5.01
1,2,3-Triazoles

S. Rachwal
Cortex Pharmaceuticals, Inc., Irvine, CA, USA
A. R. Katritzky
University of Florida, Gainesville, FL, USA

5.01.1 Introduction

The present chapter is devoted to 1,2,3-triazole and benzotriazole and their various derivatives. Triazolines (4,5-dihydro-1*H*-1,2,3-triazoles) are discussed in Section 5.01.6. Tautomeric forms of the parent molecules and atom numbering are given in **Figure 1**.

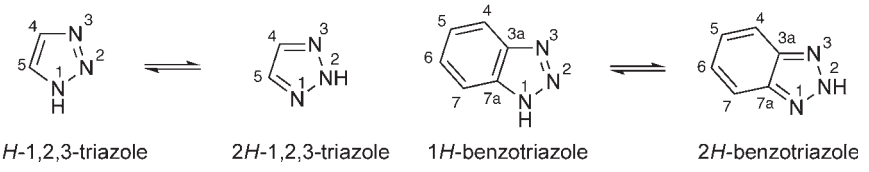


Figure 1 Tautomeric forms and atom numbering for 1,2,3-triazole and benzotriazole.

In CHEC(1984) <1984CHEC(5)669>, Chapter 4.11 on 'Triazoles and their Benzo Derivatives' (64 pages) covered the literature through 1982 and was strongly aligned to the monocyclic 1,2,3-triazoles with the considerable emphasis on ring-reduced derivatives. In CHEC-II(1996) <1996CHEC-II(4)1>, the corresponding 126-page chapter covered the literature from 1982–94, when the position had already changed significantly with the realization of the utility of benzotriazole as a synthetic auxiliary.

The present chapter is heavily biased toward benzotriazole as a consequence of numerous synthetic methods developed with the help of this molecule. It has been impossible to cover the field in a comprehensive manner in the pages available. We refer readers to the following reviews that have appeared during the last ten years:

(1) 'Properties and Synthetic Utility of Substituted Benzotriazoles' <1998CRV409> – this review covers the literature in a comprehensive manner through 1996;
(2) 'Benzotriazole-Based Reagents for Efficient Organic Synthesis' <1998ALD33> – another review of some of the synthetic applications;
(3) 'Benzannulations' <1999T8263> – specifically deals with benzotriazole mediated benzannulations;
(4) 'Michael Additions of Benzotriazole-Stabilized Carbanions' <1998CCC599>;
(5) 'The Generation and Reactions of Non-stabilized α-Aminocarbanions' <1998T2647> – includes significant amount of benzotriazole chemistry;
(6) 'Designing Efficient Routes to Poly-functionality' <2000PAC1597> – deals with benzotriazole derivatives;
(7) 'The Preparation of Mono-, 1,1-Di-, *trans*-1,2-Di- and Tri-Substituted Ethylenes by Benzotriazole Methodology' <2001SL458>;
(8) 'Benzotriazole an Ideal Synthetic Auxiliary' <2003CEJ4587> – gives some highlights,
(9) 'Benzotriazole-Mediated Amino-, Amido-, and Alkylthio-Alkylation' <2005T2555>; and
(10) 'Benzotriazoles as Advantages N-, C-, S-, and O-Acylating Agents' <2005SL1656>.

5.01.2 Theoretical methods

Experimental dipole moments and acidities of azoles, including 1,2,3-triazole, show linear correlations with their π-electron excess calculated by the semiempirical AM1 method <2003CHE71>. Experimental dipole moments of azoles agree well with those calculated by the DFT program ALLCHEM <2003PCA4172>. Calculated dipole moments μ (in units of Debye,D) of a few selected azoles are listed below:

Pyrrole	1.93
Pyrazole	2.33
Imidazole	3.84
1*H*-1,2,3-triazole	4.55
2*H*-1,2,3-triazole	0.12
1*H*-1,2,4-triazole	2.93
4*H*-1,2,4-triazole	5.81

Ab initio optimized geometries at B3LYP/6-311+G levels suggest that aromatic stabilization of 2*H*-1,2,3-triazole is the highest of all azoles <2003T1657>. Some values (in units of kcal mol^{-1}) are given below for comparison:

Pyrrole	18.04
Pyrazole	20.46
Imidazole	16.18
1*H*-1,2,3-triazole	20.21
2*H*-1,2,3-triazole	22.21
4*H*-1,2,4-triazole	12.19
1*H*-tetrazole	14.13

Bond dissociation energies for several heterocyclic systems calculated by two *ab initio* methods, CBS-Q, G3 and G3B3, show similar values <2003JPO883>. The G3B3 data for three selected azoles are as follows:

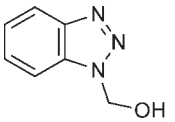
Pyrrole	N(1)-H	95.2 (kcal mol^{-1})
	C(2)-H	119.7
	C(3)-H	119.2
Pyrazole	N(1)-H	109.2
	C(3)-H	117.8
	C(4)-H	121.0
	C(5)-H	119.9
1*H*-1,2,3-triazole	N(1)-H	109.5
	C(4)-H	121.5
	C(5)-H	122.7

Potassium cation affinities of several azoles and other compounds in the gas phase were calculated by hybrid density functional theory [B3-LYP with 6-311 + G(3df , 2p) basis set] <2003CEJ3383>. There is a striking difference in binding energies of 1*H*- and 2*H*-1,2,3-triazoles. Some of the collected data are as follows:

Pyrrole	77.1 (kJ mol^{-1})
Pyrazole	90.5
1-methylpyrazole	94.5
3-methylpyrazole	92.8
1,4-dimethylpyrazole	100.0
1,3,5-trimethylpyrazole	103.4
Imidazole	111.1
1*H*-1,2,3-triazole	118.6
2*H*-1,2,3-triazole	64.5
1*H*-tetrazole	109.7
2*H*-tetrazole	88.5

Monte Carlo calculations of interactions of 1*H*-benzotriazole with water reveal significant electronic polarization of the heterocycle. The dipole moment is increased by 2.89 D for the ground state and 2.75 D for the excited state to the total values of 6.89 and 6.40 D, respectively. Direct measurements of dipole moments in water are not possible, but these numerical results are supported by experimental solvatochromic blue shift of the $\pi \rightarrow \pi^*$ transition <2003IJQ572>.

Theoretical calculations at the B3LYP/6-31G* and B3LYP/6-311++G** levels concluded that 2-(hydroxymethyl)-benzotriazole **2** is slightly more stable than 1-(hydroxymethyl)benzotriazole **1**. The energy difference of 0.22 kcal mol^{-1} suggests that both isomers should be almost equally abundant; however, in solid state and in solutions, only isomer **1** is observed. One of the possible explanations of this phenomenon is formation of strong intermolecular hydrogen bonding between the OH group and N-3 in condensed phase of derivative **1**. Less basic nitrogen atoms in derivative **2** do not provide such stabilization <2004JHC285>.



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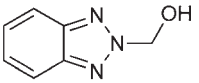

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Atomic charges of anions **3** and **4** have been evaluated at the HF/6-31G* level using several partitioning schemes. The data obtained from the natural population analysis (NPA) method are listed below. The electron-withdrawing power of the CN groups is clearly demonstrated by the total charge of the ring change from −1.34 to −0.84 <2003SSI129>.

	3	**4**
N-1	−0.41	−0.31
N-2	−0.18	−0.12
C-4	−0.17	−0.05
Σ_{ring}	−1.34	−0.84

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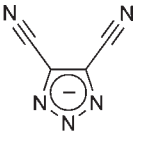

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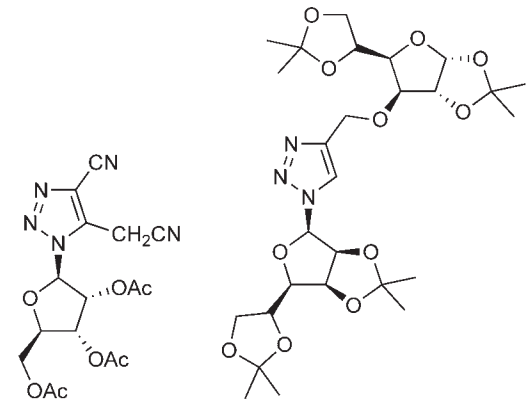
5.01.3 Experimental Structural Methods

5.01.3.1 X-Ray Crystal Structure

X-Ray crystallographic data for several basic derivatives of 1*H*-1,2,3-triazole and benzotriazole are included in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)669, 1996CHEC-II(4)1>. Hundreds of new 1*H*-1,2,3-triazole structures have been analyzed since; some crystallographic data for representative examples (structures **5–12**) are collected in **Table 1**.



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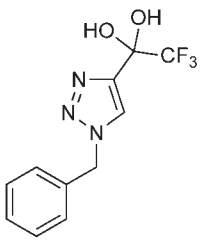

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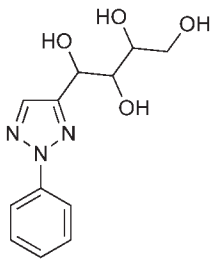

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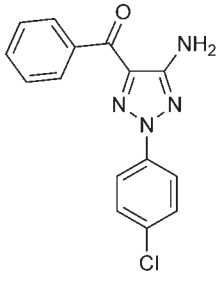

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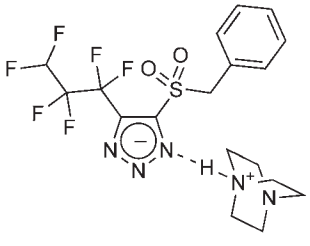

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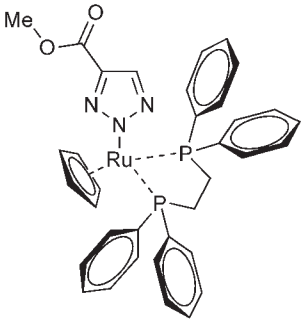

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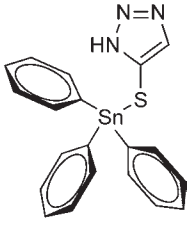

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Table 1 Selected bond lengths (in Å) for 1,2,3-triazole derivatives **5–12**

Compound	*N(1)–N(2)*	*N(2)–N(3)*	*N(3)–C(4)*	*N(1)–C(5)*	*C(4)–C(5)*	*Other*	*Reference*
5	1.359	1.293	1.359	1.351	1.373	1.486:N(1)–Cα	2004NN521
6	1.354	1.303	1.361	1.351	1.372	1.442: N(1)–Cα, 1.493: C(4)–Cα	2005H(65)1035
7	1.342	1.309	1.365	1.344	1.342	1.484: N(1)–Cα, 1.503: C(4)–Cα'	2002JFC(116)81
8	1.341	1.333	1.329	1.339	1.399	1.422: N(2)–Cα, 1.490: C(4)–Cα'	2002BMC963
9	1.324	1.358	1.338	1.340	1.417	1.416: N(2)–Cα, 1.356: C(4)–Nα	2006ARK(xv)53
10	1.334	1.321	1.351	1.334	1.368	1.477: C(4)–Cα, 1.749: C(5)–S	2001CHE470
11	1.332	1.331	1.352	1.351	1.400	2.090: N(2)–Ru	2003OM3107
12	1.316	1.329	1.317	1.348		0.858: N(1)–H, 1.746: C(5)–S	2004POL1981

As can be seen in Table 1, for N-1 substituted triazoles (structures 5–7), the N(1)–N(2) bonds (1.342–1.359 Å) are significantly longer than the N(2)–N(3) bonds (1.293–1.309 Å), reflecting more single- and more double-bond character, respectively. An electron-withdrawing substituent at C-4 (compound 5 vs. 6) shortens slightly the N(2)–N(3) bond and stretches the N(1)–Cα bond indicating that such derivatives should dissociate more easily. In 2-substituted triazole 8, both N–N bonds are approximately equal. However, when two substituents of different electronic properties are attached, as in compound 9, the N–N bonds differ substantially, with that closer to an electron-withdrawing substituent being shortened and that closer to an electron donor being elongated. This observation can be rationalized by contribution of resonance forms involving the amino and carbonyl groups at C-4 and C-5, respectively. For the same reason, the C(4)–C(5) bond in derivative 9 is the longest one in the series suggesting diminished aromatic character for this molecule.

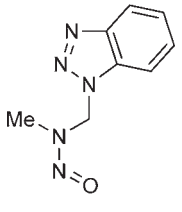
Because substituents of the ring may have different effects on the individual bonds, it is informative to compare averages of the five ring bond lengths. In this aspect, the average bond of the triazole system in compound 9 (1.355 Å) is the longest in the series 5–12 supporting the low aromatic character of this molecule. For comparison, the average bond length in molecule 8 is 1.348 Å. Triazole anion structure 10 reveals relatively short bonds with an average bond length of 1.341 Å. The triazole ring in ruthenium complex 11, with average bond length of 1.353 Å, exhibits similar character to that of molecule 9 due in part to its resonance involving the carbonyl group at C-4. In the relatively simple and electron-rich molecule 12, the average N–N bond (1.322 Å) and N–C bonds (1.332 Å) are the shortest in the whole series.

Table 2 lists bond lengths for the heterocyclic ring of the benzotriazole systems in derivatives 13–21. In comparison with 1,2,3-triazoles, N-1 substituted benzotriazoles have significantly longer N(1)–N(2) bonds (average 1.364 Å vs. 1.352 Å) and somewhat longer N(2)–N(3) bonds (average 1.307 Å vs. 1301 Å). In general, the C–N bonds and C–C bonds in the heterocyclic ring of benzotriazole derivatives are also slightly longer than the corresponding bonds in 1,2,3-triazoles. This causes the average heterocyclic ring bond in the whole series of benzotriazole derivatives 13–21 (1.361 Å) to be significantly longer than that in 1,2,3-triazole derivatives 5–12 (1.346 Å), reflecting the diminished aromatic character and therefore the higher reactivity of the benzotriazole system.

Table 2 Selected bond lengths (in Å) for benzotriazole derivatives 13–21

Compound	*N(1)–N(2)*	*N(2)–N(3)*	*N(3)–C(3a)*	*N(1)–C(7a)*	*C(3a)–C(7a)*	*Other*	*Reference*
13	1.368	1.296	1.367	1.361	1.391	1.440[a]	2001RCB1630
14	1.349	1.309	1.373	1.365	1.404	1.468[a]	2001JOC6787
15	1.377	1.310	1.383	1.371	1.410	1.434[a]	2001JOC6787
16	1.373	1.307	1.380	1.367	1.407	1.471[a]	2001JOC6787
17	1.369	1.299	1.374	1.367	1.388		2003ANS973
18	1.344	1.326	1.381	1.343	1.376	1.457[a]	2003JOC5713
19	1.368	1.302	1.380	1.377	1.391	1.431[a]	2003JOC407
20	1.336	1.353	1.354	1.356	1.381	1.413[b]	2001JCX217
21	1.351	1.296	1.374	1.363	1.411	1.477[a]	2006OM416
						1.455[c]	

[a]N(1)–Cα.
[b]N(2)–Nα.
[c]N(2)–Cα'.



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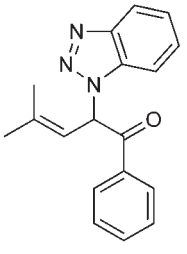

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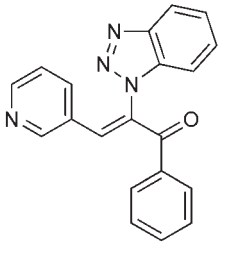

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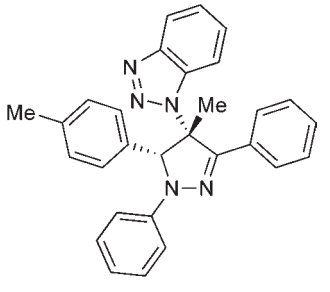

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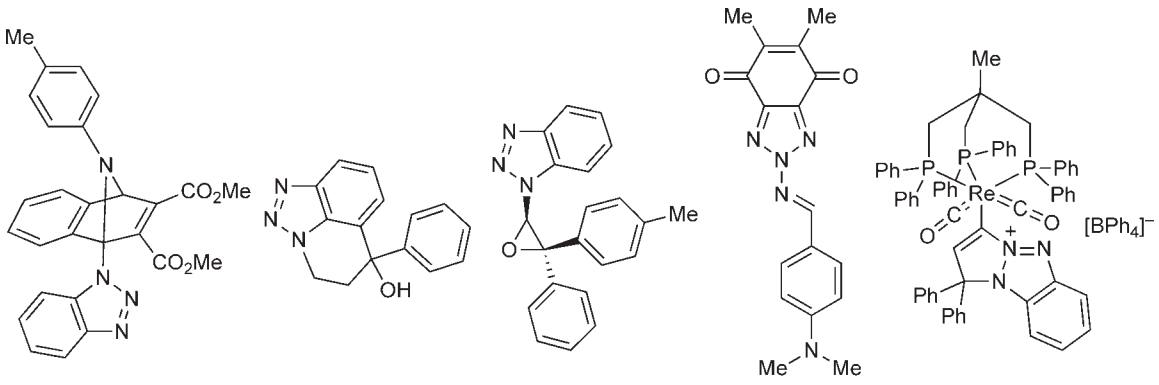
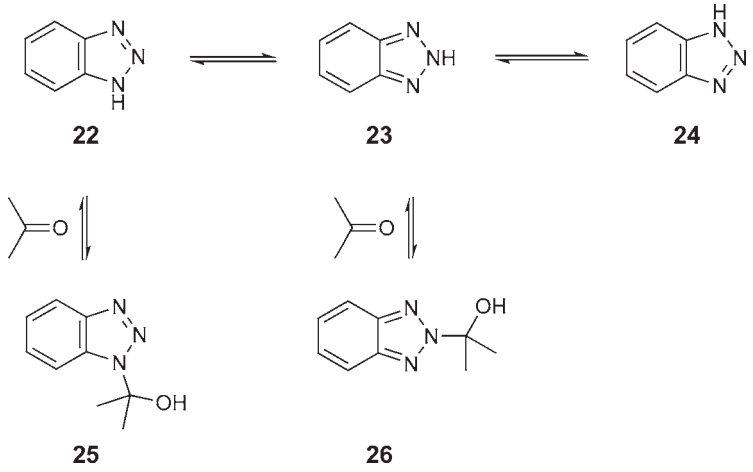


17 18 19 20 21

5.01.3.2 ^{1}H NMR Spectroscopy

Due to rapid proton exchange between forms **22**, **23**, and **24** (**Scheme 1**), benzotriazole exhibits at room temperature just two C–H signals, each for two protons, in its ^{1}H NMR spectra. However, when the temperature is lowered, the signals broaden and finally split into four separate resonances of the four individual C–H protons. The results of such study for an acetone solution of benzotriazole are given in **Table 3** <2002T9089>. The situation is additionally complicated by formation of adducts **25** and **26**, which at −90 °C contribute 25% and 5%, respectively, to the total molecular population.

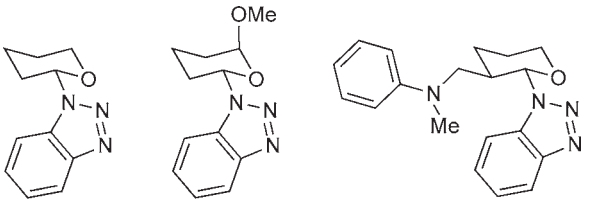


Scheme 1

Table 3 ^{1}H NMR chemical shifts in ppm for acetone-d_6 solutions of benzotriazole

Compound	*Temperature*	*H-4*	*H-5*	*H-6*	*H-7*
22–24	21 °C	8.00	7.44	7.44	8.00
22–24	−85 °C	8.11	7.48	7.48	8.05
25	21 °C	8.20	7.36	7.47	8.06
25	−85 °C	8.28	7.45	7.56	8.11

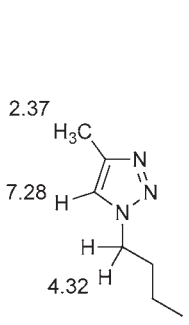
To illustrate the ^{1}H NMR assignment of benzotriazole derivatives, spectral data for three benzotriazol-1-yl derivatives of tetrahydropyran, **27–29**, are presented in **Table 4** <2001CJC1655>. Chemical shifts (in ppm) for the ring protons as well as the α-hydrogen atoms of the attached substituents in triazole derivatives **30** <2004TL6129>, **31** <2002BMC947>, **32** <2005JCO490>, **33** <2006T8115>, **34** <2006SC951>, **35** <2006OL3227>, **36** <2006OL3227>, **36** <2005JA15998>, and **38** <2005JA15998> are also shown below together with the structures.



27 **28** **29**

Table 4 ^{1}H NMR chemical shifts (ppm), multiplicity and coupling constants (Hz) for benzotriazol-1-yl derivatives **27–29**

Compound	*H-4*	*H-5*	*H-6*	*H-7*	*H-α*
27	8.05 dt (8.2, 0.9)	7.37 ddd (8.2, 6.9, 0.9)	7.48 ddd (8.4, 6.9, 0.9)	7.74 dt (8.4, 0.9)	6.02 dd (8.3, 3.0)
28	8.07 dt (8.2, 0.9)	7.38 ddd (8.2, 6.9, 0.9)	7.50 ddd (8.2, 6.9, 0.9)	7.73 dt (8.2, 0.9)	6.41 dd (10.7, 2.7)
29	8.08 dt (8.3, 0.9)	7.39 ddd (8.2, 7.0, 0.9)	7.48 ddd (8.2, 7.0, 0.9)	7.67 dt (8.3, 0.9)	5.87 d (7.5)



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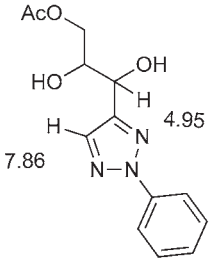

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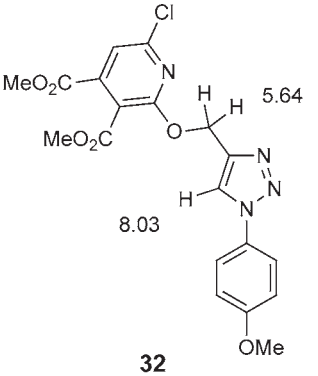

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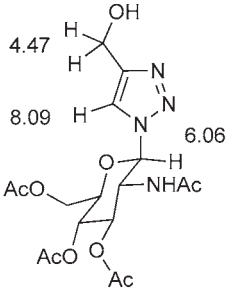

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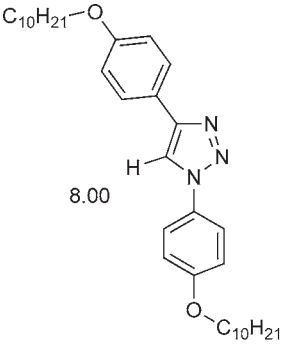

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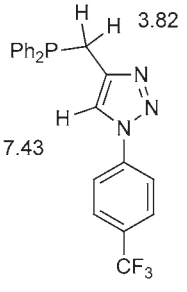

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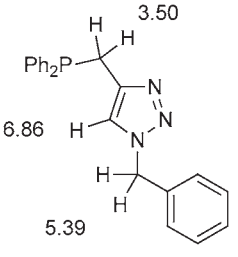

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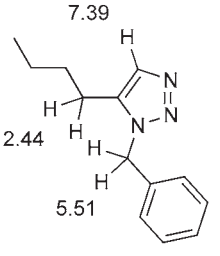

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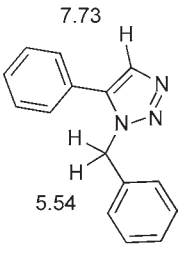
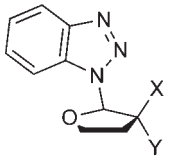


38

5.01.3.3 ^{13}C NMR Spectroscopy

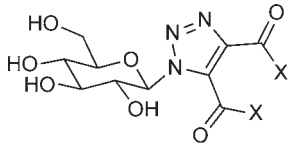
To illustrate signal assignments in ^{13}C NMR spectra of the benzotriazol-1-yl system, chemical shifts for five α-(benzotriazol-1-yl)tetrahydrofurans (structures **39–43**) <2003JPO158> and three corresponding tetrahydropyrans (structures **27–29**) <2001CJC1655> are listed in **Table 5**. Selected ^{13}C NMR spectral data for triazolyl nucleoside analogs **44–50** <2003SPL461> are collected in **Table 6**.



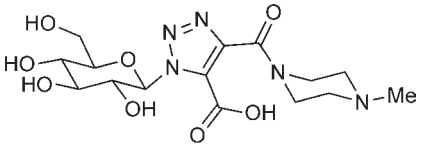
39: X = Y = H
40: X = Cl, Y = H
41: X = H, Y = Cl
42: X = CH_2NEt_2, Y = H
43: X = H, Y = CH_2NEt_2

Table 5 ^{13}C NMR chemical shifts (in ppm) for the benzotriazol-1-yl and α-carbon atoms in the spectra of derivatives **27–29** and **39–43** taken in $CDCl_3$

Compound	*C-α*	*C-4*	*C-5*	*C-6*	*C-7*	*C-7a*	*C-3a*
27	85.5	119.6	124.0	127.1	110.7	132.1	146.3
28	80.2	120.0	124.1	127.5	110.6	132.2	146.1
29	87.9	120.2	124.3	127.9	110.1	132.2	146.6
39	87.9	119.8	124.1	127.4	110.4	132.8	146.2
40	88.8	119.8	124.0	127.6	110.3	133.4	145.4
41	93.6	119.9	124.4	128.1	109.9	132.7	145.9
42	88.3	119.5	123.8	126.9	110.1	133.2	145.1
43	90.6	119.7	124.1	127.4	110.6	132.9	146.2



44: X = OH
45: X = NH_2
46: X = NHMe
47: X = NHBu
48: X = $NHCH_2Ph$
49: X = $NHCH_2CH_2OH$



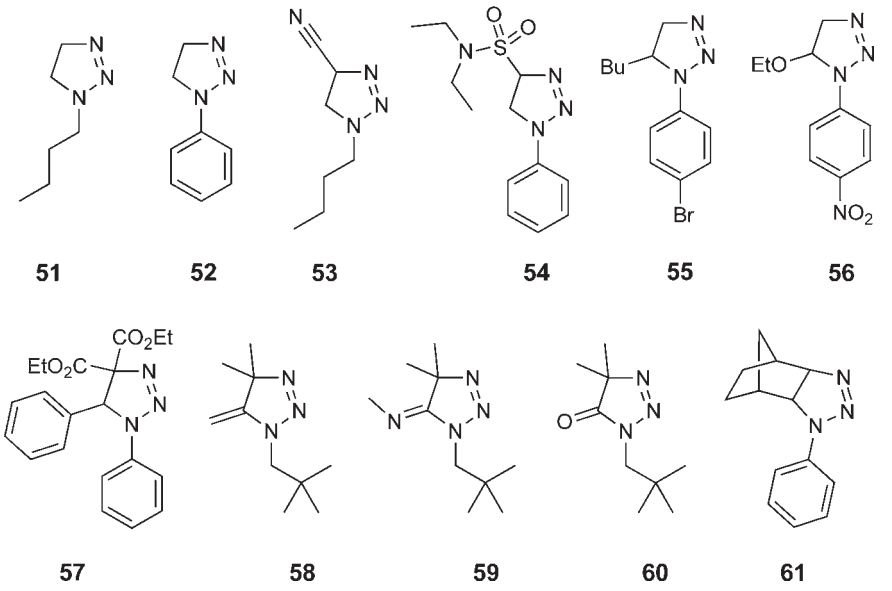
50

Table 6 Chemical shifts (ppm) for selected carbon atoms of derivatives **44–50** in their ^{13}C NMR spectra taken in DMSO-d_6

Compound	*C-4*	*C-5*	*C-1α*	*C-4α*	*C-5α*
44	143.1	140.0	87.9	180.0	180.0
45	138.9	132.2	86.2	163.1	158.0
46	138.5	133.0	86.4	161.2	156.9
47	138.7	132.0	86.4	160.7	156.2
48	138.7	132.3	86.5	160.7	156.5
49	138.7	132.1	86.2	160.8	156.4
50	144.3	135.3	85.2	163.5	176.7

5.01.3.4 ^{15}N NMR Spectroscopy

In the previous issue of *Comprehensive Heterocyclic Chemistry* <1996CHEC-II(4)1>, the ^{15}NMR spectra of 1,2,3-triazoles and benzotriazoles are extensively discussed, but 1,2,3-triazolines are only briefly mentioned. To clarify the picture, data for typical 4,5-dihydro-1*H*-1,2,3-triazoles (**51–61**) <2002J(P2)126> are collected in **Table 7**. For the ring nitrogen atoms, the highest field resonance is always assigned to N-1. To distinguish positions of N-2 and N-3 resonances, which sometimes come close to each other, isotopic labeling at N-1 and N-2 is used.



51 52 53 54 55 56

57 58 59 60 61

Table 7 ^{15}N Chemical shifts in ppm for 4,5-dihydro-1*H*-1,2,3-triazoles **51–61** taken in $CDCl_3$ with nitromethane as external reference ($\delta = 0$ ppm)

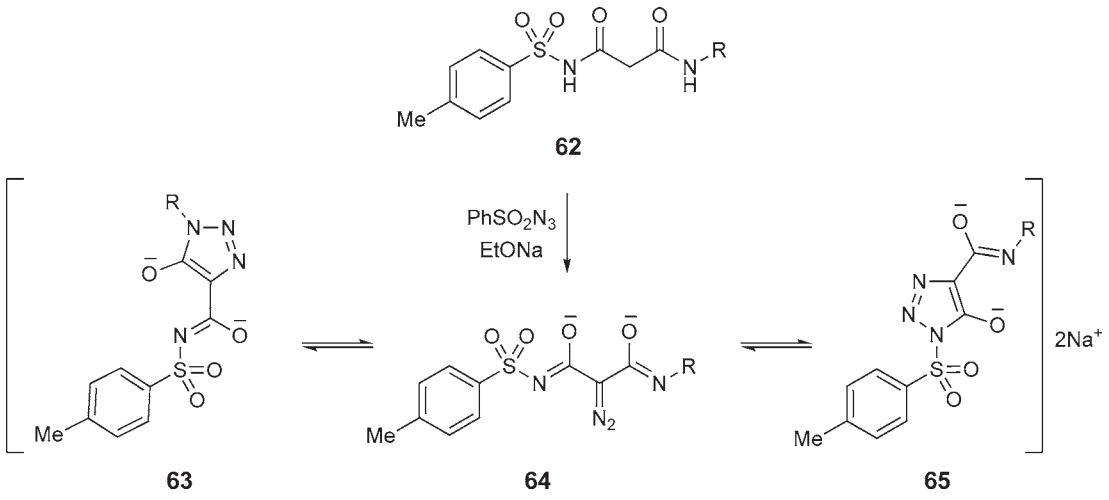
Compound	*N-1*	*N-2*	*N-3*	*Other nitrogens*
51	−195.5	54.6	−31.4	
52	−182.8	35.0	−29.3	
53	−195.5	52.8	−56.2	−127.1 (CN)
54	−182.5	37.6	−50.7	−286.4 (NEt_2)
55	−175.4	34.6	−30.4	
56	−168.3	32.7	−17.6	−12.7 (NO_2)
57	−176.9	35.8	−46.8	
58	−179.7	32.4	−6.9	
59	−172.9	36.4	3.5	−160.4 (NMe)
60	−163.1	44.0	32.8	
61	−173.9	33.5	−27.5	

The data presented indicate that change of a N-1 substituent from aliphatic to aromatic causes moderate downfield shifts of the N-1 and N-3 resonances and a strong upfield shift of the N-2 resonance. This feature can be explained by the resonance effect of the aromatic ring. Electron-withdrawing substituents at C-4 shift strongly upfield the N-3 signals but do not significantly change the N-1 and N-2 resonances. Substituents at C-5 shift significantly upfield the N-1 resonances. An sp^2 C-5 atom shifts the N-3 resonance dramatically downfield, especially when a heteroatom is attached (structures **58–60**).

5.01.4 Thermodynamic Aspects

5.01.4.1 Ring-Chain Equilibriums

Mixed malondiamide **62** on reaction with benzenesulfonyl azide and sodium ethoxide in ethanol is converted into open-chain diazo-derivative **64**, which readily cyclizes to triazoles **63** and **65** (**Scheme 2**). Rapid equilibration in solution prevents separation of individual components of the reaction mixture. NMR studies of the equilibrium between products **63**, **64**, and **65**, carried out in DMSO-d_6 are summarized in **Table 8**. It is evident from the collected data that the equilibrium depends strongly on the substituent R. Electron-withdrawing substituents on the phenyl ring destabilize structure **63** but stabilize form **65**. *Ortho*-substituents on the aromatic ring, both electron-donating and electron-withdrawing, strongly destabilize triazoles **63**, but they stabilize open-chain form **64**. The benzyl derivative exists almost exclusively in the triazole form **63** <2003CHE168>.



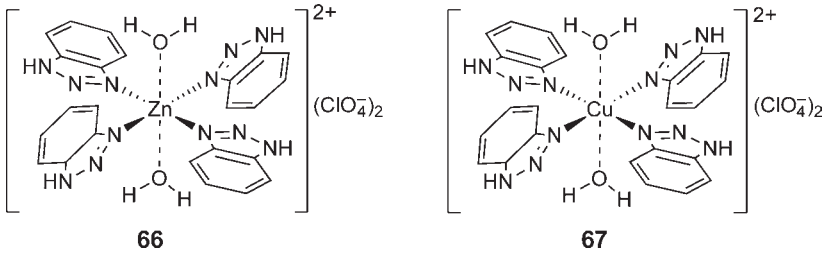
Scheme 2

Table 8 Ratio between compounds **63–65** in DMSO-d_6 solutions

Substituent R	**63** (%)	**64** (%)	**65** (%)
Ph	35	35	30
4-$MeOC_6H_4$	42	42	16
4-BrC_6H_4	25	40	35
3-$(NO_2)C_6H_4$	0.8	0.2	99
2-$MeOC_6H_4$	<0.1	58	42
2,4,6-$Cl_3C_6H_2$	<0.1	90	10
$PhCH_2$	99.6	0.2	0.2

5.01.4.2 Mononuclear Complexes

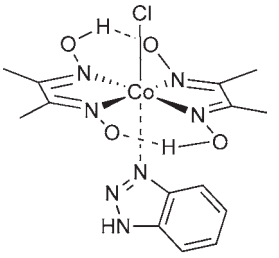
The strong coordination of benzotriazole and its derivatives to metal ions makes them attractive ligands. Thus, slow concentration of an aqueous solution of benzotriazole and zinc perchlorate results in formation of colorless prism crystals of composition $Zn[(BtH)_4(H_2O)_2](ClO_4)_2$, where BtH = benzotriazole. X-Ray crystal structure analysis shows that the crystals belong to monoclinic *C2/c* space group, with lattice parameters $a = 13.838$ Å, $b = 13.374$ Å, and $c = 16.944$ Å, $\beta = 103.206°$, $V = 3053.1$ Å^3, $Z = 4$, $R_1 = 0.0411$. The zinc ion is coordinated by four nitrogen atoms from four benzotriazole molecules and two oxygen atoms from water molecules to form an octahedral coordination polyhedron of complex **66**. Detailed analysis of the X-ray data indicates that the complex consists of two pairs of identically bonded benzotriazolyl systems located on the opposite sides of the central atom with the Zn–N bond lengths of 2.119 and 2.223 Å, respectively. The Zn–O bond length is 2.157 Å. The difference in Zn–N bond lengths is attributed to strong hydrogen bonding of two of the benzotriazolyl substituents with the perchlorate anions that decreases electron density on the N-3 atoms and weakens their bonding with the Zn ion. A similar complex, structure **67**, is obtained from copper (II) perchlorate with the Cu–N bond lengths of 2.009 and 2.090 Å, and the Cu–O bond length of 2.393 Å. The much longer Cu–O bond of complex **67** in comparison with the Zn–O bond in complex **66** is attributed to strong Jahn–Teller effect in the copper complex <2002ICC453>.



Concentration of an ethanolic solution of dimethylglyoxime, cobalt(II) chloride and benzotriazole results in deposition of crystalline complex **68**. The product is stable at room temperature; however, it slowly decomposes upon heating. Thermal analysis reveals that the compound releases first the chlorine atom and 50% of the benzotriazole content to form a new complex that is stable to 225 °C. Probably in this new form, the benzotriazole moiety coordinates two cobalt ions simultaneously. Further heating to 350 °C removes the benzotriazolyl moieties completely <2003JPY699>. The first step of decomposition can be summarized as follows:

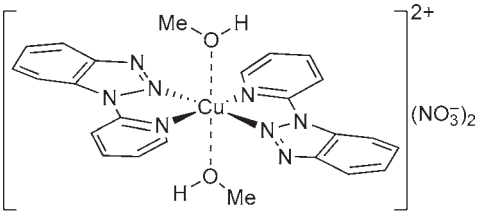
$$[Co(dmgH)_2(BtH)Cl] \rightarrow [Co(dmgH)_2(Bt)_{0.5}]$$

where dmgH = dimethylglyoxime anion, BtH = benzotriazole.



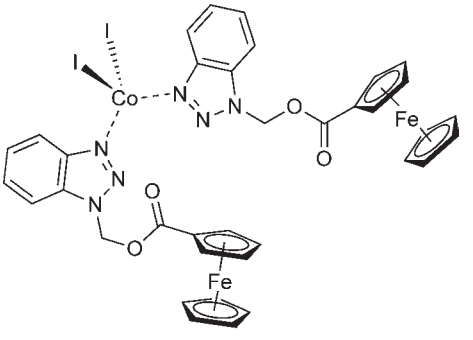
68

A reaction of 2-(benzotriazol-1-yl)pyridine with copper(II) nitrate, carried out in methanol, provides complex **69**. The product crystallizes in monoclinic space group $P2_1/n$. The copper atom lies in the crystallographic center of inversion, and it is coordinated to two chelating ligands and two methanol molecules. In structures **66–68** discussed above, the benzotriazolyl N-3 atom is involved in bonding. By contrast, in structure **69**, the benzotriazolyl N-2 atom is used to coordinate to the copper ion, with the bond length of 2.047 Å. The bond length of pyridyl-N-Cu is 2.034 Å. In analogy to structure **67**, the axial Cu–O bonds in complex **69** are elongated (2.298 Å) <2003JCD992>.



69

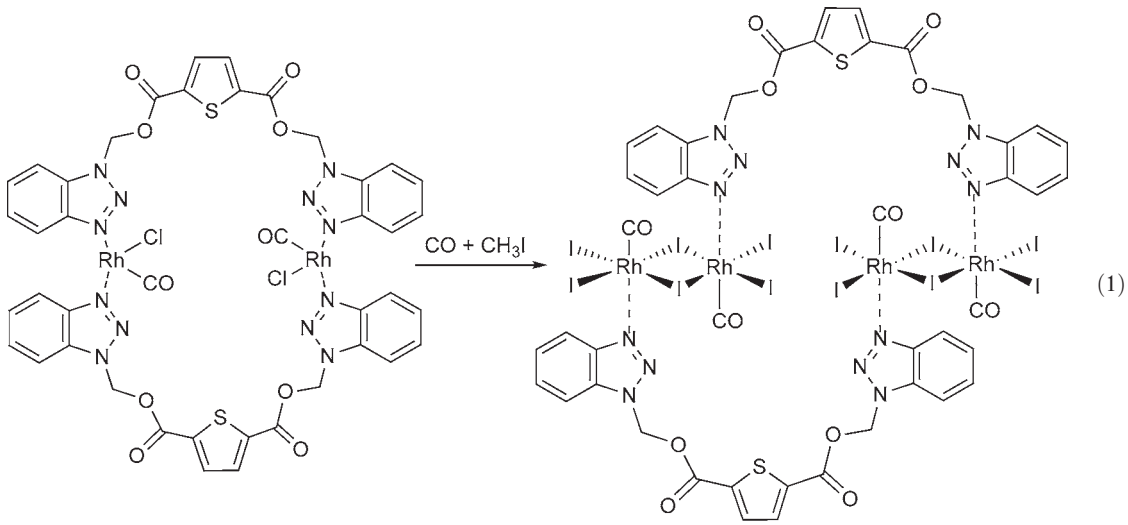
The ester derived from (benzotriazol-1-yl)methanol and ferrocenecarboxylic acid reacts in dichloromethane with cobalt(II) iodide to provide complex **70** in quantitative yield, which recrystallizes from dichloromethane/hexane to give green air-stable crystals. The X-ray structure analysis reveals that the cobalt center is coordinated to two iodine atoms and the N-3 atoms of two benzotriazole ligands. The angles N–Co–N, N–Co–I, and I–Co–I of 103.5°, 109.0° (average), and 116.2°, respectively, are close to the ideal tetrahedral angle. Some deviation from the tetrahedral geometry is indicated by the relatively large I–Co–I and relatively small N–Co–N angles; this is presumably caused by strong repulsion between the iodide anions. The bond lengths, Co–N 2.033 and 2.044 Å and Co–I 2.551 and 2.569 Å, are typical for this type of complexes <2002JOM(658)251>.



70

5.01.4.3 Di-, Tri-, and Polynuclear Complexes

(Benzotriazol-1-yl)methyl 2,5-thiophenedicarboxylate reacts with $[RhCl(CO)_2]_2$ in toluene at room temperature to give quantitatively rhodium(I) complex **71** as an air-stable yellow solid. The dimeric nature of the molecule is clearly indicated by its ESI molecular peak at $m/z = 1220$. Complex **71** catalyzes methyl iodide promoted carbonylation of methanol to give acetic acid and methyl acetate with much higher catalytic activities than the classical rhodium catalysts. Treatment with carbon monoxide and methyl iodide converts compound **71** into complex **72** in high yield (Equation 1). In a single-crystal X-ray analysis, complex **72** turns out to be a macrocycle containing two dinuclear iodo-bridged Rh(III) units. The four rhodium atoms have distorted octahedral geometries. The four Rh–N bonds are almost equal in length (2.091, 2.102, 2.128, and 2.139 Å). The Rh–C bond lengths are 1.840–1.867 Å. The bond lengths for each of the Rh_2I_6 units (2.605–2.692 Å) are typical for that type of structures. In contrast to Rh(I) macrocycle **71**, Rh(III) complex **72** does not catalyze the carbonylation of methanol <2001EJI3005>.

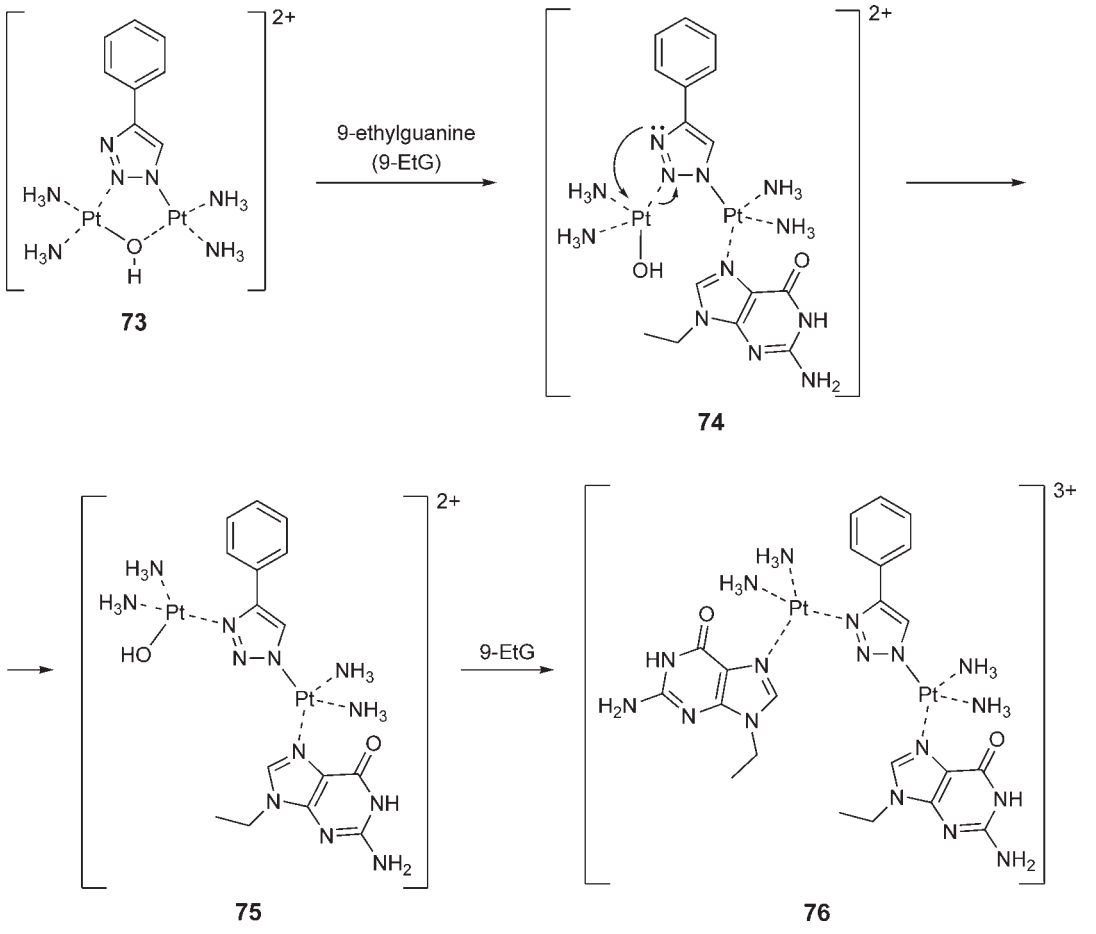


71 **72** (1)

Cisplatin is one of the most frequently used anticancer agents despite several drawbacks including acquired drug resistance and serious side effects. To overcome these problems, an intensive search is going on to find safer alternatives. In one such approach, dinuclear Pt(II) complex **73** is obtained as dinitrate salt from a reaction of [*cis*-$Pt(NH_3)_2(\mu\text{-}OH)_2](NO_2)_2$ with 4-phenyl-1,2,3-triazole. According to X-ray structure determination, the coordination of the Pt atoms is square planar with the Pt–N(ammine) distances slightly longer (2.015–2.044 Å) than the Pt–N(triazole) distances (1.985–1,996 Å). The Pt–O bond lengths are 2.027 and 2.028 Å. A weak intramolecular hydrogen bond is observed between one of the ammine groups as donor and the triazole N-3 atom as acceptor <2002JA4738>.

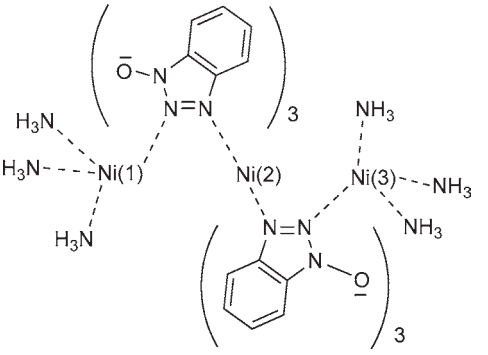
Compound **73** and its simpler analog without any substituent on the triazole ring exhibit higher cytotoxicity to L1210 murine leukemia cells than cisplatin. To explain the effect of its action on DNA, a reaction of complex **73** with 9-ethylguanine, as a model nucleobase, was studied using NMR. In the first step, the hydroxyl bridge is broken and 9-ethylguanine is attached to one of the platinum centers to give intermediate **74**. In the following step, the freed diamminohydroxyplatinum group migrates to N-3 of the triazole ring to provide thermodynamically more stable intermediate **75**. Finally, a reaction with another molecule of 9-ethylguanine provides final adduct **76** (**Scheme 3**) <2002JA4738>.

Reaction of $Ni(NO_3)_2 \cdot 6H_2O$ with 1-hydroxybenzotriazole (BtOH) and NH_3 in DMF provides trinuclear complex $[Ni_3(BtO)_6(NH_3)_6]$ **77**. Variation of the solvent and the BtOH/Ni(II) ratio afford the same complex, in various solvated forms, as the only product isolated. According to the X-ray analysis, the central Ni atom, Ni-2, in the trinuclear molecule is joined to each of the other two Ni atoms, Ni-1 and Ni-3, by three bridging BtO^- ligands. Each BtO^- ion is coordinated to Ni-2 via the N-3 atom of the benzotriazole ring and to one of the terminal Ni atoms via N-2. The ammonia ligands complete the six-coordination pattern at each of the terminal Ni atoms. The metal centers have slightly distorted octahedral geometries. The molecule is almost linear, with the Ni(1)–Ni(2)–Ni(3) bond angle of 177.9°. The Ni–N(ammine) bond distances (2.074–2.123 Å) are very close to the Ni–N(Bt) bond lengths (2.087–2.160 Å) <2002TMC377>.



73 **74** **75** **76**

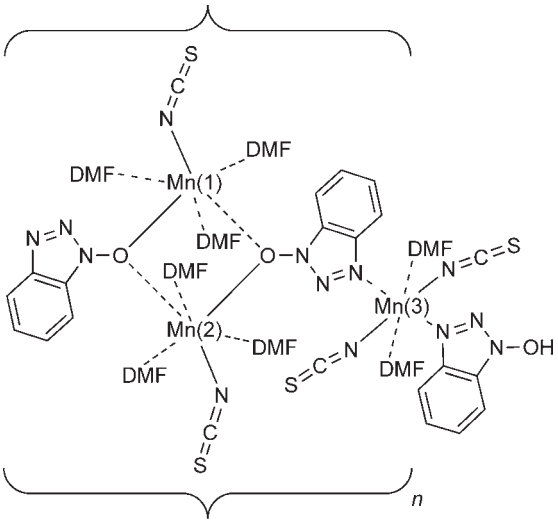
Scheme 3



77

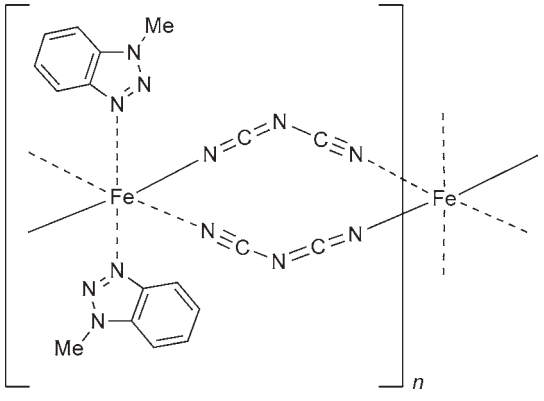
Heating of a suspension of powdered manganese in a DMF solution of 1-hydroxybenzotriazole and ammonium thiocyanate in air results in formation of a polymeric complex 78 of general formula $[Mn_3(BtO)_2(NCS)_4(DMF)_8]_n$. In this reaction zero-valent manganese is oxidized by oxygen from the air to Mn(II). Composition of this complex does not depend on the reagent ratio indicating that complex 78 is a thermodynamic product. According to X-ray analysis, complex 78 consists of dinuclear subunits of two Mn(II) atoms bridged by two oxygen atoms from BtO^- ligands, forming a planar four-membered ring [–Mn(1)-O-Mn(2)-O–]. The octahedral coordination of each of these manganese atoms is completed by three oxygen atoms from DMF molecules and one nitrogen atom from the NCS^- anion.

The dinuclear subunits in polymer **78** are connected via mononuclear subunits containing atoms Mn(3) coordinated by N-3 atoms of two anions derived from 1-hydroxybenzotriazole. The octahedral coordination of the Mn(3) atom is completed by two oxygen atoms from DMF molecules and two nitrogen atoms from NCS^- anions. The Mn(1)-O(BtO) bond lengths are 2.186 and 2.206 Å, which is a little more than the Mn(1)-O(DMF) bond lengths of 2.176 Å. The Mn(3)-N(BtO) bonds (2,262 and 2.277 Å) are also longer than the Mn(3)-N(NCS) bonds (2.199 and 2.218 Å) <2002EJI2488>.



78

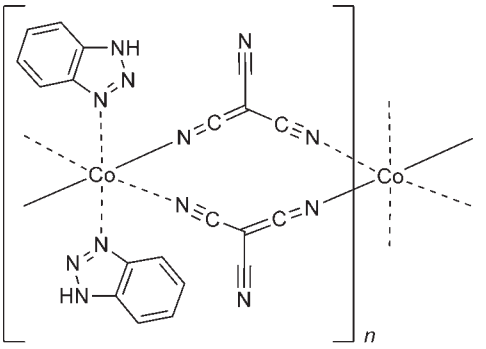
Addition of a methanolic solution of 1-methylbenzotriazole (BtMe) to an aqueous solution of $Fe(II)(ClO_4)_2 \cdot xH_2O$ and sodium dicyanamide (Nadca) results in slow deposition of crystalline complex $[Fe(BtMe)_2(dca)_2]$. X-Ray analysis reveals that the obtained complex (structure **79**) consists of one-dimensional linear chains, in which the Fe(II) centers are bridged by the dicyanamide anions. The coordination sphere at each Fe(II) center is completed by two 1-methylbenzotriazole ligands occupying the axial positions. Coordination geometry around the Fe(II) atom is distorted octahedral with the Fe-N(dca) bond length of 2.136 Å and the Fe–N(BtMe) bond length of 2.208 Å. Similar linear polymeric complexes are obtained from Mn(II) and Cu(II) salts <2006POL360>.



79

A similar complex **80** is also produced in a reaction of cobalt(II) nitrate with potassium tricyanomethanide (Ktcm) and benzotriazole (BtH). According to the X-ray data for this complex, the CoN_6 octahedron is only slightly distorted, having the N–Co–N′ angles in the range of 88.37–91.16°. The equatorial Co–N(tcm) distances (2.106 and 2.110 Å) are

slightly shorter than the axial Co–N(Bt) bonds (2.149 Å). The polymeric one-dimensional chains are cross-linked by hydrogen bonding between the benzotriazole NH atoms and the uncoordinated CN groups of the bridging ligands in the adjacent chains <2004AXC250>.

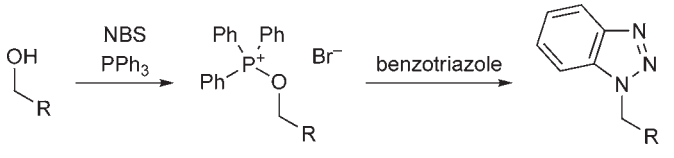


80

5.01.5 Reactivity of Fully Conjugated Rings

5.01.5.1 Nucleophilic Aliphatic Substitution

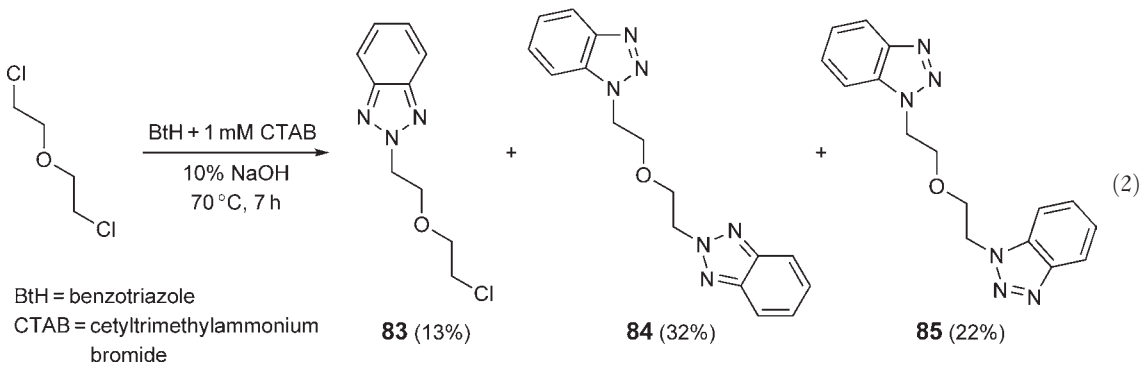
Alkylation reactions of 1,2,3-triazole and benzotriazole are exhaustively discussed in CHEC(1984) and CHEC-II(1996). The electrophilic reagents, usually alkyl halides, sulfates or sulfonates, attack N-1 or N-2 atoms of the ring producing mixtures of the corresponding 1-alkyl- and 2-alkyl triazoles <1984CHEC(5)669, 1996CHEC-II(4)1>. Some progress in this field provides finding of direct alkylation of benzotriazole with alcohols in the presence of triphenylphosphine and NBS <1997SC1613>. Presumably, the first step is formation of a reactive intermediate **81** that is attacked later by benzotriazole in the S_N2 fashion to give derivative **82** (**Scheme 4**). The reaction is regioselective and provides exclusively 1-alkyl-, 1-(arylmethyl)-, 1-(2-alken-1-yl)-, and 1-(2-alkyn-1-yl)benzotriazoles, respectively. Secondary alcohols give the corresponding alkyl derivatives in low yields, while tertiary alcohols do not alkylate benzotriazole under these conditions.



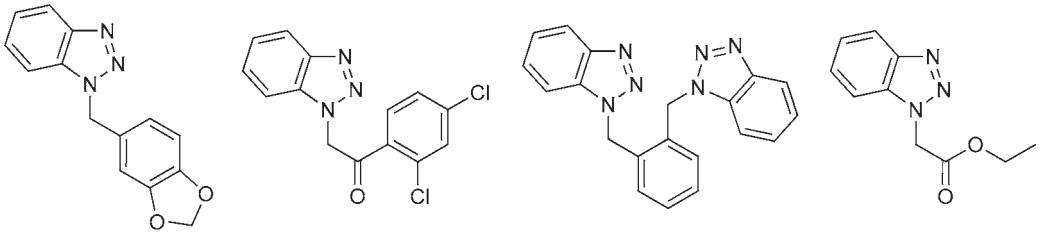
81 **82**

Scheme 4

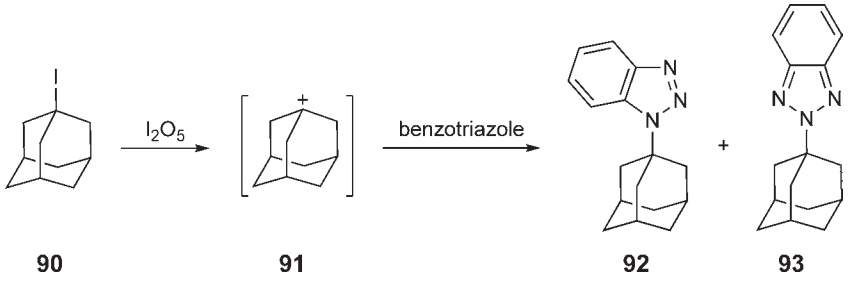
In aqueous micellar medium using cetyltrimethylammonium bromide as a surfactant, benzotriazole is alkylated regioselectively at N-1 with *n*-propyl and *n*-butyl bromides, but activated alkylating agents (benzyl chloride, allyl bromide, phenacyl chloride, etc.) produce mixtures of benzotrizol-1-yl and -2-yl isomers in ratios varying from 55:45 to 80:20, respectively <2001BCJ2133>. Alkylation of benzotriazole with bis(2-chloroethyl) ether under these conditions provides a mixture of derivatives **83–85** with isolated yields of 13%, 32% and 22%, respectively (Equation 2). Use of ionic liquids as media for alkylation of benzotriazole provides generally higher regioselectivity; however, the trend is opposite to that under micellar conditions with phenacyl bromide and similar compounds providing exclusively benzotriazol-1-yl derivatives and *n*-alkyl halides giving mixtures of benzotriazol-1-yl and -2-yl derivatives in a ratio of 15:1 <2004H(63)1077>.



Microwave irradiation can facilitate alkylation of benzotriazole. Thus, compound **86** is cleanly prepared in 95% yield upon irradiation of a solution of benzotriazole and the corresponding benzyl bromide in DMF for 40 s <2006BML999>. Very often microwave-assisted alkylation of benzotriazole works best when no solvent is used; for example, derivative **87** is prepared this way in 94% yield <2003T865>. Phase-transfer catalysis can also be used to increase the yield and improve regioselectivity of the alkylation process as it is illustrated by preparation of compound **88** in 72% yield in the presence of a pyridinophane <2006S654>. In another example, a reaction of benzotriazole with ethyl chloroacetate and K_2CO_3 in ethyl acetate is catalyzed by polyethylene glycol (PEG 400) to give a mixture of ethyl (benzotriazol-1-yl)acetate **89** (56%) and its benzotriazol-2-yl isomer (15%) <2002SRI265>.



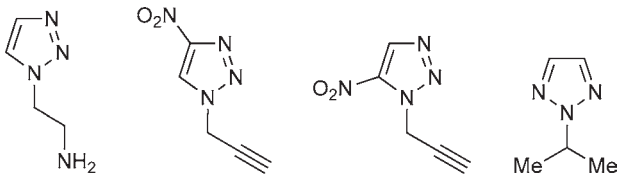
Adamantylation of benzotriazole represents a special case because direct substitution in adamantanyl halides by an S_N2 mechanism is impossible, and an S_N1 mechanism is improbable. In this case, reactive cation **91** is generated by oxidative cleavage of the C-I bond in 1-iodoadamantane **90**. Benzotriazole added to the reaction mixture binds cations **91** to afford a mixture of benzotriazol-1-yl **92** and -2-yl **93** derivatives in a ratio of 26:74 and the total yield of 67% (**Scheme 5**) <2001RJO1762>.



Scheme 5

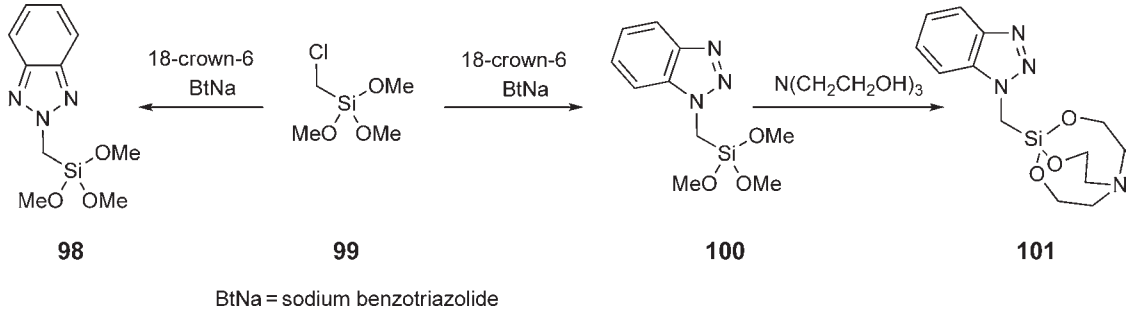
Alkylation of 1,2,3-triazole with *N*-(2-bromoethyl)phthalimide in the presence of Cs_2CO_3 followed by cleavage of the phthalyl moiety with hydrazine provides 1-(2-aminoethyl)-1,2,3-triazole **94** in 51% yield <2003JME1116>. A reaction of 4-nitro-1,2,3-triazole with propargyl bromide in the presence of KOH gives a mixture of isomeric 1-propargyl-1,2,3-triazoles **95** and **96** in the equimolar ratio <2003RJO1792>. However, in acidic media, when N-1

and N-3 positions are protonated, 2-substituted derivatives of 1,2,3-triazole are formed regioselectively. Thus, isopropyl alcohol reacts with 1,2,3-triazole in 95% sulfuric acid to provide 2-isopropyl-1,2,3-triazole **97** in 80% yield <2002JHC1111>.



94 **95** **96** **97**

Alkylation of benzotriazole with (chloromethyl)trimethoxysilane **99** provides a mixture of its derivatives **98** and **100** in a ratio of 1:3. In a reaction with tris-(2-hydroxyethyl)amine, compound **100** is converted to derivative **101** in nearly quantitative yield. Compound **98** reacts with tris-(2-hydroxyethyl)amine similarly (**Scheme 6**) <2003ARK(xiii)125, 2003CHE1639>.



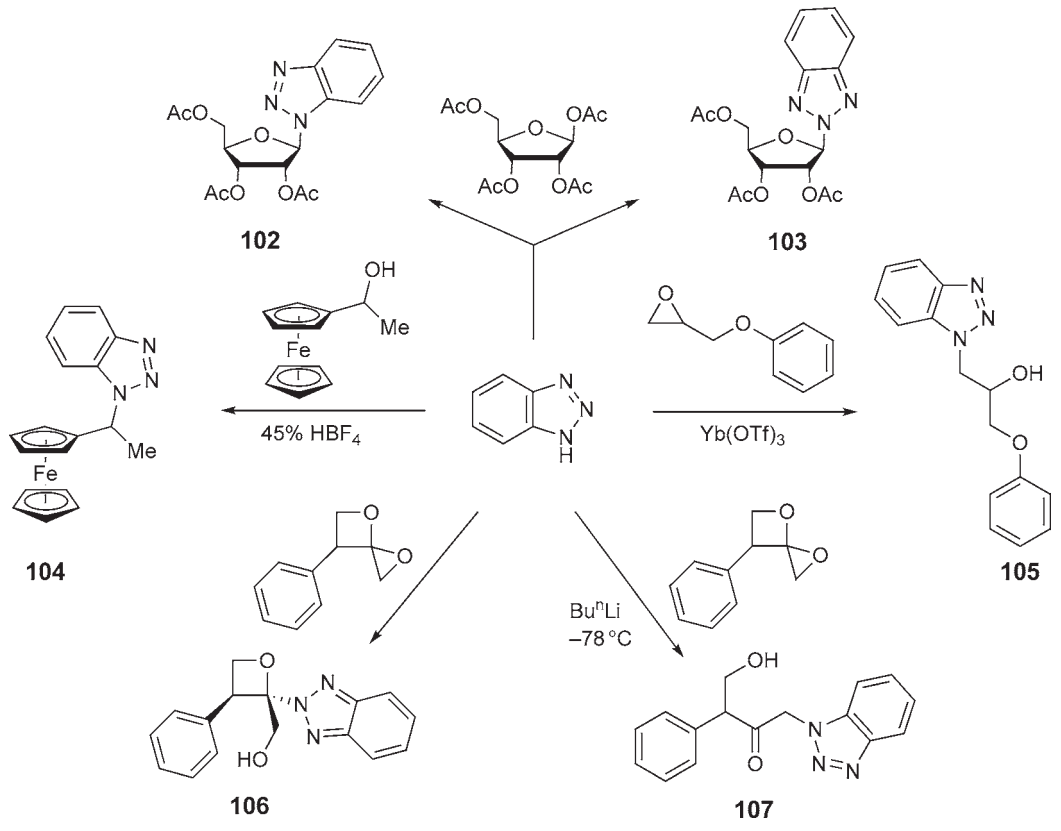
98 **99** **100** **101**

Scheme 6

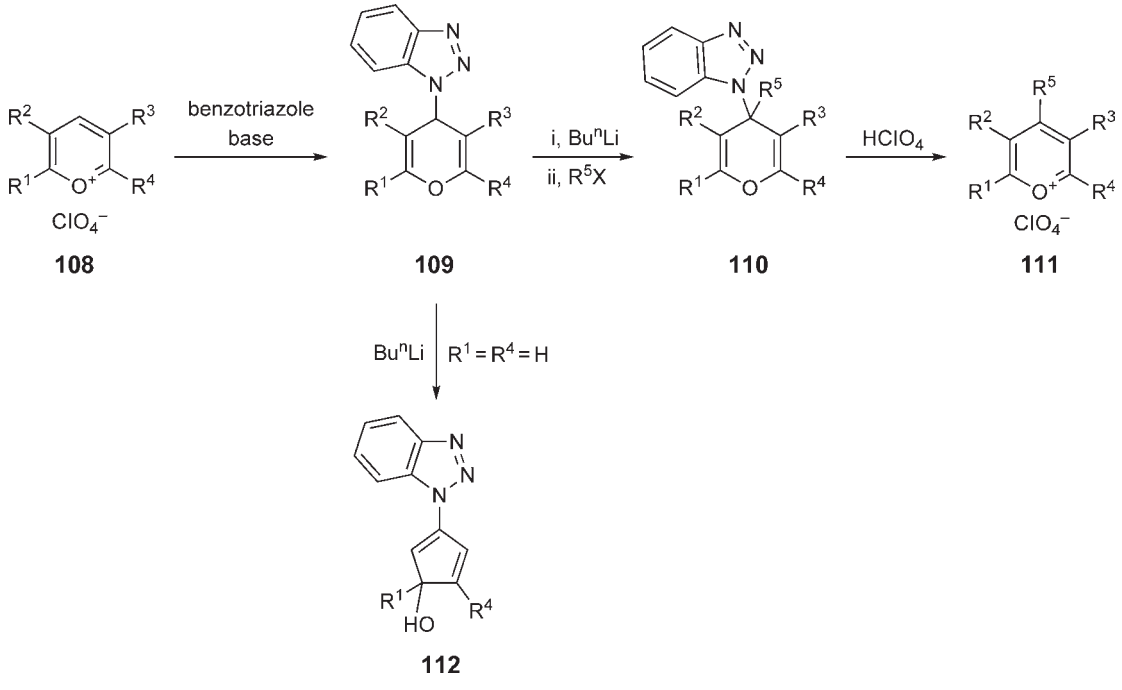
When positive charge of the reaction center is stabilized by an adjacent atom, even the acetoxy anion can be a good leaving group. Such a situation is typical in derivatives of sugars. Thus, heating of an equimolar mixture of benzotriazole and tetraacetylribose at 150 °C for 15 min results in formation of products **102** (63%) and **103** (3%) <2002NN73>. Due to strong electron-donating abilities of the ferrocene system, ferrocenyl methyl carbinol reacts eagerly with benzotriazole in the presence of 45% fluoroboric acid to give 1-(α-ferrocenylethyl)benzotriazole **104** in 93% yield (**Scheme 7**) <2004JOM(689)2473>. Catalyzed by ytterbium triflate, (phenoxymethyl)oxirane reacts with benzotriazole to afford derivative **105** in 71% yield <2003SC2989>. 1,5-Dioxaspiro[3,2]hexane with remarkably strained molecules reacts directly with benzotriazole without any catalyst to give oxetane derivative **106** as the main product in 41% isolated yield. The preference for N-2 substitution in product **106** seems to result from steric hindrance at the reaction center. However, under basic conditions, the same reagent gives product **107** (isolated yield 27%) as a result of a regular S_N2 attack on the oxirane methylene carbon atom <2003JOC1480>.

5.01.5.2 Nucleophilic Attack on Aromatic Rings

The anion derived from benzotriazole attacks electron-deficient aromatic rings of pyrylium salts **108** in position *para* to oxygen to give *4H*-pyrans **109** in high yields. Positions *ortho* in salts **108** are blocked by aryl groups ($R^1 = R^4 = Ar$) to avoid reactions there <1999JPR152>. Derivatives **109** have been found to be very useful in the synthesis of corresponding 4-alkyl pyrylium salts **111**, via 4-alkyl-4-(benzotriazole-1-yl)-*4H*-pyrans **110** (**Scheme 8**). Benzo[*b*]pyrylium <1997JOC8198, 1998EJO2623> and xanthylium <1997JOC8198> salts react similarly. Derivatives similar to adducts **109** were also obtained from nitrogen (*N*-methylacridinium) and sulfur (thioxanthylium) cationic heterocyclic systems <1999JHC927>. When $R^1 = R^4 = H$, the anions derived from pyrans **109** may also rearrange to 1,2-diaryl-2,4-cyclopentadien-1-ols **112** <1999JPR152>.

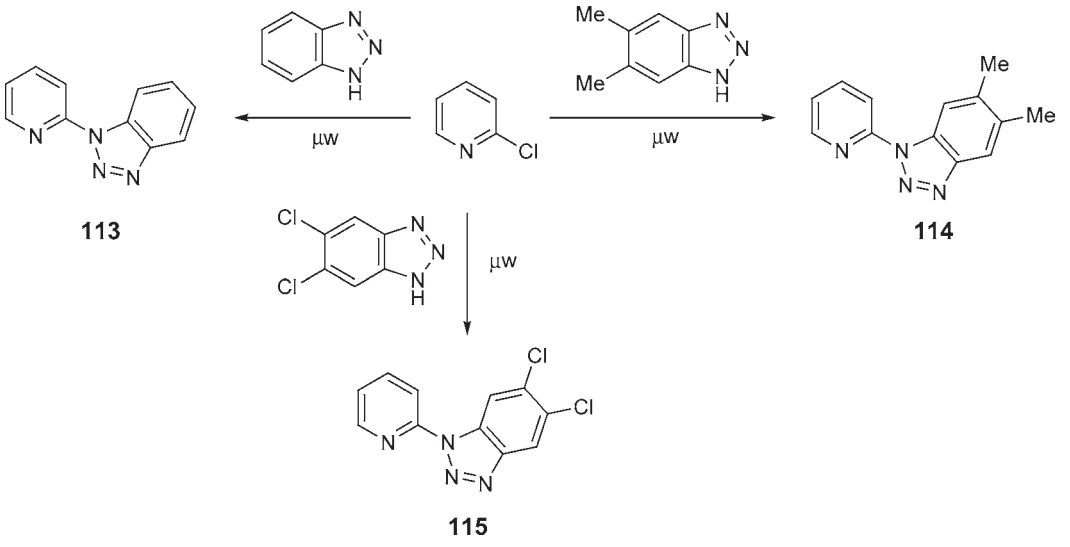


Scheme 7



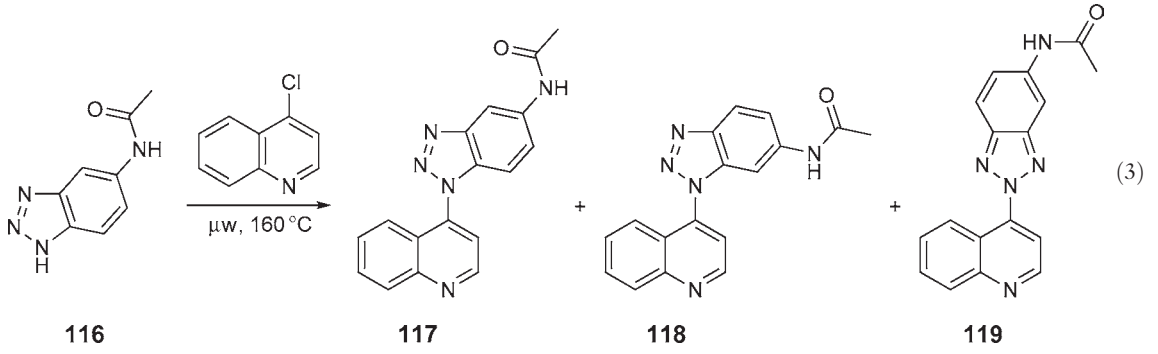
Scheme 8

Upon microwave (μw) irradiation, benzotriazole and its derivatives react readily with 2-chloropyridine to afford products **113-115** in 87%, 72%, and 70% yield, respectively (**Scheme 9**). 2-Chloroquinoline reacts similarly. 2-Bromopyridine and 2-bromoquinoline give generally lower yields in these reactions <2006OL415>.



Scheme 9

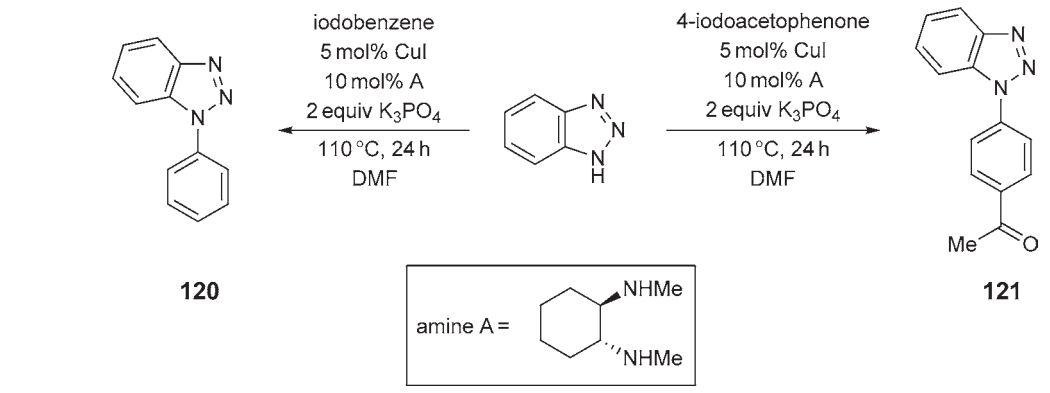
Microwave-induced reaction of 5-acetamidobenzotriazole **116** with 4-chloroquinoline gives a mixture of products **117** (43%), **118** (30%), and **119** (10%) (Equation 3). Interestingly, the product ratio does not depend on the solvent used (toluene, DMF, NMP) <2006T1895>.



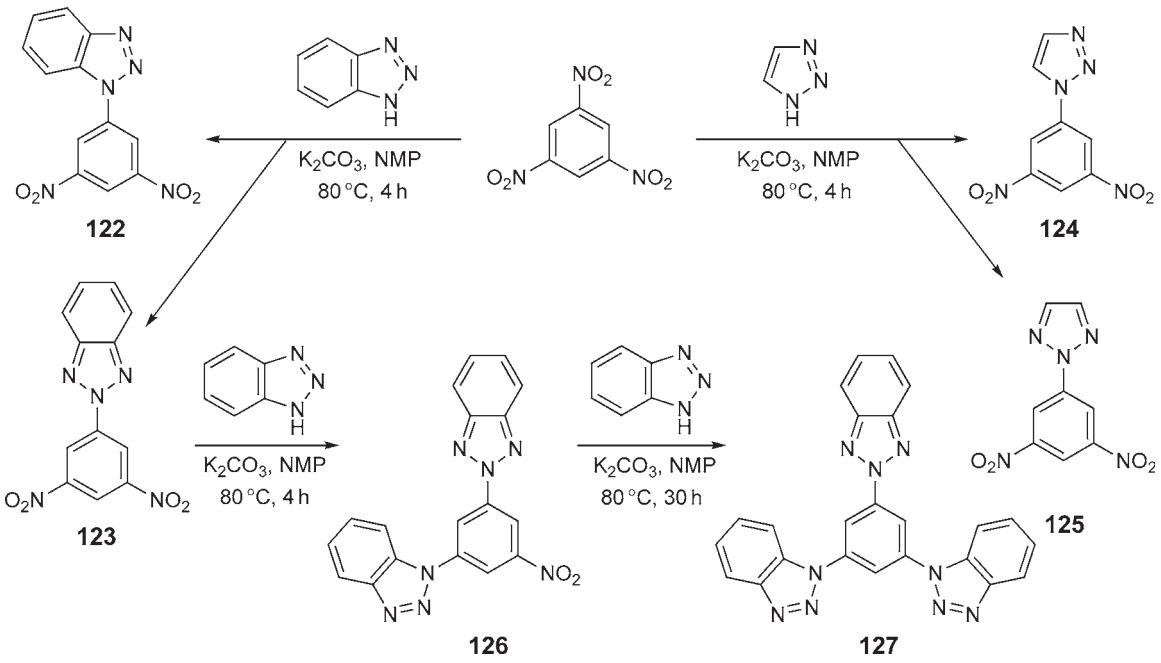
(3)

Catalyzed by a copper–diamine complex, benzotriazole reacts well even with nonactivated aromatic iodides. The case is illustrated in **Scheme 10** by formation of 1-phenylbenzotriazole **120** in 90% yield. The acetyl group as an electron-withdrawing substituent in *para* position has surprisingly negative effect on the product yield as derivative **121** is isolated in only 63% yield. Potassium phosphate is used as a base. The reactions are highly regioselective with the benzotriazol-1-yl to benzotriazol-2-yl isomer ratio higher than 25: 1 <2004JOC5578>.

Nucleophilic substitution of a nitro group by benzotriazole or triazole in strongly electron-deficient aromatic systems can also be easily achieved. Thus, heating of an equivalent mixture of 1,3,5-trinitrobenzene with benzotriazole and K_2CO_3 in NMP at 80 °C for 4 h affords products **122** and **123** in a ratio of 2:3 with 96% total yield. A similar reaction of 1,3,5-trinitrobenzene with 1,2,3-triazole gives a mixture of derivatives **124** and **125** in a molar ratio of 1:9. Surprisingly, only N-2 substitution is observed when 2-(3,5-dinitrophenyl)benzotriazole **123** is heated with benzotriazole and K_2CO_3 to give product **126** in 92% yield. Substitution of the last nitro group is also possible, but the reaction is much slower. Insoluble in most common solvents, 1,3,5-tribenzotriazolylbenzene **127** is isolated in analytically pure form in 62% yield. It can be concluded that electron-withdrawing abilities of benzotriazolyl substituents are comparable to those of a nitro group to activate aromatic rings for nucleophilic substitution (**Scheme 11**) <2004RCB588>.



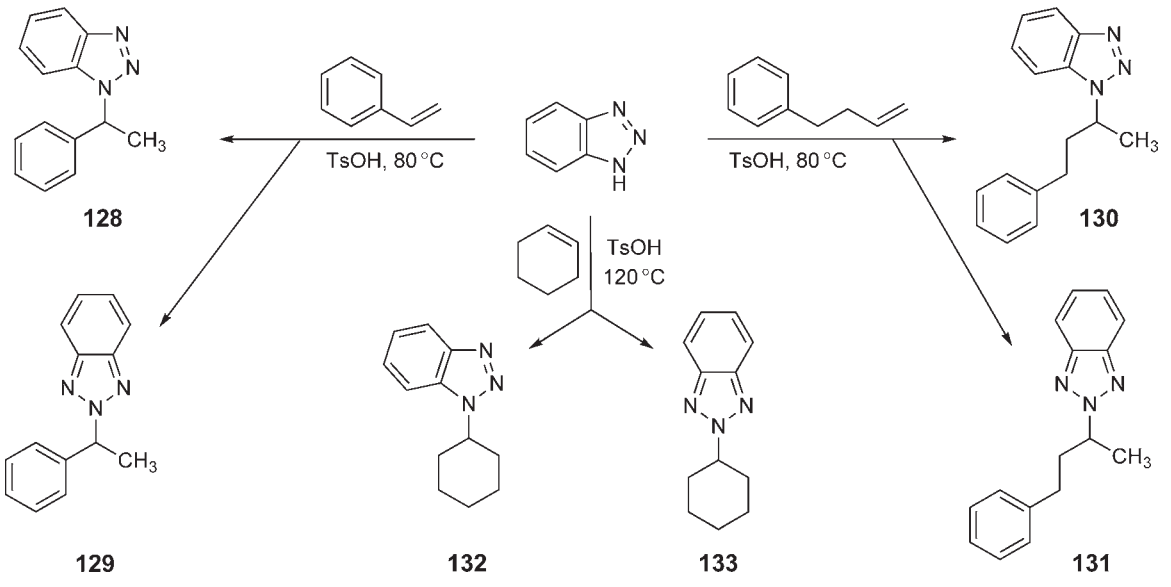
Scheme 10



Scheme 11

5.01.5.3 Addition to Multiple Bonds

Under strongly acidic conditions (10% molar equivalent of TsOH), benzotriazole adds to unactivated alkenes to afford a mixture of 1-alkyl- and 2-alkylbenzotriazoles. Because protonation of the double bond with formation of the corresponding carbocation is the first step in these additions, Markovnikov's rule is followed, and derivatives with a benzotriazolyl substituent at the terminal carbon atom are not observed. Three examples of such additions are depicted in **Scheme 12**. Thus, in a reaction with styrene, benzotriazol-1-yl **128** and -2-yl **129** are formed in a ratio of 6.5:1 and total yield of 46%. In a reaction with 4-phenylbutene, derivatives **130** and **131** are obtained in a ratio of 1.9:1 and total yield of 65%. Normal terminal alkenes give the corresponding benzotriazol-1-yl and benzotriazol-2-yl derivatives as well, but the total yields are significantly lower (25% from 1-octene and 29% from 1-decene). Increasing the amount of TsOH from 10 to 100 mol% improves slightly the overall yield, but it also results in more complex mixtures of the products due to rearrangements of the original carbocations. Cyclohexene does not react with benzotriazole at 80 °C; however, at 120 °C, a mixture of derivatives **132** and **133** is obtained in a ratio of 1.1:1 and total isolated yield of 56% <1995J(P2)1645>.



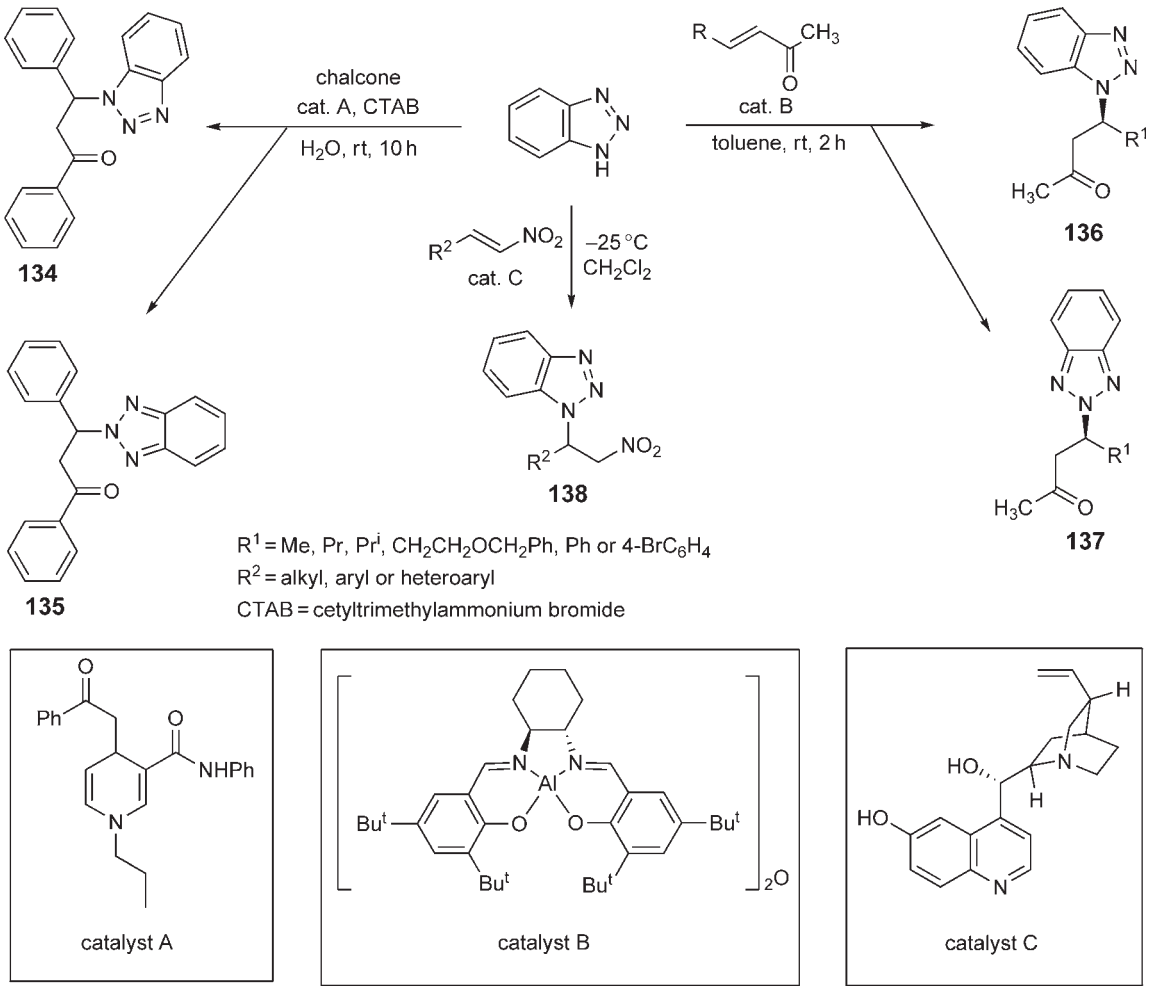
Scheme 12

Michael addition of benzotriazole to electron-deficient double bonds is described in CHEC-II(1996) <1996CHEC-II(4)1>. One of the innovations in this field is running the reaction of benzotriazole with chalcone in a micellar medium to afford a mixture of derivatives **134** and **135** in the molar ratio of 4:1 and total yield of 75% (**Scheme 13**) <2003CL1064>. Even more important innovation is running such reactions enantioselectively with application of optically active bases as catalysts. Thus, addition of benzotriazole to α,β-unsaturated ketones derived from acetone in the presence of catalyst B produces mixtures of products **136** and **137** in ratios varied from 3:1 to 2:1 with total yields in the range of 53–75% and high enantioselectivity (70–98% = ee) <2005AGE2393>. Addition of benzotriazole to 1-nitro-1-alkenes proceeds enantioselectively in the presence of catalyst C to provide exclusively benzotriazol-1-yl derivatives **138** in the average yield of 77% and high ee (64–94%) <2006OL1391>.

When the electron-deficient alkene contains a good leaving group X at the double bond, addition of benzotriazole may be followed by elimination of X (or HX) with restoration of the double bond. The total effect is a nucleophilic substitution of group X by benzotriazolide anion. Four examples of such reactions are gathered in **Scheme 14**. Thus, benzotriazolyl nitronyl nitroxide **139** must result from addition of the benzotriazolide anion to C-2 of 2-bromo-4,4,5,5-tetramethyl-4,5-dihydro-1*H*-imidazole-3-oxide-1-oxyl followed by elimination of Br^- <2004T99>. Sometimes, the intermediate adducts are stable enough to be isolated and characterized. Such is the case of adduct **140** that is obtained from a low temperature reaction of benzotriazole with methyl 2-(trifluoroacetyl)vinyl sulfone. At slightly elevated temperature, adduct **140** eliminates spontaneously methanesulfinic acid to give product **141** <2003RCB1791>. Addition of a benzotriazolide anion to carbon α of (*E*)-(2-phenylvinyl)phenyliodonium tetrafluoroborate results in unstable benzyl anion **143** that rapidly eliminates iodobenzene to afford (*E*)-1-(2-phenylvinyl)benzotriazole **142** <2002JCM388>. Heating a mixture of benzotriazole, 2-chloro-1,1,1-trifluoroethane, KOH and DMSO at 80 °C for 8 h leads to (*E*)-1-(2-chloro-1-fluorovinyl)benzotriazole **145**. The proposed mechanism for this reaction involves elimination of HF from the starting material and trapping of the evolved 2-chloro-1,1-difluoroethene by benzotriazolide anion to form intermediate anion **144** that spontaneously eliminates F^- to give product **145** <2002T4077>.

Application of catalysts allows sometimes executing this addition/elimination process even with alkenes without any electron-deficient substituent attached. Such case is illustrated by an example in **Scheme 15**. In the presence of mercury-(II) acetate and trifluoroacetic acid, 1,2,3-triazoles **146** react with vinyl acetate at 70 °C to give vinyl derivatives **148** in good yields (70–88%) <2002RJO1056>. Adducts **147** are presumed to be intermediates in this process.

In the presence of triphenylphosphine as a catalyst, benzotriazole adds readily to activated allenes. Its reaction with ethyl 2,3-butadienoate produces a mixture of adducts **149** (54%) and **150** (20%). Both derivatives form exclusively as *(E)*-isomers <2006T3710>. In a reaction of benzotriazole with dibenzoylacetylene and

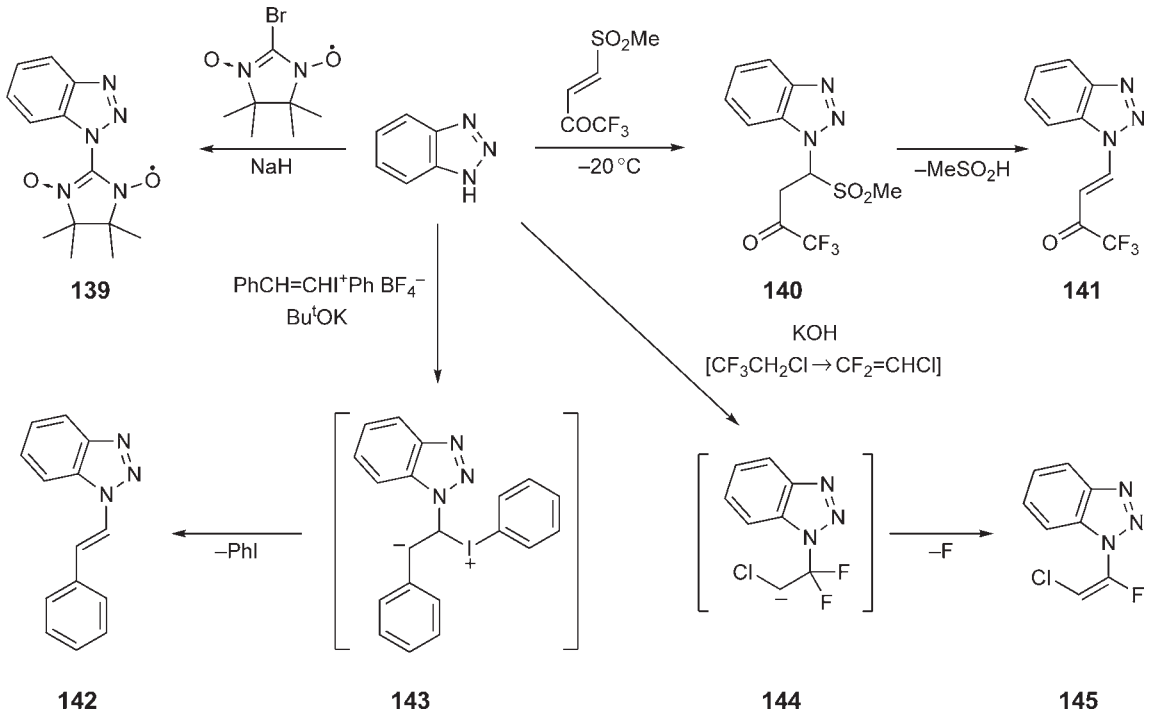


Scheme 13

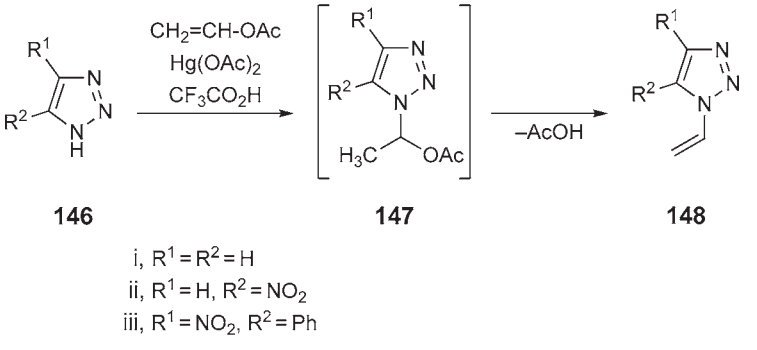
triphenylphosphine (used in the equimolar amount), a mixture of compounds **151** (40%) and **152** (45%) is obtained (**Scheme 16**). Neither open-chain benzotriazol-2-yl analog of **151** nor benzotriazol-1-yl analog of furan derivative **152** is detected <2002TL9449>. It seems to be the steric hindrance in reaction intermediates solely responsible for that distinction. To make the cyclization to a furan system possible, the molecule **151** must first assume (*E*)-configuration, and than bring the carbonyl groups to close proximity. Switching between (*Z*)- and (*E*)-configurations in compound **151** seems to be relatively easy by addition of another molecule of benzotriazole to the double bond followed by its elimination, but rotation of the α-benzoyl group would impose much strain on the molecule due to steric repulsion between its phenyl and the benzotriazolyl benzenoid ring. The less bulky benzotriazol-2-yl substituent in the original adduct of benzotriazole to the triple bond allows for such transformations without high energetic barriers.

5.01.5.4 Complexes with Borane

1-Benzylbenzotriazole **153** reacts rapidly with borane to form complex **154** in quantitative yield. Complex **154** and its analogs derived from 1-alkylbenzotriazoles are inert to water and air at room temperature and easy to handle solids. Treatment with Bu^nLi followed by iodomethane converts complex **154** into its α-methylated product **155**. In the case of a sterically hindered and less acidic substituent (compound **157**), the corresponding complex with BH_3 **158** undergoes lithiation in position 4 to afford compound **159**. Refluxing in ethanol removes the borane group from N-3 to restore the benzotriazole system (products **156** and **160**) (**Scheme 17**) <1998OPP325>.



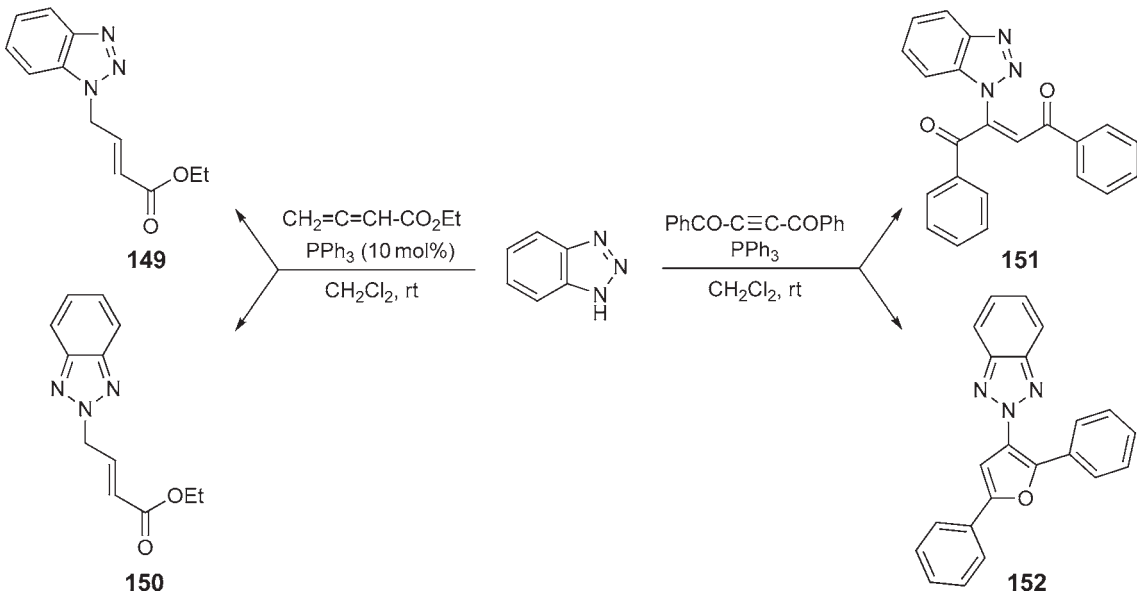
Scheme 14



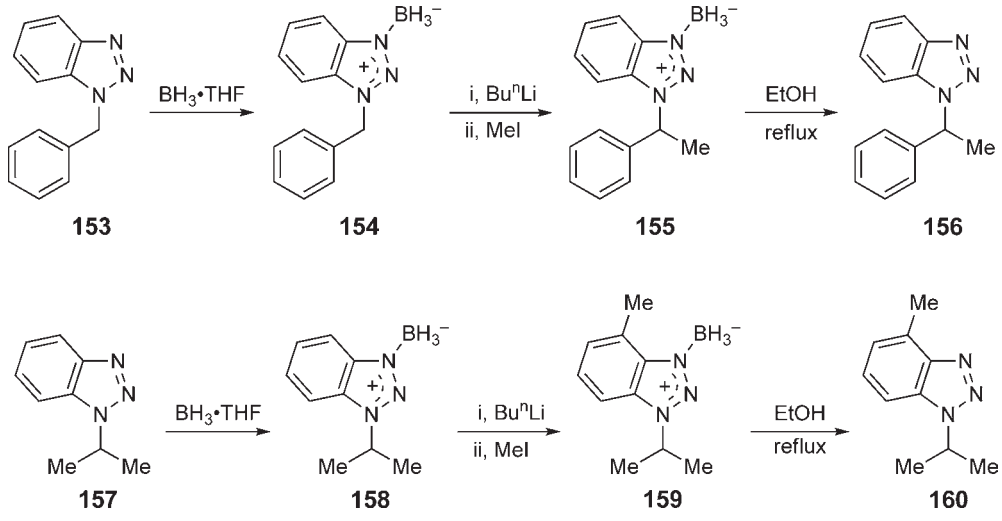
Scheme 15

5.01.5.5 N-Oxides

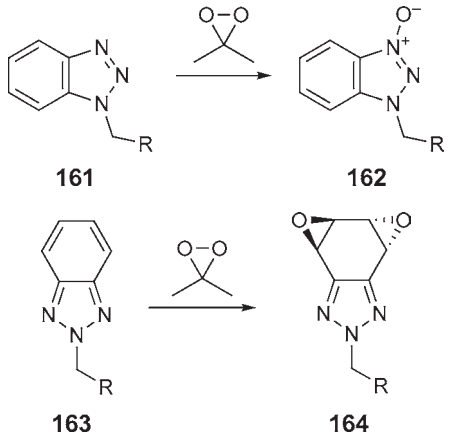
Oxidation of 1-alkylbenzotriazoles **161** with dimethyldioxirane leads to the corresponding oxides **162**, generally in high yield (Equation 4); however, in comparison with pyridine, the reaction is much slower <2001JOC5585>. Electron-deficient substituents R make the oxidation process more difficult and the yields of products **162** are compromised (e.g., 40% for R = CN). 1-Benzoylbenzotriazole is not oxidized by this reagent. n-Butyllithium lithiates oxides **162** predominantly in position 7. Refluxing in acetic anhydride converts oxides **162** into starting 1-alkylbenzotriazoles. 2-Alkylbenzotriazoles **163** react differently with dimethyldioxirane; instead of the nitrogen, carbon atoms of the benzene ring are attacked to give dioxiranes **164** (Equation 5).



Scheme 16



Scheme 17

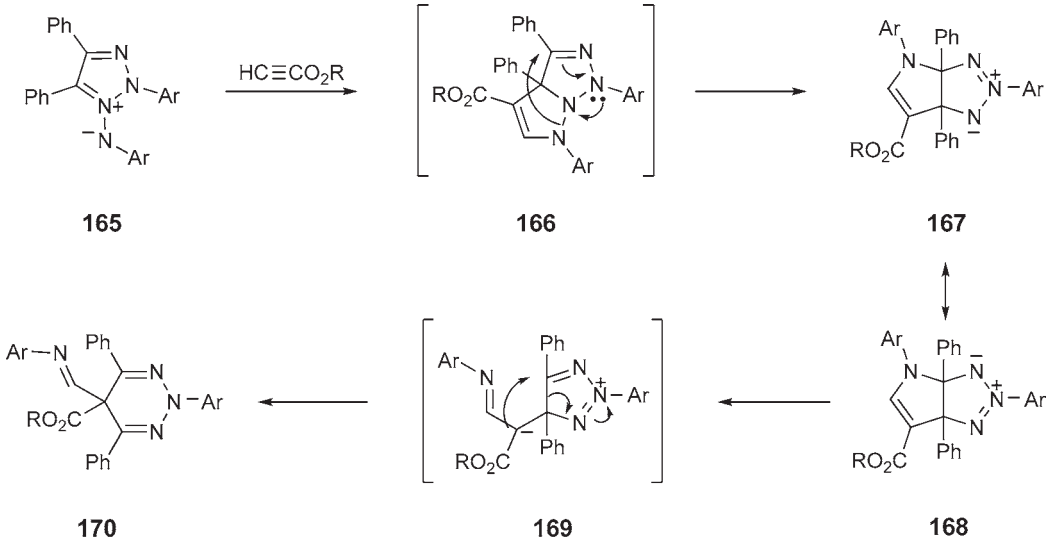


(4)

(5)

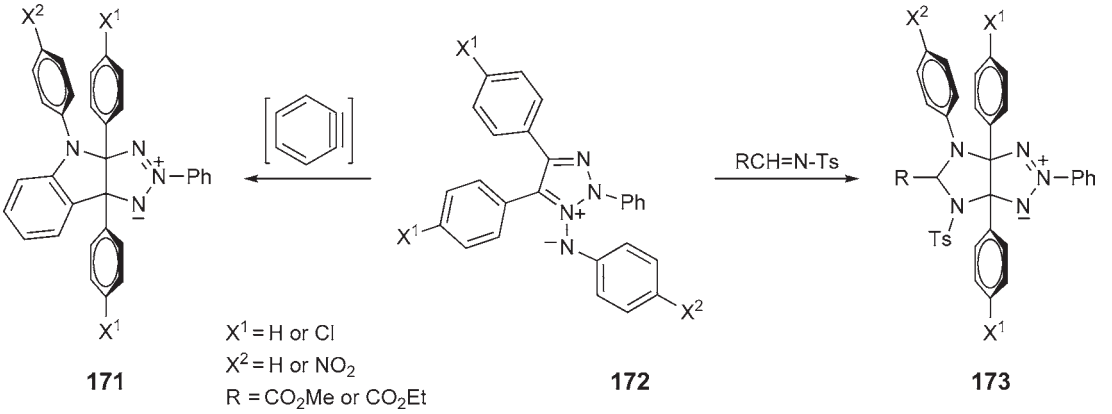
5.01.5.6 Triazolium Aminides

Aza analogs of *N*-oxides, aminides, are reactive 1-3-dipoles. In an example given in **Scheme 18**, 1,2,3-triazolium-1-aminides **165** undergo cycloaddition to esters of propiolic acid to give unstable adducts **166** that under the reaction conditions, reflux in acetone, rearrange to fused pyrrolo[2,3-*d*]-1,2,3-triazolines (mesomeric forms **167** and **168**). Prolonged heating causes cleavage of the C–N bond (between C–3a and N-4) in **168** and rearrangement of the obtained betaines **169** to more stable 2,5-dihydro-1,2,3-triazines **170**. This relatively complex process produces triazines **170** in moderate yields (35–52%) <2006TL1721, 2006JOC5679>.



Scheme 18

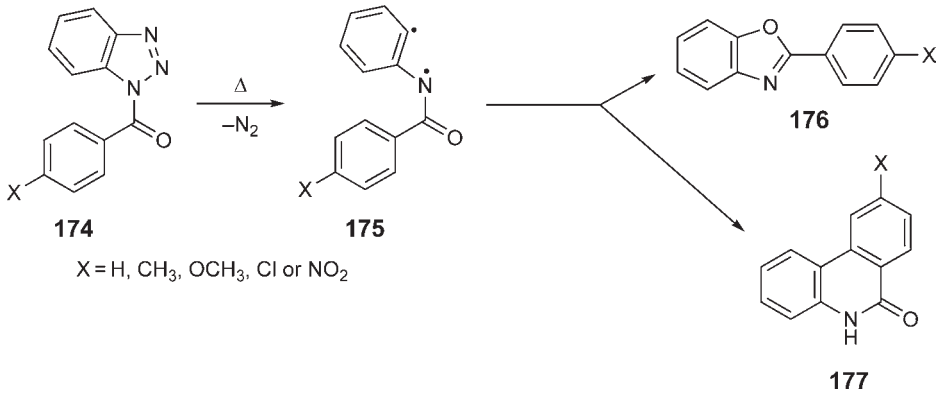
Benzyne generated *in situ* by diazotization of anthranilic acid adds readily to aminides **172** to provide cycloadducts **171**. Introduction of a nitro group into *para* position of the phenyl ring on the nitrogen terminus of the 1,3-dipole ($X^2 = NO_2$) stabilizes the system and results in higher yields of product **171** (70% vs. 50% for $X^2 = H$). Electron-deficient imines react also with aminides **172**, but the yields of isolated adducts **173** are relatively low (10–26%) (**Scheme 19**) <2003ARK(vii)110>.



Scheme 19

5.01.5.7 Thermolysis of Benzotriazole and Triazole Derivatives

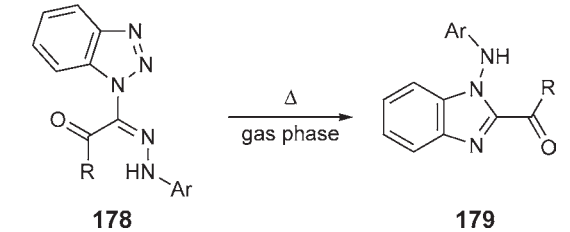
Thermolysis of benzotriazole derivatives involves cleavage of the heterocyclic ring with extrusion of a molecule of nitrogen and formation of a diradical. If the substituent at N-1 of benzotriazole is suitable for trapping radicals, cyclization to a new heterocyclic system is usually the main route for quenching the diradical. Thus, gas-phase thermolysis of 1-aryloxybenzotriazoles **174** proceeds via diradical **175**. The most favorable next step is formation of a bond between the carbonyl oxygen and the *ortho* carbon atom resulting in benzoxazole **176**. In another route, a bond forms between the ortho carbon atoms from both rings to give phenanthradinone derivative **177** (**Scheme 20**) <2005T8257>. Distribution of the products is not affected much by substituents X supporting radical mechanism of the reactions.



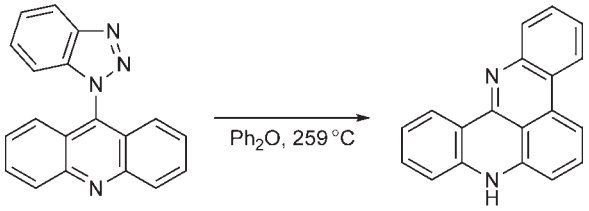
174 175 176 177

Scheme 20

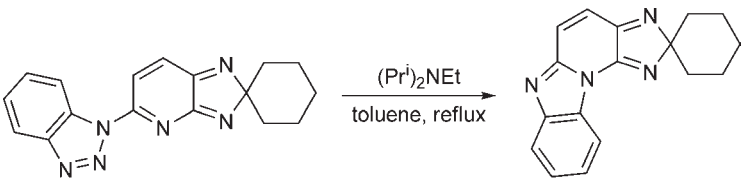
The picture can be generalized. If the substituent is attached to benzotriazolyl N-1 by an sp^2 hybridized carbon atom, the produced diradical is relatively stable, and a product resulting from simple cyclization predominates, like in an example given in **Scheme 20**. Three additional examples of such reactions are shown in Equations (6)–(8). Thus, gas-phase thermolysis of hydrazones **178** (R = Me or Ph, Ar = Ph or *para* substituted Ph) produces benzimidazoles **179** as the main products in 27–50% yields. Minor side products result mostly from cleavage of other bonds in the molecule not involving benzotriazole, and no products resulting from direct radical trapping by the carbonyl group are detected <2003T9455>. For a preparative purpose, it is more convenient to carry out pyrolysis of benzotriazole derivatives in high boiling solvents. This way, 8*H*-quino[4,3,2-*kl*]acridine **181** is obtained by refluxing a solution of 9-(1*H*-1,2,3-benzotriazol-1-yl)acridine **180** in diphenyl ether <2002JME590, 1997J(P1)2739>. Similar thermal conversions of 9-(5′-substituted-1′,2′,3′-triazol-1′-yl)acridines generate corresponding 7*H*-pyrido[4,3,2-*kl*]acridines <2003JCM75, 2001J(P1)3174>. Base catalysis may help the thermolysis, as it is illustrated by conversion of 5′-(benzotriazol-1-yl)-spiro[cyclohexane-1,2′-2′*H*-imidazo[4,5-*b*]pyridine **182** into the corresponding fused benzimidazole derivative **183** occurring in refluxing toluene <2002JCM153>.



178 179 (6)

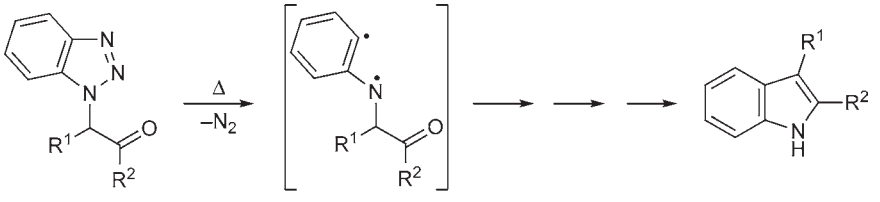


180 181 (7)



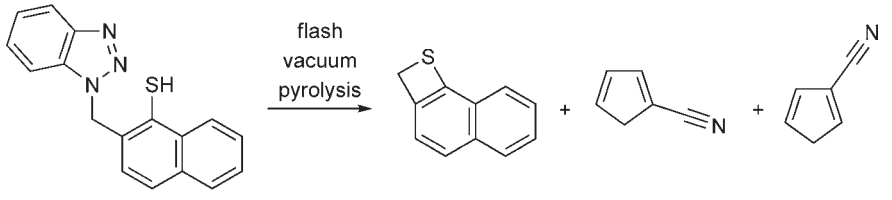
182 183 (8)

In other cases, extrusion of N_2 creates higher energy diradicals that are suitable for more complex rearrangements. Such situation is represented in **Scheme 21** by gas-phase thermolysis of ketones **184**. Diradical **185** created in the first step of this process undergoes a series of transformations that ends on stable molecule of indole **186** <2004JPO267>. Flash vacuum pyrolysis of naphthalenethiol **187** at 750 °C causes elimination of benzotriazole with formation of *2H*-naphtho[1,2-*b*]thiete **188**. Under the conditions applied, the liberated benzotriazole extrude a molecule of nitrogen end undergoes subsequent ring contraction to thermally more stable cyclopentadienecarbonitriles **189** and **190** (Equation 9) <1998JHC1505>.



184 185 186

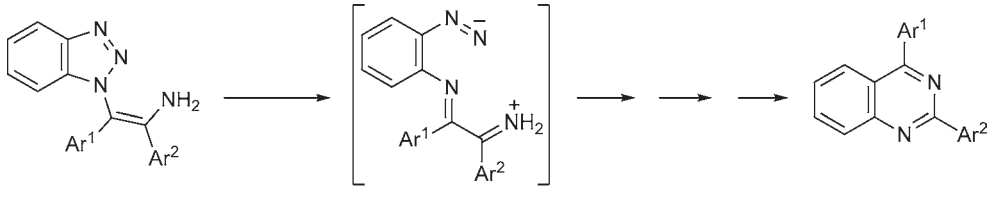
Scheme 21



187 188 189 190 (9)

5.01.5.8 Ionic and Radical Ring Opening with Loss of Nitrogen

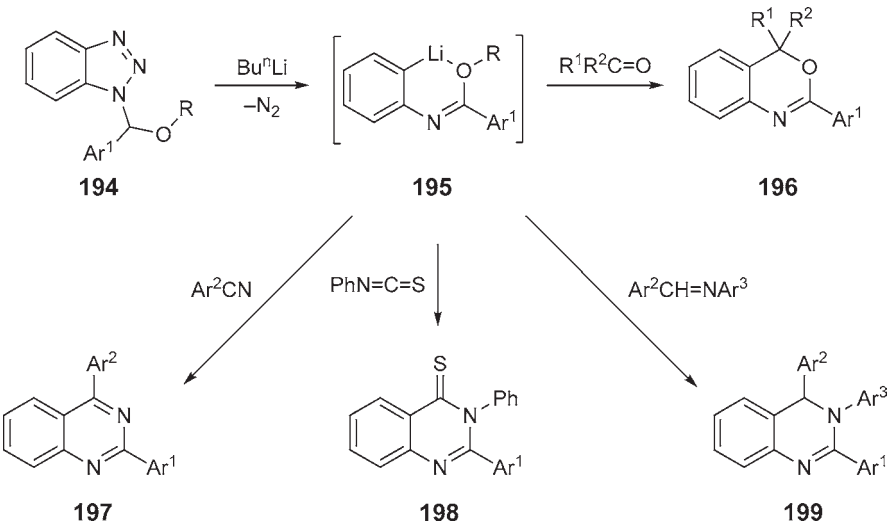
The presence of an electron-donating group adjacent to the benzotriazol-1-yl system renders the triazole ring susceptible to opening at elevated temperatures. Thus, upon heating to reflux in toluene, enamines **191** undergo ring scission between the N-1 and N-2 atoms to form betaines **192**. The consecutive loss of a molecule of nitrogen followed by cyclization and rearrangement leads to quinazolines **193** (**Scheme 22**) <1995JOC246>.



191 192 193

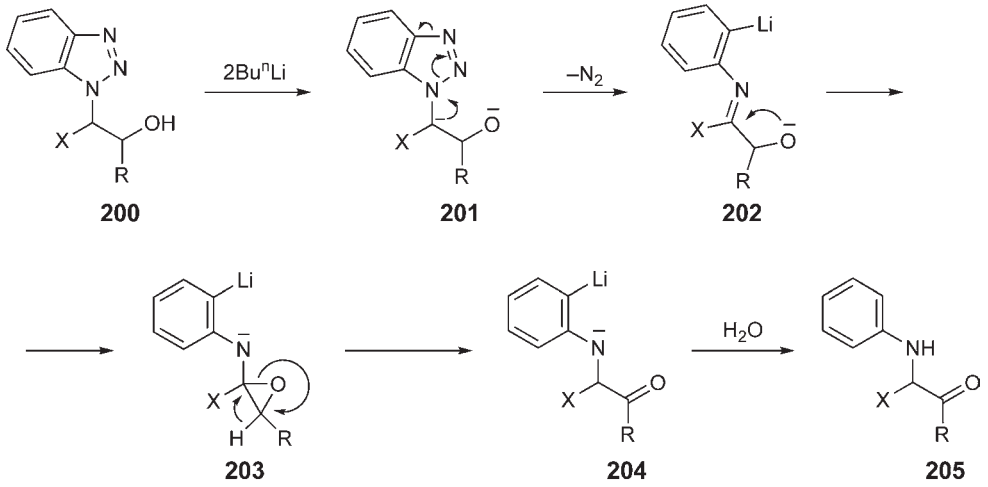
Scheme 22

Anions obtained by lithiation of 1-(α-alkoxyalkyl)benzotriazoles **194** undergo ring cleavage followed by extrusion of nitrogen to give *ortho*-iminophenyl anions **195**. These anions can be trapped by various electrophiles to provide practical synthetic methods for several heterocyclic systems **196–199** (**Scheme 23**) <1995JOC7625>.



Scheme 23

Dianion **201**, generated by treatment of alcohol **200** with 2 molar equivalents of Bu^{n}Li at −78 °C, undergoes ring opening with extrusion of N_2 and formation of new anion **202**. Cyclization to oxirane **203** and hydrogen shift creates anion **204** that is hydrolyzed during work-up to aniline derivative **205** (**Scheme 24**) <1998H(48)187>.

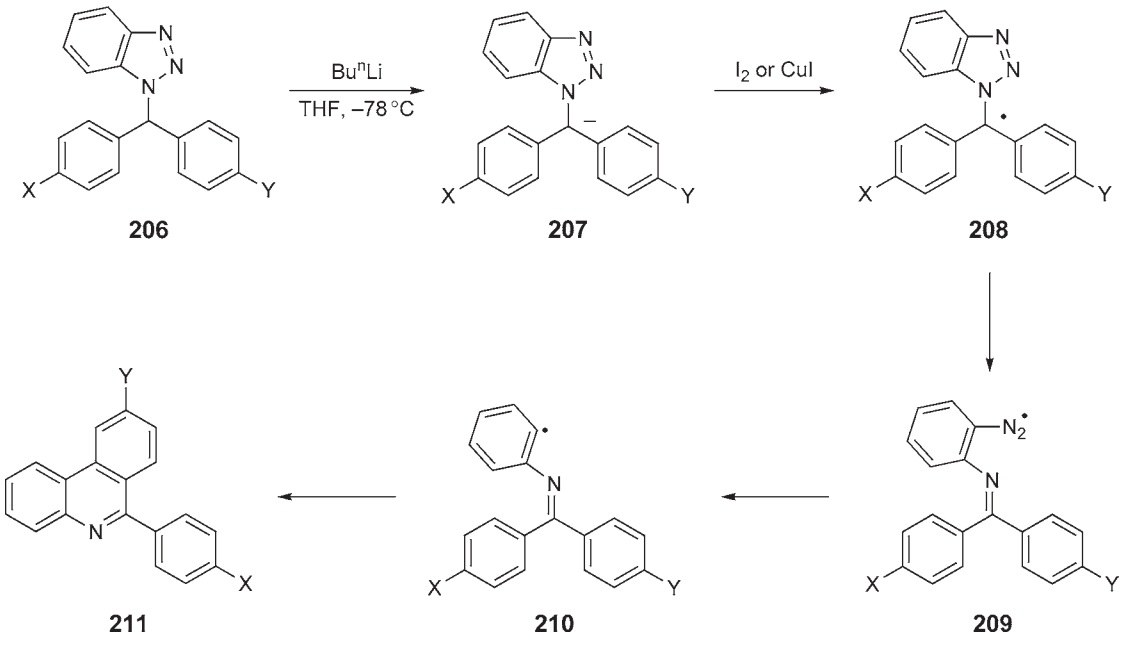


X = Ph, carbazol-9-yl or indol-1-yl
R = Ph, 4-MeC$_6$H$_4$ or *n*-C$_7$H$_{15}$

Scheme 24

Anions **207**, derived from 1-(diarylmethyl)benzotriazoles **206**, can be oxidized with mild oxidants to relatively stable triaryl radicals **208**. One of the possible reactions of radicals **208** is ring opening to give radicals **209**. Elimination of nitrogen from **209** produces unstable species **210** that undergo intramolecular cyclization to phenanthridines **211** (**Scheme 25**) <1996JHC607, 1998JOC1467>. When substituents X and Y are identical, products **211**

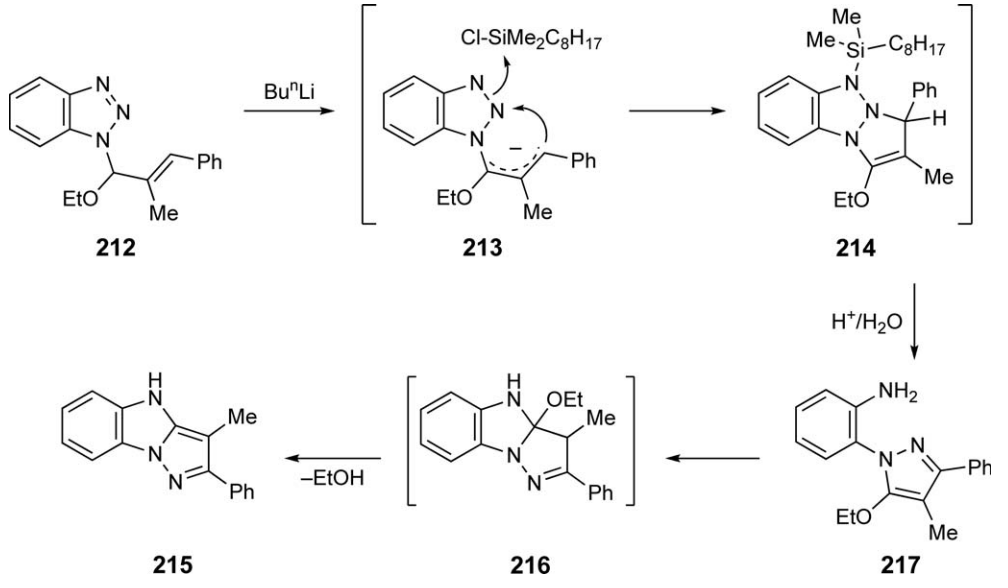
are obtained with average yield of 50%. When X and Y are different but of similar electronic character, mixtures of two isomeric phenanthridines are formed. Polycyclic phenanthridines are formed in these reactions when tricyclic analogs of **206** derived from acridine, xanthene, or thioxanthene are used as starting materials <1999JHC927>. Another possible reaction of radicals **208** is their dimerization resulting from combining one radical with another in position *para* of the aromatic ring (when X = H) <1998JOC1467>.



Scheme 25

5.01.5.9 Intramolecular Electrophilic Attack on N-2

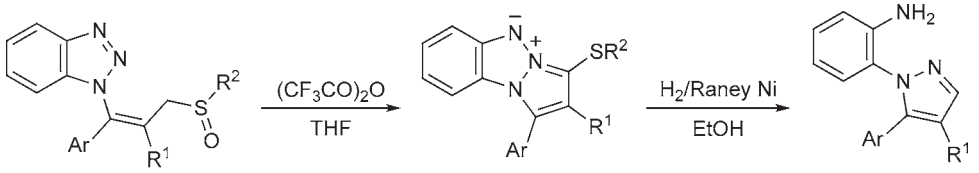
Treatment of 1-(α-ethoxyalkyl)benzotriazoles **212** with n-butyllithium and dimethyloctylsilyl chloride followed by acidic hydrolysis of the intermediates gives a mixture of pyrazoles **215** and **217** (**Scheme 26**). The probable reaction



Scheme 26

pathway involves allylic anion **213** which undergoes cycloaddition to N-2 of the benzotriazole system assisted by simultaneous reaction of N-3 with the silyl chloride to give intermediate **214**. Acidic cleavage of the bond between N-2 and N-3 leads to (2-aminophenyl)pyrazole **217**. Under acidic conditions, derivative **217** rearranges slowly to pyrazole[5,1-*b*]benzimidazole system **215**, via intermediate **216** <1996KGS775>.

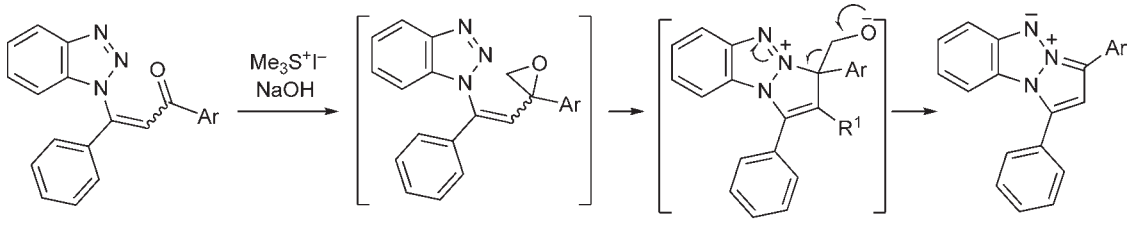
Treated with trifluoroacetic anhydride, sulfoxides **218** undergo conversion to triazapentalenes **219** with high yields. The process must involve acylation of the sulfoxide oxygen atom and generation of a carbocation that attacks the N-2 atom of benzotriazole. Hydrogenation over Raney nickel cleaves the C–S and one of the N–N bonds to generate *ortho*-substituted anilines **220** (**Scheme 27**) <2002EJO493>.



Ar = Ph, 4-FC_6H_4 or 4-$MeOC_6H_4$
R^1 = Me, Bu^t, Ph, 4-MeC_6H_4 or 2,5-$Me_2C_6H_3$
R^2 = Pr^n, Ph, or 4-MeC_6H_4

Scheme 27

Addition of benzotriazole to 1-phenyl-2-aroylacetylenes gives α,β-unsaturated ketones **221** in high yields. By treatment with dimethylsulfonium ylide, ketones **221** are converted to epoxides **222**, Opening of the oxirane ring and electrophilic attack of the obtained tertiary carbocation on N-2 of the benzotriazole system leads to betaines **223** that consecutively eliminate formaldehyde to give triazapentalenes **224** (**Scheme 28**) <2004ARK(iii)109>.



Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4 or 2-thienyl

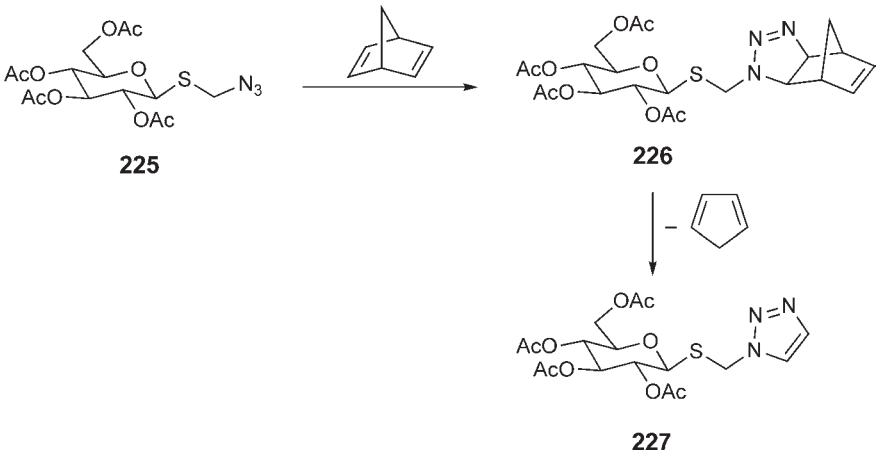
Scheme 28

5.01.6 Reactivity of Nonconjugated Rings

5.01.6.1 Conversion of Triazolines to Triazoles

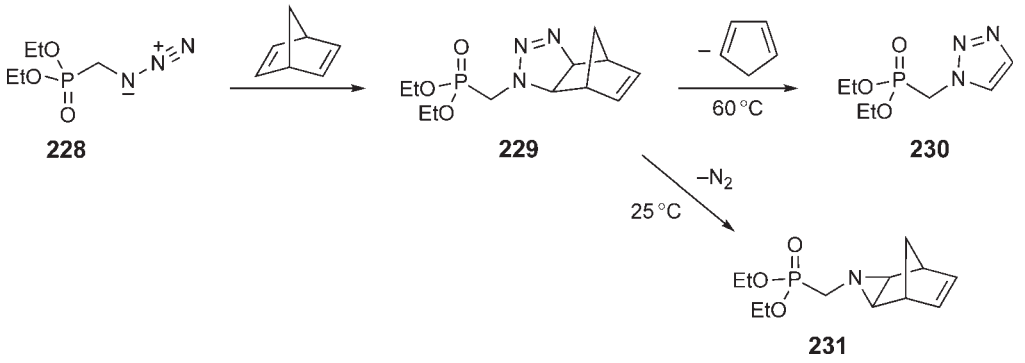
5.01.6.1.1 Retro Diels–Alder reaction

A convenient synthetic method for 1,2,3-triazoles unsubstituted at C-4 and C-5 utilizes a reaction of azides with norbornadiene, for example, **Scheme 29** <2004JOC1081>. The process is performed in refluxing dioxane. In the first step, norbornadiene undergoes 1,3-dipolar cycloaddition to glucose-derived azide **225** to give triazoline **226**. The following retro Diels–Alder reaction results in the elimination of cyclopentadiene to furnish triazole derivative **227** in 79% yield.



Scheme 29

Diethyl azidomethanephosphonate **228** reacts with norbornadiene at room temperature to give triazoline **229** in 86% yield. When heated at 60 °C, derivative **229** decomposes with elimination of cyclopentadiene to provide (1,2,3-triazol-1-yl)methanephosphonate **230** in 74% yield. However, when it is left at room temperature for an extended period of time, triazoline **229** undergoes slow conversion to aziridine **231** with elimination of nitrogen (**Scheme 30**) <1995H(40)543>.

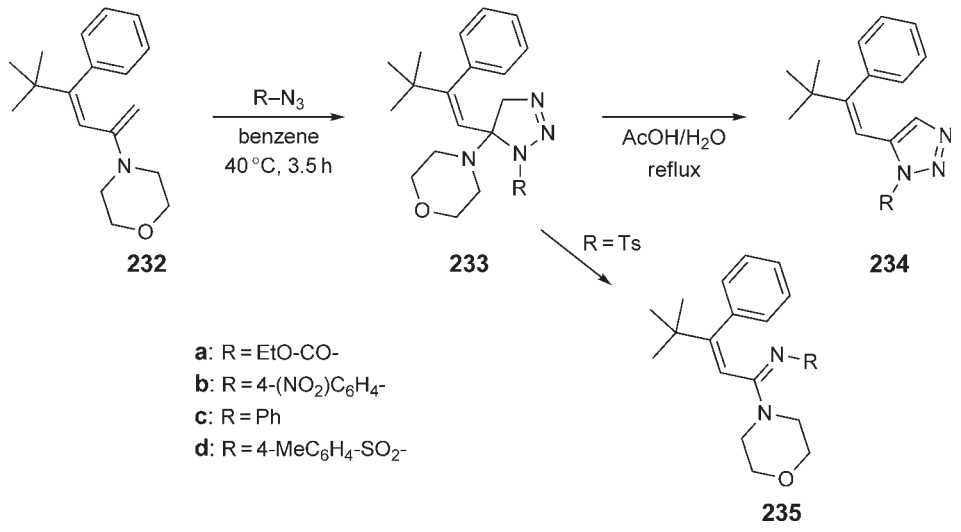


Scheme 30

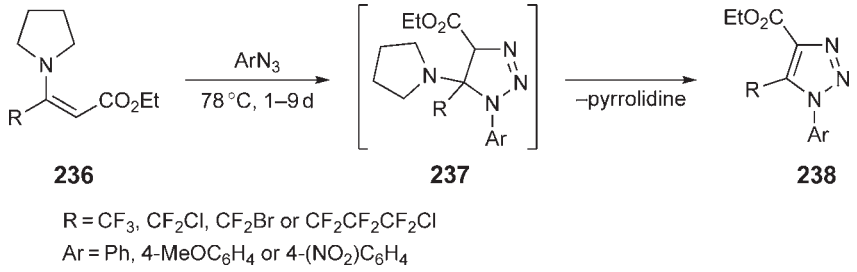
5.01.6.1.2 Elimination of amines

1,3-Dipolar cycloaddition of 2-morpholino-1,3-diene **232** to azides provides triazolines **233** (**Scheme 31**). Triazolines **233a** and **233b**, derived from 4-(ethoxycarbonyl)- and 4-nitro-phenyl azides, respectively, are stable under the reaction conditions (benzene, 40 °C); they can be isolated in good yields and fully characterized. However, phenyl derivative **233c** is less stable and spontaneously eliminates morpholine to give triazole **234c**. To eliminate morpholine from triazolines **233a** and **233b**, they are heated to reflux in aqueous acetic acid. Strong electron-withdrawing effect of the tosyl group in triazoline **233d** promotes cleavage of the ring with elimination of diazomethane to furnish α,β-unsaturated carboximidamide **235**. 1,5-Substitution of the triazole ring in derivatives **234** is confirmed by NMR studies <2005HCA1813>.

