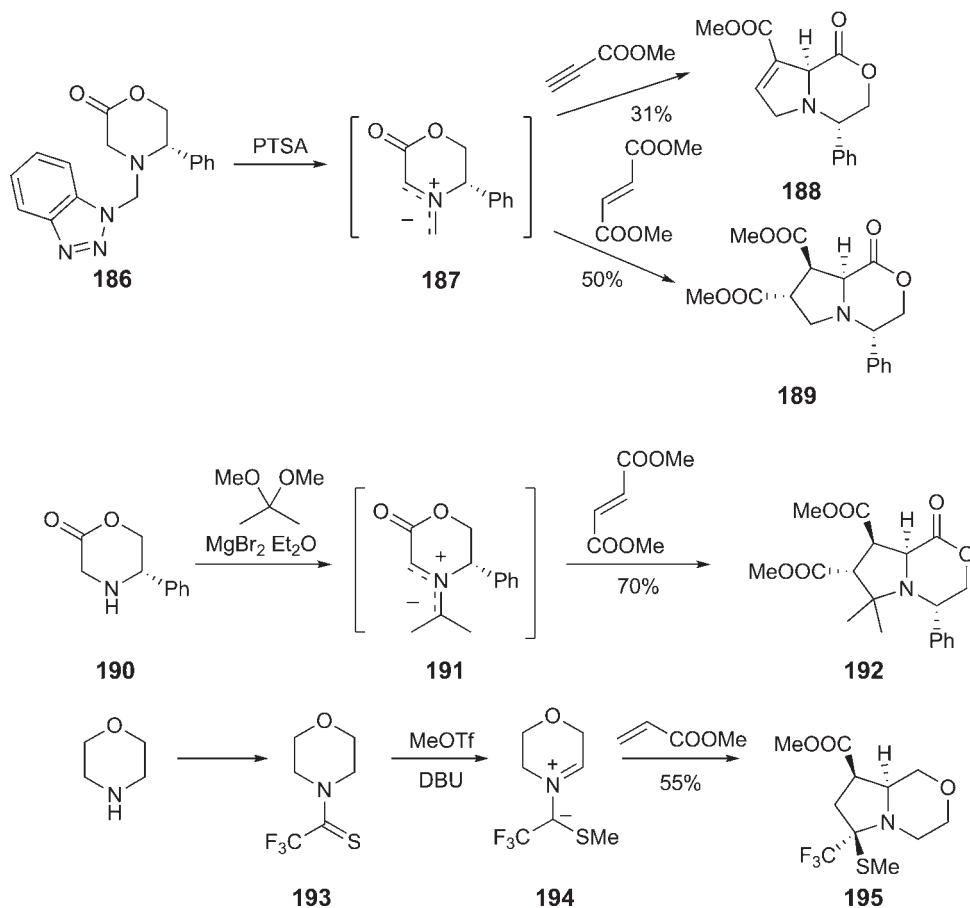
A similar radical-type cyclization induced by triethylborane and air was carried out on different oxauracils functionalized with an acyl selenide moiety as radical generators. Oxathymine **178** was alkylated in a Michael-type reaction and transformed into the corresponding acyl selenides (or bromides) **179** under standard conditions. Treatment of **179b** with tris(trimethylsilyl)silane and triethylborane in the presence of air gave the corresponding azabicyclic compound **180** with high stereoselectivity <2000JA11009>. The same reaction was applied to different suitably protected acyl or iodoalkyl derivatives of thymine **181** to form bicyclic **182** with high diastereoselectivity <2001TL6637>. In the last case, however, the radical cyclization was initiated thermally (2,2'-azobisisobutyronitrile (AIBN), in refluxing benzene) and the H-radical came from Bu₃SnH. These compounds were further elaborated to produce the new conformationally rigid nucleoside **183** <2006CC844>. Another radical cyclization was described starting from morpholinone **185**, obtained by lithiation of compound **184** and further reaction with phenyldisulfide (Scheme 27). This compound, obtained as a mixture of diastereoisomers, cyclized via a diastereoselective 5-*exo-trig*-radical process to give exclusively compound **82**. This intermediate was then employed for the preparation of substituted prolines (Section 11.11.6.3) <2003SL1058>.



Scheme 27

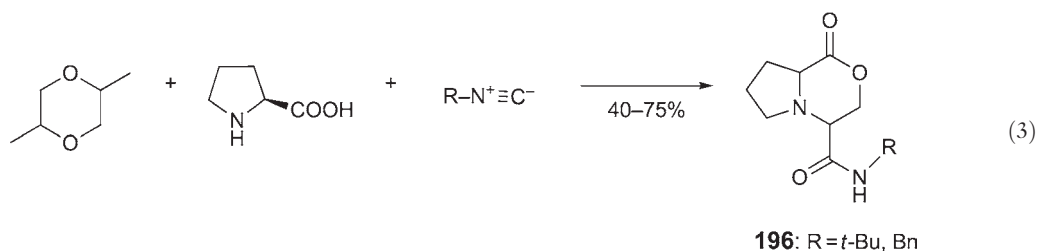
A series of analogous pyrrolo[2,1-*c*][1,4]oxazine-8-carboxylates **188** and **189** (Scheme 28) were obtained by cycloaddition of azomethine ylide **187** with dipolarophiles. The ylide was formed by *p*-toluene sulfonic acid-mediated reaction of the benzotriazolyl chiral morpholinone **186**, which can be considered as a stable crystalline azomethine ylide precursor <2001SL1841>. This procedure was applied also to morpholinone **190** that generated ylide **191** by reaction with

2,2-dimethoxypropane in the presence of MgBr_2 as the Lewis acid. Trapping of the intermediate with dipolarophiles, such as dimethyl fumarate, gave **192** in good yields [<2001SL1836>](#). However, ylide **191** did not react with acetylenic dipolarophiles. Another azomethine ylide derived from morpholine was used in the preparation of the pyrrolo[2,1-*c*][1,4]oxazine **195** (Scheme 28). In this case, the procedure started with the trifluoroacetothiamide **193** derived from morpholine. This compound was transformed into the trifluoromethyl thioamidinium triflate with MeOTf and this salt was deprotonated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to generate the ylide **194** that underwent cycloaddition with different dipolarophiles such as methyl acrylate. The reaction proceeds with high stereoselectivity that depends on the reaction conditions (amounts of MeOTf and DBU, reaction time, etc.) [<2002T3543>](#).

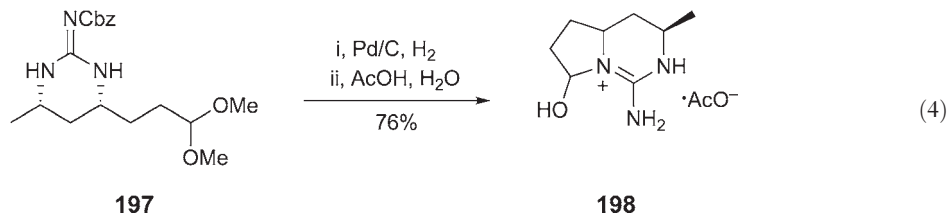


Scheme 28

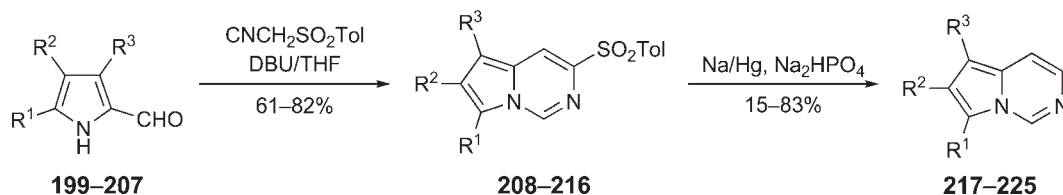
A series of 1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-ones **196** are also the product of an Ugi multicomponent reaction between proline (and also other α -amino acids that gave the corresponding monocyclic compounds) and several isonitriles in the presence of commercially available glycolaldehyde dimer (Equation 3) [<2001OL4149>](#).



Six-membered cyclic guanidine **197** was transformed into the corresponding bicyclic guanidine hemiaminal after deprotection of the Cbz and contemporary cyclization on the masked aldehyde function (Equation 4). This product, **198**, was then employed in a Biginelli reaction to form a precursor of alkaloid batzelladine F <1999JOC1512>.



A series of unsaturated pyrrolo[1,2-*c*]pyrimidines **217–225** was prepared starting from pyrrol-2-carboxaldehydes **199–207** that were reacted with tosylmethyl isocyanide (TOSMIC) to give the cyclocondensation products **208–216** in good yield (Scheme 29). Further removal of the tosyl group was obtained using 6% sodium amalgam and Na₂HPO₄ in THF–MeOH. Under these conditions, compounds **217–225** were obtained in 15–83% yields depending on the nature of the substituents (Table 1) <1996TL4263>.



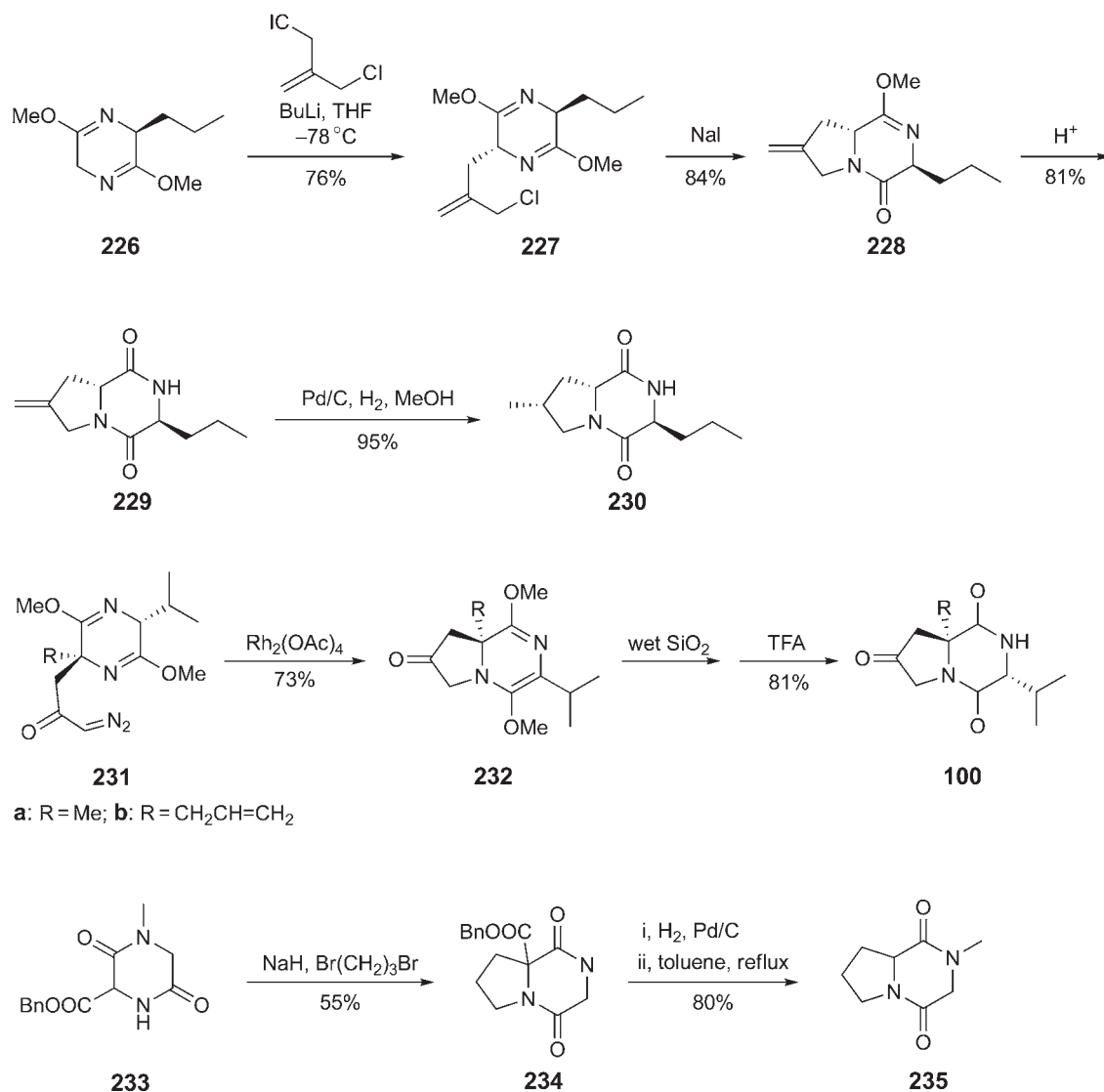
Scheme 29

Table 1 Preparation of unsaturated pyrrolo[1,2-*c*]pyrimidine (Scheme 29)

<i>R</i> ¹	<i>R</i> ²	<i>R</i> ³	Pyrrole	3-Tosyl (Yield, %)	Pyrrolo[1,2- <i>c</i>]pyrimidine (Yield, %)
H	H	H	199	208 (82)	217 (51)
H	Br	H	200	209 (79)	218 (15)
H	Me	H	201	210 (58)	219 (77)
H	Bu	H	202	211 (73)	220 (54)
H	CH ₂ =CHCH ₂ –	H	203	212 (61)	221 (46)
H	COOMe	H	204	213 (69)	222 (12)
Me	Et	Me	205	214 (69)	223 (83)
Me	H	H	206	215 (76)	224 (74)
	H	H	207	216 (80)	225 (55)

Schöllkopf's auxiliary has been widely used for the preparation of enantiomerically pure nonproteinogenic amino acids and these products have often been employed in the synthesis of diketopiperazine bicyclic derivatives. For example, the synthesis of a series of diketopiperazines derived from D-proline has been performed by alkylation of the (*S*)-**226** with methylalyl dichloride that gave the *trans*-derivative **227** with 90% de. Cyclization of **227** occurred directly by nucleophilic substitution after treatment with NaI. The acid degradation of the lactim ether **228** gave an opened intermediate that was then cyclized under nonpimerizing conditions to give diketopiperazine **229** in good yield. Hydrogenation of the double bond gave compound **230** that was used for a revision of the structure of a natural

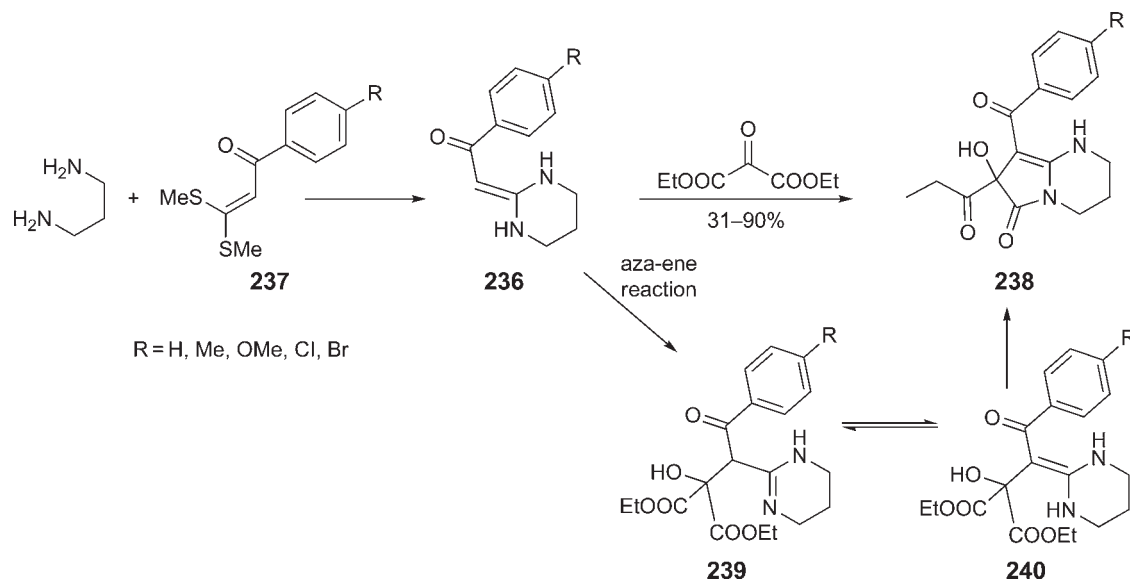
product isolated from the sponge *Calyx* cf. *podatypa*. <1998J(P1)2313>. Intramolecular rhodium(II)-catalyzed reactions in geminally disubstituted β -carbonyl diazo derivatives such as **231** (Scheme 30) occurred with complete chemoselectivity at the adjacent annular nitrogen, even in the presence of a potentially reactive carbon–carbon double bond as in **231b**. The products of this reaction, **232a** and **232b**, were submitted to two consecutive acid hydrolyses, leading to compounds **100a** and **100b**, which are valuable intermediates for the preparation of quaternary cyclic α -amino acid derivatives (Section 11.11.6.3) <2004TA1301>.



Scheme 30

The formation of a second ring, based on the generation of a six-membered carbanion followed by alkylation with a difunctional electrophile and further cyclization, was also exploited in the synthesis of hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione **235** starting from alkoxy carbonyl piperazine-2,5-dione **233**. When the key precursor was treated with 2 equiv of NaH and 1,3-dibromopropane, the bicyclic compound **234** was obtained in acceptable yield and further transformed into compound **235** by deprotection and decarboxylation (Scheme 30) <2005T8722>.

An interesting pyrrolo[1,2-*a*]pyrimidine was described as the product of the reaction of the heterocyclic ketene-aminals **236** that was synthesized by cyclocondensation of ketene dithioacetals **237** and 1,3-diamino propane. These compounds reacted with diethyl oxomalonate that behaves as a hetero-enophile, yielding the corresponding products **238** in acceptable to good yield (Scheme 31). A mechanism that involves an aza-ene reaction, via adduct **239** which isomerizes to ketene aminal **240** to produce the lactam ring of **238**, has been proposed <1999J(P1)321>.



Scheme 31

11.11.7.4 Synthesis from a Preformed Five-Membered Ring

2*H*-Pyrrolo[1,2-*b*][1,2]oxazines are a class of compounds with very few references regarding synthesis and reactivity. An interesting preparation has been described by intramolecular cyclization of *N*-hydroxy pyrrolidines carrying a methoxyallene substituent at C-2 (**242**, Scheme 32). These compounds were obtained by addition of a lithiated allene to chiral cyclic nitrones **241**. Cyclization occurred spontaneously after some days at relatively high dilution (0.05 M). Compounds **243** (obtained with excellent diastereoselectivity) can be submitted to further elaboration of the double bond or to hydrogenolysis of the N–O bond to form chiral pyrrolidine derivatives (Section 11.11.6.1) <2003EJO1153>.

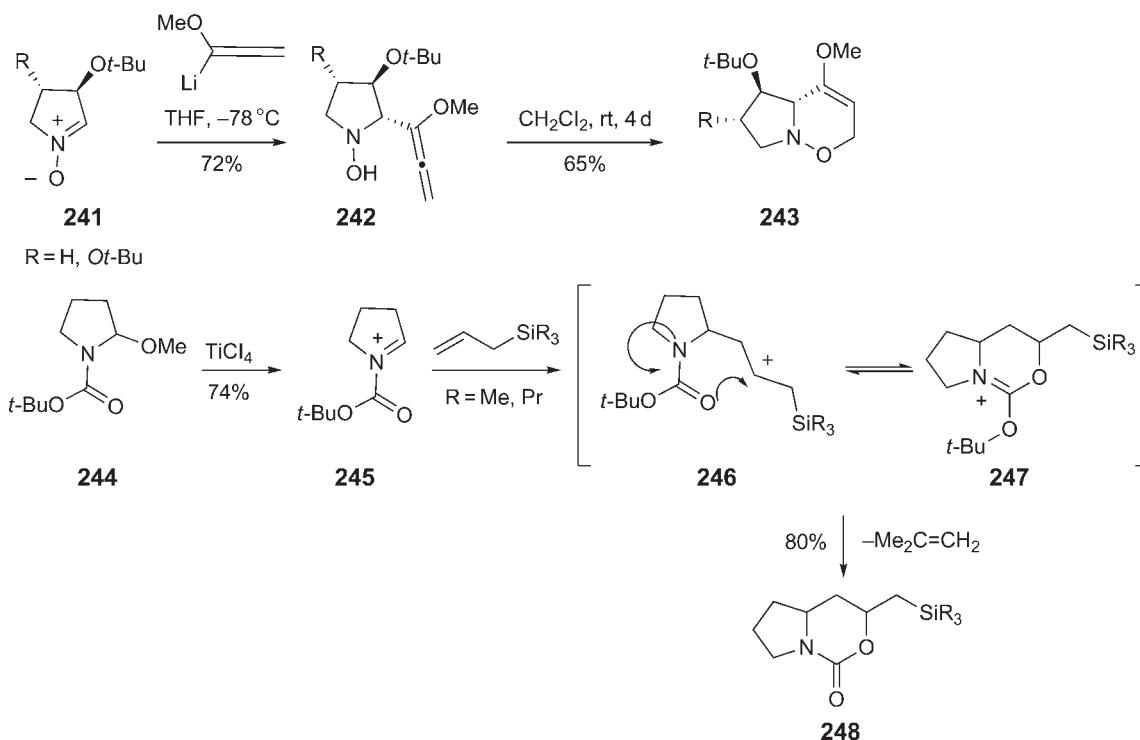
Pyrrolo[1,2-*c*][1,3]oxazin-1-one **248** has been obtained by reaction of allylsilanes with a pyrrolidine-*N*-acyliminium ion **247** (Scheme 32), formed by addition of a Lewis acid on compound **244**. The β -silyl carbocation formed by the reaction with allylsilane **246** reacted with the oxygen of the *N*-BOC group followed by the loss of 2-methylpropene. The reaction was not very stereoselective when trimethylsilane was used, whereas with larger group on the silicon the selectivity was increased <1997J(P1)2163>.

Another synthesis of this class of heterocycles has been described to prepare an intermediate for the total synthesis of allopumillotoxin. Proline-derived aldehyde **249** was reacted with lithium alkynes and the intermediate alcohols **250a** and **250b** treated with AgNO₃ in EtOH at room temperature to produce compounds **251a** and **251b**. Product **250b** was then elaborated to the required complex natural product (Scheme 33) <1996JA9073>.

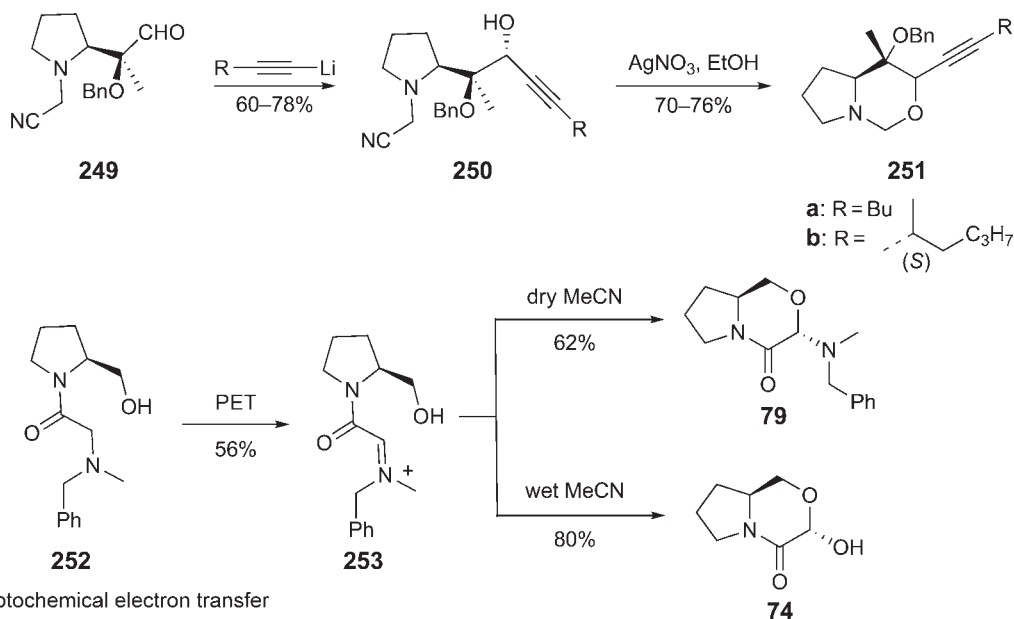
The oxazinones **74** and **79**, already described as chiral glycine templates in Section 11.11.6.3, have been prepared by the PET cyclisation of **252** by irradiation in the presence of 1,4-dicyanonaphthalene as the electron acceptor and methyl viologen as electron-transfer mediator. When the reaction was carried out under strictly anhydrous conditions, compound **79** was isolated, whereas when the reaction was carried out in wet MeCN, compound **74** was the exclusive product (Scheme 33). In any case, the products were obtained with high stereoselectivity, which is the condition required to use them as chiral auxiliaries <2000EJO657>.

A series of enantiomerically pure tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,4(3*H*)-diones **86a–d** have been prepared by bromolactonization of acrylamides derived from proline mediated by NBS (Equation 5). These compounds

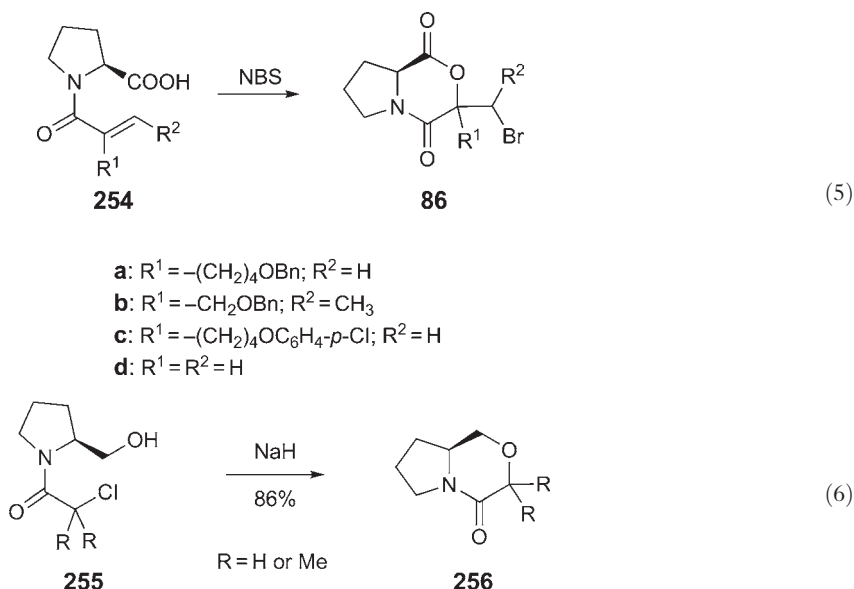
have been mainly used as key intermediates in the synthesis of biologically active molecules [<2005BMC6195, 2004TL9475, 2000JME581>](#). A similar approach derived from prolinol gave the pyrrole oxazine **256** (Equation 6), via a simple nucleophilic substitution of the α -chloro ester with the OH function derived from prolinol [<1997BMC2069>](#).



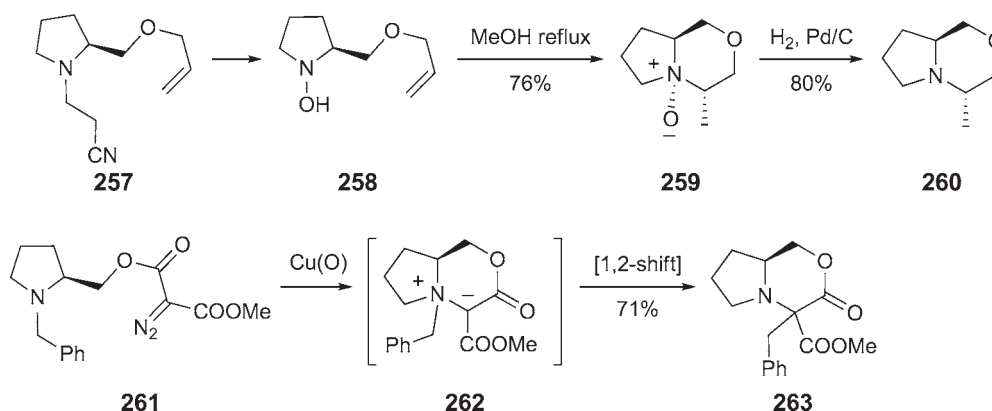
Scheme 32



Scheme 33

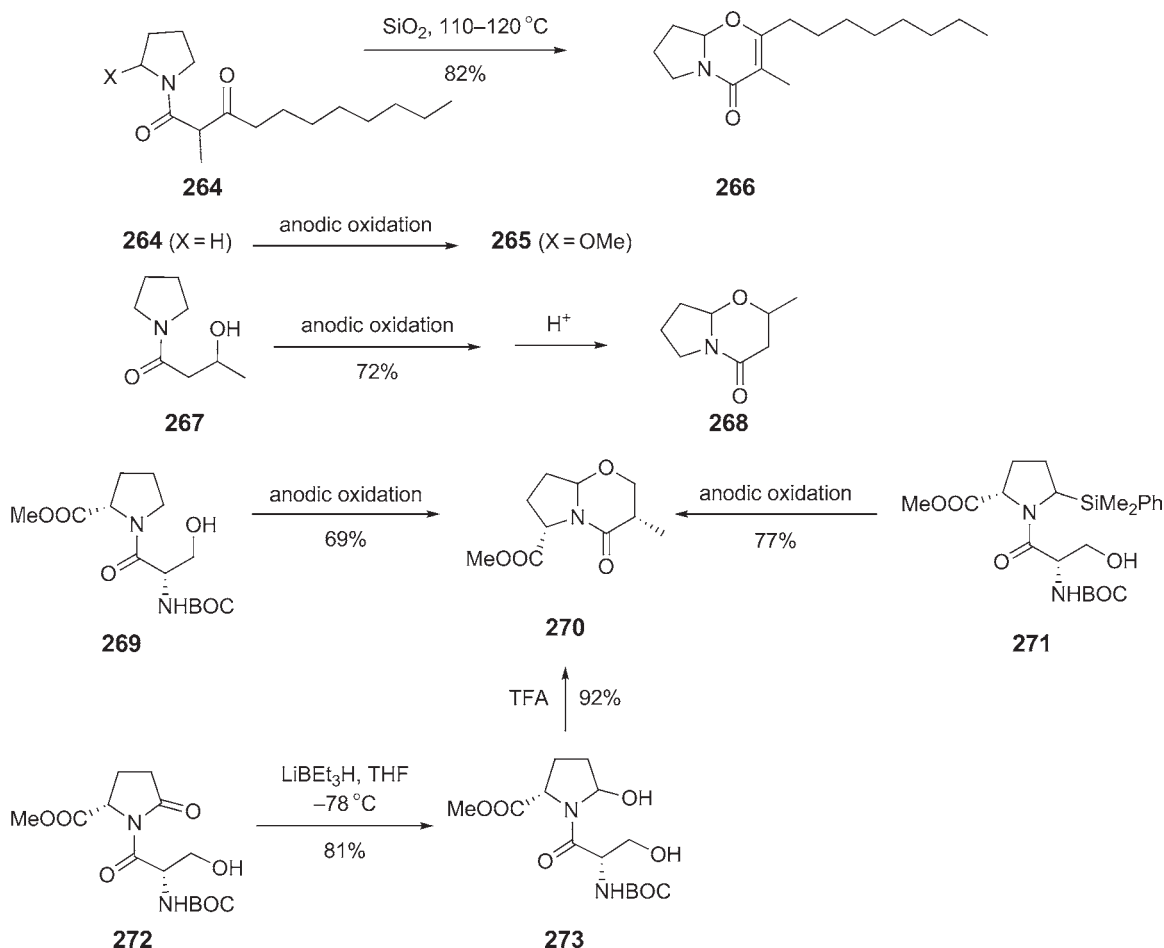


Oxazines **260** and **263** (Scheme 34) were also obtained via cyclization mediated by a charged nitrogen derivative of pyrrolidine. Prolinol was in fact transformed to the cyanoethyl derivative **257** that, upon oxidation with *m*-chloroperbenzoic acid (MCPBA), formed the hydroxylamine **258**. Heating in refluxing MeOH under nitrogen, **258** gave a reverse Cope elimination affording the pyrrolooxazine *N*-oxide **259** as a single diastereoisomer. The product was then reduced to give chiral oxazine **260** <2004TL3655>. *N*-Benzyl-prolinol was transformed into the diazomalonate **261** that was subjected to a copper-catalyzed carbene-transfer reaction. The cyclic ammonium ylide **262** was obtained and immediately transformed, via a [1,2]-shift of the exocyclic substituent on the nitrogen, into oxazine carboxylate **263**, albeit with modest stereoselectivity <2003TA917>.



Scheme 34

Several syntheses of diverse 2*H*-pyrrolo[2,1-*b*][1,3]oxazines have been described with a common strategy based on the cyclization of an OH function on the iminium ion derived from differently substituted pyrrolidines. The main difference in these syntheses lies in the method of generating the iminium ion (Scheme 35). Many reports described the use of anodic oxidation of the carbon close to pyrrolidine for this functionalization. A natural product with anti-juvenile hormone activity, **266**, has been synthesized. The β -keto amide derived from pyrrolidine **264** was submitted to anodic oxidation at 20 mA in the presence of tetrabutylammonium tosylate as the supporting electrolyte. The methoxy derivative **265** was then cyclized in acidic conditions to give product **266** <1999EJO221, 1998JOC8530>. A similar reaction was carried out by parallel electrosynthesis of alkoxy-pyrrolidine amide **268** using a spatially addressable



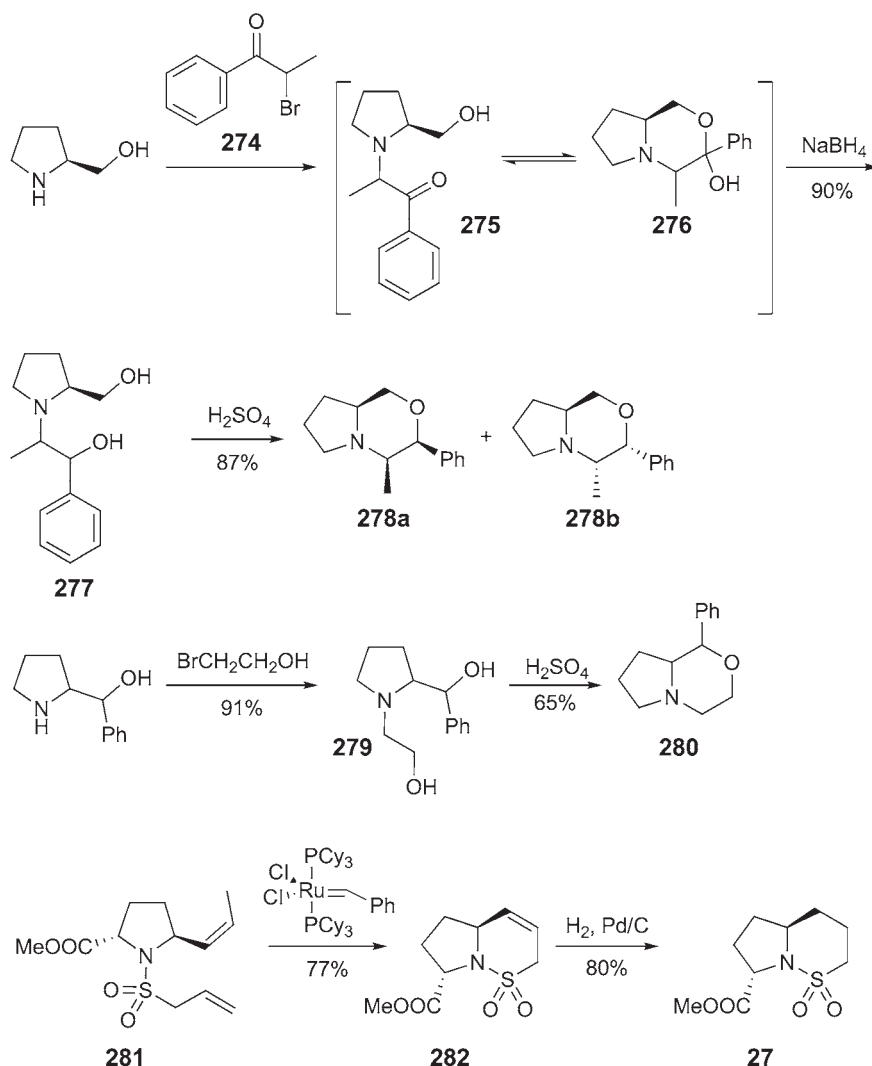
Scheme 35

electrolysis platform [<2000JCO545>](#). Analogously, conformationally constrained reverse-turn peptidomimetic **270** was obtained directly by oxidation of the suitably protected dipeptide Pro-Ser **269**. Best conditions in this case were the use of two platinum foil electrodes, a constant current of 14mAcm^{-2} , and the use of MeCN as the solvent with tetrabutylammonium fluoroborate (TBABF₄) as the supporting electrolyte. Compound **270** behaves as an amino acid and can be inserted into a peptide strain to induce the constraint [<1996JOC1198>](#). Compound **270** was also obtained by anodic oxidation of the silylated proline derivative **271** (Scheme 35). The introduction of silicon was required as the authors observed that first attempts to oxidize the proline directly failed [<2002OL1547>](#). Product **270** was obtained in a somehow complementary approach starting from the dipeptide derived from serine and pyroglutamic acid **272**. The cyclic carbonyl group was selectively reduced with LiBEt₃H to give hemiaminal **273** that cyclized in the presence of TFA to give **270** [<2001TL4943>](#).

Prolinol has been also the starting material in a synthesis of pyrroloxazines that are cyclized through an etherification mediated by H₂SO₄. Alkylation at the nitrogen with propiophenone **274** gave the substituted prolinol **275** that resulted in an equilibrium with the lactol form **276**. Reduction of the carbonyl gave the diol **277** that cyclized to the 3,4-*trans*-product as a mixture of diastereoisomers **278a** and **278b** (Scheme 36). On the other hand, starting from the substituted proline alkylated at the nitrogen **279**, H₂SO₄-mediated cyclization gave 1-phenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine **280** [<1997JHC1813>](#).

A series of bicyclic sulfonamides such as **282** and the corresponding reduced compounds were synthesized from 4-alkenyl *N*-alkenylsulphonyl prolines **281** using a ring-closing metathesis (Scheme 36). The synthesis of the starting material was previously described by the same authors [<2003T7047>](#).

Guanidine functionality has been found in a high number of pharmacologically active natural compounds and some of them contain the pyrrolo[1,2-*c*]pyrimidin-1(2*H*)-imine fragment. Consequently different synthetic approaches

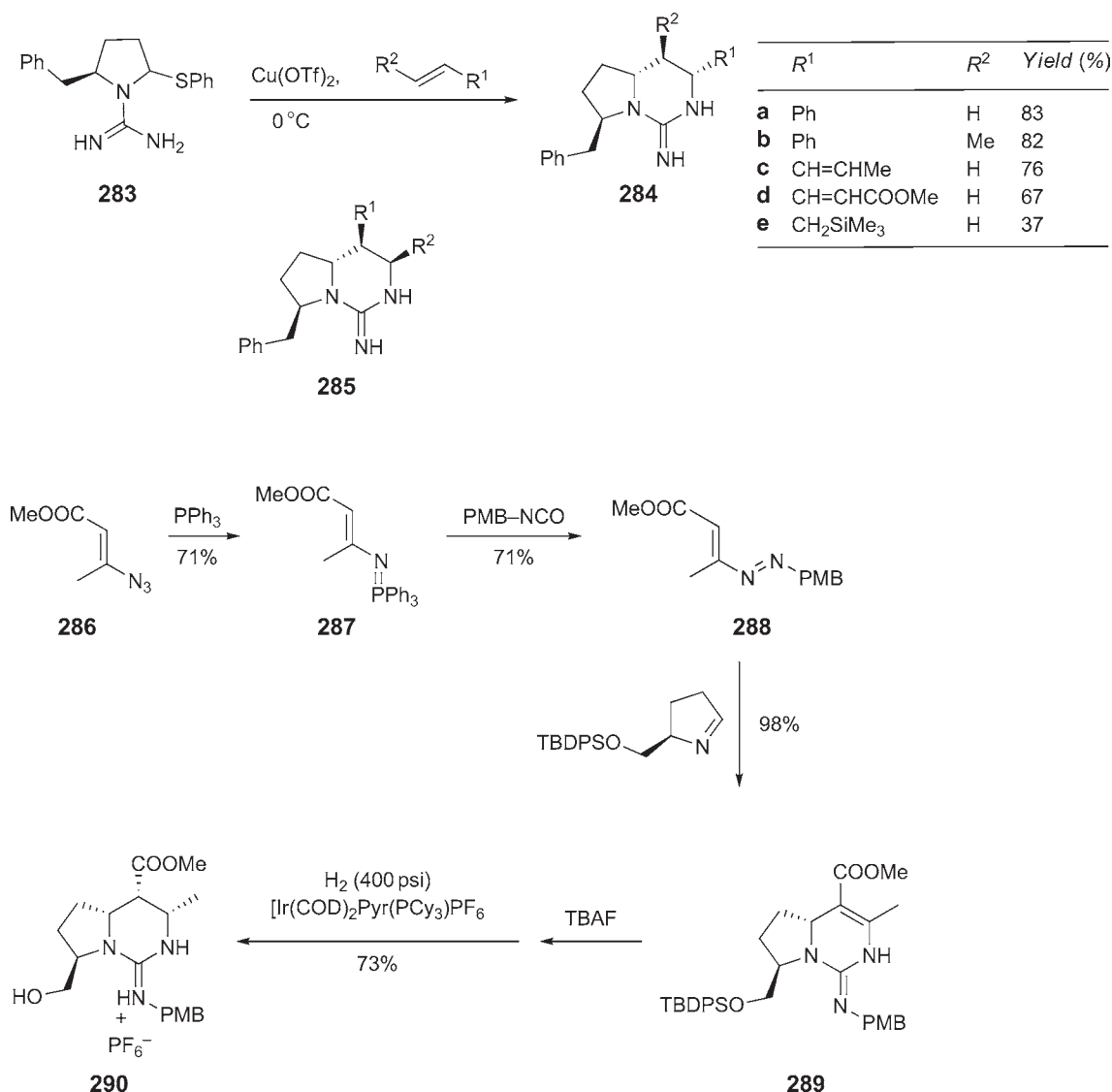


Scheme 36

have been described to access this heterocyclic system. One of the first (and also more profitable) methods employed was the generation of an *N*-amidinium ion to be used in cycloaddition procedures (Scheme 37). Starting from the thioaminal **283**, it was possible to generate with $\text{Cu}(\text{OTf})_2$ the amidinium ion that was trapped with different alkenes to give compounds **284a–e** with an acceptable stereoselection. The reaction proved to be stereospecific exclusively with (*E*)-alkenes. In fact, when (*Z*)-alkenes were used, an equimolecular mixture of compounds **284** and **285** was obtained <2001JOC3167>.

Another example of the use of a cycloaddition reaction to form this bicyclic system was based on the annulation of vinylcarbodiimides with imine. Carbodiimide **288** was prepared from the corresponding azide **286** and PPh_3 followed by an aza-Wittig reaction with a benzylisocyanate. The [4+2] annulation with a chiral dihydropyrrole provided efficiently the (*S,S*)-diastereoisomer **289**, a substructure related to batzelladine alkaloids with the requisite *anti*-relationship of the hydrogens at C-8 and C-11. Further hydroxy-directed hydrogenation with Crabtree's catalyst provided the guanidino ester **290** as a single diastereoisomer in 73% yield <2005JA6924>.

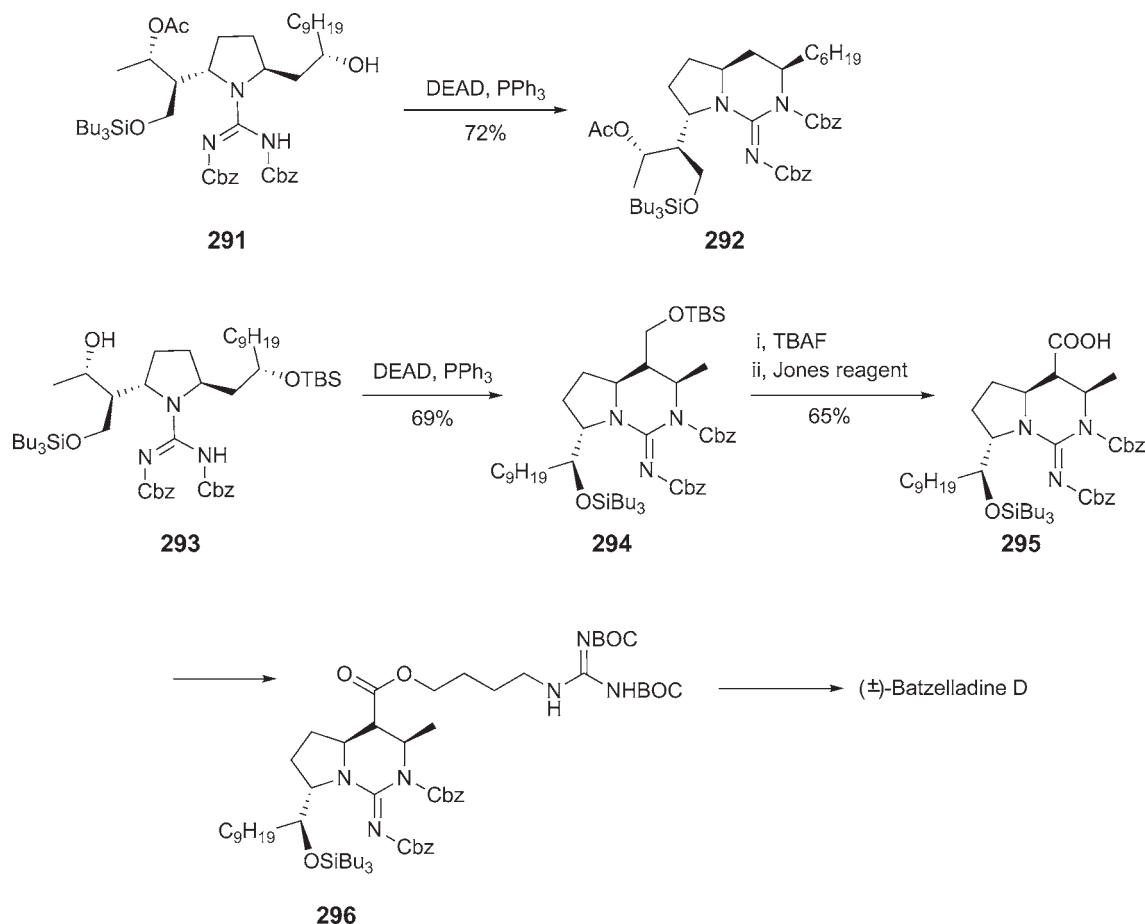
A practicable alternative to the above-mentioned approaches is the possibility to close the second ring when some of the functional groups are already installed in the molecule. Compound **291** (in a racemic form), obtained from pyrrolidine-derived nitrone in eight steps, was cyclized under classical Mitsunobu condition (DEAD, PPh_3 in THF) to give guanidine **292** <2001TL4155, 2002TL6383>. In a complementary approach, the guanidine **293** was cyclized via a Mitsunobu reaction to afford the bicyclic compound **294**. Selective cleavage of the primary silyl ether followed



Scheme 37

by Jones oxidation gave bicyclic guanidine carboxylic acid **295**. This compound was esterified with a long-chain ω -*N*-BOC guanidine alcohol (whose preparation is described in the paper), and intermediate **296** was additionally cyclized via a second Mitsunobu reaction to give ($\pm$)-batzelladine D (Scheme 38) <2002OL2921>. The same synthetic steps, relative to the formation of the hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-imine intermediate, were repeated with further variations in the synthesis of other biologically active members of this class of polycyclic guanidine alkaloids, isolated from Bahamian and Jamaican sponges, such as (+)-batzelladine A <2004AGE1559> and (–)-batzelladine D <2005CEJ6878>.

In a completely different approach to the same family of alkaloids, based always on the same hexahydropyrrolo[1,2-*c*]pyrimidin-1(2*H*)-imine intermediate, Overman *et al.* investigated a series of inter- and intramolecular Biginelli reactions on guanidine derivatives. The key reaction was a tethered Biginelli reaction of guanidine masked cyclic aldehyde such as **298**, obtained by oxidative cleavage of the double bond of unsaturated guanidine **297**, with β -ketoester **299** <2004OL1253>. The bicyclic compound **300** was then elaborated in different ways for the synthesis of several members of the family of guanidine alkaloids. The five-membered cyclic guanidine can also be a simple intermediate and the reaction carried out in one overall step as in the synthesis of **303**. The imidazole-based guanylation agent was reacted with amino acetal **301** and the intermediate **302** immediately condensed with allyl acetoacetate to provide the



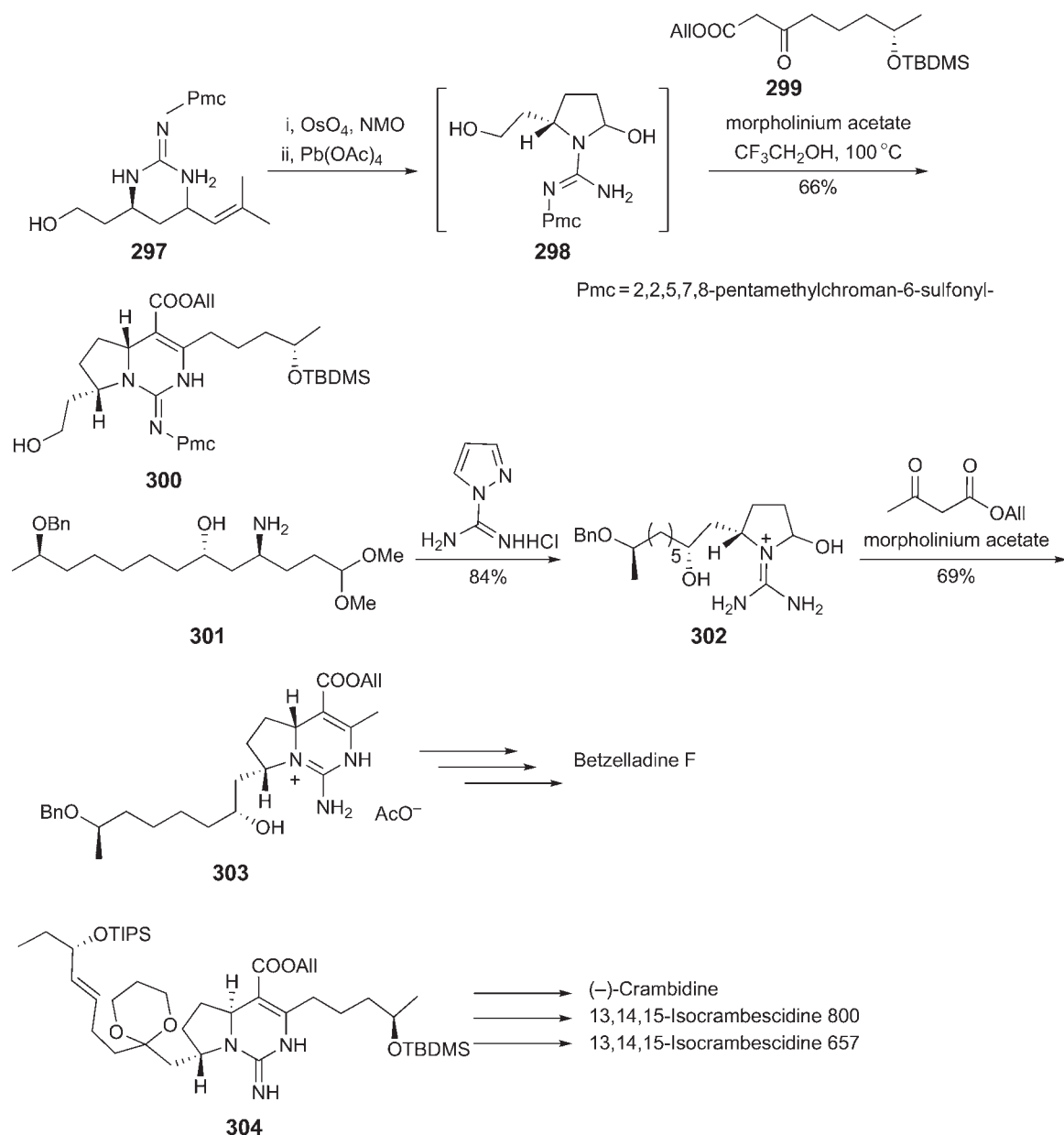
Scheme 38

Biginelli product in 45% yield as an 8:1 mixture of diastereoisomers. This intermediate **303** was used for the synthesis and the structural revision of batzelladine F [\[2006JA2594\]](#). A variation in the structural moiety of the starting cyclic masked guanidine and in the ketoester employed in the Biginelli reaction produced compound **304** (Scheme 39) that was employed in the synthesis of other members of the family such as two isocrambescidines [\[2000JA4904\]](#), and the (3*S*,8*S*,10*S*,19*R*,43*S*)- and (3*S*,8*S*,10*S*,19*R*,43*R*)-isomers of crambidine [\[2005JA15652\]](#).

A double tethered Biginelli reaction was carried out on the simple five-membered urea aldehyde **305** that reacted with the aliphatic and aromatic bis-ketoesters **306** and **307** giving compounds **308** and **309**, respectively, in good yield, albeit with a diastomeric ratio of 1:3. A series of different polycyclic bis-guanidines resembling batzelladine alkaloids were prepared [\[2003OL4485\]](#).

A similar but simpler 4-imino-hexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one **311** was prepared starting from the product obtained by nucleophilic substitution of a primary amine to the bromoacetamide of the L-prolylnitrile **310** (Scheme 40). The cyclization occurred directly in basic medium by refluxing for 96 h in EtOAc. This compound showed a potent activity as an orally bioavailable dipeptidyl peptidase IV inhibitor with anti-hyperglycemic properties [\[2003JME2774\]](#).

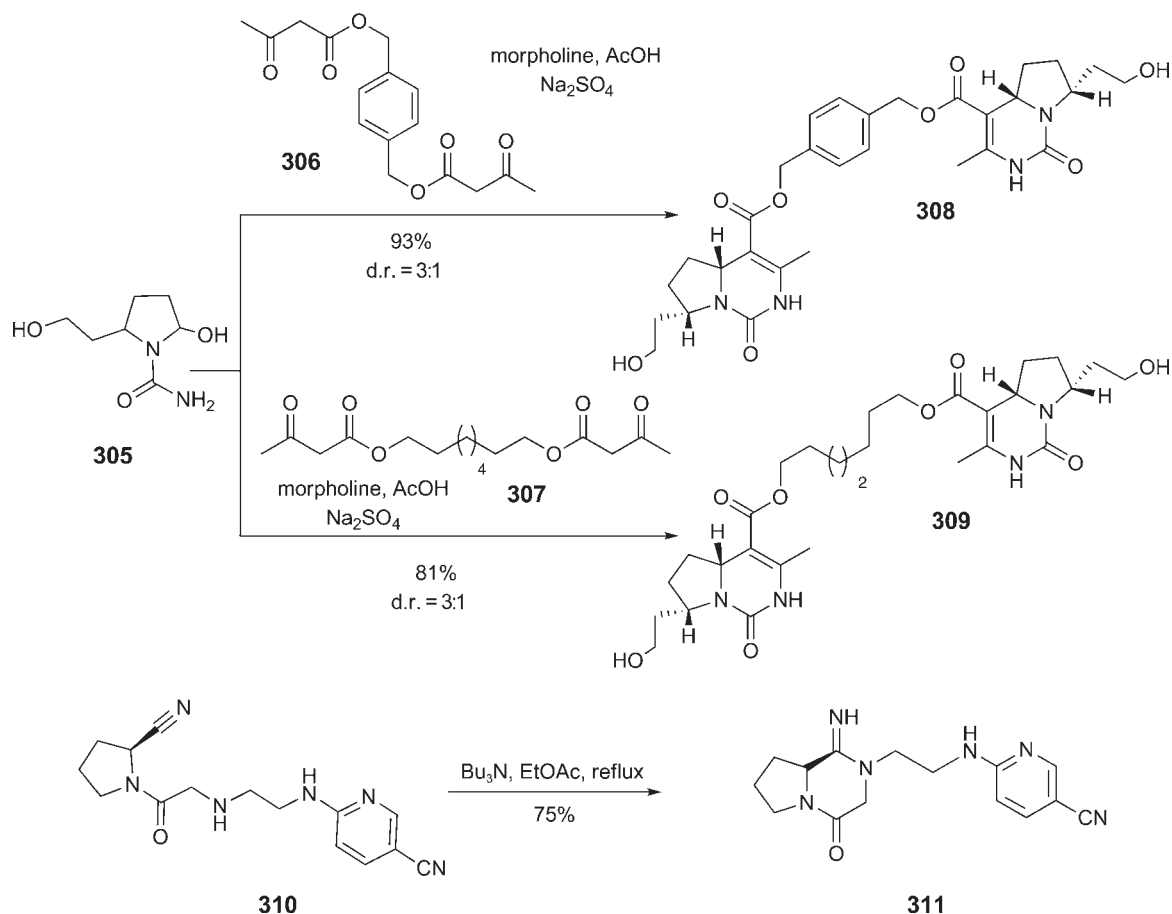
The octahydropyrrolo[1,2-*a*]pyrazine **314** was prepared by intramolecular cyclization on the intermediate unstable aldehyde **313**, obtained by ozonolysis of alkenylproline dipeptide **312**. Cyclization occurred after deprotection of the NHCbz by hydrogenolysis. The imine formed was immediately reduced (H₂, Pd on BaSO₄) to give compound **314**. The use of the Cbz protecting group proved to be important for the cyclization step. In fact, when an analogous reaction was attempted on the *N*-BOC derivative, the monocyclic hydroxyalkylamide derived from ozonolysis was recovered without subsequent reduction with hydrogen. The bicyclic system **314** was introduced as a constraint in the place of Phe⁷ or Phe⁸ in substance P to prepare a series of analogues as **315** (Scheme 41) [\[2000JOC2484\]](#).



Scheme 39

A similar scaffold for the preparation of peptidomimetics was prepared by Mitsunobu cyclization of the molecule coming from the coupling of 4-benzylprolinol and *N*-nosyl(*o*-nitrobenzensulfonyl) tryptophan **316** (Scheme 41). A Mitsunobu cyclization occurred easily due to the acidity of the NH of the nosyl group that could be further selectively deprotected under very mild conditions. The so-formed bicyclic amine **317** can be further coupled with different amino acids to give compounds **318**, employed in the search of a new somatostatin pharmacophore <2005BML4033>.

A nucleophilic alcoholic function was also used in the cyclization carried out on the epoxide prepared from the cinnamide **319** derived from prolinol. Epoxidation was done with *tert*-butylhydroperoxide and butyllithium. The presence of the strong base allowed the contemporary formation of the alkoxy salt that gave the ring opening of the epoxide and cyclization. The reaction proved to be highly stereoselective, giving compound **321** almost enantiopure. The same behavior was observed with the cinnamyl derivative of proline amide giving the corresponding



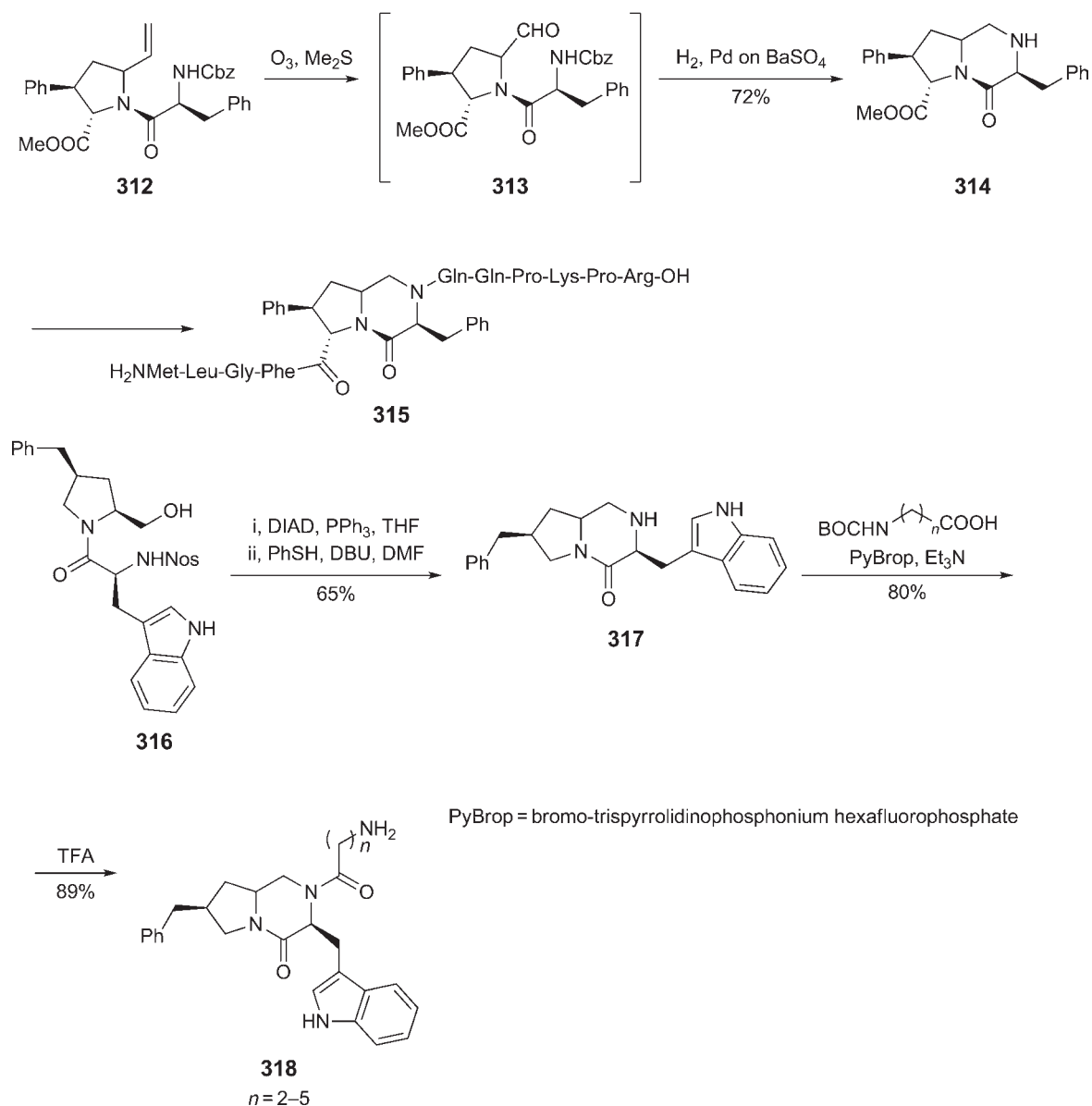
Scheme 40

diketopiperazine **322** <2000CC495>. An analogous attempt to cyclize the crotonyl amide of prolinamide **323** was tried using a phenylselenium-induced lactamization with PhSeBr in the presence of AgOTf. The diketopiperazine **324** was obtained as a mixture of diastereoisomer. The cyclization to give the second six-membered ring occurred exclusively with (*S*)-*trans*-crotonyl derivatives, whereas a different pattern of substituents and stereochemical arrangements generated the seven-membered bis-lactam **325** <1998J(P1)969>.

The amide derived from L-proline methyl ester and pyruvic acid **326** (Scheme 42) has been treated with ammonia in DME to give the intermediate diketopiperazine **327** as a mixture of diastereoisomers. The treatment of this product with BOC₂O in the presence of DMAP gave the dehydrated *O*-BOC product **113**. This compound was reactive toward different dienophiles giving the corresponding adducts in high yield on heating (Section 11.11.6). An analogous methoxy derivative **117** was prepared starting from the amide derived from *N*-Cbz proline and dimethylamino malonate **328**. Hydrogenolysis gave directly the diketopiperazine **329** that was then alkylated at the C-3 position with an unsaturated bromide. Further settlement of functional groups gave product **117**, the model compound for intramolecular cycladdition studies <2000T6345>.

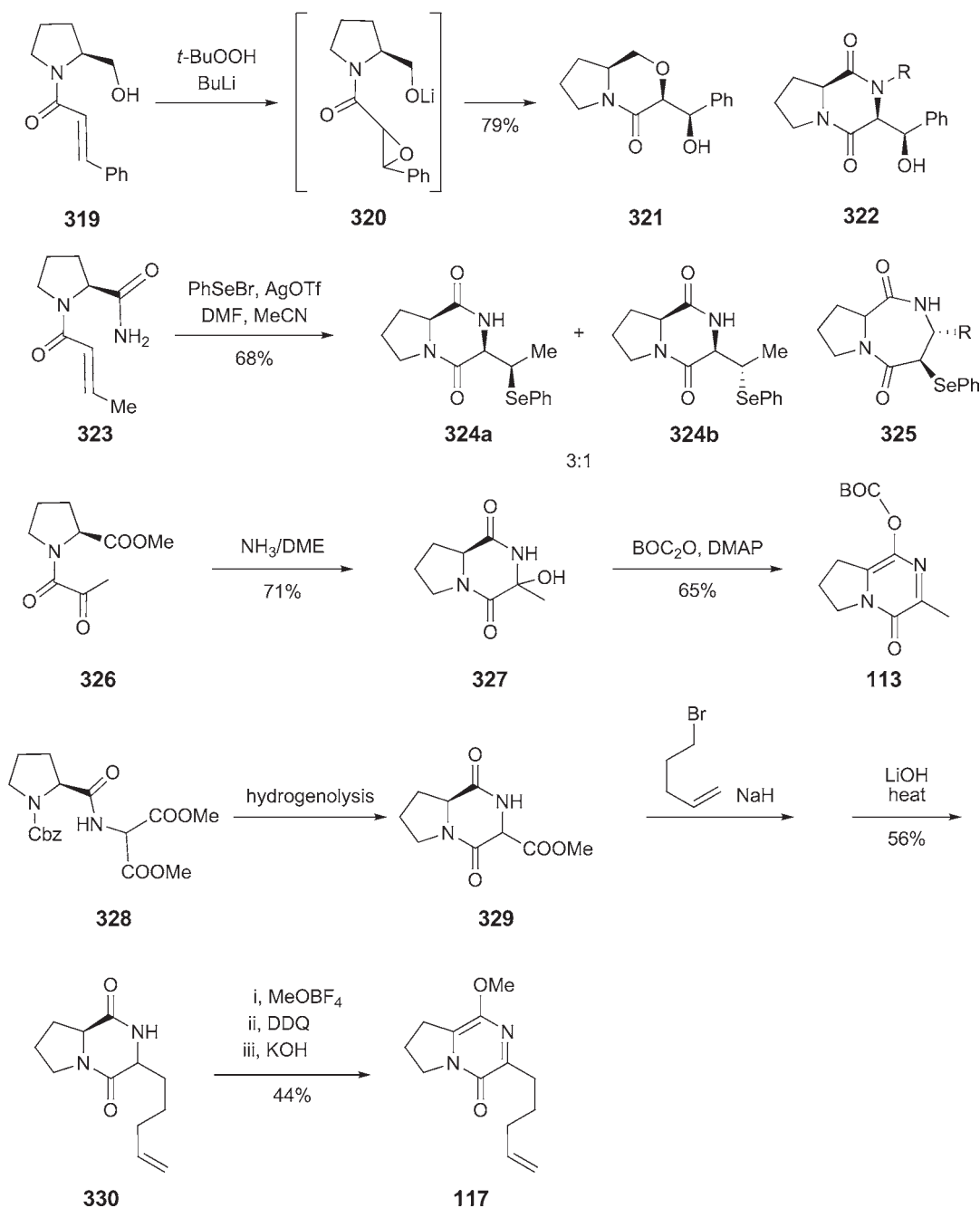
The most common bicyclic 5-6 system with one bridgehead N–O and one extra heteroatom described in the period covered in this chapter has been the diketopiperazine derived from proline as it is present in natural products, in biologically active synthetic molecules, and has been used as starting material for the preparation of conformationally constrained peptidomimetics. The classical approach to this class of molecule is the ring closing of the dipeptide derived from proline and another amino acid via nucleophilic attack of the NH₂ to the activated carboxylic group. This method has been applied several times to prepare different diketopiperazines for different uses.

Compound **331** was prepared using the free amino acid derived by coupling the product between proline and a substituted tryptophan. It was employed for studies on the biosynthesis of the anthelmintic agent paraherquamide <2001T5303>. Compound **332** was obtained by TFA-mediated reaction from the corresponding NH-*t*-Bu dipeptide



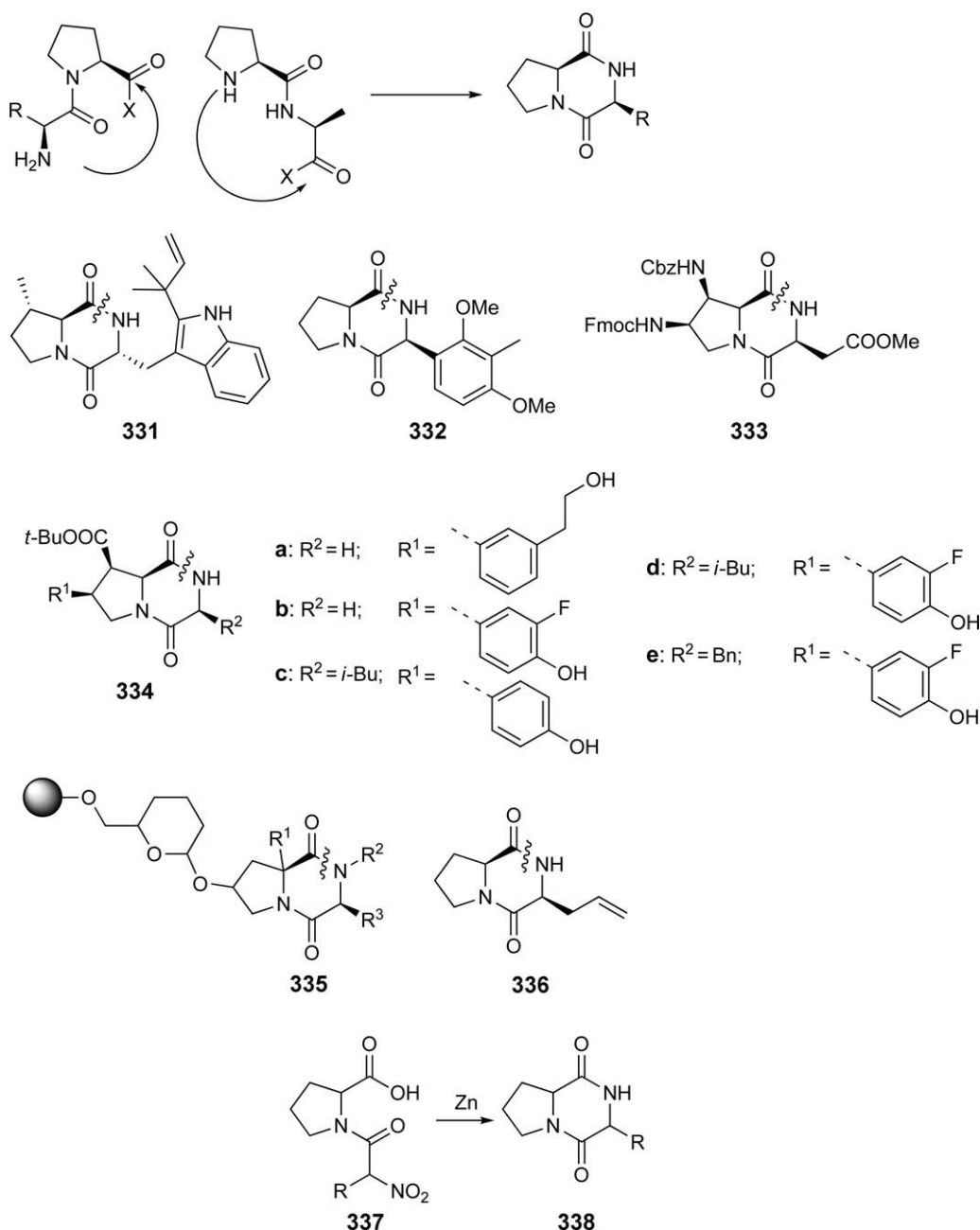
Scheme 41

methyl ester, obtained by Ugi reaction of proline, *t*-BuNC, and differently substituted aromatic aldehydes. This approach provided a series of unnatural amino acids (with the (*S*)-stereochemistry) as the second moiety linked to proline. Compound **332** was prepared in order to define the absolute and relative configuration of the products by single crystal X-ray diffractometry [\[2004OL3281\]](#). The same synthetic approach was used in the cyclization of the dipeptide prepared from (2*S*,3*R*,4*S*)-diaminoproline and L-aspartic acid. The template **333**, obtained by heating the diprotected peptide methyl ester [\[2000HCA444\]](#), was then incorporated into a cyclic loop mimetic in order to induce a stable β -hairpin conformation in solution [\[1998CC1977\]](#). A library of diketopiperazines with general formula **334a-e** was prepared on solid phase via a convergent diversity-oriented synthesis always based on cyclization of the amino acid dipeptide. These molecules can be considered as hybrids containing groups and moieties present in natural bioactive compounds [\[2005AGE2249\]](#). A library of diketopiperazines derived from 4-hydroxy-L-proline has been prepared on solid phase using a polystyrene-divinylbenzene (PS-DVB) resin with a tetrahydropyran (THP)-type linker. The synthesis procedure on solid phase was based on a series of alkylation, *N*-acylation, cyclization, and amide-bond alkylation. In this way, the three centers of diversity, R^1 , R^2 , and R^3 , were installed on **335** [\[2000JOC2179\]](#).



Scheme 42

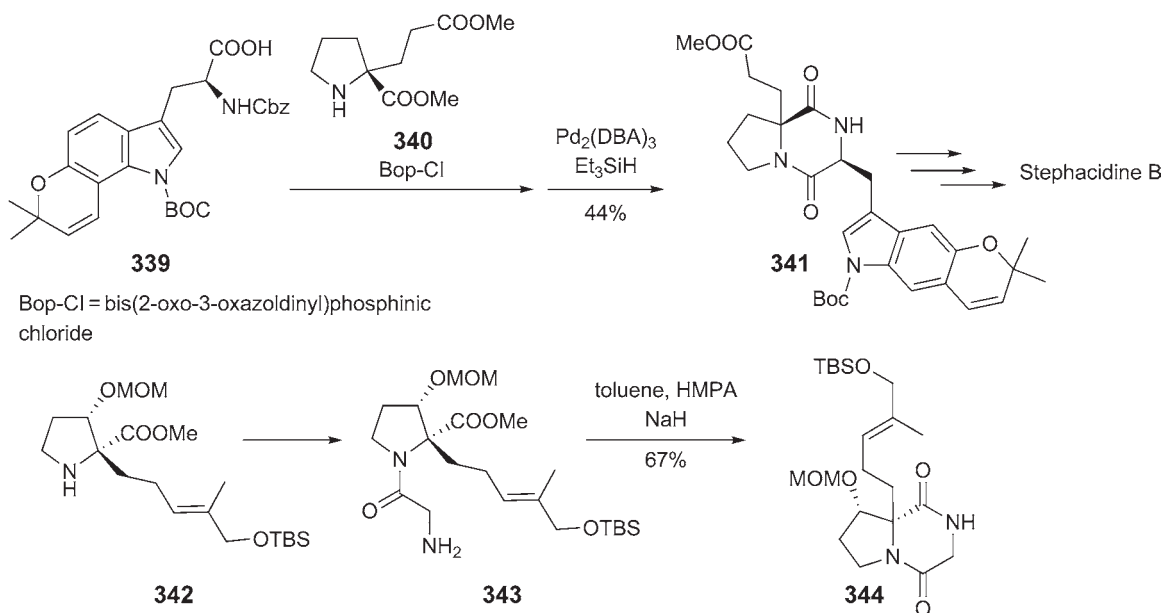
The various steps of this synthesis were also monitored by high-resolution magic angle NMR spectroscopy [\[2000JCO681\]](#). As the cyclization for preparing diketopiperazines occurs under heating, the influence of microwaves was investigated based on the nature of the substituents. The comparison was done with conventional heating and the best conditions for cyclization found were to start from *N*-BOC dipeptides and carry out thermal deprotection and cyclization under microwave irradiation without solvent [\[2005SS3412\]](#). Compound **336** was obtained as a reference compound from an intermediate, derived from proline, employed for preparation of the synthetically useful amino acid allylglycine [\[2004ASC1335\]](#). Finally, diketopiperazines **338** have also been obtained by reduction of *N*-nitroacetyl derivatives of L-proline methyl esters **337** by aqueous Zn–NH₄Cl mixture (Scheme 43) [\[1998J\(P1\)1319\]](#).



Scheme 43

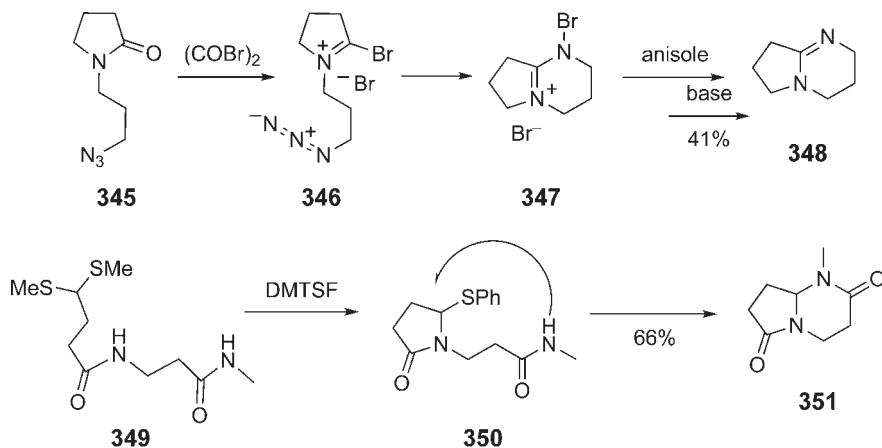
This classical approach has been also applied in the synthesis of relatively complex diketopiperazines that were then employed in the synthesis of complex polycyclic natural products. Compound **341**, obtained from **339**, was in fact used for the total synthesis of stephacidine B, an interesting prenylated alkaloid containing 15 rings, nine stereogenic centers around two octahydropyrrolo[1,2-*a*]pyrazine nuclei, and two oxindole substructures. On **339**, the amino acid coupling was carried out with Bop-Cl followed by Cbz deprotection achieved by Et_3SiH , mediated by $\text{Pd}_2(\text{DBA})_3$ (DBA = dibenzylideneacetone). Final cyclization by heating the resulting amino ester gave product **341** in good yield [\[2005AGE3892\]](#). The polysubstituted diketopiperazine **344**, the key intermediate for the synthesis of paraherquamide A, a fungal metabolite containing a bicyclo[2.2.2]diazaoctane core and a *spiro*-oxindole nucleus,

was analogously prepared. The synthetic approach was based on the preparation of the polysubstituted α -amino acid **342**; coupling and classical cyclization of the free NH_2 on the ester group was carried out in toluene/hexamethylphosphoramide (HMPA) and in the presence of NaH. These relatively unusual harsh conditions were required for the formation of a *cis*-structure such as **344** (Scheme 44) <2003JA12172>.



Scheme 44

A very convenient synthesis of hexahydropyrrolo[1,2-*a*]pyrimidines **348** (called also bicyclic amidines) has been described starting from a lactam having an azido group as in **345** (Scheme 45). Oxalyl chloride or bromide was very effective for the formation of a chloroiminium intermediate and gave the bicyclic compound **348** in high yield at room temperature. The reaction involves through an *N*-Br cyclic intermediate **347**, from which the bromine was scavenged at the end of the reaction with anisole, in order to obtain a clean compound <2004AGE478>.

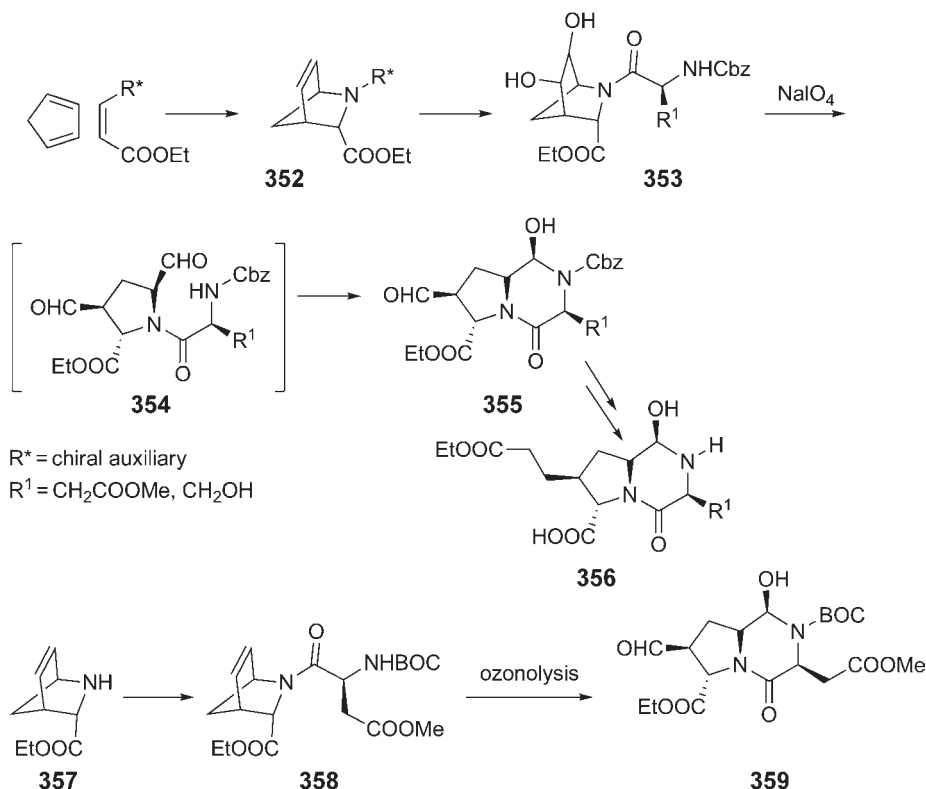


Scheme 45

Cyclisation of an NH amide toward a cyclic thionium ion was described for the synthesis of a tetrahydropyrrolo-[1,2-*a*]pyrimidine-2,6(1*H*,7*H*)-dione **351**. Compound **349** was transformed to **351** in two steps. The first one is the formation of a transient alkylthio-substituted lactam **350** from amidothioacetal **349** in the presence of dimethyl-(methylthio)sulfonium tetrafluoroborate (DMTSF) followed by intramolecular cyclization <2000JOC235>.

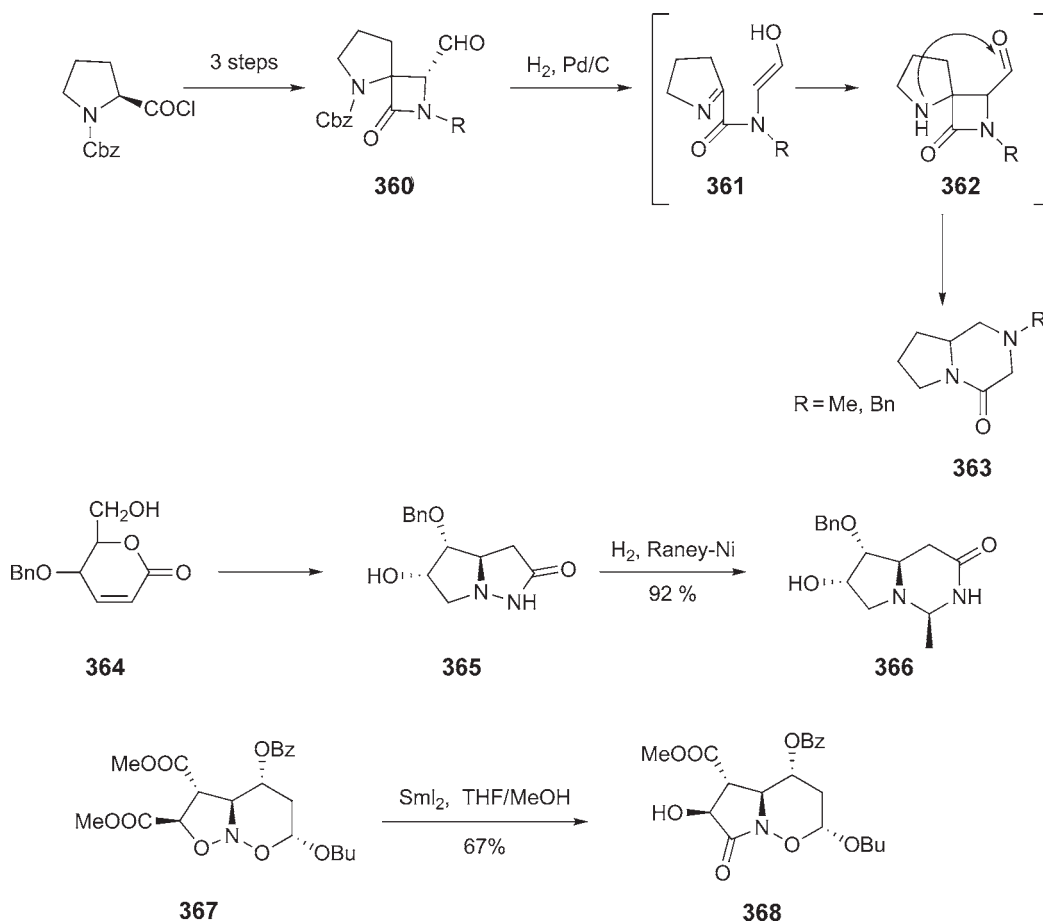
11.11.8 Ring Synthesis by Transformation of Another Ring

The stereoselective synthesis of different aldehydes of a hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one scaffold for modular dipeptide mimetics such as **353** has been reported starting from enantiomerically pure azabicyclic alkenes **352**. These intermediates were diols and coupled with a second amino acid. The product **353** was cleaved at the level of the 1,2-diol with NaIO₄ to give aldehyde **355**. The CHO function was then functionalized to produce a number of dipeptide mimetics with defined stereochemistry such as **356** <2004EJO1527>. The same authors later reported a successful preparation of azabicycloalkene **357** from which the product **358** could be prepared following standard peptide chemistry. This compound, when submitted to ozonolysis, gave the bicyclic aminal **359** in almost quantitative yield (Scheme 46). Also, this product could be transformed into polyfunctionalized bicyclic dipeptide mimetics <2006OL1681>.



Scheme 46

The nucleus of 2-substituted-hexahydropyrrolo[1,2-*a*]pyrazin-4(1*H*)-one was obtained by the rearrangement of easily available 4-formyl spiro- β -lactams protected as *N*-Cbz such as **360** (Scheme 47). When the hydrogenolysis catalyzed by Pd/C was carried out, the deprotection took place and compounds **363** were obtained probably through a ‘retro-Mannich’ process that involves the ring opening of the β -lactam. The intermediate imine **361** was reduced and the secondary amine **362** gave the cyclization via reductive amination. An enantiomerically pure version of this reaction has also been reported <2004TL4657>. A similar reductive rearrangement was observed during hydrogenolysis of the N–N bond of bicyclic pyrazolidinones **365**, obtained from α,β -unsaturated sugar lactones **364**, using H₂ and Raney-Ni. The reaction gave a hydroxy amide intermediate that cyclized *in situ* to the hydropyrrolo[1,2-*c*]pyrimidin-3(4*H*)-one **366** (Scheme 47) <1999JOC1347>.



Scheme 47

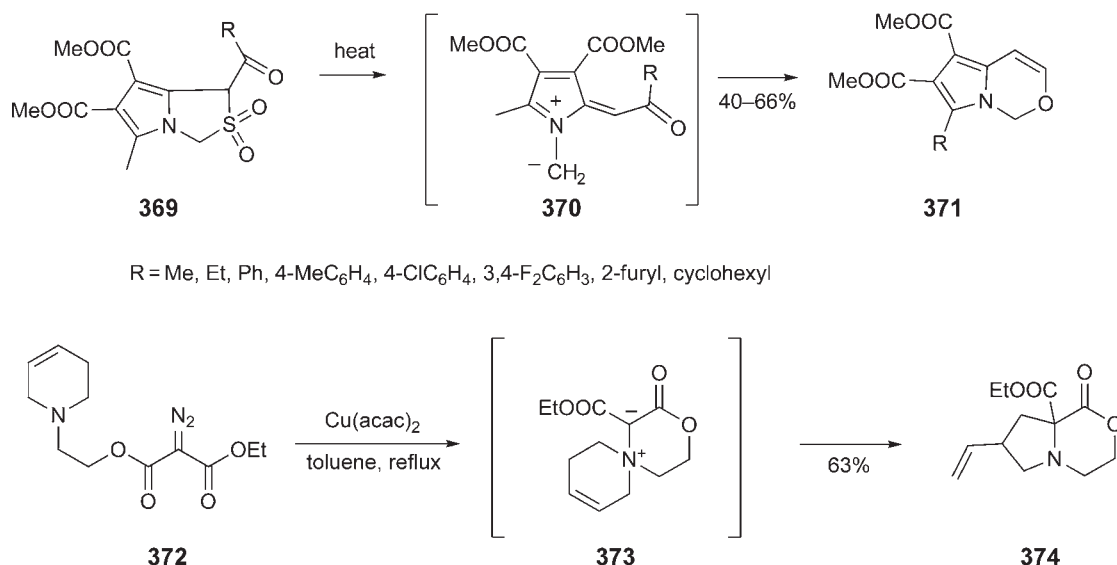
Hexahydro-2*H*-pyrrolo[1,2-*b*][1,2]oxazine-5-carboxylate **368** was obtained by ring opening of nitroso acetal **367** (obtained from a tandem double intramolecular cycloaddition) with SmI_2 (3 equiv). The ring opening by cleavage of the N–O at C-2 gave a hydroxy dicarboxylate intermediate that cyclized immediately to the hydroxylactam with complete retention of configuration [<2001CJC1606>](#).

A series of novel pyrroloxazines were prepared by thermal extrusion of sulfur dioxide from pyrrolo[1,2-*c*][1,3]thiazole 2,2-dioxides. The reaction on the acyl derivatives **369**, carried out at 600 °C and 10^{-3} mmHg, generated a transient azafulvenium methide **370** that electrocyclicized to oxazines **371** [<2001J\(P1\)1795>](#). The reaction was compatible with different aromatic and aliphatic groups [<2000CC675>](#).

Ylide **373** was also the intermediate for the Cu(I)-catalyzed transformation of the diazo malonyl ester of the tetrahydropyridine **372** to the 7-vinylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-8*a*-carboxylate **374** (Scheme 48) [<2005OL2075>](#).

11.11.9 Synthesis of Particular Class of Compounds and Critical Comparison of Various Routes Available

Saxitoxin is a small tricyclic structure isolated from oceanic red tides; it has attracted much interest for its peculiar structure and toxicity as a paralytic agent. The core structure that is related to a 1-iminoctahydropyrrolo[1,2-*c*]-pyrimidine nucleus was prepared by rearrangement after oxidation of a double bond contained in a medium-size guanidine ring. This key intermediate in the synthesis was prepared from azide **376** with a judicious use of Mbs



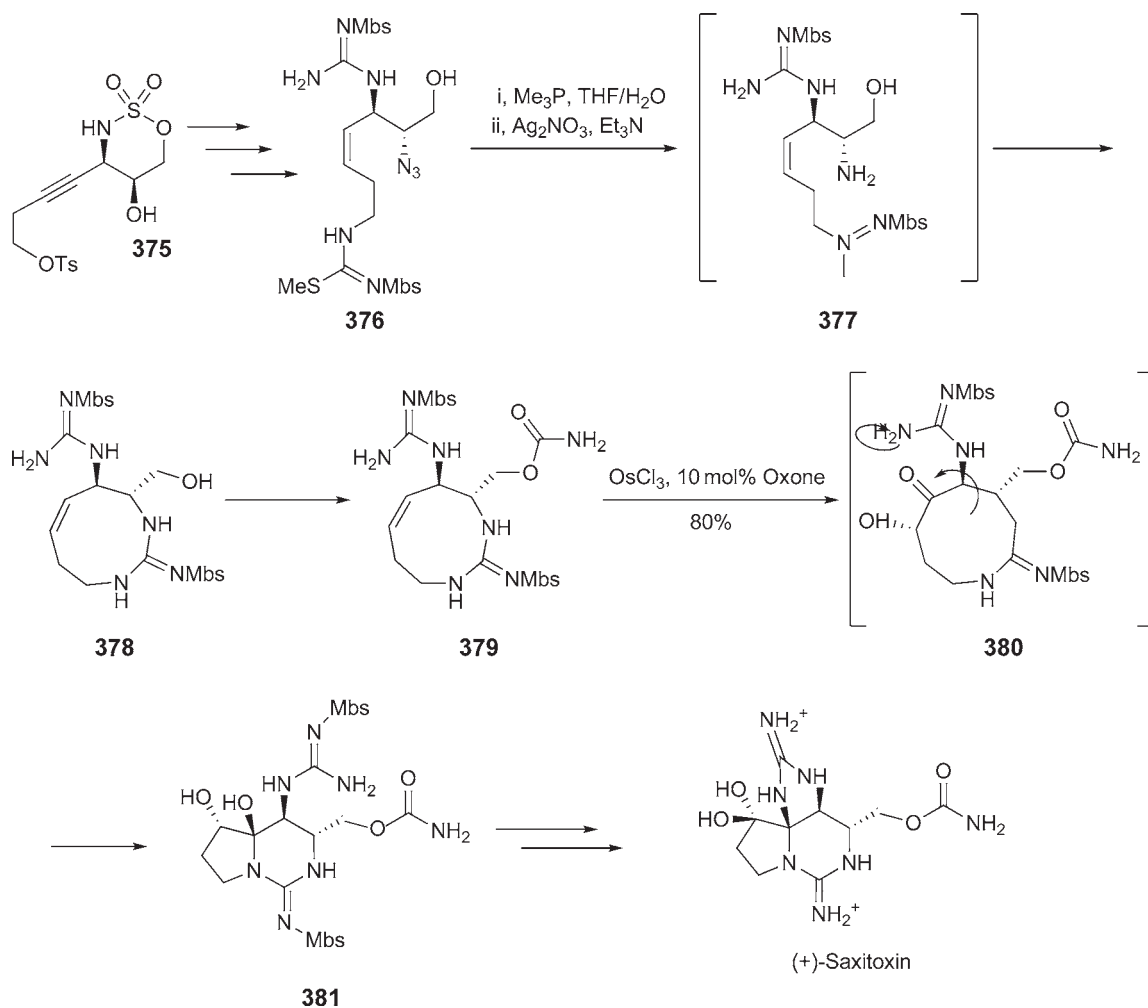
Scheme 48

(*p*-MeOC₆H₄SO₂⁻) protection on the guanidine and the pseudo thiourea functions. Azide **376** was prepared starting from easily available enantiomerically pure glycerol acetonide that produced intermediate oxathiazine dioxide **375** as a single isomer. Elaboration of the functional groups followed by reaction of the reduced azide with the carbodiimide function of **377** gave the nine-membered guanidine **378**. Functionalization at the C-13 OH with Cl₃CCONCO introduced the carbamate and selective oxidation with OsCl₃ and Oxone gave the hydroxyketone **380** that immediately cyclized to the required iminopyrrolo[1,2-*c*]pyrimidine **381**. Final cyclization of the third cycle and functional groups elaboration gave (+)-saxitoxin (Scheme 49) <2006JA3926>.

Tryprostatins A **386a** and B **386b** are indole alkaloid-based antifungal agents that act in the G2/M phase of the cell cycle, isolated from the fermentation broth of marine fungal strain of *Aspergillus fumigatus* BM939. They contain an isoprenyltryptophan moiety and a diketopiperazine unit fused with a proline. The classical approach to this class of molecule is based at first on the prenylation of tryptophan followed by classical formation of the dipeptide and ring closing to diketopiperazine (Scheme 50). For the synthesis of the unusual tryptophan structure **385a** and **385b**, the Schöllkopf auxiliary was employed for the contemporary introduction and protection of the amino acid function <2002JME1559>. Peptide coupling and ring closing gave **386a** and **386b**. A solid-phase synthesis of **386b** following this general approach has also been reported <2001TL1463>. An interesting alternative has also been reported based on the formation of the Trp-Pro diketopiperazine **387** followed by prenylation of the C-2 position of the indole ring. The required tryprostatin B was obtained in only 22% yield together with an inseparable mixture of the pentacyclic compound **388** arising from alkylation of the indole ring at C-3 and subsequent cyclization by nucleophilic attack of the neighboring piperazinedione nitrogen. It was possible, however, to recover additional tryprostatin B by TFA-mediated rearrangement of **388** that gave the trifluoroacetic ester **389**, easily transformed into the required compound **386b** by treatment with Et₃N in MeOH (Scheme 50) <2003JOC6944>.

Spirotryprostatin **394** has been isolated among secondary metabolites derived from *A. fumigatus*. Overman and Rosen have reported its synthesis using a substituted diketopiperazine as the key intermediate. The aldehyde **391** (prepared in six steps from allylic alcohol **390**) was coupled with the phosphonate derived from a Gly-Pro diketopiperazine **121**. Cyclization mediated by Pd₃(DBA)₂ on the aromatic ring gave the spiroindole **393** in good yield as a mixture of diastereoisomers. After deprotection and column chromatography to separate the diastereoisomers formed, natural (–)-spirotryprostatin **394** was isolated <2000AGE4596> (Scheme 51).

The total synthesis of paraherquamide A, the parent member of the family of fungal natural products isolated from a culture of *Penicillium parherquei* possessing potent anthelmintic and antinematodal properties, has been reported using a diketopiperazine as the scaffold for assembling the structure just before the cyclization. Compound **395** was prepared from α-amino acids following a standard procedure and then an additional carboxylic group was stereoselectively introduced at the C-3 position. Somei–Kametani <1981H(16)941> coupling of **396** with the gramine derivative **397**, in the presence of tributylphosphine, gave compound **398** as a mixture of diastereoisomers that were

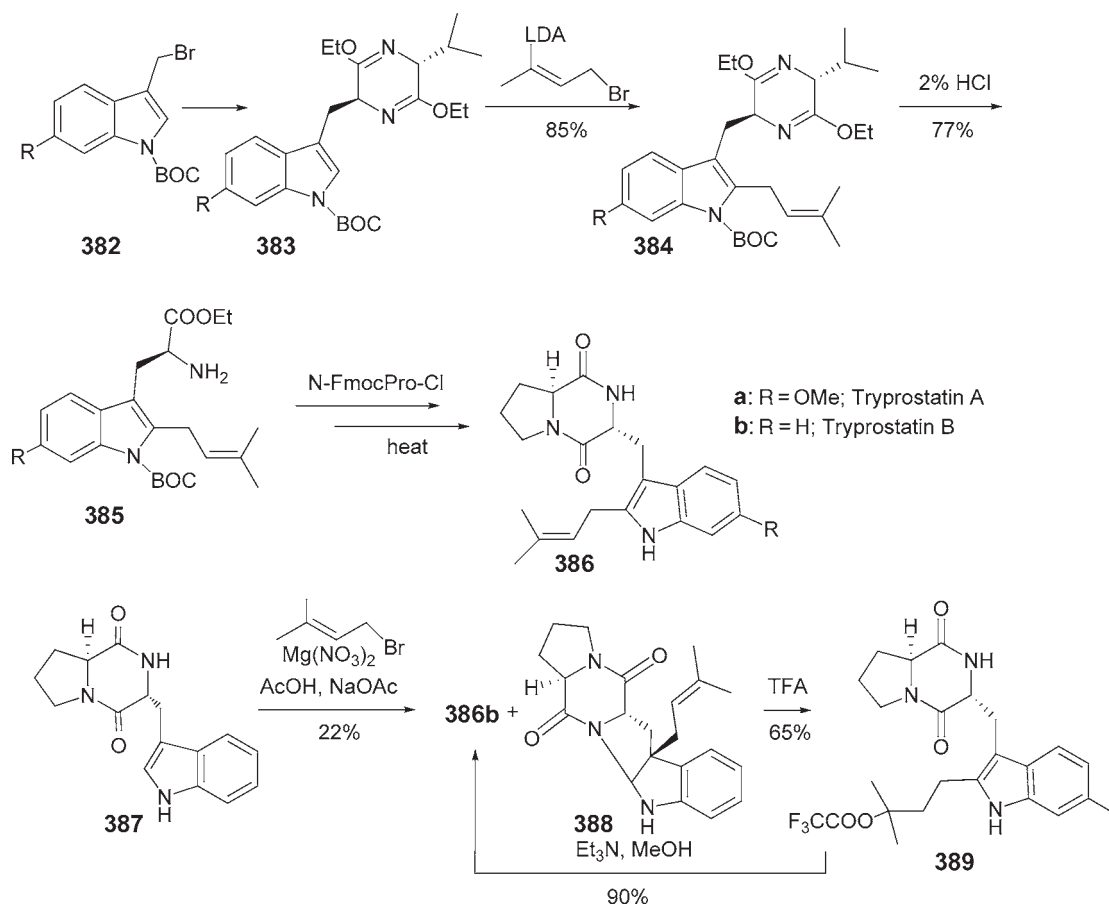


Scheme 49

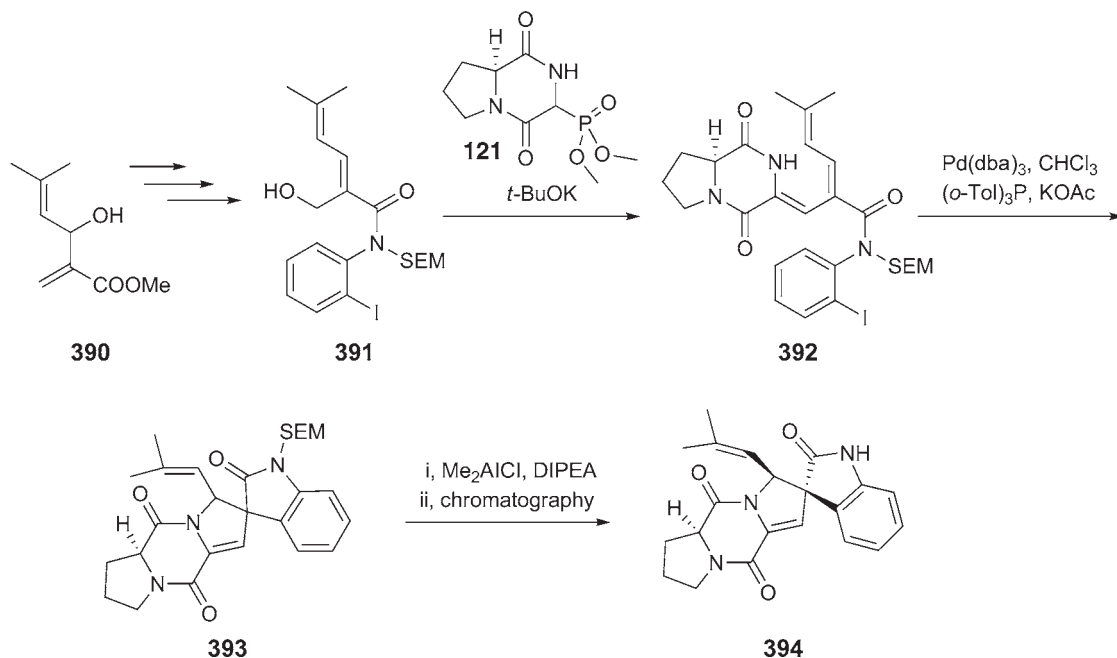
then decarboxylated to give **399** as a mixture of two isomers epimeric at the dioxepine alcohol. As this position was not a stereogenic center in the final compound, the synthesis was continued on the mixture. Product **399** was then elaborated through reorganization of functional and protective groups to afford **400** as a mixture of three different diastereoisomers. This product was ready for intramolecular nucleophilic substitution on the allylic chloride that was carried out with NaH in refluxing THF and that gave exclusively the *syn*-isomer **401**. Ring closing of the double bond on the indole ring and further rearrangement to give the spiroindole were the last important steps for the completion of the synthesis (Scheme 52) <2000AGE2540, 2003JA12172>.

An analogous approach has been employed for the synthesis of VM55599, another member of the same family of natural products. Diketopiperazine **402** was protected at the nitrogen as *N*-methylthiomethyl derivative and **403** was deprotonated at the C-3 position to react with a suitably protected prenyl-indole aldehyde **404**. The alcohol **405** was formed and further dehydrated and deprotected to give compound **406** that underwent intramolecular Diels–Alder reaction after reaction with AcCl for 14 days. The acetylation of the diketopiperazine gave a lactim intermediate **407** that tautomerizes to the other intermediate compound **408** that has the electronic and structural features to give the cycloaddition. Compound **14** was then rapidly transformed by reduction of one of the carbonyl groups into the required natural product (Scheme 53) <2000JA1675>.

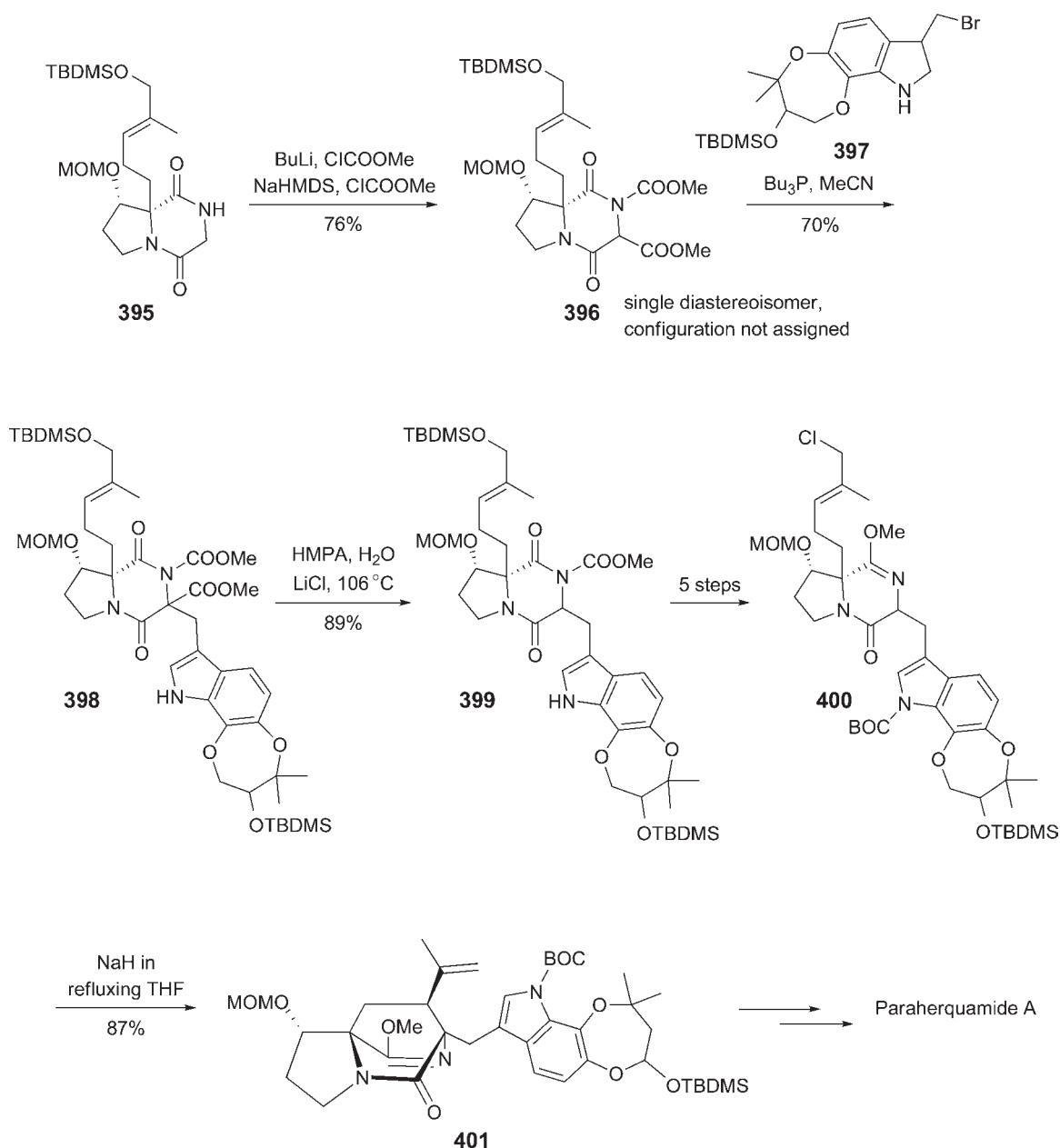
Brevioxime **25** is a natural product isolated from *Penicillium brevicompactum* and displays *in vitro* inhibition of juvenile hormone biosynthesis. Two different synthetic approaches have been described for this molecule. Different authors carried out the cyclization of the unsaturated ketoamide **409** in the presence of nitrosyl chloride that directly produced cyclization and led to the oxime <2001SL257, 2001T8699>. Starting from the same



Scheme 50



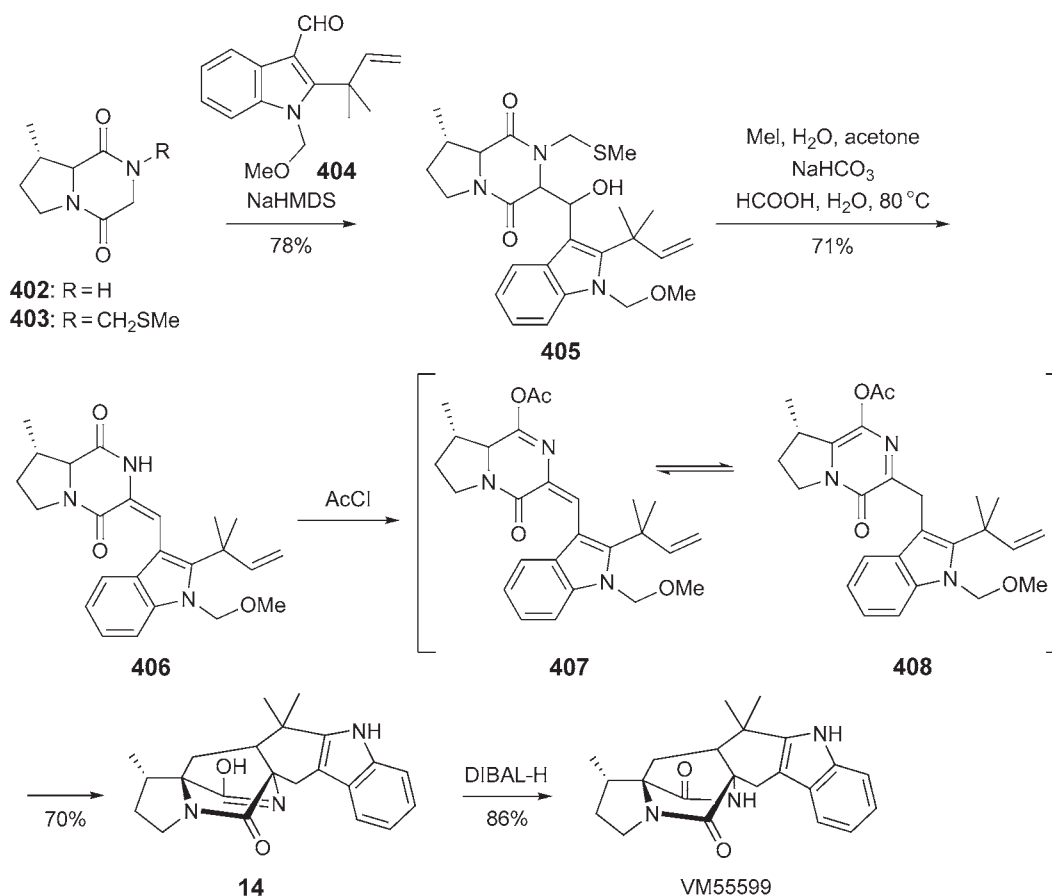
Scheme 51



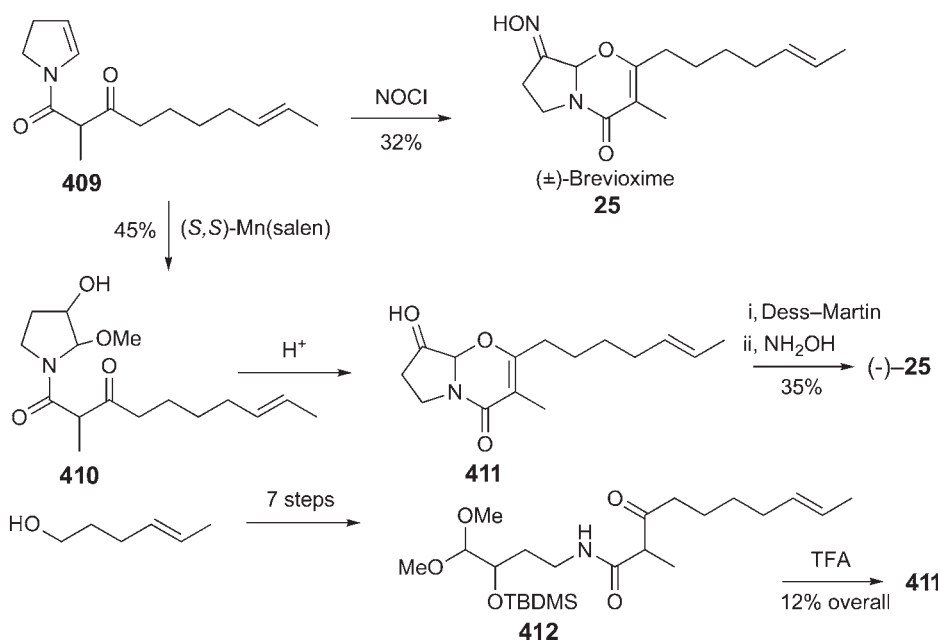
Scheme 52

intermediate amide, enantioselective oxidation of the pyrrolidine double bond gave the chiral amina **410** that was cyclized to alcohol **411** and then transformed to (–)-brevioxime, albeit in low yields and ee [\[2000T6181\]](#). Alternatively the cyclization was carried out directly on acyclic amide **412**, prepared in seven steps from 4-hexen-1-ol [\[1999CC2251\]](#). Cyclization with TFA gave directly the acetal hydrolysis, and after cyclization compound **411** was produced, from which brevioxime could be prepared as previously reported (Scheme 54) [\[2000JOC4923\]](#).

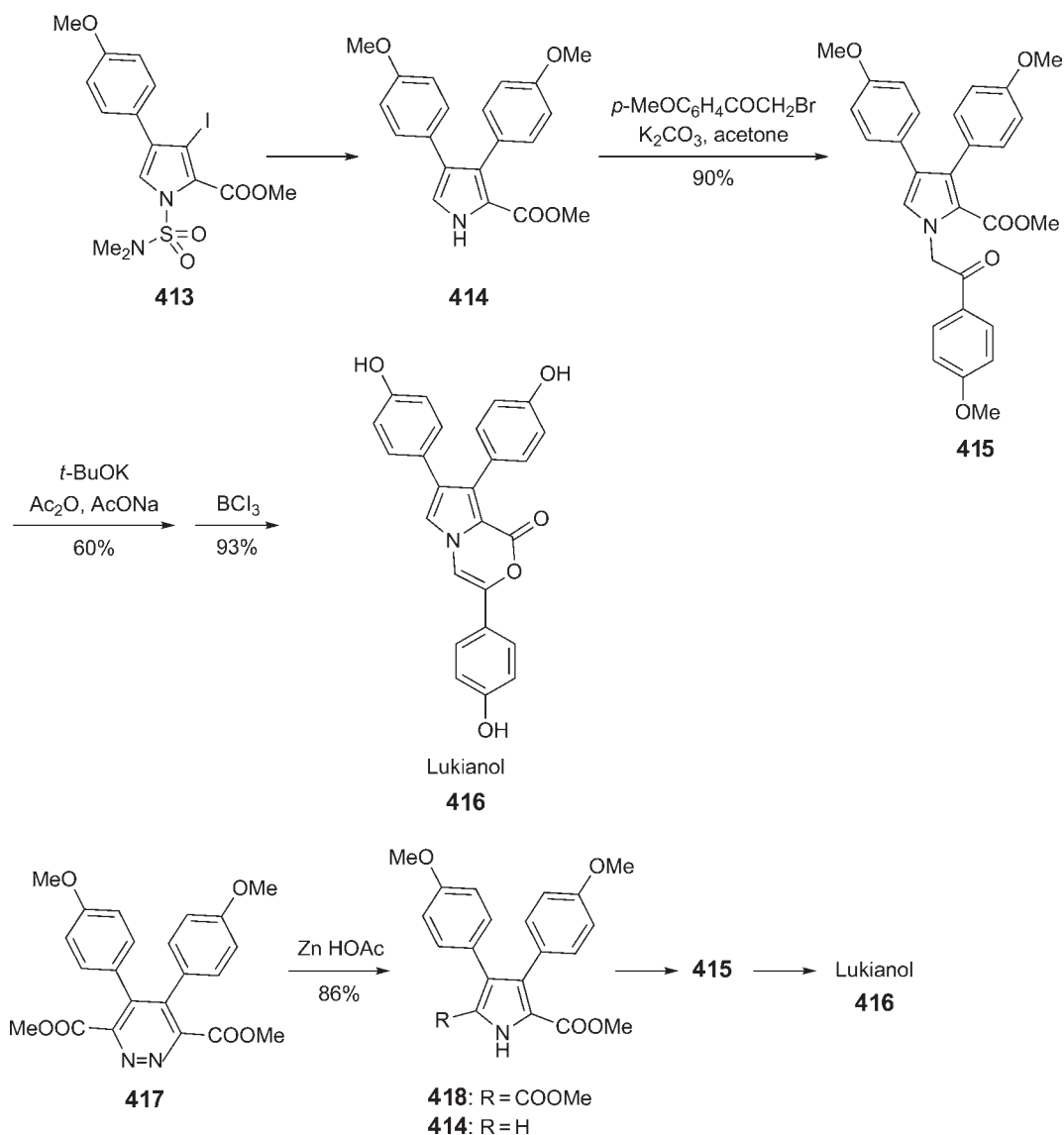
Different approaches for the preparation of polysubstituted pyrrole precursor of leukianol **416** have been described. Iodopyrrole **413** was coupled by using a Suzuki reaction to produce compound **414** that was alkylated, cyclized with *t*-BuOK, and finally deprotected to give lukianol [\[2000JOC3587\]](#). The intermediate **415** was obtained from 1,2-diazine **417** (available by cycloaddition of a symmetrical diaryl alkyne and 1,2,4,5-tetrazine). Decarboxylation and alkylation gave product **415** that was cyclized to lukianol as previously described (Scheme 55) [\[1999JA54\]](#).



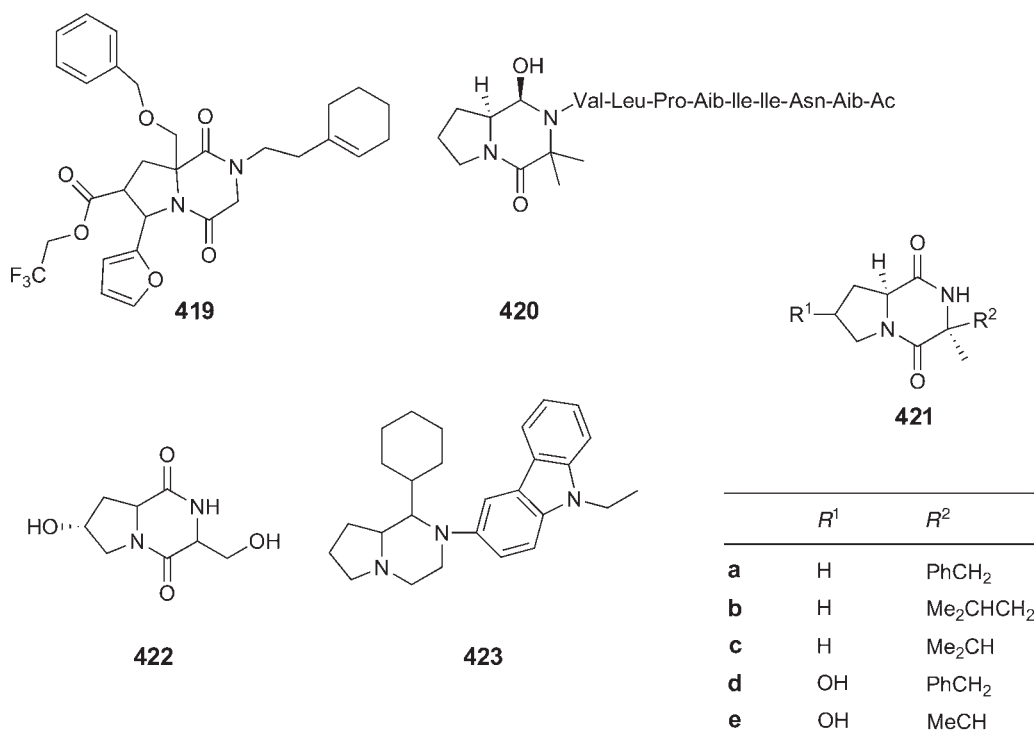
Scheme 53



Scheme 54



In addition to compounds with different biological properties already described in this chapter, different diketopiperazines showed important applications, mainly in the field of medicinal chemistry. Among an array of 6-(furan-2-yl)-hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione inhibitors of human hormone-sensitive lipase, a vital enzyme in lipid metabolism, compound **419** was active at 0.12 μM concentration [<2003JME1120>](#). Different diketopiperazines, isolated from different natural sources, showed antimicrobial properties. Aib (2-amino isobutyric acid) containing peptide **420** behaves as peptaibols that modify bacterial membranes. [<2000PES519>](#). (D,D)-Diketopiperazines **421a–e**, isolated from different marine bacteria, showed antibiotic activity against *Vibrio anguillarum* with a minimum inhibitory concentration (MIC) of 0.03–0.07 μM [<2003JNP1299>](#). Compound **422**, formally derived from a dipeptide formed by hydroxyproline and serine, exhibits a potent antihepatitis activity after oral administration [<2000JEP510>](#). A series of 1-cyclohexyl-octahydropyrrolo[1,2-*a*]pyrazines, with different substituents at C-2 position, showed a high activity as inhibitors of human *N*-myristoyltransferase 1. Best results were obtained with polar substituents, as in the case of compound **423** (Scheme 56) [<2004JEP340>](#).



Scheme 56

11.11.11 Further Developments

Most recent advances in the chemistry of the bicyclic heterocycles covered in this chapter include natural products synthesis. A new diastereoselective total synthesis of (+)-batzelladine A and (–)-batzelladine D has been described based on [4+2] annulation of vinyl carbodiimide with chiral N-alkyl amines <2006JA13255>. Lukianol has also been prepared by oxidative condensation of pyruvic acids with ammonia <2007S608>. Different complex natural products as stephacidin and parerquamides have been prepared through a cationic cascade starting from a diketopiperazine <2007JA6336, 2006TL8413>. For some recent application of diketopiperazine in asymmetric transformations see <2007TA464, 2006HCA1894>. Finally some synthetic biologically active diketopiperazines have been described such as peptidomimetic targeting the melanocortin receptors <2006BML5462> or as inhibitors of soluble epoxide hydrolase <2006BM6586>.

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Biographical Sketch



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11.12

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 1:1

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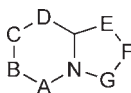
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11.12.1 Introduction

This chapter follows a similar structure to that in CHEC-II(1996) <1996CHEC-II(8)345> and covers the literature which has appeared since 1995. As discussed previously, the ring systems **1–62** shown in **Table 1** have, with a few exceptions, received relatively little attention, and in many cases there has been no further report since 1995. In other cases relevant recent references are shown in **Table 1**. Ring systems **1**, **2**, and **60** have received somewhat more coverage, and ring system **42** continues to be the focus of much attention. The isoxazolo[2,3-*b*][1,2]oxazine **1** ring

Table 1 Ring systems **1–62**



<i>Compound name and number</i>	<i>Heteroatom location</i>	<i>Reference (comments)</i>
Isoxazolo[2,3- <i>b</i>][1,2]oxazine 1	A=G=O	Several references, e.g., <1999JOC884, 1999JOC1494, 2001EJO553>
Isoxazolo[3,2- <i>c</i>][1,4]oxazine 2	C=G=O	Several references, e.g., <1997T11869, 2000JOC8544, 2001TL5343, 2003OBC4302, 2005JOC4569, 2005TL2619, 2006EJO3235>
Isoxazolo[3,2- <i>b</i>][1,3]oxazine 3	D=G=O	<1998TL1255>
Isoxazolo[2,3- <i>c</i>][1,3]oxazine 4	B=G=O	<1998CAR505, 1998J(P2)2699, 1998MI1395, 2002HCA2138>
Oxazolo[2,3- <i>c</i>][1,4]oxazine 5	C=E=O	<1997TL4521, 2004EJO4802>
Oxazolo[4,3- <i>c</i>][1,4]oxazine 6	C=F=O	<1995TL6235, 1998CC2641, 1998T6089, 2003TA917, 2005S3271>
Oxazolo[3,4- <i>c</i>][1,3]oxazine 7	B=F=O	<1999TA1135, 2000JOC5668, 2003AXC225, 2003CAR1591>
Oxazolo[3,2- <i>c</i>][1,3]oxazine 8	B=E=O	<1995SL1027, 1997JOC2106, 1999TL4539, 2000T367, 2000TL8301, 2002EJO29>
Oxazolo[2,3- <i>b</i>][1,3]oxazine 9	D=E=O	No references since 1995
Oxazolo[2,3- <i>c</i>][1,4]thiazine 10	C=S, E=O	No references since 1995

(Continued)

Table 1 (Continued)

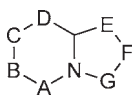
<i>Compound name and number</i>	<i>Heteroatom location</i>	<i>Reference (comments)</i>
Oxazolo[4,3- <i>c</i>][1,4]thiazine 11	C=S, F=O	No references since 1995
Oxazolo[3,4- <i>b</i>][1,2]thiazine 12	A=S, F=O	No references since 1995
Oxazolo[3,2- <i>c</i>][1,3]thiazine 13	B=S, E=O	No references since 1995
Oxazolo[2,3- <i>b</i>][1,3]thiazine 14	D=S, E=O	No references since 1995
Isoxazolo[2,3- <i>a</i>]pyrazine 15	C=N, G=O	<1996TL7339, 1996TL7343, 1998J(P1)1, 2000T7229, 2001JOC6046, 2003OBC1122, 2004EJO2321, 2005S465>
Isoxazolo[2,3- <i>a</i>]pyrimidine 16	D=N, G=O	<1995JOC5250, 1996JOC3212, 1997J(P1)1069, 2000BMC751, 2004JOC4996, 2004JOC5490>
Isoxazolo[2,3- <i>c</i>]pyrimidine 17	B=N, G=O	No references since 1995
Oxazolo[3,4- <i>a</i>]pyrazine 18	C=N, F=O	<1996S833, 1997TA1633, 1997TL45643, 1999J(P1)1677, 1999S1739, 2001T4359, 2001TA1293, 2004BMC3299, 2004JOC8805>
Oxazolo[3,2- <i>a</i>]pyrazine 19	C=N, E=O	<1998JA12783, 2000TL8735, 2003JCO278, 2003JME5117, 2003OL2727>
Oxazolo[3,4- <i>b</i>]pyridazine 20	A=N, F=O	<1995JA9190, 1996TL7951, 1997TL4947, 1999J(P1)3323, 2006JOC2293>
Oxazolo[3,2- <i>b</i>]pyridazine 21	A=N, E=O	<1996ZOR591, 2004JFL443, 2005HAC56>
Oxazolo[3,4- <i>c</i>]pyrimidine 22	B=N, F=O	<2000JOC5668, 2003OBC1532>
Oxazolo[3,2- <i>a</i>]pyrimidine 23	D=N, E=O	<1997JOC3109, 1997TL3323, 1998JOM(562)35, 2000OL633, 2001JHC823, 2001T195, 2001T3979, 2002SL1249, 2004PS1769>
Oxazolo[3,2- <i>c</i>]pyrimidine 24	B=N, E=O	<1997CC2311, 1998TL5373, 1998TL8911, 1999J(P1)3157, 2000MI413, 2001T10139, 2003CC844, 2005BMC3185, 2005BML1407, 2006PS(181)381>
[1,3]Azaphospholo[1,2- <i>a</i>] pyrazine 25	C=N, E=P	No references since 1995
[1,3]Azaphospholo[1,5- <i>a</i>] pyrazine 26	C=N, F=P	No references since 1995
[1,3]Azaphospholo[1,2- <i>b</i>] pyridazine 27	A=N, E=P	No references since 1995
[1,3]Azaphospholo[1,5- <i>b</i>]pyridazine 28	A=N, F=P	No references since 1995
Thiazolo[2,3- <i>c</i>][1,4]oxazine 29	C=O, F=S	<2002WO2002062301>
Thiazolo[4,3- <i>b</i>][1,3]oxazine 30	D=O, F=S	No references since 1995
Thiazolo[3,4- <i>c</i>][1,3]oxazine 31	B=O, F=S	No references since 1995
Thiazolo[3,2- <i>c</i>][1,3]oxazine 32	B=O, E=S	No references since 1995
Thiazolo[2,3- <i>b</i>][1,3]oxazine 33	D=O, E=S	<1995T10715, 2005OL1019, 2006S659>
Thiazolo[2,3- <i>c</i>][1,4]thiazine 34	C=E=S	<1995CPB78>
Thiazolo[4,3- <i>c</i>][1,4]thiazine 35	C=F=S	No references since 1995
Thiazolo[4,3- <i>b</i>][1,3]thiazine 36	D=F=S	No references since 1995
Thiazolo[2,3- <i>b</i>][1,3]thiazine 37	D=E=S	No references since 1995
Isothiazolo[2,3- <i>a</i>]pyrimidine 38	D=N, G=S	<2005PS(180)2291>
Thiazolo[3,4- <i>a</i>]pyrazine 39	C=N, F=S	<1995MI161, 1995T4763, 1997JHC49, 1997T12729, 1998TL2925, 2003SL817, 2005T66, 2006H(68)679>
Thiazolo[3,2- <i>a</i>]pyrazine 40	C=N, E=S	<1995MI161, 1995TL9313, 2002BML1047>
Thiazolo[3,2- <i>b</i>]pyridazine 41	A=N, E=S	<2006S103>
Thiazolo[3,2- <i>a</i>]pyrimidine 42	D=N, E=S	Many references, e.g. <2002SR47 (Review), 2003JOC4912, 2003T5411, 2003T7141, 2005PS(180)1713, 2005T6309, 2005T10774, 2006SC495>
Thiazolo[3,2- <i>c</i>]pyrimidine 43	B=N, E=S	<1997JHC435, 1999SL1379, 2001PS(170)87, 2003SUL35, 2005BMC3185, 2005BML1407, 2005PS(180)2407, 2005TL2045, 2006S37>
Thiazolo[3,4- <i>a</i>]pyrimidine 44	D=N, F=S	<2002SR47> (Review)
Selenazolo[3,2- <i>a</i>]pyrimidine 45	D=N, E=Se	<B-2001SOS(11)941> (Review)
Imidazo[2,1- <i>c</i>][1,4]oxazine 46	C=O, E=N	<1999T3987, 2001CHE1054, 2003CHE1084, 2006JME4623>
Imidazo[5,1- <i>c</i>][1,4]oxazine 47	C=O, F=N	<1998TL475>
Imidazo[5,1- <i>b</i>][1,3]oxazine 48	D=O, F=N	No references since 1995
Imidazo[1,2- <i>c</i>][1,3]oxazine 49	B=O, E=N	No references since 1995

(Continued)

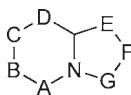
Table 1 (Continued)

Compound name and number	Heteroatom location	Reference (comments)
Imidazo[1,5- <i>c</i>][1,3]oxazine 50	B=O, F=N	<1997USP5643855>
Imidazo[2,1- <i>b</i>][1,3]oxazine 51	D=O, E=N	<2000NAT962, 2005T2645, 2006T3435>
Pyrazolo[5,1- <i>c</i>][1,4]oxazine 52	C=O, G=N	<2003TL5867, 2006JME4623>
Pyrazolo[5,1- <i>b</i>][1,3]oxazine 53	D=O, G=N	<2004BMC1357, 2004BML4945, 2004JOC7058, 2006JME4623>
Pyrazolo[1,5- <i>c</i>][1,3]oxazine 54	B=O, G=N	<2002T1199>
Imidazo[2,1- <i>c</i>][1,4]thiazine 55	C=S, E=N	<1999JCM322, 2006JME4623>
Imidazo[5,1- <i>c</i>][1,4]thiazine 56	C=S, F=N	<2002MI30>
Imidazo[5,1- <i>b</i>][1,3]thiazine 57	D=S, F=N	<2003OBC134, 2005JCO503, 2005JCO947>
Imidazo[1,2- <i>c</i>][1,3]thiazine 58	B=S, E=N	No references since 1995
Imidazo[1,5- <i>c</i>][1,3]thiazine 59	B=S, F=N	No references since 1995
Imidazo[2,1- <i>b</i>][1,3]thiazine 60	D=S, E=N	Several references, e.g. <1996JST(377)277, 1998CHE882, 2003CHE960, 2003EJO421, 2003JOC4912, 2003T7141, 2004AGE621, 2005PS(180)407, 2006PS(181)53>
Pyrazolo[5,1- <i>c</i>][1,4]thiazine 61	C=S, G=N	<2006JME4623, 2006TL7893>
Pyrazolo[5,1- <i>b</i>][1,3]thiazine 62	D=S, G=N	<1995H(41)1235, 2002TL1015, 2003OBC134>

system has been studied as the product of tandem [4+2]/[3+2] cycloaddition reactions, for example, <1999JOC884, 1999JOC1494, 2001EJO553>. Several groups have investigated the formation of the isoxazolo[3,2-*c*][1,4]oxazine **2** ring system by the cycloaddition of oxazine- and oxazinone-*N*-oxides to alkenes (see references in **Table 1**). The thiazolo[3,2-*a*]pyrimidine **42** ring system has received much attention, with many pharmacological studies appearing: this ring system is present in the atypical antipsychotic drug ritanserine, which is a 5-HT₂ receptor antagonist <1997BJP1105>. Ring system **42** has been reviewed <2002SR47>, and selected references on recent synthetic work are shown in **Table 1**. For the ring systems **63–74** shown in **Table 2**, all three heteroatoms present in the bicyclic system are nitrogen. These ring systems have received much more coverage than those shown in **Table 1**, because they can form fully delocalized aromatic systems, and this chapter will concentrate mainly on these systems. **Table 3** shows a small number of ring systems **75–83** which are new since 1995, but which generally are each covered by only one or two reports.

Table 2 Imidazodiazines **63–70** and pyrazolodiazines **71–74**

Compound name and number	Heteroatom location
Imidazo[1,5- <i>d</i>]pyrazine 63	C=F=N
Imidazo[1,2- <i>d</i>]pyrazine 64	C=E=N
Imidazo[1,2- <i>i</i>]pyridazine 65	A=E=N
Imidazo[1,5- <i>b</i>]pyridazine 66	A=F=N
Imidazo[1,2- <i>a</i>]pyrimidine 67	D=E=N
Imidazo[1,2- <i>c</i>]pyrimidine 68	B=E=N
Imidazo[1,5- <i>a</i>]pyrimidine 69	D=F=N
Imidazo[1,5- <i>c</i>]pyrimidine 70	B=F=N
Pyrazolo[1,5- <i>a</i>]pyrazine 71	C=G=N
Pyrazolo[1,5- <i>b</i>]pyridazine 72	A=G=N
Pyrazolo[1,5- <i>c</i>]pyrimidine 73	B=G=N
Pyrazolo[1,5- <i>a</i>]pyrimidine 74	D=G=N

Table 3 New ring systems 75–83

Compound name and number	Heteroatom location	Reference (comments)
Oxazolo[3,4- <i>b</i>][1,2]oxazine 75	A=F=O	<1999TL4391, 2001TL8535>
[1,3]Azaphospholo[1,5- <i>c</i>]pyrimidine 76	B=N, F=P	<2004IJB2431>
Thiazolo[3,4- <i>c</i>]pyrimidine 77	B=N, F=S	<1996H(43)1653, 2002SR47 (Review)>
Pyrazolo[1,5- <i>c</i>][1,3]thiazine 78	B=S, G=N	<1995PS(107)1>
Isothiazolo[2,3- <i>a</i>]pyrazine 79	C=N, G=S	<1998WO9858947>
[1,3]Azasilolo[1,5- <i>a</i>]pyrazine 80	C=N, F=Si	<2000JOM(613)19, 2006MI621>
Thiazolo[4,3- <i>c</i>][1,4]oxazine 81	C=O, F=S	<1997JHC49, 1997TL3611>
Oxazolo[3,4- <i>a</i>]pyrimidine 82	D=N, F=O	<1998TL93, 1998TL2985, 2002SL1831>
Isothiazolo[3,2- <i>b</i>][1,3]thiazine 83	D=G=S	<2003PS(178)2255>

11.12.2 Theoretical Methods

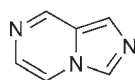
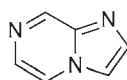
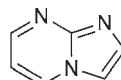
Recent applications of theoretical methods have been directed toward certain specific problems. Gaussian 94 HF/3-21G calculations on derivatives of **63** have been used to evaluate electrostatic potential maps, with the intention of correlating these with biological activities as corticotropin-releasing hormone receptor-binding ligands <2002BML291>. Semi-empirical AM1-COSMO calculations on various 3-oxo derivatives of **64** were found to reproduce the structures obtained by X-ray crystallography, with long C=O bond lengths consistent with increased zwitterionic aromatic character <2003BCJ2361>. The same study also included nuclear magnetic resonance (NMR) and UV/visible spectroscopy, aimed at understanding luminescent properties. Very similar 3-oxo derivatives of **64** have also been studied by *ab initio* HF/6-31G* calculations, and these have been correlated with antioxidant activities <2001BML2305>. The transition state structures for the retro-ene formation of 2,3-dihydro-5-oxo derivatives of **67** (see Section 11.12.9.5.2, Scheme 5) have been studied using B3LYP/6-31G** calculations <2005T5303>, showing that the bond breaking is asynchronous.

11.12.3 Experimental Structural Methods

11.12.3.1 NMR Studies

11.12.3.1.1 Proton spectra

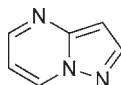
Proton and ¹³C NMR spectral data of 33 derivatives of **64** have been tabulated and assigned <1996MRC409>. Several 3-oxo derivatives of **64** have been studied by proton and ¹³C NMR spectroscopy as part of a comprehensive investigation of their structural and spectroscopic properties <2003BCJ2361>. The regioselectivity of the formation of the six-membered ring in derivatives of **67** from 1,3-diketones has been established by proton NMR spectroscopy and nuclear Overhauser effects <1997CHE535>.

**63****64****67**

11.12.3.1.2 ¹³C and ¹⁵N spectra

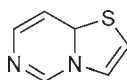
¹³C NMR spectroscopy has been used to establish the structures of intermediates formed during the photo-oxygenation of ¹³C-labeled derivatives of **64** related to bioluminescent luciferins <1996T12061>. The mechanism of the formation of 3-oxo derivatives of **64** related to the chemistry of bioluminescence has been studied by low-temperature ¹³C (together with variable temperature proton) NMR spectroscopy <1997J(P2)1831>. The ¹³C and ¹⁵N

spectra of several oxo-derivatives of **67** (with the oxygen in different positions) have been tabulated and assigned, and studied together with infrared (IR) data <1995MRC389>. Proton, ^{13}C and ^{15}N spectral data for several derivatives of **74** have also been published <2002MRC480>.

**74**

11.12.3.2 Mass Spectrometry Studies

Mass spectrometry has generally been employed in this series of compounds mainly for routine structure determination. The fragmentation pathways of some derivatives of **43** have been studied using accurate mass and metastable-transition measurements <1997JHC435>.

**43**

11.12.3.3 Electronic, IR, and Photoelectron Spectroscopy

The majority of UV-visible spectroscopy studies in this series of compounds have been carried out on 3-oxo derivatives of **64**, because of the importance of this ring system in bio- and chemi-luminescence. Electronic spectroscopy has been included in a more extensive structural and spectroscopic study of this ring system (see above) <2003BCJ2361>. The effects of substituents in different positions on the ring on solvatochromism have been studied <2004TL8531, 2005T10073>. IR spectroscopy has been applied to several oxo-derivatives of **67**, and used to interpret the degree of amide-type conjugation <1995MRC389>. IR spectra of derivatives of **67** have been calculated using *ab initio* methods, a detailed assignment of the bands made, and good correlation was found with experimental (FTIR) spectra <2003SAA1867>.

11.12.3.4 X-Ray Studies

Although there have been several X-ray structure determinations of ring systems covered by this chapter, these have been mostly used to establish structures, and in general do not show unusual features.

11.12.3.5 Magnetic Circular Dichroism Studies

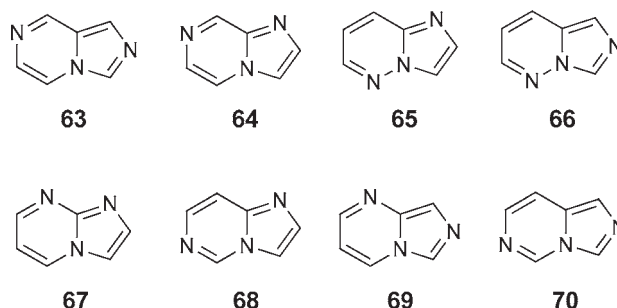
No magnetic circular dichroism studies have been reported during the period covered by this review, and only one study was reported in CHEC-II(1996) <1996CHEC-II(8)345>.

11.12.4 Thermodynamic Aspects

The first and second $\text{p}K_{\text{a}}$ values have been determined for the protonation of **74**, and AM1 calculations used to suggest the site of the first protonation <2000CHE714>. The $\text{p}K_{\text{a}}$ values of several 4-(aryloxy)-5-oxo derivatives of **74** have been obtained in different media from the variation of their UV-visible absorbances with pH <2003CED652>.

11.12.5 Reactivity of Fully Conjugated Rings

As described in CHEC-II(1996) <1996CHEC-II(8)345>, the ring systems **63–70** in which all three heteroatoms are nitrogen are the only ones which can achieve a neutral fully delocalized 10π -electron aromatic system. In these systems, the five-membered ring is electron rich and tends to be attacked by electrophiles, whereas the six-membered ring is electron deficient, and is prone to attack by nucleophiles. The reactivity of these systems has been reviewed both in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)305, 1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>.



11.12.5.1 Thermal and Photochemical Reactions

As noted in CHEC-II(1996) <1996CHEC-II(8)345>, this topic has been little studied, and there are no new developments to report.

11.12.5.2 Electrophilic Attack at Nitrogen (and/or Carbon)

Electrophilic substitution generally occurs on the more electron-rich five-membered ring in compounds based on ring systems **63–70** <1984CHEC(5)305, 1984CHEC(5)607, 1996CHEC-II(8)345>. For derivatives of systems **64**, **65**, **67**, and **68** (i.e., where heteroatom E=N in Table 2), substitution occurs at position 3 unless it is blocked <B-2002SOS(12)613> (Figure 1). Bromination of **69** with *N*-bromosuccinimide (NBS) gives the dibromo derivative **84**. Halogenation of the 3-methyl derivative of **63** with either NBS or *N*-chlorosuccinimide (NCS), and also Mannich reaction all take place at position 1, giving **85–87**.

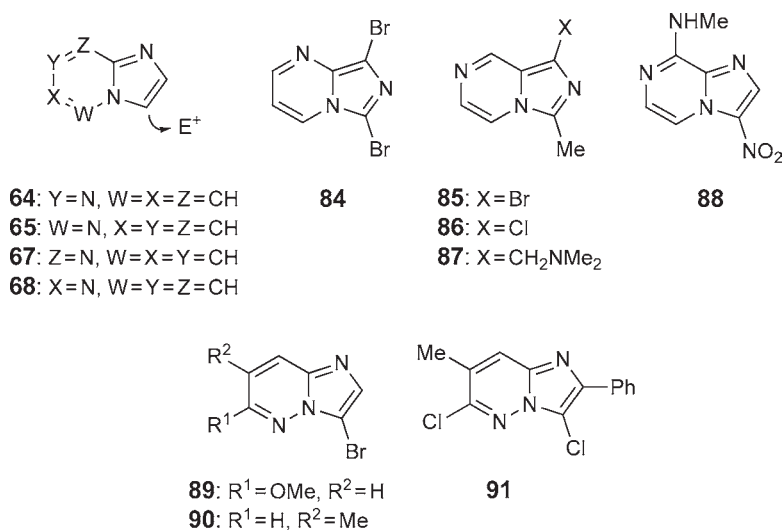
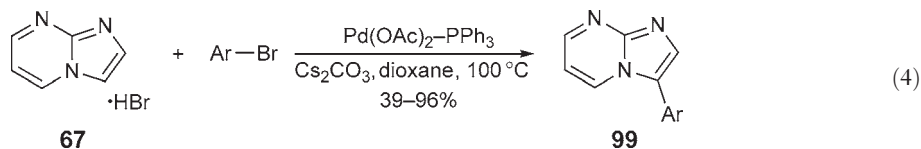
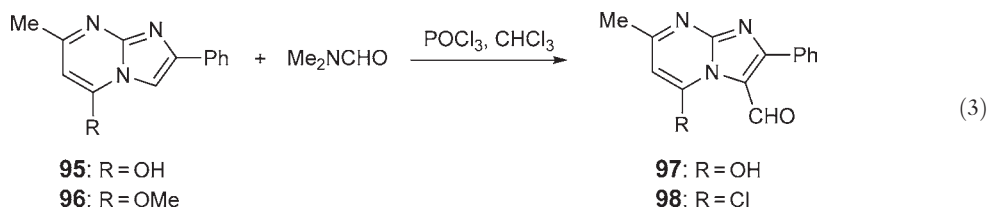
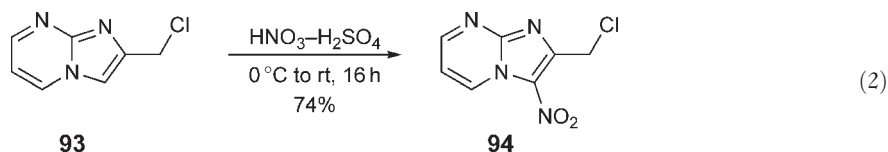
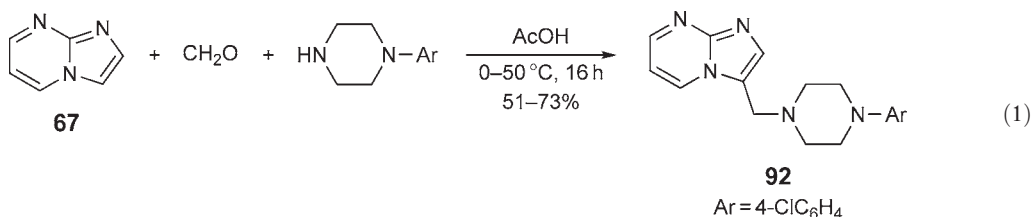


Figure 1

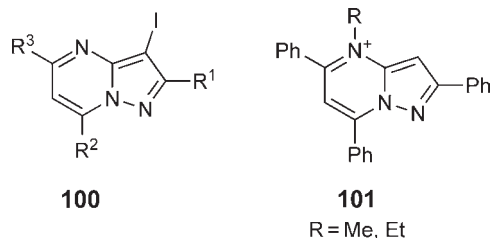
The parent ring system **64** is considerably deactivated toward electrophilic substitution, and does not undergo nitration under standard conditions <1997JHC701>. However, electron-donating groups at position 8 in the six-membered ring activate the five-membered ring toward substitution at the 3-position, allowing formation of, for example, **88** by nitration (Figure 1). These results were correlated with ^{13}C NMR studies and theoretical calculations. Other electrophiles have also been reacted similarly at the 3-position of 8-activated derivatives of **64** <1999BMC1059>.

In ring system **65**, the 6-methoxy derivative is brominated at the 3-position with NBS to give **89** <2004BML2249> and the 7-methyl derivative reacts similarly with Br_2 to give **90** <2006JME1235> (Figure 1). 2-Aryl derivatives of **65** have been nitrated or chlorinated at the 3-position to give for example, **91**, although the yields are sometimes low, and electrophilic attack can also occur on the 2-aryl substituent <2002JHC737>.

Ring system **67** also shows a similar propensity toward electrophilic substitution at the 3-position: for example, the parent ring **67** undergoes a Mannich reaction to give **92** (Equation 1) <1999BML97>. 2-Substituted derivatives of **67** also react at C-3: for example, nitration of **93** gives **94** (Equation 2) <1995T9643> and Vilsmeier formylation of **95** and **96** gives **97** and **98**, respectively, with concomitant replacement of OMe by Cl in the latter case (Equation 3) <2000JHC1265>. Palladium-catalyzed arylations of **67** show the same pattern of reactivity as electrophilic substitutions, and give 3-aryl derivatives **99** (Equation 4) <2003OL4835>. This reaction has recently been used in the production of a selective gamma-aminobutyric acid (GABA) receptor agonist <2005JOC6034>. These arylation reactions of **67** are also catalyzed by palladium hydroxide on carbon, and evidence has been presented that a homogeneous catalyst is involved <2005JOC7578>.

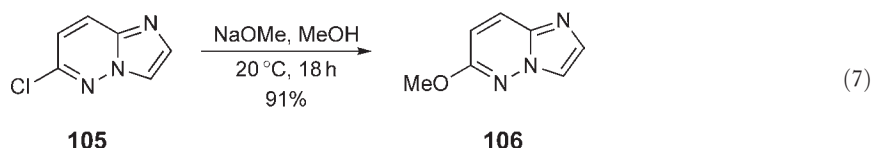
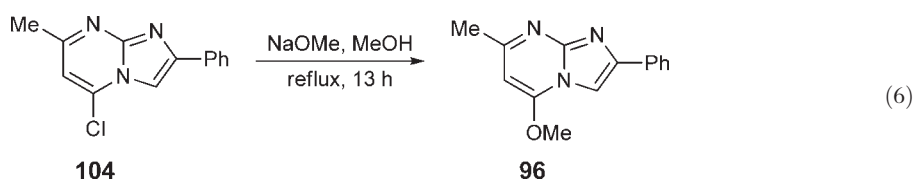
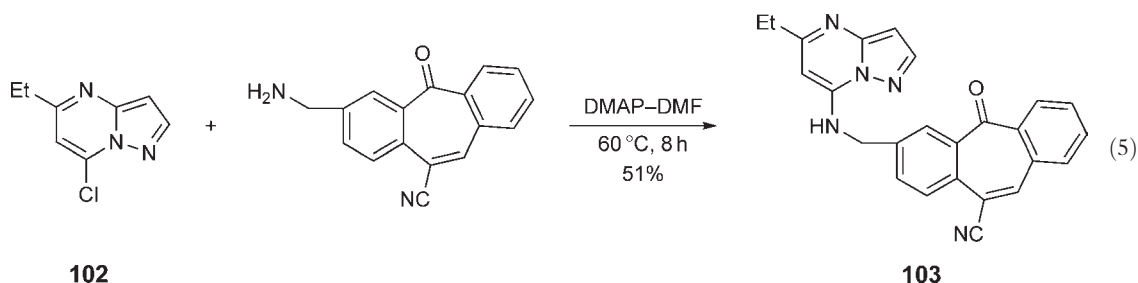


Several substituted derivatives of **74** have been iodinated at the 3-position using *N*-iodosuccinimide (NIS) to give **100** <2004S2329>. The regioselectivity of *N*-alkylation has been studied for the 2,6,8-triphenyl derivative of **74**, and this occurs selectively on N-4 of the pyrimidine ring to give **101** <2002CHE581>. Similar results are obtained with the 6,8-dimethyl-2-phenyl derivative.

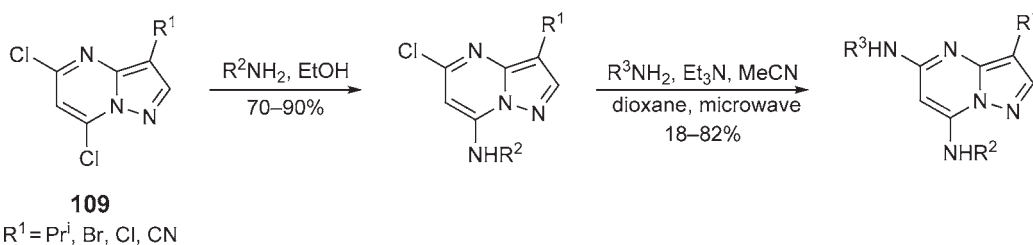
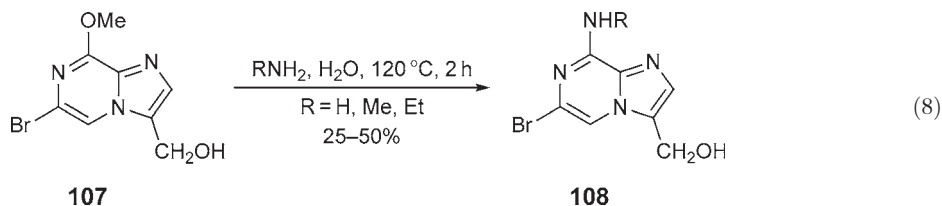


11.12.5.3 Nucleophilic Attack at Carbon

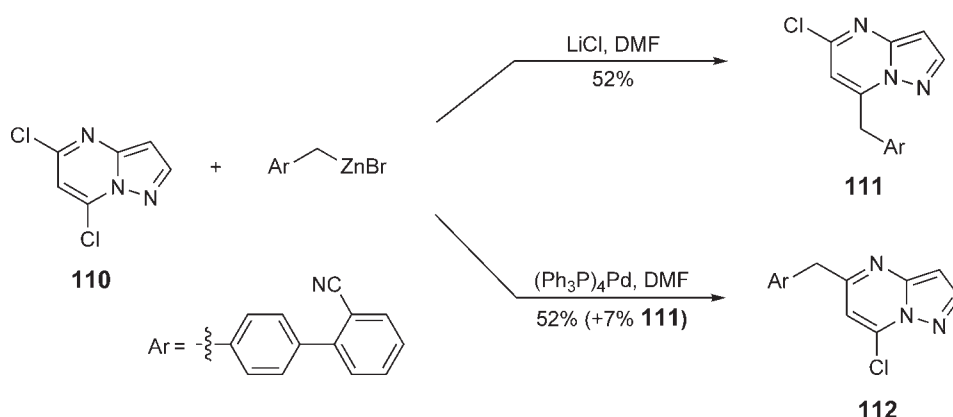
There have been extensive investigations of nucleophilic substitutions of halogens and methylthio groups in ring systems **63–74**, and these have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)305, 1984CHEC(5)607, 1996CHEC-II(8)345> and elsewhere <B-2002SOS(12)613>. Some recent examples include the replacement of the chlorine atom in **102** by an amine to give **103** (Equation 5) <1995JMC2728>, and that in either **104** or **105** by OMe to give **96** (Equation 6) <2000JHC1265> and **106** (Equation 7) <2004BML2249>, respectively. In derivatives of **74** chloro substituents at C-7 have also been replaced by amines <1998BML2067, 2000BMC181>.



In the bromomethoxy compound **107**, the OMe group is substituted selectively in preference to the Br atom to give **108** (Equation 8), and the same regioselectivity is observed with similar dibromo and bromochloro compounds <1999BMC1059>. The two chlorine atoms in a range of compounds **109** undergo sequential replacement with two different amines (or an amine and then an alcohol), reacting first at C-7 and then at C-5 (Scheme 1) <2005BML863>. The parent dichloro compound **110** shows a similar selectivity at C-7 toward an organozinc reagent in the presence of LiCl giving **111** (Scheme 2); however, this is reversed to give **112** by C-5 substitution using the same organozinc reagent, but with a palladium catalyst <1999JOC453>. In both **111** and **112**, the remaining chlorine atom was then replaced by a phenyl group using a Suzuki coupling reaction.



Scheme 1



Scheme 2

Nucleophilic attack of hydride reducing agents, for example, NaBH₄ or LiBH₄, usually results in partial reduction of the six-membered ring in these systems, and this has been reviewed [<B-2002SOS\(12\)613>](#). Various methods of reduction of derivatives of **74**, including NaBH₄, LiBH₄, catalytic hydrogenation, and electrochemical reduction, have been compared [<1995JHC1793>](#).

11.12.5.4 Reactions at Surfaces

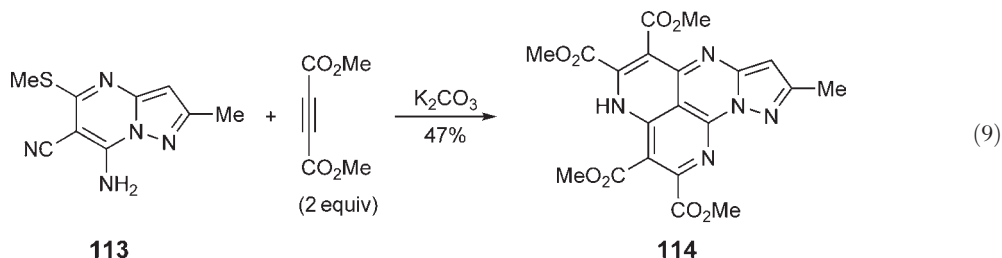
There are no new developments to report in this section.

11.12.5.5 Reactions with Radicals

There are no new developments to report in this section.

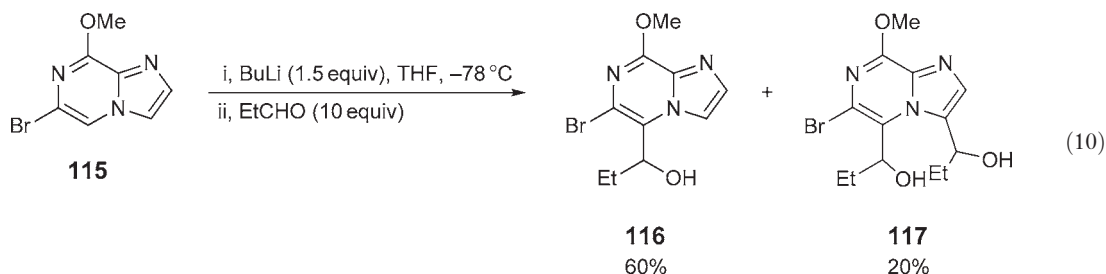
11.12.5.6 Reactions with Cyclic Transition States

Cycloaddition of **113** with two molecules of dimethyl acetylenedicarboxylate (DMAD) gives **114** in 47% yield (Equation 9) [<1996H\(42\)53>](#).



11.12.5.7 Nucleophilic Attack at Hydrogen

The bromomethoxy compound **115** undergoes lithiation by attack at hydrogen when treated with BuLi, rather than transmetalation of the bromine atom (Equation 10). Reaction with propanal then gives a mixture of **116** and **117**, suggesting that both mono- and di-lithiation have occurred [<1998T6485>](#). Lithium tetramethyl piperidine was less satisfactory than BuLi, and gave low yields after reaction with propanal. Neither the parent compound **64** nor the 8-methoxy derivative reacted with BuLi.