Less reactive *(Z)*-ethyl 3-fluoroalkyl-3-pyrrolidinoacrylates **236** require prolonged heating with azides to afford triazoles **238** in good yields (66–97%). The reactions give the best results when mixtures of reagents are heated neat, without any solvent added. Intermediate triazolines **237** do not survive under such conditions and spontaneously eliminate pyrrolidine to form triazoles **238**. The reactions are proved to be strictly regioselective with the ethoxycarbonyl group always located at C-4 of the triazole system (**Scheme 32**) <2003T4395>.

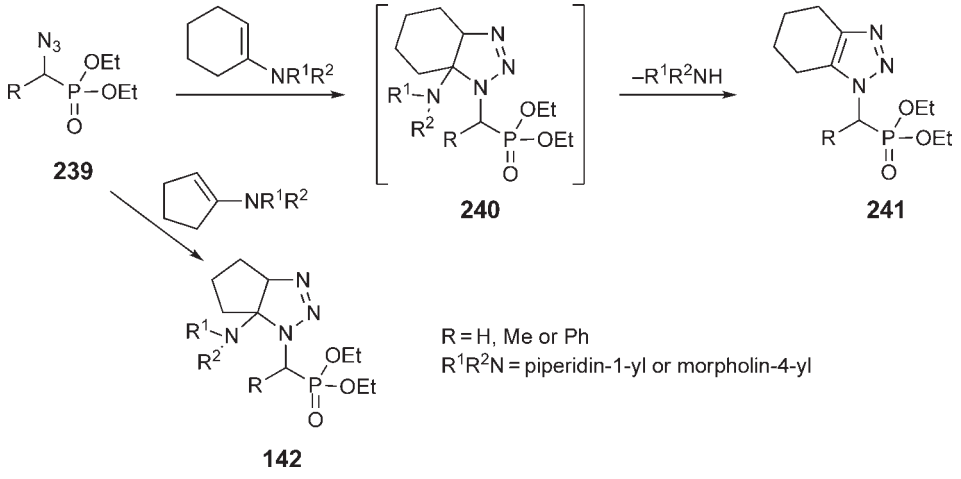


Scheme 31



Scheme 32

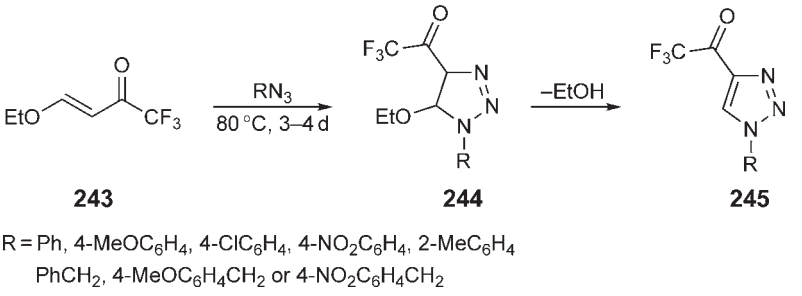
Scheme 33 illustrates the difference in reactivity between triazolines obtained from cyclohexanone and cyclopentanone enamines. Thus, the reactions of azidophosphonates **239** with cyclohexanone enamines produce unstable aminotriazolines **240** that cannot be isolated due to their spontaneous elimination of amines to provide triazoles **241**. Contrary to that, triazolines **242**, derived from cyclopentanone enamines, are isolated in good yield (76–88%) and cannot be converted to the corresponding triazoles even by thermolysis <1995H(40)543>. Probably, introduction of a double bond between two five-membered rings would involve too much molecular strain.



Scheme 33

5.01.6.1.3 Elimination of alcohols or water

2-Ethoxyvinyl trifluoromethyl ketone **243** reacts slowly at elevated temperature with aryl and benzyl azides to provide triazoles **245** in good yield (51–88%). The reactions, carried out neat, are completed usually in 2–3 d(days). However, a longer reaction time (6 d) is required for 2-methylphenyl azide due to its steric hindrance. 5-Ethoxytriazolines **244**, the expected intermediates in this process, readily eliminate ethanol under the reaction conditions and cannot be isolated (**Scheme 34**) <2002JFC(116)81>.

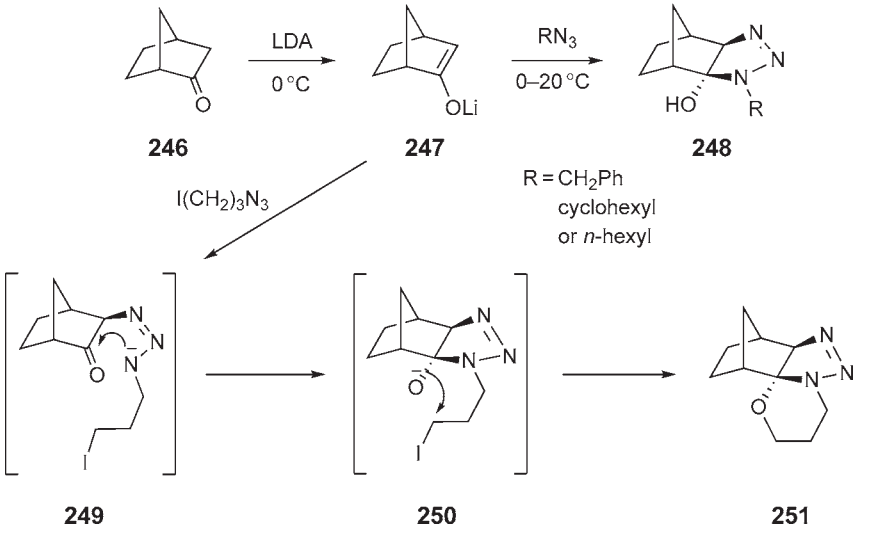


243 **244** **245**

R = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-MeC_6H_4
$PhCH_2$, 4-$MeOC_6H_4CH_2$ or 4-$NO_2C_6H_4CH_2$

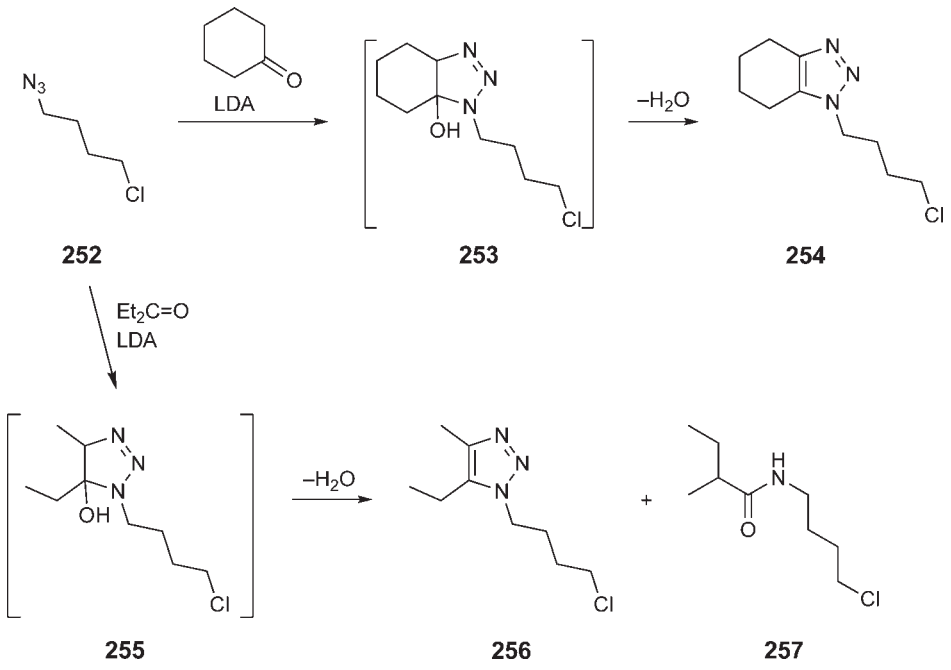
Scheme 34

In reactions with azides, ketones are directly converted to 5-hydroxytriazolines. Ketone enolate **247**, generated by treatment of norbornanone **246** with LDA at 0 °C, adds readily to azides to provide hydroxytriazolines **248** in 67–93% yield. Interestingly, 1-azido-3-iodopropane subjected to the reaction with enolate **247** gives tetracyclic triazoline derivative **251** in 94% yield. The reaction starts from an electrophilic attack of the azide on the ketone α-carbon atom. The following nucleophilic attack on the carbonyl group in intermediate **249** results in triazoline **250**. The process is completed by nucleophilic substitution of the iodine atom to form the tetrahydrooxazine ring of product **251** (**Scheme 35**) <2004JOC1720>.



Scheme 35

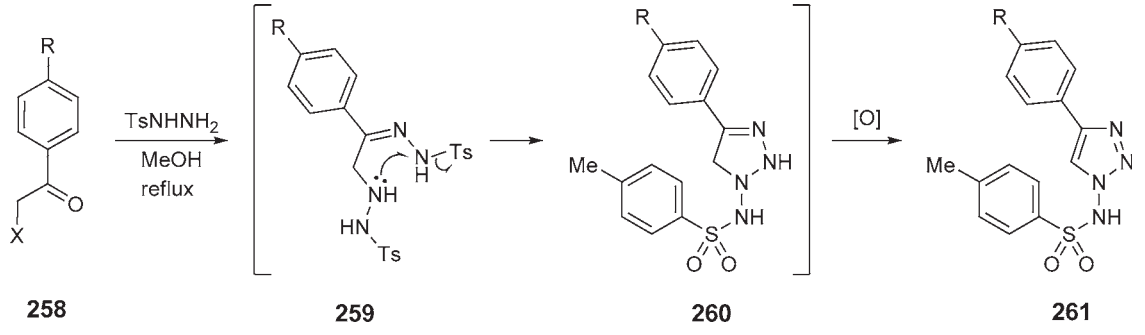
In contrast to the triazolines from **Scheme 35**, 5-hydroxytriazolines obtained from regular, unstrained ketones are unstable, eliminating rapidly water to furnish the corresponding triazoles. In an example given in **Scheme 36**, azide **252** reacts readily with cyclohexanone enolate to provide triazole **254** in 95% yield. Triazoline intermediate **253**, formed in the first step of this reaction, is very unstable and cannot be isolated. The case of open-chain ketones is illustrated by a reaction of azide **252** with diethyl ketone. Again, intermediate 5-hydroxytriazoline **255** decomposes rapidly to give, in part, triazole **256**. However, a more complex process involving elimination of nitrogen and rearrangement to amide **257** competes with the main reaction, making this synthesis less attractive <2004JOC1720>.



Scheme 36

5.01.6.1.4 Oxidation

When a solution of phenacyl halide **258** and excess tosyl hydrazide in methanol is heated to reflux, 1-(tosylamido)-4-aryltriazole **261** is formed. The reaction proceeds presumably via dihydrazide derivative **259** that subsequently undergoes intramolecular cyclocondensation to triazoline **260**. In the following step, the triazoline must be oxidized to the final triazole product **261**. Mechanism of the oxidation is not quite clear, but the probable oxidant is the starting phenacyl halide, as a half of it is converted to the corresponding acetophenone tosylhydrazone that is isolated as the main side product of the reaction (**Scheme 37**) <2004H(63)1175>.



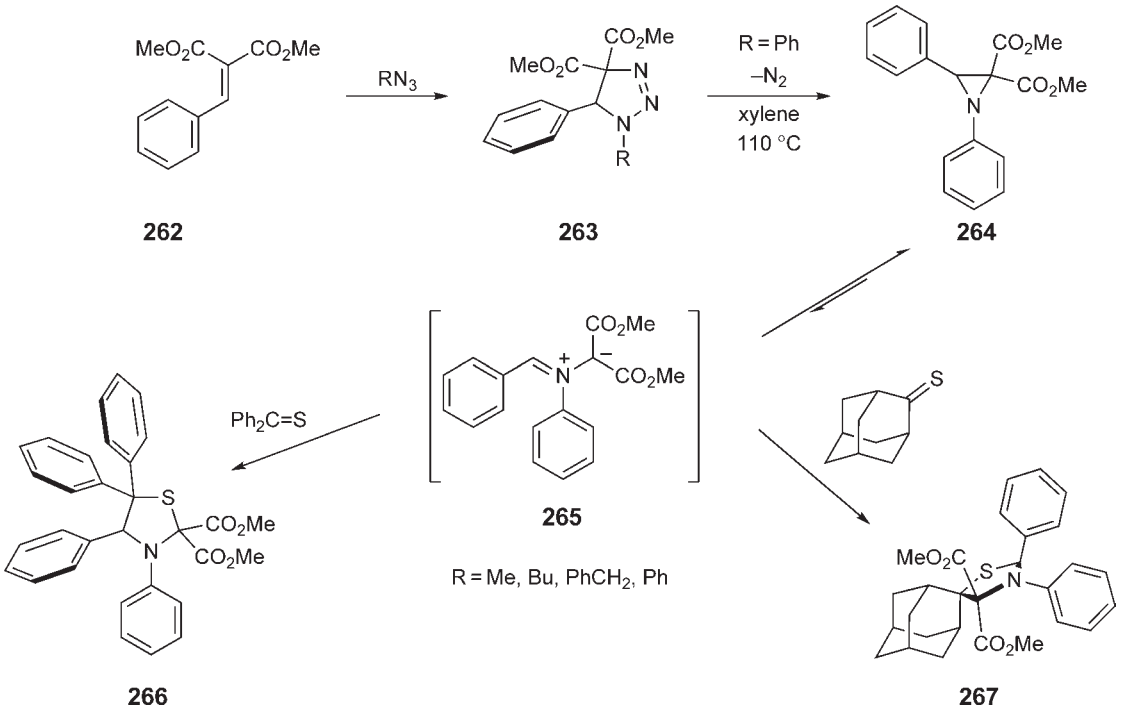
R = H, Me, Ph, MeO, Cl or F
X = Cl or F

Scheme 37

5.01.6.2 Elimination of N_2

Cycloaddition reactions of dimethyl benzylidenemalonate **262** with azides provide triazolines **263**. All compounds **263**, except one with R = Ph, are stable in xylene at 110 °C. The phenyl derivative eliminates molecular nitrogen to give dimethyl 1,3-diphenylaziridine-2,2-dicarboxylate **264**. At elevated temperature, the aziridine system is not

quite stable and may partially exist as open ylide form **265**. Thioketones added to the reaction mixture trap species **265** to provide tetrahydrothiazoles. Two examples of such reactions – with thiobenzophenone to give thiazolidine **266** and with adamantanethione to furnish derivative **267** – are presented in **Scheme 38** <2002HCA2056, 2002HCA2644>.



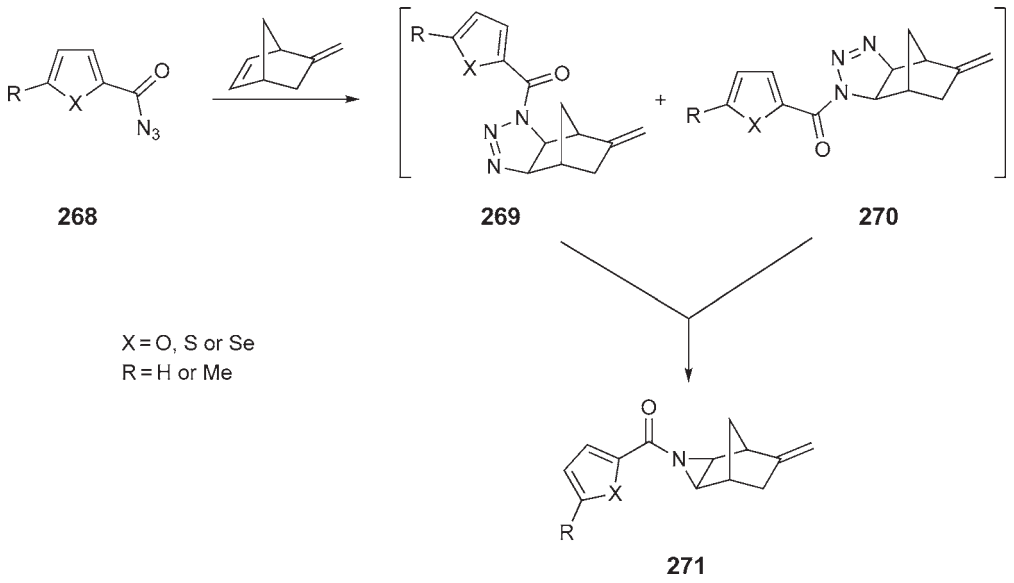
Scheme 38

Acyl azides **268**, derived from furan, thiophene and selenophene, add slowly at room temperature to the strained double bond of 5-methylenebicyclo[2.2.1]hept-2-ene. Two regioisomeric triazolines, **269** and **270**, which form in the first step, are unstable and decompose with elimination of nitrogen to provide aziridine derivatives **271**. Products **271** are isolated in good yield (73–85%). It is worthy to note that not only the terminal, unstrained double bond in the starting material, 5-methylenebicyclo[2.2.1]hept-2-ene, is unaffected, but also the typical dipolarophiles like esters of crotonic, propiolic and byt-2-ynoic acids do not react with azides **268** under these conditions (**Scheme 39**) <2002J(P1)1420>.

1-(Azidomethyl)benzotriazole **272** reacts with *N*-methylmaleinimide in refluxing toluene to give, after 3 h, exclusively triazoline derivative **273**, together with the unreacted starting materials. Prolonged heating of the starting materials results in formation of more triazoline **273**; however, products of its decomposition to derivatives **274** and **275** are also present. Refluxing of a solution of triazoline **273** in toluene for 24 h leads to a mixture of aziridine **274** and its opened isomer **275** in 4:1 ratio (**Scheme 40**) <1996JHC335>.

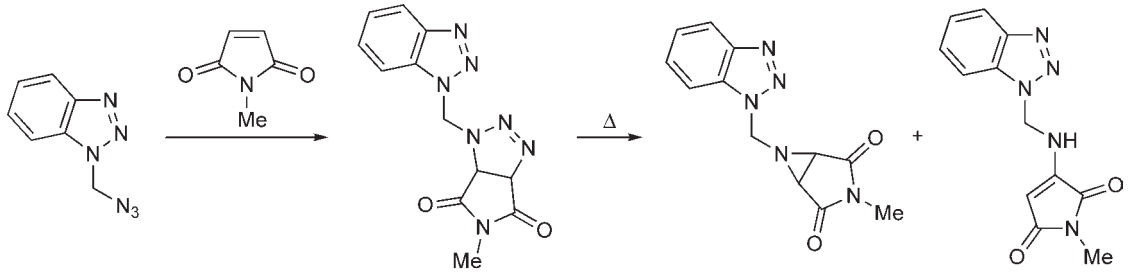
Triazolines **277** are isolated in high yield (87–94%) when the reactions of glucal **276** with azides are carried out in refluxing trimethyl or triethyl orthoformate. In all other solvents, triazolines **277** undergo immediate conversion to triazoles **278**. It is believed that the orthoformates act as nonbasic acid-scavenging solvents. Irradiated with UV light in acetone, triazolines **277** are smoothly converted to aziridines **279**. Without isolation, aziridines **279** are treated with nucleophiles in the presence of a Lewis acid to provide aminoglycosides **280** in high yield (**Scheme 41**) <2004JA8356>.

Fluoroalkanesulfonyl azides **281** add readily to vinyl ethers to provide triazolines **282** in good yield (67–84%). At room temperature, slow decomposition of the products is observed with evolution of nitrogen and formation of piperazine derivatives **284**. No other products are observed. Formation of piperazines **284** must involve cleavage of the triazoline ring with formation of zwitterionic intermediates **283** (**Scheme 42**) <2004JFC(125)445>.



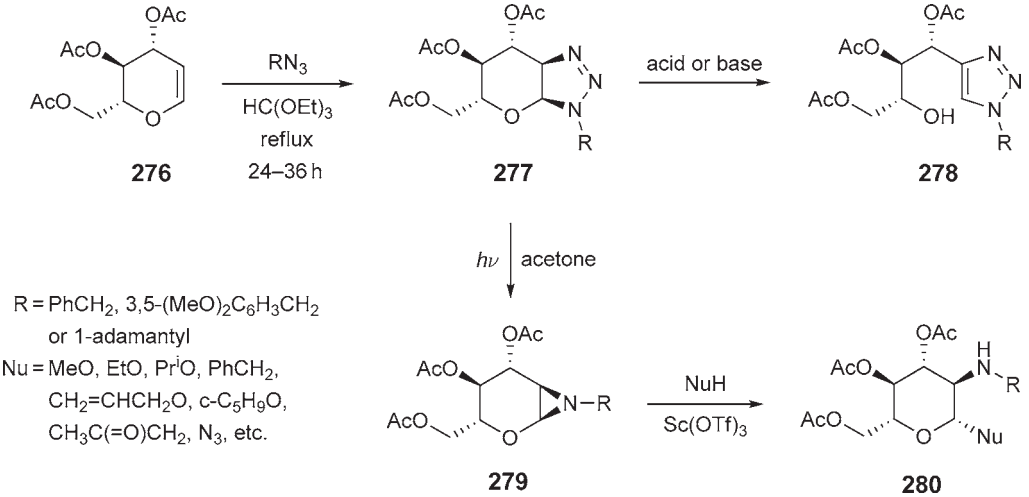
268 269 270 271

Scheme 39



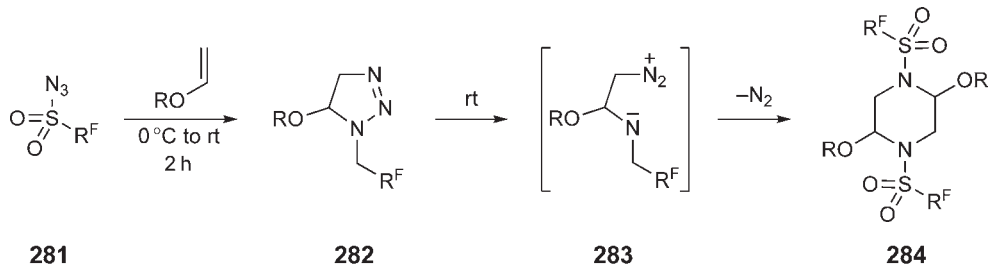
272 273 274 275

Scheme 40



276 277 278 279 280

Scheme 41

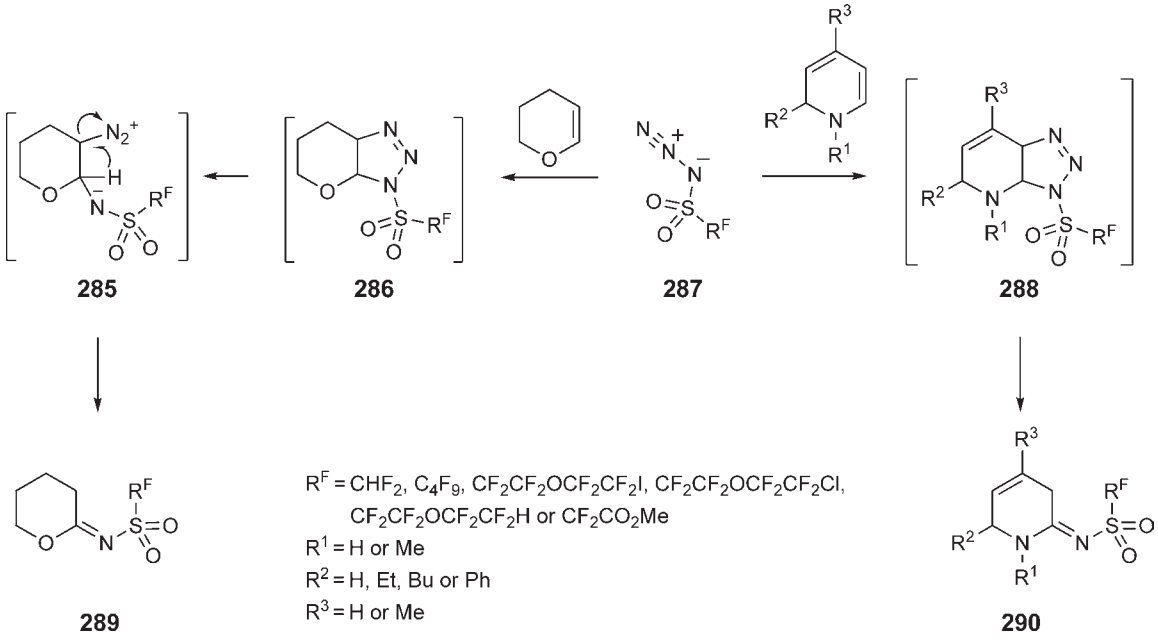


281 **282** **283** **284**

$R^F = C_4F_9$, Me_2CHOCF_2, $ClCF_2CF_2OCF_2CF_2$ or $ICF_2CF_2OCF_2CF_2$
R = Et or Me_2CHCH_2

Scheme 42

Reactions of fluoroalkanesulfonyl azides **287** with tetrahydropyran proceed fast in dichloromethane at room temperature. Evolution of nitrogen is observed together with formation of *N*-(fluoroalkanesulfonyl)-2-tetrahydropyranoimines **289**. The reactions are believed to involve 1,3-dipolar cycloaddition of tetrahydropyran to azides **287** with formation of relatively unstable triazolines **286**. Opening of the triazoline ring results in zwitterionic structure **285** that is losing molecular nitrogen and rearranges to final product **289** by 1,2-hydrogen shift <2003JFC(120)65>. In a similar manner, reactions of azides **287** with dihydropyridines lead to *N*-alkanesulfonylimines **290**, via labile triazolines **288** (**Scheme 43**) <2000JFC(106)133>.



285 **286** **287** **288** **289** **290**

$R^F = CHF_2$, C_4F_9, $CF_2CF_2OCF_2CF_2I$, $CF_2CF_2OCF_2CF_2Cl$,
$CF_2CF_2OCF_2CF_2H$ or CF_2CO_2Me
R^1 = H or Me
R^2 = H, Et, Bu or Ph
R^3 = H or Me

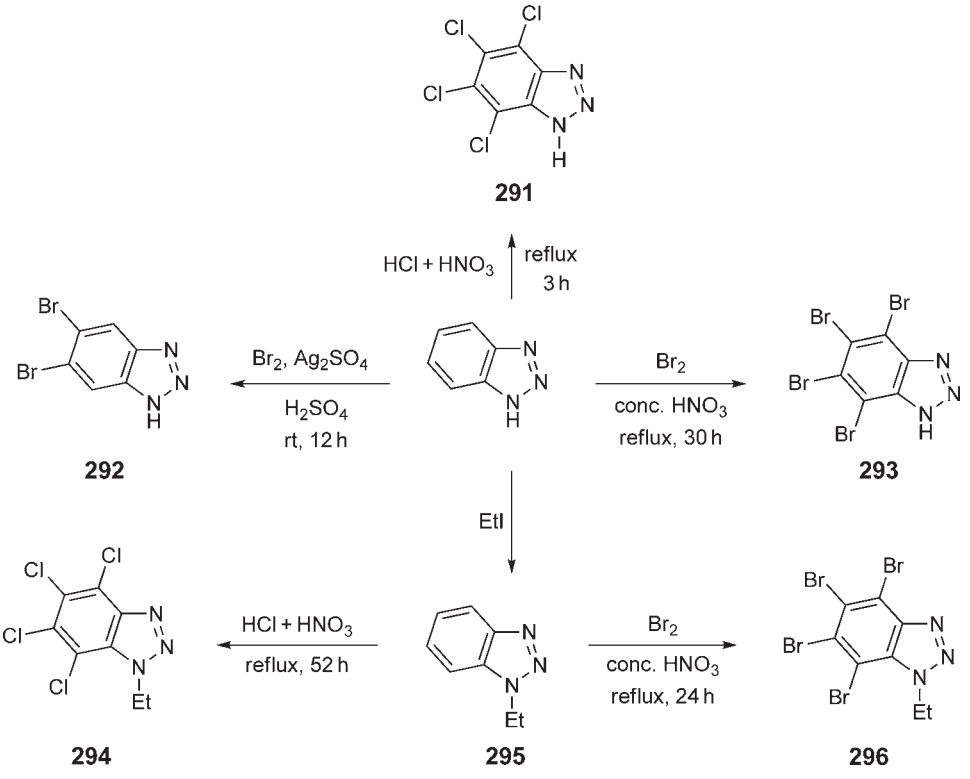
Scheme 43

5.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5.01.7.1 Reactions of the Benzenoid Ring of Benzotriazole

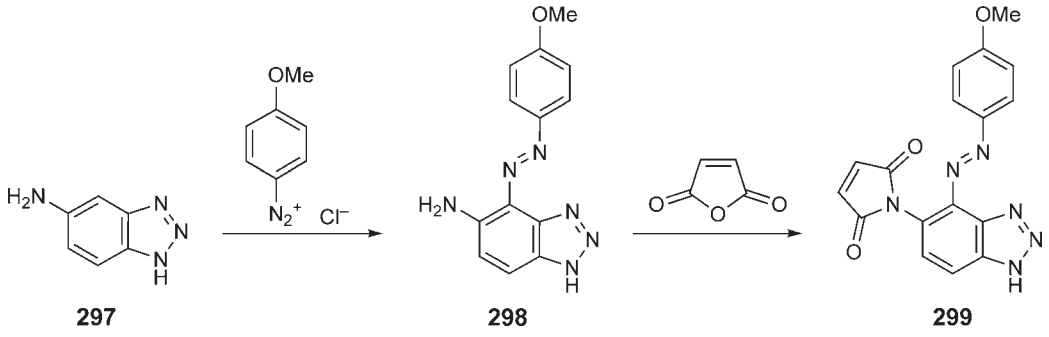
Tetrachlorobenzotriazole **291** is readily prepared in 87% yield by heating a solution of benzotriazole in a mixture of hydrochloric and nitric acids <1955JA5105>. 5,6-Dibromobenzotriazole **292** is prepared in 62% yield by treatment of benzotriazole with bromine and silver sulfate in concentrated sulfuric acid <2004BMC2617>. Under more forcing conditions, when the reaction is run in refluxing nitric acid, 4,5,6,7-tetrabromobenzotriazole **293** is formed

(**Scheme 44**) <1957JA4395>. 1-Ethylbenzotriazole **295** <1984CHEC(5)669, 1996CHEC-II(4)1> is chlorinated by refluxing in a mixture of concentrated hydrochloric and nitric acids to give 1-ethyl-4,5,6,7-tetrachlorobenzotriazole **294** in 81% yield <1957JA4395>. A reaction of derivative **295** with bromine in refluxing concentrated nitric acid provides 1-ethyl-4,5,6,7-tetrabromobenzotriazole **296** in 68% yield <1957JA4395>.



Scheme 44

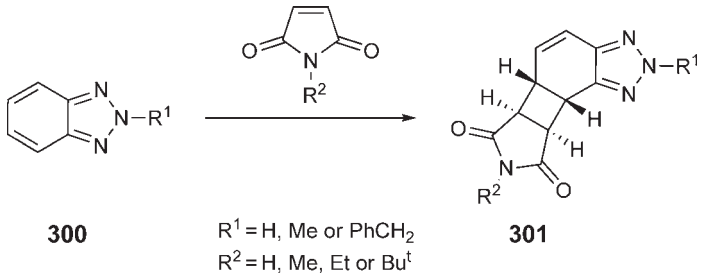
Coupling of 5-aminobenzotriazole **297** with a diazonium salt derived from 4-methoxyaniline generates diazo derivative **298**. Conversion of the amino group into maleinimide produces dye **299** (**Scheme 45**). Diels–Alder cycloadditions of dye **299** to diene tagged nucleotides allows for their efficient labeling <2002CC2100>.



Scheme 45

Benzotriazole and its 2-alkyl derivatives **300** undergo [2+2] cycloaddition to maleinimide when irradiated with UV light at λ>290 nm to give photoadducts **301** (Equation 10). In all cases, only *exo* diastereomers are formed. Since 1-alkylbenzotriazoles are completely unreactive under such conditions, unsubstituted benzotriazole must react as its

2-H tautomer. This remarkable difference in reactivity originates from a greater differentiation in bond lengths in the benzenoid ring of 2-substituted benzotriazoles in comparison with their benzotriazol-1-yl analogs. Bonds C(4)–C(5) in derivatives **300** are relatively short (1.377 Å); this renders them more double bond character and makes more susceptible to [2+2] cycloadditions <2002OL1487>.



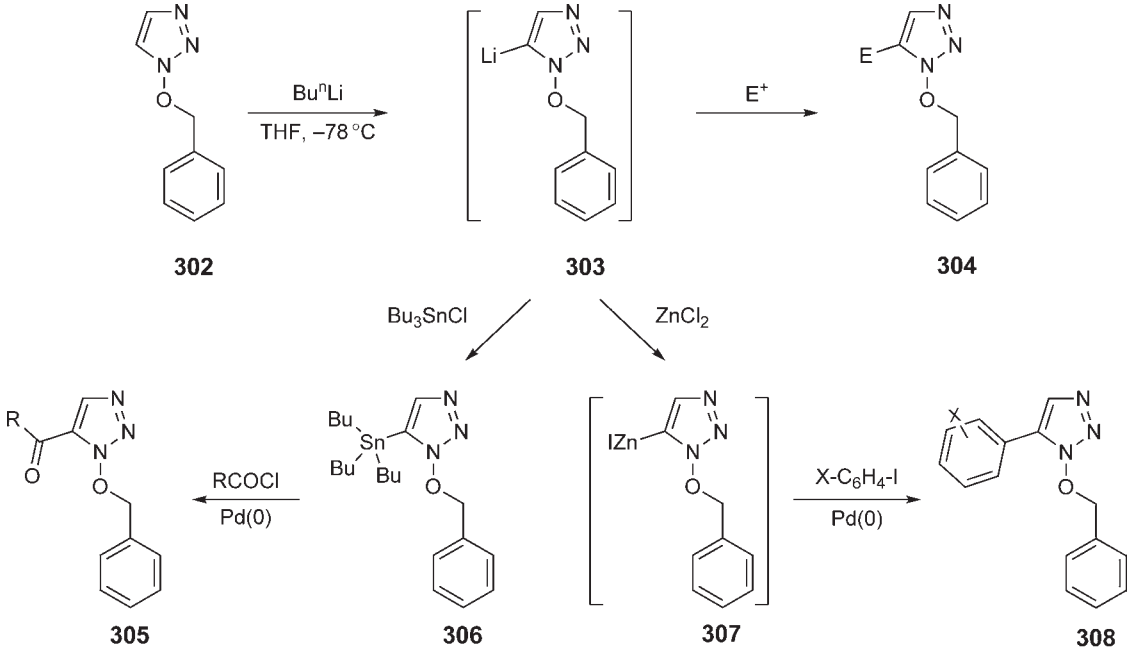
300 **301**

R^1 = H, Me or $PhCH_2$
R^2 = H, Me, Et or Bu^t

(10)

5.01.7.2 Organometallic Derivatives and Their Reactions with Electrophiles

1-Benzyloxytriazole **302** is lithiated exclusively at C-5. Treatment of lithio derivative **303** with electrophiles provides an easy access to 5-substituted triazoles **304**, which are obtained in 67–97% yield (**Scheme 46**) <1997JOC9177>. Tetrabutyltin derivative **306** becomes a convenient intermediate in the synthesis of ketones **305** (yield 59–93%) <1998S1181>. Organozinc intermediate **307** is suitable for palladium coupling with aryl iodides to provide products **308** in 71–87% yield. Apart of derivatives **308** with phenyl substituents that listed in **Scheme 46**, 5-aryltriazoles derived from pyridine, thiophene, and pyrazole are also prepared this way.

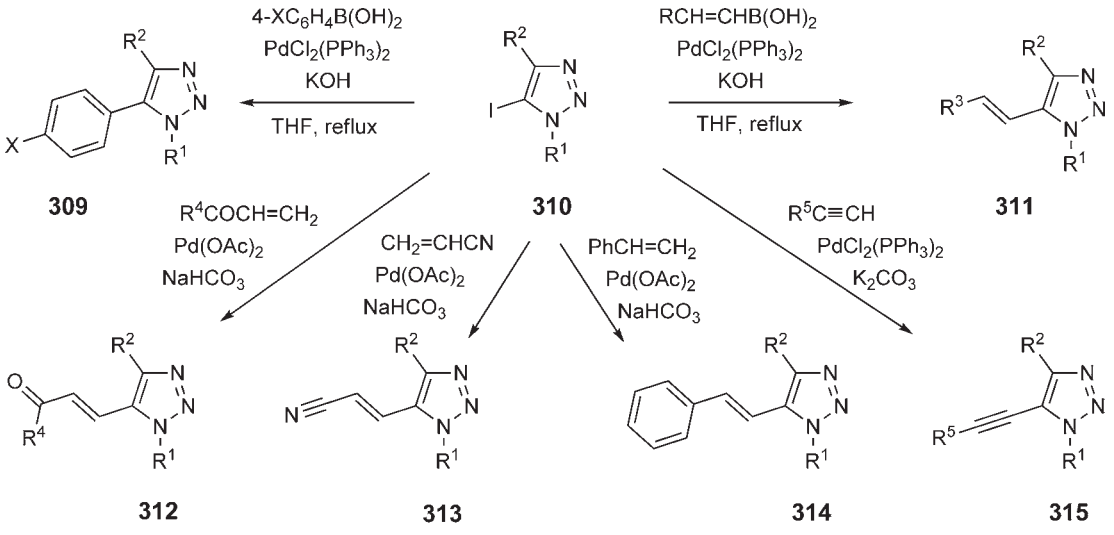


E^+ = MeI, DMF, $ClCO_2Me$, $ClCONMe_2$, C_2Cl_6, Br_2, I_2, or Me_2S_2
R = Me, *n*-$C_{11}H_{23}$, Bu^t, Ph
X = H, 2-F, 2-NH_2, 4-OH, 4-OMe, 4-NO_2

Scheme 46

5.01.7.3 Iodo Derivatives

5-Iodo-1,2,3-triazoles **310** are found to be versatile starting materials for derivatization of the triazole ring with sp^2 and sp carbon substituents. In Suzuki coupling with areneboronic acids, 5-aryltriazoles **309** are obtained in 64–98% yield. The reaction is catalyzed by palladium dichloride–triphenylphosphine complex and proceeds well in the presence of KOH as a base. In reactions with alkeneboronic acids, 5-(alken-1-yl)-1,2,3-triazoles **311** are generated in 59–95% yield. In a Heck reaction with methyl vinyl ketone, 5-iodotriazoles **310** are converted to unsaturated ketones **312** in 87–98% yield. Acrolein gives aldehyde **312** ($R^4 = H$) in only 62% yield, but the yields of products **312** obtained from a reaction of iodide **310** with methyl acrylate ($R^4 = OMe$) are much higher (92–98%). Acrylonitrile reacts well; however, mixtures of *(E)*- and *(Z)*-isomers of nitriles **313** are obtained. Heck coupling of iodide **310** with styrene is much slower, but product **314** is obtained as a single *(E)*-isomer in 92% yield. In a Sonogashira reaction, 5-iodotriazoles **310** are coupled with alkynes to provide derivatives **315** in 71–99% yield (**Scheme 47**) <2005S2730>.



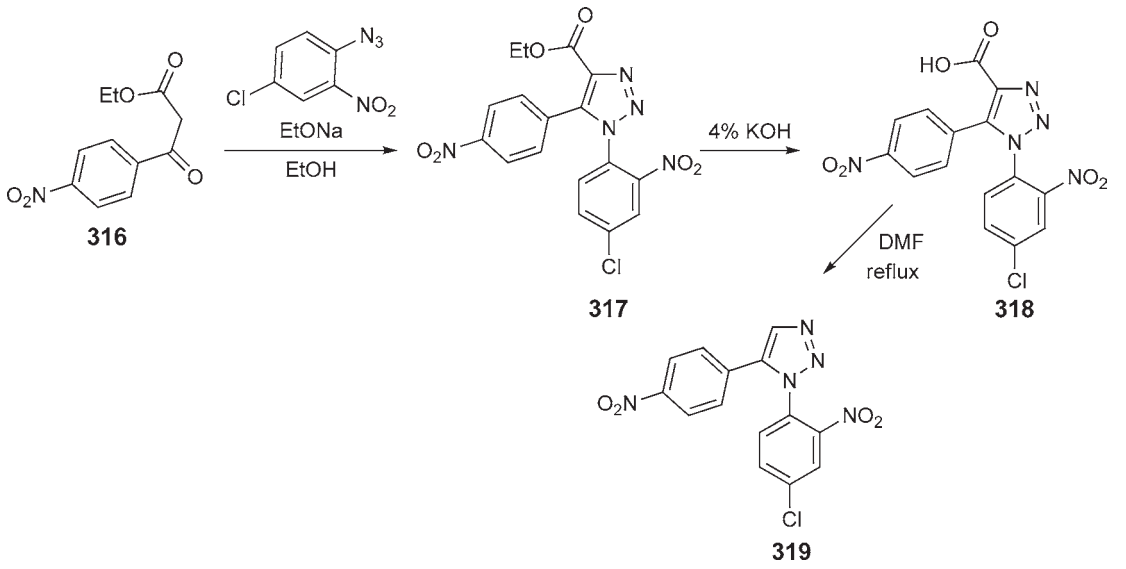
R^1 = $PhCH_2$, *n*-C_8H_{17}, CF_3CH_2, or $HCF_2CF_2CH_2$
R^2 = Ph or *n*-C_4H_9
R^3 = *n*-C_5H_{11} or $PhCH_2OCH_2$
R^4 = H, Me or MeO
R^5 = *n*-C_4H_9, Ph, $HOCH_2$, or TMS
X = H, CF_3, Cl or MeO

Scheme 47

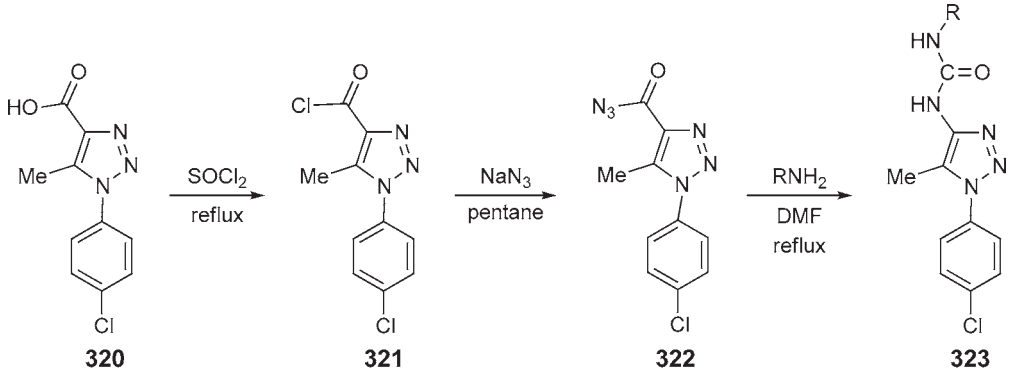
5.01.7.4 Carboxylic Acids and Their Derivatives

Esters of 1,2,3-triazolecarboxylic acids are the most common derivatives of triazole (Section 5.01.9); therefore, their conversions to other, more useful, functionalities are of great importance. In an example given in **Scheme 48**, 4-triazolecarbocylic ester **317**, obtained from a reaction of β-ketoester **316** with 4-chloro-2-nitrophenyl azide, is hydrolyzed to free acid **318** (82% yield) by 4% KOH. Heated to reflux in DMF for 3 h, acid **318** undergoes decarboxylation to triazole derivative **319** with 81% isolated yield <2004FA397>.

Acid chloride **321**, obtained in 85% yield by refluxing a solution of carboxylic acid **320** in thionyl chloride, is converted to azide **322** in 86% yield by treatment with sodium azide in pentane. Reactions of azide **322** with amines of low nucleophilicity in refluxing DMF provide ureas **323** in 24–90% yield via Curtius rearrangement. In these reactions, 3-bromo- and 4-bromoaniline give also the corresponding amides, which are formed by simple substitution of the N_3 group in azide **322** with amines, as the side products. Secondary amines and primary amines with more nucleophilic NH_2 groups (e.g., *p*-anisidine and *t*-butylamine) provide exclusively the corresponding amides (**Scheme 49**) <2003JCCS1215>.



Scheme 48

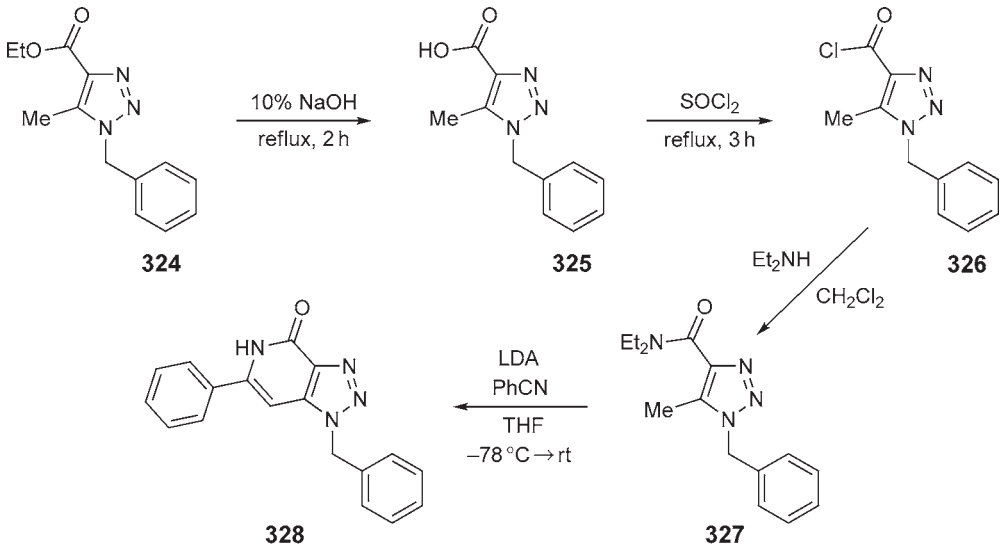


Scheme 49

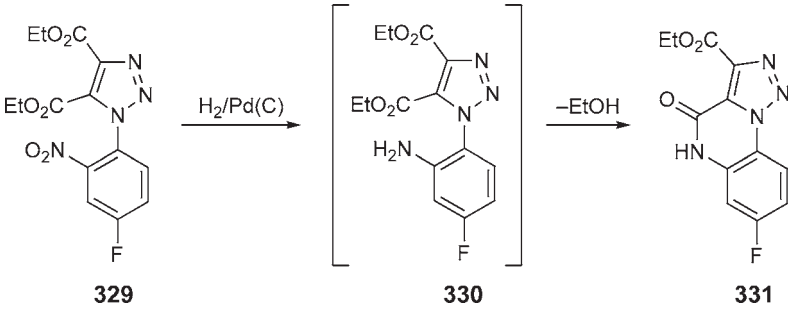
Ester **324** is hydrolyzed to acid **325** by refluxing in 10% NaOH. In a reaction with thionyl chloride, acid **325** is converted to acid chloride **326**, which is isolated as a solid in 96% yield and consecutively converted into amide **327** in 85% yield. Treatment of amide **327** with LDA extracts a proton from the methyl group. The generated anion is trapped by added benzonitrile. Subsequent cyclocondensation of the obtained imine anion with the amide group provides derivative **328** in 62% isolated yield (**Scheme 50**) <2003EJM983>.

In an example given in **Scheme 51**, tricyclic system **331** is generated by cyclocondensation between the ethoxycarbonyl group at C-5 of the triazole ring and the amino group of the substituent at N-1. The process that starts from catalytic reduction of the nitro group in derivative **329** does not stop at amine **330**, but the subsequent spontaneous cyclocondensation leads directly to product **331** that is isolated in 60% yield <2002EJM565>.

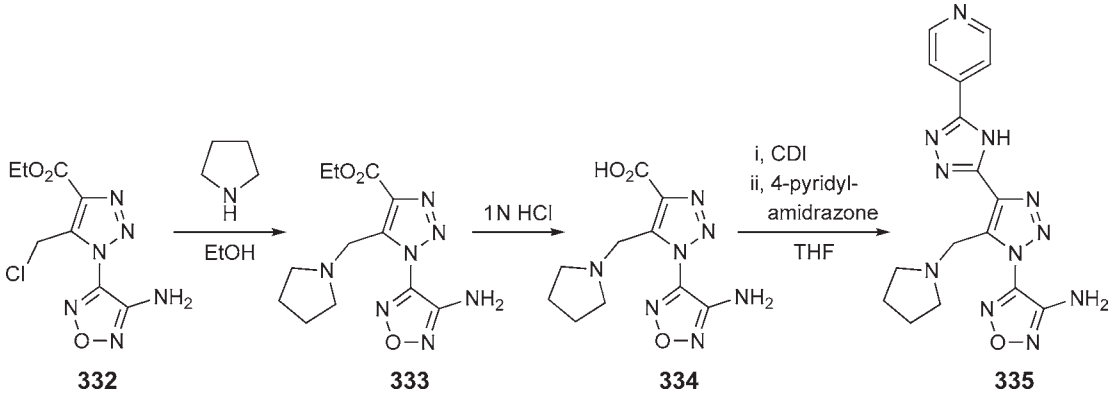
Ethyl 5-chloromethyl-1,2,3-triazole-4-carboxylate **332**, obtained by cyclocondensation of 3-amino-4-azidofurazan with ethyl 4-chloroacetoacetate, is converted to pyrrolidine derivative **333** in 97% yield. Heating at reflux with 1 N HCl deprotects the carboxylic group. The obtained acid **334** is treated with carbonyldiimidazole followed by pyridine-4-carboxylic acid amidrazone to provide product **335** in 25% yield. Compound **335** is a potent inhibitor of glycogen synthase kinase-3 (GSK-3) (**Scheme 52**) <2003JME3333>.



Scheme 50



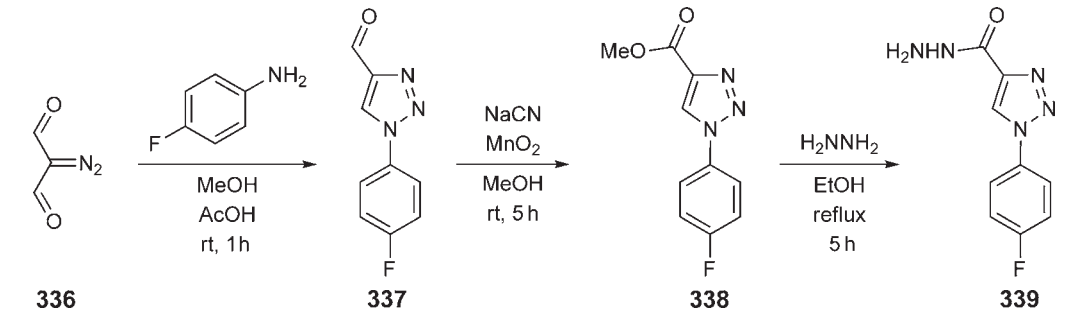
Scheme 51



Scheme 52

5.01.7.5 Carbaldehydes

Cyclocondensation of diazomalonaldehyde **336** with 4-fluoroaniline carried out in methanol-acetic acid provides 1-(4-fluorophenyl)-1,2,3-triazole-1-carbaldehyde **337** in 78% yield. Oxidation with MnO_2 in the presence of sodium cyanide in methanol converts aldehyde **337** into methyl ester **338** with 79% yield. Hydrazide **339** (84% yield) is obtained in a reaction of ester **338** with hydrazine. Product **339** reacts with various aromatic aldehydes to give hydrazones possessing interesting antiplatelet activity (**Scheme 53**) <2003BMC2051>.

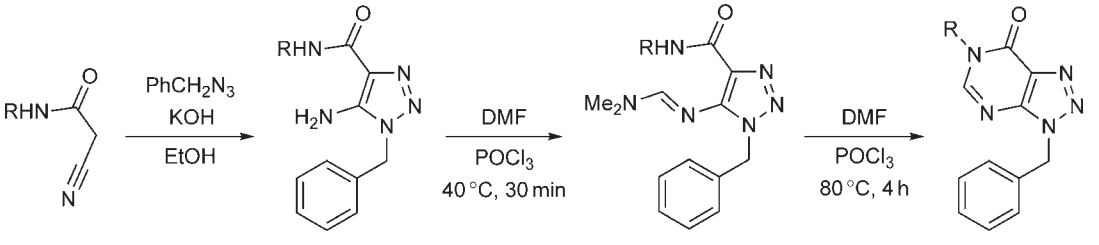


336 337 338 339

Scheme 53

5.01.7.6 Amines

1,2,3-Triazoles substituted with an amino group at C-5 are readily available from cycloaddition of nitriles to azides. They have become convenient intermediates in synthesis of biologically active compounds. In an example given in **Scheme 54**, cycloaddition of anions derived from cyanoacetamides **340** to benzyl azide provides 5-amino-1,2,3-triazole derivatives **341** in 75–91% yield. Catalyzed by phosphorus oxychloride, amines **341** undergo cyclocondensation with DMF under mild conditions (40 °C) to give amidines **242**. At higher temperature (80 °C), cyclocondensation occurs with elimination of dimethylamine to form 1,2,3-triazolo[4,5-*d*]pyrimidin-5-ones **343**, which are isolated in 71–85% yield. However, lower yield (30%) is obtained for R = 2-$MeOC_6H_4$. For R = H, simple heating of the corresponding amine **341** with formamide at 210 °C provides derivative **343** in good yield <2003RCB1770>.

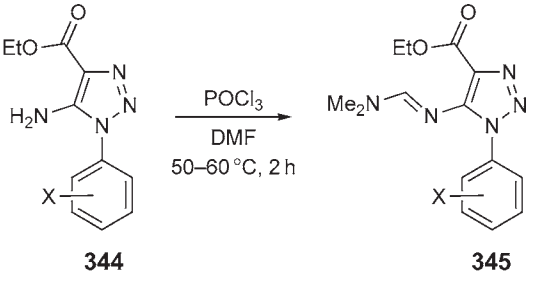


340 341 342 343

R = H, Me, $PhCH_2$, Ph, or 2-$MeOC_6H_4$

Scheme 54

In a synthesis similar to that depicted in **Scheme 54**, aminoesters **344** dissolved in DMF are treated with $POCl_3$ and heated at 50–60 °C for 2 h. The simple work-up procedure involves pouring into ice-water, neutralization with NaOH and separation of the precipitate by filtration to afford amidines **345** in 66–86% yield (Equation 11). Some of the obtained amidines exhibit selective antibacterial activity <2003SC3969>.

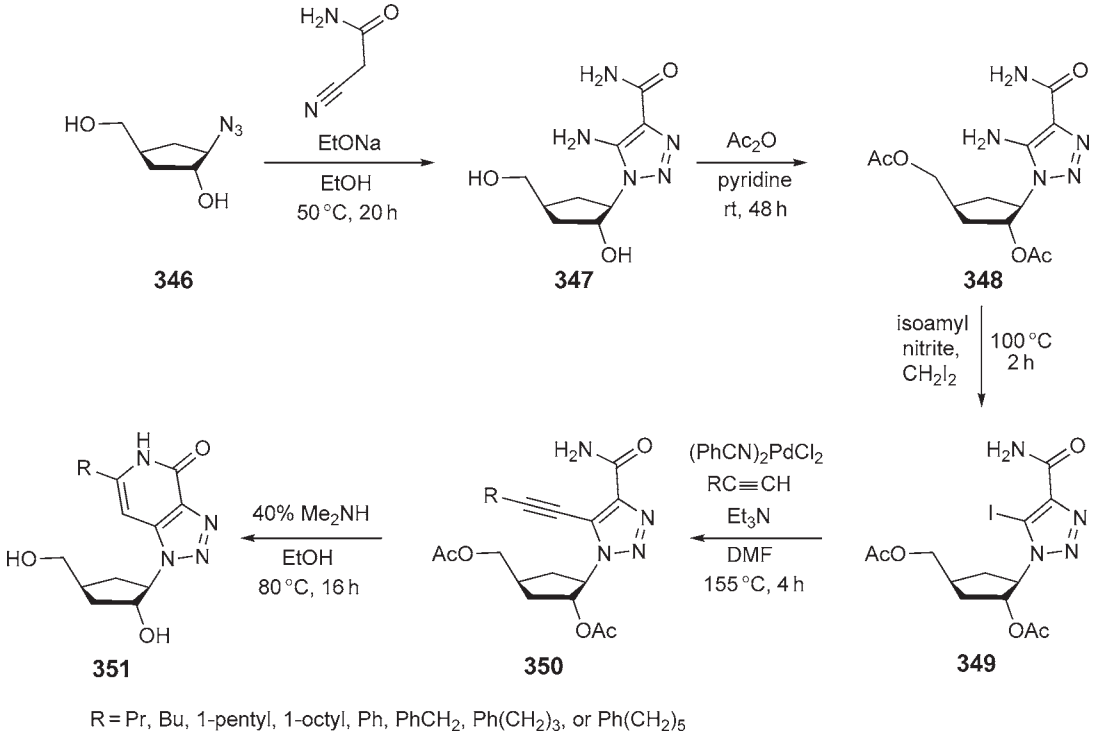


(11)

344 345

X = H, *p*-Me, *p*-MeO, *p*-EtO, *p*-MeCO, *p*-NO_2, *p*-Cl, *m*-F, *m*-Cl, *m*-Br, *m*-CF_3, or *m*-NO_2

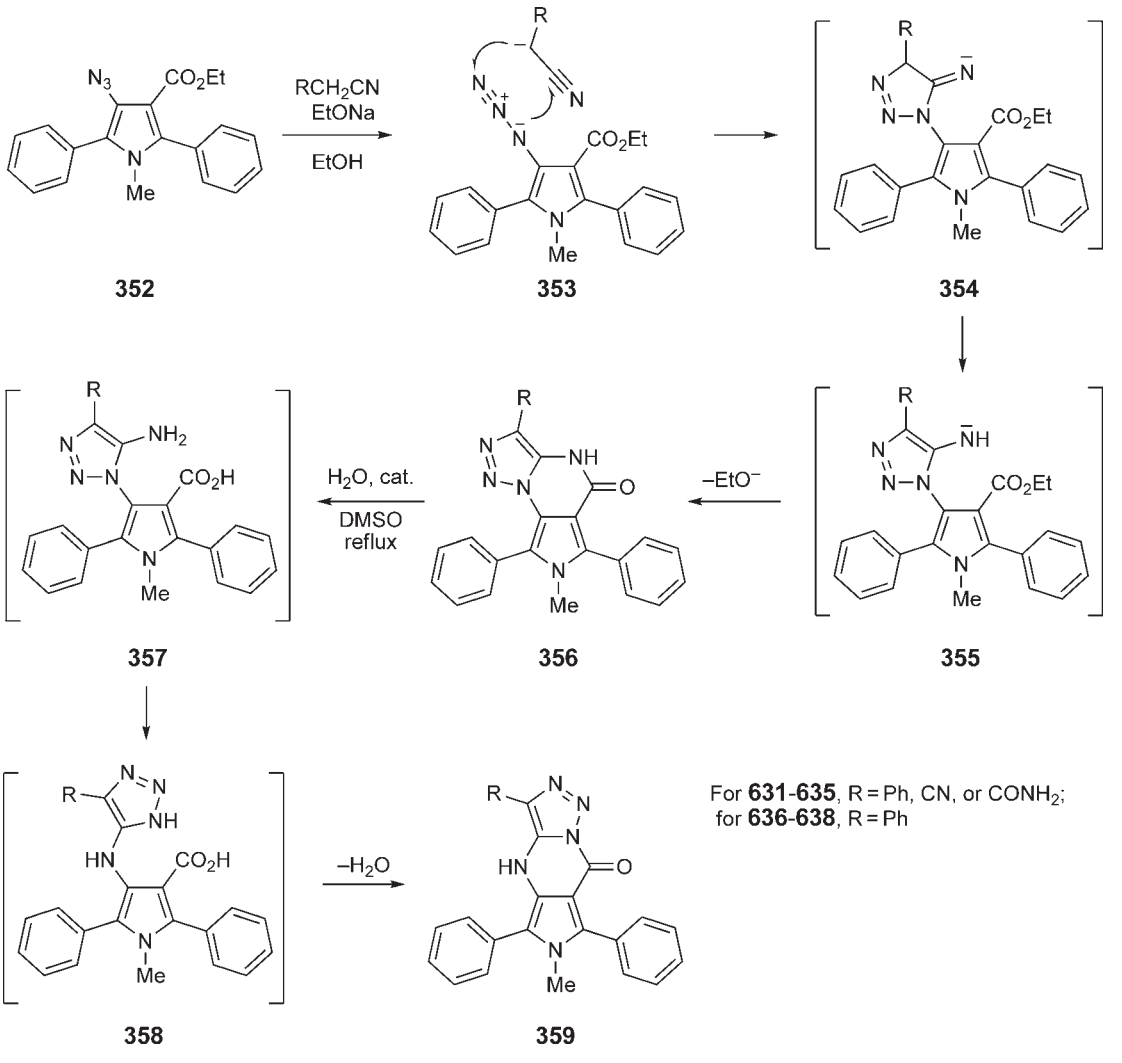
1,3-Dipolar cycloaddition of 2-cyanoacetamide to 2-azido-4-(hydroxymethyl)-cyclopentanol **346**, carried out in ethanol in the presence of sodium ethoxide, provides regioselectively 5-amino-1,2,3-triazole derivative **347** in 52% yield. In the following step, the hydroxy groups are protected by acetylation with acetic anhydride in pyridine to give diester **348** in 75% yield. Surprisingly, the amino group is not nucleophilic enough to be acetylated under such conditions. Diazotization (isoamyl nitrite) and substitution with iodide (diiodomethane) converts amine **348** into 5-iodo derivative **349** that is isolated in 55% yield. By coupling with terminal alkynes under modified Sonogashira conditions, iodide **349** is converted to alkynes **350** in 52–77% yield. Treated with 40% aqueous dimethylamine in ethanol at 80 °C in sealed tubes, amido groups in derivatives **350** undergo intramolecular cycloaddition to alkynes resulting in formation of pyridine rings. In the same step, the hydroxy groups are deprotected to provide 6-substituted 1,2,3-triazolo[4,5-*c*]pyridin-4-ones **351** in 51–72% yield (**Scheme 55**) <2005T11744>.



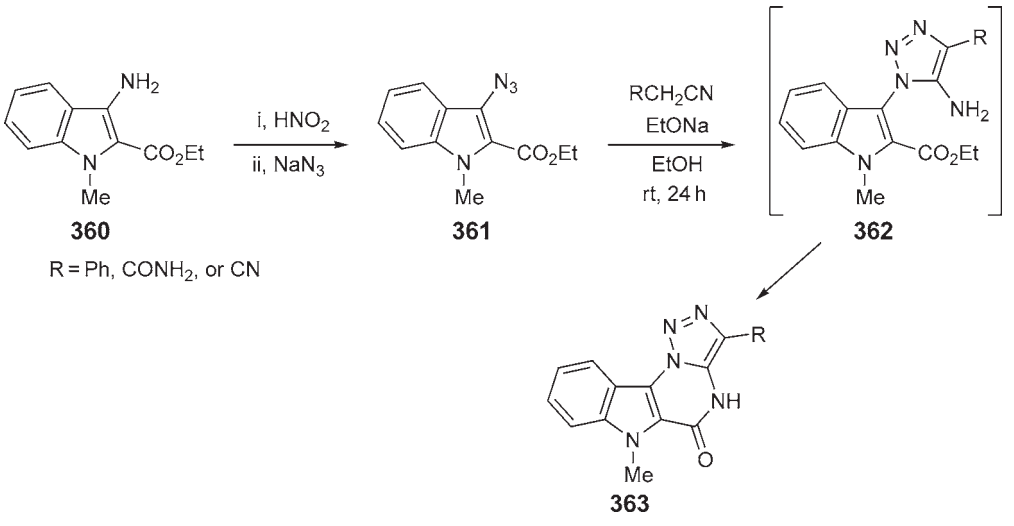
Scheme 55

When a solution of azide **352** and nitrile RCH_2CN in ethanol is treated with sodium ethoxide, the anion derived from nitrile undergoes 1,3-dipolar cycloaddition to azide **353**. Generated anion **354** tautomerizes to more stable aromatic form **355**. Nucleophilic attack of the triazoloamine anion on the ethoxycarbonyl group in intermediate **355** results in elimination of an ethoxy anion and ring closure to give pyrrolo[3,4-*e*]1,2,3-triazolo[1,5-*a*]pyrimidin-5-one **356** in high yield. Heating of compound **356** (R = Ph) in DMSO in the presence of traces of water results in its hydrolysis to aminoacid **357**. Under the reaction conditions, 5-aminotriazole system **357** undergoes Dimroth rearrangement to more stable derivative **358**. Spontaneous cyclocondensation between the carboxylic group and the triazole ring in **358** leads to 6-methyl-3,5,7-triphenyl-4,6-dihydro-8*H*-pyrrolo[3,4-*d*]1,2,3-triazolo[1,5-*a*]pyrimidin-8-one **359** that is isolated in almost quantitative yield (**Scheme 56**) <2000JHC747> . Similar transformations are reported for ethyl 1-benzyl-3-azido-4-phenylpyrrolocarboxylate <2002T9723>.

Ethyl 3-azido-1-methyl-1*H*-indole-2-carboxylate **361** is prepared in 70% yield by diazotization of amine **360** followed by substitution of the created diazonium group with sodium azide. In cycloadditions with nitrile anions, azide **361** forms triazole intermediates **362**. However, under the reaction conditions, cyclocondensation of the amino and ethoxycarbonyl groups in **362** results in formation of an additional ring. This domino process provides efficiently 4*H*-indolo[2,3-*e*]1,2,3-triazolo[1,5-*a*]pyrimidines **363** in 70–80% yield (**Scheme 57**) <2006TL2187>.

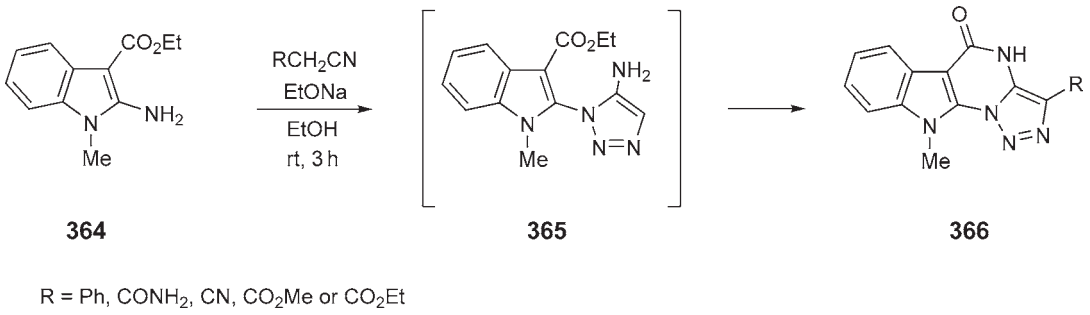


Scheme 56



Scheme 57

In a similar tandem reaction, ethyl 2-azido-1-methyl-1*H*-indole3-carboxylate **364** is converted to indolo[3,2-*e*]1,2,3-triazolo[1,5-*a*]pyrimidin-5-ones **366** via triazole intermediates **365** that are not separated (**Scheme 58**). Products **366** are obtained in 80-90% yield as potential intercalates of DNA <2003H(60)2669>.

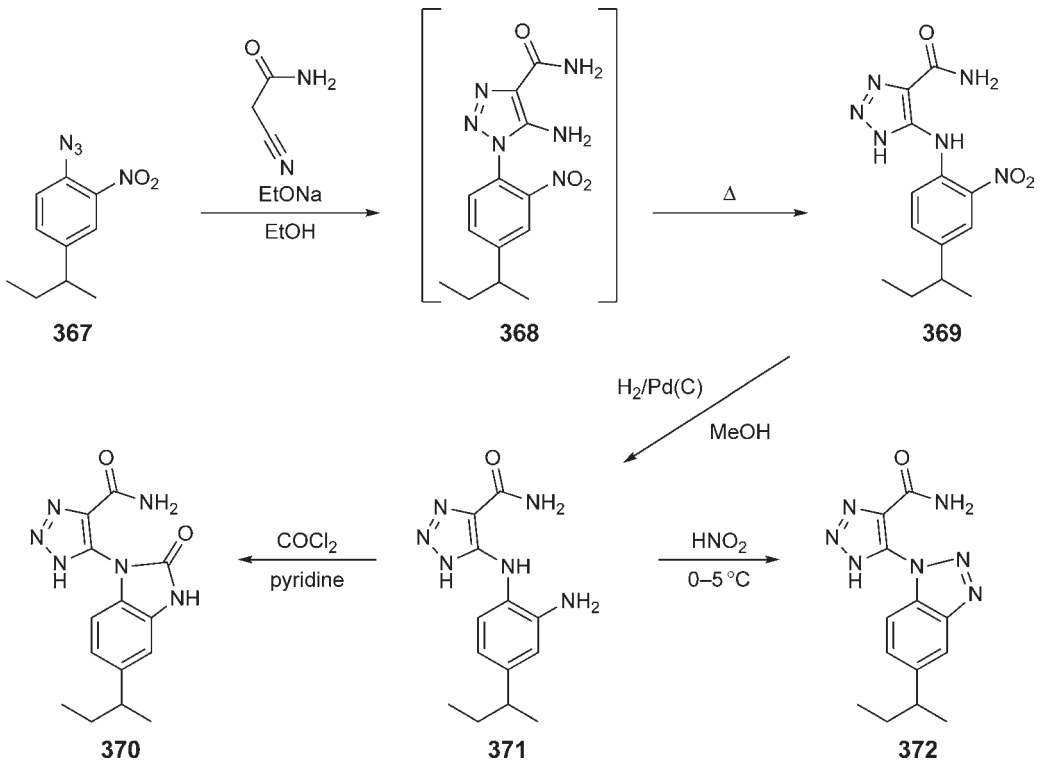


364 **365** **366**

R = Ph, $CONH_2$, CN, CO_2Me or CO_2Et

Scheme 58

Azide **367** is prepared from 4-*sec*-butyl-2-nitroaniline in 76% yield by its diazotization followed by treatment with sodium azide. In a 1,3-dipolar cycloaddition with cyanoacetamide, azide **367** is converted to triazole **368** that without separation is directly subjected to Dimroth rearrangement to give derivative **369** in 46% yield. Reduction of the nitro group provides *ortho*-phenylenediamine **371** in 91% yield <2000EJM715>. Cyclocondensation of diamine **371** with phosgene furnishes benzimidazol-2-one **370** in 39% yield, whereas its reaction with sodium nitrite in 18% HCl leads to benzotriazole derivative **372**, which is isolated in 66% yield (**Scheme 59**). Products **370** and **372** exhibit potassium channel activating ability <2001FA841>.

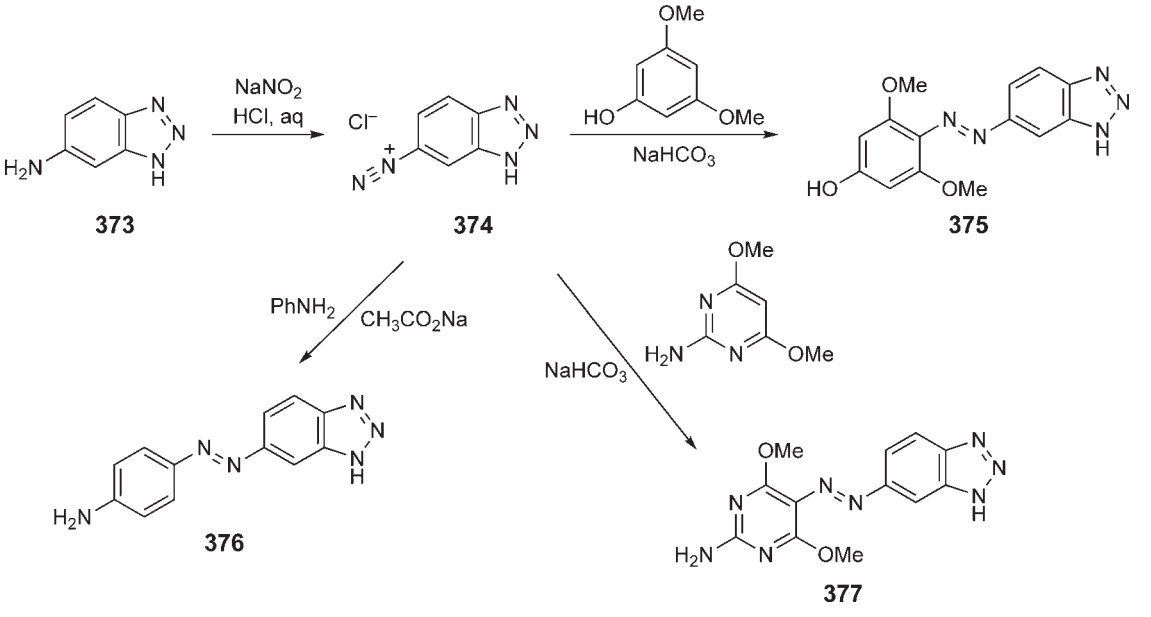


367 **368** **369**

370 **371** **372**

Scheme 59

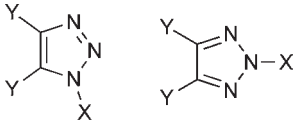
Amino groups on the benzenoid ring of benzotriazole behave similarly to those of typical aromatic amines. 4-Aminobenzotriazole **373** is readily diazotized to provide diazonium chloride **374**. In couplings with phenols or aromatic amines, diazonium derivative **374** is converted to the corresponding azo dyes. Three examples of such reactions providing dyes **375** (67%), **376** (84%) and **377** (64% yield) are shown in **Scheme 60** <2002AN838>. Dyes of this type are used for labeling of nucleotides <2003TL1339>.



Scheme 60

5.01.8 Reactivity of Substituents Attached to Ring Nitrogens

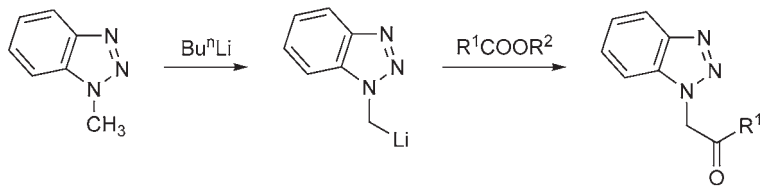
Functional groups can be attached to the ring nitrogen atoms in position 1 or 2 of unsubstituted or symmetrically substituted aromatic rings of 1,2,3-triazoles and benzotriazoles giving rise to distinctive regioisomers **378** and **379**, respectively. In most cases, isomers **378** form kinetically in predominant amounts. In some instances, there is a rapid equilibrium between isomers **378** and **379** in solution <1996CHEC-II(4)1>. For many reactions, there is no different outcome if pure isomers **378**, **379** or their mixtures are employed. For these reasons and clarity of the treatment, in the following paragraphs, only triazol-1-yl and benzotriazol-1-yl **378** isomers are depicted in schemes, even if the corresponding triazol-2-yl **379** isomers are also present in the mixtures. If the chemistry of isomers **378** and **379** differs remarkably, they are treated separately.



378 **379**

5.01.8.1 Ring N-C(sp^3)-R, R = C(sp^3), or H

Upon treatment with n-butyllithium at −78 °C, 1-methylbenzotriazole **380** is lithiated on the methyl group to give 1-(lithiomethyl)benzotriazole **381**. Rapid addition of a carboxylic ester to the solution provides α-(benzotriazol-1-yl)alkyl ketone **382** in high yield (**Scheme 61**) <1997JOC4142>. This easy access to ketones **382** and their reactivity makes them valuable intermediates in several syntheses. Their chemistry is discussed separately in Section 5.01.8.4.



380 381 382

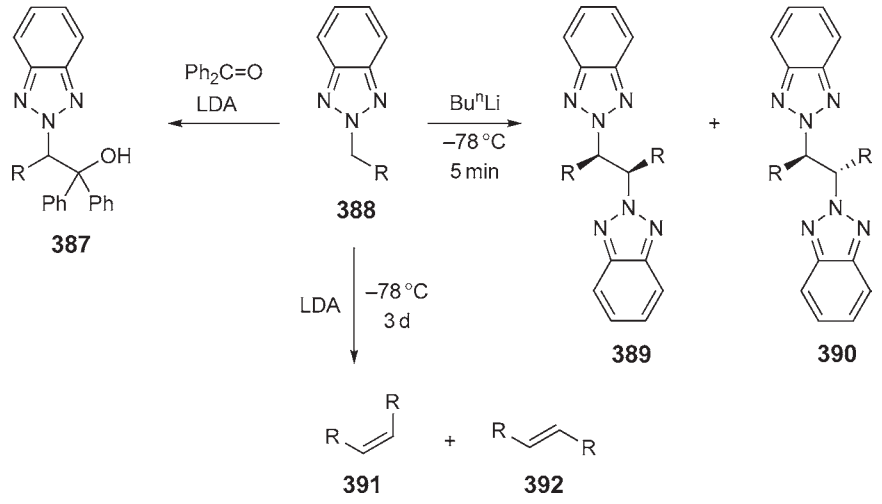
Scheme 61

When treated with Bu^{n}Li, 1-(3-chlopropyl)benzotriazole **383**, obtained from a reaction of benzotriazole with 1-bromo-3-chloropropane and NaOH, undergoes cyclization to 1-cyclopropylbenzotriazole **384** <1998JOC6710>. Further lithiation followed by treatment with ketones provides alcohols **385** (**Scheme 62**). Upon heating at 60 °C with low valent titanium <1998JOC6704>, alcohols **385** are converted into interesting cyclopropylidene derivatives **386**. 1-(3-Chloro-2-methylpropyl)benzotriazole gives analogous products with a methyl group on the cyclopropane ring <1998JOC6710>.

383 384 385 386

Scheme 62

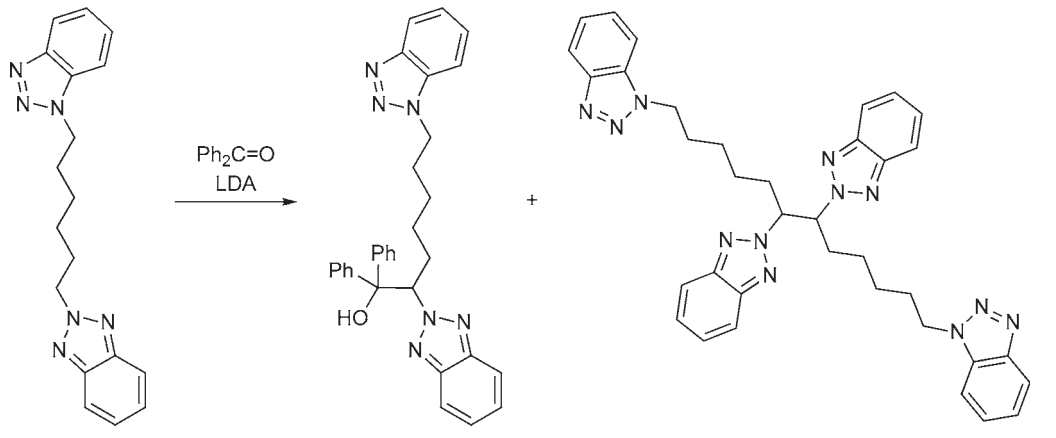
Perhaps due to oxidizing quinoid type electronic structure of benzotriazol-2-yl derivatives, some of their properties are completely different from those of isomeric benzotriazol-1-yl derivatives. Thus, anions derived from 2-alkylbenzotriazoles **388** are rapidly converted to appropriate radicals that undergo coupling to form dimers as mixtures of racemic **289** and meso **390** forms <1996LA745>. When the reaction mixture is kept for an extended period of time at −78 °C, *(Z)*- **391** and *(E)*- **392** alkenes are formed. When benzophenone is added to the reaction mixture, alcohols **387** are obtained in good yields; however, benzaldehyde does not react under these conditions (**Scheme 63**).



387 388 389 390 391 392

Scheme 63

In a direct comparison of the reactivity of 1-alkyl- and 2-alkylbenzotriazoles, compound **393** was lithiated in the presence of benzophenone with 1 equiv of LDA to give a mixture of alcohol **394** and dimer **395** (Equation 12) <1996LA745>. No reaction was detected at the carbon adjacent to the benzotriazol-1-yl moiety. When benzaldehyde was used instead of benzophenone, only dimer **395** was obtained. This suggests that α-benzotriazol-2-yl carbon radical reactions are much faster than those of α-benzotriazol-1-yl) carbanions.



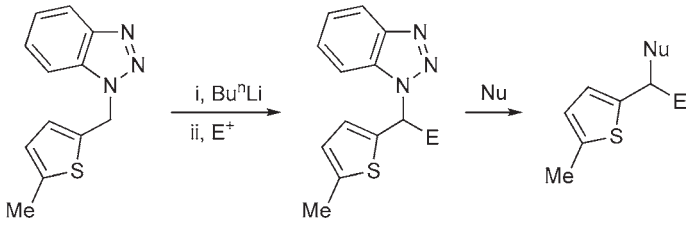
(12)

393 **394** **395**

5.01.8.2 Ring N–C(sp^3)-C=C

5.01.8.2.1 Ring N–C(sp^3)-Ar. No reaction on Ar

Easy synthesis of (benzotriazol-1-yl)methylarenes and –heteroarenes, and their reactivity, makes them convenient starting materials for further transformations. Benzotriazole assisted side-chain elaboration of alkylarenes can be illustrated by reactions carried out on 2-(benzotriazol-1-yl)methyl-5-methylthiophene **396** (**Scheme 64**). Starting material **396** can be readily obtained by refluxing a solution of 1-(hydroxymethyl)benzotriazole, 2-methylthiophene and a catalytic amount of TsOH in dioxane. α-Deprotonation of derivative **396** with Bu^{n}Li followed by treatment with an electrophile leads to product **397**. Phenyl isocyanate, phenyl isothiocyanate, benzaldehyde, alkyl iodides, benzyl bromide, and cyclohexanone have been used as electrophiles. Upon treatment with nucleophiles, the benzotriazole moiety in compounds **397** can be substituted to give products **398**. To replace the benzotriazolyl group with hydrogen, derivatives **397** are treated with zinc in refluxing acetic acid <1997JOC6215>. Similar benzotriazole-assisted side-chain transformations are reported for benzene <1997JOC721>, pyrrole <1996JOC1624, 1996TL5641>, and indole <1995JOC3401, 1995SC539, 1996JOC7558>.



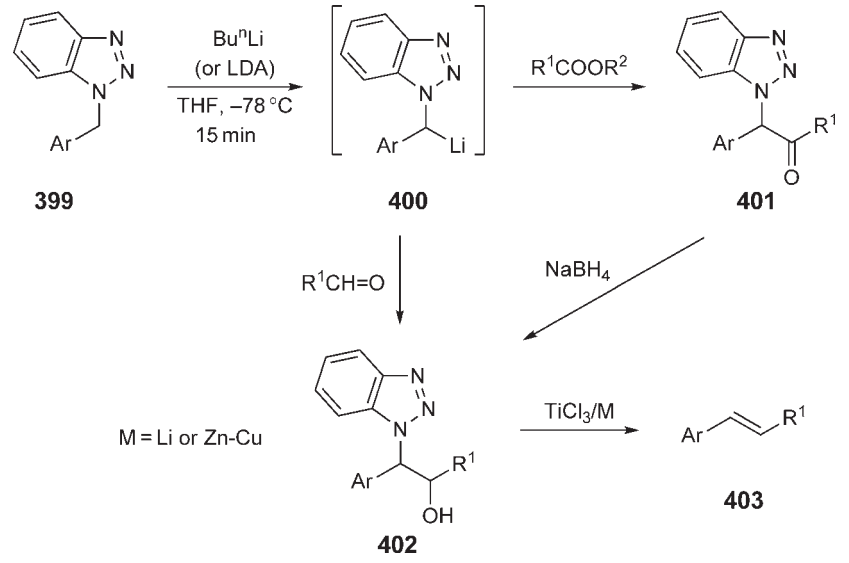
396 **397** **398**

E^+ = RI, $PhCH_2Br$, PhCH=O, PhN=C=O, PhN=C=S, and cyclohexanone

Scheme 64

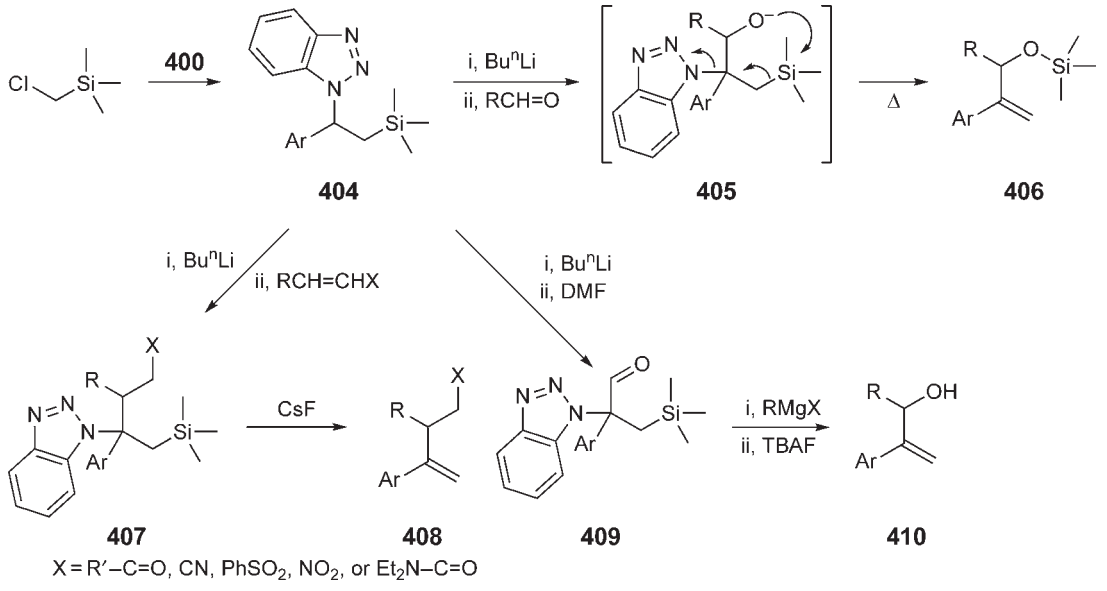
An additional stabilization of the negative charge provided by the adjacent aryl group in aryllithiomethyl intermediates **400** makes 1-(arylmethyl)benzotriazoles **399** attractive starting materials for many syntheses. Thus, reaction of anions **400** with esters of carboxylic acids leads to α-(benzotriazole-1-yl) ketones **401**, which can be easily reduced to carbinols **402**

<1998JOC3438>. In another approach, adducts **402** are produced directly by addition of anions **400** to carbonyl groups of aldehydes or ketones <1997JOC238, 1998JOC6704>. Low valent titanium, generated by reduction of $TiCl_3$ with lithium or Zn–Cu couple metals, converts carbinols **402** into olefins **403** (**Scheme 65**). The reaction sequence depicted in **Scheme 65** allows introduction of a variety of substituents R^1: for example, chiral allylamines are produced from aminoacids, or dienes are formed stereoselectively from α,β-unsaturated aldehydes or ketones. Reaction of lithio derivatives **400** with tosylhydrazones of aldehydes leads directly to *(E)*-stilbenes in a stereospecific manner <1999JOC3332>.



Scheme 65

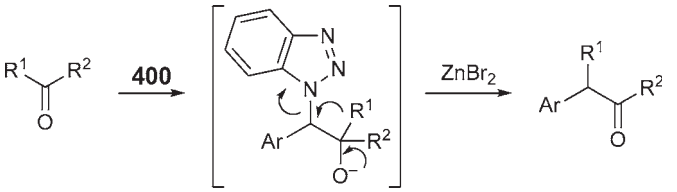
Reaction of anions **400** with chloromethyltrimethylsilane provides very useful intermediates **404** <1997JA9321>. Consecutive α-lithiation followed by addition to a carbonyl group of an aldehyde leads to alkoxide **405**. During heating, anions **405** undergo an intramolecular rearrangement with elimination of benzotriazole to produce silylated allyl alcohols **406** (**Scheme 66**) <1998JOC9978>. This approach provides a general method for the synthesis of allyl alcohols substituted with an aryl or heteroaryl group in the β position.



Scheme 66

Additions of lithiated silyl derivatives **404** to α,β-unsaturated compounds bearing electron-withdrawing substituents X provide silyl derivatives **407** with high 1,4-regioselectivity. Elimination of trimethylsilyl and benzotriazolyl groups facilitated by heating with CsF leads to γ,δ-unsaturated ketones, nitriles, sulfones, nitroalkanes, or amides **408** <1998JOC9987>. Formylation of intermediates **404** produces masked acroleins **409** that provide easy access to 2-substituted allyl alcohols **410**. Imines obtained from condensation of aldehydes **409** with arylamines can be similarly converted to the corresponding allylamines <1999JOC6080>.

Additions of anions **400** to carbonyl groups of aldehydes or ketones produce anions **411** that upon treatment with $ZnBr_2$ eliminate benzotriazole at elevated temperature and rearrange to ketones **412** (**Scheme 67**) <1996JOC7571>. This insertion of carbons carrying aryl or heteroaryl substituents provides a convenient method for one-carbon chain extension or ring expansion for aldehydes and ketones. The reaction is characterized by significant regioselectivity; of two groups R^1 and R^2, preferences for the migration are in the order: H > aryl > alkyl and *tert*-alkyl > *sec*-alkyl > n-alkyl.



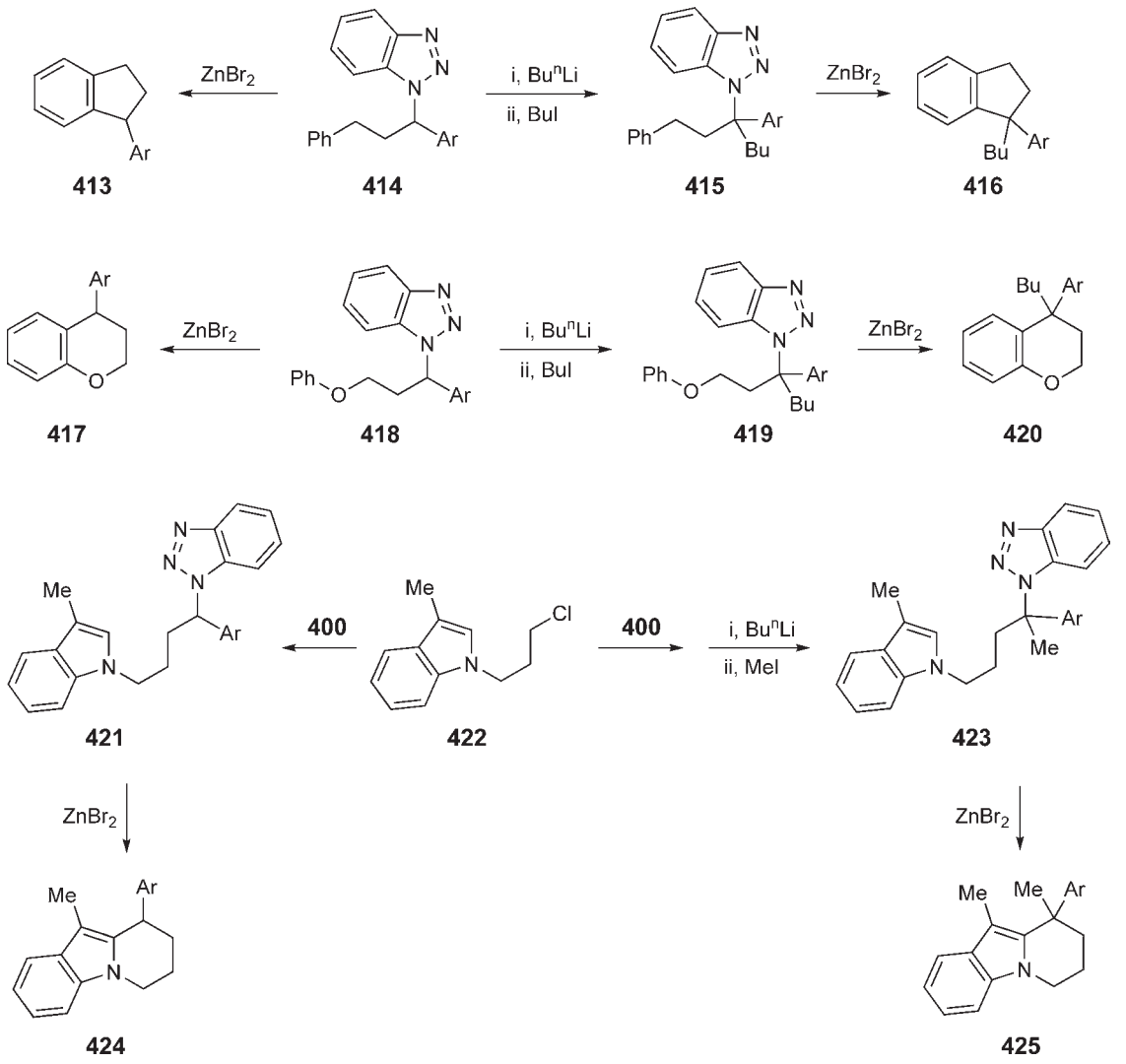
411 **412**

Scheme 67

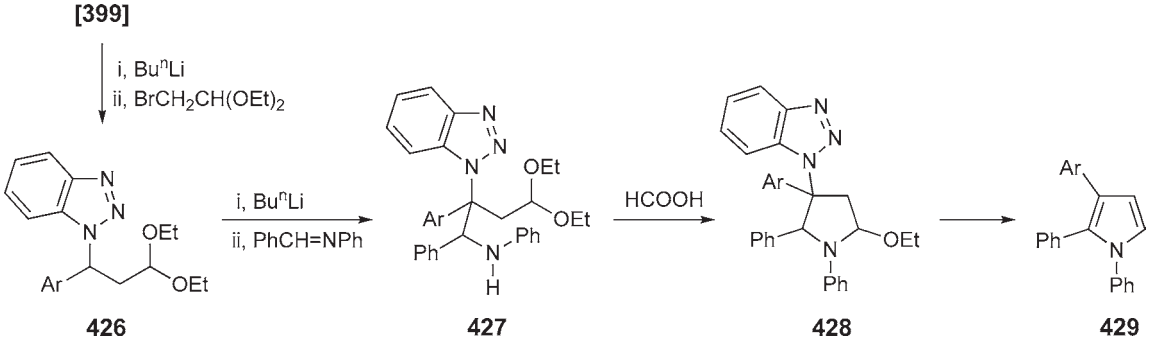
Substitution of one of the α-hydrogens in 1-(arylmethyl)benzotriazole **399** with an alkyl bearing an aromatic ring opens new frontiers. When the distance is right, an intramolecular electrophilic attack of α-carbon on an *ortho* atom of the aromatic ring is possible. Examples of such annulation reactions are given in **Scheme 68**. Thus, treatment of derivative **414**, obtained by alkylation of intermediate **400** with (2-bromoethyl)benzene, with zinc bromide results in formation of indane **413**. Alternatively, intermediate **414** can be first alkylated to product **415** and then annulated to 1,1-disubstituted indane **416**. For effective annulation, the link between the aromatic ring and α-carbon must consist of two or three atoms. Heteroatoms are also accepted, as exemplified by phenoxy derivatives **417–420**. Heterocyclic aromatic rings can be used as well; for example, annulated products **424** and **425** are obtained from 1-(3-chloropropyl)-3-methylindole **422** via intermediate **421** or its methylated analog **423**, respectively <1998JOC3445>. Similar annulation reactions involving thiophene are also described <1997JOC6215>.

Two sequential lithiations and treatments with different bifunctional electrophiles make possible one-pot syntheses of relatively complex molecules. Thus, in the [1+2+2] annulation depicted in **Scheme 69**, alkylation of 1-benzylbenzotriazole **399** with 2-bromoacetaldehyde diethyl acetal to give intermediate **426** is followed by alkylation with *N*-benzylideneaniline to produce derivative **427**. Following treatment with formic acid causes cyclization to ethoxypyrrolidine **428** that subsequently eliminates ethanol and benzotriazole to give pyrrole **429** <1997JHC1379>.

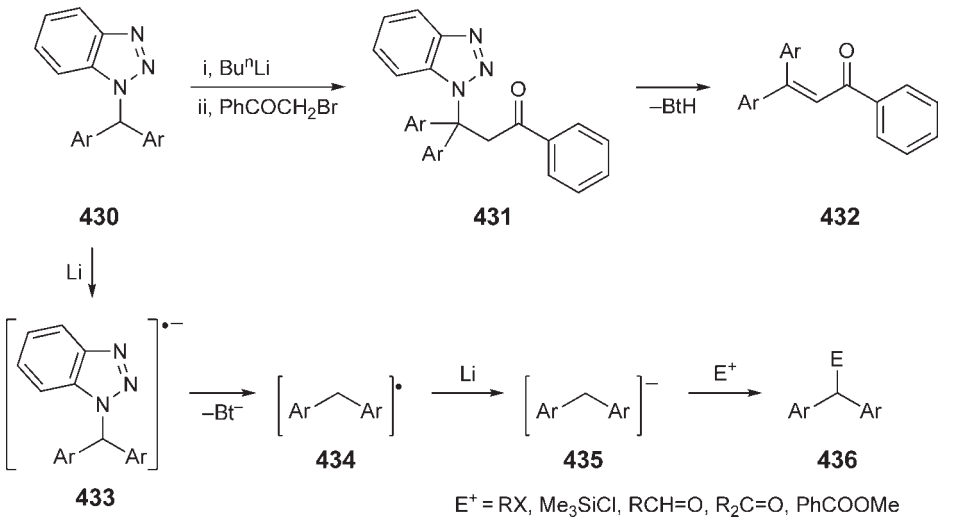
Anions derived from treatment of (diarylmethyl)benzotriazoles **430** with Bu^nLi are readily trapped by bromoacetophenone to produce ketones **431**. Increased acidity of the hydrogens in β-position, with respect to the benzotriazolyl moiety, renders derivatives **431** susceptible to elimination of benzotriazole to give diarylvinyl ketones **432** (**Scheme 70**). Both benzotriazol-1yl and -2-yl derivatives, and their mixtures, can be employed in these reactions <1998JOC3450>. Treatment of (diarylmethyl)benzotriazoles **430** with metallic lithium and electrophiles results in substitution of benzotriazole with formation of derivatives **436**. The yields are generally good, and variety of electrophiles can be employed. Some unusual outcome of these reactions can tentatively be explained by a single-electron transfer (SET) from lithium to starting compounds **430** to give radical anions **433** which eliminate benzotriazole to form relatively stable radicals **434**. Following reduction with metallic lithium (another SET) converts radicals **434** into anions **435** that are finally trapped by electrophiles to give products **436** <1997JOC4116>.



Scheme 68



Scheme 69

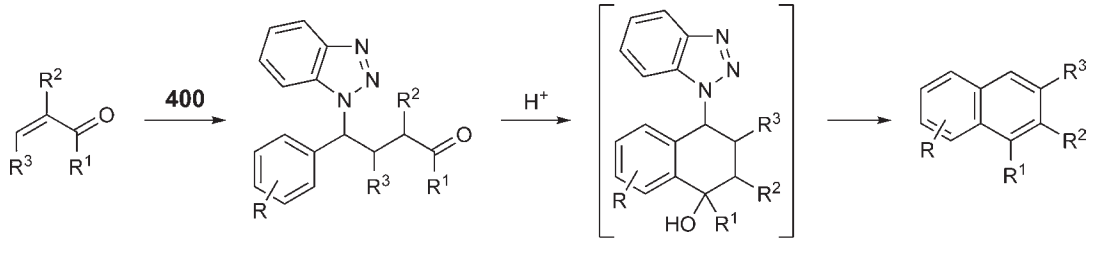


430 **431** **432** **433** **434** **435** **436**

Scheme 70

5.01.8.2.2 Ring N–C(sp^3)-Ar. Reactions on Ar

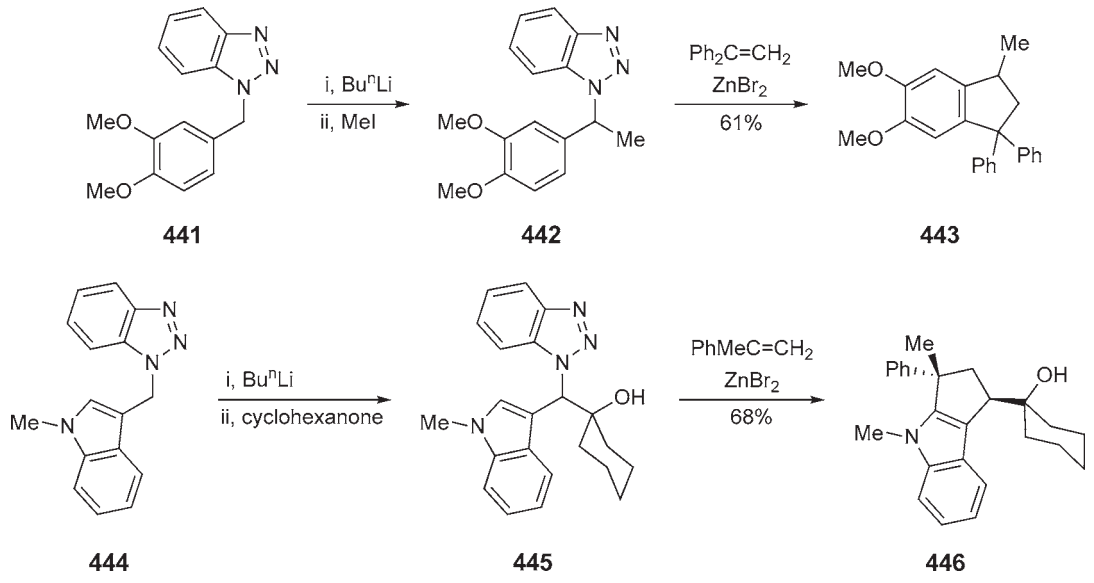
Lithiated 1-(arylmethyl)benzotriazoles **400** (Ar = phenyl, tolyl, or anisyl) readily undergo Michael additions to α,β-unsaturated aldehydes or ketones **437** to give γ-carbonyl-alkyl derivatives **438**. Upon treatment with acids, the carbonyl group of intermediate **438** is activated for an electrophilic attack on the *ortho* carbon of the ring to produce tetrahydronaphthalene derivative **439** which eliminates consecutively water and benzotriazole to give the naphthalene **440** (**Scheme 71**) <1997JOC721>. Substitution of one of the α protons in compound **400** with an alkyl group allows the introduction of substituents to C-4 of naphthalene. Analogous reactions of 1-[(1-methylindol-3-yl)methyl]-benzotriazole lead to corresponding carbazoles <1996JOC7558>. Similar [3+3] benzannulation reactions are occur for furans <1997JOC8205>, indolizines <2000JOC8059>, pyrroles <1996TL5641, 1997JOC4148>, thiazoles <2000JOC8059>, and thiophenes <1997JOC6215>; several examples of which can be found in review articles <1999T8263, 1998CCC599>.



437 **438** **439** **440**

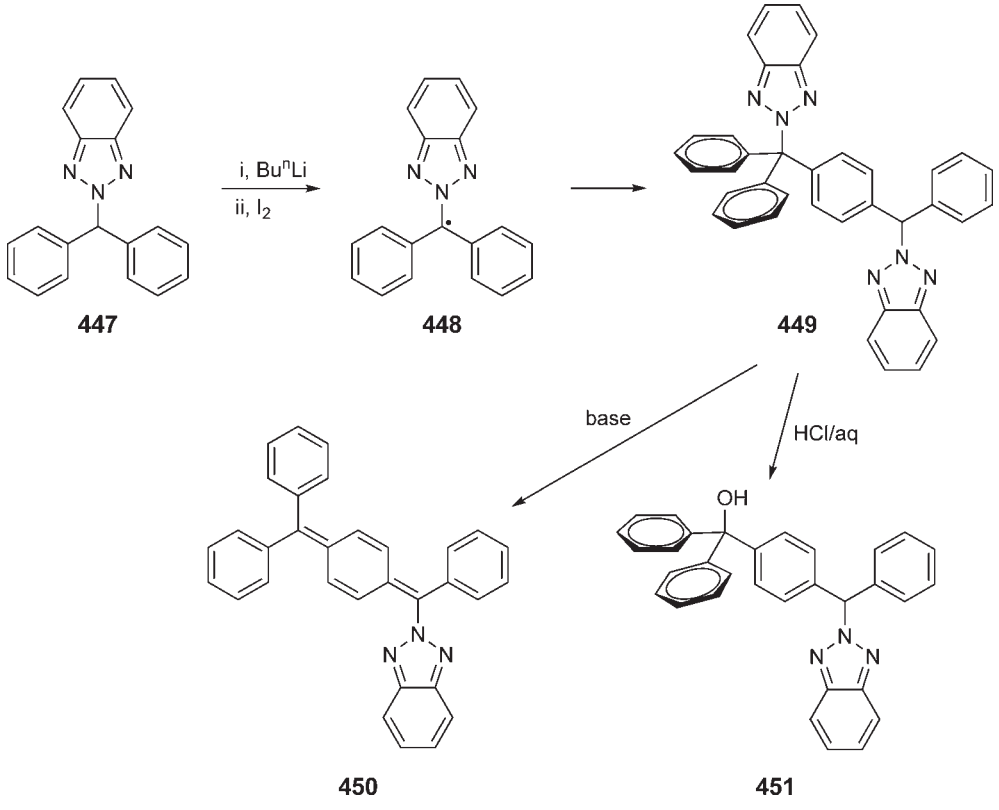
Scheme 71

Derivatives **400** containing electron-rich aromatic rings undergo readily [3+2] cycloaddition with styrenes. Two examples of such reactions are presented in **Scheme 72**. Thus, alkylation of an anion derived from benzylbenzotriazole **441** gives derivative **442**. Following treatment with $ZnBr_2$ cleaves the bond with benzotriazole to generate the corresponding benzyl cation which is then trapped by styrene to give a new cation that finally cyclizes on to the aromatic ring at its *ortho* position to furnish indan **443** <1997SC2467>. A similar process converts 1-methyl-3-[(benzotriazole-1-yl)methyl]indole **444** into tricyclic system **446**, via intermediate **445** <1996JOC7558>.



Scheme 72

Treatment of anions derived from 2-(diphenylmethyl)benzotriazole **447** with iodine generates relatively stable radicals **448** which undergo spontaneous dimerization to adducts **449** (**Scheme 73**) <1998JOC9992>. When one of the phenyl rings in starting material **447** is substituted in the *para* position, similar dimerization occurs readily, but it

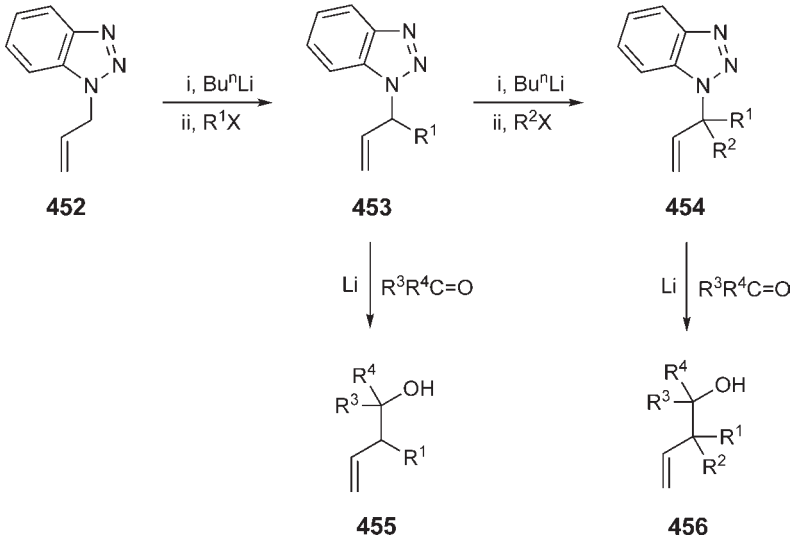


Scheme 73

is prevented by substitution of both *para* positions. Contrary to the behavior of an analogous adduct obtained by dimerization of triphenylmethyl radicals <1925CRV91, 1968TL249>, adduct **449** does not dissociate back to radicals **448**, indicating different characters of these two species. Treated with bases, adduct **449** eliminates one benzotriazole to give highly conjugated system **450**, red in color. Acidic hydrolysis converts adduct **449** into carbinol **451**. Radicals similar to **448** can be also generated from 1-(diarylmethyl)benzotriazoles, but they are less stable undergoing easily ring opening with extrusion of nitrogen <1998JOC1467>.

5.01.8.2.3 Ring N–C(sp^3)-C=C, nonaromatic

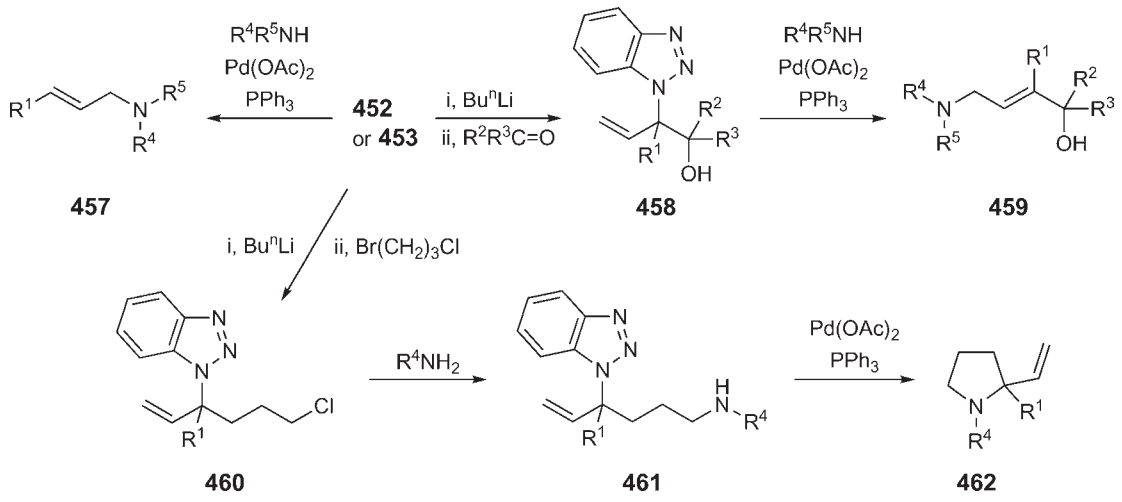
N-Allylbenzotriazoles (**452** and its benzotriazol-2-yl analog) behave somewhat similarly to *N*-benzylbenzotriazoles. Anions derived from compounds **452** upon treatment with n-butyllithium undergo alkylation exclusively at the position α to the benzotriazole moiety to give products **453** (**Scheme 74**). The lithiation and alkylation steps can be repeated to produce dialkylated derivatives **454**, possibly with two different alkyl groups. Although only benzotriazol-1yl compounds are shown in **Scheme 74**, in this case, both benzotriazol-1-yl and benzotriazol-2-yl derivatives have similar reactivity and their mixtures can be used effectively in the reactions next mentioned without separation <1998TL363>. Treatment of compounds **453** and **454** with metallic lithium in the presence of aldehydes or ketones cleaves the bonds with benzotriazole creating allylic anions that are trapped by the carbonyl groups to produce carbinols **455** and **456**, respectively, in high yields.



Scheme 74

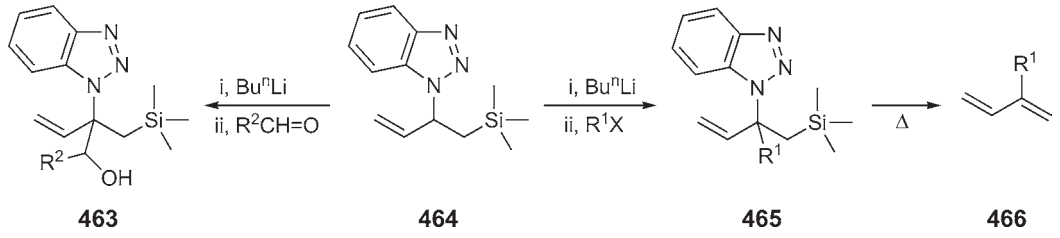
In the presence of a palladium catalyst, the benzotriazole moiety in derivatives **452**, **453** (and also in compound **454**) can be substituted with amines to give allylamines **457** (**Scheme 75**) <1998JOC5232>. Sulfonamides can also be N-allylated this way when triphenyl phosphite is used in place of triphenylphosphine as a complexing catalyst agent <2000JOC8063>. Palladium-catalyzed reactions of derivatives **453** and **454** with enamines lead to γ,δ-unsaturated ketones <1999JOC7625>. Lithiated allylbenzotriazoles **452** and **453** react with aldehydes and ketones to form alcohols **458** <2000JOC8063>. Following treatment with amines and the catalyst converts alcohols **458** into unsaturated aminoalcohols **459**.

The reaction of allylbenzotriazoles with amines can also be carried out intramolecularly. Thus, alkylation of derivatives **452** or **453** with 1-bromo-3-chloropropane gives chloropropyl derivative **460**. Subsequent substitution of the chlorine atom with an alkylamino group is easily accomplished by heating a solution of derivative **460** and amine R^4NH_2 in DMF. Intramolecular substitution of the benzotriazole moiety by the amino group in amines **461** occurs at room temperature in the presence of a palladium catalyst to furnish 2-vinylpyrrolidines **462** (**Scheme 75**) <1999JOC6066>. Similarly, alkylation of derivatives **452** and **453** with 1-bromo-4-chlorobutane and the following transformations lead to 2-vinylpiperidines <1999JOC6066>.



Scheme 75

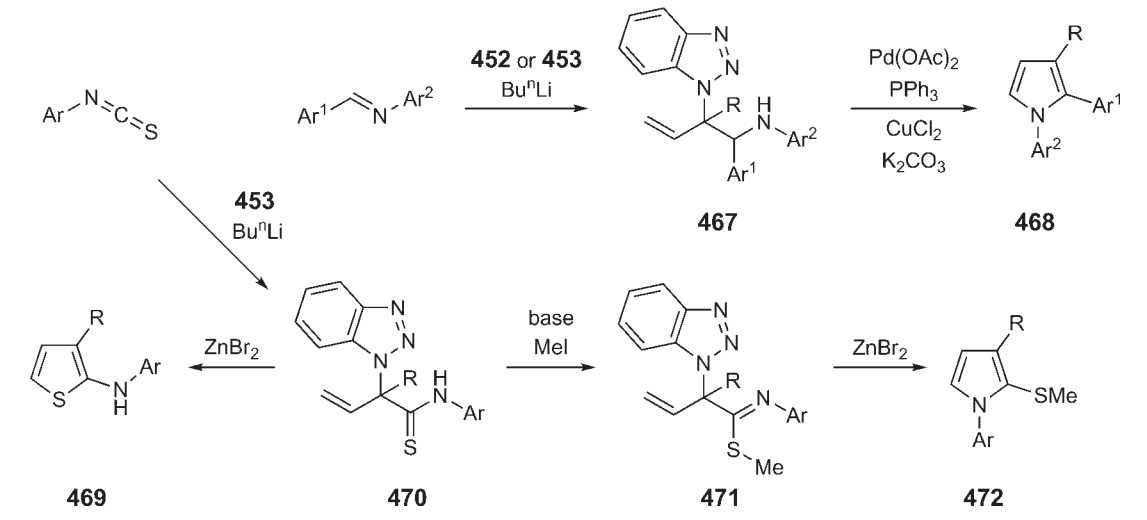
Reaction of lithiated allylbenzotriazole **452** with chloromethyltrimethylsilane yields silyl derivative **464** which can be further alkylated to give compound **465** (**Scheme 76**) <1999JOC1888>. Upon heating, product **465** is readily converted to diene **466** via vicinal elimination of benzotriazolyl and silyl substituents. Additions of lithiated silyl derivative **464** to carbonyl groups of aldehydes lead to alcohols **463** which readily eliminate benzotriazole and silane to furnish 2-(1-hydroxyalkyl)butadienes **466** (R^1 = 1-hydroxyalkyl).



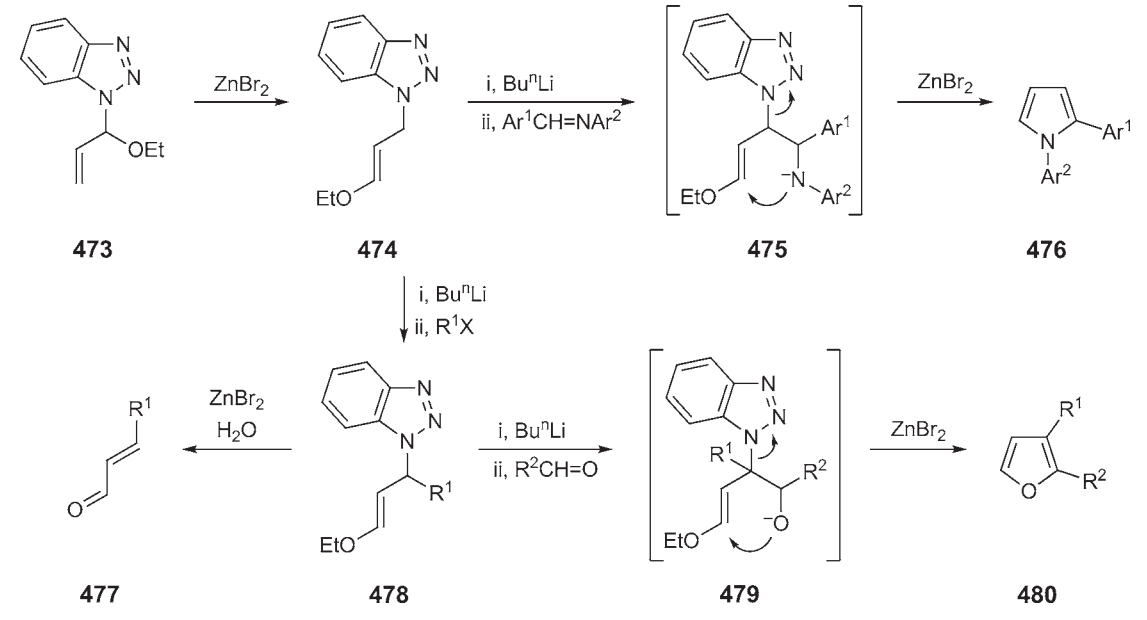
Scheme 76

Lithiated *N*-allylbenzotriazoles **452** and **453** add readily to the C=N bond of Schiff bases derived from aromatic or heteroaromatic aldehydes and amines to give amines **467**. In the presence of a palladium catalyst and copper(II) oxidizing agent, amines **467** are smoothly converted to pyrroles **468** (**Scheme 77**) <2000JOC8074>. Addition of lithiated allylbenzotriazoles **453** to the C=N bond of isothiocyanates leads to thioamides **470**. Catalyzed by $ZnBr_2$, thioamides **470** undergo cyclization to aminothiophenes **469** <2001JOC2850>. When the nucleophilic attack of the sulfur atom on the allylic system is blocked by methylation as in compound **471**, the nitrogen atom takes the leading role and 2-(methylthio)pyrroles **472** are formed instead.

When an additional leaving group is present at the allylic system, conversion of *N*-allylbenzotriazoles to five-membered heterocyclic rings is facilitated. Thus, α-ethoxy derivative **473** undergoes smooth rearrangement promoted by $ZnBr_2$ to give (γ-ethoxyallyl)benzotriazole **474**. After lithiation, the obtained anion is trapped by a Schiff base to give anion **475**. Catalyzed by $ZnBr_2$, intermediate **475** undergoes cyclization with elimination of benzotriazole and ethanol to furnish 1,2-diarylpyrrole **476** (**Scheme 78**) <1995S1315>. Alkylation of (γ-ethoxyallyl)benzotriazole **474** occurs exclusively at the carbon α producing derivatives **478**, which, in their lithiated forms, add readily to the carbonyl group of aldehydes. Obtained anions **479** are rapidly converted to 2,3-disubstituted furans **480** upon treatment with $ZnBr_2$ <1995S1315>. Treatment with $ZnBr_2$ and water converts ethoxyallyl derivatives **478** into α,β-unsaturated aldehydes **477**.



Scheme 77

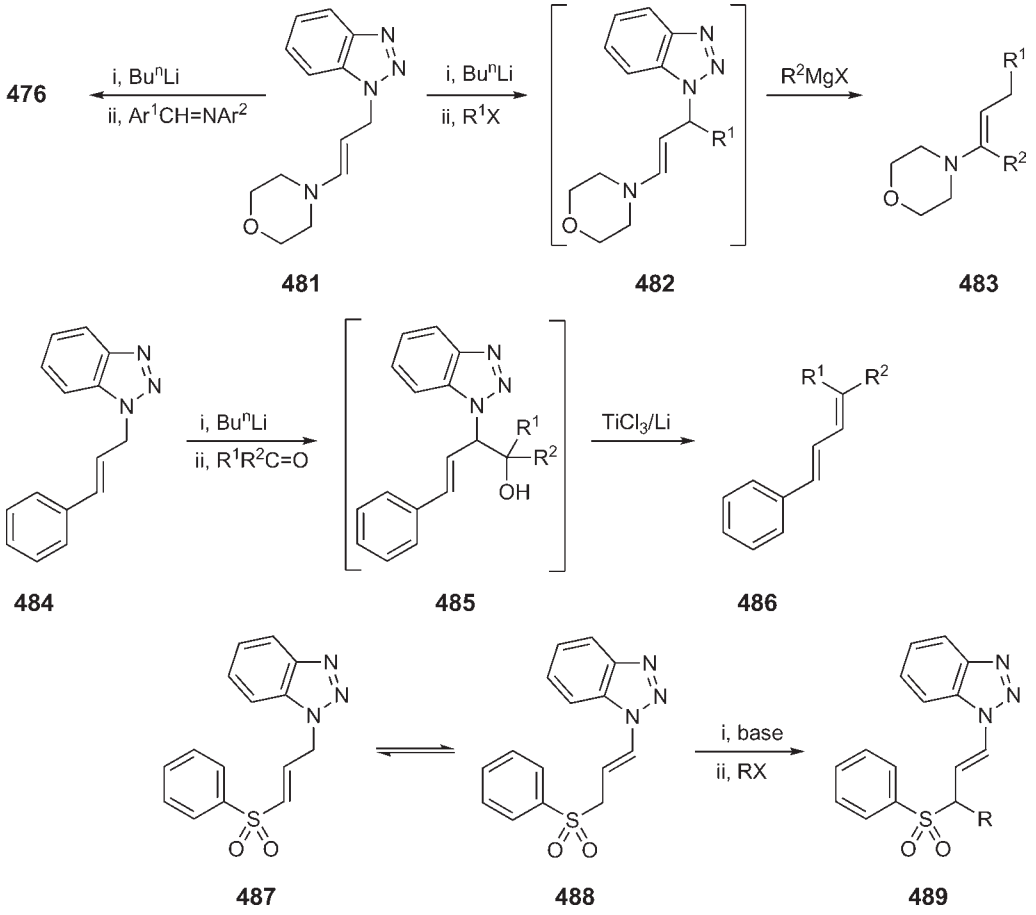


Scheme 78

The morpholin-4-yl substituent in γ-position behaves similarly to the ethoxy group. Compound **481** is easily prepared by double addition of benzotriazole to acrolein followed by elimination of one of the benzotriazolyl moieties induced by treatment with NaH. Lithiation of derivative **481** followed by addition to a Schiff base results in formation of diarylpyrrole **476**. Lithiated product **481** is alkylated exclusively at the carbon α, in relation to the benzotriazolyl substituent, giving intermediate **482**. Subsequent treatment with a Grignard reagent leads to enamine **483** (**Scheme 79**) <1995TL343>.

A phenyl substituent at the γ-carbon atom is a much weaker electron donor in comparison with the discussed above ethoxy and morpholin-4-yl groups. Nevertheless, 1-(γ-phenylallyl)benzotriazole **484** is still lithiated exclusively at the carbon α as it is evident from its reaction with aldehydes and ketones leading to dienes **486**, resulting from

elimination of benzotriazole and water from intermediate carbinols **485** <1997JOC238>. However, the strongly electron-withdrawing phenylsulfonyl group at the γ-carbon shifts the equilibrium from form **487** to form **488**, which upon its alkylation gives sole product **489** (**Scheme 79**) <1998JHC173>.

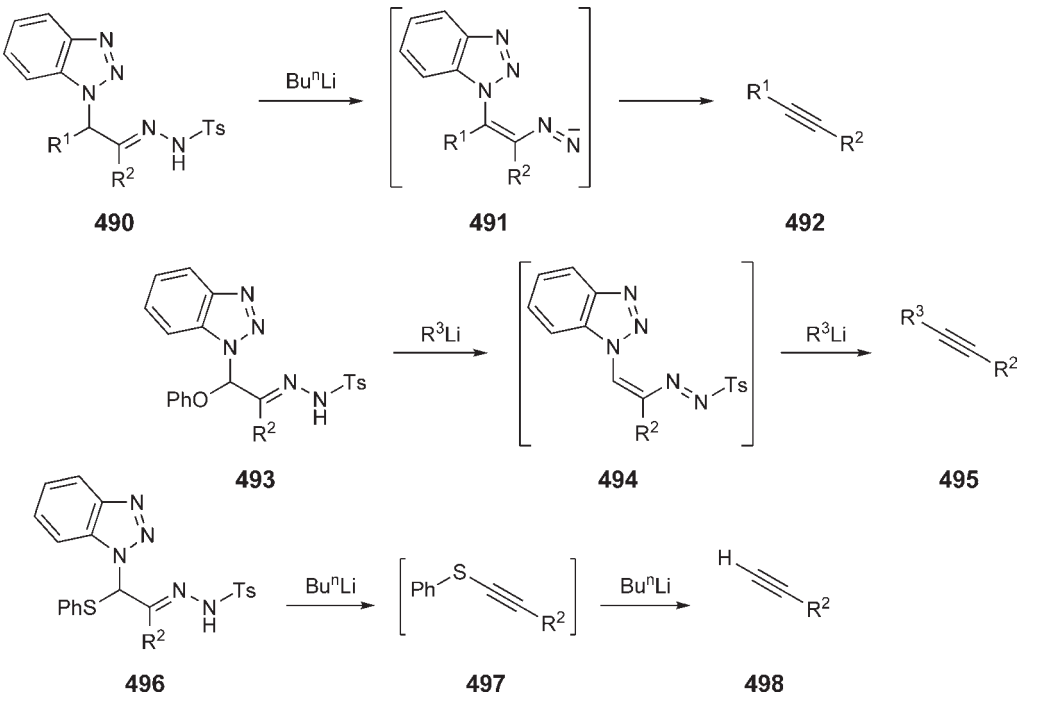


Scheme 79

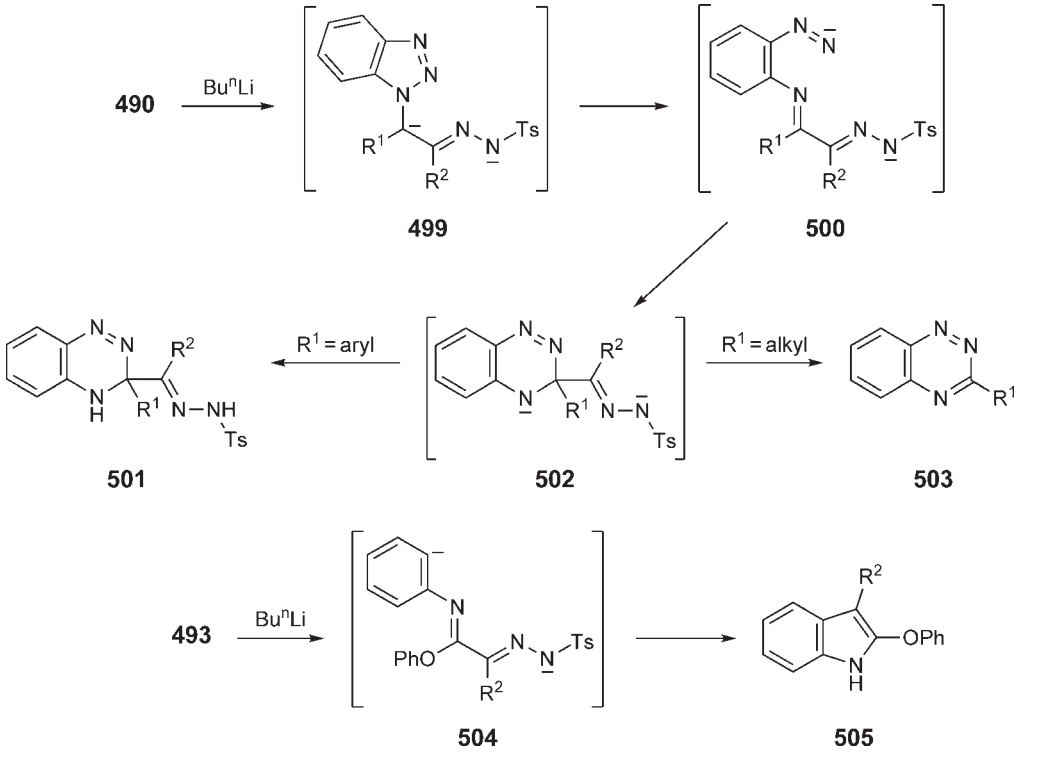
5.01.8.3 Ring N–C(sp^3)-C=N

Hydrazones **490** are readily obtained from the corresponding ketones. Upon treatment with 6 molar equivalents of n-butyllithium, they are deprotonated to dianions which lose rapidly the tosyl moiety to form anions **491** that further eliminate spontaneously N_2 and benzotriazole to give alkynes **492** (**Scheme 80**). In the special case, when R^1 = PhO (compound **493**), organolithium reagents eliminate first the phenoxy group to give intermediates **494**. Addition of group R^3 to **494** followed by elimination of tosylate, nitrogen and benzotriazole provides alkynes **495**. Due to the stronger electron-donating influence of the phenylthio group in compound **496**, the benzotriazolyl moiety is eliminated preferentially leading to unstable sulfide **497**, which is converted by excess Bu^{n}Li to acetylene **498** <1997JOC4142>.

Treated with only 3 molar equivalents of Bu^{n}Li, hydrazones **490** behave differently. Bond cleavage between N-1 and N-2 of the benzotriazole ring in the initial dianion **499** leads to dianion **500**. Following ring closure produces benzotriazine system **502**. The next step of the transformation sequence depends on substituent R^1. When R^1 is an aryl, the structure is stable enough to survive work-up as dihydrobenzotriazine **501**. When R^1 is an alkyl, the whole hydrazone group is eliminated producing benzotriazine **503** (**Scheme 81**) <1997SC3963>. When phenoxy derivative **493** is subjected to such treatment, the dianion formed, analogous to **500**, loses molecular nitrogen to give energetic dianion **504** that quickly undergoes cyclization/elimination to furnish indole **505**.



Scheme 80

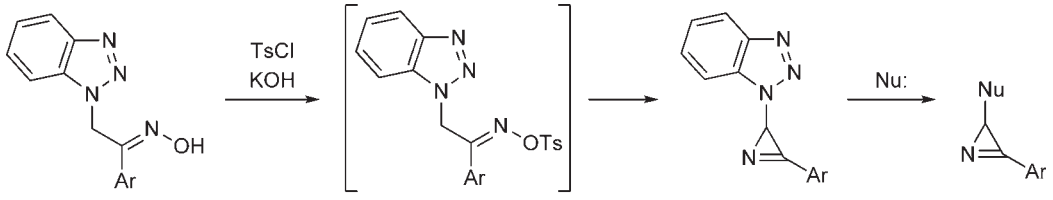


Scheme 81

Treated with thionyl chloride, hydrazones **490** ($R^1 = H$, $R^2 =$ aryl) undergo cyclocondensation to thiadiazoles **506**; whereas from aliphatic derivatives **490** ($R^1 = H$, $R^2 =$ alkyl), mixtures of thiadiazoles **507** and **508** are formed <2002H(58)311>.

506 **507** **508**

Oximes **509** can be converted to their tosylates **510**, but use of a large excess of KOH converts them directly into *2H*-azirines **511** (**Scheme 82**) <2003JOC9105>. The benzotriazolyl moiety in azirines **511** can be substituted by nucleophiles (organomagnesium reagents, potassium phthalimides, and sodium thiophenoxide) to give disubstituted azirines **512**.



509 **510** **511** **512**

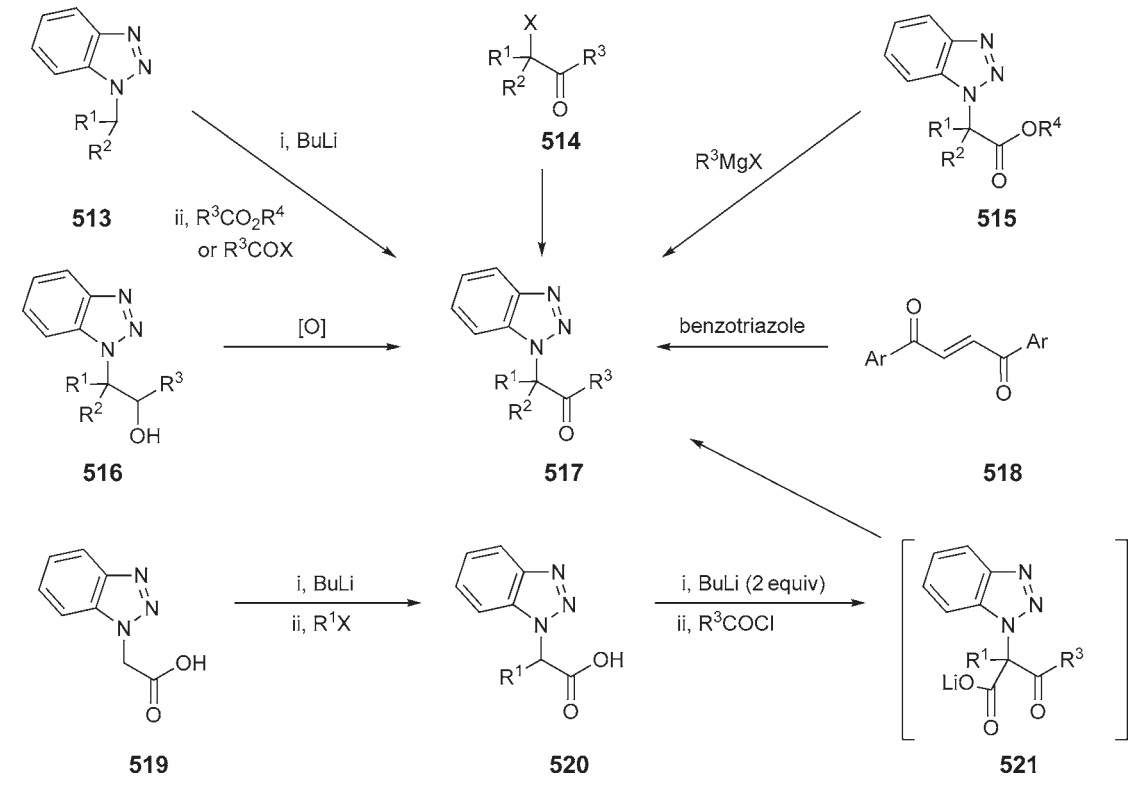
Scheme 82

5.01.8.4 Ring N–C(sp^3)-C═O

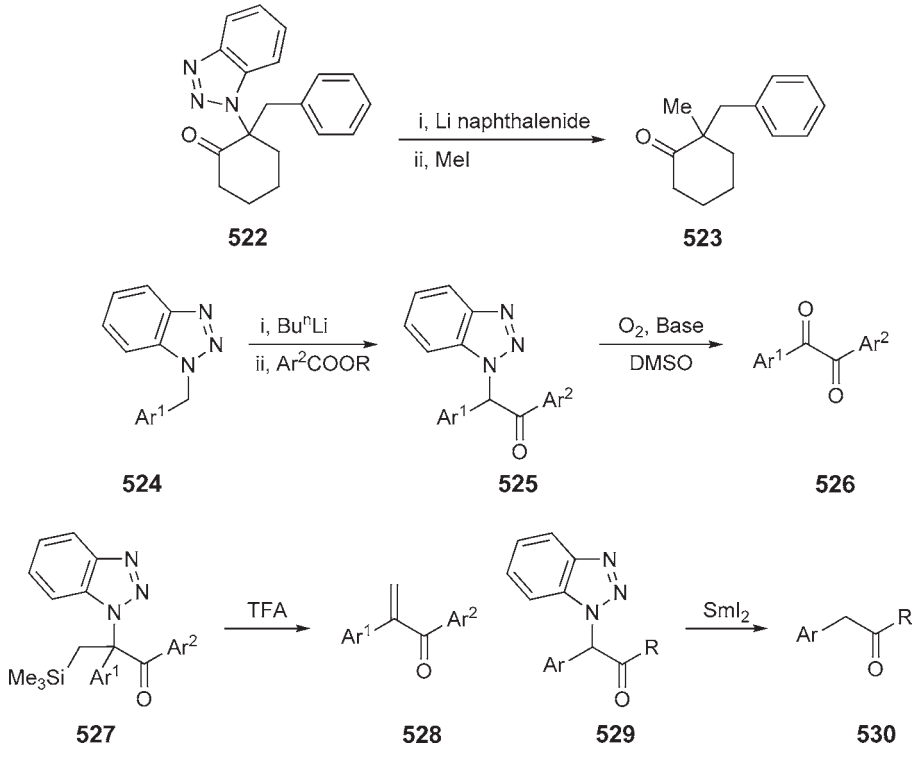
There are several methods available that lead to α-benzotriazolyl ketones **517** (**Scheme 83**). Thus, the anions derived from *N*-alkylbenzotriazoles **513** can be trapped by acid chlorides or esters <1998JOC3438, 1998H(48)1567>. Alternatively, in reactions with aldehydes, *N*-alkylbenzotriazoles **513** are converted to β-benzotriazolyl alcohols **516** that are consecutively oxidized to ketones **517** <1996LA1235>. Other approaches include substitution of halogens in α-haloketones **514** by benzotriazole, <2000JHC167, 2002ARK(iii)46>, reactions of esters of α-benzotriazolylcarboxylic acids **515** with Grignard reagents <1997JOC4142>, addition of benzotriazole to but-2-ene-1,4-diones **518** <1992PJC1633>, and reactions of *N*-chlorobenzotriazole with trimethylsilyl derivatives of the corresponding ketones <1998JCM334>. In an interesting modification of the above methods, benzotriazoleacetic acid **519** <1935LA113> is alkylated to produce carboxylic acids **520**, which are then dilithiated and treated with acyl halides to give ketones **517**, via unstable intermediates **521** <2004ARK(iii)22>.

Removal of the benzotriazole moiety from ketones **517** can be accomplished in several modes. Thus, treatment of derivative **522** with lithium naphthalenide followed by methyl iodide provides ketone **523** in 51% yield (**Scheme 84**) <2002ARK(iii)46>. Upon treatment with buthyllithium, anions derived from 1-(arylmethyl)-benzotriazoles **524** can be trapped by esters of arylcarboxylic acids to give ketones **525** which are readily oxidized with molecular oxygen under mild conditions to give diaryl 1,2-diketones **526** in good yields. This provides a convenient synthetic method for unsymmetrical 1,2-diketones, especially valuable when Ar^1 and Ar^2 are heterocyclic systems <2005JOC3271>. When trimethylsilyl derivatives **527** are treated with TFA in dichlorometane, both the trimethylsilyl and benzotriazolyl groups are eliminated to provide 1,2-diarylpropen-1-ones **528** in high yields <1998JOC9983>. Heating of ketones **527** with CsF in DMF yields also propenones **528**, but usually a rearrangement occurs and the corresponding chalcones are the main products <1998J(P2)2515>. Samarium iodide induced removal of benzotriazole from ketones **529** works well with variety of groups R to provide ketones **530** in high yield under mild reaction conditions <1998H(48)1567>.

[3+3] Annulation reaction of (benzotriazol-1-yl)acetone **531** with chalcones provides an efficient route to 3,5-diarylphenols **538**. The reaction is catalyzed by NaOH in ethanol. In the first step, Michael addition of ketone **531** to the C═C bond of a chalcone gives diketone **532**. In the second step, condensation between the carbonyl

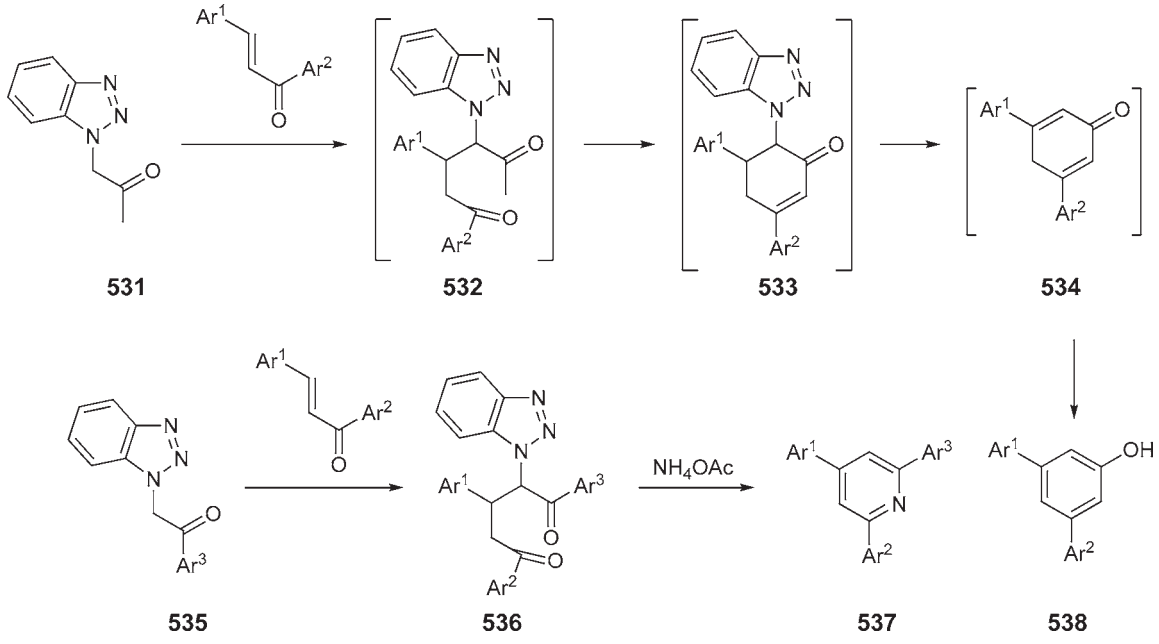


Scheme 83



Scheme 84

group at Ar^2 with the methyl group gives cyclohexenone **533**. In the following steps, benzotriazole is eliminated, and the obtained cyclohexadienone **534** rearranges to phenol **538** (**Scheme 85**) <1997JOC8215>. Diketones **536**, obtained by Michael addition of (benzotriazol-1-yl)acetophenones **535** to chalcones, cannot undergo such cyclocondensation to form phenols, but they react readily with ammonium acetate to give pyridines **537** <1999S2114>.



Scheme 85

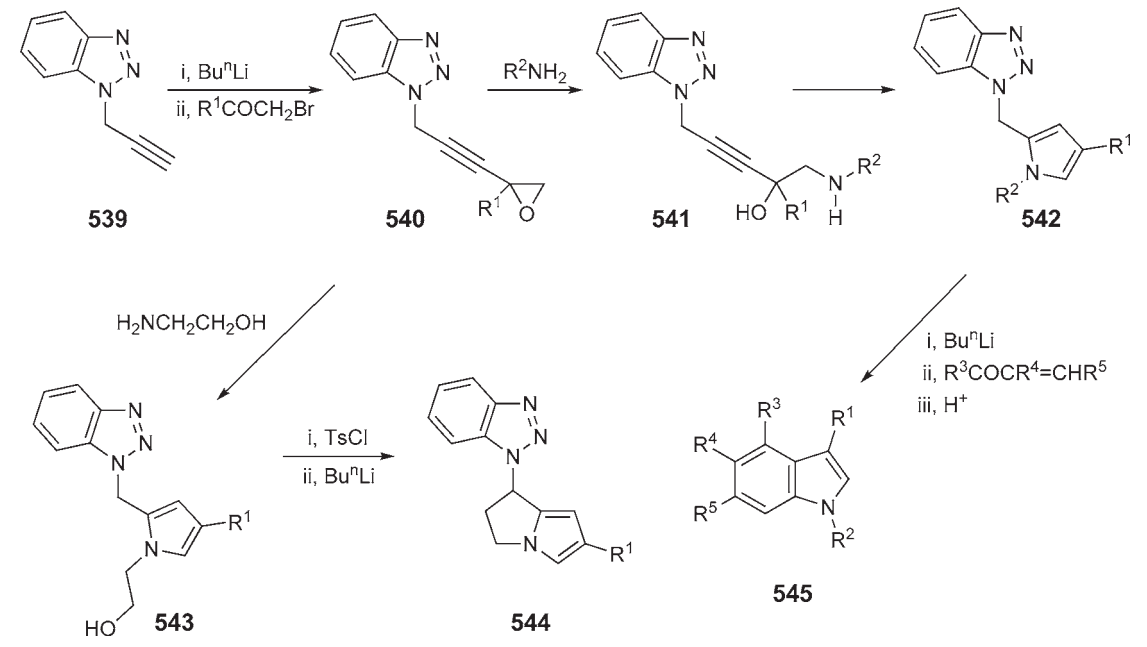
5.01.8.5 Ring N–C(sp^3)-C(sp)

Some chemistry of propargylbenzotriazole **539** and its applications in organic synthesis is already described in CHEC-II(1996) <1996CHEC-II(4)1>. Further development in this field led to very useful oxirane derivatives **540** <1995JOC638>. Primary amines in refluxing isopropanol cause opening of the oxirane ring with addition of the amine to form aminoalcohols **541** that undergo spontaneous intramolecular cyclocondensation to give pyrroles **543** (**Scheme 86**). The benzotriazolyl moiety in **542** can be directly substituted with nucleophiles or the molecule can be first lithiated at its α-carbon then treated with electrophiles and finally the benzotriazolyl group be removed to provide further classes of substituted pyrroles <1996JOC1624>.

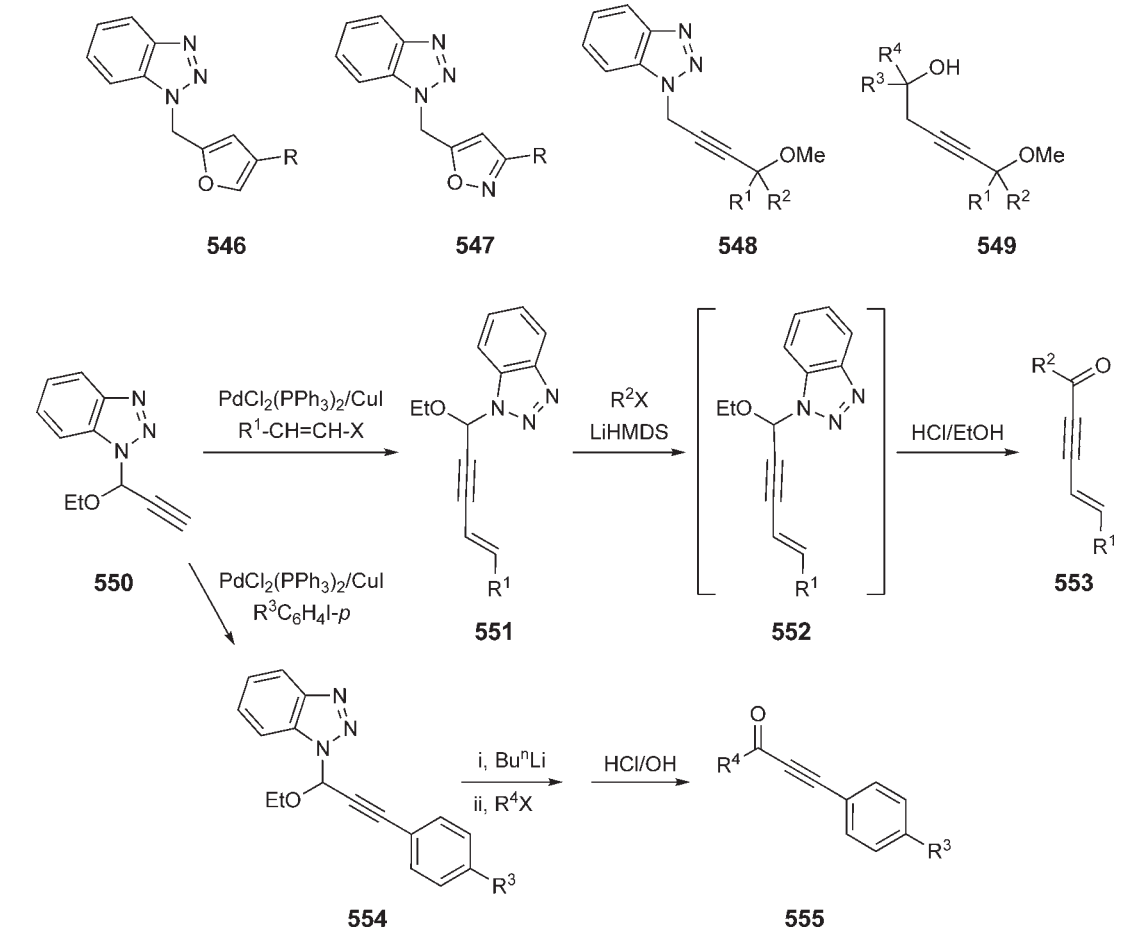
1-(2-Hydroxyethyl)pyrroles **543** obtained from reactions of oxiranes **540** with 2-aminoethanol are readily converted to 2,3-dihydro-1*H*-pyrrolo[1,2-a]pyrroles **544** <1997JOC4148>. Analogously, 1-(3-hydroxypropyl)pyrroles give homologous 5,6,7,8-tetrahydropyrrolo[1,2-a]pyridines. Easy manipulation with the benzotriazolyl moiety allows for convenient synthesis of a wide variety of fused [1,2-a]pyrroles. A similar chemistry of indoles is also described <1997JOC4148>.

Lithiated pyrrole derivative **542** undergoes Michael addition to α,β-unsaturated aldehydes or ketones, and the obtained adducts readily undergo cyclization to indoles **545** in the presence of acids as catalysts <1996TL5641>. Similarly, lithiated 2-[(benzotriazol-1-yl)methyl]furans **546**, obtained from oxiranes **540** by their cyclization promoted by Bu^{t}OK, react with α,β-unsaturated aldehydes or ketones to provide benzofurans <1997JOC8205>. 1,3-Dipolar cycloaddition of propargylbenzotriazole **539** to nitrile oxides (R-C≡C-N═O) gives oxazoles **547** in excellent yields <2000JHC1505>. Addition of lithiated propargylbenzotriazole **539** to aldehydes or ketones followed by methylation with iodomethane provides ethers **548**. Treatment with metallic lithium and the same or different aldehydes or ketones R^3R^4C═O converts ethers **548** into protected alkynediols **549** <1999TL253>.

Introduction of an alkoxy group to the α-carbon opens new possibilities regarding transformation and benzotriazole removal process from 1-propargylbenzotriazole. Thus, ether **550** <1995JOC7612> can be coupled with vinyl triflates or bromides to give enynyl products **551**. Following alkylation at the carbon α gives unstable derivatives **552** that are readily hydrolyzed to enynyl ketones **553**. In another approach, alkynes **550** are coupled with aryl iodides, and the obtained ethers **554** are alkylated and hydrolyzed to ketones **555** (**Scheme 87**) <1997JOC8201>.

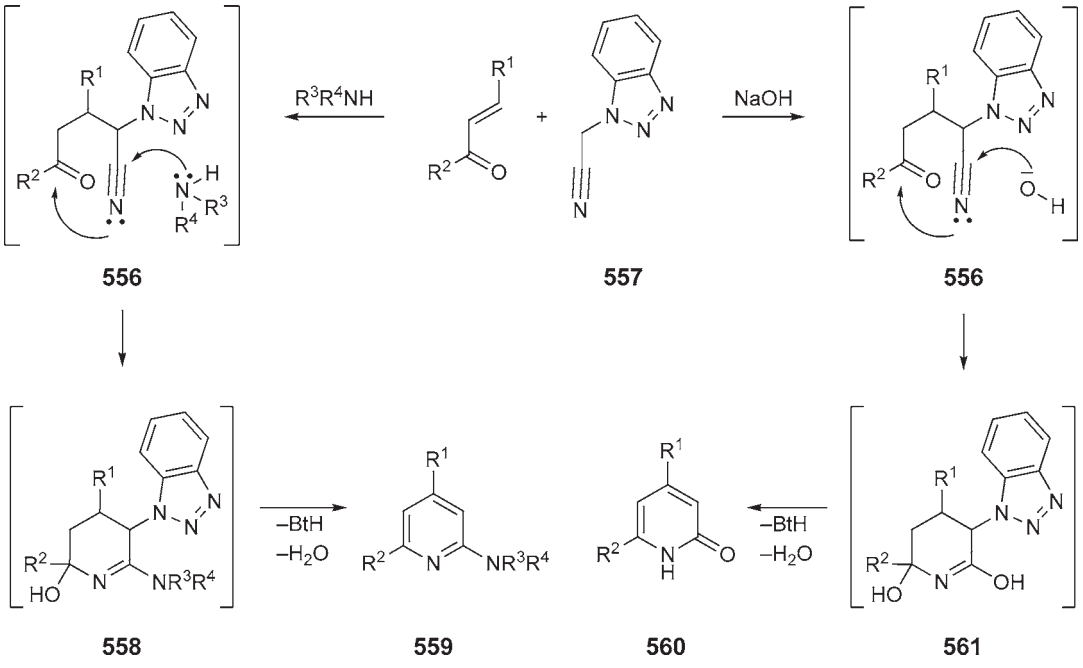


Scheme 86



Scheme 87

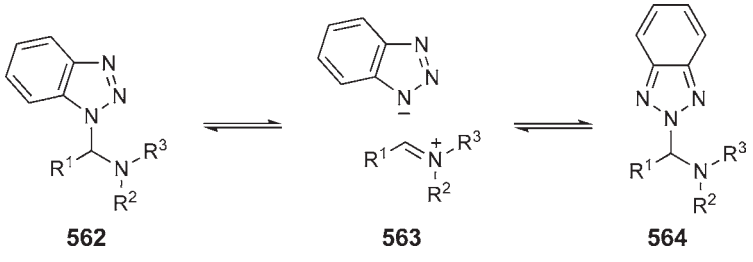
Michael addition of (benzotriazol-1-yl)acetonitrile **557** to α,β-unsaturated ketones followed by heterocyclization provides new means for preparation of 2,4,5-trisubstituted pyridines. The reaction is catalyzed by bases. In the presence of secondary amines, a nucleophilic attack of amine on the CN group in adduct **556** initiates the cyclization to tetrahydropyridine **558** that subsequently eliminates water and benzotriazole to give pyridine **559**. Analogously, in the presence of NaOH, pyridone **560** forms, via intermediate **561** (**Scheme 88**) <1997JOC6210>.



Scheme 88

5.01.8.6 Ring N–C(sp^3)-N

In solution, 1-(α-aminoalkyl)benzotriazoles **562** are in equilibrium with iminium cation **563** and hence with their benzotriazole-2-yl isomers **564** (**Scheme 89**). Protonation or complexation of the benzotriazolyl moiety (e.g., Mg, Zn, B, Al reagents) facilitates the transformation. Intermediate iminium cations **563** can be trapped by nucleophiles providing synthetic pathways to various amines. Many such reactions are described in CHEC-II(1996) <1996CHEC-II(4)1>, and some newer results are compiled in reviews <2005T2555>.

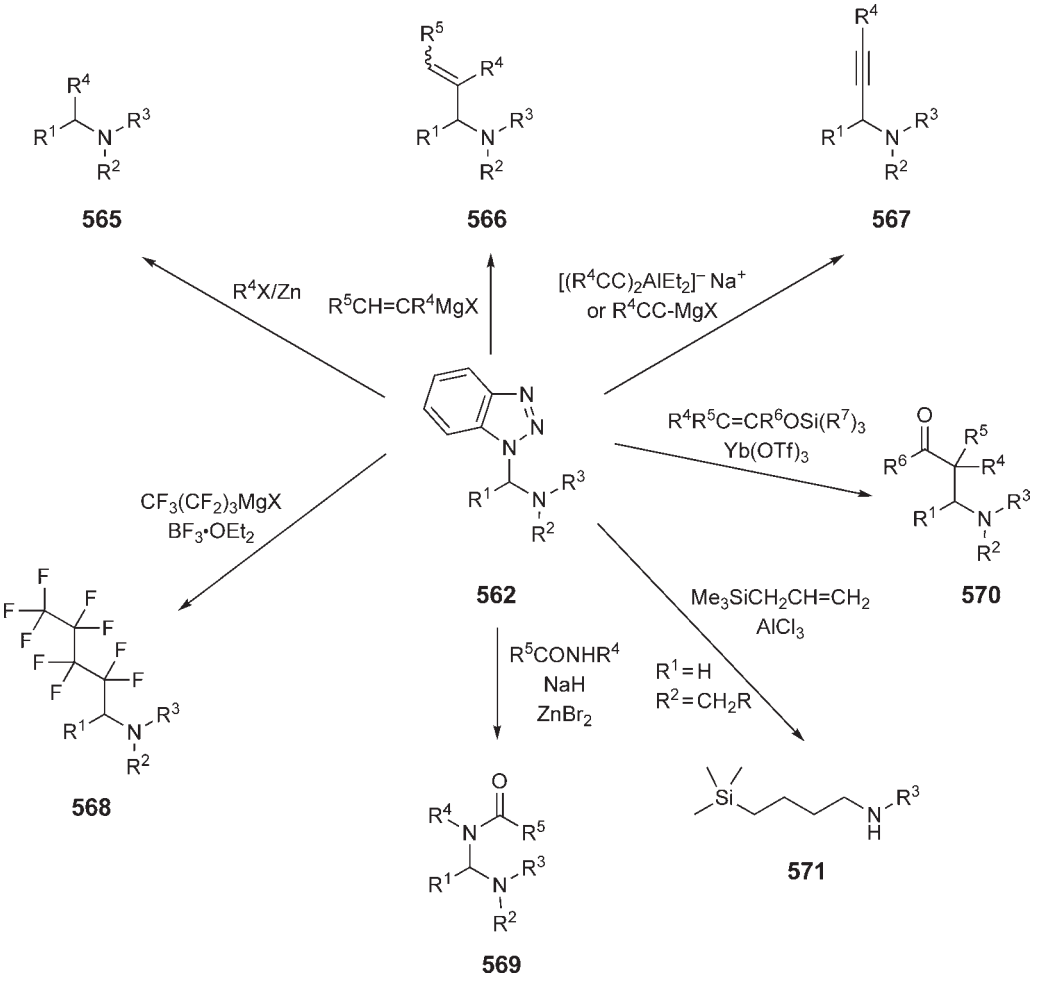


Scheme 89

For clarity, in the following schemes of this subsection, the benzotriazol-2-yl structures are often omitted when such derivatives are present in the reaction mixtures, and their chemistry is not different from that of the benzotriazol-1-yl derivatives. When there is a clear distinction in chemistry, the benzotriazol-2-yl isomers are treated separately.

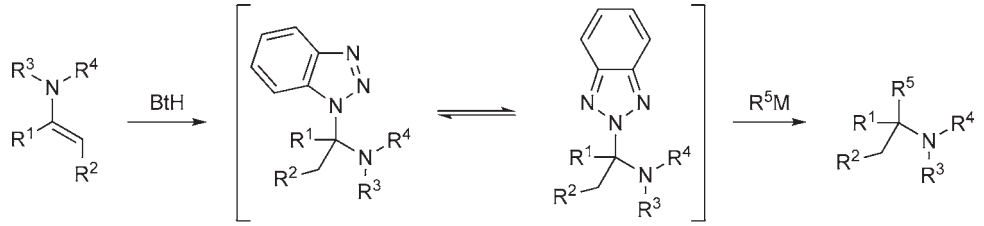
5.01.8.6.1 Substitution of benzotriazole with nucleophiles

Since the publication of CHEC-II(1996), the range of nucleophiles used for substitution of the benzotriazolyl moiety in derivatives **562** and applied reaction conditions have been widely expanded. Thus, treatment of benzotriazolyl amines **562** with organozinc bromoacetate, provides conveniently amines **565** (**Scheme 90**) <1998T7167. This extends the scope of this reaction to substituents bearing groups sensitive to organomagnesium reagents previously used for this purpose <1996CHEC-II(4)1>. Reactions of intermediates **562** with alkenylmagnesium and alkynylmagnesium reagents carried out in toluene lead to allylamines **566** and propargylamines **567** in excellent yield <2002S199>. Less stable perfluoroalkylmagnesium reagents give amines **568** when the reactions are carried out at low temperature with additional activation of derivatives **562** with trifluoroboron etherate <1997TL7015>. Propargylamines **567** can be also conveniently prepared in reactions of compound **562** with dialkynyldiethylaluminates <1999JOC488>. Treatment of benzotriazolyl derivatives **562** activated by addition of $ZnBr_2$ with sodium salts of amides allows preparation of acylaminals **569** <1998S1421>. *N*-(α-Aminoalkyl)benzotriazoles **562** react smoothly with silyl enolates in the presence of lanthanide catalysts to provide aminoketones **570** (R^6 = Ph) or aminoesters **570** (R^6 = alkoxy or phenoxy group) in practically quantitative yields <1996TL3731>. In the presence of aluminium chloride, the iminium cations derived from 1-[(dialkylamino)methyl]benzotriazoles **562** (R^1 = H) add to the C-3 atom of allyltrimethylsilane, and the obtained adducts rearrange to aminosilanes **571** via a 1,5-hydride shift from group R^2 to C-2 of the allyl system <1999OM4270>. Polymer-bound derivatives **562** provide a convenient tool for combinatorial synthesis of compound libraries <1999JCO173>.



Scheme 90

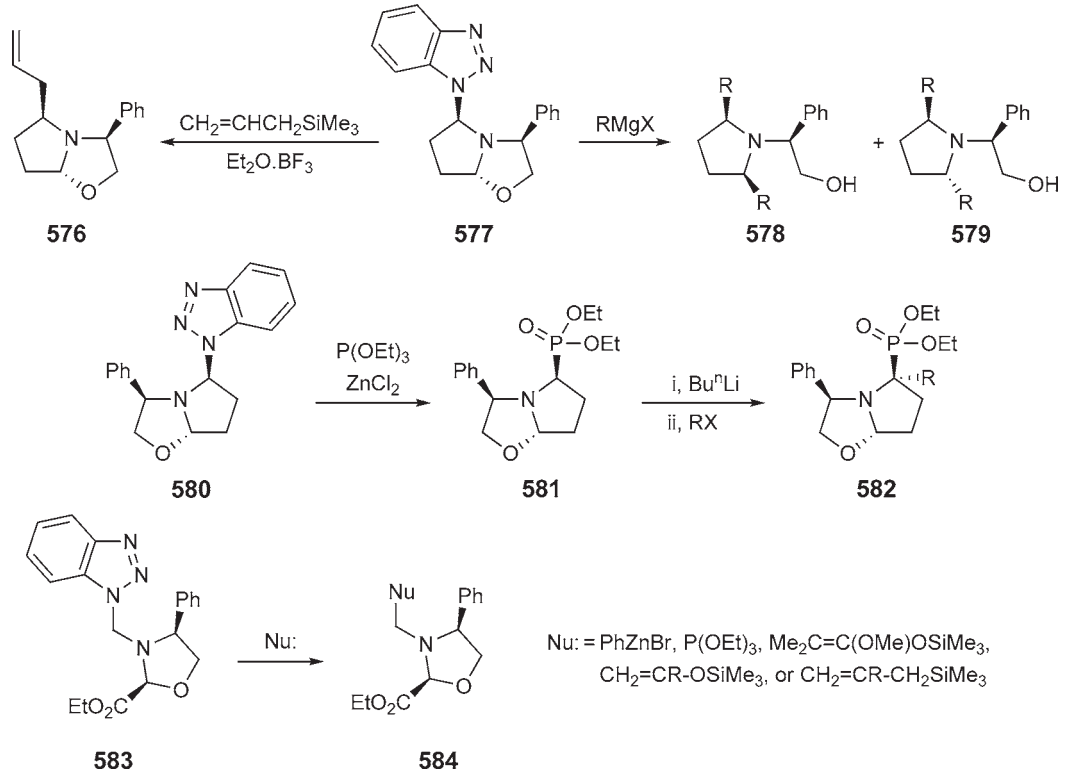
Addition of benzotriazole to enamines **572** derived from cyclic or acyclic dialkyl ketones gives α-aminoalkylbenzotriazoles **573–574**, in which the benzotriazole moiety can be easily substituted by an alkyl, aryl, alkenyl, or alkynyl group in reactions with appropriate organomagnesium or organolithium reagents to form corresponding tertiary amines **575** (**Scheme 91**). This approach extents the scope of *tert*-alkylation of secondary amines <2005JOC286>.



572 **573** **574** **575**

Scheme 91

Condensation of succinaldehyde (obtained by hydrolysis of 2,5-dimethoxyfuran) with benzotriazole and (*S*)-2-phenylglycinol provides (*3S,5R,7aR*)-5-(benzotriazole-1-yl)-3-phenyl[2,1-*b*]oxazolopyrrolidine **577** (**Scheme 92**). Oxazolopyrrolidine **577** is a convenient synthon for asymmetric syntheses of 2-substituted and 2,5-disubstituted pyrrolidines. Thus, in a reaction with allyltrimethylsilane, the benzotriazolyl moiety is substituted with an allyl group to provide derivative **576**. Hydrogenation of product **576** cleaves the chiral auxiliary to give (*2R*)-2-propylpyrrolidine. Alternatively, reactions of intermediate **576** with Grignard reagents lead to chiral 2,5-disubstituted pyrrolidines <1999JOC1979>. Direct treatment with organomagnesium reagents converts oxazolopyrrolidine **577** into mixtures of *cis* **578** and *trans* **579** 2,5-disubstituted pyrrolidines that can easily be separated by chromatography



576 **577** **578** **579**

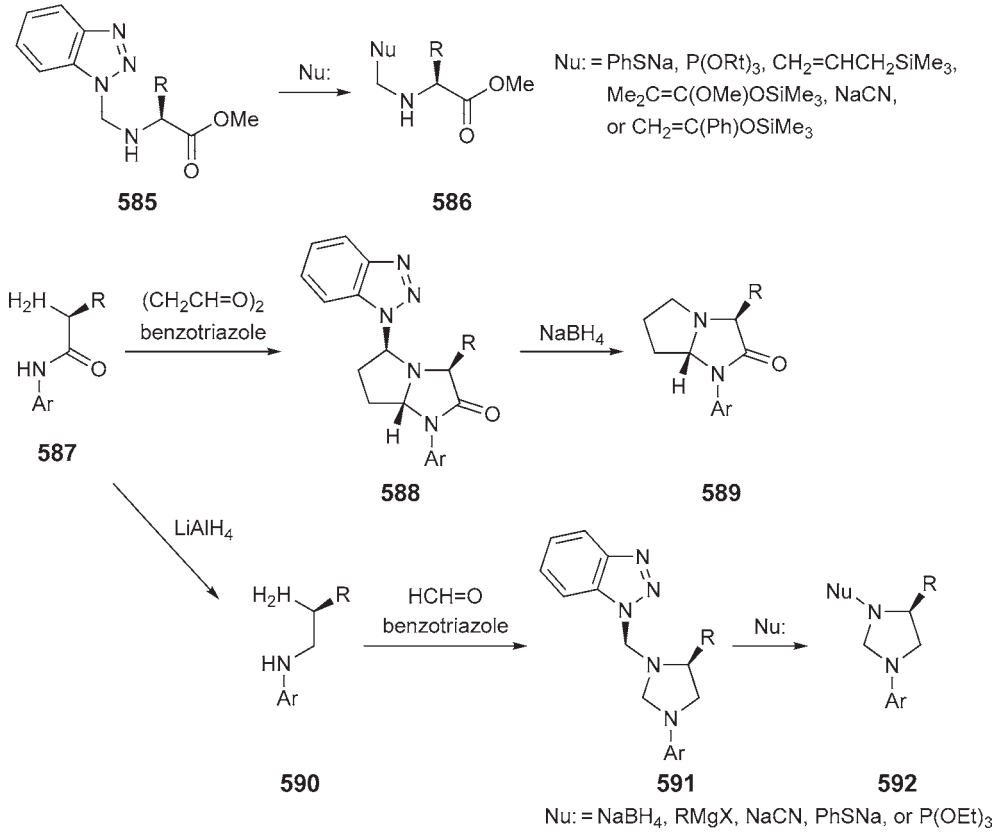
580 **581** **582**

583 **584**

Scheme 92

<1998TL1697>. Again, hydrogenation removes readily the chiral auxiliary from the nitrogen atom in intermediates **578** and **579**. Similar treatment of the piperidine analog of compound **577**, obtained by condensation of glutaraldehyde with benzotriazole and (*S*)-2-phenylglycinol leads to chiral 2,6-disubstituted piperidines <1998JOC6699>. Chiral (pyrrolidin-2-yl)-phosphonates are obtained from oxazolopyrrolidine **580** (prepared by condensation of 2,5-dimethoxytetrahydrofuran with benzotriazole and (*R*)-phenylglycinol) which reacts with triethyl phosphite to give intermediate **581** that is alkylated to produce derivatives **582** and finally deprotected by hydrogenation <2004TL5175>. Condensation of ethyl glyoxylate with (*S*)-2-phenylglycinol and formaldehyde gives *N*-[(benzotriazol-1-yl)methyl]oxazolidine **583** in which the benzotriazolyl moiety can be substituted with various nucleophiles in the presence of $ZnBr_2$ to provide chiral N-substituted oxazolidines **584** <1999JCM162>.

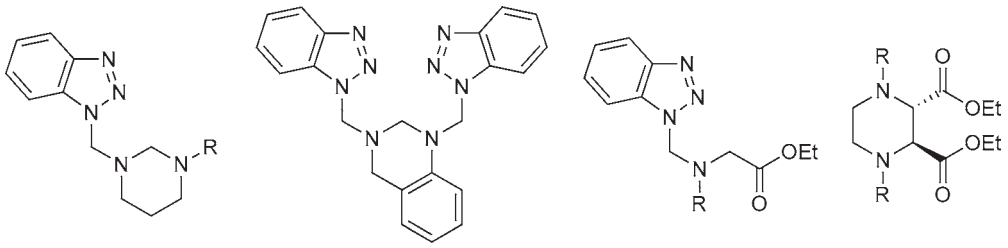
Derivatives of optically active α-aminocarboxylic acids are also used successfully in reactions with aldehydes and benzotriazole. Condensation of esters of α-aminocarboxylic acids with formaldehyde and benzotriazole gives derivatives **585** in which the benzotriazolyl moiety can be substituted by nucleophiles to give various products **586** (**Scheme 93**) <2003JOC9088>. Amides **587** derived from α-aminocarboxylic acids undergo condensation with succinaldehyde and benzotriazole to give benzotriazolyl derivatives **588** from which the benzotriazolyl group can be readily removed by treatment with sodium borohydride to furnish optically active tetrahydro-1*H*-pyrrolo[1,2-*a*]-imidazol-2-ones **589** <2002JOC4951>. Analogous reactions with glutaraldehyde provide corresponding hexahydro[1,2-*a*]pyridin-2(3*H*)-ones <2002JOC4951>. Diamines **590** obtained by reduction of amides **587** with lithium aluminium hydride undergo condensation with benzotriazole and two molecules of formaldehyde to give derivatives **591** in which the benzotriazolyl moiety is easily substituted by various nucleophiles to provide unsymmetrically substituted chiral imidazolidines **592** <2002JOC3109>.



Scheme 93

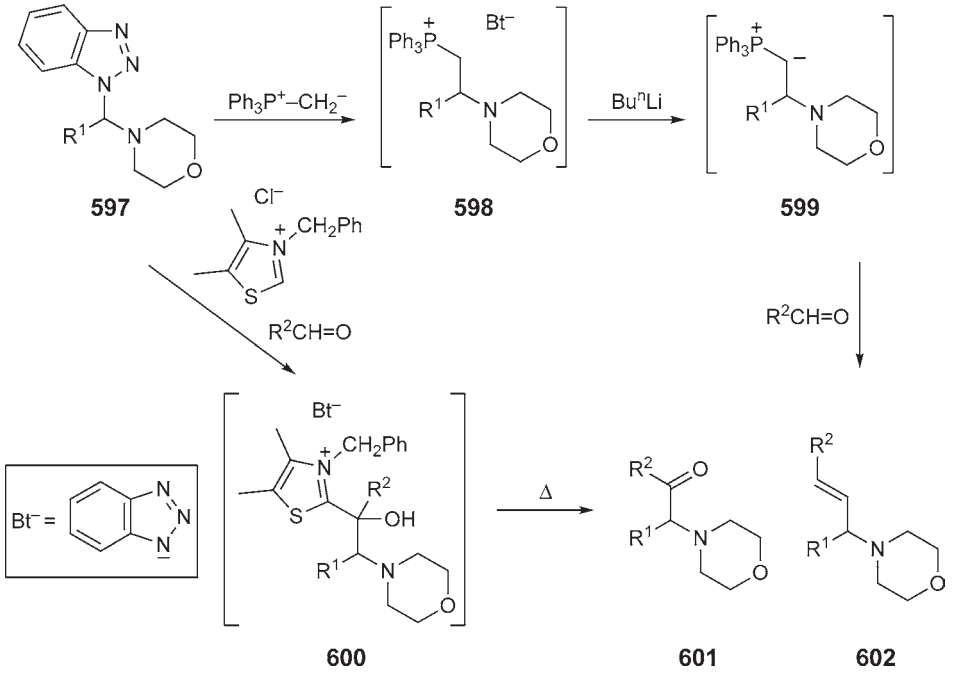
Similarly to imidazolines **591**, derivatives **593**, obtained by condensation of monosubstituted 1,3-propanediamines with formaldehyde and benzotriazole, react with organomagnesium reagents to give corresponding hexahydropyrimidines bearing two different substituents on the nitrogen atoms <2002JOC3115>. Analogously, condensation of

2-aminobenzylamine with formaldehyde and benzotriazole produces compound **594** in which the benzotriazolyl groups can be substituted by treatment with organomagnesium reagents or other strong nucleophiles. The conversion can be carried out stepwise with two different Grignard reagents, first substituting the more reactive benzotriazolyl group connected to the nitrogen atom in position 3 <2002JOC3115>. Treatment of benzotriazolyl derivatives **595**, originating from glycine, with sodium hydride in refluxing THF results in esters of *trans*-2,3-piperazinedicarboxylic acid **596**, although formation of aziridine systems could be anticipated <1996HCO1996>. The molecular structure of products **596** is confirmed by NMR and X-ray crystallographic data, but the mechanism of their formation is not yet clear.



593 **594** **595** **596**

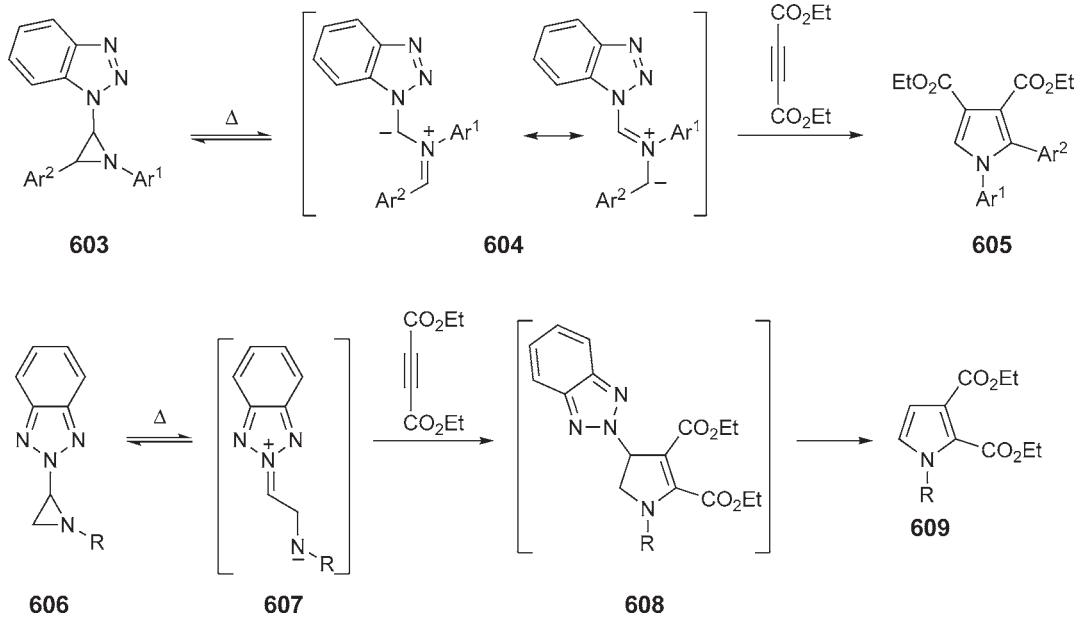
The ylide obtained from (methyl)triphenylphosphonium bromide reacts with morpholine derivatives **597** to give phosphonium salts **598** which upon treatment with *n*-butyllithium are converted to new ylides **599**. In a reaction with aldehydes, ylides **599** form *N*-(1,3-disubstituted allyl)-morpholines **602** (**Scheme 94**) <1996AQ138>. Another less common nucleophile that can be used for substitution of the benzotriazolyl moiety in *N*-(α-aminoalkyl)benzotriazoles is an adduct of *N*-benzylthiazolium salt to an aldehyde which reacts with compounds **597** to produce adducts **600**. Under the reaction conditions, refluxing in acetonitrile, salts **600** decompose to liberate aminoketones **601** <1996H(42)273>.



597 **598** **599** **600** **601** **602**

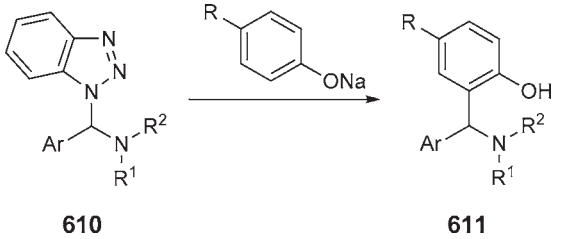
Scheme 94

Due to the high strain energy of a three-membered ring, an interesting case is represented by benzotriazolylaziridines. Upon heating, the C–C bond of the aziridine ring in (benzotriazol-1-yl)aziridines **603** is cleaved to give azomethine ylides **604** that can be trapped by diethyl acetylenedicarboxylate to form unstable pyrroline intermediates which consecutively eliminate benzotriazole to furnish pyrroles **605** (**Scheme 95**). By contrast, in (benzotriazol-2-yl)aziridines **606**, the C-N bond is cleaved, and the dipolar species **607** undergo [3+2] cycloaddition to acetylenedicarboxylate to form pyrrolines **608** that aromatize to pyrroles **609** by elimination of benzotriazole <1999JOC346>.



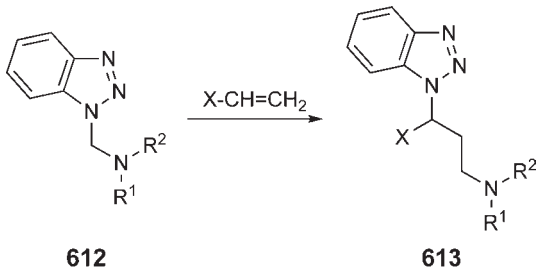
Scheme 95

1-[α-(Dialkylamino)benzyl]benzotriazoles **610**, obtained by condensation of benzaldehydes with benzotriazole and dialkylamines, react with sodium phenoxides to produce 2-[α-(dialkylamino)benzyl]phenols **611** (Equation 13). Derivatives of heterocyclic aldehydes (Ar = pyridin-4-yl, pyridin-3-yl, or thiophen-2-yl) react similarly <1999JOC6071>. As a practical example of such approach may serve derivatization of 4,13-diaza-18-crown-6-ether that is first condensed with benzotriazole and formaldehyde, and then the benzotriazolyl moiety is substituted with 7-hydroxycoumarin <1996JOC7585>.



(13)

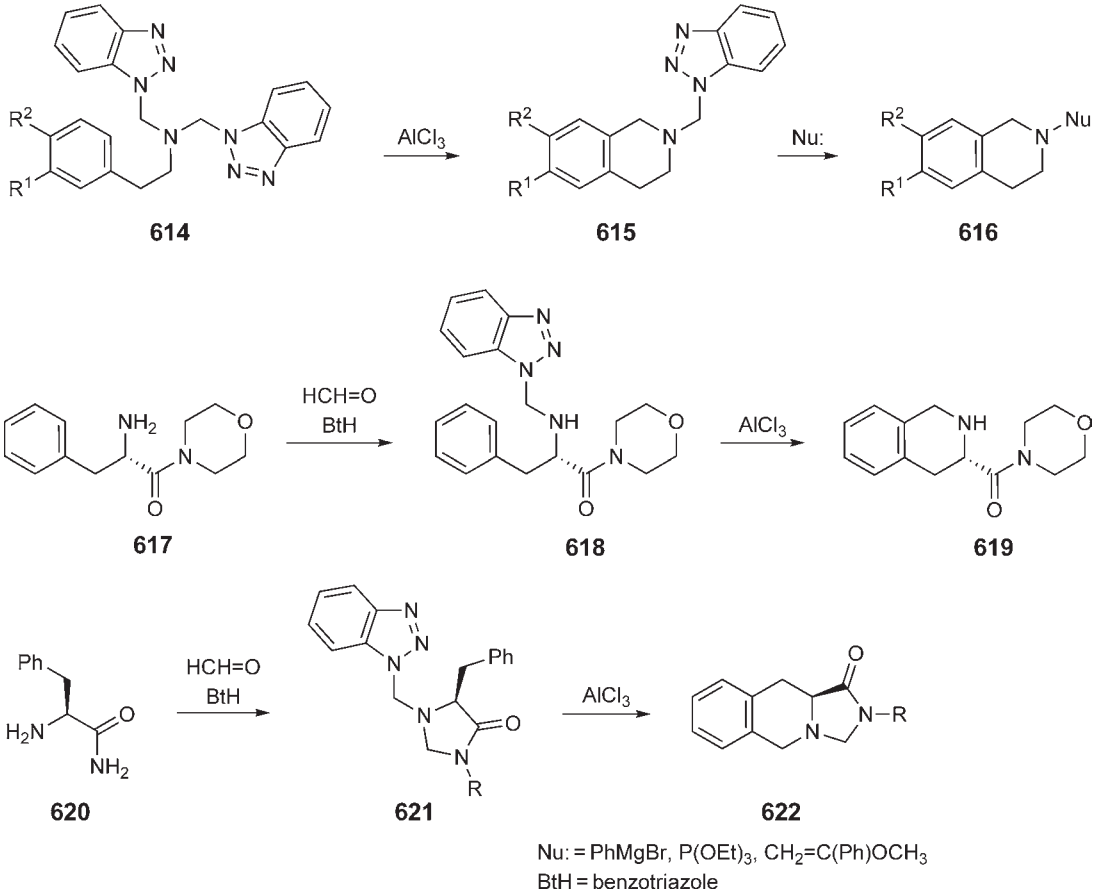
1-(Aminomethyl)benzotriazoles **612** react with electron-rich vinyl groups to give adducts **613** in which the link between the benzotriazolyl moiety and the amine nitrogen atom is extended by two atom units (Equation 14). The benzotriazolyl in its new position still can be substituted with various nucleophiles allowing rapid building of interesting molecules <1996JOC7585>.



(14)

5.01.8.6.2 Cyclocondensation

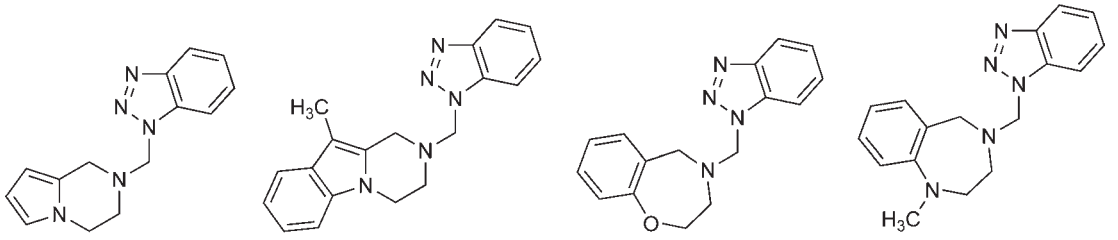
When a nucleophile is already attached to the molecule of *N*-(α-aminoalkyl)benzotriazole **562** (**Scheme 89**) as substituent R^2 or R^3, it may trap liberated iminium cation **563** with formation of a heterocyclic ring. The simplest case is represented by derivatives **562** with an electron-rich aromatic ring in a proper distance on one of the amino group substituents. Three examples of [5+1] cyclocondensation of this type (the five-atom unit comes from phenethylamines and the one atom piece comes from formaldehyde) are shown in **Scheme 96** <2001TA2427>. Thus, upon treatment with $AlCl_3$, an iminium cation generated from *N*,*N*-bis[(benzotriazol-1-yl)methyl]phenethylamine **614**, by cleavage of one of the bonds with benzotriazole, attacks the phenyl ring in its *ortho* position to produce *N*-[(benzotriazol-1-yl)methyl]-tetrahydroisoquinoline **615**. The second benzotriazolyl group can be removed by regular substitution with nucleophiles as discussed above to give tetrahydroisoquinoline **616**. Two additional



Scheme 96

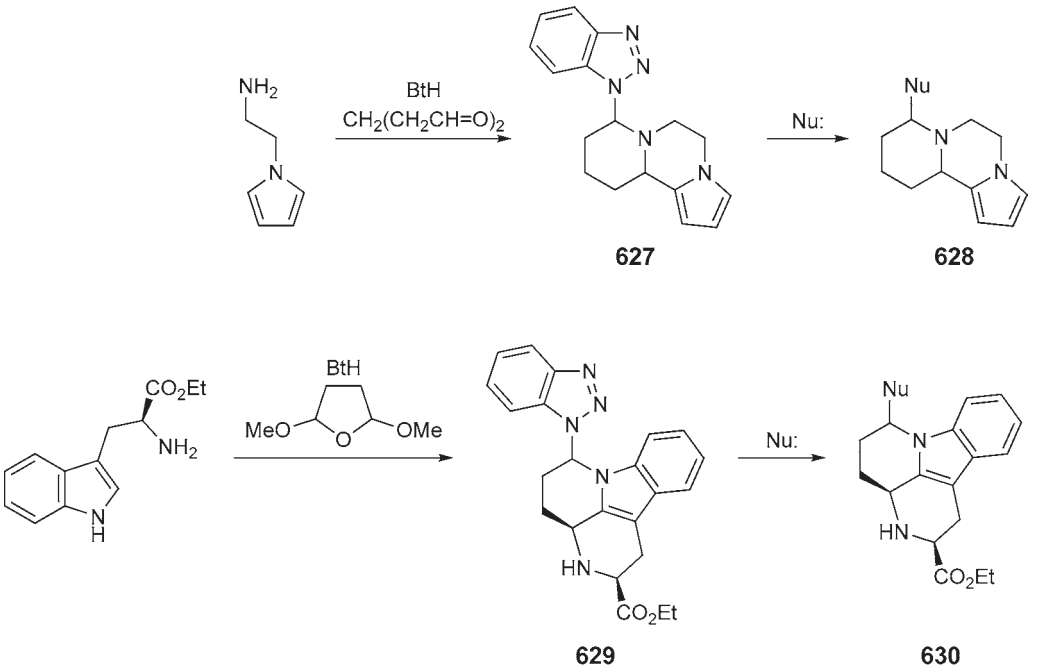
examples in **Scheme 96** show that the cyclization is not affected by even relatively complex substituents on the carbon α of the phenethylamine system, and the stereochemistry can be carried from the starting amines (**617, 620**) through the benzotriazolyl intermediates (**618, 621**) to the final products (**619, 622**) <2001TA2427, 2002JOC8224>. Some of the nucleophiles used for substitution of benzotriazole in derivatives of type **615** are listed in **Scheme 96**, but many others can be successfully employed as well <2002S601>.

Electron-rich heterocyclic rings are also used in such cyclocondensations. Thus, 1-(2-aminoethyl)pyrazole reacts with formaldehyde and benzotriazole to give bicyclic system **623** <2002JOC8220>, and an analogous reaction of 1-(2-aminoethyl)-3-methylindole leads to tricyclic system **624** <2003JOC4938>. Seven-membered rings are also formed as a result of analogous [6+1] cyclocondensations. Compound **625** was obtained from a reaction of 3-phenoxyethylamine with formaldehyde and benzotriazole, and compound **626** was obtained from a similar reaction *N*-(2-aminoethyl)-*N*-methylaniline <2002J(P1)592>. In all of these derivatives, the remaining benzotriazolyl moiety can be easily substituted with various nucleophiles.



623 **624** **625** **626**

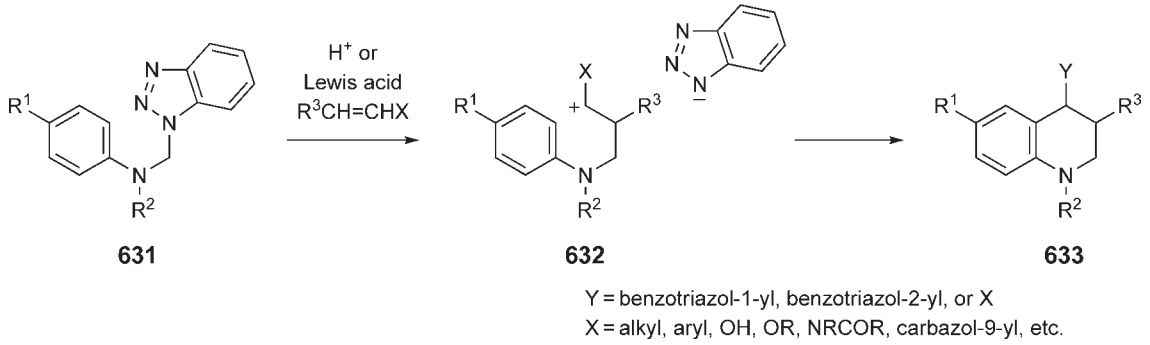
Reactions with dialdehydes allow the introduction of two additional rings in one step. Thus, condensation of 1-(2-aminoethyl)pyrrole with glutaraldehyde and benzotriazole gives tricyclic intermediate **627** in which the benzotriazolyl moiety can be readily substituted with nucleophiles to give products **628** (**Scheme 97**) <2002JOC8220>. Condensation of ethyl ester of *L*-tryptophan with 2,5-dimethoxytetrahydrofuran and benzotriazole in acetic acid gives tetracyclic intermediate **629** which upon treatment with nucleophiles (silyl derivatives) is converted to products **630** <1999T3489>.



BtH = benzotriazole
Nu: = $NaBH_4$, RMgX, NaCN, CH_2=CR-OSiMe$_3$ or CH_2=CR-CH_2SiMe$_3$

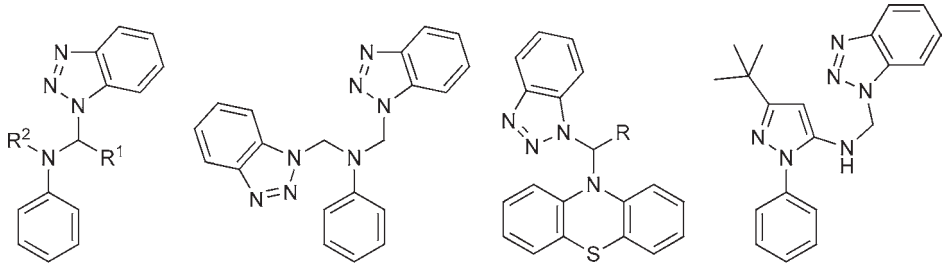
Scheme 97

Cyclocondensations of *N*-(benzotriazolylmethyl)anilines **631** with electron-rich unsaturated compounds of the type $R^3CH{=}CHX$ lead to 1,2,3,4-tetrahydroquinolines **633** (**Scheme 98**). In the first step, an iminium cation generated by dissociation of derivative **631** attacks the double bond of compound $R^3CH{=}CHX$ to generate cation **632**. In the second step, an intramolecular electrophilic attack of cation **632** on the *ortho* atom of the aniline ring furnishes tetrahydroquinoline **633**. Depending on the reaction conditions and nature of the group X, benzotriazol-1-yl (and benzotriazol-2-yl) or group X remains as the substituent in position 4 of tetrahydroquinoline **633**. For compounds lacking good leaving group, like styrenes <1997JHC1259>, alkenes <1999JHC371, 1997JHC1259>, *N*-vinylamides <1995JOC3993, 1999JHC755> and 9-vinylcarbazole <1995JOC3993>, it is the group X that remains. In the case of enolizable aldehydes <1995JOC7631> or vinyl ethers <1995JOC2588>, the benzotriazolyl moiety is usually retained as a substituent at the C-4 atom of tetrahydroquinoline **633** allowing further derivatization by substitution of benzotriazole with nucleophiles. Comparison of this new synthetic method for 1,2,3,4-tetrahydroquinolines with more classical ones has been reviewed <1996T15031>.

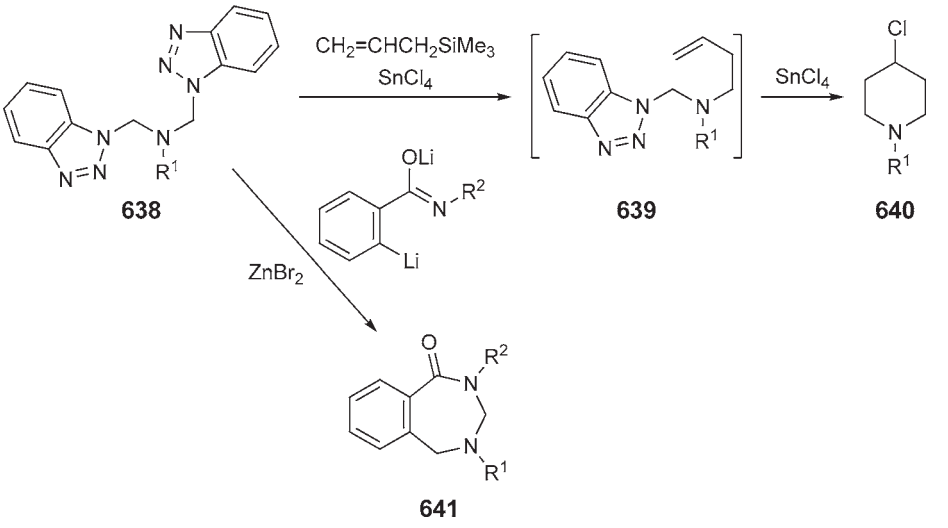


Scheme 98

Derivatives of higher aldehydes (**634**, $R^1 \neq H$) allow introduction of an additional substituent into position 2 of tetrahydroquinolines making variation of the tetrahydroquinoline system very versatile <1995JOC7631>. In *N*,*N*-bis(benzotriazolylmethyl)anilines **635**, both benzotriazolylmethyl groups may be involved in the cyclocondensation process producing julolidines <1996JOC3117, 1999JOC3328>. When the nitrogen atom supporting the benzotriazolylalkyl group is already incorporated into a ring, like in structure **636**, an additional ring is added to the heterocyclic ring system <1998S1487, 1999JHC473>. Use of alkynes instead of alkenes in the reaction depicted in **Scheme 98** results in formation of 1,2-dihydroquinolines <1998JHC467>. Derivatives of aminoheterocycles, like compound **637** <2004T8839> also undergo readily [4+2] cyclocondensation with enol ethers and vinylamides.

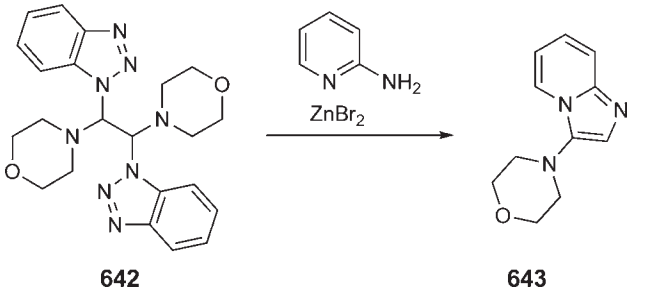


N,*N*-Bis(benzotriazolylmethyl)amines **638** derived from benzyl or phenethylamines undergo cyclocondensation with allylsilanes catalyzed by $SnCl_4$ to give 4-chloropiperidines **640** (**Scheme 99**) <1999JOC3328>. This [3+3] cyclocondensation is assumed to proceed in two steps via intermediate **639**. [3+4] cyclocondensation of derivatives **638**, originating from various aromatic and aliphatic amines, with dilithiated benzamides leads to 2,4-benzodiazepin-1-ones **641** <2002JOC8237>.



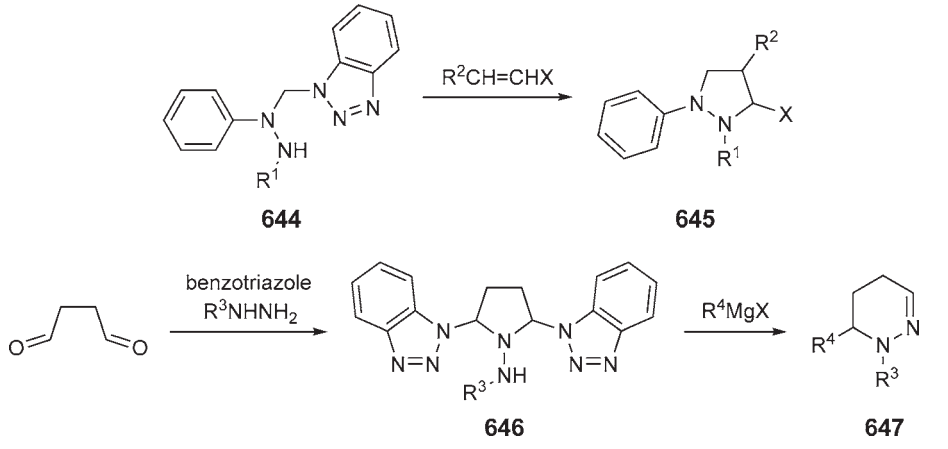
Scheme 99

Compound **642**, obtained by condensation of glyoxal with benzotriazole and morpholine undergoes interesting [2+3] cyclocondensation with 2-aminopyridine to give imidazo[1,2-*a*]pyridine **643** (Equation 15) <2003JOC4935>. Similar derivatives of piperidine and pyrrolidine are also described. 2-Amino- and 6-aminopyrimidines react similarly to give imidazo[1,2-*a*]- and imidazo[1,2-*c*]pyrimidines, respectively.



(15)

Introduction of hydrazines opens new possibilities in the cyclocondensation pattern when both nitrogen atoms of hydrazines can be involved in the process. Thus, hydrazine derivative **644** reacts with electron-rich unsaturated compounds according to [3+2] cyclocondensation pattern to produce pyrazolidines **645** (**Scheme 100**)

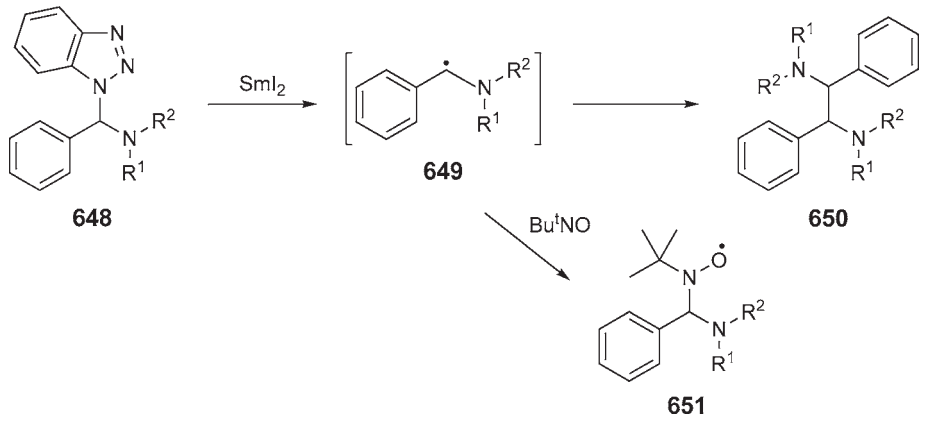


Scheme 100

<1997JOC8210>. Condensation of succinaldehyde with arylhydrazines and benzotriazole gives 1-aminopyrrolidines **646** that upon treatment with organomagnesium reagents rearrange to 1,4,5,6-tetrahydropyridazines **647** <1998S1627>.

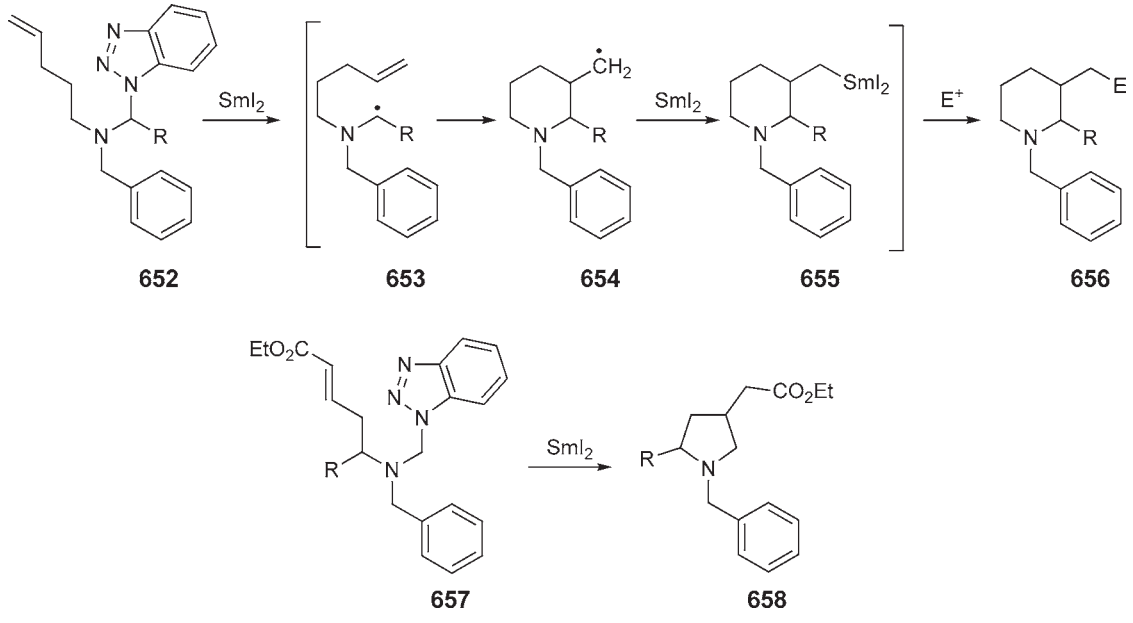
5.01.8.6.3 Reduction to α-amino radicals and α-amino anions

Treatment of *N*-(α-aminobenzyl)benzotriazoles **648** with samarium diiodide generates radicals **649** that undergo coupling to form vicinal diamines **650** (**Scheme 101**) <1992TL4763>. Formation of intermediate radicals **649** at low temperature is confirmed by EPR <1999OL1755>. Short-living radicals **649** are readily converted to more stable radicals **651** by treatment with 2-methyl-2-nitrosopropane.



Scheme 101

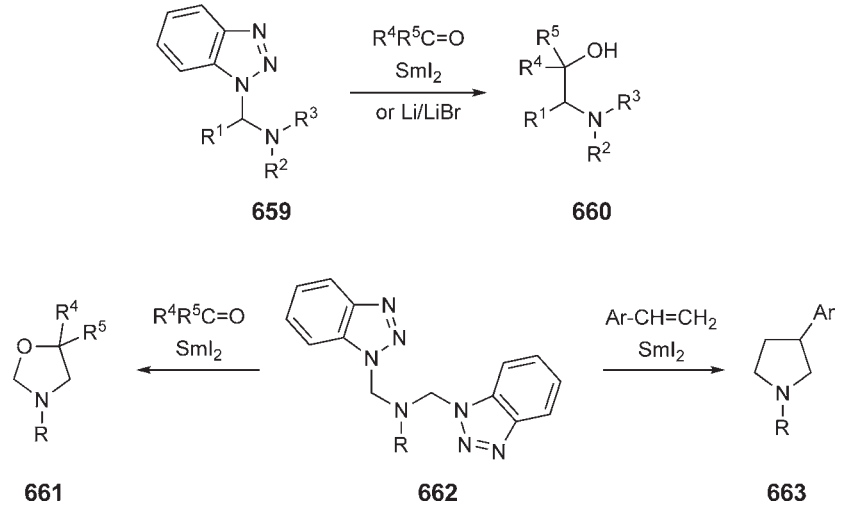
When one of the substituents on the amine nitrogen atom is ready to trap a radical formed by treatment of *N*-(α-aminoalkyl)benzotriazole with SmI_2, cyclization may occur. Such a situation is depicted in **Scheme 102**. Thus, (4-penten-1-yl)amine derivative **652** is reduced to radical **653** that is then rapidly trapped by the alkenyl group and



Scheme 102

converted to radical **654**. The following reaction with excess SmI_2 gives samarium intermediate **655**. During aqueous work-up, derivative **655** is hydrolyzed to 3-methylpiperidine **656** (E = H). Alternatively, treatment with electrophiles converts intermediate **655** to piperidines **656** with various substituents at C-3 <2000J(P2)1375>. Similarly, SmI_2 converts γ,δ-unsaturated amines **657** to pyrrolidines **658** with good yields<2002T6837>.

α-Aminocarbanions generated by treatment of *N*-(α-aminobenzyl)benzotriazoles **659** with SmI_2 (or Li/Br) can be readily trapped by aldehydes or ketones to provide β-aminoalcohols **660** (**Scheme 103**) <1997JOC4121>. A similar reaction performed on *N*,*N*-bis(benzotriazolylmethyl)amines **662** results in formation of oxazolines **661**, but the yields are low <1998TL6835>. However, when styrenes are used to trap generated radicals (or anions), pyrrolidines **663** are obtained in good yields <1998H(48)2535>.

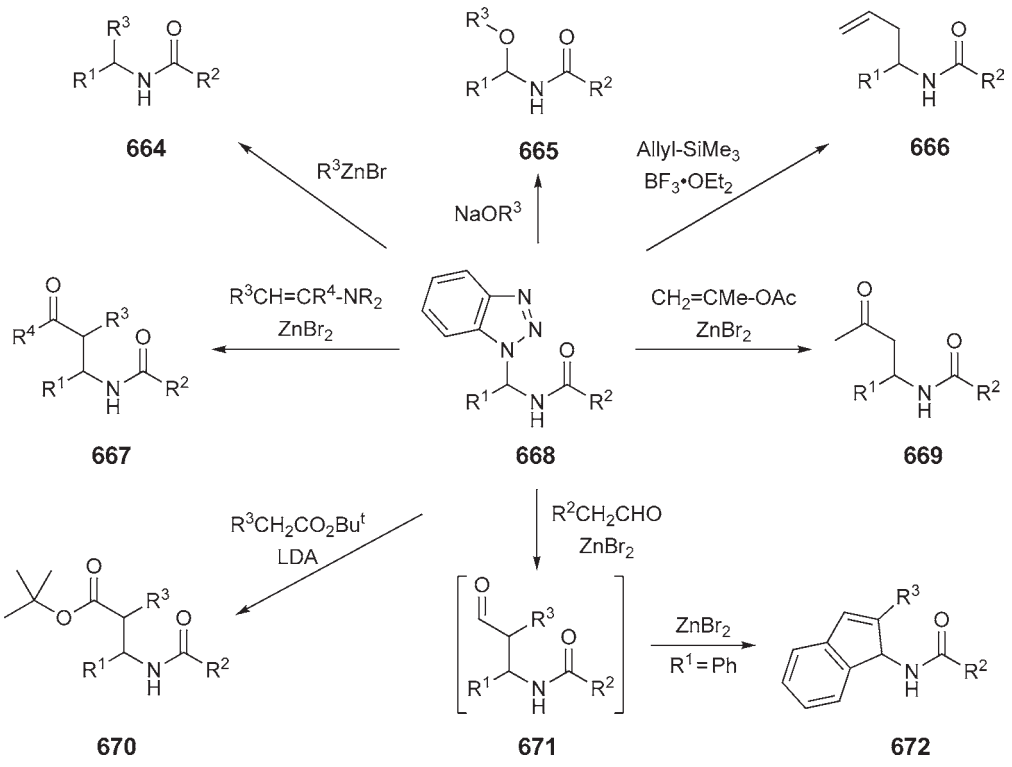


Scheme 103

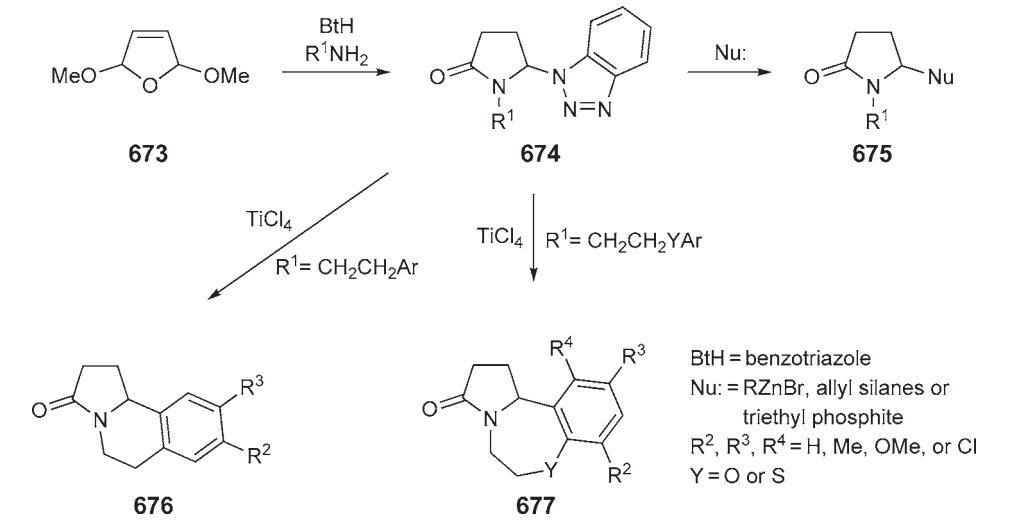
5.01.8.6.4 Derivatives of amides, thioamides, sulfonamides, and related compounds

Benzotriazolylalkyl amides **668** are easy to prepare by condensation of amides with aldehydes and benzotriazole. The chemistry of compounds **668** is to some extent similar to that of the corresponding amines discussed above; however, increased stability of derivatives **668** and higher stability of the products of their reactions bring additional synthetic possibilities. Thus, the reaction with organozinc reagents, usually prepared *in situ* from zinc powder and alkyl bromides, leading to amides **664** is analogous to the reaction of the corresponding amines (**Scheme 104**) <1998T7167, 2000TL9691>. By contrast, the reaction with sodium alkoxides producing *N*-(α-alkoxyalkyl)amides **665** is unique to derivatives **668** <1995JOC4002, 2003JOC4338>. Similarly to the amine analogs, allylation with allyltrimethylsilane converts compounds **668** to unsaturated amines **666** <1995JOC4002>, but the reaction with enamines leading to ketoamides **667** <1999JOC7622> has little precedent among the corresponding derivatives of amines. Enol esters derived from ketones react as well, as it is illustrated by the example of acetone derivative **669** <1995JOC4002>. Anions derived from *t*-butyl esters can also be used for substitution of benzotriazole to give β-amidoesters **670** <2002JOC4957>. Enolizable aldehydes can be used for substitution of benzotriazole in derivatives **668** as well. Although the original product, **671**, is unstable under the reaction conditions, in the case of R^1 being a reactive aromatic ring, subsequent cyclocondensation leads to a stable N-acylated 1-aminoindene **672** <2000JOC8066>.

Condensation of 2,5-dimethoxy-2,5-dihydrofuran **673** with benzotriazole and an amine carried out in refluxing acetic acid produces 5-benzotriazolylpyrrolidin-2-one in good yield and with strong prevalence of benzotriazol-1-yl isomer **674** <2000JOC4364>. Substitution of the benzotriazole moiety with nucleophiles gives 5-substituted 2-pyrrolidinones **675** (**Scheme 105**). When a reactive aromatic ring is attached to the nitrogen atom of 2-pyrrolidinone **674** by a two- or three-atom linker, the *ortho* carbon of the ring may serve as a nucleophile providing tricyclic systems **676** <2001JOC148> or **677** <2001JOC5590>, respectively.

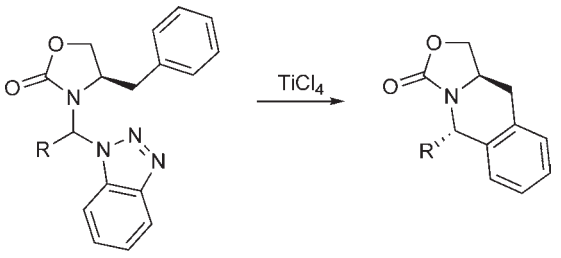


Scheme 104

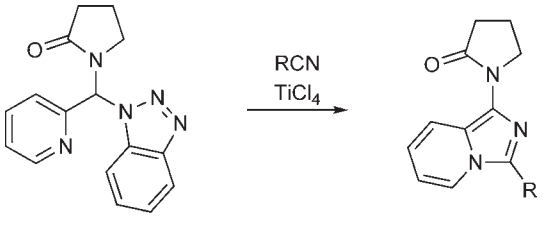


Scheme 105

Formation of polycyclic systems is also possible when benzotriazole is attached to carbon α of the nitrogen substituent in the cyclic amide. As shown in Equation (16), cyclocondensation of 5-benzyloxazolidin-2-ones **678** promoted by $TiCl_4$ stereospecifically gives tricyclic system **679** that represents the core structure of many important natural products <1999TA255, 2004EJO3611>. In a specific case of 2-pyridyl derivatives **680**, cyclocondensation with nitriles involves only the group attached to the amide nitrogen atom giving imidazo[1,5-*a*]pyridines **681** with the pyrrolidinone substituent in position 1 unchanged (Equation 17) <2001JOC2862>.

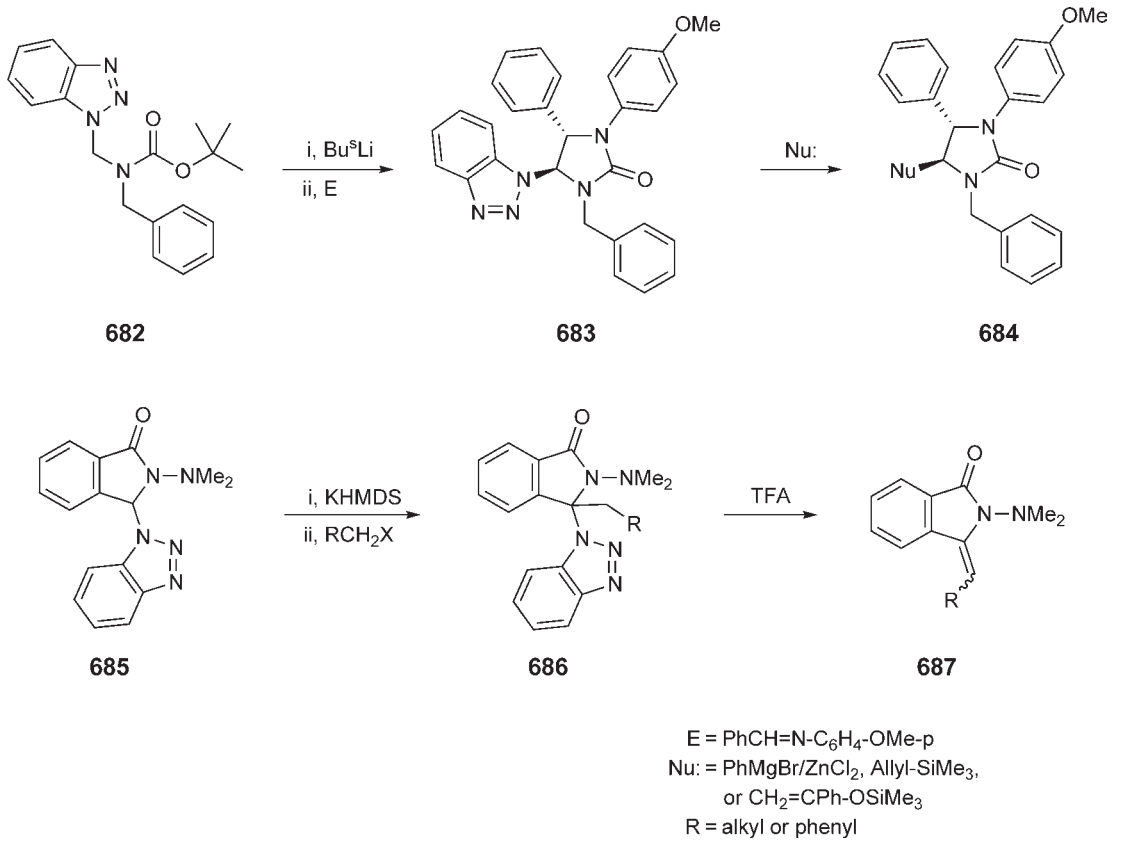


678 679 (16)



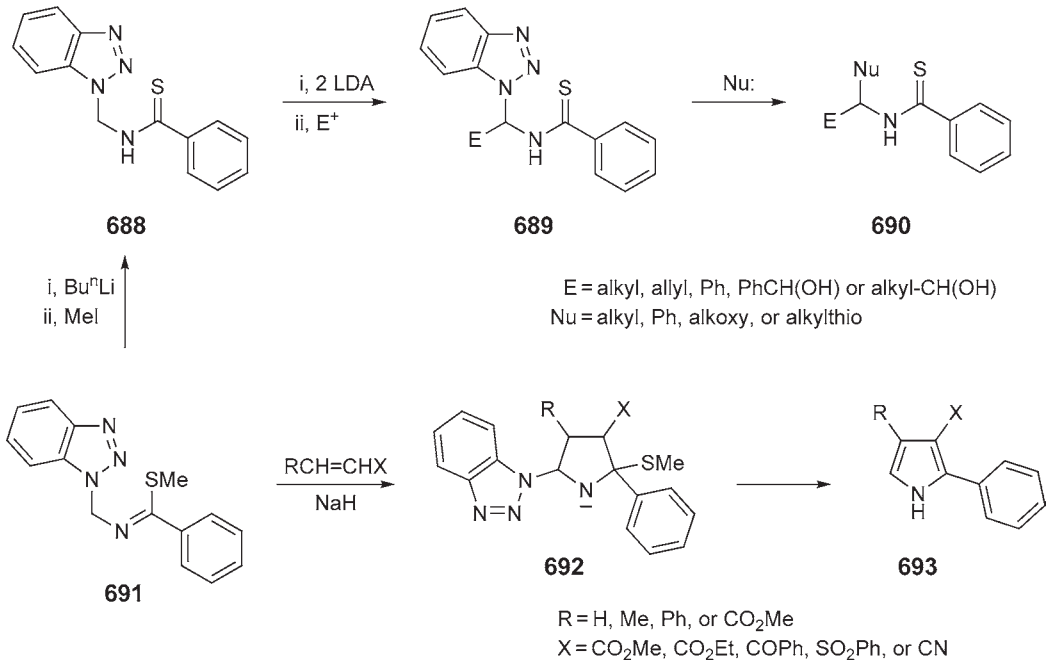
680 681 (17)

N-(Benzotriazol-1-yl)methyl derivatives of BOC-protected amines behave similarly to amides. Thus, treatment of an anion derived from compound **682** with methoxychalcone leads to 2-imidazolidinone **683** with the substituents at C-4 and C-5 oriented *trans*. Subsequent treatment with nucleophiles gives product **684** stereoselectively (**Scheme 106**) <2001JOC2858>. In the second reaction presented in **Scheme 106**, alkylation of compound **685** at the carbon α gives derivative **686** which upon treatment with TFA eliminates readily benzotriazole leading to 3-alkylidene-2,3-dihydro-1*H*-isoindolo-1-ones **687** <2002TL8055>.



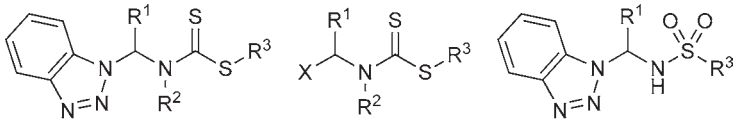
Scheme 106

The double anion, obtained from thioamide **688** upon its treatment with LDA or Bu^{n}Li, reacts with alkylating agents to give α-alkyl derivatives **689** (E = alkyl) or with aldehydes to give α-(1-hydroxyalkyl) derivatives **689** [E = RCH(OH)] (**Scheme 107**) <1995T8703>. The following substitution of benzotriazole with nucleophiles results in thioamides **690**. This simple process allows introduction of two different groups to the carbon atom attached to the thioamide nitrogen. Use of only 1 molar equivalent of the base makes possible selective methylation of the sulfur atom to give thioamidate **691**. The anion derived from compound **691** upon its treatment with sodium hydride adds readily to electron-poor double bonds to create unstable intermediate anion **692** that spontaneously eliminates benzotriazole and thiomethoxide to generate pyrrole **693** <1995T13271, 2000JOC8819>.



Scheme 107

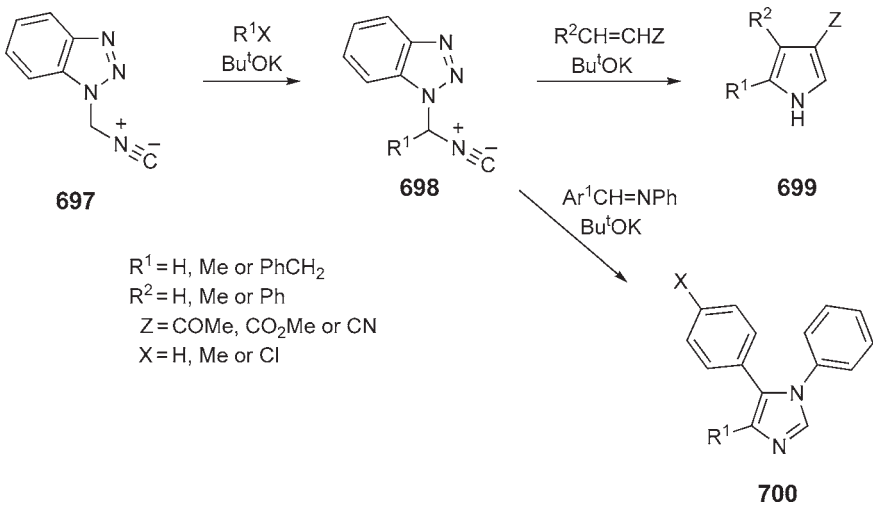
In the presence of $ZnBr_2$, the benzotriazole moiety in dithiocarbamates **694** can be readily substituted by mercaptans or phosphites providing new access to derivatives **695** <2005ARK(ix)63>. Cyclic analogs of **694**, 1,3-thiazolidine-2-thione and tetrahydro-2*H*-1,3-thiazine-2-thione, react similarly. Substitution of the benzotriazolyl group in sulfonamide derivatives **696** with cyanides occurs under mild conditions in DMSO, alcohol or even water providing a good way for preparation of *N*-(α-cyanoalkyl)sulfonamides <1997SC907>.



694 **695** **696**

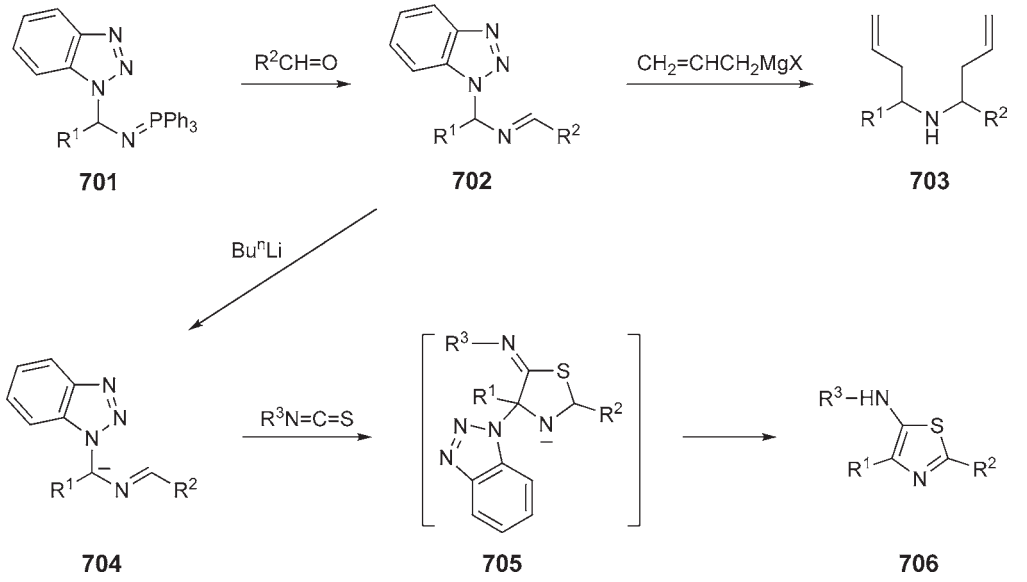
5.01.8.6.5 Imines and related compounds

In the presence of Bu^{t}OK, (benzotriazole-1-yl)methyl isocyanide (BetMIC) **697** undergoes alkylation on the methylene group to give isocyanide **698**. The anion derived from **698**, upon its treatment with Bu^{t}OK, adds to the electron-deficient double bonds of α,β-unsaturated ketones, esters or nitriles to produce pyrroles **699**. A similar reaction of isocyanide **698** with Schiff bases provides imidazoles **700**. In both cases, use of unsubstituted isonitriles **697** in the reactions leads to heterocycles **699** and **700** with R^1 = H (**Scheme 108**) <1997H(44)67>.



Scheme 108

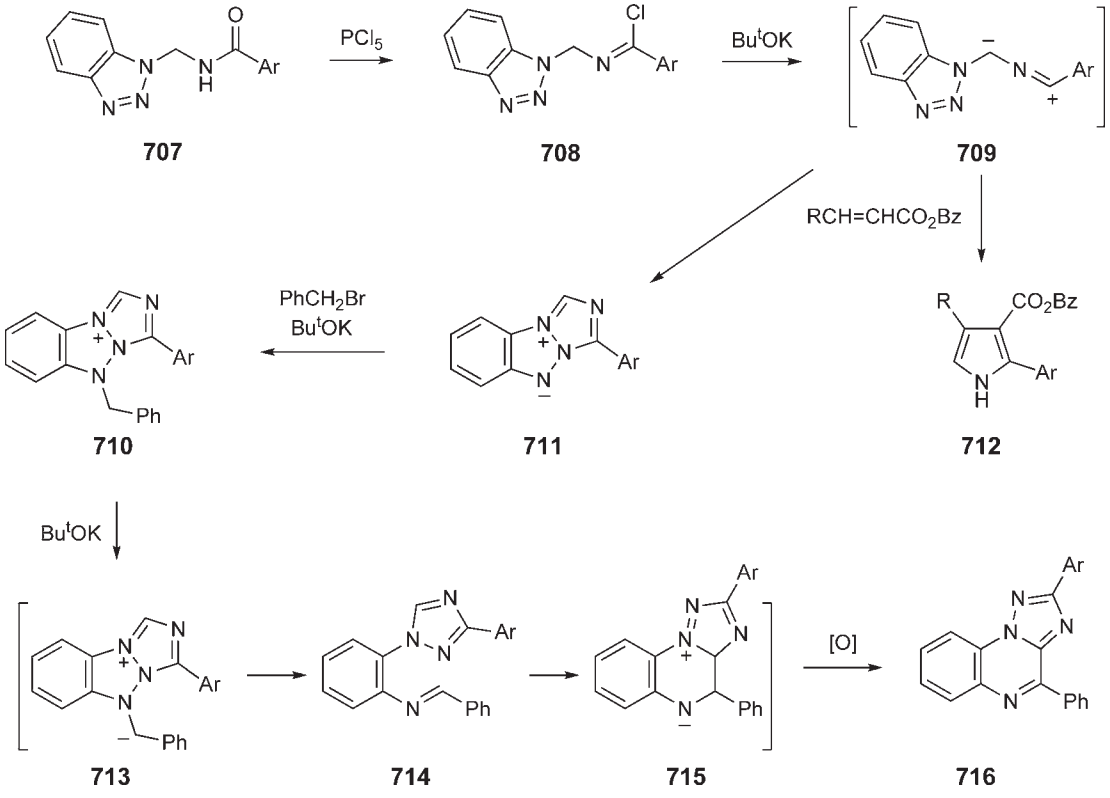
The rich chemistry of parent iminophosphorane **701** ($R^1 = H$), BetMIP, is described in CHEC-II(1996) <1996CHEC-II(4)1> and in a review article <1996JPR684>. Aza-Wittig reactions of iminophosporanes **701** with aldehydes provide imines **702**. Treated with an excess of allylmagnesium reagent, imines **702** are converted into *N*,*N*-bis(3-butenyl)amines **703**, interesting intermediates for construction of heterocyclic systems (**Scheme 109**) <2002JOC7530>. Imines **702**, particularly with $R^1 = R^2 =$ aryl, can be also conveniently prepared by direct condensation of aldehydes with benzotriazole and ammonia <2000JOC8077>. Treatment of imine **702** with *n*-butyllithium produces anion **704** that adds readily to isothiocyanates to give intermediate anion **705**. Loss of a benzotriazole anion followed by tautomerization leads to aminothiazole **706**. This way, 5-aminothiazoles **706** bearing aryl or heteroaryl substituents at C-2 and C-4 can be easily prepared in good yields <2000JOC8077>.



Scheme 109

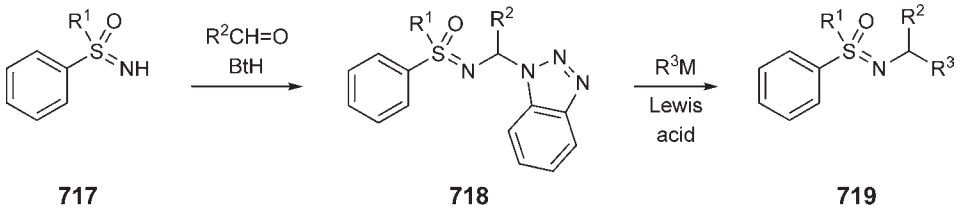
Reaction of *N*-[(benzotriazol-1-yl)methyl]amide **707** with PCl_5 gives chloroimine **708**, which upon treatment with Bu^tOK is converted to nitrile ylide **709**. Benzyl esters of α,β-unsaturated acids used as dipolarophiles trap species **709** to generate pyrroles **712** (**Scheme 110**) <2002JHC759>. When no trapping agent is added, the N-2 atom of benzotriazole act as a nucleophile, and tricyclic system **711** is formed <2001TL9109>. Addition of benzyl bromide

to the reaction mixture causes formation of a new tricyclic system that, according to the X-ray diffraction analysis, has structure **716** <2002JOC3118>. A reasonable explanation of this phenomenon is as follows. Benzylation of species **711** creates cation **710** that, affected by excess Bu^{t}OK, loses its acidic benzylic proton to form betaine **713**. Electron shift towards the positive charge causes breaking of the N–N bond. Freed 1,2,4-triazolyl group in intermediate **714** rotates to a more favorable position, and a bond between carbon atoms forms. Finally, oxidation of newly formed betaine **715**, probably by atmospheric oxygen during work-up, results in stable heterocyclic system **716**. Another possible mechanism, proposed by authors of the report <2002JOC3118>, starts from formation of the C–C bond by direct benzylation of nitrile ylide **709** that is followed by several rearrangements to produce final product **716**.



Scheme 110

Condensation of sulfoximine **717** with an aldehyde and benzotriazole produces *N*-[α-(benzotriazol-1-yl)alkyl]sulfoximine **718**. Treatment with allyl silanes in the presence of BF_3 etherate or with organozinc reagents allows substitution of the benzotriazolyl moiety in compound **718** to produce variety of substituted sulfoximines **719** (**Scheme 111**) <2003ARK(xv)115>.

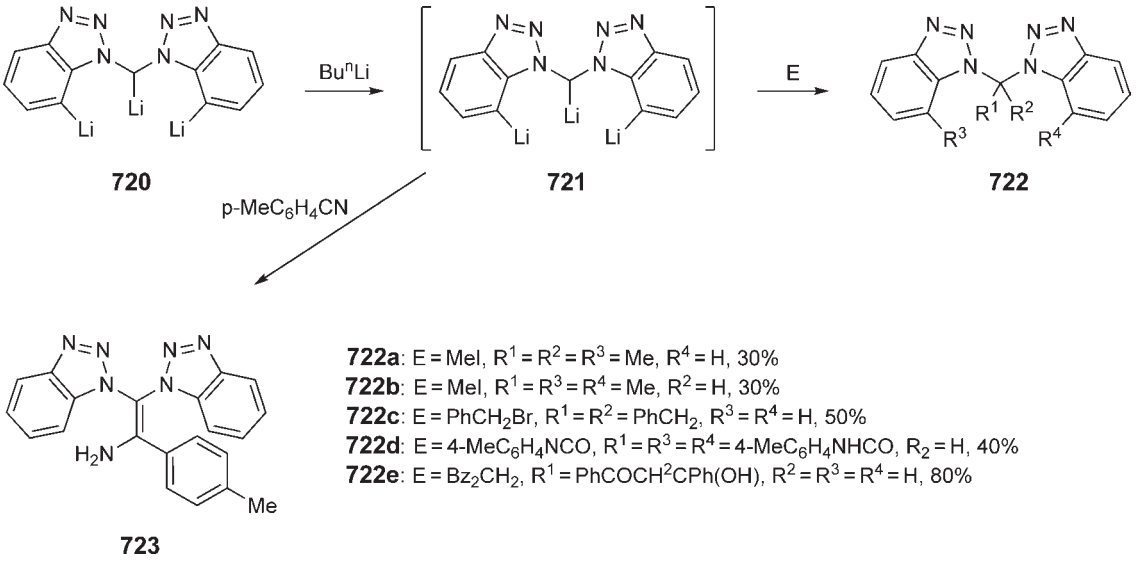


R^1 = Me or Ph
R^2 = H or CO_2Et
R^3M = CH_2=CH-CH_2SiMe_3, CH_2=CMe-CH_2SiMe_3, CH_2=CH-CH_2ZnCl, $PhCH_2ZnCl$, or PhZnCl

Scheme 111

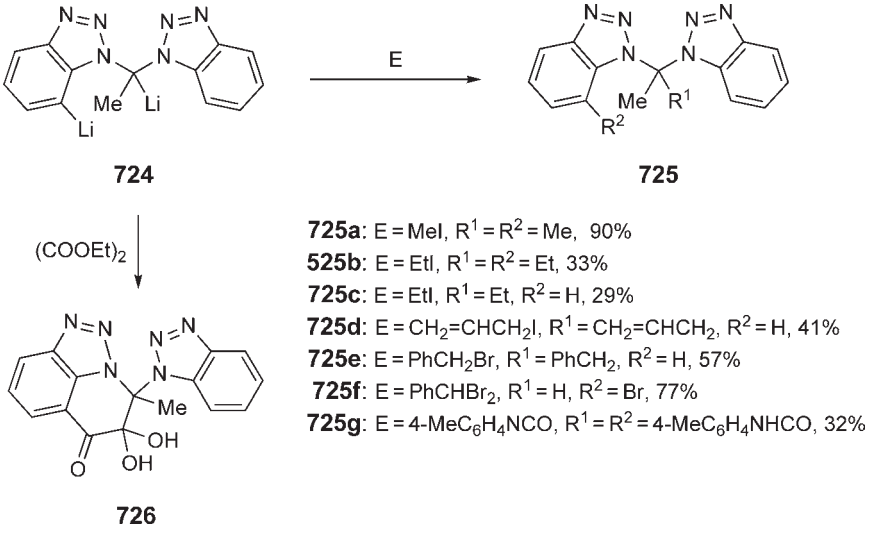
5.01.8.6.6 Bis(heterocycle-N-yl)alkanes

One of the simplest molecules belonging to this category is that of *bis*(benzotriazol-1-yl)methane **720**. Treated with an excess of Bu^nLi, molecule **720** generates polyanion **721** which, when subjected to reactions with various electrophiles, gives C-α and/or C-7 substituted derivatives **722**; an equimolar mixture of C-α, C-α, C-7 (**722a**) and C-α, C-7, C-7 (**722b**) trimethylated products forms in a reaction with iodomethane (**Scheme 112**). Under these conditions, reaction of 4-methylbenzonitrile with **721** gives enamine **723** in 70% yield <2005T3305>.



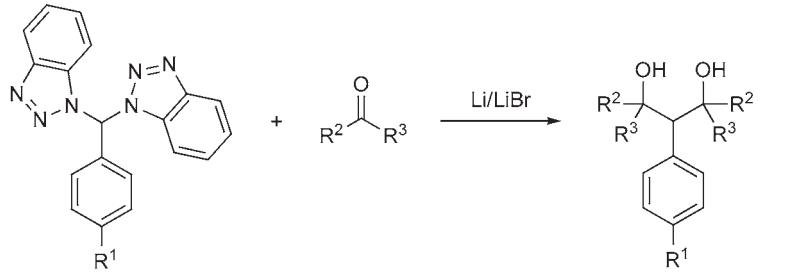
Scheme 112

1,1-Bis(benzotriazol-1-yl)ethane treated with 2 molar equivalents of BuLi undergoes lithiation at C-α and C-7 to give intermediate **724** (**Scheme 113**). Consecutive treatment of the reaction mixture with iodomethane leads to dimethylated product **725a** in high yield. In a reaction with iodoethane, apart of diethylated product **725b**, mono-ethylated derivative **725c** is also formed. Allyl iodide and benzyl bromide gives exclusively substitution at C-α (**725d** and **725e**, respectively). Reaction with benzylidene bromide leads to bromination at C-7 (**725f**). Reaction with *p*-tolyl isocyanate gives diamide **725g**, and that with diethyl oxalate produces triazoloquinolone **726** <2005T3305>.



Scheme 113

Condensation of benzaldehydes with benzotriazole in the presence of thionyl chloride readily gives α,α-*bis*(benzotriazol-1-yl)toluenes **727** that can be considered as 1,1-*gem*-dicarbanion equivalents. Thus, treatment of derivatives **727** with ketones and lithium metal suspended in THF at −78 °C generates substituted propylene glycols **728** (Equation 18) <1998TL2289>.



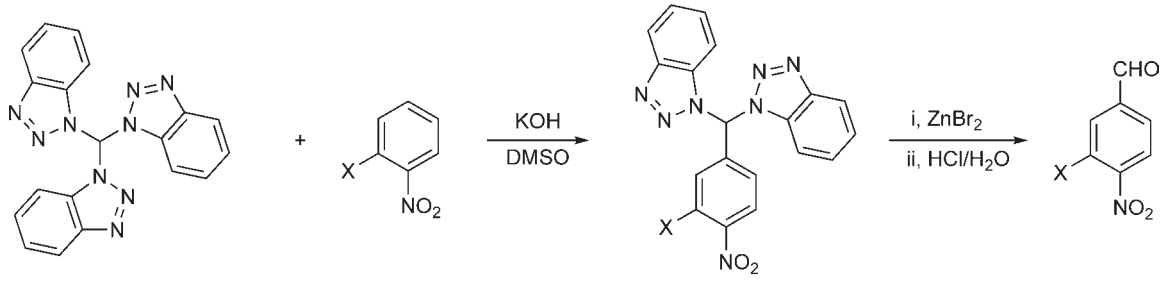
(18)

727 **728**

R^1 = H or Me;

$R^2R^3C{=}O$ = cyclopentanone, cyclohexanone, 2-pentanone, 3-pentanone, or 4-heptanone

In the presence of KOH, *tris*(benzotriazol-1-yl)methane **729** reacts with nitrobenzenes to produce *p*-[*bis*(benzotriazol-1yl)methyl]nitrobenzenes **730** (**Scheme 114**) <1996TL347>. This vicarious nucleophilic substitution of hydrogen <1991S103> can be considered as a convenient way to *p*-nitrobenzaldehydes **731**. *Meta* and *para* substituted nitrobenzenes do not react with compound **729** under these conditions, probably due to steric reasons, but 1-nitronaphthalene reacts producing a naphthalene analog of derivative **730**.



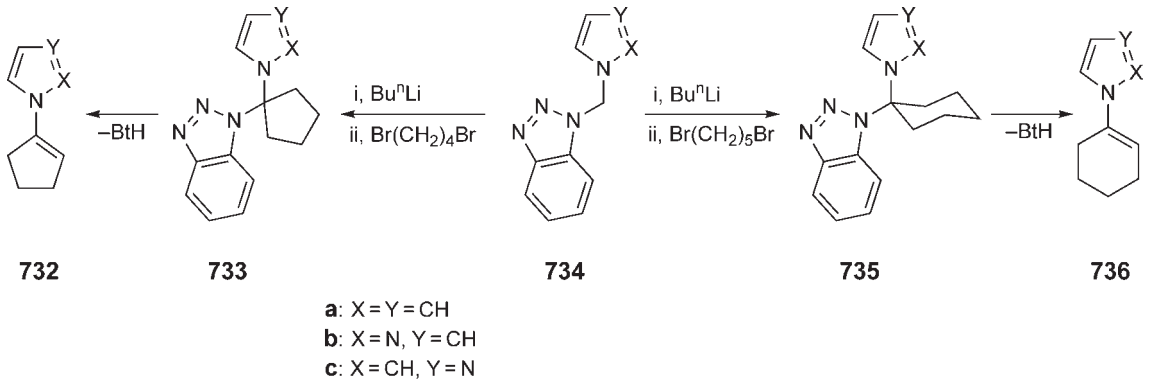
729 **730** **731**

X = H, Cl, Br, or Ph

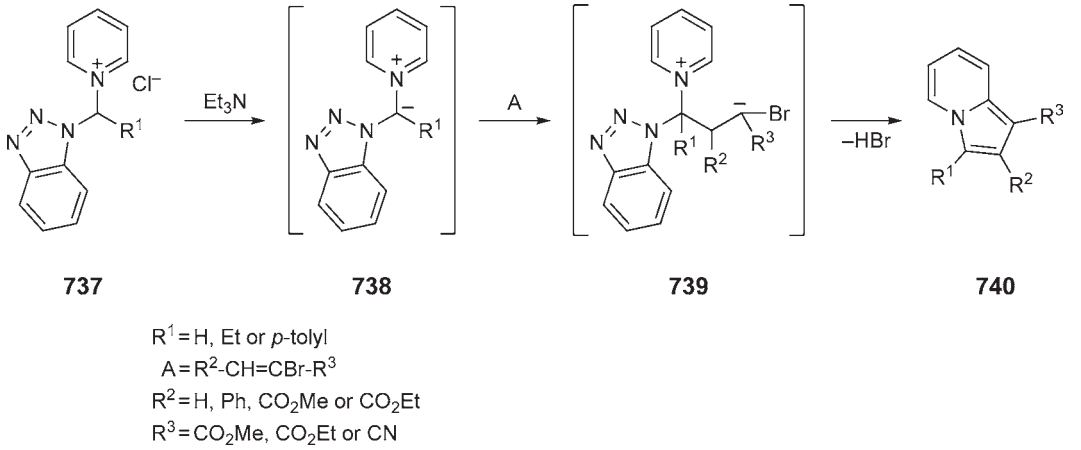
Scheme 114

N-[(Benzotriazol-1yl)methyl]azoles **734** are dialkylated with 1,4-dibromobutane to give 1,1-disubstituted cyclopentanes **733**. 1,5-Dibromopentane reacts similarly producing cyclohexanes **735** (**Scheme 115**) <2002JOC8230>. Two alternative methods are used for elimination of benzotriazole: treatment with $ZnBr_2$ or with KOH. In some cases, acidic elimination works better, in others, basic elimination is preferred. Both methods convert cyclopentane derivatives **733** to 1-(cyclopenten-1yl)azoles **732** and their cyclohexane analogs **735** to 1-(cyclohexen-1-yl)azoles **736**.

α-Protons in pyridinium salts **737** are acidic enough to be removed by weakly basic triethylamine. Obtained ylides **738** add to esters of 2-bromo-2-alkenecarboxylic acids or analogous benzonitriles to give intermediate betaines **739**. A nucleophilic attack of the anionic site on C-2 of the pyridinium system followed by elimination of HBr leads to indolizines **740** (**Scheme 116**) <1999JOC7618>. When esters of ordinary α,β-unsaturated acids (no Br at C-2) are used in these reactions, indolizines **740** are also formed but with much lower yields due to the oxidation required of the intermediate dihydro analogs of derivatives **740** that form first.

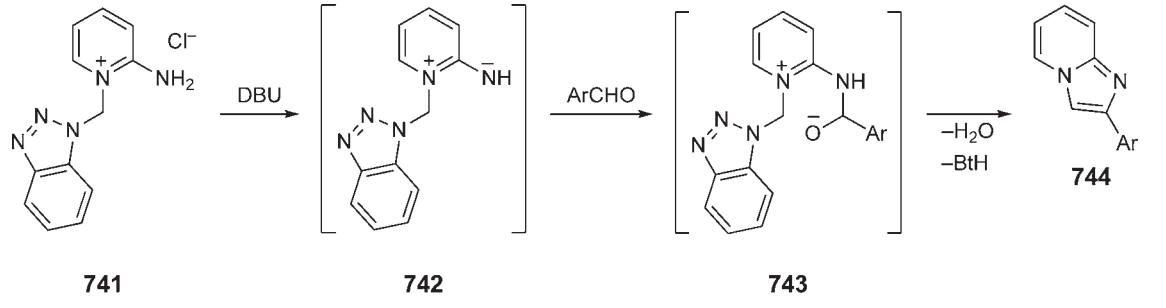


Scheme 115



Scheme 116

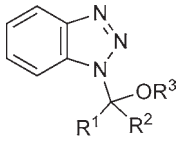
When treated with DBU at elevated temperature, 1-[(benzotriazol-1-yl)methyl}-2-aminopyridine salts **741** eliminate rather the N–H proton than the C–H one. Intermediates **742** can be trapped with aromatic aldehydes to create betaines **743**. The consecutive cyclocondensation and elimination of benzotriazole results in formation of imidazolo[1,2-*a*]pyridines **744** in good yields (**Scheme 117**) <2000JOC9201>. Aldehydes with enolizable α-protons fail to give bicyclic systems **744**, producing corresponding enamines instead.



Scheme 117

5.01.8.7 Ring N–C(sp^3)-O

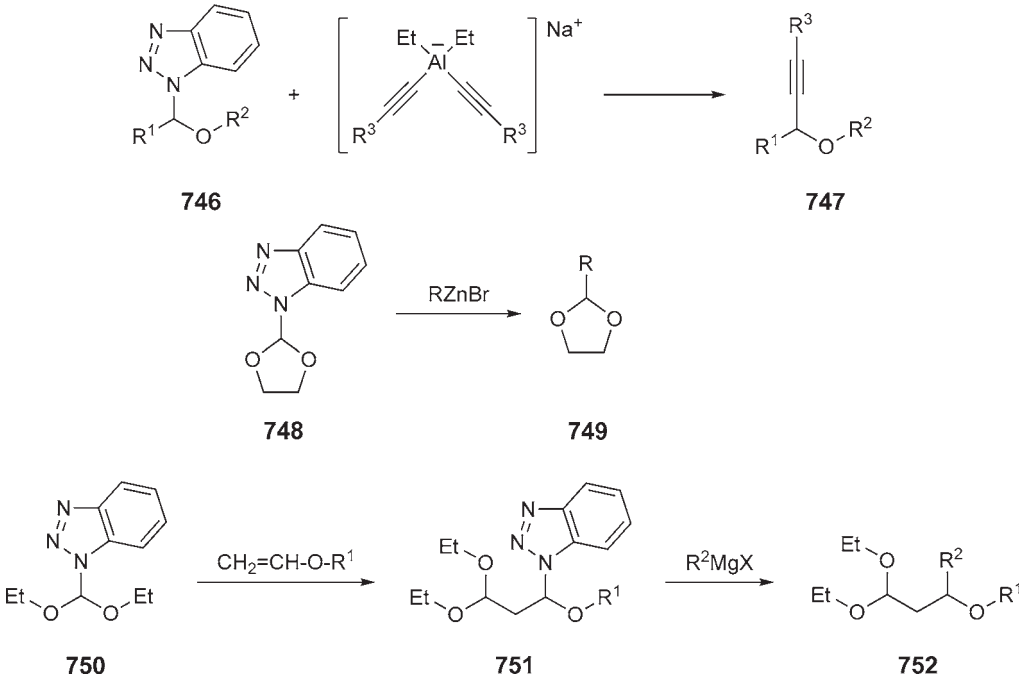
Compounds of general structure **745** (and their benzotriazol-2-yl analogs) are discussed in this subsection.



745

5.01.8.7.1 Reactions with nucleophiles

Substitution of the benzotriazole moiety in compounds **745** with organomagnesium reagents has been discussed previously <1996CHEC-II(4)1>. Newer applications of organometallic reagents to reactions with α-benzotriazolyl ethers are outlined in **Scheme 118**. Thus, reactions of benzotriazolyl ethers **746** with sodium dialkynyldiethylaluminates provide propargylic ethers **747** in high yields <1999JOC488>. 2-Benzotriazolyl-1,3-dioxolane **748** is a convenient equivalent of the formyl cation; its reactions with organozinc reagents lead to masked formylated products **749** <2000JOC1886>. In the presence of Lewis acids, *N*-(diethoxymethyl)benzotriazole **750** undergoes addition to enol ethers to produce 1-(benzotriazol-1-yl)-1,3,3-trialkoxypropanes **751**. Reactions with Grignard reagents convert derivatives **751** into β-alkoxyalkanal acetals **752** <1997JOC700>.



746 **747**

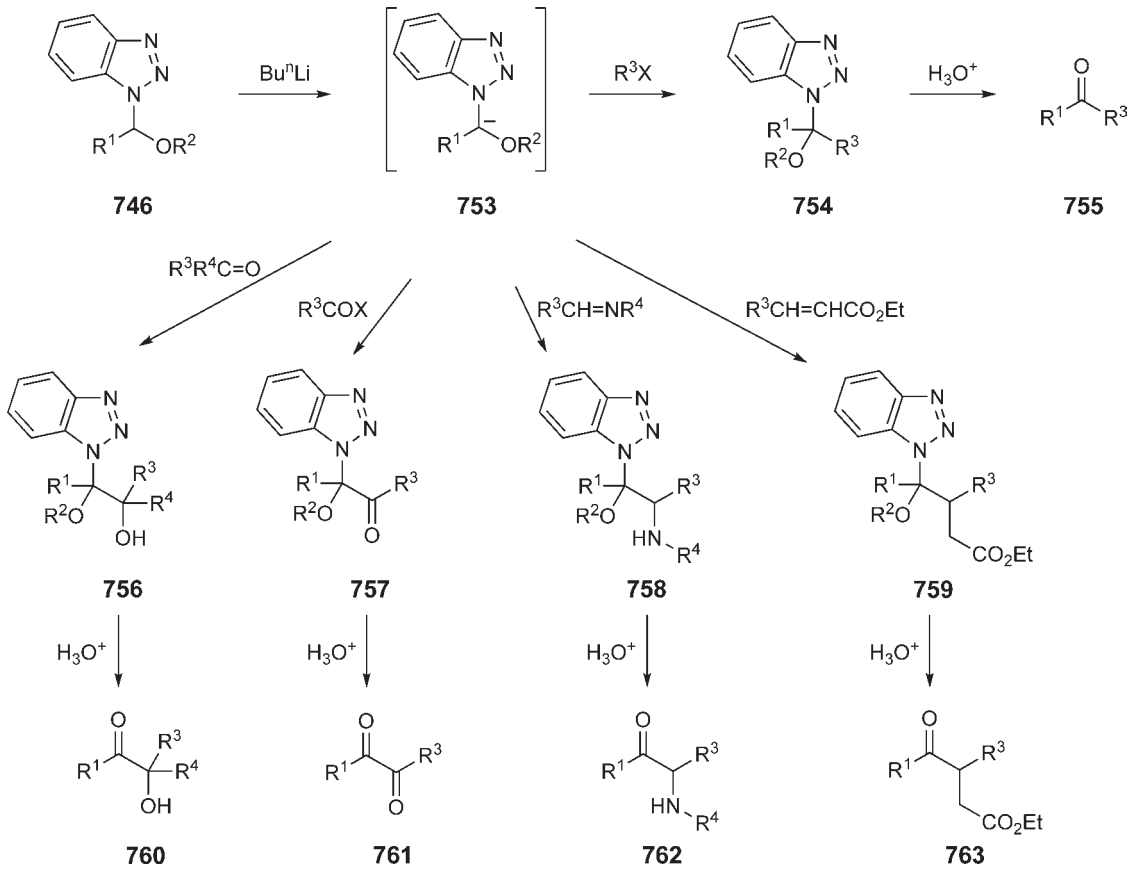
748 **749**

750 **751** **752**

Scheme 118

5.01.8.7.2 Reactions with electrophiles

α-Protons in alkoxy derivatives **746** are acidic enough to be pulled out by Bu^{n}Li. Nascent anions **753** can be trapped with alkylating agents to give α-alkylated products **754**. Geminal benzotriazol-1-yl and alkoxy substituents in compound **754** behave as a protected carbonyl group; they can be removed by acidic hydrolysis to furnish ketones **755** (**Scheme 119**). In this way, a conversion is made from aldehydes R^{1}CH═O (the precursor of **746**) to ketones R^{1}R^{2}C═O. Analogously, use of chlorosilanes as alkylating agents R^{3}X leads to acylsilanes **755** (R^1 = aryl, R^3 = SiMe$_2$R) in good yields <1996OM486>.



Scheme 119

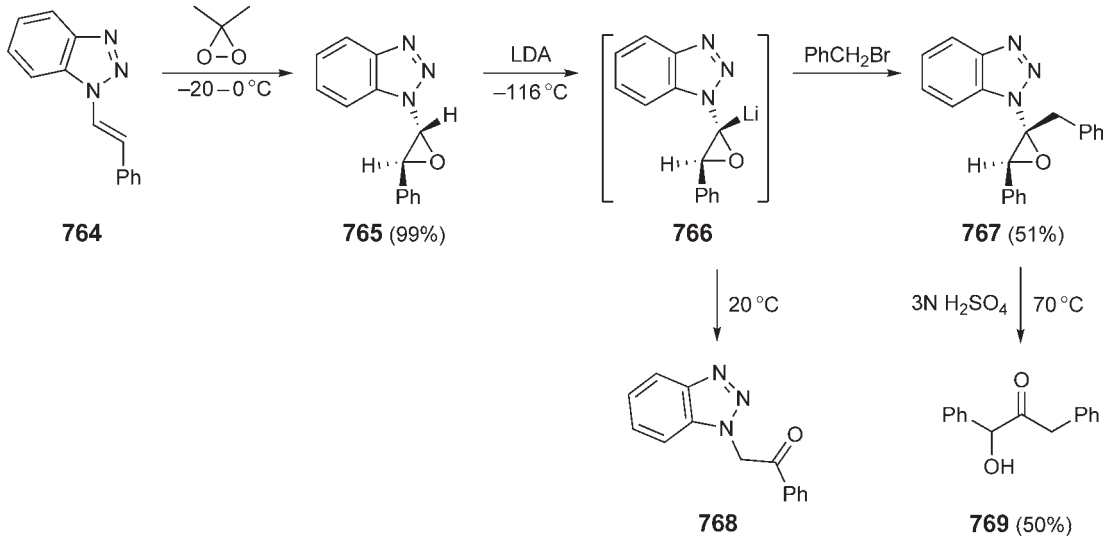
Many other electrophiles can be used to trap anions **753**; four classes of such compounds are presented in **Scheme 119**. Thus, the reactions with aldehydes or ketones lead to α-hydroxyketones **760** via intermediates **756**. The reactions with acylating agents lead to vicinal diketones **761** via intermediates **757**. The reactions with imines give α-aminoketones **762** via intermediates **758**, and those with esters of α,β-unsaturated carboxylic acids give γ-ketoacids **763** via intermediates **759**. Examples of representative products **754–763** are collected in **Table 9**. Other electrophiles used in such reactions that are not shown in **Table 9** include chlorotrimethylsilane <1995JOC7612>, isocyanates <1995JOC7612, 1998JOC1473>, isothiocyanates <1998JOC1473>, diethyl carbonate <1995JOC7612>, and ethyl chloroformate <1998JOC1473>.

Benzotriazolyloxiranes can be prepared in practically quantitative yields by epoxidation of the corresponding alkenes with dimethyldioxirane, for example, conversion of alkene **764** to oxirane **765** (**Scheme 120**). At very low temperatures, substitution of the α-proton in oxirane **765** is possible; just its treatment with LDA at −116 °C followed by benzyl bromide leads to α-benzyloxirane **767**, via lithiated intermediate **766**. At higher temperatures, rearrangement of lithiated oxirane **766** to ketone **768** is observed. Stereochemistry of the molecule is preserved during these transformations. Significant stabilization of the oxirane ring by the benzotriazolyl substituent makes its opening difficult; thus, heating in 3 N sulfuric acid was required to convert oxirane **767** into hydroxyketone **769** <2001ARK(v)68>.

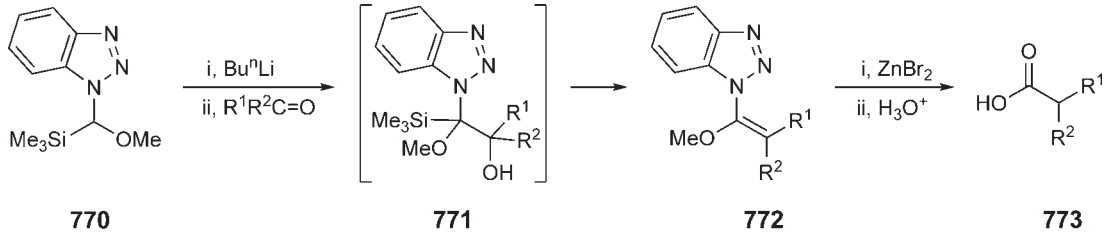
Addition of a silyl substituent into α-position of the α-(benzotriazol-1-yl)alkyl ether brings additional possibilities. Thus, lithiation of silyl ether **770** followed by treatment with an aldehyde or ketone gives unstable β-hydroxy-α-silyl-α-(benzotriazol-1-yl)alkyl ether **771** that spontaneously eliminates silanol to give vinyl ether **772** (**Scheme 121**). Treatment with $ZnBr_2$ followed by hydrolysis with a diluted acid removes both the benzotriazolyl and the methyl groups to furnish carboxylic acid **773**. In this way, in a simple manner, aldehydes and ketones are converted to one-carbon homologated carboxylic acid <1996S1425>.

Table 9 *N*-(α-Alkoxyalkyl)benzotriazoles and products of their hydrolysis

Compound	*Substituents*	*Yield (%)*	*Reference*
754a	$R^1 = Ph$, $R^2 = Me$, $R^3 = Br(CH_2)_4$	82	1999JOC2124
754b	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = Bu$	90	1996SC4049
755a	$R^1 = Ph$, $R^3 = Et$	94	1995JOC7619
755b	$R^1 = CH_2{=}CH$, $R^3 = PhCH_2CH_2$	71	1995JOC7589
755c	$R^1 = 2$-Furyl, $R^3 = Br(CH_2)_4$	89	2002JOC8489
756a	$R^1 = CH_2{=}CH$, $R^2 = Et$, $R^3 = PhCH_2$, $R^4 = H$	48	1995JOC7589
756b	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = R^4 = Me$	66	1995JOC7612
757a	$R^1 = PhC{\equiv}C$, $R^2 = Et$, $R^3 = Ph$	63	1997JOC4125
757b	$R^1 = n\text{-}C_6H_{13}$, $R^2 = Ph$, $R^3 = Bu^t$	86	1997JOC4125
758	$R^1 = PhCH(OEt)CH_2$, $R^2 = Ph$, $R^3 = p\text{-}MeC_6H_4$, $R^4 = Ph$	92	1998JOC1473
760	$R^1 = PhC{\equiv}C$, $R^3 = R^4 = Me$	100	1995JOC7612
761	$R^1 = n\text{-}C_6H_{13}$, $R^3 = Bu^t$	83	1997JOC4125
762a	$R^1 = PrCH{=}CH$, $R^2 = Et$, $R^3 = R^4 = Ph$	71	1997JOC706
762b	$R^1 = PhCH(OEt)CH_2$, $R^3 = p\text{-}MeC_6H_4$, $R^4 = Ph$	64	1998JOC1473
763	$R^1 = PrCH{=}CH$, $R^2 = Et$, $R^3 = Me$	50	1997JOC706



Scheme 120

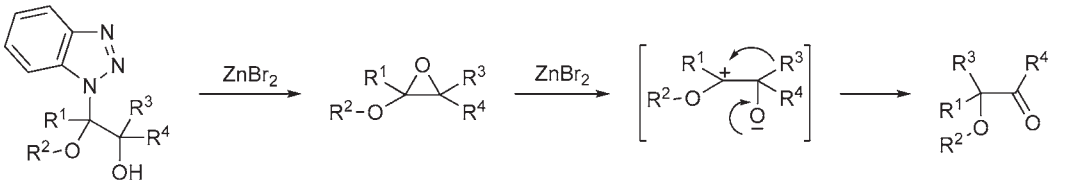


R^1 = Aryl or PhCH(Me)
R^2 = H, Me, Et or Ph
or $R^1R^2 = -C_5H_{10}-$

Scheme 121

5.01.8.7.3 Rearrangements

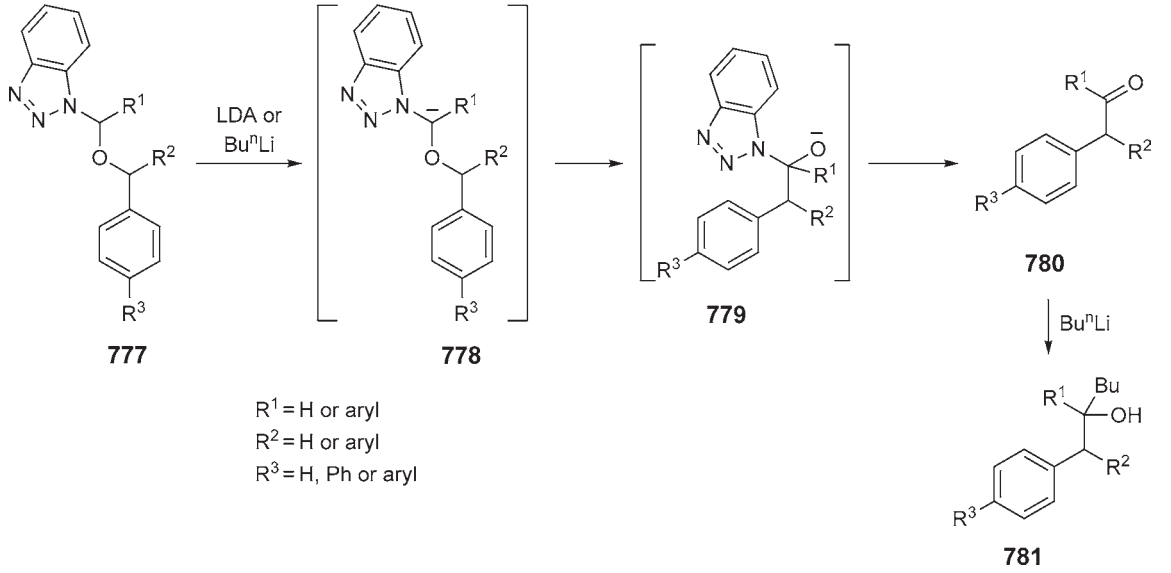
When crude reaction mixtures containing derivatives **756** (**Scheme 119**) are treated with three-fold excess of $ZnBr_2$ and heated to reflux, benzotriazole is eliminated and the products rearrange to α-alkoxyketones **776** (**Scheme 122**). The proposed mechanism involves formation of oxiranes **774** (in some cases isolated intermediates) which then open to betaines **775**. Subsequent migration of substituent R^3 furnishes α-alkoxyketone **776**. The conversion is characterized by remarkable regioselectivity with only one regioisomer formed from intermediates with $R^3 \neq R^4$ with the order of migration: H > Ar > alkyl (*tert*-alkyl > *sec*-alkyl > *n*-alkyl) <1996JOC7564>. A similar rearrangement of derivatives **756** (R^1 = H, R^2 = Ph, R^3 = H, R^4 = alkyl) is promoted by treatment with *p*-TsOH in acetic acid <1995TL841>.



756 **774** **775** **776**

Scheme 122

Treated with strong bases, α-(benzotriazol-1-yl)alkyl ethers **777** derived from benzyl alcohols undergo [1,2]-Wittig rearrangement to ketones **780** (**Scheme 123**). For the derivatives of aromatic aldehydes (R^1 = aryl), LDA is a base strong enough to pull the benzylic proton from ether **777** to give anion **778**. The subsequent [1,2]-Wittig rearrangement produces alkoxide **779** which spontaneously expels benzotriazole anion to furnish ketone **780** <2002ARK(vii)146>. In the case of formaldehyde derivatives (R^1 = H), a stronger base, Bu^nLi, is required to do the job; however, it is difficult to stop the reaction sequence at the ketone stage, and alcohols **781** are obtained as the major products <2000H(53)1783>.

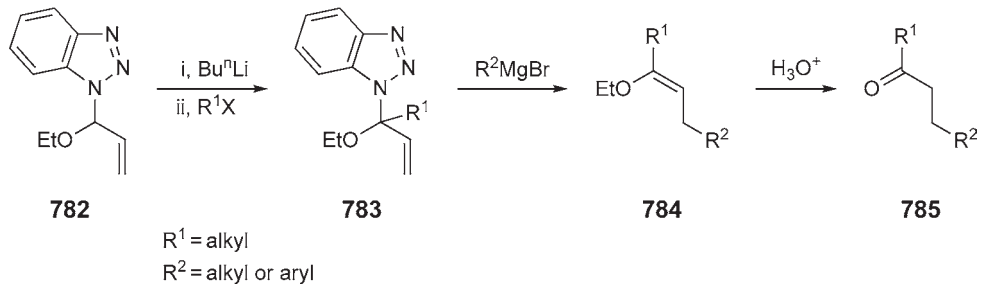


777 **778** **779** **780** **781**

Scheme 123

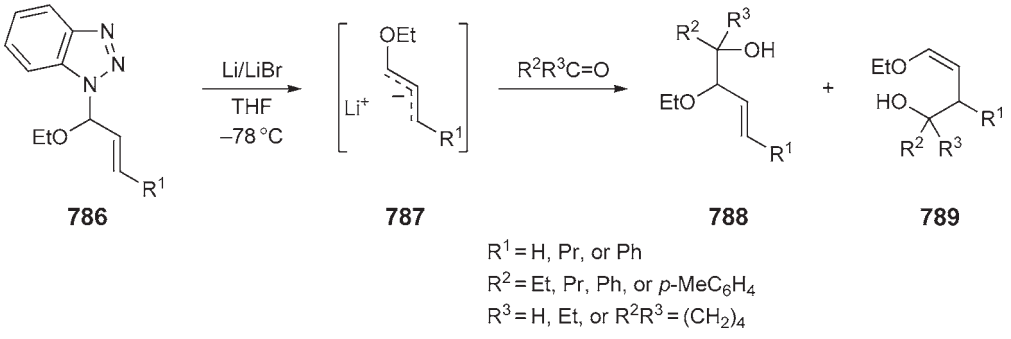
5.01.8.7.4 Allyl ethers

α-(Benzotriazol-1-yl)allyl ethyl ether **782** can be readily alkylated to give tertiary ethers **783**. Grignard reagents attack ethers **783** exclusively in γ-position (S_N2' reaction) producing enol ethers **784** which are hydrolyzed during acidic work-up to ketones **785** (**Scheme 124**). High regioselectivity of these reactions is rationalized by substitution of the α-carbon atom with bulky groups <1995JOC7605>.