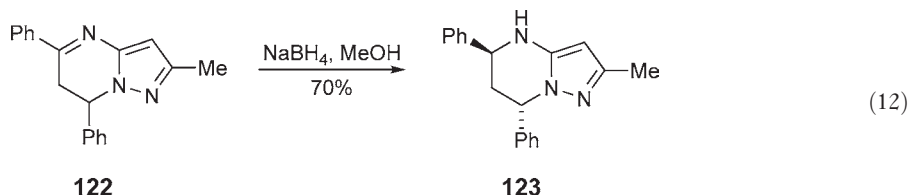
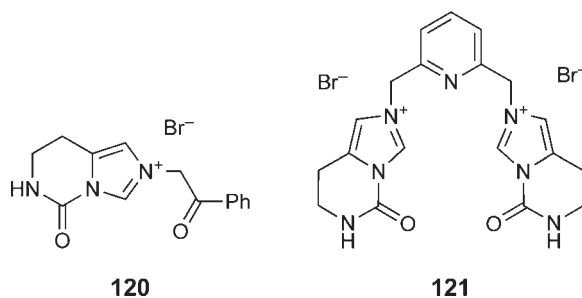
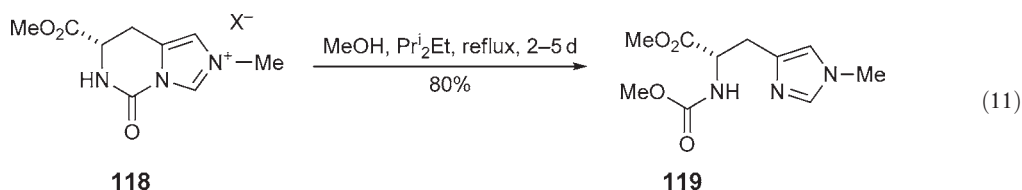


11.12.6 Reactivity of Nonconjugated Rings

This area has received much less attention in the literature than the reactivity of conjugated systems. As noted in CHEC-II(1996) <1996CHEC-II(8)345>, most of the examples studied contain one or two oxo groups in the six-membered ring and are cyclic amide tautomers of the corresponding hydroxyl compounds.

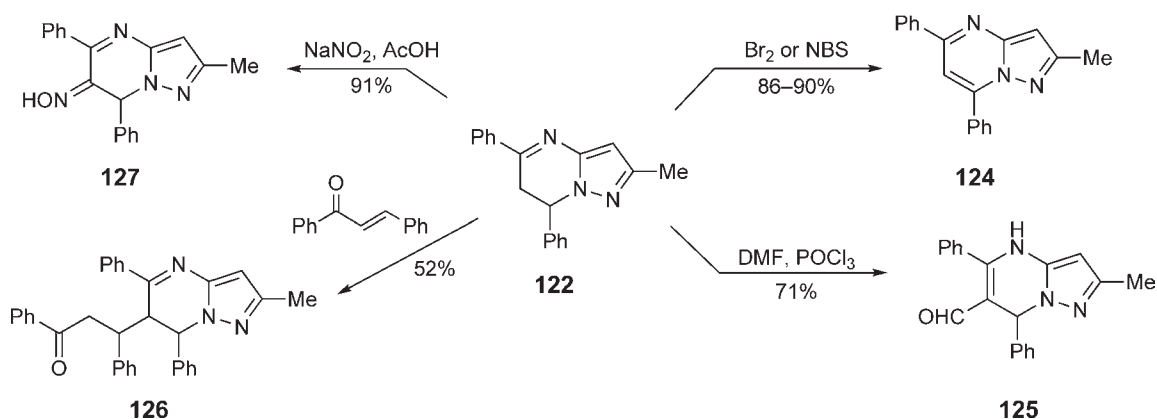
11.12.6.1 Nucleophilic Attack at Carbon

Nucleophilic attack of methanol on the carbonyl group in **118** is followed by regioselective ring cleavage toward the imidazole ring, giving **119** in which the side-chain nitrogen atom remains protected (Equation 11) <1996T5363, 1998HCA491>. A similar strategy has been employed using *tert*-butanol on **120** <2001JCM195>, and to open both of the bicyclic rings in **121** <2005T97>. Stereoselective nucleophilic hydride reduction of the dihydro compound **122** results in a fully saturated six-membered ring in **123** (Equation 12) <2005CHE492>.



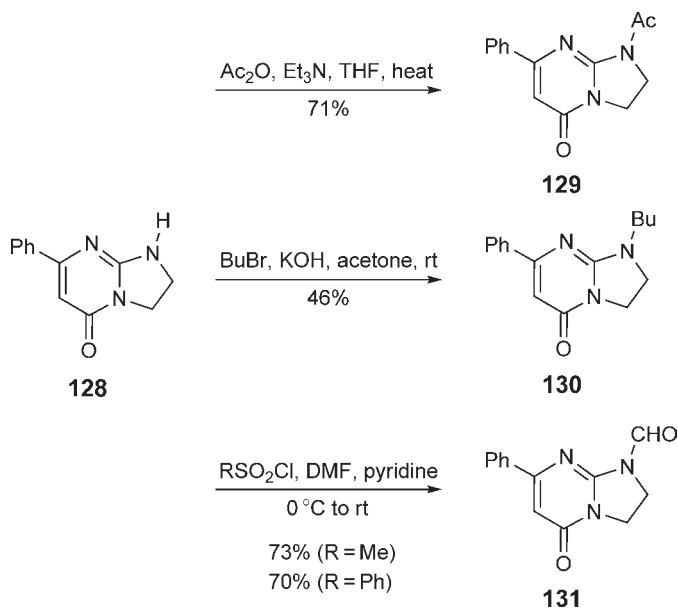
11.12.6.2 Electrophilic Attack at Nitrogen (and/or Carbon)

The dihydro compound **122** has been reacted with a variety of electrophiles (Scheme 3) <2005CHE492>. Oxidation with bromine results in the fully aromatized product **124**. Vilsmeier formylation, Michael addition, and nitrosation all occur at C-6, giving products **125–127**.

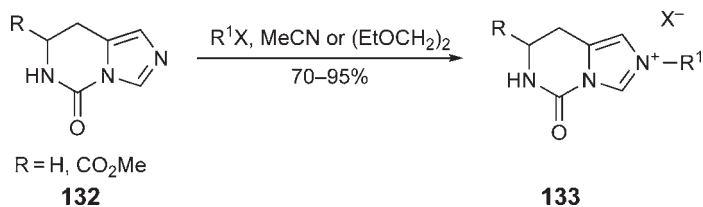


Scheme 3

The dihydro compound **128** reacts with electrophiles at N-1 (Scheme 4), with **129** and **130** resulting from acetylation and benzylation, respectively <2005T5303>. Reaction with sulfonyl chlorides in dimethylformamide (DMF) unexpectedly resulted in formylation at N-1 to give **131**. Cyclic ureas **132** react with alkylating agents on N-1 to give quaternary salts **133** (Equation 13), and improved conditions for the reaction with a variety of higher alkyl halides have been developed <1996T5363>.



Scheme 4



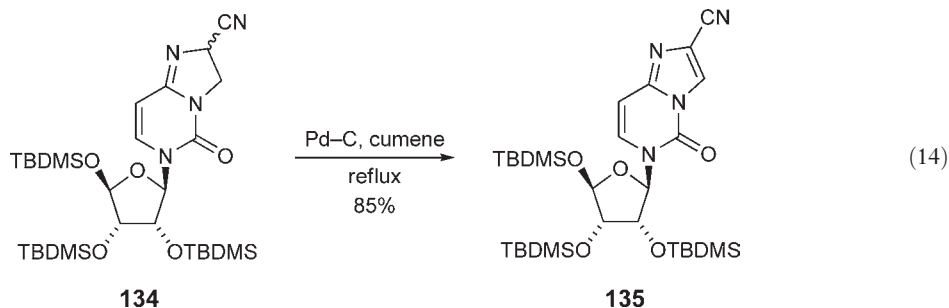
(13)

11.12.6.3 Nucleophilic Attack at Hydrogen

There are no new developments to report in this section.

11.12.6.4 Reaction with Radicals and at Surfaces

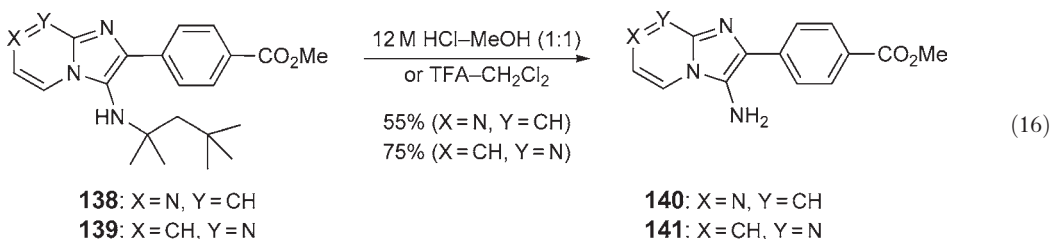
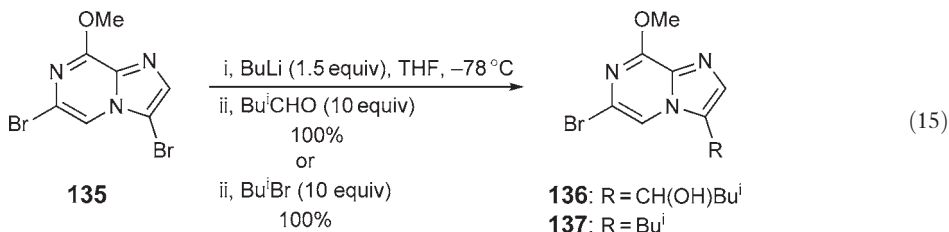
Aromatization of the nucleoside analogue **134** has been achieved by dehydrogenation over palladium on carbon in refluxing cumene (Equation 14) <2004BMC4245>.

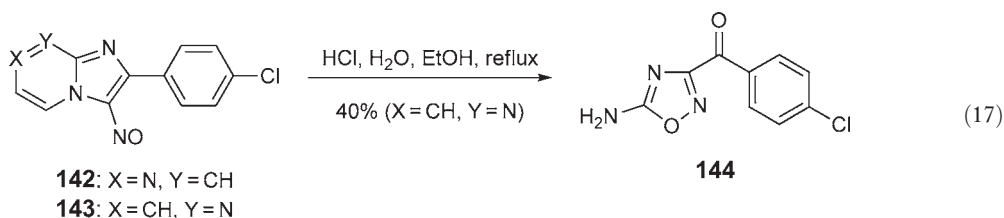


11.12.7 Reactivity of Substituents Attached to Ring Carbon Atoms

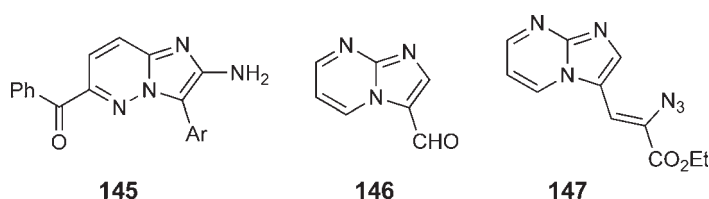
CHEC-II(1996) <1996CHEC-II(8)345> covered a range of reactions of substituents, including hydrolyses of esters to carboxylic acids and geminal dihalides to aldehydes, reduction of aldehydes and halogens directly attached to the ring, *O*-methylation with diazomethane, and reduction of nitroso compounds. A selection of reactions which have appeared since 1995 is presented here.

Halogen–metal exchange of the dibromide **135** with BuLi is completely selective for the bromine atom at C-3, and the resulting organolithium species can be reacted with an aldehyde or an alkyl halide to give **136** and **137** (Equation 15) <1998T6485> (cf. Section 11.12.5.7). Secondary amines **138** and **139** undergo dealkylation by acid to afford the primary amines **140** and **141** (Equation 16) <2000TL1495>: the alkyl group arises from the ring synthesis by three-component coupling (see Section 11.12.9.5.1) and extends this approach to allow access to primary amines. Treatment of the nitroso compound **143** with acid causes a ring-opening reaction to give **144** (Equation 17), whereas **142** undergoes decomposition under the same conditions <2000T6527>.

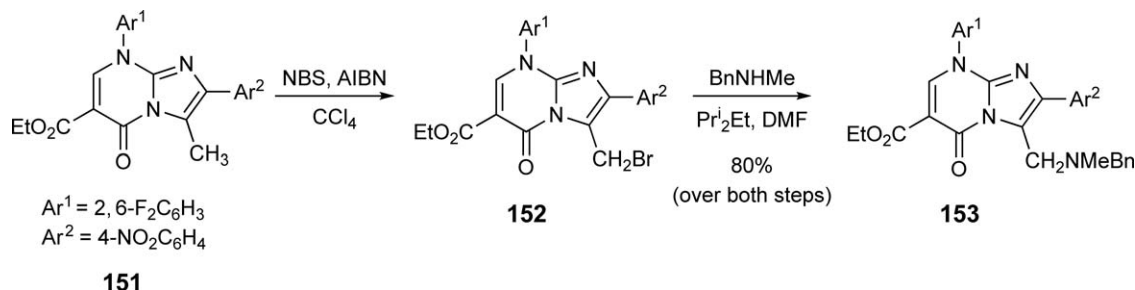
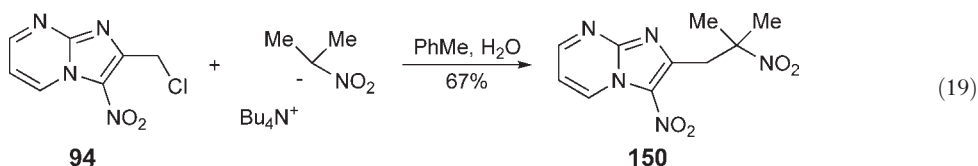
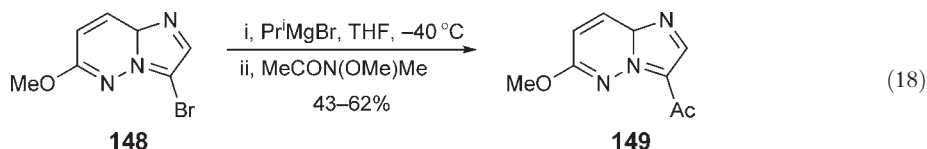




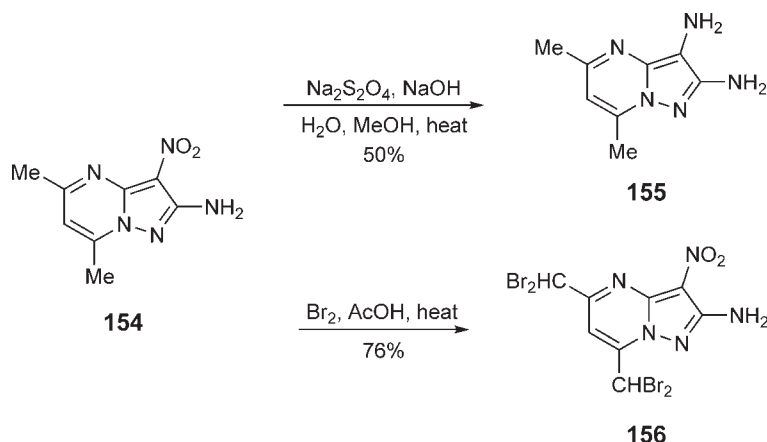
The benzoyl group in **145** has been shown to undergo a number of standard carbonyl group transformations, including oxime and hydrazone formation, and also alkene synthesis with a Horner–Wadsworth–Emmons stabilized anion [<2003JME4333>](#). The aldehyde group in **146** undergoes an aldol reaction with ethyl azidoacetate to give the α,β -unsaturated ester **147** [<1997JOC4085>](#).



The bromide **148** has been converted into the corresponding Grignard reagent using Pr^iMgBr ; treatment with a Weinreb amide then afforded the acetylated ring **149** (Equation 18) [<2004BML2249>](#). The chloromethyl group in **94** alkylates the anion of 2-nitropropane by an $\text{S}_{\text{RN}}1$ mechanism under phase-transfer conditions to give **150** (Equation 19) [<1995T9643, 2002JHC173>](#). Free radical bromination of the methyl group in **151** affords the bromomethyl compound **152** which is then substituted by an amine to give **153** (Scheme 5) [<2002BML2073>](#). The nitro group in **154** has been reduced with $\text{Na}_2\text{S}_2\text{O}_4$ to give the diamine **155** (Scheme 6); alternatively, bromination of both methyl groups in **154** with excess bromine gives the tetrabromide **156** [<1997CHE276>](#).

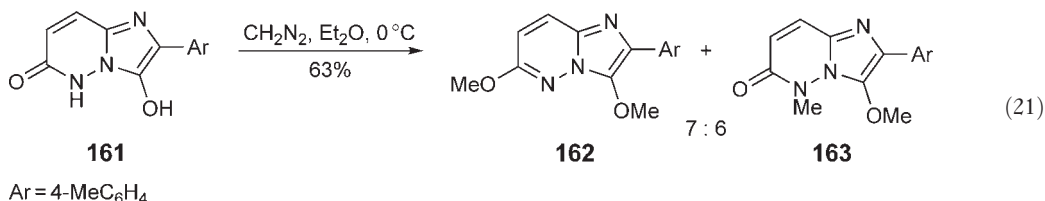
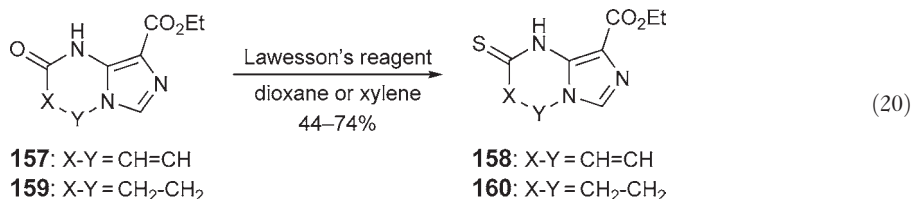


Scheme 5

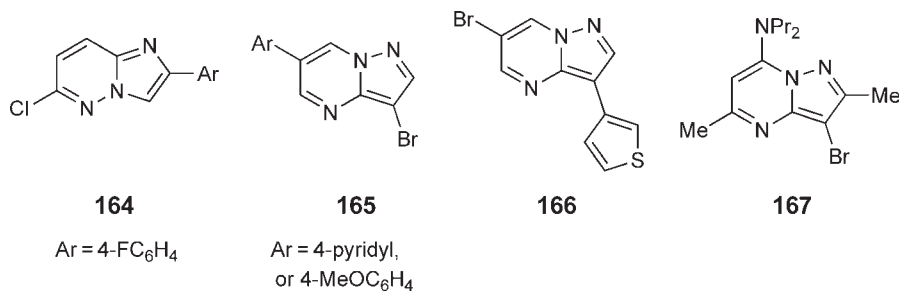


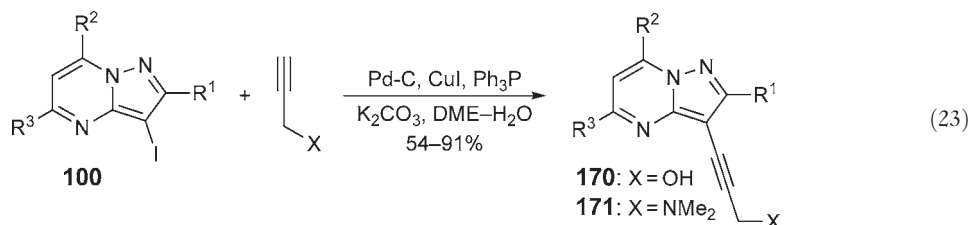
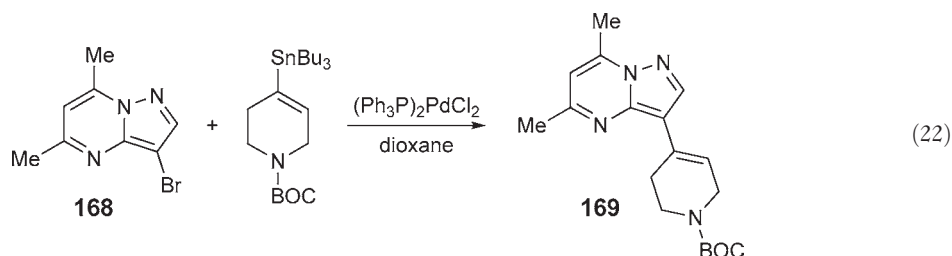
Scheme 6

Treatment of the cyclic amide **157** or the dihydro compound **159** with Lawesson's reagent gives the corresponding thioamides **158** and **160** (Equation 20) <1999JME1661>. Methylation of the cyclic amide **161** with diazomethane gives a mixture of *O,O*- and *N,O*-dimethyl products **162** and **163** in a ratio of 7:6 (Equation 21) <1996EJM651>.



An active new area of chemistry in this section is that of palladium-catalyzed coupling reactions of halo derivatives. The chloro group in **164** is more reactive than in a simple aryl chloride, and participates in Suzuki coupling reactions with aryl and heteroaryl boronic acids, with the best yields being obtained using NaOH as the base <2001S595>. Suzuki coupling reactions have been accomplished using the chloro compounds **111** and **112** <1999JOC453>, and also the bromides **90** <2006JME1235>, **165** <2002BML2767>, **166** <2002BML3537>, and **167** <2003JLR1055>. Other palladium-catalyzed coupling reactions which have been reported include a Stille coupling on bromide **168** with a heterocyclic alkenyl stannane to give **169** (Equation 22) <2005BML2129>, Heck couplings between iodides **100** and alkenes <2004S2329>, and also Sonogashira couplings between iodides **100** and propargyl amines or alcohols, to give, for example, **170** and **171** (Equation 23) <2005S131>.





11.12.8 Reactivity of Substituents Attached to Ring Heteroatoms

As with CHCE-II(1996), this area continues to receive little attention in the literature.

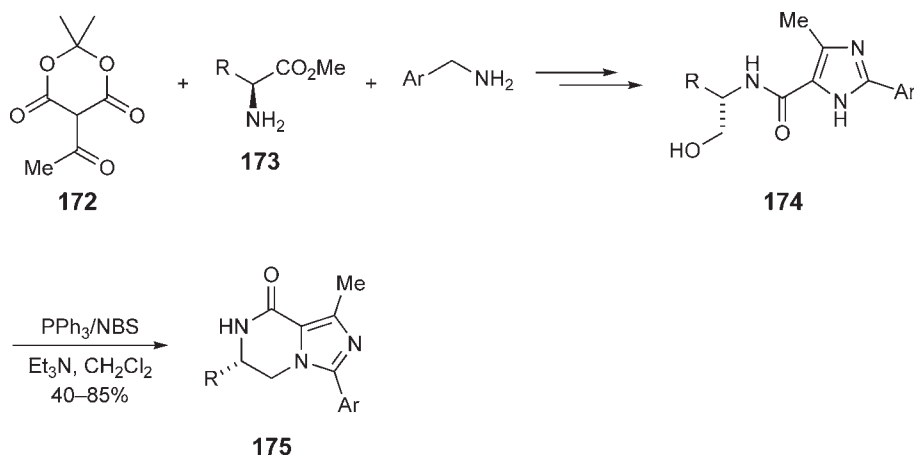
11.12.9 Ring Syntheses Classified by Number of Ring Atoms in Each Component

11.12.9.1 Imidazo[1,5-a]pyrazine 63

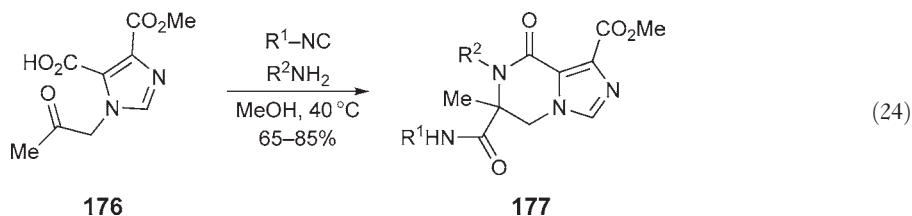
Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>. The most usual approach to this ring system is from 2-(aminomethyl)pyrazines, which are converted into the corresponding amides, and then cyclized by dehydration, with, for example, POCl₃ or polyphosphoric acid. Direct cyclization of 2-(aminomethyl)pyrazines is also possible using CS₂.

11.12.9.1.1 Closure of the pyrazine ring

Acetylated Meldrum's acid **172** and α -aminoesters **173** have been used as the building blocks to prepare the substituted imidazoles **174**, which are then cyclized to give optically active dihydro products **175** <2003OL3907> (Scheme 7). A modified four-component Ugi reaction has been used to prepare dihydro products **177** from the intermediate functionalized imidazole **176**, isonitriles, and amines (Equation 24) <2005EJO4670>.

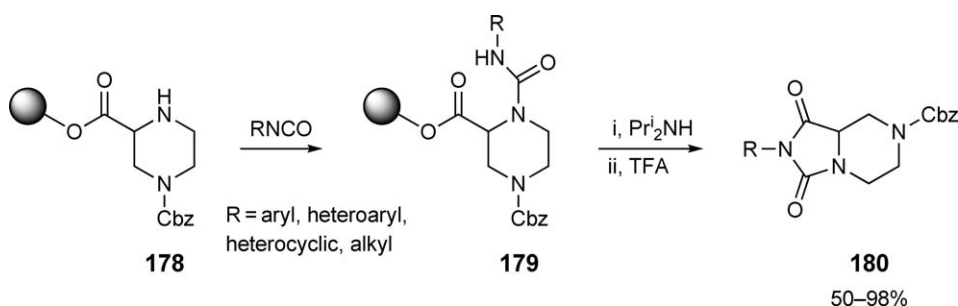


Scheme 7

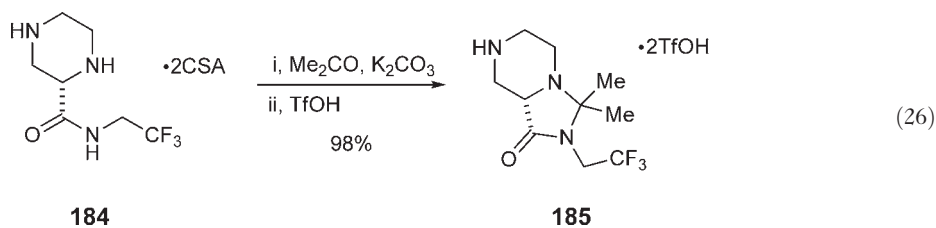
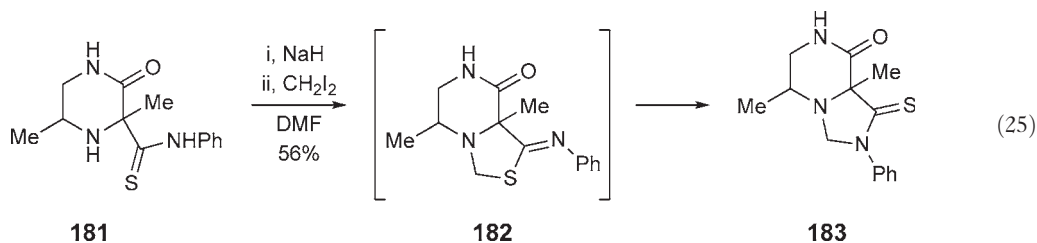


11.12.9.1.2 Closure of the imidazole ring

The monoprotected piperazine attached to a solid support **178** reacts with isocyanates generated from carboxylic acids by the Curtius rearrangement, to give intermediates **179** which cyclize to **180** during cleavage from the support (Scheme 8) <2000OL3309>. The piperazin-3-one **181** cyclizes when treated with NaH and CH₂I₂, and the resulting intermediate **182** undergoes a Dimroth rearrangement to give **183** (Equation 25) <2004S2169>. The piperazine carboxamide **184** forms the saturated heterocyclic aminal **185** when treated with acetone and acid (Equation 26) <2005TL1867>.

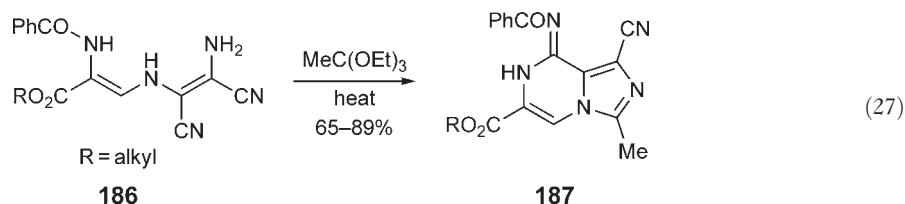


Scheme 8



11.12.9.1.3 Formation of both rings simultaneously

The diaminomaleonitrile derivative **186** is transformed into **187** by treatment with triethyl orthoacetate (Equation 27) <2006S3437>. Other orthoesters react similarly.

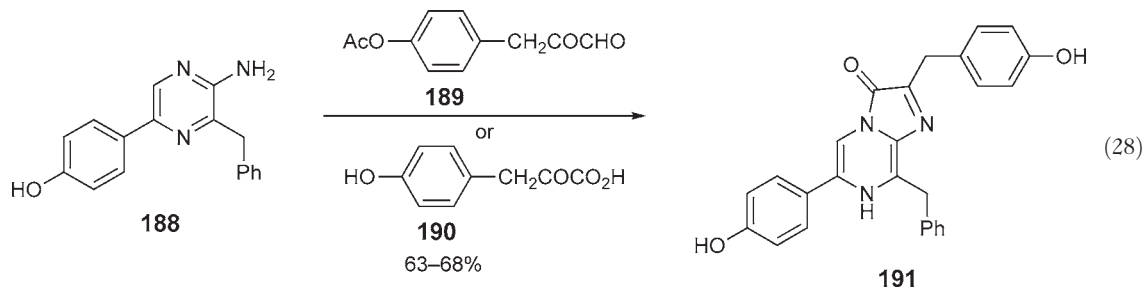


11.12.9.2 Imidazo[1,2-a]pyrazine 64

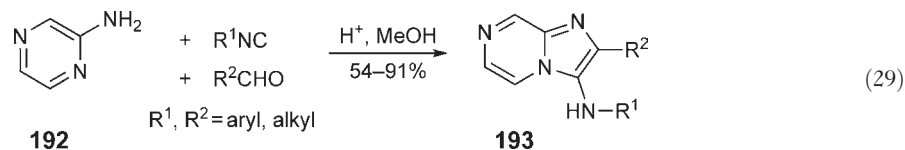
Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and also more recently <B-2002SOS(12)613>. There is also a review devoted to this ring system, containing a comprehensive survey of synthetic methods <1997RCR187>. The most usual approach to this ring system is to construct the imidazole ring onto a 2-aminopyrazine, using an α -oxoacid, α -oxoester or α -oxoaldehyde, or, most widely, an α -halocarbonyl compound. Closure of the pyrazine ring has been used much more rarely, and often starts from an imidazole bearing an acyl, amide, or aldehyde group at the 2-position, which is reacted with a component that contributes two carbon atoms to the new ring.

11.12.9.2.1 Closure of the imidazole ring

Coelenterazine **191**, an important naturally occurring bioluminescent luciferin, has been synthesized using both the established method of reacting the 2-aminopyrazine **188** with a glyoxal **189** <1997CC323>, and also by using an excess of the commercially available *p*-hydroxyphenylpyruvic acid **190** in place of the aldehyde **189** <1998H(48)1669> (Equation 28). The pyruvic acid **190** also appears to serve as a reducing agent and avoids the need for a multistep synthesis of **189**.



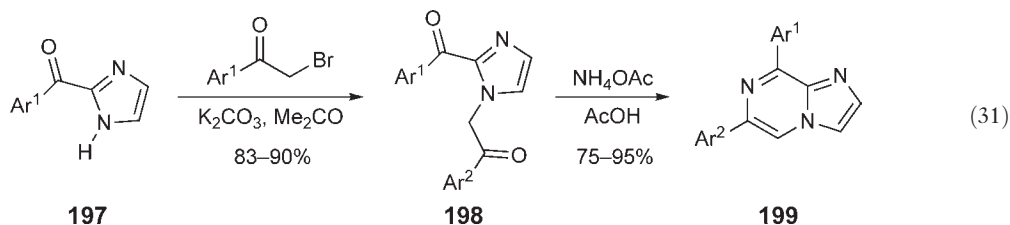
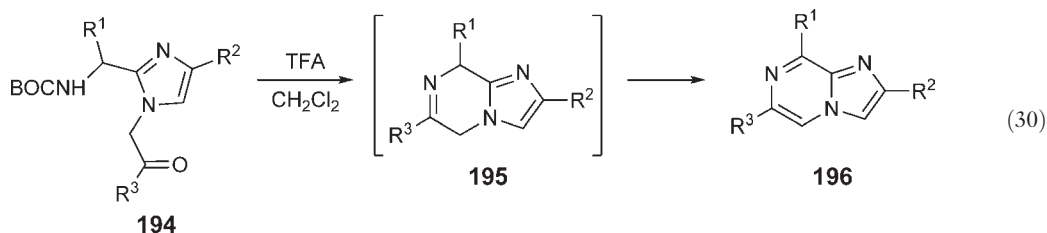
A three-component Ugi-type coupling method is gaining widespread use for the preparation of this ring system, and involves reaction between a 2-aminopyrazine **192**, an aldehyde, and an isonitrile to give **193** in one step (Equation 29) <1998AGE2234, 1998SL661>. Replacing the 2-aminopyrazine **192** with a 2-aminopyrimidine also allows the synthesis of ring system **67** (Section 11.12.9.5.1). Scandium triflate can be used to promote this reaction instead of a protic acid <1998TL3635>. The method is well suited to high-throughput parallel synthesis, and has been carried out with the isonitrile component attached to a solid support <1998TL5469, 2001SL1263>. These coupling reactions are accelerated by microwave irradiation, in the presence of either montmorillonite clay <1999TL7665> or scandium triflate <2003TL4369>.



Preparation of 2-unsubstituted products by this method would require the use of formaldehyde as the aldehyde component, which gives low yields. However, the use of glyoxylic acid, either as the free acid or bound to macroporous polystyrene carbonate, results in satisfactory formation of the 2-unsubstituted products through an *in situ* decarboxylation <2004OL4989>. The use of a nonpolar solvent (toluene) has been reported to reduce the formation of side products in this type of reaction <2006TL947>.

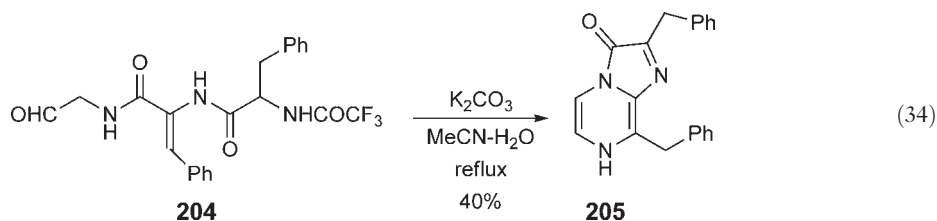
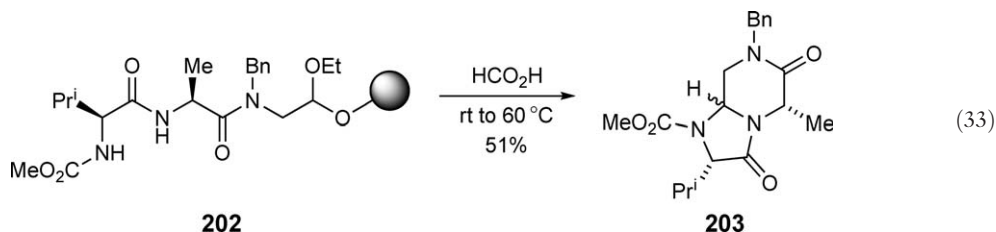
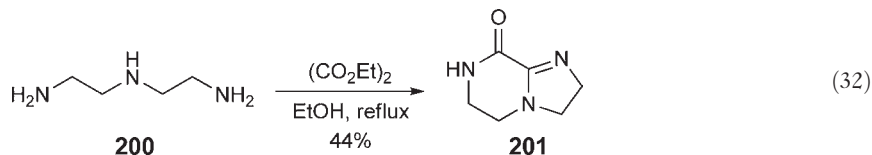
11.12.9.2.2 Closure of the pyrazine ring

Closure of the pyrazine ring has been much less well used for the preparation of this ring system. Deprotection of the aminoalkyl-substituted imidazoles **194** results in formation of the cyclic imine intermediates **195**, which undergo spontaneous oxidation to the aromatic products **196** (Equation 30) <2001BML741>. The intermediate **195** can also be intercepted by reduction with NaBH₄ to give analogous tetrahydro products. Alkylation of 2-arylimidazoles **197** gives the intermediate diketo compounds **198** which are cyclized to give the diarylheterocycles **199** using ammonium acetate in acetic acid (Equation 31) <2005JHC319>.



11.12.9.2.3 Formation of both rings simultaneously

Diethylenetriamine **200** reacts with diethyl oxalate to form **201** rather than the nine-membered macrocycle, even at high dilution (Equation 32) <1999J(P1)1211>. Tripeptide derivatives have previously been cyclized to form imidazopyrazines <1997RCR187>, and a conceptually similar approach has been used in the formation of **203** during cleavage of the linear precursor **202** from the solid support (Equation 33) <1998JOC3162>, and in the formation of coelentarazine analogues, for example, **205** from precursor **204** (Equation 34) <2002TL3161>.

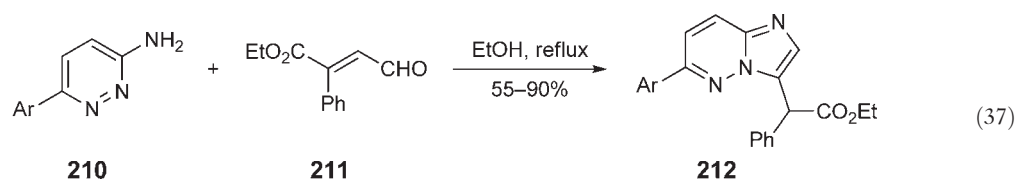
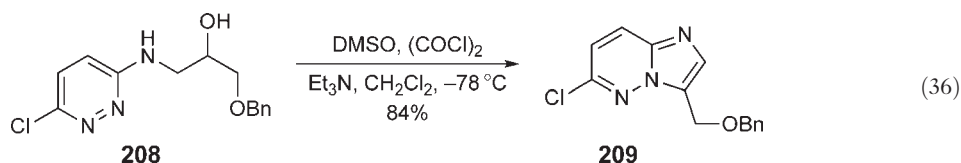
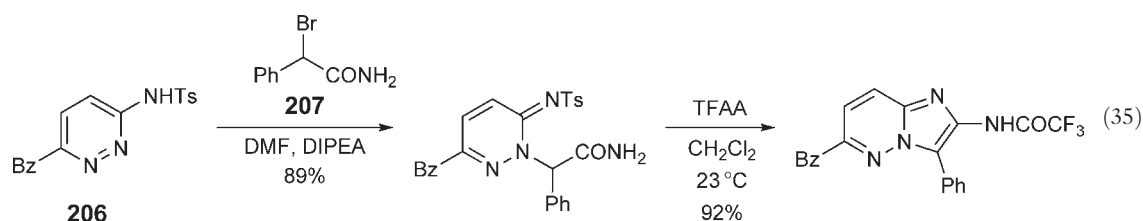


11.12.9.3 Imidazo[1,2-*b*]pyridazine 65

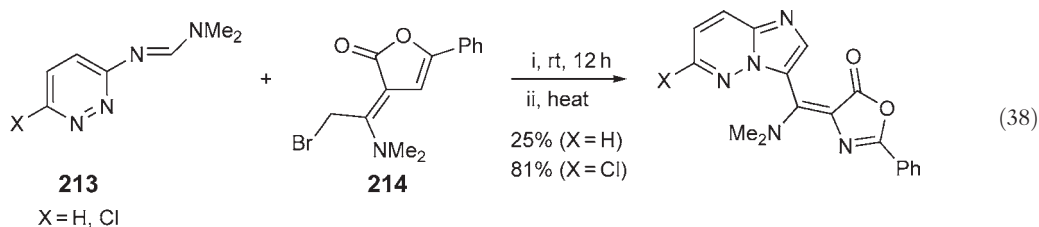
Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>. The most usual approach to this ring system involves reaction of a 3-aminopyridazine with either an α -halocarbonyl compound or, alternatively, an α -oxocarbonyl compound.

11.12.9.3.1 Closure of the imidazole ring

Recent examples of the standard cyclization of a 3-aminopyridazine with an α -halocarbonyl compound include the use of 1,3-dichloroacetone <2002JHC173> and chloroacetaldehyde <2004BML2249>. An example where the alkylation and ring-closure steps can be carried out separately is shown in Equation (35) and starts from a 3-tosylaminopyridazine **206** and α -bromophenylacetamide **207** <2003JME4333>. The aminopyridazine **208**, formed by reaction of 1,4-dichloropyridazine and an aminoalcohol, is cyclized to **209** under Swern oxidative conditions (Equation 36) <2003TL2919>. However, the ketone formed by oxidation of the alcohol is not thought to be an intermediate, and is not cyclized to **209** under these conditions. Reaction of various aryl 3-aminopyridazines **210** with the α,β -unsaturated aldehyde **211** gives the substituted phenylacetate esters **212** (Equation 37) <1995H(41)1491>. Lastly, the imidazole ring can be built up sequentially from three components, with the formamidines **213** being prepared from the corresponding 3-aminopyridazines and DMF dimethyl acetal, and then cyclised by reaction with the oxazolone **214** (Equation 38) <1998JHC971>.

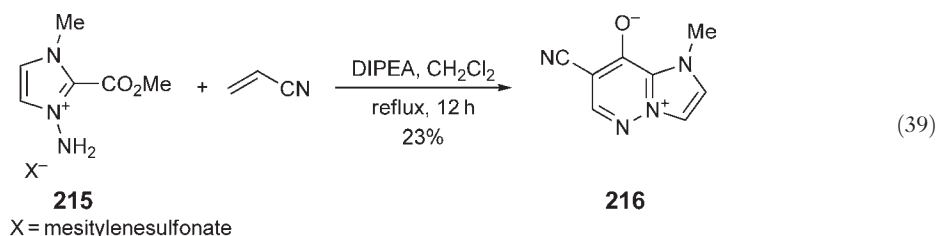


Ar = Ph, 4-X-C₆H₄: X = Cl, OMe



11.12.9.3.2 Closure of the pyrazine ring

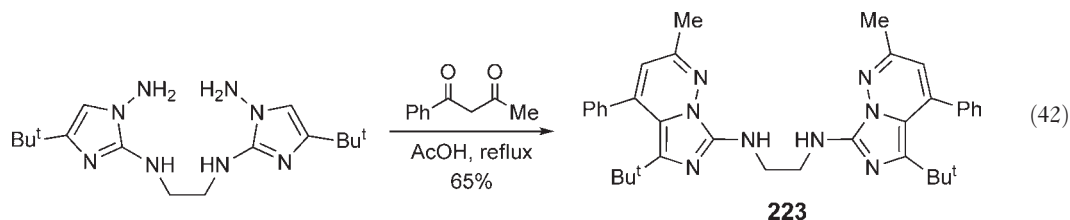
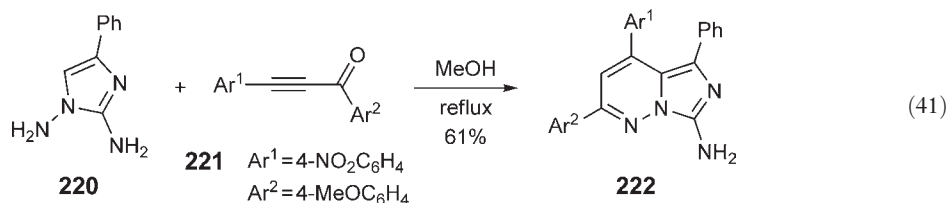
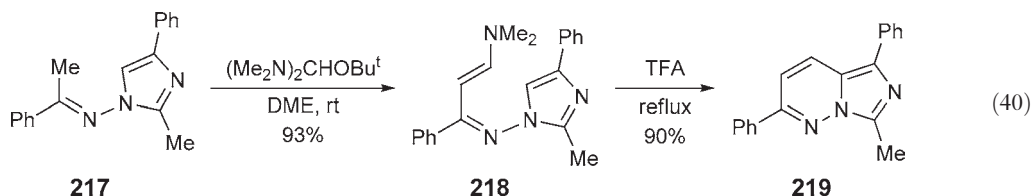
Reaction of the salt **215** with acrylonitrile produces **216** in moderate yield (Equation 39) <2001JOC8528>. Diethyl fumarate reacts similarly, but in lower yield (11–16%), together with some aromatized product.



11.12.9.4 Imidazo[1,5-*b*]pyridazine 66

This continues to be one of the least-studied imidazodiazine ring systems, with few reports having appeared <1984CHEC(5)607, 1996CHEC-II(8)345>.

The imine **217**, formed from acetophenone and the 1-aminoimidazole, has been transformed into the enamine **218** which is then cyclized to **219** in trifluoroacetic acid (TFA) (Equation 40) <1995SC3271>. The diaminoimidazole **220** reacts with ynone **221** to form **222** (Equation 41) <1998CHE1189>. Bromochalcones and chalcone dibromides can also be used in place of the ynone. Similar reactions have been used to prepare the dihydro analogues of **222** <1999CHE1207>. The reaction between 1-aminoimidazoles and 1,3-diketones has been extended to prepare bis-heterocyclic compounds, for example, **223** as ligands for transition metals (Equation 42) <2005EJI4382>.

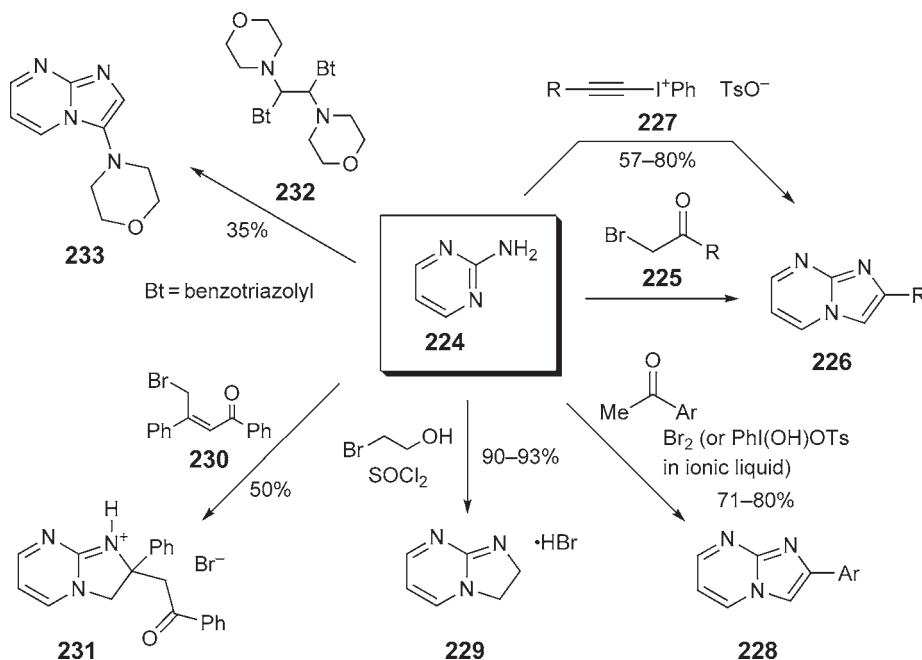


11.12.9.5 Imidazo[1,2-*a*]pyrimidine 67

Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>. The most usual approaches to this ring system are from the reaction of 2-aminopyrimidines with α -halocarbonyl compounds, or 2-aminoimidazoles with β -dicarbonyl compounds.

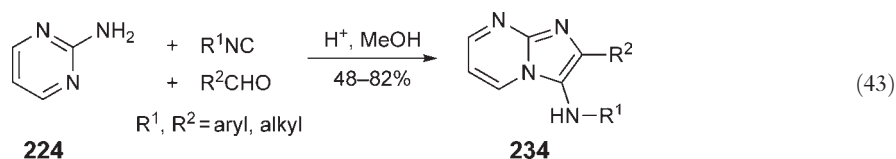
11.12.9.5.1 Closure of the imidazole ring

A number of transformations starting from 2-aminopyrimidine **224** are shown in **Scheme 9**. The established method of using α -halocarbonyl compounds **225** to give **226** can be varied by using alkynyl phenyl iodonium salts **227** <2003JHC909>. The α -halocarbonyl component **225** has been attached to a solid support before reaction with the 2-aminopyrimidine <2003TL6265>. Alternatively, the conventional reaction between **224** and **225** can be carried out on alumina without solvent <2005SC901>, or in ionic liquids <2003JCM645>. Aryl methyl ketones can be used with a halogen to give 2-aryl products **228** <2000CHE1437>, or instead of the halogen, $\text{PhI}(\text{OH})\text{OTs}$ in an ionic liquid has been employed <2005SC1741>. The dihydro product **229** can be obtained by using bromo- or chloro-ethanol, followed by thionyl chloride, or by using 1,2-dibromoethane <2001CHE224>. Use of a vinylogous bromoketone **230** gives the salt **231** <2004SC3609>, and the bis-benzotriazolylethylenediamine **232** affords **233** <2003JOC4935>. Reaction of ethyl bromoacetate with 2-aminotetrahydropyrimidines gives 3-oxotetrahydro derivatives of **67** <2005SL848>.

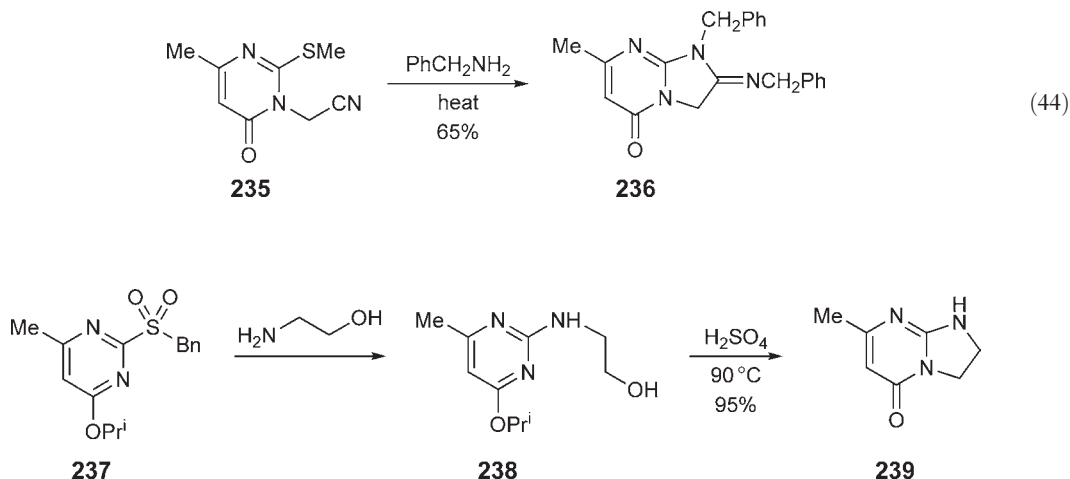


Scheme 9

The same type of the three-component Ugi-type coupling method reported in **Section 11.12.9.2.1** for the preparation of ring system **64** (Equation 29) can also be used for ring system **67**, by changing the starting aminoheterocycle to 2-aminopyrimidine **224**, which gives 3-amino-substituted products **234** (Equation 43) <1998AGE2234, 1998SL661>. The same developments described earlier also apply in this ring system: scandium triflate can be used to promote the coupling reactions <1998TL5469>, the reactions can be carried out with the isonitrile component attached to a solid support <1998TL5469, 2001SL1263>, the reactions are accelerated by microwave irradiation <1999TL7665, 2003TL4369>, and the use of a nonpolar solvent reduces the formation of side products <2006TL947>. One problem with this three-component coupling reaction when applied to 2-aminopyrimidine **224** is that mixtures of products can be formed, depending on whether the primary amino group or a ring nitrogen atom in **224** reacts with the aldehyde component <2002TL4267>.



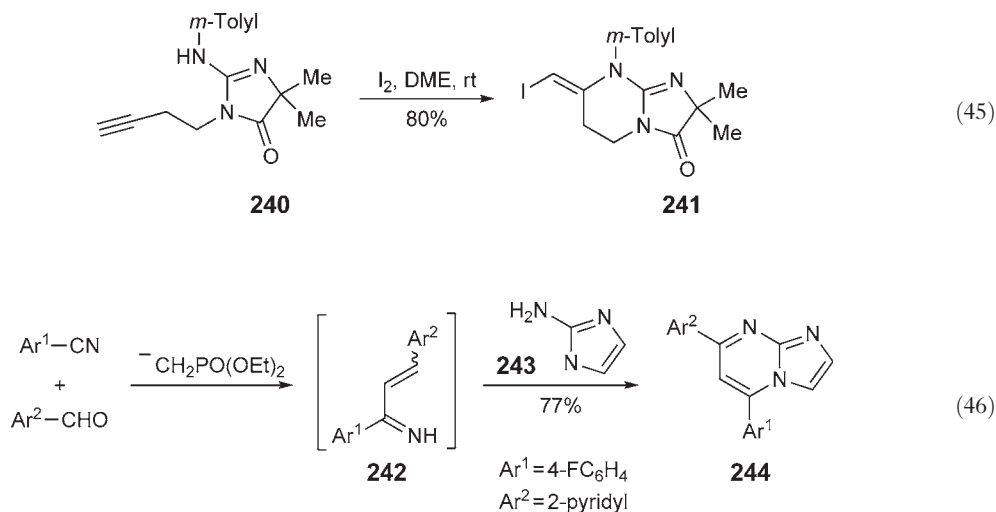
An alternative strategy toward ring **67** involves the use of pyrimidines with a leaving group at the 2-position. The 2-(methylthio)pyrimidine **235** (prepared by an alkylation reaction using chloroacetonitrile) reacts with amines and cyclizes to give, for example, **236** (Equation 44) <1996CHE605>. The 2-sulfonyl group in pyrimidine **237** can be replaced by 2-hydroxyamines, and the intermediates (e.g., **238**) are cyclized regioselectively in acid to give the dihydro products, for example, **239** (Scheme 10) <2006T1433>. Using Mitsunobu conditions, regioisomeric mixtures are obtained.

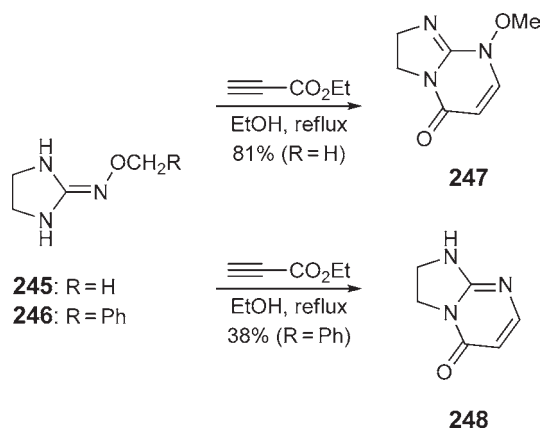


Scheme 10

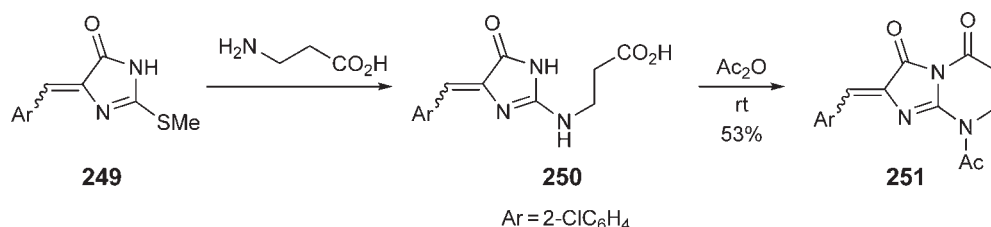
11.12.9.5.2 Closure of the pyrimidine ring

6-*exo*-Iodocyclization of the alkynyl imidazolinone **240** gives the iodomethylene product **241** (Equation 45) <1996T6581>. The α,β -unsaturated imine **242**, formed *in situ* from a nitrile, an aldehyde, and a phosphonate anion, reacts with 2-aminoimidazole **243** to give **244** (Equation 46) <2006TL2611>. The methoxyiminoimidazolidine **245** reacts with ethyl propiolate to give **247** in high yield, whereas the benzyloxy analogue **246** also loses benzaldehyde via a retro-ene reaction to give **248** in much lower yield (Scheme 11) <2005T5303>. The methylthio group in **249** is displaced by 3-aminopropanoic acid, and the intermediate **250** cyclizes upon treatment with acetic anhydride to give **251** (Scheme 12) <2001EJM407>. The three-component coupling reaction shown in Equation (47) gives reduced oxo-products **252** with an unusual bridgehead hydrogen <2004SL1086>.

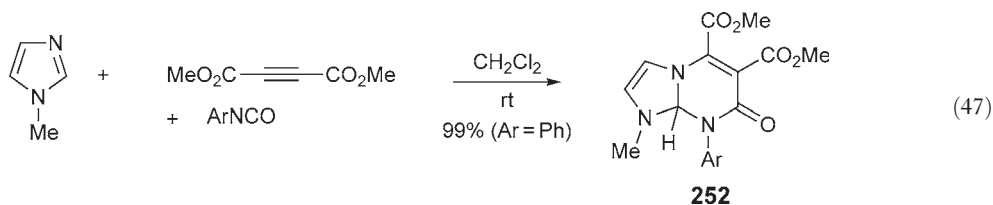




Scheme 11



Scheme 12



11.12.9.5.3 Formation of both rings simultaneously

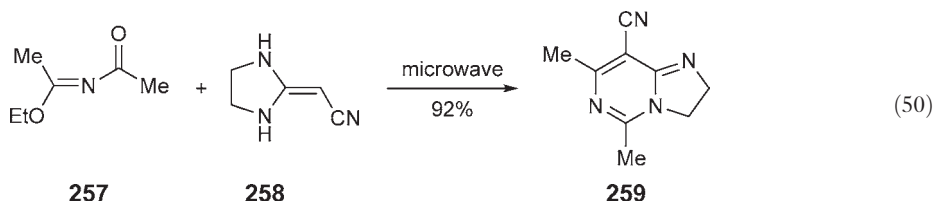
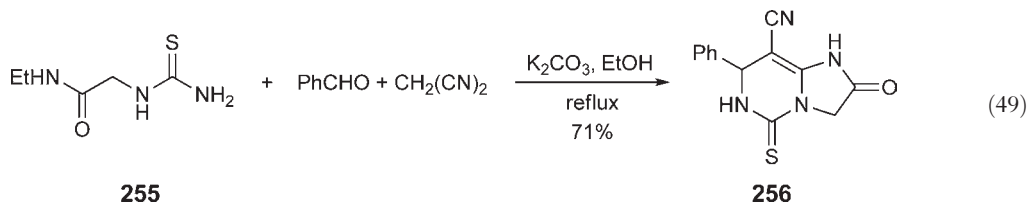
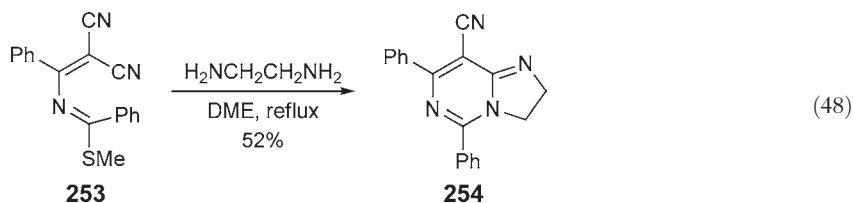
Reaction between ethyl 3-aminopropanoate, cyanamide, and D-aldoses gives (imidazo[1,2-*a*]pyrimidin-7(8*H*)-on-2-yl)-sugars in one step [<1997CL367>](#).

11.12.9.6 Imidazo[1,2-*c*]pyrimidine 68

Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) [<1984CHEC\(5\)607, 1996CHEC-II\(8\)345>](#), and elsewhere [<B-2002SOS\(12\)613>](#). The most usual approach to this ring system involves reaction of a 4-aminopyrimidine with an α -halocarbonyl compound or an α -haloacetal. Alternatively, a 4-halopyrimidine can be treated with a 2-chloroethylamine to give a 4-(2-chloroethyl)amino derivative, which can then be cyclized. Variations of this method include the use of a γ -aminoenoate ester, with ring closure then taking place by conjugate addition [<1998J\(P1\)2255>](#), and also use of a propargylamine nucleophile, with final ring closure onto the alkyne triple bond [<2006PS\(181\)1345>](#). In the reaction between a 4-aminopyrimidine and an α -chloro- β -ketoester, the regioselectivity of the ring closure has been controlled by varying the reaction conditions [<1999JOC634>](#).

Reaction between the 2-azadiene **253** and ethylenediamine results in the formation of both rings in the dihydro product **254** (Equation 48) [<1996H\(43\)1943>](#). A three-component coupling between the thiourea derivative **255**,

benzaldehyde, and malononitrile produces the thiono product **256** in one pot (Equation 49) <2002T7241>. Reaction of the *N*-acylimide **257** with the cyclic ketene aminal **258** under microwave irradiation without solvent gives the dihydro product **259** (Equation 50) <1996SC453>.

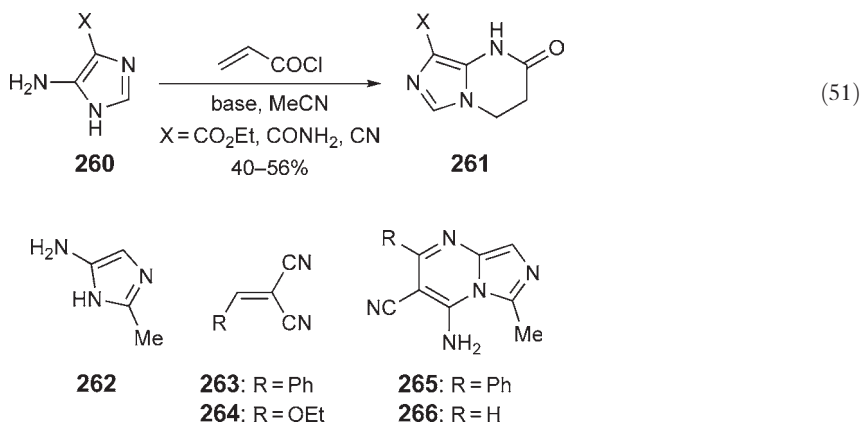


11.12.9.7 Imidazo[1,5-a]pyrimidine **69**

Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>. This ring system continues to receive little attention in the literature, and the most used method of preparation involves the reaction between a 4-aminoimidazole and a three-carbon unit.

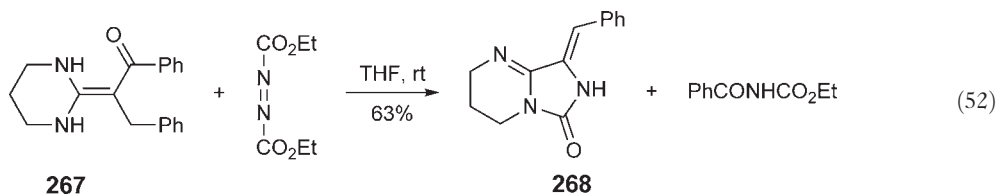
11.12.9.7.1 Closure of the pyrazine ring

Syntheses involving closure of the pyrazine ring have continued to use variations on the classical approach described above. Microwave irradiation has been used in the reaction between a 4-aminoimidazole and a α,β -unsaturated ketone <1995S389>. Treatment of the imidazoles **260** with acryloyl chloride affords the reduced heterocycles **261** (Equation 51), whereas the use of a bis-succinimidyl derivative of propionic acid gives the corresponding dihydro products <1999JME1661>. Reaction of 4-amino-2-methylimidazole **262** with benzylidenemalononitrile **263** or ethoxymethylenemalononitrile **264** gives **265** and **266**, respectively <2003HAC503>.



11.12.9.7.2 Closure of the imidazole ring

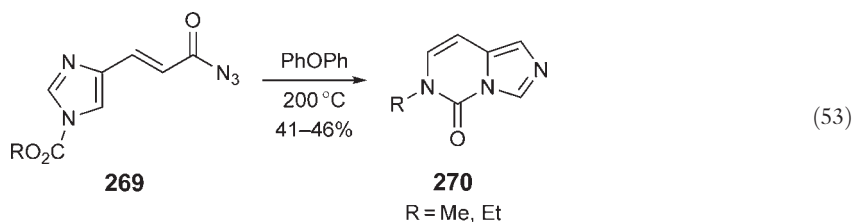
Treatment of the cyclic ketene aminal **267** with diethyl azodicarboxylate results in formation of the reduced ring system **268** (Equation 52), probably via an initial aza-ene reaction, followed by fragmentation and ring closure <2002T7791>.



11.12.9.8 Imidazo[1,5-c]pyrimidine 70

Methods of preparation for this ring system have been reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)607, 1996CHEC-II(8)345>, and elsewhere <B-2002SOS(12)613>. This ring system has not received a great deal of attention, and routes for its synthesis usually employ closure of the pyrimidine ring onto a histidine derivative or, alternatively, closure of the imidazole ring by cyclization of a 4-(aminomethyl)pyrimidine derivative.

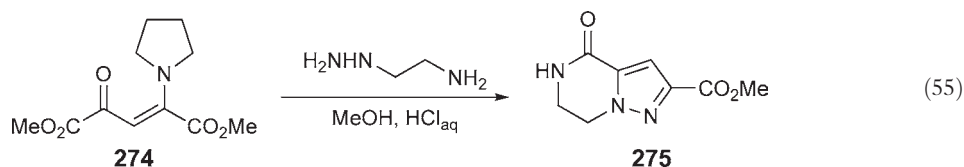
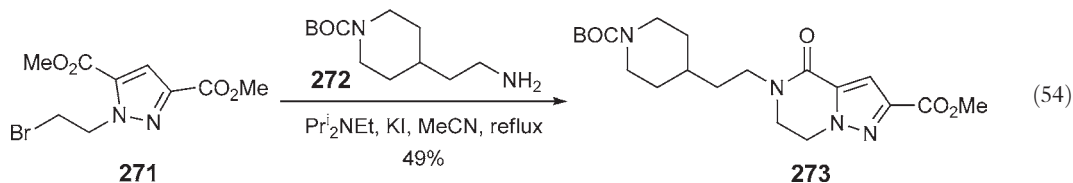
The azide derivatives **269** of urocanic acid undergo thermolysis to give **270** in moderate yields, presumably via cyclization of the isocyanate and migration of the alkyl group R (Equation 53) <2002TL5879>. When R is larger than ethyl, a different ring system is formed instead.



11.12.9.9 Pyrazolo[1,5-a]pyrazine 71

This ring system has received little attention, with previous reviews revealing no material on ring synthesis <1984CHEC(5)607, 1996CHEC-II(8)345>, and a benzo-fused example being reported elsewhere <B-2002SOS(12)613>.

The (bromoethyl)pyrazole **271** reacts with amine **272**, closing the six-membered ring to give **273** (Equation 54) <1997JME1779>. Reaction of (2-aminoethyl)hydrazine with the enaminone **274** results in the formation of both of the rings in **275** (Equation 55) <2003TL5867>.

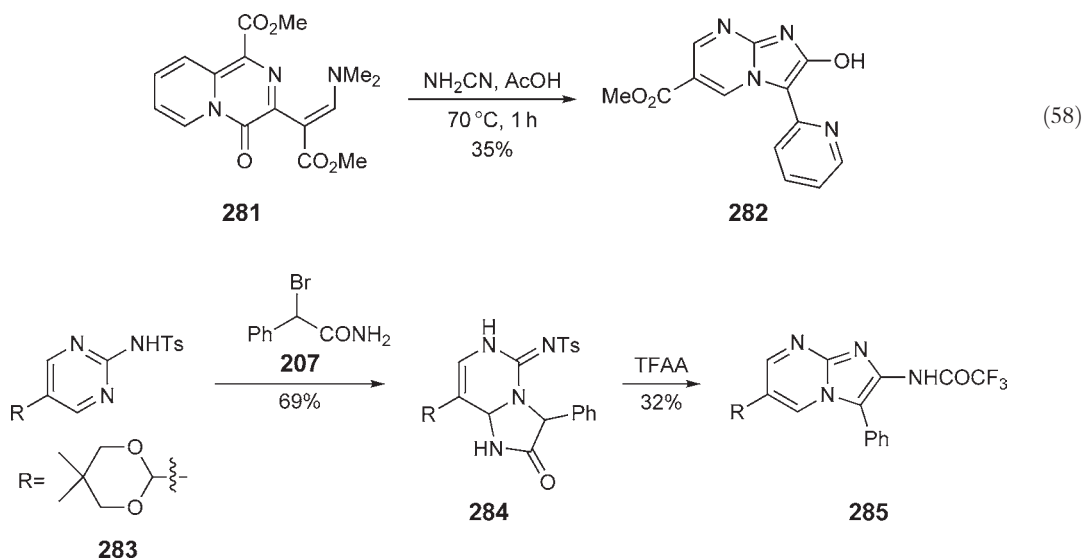


11.12.10 Ring Syntheses by Transformation of Another Ring

There have been relatively few new examples of ring synthesis by transformation of another ring published since 1995.

11.12.10.1 Imidazo[1,2-*a*]pyrimidine 67

The pyrido[1,2-*a*]pyrazine **281** reacts with cyanamide in acetic acid at 70 °C to give the imidazo[1,2-*a*]pyrimidine **282** in a process which involves formation of both of the rings in **282** and cleavage of the pyrazine ring in **281** (Equation 58) <1996JHC639>. Under different conditions, the same starting material **281** can be transformed into other heterocyclic ring systems which are outside the scope of this chapter. When the *N*-tosylaminopyrimidine **283** is treated with α -bromophenylacetamide **207**, the bicyclic product **284** (a derivative of ring system **68**) was unexpectedly formed (Scheme 13) <1999S2124>. When **284** is treated with trifluoroacetic anhydride (TFAA), ring transformation to **285** occurs.



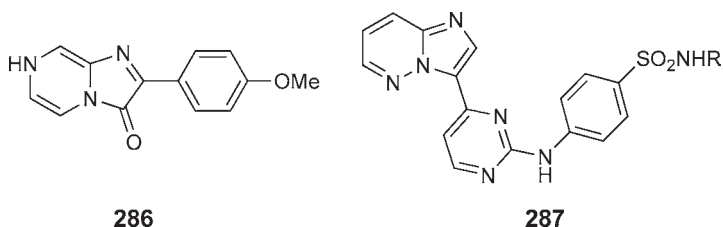
Scheme 13

11.12.11 Important Compounds and Applications

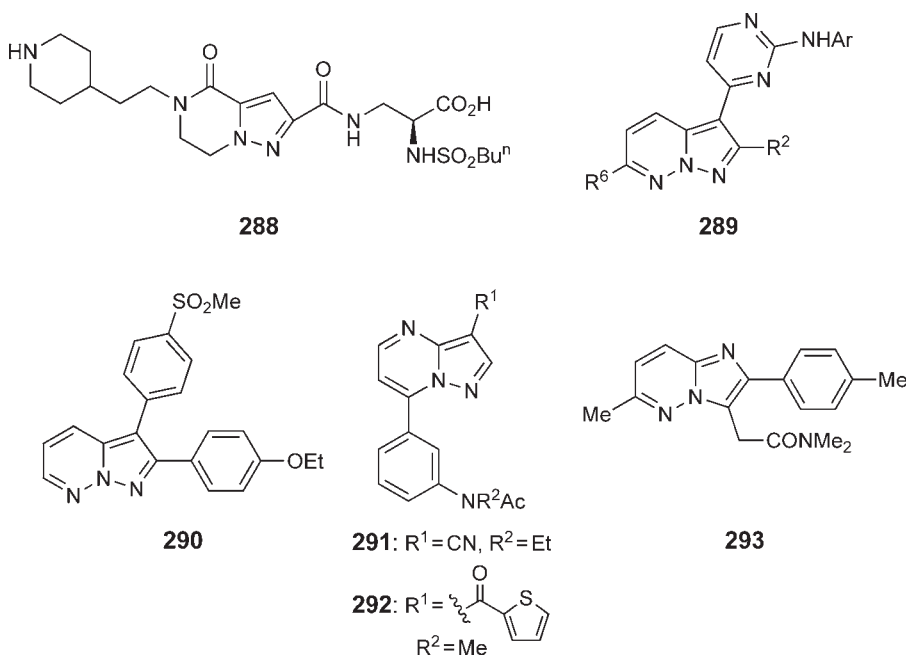
Ring systems **63–74** have attracted much attention from medicinal chemists, and examples of biological activities for a large range of new derivatives have been published for several of these systems since 1995. A selection of these is presented below.

The naturally occurring bioluminescent chromophore coelenterazine **191** is a derivative of ring system **64**, and has prompted a number of spectroscopic and synthetic studies on this and similar luciferins (e.g., <2000T2629, 2006TL753>). Related structures, for example, **286**, have antioxidant properties <2001BML2305> and are effective at preventing reperfusion injury <2003BML653>. Other analogues of ring system **64** have been studied as cyclic nucleotide phosphodiesterase inhibitors <1999BMC1059>, selective GABA_A receptor agonists <2006BML1582>, anti-inflammatory agents <1997EJM195>, and selective somatostatin receptor agonists <2001BML741>. An extensive series of papers on the effectiveness of a wide range of analogues of imidazo[1,2-*b*]pyridazine **65** as competitors for diazepam at benzodiazepine receptors has continued <1997AJC779>. Other analogues of ring system **65** have been investigated as cyclin-dependent kinase inhibitors, for example, **287** <2004BML2249>, and as CCR5 receptor antagonists <2005BML2129>. Several different types of biological activity have been studied for derivatives of imidazo[1,2-*a*]pyrimidine **67**, including antagonism of luteinising hormone-releasing hormone <2002BML2073, 2003JME1769>, MAP kinase inhibition <2003BML347>, and selective GABA_A receptor binding for the treatment of anxiety disorders <2006JME35>. Derivatives of imidazo[1,2-*c*]pyrimidine **68** have been incorporated into nucleoside analogues, which have been found to have potent activity against hepatitis B virus <1997BML303>, and other analogues can be incorporated into oligonucleotide analogues which may have carcinogenic activity <2000CRT208>.

Some thiocarbonyl derivatives of **68** have been shown to have analgesic activity <2005BMC3185>, whereas certain thiocarbonyl derivatives of imidazo[1,5-*a*]pyrimidine **69** have antitumor activity <1999JME1661>.



The oxo derivative **288** of pyrazolo[1,5-*a*]pyrazine **71** is a nonpeptide fibrinogen receptor antagonist which inhibits platelet aggregation <1997BML1531>. Derivatives of pyrazolo[1,5-*b*]pyridazine **72** incorporating a pyrimidine substituent, as in **289**, are selective glycogen synthase kinase 3 inhibitors <2004JME4716>, whereas the 2,3-diaryl derivative **290** entered clinical evaluation as a COX-2 inhibitor <2004BML5445>. Derivatives of pyrazolo[1,5-*a*]pyrimidine **74** have recently received considerable attention for their wide ranging biological activities. Zaleplon **291** is a hypnotic which is currently marketed for insomnia <2000MI413>, and the related compound indiplon **292** is in late development <2004JPE547>. Other derivatives of **74** have been investigated as angiotensin II receptor antagonists <1995JME2728>, corticotropin-releasing factor receptor antagonists <2004JME4787>, and peripheral benzodiazepine receptor ligands <2005BMC4821>. Compound **293** is an aza-analogue of the marketed hypnotic drug zolpidem and shows selective binding to certain subtypes of the GABA_A receptor <2005JME6756>. Other derivatives of **74** act as KDR kinase inhibitors <2002BML2767>, estrogen receptor antagonists <2004JME5872>, antiproliferative agents <2005BML863>, cyclin-dependent kinase 2 inhibitors <2005BML863>, COX-2-selective inhibitors <2001JME350>, and as inhibitors of coxsackievirus B3 replication <2005BML37>.



11.12.12 Further Developments

A comprehensive review of the bioluminescence of 7-oxo derivatives of ring system **64** has appeared <2007BOC82>. The three-component coupling reaction between 2-aminopyrazines, aldehydes and isonitriles, used to form examples of ring system **64** (Section 11.12.9.2.1), has been employed to prepare a combinatorial library, and selective hydrogenation of the six-membered ring in the products was also achieved <2007JCO1177>. A related three-component coupling reaction uses trimethylsilyl cyanide in place of the isonitrile component, employs an ionic liquid as a

promoter, and has been used to prepare examples of both ring systems **64** and **67** <2007M51>. Several chiral imidazolium salts based on ring system **64** have been synthesised as ionic liquids <2007TL1999>.

Baylis–Hillman adducts formed from acrylonitrile derivatives have been used to prepare reduced 2-oxo-derivatives of ring system **67**, with both rings being formed in the same reaction with cyanogen bromide <2007T9448>. The three-component coupling reaction mentioned above, and also used to prepare examples of ring system **67** (Section 11.12.9.5.1) has been combined with a subsequent Dimroth rearrangement to transform 3-amino-2-aryl (or alkyl) derivatives of **67** into the reversed regioisomers with high selectivities <2007TL2041>. Various five-membered ring amino-heterocycles have been reacted regioselectively with α -cyanocinnamionitriles to give examples of ring systems **67**, **69**, and **74** <2007TL6360>.

Reduced 5-oxo derivatives of ring system **68** have been prepared by reaction between an *N,N*-nitroketene acetal and α -chloroisocyanates <2007S835>. Attempts to form examples of ring system **68** using the three-component coupling method referred to above result in zero or very low yields; however by pre-forming an imine intermediate from the aminoheterocycle and the aldehyde, which is then reacted with the isonitrile component, satisfactory yields can be obtained <2007TL2213>.

An improved synthesis of a COX-2 inhibitor based on ring system **72** involves the cyclization of an imine intermediate formed between a 1-aminopyridazine salt and a benzyl ketone <2007TL911>. A tetrahydro derivative of ring system **73** has been prepared by dipolar cycloaddition of an *N*-sulfonylimine to a diazafulvenium methide <2007JOC4406>.

5-Oxo and 7-oxo derivatives of ring system **74** have been prepared from aminopyrazoles, with the regioselectivities being altered by changes in electrophile and reaction conditions <2007JOC1043>. Another regioselective synthesis of ring system **74** also employs reactions of aminopyrazoles, but with a 2-alkenyl-1,3-diketone as the electrophile under solvent-free conditions <2007TL6352>. Finally, the regioselectivities of formation of derivatives of **74** by reaction of an aminopyrazole with trifluoromethyl-1,3-diketones have been established by a multi-nuclear NMR study <2007MRC513>.

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Biographical Sketch



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11.13

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 2:0

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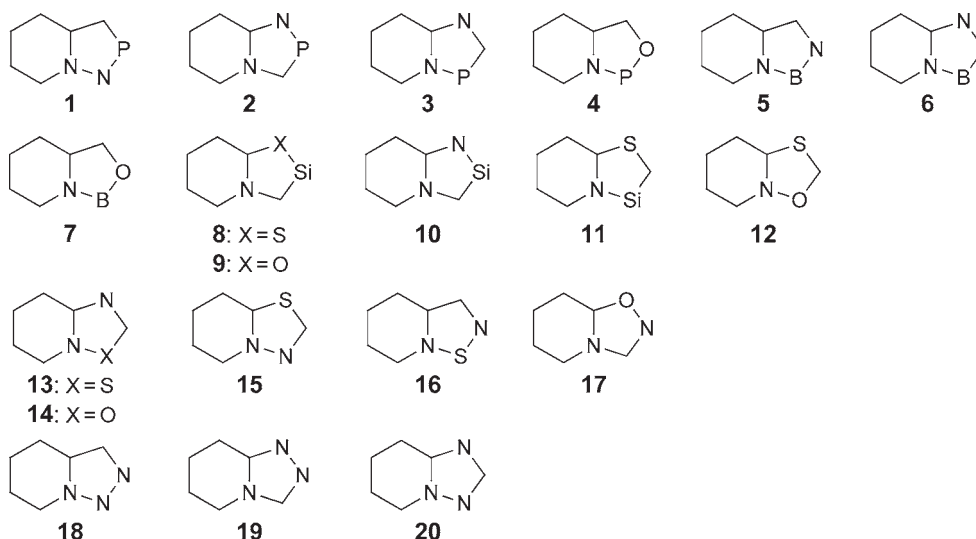
11.13.1 Introduction

This chapter reviews bicyclic systems containing fused five- and six-membered rings with one ring junction nitrogen atom and two extra heteroatoms in the five-membered ring. These heteroatoms are often both nitrogen. Systems containing other heteroatoms such as oxygen, sulfur, phosphorus, silicon, or boron are also presented. The total number of different ring systems falling within the scope of this chapter is 20 ([Scheme 1](#)). As only few reports during the period 1995–2006 deal with exotic ring systems [1–12](#), these are all briefly treated. Systems [13–17](#) were more studied for the characterization of mesoionic compounds or betaines.

By far, the most studied compounds are the triazolopyridines [18–20](#), that can form fully aromatic, neutral molecules. Worth noting are the pharmacological applications of these systems, in particular the antidepressant trazodone based on a [1,2,4]triazolo[4,3-*a*]pyridine motif, marketed worldwide. Many analogs of this triazolopyridine were synthesized to study their structure–activity relationship. As the previous editions [<1996CHEC-II\(8\)367, 1984CHEC\(5\)847>](#) have thoroughly covered syntheses and reactivities of these heterocycles, this chapter focuses on the literature of the past decade, that is, already-known preparations but using new experimental conditions, or newly discovered syntheses and properties. In the interest of saving space, preparations of the most studied [1,2,4]triazolo[4,3-*a*]pyridines [19](#) are presented in tables rather than in a detailed report.

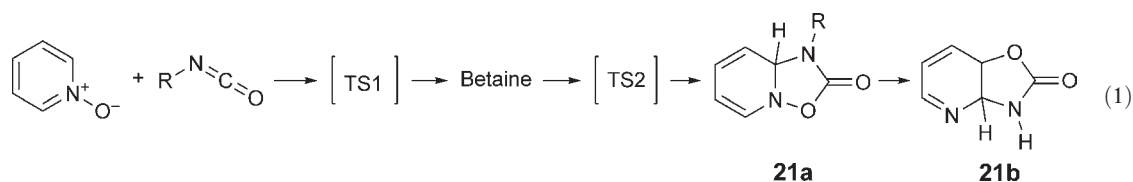
11.13.2 Theoretical Methods

Calculations were performed with few of these systems, either for their formation or properties. Thus, PM3 calculations of the cycloaddition of pyridine-*N*-oxide with an isocyanate were performed, with R = H for simplification. Two consecutive transition states were postulated, pointing out a nonsynchronous process for this reaction, via a

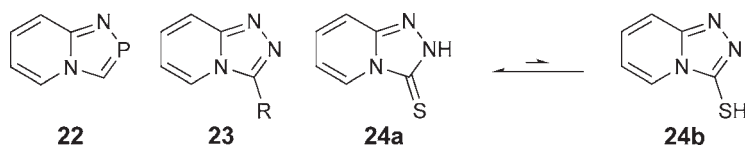


Scheme 1

transient betaine resulting from the nucleophilic attack of the *N*-oxide oxygen atom to the carbon of the isocyanate (Equation 1). The zwitterionic character of the intermediate structure is consistent with these dipolarophiles. Subsequent formation of the N–C bond afforded compound **21a** <1995T6451>. The latter subsequently undergoes a sigmatropic rearrangement which gives the more stable **21b**, with a calculated gain in energy of 35.25 kcal mol⁻¹.



Other calculations were aimed at predicting the reactivity of some bicyclic 5-6 systems. For instance, the rare [1,4,2]diazaphospholo[4,5-*a*]pyridine **22** (Scheme 2) was examined for its reactivity (C=P bond) toward dienes in cycloaddition reactions <2005T10521>. The results of density functional theory (DFT) calculations were in good agreement with the experimentally obtained regioselectivity when using unsymmetrical dienes.



Scheme 2

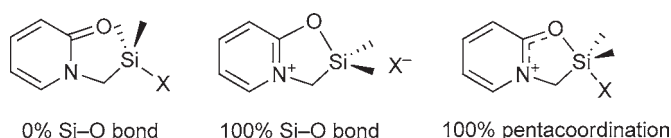
Physicochemical properties rather than reactivities were also explored. Molecular electrostatic potential (MEP) was calculated for the [1,2,4]triazolo[4,3-*a*]pyridine fragment **23**, according to the CHELPG algorithm. This afforded a prediction of its H-bond acceptor ability in view of the synthesis of p38 MAP kinase inhibitors <2005JME5728>. Tautomerism was also examined for compound **24**, also postulated as two possible acyclic structures. The *ab initio* self-consistent field (SCF)-calculated energies support **24a** as the most stable tautomer <1999MRC493>.

11.13.3 Experimental Structural Methods

11.13.3.1 NMR Studies

Chemical shifts for ¹H, ¹³C, and sometimes ¹⁵N are provided in most articles as a way of structural assignment. For instance, a thorough assignment of all protons and carbons is provided for the synthesis of [1,2,4]triazolo[4,3-*a*]pyridines

<1999T5441>. More complex, asymmetric molecules required structural determination using nOe effects <1996T4467, 2002TA821>. ^1H , ^{13}C , and ^{15}N chemical shifts of compounds **24** were calculated for each tautomer and for the two possible acyclic isomers. Experimental measurement also supported **24a** as the major tautomer <1999MRC493>. Another use of nuclear magnetic resonance (NMR) spectroscopy consisted in measuring the rate of formation of Si–O bonds in pyridones and thiopyridone derivatives <1999J(P2)2099, 2000J(P2)1059, 2000JOM125> as a function of the chemical shifts. The limits are represented in Scheme 3.

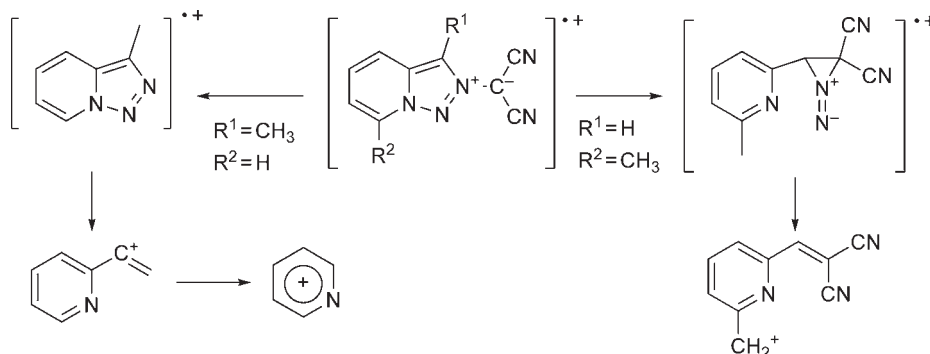


Scheme 3

These percentages were determined using ^{29}Si and ^{13}C NMR spectroscopies, the highest rates of Si–O bond formation being observed with $\text{X} = \text{OTf}$, whereas chlorosilanes rather led to pentacoordinated compounds.

11.13.3.2 Mass Spectrometry Studies

The use of mass spectrometry is generally limited to structural confirmation and measurement of molecular ion. However, a more detailed fragmentation pattern was proposed for [1,2,3]triazolo[1,5-*a*]pyridines, which exhibit a propensity for nitrogen shift (Scheme 4). This can occur before or after the loss of other substituents, according to their initial structures <1996T10519>.



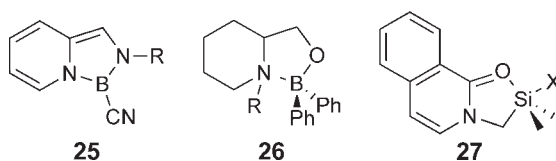
Scheme 4

11.13.3.3 Electronic, IR, and Photoelectron Spectroscopy

Electron paramagnetic resonance (EPR) spectra were recorded when these systems serve as ligands for a metal, for instance, copper <1999POL3129> or iron in ferrocene derivatives <1999T5441>. Attempts at determining a mechanism for the decomposition of triazolopyridines did not afford straight evidence for the expected radical, but for the species resulting from trapping with nitrosobenzene <1998T9785>. Infrared (IR) and Raman spectral data were assigned for some compounds, [1,2,4]triazolo[4,3-*a*]pyridine <2003IJB2567> or [1,2,4]triazolo[1,5-*a*]pyridine <2004SAA2343>.

11.13.3.4 X-Ray Studies

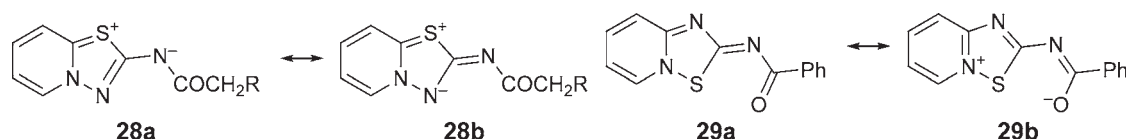
Many X-ray data are given for these bicyclic 5-6 systems, as a method for structure confirmation or elucidation of unexpected reaction products. Analysis of compound **25** (Scheme 5) revealed a planar molecule, in which the B–N distances (1.420 and 1.429 Å) indicate a multiple bond character, since in diazaboroles they range from 1.395 to 1.450 Å

**Scheme 5**

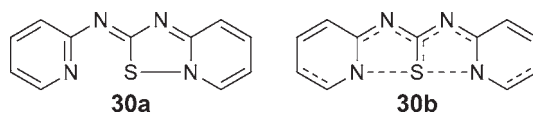
<2001JCD378>. B–N distances were also measured for compound **26**, showing a weaker bond with tertiary amine ($R = \text{CH}_3$).

In silicon derivatives, X-ray studies of compound **27** were consistent with a covalently bonded trigonal bipyramidal molecule <2000CC565>. In addition, nucleophilic substitution at silicon for similar compounds was modeled either by NMR or X-ray techniques and both methods correlate in the calculation of % Si–O bond formation <2003JOM66, 2003JOM154>.

Conclusions about mesomeric forms arose from X-ray analysis of mesoionic *N*-[2-(5-methyl-1,3,4-thiadiazolo[3,2-*a*]pyridinio)]acetamitate **28** (Scheme 6). Among the six possible delocalized structures, a large contribution of the 1,3,4-thiadiazolium structures **28a** and **28b** was observed, rather than pyridinium structures. These two mesomeric forms are in agreement with the high double-bonded character of the S–C6 bond <1996BCJ1769>.

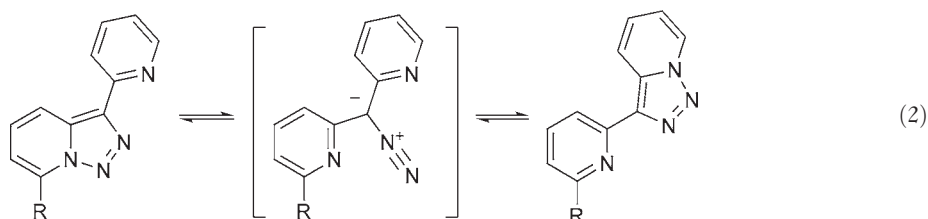
**Scheme 6**

Similarly, X-ray studies on the oxidation product of 1-benzoyl-3-(pyridin-2-yl)-thiocarbamide revealed that compound **29** has a planar structure, best represented by **29a** and **29b** due to conjugation with the benzoyl group <2003K576>. Even in the absence of added oxidizing agent, the formation of symmetrical 2-pyridylthioureas resulted in a compound which lacks the NH protons. X-ray analysis of this molecule showed a delocalization throughout the tricyclic system, indicating that the [1,2,4]thiadiazolo[2,3-*a*]pyridine **30a** obtained can be represented by symmetrical structure **30b** (Scheme 7). This was determined by the higher length of the C–S bond and a breakdown in the aromaticity of the pyridyl rings <2000CSC687>.

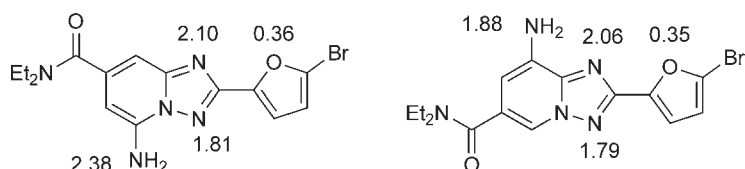
**Scheme 7**

11.13.4 Thermodynamic Aspects

Cycloaddition of pyridine *N*-oxides (see Section 11.13.2) led to careful examination of thermodynamic aspects, though no experimental measurement was provided. Thermodynamic profile for the ring-chain isomerization of [1,2,3]triazolo[1,5-*a*]pyridines via a ring-opening pathway (Equation 2) was calculated. Based on this computational study, a multistep mechanism was proposed <2005OBC3905>.



For pharmacological purposes, a mapping of the abilities of heteroatoms to behave as H-bond donors/acceptors was calculated for the molecules shown in [Scheme 8](#) <2004BML3307>.



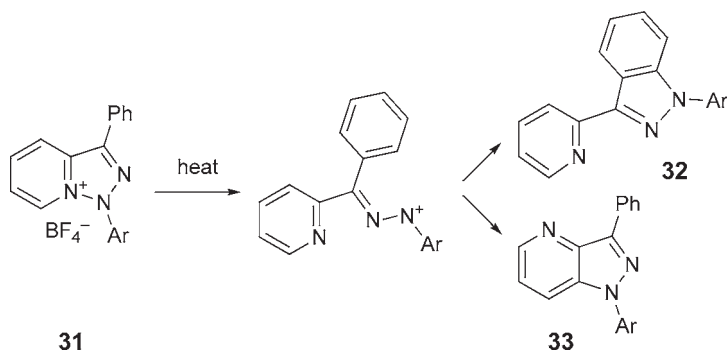
Scheme 8

The reference used is water with a value of 1.748. This means that atoms with a value <1.748 are weaker donors/acceptors than water and vice versa. The role of the nitrogen atom of the triazole ring as a H-bond acceptor appeared crucial for the interactions with the studied enzyme.

11.13.5 Reactivity of Fully Conjugated Rings

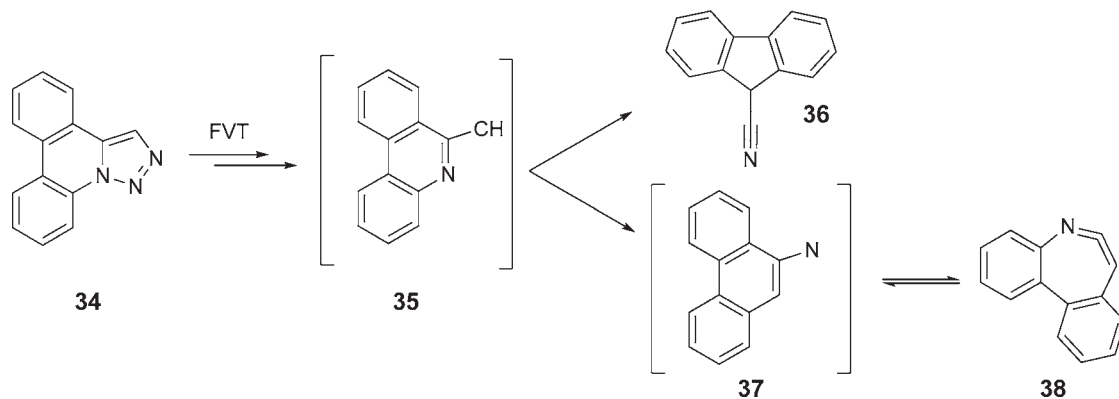
11.13.5.1 Thermal and Photochemical Reactions

Thermal decomposition of the triazolopyridinium salt **31** in dichlorobenzene at 180 °C resulted in compounds **32** and **33** ([Scheme 9](#)), providing convincing support for the intermediate formation of a nitrenium cation <1997JOC1136>.



Scheme 9

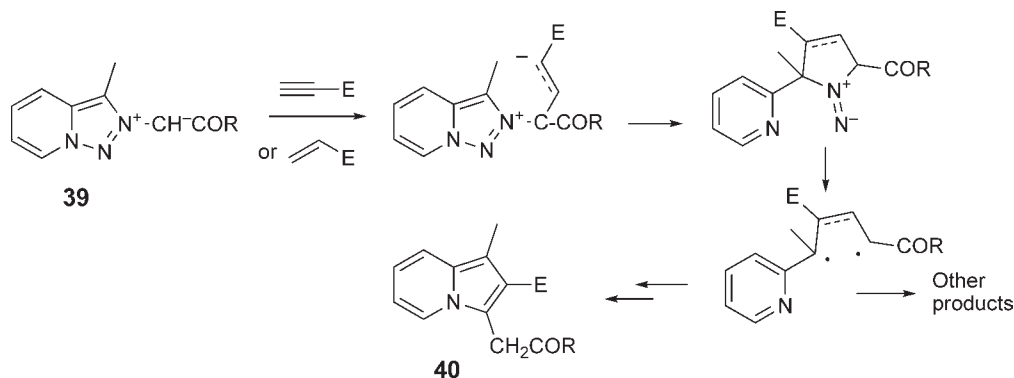
In a recent article <2005JOC7947>, the products arising from the decomposition of the triazolopyridine **34** were examined ([Scheme 10](#)). The transient carbene **35** further led to 9-cyanofluorene **36** as the main product, along with



Scheme 10

the unstable ketenimine **38**, assigned by observation of its IR band at 1932 cm^{-1} . Nitrene **37** was observed by electron spin resonance (ESR) spectroscopy, during thermal decomposition by flash vacuum thermolysis (FVT) at $600\text{--}750^\circ\text{C}$. Photolysis at 308 nm allowed the observation of carbene **35**.

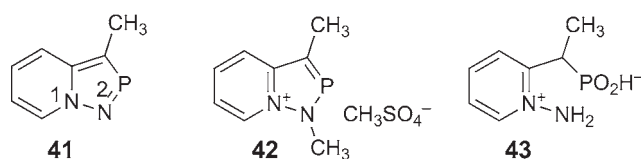
As depicted in **Scheme 11**, ylides **39** derived from 4-methyl-[1,2,3]triazolo[1,5-*a*]pyridine react with Michael acceptors, which, upon nucleophilic attack at C3 and ring opening, lead to nucleophilic displacement of nitrogen. The intermediate diradical led to a mixture of compounds, including alkenes and a cyclobutane derivative when methyl acrylate was used, and the indolizine **40** with methyl propiolate as the electrophile [<1998T9785>](#). Heating 4-methyl triazolopyridine with benzenesulfonyl chloride in acetone also confirmed decomposition via a radical pathway.



Scheme 11

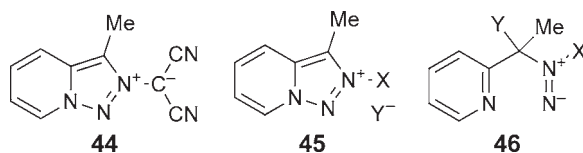
11.13.5.2 Electrophilic Attack at Nitrogen (and/or Carbon)

4-Methyl[1,2,3]diazaphospholo[1,5-*a*]pyridine **41** undergoes electrophilic attack at N-2 (**Scheme 12**). Dimethyl sulfate in the absence of nucleophile led to the salt **42**, whereas upon treatment with water, protonation of the same atom was followed by nucleophilic attack at phosphorus and consecutive ring opening to produce **43** [<1995S173>](#).



Scheme 12

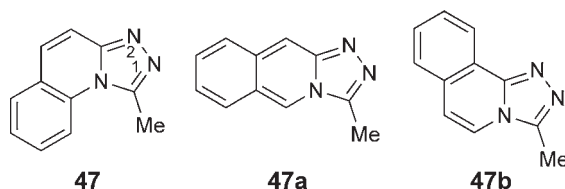
[1,2,3]Triazolo[1,5-*a*]pyridines react with various electrophiles which attack at N-2. As shown in **Scheme 13**, reacting 4-methyl[1,2,3]triazolo[1,5-*a*]pyridine with tetracyanoethylene oxide in ethyl acetate at 0°C provided the ylide **44** [<1996T10519>](#). Treatment of the same starting material with hydrogen chloride or bromide gave **45**



Scheme 13

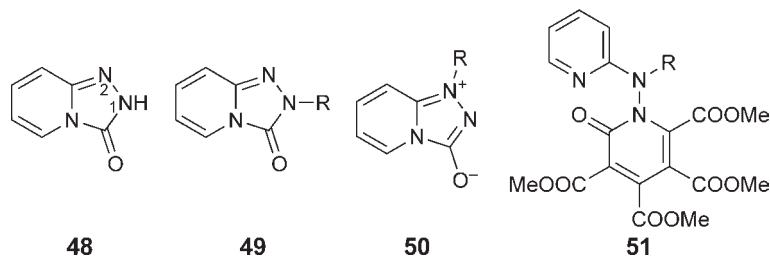
(X = H, Y = Cl or Br), which upon heating decomposed to **46** (X = H, Y = Cl[−] or Br[−]) and subsequent compounds resulting due to nitrogen shift. Similarly, methyl iodide could also provide the salt **45** (X = Me, Y = I) and benzene-sulfonyl chloride afforded **45** (X = SO₂Ph, Y = Cl) which decomposed to various products via the intermediate **46** (X = SO₂Ph, Y = Cl) <1998T9785> (see Section 11.13.5.1).

[1,2,4]Triazolo[3,4-*a*]pyridines, fused with a benzene ring, were alkylated with dimethyl sulfate. In all cases, methylation occurred predominantly at N-2 (Scheme 14), but was also observed at N-1 in ratios of 70:30 for **47**, 95:5 for **47a**, and 80:20 for **47b** <1996T1399>.



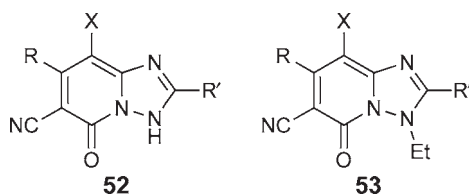
Scheme 14

Electrophilic substitution was observed at nitrogen with triazolopyridone derivatives (Scheme 15). Pyridotriazolone **48** was alkylated at N-1 and N-2, in ratios depending on the alkylating agent (MeI or PhCH₂Br) and the solvent. Mixtures of **49** and **50** were obtained, except in the case of MeI/acetone, which led exclusively to **49**. Dimethyl acetylenedicarboxylate (DMAD) reacted with betaine **50** at N-1, leading, after trapping the allenic enolate with a second equivalent of DMAD, to a ring opening by nucleophilic attack onto the triazole carbonyl, affording **51**. This result pointed out the low degree of 1,3-dipolar character for betaine **50**, and its ability to behave as a masked 1,3-dipole <2000H(53)265>.



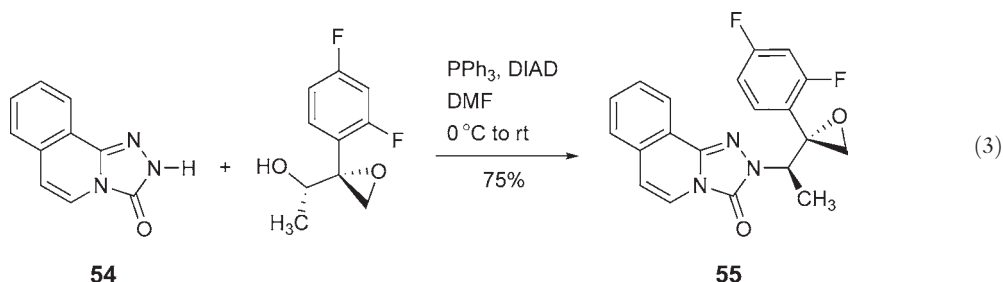
Scheme 15

A similar alkylation of triazolopyridone **52** gave **53** upon treatment with triethyl orthoformate or orthoacetate in acetonitrile (Scheme 16) <2003MI223>.

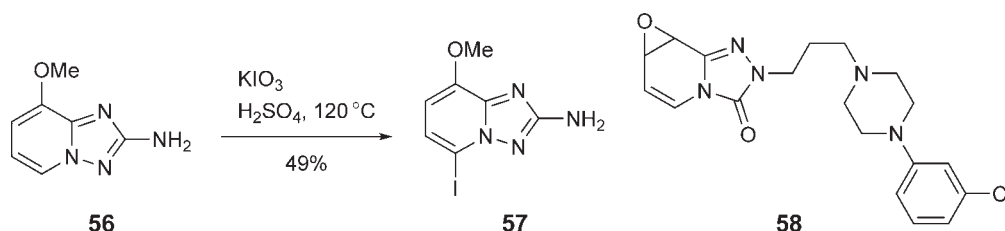


Scheme 16

More recently, a preparation of *N*-alkylated pyridotriazolones was developed using a Mitsunobu protocol, pointing out the acidity of the NH group. Compound **54** (Equation 3) displaced the hydroxyl group with classical inversion at carbon, leading to **55** <2005SC2939>.

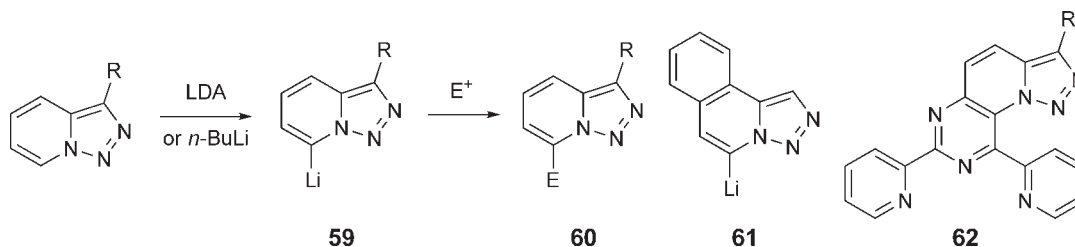


Direct electrophilic attack at carbon requires electron-rich [1,2,4]triazolo[1,5-*a*]pyridines; for instance, iodination of **56** (Scheme 17) was obtained by heating with potassium iodate in H₂SO₄ at 120 °C, affording **57** in 49% yield <2003S1649>. In a biochemical context, epoxidation of the benzenic ring of trazodone gave **58** <2005MI10>. This metabolic pathway involving cytochrome P4503A4 often accounts for the toxicity of aromatic compounds, due to the high reactivity of the epoxide.

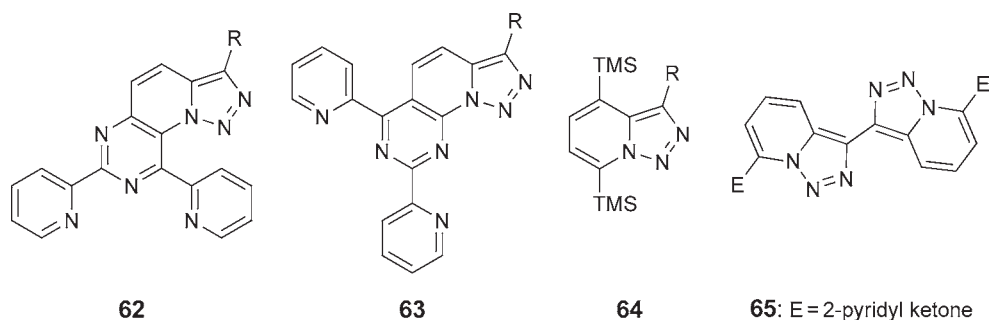


Scheme 17

When used as a versatile tool in synthesis, electrophilic substitution at carbon is generally obtained in a nondirect pathway which first involves regioselective metallation with a strong lithium base (Scheme 18). Thus, numerous examples illustrate this methodology, either using LDA/THF at −40 °C or *n*-BuLi/toluene for the lithiation (LDA = lithium diisopropylamide, THF = tetrahydrofuran). Lithiation also occurs when system **18** is fused with a benzene ring, for example, **61** <2004T4887>. Electrophilic trapping of the lithiated species **59** was performed with CO₂, dimethylformamide (DMF) <1995JHC787>, TMSCl <1998T15287> (TMS = trimethylsilyl), dibromotetrachloroethane (E = Br) <1997T8257>, aromatic aldehydes <2002ARK9> (in some cases followed by air oxidation), 2004T5785>, ethyl esters for acylation <2005OBC3905>, triisopropyl borate <2004T4887>, or pyridine-2-carbonitrile. With the latter, some readdition of the nitrile occurred, leading to a fused pyrimidine (Scheme 19), besides the formation of the expected aromatic ketone after imine hydrolysis. At first, this fused pyrimidine was believed to be compound **62** <2002ARK52>, but a recent obtention of crystals suitable for X-ray analyses revealed that its structure corresponded to the isomer **63**. A mechanism for this rearrangement was proposed <2005ARK71>. Double metallations were also observed either for the same bicyclic 5-6 system, for example, **64** obtained with TMSCl using excess LDA <1995T10969>, or with an excess of *n*-BuLi for metallation of both bicyclic 5-6 systems in the symmetrical structure **65** <2004T5785>.



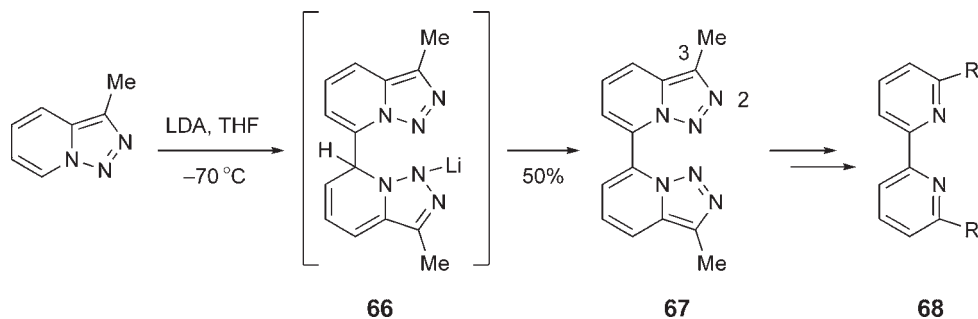
Scheme 18



Scheme 19

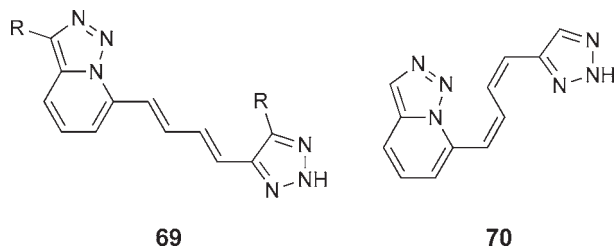
11.13.5.3 Nucleophilic Attack at Carbon

Reported nucleophilic attacks at carbon consist of aromatic substitutions of leaving groups such as halogens, rather than direct attack followed by oxidative rearomatization. Thus, metallation of systems **18** allowed substitution at C-7 with chlorine or bromine, and subsequent nucleophilic substitution with thiophenoxide, phenoxide, hydrazine, secondary amines, or methoxide ion (starting with compound **60** with E = Br and R = CONMe₂ or CONEt₂) <1997T8257>. These systems also allow further hydrolysis or the triazole ring, with loss of nitrogen. This reaction reported earlier consists of a nucleophilic attack (by water or acetic acid) at C-3, rendered possible by protonation at N-2 <1998T9785>. Also worth noting, the metallation of [1,2,3]triazolo[1,5-*a*]pyridines at -70 °C rather than -40 °C can be followed by nucleophilic attack of the lithiated species at C-7 and rearomatization of **66** via hydride shift, thus leading to the corresponding dimer **67** (Scheme 20). After subsequent hydrolytic treatment as for nondimeric structures (with aq. H₂SO₄, R = CH(OH)CH₃; with refluxing AcOH, R = CH(OAc)CH₃) or oxidation with SeO₂ (R = COCH₃), symmetrical 6-substituted 2,2'-bipyridines **68** were obtained <1997T8257, 1998T15287, 2004T5785>.



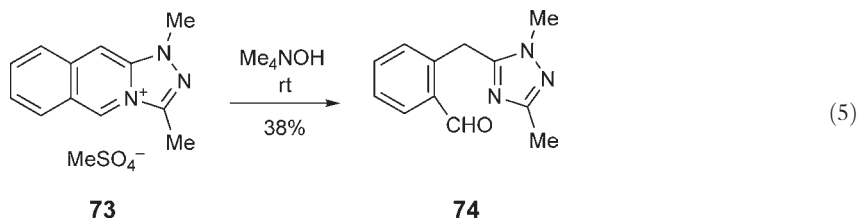
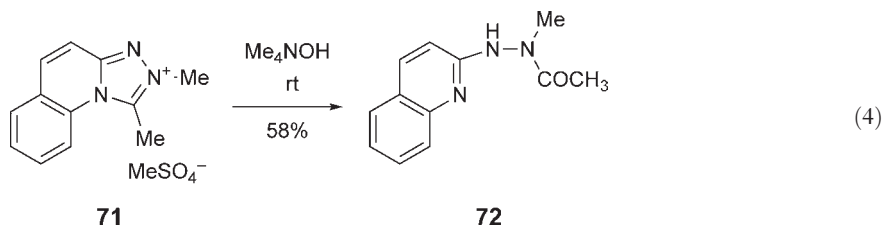
Scheme 20

The intermediate **66** may also lead to opening of the pyridine ring <1998T15287>, resulting in the formation of dienes **69** and **70** (Scheme 21), whose stereochemistries were assigned with accuracy <2002ARK146>.



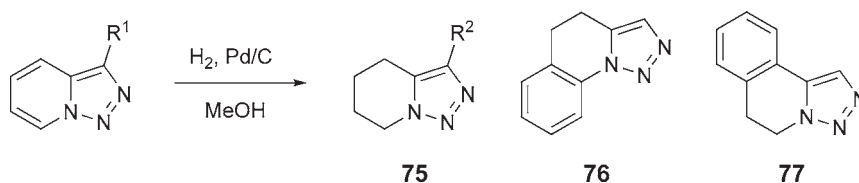
Scheme 21

With system **19**, nucleophilic attack at carbon generally involves a hydrolytic pathway after quaternarization of one of the nitrogen atoms. Thus, hydrolysis of the cationic species **71** led to ring opening (Equation 4). Whether the ring opening involves the triazole or pyridine ring depends on the initial structure. Indeed, substituents and position of the benzene ring greatly influence the opening; for instance, **71** and **73**, upon alkaline treatment with tetramethylammonium hydroxide in a mixture of water and CH₃CN, led to **72** and **74**, respectively (Equation 5). Nucleophilic attack (Nu = OH[−] or BH₄[−]) at the carbon of the bicyclic junction can also be obtained, thus providing either neutral bicyclic 5-6 system or pyridone derivatives <1996T1399>.



11.13.5.4 Reactions at Surfaces

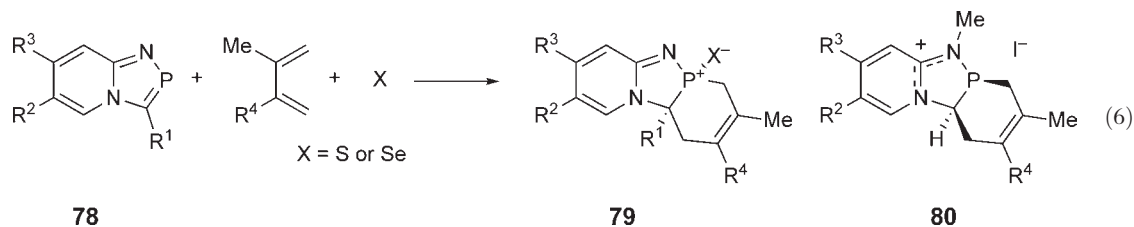
There is one new report <1999T12881> dealing with hydrogenation of [1,2,3]triazolo[1,5-*a*]pyridines substituted at C-3 (Scheme 22) and affording the piperidinotriazole **75**. The substituent R¹ can be an alkyl group, alkene, nitro, nitrile, ester, or aromatic ring and, if sensitive to hydrogenation, they will be reduced in the same step. Whatever the substituent, and whether the pyridine is fused with a benzene ring or not (compounds **76** and **77**), the pyridine is always the only ring reduced.



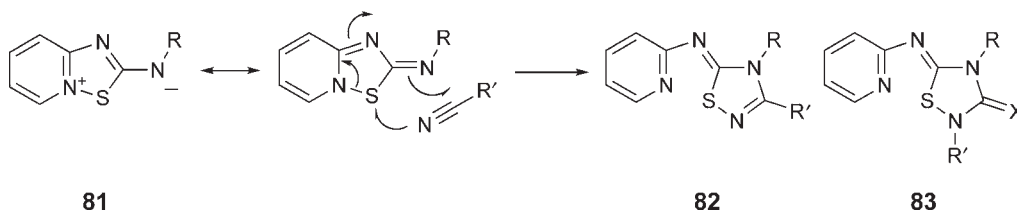
Scheme 22

11.13.5.5 Reactions with Cyclic Transition States

[1,4,2]diazaphospholo[4,5-*a*]pyridines **78** underwent [4+2] cycloaddition with *endo*-stereoselectivity (Equation 6). The reaction was carried out in the presence of electrophiles, either sulfur or selenium for an attack at phosphorus and obtention of **79**, or methyl iodide which quaternarized at N-1, giving the salt **80** <2005T10521>.



Betaine **81** or its neutral mesomeric form (Scheme 23) reacted with nitriles affording the thiadiazole **82**, and a dipolar addition was suggested <1996H2657>. In a similar reaction, isocyanates and isothiocyanates gave oxo and thiono thiadiazoles **83** (X = O, S) <1997BMC1275>.



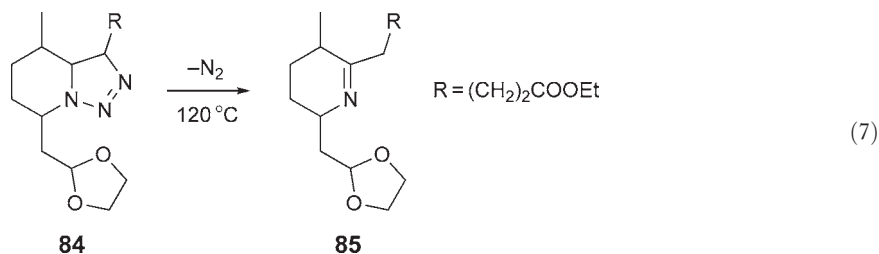
Scheme 23

Alkyne dipolarophiles such as methyl propiolate or DMAD reacted with ylides derived from [1,2,3]triazolo[1,5-*a*]-pyridines, but the mechanism proposed involved a Michael addition and subsequent nucleophilic attack rather than a concerted [4+2] cycloaddition <1996T10519> (see Section 11.13.8).

11.13.6 Reactivity of Nonconjugated Rings

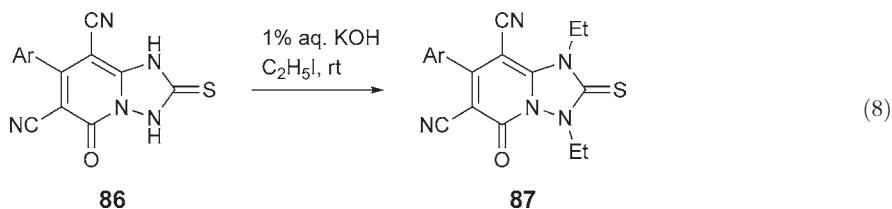
11.13.6.1 Thermal and Photochemical Reactions

As an example of nonaromatic triazolopyridine, **84** underwent a nitrogen shift upon heating in C₆D₆ (sealed tube at 120 °C) (Equation 7). The transformation was slow and gave the tetrahydropyridine **85** after 38 h <1998JOC9910>.



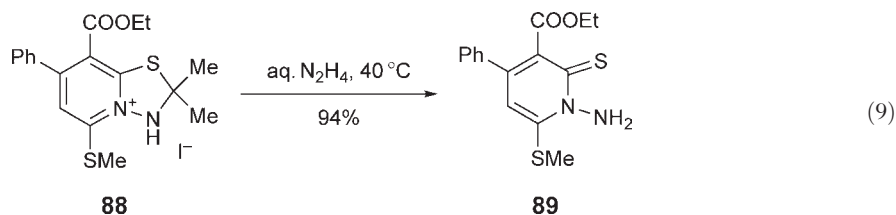
11.13.6.2 Electrophilic Attack at Nitrogen (and/or Carbon)

Alkylation of **86** with ethyl iodide in the presence of 1% aqueous KOH afforded the *N,N*-diethyl product **87** (Equation 8) <2004CPA276>.

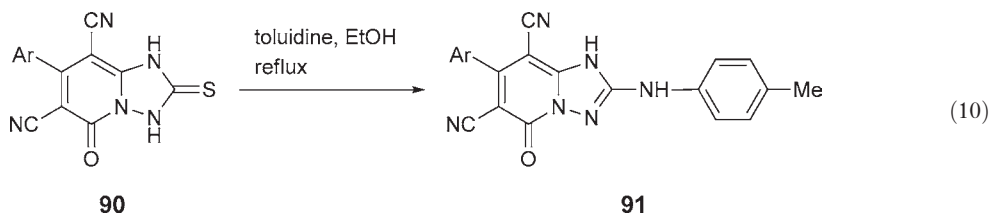


11.13.6.3 Nucleophilic Attack at Carbon

Transhydrazination of **88** with aqueous hydrazine afforded **89** through acetone removal (Equation 9) <1996JPR516>.



Condensation of **90** with *p*-toluidine resulted in nucleophilic attack at C-3, affording **91** (Equation 10) <2004CPA276>.



11.13.6.4 Reactions at Surfaces

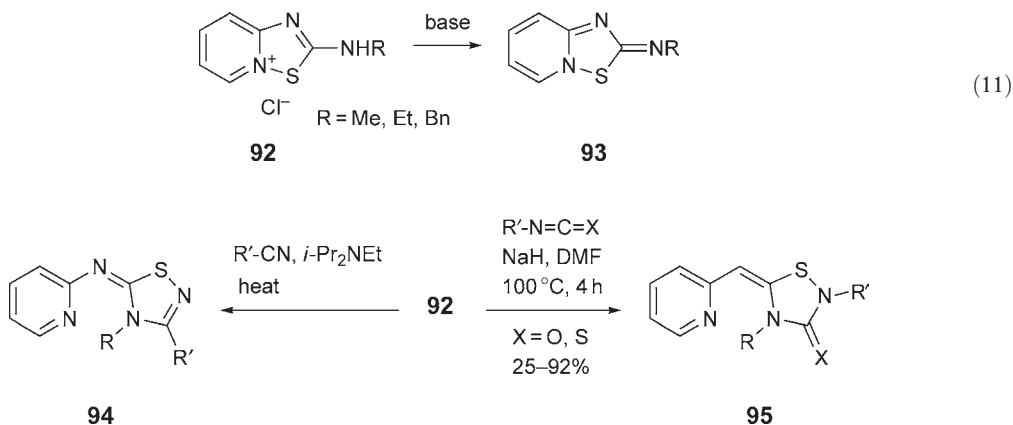
No new reaction at surfaces, neither hydrogenation nor electrochemical reaction, was found for the systems falling within the scope of this chapter.

11.13.6.5 Reactions with Cyclic Transition States

No new reaction involving cyclic transition states was reported for not fully conjugated systems during the period of time covered.

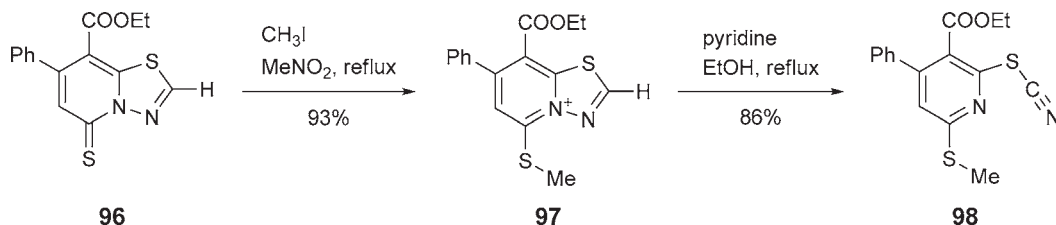
11.13.7 Reactivity of Substituents Attached to Ring Carbon Atoms

The [1,2,4]thiadiazolo[2,3-*a*]pyridinium salt **92** is stable but gives a neutral compound **93** (Equation 11) in the presence of a base (a tertiary amine or sodium hydride), thus enhancing the reactivity of the exocyclic nitrogen <1996H432657, 1997JHC337>. Further attack of the latter onto electrophiles such as nitriles or isocyanates resulted in the opening of the thiadiazole ring (Scheme 24) (see Section 11.13.5.5). This was used as a method of preparation of arylimino-1,2,4-thiazolines **94** and arylimino-1,2,4-thiazolidinones **95** as potassium channel openers <1997BMC1275>.



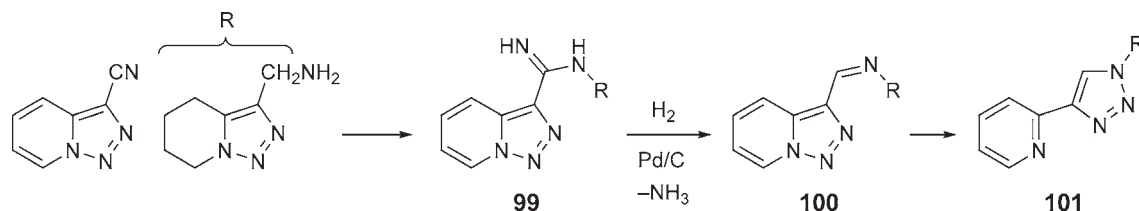
Scheme 24

[1,3,4]Thiadiazolo[3,2-*a*]pyridin-thiones **96** can be methylated at the pyridinethione sulfur atom, with methyl iodide in nitromethane (**Scheme 25**). The obtained salt **97** displays a particular reactivity for the thiadiazole hydrogen, which can be abstracted by pyridine to afford ring opening and formation of isocyanate **98** <1996JPR516>.



Scheme 25

Most reactions in the scope of this chapter account for substituents attached to the [1,2,3]triazolo[1,5-*a*]pyridine system. Classical functional group transformations were reported, such as acylation of amines <2003S1649>, or reaction of an ester on the triazole. For instance, methyl esters at the triazole were reduced <2000TL7805>, reduced for further phosphorylation purposes <2002AGE3041>, or simply hydrolyzed <1997TA3807>. Nitriles attached at the same position were transformed into sulfonylamidines or ketones <1995T10969>. Nucleophilic addition of a primary amine (formed *in situ* by hydrogenation of a nitrile) onto the remaining nitrile was also observed (**Scheme 26**); the amidine **99** obtained was further reduced to the imine **100** with loss of ammonia. This imine underwent rearrangement with ring opening and subsequent cyclization to afford a 1,2,3-triazole **101** <1999T12881>.



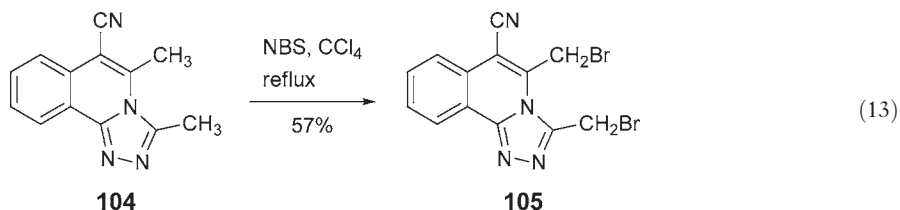
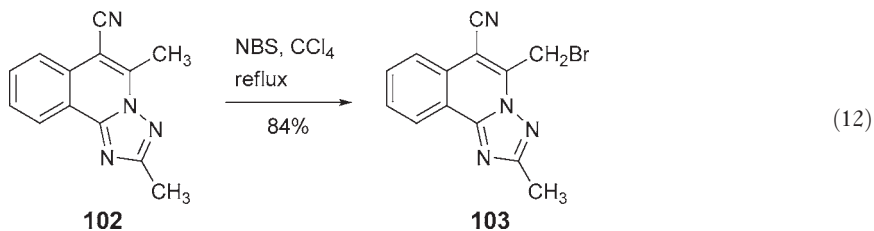
Scheme 26

Esters attached to the pyridine were used as precursors of amides <2003TL1675> and aldehydes on the pyridine ring underwent Horner–Emmons conversion to acrylates <1995JHC787>.

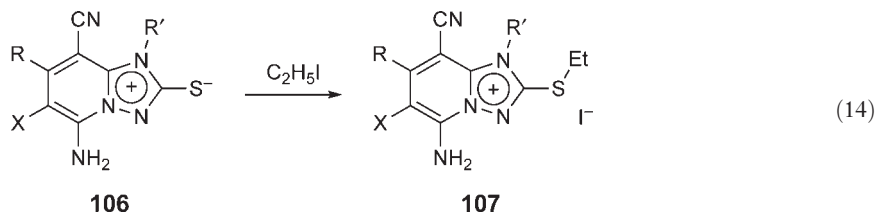
More specific to this system, the transformation of a 2-pyridyl ketone into another [1,2,3]triazolo[1,5-*a*]pyridine was used in the synthesis of poly[1,2,3]triazolo[1,5-*a*]pyridines <2002ARK52, 2004T5785, 2005OBC3905>. Metallations at C-7 are commonly employed (see [Section 11.13.5.3](#)), and boronates can be obtained by this method and further engaged in coupling reactions, especially Suzuki coupling. This led to 7-aryl compounds with generally low yields, (11–49%) <2001SL1917> and (11–83%) <2003S1649>. This result can be explained by the obtention of side products which are often the major products themselves, and result from reductive deboration or dimerization <2004T4887>.

A [1,2,4]triazolo[4,3-*a*]pyridine bearing a sugar residue on the triazole was oxidized, the sugar being transformed to an aldehyde without degradation of the bicyclic 5-6 system <1998PHA294>. Radical bromination with further oxidation of a methyl group attached to the pyridine was reported, with the participation of an adjacent nitrile in the formation of a 5-hydroxypyrrolidone. A difference in reactivities of methyl groups attached to triazole and pyridine rings was observed, for isomeric systems **18** and **19**. Indeed, radical substitution on **102** with

N-bromosuccinimide (NBS) led to monobromide **103** (Equation 12), whereas with **104**, both methyl groups were transformed, giving the dibromide **105** (Equation 13) <2004JHC549>.

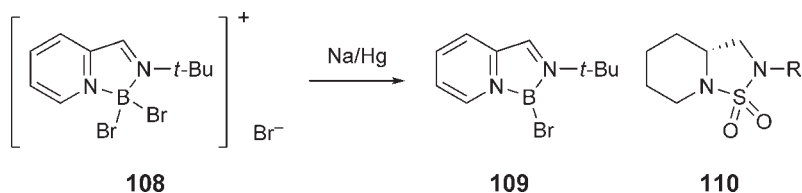


Nitriles attached to [1,2,4]triazolo[1,5-*a*]pyridones were also converted to hydrazide adducts or 1,3,4-triazoles <2004CPA260>. Sulfur in zwitterionic structure **106** was readily alkylated with ethyl iodide (Equation 14), affording the salt **107** <2003JCM755>.



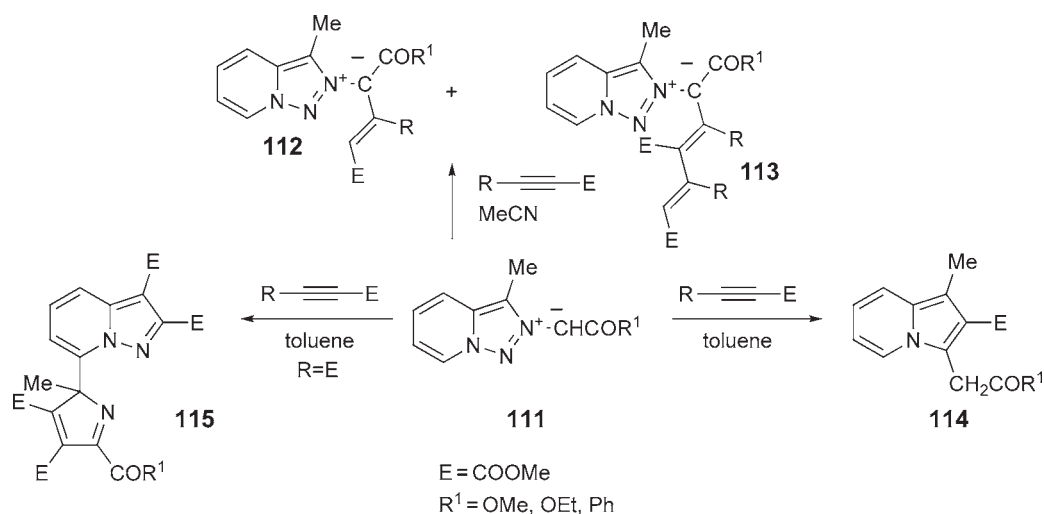
11.13.8 Reactivity of Substituents Attached to Ring Heteroatoms

Boron substituents in the [1,3,2]diazaborolo[1,5-*a*]pyridine derivative **109** were studied. This compound was obtained via reduction of its precursor **108** with sodium amalgam (Scheme 27). The bromide attached to the boron atom was further displaced with various halide, hydride, sulfur, and carbon nucleophiles <2001JCD378>. [1,2,5]thiadiazolo[2,3-*a*]pyridine derivative **110** was deprotected (R = Cbz to R = H) by classical hydrogenolysis <2002AGE3866>.



Scheme 27

[1,2,3]Triazolo[1,5-*a*]pyridines bearing an active methylene at N-2 can form ylides **111** which were reviewed in CHEC-II(1996) <1996CHEC-II(8)367>. Their reactions with alkyne Michael acceptors lead to monoadducts **112** or bis-adducts **113** at the ylide carbon, indolizines **114**, or other rearrangement products such as **115** (Scheme 28). Other ylides stabilized by a 1,3-dinitrile (malononitrile) system were reported <1996T10519>. The mechanism (see Section 11.13.5.1) of further transformations for various ylides was discussed <1998T9785>.

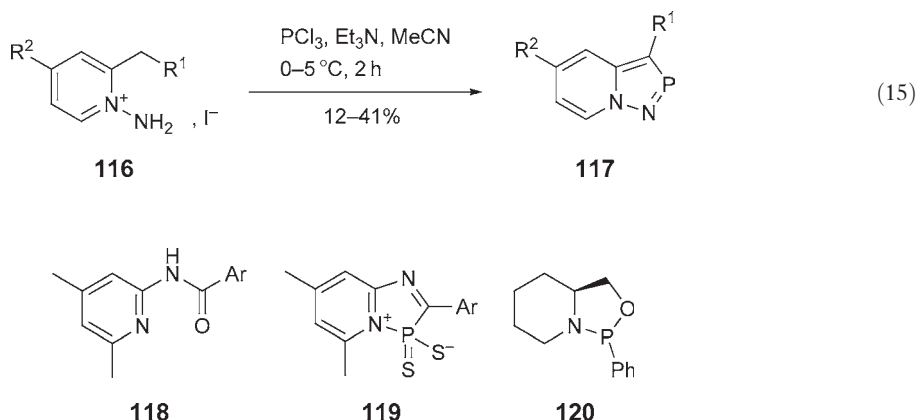


Scheme 28

11.13.9 Ring Syntheses Classified by Number of Ring Atoms in Each Component

11.13.9.1 [1,2,3]Diazaphospholo[1,5-*a*]pyridines of Type 1, [1,4,2]Diazaphospholo[4,5-*a*]pyridines of Type 2, [1,4,2]Diazaphospholo[1,5-*a*]pyridines of Type 3, [1,3,2]Oxazaphospholo[3,4-*a*]pyridines of Type 4

[1,2,3]Diazaphospholo[1,5-*a*]pyridine **117** with R^1 and $R^2 = H, CH_3$ resulted in treatment of 2-substituted *N*-aminopyridinium iodide **116** with PCl_3/Et_3N in acetonitrile at $0^\circ C$ (Equation 15) <1995S173>. Compound **119** (Ar = Ph, 2-thienyl) was obtained as a by-product, upon heating the arylamide **118** with Lawesson's reagent (Scheme 29) <1995EJM915>. Fully saturated [1,3,2]oxazaphospholo[3,4-*a*]pyridine **120** was obtained by refluxing (2*S*)-piperidine-methanol with $PhP(NMe_2)_2$ in toluene <1997JOM285>. An example of [1,4,2]diazaphospholo[4,5-*a*]pyridine of type 2 is described in Section 11.13.5.5; its synthesis is anterior to the period of time covered by this chapter.

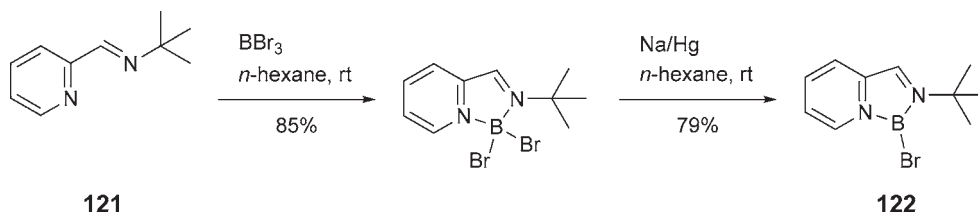


Scheme 29

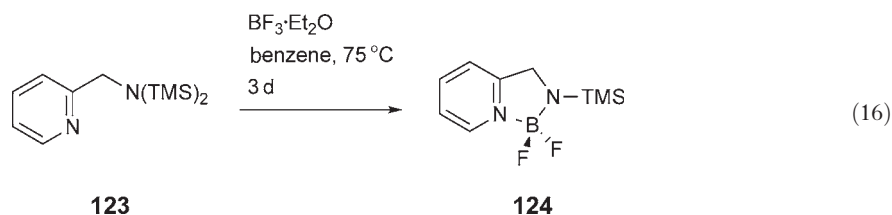
11.13.9.2 [1,3,2]Diazaborolo[1,5-*a*]pyridines of Type 5

Treatment of imine **121** with BBr_3 followed by sodium amalgam-mediated reduction led to diazaborolopyridines **122** (Scheme 30). Likewise, the 1:2 complex between **121** and BF_3 was reduced in a similar way <2001JCD378>.

Internal complex **124** was obtained by reacting BF_3 with 2-bis(trimethylsilyl)aminomethyl-pyridine **123** during 3 days at 75 °C in benzene (Equation 16) [<2002NJC677>](#).

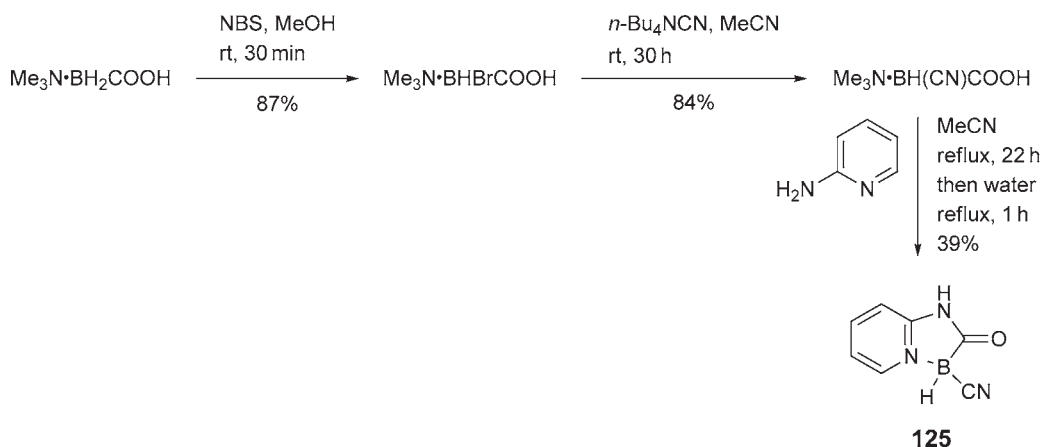


Scheme 30



11.13.9.3 [1,4,2]Diazaborolo[1,5-a]pyridines of Type 6

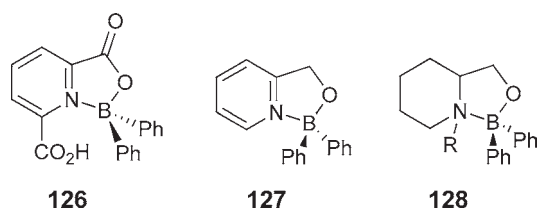
The unusual structure **125** displays an acylborane group; the latter was formed from carboxyborane as a complex with secondary or tertiary amines, imidazole, or pyridine derivatives. The synthetic pathway (**Scheme 31**) consisted in an oxidation with NBS, substitution with cyanide, then treatment with 2-aminopyridine [<2004JOM3567>](#).



Scheme 31

11.13.9.4 [1,3,2]Oxazaborolo[3,4-a]pyridines of Type 7

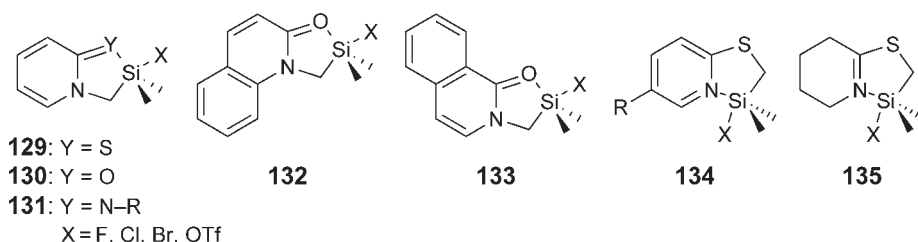
Only two illustrative reports were found over this period of time. These compounds are internal nitrogen–boron complexes (**Scheme 32**). They were obtained by condensations at low temperatures, using diphenylborinic acid $\text{Ph}_2\text{B}-\text{OH}$, prepared from aminoethyldiphenylborinate. Pyridine 2,6-dicarboxylic acid at -78°C and pyridinemethanol led to **126** and **127**, respectively [<1998JOM21>](#), while piperidinemethanol in CH_2Cl_2 at -60°C provided **128** ($\text{R} = \text{H}$ or CH_3) [<1998JOM21>](#).



Scheme 32

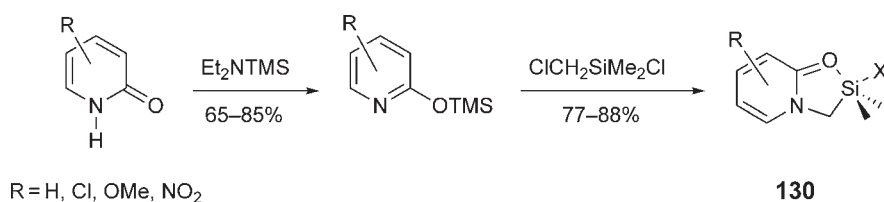
11.13.9.5 [1,4,2]Thiazasilolo[4,5-*a*]pyridines of Type 8, [1,4,2]Oxazasilolo[4,5-*a*]pyridines of Type 9, [1,4,2]Diazasilolo[4,5-*a*]pyridines of Type 10, [1,4,3]Thiazasilolo[4,5-*a*]pyridines of Type 11

The literature on these structures is sparse, and generally the articles report preparations of several of them in similar ways. These compounds are constituted by oxygen, sulfur, or nitrogen adducts at the silicon atom, thus providing pentacoordinated silicon compounds or structural analogs (Scheme 33).



Scheme 33

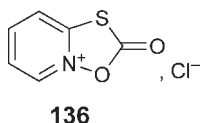
They were prepared by alkylation of 2-trimethylsilyloxy <1999J(P2)2099, 2000J(P2)1059> or 2-trimethylsilylsulfanyl pyridine (Scheme 34), quinoline <2003JOM66>, or isoquinoline <2000CC565>, with a chloromethyldimethylsilane derivative, generally a chloride, the latter being further replaced by another halide or triflate. Alkylations of 2-OTMS pyridine resulted in *N*-alkylation, whereas 2-STMS pyridine could afford both *N*- and *S*-alkylated species <2000J(P2)1059> such as 134, R = H or CF₃ <2003JOM66>, by analogy with alkylation of *S*-TMS thiolactame derivatives which provide *S*-alkylated compound.



Scheme 34

11.13.9.6 [1,4,2]Oxathiazolo[2,3-*a*]pyridines of Type 12

Compound 136 (Scheme 35) is classically used as a reagent for Barton's reductive decarboxylation, in the presence of triethylamine and *t*-BuSH <1995JOC6237, 1996JOC6189, 2003T6797>.

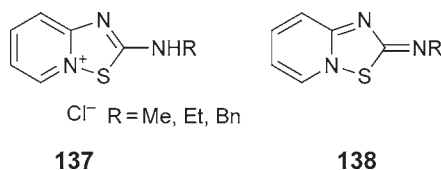


Scheme 35

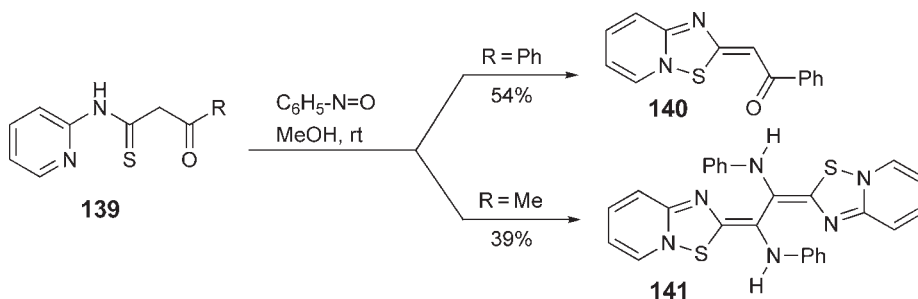
11.13.9.7 [1,2,4]Thiadiazolo[2,3-*a*]pyridines of Type 13

11.13.9.7.1 Closure of the thiadiazole ring

5-Substituted [1,2,4]thiadiazolo[2,3-*a*]pyridinium chlorides **137** are commonly prepared by oxidative cyclization of their *N*-2-pyridyl thiourea precursors with sulfuryl chloride at room temperature <1996H432657>. Other reagents were used for the oxidation of the sulfur atom, for example, bromine in acetic acid or potassium hexacyanoferrate(III) <2003JHC261>. The same reaction performed with various oxidants gave a better yield for bromine, compared to H₂O₂ or hydroxylamine <2003K576>. This was even observed with no added oxidative reagent, except, presumably by air itself under heating <2000CSC687>. These compounds also exist in a nontautomerizable form, with an *N,N*-dialkylamino group at the thiadiazole ring <1999JHC991>. Furthermore, when R = CPh, only the neutral 5-acylimino compound **138** was obtained (Scheme 36) <2003JHC261>. The formation of the thiadiazole ring was also examined with β -keto thioamides **139** instead of thioureas (Scheme 37). When R = Ph, mild oxidation with nitrosobenzene led to the exomethylene-bearing heterocycle **140**. With the methyl ketone, further enolization and reaction with nitrosobenzene led to the dimer **141** <2004S2975>.



Scheme 36

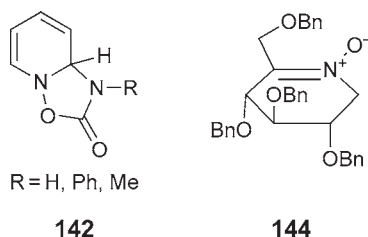


Scheme 37

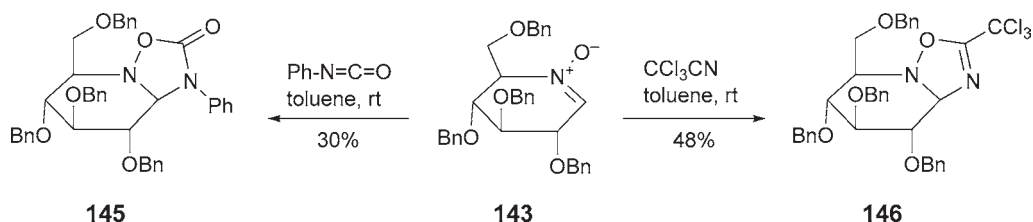
11.13.9.8 [1,2,4]Oxadiazolo[2,3-*a*]pyridines of Type 14

11.13.9.8.1 Closure of the oxadiazole ring

Closure of the oxadiazole ring is still achieved through cycloaddition between pyridine *N*-oxides and isocyanates, affording adducts such as **142** (Scheme 38) <1995T6451>. Nonaromatic imine *N*-oxides exhibited similar reactivities, since azasugar-derived *N*-oxides as a mixture of **143** and **144** underwent cycloaddition reactions in the presence of phenyl isocyanate or trichloroacetoneitrile. Compounds **145** and **146** (Scheme 39) were obtained from the aldoxime *N*-oxide **143**; two other regioisomeric heterocycles arose from the ketoxime derivative **144** <1996T4467>.



Scheme 38

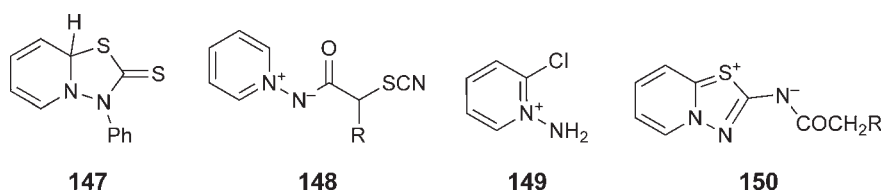


Scheme 39

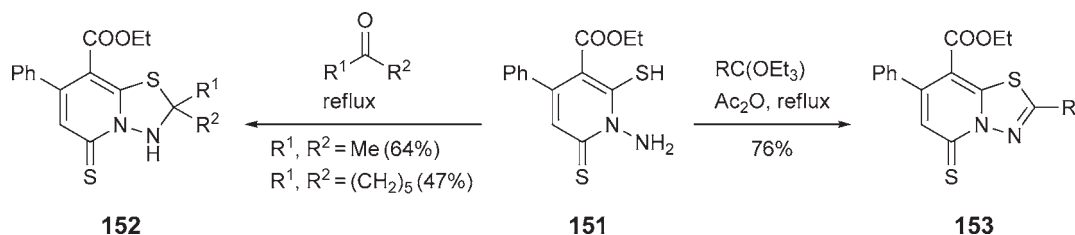
11.13.9.9 [1,3,4]Thiadiazolo[3,2-a]pyridines of Type 15

11.13.9.9.1 Closure of the thiadiazole ring

1,3-Dipolar addition of pyridinium *N*-phenyl imide with carbon disulfide led to the reversible formation of the unstable, nonaromatic adduct **147** (Scheme 40), which decomposed on exposure to air [<1999HAC79>](#). Previous examples concerned unsubstituted azomethine imines which upon the same reaction afforded more stable, conjugated species. Alternatively, the fully conjugated mesoionic form **150** was obtained via cyclization of pyridinium *N*-ylides bearing a thiocyanate group **148** or by treatment of *N*-amino-2-chloropyridinium salt **149** with potassium thiocyanate and an acylating agent [<1996BCJ1769>](#). Another route to the thiadiazole ring was proposed, through condensation of the 1-amino-2-mercaptopyridin-6-thione **151** (Scheme 41), either with a ketone or an orthoformate, leading to **152** and **153**, respectively [<1996JPR516>](#). Forcing the aromatization of both pyridine rings by methylation (CH_3I) of the sulfur atom in the pyridinthione resulted in the formation of pyridinium iodides, with no change in the thiadiazole ring.



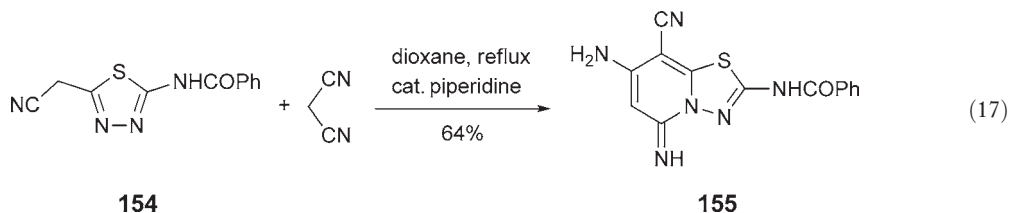
Scheme 40



Scheme 41

11.13.9.9.2 Closure of the pyridine ring

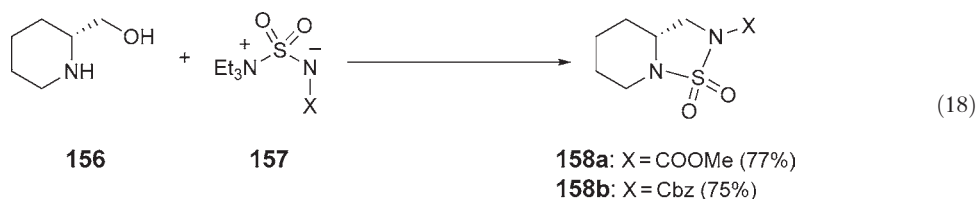
Compound **155**, analogous to structure **153**, was prepared by a piperidine-mediated condensation of the 1,3,4-thiadiazole **154** with malononitrile (Equation 17) [<1995PS51>](#).



11.13.9.10 [1,2,5]Thiadiazolo[2,3-*a*]pyridines of Type 16

11.13.9.10.1 Closure of the thiadiazole ring

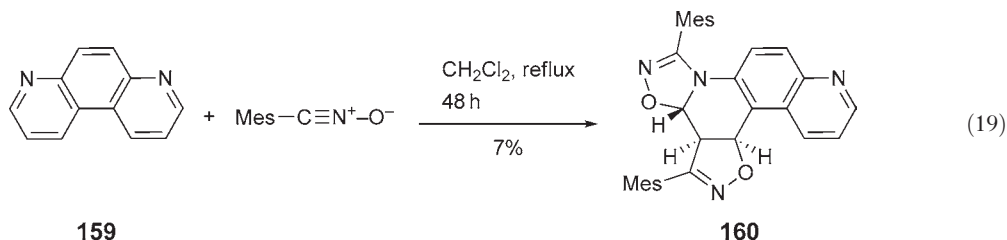
The unsymmetrical cyclic sulfonylurea **158** was prepared from its β -amino alcohol precursor **156** and a Burgess-type reagent **157** (Equation 18). This reagent served both as an activating reagent for the transformation of the amino alcohol into a transient sulfamidate, and as a source of nucleophilic nitrogen in the cyclization process <2002AGE3866>. The nitrogen atom bearing the carbamate can be further deprotected <2004CEJ5581>.



11.13.9.11 [1,2,4]Oxadiazolo[4,5-*a*]pyridines of Type 17

11.13.9.11.1 Closure of the oxadiazole ring

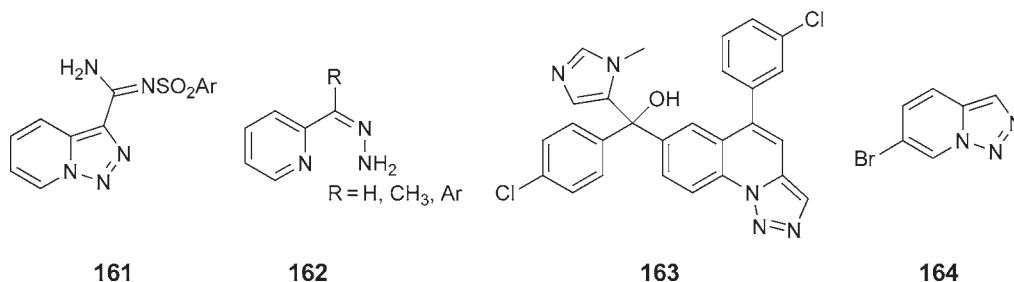
1,3-Dipolar addition of mesitylene nitrile oxide with 4,7-phenanthroline **159** gave a 2:1 adduct **160** with a very low yield (Equation 19), the dearomatization of the pyridine ring giving rise to a more reactive double bond which, in turn, underwent cyclization <1998T9187>.



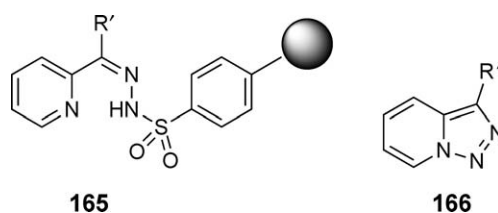
11.13.9.12 [1,2,3]Triazolo[1,5-*a*]pyridines of Type 18

11.13.9.12.1 Formation of the triazole ring

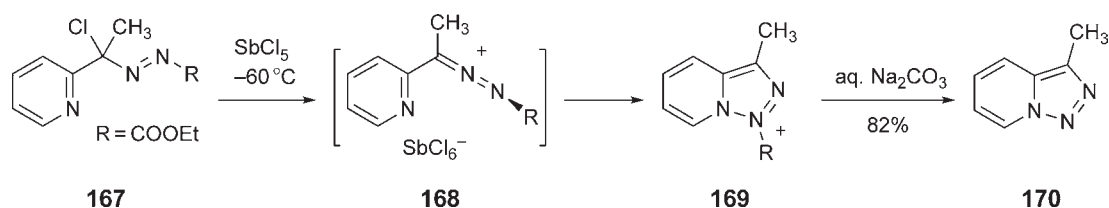
This system is widespread and methods for its preparation were reviewed. Treatment of 2-pyridyl acetonitrile with arylsulfonyl azide in the presence of NaOEt led to the formation of the triazole ring, with concomitant release of arylsulfonylamide anion. The latter, upon addition onto the nitrile, led to a sulfonylamidine at C-4 **161** (Scheme 42) <1995T10969>. In a more general pathway, oxidation by K₃Fe(CN)₆ <1996MI145>, MnO₂ <2002ARK52, 2004T5785, 2005OBC3905>, or hypervalent iodine reagents <2000SC417> of hydrazones **162** derived from 2-formylpyridine or its keto analog led to the triazole ring. Unexpected formation of [1,2,3]triazolo[1,5-*a*]pyridine was also observed and presumably due to air-induced oxidation of the hydrazone <2005POL807>. In the quinoline <2003BML4365> or pyridine series <1997T8257>, treatment of a 2-carbaldehyde with *p*-tolylsulfonylhydrazine gave the heterocycles **163** and **164**. In this case, as an arylsulfinate is attached to the intermediate hydrazone, oxidative conditions are not required since the sulfur atom is reduced in the sulfinate leaving group. Similarly, under solid-phase conditions (Scheme 43), polymer-bound arylsulfonyl hydrazones **165** were transformed into triazolopyridines **166** by treatment with morpholine at 95 °C <2004TL6129>. Another synthesis was described in strong Lewis acid conditions (Scheme 44), since the formation of 1-azo-2-azonia-allene salts **168** from halide **167** with an adjacent 2-pyridine led to a [1,2,3]triazolo[1,5-*a*]pyridinium **169**, with a subsequent *N*-deprotection giving **170** (R = COOEt or 2,4,6-trichlorophenyl) under aqueous alkaline conditions <1998M1293>.



Scheme 42



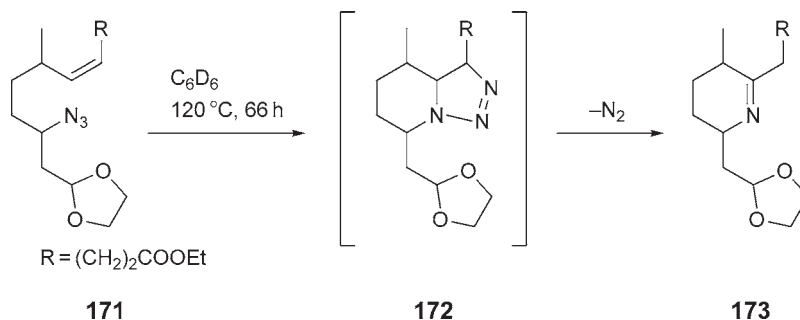
Scheme 43



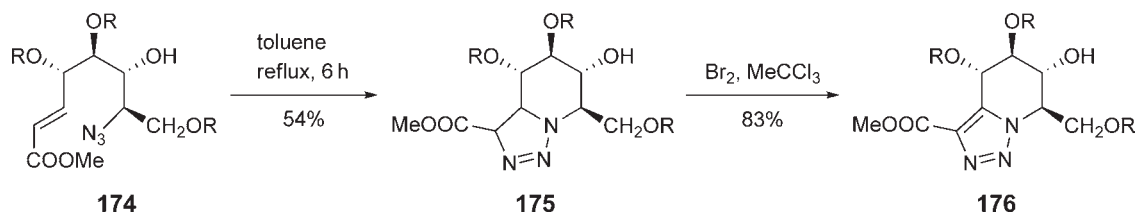
Scheme 44

11.13.9.12.2 Formation of both rings

Nonaromatic heterocycles, in which the pyridine ring is saturated, can be obtained via a simultaneous formation of both rings, involving the intramolecular 1,3-dipolar addition of an azide onto a double bond. Unactivated double bond in **171** (Scheme 45) required harsh conditions and prolonged heating of the observed intermediate **172** resulted in loss of nitrogen, providing the 3,4,5,6,-tetrahydropyridine **173** <1998JOC9910>. Conjugated double bonds behaved as more efficient dipolarophiles, and, for instance, the same cyclization (Scheme 46) was performed in milder conditions using

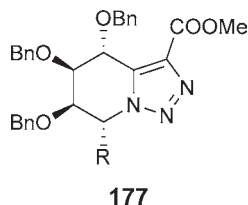


Scheme 45



Scheme 46

sugar-derived azides **174** <1997TA3807>. Formation of the triazole ring **176** required a further aromatization step which was achieved by oxidation of **175** with bromine, or tetrapropylammonium perruthenate/*N*-methyl morpholine oxide for derivatives of D-arabinose and L-fucose derivative **177** (R = H or CH₃) <2000TL7805>.

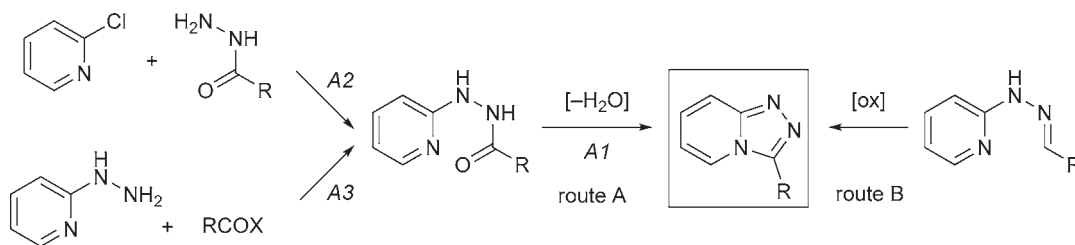


11.13.9.13 [1,2,4]Triazolo[4,3-a]pyridines of Type 19

11.13.9.13.1 Closure of the triazole ring

Due to the important pharmacological applications of this system, in particular the antidepressant trazodone, numerous articles deal with either its synthesis, or its incorporation into more complex substances, as a pharmacophore (see Section 11.13.12). Synthetic methods have been reviewed <1996CHEC-II(8)367>, and most of them are still in use or have been modified. Recent literature essentially focuses on the formation of the triazole ring.

Most preparations can be divided into two distinct routes (Scheme 47), either a condensation pathway (route A), or an oxidative cyclization starting from the corresponding hydrazone (route B).



Scheme 47

As the literature in this field is extensive, these preparations are summarized in Tables 1 and 2. Condensations are listed in Table 1. The hydrazides required can be first isolated (method A1, Scheme 48), prepared by S_NAr of a 2-chloropyridine derivative with a hydrazide nucleophile (method A2, Scheme 49), or simply via a preformed 2-hydrazinopyridine (method A3, Schemes 50 and 51).

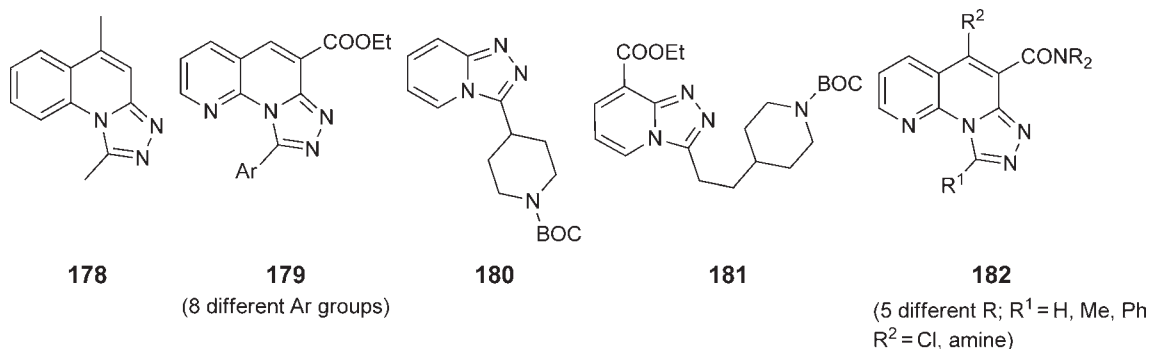
These protocols were applied to pyridines, quinolines, and naphthyridines. They are compatible with other functional groups, for instance, acid derivatives. Dehydration can be effected by a chemical process (chlorinating agents), or simply by heating. Method A3 generally required harsh conditions, since in most examples no base was added for HCl consumption, therefore lowering the reactivity of the pyridine nitrogen, present as its hydrochloride salt.

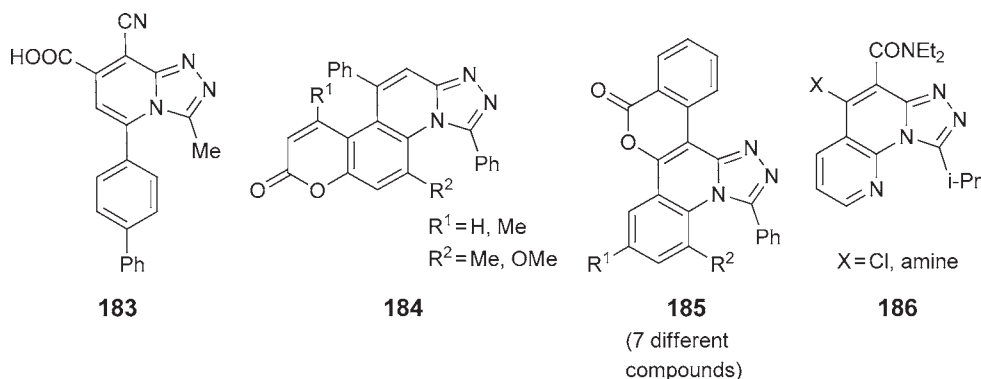
Table 1 Syntheses of [1,2,4]triazolo[4,3-*a*]pyridines by condensation

Entry	Compound	Method	Conditions	Reference
1	178	A1	Heating > m.p.	1998IJB174
2	179	A1	POCl ₃ , 130 °C	2003IJB1746
3	180	A1	Ph ₃ PCl ₂ , Et ₃ N, MeCN	2005BML2129
4	181	A1	AcOH, toluene, reflux	2000TL4533
5	182	A2	160 °C	1997FA49
6	183	A2	BuOH, reflux	2001MI149
7	184	A2	BuOH, reflux	2003IJB358
8	185	A2	EtOH, reflux	2003IJB2567
9	186	A2	Dowtherm A, 155 °C	2005EJM155
	182 (R ² = amine)	A2	Dowtherm A, 160 °C	2000EJM1021
10	187		EtOH, Et ₃ N, sealed tube, 120 °C	2005JME5001
11	188	A3	ArCOCl RCOOH, reflux	1996IJB106
12	189	A3	ArCOCl, pyridine, reflux	1996JPS263
13	190	A3	PhCHO, dioxane:AcOH, reflux	1997CHE609
14	191	A3	HC(OEt) ₃ , dioxane, reflux	2001MI1135
15	192	A3	PhCOCl, HMPA, 220 °C	2003IJB1937
16	193	A3	<i>i</i> -BuCOCl, reflux	2005JME5728

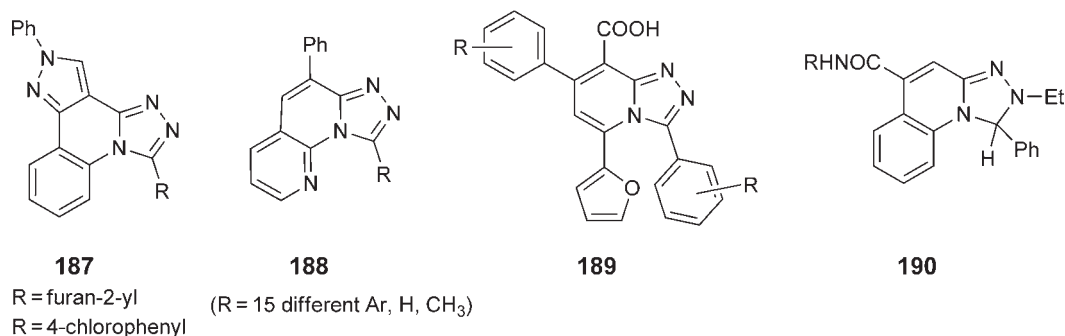
Table 2 Syntheses of [1,2,4]triazolo[4,3-*a*]pyridines by means of hydrazone oxidation

Entry	Compound	Reagent	Reference
1	189	Br ₂	1996JPS263
2	208	Br ₂	2002TA821
3	209	Br ₂	2004NN567
4	210	PhI(OAc) ₂	2001SC1511
5	211 : R = <i>p</i> -OMe	PhI(OAc) ₂	2002SC2377
6	211 : R = <i>p</i> -Cl	PhI(OAc) ₂	2002IJB1894
7	212 , 213 : R = H	PhI(OAc) ₂	2003EJM533
8	188	Chloramine T/MW	2004JRM145
9	212	Thianthrene ⁺	1997BKC604
10	212 : R = H; Ar = ferrocenyl	DMAD or NTS	1996T5441
11	211 : R = <i>m</i> -Cl	PhNO ₂	1996IJB106
12	213 : R = H	NaNO ₂ /AcOH	2003IJB1456
13	211 : R = <i>p</i> -NO ₂	NaNO ₂ /AcOH	2004IJB2641
14	213 : R = Cl	Pb(OAc) ₄	1998PHA294
15	210	Pb(OAc) ₄	2001SC1511
16	214	Pb(OAc) ₄	2005TA2927
17	211 : R = <i>o</i> -Cl	Hg(OAc) ₂ /MW	2004HCO363
18	213 : R = H	Tl(OAc) ₃	2001IJB262
19	191	FeCl ₃	1997CHE609
20	212 : R = H	CuCl ₂	2005T5942

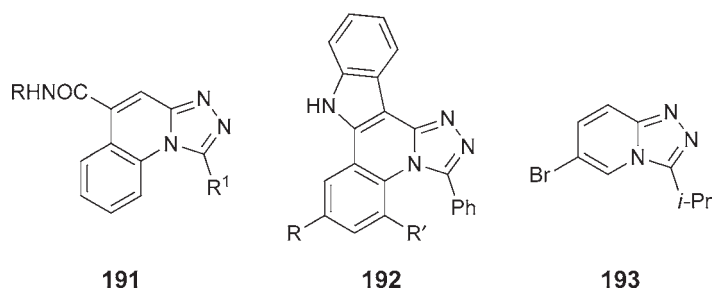
**Scheme 48**



Scheme 49

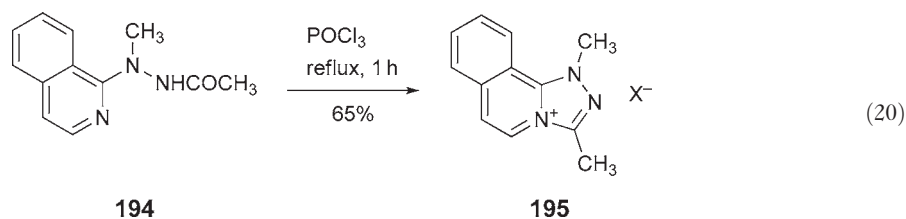


Scheme 50

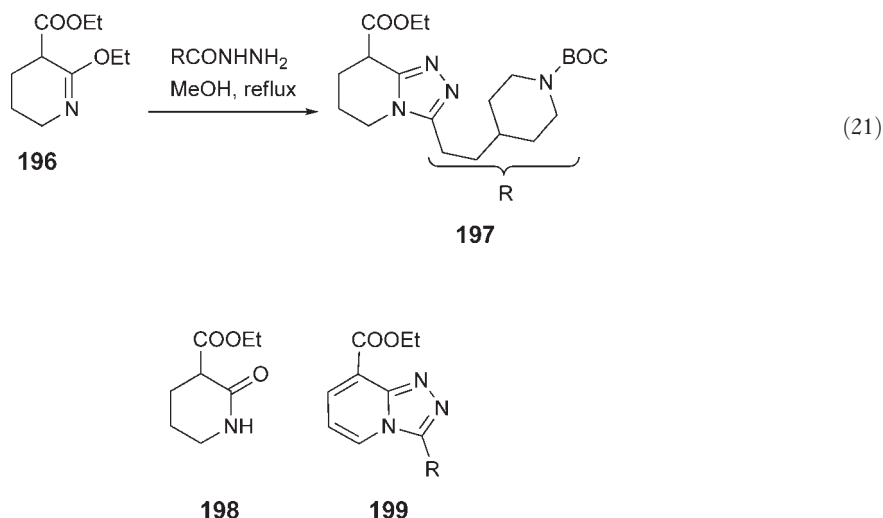


Scheme 51

Owing to the possibility of a proton loss from both nitrogen atoms, cyclization generally resulted in neutral compounds. *N*-Substituted starting materials led to cationic species with no possibility of subsequent tautomerization. For instance, *N*-methyl acetic hydrazide **194** gave the triazolopyridinium **195** upon treatment with POCl₃ (Equation 20) <1996T1399>.

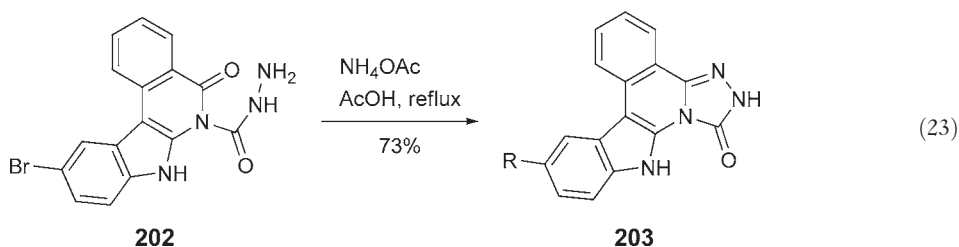
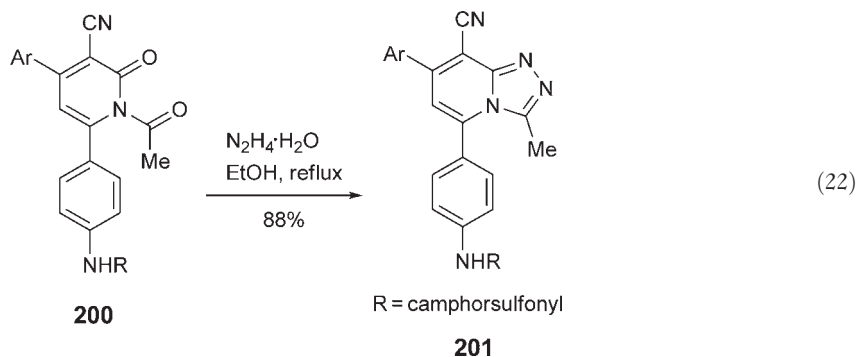


In nonaromatic series, iminoether precursors were used, due to their higher stability compared to chloroimines. Piperidinone derivatives underwent condensation with release of methanol; for instance, iminoether **196** gave **197** in the presence of the appropriate carbazide (Equation 21) <2001BML2619>. Similarly, lactam **198** was activated by Me_3OBF_4 in CH_2Cl_2 at room temperature, then condensed with a hydrazide in methanol, also yielding **197** (Equation 21). Fully conjugated compound **199** was obtained via $\text{S}_{\text{N}}\text{Ar}$ between ethyl 2-chloropyridin-3-carboxylate and hydrazine (Scheme 52), followed by 1-ethyl-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride(EDC)-mediated coupling with RCOOH <2000TL4533>.

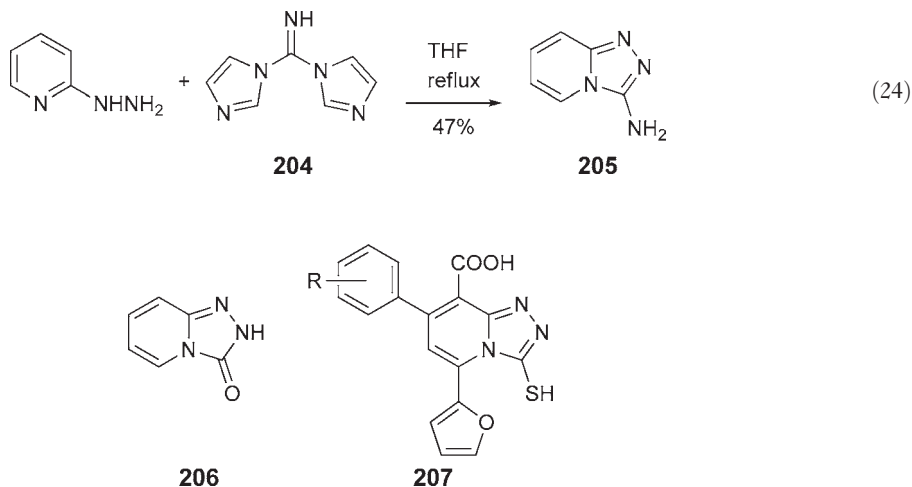


Scheme 52

Other condensations were described using pyridin-2-ones instead of 2-chloropyridines, but they need to be rendered more electrophilic by *N*-acylation. Thus, the reaction of *N*-acetyl pyridin-2-one **200** with hydrazine led to **201** (Equation 22) <2003PS1129>. Similarly, the intramolecular cyclization of **202** afforded the pyridotriazolone **203** (Equation 23) <1995JIC735>.

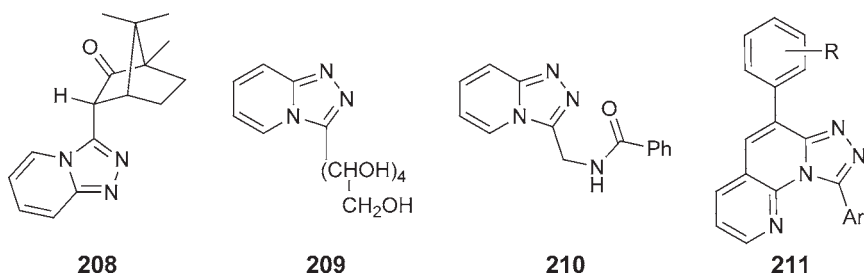


Other [1,2,4]triazolo[4,3-*a*]pyridines, substituted at C-3 by a heteroatom, were synthesized by condensation of carbonic acid derivatives. The amino-substituted compound **205** was obtained from 2-hydrazinopyridine and di(imidazole-1-yl)methanimine **204** (Equation 24) <2003JHC191>, whereas condensation of the same starting material with urea afforded **206** (Scheme 53) <2000H53265>. A similar oxo compound, that is, **206** with *N*-Ar instead of *N*-H, was obtained by reacting Ar-hydrazinopyridine with phosgene <2001MI3>. In addition, the 3-mercapto derivative **207** was obtained with a 42–45% yield (*R* = 4-Br or 4-CH₃), by treating its 2-hydrazinopyridine precursor in the presence of potassium hydroxide in refluxing ethanol <1996JPS263>.

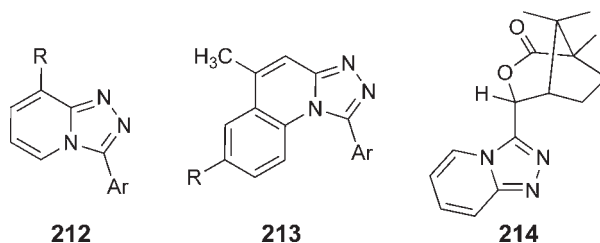


Scheme 53

Oxidative processes (route B) represent another common route to triazolopyridines (compounds described in Schemes 54 and 55). These preparations all start from aldehyde hydrazones and use different oxidative reagents for the cyclization (Table 2). Generally, those conditions are milder than condensation methods. Moreover, the oxidizing reagents are compatible with other moieties, even the sugar-derived polyol **209**. In the case of compound **208**, the hydrazone (major diastereomer) was obtained by tautomerization of the corresponding enhydrazine, the



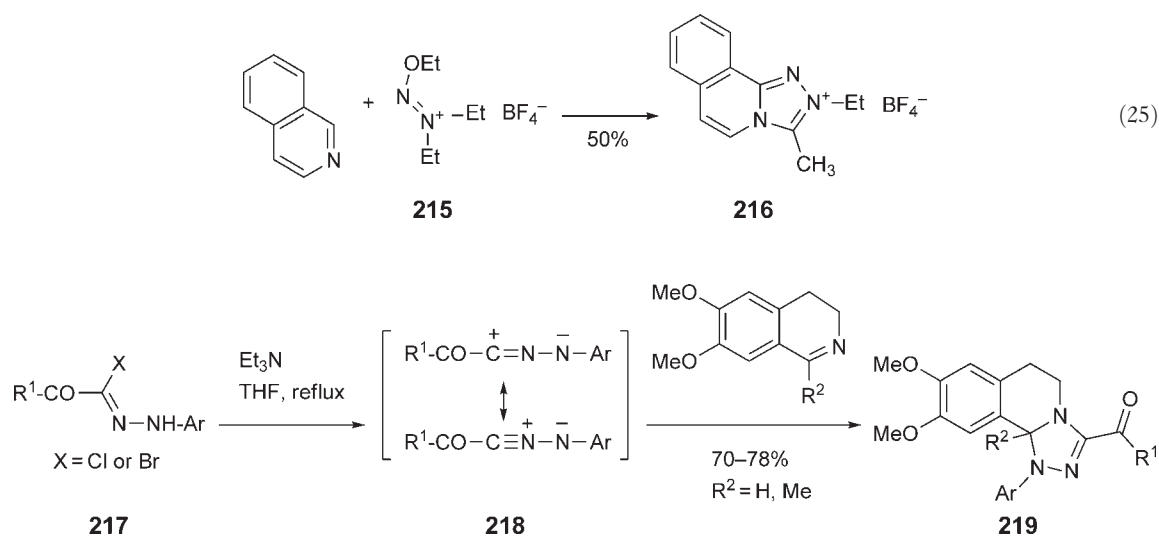
Scheme 54



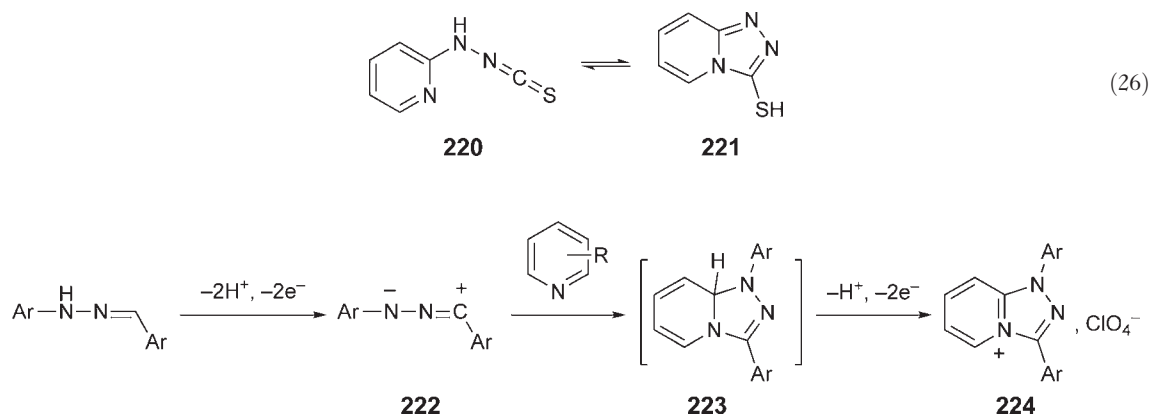
Scheme 55

latter being prepared by transamination of the *N,N*-dimethylenamine. These compounds were further studied for the stereoselective reduction (borane reagents) of the ketone, the stereochemical outcome of the reaction being due to complexation of the boron with the triazole ring <2006TA79>. Apparently, no specific work seems to rule the choice of the reagent, since they were rarely compared to each other. Nonetheless, Pb(OAc)₄ could efficiently replace bromine in the oxidation process with camphor-derived compound **214** <2005TA2927>, and most side reactions were avoided with this reagent. When dimethyl azidicarboxylate or ω -nitrostyrene (NTS) were used (Table 2, entry 10), the triazolopyridine was obtained instead of the expected dipolar addition product.

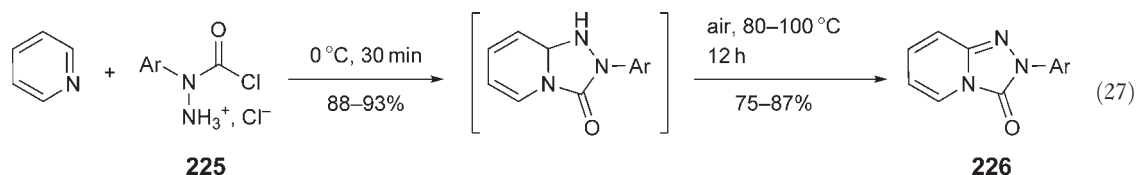
Triazolopyridines are also accessible via addition rather than condensation. Thus, the pyridotriazolium **216** was produced by reaction of isoquinoline with 1,1-diethyl-2-ethoxy-diazenium fluoroborate **215** (Equation 25) <1996T1399>. Nonaromatic dipolarophiles were also employed. The cycloaddition of the nitrilimine **218** generated from halide **217**, with 3,4-dihydro-6,7-dimethoxy-isoquinoline, afforded **219** (Scheme 56) <1996T3451>. Similar reaction intermediates were proposed under conditions of anodic oxidation. For instance (Scheme 57), the nitrilimine **222** formed the adduct **223** with a substituted pyridine, which further aromatized to yield the pyridinium **224** <2005MI2753>. In addition, an intramolecular process involving the addition of *N*-aminoisothiocyanate **220** onto the pyridine nitrogen provided 5-mercapto[1,2,4]triazolo[4,3-*a*]pyridine **214** (Equation 26) which was observed in several tautomeric forms <1999MRC493>. Recently, another synthesis (Equation 27) was proposed via a direct addition of a chloroformylhydrazine **225**, generated with phosgene, onto an unsubstituted pyridine ring, followed by air-induced aromatization to yield the pyridotriazolone **226** <2001MI3, 2002MI239>.



Scheme 56

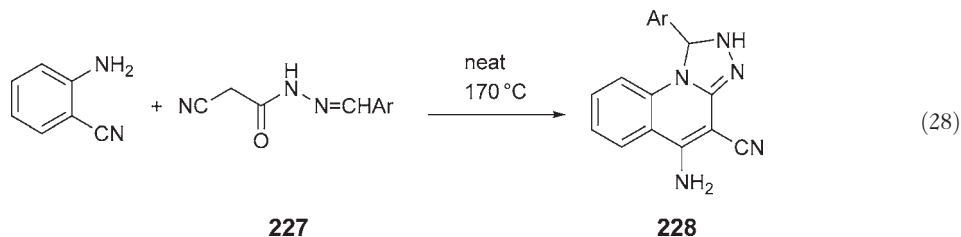


Scheme 57



11.13.9.13.2 Closure of both rings

Though rarely used, this methodology can be illustrated (Equation 28) by reaction at high temperature between 2-aminobenzonitrile (anthranilonitrile) and various cyanoacetic hydrazides of general structure **227** (Ar = Ph, 4-ClC₆H₄, 4-MeOC₆H₄). The 4,5-dihydro-[1,2,4]triazolo[4,3-*a*]quinolines **228** were obtained in this way <2005SC2481>.

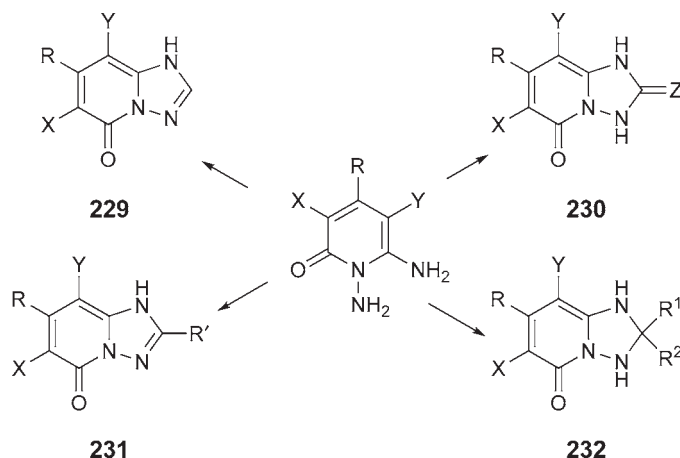


11.13.9.14 [1,2,4]Triazolo[1,5-*a*]pyridines of Type 20

11.13.9.14.1 Closure of the triazole ring

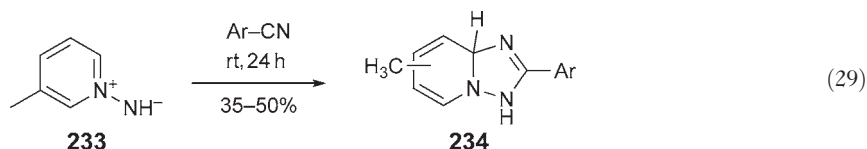
Closure of the triazole ring can be achieved either by oxidative formation of the N–N bond, or condensation of an *N*-aminopyridone. The latter was formed by *N*-amination of pyridines with mesitylhydroxylamine (MSH), or by forming the pyridine ring, starting from cyanoacetic hydrazide with malononitrile or 2-cyanoacrylates.

This common intermediate (X, Y = electron-withdrawing groups; R = alkyl or aryl) is very widespread in these syntheses. As depicted in Scheme 58, condensations with a formic acid equivalent gave **229** from the imino ether PhCO-NH-NH=CH-OEt <2004CPA260>, DMF/ClCOOEt <2003MI223> or formic acid itself <2004CPA276>. Compounds **230**, bearing a heteroatom at C-3, were obtained by condensing isothiocyanates (Z = N–R', H₂S shift), phenyl isocyanate (Z = O, PhNH₂ loss) <1999AF377>, or diethylcarbonate (Z = O) <1998SC3331>. Structure **231** resulted from condensations with acid derivatives, such as acetyl or benzoyl chloride, orthoesters <1998H(48)1185>, acetic anhydride, or RCOOH in the presence of polyphosphoric acid <2004CPA260>. Half-conjugated system **232** was obtained either with formaldehyde or dibromomalononitrile <1998SC3331>.

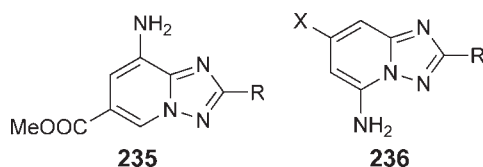


Scheme 58

N-Amino pyridinone can be replaced by an *N*-aminopyridinium salt. Deprotonation of the latter by KOH in ethanol/water yielded the ylide **233**, which underwent a dipolar cycloaddition onto an aromatic nitrile to provide **234** (Equation 29) with subsequent oxidative rearomatization <2002JCM560, 2002BML2411>.

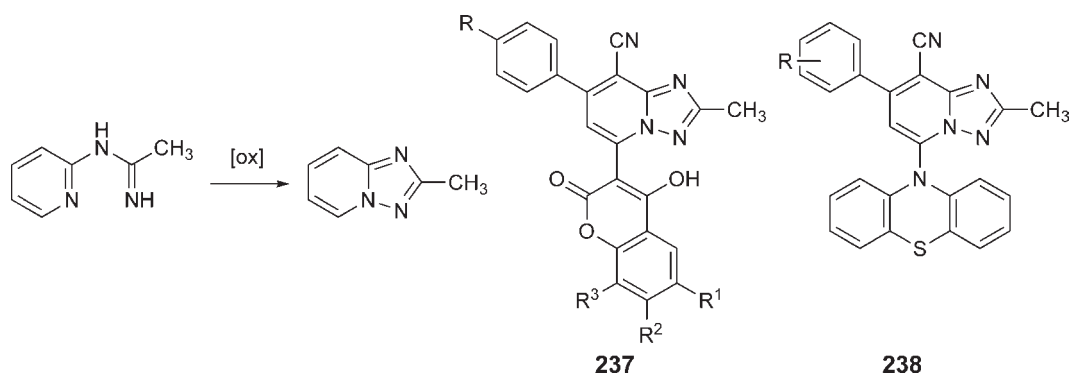


Recent literature also focused on condensations of *N*-aminopyridiniums with aldehydes. In this case, a further rearomatization step is required, in general with air in alkaline conditions. Most pyridines used in these preparations are 2,3- or 2,6-diaminopyridines, leading to isomers **235** <2004BML3307> and **236** (X = COOMe <2003TL1675, 2003JCO233> or Br <2001SL1917>, respectively) (Scheme 59).



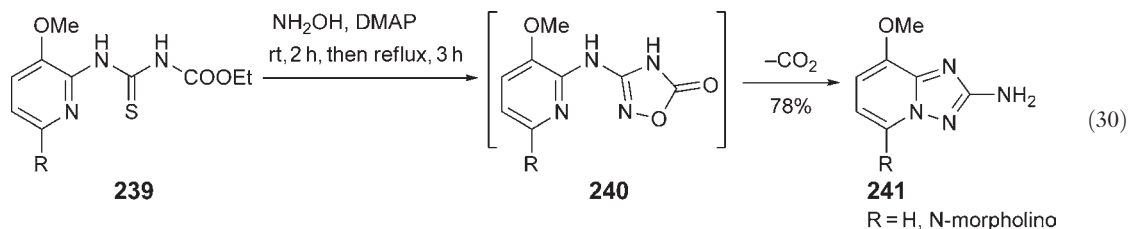
Scheme 59

A different strategy (see Scheme 60) consisted in forming the N–N bond by oxidation of an amidine with MnO₂. The amidine was obtained by AlCl₃-mediated addition of a 2-aminopyridine on acetonitrile. A series of compounds **237** <2003IJB2901> and **238** was obtained in this way <2005ARK21>.

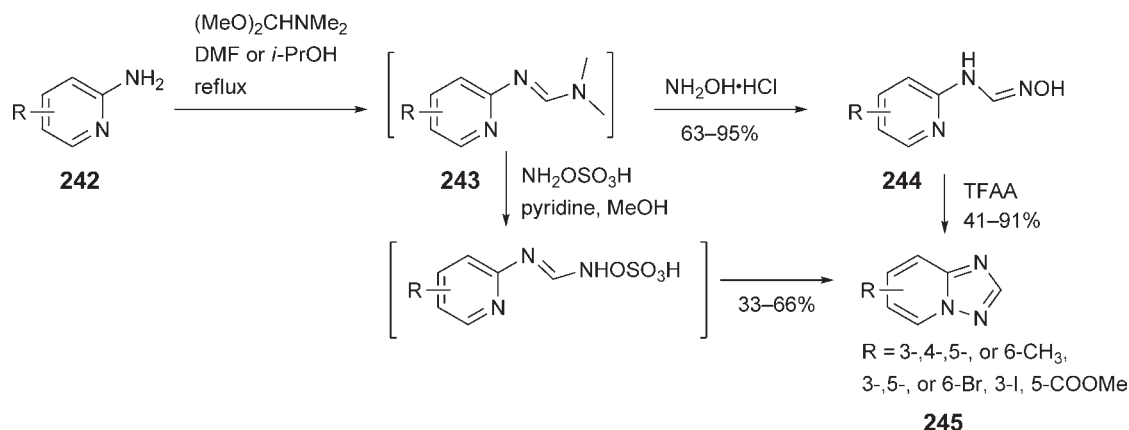


Scheme 60

Another preparation employed the condensation of hydroxylamine with a substituted thiourea **239**. In this example (Equation 30), no oxidation was required, since the central nitrogen atom is already in a higher oxidation state via its hydroxylamine derivative **240**. Nucleophilic attack of the pyridine nitrogen atom resulted in ring closure, affording **241** accompanied by decarboxylation <2003S1649>.



A similar strategy used the transamination of formylamidines by $\text{NH}_2\text{OSO}_3\text{H}$. Recently, this method was modified and afforded an extended scope of substituents on the pyridine ring. As depicted in **Scheme 61**, treatment of a substituted 2-aminopyridine **242** with DMF dimethylacetal afforded the amidine intermediate **243** which underwent transamination with hydroxylamine. The subsequent dehydrative cyclization step was optimized; the best conditions obtained consisted in treating formamidoxime **244** with trifluoroacetic anhydride (TFAA) at room temperature during 1 h [<2005EJO3761>](#). Similarly, classical treatment of the amidine **243** with $\text{NH}_2\text{OSO}_3\text{H}$ was used in the synthesis of **245**, which represents a key building block in the preparation of DPP(iv) (DPP = dipeptidylpeptidase) inhibitors [<2006JME3614>](#).

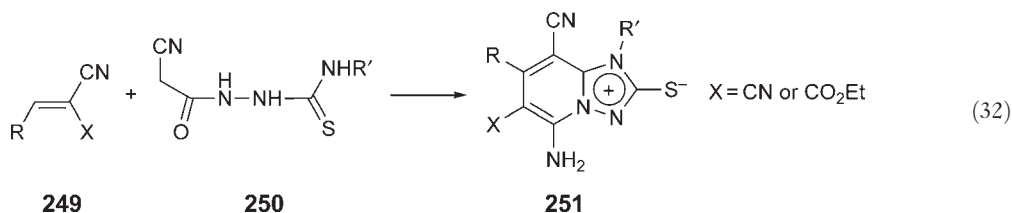
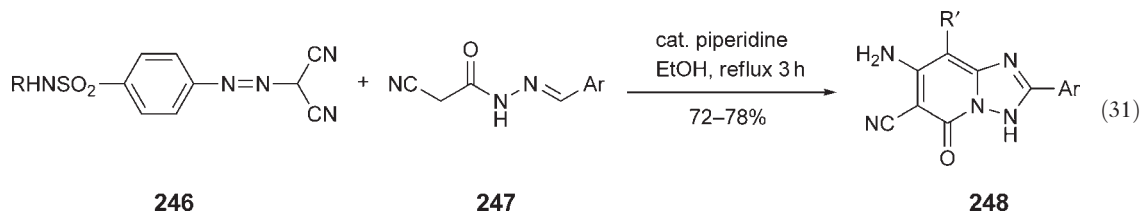


Scheme 61

11.13.9.14.2 Closure of both rings

Condensation of active methylene compounds with cyanoacetic hydrazide-derived hydrazones led to a one-pot formation of pyridine and triazole rings.

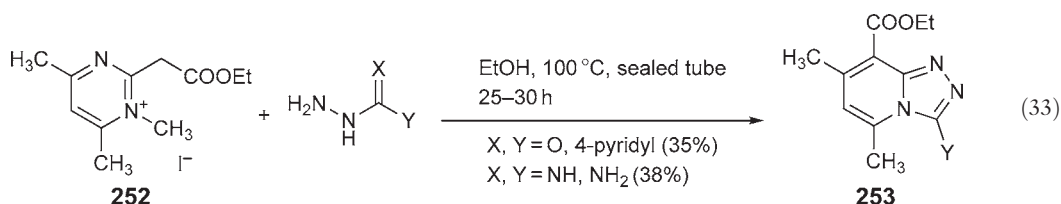
Malononitrile derivative **246** in the presence of hydrazone **247** led to the formation of both rings in compound **248** ([Equation 31](#), $\text{R}' = \text{N}=\text{N}-\text{C}_6\text{H}_4-p-\text{SO}_2\text{NHR}$) [<2000MI1273>](#), whereas unsubstituted malononitrile, refluxed in ethanol with cyanoacetic hydrazide and the appropriate aldehyde, led to the same compound with $\text{R}' = \text{H}$ [<1996AFF410, 1996PHA982>](#). Similarly, mesoionic [1,2,4]triazolo[1,5-*a*]pyridin-4-ium-2-thiolates **251** were synthesized ([Equation 32](#)) by reacting **249** and **250** in the presence of triethylamine [<2003JCM755>](#).



11.13.10 Ring Syntheses by Transformation of Another Ring

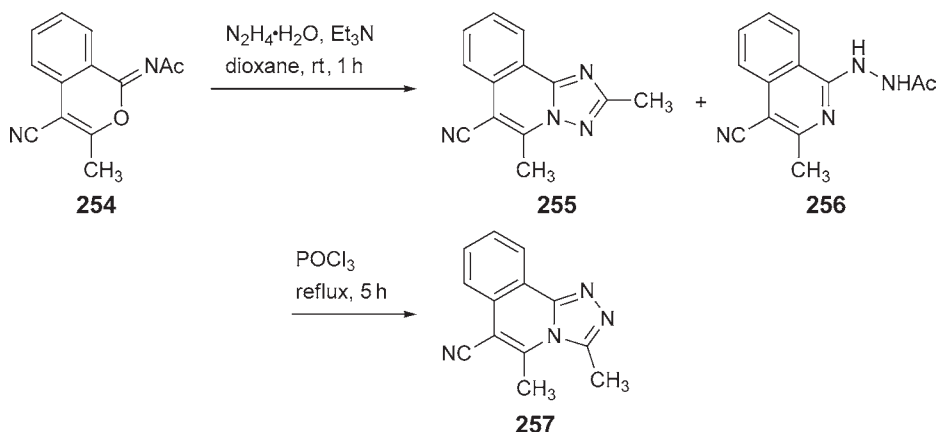
11.13.10.1 [1,2,4]Triazolo[4,3-*a*]pyridines of Type 19

By analogy with the conversion of 1,2-dialkylpyridinium salts into 2-alkylaminopyridines known as the Kost–Sagitullin rearrangement, the pyridinium salt **252** was treated with two different hydrazides (Equation 33). The [1,2,4]triazolo[4,3-*a*]pyridines **253** with Y = 4-pyridyl and NH₂ were obtained with 35% and 38% yields, respectively <2003CHE275>.



11.13.10.2 [1,2,4]Triazolo[1,5-*a*]pyridines of Type 20

Compound **254** can be considered as a masked β -ketonitrile. Treatment of the latter with hydrazine hydrate led to nucleophilic opening and recyclization to give the triazolopyridine **255** along with **256** which was converted to the [1,2,4]triazolo[4,3-*a*]pyridine **257** (Scheme 62) <2004JHC549>.



Scheme 62

11.13.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

This Section focuses on systems **18–20**, as several syntheses exist for these compounds. [1,2,3]Triazolo[1,5-*a*]pyridines of type **18** are prepared either by oxidation of hydrazones or using arylsulfonyl hydrazones. In this case, the elimination of an arylsulfinate can be viewed as a sulfur ‘umpolung’, since the nitrogen is oxidized and the sulfur atom reduced. The latter method avoids the use of oxidizing agents which might not be compatible with other functional groups. In addition, the solid-phase synthesis developed for the preparation of such compounds allows a large chemical diversity (see Section 11.13.9.12). Furthermore, their functionalization at C-7 is best achieved by lithiation methods (see Section 11.13.5.2).

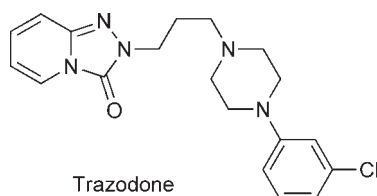
[1,2,4]Triazolo[4,3-*a*]pyridines of type **19** have attracted most attention for their synthesis. Among both main methods of preparation, the condensation of hydrazides generally requires too harsh conditions to be compatible with complex structures. Though, dehydration with mild chlorinating agents such as PPh₃·Cl₂ seems promising. The other main preparation used C-oxidation of aldehyde hydrazones. This proceeds in generally mild conditions, though many toxic metals are often employed and can be advantageously replaced with sodium nitrite or hypervalent iodine reagents (see Section 11.13.9.13).

[1,2,4]Triazolo[1,5-*a*]pyridines of general structure **20**, if highly substituted on the pyridine ring, are rapidly synthesized by condensation of *N*-amino pyridones, themselves prepared by means of condensation. If

nonsubstituted compounds are required, oxidation of amidine with MnO_2 , as well as nucleophilic attack of thioureas or amidines with hydroxylamine or its O-activated derivatives, are efficient procedures (see Section 11.13.9.14).

11.13.12 Important Compounds and Applications

Bicyclic 5-6 systems having potential biological activities are represented by triazolopyridines, since many other systems among 1–17 were studied only for synthesis purposes or physicochemical studies. A marketed [1,2,4]triazolo[4,3-*a*]pyridine is illustrated by trazodone (Scheme 63), an antidepressant that acts as an antagonist of 5-HT and blocks its reuptake. Trazodone is marketed under the brand names Desyrel, Trazon, Trialodine, Trittico, and Thombran. This molecule is well described in CHEC-II(1996) <1996CHEC-II(8)367>, since much research on this topic was done during the 1980s. Recent reports deal with various activities of triazolopyridines, generally employed as the central pharmacophore, often fused with another aromatic ring (quinoline or naphthyridine derivatives), or simply used as a substituent to modulate the activity. In order to clarify the literature on this topic, the expected properties for these bicyclic 5-6 compounds are presented in Table 3.



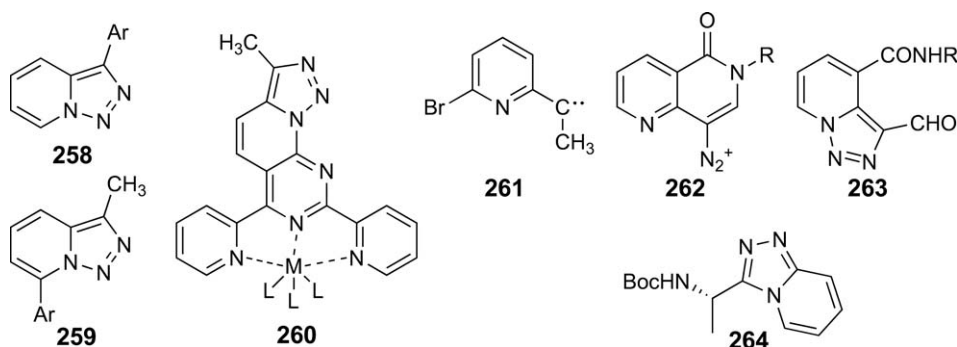
Scheme 63

Table 3 Biological activities of some triazolopyridines

Entry	Compound category	Biological activity studied	Reference
1	18	Inhibitor of photosystem II	1996MI143
2	18	Inhibitors of farnesyl protein transferase	2003BML4365
3	18 (compound 176, Section 11.13.9.12.2)	Anionic sugar mimics	1997TA3807
4	(analogue of 176)	Inhibitors of α -1,3-fucosyltransferase	2002AGE3041
5	18	Potential helicating agents	1998T15287 2004T5785
6	18	Cardiovascular agents	2002ARK9
7	19	Anti-inflammatory and analgesic agents	1997FA42 2000EJM1021 2001MI1135 2005EJM155
8	19	Conformationally constrained tertiary amides analog	2000TL4533
9	19	Constrained templates for fibrinogen receptor (GPIIb/IIIa) antagonists	2001BML2619
10	19	CCR5 receptor antagonists for antiviral activity	2005BML2129
11	19	Antibacterial agents	2003EJM533
12	19	Matrix metalloprotease inhibitors	2003JME3840
13	19	HIV-1 integrase inhibitors	2004JME385
14	19	Human A_3 adenosine receptor antagonists	2005JME5001
15	19	P38 MAP kinase inhibitors	2005JME5728
16	19	Inhibitors of DNA methyltransferase	2006JME678
17	19	Human lipoxigenase inhibitors	2006JME1356
18	19 and 20	Dipeptidyl peptidase(IV) inhibitors	2006JME3614
19	20	Nonsteroidal pregnancy-terminating agents	2002BML2411
20	20	Purinergic receptor (A_2A) antagonists	2003JCO233
21	20	Adenosine receptor inhibitors	2001SL1917 2003SI649 2004BML3307
22	20	Antimicrobial agents	2005ARK21
23	20	Treatment of <i>Toxocara canis</i>	2005MI134

11.13.13 Further Developments

[1,2,3]Triazolo[1,5-*a*]pyridines **258** and **259** bearing an aryl or heteroaryl substituent at C-3 or C-7 (**Scheme 64**) have been studied for their fluorescence properties. These aryl substituents were introduced using Suzuki cross-coupling reaction. Halide precursors were prepared for this purpose, iodine at C-3 was obtained by a direct iodination (I_2 , DMF, KOH), whereas synthesis of bromides at C-7 required a prior metallation step (*n*-BuLi/toluene) <2006TL8101>. [1,2,3]Triazolo[1,5-*a*]pyridines incorporated in polycyclic structures such as compound **260** (**Scheme 64**), were recently used in designing sensors for anions <2006JOC9030>. In those systems, the metal ligand consists of the terpyridine unit, the [1,2,3]triazolo[1,5-*a*]pyridine is not involved in the chelation. Zinc and copper cations produce a quenching of the fluorescence, further restored by additional complexation with different anions. Another example of spectroscopic use of these compounds is illustrated by luminescent rhenium complexes of a compound bearing a [1,2,4]triazolo[4,3-*a*]pyridine of type **19** <2006POL2289>. In this case, one of the nitrogen atoms of the triazole participates in the complexation.

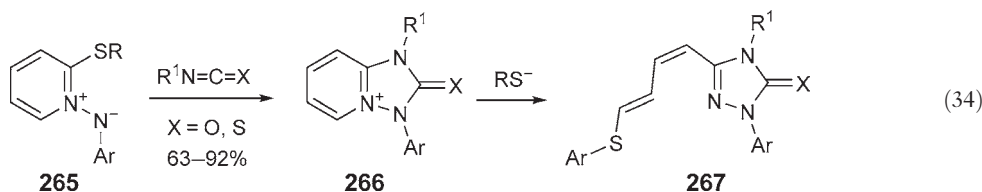


Scheme 64

Thermal decomposition of 7-bromo-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine was carried out at 100 °C under 1.7 atm during 5 days. Separation of the products and careful analysis provided evidence for a carbene intermediate **261** and products arising from its rearrangement, including cyclopropane derivatives <2007ARK297>. Recent preparations were also published for this ring system. Annulation of the triazole ring after diazotation of an amine moiety attached to an adjacent ring fused with the pyridine afforded the diazonium **262** which led to the [1,2,3]triazolo[1,5-*a*]pyridine ring system with a concomitant hydrolytic opening of the pyridone ring, leading to compound **263** <2006T2313>.

New, mild conditions were published for the closure of the triazole ring in the case of [1,2,4]triazolo[4,3-*a*]pyridines of type **19** from 2-pyridyl hydrazides. Starting from carboxylic acids, the hydrazides were obtained by coupling with 2-hydrazinopyridine. The key-step of the synthesis was the conversion of hydrazides to thiohydrazides, using Lawesson's reagent. In this case, the elimination of H_2S during the condensation process is much easier than a classical dehydration. Thus, the heterocycle formation from the carboxylic acid even proved compatible with an aminoacid. In the case of alanine (compound **264**, **Scheme 64**), no racemization was noticed since further *N*-coupling with valine did not reveal the other diastereoisomer <2006TL7591>. Most recently, the early step in the preparation of the same ring system from carboxylic acids was facilitated by the use of a polymer-supported reagent. The carboxylic acid was coupled to 2-hydrazinopyridines with trichloroacetonitrile/polymer-supported phosphine activation, followed by microwave-assisted condensation <2007TL2237>.

New derivatives of [1,2,4]triazolo[1,5-*a*]pyridines of type **20** were also prepared recently. A dipolar addition of 2-sulfanyl-*N*-aminopyridinium ylide **265** (generated from a tetrazolopyridine precursor) was observed with aryl isocyanates or isothiocyanates as the dipolarophiles (**Equation 34**). Further elimination of the thiolate resulted in the formation of [1,2,4]triazolo[1,5-*a*]pyridinium salts **266**. Further attack of a thiolate ion at the pyridine ring resulted in opening of the latter and obtention of a diene **267** <2006JOC7805>. More classical synthesis was adapted to polymer-supported 2-aminopyridines, which were treated with *N*-amination reagents, especially *O*-(2,4-dinitrophenyl)hydroxylamine, more suitable in those conditions than *O*-mesitylenesulfonyl hydroxylamine. This amination step was followed by closure of the triazole ring by condensation with various aldehydes and rearomatization <2006MI961>. Though rarely used, a closure of the pyridine ring via radical addition of the triazole onto an adjacent benzenic ring was also described <2006CEJ8378>.



Most recent biological properties were checked for [1,2,3]triazolo[1,5-*a*]pyridines of type **18** fused in more complex structures. For instance, triazoloacridinones were studied as inhibitors of human NAD(P)H quinone oxidoreductase. They were first predicted from in silico docking then synthesized and evaluated <2006BMCL6246>. Asymmetrical bisintercalators incorporating the [1,2,3]triazolo[4,5,1-*de*]acridine-6-one motif exhibited promising DNA-binding properties <2006JME7198>. Another compound in this structural category was able to stop the cell cycle at the G2/M phase, responsible for its antitumor activity <2006MI1668>.

[1,2,4]Triazolo[4,3-*a*]pyridines of type **19**, bearing an oxazol-5-yl at C5 afforded good leads as p38 kinase inhibitors <2006BMCL4339>. 6-(4-(2,5-Difluorophenyl)oxazol-5-yl)-3-isopropyl-[1,2,4]-triazolo[4,3-*a*]pyridine was selected as a p38a MAP kinase inhibitor <2006MI371>. In addition, 2-aryl-1,2,4-triazolo[1,5-*a*]pyridines displayed antifungal activities against *C. albicans* and *T. rubrum* <2006MI262>. In addition, this ring system was formed in the course of the decomposition of Alprazolam tablets <2006MI2360>.

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Biographical Sketch



Professor Laurent Bischoff was born in France in 1969. Following chemistry studies at the Ecole Nationale Supérieure de Chimie de Paris, he worked on electrophilic amination with Professor J.-P. Genêt and received his Ph.D. degree from Paris 6 University in 1994. Then he joined Professor Jack Baldwin's group in Oxford, for a postdoctoral fellowship, working on a biosynthetic approach toward manzamine alkaloids. He got an associate professor position in the Faculty of Pharmacy in 1995 with Professor Bernard-Pierre Roques. His area of research was the design of new series of aminopeptidase A inhibitors for the central control of hypertension. Five years later, he started a new topic, focusing on the cell cycle via the study of Cdc 25 inhibitors with Professor C. Garbay. In 2003, he moved to Rouen for a professor position in the group of Professor Francis Marsais (ECOFH – IRCOF). His main topics of interest are bioorganic chemistry (peptidomimetics, peptide labeling, unnatural aminoacids) and short syntheses of heterocyclic building blocks.

11.14

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Two Extra Heteroatoms 0:2

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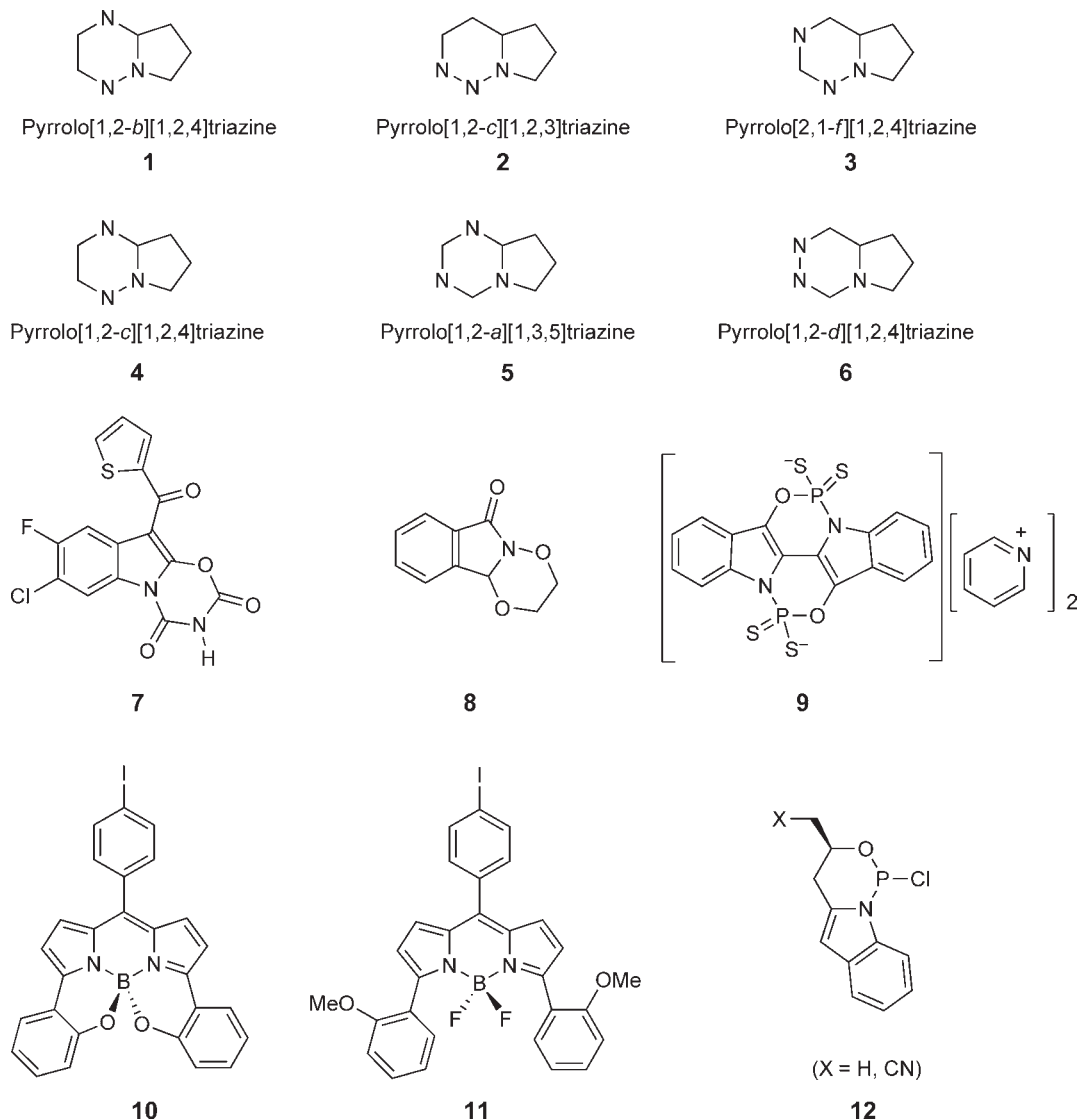
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11.14.1 Introduction

This chapter covers the bicyclic 5-6 systems with one ring junction nitrogen and two extra heteroatoms in the six-membered ring. The heteroatoms are primarily nitrogen, but a limited number of oxygen-, boron-, and phosphorus-containing systems have also been studied. There is one related chapter in CHEC-II(1996) <1996CHEC-II(8)389>. No general review of the topic exists, but some of these bicyclic systems such as pyrrolotriazine derivatives have been covered in various book chapters <2005SOS(18)665, 2005SOS(22)379, 2005SOS(22)795, 2004SOS(17)223>. This review will concentrate on the literature which has appeared since 1995.

Of the large number of theoretically possible systems falling within the scope of this chapter, only few of them have been reported in the literature. By far the greatest number of citations was devoted to all the regioisomeric pyrrolotriazines 1–6, both fully conjugated and nonconjugated, and related benzo derivatives. The other systems

known include the cyclic carbamate **7**, analogous to the piroxicam prodrug droxicam <1996JME10>, the fused six-membered-dioazaring compound **8** <1999TL2117>, the salt **9** derived from dithioindigo <2002J(P1)330>, the dye **10** and its parent system **11** <1999CC1889>, and phosphorochloridite **12** resulting from reaction of PCl_3 with various chiral indolo alcohols <1997TL705, 1997TL3797, 1998TL6433, 1999JOC2595, 2004AGE4521>.

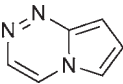


Little attention has been paid to systematic studies of spectral properties, X-ray structure, or thermodynamic aspects for these systems. Thus, little space is devoted to these subjects unless some feature warrants special note. On the contrary, synthesis and chemical reactivity of pyrrolo[1,2,4]triazines will be methodologically reviewed.

11.14.2 Theoretical Methods

Heats of formation can be obtained experimentally, but when a compound is unstable or difficult to purify, experimental values become increasingly difficult to measure. Therefore, heats of formation of various aromatic nitrogen heterocycles have been calculated, using both well-established semi-empirical methods (modified neglect of diatomic overlap (MNDO), AM1, and PM3) and *ab initio* methods (4-31G and 6-31G**) <1997JMT9>. These methodologies were applied to azolotriazines suggesting, in this particular case, a reasonable agreement between the corrected PM3 and *ab initio* heats of formation (Table 1).

Table 1 Semi-empirical and *ab initio* azolotriazine heats of formation (ΔH_f , kcal mol⁻¹)

Compound	Semi-empirical			<i>Ab initio</i> ^b
	MNDO	AM1	PM3	
	78.7	107.5	85.1	104.5
	106.8 ^a		99.2 ^a	

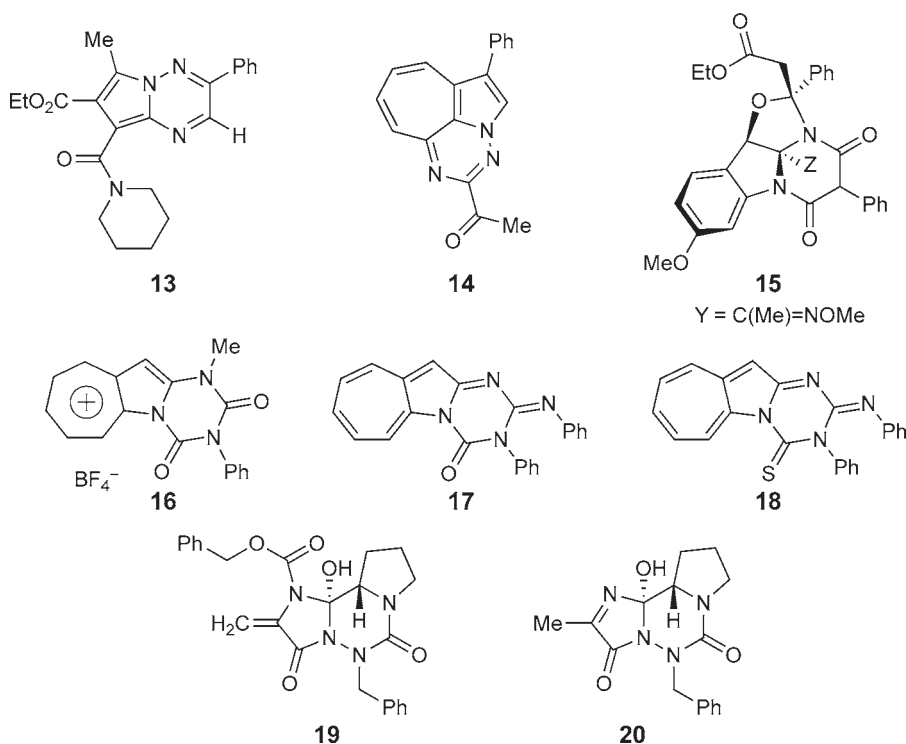
^aCorrected semi-empirical values.^bAverage of 4-31G and 6-31G** results.

Azolotriazines can be formed by cycloaddition reactions between diazoazoles and various substituted alkynes. In order to determine the mechanism of these reactions, semi-empirical AM1, MNDO, and PM3 calculations were run <1999JMT103>. Depending on the nature of the alkyne partner, these condensations may be viewed either as [7+2] cycloadditions, directly forming azolotriazines, or as [3+2] cycloadditions forming spirobicyclic intermediates, which quickly rearrange to azolotriazines.

11.14.3 Experimental Structural Methods

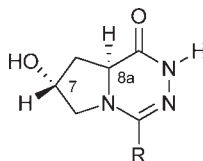
11.14.3.1 X-Ray Studies

The structures of several compounds containing the pyrrolo[1,2,4]triazine moiety have been established by X-ray crystallography, as for example pyrrolo[1,2-*b*][1,2,4]triazine **13** <1997J(P1)1829>, 4-acetyl-1-phenyl-2a,3,5-triazabenz[*c,d*]azulene **14** <2000H(53)323>, heterodiquinane **15** <1998CL1135>, cation **16** derived from methylation of 3-phenylcyclohepta[4,5]pyrrolo[1,2-*a*][1,3,5]triazine-2,4(3*H*)-dione <2005H(65)1629>, 2-phenyl-3-phenyl-2,3,4,4a-tetrahydro-1,3,4a-triazabenz[*a*]azulen-4-one **17** and its thioisomer **18** <2006H(67)337>, pseudopeptidic aza-cyclol **19** and its imino aza-cyclol derivative **20** <1997J(P1)2223>.



11.14.3.2 NMR Spectra

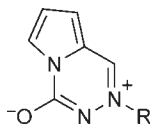
A detailed assignment and analysis of the ^1H nuclear magnetic resonance (NMR) spectra of compounds **16** and **17**, with some other derivatives of the same series, has been reported <2005H(65)1629>. On the basis of ^1H NMR spectroscopy, the stereochemistry at C-5 of compound **15** was determined as *endo*-ethoxycarbonylmethyl and *exo*-phenyl configuration with respect to the *cis*-fused indoline-oxazolidine ring. In fact, the ethoxyl protons resonated at higher field due to the diamagnetic anisotropy of the phenyl ring. Stereochemistry of compounds **21** was established from nuclear Overhauser effect (NOE) experiments, concluding that the hydrogen atoms of carbons C-7 and C-8a are in a 1,3-*trans*-relationship. A detailed assignment and analysis of the ^1H and ^{13}C NMR spectra of compounds **19** and **20**, with some other derivatives of the same series, has been reported <1997J(P1)2223>.



21

R = H, Me Et, Ph

The structure of betaine **22** (R = Me) was deduced from ^1H and ^{13}C NMR spectral data and elemental analysis <1999T13703>. A singlet at δ 8.23 ppm in the ^1H NMR spectrum was assigned to the proton at C-1, the signal of which appeared at δ 127.3 ppm in the ^{13}C NMR spectrum. These chemical shifts were slightly shifted to lower magnetic field than those of the corresponding atoms of the precursor pyrrolo[1,2-*d*][1,2,4]triazin-4-one, reflecting the mesomeric effect of the cation in **22** (R = Me). In addition, a singlet (δ 4.05 ppm) of the methyl group was observed at lower field in comparison with a methyl group attached to a neutral nitrogen-containing functional group, such as amino or amide group. This lower-field shift is caused by the quaternized iminium cation in the vicinal position.



22

11.14.3.3 Mass Spectrometry Studies

The use of mass spectrometry in the series of systems falling within this chapter has been mainly restricted to molecular ion determination and structure determination <1996CHEC-II(8)389>. No systematic study of this family has been made.

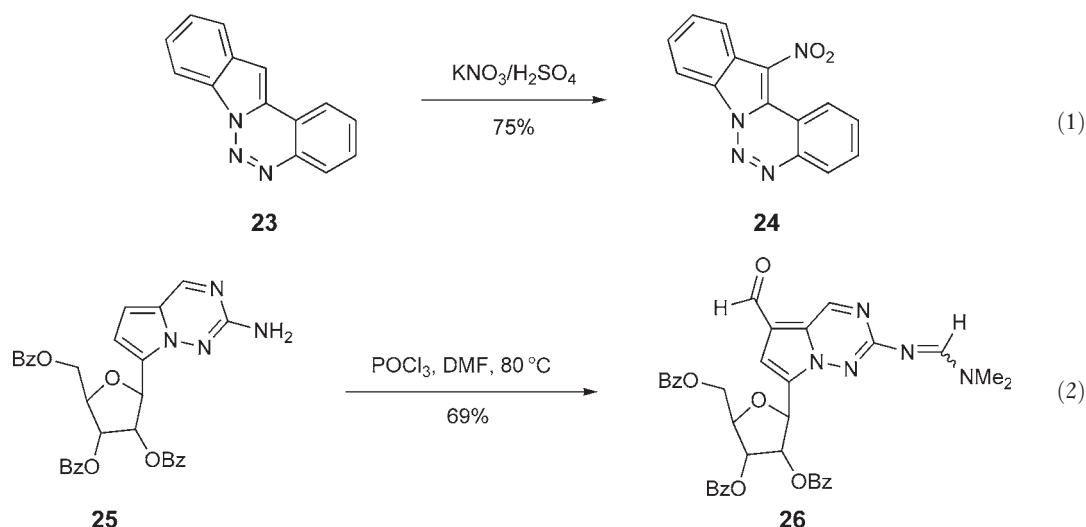
11.14.4 Thermodynamic Aspects

Thermodynamic aspects of bicyclic compounds falling with the scope of this chapter have not been the subject of systematic study.

11.14.5 Reactivity of Fully Conjugated Rings

11.14.5.1 Electrophilic Attack at Carbon

The pyrrolotriazine scaffold can be viewed as a five-membered π -electron-rich heterocyclic ring fused to a six-membered π -electron-deficient ring. Therefore, the chemistry of these fully conjugated systems consists essentially of electrophilic attacks to the pyrrole carbons. As a first illustration of this process, the indolobenzotriazine **24** was obtained in 75% yield by direct nitration in sulfuric acid of the corresponding unsubstituted indolobenzotriazine **23** (Equation 1) <1999JME2561>. Another example of such reactivity is the Vilsmeier formylation of the aromatic nucleus of pyrrolo[2,1-*f*][1,2,4]triazine **25**, which resulted in the formation of compound **26** (Equation 2) <2001CAR77>.



11.14.5.2 Electrophilic Attack at Heteroatom

Concerning the reactivity of fully conjugated bicyclic compounds, there have been no systematic studies on electrophilic attack at nitrogen by proton acids, alkylating or acylating agents, halogen, peracids, Lewis acids, or aminating agents. The only reported studies in this field deal with the preparation of betaines **22** by alkylation of the pyrrolo[1,2-*d*][1,2,4]triazin-4-one **27**. 2-Alkylpyrrolo[1,2-*d*][1,2,4]triazinium-4-olates **22** were obtained as major products along with the 3-alkylated products **28** (Equation 3; Table 2) <1999T13703>.

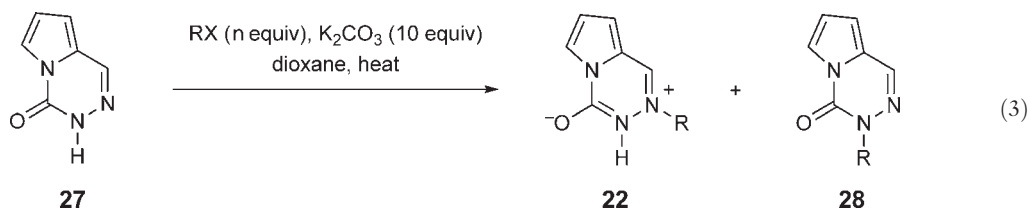


Table 2 Betaine synthesis via alkylation of pyrrolo[1,2-*d*][1,2,4]triazin-4-one **27**

<i>R</i>	<i>X</i>	<i>n</i>	Reaction time (h)	Temperature (°C)	Yield of 22 (%)	Yield of 28 (%)
Me	I	10	10	40	80	16
PhCH ₂	Br	3	6	80	85	15

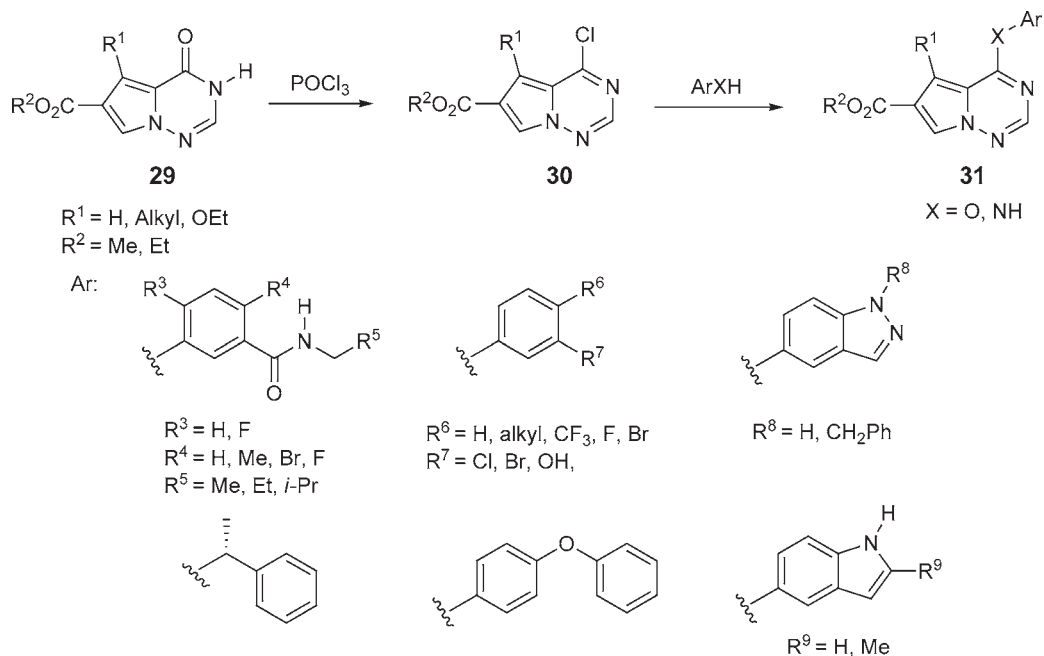
11.14.6 Reactivity of Nonconjugated Rings

The majority of references dealing with the reactivity of nonconjugated bicycles covered by this chapter primarily deals with those systems containing one or two oxo groups in the six-membered ring. Thus, most of the substrates engaged in the following reactions behave as cyclic amides, and strong nucleophiles of the type that attack amides generally do react with these systems.

11.14.6.1 Nucleophilic Attack at Carbon

Most of the reported reactions consist of nucleophilic attack at the carbon atom of the carbonyl group, resulting in substitutions rather than ring openings. Thus, in a series of recent publications, it was shown that pyrrolotriazinones **29** could be easily converted to the corresponding fully aromatic chloro derivatives **30**. These chloroimides readily

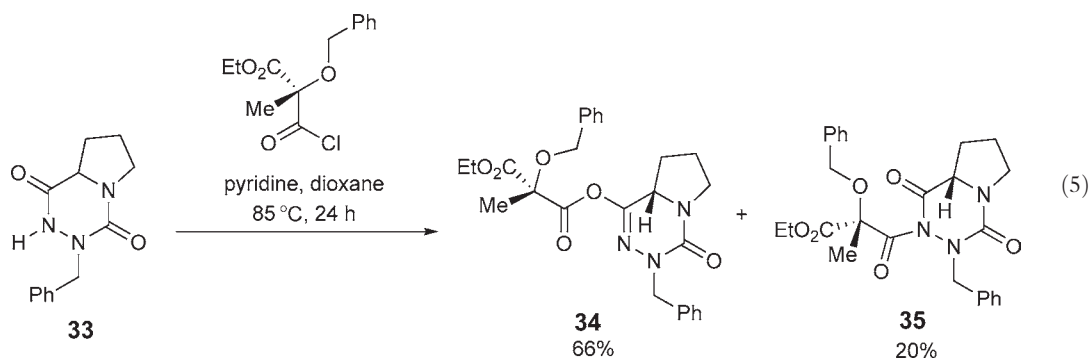
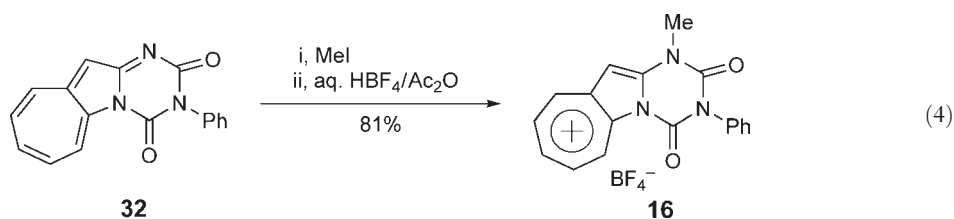
undergo nucleophilic substitutions with the appropriately functionalized aryl alcohols or aryl amines to furnish the corresponding analogues **31** in good overall yield (Scheme 1) <2004JME4054, 2005BML4774, 2005JME3991, 2005BML1429, 2006JME2143>.



Scheme 1

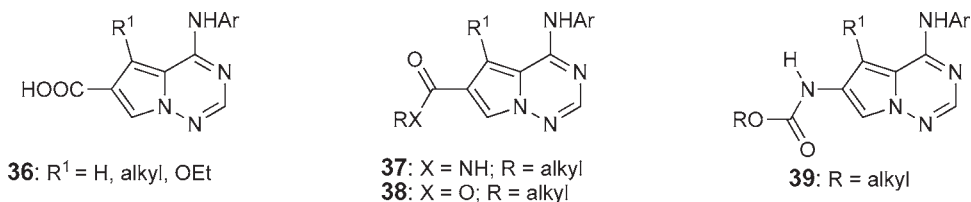
11.14.6.2 Electrophilic Attack at Carbon and Nitrogen

In systems with two oxo moieties, electrophilic attack occurs at the nitrogen of the cyclic amide. As an illustration, triaziridine dione **32** was converted in good yield to the salt **16** upon treatment with MeI and followed by ion exchange (Equation 4) <2005H(65)1629>. Similar reactivity was observed with substrate **33**, but in this case a 3/1 mixture of *O*-acylated and *N*-acylated products **34** and **35** was obtained (Equation 5) <1997J(P1)2223>.

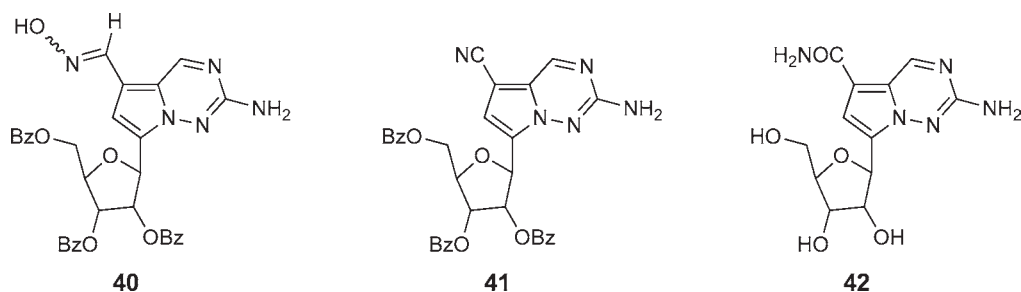


11.14.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Various functional groups were introduced in the 6-position of pyrrolo[2,1-*f*][1,2,4]triazines. Saponification of **31** (X = NH) with LiOH afforded the corresponding carboxylic acids **36**, which were coupled to amines or alcohols via the corresponding acid chlorides to afford a series of amides **37** or esters **38**. Alternatively, Curtius rearrangement of **36** with diphenylphosphoryl azide (DPPA) and reaction of the intermediate isocyanate with an alcohol afforded a series of carbamates **39** <2005BML4774, 2005JME3991, 2005BML1429>.



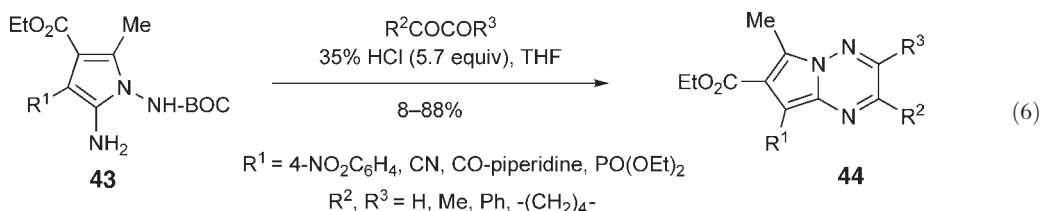
Aldehyde **26** was treated with hydroxylamine hydrochloride in refluxing methanol to give a mixture of (*E*)- and (*Z*)-pyrrolotriazine **40** in 59% and 21% yield, respectively. Dehydration of aldoxime **40** with trifluoromethanesulfonic anhydride and triethylamine in dichloromethane afforded triazine **41**. Conversion of the nitrile **41** to the deprotected amide **42** was accomplished in 96% yield on treatment of **41** with basic hydrogen peroxide in ethanol <2001CAR77>.



11.14.8 Ring Syntheses Classified by Number of Ring Atoms in Each Component

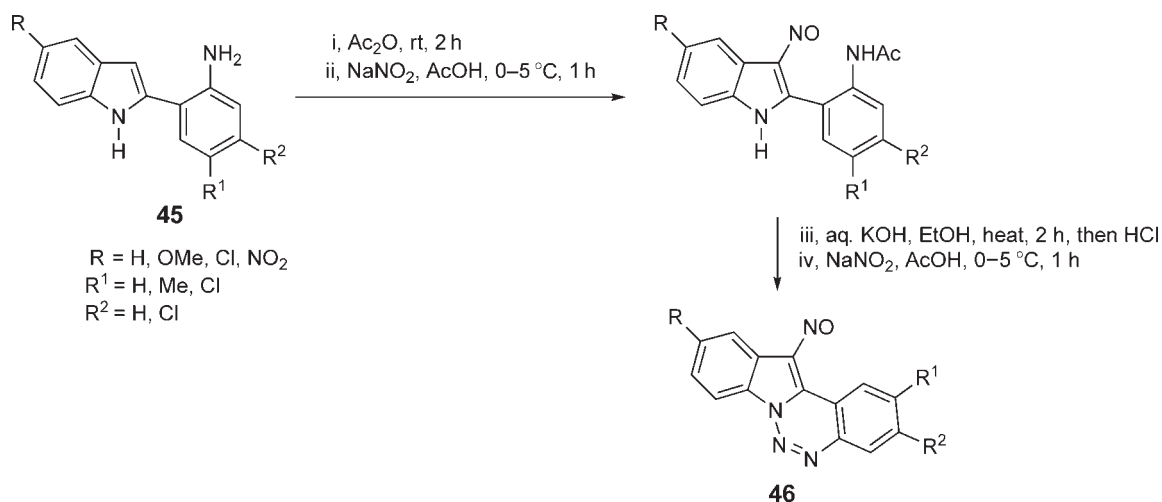
11.14.8.1 Pyrrolo[1,2-*b*][1,2,4]triazine

Highly substituted pyrrolo[1,2-*b*][1,2,4]triazines were synthesized from pyrrole derivatives, by closure of the triazine ring. Thus, hydrolytic cleavage of some 1,2-diaminopyrroles having a 1-NH-BOC-protected amino function **43** followed by reaction with 1,2-dicarbonyl compounds afforded a one-pot access to the corresponding bicyclic heterocycles **44** (BOC = *t*-butoxycarbonyl; Equation 6) <1997J(P1)1829>.



11.14.8.2 Pyrrolo[1,2-*c*][1,2,3]triazine

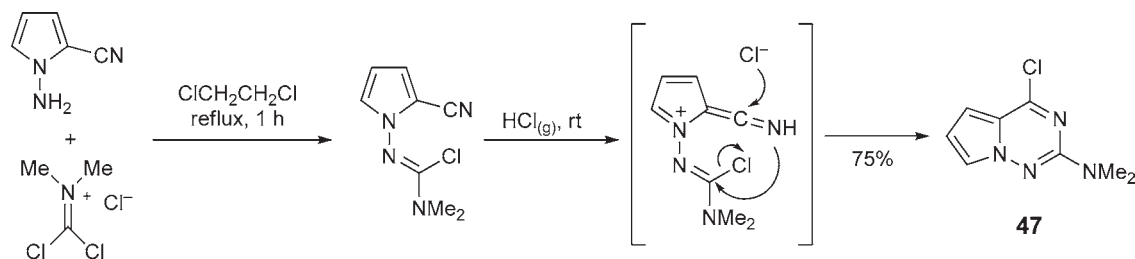
Among all the pyrrolotriazines described in literature, little attention has been given to the preparation of derivatives containing the pyrrolo[1,2-*c*][1,2,3]triazine skeleton. Nevertheless, derivatives of the ring system indolo[1,2-*c*]benzo[1,2,3]triazine **46** were synthesized by diazotization of substituted 2-(2-aminophenyl)indoles **45** followed by an intramolecular coupling reaction of the diazonium group with the indole nitrogen (Scheme 2) <1999JME2561>.



Scheme 2

11.14.8.3 Pyrrolo[2,1-f][1,2,4]triazine

Various methods for the preparation of pyrrolo[2,1-f][1,2,4]triazine derivatives have been reported in the literature, but all of them were based on the same strategy, consisting in closure of the triazine ring. For example, reaction of *N*-aminopyrrolonitrile with phosgeniminium salt in refluxing 1,2-dichloroethane for 1 h and subsequent treatment with hydrogen chloride provided a direct one-pot synthesis of the substituted pyrrolo[2,1-f][1,2,4]triazine **47** in 75% yield (Scheme 3) <1996T3037>.

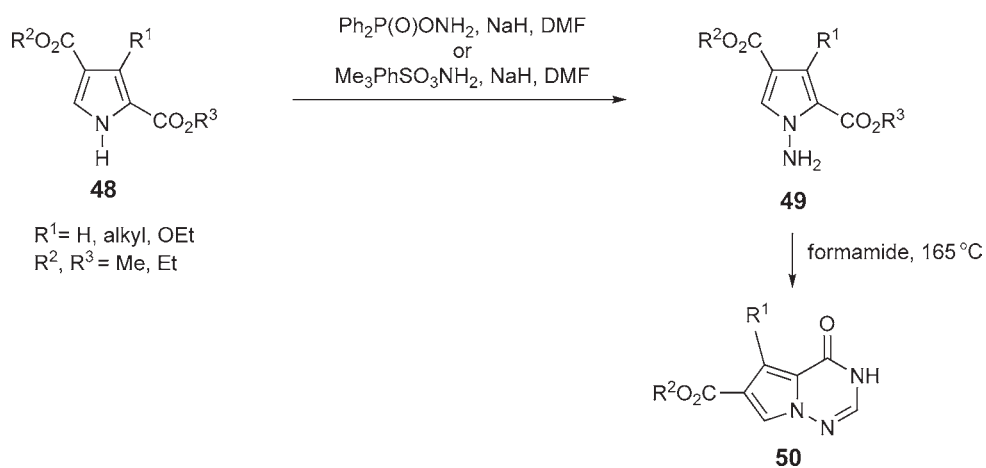


Scheme 3

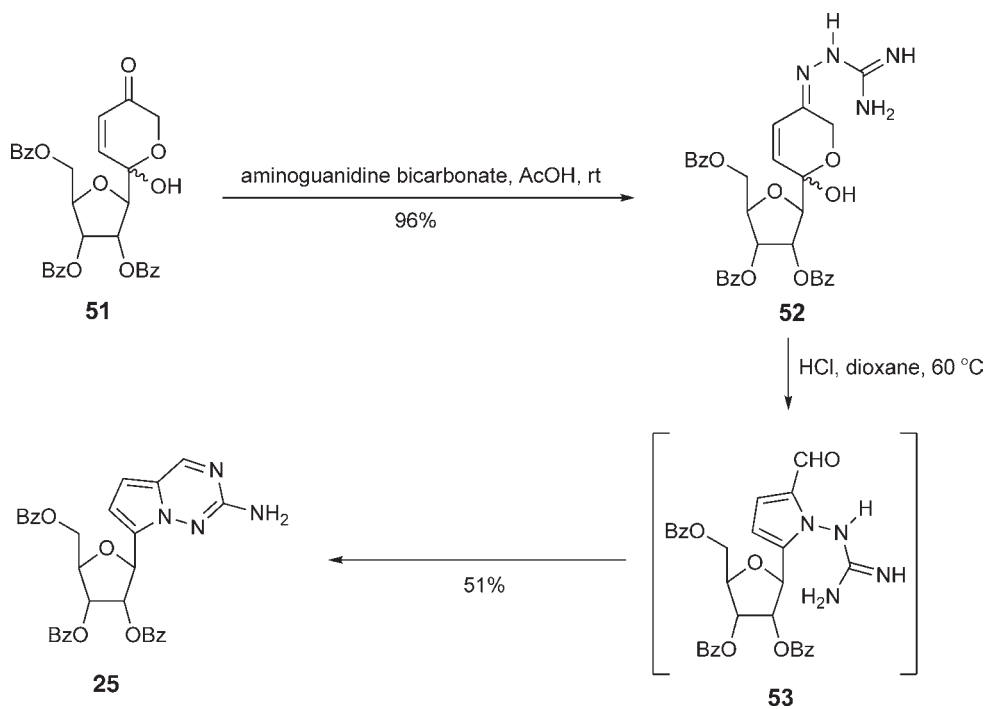
Various versatile syntheses of suitably functionalized pyrrolo[2,1-f][1,2,4]triazine nuclei have been described through the intermediacy of the requisite pyrrolotriazinones **50** <2004JME4054, 2005BML1429, 2005BML4774, 2005JME3991>. *N*-Amination of substituted 1*H*-pyrroles **48** using either *O*-(diphenylphosphinyl)hydroxylamine or *O*-(mesitylenesulfonyl)hydroxylamine provided aminopyrroles **49**. Cyclization of **49** upon heating in formamide generated the desired bicycle **50** (Scheme 4).

It is also important to note that C-nucleosides incorporating the pyrrolo[2,1-f][1,2,4]triazine system are known. Thus, treatment of pyranulose glycoside **51** with aminoguanidine in acetic acid gave the corresponding semicarbazone **52** in 96% yield. The ring transformation of the semicarbazone in dioxane through **53** afforded a 51% yield of 2-amino-7-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl) pyrrolo[2,1-f][1,2,4]triazine **25** (Scheme 5) <2001CAR77>.

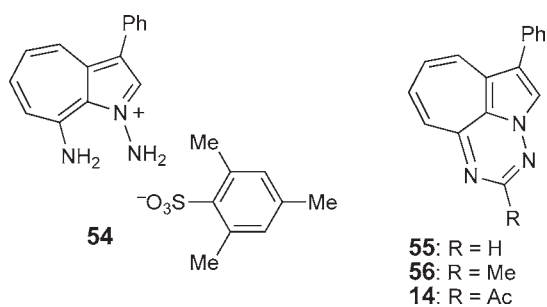
Finally, the pyrrolo[2,1-f][1,2,4]triazine moiety was also encountered in azulene derivatives. Reactions of 1,8-diamino-3-phenyl-1-azaazulenium salt **54** with triethyl orthoformate and acetic anhydride gave 1-phenyl-2a,3,5-triazabenz[*c,d*]azulenes **55** and **56**. The reaction of the same salt with ethyl pyruvate gave 4-acetyl-1-phenyl-2a,3,5-triazabenz[*c,d*]azulene **14** <2000H(53)323>.



Scheme 4



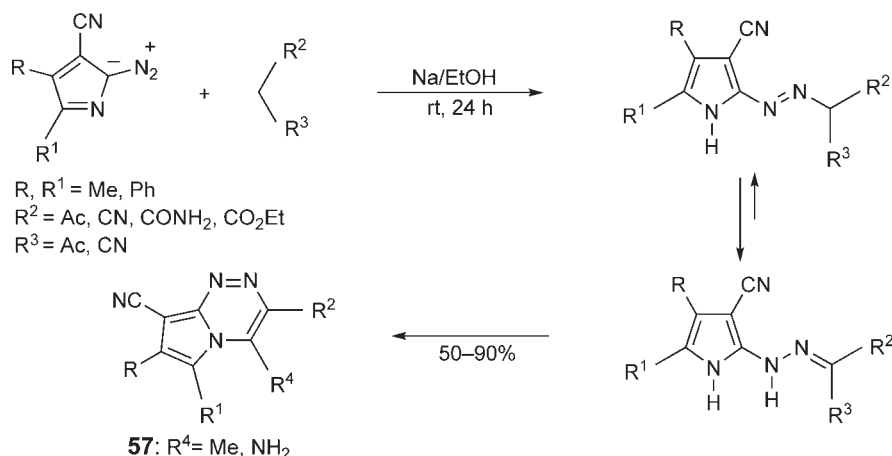
Scheme 5



11.14.8.4 Pyrrolo[1,2-*c*][1,2,4]triazine

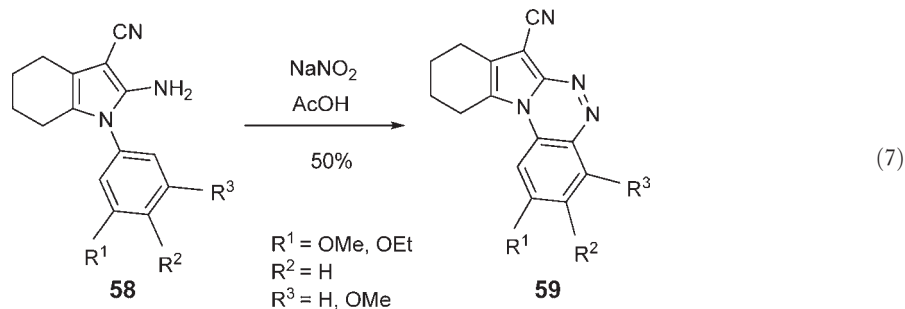
1,2,4-Triazines have been the subject of a recent and highly documented review [<2004SOS\(17\)223>](#). Due to the great biological interest of these polyheterocycles, their synthesis has long been an area of intense development, and still constitutes to be an active domain from the academic and industrial points of view.

Pyrrolo[1,2-*c*][1,2,4]triazine **57** were directly obtained from the reaction of 2-diazopyrroles with sodium salts of β -diketones, β -carbonitriles, and β -dinitriles [<2002EJM267>](#) (Scheme 6). Similar reactions have been developed from 2-diazoindoles, leading access to the corresponding ring systems indolo[1,2-*c*][1,2,4]triazines [<2002FA97>](#).

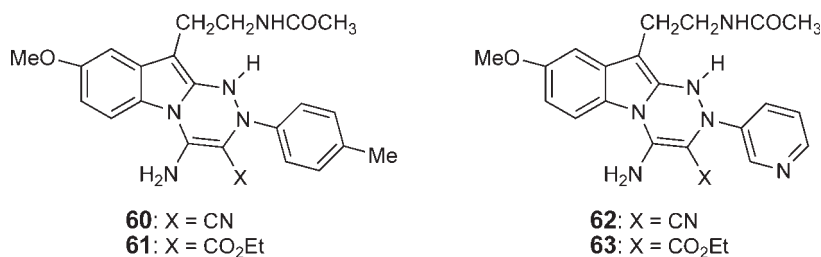


Scheme 6

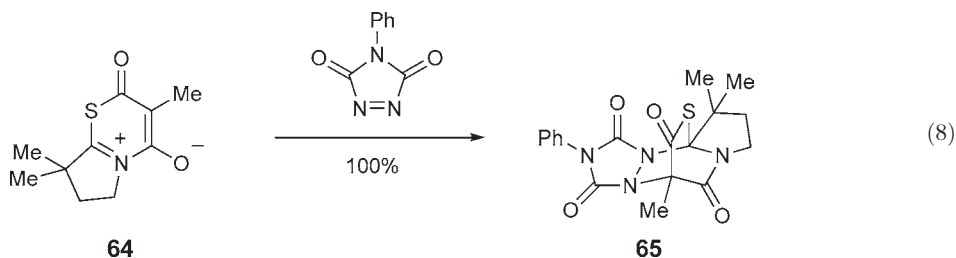
A series of indolo[2,1-*c*]benzo[1,2,4]triazine derivatives **59** were synthesized by diazotization of 2-amino-1-aryl-1,2,3,4-tetrahydroindoles **58** followed by an intramolecular coupling of the diazonium group with the aryl moiety (Equation 7) [<2003H\(60\)2519>](#). However, products were obtained in reasonable yields only in the case of amines in which an electron-donating group on the phenyl ring was suitably placed to activate the position 6 to undergo the electrophilic attack by the diazonium group.



Reaction of melatonin with various aryldiazonium chlorides in ethanolic sodium acetate solution afforded arylazo-melatonin derivatives. Reactions of these products with either malonitrile or ethyl cyanoacetate formed the corresponding arylaminotriazino[4,3-*a*]indole scaffolds **60–63** [<2005BMC1847>](#).

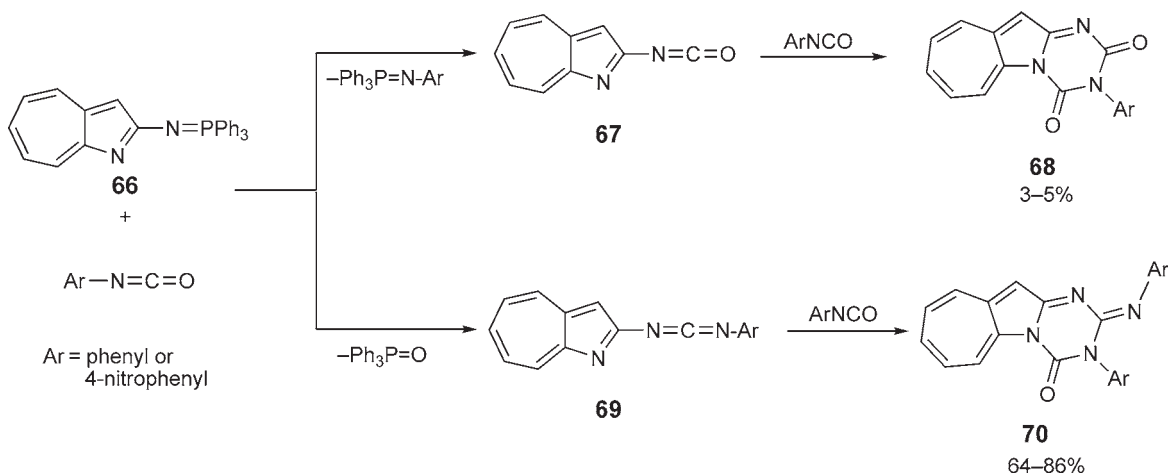


Cycloaddition reactions of betaine **64** with electron-deficient dipolarophiles, such as the extremely reactive 4-phenyl-1,2,4-triazoline-3,5-dione, gave the corresponding cycloadduct **65** isolated in quantitative yield (Equation 8) <1995T6651>.

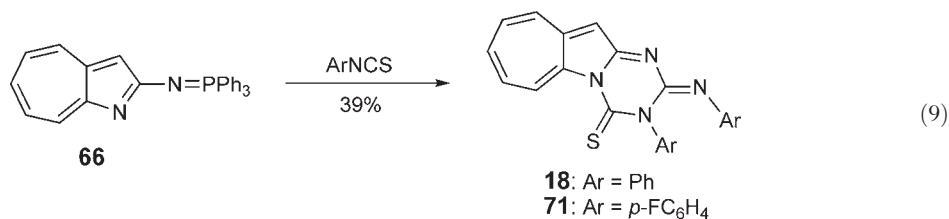


11.14.8.5 Pyrrolo[1,2-*a*][1,3,5]triazine

3-Phenyl- and 3-(4-nitrophenyl)cyclohepta[4,5]pyrrolo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones **68** and the corresponding arylimino derivatives **70** were synthesized by the reaction of (1-azaazulen-2-yl)imino-triphenylphosphorane **66** with aryl isocyanates and subsequent heterocyclization with a second isocyanate <2005H(65)1629>. Both intermediates **67** and **69** can be postulated in this sequence. Formation of **67** involves loss of aryliminotriphenylphosphorane as the abnormal aza-Wittig product, while carbodiimides **69**, which predominate over the formation of **67**, are the normal aza-Wittig products (Scheme 7). Similar treatments of (1-azaazulen-2-yl)imino-triphenylphosphorane with aryl isothiocyanates gave the corresponding 2-arylimino-3-aryl-2,3,4,4a-tetrahydro-1,3,4a-triazabenz[*a*]azules-4-thiones **18** and **71** (Equation 9).

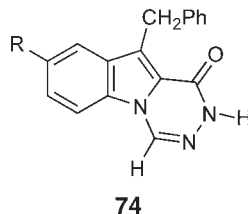
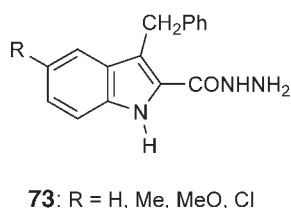
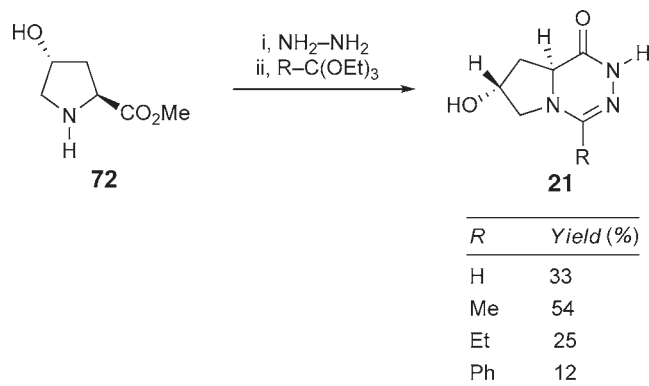


Scheme 7

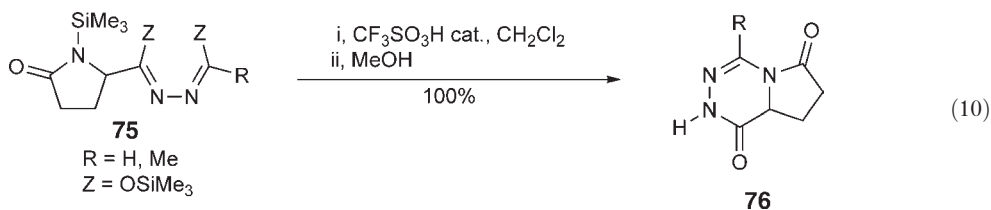


11.14.8.6 Pyrrolo[1,2-*d*][1,2,4]triazine

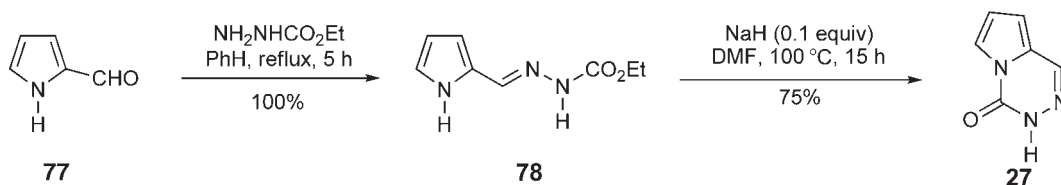
Pyrrolo[1,2-*d*][1,2,4]triazinones **21** were synthesized from methyl ester of *trans*-4-hydroxy-L-proline **72**. The synthetic route involved formation of hydrazones followed by cyclisation with orthoesters <1998BMC349>. Similar reactions have been developed with 3-benzylindole-2-carbohydrazides **73** in reaction with triethyl orthoformate, giving the corresponding ring systems indolo[1,2-*c*][1,2,4]triazin-4-ones **74** <2004JHC7>.



The pyrrolo[1,2-*d*][1,2,4]triazinone skeleton **76** was also accessible in quantitative yield through a triflic acid-catalyzed heterocyclization of trisilylated diacylhydrazines **75** derived from pyroglutamic acid (Equation 10) <1996JHC1073>.

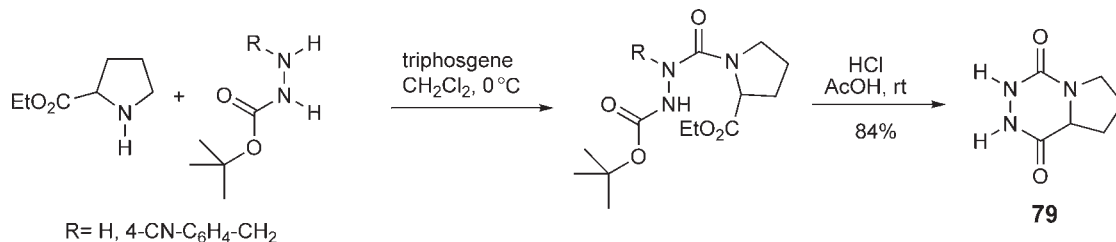


Dehydrative condensation of pyrrole-2-carboxaldehyde **77** and ethyl carbazate afforded carbethoxyhydrazone **78** in quantitative yield. Cyclization of **78** in the presence of a catalytic amount of sodium hydride (10 mol%) in dimethylformamide (DMF) at 100 °C led to the formation of pyrrolo[1,2-*d*][1,2,4]triazin-4-one **27** in 75% yield (Scheme 8) <1999T13703>.



Scheme 8

Reaction of *tert*-butyl 1-hydrazinecarboxylates with triphosgene and ethyl 2-pyrrolidinecarboxylate, followed by removal of the BOC-protecting group with gaseous hydrogen chloride in anhydrous acetic acid, yielded hexahydro-pyrrolo[1,2-*d*][1,2,4]triazin-1,4-dione **79** (Scheme 9) <2003SC1011>.



Scheme 9

11.14.9 Ring Synthesis by Transformation of Another Ring

Irradiation of urazole **80** and β -ketoesters **81** in acetonitrile containing triethylamine gave a mixture of two products **82** and **15** <1998CL1135>. The photoproduct **82** had previously been identified as a rearranged product in the photochemical reactions of **80** without nucleophiles <1996BCJ3533>. Compounds **15** presented an intricate hetero-diquinane framework containing a triazinoindolinone and an oxazolidinone skeletons. When ethyl acetoacetate was used as nucleophile, competitive dimerization of product **82** occurred to give **84** as a third product (Table 3).

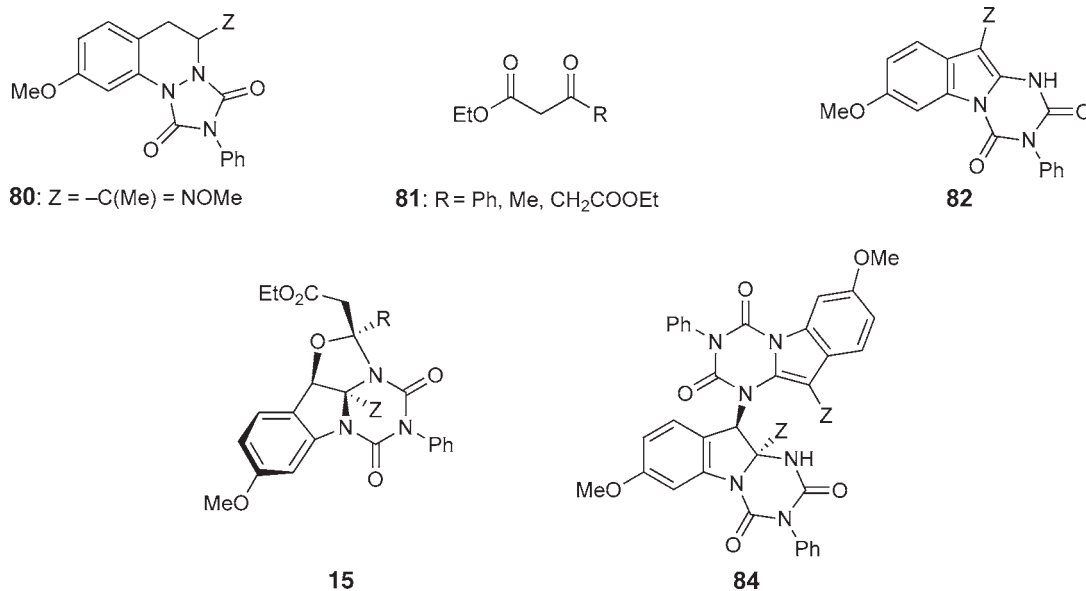


Table 3 Photoreactions of urazole **80** with β -ketoesters in the presence of triethylamine

β -Ketoester 81	Irradiation time (h)	Isolated yield (%)		
		82	15	84
R = Ph	6	14	66	0
R = Me	6	4	42	33
R = CH ₂ CO ₂ Et	10	4	62	0

11.14.10 Important Compounds and Applications

All the heterocycles containing a ring junction nitrogen atom and two extra nitrogen atoms in the six-membered ring described in this chapter exhibited a diverse array of biological activities. By far the greatest amount of activity has been found to be associated with the pyrrolo[2,1-*f*][1,2,4]triazine nucleus. In the last few years, numerous patents have been deposited on processes for the preparation of pyrrolotriazine kinase inhibitors for the treatment of inflammation, cancer, and proliferative diseases <2006USP6084650, 2006USP6089358, 2006USP6019928, 2006WO6007468, 2006USP6014741, 2006USP6009454, 2005USP5288289, 2005WO5066176>.

Another important series of biologically active compounds relative to this chapter are molecules containing the pyrrolo[1,2-*d*][1,2,4]triazine skeleton. Such compounds exhibited various activities such as kinase inhibition <2006WO6047354>, modulation of nuclear hormone receptor function <2004USP4077606, 2003USP3114420, 2002WO2000653>, inhibition of poly(ADP-ribose)polymerase <2003WO3070707>, immunostimulation <1998BMC349>, treatment of symptoms of cholinergic insufficiency involving cognitive disorders <1998USP5750522>, and inhibition of chymase and nitric oxide production <1996EP713876>.

Some pyrrolo[2,1-*c*][1,2,4]triazines were evaluated against a panel of human cancer cell lines and some of them demonstrated inhibitory effects in the growth of a wide range of cancer cell lines generally at 10^{-5} M concentration and in some cases at micromolar concentrations <2002EJM267, 2002FA97>.

Finally, indolo[1,2-*c*]benzo[1,2,3]triazines **46** proved to be fairly potent and selective inhibitors of *Streptococcus* and *Staphylococcus*, up to 80 times more potent than the reference drug streptomycin, and inhibited the growth of the above Gram-positive bacteria at concentrations far lower than those cytotoxic for animal cells <1999JME2561>.

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Biographical Sketch



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11.15

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 3:0

G. Hajós and Z. Riedl

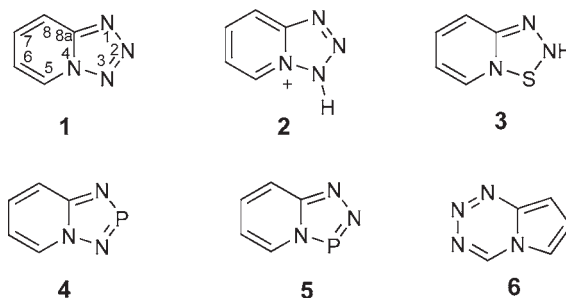
Institute of Biomolecular Chemistry, Chemical Research Center, Budapest, Hungary

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11.15.1 Introduction

In this chapter only six ring systems and/or their benzologues are discussed. As to the ring systems of 3:0 heteroatom arrangement three types – tetrazolo[1,5-*a*]pyridine **1**, its protonated (quaternized) derivative **2**, and thiatriazolopyridine **3** – have already been discussed in CHEC-II(1996) <1996CHEC-II(8)405>, whereas two new ring systems – two differently fused triazaphospholes **4** and **5** have recently been synthesized. Very little material has appeared on ring systems with 3:0 heteroatom variation, and all of this in the past period has concerned the earlier known pyrrolo[1,2-*d*][1,3,4,5]tetrazine **6** skeleton (**Scheme 1**).

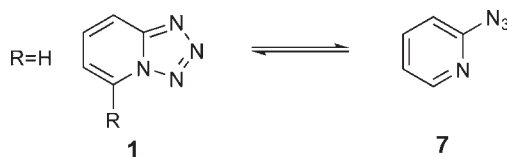


Scheme 1

11.15.2 Theoretical Methods

Novel calculations on the tetrazolo[1,5-*a*]pyridine–2-azidopyridine equilibrium (Scheme 2, 1–7) in the case of 5-substituted derivatives using *ab initio* (6-31G**/MP2) methods appeared recently <2000T8775>. It has been shown that these substituents sensitively influence the equilibrium as revealed by the calculated energies shown in Table 1.

These data reveal that in the case of the methyl derivative, the tetrazole form is substantially more stable than the azide, whereas a dominant preference for the azide form was found with some other substituents. These theoretical conclusions are nicely supported by the experimental findings.



Scheme 2

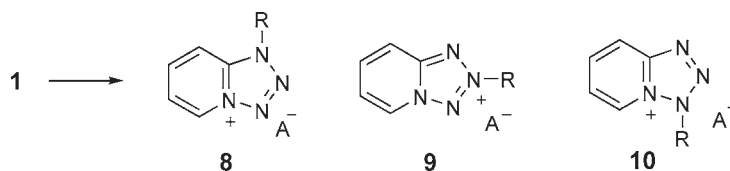
Whitehead *et al.* carried out novel calculations on the tetrazole–azide equilibrium 1–7, (Scheme 2) and found that PM3 provided the best results <2001JMT199>. The computed heats of formation showed that the equilibrium is shifted to the ring-closed form in the case of electron-donating substituents in *meta* position to the pyridine nitrogen atom.

Table 1 Differences of energy values (kcal mol^{−1}) of 5-substituted tetrazolo[1,5-*a*]pyridines **1** and their azido valence bond isomers **7** calculated by *ab initio* (6-31G**/MP2) method

<i>R</i>	<i>E</i> (tetrazole)– <i>E</i> (azide) Kcal.mol ^{−1}
H	−3.9
CH ₃	−5.8
OH	1.8
Cl	1.5
OCH ₃	2.4
NO ₂	7.0
COOH	−0.3

Theoretical studies on the experimentally observed selectivity of alkylation of tetrazolo[1,5-*a*]pyridine **1** and its benzologues to alkyltetrazolo[1,5-*a*]pyridinium salts revealed that the site of the alkylation can be fairly well predicted by the help of molecular electronic potential (MEP) maps <1998JMT191>. Earlier it was shown that transformation of **1** to the three possible alkyl-substituted salts **8–10** (Scheme 3) results in a mixture containing high

amount of 1-alkyl **8** and only traces of 2-alkyl **9** salts <1996CHEC-II(8)408>. The recent calculations showed that the MEP minimum is significantly the lowest at N-1.



Scheme 3

A substantial amount of theoretical work in the context of some nuclear magnetic resonance (NMR) studies has been carried out by a Polish research group <1999JST165, 2002JST33>. These authors found that ^{13}C and ^{15}N chemical shifts calculated for tetrazolo[1,5-*a*]pyridine **1** and 2-azidopyridine **7** (Scheme 2) by the GIAO-CPHF *ab initio* method were in good agreement with the experimentally observed values. These studies also revealed that tetrazolo[1,5-*a*]pyridine **1** – as well as a number of related azaindolizine – undergoes protonation exclusively at position 1, which significantly changes the electronic distribution at atoms in positions 1, 2, 8, and 8a.

11.15.3 Experimental Structural Methods

While numerous studies dealt earlier with ^1H and ^{13}C NMR investigation of the tetrazolo[1,5-*a*]pyridine-2-azidopyridine equilibrium as discussed in CHEC-II(1996), ^{15}N NMR investigations appeared only during the past period. ^{15}N NMR shifts of a set of 6- and 8-substituted tetrazolo[1,5-*a*]pyridines have been described by Cmoch *et al.* <1997MRC237>. Comparison of the values measured in trifluoroacetic acid (TFA) solutions (Table 2) shows a predominant downfield shift (by 30–90 ppm) of the N-1 signals of the tetrazole forms compared to those measured in the DMSO solutions. This finding strongly supports the suggestion that protonation takes place at N-1. Further related studies of these authors also appeared <1999JST165, 2002JST33>.

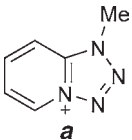
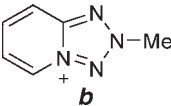
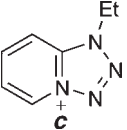
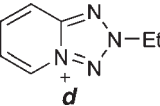
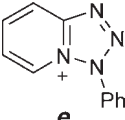
Table 2 ^{15}N NMR shifts in DMSO and TFA solutions of some 6- and 8-substituted tetrazolo[1,5-*a*]pyridines

R	Solvent	N-1		N-2		N-3		N-4	
		A	T	A	T	A	T	A	T
H	DMSO		–67.8		–18.3		–31.8		–128.3
	TFA		–161.3		–13.5		–34.9		–131.3
6-NO ₂	DMSO		–66.8		–26.2		–26.2		–130.7
	TFA	–276.1	–94.8	–152.8	–7.8	–130.3	–28.8	–191.8	–133.8
6-Br	DMSO		–67.0		–18.8		–31.4		–121.6
	TFA	–275.0	–94.8	–152.1	–7.8	–131.8	–28.8	–201.4	–133.8
8-NO ₂	DMSO		–67.3		–20.7		–30.3		–122.9
	TFA		–106.5		–1.1		–31.8		–126.0

A = azide form; T = tetrazole form.

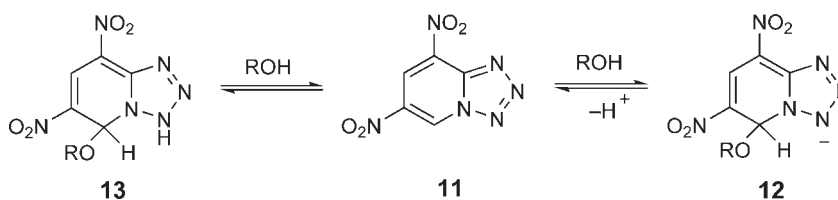
NMR shifts (^1H , ^{13}C , and ^{15}N) of 1-alkyl-, 2-alkyl-, and 3-aryltetrazolo[1,5-*a*]pyridinium salts have also been measured <1999JST119>. The data are compiled in Table 3. The ^{15}N shifts of these salts seemed of particular importance as they revealed quite big shielding changes for the nitrogen nuclei. These chemical shifts were also calculated by the *ab initio* GIAO-CHF method, and the result was found to be in fairly good agreement with the experimental values.

Table 3 The ^1H , ^{13}C , and ^{15}N chemical shifts of 1-alkyl, 2-alkyl-, and 3-aryltetrazolo[1,5-*a*]pyridinium salts

					
^1H chemical shifts (ppm)					
$\text{CH}_3(\text{N})$	4.51	4.89	1.64	1.75	
$\text{CH}_2(\text{N})$			4.93	5.19	
H-5	9.75	9.68	9.73	9.65	9.48
H-6	8.00	8.03	7.98	8.01	8.18
H-7	8.57	8.36	8.55	8.34	8.60
H-8	8.67	8.66	8.68	8.65	9.05
^{13}C chemical shifts (ppm)					
$\text{CH}_3(\text{N})$	35.9	44.0	13.4	13.4	
$\text{CH}_2(\text{N})$			45.2	53.4	
C-1a	140.4	149.2	140.0	149.3	149.1
C-5	128.9	127.4	129.0	127.5	124.7
C-6	121.3	123.2	121.4	123.1	124.7
C-7	141.3	137.9	141.3	137.8	139.3
C-8	111.6	116.4	111.5	111.6	118.3
^{15}N chemical shifts (ppm)					
N-1	-165.8	-78.4	-154.6	-81.0	-57.6
N-2	-12.8	-95.3	-14.8	-84.7	+0.6
N-3	-39.7	-42.4	-39.1	-43.6	-124.7
N-4	-129.0	-132.2	-128.6	-132.6	-145.9

11.15.4 Thermodynamic Aspects

Thorough thermodynamic and kinetic investigation of solvolysis of 4,6-dinitrotetrazolo[1,5-*a*]pyridine **11** in water and methanol has been carried out [\[2003OBC2764\]](#). It has been shown that in water the anionic σ -complex **12** is formed exclusively, whereas addition of methanol results in partial formation of the neutral carbinolamine-type adduct **13** at low pH ([Scheme 4](#)). All these results indicate that **11** is an even more powerful electrophile than dinitrobenzofuroxane.

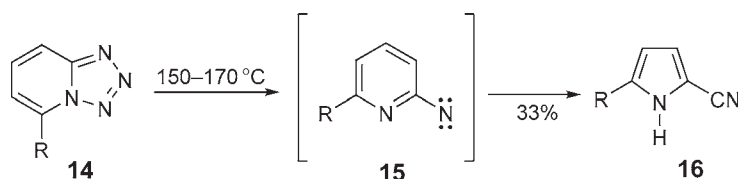
**Scheme 4**

Quite recently, the same research group compared the electrophilicity of 6-nitro-tetrazolo[1,5-*a*]pyridine and 6,8-dinitrotetrazolo[1,5-*a*]pyridine **11** with a series of electron-deficient aromatic and heteroaromatic compounds [\[2005JOC6242\]](#). As reference nucleophiles, *N*-methylpyrrole, indole, *N*-methylindole, and some morpholino enamines were used. The reactivity of the electrophiles studied followed the linear-free energy relationship defined by Mayr *et al.* [\[2003ACR66\]](#).

11.15.5 Reactivity of Fully Conjugated Rings

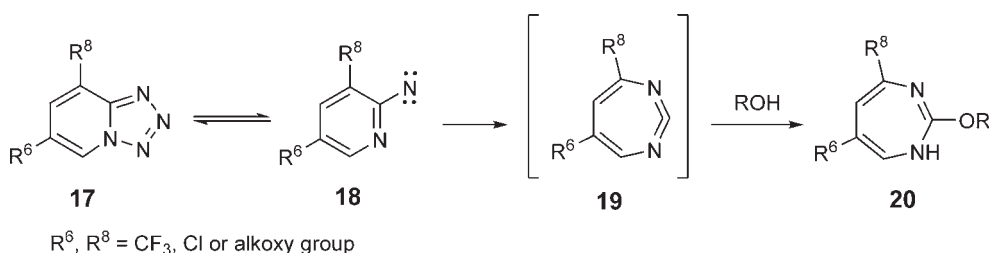
11.15.5.1 Ring Contractions and Ring Enlargements

Simoni *et al.* described [\[2000TL2699\]](#) that some fused tetrazoles readily participate in thermolytic ring contraction reactions which result in the formation of cyanopyrroles ([Scheme 5](#)). Thus, heating of tetrazolo[1,5-*a*]pyridine derivatives **14** at 150–170 °C yields the corresponding 2-cyanopyrrole **16**. The process is believed to proceed via a nitrene intermediate **15**.



Scheme 5

A series of experiments on ring expansions under photochemical conditions has been published by Wentrup *et al.* <1996CC813, 1998J(P1)2247, 2004OBC246, 2004OBC1227>. Schematic representation of these transformations is shown in Scheme 6.



Scheme 6

Tetrazolo[1,5-*a*]pyridines bearing trifluoromethyl, alkoxy, or chloro substituents in positions 6 and/or 8 such as in **17** were subjected to photolysis in a dioxane solution in the presence of some alcohols at low temperature (ice bath). After irradiation with a high pressure Hg/Xe lamp the reaction mixtures were worked up to yield 2-alkoxy-1*H*-1,3-diazepines **20** in medium to good yield. The transformations proceed via nitrogen elimination of the starting tetrazole–azide system to give a nitrene **18**, which undergoes an insertion reaction into the adjacent C–C bond to yield a diazacyclohepta-1,2,4,6-tetraene **19** as a reactive intermediate <1996JA4009>. This intermediate can be trapped by addition of a nucleophile (e.g., alcohol) to afford the final product **20**. This reaction pathway is strongly reminiscent of that found earlier by the same authors under flash vacuum pyrolytic conditions <1996CHEC-II(8)408>.

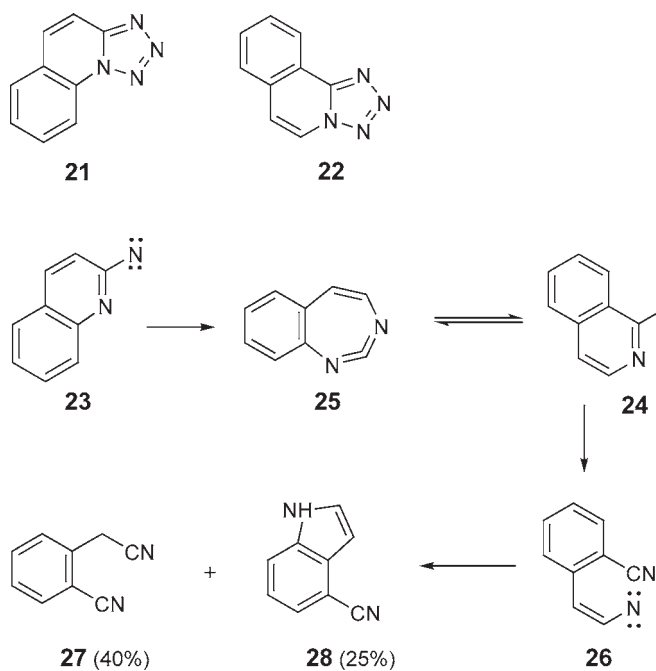
Similar observations with tetrazolo[1,5-*a*]pyridines bearing a phenylurea side chain have independently been reported by a French research group <1996JHC1035>.

Extension of these studies to benzologues of tetrazolo[1,5-*a*]pyridine, that is, for tetrazolo[1,5-*a*]quinoline **21** and tetrazolo[5,1-*a*]isoquinoline **22**, led to interesting results <2003JOC1470> as shown in Scheme 7. Both of these fused tetrazoles resulted in formation of a nitrene **23** and **24**, respectively, which could be interconverted via formation of the fused cyclic carbodiimide derivative **25**. Isoquinolynitrene **24**, furthermore, was found to undergo subsequent reactions: ring opening afforded the vinylnitrene **26**, which was transformed to *o*-cyanophenylacetonitrile **27** by a 1,2-H shift and to 4-cyanoindole **28** by an intramolecular cyclization in 40% and 25% yields, respectively.

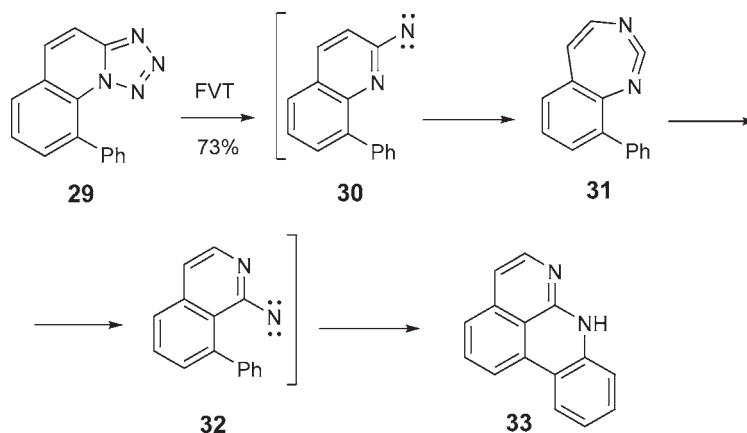
A series of transformations via nitrene formation similar to the previously discussed case was also found under flash vacuum thermolytic (FVT) conditions by the same team as shown in Scheme 8 <2003JOC1470>. 9-Phenyltetrazolo[1,5-*a*]quinoline **29** underwent nitrene **30** and cyclic carbodiimide **31** formation, and this intermediate – similar to the previous case – could open up to the isoquinoline nitrene **32** in which, however, proximity of the nitrene to the phenyl substituents allowed the ring closure to the stable tetracyclic ring system **33** which was obtained in 73% yield.

11.15.5.2 Ring Opening of the Six-Membered Moiety

As a continuation of earlier studies on electrocyclic ring opening of the pyridine moiety of 3-aryltetrazolo[1,5-*a*]pyridinium salts **34** <1996CHEC-II(8)409> further extension of this type of transformation was published by a

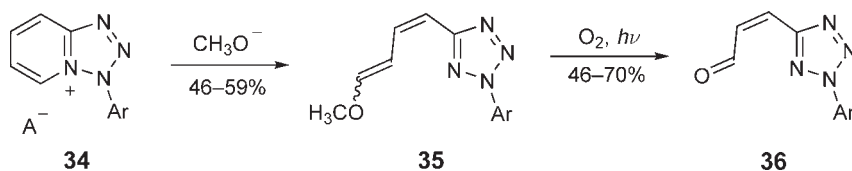


Scheme 7



Scheme 8

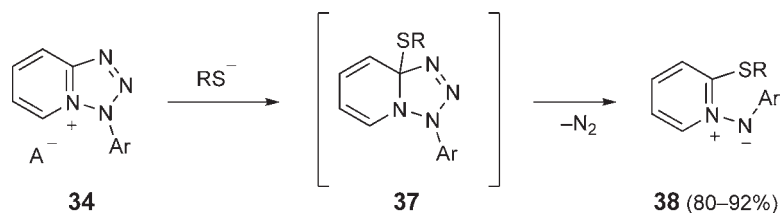
Hungarian group <2003T7485>. These authors described that ring opening of **33** with methoxide anion gave a methoxydiene **35** which can be subjected to oxidative photodegradation to tetrazolylacroleine **36** (Scheme 9). This product seemed of special preparative importance because of the presence of the reactive aldehyde function and proved to be suitable starting compound for a series of tetrazolyldienes and trienes <2004H2287>.



Scheme 9

11.15.5.3 Ring Opening of the Five-Membered Moiety

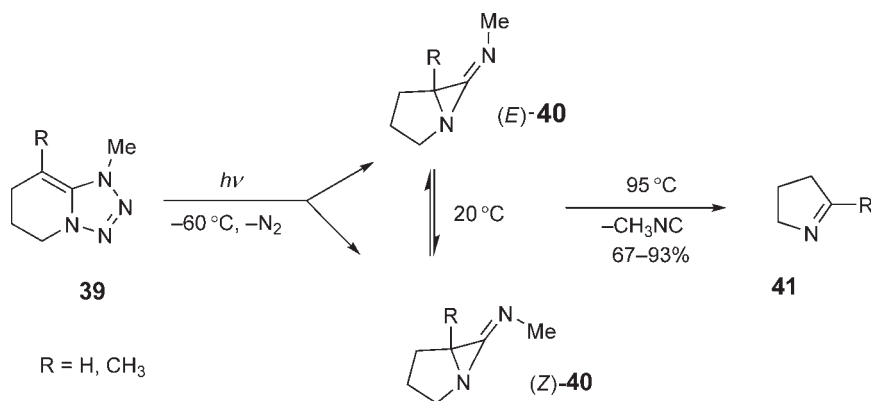
Investigations of reactivity of 3-aryltetrazolo[1,5-*a*]pyridinium salts **34** with aryl- and aralkylthiolates as nucleophiles recently lead to the preparation of synthetically valuable new mesomeric betaines **38** (Scheme 10) <2002T3613, 2003JOC5652>.



Scheme 10

The first step of the reaction sequence is the addition of the nucleophilic anion to position 8a of the starting salt **34** to give an intermediate **37** which rapidly undergoes nitrogen elimination to yield the zwitterionic product **38** as a relatively stable brilliant red crystalline substance in high yield. The strong dipolar character of **38** allowed further transformations via 1,3-dipolar cycloadditions and related reactions <2003JOC5652>.

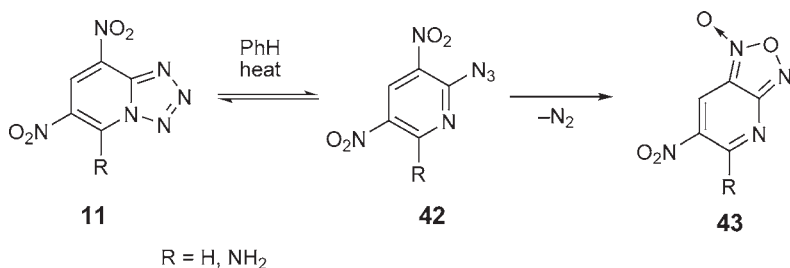
A photoextrusion of a nitrogen molecule from a partially saturated tetrazolo[1,5-*a*]pyridine derivatives has been described by Quast *et al.* <1998EJO317> (Scheme 11). The starting bicyclic compound **39** when irradiated at low temperature (at -60°C) afforded annulated iminoaziridine **40** as a mixture of (*E*)- and (*Z*)-isomers. These two geometric isomers equilibrated at higher temperature (20°C). Upon heating of the mixture of (*E*)-**40** and (*Z*)-**40**, a thermal cycloreversion took place with methyl isocyanide elimination to afford the dihydropyrrole **41**.



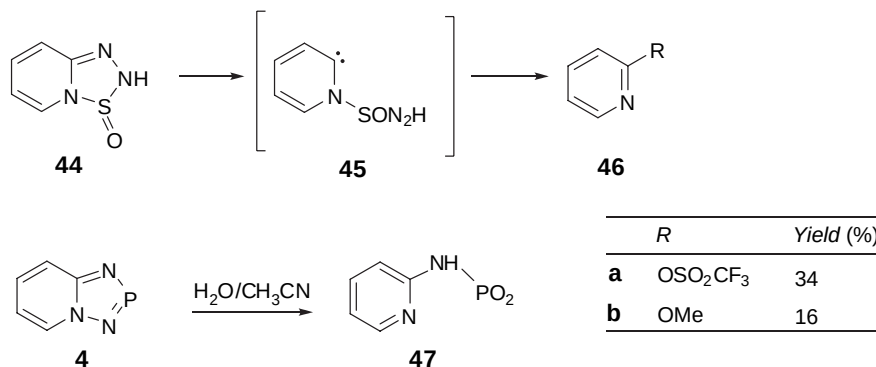
Scheme 11

Transformation of some dinitroaminotetrazolo[1,5-*a*]pyridines to benzofuroxanes has been reported by a German team <1995JHC585> (Scheme 12). Tetrazole **11** when refluxed in benzene for 90 min gave the pyridofuroxane derivative **43** in high yield. The reaction proceeds obviously through the azide compound **42** which yields a nitrene upon heating and, then, attachment of the nitrene to the nitro oxygen atom gives rise to formation of the product **43**. The finding proved to be in accordance with earlier similar observations discussed in CHEC-II(1996) <1996CHEC-II(8)411>.

Little information has appeared on derivatives of [1,2,3,5]thiatriazolopyridines as mentioned also in CHEC-II(1996) <1996CHEC-II(8)405>. In a recent study, the thermal decomposition of the sulfoxide derivative **44** in methanol in the presence of sodium triflate was investigated <1996JFC161> (Scheme 13). After a prolonged reflux, two products: 2-pyridyl triflate **46a** and 2-methoxypyridine **46b**, was isolated in 34% and 16% yields, respectively. The authors concluded that the first step of this transformation is a thermal ring opening of **45** to a carbene intermediate.



Scheme 12



Scheme 13

The recently synthesized phosphatriazolo[1,5-*a*]pyridines **4** can also participate in reactions involving the ring opening of the five-membered ring <1995ZNB558>. When the unsubstituted phospho-heterocycle is treated with aqueous acetonitrile, a hydrolysis occurs and the open-chained phosphenic amide **47** can be obtained in acceptable yield (Scheme 13).

The fact that tetrazolo[1,5-*a*]pyridine reacts with phosphines – via ring opening to the valence bond isomer azide – to give a phosphorane has been long recognized. Some novel applications of this transformation have been published during the recent period. The fused tetrazoles subjected to this reaction, the resulting phosphoranes, and the literature sources are summarized in Table 4.

11.15.5.4 Participation in Cyclization Reactions

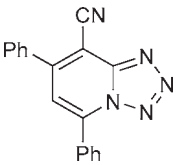
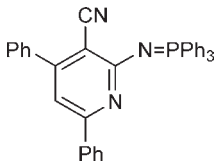
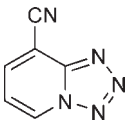
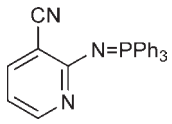
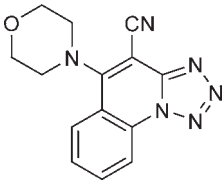
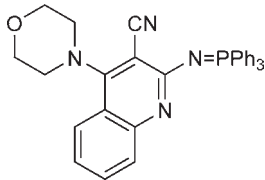
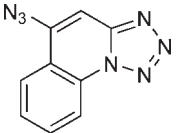
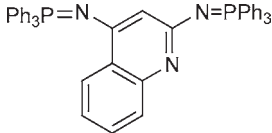
As mentioned already in CHEC-II(1996) <1996CHEC-II(8)411>, some tetrazolo[1,5-*a*]pyridines can react with their C(5)–C(6) and C(7)–C(8) double bonds as dienophiles in Diels–Alder reactions. A novel study again supported this recognition: Goumont *et al.* described that 6,8-dinitrotetrazolo[1,5-*a*]pyridine **11** easily react with some 2,3-disubstituted butadienes to give bis-cycloadducts **48** <2002T3249>. These products when treated with potassium *t*-butoxide undergo base catalyzed elimination of nitric acid followed by oxidation reaction to yield the fully aromatic tetracyclic compounds **49** (Scheme 14).

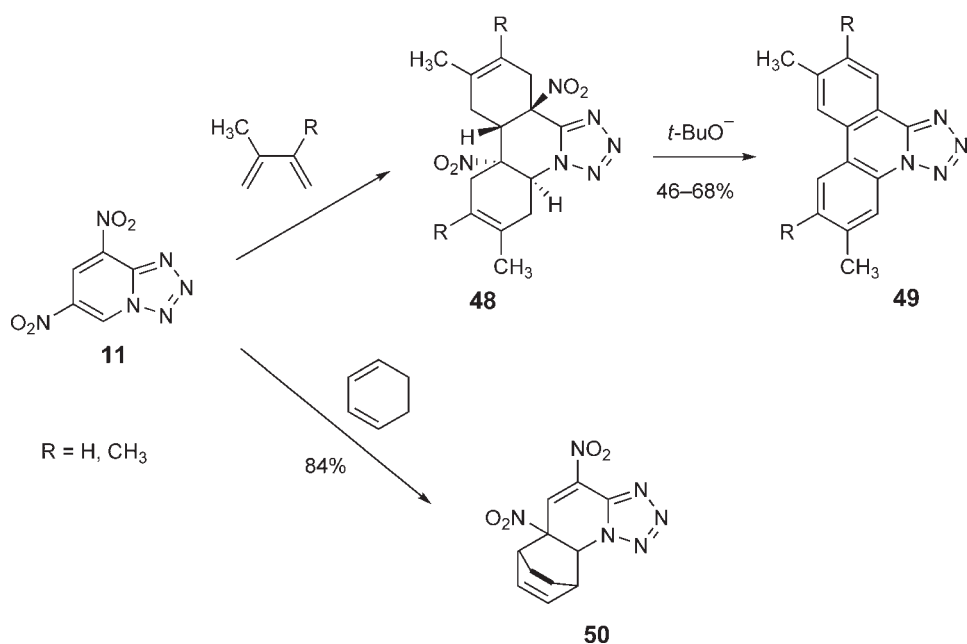
The same authors found quite recently that the tetrazole compound **11** when reacted with 1,2-dihydrobenzene, the monocycloadduct **50** as a racemate is formed in high yield (84%) <2005TL8363>.

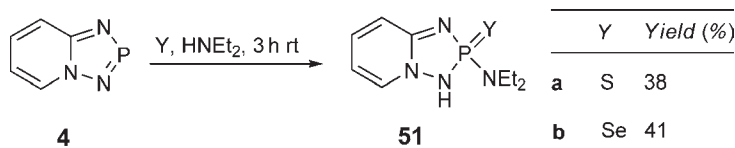
11.15.5.5 Addition Reactions on Ring-Phosphorus Atom

Bansal *et al.* found that the recently synthesized phosphatriazolo[1,5-*a*]pyridines can undergo addition reaction on the phosphorus atom when treated with sulfur or selenium in the presence of a secondary amine <1995ZNB558> (Scheme 15). Thus, reaction of **4** with these reagents yields under mild conditions the sulfur- or selenium containing addition products **51a** and **51b** in fair yield.

Table 4 Synthesis of some phosphoranes from tetrazolo[1,5-*a*]pyridines and its benzologues

Starting tetrazole	Product	Yield (%)	Reference
		78	<1994PHA322>
		90	<1994JHC1503>
		96	<1994BSF279>
		81	<1994JPR311>

**Scheme 14**



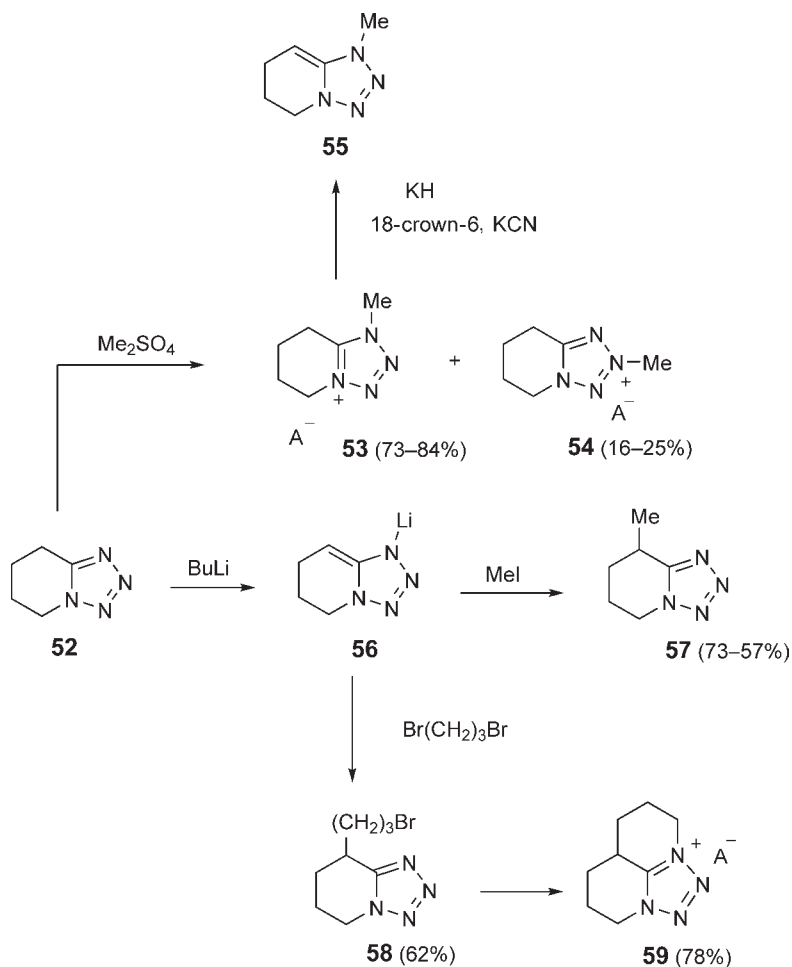
Scheme 15

11.15.6 Reactivity of Nonconjugated Rings

Fairly limited amounts of novel information on the reactivity of partially conjugated tetrazolo[1,5-*a*]pyridines was published during the recent period, and all by Quast *et al.* <1997LA671, 1998EJO317>. The most important aspects of the results are shown in Scheme 16.

5,6,7,8-Tetrahydrotetrazolo[1,5-*a*]pyridine **52** was reacted with dimethyl sulfate to give a mixture of quaternary salts: 1-methyl **53** and 2-methyl compounds **54** from which the 1-alkyl compound was separated as a crystalline hexafluorophosphate salt **53** (A = PF₆) in good yield. This salt when treated with potassium hydride in the presence of 18-crown-6 and KCN underwent deprotonation to give the saturated six-membered ring **55**.

5,6,7,8-Tetrahydro[1,5-*a*]pyridine **52** was also subjected to lithiation by reaction with butyllithium and gave the 1-lithio derivative **56**. This compound when treated with methyl iodide afforded the 4-methyl derivative **57**. Further interesting transformations of **56** have also been carried out: reaction with 1,3-dibromopropane gave first the

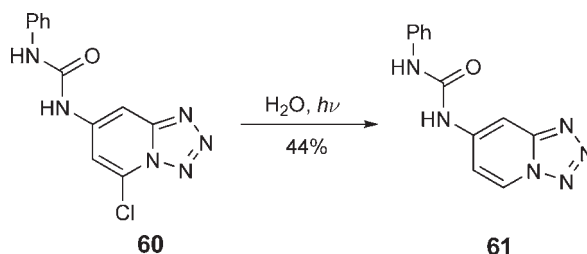


Scheme 16

4-bromoalkyl compound **58** which underwent intramolecular nucleophilic substitution at the alkyl chain and gave the peri-fused tetracyclic quaternary product **59**.

11.15.7 Reactivity of Substituents Attached to Ring Carbon Atoms

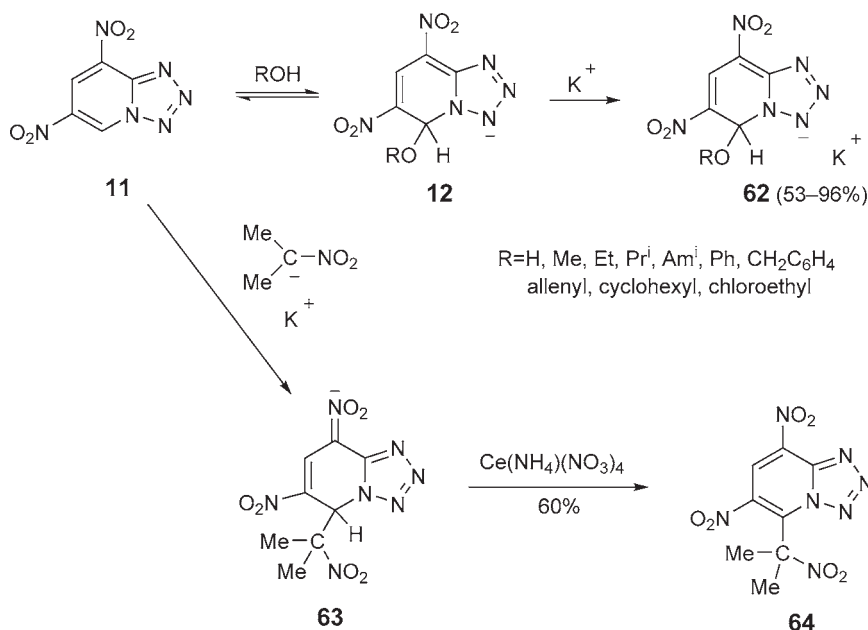
A photolytic reduction of the 5-chloro-substituted tetrazolo[1,5-*a*]pyridine derivative **60** was observed by Dias *et al.* <1996JHC1035> (Scheme 17). These authors found that the photolysis of the starting compound **60** when carried out with unfiltered light followed an unusual pathway: instead of a ring-enlargement reaction experienced with use of Pyrex filter in many cases, a photolytic reduction takes place in 44% yield, and the chlorine substituent is replaced by a hydrogen atom to afford a 5-H product **61** (Scheme 17).



Scheme 17

As discussed in Section 11.15.4 on thermodynamic aspects, dinitrotetrazolo[1,5-*a*]pyridines **11** are electrophiles and can react with nucleophilic species in addition reactions as shown in Scheme 18 <1994IZV1278, 2003OBC2764>. In the presence of alcohols on addition of the alcoholate anion in position 5 of tetrazolo[1,5-*a*]pyridine takes place. The primary addition product **12** formed in an equilibrium was characterized by its ¹H NMR spectrum and can be isolated in the form of potassium salts **62** in good to high yields 53–96% <1994IZV1278>.

Goumont *et al.* exploited this kind of reactivity for the nucleophilic substitution of the hydrogen atom in position 5 by carbon nucleophiles <2003OBC2192> (Scheme 18). These authors reported that 6,8-dinitrotetrazolo[1,5-*a*]pyridine **11** easily reacts with potassium nitropropenide to yield an adduct similar to those obtained with alcohols **12**. This adduct when oxidized by cerium ammonium nitrate yields the nitroalkyl-substituted aromatic compound **64**.

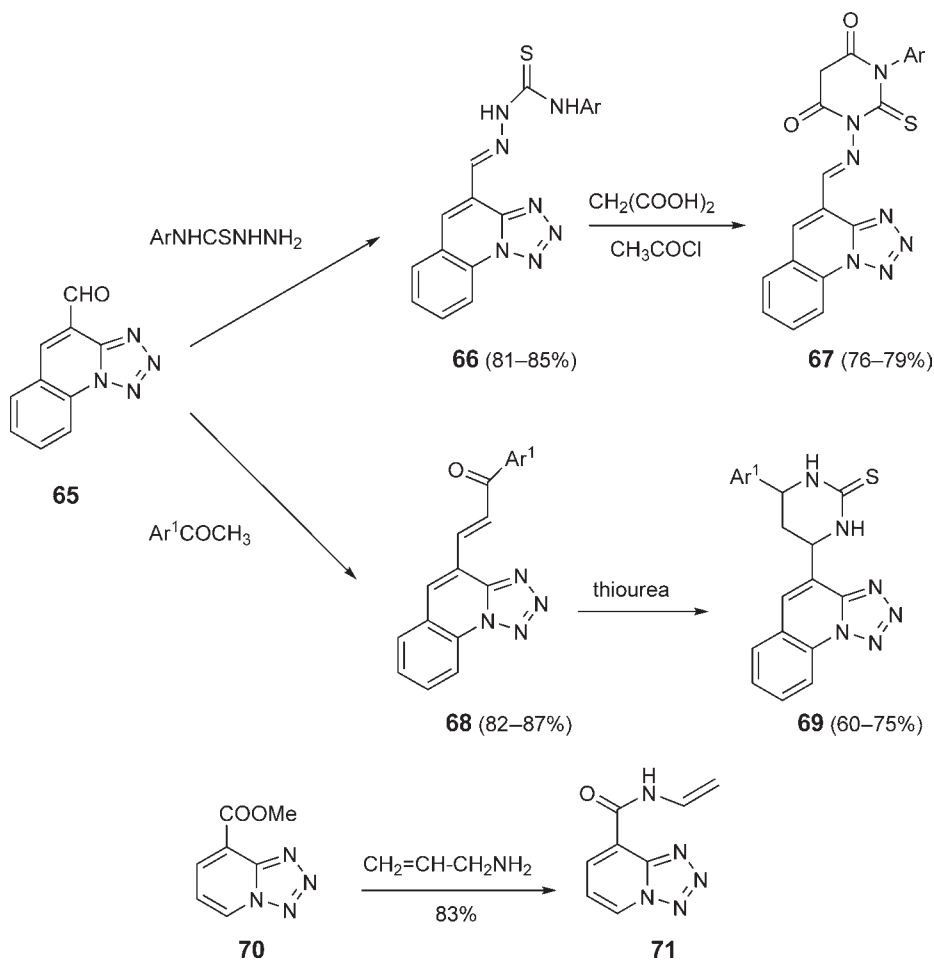


Scheme 18

Some more or less routine transformations with side chains of tetrazolo[1,5-*a*]pyridine or its benzologue have also been published during the recent period, and these results are shown in **Scheme 19**.

As part of an Egyptian–Korean cooperation, 4-formyltetrazolo[1,5-*a*]quinoline **65** was subjected to various transformations of the formyl group to afford cyclization reactions in this side chain <2004EJM249>. Thus, reaction with thiosemicarbazide gave the thiosemicarbazone **66** which was treated with malonic acid and acetyl chloride to give a new six-membered heterocycle on the side chain **67**. The same aldehyde **65** was also subjected to condensation reaction with acetophenones to give 1,2-unsaturated ketones **68** which reacted with thiourea to give a partially saturated pyrimidine-thione **69**.

Based on earlier experiences ring opening of the pyridine moiety in methyl 4-tetrazolo[1,5-*a*]pyridine carboxylate **70** on reaction with allylamine was predicted by Okawa *et al.* <1997T16061> (**Scheme 19**). Instead of the expected major structural change, however, a routine aminolysis was found to yield the allylamide **71**.



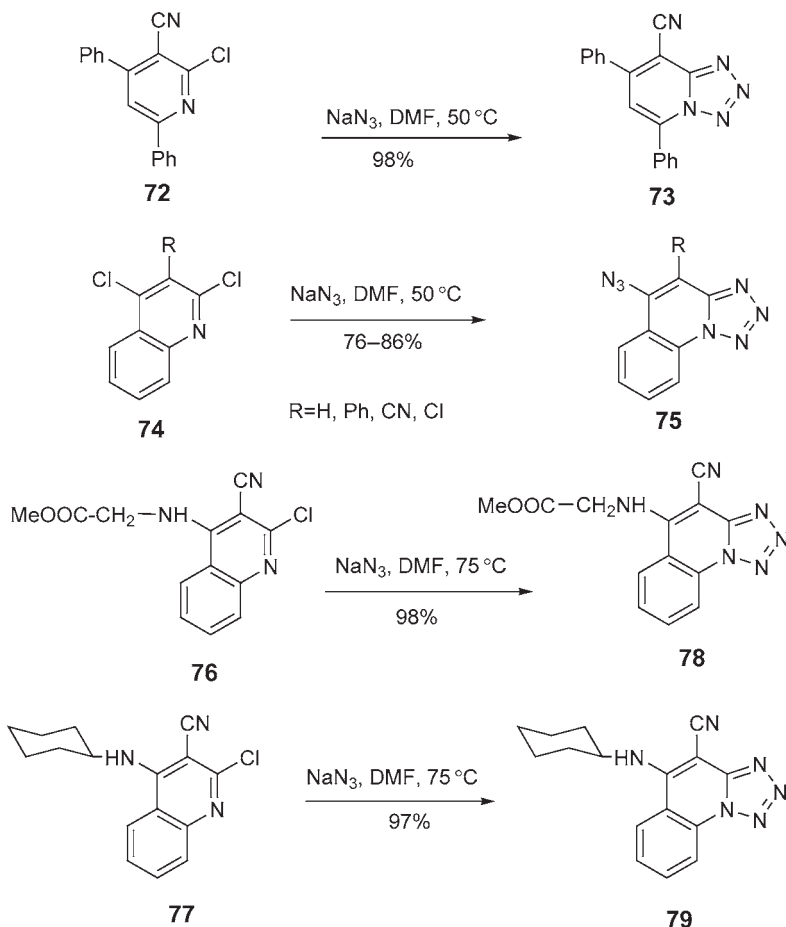
Scheme 19

11.15.8 Ring Synthesis

11.15.8.1 Ring Synthesis of Fused Tetrazoles

11.15.8.1.1 Ring synthesis involving formation of the tetrazole ring via azide–tetrazole equilibrium
As discussed in CHEC-II(1996) <1996CHEC-II(8)412>, the most widely established synthetic pathway to fused tetrazoles involves the synthesis of a 2-azidoazine participating in the equilibrium with the fused tetrazole. This equilibrium is – in most cases – shifted to the tetrazole form. The easiest way to the 2-azides is either a nucleophilic

exchange of a halogen atom in this position by azide anion or treatment of a 2-hydrazino compound by nitrous acid. Numerous applications of these well-established approaches have appeared during the past decade, and these are summarized in the following **Scheme 20**.

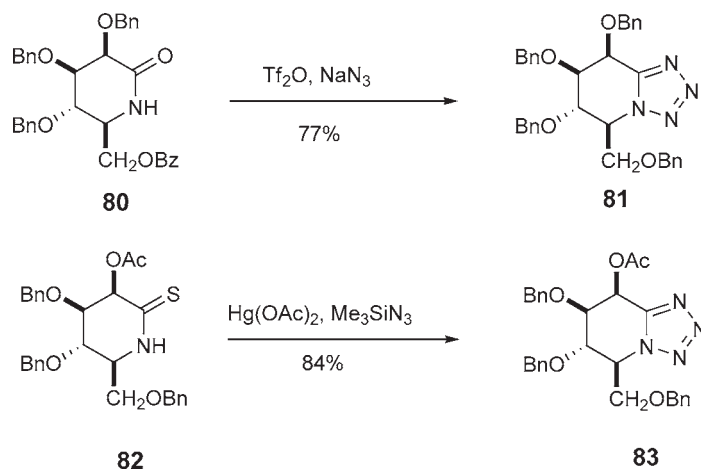


Scheme 20

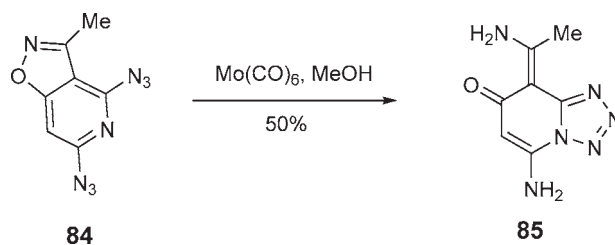
In all the four cases shown in **Scheme 20** the azido group in the desired positions have been introduced by reaction of sodium azide and 2-chloroheterocycles to give the appropriate tetrazoles in high yields. Thus, chloropyridine derivative **72** gave a tetrazolo[1,5-*a*]pyridine compound **73** <1994PHA322>. Reaction of the 2,4-dichloroquinoline derivative **74** with sodium azide yielded a tetrazolo[1,5-*a*]quinoline derivative **75** bearing an azido moiety in position 4 <1994JPR311>. Also, the 4-amino-substituted 2-chloroquinolines **76**, **77** reacted similarly and afforded the corresponding fused tetrazoles **78** and **79**, respectively <2000S2078, 2001S97>.

The same principle was also applied with the synthesis of partially saturated ring systems as shown in **Scheme 21**. Vasella *et al.* reported that some manno lactams **80** can be transformed to the appropriate 5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridines **81** by treatment with triflic anhydride followed by sodium azide <1999SC551>. The product was obtained in high yield (77%). Similarly, reaction of mannothiolactam **82** with mercury(II) acetate and, subsequently, with trimethylsilylazide gave rise to the fused tetrazole **83** also in high yield (84%) yield <2000HCA513>. Other studies by the same research group on related ring systems also appeared <1995HCA514, 1996HCA2190>.

Scheme 22 illustrates a special application of the azide-tetrazole ring closure described by Ponticelli *et al.* <2004JHC761>. The diazido compound **84** exists as an azide valence bond isomer. When this compound, however, is subjected to reduction by molybdenum hexacarbonyl, one azido group undergoes reduction selectively to an



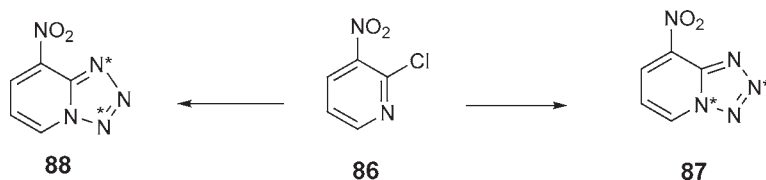
Scheme 21



Scheme 22

amine, the isoxazole moiety is simultaneously also reduced to an open chain form, and because of the new substitution pattern of the pyridine ring, the remaining azide group undergoes ring closure to the tetrazolo[1,5-*a*]pyridine derivative **85**.

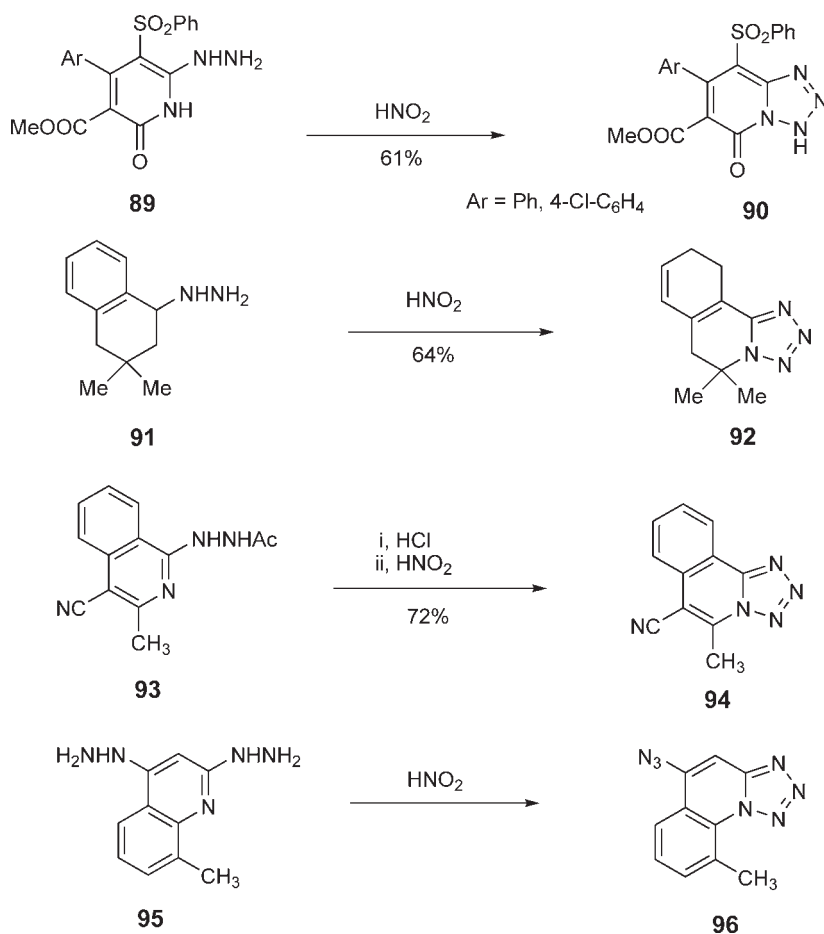
A special, isotope-labeled case of the azide–tetrazole equilibrium was studied by Cmoch *et al.* [<2000JPO480>](#), and the results are shown in [Scheme 23](#). 2-Chloro-3-nitropyridine **86** was treated with potassium azide containing a doubly labeled (¹⁵NN¹⁵N) azide anion. The authors detected formation of two differently labeled tetrazolopyridines: the 2,4- **87** and the 1,3-labeled **88** derivatives.