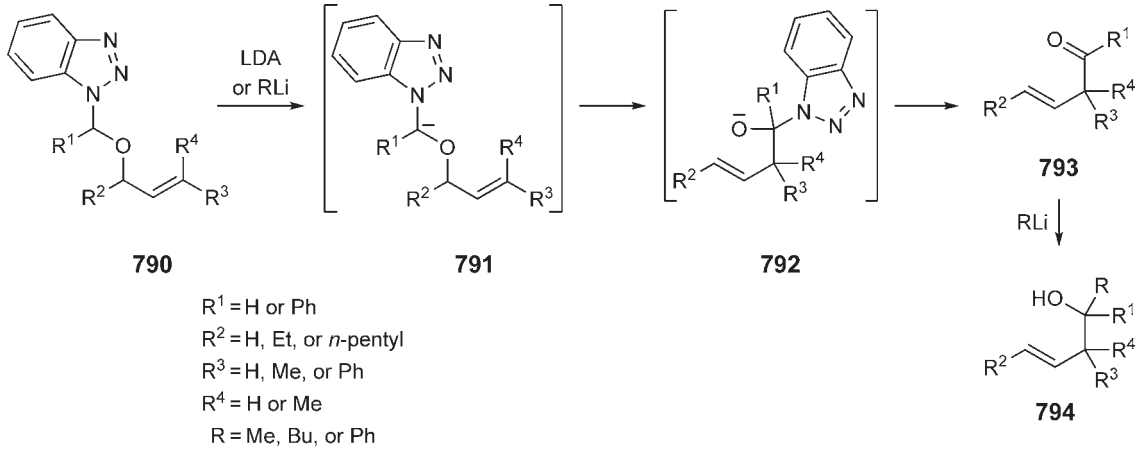
Scheme 124

Treated with a suspension of metallic lithium at low temperatures, ethers **786** are reduced to anions **787**. Addition of an aldehyde or ketone to the reaction mixture allows trapping these anions with formation of β-hydroxyethers **788** and enol ethers **789** (**Scheme 125**). For $R^1 = H$, in reactions with aliphatic aldehydes and ketones, the α-attack prevails to give hydroxyethers **788** as the major products. In other cases, products **789** resulting from the γ-attack of anion **787** on a carbonyl group become dominant. Stereochemistry of products **789** (*cis* : *trans)* also depends strongly on substituents R^1 with the *cis* geometry prevailing (98:2 to 4:2) for $R^1 = H$ or Pr. When $R^1 = Ph$, mostly *trans* isomers (1: 2) are formed <1998TL6437>.



Scheme 125

For allyl ethers **790** with $R^1 = Ph$, treatment with LDA generates anions **791** which undergo [2,3]-Wittig rearrangement to more stable alkoxides **792** (**Scheme 126**). Spontaneous expulsion of benzotriazole anion from **792** generates β,γ-unsaturated ketones **793** that are isolated in high yields (86–92%) <1996JOC4035>. In the case of

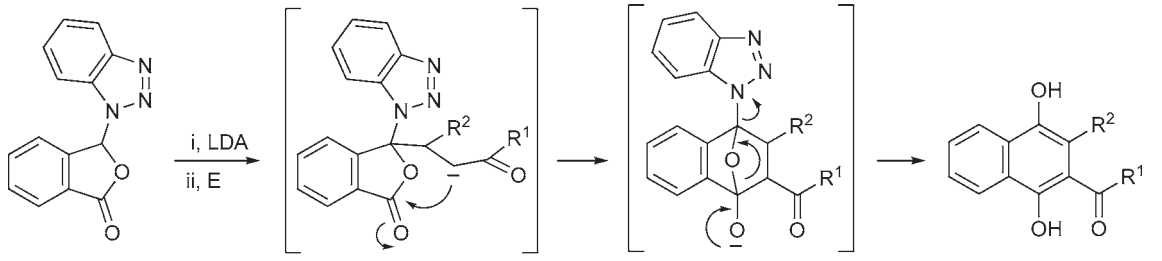


Scheme 126

R^1 = H, stronger bases required to pull the α-proton from ethers **790** react also with intermediate aldehydes **793** to convert them into alcohols **794**. In all these reactions, exclusive formation of the products with the *(E)* configuration is observed.

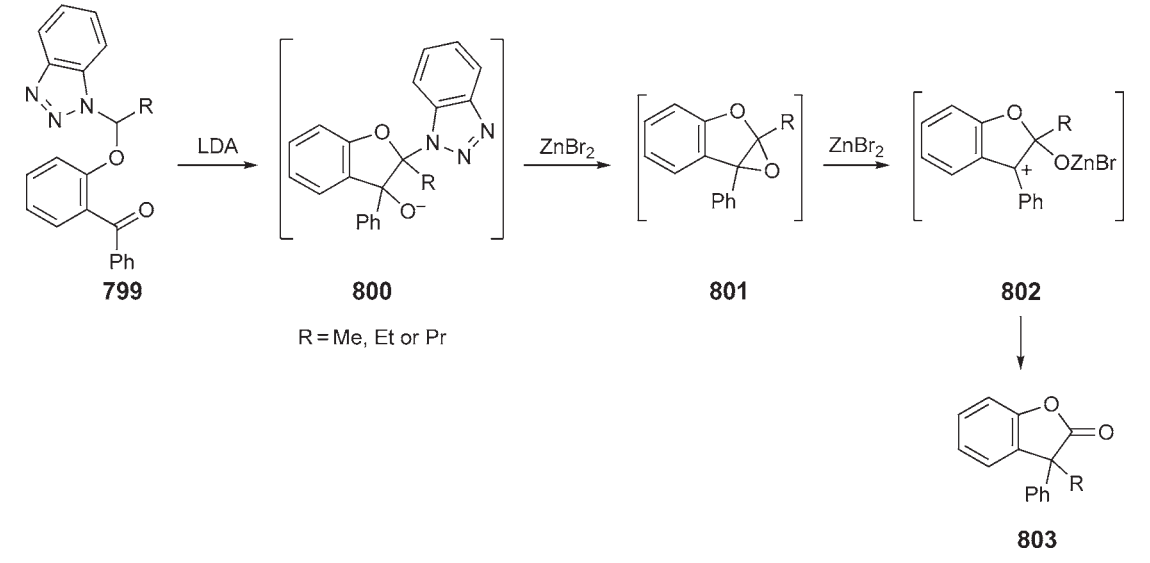
5.01.8.7.5 Cyclocondensations

Condensation of benzotriazole with 2-carboxybenzaldehyde gives 3-(benzotriazol-1-yl)phthalide **795** (**Scheme 127**). The anion derived from phthalide **795** adds to the β-carbon atom of α,β-unsaturated carbonyl compounds *E* to produce anion **796** that by intramolecular nucleophilic attack on the phthalide carbonyl group is converted to anion **797**. Spontaneous expulsion of benzotriazole from molecules **797** followed by aromatization leads to 1,4-dihydroxynaphthalenes **798** <1997SC3951>.



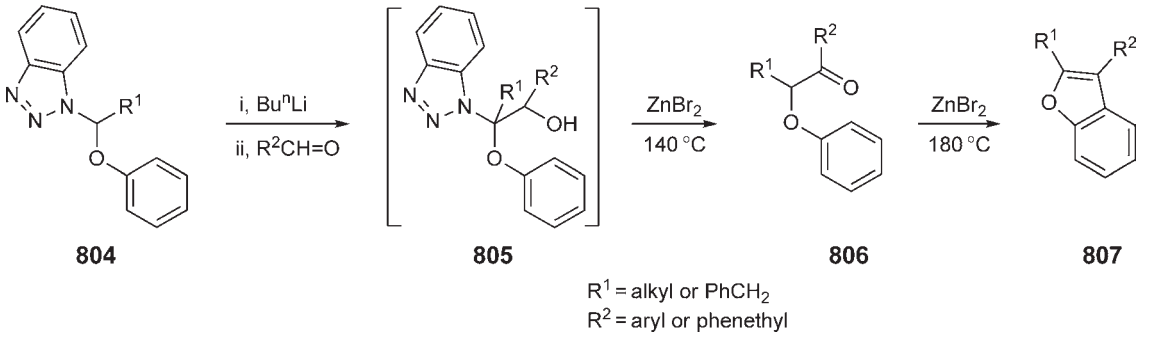
Scheme 127

Alkylation of 2-hydroxybenzophenone with 1-(α-chloroalkyl)benzotriazoles provides ethers **799**. Treated with LDA, ethers **799** lose α-proton. Nucleophilic intramolecular attack of the obtained anions on the carbonyl group leads to alkoxides **800** (**Scheme 128**). When a treatment with $ZnBr_2$ follows, an arrangement occurs resulting in formation of 2,3-dihydrobenzofuran-2-ones **803**. The suggested mechanism involves elimination of benzotriazole with formation of epoxides **801**. Promoted by $ZnBr_2$, the epoxides open to cations **802** which rearrange to final products **803** <2004ARK(vi)27>.



Scheme 128

Two examples discussed above involve participation of an *ortho* substituent on the aromatic ring in the cyclization process; however without such a substituent, α-(benzotriazol-1-yl)alkyl aryl ethers can also be employed as the starting materials for introduction of an additional ring. Thus, lithiation of ether **804** followed by treatment with an aldehyde generates β-hydroxyether **805** (**Scheme 129**). Treated with $ZnBr_2$ and heated at 140 °C, derivatives **805** eliminate benzotriazole and rearrange to α-aryloxyketones **806**. When heating with $ZnBr_2$ is continued at even higher temperature (175–180 °C), cyclocondensation of ketones **806** with involvement of the phenyl *ortho* carbon atom leads finally to benzofurans **807** <1998J(P1)1059>.



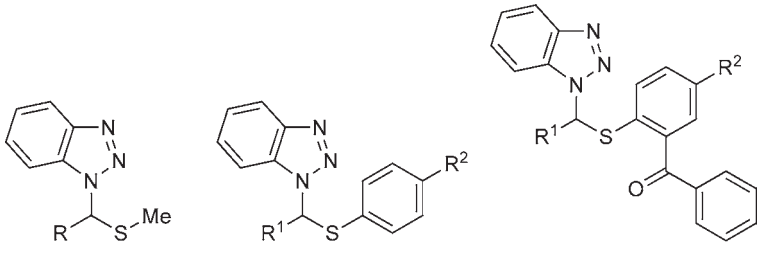
804 **805** **806** **807**

Scheme 129

5.01.8.8 Ring N–C(sp^3)-X (X = heteroatom ≠ N or O)

5.01.8.8.1 Sulfur derivatives

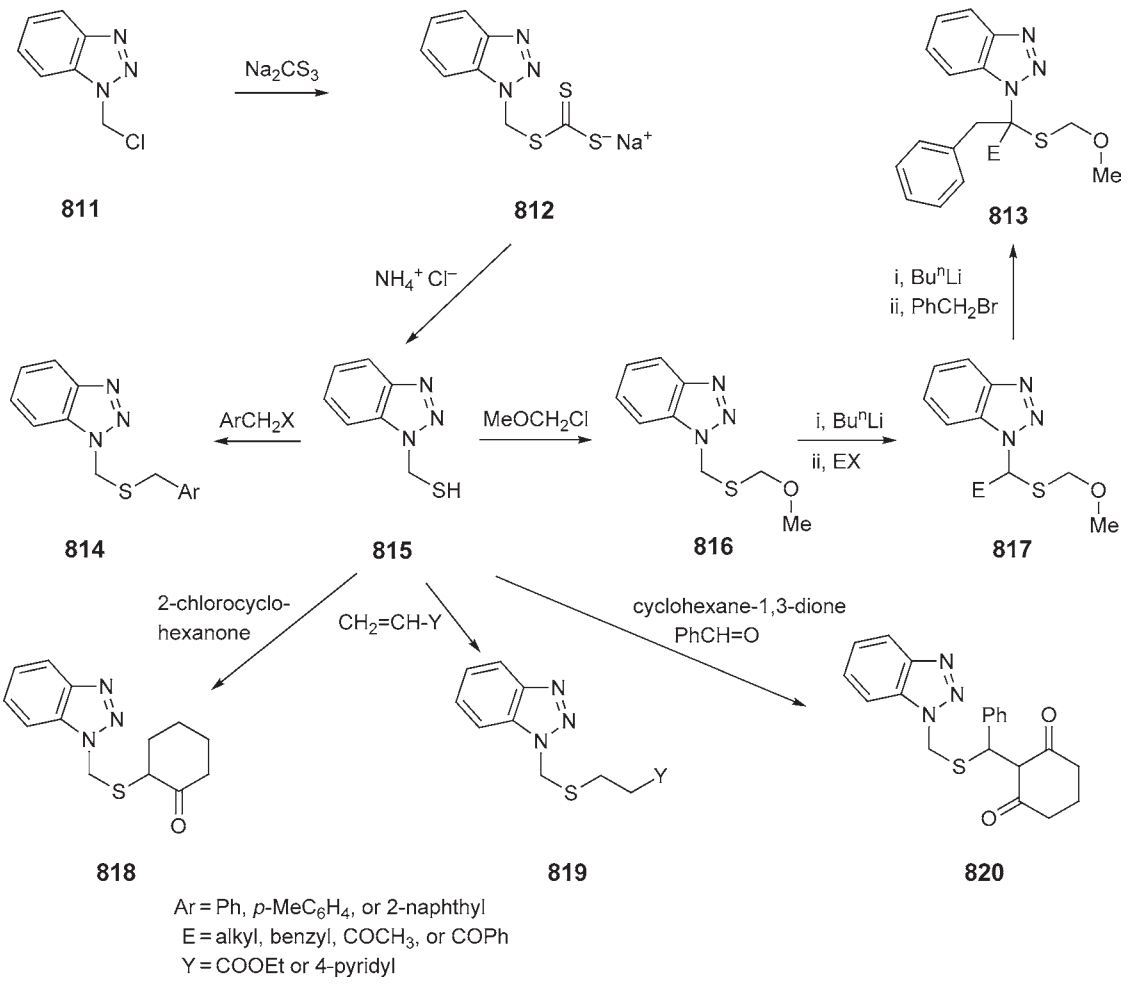
The preparation of α-(benzotriazol-1-yl)alkyl thioethers and their reactions with nucleophiles have been discussed before <1996CHEC-II(4)1>. To some extent, α-(benzotriazol-1-yl)alkyl thioethers react similarly to the related ethers. Thus, thioether **808** can be lithiated with Bu^{n}Li then treated with an aldehyde or a ketone to give a sulfur analog of α-(benzotriazol-1-yl)-β-hydroxyalkyl ether **756**. Similarly to ethers **756**, their sulfur analogs can be hydrolyzed to α-hydroxyketones **760** (**Scheme 119**) <1998JOC2110, 2004JOC303>. Lithiated, then treated with an aldehyde or ketone followed by $ZnBr_2$, thioether **809** is converted to the corresponding benzothiophene <1998J(P1)1059>, in analogy to conversion of ether **804** to benzofuran **807**. Similarly to conversion of ethers **799** to 2,3-dihydrobenzofuran-2-ones **803** (**Scheme 128**), thioethers **810** are converted to the corresponding 2,3-dihydrobenzothiophen-2-ones <2004ARK(vi)27>. In general, due to better stabilization of the adjacent carbocation than it is possible in ethers, properties of α-(benzotriazol-1-yl)alkyl thioethers resemble in some aspects those of α-(benzotriazol-1-yl)alkylamines. However, in other aspects, properties of thioethers are quite unique.



808 **809** **810**

1-(Mercaptomethyl)benzotriazole **815** is conveniently prepared by treatment of 1-(chloromethyl)benzotriazole **811** with sodium trithiocarbonate followed by hydrolysis of the obtained hemi ester **812** with ammonium chloride (**Scheme 130**). In the presence of triethylamine, mercaptan **815** reacts readily with arylmethyl halides to give sulfides **814** in high yields. Alkylation of mercaptan **815** with chloromethyl methyl ether provides methoxymethyl thioether **816** that can be substituted at the α-carbon atom by treatment with Bu^{n}Li followed by an electrophile to

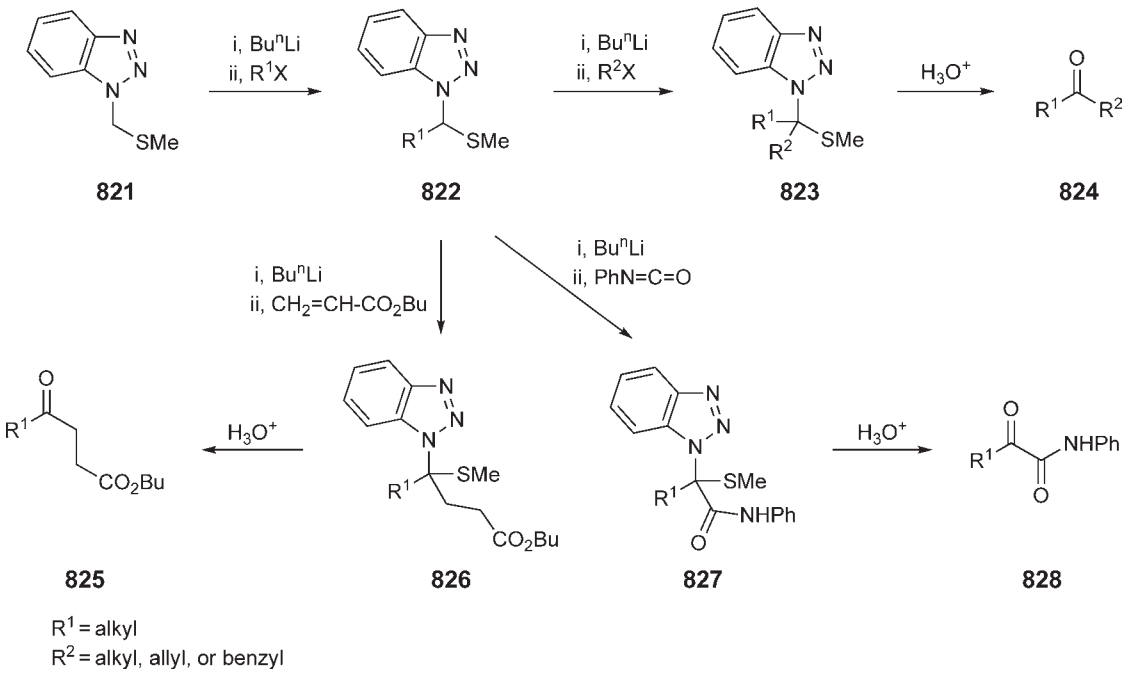
furnish thioethers **817**. Repeated treatment with Bu^nLi and an electrophile (benzyl bromide) allows substitution of the remaining α-proton to get derivative **813**. Among other reactions performed on mercaptan **815** are substitution of the chlorine atom in 2-chlorocyclohexanone to give product **818**, addition to electron deficient vinyl groups (products **819**) and condensation/addition with 1,3-cyclohexanedione and benzaldehyde to produce derivative **820** <1996JHC1927>.



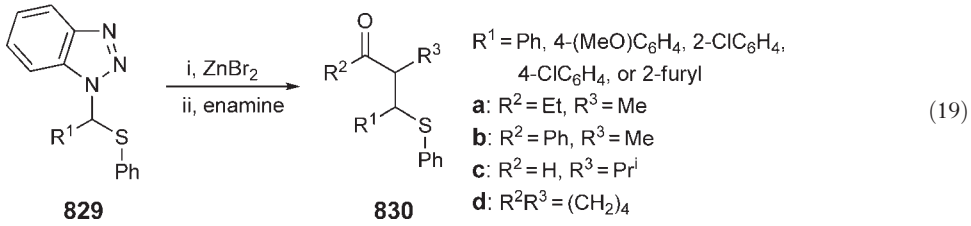
Scheme 130

The readily available benzotriazolyl derivative of dimethyl sulfide, compound **821**, can be alkylated on α-carbon in a stepwise manner to provide (α,α-disubstituted)alkyl thioethers **823** (**Scheme 131**). Hydrolysis of these thioethers under mild conditions (5% H_2SO_4 at room temperature) furnishes ketones **824** in high yields. The anion derived from mono substituted (benzotriazol-1-yl)methyl thioether **822** adds to butyl acrylate to give intermediate **826** that can be hydrolyzed to γ-ketoester **825**. In another example of reactivity of α-(benzotriazol-1-yl)alkyl thioethers, treatment of thioether **822** with Bu^nLi followed by phenyl isocyanate converts it into α-ketoanilide **828**, via intermediate adduct **827** <1998JOC2110>.

Treated with $ZnBr_2$ followed by enamines, phenyl thioethers **829** derived from aryl aldehydes are converted to β-(phenylthio)alkyl ketones or aldehydes **830** in moderate to good yields (Equation 19). Enamines used in these syntheses are: (1) morpholine enamine derived from diethyl ketone, (2) diethylamine enamine of propiophenone, (3) piperidine enamine derived from isovaleraldehyde, and (4) pyrrolidine enamine of cyclohexanone <2000H(53)331>.



Scheme 131

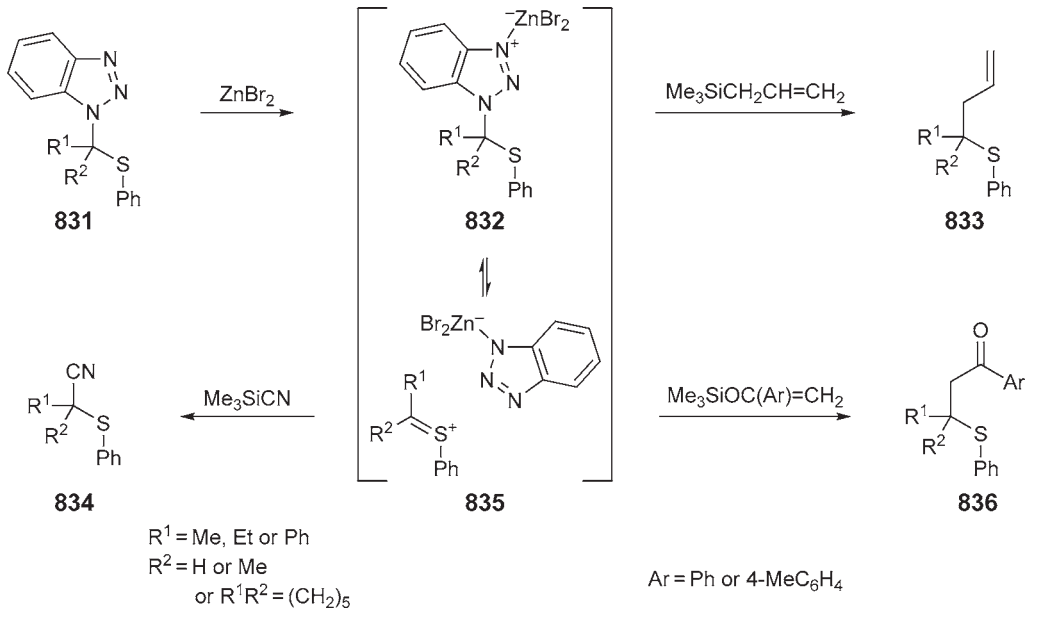


(19)

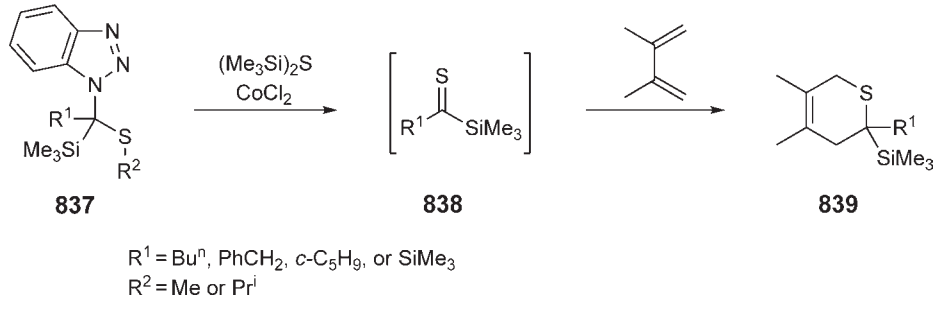
Treatment of α-(benzotriazol-1-yl)alkyl thioethers **831** with $ZnBr_2$ weakens the bond with benzotriazole, and the obtained complex **832** may partially dissociate to thionium cation **835** that can be trapped by even mild nucleophiles. Thus, trimethylsilyl cyanide added to the reaction mixture causes substitution of the benzotriazole moiety by the CN group to give α-(phenylthio)carbonitrile **834**. In a similar manner, treatment with allylsilane leads to γ,δ-unsaturated thioether **833**. Addition of species **835** to the double bond of a trimethylsilyl α-arylvinyl ether followed by hydrolysis of the silyloxy group furnishes β-(phenylthio)alkyl aryl ketones **836** (**Scheme 132**) <1996TL6631>.

Introduction of trimethylsilyl substituents attached directly to the α-carbon atom of α-(benzotriazol-1-yl)alkyl thioethers provide new opportunities. Thus, treatment of lithiated monosubstituted α-(benzotriazol-1-yl)alkyl thioethers with chlorotrimethylsilane produces α-(trimethylsilyl)alkyl thioethers **837**. In reactions with hexamethyldisilathiane and cobalt dichloride, thioethers **837** are converted to thioacylsilanes **838** that can be trapped in a Diels–Alder reaction with 2,3-dimethylbutadiene to form 2-alkyl-4,5-dimethyl-2-trimethylsilyl-3,6-dihydro-2*H*-thiopyrans **839** (**Scheme 133**) <2000JOC9206>.

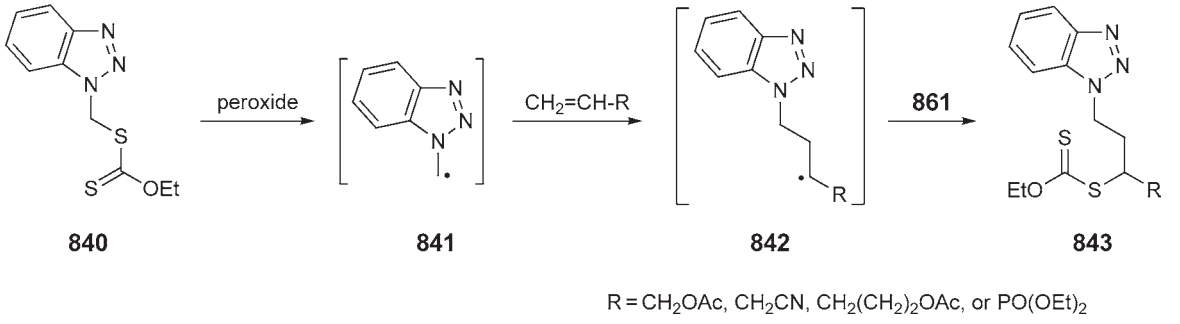
All reactions of benzotriazole derivatives of the type Bt-CR^1R^2-S discussed above are based on electrophilic or nucleophilic substitutions at the α-carbon, but radical reactions are also possible. Thus, the first report on unsubstituted carbon-centered (benzotriazol-1-yl)methyl radical **841** involves derivatives of (benzotriazol-1-yl)methyl mercaptan. *S*-(Benzotriazol-1-yl)methyl-*O*-ethyl xanthate **840** is readily prepared in a reaction of 1-(chloromethyl)-benzotriazole with commercially available potassium *O*-ethyl xanthate. Upon treatment with radical initiators (lauroyl peroxide), the C–S bond is cleaved to generate radical **841** that can be trapped by alkenes to generate new radicals **842**. By taking the xanthate moiety from the starting material, radicals **842** are converted to final products **843** with regeneration of radicals **841** allowing repetition of the process (**Scheme 134**). Maleinimides are also satisfactorily used as radical traps in these reactions <2001H(54)301>.



Scheme 132



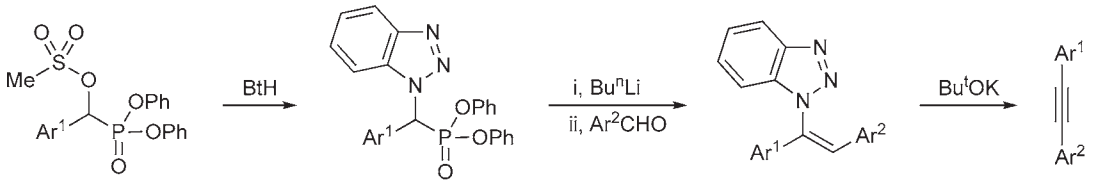
Scheme 133



Scheme 134

5.01.8.8.2 Phosphorus derivatives

Methanesulfonates **844**, obtained by addition of diphenyl phosphite to aldehydes Ar^1CHO and mesylation of the hydroxyl group of the adducts, react with benzotriazole to give diphenyl α-(benzotriazol-1-yl)benzylphosphonates **845**. Lithiation and treatment with aldehydes Ar^2CHO converts phosphonates **845** into stilbenes **846**, which can eliminate benzotriazole to give diarylacetylenes **847** (**Scheme 135**) <2002ARK(xiii)17>.

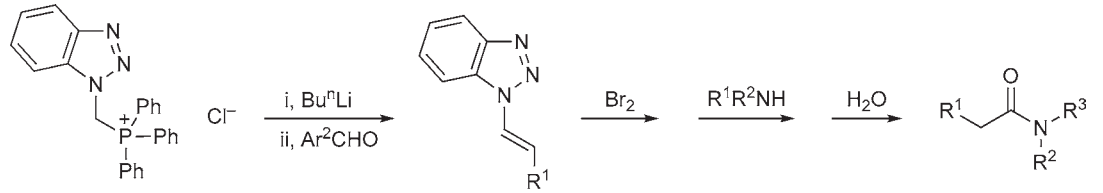


844 **845** **846** **847**

BtH = benzotriazole
Ar^1 = Ph, 4-MeC$_6$H$_4$, or 4-ClC$_6$H$_4$
Ar^2 = Ph, 4-MeC$_6$H$_4$, 4-(NO$_2$)C$_6$H$_4$, 1-naphthyl,
2-furyl, 2-thienyl, 2-pyridyl, or 3-pyridyl

Scheme 135

[(Benzotriazol-1-yl)methyl]triphenylphosphonium chloride **848** reacts with Bu^{n}Li and aldehydes to give 1-(alken-1-yl)benzotriazoles **849**. Addition of bromine to the double bond of derivatives **849** followed by a reaction with amines furnishes amides **850**. A variety of primary or secondary amines can be used. This way aldehydes are conveniently homologated and converted to amides with a one-atom longer chain (**Scheme 136**) <2004ARK(ix)44.



848 **849** **850**

R^1 = Et, Pr^i, Ph, or 2-thienyl
R^2 = various alkyl, aryl or heteroaryl, and R^3 = H
or R^{1}R^2 = (CH$_2$)$_5$, (CH$_2$)$_2$O(CH$_2$)$_2$, or (CH$_2$)$_2$NMe(CH$_2$)$_2$

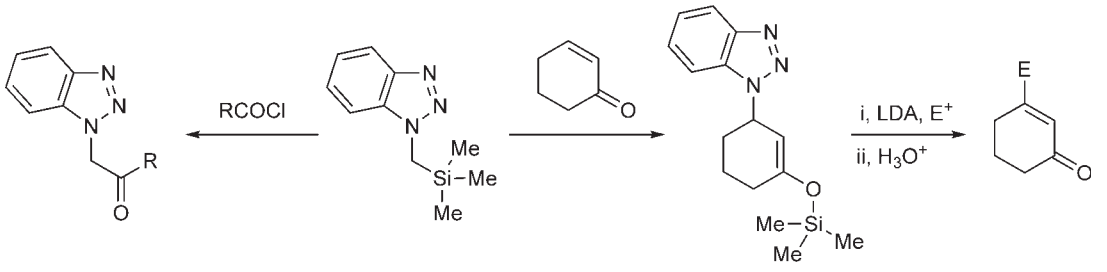
Scheme 136

5.01.8.8.3 Silicon derivatives

[(Benzotriazol-1yl)methyl]trimethylsilane **852** reacts with acyl chlorides under mild conditions to provide (benzotriazol-1-yl)methyl ketones **851** in high yields (**Scheme 137**) <2001J(P1)2483, 2001JOC5606>. Reactivity of benzotriazolyl derivatives of type **851** and their application in organic synthesis are discussed in Section 5.01.8.4. 1,4-Adition of silane **852** to 2-cyclohexen-1-one produces derivative **853** that is unstable to the air; however, direct treatment of the reaction mixture with a base generates an anion that can be trapped by various electrophiles. Final hydrolysis of the silyloxy group and elimination of benzotriazole give rise to 3-substituted 2-cyclohexen-1-ones **854** <1995TL5491>.

5.01.8.8.4 1-(Chloromethyl)benzotriazole

1-(Chloromethyl)benzotriazole **856** is an important starting material for preparation of many derivatives of benzotriazole that are discussed in this section. All these reactions rely on the nucleophilic substitution of chlorine in **856** with nucleophiles to give derivatives **855** <1996CHEC-II(4)1>. However, it appears that compound **856** can also be converted into its anion by treatment with LDA at −40 °C. The anions generated this way can be trapped by ketones to provide a convenient method for the synthesis of (benzotriazol-1-yl)oxiranes **857** (**Scheme 138**) <2003JOC407>.

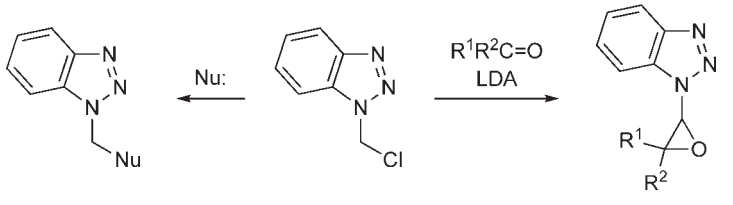


851 **852** **853** **854**

R = alkyl, aryl, or $ClCH_2$

E = alkyl, $ArCH_2$, PhCO, PhCHOH, Ph_2COH, or ArNHCS

Scheme 137



855 **856** **857**

R^1 = Me, Et, Ph, 4-MeC_6H_4 or 4-ClC_6H_4

R^2 = Et or Ph, or

R^1R^2 = $(CH_2)_5$

Scheme 138

5.01.8.9 Ring N–C(sp²)═C

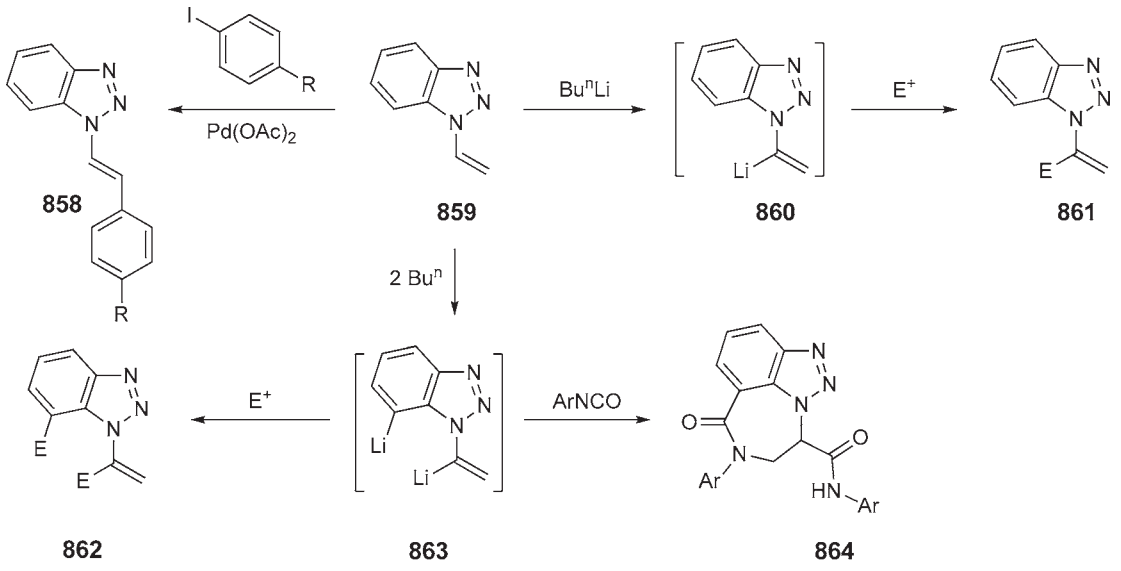
5.01.8.9.1 Alkenyl group not activated

In the presence of a palladium catalyst, 1-vinylbenzotriazole **859** reacts with iodoarenes to give derivatives **858** (**Scheme 139**). Exclusive addition to the β-carbon and *(E)* geometry of molecules **858** are confirmed by NMR data <1999H(50)767>. To introduce substituents on the α-carbon, 1-vinylbenzotiazole is lithiated first with 1 molar equivalent of Bu^nLi to give intermediate **860** and then treated with electrophiles to furnish products **861** <2003JOC5713>. Use of *2* equiv of Bu^nLi produces dilithiated intermediate **863** giving rise to disubstituted products **862**. When reagents with two electrophilic centers are used, like $(PhCO)_2$ or $(PhCO)_2CH_2$, an additional ring is added to the heterocyclic system involving atoms C-*α* and C-7. Initial addition of two isocyanate groups to C-*α* and C-7 is followed by an intramolecular nucleophilic addition of the amide N-H to the vinyl bond resulting in products **864** <2003JOC5713>.

1-Alkenylbenzotriazoles **865** are readily prepared by isomerization of the corresponding allyl derivatives catalyzed by Bu^tOK. Lithiated compounds **865** are treated with electrophiles to provide α-substituted derivatives **866**. Epoxidation of the double bond with *m*-chloroperbenzoic acid converts intermediates **866** into oxiranes **867** that can be hydrolyzed to furnish α-hydroxyketones **868** in good yields (**Scheme 140**) <1996SC2657>.

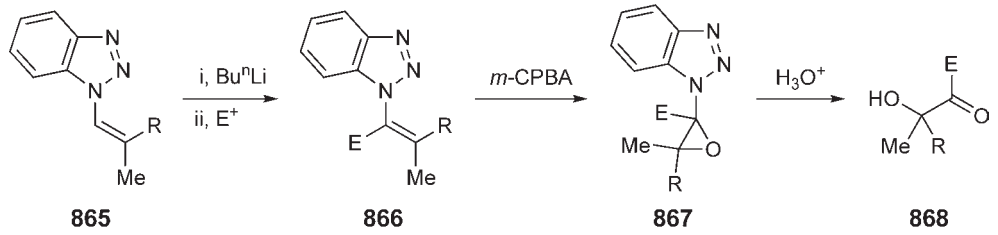
5.01.8.9.2 Electron-withdrawing substituents

Compounds of this type with an electron-withdrawing substituent at C-α can be easily prepared by condensation of 2-(benzotriazol-1-yl)acetophenone **869** with aldehydes. Exclusively *(E)* isomers of α,β-unsaturated ketones **870** are formed. Treatment with hydrazines converts derivatives **870** into pyrazolines **871**. Elimination of benzotriazole from **871** in the presence of mild bases furnishes pyrazoles **872**. When in these reactions hydroxylamine is used instead of hydrazines, the corresponding isoxazoles are obtained (**Scheme 141**) <2001JOC6787>.



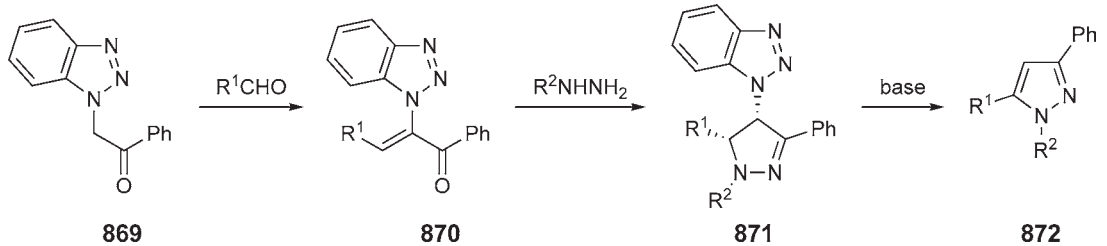
R = Me or OMe
E^+ = 4-MeC_6H_4CHO, PhCOCH=CHPh, or 4-MeC_6H_4NCO
Ar = Ph or 4-MeC_6H_4

Scheme 139



R = H or Me
E = octyl, 4-$BrC_6H_4CH_2$, PhCHOH, Ph_2COH, or 1-hydroxycyclohexyl

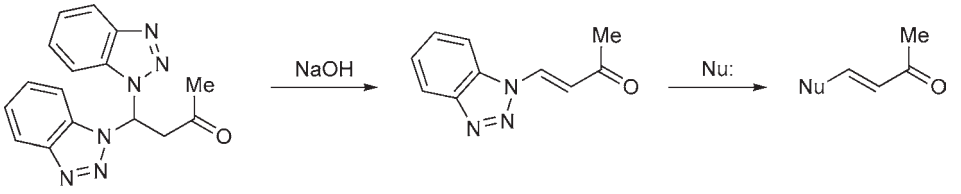
Scheme 140



R^1 = Pr^i, Ph, 4-MeC_6H_4, or 3-pyridyl
R^2 = Me or Ph

Scheme 141

Compound **874**, as a representative of derivatives with an electron-withdrawing substituent at C-β of the vinyl group, is easily prepared by elimination of one benzotriazole from 2,2-*bis*(benzotriazol-1-yl)ethyl methyl ketone **873**. The stereoselective elimination catalyzed by NaOH gives exclusively the *(E)* isomer of derivative **874**. Addition of nucleophiles to the double bond of vinyl ketone **874** followed by elimination of benzotriazole leads to α,β-unsaturated ketones **875**. Amines used as nucleophiles do not need any catalysis, but reactions with carbon and sulfur nucleophiles require addition of a base. The total effect is nucleophilic substitution of the benzotriazolyl group at the β-carbon of α,β-unsaturated ketone (**Scheme 142**) <1996SC3773>.



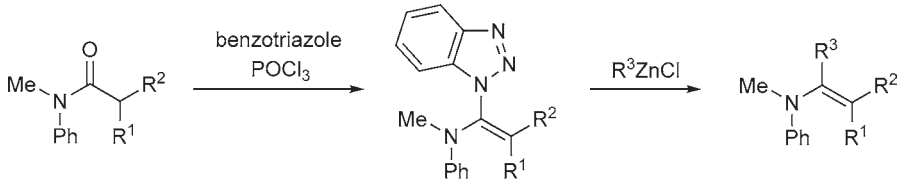
873 **874** **875**

Nu: = piperidine, morpholine, 2-nitropropane, $MeCH(CO_2Et)_2$, $Ph(CH_2)_3CN$, or PhSH

Scheme 142

5.01.8.9.3 Electron-donating substituents

α-(Benzotriazol-1-yl)enamines **877** can be conveniently prepared in reactions of amides **876** with benzotriazole and $POCl_3$. Enamines **877** are stable enough to be separated by column chromatography as pure stereoisomers; however, their long storage in a solution showed partial isomerization between benzotriazol-1-yl and benzotriazol-2-yl isomers. Nucleophilic substitution of benzotriazole with organozinc reagents furnishes enamines **878** (**Scheme 143**) <2000ARK(v)667>.

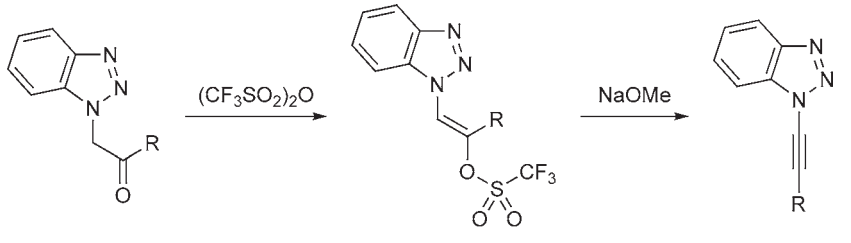


876 **877** **878**

R^1 = H or Me
R^2 = Me or Et
R^3 = Me or PhCC

Scheme 143

Triflate **880** can be formally considered as an ester of the enol form of ketone **879**. Treatment with a base causes elimination of the triflate group to afford 1-(benzotriazol-1-yl)alkynes **881** (**Scheme 144**) <2000OL3789>.



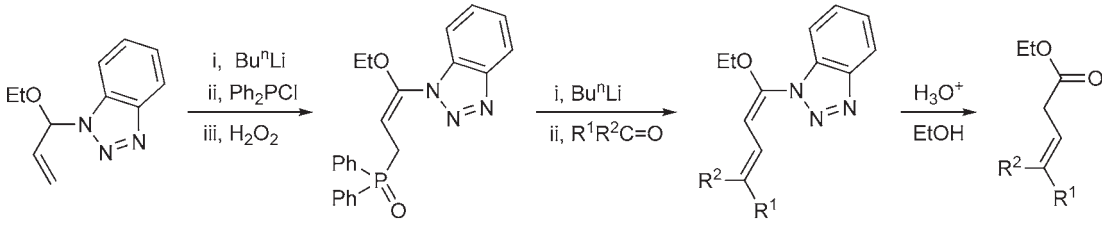
879 **880** **881**

R = alkyl or aryl

Scheme 144

5.01.8.9.4 Allylic derivatives

The benzotriazolyl derivative of acrolein acetal, compound **882**, is lithiated, treated with chlorodiphenylphosphine, and the obtained intermediate is oxidized with hydrogen peroxide to phosphine oxide **883** (**Scheme 145**). The relatively acidic proton in derivative **883** is easily removed by a base, and the obtained anion adds to a carbonyl group of aldehyde or ketone. Subsequent rearrangement and elimination of the phosphorane group generates diene **884**. For the derivatives of aldehydes (**884**, $R^2 = H$), *(E)–(E)* stereoselectivity of the elimination is observed. Acidic alcoholysis of dienes **884** affords esters of β,γ-unsaturated carboxylic acids **885** < 1997JOC4131>.

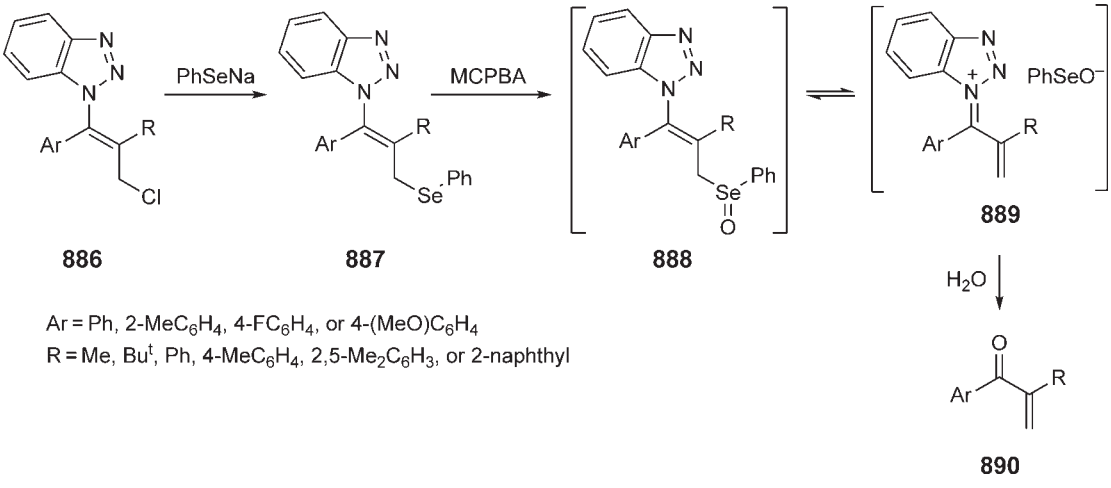


882 **883** **884** **885**

R^1 = *n*-C_3H_7, *n*-C_7H_{15}, Ph, or $PhCH_2CH_2$
R^2 = H, Me, *n*-C_3H_7, or Ph, or
$R^1R^2 = (CH_2)_5$

Scheme 145

The allylic chlorine atom in derivatives **886** can be easily substituted by nucleophiles <2002EJO493>. Reactions of chlorides **886** with sodium benzeneselenide provide allylic selenides **887**. Oxidation of the selenium atom in selenides **887** with *m*-chloroperbenzoic acid generates unstable selenoxides **888**. Contrary to the corresponding sulfoxides <2002EJO493>, and due to good leaving ability of the benzeneselenate moiety, selenoxides **888** may dissociate to cations **889** that are readily hydrolyzed to vinyl ketones **890** (**Scheme 146**) <2002TL3021>.



886 **887** **888** **889** **890**

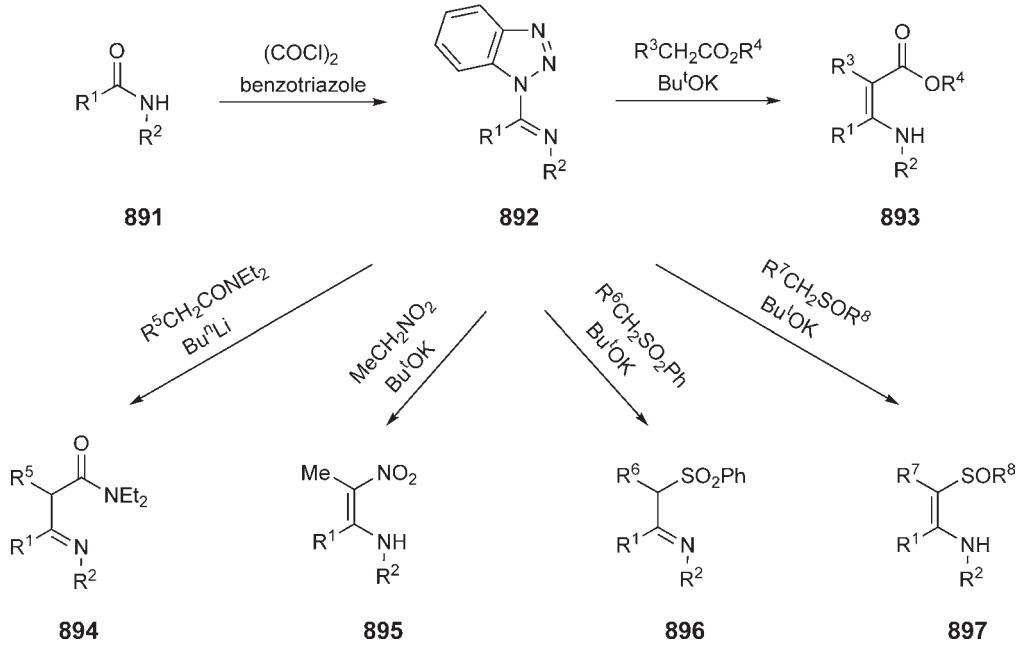
Ar = Ph, 2-MeC_6H_4, 4-FC_6H_4, or 4-$(MeO)C_6H_4$
R = Me, Bu^t, Ph, 4-MeC_6H_4, 2,5-$Me_2C_6H_3$, or 2-naphthyl

Scheme 146

5.01.8.10 Ring N–C(sp^2)═N

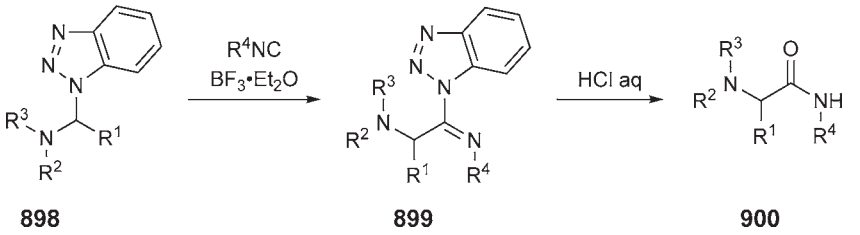
1-Imidoylbenzotriazoles **892** are prepared in good yield (50–90%) in reactions of amides **891** with benzotriazole and oxalyl chloride in the presence of pyridine <2006JOC3375>. Derivatives **892** are convenient reagents for imidoylation of methylene groups activated by electron-withdrawing substituents. Thus, in their reactions with ester enolates,

generated from the corresponding esters by addition of Bu^{t}OK, 1-imidoylbenzotriazoles **892** give β-enaminoesters **893** in 77–88% yield. Similarly, β-iminoamides **894** are obtained in 48–69% from reactions of compounds **892** with amides deprotonated by Bu^{n}Li. The anions generated from nitroethane, alkyl phenyl sulfones, or sulfoxides by action of Bu^{t}OK react with 1-imidoylbenzotriazoles **892** to provide derivatives **895**, **896**, and **897**, respectively, in generally good yields. All of these products can exist in equilibria between the enamine and imine forms; however, the NMR data indicate that the enamine forms are strongly predominant for derivatives **893**, **895**, and **897** (**Scheme 147**) <2007ARK(v)263>.



Scheme 147

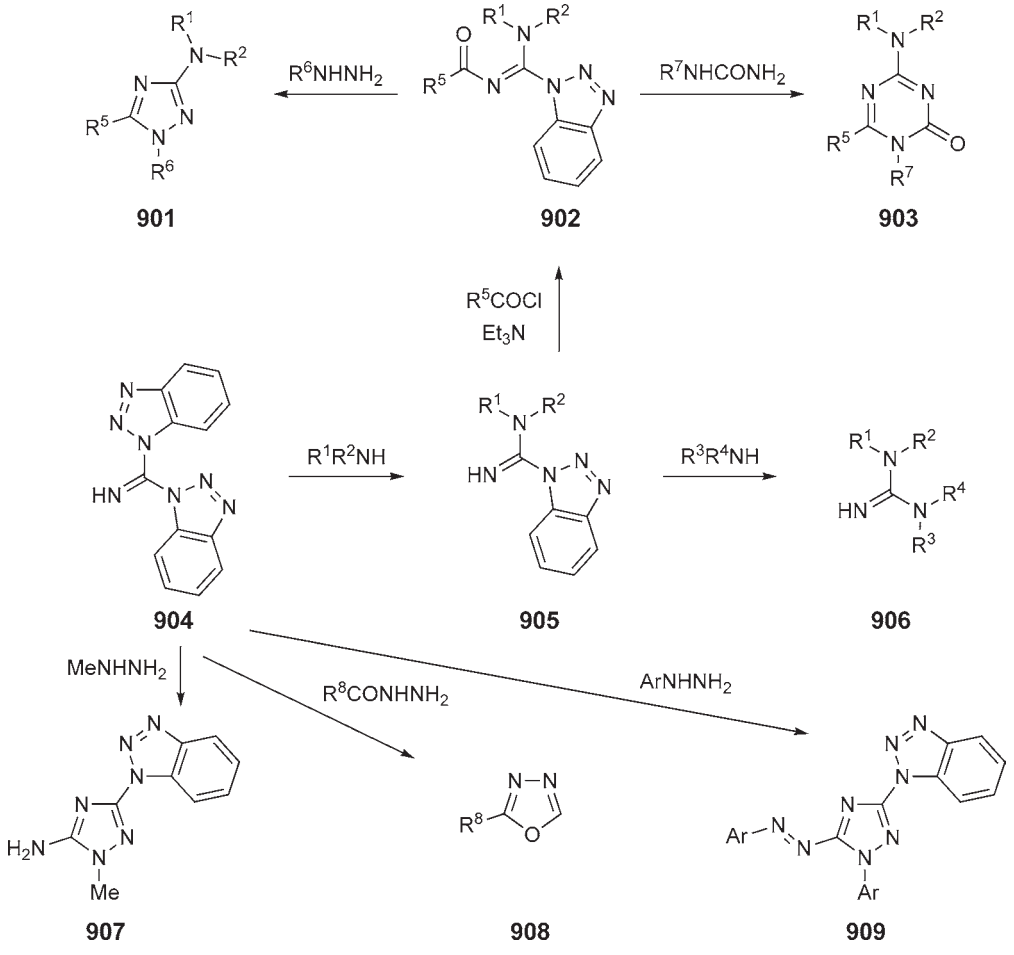
Reactions of *N*-(α-aminoalkyl)benzotriazoles **898** with isonitriles catalyzed by boron trifluoride etherate give *N*-(α-aminoalkylimidoyl)benzotriazoles **899** in high yield. Upon treatment with hydrochloric acid, derivatives **899** are conveniently converted to α-aminoamides **900** (**Scheme 148**) <2005JSC319>.



Scheme 148

A reaction of benzotriazole with cyanogen bromide carried out in ethanol in the presence of NaOH provides dibenzotriazolylmethanimine **904** as a mixture of benzotriazol-1-yl and 2-yl isomers <1996POL4011, 2000JOC8080>. To simplify the picture, only the benzotriazol-1-yl isomer is shown in **Scheme 149**. Treatment with amines converts methanimine **904** under mild conditions into carboxyimidamides **905** as sole benzotriazol-1-yl isomers. Upon treatment with other amines at slightly elevated temperature, the second benzotriazolyl moiety can be replaced to provide guanidines **906** bearing up to four different groups <2000JOC8080>. Acyl derivatives **902** undergo cyclocondensation with alkyl or aryl hydrazines to give 3-amino-1,2,4-triazoles **901** in good yields

<2001S897>. Cyclocondensation of derivative **902** with ureas provides 1,3,5-triazin-2-ones **903**, whereas a similar reaction with thioureas gives 1,3,5-triazin-2-thiones <2001JOC6797>. Hydrazides derived from aromatic carboxylic acids react with imine **904** to give oxadiazoles **908** almost quantitatively, whereas only 42% yield was achieved in an analogous reaction of acetyl hydrazide <2002ARK(vi)82>. Cyclocondensation of imine **904** with methylhydrazine produces 1,2,4-triazole **907**; however, in the case of arylhydrazines, a more complex process involving condensation of **904** with two molecules of hydrazine, elimination of ammonia and oxidation with atmospheric oxygen leads to azo derivatives **909** <2002ARK(vi)82>.

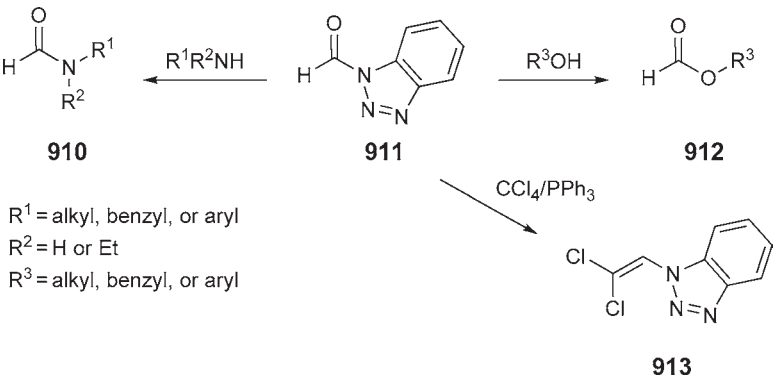


Scheme 149

5.01.8.11 Ring N–C(sp^2)═O

5.01.8.11.1 Ring N–(C═O)-H

Considering benzotriazolyl moiety in compounds of the general structure R-(C═O)-X (X = benzotriazol-1-yl or benzotriazol-2-yl) as a synthetic equivalent of a halogen atom, the formyl derivative (R = H) is of special interest due to unavailability of the halogen analogs. 1-Formylbenzotriazole **911** can be conveniently prepared in a reaction of benzotriazole with formic acid in the presence of dicyclohexylcarbodiimide <1995S503>. Its reactions with amines provide conveniently formamides **910** under mild conditions <1995S503, 2002JA12950>. Even unreactive 2-nitroaniline and 2-aminopyridine can be efficiently formylated this way (**Scheme 150**) <1995S503>. In reactions of 1-formylbenzotriazole **911** with alcohols, the corresponding formates **912** are readily obtained <1995S503>. Treatment of compound **911** with triphenylphosphine and CCl_4 results in formation of 1-(2,2-dichlorovinyl)benzotriazole **913**, a convenient starting material in the synthesis of 1-ethynylbenzotriazoles (see Section 5.01.8.13) <2006T3794>.

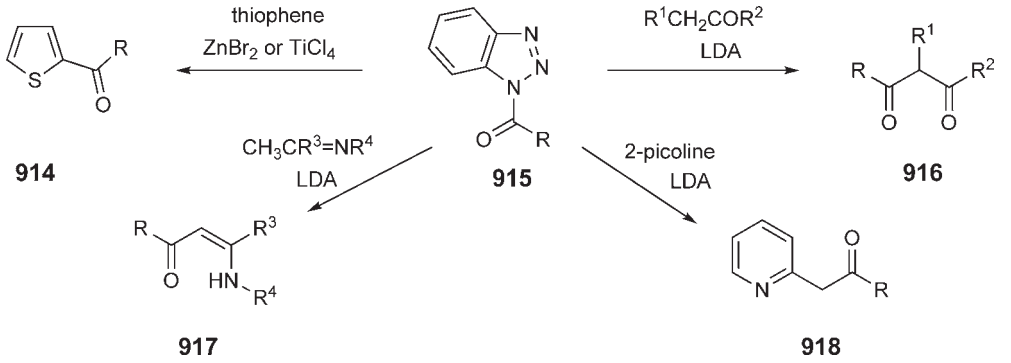


Scheme 150

5.01.8.11.2 Ring N-(C═O)-R, C-acylation

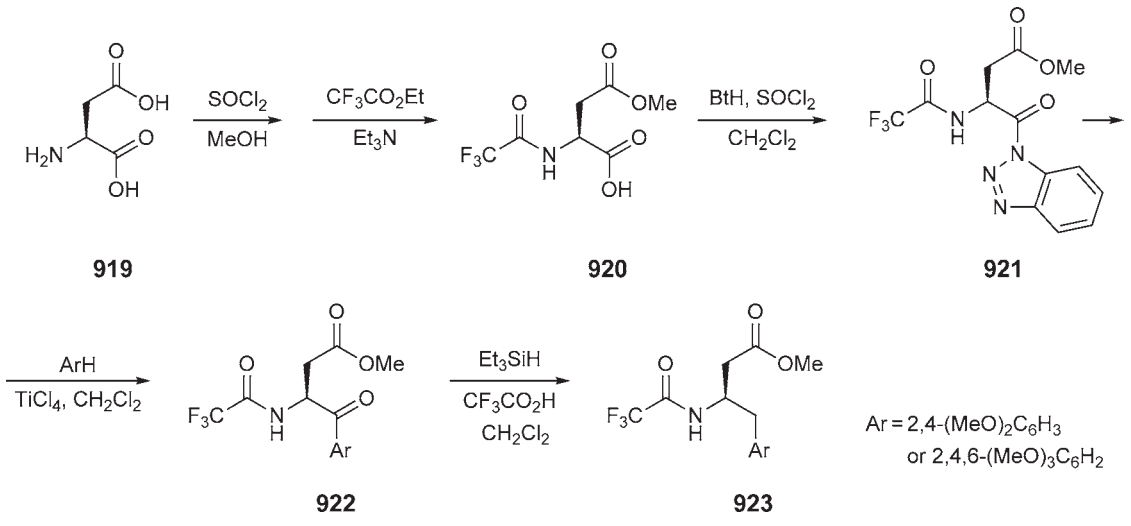
A wide range of *N*-acylbenzotriazoles **915** have been prepared under mild conditions in reactions of carboxylic acids with thionyl chloride in the presence of fourfold excess of benzotriazole, including R = alkyl, α-haloalkyl, α-alkoxyalkyl, alkenyl, alkinyl, aryl, and heteroaryl <2003S2795, 2004RQM275>. They represent convenient acylating agents for variety of nucleophiles. Synthetic applications of such compounds have been reviewed <2005SL1656>.

Some examples of C-acylation by 1-acylbenzotriazoles **915** are collected in **Scheme 151**. Thus, acylation of aromatic rings involves reactions of derivatives **915** with thiophene in the presence of $ZnBr_2$ or $TiCl_4$ to give corresponding 2-acylthiophenes **914** in high yield <2004CCA175>. Furan reacts similarly. C-2 acylation of pyrroles and C-3 acylation of indoles under these conditions does not require N-protection <2003JOC5720>. Ketones are acylated in the presence of LDA to give β-diketones **916** <2000JOC3679>; the reaction can also be carried out on a polymer support <2001JCO167>. Acylation of aliphatic nitriles leads to the corresponding β-ketonitriles <2003JOC4932> and that of sulfones to β-ketosulfones <2003JOC1443>. Imines delivered from methyl ketones are effectively acylated by derivatives **915** on their methyl groups to give enaminones **917** <2000S2029>. 2-Picoline is readily acylated by **915** to produce (pyridin-2-yl)methyl ketones **918**; 4-picoline, 4-methylquinoline and the corresponding benzyl derivatives react similarly <2005ARK(vi)329>.



Scheme 151

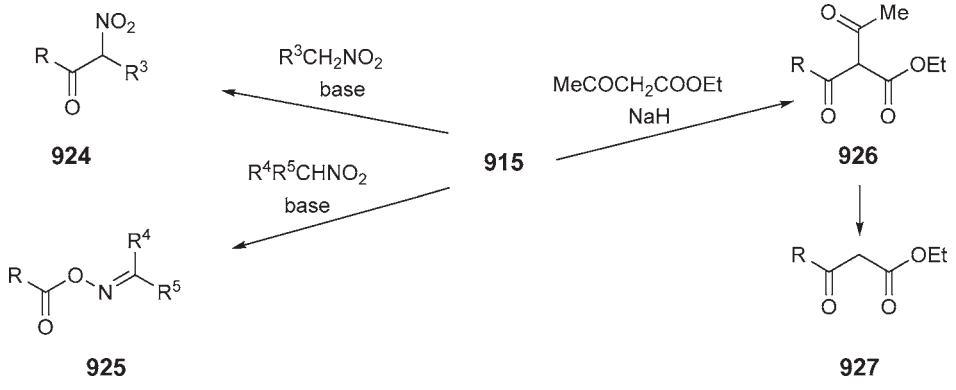
In a reaction with thionyl chloride and methanol, L-aspartic acid **919** is converted to its monoester, which is subsequently treated with ethyl trifluoroacetate to give N-protected aminoacid **920**. Upon treatment with benzotriazole and thionyl chloride, acid **920** is converted to 1-acylbenzotriazole **921** that can be used as an acylating agent for electron-rich aromatics. Thus, in its reaction with di- and trimethoxybenzene, the corresponding γ-keto-β-aminocarboxylic acid esters **922** are obtained in 35% and 50% yield, respectively. Ketones **922** are smoothly reduced with triethylsilane to β-aminoacid derivatives **923** (78–79% yield). Higher yields of ketones **922** (54–89%) are obtained from reactions of acylating agent **921** with reactive heteroaromatics like pyrrole, indole and their *N*-methyl derivatives. Starting from glutamic acid, an analogous reaction sequence provides derivatives of the corresponding γ-aminoacids (**Scheme 152**) <2007JOC407>.



919 **920** **921** **922** **923**

Scheme 152

N-Acylbenzotriazoles **915** delivered from aliphatic, aromatic or N-protected α-amino carboxylic acids react with primary nitroalkanes under basic conditions to give corresponding α-nitroalkanes **924** in good yields <2005JOC9211>. Under similar conditions, secondary nitroalkanes are converted to O-acylated oximes **925**. Treatment of ethyl acetoacetate with aromatic *N*-acylbenzotriazoles **915** (R = Ar) leads to 3-aryl-β-ketoesters **927**, presumably via three-carbonyl intermediates **926** (**Scheme 153**) <2004JOC6617>. Analogous reactions of α-acetylketones produce higher β-diketones.

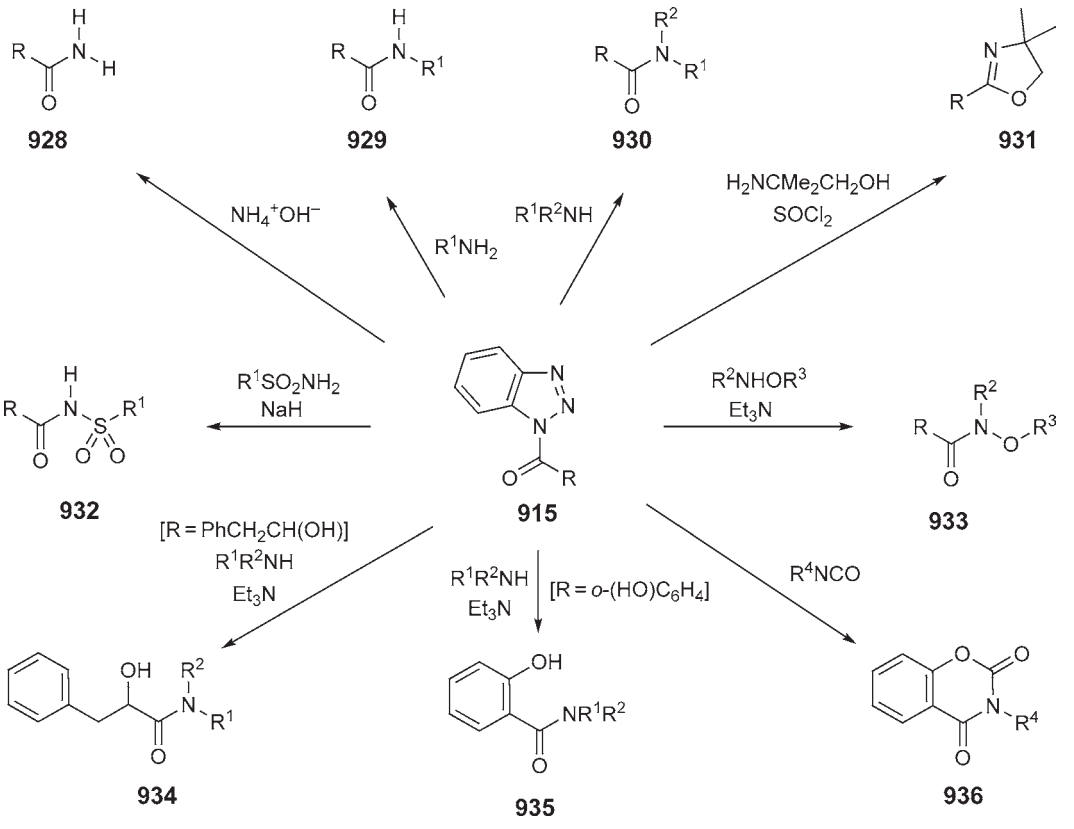


924 **915** **926** **925** **927**

Scheme 153

5.01.8.11.3 Ring N-(C═O)-R, N-acylation

Acylbenzotriazoles **915** are convenient acylating agents for all kinds of amines. Thus, in their reactions with ammonia (30% aqueous solution), primary amides **928** are formed in high to quantitative yields. Primary amines react similarly well to give amides **929**. In the case of secondary amines, the yields of amides **930** are generally high, except when there is too much steric hindrance; for example, *N*-ethylisopropylamine does not react at all (**Scheme 154**) <2000JOC8210>. Reactions of compounds **915** with 2,2-dimethyl-2-aminoethanol produce oxazolines **931** <2004JOC811>. Analogously, thiazolines are formed in reactions of acylbenzotriazoles **915** with 2-aminoethanethiol <2004JOC811>. Due to simplicity and high efficiency of these reactions, 1-acylbenzotriazoles **915** are currently used in drug derivatization <2001IJP129, 2003CCA335> and preparation of ^{14}C-labeled compounds <2003JLR449>. The synthesis of amides **928–930** can be further facilitated by application of microwaves <2006JOC3375> or a solid phase support <2002BML1809>.



Scheme 154

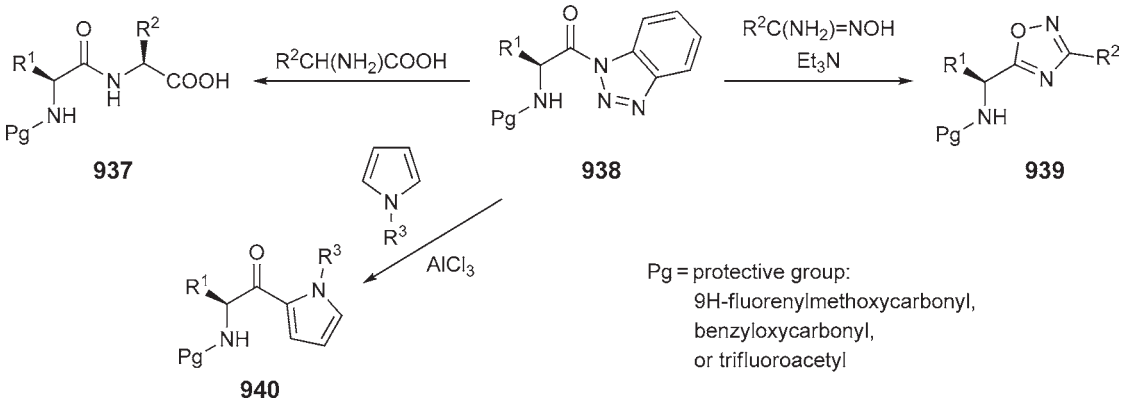
N-Acylation by derivatives **915** is applicable to the formation of *N*-acylsulfonamides **932** <2004ARK(xii)14>, hydroxamic acids and Weinreb amides **933** <2002ARK(xi)39, 2003S2777> in high yields (**Scheme 154**). Application of this methodology allows direct conversion of hydroxy carboxylic acids into their amides without any protection on the hydroxy group. Thus, in reactions with amines, compound **915** derived from 2-hydroxy-3-phenylpropionic acid gives amides **934** in 72–75% yield <2006JOC3364>. 1-Acylbenzotriazole **915** derived from salicylic acid reacts smoothly with amines to give salicylamides **935** <2006JOC3364> and with isocyanates to afford benzoxazine-2,4-diones **936** <2007ARK(vi)6>. Many other hydroxy carboxylic acids, with various distances between the hydroxy and carboxylic groups, produce similarly good results <2006JOC3364>.

N-Protected 1-(α-aminoacyl)benzotriazoles **938** derived from chiral α-aminocarboxylic acids can be conveniently prepared by mixing 4 molar equivalents of benzotriazole with 1 equiv of thionyl chloride followed by addition of 1 equiv of N-protected α-aminocarboxylic acid. Acylbenzotriazoles **938** react with chiral amines to give corresponding amides with retention of chirality <2002ARK(viii)134>. Condensation of **938** with unprotected α-aminocarboxylic acids in MeCN/H_2O in the presence of triethylamine at room temperature gives readily chiral dipeptides **937** <2004S2645, 2005S397, 2005TL6537>. The methodology can be readily extended to tripeptides <2006S411>. Reactions of derivatives **938** with amidoximes lead to 5-(α-aminoalkyl)-1,2,4-oxadiazoles **939** in high yields and with preservation of chirality <2005ARK(vii)36> (**Scheme 155**). Reactions of aminoacylbenzotriazoles **938** with pyrrole and *N*-methylpyrrole in the presence of $AlCl_3$ give chiral 2-(aminoacyl)pyrroles **940**. Analogous reactions with indoles lead to their 3-(aminoacyl) derivatives <2005JOC4993>.

5.01.8.11.4 Ring N-(C═O)-R, O-, and S-acylation

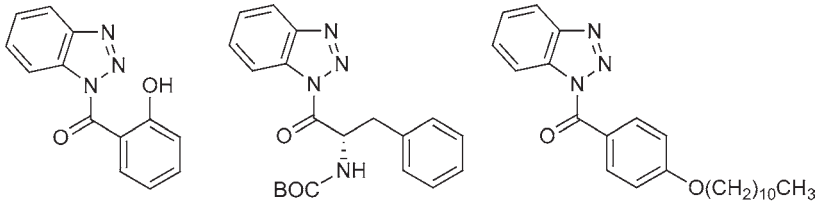
Despite the many simple methods for preparation of carboxylic esters and thioesters, in some instances, use of 1-acylbenzotriazoles **915** as O and S acylating agents may be advantageous. For example, easy to prepare salicylic acid derivative **941** reacts with cyclopentanol under microwave irradiation to give 92% yield of cyclopentyl salicylate in 10 min <2006JOC3364>. In another example, L-phenylalanine derivative **942** reacts with benzyl mercaptan

and triethylamine at 25 °C for 1 h to produce the corresponding thioester in 97% yield <2004S1806>. 1-(4-Undecyloxybenzoyl)benzotriazole **943** is conveniently used for acylation of a complex phenol in preparation of liquid crystals <2004JA1161>. Esters are also formed with good yields in reactions of 1-acylbenzotriazoles **915** with organozinc reagents in the presence of a palladium catalyst <2001ARK(xi)41>. The unusual course of these reactions must involve oxidation of the intermediates with atmospheric oxygen.



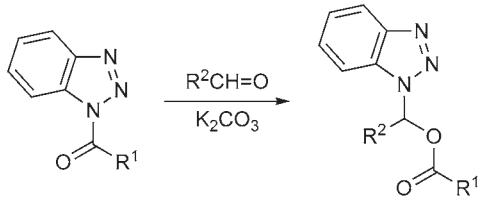
937 **938** **939** **940**

Scheme 155



941 **942** **943**

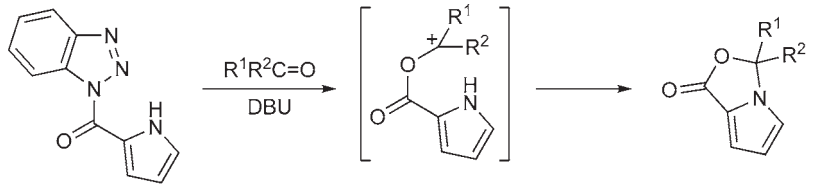
Carbonyl oxygen atoms of aldehydes can also be efficiently acylated by 1-acylbenzotriazoles **915** in the presence of mild bases (K_2CO_3, Et_3N). The released benzotriazolide anions are consecutively attached to the aldehyde carbonyl carbon atoms to produce esters **944** (Equation 20). Aliphatic aldehydes react quickly at room temperature, but aromatic aldehydes require elevated temperatures. The yields are good to quantitative. The amounts of benzotriazol-2-yl isomers of esters **944** in the products mixtures is strongly dependent on the reaction conditions and the character of groups R^1 and R^2, and it may vary from 5% to 25% <1999JHC777>.



915 **944** (20)

R^1 = Me, Bu^t, $ClCH_2$, $Cl(CH_2)_3$, Ph, 4-$MeOC_6H_4$, or 2-furyl
R^2 = Et, Pr, Bu^t, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$(CN)C_6H_4$, 4-$(NO_2)C_6H_4$, 4-$(CO_2Me)C_6H_4$, 2-furyl, or 3-furyl

Similarly to the reaction depicted in Equation (20), acylation of the oxygen atom of aldehydes or ketones by pyrrole derivative **945** produces intermediate cations **946**. However, instead of being trapped by benzotriazole to give ester **944**, the intramolecular electrophilic attack of the cation on the pyrrole nitrogen atom produces pyrrolo[1,2-oxazol-1-one] **947**. According to an alternative path, the adduct of pyrrole to the carbonyl group of aldehyde is formed first, and then its oxygen atom is intramolecularly acylated to give product **947**. The reaction is catalyzed by DBU. The indole analog of **945** reacts similarly with aldehydes and ketones to produce tricyclic systems (**Scheme 156**) <2004JOC9313>.

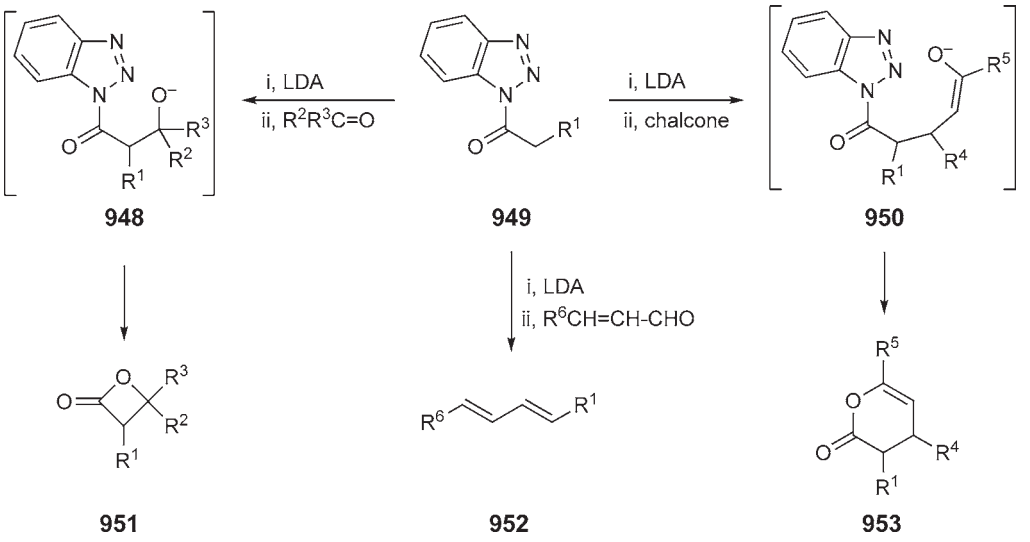


945 **946** **947**

$R^1R^2C{=}O$ = $Pr^iCH{=}O$, 4-$MeC_6H_4CH{=}O$, 2-furyl-CH=O, $Me_2C{=}O$, $Et_2C{=}O$, cyclohexanone, or acetophenone

Scheme 156

Intramolecular acylation of oxygen atoms plays also an important role in reactions of carbanions derived from acylbenzotriazoles **949** with aldehydes and ketones. Thus, anion **948** obtained in the first step undergoes intramolecular cyclocondensation to β-lactone **951** (**Scheme 157**) <1996LA881>. A similar addition of anions derived from acylbenzotriazoles **949** to cinnamaldehydes provide unstable β-lactones that undergo spontaneous ring opening and decarboxylation to dienes **952** (a mixture of (*E*,*E*) and (*E*,*Z*) isomers). However, in the case of chalcones, the nucleophilic attack goes on the β-carbon atom to yield 3,4-dihydropyran-2-ones **953**, via intramolecular acylation of the oxygen atom in anionic intermediates **950** <2002JOC3104>.



948 **949** **950**

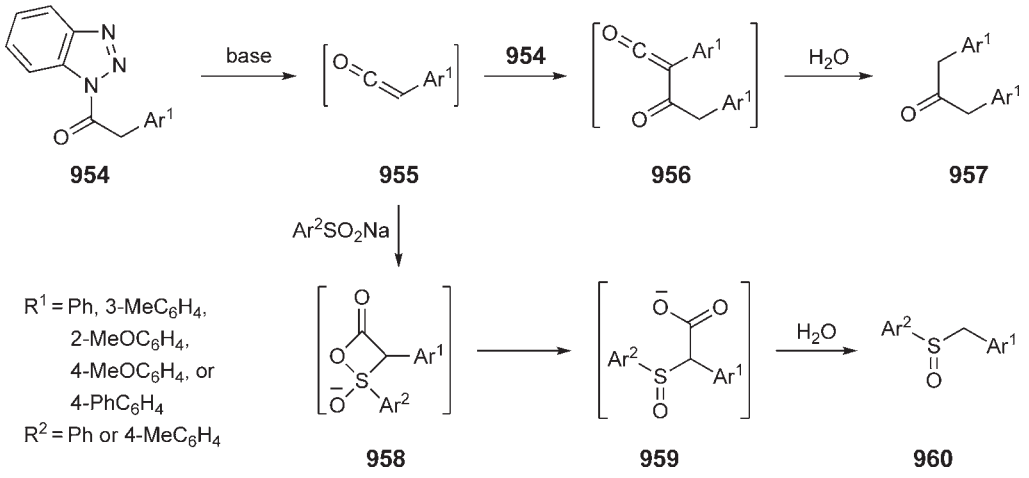
951 **952** **953**

Scheme 157

5.01.8.11.5 Ring N-(C═O)-R, elimination of benzotriazole

Treated with a base, 1-(arylacetyl)benzotriazoles **954** eliminate benzotriazole to form ketenes **955**. When no other reagent is added, ketene **955** is acylated by another molecule of **954** to produce α-ketoketene **956** which upon addition of water and decarboxylation during the work-up is converted to symmetrical dibenzyl ketone **957**

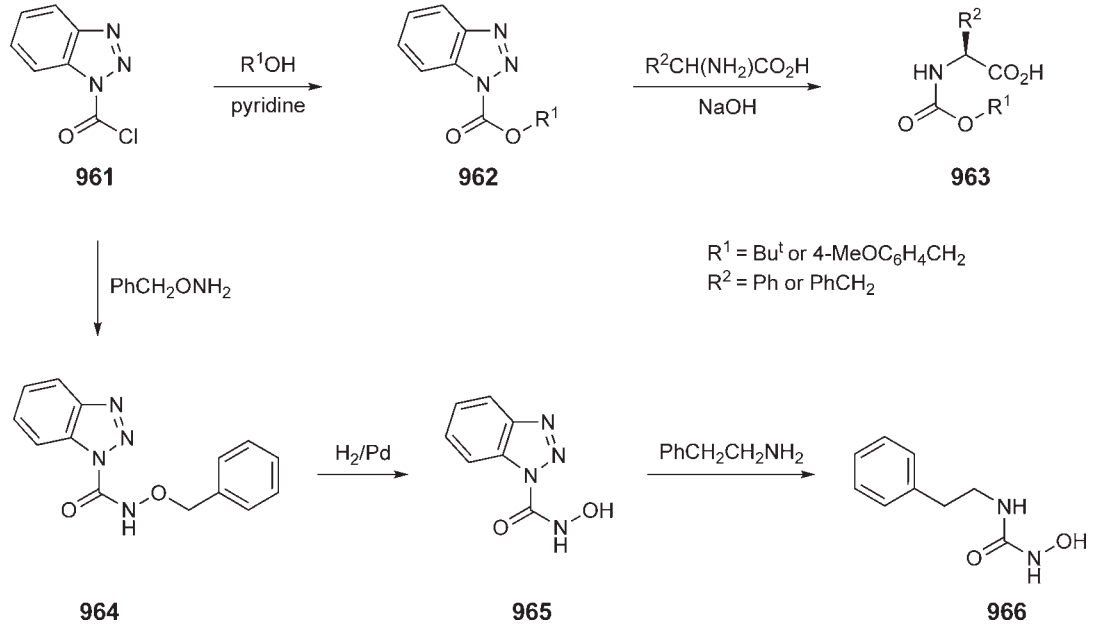
(**Scheme 158**) <1996HAC365>. Trapping of ketenes **955** by arenesulfinates generates unstable adducts **958** that consecutively undergo ring opening (intermediate **959**) and decarboxylation to aryl benzyl sulfoxides **960** <1996SL701>. Upon heating at 210 °C, even simple acylbenzotriazoles **949** (R^1 = alkyl) eliminate benzotriazole and generate corresponding ketenes that can be conveniently trapped by isocyanates <2000JOC8069>.



Scheme 158

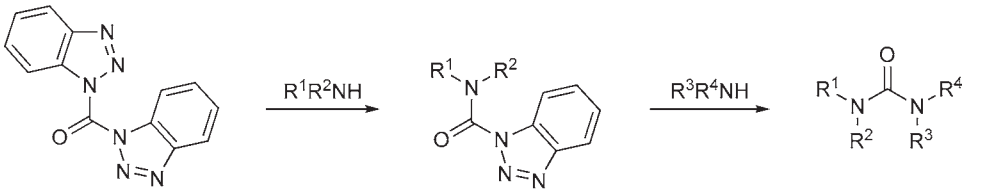
5.01.8.11.6 Ring N-(C═O)-X

1-Chloroformylbenzotriazole **961** is prepared in a reaction of benzotriazole with phosgene <1997SC1623, 2000CCA569> or more conveniently with triphosgene <2003CCA217>. In reactions with alcohols in the presence of pyridine, the chlorine atom in derivative **961** is substituted by an alkoxy group. Obtained esters **962** react with aminoacids to provide their N-protected forms **963** (**Scheme 159**) <1997SC1623>. The reaction of compound **961** with benzyloxyamine provides 1-(benzyloxycarbamoyl)benzotriazole **964**. Deprotection of the hydroxy group by hydrogenation gives acid **965** that is treated then with phenethylamine to afford *N*-hydroxy-*N*′-phenethylurea **966** <2000CCA569>.



Scheme 159

1,1′-Carbonyldibenzotriazole **967** is conveniently prepared by stirring a THF solution of 2 molar equivalents of benzotriazole and 1 equiv of phosgene for 3 d. Successive treatment with two different amines provides an efficient synthetic method for asymmetrically substituted ureas **969** via intermediate amidobenzotriazoles **968** (**Scheme 160**) <1997JOC4155>. The benzotriazole moiety in amides **968** can be readily displaced by aryl and heteroaryl organomagnesium or organolithium reagents to provide benzamides (or heterocyclic amides) **970** in moderate to good yields <1999JCM230>.

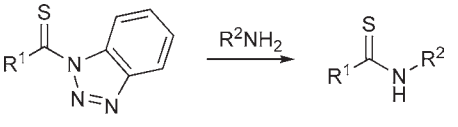


For **969**: R^1R^2NH = Bu^nNHMe, $PhNH_2$, morpholine, or 1-methylpiperazine
R^3R^4NH = *n*-$C_8H_{17}NH_2$, Bu^nNHMe, PhNHMe, Ph_2NH, morpholine, or piperidine;
For **970**: R^1R^2NH = PhNHMe, Ph_2NH, morpholine, or 1,2,3,4-tetrahydroisoquinoline
R^5 = aryl or heteroaryl

Scheme 160

5.01.8.12 Ring N-C(sp²)═S

Benzotriazole thioamides **971** react with amines to produce thioamides **972** under mild conditions (Equation 21). It is the preferred route to thioamides with reactive groups R^1 and R^2 where direct conversion of the corresponding amides to thioamides **971** is not feasible <2002J(P1)2243>. More stable 6-nitrobenzotriazolyl analogs of **971** are more convenient to use in some instances <2005TA1905, 2005JOC7866>. A significant drawback of this method is lengthy preparation of derivatives **971** <2002J(P1)2243> or their 6-nitrobenzotriazolyl analogs <2005JOC7866> involving several steps that start from the corresponding *ortho*-phenylenediamine and include formation of the triazole ring (see Section 5.01.9).

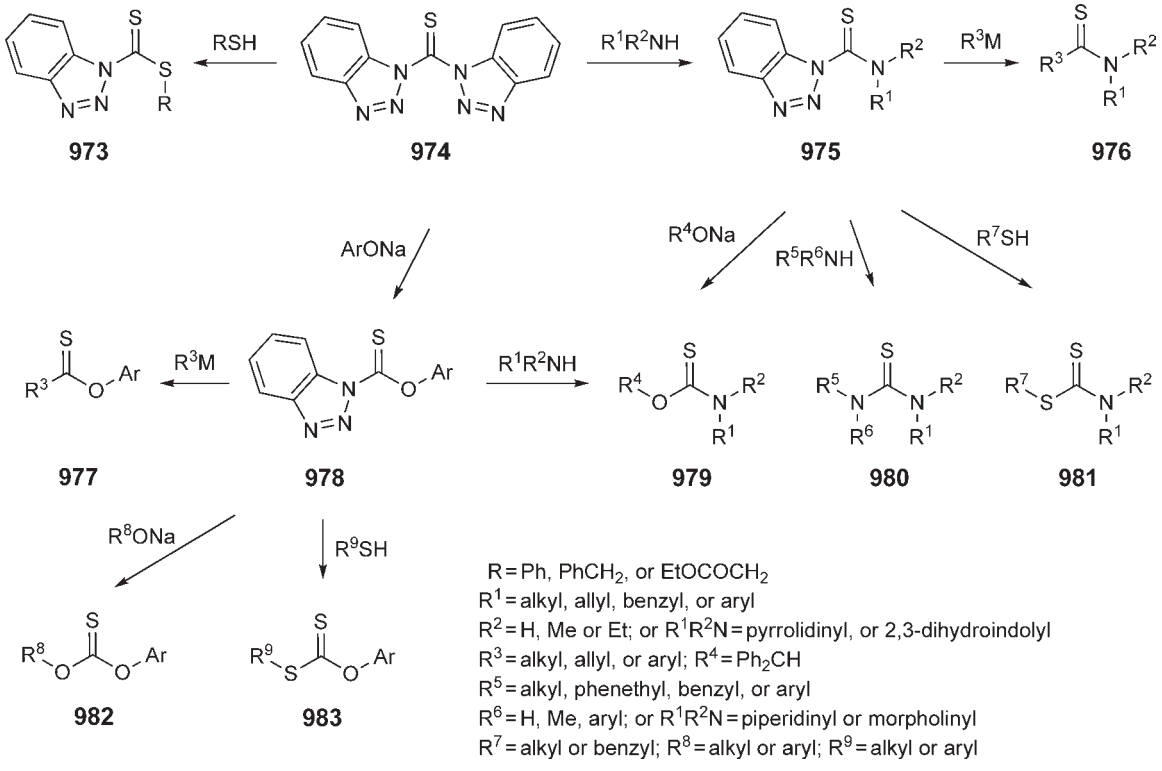


(21)

Bis(benzotriazol-1yl)methanethione **974** is easily prepared from thiophosgene and 1-(trimethylsilyl)benzotriazole <1978JOC337>. In reactions with thiols and triethylamine, thiones **974** are converted to derivatives **973** in modest yields; the main side products result from nucleophilic attacks of the thiolate anions on the thione sulfur atom to produce disulfides <2005JOC7866>. In reactions with amines, compounds **974** are smoothly converted to 1-(thiocarbamoyl)benzotriazoles **975** <2004JOC2976>. Substitution of one of the benzotriazolyl groups in **974** by phenolate anions yields 1-(aryloxythioacyl)benzotriazoles **978** (**Scheme 161**) <2005JOC7866>.

Reactions of thiocarbamoyl benzotriazoles **975** with organolithium or Grignard reagents provide thioamides **976** in moderate to good yields <2005JOC7866>. Substitution of the benzotriazolyl moiety in **975** by alkoxide anions leads to thiocarbamates **979** <2005JOC7866>. In reactions with amines, substitution of the first benzotriazolyl group in

bis(benzotriazol-1yl)methanethione **974** occurs readily at room temperature to give 1-(thiocarbamoyl)benzotriazoles **975**. However, when the amines are used in 2:1 molar ratio, and the reaction mixtures in dichloromethane are heated at reflux, symmetrical thioureas **980** ($R^1 = R^6$ and $R^2 = R^5$) are obtained. Unsymmetrical thioureas **980** are prepared in good yields by reactions of intermediates **975** with different amines <2004JOC2976, 2005JOC7866>. In the presence of triethylamine, 1-(thiocarbamoyl)benzotriazoles **975** react with mercaptans to give dithiocarbamates **981** <2005JOC7866>. Similarly to their amine analogs **975**, the benzotriazolyl moiety in oxygen derivatives **978** can be readily substituted with organometallic reagents to provide thionoesters **977**, with amines to give thiocarbamates **979**, with alkoxides to afford thiocarbonates **982** and with mercaptans to yield dithiocarbonates **983** (**Scheme 161**) <2005JOC7866>.



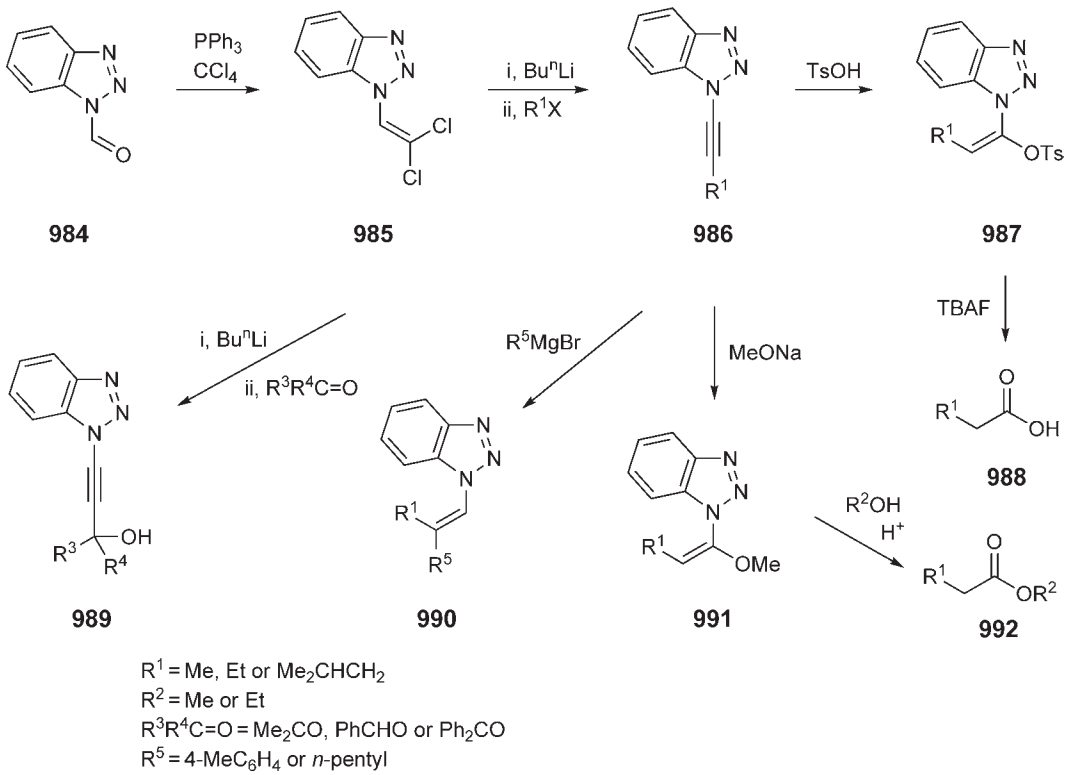
Scheme 161

5.01.8.13 Ring N–C(sp)

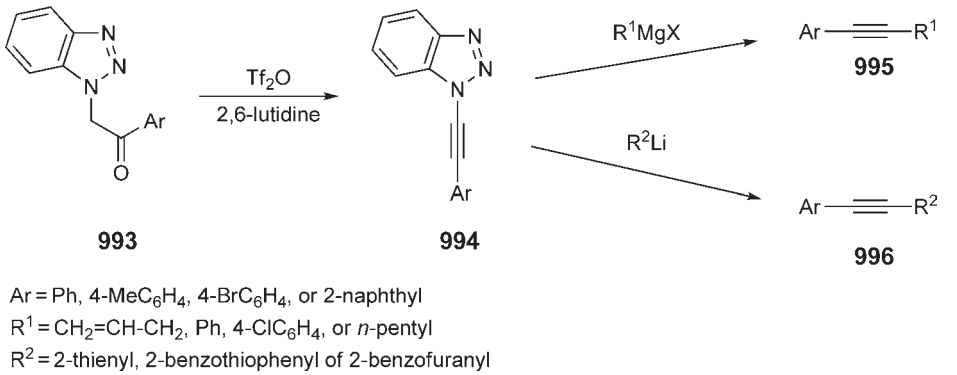
5.01.8.13.1 Ring N–C≡C–R

1-Formylbenzotriazole **984** reacts with triphenylphosphine and CCl_4 to provide 1-(2,2-dichloroethenyl)benzotriazole **985** in 68% yield as a crystalline solid. Treatment of derivative **985** with 2 molar equivalents of Bu^nLi followed by alkylating agents leads to 1-alkynylbenzotriazoles **986** in 58–84% yield. Alternatively, propargyl alcohols **989** (32–84% yield) are obtained in a reaction of **985** with Bu^nLi and aldehydes or ketones. *p*-Toluenesulfonic acid adds readily to the triple bond of derivatives **986** to give intermediates **987** that are easily hydrolyzed to carboxylic acids **988**. Similarly, esters **992** are obtained by addition of methanol to derivatives **986** under basic conditions followed by acidic alcoholysis of intermediate **991**. Addition of Grignard reagents to alkynes **986** provides alkenes **990** in 72-91% yield (**Scheme 162**) <2000OL3789, 2002JOC7526, 2006T3794>.

1-(Arylethynyl)benzotriazoles **994** are prepared conveniently in a reaction of aryl (benzotriazol-1-yl)methyl ketones **993** with triflic anhydride in the presence of 2,6-lutidine. Nucleophilic attacks in derivatives **994** occur on the C-α atoms; thus, their reactions with Grignard reagents give alkynes **995** in 51–83% yield. Lithiated heteroaromatics react similarly to give alkynes **996** in 58–70% yield (**Scheme 163**) <2002JOC7526>.



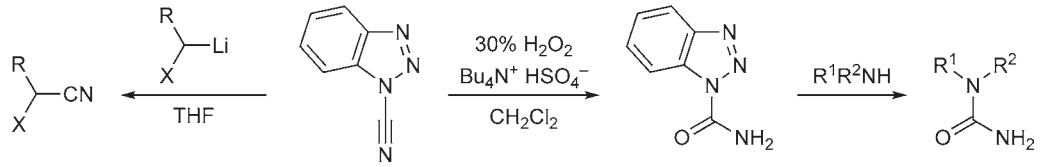
Scheme 162



Scheme 163

5.01.8.13.2 Ring N–C≡N

1-Cyanobenzotriazole **998** is readily prepared in 92% yield by treatment of benzotriazole with sodium hydride followed by cyanogen bromide. Solid and stable derivative **998** is a convenient reagent for introduction of the nitrile functional group into activated methylene compounds R-CH_2-X, which are lithiated with LDA prior to the reaction. Less acidic materials such as Ph-CH_2-Ph and 2-pyridyl-CH_2-Me are lithiated with Bu^nLi. Nitriles **997** are obtained under mild conditions in average 65% yield (**Scheme 15**) <2007ARK(iii)5>. Hydrolysis of 1-cyanobenzotriazole **998** with 30% H_2O_2 provides (benzotriazol-1-yl)carboxylic acid amide(**999** in 79% yield. Substitution of the benzotriazolyl moiety in product **999** by amines occurs readily at room temperature to furnish ureas **1000** in 61–96% yield (**Scheme 164**) <2003ARK(viii)8>.



R-CH_2-X = Ph-CH_2-CN, $PhCH_2$-CH_2-CN, Ph-CH_2-CO_2Et, 1-naphthyl-CH_2-CO_2Me, Ph-CH_2-COPh, Ph-CH_2-Ph, 2-pyridyl-CH_2-Me, Ph-CH_2-SO_2Ph, $PhCH_2$-CH_2-SO_2Ph, or 2-tolyl-CH_2-SO_2Ph

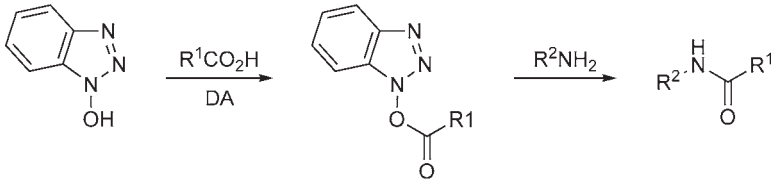
R^1R^2NH = 4-$MeOC_6H_4NH_2$, $PhCH_2NH_2$, $PhCH_2CH_2NH_2$, *n*-pentyl-NH_2, Bu_2NH, Pr^i_2NH, or $(PhCH_2)_2NH$

Scheme 164

5.01.8.14 Ring N–X (X = heteroatom)

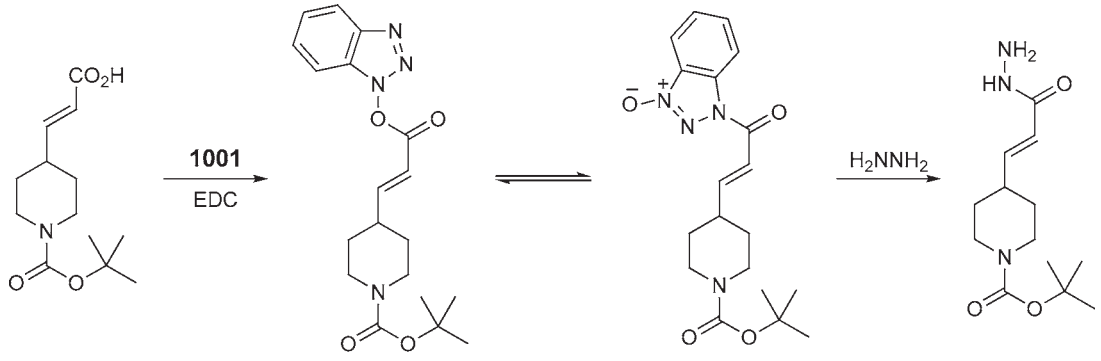
5.01.8.14.1 Ring N–O

Due to its wide application in peptide synthesis, 1-hydroxybenzotriazole **1001** is the most commonly used benzotriazole derivative with hundreds of references in *Chemical Abstracts* each year. Utility of compound **1001** comes from its readiness to form esters with carboxylic acids in the presence of dehydrating agents (DAs). Obtained esters **1002** react eagerly with amines to produce amides **1003** in high yields (**Scheme 165**). More details about this application are given in Section 5.01.12.



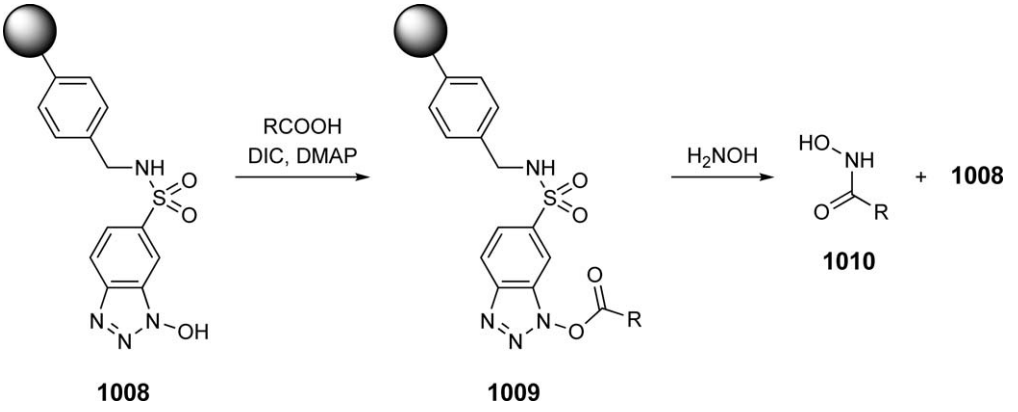
Scheme 165

Scheme 166 shows application of this methodology for preparation of hydrazide **1007**. Thus, the reaction of acid **1004** with 1-hydroxybenzotriazole and EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride] gives ester **1005** that can be separated and characterized, but it rearranges slowly to isomeric form **1006** in solutions. However, both derivatives, **1005** and **1006**, are found to be equally reactive toward hydrazine and afford hydrazide **1007** in 98% isolated yield <2002JOC9471>.



Scheme 166

Polymer-bound 1-hydroxybenzotriazole **1008** reacts with carboxylic acids in the presence of 1,3-diisopropylcarbodiimide (1,3-DIC) and DMAP to produce esters **1009**. Treated with hydroxylamine, esters **1009** are converted to hydroxamic acids **1010** (**Scheme 167**) <2003OBC850>. Starting 1-hydroxybenzotriazole **1008** is recycled in the process and can be used for other syntheses. This method is well suited for automated synthesis of a library of hydroxamic acids. In similar applications of polymer-supported 1-hydroxybenzotriazole **1008**, a wide variety of amides is synthesized <1997JOC2594, 2002JCO576>.



Scheme 167

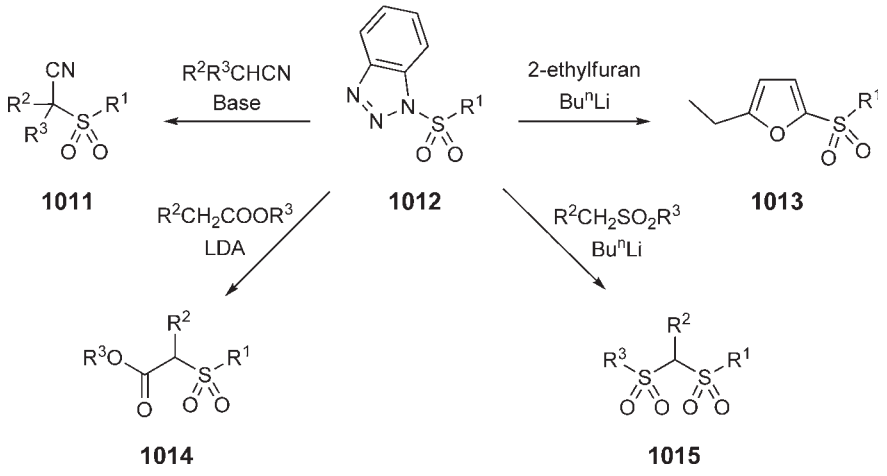
Although most common, application of esters **1002** is not limited to formation of C–N bonds. Such esters are also effectively used for regioselective benzoylation of sugars <2004CEJ399> and even for acylation of activated methylene groups <2003S2015>. Biological activity of some esters of the 1-hydroxybenzotriazole against SARS virus is attributed to their ability to acylate the cysteine sulfur atom in a key viral enzyme <2006CBO261>. Esters of 1-hydroxybenzotriazole **1001** with phosphoric acid are used for phosphorylation of nucleosides in a viral genome linked peptide <2003T1589>.

5.01.8.14.2 Ring N–S

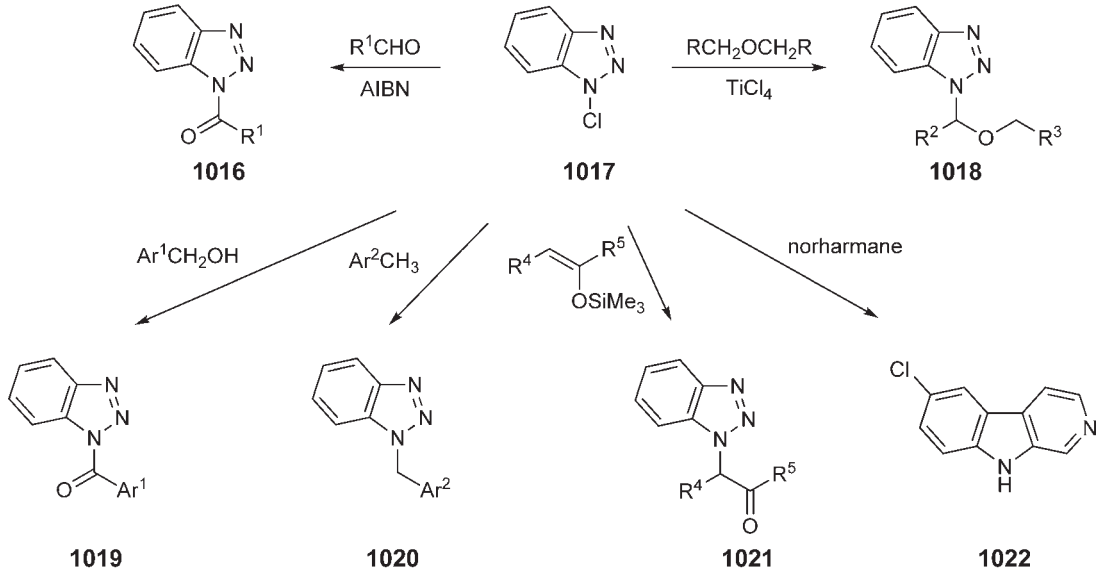
1-Sulfonylbenzotriazoles **1012** are readily available from reactions of benzotriazole with sulfonyl chlorides <2000JOC8210> or reactions of 1-chlorobenzotriazole with sulfinic acids <2004JOC1849>. Condensation of **1012** with primary or secondary nitriles under basic conditions provides corresponding α-cyanoalkyl sulfones **1011** in good to excellent yields (**Scheme 168**). In a convenient manner, sulfonyl derivatives **1012** convert lithiated heterocycles into heterocyclic sulfones; for example, 2-ethylfuran is converted to sulfone **1013**. In similar reactions, alkylheterocycles give α-(sulfonylalkyl)heterocycles, enolizable carboxylic esters give α-sulfonylcarboxylic esters **1014**, and sulfones give α-sulfonylalkyl sulfones **1015** <2005JOC9191>.

5.01.8.14.3 Ring N–Cl

1-Chorobenzotriazole **1017** is known as a mild oxidizing and chlorinating agent. Its reactions with aldehydes in the presence of catalytic amounts of AIBN lead to acylbenzotriazoles **1016** (**Scheme 169**) <2003ARK(xiv)131>. 1-Benzoylbenzotriazoles **1019** can also be obtained by oxidation of the corresponding benzyl alcohols with 2 equiv of compound **1017** <2003ARK(xiv)131>. Under similar conditions, toluenes are converted to the corresponding benzylbenzotriazoles **1020** <2003ARK(xiv)131>. Catalyzed by $TiCl_4$ and other Lewis acids, reactions of chlorobenzotriazole **1017** with ethers provide 1-(α-alkoxyalkyl)benzotriazoles **1018** <1999H(50)1877>. Reactions of **1017** with ketone silyl enol ethers give 1-(α-acylalkyl)benzotriazoles **1021** <1998JCM334>. Reactive aromatic rings can be efficiently chlorinated by chlorobenzotriazole **1017** as it is demonstrated by chlorination of norharmane, one of β-carbolines, to its chloro-derivative **1022** in 83% yield <2003JHC419>.



Scheme 168



R^1 = alkyl, aryl, or heteroaryl; Ar^1 = Ph or 4-PhC_6H_4; Ar^2 = Ph, 4-ClC_6H_4, or 4-$(NC)C_6H_4$
$R^2CH_2OCH_2R^3$ = Et_2O, $Bu^n{}_2O$, $(ClCH_2CH_2)_2O$, $(PhCH_2)_2O$, Bu^nOEt, dioxane, THF, THP, or isochroman
R^4 = H, Me, or Ph; R^5 = alkyl, aryl, or heteroaryl; or R^4R^5 = 2-$C_6H_4CH_2$, or 2-$C_6H_4CH_2CH_2$

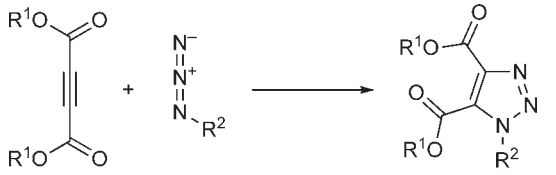
Scheme 169

5.01.9 Ring Synthesis from Acyclic Compounds

5.01.9.1 Ring Synthesis from Acetylenedicarboxylates

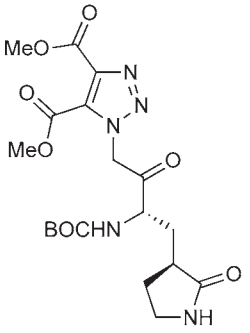
Cycloadditions of azides to alkynes and their derivatives <1996CHEC-II(4)1> continue to be the main synthetic route to 1,2,3-triazoles. Some aspects of these reactions with focus on cycloadditions at low temperature are discussed in a review <2003H(60)1225>. Recent advances in this area make the synthesis easy and high yielding to allow quick assembly of complex structures from relatively simple fragments. Drug design, proteomics, and nanotechnology are the scientific fields of great contemporary interest in such synthesis.

Esters of acetylenedicarboxylic acid **1023** are commercially readily available, are very reactive as dipolarophiles, and the carboxylic groups in products of their reactions can be easily converted to many other functionalities. Therefore, they are often the first choice as substrates for 1,3-dipolar cycloaddition to azides **1024** (Huisgen reaction). The reactions are carried out at room or elevated temperature, and the yields of 1,2,3-triazoles **1025** are usually high to quantitative (Equation 22). Several products obtained in this way are presented as structures **1026–1034**. Some details about the reactions leading to these products are given in **Table 10**.

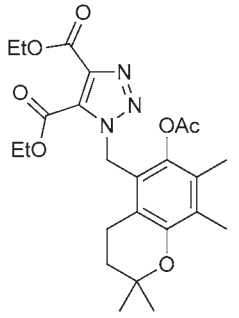


(22)

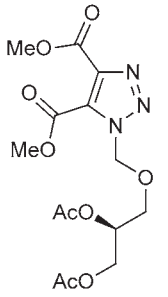
1023 **1024** **1025**



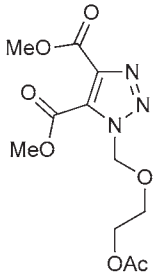
1026



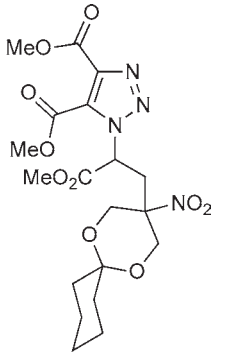
1027



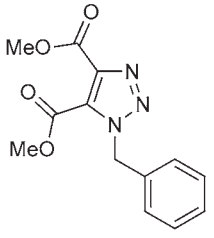
1028



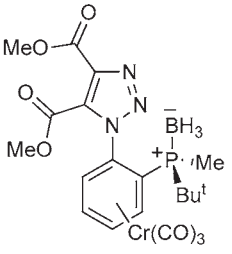
1029



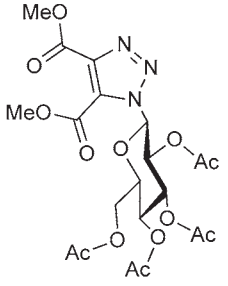
1030



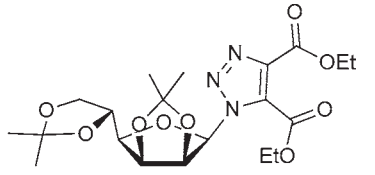
1031



1032



1033

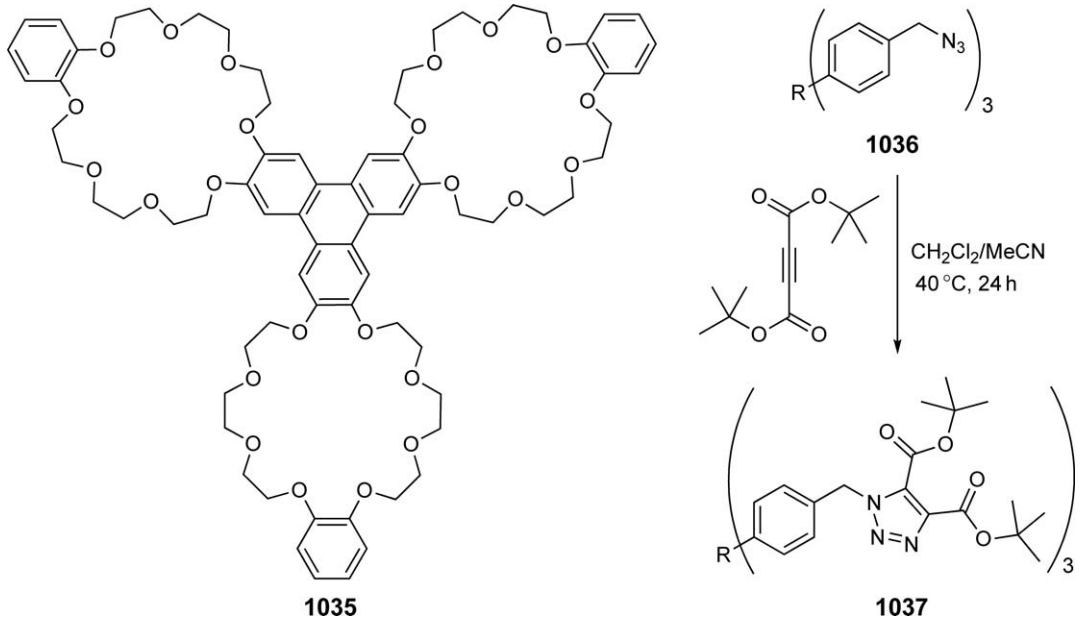


1034

Table 10 [3+2] Cycloaddition reactions of azides with acetylenedicarboxylates

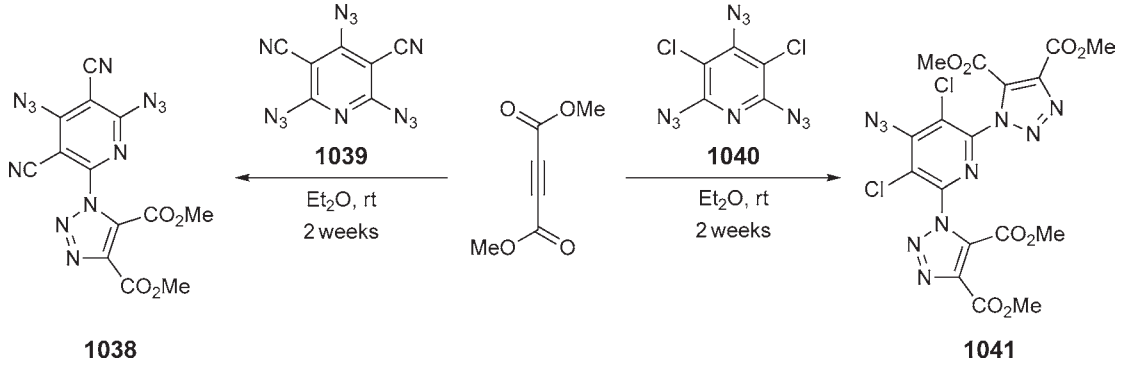
Product	*Reaction conditions*	*Yield (%)*	*Purpose*	*Reference*
1026	toluene, r.t., 72 h	100	inhibitor of hepatitis A virus 3C proteinase	2004BML3655
1027	toluene, reflux, 24 h	90	derivatives of α-tocopherol	2006EJO2081
1028	toluene, reflux, 72 h	73	nucleoside analogs	2002BKC437
1029	toluene, reflux, 72 h	73	nucleoside analogs	2002JCM264
1030	benzene, reflux, 3 h	100	nucleoside analogs	2002TL8351
1031	toluene, µw, 10 min	95	study of microwave methodology	2003MDV171
1032	toluene, 130 °C, 40 h	65	asymmetric catalysis	2005T4701
1033	toluene, 80 °C, 24 h	84	antitumor nucleoside analog	2002NN361
1034	toluene, reflux, 24 h	90	disaccharide carbohybrids	2005H(65)1035
(1,2,3-triazol-1-yl)calix[4]arenes	CH_2Cl_2, reflux, 6 h	84	molecular hosts	2002JOC6136

An example of application of the [1,3]-dipolar cycloaddition reactions between azides and esters of acetylenedicarboxylic acid in nanotechnology is given in **Scheme 170**. In solutions, molecules of tris(crown ether) **1035** and tris(benzyl azide) **1036**, where R is a large template of C_3 symmetry, are self-assembled into a bundle with benzyl azide groups poking through the crown-ether rings. When di(*tert*-butyl) acetylenedicarboxylate is added, the azide groups are converted to triazoles **1037**, that are too bulky to be pulled out of the crown-ether rings, and the assembly remains permanently mechanically interlocked <2004CEJ1926>.



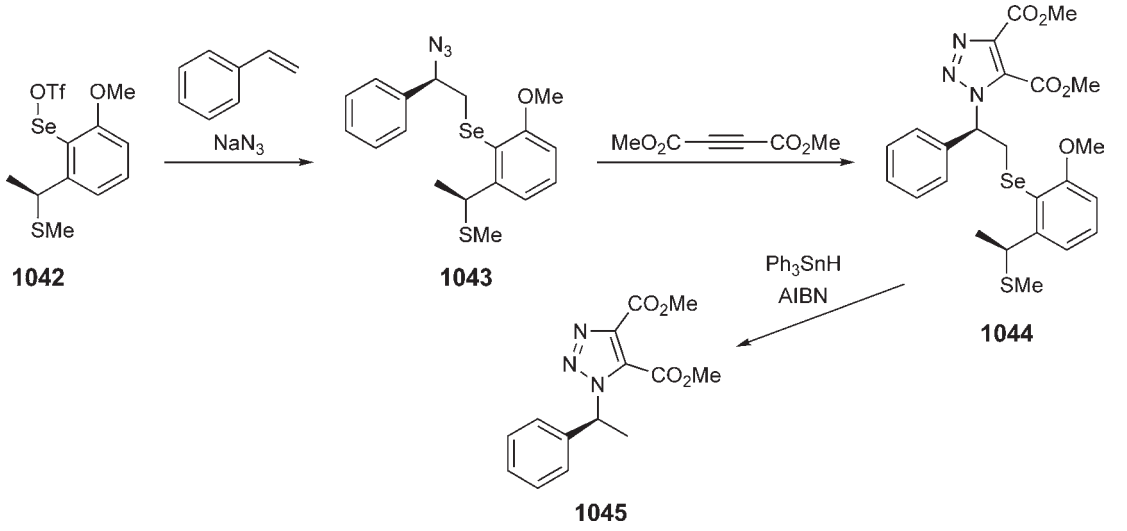
Scheme 170

Reactivity of azides towards acetylenedicarboxylates is very dependent on their electron density (energy HOMO). Thus, strongly electron-deficient 3,5-dicyano-2,4,6-triazidopyridine **1039** reacts slowly with dimethyl acetylenedicarboxylate to give triazole derivative **1038** in 34% yield with most of the starting material recovered unchanged. Under comparable conditions, less electron-deficient 3,5-dichloro-2,4,6-triazidopyridine **1040** reacts with dimethyl acetylenedicarboxylate to provide 2,6-bis(1,2,3-triazol-1yl)pyridine derivative **1041** in 75% yield (**Scheme 171**) <2001CHE861>.



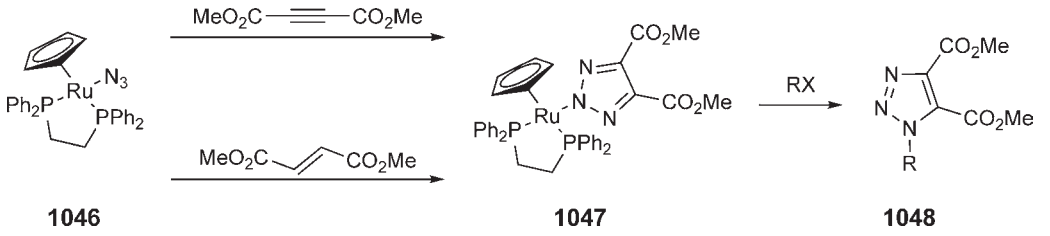
Scheme 171

An example of asymmetric synthesis involving cycloaddition of an azide to dimethyl acetylenedicarboxylate is depicted in **Scheme 172**. Thus, asymmetric auxiliary **1042** reacts with styrene and sodium azide to generate azide **1043** in 90% yield and 94% diastereomeric purity. The following reaction (**Scheme 172**) with dimethyl acetylenedicarboxylate converts azide **1043** into triazole **1044** in 75% yield. Finally, the bond with selenium is cleaved by treatment with triphenyltin hydride and AIBN to furnish triazole **1045** in 80% yield and preserved optical purity (94%) <2003AGE3131>.



Scheme 172

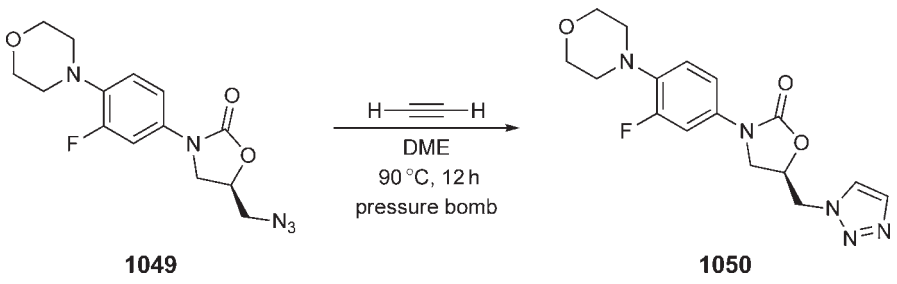
Treatment of ruthenium azido complex **1046** with dimethyl acetylenedicarboxylate in CH_2Cl_2 at room temperature for 24 h results in ruthenium triazole complex **1047** with 90% isolated yield. Surprisingly, product **1047** forms also in reactions of complex **1046** with dimethyl fumarate and dimethyl maleate in comparable yields, but the reactions are slower and require one week for completion. Presumably, the intermediate that forms in cycloaddition of azide **1046** to the double bond of fumarate undergoes consecutive dehydrogenation catalyzed by ruthenium. Treatment with alkylating agents cleaves the ruthenium–nitrogen bond and releases N-1 alkylated triazoles **1048** (**Scheme 173**) <2003OM3107>.



Scheme 173

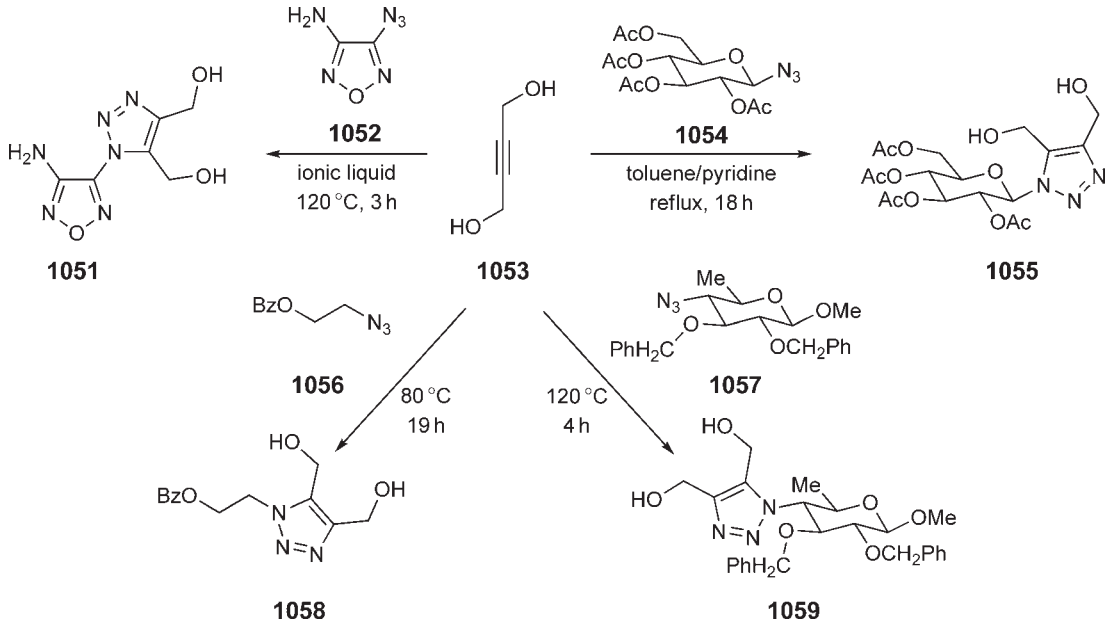
5.01.9.2 From other Symmetrically Substituted Acetylenes

Use of unsubstituted acetylene as a substrate in 1,3-dipolar cycloadditions with azides results in 4,5-unsubstituted triazoles. The reactions have to be carried out under pressure. In an example given in Equation (23) showing synthesis of an antibacterial agent, a solution of azide **1049** in dimethoxyethane is transferred to a pressure bomb that is then charged with acetylene and heated at 90 °C for 12 h to give triazole derivative **1050** in 74% yield <2003BMC35>.



1049 1050 (23)

2-Butyn-1,4-diol **1053** is a common 1,3-dipolarophile used in cycloadditions with azides; however, its reactivity is lower in comparison with esters of acetylenedicarboxylic acid, and the yields of its cycloaddition products are also lower. The advantage of using it in syntheses is direct introduction of two hydroxymethyl groups in positions 4 and 5 of the triazole system that may be useful as anchoring points for assembly of more complex structures. In the first example given in **Scheme 174**, cycloaddition of alkyne **1053** to 3-azido-4-aminofurazan **1052** is carried out in an ionic liquid at 120 °C to give triazole **1051** in 65% yield <2002MC83>.

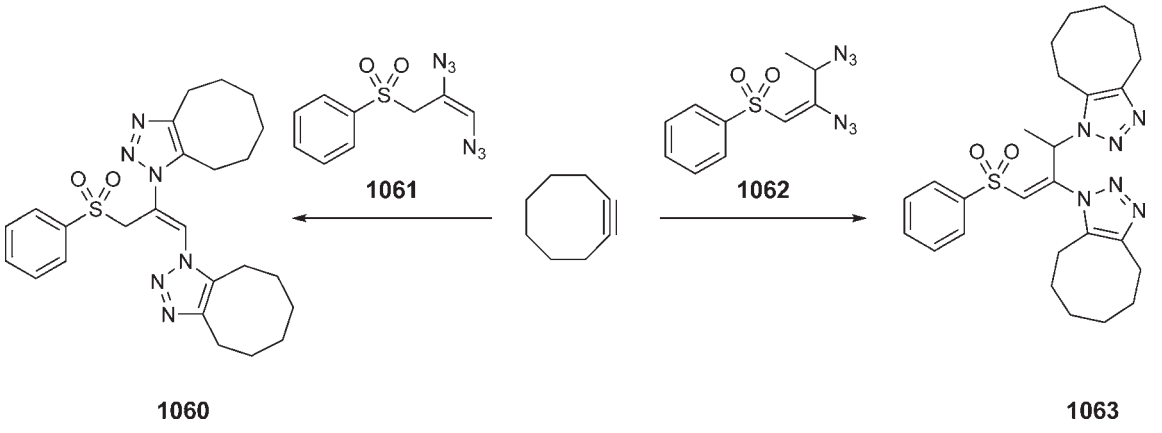


Scheme 174

In the second example, azide **1054** derived from acetylated glucose reacts with alkyne **1053** in refluxing toluene/pyridine mixture to afford triazole derivative **1055** in 38% yield which is used as an intermediate in synthesis of anticancer agents <2002TL4021>. Alternatively, the same final product is obtained when more reactive dimethyl acetylenedicarboxylate is used as the polarophile in cycloaddition with the glucose derived azide, and the carbomethoxy groups are consecutively reduced to hydroxymethyls. However, in the second approach, a different protection of the hydroxy groups in glucose is required adding a couple of additional steps to the process <2002TL4021>.

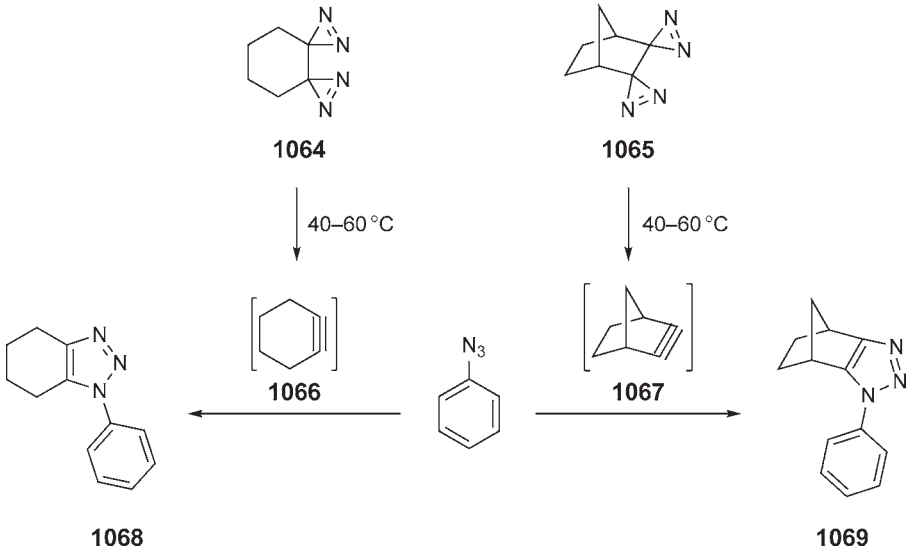
In the third example, the reaction of alkyne **1053** with protected hydroxyethylazide **1056** is carried out by heating a neat mixture of the reagents at 80 °C to give triazole **1058** in 65% yield <2005T9118>. The same neat approach is used in synthesis of sugar derivative **1059** that is obtained in 85% yield from a reaction of alkyne **1053** with protected sugar azide **1057** <2005T9118>.

Due to molecular strain, cyclooctyne is a very reactive species. Its reactions with azides proceed rapidly even at room temperature making it a convenient tool for probing structures of unstable azides. Thus, the reaction of cyclooctyne with diazide **1061** carried out in CH_2Cl_2 at room temperature is accomplished within 2 h and provides ditriazolyl derivative **1060** in 76% yield. A similar reaction of cyclooctyne with diazide **1062** leads to ditriazolyl derivative **1063** in 90% yield (**Scheme 175**) <2005T8904>.



Scheme 175

Scheme 176 represents the opposite situation, with stable phenyl azide used as a probe to trap very reactive and short living alkynes. Thus, diazirine **1064** generates cyclohexyne **1066** that is too reactive to be isolated and characterized. However, when phenyl azide is added to the reaction mixture, it traps species **1066** *in situ* to give triazole **1068** in 84% yield. Similarly, even more strained norbornyne **1067**, generated from diazirine **1065**, is trapped by phenyl azide to afford triazole **1069** in 22% yield <2006AGE309>.

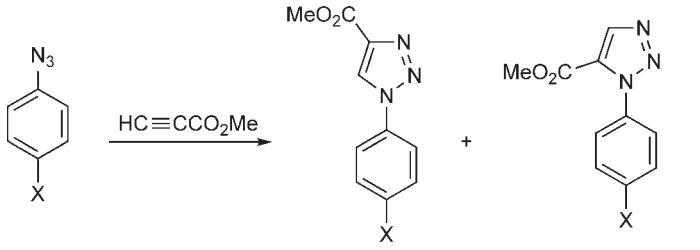


Scheme 176

5.01.9.3 From Nonsymmetrical Acetylenes – Problem of Regioisomers

After acetylenedicarboxylates, esters of propiolic acid are the second common group of reagents for 1,3-dipolar cycloaddition with azides. They react fast, and the yields of products are high. However, because the reacting

partners can approach each other in two ways, two regioisomers are formed, with the 4-alkoxycarbonyl derivative usually strongly predominant. The results of an interesting study investigating influence of substituents in arylazides **1070** on a cycloaddition reaction with methyl propiolate are presented in Equation (24). The reactions are carried out in refluxing CCl_4, and the combined yields of products **1071** and **1072** are 91–96%. To explain product distribution between the regioisomers, authors calculate chemical potential differences between the reactants and energies of their transition states <2003CEJ2770>.

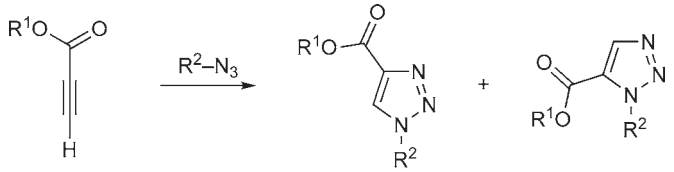


1070 **1071** **1072**

X	1071/1072
H	75:25
Me	73:27
MeO	68:32
F	70:30
Cl	68:32
NO_2	55:45

(24)

Some examples of the reactions between propiolates **1073** and azides leading to triazoles **1074** and **1075** (Equation 25) are collected in **Table 11**. As can be seen (entries 1 and 2), water as a reaction medium can improve the product yield, but it does not improve the regioselectivity. Microwave assisted synthesis (entry 3) can reduce dramatically the reaction time, but the regioselectivity is poor. Larger aliphatic groups in azides do not affect much the reactions (entries 4–7). An interesting novel approach to the problem of regioselectivity represents entry 8 where cycloaddition between 2-aminophenyl azide and ethyl propiolate is carried out in polymer nanocavities imprinted by regioisomer **1074** used as a template. In comparison with a regular reaction carried out in a solvent (entry 9), entry 8 shows a great improvement.



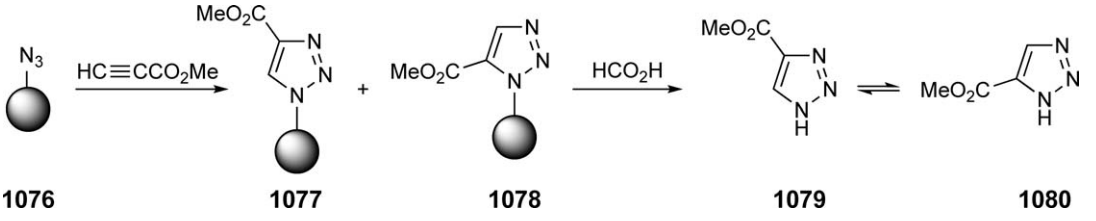
1073 **1074** **1075**

(25)

Table 11 Reactions of propiolates **1073** with azides

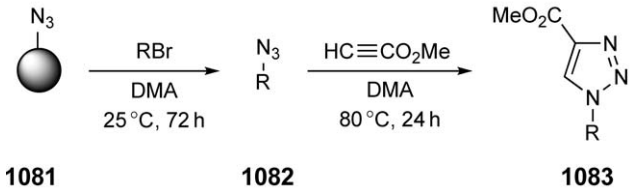
Entry	R^1	R^2	*Reaction conditions*	*Total yield(%)and ratio of* **1074**:**1075**	*Reference*
1	Et	Ph	EtOH, reflux, 8 h	69, 83:17	2004AP156
2	Et	Ph	H_2O, 120 °C, 24 h	90, 85:15	2003CC2450
3	Et	$PhCH_2$	Toluene, μW, 5 min	89, 64:36	2003MDV171
4	Me	$AcO(CH_2)_2OCH_2$	Toluene, reflux, 72 h	66, 92:8	2002JCM264
5	Me	$MeO(CH_2)_2O(CH_2)_2$	Toluene, 65 °C, 48 h	83, 80:20	2005T4983
6	Me	(1*S*,2*S*) $(MeO)_2P(O)$-$CH(OH)CH(OBn)CH_2$	Toluene, 100 °C, 4 h	98, 80:20	2004TA1457
7	Me	(1*R*,2*S*) $(MeO)_2P(O)$-$CH(OH)CH(OBn)CH_2$	Toluene, 100 °C, 4 h	100, 86:14	2004TA1457
8	Et	2-NH_2-C_6H_4	Imprinted polymer nanoreactor	94:6	2006JA4178
9	Et	2-NH_2-C_6H_4	In solution	70:30	2006JA4178

In a new approach to the synthesis of 1,2,3-triazoles, polymer supported azide **1076**, based on monomethyl ether of polyethylene glycol with molecular weight of 5000 Da, reacts with methyl propiolate in refluxing toluene to give a mixture of two regioisomeric triazoles **1077** and **1078** in 98% yield. However, the ratio of isomer **1077** to **1078**, 83:17, is not improved and remains comparable to that observed in simple addition of alkyl azides to methyl propiolate. The advantage of this method is high yield of the products and easy separation by precipitation from a solution in diethyl ether. Deprotection from the polymer is easily accomplished by treatment the mixture with formic acid. Both regioisomers give the same monosubstituted product which is a rapidly equilibrating mixture of tautomers **1079** and **1080** (**Scheme 177**) <2003TL1133, 2005T4983>.



Scheme 177

A simple procedure is developed for conversion of aliphatic bromides into methyl 1-alkyl-1,2,3-triazole-4-carboxylates **1083**. In the first step, alkyl bromide reacts with polymer-supported azide **1081** to provide a solution of azide **1082** in DMA. The best results are obtained with Merrifield resin. After the first step, the resin is simply filtered off, and the solution of azide **1082** is used directly in the next step for a reaction with methyl propiolate. In this way, the procedure is significantly simplified, and alkyl azides, that may be explosive in a concentrated form, do not require any additional work-up. As can be seen from the examples given in **Scheme 178**, the yield and purity of products **1083** are high <2003TL2153>.

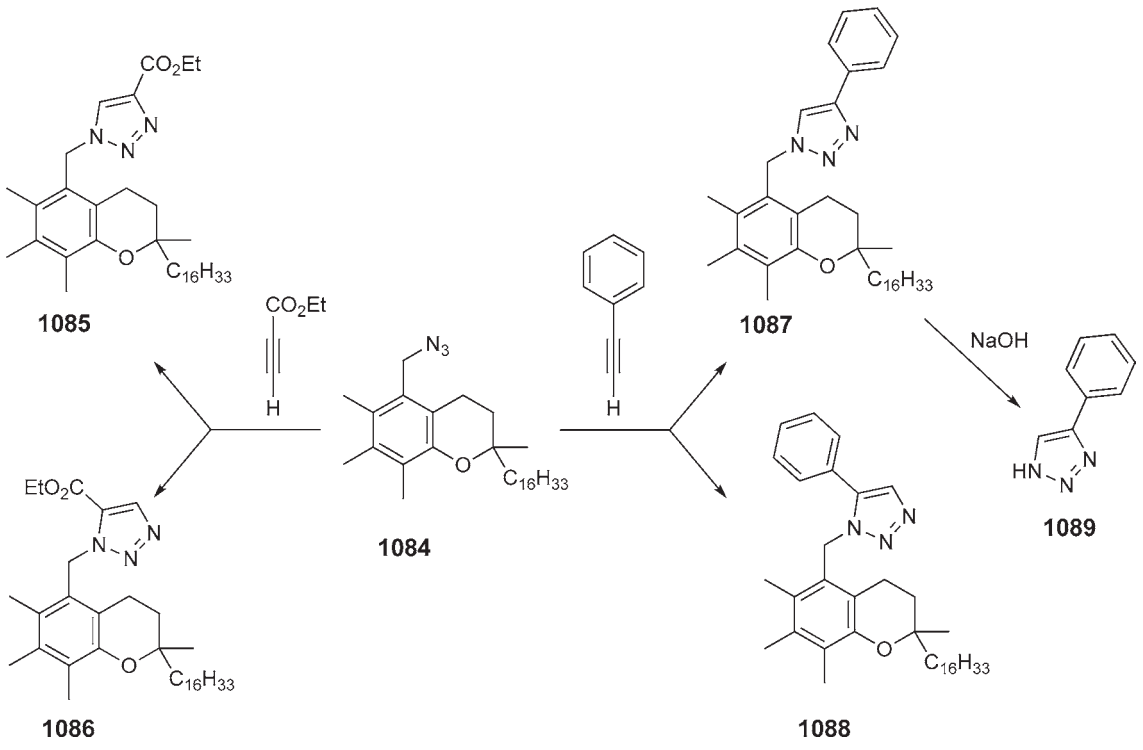


Entry	R	1083 Yield (%)	1083 Purity (%)
1	$Me_2CHCH_2CH_2$	73	99
2	c-$C_6H_{11}CH_2CH_2$	99	95
3	$Me_2C{=}CHCH_2$	88	84
4	$MeO_2C(CH_2)_4$	99	85
5	$PhCH_2$	98	97
6	$PhOCH_2CH_2$	100	75

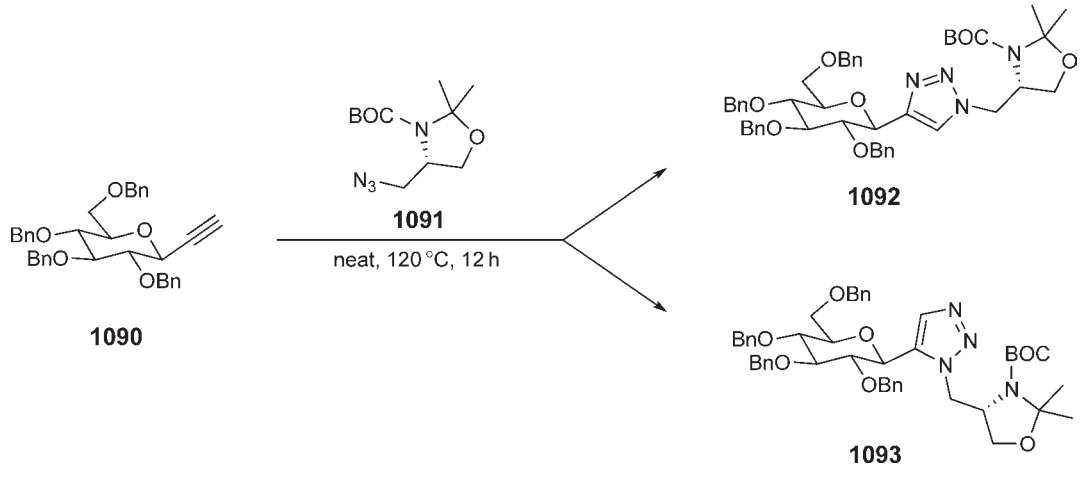
Scheme 178

Regioselectivity in reactions of acetylenes with azides depends strongly on electronic and steric factors of both reagents. Usually less electron-deficient and therefore less reactive acetylenes tend to be less regioselective. To compare reactivity of ethyl propiolate and phenylacetylene, reactions of both with tocopheryl azide **1084** are presented in **Scheme 179**. The reactions are carried out in refluxing toluene for 1–3 d. From the reaction with ethyl propiolate, 1,4-disubstituted triazole **1085** is obtained in 55% isolated yield and 1,5-disubstituted derivative **1086** in 28% yield. For phenylacetylene, the regioselectivity is slightly higher in this reaction, although the isolated yields of products are lower: 52% for derivative **1087** and 18% for isomer **1088**. Hydrolysis of derivative **1087** with 10% NaOH in methanol cleaves the bond with tocopherol releasing 4-phenyl-1,2,3-triazole **1089** <2006EJO2081>.

Not always 1,4-regioisomers are predominant in 1,3-cycloadditions of azides to alkynes. Thus, in preparation of new building blocks for glycopeptides, ethynyl *C*-glucoside **1090** is subjected to a reaction with azide **1091** to give a mixture of triazole derivatives **1092** (32%) and **1093** (48%). For the ethynyl *C*-galactoside analog of **1090**, the ratio between the products is shifted even more towards the 1,5-regioisomer (**Scheme 180**) <2004OL2929>.



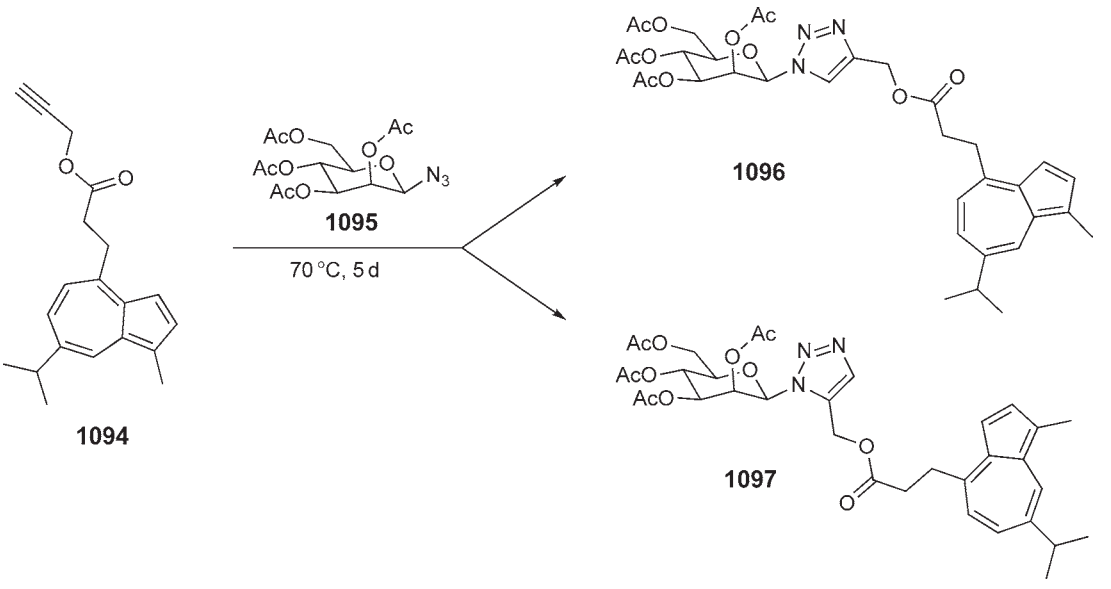
Scheme 179



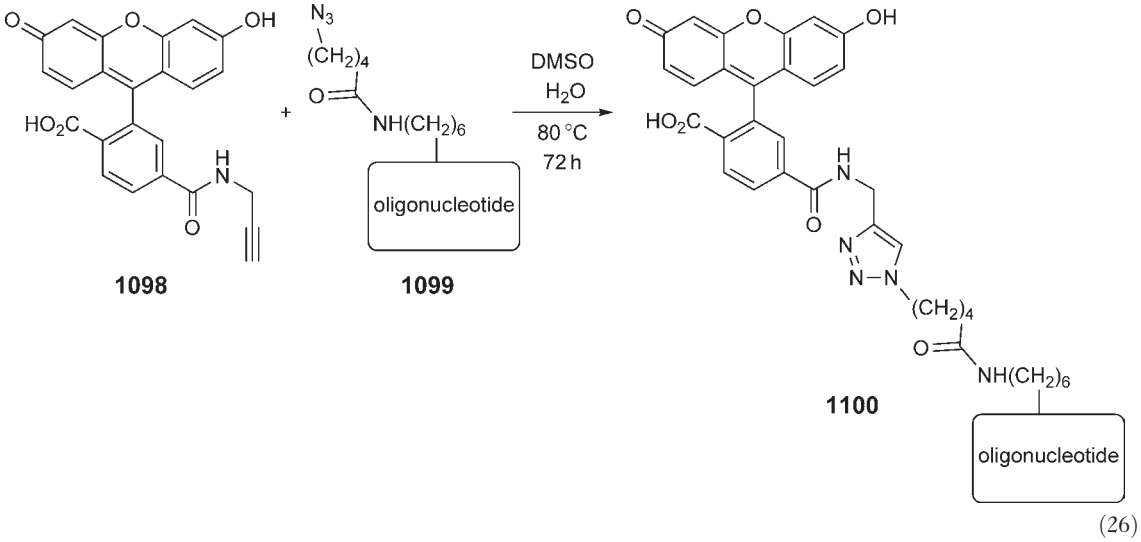
Scheme 180

To facilitate parallel synthesis and purification of triazolyl derivatives of sugars, the products are tagged with an azulene chromophore. For this purpose, guajazulene, an inexpensive azulene, is converted to propargylic ester **1094** and reacted with mannose derivative **1095** to provide a mixture of regioisomers **1096** (44%) and **1097** (32%). Separation of the products can be easily achieved by chromatography because they are visible on the column (**Scheme 181**) <2006EJO1103>.

To facilitate DNA sequencing, oligonucleotides are tagged with fluorophores. For this purpose, azido-labeled DNA **1099** is subjected to a reaction with alkyne **1098**, derived from 6-carboxyfluorescein and propargylamine, to give derivative **1100** (together with its 1,5-regioisomer) in 91% total isolated yield (Equation 26) <2003JOC609>.



Scheme 181

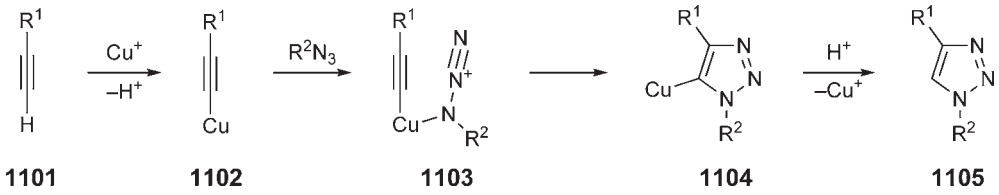


(26)

5.01.9.4 Copper Catalysis in Cycloadditions of Alkynes to Azides

Discovery of copper(I) catalysis in 1,3-dipolar cycloadditions of terminal alkynes to azides in 2002 <2002AGE2596, 2002JOC3057> has revolutionized the field. The so-called 'click chemistry' has become very popular creating a new 'gold rush' resulting in hundreds of scientific publications on the subject. It is not only that the catalyzed reactions proceed faster under mild conditions, but full regioselectivity of the products is achieved as well. Terminal alkynes generate only 1,4-disubstituted triazoles. Some aspects of this new methodology are discussed in a recent review <2007ALD7>.

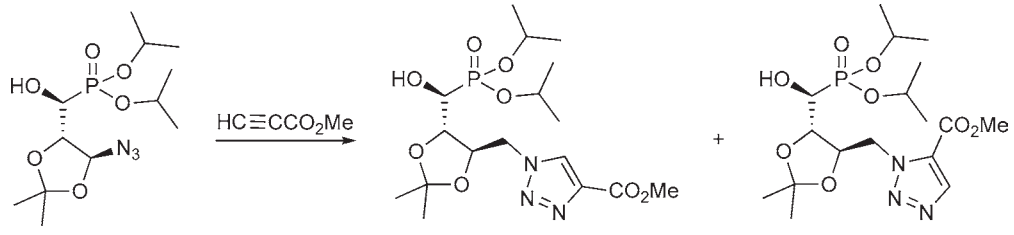
The fact that only reactions of terminal alkynes with azides are catalyzed by Cu(I) suggests participation of Cu acetylenides in the catalytic process. This conclusion is supported quantum-mechanical calculations of the transition state energies <2005JA210>. Brief outline of the reaction mechanism is given in **Scheme 182**. Thus, alkyne **1101** reacts with Cu^{+} to give copper(I) acetylenide **1102**. In the key step, copper coordinates additionally a molecule of azide to form a complex **1103**. Both entities brought to close proximity undergo facile cycloaddition to give triazole organocopper derivative **1104**. Final exchange with proton generates neutral triazole **1105** and releases the copper catalyst.



1101 1102 1103 1104 1105

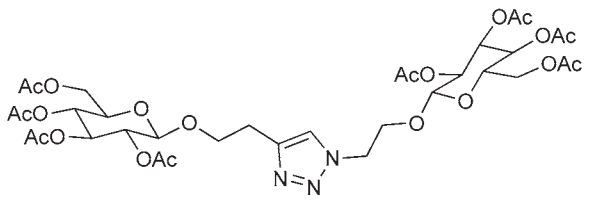
Scheme 182

There are many studies comparing thermal and catalytic 1,3-dipolar cycloadditions between alkynes and azides. In an example given in Equation (27), azide **1106** reacts with methyl propiolate in refluxing toluene to give a mixture of regioisomeric triazoles **1107** and **1108** in total yield of 59% and the ratio of 75:25, respectively. The same reaction carried out in water at room temperature with 10 mol% of a CuI catalyst, added as a suspension, results in exclusive formation of regioisomer **1107** with 94% isolated yield (Equation 27) <2005TA4056>.

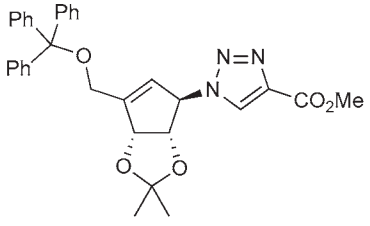


1106 1107 1108 (27)

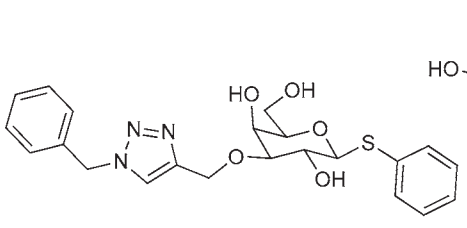
In one approach to catalytic synthesis of 1,2,3-triazoles, copper(I) is introduced to the reaction mixture as CuI. Compounds **1109–1115** are obtained this way. As can be seen in **Table 12**, a tertiary amine is often added as a base. The reaction conditions are mild and yields of the products are high. In some cases, the reaction can be carried out in water (compound **1115**). For the synthesis of triazole **1116**, addition of Cu powder is enough to generate catalytic amounts of Cu(I).



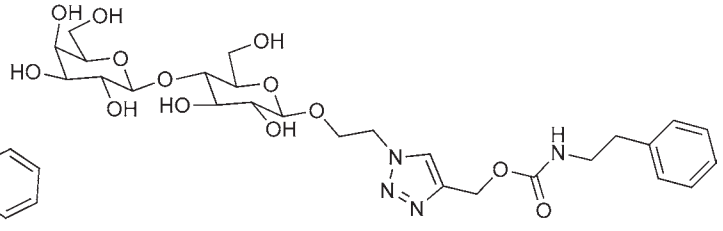
1109



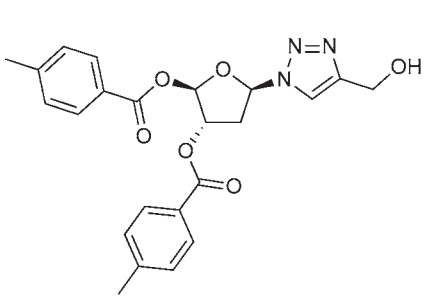
1110



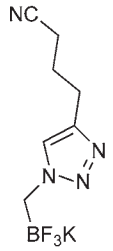
1111



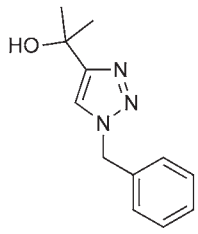
1112



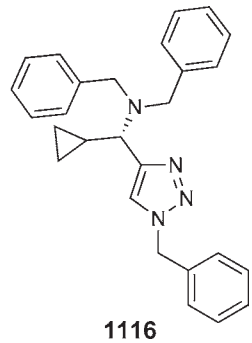
1113



1114



1115

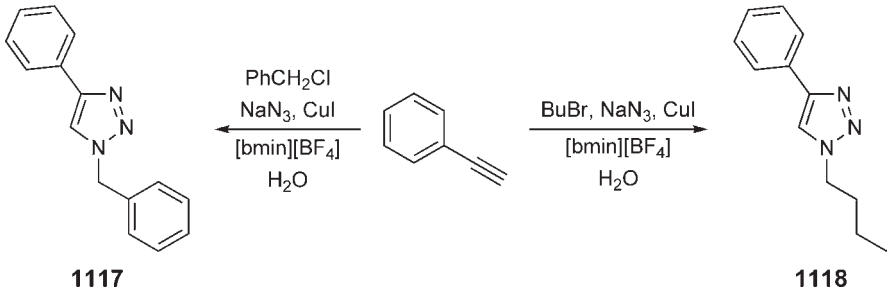


1116

Table 12 Synthesis of triazoles **1109–1116**

Product	*Reaction conditions*	*Yield (%)*	*Purpose of synthesis*	*Reference*
1109	CuI, Pr^i_2NEt, MeCN, rt, 2 h	96	Bioactive glycoconjugates	2006JOC3664
1110	CuI, Et_3N, THF, rt, 12 h	98	Antiviral nucleosides	2006JME1140
1111	CuI, Pr^i_2NEt, THF	97	Inhibitors of galectins-1 and -3	2006CC2379
1112	CuI, Pr^i_2NEt, MeCN, rt, 6 d	80	Inhibitors of galectin-1	2006CAR1353
1113	CuI, Pr^i_2NEt, silica gel, microwave	95	Triazolyl nucleosides	2006TL4807
1114	CuI, DMSO, 80 °C, 1 h	90	Novel organotrifluoro-borates	2006OL2767
1115	CuI, H_2O, rt, 20 h	100	Synthesis of 1,2,3-triazoles in water	2006SL957
1116	Cu powder, BuOH/H_2O (2:1), 40 °C, 24 h	95	Chiral 4-(α-aminoalkyl)-1,2,3-triazoles	2005SL2796

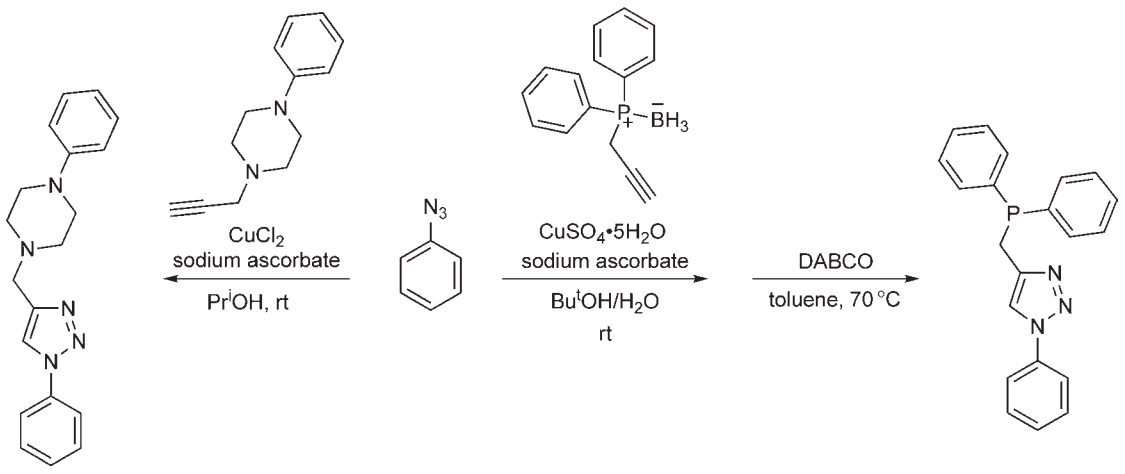
A separate preparation of azides is not always necessary. **Scheme 183** illustrates a case where azides are generated *in situ* from the corresponding halides. The reactions are carried out in ionic liquid–water system. Triazole **1117** is obtained in 94% yield from a reaction carried out at room temperature for 4 h. Butyl derivative **1118** is obtained in 90% yield under similar conditions <2006TL1545>.



1117 1118

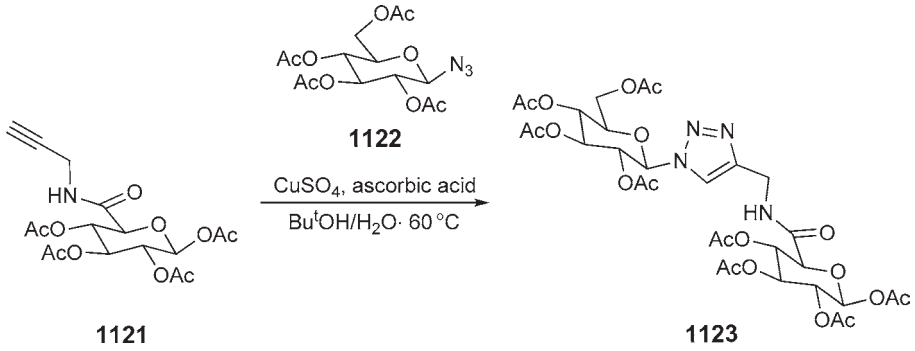
Scheme 183

In another approach, Cu(II) salts which are more soluble and easier to handle are used together with reducing agents to generate catalytic amounts of Cu(I) in reacting mixtures. In the first such example, presented in **Scheme 184**, phenylazide reacts with 1-phenyl-4-propargylpiperazine in isopropanol to give triazole **1119** in 65% yield <2006BML2955>. The reaction is catalyzed by the $CuCl_2$–sodium ascorbate system. In the second example, borane complex with propargyl-diphenylphosphine reacts with phenyl azide in a mixture of *tert*-butanol and water. The reaction is catalyzed by $CuSO_4$–sodium ascorbate and provides triazole derivative **1120**–borane complex in 96% yield. Treatment of the product with DABCO removes borane protection to give free triazole **1120** in 89% yield <2006OL3227>. In one more example of the reaction catalyzed by copper(II)–ascorbic acid system, propargylamide **1121**, derived from protected glucoronic acid, reacts with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide **1122** to give triazole derivative **1123** in 91% yield (Equation 28) <2006CAR1081>.



1119 **1120**

Scheme 184

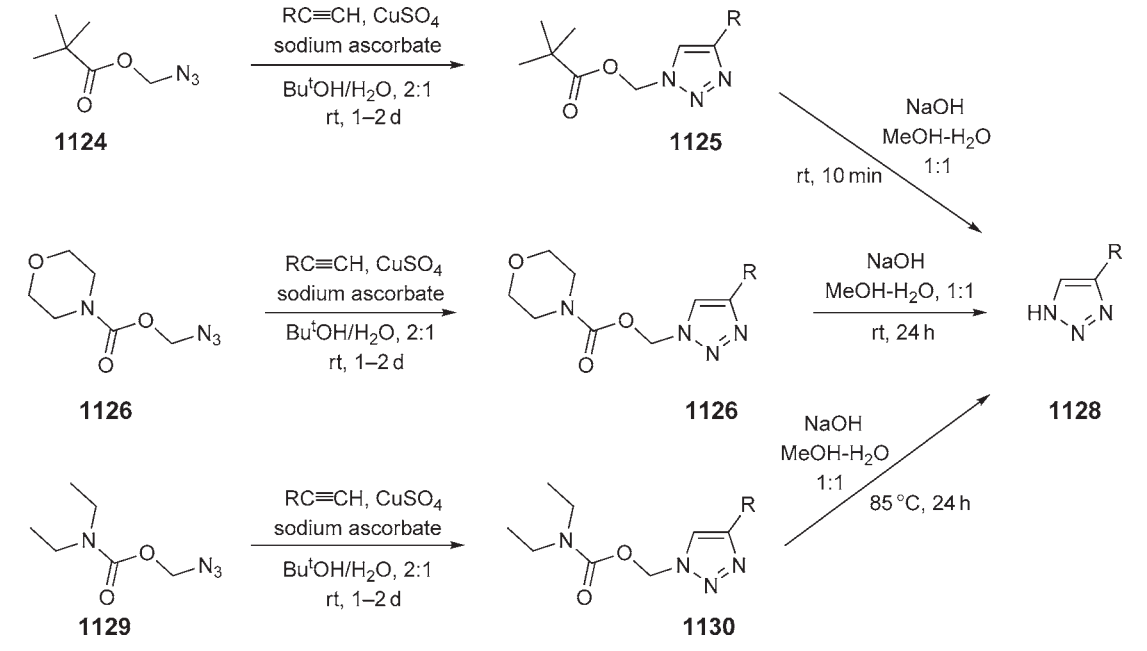


1121 **1122** **1123**

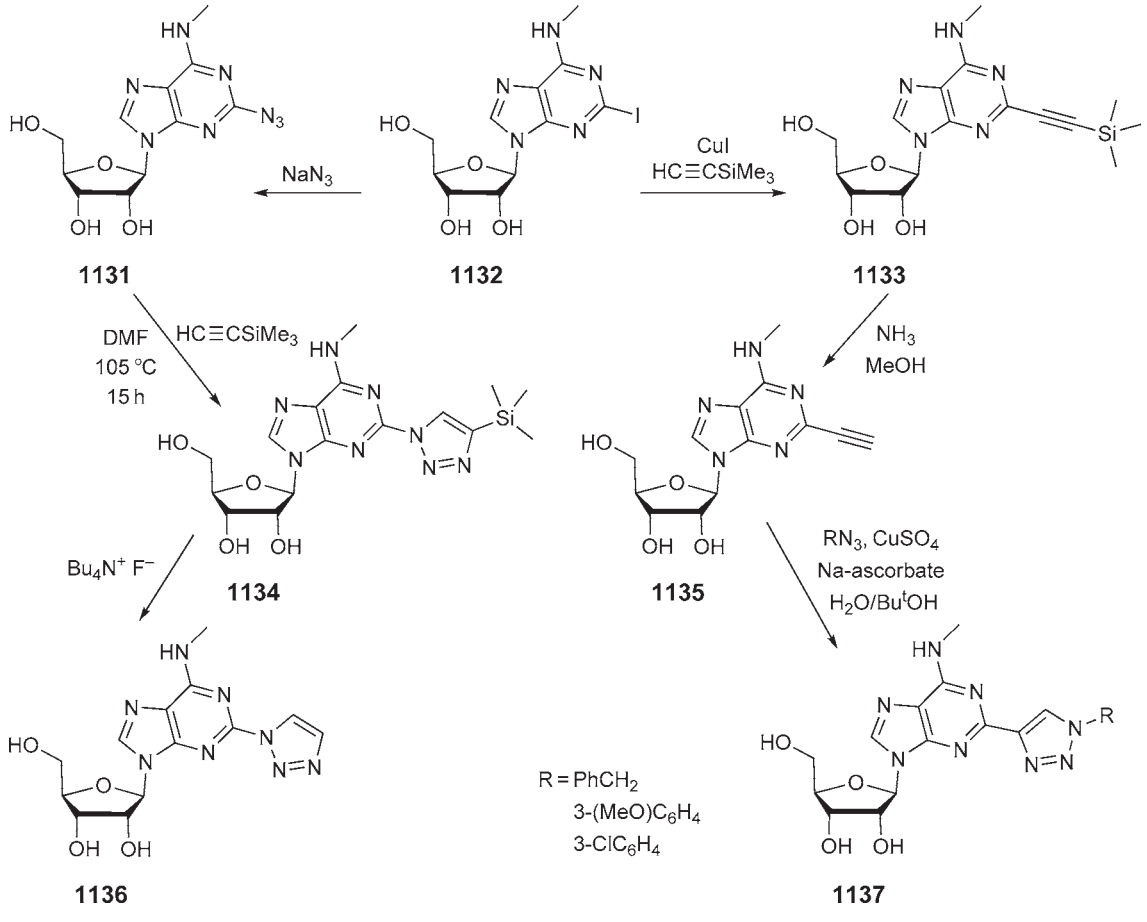
(28)

To obtain N-unsubstituted triazoles by this method, readily available azidomethyl *tert*-butyrate **1124** or carbamates **1126** and **1129** are treated with alkynes to provide triazolyl derivatives **1125**, **1127**, or **1130**, respectively. The N-protecting groups can be easily removed by treatment with NaOH to give monosubstituted triazoles **1128**. Compound **1125** is very sensitive to bases and loses its protecting group after 10 min treatment with 2.2 molar equivalents of NaOH in methanol–water. Deprotection of derivative **1127** is much slower under these conditions, and deprotection of **1130** requires heating at 85 °C. For base sensitive groups R, use of protection **1125** gives the best results. However, in other cases, more stable protections **1127** and **1130** provide better yield of products **1128** (**Scheme 185**) <2005SL2847>.

(Trimethylsilyl)acetylene is a versatile reagent in triazole synthesis. Two ways of its application in synthesis of adenosine agonists are depicted in **Scheme 186** <2006JME7373>. Thus, iodide **1132** is first treated with sodium azide to be converted to azide **1131**. Thermal cycloaddition of (trimethylsilyl)acetylene to azide **1131** gives C-silylated triazole **1134** (and possibly its regioisomer). Regioselectivity in this reaction is not important because the trimethylsilyl group is subsequently removed by treatment with tetrabutylammonium fluoride to give triazol-1-yl derivative **1136** without additional substituents on the ring. Alternatively, iodide **1132** is treated with (trimethylsilyl)acetylene in the presence of CuI and a palladium–phosphine complex as a catalyst to give (trimethylsilyl)ethynyl derivative **1133**. Removal of the silyl protection by treatment with methanolic ammonia to give compound **1135** followed by regular cycloadditions with benzyl azides, catalyzed by $CuSO_4$–sodium ascorbate, furnishes triazolyl derivatives **1137** in 73–80% yield.



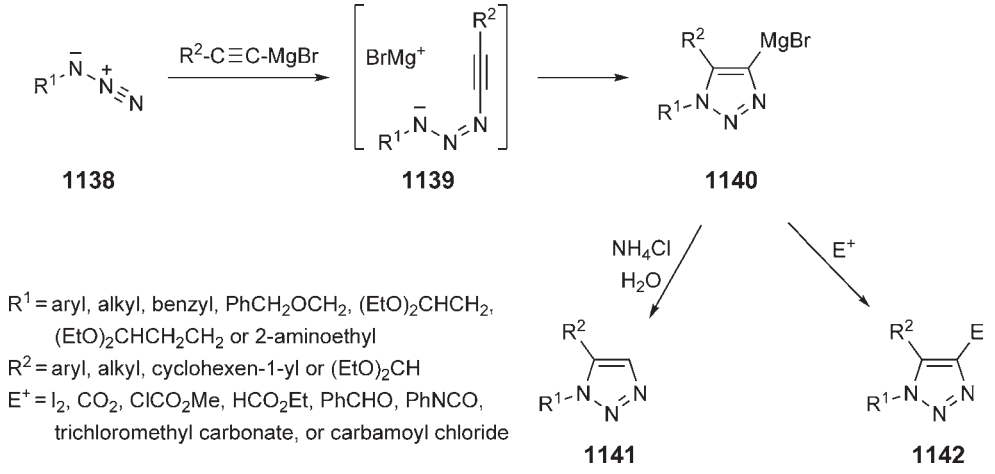
Scheme 185



Scheme 186

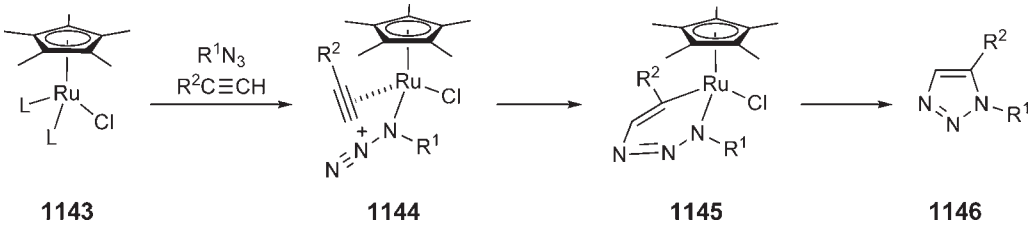
5.01.9.5 Reverse Regioselectivity

1,5-Disubstituted 1,2,3-triazoles are the minor products of thermal cycloaddition of terminal alkynes to azides, and they are completely absent when the reactions are catalyzed by Cu(I). However, under strongly basic conditions, when magnesium or lithium acetylenides are used as the substrates, reverse regioselectivity is observed, and 1,5-disubstituted triazoles are separated as the only products. The proposed mechanism begins with a nucleophilic attack of the alkyne anion on the terminal nitrogen atom of azide **1138**. The resulting intermediate anion **1139** undergoes spontaneous cyclization to organomagnesium derivative **1140**. Work-up with aqueous ammonium chloride furnishes 1,5-disubstituted triazoles **1141**. When instead of work-up, the reaction mixture is treated with an electrophile, 1,4,5-trisubstituted triazoles **1142** are obtained (**Scheme 187**) <2004OL1237>. The reactions are typically carried out in THF at room temperature. In the case of more reactive azides with electron-deficient groups R^1, the reactions are exothermic and can be accomplished in less then 1 h. Less reactive azides require longer, 1 d, time to completion. The yields are high to quantitative <2004OL1237, 2005OL4907, 2006JOC3928>.



Scheme 187

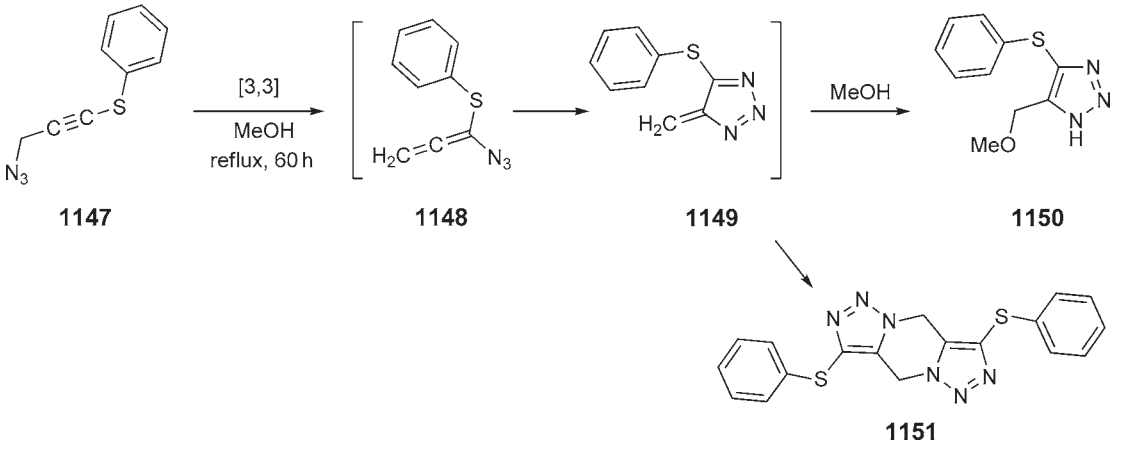
According to the recent finding <2005JA15998>, catalysis by ruthenium complexes used in 1 mol% amounts leads also exclusively to 1,5-disubstituted 1,2,3-triazoles. The reactions, carried out in benzene or dioxane, are relatively fast (typically 2–4 h) and high yielding (80–94%). The method tolerates groups that may not be compatible with organomagnesium reagents. Contrary to the copper(I) catalysis, this method works also well with disubstituted acetylenes to provide 1,4,5-trisubstituted 1,2,3-triazoles. The suggested mechanism <2005JA15998> is presented in **Scheme 188**. Simultaneous replacement of two ligands in ruthenium catalyst **1143** (e.g., triphenylphosphine) by the azide and alkyne molecules generates active transition state **1144** promoting bond formation between the terminal atoms of the new ligands to give a six-membered ruthenocycle **1145**. Finally, formation of the second bond between the reacting partners releases a molecule of triazole **1146** and recycles the catalyst.



Scheme 188

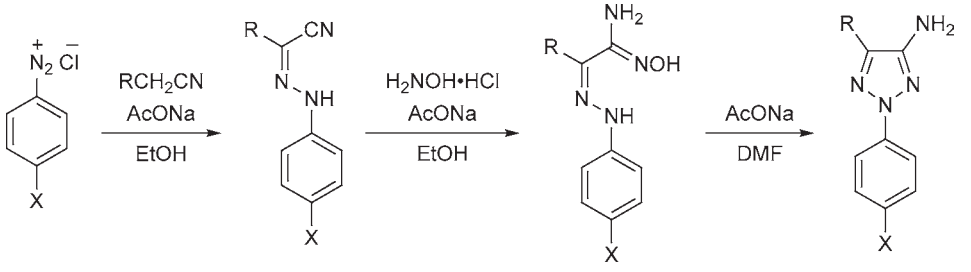
5.01.9.6 Other Synthetic Methods for 1,2,3-Triazoles

Heated in methanol for an extended period of time, propargyl azide **1147** experiences a [3,3] sigmatropic shift to allenyl azide **1148** that undergoes rapid cyclization to triazafulvene **1149**. Addition of a molecule of methanol converts reactive intermediate **1149** to triazole **1150** that is isolated in 68% yield. In concentrated solutions, two molecules of intermediate **1149** may undergo cycloaddition to form dimer **1151** as a side product (**Scheme 189**) <2005EJO3704>.



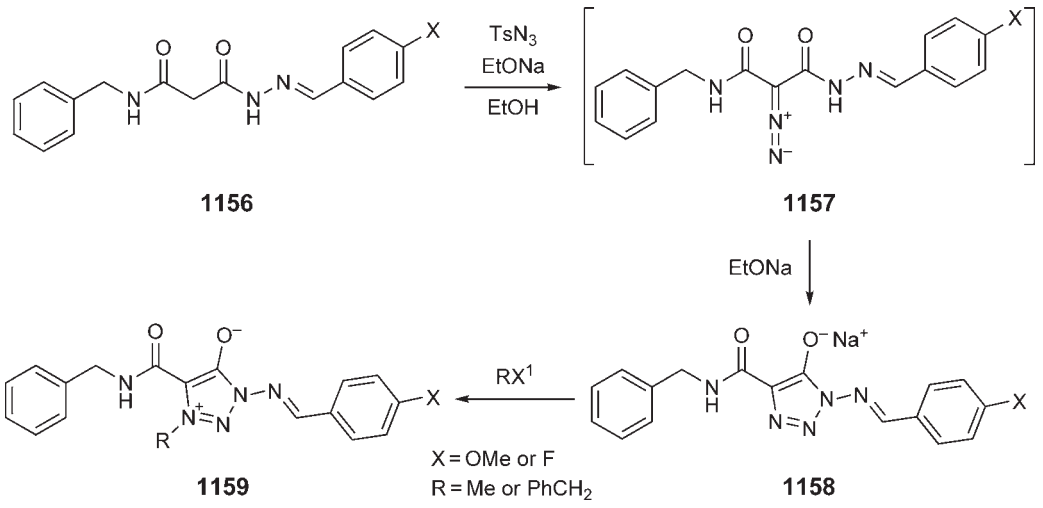
Scheme 189

Condensation of diazonium salts **1152** with activated nitriles provides hydrazones **1153**. Treatment of hydrazones **1153** with hydroxylamine affords amidoximes **1154** in high yield. Upon heating with anhydrous sodium acetate in refluxing DMF, compounds **1154** undergo intramolecular cyclocondensation to provide 5-substituted 4-amino-2-aryl-2*H*-1,2,3-triazoles **1155** in 75–85% yield (**Scheme 190**) <2006ARK(xv)53>.



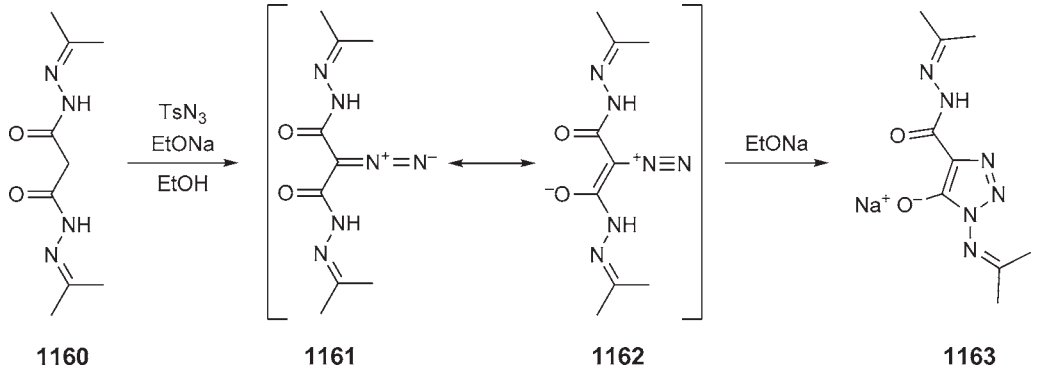
Scheme 190

Upon heating with tosyl azide and sodium ethoxide in ethanol, amidohydrazides **1156** derived from malonic acid are converted into diazo compounds **1157**. Under the reaction conditions, derivatives **1157** undergo cyclization to triazoles **1158**. Salts **1158** are isolated in good yield (52% for X = OMe and 82% for X = F). Methylation and benzylation of products **1158** occurs selectively on the triazole N-3 atom giving rise to mesoionic systems **1159** (**Scheme 191**) <2002J(P1)211>. Under similar reaction conditions, dihydrazide **1160** is converted to triazole **1163** via intermediate diazo derivative **1161** (**Scheme 192**) <2004T5367>. Resonance form **1162** and others with definitely positive charge on the diazo nitrogen atoms seem to be responsible for the cyclization.



1156 1157 1158 1159

Scheme 191



1160 1161 1162 1163

Scheme 192

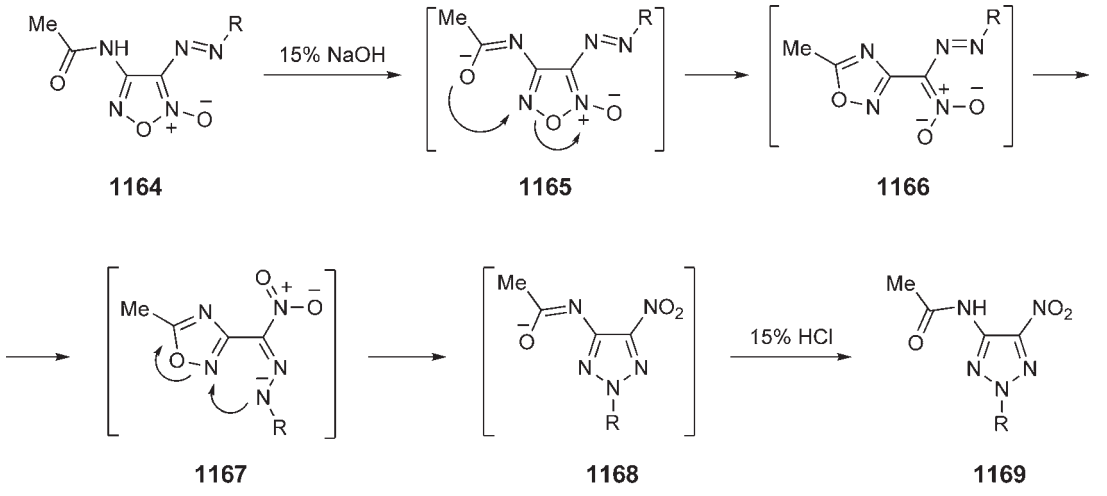
5.01.10 Ring Syntheses by Transformation of Other Rings

5.01.10.1 1,2,3-2H-Triazoles from 1,2,5-Oxadiazoles

Treatment of 4-acetamido-3-arylazo-1,2,5-oxadiazole 2-oxides (furoxans) **1164** with aqueous NaOH results in formation of 4-acetamido-2-aryl-5-nitro-2*H*-1,2,3-triazoles **1169**. According to the proposed mechanism, the anion derived from the acetamido group attacks N-5 of the furoxan system (form **1165**) causing ring opening and formation of another oxadiazole ring (form **1166**). Rotation of the large substituent at C-3 in oxadiazole **1166** brings the arylazo group to proximity of the ring (form **1167**). In the following step, which is reverse to that shown as form **1165**, an intramolecular attack of the arylazo group on oxadiazole **1167** causes ring opening with release of the acetamido group and formation of a new ring (form **1168**). Acidification with hydrochloric acid stabilizes the system as triazole derivative **1169**. This cascade rearrangement is fast (20 min at room temperature) and provides triazoles **1169** in 54–62% yield (**Scheme 193**) <2001MC230>.

Reaction of amines **1170** with ethoxycarbonyl isocyanate, carried out in ethyl acetate at −20 °C, provides 3-arylazo-4-(3-ethoxycarbonylureido)furoxans **1171** in 82–86% yield. Compounds **1171** are much less reactive than their acetamido analogs **1164**. To promote a cascade rearrangement similar to that depicted in **Scheme 193**, furoxans **1171** have to be heated with potassium *tert*-butoxide in DMF. The probable reason for reduced reactivity of anion **1172** is the fact that it can exist in several tautomeric and resonance forms rendering the carbonyl oxygen atom less nucleophilic. However, at 100 °C, a nucleophilic attack of the oxygen atom on N-5 of the furoxan system results in its ring opening and formation of a new ring of oxadiazole **1173**. By rotation of the substituent at C-3, the arylazo group comes to a suitable position for

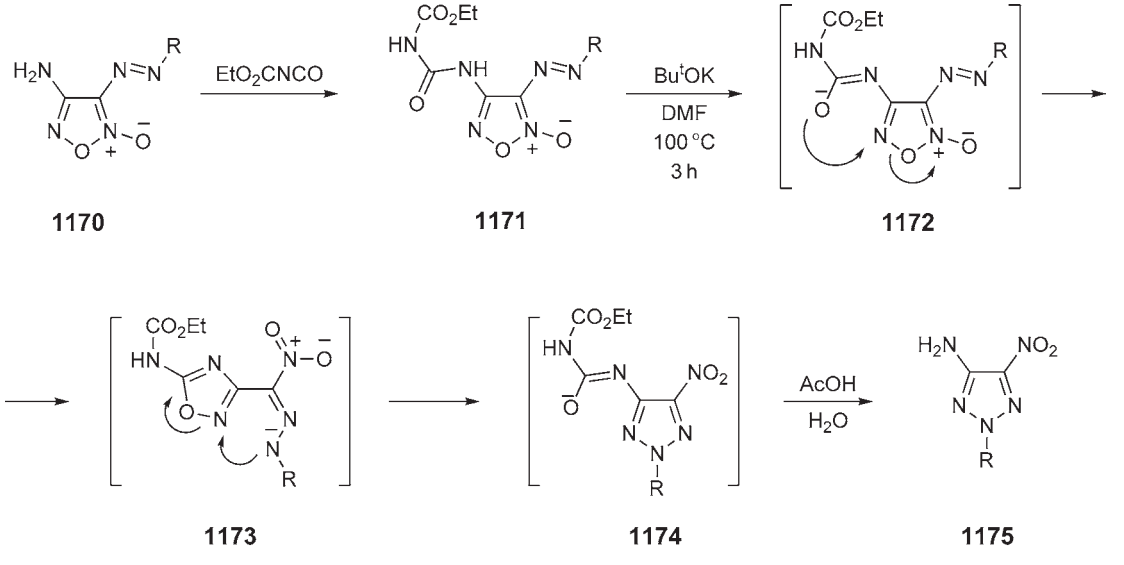
nucleophilic attack on N-2 resulting in opening of the oxadiazole ring and formation of triazole **1174**. During work-up, even under very mild conditions, the ureido group is hydrolyzed and 3-amino-2-aryl-4-nitro-2*H*-1,2,3-triazole **1175** is obtained. Compounds **1175** are isolated in 45–65% yield (**Scheme 194**) <2003RCB1829>.



1164 **1165** **1166** **1167** **1168** **1169**

R = 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$, or 2,4,6-Me$_3$C$_6$H$_2$

Scheme 193

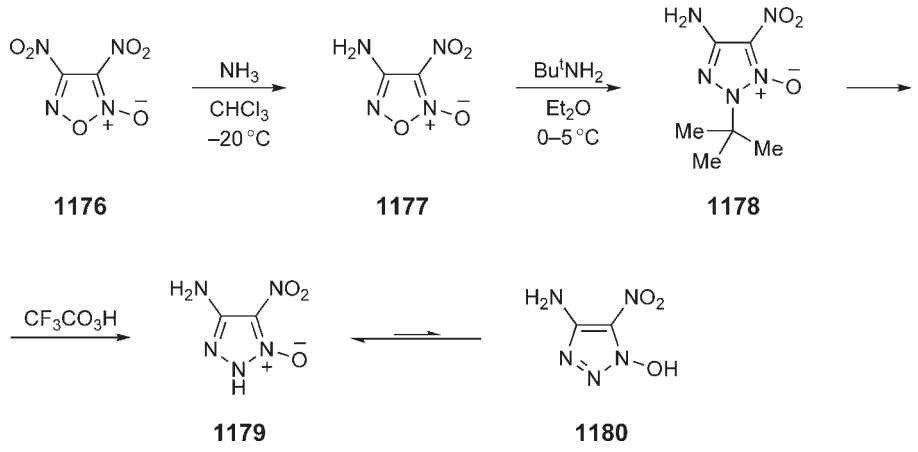


1170 **1171** **1172** **1173** **1174** **1175**

R = 4-MeOC$_6$H$_4$, 4-EtOC$_6$H$_4$, or 2,4,6-Me$_3$C$_6$H$_2$

Scheme 194

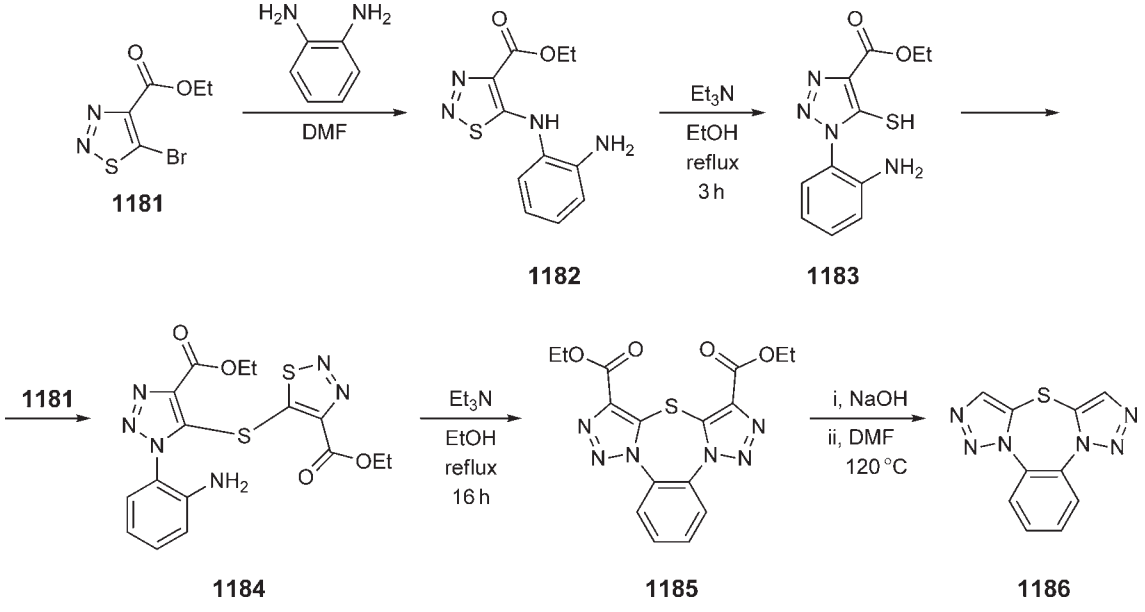
Substitution of the 4-nitro group in 3,4-dinitrofuroxan **1176** by ammonia occurs readily, even at low temperature. Subsequent treatment of the obtained amine, product **1177**, with *t*-butylamine results in formation of 4-amino-2-(*t*-butyl)-5-nitro-1,2,3-triazole 1-oxide **1178**. However, there must be some additional side products in the reaction mixture, as the isolated yield of compound **1178** is only 17%. Upon treatment with trifluoroperacetic acid, the *t*-butyl group is removed. The obtained triazole system can exist in two tautomeric forms, **1179** and **1180**; however, the 1-oxide form **1179** is strongly favored (**Scheme 195**) <2003CHE608>.



Scheme 195

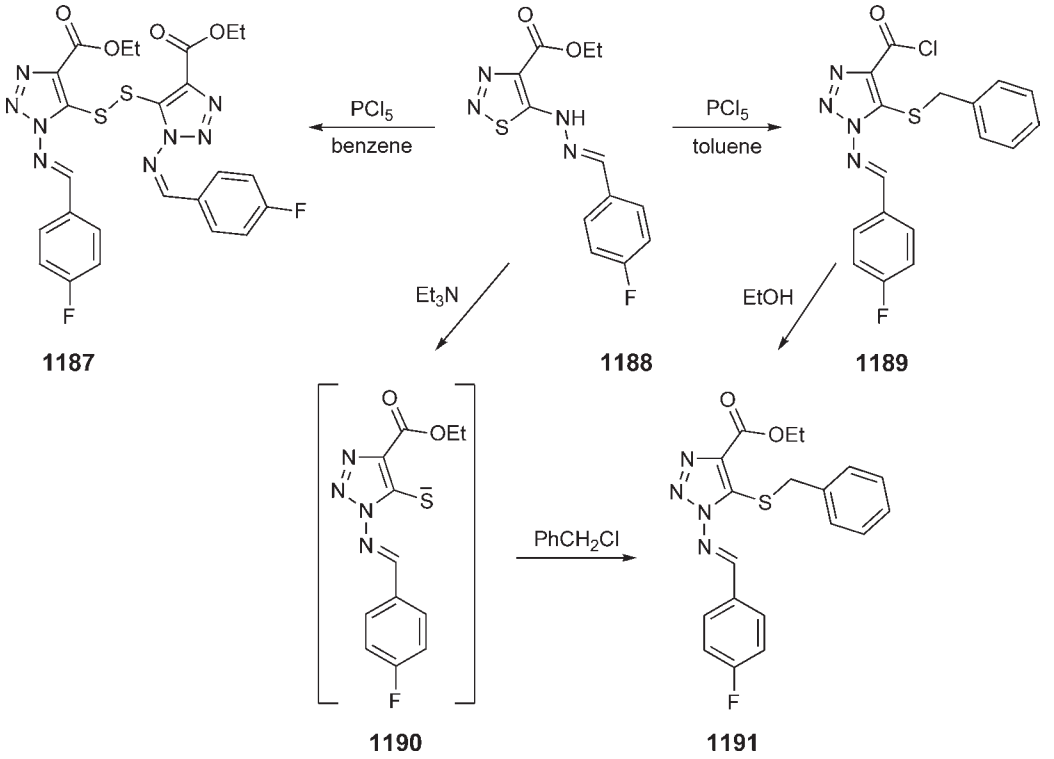
5.01.10.2 1,2,3-1H-Triazoles from 1,2,3-Thiadiazoles

In a reaction with *ortho*-phenylenediamine, carried out in DMF at room temperature, ethyl 5-bromo-1,2,3-thiadiazole-4-carboxylate **1181** is converted to ethyl 5-[(2-aminophenyl)amino]-1,2,3-thiadiazole-4-carboxylate **1182** with 76% yield. Upon treatment with a mild base, amine **1182** undergoes Dimroth rearrangement to 5-mercapto-1,2,3-triazole **1183** (isolated in 93% yield). In a reaction with second molecule of bromide **1181**, mercaptan **1183** is converted to sulfide **1184** (93% yield). Treatment of derivative **1184** with Et_3N in refluxing ethanol leads to a nucleophilic attack of the amino group on the thiadiazole ring resulting in elimination of hydrogen sulfide and formation of the second benzotriazole ring. Benzothiadiazepine **1185** obtained this way is isolated in 54% yield. Hydrolysis of the carbethoxy groups in derivative **1185** followed by decarboxylation of the obtained acid furnishes di[1,2,3]triazolo[1,5-*a*:5′1′-*d*][3,1,5]benzothiadiazepine **1186** (**Scheme 196**) <2002J(P1)1574>.



Scheme 196

Treatment of 1,2,3-thiadiazole derivative **1188** with PCl_5 in refluxing benzene results in formation of the 1,2,3-triazol-5-yl disulfide **1187**. The reaction must proceed by Dimroth rearrangement of the thiadiazole ring followed by oxidation of the obtained thiol, possibly with PCl_5. However, when the reaction is carried out in refluxing toluene, triazole derivative **1189** is obtained instead (isolated yield 65%). In this case, apart of Dimroth rearrangement of the starting material, a reaction of PCl_5 with the solvent generates benzyl chloride that benzylates the thiol group. Hydrogen chloride released in this reaction converts the ethoxycarbonyl group into an acid chloride function in product **1189**. To prove the structure of derivative **1189**, it is converted to ester **1191**, which appears to be the same compound as the product obtained by regular Dimroth rearrangement of thiadiazole **1188** catalyzed by Et_3N followed by treatment of intermediate **1190** with benzyl chloride (**Scheme 197**) <2003CHE126>.

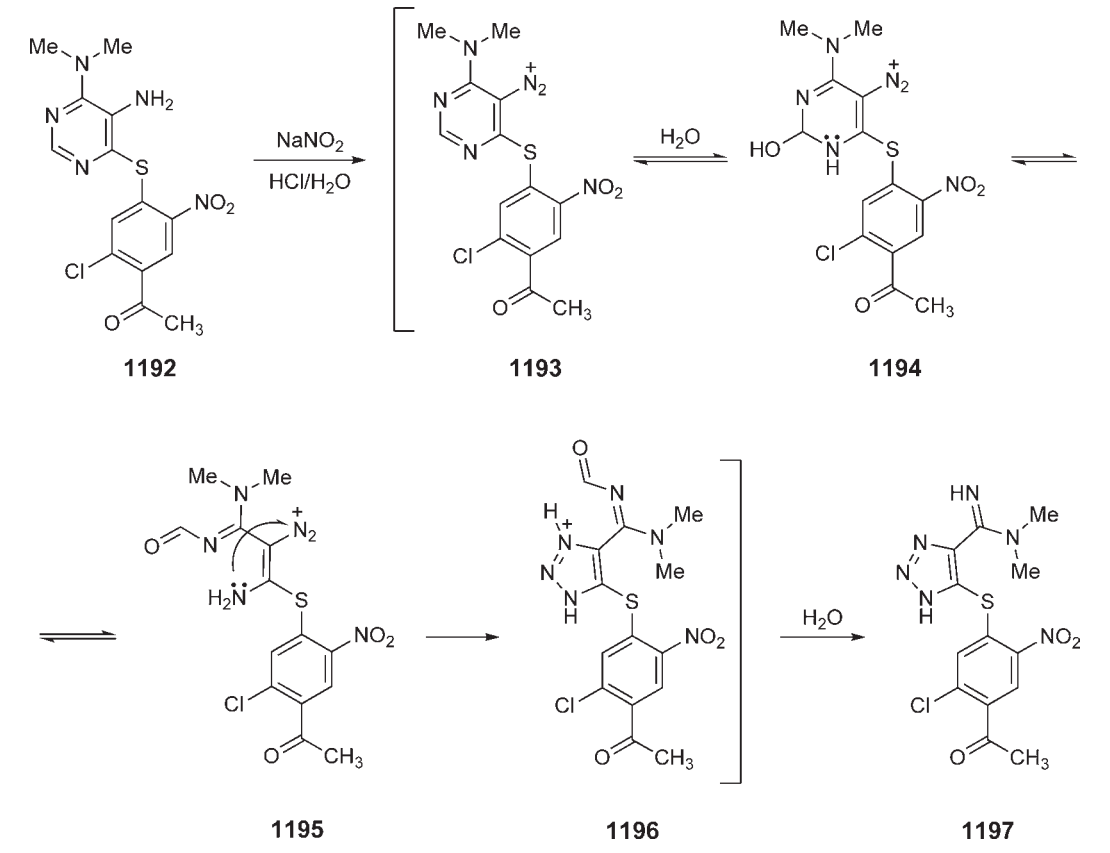


Scheme 197

5.01.10.3 1,2,3-Triazoles from Pyrimidine Derivatives

Diazotization of the 5-aminopyrimidine **1192** gives the diazonium cation **1193**. Due to strong electron deficiency at C-2 of the pyrimidine system, species **1193** exists partially as the covalent hydrate **1194**. Under acidic conditions, the 1,2-dihydropyrimidine ring of intermediate **1194** can be easily opened. One of such open forms is structure **1195**. Among many tautomeric forms of species **1195**, there are structures with a single bond between the carbon atoms, which allow free rotation to bring the NH_2 and N_2^+ groups to close proximity. Nucleophilic intramolecular attack of the amine N atom on the diazonium group leads to triazolyl derivative **1196**. In the aqueous hydrochloric acid reaction medium, **1196** is hydrolyzed to (1,2,3-triazol-4-yl)amidine **1197** (**Scheme 198**) <2003PCJ298>.

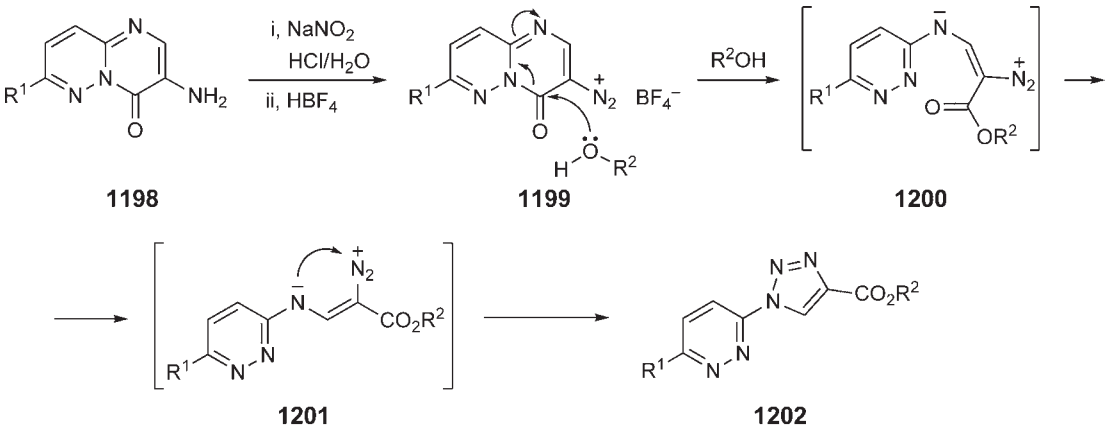
As shown in **Scheme 199**, the 5-aminopyrimidine structure may be also incorporated into a more complex bicyclic system. Thus, diazotization of 3-amino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazines **1198** followed by treatment with 50% aqueous tetrafluoroboric acid results in precipitation of salts **1199**. When heated with alcohols, nucleophilic attack on the carbonyl group opens the pyrimidine ring. The obtained species **1200** assume conformation **1201** that is more suitable for bond formation between the opposite charged nitrogen atoms. Alkyl 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **1202** are obtained in 31–66% yield <2002ARK(viii)143>.



1192 1193 1194

1195 1196 1197

Scheme 198



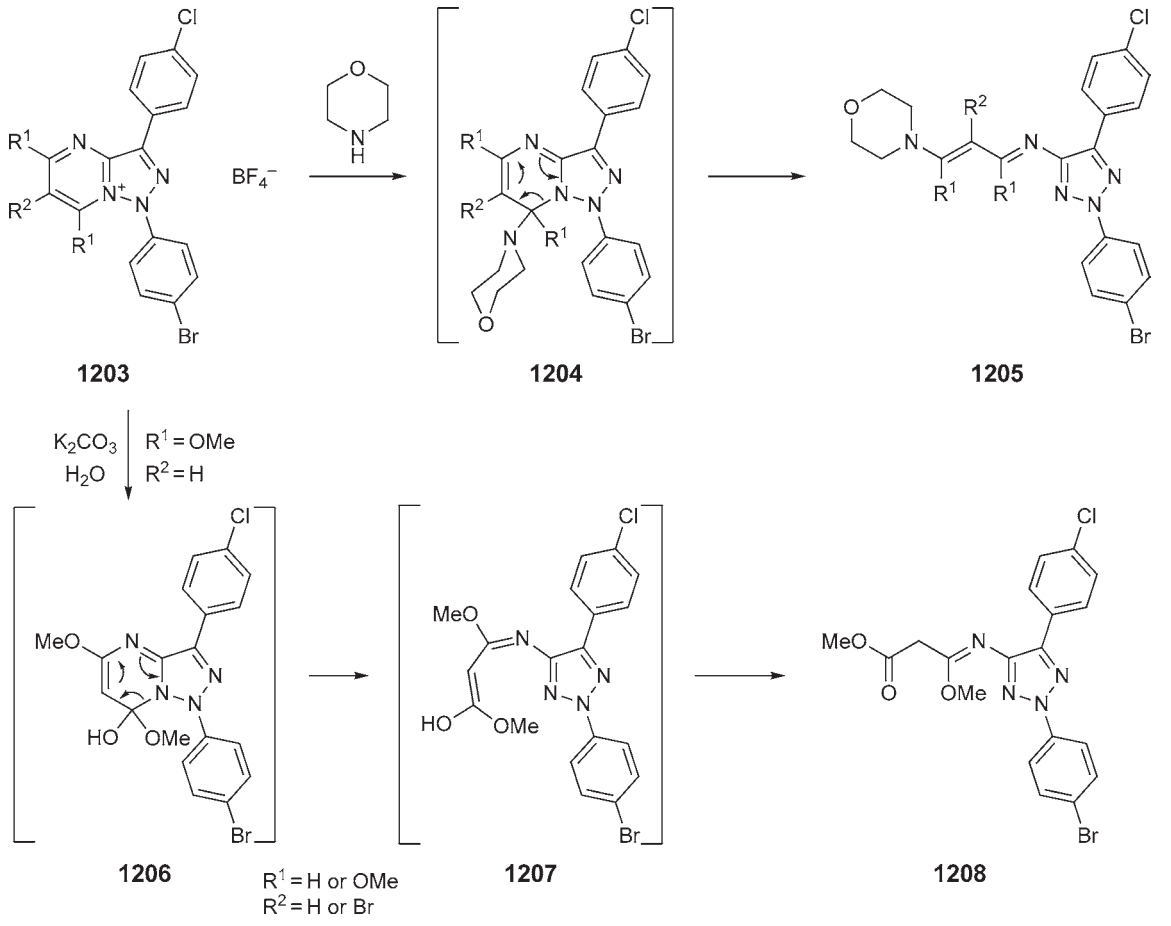
1198 1199 1200

1201 1202

R^1 = H or Ph
R^2 = Me, Et, Pr^n, Bu^n, or *n*-pentyl

Scheme 199

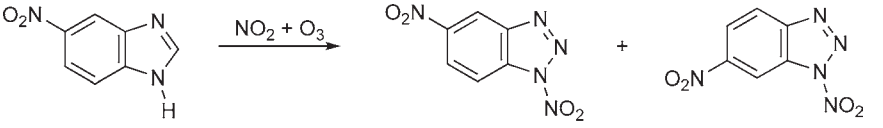
A nucleophilic attack of morpholine on the pyrimidine ring in 1,2,3-triazolo[1,5-*a*]pyrimidinium salts **1203** leads to unstable intermediates **1204**. Spontaneous opening of the pyrimidine ring results in formation of 1,2,3-triazole derivatives **1205** that are isolated in 80–85% yield. A similar nucleophilic attack of the hydroxide anion (from aq. K_2CO_3) on dimethoxy derivative **1203** provides transition species **1206** that opens to intermediate **1207**, and finally tautomerizes to ester **1208**, isolated in 87% yield (**Scheme 200**) <2003T4297>.



Scheme 200

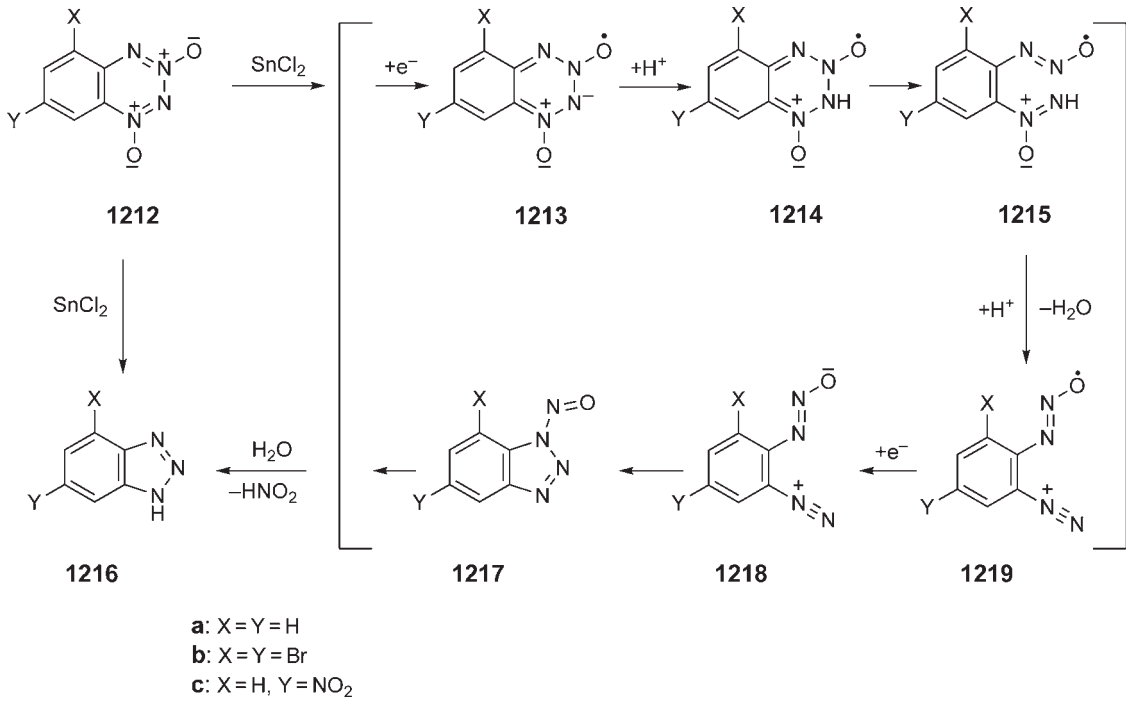
5.01.10.4 Benzotriazoles and Higher Fused Systems

Treatment of benzimidazole with ozone and NO_2 results in a complex mixture of mono- and di-nitrated benzimidazoles and triazoles. However, nitration of 5-nitrobenzimidazole **1209** under such conditions leads to two major products, benzotriazoles **1210** and **1211**. The mechanism of ring conversion from benzimidazole to benzotriazole is not clear (Equation 29) <2004CPB570>.



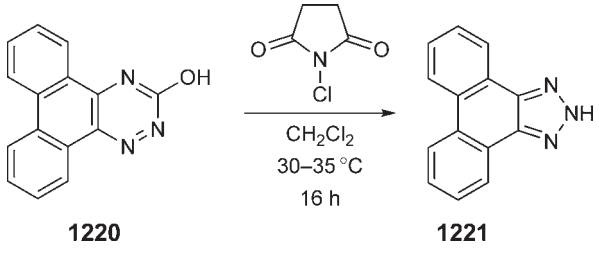
1209 **1210** **1211** (29)

Reduction of benzo-1,2,3,4-tetrazine 1,3-diones **1212** results in formation of benzotriazoles **1216**, which are isolated in high yield (95–98%). Common agents used for reduction of nitro groups, $Na_2S_2O_4$, $SnCl_2$, or Fe/HCl, work well here; however, the required reaction conditions are milder allowing a nitro group survive untouched in product **1216c**. The proposed mechanism starts from a single electron transfer with generation of radical **1213**. After protonation leading to intermediate **1214**, the N(2)–N(3) bond is cleaved furnishing form **1215**. Another protonation and elimination of water leads to diazonium ion **1219**. Transfer of a second electron converts radical **1219** into anion **1218** that is in position to undergo cyclization to *N*-nitrosobenzotriazole **1217**. Under the reaction conditions, intermediate **1217** hydrolyzes to benzotriazole **1216**. Intermediacy of nitroso derivatives **1217** is proven by running the reaction in the presence of morpholine with 4-nitrosomorpholine being isolated as the only side product (**Scheme 201**) <2002OL3227>.



Scheme 201

1,2,3-Triazoles fused with larger aromatic systems can be also obtained this way. Thus, in an example given in Equation (30), 2*H*-phenanthro[9,10-*d*]-1,2,3-triazole **1221** is obtained in 84% yield from a reaction of 3-hydroxyphenanthro-1,2,4-triazine **1220** with NCS <2000H(53)203>.



(30)

5.01.11 Synthesis of Particular Classes of Compounds

5.01.11.1 Derivatives of 1,2,3-Triazole

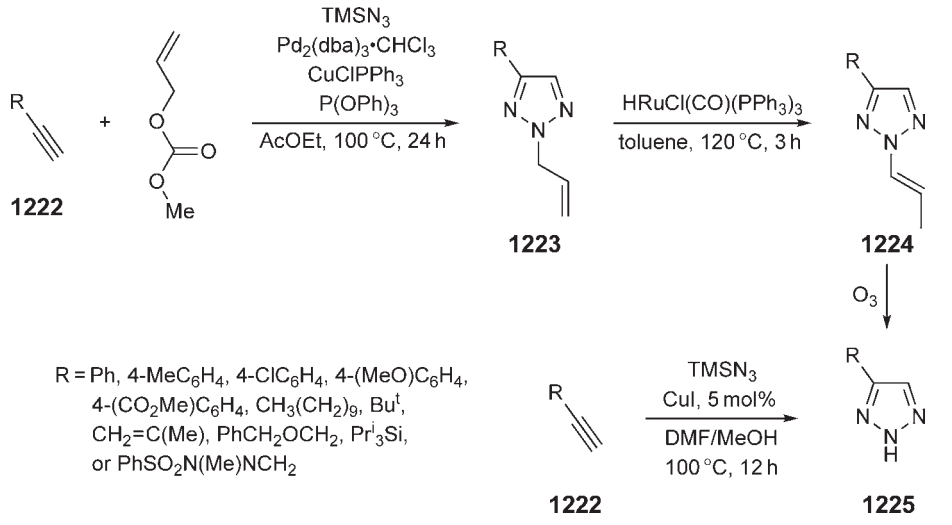
5.01.11.1.1 N-Substituted 1,2,3-triazoles

Reactions of salts of 1,2,3-triazole with electrophiles provide an easy access to 1,2,3-triazol-*N*-yl derivatives; although, usually mixtures of N-1 and N-2 substituted triazoles are obtained that have to be separated (see Section 5.01.5). Another simple method for synthesis of such derivatives is addition of 1,2,3-triazole to carbon–carbon multiple bonds (Section 5.01.5). N-1 Substituted 1,2,3-triazoles can be selectively prepared by 1,3-dipolar cycloaddition of acetylene or (trimethylsilyl)acetylene to alkyl or aryl azides (Section 5.01.9).

5.01.11.1.2 C-Substituted 1,2,3-triazoles

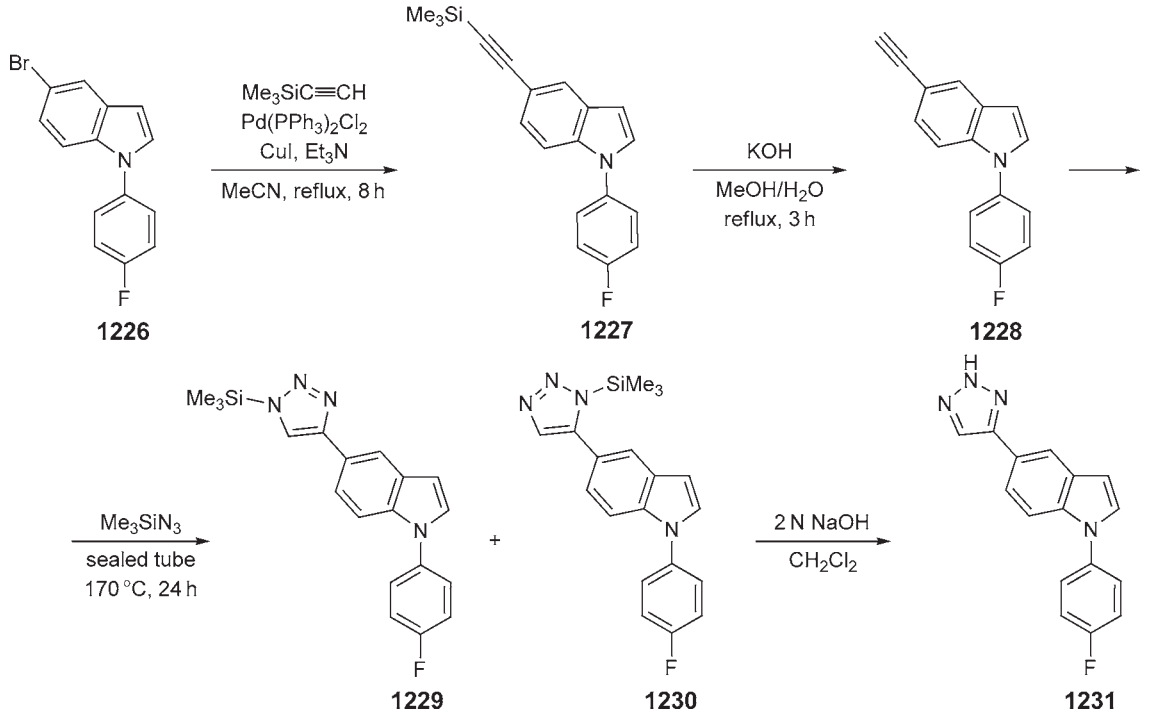
In the presence of copper and palladium catalysts, terminal alkynes **1222** react with trimethylsilyl azide and allyl methyl carbonate to provide 2,4-disubstituted 1,2,3-triazoles **1223** in moderate to good yield. Isomerization of the allyl substituent in the presence of a ruthenium catalyst gives 4-substituted 2-(1-propen-1-yl)-2*H*-1,2,3-triazoles **1224**.

Deprotection of N-2 by ozonolysis furnishes triazoles **1225** (**Scheme 202**) <2003JA7786>. Finding that 1,3-dipolar cycloaddition of alkynes **1222** to trimethylsilyl azide, carried out in DMF/MeOH in the presence of CuI as a catalyst, leads directly to products **1225** with much higher yields provides a significant progress to the synthesis of N-unsubstituted 1,2,3-triazoles <2004EJO3789>.



Scheme 202

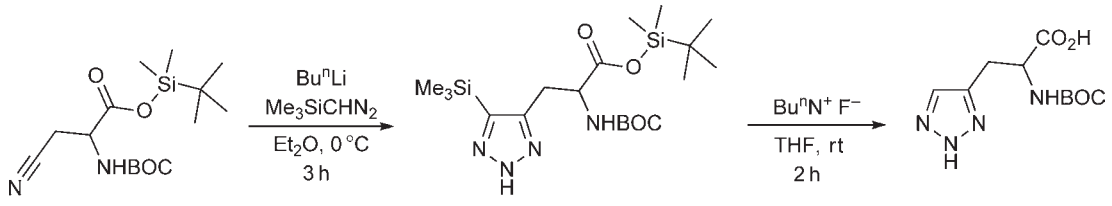
Scheme 203 provides a methodology for the conversion of aryl bromides onto 4-aryl-1,2,3-triazoles. In the given example, palladium–copper catalyzed substitution of the bromine atom in indole **1226** by trimethylsilylacetylene provides intermediate **1227**. Hydrolysis of the trimethylsilyl protecting group releases terminal alkyne **1228**, isolated



Scheme 203

in 35% yield (two steps). 1,3-Dipolar cycloaddition of alkyne **1228** to trimethylsilyl azide leads to a mixture of regioisomeric triazoles **1229** and **1230**, which is directly hydrolyzed by 2 N NaOH to give quantitatively triazole **1231** <2003JME265>.

In a quite different approach, shown in **Scheme 204**, cycloaddition of nitrile **1232** to trimethylsilyldiazomethane provides silylated triazole **1233**, isolated in 75% yield. Treatment with tetrabutylammonium fluoride removes the trimethylsilyl group and simultaneously the silyl protection of the carboxylic group to afford 4-substituted triazole derivative **1234** in 81% yield <2003PEN699>.



1232 **1233** **1234**

Scheme 204

5.01.11.1.3 1,4-Disubstituted 1,2,3-triazoles

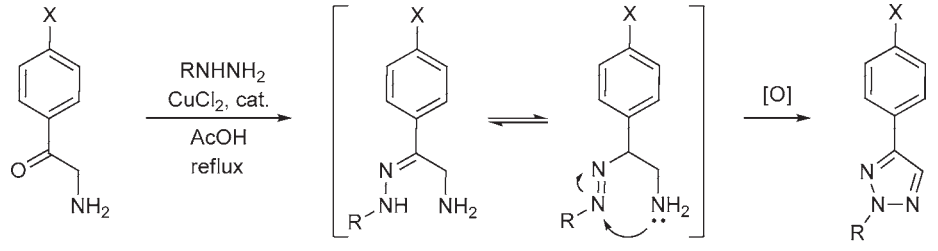
1,4-Disubstituted 1,2,3-triazoles are exclusive products of copper catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. A variety of substituents can be introduced in this way. Many examples of such reactions are discussed in Section 5.01.9.

5.01.11.1.4 1,5-Disubstituted 1,2,3-triazoles

1,5-Disubstituted 1,2,3-triazoles are formed in 1,3-dipolar cycloaddition of alkynylmagnesium reagents to azides. This reverse regioselectivity is also achieved in ruthenium-catalyzed cycloadditions. Examples of such reactions can be found in Section 5.01.9.

5.01.11.1.5 2,4-Disubstituted 1,2,3-triazoles

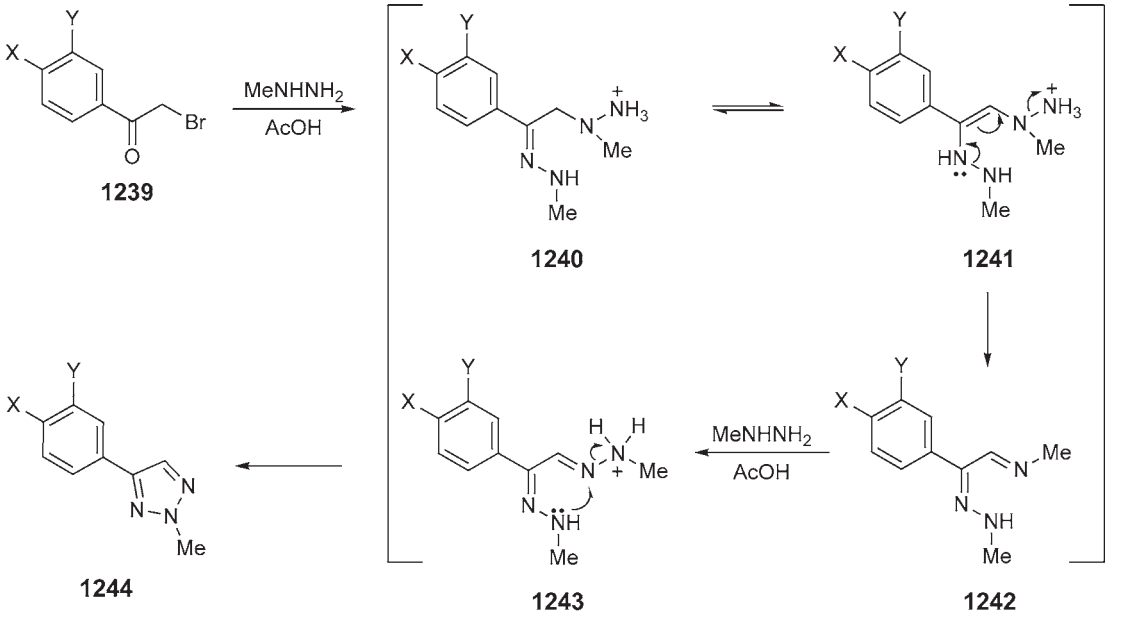
2,4-Disubstituted 1,2,3-triazoles are usually minor components in the product mixtures obtained from reactions of triazole with electrophiles (see Section 5.01.5). The few regioselective syntheses of such compounds include a reaction of aminoacetophenones **1235** with hydrazines. The reaction with methylhydrazine proceeds well without any catalysis, but that with phenylhydrazine requires cupric chloride as a catalyst. It is assumed that hydrazone **1236** that forms in the first step is in a tautomeric equilibrium with its azo form **1237**. However, it is not clear how bond formation between the nitrogen atoms and oxidation to the triazole system occurs. 4-Aryltriazoles **1238** are obtained in 50–66% yield (**Scheme 205**) <2003SC3513>.



1235 **1236** **1237** **1238**

Scheme 205

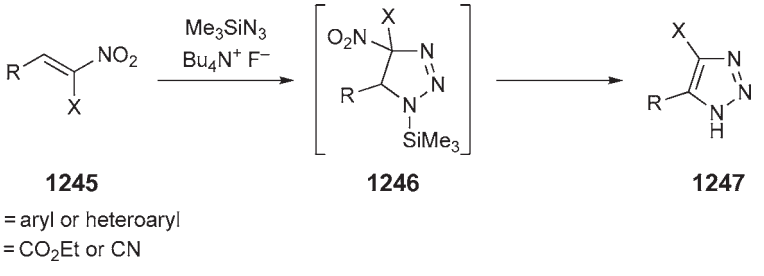
It appears that treatment of phenacyl bromides **1239** with methylhydrazine in refluxing acetic acid leads also to 1,4-disubstituted triazoles **1244**. Fivefold excess of methylhydrazine is used in these reactions. According to the proposed mechanism, structures **1240–1243**, methylhydrazine has a double role, as a condensing agent and an oxidant. In the final account, three molecules of methylhydrazine have to be used to produce one molecule of triazole **1244**, two molecules of methylamine and one molecule of ammonia. The basic triazole **1244** (X = Y = H) is separated in 59% yield. The reactions go well with electron-donating substituents (for X = OH, the yield is 81%), but electron-withdrawing substituents can lower the yield dramatically (11% for $X = NO_2$) (**Scheme 206**) <2003JCM96>.



Scheme 206

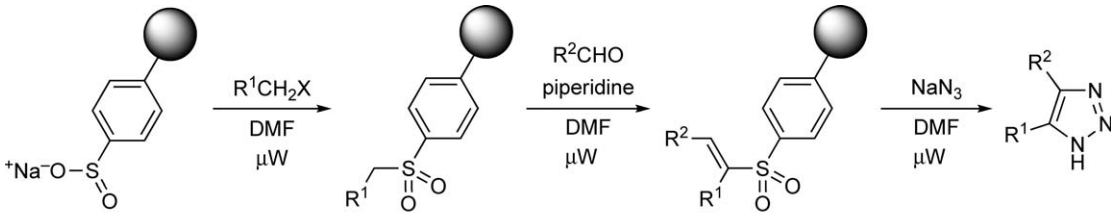
5.01.11.1.6 4,5-Disubstituted 1,2,3-triazoles

A simple procedure for the synthesis of 4,5-disubstituted 1,2,3-triazoles **1247** involves stirring a mixture of nitroethene **1245** with trimethylsilyl azide and tetrabutylammonium fluoride at 30 °C for 3 h. No solvent is needed. Triazoline **1246**, which forms in the first step of the reaction, eliminates nitrous acid, and the trimethylsilyl group is cleaved off by the fluoride anion to afford triazole **1247**. Various aryl and heteroaryl substituents R are used providing triazoles **1247** in 70–90% yield (**Scheme 207**) <2005JOC6526>.



Scheme 207

The synthesis of 4,5-disubstituted triazoles shown in **Scheme 208**, carried out on a polymer support with microwave assistance, is based on a similar principle. In the first step, sulfinate **1248** is converted to sulfone **1249**. Condensation with aldehydes provides vinyl sulfones **1250**. Cyclocondensation of sulfones **1250** with sodium azide generates corresponding triazoline intermediates that eliminate sulfinate **1248** to provide triazoles **1251** in moderate to good yield <2006OL3283>.

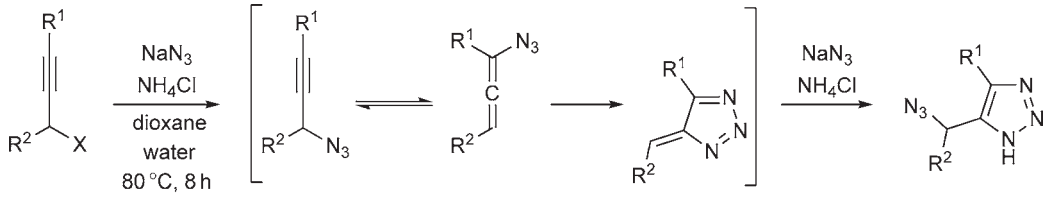


1248 **1249** **1250** **1251**

R^1 = CN, Ac, CO_2Me or $CONH_2$
R^2 = Ph, 4-$(NO_2)C_6H_4$, 2-pyridyl, 3-pyridyl, 2-furyl or 2-thienyl

Scheme 208

Azides **1253** obtained from propargyl halides or sulfonates **1252** undergo sigmatropic rearrangement to azidoallenes **1254**, which subsequently undergo cyclization to triazafulvenes **1255**. Under the reaction conditions, species **1255** react with another molecule of sodium azide to furnish triazoles **1256**. Products **1256** are isolated in 65–97% yield (**Scheme 209**) <2005S1514>.



1252 **1253** **1254** **1255** **1256**

R^1 = H, Et, Ph, CH_2OH, CH_2Cl, *n*-C_5H_{11}, or phthalimidyl-CH_2
R^2 = H, Me, or Pr
X = Cl, Br, MsO, or TsO

Scheme 209

5.01.11.1.7 Tri-substituted 1,2,3-triazoles

Compounds of this type are the most common products obtained from thermal 1,3-dipolar cycloaddition of disubstituted alkynes to azides. Many examples of such reactions can be found in Section 5.01.9.

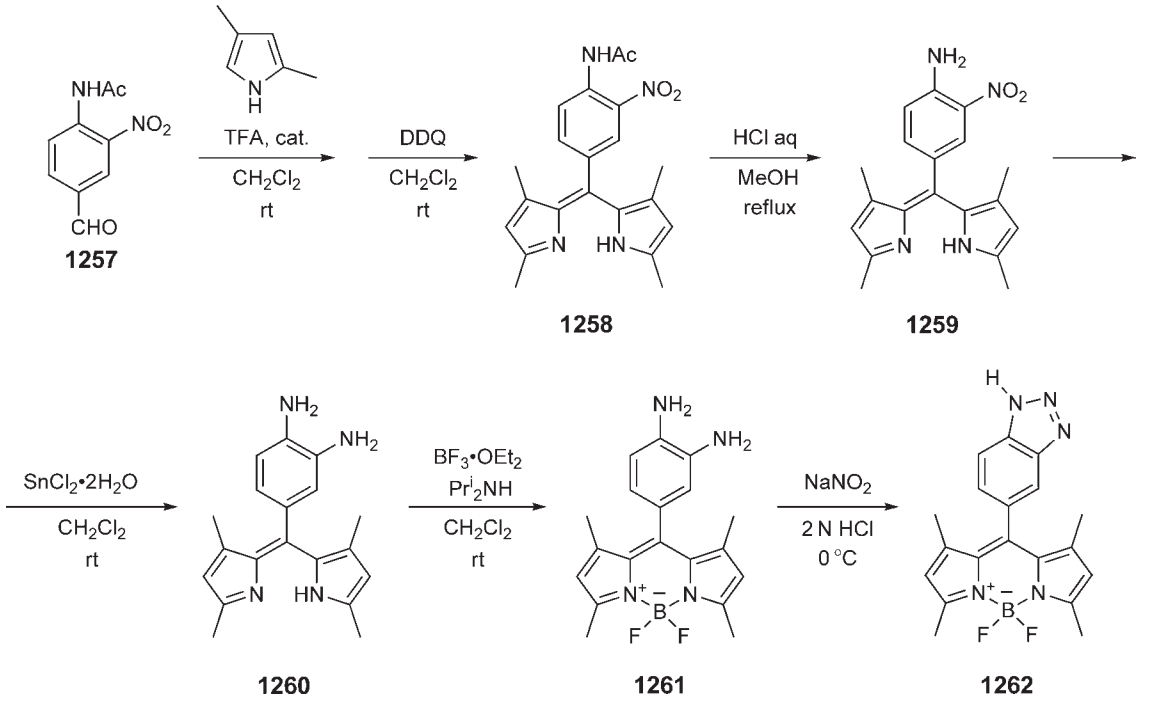
5.01.11.2 Derivatives of Benzotriazole

5.01.11.2.1 N-Substituted benzotriazoles

Preparation of benzotriazolyl derivatives substituted at N-1 (or N-2) with variety of functional groups is described in detail in Sections 5.01.5 and 5.01.8. The basic strategy starts from a reaction of benzotriazole with an electrophile. In most cases, the reaction produces a mixture of benzotriazol-1-yl and benzotriazol-2-yl derivatives that is not difficult to separate. Further modification of the substituent in subsequent steps leads to the desired product.

5.01.11.2.2 C-Substituted benzotriazoles

There are only few commercially available C-substituted benzotriazoles. In some situations, the substituents can be readily converted to more complex groups in the desired products. However, in many instances, it is more convenient to design first the right substituent and build the heterocyclic ring later. An example of such approach is shown in **Scheme 210**. Thus, in a reaction with 2,4-dimethylpyrrole, followed by treatment with DDQ, benzaldehyde **1257** is converted to product **1258** in 26% overall yield. Deprotection of the amino group gives *ortho*-nitroaniline **1259** that is subsequently reduced to *ortho*-phenylenediamine **1260** with 95% yield. Complexation of the dipyrrolyl moiety with boron trifluoride gives product **1261** (71% yield), which by treatment with sodium nitrite in 2 N HCl is converted to desired triazole derivative **1262** in 29% yield <2004JA3357>.

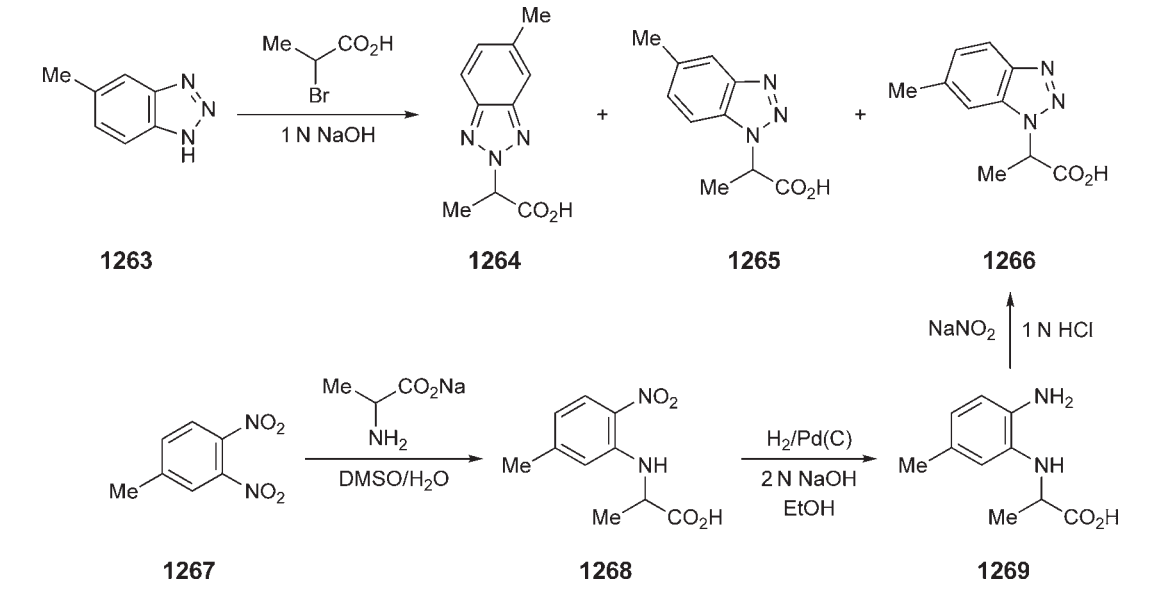


Scheme 210

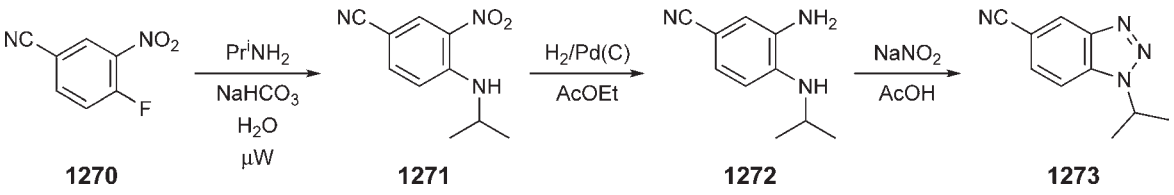
5.01.11.2.3 C,N-Disubstituted benzotriazoles

Direct N-substitution of benzotriazole in its reactions with electrophiles is a common practice. However, that strategy usually does not work well when a C-substituted benzotriazole is used as the starting material. Thus, in an example shown in **Scheme 211**, reaction of 5-methylbenzotriazole **1263** with 2-bromopropionic acid provides a mixture of three products **1264–1266** with the N(2)-substituted benzotriazole derivative **1264** being strongly predominant. Thus, the use of this approach for the synthesis of desired compound **1266**, which appears to be the least abundant in the mixture, is very impractical. Synthesis of the benzotriazole system starting from 3,4-dinitrotoluene **1267** is a much better alternative. In the first step, heating of a solution of compound **1267** and sodium 2-aminopropionate in DMSO allows for selective substitution of the nitro group in position *meta* to provide 2-nitroaniline **1268**. Reduction of the remaining nitro group to give diamine **1269** followed by cyclocondensation with nitrous acid furnishes the desired product **1266** <2003FA33>.

A similar approach, synthesis of a selectively substituted benzotriazole from the corresponding *ortho*-nitroaniline, is depicted in **Scheme 212**. The process starts from a microwave-assisted substitution of the fluorine atom in 4-fluoro-3-nitrobenzonitrile **1270** by isopropylamine to give *ortho*-nitroaniline **1271** in 99% yield. Reduction of the nitro group provides *ortho*-phenylenediamine **1272** that is directly converted to 5-cyano-1-isopropylbenzotriazole **1273**, which is isolated in 83% yield <2006JME1227>.



Scheme 211



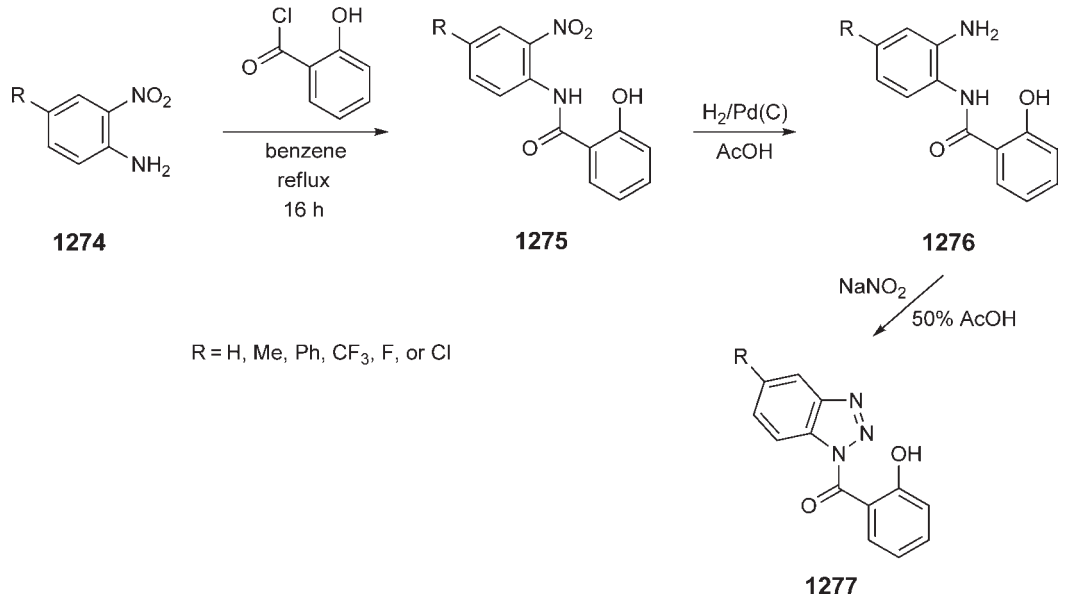
Scheme 212

A series of *para*-substituted *ortho*-nitroanilines **1274** is converted in this way to benzotriazolyl derivatives **1277**, which are of interest as potassium channel activators. In the first step, nitroanilines **1274** are treated with salicylyl chloride to provide salicylamides **1275** in 70–95% yield. The nitro group is catalytically reduced, and the obtained intermediates **1276** are subjected to a reaction with nitrous acid, generated *in situ* from $NaNO_2$, to afford 5-substituted 1-(2-hydroxybenzoyl)-1*H*-benzotriazoles **1277** in 52–96% yield (**Scheme 213**) <2001FA827>.

5.01.11.2.4 C,C-Disubstituted benzotriazoles

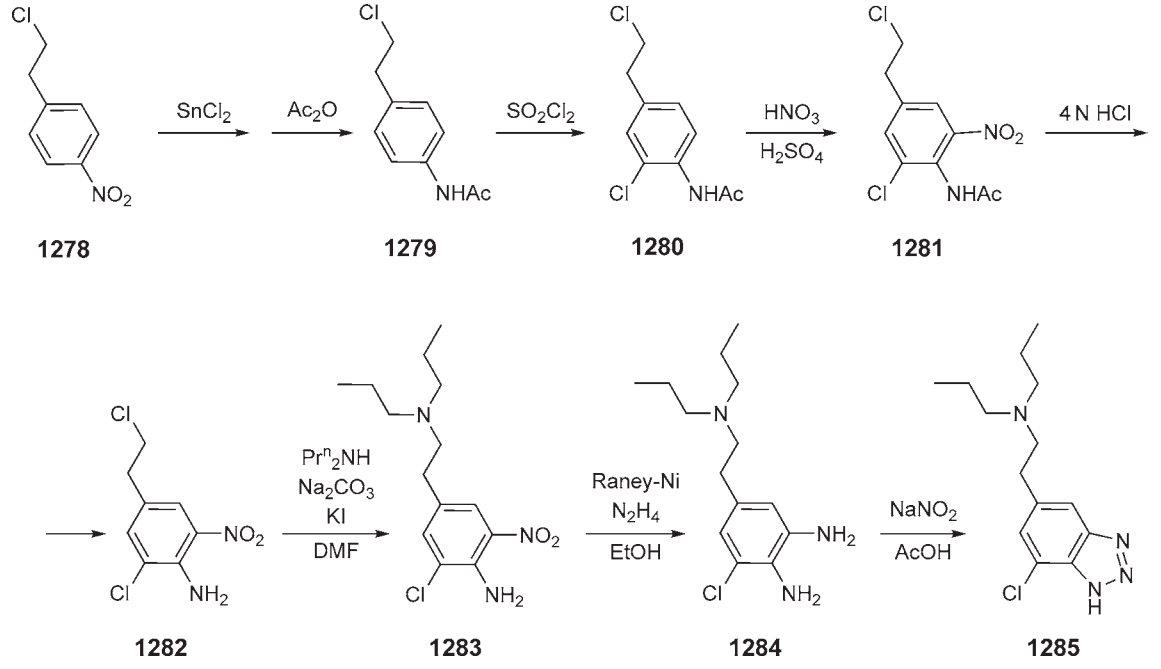
C-Derivatization of benzotriazole is rather difficult, and a benzotriazole system selectively substituted at the benzenoid ring is usually constructed from scratch. An illustration of this case is depicted in **Scheme 214**. The process starts from a relatively simple molecule of 4-(2-chloroethyl)nitrobenzene **1278** that is reduced to the corresponding aniline and acetylated to give acetanilide **1279**. Chlorination with $SOCl_2$ provides derivative **1280** in 75% yield that is subsequently nitrated to give product **1281** in 70% yield. Deprotection of the amino group gives nitroaniline **1282**, In the following steps, the 2-chloroethyl substituent is converted into 2-(dipropylamino)-ethyl group (compound **1283**), the nitro group is reduced, and the obtained *ortho*-phenylenediamine **1284** is subjected to cyclocondensation with nitrous acid to furnish benzotriazole **1285** with the last step yield of 61% <2004AP376>.

Instead of sodium nitrite, isoamyl nitrite is sometimes used as a nitrosating agent in synthesis of the benzotriazole ring. With this reagent, the reaction conditions are very mild allowing survival of acid sensitive groups. In an example of such a reaction, methyl 3,4-diamino-2-methoxybenzoate **1286** is treated with isoamyl nitrite at room temperature. The reaction is fast and provides methyl 4-methoxybenzotriazole-5-carboxylate **1287** in 62% yield, isolated by simple filtration off the precipitate (Equation 31) <2006JME4762>.



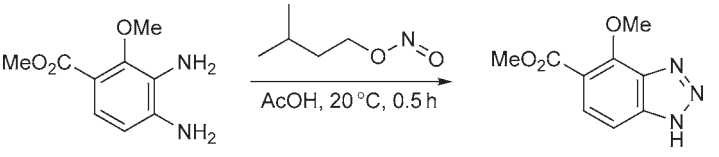
1274 **1275** **1276** **1277**

Scheme 213



1278 **1279** **1280** **1281** **1282** **1283** **1284** **1285**

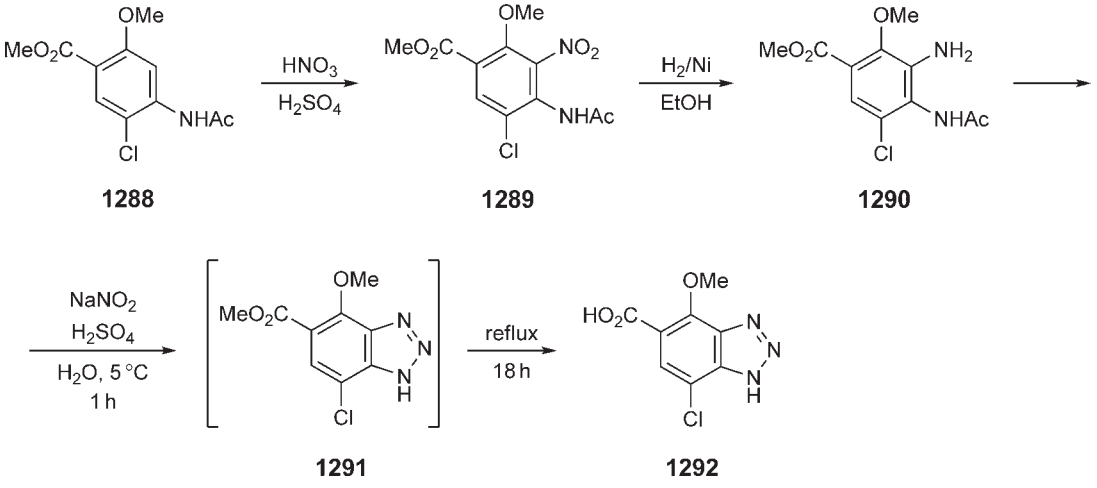
Scheme 214



1286 **1287** (31)

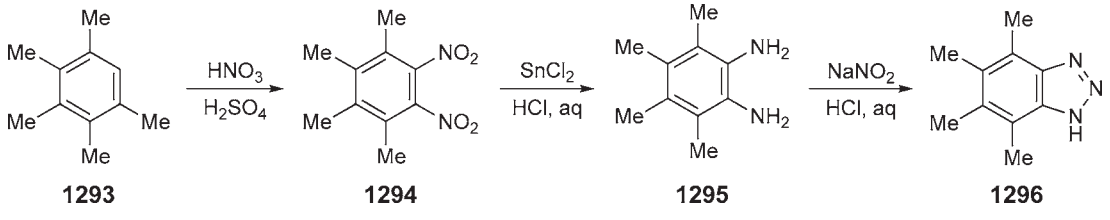
5.01.11.2.5 Three or more substituents

To get a complex set of substituents by direct derivatization of benzotriazole is not feasible. In such situations, it is better to have all the substituents in place first and later construct the heterocyclic ring. High reactivity of anilines and their well-developed chemistry makes them good stating materials. In an example shown in **Scheme 215**, acetanilide **1288** is nitrated to afford nitro derivative **1289** in 73% yield. Catalytic reduction of the nitro group provides methyl 4-acetylamino-3-amino-5-chloro-2-methoxybenzoate **1290** in 96% yield. Nitrosation of compound **1290** in diluted sulfuric acid leads to intermediate **1291**, which without separation is heated to be converted to 7-chloro-4-methoxy-1*H*-benzotriazole-5-carboxylic acid **1292**, isolated in 64% yield <2002CPB941>.



Scheme 215

Preparation of 4,5,6,7-tetrabromobenzotriazole and its tetrachloro analog by direct bromination or chlorination of benzotriazole is described in Section 5.01.7. However, other tetra-substituted benzotriazoles have to be constructed from a suitably substituted benzene ring. Thus, treatment of pentamethylbenzene **1293** with fuming nitric acid in concentrated sulfuric acid provides 3,4,5,6-tetramethyl-1,2-dinitrobenzene **1294** in 66% yield. Using routine procedures, derivative **1294** is reduced with $SnCl_2$ in aqueous HCl, and the obtained diamine **1295** is subsequently treated with $NaNO_2$ (in aq. HCl) to provide 4,5,6,7-tetramethyl-1*H*-benzotriazole **1296** (**Scheme 216**) <2004BMC2617>.



Scheme 216

5.01.12 Important Compounds and Applications

5.01.12.1 Benzotriazole Methodology in Organic Synthesis

The last two decades have witnessed rapid development of organic synthetic methods based on benzotriazole derivatives. Thus, introduction of benzotriazole moiety to organic molecules provides several practical advantages. Among other benefits, a benzotriazolyl substituent activates the reaction center, stabilizes intermediates, increases regio- and stereoselectivity, and simplifies separation and purification of the products. After the desired molecular assembly is constructed, the bond with benzotriazole is cleaved off to provide the final product. A vast variety of

molecular structures is conveniently prepared in this way. The largest section of this chapter (Section 5.01.8) is devoted specifically to this topic. For this reason, benzotriazole itself and a hundred of its basic derivatives that are commercially available now have become important materials in organic synthesis.

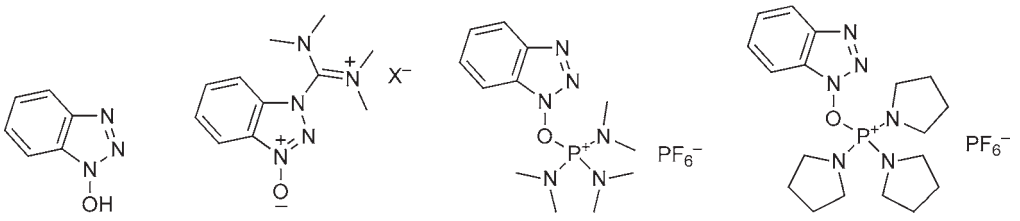
5.01.12.2 Peptide Coupling Reagents

I-Hydroxybenzotriazole (HOBt) **1297** <1996CHEC-II(4)1> has become an everyday reagent in many chemistry labs, and the number of reports of its application in organic synthesis is boosted to hundreds per year. Combined with a dehydrating agent and a tertiary amine, HOBt is an excellent auxiliary in preparation of amides (**Table 13**). The mechanism of its interaction with carboxylic acids is discussed in Section 5.01.8. Some of the dehydrating agents used in the process are also derivatives of HOBt **1298–1301**. In some instances, these derivatives, HBTU **1298** <2002JOC1184, 2004NAR623>, TBTU **1299** <2005HCA447, 2005HCA1040, 2005TL6239, 2006OL2851, 2006TL1737> and BOP **1300** <2005JA17894, 2005JOC3660, 2006JA3011, 2006OL239, 2006OL511> are used alone without addition of HOBt. Combinations of HOBt with dehydrating agents, especially DIC <2005JOC9622, 2005TL7443, 2006JCO150, 2006JME1833, 2006JME2388>, HBTU <2005AGE2534, 2005JCO697, 2005JOC7654, 2005TL4053, 2006TL2671> and BOP <2002BML2855, 2005AGE2887, 2005JCO703> are common reagents in solid-phase synthesis of peptides. Use of HOBt together with DCC <2005CEJ6666, 2005JOC5339, 2005JOC6313, 2005TL4377, 2005TL6791>, EDC <2005AGE5710, 2006JME2333, 2006OL531, 2006OL797, 2006SC1317> or HBTU <2001NN1347, 2006JME2593> in preparation of carboxylic esters is also relatively common. HOBt can likewise promote formation of C–C bonds in coupling of carboxylic acids with cyanoacetates <2002BCJ2691> and acetoacetates <2002SL1736>. In the presence of HBTU, aminoacids react with diazomethane to give their higher homologs <2003PES230>.

Table 13 Some of the recent applications of 1-hydroxybenzotriazole in the synthesis of amides

Example	*Character of* R^1COOH	*Character of* R^2NH_2	*Dehydr. agent*	R^1CONHR^2 *application*	*Yield* (%)	*Reference*
1	Aminoacid	Aminoacid	EDC	Peptide	97	2005CC4908
2	Aminoacid	Peptide	EDC	Cyclic peptide	90	2005JOC9626
3	Dipeptide	Amino thioester	DCC	Peptide thioacid	93	2006OL823
4	Oxazolidine-COOH	L-Ser-OMe	DDC	Telomerase inhibitor	79	2006S1289
5	Fmoc-Leu-OH	PS-R-NH_2	TBTU	Oxazole tripeptide	87	2006OL2417
6	Cyclopentane-carboxylic acid	Methyl glycinate	TBTU	Peptides	98	2005HCA1711
7	Aminosugar acid	Aminosugar	HBTU	Oligosaccharide mimic	89	2005AGE2096
8	Arenoxyacetic acid	Methyl glycinate	DCC	Heteroditopic receptors	71	2006CJC58
9	Aminoacid	Aminoacid	DCC	Opioid receptor agonist	96	2006JME1773
10	Aminoacid	Aminosugar	EDC	Antibiotics	91	2006OL887
11	Succinic acid	Ar-1,3-di-[$O(CH_2)_3$]-NH_2	EDC	Dentronized polymer	76	2006JA5091
12	RCH(Bu^t)-COOH	$ArCH_2NHNH_2$	EDC	HIV protease inhibitor	76	2006JME1828
13	Fmoc-Gly-OH	$R_2C(CO_2Me)$-NH_2	DIC	6-Spiro-1,4-diazepane	98	2005EJO907
14	ArCOCOOH	$R^1R^2NH_2$	EDC	FKBP12 ligand	68	2006JME1202
15	ArCOOH	Morpholine	EDC	Growth factor-β inhibitor	73	2006JME2210
16	2-Indole-carboxylic acid	2,3-Dihydro-indole	EDC	Antitumor antibiotic	96	2006JA7136

DCC = 1,3-dicyclohexylcarbodiimide, DIC = 1,3-diisopropyl-carbodiimide, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.



1297

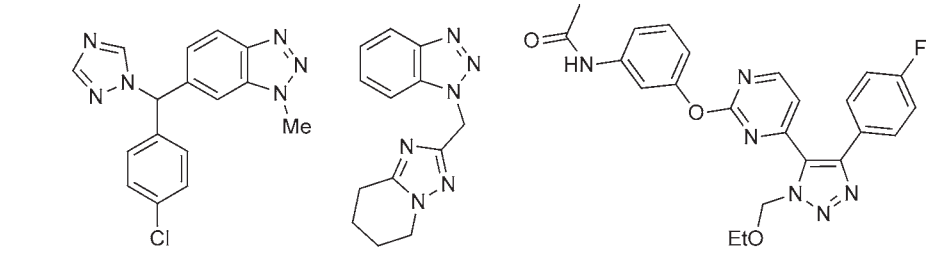
1298: $X^- = PF_6^-$ (HBTU)
1299: $X^- = BF_4^-$ (TBTU)

1300: BOP

1301: PyBOP

5.01.12.3 Biologically Active Derivatives

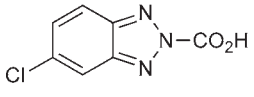
Due to their easy access and high enzymatic stability, benzotriazole and 1,2,3-triazole systems are frequently used as building blocks in drug design. Among antitumor agents, vorozole (structure **1302**) is a high-affinity competitive aromatase inhibitor, designed for inhibiting estrogen synthesis in patients with breast cancer <2001CNR8452, 2002JON1026, 2003STE1139>. Benzotriazole derivative **1303** exhibits remarkable activity against leukemia, ovarian, renal, and lung cancers <2003BMC1701>. The structures may be complex, like compound **1304** <2003BML1665>, or simple, like compound **1305** <2003FA33>, both of them exhibiting anti-inflammatory activities, although based on different principles. Nucleoside analog **1306** inhibits strongly helicase activity of hepatitis C virus <2003EJB1645>, whereas compound **1307** and several of its analogs show strong activity against respiratory syncytial virus (RSV) <2003BML2141>.



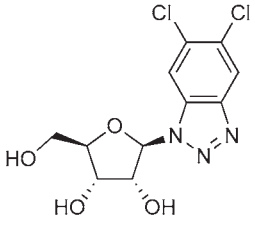
1302

1303

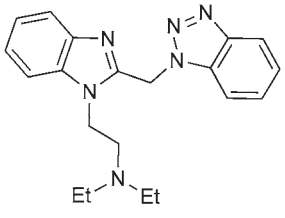
1304



1305



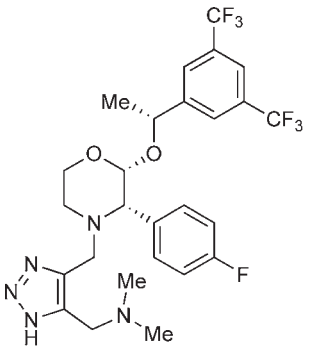
1306



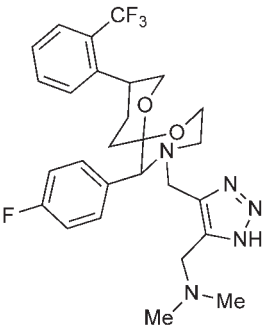
1307

Very simple derivatives of benzotriazole with biological activity include 5,6-dimethylbenzotriazole, a very effective agent against cysts of *Acanthamoeba castellanii* <2004BMC2617>, tetrabromobenzotriazole, which provides selective inhibition of protein kinase CK2 <2001PSC2200> and induces apoptosis of Jurkat cells <2002BJ41>, 1-salicylyl-4-methylbenzotriazole, potassium channel activator <2001FA827> and 1-isopropyl-1*H*-benzotriazole-4-carboxylic acid, a selective agonist of human orphan G-protein-coupled receptor GPR109b <2006JME1227>.

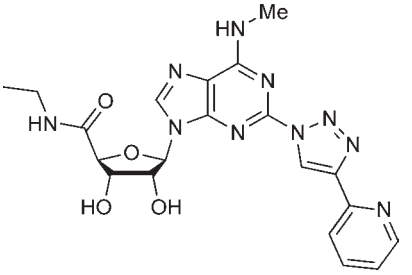
Several 1,2,3-triazole derivatives have been designed to target G-protein-coupled receptors. Among them are neurokine NK_1 antagonists **1308** <2001JME4296, 2002JEP536> and **1309** <2002BML2515>, selective A_3 adenosine receptor agonist **1310** <2006JME7373> and highly selective α_1 adrenoreceptor antagonists <2003JME265>. Other 1,2,3-triazole derivatives are of interest as inhibitors of some key enzymes: acetylcholinesterase <2004JA12809>, glycogen synthase kinase-3 <2003JME3333>, glycosidase <2005T9118>, galectin-1 <2006CAR1353, 2006CC2379> and α-2,3-sialyltransferase <2006CC629>.



1308



1309



1310

There are also 1,2,3-triazoles with antiviral <2006BML2693, 2006JME1140>, antibacterial <2002BML2771, 2003BMC35>, antithrombotic <2004AP156>, or antiplatelet <2003BMC2051> activities. Some triazoles work as potassium channel activators <2004FA397>, others as calcium signal transduction inhibitors <2002CLC86>. 1,5-Diaryl-Δ^2-1,2,3-triazolines are recognized anticonvulsant agents <2003CME2081, 2004JLR31>. Among biologically active benzotriazoles are also inactivators of the severe acute respiratory syndrome 3CL protease <2006CBO1261>, trichostatin suppressors <2003CBO397>, antagonists of the gonadotropin releasing hormone <2002BML827>, and nonpeptide inhibitors of protein tyrosine phosphatase 1B <2004BML1043>.

5.01.12.4 Other Applications

Due to strong complexing affinities to copper and some other ions, benzotriazole and its derivatives have found wide application in anticorrosion formulations. Hundreds of patents covering this subject are registered each year. One of the major applications of such formulations is in electronics that include thiol passivation of copper interconnects during semiconductor manufacturing, grinding composition for polishing of semiconductor devices, corrosion-preventing agents for etching of insulator films in manufacture of semiconductor devices, cleaning solutions for electrohydrodynamic cleaning of semiconductors, components of polymer coatings for silver-plated circuits, and in dispersants for preparation of nickel-coated copper powder for electricity-conducting inks. Benzotriazole is also commonly used as an unticlogging agent in jet inks for forming high-quality images.

Anticorrosion abilities of benzotriazole and its derivatives are also widely utilized in fluids for all kind of machinery. They are important antifriction–antiwear additives for engine oils, components of antirusting grease for aircraft, biodegradable lubricants for turbines, brake liquids based on polyoxyalkylene synthetic oils, metal corrosion inhibitors in aqueous coolants containing acetic acid and propylene glycol, grease for gas compressors for fuel cell systems, emulsifiable oil for preparation of noncombustible oil–water hydraulic emulsions for coal mining, environment-protecting lubricating oil for refrigerators, antifreeze composition for diesel engines, and lubricating oil compositions for hot rolling aluminium plates. Benzotriazole derivatives can be also found in machine dishwashing detergents containing nonionic surfactants, corrosion inhibitors for thermoplastic polyurethanes in contact with metals, and in anticorrosion polymer coatings for guitar strings.