Scheme 23

Reaction of hydrazinoazines with nitric acid has also proved to be suitable route to form azido moieties to complement the nucleophilic exchange reaction of a halide for an azide. This approach has also been applied recently for the synthesis of fused tetrazoles, and these transformations are shown in [Scheme 24](#).

Thus, the 2-hydrazinopyridone compound **89** was transformed to the corresponding fused tetrazolo[1,5-*a*]pyridine **90** in 61% yield [<2000J\(P1\)3686>](#), and the partially saturated 1-hydrazinoisoquinoline compound **91** when reacted with nitric acid gave the appropriate tetrazole **92** in 64% yield [<1994KGS511>](#). In the case of the acylhydrazino isoquinoline derivative **93**, a deprotection of the hydrazine group was carried out first followed by treatment with



Scheme 24

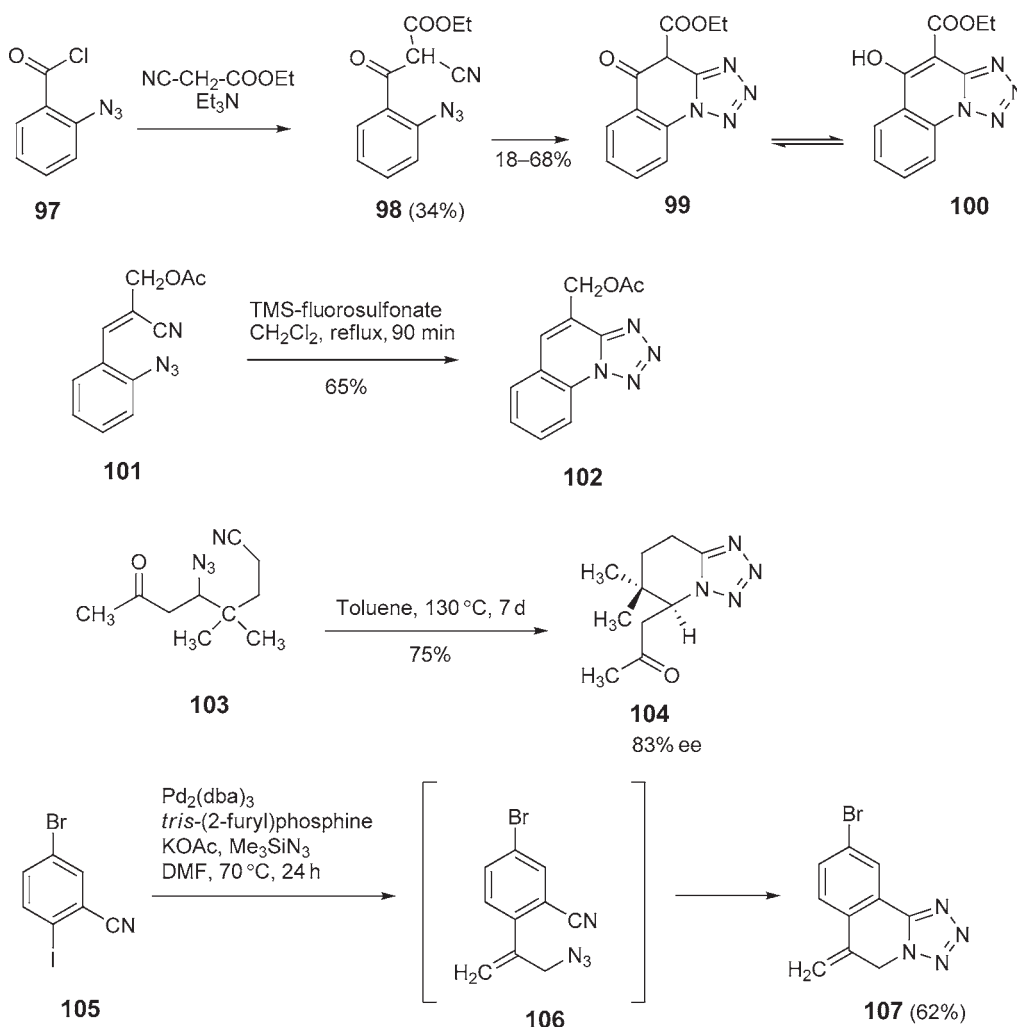
nitric acid to form 5-methyl-6-cyanotetrazolo[1,5-*a*]quinoline **94** in 72% yield [\[2004JHC549\]](#). In the case of the quinoline derivative **95**, a similar transformation has been described: one of the hydrazine groups was reacted to yield the tetrazole and; simultaneously, the other hydrazine substituent was also transferred to an azide to form 5-azidotetrazolo[1,5-*a*]quinoline **96** [\[2000MOL1224\]](#).

11.15.8.1.2 Ring synthesis including formation of the tetrazole ring by intramolecular 1,3-dipolar cycloadditions

1,3-Dipolar cycloaddition between azides and nitriles is also a well-established route to tetrazoles. If these two functional groups are closely located within one molecule, intramolecular cyclization can occur to yield fused tetrazoles. The present survey of the recent literature shows that this approach has also been successfully applied in some cases and led to the synthesis of novel ring systems belonging to this chapter. These results are depicted in [Scheme 25](#).

Smalley *et al.* reported the synthesis of the cyano-containing keto ester **98** by reaction of *o*-azidobenzoyl chloride **97** with cyanoacetic ester in the presence of triethylamine. This keto ester was then heated in acetonitrile for 30 min and gave the ring closed product **99** which was isolated in the fully aromatic tautomeric form **100** [\[1997S773\]](#). A similar approach to tetrazolo[1,5-*a*]quinolines has been applied by a Korean research group: in this case a reflux of the cyano-azido compound **101** for a longer period was needed in order to accomplish the cyclization to 4-acetoxymethyl-tetrazolo[1,5-*a*]quinoline **102** [\[2003JHC1103\]](#).

The enantiomerically pure open-chained cyano-azido compound **103** also underwent cyclization to the tetrahydrotetrazolo[1,5-*a*]pyridine derivative **104** when heated in a toluene solution at 130 °C for 7 days. The reaction was found to proceed in 75% yield and with an enantiomeric excess of 83% [\[2005JA1313\]](#).



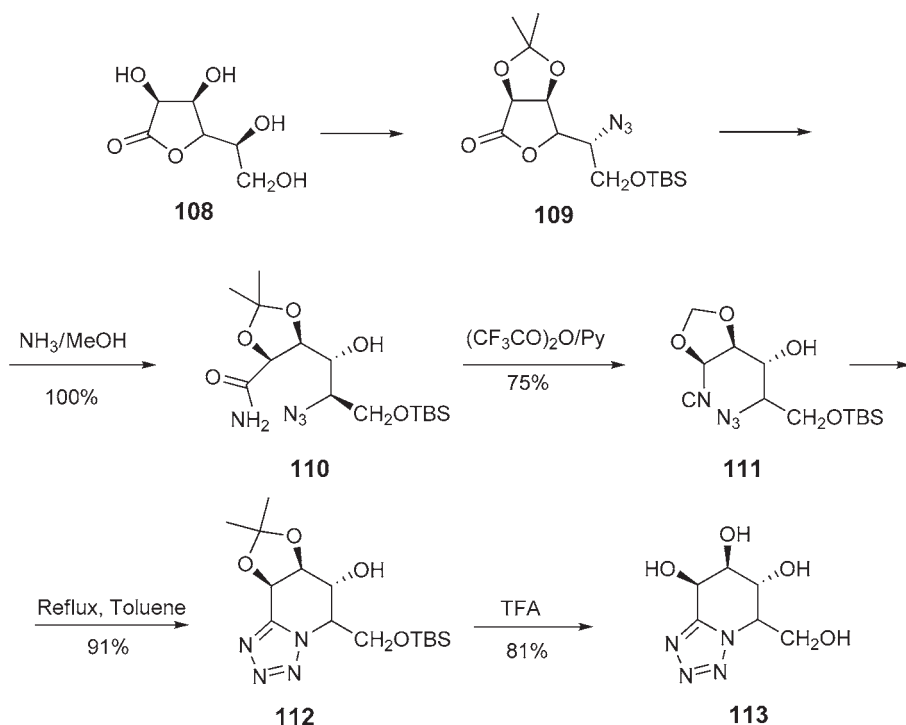
Scheme 25

An interesting palladium-catalyzed allene/azide incorporation and intramolecular 1,3-dipolar cycloaddition cascade to tetrazolo[5,1-*a*]isoquinoline has been published by Grigg *et al.* <2005TL5899>. In the first step of the events, 3-bromo-6-iodobenzonitrile **105** was reacted with the allene/trimethylsilylazide system in the presence of palladium(0) catalyst to yield a coupling product **106** which under the reaction conditions applied (DMF, 70°C for 24 h) gave **107**.

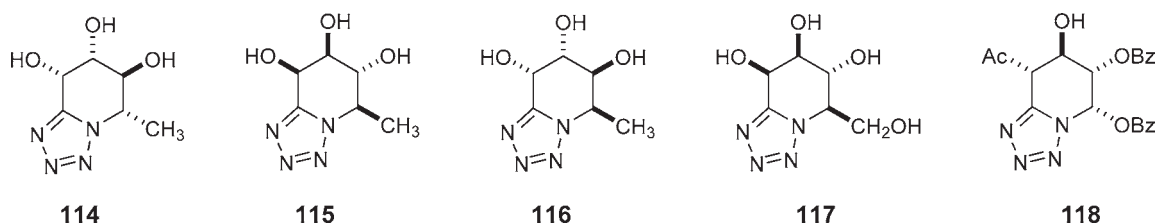
A substantial amount of research has been carried out in the field of tetrazole-fused sugars (rhamnose, mannose, and glucose derivatives) – mostly because of the biological importance of these derivatives. In many of these cases synthesis of the fused tetrazole moieties has been perfected by intramolecular 1,3-cycloaddition reactions with participation of a cyano and azido group. Some of these results are shown in Schemes 26 and 27.

Scheme 26 depicts a representative synthetic pathway to a mannopyranotetrazole **113** described by Davis *et al.* <1995TL7511, 1999T4489>. The synthesis was started from the L-gulonolactone **108** which was converted to an azide **109** with simultaneous protection of the remaining hydroxy groups. This compound **109** was then treated with ammonia to result in a ring opening of the furan ring to **110**. In the next step the amido function of this intermediate was converted into a nitrile function: intermediate **111** was formed containing the azide and nitrile functions in proper vicinity to allow the ring closure to the desired tetrazole **112** which was accomplished in refluxing toluene in high yield. Finally, removal of the protecting groups by TFA yielded the free mannottetrazole **113**.

A great number of related tetrazolo sugars have been obtained by a similar synthetic strategy, and these structures are shown in Scheme 27. Thus, the D-rhamnotetrazole **114** and its L-enantiomer **115** <1999T4489>, the epimeric



Scheme 26



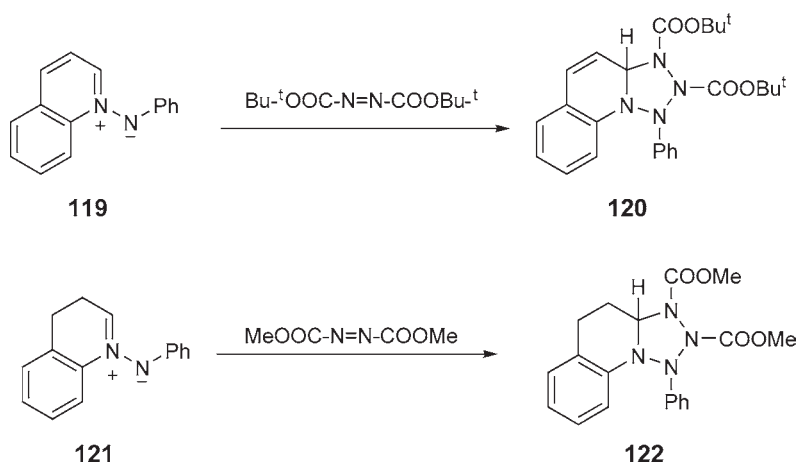
Scheme 27

116 compound [\[1996TL8569, 1998TA2947\]](#), the mannotetrazole **117** [\[1995TL7511\]](#), as well as the protected mannotetrazole **118** [\[1995HCA514\]](#) have been synthesized and investigated.

Besides the numerous applications of 1,3-dipolar cyclizations to tetrazoles taking place between nitriles and azides, cycloaddition with a totally new atomic variation leading to the tetrazole ring has also been recently found. Huisgen *et al.* [\[1998EJO379\]](#) found in the course of their extended studies on isoquinolinium *N*-arylimides that these compounds can also react as 1,3-dipoles with azodicarboxylate esters as the dipolarophile. Thus, the red color of the solution of the phenylimide compound **119** in dichloromethane when treated with *t*-butyl azodicarboxylate disappeared and the cycloadduct **120** was isolated in the form of yellow cubes. When a solution of this product was heated, its color turned to red again indicating that the retrocyclization takes place at higher temperature. Similarly to this observation, the 3,4-dihydroisoquinolinium *N*-phenylimide **121** also underwent cycloaddition with dimethyl azodicarboxylate to yield the cycloadduct **122**. To the best of the knowledge of these authors, this compound is probably the first representative of a tetrazolidine ([Scheme 28](#)).

11.15.8.1.3 Ring synthesis involving ring closure of the pyridine ring

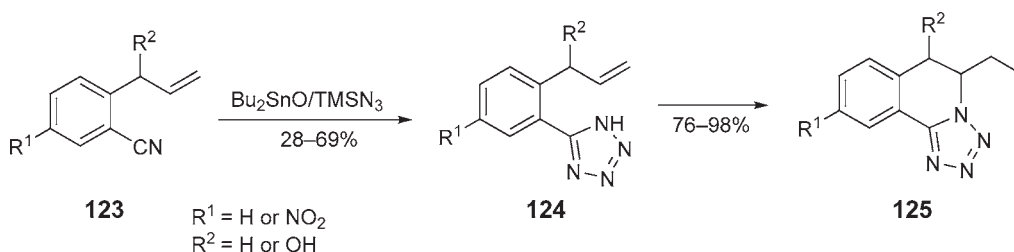
In contrast to the cyclization strategies where ring closure of the tetrazole part of tetrazolo[1,5-*a*]pyridines and benzologues has been carried out, much less attention has been paid to reaction pathways starting from appropriate



Scheme 28

tetrazole derivatives and cyclization of the pyridine moiety. In this section a few results based on this approach are summarized.

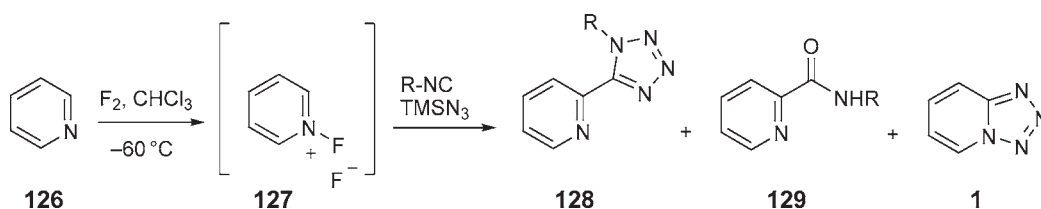
A novel methodology for cyclization to partially reduced tetrazolo[5,1-*a*]isoquinolines has been elaborated by Ek *et al.* <2003T6759> as shown in Scheme 29. The key step is the iodocyclization of an allylphenyltetrazole compound **124** – conveniently synthesized from the appropriate allyl-substituted benzonitrile **123** – under very mild conditions (iodine, acetonitrile solution, 0 °C, 3 h) to give the iodomethyl-substituted product **125**.



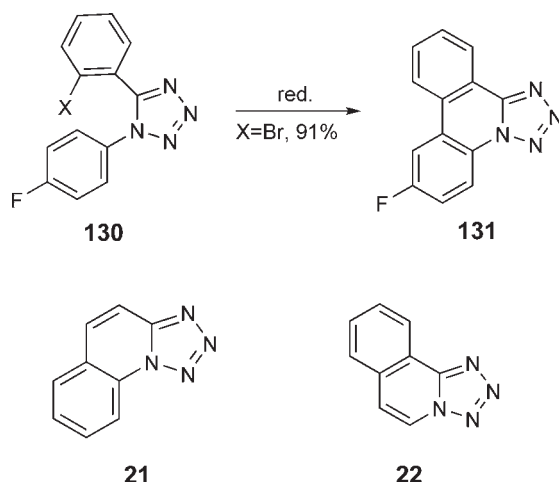
Scheme 29

In studying the reactivity of *N*-fluoropyridinium fluoride **127** obtained from pyridine **126** by treatment with fluorine gas in chloroform at low temperature (Scheme 30), Kiselyov studied reactions with isocyanides in the presence of trimethylsilylazide <2005TL4851>. A mixture of products was obtained in which, besides tetrazolylpyridine **128** and a nicotinamide derivative **129** also tetrazolo[1,5-*a*]pyridine **1** was obtained in very poor yield (5–10%).

A radical cyclization using electrochemical methods has been applied to fluorine-substituted tetrazolo[1,5-*a*]phenantiridines **131** as described by Grimshaw *et al.* <1994CC2171> and shown in Scheme 31. These authors found that the 1,5-diaryltetrazole **130** bearing an *ortho* halogen atom on the 5-phenyl ring, undergo reductive cyclization to



Scheme 30

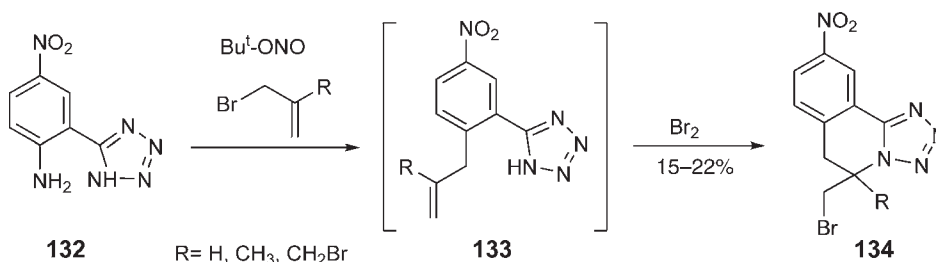


Scheme 31

the tetracyclic product when subjected to electrochemical reduction (Scheme 31). As a cathode, mercury, cadmium, zinc, and mild steel were used, whereas the halogen atom was chlorine, bromine, and iodine. Yields were moderate to excellent (50–91%), and the best result (91%) was obtained with reduction of the bromo compound on mild steel. Besides the heteroaromatic product **131**, some partially reduced dihydro compounds have also been formed. The benzologous tetrazolo[1,5-*a*]quinoline **21** and tetrazolo[5,1-*a*]isoquinoline **22** have also been obtained from unsubstituted isoquinoline and quinoline, respectively, in low yields (14% and 19%).

The same chemical transformation was also realized later by radical reaction using tributyltin hydride and azoisobutyronitrile <1999ACS913>, although the yield was moderate and the ratio of the reduced by-products was much higher (45%).

In the course of studies on diazotizative allylation reactions (called ‘DiazAll reactions’) Frejd *et al.* found an interesting route to 5,6-dihydrotetrazolo[5,1-*a*]isoquinolines starting from aniline-substituted tetrazoles <2003JOC1911>. These authors found that 5-(2-[4-nitroanilino])tetrazole **132** when treated with some 3-bromoprop-1-ene derivatives yielded the corresponding tricyclic fused tetrazole **134** in rather poor yields. An interesting feature of this conversion is that during the formation of the intermediate **133** elemental bromine is formed which again enters into reaction with this intermediate and leads to the oxidative cyclization (in a process similar to bromolactonization) to the final product **134** (Scheme 32).

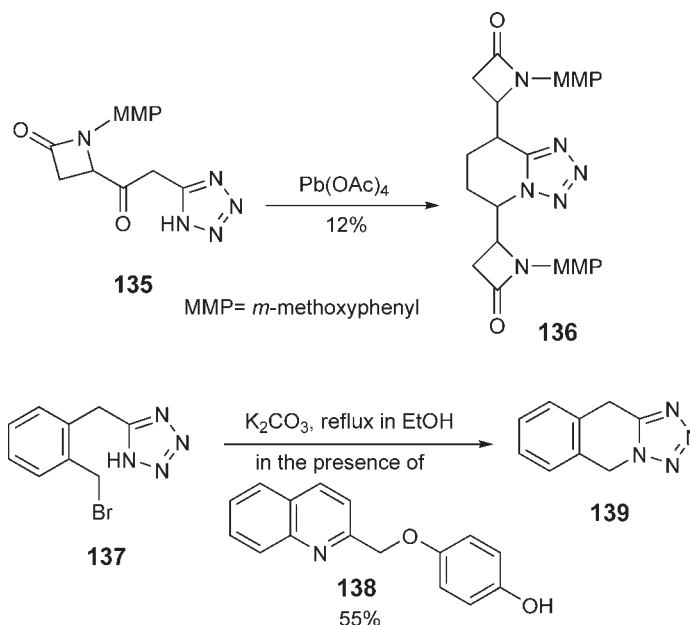


Scheme 32

A Hungarian research group observed a nonexpected formation of a tetrazolo[1,5-*a*]derivative <2001J(P1)1131>. These authors found that treatment of the β -lactam-substituted tetrazolylmethyl ketone **135** with lead tetraacetate results in a ring closure to pyridine ring fused to tetrazole, and product **136** was formed as a mixture of diastereomers in low yield (Scheme 33).

Another unexpected ring closure implying cyclization to a fused pyridine moiety was found by Sledeski *et al.* <1997TL1129>, and the result is shown in Scheme 33. These authors studied a series of transformations of the

phenyl ether **138** and found that reaction of the tetrazolyl derivative **137** in the presence of **138** under basic conditions (50 °C in ethanol in the presence of potassium carbonate) does not yield any coupling product as expected, but, instead, an intermolecular cyclization of **137** occurs and the linearly fused 5,10-dihydro-tetrazolo[1,5-*b*]isoquinoline **139** is formed in 55% yield.



Scheme 33

11.15.8.1.4 Miscellaneous ring closures to fused tetrazoles

In this section three recently published studies will be referred to which would have been difficult to categorize in any of the above classifications. The chemical transformations carried out are shown in **Scheme 34**.

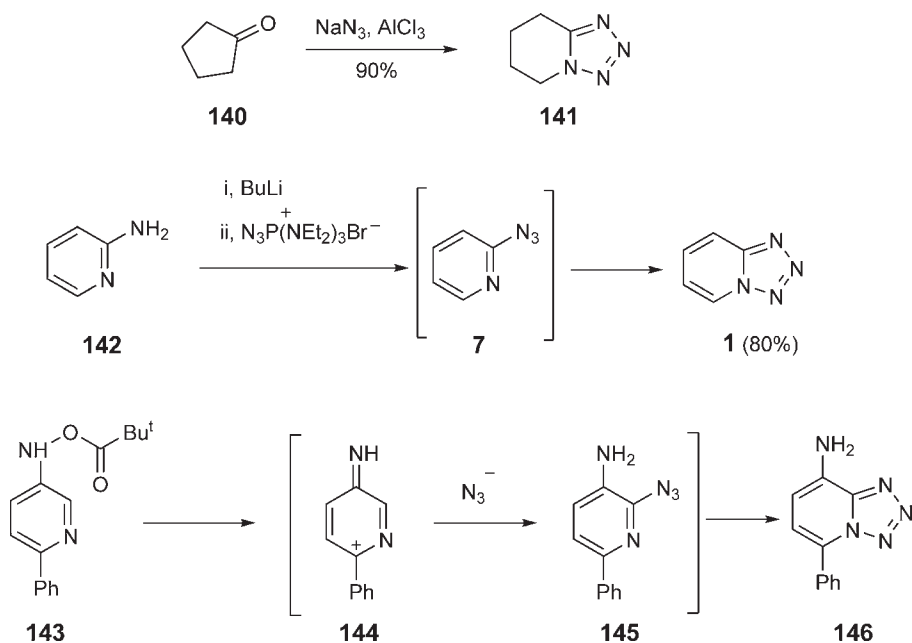
Reaction of cyclopentanone **140** with sodium azide in the presence of a Lewis acid to give 5,6,7,8-tetrahydro[1,5-*a*]pyridine **141** has already been reviewed in CHEC-II(1996) <1996CHEC-II(8)414>. In a recent paper of Eshgi *et al.* <2005SC1115> it has been reported that the yield of this transformation can be dramatically improved by using aluminium trichloride instead of titanium tetrachloride as a Lewis acid. The new reaction conditions allow the synthesis of the product within 10 min in 90% yield. This method also allowed the synthesis of tetrazoles fused to azacycloheptane, -cyclooctane, and -cyclononane rings in high yields (75–95%) <2005SC1115>.

Conversion of aromatic amines to azides was studied by Seechter *et al.* <2002TL8421> and these studies lead to the recognition of a new approach to tetrazolo[1,5-*a*]pyridine. Thus, reaction of 2-aminopyridine **142** with butyllithium followed by treatment with azidotris(diethylamino)phosphonium bromide gave rise to tetrazolo[1,5-*a*]pyridine **1** in 80% yield. The first intermediate is obviously the azide **7**.

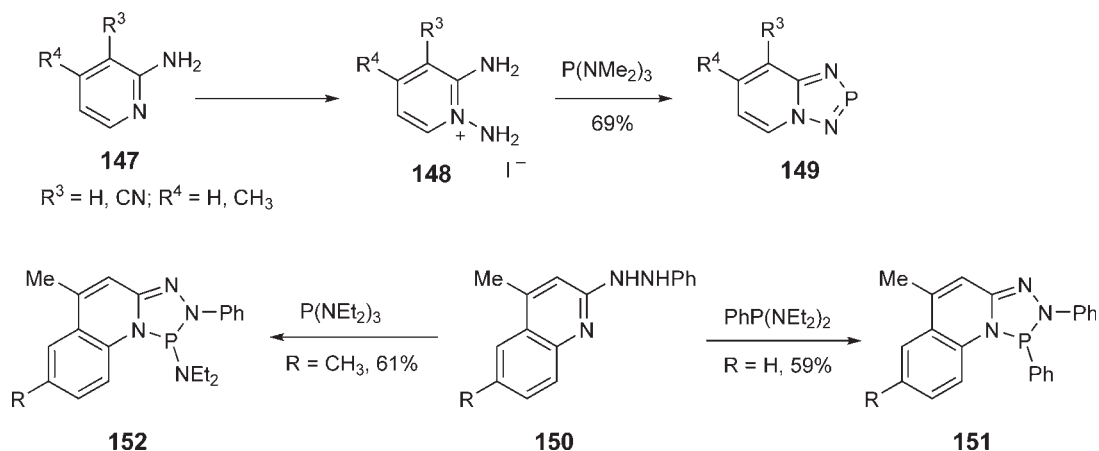
Novak *et al.* <1998JA1643> devised a novel approach to amino-substituted tetrazolo[1,5-*a*]pyridine which provides a really unique pathway (**Scheme 34**). These authors studied the possibility of formation of nitrenium ions from the pivaloylhydroxylamine **143** and found that if azide anion is present in the main reaction route is the formation of tetrazolo[1,5-*a*]pyridine **146**. The authors concluded that the first intermediate is the formation of the carbonium cation **144** which captures the azide anion to yield 2-azidopyridine **145**, that is, the valence bond isomer of the product **146**.

11.15.8.2 Ring Synthesis of Fused Triazaphospholes

Two types of phosphorus-containing five-membered heterocycles – both entirely new and not referred to in CHEC-II(1996) – have been synthesized during the past years. These syntheses are summarized in **Scheme 35**.



Scheme 34



Scheme 35

Studies on the synthesis of [1,2,4,3]triazaphospholo[1,5-*a*]pyridines have been reported by Schmidpeter *et al.* <1993JPR458, 1994PS381, 1995ZNB558>. The reaction pathway starts from 2-aminopyridine **147** which is first subjected to an N -amination reaction to give 1,2-diaminopyridinium iodide **148**, and this compound is treated with tris(dimethylamino)phosphine to yield the five-membered phosphorus-containing heterocycle **149**.

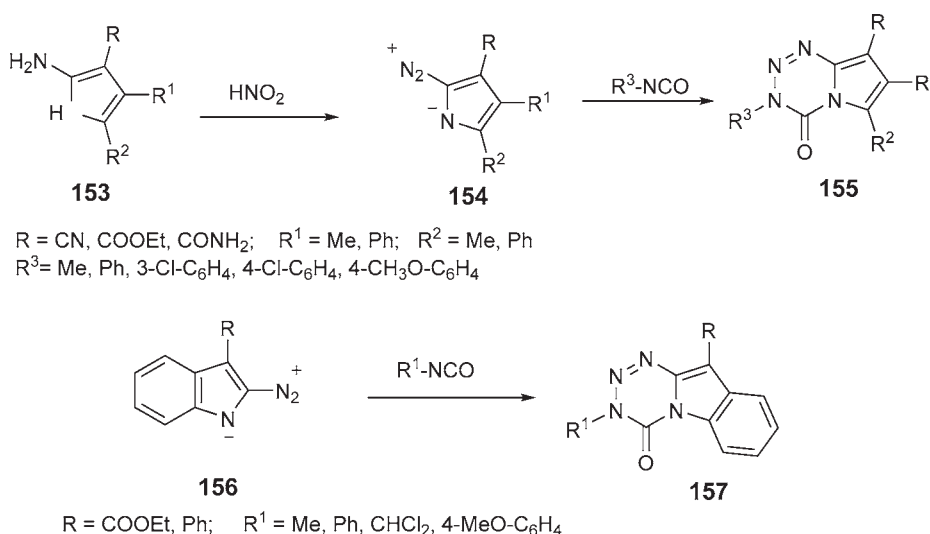
Also triazaphospholes but with another arrangement of the heteroatoms fused to quinoline have been synthesized by a Russian team <1998ZOB1576>. These authors described that N -(2-quinolyl)- N' -phenylhydrazines when reacted with appropriate phosphorus-containing reagents give rise to new fused triazaphospholes. Thus, reaction of the methylquinolylhydrazine **150** ($\text{R} = \text{H}$) with phenylphosphorus acid bis-diethylamide gave rise to 1,2-diphenyl-1,2-dihydro[1,2,4,3]triazaphospholo[4,5-*a*]quinoline **151**, whereas the dimethylquinoline derivative **155** ($\text{R} = \text{CH}_3$) when reacted with phosphorus acid tris-diethyldiamide methyl ester yielded 1-diethylamino-2-phenyl-1,2-dihydro[1,2,4,3]triazaphospholo[4,5-*a*]quinoline **152**. Both conversions have been described to proceed in boiling benzene in good yield (59–61%).

11.15.8.3 Ring Synthesis of Pyrrolotetrazines

The only ring system with a 0:3 nitrogen atom arrangement that has been studied in the past period is pyrrolo[2,1-*d*][1,2,3,5]tetrazine, which was not synthesized earlier. The first synthesis was presented by Cirrincione *et al.* in two successive publications <1999S2082, 2003BMC2371>. The results are depicted in **Scheme 36**.

The synthesis is started from a 2-aminopyrrole **153** which is first diazotized to an azine **154** formulated here by a dipolar valence bond structure in order to rationalize its further reactivity. This compound when reacted with an isocyanate undergoes ring closure to give the fused tetrazine **155** in good yield in most of the cases. Although with other related ring systems (e.g., aza-analogues-fused imidazoles) alternative synthetic routes have also been found (cf. Chapter 11.19) such efforts with the present ring system proved to be unsuccessful. From the increased rate of the reaction with dipolar solvents, the authors concluded that addition of the isocyanate proceeds by a two-step mechanism rather than in a synchronous reaction.

The same research group has also published the synthesis of the related benzologue <2005BMC295>. The synthesis of this tricyclic ring system **157** has been accomplished in analogous way: the indole-azine **156** was prepared first and was then reacted with isocyanates.

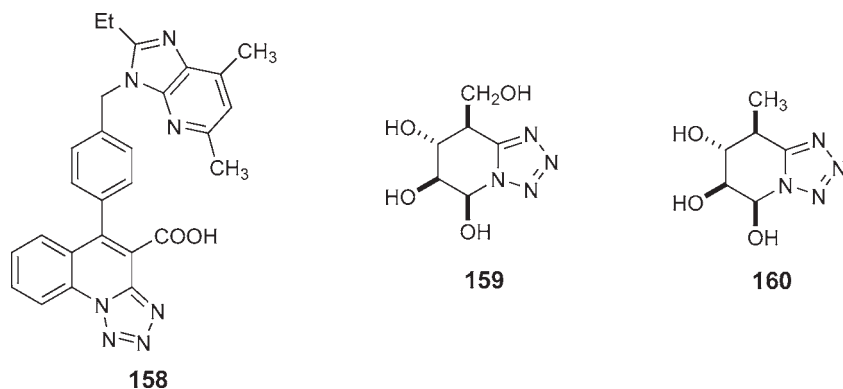


Scheme 36

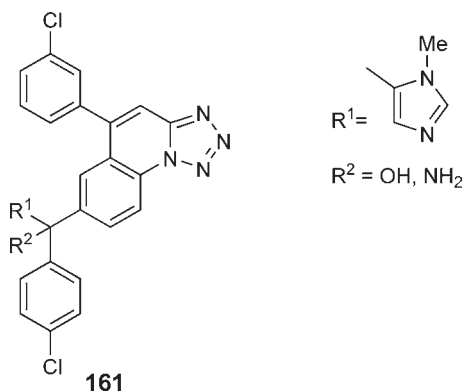
11.15.9 Important Compounds and Applications

Several biologically useful derivatives of ring systems belonging to this chapter have been found recently. The most important representatives are shown in **Scheme 37**. Thus, the tetrazolo[1,5-*a*]quinoline derivative **158** bearing an imidazopyridinylbenzyl side chain has been found to inhibit the angiotensin II-induced contraction in rabbit aortic strips <2004JMC2574>. Tetrazole derivatives of some carbohydrates turned out to be active inhibitors of glycosidases. In this respect, the mannotetrazole **159** and rhamnotetrazole **160** derivatives should be emphasized as described by Brandstetter *et al.* <1995TL7511, 1999T4489>. Upon measurement of a series of carbohydrate-based tetrazole derivatives these authors came to the conclusion that, in contrast to the glycosidase-inhibitory activity of some pyranoses, furanotetrazoles have no effect on any glycosidase.

Angibaud *et al.* carried out thorough studies on the farnesyl protein transferase inhibitory activity of substituted azoloquinolines <2003BML4365>. These authors found that some tetrazolo[1,5-*a*]quinolines **161** (**Scheme 38**) are promising agents for oral *in vivo* inhibition.



Scheme 37



Scheme 38

11.15.10 Further Developments

Two important transformations of tetrazolo[1,5-*a*]pyridine derivatives should be mentioned in this respect; both can be regarded as ring transformations. Thus, Chan and Faul described a general method for treatment of acid chloride derivatives of tetrazolo[1,5-*a*]pyridine by acid amides and triphenylphosphine to give pyrido[2,3-*d*]pyrimidines in medium to good yields (30–76%) [<2006TL3361>](#). Also a new ring transformation has recently been reported by a Hungarian group: reaction of 3-substituted tetrazolo[1,5-*a*]pyridinium salts with aryl isothiocyanates and isocyanates resulted in formation of new oxo- and thioxo[1,2,4]triazolo[1,5-*a*]pyridinium salts [<2006JOC7805>](#).

Recently a new synthetic pathway to tetrazolo[1,5-*a*]pyridine has been explored by Keith [<2006JOC9540>](#). According to this new procedure, pyridine *N*-oxides can be treated by sulfonyl or phosphoryl azide to furnish tetrazolo[1,5-*a*]pyridines in one reaction step in medium to good yields (30–100%).

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Biographical Sketch



György Hajós received his Ph.D. degree with Prof. A. Messmer at Eötvös University in Budapest in 1974. Since this time he has been working for the Chemical Research Center, Hungarian Academy of Sciences, first as a scientific investigator, later as head of Laboratory for Heterocyclic Chemistry and since 2005 he is director of the Institute of Biomolecular Chemistry. He spent 2 years in Germany with Prof. Günther Snatzke (1975 and 1985) as DFG- and Humboldt-fellow. In 1992 he acquired the Doctor of Science degree from the Hungarian Academy of Sciences. He made his Habilitation at Debrecen University in 1995 and he is appointed university professor at Debrecen University, University of Technology and Economics, as well as Eötvös University in Budapest. He has been awarded a Zemplén-prize by the Hungarian Academy of Sciences in 1996. His research interest implies synthetic heterocyclic chemistry, cyclization and ring-opening reactions, elaboration of selective procedures, synthesis of biologically active derivatives, semi-empirical rationalization of chemical transformations.



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11.17

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 1:2

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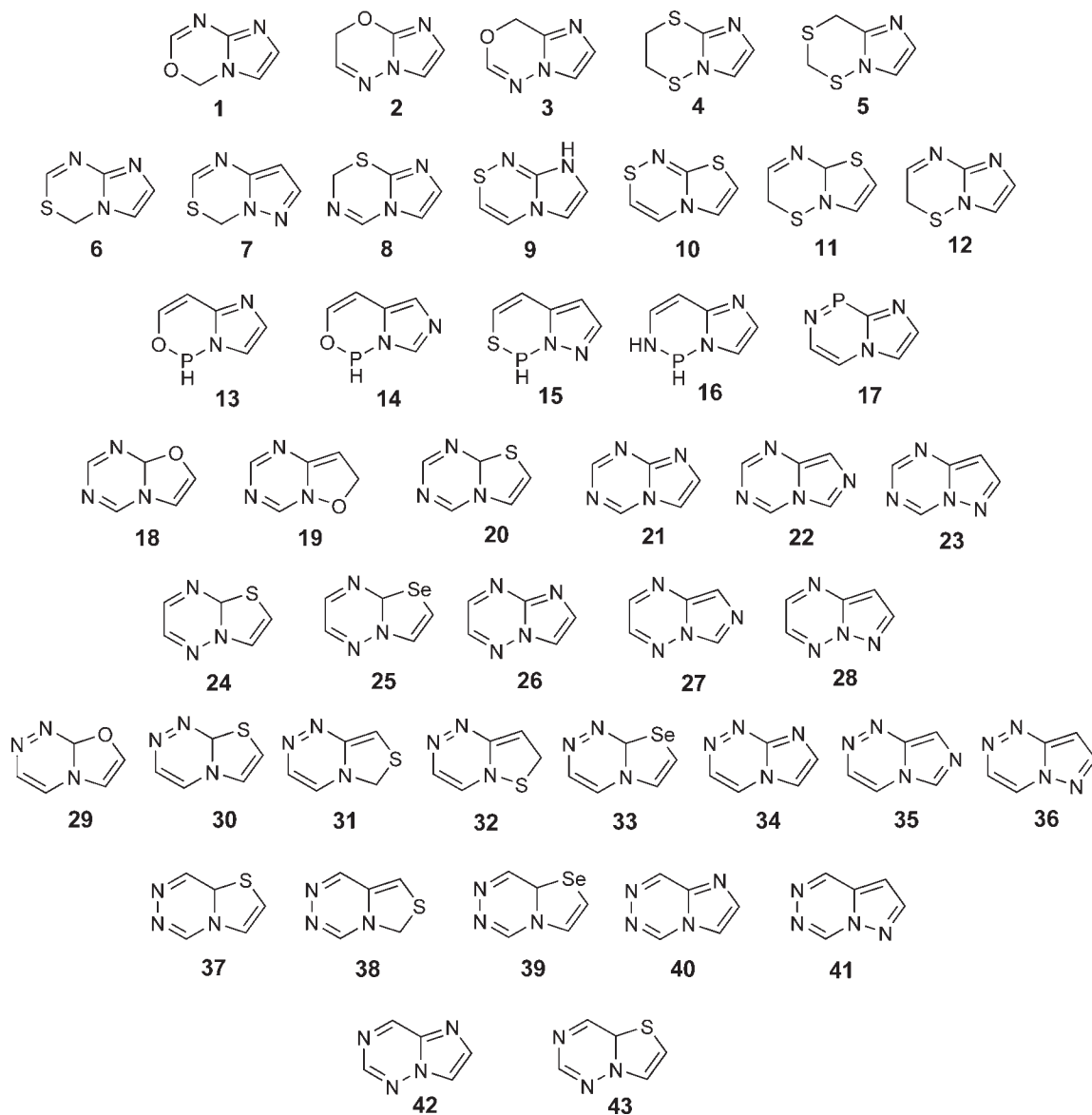
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11.17.1 Introduction

A large variety of ring systems of the title arrangement of heteroatoms exist and have been studied during the past period. Ring systems treated in this chapter are summarized in [Scheme 1](#).



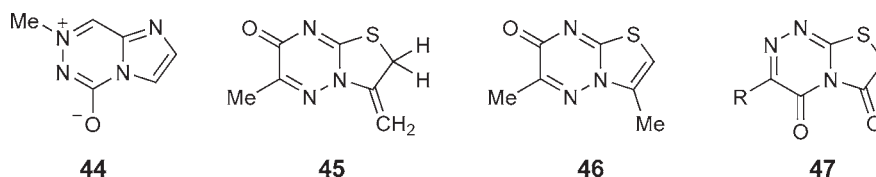
Scheme 1

The compilation of ring systems in [Scheme 1](#) consists of all the ring systems discussed in this chapter. The first three lines of structures are fused oxadiazines, dithiazines, and thiadiazines, these ring systems are followed by various fused

phosphinines with different heteroatomic arrangements. The majority of the ring systems of the present chapter involve different fused triazines, [1,3,5]triazines and *b*-, *c*-, *d*-, and *f*-fused [1,2,4]triazines, as shown by the last five entries of this scheme. The five-membered heterocycles can be oxazoles or isoxazoles (18, 19, 29), thiazoles or isothiazoles (10, 11, 20, 24, 30, 31, 32, 37, 38, 43), selenazoles (25, 33, 39), imidazoles (1, 2, 3, 4, 5, 6, 8, 9, 12, 13, 14, 16, 17, 21, 22, 26, 27, 34, 35, 40, 42), and pyrazoles (7, 15, 23, 28, 36, 41). Besides these bicyclic rings, some of their benzologues will also be discussed. There are several other ring systems of a heteroatomic arrangement that would belong to this chapter which were published earlier <1996CHEC-II(8)445> but no novel results appeared since 1996.

11.17.2 Theoretical Methods

In the course of investigation of reactivity of the mesoionic compound **44** (Scheme 2) the question arose if this bicyclic system participates in Diels–Alder reactions as an electron-rich or an electron-poor component <1999T13703>. The energy level of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) orbitals were calculated by PM3 method. Comparison of these values with those of two different dienophiles (dimethyl acetylenedicarboxylate (DMAD) and 1,1-diethylamino-1-propyne) suggested that a faster cycloaddition can be expected with the electron-rich ynamine, that is, the Diels–Alder reaction of inverse electron demand is preferred. The experimental results seemed to support this assumption.



Scheme 2

A Russian team, when investigating the ring-closure reaction to some tiazolo[3,2-*b*][1,2,4]triazinones **45** and **46**, carried out AM1 calculations for these molecules <2000ZOB650>. With the help of the quantum-chemical results, infrared (IR) spectra of these compounds have been calculated and compared with the experimentally observed spectra. Thus, clear differentiation is possible between the two tautomeric structures.

Theoretical calculations were carried out for the rationalization of the ring closure reactions yielding thiazolo[2,3-*c*][1,2,4]triazinones **47** <2003PS1143>. PM3 and AM1 methods were applied which revealed that the observed regioselective cyclization is in accordance of the charge control of the reaction.

11.17.3 Experimental Structural Methods

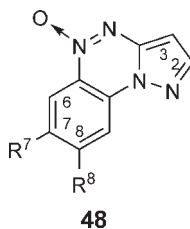
11.17.3.1 NMR Investigations

A great number of nuclear magnetic resonance (NMR) assignments appeared but space limitations of this chapter would not allow a complete discussion. In three cases, more detailed analyses of the measured data appeared; these are summarized below.

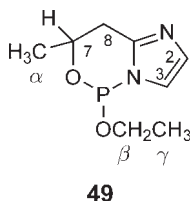
Costanzo *et al.* <1994JHC1369> published the synthesis of a series of pyrazolo[5,1-*c*]benzo[1,2,4]triazine-5-oxides **48** and compared the ^{13}C NMR chemical shifts of these products. These values for a set of four derivatives are shown in Table 1.

Also, ^{13}C NMR assignments have been published for a recently synthesized phosphorus-containing ring system: imidazo[1,2-*c*][1,3,2]oxazaphosphinine **49** <1996TL977>. The chemical shifts as well as the $J_{\text{C-P}}$ coupling constants are shown in Table 2.

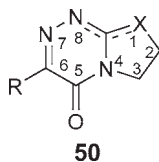
Systematic NMR studies of a set of heterocycles containing guanidine and thiourea structural moiety have been published by an English team <1995MRC389>. In the frame of these investigations, some imidazo- and tiazolo-[1,2,4]triazinones having the general structure **50** have been analyzed by ^{13}C and ^{15}N NMR spectroscopy. The chemical shifts of some derivatives are compiled in Table 3.

Table 1 ^{13}C NMR chemical shifts (300 MHz) of some pyrazolo[5,1-*c*]benzo[1,2,4]triazine-5-oxides **48** measured in CDCl_3 solution

R^8	R^7	$C-2$	$C-3$	$C-6$	$C-7$	$C-8$	$C-9$
H	H	144.8	99.8	123.5	127.4	136.0	115.8
Cl	H	145.3	100.2	125.1	128.0		115.8
H	Cl	145.1	100.2	123.1		136.4	117.4
H	NO_2	146.7	101.4	130.2		120.5	117.5

Table 2 ^{13}C chemical shifts (with respect to the residual signal of CDCl_3 at 77.0 ppm) as well as the $J_{\text{C-P}}$ coupling constants of the imidazo[1,2-*c*][1,3,2]oxazaphosphinine derivative **49**

	$C-2$	$C-3$	$C-7$	$C-8$	$C\alpha$	$C\beta$	$C\gamma$
^{13}C NMR shift (ppm)	127.57	115.07	65.94	32.74	20.38	60.23	15.53
Coupling constant (H-2)	$^3J_{\text{C-P}} = 5.2$	$^2J_{\text{C-P}} = 18.1$	$^2J_{\text{C-P}} = 6.3$	$^3J_{\text{C-P}} < 0.3$	$^3J_{\text{C-P}} = 4.1$	$^2J_{\text{C-P}} = 19.4$	$^3J_{\text{C-P}} = 5.0$

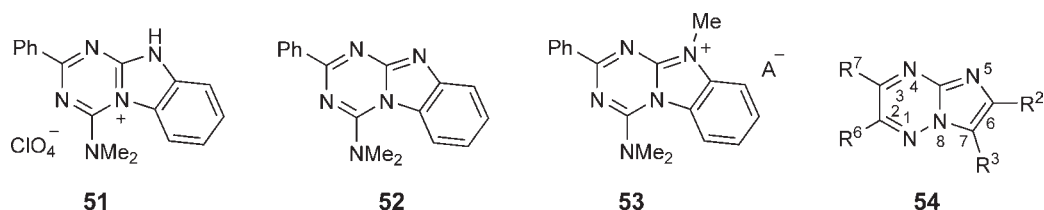
Table 3 ^{13}C and ^{15}N NMR data of some imidazo- and thiazolo[1,2,4]triazinones **50** measured in dimethyl sulfoxide (DMSO) solution

Entry	X	R	$N-1$	$N-4$	$C-5$	$C-6$	$N-7$	$N-8$
1	NMe	Me	n.d.	n.d.	154.1	147.5	n.d.	n.d.
2	NMe	Ph	-314.23	-232.89	n.d.	n.d.	+4.53	-141.72
3	S	Me		-213.57	154.0	152.1	-8.5	-111.62
4	S	Ph		-208.64	n.d.	n.d.	-0.25	-109.12

The ^{13}C shifts are related to TMS; the ^{15}N shifts are compared to neat nitromethane.

11.17.3.2 Optical Spectroscopic Studies

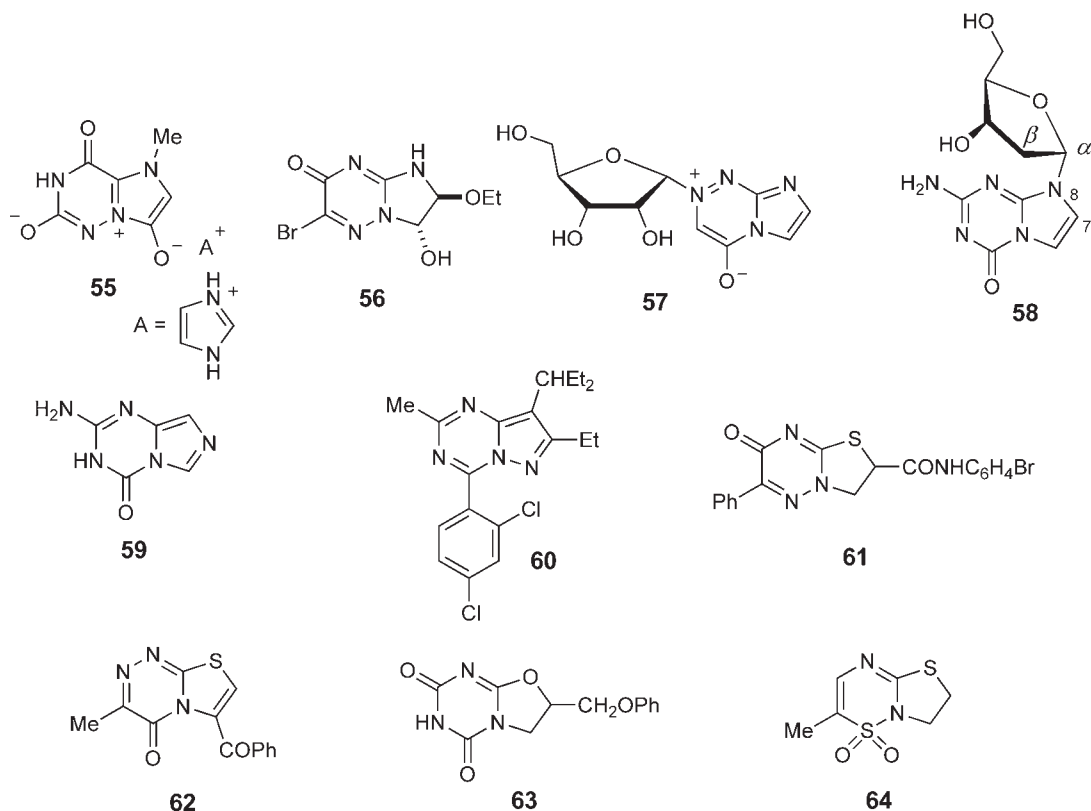
The effect of methylation of **51** and **52** to give **53** on the UV spectrum was studied (Scheme 3) <1995JHC1833>. The result indicated that in contrast to related cases no dominant change occurs.

**Scheme 3**

Fluorescence and luminescence spectroscopic studies on imidazo[1,2-*b*][1,2,4]triazines **54** have been published by a Russian team [\[1994ZOB327, 1994ZOB497\]](#). The experimental data reveal that protonation of **54** can take place either on N-4 or on N-5 and is strongly dependent on the solvent used.

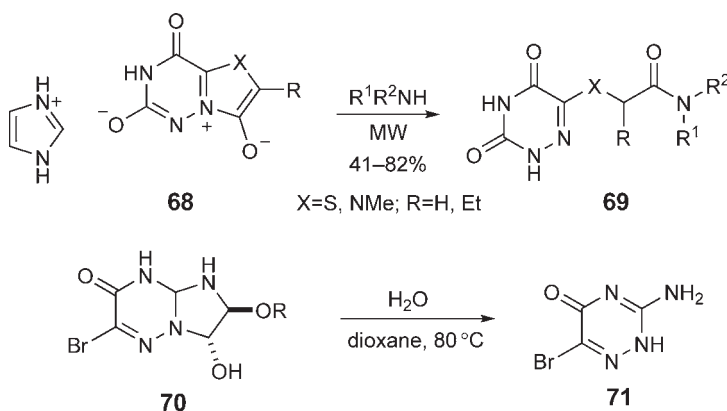
11.17.3.3 X-Ray Elucidations

X-Ray structure elucidations in order to provide unambiguous proof for the particular structures have been carried out in several cases. Ten such studies are reviewed in this section, and every piece of work relates to a different ring system. Structures of these compounds are shown in [Scheme 4](#).

**Scheme 4**

Structure of the mesoionic derivative of the imidazo[2,1-*f*][1,2,4]triazine ring system **55** has been determined [\[2005TL5325\]](#). The X-ray analysis unequivocally revealed the zwitterionic character.

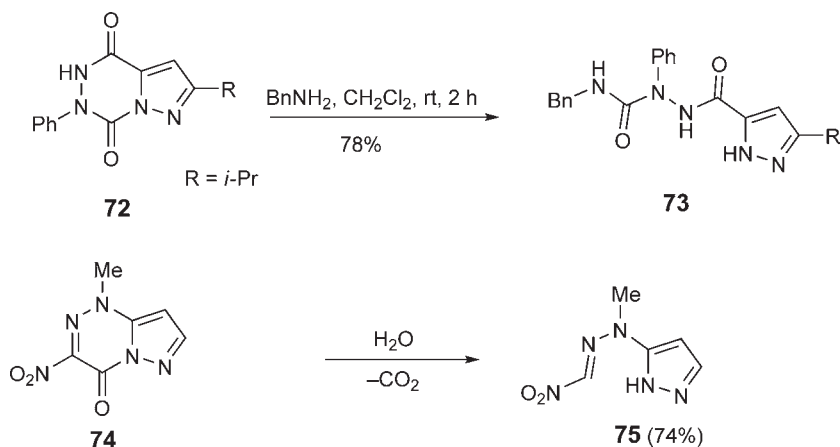
Investigation of 1,2,3,7-tetrahydroimidazo[1,2-*b*][1,2,4]triazin-7-one **56** revealed the *trans*-relationship between the substituents in positions 2 and 3 [\[2003OL4595\]](#). The (OH)O-*C*(3)-*C*(2)-O(OEt) dihedral angle confirmed this geometric feature, whereas it has been shown that the imidazole ring is nearly planar.



Scheme 6

Hydrolytic ring opening of the five-membered ring of an imidazo[1,2-*b*][1,2,4]triazine derivative was described by Garnier *et al.* <2003OL4595> (Scheme 6). When a solution of the 2-ethoxy compound **70** (R = OEt) in dioxane was treated with water, formation of the aminotriazinone compound **71** was experienced. Detailed investigations on the reaction mechanism revealed that the ring-opening process proceeds via the dihydroxy intermediate **70** (R = H).

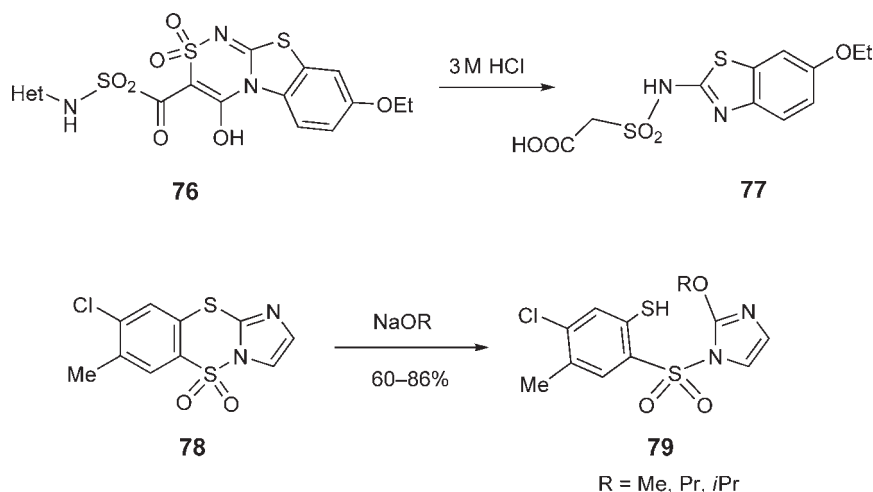
In Scheme 7, ring-opening reactions of some fused pyrazoles are shown. Thus, Baraldi *et al.* <1999S453> described that the pyrazolo[1,5-*d*][1,2,4]triazine-dione derivative **72** is sensitive toward nucleophiles: its reaction with benzylamine at room temperature gives rise to the acyl semicarbazide **73** in high yield (78%).



Scheme 7

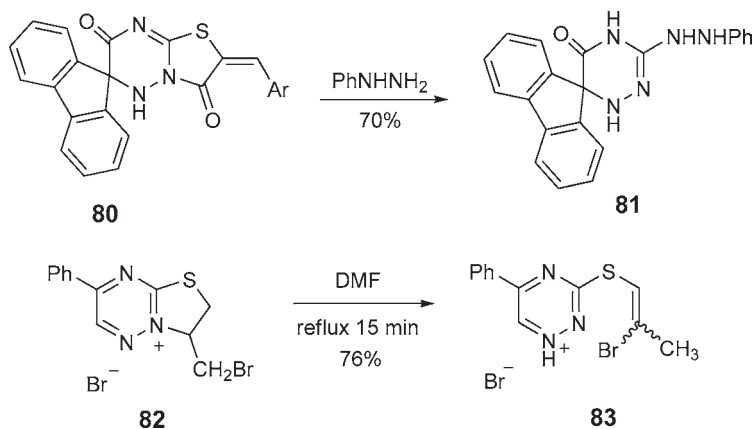
Rusinov *et al.* <1996ZOR770> found that the nitro-substituted pyrazolo[5,1-*c*][1,2,4]triazinone compound **74** undergoes ring opening when boiled in water to yield a hydrazone **75**. During the reaction, carbon dioxide is eliminated.

Ring-opening reactions of some sulfur-containing heterocyclic rings are shown in Scheme 8. Acidic hydrolysis of the benzothiazolothiadiazine derivative **76** to the sulfonamide **77** was described by Scarborough *et al.* <2001BML1805>. The structure of this product **77** provided an important support to the structure elucidation of **76**. Ring opening of imidazodithiazines has been studied by Brzozowski and Kornicka <1999APH135>. When the tricyclic sulfones **78** were heated with various sodium alkoxides, the central six-membered ring opened up to yield phenylsulfonylimidazoles **79** containing the alkoxide group on the imidazole ring in good to excellent yields (60–86%). Similar ring opening of related imidazodithiazines under acidic conditions has also been studied by the same authors <1999APH135>.



Scheme 8

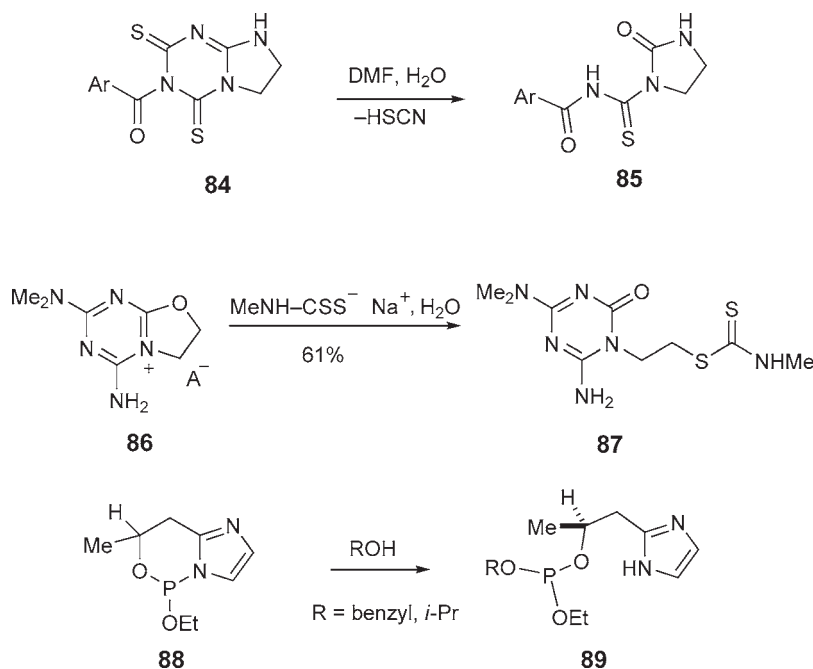
In **Scheme 9**, ring-opening reactions of two fused thiazoles are shown. The spiro-substituted fused thiazolone **80** was found to react with phenylhydrazine at 150 °C to yield a substituted hydrazinotriazine **81** in high yield (70%) <1994PHA729>. Rudakov *et al.* investigated the reactivity of the dihydrothiazolo[3,2-*b*][1,2,4]triazinium derivative **82**. This compound, when refluxed in DMF for 15 min, underwent ring opening and the vinylsulfide **83** was formed in high yield <1997ZOR1103>.



Scheme 9

In **Scheme 10**, miscellaneous ring openings are demonstrated. The interesting feature of ring opening of the imidazo[1,3,5]triazine derivative **84** is that along the ring opening process rhodanic acid is eliminated <1994H(37)689>. The reaction takes place in refluxing aqueous DMF and yields the 2-oxoimidazoline **85**. This compound, which has already been synthesized earlier by an independent route, has provided an important support to determination of the exact structure of the starting cyclic compound **84**.

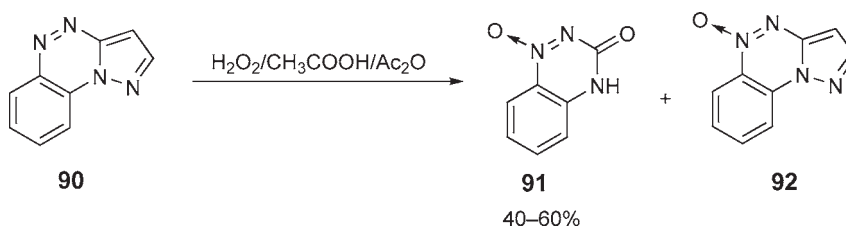
The ring opening of the oxazolotriazinium salt **86** with sodium dithiocarbamate was reported by Dovlatyan *et al.* <1996KGS1417>. The reaction takes place in water at room temperature to yield a dithiocarbamoylethyl-substituted triazinone **87**.



Scheme 10

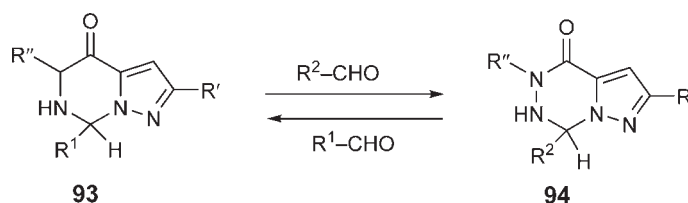
Ring opening of the recently synthesized imidazooxaphosphinine **88** was experienced to occur in the presence of alcohols [<1996TL977, 1998NN939>](#). Diastereoselective reaction took place in dichloromethane solution between 2 and 30 min depending on the alcohol used to yield the triester **89**.

Oxidative degradation of a fused pyrazole ring was reported by Costanzo *et al.* [<1998EJM237>](#), as shown in [Scheme 11](#). Studies on oxidation of the tricyclic ring system **90** aimed at preparation of some *N*-oxides (e.g., **92**). These authors found, however, that oxidation by using hydrogen peroxide in the presence of acetic acid and acetic anhydride yielded a mixture of **91** and **92**, where in most cases the ring-opened triazinone **91** containing the *N*-oxide function as a main product was separated from the reaction mixture. Yields were found to be moderate (40–60%).



Scheme 11

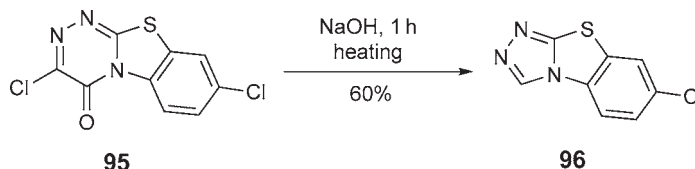
Wipf *et al.* [<2005OL4483>](#) elaborated a new metathesis method including ring opening in order to generate dynamic combinatorial libraries. The transformation is shown in [Scheme 12](#). The essence of this method is the recognition that an equilibrium takes place with **93** and an aldehyde in aqueous conditions at pH 4 in a phosphate buffer. With the help of this transformation, a series of new R^2 -substituted products **94** – not available via direct ring closure – have been synthesized.



Scheme 12

11.17.5.2 Ring Contraction

Ring contraction reaction of the benzthiazolo[2,3-*c*][1,2,4]triazin-one derivative **95** has been reported by Kuberkar *et al.* <2005JCM632> (Scheme 13). This compound when heated in aqueous sodium hydroxide underwent ring opening and a subsequent ring closure to result in formation of the fused [1,2,4]triazole ring system **96** in good yield (60%).



Scheme 13

11.17.5.3 Formation of Further Condensed Rings

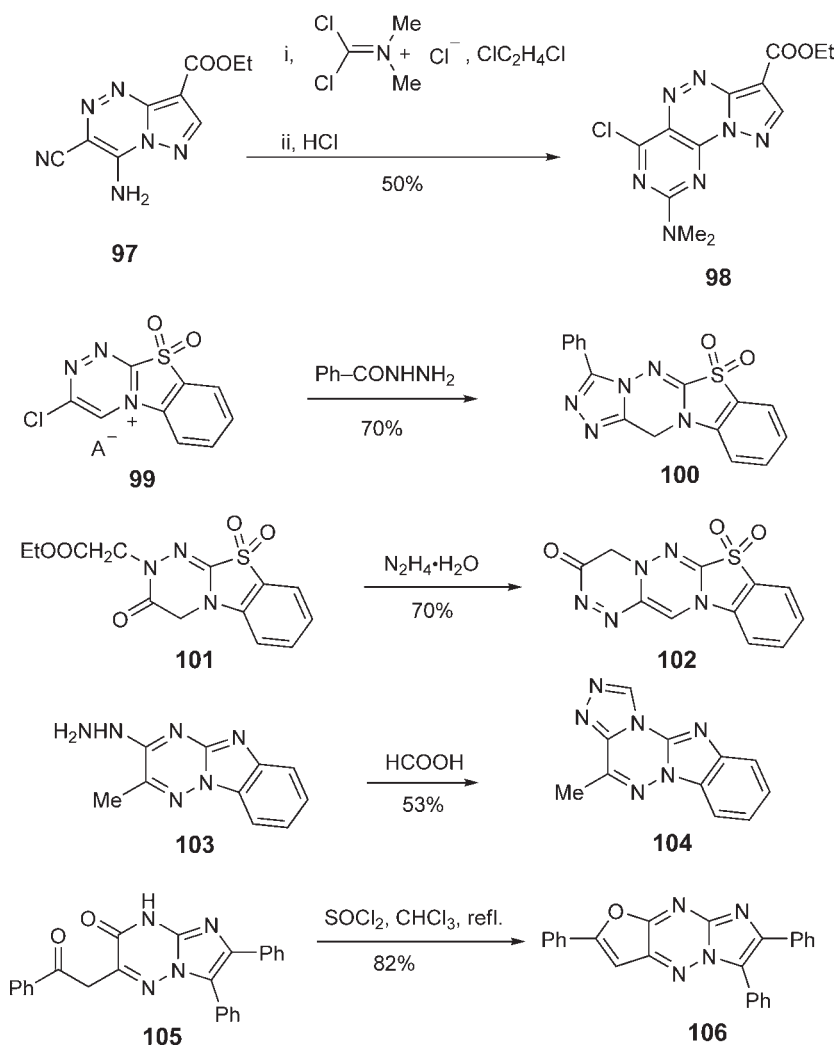
Further condensed five- and six-membered rings have been synthesized in several cases as shown in Scheme 14. As reported by Quintela and Moreira <1996T3037>, in the case of the pyrazolo[3,2-*c*][1,2,4]triazine ring system, a fused pyrimidine ring can be formed by transformation of the cyano and amino groups in adjacent positions. Thus, treatment of **97** with dimethyl phosgeniminium chloride and, subsequently, by hydrogen chloride gas gave rise to the tricyclic product **98** in good yield.

Formation of two different fused rings in the case of the ring system benzthiazolo[2,3-*c*][1,2,4]triazine derivatives has been reported. The chloro derivative **99** when reacted with benzhydrazide resulted in formation of a fused [1,2,4]triazole ring **100** <2003HCO181> in good (70%) yield. The same authors also described that the oxotriazine compound **101** bearing an appropriate functional group (*N*-ethoxy-carbonylmethylene moiety) in the adjacent position was reacted with hydrazine hydrate to form a tetracyclic product containing a new fused [1,2,4]triazine ring **102**. A fused [1,2,4]triazole moiety was formed by reaction of the hydrazine-substituted benzimidazolo[1,2-*b*][1,2,4]triazine compound **103** with formic acid. The tetracyclic product **104** was obtained in acceptable yield (53%) <2000KGS112>.

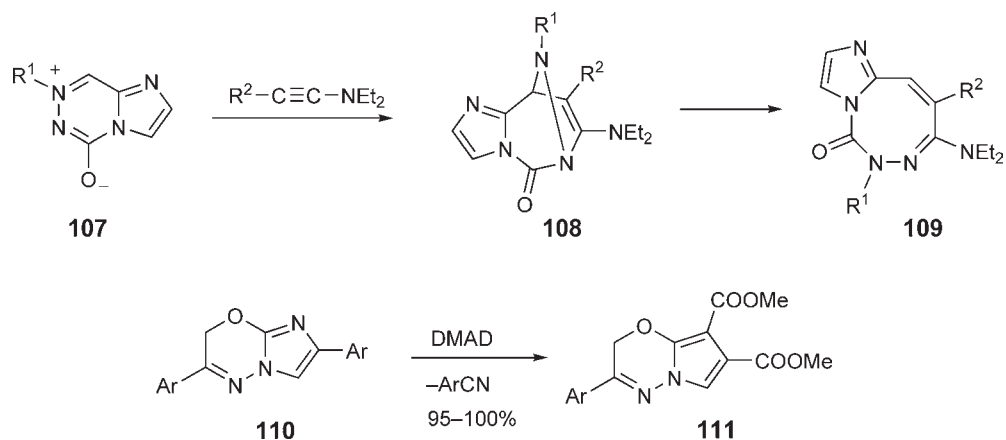
Ring closure to a fused furan was carried out by Kruglenko *et al.* <1998KGS258>: the fused triazinone derivative **105** was treated with thionyl chloride under reflux conditions in chloroform to yield the tricyclic compound **106** in excellent yield.

11.17.5.4 Cycloadditions

The betainic imidazo[1,2-*d*][1,2,4]triazinium-olate **107** was found to react as a 1,3-dipole in 1,3-dipolar cycloaddition with ynamines to yield a bridged skeleton **108** <1999T13703> as shown in Scheme 15. This cycloadduct **108** underwent subsequent rearrangement upon heating, and resulted in formation of a fused eight-membered heterocycle **109**. With acetylenes other than ynamines, the transformation was found to proceed slowly and in bad yields. The fact that ynamines were used successfully, as well as theoretical considerations (cf. Section 11.17.2) in this chapter, indicated that these Diels–Alder reactions are of inverse electron demand.



Scheme 14

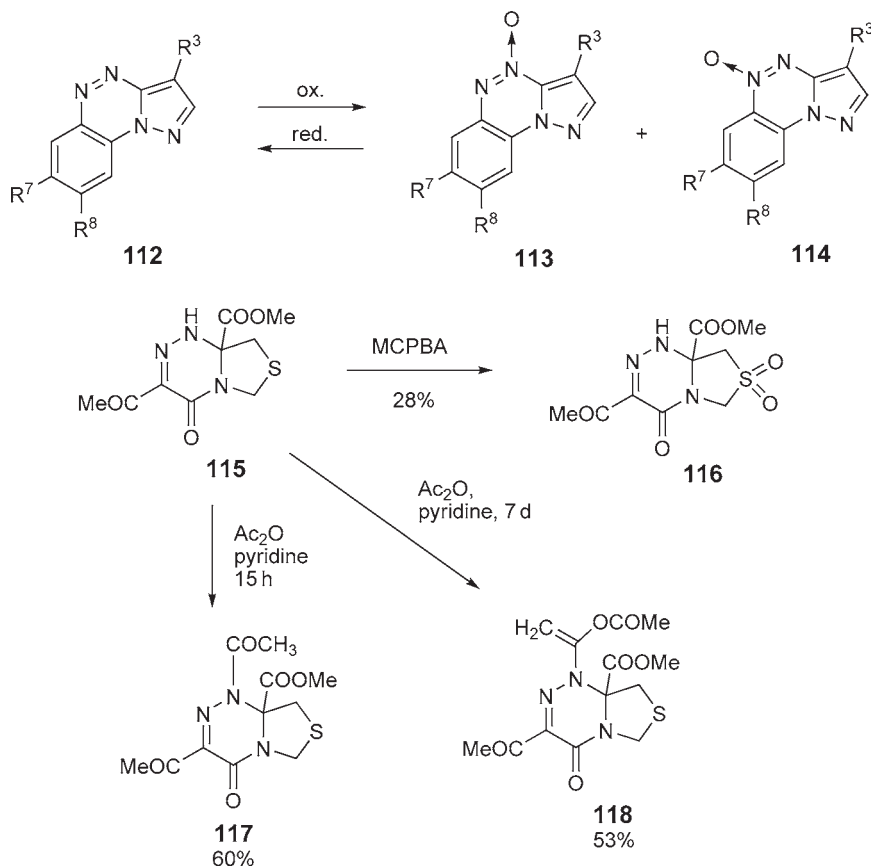


Scheme 15

In the case of the imidazo[1,2-*b*][1,3,4]oxazine compound **110**, a Diels–Alder cycloaddition was also reported <1994S555>. In this compound, the five-membered ring reacted as a diene, and DMAD acted as a dienophile. The primary cycloadduct spontaneously underwent benzonitrile elimination and led to the ring transformation product **111** in almost quantitative yield (95–100%).

11.17.5.5 Reactions of the Ring Heteroatoms

Oxidations of ring nitrogen and sulfur atoms are shown in **Scheme 16**. In **Section 11.17.5.1**, it has already been discussed that detailed investigations on oxidation of the ring system **112** were carried out by Costanzo *et al.* <1999MI223, 1998EJM237, 1996EJM259>, and this research group also published the synthesis of *N*-oxides.



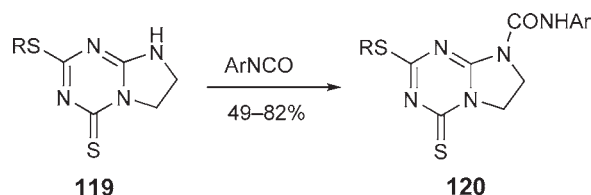
Scheme 16

As shown in **Scheme 16**, the *N*-oxidations of **112** can yield 4-oxides **113** and/or 5-oxides **114** can be formed. In some special cases (e.g., if $R^3 = Br$), formation of exclusively **114** was experienced. The reverse transformation was also carried out: reduction of the *N*-oxides (**113**, **114**) by triethylphosphite or Zn/acetic acid yielded the deoxy compound **112**.

Oxidation of the partially saturated derivative of the thiazolo[4,3-*c*][1,2,4]triazine ring system **115** was studied by Stoodley *et al.* <1999J(P1)1067>. Reaction of **115** with *m*-chloroperbenzoic acid gave rise to the cyclic sulfone **116** in poor yield (28%).

In the case of ring-nitrogen atoms, *N*-acylation and *N*-alkylation reactions have been described. Thus, **Scheme 16** shows that compound **115** was subjected to acetylation <1999J(P1)1067>. If the reaction is carried out with acetic anhydride in pyridine under an argon atmosphere for 15 h, the acetyl compound **117** can be obtained. The same reaction mixture, however, when left to stand for 7 days, undergoes a further acetylation step to yield the acetate **118**.

If the ring nitrogen atom forms a secondary amine, its reaction with aryl isocyanate can yield substituted ureas and this transformation is strongly related to a N-acylation. In this respect, a publication by Saczewski and Nasal <1995APH237> should be mentioned here: these authors described the transformation of **119** with a number of arylisocyanates to the urea **120** in medium to high yields (49–82%) (Scheme 17).



Scheme 17

Alkylation reactions on ring nitrogen atoms have been carried out in many cases. In the majority of these transformations, well-established methods have been applied. A compilation of ring nitrogen alkylations is shown in Table 4, where the structures of the starting compounds, products, yields, and references are summarized. Ribosidation of these ring systems as well as rearrangement of these products have also been reported <1996TL901>.

Table 4 Alkylation reaction on ring nitrogen atom: a summary of the structures of the starting compounds, products, yields, and references

Entry	Starting compound	Product	Yield (%)	References
1			47–57	1999T13703
2			85	1994JRM644
3			78–83	2003AP413 2000JME96
4			75–80	1996JB842 2001JME4359 2005JCM632
5			96	1995JHC1833

(Continued)

Table 4 (Continued)

Entry	Starting compound	Product	Yield (%)	References
6			21–62	1997JHC429
7			24–70	2004HCA1239 2001JOC5012
8			55–65	2004HCA1239
9			75–96	1995APH237

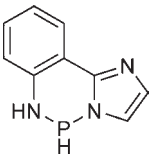
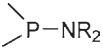
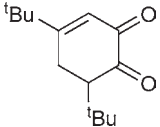
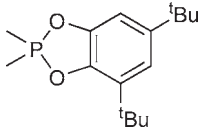
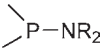
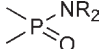
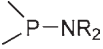
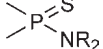
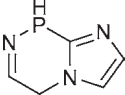
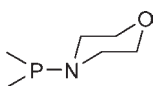
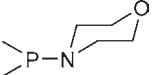
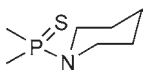
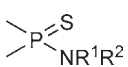
Although fused phosphinines have been first synthesized only in the recent years, almost every study in this area also involved some reactions with the ring phosphorus atoms. These transformations are compiled in [Table 5](#). In this table, the starting and product P-functions, the reagents, yields (if published), and references are listed.

Table 5 Transformations of oxaza- and diazaphosphinines: a listing of the starting and product P-functions, reagents, yields (if published), and references

Ring system	Starting P-function	Reagent	Product	Yield (%)	Reference
		S ₈		n.d.	2002PS1767
		Beaucage's reagent		n.d.	1998NN939
		S ₈		n.d.	1996TL977
				67	2004HAC307
		S ₈		100	2004HAC307
		Se		100	2004HAC307

(Continued)

Table 5 (Continued)

Ring system	Starting P-function	Reagent	Product	Yield (%)	Reference
				100	2004HAC321
		ox		n.d.	2004HAC321
		S ₈		97	2004HAC321
		Morpholine		n.d.	2002KGS385
		S ₈		n.d.	2002KGS385
		HNR ¹ R ² + S ₈		48–91	2002HAC84
		S ₈		32	2002HAC84

11.17.5.6 Reactivity of the Ring Carbon Atoms

11.17.5.6.1 Halogenations, nitrations, and other electrophilic reactions

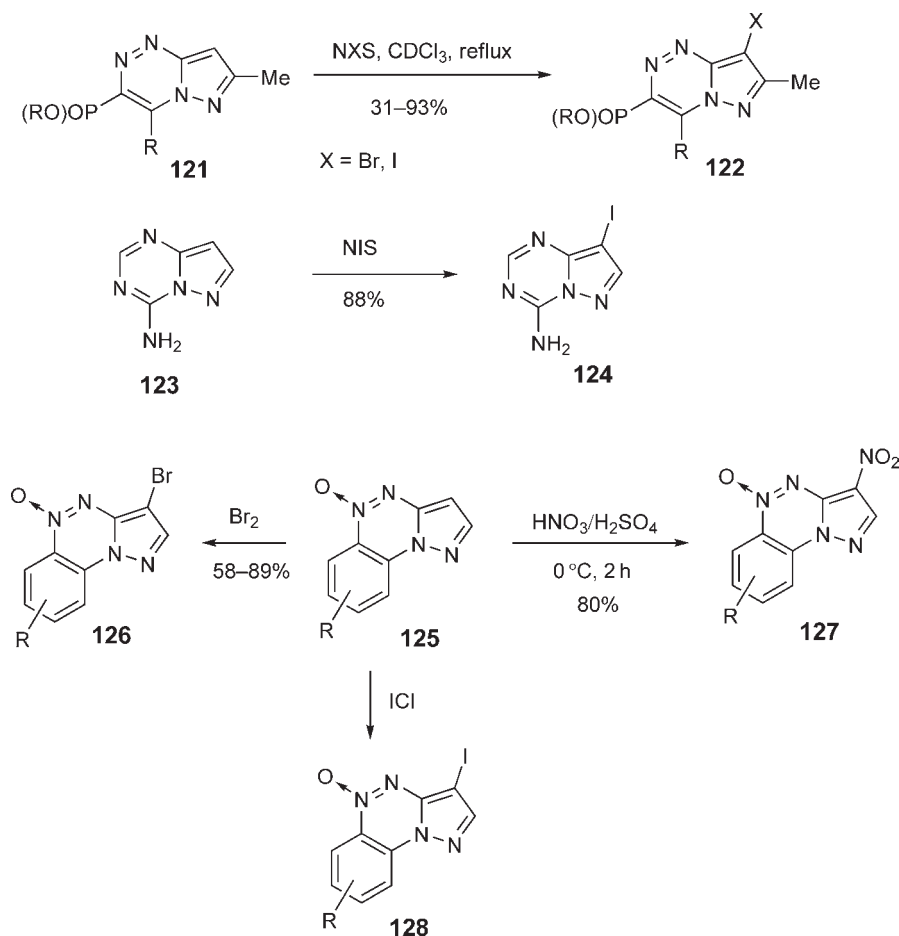
Halogenations of pyrazolo[3,2-*c*][1,2,4]triazines and pyrazolo[2,3-*a*][1,3,5]triazines have been published during the past period and carried out with *N*-bromo- and *N*-iodosuccinimide, as shown in [Scheme 18](#). All of these transformations result in halogenation in position 3.

Neidlein and Ankenbrand reported [<1999H\(51\)513>](#) that compound [121](#) undergoes halogenation with both of these reagents to yield 3-bromo and 3-iodo derivatives [122](#). The reaction is carried out in refluxing chloroform. Similar conditions have been applied for iodination of the amino derivative [123](#) [<1995NN105>](#) which took place in DMF at 65 °C to yield the iodo product [124](#) in high yield. Similar procedure of related derivatives taking place with the same regioselectivity and in good yield was also published [<2002JOC8063>](#).

Bromination and nitration of pyrazolo[5,1-*c*]benzo[1,2,4]triazine-5-oxide [125](#) was described by Costanzo *et al.* [<1996EJM259, 1999MI223>](#). Bromination was carried out with elemental bromine to give 3-bromo derivatives [126](#) in good to excellent yields, and nitration according to classical methods yielded the 3-nitro compound [127](#) also in high yield, and iodination was carried out by using iodonium chloride in good yield (56%) [<2002MI87>](#) to give [128](#).

Eschenmoser and coworkers dealt with electrophilic substitution of imidazo[1,5-*a*][1,3,5]triazines [<2003OL2067, 2003OL2071>](#) ([Scheme 19](#)). These authors found that some iminium salts (e.g., [130](#)) smoothly react with this ring system [129](#): the σ -complex [131](#) is strongly stabilized by the ammonium cation on the triazine ring and, then, deprotonation yields the substitution product [132](#). Deuteration to [133](#) and introduction of the pyrrolidine ring to [134](#) also take place according to this mechanism in high yields.

The same authors also published the synthesis of two nucleosides [135](#) and [136](#) by application of this process [<2003OL2067>](#). In these cases, the reagent iminium salts were generated *in situ* by adding the appropriate sugar and ammonium chloride to the reaction mixture which allowed the intermediate ring closure of the cyclic carbohydrate to an open-chained iminium salt.



Scheme 18

Friedel–Crafts acylation of a pyrazolo[1,5-*a*][1,3,5]triazine derivative **137** was published by Raboisson *et al.* <2002TL9501> and the transformation is shown in **Scheme 20**. The electrophilic attack of various acyl chlorides took place in position 3 to yield the new ketones **138** in moderate to excellent yields.

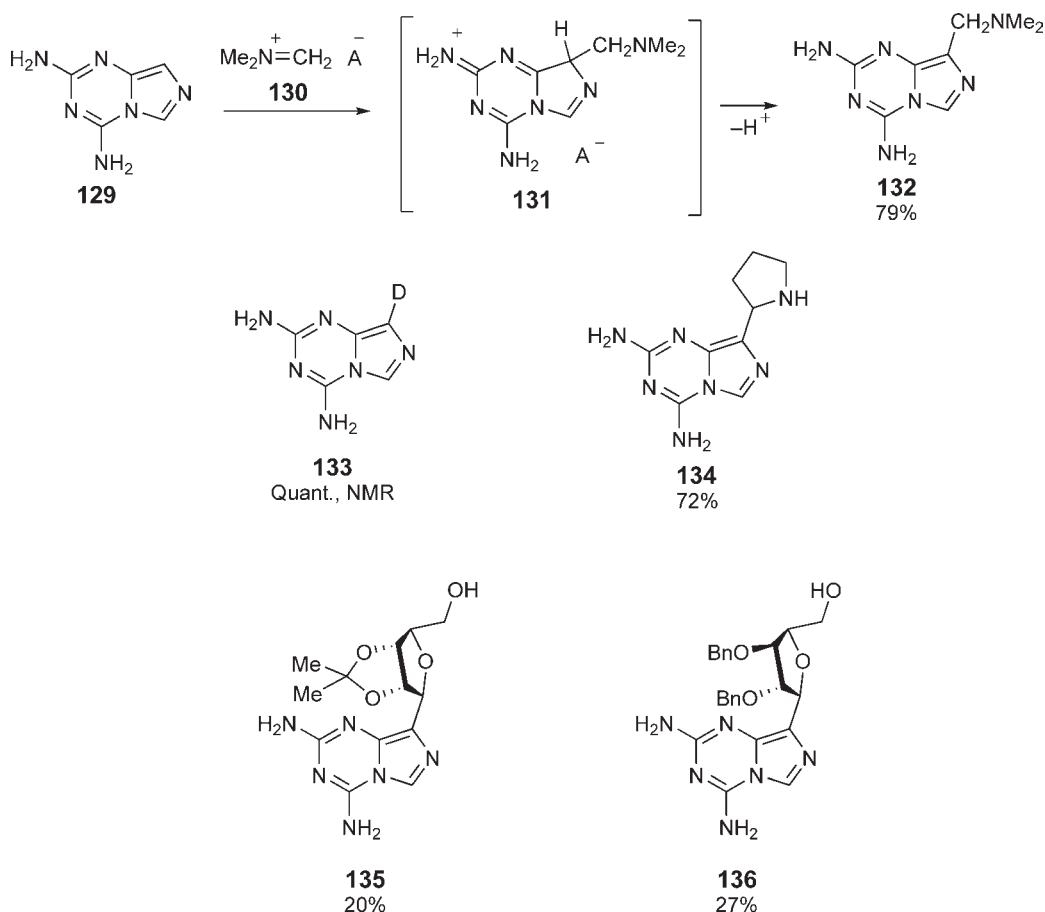
11.17.5.6.2 Nucleophilic substitutions

Nucleophilic substitutions are in many cases facile processes in heterocyclic chemistry. Also, in the area of the present chapter, many such routine transformations have been carried out. Such transformations are summarized in **Table 6**, where the structures of the starting compounds, products, the reagents, yields, and references are listed. These include reactions of halogen, methoxy, and methylsulfanyl derivatives with amines or alkoxides. One exceptional case (**Table 6**, entry 9) should be pointed out: this exchange reaction, unlike the others in this table, proceeds via an elimination–addition mechanism. A few related transformations that follow more complicated pathways and therefore could not be classified unambiguously into this table, can be found in **Table 7** in **Section 11.17.5.6.5**.

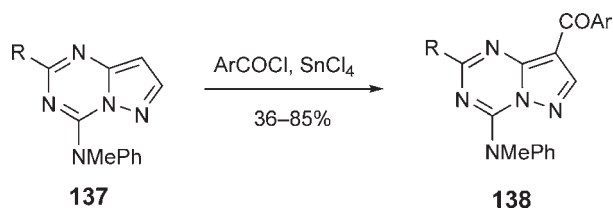
11.17.5.6.3 Cross-coupling reactions

Many of the recently elaborated cross-coupling methodologies have been applied to the ring systems of the present chapter. These transformations are shown in **Scheme 21**.

Raboisson *et al.* <2002JOC8063> elaborated a new general approach to pyrazolo[1,5-*a*][1,3,5]triazine-based C-nucleosides **140** by application of palladium-mediated cross-coupling reaction. The reaction of **139** was carried out by using bis(dibenzylideneacetone)Pd(0), triphenylarsine, and triethylamine to give the product **140** in high yield (75%).



Scheme 19



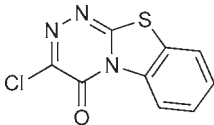
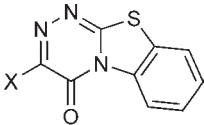
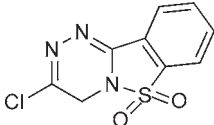
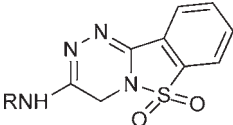
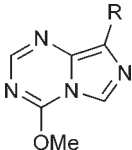
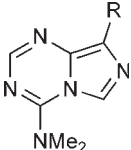
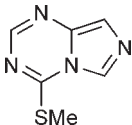
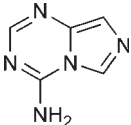
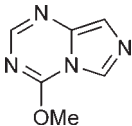
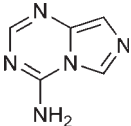
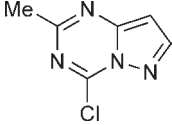
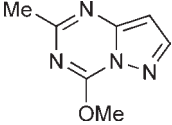
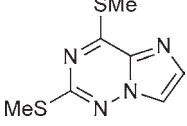
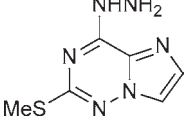
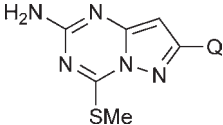
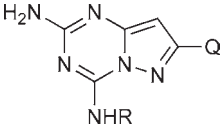
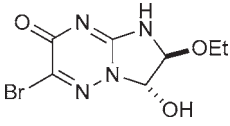
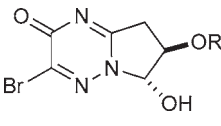
Scheme 20

Similar cross-coupling reaction of another derivative of the same ring system **141** with dihydrofuran has also been described. In this case, palladium diacetate, tributylamine, triphenylphosphine, and tetrabutylammonium chloride were used to afford the product **142** in high yield (70%) [<1995NN105>](#).

A Sonogashira coupling of **143** was reported by Neidlein and Ankenbrand [<1999H\(51\)513>](#). The new acetylenic compounds **144** were prepared in variable yields (11–74%).

Costanzo *et al.* [<2002MI87>](#) published the synthesis of the furyl-substituted pyrazolo[3,2-*c*][1,2,4]triazine derivative **146** by Suzuki coupling of the iodo compound **145** with 2-furylboronic acid. The yield was found to be moderate (38%). It may be important to mention that these authors also tried to transform **145** to a heteroaromatic boronic acid and to carry out cross-coupling of this compound with 3-bromofuran. Unfortunately, however, this approach failed and only homo-coupling occurred.

Table 6 Nucleophilic substitution at ring carbon atom: starting compounds, reagents, products, yield and references are listed

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1		HNR^1R^2 or NaN_3	 $\text{X} = \text{R}^1\text{R}^2$ or N_3	65–70	1996JJC842 2005JCR(S)632
2		RNH_2		45–75	2003HCO181
3		Me_2NH		50–60	1995JMC3558
4		NH_3		50	1995JMC3558
5		NH_3		72	1995JMC3558
6		MeOH		54	2002JOC8063
7		N_2H_4		89	1999JCS(P1)2929
8		RNH_2 $\text{R} = \text{Ar}, \text{NH}_2$		70–87	2001JCR(S)439 2001SC3453
9		ROH		36–87	2003OL4595

(Continued)

Table 6 (Continued)

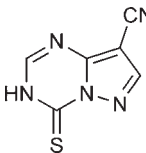
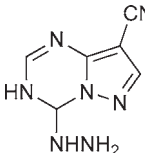
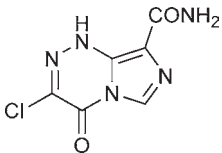
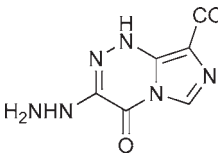
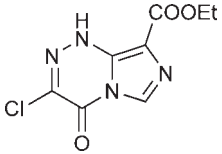
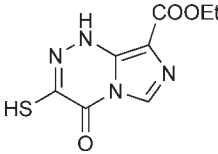
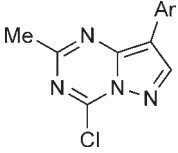
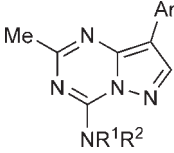
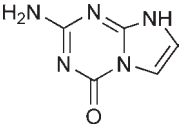
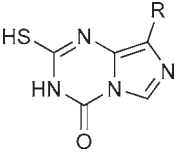
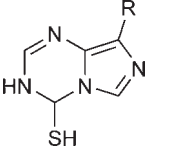
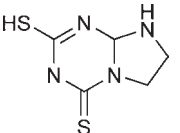
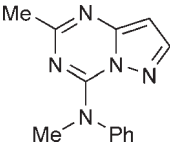
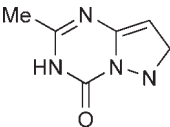
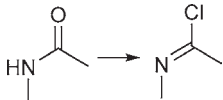
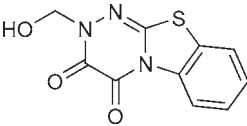
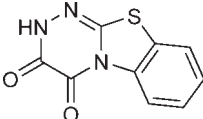
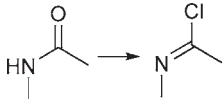
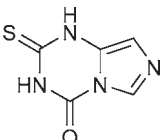
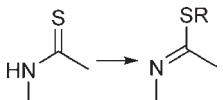
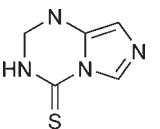
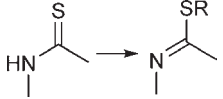
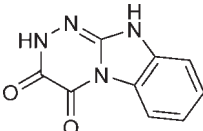
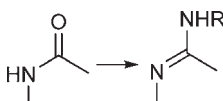
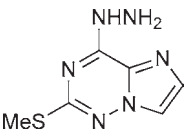
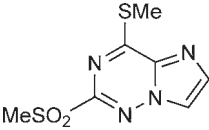
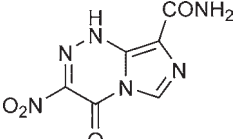
Entry	Starting compound	Reagent	Product	Yield (%)	Reference
10		N_2H_4		60	1997JCR(M)2255
11		$\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$		77	1999KGS1544
12		H_2NCSNH_2		52	1999KGS1544
13		HNR^1R^2		46–68	2000JMC449

Table 7 Other substituent transformations: a listing of the starting compound, functional group transformation, and references

Entry	Starting compound	Transformation	References
1		$\text{NH}_2 \rightarrow \text{NHBu}^t$	2004HCA1239
2		$\text{SH} \rightarrow \text{H}$	1995JME3558
3		$\text{SH} \rightarrow \text{OMe}$	1995JME3558 1994JRM644
4		$\text{SH} \rightarrow \text{SCH}_2\text{CONHAr}$	1995APH237

(Continued)

Table 7 (Continued)

Entry	Starting compound	Transformation	References
5		NMePh $\rightarrow$ H	2002JOC8063 2003TL703
6			2002JOC8063
7		OH $\rightarrow$ NR ¹ R ²	2005JCM632
8			2005JCM632 1996IJB842
9			1994JRM644
10			1994JRM644
11			2003AP413
12		NHNH ₂ $\rightarrow$ H	1999J(P1)2929
13		MeSO ₂ $\rightarrow$ H	1999J(P1)2929
14		C=O $\rightarrow$ =C-Cl	1999KGS1544

(Continued)

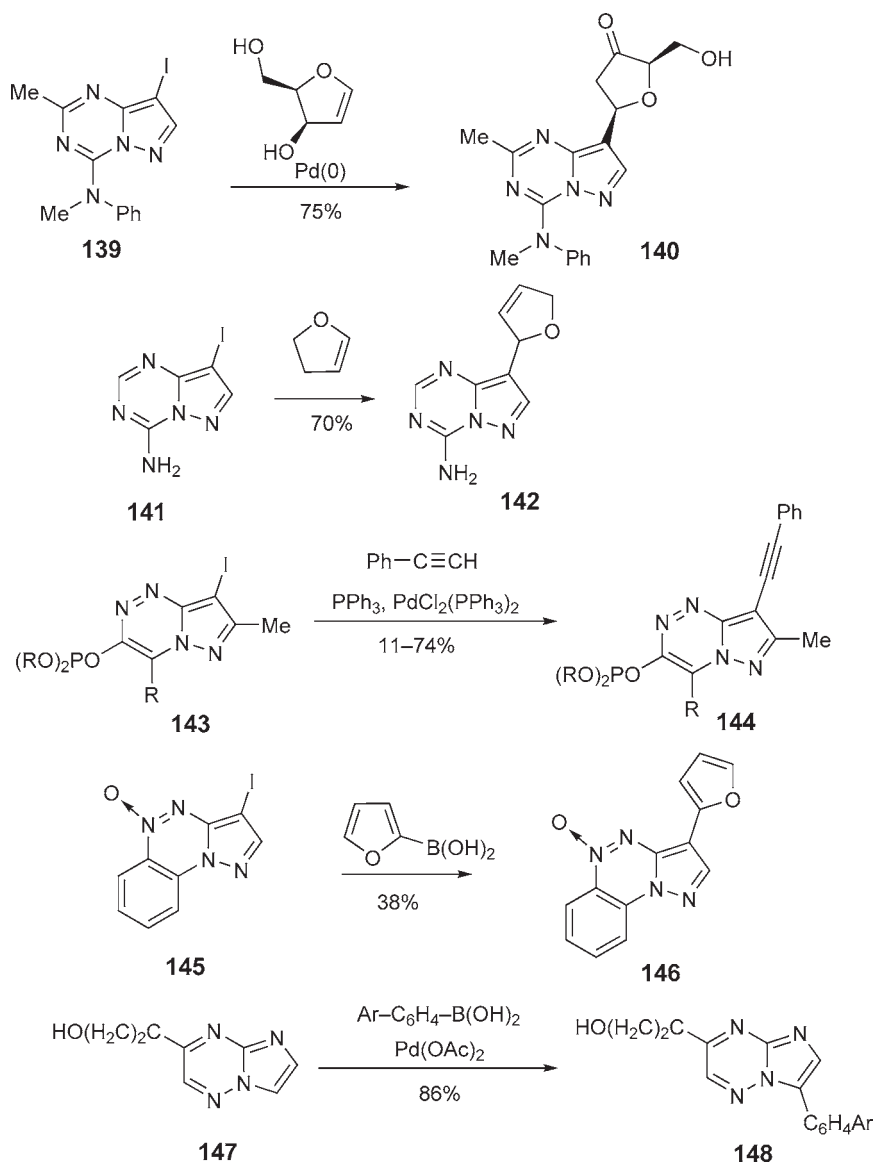
Table 7 (Continued)

Entry	Starting compound	Transformation	References
15		$\text{NO}_2 \rightarrow \text{Cl}$	1999KGS1544
16		$\text{Cl} \rightarrow \text{OH}$	1999KGS1544
17			2003C248
18		$\text{SMc} \rightarrow \text{OPh}$	2000BML821
19		$\text{NH}_2 \rightarrow \text{OH}$	2002IZV1594
20			1998JME3128
21			1997JRM2255

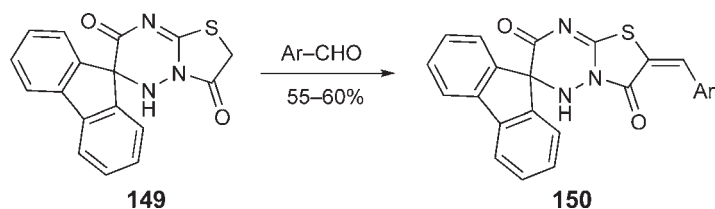
Gauthier *et al.* <2005JOC5938> elaborated a synthetic route to **148**, which is an important biologically active compound. These authors found that **147** can be subjected directly to cross-coupling process with the appropriate boronic acid, and there is no need for the halogenation of **147** to an intermediate for this cross-coupling. The product **148** was obtained in kilogram quantities in almost quantitative yield.

11.17.5.6.4 Condensation reactions

The condensation reaction of the spiro-substituted partially saturated thiazolo[3,2-*b*][1,2,4]triazine compound **149** was published by Abdel-Rahman *et al.* <1994PHA729>, as shown in **Scheme 22**. The transformation was carried out in glacial acetic acid under heating to yield the ethenyl derivative **150** in acceptable yields (55–60%).



Scheme 21

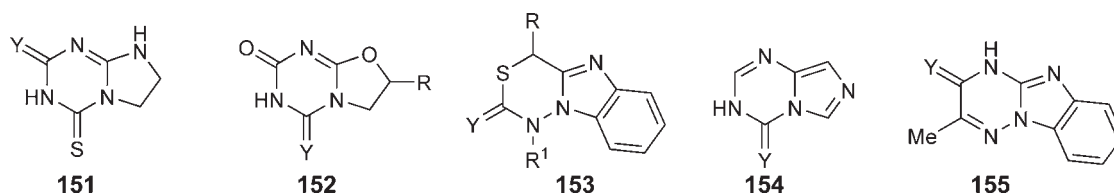


Scheme 22

11.17.5.6.5 Transformations of substituents

A great number of transformations of substituents – mostly by well-established routine methods – have been applied. In this section, those reactions are reviewed where the atom of the substituent attaching to the ring carbon atom of the heterocycle is changed in the course of the transformation, and could not be classified into the previous sections. Reactions of substituent where the transformation occurs in the side chain are summarized in [Section 11.17.5.7](#).

Transformation of oxoazines to thioxoazines, and the reverse, is well documented in the literature and has also been treated in CHEC-II(1996) <1996CHEC-II(8)445>. **Scheme 23** shows some compounds that have been synthesized by the use of this type of transformation. In the cases of Y = S substituents (**151** <1995APH237>, **152** <1997MI291>, **153** <1996IJB748>), the thioxo derivatives were oxidized to oxo compounds by hydrogen peroxide or mercury oxide, whereas in the cases of **154** <1995JME3558> and **155** <2000KGS112> (where Y = O), the oxo compounds were treated with Lawesson's reagent or phosphorus pentasulfide to yield thioxo derivatives.



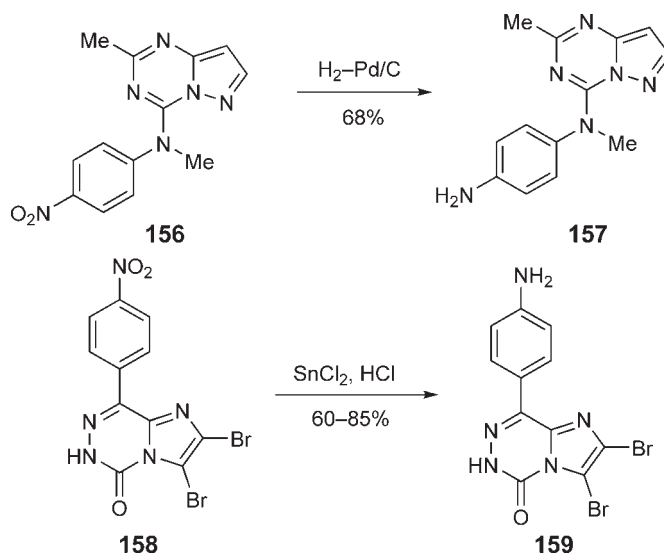
Scheme 23

In **Table 7**, a great variety of other substituent transformations are summarized that have been published during the recent years.

11.17.5.7 Transformations of the Substituents and Side Chains

11.17.5.7.1 Reduction of nitro groups

Scheme 24 illustrates two examples for reduction of nitro groups as side-chain substituents to amino functions.



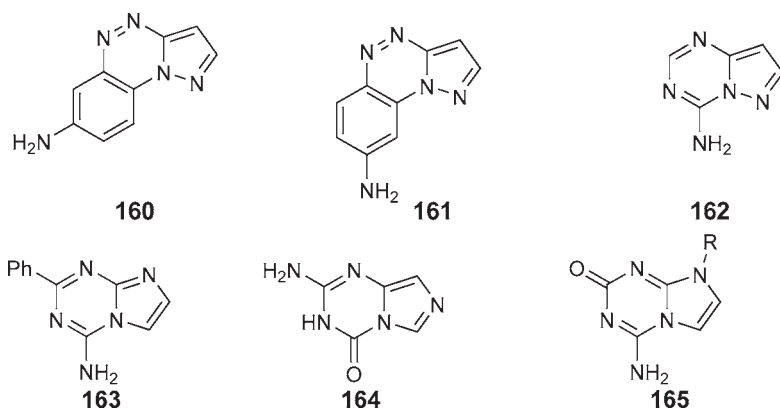
Scheme 24

Reduction of **156** to the amine **157** was carried out by palladium/charcoal <2003TL703>, whereas **158** was reduced by stannous dichloride to give **159** <1997BML89>, and both transformations proceeded in good to excellent yields.

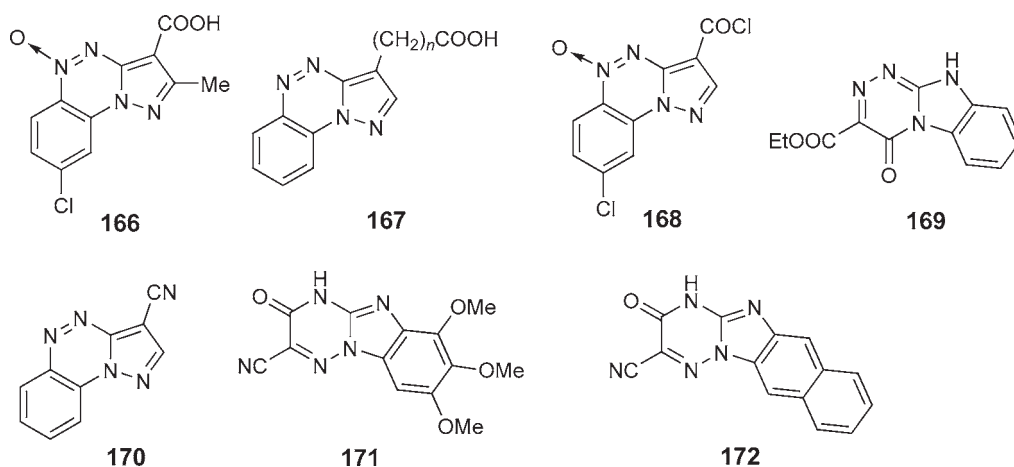
In cases of some derivatives bearing an amino substituent, conversions to acylamines, alkylamines, and amidines have been reported. These substrate amines include the above-mentioned two amino compounds **157** and **159** as well as other compounds shown in **Scheme 25**.

Thus, acylations of **157** <2003TL703>, **159** <1997BML89>, **160**, **161** <1996EJM259>, and **162** <1995NN105>, and alkylation of **163** <2002JME5030> have been published. Furthermore, transformations of the amines **164** <2004OL3691> and **165** <1996HCA1881> with dimethylformamide diethylacetal was reported to yield the corresponding amidines.

A further group of related transformations concern the conversion of various acidic functions (acid, acid chloride, ester, nitrile, etc.) to each other. The starting compounds of these reactions are shown in **Scheme 26**.



Scheme 25



Scheme 26

The carboxylic acid **166** <1999FA375> was converted to an acid chloride **168**, and the related acid **167** was transformed to various esters <2002JME5710>. Reaction of the acid chloride **168** to some esters by treatment of the respective alcohol has been carried out <1999FAS375>. The ester **169** was reacted with a large set of aniline derivatives at high temperature in xylene <2003AP413> to form amides in good to excellent yields (60–86%). Hydrolysis of the nitrile **170** <1999FA375> to the amide, transformations of the nitriles **171** <2004HCO67> and **172** <2002HCO123> to acids by acidic hydrolysis, and conversion of **172** to a hydroxamides by treatment with hydroxylamine <2002HCO123> have also been reported.

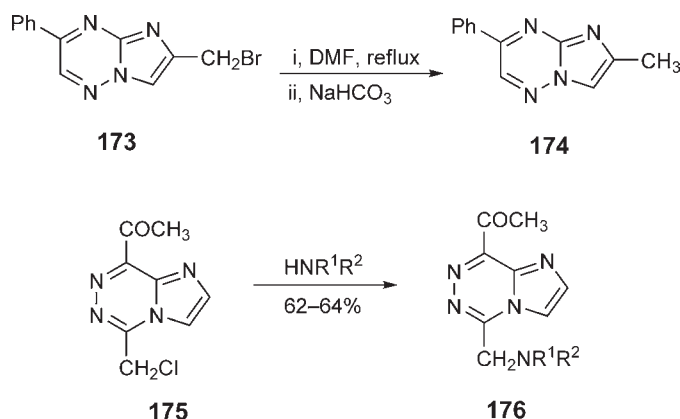
Finally, two further transformations are shortly mentioned which do not belong to any of the above categories. These are shown in **Scheme 27**. The reduction of the bromomethyl compound **173** to the methyl derivative **174** was described by Rudakov *et al.* <1998KGS110>. Also, the halomethyl derivative of another related ring system **175** was investigated in order to synthesize methylenamino derivatives **176** <1997SC2433>. These transformations proceeded at 100 °C in acceptable yields (62–64%).

11.17.6 Ring Synthesis from Acyclic Compounds

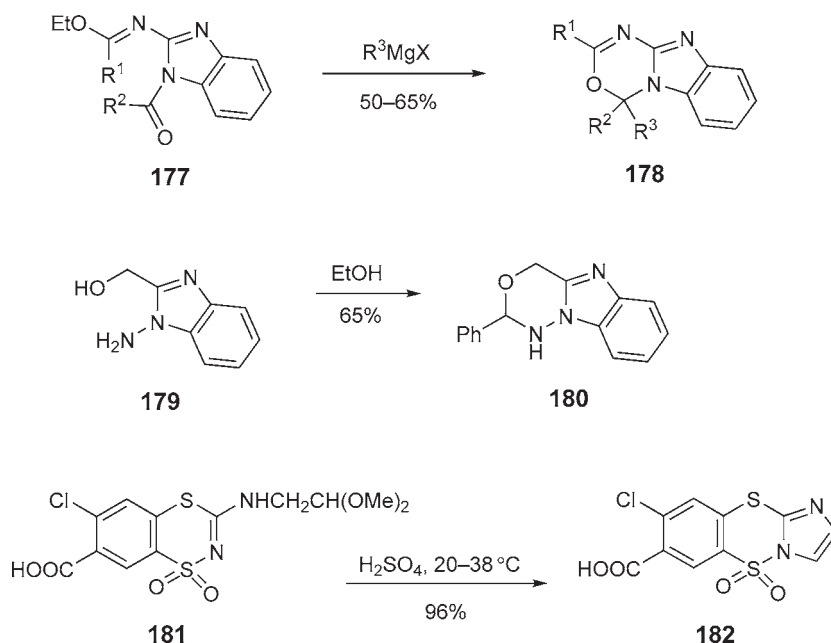
11.17.6.1 Synthesis of Fused Oxadiazines, Dithiazines, and Thiadiazines

The formation of two fused oxadiazine ring systems and one fused dithiazine ring system is illustrated in **Scheme 28**.

Abderrahim *et al.* <1997SC3039> found that treatment of the ethylenediaminobenzimidazole compound **177** with a Grignard reagent is a convenient tool for the synthesis of the partially saturated benzimidazo[2,3-*d*][1,3,5]oxadiazine



Scheme 27



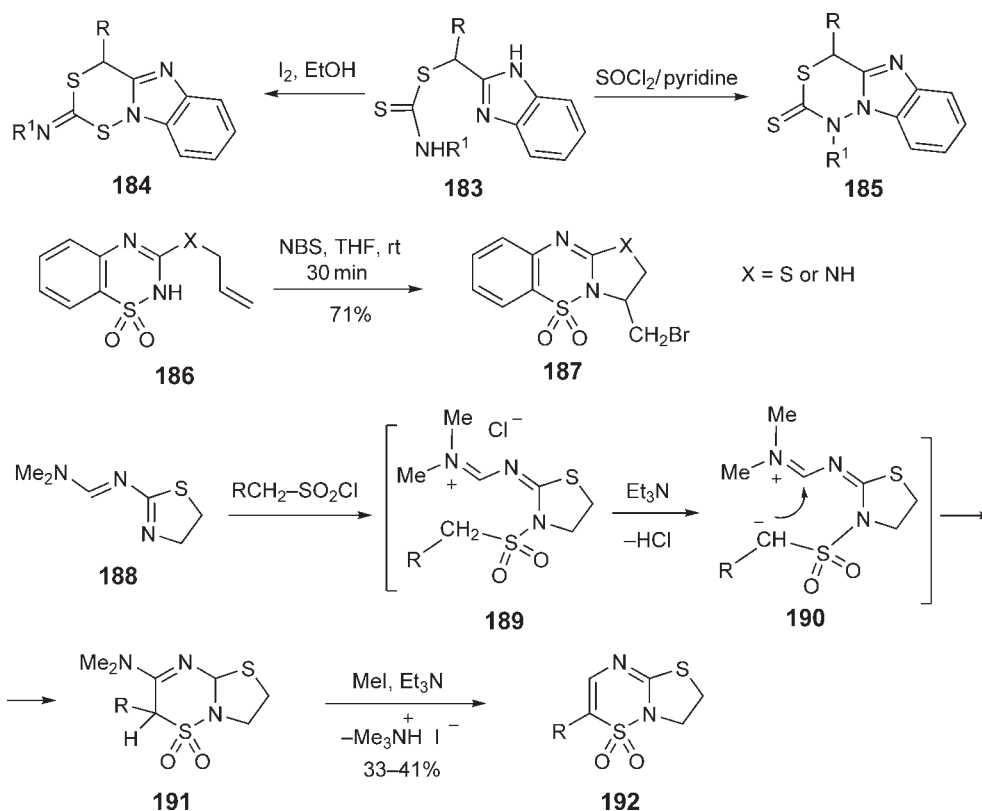
Scheme 28

ring system **178**, a benzologue of the parent bicyclic imidazo[2,3-*d*][1,3,5]oxadiazine skeleton. The similar ring closure was later also observed under electrochemical conditions, and compounds **178** were obtained in acceptable yields (50–65%) [\[2002SC241\]](#). A synthetic procedure for the related ring system benzimidazo[1,2-*d*][1,3,4]oxadiazine was described by Essassi *et al.* [\[1994BSB83\]](#). According to this publication, 1-amino-2-hydroxymethylbenzimidazole **179** undergoes cyclization when heating in ethanol to give the fused oxazine **180**.

Imidazole-fused dithiazines were synthesized by Brzozowski and Saczewski [\[2002JME430\]](#). The ring-closure reaction of the acetal **181** took place in sulfuric acid to yield the tricyclic product **182** in almost quantitative yield.

Investigations of transformations with the imidazole-containing dithiocarbamate **183** (Scheme 29) also led to recognition of formation of a fused dithiazine ring system as described by Yadav and Pal [\[1996IJB748\]](#). This compound **183**, when treated with iodine in ethanol, underwent ring closure to **184**. These authors also reported that the same starting compound **183** can undergo a different cyclization when treated with thionyl chloride in pyridine. In this case, it is the carbamate nitrogen atom that participates in the cyclization to yield the fused thiadiazine **185**.

For ring closure to *b*-fused [1,2,4]thiadiazines, two approaches were published during recent years. Chern *et al.* [\[1998JME3128\]](#) reported that derivatives **186** containing allylamino or allylsulfanyl group in position 3 of the

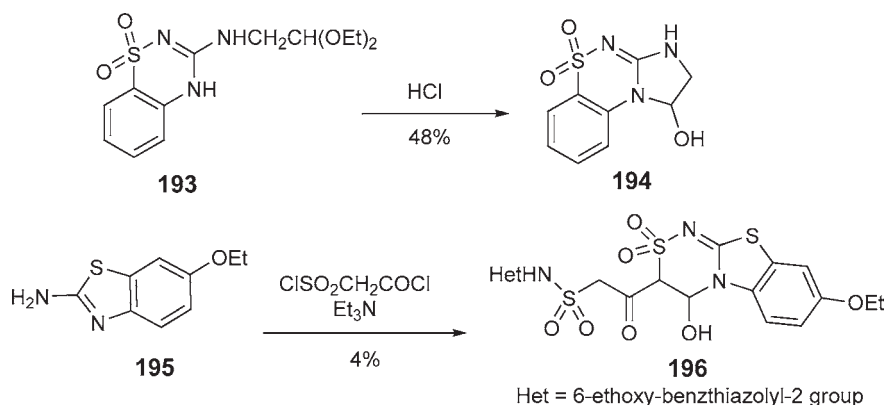


Scheme 29

benzo[1,2,4]thiadiazine ring system undergo smooth reaction with *N*-bromosuccinimide (NBS) at room temperature to afford fused imidazoles and thiazoles **187**, respectively.

Scheme 29 shows also another synthetic approach to the bicyclic thiazolo[3,2-*b*][1,2,4] ring. This mild transformation was published by Deniaud and co-workers [<2002TL4099>](#). The preparative route starts from the amidine-containing thiazolidine derivative **188** which can be treated with various sulfonyl chlorides. The authors concluded that the first step is acylation of the thiazole nitrogen atom to give a salt **189**, which, in the presence of triethylamine, undergoes the deprotonation to the zwitterion **190**. This intermediate – as shown by the arrow – undergoes cyclization to the isolable product **191**. Treatment of **191** with methyl iodide affords the final product **192** with the unsaturated six-membered thiadiazine ring.

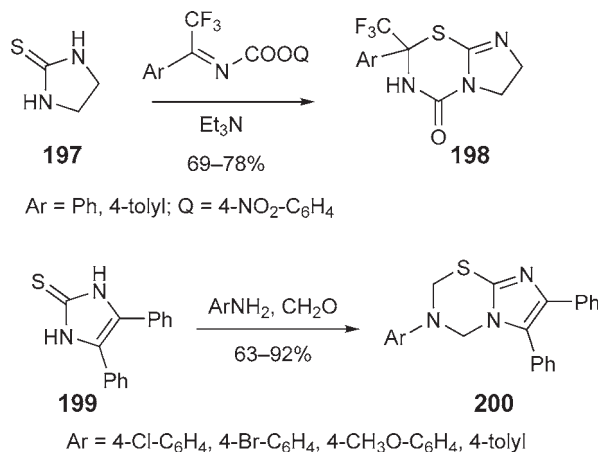
Two different *c*-fused [1,2,4]thiadiazines were synthesized nearly at the same time, and the syntheses are shown in **Scheme 30**. Boverie *et al.* [<2001JPL973>](#) reported a procedure for the imidazole ring closure, which is fairly



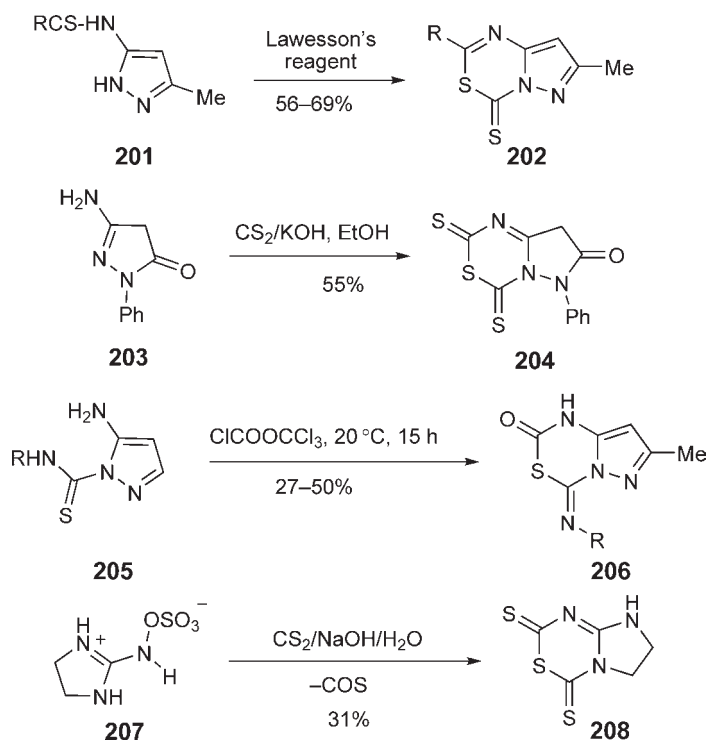
Scheme 30

reminiscent of formation of **182** discussed above: reaction of the acetal **193** with acid (in this case, hydrochloric acid) results in the ring closure to **194** in medium yield (48%). A derivative of the related thiazolo-fused ring system of fairly complicated substitution pattern was studied in more details because of its biological importance by Scarborough *et al.* <2001BML1805>. In this case, the synthetic pathway followed the ring closure of the six-membered ring: the benzthiazole compound **195** was treated with chloresulfonylacetly chloride to give **196** in very low yield (4%).

Several syntheses appeared leading to fused [1,3,5]thiadiazines. These are summarized in **Schemes 31 and 32**. The imidazo[2,1-*b*][1,3,5]triazine skeleton was synthesized by two independent groups. Vovk *et al.* <2004KGS282> reported that treatment of imidazoline-2-thione **197** with some carbamic esters in the presence of triethylamine yields the ring-closed product **198** in good yield (69–78%). In the other procedure <2000JRM401>, 2-mercapto-4,5-diphenylimidazole **199** was reacted with various anilines in the presence of formaldehyde to afford the imidazothiadiazines **200** in good to high yields (63–92%).



Scheme 31



Scheme 32

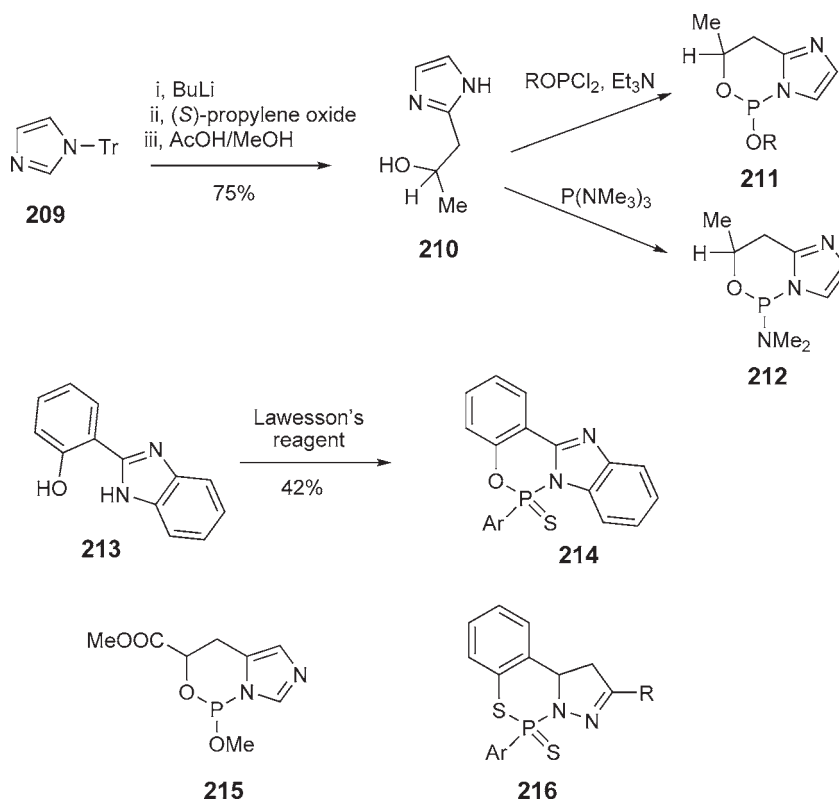
More intensive investigations have been carried out with synthesis of *c*-fused [1,3,5]thiadiazines, and the transformations are shown in [Scheme 32](#).

The pyrazolylthiocarbamate **201** when reacted with Lawesson's reagent gave rise to ring-closed thiadiazines **202** in moderate yield [\[1994JHC1477\]](#). The same authors, in another publication, reported on ring closure of another pyrazole derivative **203** by the use of thiophosgene to obtain a new pyrazolothiadiazine product **204** [\[2002JFA4839\]](#). In another procedure [\[2003HAC211\]](#), 1-phenyl-3-aminopyrazol-5(4*H*)-one was reacted with carbon disulfide to yield the bicyclic product **204**. In the third approach described by Vicentini *et al.* [\[2004JFA1898\]](#), a urea **205** was used as a starting compound: its treatment with trichloromethyl chloroformate at room temperature gave rise to the pyrazolylthiadiazine product **206**, unfortunately in poor to medium yields only (27–50%).

Investigation of transformations of the zwitterion **207** led to the elaboration of a new synthetic route to imidazo[1,2-*c*]-thiadiazines [\[2003JOC4791\]](#). Treatment of this compound **207** with carbon disulfide in the presence of sodium hydroxide resulted in elimination of carbon oxide sulfide and in formation of the cyclized product **208**.

11.17.6.2 Synthesis of Fused Oxazaphosphinines and Diazaphosphinines

Novel bicyclic imidazo-oxazaphosphinines have been synthesized in high diastereoselectivity by Marsault and Just [\[1996TL977\]](#). In the first step, *N*-tritylimidazole **209** was lithiated and, subsequently, treated with (*S*)-propylene oxide as a chiral auxiliary and acetic acid to give the intermediate **210**, which was reacted with alkyl dichlorophosphate to yield the ring-closed product **211** as a single diastereomer ([Scheme 33](#)). Extension of these approaches for further derivatives **212** has also been published [\[1998NN939\]](#).

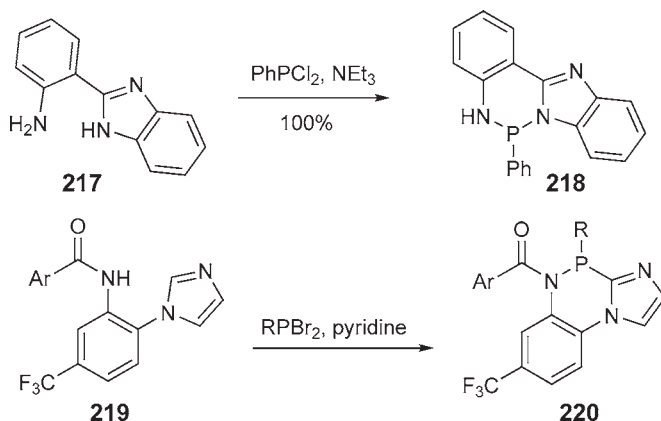


Scheme 33

In [Scheme 33](#), ring closure to a related benzologue is also shown [\[2002PS2675\]](#): reaction of 2-(2'-hydroxyphenyl)benzimidazole **213** with Lawesson's reagent yielded the tetracyclic product **214** in one single step in medium

yield (42%). Another study applying similar methodology also appeared [\[2004HAC307\]](#). These cyclization techniques resulting in formation of imidazo[1,2-*c*][1,3,2]oxazaphosphinines have also been successfully applied for other related ring systems. Thus, the imidazo[3,4-*c*][1,3,2]oxazaphosphinine derivative **215** [\[1998NN939\]](#) and pyrazolo[2,3-*c*][1,3,2]oxazaphosphinine compound **216** [\[2005JHC1143\]](#) have been obtained by analogous procedures.

Synthesis of two different diazaphosphinine ring systems has been accomplished recently, as shown in [Scheme 34](#). The synthesis of **218** was achieved by treatment of the aminophenylbenzimidazole compound **217** with dichlorophenylphosphine [\[2004HAC321\]](#). The product was obtained in quantitative yield. The synthesis of the related ring system **220** was studied by a Ukrainian research group [\[2002HAC84, 2002KGS385, 2002PS1767\]](#). In all of the syntheses described in these publications, an imidazole derivative functionalized by an acylaminoanilino side chain attached to the imidazole ring nitrogen atom was transformed under appropriate conditions. Thus, treatment of **219** with dibromoalkylphosphine in pyridine gave rise to formation of **220**.

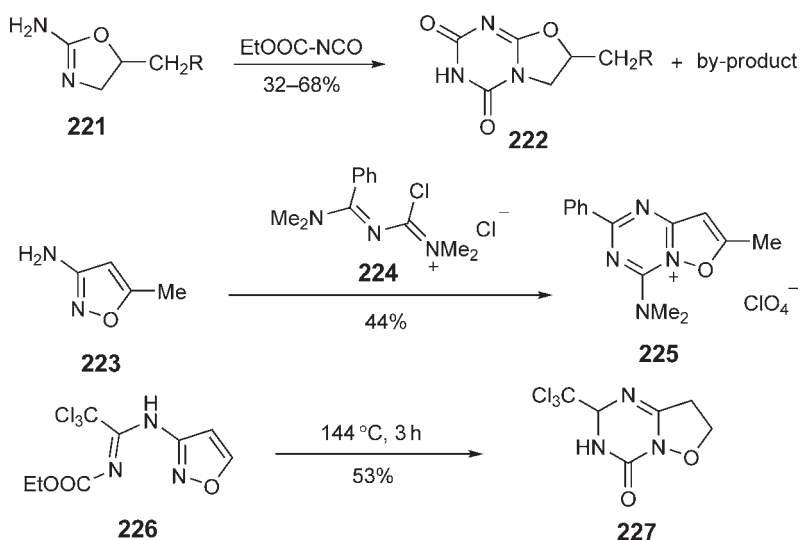


Scheme 34

11.17.6.3 Synthesis of Fused [1,3,5]Triazines

11.17.6.3.1 Oxazolo- and isoxazolo[1,3,5]triazines

Synthetic routes to these ring systems have already been discussed in CHEC-II(1996) [\[1996CHEC-II\(8\)445\]](#). Some recently described procedures are shown in [Scheme 35](#).



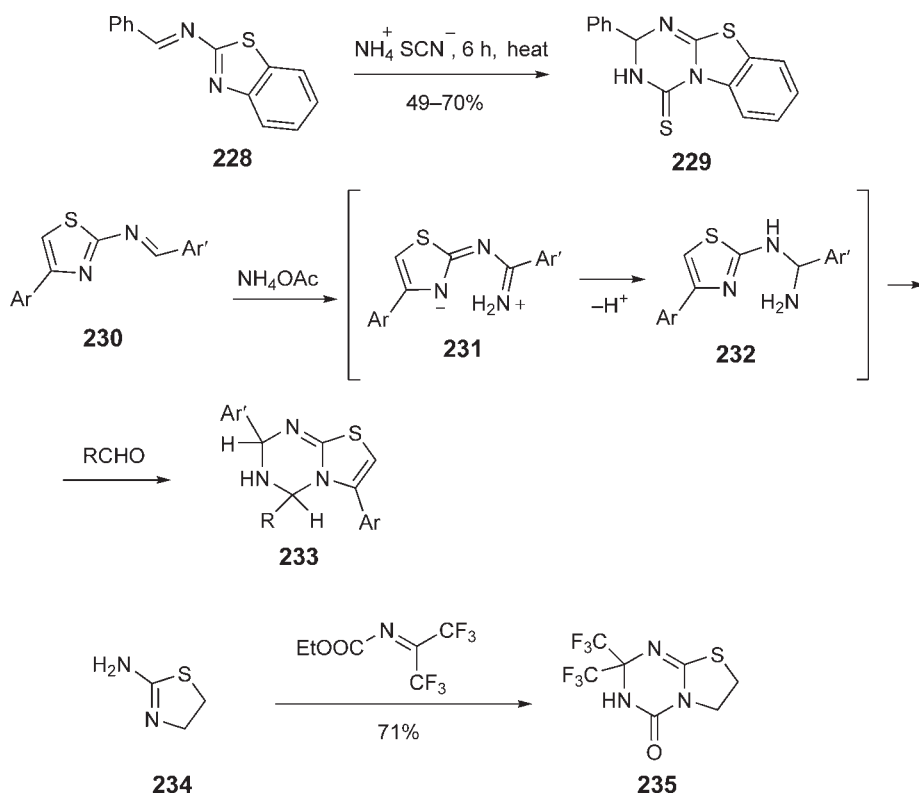
Scheme 35

Transformation of the aminooxazoline **221** by ethoxycarbonyl isocyanate to the ring-closed product **222** is modification of an earlier recognized methodology <1997JHC429, 1997MI291, 1998MI9>. The cyclized products were separated from a undesired by-product and were isolated in low to medium yield (32–68%). A similar technique was also applied to the synthesis of the benzologous system <2001KGS567>.

Two new syntheses to fused isoxazoles are worth mentioning. In a study for the synthesis of various related fused [1,3,5]triazinium salts, Okide described <1994JHC535> the conversion of 3-amino-5-methylisoxazole **223** with the iminium salt **224**. The quaternary perchlorate salt **225** was obtained in medium yield (44%). A Russian research group <2004KGS592> reported that the isoxazole derivative **226** undergoes thermal cyclization when heated in xylene at higher temperature for an extended time, and the cyclized product **227** can be obtained in 53% yield.

11.17.6.3.2 Thiazolo[1,3,5]triazines

Research on only one ring system, thiazolo[3,2-*a*][1,3,5]triazine, was published in recent years. Although in CHEC-II(1996) <1996CHEC-II(8)445> ring closures to this skeleton ring were already discussed, some new approaches also appeared. These are shown in Scheme 36.



Scheme 36

Kriplani *et al.* <2005HCO527> published that Schiff bases formed from 2-amino-benzothiazoles **228** easily undergo ring closure to fused triazine-thiones **229** when treated with ammonium thiocyanate in dioxane under heating. The products were obtained in medium to good yields (49–70%).

Yadav and Kapoor <2003TL8951> reported on a microwave-assisted ring closure leading to novel thiazolo[1,3,5]-triazines, as shown in Scheme 36. This three-component one-pot procedure started from the thiazolyl Schiff base **230**, to which ammonium acetate and an aldehyde was added. In the first step, the azomethine moiety of the Schiff base reacted with ammonia to give the zwitterionic first intermediate **231**, which underwent deprotonation to the amine **232**, and, finally, reaction of this second intermediate with the aldehyde involving the ring-closure step afforded the product **233**. It is important to emphasize that the MW-assisted technique ensured high yields (76–88%)

and high selectivities (>97%) concerning formation of the possible *cis-trans*-geometric isomers (*cis* proved to be highly preferred), whereas similar transformations under thermal conditions proceeded in poor yield and with low selectivities.

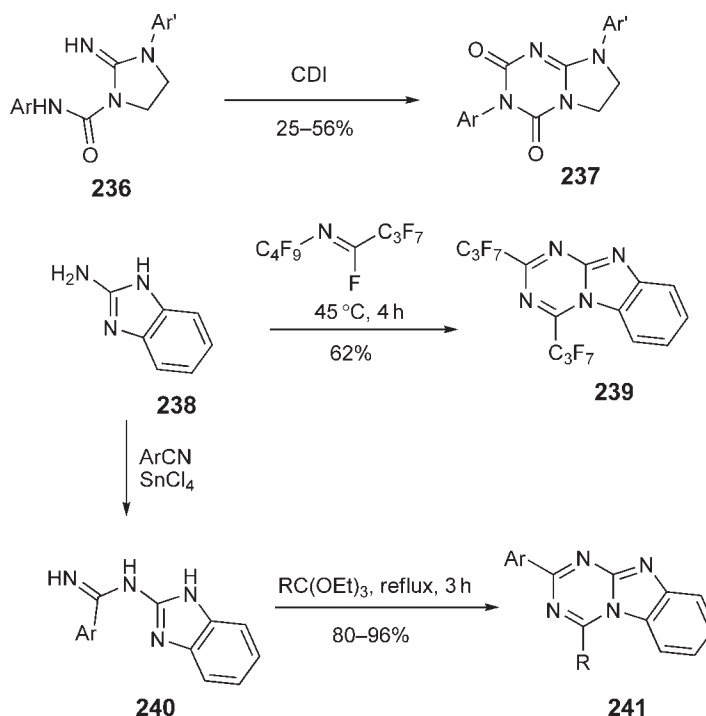
Sokolov and Aksinenko described a series of transformations of 2-aminoazoles and azines with *N*-ethoxycarbonyl-hexafluoroacetone imine <2003IZV2053>. In this research, these authors found that 2-aminothiazoline **234** can be transformed to the ring-closed compound **235** in good yield (71%).

Some other synthetic research on thiazolo[3,2-*a*][1,3,5]triazines has also appeared <1995ZOB480, 1997JIC818, 1997ZOR96, 1998IZV1670, 2003PS2563, 2003JCCS1085>.

11.17.6.3.3 Imidazo[1,2-*a*][1,3,5]triazines

Various ring-closure reactions leading to this ring system were described in CHEC-II(1996) <1996CHEC-II(8)445>, but also some new approaches were published during the recent period.

Novel cyclizations implying the ring closure of the six-membered triazine ring are shown in Scheme 37.



Scheme 37

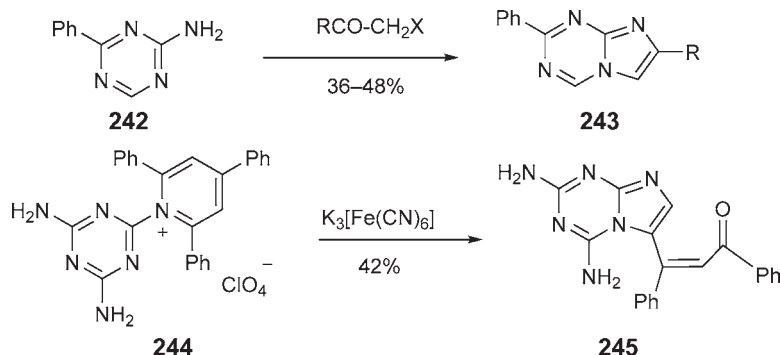
A Polish research group synthesized a large set of derivatives of the title ring system by treatment of the imidazoline derivative **236** with 1,1'-carbonyldiimidazole (CDI) <2002EJM761>. The reaction took place in DMF in 3 h under heating to give the products **237** in poor to medium yields (27–56%). These authors also carried out the cyclization with an *N*-carbamoyl derivative related to **236** by using phosgene as a cyclizing agent.

Synthesis of benzimidazolo[1,2-*a*][1,3,5]triazine bearing fluorosubstituents has also been published <2000JFC105, 2000ZOR120>: 2-aminobenzimidazole **238** was reacted with a perfluoroazomethine at 45 °C to give the product **239** in good yield (62%).

Indian authors reported the ring closure of the imidazolylamidine **240** to the tricyclic fused triazine **241** <1998IJB1283>. The reaction with aliphatic orthoesters was carried out under reflux conditions to yield the products in excellent yields.

In Scheme 38, two novel cyclizations are shown where the five-membered ring is formed during the reactions. Thus, some 2-amino[1,3,5]triazines **242** were subjected to ring closure by reaction with various halomethylcarbonyl compounds

(phenacyl bromide, chloroacetone, etc.) to give the cyclized products **243**, mostly in medium yield (36–48%). Another procedure [<1996CCC770>](#) starts from the quaternary salt **244**. This compound was oxidized by potassium ferricyanide to give **245** in modest yield (42%).

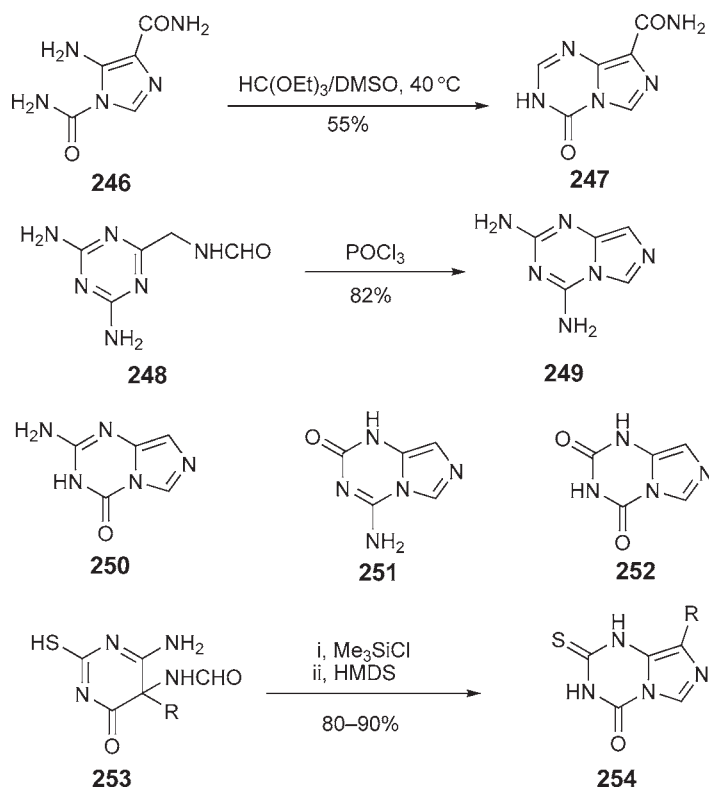


Scheme 38

Some other syntheses of imidazo[1,2-*a*][1,3,5]triazines or its benzologues have also appeared [<1994H\(37\)689, 1997AP59, 2001JOC5012, 2003TL3705, 2005AP365, 2005T6073>](#).

11.17.6.3.4 Imidazo[1,5-*a*][1,3,5]triazines

In CHEC-II(1996) only one cyclization procedure was discussed in more detail [<1996CHEC-II\(8\)445>](#). During the recent years, however, some basically new approaches were reported, and these are shown in [Scheme 39](#).



Scheme 39

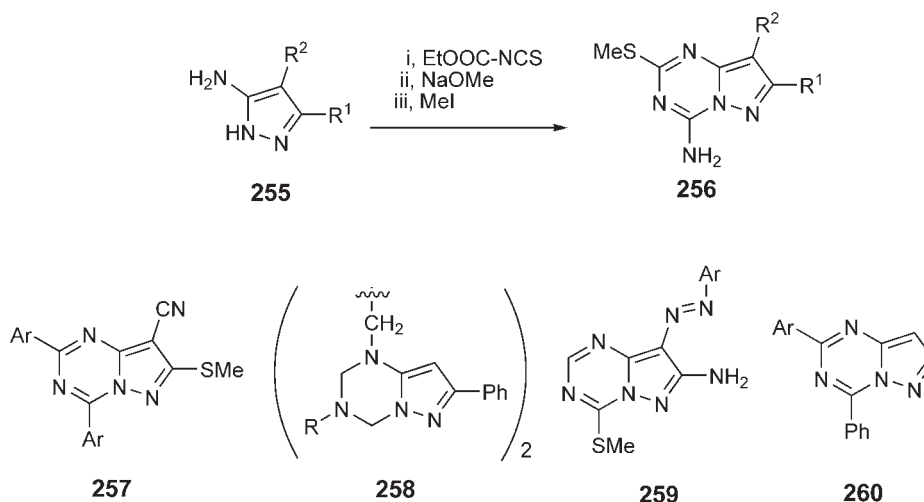
An English research group described the ring closure to give the title skeleton by closure of the six-membered triazine ring <1996BML185>. In this procedure, the imidazole derivative **246** was transformed by triethyl orthoformate to give the fused triazine compound **247**. The same research group later published a modified procedure <1998J(P1)1669>, which allowed the extension of the cyclization to several substituted derivatives in moderate yields (35–48%).

Eschenmoser and co-workers <2003OL2067, 2004OL3691, 2005HCA1960> carried out thorough synthetic studies for preparation of some imidazo[1,5-*a*][1,3,5]triazines with particular substitution patterns such that these compounds could be considered as nitrogen-positional isomers of some nucleobases. One of the typical synthetic steps is treatment of the diaminotriazine derivative **248** with phosphorus oxychloride to give the cyclized purinoid **249** in high yield (82%). Modification of this procedure also allowed preparation of the various oxo- and amino-related derivatives **250–252**.

Golankiewicz *et al.* <1995JME3558> described a synthesis of the title ring system by ring closure of the five-membered ring. In this case, the pyrimidine compound **253** was treated first with trimethylchlorosilane and, then, with hexamethyldisilazane, and as a consequence of a quite complicated rearrangement the imidazotriazine compound **254** was obtained in excellent yield (80–90%).

11.17.6.3.5 Pyrazolo[1,5-*a*][1,3,5]triazines

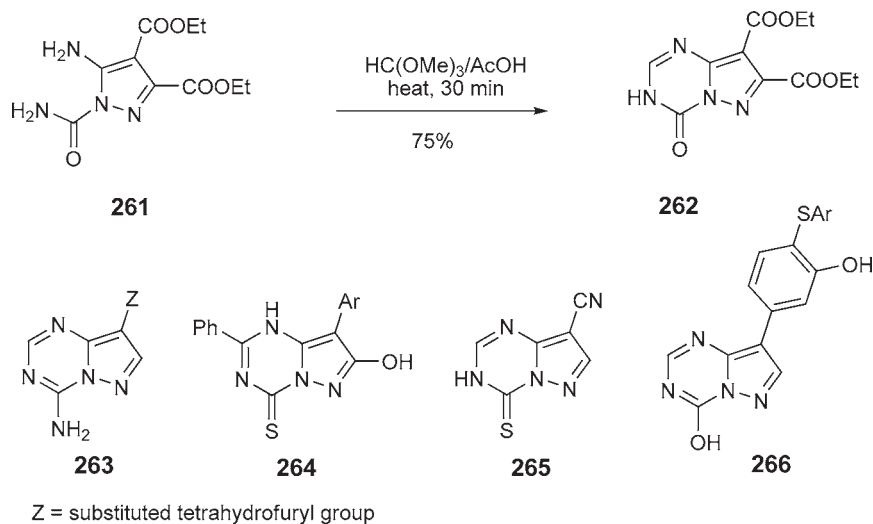
In contrast to the fact that only limited amount of information on the synthesis of this ring system appeared in CHEC-II(1996) <1996CHEC-II(8)445>, fairly substantial synthetic work in this area has been published recently and some research closely related to established methodologies also appeared recently <2001SC3453, 2004SC805>. The main reason for this increased interest is obviously the biological importance of some derivatives. Interestingly, these procedures start from, without exception, aminopyrazoles. Three strategic pathways have been realized depending on the different compilations of the ring nitrogen atoms: (1) transformation of 3-aminopyrazoles with reagents providing one more nitrogen atom, (2) transformation of aminopyrazoles bearing also a functional group containing nitrogen atom, and (3) transformation of a pyrazole compound bearing an amidine side chain. Some representative cyclization reactions are shown in Schemes 40, 41, and 42, respectively, with concise references for some other synthetic work applying a similar synthetic strategy.



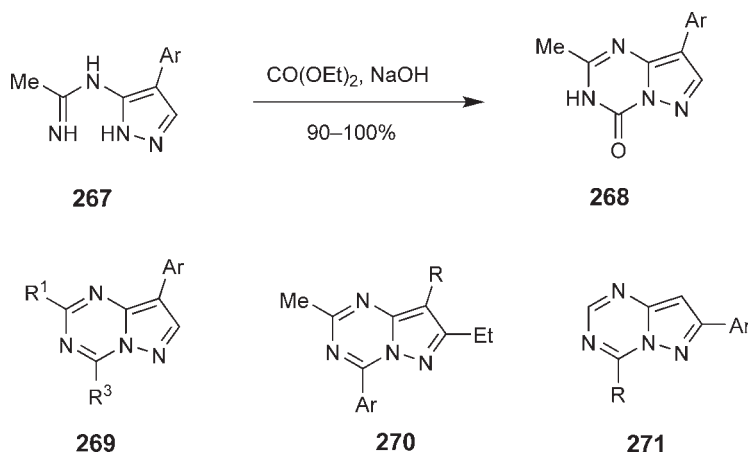
Scheme 40

11.17.6.3.5(i) Method (1)

A typical cyclization reaction starting from a 3-aminopyrazole is the transformation of **255** <2000BML821>. This compound was treated first with ethoxycarbonyl isothiocyanate followed by sodium methoxide to yield a cyclic intermediate which was methylated by methyl iodide to give the stable product **256**. In the cases of the synthesis of **257** <1995PHA675>, the dimeric **258** <2005JHC975>, the azo-substituted **259** <2001JCM439>, and the diaryl



Scheme 41



Scheme 42

compound **260** <2005AP365>, aminopyrazole was used as starting compound. Some other modifications of the same synthetic strategy is that an intermediate of the reaction of the 3-aminopyrazole with an appropriate reagent (e.g., isocyanate) is first isolated and this compound is subjected directly to the ring closure <2001SC3459, 2003C248>.

11.17.6.3.5(ii) Method (2)

In this category of syntheses, the starting compound is an aminopyrazol bearing also a functional group containing one nitrogen atom. Such a reaction is shown in **Scheme 41**. Thus, a Japanese group <1998H(48)2095> reported that the aminopyrazole **261**, also containing a carbamoyl group on the ring nitrogen atom, can be subjected to ring closure by treatment of trimethyl orthoformate to give the diester **262**. Four derivatives, **263** <1996NN1223>, **264** <1998PHA368>, **265** <1997JRM2255>, and **266** <1997PS305>, have also been synthesized from starting pyrazole compounds of a similar heteroatom pattern.

11.17.6.3.5(iii) Method (3)

In **Scheme 42**, results of ring-closure reactions of amidine-containing pyrazoles are summarized. A typical procedure was published by Gilligan and co-workers <2000JME449>: the pyrazolylamidine **267** was treated with diethyl carbonate in the presence of sodium hydroxide to afford the ring-closed product **268** in almost quantitative yields. Compound **269** <2001JME350> was synthesized with the use of orthoester as a reagent, whereas the syntheses of **270** also started from an amidine, and acid chloride was the ring-closing agent <2003BMC4093>. (In this latter case, an alternative procedure starting from 2-aminopyrazole was also described.) Compound **271** was prepared – also starting from an amidine – via a somewhat more sophisticated mechanism <2003SI201>.

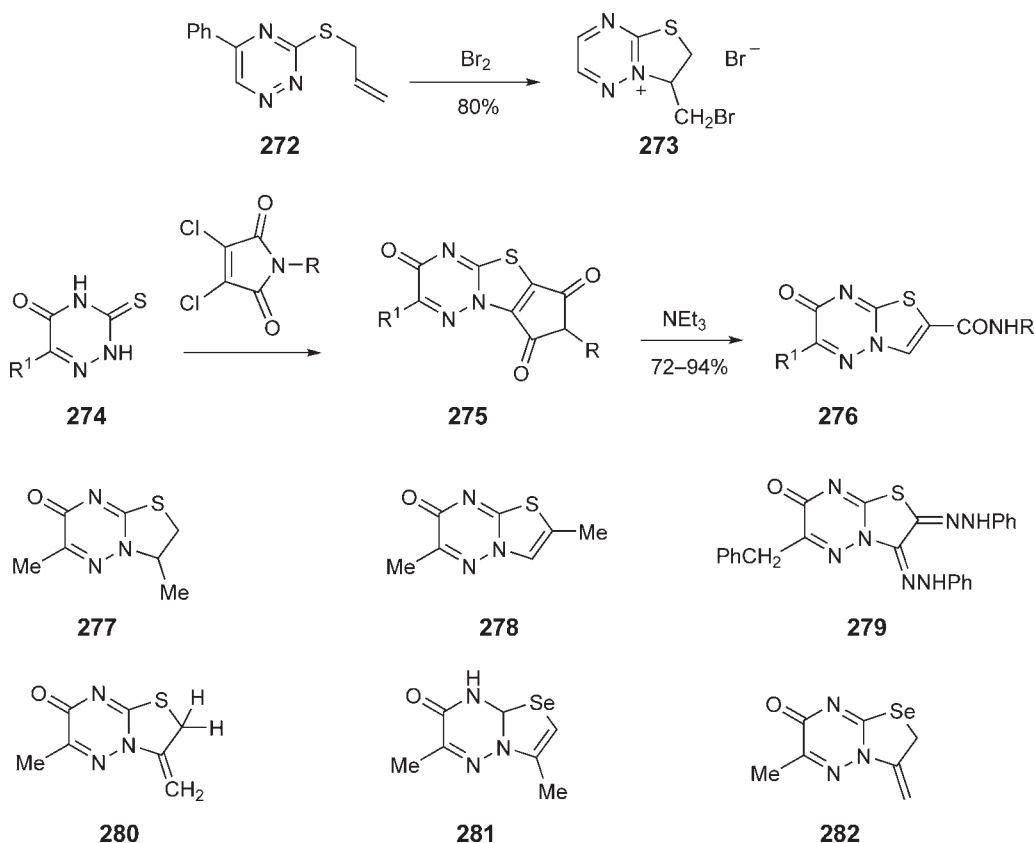
11.17.6.4 Synthesis of Fused [1,2,4]Triazines

11.17.6.4.1 *b*-Fused [1,2,4]triazines

11.17.6.4.1(i) Fused thiazoles and selenazoles

Research work in this area was concentrated to synthesis of thiazolo[3,2-*b*][1,2,4]triazine ring system and its selenazole analogue. While only three such procedures were discussed in CHEC-II(1996) <1996CHEC-II(8)445, 1984J(P1)2707, 1985KGS1497, 1987KGS554>, quite substantial new literature data have appeared in recent years. Two typical synthetic approaches are shown in **Scheme 43**, and reference to six further derivatives is also provided.

A Russian team <1997ZOR1103> reported that the allylthiotriazine compound **272** is a convenient starting compound for ring closure to the bicyclic ring system: treatment of this compound with bromine under mild conditions results in formation of the salt **273** in high yield (80%). A Ukrainian research group found a different approach to thiazolotriazines starting also from a [1,2,4]triazine derivative <2001H(55)2189>: **274** was reacted with dichloromaleinimide to give a tricyclic intermediate first **275**, which was subjected to a further transformation by triethylamine to yield the bicyclic product **276**.



Scheme 43

Several other procedures to derivatives of this ring system have been published; in most of these, basically the above or related synthetic techniques were used. These have been applied to the synthesis of **277** <2000PS95>, its unsaturated analogue **278** <2000PS239, 2000JCM464>, the bishydrazone **279** <2002JCCS1035>, and the derivative **280** <2000ZOB650>. The two analogous selenazoles **281** and **282** have also been synthesized <1998SC233, 1998IJB587>.

11.17.6.4.1(ii) Fused imidazoles

Concerning the synthetic procedures to these ring system, various methods have been published in CHEC-II(1996) <1996CHEC-II(8)445>. The recently reported approaches can be categorized basically into two groups: (1) ring closure of the six-membered triazine ring by reaction of a 1,2-diaminoimidazole with an α -bifunctional reagent and (2) conversion of a 3-amino[1,2,4]triazine derivative with an appropriate reagent to form the imidazole ring. The novel syntheses are shown in **Scheme 44**. The first three examples belong to group (1), whereas the further syntheses represent group (2).

Ring closure of the 1,2-diaminoimidazole compound **283** to **284** was carried out in boiling methanol in medium to excellent yields <2004SL549>, whereas transformation of a related diaminoimidazole **285** was accomplished with a 2,4-dioxobutyric acid reagent in acetic acid to give the bicyclic product **286** in good to high yield (64–84%) <1998KGS258>. In the case of the benzologue diaminobenzimidazole **287**, ring closure with diethyl dicyanobutenedioate was described to give the tricyclic fused triazine **288** in poor yield (20%) <1999JHC1317>. Spectroscopic studies indicate the presence of an internal hydrogen bond.

In the other cases shown in **Scheme 44**, aminotriazine or its derivatives serve as starting compound for the ring closures. Thus, substituted 3-amino[1,2,4]triazines **289** were reacted with appropriate azulene derivatives bearing a halomethylenecarbonyl substituent (a reagent analogous to phenacylbromide) to yield **290** <2003H(59)359>, the two closely related 3-amino-5-ethenyltriazines **291** and **293** were cyclized with diethyl oxalate and 2-ethoxyethanol, respectively, to yield a dioxo-substituted **292** and a saturated imidazole moiety **294** <1999PHA347>.

Various derivatives of 3-amino[1,2,4]triazin-5-one **295** were transformed by reaction with glyoxal in the presence of alcohols, thiols, or amines to give a dihydroimidazole ring-containing product with a moiety provided by the co-reagent in position 2 **296** <2003OL4595>. The reaction takes place overnight at 80 °C in dioxane in high yields (80–90%). Ring closure of **297** bearing the 1-aminonaphthyl substituent does not follow the same synthetic pattern as above, still the strategy of compilation of the five-membered ring is similar: upon heating in acetic acid, the amino group of the naphthalene ring attacks the adjacent oxo function, and the condensation gives rise to the tetracyclic product **298** in high yield <2002HCO123>. The procedure was also applied in other analogous cases <2004HCO67>. Bromination of **299** also represents an outstanding pathway: the rapid reaction affords the quaternary salt **300** in high yield <1998KGS110>. Synthesis of two camphor-related imidazotriazines **301** <2001JHC379> and **302** <1998JHC293> should also be mentioned here. In both cases, some of the earlier established ring closures were applied.