Due to strong UV absorption, benzotriazole derivatives have found application in cosmetic formulas for skin photoprotection, in cosmetic sunscreen compositions, in multifunctional eyeglass lenses with UV absorbers, in UV protecting films for radiation detectors in personal instant alert dosimeters, in polyester compositions reducing UV light penetration for production of bottles, in UV absorbers for decorative polyolefin sheets with improved weather resistance, in protective coatings containing UV absorbers for microporous sheets, in UV absorbers for plant protecting covers, in photographic emulsion of light-sensitive materials, and as UV absorber for a multilayer golf ball with a translucent cover.

5.01.13 Further Developments

Novel applications of benzotriazole methodology in organic synthesis include regiospecific preparation of 1,4,5-trisubstituted pyrazoles <2007ARK(i)9>, efficient synthesis of 1,5-disubstituted tetrazoles <2007SL1204>,

amidoalkylations of nitroalkanes, nitriles, alkynes, and esters <2007ARK(xi)96>, thioamidoalkylation of 1,3-dicarbonyl compounds, enol silyl ethers, and enamines <2007S1655>, C-aminoimidoylation and C-thiocarbamoylation of esters, sulfones, and ketones <2007JOC6742>, synthesis of cyano derivatives of *N*-alky and *N*-aryl piperazines <2007EJM471>, and preparation of polyfunctional acyl azides <2007JOC5802>. *N*-Acyl derivatives of benzotriazole are used for efficient peptide coupling of sterically hindered aminoacids <2007JOC5794> and 5-amino-1-methyl-1*H*-[1,2,4]-triazole-3-carboxylic acid <2007SC1917, expedient synthesis of *N*-*Z*-pyroglutamyl-aminoacid derivatives <2007BML6000>, synthesis of (+)-aphanorphine <2007H(72)497>, and as Mosher-Bt reagents <2007JOC4268>.

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Biographical Sketch

Stanislaw Rachwal was born in Jodlowka, Poland, in 1949 and raised in Krakow, Poland. In 1978, he received a PhD in organic chemistry from Jagiellonian University in Krakow and was nominated to a position of an Adjunct Professor at that university in 1980. His main research at that time was focused on chemistry of ferrocenophanes. During a sabbatical leave in 1984, he joined Professor Alan R. Katritzky at the University of Florida to lay a foundation for application of benzotriazole in organic synthesis. He returned to the University of Florida in 1988, where, as a group leader, he pushed forward the research on derivatives of benzotriazole. His collaboration with Professor Katritzky till 1993 resulted in 36 scientific papers on benzotriazole. Since1993, he has been working in pharmaceutical industry specializing in CNS drugs with the primary focus on heterocyclic compounds.

Alan Katritzky was born in London, UK and educated at St. Catherine's College, Oxford, of which he became, in 2006, an Honorary Fellow. He was a Founder Fellow of Churchill College, Cambridge, and then founding of Professor/Dean of the School of Chemical Sciences at the University of East Anglia before crossing the Atlantic in 1980 to become Kenan Professor and Director of The Center for Heterocyclic Compounds at the University of Florida. He has researched, published, lectured, and consulted widely in heterocyclic chemistry, synthetic methods, and QSPR. He created the not-for-profit foundation ARKAT and since 2000 has been organizing the annual 'Florida Heterocyclic and Synthetic Conferences' (Flohet) and publishes *Archive for Organic Chemistry* (Arkivoc) completely free on the Internet at arkat-usa.org. His honors from 20 countries include 14 honorary doctorates.

5.02
1,2,4-Triazoles

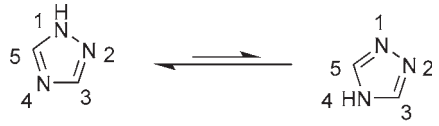
A. D. M. Curtis and N. Jennings
Keele University, Keele, UK

5.02.1 Introduction

This chapter surveys the chemistry of 1,2,4-triazoles as detailed in the literature during the period 1995–2007. This class of compounds has been reviewed previously in CHEC(1984) <1984CHEC(5)733> and CHEC-II(1996) <1996CHEC-II(4)127>, and other review articles as cited therein. The synthesis of monocyclic 1,2,4-triazoles has been the subject of a recent review <2004SOS(13)603>. 1,2,4-Triazoles with specific substituents or substitution patterns have also been the subject of review articles: for example, the chemistry of 5-amino-3-nitro-1,2,4-triazole (ANTA) and derivatives <2002RJO1231, 2002ZOR1289>, and the synthesis of fluorinated triazoles <1999JCM300, 1999JRM1301>. The chemistry of metal complexes of ligands containing 1,2,4-triazole residues has also been reviewed <2000CCR131>.

In view of the nature of this edition as a whole, the content of this chapter is restricted to describing the chemistry of monocyclic 1,2,4-triazole systems. Readers are directed to the relevant chapters elsewhere in this edition for details of the chemistry of fused heterocyclic systems that contain a 1,2,4-triazole moiety; examples of fused systems are only cited in this chapter where relevant.

As is customary with works covering this particular class of heterocycle, this review must begin with an explanation of the structure and naming conventions for 1,2,4-triazoles and derivatives. The parent compound, 1,2,4-triazole **1**, possesses a five-membered aromatic ring that contains three nitrogen atoms arranged as shown in Equation (1). However, two tautomeric forms, 1*H*-1,2,4-triazole **1a** and 4*H*-1,2,4-triazole **1b**, can be envisaged and this has led to some ambiguity in nomenclature, as detailed eloquently in CHEC(1984) <1984CHEC(5)733>. In fact, structure **1a** predominates and much of the chemistry of 1,2,4-triazoles reflects this.



1a **1b** (1)

1,2,4-Triazol-5-ol **2a** and the corresponding thiol **3a** exist predominantly as the 5-oxo- or 5-thioxo-tautomers **2b** and **3b**, respectively (Equation 2).

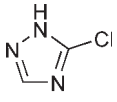
2a: X = O
3a: X = S
2b: X = O
3b: X = S (2)

Any further details concerning structure and nomenclature may be found within the body of this review, otherwise the reader is again directed to previous works <1984CHEC(5)733, 1996CHEC-II(4)127>.

5.02.2 Theoretical Methods

With the advent of ever more sophisticated computational methods for the modeling of molecular structures and properties, it is unsurprising that 1,2,4-triazoles have been examined, mostly as an aid to confirm the findings from experimental structural methods. Many of the studies are on simple, model systems used to give an insight into the properties of much larger molecules, though the methodologies used have been extended to larger systems containing triazole moieties.

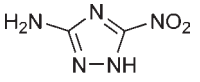
The tautomeric forms of 5-chloro-1,2,4-triazole **4** were investigated using Hartree–Fock and Meller–Plesset methodology in the 6-31G(d) basis, and the ^{35}Cl nuclear quadrupole resonance (NQR) frequencies were calculated subsequently. These calculations suggest that tautomer **4** is predominant <2001CHE95, 2001KGS99>.



4

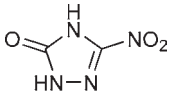
Of course, experimental methods are used to determine the molecular properties of 1,2,4-triazoles but computational studies, particularly density functional theory (DFT) calculations, are frequently carried out to predict and confirm the experimental findings. Calculation of the fundamental vibrational frequencies using the 6-311G(d,p) basis set has been used to support a comprehensive study of the vibrational spectra of 1,2,4-triazole <2000JST(530)183>.

Highly energetic compounds with potential use in explosive devices must be characterized completely and safely, particularly as the explosive character may be linked directly to vibrational modes in the molecular structure, hence the application of computational methods to complement experimental observations. ANTA **5** has been the subject of various studies and, as an adjunct to one of these and to confirm the results of an inelastic neutron scattering experiment, an isolated molecule calculation was carried out using the 6-311G** basis set <2005CPL(403)329>.



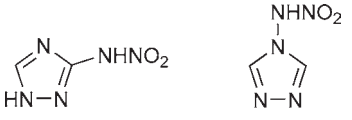
5

Similarly, the structure of 5-nitro-2,4-dihydro-3*H*-1,2,4-triazol-3-one (NTO) **6** has been scrutinized using molecular orbital calculations using the 6-31+G* and 6-311+G** basis sets. These calculations examined the various tautomers of NTO and give an insight into the molecular mechanisms involved in its explosive decomposition <1996JA8048>.



6

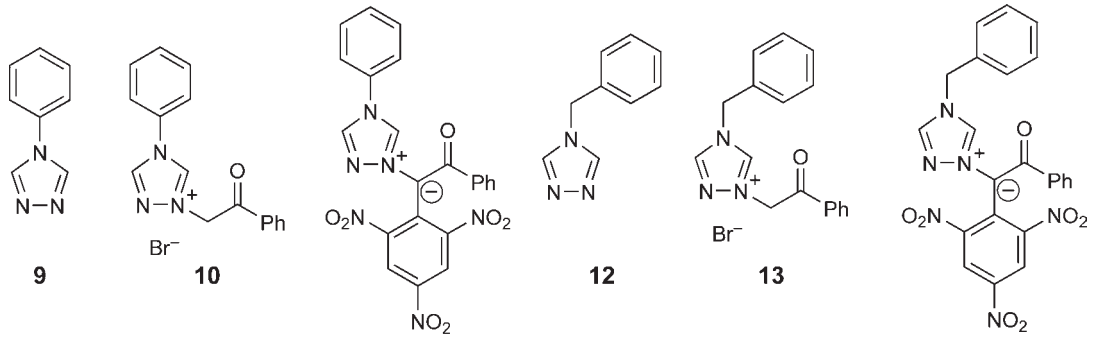
The thermal decomposition of nitramino-1,2,4-triazoles **7** and **8** has been modeled and detailed decomposition pathways proposed for a number of tautomeric forms of these compounds <2006CHE1267, 2006KGS1467>. The chemistry of 4-nitramino-1,2,4-triazole **8** has been studied in depth but no decomposition studies on its derivatives have been documented <2002RJO1343, 2002ZOR1397>.



7 **8**

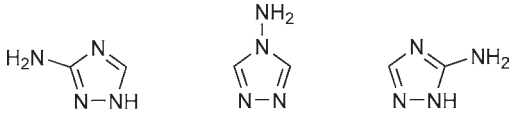
The aromaticity of 1,2,4-triazoles has been investigated and quantified using the harmonic oscillator model of aromaticity (HOMA) index, where a value of 1 is assigned to a molecule that is fully aromatic, 0 for a nonaromatic molecule, and a negative value for a molecule that is antiaromatic; the data obtained were compared to other small-molecule heteroaromatics. It was determined that different tautomers of substituted and unsubstitued 1,2,4-triazoles have individual HOMA indices <2000JST(524)151>.

1-Phenyl-1,3,4-triazole **9**, the corresponding triazolium salt **10**, and methylide **11** have been studied by PM3 and DFT methods using the 6-31G* basis set to determine their potential use as component molecular systems in conducting materials; this study accompanied corresponding experimental conductivity measurements <2004JST(699)31>. The analogous benzyltriazole derivatives **12–14** were also investigated in a similar study <2005MI106>.



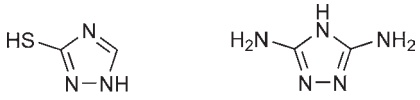
9 10 11 12 13 14

A comprehensive study into the structures and molecular properties of 3-amino-1*H*-1,2,4-triazole **15**, 4-amino-4*H*-1,2,4-triazole **16**, and 5-amino-1*H*-1,2,4-triazole **17** has been undertaken using *ab initio* methods, both to predict and confirm data obtained from microwave spectroscopy of these compounds <2004JST(705)177>.



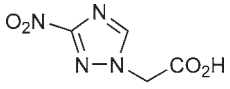
15 16 17

Computational methods were employed to predict molecular vibrations in 3-mercato-1,2,4-triazole **18** and 3,5-diamino-1,2,4-triazole **19** in order to fully assign the Fourier transform infrared (FTIR) and FT–Raman spectra of these molecules <2004SAA709, 2005SAA261>.



18 19

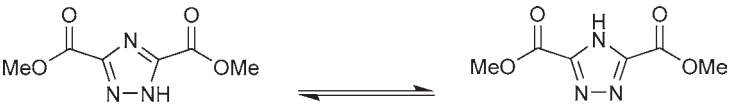
DFT calculations using the 6-311G** and LANL2DZ basis sets were carried out on 3-nitro-1,2,4-triazolylethanoic acid **20**, again to aid in the assignment of data from FTIR, FT–Raman, and surface enhanced Raman scattering (SERS) spectroscopy <2005CPL(402)361>.



20

As part of a study to determine the tautomerization of 1,2,4-triazole residues in macrocyclic assemblies, the tautomerism of simple 1,2,4-triazoles was determined by calculation using the 6-31G* basis set. The findings confirmed that the 1*H*-tautomer of the parent 1,2,4-triazole **1a** is preferred over the corresponding 4*H*-tautomer **1b** with a difference in the calculated energies of 6.89 kcal mol^{-1}. Similar results were obtained when model systems were examined: the calculated energy differences between the preferred tautomers **21a** and **21b**, and the corresponding tautomers **22a** and **22b** are 4.32 and 6.27 kcal mol^{-1}, respectively. However, the findings also confirmed that incorporation of the triazole moiety into a macrocyclic crown ether favors the 4*H*-tautomer (Equations 3 and 4) <2001JHC1387>.

21a 21b (3)



22a 22b (4)

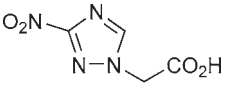
5.02.3 Experimental Structural Methods

The characterization of molecular systems containing 1,2,4-triazole moieties has continued to employ familiar spectroscopic techniques, supplemented by more recent developments in the field. Other techniques, including electrochemistry, have also been described for triazoles that have been designed for or deployed in specific, applied environments; such functional molecules are described later in this chapter.

5.02.3.1 Infrared and Raman Spectroscopies

A comprehensive study of the vibrational spectra of 1,2,4-triazole in comparison to those of 1,2,3-triazole and tetrazole has been carried out <2000JST(530)183>. The tautomerism displayed by simple 1,2,4-triazole thiones has also been studied using vibrational spectroscopic techniques and the preferred tautomers present in the solid state determined <1997SAA699>.

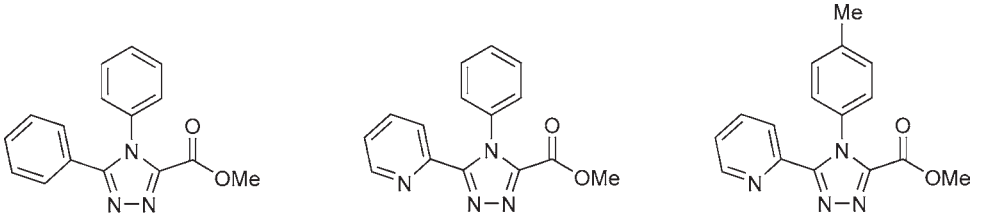
The FTIR and FT–Raman spectra of 3-nitro-1,2,4-triazolylethanoic acid **23** were acquired and analyzed using data predicted by theoretical calculations. Additionally, SERS spectroscopy was employed to examine the behavior of acid **23** in the presence of silver: enhancements in the intensities of signals assigned to stretching vibrations of the carboxylate and nitro substituents indicated that these groups are involved in the association of acid **23** to the metal surface. Further, it can be deduced that the triazole ring is aligned parallel to the metal surface to enable interaction of the π-electrons with the metal <2005CPL(402)361>.



23

5.02.3.2 Nuclear Magnetic Resonance Spectroscopy

A comprehensive structural study of 1,2,4-triazoles **24–26** was carried out and the ^{1}H, ^{13}C, and ^{15}N chemical shifts of all atoms determined in solution using 1D and 2D heteronuclear correlation experiments, and in the solid phase using cross-polarization magic angle spinning experiments. Any deductions made about the structures of triazoles **24–26** from the nuclear magnetic resonance (NMR) data were confirmed using X-ray diffraction analysis of triazole **24** <2001JST(562)167>.

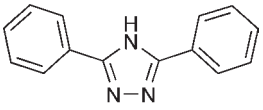


24 **25** **26**

5.02.3.3 X-Ray Photoelectron Spectroscopy

X-Ray photoelectron spectroscopy (XPS) was used to examine the surface of steel that had been exposed to 1.0 M hydrochloric acid in the presence of 3,5-diphenyl-4*H*-1,2,4-triazole **27** as corrosion inhibitor. These measurements demonstrated that the inhibitor **27** was chemisorbed on to the metal surface; the protection afforded by **27** was still

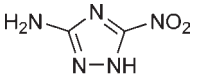
observed after the metal sample had been removed from the acidic medium, washed and replaced in acidic medium that did not contain any additional inhibitor <2000MI194>.



27

5.02.3.4 Inelastic Neutron Scattering Spectroscopy

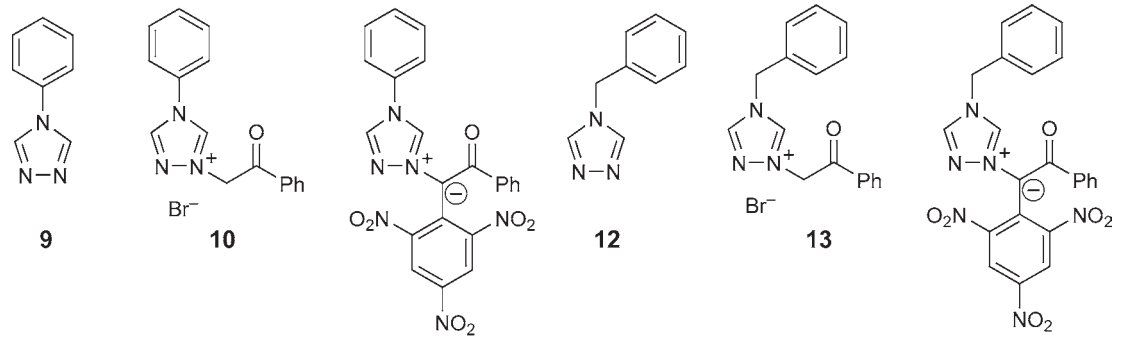
Supplementary to other vibrational spectroscopies, inelastic neutron scattering (INS) spectroscopy is a very useful technique for studying organic molecules as it is extremely sensitive to the vibrations of hydrogen atoms. INS spectroscopy has been used to analyze the molecular dynamics of the energetic compound ANTA **5** <2005CPL(403)329>.



5

5.02.3.5 Electrochemical Measurements

The conductivities of 1-phenyl-1,3,4-triazole **9**, the corresponding triazolium salt **10**, and methylide **11** have been studied across a range of temperatures and, in the case of methylide **11**, a range of pH. The experiments, supported by theoretical calculations, showed that a 1:1 mixture of triazolium salt **10** and methylide **11** is the most promising for further study <2004JST(699)31>. Similar experiments involving the analogous benzyltriazole derivatives **12–14** again showed that a mixture of triazolium salt and ylide, in this case **13** and **14**, had the better conductivity <2005MI106>.



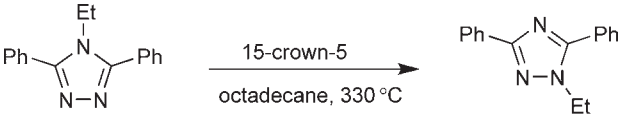
9 **10** **11** **12** **13** **14**

Electrochemical polarization studies and electrical impedance spectroscopy (EIS) are carried out routinely in the investigation of small-molecule inhibitors of corrosion of metals in aqueous environments. A wide variety of substituted 1,2,4-triazoles have been investigated as corrosion inhibitors for the protection of steel, copper, and other metals, and a considerable body of data has been published. The reader is directed to the primary literature for further details as to the scope and results of these experiments <2000MI187, 2002MI63, 1999MI237, 2000MI194, 2002MI1, 2004MI214, 1998MI391, 1999MI789, 2000MI773, 2002MI573, 2002MI997, 2003MI309, 2003MI371, 2004MI2455, 2004MI2701, 2005MI151, 2005MI663, 2005MI3368, 2006MI608, 2002MI4339, 2004MI811, 2004MI2771, 2005MI47, 2006MI3957, 2001MI283, 2002MCH489, 2002MCH655, 2002MI18, 2005MI269, 2003MAL4547, 2000MI207, 2003MI63, 2004MI149, 2004MI322>.

5.02.4 Thermodynamic Aspects

The parent 1,2,4-triazole has been investigated as a potential reference compound for use in combustion experiments of compounds that contain nitrogen atoms using a micro-bomb calorimetry experiment. Urea was used previously as a standard but the chemical and physical stability of 1,2,4-triazole lends itself to such a role <2000MI949>.

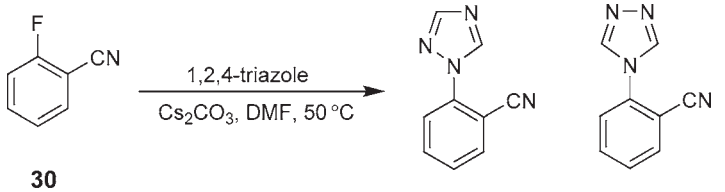
The kinetics of the thermally induced rearrangement of 4-ethyl-3,5-diphenyl-4*H*-1,2,4-triazole **28** to the corresponding 1-ethyl-substituted compound **29** in the presence of 15-crown-5 in octadecane at 330 °C has been studied (Equation 5). A mechanism for the rearrangement was proposed that involved an intermediate triazolium triazolate species <2001JHC955>.



28 **29** (5)

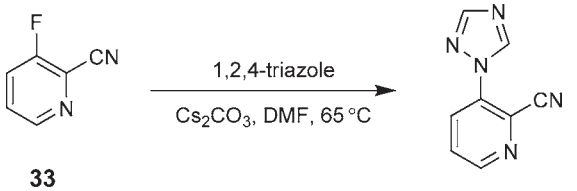
5.02.5 Reactivity of Fully Conjugated Rings

Nucleophilic substitution of the fluorine atom in 2-fluorobenzonitrile **30** by 1,2,4-triazole gave a 10:1 mixture of 2-[1,2,4]-triazol-1-yl benzonitrile **31** and the corresponding 4-isomer **32** in crude yield of 66% (Equation 6) <2004JME2995>.



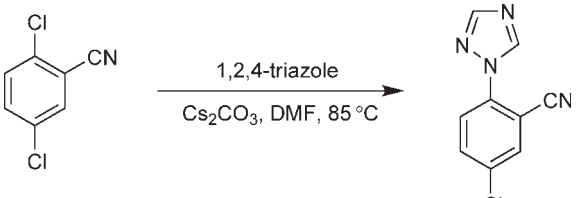
30 **31** **32** (6)

A similar reaction of 1,2,4-triazole with 2-cyano-3-fluoropyridine **33** gave 3-[1,2,4]-triazol-1-yl-pyridine-2-carbonitrile **34** in a yield of 92% after purification (Equation 7) <2004JME2995>.



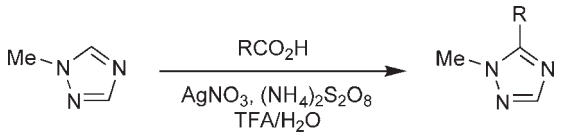
33 **34** (7)

Reaction of 2,5-dichlorobenzonitrile **35** with 1,2,4-triazole gave 5-chloro-2-[1,2,4]triazol-1-ylbenzonitrile **36** as the sole product in quantitative yield (Equation 8) <2004JME2995>.



35 **36** (8)

Alkylation of the 1,2,4-triazole ring by alkyl radical species has been achieved: reaction of 1-methyl-1,2,4-triazole **37** with alkyl carboxylic acids in the presence of a silver catalyst gave the corresponding 2-alkylated triazoles **38a–e** in moderate yields (Equation 9 and **Table 1**) <2001TL7353>.

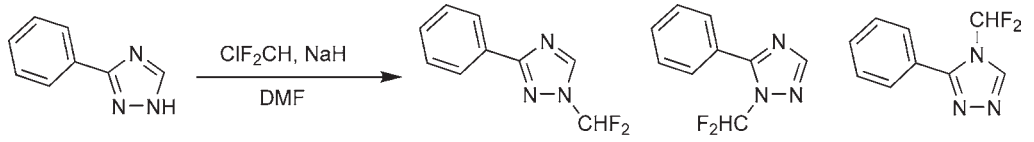


37 **38a–e** (9)

Table 1 Alkylation of 1-methyl-1,2,4-triazole **37** using radical species (Equation 9)

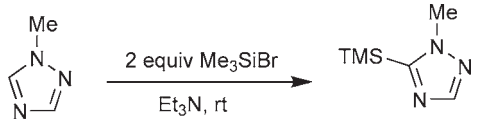
Entry	*R*	*Triazole* **38**	*Isolated yield* (%)
1	Cyclopropyl	**a**	60
2	Cyclobutyl	**b**	54
3	Cyclopentyl	**c**	35
4	Cyclohexyl	**d**	54
5	Isopropyl	**e**	53

Regioselective N-difluoromethylation of 3-phenyl1,2,4-triazole **39** has been achieved using chlorodifluoromethane in the presence of a base. The reaction yielded a mixture of the three possible products **40–42** and proceeds by the insertion of a difluorocarbene into an N–H bond (Equation 10) <1998JFC(92)141>.



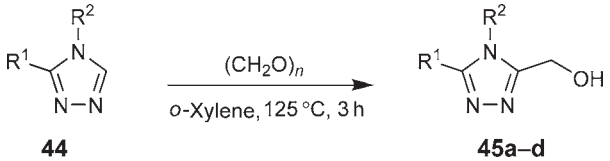
39 **40** 66% **41** 14% **42** 20% (10)

1-Methyl-1,2,4-triazole **37** underwent electrophilic substitution to give 1-methyl-5-trimethylsilyl-1*H*-1,2,4-triazole **43** in 56% yield (Equation 11) <2006S1279>.



37 **43** (11)

3-Hydroxylmethyl-1,2,4-triazoles **45a–d** may also be prepared by electrophilic substitution by the reaction of the parent 1,2,4-triazoles **44** with paraformaldehyde in refluxing xylene (Equation 12 and **Table 2**) <2006S156>.



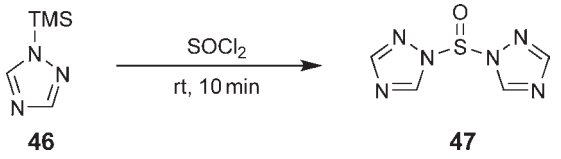
44 **45a–d** (12)

Table 2 Hydroxymethylation of 1,2,4-triazole derivatives using paraformaldehyde (Equation 12)

Entry	*Triazole* **45**	R^1	R^2	*Yield* (%)
1	**a**	Me	Me	50
2	**b**	Me	Ph	90
3	**c**	Ph	Me	96
4	**d**	Ph	Ph	81

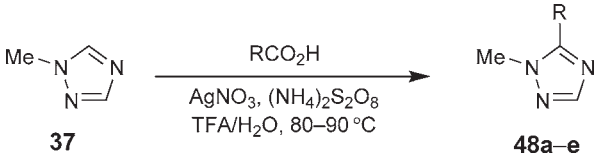
The yield of 3-hydroxymethyl-4,5-dimethyl-4*H*-1,2,4-triazole **45a** could be increased to 73% by reacting the precursor 1,2,4-triazole in 37% aqueous formalin at 90 °C for 3 h <2006S156>.

The facile synthesis of bis(1,2,4-triazolyl)sulfoxide **47** was achieved from the reaction of 1-trimethylsilyl-1,2,4-triazole **46** with thionyl chloride (Equation 13). This compound was then used as a triazole-donor reagent in the synthesis of 1,1-bis(1,2,4-triazolyl) derivatives of carbonyl compounds <2000JHC743>.



46 **47** (13)

1-Methyl-1,2,4-triazole **37** undergoes radical alkylation to give monoalkylated 1-methyl-1,2,4-triazoles **48a–e** in which the new substituent is in the 5-position; no addition products resulting from alkylation in the 3-position were observed (Equation 14 and **Table 3**) <2001TL7353>.



37 **48a–e** (14)

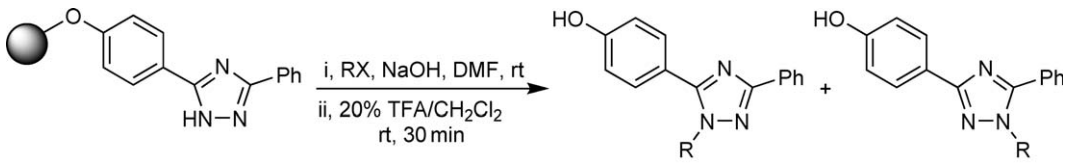
Table 3 Alkylation of 1-methyl-1,2,4-triazole **37** using radical species (Equation 14)

Entry	*Triazole* **48**	*R*	*Isolated yield* (%)
1	**a**	Cyclopropyl	60
2	**b**	Cyclobutyl	54
3	**c**	Cyclopentyl	35
4	**d**	Cyclohexyl	54
5	**e**	Isopropyl	53

Alkylation of 1,2,4-triazole has been investigated in some depth: as was expected, reaction of 1,2,4-triazole with a wide variety of electrophilic reagents in the presence of an equally diverse array of basic reagents gave both 1-alkyl-1,2,4-triazole and 4-alkyl-1,2,4-triazole products but always in the approximate ratio of 90:10 in favor of the 1-alkylated product <2000TL1297>.

The reaction of 1,2,4-triazole with alkenes has also been studied: 1,2,4-triazole was reacted with a variety of electrophilic and nucleophilic alkenes, both in the presence and absence of a catalyst, and the yield of the corresponding 1-alkyl-1,2,4-triazoles determined <2002CHE981, 2002KGS1122>.

Supported 1,2,4-triazoles undergo reaction with alkyl halides on the solid support. For example, 3-methyl-5-aryl-1*H*-1,2,4-triazole **49** reacted with a variety of alkyl halides to give, after cleavage from the solid support, mixtures of the corresponding alkyltriazoles **50a–h** and **51a–h**. The mass yield of the triazoles **50** and **51** was virtually quantitative following cleavage from the solid support but the major isomer obtained from each reaction following cleavage was not determined (Equation 15 and **Table 4**) <1999OL1189>.



(15)

49 **50a–h** **51a–h**

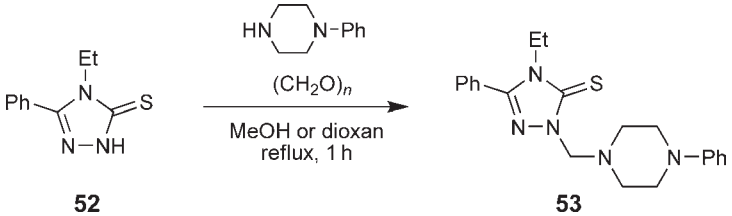
Table 4 Alkylation of solid-supported 1,2,4-triazole derivatives (Equation 15)

Entry	*Triazoles* **50** *and* **51**	*R*	*Purity (%)*	*Isomer ratio*
1	**a**	Bu^n	82	56:44
2	**b**	Pr^i	90	48:52
3	**c**	*c*-C_5H_9	71	51:49
4	**d**	$H_2C{=}CHCH_2$	78	50:50
5	**e**	$C_6H_5CH_2$	54	64:36
6	**f**	*n*-$C_6H_{13}(CH_3)CH$	88	49:51
7	**g**	$C_6H_5(CH_3)CH$	70	40:60
8	**h**	*c*-$C_3H_5CH_2$	77	38:62

5.02.6 Reactivity of Non-Conjugated Rings

The alkylation of 4-amino-1,2,4-triazolo-3-thione derivatives using haloalkyl nitriles to give the S-alkylated product as a result of alkylation of the 3-mercato-1,2,4-triazole tautomer, or the corresponding N-alkylated product resulting from reaction with the 3-thione tautomer, has been studied extensively; optimum conditions have been developed to provide either the S- or the N-alkylated products in good yields <2000PS(167)219, 2003BML2601>.

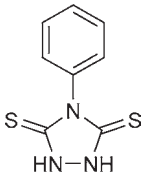
The Mannich reaction has been applied to the synthesis of a wide array of *N*-aminomethyl-1,2,4-trialozethiones. For example, 1,2,4- triazolo-3-thione **52** reacts with *N*-phenylpiperidine in the presence of 40% formalin to give the corresponding N-substituted 1,2,4-triazolo-3-thione **53** in 77% yield (Equation 16) <2005PS(180)537, 2000PS(164)67>.



(16)

52 **53**

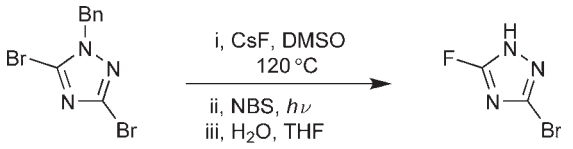
The Mannich reaction has also been applied to the aminoalkylation of 4-phenyl-1,2,4-triazolidine-3,5-dione **54** <2000CHE1058, 2000KGS1214>.



54

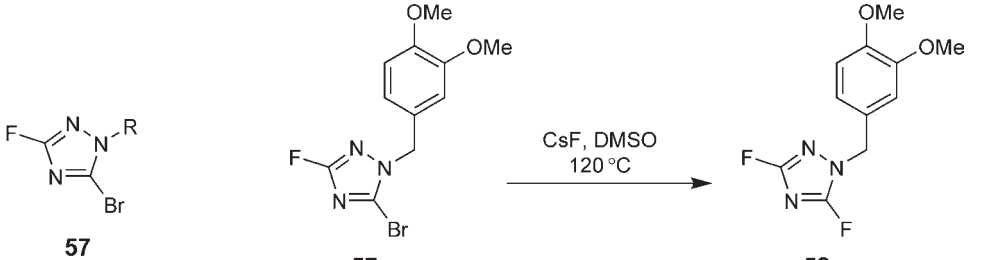
5.02.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Halogen exchange followed by debenzylation of 1,2,4-triazole **55** was employed in the preparation of 3-bromo-5-fluoro-1*H*-1,2,4-triazole **56** in 59% overall yield (Equation 17) <1998S1357>.



55 **56** (17)

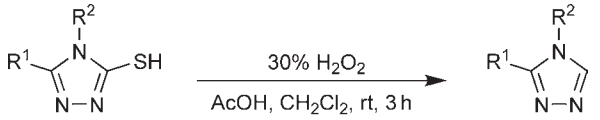
As may be expected, the bromine substituent in 3-bromo-5-fluoro-1*H*-1,2,4-triazoles **57a–c** can be displaced using a variety of nucleophiles. In particular, treatment of compound **57c** with cesium fluoride gave the corresponding difluoro derivative **58** (Equation 18) <1998S1357>.



57 **57c** **58** (18)

a: R = Me
b: R = Bn
c: R = 3,4-$(MeO)_2C_6H_4CH_2$

The thiol group was displaced from 3-mercapto-1,2,4-triazoles **59** using oxidation to yield the corresponding 3-unsubstituted compounds **60a–d** in good yield (Equation 19) (**Table 5**) <2006S156>.

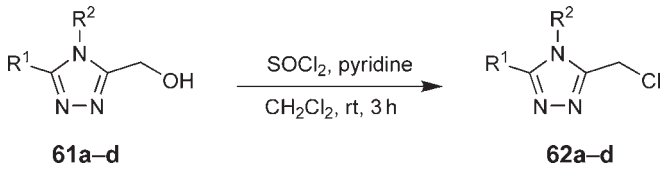


59 **60a–d** (19)

Table 5 Oxidation of 3-mercapto-1,2,4-triazole derivatives using hydrogen peroxide (Equation 19)

Entry	*Triazole* **60**	R^1	R^2	*Yield* (%)
1	**a**	Me	Me	82
2	**b**	Me	Ph	83
3	**c**	Ph	Me	83
4	**d**	Ph	Ph	86

3-Chloromethyl-1,2,4-triazoles can be valuable intermediates in the synthesis of more complex compounds containing a 1,2,4-triazole moiety, and they can be accessed using a number of established methods for the synthesis of the triazole ring system. However, these processes often give variable yields and require much work to construct the starting material. A more convenient procedure has been developed, by which a hydroxymethyl-1,2,4-triazole is converted to the chloromethyl derivative by reaction with thionyl chloride (Equation 20 and **Table 6**) <2006S156>.

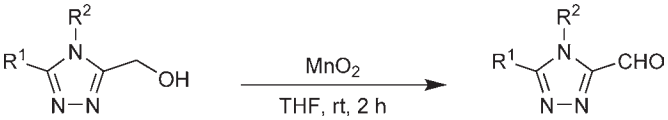


61a–d 62a–d (20)

Table 6 Reaction of 3-hydroxymethyl-1,2,4-triazole derivatives with thionyl chloride (Equation 20)

Entry	*Triazole* **61**	R^1	R^2	*Triazole* **62**	*Yield* (%)
1	**a**	Me	Me	**a**	21
2	**b**	Me	Ph	**b**	75
3	**c**	Ph	Me	**c**	88
4	**d**	Ph	Ph	**d**	96

3-Hydroxymethyl-1,2,4-triazoles may also be oxidized under mild conditions to give the corresponding aldehydes; this method is particularly convenient as it avoids exposure to alcohols and the consequent formation of acetals (Equation 21 and **Table 7**) <2006S156>.

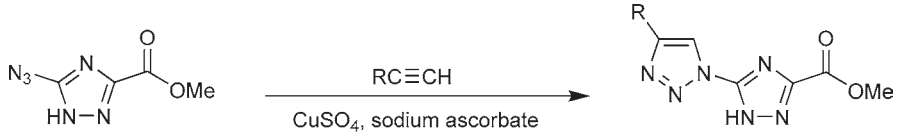


63a–d **64a–d** (21)

Table 7 Oxidation of 3-hydroxymethyl-1,2,4-triazole derivatives using manganese dioxide

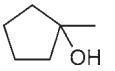
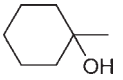
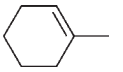
Entry	*Triazole* **63**	R^1	R^2	*Triazole* **64**	*Yield* (%)
1	**a**	Me	Me	**a**	94
2	**b**	Me	Ph	**b**	77
3	**c**	Ph	Me	**c**	71
4	**d**	Ph	Ph	**d**	75

Azide groups attached in the 5-position of a 1*H*-1,2,4-triazole will react with terminal alkynes under mild, copper-catalyzed conditions to yield 3-(1,2,3-triazol-1-yl)-1,2,4-triazoles. The 1,2,4-triazoles **66a–j** were prepared in this manner from the azido-1,2,4-triazole **65** in good yields (Equation 22 and **Table 8**) <2006BML2693>.

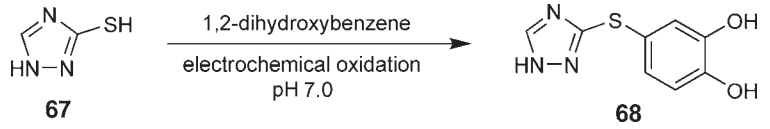


65 **66a–j** (22)

Table 8 Cycloaddition reactions of 5-azido-1,2,4-triazole derivatives with alkynes (Equation 22)

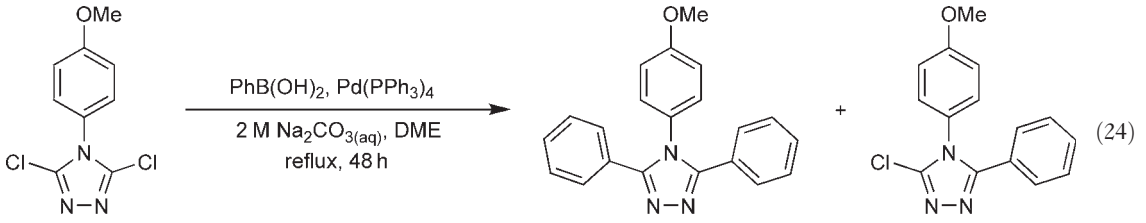
Entry	*Triazole* **66**	*R*	*Yield* (%)
1	**a**	EtO_2C	85
2	**b**	$CH_3CO_2CH_2$	92
3	**c**		78
4	**d**		78
5	**e**		85
6	**f**	C_6H_5	85
7	**g**	4-MeC_6H_4	85
8	**h**	4-$MeOC_6H_4$	83
9	**i**	4-FC_6H_4	70
10	**j**	4-*n*-$C_5H_{11}C_6H_4$	82

3-Mercapto-1,2,4-triazole **67** reacted in a standard coulometric cell with the *ortho*-quinone generated electrochemically from 1,2-dihydroxybenzene to give 4-(1*H*-1,2,4-triazole-3-ylsulfanyl)-1,2-benzenediol **68** via a Michael addition (Equation 23) <2005MI68>.



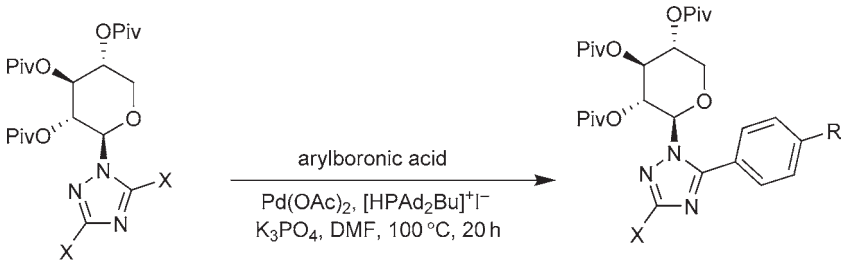
67 **68** (23)

Metal-catalyzed cross-coupling reactions are now ubiquitous in organic synthesis and several standard methods are used routinely for the formation of aryl–aryl bonds. Such methods have also been used to cross-couple heterocyclic species and this area of research has been reviewed <2005T2245>. However, the cross-coupling of halogenated 1,2,4-triazoles has only recently been reported. Typical Suzuki coupling conditions were employed in the reaction of 3,5-dichloro-4(4-methoxyphenyl)-4*H*-1,2,4-triazole **69** and phenylboronic acid: the reaction proceeded to give the 3,5-diaryltriazole **70** in 37% yield. However, this was accompanied by the undesired product **71** which was obtained in 47% yield. It should be noted that the reaction conditions were unoptimized and were not investigated further in this report (Equation 24) <2006T2677>.



69 **70** **71** (24)

In a more sophisticated study, reaction of the glycosides **72a** and **72b** with a range of arylboronic acids under Suzuki coupling conditions gave the corresponding aryl-substituted 1,2,4-triazoles in good yield; in all cases arylation took place predominantly at position 5 on the triazole ring, though some 3-substituted and 3,5-disubstituted products were observed as minor by-products (Equation 25 and **Table 9**) <2006T3301>.



72a: X = Cl
72b: X = Br

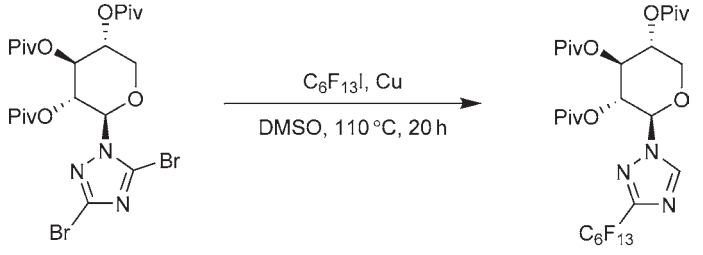
73a–e

(25)

Table 9 Reaction of arylboronic acids with 3,5-dihalo-1,2,4-triazole derivatives under Suzuki coupling conditions (Equation 25)

Entry	*Triazole* **72**	*X*	*R*	*Triazole* **73**	*Yield* (%)
1	**a**	Cl	H	**a**	63
2	**a**	Cl	CH_2=CH	**b**	78
3	**a**	Cl	MeO	**c**	44
4	**b**	Br	CH_2=CH	**d**	67
5	**b**	Br	*n*-$C_6H_{13}O$	**e**	53

Addition of a fluorinated pony-tail to the dibrominated 1,2,4-triazole glycoside **74** proceeded well using a copper-catalyzed coupling reaction but produced a yield of 37% of the 3-perfluorohexyl-1,2,4-triazole **75**. As position 5 on the 1,2,4-triazole ring is the most reactive than one would expect that the perfluoroalkyl group would be attached here; instead, the competing hydrodebromination at position 5 proceeds at a faster rate than the coupling reaction; hence, the perfluoroalkyl group appears in the 3-position (Equation 26) <2006T3301>.

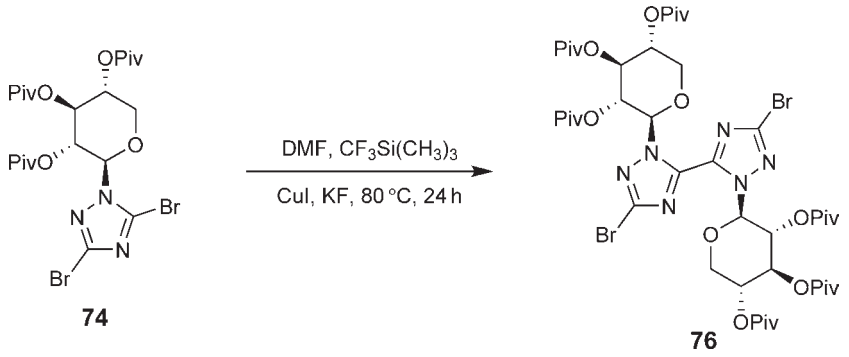


74

75

(26)

A potentially profitable discovery was that dibromide **74** will undergo an Ullman-type coupling to give the corresponding bis(1,2,4-triazole) **76** in 51%; the reaction conditions employed were chosen in order that a trifluoromethyl substituent could be introduced but this reaction did not occur, the biaryl bond formation being preferred (Equation 27) <2006T3301>.

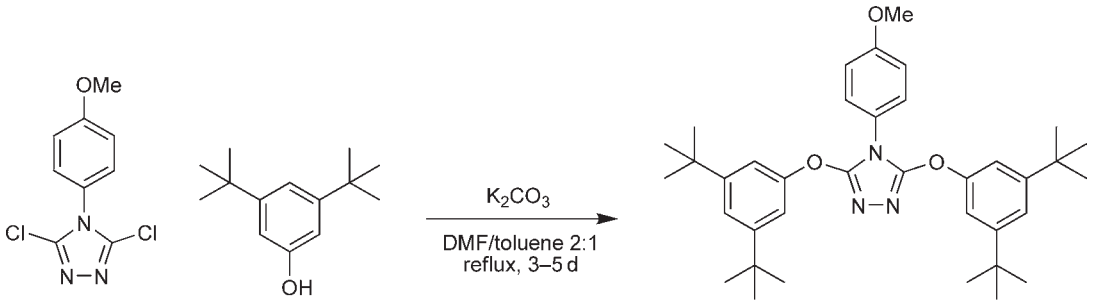


74

76

(27)

As part of a program directed toward the synthesis of dendrimeric structures containing the 1,2,4-triazole moiety, 3,5-dichloro-4(4-methoxyphenyl)-4*H*-1,2,4-triazole **69** was reacted with phenol **77** under basic conditions to give the dendron **78** in a yield of 80% (Equation 28) <2006T2677>.



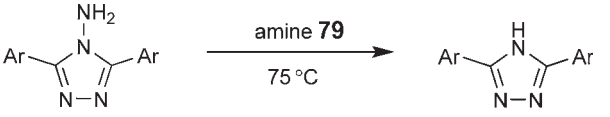
69 **77** **78** (28)

A range of L-cysteine derivatives bearing a 1,2,4-triazolyl residue on the sulfur atom has been prepared by the asymmetric Michael addition of 4,5-dialkyl-3-mercapto-1,2,4-triazoles to a nickel Schiff base complex. The enantiomeric excesses of the product aminoacids were measured and found to be greater than 98.5% in some cases <2004TA705, 2004RCB932, 2004IZV894>.

The regioselective alkylation and acylation of 3,5-diamino-1,2,4-triazole **19** using a simple protecting group strategy has been described in detail <2006RJA624, 2006ZPK632>.

5.02.8 Reactivity of Substituents Attached to Ring Nitrogen Atoms

The synthesis of 4-amino-3,5-diaryl-1,2,4-triazoles is well documented but deamination using sodium nitrite in aqueous nitric acid typically gives low yields and is restricted in its scope. A more efficient method of deamination using aqueous hypophosphorous acid has been reported: the intermediate diazonium salt formed in this reaction is reduced quickly within the reaction mixture, leading to high yields (Equation 29 and **Table 10**) <2002JHC93>.

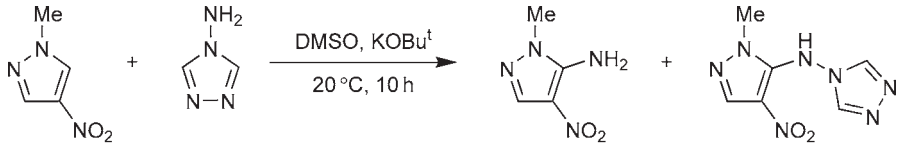


79a–m **27**, **80a–l** (29)

Table 10 Reaction of hypophosphorus acid with 4-amino-1,2,4-triazole derivatives (Equation 29)

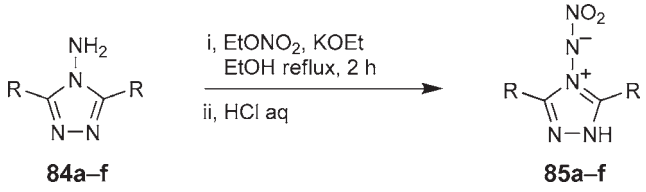
Entry	*Aminotriazole* **79**	*Ar*	*Triazole*	*Yield* (%)
1	**a**	C_6H_5	**27**	99
2	**b**	2-MeC_6H_4	**80a**	91
3	**c**	3-MeC_6H_4	**80b**	80
4	**d**	4-MeC_6H_4	**80c**	99
5	**e**	2-HOC_6H_4	**80d**	76
6	**f**	4-HOC_6H_4	**80e**	98
7	**g**	3-$MeOC_6H_4$	**80f**	99
8	**h**	4-$MeOC_6H_4$	**80g**	99
9	**i**	4-$MeSC_6H_4$	**80h**	79
10	**j**	2-ClC_6H_4	**80i**	84
11	**k**	4-ClC_6H_4	**80j**	98
12	**l**	2-Pyridyl	**80k**	81
13	**m**	4-Pyridyl	**80l**	76

4-Amino-4*H*-1,2,4-triazole **16** was employed as an aminating agent in a reaction with 1-methyl-4-nitropyrazole **81**: the reaction gave a mixture of the 5-amino-4-nitropyrazole **82** and the adduct **83** in low yields of 20% and 13%, respectively (Equation 30) <2000CHE476, 2000KGS551>.



(30)

Nitration of the amino group of 4-amino-3,5-diaryl-1,2,4-triazoles has been achieved: reaction of 4-imino-1,2,4-triazoles **84a–f** with ethyl nitrate gives the corresponding triazolium nitroimides **85a–f** in good yield (Equation 31 and **Table 11**) <2001RCB2481, 2001IZV2367>. The chemistry of 4-nitrimido-1,2,4-triazoles has been further investigated in depth <2003RCB467, 2003IZV446, 2003IZV695, 2003RCB665>.

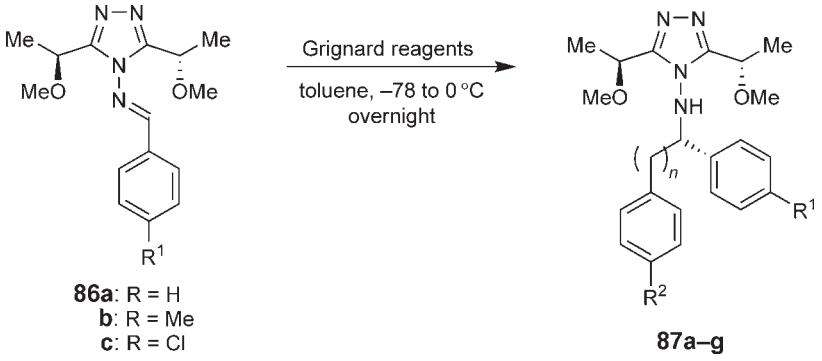


(31)

Table 11 Reaction of ethyl nitrate with 4-amino-1,2,4-triazole derivatives (Equation 31)

Entry	*Aminotriazole* **84**	*R*	*Triazole* **85**	*Yield* (%)
1	**a**	Me	**a**	50
2	**b**	Et	**b**	43
3	**c**	Pr^n	**c**	52
4	**d**	Ph	**d**	67
5	**e**	$PhOCH_2$	**e**	65
6	**f**	$PhCH_2SCH_2$	**f**	51

The asymmetric alkylation of hydrazones bearing a chiral auxiliary derived from 4-amino-1,2,4-triazole has been investigated. Treatment of hydrazones **86a–c** with Grignard reagents gave the corresponding amines **87a–g** in good yields and with high diastereoselectivities (Equation 32 and **Table 12**) <1996TA1621>.



(32)

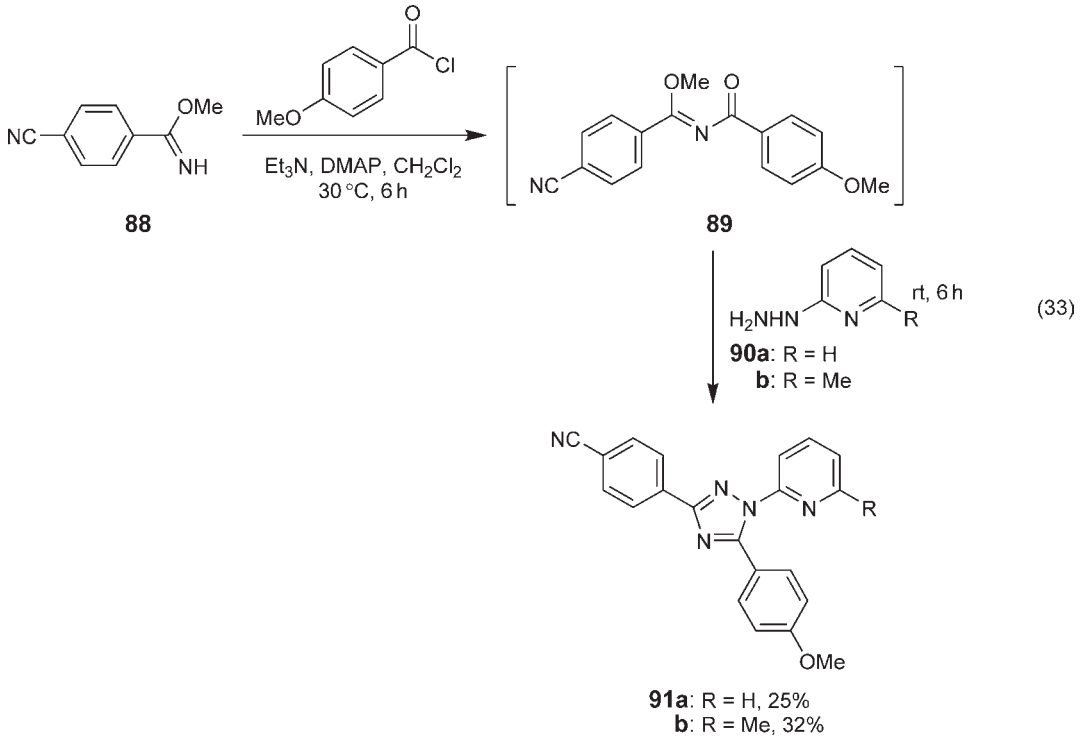
Table 12 Reaction of chiral 4-amino-1,2,4-triazole derivatives with Grignard reagents (Equation 32)

Entry	*Aminotriazole* **87**	R^1	R^2	*n*	*Yield* (%)	*de* % (*GC*)
1	**a**	H	Me	0	67	93
2	**b**	Me	H	0	76	70
3	**c**	Cl	Me	0	70	96
4	**d**	H	H	1	71	96
5	**e**	Cl	H	1	69	98
6	**f**	H	H	2	65	83
7	**g**	Cl	H	2	60	>99

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

5.02.9.1 Fragments Contributing Two Ring Atoms

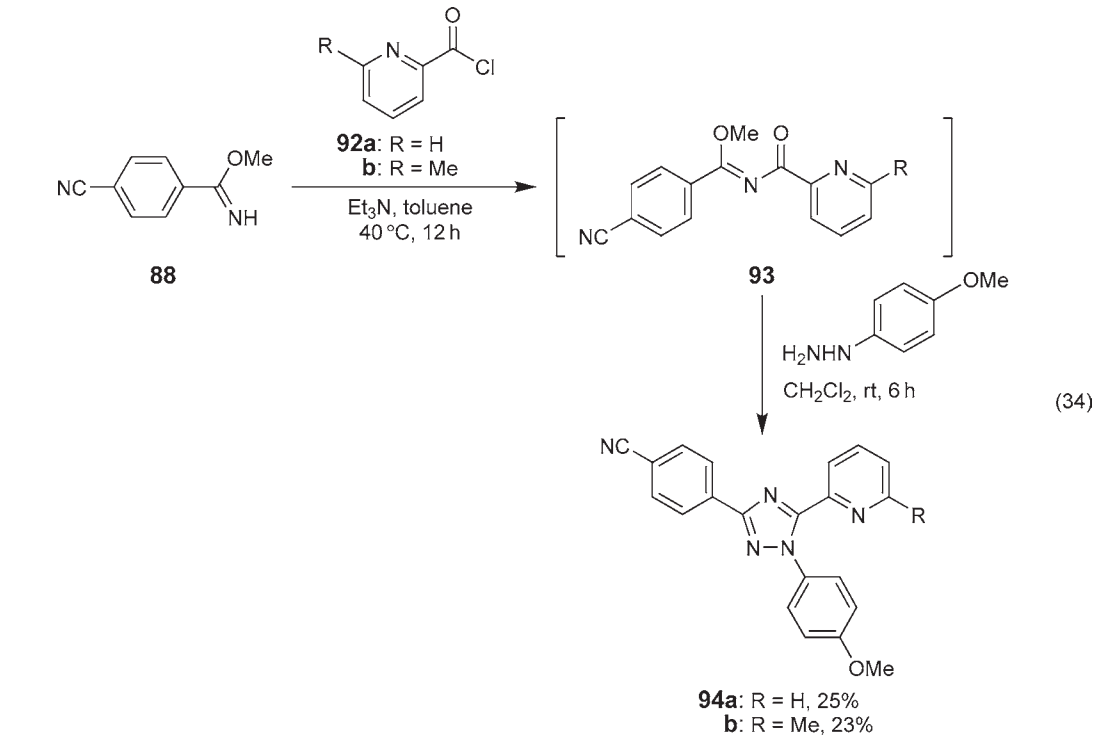
The synthesis of a series of 2-pyridyl-substituted 1,2,4-triazoles was achieved from methyl 4-cyanobenzimidate **88** by reaction with the appropriate acid chloride and hydrazine via the unstable *N*-aroylimidate intermediate. For example, reaction of **88** with 4-methoxybenzoyl chloride gave the imidate **89**, subsequent reaction of which with pyridylhydrazines **90a** and **90b** gave 1,2,4-triazoles **91a** and **91b** (Equation 33) <2004BMC2013>.



Scheme 1a

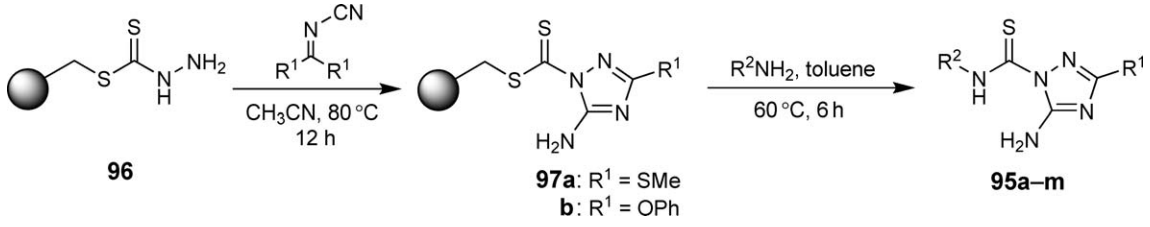
Alternatively, reaction of methyl 4-cyanobenzimidate **88** with picolinoyl chloride **92a** or 6-methylpicolinoyl chloride **92b** delivered the intermediates **93**. The subsequent reaction of imidates **93** with 4-methoxyphenylhydrazine gave 1,2,4-triazoles **94a** and **94b** (Equation 34) <2004BMC2013>.

5-Amino-1,2,4-triazoles **95a–m** have been prepared using solid-phase parallel, traceless synthesis via the reaction of supported dithiocarbazate **96** with cyanocarbodiimides to give the 1,2,4-triazoles **97a** and **97b**. The target 1,2,4-triazoles were cleaved from the solid support by nucleophilic substitution using a range alkylamines in modest yields but with high levels of purity (**Scheme 2** and **Table 13**) <2005JCO136>.



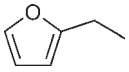
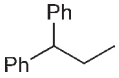
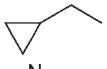
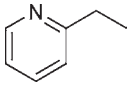
(34)

Scheme 1b



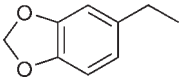
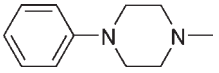
Scheme 2

Table 13 Solid-phase synthesis of substituted 5-amino-1,2,4-triazole derivatives (**Scheme 3**)

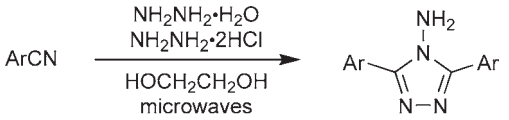
Entry	*Triazole* **95**	R^1	R^2	*Yield* (%)	*Purity* (%)
1	**a**	SMe	2-$MeC_6H_4CH_2$	26	98
2	**b**	SMe		23	100
3	**c**	SMe	4-$MeOC_6H_4CH_2$	27	97
4	**d**	SMe	Pr^i	20	98
5	**e**	SMe	Piperidino	28	96
6	**f**	SMe	2-$ClC_6H_4CH_2$	22	93
7	**g**	SMe		19	81
8	**h**	SMe	Bu^i	27	98
9	**i**	SMe		24	100
10	**j**	OPh		18	94

(*Continued*)

Table 13 (Continued)

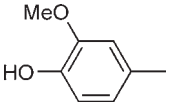
Entry	*Triazole* **95**	R^1	R^2	*Yield* (%)	*Purity* (%)
11	**k**	OPh	Morpholino	23	92
12	**l**	OPh		25	85
13	**m**	OPh		22	87

Microwave irradiation of a reaction mixture containing aromatic nitriles, hydrazine hydrate, hydrazine dihydrochloride, and ethylene glycol as solvent in a one-pot process gave 3,5-disubstituted 4-amino-1,2,4-triazoles **98a–i** in excellent yields (Equation 35 and **Table 14**) <2000TL1539>.



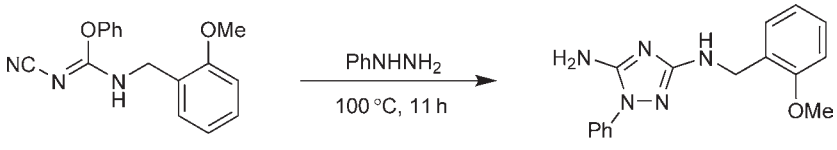
98a–i (35)

Table 14 Synthesis of 3,5-disubstituted 4-amino-1,2,4-triazoles using microwave irradiation (Equation 35)

Entry	*Triazole* **98**	*Ar*	*Yield* (%)
1	**a**	C_6H_5	85
2	**b**	4-MeC_6H_4	88
3	**c**	4-$NH_2C_6H_4$	78
4	**d**	4-HOC_6H_4	75
5	**e**		90
6	**f**	4-MeC_6H_4	77
7	**g**	4-ClC_6H_4	61
8	**h**	2-Pyridyl	81
9	**i**	4-Pyridyl	75

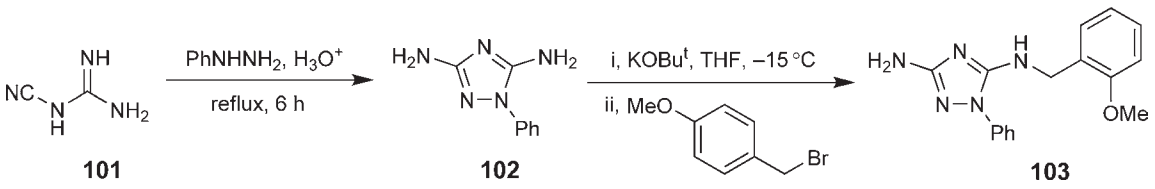
5.02.9.2 Fragments Contributing Three Ring Atoms

An investigation into the synthesis of 3,5-diamino-1,2,4-triazoles provided regiospecific routes toward the target triazoles that enables the isolation of single isomers: despite obvious expectations, reaction of cyanoisourea **99** with phenylhydrazine gave 1,2,4-triazole **100** as a single regioisomer in 86% yield (Equation 36) <1998TL7983>.



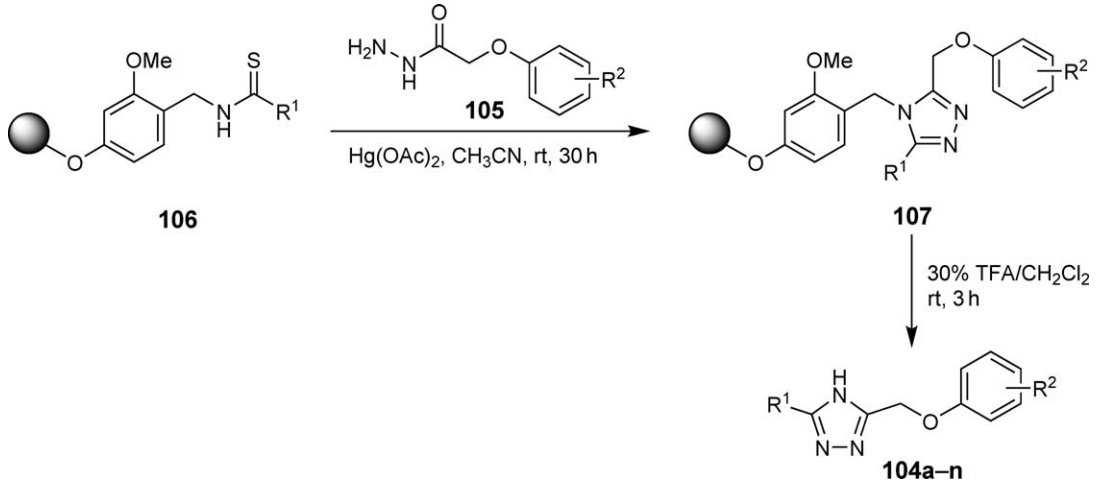
99 **100** (36)

However, reaction of *N*-cyanoguanidine **101** with phenylhydrazine gave 1,2,4-triazole **102**, again as a single regioisomer in 41% yield. Alkylation of compound **102** was also regiospecific, exploiting the difference in pK_a of the amino groups in positions 3 and 5, giving 1,2,4-triazole **103** as a single isomer in 30% yield (**Scheme 3**) <1998TL7983>.



Scheme 3

3,5-Disubstituted 1,2,4-triazoles **104a–n** have been prepared using a soluble polymer support (PEG6000): using established methodology for their synthesis via the reaction of aryloxyacyl hydrazides **105** with a polymer-supported thioamide **106** in the presence of mercury diacetate, a range of supported 1,2,4-triazoles **107** was prepared. The triazole products **104a–n** were cleaved readily from the polymer in this diversity-oriented, traceless route (**Scheme 4** and **Table 15**) <2005TL8479>.

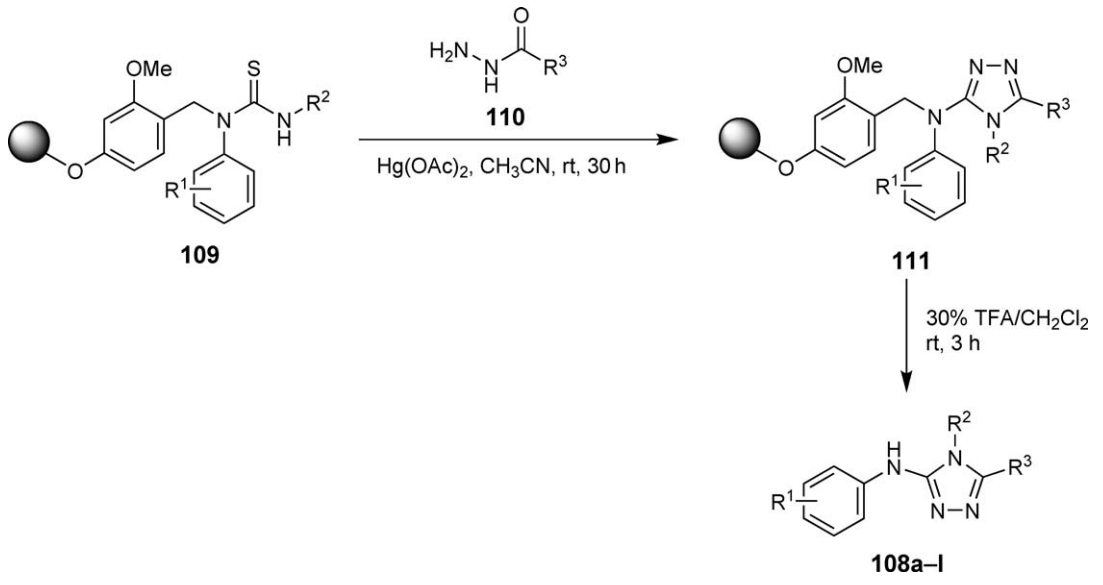


Scheme 4

Table 15 Solid-phase synthesis of 3,5-disubstituted 1,2,4-triazole derivatives (**Scheme 4**)

Entry	*Triazole* **104**	R^1	R^2	*Cleaved* (%)	*Purity* (%)
1	**a**	C_6H_5	4-CH_3	90	87
2	**b**	C_6H_5	4-Cl	94	88
3	**c**	C_6H_5	H	85	90
4	**d**	C_6H_5	4-CH_3	79	96
5	**e**	C_6H_5	4-Br	85	83
6	**f**	2-ClC_6H_4	4-CH_3	80	86
7	**g**	2-ClC_6H_4	4-Cl	88	81
8	**h**	2-ClC_6H_4	H	89	94
9	**i**	2-ClC_6H_4	4-CH_3	77	83
10	**j**	2-ClC_6H_4	4-Br	81	84
11	**k**	2-ClC_6H_4	4-NO_2	79	95
12	**l**	4-$CH_3C_6H_4$	4-NO_2	76	94
13	**m**	4-$CH_3C_6H_4$	4-CH_3	90	85
14	**n**	4-$CH_3C_6H_4$	4-Cl	88	94

In an alternative traceless route, 4,5-disubstituted 3-amino-1,2,4-triazoles **108a–l** were also prepared on a PEG6000 support, though this time via the reaction of a polymer-supported thiourea **109** with arylacyl hydrazides **110** in the presence of mercury diacetate, with three possible points of diversity. A range of supported 1,2,4-triazoles **111** were obtained and the free 1,2,4-triazoles **108a–l** were cleaved from the polymer in high yield (**Scheme 5** and **Table 16**) <2005TL5139>.

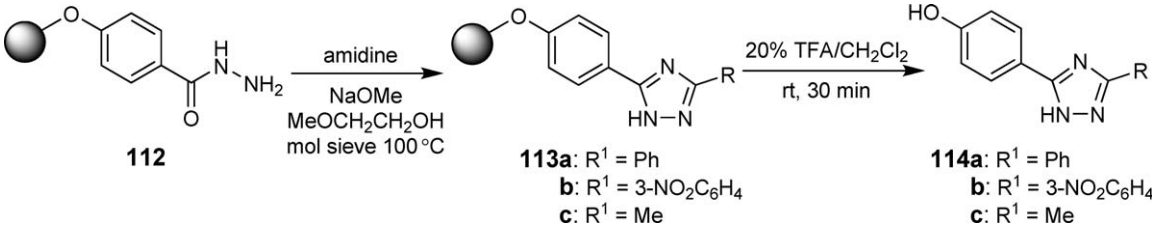


Scheme 5

Table 16 Traceless polymer-supported synthesis of 4,5-disubstituted 3-amino-1,2,4-triazole derivatives (Scheme 5)

Entry	*Triazole* **108**	R^1	R^2	R^3	*Cleaved* (%)	*Purity* (%)
1	**a**	H	$C_6H_4CH_2$	4-$NO_2C_6H_4$	56	87
2	**b**	H	$C_6H_4CH_2$	C_6H_5	80	90
3	**c**	H	$C_6H_4CH_2$	4-$MeOC_6H_4$	87	92
4	**d**	H	$C_6H_4CH_2$	4-MeC_6H_4	86	86
5	**e**	H	*n*-C_4H_9	C_6H_5	78	83
6	**f**	$4CH_3O$	*n*-C_4H_9	4-MeC_6H_4	81	86
7	**g**	4-CH_3	*n*-C_4H_9	4-$NO_2C_6H_4$	77	90
8	**h**	4-CH_3	$C_6H_4CH_2$	C_6H_5	89	80
9	**i**	4-CH_3	$C_6H_4CH_2$	4-$MeOC_6H_4$	96	88
10	**j**	4-CH_3	$C_6H_4CH_2$	4-BrC_6H_4	89	81
11	**k**	4-CH_3	$C_6H_4CH_2$	2-Naphthyl	84	89
12	**l**	$4CH_3O$	$C_6H_4CH_2$	CH_3	92	93

5-Hydroxyphenyl-1,2,4-triazoles have been prepared using mild conditions on a solid-phase polymer support: acylhydrazine **112**, linked to a Wang resin, was reacted with a variety of amidines to give the 3,5-disubstituted-1,2,4-triazoles **113a–c**. These were then liberated from the solid support under acidic conditions to give the free triazoles **114a–c** in high yield (Scheme 6 and Table 17) <1999OL1189>.

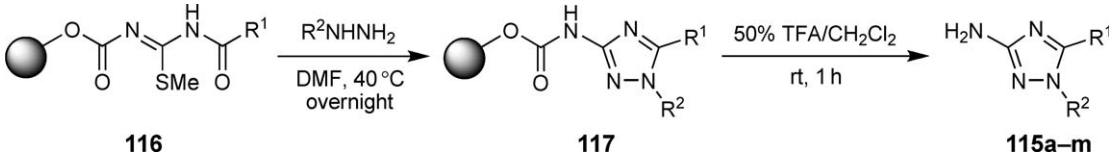


Scheme 6

Table 17 Solid-phase synthesis of 5-hydroxyphenyl-1,2,4-triazole derivatives (**Scheme 6**)

Entry	*Triazole* **114**	*R*	*Cleaved* (%)	*Purity* (%)
1	**a**	C_6H_5	100	85
2	**b**	3-$NO_2C_6H_4$	95	90
3	**c**	Me	90	75

5-Amino-1,2,4-triazoles **115a–m** bearing a variety of substituents have been prepared on a carbonate solid support via the reaction of supported acylisothioureas **116** with hydrazines under mild conditions to give the 1,2,4-triazoles **117**. The target 1,2,4-triazoles were cleaved from the solid support using trifluoroacetic acid in high yield and high levels of purity. Again, this is an excellent example of a traceless synthesis of this particular class of azoles (**Scheme 7** and **Table 18**) <2003TL7481>.



Scheme 7

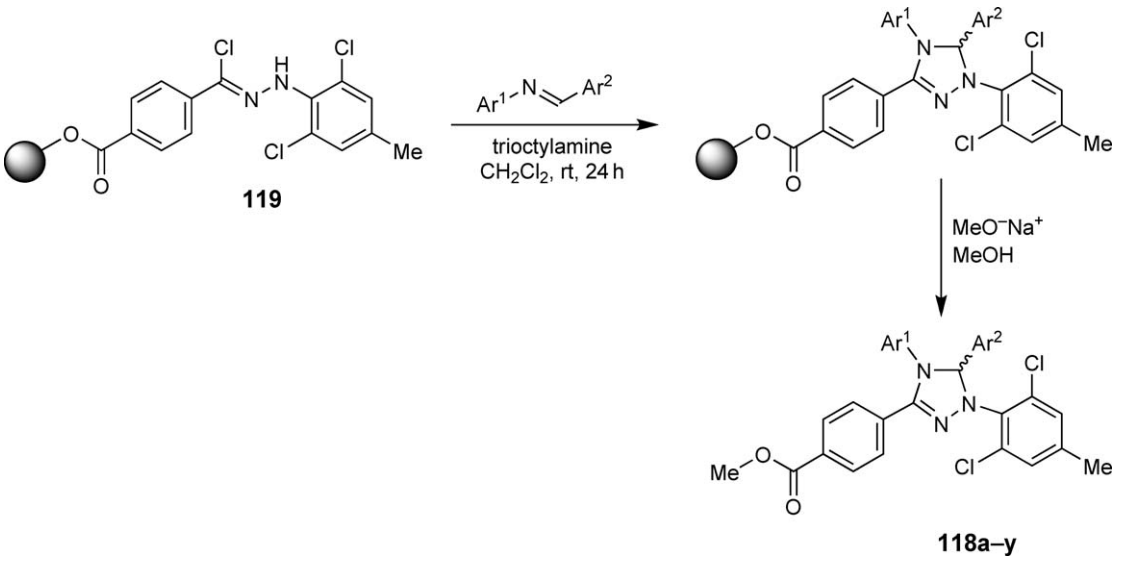
Table 18 Solid-phase synthesis of 5-amino-1,2,4-triazole derivatives (**Scheme 7**)

Entry	*Triazole* **115**	R^1	R^2	*Yield* (%)	*Purity* (%)
1	**a**	3,5$(CF_3)_2C_6H_3CH_2$	C_6H_5	62	82
2	**b**	$C_6H_5CH_2$	C_6H_5	65	85
3	**c**	3-$FC_6H_4CH_2$	C_6H_5	63	83
4	**d**	3-$FC_6H_4CH_2$	H	71	79
5	**e**	3-$FC_6H_4CH_2$	C_6H_5	68	82
6	**f**	4-MeC_6H_4	C_6H_5	58	80
7	**g**	4-MeC_6H_4	H	65	83
8	**h**	Pr^i	C_6H_5	73	88
9	**i**	Bu^s	C_6H_5	63	74
10	**j**	4-$EtOC_6H_4CH_2$	H	59	87
11	**k**	4-$EtOC_6H_4CH_2$	C_6H_5	62	79
12	**l**	4-$NO_2C_6H_4(CH_2)_3$	H	75	82
13	**m**	$C_6H_5(CH_2)_3$	H	68	86

Highly functionalized tetraaryl-4,5-dihydro-1,2,4-triazoles **118a–y** have been prepared on a soluble polymer support (PEG4000) from the cycloaddition of diarylimines with a nitrile imine, prepared *in situ* from the arylhydrazone **119**. The triazole products are highly fluorescent and several have reasonable fluorescence quantum yields (**Scheme 8** and **Table 19**) <2005S3535>.

A mild and 'greener' approach to the synthesis of 1,2,4-triazoles by the dipolar cycloaddition of nitrilimines with nitriles has been reported. The nitrilium intermediates were generated *in situ* from hydrazonyl chlorides **120** and reacted with the nitriles in a one-pot process. Yields of the 1,3,5-trisubstituted products **121a–o** were good in the majority of cases (Equation 37 and **Table 20**) <2005H(65)1183>.

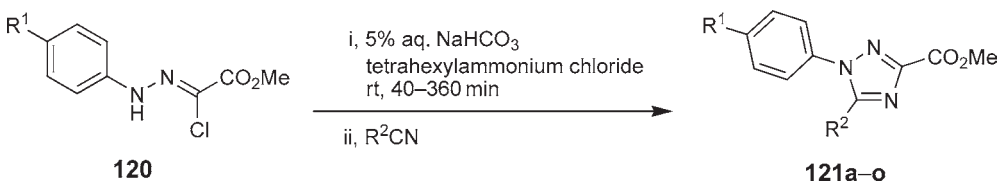
A series of 3,5-disubstituted 1,2,4-triazoles **122a–l** have been prepared by the reaction of nitriles **123** with acylhydrazides **124** in butanol and the presence of catalytic potassium carbonate; the reaction mixture was heated to 150 °C by irradiation with microwave radiation. The reaction conditions enabled a wide variety of starting materials to be employed, including nitriles that would otherwise seem unreactive. In the majority of cases the yields from this process were comparable, if not higher than the corresponding process in which the materials were heated together in an oil bath for a longer period of time without irradiation (Equation 38 and **Table 21**) <2005TL3429>.



Scheme 8

Table 19 Polymer-supported synthesis of tetraaryl-4,5-dihydro-1,2,4-triazole derivatives (Scheme 8)

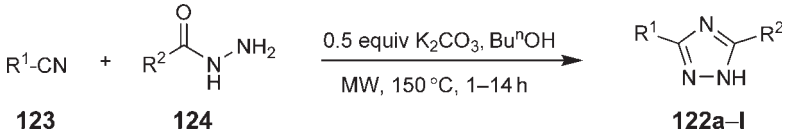
Entry	*Triazole* 118	Ar^1	Ar^2	*Cleaved* (%)	*Purity* (%)
1	a	4-$MeOC_6H_4$	4-FC_6H_4	94	95
2	b	4-$MeOC_6H_4$	4-BrC_6H_4	95	93
3	c	4-MeC_6H_4	4-BrC_6H_4	83	81
4	d	C_6H_5	4-BrC_6H_4	80	79
5	e	4-FC_6H_4	4-BrC_6H_4	79	82
6	f	4-MeC_6H_4	4-MeC_6H_4	75	70
7	g	4-$MeOC_6H_4$	4-MeC_6H_4	89	90
8	h	4-$MeOC_6H_4$	4-$Me_2NC_6H_4$	76	78
9	i	4-FC_6H_4	4-FC_6H_4	83	85
10	j	4-MeC_6H_4	4-FC_6H_4	85	84
11	k	C_6H_5	4-FC_6H_4	78	77
12	l	4-BrC_6H_4	4-BrC_6H_4	83	83
13	m	4-ClC_6H_4	4-BrC_6H_4	82	84
14	n	4-ClC_6H_4	4-ClC_6H_4	83	83
15	o	4-ClC_6H_4	4-FC_6H_4	86	88
16	p	4-$MeOC_6H_4$	4-ClC_6H_4	89	90
17	q	4-ClC_6H_4	4-MeC_6H_4	88	90
18	r	4-FC_6H_4	4-ClC_6H_4	83	83
19	s	C_6H_5	C_6H_5	90	90
20	t	C_6H_5	4-MeC_6H_4	86	87
21	u	4-FC_6H_4	C_6H_5	83	83
22	v	4-$MeOC_6H_4$	C_6H_5	92	94
23	w	4-$MeOC_6H_4$	4-$MeOC_6H_4$	95	98
24	x	4-$MeOC_6H_4$	C_6H_5	93	96
25	y	C_6H_5	4-ClC_6H_4	90	94



(37)

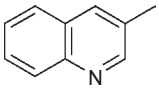
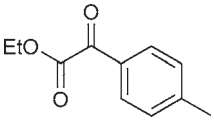
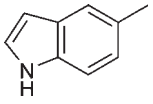
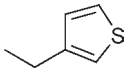
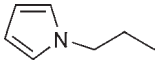
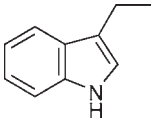
Table 20 Cycloaddition reaction of *in situ*-generated nitrilimines with nitriles to give 1,3,5-trisubstituted 1,2,4-triazole derivatives (Equation 37)

Entry	R^1	R^2	*Triazole* **121**	*Yield* (%)
1	H	CO_2Et	**a**	79
2	Me	CO_2Et	**b**	78
3	F	CO_2Et	**c**	95
4	Cl	CO_2Et	**d**	82
5	NO_2	CO_2Et	**e**	59
6	H	CO_2Bn	**f**	76
7	Me	CO_2Bn	**g**	74
8	F	CO_2Bn	**h**	84
9	Cl	CO_2Bn	**i**	74
10	NO_2	CO_2Bn	**j**	67
11	H	CCl_3	**k**	46
12	Me	CCl_3	**l**	41
13	F	CCl_3	**m**	49
14	Cl	CCl_3	**n**	56
15	NO_2	CCl_3	**o**	24



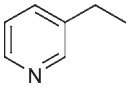
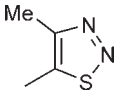
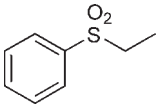
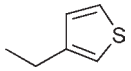
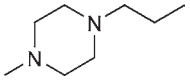
(38)

Table 21 Reaction of nitriles with acylhydrazides to give 3,5-disubstituted 1,2,4-triazole derivatives (Equation 38)

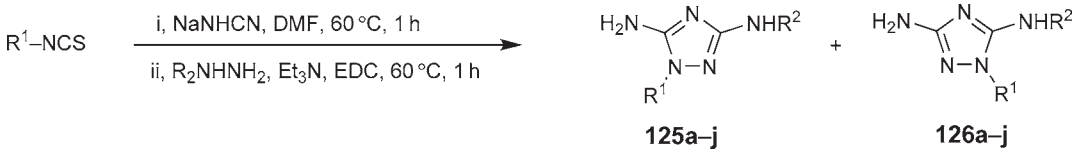
Entry	*Triazole* **122**	R^1	R^2	*Yield* (%)
1	**a**		4-$MeOC_6H_4$	83
2	**b**	4-ClC_6H_4	4-FC_6H_4	61
3	**c**	4-FC_6H_4	4-$Me_2NC_6H_4$	50
4	**d**	C_6H_5	4-pyridyl	57
5	**e**		3-BrC_6H_4	82
6	**f**		2-ClC_6H_4	41
7	**g**	3-$MeOC_6H_4$		50
8	**h**		4-$MeOC_6H_4$	74
9	**i**		C_6H_5	45

(*Continued*)

Table 21 (Continued)

Entry	*Triazole* **122**	R^1	R^2	*Yield* (%)
10	**j**			45
11	**k**			62
12	**l**		2-FC_6H_4	34

3,5-Diamino-1,2,4-triazoles are prepared in good to high yields in an efficient, one-pot process from the reaction of sodium salts of *N*-cyanothioureas, prepared *in situ* from isothiocyanates and sodium hydrogen cyanamide in dimethylformamide (DMF), and substituted hydrazines in the presence of catalytic 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). The products, 1,2,4-triazoles **125a–j** and **126a–j**, are obtained as a mixture of regioisomers, but isomer **125a–j** predominates in each case (Equation 39 and **Table 22**) <2003TL1409>.

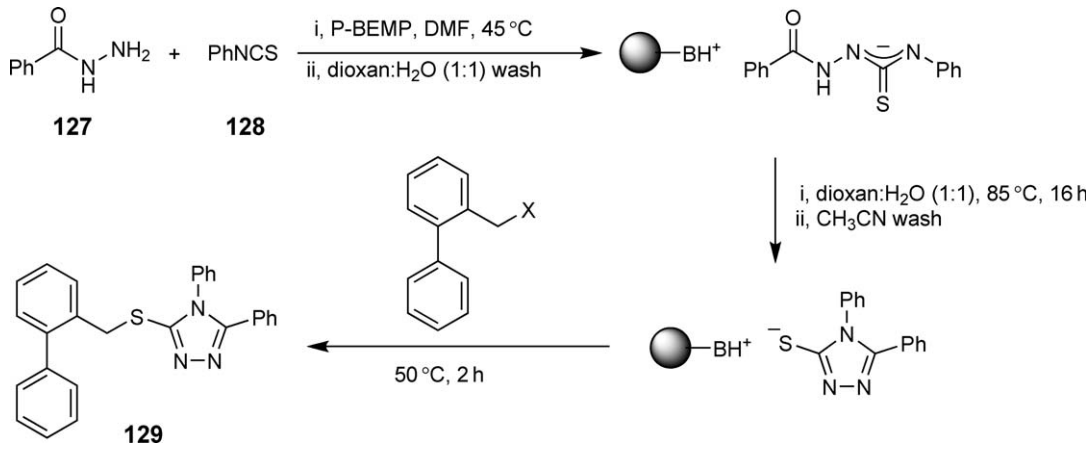


(39)

Table 22 One-pot synthesis of 3,5-diamino-1,2,4-triazole derivatives (Equation 39)

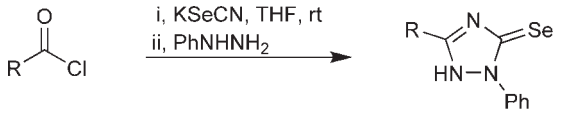
Entry	*Triazoles*	R^1	R^2	*Yield* (%)	*Ratio* **125**:**126**
1	**125,126a**	C_6H_5	CH_2CH_2CN	72	3.6:1
2	**125,126b**	C_6H_5	Cyclohexyl	82	3:1
3	**125,126c**	C_6H_5	Bu^t	90	20:1
4	**125,126d**	C_6H_5	C_6H_5	73	19:1
5	**125,126e**	C_6H_5	4-$CF_3C_6H_4$	70	Xe only
6	**125,126f**	C_6H_5	4-$MeOC_6H_4$	79	12:1
7	**125,126g**	4-$MeOC_6H_4$	Cyclohexyl	85	3.9:1
8	**125,126h**	2,4$(Cl)_2C_6H_3$	Cyclohexyl	90	4:1
9	**125,126i**	Pr^n	Bu^t	52	14:1
10	**125,126j**	$C_6H_5CH_2$	C_6H_5	42	20:1

The polymer-bound reagent P-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene) has been used as the base in an interesting synthesis of 3-thio-1,2,4-triazole derivatives using a so-called 'catch, cyclize, release' method that combines the advantages of solid-supported reagents with a diversity-oriented synthesis: acylhydrazides react with isothiocyanates in DMF in the presence of P-BEMP to give the corresponding acylimidosemicarbazide intermediate bound to the polymer as an ion pair. Cyclization to yield the corresponding 1,2,4-triazole also leaves the product heterocycle associated with the polymer, to be released by the reaction of the polymer-bound 1,2,4-triazole with an electrophilic reagent; in this study alkylating agents were employed to deliver 3-thioalkyl-1,2,4-triazoles. The method allows for a wide range of hydrazides, isothiocyanates, and electrophiles to be used and a variety of complex substitution patterns were obtained. For example, acylhydrazide **127** and isothiocyanate **128** reacted in the presence of P-BEMP to give 1,2,4-triazole **129** in a crude yield of 75% and purity of 100% after cleavage using the appropriate alkyl halide (**Scheme 9**) <2002TL5305>.



Scheme 9

2-Phenyl-1,2-dihydro-3*H*-1,2,4-triazole-3-selenones **130a–d** were delivered as minor products from the reaction of a range of acyl chlorides with potassium isoselenocyanate (Equation 40 and **Table 23**) <2006H(68)1191>.



130

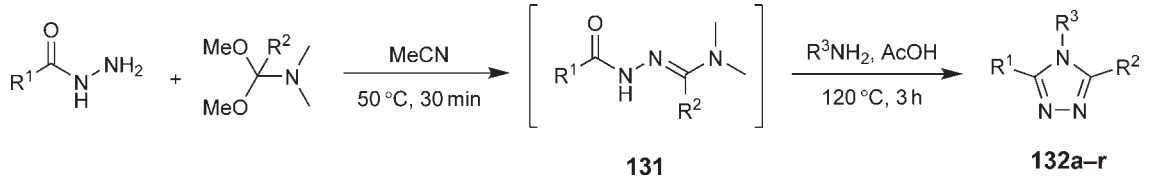
a: R = 4-$CH_3C_6H_4$
b: R = Ph
c: R = 4-$MeOC_6H_4$
d: R = 4-ClC_6H_4

(40)

Table 23 Reaction of acyl chlorides with potassium isoselenocyanate (Equation 40)

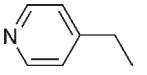
Entry	*R*	*Yield* (%) **130**
1	4-$CH_3C_6H_4$	38
2	Ph	5
3	4-$MeOC_6H_4$	15
4	4-ClC_6H_4	20

1,2,4-Triazoles have been prepared using a one-pot method that has a wide scope and can deliver highly-functionalized heterocycles in yields ranging from 9–87%. The three-component reaction involves the formation of an intermediate species **131** that undergoes further reaction with an amine to give 1,2,4-triazoles **132a–r**. An alternative mechanism was proposed that involved the formation of an oxadiazole intermediate but this was discounted (**Scheme 10** and **Table 24**) <2004OL2969>.

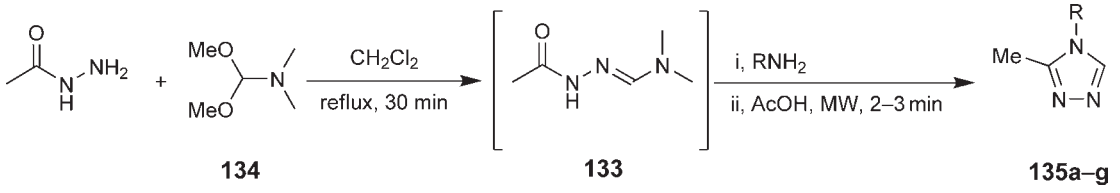


Scheme 10

Table 24 One-pot synthesis of 1,2,4-triazole derivatives (**Scheme 10**)

Entry	*Triazole* **132**	R^1	R^2	R^3	*Yield* (%)
1	**a**	Me	Me	4-$FC_6H_4CH_2$	69
2	**b**	Me	H	4-$FC_6H_4CH_2$	68
3	**c**	Me	H	$C_6H_5CH_2$	39
4	**d**	Me	H	4-$MeOC_6H_4CH_2$	22
5	**e**	Me	H	4-$NO_2C_6H_4CH_2$	48
6	**f**	Me	H	C_6H_5	64
7	**g**	Me	Me	C_6H_5	55
8	**h**	Me	H	4-$MeOC_6H_5$	87
9	**i**	Me	Me	4-$MeOC_6H_5$	60
10	**j**	Me	H	$EtO_2CC_6H_4$	43
11	**k**	4-MeC_6H_4	H	4-$FC_6H_4CH_2$	65
12	**l**	4-$MeOC_6H_4$	H	4-$FC_6H_4CH_2$	33
13	**m**	4-$NO_2C_6H_4$	H	4-$FC_6H_4CH_2$	51
14	**n**	Me	H		42
15	**o**	Me	H	$H_2C{=}CHCH_2$	56
16	**p**	Me	H	$HC{\equiv}CCH_2$	13
17	**q**	Me	H	c-C_6H_{11}	9
18	**r**	4-MeC_6H_4	H	c-C_6H_{11}	13

Microwave-assisted synthesis has been employed in an attempt to improve upon the one-pot synthesis of 1,2,4-triazoles reported previously by Stocks *et al.* hopefully to enable the preparation of substituted compounds in a cleaner, greener manner. The reaction of hydrazonoformamide **133**, prepared *in situ* from acetylhydrazine and acetal **134**, with a variety of amines followed by microwave irradiation was investigated: the corresponding 3-substitued 1,2,4-triazoles **135a–g** were obtained in excellent yields, many of which were indeed greater than the similar process without irradiation (**Scheme 11** and **Table 25**) <2005H(65)1957>.



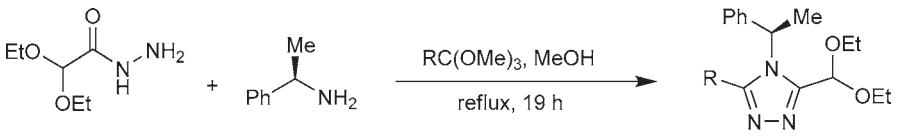
134 **133** **135a–g**

Scheme 11

Table 25 Microwave-assisted one-pot synthesis of 1,2,4-triazole derivatives (**Scheme 11**)

Entry	*Triazole* **135**	*R*	*Yield* (%)
1	**a**	C_6H_5	77
2	**b**	Cyclohexyl	72
3	**c**	$C_6H_4CH_2$	81
4	**d**	4$MeOC_6H_4$	97
5	**e**	$EtO_2CC_6H_4$	55
6	**f**	4-$MeOC_6H_4CH_2$	72
7	**g**	4-$FC_6H_4CH_2$	82

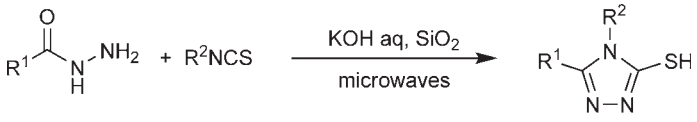
Optically active 4-substituted 1,2,4-triazoles **136a** and **136b** have been prepared using a simple one-pot strategy (Equation 41) <1998CRC63>.



136a: R = H, 62%
136b: R = Me, 90%

(41)

Acylhydrazides reacted with isothiocyanates in a one-pot procedure using microwave irradiation of the starting materials in the presence of either silica or montmorillonite K10 to give the 3-mercapto-1,2,4-triazoles **137a–f** in high yields (Equation 42 and **Table 26**) <2006PS(181)1839>.



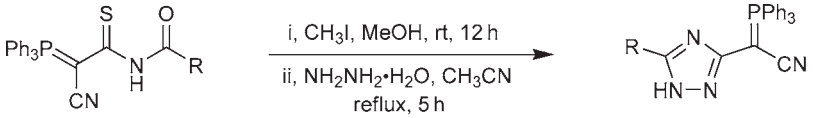
137a–f

(42)

Table 26 Reaction of acylhydrazides with isothiocyanates (Equation 42)

Entry	*Triazole* **137**	R^1	R^2	*Yield (%) (silica)*	*Yield (%) (K10)*
1	**a**	C_6H_5	C_6H_5	85	86
2	**b**	4-ClC_6H_4	C_6H_5	88	87
3	**c**	C_6H_5	Me	78	81
4	**d**	4-ClC_6H_4	Me	75	78
5	**e**	4-$NO_2C_6H_4$	C_6H_5	90	88
6	**f**	Me	C_6H_5	77	72

Methylation of ylides **138a** and **138b** followed by reaction of the intermediate formed *in situ* with hydrazine gave 1,2,4-triazoles **139a** and **139b** (Equation 43). Triazoles **139a** and **139b** were reacted with 4-methoxybenzaldehyde to demonstrate that they could participate in the Wittig synthesis of alkenes <2001RJC1157, 2001ZOB1227>.

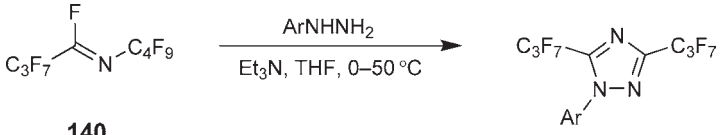


138a: R = Me
b: R = 4-MeC_6H_4

139a: R = Me, 60%
b: R = 4-MeC_6H_4, 87%

(43)

Fluorinated triazole derivatives have been prepared by a somewhat deceptive route that starts with imine perfluoro(5-aza-4-nonene) **140**: reaction of **140** with aromatic hydrazines gives 1,2,4-triazoles **141a–g** in good yields (Equation 44 and **Table 27**) <2001RJO1621, 2001ZOR1693>.



140

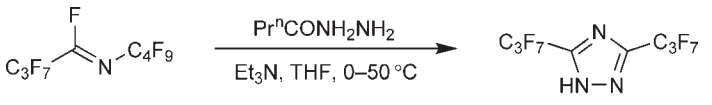
141a–g

(44)

Table 27 Reaction of perfluoro(5-aza-4-nonene) with aromatic hydrazines (Equation 44)

Entry	*Triazole* **141**	*Ar*	*Yield* (%)
1	**a**	C_6H_5	83
2	**b**	2-$NO_2C_6H_4$	83
3	**c**	2,4-$(NO_2)_2C_6H_3$	53
4	**d**	C_6F_5	90
5	**e**	4-HC_6F_4	72
6	**f**	4-BrC_6F_4	57
7	**g**	4-$CF_3C_6F_4$	84

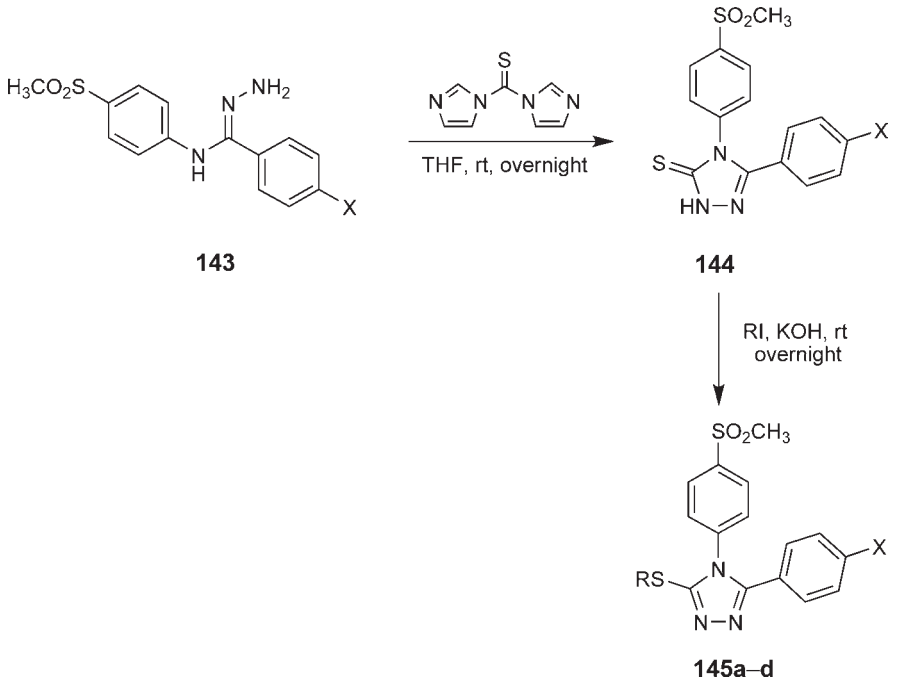
The reaction of perfluoro(5-aza-4-nonene) **140** with propionyl hydrazine under the conditions outlined above gives the parent 1*H*-1,2,4-triazole **142** in 42% yield via spontaneous loss of the propionyl group (Equation 45) <2001RJO1621, 2001ZOR1693>.



140 **142** (45)

5.02.9.3 Fragments Contributing Four Ring Atoms

Reaction of carbohydrazonamides **143** with 1,1′-thiocarbonyldiimidazole as the donor of the remaining carbon atom required in tetrahydrofuran gave the corresponding 1,2,4-triazol-5-thiones **144**, subsequent reaction of which with electrophiles gave 3-alkylthio-1,2,4-triazoles **145a–d** in reasonable overall yield (**Scheme 12**) (**Table 28**) <2006BMC2507>.



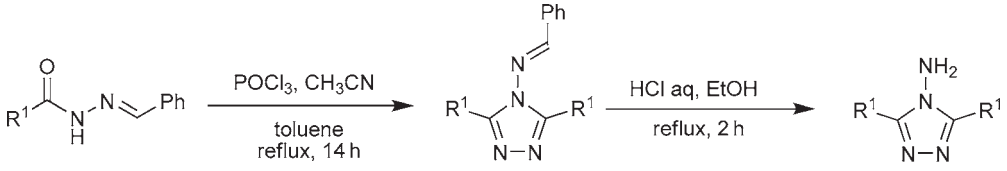
143 **144** **145a–d**

Scheme 12

Table 28 Reaction of carbohydrazonamides with 1,1'-thiocarbonyldiimidazole (**Scheme 12**)

Entry	*Triazole* **145**	*R*	*X*	*Yield* (%)
1	**a**	Me	F	41
2	**b**	Me	Me	44
3	**c**	Et	F	42
4	**d**	Et	Me	47

Reaction of arylidinehydrazides **146** with phosphorus oxychloride gave the corresponding 4-arylidineamino-1,2,4-triazol-5-thiones **147a–e**, subsequent hydrolysis of which gave 4-amino-1,2,4-triazoles **148a–e** (**Scheme 13** and **Table 29**) <2001CHE1107, 2001KGS1207>.

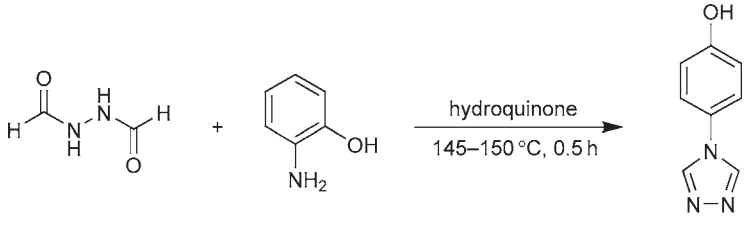


Scheme 13

Table 29 Reaction of arylidinehydrazides with phosphorus oxychloride (**Scheme 13**)

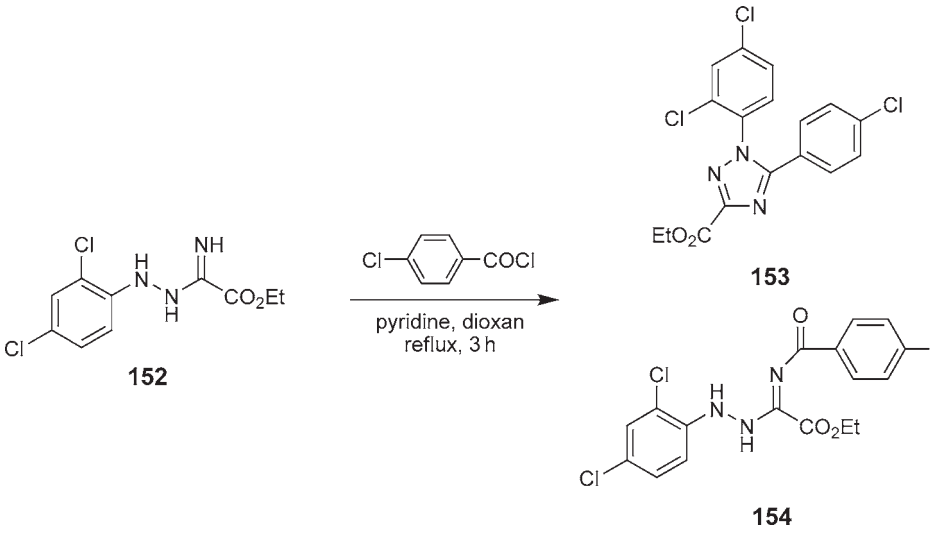
Entry	*R*	*Triazole* **147** (*Yield* (%))	*Triazole* **148** (*Yield* (%))
1	C_6H_5	**a** (83)	**a** (93)
2	3-MeC_6H_4	**b** (92)	**b** (91)
3	3-ClC_6H_4	**c** (78)	**c** (88)
4	3-$MeOC_6H_4$	**d** (90)	**d** (90)
5	3-$NO_2C_6H_4$	**e** (71)	**e** (86)

Fusion of diformylhydrazine **149** with aminophenols at high temperature yields the corresponding 4-aryl-1,2,4-triazoles. For example, diformylhydrazine **149** and 2-aminophenol **150** were heated in the prescence of hydroquinone to give triazole **151** in 46% yield after work-up (Equation 46) <2006RJC158, 2006ZOB161>.



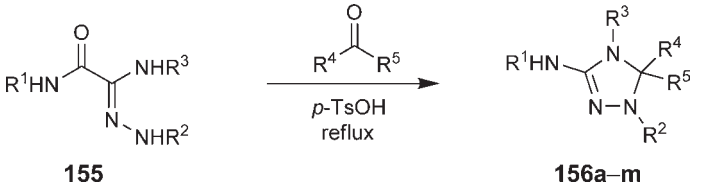
(46)

Treatment of the iminoacetate **152** with 4-chlorobenzoyl chloride in the presence of a base gave the desired ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazolecarboxylate **153** and the uncyclised ethyl 2-(4-chlorobenzamido)-2-(2-(2,4-dichlorophenyl)hydrazinyl)acetate **154** in 36% and 6% yield, respectively. The undesired compound **154** was subsequently converted to 1,2,4-triazole **153** in 93% yield by further treatment with pyridine (Equation 47) <2006EJM114>.



(47)

Arylhydrazonoacetamides **155** undergo acid-catalyzed condensation with ketones to give the corresponding 4,5-dihydro-1,2,4-triazoles **156a–m** in good yields (Equation 48 and **Table 30**) <2002T5317>.

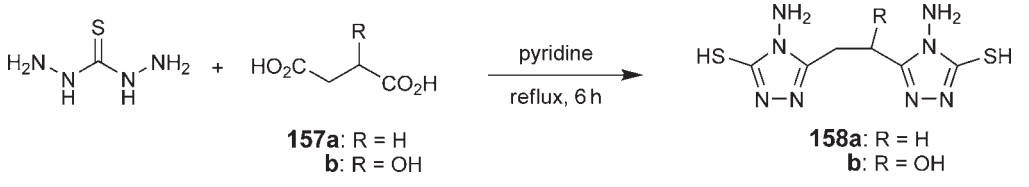


(48)

Table 30 Acid-catalyzed condensation of arylhydrazonoacetamides with ketones to give 4,5-dihydro-1,2,4-triazole derivatives (Equation 48)

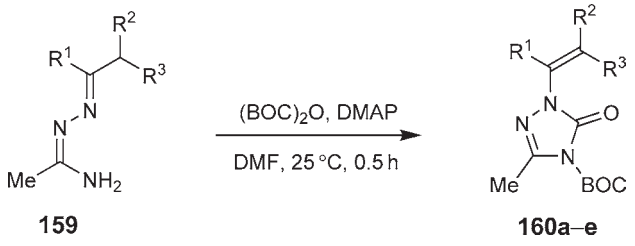
Entry	*Triazole* **156**	R^1	R^2	R^3	R^4	R^5	*Yield* (%)
1	**a**	Ph	Ph	H	Me	Me	26
2	**b**	Ph	Ph	Me	Me	Me	43
3	**c**	Ph	3-FC_6H_4	H	Me	Me	73
4	**d**	Ph	4-MeC_6H_4	Me	Me	Me	75
5	**e**	Ph	4-ClC_6H_4	Me	Me	Me	35
6	**f**	Ph	4-FC_6H_4	H	Me	Me	55
7	**g**	2-ClC_6H_4	Ph	H	Me	Me	60
8	**h**	2-ClC_6H_4	Ph	H	Me	Et	45
9	**i**	2-ClC_6H_4	Ph	4-ClC_6H_4	Me	Me	14
10	**j**	2-ClC_6H_4	3-ClC_6H_4	H	Me	Me	71
11	**k**	2-ClC_6H_4	3-ClC_6H_4	H	Me	Me	48
12	**l**	4-ClC_6H_4	3-ClC_6H_4	H	Me	Me	36
13	**m**	4-FC_6H_4	3-$MeCOC_6H_4$	H	Me	Me	50

Two 4-amino-3-mercapto1,2,4-triazole residues linked by a two-carbon bridge have been prepared by the reaction of thiocarbohydrazide with succinic acid **157a** or malic acid **157b** to give 1,2-bis-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethan-1-ol **158a** or 1,2-bis-(4-amino-5-mercapto-4*H*-1,2,4-triazol-3-yl)ethane **158b** in yields of 56% and 60%, respectively (Equation 49) <2006PS(181)2361>.



(49)

Aminoethylidenehydrazones **159** reacted with di-*tert*-butyl dicarbonate in the presence of 4-dimethylaminopyridine (DMAP) to give the corresponding 2*H*-1,2,4-triazol-3(4*H*)-ones **160a–e** (Equation 50 and **Table 31**) <1999JHC1235>.

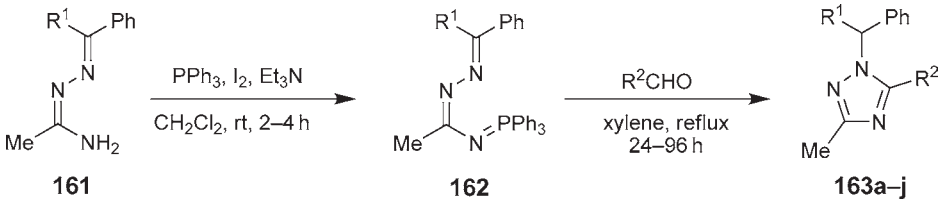


159 **160a–e** (50)

Table 31 Reaction of aminoethylidenehydrazones with di-*tert*-butyl dicarbonate to give 2*H*-1,2,4-triazol-3(4*H*)-one derivatives (Equation 50)

Entry	*Triazole* **160**	R^1	R^2	R^3	*Yield* (%)
1	**a**	Ph	H	H	34
2	**b**	Ph	Me	H	30
3	**c**	Ph	$-CH_2CH_2-$		28
4	**d**	2-Furyl	H	H	43
5	**e**	2-Thienyl	H	H	40

Aminoethylidenehydrazones **161** react with triphenyl phosphine to give the azinoiminophosphorane intermediates **162** which cyclize via an aza-Wittig reaction with benzaldehydes to give the corresponding 1,2,4-triazoles **163a–j** (**Scheme 14** and **Table 32**) <2002JHC845>.



161 **162** **163a–j**

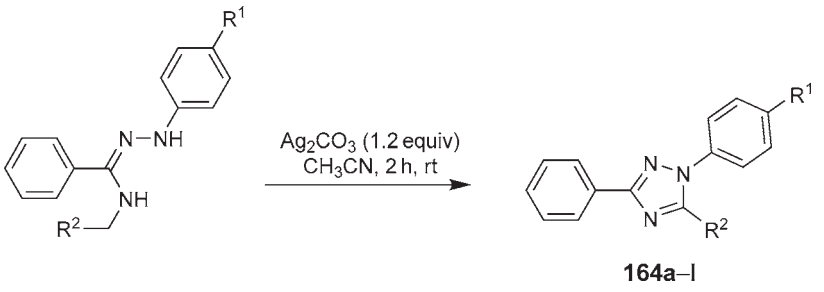
Scheme 14

Table 32 Aza-Wittig cyclization of azinoiminophosphorane intermediates with benzaldehydes to give 1,2,4-triazoles derivatives (**Scheme 14**)

Entry	*Triazole* **163**	R^1	R^2	*Yield* (%)
1	**a**	Ph	Ph	82
2	**b**	Ph	4-ClC_6H_4	67
3	**c**	Ph	4-$NO_2C_6H_4$	43
4	**d**	Ph	4-MeC_6H_4	59
5	**e**	Ph	4-$MeOC_6H_4$	43
6	**f**	Me	Ph	77
7	**g**	Me	4-ClC_6H_4	70
8	**h**	Me	4-$NO_2C_6H_4$	44
9	**i**	Me	4-MeC_6H_4	53
10	**j**	Me	4-$MeOC_6H_4$	47

5.02.9.4 Fragments Contributing Five Ring Atoms

Recent studies toward the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles from amidrazones have described the use of various oxidizing agents, including Ag_2CO_3 and the Dess–Martin periodinane, to accomplish the ring-closing reaction and deliver the corresponding 1,2,4-triazoles **164a–l** in good yield (Equation 51 and **Table 33**) <2000T8071, 2001T9677, 2002TL8925>.

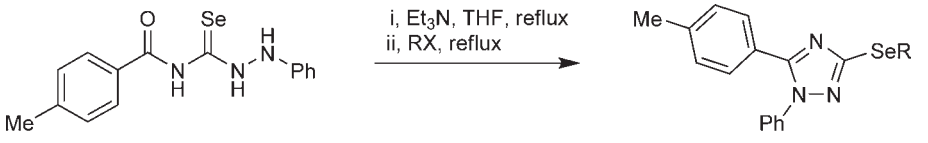


164a–l (51)

Table 33 Oxidation of amidrazones to give 1,3,5-trisubstituted 1,2,4-triazole derivatives (Equation 51)

Entry	R^1	R^2	*Triazole* **164**	*Yield* (%)
1	H	Ph	**a**	69
2	H	$PhCH_2$	**b**	62
3	H	Ph-CH-Ph	**c**	5
4	H	Me-CH-Me	**d**	40
5	H	$H_2C{=}CH$	**e**	51
6	H	3-Pyr	**f**	47
7	H	1-Mor-CH_2	**g**	37
8	H	$MeO_2CCH_2CH_2$	**h**	73
9	MeO	Ph	**i**	66
10	MeO	$PhCH_2$	**j**	48
11	NO_2	Ph	**k**	78
12	NO_2	$PhCH_2$	**l**	60

The selenosemicarbazides **165** were cyclized to yield the corresponding 3-alkylseleno-1*H*-1,2,4-triazoles **166a–g** (Equation 52 and **Table 34**) <2006H(68)1191>.

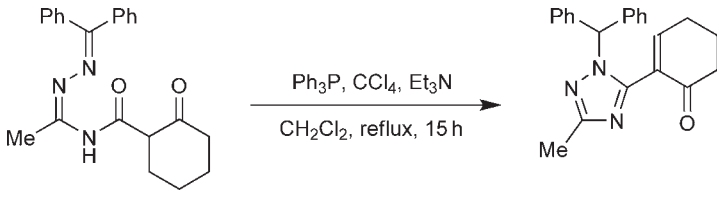


165 **166a–g** (52)

Table 34 Cyclization of selenosemicarbazides to give 3-alkylseleno-1*H*-1,2,4-triazole derivatives (Equation 52)

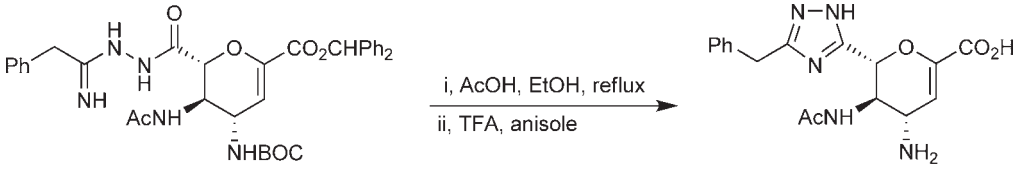
Entry	*RX*	*Triazole* **166**	*Yield* (%)
1	MeI	**a**	70
2	EtI	**b**	86
3	Pr^nI	**c**	71
4	Pr^nBr	**c**	35
5	Pr^iI	**d**	61
6	cHexI	**e**	55
7	BnBr	**f**	61
8	$CH_2{=}CHCH_2Br$	**g**	59

Cyclization of the aminomethylhydrazone derivative **167** in the presence of base gave the 1,3,5-trisubstituted 1,2,4-triazole **168** in 50% yield; a mechanism for the formation of triazole **168** also accounts for the formation of accompanying di- and tricyclic by-products (Equation 53) <1997S1461>.



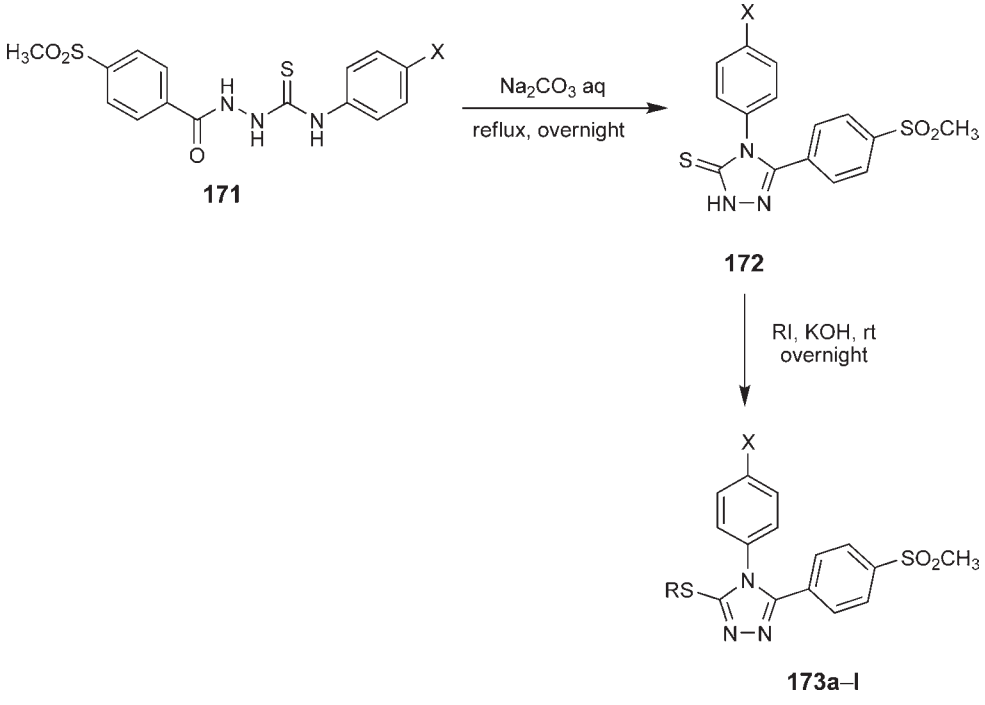
167 **168** (53)

Complex imide **169** was prepared during an investigation into the preparation of analogues of the antiviral compound zanamivir: Cyclization of imide **169** in acidic media, followed by treatment with trifluoroacetic acid, gave the corresponding 1,2,4-triazole **170** in a yield that was reported to be high (Equation 54) <1997BML2239>.



169 **170** (54)

Cyclization of aroylsemicarbazides **171** in the presence of aqueous sodium carbonate gave the corresponding 1,2,4-triazol-5-thiones **172**, subsequent reaction of which with electrophiles gave 3-alkylthio-1,2,4-triazoles **173a–l** in high overall yield (**Scheme 15** and **Table 35**) <2006BMC2507>.



Scheme 15

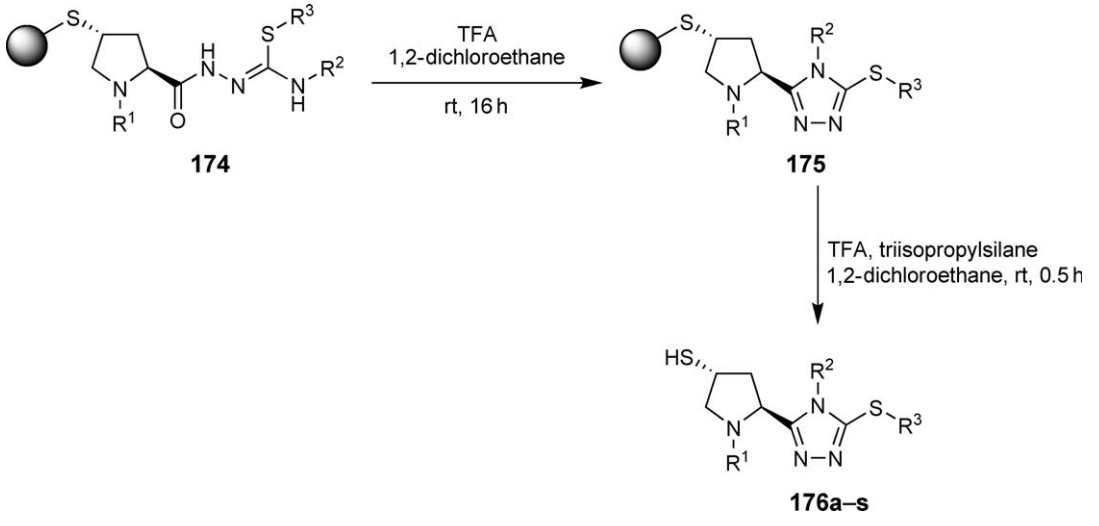
Table 35 Cyclization of aroylsemicarbazides and reaction of the corresponding 1,2,4-triazol-5-thiones with electrophiles to give 3-alkylthio-1,2,4-triazole derivatives (**Scheme 15**)

Entry	*Triazole* **173**	*R*	*X*	*Yield* (%)
1	**a**	Me	H	81
2	**b**	Me	F	85
3	**c**	Me	Cl	73
4	**d**	Me	Br	72
5	**e**	Me	OMe	65
6	**f**	Me	Me	74
7	**g**	Et	H	83
8	**h**	Et	F	79
9	**i**	Et	Cl	78
10	**j**	Et	Br	75
11	**k**	Et	OMe	68
12	**l**	Et	Me	68

1,2,4-Triazoles bearing a pyrrole substituent in position 3 have been prepared on a solid support using mild conditions by acid-catalyzed cyclisation of intermediate **174** and subsequent cleavage of the supported 1,2,4-triazoles **175** to give target compounds **176a–s**. The overall yields reported following purification are modest to low but do include all steps leading up to the final cyclization and cleavage of the triazole, which one would expect to be reasonably efficient (**Scheme 16** and **Table 36**) <2002BML1727>.

4-Substituted 3-thio-1,2,4-triazoles were prepared by the base-catalyzed cyclization of acylsemicarbazides **177** to give the corresponding 1,2,4-triazoles **178a–g** in excellent yields (Equation 55 and **Table 37**) <2004EJM535>.

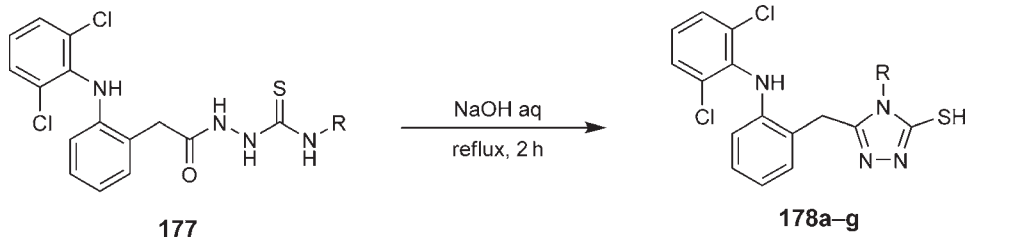
The reaction of hydriodobenzimidohydrazide with D-glucose, D-galactose, and D-arabinose in aqueous media has been studied with the goal of preparing *N*-glycosides of 1,2,4-triazoles. The reaction with D-glucose yielded the pyranosyl nucleoside **179**, whereas reaction with D-galactose gave the unexpected furanosyl nucleoside **180**; the outcome of the reactions seems to be dependent upon the carbohydrate and not the conditions employed. However, reaction of hydriodobenzimidohydrazide **181** with D-arabinose **182** gave intermediate compound **183** which was reacted further with ethanoic anhydride in the presence of pyridine to give nucleoside **184**. Under the conditions employed the triazole ring forms first, allowing attack of ethanoate at C-1^1 to give the favoured D-manno configuration. The outcomes of these reactions were confirmed by NMR spectroscopy, mass spectrometry, and X-ray crystallography (Equation 56) <2000J(P1)829>.



Scheme 16

Table 36 Solid-supported synthesis of 1,2,4-triazole derivatives (**Scheme 16**)

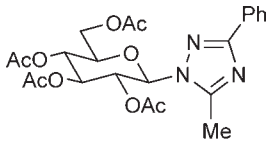
Entry	*Triazole* **176**	R^1	R^2	R^3	*Yield* (%)
1	**a**	2-NaphthylSO$_2$	Ph	Me	24
2	**b**	4-Pr^{n}C$_6$H$_4$SO$_2$	Ph	Me	23
3	**c**	4-ClC$_6$H$_4$SO$_2$	Ph	Me	9
4	**d**	4-CF$_3$C$_6$H$_4$SO$_2$	Ph	Me	42
5	**e**	Bu^{n}OCO	Ph	Me	39
6	**f**	4-MeC$_6$H$_4$SO$_2$	Ph	Me	5
7	**g**	4-FC$_6$H$_4$SO$_2$	Ph	Me	21
8	**h**	MeSO$_2$	Ph	Me	15
9	**i**	4-FC$_6$H$_4$NHCO	Ph	Me	17
11	**k**	(Me)$_2$NSO$_2$	Ph	Me	28
12	**l**	2-NaphthylSO$_2$	Ph	Pr^n	44
13	**m**	2-NaphthylSO$_2$	Ph		45
14	**n**	2-NaphthylSO$_2$	Ph	Bu^i	33
15	**o**	2-NaphthylSO$_2$	4-FC$_6$H$_4$CH$_2$	Me	18
16	**p**	2-NaphthylSO$_2$	2,3,5,6-F$_4$C$_6$H	Me	8
17	**q**	2-NaphthylSO$_2$	4-FC$_6$H$_4$	Me	10
18	**r**	2-NaphthylSO$_2$	3-Cl-4-FC$_6$H$_3$	Me	7
19	**s**	2-NaphthylSO$_2$	Me	Me	10



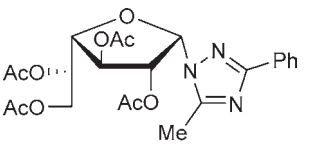
177 **178a–g** (55)

Table 37 Cyclization of acylsemicarbazides to give 4-substituted 3-thio-1,2,4-triazole derivatives (Equation 55)

Entry	*Triazole* **178**	*R*	*Yield* (%)
1	**a**	Bu^n	74
2	**b**	Cyclohexyl	82
3	**c**	4-ClC$_6$H$_4$	80
4	**d**	4-FC$_6$H$_4$	78
5	**e**	4-MeC$_6$H$_4$	68
6	**f**	2-MeC$_6$H$_4$	65
7	**g**	2-MeOC$_6$H$_4$	72



179



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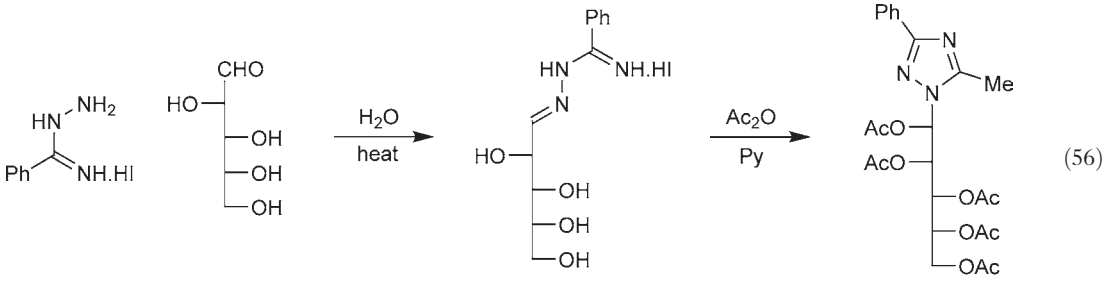
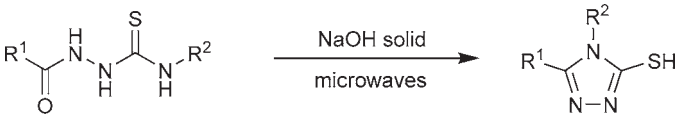


181 182 183 184

(56)

Cyclization of semicarbazide derivatives **185** was achieved using microwave irradiation in the presence of sodium hydroxide for 2–4 min to give the corresponding 3-mercapto-1,2,4-triazoles **186a–f** in high yields (Equation 57 and **Table 38**) <2006PS(181)1913>.



185 186a–f

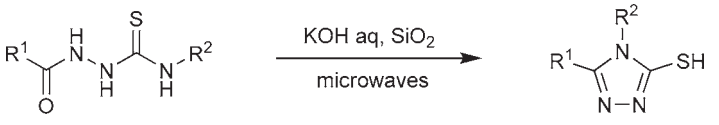
(57)

Table 38 Microwave-assisted cyclization of semicarbazides to give 3-mercapto-1,2,4-triazole derivatives (Equation 57)

Entry	*Triazole* **186**	R^1	R^2	*Yield* (%)
1	**a**	2-Pyridyl	$C_6H_5CH_2$	85
2	**b**	3-Pyridyl	$C_6H_5CH_2$	75
3	**c**	4-Pyridyl	$C_6H_5CH_2$	75
4	**d**	2-Pyridyl	$2\text{-}MeC_6H_4$	72
5	**e**	3-Pyridyl	$2\text{-}MeC_6H_4$	95
6	**f**	4-Pyridyl	$2\text{-}MeC_6H_4$	86

An alternative procedure, again using microwave irradiation but in the presence of aqueous potassium hydroxide and silica, caused cyclization of semicarbazide derivatives **185** to give 3-mercapto-1,2,4-triazoles **186a–f** in high yields (Equation 58 and **Table 39**) <2006PS(181)1839>.

Dimethyl succinate derivatives **187** eliminate a molecule of methyl ethanoate upon heating to give 1,2,4-triazoles **188a–e** in reasonable yield. The reaction also produces the corresponding triazines but these are readily separated from the desired triazoles (Equation 59 and **Table 40**) <2001EJM93>.

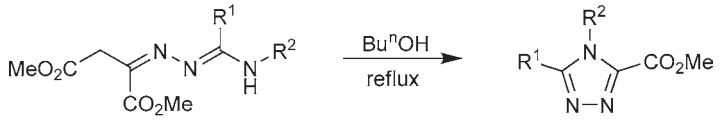


185 186a–f

(58)

Table 39 Microwave-assisted cyclization of semicarbazides to give 3-mercapto-1,2,4-triazole derivatives (Equation 57)

Entry	*Triazole* **186**	R^1	R^2	*Yield* (%)
1	**a**	C_6H_5	C_6H_5	82
2	**b**	4-ClC_6H_4	C_6H_5	80
3	**c**	C_6H_5	Me	70
4	**d**	4-ClC_6H_4	Me	75
5	**e**	4-$NO_2C_6H_4$	C_6H_5	85
6	**f**	Me	C_6H_5	70

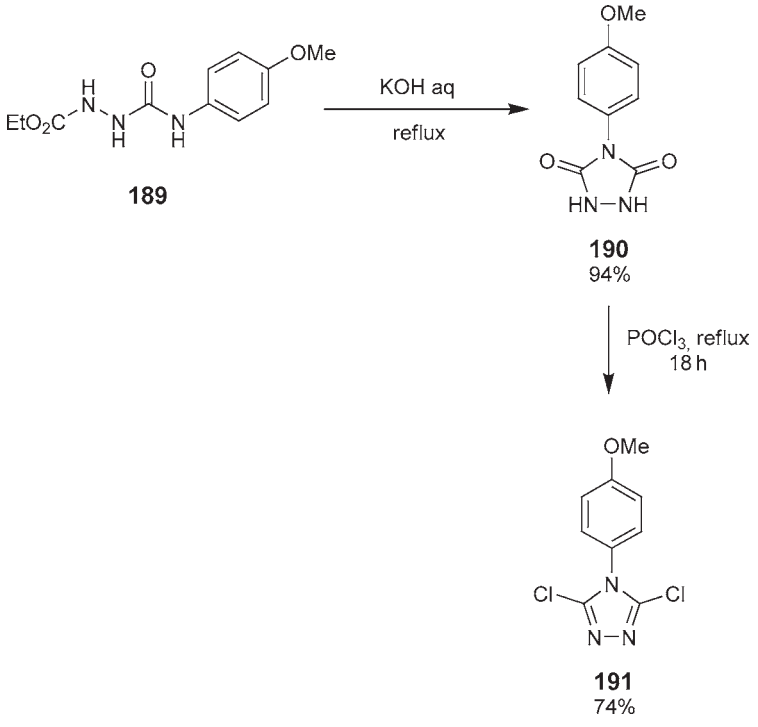


187 **188a–e** (59)

Table 40 Reaction of dimethyl succinates to give 1,2,4-triazole derivatives (Equation 59)

Entry	*Triazole* **188**	R^1	R^2	*Yield* (%)
1	**a**	C_6H_5	C_6H_5	38
2	**b**	C_6H_5	4-MeC_6H_4	32
3	**c**	2-Pyridyl	C_6H_5	35
4	**d**	2-Pyridyl	4-MeC_6H_4	30
5	**e**	2-Pyridyl	4-$NO_2C_6H_4$	37

Base-catalyzed cyclization of semicarbazide **189** gave the triazolidine 3,5-dione **190**, subsequent treatment of which with phosphorus oxychloride gave 3,5-dichloro-4-aryl-1,2,4-triazole **191** (**Scheme 17**). <2006T2677>.