11.17.6.4.1(iii) Fused pyrazoles

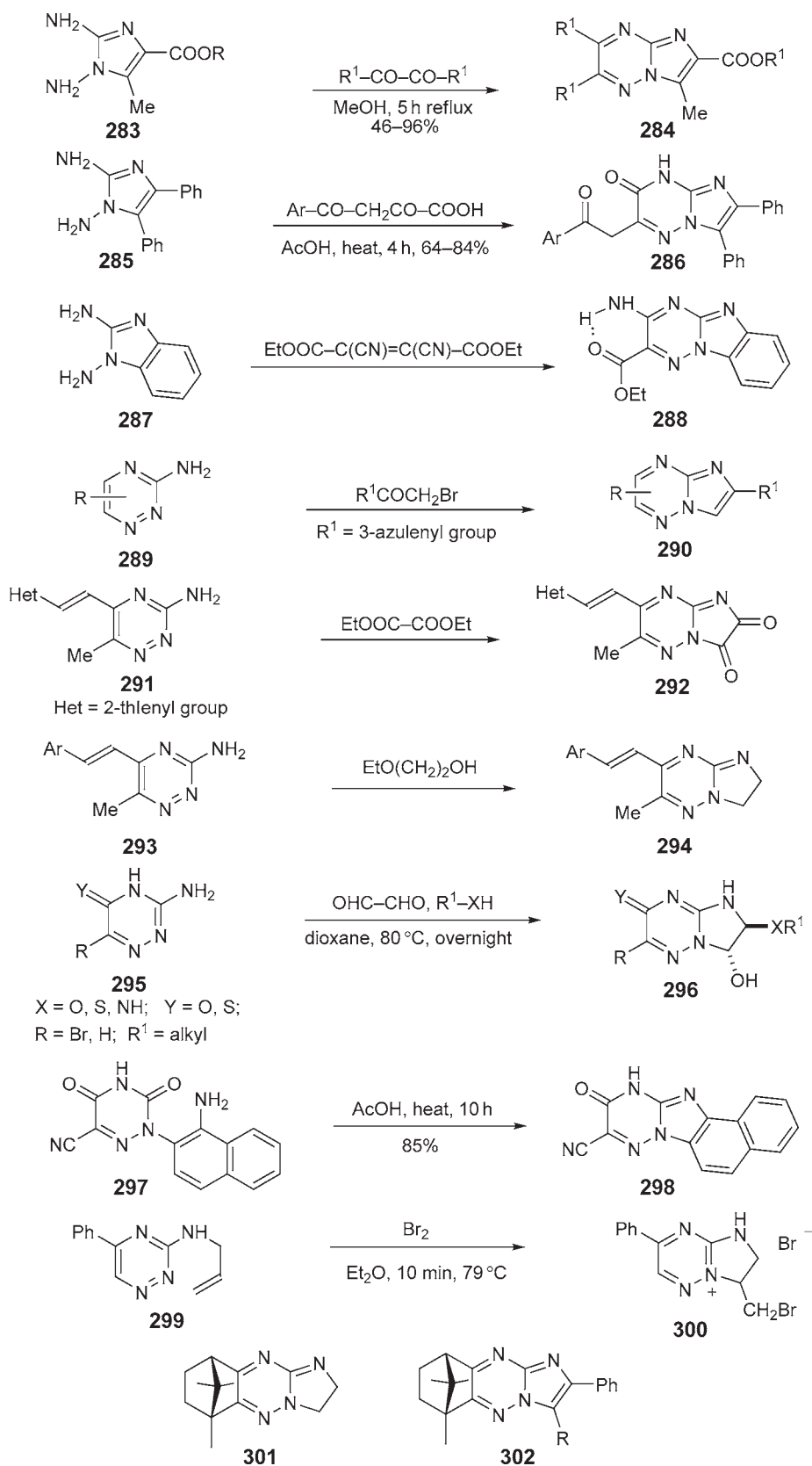
Synthesis of 2,3-disubstituted 7-*tert*-butylpyrazolo[1,5-*b*][1,2,4]triazines were reported by McNab and co-workers <2003OBC4268>. The reaction (**Scheme 45**) followed an earlier pathway: the 1,5-diaminopyrazole derivative **303** was reacted with a dioxo reagent (diacetyl or benzyl) to yield the ring-closed product **304** in poor to medium yield (27–54%).

11.17.6.4.2 c-Fused [1,2,4]triazines

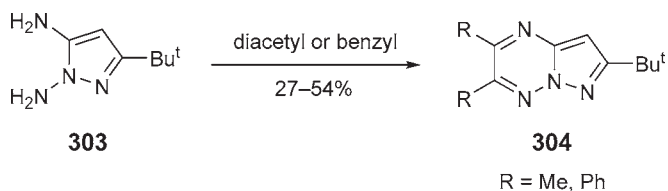
11.17.6.4.2(i) Fused oxazoles, thiazoles, and selenazoles

A fairly substantial amount of preparative work on the title ring systems has been published in the recent years. Some procedures are closely related to earlier elaborated methods reviewed in CHEC-II(1996) <1996CHEC-II(8)445>, but some new approaches have also been recognized. The majority of the available literature relates to one ring system, thiazolo[2,3-*c*][1,2,4]triazine, whereas synthesis of four others have also been reported. Synthetic routes to these four ‘outstanding’ ring systems are discussed first and shown in **Schemes 46** and **47**.

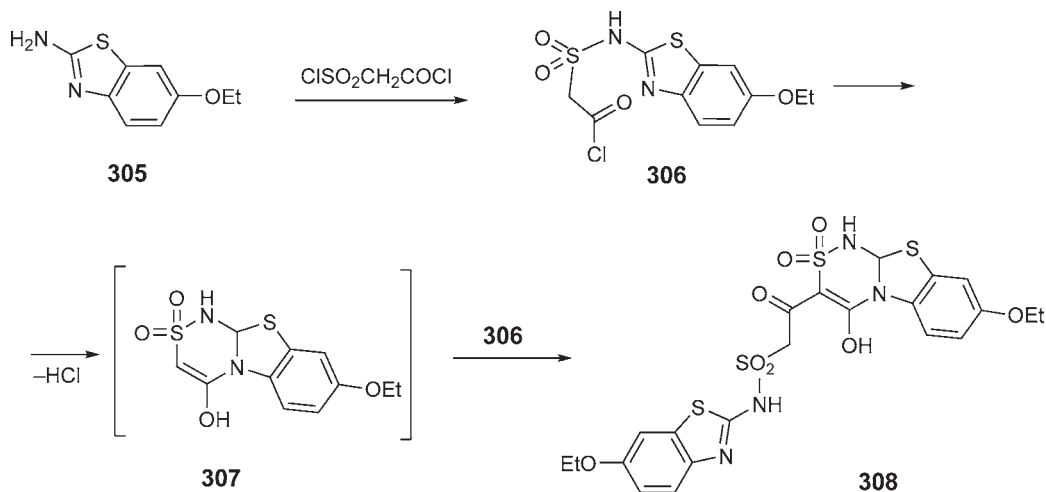
Because of its importance in biological areas, special efforts have been made with the synthesis of the thiazolo[2,3-*c*]-[1,2,4]thiadiazole derivative **308** <2001BML1805>. The pathway started from the benzothiazole derivative **305** which was treated with chlorosulfonylacetyl chloride to form an intermediate **306**, which underwent cyclization to a second intermediate **307** with hydrogen chloride elimination. The last step is the attack of the first intermediate **306** at the thiadiazine carbon atom to form the final product **308**.



Scheme 44

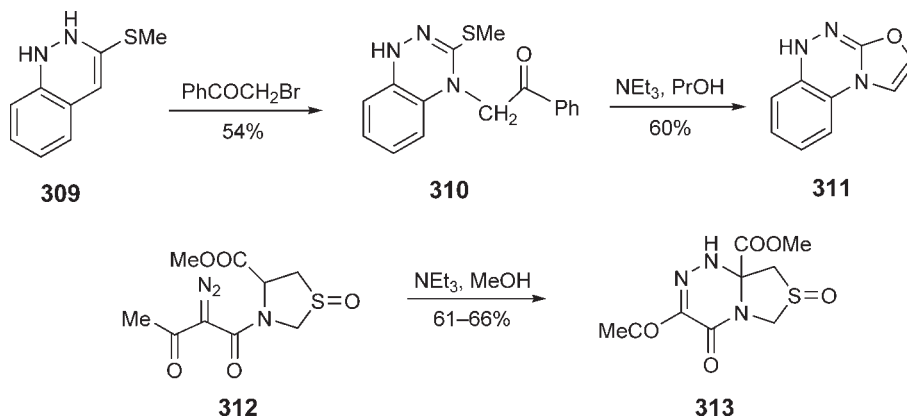


Scheme 45



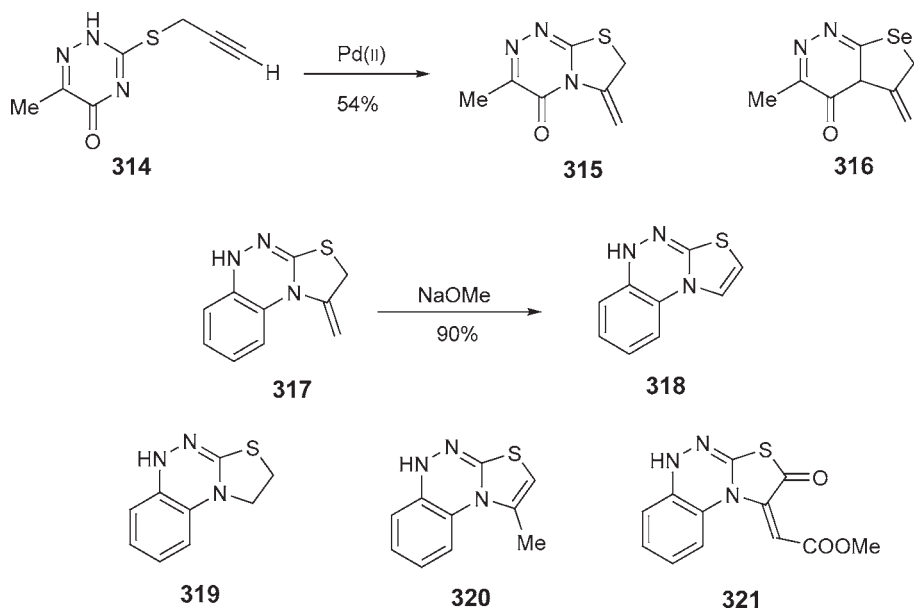
Scheme 46

Indian authors reported a synthetic route to the novel ring system oxazolo[2,3-*c*]benzo[1,2,4]triazine <1998IJB585> (Scheme 47). Thus, 1,2-dihydro-3-methylsulfanobenzo[1,2,4]triazine **309** was alkylated with phenacyl bromide selectively at nitrogen N-4 to give **310**, and this compound underwent cyclization when refluxed in a mixture of propanol and triethylamine for a prolonged period (72 h) to yield **311** in medium yield (60%). Stereoselective transformation of the partially saturated thiazolo[4,3-*c*][1,2,4]triazine derivative **312** was reported by Stoodley *et al.* <1999J(P1)1067>. The reaction of **312** was carried out in refluxing methanol in the presence of triethylamine to yield the product **313** retaining the stereochemistry of the starting compound in medium yield (61–66%).



Scheme 47

Most of the chemical transformations shown in **Scheme 48** were described by an Irani research group during the past decade. All these efforts were aimed at elucidation of synthetic routes to thiazolo[2,3-*c*][1,2,4]triazine compounds and also to its selenazo analogues.



Scheme 48

The basic method of Heravi *et al.* <1996IJB1260, 2002PS2491> is the palladium-catalyzed transformation of the *S*-propargyl compound **314**: its treatment with a Pd(II) catalyst resulted in the ring closure to the thiazole part containing an *exo*-methylene moiety **315**. The related selenazole **316** was also synthesized <1998IJB587, 2001PS87>.

Similar reactions proved to be successful with the benzologue **317** <1997M1143, 1998SC233, 2001PS87>, as shown in **Scheme 48**. This compound, interestingly, was converted by sodium methoxide to the more stable tautomeric form **318**. Further work carried out by the same research group also resulted in the synthesis of thiazolo[2,3-*c*]benzo[1,2,4]triazines with different extent of saturation and different substitution pattern in the thiazole ring (**319**, **320**, **321**) <2003PS797>. These compounds were synthesized starting from 1,2-dihydro-3-mercaptopbenzo[1,2,4]triazines by using 1,2-dichloroethane, propargyl bromide, and DMAD, respectively, as reagents.

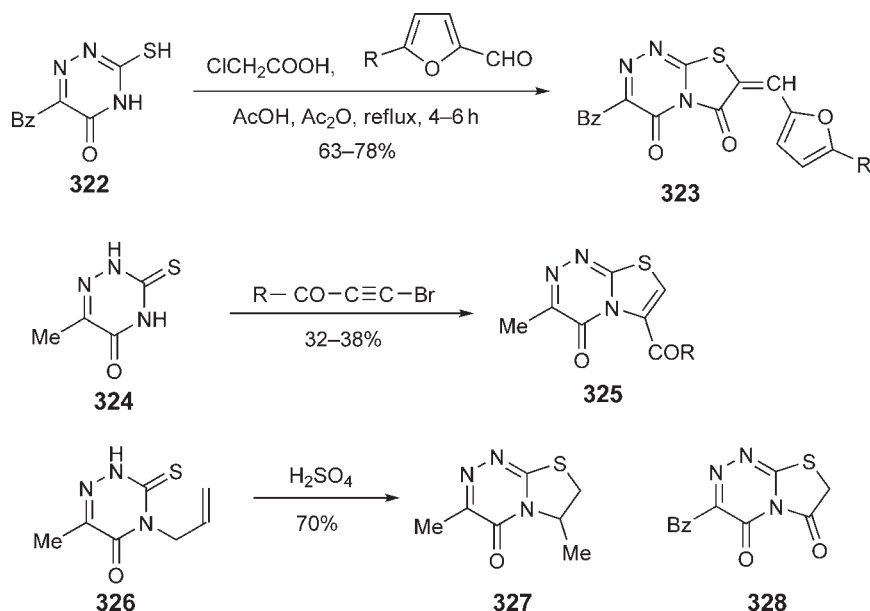
A novel three-component synthesis of triazinothiazolones was reported by Sarojini and co-workers <2005SC333> (**Scheme 49**). The triazinone compound **322** was treated with chloroacetic acid in the presence of 5-arylfuran carboxaldehyde in a mixture of acetic acid and acetic anhydride under reflux conditions to give the cyclized products **323** in good yields (63–78%). Two other syntheses of these derivatives are also shown in this scheme: reaction of the triazinethione compound **324** with some bromoalkynylketone reagents yielded the thiazolotriazinones **325** in relatively low yield <1996IZV2971>, whereas ring closure of **326** in sulfuric acid at 50°C was reported <2000PS95> to give **327** in good yield (70%). Ring closure to **328** <2003PS1143> as well as other related compounds <2005JCM632, 1995IJB423> also appeared.

11.17.6.4.2(ii) Fused imidazoles

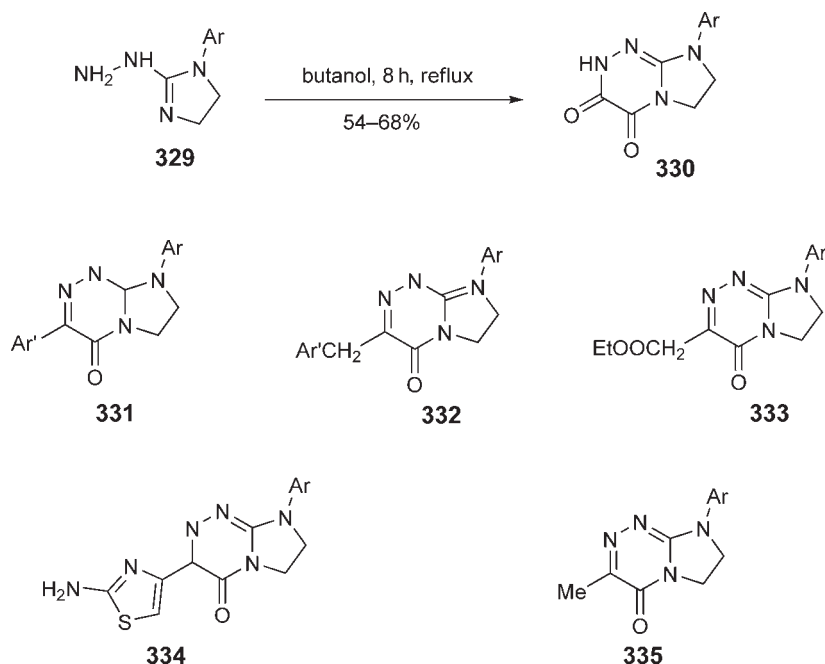
Two different fused imidazoles, imidazo[2,1-*c*][1,2,4]triazines (extensive literature data) and imidazo[5,1-*c*][1,2,4]triazines (much less information), are discussed in this section.

All synthetic approaches to imidazo[2,1-*c*][1,2,4]triazines published during recent years utilize the ring closure of the six-membered triazine ring by conversion of a properly functionalized imidazole compound.

Thorough studies on this ring system have been carried out by Sztanke *et al.* during the past decade. The representative cyclization step is shown in **Scheme 50**: the 2-hydrazinoimidazoline compound **329** when reacted with diethyl oxalate in butanol under reflux conditions gave rise to formation of triazin-diones **330** <2005EJM127>



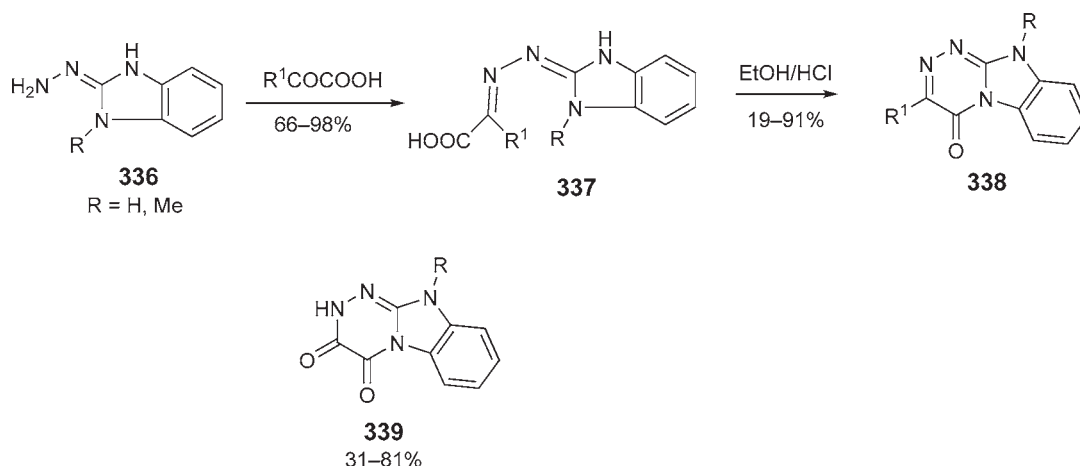
Scheme 49



Scheme 50

in medium to good yields. Besides this reagent, a number of other α -bifunctional reagents were successfully used by the same research group to prepare other derivatives with different substitution patterns. Thus 6-aryl-5-oxo compounds **331** <1995APH123, 2004APH373>, 6-benzyl-5-oxo derivatives **332** <1997APH71>, oxo esters **333** <1997APH147>, thiazolyl-substituted compounds **334** <1997APH223>, and 6-methyl-5-oxotriazines **335** <2002APH235> have been synthesized.

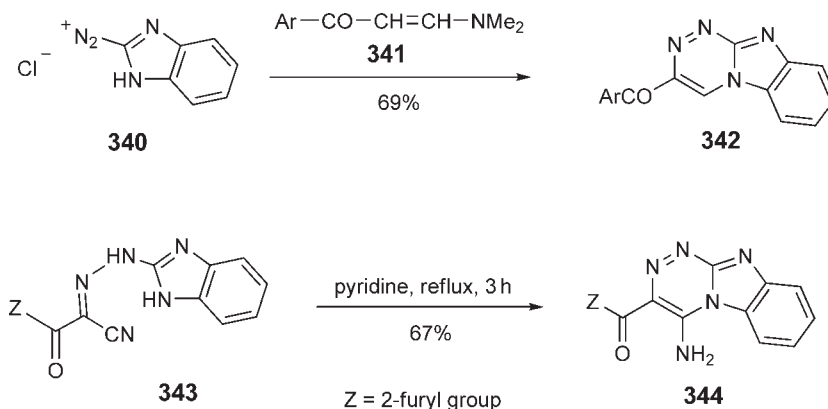
A similar synthetic strategy described by Primofiore *et al.* proved to be straightforward for the synthesis of benzologues as shown in [Scheme 51](#).



Scheme 51

2-Hydrazinobenzimidazole derivative **336** was treated with oxocarboxylic acids to give a hydrazone **337** which underwent ring closure to the fused triazinone **338** <2000JME96, 2001JME316>. Reaction with dialkyl oxalate allowed the synthesis of the triazinedione derivative **339** <2001JME4359>.

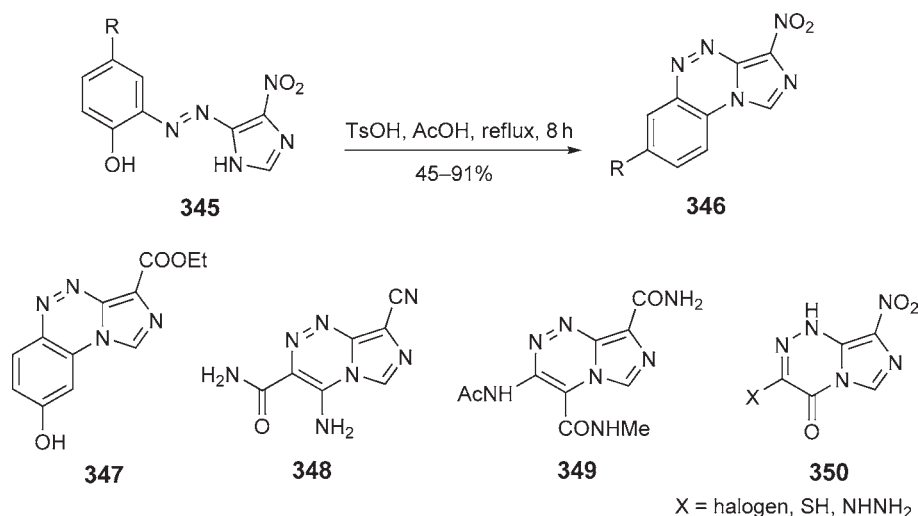
Two further cyclization methods to fused imidazoles are shown in Scheme 52. Al-Shiekh *et al.* <2004JCM174> reported that reaction of the diazonium salt **340** with the carbonyleneamine **341** leads to formation of the benzimidazotriazine compound **342** in good yield (69%). Transformation of **343** to the ring-closed **344** as described by Farag *et al.* <2004JCM808> proceeds via nucleophilic attack of the imidazole nitrogen atom on the adjacent cyano group to result in formation of an amine **344**. This latter strategy has also been applied in other related cases <1996T7893, 2000JRM622, 2005JCM378>.



Scheme 52

As mentioned above, much less new information on imidazo[5,1-*c*][1,2,4]triazines appeared during the past years. Only one Russian team reported synthetic pathways to this ring system, and the results are summarized in Scheme 53.

The representative transformation is ring closure of the azo compound **345** <2000KGS540>. This imidazole derivative when refluxed in acetic acid in the presence of *p*-toluenesulfonic acid for 8 h undergoes cyclization to the tricyclic heteroaromatic ring **346**. The yields are between medium to excellent. Similar ring-closure reactions have been carried out for the synthesis of the ester **347** <2005IZV348>, the cyanoimidazotriazine **348**, and carboxamide **349** <1998KGS805>, as well as a series of imidazotriazin-4-ones containing various substituents in position 3 **350** <1999KGS1544>.

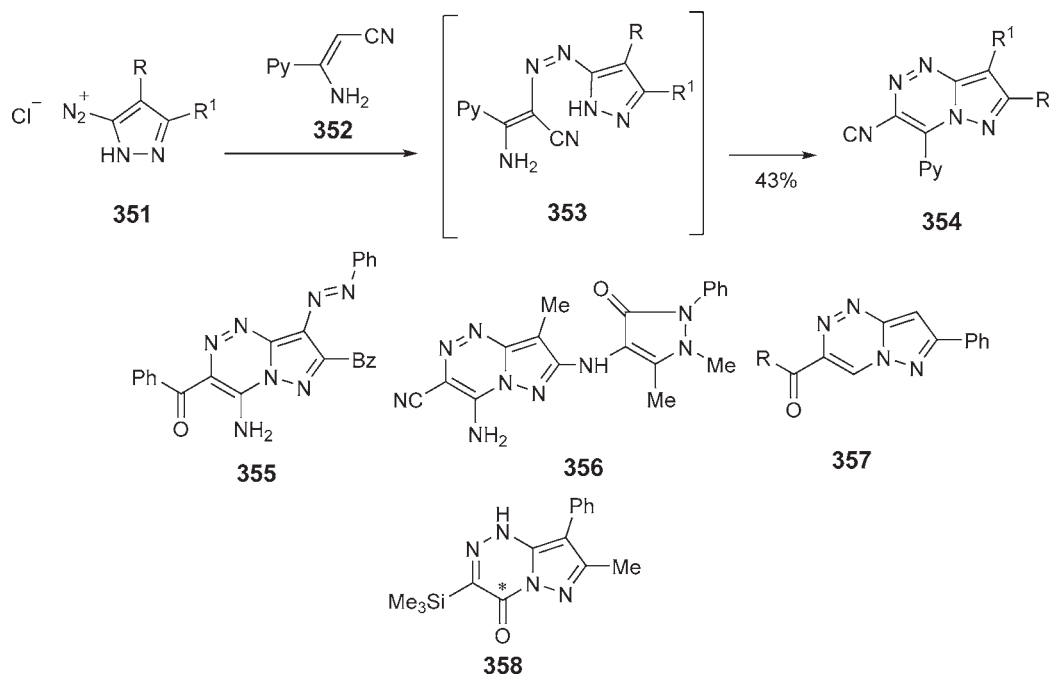


Scheme 53

11.17.6.4.2(iii) Fused pyrazoles

A few syntheses to these ring systems were reviewed in CHEC-II(1996) <1996CHEC-II(8)445>. In contrast to this limited amount of synthetic information, a great number of publications on ring closures to pyrazolo[5,1-*c*][1,2,4]triazines appeared during the past years. These novel approaches are classified into four groups of transformations depending on the main structural feature of the starting compound.

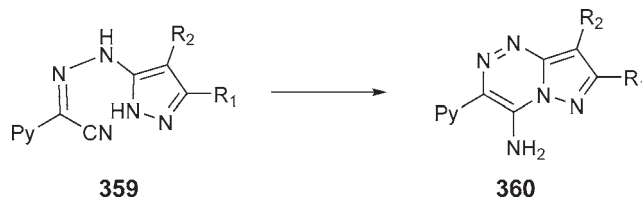
- Many syntheses have been accomplished by transformation of 3-diazopyrazoles, which can also be represented by their protonated species as diazonium salts. These methods are, in part, summarized in Scheme 54. One such typical ring closure was published by Ghazlan and Hassanien <2002T9423>: the diazonium salt **351** was treated with the cyanoenamine **352** to afford an azo intermediate **353**, which underwent cyclization to **354** in a net yield of



Scheme 54

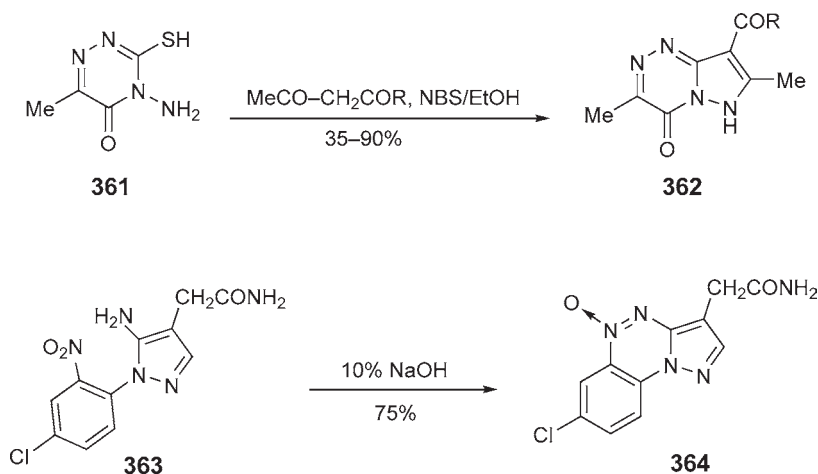
43%. This and similar strategies have been also applied for preparation of the phenylazo derivative **355** <1997JRM1377>, for the pyrazolamine-substituted compound **356** <1998IJB484>, and for the pyrazolotriazinyl ketone **357** <2004JCM174>. The derivative **358** having a ^{11}C isotope in position 4 has also been prepared by the use of a new isotope-containing precursor: $[^{11}\text{C}]$ lithium trimethylsilylnolate <1999JLRS123>. Azopyrazoles have been applied for ring closure in many other cases <1994PHA482, 1999ZOR1384, 1999H(51)513, 2001JME350, 2002IZV1594, 2003JRM1161, 2004JCCS575, 2004JCM174, 2004JCM789>.

- In another group of cyclizations to the title compounds, 3-pyrazolylhydrazones were used that contain a functional group which is able to undergo ring closure with participation of the pyrazole ring nitrogen atom. A typical transformation is the ring closure of **359** <2003JHC71> shown in **Scheme 55**. In this compound, the ring closure is possible by the nucleophilic attack of the ring nitrogen atom to the C-atom of the cyano group to result in formation of the amino compound **360**. Principally, the same approach was utilized in many other cases <1995JCM96, 1996T7893, 1996JCCS493, 2000IJB202, 2001JRM901, 2002PS2497, 2003JCCS1189, 2004JCM808>.



Scheme 55

- A third, not too widely used, approach is transformation of an *N*-aminotriazine compound, as shown in **Scheme 56**. The 3-mercapto-4-amino[1,2,4]triazine derivative **361** was treated with an active methylene ketone and NBS in ethanol to yield the cyclized product **362** in moderate to excellent yield <2001JHC711>. A similar synthetic strategy was also applied in another case <2003KGS1844>.



Scheme 56

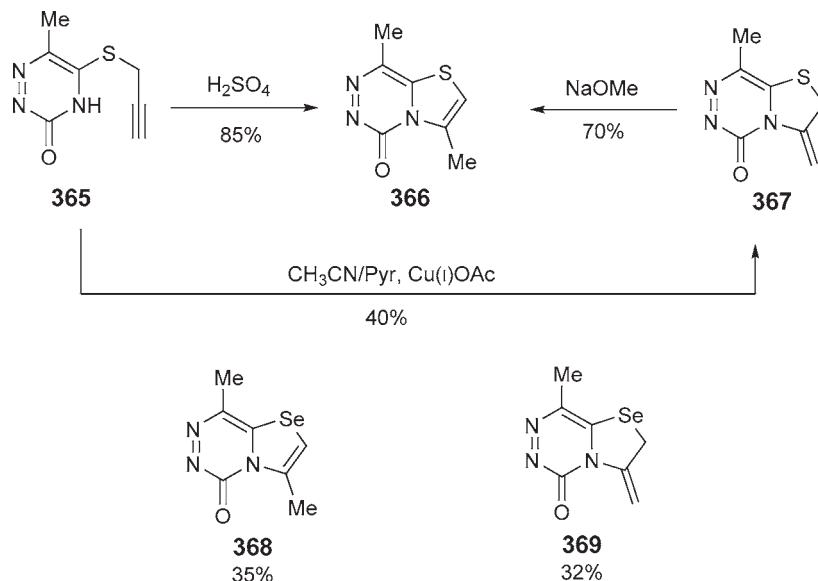
- It is also possible to carry out the ring closure of the triazine moiety, and such a reaction was already concisely mentioned in CHEC-II(1996) <1996CHEC-II(8)445>. Transformation of **363** to **364** reported by Costanzo *et al.* <1999JME2218> also belongs to this type of cyclization.

11.17.6.4.3 *d*-Fused [1,2,4]triazines

11.17.6.4.3(i) Fused thiazoles and selenazoles

Two kinds of fused thiazoles belonging to this section, thiazolo[3,2-*d*][1,2,4]triazines and thiazolo[3,4-*d*][1,2,4]triazines, as well as their selenazole analogues have been prepared during the past years.

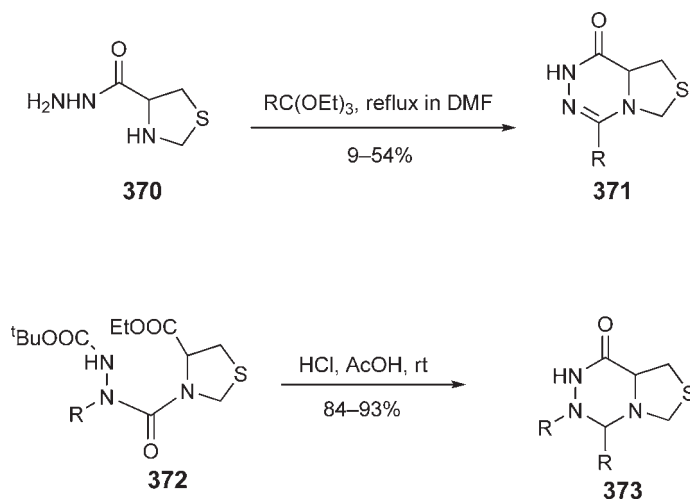
Progress in the field of thiazolo[3,2-*d*][1,2,4]triazines has been published by an Iranian research group. The results are shown in [Scheme 57](#).



Scheme 57

Heravi *et al.* reported that treatment of a triazine compound containing a propargylsulfanyl side chain **365** can lead to two different products [\[1998IJB587, 1998SC233, 2000JCM464\]](#): reaction with sulfuric acid under irradiation yields **366** whereas transformation under different reaction conditions (e.g., in acetonitrile–pyridine in the presence of copper(I) acetate) affords the tautomeric **367** containing an *exo*-methylene bond in the thiazole ring. This compound when reacted with sodium methoxide undergoes tautomerism to give **366**. The two selenazol derivatives **368** and **369** have been obtained similarly.

Two new procedures have been reported to partially saturated derivatives of the thiazolo[3,4-*d*][1,2,4]triazine ring system. The results are shown in [Scheme 58](#).

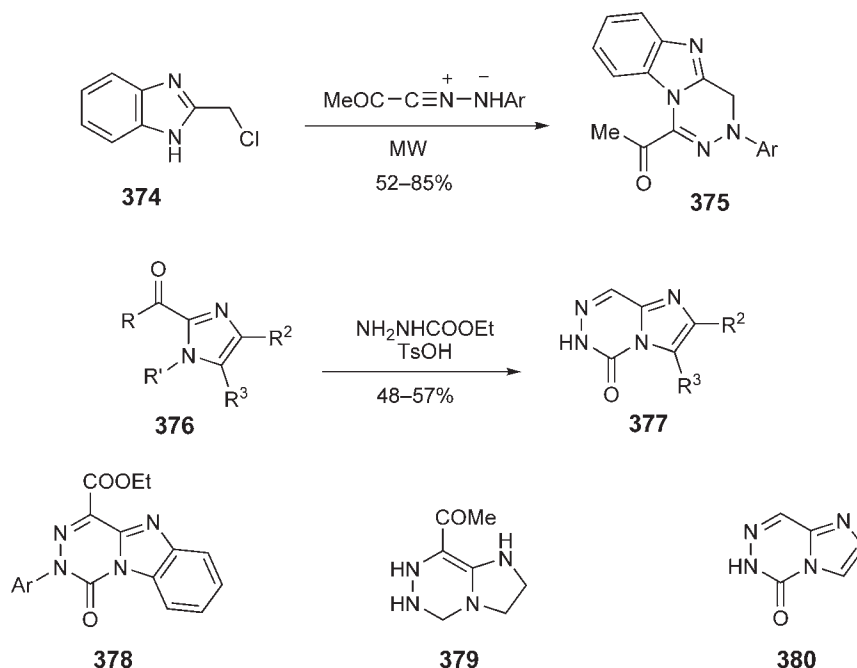


Scheme 58

Couquelet and co-workers described the cyclization of the tetrahydrothiazolyl acid hydrazine **370** <1998BMC349>: when this compound was refluxed in DMF in the presence of an orthoester, cyclization to **371** took place. The yield in certain cases was very low, in some other cases poor to medium (9–54%). A different synthetic strategy to a related derivative of the same ring system was published by Obreza and Urleb <2003SC1011>. These authors treated the N-substituted tetrahydrothiazole derivative **372** with hydrochloric acid in acetic acid solution. Cyclization to **373** took place in excellent yields (84–93%).

11.17.6.4.3(ii) Fused imidazoles

An interesting new ring-closure reaction to 1,4,5,6-tetrahydrobenzimidazo[1,2-*d*][1,2,4]triazines by using microwave irradiation has been described by a Jordanian–German joint research group <2005TL1725>, as summarized in Scheme 59.



Scheme 59

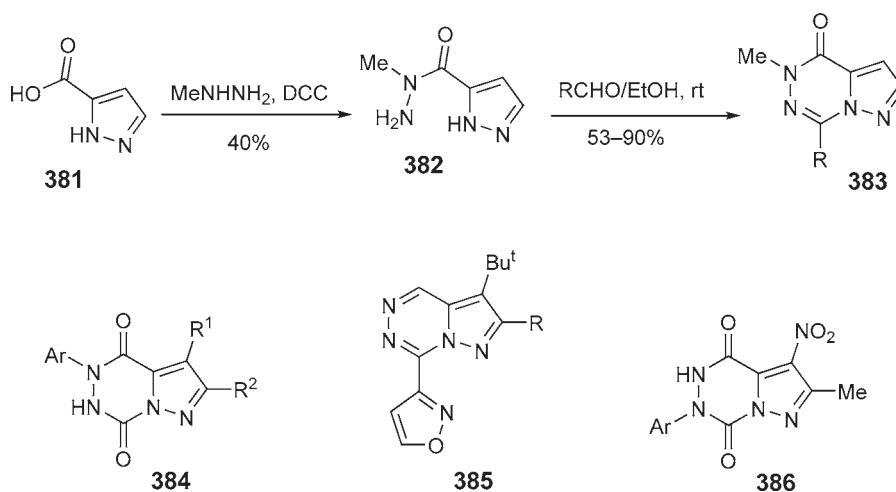
Thus, 2-chloromethylbenzimidazole **374** was treated with various aryl nitrilimines on a silica support. The reactions took place within 4 min and the ring-closed products **375** were formed in high yields (52–85%).

According to another synthetic strategy, an imidazolyl ketone hydrazone is subjected to ring closure. A typical example for this approach is the transformation of the ketone **376** <1997BML89>. This compound was transformed to a hydrazone by treatment with ethoxycarbonylhydrazine, upon which formation of an intermediate hydrazone and a spontaneous cyclization took place to **377** in medium yields (48–57%). Similar ring closures were carried out for the synthesis of the derivatives **378** <2000IJB202>, **379** <1997SC2433>, and **380** <1999T13703>.

11.17.6.4.3(iii) Fused pyrazoles

Synthetic routes to these derivatives – as also discussed earlier in CHEC-II(1996) <1996CHEC-II(8)445> – utilize the reaction of a 3-substituted pyrazole derivative bearing a carbonylhydrazine or hydrazone side chain with an appropriate reagent providing a one-carbon-atom structural unit. Scheme 60 summarizes the recent results.

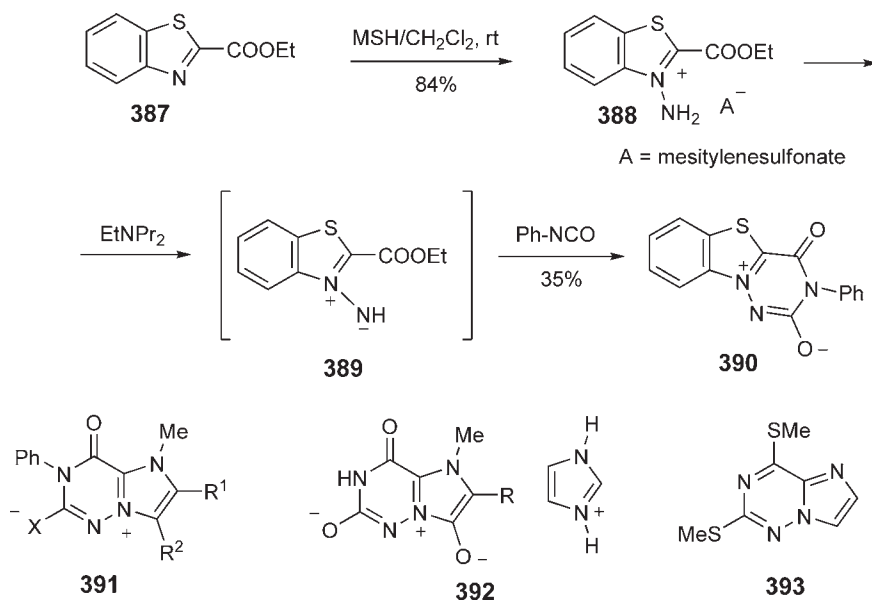
The ring-closure reactions starting from pyrazole 3-carboxylic acid **381** were published by Wipf *et al.* <2005OL4483>. This compound was reacted with methylhydrazine in the presence of dicyclohexylcarbodiimide (DCC) to give the hydrazide **382**, which underwent ring closure upon reaction with aldehydes to yield **383**. Ring-closure reactions to **384** <1999S453, 2002ZOR630>, **385** <2004JME5829>, and **386** <1999AF997> followed similar or closely related protocols.



Scheme 60

11.17.6.4.4 *f*-Fused [1,2,4]triazines

Alvarez-Builla and co-workers described a straightforward synthesis of some new betainic [1,2,4]triazine[6,1-*b*]benzothiazolium-2-olates, as shown in [Scheme 61](#).



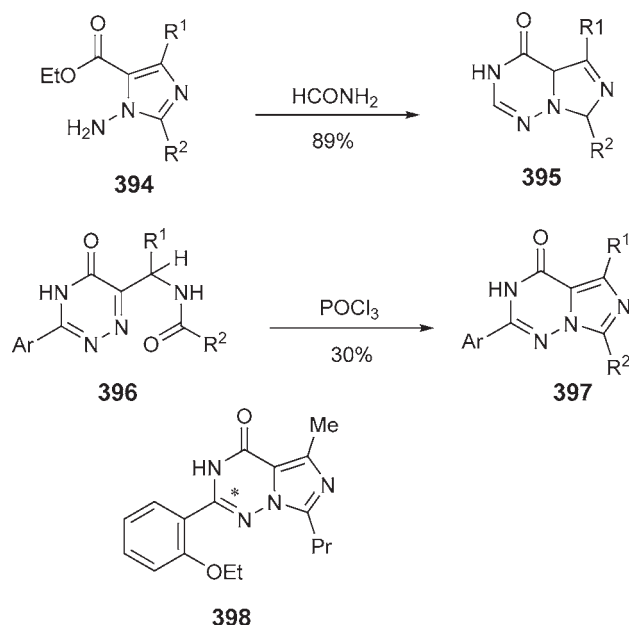
Scheme 61

The starting benzothiazole carboxylic ester **387** was subjected to a *N*-amination by using mesityl hydroxylamine to give an *N*-amino salt **388**, which was treated with a tertiary amine to give the deprotonated intermediate **389**. This species when reacted with phenylisocyanate yielded the final product **390** in moderate yield [\[2001JOC8528\]](#).

The same authors also reported the synthesis of the bicyclic analogue **391**. Synthesis of a closely related zwitterionic compound, the imidazolium salt **392** [\[2005TL5325\]](#), was reported by Lakner *et al.* Ring closure to **393** has also been described [\[1999J\(P1\)2929\]](#).

Syntheses of imidazo[[5,1-*f*][1,2,4]triazines are shown in [Scheme 62](#). Heim-Reither elaborated an easy access to these compounds [\[2005JOC7331\]](#). The ring-closure step of the reaction pathway is treatment of the

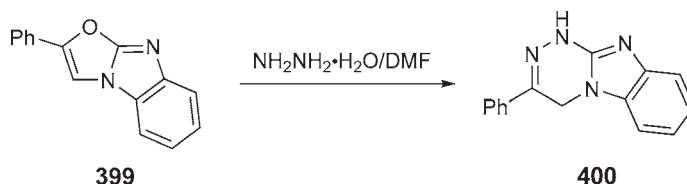
N-aminoimidazole ester **394** with formamide to yield the ring-closed product **395** in 89% yield. In a procedure reported by Haning *et al.* <2002BML865, 2002BML3900>, the triazinone **396** was subjected to transformation with phosphorus oxychloride. The imidazotriazine product **397** was obtained in low yield. A ^{14}C -labeled derivative of this ring system **398** has also been prepared <2001JLR947, 2003JLR1019>.



Scheme 62

11.17.6.5 Formation of Ring from Ring

Ring transformation of **399** to the imidazotriazine derivative **400** was reported <2001KGS1284>, as shown in Scheme 63. The reaction takes place with hydrazine hydrate in DMF under heating for 4 h.

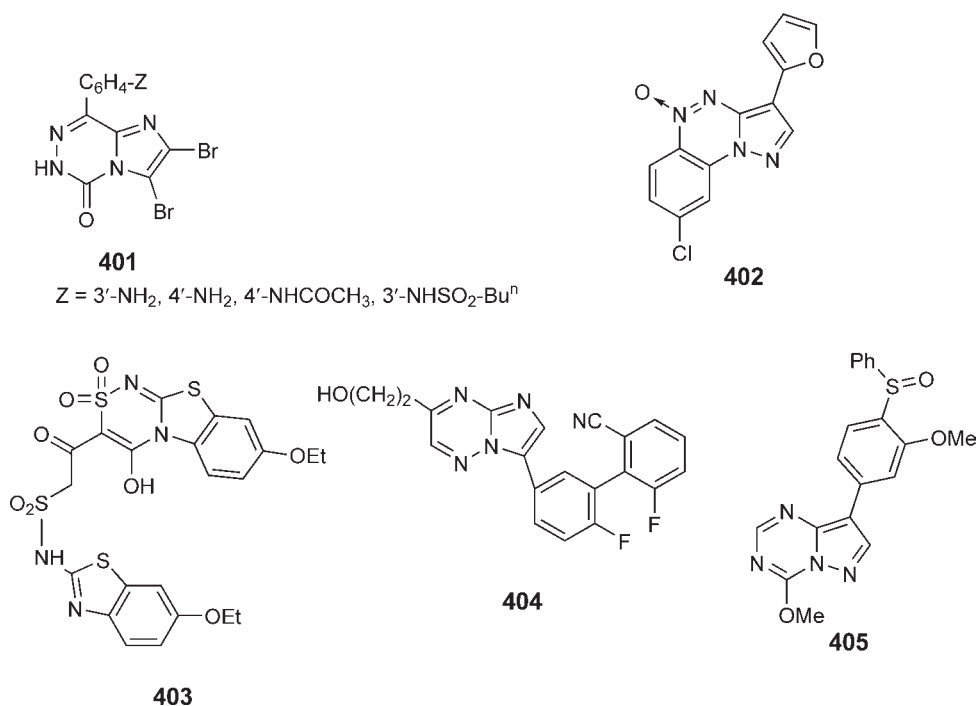


Scheme 63

11.17.7 Important Compounds and Applications

Several derivatives of the ring systems involved in this chapter exhibited valuable biological properties. Structures of the most important compounds are shown in Scheme 64.

Thus, studies on some imidazo[1,2-*d*][1,2,4]triazinones revealed that some of these compounds **401** (Scheme 64) are inhibitors of the Ca^{2+} -calmoduline sensitive phosphodiesterase. Predictions based upon structure–activity relationship investigations suggested and, interestingly, biological studies verified that the $\text{Z} = 3'\text{-NHSO}_2\text{-Bu}^n$ derivative of **401** was the most potent compound <1997BML89>. Studies on pyrazolo[5,1-*c*][1,2,4]triazines as benzodiazepine receptor ligands <2002JME5710> revealed that the furyl derivative **402** is a functionally selective ligand *in vivo*: it exhibited anxiolytic activity in the conflict models similar to diazepam, but without any sedative and amnesiac properties or interference from alcohol.



Scheme 64

The benzothiazole-fused thiadiazine derivative **403** was considered as the first reversible purinergic receptor-specific, non-nucleoside-based potent antagonist of the platelet P2Y₁₂ receptor [\[2001BML1805\]](#). The imidazo[1,2-*b*]-[1,2,4]triazine derivative **404** was recognized as an $\alpha_{2/3}$ -selective γ -aminobutyric acid (GABA) agonist [\[2005JOC5938\]](#); the pyrazolo[1,5-*a*][1,3,5]triazine compound **405** was found as a xanthine dehydrogenase inhibitor [\[1995TA2991\]](#). Other derivatives of the same ring system [\[2003BMC4093\]](#) and its benzologues [\[1996EJM259\]](#) also proved to exhibit valuable biological properties in the area of benzodiazepine receptor and corticotropin-releasing factor receptor-binding affinity, respectively.

11.17.8 Further Developments

A detailed experimental and theoretical study on a ternary tautomeric equilibrium of [1,2,4]triazino[2,3-*a*]benzimidazol-5(4*H*)-3-ones (i.e., compounds related to structure **288**) has been carried out [\[2006RCB492\]](#).

Stereoselective synthesis of 3'-substituted 2'-deoxy C-nucleoside pyrazolo[1,5-*a*][1,3,5]triazines and their 5'-phosphate nucleotides starting from related 3'-ketonucleosides have been accomplished [\[2006TL5099\]](#). Regioselective ring closure to derivatives of the same ring system – reminiscent of those discussed in Section 11.17.5.3.5 – has been described [\[2006TL5441\]](#).

New synthetic pathways have been elaborated for imidazo[1,2-*b*][1,2,4]benzodithiazines (i.e., analogues of **182**) [\[2006BML2985, 2006BML5298\]](#). The new derivatives exhibited remarkable antitumor and anti-HIV-1 activity.

New cyclizations to benzimidazolo[1,2-*a*][1,3,5]triazines involving ring closure of both the six-membered [\[2006BML3401\]](#) and the five-membered heterocycles [\[2005JFC759\]](#) as discussed in Section 11.17.5.3.3 have been published. These syntheses allowed the biological evaluation of lisofylline analogues as a potential treatment for Type 1 diabetes. Derivatives of this ring system as well as those of some fused oxazole and thiazole analogues have recently synthesized by a microwave-assisted technique mostly in very high yields [\[2006S597\]](#).

In the area of pyrazolo[5,1-*c*][1,2,4]triazines partially saturated fluororous derivatives have been synthesized by ring closure reactions [\[2005JFC1230\]](#).

Biologically valuable (selective GABA_A antagonists also applicable for treatment of anxiety) derivatives of the imidazo[1,2-*b*][1,2,4]triazine, imidazo[1,5-*d*][1,2,4]triazine, imidazo[2,1-*f*][1,2,4]triazine, and pyrazolo[1,5-*d*]-[1,2,4]triazine ring systems have recently been recognized <2006BML1477, 2006JMC1235, 2006BML1582, 2006BML3550>. Anticancer and antiproliferative activity of some new derivatives of the imidazo[1,2-*c*][1,2,4]triazine (34) ring system has been disclosed <2006EJM539, 2006EJM1373>.

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Biographical Sketch



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11.16

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Three Extra Heteroatoms 2:1

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11.16.1 Introduction

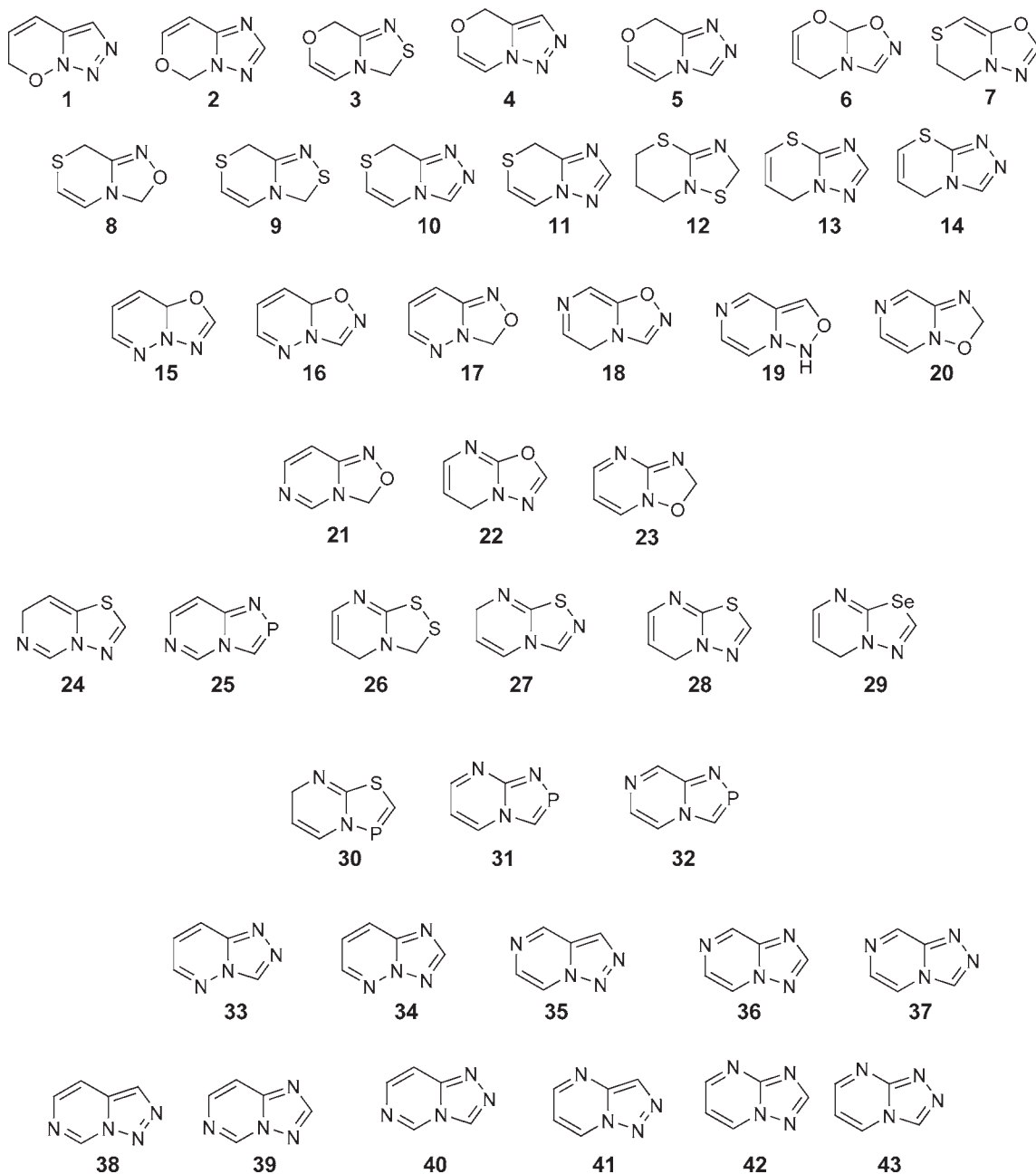
In [Scheme 1](#), all the ring systems belonging to this chapter are depicted. The six-membered rings can be oxazine, thiazine, pyridazine, pyrazine, and pyrimidine, whereas the five-membered fused ring can contain oxygen, sulfur, selenium, phosphorus, and nitrogen atoms in various arrangements.

Further ring systems that have not been reported during the recent period can be found in CHEC-II(1996) <1996CHEC-II(8)421>.

11.16.2 Theoretical Methods

Kleinpeter *et al.* carried out *ab initio* and semi-empirical (PM3) calculation in order to rationalize the tautomeric equilibria of 7-hydroxy-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine <1995JST(335)273, 1997JST(435)65>. This compound can exist in four tautomeric forms **a–d** ([Figure 1](#)). The authors concluded that the high computational level available can sufficiently reproduce the position of tautomeric equilibria in solution and, thus, can serve as a useful tool instead of time-consuming experimental studies.

In the course of some crystallographic studies (cf. [Section 11.16.3.2](#)), a Spanish–French joint team carried out theoretical calculations on some [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives <1997JST(415)285, 2000JST(519)165>. Thus, semi-empirical calculations and full geometry optimizations have been carried out on derivative **62** shown in [Scheme 4](#). The calculated net charges proved to be relatively high values and ranged between –0.25 and +0.17 <1997JST(415)285>. Similar calculations have been also carried out for the related derivative **57** shown also in [Scheme 4](#) <2000JST(519)165>. With this derivative, similar charge distribution (relatively high values) was obtained. Based on the calculated heats of formation, reliable predictions could be made for the most stable tautomeric form.



Scheme 1

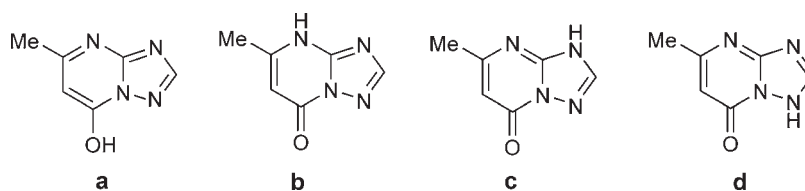


Figure 1 Tautomeric forms of 7-hydroxy-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine.

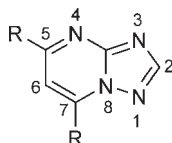
11.16.3 Experimental Structural Methods

11.16.3.1 NMR Investigations

Several studies on nuclear magnetic resonance (NMR) investigations of derivatives belonging to this chapter have already been summarized in CHEC-II(1996) <1996CHEC-II(8)421> and, also recently, a fairly substantial amount of new experimental work has been published.

Most of these studies relate to derivatives of one ring system: triazolo[1,5-*a*]pyrimidine. ^{13}C and ^{15}N chemical shifts of some 5,7-disubstituted [1,2,4]triazolo[1,5-*a*]pyrimidines substituted in the pyrimidine ring (and also some of their Au(III) chloride complexes) were published by Szytk *et al.* <2002MRC529>; the data are shown in Table 1.

Table 1 ^{15}N and ^{13}C NMR data of some [1,2,4]triazolo[1,5-*a*]pyrimidines substituted in the pyrimidine ring



	<i>N</i> -1	<i>N</i> -3	<i>N</i> -4	<i>N</i> -8	<i>C</i> -2	<i>C</i> -3a	<i>C</i> -5	<i>C</i> -6	<i>C</i> -7
R = H	−106.0	−151.3	−103.2	−154.3	156.7	156.0	156.1	111.1	138.0
R = Me	−111.9	−153.9	−124.4	−157.9	155.9	155.8	165.4	111.5	148.0
R = Ph	−110.5	−150.7	−120.4	−157.9	156.8	157.1	161.7	107.5	148.6

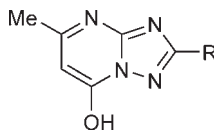
Chemical shifts in DMF solution.

All chemical shifts are given in ppm.

Comparison of the ^{15}N NMR shifts reveal that the *N*-3 and *N*-8 shifts appear at significantly lower fields in contrast to the shifts of *N*-1 and *N*-4 atoms. The results of these measurements are in good accordance with the earlier study of Grodzicki *et al.* <1996MRC725>.

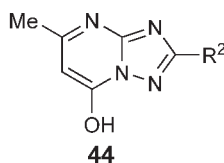
Kleinpeter *et al.* <1997JST(435)65> investigated the effect of substituents in position 2 on the ^{13}C and ^{15}N chemical shifts of 7-hydroxy-substituted derivatives. Some representative data are listed in Table 2. These authors found a good coincidence between the calculated chemical shifts and the experimental values.

Table 2 ^{15}N and ^{13}C NMR data of some 5-hydroxy[1,2,4]triazolo[1,5-*a*]pyrimidines substituted in the triazole ring

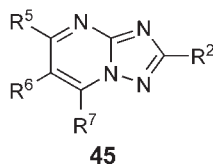


<i>R</i>	<i>N</i> -1	<i>N</i> -3	<i>N</i> -4	<i>N</i> -8	<i>C</i> -2	<i>C</i> -3a	<i>C</i> -5	<i>C</i> -6	<i>C</i> -7
H	110.6	165.4	252.3	115.0	151.9	150.6	151.7	98.2	115.9
OH					163.9	151.6	149.3	99.2	154.7
COOH	101.7	162.4	252.9	153.6	154.0	150.9	152.4	98.5	155.6
CH ₂ OCH ₂ COOH	124.3	165.4	253.0	156.5	160.4	151.5	151.5	98.2	155.7
C ₇ H ₁₅	117.4	187.6	253.9	156.2	164.1	150.7	151.0	98.1	155.6

A huge amount of informations on chemical shifts of various derivatives appeared in the publications of Kleinpeter *et al.* <1995JST(335)273> and Reiter *et al.* <1995JHC407>. The structures of molecules investigated are shown in Scheme 2.



$R^2 = \text{H, OH, SH, NH}_2, \text{NHNO}_2, \text{alkyl, SMe, SO}_2\text{Me}$



$R^2 = \text{H, SMe, BuS, morpholino, NMe}_2, \text{pyridylmethylamino}$

$R^5 = \text{Me, Bu, Ph, acetyl}$

$R^6 = \text{H, COCH}_3$

$R^7 = \text{Me, Bu, Ph, acetyl}$

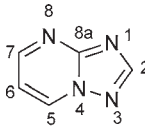
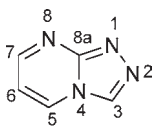
Scheme 2

In the case of the 7-hydroxy-substituted compounds **44** (Scheme 2), 54 different derivatives were investigated by ^{13}C NMR spectroscopy and, in some cases, also by ^{15}N NMR spectroscopy <1995JST(335)273>. With the help of proton-coupled ^{13}C NMR spectra, semi-selective INEPT (insensitive nuclei enhanced by polarization transfer) experiments, and heteronuclear multiple bond correlation (HMBC) two-dimensional 2D-NMR spectra, all shifts could be unequivocally assigned. While the C-7 shifts did not allow the existing tautomeric situation to be determined, a clear decision could be made by ^1H NMR spectroscopy in this respect. The ^{15}N NMR spectra revealed an equilibrium between the N(4)H and N(3)H tautomeric forms, which is fast on the NMR timescale.

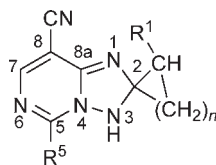
In the study on tetrasubstituted [1,2,4]triazolo[1,5-*a*]pyrimidines **45**, ^1H and ^{13}C NMR spectra of 35 different compounds have been recorded <1995JHC407>. Substituents in position 2 were various amines and sulfano groups, whereas the other substituents (R^5 , R^6 , and R^7) were alkyl, phenyl, and acetyl groups.

Wiench *et al.* investigated chemical shifts of a set of positional isomers of azaindolizines <1994MRC373>. In Table 3, ^{13}C and ^{15}N NMR chemical shifts of two related ring systems, the unsubstituted [1,2,4]triazolo[1,5-*a*]pyrimidine **A** and [1,2,4]triazolo[3,2-*a*]pyrimidine **B**, are compared.

Table 3 ^{13}C and ^{15}N NMR chemical shifts of unsubstituted [1,2,4]triazolo[1,5-*a*]pyrimidine **A** and [1,2,4]triazolo[3,2-*a*]pyrimidine **B** measured in $\text{DMSO}-d_6$ solutions

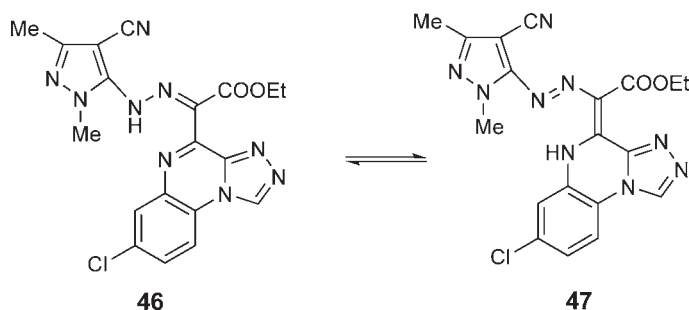
	 A					 B					
	N-1	N-2	N-3	N-4	N-8	C-2	C-3	C-5	C-6	C-7	C-8a
A	-149.4		-102.1	-153.5	-105.0	155.8		137.4	110.9	155.5	154.6
B	-84.3	-49.4		-196.9	-103.5		135.7	133.9	109.9	155.4	152.8

Miyamoto and Yamazaki elaborated a general synthetic method to spiro-substituted [1,2,4]triazolo[1,5-*c*]pyrimidines bearing alicyclic rings of different sizes and bearing different (amino and sulfano) substituents in position 5 <1997JHC871>. ^{13}C NMR chemical shifts of the ring carbon atoms of some selected derivatives are compiled in Table 4.

Table 4 ^{13}C NMR chemical shifts of ring carbon atoms of some spiro(cycloalkane-1,2'-[1,2,4]triazolo[1,5-c]pyrimidine carbonitriles measured in $\text{DMSO}-d_6$ solutions

R^1	R^5	n	$C-2$	$C-5$	$C-7$	$C-8$	$C-8a$
H	SMe	3	86.3	161.3	157.0	97.1	145.8
Me	SMe	3	86.1	161.0	157.0	98.3	145.5
H	SMe	4	89.3	161.6	156.9	86.6	145.7
H	NH_2	3	78.1	147.2	159.8	95.8	151.8
H	NHMe	3	78.8	147.3	154.4	96.0	150.7
H	NH_2	4	78.3	147.1	159.8	87.9	152.1
H	NHMe	4	79.0	147.1	159.5	88.1	150.9
Me	NH_2	3	77.9	147.2	159.8	96.9	151.7

Kim and Okamoto carried out studies on a tautomeric equilibrium between a hydrazono and azo derivative, **46** and **47** respectively, by means of NMR spectroscopy (Scheme 3) <1994JHC233>. The ^{13}C and ^1H NMR values could be well assigned to the particular carbon and hydrogen atoms. The equilibria were determined in dimethyl sulfoxide (DMSO) and aqueous trifluoroacetic acid.

**Scheme 3**

Schmidpeter *et al.* studied the synthesis of various diazaphospholodiazines, and investigated the products by NMR spectroscopy <1995CB581>. In Table 5, ^{31}P and ^{13}C NMR chemical shifts as well as (P,C) coupling constants of three ring systems, [1,4,2]-diazaphospholo[4,5-*a*]pyrimidine **e**, [1,4,2]-diazaphospholo[4,5-*e*]pyrimidine **f**, and [1,4,2]-diazaphospholo[4,5-*a*]pyrazine **g**, are compared.

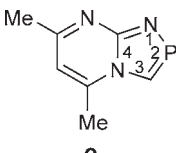
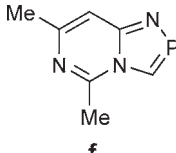
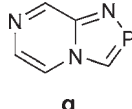
11.16.3.2 X-Ray Studies

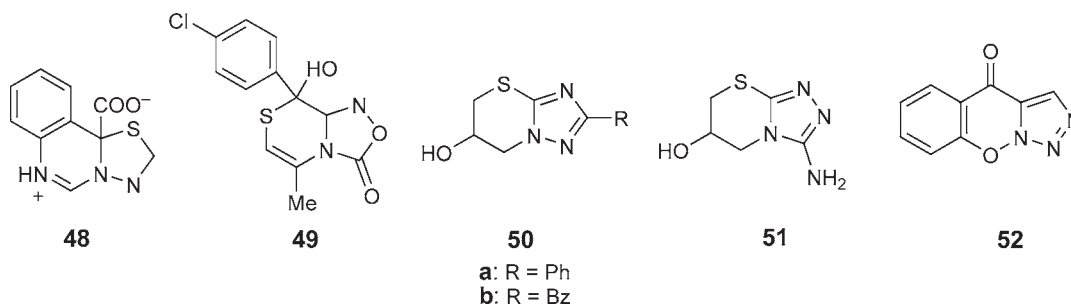
A considerable amount of X-ray structure elucidation work has been published in the field of the ring systems of this chapter. Because of the relatively high diversity of the structures studied, this part of the chapter is divided into several subsections depending on the main structural units.

11.16.3.2.1 X-Ray studies of oxygen- and sulfur-containing ring systems

Derivatives of various oxygen- and sulfur-containing ring systems investigated by X-ray crystallography are shown in Scheme 4.

Table 5 ^{31}P and ^{13}C NMR chemical shifts as well as (P,C) coupling constants (J in Hz) of [1,4,2]-diazaphospholo[4,5-*a*]pyrimidine **e**, [1,4,2]-diazaphospholo[4,5-*e*]pyrimidine **f**, and [1,4,2]-diazaphospholo[4,5-*a*]pyrazine **g** measured in CDCl_3 solutions

			
P	198.0	204.5	207.9
C3	146.3	147.1	151.1
$J_{(\text{P,C})}$	63.8	64.5	71.1
C5	143.8	147.0	120.7
$J_{(\text{P,C})}$	3.5	2.9	
C6	109.2		129.6
$J_{(\text{P,C})}$	1.9		1.2
C7	161.5	150.1	
$J_{(\text{P,C})}$			
C8		109.1	144.9
$J_{(\text{P,C})}$		7.3	10.2
C8a	153.6	152.8	146.8
$J_{(\text{P,C})}$	16.1	13.9	14.2

**Scheme 4**

Zhang *et al.* <1997AXC325> investigated the structure of 2-amino-5-methyl-10b*H*[1,3,4]thiadiazolo[3,2-*c*]quina-zolin-6-ium-10b-carboxylate **48** which was isolated as a crystalline hydrate. These authors found that the two six-membered rings are approximately coplanar, but because of the presence of the sp^3 carbon atom in the bridgehead position there is a marked nonplanarity between the thiadiazole and pyrimidine rings with a dihedral angle of 23.1° . Because of this asymmetrical feature the molecule is chiral and the crystal structure is a racemate incorporating two molecules of water for each *R/S* pair of the molecules.

X-Ray elucidation provided a final proof for the structure elucidation of 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one **49**, which was obtained as a product of ring-transformation reaction <1997J(P2)2407>. This analysis revealed that the oxadiazole ring is planar, whereas the thiazine ring is in a distorted half-chair conformation with a displacement asymmetry parameter ΔC_2 ($\text{S}-\text{C}(3)$) = 0.031. The structure analysis represents the first X-ray elucidation of a [1,4]thiazine ring fused to a [1,2,4]triazole moiety.

Glowka *et al.* <1994JCX273, 1994JCX527> carried out studies with several derivatives of the [1,2,4]triazolo[3,2-*b*]-[1,3]thiazine ring systems **50**. The experimental data revealed that **50a** and **50b** had similar geometries implying flat triazole rings, sofa conformations of the thiazine moiety, and axial hydroxyl groups. In the crystals, infinite chains are formed with participation of the OH groups and N-4 atoms. This formation is enantiomeric in the case of **50a** and, interestingly, racemic in **50b**.

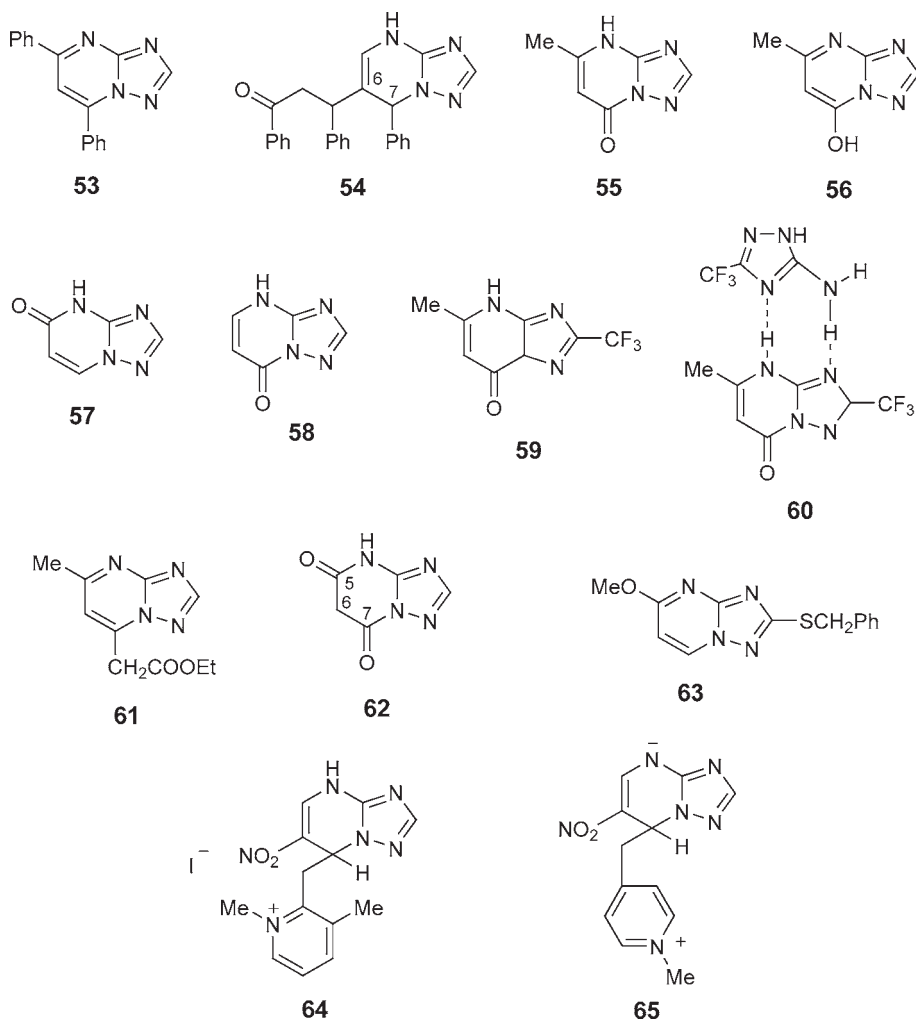
The same type of ring-closure reaction that leads to the [3,2-*b*]-fused **50** can also result, in principle, in formation of a [3,4-*b*]-fused ring system (see Sections 11.16.5.2 and 11.16.7). This case has been found when an amino group was present in the triazole ring, and formation of **51** has been supported by X-ray diffraction. The crystalline structure

indicated that this molecule has less aromatic character and smaller delocalization of π -electrons of the triazole ring compared to other isomeric [3,2-*b*] fused triazoles.

The crystal structure of the tricyclic triazolo[1,5-*b*][1,2]oxazinone **52** was determined by Begtrup *et al.* <2002T2397>. This compound was obtained as a product of a designed ring-closure reaction, and it was the X-ray analysis that provided a firm support for the outcome of the transformation.

11.16.3.2.2 X-Ray studies of [1,2,4]triazolo[1,5-*a*]pyrimidines

X-Ray diffraction data are most prevalent in the area of the title ring system. Altogether, structures of 13 derivatives of this skeleton have been elucidated by crystallography. These structures are summarized in Scheme 5.



Scheme 5

Surdykowski *et al.* described the crystal structure of the diphenyl derivative **53** <1999AXC1337>. These authors found that the two phenyl substituents form interplanar angles 27.38° and 55.76° with the core plane. Lipson *et al.* investigated the structure of the derivative **54** bearing an oxoalkyl chain as a substituent on the six-membered ring <2003JHC1081>. Analysis of the results showed that the conformation of the dihydropyrimidine ring can be described as a flattened boat which may be the consequence of a considerable strengthening of the 1,2-allyl interactions along the C(7)–C(6) bond.

Hydroxy-triazolopyrimidines and their oxo tautomers **55–58** have been investigated by a joint French–Spanish group <1996JCX847, 1997JCD2321, 2000JST(519)165>. In the case of derivative **55**, X-ray crystallography revealed the

existence of a hydrogen-bonded polymeric chain, whereas mass spectrometry and ^{15}N NMR spectra can suggest the existence of a dimeric structure. Complexes of **55** and silver(I) salts have also been studied <1997JCD2321>. The same team dealt with palladium(II) and platinum(II) tetrakisithiourea complexes of **56** <1996JX847>. Comparison of powder diffraction data of these complexes indicated the isomorphous character of the complexes. X-Ray elucidation of the two isomeric fused pyrimidones supported the presence of NH tautomers **57** and **58** in accordance with the theoretical predictions <2000JST(519)165>.

In the course of the synthetic efforts to isolate **59**, a co-crystal containing the starting aminotriazole compound **60** could be obtained depending on the mode of purification (chromatography or crystallization) <2004AXC733>. Crystallographic study of these products showed that the molecules **59** are linked into simple chains, whereas in **60** the components are linked by combination of two-center $\text{N}-\text{H}\cdots\text{N}$ and $\text{N}-\text{H}\cdots\text{O}$ hydrogen bonds.

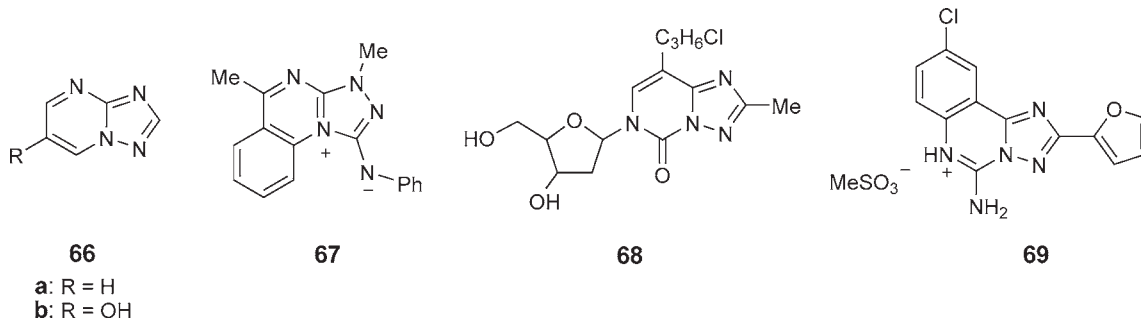
In the case of the ester derivative **61**, formation of a different isomeric structure could also be possible <1996AXC1031>. X-Ray crystallography of this compound unambiguously excluded an alternative structure and supported the existence of **61**. The experimental data revealed that the two ring moieties are planar, and the bond lengths and angles are in good agreement with data reported for closely related derivatives of the same ring system.

The monosodium salt of 4,5,6,7-tetrahydro-5,7-dioxo-[1,2,4]triazolo[1,5-*a*]pyrimidine **62** was subjected to X-ray crystallographic studies <1997JST(415)285>. The measurements revealed the formation of a polymeric chain in the crystal structure, and the chains were linked to one another via the heterocyclic moieties, which were attached to two sodium atoms from one chain and to a sodium atom from another chain to generate a 3-D network. The whole heterocyclic system was found to be planar. Due to the conjugated negative charge, no significant changes in the bond distances $\text{C}(5)-\text{O}(5)$, $\text{C}(5)-\text{C}(6)$, $\text{C}(6)-\text{C}(7)$, and $\text{C}(7)-\text{O}(7)$ were observed.

In the course of elaboration of effective new synthetic routes, the compound **63** had been synthesized <1999JHC183>. X-Ray structure analysis provided a final and firm proof of the structure and, thereby, the applicability of the invented method. Rusinov *et al.* <1998ZOR290> investigated the structures of the cation of salt **64** and the zwitterionic compound **65** obtained by an addition of triazolopyrimidine derivatives on *N*-methylpyridinium compounds. The cation **64** was found to form hydrogen-bonded dimers, whereas **65** formed a co-crystal with acetonitrile.

11.16.3.2.3 X-Ray studies of other types of triazolopyrimidine ring systems

In three studies, X-ray investigations of triazolopyrimidine derivatives, different from the ring system discussed above, appeared. The structures determined by crystallography are shown in Scheme 6.



Scheme 6

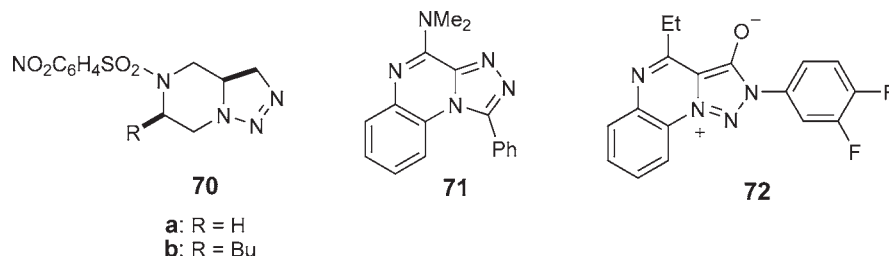
Glowka *et al.* studied two tetrahydro[1,2,4]triazolo[4,3-*a*]pyrimidine derivatives **66a** and **66b** by X-ray diffraction <1994JCX375>. In the solid state, both molecules had the same conformation and were found to be packed in similar manner. The triazole rings proved to be planar, and the conjugation of the π -electrons with the lone pair of the N-8 atom was assumed to be the reason of the sofa conformation of the saturated six-membered ring.

A zwitterionic derivative of the benzologue ring system [1,2,4]triazolo[4,3-*a*]quinazolinium skeleton **67** was also subjected to X-ray analysis <1999J(P1)1517>. The fused heterocyclic ring system was found to be not strictly planar and a pronounced fold at the junction of the triazole and quinazoline rings was observed. The *N*-phenyl ring deviated from the coplanarity with the triazole ring only by 7.21° and, thus, a high degree of π -conjugation was maintained throughout the whole molecule.

The pyrimidine nucleoside **68** was formed by a Dimroth rearrangement <1999J(P1)1333>. This interesting transformation was verified by the X-ray structure elucidation. Representative of the benzologue of the same ring system as an adenosine receptor ligand, compound **69** was investigated by crystallography. This molecule was found to be roughly planar; protonation took place at the imino nitrogen of the pyrimidine ring to form strong hydrogen bonds with two oxygens of the methane sulfate ion.

11.16.3.2.4 X-Ray studies of various triazolopyrazines

Three such studies appeared during the past period of time, and the structures investigated are shown in **Scheme 7**.

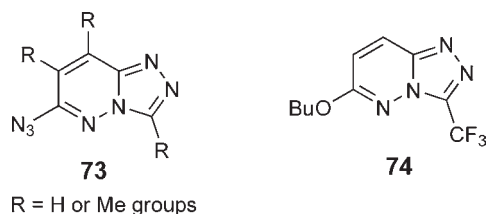


Scheme 7

Derivatives **70** of the saturated triazolopiperazine ring were obtained as a result of an interesting intramolecular cyclization and it was the X-ray elucidation that provided a firm support for the structure of the two related compounds **70a** and **70b** <2005TL1205>. In two other cases, derivatives of the benzologue ring system [1,2,4]triazolo[4,3-*a*]quinoxaline have been subjected to crystallographic studies. Thus, the structure of **71** was described by Mustaphi *et al.* <2004PS2265>, whereas the structure of the zwitterionic olate **72** was analyzed by Abbott *et al.* <2002T3185>. In the case of this latter compound it is interesting to note that the C–O bond distance was found to be 1.23 Å which is intermediate between a carbonyl (1.20 Å) and a carboxylate bond distance (1.25 Å). This finding is in accordance with the proposed mesoionic structure **72**.

11.16.3.2.5 X-Ray studies of various triazolopyridazines

Some derivatives of the [1,2,4]triazolo[4,3-*b*]pyridazines have been investigated by X-ray crystallography. These structures are shown in **Scheme 8**.



Scheme 8

In the course of studies on azide–tetrazole equilibria, some azido derivatives **73** of this ring system have been subjected to X-ray structure elucidation <2005JST(751)65>. These derivatives proved to be mainly planar and the least planar part of these molecules were the azide moieties. In both cases (**72**: R = H and Me), formation of hydrates were also observed. Crystallographic analysis of the trifluoromethyl compound was described by Lange *et al.* <1997APH299>, and structure elucidation of the nucleoside analogue **74** was reported by Stanovnik *et al.* <1998JHC513>.

11.16.3.3 Mass Spectrometry

Mass spectral fragmentation of [1,3,4]thiadiazolo[3,2-*a*]pyrimidinium perchlorate **h** was studied by Takenaka and Tsuji <1996JHC1367>. The result is shown in **Figure 2**.

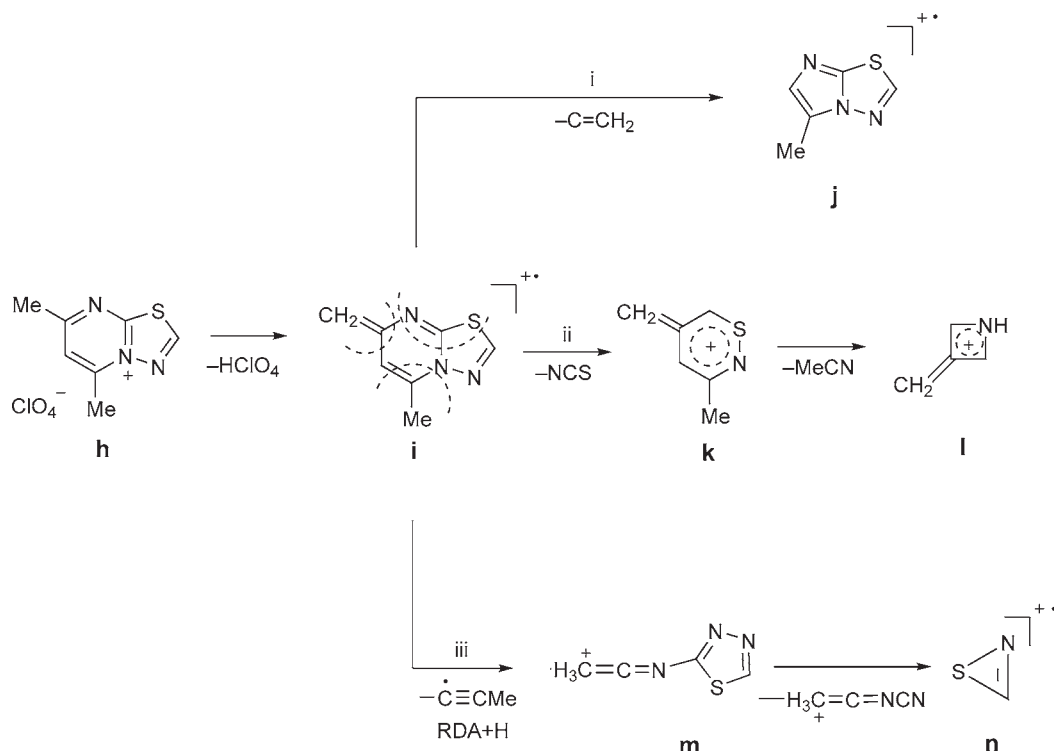


Figure 2 Mass spectral fragmentation of [1,3,4]thiadiazolo[3,2-a]pyrimidinium perchlorate.

These authors described that appearance of the intense peak of the free base ion (**i**, $\text{M}^+ - \text{HClO}_4$) and three fragmentation pathways, all originating from **i**, can be observed. Path (i) is loss of a $\text{C}=\text{CH}_2$ fragment to yield **j**, path (ii) is an *N*-chlorosuccinimide (NCS) radical extrusion (formation of **k** followed by removal of acetonitrile to **l**, whereas in path (iii) a retro-Diels-Alder (DA) cleavage accompanied by hydrogen transfer occurs to give **m** followed by a ring contraction to **n**.

11.16.4 Thermodynamic Aspects

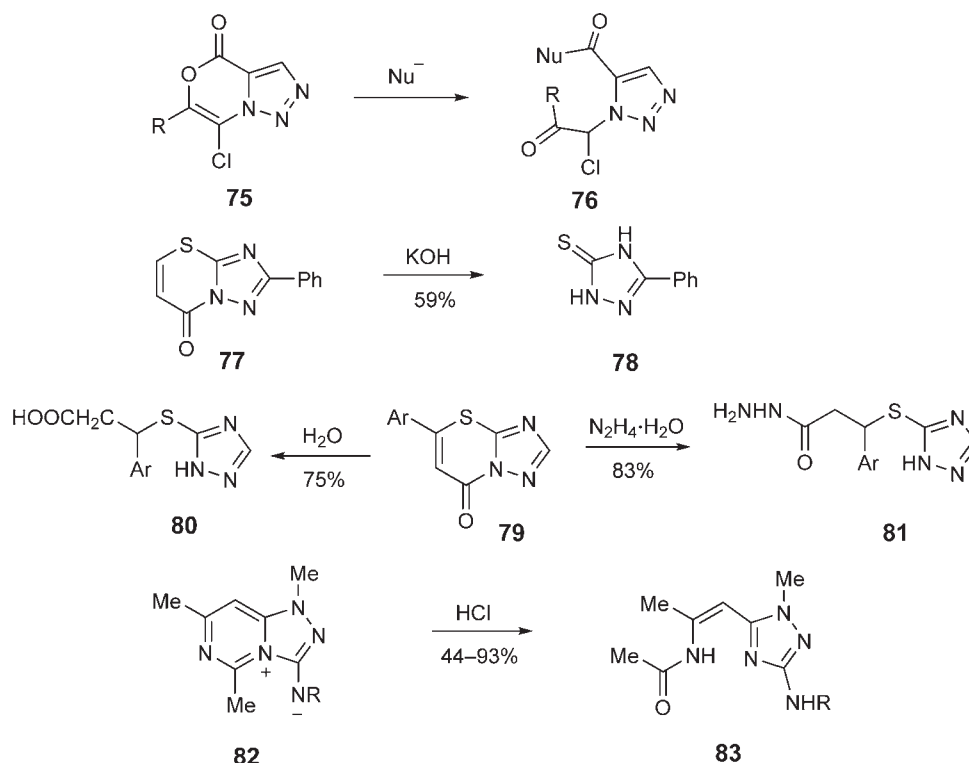
A few pieces of information in this respect appeared during the past period of time. Thus, strain energies of different conformations of some triazolopyrimidines (derivatives **148**, Scheme 17) have been calculated and compared in order to assess the existing conformer <1999IZV1573>. For other derivatives, heats of formation have been calculated and compared for different tautomeric forms <1995JST(335)273, 2000JST(519)165>. Existence of an equilibrium between a stable fused triazole and a reactive diazaallenium cation under thermal conditions has been explored by a Hungarian team <1999JOC5499>; the chemical consequences are shown in Scheme 13 (Section 11.16.5.1.2).

11.16.5 Reactivity of Fully Conjugated and Nonconjugated Rings

11.16.5.1 Ring-Opening Reactions

11.16.5.1.1 Ring opening of oxygen- and sulfur-containing ring systems

Most of these ring-opening reactions occur as a consequence of a nucleophilic attack. The nucleophile can be an amine, hydroxide ion, or the solvent (e.g., alcohol, water). These reactions can be categorized into two main groups depending on whether it is the six-membered or five-membered ring that undergoes opening (Scheme 9).



Scheme 9

Opening of the six-membered oxazine moiety of some [1,2,3]triazolo[5,1-*c*][1,4]oxazines was studied by Hoornaert *et al.* <1994TL9767, 1996T8813>, and the result is shown in **Scheme 9**. Ring opening of **75** took place in alcohol or refluxing aqueous acetonitrile for 15 min to yield the [1,2,3]triazole derivative **76** in most cases in high yield. As nucleophiles, aliphatic alcohols, ammonia, or water were used.

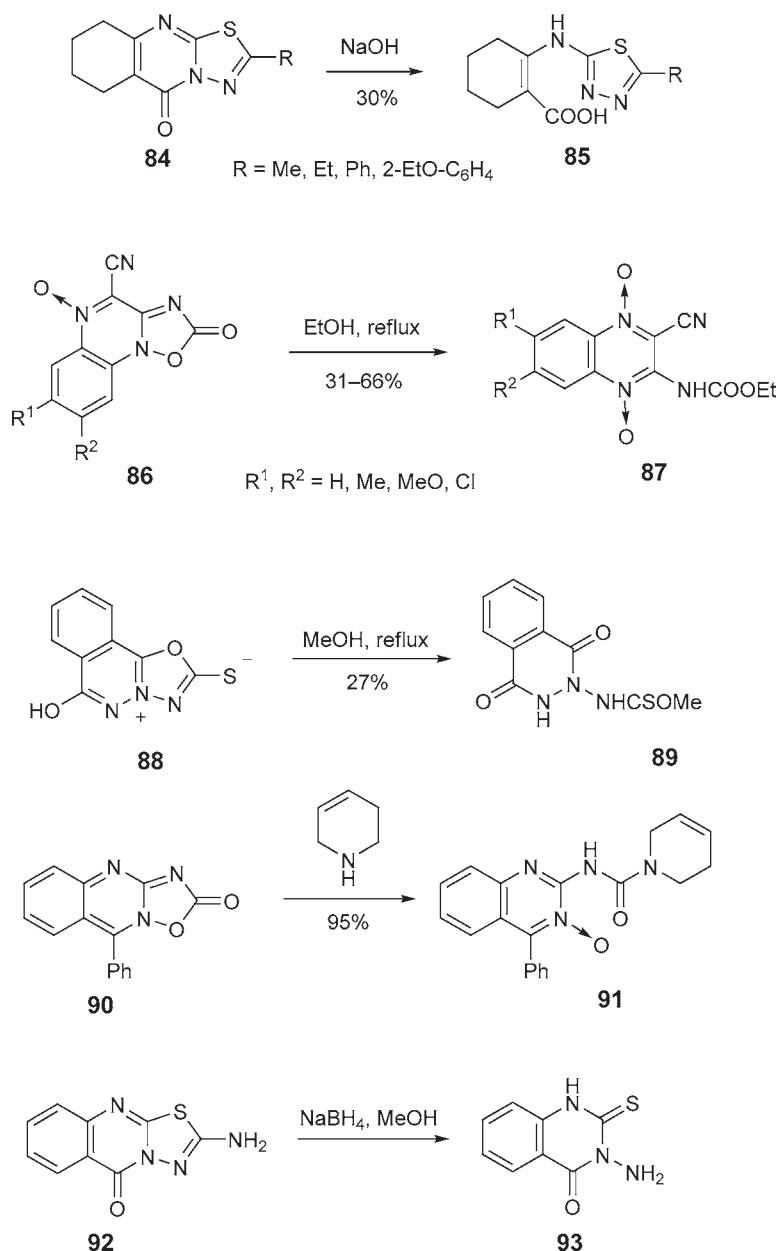
Basic hydrolysis of the [1,2,4]triazolo[5,1-*b*][1,3]thiazine derivative **77** was described to yield triazole-thione **78**, the reaction proceeding in 59% yield <2005ZOR1092>. Related partially saturated triazolothiazines **79** were also subjected to ring-opening reaction: aqueous hydrolysis afforded the acid **80** <2004KGS1256>, whereas reaction of **79** with hydrazine hydrate yielded the acid hydrazine **81** <2004ZOR260>. Both transformations took place in high yields.

A very interesting ring opening involving opening of the pyrimidine ring as well also was reported by Crabb *et al.* <1997J(P2)49>. These authors observed that the betaine **82** when treated with aqueous hydrochloric acid gives rise to ethenyltriazole **83**. The whole transformation is strongly reminiscent of the temporary ring openings taking place with Dimroth rearrangements.

Ring opening of the tricyclic thiadiazoloquinazolone derivative **84** was described by Santagati *et al.* <1994PHA880>; the transformation is shown in **Scheme 10**. When this compound was heated with sodium hydroxide in a mixture of ethanol and dioxane, the central pyrimidine ring underwent hydrolytic ring opening, and the substituted thiadiazole derivative **85** was formed.

In contrast to the above ring-opening reactions, in some cases, the opening of the five-membered ring component was experienced. Such transformations are also shown in **Scheme 10**.

An English–Spanish joint team investigated the ring-opening reaction of some [1,2,4]oxadiazolo[2,3-*a*]quinoxalines **86** <1996JHC1671>. These authors described that the treatment of **87** with refluxing ethanol results in the opening of the oxadiazole ring and leads to the formation of an ethyl carbamate quinoxaline derivative **87** in medium to good yield depending on the substituents on the fused benzene ring. A similar reaction was also described for methanol <2002AF113> and dimethylaminoethylamine <1999AF55> as the reagents; these transformations afforded methylcarbamate and substituted urea derivatives, respectively. A mesoionic derivative of the positional isomeric ring system **88** was reported by a Korean team <1997H(45)2101>: refluxing **88** in methanol gave rise to the formation of the thiocarbamate **89** in poor yield (27%).



Scheme 10

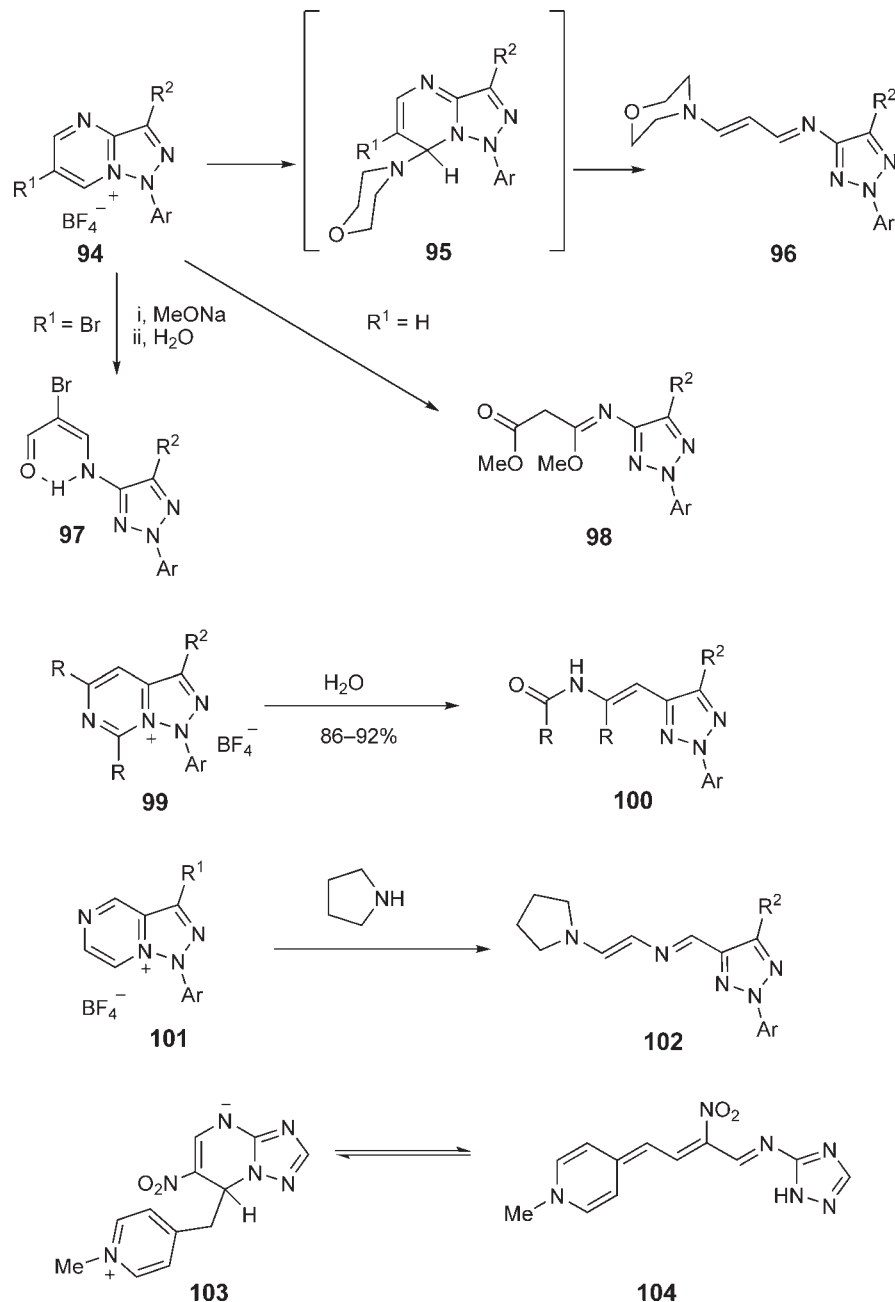
The linearly fused oxadiazoloquinazoline derivative **90** also underwent ring opening with nucleophiles: treatment of a toluene solution of this compound with tetrahydropyridine (refluxing conditions for 15 min followed by storage overnight at room temperature) yielded the urea-substituted quinazoline compound **91** in almost quantitative yield <2000S2009>.

A reductive ring opening of a linearly fused thiadiazole derivative **92** was reported by Nawrocka and Stasko <1997PJC792>. Reaction of this compound with sodium borohydride in methanol under heating afforded the *N*-aminoquinazolone-thione **93**.

11.16.5.1.2 Ring opening of various triazolodiazines

Similarly to the ring systems treated in Section 11.16.5.1.1, both the six-membered and the five-membered moieties can undergo ring-opening reactions.

As a continuation of earlier research activities as reviewed in CHEC-II(1996) <1996CHEC-II(8)421>, Messmer *et al.* described several ring-opening reactions for fused [1,2,3]triazoloazinium salts <1997T9393, 2003T4297>. The results are shown in **Scheme 11**.



Scheme 11

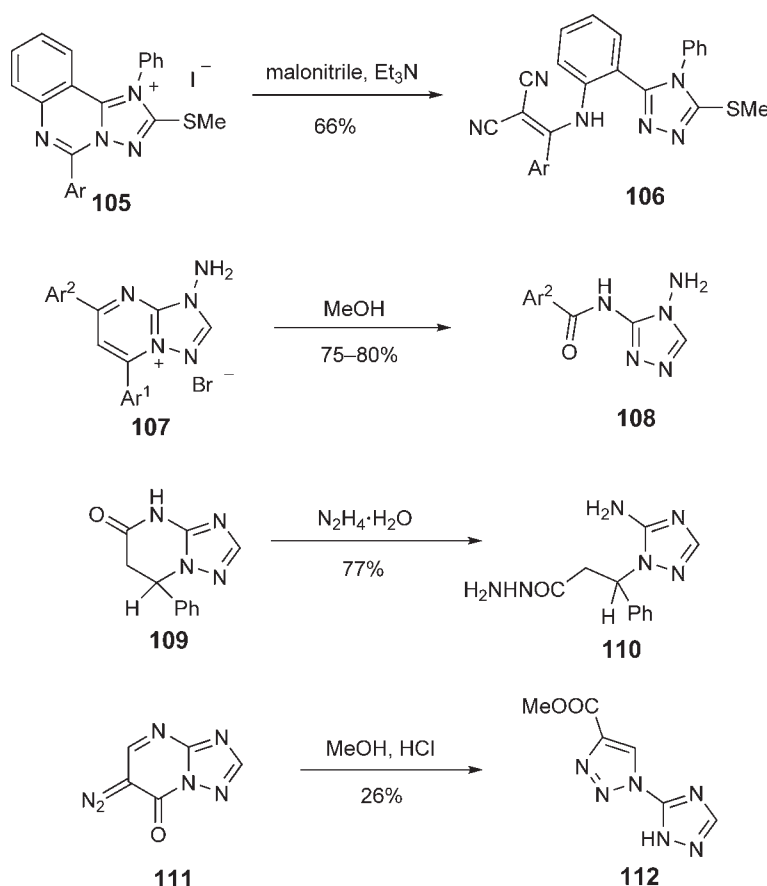
These authors found <2003T4297> that [1,2,3]triazolo[1,5-*a*]pyrimidinium salts easily undergo ring opening when treated with nucleophiles. Thus, reaction of **94** with morpholine yields the morpholineenamine **96** in good yield. The reaction was interpreted by intermediate formation of an addition product **95** which can undergo a retro-electrocyclic opening to give the azadiene. A similar transformation has already been reported in CHEC-II(1996)

<1996CHEC-II(8)421>. Reaction of **94** with water can proceed by two different routes depending on the substitution pattern: in the case of the bromo-substituted derivative the unsaturated ketone **97** was formed in high yield, whereas the derivative being unsubstituted at the pyrimidine moiety gave the methyl ester **98**, also in very good yield.

Hydrolytic ring opening of the isomeric [1,2,3]triazolopyrimidinium salt **99** yielded the amide **100**. The same team also described <1997T9393> the analogous transformation of the [1,2,3]triazolo[1,5-*a*]pyrazinium salts **101**: reaction of this quaternary salt with a secondary amine (e.g., with pyrrolidine) led to the formation of the azadieneamine **102**. For the formation of this product, a similar mechanism to that with **96** was anticipated.

Rusinov *et al.* <1998ZOR290> reported a ring-opening process strongly reminiscent of the previous case. These authors described that the zwitterions **103** undergo ring opening to give **104** in refluxing in dimethylformamide (DMF) for 5 min. When the pure **104** was dissolved in DMSO-*d*₆ for NMR measurement, the reverse reaction to **103** took place to result in an equilibrium mixture.

In Scheme 12 several ring openings are summarized that proceed via solvolysis or nucleophilic attack at the six-membered moiety. These reactions take place under relatively smooth conditions in the case of azoloazinium salts or the electron-deficient azinones, but neutral bicyclic heterocycles can also react with strong nucleophiles.



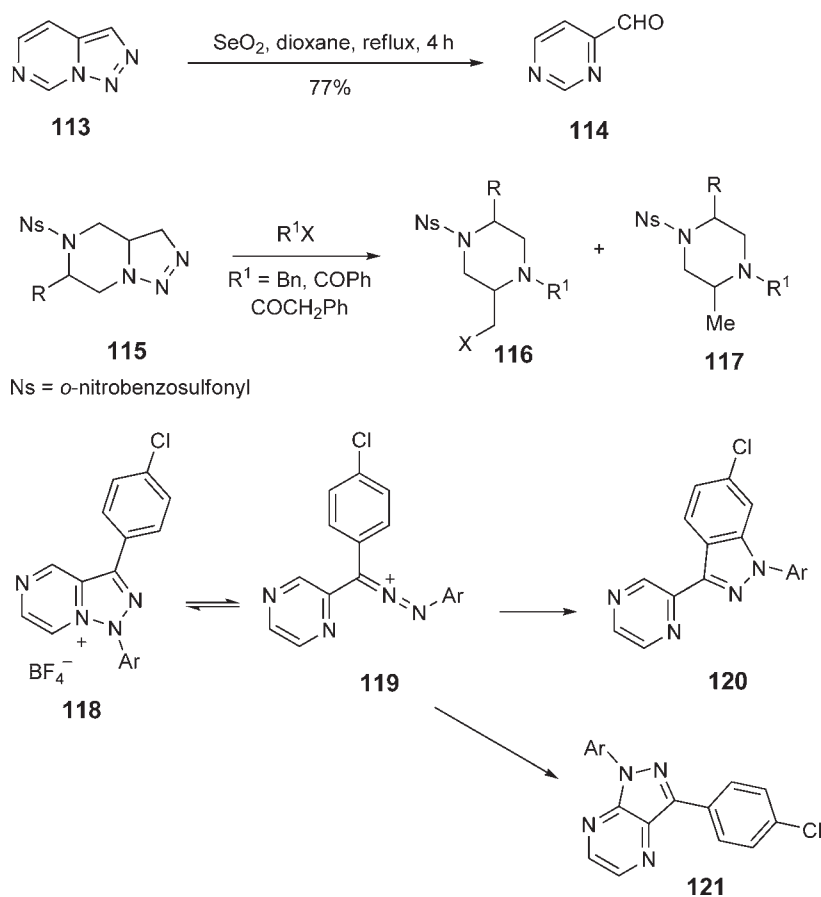
Scheme 12

The ring opening of the fused triazolium salt **105** with malonitrile was reported by Wasfy <2003HAC581>: the anion of the reagent was generated by Et₃N, and the transformation to **106** took place in acetonitrile under heating for 24 h in 66% yield. Similar hydrolysis of other derivatives of this ring system has also been reported <1994H(39)693>.

Ring opening of the *N*-aminotriazolopyrimidinium salts **107** to the amides **108** occurred in high yields <1999KGS796>. The partially saturated derivative of the same ring system **109** also underwent ring opening when reacted with hydrazine hydrate <2000KGS1542> and the open-chained hydrazide **110** was obtained in 77% yield.

An interesting route to [1,2,3]triazolo[1,2,4]triazoles starting from azine derivatives of the [1,2,4]triazolo[1,5-*a*]-pyrimidine ring system was reported by Stanovnik *et al.* <2005JHC1167>. The starting compound **111** when reacted with hydrogen chloride in methanol undergoes ring opening and, subsequently, a 1,5-dipolar cyclization takes place with participation of the azine moiety to result in formation of a [1,2,3]triazole ring **112**. The yield in this case was low (26%), but it was found to be essentially higher with some related ring systems.

Ring-opening reactions with opening of the five-membered moiety can occur in the cases of several fused [1,2,3]triazines. Such transformations are depicted in Scheme 13.

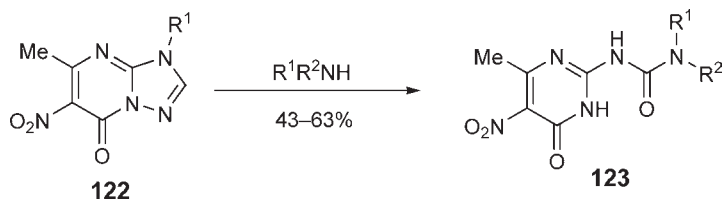


Scheme 13

Thus, oxidation of [1,2,3]triazolo[1,5-*c*]pyrimidine **113** with selenium dioxide resulted in opening of the triazole moiety <2001T10111>, and pyrimidin-4-aldehyde **114** was formed in high yield. Ring opening of the partially saturated derivative **115** of a related (i.e., pyrazine-fused) ring system has also been carried out <2005TL1205>. Treatment of this saturated compound with various acyl- or alkyl chlorides afforded two kinds of products: **116** as the main product and **117** as a side product. In some cases (e.g., R = *i*-Pr or Bn; R¹ = COOCH₂Ph or COPh), the reactions proved to be entirely selective and the product **116** was formed in pure form and good to excellent yields (62–95%).

In the course of studies on a series of azoloazinium salts, Messmer *et al.* observed <1999JOC5499> that [1,2,3]triazolo[1,5-*a*]pyrazinium salts **118** – similarly to several other fused [1,2,3]triazolium salts with bridgehead nitrogen atoms – undergo valence-bond isomerism under thermal conditions (in refluxing dichlorobenzene or refluxing trifluoroacetic acid) to result in an equilibrium with the reactive species diazaallenium cation **119**. Although **119** could not be detected directly, the two products **120** and **121** unambiguously supported its intermediate existence. Compounds **120** and **121** were considered as products of attack by the diazaallenium cation on the *p*-chlorophenyl and pyrazine rings, respectively. Formation of **120** was rationalized by an electrophilic attack on the phenyl ring, whereas formation of the pyrazolopyrazine ring was considered as a pseudo-electrocyclization process.

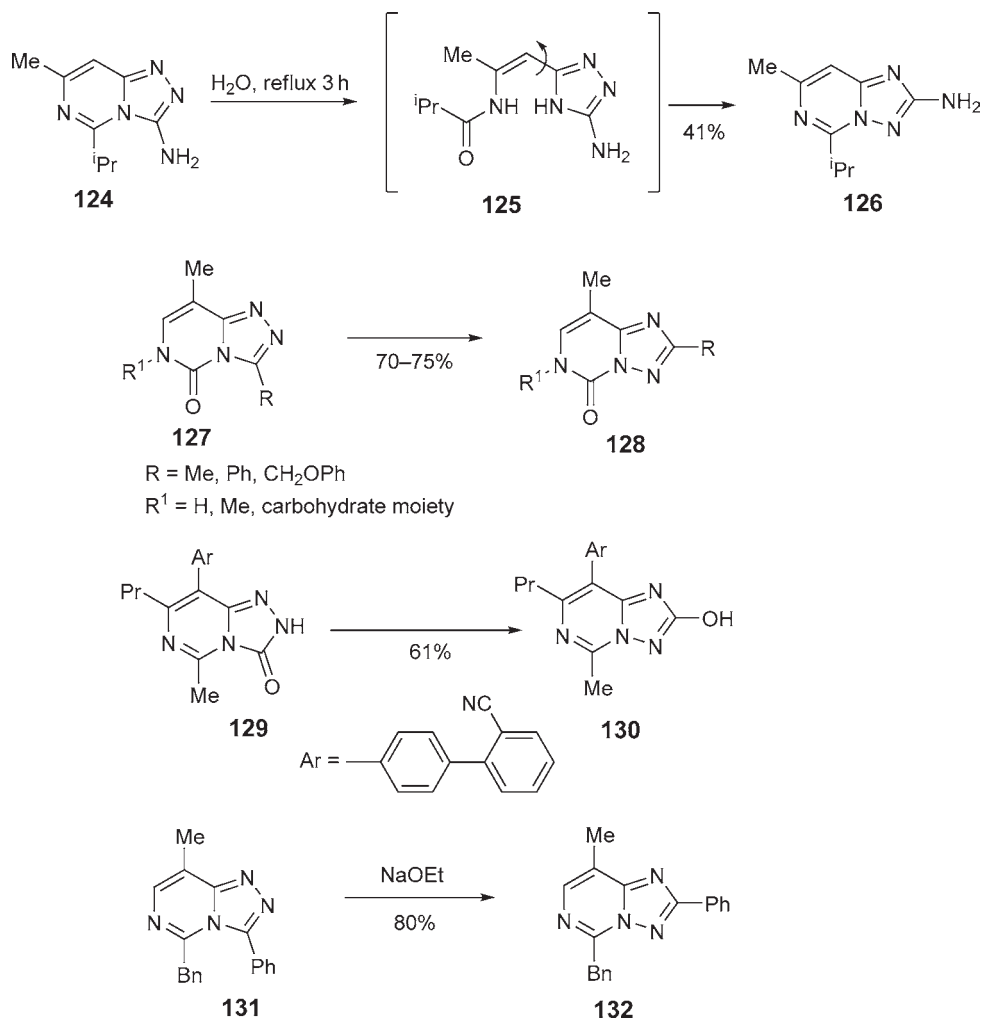
Ring opening of also a fused [1,2,4]triazole system by secondary amines has been reported. Chupakhin *et al.* described that 5-methyl-6-nitro[1,2,4]triazolo[1,5-*a*]pyrimidin-7(8*H*)one **122** underwent ring opening when treated with various secondary amines to yield pyrimidyl urcas **123** in medium to good yield <2001IZV655>, as shown in Scheme 14.



Scheme 14

11.16.5.2 Ring Transformations

The best-documented ring transformation of the systems presented in this chapter is the Dimroth rearrangement of fused [1,2,4]triazoles. Such transformations were discussed in CHEC-II(1996) <1996CHEC-II(8)421> and, also, several novel cases have also been discovered. These are depicted in Scheme 15.

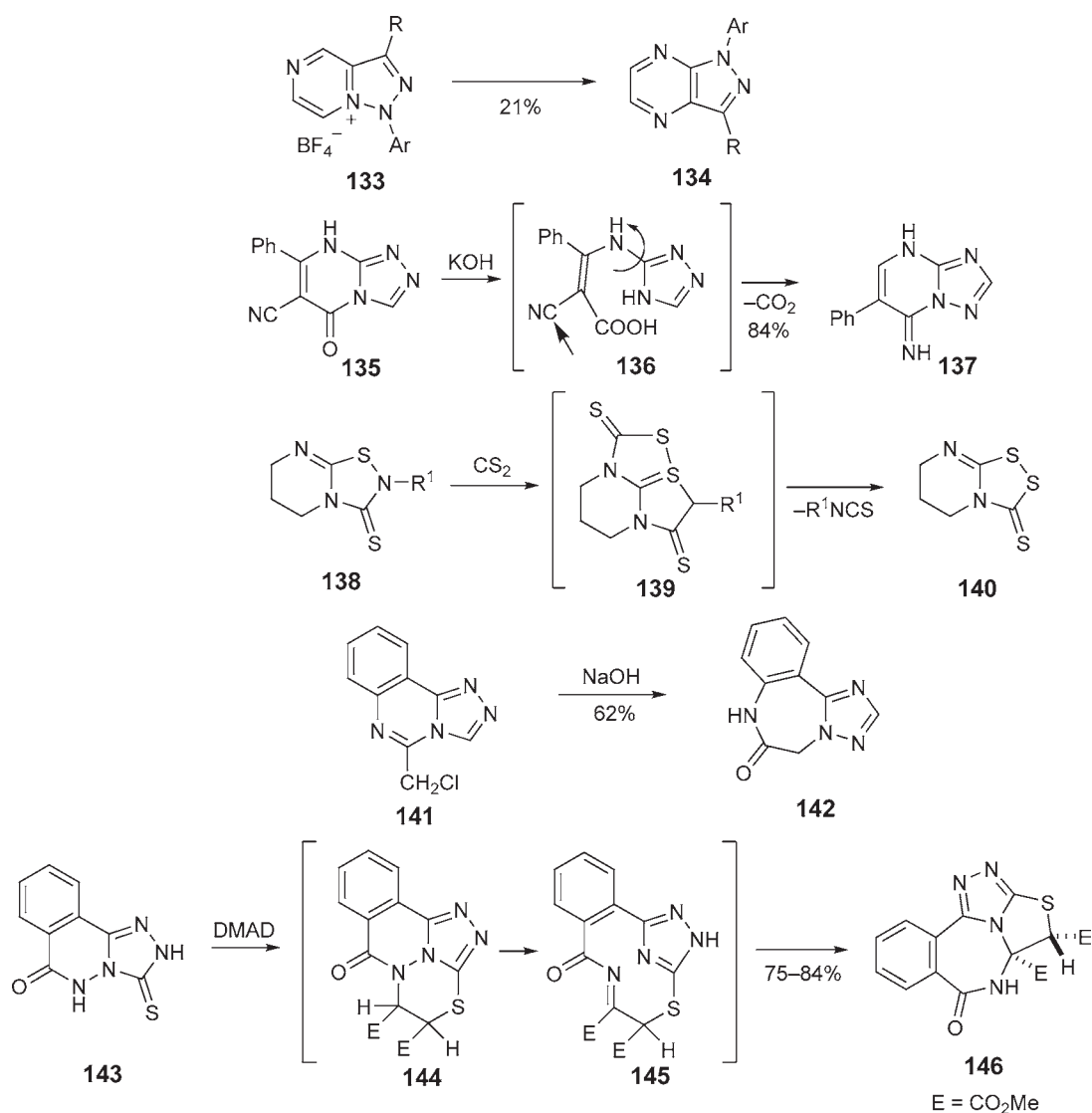


Scheme 15

A typical case is the ring transformation of 3-amino-5-isopropyl-7-methyl[1,2,4]triazolo[4,3-*c*]pyrimidine **124** to the correspondingly substituted [1,2,4]triazolo[1,5-*c*]pyrimidine derivative **126** <1997J(P2)49>. The main step of this transformation is the hydrolytic ring opening of the pyrimidine ring to the intermediate **125**, in which the triazole ring can rotate and, then, a reverse ring closure occurs with participation of a different nitrogen atom. As a consequence, all of the substitution pattern remains the same, and it is only the fusion site of the triazole ring that will be different in the product **126** compared to the starting material **124**.

Several other Dimroth rearrangements with various derivatives of the same ring system have been realized. Thus, some fused pyrimidones **127** were transformed to the corresponding [1,5-*c*]fused products **128** <2002H(57)631>, including some nucleoside analogues (R = carbohydrate moiety) <1999J(P1)1333>. Also, biphenyl-substituted fused triazolones **129** gave the isomeric derivatives **130** as potent angiotensin II antagonists <1996JHC1307>, and 5-benzyl-substituted derivatives **131** were reacted analogously to **132** <2000KGS225>.

Besides these 'conventional' transformations, some ring transformations proceeding by more complicated reaction mechanisms have also been reported, and these are summarized in **Scheme 16**.



Scheme 16

The ring transformation of the fused triazolium salt **133** to the pyrazolopyridine derivative **134** proceeds via ring opening according to a valence-bond isomerization <1999JOC5499> and was already discussed in Section 11.16.5.1.

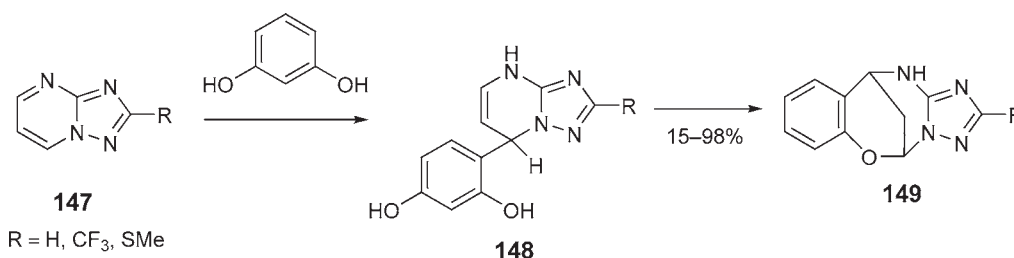
A highly interesting ring transformation of **135** to **137** was reported by El Ashry *et al.* <1998ZNB1203>. This ring transformation is basically also a Dimroth rearrangement, and in the first step results in the formation of intermediate **136** in which – according to the usual Dimroth protocol – the triazole ring rotates as shown by the arrow. The interesting feature of the conversion is, however, that after the rotation the triazole ring-nitrogen atom attacks the cyano carbon atom rather than the carboxylic one. The ring closure takes place, the intact carboxyl group is removed by decarboxylation, and the imine **137** is formed.

Transformation of the thiadiazolopyrimidine compound **138** to the fused dithiazole **140** also follows a fairly complicated pathway <2004JHC99>. When the derivative **138** is treated with carbon disulfide, a cyclization reminiscent of 1,3-dipolar cyclization takes place with the reagent acting as a dipolarophile to give a *peri*-fused tricyclic intermediate containing a hypervalent sulfur atom **139**. This intermediate can undergo isothiocyanate elimination to furnish **140**. It is interesting to note that the sulfur atom of the thione moiety in the product is derived from carbon disulfide.

Finally, three ring-enlargement reactions should be referenced in this section. Gerecke *et al.* reported <1994H(39)693> that treatment of the 5-chloromethyl-substituted triazolo[4,3-*c*]quinazoline compound **141** with sodium hydroxide results in the formation of a seven-membered diazepine ring **142** in good yield.

Csámpai *et al.* investigated the reactivity of [1,2,4]triazolo[4,3-*b*]pyridazine-6(5*H*)-one-3-(2*H*)-thiones **143** with dimethyl acetylenedicarboxylate <2001T7191>. An interesting sequence of transformations was experienced: first a cycloaddition occurred to give the first intermediate **144**, which underwent an inner ring opening to a doubly fused ten-membered ring **145** and, finally, the attack of the triazole nitrogen atom at the imine carbon atom leads to compound **146**. The two ester groups were found in a relative *cis*-stereochemistry. The yields – in contrast to the seemingly complicated mechanism – were high (75–84%).

Chupakhin *et al.* investigated the reactivity of some [1,2,4]triazolo[1,5-*b*]pyrimidines with resorcinol (Scheme 17) <1999IZV1573>. These authors found that **147** reacts with resorcinol to give at first the addition product **148** which undergoes an intramolecular cyclization to produce the bridged skeleton **149**.



Scheme 17

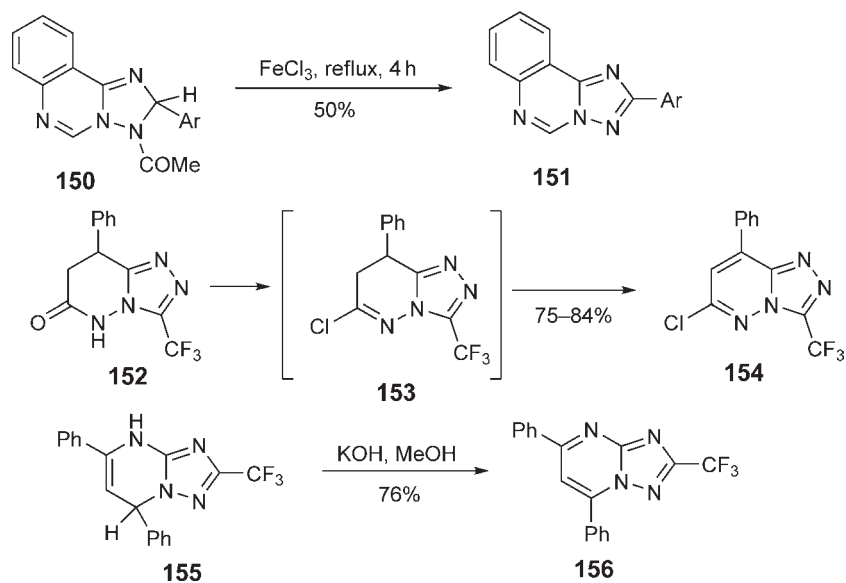
11.16.5.3 Oxidations and Reductions of the Ring

Some transformations involving oxidation of the heterocyclic ring have been reported. These oxidations created full heteroaromaticity in the rings. These reactions are depicted in Scheme 18.

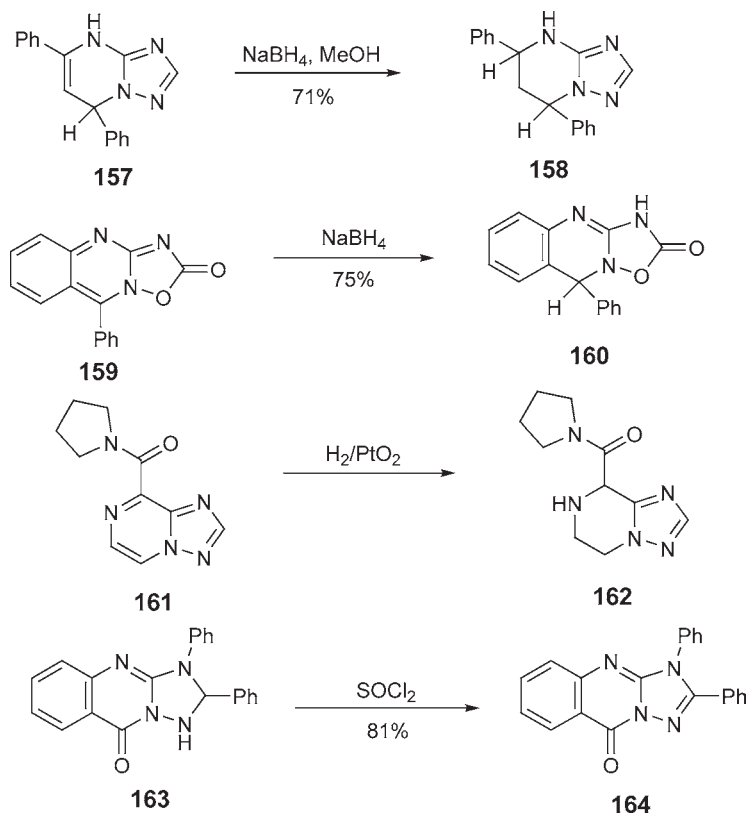
In the course of a study in the area of medicinal chemistry, the *N*-acetyl tricyclic compound **150** was obtained <2005JME6409>, which could be oxidized by FeCl₃ to give the heteroaromatic triazoloquinazoline derivative **151** in medium yield (50%). Transformation of the partially saturated triazolopyridazine derivative **152** with a mixture of phosphorus oxychloride and phosphorus pentachloride not only resulted in exchange of the lactam moiety for an imine chloride **153**, but also a subsequent spontaneous oxidation took place to the heteroaromatic chloro compound **154** <1997APH299>. Also a ring oxidation took place when the partially saturated triazolopyrimidine derivative **155** was treated with methanolic potassium hydroxide under heating for 20 min. The fully conjugated product **156** was obtained in high yield (76%).

Ring-reduction transformations were also reported in CHEC-II(1996) <1996CHEC-II(8)421>, and some novel similar transformations also appeared during the recent years. These reactions are shown in Scheme 19.

Two ring reductions using sodium borohydride were reported. The reduced derivative **157** underwent further reduction in the six-membered ring with methanolic sodium borohydride under heating for 15 min to give the



Scheme 18



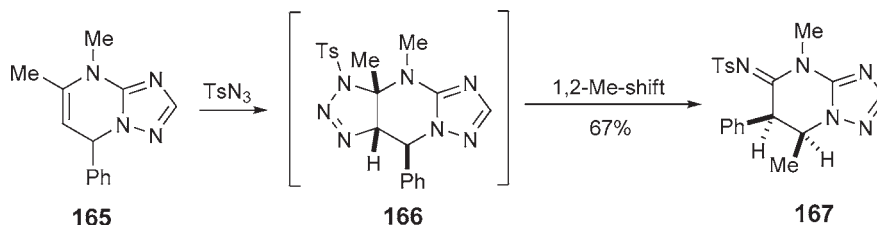
Scheme 19

tetrahydro compound **158** in high yield (71%) <1994KGS981>, whereas reduction of the tricyclic fused oxadiazole **159** was accomplished in DMF at rt for 30 min to afford the dihydro product **160** in high (75%) yield <2000S2009>. Catalytic hydrogenation of the [1,2,4]triazolo[1,5-*a*]pyrazine derivative **161** over PtO₂ was reported to yield **162** containing a saturated pyrazine ring <1995FA405>.

Oxidation of the ring was also observed: in reaction of **163** with thionyl chloride <1997BCJ2209>, **164** was obtained in 81% yield (Scheme 19).

11.16.5.4 Cycloaddition

A 1,3-dipolar cycloaddition of a partially saturated [1,2,4]triazolo[1,5-*a*]pyrimidine derivative **165** was reported by a German–Ukrainian team <2000JHC195>. The reaction pathway is shown in Scheme 20.



Scheme 20

Derivative **165** was treated with tosyl azide at room temperature for 48 h to give **167**. Formation of this product was rationalized by a 1,3-dipolar cycloaddition with participation of the C=C bond in the pyrimidine ring in **165** to form a cycloadduct **166** at first, which underwent a [1,2]-methyl shift and a nitrogen elimination to yield **167**. Structure elucidation of this product revealed the relative *cis*-stereochemistry of the phenyl and methyl substituents.

11.16.5.5 Formation of Further Condensed Rings

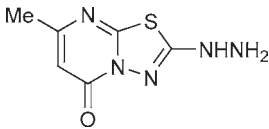
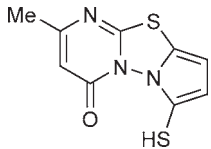
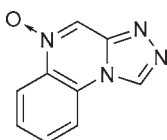
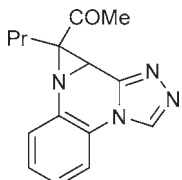
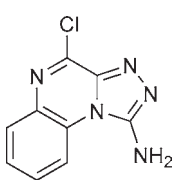
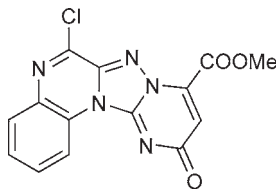
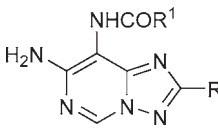
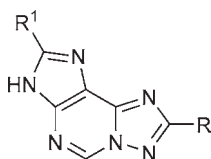
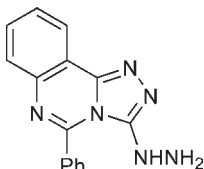
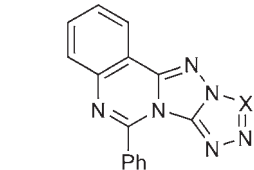
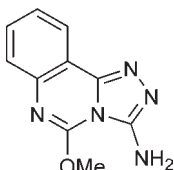
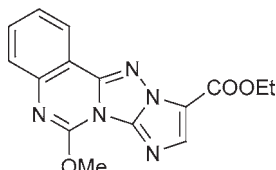
In comparison to the examples in CHEC-II(1996) <1996CHEC-II(8)421>, a lot of synthetic work has been reported where a new ring was created. As most of these ring closures have been perfected by routine transformations, no detailed mechanistic discussion is provided here but, instead, these transformations are compiled in Table 6.

Table 6 Reactions with formation of further condensed rings: starting compounds, products, yields, and literature references

Entry	Starting compound	Product	Yield (%)	Reference
1	R = H, Me	R¹ = Ph, 4-F-C₆H₄, 2-furyl	60–72	1999IZV66
2		E = COOMe or COOEt	23–43	1996H(42)53, 2001JHC1135

(Continued)

Table 6 (Continued)

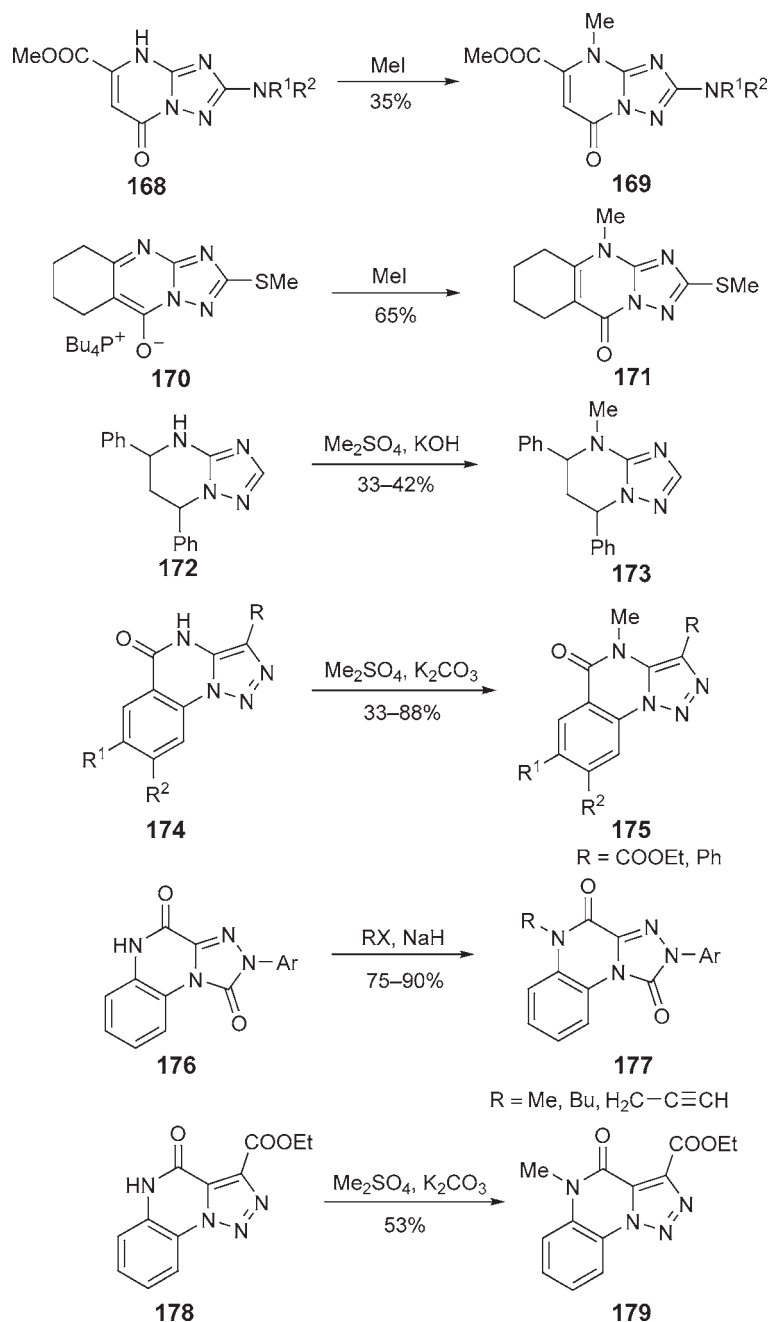
Entry	Starting compound	Product	Yield (%)	Reference
3			78	1994KGS560
4			17	1994CCC2493
5			61	2002AP389
6			50–68	1994JHC1171
7		 X = N or C-R R = H, Me, SH, NHPH, 5-nitrofuryl, 4-nitrophenyl	52–93	1995M767
8			53	2003AP560

11.16.5.6 Reactions at the Ring Heteroatoms

11.16.5.6.1 Alkylation of ring nitrogen atoms

N-Alkylations of ring nitrogen atoms were reviewed in CHEC-II(1996) <1996CHEC-II(8)421> and recently several such transformations have also been published. Most of these reactions were carried out by using methyl iodide and dimethyl sulfate. In one case, alkyl chlorides and sodium hydride were used. The transformations are shown in **Scheme 21**.

Six different alkylations are depicted in **Scheme 21**. The first four cases show alkylation of various [1,2,4]triazolo-[1,5-*a*]pyrimidines or their benzologues. Thus, reaction of **168** with methyl iodide gave **169** <1999MI227>; the cyclohexa-fused analogous derivative **170** reacted in similar manner and afforded the 4-methyl product **171** <2001JHC237>. Compounds **172** and **174** were methylated with dimethyl sulfate to give **173** <1994KGS981> and **175** <1996FA131, 2000EJM333>, respectively.

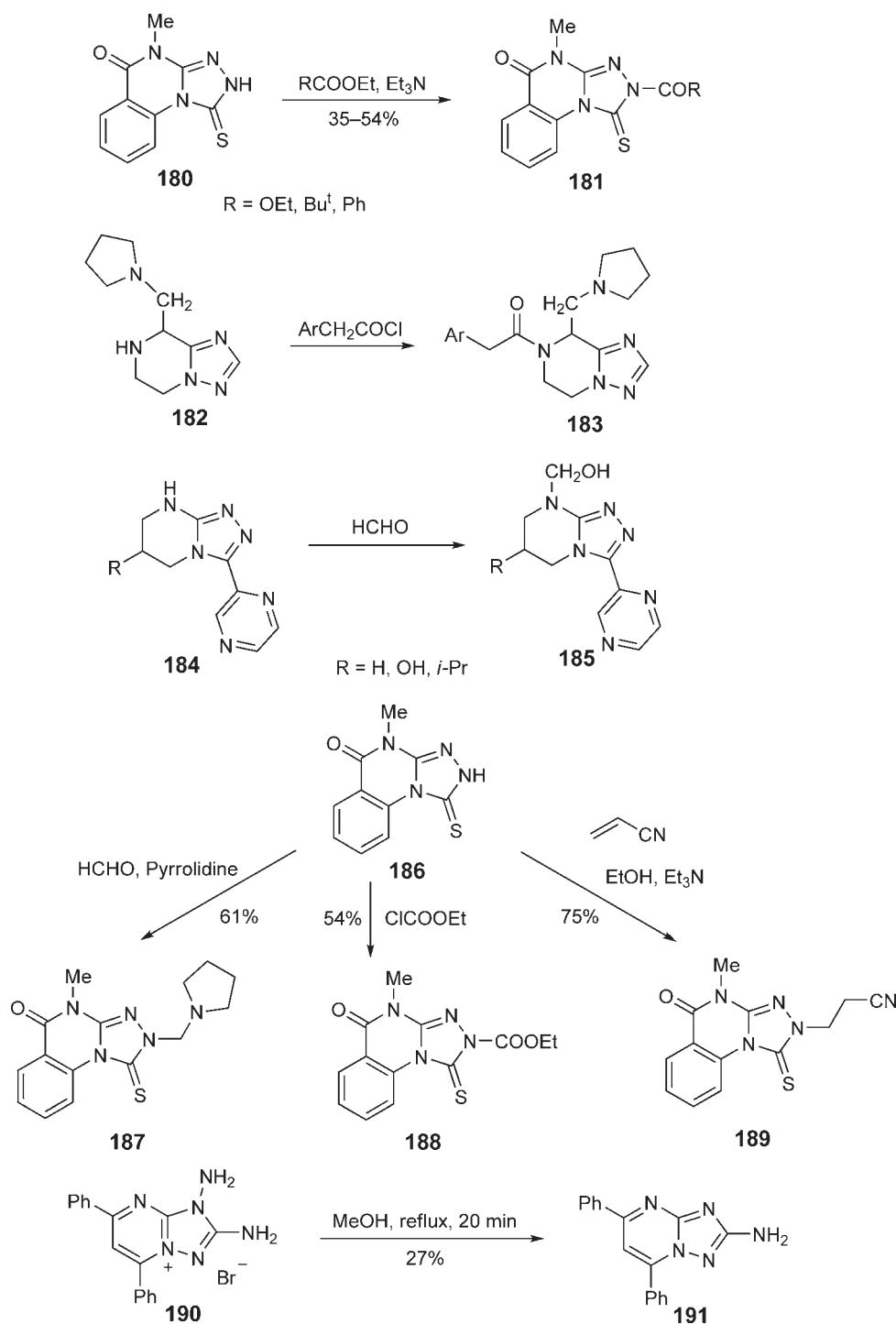


Scheme 21

In the case of the [1,2,4]triazolo[4,3-*a*]quinazole derivative **176** sodium hydride was used as the deprotonating agent and the alkylation was carried out with different alkyl (or propargyl) chlorides to result in alkylation on the pyrimidine nitrogen atom (**177** was formed) in high yield <2000JME1158>. Alkylation of another derivative **178** of this same ring system with dimethyl sulfate and potassium carbonate as a base was reported to give **179**.

11.16.5.6.2 Other transformations on ring nitrogen atoms

Two examples for acylation of ring nitrogen atom are shown in Scheme 22. Reaction of **180** with various esters was described <2000MOL1210>. The transformations took place on the N-2 triazole nitrogen atom to give **181** in poor to medium yields (Scheme 22).



Scheme 22

In contrast to the previous transformations where the reaction took place at the five-membered ring, acylation of **182** at the pyrazine nitrogen atom was reported <1995FA405> to yield **183**.

N-Formylation of **184** was carried out by Sitarz *et al.* <2005KGS230>. The reaction was carried out with formaldehyde, and the Mannich reaction resulted in formation of **185** in 76% yield.

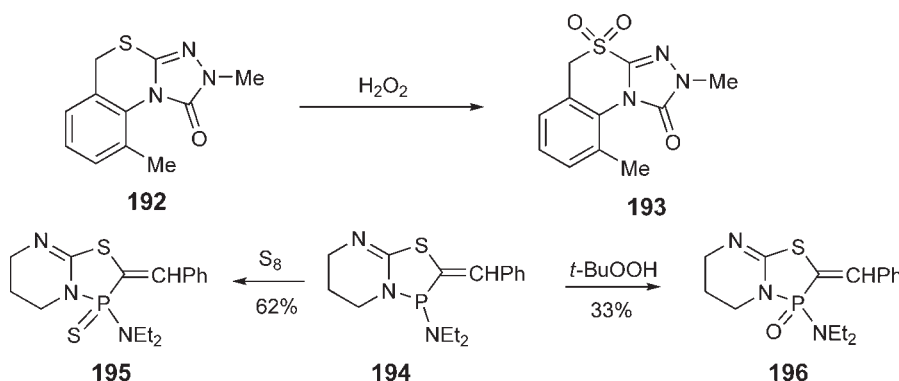
Fathalla *et al.* reported that some [1,2,4]triazolo[4,3-*a*]quinazoles can be subjected to various transformations involving the triazole nitrogen atom <2000MOL1210>. Thus, treatment of **186** with formaldehyde and pyrrolidine

resulted in a Mannich reaction to give **187**; reaction with ethyl chloroformate gave **188**, whereas reaction with acrylonitrile in the presence of Et_3N afforded the cyanoethyl derivative **189**.

Removal of an *N*-amino substituent was also reported in one case <1999KGS796>. Kolos *et al.* found that heating of the diamino compound **190** in methanol for 20 min results in removal of the *N*-amino moiety to give **191** in 27% yield (Scheme 22).

11.16.5.6.3 Reactions on ring sulfur and phosphorus atoms

A few routine transformations on ring sulfur and phosphorus atoms were reported during the past period of time, and these are shown in Scheme 23.



Scheme 23

Oxidation of the fused thiazine **192** by hydrogen peroxide yielded the cyclic sulfone **193** <2004T4361>. Oxidation of the fused thiazaphosphole **195** was accomplished by *t*-butyl peroxide to yield **196** in relatively low yield (33%), whereas reaction of **194** with elemental sulfur yielded the *P*-sulfide **195** in 62% yield <1994PS59>.

11.16.5.7 Reactivity at Ring Carbon Atoms

11.16.5.7.1 Electrophilic substitutions

Several electrophilic substitutions were reviewed in CHEC-II(1996) <1996CHEC-II(8)421> and some similar transformations have been reported more recently. These include nitrations, nitrosations, azo couplings, and Friedel–Crafts-related transformations.

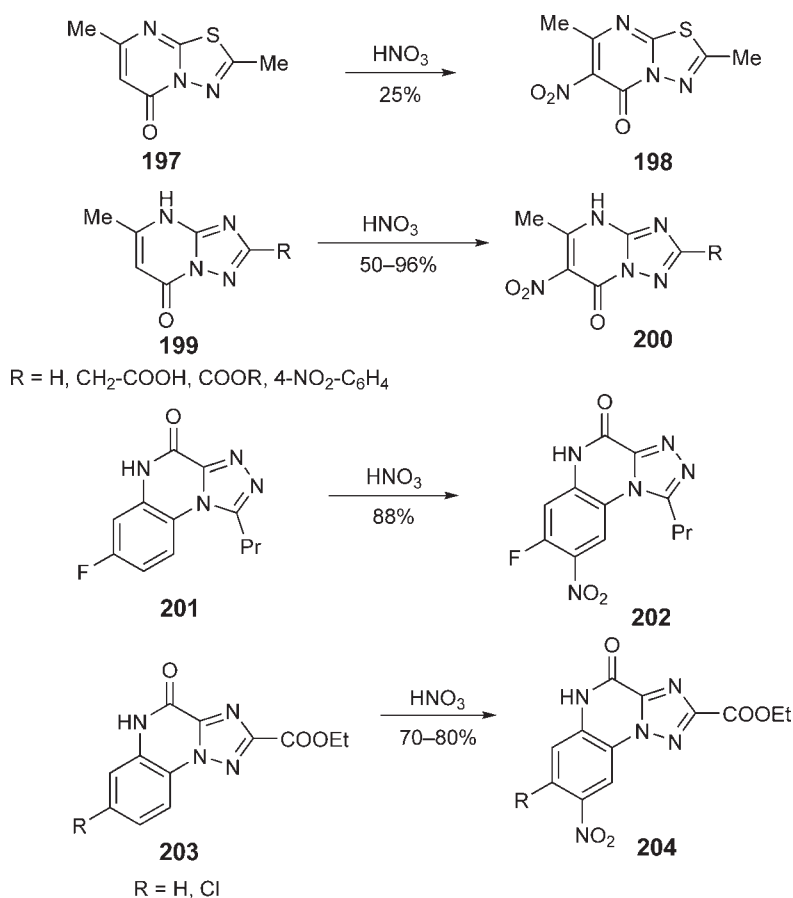
The recently published nitrations are shown in Scheme 24. All of these reactions have been carried out with nitric acid.

Thus, the thiadiazolopyrimidine derivative **197** gave 6-nitro compound **198** <1999IZV1154>; the related fused triazole with a similar heteroatomic arrangement **199** reacted also in the same position to give **200** <1997ZOR1867>. Nitration of two benzologues of this ring system have also been reported and both reacted at the fused benzene ring: **201** gave **202** <1997JME2053> whereas the ester **203** yielded the nitro compounds **204** <2000JME3824, 2001JME3157>.

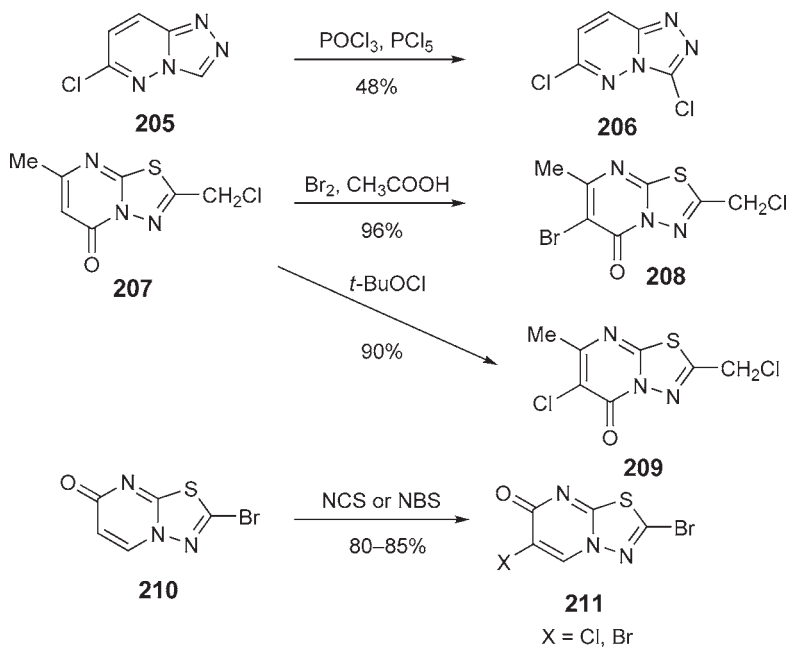
Some halogenations are shown in Scheme 25. Treatment of the triazolopyridazine derivative **205** with a mixture of phosphorus oxychloride and phosphorus pentachloride led to 3-chloro derivative **206** <1994PJC683>. For derivative **207**, both bromination and chlorination were reported <1994IZV908>; treatment with elemental bromine in acetic acid gave **208** in almost quantitative yield, whereas reaction with *t*-butyl hypochloride yielded the chloro compound **209**. For the thiadiazolopyrimidine derivative **210** both chlorination and bromination have also been described <2005JHC1105> taking place on the thiadiazole ring; reactions with *N*-chloro- and *N*-bromosuccinimide gave rise to the 6-halogeno-substituted products **211** in high yields.

A few other electrophilic substitution reactions of the ring systems in this chapter are shown in Scheme 26 also.

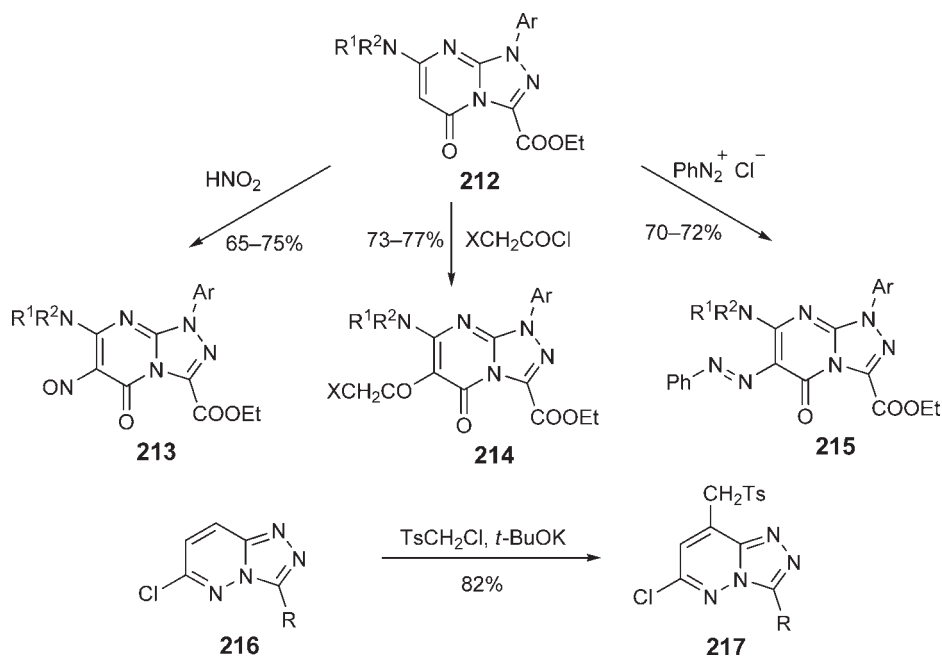
For the triazolopyrimidine derivative **212** three different types of electrophilic substitutions were reported <2003HCA739, 1997JRM2378>: nitrosation gave **213**, reaction with chloroacetyl chloride (Friedel–Crafts reaction) yielded **214**, whereas azo coupling afforded the phenylazo derivative **215**. All of these transformations proceeded in good yields (65–77%). In one case, electrophilic substitution with tosylmethyl chloride was also reported <1996PJC1279>: treatment of **216** with this reagent yielded the tosylmethyl derivative **217** in high yield (82%).



Scheme 24



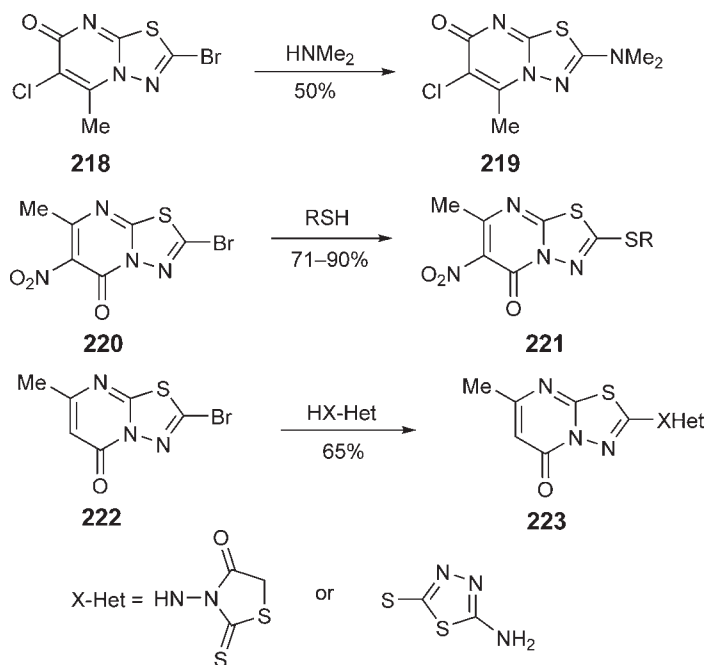
Scheme 25



Scheme 26

11.16.5.7.2 Nucleophilic substitutions

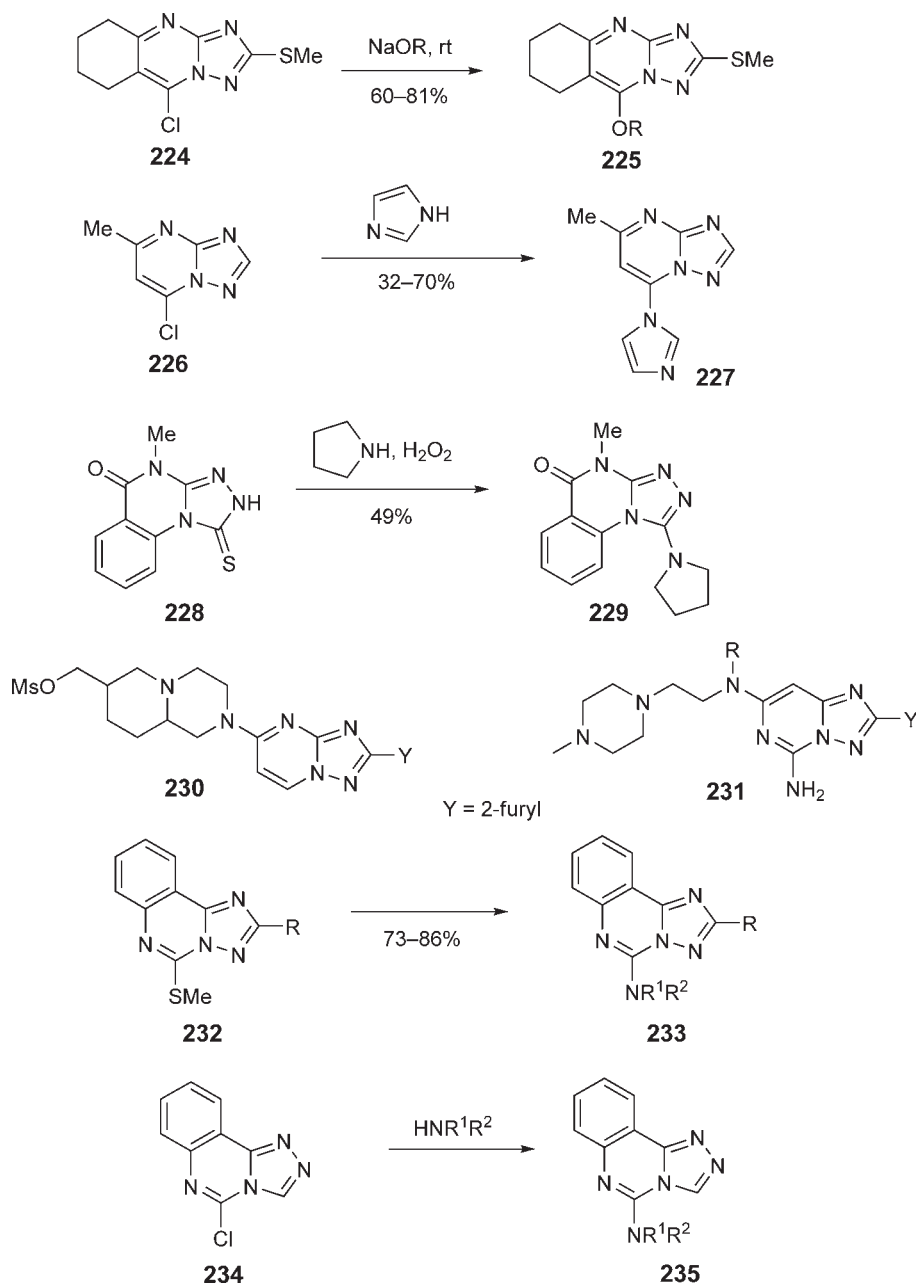
Numerous nucleophilic substitutions of derivatives of the title ring systems have been carried out during the past period of time. These are summarized in [Schemes 27–29](#).



Scheme 27

Transformations of various 2-bromo-substituted derivatives of [1,3,4]thiadiazolo[3,2-*a*]pyrimidines are shown in [Scheme 27](#). Thus, reaction of **218** with dimethylamine gave **219** in medium yield <2005JHC1105>, treatment of **220** with mercaptans afforded **221** in good yield <1999IZV1154>, whereas reaction of **222** with hetarylamines and hetarylmercaptanes yielded **223** <1993IZV1954, 1994KGS560>.

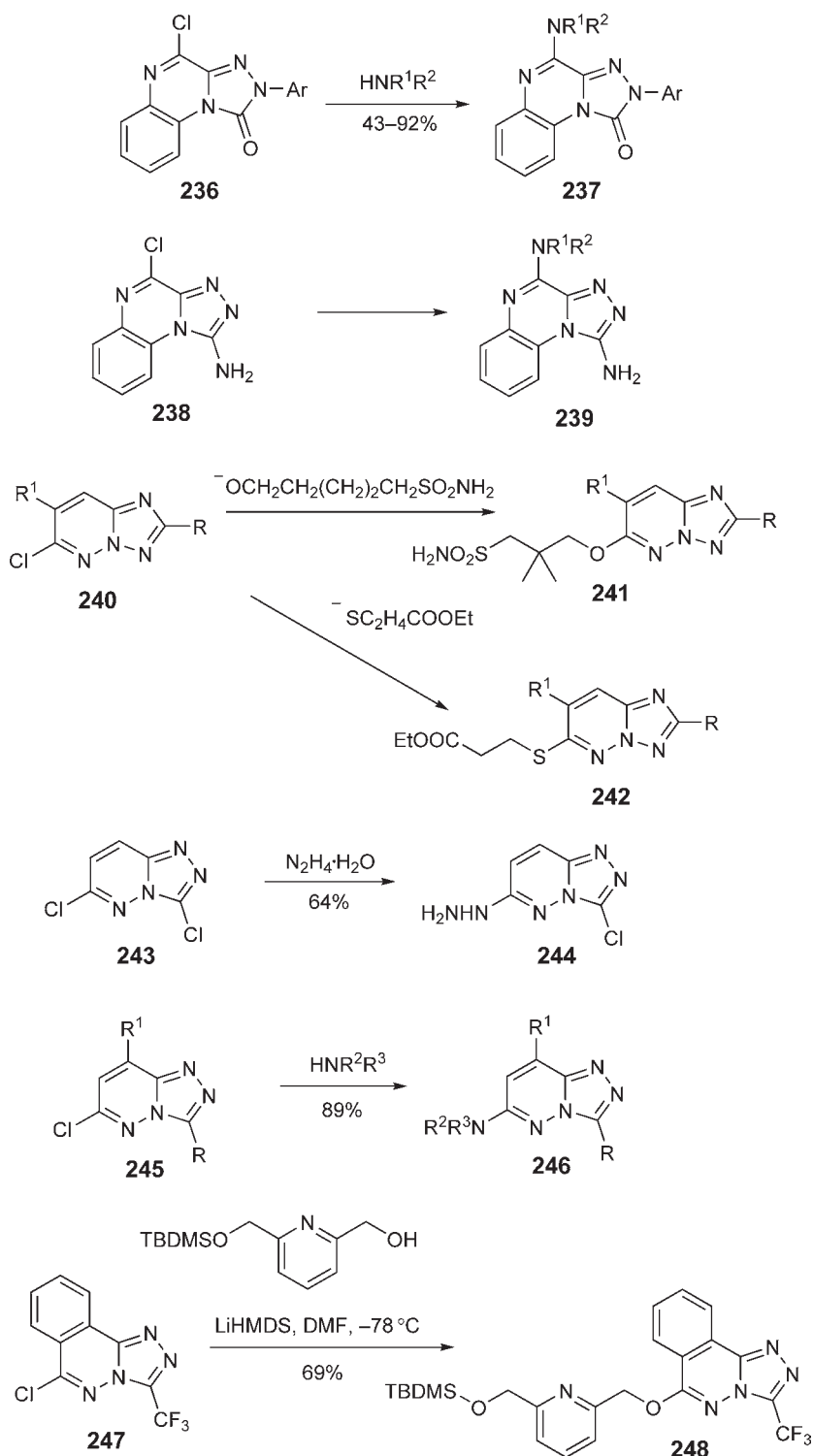
Some nucleophilic substitutions of triazolopyrimidines and their benzologues are compiled in [Scheme 28](#). Thus, the cyclohexa-fused [224](#) reacted with alkoxides selectively displacing the halogen substituent to give the alkoxy derivative [225](#) [<2001JHC237>](#), and the chloro compound [226](#) also underwent a similar transformation in reaction with imidazole in the presence of a base to yield imidazolyl derivatives [227](#) in poor to high yields (32–70%) [<2000ZOR899>](#). Reaction of [228](#) with pyrrolidine was accomplished in the presence of hydrogen peroxide – that is, via intermediate formation of a sulfonic acid – to afford the pyrrolidinyl-substituted product [229](#) [<2000MOL1210>](#).