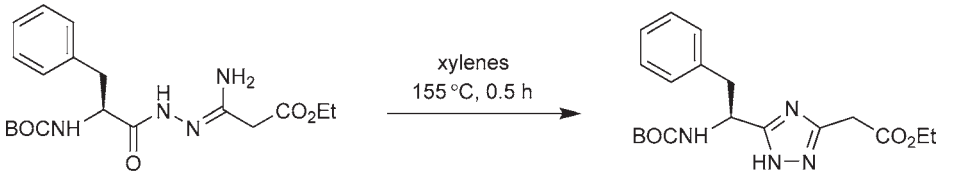
189

190
94%

191
74%

Scheme 17

Cyclization of racemic acylimidrazone **192**, prepared from the corresponding acylhydrazone of phenylalanine, gave the protected amino acid **193** in an overall yield of 57% (Equation 60) <1999JME4331>.

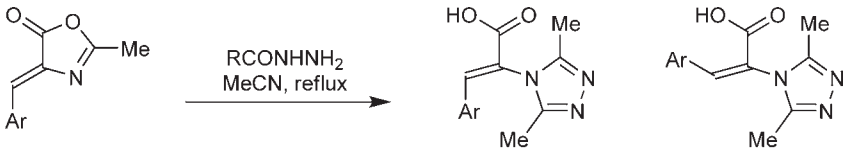


192 **193** (60)

5.02.10 Ring Syntheses by Transformation of Another Ring

5.02.10.1 (4*H*)-1,3-Oxalones

(*Z*)-4-Arylmethylene-5(4*H*)-oxazolones **194** undergo ring opening and subsequent closure to yield substituted 1,2,4-triazoles **195a–g** and **196a–g** when reacted with hydrazide derivatives (Equation 61 and **Table 41**). The mechanism of the reaction was elucidated and confirmed using computational methods <2004H(63)1273>.



194 **195a–g** **196a–g** (61)

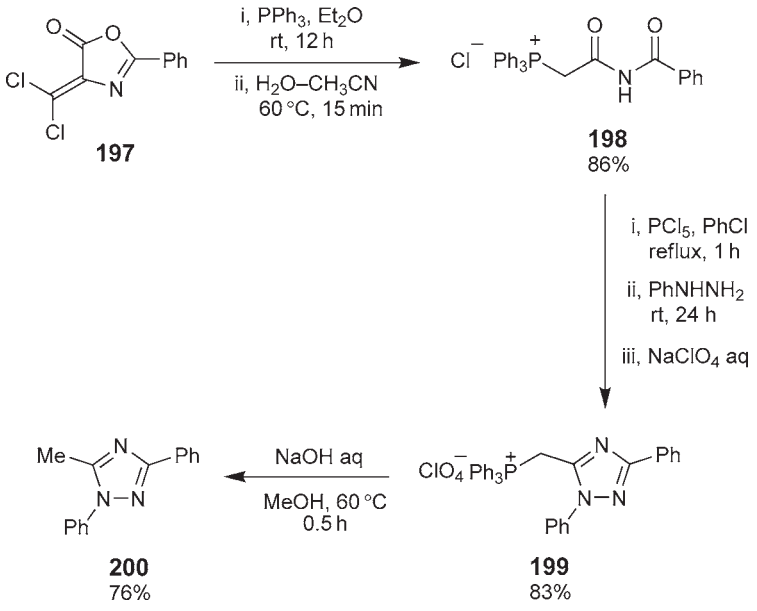
Table 41 Reaction of (*Z*)-4-arylmethylene-5(4*H*)-oxazolones with hydrazides to give substituted 1,2,4-triazole derivatives (Equation 61)

Entry	*Oxazolone* **194**	*R*	*Yield* **195***a–g* (%)	*Yield* **196***a–g* (%)
1	**a**	Me	>99	<1
2	**b**	Me	92	8
3	**b**	Ph	76	19
4	**b**	4-$MeOC_6H_4$	68	23
5	**b**	4-$MeOC_6H_4$	>99	<1
6	**b**	$PhCH_2$	83	17
7	**b**	H	>99	<1

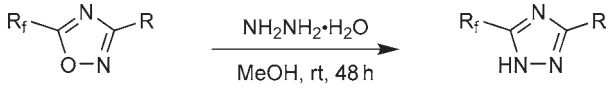
(*Z*)-4-dichloromethylene-5(4*H*)-oxazolones also undergo a ring transformation subsequent to sequential treatment with triphenylphosphine, phophorus pentachloride and hydrazines: for example, reaction of oxazolone **197** with triphenylphosphine gives the intermediate triphenylphosphonium chloride salt **198**. Reaction of salt **198** with phosphorus pentachloride, followed by phenylhydrazine and sodium perchlorate yielded the perchlorate salt **199**, basic hydrolysis of which gave the corresponding 1,2,4-triazole **200** (**Scheme 18**) <2004RJC1328, 2004ZOB1434>.

5.02.10.2 1,2,4-Oxadiazoles

Reaction of the fluorinated 1,2,4-oxadiazoles **201** with hydrazine gave the corresponding 1,2,4-triazoles **202a–d** in good yield via a ring-opening rearrangement of the oxadiazole (Equation 62 and **Table 42**) <2003JOC605>.



Scheme 18

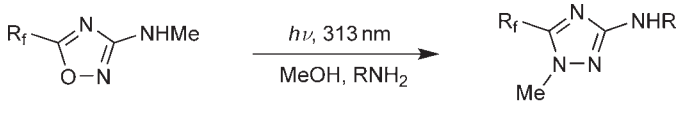


(62)

Table 42 Reaction of fluorinated 1,2,4-oxadiazoles with hydrazine to give 1,2,4-triazole derivatives (Equation 62)

Entry	*Oxadiazole* **201**	*R*	R_f	*Triazole* **202**	*Yield* (%)
1	**a**	Ph	CF_3	**a**	44
2	**b**	Ph	C_3F_7	**b**	58
3	**c**	Ph	C_7F_{15}	**c**	88
4	**d**	$C_{11}H_{23}$	CF_3	**d**	68

The photochemical rearrangement of 1,2,4-oxadiazoles to give substituted 1,2,4-triazoles has been employed in the synthesis of a wide range of fluorinated triazole derivatives. 1,2,4-Oxadiazoles **203a** and **203b** bearing perfluoroalkyl substituents in the 5-position were irradiated at 313 nm in the presence of an amine to give the corresponding 1,2,4-triazoles **204a–e** in modest yield (Equation 63 and **Table 43**) <2004JOC4108>.

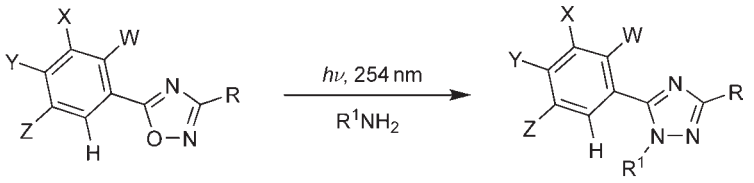


(63)

Table 43 Photochemical rearrangement of 1,2,4-oxadiazoles to give substituted 1,2,4-triazole derivatives (Equation 63)

Entry	*Oxadiazole* **203**	*R*	R_f	*Triazole* **204**	*Yield* (%)
1	**a**	Me	C_7F_{13}	**a**	25
2	**b**	Me	Ph	**b**	27
3	**a**	H	Ph	**c**	24
4	**a**	Pr^n	Me	**d**	21
5	**a**	$(CH_2)_4$	Me	**e**	23

Irradiation of 1,2,4-oxadiazoles **205** bearing fluorinated substituents in the 3- or 5-positions in the presence of an amine delivered the corresponding 1,2,4-triazoles **206a–e** and **207a–e** via a photochemical rearrangement. Several other competing reactions served to divert some of the reactive intermediates and, hence, yields of the fluorinated triazoles were modest (Equation 64 and **Table 44**) <2005H(65)387>.



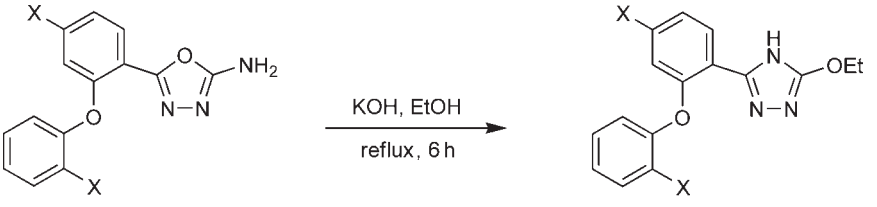
205 **206a–e**: R^1 = Me; **207a–e**: R^1 = Pr^n (64)

Table 44 Photochemical rearrangement of fluorinated 1,2,4-oxadiazoles to give substituted 1,2,4-triazole derivatives (Equation 64)

Entry	*R*	*W*	*X*	*Y*	*Z*	R^1	*Triazole*	*Yield* (%)
1	C_6H_5	H	H	H	H	Me	**206a**	35
2	Ph	F	F	F	F	Me	**206b**	37
3	Ph	F	F	F	H	Me	**206c**	45
4	Me	F	F	F	F	Me	**206d**	35
5	Me	F	F	F	H	Me	**206e**	46
6	C_6H_5	H	H	H	H	Pr^n	**207a**	34
7	Ph	F	F	F	F	Pr^n	**207b**	36
8	Ph	F	F	F	H	Pr^n	**207c**	43
9	Me	F	F	F	F	Pr^n	**207d**	34
10	Me	F	F	F	H	Pr^n	**207e**	49

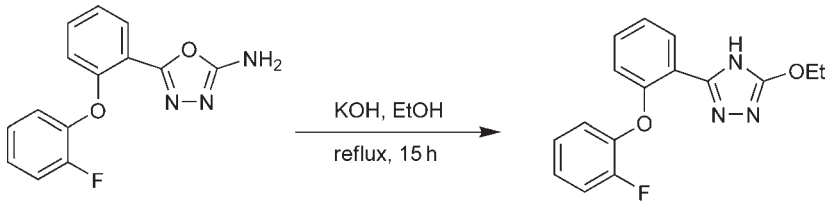
5.02.10.3 1,3,4-Oxadiazoles

The rearrangement of 1,3,4-oxadiazoles **208a** and **208b** in the presence of a base was employed in the synthesis of the phenoxyphenyl 1,2,4-triazoles **209a** and **209b** (Equation 65) <2003BMC769>.



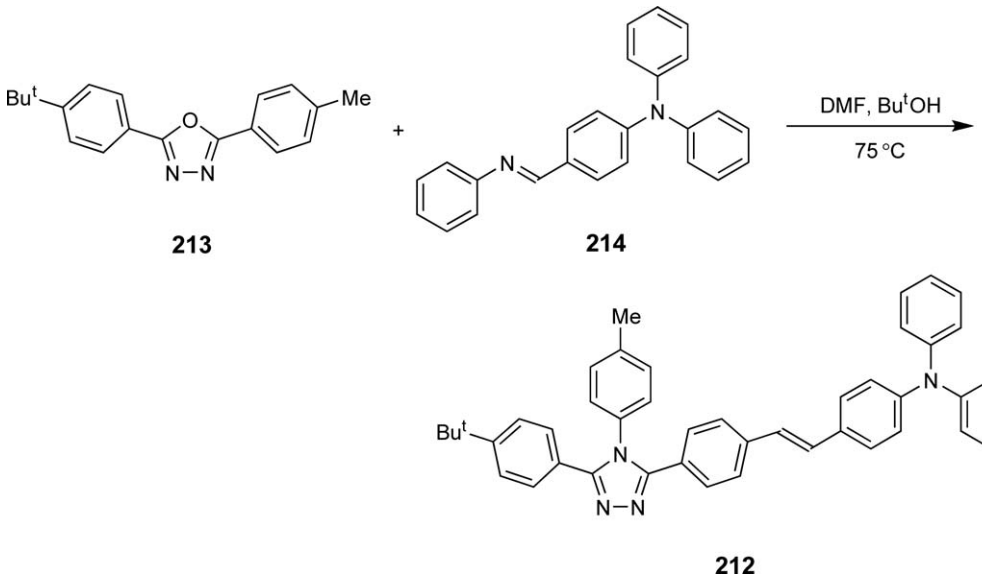
208a: X = H; **b**: X = Cl **209a**: X = H; **b**: X = Cl (65)

In a similar fashion, 1,3,4-oxadiazole **210** was transformed into 1,3,4-triazole **211** (Equation 66) <2004BML6057>.



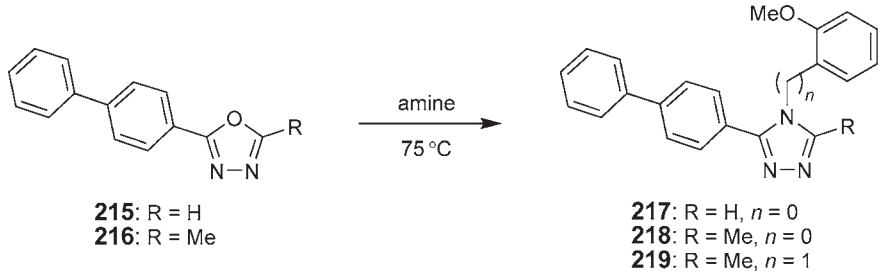
210 **211** (66)

The Siegirst reaction was deployed in the synthesis of highly functionalized triazole **212**: 2-(*p-tert*-butylphenyl)-5-(*p*-tolyl)-1,3,4-oxadiazole **213** was reacted with Schiff's base **214** in the presence of potassium *tert*-butoxide to give 1,2,4-triazole **212** in a yield of 90% after recrystallization (Equation 67) <2004MI209>.



(67)

Reaction of 1,3,4-oxadiazoles **215** and **216** with either 2-methoxyphenylamine or 2-methoxybenzylamine with heating delivered the corresponding 1,2,4-triazoles **217–219** in low yields (Equation 68 and **Table 45**) <2002BMC1905>.



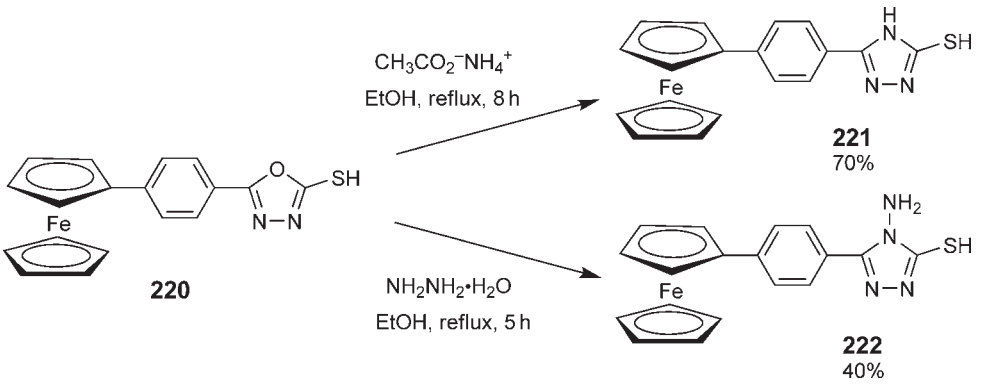
(68)

Table 45 Reaction of 1,3,4-oxadiazoles with 2-methoxyarylamines (Equation 68)

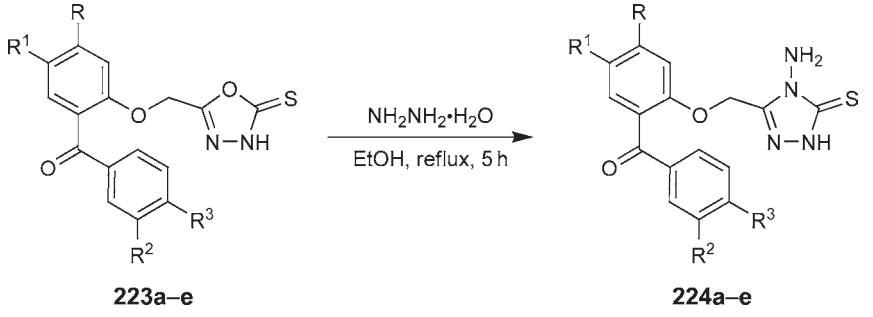
Entry	*Oxadiazole*	*R*	*Amine*	*Triazole*	*Yield* (%)
1	**215**	H	2-Methoxyphenylamine	**217**	31
2	**216**	Me	2-Methoxyphenylamine	**218**	12
3	**216**	Me	2-Methoxybenzylamine	**219**	28

1,3,4-Oxadiazole **220** bearing a ferrocenyl substituent was reacted with ammonium ethanoate and hydrazine to yield the corresponding 1,2,4-triazoles **221** and **222** in reasonable yield (**Scheme 19**) <2003JOM(675)1>.

This time using hydrazine hydrate as the amine donor, reaction with 1,3,4-oxadiazole-2-(3*H*)-thiones **223a–e** under heating in ethanol yielded the corresponding 1,2,4-triazole-2-(3*H*)thiones **224a–e** (Equation 69 and **Table 46**) <2005EJM1156>.



Scheme 19

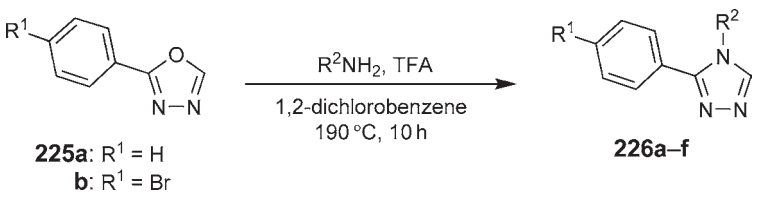


(69)

Table 46 Reaction of 1,3,4-oxadiazole-2-(3*H*)-thiones with hydrazine hydrate (Equation 69)

Entry	*Oxadiazole* **223**	*R*	R^1	R^2	R^3	*Triazole* **224**	*Yield* (%)
1	**a**	H	Me	Cl	H	**a**	75
2	**b**	H	Cl	H	H	**b**	
3	**c**	Br	H	H	H	**c**	
4	**d**	H	Me	H	OMe	**e**	
5	**e**	H	Me	H	Me	**f**	

Reaction of 2-aryl-1,3,4-oxadiazoles **225a** and **225b** with arylamines in the presence of trifluoroacetic acid gave the corresponding 3,4-diaryl-1,2,4-triazoles **226a–f** in good yields (Equation 70 and **Table 47**) <2005CHE866, 2005KGS1026>.



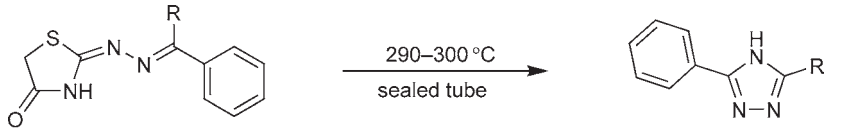
(70)

Table 47 Reaction of 2-aryl-1,3,4-oxadiazoles with arylamines to give 3,4-diaryl-1,2,4-triazoles (Equation 70)

Entry	*Triazole* **226**	R^1	R^2	*Yield* (%)
1	**a**	H	C_6H_5	90
2	**b**	H	4-BrC_6H_4	60
3	**c**	H	4-MeC_6H_4	57
4	**d**	H	1-Naphthyl	36
5	**e**	Br	C_6H_5	52
6	**f**	Br	4-BrC_6H_4	77

5.02.10.4 5(4*H*)-Thiazolones

A novel approach toward the synthesis of 1,2,4-triazoles via a thermally induced fragmentmentation reaction of 4(5)-thiazolone derivatives **227a** and **227b** and subsequent rearrangement of the resulting diradical intermediates yielded mono- and disubstituted triazoles **228a** and **228b** in moderate yields, considering the harsh conditions employed (Equation 71) <1998JPY1>.



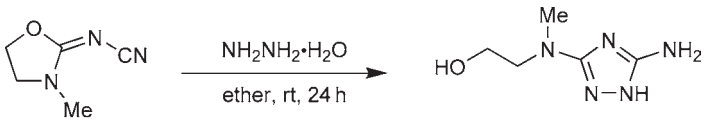
227a: R = Me
b: R = Ph

228a: R = Me, 28%
b: R = Ph, 25%

(71)

5.02.10.5 Oxazolidinones

Reaction of iminooxazolidinone **229** with hydrazine gave the 1,2,4-triazole **230** in an overall yield of 62% (Equation 72) <2002JHC319>.



229 **230**

(72)

5.02.11 Synthesis of Particular classes of Compounds and Critical Comparison of the Various Routes Available

1,2,4-Triazoles can be accessed by a number of well-established synthetic routes, and it is true that the majority of reports encompassed by the time frame of this review employ these methods with little variation; in general, the starting materials for these routes are accessible, the conditions required are accommodating and good yields result. The individual merits of these routes have been covered in CHEC(1984) and CHEC-II(1996) <1984CHEC(5)733, 1996CHEC-II(4)127, 2004SOS(13)603>.

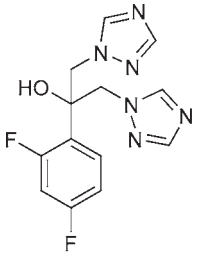
Perhaps the most important issues to consider now are the application of novel methodologies, molecular diversity, and synthetic convenience. There have been several reports of novel, one-pot procedures for the preparation of 1,2,4-triazoles with diverse structures. Synthesis of 1,2,4-triazoles on polymeric supports, in both solution and solid phase, represents a step toward the combinatorial synthesis of these heterocycles. It is these novel applications of technology to organic synthesis that perhaps lead the way in 1,2,4-triazole chemistry.

5.02.12 Important Compounds and Applications

Compounds containing a 1,2,4-triazole moiety find use in a wide range of applications and substituted 1,2,4-triazoles are becoming more prevalent in functional materials that are at the cutting edge of new technology: The biological activity of 1,2,4-triazole derivatives is well documented and important discoveries continue to be made in this area, though the electron donor and coordinating ability of 1,2,4-triazoles has also seen an increase in their use as ligands, functional polymers, and in industrial coatings. CHEC-II(1996) highlights many cases where 1,2,4-triazoles have become ubiquitous; some of the more significant, recent developments are detailed below, together with a selection of supporting references.

5.02.12.1 Pharmaceuticals

A wide variety of antifungal agents have been further developed that contain a 1,2,4-triazole moiety; fluconazole **231** is probably the most widely recognized with voriconazole **232**, ketoconazole **233**, itraconazole **234**, and posaconazole **235** being developed subsequently <2002MI550, 2003MI272, 2005MI1553, 2005MI91, 2005MI1215, 2005JIB1558, 2005MI775, 2006MI483, 2006MI579>.



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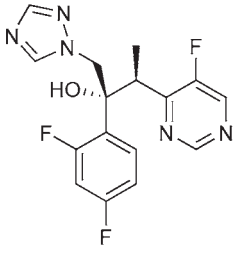

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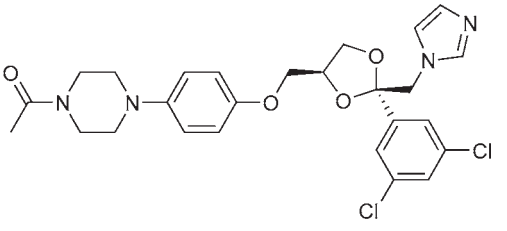

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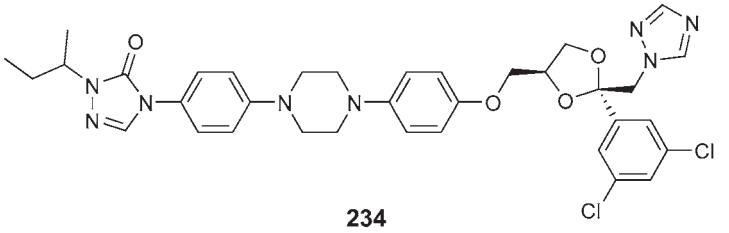

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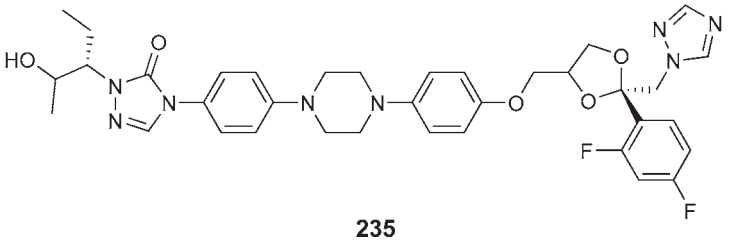
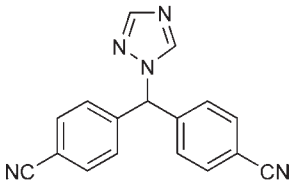


235

The link between estrogen levels and the development of breast cancer is well established and several drugs have been developed to regulate estrogen synthesis by inhibiting the enzyme aromatase; aromatase catalyzes the final step in steroid biosynthesis and is thus an excellent target. Several nonsteroidal aromatase inhibitors have been developed, including letrozole **236** and anastrozole **237** <2002MI61>.



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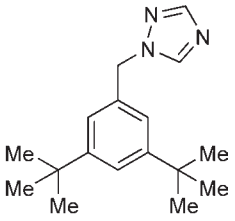
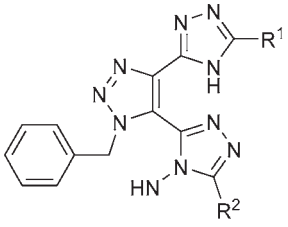


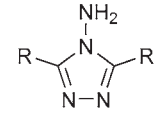
237

5.02.12.2 Corrosion Inhibitors

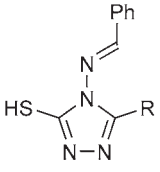
In addition to the parent compound, a wide variety of 1,2,4-triazoles have been studied and employed as inhibitors of the corrosion of metals and alloys under a variety of conditions; these include 'simple' amino- and aryl-substituted triazoles and more complex compounds, **238–241** for example. Literature reports are usually supported by comprehensive characterization of the molecules and systems, typically including electrochemical studies. As yet, there appears not to have been any systematic review of the field <2000MI187, 2002MI63, 1999MI237, 2000MI194, 2002MI1, 2004MI214, 1998MI391, 1999MI789, 2000MI773, 2002MI573, 2002MI997, 2003MI309, 2003MI371, 2004MI2455, 2004MI2701, 2005MI151, 2005MI663, 2005MI3368, 2006MI608, 2002MI4339, 2004MI811, 2004MI2771, 2005MI47, 2006MI3957, 2001MI283, 2002MCH489, 2002MCH655, 2002MI18, 2005MI269, 2003MAL4547, 2000MI207, 2003MI63, 2004MI149, 2004MI322>.



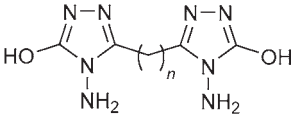
238a: $R^1 = R^2 = H$
b: R^1 = Me, R^2 = SMe



239a: R = Ph
b: R = 3-C_6H_4Me
c: R = 2-pyridyl
d: R = 3-pyridyl
e: R = 4-pyridyl
f: R = 2-thiophenyl



240a: R = H
b: R = Me
c: R = Et
d: R = Ph



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5.02.12.3 Macrocycles and Polyheterocycles

Triazole residues continue to be incorporated into a variety of heteromacrocyclic ligands <1995JOC6097, 1995SL757, 1996SL285, 2002S260, 1999SC1711, 2000T885, 2004T1541, 1998TL1067>.

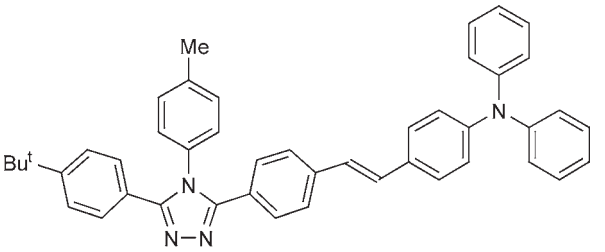
1,2,4-Triazoles have also been incorporated into metallo phthalocyanines and the photophysical properties of the nitrogen-rich heterocycles elucidated <2001JOC89>.

5.02.12.4 Functional Materials

A range of ionic liquids containing a 1,2,4-triazolium moiety has been developed and a variety of processes investigated using such compounds <2002JOC9340, 2006CEJ4630, 2005EJI2573, 2005CC868>.

Despite early, unsuccessful attempts to further expand the range of dendrimeric compounds that contain heterocyclic residues, 1,2,4-triazoles were eventually incorporated into large dendrimeric arrays <2002ARK17, 2002JOM(660)50, 2006T2677>.

Light emitting displays are ubiquitous in electronic devices. Organic polymers have been investigated for use in these devices, including copolymers containing 1,2,4-triazole moieties; such polymers were found to fluoresce at different wavelengths whether they were in solution or in the solid state <2003SM(137)1113>. Thin solid films containing triazole derivative **212** are of interest in the development of organic light emitters; **212** luminescence strongly at 484 nm when a low voltage is applied <2004MI209>.



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Biographical Sketch

Originally from the Black Country, Dr. Anthony D.M. Curtis spent his formative years in Redditch in rural north Worcestershire. He left for the city in 1984 and undertook his undergraduate and postgraduate studies, under the supervision of Richard Stoodley, at the University of Manchester, Faculty of Technology (UMIST), graduating with a PhD in 1990. Tony then moved to the USA to work as a postdoctoral fellow in the laboratory of T. Ross Kelly at Boston College, before returning to the UK in 1993 to take up a Lectureship at Keele University. Tony is now Director of Undergraduate Studies (Pharmaceutical Science) in the Keele School of Pharmacy, a role that enables him to work at the interface between the Physical and Life Sciences, and maintain his research interests in organic and medicinal chemistry. Aside from his family, Tony's other interests include rugby union and steam railways.

Born and raised in Stoke-on-Trent, Dr. Nicola Jennings undertook her undergraduate degree in biological and medicinal chemistry and biochemistry at Keele University. Remaining at Keele, under the supervision of Prof. Jim Howell, she graduated with a PhD in organometallic chemistry in 2007. Nicola has remained at Keele University and her position of laboratory assistant enables her to share her expertise with undergraduate students on chemistry, forensic science, and pharmacy undergraduate programmes, and maintain her interest in organic synthesis and analysis. Nicola's other interests include her family, interior design, and classic minis.

5.03
1,2,3-Oxadiazoles

W. Fraser
Aston University, Birmingham, UK

5.03.1 Introduction

"Can 1,2,3-Oxadiazole be Stable?" <1985AGE713>. *Ab initio* calculations suggest that 1,2,3-oxadiazole cannot be isolated as a discrete species, even in an inert matrix at low temperature. With few exceptions, simple 1,2,3-oxadiazoles remain unknown <1997AHC2, 2000AHC157>. Despite this, many substituted derivatives are accessible and the purpose of this chapter is bring the previous coverage of the subject in CHEC(1984) <1984CHEC(6)365> and CHEC-II(1996) <1996CHEC-II(4)165> up to date with a survey of the literature from mid-1995 to mid-2007. Recent advances include the preparation of the first neutral 1,2,3-oxadiazolines and 1,2,3-oxadiazolidines (Section 5.03.9.4), the formation of stable 1,2,3-oxadiazole 3-oxides by a new reaction between nitric oxide and alkynes (Section 5.03.9.1), the regiospecific 1,3-dipolar cycloaddition of sydnones and unsymmetrical alkynes (Section 5.03.5.2.6), and the synthesis of new sydnone and sydnonimine derivatives endowed with biological activity (Section 5.03.12).

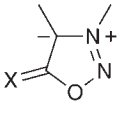
5.03.2 Theoretical Methods

The chemistry of 1,2,3-oxadiazoles is dominated by mesoionic sydnone **1** and sydnonimine **2** derivatives <B-1997MI1, B-2000MI1, 1995PAC1307, 2002ARK224>. Of the various resonance forms that may be drawn for the sydnone ring system, structure **1** appears to be the best single representation <1984CHEC(6)365, 1996CHEC-II(4)165> and, as such, sydnones are not regarded as delocalized aromatic <1998JOC2497, 2001CRV1421> ring systems. *Ab initio* calculations suggesting that 1,2,3-oxadiazole **3** cannot be isolated as a discrete species, even in an inert matrix at low temperature, were reinforced by calculations on an optimized system performed at various higher levels of theory <1998JOC5801>.

A 'nearly barrier-less' ring opening of structure **3** was predicted and a pseudopericyclic nonrotatory pathway the likely mode for theoretical cyclization of molecule **4** to 1,2,3-oxadiazole **3** <1998JOC5801>. The 1,3-dipolar cycloaddition of nitrous oxide (N_2O) to acetylene has been studied <2001JOC6096>. Calculations predicted formation of 1,2,3-oxadiazole **3** as an intermediate that gives formyldiazomethane **4** on ring opening. In this case, the dipolar addition process is controlled by the highest occupied molecular orbital (HOMO) of the dipolarophile and lowest unoccupied molecular orbital (LUMO) of the dipole with the frontier molecular orbital (FMO) coefficients product being the best predictor of regioselectivity when unsymmetrical alkynes are reacted with N_2O <2001JOC6096>.

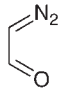
The mechanism of direct oxidation of cyclohexene to cyclohexanone by N_2O mediated oxidation was analyzed by density functional theory (DFT) using B3LYP/6-31G approximation. A two-step reaction mechanism was predicted where the substituted 1,2,3-oxadiazoline ring system **5** forms as the first intermediate in the process before subsequent conversion to the cyclohexanone <1999JOC6710, 2003CC42, 2005MI177>.

Formation of 1,2,3-oxadiazolidines **6** is possible, in principle, by [3+2] cycloaddition of diazine oxide **7** to alkenes. The calculated energy barrier for diazine oxide addition to ethylene is approximately 5 kcal mol^{-1} lower than the calculated value of 27 kcal mol^{-1} for the addition of ethylene to butadiene <1997JHC1383>. However, the 1,2,3-oxadiazolidine **6** ring system is unstable. The calculated activation energy for retro 1,3-dipolar addition to ethylene and diazine oxide **7** is 7.2 kcal mol^{-1}. When the ring system is confined to a caged structure, the activation energy for the retro 1,3-dipolar cycloaddition increases significantly as evidenced experimentally by the successful preparation and characterization of such caged structures featuring the substituted 1,2,3-oxadiazolidine ring system **6** (Section 5.03.9.4) <1995LA1801, 2000EJO743>.



1: X = O
2: X = NH

3



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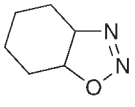

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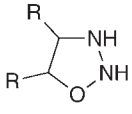

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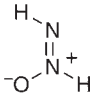
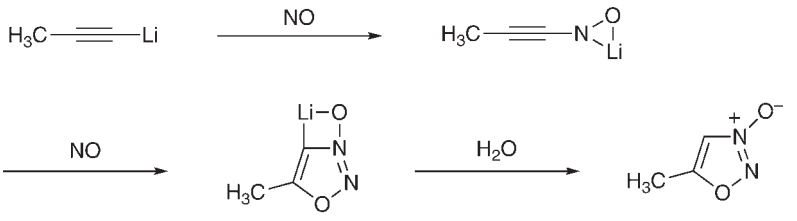


7

The formation of 5-methyl-1,2,3-oxadiazole 3-oxide **9** by the fixation of nitric oxide (NO) using propynyllithium has been investigated using *ab initio* (U)MP2 and DFT/(U)B3LYP methods (**Scheme 1**) <2005JOC5045>.



8 **9**

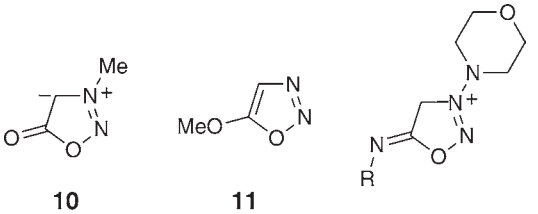
Scheme 1

Formation of the bicyclic lithiated intermediate **8** is considered to be a two-step process whereby the nitrogen atom of nitric oxide attaches to the C1 atom of propynyllithium. Addition of a second molecule of nitric oxide gives intermediate **8** that on reaction with water produces 5-methyl-1,2,3-oxatriazole 3-oxide **9** (**Scheme 1**). Calculated, optimized geometry and bond lengths for structure **9** together with calculated infrared (IR) and Raman spectra are reported <2005JOC5045>.

The solvent effects on the nitrogen shieldings of 3-methylsydnone **10** and the hypothetical 5-methoxy-1,2,3-oxadiazole **11** were calculated <2000MRC580, 2001AHC1>. For structure **10**, there is excellent linear correlation between the calculated and the experimentally determined chemical shift values for N2 and N3.

When the iterative maximum localization extended Hückel (IML-EH) method is applied to the drug molsidomine **12** (Section 5.03.12), the angle widening at N2–N3–C4 observed by X-ray analysis, 115° instead of the typical 108°, is due to induced polarization <1998JMT291>. The N3 position is the most electron deficient, followed by C-5. The N^{+}–N bond connecting N3 to the morpholine ring has no π character despite the electron deficiency at N3 and the distortion toward planarity.

Calculated bond lengths and bond orders confirm that N3 carries the positive charge in SIN-1 **13**, the metabolite of molsidomine **12**, and that the structure exists in cyclic form and not as the ring-opened isomer <1996CHE1358>. The 1,2,3-oxadiazole ring system was included in a total set of 100 heterocyclic ring systems studied in a principal component analysis correlating the *in vitro* biological activities of HIV-1 reverse transcriptase inhibitors with the chemical structures of the heterocyclic ring systems <1996JME4065>.



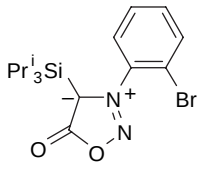
10 **11**

12: R = EtO_2C
13: R = H·HCl

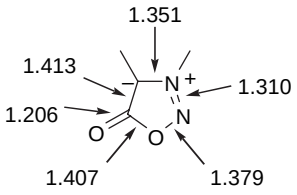
5.03.3 Experimental Structural Methods

5.03.3.1 X-Ray Crystal Structures

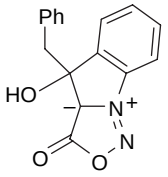
Various X-ray crystal structures have been reported since the last survey <1996CHEC-II(4)165>. X-ray crystal structure analysis of 3-(2-bromophenyl)-4-(triisopropyl)sydnone **14** reveals that the sydnone and phenyl rings are themselves planar and that they lie almost perpendicular to each other with a dihedral angle of 80.62(10)° <2001AXEo985>. The bond distances between each of the atoms are within the accepted values. The average bond distances (angstrom) in disubstituted sydnone rings are represented in structure **15** <1995JPC1923, 2003AXEo894>.



14

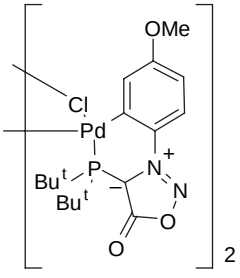


15

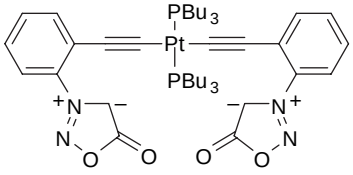


16

Typical bond distances and angles are also observed in 4-hydroxy-4-benzylsydno[3,4-*a*]indole **16** indicating that substituents in this fused ring system are not destabilizing to the sydnone ring <2004AXEo1568>. In the six-membered metallocycle **17** (Section 5.03.7.1.1), the bonds O1 to N2, and N3 to aryl ring are shortened whereas N3–C4 and C4–O5 are lengthened compared with the average values <1997OM1803>. Other palladium complexes containing the sydnone ring system have been described <2000JOM1, 2002MI9>. Bond lengths and bond angles in the sydnone rings of the platinum complex **18** are similar to the average values <2005JPC999>.

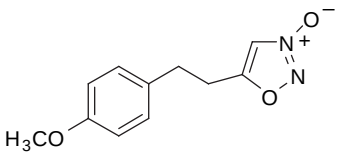


17

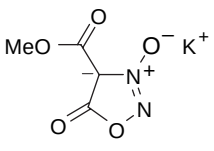


18

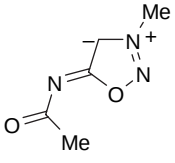
The X-ray crystal structures of the two N3 oxides, 5-(4-methoxyphenethyl)-1,2,3-oxadiazole 3-oxide **19** <2004CC216> and 4-carboxymethylsydnone 3-oxide **20** <2002AGE2089>, have been reported. In the new type of 1,2,3-oxadiazole structure **20**, the C5 bond to the exocyclic oxygen is only slightly lengthened compared with the ester carbonyl bond. The cautionary note here is that compound **20** forms dense crystals that decompose exothermally at high temperatures <2002AGE2089>. The X-ray crystal structure of the picrate salt of *N*-acetyl-3-methylsydnonimine **21** shows the exocyclic amide group to have the same conformation as that determined by nuclear magnetic resonance (NMR) analysis <2000MRC617>.



19

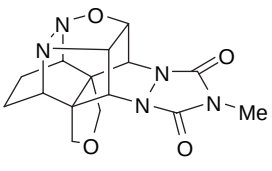


20

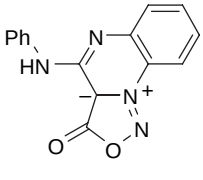


21

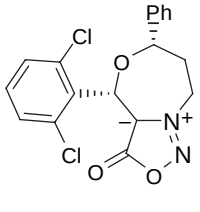
The first oxadiazolidine ring to be studied by X-ray crystallography features in the caged structure **22**, which is formed by [3+2] cycloaddition of a diazine oxide group and the adjacent C=C bond <2000EJO743>. Fused ring sydnone structure **23** <2004AXEo258>, bicyclic structure **24** <2005H(65)2649>, the N3 monosubstituted sydnones **25–28** listed in **Table 1**, and the disubstituted sydnones **29** to **57** listed in **Table 2** represent the other structures that have been determined by X-ray crystallography since the last review of the subject <1996CHEC-II(4)165>.



22

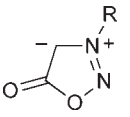


23



24

Table 1 Structures of monosubstituted syndrones **25–28** that have been determined by X-ray crystallography



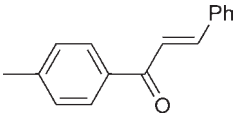
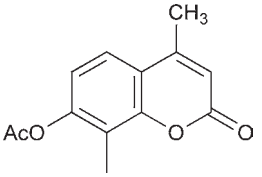
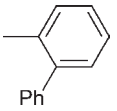
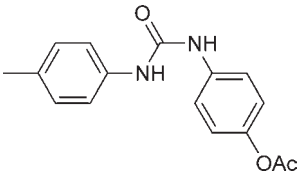
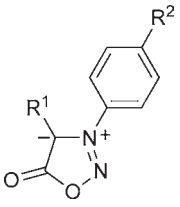
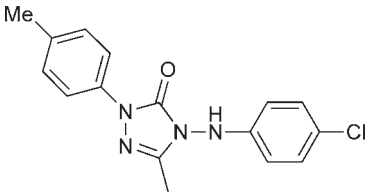
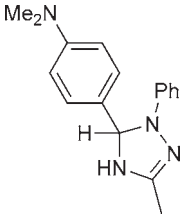
Compound	*R*	*Reference*
25		2003AXEo1762
26		2004AXEo701
27		2004AXEo977
28		2004AXEo1015

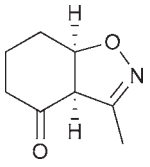
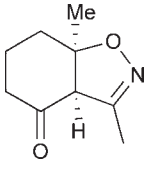
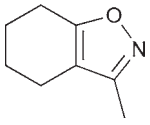
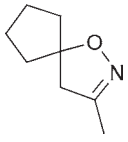
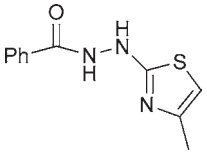
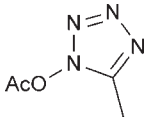
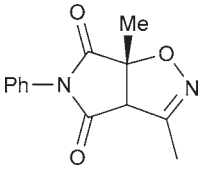
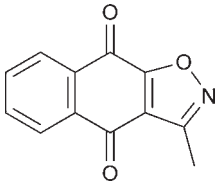
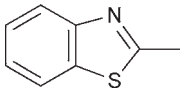
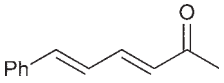
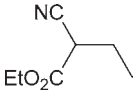
Table 2 Structures of disubstituted syndrones **29–57** that have been determined by X-ray crystallography



Compound	R^1	R^2	*Reference*
29		Me	2000MI227
30		MeO	2001MI883

(*Continued*)

Table 2 (Continued)

Compound	R^1	R^2	*Reference*
31		Me	2001MI1143
32		Me	2001MI1143
33		Me	2001MI1143
34		Me	2001MI1143
35		H	2002AXEo784
36		H	2002MI361
37		OEt	2002T10437
38		H	2002T10437
39		H	2002T10437
40		OMe	2003AXEo894
41		OEt	2003T4103

(*Continued*)

Table 2 (Continued)

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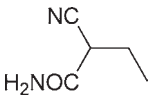
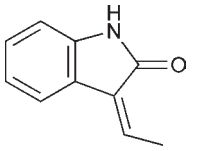
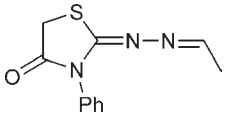
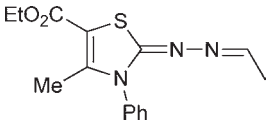
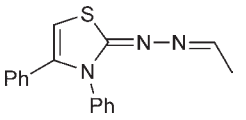
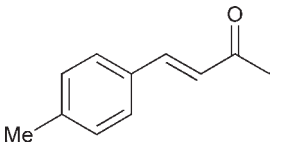
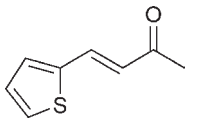
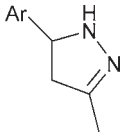
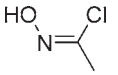
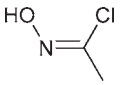
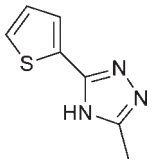
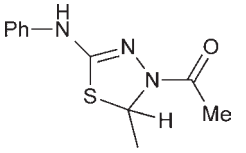
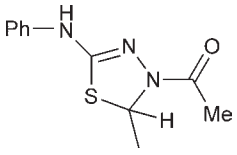
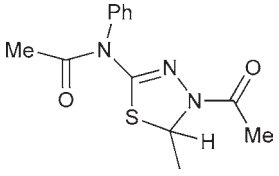
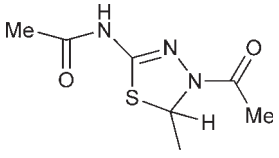
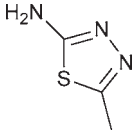
42		Me	2003T4103
43		H	2003T4103
44		OMe	2004BMC4633
45		Me	2004MC4633
46		OMe	2004MC4633
47		Me	2004S26
48		OMe	2004S26
49		Me	2004S26
50		H	2004S2877
51		Me	2004S2877
52		Me	2004S2877
53		H	2005T10917

(*Continued*)

Table 2 (Continued)

Compound	R^1	R^2	*Reference*
54		OEt	2005T10917
55		H	2005T10917
56		OMe	2005T10917
57		H	2005T10917

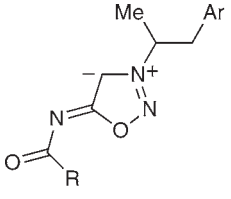
5.03.3.2 NMR Spectra

Synthesis and complete ^{1}H and ^{13}C assignments of the first *cis*- and *trans*-sydnonylstilbene derivatives have been reported with the H4 and C4 signals clearly distinguished from those of the stilbene rings <2004MRC1053>. Solvent effects on nitrogen shielding in 3-methylsydnone **10** were calculated and show excellent correlation with those recorded experimentally <2000MRC580, 2001AHC1>. The solvent effects on the nitrogen shieldings of 3-methylsydnone 10 by high-precision ^{14}N NMR were found to be significantly different from other stable isomers of 1,2,3-oxadiazole <1996MR148>.

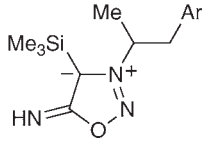
Multinuclear NMR data have been recorded for molsidomine **12** and its metabolite SIN-1 **13**, confirming that both are closed ring structures and that the positive charge is accommodated at the N3 position <1996CHE1358>. The $^{1}J_{c-c}$ C4–C5 coupling constants for selected 1,2,3-oxadiazoles lie between 69.4 and 89 Hz, but correlation of these values with measures of bond order and aromaticity is difficult due to substituent effects <2000MRC617, 2002JST269>.

5.03.3.3 Mass Spectra

Molecular ions were observed by gas chromatography–mass spectrometry (GC–MS) analysis for trifluoroacetyl **58** and trimethylsilyl **60** derivatives of mesocarb (sydnocarb) **59** (Section 5.03.12) <1999JMP1079>. Unlike the silyl derivative **60** and sydnones <1996CHEC-II(4)165>, no $[M^+-NO]$ ion was observed for trifluoroacetyl derivative **58**. The characteristic ions $PhCH_2(Me)CH^+$ (*m/z* 119) and $PhCH_2^+$ (*m/z* 91) were observed for both derivatives **58** and **60**.



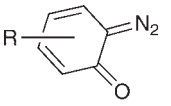
58: R = CF_3
59: R = NHPh



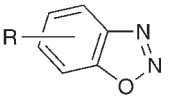
60

5.03.3.4 UV and IR Spectra

An ultraviolet (UV) study of 2-benzoquinones supports the ring open structures **61–63** over the 1,2,3-benzoxadiazole forms **64–66**. Results from an *ab initio* study were in agreement with the experimental findings <2000IJQ52, 2004MI1082>. Absorption spectra of sydnone complexes of pentacyanoferrate(II) were determined and showed strong metal-to-ligand charge-transfer bands in the visible region <1998MI77>.



61: R = H
62: R = NO_2
63: R = CO_2H



64: R = H
65: R = NO_2
66: R = CO_2H

In the IR, carbonyl stretching frequencies of sydnones occur over a wide range of 1720–1790 cm^{-1} <1996CHEC-II(4)165>, with typical values centered around 1750 cm^{-1} in the 3-arylsydnone series <2001AP263, 2002SC2203, 2004AP164, 2006H(68)175>. When 3-arylsydnones react with butyllithium at −70 °C to form C4 lithiated derivatives, Fourier transform infrared (FTIR) analysis has revealed that the lithium atom at C4 and exocyclic oxygen at C5 are chelated <1997MI381>.

5.03.3.5 Dipole Moments and Dielectric Constants

The dipole moments of both 3- and 4-phenylsydnones containing dimethylamino and nitro substituents were calculated (*ab initio* 3-21G basis set); the magnitude increases with the electron donor attached to the phenyl ring <1995JPC1923>. Quadrupole moments, octopole moments, and polarizability of 1,2,3-oxadiazole have been determined by *ab initio* calculations and simple models <1996JPC8752, 1999JPC10009>.

Some physical properties of 3-propyl-4-ethylsydnone have been determined at various temperatures <1997BCJ315>. The dielectric constant ($\varepsilon = 64.6$ at 25 °C) is high compared to many organic solvents and close to that of propylene carbonate ($\varepsilon = 64.9$), a typical nonaqueous polar solvent.

5.03.4 Thermodynamic Aspects

1,2,3-Benzoxadiazole **64** is calculated to be 1 kcal mol^{-1} less stable than its ring open form **61** <2004MI1082> and is mirrored by the 4-nitro **65** and 6-carboxyl **66** substituted analogs that exist exclusively as the ring open isomers **62** and **63** <2000IJQ52> (Section 5.03.3.4).

5.03.5 Reactivity of Fully Conjugated Systems

5.03.5.1 Benzo-1,2,3-oxadiazoles and Naphtho[2,3-*d*]-1,2,3-oxadiazole

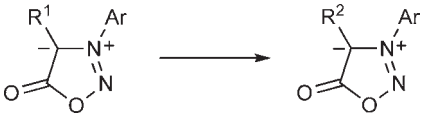
No further reports on the reactions of these systems have appeared since last review of the subject <1996CHEC-II(4)165>.

5.03.5.2 Sydnones

The chemistry of the 1,2,3-oxadiazole ring system remains dominated but not entirely confined to sydnones, sydnonimines, and their derivatives. Although the charge distribution on the rings varies according to the nature of the substituents present, there is usually a duality of effects where C4 is generally electron releasing and N3 electron attracting.

Sydnones undergo a range of useful reactions despite their susceptibility to acid-catalyzed hydrolysis and instability in basic media. Since the last review of the subject <1996CHEC-II(4)165>, some novel methods have appeared and these are presented in the following sections. **Table 3** provides a short summary of some recent transformations applied to 3-arylsydnones.

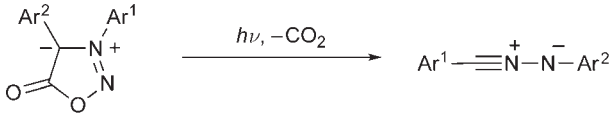
Table 3 Some methods for functionalization at the C4 position of 3-arylsydnones



R^1	R^2	*Conditions*	*Yield (%)*	*Reference*
H	Cl	Et_3N, $PhICl_2$, CH_2Cl_2, rt	51–86	1996SC1441
H	I	ICl, AcOH, AcONa, rt	70–85	1997LA2613
H	AcO	Ac_2O, montmorillonite K-10, 110 °C, overnight	25–86	1996SC2757
H	RS	S_8, BuLi, THF	54–76	2002RCB899
H	H_2NCO	$ClSO_2NCO$, MeCN, 0 °C, 10 min, 0 °C to rt, 90 min	55–81	1998SC931
H	R_3Si	LDA, R_3SiCl, −78 °C, 1 h	79–85	2003SC2061
H	$ArNHCH_2$	HCHO, $ArNH_2$, HCl, EtOH	31–90	2002MI283
Br	ArC≡C	CuI, $Pd(PPh_3)_4$, ArC≡CH, Et_3N, rt, 10 h	79–94	2003SC2209
Me_3SiC≡C	ArC≡C	i, Bu^n_4NF, $3H_2O$, THF, 20 °C; ii, 5% $Pd(PPh_3)_4$–5% CuI, Et_3N, THF, 20 °C, 2–24 h	0–97	1997MC93

5.03.5.2.1 Unimolecular ring cleavage

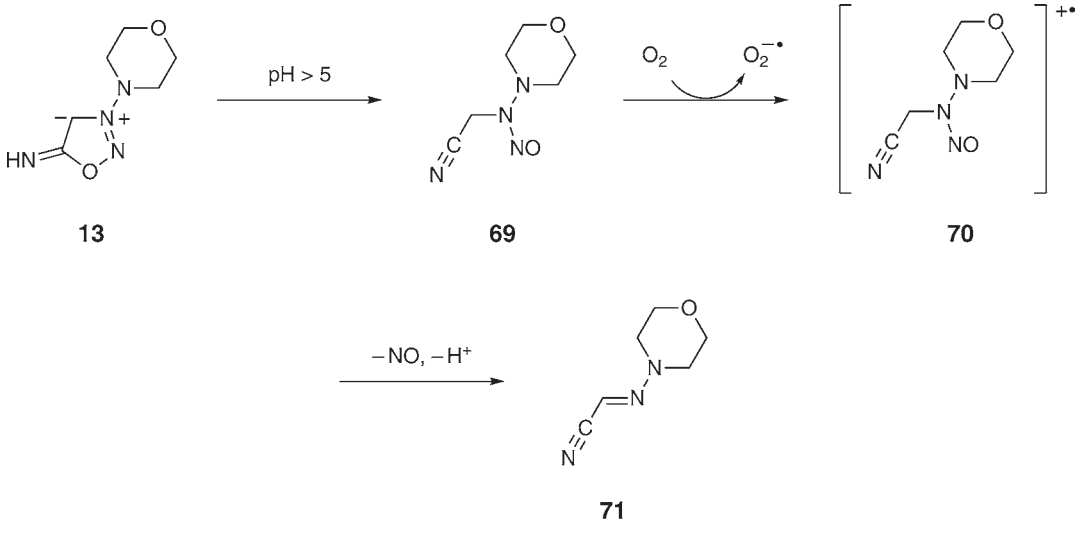
The sydnone and sydnonimine ring systems are stable in acid solution at room temperature but are rapidly hydrolyzed in basic media <1984CHEC(6)365>. 3,4-Diarylsydnones **67** lose carbon monoxide on photolysis giving nitrile imines **68** that can be intercepted by dipolarophiles (Equation 1) <2004TL9057>.



(1)

67 **68**

Under physiological conditions, the nitric oxide-releasing compound SIN-1 **13** (Section 5.03.12) undergoes spontaneous ring opening to SIN-1A **69** that then forms a cation **70** in the presence of oxygen to release nitric oxide giving SIN-1C **71** (**Scheme 2**) <1997MI882, 2002CRV1091, 2003JHC943, 2004MI121>. The effect of pH on



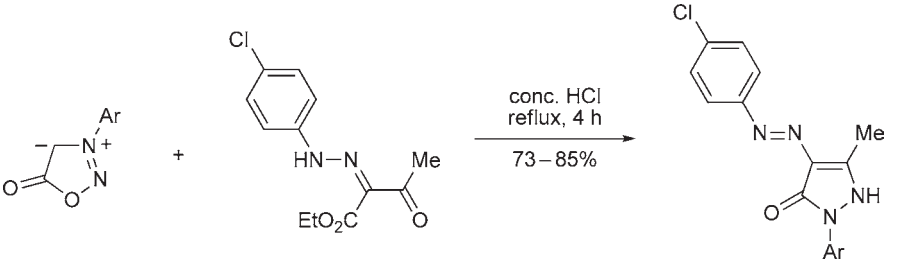
13 **69** **70** **71**

Scheme 2

the ring opening of sydnonimines has been studied by polarimetry. Unlike the psychotropic drug sydnocarb **59** (Sections 5.03.3.3 and 5.03.12), 3-isopropylsydnonimine was shown to be completely stable in the pH range 1–7 <2004CHE507>.

5.03.5.2.2 Acid-catalyzed ring cleavage

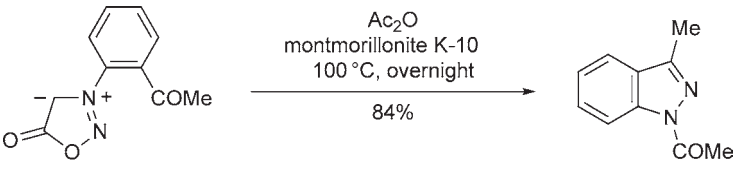
The susceptibility of the sydnone ring to acid-catalyzed hydrolysis at elevated temperature is exploited for the preparation of hydrazines <2000MI227>. Primary amines are first converted to sydnones, which are then hydrolyzed to give hydrazines that may be isolated or reacted further without isolation <1996CHEC-II(4)165>. As 'masked' hydrazines, 3-arylsydnones are firstly subjected to acid-catalyzed ring opening and then allowed to react further *in situ* with 2-(4-chlorophenyl)hydrazono-3-oxo-butyric acid to form substituted pyrazolidinones (Equation 2) <2005SC2169>.



(2)

Acid-catalyzed ring opening of 3-aroylethylsydnones gives 3-arylpyrazolines or the 1-aroylethyl-3-arylpyrazolines depending on the exact conditions used <1998CCL803, 2001MI388>. Similarly, when heated with excess arylhydrazine in the presence of aqueous HCl, 4-acetyl-3-arylsydnones initially form hydrazones that isomerize to give 4-arylhydrazo-1,2-pyrazolin-5-ones <2000MI1171>.

The formation of triazoles by acid-catalyzed ring opening and isomerization of various other C4-substituted sydnones has also been explored <2001MI769>. When applied to 3-(2-acetylphenyl)sydnone, conditions that are successful for C4 acylation of other 3-arylsydnones result unexpectedly in the formation of the *N*-acetyl-3-methylindazole **72**. Initial protonation of the carbonyl in the *ortho*-acetyl group triggers attack by the N2 position of the sydnone ring and concludes with hydrolysis and loss of carbon dioxide (Equation 3) <1996SC2757>.

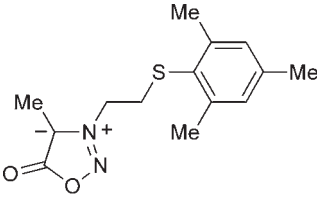


(3)

72

5.03.5.2.3 Oxidative ring cleavage

The sydnone TTMS **73** (Section 5.03.12) has been shown to undergo oxidative ring cleavage by cytochrome P450 <1998MI739>.

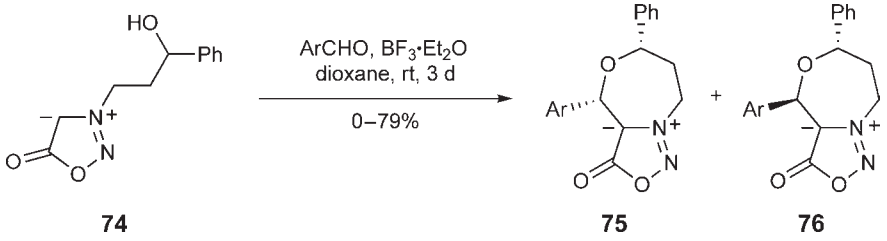


73

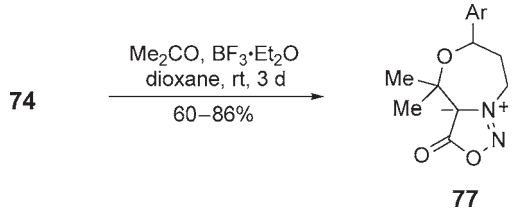
5.03.5.2.4 Electrophilic substitution at C4

There are many examples where electrophiles have been introduced directly into sydnones unsubstituted at C4 <1984CHEC(6)365, 1996CHEC-II(4)165>. Some recent examples of electrophilic substitution at C4 involving 3-arylsydnones are summarized in **Table 3** (Section 5.03.5.2). The hydrogen at C4 in sydnones may be substituted in good yield by chlorine <1996SC1441>, bromine <2002ARK80, 2006S1123>, iodine <1997LA2613, 2002MI237, 2002RRC315>, acetyl <1996SC2757, 1999RRC249>, and acetamide <1998SC931>.

Intramolecular electrophilic substitution at C4 provides a route to fused structures where the sydnone ring directs lithiation *ortho* in the phenyl substituent <1996S1183>. This and other methods whereby electrophiles may be introduced at C4 involving organo metallic intermediates are described in Section 5.03.7.1.1. The electron-rich C4 position of 3-(3-phenyl-3-hydroxypropyl)sydnone **74** is exploited in an interesting application of the oxa-Pictet–Spengler reaction, whereby sydnone **74** reacts with aromatic aldehydes using $BF_3{\cdot}Et_2O$ under mild conditions to form predominantly *cis*-configured products **75** over the *trans*-**76** (Equation 4) <2005H(65)2649>. Yields for this cyclization reaction were higher for aldehydes with electron-withdrawing groups. Use of acetone instead of an aryl aldehyde places geminal dimethyl groups in the seven-membered ring **77** (Equation 5) <2002SC2203>.



74 **75** **76** (4)



74 **77** (5)

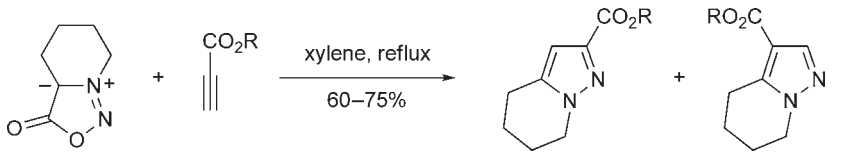
5.03.5.2.5 Nucleophilic attack at hydrogen (deprotonation)

Metallation reactions at C4 of sydnones and sydnonimines are used as a means of achieving electrophilic substitution. Examples that have appeared since the last review of the subject <1996CHEC-II(4)165> are given in Section 5.03.7.1.1.

5.03.5.2.6 1,3-Dipolar cycloaddition reactions

Sydnones can be regarded as a cyclic azomethine imines and participate widely in thermal 1,3-dipolar cycloaddition reactions <2000TL1687>. They react with acetylenic dipolarophiles to give intermediate cycloadducts that form pyrazoles on spontaneous loss of carbon dioxide. Similarly, 1,3-dipolar cycloaddition of sydnones to acetic anhydride gives 1,3,4-oxadiazolones <2000FA65, 2006MI191, 2006JSC331, 2007HAC61>. Many examples of 1,3-dipolar cycloaddition reactions have appeared since the last review <1997LA2613, 2002ARK80, 2000MI131, 2001MI183, 2001OPP100, 2002MI237, 2002RRC315, 2003AXEo44, 2003MI747, 2005JCM592, 2006JHC287, 2007JC(B)375, 2007JOC000>.

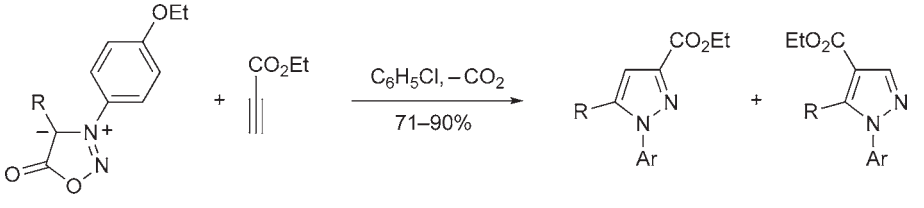
In the cycloaddition of sydnones to dipolarophiles containing electron-withdrawing groups, interaction between the HOMO of the sydnone and the LUMO of the dipolarophile is dominant <B-1997MI1, 1996CHEC-II(4)165, 2006OPRD712, 1997LA2613, 2000T4261>. Reaction of 3-methylsydnone with methyl propiolate, for example, gives a good yield of 3-carboxymethyl-1-methylpyrazole as a single isomer <1998BKC725>. Other cycloaddition reactions usually show poorer regioselectivity when unsymmetrical alkynes are used <1996CHEC-II(4)165>. Substituted pyrazoles **79** and **80** are formed when the bicyclic sydnone **78** is reacted thermally with different esters of acrylic acid (Equation 6) <2000BKC761>.



78 79 80 (6)

R = Me	67	33
Et	75	25
Bu^n	63	37
$PhCH_2$	69	21
$PhCH_2CH_2$	66	34

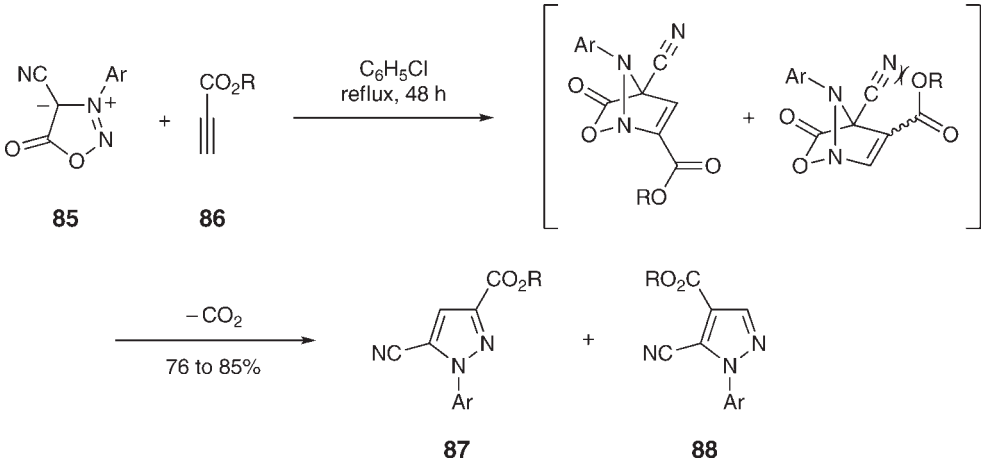
The yields from these reactions (Equation 6) are good and pyrazole **79** predominates. However, the distribution of regioisomers varies depending on the acrylamide ester used <2000BKC761>. Substituents on the sydnone and on the dipolarophile also play a key role and this has been exploited effectively as a means of discouraging formation of the unwanted regioisomer. The sizes of the substituents attached at C4 in the 3-arylsydnones **81** have a strong influence on the regioselectivity of cycloaddition with ethyl propiolate **82** <2006H(68)1007>. Bulky substituents at C4 encourage formation of isomer **84** at the expense of isomer **83** (Equation 7).



81 82 83 84 (7)

R = H	76	24
I	56	44
CN	58	42
CH_2Ph	63	37
SPh	52	48

Steric effects and FMO control have been combined in an elegant way to achieve regiospecific synthesis of pyrazole inhibitors of dihydroorotate dehydrogenase <2006SL901>. When the size of the propargylic acid ester **86** is increased from ethyl to diphenylmethyl, pyrazole **87** is formed from compound **85** regiospecifically (**Scheme 3**; **Table 4**) <2006H(68)1007>.



85 86 87 88

Scheme 3

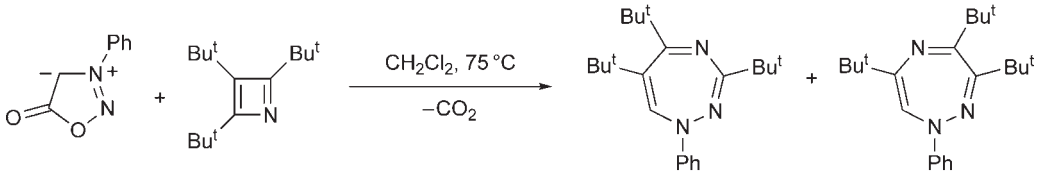
Table 4 1,3-Dipolar cycloaddition of propargyl esters **86** to sydnone **85** (**Scheme 3**) <2006H1007, 2006SL901>

R	*Ar*	*Ratio* **87**:**88**	*Total yield (%)*
Et	4-$EtOC_6H_4$	58:42	80
Bu^t	4-$EtOC_6H_4$	78:22	79
CH_2Ph	4-$EtOC_6H_4$	57:43	76
$CHPh_2$	4-$EtOC_6H_4$	100:0	85
$CHPh_2$	Ph	100:0	80

Preparation of the antidepressant drug FS-32 by an intramolecular 1,3-dipolar cylcoaddition reaction of the appropriately functionalized sydnone has been reported <2001S1775>. 3-Phenyl- and 3-(4-halophenyl)sydnones, but not the more electron-rich 3-methyl- or 3-(4-methoxyphenyl)sydnone, undergo cycloaddition involving the P=C bond in ferriophosphaalkene complexes to give stable derivatives <1997OM2958>. 3-Phenylsydnone reacts with reluctance when refluxed in mixtures of cyclopentadiene and dicyclopentadiene to give resulting mixtures of pyrazole-fused norbornene isomers <2003MI95>. When the reaction yields are high, the cycloaddition of dipolarophiles to sydnones represents good atom economy where the carbon dioxide lost from the cycloadduct to form the pyrazole product accounts for the only 'unused' atoms.

A proposed 'greener' version of cycloaddition between 3-phenylsydnones and diethyl or dimethy acetylenedicarboxylate, employing supercritical or near-supercritical carbon dioxide as the solvent, has been investigated. This gave the 1-phenyl-pyrazole-3,4-dicarboxylic acid esters in yields comparable to those from traditional methods <2001OPP100>. When methyl propiolate is used as the dipolarophile, two regioisomers (3- and 4-carboxymethyl-1-phenylpyrazole) are formed; lower pressure and higher temperature give higher reaction yields, whereas higher pressure and lower temperature give greater selectivity in favor of the 3-carboxymethyl isomer <2000MI131>.

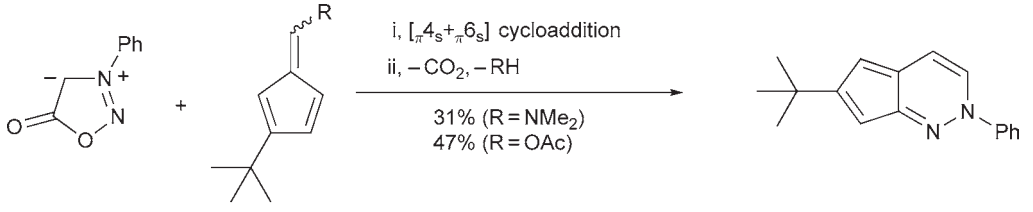
3-Phenylsydnone **89** is not restricted to [3+2] cycloaddition. Reaction of sydnone **89** and its derivatives with the substituted azete **90** gives isomeric 1*H*-triazepines after extrusion of carbon dioxide (Equation 8).



(8)

89 **90** 32% 48%

Photolysis of the triazepine products produces 2,2-dimethylpropanenitrile and the corresponding pyrazole in quantitative yield <1997BSF927>. Reaction of sydnone **89** with fulvene **91** proceeds by [$\pi 4_s + \pi 6_s$]-cycloaddition followed by spontaneous loss of carbon dioxide and a molecule of dimethylamine or acetic acid from the 'pseudo-azulene', cyclopenta[*d*]pyridazine **92** (Equation 9) <1996CC1011, 1997T9921>.



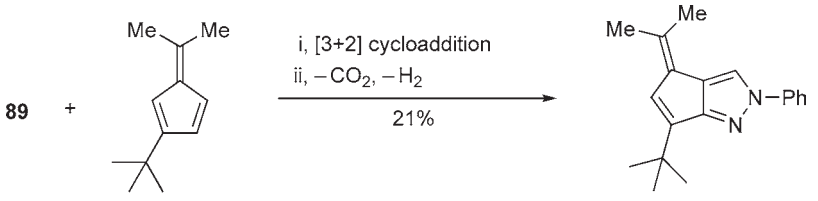
(9)

89 **91** **92**

R = NMe_2 or OAc

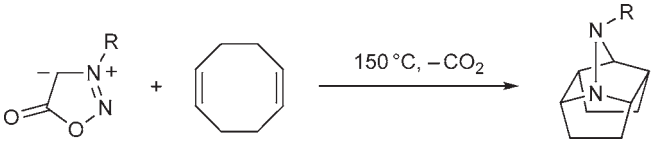
Dimethylfulvene **93** also reacts with sydnone **89**, albeit sluggishly, to form the dihydrocyclopenta[*c*]pyrazole **94** after elimination of carbon dioxide and hydrogen (Equation 10). Molecular orbital energies and coefficients of 3-phenylsydnone **89** and fulvenes **91** and **93** have been calculated (PM3-MNDO), but when orbital symmetries

were taken into consideration, no adequate explanation was possible for the different cycloaddition preferences of fulvenes **91** (R = NMe_2 or OAc) compared with **93** on reaction with sydnone **89** <1997T9921>.



93 **94** (10)

The Weintraub reaction was revisited to form additional members of the series of diazatetracycloundecanes by tandem 1,3-dipolar cycloaddition of sydnones and 1,5-cyclooctadiene (Equation 11) <1996JHC719>.



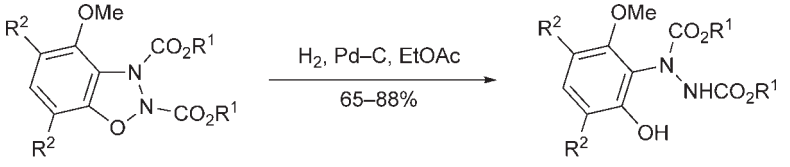
(11)

R = (3,4-di-MeO)C_6H_3 (12%)
R = Me (51%)
R = Bu^t (20%)

5.03.6 Reactivity of Nonconjugated Rings

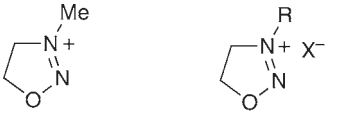
Until very recently, the known chemistry was confined to 4,5-dihydro-3-methyl-1,2,3-oxadiazolium salts used to study mechanisms of DNA alkylation <1997CRV829> by anticancer agents such as the (β-hydroxyethyl)nitrosamines <1996JA10995> and the 1-(2-chloroethyl)-1-nitrosoureas <1996JME796, 1996MI208, 1999MI965>. The 4,5-dihydro-3-methyl-1,2,3-oxadiazolium cation **95** has been shown to react principally with the guanine bases in DNA where it undergoes attack at C5 by the amino group of guanine to create an N7 modified base that carries the entire nitrosamine fragment <1996JA10955>. The cation also undergoes attack at its methyl group but to a lesser extent.

The 3-methyl- and 3-phenyl-1,2,3-oxadiazolinium salts **96** and **97** are capable of oxidizing thiols to disulfides <1995MI817>. New dihydro-1,2,3-benzoxadiazoles, prepared by the reaction of 1,2-benzoquinones with diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) in the presence of triphenylphosphine (Section 5.03.9.4), have been shown to undergo catalytic hydrogenolysis to give phenols (Equation 12) <2005OL5139>.



(12)

R^1 = Et or Pr^i; R^2 = Bu^t or $(4\text{-}ClC_6H_4)_2CH$



95

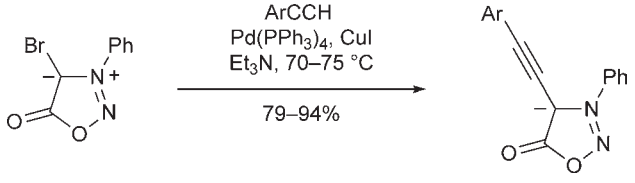
96: R = Me; X = Ts
97: R = Ph; X = Tf

5.03.7 Reactivity of Substituents Attached to Ring Carbon Atoms

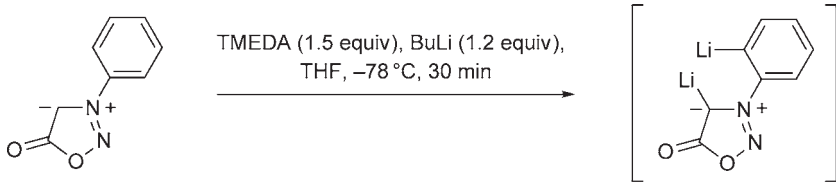
5.03.7.1 Reactivity of Substituents Attached to C4

5.03.7.1.1 Reactions of C4 metallated species

Modified Sonogashira coupling conditions give excellent yields of alkynylsydnones when 4-bromo-3-phenylsydnone is reacted with terminal alkynes (Equation 13) <2003SC2209>. The sydnone ring acts as an *ortho*-director of lithiation when 3-phenylsydnone **89** is dilithiated to give intermediate **98** upon reaction with butyllithium in tetramethylethylenediamine [1,2-bis(dimethylamino)ethane] (TMEDA) (Equation 14). By judicious choice of reaction conditions and electrophiles, C4 monosubstituted **99** <1998HAC549>, *ortho* monosubstituted **100** <1998TL1509>, disubstituted **101** <1997TL1165, 2007SC915>, and fused ring **102** <1996S1183> products may be obtained separately and in high yield.

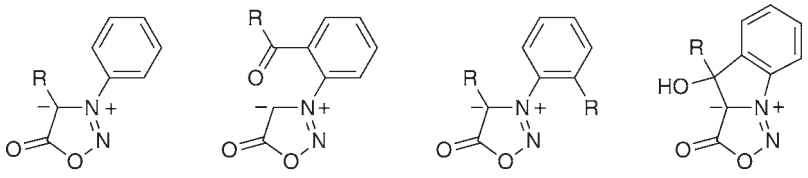


(13)



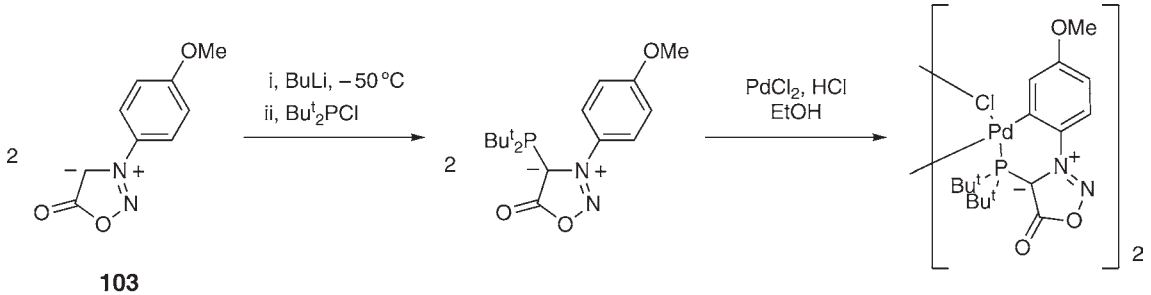
(14)

89 **98**



99 **100** **101** **102**

Palladium insertion into the phenyl ring of 3-(4-methoxyphenyl)sydnone by lithiation of compound **103**, phosphination at C4, then insertion of palladium at the *ortho* C–H bond to give product **17** has been achieved (**Scheme 4**) <1997OM1803>.

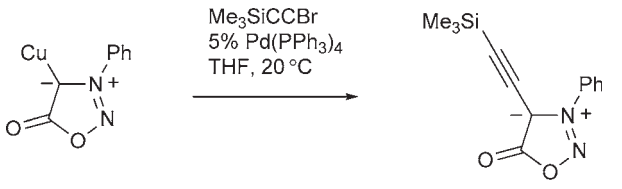


103 **17**

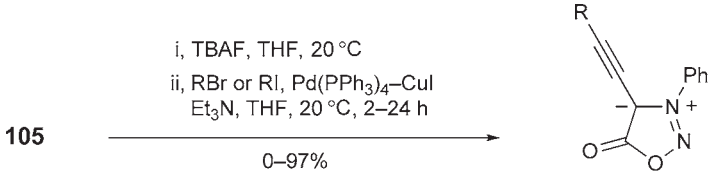
Scheme 4

4-Alkynyl-substituted sydnones **106** are prepared from the new trimethylsilylethynyl derivative **105**. 4-Cuprio-3-phenylsydnone **104** <1996CHEC-II(4)165> reacts with 1-bromo-2-trimethylsilyl acetylene to give product **105**,

which undergoes palladium(0)-catalyzed cross-coupling with alkyl or vinyl halides (Equations 15 and 16) <1997MC93>.



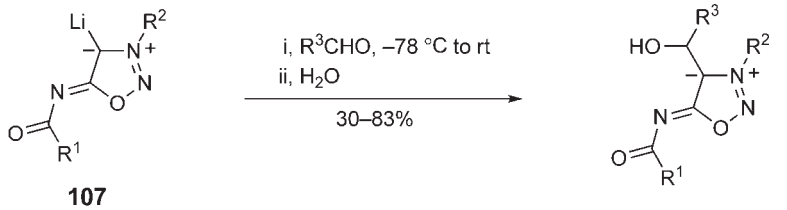
104 105 (15)



105 106 (16)

R = aryl, vinyl; X = Br, I

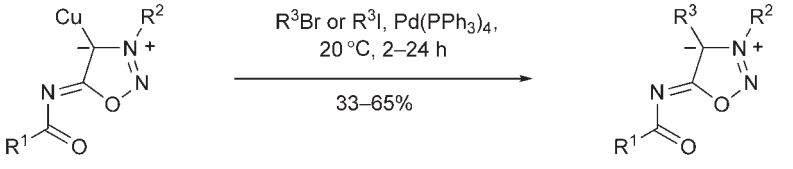
Use of iodides to form the C4 alkynyl-substituted sydnones **106** gives moderate to high yields, whereas use of bromides gives moderate to low yields. Usually, the most productive synthesis of sydnonimines relies on cyclization of the appropriately substituted *N*-nitroso-α-aminonitriles in acid (Section 5.03.9.3). When the required α-aminonitrile is not easily obtainable or when substituents hamper its cyclization, direct attachment of substituents to the organometallic derivatives **107** or **108**, formed from the corresponding C4 unsubstituted sydnonimine starting materials, provides an alternative method (Equations 17 and 18) <2000MC181, 2000DOC175>. The 4-lithio sydnonimines **107** are thermally unstable, decomposing above −78 °C, and their poor nucleophilicity renders them unreactive toward highly electrophilic reagents such as trimethylsilyl chloride, methyl iodide, and allyl bromide. The 4-cuprio sydnonimines **108** are thermally stable and mirror the reactivity displayed in the sydnone series <2000DOC175>.



107 (17)

R^1 = Me_3C, Ph, F_3C, Me, MeO, 4-MeC_6H_4
R^2 = *cyclo*-C_6H_{11}, 1-morpholine

R^3 = H, Ph, 4-ClC_6H_4, 2-furyl



108 (18)

R^1 = Me_3C, Ph, CF_3
R^2 = Me, *cyclo*-C_6H_{11}

R^3 = Ph, PhCHCH, 4-$O_2NC_6H_4$, MeCO, vinyl

Elemental sulfur, used together with alkyl or aryl halides, provides a route to 4-alkylthio- and 4-arylthiosydnones from 4-lithiosydnones <2002RCB899>.

5.03.7.1.2 Replacement of C4 substituents by hydrogen

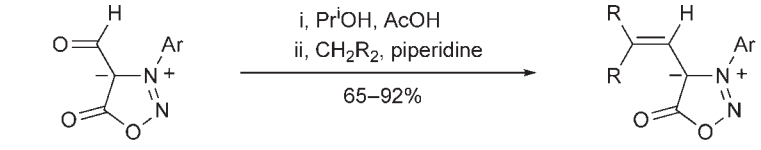
Use of sodium sulfite allows selective replacement of iodine by hydrogen at C4 without affecting the *ortho*-position in 4-iodo-3-(2-iodophenyl)sydnone <2005SC639>. Acrylate groups attached at the C4 position of 4-arylsydnones reacted with guanidine hydrochloride but the result was replacement of the C4 substituent by hydrogen instead of formation of the planned pyrimidinone products <2003T4103>.

5.03.7.1.3 Other reactions

Standard functional group transformations of 4-acetyl-3-arylsydnones include reduction with sodium borohydride to give secondary alcohols <1995M4987>, bromination <2001AP263>, and Claisen–Schmidt condensation using aldehydes in the presence <2003AXEo894, 2004S26> and absence <2003IJB2556> of solvent. 4-(3-Arylpropenoyl)sydnones, prepared by Claisen–Schmidt condensation, successfully undergo Robinson annelation without solvent to form sydnones with arylcyclohexanone substituents <2003SC3589>.

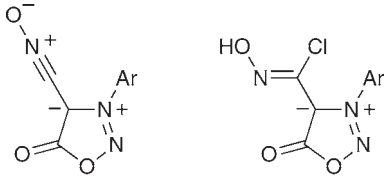
4-Bromoacetyl-3-phenylsydnones, which are formed photochemically by bromination of 4-acetyl-3-arylsydnones, undergo Hantzch reaction with thioamides and their derivatives to give various C4 substituted sydnones <1997PJC1049, 2000RRC71, 2001AP263, 2002AXEo784, 2003AXEo1762>.

4-Formylsydnones undergo Claisen–Schmidt condensation with ketones such as acetone and acetophenone as reactants <2004S26>. Additionally, 4-formylsydnones undergo Knoevenagel condensation with active methylene compounds to provide a useful complement to the standard functional group transformations. Addition of glacial acetic acid before the addition of active methylene compound and piperidine to the 4-formylsydnone is necessary to avoid decomposition of the sydnone ring (Equation 19) <2003T4103>. Use of isopropyl alcohol instead of ethanol serves to improve the reaction yield by encouraging precipitation of the product.



(19)

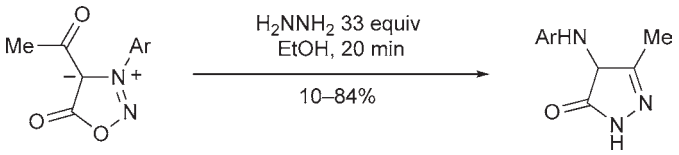
Examples of ring systems that have been introduced at the C4 position of sydnones by various standard methods include: indolone <2003T4103>, isoxazole <2001MI1143, 2002T10437>, isoxazoline <2001MI1143>, oxazole <2002T10437>, oxadiazole <1999MI63>, pyrazole <1995IJH19>, pyrazoline <2004S26>, pyrrole <1999MI163>, tetrazole, thiadiazole, thiadiazolidine, thiazole <1995IJB346, 1996IJH107, 2001IJB742, 2000IJH217, 2004SC4055, 2006JSC851>, thiazolidine, thiazoline, 1,2,4-triazole <2001MI883, 2004IJH127, 2004S2877>, triazolone <2000MI227, 2002MI361, 2004BMC4633, 2005T10917>, and other fused <1998IJH277, 2002IJB1712, 2003IJB1141, 2003IJH241, 2003MI355> and spiro ring systems <2000JCR(S)546>. X-ray crystal structures of several such compounds have been reported (Section 5.03.3.1). The nitrile oxides **109** can be generated from the corresponding hydroxamic chlorides **110** <2002T10437>.



109 **110**

When the nitrile group in 4-cyano-3-arylsydnones is reduced electrochemically to 4-aminomethylene using quaternary ammonium salt buffer solutions, the heterogeneous rate constant for the reduction increases with cation size <2003MI123>. Alkoxyphenylsydnones may be cleaved using acid to the hydroxyphenylsydnones <1998MI387>.

Diazotization of 3-(4-aminophenyl)sydnones followed by reaction with 1- or 2-hydroxynaphthalene provides azo dyestuff materials <1998MI209>. A new type of reaction between 4-acetyl-3-arylsydnones and hydrazine yields substituted pyrrolidinones by a cycloaddition process involving loss of nitric oxide (Equation 20) <1999H(51)95, 2001AHC73>.



(20)

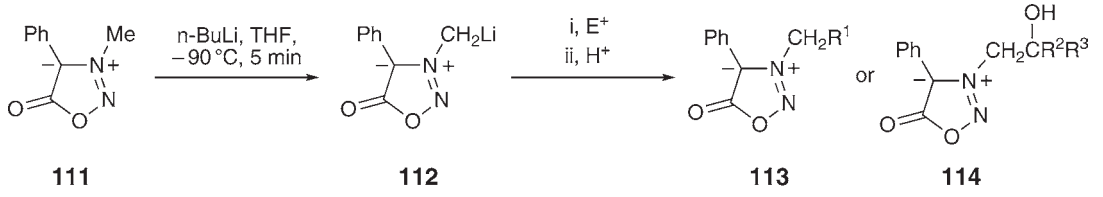
5.03.7.2 Reactivity at C5

The nitric oxide donor SIN-1 **13** (Section 5.03.12) reacts with 4-nitrophenyl chloroformate to give the N-acylated product that also acts as a potent nitric oxide donor. Further derivatives with trypanocidal activities may be prepared by transesterification with various alcohols <2003JHC943>.

5.03.8 Reactivity of Substituents Attached to Ring Heteroatoms

Even though the sydnone ring is electron releasing at the C4 position, 3-(2,4,6-trimethylphenyl)sydnone and all of the possible isomers of 3-(dimethylphenyl)sydnone undergo nitration exclusively in the aryl ring <1996JHC485>. 3-(2-Acylphenyl)sydnones are accessible in good to moderate yield by displacement of succinimidooxy-, tribromomethyl-, or chloromethylcarbonyl groups at the C2 position of the phenyl ring by nitrogen or oxygen nucleophiles <2000JHC383>.

Preparation of the new compound 3-lithiomethyl-4-phenylsydnone **112** exploits the C–H bond activation by the positive charge at N3 in sydnone **111** <1998RCB1725>. Although compound **112** decomposes above −90 °C, it can be readily prepared from sydnone **111** using *n*-butyllithium in THF, and reacted with a choice of electrophiles to give stable products, such as sydnones **113** and **114** <1998SL667> (**Scheme 5**).



$R^1 = CH_2CHCH_2$ (67%), CO_2Me (21%), $SiMe_3$ (36%), CO_2H (70%); $R^2 = H$, $R^3 = 4\text{-}ClC_6H_4$ (80%); $R^2 = Me$, $R^3 = Ph$ (12%); $R^2 = R^3 = Ph$ (70%)

Scheme 5

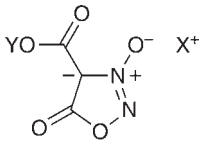
Formation of a homologous series of alkyl-substituted biphenylsydnones is achieved when 3-(4-bromophenyl)sydnone is subjected to Suzuki coupling with boronic acids <2005CC1552>. 3-(Aroylethyl)sydnones are reduced by sodium borohydride to secondary alcohols. The secondary alcohol products may be acylated or reoxidized <1998JCM626>. Amides are formed when 3-(4-aminophenyl)sydnones are reacted directly with acid chlorides <2004MI2523> or with carboxylic acids in the presence of $SiCl_4$ <2000MI280>. Substitution of bromine by trialkylsilyl groups occurs in high yield by lithium-induced silyl migration from the C4 position of the sydnone ring to the *ortho*-position of the phenyl group in 3-(2-bromophenyl)-4-trialkylsydnones <2003SC2061>.

3-(2-Ethynylphenyl)sydnone has been prepared from 3-(2-iodophenyl)sydnone and serves as a basis for the preparation of sydnone containing oligomeric areneynes by iterative Sonogoshira coupling reactions <2005SC639>. The effect of solvent on the rate of nucleophilic substitution of 3-(4-chloro-3-nitrophenyl)sydnone compared with 1-chloro-2,4-dinitrobenzene has been examined in a kinetic study <1996HCO507>.

5.03.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

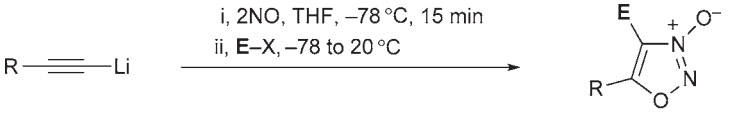
5.03.9.1 N3 Oxides

Structure **20** and salts **115** and **116** are formed by condensation of nitric oxide with diethylmalonate. Arulsamy and Bohle warn that this new type of compact ring structure forms dense crystals, and compounds **20**, **115**, and **116** are potential energetic materials which decompose violently at high temperatures" <2002AGE2089>.



20: X = K; Y = Me
115: X = K; Y = K
116: X = Na; Y = Na

A new reaction of nitric oxide with a variety of alkynes produces 5-substituted 1,2,3-oxadiazole 3-oxides **117** on quenching with water (Equation 21; **Table 5**) <2004CC216>. The 4-trimethylsilyl and 4-deuteriated derivatives are formed when the reaction is concluded by quenching with TMS-Cl or D_2O. The likely mechanism begins by nucleophilic attack or by one-electron transfer from the alkynyllithium reagent to nitric oxide giving an unstable intermediate that may then isomerize to reduce electron repulsion between the oxygen and nitrogen atoms (**Scheme 6**). The process is then likely to conclude by a 5-*endo*-*dig*-cyclization <2004CC216>.

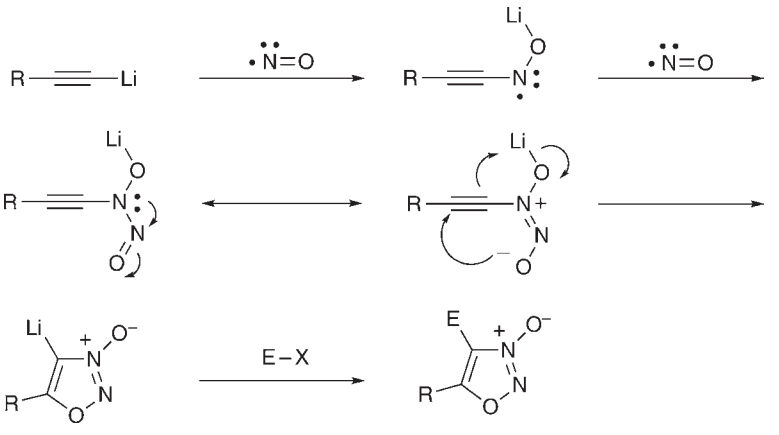


(21)

117

Table 5 1,2,3-Oxazolidinone 3-oxides **117** by reaction of nitric oxide with alkynyllithium reagents (Equation 21) <2004CC16>

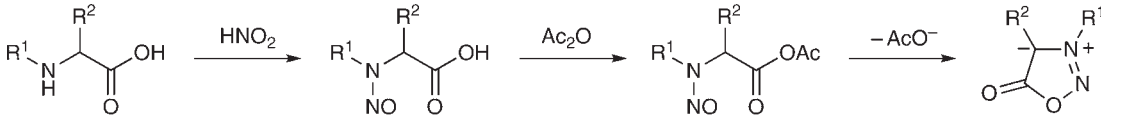
R	*E*–*X*	*Yield* (%)
n-C_8H_{17}	**H**–OH	84
n-C_8H_{17}	**D**–OD	82
n-C_8H_{17}	**Me_3Si**–Cl	88
Ph	**H**–OH	72
Ph	**Me_3Si**–Cl	78
4-$MeOC_6H_4$	**H**–OH	82
4-$MeOC_6H_4$	**D**–OD	79
4-$MeOC_6H_4$	**Me_3Si**–Cl	85
$BnOCH_2CH_2$	**H**–OH	80
$BnOCH_2CH_2$	**Me_3Si**–Cl	79
$PhCCCH_2OCH_2$	**H**–**OD**	72
$PhCCCH_2OCH_2$	**Me_3Si**–Cl	88
CH_2CHCH_2 (Ts) NCH_2	**H**–OH	82



Scheme 6

5.03.9.2 Sydnones

Entry into this class of compounds remains dominated by the standard method (**Scheme 7**). Nitrosation of the appropriately substituted glycine **118** to give *N*-nitroso derivative **119** is followed by mixed anhydride formation to give intermediate product **120** that cyclizes to give the sydnone **121** <1996JHC485, 1996JHC719, 2002ARK80, 2002MI237, 2002SC2203, 2003BMCL2899, 2004AP164, 2004AP427>.



118 **119** **120** **121**

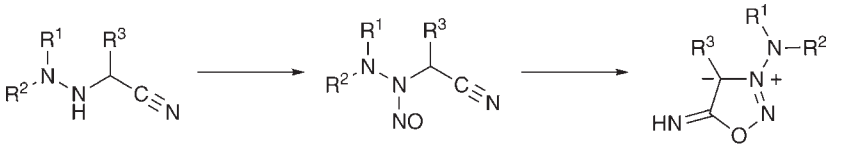
R^1 and R^2 = alkyl or aryl

Scheme 7

Mixed anhydride formation is bypassed in a synthesis of 3-phenylsydnone where *N*-nitroso-*N*-phenylglycine is cyclized directly in the presence of 2-chloro-1,3-dimethylimidazolium chloride <1999JOC6989> or 1,3-dibromo-5,5-methylhydantoin <2006H(68)175, 2006S1123> as dehydrating agents. The standard synthesis of sydnones has also benefited from the use of microwave irradiation to form the necessary *N*-arylglycine starting materials <2006H(68)175>.

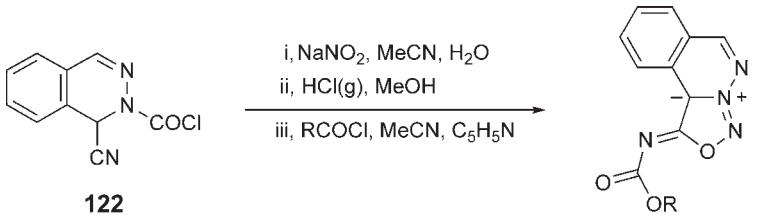
5.03.9.3 Sydnonimines

Sydnonimimes are prepared in a similar way to sydnones (Section 5.03.9.2) but rely on the availability of the appropriate aminonitrile (**Scheme 8**) <2002CRV1091>. Substituted dihydro- and tetrahydrophthalazine **122** and **124**, formed from phthalazine by modification of the Reissert reaction, were converted to the novel sydnonimines **123** and **125** (Equation 22) <1995JHC643>.



R^1, R^2, and R^3 = alkyl or aryl

Scheme 8

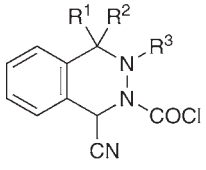


122

R = Et (7%)
R = 4-MeOC$_6$H$_4$ (7%)

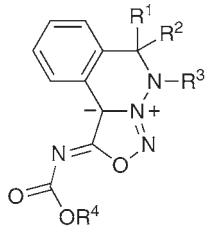
123

(22)



124

R^1 = H or Me
R^2 = H or Me
R^3 = Me or Bu

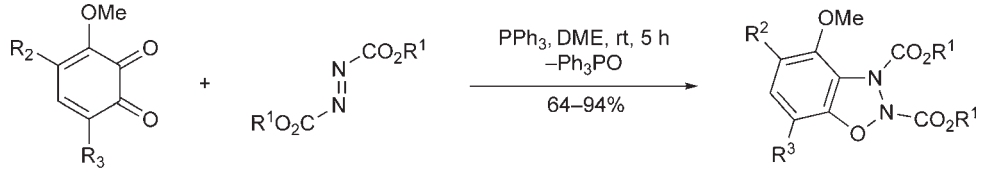


125

R^1 = H or Me
R^2 = H or Me
R^3 = Me or Bu
R^4 = Et or 4-MeOC$_6$H$_4$

5.03.9.4 2,3-Dihydro-1,2,3-oxadiazoles

This class of compound is represented by 2,3-disubstituted-1,2,3-benzoxadiazoles and new caged structures. 2,3-Disubstituted-1,2,3-benzoxadiazoles **128** were prepared in high yield when the Huisgen zwitterion, formed between dialkyl azodicarboxylates **127** and triphenylphosphine, was reacted with 3-methoxy-4,6-disubstituted-1,2-benzoquinones **126** (Equation 23; **Table 6**) <2005OL5139>.



126 127 128

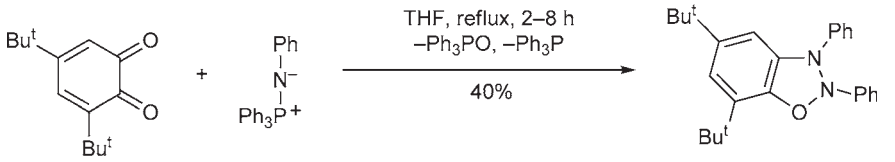
(23)

Table 6 Dihydro-1,2,3-benzoxadiazoles by reaction 3-methoxy-4,6-disubstituted-1,2-benzoquinones (Equation 23) <2005OL5139>

R^1	R^2	R^3	*Yield* (%)
Et	Bu^t	Bu^t	75
Et	Ph_2CH	Ph_2CH	78
Et	Bu^t	H	91
Et	(4-ClC$_6$H$_4$)$_2$CH	(4-ClC$_6$H$_4$)$_2$CH	73
Pr^i	Bu^t	H	94
Pr^i	Ph_2CH	Ph_2CH	85
Pr^i	(4-ClC$_6$H$_4$)$_2$CH	(4-ClC$_6$H$_4$)$_2$CH	64
Pr^i	Me_2PhCH	Me_2PhCH	85
Pr^i	Bu^t	Bu^t	86

The proposed mechanism involves attachment of the zwitterion to the C2 of the quinone to form a tetrahedral intermediate that rearranges by a Wittig-type process to give a spirooxadiazoline intermediate. Elimination of triphenylphosphine oxide on subsequent ring opening and aromatization is followed by ring closure to give the 2,3-disubstituted-1,2,3-benzodiazole <2005OL5139>.

A new oxadiazole derivative **131** has been prepared in 40% yield by reacting the 1,2-benzoquinone **129** with 1 equiv of *N*-phenyliminophosphorane **130**; product yield rises to almost 80% when 2 equiv of phosphorane **130** is used (Equation 24) <2002SC2779>.

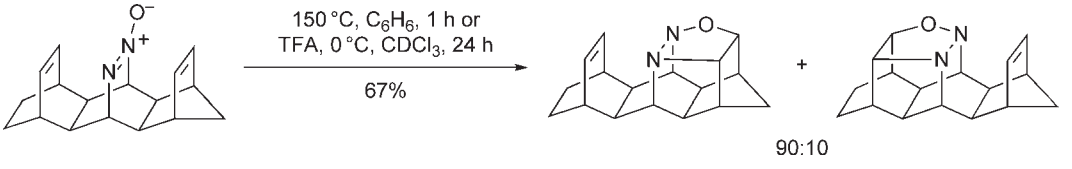


(24)

129 **130** **131**

^{13}C-NMR analysis revealed signals at $\delta = 142.5$ and 135.7 ppm due to C7a and C3a respectively, and molecular ion $m/z = 386$ was observed as the base peak in the mass spectrum. Although formation of oxadiazolines is possible in principle by the [3+2] cycloaddition of azoxides and alkenes, they are predicted to be unstable with the likely mode of decomposition being the retro 1,3-dipolar addition to the azoxide and alkene (Section 5.03.2).

The first examples of stable oxadiazolidine structures are the regioisomers **133** formed by intramolecular [3+2]-cycloaddition of **132** (Equation 25) <1995LA1801, 1997JHC1383>. Further examples of cage structures featuring the oxadiazolidine ring have been reported together with the crystal structure of compound **22** (Section 5.03.3.1) <2000EJO743>.

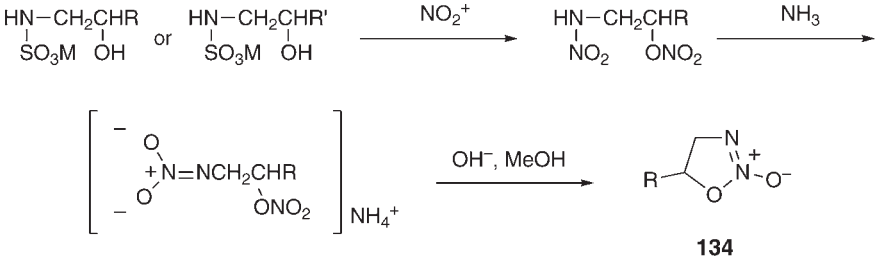


(25)

132 **133**

5.03.9.5 4,5-Dihydro-1,2,3-oxadiazoles

A new approach to functionally substituted 4,5-dihydro-1,2,3-oxadiazole 2-oxides **134** has been described (**Scheme 9**) <2005RJO120>. The method allows access to new derivatives and better access to the known derivatives that relied on 'difficult-to-prepare' starting materials such as *N*-nitrosulfamides and *N*-nitro-2-cyanoethylalkylamines.



134

M = Na, K
R' = CH_2OH, $CH_2N(OH)Me$
R = H (44%), CH_2OMe (44%), CH_2Cl (56%), CH_2N_3 (45%), CH_2ONO_2 (51%), $CH_2N(NO_2)Me$ (36%)

Scheme 9

Thus nitration of readily accessible hydroxysulfamates followed by conversion to their ammonium salts gave 4,5-dihydro-1,2,3-oxadiazole 2-oxides **134** on cyclization using methanolic alkali. The structure of one derivative ($R = CH_2N(NO_2)Me$) (**Scheme 9**) was further confirmed by two-dimensional $^{1}H-^{15}N$ correlation NMR <2005RJO120>.

5.03.10 Ring Syntheses by Transformation of Another Ring

There have been no reports of 1,2,3-oxadiazoles synthesized by transformation of another ring since the last survey <1996CHEC-II(4)165> other than those involving cyclization of substituents attached to benzene (Section 5.03.9).

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

The chemistry of 1,2,3-oxadiazoles is dominated by the sydnones, sydnonimines, and their analogs. There are many examples that employ the standard route to sydnones; the method remains unsurpassed. Methods for cyclization have been described that bypass the need for mixed anhydride formation, helping to shorten the standard route (Section 5.03.9.2).

The *ortho*-directed lithiation protocol allows selective functionalization of 3-arylsydnones in the aryl ring, the C4 position of the sydnone ring, or both simultaneously. The method allows access to fused ring structures (Sections 5.03.5.2.4 and 5.03.7.1.1). Reliable routes to otherwise unknown oxadiazolidines have been established (Section 5.03.9.4). Regiospecificity can now be achieved by judicious choice of substituents when propargylic esters react with sydnones to form pyrazoles (Section 5.03.5.2.6).

5.03.12 Important Compounds and Applications

1,2,3-Oxadiazole derivatives display a wide range of biological activities. The series of important compounds that were included in the last survey <1996CHEC-II(4)165> continues to have importance and is extended by several new derivatives. The therapeutic uses of sydnonimines as antihypertensive agents stem largely from their important role as donors of nitric oxide in biological systems and are documented in recent reviews <B-2004MI1, B-2005MI1, 1998MI113, 1999FA316, 2000MI200, 2000MI559, 2000MI701, 2000TH, 2002CRV1091, 2002MI385, 2004MI849>.

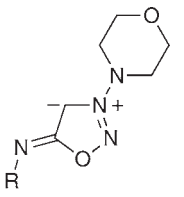
Molsidomine **12** and other *N*-acyl derivatives of sydnonimines are stable solids that can be stored at room temperature when protected from light. Molsidomine has a long-term vasodilatory effect in reducing the venous return, cardiac output, ventricular work, and myocardial oxygen consumption. Its own vasoactivity is poor *in vitro* but when metabolized by esterase hydrolysis, the potent vasorelaxant compound SIN-1 **13** is revealed (Section 5.03.5.2.1). SIN-1 **13** has been shown to have potent vasorelaxant effect on the isolated human radial artery and shows no cross-tolerance with nitrates <1998MI212, 2002MI1>. It has been further shown to have a hyperpolarizing effect on locus coeruleus neurons in the brain <1998MI3508>. Irradiation with visible light markedly enhances the release of nitric oxide by SIN-1 **13** <1997MI66> and in aerosolized form it exhibits dose-dependent, sustained vasodilation in the pulmonary circulation <1997MI985>.

Pirsidomine **135** has antiischaemic and antianginal properties, and is similar in action to molsidomine, undergoing bioactivation *in vivo* to compound **136** <1996MI4937>. Sydnocarb (mesocarb) **59** acts on the central nervous system (CNS) and has been used as a psychotropic drug and antidepressant <2004CHE507>.

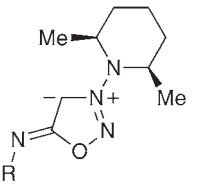
Arylthioethylsydnone **73** (TTMS) is known to act as a mechanism-based inhibitor of some cytochrome P450 isozymes and as an inducer of cytochrome P450 3A <1996MI676, 1996MI872, 1998MI739>.

Sydnonimines with alkylamine substituents at position N3 were shown to be considerably more potent donors of nitric oxide compared with analogs having alkyl or aralkyl groups at the same position <2004RCB2840>.

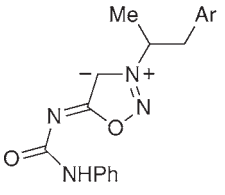
Various new 3-arylsydnone derivatives represented by general formula **137** have been prepared and are reported to possess anti-inflammatory <1995MI243>, antiviral <2006MI399>, antimicrobial <1995IJB346, 2000FA65, 2001MI297, 2004AP164, 2004AP427>, antifungal <1995IJB346, 1996IJH107, 2000FA406>, bactericidal <1995MI327>, CNS depressant <2001AP263>, trypanocidal <2003JHC943>, and radical scavenging <2004BMC4633> properties.



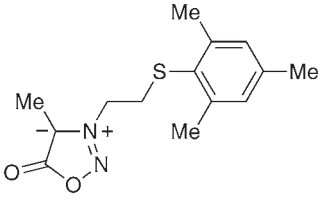
12: R = EtO_2C
13: R = H·HCl



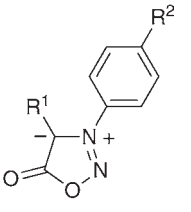
135: R = 4−$MeOC_6H_4CO$
136: H·HCl



59



73

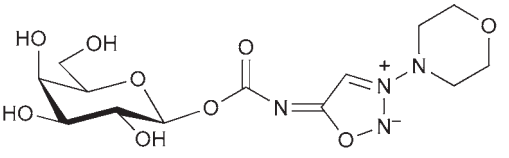


137

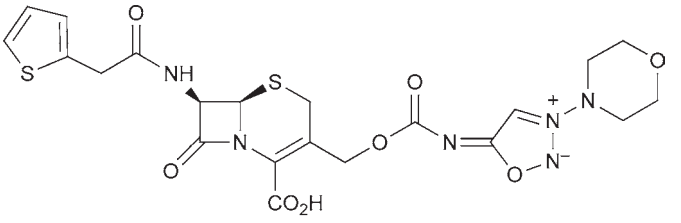
A short series of 3-(4-amino-3-nitrophenyl)sydnones was prepared and screened for antitumor activity against selected cell lines <2003BML2899>. Alkanediamines that inhibit aggregation of human blood cells lose antiplatelet activity when the pendant amino groups are converted to sydnonimine groups <1996AP191>.

Synthesis of glycoside **138**, a galactose conjugate of SIN-1 **13**, has been achieved and its role as β-galactosidase-mediated nitric oxide donor has been evaluated <2005JOC3518>.

Structure **139** represents a cephalosporin conjugate of SIN-1 **13** that has been synthesized and evaluated as a β-lactamase-dependent, nitric oxide-releasing conjugate with potential application in antibody-directed enzyme prodrug therapy (ADEPT) <2003BML1687>.



138



139

3-Methyl- and 3-ethylsydnone have been used as aprotic solvents for electrolytes <2000MI20, 2002MI334>, whereas 3-phenylsydnone has been employed as a filter for recording the absorption spectra and refractive indexes of polymer films containing other mesoionic compounds <2002MI2290>.

Synthesis of the first mesoionic nematic and smectic A liquid crystals derived from sydnones has been described and their self-organization into liquid crystal phases has been studied by optical, calorimetric, and powder X-ray diffraction methods <2005CC1552>.

5.03.13 Further Developments

The acylation of 3-arylsydnones (Section 5.03.5.2.4) at position C4 occurs under neutral conditions and in satisfactory yield, in the presence of acetic anhydride and 1,3-dibromo-5,5-dimethylhydantoin as an efficient promoter <2007JHC467>.

Electrochemical reduction of 3-phenylsydnone **89** and its 3-(4-methoxy)phenyl and 3(4-methyl)phenyl analogues represents a new method for the preparation of 2,4-dihydro-3-aryl-1,2,3-oxadiazole-5-ones <2006CCA273, 2006MI776>. The products were isolated in 82 to 88% yield, and their proposed structures are supported by melting point, elemental analysis, IR, proton NMR, and mass spectral data.

Unlike simple dipolarophiles, 1-aryl-3-(5-nitro-2-furyl)propynones undergo regiospecific 1,3-dipolar cycloaddition with 3-arylsydnones (Section 5.03.5.2.6) to form new 1-aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles (72–73%) <2007SC1285>. The formation of pyrazole-fused norbornenes by the reaction of 3-phenylsydnone **89** and 3-aryl analogues with cyclopentadiene (Section 5.03.5.2.6), is strongly dependant on the nature of the aryl substituents, which affect the rate of dehydrogenation of the dihydropyrazole intermediate <2006MI1557>.

Silver and tetra(n-butyl)ammonium salts of 4-carboxymethylsydnone 3-oxide **20** (Section 5.03.9.1) have been prepared <2007CJC105>. The acid and base stability of these *N*-oxides and their reluctance to undergo cycloaddition with dipolarophiles is noteworthy. X-ray diffraction data and estimation by density functional theory suggest a degree of aromaticity in compound **20** and in its silver salt as evidenced by planarity of the sydnone ring and delocalization of double bonds. Cyclic voltametry data suggest that these sydnone derivatives may be oxidized with a suitable reagent and differential scanning calorimetry data demonstrate thermal stability at ambient temperature but exothermic decomposition above *229* °C. The tetra(n-butyl)ammonium salt of **20** is soluble in a range of organic solvents and undergoes *O*-methylation with dimethyl sulfate to give the kinetic product (85.4%). Alternatively, *N*-methylation can be achieved using methyl iodide as alkylating agent to give the thermodynamic product (61%) or by isomerization of the *O*-alkylated analogue (*2* h, 140 °C). The regioselectivity of these reactions was confirmed by X-ray crystallography <2007JOC3625>.

The standard synthesis of sydnones (Section 5.03.9.2) has benefited from the use of *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide (TBBDS) as an efficient promoter of the one-pot conversion of various *N*-arylglycines to sydnone products <2006H(68)2343>. Conversion of *N*-arylglycines to sydnones was achieved in 85 to 95% yield using a combination of $NaNO_2$ and Ac_2O in CH_2Cl_2 promoted by TBBDS, under mild and neutral conditions.

The *N*-acyl sydnonimine derivative molsidomine **12** has been used for many years in several countries for the treatment of stable angina pectoris. The efficacy and safety of molsidomine **12** given once-daily <2006MI107>, and its long-term tolerability <2006MI601>, have been established in recent clinical trials. The *N*-deacyl analogue SIN-1 **13** is a potent nitric oxide donor that has been used to study nitrotyrosine *O*-sulfate production by human hepatoma cells <2007BJ497>, dynorphin-mediated antinociceptive effects of L-arginine in mice <2006MI245>, and kynurenic acid production in rat brain <2007MI130>.

The same urethane linker group that is a feature of conjugates **138** and **139** (Section 5.03.12) has also been used to provide SIN-1 **13** conjugates of two vitamin E analogues, *δ*-tochopherol and Torolox®, that undergo enzymatic bioactivation in the presence of porcine liver esterase to release nitric oxide <2006MI363>.

Polymethyl(methacrylate) doped with 4-substituted 3-arylsydnones provide a promising class of nonlinear optical materials with various potential applications <2007SM142>.

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Biographical Sketch

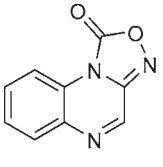
William Fraser was born in Hamilton. He studied at the other of the two local universities, Strathclyde, where he obtained a first class B.Sc. honors degree in 1986 and Ph.D. in 1989 under the direction of Professor Colin J. Suckling and Professor Hamish C. S. Wood. He was awarded a Royal Society European Exchange Postdoctoral Fellowship and worked in the laboratories of Professor Albert Eschenmoser at the ETH, Zürich. In 1991, he took up his present position as lecturer in medicinal chemistry at Aston University, Birmingham. His scientific interests include nucleoside and nucleic acid chemistry, solid-supported, synthesis, and study of base-modified antigene oligonucleotides targeted to DNA.

5.04
1,2,4-Oxadiazoles

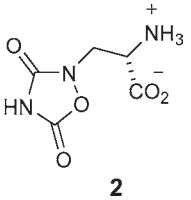
K. Hemming
University of Huddersfield, Huddersfield, UK

5.04.1 Introduction and Literature on 1,2,4-Oxadiazoles

1,2,4-Oxadiazoles were reviewed previously in CHEC(1984) <1984CHEC(6)365> and in CHEC-II(1996) <1996CHEC-II(4)179>, and these contain references to earlier comprehensive reviews. The present chapter updates the previous work and reviews the literature from 1995 onward, concentrating on major new advances, preparations, reactions, uses, and concepts. Each main section contains, where appropriate, a short paragraph to explain any major advances that have occurred since the appearance of CHEC-II(1996). Since the appearance of CHEC-II(1996), three major reviews dealing specifically with 1,2,4-oxadiazoles have appeared <2001JCM209, 2004HOU(13)127, 2005MI328>, the latter of which deals with mass spectrometric analysis; one other review deals with the uses of oximes for the synthesis of heterocycles in general, but includes significant sections on 1,2,4-oxadiazoles <2000H(53)2285>. Since CHEC-II(1996), the use of the 1,2,4-oxadiazole ring as a peptidomimetic, as a stable ester and amide isostere, together with the use of specific 1,2,4-oxadiazoles as inhibitors in several biological systems, has led to a huge upsurge in interest in this class of heterocycle, with over 1700 publications since 1995. Of these, just over 1000 deal with applications of the soluble guanylyl cyclase inhibitor 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) **1**, and a further 200 deal with applications of neuroexcitatory natural product quisqualic acid **2**.



1



2

5.04.2 Theoretical Methods

^{13}C nuclear magnetic resonance (NMR) chemical shifts of a series of (1,2,4-oxadiazolyl-5-yl)-1,2,5-oxadiazole 2-oxides were calculated using gauge-independent atomic orbital (GIAO) methods and found to be within 4 ppm of experimental values <2000J(P2)473>. Semi-empirical calculations (AM1) on a 3-(*p*-tolyl)-1,2,4-oxadiazole predicted the *p*-tolyl and 1,2,4-oxadiazole rings to be coplanar, a feature confirmed by X-ray crystallographic studies <2004T10761>. Both semi-empirical (PM3 and AM1) and *ab initio* (B3LYP/6-31G and HF/6-31G) molecular orbital

calculation have been performed for 3,5-diaryl-1,2,4-oxadiazoles and 3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles <2003JST149>, [3-phenyl-1,2,4-oxadiazol-5-yl]propionamides <2002JST177>, 2-acetyl-4,5-dihydro- and 4-acetyl-2,5-dihydro-1,2,4-oxadiazoles <2001JST29>, and 3-phenyl-[1,2,4]-oxadiazole-5-benzo[1,3]dioxol-5-ylmethylene-carbohydrazides <2005HCO29>. The *ab initio* calculations give values close to those obtained by crystallographic techniques and NMR spectroscopy. Resonance valence bond theory, volume calculations, semi-empirical (AM1) and *ab initio* (STO-3G and 6-31G) molecular orbital calculations have been reported for a series of analgesic 1,2,4-oxadiazolo-phthalimides <2003JST1, 2000JCX131>, leading to new suggestions for mechanisms of activity. Intermolecular perturbation theory and distributed multipole analysis have been used to establish the directionality and strength of hydrogen bonds formed between methanol and the 1,2,4-oxadiazole ring <1997JCC2060>. A theoretical treatment of the Boulton–Katritzky rearrangement involving 3-formylamino-1,2,4-oxadiazole compares and contrasts semi-empirical and *ab initio* treatments, offering some useful insights into the reaction pathway <1998JMT67>.

5.04.3 Experimental Structural Methods

5.04.3.1 X-Ray Diffraction

Recent X-ray crystal structures <2000J(P2)473, 2000TA1527, 2005NN1919, 2005BMC353, 2004T10761, 2003JST361, 2000JCX131> confirm earlier studies <1984CHEC(6)365, 1996CHEC-II(4)179> that the 1,2,4-oxadiazole ring is planar. **Table 1** shows some typical selected bond lengths and angles for the 1,2,4-oxadiazoles **3–9** shown in **Figure 1** <2000CCHT131, 2000JP2473, 2003JST361, 2005BMC353, 2005NN1919>. It is of further interest to note in compounds **3** and **7** that the aromatic substituent and 1,2,4-oxadiazole ring are coplanar. The dihedral angles between the heterocyclic rings in compounds **4** and **5** are 4.56° and 9.43°, respectively. Compound **6** has the two aryl substituents almost coplanar with dihedral angles of 11.13° and 2.28° for the C-5 and C-3 substituents, respectively.

Table 1 Selected bond lengths and angles for 1,2,4-oxadiazoles **3–9** (see **Figure 1**)

1,2,4-Oxadiazole	**3**	**4**	**5**	**6**	**7**	**8**	**9**
O(1)–N(2) bond length (Å)	1.421	1.414	1.391	1.415	1.415	1.404	1.423
N(2)–C(3) bond length (Å)		1.294	1.300	1.310	1.293	1.304	1.304
C(3)–N(4) bond length (Å)	1.396	1.370	1.373	1.385	1.372	1.377	1.387
N(4)–C(5) bond length (Å)		1.283	1.287	1.298	1.293	1.297	1.297
C(5)–O(1) bond length (Å)		1.362	1.342	1.347	1.339	1.345	1.342
O(1)–N(2)–C(3) bond angle (°)		102.46	101.5	103.51	103.64		
N(2)–C(3)–N(4) bond angle (°)		115.9	116.9	114.1	114.42		
C(3)–N(4)–C(5) bond angle (°)	102.2	101.08	102.1	102.83	102.91		
N(4)–C(5)–O(1) bond angle (°)		113.9	112.8	113.3	113.19		
C(5)–O(1)–N(2) bond angle (°)	105.9	106.6	106.7	106.25	105.81		

The 4,5-dihydro-1,2,4-oxadiazole ring in compounds **10** <1999AXC650> and **11** <2001JST29> (see **Figure 2**) are in an envelope conformation, with the O-1 atom in compound **10** 0.110 Å above the common plane occupied by N-2, C-3, N-4, and C-5. In compound **10**, the C-3 phenyl substituent and heterocyclic ring are no longer coplanar, and show a dihedral angle of 36.3°. The fused 4,5-dihydro-1,2,4-oxadiazole **12** <1999AXC685> shows the oxadiazole ring with a twisted envelope conformation, whereas the fused system **13** has an envelope conformation with the C-5 atom 0.226 Å out of the plane described by O-1, N-2, C-3, and N-4 <2002AXE548>. As shown in **Table 2**, the N(4)–C(5) bond in 4,5-dihydro compounds **10–13** is, as expected, longer than that in the fully conjugated systems shown in **Table 1**. Crystal structures for a series of 2,3-dihydro-1,2,4-oxadiazole complexes **14** have been reported <2001IC264>, and details are shown in **Table 2** for one such compound, complex **15**, which shows the expected increased bond length for N(2)–C(3), together with a dihydro-1,2,4-oxadiazole ring in an envelope conformation with N-2 out of the plane and the other ring slightly twisted on N(2)–C(3). Finally, structures for the two 2,5-dihydro-1,2,4-oxadiazoles **16** and **17** have been reported <2001JST29>, showing dihedral angles between the heterocyclic ring and the C-3 aryl substituent of 28.83° and 27.82°, respectively, and bond lengths and angles as listed in **Table 2**.

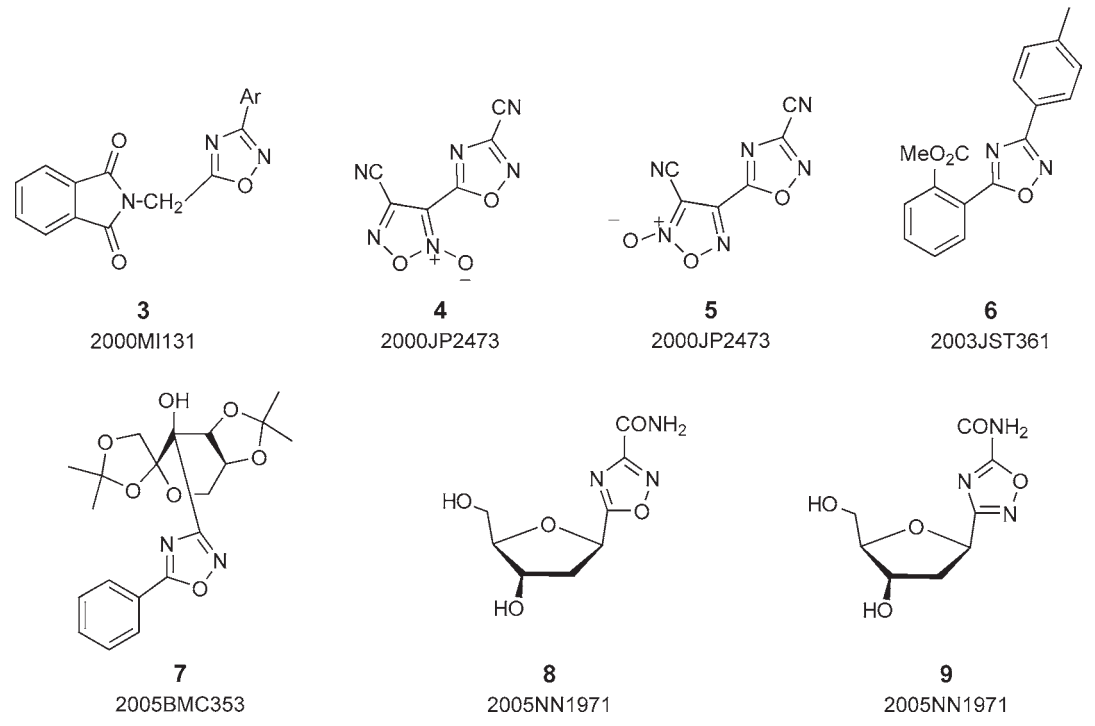


Figure 1 1,2,4-Oxadiazoles with recently reported X-ray crystal structures (see **Table 1**).

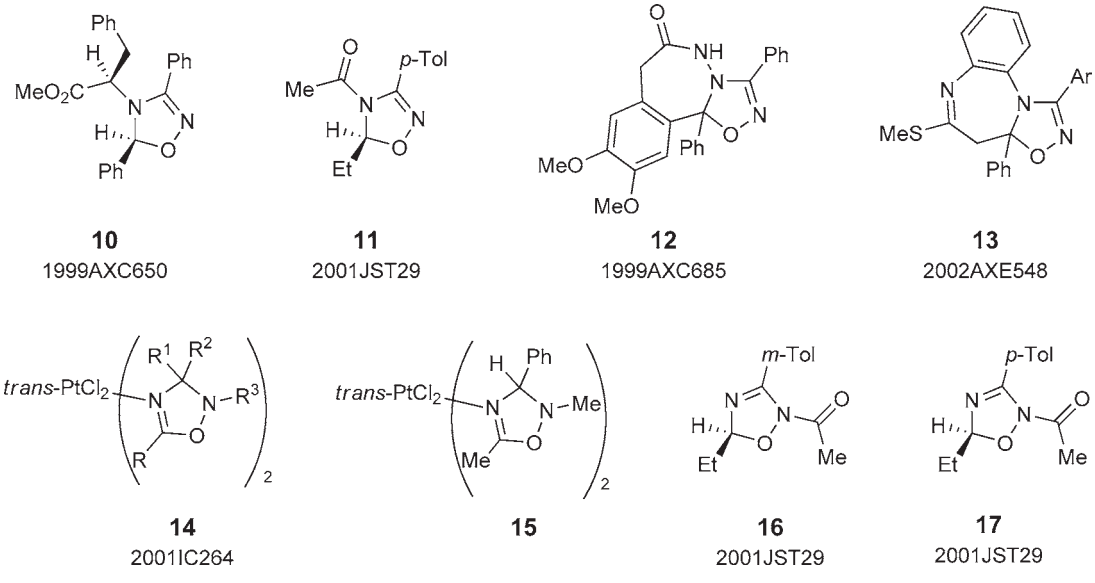


Figure 2 Dihydro-1,2,4-oxadiazoles with recently reported crystal structures (see **Table 2**).

5.04.3.2 NMR Spectroscopy

In line with its importance in characterization, this section has been expanded and updated and includes a more detailed analysis than that in CHEC-II(1996) and CHEC(1984), which contain, nonetheless, important data on proton NMR shifts of C-3- and C-5-unsubstituted fully conjugated 1,2,4-oxadiazoles. A major advance since CHEC-II(1996) is the appearance of a large amount of fully assigned ^{13}C data for C-3/C-5-disubstituted fully conjugated 1,2,4-oxadiazoles <1996JHC1583,

Table 2 Selected bond lengths and angles for dihydro-1,2,4-oxadiazoles **10–13** and **15–17** (see **Figure 2**)

Dihydro-1,2,4-Oxadiazole	**10**	**11**	**12**	**13**	**15**	**16**	**17**
O(1)–N(2) bond length (Å)	1.431	1.430	1.443		1.495	1.421	1.427
N(2)–C(3) bond length (Å)	1.287	1.280	1.285	1.282	1.486	1.412	1.414
C(3)–N(4) bond length (Å)	1.389	1.403	1.405		1.499	1.267	1.270
N(4)–C(5) bond length (Å)	1.473	1.455	1.484		1.277	1.449	1.444
C(5)–O(1) bond length (Å)	1.439	1.429	1.449		1.348	1.456	1.450
O(1)–N(2)–C(3) bond angle (°)	105.8	107.6	106.41		103.1	104.9	103.9
N(2)–C(3)–N(4) bond angle (°)	115.6	112.2			103.9	114.0	113.3
C(3)–N(4)–C(5) bond angle (°)	105.2	105.4	104.02		108.6	107.3	107.6
N(4)–C(5)–O(1) bond angle (°)	103.1	102.3			115.5	105.7	105.8
C(5)–O(1)–N(2) bond angle (°)	109.71	110.3	106.78		106.4	104.5	103.9

1998JHC161, 1999CAR157, 1999FES747, 2000HCO41, 2000J(P2)473, 2002JST177, 2003CAR257, 2006TL2965>. **Table 3** summarizes the data for some 50 oxadiazoles represented by structures **18–24** (**Figure 3**). Analysis of the data reveals that the more deshielded C-5 (OCN) is downfield of the C-3 (NCN). It is interesting to note that the assignments for 1,2,4-oxadiazole **19** were made on the basis of careful INEPT and $^{13}C\{^{1}H\}$ nuclear Overhauser effect (NOE) experiments. In a series of bis-aryl 1,2,4-oxadiazoles **24**, the presence of electron-withdrawing or -donating groups on the aryl rings has little effect on the C-3 or C-5 ^{13}C shifts. Similarly, switching the furanose ring in compound **20** for pyranose maintains the C-3 shift at ~171 ppm <2003CAR257>, whereas the presence of a C-3 nitrile group gives an upfield shift to ~149 ppm. Alkyl substituents give the most downfield signals for the C-5 carbon, with an approximate 10 ppm upfield shift for an aryl group, and a further 5–10 ppm upfield shift for a heteroaryl or amide group. A study of ^{14}N chemical shifts (nitrogen NMR shielding) of the parent system **25** shows N-2 at 9.41–22.10 ppm and N-4 at 135.11–145.56 ppm (referenced to neat nitromethane) when studied in 0.2 M solutions of various solvents <1996JMR148>.