Scheme 28

The triazoloquinazolinone derivatives [230](#) and [231](#) were also prepared via nucleophilic substitution of halogenotriazolopyrimidines by piperidines [<2004JME6218, 2004BML4835>](#) and related amines [<2004BML4831>](#). Nucleophilic substitution of the methylsulfanyl group in compound of type [232](#) afforded the amines [233](#) in high yield [<2003EJO182>](#). The similarly substituted chloro derivative [234](#) was also reacted with secondary amines to give the substituted products [235](#) [<2003AP560>](#).

Some nucleophilic substitutions of benzologues of the ring system [1,2,4]triazolo[4,3-*a*]pyrazines are shown in **Scheme 29**. The chloro triazolone compound **236** was reacted with a series of amines to give **237** in medium to high yields <2000JME1158, 1999AP39>. Similarly, reaction of **238** with secondary amines gave **239** <2002AP389> (**Scheme 29**).

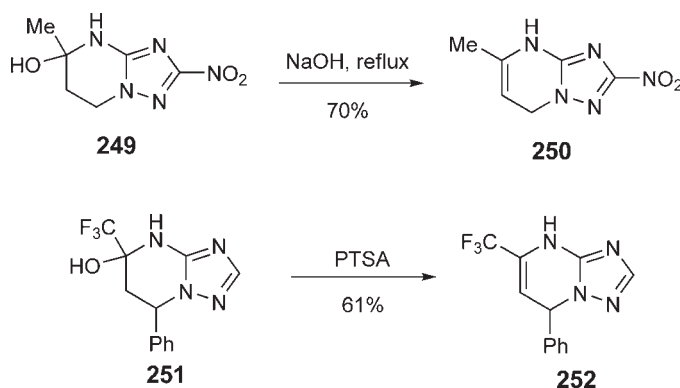


Scheme 29

Nucleophilic substitutions of some triazolopyridazines are shown in [Scheme 29](#). Similarly to the previous cases, halogen atoms were substituted in these conversions to give amines and sulfanyl compounds. Thus, reaction of **240** ($R^1 = \text{Me}$) with a substituted amyl alkoxide gave **241** <1997CPB1447>, whereas reaction of **240** ($R = \text{H}$) with a thiolate afforded **242** <2003CPB122>. Reaction of the dichlorotriazolopyrimidine derivative **243** with hydrazine hydrate yielded selectively **244** <1994PJC683>. Reactions of other substituted 6-chloro[1,2,4]triazolo[4,3-*b*]pyridazines **245** with various amines to give substituted products **246** have been published <1996PJC1279, 1997APH299, 2001APH217>. Similar substitution with the benzologue **247** was reported <2004BML2463>: reaction with a substituted pyridylmethanol gave **248**.

11.16.5.7.3 Eliminations

Elimination of water to afford a higher level of unsaturation was reported in some cases as shown in [Scheme 30](#). Thus, the hydroxy compound **249**, when treated with sodium hydroxide, gave **250** <1994ZOR774>, whereas treatment of **251** with *p*-toluenesulfonic acid gave rise to formation of **252** <2004KGS71>.



Scheme 30

11.16.5.7.4 Cross-couplings

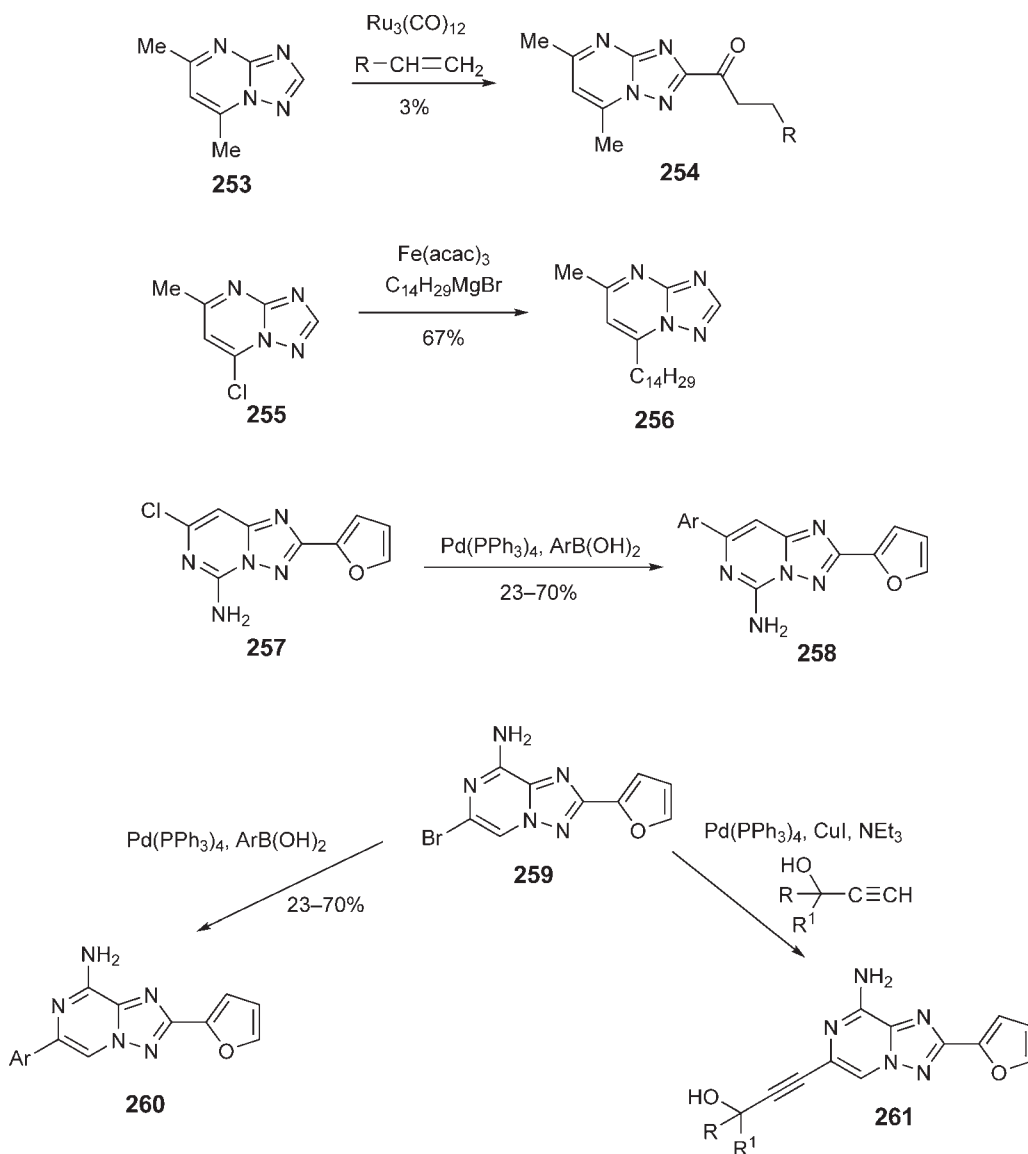
More recently, several transition metal-catalyzed cross-couplings have been described. As a result of these transformations new substituents can be introduced. Such transformations are depicted in [Scheme 31](#).

In the course of a study on creation of a library of a great number of hetaryl ketones and related derivatives, Szewczyk *et al.* <2001AGE216> elaborated a ruthenium-catalyzed transformation of heterocycles with activated C–H bond by reaction with olefins and carbon monoxide. Thus, **253** gave **254**, albeit in very poor yield. Synthetically, the more straightforward iron-catalyzed transformation was described by Fürstner *et al.* <2002JA13856>. These authors reacted **255** with a Grignard reagent in the presence of $\text{Fe}(\text{acac})_3$ to afford the 7-alkyl-substituted derivative **256** in reasonable yield (acac = acetylacetonate).

Halogen derivatives of both related ring systems, the fused pyrimidine **257** and the fused pyrazole **259**, were subjected to Suzuki coupling with arylboronic acids and palladium tetrakis(triphenyl)phosphine as the catalyst. Thus, coupling of the 7-chloro compound **257** yielded the 7-aryl derivative **258** <2005BML3670>, whereas treatment of the bromo-substituted **259** gave **260**. The latter starting compound (**259**) was also subjected to Sonogashira coupling in the presence of cuprous iodide to yield **261**.

11.16.5.7.5 Miscellaneous transformations

Some transformations of the ring carbon atom that cannot be classified into the above categories are illustrated in [Scheme 32](#).

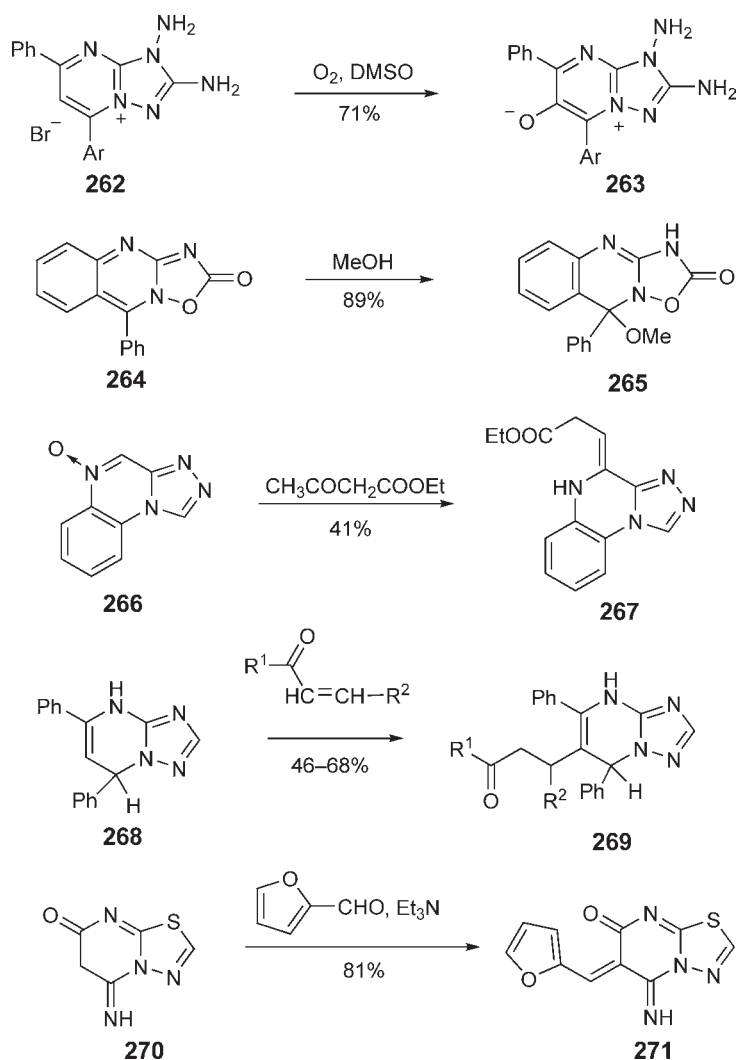


Scheme 31

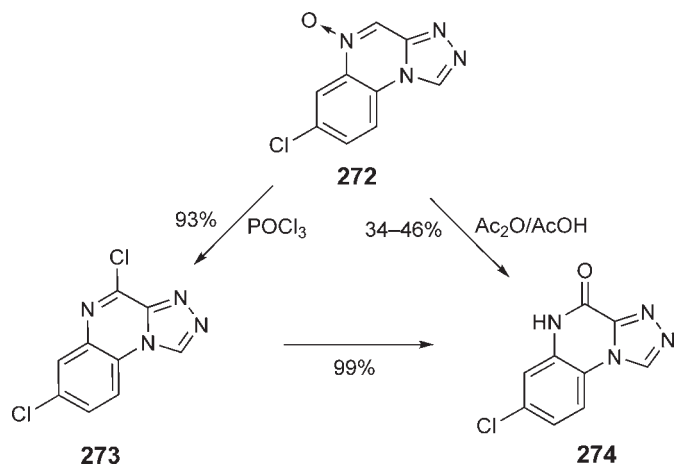
Oxidation of the pyrimidine ring was observed with treatment of **262** with air [\[2001KGS368\]](#): heating of this compound in a DMSO solution for 40 h gave rise to the 6-olate **263** in 71% yield. The tricyclic fused oxadiazole reacted with methanol to give the addition product **265** [\[2000S2009\]](#). A fairly complicated transformation of **266** when treated with acetoacetic ester was observed [\[1994CCC2493\]](#) and the *exo*-double-bond-containing product **267** was obtained in medium yield. A C–C coupling of compound **268** was reported [\[2003JHC1081\]](#): treatment with unsaturated ketones yielded **269** in medium to good yields. Finally, a condensation between **270** and furyl aldehyde was reported to give *exo*-ethenyl derivative **271** in high yield [\[1996IZV366\]](#).

Introduction of chloro and oxo substituents into position 7 of [1,2,4]triazolo[4,3-*a*]quinoxalines by transformation of the neighboring *N*-oxide function has been reported by Kurasawa *et al.* (Scheme 33) [\[1994JHC1697\]](#).

The *N*-oxide derivative **272** when treated with phosphorus oxychloride yielded a 7-chloro compound **273** with simultaneous reduction of the *N*-oxide function which could be hydrolyzed by sodium hydroxide to the 7-oxo derivative **274**. This compound **274** also formed directly from **272** upon treatment with acetic anhydride–acetic acid.



Scheme 32



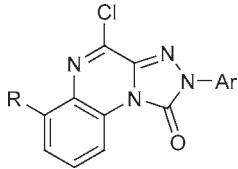
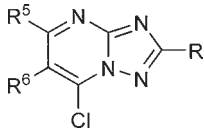
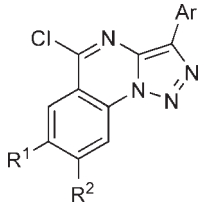
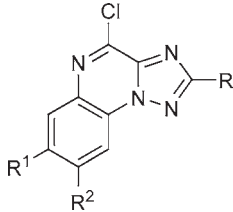
Scheme 33

11.16.5.7.6 Transformations of substituents

Numerous transformations of substituents have been carried out by applying established routine reactions. In this section, a concise survey on these transformations is provided.

In **Table 7**, the α -chloro heterocycles that have been obtained from the corresponding hydroxyl compounds are summarized. These reactions can be carried out by phosphorus oxychloride in most cases.

Table 7 Synthesis of chlorotriazolodiazines from the corresponding hydroxyl derivatives (or their lactam forms)

Entry	Product	Yield (%)	Reference
1		95	1999AP39, 2004JME3580, 2003BMC3541
2		81–85	1999JHC183, 2002JHC703
3		19–81	2000EJM333
4		30–65	1995EJM133

Other conversions of hydroxyl-substituted compounds (or their lactam tautomers), their thio analogues, as well as amines are listed in **Table 8**. These reactions involve *O*-, *N*-, or *S*-alkylations or acylations, *O*–*S* exchange reactions, or other analogous processes.

In **Table 9**, some conversions of heterocyclic carboxylic acids and esters are shown. The reactions involve amide formation, hydrolysis, and decarboxylation.

A great number of other different, mostly routine transformations have also been reported. In **Table 10**, these conversions are summarized: the structure of the starting compound is shown as well as the essence of the structural change, together with yields and references.

Finally, some more complicated functional group transformations should be mentioned. These are shown in **Scheme 34**.

Two transformations should be discussed in more detail: (1) presence of the amino group in **275** was utilized for the synthesis of the fused isoquinolinium salt **276** bearing the bicyclic heterocycle as an *N*-substituent <2003JHC1041>; (2) selective nucleophilic substitution of **277** with pyrrolidine was reported <2001ZOR604> to yield only substitution on the phenyl substituent without formation of an amide from the ester group **278**.

The other structures in **Scheme 34** just indicate that various transformations of the marked functional groups were carried out without any change of the bicyclic or tricyclic heterocycle. Thus, the hydrazine compounds **279** <1997SC2637, 2000H(53)339, 2005HCO321>, **280** <1995PHA33>, **281** <1994KGS560>, and **282** <1995M767> were subjected to some routine transformations (e.g., conversion to hydrazones), the amine **283** was reacted with an aromatic aldehyde to give a Schiff base <2002AP389>, and the oxime **284** was subjected to an *O*-alkylation <1997JHC1519>.

Table 8 Various chemical transformations of hydroxyl-substituted compounds (or their lactam forms), their thioxo analogues, and amines

Entry	Starting compound	Product	Reagent	Yield (%)	Reference
1			Lawesson's reagent	90	1994PHA880
2			Mitsunobu reagent	30–74	2001SL712
3			Me ₂ SO ₄	46	1996FA131
4			RBr	24–54	1994PHA21
5			RBr		2004JME1807
6			ArCOCl		1997APH299
7			Bu ₄ NHSO ₄ , MeI	86	2001JHC237
8			RBr	40–82	2003MI79, 2001MOL557
9			MeI	72–99	2003EJO182, 1999JHC1327

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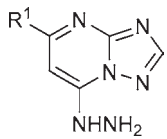
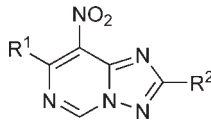
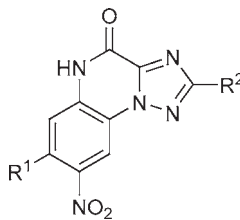
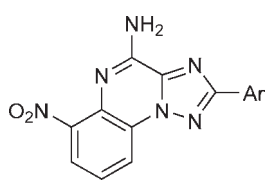
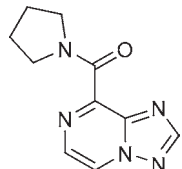
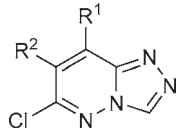
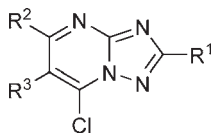
Table 8 (Continued)

Entry	Starting compound	Product	Reagent	Yield (%)	Reference
10			MeI	87–91	2003HAC581
11			MeI	58	2005HAC278
12			acrolein derivative, AcOH	54	1997PJC792

Table 9 Conversions of heterocyclic carboxylic acids and esters

Entry	Starting compound	Transformation	Yield (%)	Reference
1		COOEt $\rightarrow$ CONH ₂	68	2001JHC1119
2		COOEt $\rightarrow$ COOH	67–94	1999JME2478
3		COOEt $\rightarrow$ H	80–86	1995H(41)2777
4		COOH $\rightarrow$ H	78–81	1998EJM113
5		COOMe $\rightarrow$ COOH	72	2005ZOR109

Table 10 Transformations of substituents of various azoloazines

Entry	Starting compound	Transformation	Reagent	Yield (%)	Reference
1		$\text{NHNH}_2 \rightarrow \text{N}_3$	HNO_2	78	1995PHA33
2		$\text{NO}_2 \rightarrow \text{NH}_2$	H_2/Pd	25–28	1994JHC1171
3		$\text{NO}_2 \rightarrow \text{NH}_2$	Fe, AcOH	44–63	2001JME3157, 2004JME262
4		$\text{NO}_2 \rightarrow \text{NH}_2$	H_2/Pd	50	1999AP39, 2004JME3580
5		$\text{CON}(\text{CH}_2)_5 \rightarrow \text{CH}_2\text{N}(\text{CH}_2)_5$	BH_3 , Me_2S		1995FA405
6		$\text{Cl} \rightarrow \text{H}$	H_2/Pd	60	1996PJC1279
7		$\text{Cl} \rightarrow \text{H}$	Zn–Cu, AcOH, MeOH	74–90	1999JHC183

(Continued)

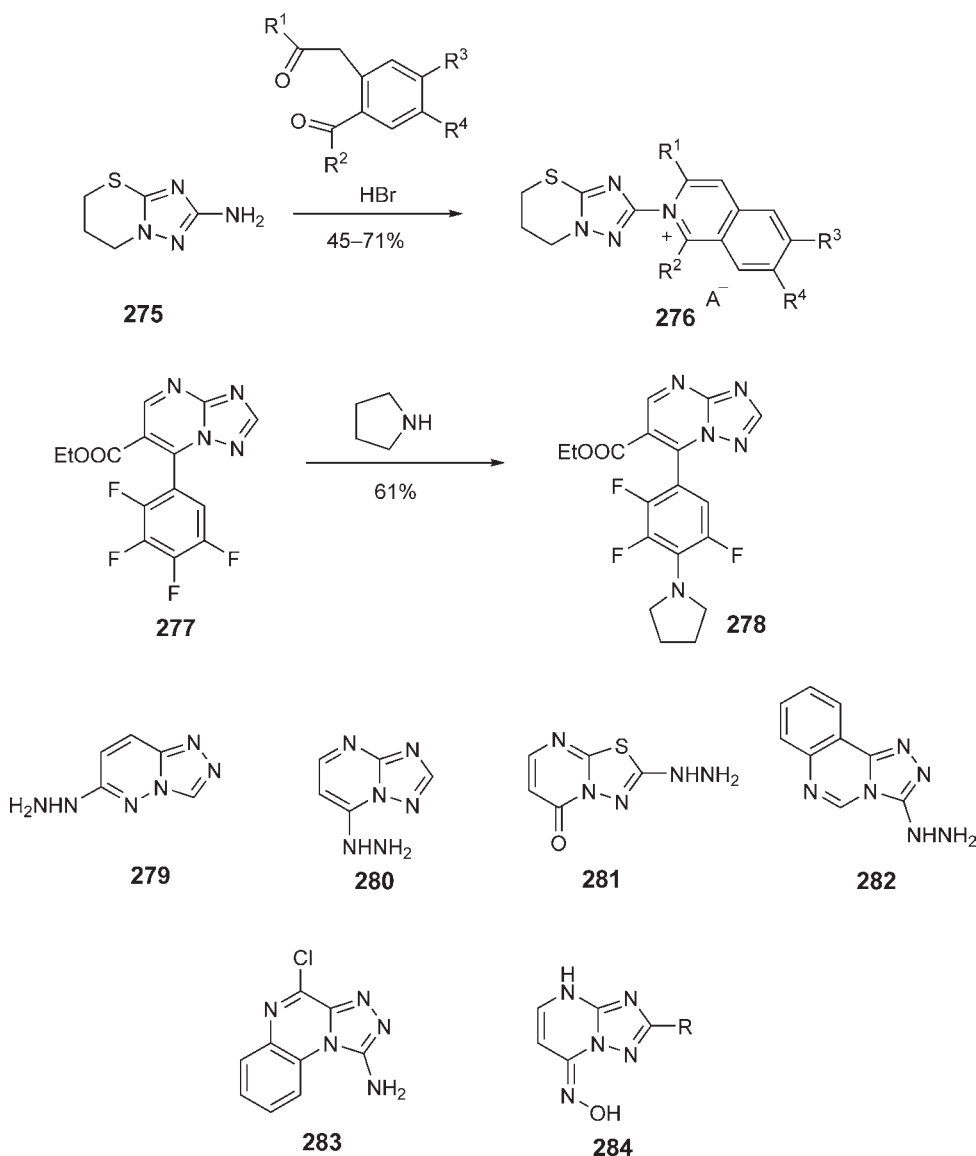
Table 10 (Continued)

Entry	Starting compound	Transformation	Reagent	Yield (%)	Reference
8		$\text{CH}_2\text{COOEt} \rightarrow \text{HC}(\text{C}(\text{S})\text{NHA}r)\text{COOEt}$	ArNCS	64	1998IZV2371
9		$\text{CH}_2\text{COOEt} \rightarrow \text{HC}(\text{CSSMe})\text{COOEt}$	CS_2 , MeI, NaH		1998IZV2371
10		$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{SA}r$	ArSH, NaOH	91	1996KGS549
11		$\text{CH}_2\text{SEt} \rightarrow \text{CH}_2\text{SO}_2\text{Ar}$	H_2O_2 , AcOH	38	1996KGS549
12		$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{N}(\text{CH}_2)_5$	Piperidine	60–65	1994IZV908
13		$\text{CH}_2\text{Cl} \rightarrow \text{CH}_2\text{CN}$	KCN	87	2005HAC278
14		$\text{CHCl}_2 \rightarrow \text{CHO}$	Morpholine	65	2003JRM835
15		$8\text{-NH}_2 \rightarrow 8\text{-NHCOR}^1$	R^1COCl	50–68	1994JHC1171
16		$\text{CH}_3 \rightarrow \text{CH}=\text{CH}-\text{NMe}_2$	DMF/DMA	86–92	1997JHC465

(Continued)

Table 10 (Continued)

Entry	Starting compound	Transformation	Reagent	Yield (%)	Reference
17		Me $\rightarrow$ CH=CHR ¹		76–91	1999IZV1154
18		Me $\rightarrow$ CH ₂ Br	Br ₂	95	1999PHA808
19		Selective transformations of the NH ₂ groups			2003BMC5509
20		HN-C=O $\rightarrow$ N=C-NHR ¹	HMDS, R ¹ NH ₂	15–22	2002EJM565
21			<i>t</i> -BuONO BF ₃ ·Et ₂ O, AcOH	93	2005JHC1167
22			MeOH, reflux	48	2005JHC1167
23		HNCOPh $\rightarrow$ NH ₂	HCl	26–32	2001SC1511
24		OMe $\rightarrow$ OH	HCl	82	1997JME2053



Scheme 34

11.16.6 Ring Synthesis from Acyclic Compounds

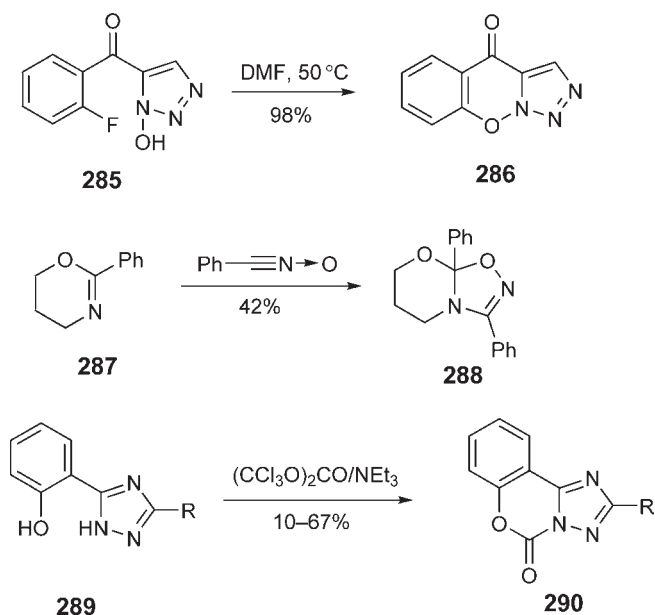
11.16.6.1 Ring Synthesis of Fused Oxazines and Thiazines

11.16.6.1.1 Synthesis of fused oxazines

Although a few synthetic approaches to fused oxazines belonging to this chapter were reviewed in CHEC-II(1996) <1996CHEC-II(8)421>, many new pathways have been invented recently. Transformations yielding fused 1,2-oxazines and 1,3-oxazines are treated first, followed by the summary of pathways leading to various fused 1,4-oxazines.

Syntheses leading to fused 1,2- and 1,3-oxazines are shown in [Scheme 35](#). Begtrup *et al.* reported <2002T2397> that the *N*-hydroxytriazolyl-fluorophenylketone **285** can conveniently be transformed to the fused triazolooxazine **286** in almost quantitative yield.

A 1,3-dipolar cycloaddition approach to this group of compounds involving reaction of a nitrilimine and C=N bond have already been mentioned in CHEC-II(1996) <1996CHEC-II(8)421>. Such a transformation has recently been elaborated by an English team <1994J(P1)3563> for the ring closure of the partially saturated oxazine **287** with nitrile oxide to yield the bicyclic product **288** in medium yield (42%).

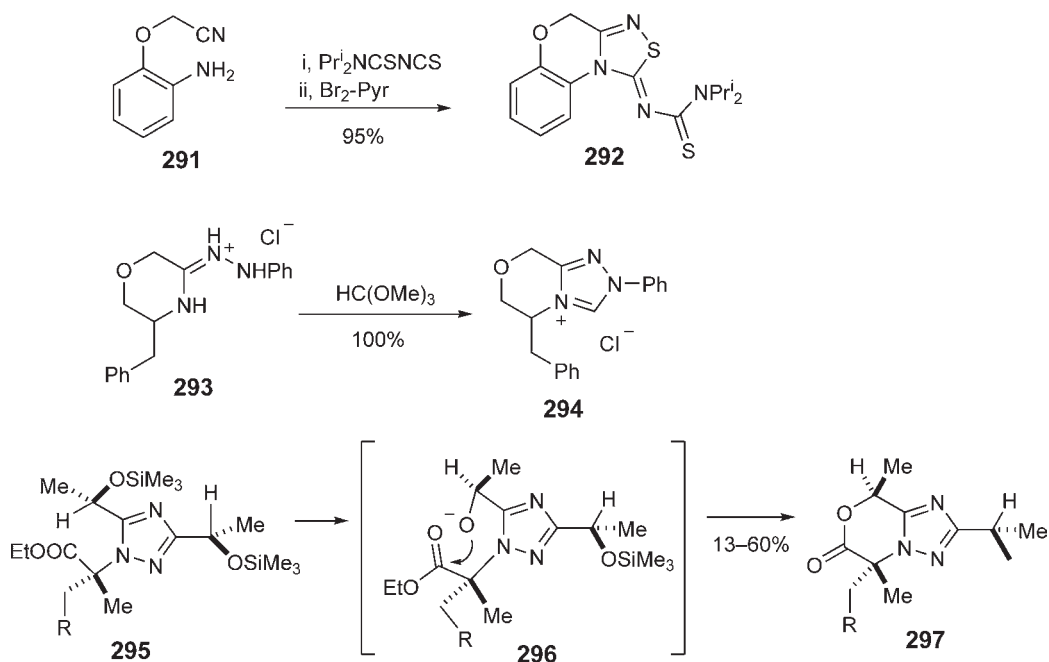


Scheme 35

Synthesis of the tricyclic [1,2,4]triazolo[1,5-*c*][1,3]benzoxazine **290** was described by an Italian group <1994FA89, 1995JME2196>. These authors reacted the triazolylphenol **289** with bis-trichloromethyl carbonate to obtain the tricyclic product **290** in poor to good yield.

New syntheses of [1,2,4]thiadiazolo- and [1,2,4]triazolo[1,4]oxazines are shown in Scheme 36.

L'abbé *et al.* elaborated a very short and efficient pathway to [1,2,4]thiadiazolo[1,4]benzoxazines, which, interestingly, follows a quite complicated pathway <1994T7019, 1996J(P1)225>. The starting compound is the cyano-substituted



R = alkyl, aryl, allyl, or propargyl groups

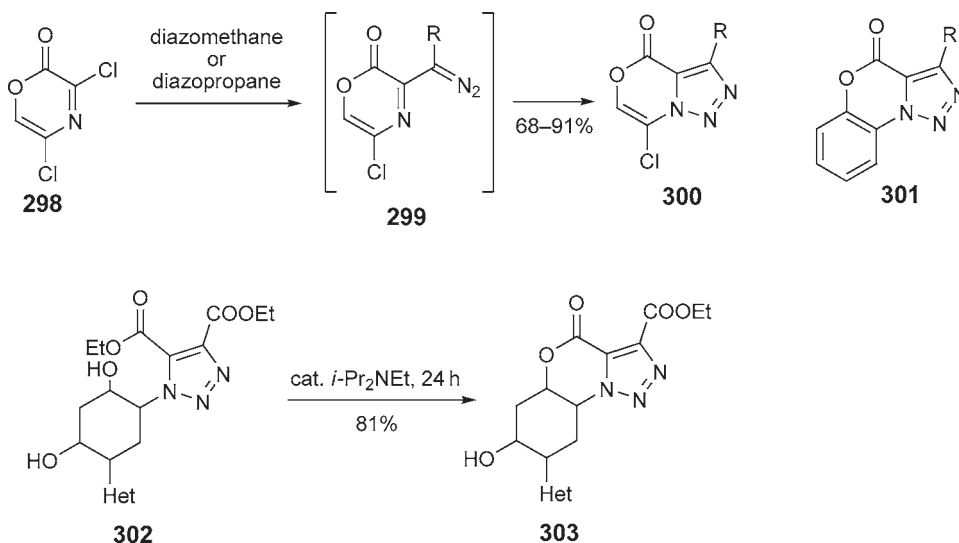
Scheme 36

aniline **291** which is treated with thiocarbamoylisothiocyanate first. The reaction mixture was then subjected to oxidation by bromine to give the tricyclic product **292**.

The triazoloxazine **294** containing the saturated oxazine moiety was synthesized by Knight and Leeper <1998J(P1)1891>: treatment of the hydrazinium salt **293** with trimethyl orthoformate yielded the product **294** in quantitative yield.

Katritzky *et al.* reported <1996TA1631> the synthesis of a partially saturated chiral triazoloxazine with high diastereoselectivity. The products were considered as useful potential synthetic intermediates for asymmetric transformations. The authors treated **295** with a base to yield an intermediate **296** which underwent intramolecular cyclization to give the product **297** in most cases in medium to good yield.

Synthesis of [1,2,3]triazolo[1,4]oxazines from oxazinyl diazomethane was mentioned in CHEC-II(1996) <1996CHEC-II(8)421> and such novel applications have appeared recently also (Scheme 37). Hoornaert *et al.* described <1994TL9767, 1996T8813> that transformation of the dichloro compound **298** with diazomethane or diazopropane to give the substituted diazomethane **299** as an intermediate which underwent ring closure to **300** in good to excellent yield. The benzologue **301** was also prepared by the same authors in a similar manner.



Scheme 37

Sharpless *et al.* also reported <2001AGE2004> the synthesis of one representative of the present class of compounds. In their studies on ‘click’ chemistry, the substituted cyclohexyltriazole **302** was prepared, which, upon treatment with a base at reflux temperature, underwent lactonization to yield the fused oxazinone **303** in high yield.

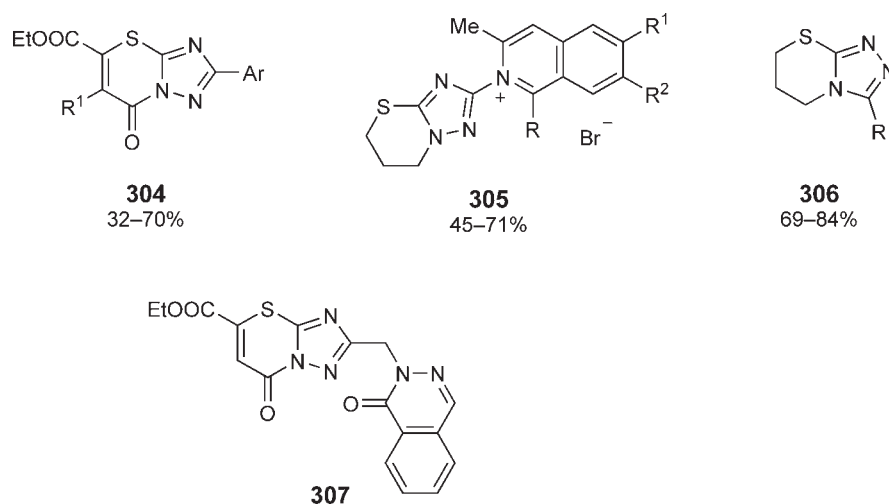
11.16.6.1.2 Synthesis of fused thiazines

In CHEC-II(1996), seven different synthetic pathways to the ring systems of the present section were reviewed <1996CHEC-II(8)421>, and recently several further applications of these methodologies have been reported. The products obtained by these approaches are shown in Scheme 38.

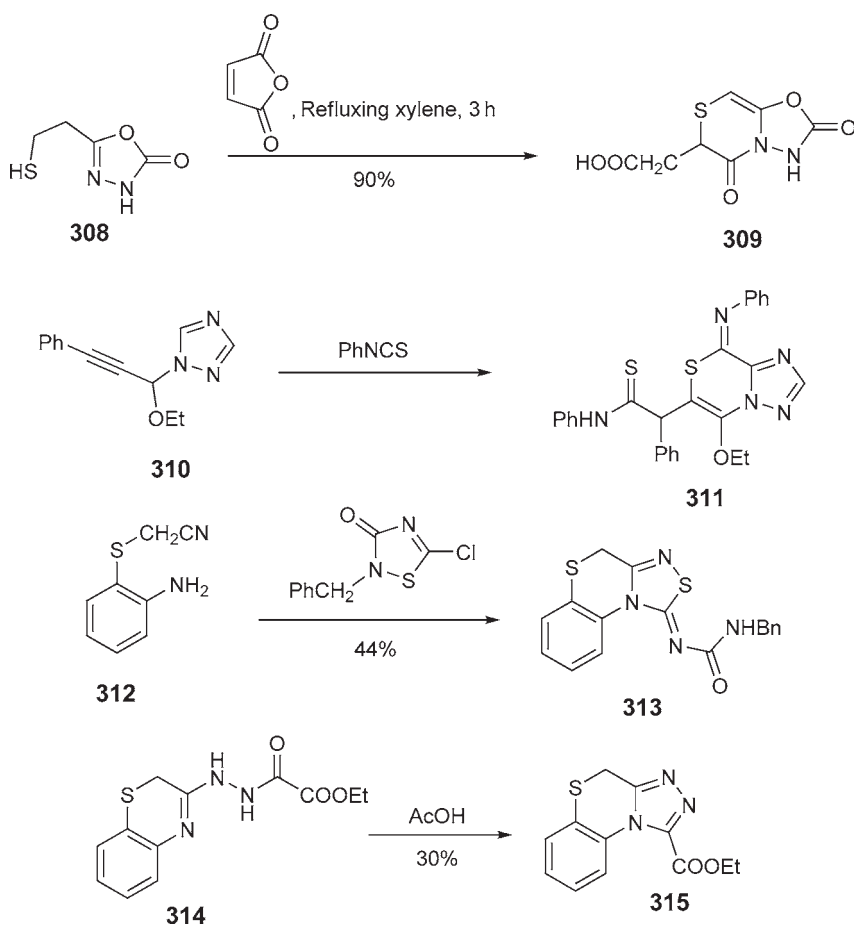
Thus, esters **304** have been obtained in medium to good yield <2002FA145, 2005ZOR109>, derivatives **305** bearing an isoquinolinium moiety have been prepared <2003JHC1041>, several derivatives of the general structure **306** have been obtained <1995PS29, 2001SC2841, 2004PS2519>, and derivatives with a phthalazinone side chain **307** have also been synthesized <2003PS1987>.

In Scheme 39, new pathways to fused [1,4]thiazines are shown. The oxadiazolone derivative with a mercapto-methyl side chain (**308**) was reported to react with maleic anhydride to the fused product **309** in high yield <1996M549>. The acetylene substituted triazole **310**, when reacted with 2 molar equiv of phenylisocyanate, afforded a polysubstituted triazolothiazine derivative **311** via a fairly complicated reaction pathway <1998CJC635>.

Ring closure of the cyano group containing aniline (**312**) to **313** <1994T7019, 1996J(P1)225> followed the same pathway as that with the oxazine analogue discussed earlier with transformation of **291** into **292**. Formation of the fused triazole **315** from **314** was also reported <1994FA245>.

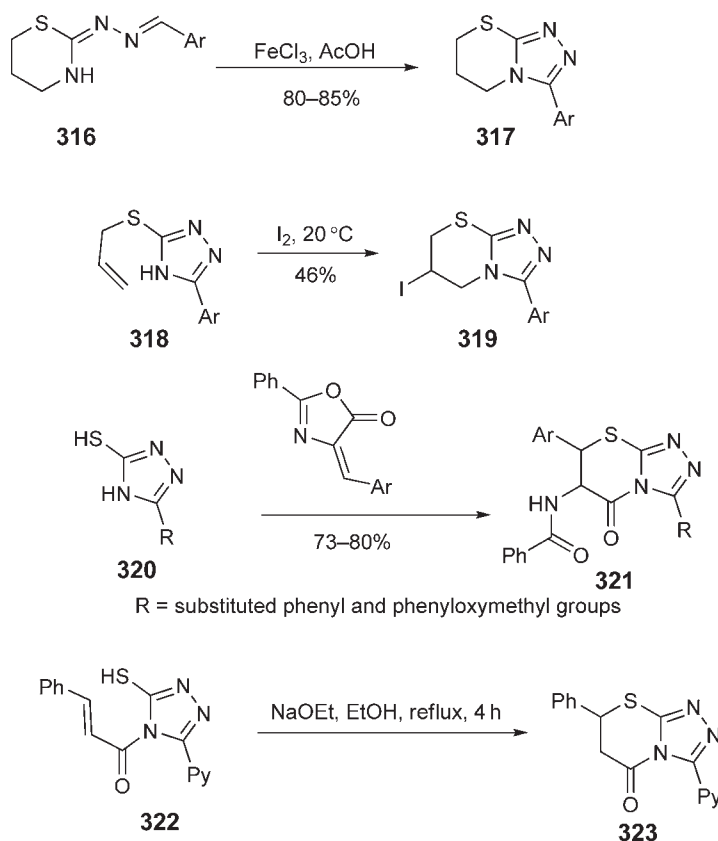


Scheme 38



Scheme 39

Several new cyclizations to [1,2,4]triazolo[3,4-*b*][1,3]thiazines have been published recently, and these are summarized in [Scheme 40](#). In all the four cases shown here, the thiazine ring is partially saturated.



Scheme 40

The 2,3-diazadiene **316** bearing the [1,3]thiazine moiety was successfully oxidized by FeCl_3 to give the ring-closed triazolothiazine **317** in high yield [\[1997AJC911\]](#). The triazole derivative **318** containing an allylthio substituent was reacted with iodine to give a mixture of four products from which **319** proved to be the main product formed in medium yield (46%) [\[2004KGS1391\]](#).

An Indian team carried out the transformation of mercaptotriazole **320** using an oxazolone reagent [\[2001IJB252\]](#) and found that a series of triazolothiazines with the substitution pattern **321** can be obtained in high yields. Treatment of the mercaptotriazole with an unsaturated ketone side chain **322** under basic conditions gave rise to ring closure to **323** [\[1998JRM2056\]](#).

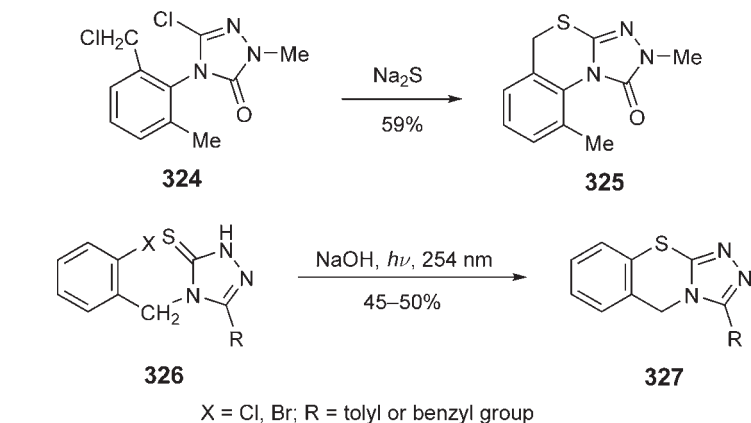
Besides these syntheses, some cyclisations leading to benzologues of this ring system have also been reported, and two such transformations are demonstrated in [Scheme 41](#). Thus, Brown *et al.* described [\[2004T4361\]](#) that treatment of **324** with sodium sulfide resulted in formation of the triazolobenzothiazinone compound **325** in acceptable yield. Ring closure of **326** took place under irradiation and basic conditions to yield **327** in medium yield [\[2002TL5119, 2004T851\]](#).

Synthetic routes to [1,3]thiazines or their benzologues fused to [1,2,4]thiadiazoles and [1,2,4]triazoles are shown in [Scheme 42](#).

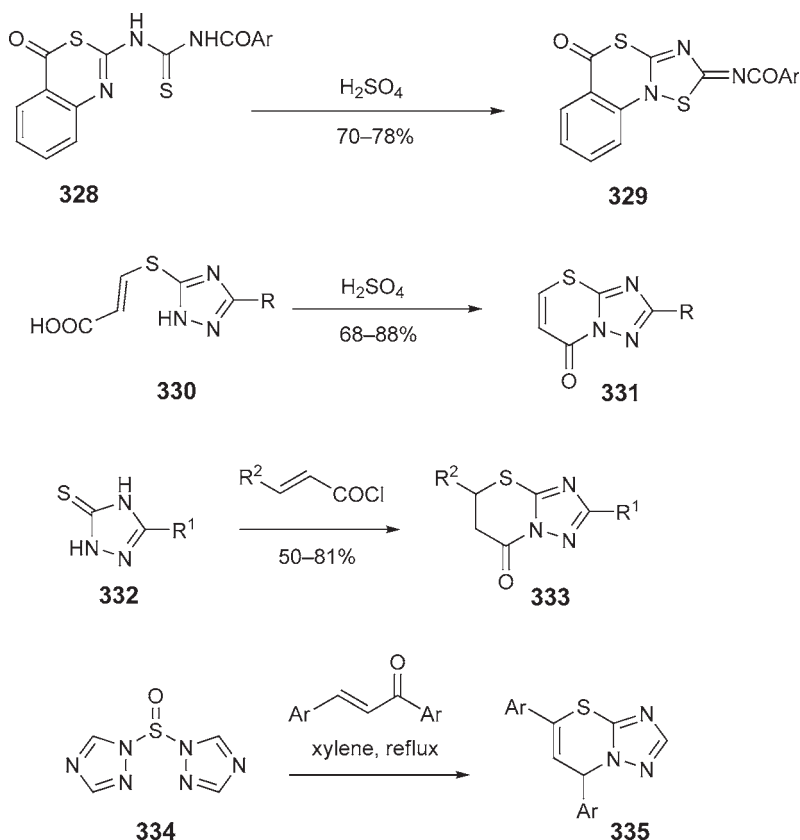
An efficient cyclization to [1,2,4]thiadiazolo[2,3-*a*][3,1]benzothiazines was reported by Gütschow [\[1996JHC355\]](#): treatment of the thiourea derivative **328** with sulfuric acid yielded the tricyclic product **329** in high yield. Heravi *et al.* described [\[2001M1225\]](#) that the triazole derivative **330** bearing a vinylsulfide side chain can be subjected to ring closure. This reaction also takes place in sulfuric acid and resulted in cyclization of the six-membered ring to yield **331** in good to high yield.

A general route to [1,2,4]triazolo[3,2-*b*][1,3]thiazines was discovered by Britsun *et al.* [\[2001ZOR1102, 2004KGS1256, 2004ZOR260\]](#). In these publications, reaction of triazole thiones **332** with various substituted acrylic chlorides was reported to yield a series of ring-closed products **333** with the substituent of the reagent in the six-membered ring at the position adjacent to the sulfur atom.

Transformation of bis-triazolylsulfoxide **334** with a chalcone should also be mentioned here [\[2000OL429\]](#). Formation of the cyclized product **335** was, unfortunately, reported to take place only in poor yield.



Scheme 41

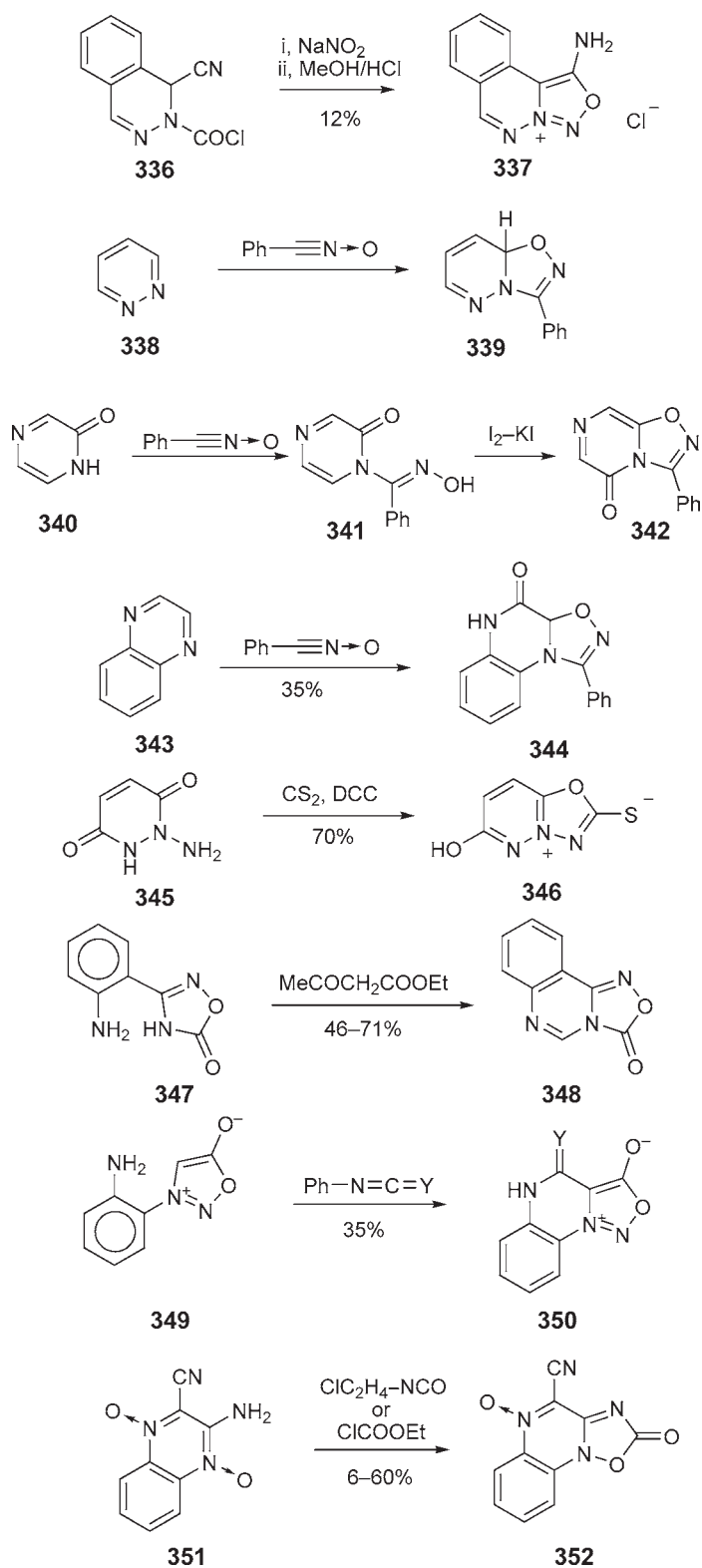


Scheme 42

11.16.6.2 Ring Synthesis of Fused Pyridazines, Pyrimidines, and Pyrazines with Oxygen, Sulfur, Selenium, and Phosphorus Atoms in the Five-Membered Ring

11.16.6.2.1 Synthesis of oxadiazolopyridazines, -pyrimidines, and -pyrazines

While syntheses of only a few such ring systems were reviewed in CHEC-II(1996) <1996CHEC-II(8)421>, a substantial amount of novel informations in this respect has appeared recently. In most of the cases – with a few exceptions – benzologues of the title systems have been prepared. The chemical transformations are illustrated in [Scheme 43](#).



Scheme 43

Ruxer *et al.* reported <1995JHC643> that treatment of the carbamoyl chloride **336** derivative first with sodium nitrite followed by gaseous hydrogen chloride gave rise to the fused quaternary salt **337**. This interesting transformation is based on an earlier recognition that carbamoyl chloride can react with sodium nitrite under neutral conditions (in acetonitrile, with nucleophilic exchange of the chloro atom for an ONO moiety followed by carbon dioxide elimination) to give an *N*-nitroso derivative <1979TL3831>. Such a nitroso intermediate is obviously also formed in the present cyclizations.

A considerable attention has been paid to the reaction of various diazines with benzonitrile oxide by different groups <1995T11855, 1996T6421, 2000H(3)69>. Such a transformation can result in the formation of a fused oxadiazole ring system. Corsaro *et al.* have shown <1996T6421> that the expected 1,3-cycloaddition between the reagent and the C=N bond of the heteroaromatic diazine ring actually takes place, but in many cases a double cyclization occurs to afford polycyclic heteroaromatics. In this respect, the pyridazine ring **338** represents an exception: its treatment with benzonitrile *N*-oxide yields the mono-cycloadduct **339** in 72% yield.

The same authors reported in a later study <2000H(3)69> that pyrazinone **340** is also a suitable starting material for a such transformation. The reaction proceeds in two steps: the starting pyrazinone **340** when treated with benzonitrile oxide yields an addition product **341** which undergoes oxidative cyclization in the presence of iodine–potassium iodide to the ring-closed [1,2,4]oxadiazolo[4,5-*a*]pyrazines **342**.

The benzonitrile oxide approach also proved to be relatively successful in the case of quinoxaline **343** <1995T11855> and led to formation of the tricyclic product **344** in modest yield (35%).

A Korean team published the synthesis of a mesoionic oxazolopyridazine derivative <1997H(45)2101>. These authors reacted the *N*-aminopyridazine dione **345** with carbon disulfide and dicyclohexylcarbodiimide (DCC) to give the product **346** in high yield (70%).

The aminophenyl-substituted oxadiazoles **347** and **349** were also used as starting compounds for cyclizations to oxadiazolobenzodiazines: reaction of **347** with ethyl acetoacetate yielded the fused quinazoline **348** <1995AP397>, whereas transformation of **349** with phenylisocyanate or phenylisothiocyanate gave rise to oxadiazoloquinoxaline-olates or thiolates **350** in medium to excellent yield <1994H(38)2023>. A Spanish–British joint team reported that some 2-aminoquinoxaline *N*-oxides are convenient derivatives for ring closure to fused oxadiazoles <1996JHC1671, 1999AF55>. Thus, transformation of **351** with either chloroethylisocyanate or ethyl chloroformate gave rise to derivatives **352** in poor to acceptable yields. The reaction in the cases of both reagents launches with attack of the amino group at the carbonyl carbon atom of the reagent to give an intermediate (a urea or carbamate) in which the *N*-oxide oxygen atom attacks the same carbon atom to result in the ring closure with simultaneous elimination of chloroethylamine or ethanol, respectively.

Synthetic routes to some [1,3,4]oxadiazoles fused to the a site of pyrimidine – or its benzologue – are shown in Scheme 44.

Yadav *et al.* <1994IJB565, 1995IJB500> carried out a series of syntheses to [1,3,4]oxadiazolo[3,2-*a*]pyrimidone derivatives. The general procedure started from a 2-aminooxadiazole **353**, which was reacted with an oxazolone reagent to give the cyclized product **354** in high to excellent yields. The method allowed the preparation of compounds with high diversity concerning the aryl group at the oxadiazole ring as well as the R-substituent at the pyrimidine ring (both can be a range of substituted phenyl groups).

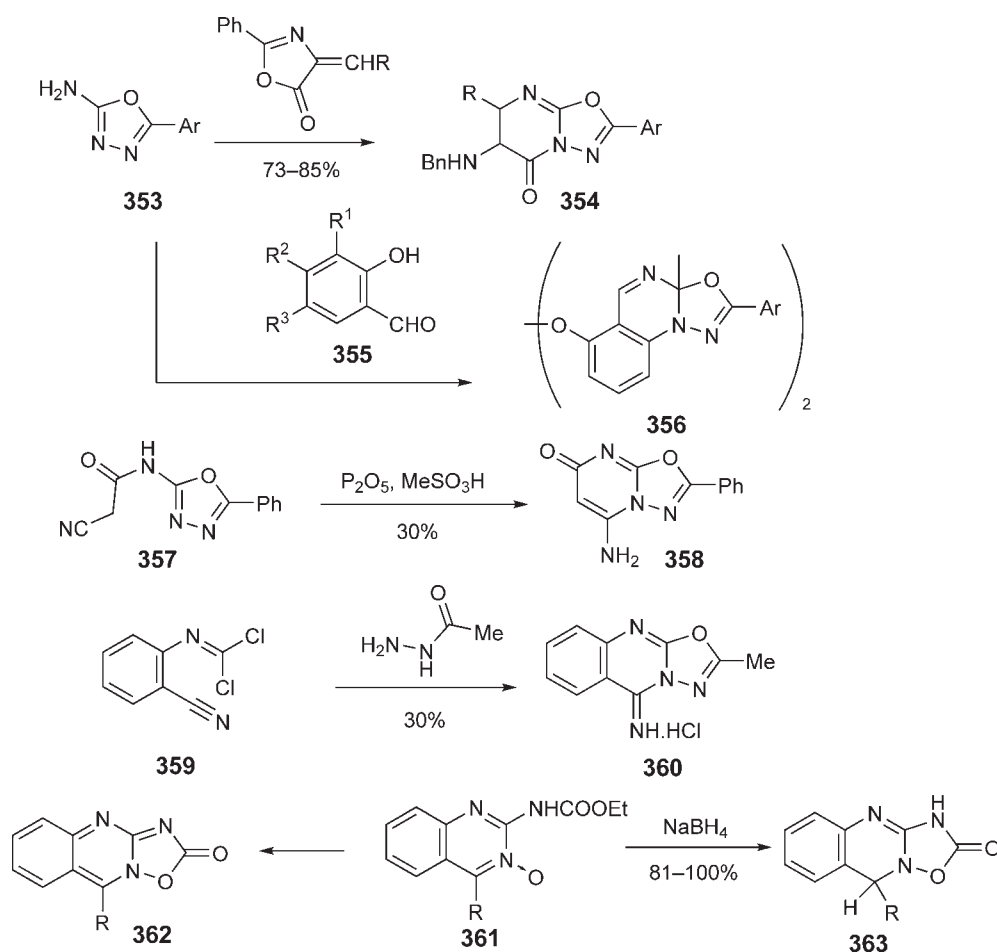
The synthesis of the dimeric oxadiazoloquinazoline **356** was described as a single-pot procedure by an Indian team <2005JHC487>. The products were obtained by reaction of the aminooxadiazoles **353** with the hydroxybenzaldehyde reagent **355**.

Synthesis of the oxadiazolopyrimidone **358** was accomplished by reaction of the amide **357** with phosphorus pentoxide and methanesulfonic acid in low yield <1994PHA880>. Also, its benzologue **360** could only be obtained in very modest yield <2004TL8741>; in the case, reaction of the benzonitrile derivative **359** with acetylhydrazine resulted in formation of the bicyclic product **360**.

Renaut *et al.* elaborated a synthetic route to linearly fused oxadiazoloquinazoles <2000S2009>. These authors reported that the *N*-oxide carbamate **361** can be subjected to ring closure to the unsaturated cyclized product **362** under fairly forcing conditions (220 °C, 0.1 Torr). Much milder reaction conditions are needed, however, to carry out a reductive cyclization: treatment of **361** in ethanol in the presence of sodium borohydride (at 50 °C) gave rise to the partially reduced product **363** in nearly quantitative yield.

11.16.6.2.2 Synthesis of thiadiazolopyrimidines and selenodiazolopyrimidines

A fairly substantial amount of new literature has appeared for the title ring systems. Most interestingly, the majority of all this information concerns one single ring system: [1,3,4]thiadiazolo[3,2-*a*]pyrimidine and its benzologues. Several synthetic pathways to such ring systems were reviewed already in CHEC-II(1996) <1996CHEC-II(8)421>. Among



Scheme 44

these established methods, two approaches have often been used during the recent period of time: (1) reaction of 2-aminothiadiazoles with bifunctional reagents or analogous compounds (i.e., ring closure of the pyrimidine ring); (2) reaction of *N*-aminopyrimidine-2-thione with a reagent providing a one-carbon atom unit (i.e., ring closure of the thiadiazole ring). Table 11 summarizes these novel transformations, and shows the starting compound, the reagent applied, and product, the yields, and literature references.

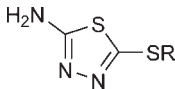
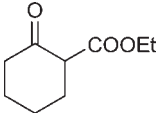
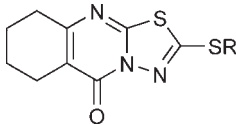
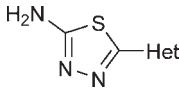
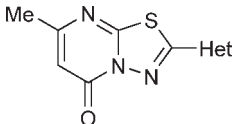
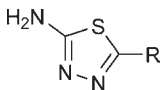
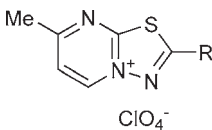
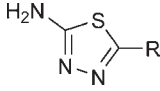
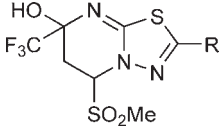
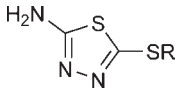
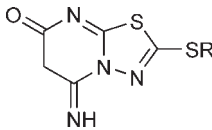
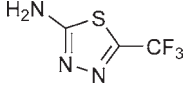
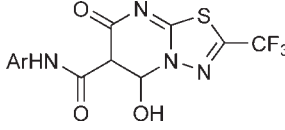
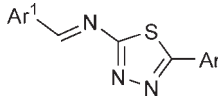
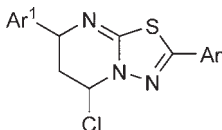
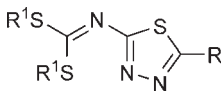
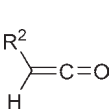
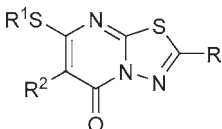
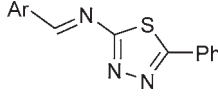
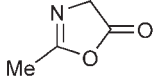
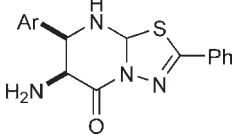
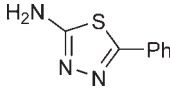
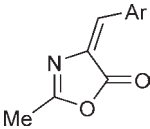
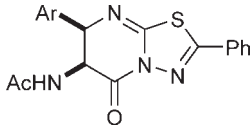
Three new synthetic pathways should be reviewed, as shown in Scheme 45.

Table 11 Novel transformations to [1,3,4]thiadiazolo[3,2-*a*]pyrimidine and its benzologues by using old methodologies

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1	<chem>Nc1nc(R)sc2nc3c(nc1O)oc(Ar)nn32</chem>	Diketene	<chem>O=C1C(=O)N(C1=CC=C2C=CC=C2)C=CC=C2</chem>	50–80	2005JHC1105
2	<chem>Nc1nc(R)sc2nc3c(nc1O)oc(Ar)nn32</chem>	<chem>MeCOCH2COOEt</chem>	<chem>MeC(=O)Nc1nc(R)sc2nc3c(nc1O)oc(Ar)nn32</chem>	75	1995PS1, 1996KGS549

(Continued)

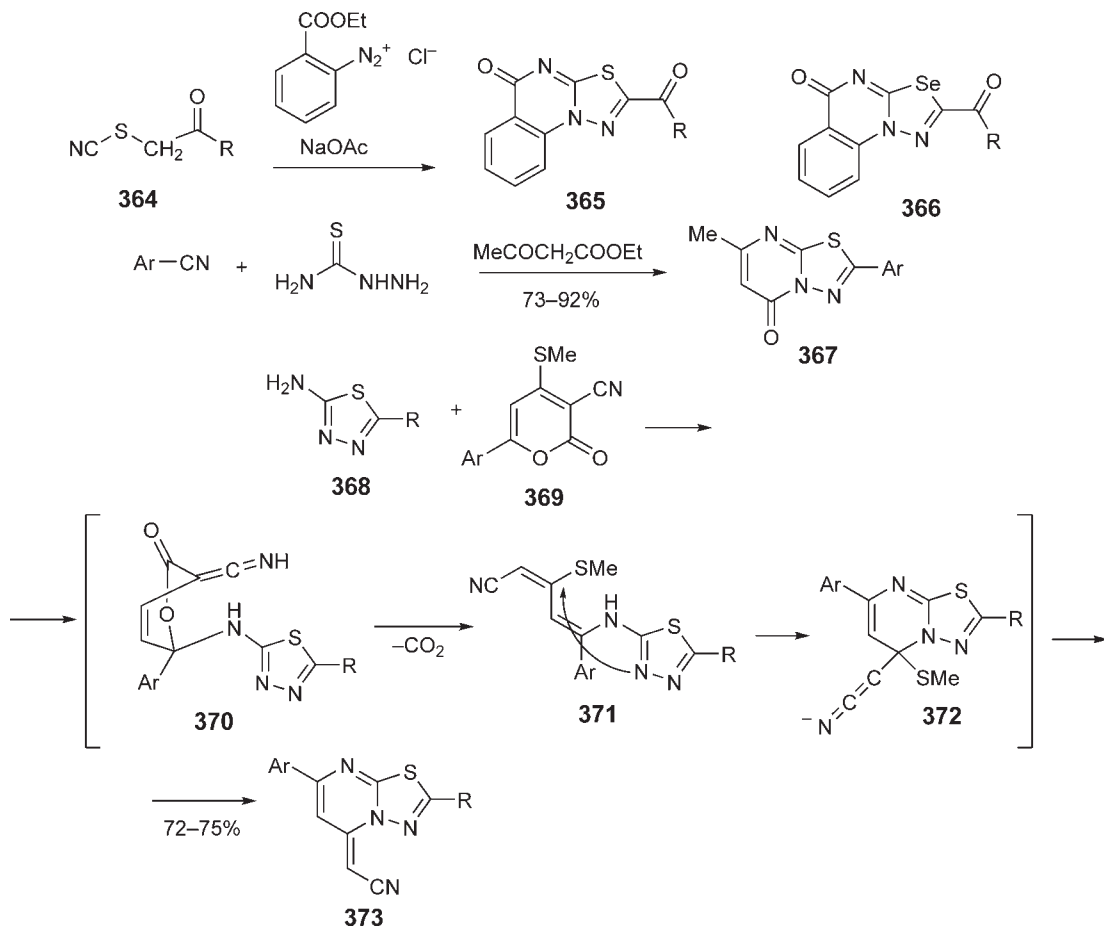
Table 11 (Continued)

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
3				39	1996IJB238
4		EtAc		93	1993IZV1954
5		MeCOCH ₂ COMeHClO ₄	 ClO ₄ ⁻	29–80	1996JHC1367
6		CF ₃ -CO-CH=CH-SO ₂ Me		90	2002KGS253
7		CN-CH ₂ COOEt		22	1996IJB238
8		EtOOC-CH-CONHAr EtOOC		50	1998BML3317
9		ClCH ₂ COCl		72–76	1996JCM36
10				54–60	1996M1273
11		 microwave conditions (MW)		89–95	2003S63
12				75	1995IJB500

(Continued)

Table 11 (Continued)

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
13		POCl_3			1994PHA880
14		$\text{AcOH}, \text{P}_2\text{O}_5$		60–80	2000PHA737, 1999JRM460
15		BrCN			1994PHA880



Scheme 45

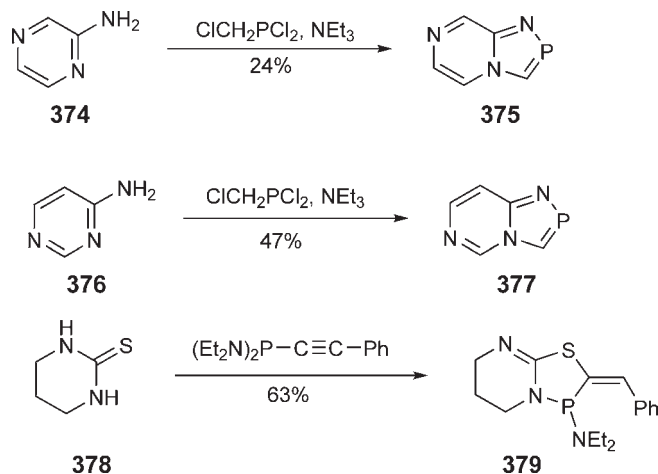
Emam *et al.* elaborated <1997PS37> a new route to thiadiazoloquinazolones **365** by reacting the thiocyanato ketone **364** with *o*-ethoxycarbonylphenyldiazonium salt. The reaction was carried out at low temperature (0–5 °C) and yielded product **365**. A similar reaction with a selenocyanate starting compound afforded the analogous selenodiazolo product **366**.

An easy access to the title compounds has been found by Shukorov *et al.* <1994IZV908, 1995IZV2035>. These authors reported that reaction of benzonitrile derivatives with thiosemicarbazide and ethyl acetoacetate in the presence of polyphosphoric acid gives rise to the cyclized products **367** in good to excellent yields.

Cyclization to cyanometheno-substituted thiadiazolopyrimidines has been described by Ram *et al.* <2003T7141>. The transformation starts from 2-aminothiadiazole derivative **368** and follows a quite complicated reaction mechanism. The first step is the reaction of **368** with pyrone **369**. In this step, a 1,4-addition of the amino group takes place at the pyran ring to yield the first intermediate **370**, which can undergo carbon dioxide elimination to a dieneamine **371**. In this second intermediate, the ring nitrogen atom of the thiadiazole ring can act as a nucleophile at the remote C=C bond of the diene chain to result in a ring closure to a third intermediate **372**, which can eliminate a methylthiolate anion to give the final product **373**. The high yields (72–75%) unambiguously reveal the preparative value of this transformation.

11.16.6.2.3 Synthesis of diazaphospholo and thiazolophospholo pyrimidines and pyrazines

Recently novel information on cyclizations to phosphorus-containing heterocycles with heteroatomic arrangement has appeared. These ring closures are shown in **Scheme 46**.



Scheme 46

Karaghiosoff *et al.* described <1995CB581> an easy access to two different phosphorus-containing ring systems. These authors found that reaction of aminodiazine with chloromethyldichlorophosphane provides an efficient route for ring closure to fused diazaphospholes. Thus, 2-aminopyrazine **374** gave **375**, whereas 4-aminopyrimidine **376** afforded **377** in poor and moderate yields, respectively. The synthesis of the thiazaphospholopyrimidine derivative **379** was accomplished by Fluck *et al.* <1994PS59>: reaction of tetrahydropyrimidin-2-one **378** with phenylethynylbis-diethylaminophosphine under low pressure yielded the ring-closed product **379** in good yield (63%).

11.16.6.3 Ring Synthesis of Triazolopyridazines and Their Benzologues

11.16.6.3.1 Synthesis of triazolopyridazines

Several ring-closure reactions to triazolopyridazines and their benzologues were reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)847, 1996CHEC-II(8)421>, and recently, a large amount of novel applications of the same basic methodologies have been reported. In **Table 12**, such syntheses affording [1,2,4]triazolo[4,3-*b*]pyridazine (entries 1–19) and [1,2,4]triazolo[1,5-*b*]pyridazines (entries 20 and 21) are compiled: the starting compounds,

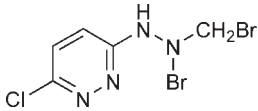
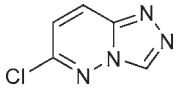
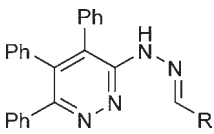
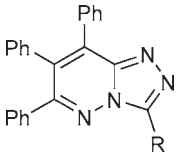
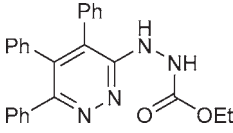
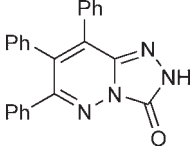
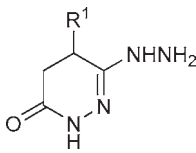
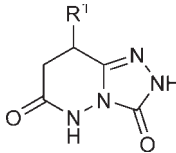
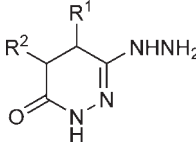
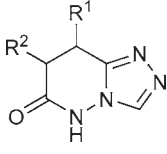
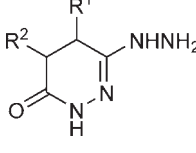
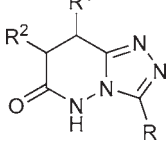
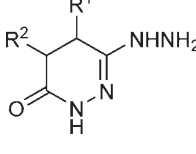
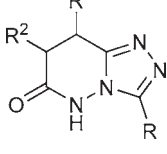
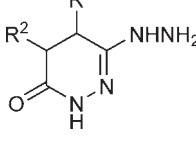
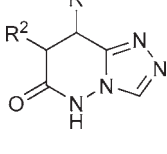
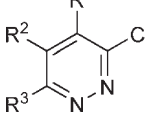
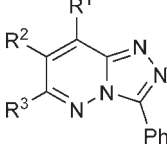
reagents, and structures of products are shown together with yields and literature references. As inspection of [Table 12](#) shows, most of these data refer to the synthesis of [1,2,4]triazolo[4,3-*b*]pyridazine derivatives, and the ring-closure reactions are perfected basically by using two approaches: (1) ring closure of the five-membered ring starting from hydrazinopyridazines, or (2) ring closure of the pyridazine ring starting from *N*-aminotriazole compounds. A review paper on triazolopyridazines and other related fused pyridazines also appeared [<2005JHC361>](#).

Table 12 Syntheses of [1,2,4]triazolo[4,3-*b*]pyridazine and [1,2,4]triazolo[1,5-*b*]pyridazine derivatives

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1		HCOOH		76	1994PHA21 , 1994PJC683 , 1997APH451 , 1994JME2153
2		ClCOOEt		42	1994PJC683
3		RCOCl		85	2005HAC278 , 1997APH451 , 1994JME2153 , 2000TL781
4		CN-CH2COOEt		92	2005HAC278
5		PhNCS or CS2		60–90	2005HAC278 , 1997APH451
6		RCONHCHCOOH		11–62	2005HCO321
7				69	1995JHC1341
8		BrCN		63–85	1994JME2153
9		RC(OEt)3		63–80	1994JME2153

(Continued)

Table 12 (Continued)

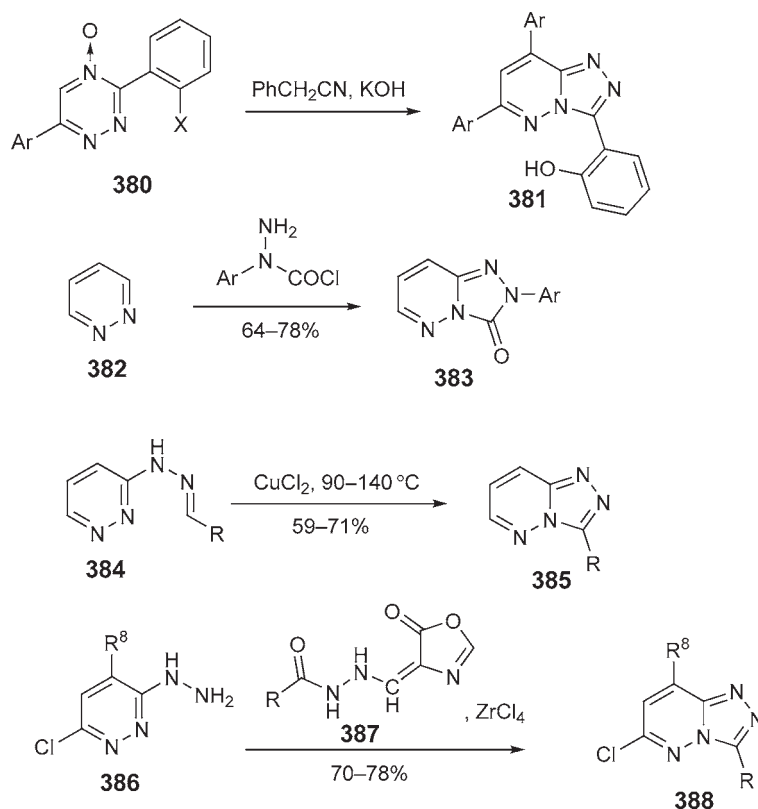
Entry	Starting compound	Reagent	Product	Yield (%)	Reference
10		AcOH, NaOAc		52	1994PJC683
11		Br ₂ , AcOH Pb(OAc) ₄ PhI(OAc) ₂		90	1998JHC513, 2005HAC278, 2001SC1511, 2003CAR2057, 1997JHC1115, 1994JHC1259
12		Heating		57	2005HAC278
13		COCl ₂		57	1996APH431
14		HCOOH			2002ZNB668, 1996APH431
15		RCOOH or RCOCl		48	1996APH431
16		RC(OEt) ₃		42	1996APH431
17		MeCOCH(Me)COOEt		86	2002PJC1577
18		PhCONHNH ₂		78	2003PS199

(Continued)

Table 12 (Continued)

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
19		NH ₂ CONHNH ₂		80	1997JPR20, 2001HCO159
20		NH ₂ OH, PPA			1997CPB1447
21		POCl ₃		30	2003CPB122

Besides the more routine cyclizations shown in [Table 12](#), some particular ring-closure reactions will be discussed separately. These transformations are shown in [Schemes 47 and 48](#).

**Scheme 47**

[Scheme 47](#) contains syntheses of [1,2,4]triazolo[4,3-*b*]pyridazine derivatives by ring closure of the triazole moiety. Kozhevnikov *et al.* reported [<2005MC31>](#) an interesting ring transformation: treatment of the

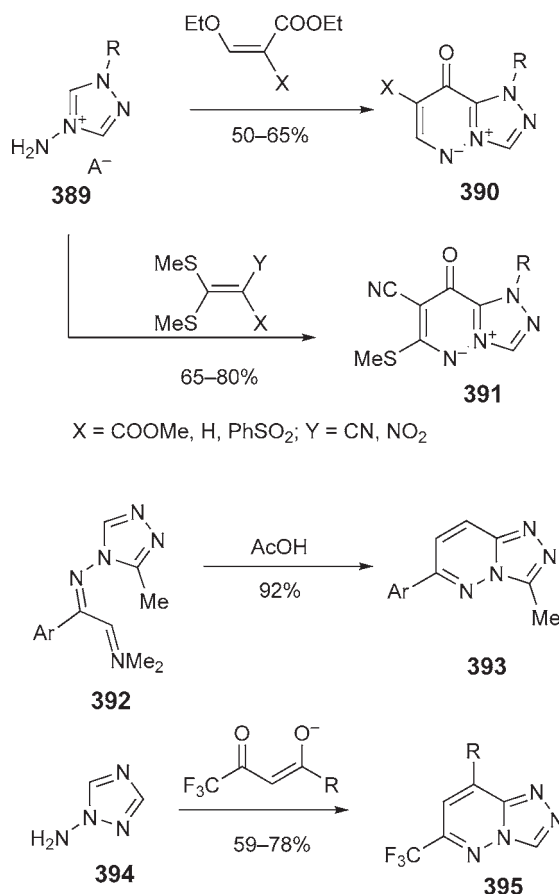
3-aryl[1,2,4]triazine-*N*-oxide **380** with benzylnitrile in the presence of potassium hydroxide afforded **381** containing an *o*-hydroxyphenyl substituent in position 3. The reaction could be only performed when the aryl group in **380** was *o*-chloro- or *o*-fluorophenyl moiety.

A Chinese group described a relatively simple route to 2-aryl[1,2,4]triazolo[4,3-*b*]pyridazine-3(2*H*)ones **383** by treatment of unsubstituted pyridazine **382** with α -chloroformylphenylhydrazine hydrochloride <2002JCCS239>. The reaction was completed in 24 h at 60 °C in isopropanol in good yield.

With the synthesis of novel [1,2,4]triazolo[4,3-*b*]pyridazine derivatives **385** from the pyridazylhydrazone **384**, Döring *et al.* followed a well-established route (cf. Table 12, entry 11) <2005T5942>. The specificity of this study is, however, the use of cupric chloride as an oxidizing agent (which has not been used before).

Kocevar *et al.* investigated the reactivity of 3-hydrazinopyridazines **386** in the presence of the oxazolone compound **387** <2001H(54)1011>. In some special cases (mostly when R⁸ = Me), formation of **388** in high yields was observed, while in other cases an entirely different transformation (formation of a pyrazolone ring as a substituent instead of the hydrazine group) was experienced.

Some special ring closures utilizing cyclization of the pyridazine ring should also be discussed in more detail; these are shown in Scheme 48.



Scheme 48

Matsuda *et al.* <1995H(41)2777> described an efficient synthesis of mesoionic [1,2,4]triazolo[4,3-*b*]pyridazines **390** and **391**. The starting compound for the synthesis is the *N*-aminotriazole **389**, which can be treated either with ethyl 2-chloro-3-ethoxyacrylate to yield **390** or with ketene dithioacetals to afford **391**. The reactions proceed in good to high yield.

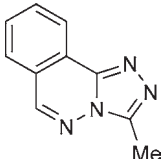
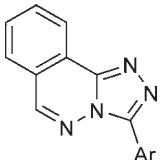
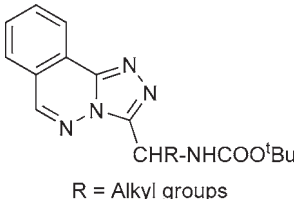
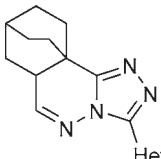
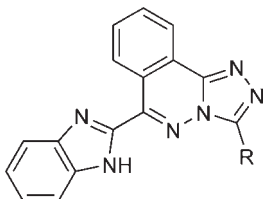
An interesting ring closure of the pyridazine moiety leading to a [1,2,4]triazolo[4,3-*b*]pyridazine derivative **393** was described by Albright and Lieberman <1994JHC537>.

The synthesis was accomplished by heating **392** in acetic acid for a prolonged period leading to compound **393** in high yield. A trifluoromethyltriazolopyridazine derivative **395** was synthesized by a Russian team <1998ZOR411>. Treatment of *N*-aminotriazole **394** with the lithium salt of trifluoroacetylacetone gave rise to the ring-closing product **395** in high yield.

11.16.6.3.2 Synthesis of triazolophthalazines

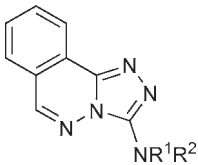
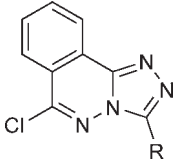
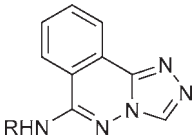
Several applications of established ring-closure methodologies have been applied for the syntheses of the benzo- analogues of the triazolopyridazine ring system – all these refer to cyclization to [1,2,3]triazolo[3,4-*a*]phthalazine derivatives. In **Table 13**, such products are shown together with yields and literature references. The product in entry 8 is somewhat outstanding in this list: these compounds have been synthesized by solid-phase methodology, and the yields refer to the amounts of the crude products mostly of 90% purity.

Table 13 [1,2,3]Triazolo[3,4-*a*]phthalazine derivatives obtained by established ring-closure techniques, including yields and literature references

Entry	Product	Yield (%)	Reference
1		40	1994SC2645
2		94–98	1999SC583
3		52–96	2004JHC387
4		30–65	2004JME3642
5		61–82	2003JRM835

(Continued)

Table 13 (Continued)

Entry	Product	Yield (%)	Reference
6		66–78	2004OPP121
7			2004JME1807
8		41–73	2005TL3107

11.16.6.4 Ring Synthesis of Triazolopyrazines

11.16.6.4.1 Synthesis of [1,2,3]triazolo[1,5-*a*]pyrazines

Novel synthetic pathways to derivatives of the title ring system are shown in [Scheme 49](#).

Vercek and co-workers described an effective approach to some 3-cyano-4-amino[1,2,3]triazolo[1,5-*a*]pyrazines starting from the *N*-substituted triazole derivatives [396](#) [<2002H\(56\)353>](#). This compound when treated either with acetic acid or triethylamine gave rise to the ring-closed products [397](#) in acceptable yield (55–66%).

A ring-closure reaction to the bicyclic triazolopyridine system implying intramolecular 1,3-dipolar cycloaddition was published by Couty *et al.* [<2004TL3725>](#). The reaction pathway started from an *N*-propargylaminoalcohol [398](#), which was treated first with thionyl chloride followed by sodium azide to give the intermediate [399](#), which underwent the desired cyclization to afford the final product [400](#). Although in other related cases (cf. Chapter 11.15 for tetrazolopyrazines) the yields were acceptable, this nitrogen positional derivative was obtained only in 20% yield.

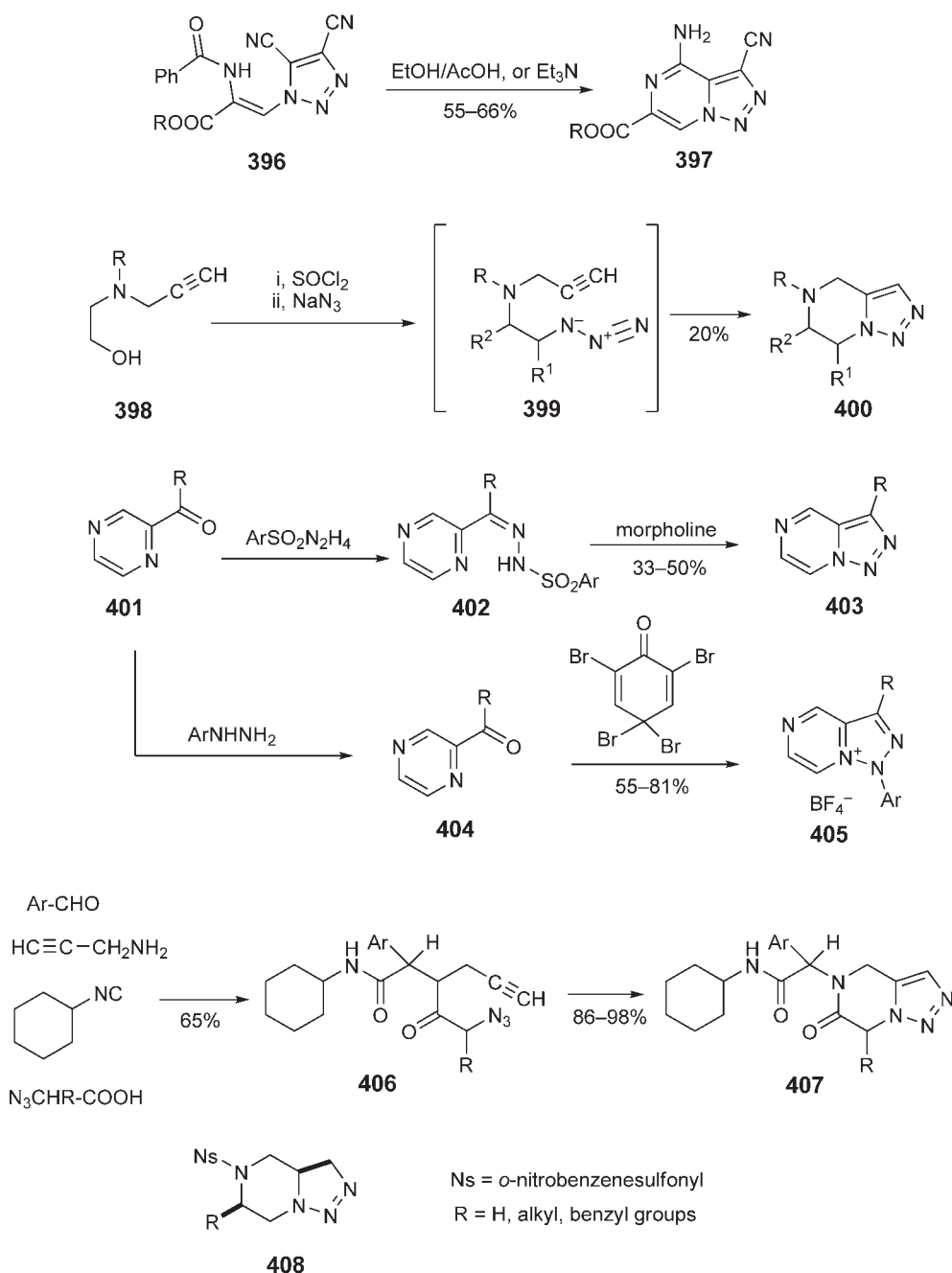
Two recent publications appeared describing synthetic routes to triazolopyrazines starting from pyrazinyl ketone hydrazones. Thus, Raghavendra and Lam reported [<2004TL6129>](#) that the tosylhydrazone [402](#) obtained from the pyrazinyl ketone [401](#) and tosylhydrazide can be subjected to cyclization to [403](#) by treatment with morpholine in modest to medium yields. A Hungarian–Austrian joint group described another type of cyclization [<1997T9393>](#): treatment of various arylhydrazones [404](#) with 2,4,4,6-tetrabromo-2,5-cyclohexadienone gave rise to formation of the quaternary bromides [405](#) in medium to high yields.

A versatile synthesis of triazolopyrazines has been elaborated by Akritopoulou-Zanze *et al.* [<2004TL8439>](#). The method involves two steps: a multicomponent Ugi reaction and a subsequent ring closure. Thus, arylaldehydes, propargylamine, cyclohexylisocyanide, and azidoacetic acid yielded the intermediate [406](#) which easily underwent cyclization to give the partially saturated derivative [407](#) in excellent yields.

Finally, the synthesis of various substituted derivatives of the general formula [408](#) should be discussed [<2005TL1205>](#). Although the cyclization step to these derivatives is basically an application of an earlier recognized intramolecular cycloaddition of an azide group [<1990JHC817>](#) as reviewed in CHEC-II(1996) [<1996CHEC-II\(8\)421>](#), and the present application allows a higher diversity of introduction of substituents.

11.16.6.4.2 Synthesis of [1,2,4]triazolo[1,5-*a*]pyrazines

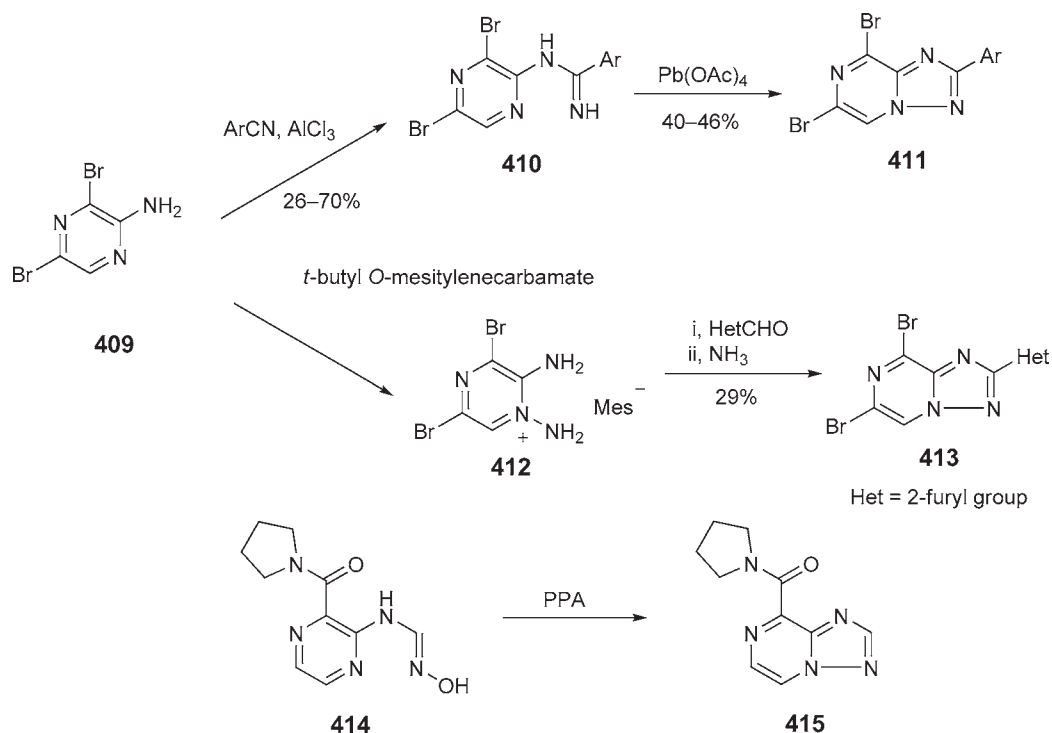
The preparation of biologically active [1,2,4]triazolo[1,5-*a*]pyrazines has been reported recently. The reaction routes are shown in [Scheme 50](#). Dowling *et al.* reported [<2005BML4809>](#) the synthesis of aryl-substituted derivatives [411](#). The first step was the transformation of the 2-aminopyrazine compound [409](#) to an amidine [410](#), which was subjected



Scheme 49

to oxidation with lead tetraacetate to furnish the product **411** in variable yields. Some hetaryl compounds have also been obtained in this way.

An alternative route to furyl compounds of similar structure was reported by Yao *et al.* <2005BML511>: the same starting amine **409** was N-aminated to the 1,2-diaminopyrazinium mesylate **412**, which was ring-closed by treatment with furylaldehyde to yield **413** in rather poor yield. The synthesis of the pyrrolidinylcarbonyl derivative **415** in a cyclocondensation reaction of **414** by use of polyphosphoric acid was reported by Giardina *et al.* <1995FA405>.



Scheme 50

11.16.6.4.3 Synthesis of [1,2,4]triazolo[4,3-*a*]pyrazines

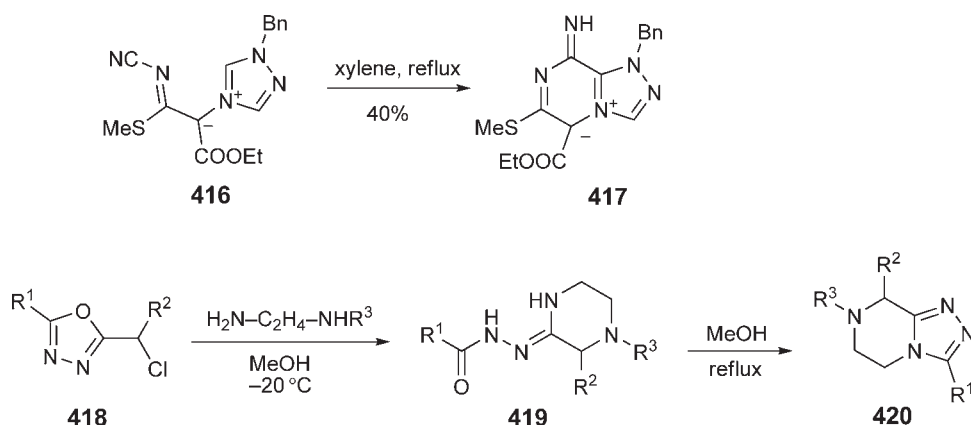
Relatively few new papers have appeared on synthetic procedures for the title ring system. Some of these follow established methodologies. Thus, three reports appeared where 2-hydrazinopyrazines – or their derivatives – were subjected to ring closure to give [1,2,4]triazolo[4,3-*a*]pyrazines. These products – with yields and references – are shown in Table 14.

Table 14 [1,2,4]Triazolo[4,3-*a*]pyrazines prepared from 2-hydrazinopyrazines or their derivatives

Entry	Product	Yield (%)	Reference
1		54	1994SC1895
2		69	2001SC1511
3		59 ^a	2002TA821

^aendo/exo-Ratio = 86/14; 72% de.

Two new procedures deserve, however, special interest; these are shown in [Scheme 51](#).



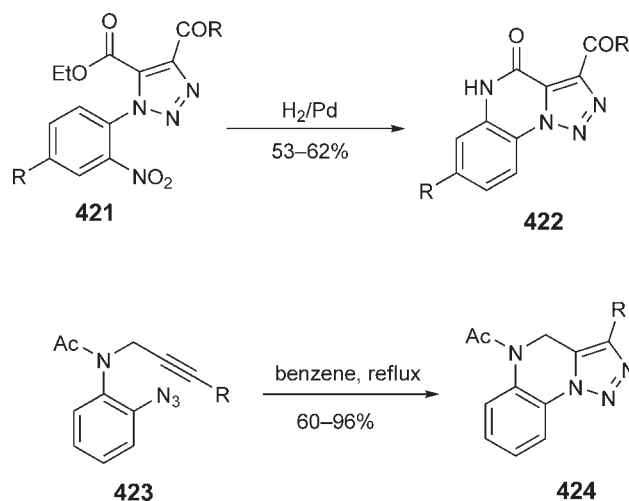
Scheme 51

Matsuda *et al.* described the cyclization to a mesoionic derivative of the title ring system [<1995H\(41\)329>](#). The starting compound of the ring-closure reaction is the anion **416**, which was easily obtainable from ethyl [1,2,4]triazol-1-ylacetate with potassium bromide. Upon heating this compound, ring closure to the zwitterionic **417** takes place in 40% yield.

Balsells *et al.* found that some chloromethyloxadiazoles are highly reactive and are suitable starting compounds for the synthesis of some tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazines [<2005OL1039>](#). These oxadiazoles **418** react with ethylenediamines at -20°C and yield a substituted piperidine **419** as a result of a fairly complicated ring-opening–ring-closure sequence. This intermediate easily undergoes cyclization reaction to the target bicyclic product **420**.

11.16.6.4.4 Synthesis of triazoloquinoxalines

Two approaches to [1,2,3]triazolo[1,5-*a*]quinoxaline compounds are shown in [Scheme 52](#).



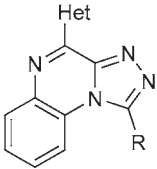
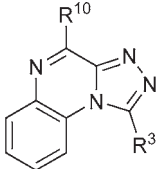
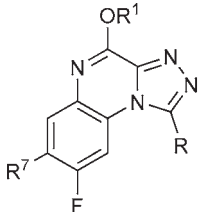
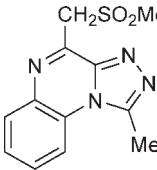
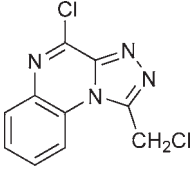
Scheme 52

Biagi *et al.* described a reductive cyclization to triazoloquinoxalinones **422** [<2002EJM565>](#). These authors found that catalytic reduction of the *o*-nitrophenyl derivative **421** – obviously via intermediate formation of the

amine – results in an intramolecular ring-closure reaction (with elimination of ethanol) to give **422**. The second synthetic pathway was published by Brogini *et al.* <1997JRM2215>. In this procedure, the *N*-propargylazidoaniline derivative **423** was transformed by heating in benzene to give various substituted tricyclic products **424** in good to excellent yields.

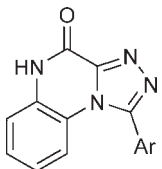
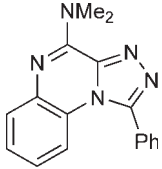
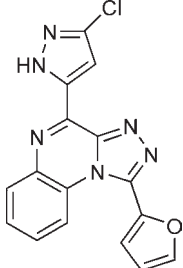
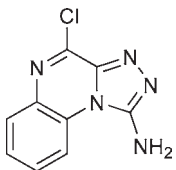
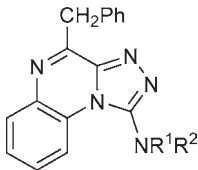
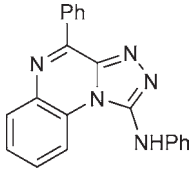
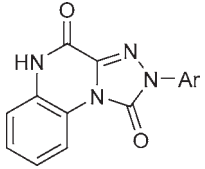
Many more results were reported in the area of the isomeric [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives. With one exception, however, all these studies applied known recognized ring-closure techniques for the synthesis of novel derivatives, in many cases of biological importance (cf. Section 11.16.8.) In Table 15, these derivatives are summarized together with the literature references.

Table 15 Structures of [1,2,4]triazolo[4,3-*a*]quinoxaline derivatives synthesized by known cyclisation methods

Entry	Product	Reference
1	 Het = subst. 1- or 3-pyrazolyl R = H, Me	1994JHC549, 2000JHC103
2	 R³ = Me, Bn, CH₂COOEt R¹⁰ = Ph, subst. phenyl or hetaryl group	1999PHA808
3	 R¹ = H or Me; R = alkyl or phenyl group; R⁷ = H, NO₂	1997JME2053, 1999IJB45, 1999IJB1371
4		1995PS1
5		2004MI175

(Continued)

Table 15 (Continued)

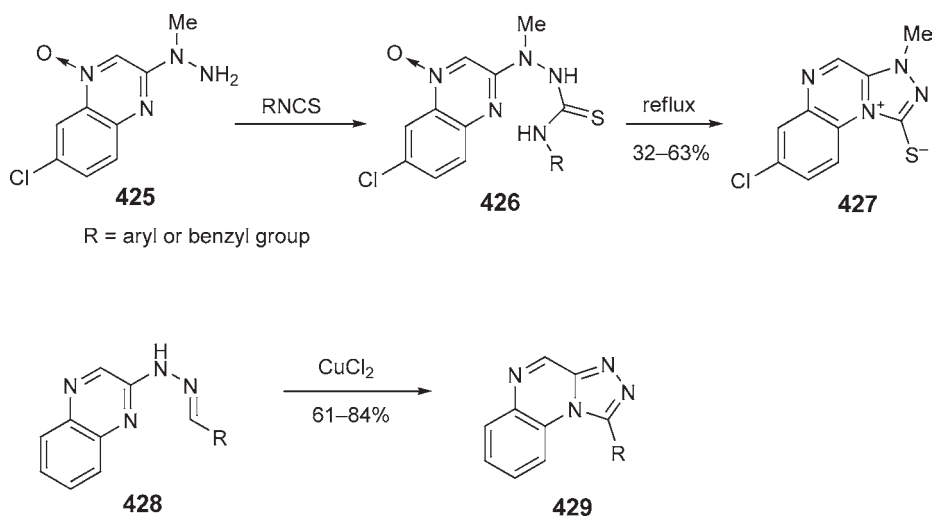
<i>Entry</i>	<i>Product</i>	<i>Reference</i>
6	 A bicyclic system consisting of a benzene ring fused to a six-membered ring containing a carbonyl group (C=O) and an NH group. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with an aryl (Ar) substituent at the 4-position.	2000IJB329
7	 A bicyclic system consisting of a benzene ring fused to a six-membered ring. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with a dimethylamino (NMe ₂) group at the 4-position and a phenyl (Ph) substituent at the 5-position.	2004PS2265
8	 A bicyclic system consisting of a benzene ring fused to a six-membered ring. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with a chlorine (Cl) atom at the 4-position and a furan ring at the 5-position.	1998AP163
9	 A bicyclic system consisting of a benzene ring fused to a six-membered ring. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with a chlorine (Cl) atom at the 4-position and an amino (NH ₂) group at the 5-position.	2002AP389
10	 A bicyclic system consisting of a benzene ring fused to a six-membered ring. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with a benzyl (CH ₂ Ph) group at the 4-position and an NR ¹ R ² substituent at the 5-position.	2004OPP121
11	 A bicyclic system consisting of a benzene ring fused to a six-membered ring. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with a phenyl (Ph) group at the 4-position and an N-phenyl (NHPh) group at the 5-position.	1997PHA594
12	 A bicyclic system consisting of a benzene ring fused to a six-membered ring containing a carbonyl group (C=O) and an NH group. A 1,2,4-triazole ring is attached to the six-membered ring at the 2-position, with an aryl (Ar) substituent at the 4-position.	2000JME1158

(Continued)

Table 15 (Continued)

Entry	Product	Reference
13		2000PHA896
14		1999AP39, 2000JME1158, 2003BMC3541, 2004JME3580
15		1997PHA436

The synthesis of an interesting mesoionic [1,2,4]triazolo[4,3-*a*]quinoxaline derivative shown in [Scheme 53](#) is noteworthy. A Korean–Japanese team described the treatment of an *N*-methylhydrazinoquinoxaline-*N*-oxide **425** by isocyanates to give a semithiocarbazide **426** which upon heating underwent cyclization to the thiolate **427** in medium to good yields [<1997JHC1539>](#).

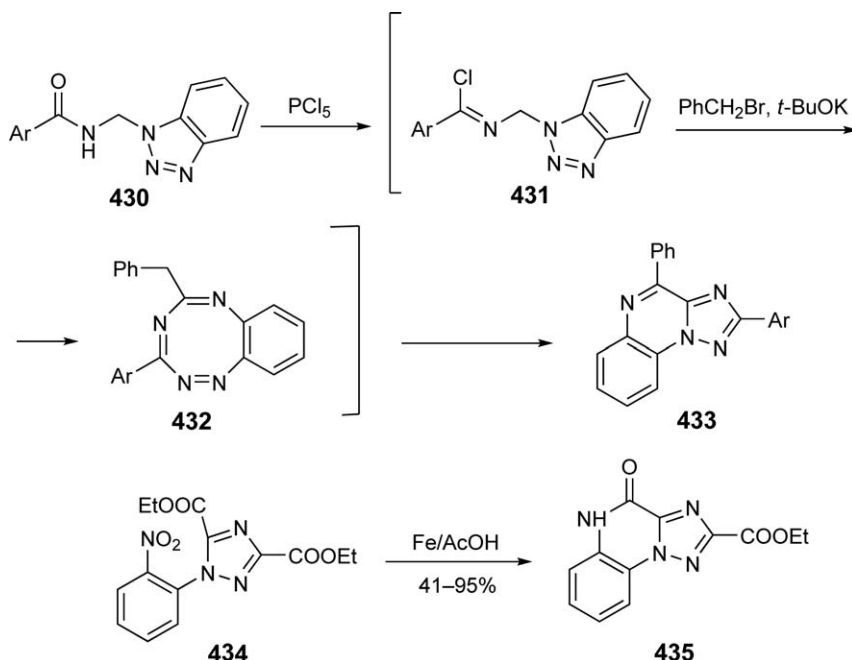


Scheme 53

Oxidative cyclization of hydrazones to fused [1,2,4]triazoles by means of cupric chloride was already discussed above for a related pyridazine derivative. The same method was also applied successfully for ring closure of **428** to **429** in good to excellent yields ([Scheme 53](#)) [<2005T5942>](#).

Two synthetic pathways to [1,2,4]triazolo[1,5-*a*]quinoxalines are shown in [Scheme 54](#). Transformation of **430** to **433** was described by Katritzky *et al.* [<2002JOC3118>](#). The ring-closure reaction proceeded via a very complicated pathway in relatively low yield (25–31%). The first intermediate is the imidoyl chloride **431** which, when treated with

benzyl bromide in the presence of potassium *t*-butoxide, undergoes a series of ring openings and ring transformations. An interesting intermediate is the eight-membered tetrazocane **432**, which again undergoes further basic ring transformations to yield finally product **433**.



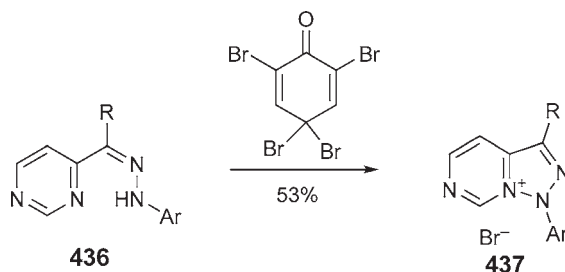
Scheme 54

An essentially more simple but, from the biological point of view, very useful ring closure has been elaborated by Catarzi *et al.* <1994JME2846, 1999JME2478, 2000JME3824, 2001JME3157>. These authors described that reduction of the nitrophenyltriazole **434** with iron in acetic acid results in the formation of an amine intermediate which immediately undergoes intramolecular cyclization to yield triazoloquinoxalines **435**. The yield varies between medium and high, but in most cases it is satisfactory.

11.16.6.5 Ring Synthesis of Triazoles Fused to the *c*-Site of Pyrimidine Ring

11.16.6.5.1 Synthesis of [1,2,3]triazolo[1,5-*c*]pyrimidines and [1,2,4]triazolo[1,5-*c*]pyrimidines

A novel approach to [1,2,3]triazolo[1,5-*c*]pyrimidines is shown in Scheme 55. Bátori and Messmer – in the course of their investigations on fused azolium salts – described a synthetic pathway to 1,3-disubstituted[1,2,3]triazolo[1,5-*c*]pyrimidinium salts <1994JHC1041>. The cyclization was accomplished by transformation of the hydrazone **436**. This compound was subjected to an oxidative ring closure by 2,4,6-tetrabromo-2,5-cyclohexadienone to give the bicyclic quaternary salt **437** in acceptable yield.

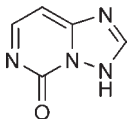
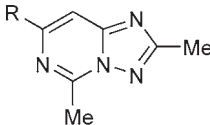
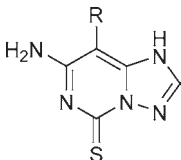


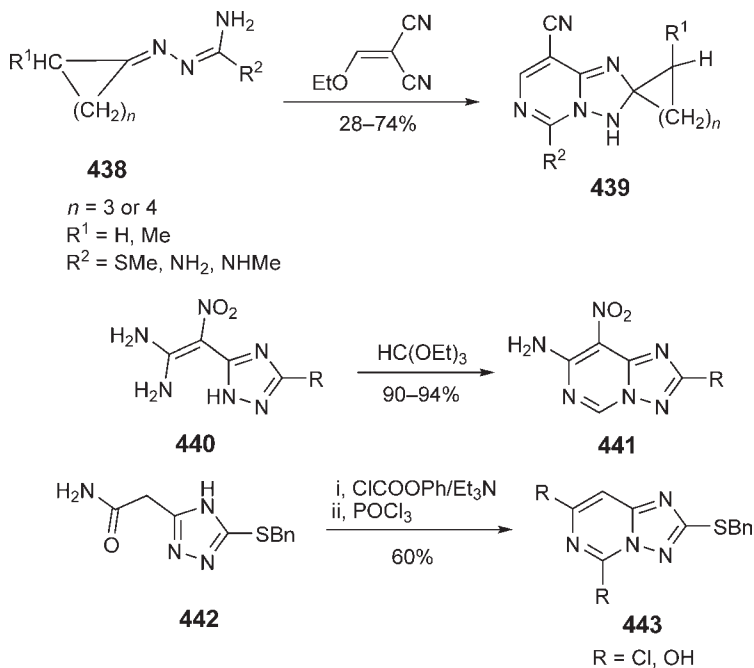
Scheme 55

More novel results were published in the area of the isomeric [1,2,4]triazolo[1,5-*c*]pyrimidine ring system. In [Table 16](#), a few applications of earlier known methodologies are shown. All these compounds were synthesized by transformation of 4-imino-3-aminopyrimidine or analogous derivatives by reagents providing a one-carbon-atom structural unit (e.g., carboxylic acids or derivatives).

Two further, more specific transformations leading to this ring system are shown in [Scheme 56](#).

Table 16 Synthesis of [1,2,4]triazolo[1,5-*c*]pyrimidines by earlier known methodologies

Entry	Product	Reference
1		2002HCA502
2	 R = COOEt, Me	2003KGS223
3		1994JME3828



Scheme 56

Miyamoto and Yamazaki described the transformation of the cyclopropane derivative **438** by ethoxymethylene malonitrile (Scheme 56) <1997JHC871>. As a result, a series of spiro-substituted triazolopyrimidines **439** were obtained in modest to good yield. The synthesis allowed a certain variation of the substituents. Another cyclization reaction to this ring system utilized the ring closure of the pyrimidine ring which was reported by Gatta *et al.* <1994JHC1171>. Thus, the enamine-substituted triazole **440** was treated by triethyl orthoformate to give **441** in almost quantitative yields.

An interesting new route to derivative of this ring system was reported by Shankar and Pews <2000H(53)1151>. Triazole derivative **442** was treated first with phenyl chloroformate in the presence of triethylamine followed by reaction with phosphorus trichloride to yield the triazolopyrimidine products **443** in good yield.

It is important to note that besides these synthetic pathways a very important access to [1,2,4]triazolo[1,5-*c*]-pyrimidine derivatives is the Dimroth rearrangement of [1,2,4]triazolo[4,3-*c*]pyrimidine compounds. This type of ring transformation is specifically discussed in Section 11.16.5.2; these possibilities are also reviewed in Section 11.16.7. As these isomerizations always take place into the direction of the [1,2,4]triazolo[1,5-*c*]pyrimidine ring, in several studies only these products are described without special (or any) note of the primarily formed [1,2,4]triazolo[4,3-*c*]pyrimidine ring. Table 17 contains the structures of some [1,2,4]triazolopyrimidines and benzologues with a fusion site of the triazole ring that have been formed via transformation of the isomeric [1,2,4]triazolo[4,3-*c*]pyrimidine compounds with or without isolation of these intermediates.

Table 17 [1,2,4]Triazolopyrimidines and benzologues with a fusion site of the triazole ring that have been formed via transformation of the isomeric [1,2,4]triazolo[4,3-*c*]pyrimidine compounds

Entry	Starting compound	Conditions	Product	Reference
1		Heat		2005BML3670
2		Ac ₂ O		2005JME6409
3		DCC and NaOH		1999J(P1)1527

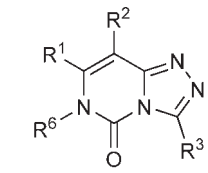
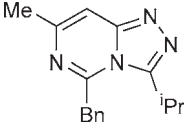
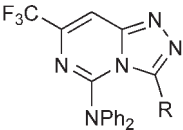
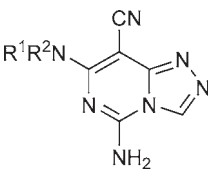
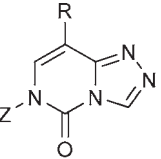
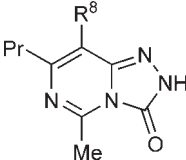
11.16.6.5.2 Synthesis of [1,2,4]triazolo[4,3-*c*]pyrimidines

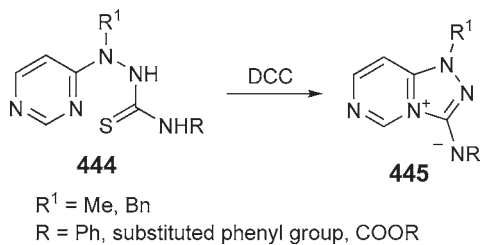
Similarly to other related fused triazoloazines that can be derived from hydrazinoazines, several studies appeared on applications of old methodologies for the synthesis of novel derivatives. Structures of such products are compiled in Table 18 including references.

One synthetic paper describing interesting mesoionic products should be discussed separately; the transformation is shown in Scheme 57.

Crabb *et al.* found <1997J(P2)49> that treatment of the triazole compound **444** – easily available from pyrimidinylhydrazine by treatment with arylisocyanates – with DCC gives rise to the triazolopyrimidinium aminide **445**.

Table 18 Synthesis of [1,2,4]triazolo[4,3-c]pyrimidine derivatives by earlier recognized methods

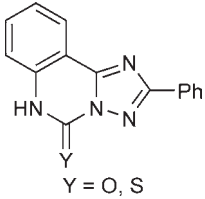
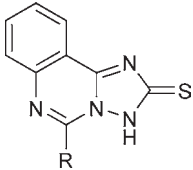
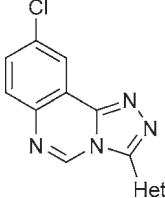
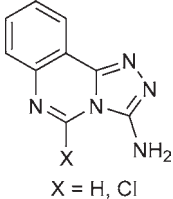
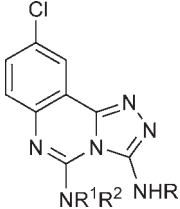
Entry	Product	Reference
1	 $R^1, R^2, R^3, R^6 = \text{H or Me}$	2002H(57)631
2		2000KGS225
3	 R = Carbohydrate group	2002SC1791
4		2000JHC707
5	 Z = Carbohydrate group	1995JOC7066, 1998TL3865
6		1996JHC1307

**Scheme 57**

11.16.6.5.3 Synthesis of triazoles fused to the c-site of quinazoline ring

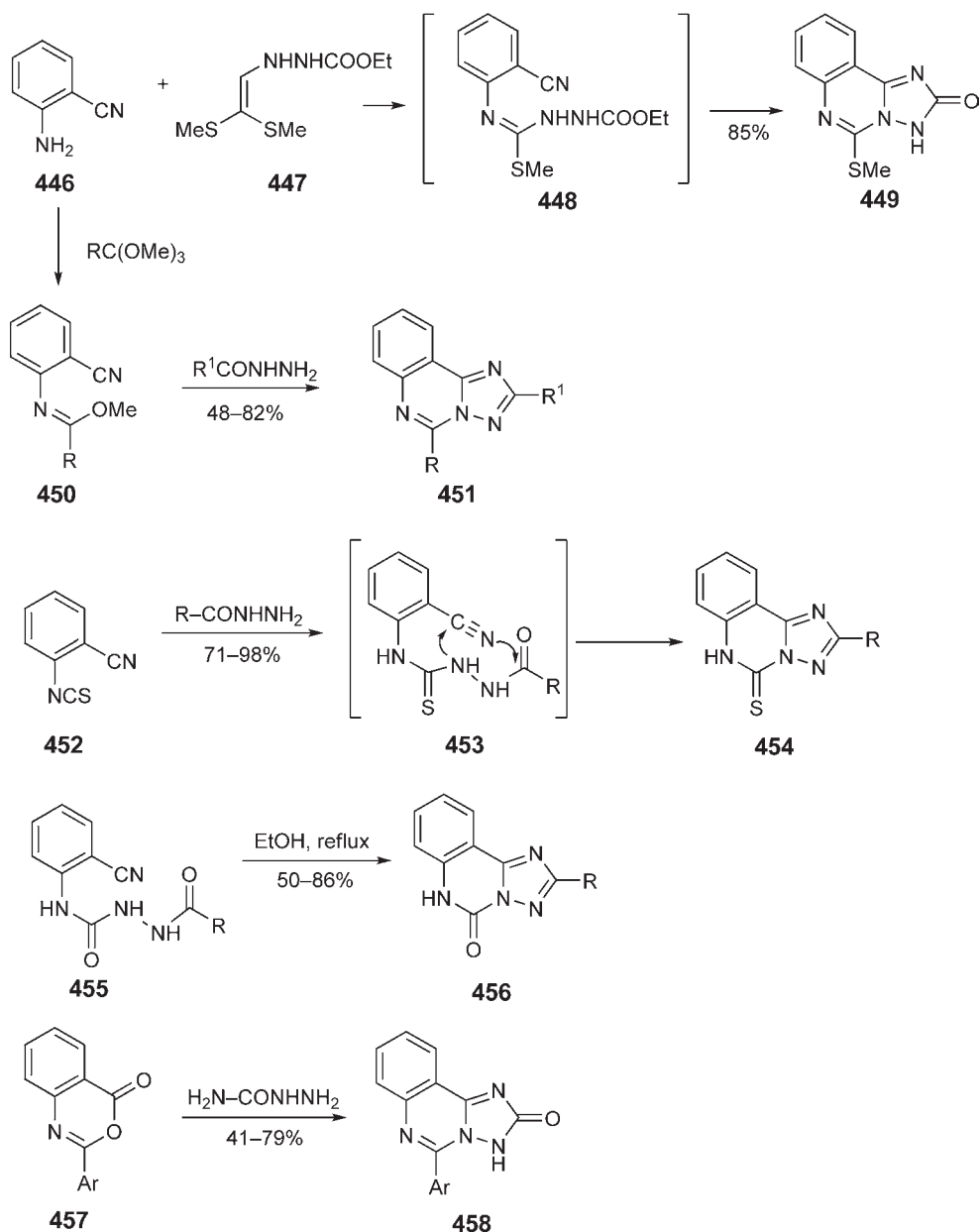
Some [1,2,4]triazolo[5-*c*]quinazoles and [1,2,4]triazolo[4,3-*c*]quinazoles were synthesized by application of earlier established methodologies, and these are summarized in [Table 19](#).

Table 19 [1,2,4]Triazolo[1,5-*c*]quinazoline and [1,2,4]triazolo[4,3-*c*]quinazoline derivatives obtained by known methods

Entry	Product	Reference
1	 Y = O, S	2000MI243, 1999JHC1327
2		1997JRM1041, 2005JHC125
3		1994CCCC243
4	 X = H, Cl	2000MI243, 2003AP560
5		1994CCC222

Several new approaches have also appeared. These transformations are illustrated in [Scheme 58](#).

Sauter *et al.* <1995H(40)851> recognized that some *N*-[bis(methylthio)methylene]amino esters (called BMMA reagents) can be usefully applied for one-pot reactions to fused heterocycles. Thus, *o*-aminobenzonitrile **446** was treated with the BMMA reagent **447** to yield the fused triazolone **449** in high yield. The reaction was rationalized by formation of the intermediate **448**. The ring-closure method to triazoloquinazolines described by Okamura *et al.* <2004BML2443> also started from *o*-aminobenzonitrile **446**: this compound was first treated with orthoester to give an iminoether **450**, which was then reacted with acylhydrazines. In this transformation, tandem formation of the fused pyrimidine and fused triazole ring can take place ('domino' reaction; for more details see example **454**) to give the correspondingly substituted tricyclic product **451**. A large set of derivatives were synthesized in medium to high yield.



Scheme 58

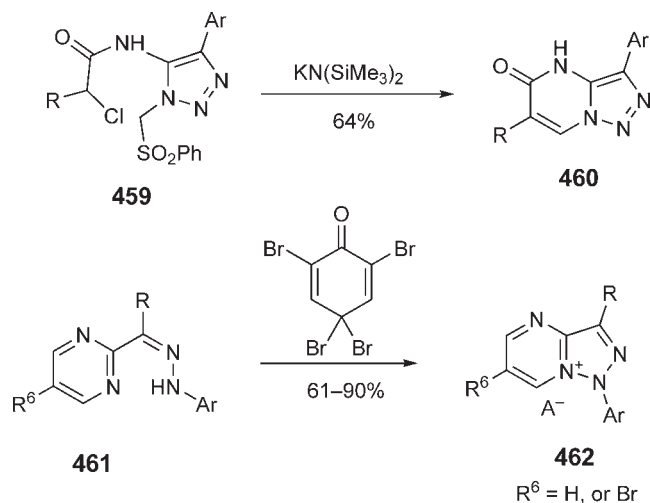
A ring closure to triazoloquinazoles described by Blank *et al.* <2003EJO182> also followed by a ‘domino cyclization’ pathway: *o*-isothiocyanatobenzonitrile **452** was treated with acylhydrazines to give the intermediate **453**, in which the formation of two N–C bonds occurs, as indicated by the arrows, to yield **454**. Compound **455** – closely related to the already-mentioned intermediate **453** – was also reported to undergo cyclization in an ethanolic solution under reflux conditions to give **456** <1994AP469>.

Ring closure to **458** starts from an unusual, benzoxazinone derivative **457** <1995MI209, 2002JCM490>. Reaction of this compound with semicarbazide involves first a ring transformation of the oxazine ring to a pyrimidine ring, and the subsequent course of the reaction follows a well-known pathway (i.e. condensation of the NH_2 group and ring C=O moiety).

11.16.6.6 Ring Synthesis of Triazoles Fused to the α -Site of Pyrimidine Ring

11.16.6.6.1 Synthesis of [1,2,3]triazolo[1,5-*a*]pyrimidines

Two results in the area of the ring system of this subsection appeared during the recent period of time; the chemical transformations are shown in [Scheme 59](#).



Scheme 59

An unusual one-pot intramolecular sulfoxide alkylation–elimination reaction was found by Gibson *et al.* <2001SL712>. These authors found that treatment of **459** with potassium bis-trimethylsilylamide resulted in a ring closure to **460** in acceptable yield. Furthermore, Bátori and Messmer found an effective method for preparation of [1,2,3]triazolo[1,5-*a*]pyrimidinium salts <1994JHC1041>: oxidative cyclization of hydrazones **461** by 2,4,4,6-tetrabromo-2,5-cyclohexadienone gave rise to the quaternary salts **462**. Under certain reaction conditions, the formation of 6-bromo-salts **462** ($\text{R}^6 = \text{Br}$) was also experienced. As neither the starting compound nor the quaternary triazolopyrimidinium salt underwent bromination in this position, the authors assumed that this bromination process occurred on one of the intermediates in the course of the above-mentioned cyclization reaction.

11.16.6.6.2 Synthesis of [1,2,4]triazolo[1,5-*a*]pyrimidines

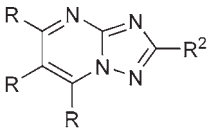
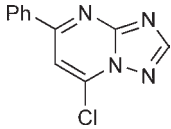
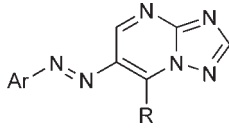
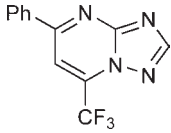
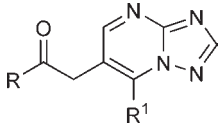
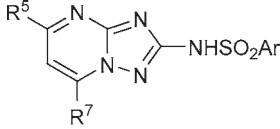
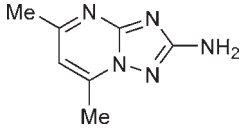
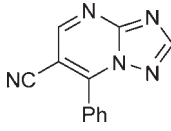
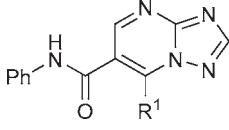
A huge amount of literature data has appeared in the context of derivatives of this ring system. The majority of the published data relates to earlier established ring-closure methodologies starting from 3-amino[1,2,4]triazoles. Two of these should be emphasized: (1) reaction of these aminotriazoles with β -oxo-ketones, esters, nitriles, or with malonic acid derivatives, and (2) reaction of these amines with α,β -unsaturated ketones or esters. These transformations are summarized in [Tables 20 and 21](#). Furthermore, other ring-closure reactions starting from 3-amino[1,2,4]triazoles by reactions of other reagents that cannot be classified into [Tables 20 and 21](#) are listed in [Table 22](#).

In [Scheme 60](#), a further few cyclizations to the title ring system are shown, none of which fits unambiguously to any categories of the above discussion (i.e., to [Tables 20, 21, or 22](#)).

McNab *et al.* published the pyrolysis of **463** <1997J(P1)1799>. Although **464** was obtained in 76% yield, the isomeric **465** was also formed and the mixture of **464** and **465** was found to be inseparable, which lowers the value of the procedure.

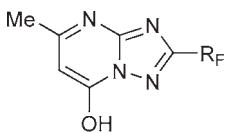
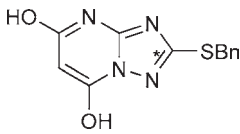
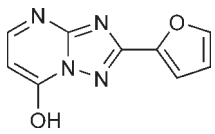
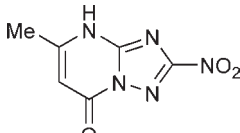
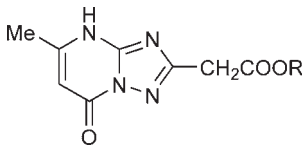
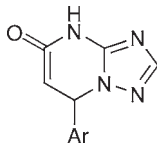
Kofman and Paketina described a simple ring closure to partially saturated [1,2,4]triazolo[1,5-*a*]pyrimidines <1994ZOR774>. Treatment of the nitrotriazole derivative bearing a γ -ketone side chain **466** with sodium hydroxide resulted in a ring closure to **467** in high yield. Another intramolecular cyclization to derivatives of this ring system was found by Lipunova *et al.* <2001ZOR604>: the tetrafluorophenyl unsaturated ketone **468** when treated with potassium fluoride yielded the ring-closed **469** in good yield. A related ring closure was described by Ahmed *et al.*

Table 20 Ring closures to [1,2,4]triazolo[1,5-*a*]pyrimidines by reaction of 3-amino[1,2,4]triazoles with β -oxo ketones, esters, nitriles, or malonic acid derivatives

Entry	Product	Reference
1	 R = alkyl or aryl groups R² = RS, morpholino or dimethylamino group	1995JHC407
2		1995PHA33
3		2004JHC647, 1998MI480, 1999IJB1371
4		2003IZV1127
5		1997IZV1226, 2005OPP223
6	 R⁷ = Me, Ph, OH R⁵ = Me, Ph	1997BML1087
7		1999EJI213
8		2000JRM173, 2000SC1985
9		2002PJC945

(Continued)

Table 20 (Continued)

Entry	Product	Reference
10	 R_F = fluororous groups	1999JFC(96)51
11 ^a		1997JLR231, 1999JHC183
12		1995IJB209
13		1997ZOR1867
14		1997ZOR1867
15		1999KGS664

^a¹⁴C-labeled derivative.

<1998JRM2056>: in this procedure, the open-chain *N*-cinnamoyl compound **470** was subjected to ring closure in the presence of sodium ethoxide to yield the bicyclic product **471**.

11.16.6.6.3 Synthesis of [1,2,4]triazolo[4,3-*a*]pyrimidines

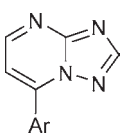
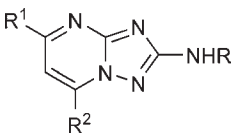
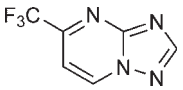
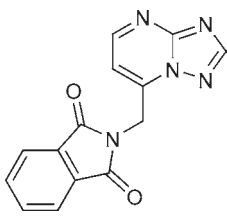
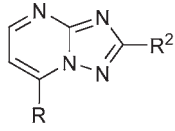
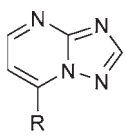
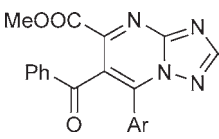
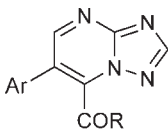
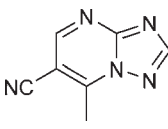
The majority of the syntheses of these ring system derivatives follows two routes: they start either from a hydrazinopyrimidine derivative or from a 3-amino[1,2,4]triazole derivative. These synthetic procedures are summarized in **Tables 23** and **24**.

In **Table 23**, [1,2,4]triazolo[4,3-*a*]pyrimidine derivatives that have been synthesized either by acidic ring closure of 2-hydrazinopyrimidine (method A) or by oxidation of a 2-pyrimidylhydrazone (method B) are compiled.

The other general route to [1,2,4]triazolo[4,3-*a*]pyrimidine derivatives is the reaction of 3-amino[1,2,4]triazole with 1,3-difunctional reagents. Five such approaches are summarized in **Table 24**. As **Table 24** reveals, the yields are high in all cases.

Three other approaches to derivatives of the title compounds of this section need more detailed discussion; these reactions are shown in **Scheme 61**.

Table 21 Ring closures to [1,2,4]triazolo[1,5-a]pyrimidines by reaction of 3-aminotriazoles with α,β -unsaturated ketones, esters, or nitriles

Entry	Product	Reference
1		2004JHC267
2		1999J(P1)1527
3		2002S901
4		2004JHC381
5	 R = alkyl, cycloalkyl, aryl, hetaryl groups R ² = alkyl or 4-pyridyl group	2002AF833
6	 R = Et, aryl group	2004JCM174
7		2003KGS949
8	 R = OEt or NH ₂	2001JHC1119
9		2005T5379

(Continued)

Table 21 (Continued)

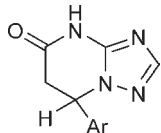
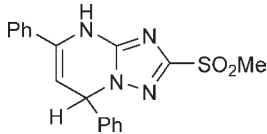
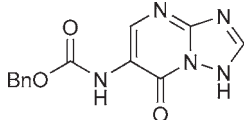
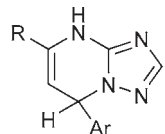
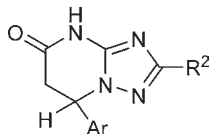
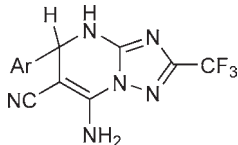
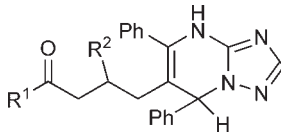
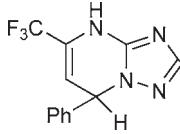
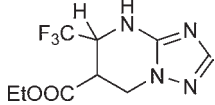
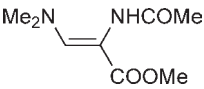
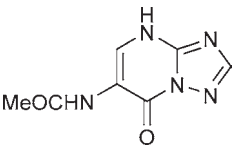
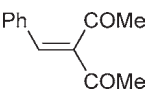
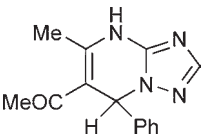
<i>Entry</i>	<i>Product</i>	<i>Reference</i>
10		1999JHC205
11		2000ZOB1553
12		2005JHC1167, 1999CCC177
13	 R = aryl or hetaryl groups	1999KGS678
14	 R ² = NH ₂ , CF ₃ , or H	2000KGS1542
15		1997JRM2378
16		2003JHC1081
17		2004KGS71
18		2004ZOR938

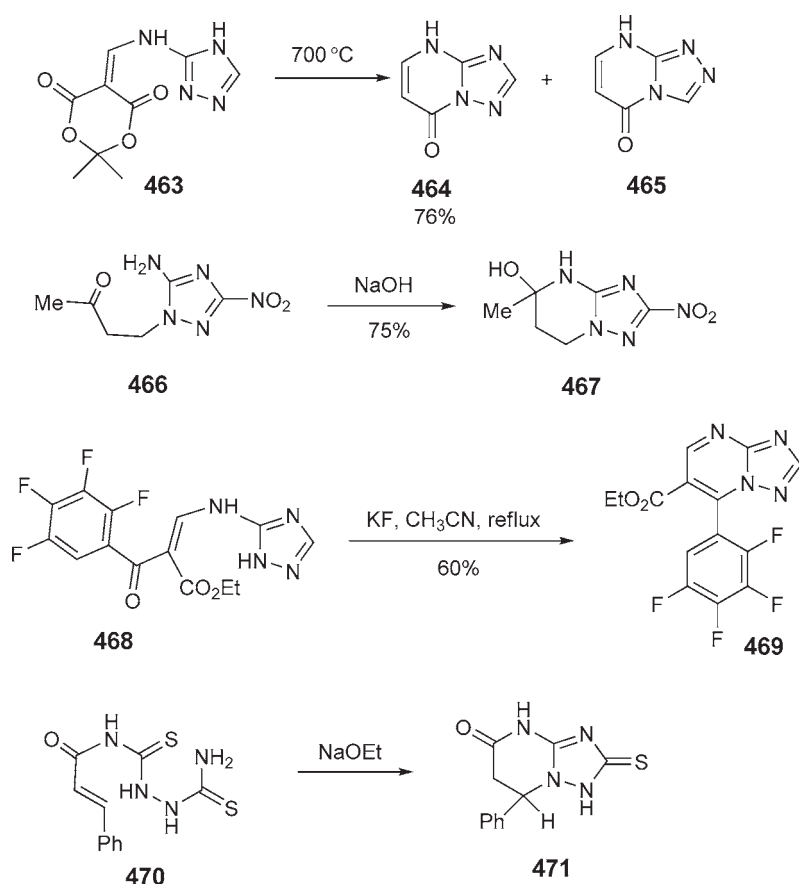
Table 22 Various ring-closure reactions to [1,2,4]triazolo[1,5-a]pyrimidines starting from 3-amino[1,2,4]triazoles

Entry	Reagent	Product	Reference
1			1994T12113, 1998H(47)689, 1995H(40)729
2			2004T4601
3			2005JHC1111
4			1995JCM290
5			1997PHA23
6	DMAD		1999MI227
7			2001KGS368, 1999KGS796
8			2005KGS246
9	MeCOCH2COOEt + ArCHO		2003IZV1677

(Continued)

Table 22 (Continued)

Entry	Reagent	Product	Reference
10			1997JHC247
11			1998JHC989



Scheme 60

Farag *et al.* published a synthetic route to [1,2,4]triazolo[4,3-*a*]pyrimidines involving reaction of 2-aminopyrimidine **472** with hetarylcarbonylhydroximoyl chloride <1997T17461>. Thus, reaction of **472** with 2-benzothiazolylcarbonylhydroximoyl chloride gave the intermediate **473**, which underwent cyclization in refluxing ethanol to give **474**.

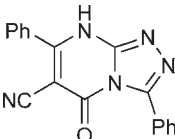
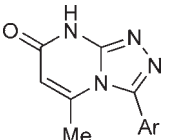
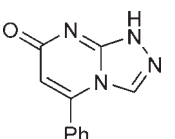
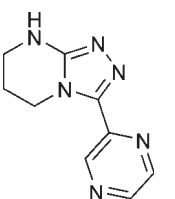
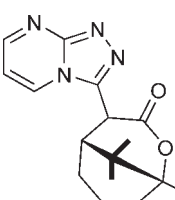
A very interesting ring-closure pathway involving Smiles rearrangement has been thoroughly studied by several Egyptian groups <2001M715, 2001SC731, 2001T10133, 2002HAC136, 2002M1297, 2003HCA739, 2004HAC107, 2006SC97>. A typical manifestation of this kind of ring closure is the transformation of the thione **475** to the

Table 23 [1,2,4]triazolo[4,3-a]pyrimidine derivatives synthesized from 2-hydrazinopyrimidines or their hydrazones

Entry	Product	Method	Yield (%)	Reference
1		B	70	1998ZNB1203
2		A	72	1996JHC229
3		B	43–63	2005T5942
Ar = substituted phenyl group				
4		B	57	2001SC1511
5		A	48–69	1994PHA27
R = alkyl or aryl, hetaryl groups				
6		A	60–65	1994IJB380
7		B	68	1995PHA784
Ch = D-ribose-1-yl group				
8		A	84	1998MI110
9		A	65	1996PS67
10		A	74–80	1998ZNB1203
R = alkyl or benzyl groups				

(Continued)

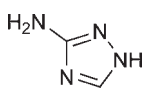
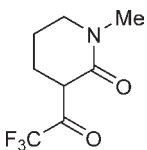
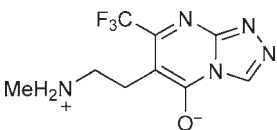
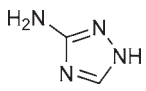
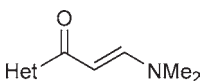
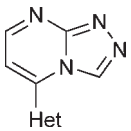
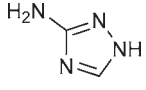
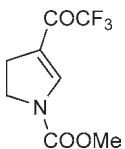
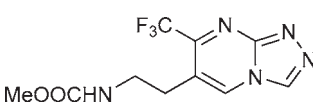
Table 23 (Continued)

Entry	Product	Method	Yield (%)	Reference
11		B	65	1998ZNB1203
12		A, B	63–78	2002KGS850, 2002KGS1296
13		A	88	1999ZNB788
14		A	37	2005KGS230
15		A	4	2005TA2927

Method A: reaction of a 2-hydrazinopyrimidine with acid chloride or related reagent.

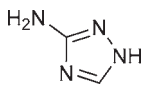
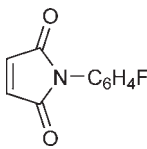
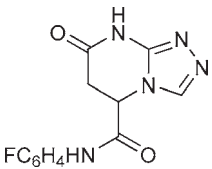
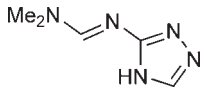
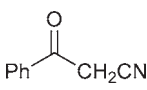
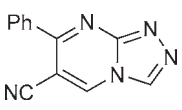
Method B: reaction of a hydrazone by oxidizing agent (e.g., bromine, ferric chloride).

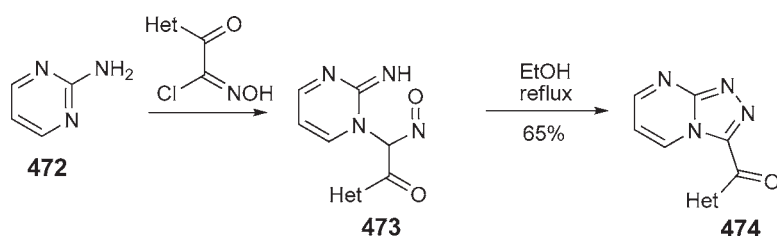
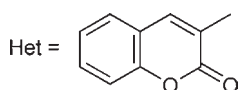
Table 24 [1,2,4]triazolo[4,3-a]pyrimidine derivatives synthesized from 3-amino[1,2,4]triazoles

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1				75	1995J(P1)2907
2				70	2001JHC981
3				82	1999TL2541

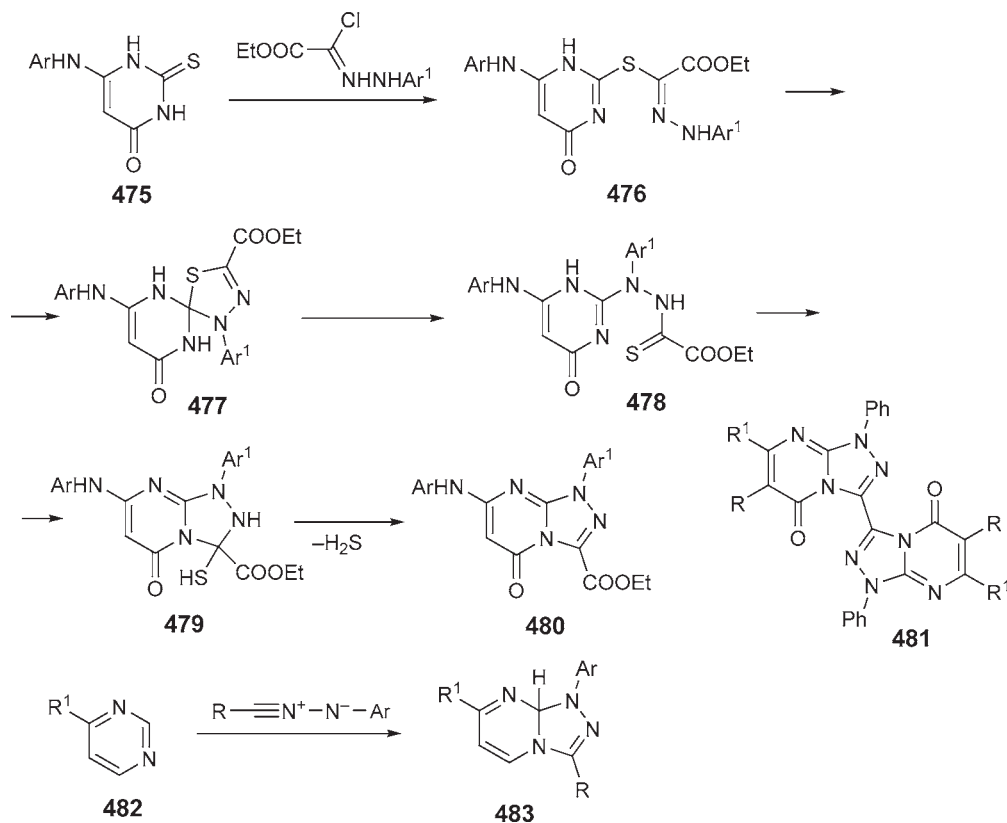
(Continued)

Table 24 (Continued)

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
4				72	2004KGS1404
5				85	1999JRM2848



Het = 2-Benzthiazolyl group



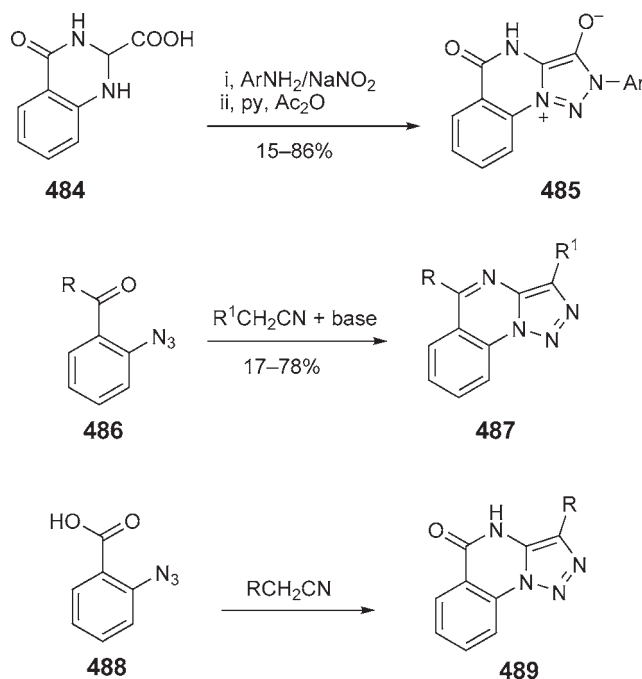
Scheme 61

ring-closed product **480** <2001T10133>. Thus, reaction of **475** with a hydrazonoyl halide gives intermediate **476** which can yield the spiro compound **477**. As a result of the 'Smiles rearrangement', the next step is formation of the hydrazine derivative **478** which can undergo ring closure to **479** followed by hydrogen sulfide elimination to yield the final product **480**. The dimeric compound **481** has also been obtained by this approach <2001M715>. Many other related derivatives containing substituents different from the ethoxycarbonyl moiety in position 3 have also been published.

The third quite unique approach to the title system is a [1,3]-dipolar cycloaddition between a substituted pyrimidine **482** and an aryl nitrilimine <1994LA1005>. In this reaction, the C=N bond of the heteroaromatic pyrimidine ring fulfills the role of the dipolarophile. A [1,3]-dipolar cycloaddition has been applied to prepare **483** <2003PS1101, 2004PS601>.

11.16.6.6.4 Synthesis of triazoles fused to the *a*- and *b*-site of quinazoline

In this section, synthesis of benzologues of various triazolopyrimidines discussed in Sections 11.16.6.6.1–11.16.6.6.3 is summarized. Because of the heteroatom arrangements, benzologues of these three kinds of fused triazoles can have either linearly (*b*-fused quinazoline) or angularly fused (*a*-fused quinazoline) ring systems. Recent synthetic work on fused [1,2,3]triazolo[1,5-*a*]quinazoles is shown in Scheme 62.

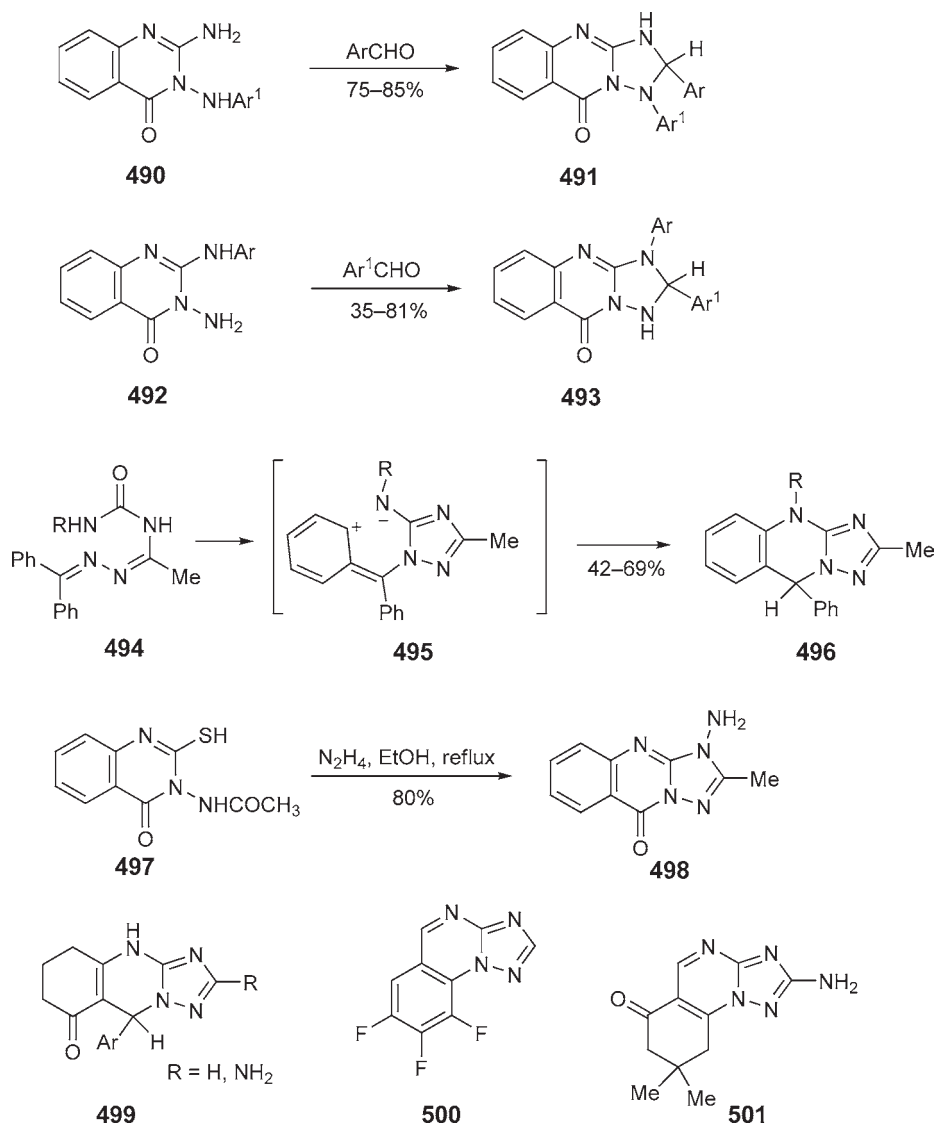


Scheme 62

The synthesis of some new mesoionic triazoloquinazoles **485** has been reported by Abbott *et al.* <2002T3185>. These authors reported that treatment of **484** with an aryl diazonium salt followed by reaction with acetic anhydride in pyridine results in a ring closure to **485**. The first step is an azo-coupling on the ring nitrogen atom, whereas the second part of the transformation is the removal of a molecule of water.

Two structurally related arylazides were also transformed similarly. Porter *et al.* described <1997S773> that ketone **486** can conveniently be transformed into **487** when treated with a substituted acetonitrile containing an active methylene group under basic conditions. The products were obtained in most cases in excellent yields. Cyclization to **489** proceeds in a similar manner as described by an Italian team <1996FA131, 2000EJM333>: the *o*-azidobenzoic acid **488** yielded the fused [1,2,3]triazole **489**.

Scheme 63 demonstrates recent synthetic results concerning two related tricyclic ring systems: [1,2,4]triazolo[1,5-*a*]-quinazoline and [1,2,4]triazolo[5,1-*b*]quinazoline. In the first two cases, the starting compound is a substituted *N*-aminoquinazoline. A series of dihydro[1,2,4]triazolo[5,1-*b*]quinazolones **491** have been prepared by treatment of 3-arylamino-2-anilinoquinazolones **490** with aromatic aldehydes [<1997BCJ2209>](#). The yields in most cases were excellent (75–85%). A closely related pathway to the same products was also reported by an Egyptian team a few years later [<2001M1063>](#).



Scheme 63

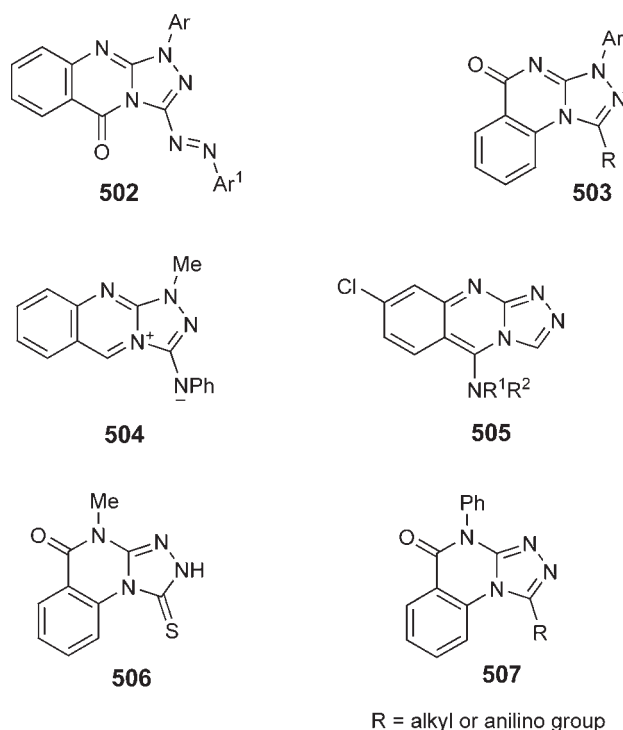
Ding *et al.* published a synthetic route to the related fully conjugated linearly fused triazoloquinazoline **493** [<2004EJO3872>](#). The synthesis started from the phosphorane **492**; treatment of this compound with arylisocyanates (via the formation of a carbodiimide side-chain intermediate) gives rise to product **493** in excellent yield.

An efficient pathway to 3,8-dihydro derivatives of the same ring system **496** was published by Lee *et al.* [<1994S1057, 1997S1461>](#): the ureido ethylidenehydrazones of type **494** were treated with triphenylphosphine in the presence of triethylamine in a carbon tetrachloride solution under refluxing conditions to yield the product **496** in acceptable yields. The transformation was rationalized to proceed via the zwitterionic intermediate **495**. It is important to note that, in the cases of $\text{R} = \text{aryl}$ group, the reaction proceeded in a totally different direction to furnish

some unusual guanidine derivatives rather than cyclic products. Saleh *et al.* described [2003JHC973](#) the formation of *N*-amino[1,2,4]triazolo[5,1-*b*]quinazolones [498](#). The synthesis was carried out by treatment of [497](#) with hydrazine hydrate under refluxing conditions to yield [498](#) in high yields.

Synthetic routes to the linearly fused [499](#) [2003KGS1383](#) as well as the angularly fused [500](#) [2005ZOR115](#) and [501](#) [2005ZOR1092](#) have also been described ([Scheme 63](#)).

Finally, structures of some new angularly fused [1,2,4]triazolo[4,3-*a*]quinazoles and linearly fused [1,2,4]triazolo[3,4-*b*]quinazoles are summarized in [Scheme 64](#). All of these derivatives were synthesized by methods described earlier for the nonbenzologous analogues. Thus, the azo compound [502](#) [2005JCM285](#) and the angularly fused [503](#) [1995H\(41\)1999](#) were obtained by transformation of 2-mercaptoquinazoles by reaction with hydrazonoyl halides by analogy with transformation of the mercaptopyrimidine derivative [475](#), and the reaction followed the ‘Smiles-rearrangement’ pathway to yield the triazoles. In the cases of derivatives [504](#) [1999J\(P1\)1517](#), [505](#) [1996MI585](#), [506](#) [1999FA486](#), [2005BML1877](#), and [507](#) [2001MOL557](#), a more general approach of transformation of hydrazinoquinazoles (by methods used for pyrimidine derivatives), shown in [Table 23](#), has been applied.

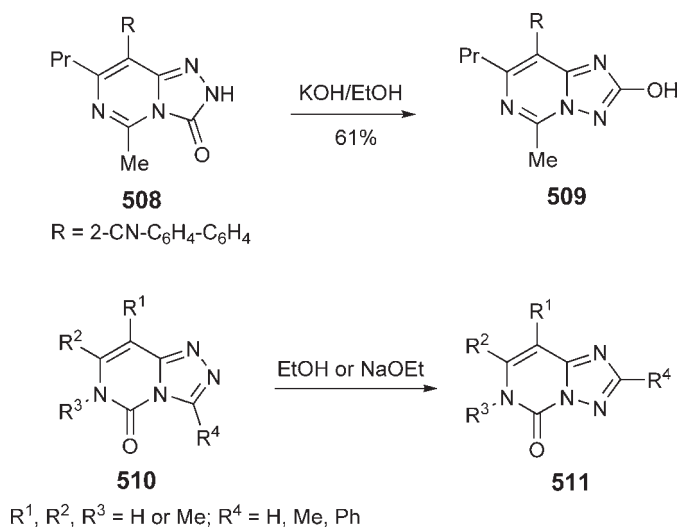


Scheme 64

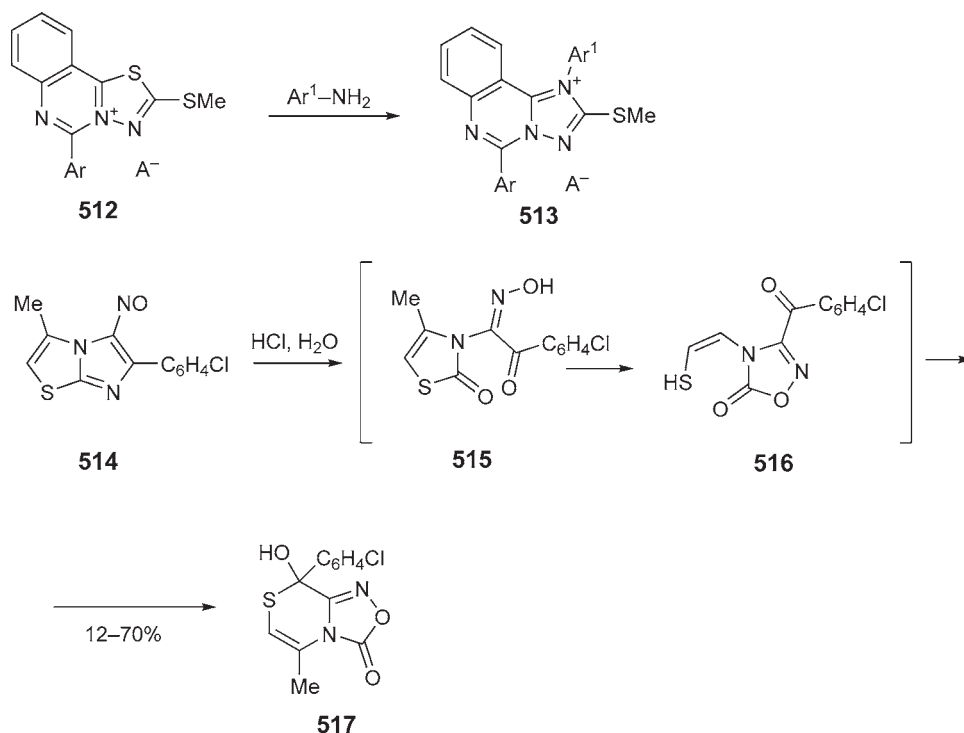
11.16.7 Ring Synthesis from Another Ring

The best known and documented ring transformation to fused [1,2,4]triazoles is the Dimroth rearrangement in which a 3,4-fused tetrazole undergoes temporary ring opening which is followed by a ring closure to the isomeric 1,5-fused tetrazole ring (for more detailed discussion, see [Section 11.16.5.2](#): transformation of [124](#) to [126](#)). Two such recent cases are shown in [Scheme 65](#). Both transformations of [508](#) to [509](#) [1996JHC1307](#) and [510](#) to [511](#) [2002H\(57\)631](#) took place in the presence of a base. In the latter case, even milder conditions (solvolysis in ethanol), proved to be enough for the success of the reaction. Some other transformations utilizing the Dimroth rearrangement were discussed above in the ‘Reactivity’ section ([Section 11.16.5.2](#)).

Other ring transformations to the ring systems of this chapter have also been published. These syntheses are depicted in [Scheme 66](#).



Scheme 65



Scheme 66

Transformation of the fused thiadiazole **512** to the triazole **513** follows a quite general ring-transformation route [<2003HAC581>](#): the aniline as a nucleophilic reagent attacks the fused cation at the bridgehead carbon atom adjacent to the positively charged nitrogen atom resulting in a ring opening and, then, a ring closure occurs with participation of the nitrogen atom of the reagent and hydrogen sulfide is eliminated.

A much more complicated pathway was described by an Italian team [<1997J\(P2\)2407, 1999T5433, 2000JHC875>](#) involving transformation of the imidazothiazole **514** to the oxadiazolothiazine **517** which takes place upon treatment

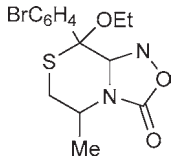
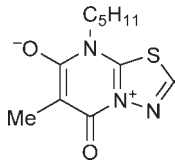
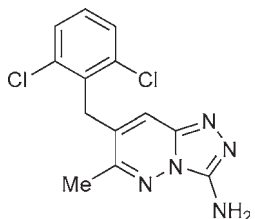
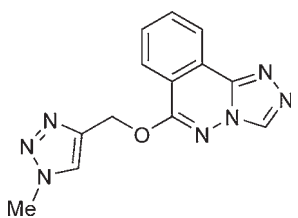
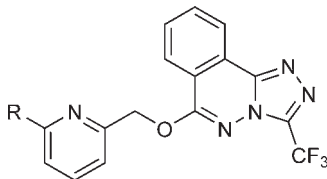
with aqueous acid. The first step here is the acidic ring opening of the imidazole ring to **515**; this step is followed by the formation of an oxadiazole ring to give intermediate **516** and, finally, addition of the mercapto sulfur atom on the carbonyl carbon atom bearing the aryl substituent occurs as a ring-chain tautomerism to yield product **517**.

A further ring transformation (formation of **140** from **138**) was discussed in Section 11.16.5.2.

11.16.8 Important Compounds and Applications

Among the derivatives of ring systems belonging to this chapter, a great number of compounds exhibited valuable biological activities. In Table 25, the most important structures are listed together with the area of the particular activity and literature references.

Table 25 Various derivatives having biological activities

Entry	Structure	Effect	Reference
1		Selective myocardial calcium channel modulator	2002JME3475, 2005JME2445
2		Platelet aggregation inhibitor	2000BMC1917
3		Anticonvulsant	1998BMC983
4		GABA $\alpha 5$ receptor inverse antagonist as cognition enhancer	2004JME2176
5		High-affinity ligand to the $\alpha 2\delta$ -1 subunit of voltage-gated calcium channel	2004BML2463

(Continued)

Entry	Structure	Effect	Reference
6		Angiotensin II antagonist	1994JME2371, 1996JHC1307
7		Adenosine antagonist	1996JME4142, 1998JME2835
8		A ₁ and A ₃ adenosine receptor antagonist	2005BMC705
9		A _{2A} adenosine receptor antagonist	2003BMC5509
10		Dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes	2005JME141

Novel ring opening reactions of the 1,3-thiazinone moiety of triazolo[5,1-*b*][1,3]thiazines (**13**) have been studied Britsun et al. <2005CHE1334>. The experienced transformations are reminiscent of formation of **81** from **79** (Section 11.16.5.1.1). In the frame of this research activity, ring contraction of the thiazine moiety to a thiazole was also observed by the same team <2005CHE782>.

Stereoselective reduction of some triazolodiazines (derivatives of ring systems **33** and **37**) bearing chiral terpene residues has been elaborated by Groselj *et al.* <2006TA79>. With catalytic hydrogenation, partial saturation of the six-membered ring was experienced, while reaction with borane–methyl sulfide resulted in formation of triazole–boron complexes.

As to the reactivity of derivatives of the ring systems discussed in the present chapter, two recent publications seem worth mentioning.

- Some derivatives of the [1,2,4]triazolo[4,3-*b*]pyridazine ring system **33** were subjected to a special type of nucleophilic substitution called “vicarious nucleophilic substitution” (VSN) <2006TL4259>. In the course of this transformation a formal substitution of az aromatic hydrogen atom – occurring *via* an addition–elimination mechanism – takes place.
- In the case of a [1,2,3]triazolo[1,5-*a*]quinazolone derivative (closely related to **489**) a direct one-step amination has been reported where the cyclic amide moiety is replaced by an amino substituted structural unit <2006OL2425>.

Some novel results in the area of ring closure reactions also appeared. Thus, an indium(III) triflate catalyzed tandem azidation/1,3-dipolar cycloadditions to derivatives of the [1,2,3]triazolo[5,1-*c*]oxazine ring system **4** has been elaborated by Yanai and Taguchi <2005TL8639>. New ring closure to derivatives of the [1,3,4]oxadiazolo[3,2-*a*]pyrimidine ring system **22** has been published <2006T5464>, and a derivative of an oxadiazolopyrazine ring system (closely related to **18** but containing the O and N atoms in the opposite positions) has also been synthesized <2006JHC579>.

New approaches have been found for cyclization to [1,2,3]triazolo[1,5-*a*]pyrimidine (**41**) <2006JHC1563> and [1,2,4]triazolo[1,5-*a*]pyrimidine (**42**) <2005RCB2903>; both ring closure reactions started from the appropriate aminotriazoles. A new method for the synthesis of [1,2,4]triazolo[4,3-*a*]quinoxalines (derivatives of the benzologue of ring system **37**) has also been reported <2006SC1873>.

Some recent publications gave account on recognition of valuable biological effects of derivatives of the present chapter. Thus, some [1,2,4]triazolo[4,3-*b*]pyridazines (derivatives of the ring system **33**) proved to be selective GABA_A $\alpha 2/\alpha 3$ agonists <2005JMC7089>. Furthermore, antiretroviral activity against HIV-1 with cytotoxicity <2006EJM1102> as well as selective human A₃ adenosine receptor antagonist activity <2006JMC3916> has been explored with [1,2,4]triazolo[1,5-*a*]quinoxaline compounds and its nitrogen positional isomers <2006JMC3916> (derivatives of the benzologues of ring systems **36** and **37**).

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Biographical Sketch



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11.18

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 3:1

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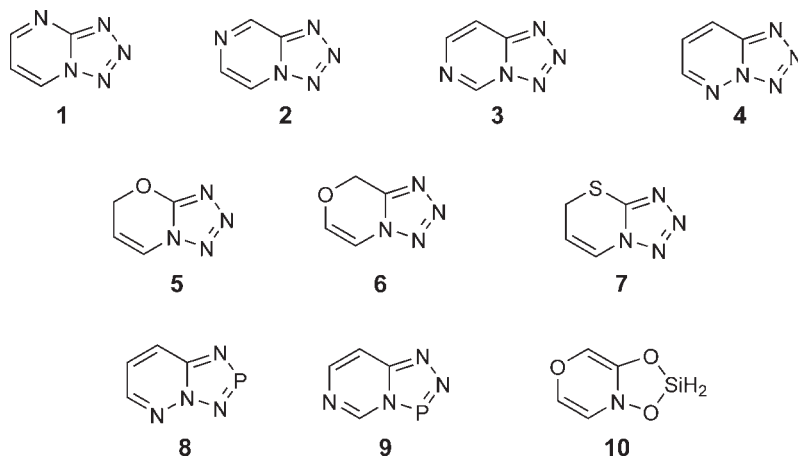
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11.18.1 Introduction

Most of the ring systems belonging to this chapter contain – with three exceptions – fused tetrazole rings. The ring systems discussed are shown in **Scheme 1** and are as follows: tetrazolo[1,5-*a*]pyrimidine **1**, tetrazolo[1,5-*a*]pyrazine **2**, tetrazolo[1,5-*c*]pyrimidine **3**, tetrazolo[1,5-*b*]pyridazine **4**, 7*H*-tetrazolo[5,1-*b*][1,3]oxazine **5**, 8*H*-tetrazolo[1,5-*d*]-[1,4]oxazine **6**, and 7*H*-tetrazolo[5,1-*b*][1,3]thiazine **7**. The outstanding three ring systems involve two fused triazaphospholes: [1,2,4,3]triazaphospholo[1,5-*b*]pyridazine **8**, [1,2,4,3]triazaphospholo[1,5-*f*]pyrimidine **9**, and a ring-closed siloxane derivative, the [1,3,4,2]dioxazasilolo[5,4-*c*][1,4]oxazine ring system **10**. Furthermore, in addition to these bicyclic systems, some of their benzologues have been published also.

This chapter covers the literature from 1995 to the present and updates earlier chapters in this series <1984CHEC(5)880, 1984CHEC(5)860, 1996CHEC-II(8)465>.



Scheme 1

11.18.2 Theoretical Methods

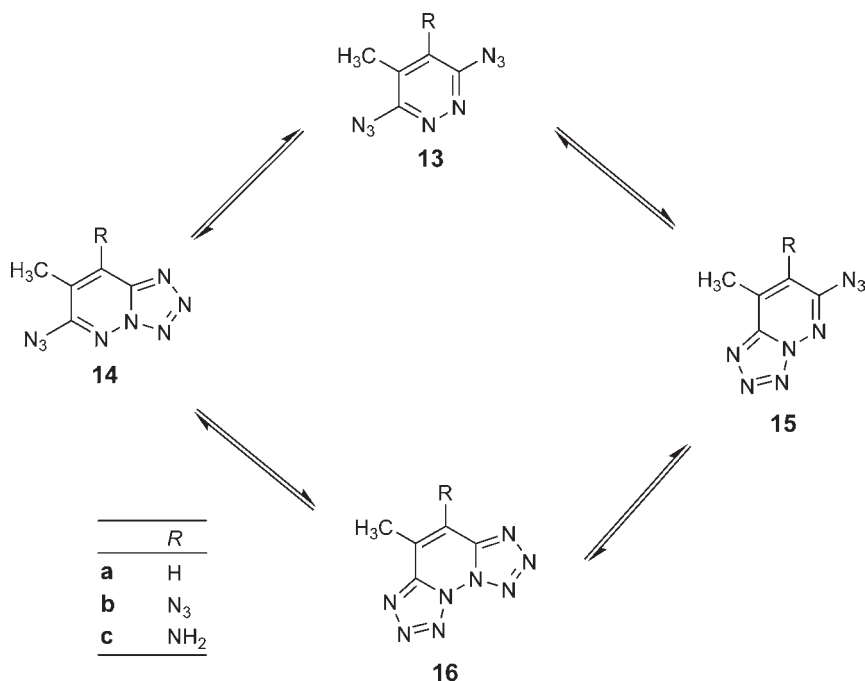
Quantum-chemical calculations (AM1, PM3) have been carried out in order to investigate the thermodynamic behavior of the possible equilibrium between variously substituted 6-azidotetrazolo[1,5-*b*]pyridazine **11** and the bis-tetrazole **12** <2005JST65> (Scheme 2). From the calculated heat of formation, the authors concluded that this value is consistently lower for the azide tautomers **11** than for the corresponding tetrazoles **12** on average by 20 kcal mol⁻¹ and, thus, the azide isomers— in full accordance with the experimental observations – are more stable than the ring-closed fused tetrazoles.



Scheme 2

Also, quantum-chemical calculations have been carried out for assessment of the relative energies of the different open-chained and ring-closed forms of 3,6-diazo-5-methylpyridazines **13a–c** (Scheme 3) <2004OBC1782>.

Because of the presence of two azide groups in positions adjacent to the ring nitrogen atoms in compound **13a**, valence bond isomerization can result in formation of 6-azido-7-methyltetrazolo[1,5-*b*]pyridazine **14a**, 6-azido-8-methyltetrazolo[1,5-*b*]pyridazine **15a**, and the bis-tetrazole compound **16a**. Calculations have been carried out by using hybrid density functional theory (B3LYP/6-311+G(d,p)) and complete basis set treatments (CBS-4M). All calculations revealed that the 8-methyl derivative **15a** is the most stable isomer. Similar studies on the triazide derivative **13b**, however, indicated that in this case the equilibrium is shifted to the 7-methyl form **14b**. All these conclusions proved to be in entire agreement with the experimental findings (see Section 11.18.3.2.).



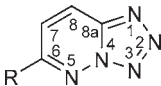
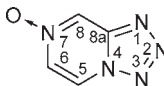
Scheme 3

11.18.3 Experimental Structural Methods

11.18.3.1 NMR Structure Elucidations

Thorough nuclear magnetic resonance (NMR) investigations of some tetrazolo[1,5-*b*]pyridazines and tetrazolo[1,5-*a*]pyrazine-7-oxides have been carried out by Cmoch *et al.* <1999MRC493, 2003MRC693>. Comparison of ¹³C and ¹⁵N NMR chemical shifts of the ring atoms are shown in Table 1.

Table 1 Comparison of ¹³C and ¹⁵N NMR shifts of the ring atoms of some tetrazolo[1,5-*b*]pyridazines and tetrazolo[1,5-*a*]pyrazine-7-oxides

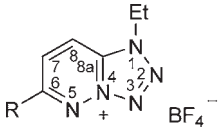
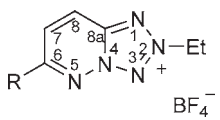
			
	<i>R</i> = <i>H</i>	<i>R</i> = <i>Cl</i>	<i>R</i> = <i>OCH</i> ₃
C-5			134.1
C-6	148.4	151.4	143.3
C-7	125.9	127.3	140.2
C-8	125.6	128.2	125.3
C-8a	143.2	142.6	141.9
N-1	−64.2	−63.1	<i>a</i>
N-2	+14.5	<i>a</i>	<i>a</i>
N-3	−25.6	<i>a</i>	<i>a</i>
N-4	−99.9	−101.6	−104.7
N-5	−68.9	−82.5	−80.7

DMSO solution.

^aNot detected in long-range ¹⁵N-¹H-correlation.

The same authors also investigated the NMR spectroscopic properties of 1- and 2-alkylated tetrazolo[1,5-*b*]-pyridazinium salts <2002MRC507> and concluded that the site of alkylation can be accurately determined from the ^{15}N NMR chemical shifts of these compounds. The obtained chemical shifts with these salts are summarized in Table 2.

Table 2 Compilation of ^{13}C and ^{15}N NMR shifts of some 1- and 2-alkylated tetrazolo[1,5-*b*]pyridazinium salts

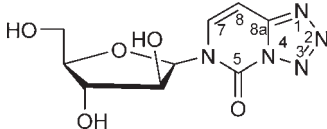
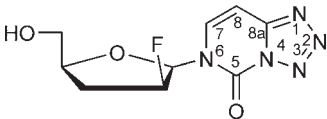
						
	$R = \text{Cl}$	$R = \text{N}_3$	$R = \text{NPPH}_3$	$R = \text{Cl}$	$R = \text{N}_3$	$R = \text{NPPH}_3$
C-6	156.6	159.5	155.8	159.0	161.2	157.4
C-7	136.1	129.0	128.9	134.1	127.2	127.1
C-8	124.4	124.2	123.5	128.7	128.3	127.8
C-8a	139.0	138.3	137.2	146.7	146.1	145.0
N-1	-150.2	-150.6	-150.8	-74.5	-75.2	-75.8
N-2	-16.2	-18.4	-19.0	-86.3	-90.2	-81.4
N-3	a	a	a	-35.1	-37.4	-37.6
N-4	-79.6	-109.1	-117.1	-82.5	-110.1	-112.3
N-5	-103.7	-107.0	-109.2	-107.2	-112.3	a

DMSO solution.

^aNot detected in long-range ^{15}N - ^1H correlation.

NMR investigations of some carbohydrate-substituted tetrazolo[1,5-*c*]pyrimidin-5(6*H*)ones as nucleotide analogues have been studied by Chu *et al.* <1997JOC7267>. The ^1H and ^{13}C chemical shifts of these derivatives are shown in Table 3.

Table 3 ^1H and ^{13}C chemical shifts of some carbohydrate-substituted tetrazolo[1,5-*c*]pyrimidin-5(6*H*)ones

				
H-7	8.0		8.11	
H-8	7.1		7.18	
C-5	151.5		151.6	
C-7	137.2		136.8	
C-8	75.4		93.0	
C-8a	143.0		143.1	

11.18.3.2 X-Ray Studies

In some cases, X-ray studies of derivatives of ring systems belonging to this chapter have been investigated. Thus, X-ray structure elucidation of the two carbohydrate-substituted tetrazolo[1,5-*c*]pyrimidin-5(6*H*)ones depicted in Table 3 have been carried out <1997JOC7267>. Similarly, X-ray diffraction studies have been carried out on 6-azido- and 6-amino-7-methyltetrazolo[1,5-*b*]pyridazine **14b** and **14c**, respectively (Scheme 3) <2004OBC1782>. The determined structures were found to be in agreement with theoretical assumptions. The authors concluded that – similarly to earlier observations – the fusion of the tetrazole moiety resulted in a strong deformation of the pyridazine ring.

11.18.4 Thermodynamic Aspects

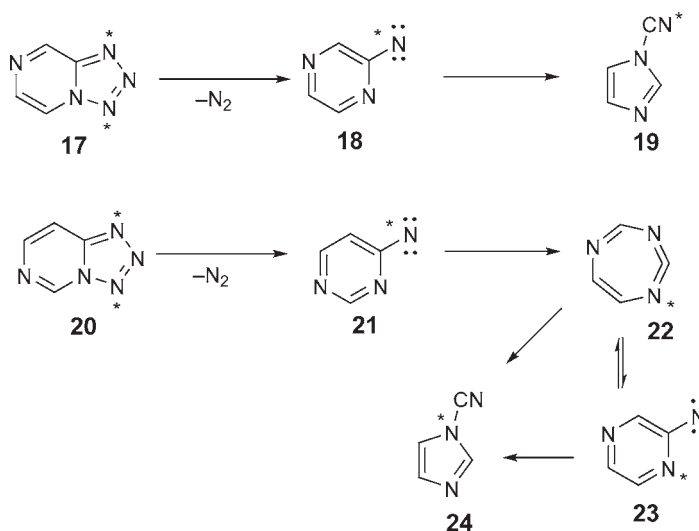
Since the publication of some results on this subject as reviewed in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)860, 1996CHEC-II(8)465>, no new results have appeared during the recent period of time.

11.18.5 Reactivity of Fully Conjugated and Nonconjugated Rings

11.18.5.1 Ring Transformations

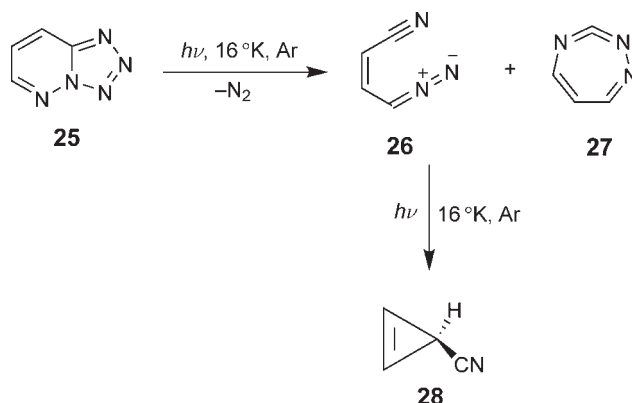
Wentrup and co-workers have carried out systematic flash vacuum thermolysis studies with a series of fused tetrazoles. Investigations of the isomeric tetrazolo[1,5-*a*]pyrazine **17** and tetrazolo[1,5-*c*]pyrimidine **20** showed that, in both cases, ring contraction takes place to afford imidazoles in high yields, but isotope labeling experiments revealed that the mechanisms of the openings of the two ring systems are different <2002JOC8538>.

Scheme 4 shows that both doubly ^{15}N -labeled tetrazoles **17** and **20** undergo first N_2 elimination in which one of the isotope nitrogen atom will be removed and, thus, the intermediate nitrenes **18** and **21**, respectively, contain the remaining ^{15}N atom in the *exo*-position. While nitrene **18** undergoes rapid ring contraction to a C^{15}N -substituted imidazole **19**, reaction of nitrene **21** is much more complicated. This intermediate is transformed first to the triazacyclohepta-1,2,4,6-tetraene compound **22**, which either directly or via a next nitrene intermediate **23** can result in the ring contraction to **24** containing the ^{15}N atom in the ring nitrogen position.



Scheme 4

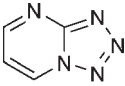
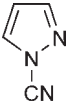
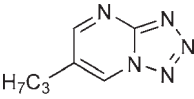
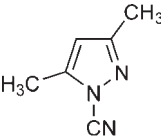
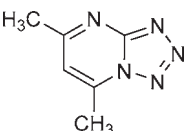
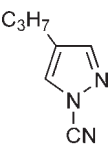
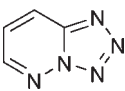
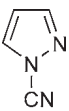
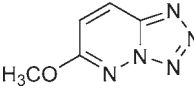
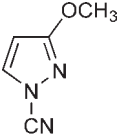
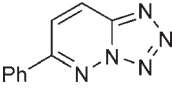
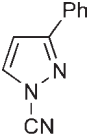
Matrix isolation photolytic studies on tetrazolo[1,5-*b*]pyridazine **25** have been reported by Hill and Platz <2003PCP1051> (**Scheme 5**) and formation of the 1-cyano-3-diazopropene **27**, triazacycloheptatetraene **28**, and cyano-cyclopropene **29** was detected. Upon the absence of electron spin resonance absorptions at 7 K, the authors concluded that triplet nitrene was not formed but, instead, the resulting singlet nitrene rapidly underwent further ring openings.



Scheme 5

Ring contraction of fused tetrazoles to *N*-cyanopyrazoles under thermal conditions has been elaborated by Simoni *et al.* <2000TL2699>. The results are compiled in Table 4.

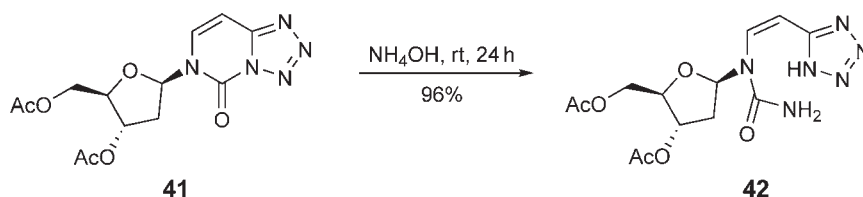
Table 4 Thermolysis of fused tetrazoles to *N*-cyanopyrazoles

<i>Fused tetrazole</i>	<i>Temperature of thermolysis (°C)</i>	<i>Product</i>	<i>Yield (%)</i>
 29	120–140	 35	66
 30	200–220	 36	86
 31	150–170	 37	60
 32	150–170	 38	70
 33	80–100	 39	78
 34	210–230	 40	55

Thus, unsubstituted, 6-propyl- and 5,7-dimethyl tetrazolo[1,5-*a*]pyrimidines **29**, **30**, and **31**, respectively, as well as unsubstituted 6-methoxy- and 6-phenyltetrazolo[1,5-*b*]pyridazines **32–34**, when heated at ambient temperature (close to their melting points), gave rise to the correspondingly substituted *N*-cyanopyrazoles **35–40** in medium to good yields.

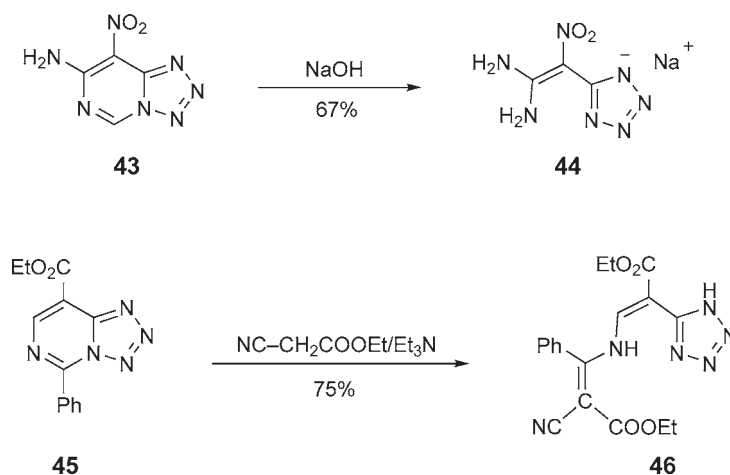
11.18.5.2 Ring Openings

A recent publication <2005JOC1961> disclosed that tetrazolo[1,5-*c*]pyrimidine derivatives obtained by ring closure of 4-azido-2-pyrimidinone nucleosides participate in hydrolytic ring opening under basic conditions (Scheme 6). As a result, the pyrimidine ring of compound **41** undergoes ring cleavage in the presence of ammonium hydroxide and the substituted open chain *N*-vinylurea **42** is formed.



Scheme 6

In two other cases, the ring opening of the pyrimidine moiety of the same ring system has also been observed, and both proceed under basic conditions. These results are shown in [Scheme 7](#). Makarov *et al.* reported that treatment of 7-amino-8-nitrotetrazolo[1,5-*c*]pyrimidine **43** with aqueous base results in the opening of the pyrimidine ring to give the vinyltetrazole **44** in the form of a sodium salt [<1994KGS976>](#). Ring opening of the pyrimidine ring of the derivative **45** was observed by Krivopalov and co-workers [<1998IZV1453>](#). This compound was reacted with ethyl cyanoacetate in the presence of triethylamine to give the tetrazole derivative **46** bearing an unsaturated side chain in good yield.



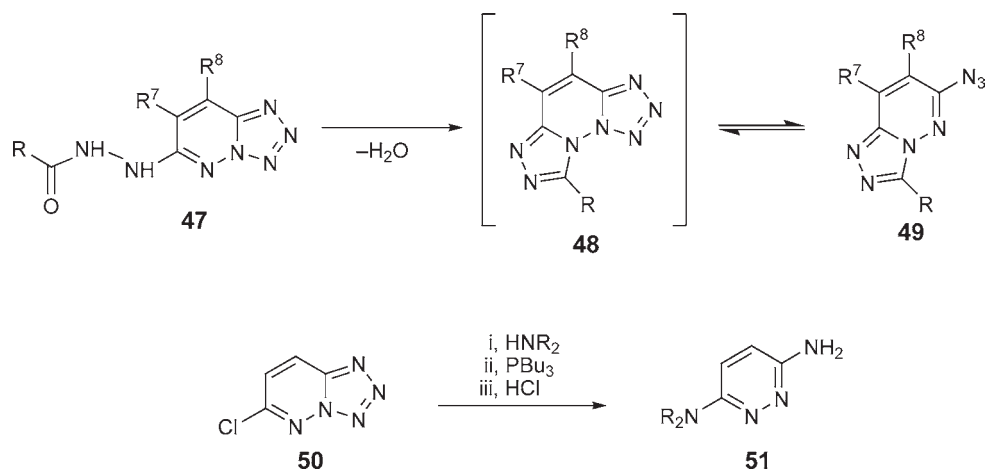
Scheme 7

Ring opening of the five-membered tetrazole ring has also been observed in several cases. The most trivial conversion is the equilibrium between the fused tetrazole and azidodiazine which, in principle, could take place with every fused tetrazole compound described in this chapter, and, therefore, no special comment on this type of ring opening needs to be discussed.

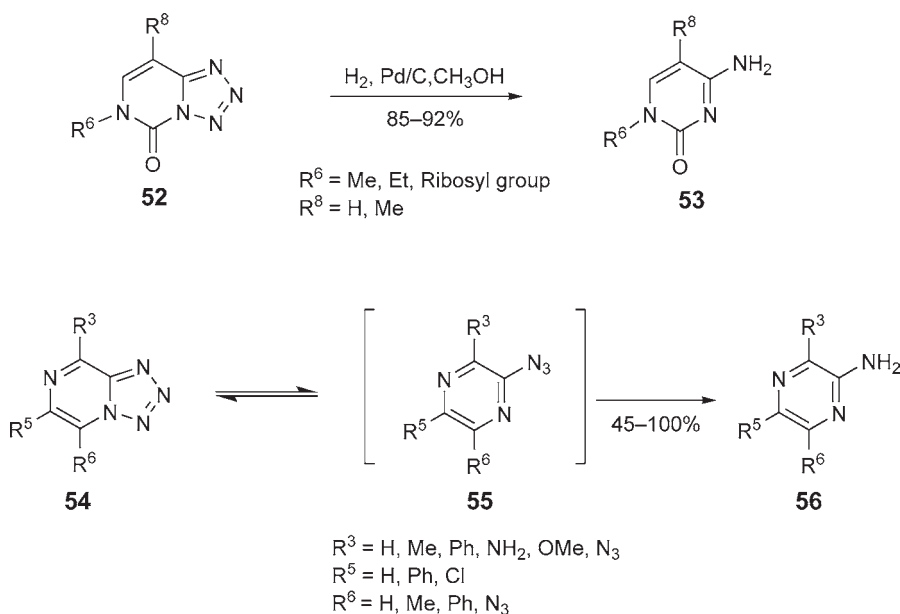
One outstanding case which is still worth mentioning is shown in [Scheme 8](#). Katrusiak *et al.* [<2005JST65>](#) investigated the ring-closure possibilities to some [1,2,4]triazole-fused pyridazines. Thus, the hydrazide **47** was treated with formic acid to form the desired triazole ring. Upon formation of the new triazole moiety, however, the tricyclic product **48** underwent ring opening at the tetrazole site and the azido compound **49** was isolated from the reaction mixture.

Some reductive ring openings of fused tetrazoles belonging to this chapter have also been described. Thus, 6-chlorotetrazolo[1,5-*b*]pyridazine **50** ([Scheme 8](#)) proved to be suitable starting material for the synthesis of 3,6-diaminopyridazines [<2005JA1719>](#). Although such pyridazine derivatives have been known before, Gong and Krische found that their synthesis from **50** by treatment with an amine is followed by application of the Staudinger reaction and, then, acidic hydrolysis proved to be more convenient. By this procedure, various 6-substituted 3-aminopyridazines **51** have been obtained.

Another study also aimed at the synthesis of aminoazines from fused tetrazoles: Golankiewicz and co-workers found that transformation of tetrazolo[1,5-*c*]pyrimidin-5(6*H*)ones **52** to 4-aminopyrimidin-2(1*H*)ones **53** ([Scheme 9](#)) can conveniently be carried out by catalytic hydrogenation in methanol in high yields (85–92%) [<1995S777>](#). This preparative method proved to be superior to other established procedures: the use of sodium borohydride gave mixture of products, whereas the Staudinger reaction by using triphenylphosphine yielded stable phosphinimines which could be decomposed to the desired amines only under forcing conditions.



Scheme 8

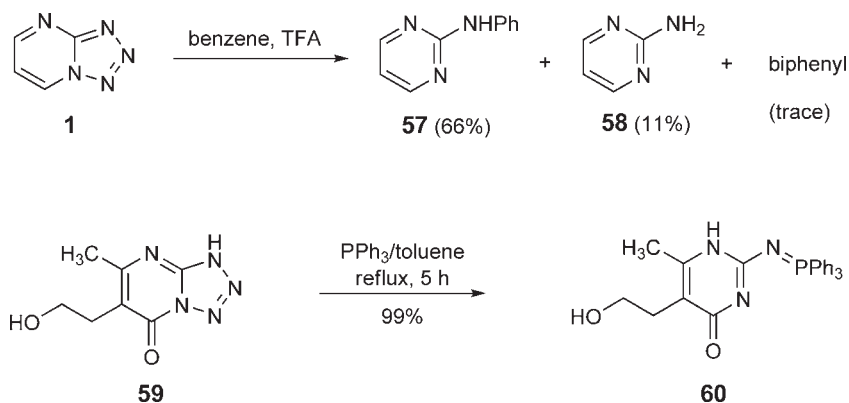


Scheme 9

Sato *et al.* carried out detailed studies on the possibilities of transformation of tetrazolo[1,5-*a*]pyrazines **54** to 2-aminopyrazines **56** <1994S931>. These authors found that the generally used methods for this conversion fail because the starting compound exists in the stable bicyclic form **54**, whereas partial formation of the azide valence bond isomer **55** would be necessary for the success of the transformation. Application of special reaction conditions succeeded, however: hydrogenation over palladium catalyst in the presence of ammonium hydroxide or treatment with stannous chloride in a mixture of methanol and hydrochloric acid solved this problem. Thus, a great number of derivatives of **54** was reduced to the corresponding 2-aminopyrazine **56** in medium to high yields (45–100%).

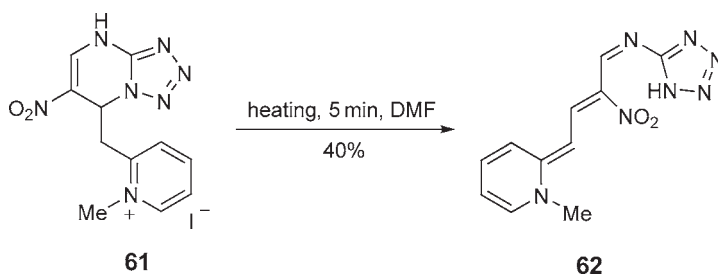
Irradiation of tetrazolo[1,5-*a*]pyrimidine **1** in benzene in the presence of trifluoroacetic acid was investigated by Takeuchi and Watanabe <1998JPO478> (Scheme 10). Formation of 2-anilinopyrimidine **57**, 2-aminopyrimidine **58**, and biphenyl was observed. The authors assumed that **57** was formed via a singlet nitrene, whereas formation of the other products may result from the triplet nitrene intermediate. In contrast to this early assumption, Hill and Platz <2003PCP1051> exclude the formation of a triplet nitrene upon spectroscopic evidence as discussed in Section 11.18.5.1.

Ring opening of the oxo derivative of the tetrazolo[1,5-*a*]pyrimidine ring system has also been reported <1996JHC229>. Treatment of the 6-hydroxyethyl-7-methyl substituted compound **59** with triphenylphosphine gave the phosphinimine derivative **60** in nearly quantitative yield (Scheme 10).



Scheme 10

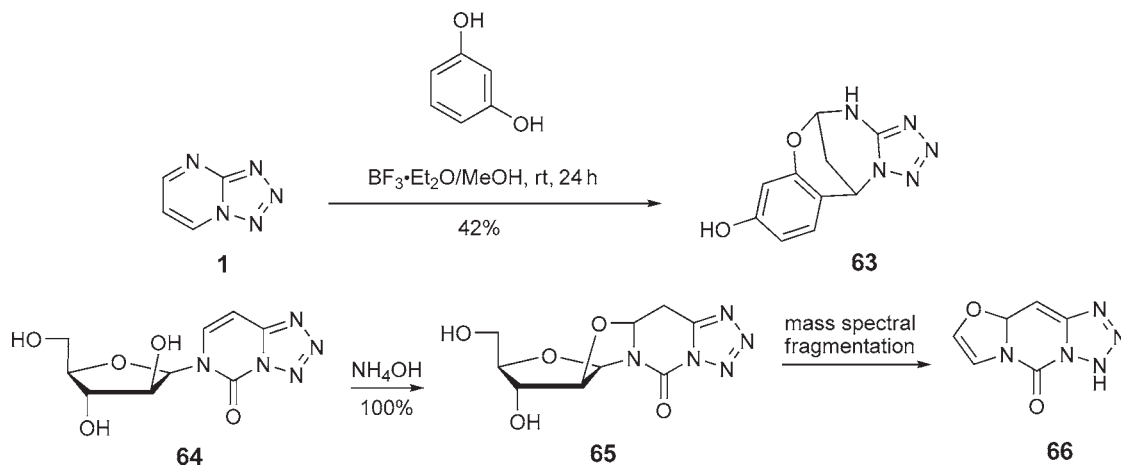
A ring opening taking place on simple heating has been observed by Chupakhin and co-workers [<1998ZOR290>](#) (Scheme 11). These authors found that the quaternary salt **61**, when heated in dimethylformamide (DMF) for 5 min, undergoes N–C cleavage, and the tetrazolylazatriene **62** is formed in medium yield.



Scheme 11

11.18.5.3 Cyclizations

Chupakhin and co-workers [<1999IZV1573>](#) reported the formation of a bridged polycycle starting from tetrazolo[1,5-*a*]pyrimidine **1** (Scheme 12): this compound was treated with resorcinol in the presence of boron trifluoride etherate at room temperature to yield a 1,3-addition product on the pyrimidine ring **63** with participation of one oxygen atom and a ring carbon atom of the reagent.

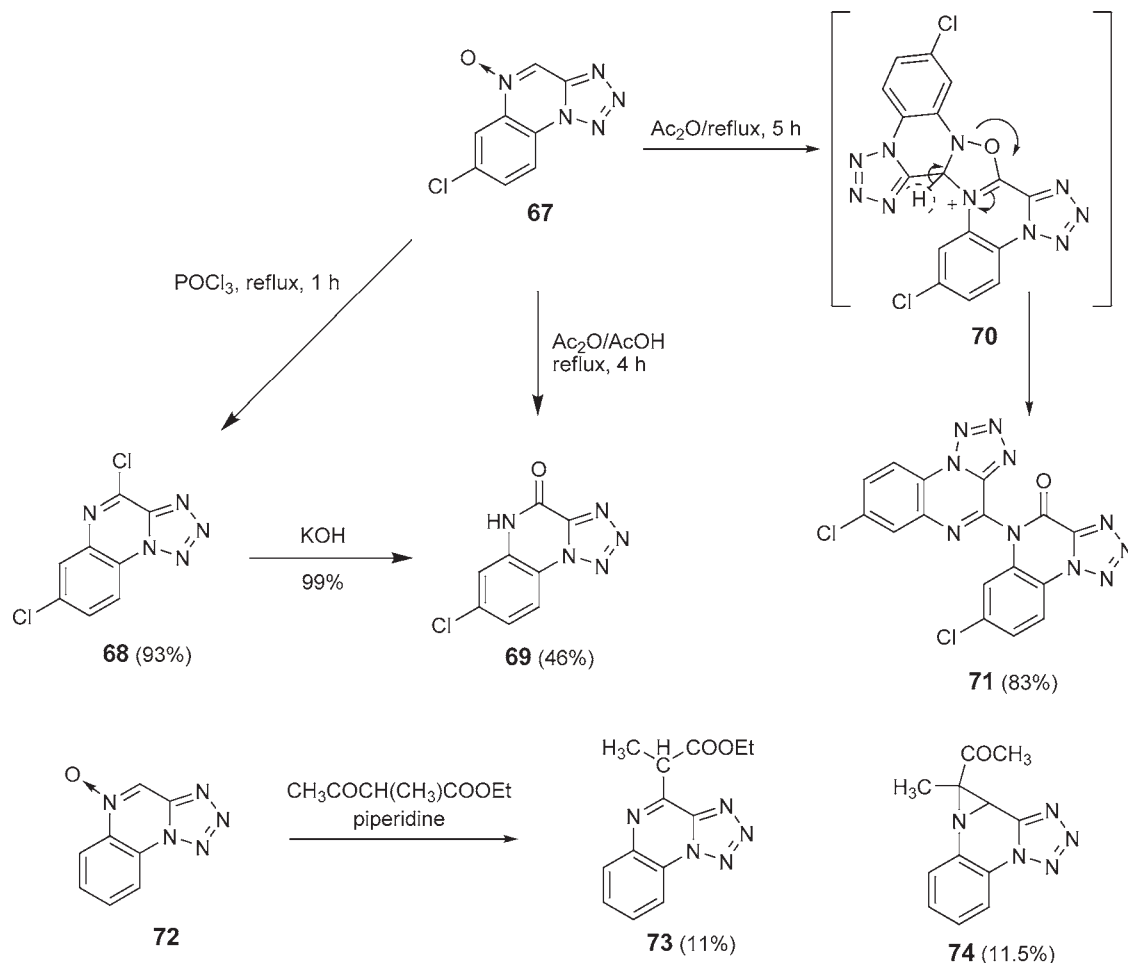


Scheme 12

An intramolecular cyclization of a tetrazole-containing nucleoside **64** has been observed by Chu and co-workers <1997JOC7267> (cf. other properties of this compound in Table 3). These authors reported that the 3-OH group on the arabinofuranose ring participates in an addition reaction at position 7 of the tetrazolo[1,5-*c*]pyrimidine ring to form **65** which is a dihydro derivative of the parent heterocycle. The final structure elucidation has been carried out with the help of the tricyclic tandem mass spectrometry (MS/MS) fragment **66**.

11.18.5.4 Miscellaneous Transformations

Transformations of the *N*-oxide derivative of the fused tetrazolo[1,5-*a*]quinoxaline **67** have been investigated by Kurasawa *et al.* <1994JHC1697>. The results are shown in Scheme 13.

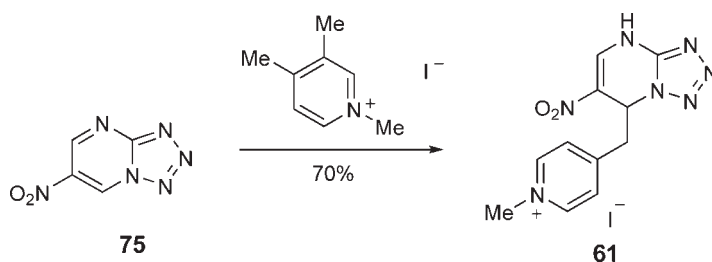


Scheme 13

The starting *N*-oxide compound **67** was found to undergo two types of transformation when treated with acetic anhydride. Thus, when a mixture of acetic anhydride and acetic acid was applied, formation of the fused quinoxalinone **69** was observed. The same compound **69** could also be prepared by an alternative route: transformation by phosphorus oxychloride gave the chlorinated product **68**, which was hydrolyzed by potassium hydroxide to give **68**. When **67** was, however, treated solely with acetic anhydride under similar reaction conditions as before (5 h, reflux), formation of the dimer **71** was experienced. The authors suggest upon mechanistic considerations that the first step is the acetylation of the *N*-oxide function followed by a nucleophilic addition of the free *N*-oxide oxygen atom of another molecule. This can lead to the formation to a positively charged cyclic intermediate **70** which can undergo deprotonation with the help of acetate anion. Finally, shifts of electron pairs as shown on the structural formula **70** leads to the final product.

Another transformation of the same *N*-oxide system was studied by a Czech group <1994CCC2493> (Scheme 13): the unsubstituted *N*-oxide compound **72** was treated with 2-methyl-substituted acetoacetic ester in the presence of piperidine. Similar to the previous example (i.e., formation of **69**), a nucleophilic attack at position adjacent to the *N*-oxide function (at position 4) took place simultaneously with removal of the oxygen atom, and the 4-substituted product was obtained, unfortunately only in low yield. This result is particularly interesting in comparison to a related transformation discussed in the previous edition of *Comprehensive Heterocyclic Chemistry*: treatment of **72** with an acetylacetone derivative gave the aziridine **74**. The authors concluded that reaction paths leading to product types **73** and **74** proceed via a common intermediate and in both reactions **72** reacts as a 1,3-dipole with the reagent as a dipolarophile, and the final outcome of the reaction depends on the substituents of the reagents.

An interesting transformation of 6-nitrotetrazolo[1,5-*a*]pyrimidine **75** was reported by Chupakhin and co-workers <1998ZOR290>, as shown in Scheme 14. The compound **75** was reacted with 1,3,4-trimethylpyridinium iodide in acetonitrile under heating to give the 5-substituted dihydro derivative of the parent heterocycle **61**. The reaction can be regarded as a formal 1,4-addition on the pyrimidine ring.



Scheme 14

11.18.6 Reactivity of Substituents Attached to Ring Carbon Atoms

11.18.6.1 Substitutions and Reductions

A limited number of such reactions have been recently published, and the results are compiled in Table 5. The first example is the reduction of azido compound **76** by sodium dithionite to the corresponding amine **77**. Furthermore, some nucleophilic substitutions of the chlorine substituents of heterocycles **78** and **80** have also been reported: these compounds, when reacted with morpholine and *m*-bromoaniline, respectively, furnished the substitution products **79** and **81**.

11.18.6.2 Transformations of the Side Chains

Various research works on more sophisticated transformations of the side chains of the heterocycles belonging to this chapter have been carried out as shown below.

Deeb *et al.* described <2003H(60)1873> a series of transformations of an ester substituent of a tetrazolo[1,5-*b*]pyridazine derivative **82** (Scheme 15).

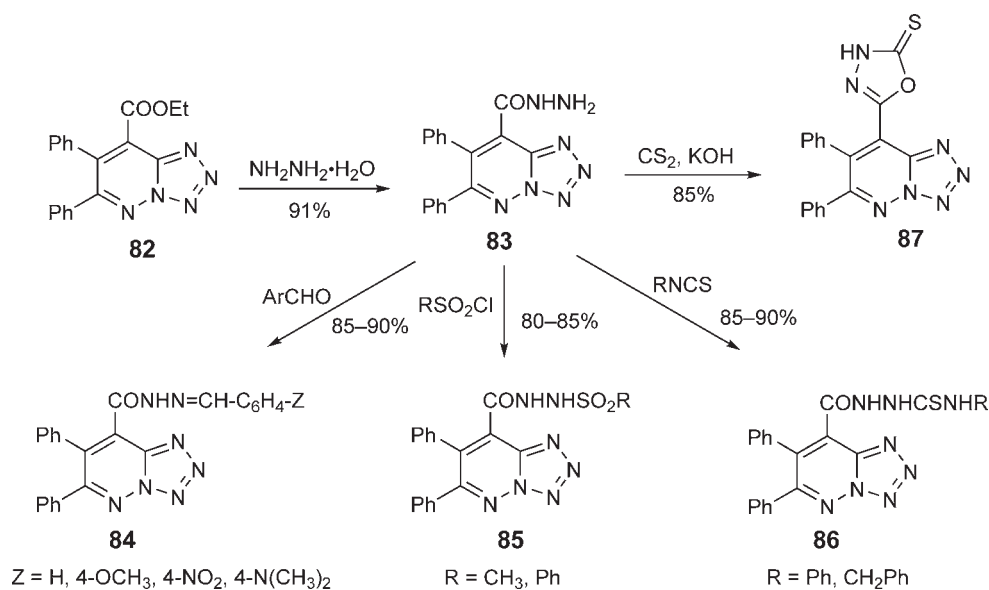
The key intermediate in these transformations was the hydrazide **83** obtained from the ester **82** by simple treatment with hydrazine hydrate. This intermediate was then transformed by aldehydes, sulfonic chlorides, and isothiocyanates to obtain various aryl hydrazones **84**, sulfonylhydrazines **85**, and thiocarbazides **86**.

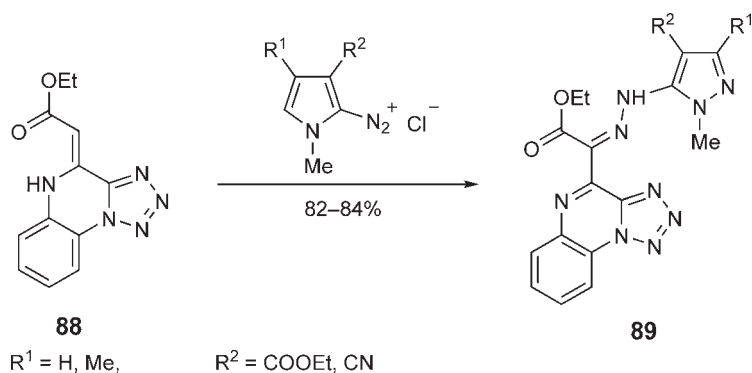
The hydrazide **83** also proved to be suitable for ring-closure reactions on the side chain: its treatment with carbon disulfide yielded an oxadiazolyl-substituted derivative **87** of the parent ring system.

Kurasawa *et al.* carried out some transformations with the α,β -unsaturated ester-containing tetrazolo[1,5-*a*]quinoxaline moiety **88** (Scheme 16) <1994JHC233>. This compound underwent azo couplings with 2-(*N*-methyl)pyrazinyldiazonium salt in the methylene position to yield hydrazones **89** in high yield.

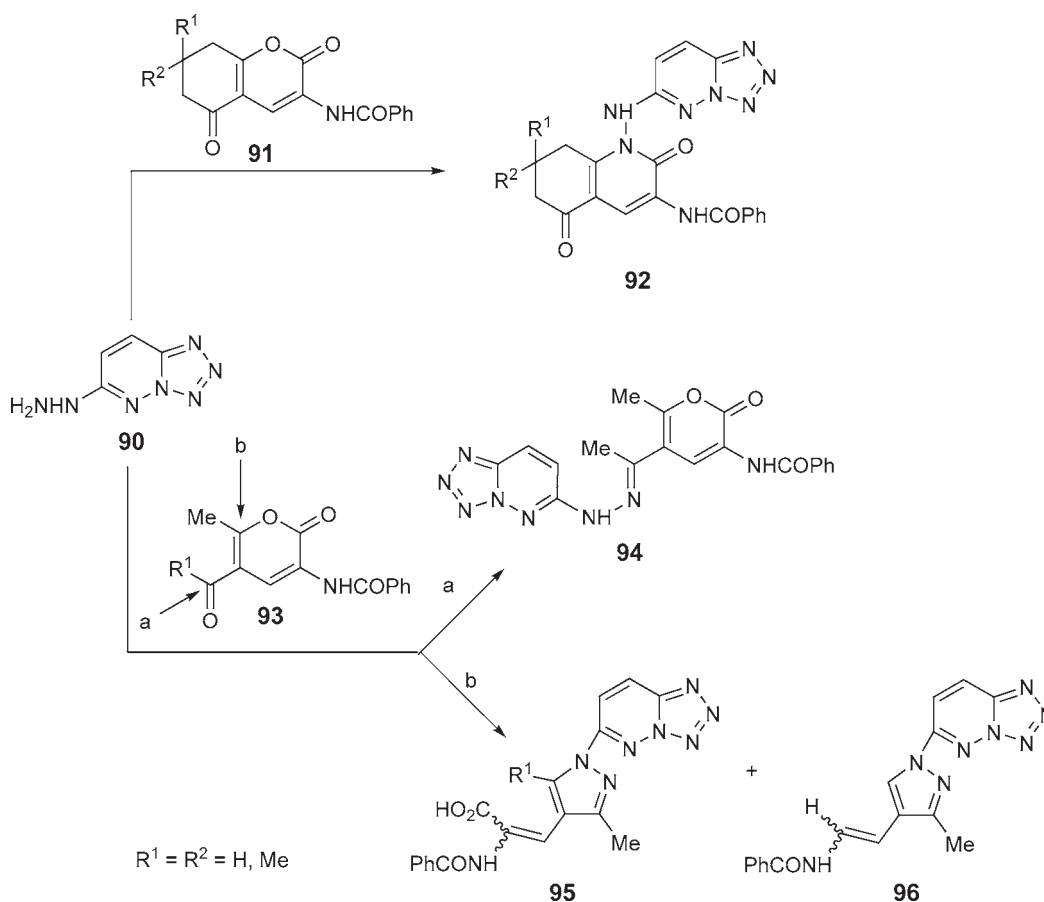
Kocevar and co-workers reported that 6-hydrazinotetrazolo[1,5-*b*]pyridazines **90** are valuable starting compounds for various transformations including some ring transformations as shown in Scheme 17 <1994SL667, 2003H(61)105, 2003H(59)129, 2002J(P1)675>.

Table 5 Reductions and substitution reactions of tetrazolodiazines





Scheme 16



Scheme 17

The hydrazine derivative **90** was reacted with the tetrahydrobenzopyran-dione derivative **91** to result in the ring transformation of the pyrone moiety and, thus, the fused-pyridine compound bearing the tetrazolo[1,5-*b*]pyridazinyldiazole structural unit **92** was obtained. The same hydrazino derivative **90** was also reacted with a 5-acyl-2-pyrone **93**. With this reagent, two types of transformations were observed depending on the site of attack (a or b) on the reagent. In the case of attack on the carbonyl carbon atom (attack a), formation of the hydrazone **94** was experienced, whereas attack b (at the ring carbon atom) led to formation of two isomeric *N*-tetrazolo[1,5-*b*]pyridazinyldiazoles having an olefinic side chain on the pyrazole ring **95** and **96**. This latter transformation obviously takes place via ring opening of the pyrone reagent.

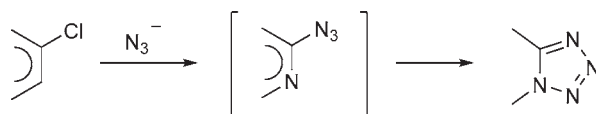
11.18.7 Ring Synthesis from Acyclic Compounds

11.18.7.1 Novel Applications of Established Methods for the Synthesis of Tetrazoloazines

The majority of the syntheses of fused tetrazoles have been realized by using the well-documented azide–tetrazole equilibrium, which has been discussed in detail in CHEC-II(1996) <1996CHEC-II(8)465>. Among these synthetic routes, differentiation can be achieved according to the various modes of accessing of the azidoheterocycles. Basically, two general routes are applied.

Method a. The most frequent approach is the treatment of α -halogenoazines by metal azides. Tetrazoles that have been synthesized recently via this methodology are compiled in Table 6. Inspection of these data reveals that all these transformations proceed in good yields.

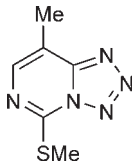
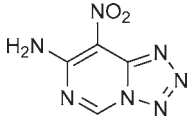
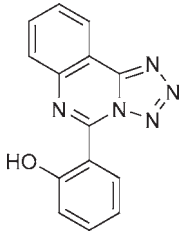
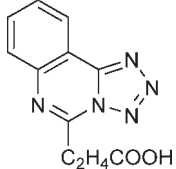
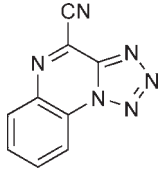
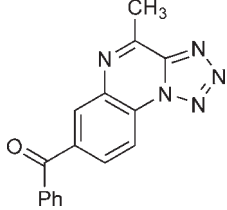
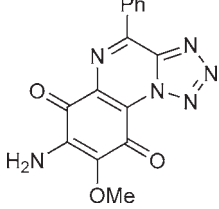
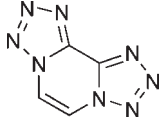
Table 6 Tetrazolopyridazines, -pyrimidines, and -pyrazines prepared by nucleophilic substitution of haloazines by azide anion



Entry	Product	Yield (%)	Reference
1		59	1997JPR20
2		73	2003H1873
3		80	1997IJB75
4		50	1994IJB491
5		68	2001HCO159

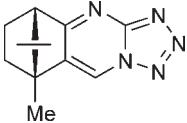
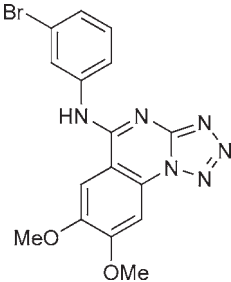
(Continued)

Table 6 (Continued)

Entry	Product	Yield (%)	Reference
6		64	2003PS67
7		69	1994KGS976
8		n.d.	1995IZV1494
9		45	1998IJB303
10		75	1990PHA896
11		60	2000MOL864
12		90	1996JHC447
13		65	1997JOC4082

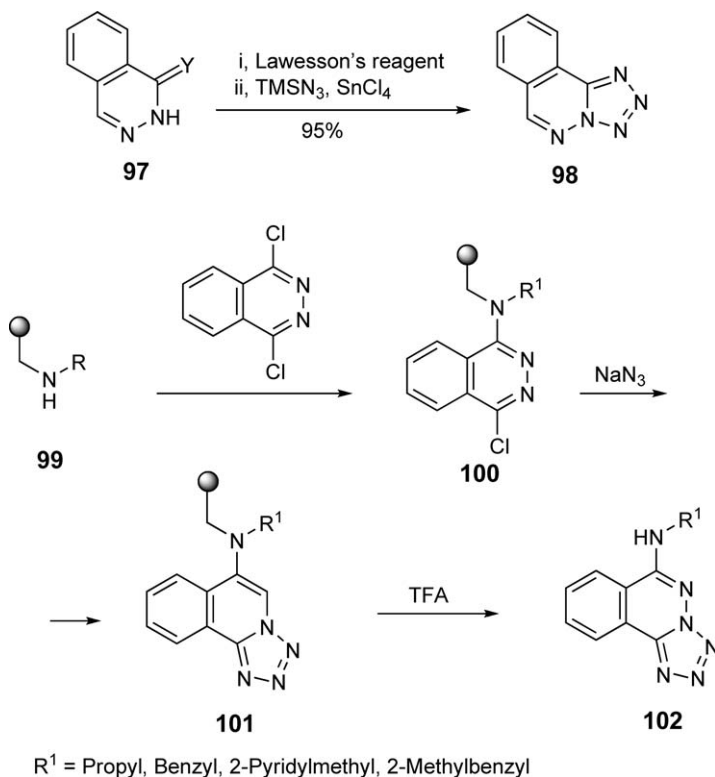
(Continued)

Table 6 (Continued)

Entry	Product	Yield (%)	Reference
14		95	1998JHC325
15		58	1997JHC1375

Method b. Another approach to azides is the treatment of α -hydrazinoazines with nitrous acid, and this procedure is almost as generally used as in the previous route. Recent applications of this methodology are shown in [Table 6](#).

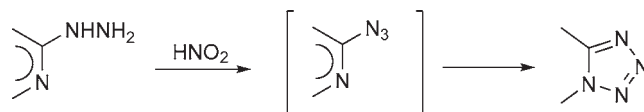
Two interesting modifications of the above methods should be discussed in more detail. These two transformations are shown in [Scheme 18](#).

**Scheme 18**

The first case was reported by Lehnhoff and Ugi [<1995H\(40\)801>](#): the starting compound was phthalazin-1(2*H*)one **97** (Y=O) which was first subjected to transformation with Lawesson's reagent to the corresponding thione **97** (Y=S), and this compound was treated with trimethylsilylazide and stannous tetrachloride to yield tetrazolo[5,1-*a*]phthalazine **98** in 95% yield.

The second special example is a simple treatment of a 1-chlorophthalazine derivative **100** with sodium azide, but the procedure has been elaborated for solid-phase synthetic application [<2005TL3107>](#). Thus, the amine **99** bearing a resin residue was reacted with 1,4-dichlorophthalazine to give, for the desired ring closure, the substrate **100**, which was reacted with sodium azide to give the fused tetrazoles **101**. Finally, cleavage of the resin to give the product **102** was carried out by treatment with trifluoroacetic acid. The purity of the products exceeded 90% in four cases – the yields were good to excellent (65–90%) ([Table 7](#)).

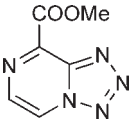
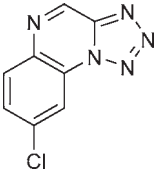
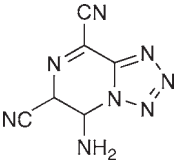
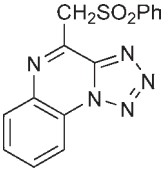
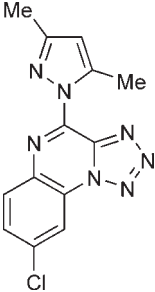
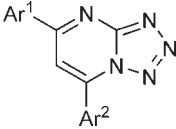
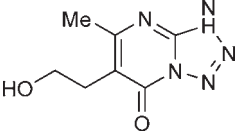
Table 7 Synthesis of fused tetrazoles starting from hidrazinodiazines



Entry	Product	Yield (%)	Reference
1		77	1996PJC1279
2		62–68	2000JHC707
3		55–84	1994JC(M)412
4		78	1997JHC1699 1998IJB651

(Continued)

Table 7 (Continued)

Entry	Product	Yield (%)	Reference
5		68	1996J(P1)247
6		74	2000JHC103
7		53	1994SC1895
8		79	1995PS1
9		74	2000JHC103
10		62–70	2004IJB667
11		85	1996JHC229

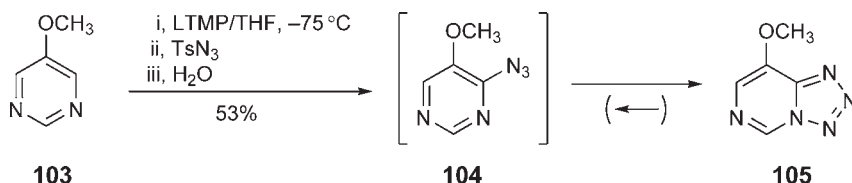
Introduction of the azido group into the azine heterocycle can also be accomplished starting with azine derivatives bearing a five-membered heterocycle as a leaving group in this position. **Table 8** shows three such conversions where the leaving groups are isoxazalone (entry a), imidazole (entry b), and triazole (entry c) substituents.

Table 8 Synthesis of fused tetrazoles starting from azolyldiazines

Entry	Starting compound	Product	Reagent	Yield (%)	Reference
1			LiN ₃ , <i>t</i> -BuOK NaN ₃ , Me(C ₈ H ₁₇) ₃ N ⁺ Cl ⁻	39 95	1995AJC1861 1992AJC2037
2			NaN ₃ , AcOH	59	1997NN993
3			LiN ₃	27	1997JOC7267

11.18.7.2 Synthesis of Tetrazoloazines via Metallation Reaction

Quéguiner and co-workers found that some diazinyldiazides suitable for formation of fused tetrazoles can be obtained via metallation of the diazine ring as shown in [Scheme 19](#) <1996S838>.

**Scheme 19**

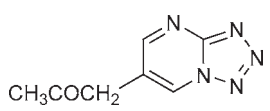
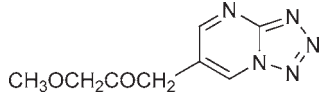
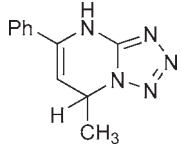
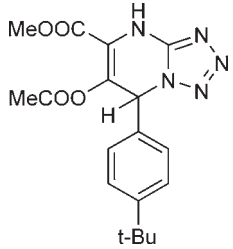
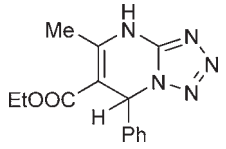
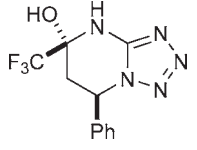
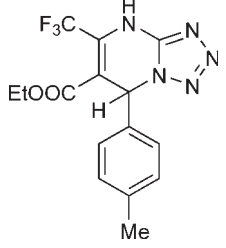
Thus, 5-methoxypyrimidine **103** when treated with lithium tetramethylpiperidide (LTMP) and subsequently by tosyl azide led to formation of the 2-azido derivative **104**, which spontaneously undergoes ring closure to 8-methoxytetrazolo[1,5-*c*]pyrimidine **105**.

11.18.7.3 Synthesis of Tetrazoloazines by Ring Closure of the Six-membered Ring

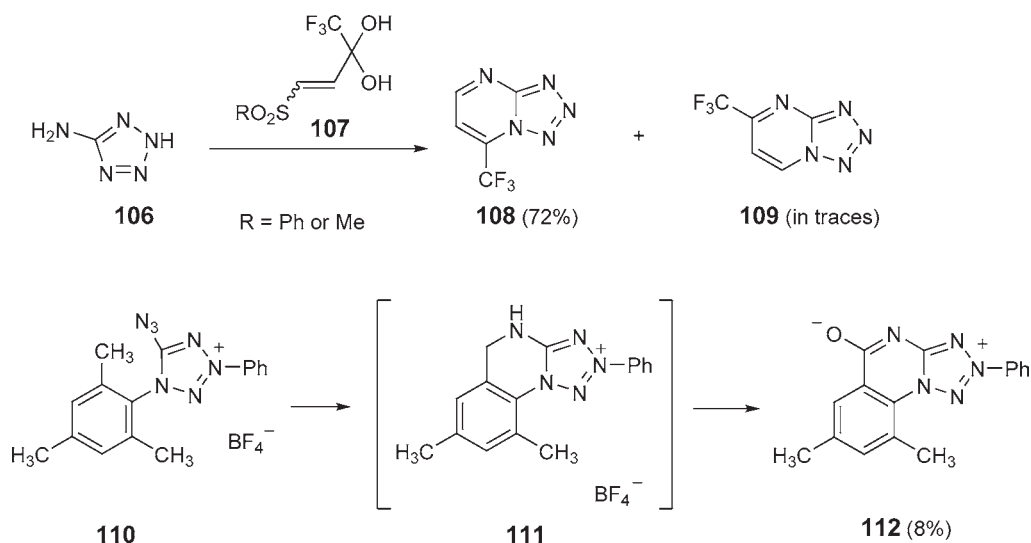
The synthetic pathway to tetrazolo[1,5-*a*]pyrimidines starting from 5-amino-tetrazoles has already been discussed in CHEC-II(1996) <1996CHEC-II(8)465>. During the recent period of time, several modifications of this approach have been described. The obtained products – among them some partly saturated derivatives – and the applied reagents as well as yields and references are summarized in [Table 9](#).

In [Scheme 20](#), another ring closure starting from 5-aminotetrazole is shown, which should be discussed in more detail. Nenajdenko and co-workers carried out studies on ring closure reactions taking place between 1,1,1-trifluoro-4-sulfonyl-but-3-ene-2,2-diols **107** and a series of aminoazoles <2002S901>. They found that the reaction can take place in two different ways and, thus, the isomers **108** and **109** can be formed. Reaction of **107** with 5-aminotetrazole **106** was found to proceed regioselectively, and yielded the 5-trifluoromethyl compound **108** as the main product in good yield (72%). The other isomer **109** was found only in traces.

Table 9 Synthesis of tetrazolo[1,5-*a*]pyrimidines starting from 5-aminotetrazole

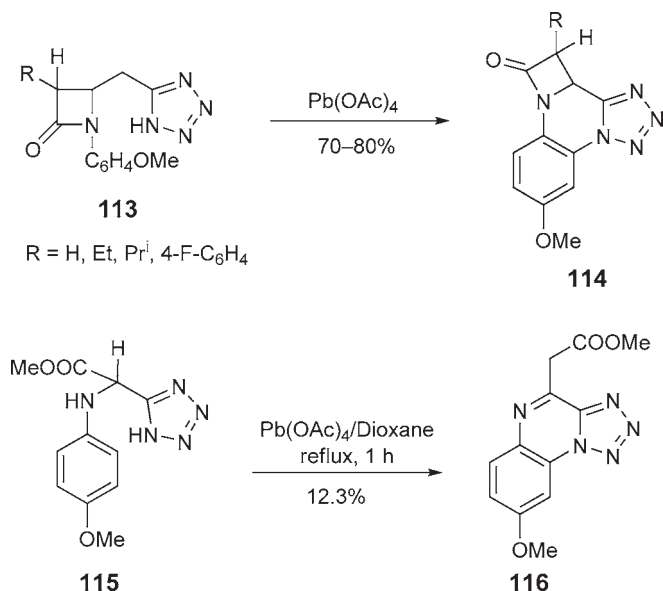
			
Reagent	Product	Yield (%)	Reference
Acetylmalonaldehyde		86	1997IZV1226
3-Hydroxy-2-(3-methoxy-2-oxopropyl)propenal		52	1997KGS807
Crotonophenone		45	2001KGS811
Methyl acetoacrylate + 4- <i>t</i> -Bu ^t -benzaldehyde		35	2003ZOR797
Ethyl acetoacrylate + benzaldehyde		61	2003IZV1677
1-Trifluoromethyl-4-phenylacrolein		72	2004KGS71
Ethyl trifluoroacetoacrylate + 4-Methylbenzaldehyde		40	2004ZOR938

A photolytic study with a 5-azidotetrazole derivative also led to the formation of a tetrazolo[1,5-*a*]quinazoline compound, although the yield was fairly low. Araki *et al.* published findings that irradiation of **110** in aqueous medium resulted in formation of the mesoionic enolate **112** in 8% yield <2000JHC1129> (Scheme 20). The authors concluded that the formation of the tricyclic structure can be rationalized by an intramolecular insertion of the triplet nitrene formed from **110** to a C–H bond of an *ortho*-methyl group to give at first intermediate **111**, which was converted under the applied reaction conditions to produce **112**.



Scheme 20

In the course of a series of studies on oxidations of β -lactam-substituted tetrazoles carried out by a Hungarian research group [<1999T8457>](#), cyclization to some fused tetrazolo[1,2-*a*]pyrazines has been observed. The results are shown in [Scheme 21](#).

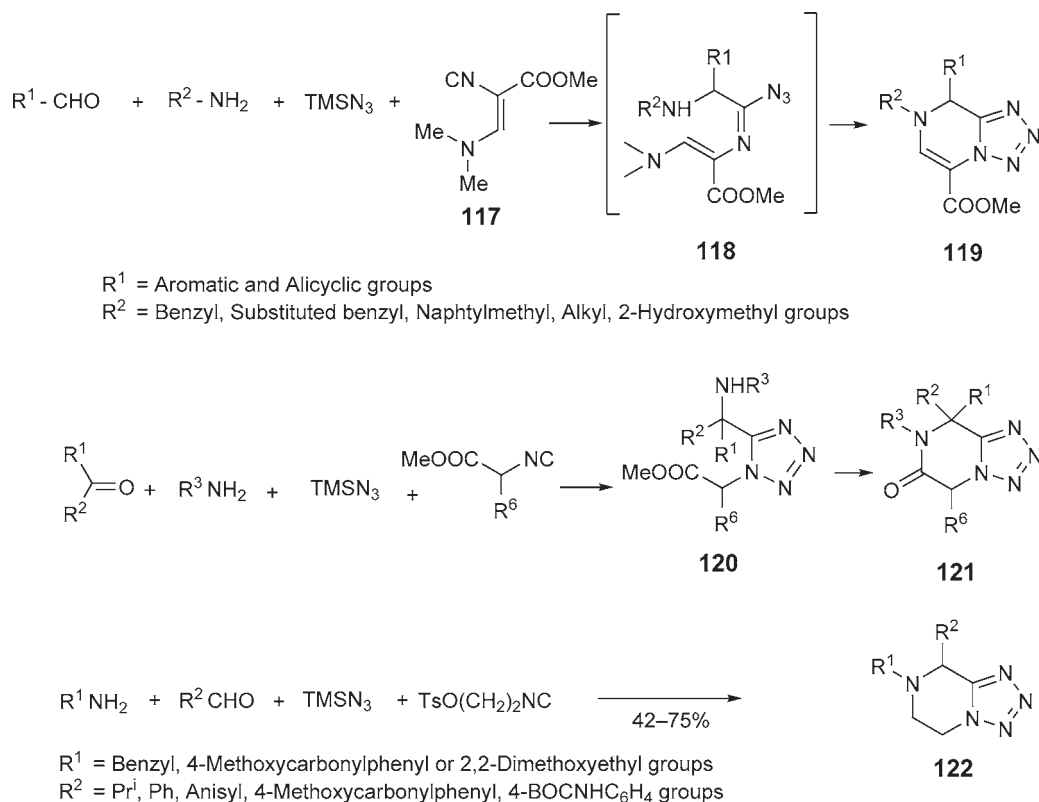


Scheme 21

Thus, the substituted tetrazoles **113** upon oxidation with lead tetraacetate gave rise to the fused tetrazoles **114**, in most cases in high yields. Tetrazole derivatives **115**, bearing an anisidine side chain, also underwent oxidative cyclization and afforded 10-methoxycarbonylmethyltetrazolo[1,5-*a*]quinoxaline **116** in good yield. This compound was obtained as a mixture of tautomers (with participation of the methylene hydrogen atoms) and the depicted tautomeric form **116** proved to be dominant.

11.18.7.4 Application of Multicomponent Reactions to the Synthesis of Tetrazolopyrazines

Synthesis of unsaturated and partially saturated tetrazolo[1,5-*a*]pyrazines by multicomponent reactions have been intensively studied during the past few years and publication on this subject by three independent groups appeared. The results are shown in [Scheme 22](#).



Scheme 22

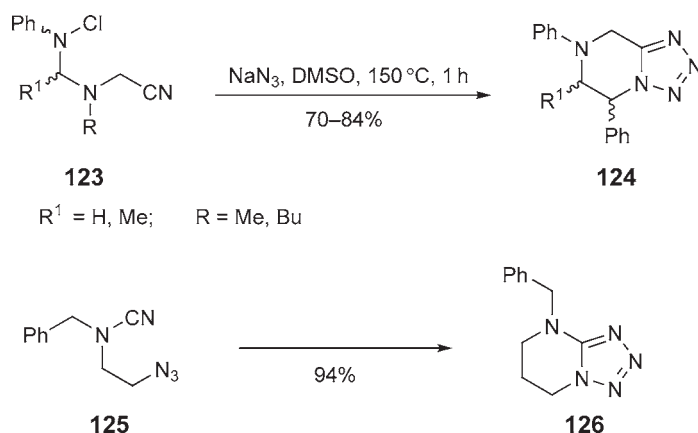
A research team at Rhône-Poulenc reported a four-component procedure for the synthesis of variously substituted heteroaromatic tetrazolo[1,5-*a*]pyrazines [<1998TL735>](#). Thus, aldehydes, primary amines, trimethylsilyl azide, and methyl β -(*N,N*-dimethylamino)- α -isocyanoacrylates **117** were reacted in a methanolic solution at room temperature to yield the product **119** in high yields. The reaction was rationalized to proceed via the formation of intermediate **118**. The procedure proved to be efficient for combinatorial chemical applications.

In addition, interest in combinatorial chemical applications led a team at AMGEN to the recognition of a related but different pathway which afforded tetrahydro tetrazolo[1,5-*a*]pyrazine-6-ones **121** ([Scheme 22](#)) [<2000TL8729>](#). In this procedure, three starting components, that is, the ketone, the primary amine, and trimethylsilyl azide, as in the previous method, were used, and the fourth component was methyl isocyanoacetate. This reaction also took place under relatively smooth conditions (methanolic solution at room temperature for 6 h followed by reflux for 24 h) to yield the products **121** in good to high yields. The reaction obviously proceeds by the formation of intermediate **120**.

The third multicomponent approach to tetrahydrotetrazolo[1,5-*a*]pyrazines elaborated by a German team is also reminiscent of the previously discussed two procedures [<2004TL3725>](#). The specific feature of this method is the use of 2-tosyl-oxyethylisocyanide instead the isocyano derivatives described above. This transformation was also carried out in methanolic solution, and simple stirring at room temperature for 24 h led to the tetrahydro products **122** in medium to good yields (42–75%).

11.18.7.5 Cyclization to Tetrazolozines by 1,3-Dipolar Cycloaddition

Two studies appeared during the recent years where fused tetrazolodiazines have been synthesized by application of intramolecular 1,3-dipolar cycloaddition of a cyano and an azido moiety. These transformations are depicted in [Scheme 23](#).



Scheme 23

Couty *et al.* [<2004TL3725>](#) found that various geometric isomers of some chlorinated aminoacetonitriles **123** can be conveniently treated with sodium azide in dimethyl sulfoxide (DMSO) at 150 °C, to produce after 1 h the corresponding tetrahydrotetrazolo[1,2-*a*]pyrazines **124** in good yields. Extension of studies on ‘click chemistry’ carried out by Demko and Sharpless [<2001OL4091>](#) also proved to be suitable for easy preparation of some ring systems belonging to this chapter. One such example is formation of 5,6,7,8-tetrahydro-8-benzyltetrazolo[1,5-*a*]pyrimidine **126** from the open-chained cyano-azido derivative **125**. The reaction proceeds at 140 °C in 94% yield. Formation of other related ring systems is discussed below in the next section.

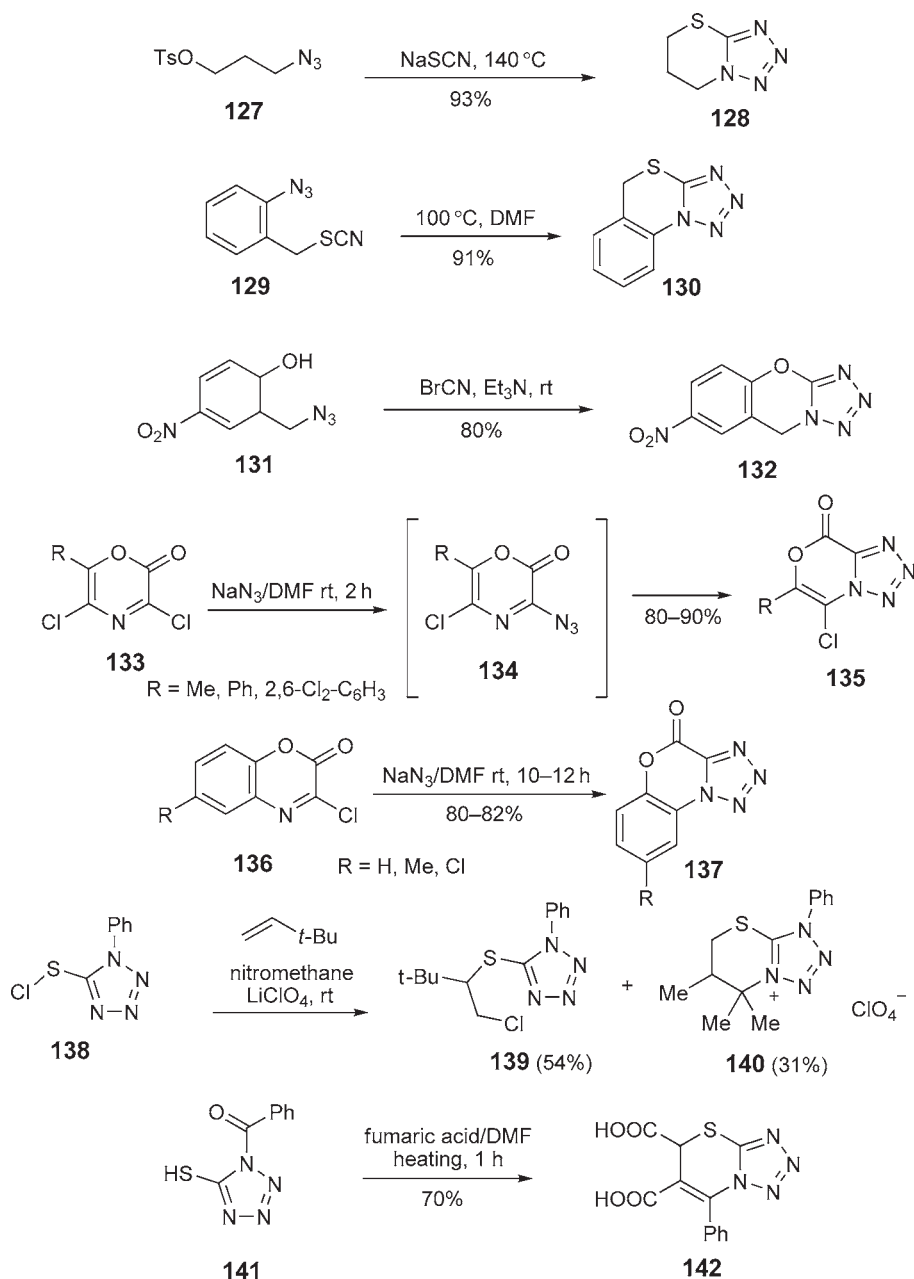
11.18.7.6 Synthesis of Tetrazolooxazines and Thiazines

As indicated in the introductory section of this chapter, some tetrazolooxazines and thiazines have also been synthesized during the past period. These results are shown in [Scheme 24](#).

The above discussed ‘click approach’ described by Demko and Sharpless [<2001OL4091>](#) allowed also the synthesis of some fused thiazines and oxazines. Thus, treatment of 3-tosyloxypropylazide with sodium thiocyanide **127** gave 5,6,7,8-tetrahydro-tetrazolo[5,1-*b*][1,3]thiazine **128**. The reaction obviously proceeds via an intermediate alkyl thiocyanide formed by nucleophilic displacement of the tosyloxy group. A similar procedure has been applied for the synthesis of the tricyclic 9*H*-tetrazolo[5,1-*b*][1,3]benzothiazine **130**, starting from compound **129** containing the cyano moiety necessary for the planned dipolar cyclization. Furthermore, 2-azidomethyl-4-nitrophenol **131** also proved to be suitable for ring-closure reaction: treatment with cyanogen bromide and trimethylamine at room temperature gave the tricyclic ring-closed tetrazolooxazine **132**.

Ring closure to the 5*H*-tetrazolo[5,1-*c*][1,3]oxazine skeleton has been reported by Hoornaert and co-workers [<1996T8813>](#). These authors treated variously substituted 2,4-dichloro[1,4]oxazin-2-ones **133** with sodium azide. The fused tetrazoles **135** obtained were formed via the formation of their azide valence bond isomer intermediate **134**. A similar approach proved to be suitable for the benzologues of these compounds. Thus, the benzoxazinone compounds **136** gave the tricyclic ring-closed tetrazoles **137**. Both reactions yielding **135** and **137** proceeded in high yields (80–90%).

Two other synthetic approaches, both resulting in ring closures to partially reduced tetrazolo[5,1-*b*][1,3]thiazines, should be mentioned. A Russian team [<1994ZOR760>](#) reported that 1-phenyltetrazole 5-sulfonyl-chloride **138**, when reacted with 3,3-dimethylbut-1-ene in the presence of lithium perchlorate, gave a mixture of two products: besides the addition product **139** a fused tetrazolothiazinium perchlorate salt **140** was also obtained in 31% yield. Formation of another derivative of the same ring system was reported by Assy [<1995PJC1022>](#), who found that reaction of 1-benzoyl-5-mercaptopotetrazole **141** with fumaric acid yields 7*H*-tetrazolo [5,1-*b*][1,3]thiazine-5,6-dicarboxylic acid **142** in 70% yield. The reaction proceeds in the presence of triethylamine in DMF under heating for 1 h.

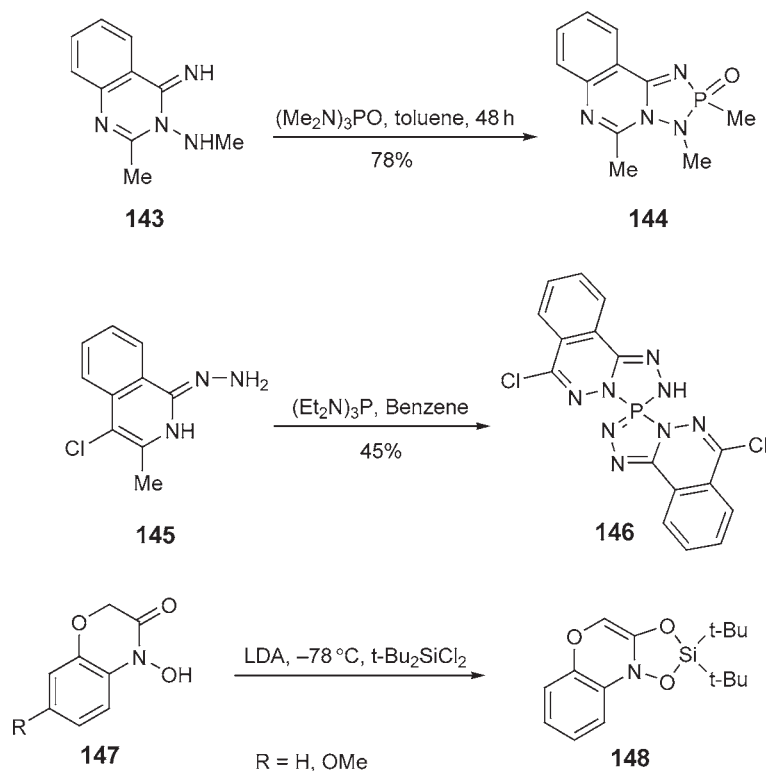


Scheme 24

11.18.7.7 Synthesis of Fused Ring Systems with Phosphorus and Silicon Ring Atoms

Two phosphorus-containing ring systems and one silicon-containing fused heterocycle belonging to the heteroatomic arrangements of this chapter have been synthesized recently. The synthetic pathways are presented in Scheme 25.

A [1,2,4,3]triazaphospholo[1,5-*f*]quinazoline derivative **144** containing a pentavalent phosphorus atom has been synthesized by Abderrahim and Boujlel <2005PS79>: the *N*-methylamino-4-iminoquinazoline compound **143** was reacted with hexamethylphosphamide under heating in toluene for 48 h to give the product in 78% yield. Formation of a spiro-fused triazaphosphole has been reported by Eliseenkova *et al.* <1998ZOB1576>. These authors found that 1-chloro-4-hydrazonophthalazine **145** can be transformed in refluxing benzene, in the presence of tris(diethylamino)phosphine, to the polycyclic product **146**.

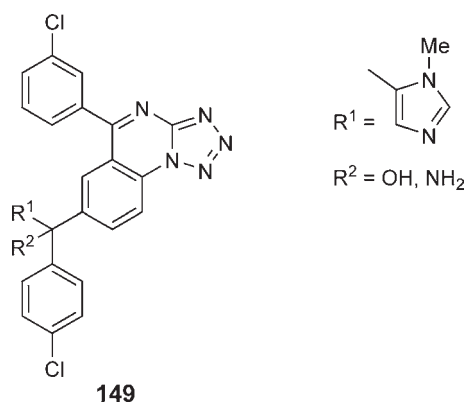


Scheme 25

Two derivatives of a cyclosilyl ether **148** have been synthesized by a German team [\[1994TL4335\]](#). The enolizable cyclic hydroxamic acid **147** when treated with 2 equiv of lithium diisopropylamide followed by reaction with di-*tert*-butyldichlorosilane in toluene yielded the stable [1,3,4,2]dioxazasilolo[5,4-*c*][1,4]oxazine derivative **148**.

11.18.8 Important Compounds and Applications

Concerning the practical importance of compounds belonging to this chapter, only one type of the derivatives is worth mentioning. Angibaud *et al.* carried out thorough studies on farnesyl protein transferase inhibitory activity of substituted azoloquinolines [\[2003BMC4365\]](#). These authors found that some tetrazolo[1,5-*a*]quinazolines **149** (Scheme 26) are promising agents for oral *in vivo* inhibition. Similar results have been obtained with some related tetrazolo[1,5-*a*]quinolines as described in Chapter 11.15 (section 11.15.12).



Scheme 26

11.18.9 Further Developments

New results has been published a “vicarious substitution” on the tetrazolopyridazine ring system <2006TL4259>. Novel observations of formation of nitrenes and diradicals from fused tetrazoles by argon matrix photolysis have been published by an Australian team <2006JOC4049>. These reactive species underwent a variety of subsequent ring enlargements, cyclizations, ring openings and other reactions. Also ring enlargement has been observed under photochemical conditions with tetrazolopyrimidines derived from 4-azidouracil nucleosides <2006JOC1742> to yield highly valuable 1,3,5-triazepine-2,4-dione nucleosides.

Some new synthetic approaches to tetrazolodiazines have recently been reported. Thus, a multi-step variation of the cyclization method discussed in Table 9 has been elaborated <2005S2597> with the aim of library synthesis.

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Biographical Sketch



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11.19

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 2:2

G. Hajós and Z. Riedl

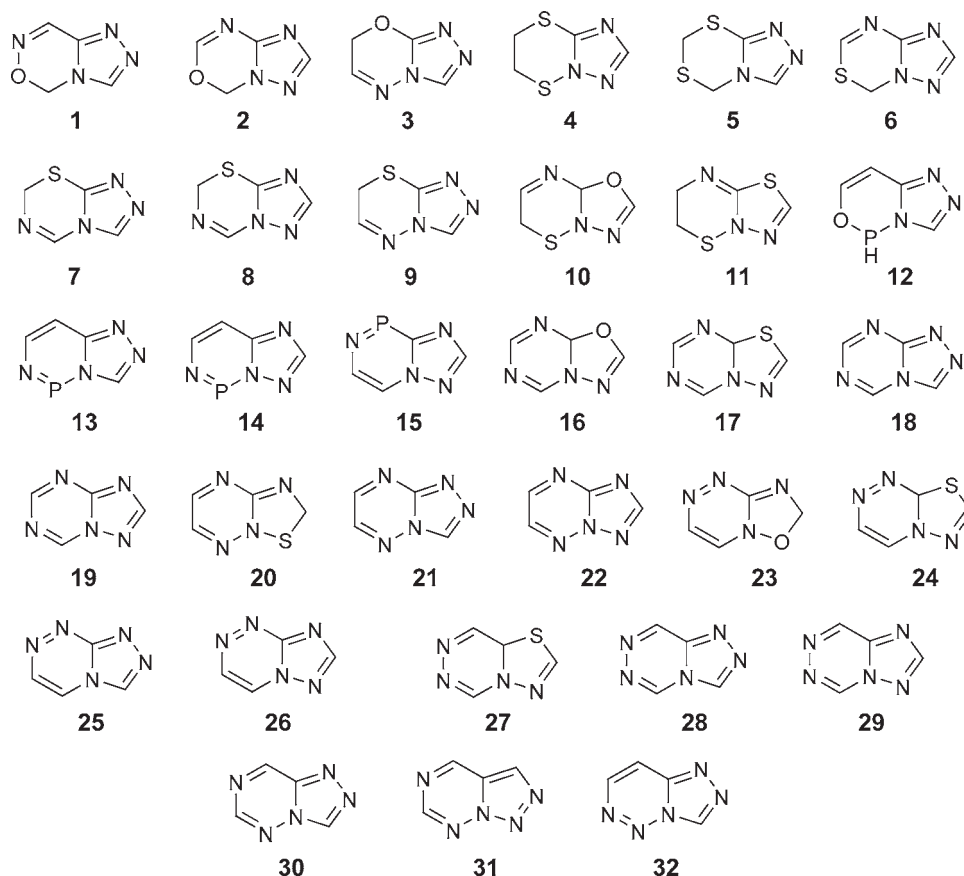
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11.19.1 Introduction

Because of the numerous possibilities of arrangements of heteroatoms in the ring systems covered in this chapter, a substantial amount of literature data appeared during the recent period. The ring systems discussed here are shown in [Scheme 1](#).



Scheme 1

These can be classified as follows:

1. triazolooxadiazines **1–3**, triazolodithiazines and thiadiazines **4–9**, as well as oxa- or thiadiazolothiadiazines **10 and 11**;
2. four different phosphorus-containing heterocycles (triazolooxazaphosphinines and –diazaphosphinines) **12–15**;
3. oxadiazolo-, thiadiazolo-, and triazolo[1,3,5]triazines **16–19**;
4. fused [1,2,4]triazines: *b*-fused systems **20–22**, *c*-fused skeletons **23–26**, *d*-fused rings **27–29**, and *f*-fused ring systems **30 and 31**.

A fused [1,2,3]triazine **32** will also be discussed.

Out of these ring systems, 14 skeletons (**11, 16, 17, 18, 19, 21, 22, 24, 25, 26, 27, 28, 29, and 30**) were discussed in CHEC-II(1996) <1996CHEC-II(8)479>.

11.19.2 Theoretical Methods

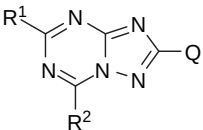
Since publication of some results on this subject as reviewed in CHEC-II(1996) <1996CHEC-II(8)479>, no new results appeared during the recent period of time.

11.19.3 Experimental Structural Methods

11.19.3.1 NMR Results

Beyond routine analytical NMR data, a relatively large set of ^{13}C NMR data is available for derivatives of the [1,2,4]triazolo[2,3-*a*][1,3,5]triazine **19** ring system <1995J(P1)801, 2002JHC327>. The experimentally observed chemical shifts are compiled in Table 1.

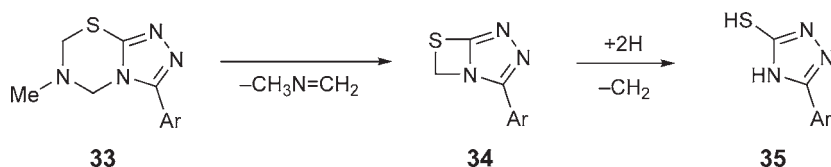
Table 1 ^{13}C NMR chemical shifts of [1,2,4]triazolo[2,3-*a*][1,3,5]triazine derivatives (all units are given in ppm)



R^1	Q	R^2	$C-2$	$C-7$	$C-5$	$C-3a$
NH ₂	H	NH-C ₃ H ₆ -NMe ₂	154.2	149.2	162.7	158.8
NH ₂	H	NH-CH ₂ -Ph	154.4	149.2	162.7	159.0
NH ₂	SMe	Morpholino	165.0	148.4	161.8	161.3
NH ₂	SMe	NHEt	165.2	148.2	162.6	159.3
NH ₂	NHEt	NHEt	165.6	148.2	162.3	158.4
NH ₂	NH-CH ₂ -Ph	NH-CH ₂ -Ph	165.9	148.5	162.3	158.7
NH ₂	NH-C ₈ H ₁₇	NH-C ₈ H ₁₇	164.8	148.6	162.4	157.8
NH ₂	NH-(CH ₂) ₂ -NMe ₂	NH-(CH ₂) ₂ -NMe ₂	165.6	148.3	162.3	158.4
NH ₂	NH-(CH ₂) ₃ -NMe ₂	NH-(CH ₂) ₃ -NMe ₂	165.7	148.3	162.3	158.3
NH ₂	Morpholino	Morpholino	165.6	148.5	161.6	160.7
SMe	2-Furyl	NH ₂	156.2	149.6	173.3	157.2
NH ₂	2-Furyl	SMe	156.8	161.0	160.5	151.5
PhO	2-Furyl	NH ₂	156.8	152.0	165.0	158.9
PhO	2-Furyl	PhO	158.0	155.0	164.4	160.1
PhO	SMe	NH ₂	166.7	151.0	164.8	158.9
PhO	SMe	NH ₂	138.2	152.3	164.4	157.4

11.19.3.2 Mass Spectrometry

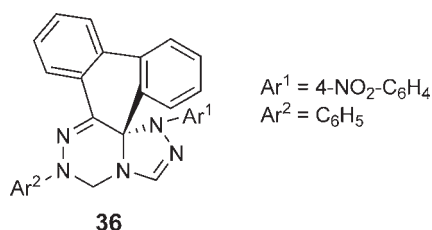
In a study on [1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines, mass spectral fragmentation of the 3-aryl-6-methyl derivative **33** (see Scheme 2) has been determined by Wang *et al.* <2001SC2841>. These authors found that elimination of the methylimine formaldehyde takes place first to form a thiazetidine ring **34** and, finally, removal of a CH₂ group the 2-mercapto-5-aryl[1,2,4]triazole **35** can be observed.



Scheme 2

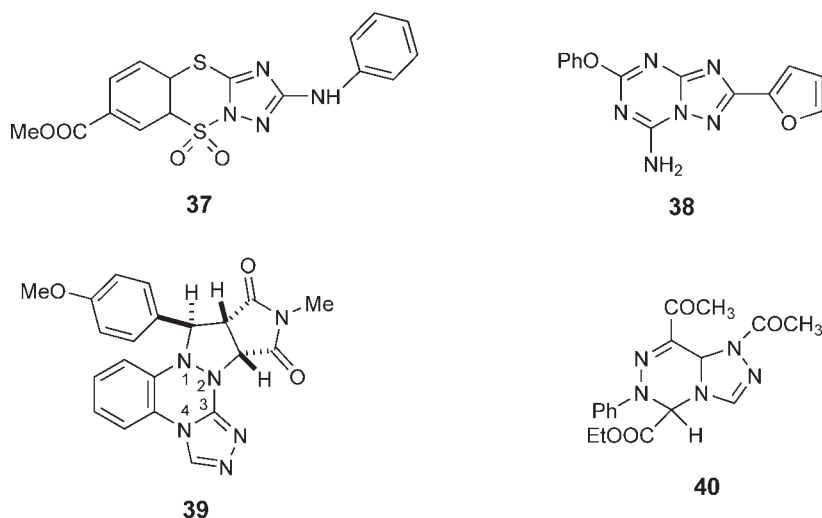
11.19.3.3 X-Ray Investigations

The structure of the partially saturated phenanthro spiro-fused triazolotriazine derivative **36** (Scheme 3) has been studied by X-ray analysis <1997J(P1)1047>. This structure elucidation revealed that between the benzene ring and the phenanthrene unit there is a small out-of-plane tilt (8.4°).



Scheme 3

In the course of investigation of potential antitumor compounds, the triazolobenzodithiazine derivative **37** seemed of special interest (Scheme 4). As no unambiguous proof could be provided by spectroscopic data (cf. Section 11.19.6.) X-Ray analysis of the crystalline product has been carried out <2003BMC1259>. The results revealed that in crystals the molecules formed centrosymmetric dimers by the help of weak NH...N hydrogen bonds. Because of the conformation of the central six-membered ring, the tricyclic molecule had a butterfly shape.



Scheme 4

Also in the case of a [1,2,4]triazolo[2,3-*d*][1,3,5]triazine derivative **38** (Scheme 4), the X-ray analysis provided the final proof for the exact structure <1995J(P1)801>. It has been found that – in accordance of the experienced coupling constants in the NMR spectrum – the 7-amino group is coplanar with the ring system.

The exact structure of a cycloadduct **39** obtained by dipolar cycloadditions of a [1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazine-based azomethine imine has been determined by X-ray investigation <2005EJO3553> (Scheme 4). The data supported the unambiguous connectivity of the particular atoms (i.e., attachment of the *p*-anisyl carbon atom to N-1) and, furthermore, the fact that the central triazine ring had a quasi-envelope structure with the N-4 atom at the top.

The substituted tetrahydro derivative of the [1,2,4]triazolo[4,3-*d*][1,2,4]triazine ring system **40** has also been investigated by X-ray crystallography <2002M1165>. The result showed a close similarity with that obtained with an earlier related derivative <1996CHEC-II(8)479>.

11.19.4 Thermodynamic Aspects

In the case of a ring-transformation reaction (discussed in detail in Section 11.19.7) <2005T7489>, negative enthalpy of activation has been determined and this finding allowed to conclude that the isomerization follows a pericyclic pathway.

Experimentally determined pK_a values have been compared with Hammett substituent constants σ_x for a set of [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles <2002PS487> (Figure 1) and an excellent correlation was found. This result provided a further support – in accord with some nuclear magnetic resonance (NMR) measurements – for existence of one particular tautomeric form (Figure 1, structure **a**) among the three possible ones (Figure 1, **a**, **b**, **c**).

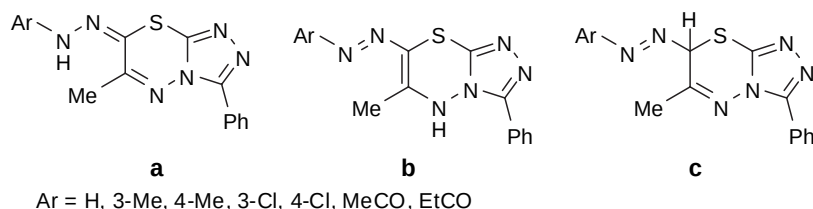
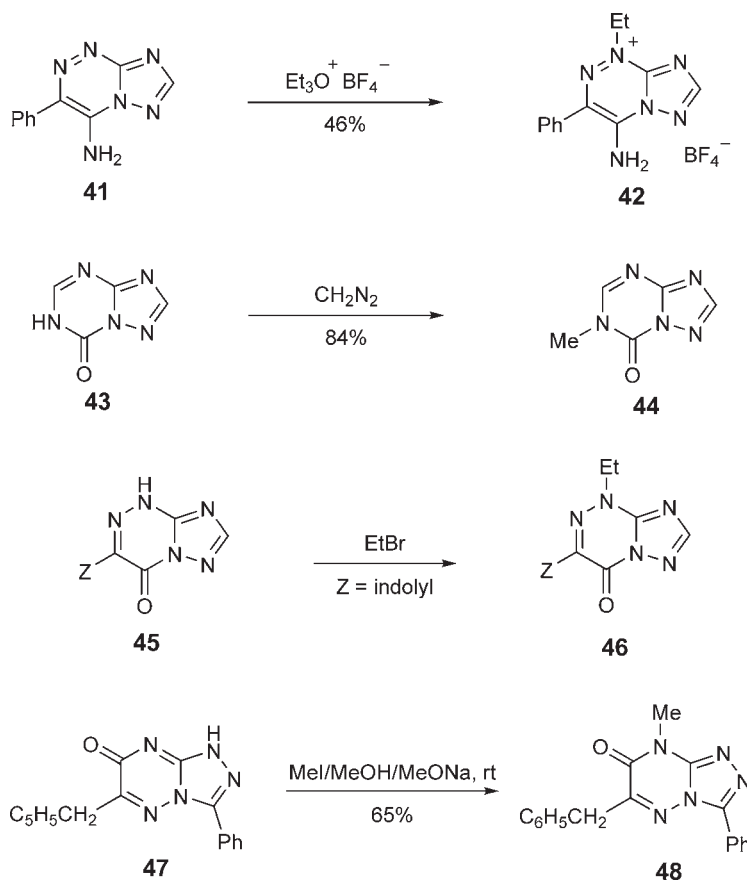


Figure 1 Tautomeric possibilities of some [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles.

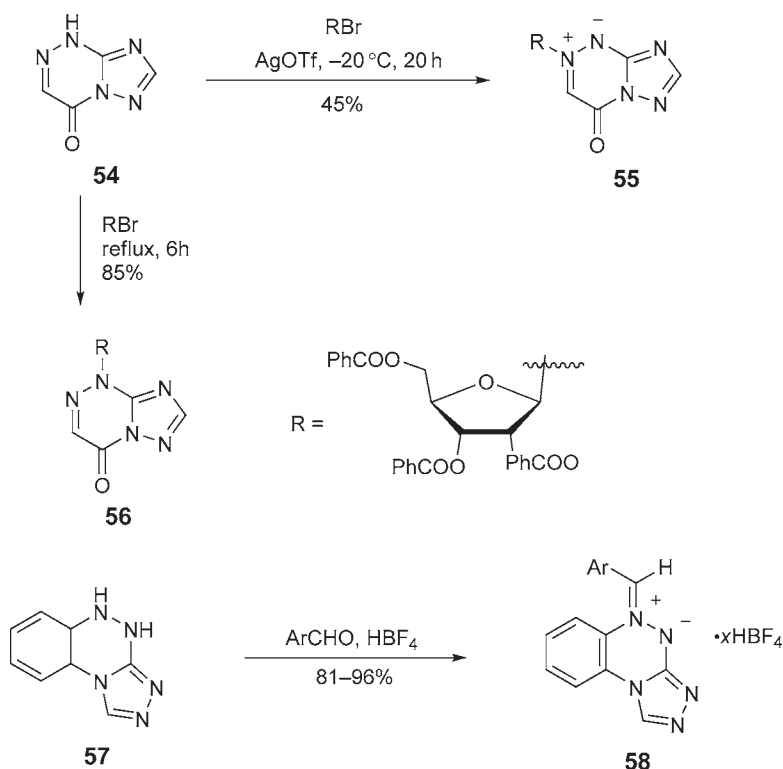
11.19.5 Reactivity

11.19.5.1 Reactions at Heteroatoms

Some alkylations of ring nitrogen atoms are shown in Scheme 5. Study on alkylation of the [1,2,4]triazolo[5,1-*c*][1,2,4]triazine derivative **41** have been carried out by Chupakhin and co-workers <2002IZV1594>. The best result was obtained with triethyloxonium tetrafluoroborate as a reagent. The ethylation was found to proceed selectively on N-4 atom in the six-membered ring to result in formation of the quaternary salt **42**.



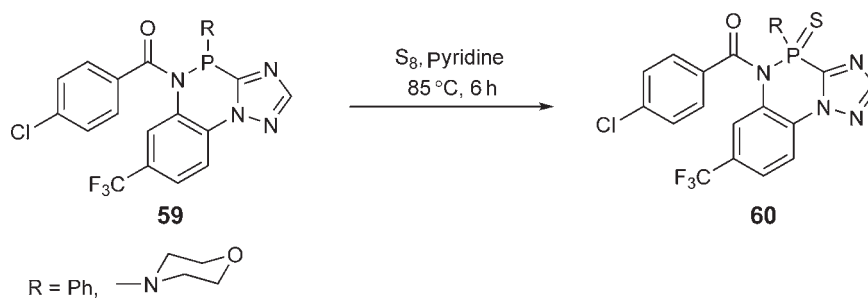
Scheme 5



Scheme 8

Some 4,5-dihydro[1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazines **57** easily reacted with aromatic aldehydes to result in the formation of synthetically valuable azomethine imines **58** <2005EJO3553>. The transformation took place at room temperature in the presence of tetrafluoroboric acid in 10 min in high yields. The product **58** was conveniently prepared and stored in the form of tetrafluoroborate salt, and was subjected to further reactions (e.g., 1,3-dipolar cycloadditions; see Section 11.19.5.4.) by *in situ* liberation of the free base prior to transformation.

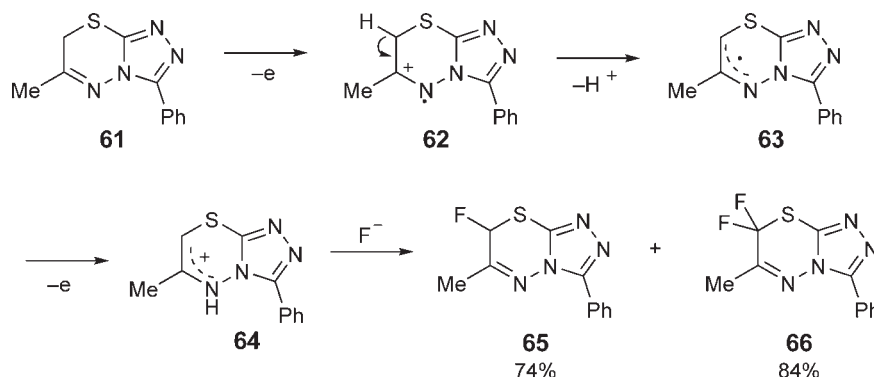
Sulfur addition on the ring phosphorus atom of [1,2,4]triazolo[5,1-*c*][1,4,2]diazabenzophosphinine derivatives **59** was described by Zarudnitskii *et al.* <2002HAC146> (Scheme 9). The transformations were carried out in pyridine at 85°C to yield the *P*-sulfanylene products **60**.



Scheme 9

11.19.5.2 Reactions at Ring Carbon Atoms

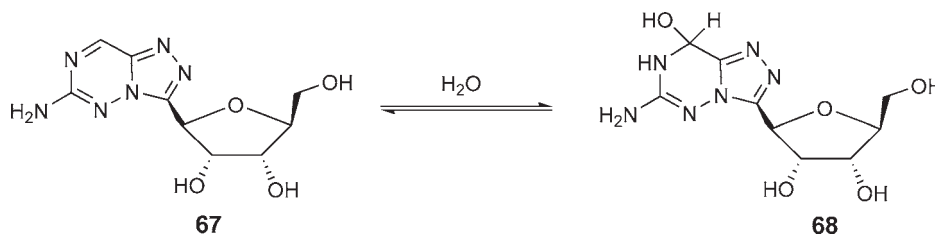
An interesting fluorination has been carried out with [1,2,4]triazolo[3,4-*b*][1,3,4]thiaziazines by electrochemical techniques <2002TL273>, as shown in Scheme 10.



Scheme 10

It has been found that the derivative **61** can undergo mono- or difluorination in position 7 to give either **65** or **66** depending on the reaction conditions. Thus, by 3 F mol^{-1} charge passed (in dimethoxyethane with tetraethylammonium fluoride–hydrogen fluoride as supporting electrolyte) the monofluoro compound **65** was obtained in 81% yield exclusively, but with higher charge (8 F mol^{-1}) under the same conditions only the difluoro derivative **66** was obtained. The reaction was interpreted by formation of intermediates **62–64**: removal of the first electron from **61** leads to a radical cation **62**, which, upon deprotonation, affords a delocalized radical **63**. This species can lose again an electron to afford a delocalized cation **64**, which is reactive enough to capture a fluoride anion at the terminal carbon atom of the delocalized triatomic moiety.

Introduction of a hydroxy group to the ring carbon atom via formation of a covalent hydrate was described by Bojack *et al.* (Scheme 11) <2001OL839>. These authors reported that derivative **67** and some analogous compounds exist in aqueous solutions as a mixture of the parent compound **67** and the covalent hydrate **68**.

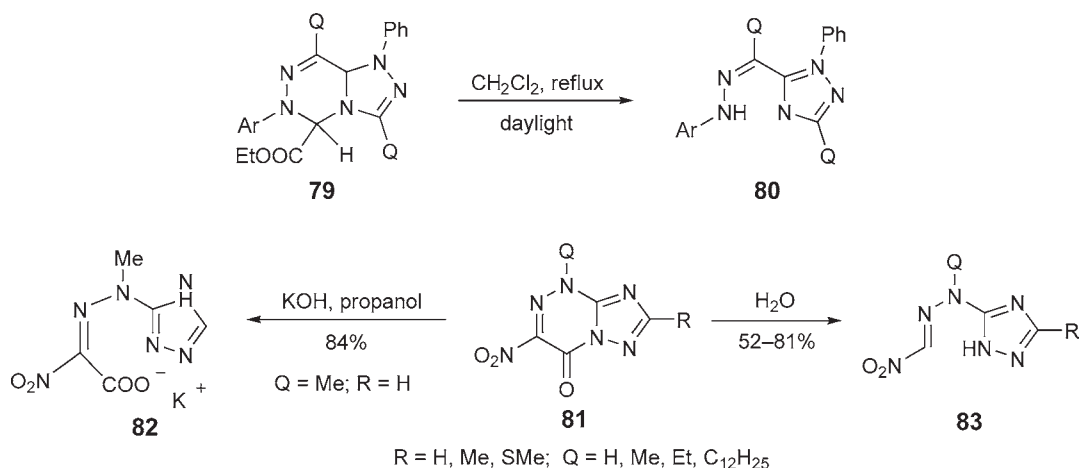


Scheme 11

In research work on the transformation of [1,2,4]triazolo[4,3-*b*][1,2,4]triazines, introduction of various moieties into position 7 of this ring system has been elaborated by Chupakhin and co-workers <2001IZV2084, 2002HCO75, 2003ZOB862>, as illustrated in Scheme 12. Some of these transformations have been carried out under acidic conditions, and in several cases basic conditions have been applied. In most cases, a formal addition of a CH moiety of the reagent to the C(7)=N(8) bond of the triazine ring occurs to result in the formation of a partially saturated triazine structure, and this transformation was followed by spontaneous oxidation to yield heteroaromatic triazine rings.

Thus, the unsubstituted starting compound **69** was treated with resorcinol in the presence of trifluoroacetic acid (TFA) to yield **70**. Then, reaction of **69** with the cyclic α,β -unsaturated ketone in the presence of lithium hydride gave the 7-substituted heteroaromatic compound **71**, and ethyl cyanoacetate afforded the cross-conjugated product **72**, whereas reaction with pyrimidine–2,4,6-trione in the presence of triethylamine yielded the addition product **73**. Indole also been reacted with **69**, and heating of the dichloromethane solution for 90 min in the presence of TFA yielded the addition product **74** in excellent yield (95%) <1998ZOR450> (Scheme 12).

Introduction of substituents to ring carbon atoms has also been carried out by condensation reactions as reported by Holla *et al.* <2001FA565> (Scheme 13). It has been shown in this study that the 7-methylene group in the [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivative **75** easily reacts with aromatic aldehydes in the presence of a base and affords cross-conjugated arylenyl products **76**. The transformations proceed in good to high yields (60–80%). The same methylene group also reacted with diazonium salts <2005HAC621>: reaction of derivative **77** with phenyldiazonium salt in pyridine yielded the phenylhydrazone **78** in high yield (72%).

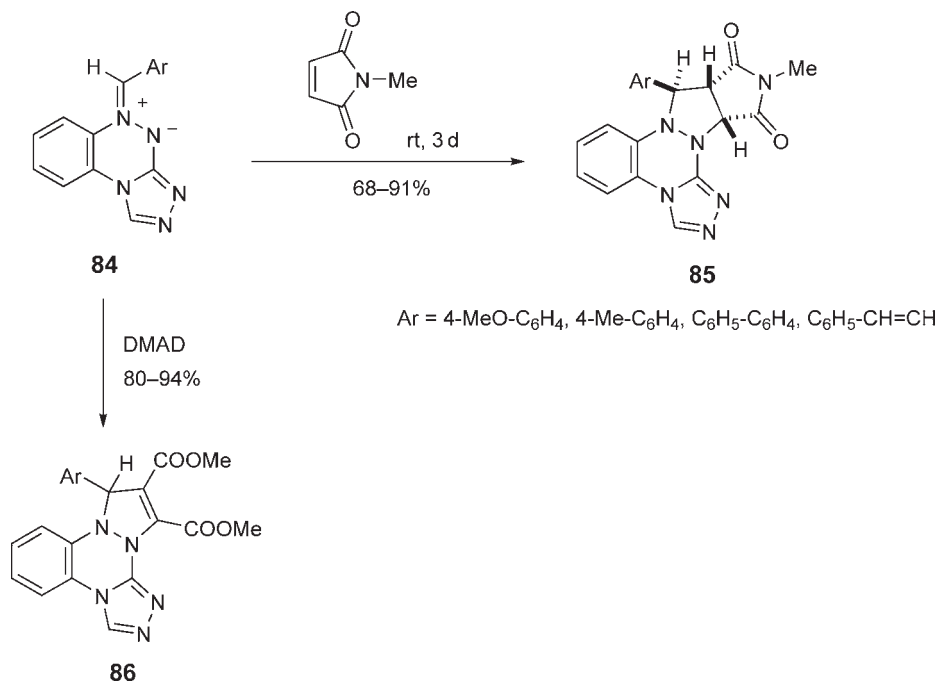


Scheme 14

A hydrolytic ring opening of some [1,2,4]triazolo[5,1-*c*][1,2,4]triazines has been observed by a Russian team [<1996ZOR770>](#). Derivative **81** (Q = Me, R = H) has been treated with aqueous potassium hydroxide in propanol for 10 min, and the six-membered triazine ring opened up to give the potassium carboxylate **82**. In contrast, however, heating some derivatives of the same starting compound **81** in water for 50 min resulted in a subsequent decarboxylation to yield **83** in moderate to high yield (52–81%).

11.19.5.4 Cycloadditions

The recently synthesized [1,2,4]triazolo[3,4-*c*][1,2,4]triazinyl azomethinimines (see [Section 11.19.5.1](#)) easily participated in 1,3-dipolar cycloadditions with various dipolarophiles, as shown in [Scheme 15 <2005EJO3553>](#).

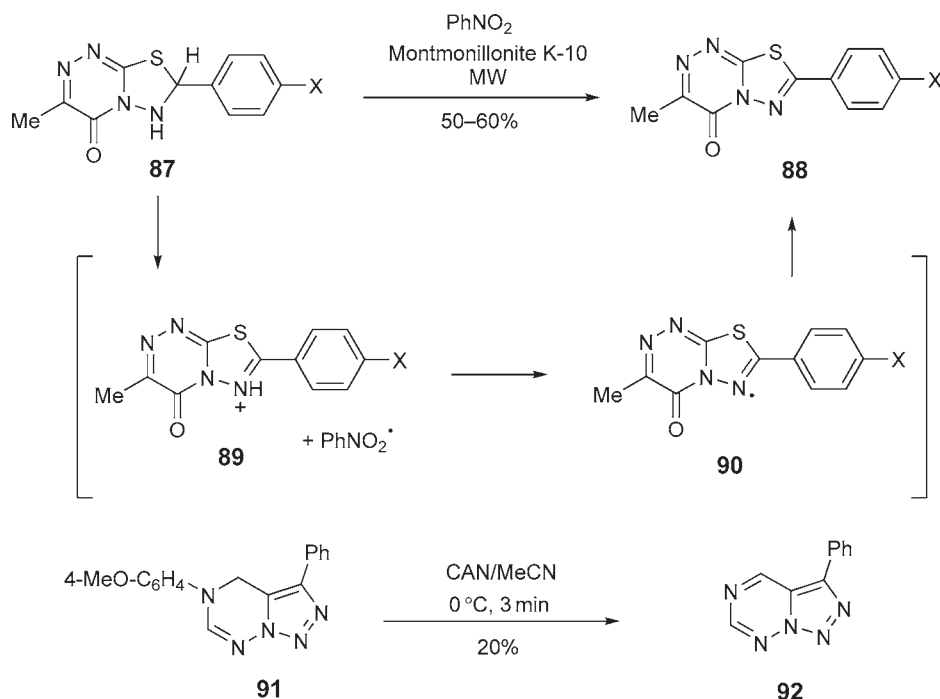


Scheme 15

Thus, derivatives of structure **84** were treated with *N*-methylmaleinide to give the cycloadducts **85** in high yields. In accordance with the concerted nature of this process, the pyrazoles and pyrrolidine-dione had a *cis*-fusion. Similar cycloaddition was also experienced with dimethyl acetylenedicarboxylate (DMAD) to afford **86** containing the partially unsaturated pyrazole ring.

11.19.5.5 Oxidation of the Ring

Two publications appeared during the past period reporting oxidation of partially saturated ring systems to fully conjugated analogues. These transformations are shown in **Scheme 16**.



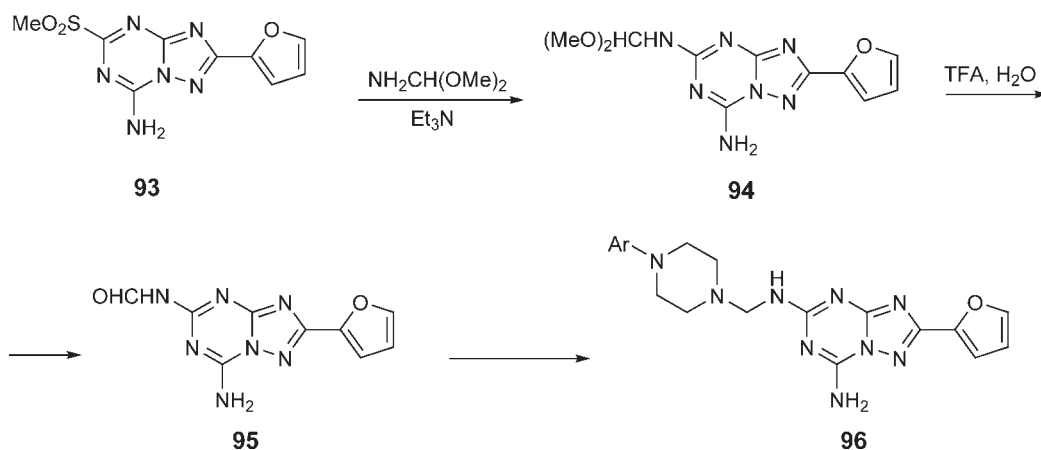
Scheme 16

An Iranian group described the synthesis of some [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazinones **88** <2002PS2399> and in the course of the synthetic pathway the dihydro derivative **87** was first obtained. These authors found that microwave irradiation of **87** on montmorillonite in the presence of nitrobenzene allowed to accomplish the final oxidative step and yielded the fully conjugated end-product in good yields (50–62%). The reaction as proceeding was interpreted by electron transfer to **89** caused by the microwave irradiation followed by the formation of the intermediate radical **90**.

A Greek team also reported on oxidation of partially saturated heterocycles to fully heteroaromatic rings <1996JHC599>: 5-*p*-anisyl-4,5-dihydro[1,2,3]triazolo[5,1-*f*][1,2,4]triazine **91**, when treated with cerium ammonium nitrate, underwent an oxidative hydrolysis giving heteroaromatic product **92** in poor yield (20%).

11.19.5.6 Substitutions

Nucleophilic substitution of the methylsulfonyl group in position 7 of the [1,2,4]triazolo[2,3-*a*][1,3,5]triazine **19** ring system has been carried out in order to obtain biologically valuable derivatives <2004BML4835, 2004JME6218, 2004JME4291> (**Scheme 17**). The reaction pathway was launched by treatment of derivative **93** with aminoacetaldehyde dimethylacetal in the presence of triethylamine under reflux conditions to give the substitution product **94**



Scheme 17

which was hydrolyzed by TFA/H₂O to the formylmethylamine **95**. This compound was then reacted with an *N*-aryl piperazine under reductive conditions (by using sodium triacetoxyborohydride) to give the corresponding arylpiperazinylethylamino compound **96**.

Some other nucleophilic substitutions have also been reported involving these which implied the substitution of chloro, methylsulfonyl, methylsulfonyl, and phenoxy groups by phenoxy, amino, or hydrazine substituents. These reactions are summarized in Table 2.

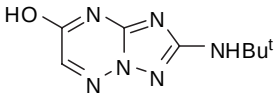
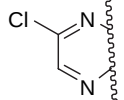
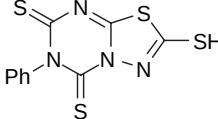
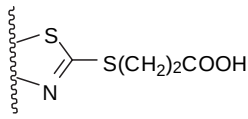
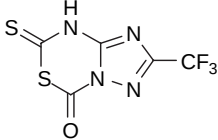
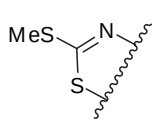
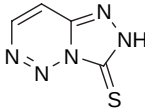
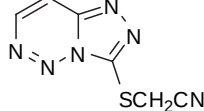
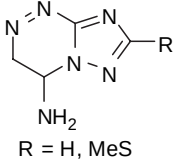
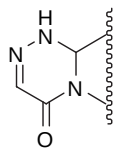
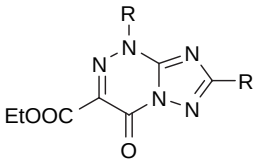
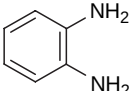
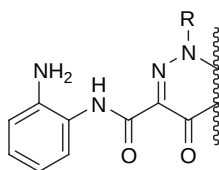
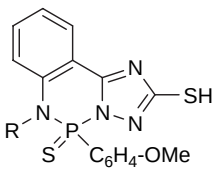
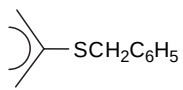
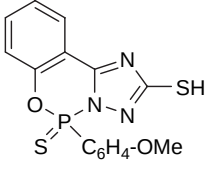
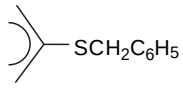
Table 2 Nucleophilic substitution reactions of some triazolo[4,5-b]pyridines

Starting compound	Reagent	Product	Yield (%)	Reference
	PhO [−]		64	1996MI145
	RNH ₂		No data	1995J(P1)801
	NH ₃ /EtOH		35–95	1995J(P1)801
	PhOH		Poor	1995J(P1)801
	N ₂ H ₄ ·H ₂ O		100	1999J(P1)2937

11.19.5.7 Transformations of Substituents and Side Chains

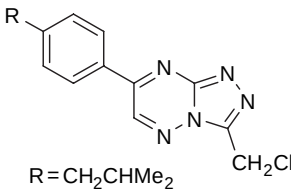
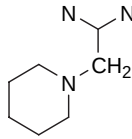
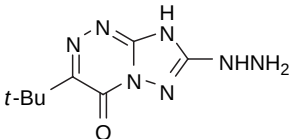
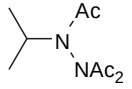
Beyond the well-defined substitutions of the heterocyclic ring systems, numerous other transformations have been carried out that cannot be simply classified into the 'substitution' category. These transformations involve side chain alkylations, exchange of substituents by more sophisticated methods, or ring closures carried out on the side chains. A set of such reactions are summarized in [Table 3](#).

Table 3 Transformation of substituents of some azolotriazines, thiadiazines, and diazaphosphinines

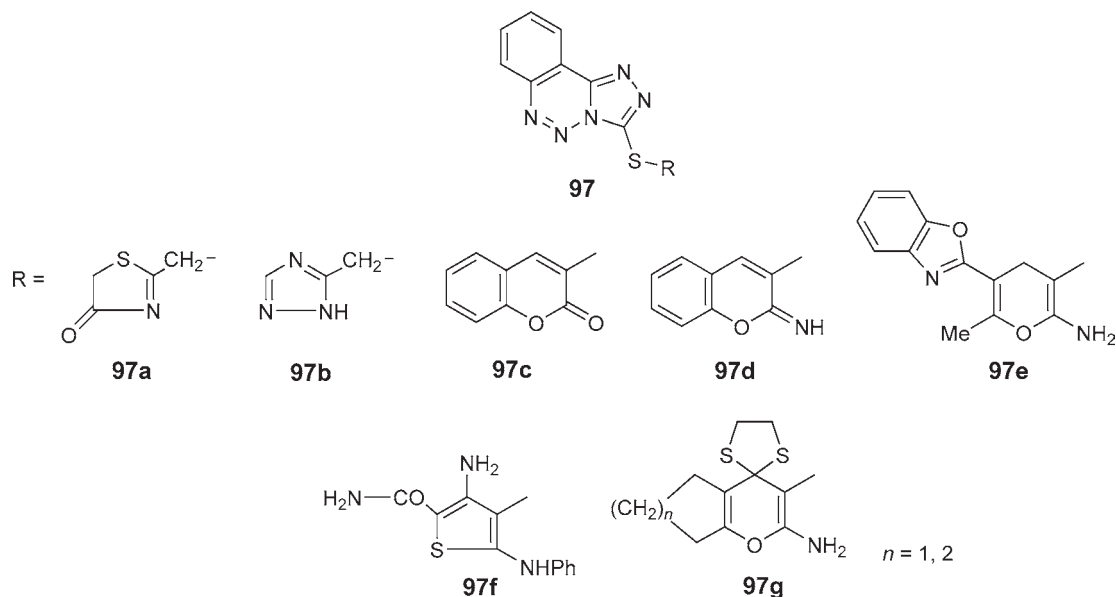
Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1		POCl ₃		93	1996MI145
2		Br(CH ₂) ₂ COOH		70	1994MI521
3		MeI/KOH		60	1998JRM2126
4		ClCH ₂ CN		84	2001SC97
5	 R = H, MeS	NaNO ₂ /H ₂ SO ₄		47–58	1999ZOR1384
6	 R = H, Me, SMe			16–65	1999ZOR1384
7	 R = H, Me	C ₆ H ₅ CH ₂ O		70	2000PS11
8	 R = H, Me	C ₆ H ₅ CH ₂ Cl		76	2000PS11

(Continued)

Table 3 (Continued)

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
9	 $R = \text{CH}_2\text{CHMe}_2$	Piperidine		84	2004AF42
10	 $t\text{-Bu}$	Ac_2O		58	1999ZOB1579

Concerning the transformation of substituents, a special note should be made on a series of ring-closure reactions carried out on the side chain of some [1,2,4]triazolo[4,3-*c*]benzo[1,2,3]triazines published by Moustafa <2001SC97>. The results are summarized in [Scheme 18](#). This scheme shows that by transformation of the R group attached to the sulfur atom of derivative **97** a fairly large set of cyclic products – involving thiazolidone **97a**, [1,2,4]triazole **97b**, coumarone and its imine **97c** and **97d**, respectively, benzoxazylpyrane, **97e**, thiophene **97f**, and cyclopenta- or cyclohexa-fused protected pyrone **97g** substituents – have been obtained.



Scheme 18

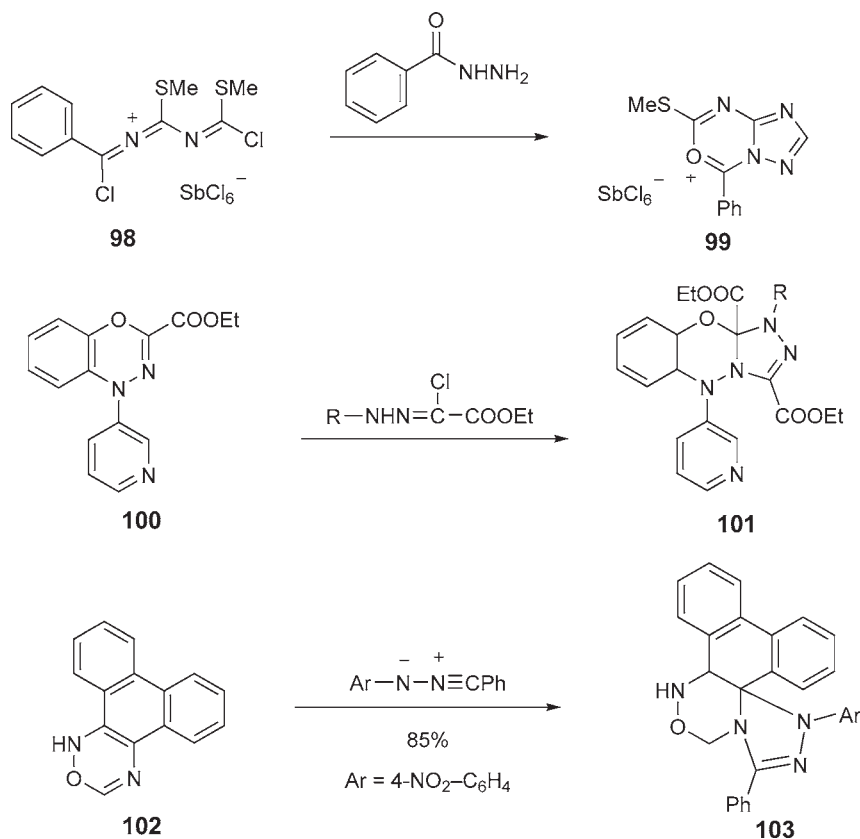
11.19.6 Ring Synthesis from Acyclic Compounds

Apart from some special cases, the ring-closure step in the course of the synthetic pathway is often condensation reaction and, thus, these transformations can be considered as ‘cyclocondensations’. Reactions following a few other mechanisms like cycloaddition, electrocyclization, and intramolecular nucleophilic addition of electron pair of an atom to a multiple bond also occur relatively often. Because of the fairly large complexity of the ring systems belonging to this chapter, the treatment according to the heteroatomic combinations seemed the most straightforward. Thus, the fused

oxadiazoles, dithiazoles, thiadiazoles, and azaphosphinines are discussed first, followed by review of the syntheses of various fused triazines. Because of the abundance of data on [1,2,4]triazines, in this case even the site of the fusion (i.e., *b*-, *c*-, *d*-, and *f*-fusion) will be differentiated.

11.19.6.1 Ring Closure of Fused Oxadiazines

Three triazole-fused oxadiazines have been synthesized during the recent period, as shown in [Scheme 19](#).



Scheme 19

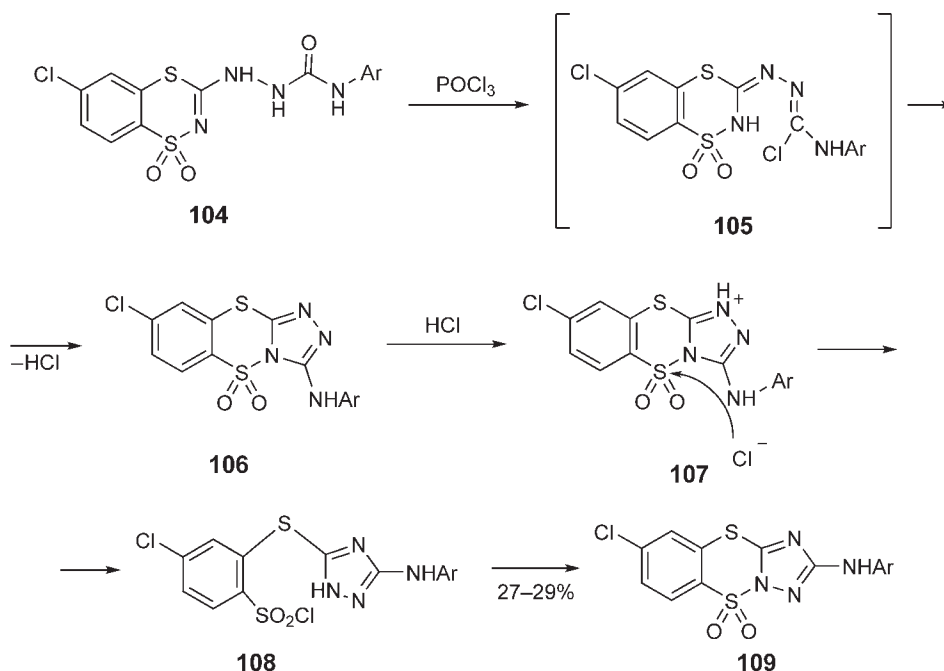
A straightforward synthesis for [1,2,4]triazolo[2,3-*c*][1,3,5]oxadiazinium salts has been described by Hamed *et al.* <1995JPR274>. The transformation of azaallenium hexachloroantimonate **98** with benzhydrazone was carried out in dichloroethane under reflux conditions to yield the fused quaternary salt **99**.

The synthesis of a derivative of the [1,2,4]triazolo[3,4-*b*][1,3,4]benzoxazine derivative **101** was reported by an Italian team <2005JCM276>. These authors have found that the transformation of the benzoxadiazine derivative **100** with ethyl 2-chloro-2-(2-methylhydrazono)acetate results in the ring closure to **101**, albeit in poor yield.

Formation of a spiro-fused triazolooxadiaine **103** was described by Butler *et al.* <1997J(P1)1047>. The transformation of **102** to **103** is a 1,3-dipolar cycloaddition carried out by *N*-(4-NO₂C₆H₄)benzonitrilimine (generated from *N*-(4-nitrophenyl)benzohydrazonoyl bromide with triethylamine) to yield the cycloadduct **103** in 85% yield.

11.19.6.2 Ring Closure of Fused Dithiazines

Synthesis of the triazolodithiazine derivative **109** has been reported by Pomarnacka and Gdaniec <2003BMC1259> ([Scheme 20](#)). Transformation of the semicarbazide **104** with phosphorus oxychloride gave the derivative of the fused heterocycle **109**. Inspection of the connectivity of the heteroatoms clearly indicates that a predominant



Scheme 20

rearrangement should take place in the course of this transformation. According to the authors' interpretation, the reaction launches by formation of the imine chloride **105** followed by cyclization to intermediate **106**. This compound can be protonated to **107**, and attack of the chloride anion can result in a ring opening to **108** and, then, a Dimroth-type rearrangement can afford the experimentally isolated product **109**.

11.19.6.3 Ring Closure of Fused Thiadiazines

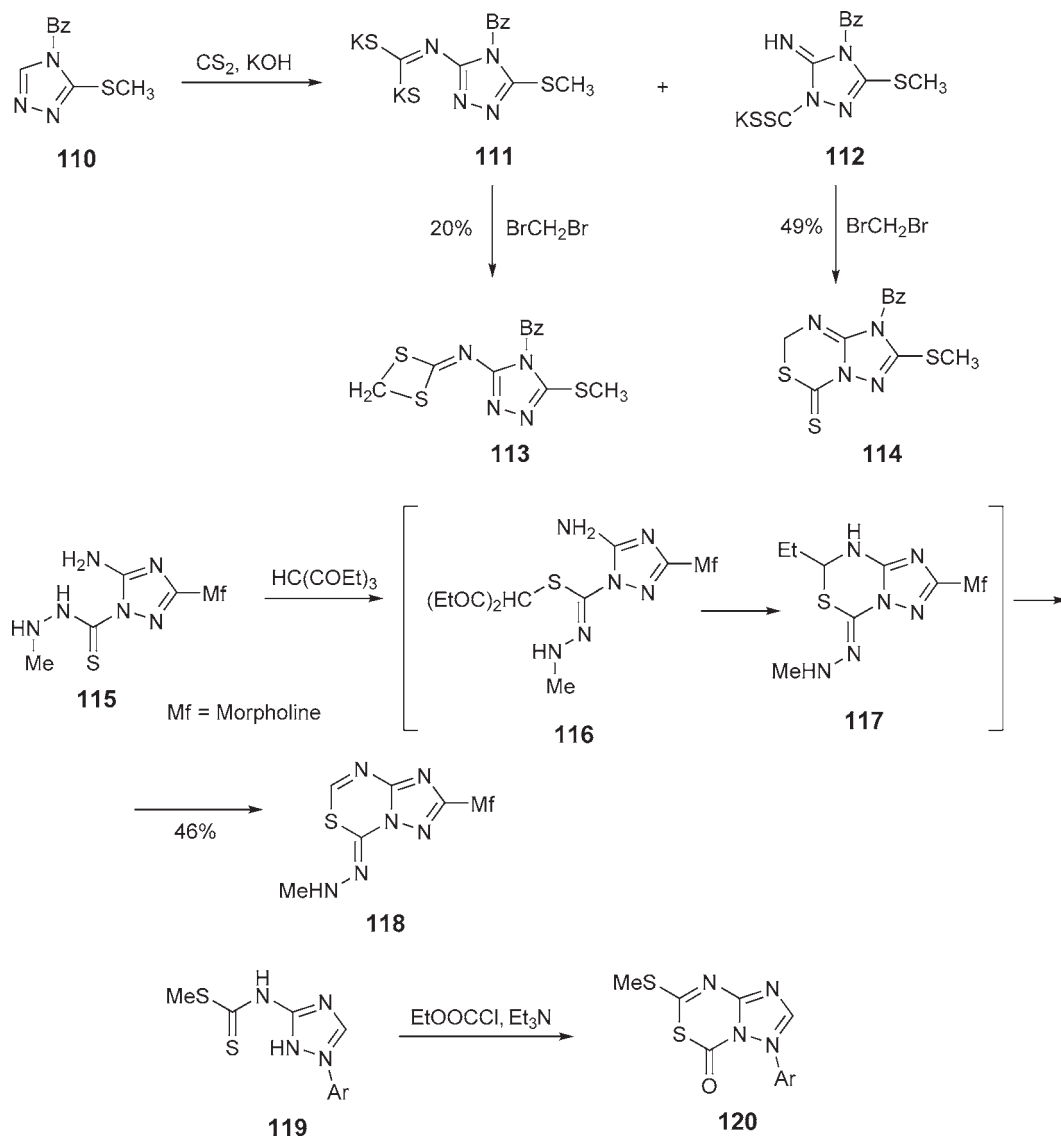
11.19.6.3.1 Thiadiazines and dithiazines with 1,3,5-heteroatomic arrangement in the six-membered ring. Syntheses of four different triazolo[1,3,5]thiadiazine ring systems are discussed in this section. The chemical transformations are shown in Schemes 21–25.

Reiter and co-workers found in the course of their extended research on fused [1,2,4]triazines <1994JHC997> that the N-protected methylthiotriazine derivative **110** when reacted with carbon disulfide under strongly basic conditions yields a mixture of two products **111** and **112**. When this mixture was treated with dibromomethane, product **113** was easily removed from the reaction mixture, and workup of the mother liquor allowed the isolation of the [1,2,4]triazolo[1,5-*c*][1,3,5]thiadiazine derivative **114** in 49% yield (Scheme 21). The same authors carried out ring closure of the ring-closed semithiocarbamide **115** to the triazolothiadiazine derivative **118** as shown in Scheme 21 <1997JHC1575>. The starting compound was treated with triethyl orthoformate. The authors assume that first intermediate **116** is formed which cyclizes to a second intermediate **117** and, finally, ethanol elimination yields the isolated product **118**.

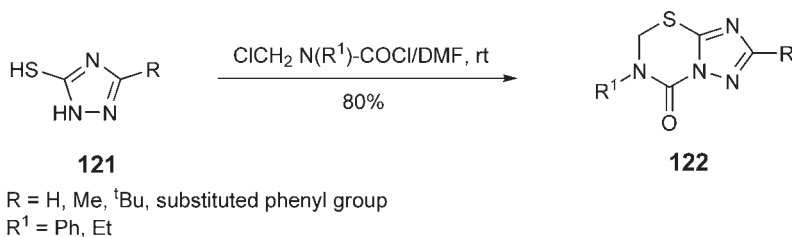
An oxo derivative of the same ring system has also been synthesized <1998JRM2126>: treatment of the dithiocarbamate derivative **119** with ethyl chloroformate in the presence of triethylamine resulted in the formation of the ring-closed product **120**.

Liu *et al.* elaborated an efficient synthetic route to [1,2,4][5,1-*b*][1,3,5]thiadiazine-7-ones **122** <2000M953, 2000JFC111> starting from 3-mercapto[1,2,4]triazoles **121**. These compounds were treated with N-substituted N-chloromethylcarbamoyl chloride in dimethylformamide (DMF) solution at room temperature for 1–2 h to give the ring-closed products in high yield (>80%) (Scheme 22).

Ring closure to [1,2,4]triazolo[3,4-*b*][1,3,5]thiadiazines by utilizing the Mannich reaction has been published by a Chinese team <1999SC2027, 2001SC2841, 2001JHC929> (Scheme 23). 5-Aryl-substituted 3-mercapto[1,2,4]triazoles **123** were treated with formaldehyde and primary amines under acidic conditions to yield the fused thiadiazines **124**. The reaction was interpreted to proceed via formation of intermediate **125** upon the reaction of **123** with a

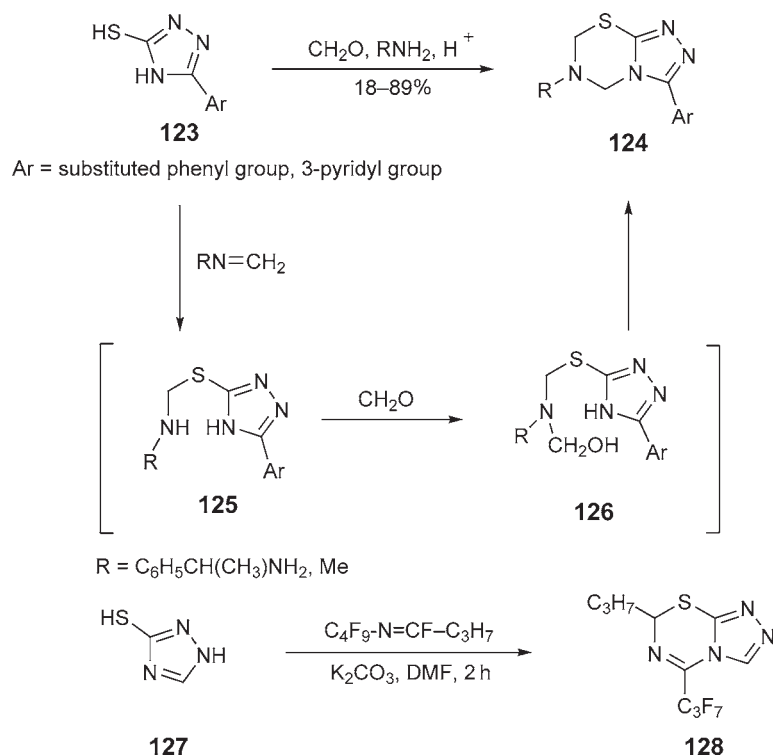


Scheme 21



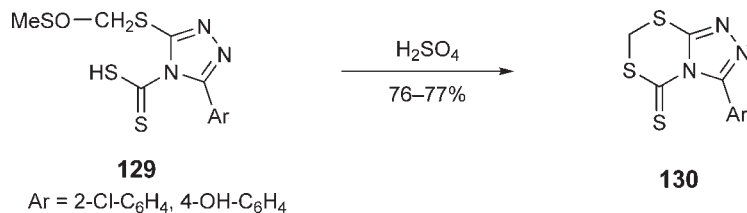
Scheme 22

Mannich base. This step was followed by reaction of **125** with a second molecule of formaldehyde to give **126**, which undergoes internal cyclization under the reaction conditions used. A fluororous derivative of this ring system has also been published [<2005ZOR441>](#): reaction of 3-mercapto[1,2,4]triazole **127** with perfluoro 5-aza-4-nonene gave the bis-perfluoropropyl substituted ring-closed compound **128**.



Scheme 23

The [1,2,4]triazolo[3,4-*d*][1,3,5]dithiazine ring system was synthesized by Yadav *et al.* [<1997IJB442>](#) as shown in [Scheme 24](#). The cyclization of the triazolyl dithio acid containing a methane sulfinylmethylsulfanyl substituent **129** was carried out in sulfuric acid to give the bicyclic compounds **130** in high yield.



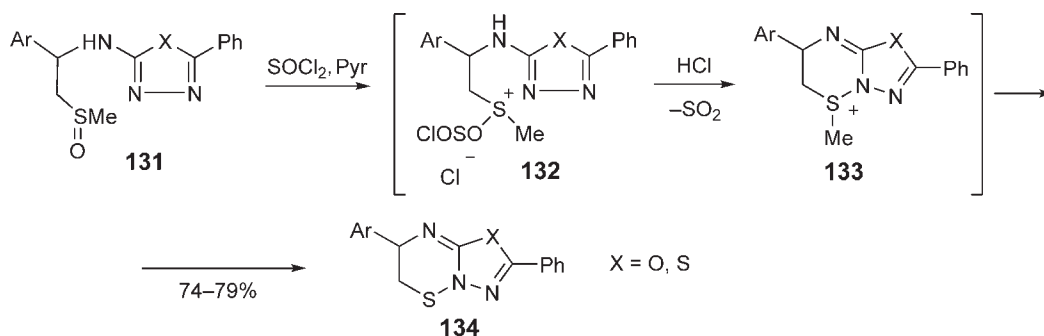
Scheme 24

11.19.6.3.2 Oxadiazolo- and thiadiazolo[1,3,4]thiadiazines

One procedure for the synthesis of these title ring systems appeared recently [<2003S1079>](#). Yadav and Kapoor described that the transformation of some oxadiazole and thiadiazole derivatives bearing specially substituted methylsulfinyl side chain **131**, when reacted with thionyl chloride, give ring-closed compounds **134**. The reaction was carried out in pyridine under reflux conditions in 74–79% yield. As shown in [Scheme 25](#), the authors assume that the first step is the formation of the sulfonium salt **132** which undergoes cyclization with hydrogen chloride and sulfur dioxide elimination to **133** and, finally, demethylation of this intermediate leads to the final product **134**.

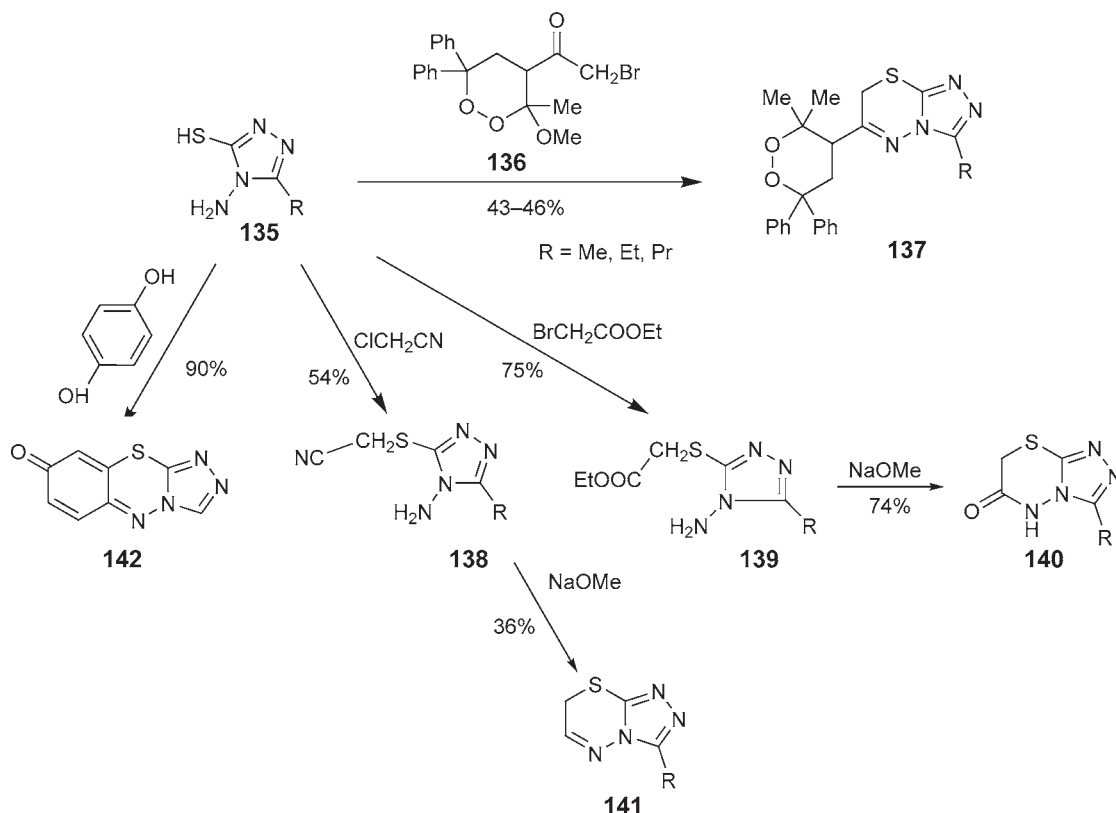
11.19.6.3.3 [1,2,4]Triazolo[3,4-*b*][1,3,4]thiadiazines

Among all the possible ring systems of this chapter, the most extended literature concerns derivatives of this ring system during the past period. Also, extensive literature data can be found in CHEC-II(1996) [<1996CHEC-II\(8\)479>](#). The huge number of the derivatives synthesized does not allow complete coverage of all particular compounds.



Scheme 25

Several ring-closure reactions for [1,2,4]triazolo[3,4-*b*][1,3,4]thiadizines have been described, and all these procedures started from 3-mercapto-4-amino[1,2,4]triazole **135** (Scheme 26). A common structural feature of the reagents is the presence of the CH_2X (X = halogen atom) moiety which allows the alkylation at the sulfur atom followed by a ring-closure reaction via an elimination step. Some typical ring closures are shown in Scheme 26.



Scheme 26

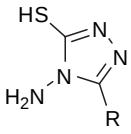
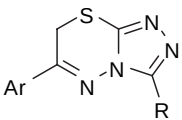
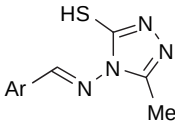
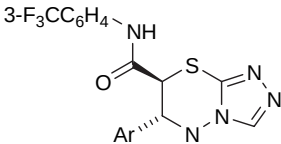
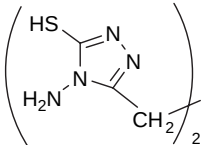
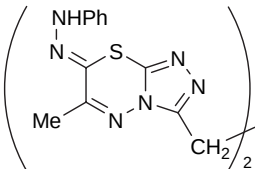
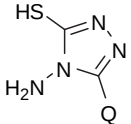
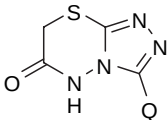
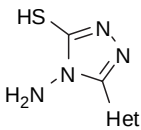
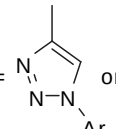
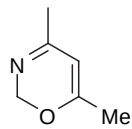
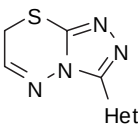
The reaction of **135** with the 1,2-dioxane derivative **136** yielded the derivative of the fused ring system **137** in moderate yield (43–46%) [2000JHC269]. Vainilavicius *et al.* have transformed **135** with chloroacetonitrile to the alkylated derivative **138** and with ethyl bromoacetate to **139** [2001M825]. They found that **139** could be ring-closed to **140** in high yield, whereas **138** when treated with sodium methoxide gave **141** in poor yield. Direct routes to **140** and **141** starting from **135** have also been elaborated.

An enzymatic procedure for the synthesis of **142**, starting from **135**, has been described by Bhalerao *et al.* <1994T4019>. The product **142** has been synthesized by the use of laccase enzyme under mild conditions (aqueous acetonitrile, rt, 12 h) in 90% yield.

Further synthetic applications of the same or similar methodologies are summarized in **Tables 4–6** followed by short description of some particular ring closure reactions illustrated in **Schemes 27, 28, and 29**.

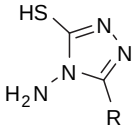
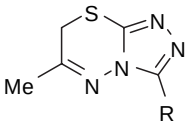
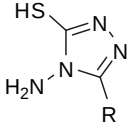
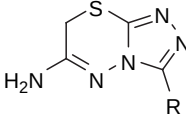
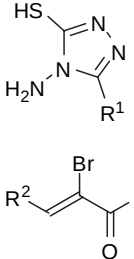
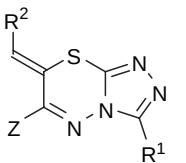
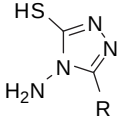
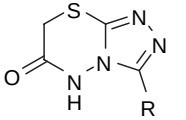
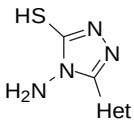
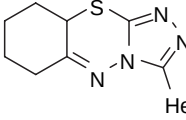
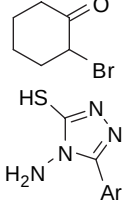
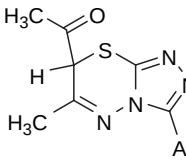
The most widely used method for the ring closure to the title ring system is the reaction of a 3-mercapto-4-amino[1,2,4]triazole compound with an α -halo-oxo reagent. The particular realizations of these syntheses are summarized in **Table 4**. Comparison of the reference lists shows that reactions with phenacylhalogenides and analogues (entry 1) is by far the best method. Synthesis of altogether more than 150 derivatives are described in

Table 4 Synthesis of [1,2,4]triazolo[3,4-b]thiadiazines by reaction of 3-mercapto-4-amino[1,2,4]triazoles with α -halo-oxo reagent

Entry	Starting compound + reagent	Product	Yield (%)	Reference
1	 ArCOCH_2Br		33–98	1996FA793, 1997PJC1049, 2005IJB628, 2003ZOR1088, 2002IJB1257, 2001FA919, 2001AF569, 1996AP427, 1995IJB939, 1995PS123, 1996PHA123, 2002SC3455, 2005JHC233, 2005HAC621, 1998IJB183, 1997IJB782, 1995IJB707, 2000PS11
2	 $3\text{-CF}_3\text{-C}_6\text{H}_4\text{-NHCOCH}_2\text{Cl}$		63–71	2003KGS631
3	 Ph-NHN=CCl-COMe		92	2002ZNB552
4	 $\text{Q} = \text{NHSO}_2\text{C}_6\text{H}_3(2,5\text{-di-Cl})$ $\text{ClCH}_2\text{COOEt}$	 $\text{Q} = \text{NHSO}_2\text{C}_6\text{H}_3(2,5\text{-di-Cl})$	72	2002HAC316
5	 $\text{Het} =$  or  ClCH_2CHO		64–88	2000JCCS1115, 2001RRC905

(Continued)

Table 4 (Continued)

Entry	Starting compound + reagent	Product	Yield (%)	Reference
6	 $\text{CH}_3\text{COCH}_2\text{Cl}$		67–70	2002PS2403, 1995IJB707
7	 ClCH_2CN		60–70	2002PS2403
8		 $\text{Z} = 5\text{-nitro-2-furanyl}$ $\text{R}^1 = \text{Me, Et, Ph, } p\text{-tolyl}$ $\text{R}^2 = \text{Ph, substituted phenyl}$	45–90	1994EJM301
9	 $\text{R} = \text{CH}_2\text{OAr, 4-MeO-3-Br-C}_6\text{H}_3$ ClCH_2COOH		65–74	1995IJB707, 2002IJB1257 1996FA793, 1998IJB183, 1997IJB782
10	 (Het = see with entry 5)		47–58	2000JCCS1115, 2001RRC905
11	 $\text{CH}_3\text{COCHClCOCH}_3$		75	2002PS487

these literature sources, and most of the transformations have been carried out in high yields. Moderate yields have been experienced only in exceptional cases. Other reagents used are chloroacetylamine (entry 2), arylhydrazonoyl chloride (entry 3), ethyl chloroacetate, chloroacetaldehyde (entry 5), chloroacetone (entry 6), chloroacetonitrile (entry 7) and 3-haloenone (entry 8), chloroacetic acid (entry 9), and 2-bromocyclohexanone (entry 10).

Ring closures of 3-mercapto-4-amino[1,2,4]triazole with benzoin or related compounds is also a well-established approach for the synthesis of the title compounds (with [Table 5](#), entry 5, (tosyloxy)methyl 2-hetarylketones were used). These procedures are summarized in [Table 5](#).

Table 5 Ring closures to [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines by reaction of 3-mercapto-4-amino[1,2,4]triazoles with benzoin or related reagents

Entry	Starting compound	Product	Yield (%)	Reference
1			25–50	1995IJB707
2			55–60	1998IJB183 , 2001IJB828
3			65–73	2001IJB640
Het = 5-Aryl-3-pyrazolyl group				
4			73	2005IJB628
5			90	1998SC3133

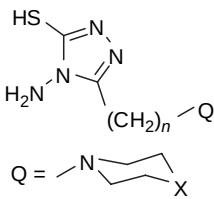
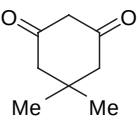
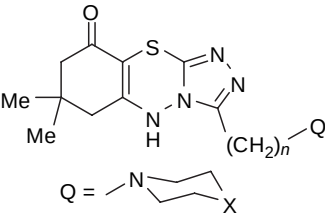
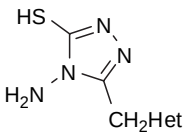
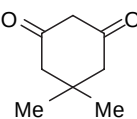
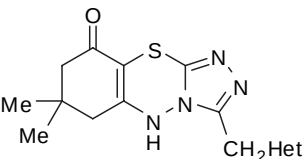
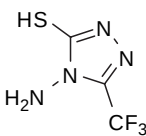
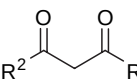
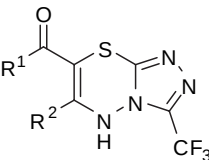
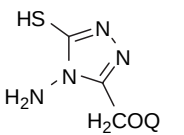
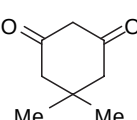
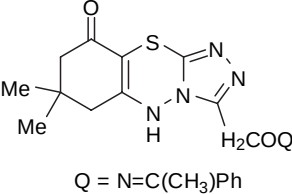
(Tosyloxy)methyl 2-hetarylketone was used as the reagent (heteroaryl groups: furan and thiophene derivatives).

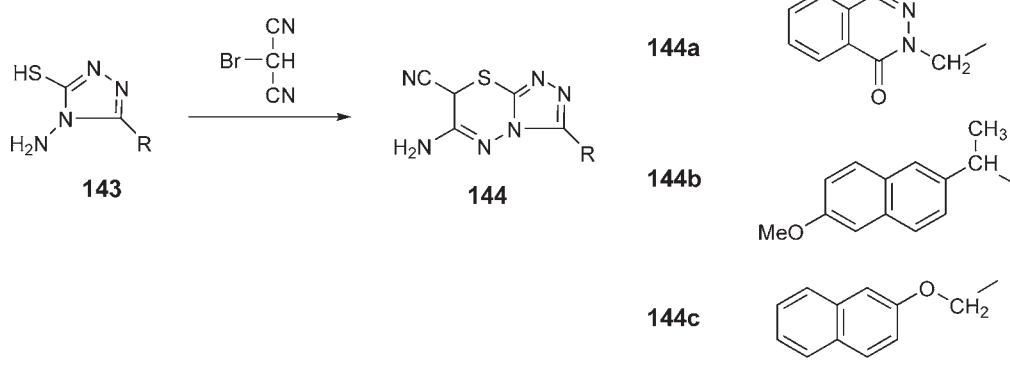
3-Mercapto-4-amino[1,2,4]triazole can also be transformed to derivatives of the title ring system by 1,3-dioxo reagents. These transformations are summarized in [Table 6](#). In most of these cases, 5,5-dimethylcyclohexane-1,3-dione was used, and, accordingly, this procedure can lead to some cyclohexenyl-fused derivatives.

Transformations of 5-substituted 3-mercapto-4-amino[1,2,4]triazoles [143](#) with bromomalonitrile are shown in [Scheme 27](#). These reactions were carried out in ethanolic potassium hydroxide to yield *N*-phthalazinemethylene [144a](#), [<2003PS1987>](#) substituted 1-naphthyl-1-ethyl [144b](#), [<2002HAC199>](#) and 2-naphthyloxymethyl derivatives [144c](#), [2001PS223>](#).

Synthetic routes to the title ring system using two other reagents, acetylene dicarboxylic ester and 2,4-dinitrochlorobenzene, are shown in [Scheme 28](#). Reaction of [145](#) with DMAD (or its ethyl analogue) yields a ring-closed

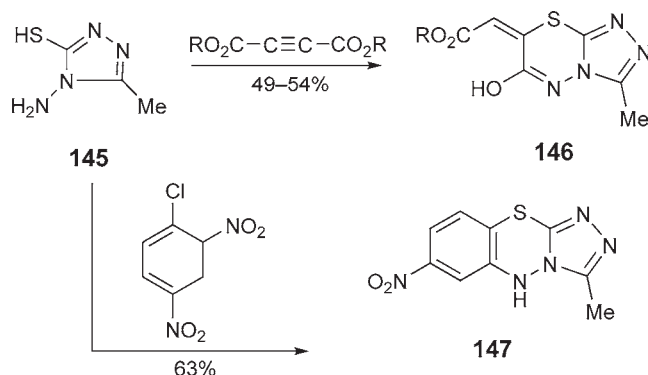
Table 6 Cyclization of 3-mercapto-4-amino[1,2,4]triazoles with β -dioxo reagents

Entry	Starting compound	Reagent	Product	Yield (%)	Reference
1				15–25	1995IJB707
2				50–70	1997IJB782
3				66–70	1998PS41
4				50	2001IJB828

**Scheme 27**

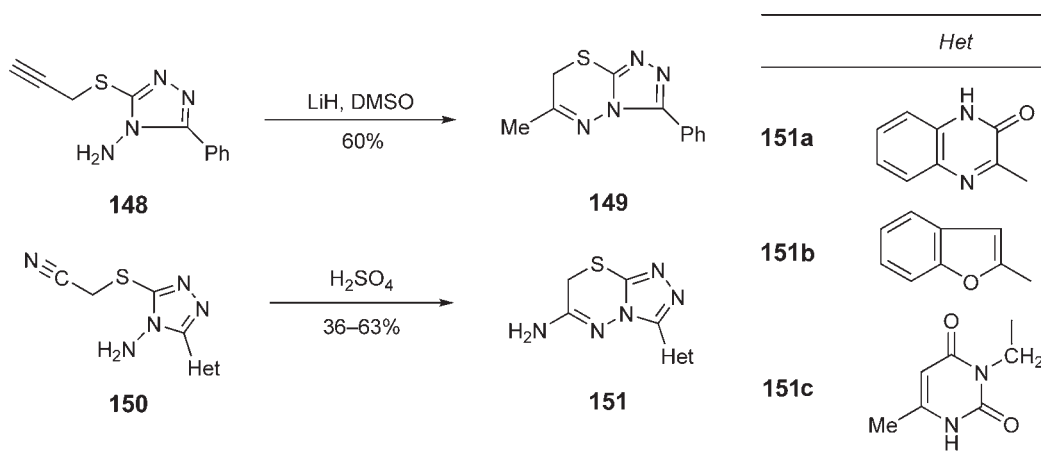
product **146** bearing a hydroxy group and an *exo*-double bond on the thiadiazine ring in medium yield <2000PS211>. The method was also applied to more complicated substituted cases <2003PS1987>.

Reaction of **145** with 2,4-dinitrochlorobenzene to give the tricyclic ring-closed product **147** can be carried out in DMF under heating for several hours; the yield is more acceptable than in the previous case <2000PS211>.



Scheme 28

In some examples – in contrast to the above cases – an internal nucleophilic attack of a triple bond can occur (in an *exo-dig*-fashion), resulting in the formation of a new six-membered ring. Such conversions are shown in Scheme 29.



Scheme 29

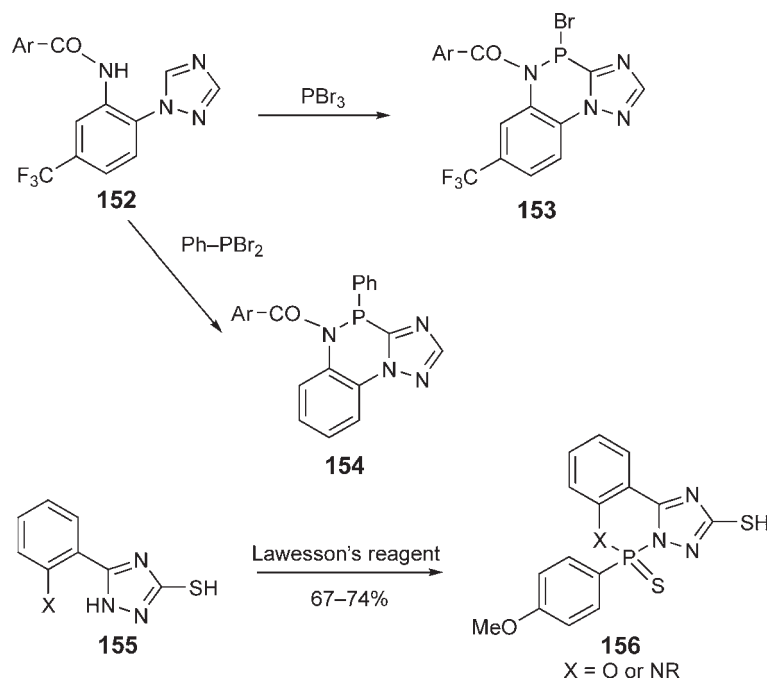
The *S*-propargyl compound **148** was found to cyclize to **149** in the presence of lithium hydride in dimethyl sulfoxide (DMSO) under heating [<2000PS211>](#), and this latter compound **149** was obtained in 60% yield. With related compounds containing the $\text{C}\equiv\text{N}$ group **150**, similar transformations were carried out to yield some hetaroaryl-substituted products. Thus, the quinoxalyl derivative **151a**, the benzofuryl compound **151b**, and the pyrimidine derivative **151c** were obtained in moderate to good yields (36–63%) [<2000PS101, 2002EJC423, 2001M825>](#).

11.19.6.4 Ring Closures to Phosphorus-Containing Heterocycles

As indicated in the introductory part, three ring systems containing phosphorus atom have been synthesized. These syntheses are shown in Scheme 30.

Reaction of the benzoylaminotriazole compound **152** with phosphorus tribromide lead to the cyclized product, to the benzologue of the [1,2,4]triazolo[5,1-*c*][1,4,2]diazaphosphinine derivative **153**, as described by Zarudnitskii *et al.* [<2002HAC146>](#). The same starting compound was also reacted with dibromophenylphosphine to yield the *P*-phenyl product **154**.

Ring closure to another phosphorus-containing benzologue ring system was reported by Moustafa [<2000PS11>](#). In this study, 2-alkylaminophenyl- and 2-hydroxyphenyl-4-mercapto[1,2,4]triazoles (**155**: X = alkylamino or O) were reacted with Lawesson's reagent. The cyclizations were reported to proceed in good yields (67–74%) to afford benzologues of [1,2,4]triazolo[4,3-*f*][1,3,2]diazaphosphinine and [1,2,4]triazolo[4,3-*f*][1,3,2]oxazaphosphinines **156** (Scheme 30).

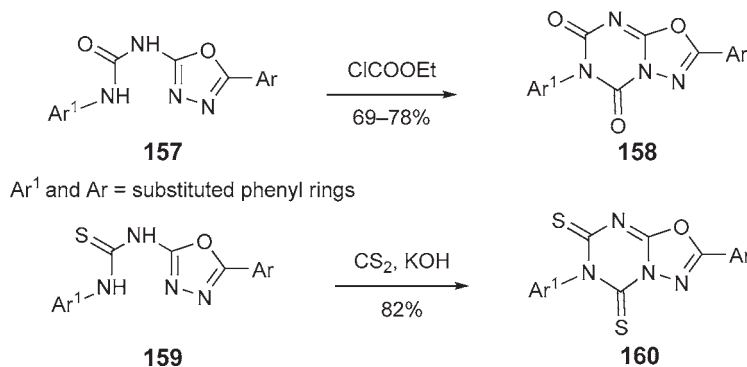


Scheme 30

11.19.6.5 Ring Closures to Fused Triazines

11.19.6.5.1 Fused [1,3,5]triazines

Four different ring systems belonging to this category have been published during the past period: synthesis of [1,3,4]oxadiazolo[3,2-*a*]triazines, [1,3,4]thiadiazolo[3,2-*a*]triazines, and two [1,2,4]triazolo[1,3,5]triazines, the [1,5-*a*] and [4,3-*a*] fused ones, are discussed here (Scheme 31).

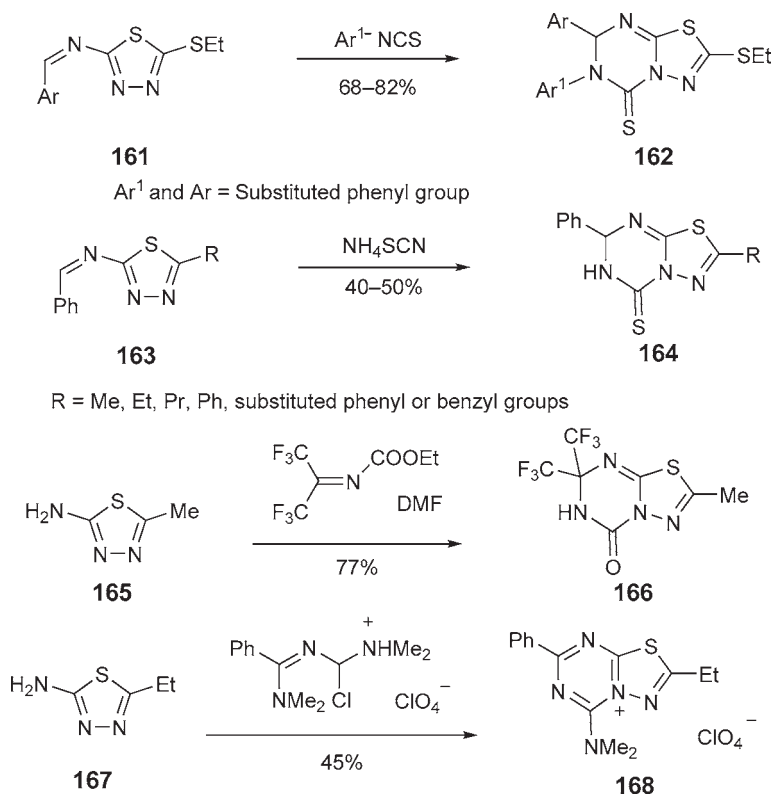


Scheme 31

Synthetic routes to [1,3,4]oxadiazolo[3,2-*a*]triazines are exemplified by two transformations, as shown in Scheme 31. Mishra *et al.* <2000JFA5465> found in the course of their studies on agrochemically important compounds that the oxadiazolylurea derivative 157 can conveniently be converted to the ring-fused [1,3,5]triazine compound 158 by reaction with ethyl chloroformate. The reaction proceeds – depending on the Ar and Ar¹ groups – generally in good yield. The transformation of the oxadiazolylthiourea 159 with carbon disulfide follows a similar pattern <2003IJB215> and leads to the dithione 160 in excellent yield (82%).

Transformations of [1,3,4]thiadiazolylazomethines to thiadiazolo[3,2-*a*][1,3,5]triazinones are demonstrated in Scheme 32. The azomethines 161 containing various aryl groups were treated with different aryl isothiocyanates

to result in ring closure to derivatives **162** <1994JFA1352> in good to excellent yields (68–82%). Reaction of the azomethine **163** bearing various R groups on the thiadiazole ring with ammonium rhodanide led to a similar result <2003IJB2583> and gave rise to a series of differently R-substituted bicyclic compounds **164**.

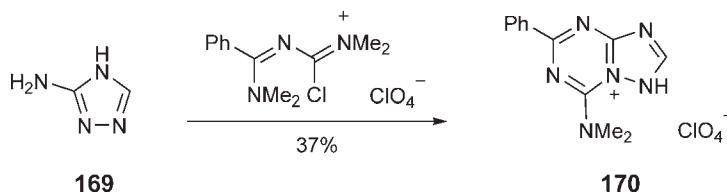


Scheme 32

Two other results should be reviewed here, too. The substituted thiadiazolo[3,2-*a*][1,3,5]triazinone compound (having two trifluoromethyl groups) was described by Sokolov and Aksinenko <2003IZV2053>: 2-amino-5-methyl[1,3,4]thiadiazole **165** was heated with *N*-ethoxycarbonyl-bis-trifluoroacetone imine in DMF in the presence of *p*-toluenesulfonic acid to yield the cyclized product **166** in good yield (77%).

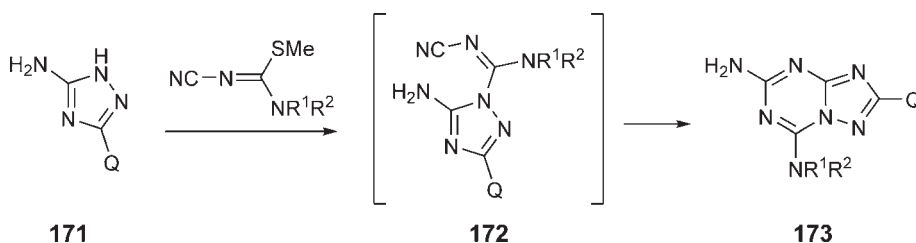
The last example for the synthesis of this ring system discussed in this section is somewhat different from the previous ones as it presents formation of a positively charged thiadiazolo[3,2-*a*][1,3,5]triazinium salt as published by Okide <1994JHC535>: the 2-amino-5-alkyl[1,3,4]thiadiazole **167** was reacted with 1-chloro-1,3-bis(dimethylamino)-3-phenyl-2-azaprop-2-enylium perchlorate (a reagent which was synthesized by the same author earlier <1992JHC1551>) to give the quaternary salt **168** in moderate yield (45%) (Scheme 32).

This synthetic strategy also proved to be also suitable for the ring closure to the related [1,3,4]triazolo[2,3-*a*][1,3,5]triazinium salts, as shown in Scheme 33 <1994JHC535, 1995JHC1833>: reaction of **169** with 1-chloro-1,3-bis(dimethylamino)-3-phenyl-2-azaprop-2-enylium perchlorate gave the quaternary salt **170** in 37% yield.



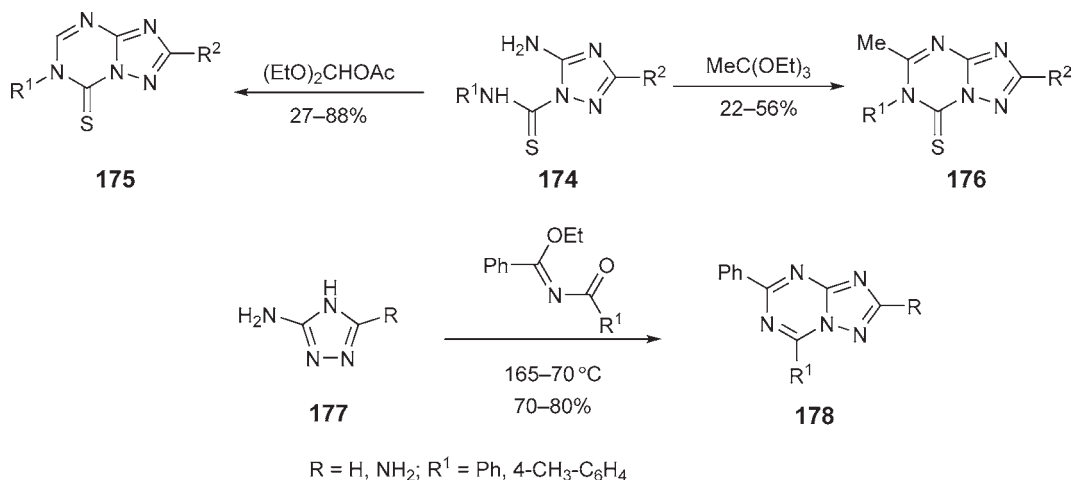
Scheme 33

Synthetic routes to [1,2,4]triazolo[1,3,5]triazines were discussed in CHEC-II(1996) <1996CHEC-II(8)479> A novel application for cyclizations to this ring system by using *N*-cyano-*N,N*-dialkyl-*S*-methylisothiourea has recently been published by Berecz *et al.* (Scheme 34) <2002JHC327>. These authors showed that this reagent can react with various 3-amino[1,2,4]triazoles **171**. The supposed intermediate **172** is a result of the attack of N-2 of the triazole ring at the carbon atom of the reagent with removal of methylmercaptan and, then, the internal nucleophilic addition of the amino group at the cyano carbon atom occurs to give the cyclized product **173**.



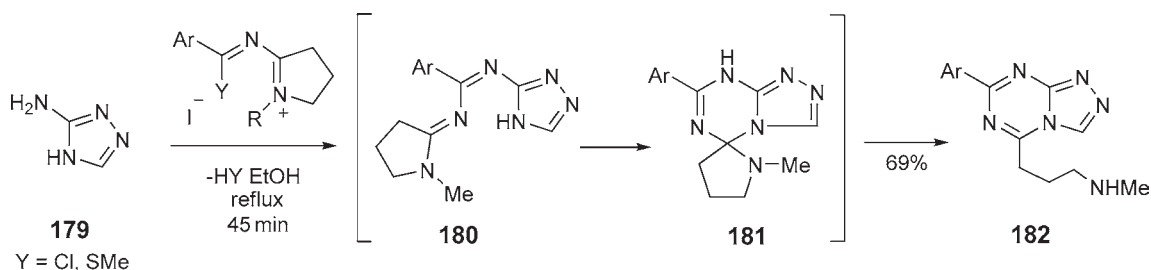
Scheme 34

Ring closure to fused triazinethiones has been described by Akahoshi *et al.* <1998JME2985> as shown in Scheme 35. The thiourea derivative **174** bearing the triazole group was treated with two different kinds of reagents: reaction with diethyloxymethyl acetate yielded **175**, whereas transformations with orthoesters lead to the 5,6-disubstituted derivatives **176**. Manifestation of the similar ring-closure principle has been observed in a side reaction by Reiter and Barkóczy <1997JHC1575>. Scheme 35 also shows a different and efficient ring-closure procedure to this ring system described by Bekircan *et al.* <2005AP365>. Differently substituted 3-amino[1,2,4]triazoles **177** were treated with an acylated iminoether reagent (i.e., with *N*-(ethoxyphenylmethylene)benzamide) at elevated temperature to yield the heteroaromatic ring-closed products **178** in high yields.

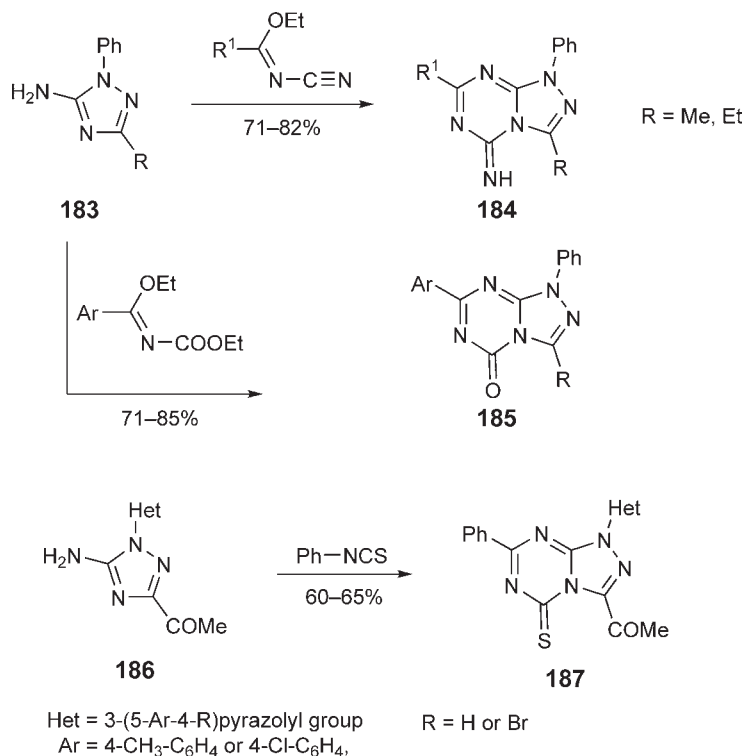


Scheme 35

Synthetic procedures to the related [1,2,4]triazolo[4,3-*a*][1,3,5]triazines are shown in Schemes 36 and 37. Liebscher *et al.* <2003S1201> reported a series of transformations starting from 3-amino[1,2,4]triazole **179** to result in formation of the ring-fused product **182**, as shown in Scheme 36. Reaction of **179** with some cyclic iminium salts gave rise to 5-aminoalkyl-7-aryl[1,2,4]triazolo[4,3-*a*][1,3,5]triazine **182** in good yield (69%). The reaction was rationalized by supposing initial formation of the diazadiene intermediate **178**, which can undergo ring closure to the spiro-fused second intermediate **180**. Finally, ring-chain tautomerism can result in formation of the heteroaromatic system of **181**.



Scheme 36

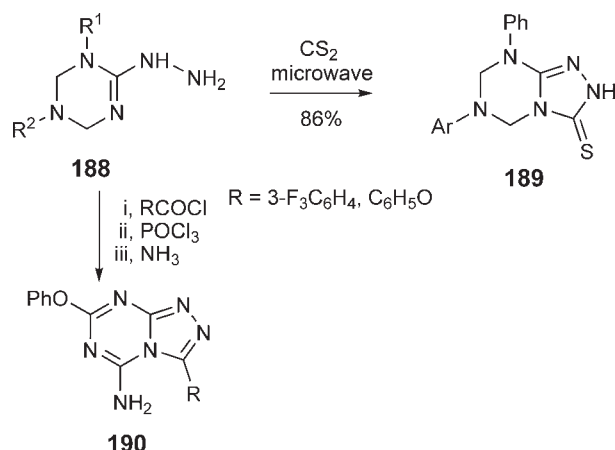


Scheme 37

Scheme 37 presents further synthetic strategies to derivatives of the same ring system. Thus, transformation of 2-phenyl-3-amino[1,2,4]triazole derivatives **183** with ethyl *N*-cyanoacetimidate yielded the correspondingly substituted 1-phenyl [1,2,4]triazolo[4,3-*a*][1,3,5]triazine-5-imine **184** in high yield, whereas the same aminotriazoles when reacted with ethyl aryl(*N*-ethoxycarbonyl)imidate yielded related fused 5-triazinones **185** <2005SC2467>. *N*-Heteroaryl-substituted aminotriazoles **186** were also treated with phenylisothiocyanate in order to synthesize the same heterocyclic ring system <1997IJB91>: heating the reaction mixture in pyridine for 3 h led to formation of the cyclized products **187** in good yield (60–65%).

In contrast to the above-discussed cyclizations, two syntheses including ring closure of the five-membered ring have been described for [1,2,4]triazolo[1,5-*a*][1,3,5]triazines. The chemical transformations are shown in **Scheme 38**. Caulkett *et al.* published that the 2-hydrazino[1,3,5]triazine derivative **188** when treated with acid chlorides underwent ring closure and subsequent treatment with ammonia yielded the 5-amino compound **190** <1995J(P1)801>.

Also, 2-hydrazino[1,3,5]triazines were found to be suitable for ring closure to give fused triazoles as described by Dandia *et al.* <2004SC1141>. These authors reported that derivative **188** (R¹ = 4-F-C₆H₄, R² = Ph) reacted with carbon disulfide under microwave irradiation and furnished the fused triazol-thione **189** in excellent yield (86%).



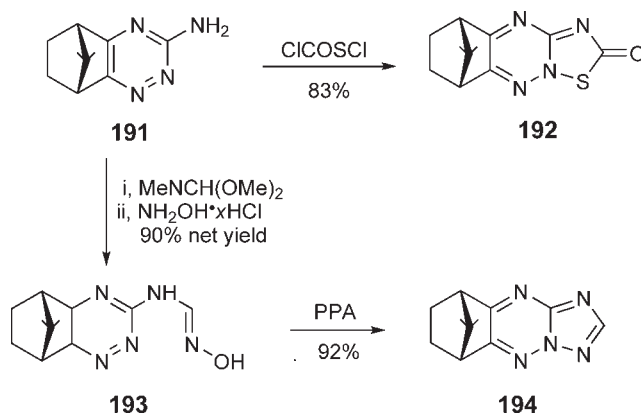
Scheme 38

11.19.6.5.2 Ring closure of *b*-fused [1,2,4]triazines

11.19.6.5.2(i) Ring closure of the five-membered ring

Three different ring systems with *b*-fusion of the [1,2,4]triazine ring (a fused thiadiazole and two different triazoles) have been described during the past period.

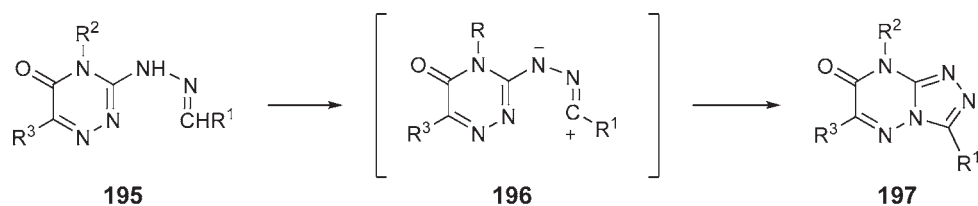
Nagai *et al.* carried out various transformations with camphor-fused amino[1,2,4]triazine **191** <1998JHC293> (Scheme 39). Reaction of **191** with chlorocarbonylsulfonyl chloride yielded the fused thiadiazolone **192** in high yield (83%). The same starting compound also proved to be suitable for the synthesis of the fused triazole derivative **193**. To this end, **191** was first subjected to two subsequent transformations: first by dimethylformamide dimethylacetal followed by treatment with hydroxylamine hydrochloride to give an *N*-hydroxyamidine **193** in 90% overall yield, and then this compound was treated with polyphosphoric acid to yield the fused triazole product **194** in 92% yield.



Scheme 39

A 1,5-dipolar cyclization route to [1,2,4]triazolo[4,3-*b*][1,2,4]triazinones has been elaborated by Shawali and Gomha <2002T8559>, and the results are summarized in Scheme 40. The direct starting compound for the ring-closure reaction is the active intermediate iminonitrilimine **196**, which is formed upon oxidation of the hydrazone **195**. Intermediate **196** undergoes 1,5-dipolar cyclization and affords the ring-closed product **197**. The transformation has been carried out both in the case of the *N*-unsubstituted ($R = H$) and in the case of the *N*-methyl ($R = CH_3$) compound.

For the synthesis of derivatives of this ring system also, several other reports appeared. These results are shown in Scheme 41.

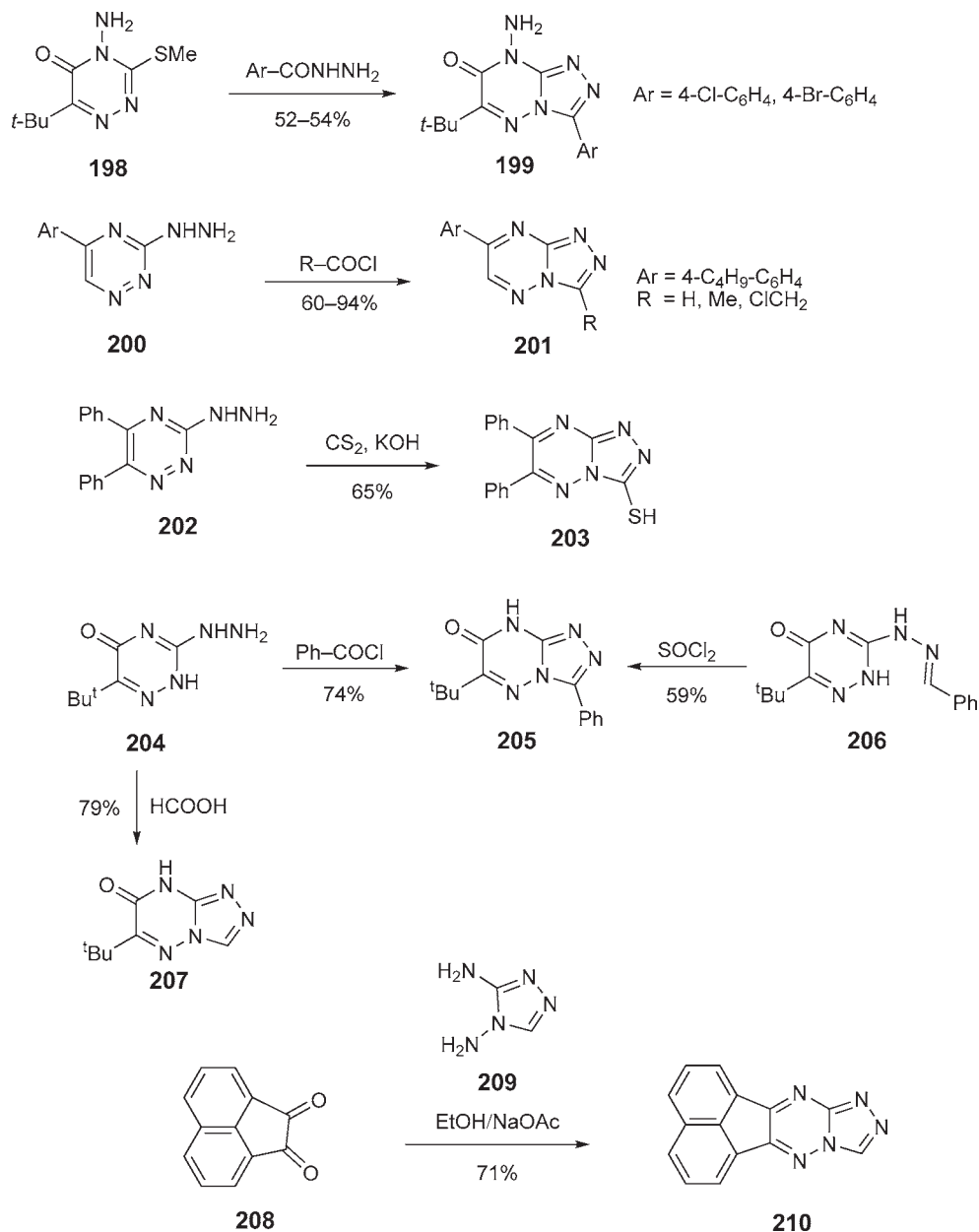


$R^1 = \text{H, Me}$

$R^2 = \text{phenyl, substituted phenyl, 3-furanyl, 2-thienyl groups}$

$R^3 = \text{C}_6\text{H}_5\text{CH}_2$

Scheme 40



Scheme 41

In the case of the 3-methylsulfanotriazine derivative **198**, a simple treatment with arylhydrazides allowed the ring closure to the 3-aryl-substituted products **199** <2003KGS950>. In other cases, the hydrazine function was first introduced to position 3 of the [1,2,4]triazine ring and these compounds were then cyclized by using various reagents.

Thus, 5-aryl-3-hydrazino[1,2,4]triazine **200** was reacted with acid chlorides to yield **201** <2004AF42>, and reaction of 5,6-diphenyl-3-hydrazino[1,2,4]triazine **202** with carbon disulfide yielded a 3-mercapto product **203** <2000PJS214>.

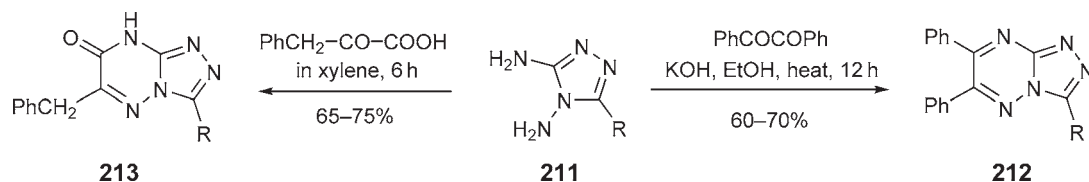
Mironovich and Ivanov found two approaches for the synthesis of the fused triazolotriazine **205** <2003ZOB1041, 2003KGS1376>: either the 3-hydrazinotriazine derivative **204** was treated with benzoyl chloride to yield **205** in high yield (74%), or the benzaldehyde triazinylhydrazone derivative **206** was subjected to transformation with thionyl chloride to afford the same product **205** in a slightly lower yield (59%). Ring closure of **204** with formic acid has also been carried out to give the product **207** with unsubstituted triazole ring.

A condensation reaction taking place between the α -diketone **208** and 3,4-diamino[1,2,4]triazole **209** has been applied for the synthesis of the pentacyclic fused triazole **210** <1994BCJ149>. The transformation was carried out in ethanol in the presence of sodium acetate and acetic acid in high yield (71%).

11.19.6.5.2(ii) Ring closure of the six-membered ring

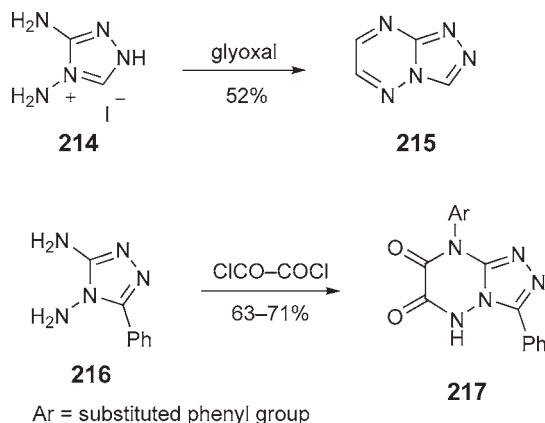
All procedures for ring closure to the title ring system by cyclization of the six-membered ring utilize the reactivity of 3,4-diamino[1,2,4]triazoles **209**: these compounds can easily react with bifunctional reagents bearing these functional groups in adjacent positions.

Holla *et al.* published <2003IJB2054> that such diamines **211** can react with benzil in the presence of alcoholic potassium hydroxide with heating and undergo ring closure to 6,7-diphenyl[1,2,4]triazolo[4,3-*b*][1,2,4]triazine derivatives **212** in good yields bearing an R group on the triazole ring depending on the starting compound applied (Scheme 42). The same authors found that 2-oxo-3-phenylpropionic acid is also a suitable reagent for the ring closure to the same ring system. In these reactions, 6-benzyl-7-oxo derivatives **213** are also formed in good yields.



Scheme 42

Two other approaches to [1,2,4]triazolo[4,3-*b*][1,2,4]triazines are shown in Scheme 43, also taking use of the reactivity of 2,3-diamino[1,2,4]triazoles. Thus, the hydroiodide salt **214** can react with glyoxal in concentrated hydrochloric acid to give the unsubstituted basic ring system **215** in 52% yield <2000KGS816>. Transformation of a 4-amino-3-anilino[1,2,4]triazole **216** to fused triazine was also described <1996SC3827>. This reaction was carried out with oxalyl chloride in the presence of triethylamine by heating for 4 h to give the fused triazine-diones **217** in good yields.



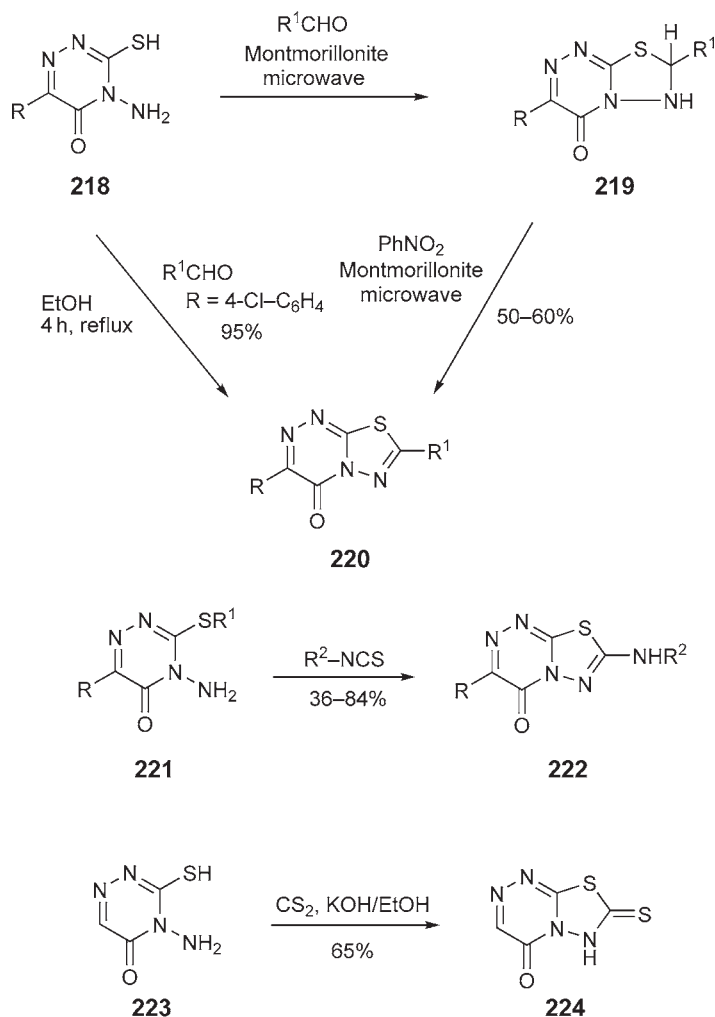
Scheme 43

11.19.6.5.3 Ring closure of *c*-fused [1,2,4]triazines

11.19.6.5.3(i) Ring closures of the five-membered ring

Most of the cyclizations of the five-membered ring relating this type of fused [1,2,4]triazines concern the synthesis of [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazines. These synthetic approaches are similar in respect to the starting compound, which is a substituted 4-amino-3-mercapto[1,2,4]triazine-5(4*H*)one **218** in each case. The ring-closure reactions can be classified into four related categories according to the reagent used: aldehyde, isothiocyanate, carbon disulfide, or an acid.

Reaction of **218** with aromatic aldehydes to give the ring-closed product **220** takes place in boiling ethanol in excellent yield (Scheme 44) <2001PHA376>. The transformation obviously proceeds via formation of a dihydrothiadiazole **219**, as also suggested for the transformation of **218** under microwave irradiation in the presence of montmorillonite <2002PS2399>.



Scheme 44

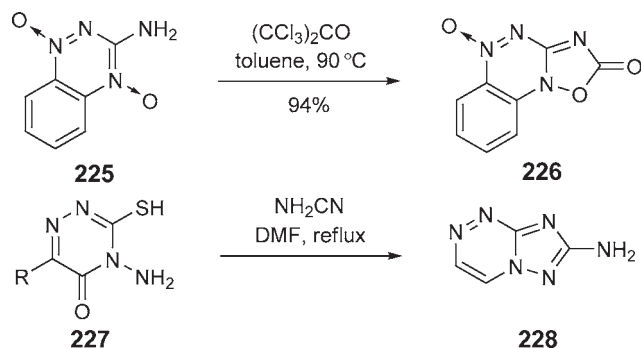
Scheme 44 also shows two further synthetic routes to [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazinones. Reaction of the 3-mercapto- or 3-methylsulfanyltriazinone **221** ($R^1 = \text{H}$ or $R^1 = \text{Me}$) with a set of isothiocyanates was reported to give the 2-amino-substituted fused ring system **222** in medium to good yield (36–84%) <1997JHC1351>. Derivative **223** was described to undergo cyclization to a fused thiadiazole **224** by treatment with carbon disulfide in the presence of potassium hydroxide in ethanol <2001PHA376>.

A high number of [1,3,4]thiadiazolo[2,3-*c*][1,2,4]triazinones **220** have been prepared by treatment of the *N*-aminomercaptotriazine **218** with various acids. The cyclization proceeds in the presence of strong acid (sulfuric acid, phosphorus oxychloride) in good to large yields. Information (R and R¹ groups, reaction conditions, yield, and references) concerning 46 different representatives of the heterocycle **220** obtained by this method are compiled in Table 7.

Table 7 Data of syntheses (R and R¹ groups, reaction conditions, yield, and references) of different representatives of the heterocycle **220**

Entry	R	R ¹	Reaction condition	Yield (%)	Reference
1	C ₆ H ₅ CH ₂	2-(5-Substituted)furyl	POCl ₃ , heat	73–82	2002IJB2690
2	Benzo[1,3]dioxid-5-ylmethyl	2-(5-Substituted)furyl	POCl ₃ , heat	80	2002IJB2690
3	Me	Ph	H ₂ SO ₄ , 120 °C	91	2004PS1469
4	Me	C ₆ H ₅ CH ₂	H ₂ SO ₄ , 120 °C	81	2004PS1469
5	Me	4-Tolyl	H ₂ SO ₄ , 120 °C	84	2004PS1469
6	Me	3-Cl-C ₆ H ₄	H ₂ SO ₄ , 120 °C	86	2004PS1469
7	Me	2-Furyl	POCl ₃ , heat	76	1997MI266
8	<i>t</i> -Bu	2-Cl-C ₆ H ₄	POCl ₃ , heat	61	1997MI266
9	4-Cl-benzyl	3-Cl-C ₆ H ₄	POCl ₃ , heat	58	1997MI266
10	Me	4-NH ₂ -C ₆ H ₄	POCl ₃ , heat	64	1997MI266
11	<i>t</i> -Bu	4-NH ₂ -C ₆ H ₄	POCl ₃ , heat	70	1997MI266
12	4-Cl-benzyl	4-NH ₂ -C ₆ H ₄	POCl ₃ , heat	56	1997MI266
13	Me	4-MeO-C ₆ H ₄	POCl ₃ , heat	57	1997MI266
14	<i>t</i> -Bu	4-MeO-C ₆ H ₄	POCl ₃ , heat	49	1997MI266
15	4-Cl-benzyl	4-MeO-C ₆ H ₄	POCl ₃ , heat	56	1997MI266
16	<i>t</i> -Bu	3-Pyridyl	POCl ₃ , heat	42	1997MI266
17	4-Cl-benzyl	3-Pyridyl	POCl ₃ , heat	45	1997MI266
18	<i>t</i> -Bu	4-F-C ₆ H ₄	POCl ₃ , heat	85	2003PS2193
19	<i>t</i> -Bu	4-F-3-PhO-C ₆ H ₃	POCl ₃ , heat	85	2003PS2193
20	<i>t</i> -Bu	2,4-Di-Cl-5-F-C ₆ H ₂	POCl ₃ , heat	80	2003PS2193
21	4-Cl-benzyl	4-F-C ₆ H ₄	POCl ₃ , heat	90	2003PS2193
22	4-Cl-benzyl	4-F-3-PhO-C ₆ H ₃	POCl ₃ , heat	78	2003PS2193
23	4-Cl-benzyl	2,4-Di-Cl-5-F-C ₆ H ₂	POCl ₃ , heat	76	2003PS2193
24	3,4-Di-MeO-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	POCl ₃ , heat	80	2003PS2193
25	3,4-di-MeO-C ₆ H ₃ CH ₂	4-F-3-PhO-C ₆ H ₃	POCl ₃ , heat	75	2003PS2193
26	3,4-di-MeO-C ₆ H ₃ CH ₂	2,4-Di-Cl-5-F-C ₆ H ₂	POCl ₃ , heat	78	2003PS2193
27	2,4-di-Cl-C ₆ H ₃ CH ₂	4-F-C ₆ H ₄	POCl ₃ , heat	82	2003PS2193
28	2,4-di-Cl-C ₆ H ₃ CH ₂	4-F-3-PhO-C ₆ H ₃	POCl ₃ , heat	80	2003PS2193
29	2,4-di-Cl-C ₆ H ₃ CH ₂	2,4-Di-Cl-5-F-C ₆ H ₂	POCl ₃ , heat	80	2003PS2193
30	Benzyl	2,4-Di-Cl-C ₆ H ₃ -OCH ₂	POCl ₃ , heat	86	1998FA395
31	Benzyl	3-Me-4-Cl-C ₆ H ₃ -OCH ₂	POCl ₃ , heat	96	1998FA395
32	Benzyl	4-Cl-C ₆ H ₄ -NCH ₂	POCl ₃ , heat	62	1998FA395
33	Benzyl	4-Br-C ₆ H ₄ -NCH ₂	POCl ₃ , heat	56	1998FA395
34	Benzyl	4-F-3-Cl-C ₆ H ₃ -NCH ₂	POCl ₃ , heat	65	1998FA395
35	Ph	4-Cl-C ₆ H ₄	POCl ₃ , heat	96	1998FA395
36	Me	2,4-Di-Cl-C ₆ H ₃	POCl ₃ , heat	78	1998FA395
37	Ph	2,4-Di-Cl-C ₆ H ₃	POCl ₃ , heat	73	1998FA395
38	Me	4-Cl-3-Me-C ₆ H ₃	POCl ₃ , heat	89	1998FA395
39	Ph	4-Cl-3-Me-C ₆ H ₃	POCl ₃ , heat	90	1998FA395
40	Me	Tolyl	POCl ₃ , heat	90	1998FA395
41	Me	4-Cl-C ₆ H ₄	POCl ₃ , heat	69	1998FA395
42	Ph	4-Cl-C ₆ H ₄	POCl ₃ , heat	88	1998FA395
43	Me	4-Br-C ₆ H ₄	POCl ₃ , heat	85	1998FA395
44	Ph	4-Br-C ₆ H ₄	POCl ₃ , heat	53	1998FA395
45	Me	4-F-3-Cl-C ₆ H ₃	POCl ₃ , heat	63	1998FA395
46	Ph	4-F-3-Cl-C ₆ H ₃	POCl ₃ , heat	57	1998FA395

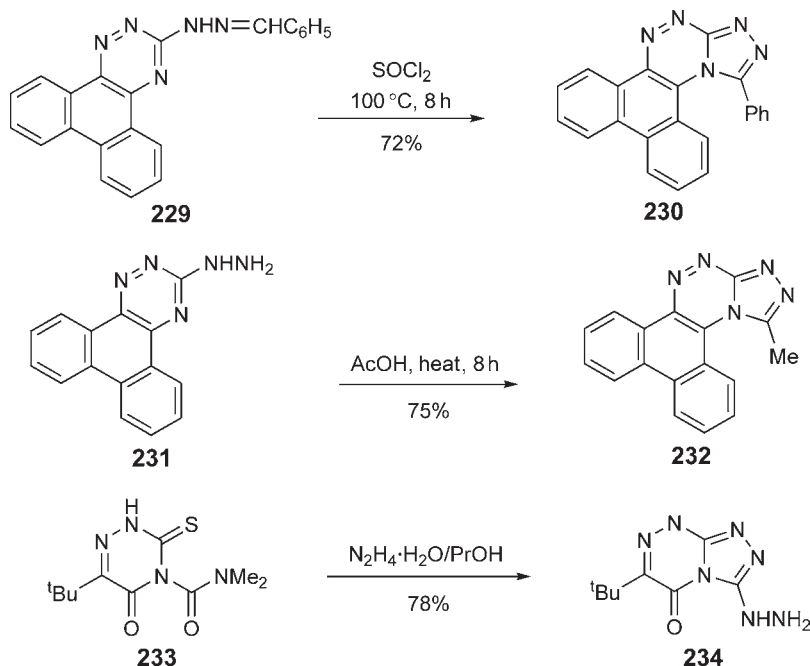
Scheme 45 presents synthetic procedures for ring systems [1,2,4]oxadiazolo[3,2-*c*][1,2,4]triazine and [1,2,4]triazolo[3,2-*c*][1,2,4]triazine published recently. 3-Aminobenzo[1,2,4]triazine-1,4-di-*N*-oxide **225** was found to participate in a ring-closure reaction when treated with bis-trichloromethyl carbonate [<1999CJC182>](#). The cyclization to **226** took place in a short reaction time in excellent yield (94%). The *N*-aminomercaptotriazine derivative **227** proved to be convenient starting compound for ring closure to [1,2,4]triazoles with different positions of heteroatoms as discussed above [<2003PS2055>](#): its reaction with cyanamide gave rise to 2-amino[1,2,4]triazolo[3,2-*c*][1,2,4]triazine **228** under reflux conditions in DMF.



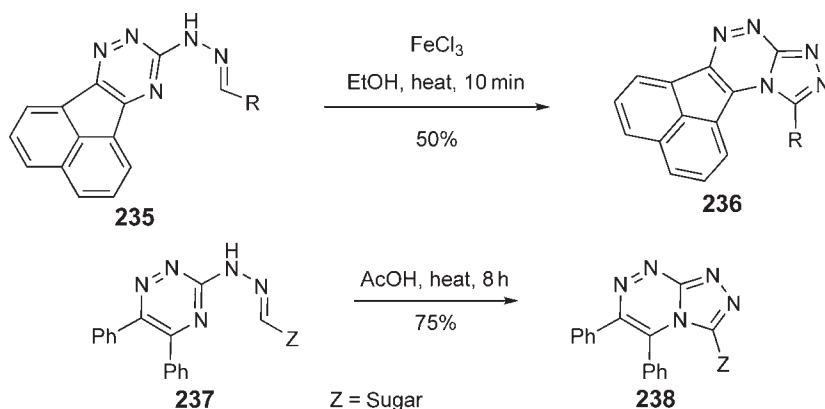
Scheme 45

Several publications from recent years can be found for synthesis of [1,2,4]triazolo[3,4-*c*][1,2,4]triazines, and these are shown in [Schemes 46 and 47](#).

Thus, the phenanthridine-fused benzaldehyde triazinyldiazine **229** was cyclized by using thionyl chloride to the phenyl substituted pentacyclic product **230** [<1998NN1385>](#). The corresponding methyl-substituted fused system **232** was obtained from the free hydrazine **231** in boiling acetic acid. Formation of a related triazinone **234** has also been described [<1994KGS1258>](#). In this quite unusual transformation, the thio-substituted cyclic urea derivative **233** was treated with hydrazine hydrate in propanol under heating. The ring-closed triazolyldiazine **234** – formed by elimination of dimethylamine – was obtained in high yield (78%).



Scheme 46



Scheme 47

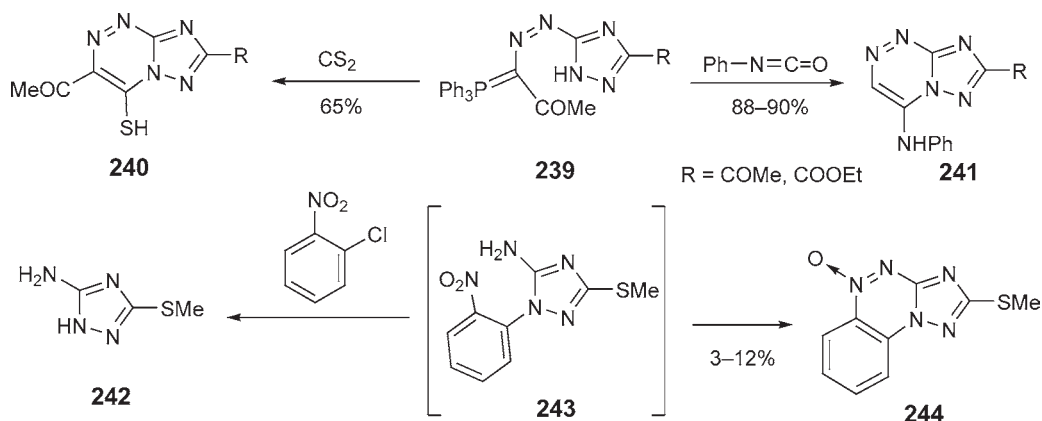
Syntheses of [1,2,4]triazolo[3,4-*c*][1,2,4]triazines by oxidation – allowing access also to some specific derivatives bearing carbohydrate side chains – are shown in [Scheme 47](#). The polycyclic triazinyldiazones of acetaldehyde **235** (R=Me) have been subjected to oxidation by ferric chloride to yield the ring-closed triazole **236** (R=Me) in moderate yield [\[1994BCJ149\]](#). Similar transformations with a sugar side chain **235** (R=sugar) have also been carried out successfully (in 60% yield) to give the corresponding substituted fused triazole **236** (R=sugar). Similar transformations have been carried out with the monocyclic triazinyldiazones **237** [\[1996PHA707\]](#): ring closures to a set of carbohydrate-substituted fused **238** were found to proceed in good yields.

11.19.6.5.3(ii) Ring closures of the six-membered ring

11.19.6.5.3(ii)(a) [1,2,4]triazolo[3,2-*c*][1,2,4]triazines

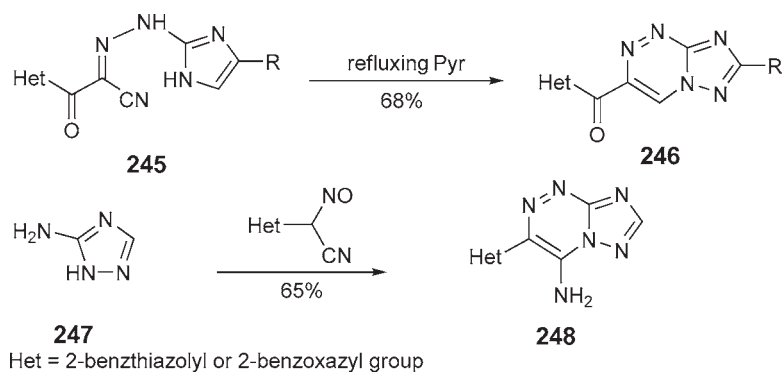
Among the *c*-fused [1,2,4]triazines, by far most of the data are available for this particular ring system, and synthetic routes have already been discussed in CHEC-II(1996) [\[1996CHEC-II\(8\)479\]](#). Novel transformations are shown in [Schemes 48–51](#).

3-[1,2,4]Triazolyazo moieties provide the correct structural connectivities of carbon and nitrogen atoms for the formation of the title ring system. Thus, the triphenylphosphono-substituted azo compound **239** was successfully cyclized to the mercapto derivative **240** by using carbon disulfide [\[2003JCCS1189\]](#) ([Scheme 48](#)). The same starting compound **239** when reacted with nitrosobenzene gave rise to the related aniline-substituted product **241**. Compilation of the nitrogen atoms of the triazine ring in a different sequence has been described by Trinka and Reiter [\[1995JHC1359\]](#). These authors carried out the arylation of 3-amino[1,2,4]triazole by 2-chloronitrobenzene to **244** formed obviously via intermediate **243**.



Scheme 48

Scheme 49 illustrates ring-closure reactions where the most important reaction step is an intramolecular nucleophilic addition of the triazole ring-nitrogen atom to the carbon atom of a cyano group to afford an *exo*-amino moiety in the product. Thus, compound **245** when refluxed in pyridine underwent a cyclization of this type to give the bicyclic product **246** bearing a benzthiazolylcarbonyl side chain in high yield (68%) <1996T7893>. The analogous benzthiazolyl derivative **248** has been prepared in a similar fashion <2002PS2497>: here the 3-amino[1,2,4]triazole **247** was treated with the appropriate nitrosoacetone nitrile to yield, obviously via formation of an intermediate hydrazono side chain with the cyano group at the end, the heteroaromatic triazolotriazine **248** in good yield (65%). Other heterocycle-substituted derivatives (e.g., 2-benzoxazolyl <1995JCM96>, 2-thiazolyl <2000JRM622>, 2-benzofuranyl <2005JCM378>, 2-benzimidazolyl <1999ZOR1384>, and 2-furyl derivatives <2004JCM808>) have also been obtained similarly.



Scheme 49

A special approach to [1,2,4]triazolo[3,2-*c*][1,2,4]triazine derivatives is the transformation of 3-diazo[1,2,4]triazoles, easily available by diazotation of aminotriazoles. These compounds already contain the five nitrogen atoms in the correct sequence in order to form the desired bicyclic ring system and, thus, their reaction with proper bifunctional reagents can give rise to the cyclized products in one single step. Such transformations are collected in **Scheme 50**.

In all these transformations, the substituted 3-diazo[1,2,4]triazole **249** is the starting compound. Thus, reaction with 1-aryl-1-formylacetonitrile leads to an amino-substituted derivative **250** <2002IZV1594>, transformation with nitroacetaldehyde gives a nitro-hydroxy compound **251** <1994KGS52>, ring closure with malonitrile yields the cyano-amino derivative **252** <1997JRM2378>, cyclization with trimethoxybenzene gives rise to the fused product **253** <2005IZV348>, use of a heteroarylacetonitrile as the reagent affords an amino- and heteroaryl-substituted product **254** <2003JRM1161>, with malonoester the cyclization leads to the ethoxycarbonyl-substituted triazinone **255** <1999ZOR1384>, whereas ring closure with ethyl diethoxyphosphorylacetate gives the cyclized product **256** bearing the phosphoryl ester side chain <1999H(51)513>. Most of these transformations proceed in good yields.

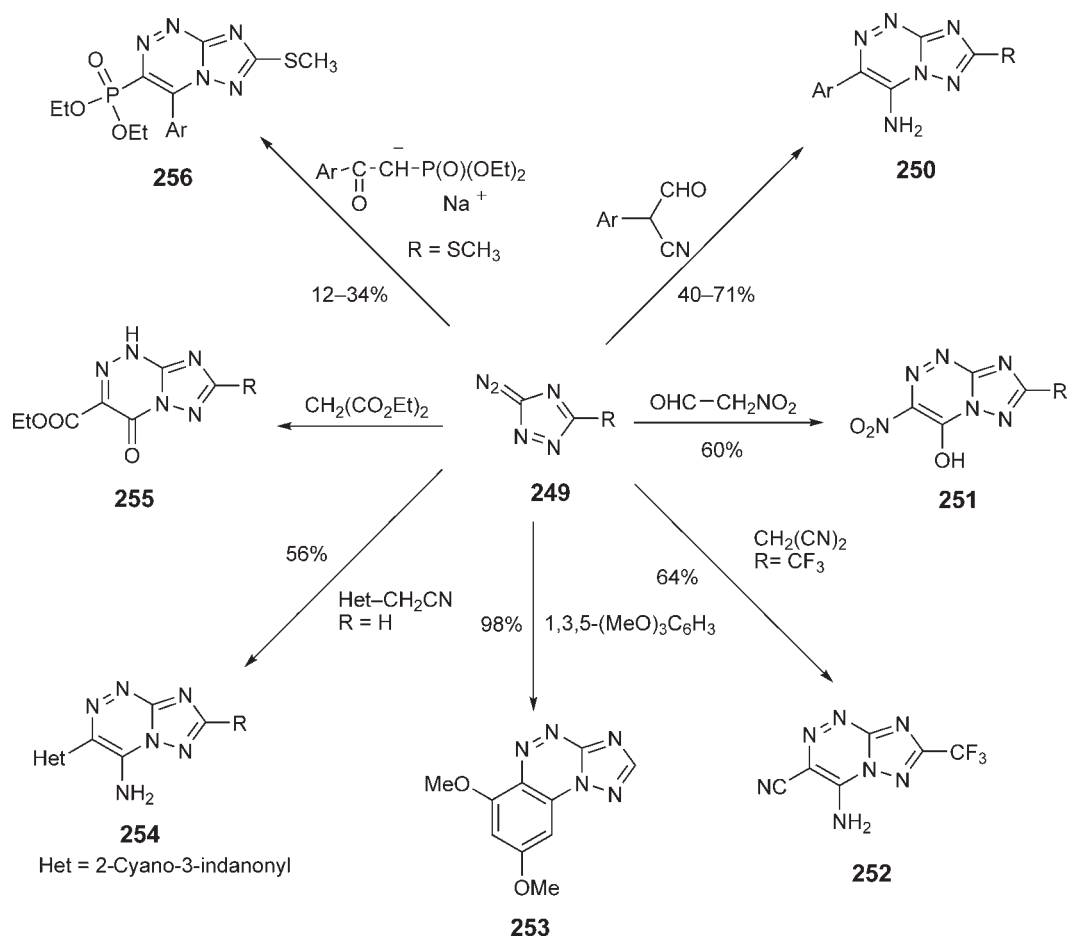
In one case, synthesis of an ^{15}N -labeled derivative has been described containing the nitrogen label in the triazole ring adjacent to the bridgehead nitrogen position <2001SC2351>. The synthesis is shown in **Scheme 51**.

The main starting compound is the labeled nitroguanidine **257** obtained from guanidine with isotope-labeled potassium nitrate. Reduction of **257** to hydrazine carboximidamide **258** was carried out with zinc and, then, ring closure to 3-amino[1,2,4]triazole **259** was carried out using formic acid. Finally, the ring closure to form the [1,2,4]triazine ring – similar to other procedures presented in **Scheme 54** – was perfected by reaction with nitrous acid followed by treatment with ethyl nitroacetate to **260**.

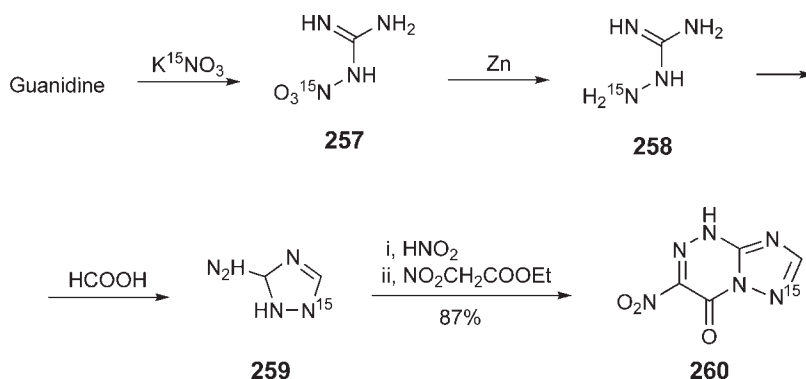
11.19.6.5.3(ii)(b) [1,2,3]Triazolo[4,3-*c*][1,2,4]triazines and [1,2,4]triazolo[3,4-*c*][1,2,4]triazines

Results concerning these ring systems are summarized in **Scheme 52**. Synthesis of a benzologue of the [1,2,3]triazolo[4,3-*c*][1,2,4]triazine ring system has been published by Abbott *et al.* <2002T3185>. The essence of the cyclization procedure is diazotation of the zwitterionic aminoaryltriazole compound **261**, whereupon an internal azo coupling takes place to yield the fused triazine **262** in low yield (24%).

Synthesis of the other ring system ([1,2,4]triazolo[3,4-*c*][1,2,4]triazine), mentioned in the title of this section, has been carried out by a procedure analogous to those shown in **Scheme 52** <2004JCM174>. Thus, the diazotriazole **263** was reacted with an α,β -unsaturated ketone in ethanolic solution in the presence of sodium acetate at room temperature to yield the cyclized product **264** in good yield (70%).



Scheme 50

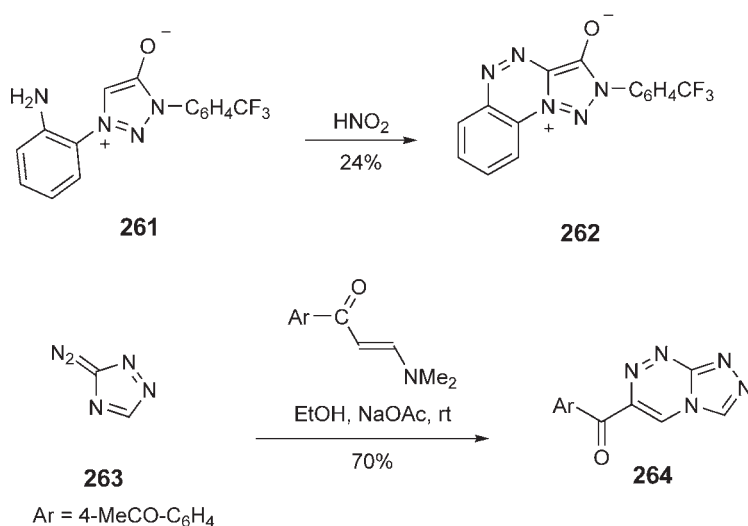


Scheme 51

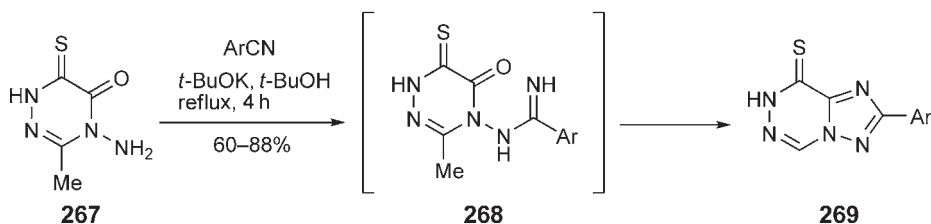
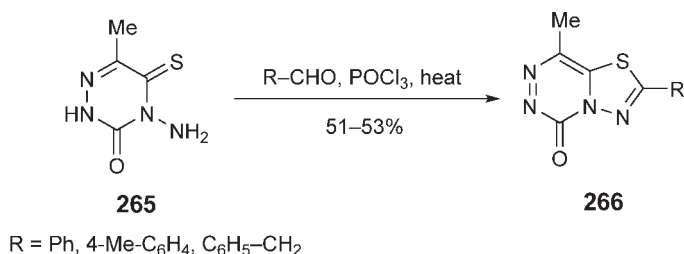
11.19.6.5.4 Ring closure of *d*-fused [1,2,4]triazines

[1,2,4]Thiadiazolo[3,2-*d*][1,2,4]triazinones have been synthesized by Heravi *et al.* <2001PS129>, and the chemical transformation is shown in Scheme 53. Thus, the *N*-aminotriazine–thione **265** reacted with aryl and benzylaldehyde to yield the ring-closed thiadiazoles **266** in medium yield (51–53%).

Synthesis of fused [1,2,4]triazoles with the same heteroatomic arrangement (i.e., [1,2,4]triazolo[2,3-*d*][1,2,4]triazines) has been published also by Heravi *et al.* <2005JHC1021>. These authors found that the *N*-aminotriazinone



Scheme 52

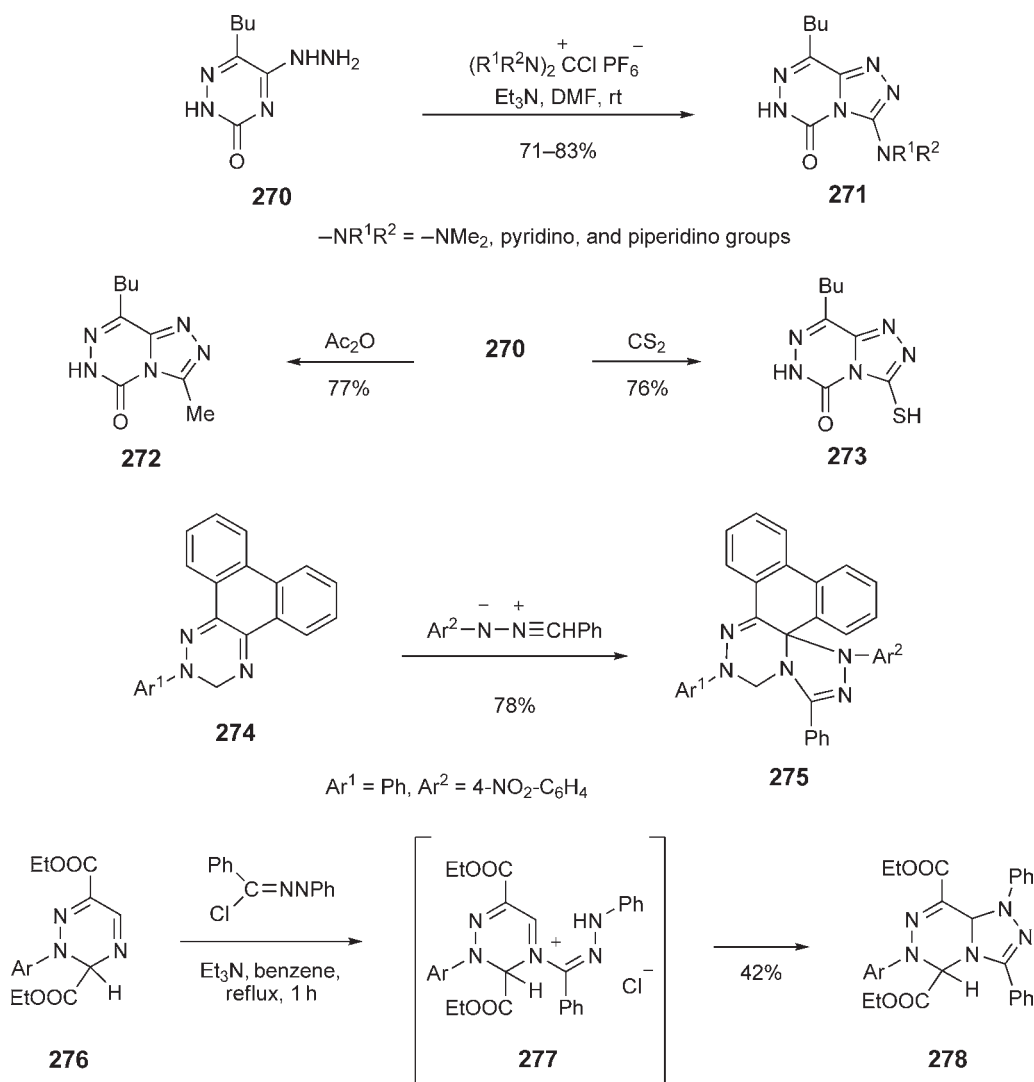


Scheme 53

267 can be conveniently transformed with a large set of aryl nitriles under basic conditions (in the presence of potassium *t*-butoxide in *t*-BuOH in refluxing conditions) to the heteroaromatic product **269** bearing the aryl group of the reagent applied in position 2. The transformation was rationalized to proceed via formation of intermediate **268**.

The synthesis of some derivatives of 8-benzyl[1,2,4]triazolo[4,3-*d*][1,2,4]triazine-5-ones has been published by Egyptian authors. Abdul-Ghani *et al.* described that the hydrazinotriazine compound **270** when treated with bisdialkylamino-chlorocarbonium hexafluorophosphate in the presence of triethylamine dimethylformamide under reflux conditions afforded the 3-substituted ring-closed product **271** bearing the amino group in position 3 of the reagent applied <2004OPP121>. The transformations were carried out in high yields (Scheme 54).

The same starting compound **270** was also subjected to ring closure by using other reagents <2003PS1143>: reaction of **270** with acetic anhydride afforded the methyl-substituted **272**, whereas reaction with carbon disulfide yielded the 3-mercapto derivative **273**.



Scheme 54

Two other synthetic routes to derivatives of this ring system should be mentioned here, and the transformations are shown in [Scheme 54](#). The phenanthrene-fused N -aryldihydro[1,2,4]triazine **274** was found to undergo 1,3-dipolar cycloaddition with diarylnitrilimine to give the cycloadduct **275** [\[1997J\(P1\)1047\]](#). This transformation is entirely analogous to that taking place with a fused oxadiazine derivative, as discussed in [Section 11.19.6.1](#).

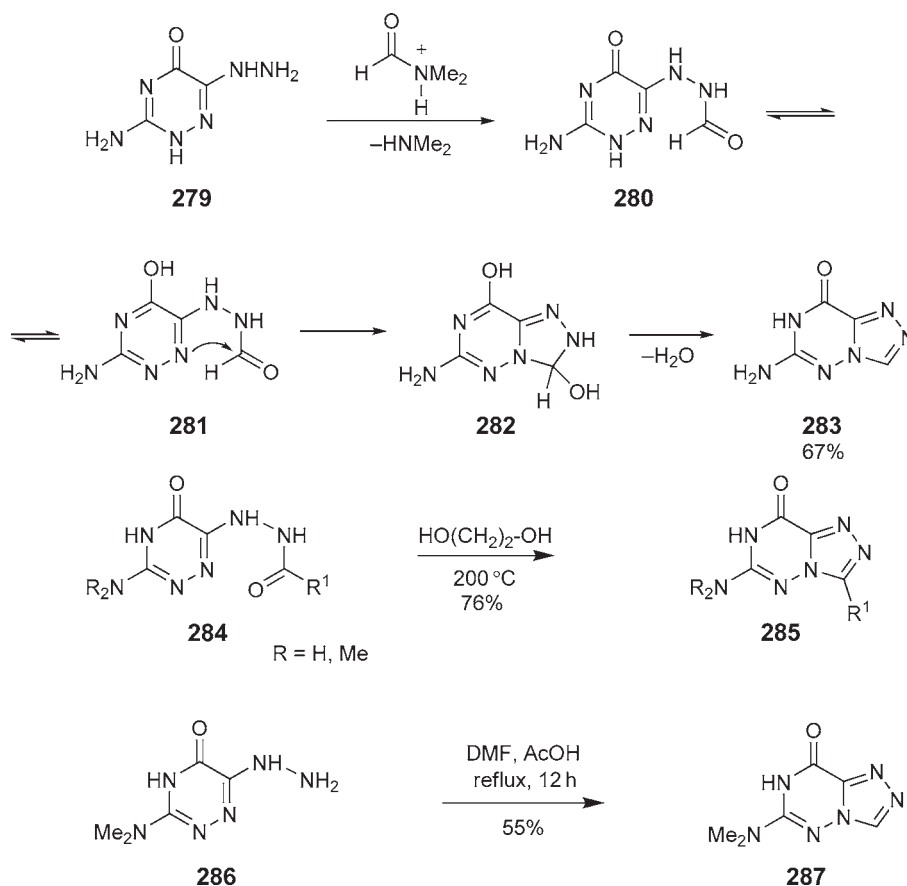
Ring closure of triazinyl diester **276** was reported by Moderhack *et al.* [\[2002M1165\]](#). This compound was treated with hydrazonoyl chloride in the presence of triethylamine in refluxing benzene. Formation of the intermediate **277** was anticipated, which, upon intramolecular cyclization, afforded the fused triazole **278** in medium yield (42%). Syntheses of other related compounds via modified synthetic routes have also been described.

11.19.6.5.5 Ring closure of *f*-fused [1,2,4]triazines

11.19.6.5.5(i) Ring closure of the five-membered ring

Very few results on the title ring systems involving cyclization of the five-membered ring have appeared in the recent years, and all reports relate to one single ring system: [1,2,4]triazolo[3,4-*f*][1,2,4]triazine. The results are shown in [Scheme 55](#).

A thorough mechanistic investigation has been published [\[2005JHC851\]](#) on transformation of the hydrazinotriazine compound **279** using DMF under acidic conditions to yield the ring-closed fused triazole **283**, as shown in [Scheme 55](#). The reaction proceeds via the tautomeric intermediates **280** and **281**, and attack of the ring nitrogen



Scheme 55

atom of the triazine moiety toward the formyl function results in a covalent hydrate **282** which spontaneously loses one molecule of water to yield the heteroaromatic product.

The acylated derivative of **279**, compound **284** ($\text{R} = \text{H}$, $\text{R}^1 = 2\text{-pentenyl}$), was also subjected to ring closure under thermal conditions [\[1995NN1601\]](#): a derivative containing a 2-pentenyl group at the R position was cyclized to **285** ($\text{R} = \text{H}$, $\text{R}^1 = 2\text{-pentenyl}$) in 76% yield.

A similar synthetic approach has also been applied by Rees *et al.* [\[1999J\(P1\)2937\]](#). These authors transformed a carbohydrate-substituted analogue of **284** ($\text{R} = \text{Me}$, $\text{R}^1 = \beta\text{-D-ribofuranosyl}$) and carried out the ring closure to a product related to **285** ($\text{R} = \text{Me}$) in high yield. The same authors found that treatment of the free hydrazine **286** with DMF and acetic acid in refluxing conditions yields the triazolotriazinone derivative **287** in medium yield (55%).

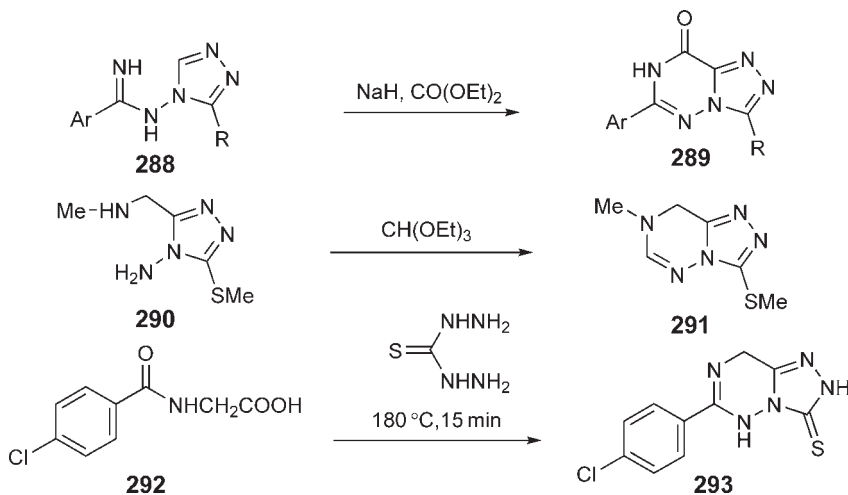
11.19.6.5.5(ii) Ring closure of the six-membered ring

Cyclizations to [1,2,4]triazolo[3,4-*f*][1,2,4]triazines by ring closure of the triazine ring have been reviewed in CHEC-II(1996) [\[1996CHEC-II\(8\)479\]](#). Such ring closure has also been reported recently, and in the course of these studies three different kinds of attachment of the ring atoms have been realized in order to create the bicyclic system. The synthetic routes are shown in [Scheme 56](#).

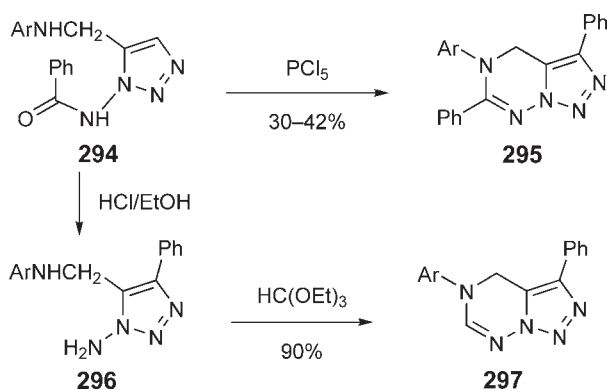
The triazole-substituted amidrazone **288** was cyclized – after deprotonation by using sodium hydride – by treatment with diethyl carbonate to yield the bicyclic product **289** [\[2005BML3900\]](#). Experimental details of this procedure have been described in the patent literature [\[2001WO047929\]](#). Two other ring closures have also been carried out: cyclization of the amino-methylamino compound **290** with triethyl orthoformate gave the *N*-methyl product **291** [\[2004KGS130\]](#), whereas reaction of *p*-chlorobenzoylglycine derivative **292** with thiocarbonohydrazide afforded the aryl-substituted product **293** [\[2002HAC316\]](#).

Synthesis of some *f*-fused [1,2,3]triazoles has been published by a Greek group [\[1996JHC599\]](#). The results are shown in [Scheme 57](#). The main starting compound was the *N*-benzoylamino derivative **294** which underwent ring

closure – with participation of the arylaminomethyl side chain – when treated with phosphorus pentachloride to the 6,7-diaryl derivative **295**. When the benzoyl group on **294** was hydrolyzed by hydrochloric acid in ethanol, the free *N*-amino compound **296** was formed which was reacted with triethyl orthoformate to give the 6-unsubstituted analogous product **297** (Scheme 57).



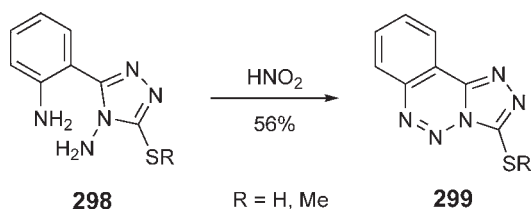
Scheme 56



Scheme 57

11.19.6.5.6 Ring closure to fused [1,2,3]triazines

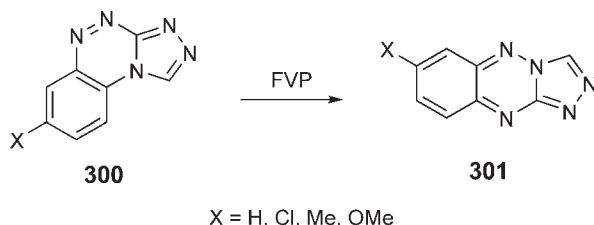
Only one publication on the synthesis of fused [1,2,3]triazines has appeared <2001SC97>. The chemical transformation is shown in Scheme 58: diazotization of **298** by using nitrous acid gave rise to the tricyclic product **299** in moderate yield.



Scheme 58

11.19.7 Ring Syntheses by Transformations of Another Ring

An Argentinian–Hungarian joint team carried out flash vacuum pyrolytic (FVP) studies with some [1,2,4]triazolo[3,4-*c*]benzo[1,2,4]triazines **300** <2005T7489> (Scheme 59). Although two N–N moieties are located in this ring system, and thus elimination of nitrogen molecule and possible rearrangements were expected, such transformation was not observed and, instead, a partial ring transformation to the linearly fused **301** was experienced.

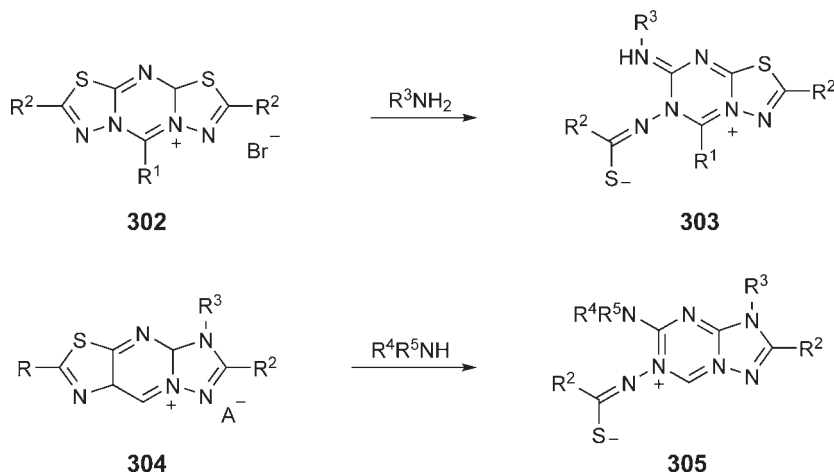


Scheme 59

FVP treatment of both isolated samples **300** and **301** resulted in a mixture containing **300** + **301**; this finding revealed that these two compounds can be mutually transformed into each other under forced conditions. Upon some kinetic measurements (determination of a negative activation entropy), the authors concluded that the ring transformation probably proceeds via a concerted sigmatropic shift to an antiaromatic diazine intermediate.

Reinvestigation of the classical synthetic route to **300** and careful analysis of the reaction mixtures revealed that the linearly fused isomers **301** can also be found in these reaction mixtures in small amounts, and these samples proved to be fully identical with those isolated from the FVP experiments.

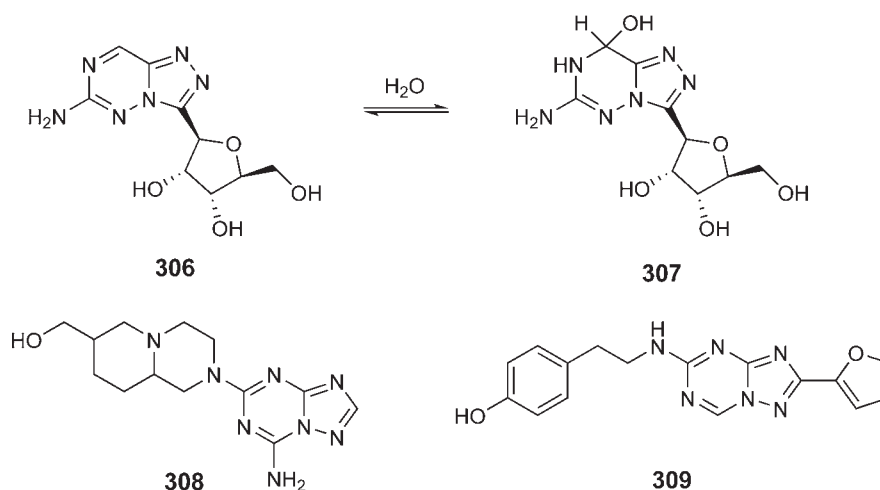
Formation of some mesoionic [1,3,4]thiazolo[3,2-*a*][1,3,5]triazines **303** and related [1,2,4]triazolo[2,3-*a*][1,3,5]triazines **305** has been observed by Anders *et al.* <2005T673>, as shown in Scheme 60. These authors reported that the quaternary salts **302** and **304** containing polyfused delocalized cations easily react with amines to result in ring opening to **303** and **305**, respectively.



Scheme 60

11.19.8 Important Compounds and Applications

Recent literature data reveal that some triazolotriazines have valuable biological properties. Some important structures are shown in Scheme 61.



Scheme 61

A recent study [<2001OL839>](#) reported that the ribosyl triazotriazine **306**, which was synthesized on the basis of preliminary computational predictions, exists predominantly as the covalent hydrate **307** in water; this compound was found to be a potent inhibitor of mammalian adenosine deaminase.

Some piperazine-containing [1,2,4]triazolo[2,3-*a*][1,3,5]triazines, for example, **308** and **309**, have been shown to be potent and selective adenosine A_{2a} receptor antagonists [<2004BML4831, 2004JME6218, 2005JME2009>](#).

11.19.9 Further Developments

During the recent period of time novel results have been published concerning five ring systems belonging to this chapter. These are summarized below.

In the area of the [1,2,4]triazolo[2,3-*b*][1,4,2]benzodithiazines (the benzologue of ring **4**) known ring closure methodologies have been applied in order to find new biologically active derivatives [<2006EJM633, 2006PJC429>](#). Also established methodologies related to those for the cyclization to **135** (see [Section 11.19.6.3.3, Table 4](#), Entry 1) have been applied in order to synthesize new, biologically active [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines (derivatives of ring system **9**) [<2005EJM1156, 2006EJM657, 2006SC1655>](#). Some of these new derivatives were regarded as potential antibacterial, antifungal, and anticancer agents.

A modified synthetic approach related to those discussed in [Section 11.19.6.5.1](#) to [1,2,4]triazolo[2,1-*c*][1,3,5]triazine-5(6*H*)ones (derivatives of ring system **18**) has been published by Abderrahim and Boujlel [<2006PS581, 2006PS995>](#), most of these derivatives have been prepared in high yields.

A new cyclization method for [1,2,4]triazolo[5,1-*c*]triazines (ring system **26**) starting from trifluoromethylated 1,2,3-triketones and resulting in formation of 4,7-dihydro derivatives has recently been published [<2005JFC1230>](#). The structure of one representative derivative has also been investigated by X-ray crystallography.

New derivatives of [1,2,4]triazolo[3,4-*f*][1,2,4]triazinones have been synthesized by earlier established cyclization methods [<2006JHC889>](#). Alkylation of the 3-mercapto group of this ring system has also been reported [<2006MI169>](#).

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Biographical Sketch



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11.20

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Four Extra Heteroatoms 1:3

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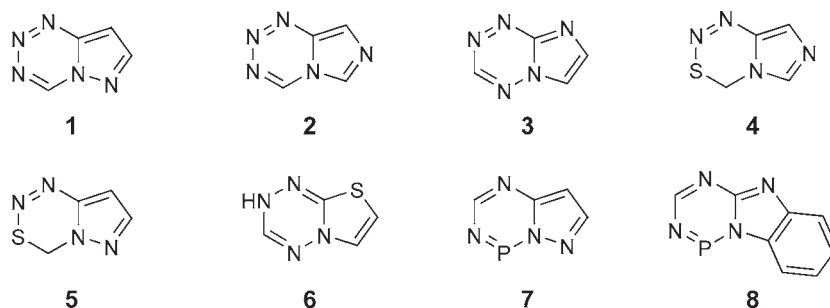
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11.20.1 Introduction

Eight ring systems: pyrazolo[3,2-*d*][1,2,3,5]tetrazine **1**, imidazo[5,1-*d*][1,2,3,5]tetrazine **2**, imidazo[1,2-*b*][1,2,4,5]-tetrazine **3**, 4*H*-imidazo[5,1-*d*][1,2,3,5]thiatriazine **4**, 4*H*-pyrazolo[5,1-*d*][1,2,3,5]thiatriazine **5**, 2*H*-thiazolo[3,2-*b*]-[1,2,4,5]tetrazine **6**, pyrazolo[1,5-*c*][1,3,5,2]triazaphosphorine **7**, and benzo[*d*]imidazo[1,2-*c*][1,3,5,2]triazaphosphorine **8** are discussed in this chapter (Scheme 1). Four of these (**1**, **2**, **3**, and **6**) have already been treated in CHEC-II(1996) <1996CHEC-II(8)493>, whereas research on the other four has appeared only recently. In several cases, partially saturated forms of these rings have been obtained. The most substantial literature relates to derivatives of ring system **2** because of the antitumor activity of these compounds.

11.20.2 Theoretical Methods

Very little amount of theoretical results were surveyed in CHEC-II(1996) <1996CHEC-II(8)493>. Since that time, no such studies have appeared.

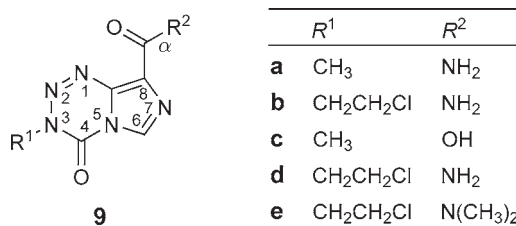


Scheme 1

11.20.3 Experimental Structural Methods

11.20.3.1 NMR Investigations

Structure elucidation of three related derivatives of ring system **2** ('temozolomide' **9a**, 'mitozolomide' **9b**, and the related acid derivative **9c**) has been carried out by ^{13}C and ^{15}N NMR spectroscopy <1995J(P1)249> (Scheme 2). The ^{15}N NMR chemical shifts measured in dimethyl sulfoxide (DMSO) solutions are listed in Table 1. For compound **9a**, Lowdin charges of the nitrogen atoms have also been calculated and found to have a linear relationship with the experimentally determined chemical shifts of these atoms. The NMR data of **9a** have been correlated with those of a series of heterocycles of related structure by the same team <2002MRC300>.



Scheme 2

Table 1 ^{15}N NMR data of derivatives **9a–c**

Compound	N-1	N-2	N-3	N-5	N-7
9a	−33.99	20.02	−180.44	−199.82	−105.64
9b	−31.88	18.19	−175.62	−200.38	−105.14
9c	−33.98	22.35	−197.10	−199.73	−101.43

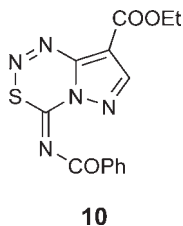
11.20.3.2 X-Ray Studies

The crystal structure of two analogues of the antitumor agent mitozolomide **9b** (i.e., **9d** and **9e**) has been determined (<1995AXC937> and <1994AXC1629> respectively).

Although a dimeric structure implying hydrogen bonds via the two carbonyl groups was expected, with **9d** the X-ray measurements showed that two molecules in an asymmetric unit occur utilizing hydrogen bonding between the carboxyl group of one molecule and the N atom and CH in the imidazo ring of the other <1995AXC937>.

With derivative **9e**, an interesting consequence of the presence of the dimethylamino group was found: although this ring system, similarly to **9b**, was found to be planar, the dimethylamide substituent did not allowed formation of a hydrogen bond and this led to rotation of this group by 45° , approximately, around the C(8)–C(α) bond <1994AXC1629>.

X-Ray structure analysis of the recently synthesized pyrazolo[1,2,3,5]thiatriazine derivative **10** (Scheme 3) (cf. Section 11.20.7.2) has been carried out <2004SL2037>. The crystalline form of **10** proved to be nearly planar, and the five-membered and the six-membered rings made an angle of 1.68°.



Scheme 3

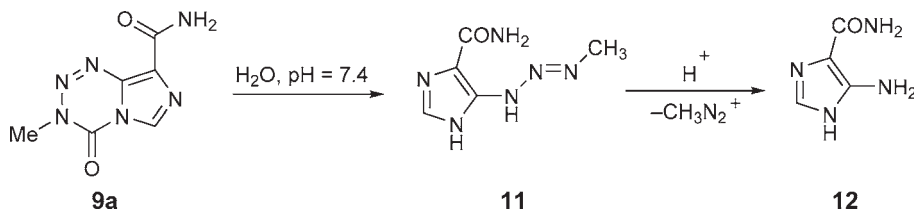
11.20.4 Thermodynamic Aspects

Results in this subject have neither been published in CHEC(1984) and CHEC-II(1996) nor during the recent period of time.

11.20.5 Reactivity of Fully and Partially Conjugated Rings

11.20.5.1 Ring Openings

Detailed investigation of the behavior of temozolomide **9a** under physiological conditions has been carried out. These studies revealed that water easily attacks **9a** at the 4-carbonyl position of the tetrazinone ring to yield a methyltriazenyl intermediate **11** (Scheme 4). This water-sensitive intermediate **11** rapidly undergoes decomposition under protic conditions to yield 5-aminoimidazole 4-carboxamide **12**, while methyldiazonium salt is liberated <2002JME5448, 2002JME5458>.

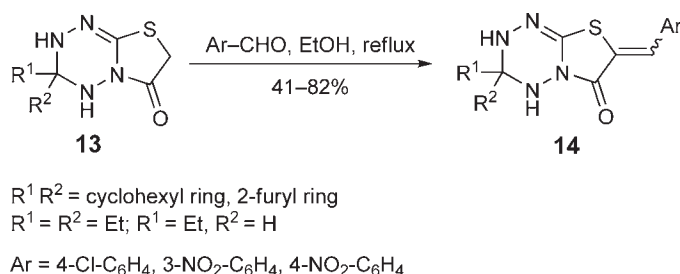


Scheme 4

11.20.5.2 Miscellaneous Transformations

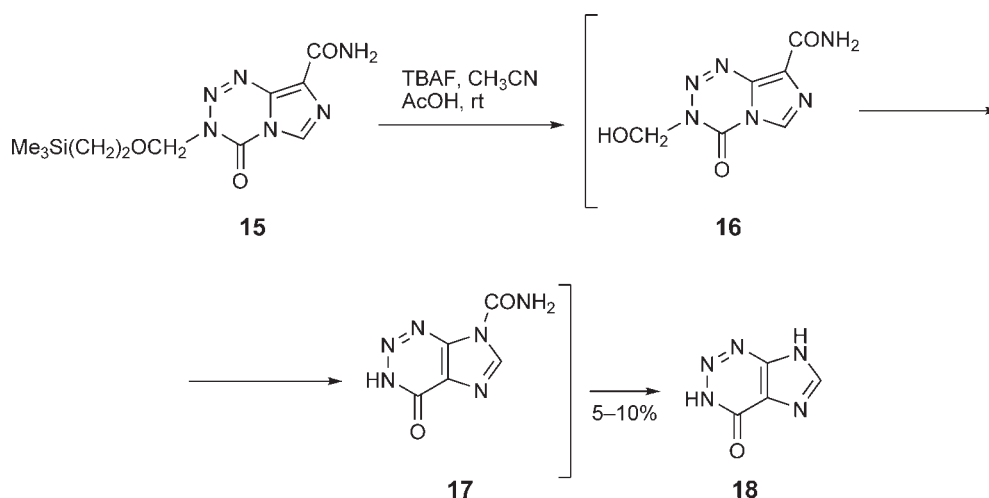
Among the sparse data available on reactivity of the ring systems belonging to this chapter, a condensation reaction, a ring transformation, and a ring closure are discussed in this section.

Mohan *et al.* carried out extensive research on 3,4-dihydro-2*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazin-6(7*H*)-one derivatives **13** <1995IJB1013, 1996IJB133, 1997IJB414, 1998IJB819, 2001IJB584, 2002IJB400> and have shown that these compounds easily participate in condensations with aromatic aldehydes to yield products such as **14** with *exo*-C=C moieties (Scheme 5). Various derivatives have been subjected to this transformation: the groups (R¹ and R²) in position 2 were H and Et or were constituents of a ring (e.g., cyclohexyl of 2-furyl ring) to form a spiro compound. Similarly, the structure of the aldehyde component was also varied (chloro and nitrophenyl groups have been applied). The reaction in most cases proceeded in medium to good yield (41–82%) in ethanolic solution in the presence of a base under reflux conditions. In some cases, this condensation reaction was coupled with the ring closure reaction to **13** and, thus, cascade reactions to produce **14** have also been elaborated (cf. Section 11.20.7.1).



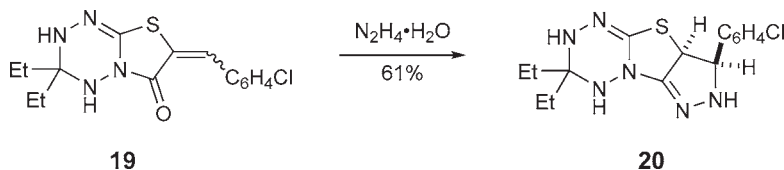
Scheme 5

In the course of investigations on imidazo[5,1-*d*][1,2,3,5]tetrazine derivatives (i.e., temozolomide analogues), Stevens *et al.* observed that after treatment of **15** with TBAF, **16** was formed but the presence of **18** was also observed in the reaction mixture <1995J(P1)2783>. This unexpected ring transformation was rationalized (Scheme 6) by the formation of intermediate **17** through Dimroth rearrangement followed by elimination of isocyanic acid (HNCO).



Scheme 6

Scheme 7 shows formation of a new fused ring described by Mohan and Kataria <1998IJB819>. These authors reported that treatment of the benzylidene compound **19** with hydrazine hydrate in acetic acid in the presence of sodium acetate gave the tricyclic fused pyrazoline derivative **20** in acceptable yield (61%). The two hydrogen atoms at the site of the ring closure were found to be *cis*.

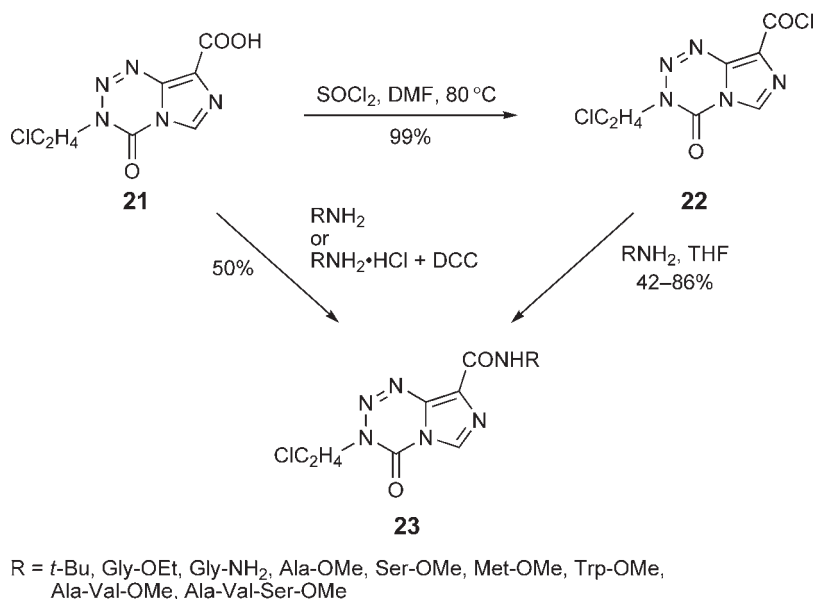


Scheme 7

11.20.6 Reactivity of Substituents Attached to Ring Atoms

Only a few publications have appeared recently that discuss the reactivity of substituents of the ring systems of this chapter. In the course of thorough investigations on mitozolamide and its analogues, Stevens *et al.* <2002JME5458>

carried out studies in order to prepare amino acid and peptide conjugates of these compounds. The transformations are depicted in [Scheme 8](#).



Scheme 8

The carboxylic acid **21** was subjected to two kinds of transformation in order to obtain the desired conjugates **23**: either a direct way was used by reacting **21** with the desired amino acid or peptide in the presence of dicyclohexylcarbodiimide (DCC) to yield **23**, or the acid chloride intermediate **22** was obtained first by treatment of **21** with thionyl chloride and, then, this compound could be smoothly converted to the target products **23** by simple treatment with the particular amino acid or peptide [\[1990JME1393\]](#). The procedure was applied for Gly, Ala, Ser, Met, and Trp conjugates, as well as for a dipeptide (Ala-Val) and a tripeptide (Ala-Val-Ser) conjugate. Most of the products have been obtained in the form of C-terminal esters. It is worth noting that in the case of the Gly conjugate, a C-terminal amide has also been prepared.

Peptide conjugates with attachment to the carboxylic function of the imidazole ring have also been synthesized [\[2002JME5458\]](#).

The same team investigated some transformations of substituents at the N-3 atom of the same ring system ([Scheme 9](#)) [\[1994CC1687, 1995JP12783\]](#). The aim of these conversions was to elaborate a feasible route to temozolomide **28** starting from the *N*-acetic ester **24**. While the expected approach (hydrolysis of the ester followed by decarboxylation) failed, a longer pathway proved to be suitable. Thus, **24** was hydrolyzed by hydrochloric acid to the *N*-acetic acid derivative **25**, which was transformed by using isobutyloxycarbonyl chloride to the active ester **26**. This compound was then subjected to the Barton protocol, as it was reacted with 2-mercaptopyridine-*N*-oxide to give intermediate **27** followed by reduction by tributyltin hydride under irradiation to yield the *N*-methyl-substituted end product (temozolomide). The overall yield of the pathway to **28** starting from **24** was 26% ([Scheme 9](#)).

Other transformations of the substituents on the N-1 atom were also reported [\[1997JOC7288\]](#) ([Scheme 9](#)): hydrolysis of the 5-cyano group of derivative **29** to a carboxamide **30** has also been reported.

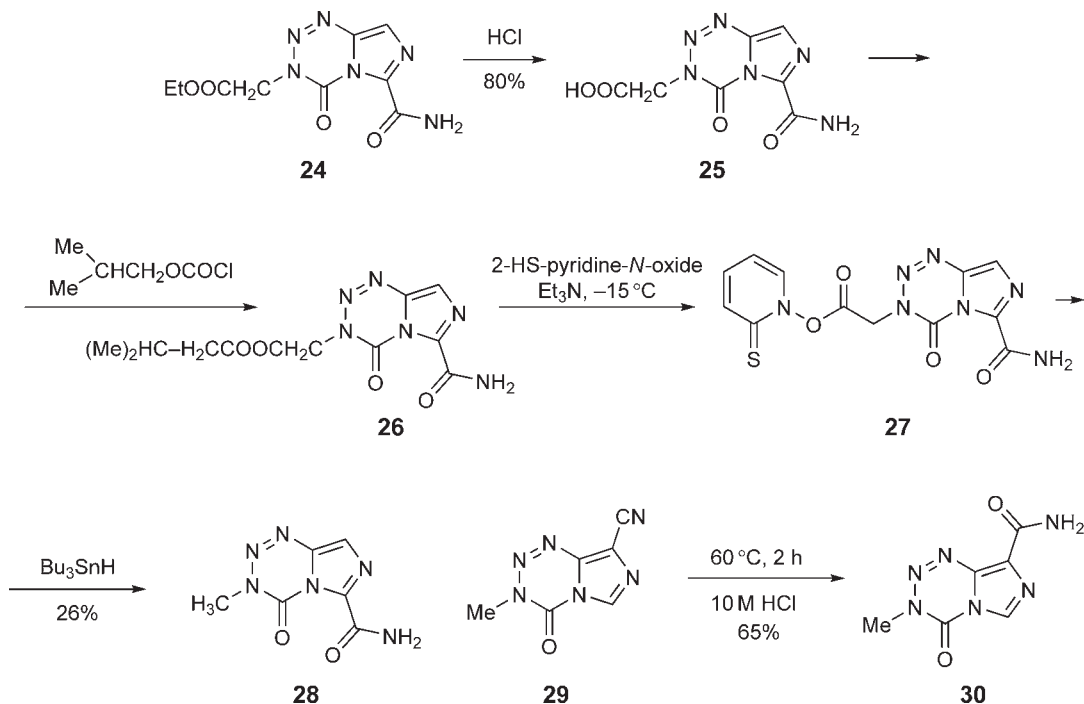
11.20.7 Ring Synthesis from Acyclic Compounds

11.20.7.1 Ring Synthesis of Azolotetrazines

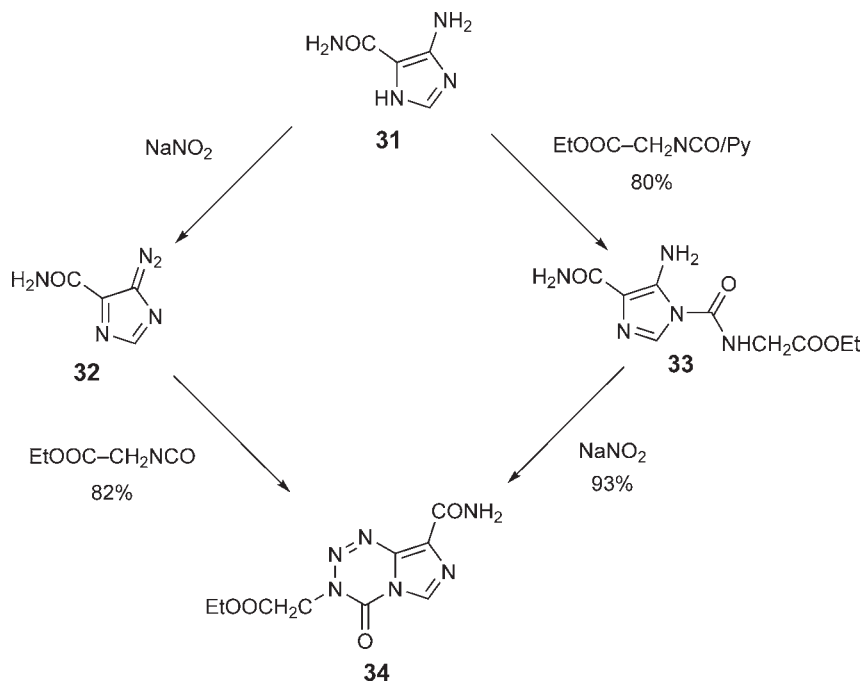
11.20.7.1.1 Synthesis of imidazo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-ones

Fairly substantial literature on synthetic methods of these derivatives appeared obviously mainly because of the valuable biological activity of these compounds. Such pathways have already been discussed in CHEC-II(1996)

<1996CHEC-II(8)496>, where, unfortunately, the numbering of the title ring system (title of Section 8.20.5.2.) appeared erroneously. During the recent period, new approaches have been found, and they are summarized below (Scheme 10).



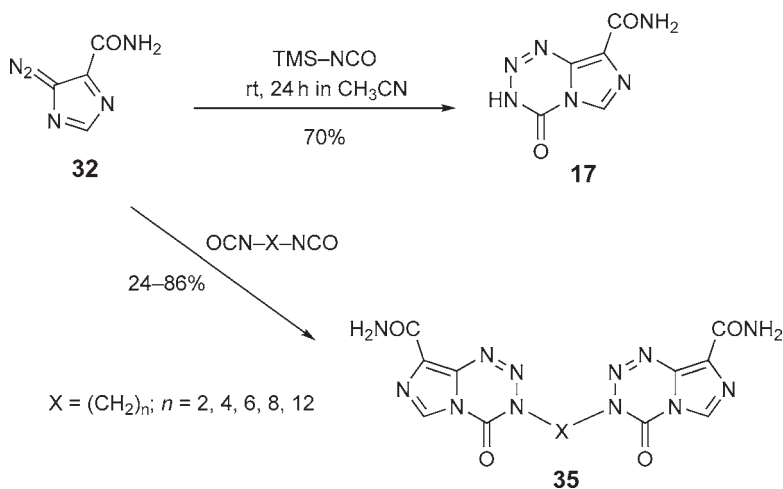
Scheme 9



Scheme 10

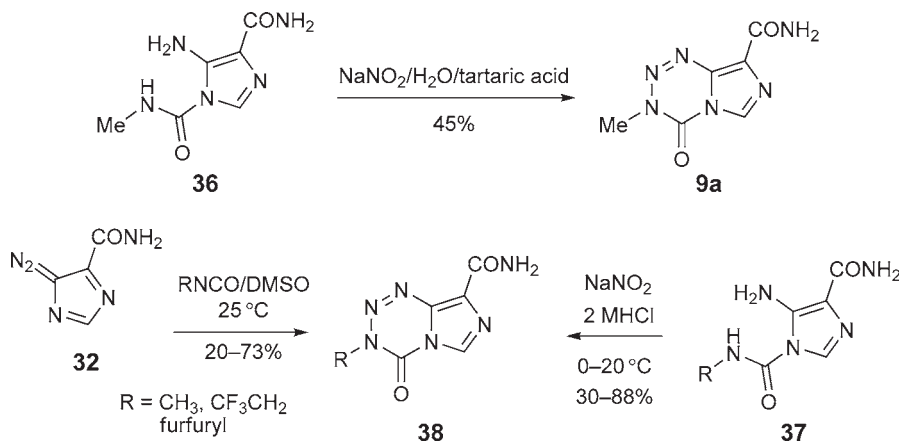
Stevens *et al.* published a series of synthetic approaches to this ring system (Scheme 10). They found that 5-aminoimidazole-4-carboxamide **31** can be transformed to imidazo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one **34** in two ways <1994CC1687, 1995J(P1)2783>: compound **31** is either diazotized to an azo derivative **32**, which can be ring-closed by ethoxycarbonylmethylisocyanate to the *N*-ethoxycarbonylmethyl bicyclic product **34**, or the same compound **31** can react first by ethyl 2-isocyanatoacetate in pyridine to give the cyclic urea derivative **33**, which, upon treatment with nitrous acid, gives rise to the same fused imidazotetrazinone **34**. This approach was later applied for a series of various isocyanates <1997CC363, 1998J(P1)1669> (Scheme 10).

The same team found that the diazoimidazole carboxamide derivative **32** can also be transformed directly to the ring-closed product **17**, being unsubstituted at N-3 by direct transformation with trimethylsilyl isocyanate (Scheme 11). Although a great number of experiments carried out in various solvents failed, recognition of a marked solvent effect led to the finding that this transformation nicely proceeds in acetonitrile under smooth conditions (rt, 24 h) in high yield (70%) <1996BML185>. The same azine **32** was also cyclised by bis-isocyanates <2000J(P1)4432>. As a result, a series of dimers **35** have been obtained bearing various spacers between the N-2 atom of the bicyclic units.



Scheme 11

Further variations for the synthesis of this ring system has been published by M. F. G. Stevens *et al.* (Scheme 12). Thus, the methyl-substituted cyclic carbamate **37** when treated with sodium nitrite in aqueous tartaric acid yielded temozolomide **9a** in average yield (45%) <1997JOC7288>. Two other approaches also proved to be applicable to the synthesis of a great number of derivatives: the diazoimidazole carboxamide **32** was reacted with various isocyanates to

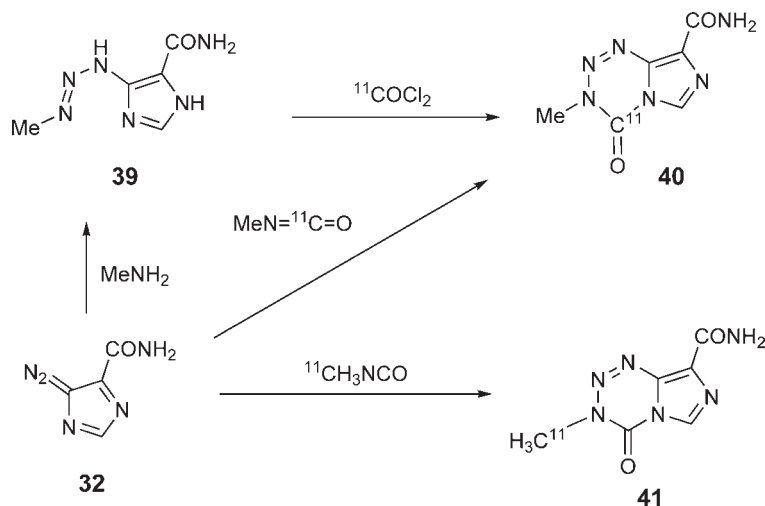


Scheme 12

give the corresponding *N*-substituted product **38** <1998J(P1)1669>, whereas the same substituted derivatives were also obtained via nitrosative cyclization of different representatives of **37**.

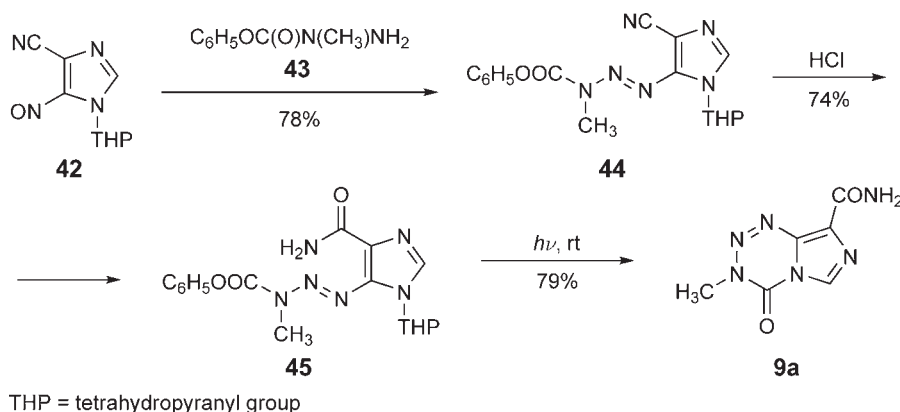
Because of the clinical application of temozolomide **9a**, the synthesis of a ^{11}C derivative **41** labeled at position 1 (i.e., the carbonyl carbon atom in the tetrazine ring) of these compounds has also been published (Scheme 13).

To this end, the diazoimidazole carboxamide compound **32** was transformed first by methylamine to the methyl-triazene derivative **39**, which was reacted with ^{11}C -phosgene to give the desired product **40** <2002JME5448>. In another approach, **32** was directly cyclized to the bicyclic product by using ^{11}C -labeled methyl isocyanate. This route allowed the synthesis of both the C-2-labeled **40** and the C-methyl-labeled samples **41** <1997JLR371, 2002JME5448> (Scheme 13).



Scheme 13

Thus, the recognition that nitrosoimidazoles and phenyl methylcarbazates can participate in an efficient condensation to give 2,8-dihydro-imidazo[5,1-*d*][1,2,3,5]tetrazine-1-one derivatives **9** led to the elaboration of a new reaction pathway to this biologically active substance <2002J(P1)1877> (Scheme 14).

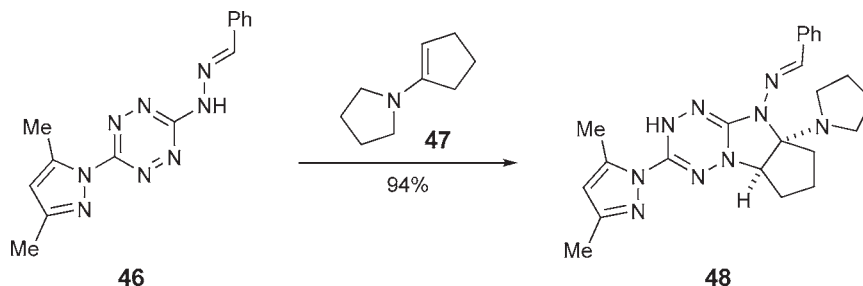


Scheme 14

The *N*-protected nitrosoimidazole carbonitrile **42** – which can easily be obtained from the commercially available 4-nitroimidazole in 4 reaction steps – was treated with phenyl methylcarbazate **43** to give a substituted triazenyli-midazole **44**. The cyano group of this compound was first hydrolyzed to an amide function to produce **45**, and then irradiation yielded the end product **9a** in high yield (79%).

11.20.7.1.2 Synthesis of imidazo[1,2-*b*][1,2,4,5]tetrazines

In a publication by a Russian team, formation of partially saturated derivatives of this ring system have been reported <2003HCO39>. The transformation is depicted in **Scheme 15**.

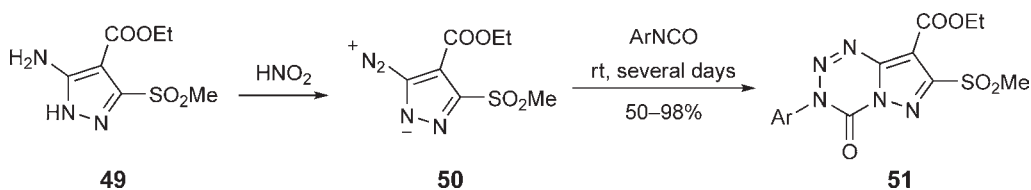


Scheme 15

These authors found that the tetrazinylhydrazone derivative **46** when reacted with pyrrolidinoenamine **47** in methanol yields the cyclopenta-fused derivative of the title ring system **48** in 94% yield. A similar transformation was carried out successfully by using morpholine-enamine in somewhat poorer yield. When the transformation was tried in acetonitrile as a solvent, a totally different reaction was observed: a regular Diels–Alder reaction between the tetrazine ring and the enamine double bond (of inverse electron demand) took place to yield pyridazines.

11.20.7.1.3 Synthesis of pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-ones

Synthetic pathways to this ring system have already been discussed in CHEC-II(1996) <1996CHEC-II(8)497>. Recently a new application of the established methodology has been successfully applied for the synthesis of a set of sulfone-containing derivatives by a Chinese research group <2005JHC609> (**Scheme 16**). The aminopyrazole derivative **49** was first diazotized to an azine **50** and, then, the ring closure to the bicyclic product **51** has been performed by using various aryl isocyanates. The new methylsulfones **51** have been obtained in average to excellent yields (50–98%).

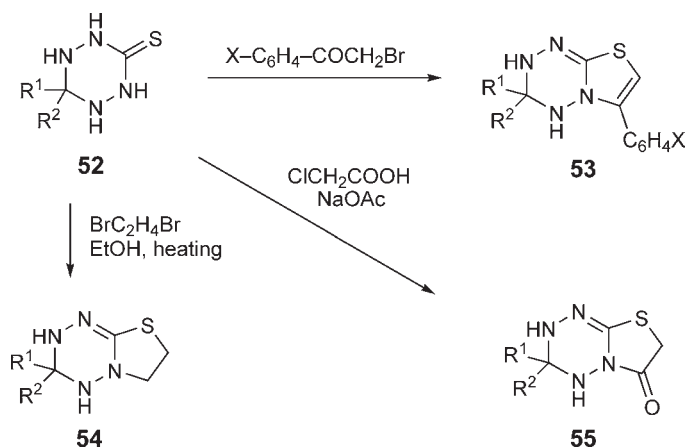


Scheme 16

11.20.7.1.4 Ring synthesis of thiazolo[3,2-*b*][1,2,4,5]tetrazines

Synthetic approaches to representatives of this ring system have been discussed in CHEC-II(1996) <1996CHEC-II(8)496>. Research activity in this area has been considerably extended during the past years. Thus, the basic starting material is a 6,6-disubstituted tetrahydro[1,2,4,5]tetrazin-3-thione **52**, which has been converted in three different ways: reaction with phenacyl bromides led to 3,3-disubstituted 3,4-dihydro-6-phenyl-2*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazines **53**, reaction of **52** with 1,2-dibromoethane gave 3,4,6,7-tetrahydro-2*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazines **54**, whereas transformation of **52** with chloroacetic acid in the presence of sodium acetate yields substituted 3,4-dihydro-1-2*H*-thiazolo[3,2-*b*][1,2,4,5]tetrazin-6(7*H*)-ones **55** <2001JJB584> (**Scheme 17**). Details are shown in **Table 2**.

Some derivatives of this ring system, which have been synthesized by these methods, are compiled in **Table 2**. These data show that the cyclizations proceed in medium to good yields in most cases.



Scheme 17

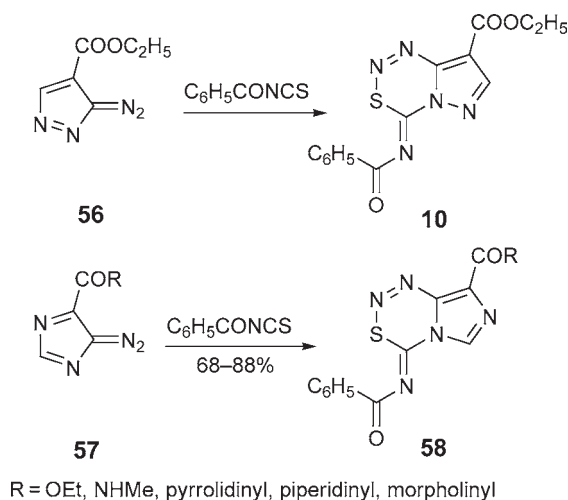
Table 2 Summary on some literature procedures to thiazolo[3,2-*b*][1,2,4,5]tetrazines 53–55

<i>R</i> ¹	<i>R</i> ²	<i>X</i>	Yield (%)	Reference
53				
Et	Et	4-Br	65	2001IJB584
Et	Et	4-C ₆ H ₅	56	2001IJB584
Et	Et	H	48	2001IJB584
H	2-Furyl	4-NO ₂	48	1997IJB414
H	Et	4-C ₆ H ₅	47	1996IJB133
H	Et	4-Cl	58	1996IJB133
54				
H	H		61	2001IJB584
H	2-Furyl		54	1997IJB414
H	Et		75	1996IJB133
55				
Et	Et		84	2001IJB584
-(CH ₂) ₅ -				1997IJB400
Spiro-9-fluorenyl				1996IJB685
Spiroadamantyl			72	2003IJB1460

As mentioned in Section 11.20.5.1 discussing the reactivity of these ring systems, the ring closure reactions to **53–55** have been coupled in several cases with subsequent condensation reactions with arylaldehydes to yield benzylidene derivatives of these ring systems (e.g., **13**) which transformations can be considered as cascade reactions.

11.20.7.2 Ring Synthesis of Fused Thiatriazines

New cyclizations starting from diazo derivatives of some pyrazoles and imidazoles (**56** and **57**, respectively) have been described to yield novel fused [1,2,3,5]thiatriazines (Scheme 18). Thus, reaction of **56** with benzoylisothiocyanate readily took place and led to the 4*H*-pyrazolo[5,1-*d*][1,2,3,5]thiatriazine derivative **10** (for the X-ray analysis of this compound, see Section 11.20.3.2), whereas the analogous reaction of **57** afforded the corresponding derivative **58** of the isomeric 4*H*-imidazo[5,1-*d*][1,2,3,5]thiatriazine ring system. In this latter case, a certain variation of the acidic functionality of the imidazole ring was also possible (Scheme 18) <2004SL2037>. All these conversions proceeded in high yield (68–88%).



Scheme 18

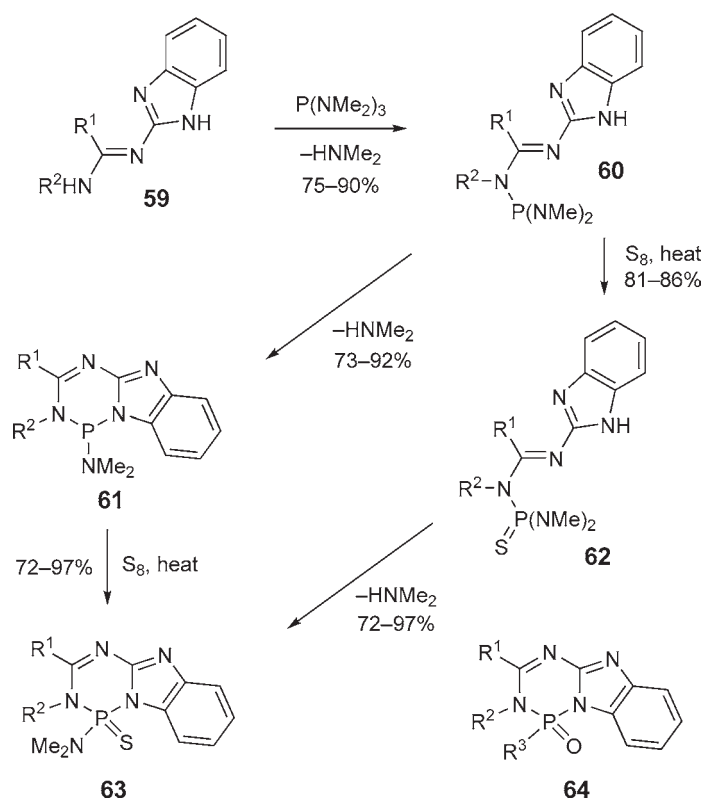
11.20.7.3 Ring Synthesis of Phosphorus-Containing Ring Systems

Synthesis of two phosphorus-containing heterocycles with the heteroatom arrangement of this chapter has been elaborated during the past years.

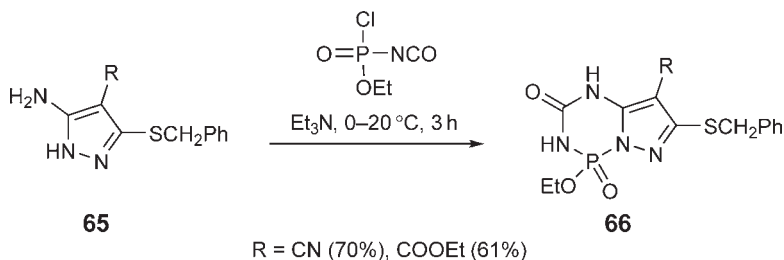
The pathways to derivatives of the benzo[*d*]imidazo[1,2-*c*][1,3,5,2]triazaphosphorine ring system are shown in Scheme 19 <2002PS1033>. In the first step, the imidazolylazomethine derivative **59** was treated with tris-dimethylaminophosphine in order to create the N–P bond in **60**. Further events can occur in two different ways: either a direct ring closure upon heating (elimination of dimethylamine) is carried out to yield the trivalent phosphorus-containing heterocycle **61** which can be transformed to the phosphorin thione **63**, or reaction of **60** with elementary sulfur is carried out first to give the thione intermediate **62**, which, upon heating, gives rise to **63**. The reactions have been applied to a great number of alkyl and aryl derivatives and have been found to proceed in good to excellent yields. This synthetic principle has also been applied successfully for the synthesis of the *P*-oxo analogue **64** <2004PS1387> (Scheme 19).

Synthesis of the other phosphorus-containing heterocycle, pyrazolo[1,5-*c*][1,3,5,2]triazaphosphorine, has been published by Yang and Lu <1994SC59> (Scheme 20).

Thus, 4-substituted 5-amino-3-benzylsulfanyl-1*H*-pyrazole **65** derivatives (R = CN or COOEt) were treated with phosphoric acid ethyl ester chloride isocyanate in the presence of triethylamine under mild conditions (0–20 °C) for 3 h to give the ring-closed product **66** in medium to good yields (70% and 61%, respectively).



Scheme 19



Scheme 20

11.20.8 Important Compounds and Applications

The most important compounds belonging to this chapter are two derivatives of the imidazo[5,1-*d*][1,2,3,5]tetrazine ring system **2**: 3-methylimidazo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)one 8-carboxamide **9a**, called temozolomide, and the 3-chloroethyl-substituted analogue **9b**, mitozolomide, which possess marked antitumor activity. Both compounds are considered as prodrugs for two cytotoxic alkylating agents that can alkylate DNA. The carboxamide substituent is believed to play an important role in DNA sequence recognition <1995JME1493, 1995AXC937, 1999JLR704>.

Another interesting biological application possibility was found by Yang *et al.* <2005JHC609>, who described that some pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones have been identified as potential herbicides.

11.20.9 Further Developments

No major developments in the area have been reported recently. Wu *et al.* have described a novel application of the ring closure reaction to pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones for trifluoromethyl substituted derivatives <2006JFC409>. The transformations were found to proceed in high yields (70–95%).

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Biographical Sketch



György Hajós received his Ph.D. degree with Prof. A. Messmer at Eötvös University, Budapest, in 1974. Since that time, he has been working for the Chemical Research Center, Hungarian Academy of Sciences, first as a scientific investigator, later as head of Laboratory for Heterocyclic Chemistry, and since 2005 he is director of the Institute of Biomolecular Chemistry. He spent two years in Germany with Prof. Günther Snatzke (1975 and 1985) as DFG and Humboldt fellow. In 1992, he acquired his Doctor of Science degree from the Hungarian Academy of Sciences. He made his Habilitation at Debrecen University in 1995 and was appointed university professor at Debrecen University, University of Technology and Economics, as well as Eötvös University in Budapest. He has been awarded a Zemplén-prize by the Hungarian Academy of Sciences in 1996. His research interest includes synthetic heterocyclic chemistry, cyclization and ring-opening reactions, elaboration of selective procedures, synthesis of biologically active derivatives, and semi-empirical rationalization of chemical transformations.



After her chemistry diploma at Eötvös University, Budapest, in 1975, Zsuzsanna Riedl received her Ph.D. degree with Prof. A. Messmer at the same university in 1980. Since that time, she has been working for the Chemical Research Center, Hungarian Academy of Sciences, where, at present, she is senior investigator at the Department of Synthetic Organic Chemistry and head of the Instrumental Organic Analytical Chemistry Laboratory since 2001. She acquired her Candidate of Science degree in 1992 and Doctor of Science (D.Sc.) degree in 2005 from the Hungarian Academy of Sciences. Between 1988 and 2002, she was visiting investigator several times at the Institute of Chemistry, Karl-Franzens University of Graz (Austria), where she worked with Prof. G. Kollenz on synthesis and ring transformation of fused furanes. In 2003 she received the investigator award for her research from the 'Kisfaludy Lajos' foundation. Her research interest implies heterocyclic ring closures and ring openings, reactivity of heteroaromatic systems, especially theoretical and experimental study of electrophilic reactions of heteroaromatics, rearrangement reactions of heterocycles, synthesis of biologically active (multidrug resistance inhibitory and intercalating) fused systems.

11.21

Bicyclic 5-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: Five Extra Heteroatoms 3:2

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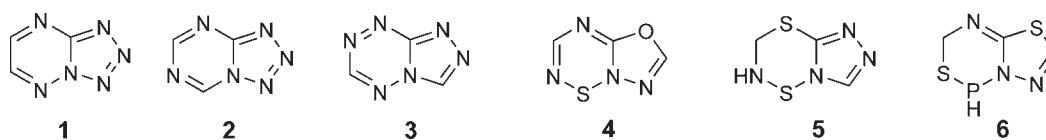
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11.21.1 Introduction

Six ring systems discussed in this chapter are shown in [Scheme 1](#). Two of these, tetrazolo[1,5-*b*][1,2,4]triazine **1**, and tetrazolo[1,5-*a*][1,3,5]triazine **2**, have a 3:2 heteroatomic arrangement, whereas the other four, [1,2,4]triazolo[4,3-*b*]-[1,2,4,5]tetrazine **3**, [1,3,4]oxadiazolo[3,2-*b*][1,2,4,6]thiatriazine **4**, [1,2,4]triazolo[4,3-*b*][1,4,2,6]dithiadiazine **5**, and [1,3,4]thiadiazolo[3,2-*c*][1,3,5,2]thiadiazaphosphinine **6**, belong to the 2:3 category, that is, in these ring systems two extra heteroatoms are located in the five-membered ring and three extra heteroatoms in the six-membered ring. Ring systems **1–3** have already been discussed in CHEC-II(1996) <1996CHEC-II(8)499>, whereas the other ring systems are new.

11.21.2 Theoretical Methods

Atomic charges have been calculated by semi-empirical method (AM1) for nitrogen atoms of two triazolo[4,3-*b*]-[1,2,4,5]tetrazines in order to assess the site of alkylation of these compounds <2000ARK259>. The results are summarized in [Table 1](#).



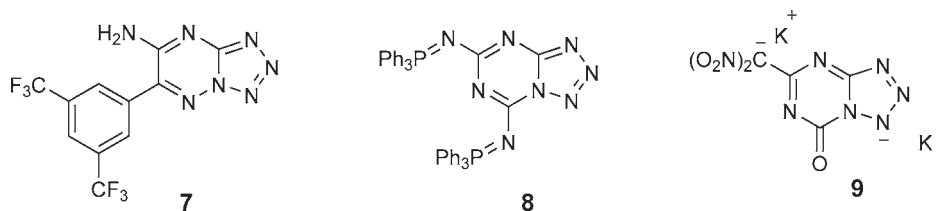
Scheme 1

Table 1 Calculated charges of nitrogen atoms in two triazolo[4,3-*b*][1,2,4,5]tetrazine derivatives

N-1	-0.41	-0.41
N-2	-0.39	-0.40
N-5	-0.30	-0.41
N-7	-0.34	-0.33
N-8	-0.29	-0.29

11.21.3 Experimental Structural Methods

In the area of the title ring systems, X-ray investigations have been carried out in two cases during the past period of time. The elucidated structures determined are shown in [Scheme 2](#).



Scheme 2

Chupakhin *et al.* investigated the structure of the tetrazolotriazine derivative **7** <2005IZV713>. The X-ray study unambiguously supported the [1,5-*b*]fusion and the fact that in the crystalline state the molecules formed dimers stabilized by hydrogen bonds. Crystallographic study on **8** <1998EJI2013> revealed that the P–N distance is between 1.614 and 1.608 Å, which corresponds to a bond order between 1 and 2. The structure of the double salt **9** has also been determined by crystallographic analysis <2005KGS259>.

In some studies, detailed nuclear magnetic resonance (NMR) analysis of the prepared compounds has been published. [Table 2](#) shows those ring systems where the NMR (^1H and ^{13}C) information exceeds the simple routine level.

Table 2 Summary of references to more detailed NMR assignments of derivatives of particular ring systems

Ring system	NMR method	Reference
1	^1H	1994ZOR126
	^1H	1998ZOR450
	^1H	2001IZV2084
3	^1H	1999ZOR1379
	^1H , ^{13}C	1998JHC1329
5	^1H	1999MI511
6	^1H , ^{13}C	1997PS299

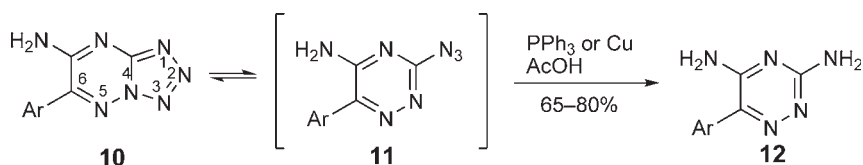
11.21.4 Thermodynamic Aspects

In the course of theoretical calculations discussed above (Section 11.21.2, Table 1), heats of formation of alkylated salts have been computed <2000ARK259>. The most favourable $\Delta\Delta$ values have been obtained for the N(1)-Me and N(2)-Me salts, and this result was in entire agreement with the experimentally observed site of alkylations (i.e., with formation of **14** and **15** as shown in Scheme 4, Section 11.21.5.2.1).

11.21.5 Reactivity

11.21.5.1 Reactivity of the Ring

Ring-opening reactions of some tetrazolo[5,1-*c*][1,2,4]triazines have been reported by Chupakhin *et al.* <2005IZV713>, as shown in Scheme 3.



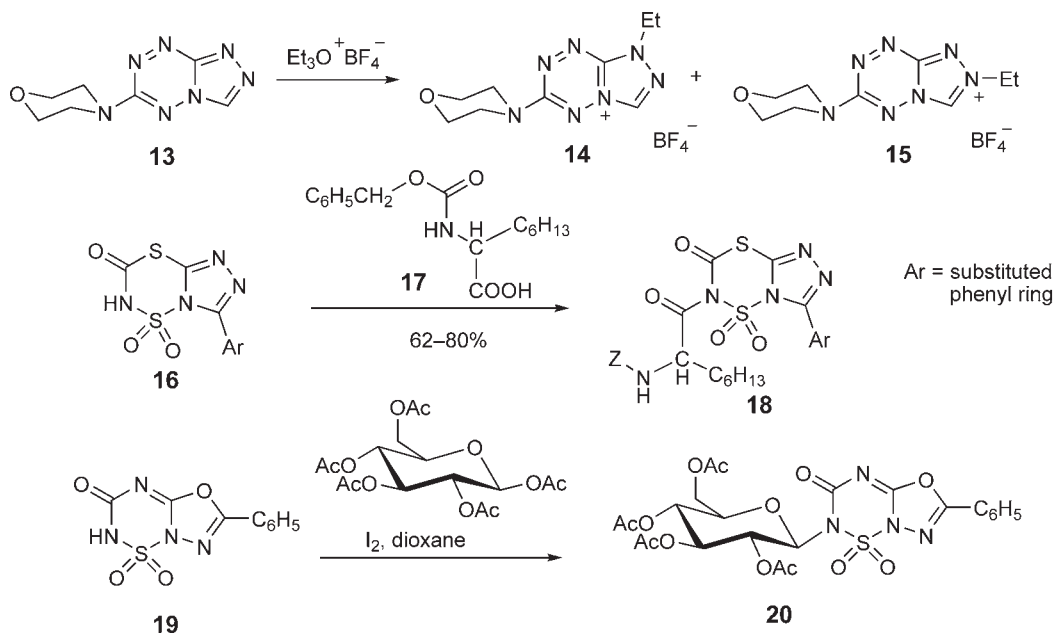
Scheme 3

The fused tetrazoles **10** containing various aryl groups in position 6 were boiled in acetic acid in the presence of either triphenylphosphine or copper and gave rise to the amino-substituted triazines **12**. The reaction proceeds obviously via valence bond isomerization of **10** to the azide **11** and is regarded as a useful synthetic route to the diamino compounds **12**.

11.21.5.2 Reactivity of the Ring Heteroatoms

11.21.5.2.1 Reactivity of ring nitrogen atom

Alkylation, acylation, and glycosidation of ring nitrogen atoms of ring systems discussed in this chapter have been reported. The transformations are depicted in Scheme 4.



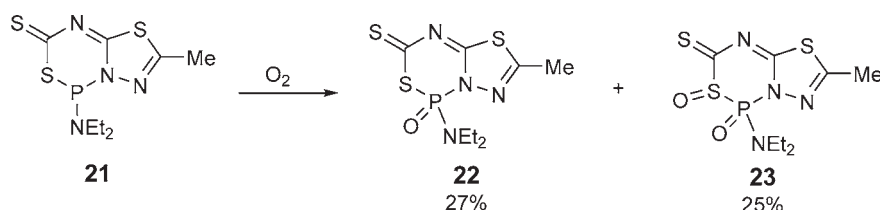
Scheme 4

In the course of studies on the synthesis of [1,2,4]triazolo[3,4-*b*][1,2,4,5]tetrazines, Kotschy *et al.* investigated the alkylation of the morpholino derivative **13** of this ring system <2000ARK259>. It has been found that ethylation carried out with triethyloxonium tetrafluoroborate took place exclusively on the five-membered ring and yielded a mixture of 1-ethyl **14** and 2-ethyl **15** quaternary salts.

Acylation of the [1,2,4]triazolo[4,3-*b*][1,4,2,6]dithiadiazine-6-dioxide compound **16** was reported by an Indian team <1999MI511>. The reaction of this compound with 2-(benzyloxycarbonylamino)octanoic acid with the help of benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate ('BOP reagent', **17**) was carried out at room temperature for 2 h to give the acylated compound **18**. Glycosidation of the [1,3,4]oxadiazolo[1,2,4,6]thiatriazole compound **19** with penta-*O*-acetyl- β -D-glucopyranose by using iodine was reported to yield the *C*-glycoside **20** <2005IJC163>.

11.21.5.2.2 Reactivity of ring oxygen and ring sulfur atoms

A Chinese research team found <1997PS299> that derivative **21** of the new [1,3,4]thiadiazolo[3,2-*c*][1,3,5,2,]thiadiazaphosphorine ring system undergoes spontaneous oxidation on air, as shown in Scheme 5. Thus, storage of the dichloromethane solution of **21** for 48 h at room temperature results in formation of a mixture of **22** and **23**.

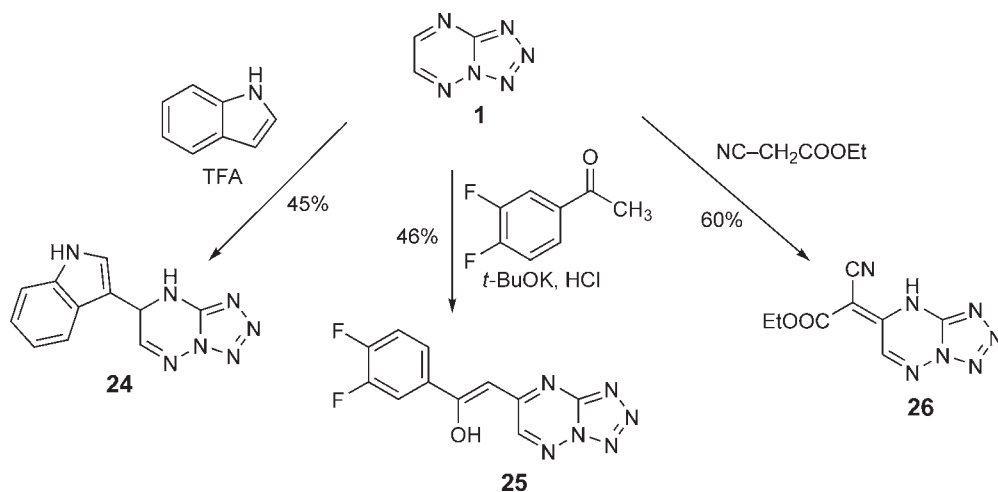


Scheme 5

11.21.5.3 Reactivity of the Ring Carbon Atom

A series of functionalizations of the ring system tetrazolo[1,5-*b*][1,2,4]triazine **1** have been reported by Rusinov *et al.*

These authors found that nucleophilic additions to the unsubstituted ring system **1** can be carried out to yield a number of 7-substituted dihydro products or, in some cases, where an oxidation can follow this addition, also 7-substituted heteroaromatic derivatives (Scheme 6). Thus, reaction of **1** with indole under acidic conditions (in trifluoroacetic acid) yields 7-(1*H*-indol-3-yl)-7,8-dihydrotetrazolo[1,5-*b*][1,2,4]triazine **24** <1998ZOR450>. Reaction of **1** with 3,4-difluoroacetophenone in the presence of potassium *tert*-butoxide in tetrahydrofuran followed by

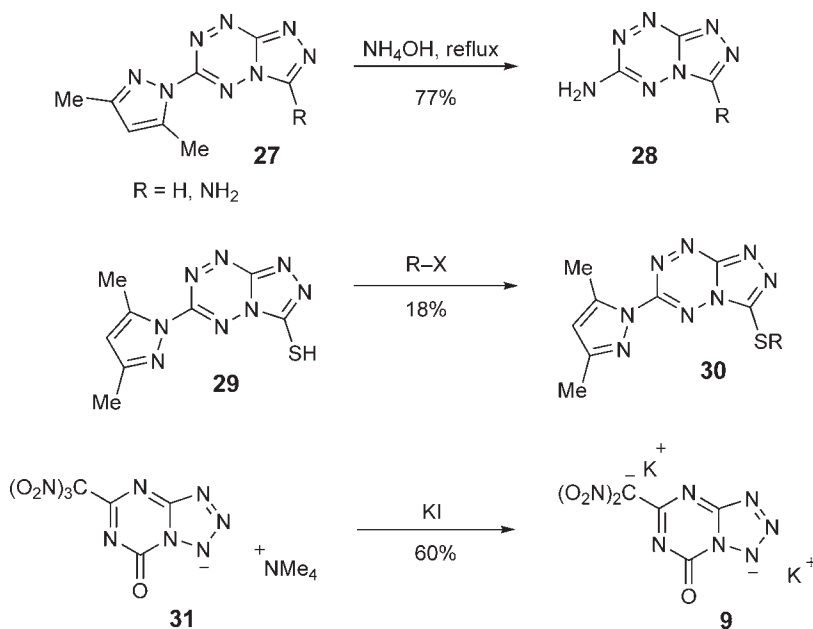


Scheme 6

treatment of aqueous hydrogen chloride gave the substituted ethenyl derivative of the bicyclic heterocycle **25** <2002HCO75>. The addition reaction of **1** with cyanoacetic acid has also been described to afford the *exo*-double-bond-containing product **26** <2001IZV2084>. Introduction of various other aryl groups to position 7 of this ring system has also been reported <1998ZOR450, 2003ZOB862>.

11.21.6 Reactivity of Substituents Attached to Ring Carbon Atoms

Reactions of substituents attached to the ring carbon atoms have only been reported sparingly. The results are shown in Scheme 7.



Scheme 7

Chavez and Hiskey studied the reactivity of the pyrazolyltriazolotetrazine derivatives **27** (R = H or NH₂) in the presence of ammonia <1998JHC1329>. These authors found that in the case of R = H, the nucleophilic substitution of the pyrazolyl group takes place on treatment with ammonium hydroxide under refluxing conditions to give the amine derivative **28** in 77% yield. In contrast to these mild conditions, the amino derivative **27** (R = NH₂), when reacted with ammonia under pressure (with heating in a steam cone for 3 h), yielded the diamino product **28** in almost quantitative yield. Alkylation of a mercapto derivative of the same ring system **29** under standard conditions to an alkylsulfano compound **30** has also been reported <1999ZOR1379>.

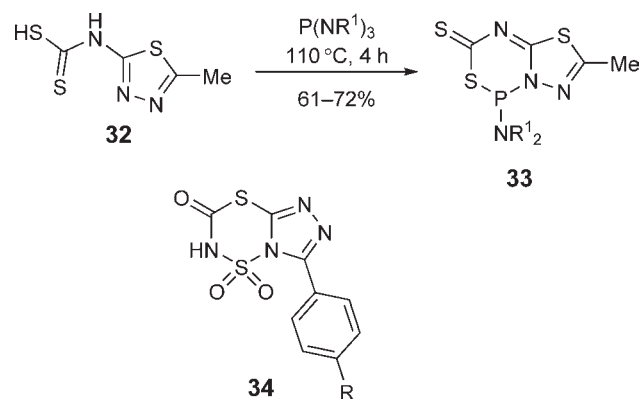
Modification of the trinitromethyl substituents of the derivative **31** was reported by a Russian team <2005KGS259>: removal of one nitro group was achieved by treatment with potassium iodide at room temperature in good yield to give the double salt **9**.

11.21.7 Ring Synthesis from Acyclic Compounds

11.21.7.1 Synthesis of Ring Systems Implying Also Oxygen, Sulfur, or Phosphorus Atoms

The fairly limited amount of novel literature data is illustrated in Scheme 8.

Representatives of an earlier unknown heterocyclic ring system, [1,3,4]thiadiazolo[3,2-*c*][1,3,5,2]thiadiazaphosphorine **33**, have been synthesized by a Chinese team <1997PS299>. The ring-closure reaction started from the



Scheme 8

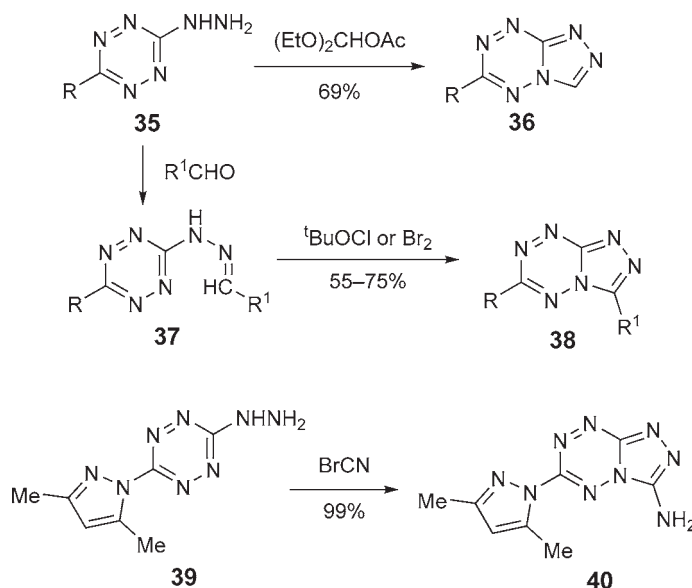
thiadiazole derivative **32**. This compound when treated with tris-trialkylphosphine at higher temperature gave rise to the new heterocyclic derivatives **33** in medium to good yield.

Advances in the area of triazolo[4,3-*b*][1,4,2,6]dithiadiazines **34** were reported by Srivastava *et al.* <1999MI511>. Although the ring-closure route to these derivatives was published many years ago <1979H(12)815>, several new derivatives of this ring system have now been prepared containing various R groups as substituents of the phenyl ring.

11.21.7.2 Synthesis of Ring Systems Implying Only Nitrogen Atoms in the Ring

11.21.7.2.1 Ring synthesis of triazolotetrazines

A novel ring-closure strategy to the synthesis of the earlier known ring system: [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine was reported by Chavez and Hiskey <1998JHC1329> (Scheme 9). These authors found that 3-hydrazino[1,2,4,5]-tetrazines **35** are suitable starting compounds for the planned purpose and, thus, their reaction with diethoxymethyl acetate gave the ring-closed products **36** in good yields. The R group can be a hydrogen atom or a heterocyclic ring. Ring closures with R = hydrazine group were also accomplished; in these cases also, this substituent underwent condensation reaction with participation of the reagent.

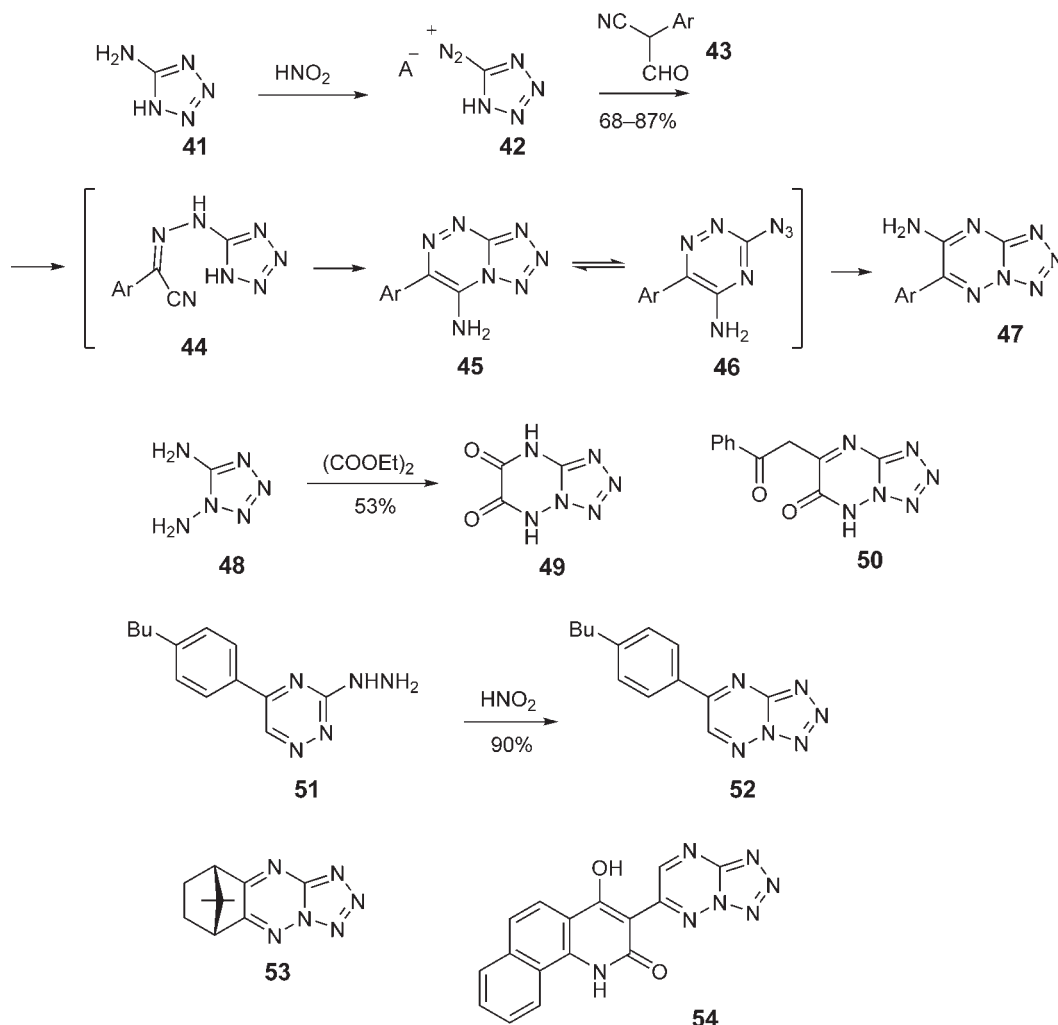


Scheme 9

A Russian team also carried out similar ring-closure reactions <1999ZOR1379>. These authors found also an alternative route: reaction of **35** with aldehydes gave hydrazones **37**, which were oxidized either with ^tBuOCl or bromine to result in the triazole ring **38**. Ring closure of particular hydrazinotetrazines **39** to give the amino-substituted triazolotetrazines **40** were performed with cyanogen bromide <1998JHC1329>. Other applications of these methodologies also appeared <2000ARK259>.

11.21.7.2.2 Ring synthesis of tetrazolo[1,2,4]triazines

All synthetic works belonging to this section relate, with one exception, to the preparation of tetrazolo[1,5-*b*]-[1,2,4]triazines. Although the final outcome of this outstanding work as published by Chupakhin *et al.* <2005IZV713> is also formation of this ring system, the reaction pathway actually involves a ring transformation reaction. The interesting result is summarized in Scheme 10.



Scheme 10

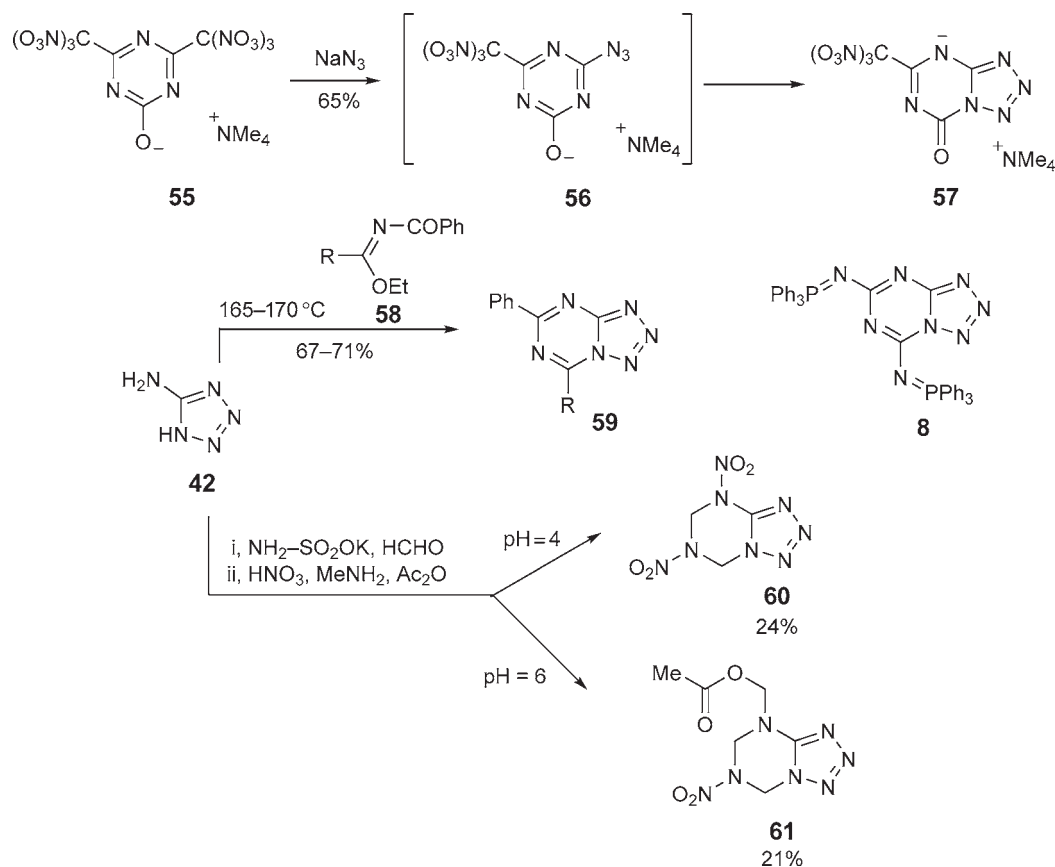
The reaction sequence starts from tetrazolyldiazonium salt **42** prepared from aminotetrazole **41** by diazotation. This compound when reacted with arylformylacetonitrile **43** leads to the intermediate formation of the condensation product **44**, which easily undergoes ring closure to **45**. This tetrazolo[5,1-*c*][1,2,4]triazine compound, however, forms an equilibrium with the valence bond isomeric azide **46**, which can participate in a different ring closure than the reverse route, and yields the tetrazolo[1,5-*b*][1,2,4]triazine product **47**. The reaction was carried out with a series of various aryl derivatives and proceeded in good to excellent yields (68–87%).

Other cyclizations to give tetrazolo[1,5-*b*][1,2,4]triazines published in recent years basically follow the established procedures discussed earlier in CHEC-II(1996) <1996CHEC-II(8)499> and belong to two categories: (1) reaction of 1,5-diaminotetrazole **42** with α -dioxo reagents, and (2) reaction of a 3-hydrazino[1,2,4]triazine derivative with nitrous acid.

Method (1) was applied with reaction of **48** with diethyl oxalate to yield a tetrazolotriazine-dione **49** <2005JIC172>. A similar route – application of 5-phenyl-furan-2,3-dione as an α -dioxo reagent – led to the ring-closed product **50** <1994ZOR126>. For method (2) also, several examples have been reported. Thus the butylphenyltriazinyldiazine compound **51** was transformed to the corresponding tetrazole **52** <2004AF42>, and, furthermore, the camphor-fused tetrazolotriazine **53** <1997H(44)117> as well as the heteroaryl-substituted compound **54** <2001CPA242> have also been prepared by this way.

11.21.7.2.3 Ring synthesis of tetrazolo[1,3,5]triazines

Synthesis of an interesting anionic derivative of the ring system tetrazolo[1,5-*a*][1,3,5]triazine was reported by Fedorov *et al.* <2005KGS259>; the ring-closure reaction is shown in **Scheme 11**.



Scheme 11

The tetramethylammonium triazine-olate **55** was treated with sodium azide, whereupon nucleophilic exchange of the trinitromethyl substituent took place to give the azide intermediate **56**, which spontaneously underwent valence bond isomerization to the fused tetrazole **57**.

Some other cyclizations have also been reported, and these apply similar strategies as have been published earlier and discussed in CHEC-II(1996) <1996CHEC-II(8)499>. Thus, Bekircan *et al.* <2005AP365> carried out the ring-closure reaction of aminotetrazole with an iminoether reagent **58** to give **59**. The transformation proceeded at 165–170 °C in good yields (67–71%). The bis-triphenylphosphine derivative **8** was synthesized from the corresponding hydrazine[1,3,5]triazine following the established methodology <1998EJI2013>.

Formation of the partially saturated nitro derivatives **60** and **61** was reported by a Russian team <1994KGS1129>. The two products were obtained under fairly complicated reaction conditions: when aminotetrazole **42** was first treated with potassium amidosulfonate and formaldehyde at pH = 4 followed by addition of nitric acid, methylamine, and acetic anhydride, product **60** was obtained in 24% yield. The same reaction, however, carried out at pH = 6 gave rise to formation of the acetoxy compound **61** in 21% yield.

11.21.8 Important Compounds and Applications

Derivative **47** and related compounds proved to stimulate the central nervous system <1997H(44)117>, and the unprotected derivatives of **53** showed fungicidal activity <1999MI511>.

11.21.9 Further Developments

New transformations (nucleophilic substitutions) of the trinitromethyl derivative of tetrazolo[1,2-*a*][1,3,5]triazine ring system have recently been studied <2005KGS582>. In the area of ring synthesis both earlier known and novel rings have been prepared. Thus, some new derivatives of the tetrazolo[1,5-*b*][1,2,4]triazine ring have been synthesized from some 3-hydrazino[1,2,4]triazines upon the analogy of the ring closure **51** → **52** (cf. Section 11.21.7.2) <2005ZOR895>, whereas ring closure to a thia analogue of the ring system **4** has also been reported <2005AJC891>.

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Biographical Sketch



György Hajós received his Ph.D. degree with Prof. A. Messmer at Eötvös University in Budapest in 1974. Since this time, he has been working for the Chemical Research Center, Hungarian Academy of Sciences, first as a scientific investigator, later as head of the Laboratory for Heterocyclic Chemistry, and since 2005 as director of the Institute of Biomolecular Chemistry. He spent two years in Germany with Prof. Günther Smatzke (1975 and 1985) as DFG- and Humboldt-Fellow. In 1992, he acquired a Doctor of Science degree from the Hungarian Academy of Sciences. He made his Habilitation at Debrecen University in 1995 and was appointed university professor at Debrecen University, University of Technology and Economics, as well as Eötvös University in Budapest. He has been awarded a Zemplén-prize by the Hungarian Academy of Sciences in 1996. His research interest includes synthetic heterocyclic chemistry, cyclization and ring-opening reactions, elaboration of selective procedures, synthesis of biologically active derivatives, and semi-empirical rationalization of chemical transformations.



Zsuzsanna Riedl, after her chemistry diploma at Eötvös University in Budapest in 1975, received her Ph.D. degree with Prof. A. Messmer at the same university in 1980. Since this time, she has been working for the Chemical Research Center, Hungarian Academy of Sciences, where at present she is senior investigator at the Department of Synthetic Organic Chemistry and head of the Instrumental Organic Analytical Chemistry Laboratory since 2001. She acquired her Candidate of Science degree in 1992 and Doctor of Science (D.Sc.) degree in 2005 from the Hungarian Academy of Sciences. Between 1988 and 2002, she was visiting investigator several times at the Institute of Chemistry, Karl-Franzens University of Graz (Austria), where she worked with Prof. G. Kollenz on synthesis and ring transformation of fused furanes. In 2003 she received an investigator award for her research from the Kisfaludy Lajos Foundation. Her research interest includes heterocyclic ring closures and ring openings, reactivity of heteroaromatic systems, especially theoretical and experimental study of electrophilic reactions of heteroaromatics, rearrangement reactions of heterocycles, and synthesis of biologically active (multidrug-resistance inhibitory and intercalating) fused systems.