Table 3 ^{13}C NMR shifts for C-3/C-5-disubstituted 1,2,4-oxadiazoles **18–24** (see **Figure 3**)

1,*2,4-Oxadiazole*	**18**	**19**	**20**	**21**	**22**	**23**	**24**
^{13}C shift for C-3	167.9–168.2	165.0	169.3–171.6	148.3–149.7	148.6–149.6	168.1–168.2	168.8–169.0
^{13}C shift for C-5	182.7–184.8	170.5	173.4–174.9	166.9–168.3	164.1–165.1	179.4–179.0	174.7–175.8
No. of examples	9	1	4	16	3	4	16
Solvent	$CDCl_3$	DMSO	DMSO	DMSO	CD_3CN	$CDCl_3$	$CDCl_3$

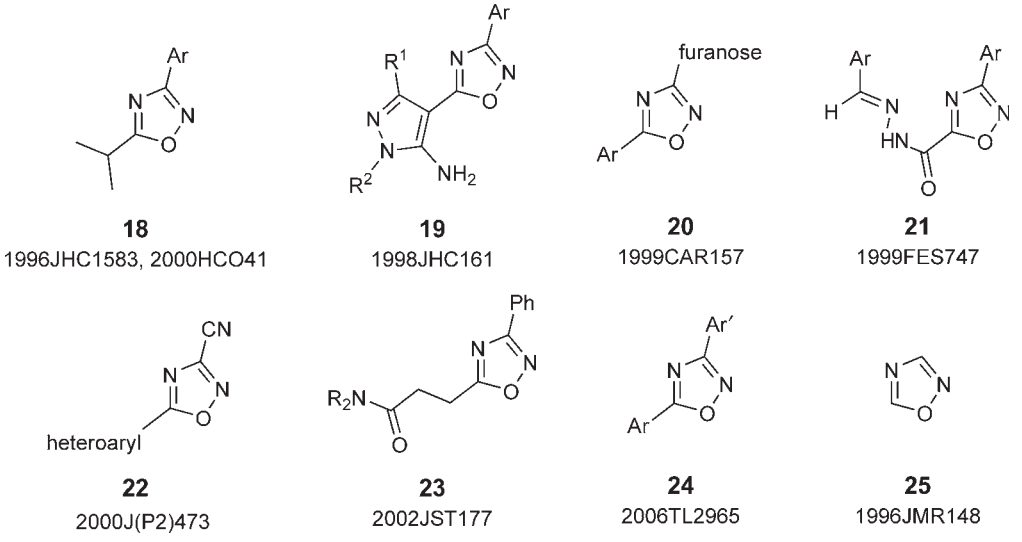


Figure 3 Selected 1,2,4-oxadiazoles with ^{13}C NMR data listed in **Table 3**.

With the 2-methyl-2,3-dihydro-1,2,4-oxadiazoles **26** (see **Figure 4**; $R^2 = Me$), the C-5 ^{13}C shift occurs at around 160 ppm, with the C-3 ^{13}C shift at 93–94 ppm. When the 2-substituent is aryl, the C-5 shift occurs at around 170 ppm, with the C-3 ^{13}C shift now at 123–124 ppm. The corresponding ^1H shifts for the C-3 proton are 5.7–5.8 and 7.2–6 ppm, respectively ($CDCl_3$) <1996H(43)1021>. The platinum(II) complexes **27** (see **Figure 4**; $R^2 = Me$ or CH_2Ph) show the C-5 ^{13}C shift at around 163–168 ppm, and the C-3 ^{13}C shift at 89–95 ppm, with the corresponding ^1H shift for the C-3 proton at 5.6–6.2 ppm. Oxidation of the complex up to Pt(IV) gives the C-5 ^{13}C shift at around 172–173 ppm, the C-3 ^{13}C shift at 91–93 ppm, with the ^1H shift for the C-3 proton now at 6.6–6.8 ppm ($CDCl_3$) <2001IC264>. In the 2,3-dihydro-1,2,4-oxadiazol-3-one **28**, the C-3 carbonyl ^{13}C shift occurs between 165.4 and 179.9 ppm ($CDCl_3$/DMSO-d_6) (DMSO = dimethyl sulfoxide) <2003JEC21>. The isopropyl-4,5-dihydro-1,2,4-oxadiazoles **29** ($R^1 = CHMe_2$) show the C-5 ^{13}C shift at 97.1–98.9 ppm, and the C-3 ^{13}C shift at 155.1–156.6 ppm, with the corresponding ^1H shift for the C-5 proton at 5.3–5.6 ppm ($CDCl_3$) <1996JHC1583, 2000HCO41>, whereas the *n*-propyl-4,5-dihydro-1,2,4-oxadiazoles **30** ($R^1 = CH_2CH_2Me$) show the C-5 ^{13}C shift at 92.0–93.2 ppm, the C-3 ^{13}C shift at 155.2–156.0 ppm, and the ^1H shift for the C-5 proton at 5.6–5.7 ppm ($CDCl_3$) <2003BMC1821>. The fused 5,5-disubstituted 4,5-dihydro-1,2,4-oxadiazoles **31** show C-5 ^{13}C shifts in the slightly more downfield range of 98.6–103.7 ppm, with C-3 at 154.6–167.5 ($CDCl_3$) <2001NJC1479>. 4,5-Dihydro-1,2,4-oxadiazol-5-ones **32** show the C-3 at ~166 and the C-5 carbonyl carbon at ~174 ppm (DMSO) <2002OPD896>. ^{13}C NMR spectra of 2,5-dihydro-1,2,4-oxadiazoles **33** show the deshielded C-5 at 97.7 ($R^2 = H$) to 107.3 ppm ($R^2 = Me$) and the C-3 at 160.2–166.1 ppm, with the ^1H NMR spectra ($R^2 = H$) showing the proton on C-5 resonating at 6.1–6.3 ppm ($CDCl_3$) <1998BCJ1231>. 1,2,4-Oxadiazolidin-3,5-diones **34** have continued to attract much attention, and heteronuclear multiple bond correlation (HMBC) studies have been able to establish that the C-5 carbonyl is slightly upfield of the C-3 carbonyl in the ^{13}C spectrum, with values in the range 150–156 ppm (C-5) and 155–162 ppm (C-3) <1997SL263, 1999JME1639, 2000HCO55>. The 2-alkyl-5-aryl-4-unsubstituted-oxadiazolidin-3-ones **35** show the C-3 carbonyl at

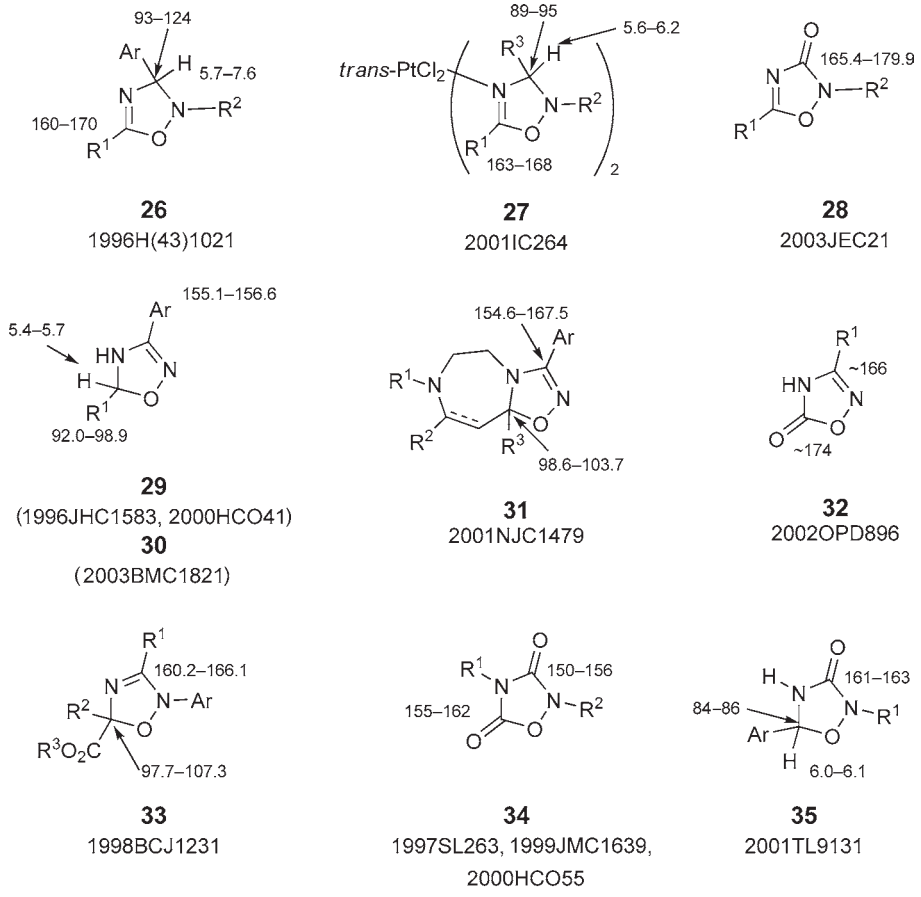
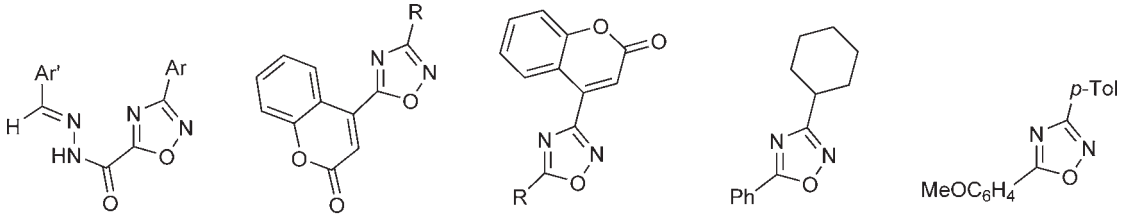


Figure 4 Representative NMR signals for non-fully conjugated 1,2,4-oxadiazoles **26–35**.

161–163 ppm in the ^{13}C NMR and the sp^3 C-5 at 84–86 ppm, with the C-5-H at 6.0–6.1 ppm in the ^1H NMR spectra <2001TL9131>. The corresponding 1,2,4-oxadiazolidin-5-ones show the C-5 carbonyl at 166–170 ppm in the ^{13}C NMR, the C-3 methine carbon at 77–81 ppm, and the C-3-H at 5.7–6.7 ppm in the ^1H NMR, with the more downfield signals attributed to the influence of an eclipsing N-2 lone pair <2006SC997>.

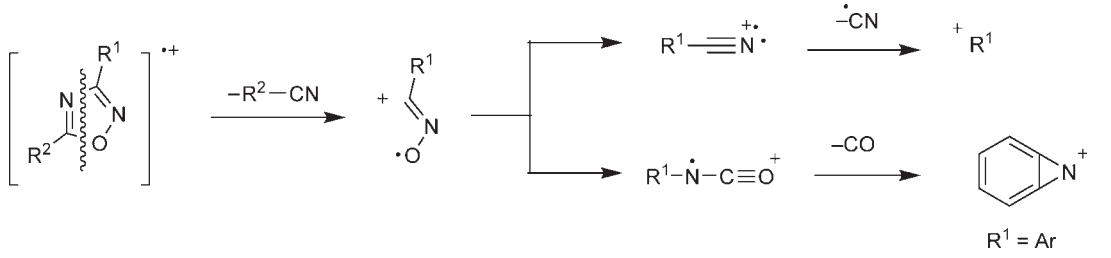
5.04.3.3 Mass Spectrometry

As discussed in CHEC-II(1996) <1996CHEC-II(4)179>, the electron impact mass spectrometry of 1,2,4-oxadiazoles is dominated by a (stepwise) 1,3-dipolar cycloreversion process, which proceeds via the initial cleavage of the 1,5 (C–O) and 3,4 (C–N) bonds, producing a nitrile oxide fragment, and recent reports highlight the continuing importance of this fragmentation <2003H(60)2287, 2000MI115, 1999BML209, 1998EJM715, 1996JHC967> in 1,2,4-oxadiazole characterization. As examples, the acyl hydrazone-substituted 1,2,4-oxadiazoles **21** (**Figure 5**) show major fragmentation to the expected nitrile oxide fragment, as well as fragmentations specific to the hydrazone side chain <2000MI115>. The coumarin regioisomers **36** and **37** also fragmented to give an aryl/alkyl nitrile oxide (depending on the R group) or a coumarinyl nitrile oxide as the major fragment, respectively <1998EJM715, 1996JHC967>. The 3-unsubstituted 1,2,4-oxadiazole **36** (R = H) fragmented with loss of an HCN fragment <1998EJM715>. A wide selection of 3-aryl/alkyl-5-phenyl-1,2,4-oxadiazoles and 3,5-bis-aryl-1,2,4-oxadiazoles show major fragmentation to a nitrile oxide fragment <2003H(60)2287, 1999BML209>, with, as typical examples, compounds **38** and **39** giving base peaks at 125 ($C_6H_{11}CNO$) and 133 (*p*-Tol-CNO), respectively. The nitrile oxide fragment itself fragments further, either by expulsion of oxygen to give a nitrile fragment which may then lose a CN fragment, or via rearrangement and expulsion of CO (**Scheme 1**). When R^1 is aromatic, these routes lead to *m/z* 77 and 90 peaks. A detailed review of the mass spectrometric analysis of 1,2,4-oxadiazoles and dihydro-1,2,4-oxadiazoles appeared in 2005 <2005MI328>.



21 2000MI115 **36** 1996JHC967 **37** 1998EJM715 **38** 2003H2287 **39** 1999BML209

Figure 5 1,2,4-Oxadiazoles that undergo fragmentation by loss of a nitrile oxide fragment.



Scheme 1

5.04.3.3.1 IR Spectroscopy

Recent reports of infrared (IR) spectra reinforce information reported in CHEC-II(1996) <1996CHEC-II(4)179>, but a number of important detailed assignments have appeared in the interim. Thus, a series of fully conjugated 1,2,4-oxadiazoles **40** have been investigated <2003BMC1821> and the relevant absorptions are shown in **Figure 6**, and have been verified by other studies that show $\nu_{C=N}$ at 1592–1603 and ν_{N-O} at 895–910 cm^{-1} <2003CAR257,

2002JST177>. The 4-oxides **41** have $\nu_{C=N}$ slightly displaced at 1576–1602 cm^{-1} <1997T1787>. 4,5-Dihydro-1,2,4-oxadiazoles **29** and **30** show ν_{N-H} at 3192–3231 cm^{-1} (KBr disc), $\nu_{C=N}$ at 1592–1606 cm^{-1}, ν_{N-O} at 830–870 cm^{-1}, and ν_{C-O} at 1089–1179 cm^{-1} <1996JHC1583, 2003BMC1821, 2003CL842>. 2,5-Dihydro-1,2,4-oxadiazoles **33** show $\nu_{C=N}$ at 1622–1645 cm^{-1} <1998BCJ1231>. 2,3-Dihydro-1,2,4-oxadiazole complexes **15** show $\nu_{C=N}$ at 1567–1611 (Pt(IV)) or 1622–1660 cm^{-1} (Pt(II)), while the free 2,3-dihydro-1,2,4-oxadiazoles show $\nu_{C=N}$ between 1670 and 1676 cm^{-1} <2001IC264, 2000JA3106>. 1,2,4-Oxadiazolidin-5-ones **42** have a carbonyl absorption in the range 1744–1774 cm^{-1} <2006SC997>, while 4-unsubstituted 1,2,4-oxadiazolidin-3-ones **35** show the carbonyl at 1705–1712 cm^{-1} <2001TL9131>. 1,2,4-Oxadiazolidin-3,5-diones **34** show carbonyl absorptions at 1814–1837 and 1738–1758 cm^{-1} <2000HCO55>.

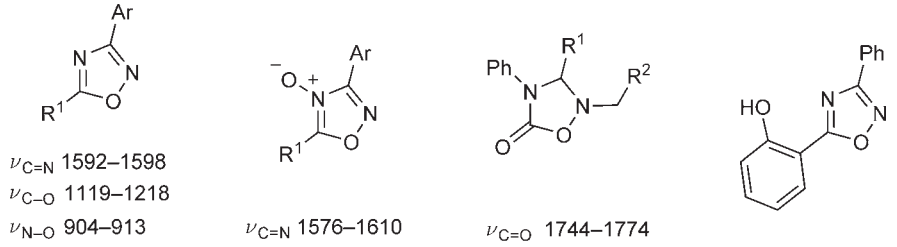


Figure 6 IR absorptions (cm^{-1}) reported for 1,2,4-oxadiazoles.

5.04.3.4 Miscellaneous

UV–Vis (ultraviolet–visible) and fluorescence spectra of Cu(II) complexes of 5-(2-hydroxyphenyl)-3-phenyl-1,2,4-oxadiazole **43** (see **Figure 6**), have been investigated and the complexes were found to fluoresce at ambient temperature via a 2:1 complex, with the Cu(II) binding to the monodentate 1,2,4-oxadiazole ring via N-4 and to the OH group <1999ICA1>. Very few other studies report UV spectra for 1,2,4-oxadiazoles, and those that are reported involve 1,2,4-oxadiazoles with aryl substituents <1996JHC1583, 2003BMC1821>. This may reflect the fact, as discussed in CHEC-II(1996) <1996CHEC-II(4)179>, that nonaryl 1,2,4-oxadiazoles have no UV absorption above 200 nm.

5.04.4 Thermodynamic Aspects

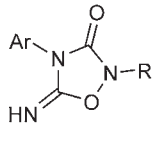
Important information on the boiling points and melting points of 1,2,4-oxadiazoles and on the relative stabilities of fully conjugated disubstituted and monosubstituted 1,2,4-oxadiazoles is contained in CHEC-II(1996) <1996CHEC-II(4)179> and is still of great relevance. Since the appearance of CHEC-II(1996), a large number of fully conjugated 3,5-disubstituted 1,2,4-oxadiazoles have been prepared and are generally reported as thermally stable solids, irrespective of the nature of the substituents <2005JHC699, 2003H(60)2287, 2003JST1, 2002SC887, 2001TL1495, 2000FES719>, although those with a simple aliphatic substituent tend to be oils <1996CHEC-II(4)179, 2000HCO41, 1999BML209>. The high stability of fully conjugated 3,5-disubstituted 1,2,4-oxadiazoles allows them to be prepared without decomposition by microwave irradiation at temperatures up to 200 °C <2005OL925, 2003TL9337>. A study of the mesomorphic phase transitions of a series of 5-(bromophenyl)-1,2,4-oxadiazoles reveals that some are able to demonstrate both smectic and nematic phases <2000MCL327>.

Fully conjugated 1,2,4-oxadiazoles are generally stable to column chromatography on silica, and gas chromatography (GC) analysis has been performed on, for example, HP-5 phenylmethylsilicone columns <1999BML209>. High-performance liquid chromatography (HPLC) at the semipreparatory level has been undertaken using a SH-C18 column in water/acetonitrile/formic acid <2003TL9337>, and analytical HPLC has been performed using YMC-ODS reverse-phase column with methanol/water/TFA (TFA = trifluoroacetic acid) <2001BML753>. Solubility is good in DMSO, ethyl acetate and chloroform; recrystallisation has been effected from ethyl acetate/ether/hexane, ethanol, chloroform or chloroform/hexane. Fully conjugated 1,2,4-oxadiazoles are used successfully as stable, hydrolysis resistant isosteres for esters and amides, and are popular peptidomimetics due to this inherent stability <2004HOU(13)127, 2001JCM209>.

Monocyclic 3,5-disubstituted 4,5-dihydro-1,2,4-oxadiazoles are thermally stable solids which are stable to chromatography on silica in the case of both 4-substituted and 4-unsubstituted examples <2002JCM131, 2000PHA22, 2000HCO41>, and several fused 4,5-dihydro-1,2,4-oxadiazoles are solids with excellent thermal and chromatographic stability <2002AXE548, 2001NJC1479, 1999AXC685>. Thermokinetic analysis (differential scanning calorimetry, DSC) of sodium and potassium 3-methyl-4,5-dihydro-1,2,4-oxadiazol-5-ones show them to be stable solids suitable for large-scale processing with melting points and onset temperatures in excess of 250 °C <2002OPD896>, and other studies have shown 4,5-dihydro-1,2,4-oxadiazol-5-ones to be stable to hydrolysis by aqueous sodium hydroxide <1995BML1903>. Several series of 2,5-dihydro-1,2,4-oxadiazoles have been synthesized and are usually isolated as stable oils that are easily purified on silica gel, showing good thermal stability (stable in boiling acetonitrile, for example) <1998BCJ1231, 2005OL1391>. 2,3-Dihydro-1,2,4-oxadiazoles have also been reported to be oils which are stable in solution in the presence of pyridine and are stable to chromatography on silica gel <2000JA3106>. 1,2,4-oxadiazolidin-3,5-diones, such as the natural product quisqualic acid **2**, are stable solids at room temperature, survive heating in DMF at 98 °C, are stable in the presence of organic acids such as TFA, and are suitable substrates for ion exchange chromatography <2000HCO55, 1996TL5225>. 3-Substituted 1,2,4-oxadiazolidin-5-ones and the related 5-thiones are chromatographically and thermally stable solids which survive heating at reflux in either toluene or dichloromethane <1998H(48)1935, 2001TL9131>, with even the 3-imino derivatives **44** being stable and isolable, surviving methanolic sodium bicarbonate, organic bases such as triethylamine (TEA), and HCl in tetrahydrofuran (THF) <2002SC803>. 4,5-Dihydro-1,2,4-oxadiazoles are stable in the presence of sodium methoxide in methanol and in the presence of 70% ethylamine in water/THF <2003CL842>, and the corresponding 4,5-dihydro-1,2,4-oxadiazol-5-ones are stable in alkaline solution <1998AP375>. The dihydro-1,2,4-oxadiazoles are generally stable in the atmosphere and require more vigorous oxidation in order to convert them into fully conjugated 1,2,4-oxadiazoles, although there are isolated examples of spontaneous oxidation when strongly electron-withdrawing substituents are present <2000PHA22>. Thus, 4,5-dihydro-1,2,4-oxadiazoles are stable in the atmosphere <2003CL842, 2002JCM131, 2002AXE548, 2001NJC1479, 2000HCO41, 2000PHA22, 1999AXC685> but can be converted into fully conjugated 1,2,4-oxadiazoles in the presence of nitric acid in chloroform <2000HCO41>.

The fully conjugated 1,2,4-oxadiazole is planar, but is often described as having 'low aromaticity', appearing, for example, lower than furan on the Bird index <2005JOC3288, 2004EJO974, 2003JOC605, 1992T335> and has appreciable heterodiene character, a feature reflected by the relevant bond lengths (see Section 5.04.3.1). This low aromaticity often manifests itself by allowing rearrangement to more thermodynamically stable ring systems and makes 1,2,4-oxadiazoles good substrates for ring-to-ring transformations, where suitable substituents exist. As discussed in Section 5.04.3.1, the non- fully conjugated dihydro-1,2,4-oxadiazoles are nonplanar, adopting an envelope conformation with one atom sitting above the plane described by the four others (see Section 5.04.3.1 for full details).

Comments in CHEC(1984) <1984CHEC(6)365> on the tautomerism of 3- and 5-hydroxy, 3- and 5-amino, and the 3- and 5-sulfur analogues are still of importance, and a further review <2000AHC157> has appeared, which, together with a recent study of amino-1,2,4-oxadiazol-3-ones <2006CEJ727>, confirms the earlier observations. An interesting addition to the literature on tautomerism is the case of the 5-aryl-4,5-dihydo-1,2,4-oxadiazoles **45** which undergo formal tautomerism with the 4-aryl-1,3-diaza-1,3-butadiene **46**, which can then be made to undergo ring closure with loss of water to form the quinazoline **47** <2003TL2015>.



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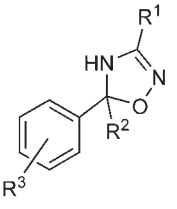

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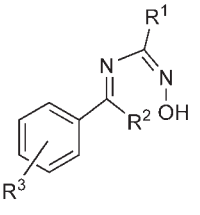

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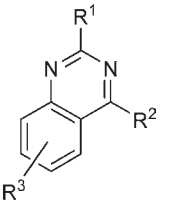

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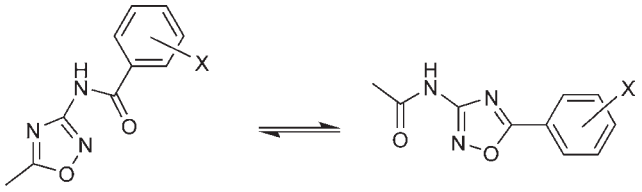
5.04.5 Reactivity of Fully Conjugated 1,2,4-Oxadiazoles

5.04.5.1 Thermal Reactions

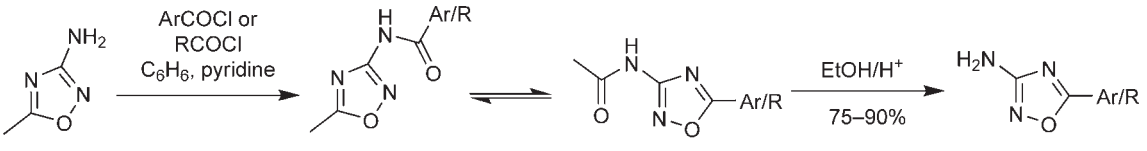
Molecular rearrangements of five-membered ring heterocycles with a three-atom side chain continue to attract much attention in the literature and new developments have become apparent since those detailed in CHEC-II(1996), including the appearance of a useful review encompassing the ring-degenerate version of the process

<2000JHC427>. Thus, a study of substituent effects in the ring-degenerate interconversions between the 3-aroylamino-5-methyl-1,2,4-oxadiazoles **48** and 3-acetylamino-5-aryl-1,2,4-oxadiazoles **49** (Equation 1) has been undertaken, showing that, in base, mixtures enriched in compound **48** are obtained, whereas in neutral conditions, mixtures richer in compound **49** are formed. The effect of the X group was found to be insignificant in neutral media, but far more marked in basic media where anions of species **48** and **49** can be invoked <1995T5133>.



48 **49** (1)

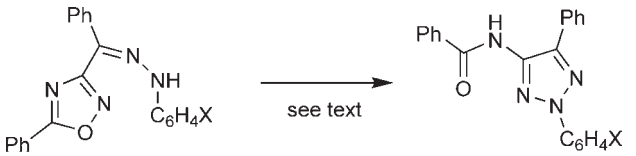
A ring-degenerate rearrangement has been exploited in the synthesis of a range of 3-amino-5-aryl-, 3-amino-5-alkyl-, and 3-amino-5-polyfluorophenyl-1,2,4-oxadiazoles **53** starting from 3-amino-5-methyl-1,2,4-oxadiazole **50** (**Scheme 2**). Aroylation or alkanoylation gave the rearrangement precursor **51**. Acid hydrolysis of the resultant equilibrium mixture gave high yields of the 3-amino-1,2,4-oxadiazole after preferential hydrolysis of the acetylamino group in intermediate **52** and re-equilibriation <2002H(57)811>.



50 **51** **52** **53**

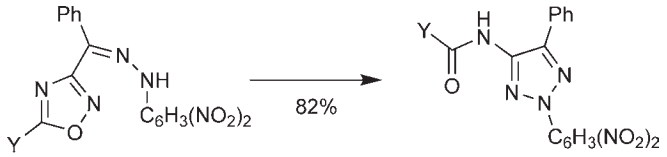
Scheme 2

The role of substituents X on the mononuclear heterocyclic rearrangement (MHR) of 20 phenylhydrazones **54** of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into the triazoles **55** (Equation 2) has been investigated, allowing the influence of X on the product distribution to be evaluated and first-order rate constants and Hammett correlations to be determined <1999T12885>.



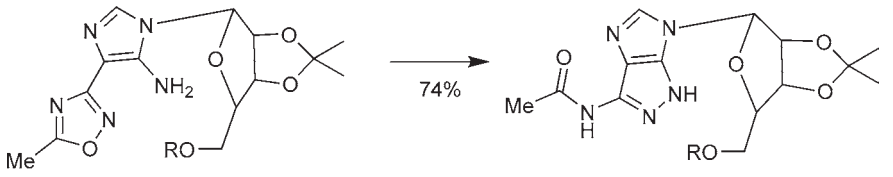
54 **55** (2)

A similar study (Equation 3) has established that, contrary to earlier work, the 2,4-dinitrophenylhydrazone **56** of 5-amino-3-benzoyl-1,2,4-oxadiazole (Y = NH_2) is converted rapidly into the triazole **57** by short heating in ethanol, and that the 5-phenyl analogue **56** (Y = Ph) behaves in the same manner <2001JOC6124>. Detailed studies of the experimental and theoretical aspects of the type of rearrangement shown in Equations (2) and (3) have been carried out <2006JOC5616, 2005T167, 2004JOC8718, 2004JPC1731>.



56: Y = NH_2 or Ph **57**: Y = NH_2 or Ph (3)

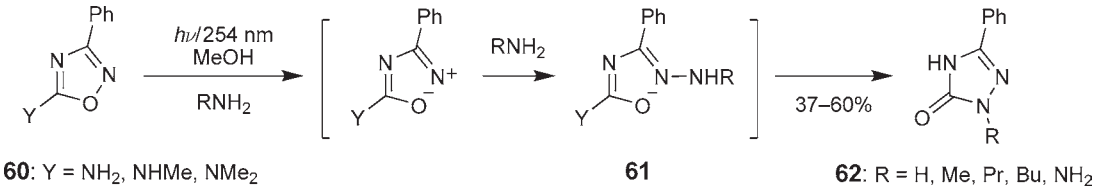
The protected 5-amino-1-ribofuranosyl-4-(5-methyl-1,2,4-oxadiazol-3-yl)imidazole **58** (Equation 4) undergoes MHR to afford the 3-acetamidoimidazopyrazole **59** in dimethyl formamide (DMF) or DMSO as solvent at 75–100 °C <2005NN1971>.



(4)

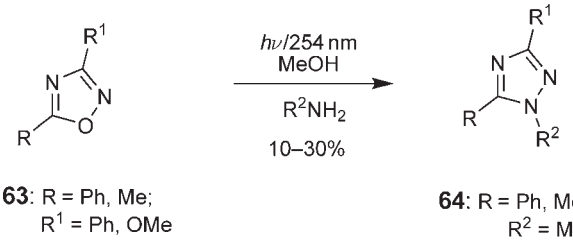
5.04.5.2 Photochemical Reactions

The irradiation of 5-amino-1,2,4-oxadiazoles **60** in the presence of nucleophilic nitrogen sources (primary amines, ammonia or hydrazine) produced 1,2,4-triazolin-5-ones **62**, a process which proceeds via cleavage of the N–O bond and addition of the nucleophile to form the intermediate **61** (**Scheme 3**) <1996JOC8397>.



Scheme 3

As detailed in Equation (5), this process can be applied to other 1,2,4-oxadiazoles **63**, hence allowing the production of triazoles **64**, albeit in low yields <1996JOC8397>.

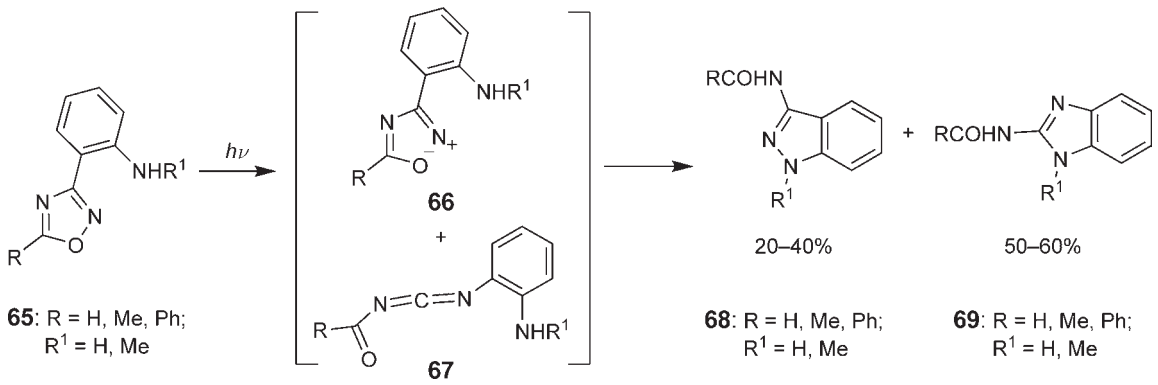


(5)

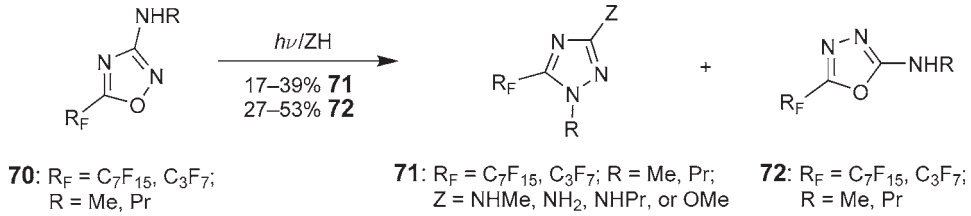
The irradiation of 3-(*o*-aminophenyl)-1,2,4-oxadiazoles **65** allowed the process to be extended to the formation of an internal N–N bond (**Scheme 4**), leading either to the indazoles **68** directly from photolytic species **66**, or to the formation of benzimidazoles **69**, which were formed from the carbodiimide **67**, the rearrangement product of photolytic species **66** <1996JOC8397>.

The fluorinated 1,2,4-oxadiazoles **70** (**Scheme 5**) gave, as the major heterocyclic components, the triazoles **71** and 1,3,4-oxadiazoles **72**, with the product formed being dependent upon the nature of ZH. Methanol in the presence of TEA, for example, gave an approximately 1:1 mixture of the appropriate 1,3,4-oxadiazole **72** and the triazole **71** (Z = OMe), whereas methanol in the presence of a nucleophilic primary amine gave the triazoles **71** (Z = NHMe, NH_2, NHPr, etc.) together with compound **72** <2004JOC4108, 2004JFC165>.

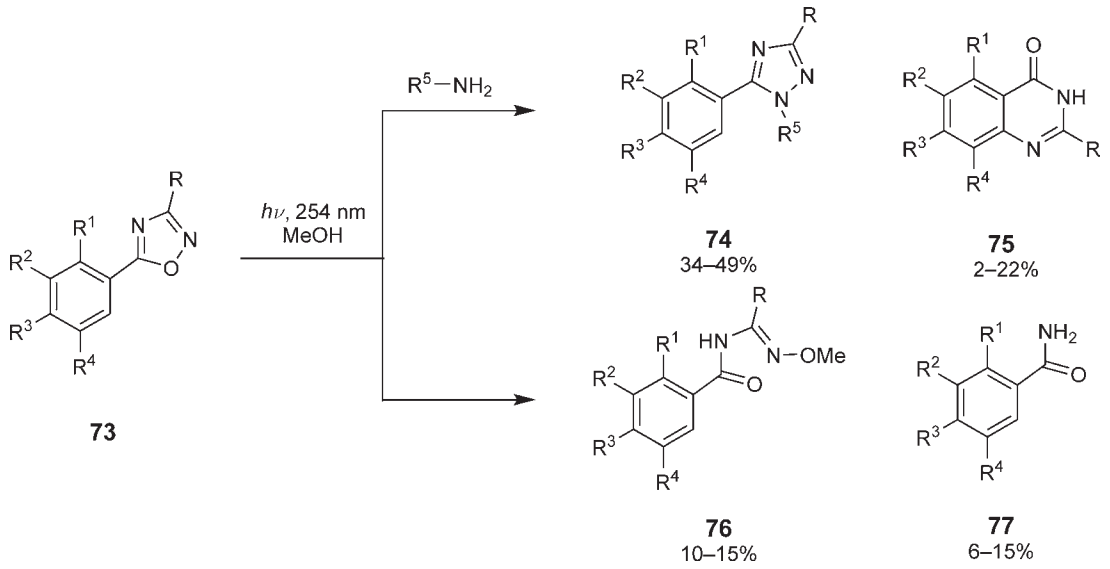
The same research group has shown that the 5-fluorophenyl-1,2,4-oxadiazoles **73** (**Scheme 6**) form the triazoles **74** as the major products in the presence of amine nucleophiles, together with varying amounts of side products **75–77**, with product **76**, for example, being formed by the competitive addition of the methanol solvent to the N–O-cleaved photolytic product <2005H(65)387>. The formation of quinazolin-4-ones **75** has been studied separately, and has been optimized to allow good yields as shown by the example in Equation (6) <1999JOC7028>.



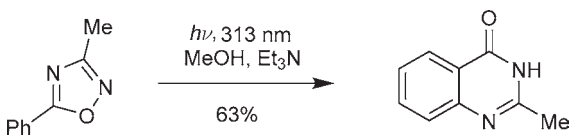
Scheme 4



Scheme 5

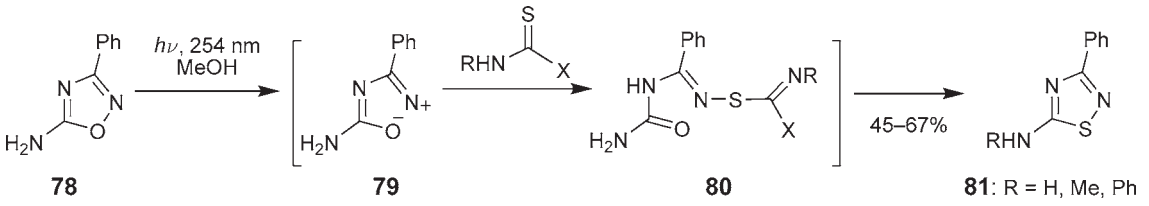


Scheme 6



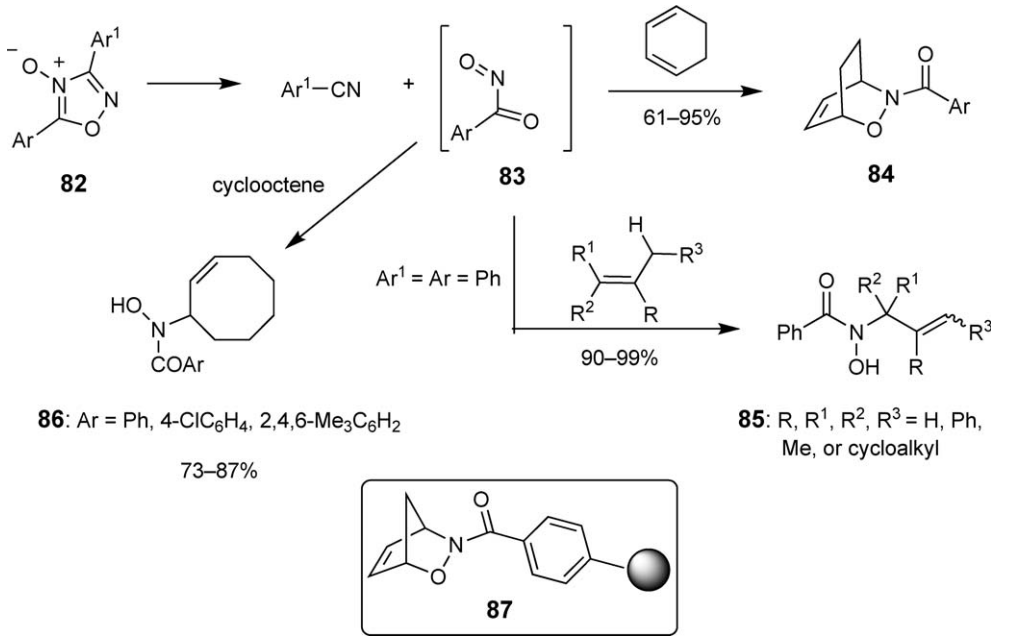
(6)

When the nitrogen nucleophile is replaced by a sulfur nucleophile, thiadiazoles can be formed. Thus, as shown in **Scheme 7**, the 5-amino-1,2,4-oxadiazole **78** gives the photolytic intermediate **79**, which is intercepted by a thiourea to give intermediate **80**, followed by ring closure and elimination to give the thiadiazoles **81** <1997T12629>.



Scheme 7

The irradiation of 1,2,4-oxadiazole-4-oxides **82** (**Scheme 8**) at 313 nm in methanol afforded excellent yields of the hetero-Diels–Alder adducts **84**, a process that involves initial formation of an isolable nitrile together with the nitrosocarbonyl **83**, where *in situ* trapping of the latter with cyclohexadiene furnishes adducts **84**. The nitrosocarbonyls could be trapped through an ene reaction, giving the ene adducts **85** in excellent yields <1999TL797>. The same group also reported that intermediate nitrosocarbonyls can be trapped by an ene reaction with cyclooctene to give the ene adducts **86** <2000TL2019>. The hetero-Diels–Alder methodology was later adapted to allow the generation of the nitrosocarbonyl intermediate on a solid support (Wang resin) to give the resin-bound cycloadduct **87** which was easily cleaved from the support <2005JCO887>.

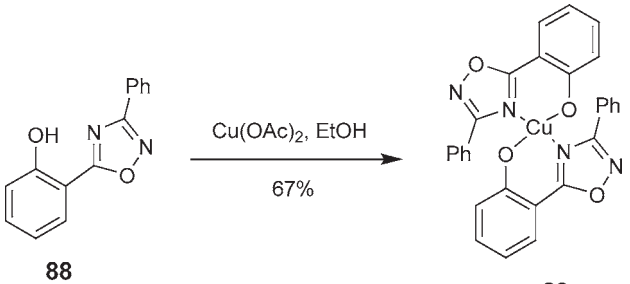


Scheme 8

5.04.5.3 Electrophilic Attack

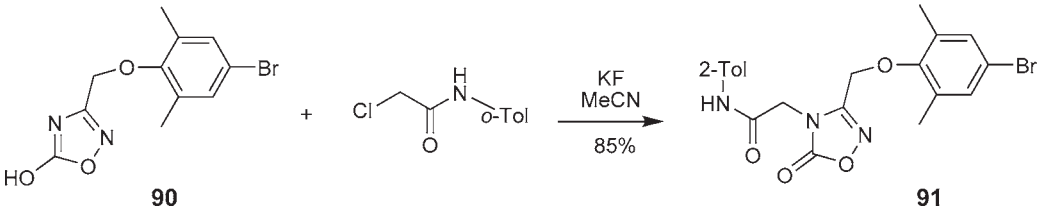
5.04.5.3.1 Electrophilic attack at nitrogen

The first synthesis of Cu(II) bis-complexes **89** of substituted 1,2,4-oxadiazoles **88** has been reported, with complexation occurring selectively on the 4-nitrogen <1999ICA1> (Equation 7).



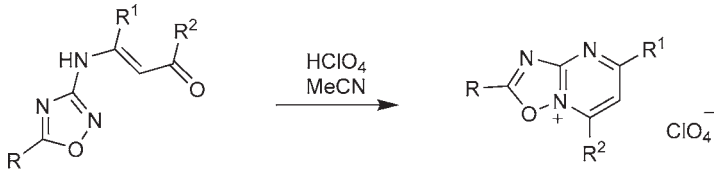
88 89 (7)

During the synthesis of a new rice blast disease fungicide, the 5-hydroxy-1,2,4-oxadiazole **90** underwent reaction on the 4-nitrogen to furnish the 4-substituted-1,2,4-oxadiazol-5-one **91** as shown in Equation (8) <2002JPES221>.



90 91 (8)

Access to oxadiazolopyrimidinium salts, for example, compound **93**, was achieved via intramolecular electrophilic attack of the 2-nitrogen of the 1,2,4-oxadiazole **92** in the presence of $HClO_4$ (Equation 9). Competing reaction at N-4 also occurs and the products are often not isolated, but used as intermediates for hydrolysis, thereby producing pyrimidines <2006T1158>.



92: R = Ph, Me;
R^1, R^2 = H, Me, CF_3

93 (9)

5.04.5.3.2 Electrophilic attack at carbon

The 1,2,4-oxadiazole ring is almost inert to electrophilic attack at carbon and there are no further examples to supplement those few important exceptions reported previously in CHEC-II(1996) <1996CHECII-(4)179>.

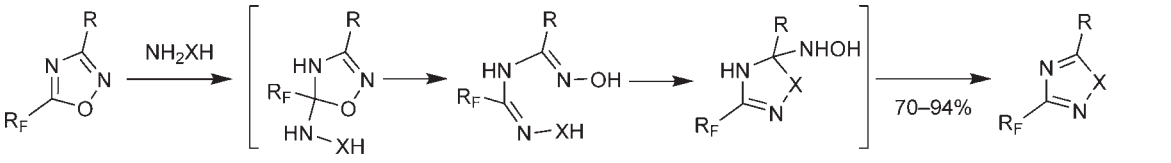
5.04.5.4 Nucleophilic Attack

5.04.5.4.1 Nucleophilic attack at the 3-position

As reported in CHEC-II(1996) <1996CHEC-II(4)179> and in more recent reviews <2001JCM209, 2004HOU(13)127>, the 3-position is remarkably stable to attack by nucleophiles and there are no additions to this aspect of the chemistry of 1,2,4-oxadiazoles since the appearance of CHEC-II(1996).

5.04.5.4.2 Nucleophilic attack at the 5-position

Unlike the 3-position, the 5-position is very susceptible to nucleophilic substitutions and additions. Thus, a series of publications report that 5-fluoroalkyl-1,2,4-oxadiazoles **94** undergo reaction with hydrazine or hydroxylamine to furnish 3-fluoroalkyl-1,2,4-triazoles **95** (X = NH) and 3-fluoroalkyl-1,2,4-oxadiazoles **95** (X = O), a reaction that proceeds via addition of the nitrogen nucleophile to the 5-position (**Scheme 9**) <2005JOC3288, 2004EJO974, 2003JOC605>.

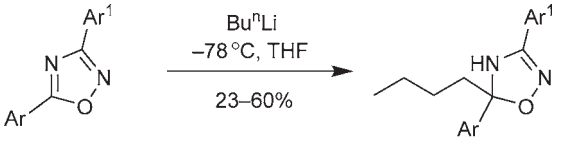


94: R = COPh, $C_{11}H_{23}$, *p*-$MeOC_6H_4$;
R_F = CF_3, C_3F_7, C_7F_{15}

95: X = NH, NMe, or O

Scheme 9

The reaction of butyllithium with a series of 3,5-diaryl-1,2,4-oxadiazoles **96** gives 5-butyl-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles **97** (Equation 10) typically in 50–60% yield. The 23% yielding reaction occurs due to competing deprotonation of the 5-hydroxyphenyl analogue <2000H(53)191, 2003JMT49>.

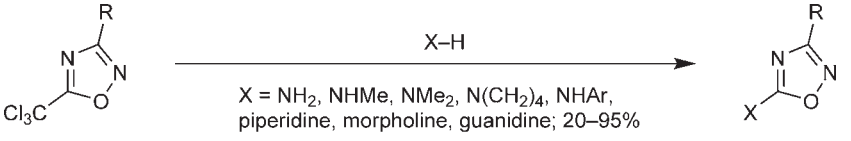


(10)

96: Ar = Ph, *o*-ClC_6H_4, *o*-HOC_6H_4;
Ar^1 = Ph, *o*-ClC_6H_4

97

The remarkable reactivity of 5-trichloromethyl-1,2,4-oxadiazoles **98** toward nucleophilic substitution by amines has continued (see also CHEC-II(1996) <1996CHEC-II(4)179>) to attract interest, producing 5-amino-1,2,4-oxadiazoles **99** in generally excellent yields, with anilines giving yields lower in the range quoted in Equation (11) <2002H(57)1891, 2001JPES60, 2002RCB1857>. 3-Methyl-5-trichloromethyl-1,2,4-oxadiazoles **98** (R = Me) reacts with the anion of benzyl alcohol to furnish the corresponding 5-benzyloxy-1,2,4-oxadiazole **99** (R = Me, X = OCH_2Ph), while reaction with KOH in ethanol gave the 3-methyl-1,2,4-oxadiazolin-5-one, which is the major tautomeric form of the corresponding 5-hydroxy-1,2,4-oxadiazole **99** (X = OH) <1995TL4471>.

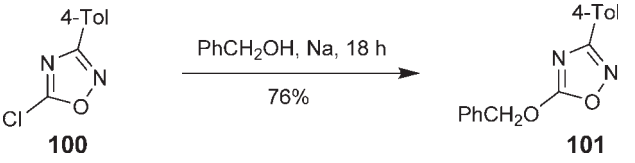


(11)

98: R = $CH_2C_6H_4Cl$, $CH_2C_6H_3Cl_2$, $CH_2C_6H_4Me$, C_7F_{15},
Ph, 4-$NO_2C_6H_4$, 2,3-$Me_2C_6H_3$, 4-$C_6H_4SO_2NH_2$

99

5-Chloro-1,2,4-oxadiazole **100** undergoes nucleophilic substitution with the anion of benzyl alcohol to give the 5-benzyloxy-1,2,4-oxadiazole **101** (Equation 12) <1995TL4471>.



(12)

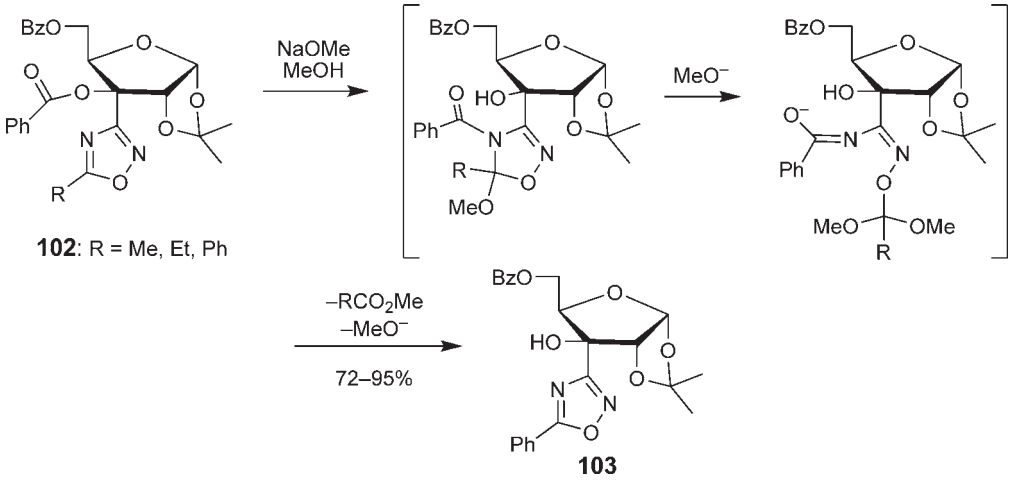
100 **101**

The attack of methoxide at the 5-position of the three 3-furanosidyl-1,2,4-oxadiazoles **102** led in each case to the 5-phenyl-1,2,4-oxadiazole **103** via the mechanism suggested in **Scheme 10**, whereby the oxadiazole 5-position is attacked twice by the methoxide anion, a process that is followed by ring closure and loss of acetate and methoxide <1999CAR157>.

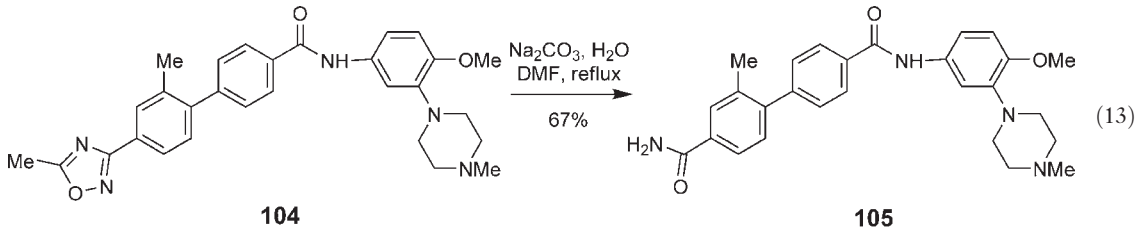
5.04.5.5 Hydrolysis of 1,2,4-Oxadiazoles

As discussed previously, 1,2,4-oxadiazoles are generally considered to be resistant to hydrolysis <2001JCM209, 2004HOU(13)127>. However, extensive treatment of the 1,2,4-oxadiazole **104** (Equation 13) in DMF in the

presence of aqueous sodium carbonate at reflux provides a rare example of a fully conjugated 1,2,4-oxadiazole undergoing hydrolysis, giving the partial hydrolysis product **105** <2000JME517>.



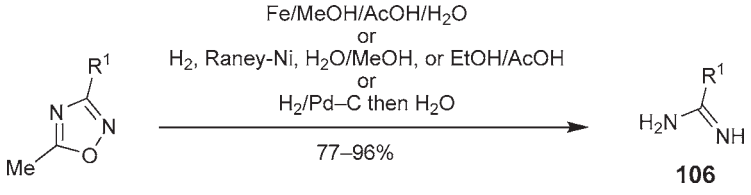
Scheme 10



(13)

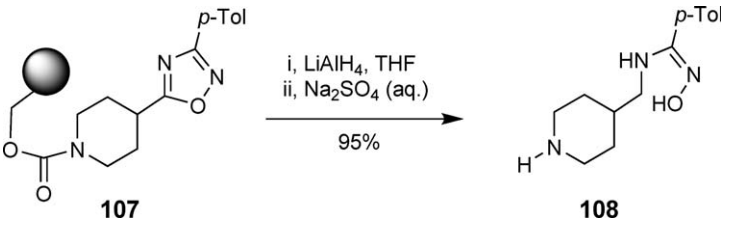
5.04.5.6 Reductions of 1,2,4-Oxadiazoles

The reduction of fully conjugated 5-methyl-1,2,4-oxadiazoles to give amidines **106** (or their HCl or acetate salts (Equation 14) has received reasonable attention since the publication of CHEC-II(1996), where it was only briefly known. Reduction has been carried out by hydrogenation over Pd–C <1995TL4471, 1996BML2425>, Raney-nickel <1998TL7619, 2000JME517>, or by the use of iron powder in aqueous solution <2003TL8697>, where the latter method seems to be the most facile and robust. These methods proceed via the initial formation of an acetylamidine which undergoes spontaneous hydrolysis to give the amidines **106** and, importantly, allows 1,2,4-oxadiazoles to be used as masked or protected amidines.



(14)

The reduction of the Wang resin-bound 1,2,4-oxadiazole **107** (Equation 15) with $LiAlH_4$ resulted in reductive cleavage from the resin and a reductive ring opening of the 1,2,4-oxadiazole to furnish the amidoxime **108** <1999BML2101>.



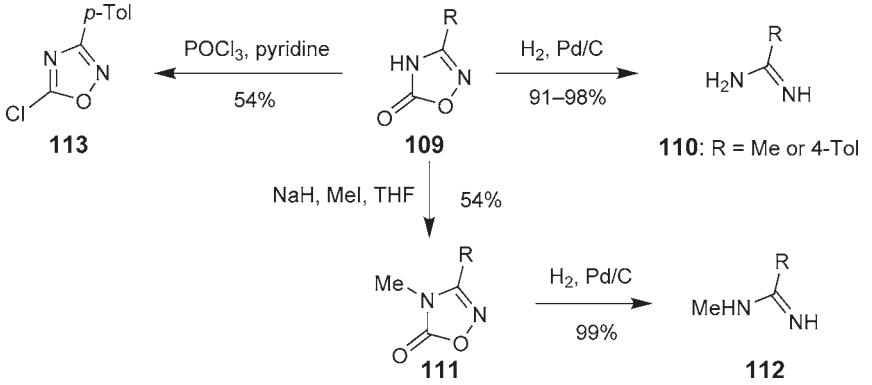
(15)

5.04.6 Reactivity of Nonconjugated 1,2,4-Oxadiazoles

CHEC-II(1996) <1996CHEC-II(4)179> showed that 4,5-dihydro-1,2,4-oxadiazoles dominated research in this area, and this pattern has continued <2001JCM209, 2004HOU(13)127>. Major advances in this field have occurred over the past 10 years, with the use of nonconjugated 1,2,4-oxadiazoles as masked amidines (see also Section 5.04.5.5) emerging as an important theme.

5.04.6.1 Reactivity of 4,5-Dihydro-1,2,4-oxadiazoles (Δ^2-Oxadiazolines)

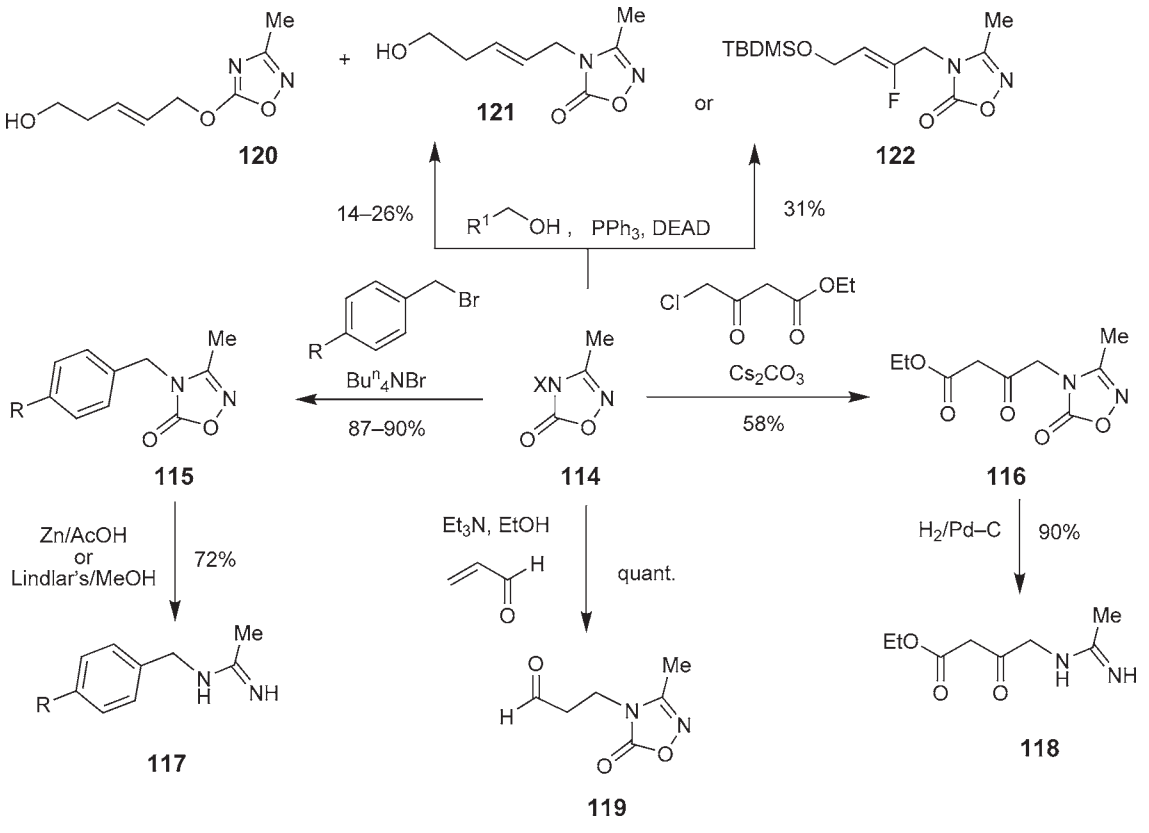
Hydrogenation of the 4,5-dihydro-1,2,4-oxadiazol-5-ones **109** (R = Me or 4-Tol) over Pd–C furnished the amidines **110** (**Scheme 11**), thereby showing that these substrates can also (see Equation 14) function as protecting groups for the amidine moiety <1995TL4471>. The pK_a (5.1–6.6) of such heterocycles renders them particularly stable to base. Methylation of the NH in compound **109** (R = 4-Tol) gave the 4-methyl analogue **111** which gave the alkylated amidine **112** after reduction <1995TL4471>. The same work also demonstrated the chlorination of the 4,5-dihydro-1,2,4-oxadiazol-5-one **109** (R = 4-Tol) to give the 5-chloro-1,2,4-oxadiazole **113**.



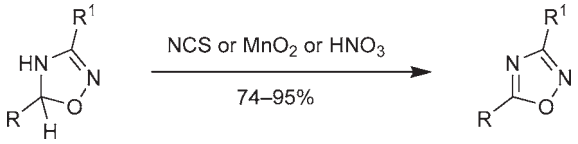
Scheme 11

Moormann *et al.* have conducted significant work with the 4,5-dihydro-1,2,4-oxadiazol-5-one **114** (X = H or K) (**Scheme 12**), demonstrating that substitution on the 4-N atom can occur with alkyl halides to give products **115** and **116**. Reduction of each of these compounds furnishes the corresponding amidines **117** and **118**. 4,5-Dihydro-1,2,4-oxadiazol-5-one **114** also reacted via Michael addition to give the Michael adduct **119**, and via Mitsunobu reaction to give the N-substituted compounds **121** or **122** (depending on the nature of R^1) plus some competing O-substituted fully conjugated product such as compound **120** <2004T10907>.

The oxidation of 4,5-dihydro-1,2,4-oxadiazoles to the corresponding fully conjugated 1,2,4-oxadiazoles (Equation 16) is a major class of reactions and is covered more fully in Section 5.04.10.1. Oxidants include *N*-chlorosuccinimide <1996JHC1583>, MnO_2 <2003BMC1821, 2000HCO41>, or concentrated HNO_3 in $CHCl_3$ <2000HCO41>.

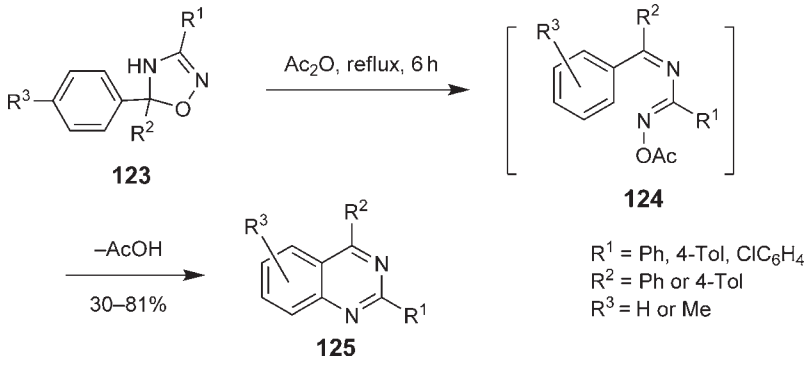


Scheme 12



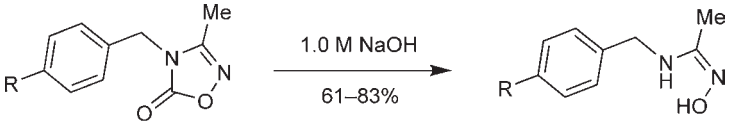
(16)

5-Aryl-4,5-dihydro-1,2,4-oxadiazoles **123** produced the quinazolines **125** on heating in acetic anhydride; this process is proposed to proceed via the acetylated diaza-1,3-butadiene intermediate **124** (**Scheme 13**) <1999AXC2158, 2002PJC1137, 2003TL2015>.



Scheme 13

As detailed in CHEC-II(1996) <1996CHEC-II(4)179>, 4,5-dihydro-1,2,4-oxadiazol-5-ones are readily hydrolyzed, and further examples (see Equation 17) of this transformation have been reported involving the synthesis of amidoximes **126** from the dihydro-1,2,4-oxadiazol-5-one **115** <2004T10907>.



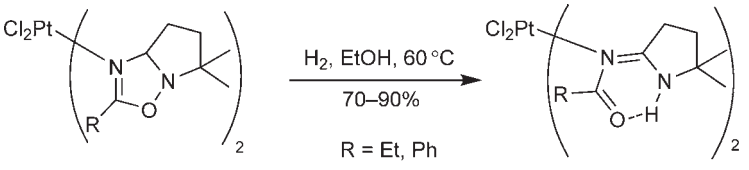
115: R = H, Br, NO_2 **126** (17)

5.04.6.2 Reactivity of 2,5-Dihydro-1,2,4-oxadiazoles (Δ^3-Oxadiazolines)

As reported in CHEC-II(1996) <1996CHEC-II(4)179>, this class of heterocycle remains unexplored in terms of its reactivity. Section 5.04.10.2 deals with the synthesis of this class of dihydro derivative.

5.04.6.3 Reactivity of 2,3-Dihydro-1,2,4-oxadiazoles (Δ^4-Oxadiazolines)

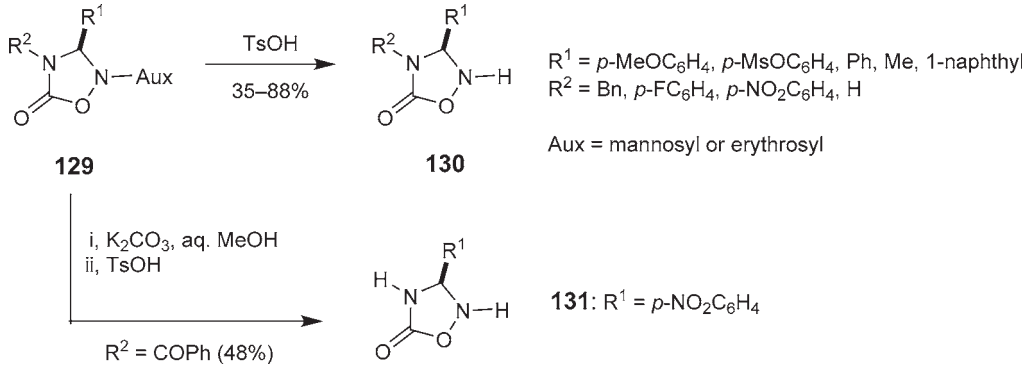
Since CHEC-II(1996) <1996CHEC-II(4)179>, when no examples were known, only one example of the reactivity of this type of system has appeared. Hence, the platinum(II) 2,3-dihydro-1,2,4-oxadiazole complexes **127** undergo rupture of the N–O bond and a 1,2-H shift in the presence of hydrogen to give the ketoimines **128** (Equation 18) as stable white solids <2004JCD2741>.



127 **128** (18)

5.04.6.4 Reactivity of the Fully Saturated System (1,2,4-Oxadiazolidines)

Important new reactions in this class have appeared since the publication of CHEC-II(1996) <1996CHEC-II(4)179>. Thus, the mannosyl- and erythrose-derived auxiliary substituted 1,2,4-oxadiazolidin-5-ones **129** undergo ready loss of the auxiliary in the presence of TsOH to yield the configurationally stable 1,2,4-oxadiazolidin-5-ones **130** (**Scheme 14**). The use of the 4-benzoyl derivative (R^2 = COPh) allows the sequential removal of the *N*-benzoyl group and the auxiliary to give the configurationally stable 2,4-unsubstituted compound **131**. This constitutes the first general synthesis of enantiomerically pure oxadiazolidinones <2005AGE936>.

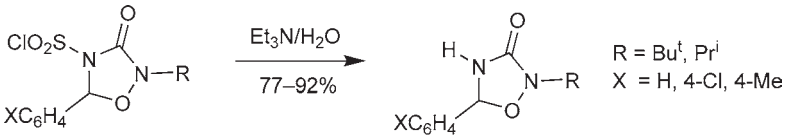


129 **130**

131: R^1 = p-$NO_2C_6H_4$

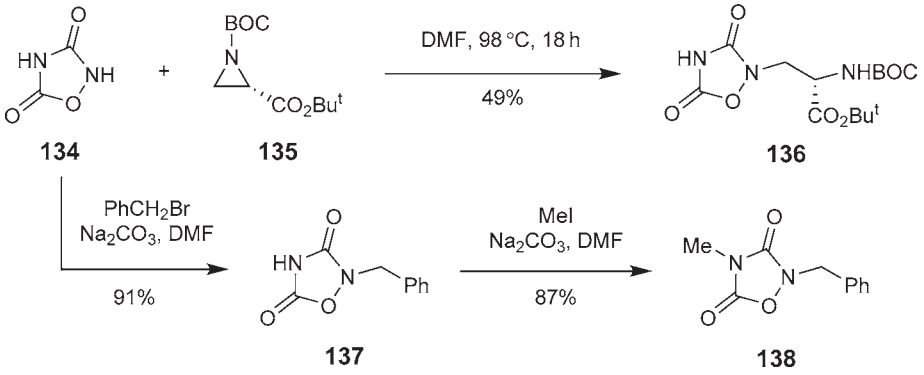
Scheme 14

The 4-chlorosulfonyl-1,2,4-oxadiazolidin-3-ones **132** undergo loss of the chlorosulfonyl moiety to give the corresponding 4-unsubstituted system **133** as shown in Equation (19) <2001TL9131>.



132 **133** (19)

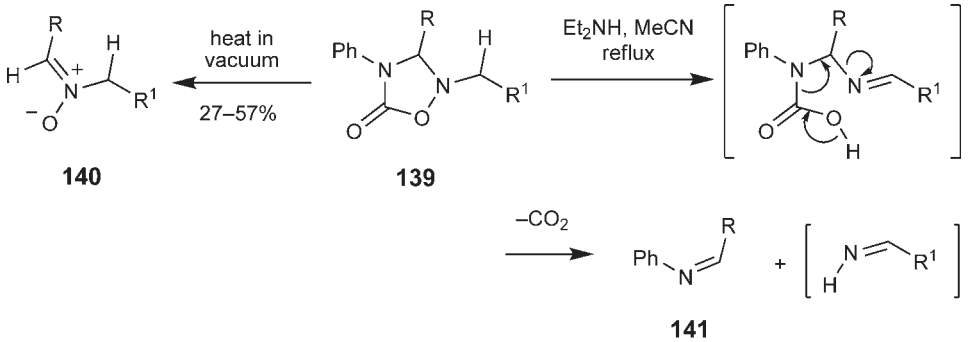
Scheme 15 shows work which reveals that in the parent unsubstituted 1,2,4-oxadiazolidin-3,5-dione **134**, N-2 undergoes alkylation in preference to N-4, hence allowing the synthesis of the protected (*S*)-quisqualic acid **136** by reaction with the (*S*)-aziridine **135** by Baldwin and co-workers <1996TL5225>. Similarly, reaction with benzyl bromide occurs at N-2 to furnish the 2-benzyl derivative **137**, which could be reacted subsequently at N-4 to give the 2,4-disubstituted-1,2,4-oxadiazolidin-3,5-dione **138**. The order of substitution was established using HMBC <1997SL263>.



134 **135** **136** **137** **138**

Scheme 15

The 1,2,4-oxadiazolidin-5-ones **139** undergo retro-1,3-dipolar cycloaddition when heated in vacuum to give the nitrones **140**. Treatment in acetonitrile in the presence of base results in attack of the exocyclic α-proton and fission of the N–O bond followed by loss of carbon dioxide and formation of the benzylidenaniline **141** in undisclosed yields via the mechanism shown in **Scheme 16** <2006SC997>.

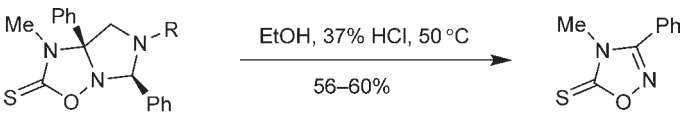


140 **139** **141**

R = 2,3-$(MeO)_2C_6H_3$; 3,4-$(MeO)_2C_6H_3$; 2-$NO_2C_6H_4$; Ph; R^1 = H, Ph, 2,3-$(MeO)_2C_6H_3$

Scheme 16

The treatment of imidazo-1,2,4-oxadiazol-5-thiones **142** (Equation 20) with ethanolic HCl results in a retro-1,3-dipolar cycloaddition of the imidazo ring to give an azomethine ylide together with the 4,5-dihydro-1,2,4-oxadiazol-5-thiones **143** <2003PS881>.



(20)

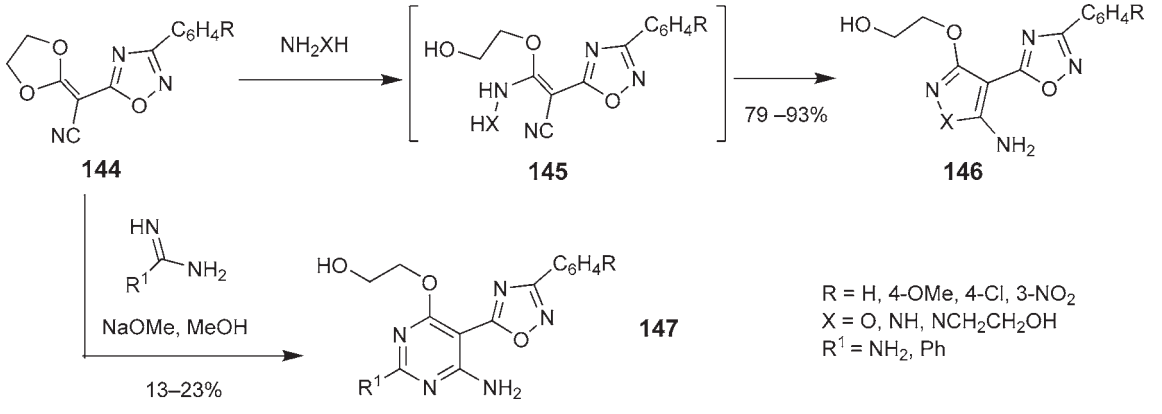
142: R = 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$ **143**

5.04.7 Reactivity of Substituents Attached to Ring Carbon Atoms

Some key reactions relevant to this section were not covered in CHEC-II(1996) <1996CHEC-II(4)179>, and hence some references to important work prior to the appearance of CHEC-II(1996) are included. Nonetheless, CHEC-II(1996) does contain many pertinent reactions of ring carbon substituents, such as important information on Curtius rearrangements and α-anion formation and reactivity.

5.04.7.1 Rearrangement Reactions

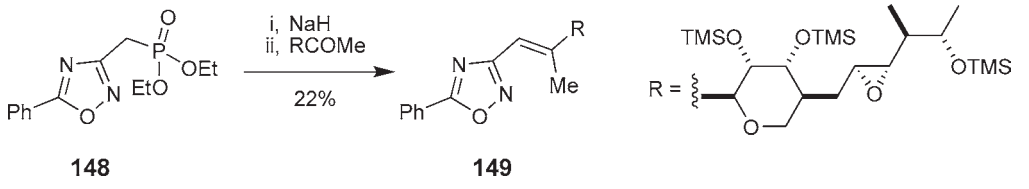
The 1,2,4-oxadiazole dioxolanes **144** react with hydroxylamine and hydrazines to form the 5-pyrazole- and isoxazole-substituted 1,2,4-oxadiazoles **146** via the dioxolane ring-opened intermediates **145** (**Scheme 17**). Reaction of compounds **144** with amidine or guanidine salts allows access to pyrimidine substituted analogues **147**, via intermediate **145** (X = C(NH)R^1), albeit in lower yield <1996JHC1943, 1998JHC161>.



Scheme 17

5.04.7.2 Reactions at the α-Carbon of Alkyl Substituents

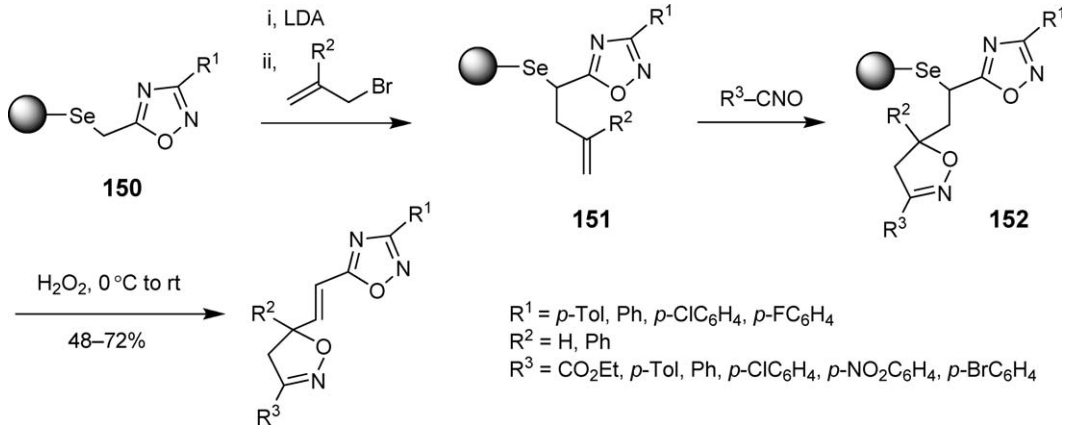
Although not widely exploited, the use of the phosphonate **148** in Wadsworth–Emmons reactions represents a process of great potential that has been used to access the 3-alkenyl-1,2,4-oxadiazole **149** (Equation 21) <1989J(P1)2047>.



(21)

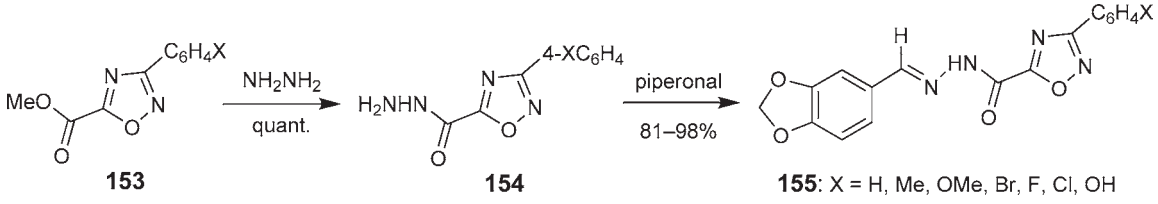
148 **149**

In another elegant approach (**Scheme 18**), a synthesis of 5-alkenyl-substituted 1,2,4-oxadiazoles relies upon a selenoxide *syn*-elimination at the 5-α-carbon of the selenium resin-supported 1,2,4-oxadiazole **152**. Access to compound **152** was achieved in two steps from the supported oxadiazole **150**, which underwent deprotonation and alkylation at the 5-α-carbon to give the α-alkylated selenium resin **151**. 1,3-Dipolar cycloaddition then gave the selenium resin-supported 1,2,4-oxadiazole **152** <2005JCO726>.

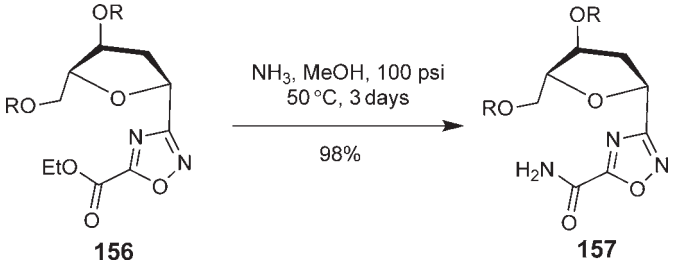


Scheme 18

Standard transformations at the α-carbon, as discussed in CHEC-II(1996) <1996CHEC-II(4)179>, proceed without incident. Selected recent examples (**Scheme 19**; Equation 22) include the conversion of the esters **153** into the hydrazides **154** and thence into the methylene carbohydrazides **155** <2005HCO29>, a process that has been shown by the same workers to apply to other aldehydes (benzaldehyde, 4-*N*,*N*-dimethylaminobenzaldehyde, furfuraldehyde, or thiophene 2-carboxaldehyde) with equal success <1999FES747>, and the conversion of the ester **156** into amide **157** <2005NN1919>, a process that demonstrates the robustness of the 1,2,4-oxadiazole ring.



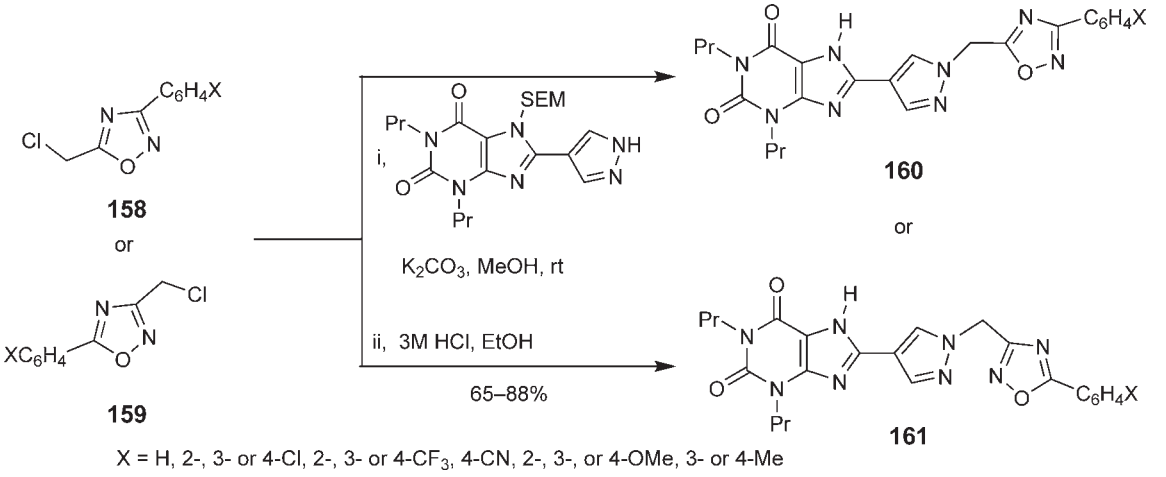
Scheme 19



(22)

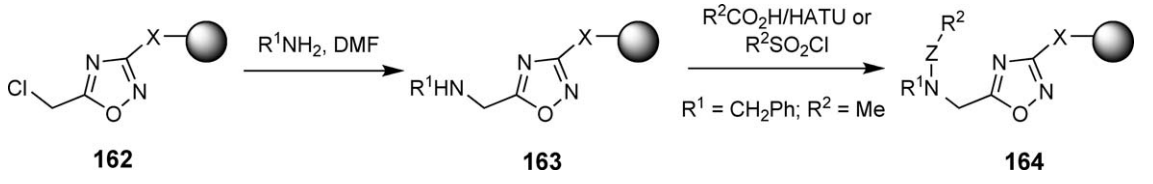
5.04.7.3 Reactions of Halomethyl Substituents

The 3- and 5-chloromethyl-1,2,4-oxadiazoles **158** and **159** react with the pyrazolyl purine shown in **Scheme 20** to give the corresponding (1,2,4-oxadiazol-5-yl)- and (1,2,4-oxadiazol-3-yl)methyl derivatives **160** and **161**, respectively <2006BML302>.



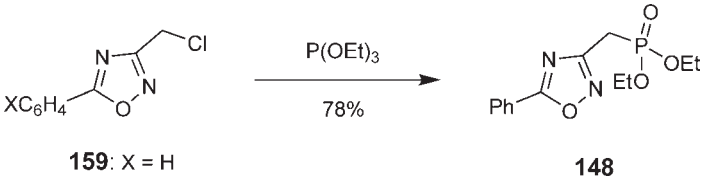
Scheme 20

The polymer-supported 5-chloromethyl-1,2,4-oxadiazole **162** undergoes easy reaction with primary amines to give the 5-aminomethyl oxadiazoles **163**, which serve as excellent substrates for the synthesis of amides or sulfonamides **164** (**Scheme 21** – yields not reported) <1999TL8547>.



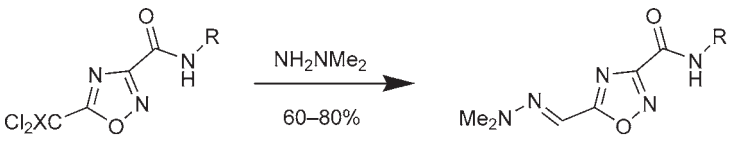
Scheme 21

As shown in Equation (23), the 3-chloromethyl-1,2,4-oxadiazole **159** (X = H) undergoes Arbuzov reaction to give the phosphonate **148** which has been used in Wadsworth–Emmons reactions as shown previously in Equation (21) <1989J(P1)2047>.



(23)

The 5-dichloromethyl- and 5-trichloromethyl-1,2,4-oxadiazoles **165** and **166** react with dimethylhydrazine to give the hydrazones **167** (Equation 24) <2002RCB1857>.



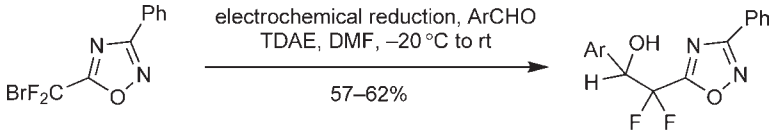
165: X = Cl
166: X = H

167

R = Ph, 3,4-$Cl_2C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2,3-$Me_2C_6H_3$, 4-$C_6H_4SO_2NH_2$

(24)

Electrochemical reduction of the 5-(bromodifluoromethyl)-1,2,4-oxadiazole **168** in the presence of tetrakis (dimethylamino)ethylene (TDAE) generates the 5-(difluoromethyl) anion which reacts with aldehydes to give the 5-*gem*-difluorinated-1,2,4-oxadiazoles **169** (Equation 25) <2001JFC39, 1998JOC5385>.



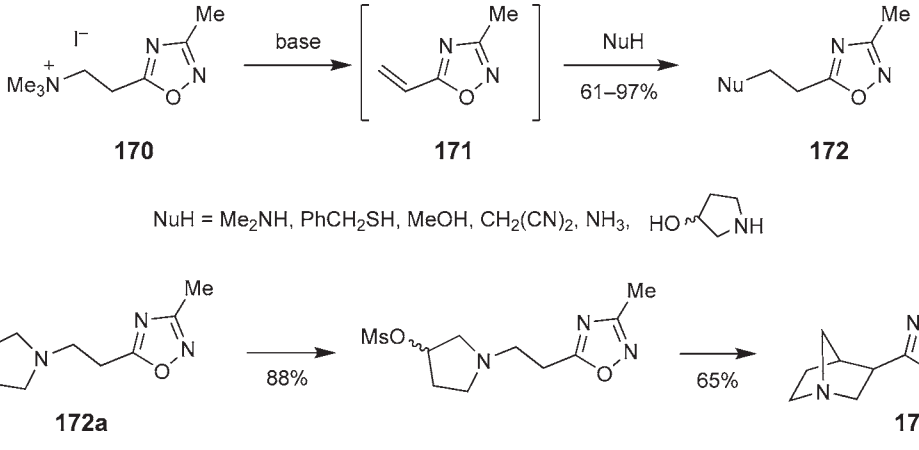
168 **169**

Ar = 3-pyridyl, 2-pyridyl, biphenyl, 4-FC_6H_4, 4-$CF_3C_6H_4$, 4-CNC_6H_4

(25)

5.04.7.4 Miscellaneous Reactions of Carbon Substituents

The reaction of 5-[2-(*N*,*N*-dimethylamino)ethyl]-1,2,4-oxadiazole with methyl iodide forms the quaternary ammonium salt **170** (**Scheme 22**), which undergoes elimination in the presence of base (diisopropylethylamine (DIEA), TEA, 1,8-diazabicyclo[4.3.0]undec-7-ene, etc.) to form an intermediate 5-vinyl-1,2,4-oxadiazole **171,** which undergoes *in situ* Michael addition with nucleophiles to furnish the Michael adducts **172**. As an example, also shown in **Scheme 22**, 3-hydroxy-pyrrolidine allows the synthesis of compound **172a** in 97% yield. Mesylation followed by deprotonation of the 1,2,4-oxadiazole methylene at C-5 enables S_N2 displacement of the mesylate to give the 5-azabicycloheptyl derivative **173**, which is a potent muscarinic agonist <1996JOC3228>.



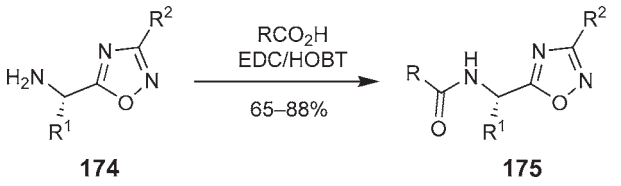
170 **171** **172**

172a **173**

Scheme 22

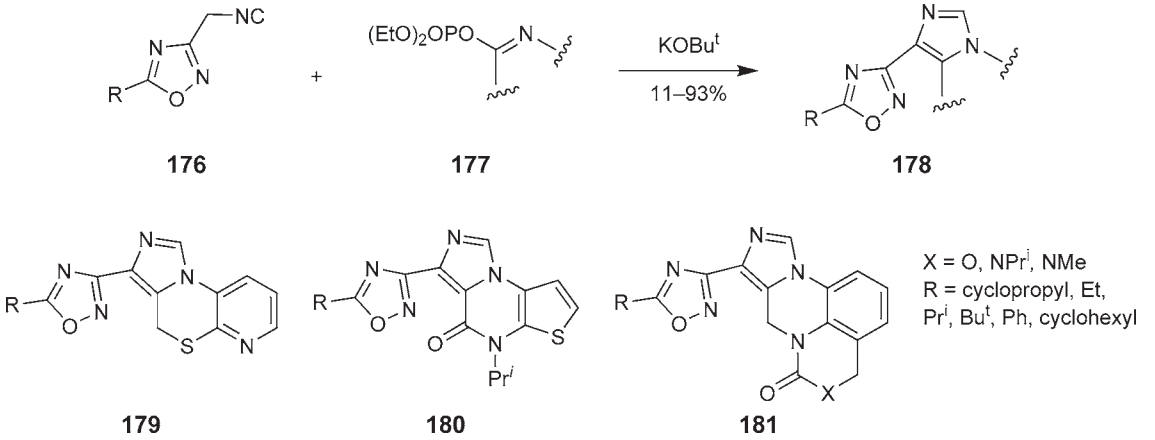
1,2,4-Oxadiazole amine **174** serves as an excellent template for the introduction of a wide variety of 5-amido side chains onto the 1,2,4-oxadiazole nucleus (Equation 26), and several such products **175** are potent inhibitors of the tyrosine kinase ZAP-70 <1999BML3009>. Amide or pseudopeptide side chains can also be introduced by the

reaction of an amine or N-protected amino acid with 1,2,4-oxadiazoles bearing a carboxylic acid side-chain using standard coupling procedures such as benzotriazol-1-yloxytris-(dimethylamino)phosphonium (BOP) <2000FES719>.



(26)

The 3-(isocyanomethyl)-1,2,4-oxadiazoles **176** (**Scheme 23**) have received widespread interest because of their ability to allow access to 3-imidazolyl-1,2,4-oxadiazoles **178** after isocyanide cyclization and phosphate elimination with imino phosphate esters **177**. Typical examples are compounds **179–181**, although well over 20 other examples have been synthesized <2002M1205, 2002M653, 2001H(40)1963, 1996JME4654>.

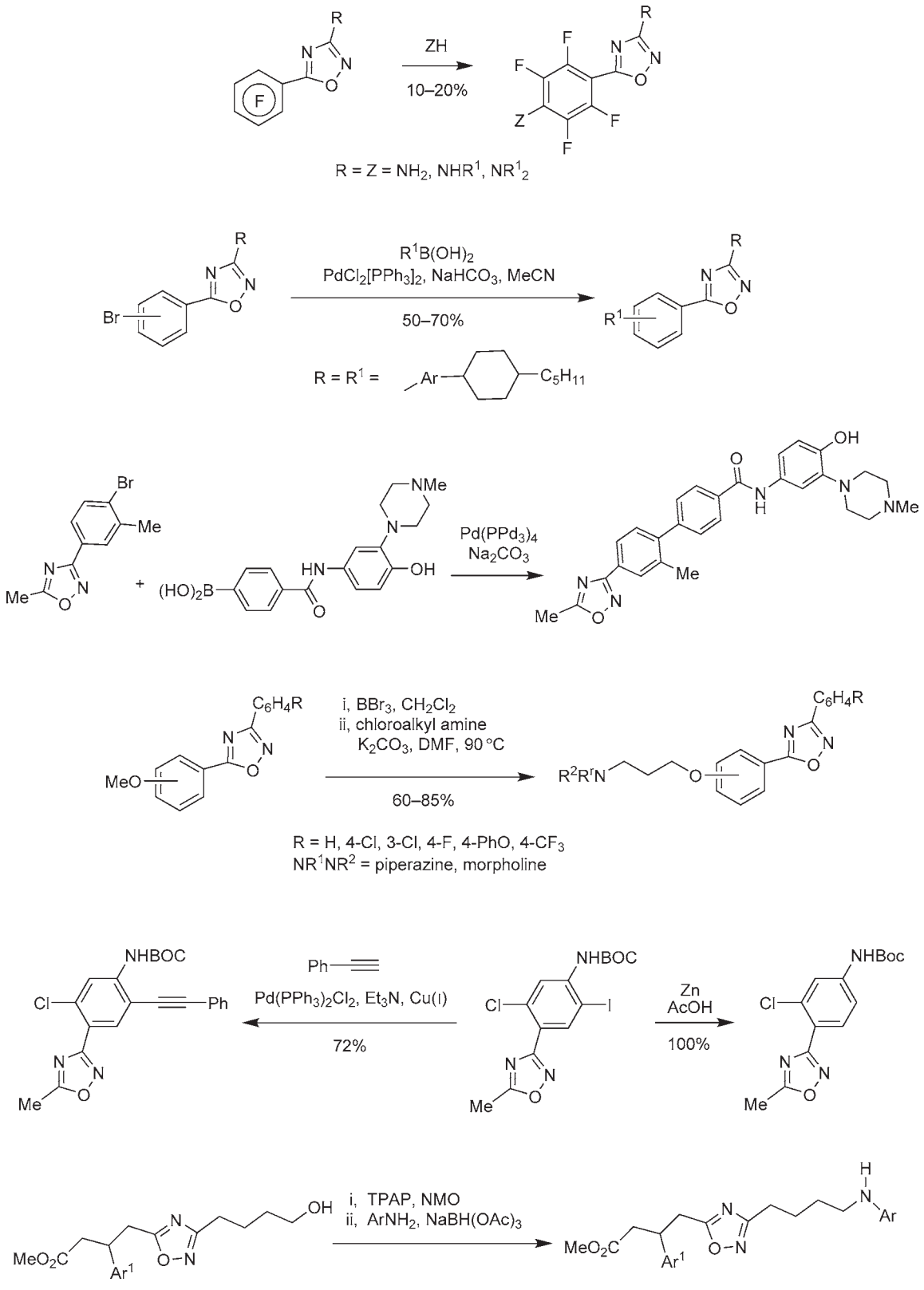


Scheme 23

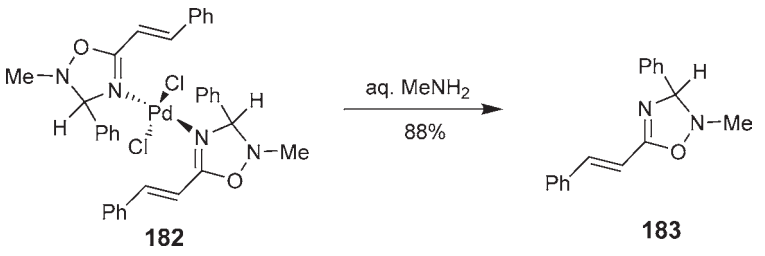
The intrinsic stability of the fully conjugated 1,2,4-oxadiazole is reflected in the number of reactions that a variety of substituents at carbons 3 or 5 of the 1,2,4-oxadiazole ring can undergo. **Scheme 24** shows a selection of these transformations including some notable arylboronic acid cross-coupling reactions <2000MCL327, 2000JME517>, aryl ether syntheses <2004BML4307, 2000JME517>, a nucleophilic attack of a pentafluorophenyl substituent that leaves the oxadiazole ring intact <2004JFC165>, a useful Sonogashira coupling and reductive deiodination <2003TL8697>, and a tetrapropylammonium perruthenate (TPAP) oxidation of a 3-hydroxy substituent which is followed by reductive aminations of the resultant aldehydes <2006BML839>.

5.04.8 Reactivity of Substituents Attached to Ring Heteroatoms

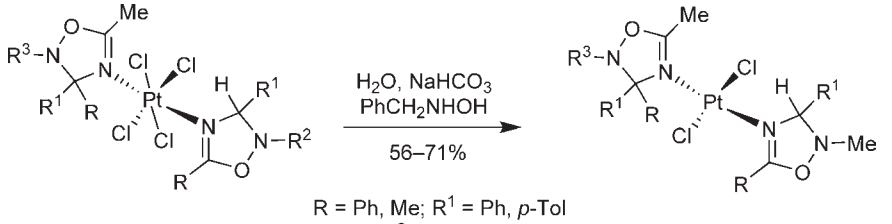
The dimeric 2,3-dihydro-1,2,4-oxadiazole palladium(II) complex **182** (Equation 27) reacts with aqueous methylamine to liberate the ligand **183** <2003JCD2544>. A similar process has also been applied to platinum(IV)-bound complexes **184**, using pyridine to liberate the 2,3-dihydro-1,2,4-oxadiazole <2000JA3106>. Reduction of the platinum(IV) complexes **184** (Equation 28) gives the corresponding platinum(II) complexes **185** <2001IC264>.


ZH
10–20%
R = Z = NH2, NHR1, NR1 2
R1B(OH)2
PdCl2[PPh3]2, NaHCO3, MeCN
50–70%
R = R1 =
Pd(PPd3)4
Na2CO3
i, BBr3, CH2Cl2
ii, chloroalkyl amine
K2CO3, DMF, 90 °C
60–85%
R = H, 4-Cl, 3-Cl, 4-F, 4-PhO, 4-CF3
NR1NR2 = piperazine, morpholine
Pd(PPh3)2Cl2, Et3N, Cu(I)
72%
Zn
AcOH
100%
i, TPAP, NMO
ii, ArNH2, NaBH(OAc)3

Scheme 24



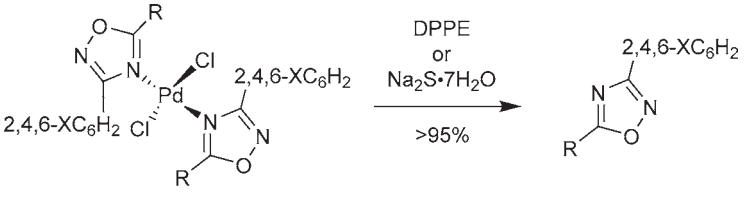
182 183 (27)



R = Ph, Me; R^1 = Ph, *p*-Tol
R^2 = Me, Bn

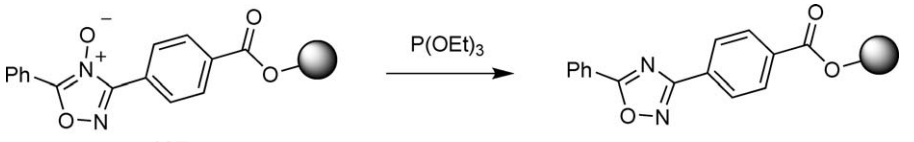
184 185 (28)

In a similar process involving the stable fully conjugated 1,2,4-oxadiazole *N*4 palladium(IV) complexes **186**, liberation from palladium was achieved either with 1,2-bis(diphenylphosphino)ethane (DPPE) or with an excess of sodium sulfide (Equation 29) <2005EJI845>.



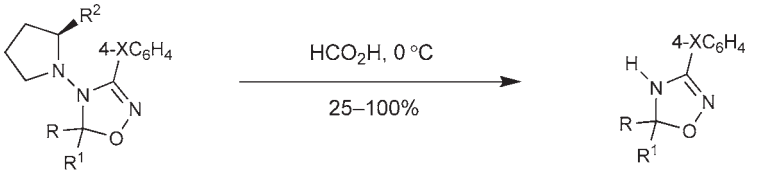
186 X = Me or OMe; R = Me, Et, CH_2CN, NMe_2, Ph (29)

The removal of oxygen from 1,2,4-oxadiazole 4-oxides and polymer-supported analogues **187** can be achieved with triethyl- or trimethylphosphite, as the example in Equation (30) shows <2005JCO887>.



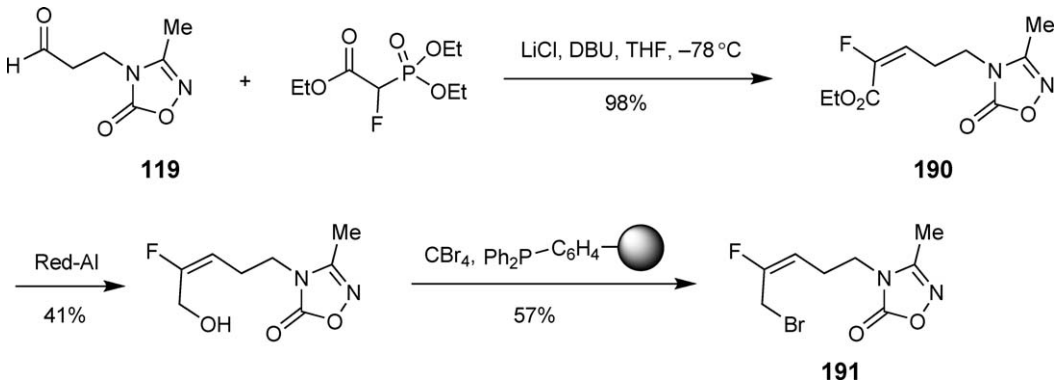
187 (30)

N–N cleavage of the 4-proline-substituted 4,5-dihydro-1,2,4-oxadiazoles **188**, shown in Equation (31), with formic acid gave the corresponding 4,5-dihydro-1,2,4-oxadiazoles **189** in good yield and with ee up to 91% <1999H(50)995>.



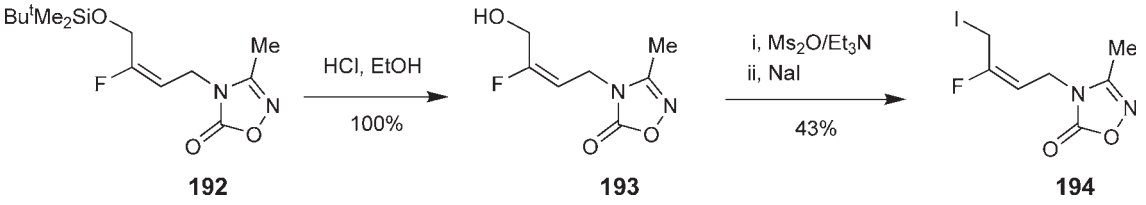
188 X = H, F, OMe; R, R^1 = cyclopentyl, alkyl/aryl
R^2 = CH_2OMe, CPh_2OMe **189** (31)

The 4,5-dihydro-1,2,4-oxadiazol-5-one **119** (see also **Scheme 12**) undergoes Wadsworth–Emmons reaction to give the alkene **190** (**Scheme 25**). Reduction of the ester with Red-Al and subsequent bromination of the alcohol gave the bromofluoroalkenyl-substituted 4,5-dihydro-1,2,4-oxadiazol-5-one **191**, demonstrating the robustness of this ring system <2004T10907>.



Scheme 25

The same research group also showed that the *t*-butyldimethylsilyl (TBDMS)-protected 4-substitued 4,5-dihydro-1,2,4-oxadiazol-5-one **192** afforded the alcohol **193** on treatment with ethanolic HCl. Mesylation and treatment of the intermediate with sodium iodide gave the iodofluoroalkenyl-substituted 4,5-dihydro-1,2,4-oxadiazol-5-one **194** (**Scheme 26**) <2004T10907>.



Scheme 26

5.04.9 Ring Syntheses of Fully Conjugated 1,2,4-Oxadiazoles

5.04.9.1 Syntheses of Fully Conjugated 1,2,4-Oxadiazoles

The high level of recent interest in the fully conjugated 1,2,4-oxadiazole ring as a hydrolysis-resistant amide and ester bioisostere and peptidomimetic <2001JCM209, 2004HOU(13)127>, coupled with the general surge in combinatorial and polymer-supported methodologies, means that the synthesis of this class of heterocycle has attracted enormous attention since the appearance of CHEC-II(1996), with many of the methods discussed therein having been refined and improved significantly. Entirely new approaches have also revealed themselves.

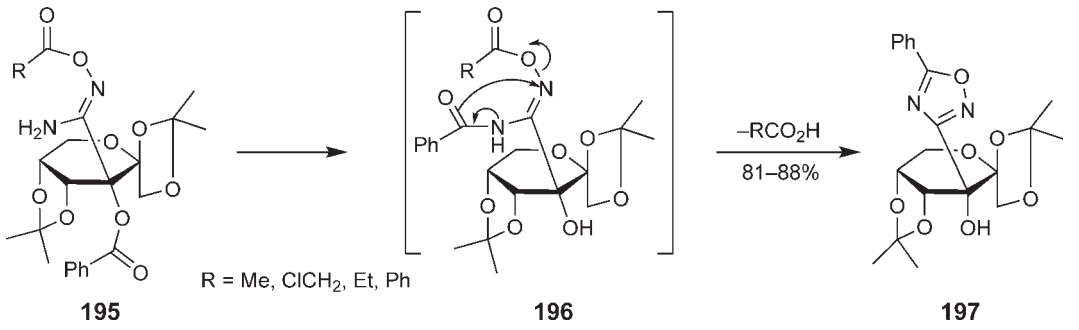
5.04.9.1.1 Ring syntheses of 1,2,4-oxadiazoles from a five-atom component

5.04.9.1.1(i) Synthesis via N–O bond formation

This is a rare approach, and only one new example has appeared since the publication of CHEC-II(1996) <1996CHEC-II(4)179>. Hence, as shown in **Scheme 27**, the O-acylated amidoximes **195** undergo an intramolecular replacement reaction via neighboring group participation of the 3-*O*-benzoyl group to give the intermediate **196**. N–O bond formation and loss of a carboxylic acid gives the 5-phenyl-1,2,4-oxadiazole **197**, the only product isolated in each of the four examples studied <2005BMC353, 2003CAR257>.

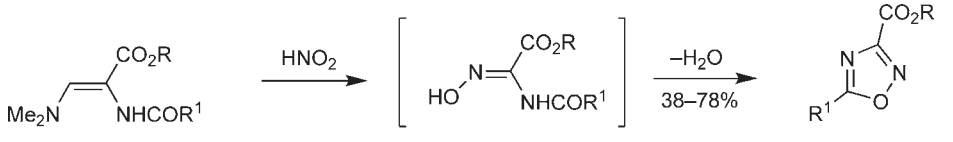
5.04.9.1.1(ii) Synthesis via C–O bond formation

Although a rare approach, new research has emerged that has given another major method of 1,2,4-oxadiazole synthesis via C–O bond formation of a five-atom component. Thus, the nitrosation of the dimethylaminopropenoates **198** (**Scheme 28**) results in the formation of the corresponding oximes **199** which undergo cyclization to give the 5-substituted 1,2,4-oxadiazole 3-carboxylates **200** <1995JHC1563, 1997JHC1705, 1999JHC1581, 2000SL1077>.



195 196 197

Scheme 27

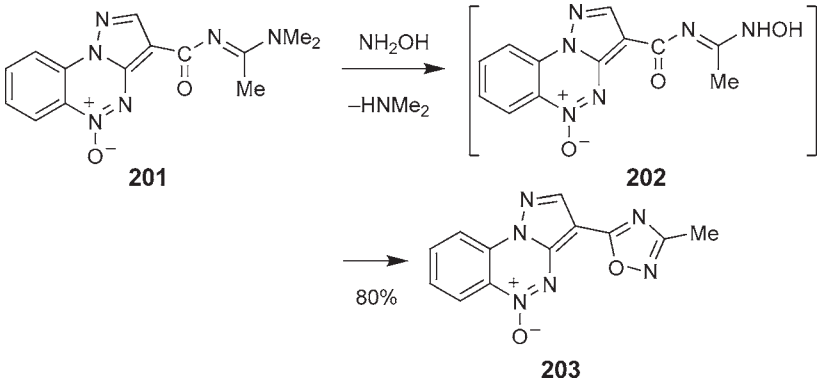


198 199 200

R = Me, Et; R^1 = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-Tol, 4-$MeOC_6H_4$, Me, styryl, 2,6-dichlorostyryl, 2-methylstyryl, 2-methoxystyryl

Scheme 28

In a related approach, the reaction of the acylamidine **201** (**Scheme 29**) with hydroxylamine results in loss of dimethylamine to give intermediate **202** which undergoes cyclization to give the 1,2,4-oxadiazole **203** <1999JME2218>.



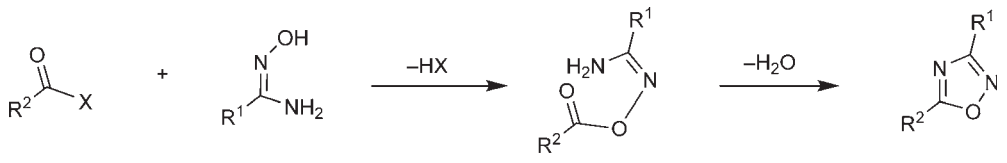
201 202 203

Scheme 29

5.04.9.1.1(iii) Synthesis via C–N bond formation

The cyclization of the five-atom component O-acylated amidoximes **204** leads to 1,2,4-oxadiazoles via C–N bond formation as shown in **Scheme 30**. The requisite O-acylated amidoximes **204** are accessed via the reaction of an amidoxime with an activated carboxylic acid or a carboxylic acid derivative. Often the O-acylated amidoxime **204** is not isolated and the cyclization is either spontaneous or occurs in a 'one-pot' process, and these approaches are dealt with in Section 5.04.9.1.2 as syntheses from a one-atom component and a four-atom component. In this section, only those methods in which the O-acylated amidoxime **204** is isolated and cyclized in a separate step are dealt with.

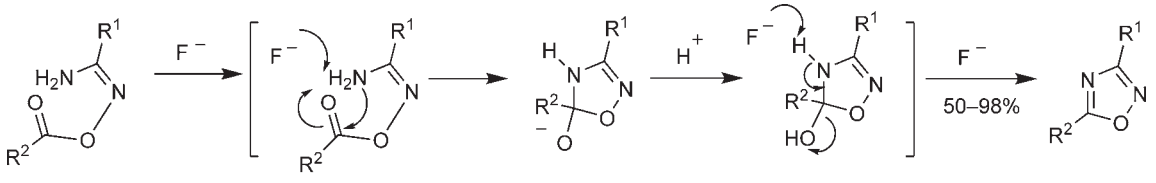
Cyclization of isolated O-acylated amidoximes **204** has been achieved thermally in glacial acetic acid at reflux <2005RCB1900, 2001BML2079>, heating in DMF at 110 °C <2001TL1495>, toluene at reflux <2006BML302, 1998EJM715>, pyridine at reflux <1999JME4088, 1999BML2359>, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at



204

Scheme 30

72 °C <1997C832>, reflux in ethanol <2005ARK36>, treatment with sodium acetate in ethanol/water at 86 °C <2003JOC7316, 2003TL6079>, heating neat at 120 °C <2001T5865>, heating at 85 °C in acetonitrile <2005OL925>, and heating at reflux in 2% sodium hydroxide <2002JPES229>. A significant advance is the use of tetra-*N*-butylammonium fluoride (TBAF) in THF at room temperature as a cyclization media, a process which occurs in the presence of 0.1–1.0 equiv of TBAF and is extremely mild and high yielding <2001TL1441, 2003TL8697>, with the fluoride ion acting as both a homogeneous and strongly basic reagent (**Scheme 31**).



204 R^1 = Ph, 2-, 3- or 4-Tol, 2-, 3- or 4-$MeOC_6H_4$, 2-, 3-, or 4-$NO_2C_6H_4$, Me, 4-$BocHNC_6H_4$, 2-Cl,5-I,4-$BocHNC_6H_2$
R^2 = Me, Ph, OMe,Bu^t, CH_2Cl, $CH_2OCH_2CH_3$, CF_3, Pr^i, 2-, 3-, or 4-$NO_2C_6H_4$, CH_2Ph

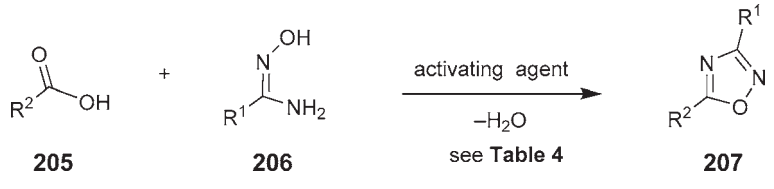
Scheme 31

5.04.9.1.2 Ring syntheses of 1,2,4-oxadiazoles from a one-atom component and a four-atom component

5.04.9.1.2(i) Syntheses from amidoximes and carboxylic acids and their derivatives

The reaction of an amidoxime **206**, the four-atom component N–C–N–O, with a carboxylic acid derivative constitutes the historically most used <1984CHEC(6)365, 1996CHEC-II(4)179> entry into the 1,2,4-oxadiazole nucleus, and this approach has continued to be popular since it was reviewed in CHEC-II(1996). The reactions discussed in this section proceed, as discussed in Section 5.04.9.1.1(iii) (see also **Scheme 30**), via a nonisolable acylated amidoxime.

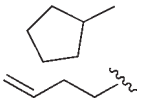
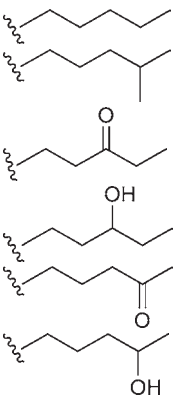
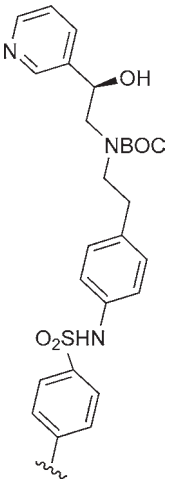
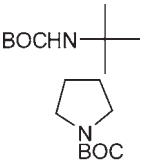
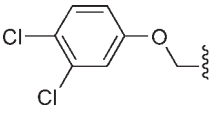
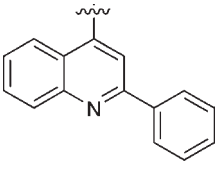
A strong recent trend toward the use of a carboxylic acid **205** (see Equation 32) that is activated *in situ* and then reacted with an amidoxime **206** has emerged since the appearance of CHEC-II(1996) <1996CHEC-II(4)179>. **Table 4** lists a range of 1,2,4-oxadiazoles **207** that are available via this method together with the range of coupling reagents that has been used. Notable among these studies are those that compare various coupling reagents <1996TL6627, 2001TL1495, 2004SC1863, 2004BML4491, 2005OL925>, those that utilize high-speed microwave irradiation <2005OL925, 2004BML4491, 2003TL9337>, those that are applicable to a large range of 1,2,4-oxadiazoles (often as libraries) <2005OL925, 2004BML4491, 2003TL9337, 2001TL1495, 2000BML1427, 1999BML209, 1996TL6627>, one that utilizes optimization on the basis of statistical design <2003TL9337>, and one that is applicable to scale up to a 30 kg scale using EDC/HOBT(EDC = 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride; HOBT = hydroxybenzotriazole) <2006OPD36>.



205 **206** **207** (32)

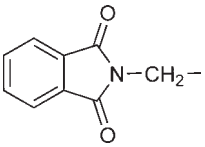
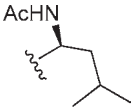
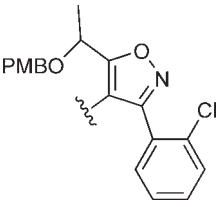
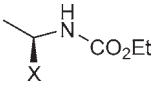
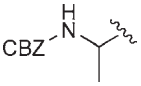
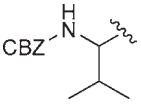
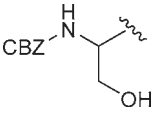
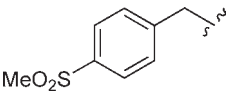
A wide variety of carboxylic acid derivatives **208** can also be used as the one-carbon fragment (Equation 33). The carboxylic acid derivative can be an ester <1996BML833, 1996JOC3228, 1999CPB120, 1999JFC127, 1999CPB876, 1999J(P1)2725, 2000BMC1443, 2000BMC1559, 2001BML2079, 2005NN1971, 2005BML4628, 2006TL3629,

Table 4 1,2,4-Oxadiazoles available from the reaction of carboxylic acids with amidoximes in the presence of an activator (see Equation 32)

R^2 (carboxylic acid)	*R^1 (amidoxime)*	*Activating agent*	*Yield of* **207** *(%)*	*References*
$4\text{-}XC_6H_4$ (X = H, Me, OMe)	4-Tol	EDC DCC BOP-Cl CDI	30–63 50–54 47–64 57–62	1996TL6627
Not defined (library)	Not defined (library)	EDC/HOBT	Not given	1997C832
$4\text{-}XC_6H_4$ (X = OMe, Br, CN)	YC_6H_4 (Y = 4-OMe, 4-Me, 4-F, 3-CF_3)	CDI	51–69	1999BML209
	YC_6H_4 (Y = 4-OMe, 4-Me, 4-F, 3-CF_3)	CDI	45–60	1999BML209
BOC-Glu, BOC-Ala, BOC-*homo*Phe, BOC-Ser, Et, CH_2-(3-indole)	Bn, $(CH_2)_2Me$, CH_2-(4-MeC_6H_4), CH_2-(4-$Pr^iC_6H_4$), CH_2-(4-ClC_6H_4), CH_2-(2,3-$Cl_2C_6H_3$), CH_2-(2,3-$Cl_2C_6H_3$), CH_2CH_2Ph	EDC/HOBT/ Hunig's base	Not given	1999JME4088, 1999BML2359
Me, Pr^n, Bu^n, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17} 		EDAC	Not given	2000BML1427, 2000BML1431
	Ph, 4-$Bu^tC_6H_4$, 4-$CF_3C_6H_4$, 3-pyridyl	TBTU/HOBT/ DIEA/DMF	66–87	2001TL1495
3-Tol, 4-ClC_6H_4 				
				

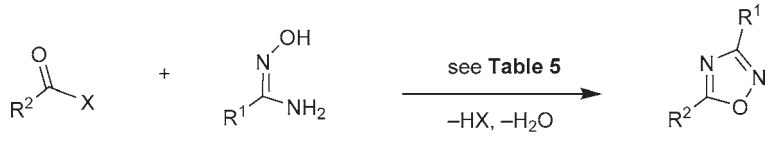
(*Continued*)

Table 4 (Continued)

R^2 (carboxylic acid)	R^1 (amidoxime)	Activating agent	Yield of **207** (%)	References
	2-, 3-, or 4-Tol, 4-XC_6H_4 (X = H, Cl, NO_2, OMe)	DCC/DME	20–82	2003JST1
Ph, 4-Tol, 4-ClC_6H_4	Ph, 4-Tol, 4-ClC_6H_4	HBTU/DIEA/ 200 °C/microwave	>90	2003TL9337
				
	4-Tol	EDC	40	2004JOC1470
 (X = Me, Bn, Bu^i, CH_2SCH_2Ph)	Ph, 4-Tol, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$	DCC/dioxane/ 100 °C	60–82	2004S1589
4-$MeOC_6H_4$, 4-CNC_6H_4, 4-$MeSO_2C_6H_4$,   	Me, 4-FC_6H_4	EDC/ HOBT	60–93	2004SC1863
4-XC_6H_4 (X = H, NO_2, OEt)	4-Tol	EDC or CDI or TBTU/HOBT or DCC/HOBT (all microwave)	27–91	2004BML4491
4-$BnOC_6H_4$, 3-$MeOC_6H_4$, $PhCH_2CH_2$, 2-furyl, 2-Tol, CH_2-cyclohexyl	3-$NO_2C_6H_4$, 3-$CF_3C_6H_4$, 3-pyridyl, Me, Bu^t, 4-Tol	PS-BEMP/HBTU/ microwave or PS-PPh_3/DIEA/ microwave	45–97	2005OL925
	Me	EDC/HOBT	90	2006OPD36

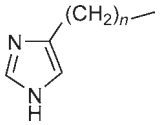
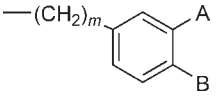
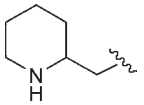
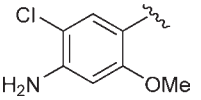
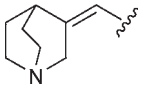
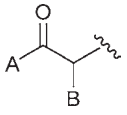
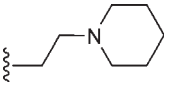
PS-BEMP = polymer-supported 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazophosphorine; EDAC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide; PS-PPh_3 = polystyrene-supported PPh_3; TBTU = 2(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate.

2006TL4271>, an acid chloride <1999CCL117, 1999FES747, 1999KGS701, 2000BML1427, 2000BML1431, 2002RCB1857, 2003CAR257, 2003H(60)2287, 2004BML4307, 2005HCO29, 2005BMC353, 2005JHC699, 2005NN1919, 2006BML302>, an acid fluoride <1999TL9359>, an acid anhydride <1995JOC3112, 1996BML2425, 1998TL7619, 1999CAR157, 1999JMC4331, 2000BML1431, 2002H(57)1891, 2003CAR257, 2005BMC353> including symmetrical acid anhydrides derived from amino acids <1995JOC3112, 1999JME4331>, and amino acids activated as succinimides <1999JME4088, 1999BML2359>. Some representative examples are shown in **Table 5**.



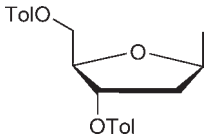
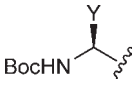
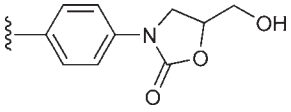
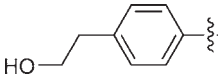
208 **206** **207** (33)

Table 5 1,2,4-Oxadiazoles available from the reaction of carboxylic derivatives with amidoximes (see Equation 33)

R^2 **208**	R^1 **206**	*X* (*conditions*)	*% Yield of* **207** (*Reference*)
 n = 1, 2, 3	 m = 1, 2; B = H, Cl; A = Cl, CF_3, OMe	OMe (NaOMe, MeOH)	19–63 (1996BML833)
$Me_2N(CH_2)_2$	Me	OMe (NaH, THF)	39 (1996JOC3228)
		OMe (NaH, DMF)	72 (1999CPB120)
BrF_2C	Ph, Me, Pr^n	OEt (heat)	24–41 (1999JFC127)
	Me, Et	OEt (NaOEt, EtOH, heat)	46–93 (2000BMC1443)
Me, Et, Pr^n, Pr^i, Bu^i, cyclopropyl	NH_2	OEt (NaOH, EtOH)	5–20 (2005BML4628)
Benzyl, 4-methylbenzyl, 4-$MeOC_6H_4$	Me, 4-Tol	OMe (K_2CO_3, toluene, reflux)	62–91 (2006TL3629)
 A = OMe, OEt, OBn, Me; B = Ph, Bn, H, CH_2CHMe_2	2-, 3-, or 4-pyridyl, CO_2Et, Me, cyclopropyl,	OMe, OEt, OBu^t (120 °C, solvent free)	47–91 (2006TL4271)
CO_2Me	Ph, 4-YC_6H_4 Y = Me, OMe, NO_2	Cl (THF, reflux)	42–52 (1999FES747, 2005HCO29)
Ph		Cl (DMSO, rt)	73 (1999KGS701)
CH_2Cl	C(O)NHR R = Ph, 4-YC_6H_4 (Y = Cl, MeO, NO_2)	Cl (Na_2CO_3, amyl acetate, reflux)	60–70 (2002RCB1857)
Me, Ph, 4-$NO_2C_6H_4$	Ph, 3- or 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, styryl, 4-$ClC_6H_4CH_2$	Cl (MgO, microwave, 1 min)	67–91 (2003H(60)2287)

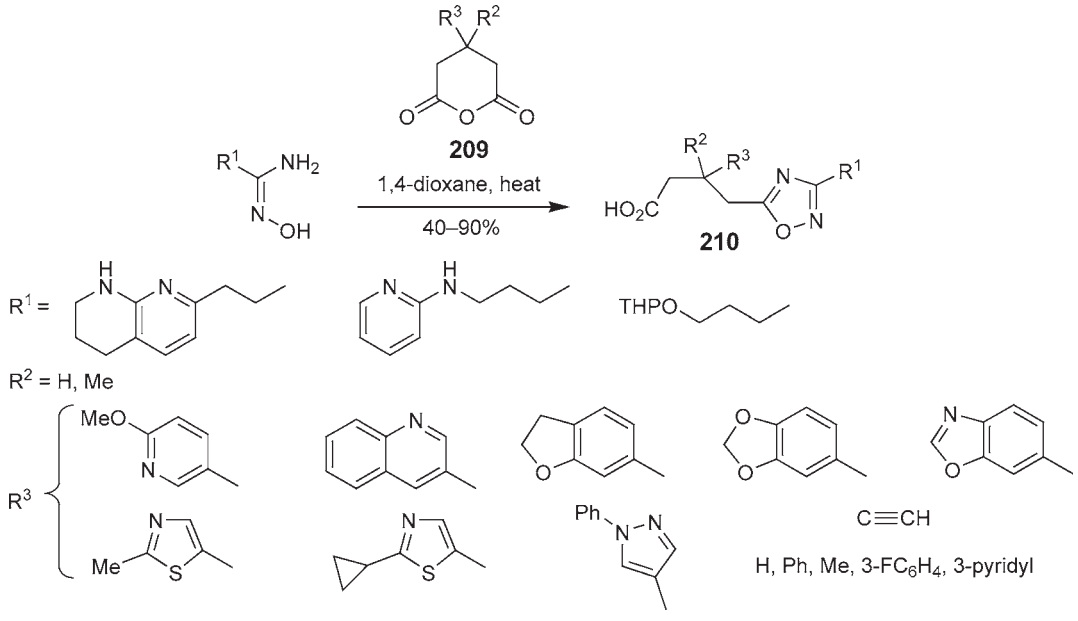
(*Continued*)

Table 5 (Continued)

R^2 **208**	R^1 **206**	*X* (*conditions*)	*% Yield of* **207** (*Reference*)
4-$MeOC_6H_4$	4-ClC_6H_4, 4-ClC_6H_4	Cl (pyridine, reflux)	70–85 (2004BML4307)
	CO_2Et	Cl (pyridine, 80 °C)	20 (2005NN1919)
Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$	Ph, 3- or 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, C_6H_{11}, 4-$ClC_6H_4CH_2$	Cl (Al_2O_3/ NH_4F, microwave, 3 min)	71–90 (2005JHC699)
	CO_2Et	$OC(O)R^2$ (pyridine, reflux)	54–81 (1995JOC3112)
Y = CH_2Ph, H, Me, CH_2SBn, CH_2OBn, CH_2CO_2Bn	$CH_2CH_2OTBDPS$		75 (1999JME4331)
Me		$OC(O)Me$ (Ac_2O, 120 °C)	80 (1996BML2425) 82 (1998TL7619)
			
CCl_3	C_7F_{15}	$OC(O)CF_3$ (CF_3COOH, 120 °C)	80 (2002H(57)1891)

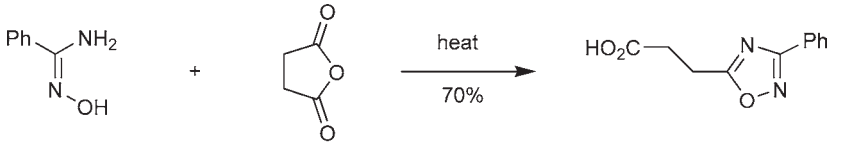
TBDPS = *tert*-butyldiisopropylsilyl.

As shown in **Scheme 32**, 3-substituted glutaric anhydrides **209** are excellent substrates for reaction with amidoximes, giving the 1,2,4-oxadiazoles **210** <2006BML839>.



Scheme 32

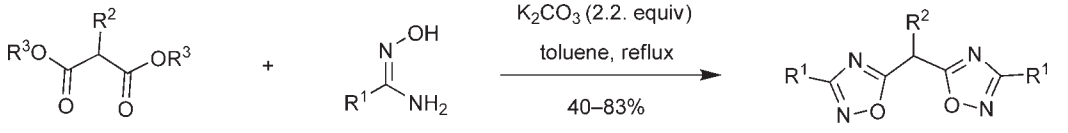
Succinic anhydride **211** reacts in the same fashion to produce the 1,2,4-oxadiazol-5-yl propanoic acids **212** (Equation 34), which function as excellent substrates for coupling to amino acid derivatives <2000FES719, 1999HCO521, 1999H(51)2961>.



(34)

211 **212**

The reaction of malonates **213** with 2 equiv of an amidoxime in the presence of potassium carbonate results in the formation of the bis-1,2,4-oxadiazoles **214** (Equation 35), a process that also gives excellent yields of the mono-1,2,4-oxadiazoles when a 1:1 ratio is employed (see **Table 5**) <2006TL3629>.

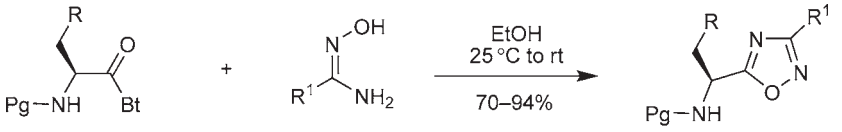


(35)

213 **214**

R^1 = Me, Et, Bn, 4-FC_6H_4, 4-$MeOC_6H_4$, cyclopropylmethyl, CH_2CH_2OMe
R^2 = H, Bn

The reaction of the stable and readily available N-protected (α-aminoacyl)benzotriazoles **215** (Equation 36) with amidoximes **206** in ethanol gave the N-protected 5-amino-substituted 1,2,4-oxadiazoles **216** in high yield, under mild conditions and with good (>97%) retention of chirality <2005ARK36>. The method is also applicable to aromatic *N*-acylbenzotriazoles, giving access to 5-aryl-1,2,4-oxadiazoles in 73–82% yield.

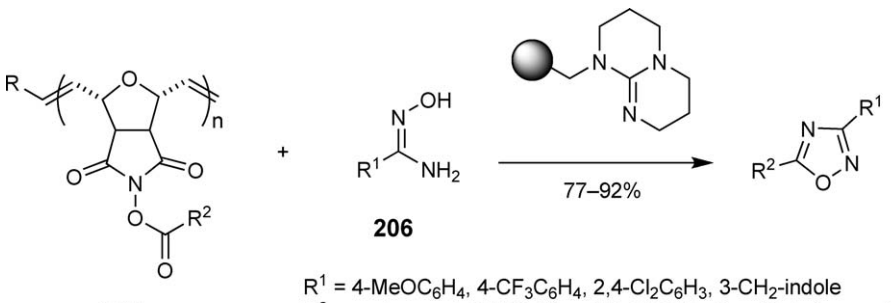


(36)

215 **206** **216**

R^1 = 4-Tol, 4-pyridyl, Bn
R from alanine, valine, phenylalanine, methionine, tryptophan, and glutamine

ROMPGEL-supported acylating agents **217** (ROMPGEL = ring-opening metathesis polymer backbone) have been used to give access to 1,2,4-oxadiazoles in high yields with minimal need for purification (Equation 37) <2000CCHT131>.



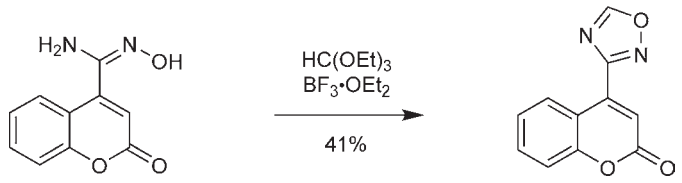
(37)

217 **206**

R^1 = 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 2,4-$Cl_2C_6H_3$, 3-CH_2-indole
R^2 = cyclopropyl, CH_2CHMe_2, 3,5-$Cl_2C_6H_4$, 3-pyridyl, 4-oxazolyl

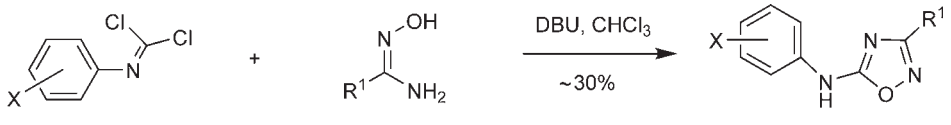
5.04.9.1.2(ii) Other methods involving a one-atom component and four-atom component

Access to 5-unsubstituted 1,2,4-oxadiazoles can be achieved by reaction of an amidoxime with ethyl orthoformate <1984CHEC(6)365, 1996CHEC-II(4)179, 2001JCR(S)209, 2004HOU(13)127>, and a recent example is shown in Equation (38) <1998EJM715>.



(38)

The imidocarbonylchlorides **218** (Equation 39) react with amidoximes in chloroform in the presence of DBU to give the 5-anilino-1,2,4-oxadiazoles **219** <2001JPES60>.

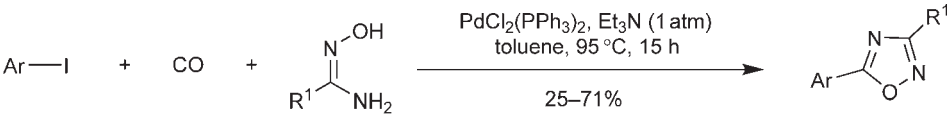


218 **206** **219**

(39)

R^1 = ZC_4H_4 or $ZC_6H_4CH_2$; Z = H, 2-Me, 2-Cl, 4-Cl, 3-Me, 2-Ph, 2,6-Cl_2
X = 4-Cl, 2-Cl, 3-Cl, 4-OCF_3, 4-Me, 3-CF_3, 4-OMe, 4-F, 4-Bu^t

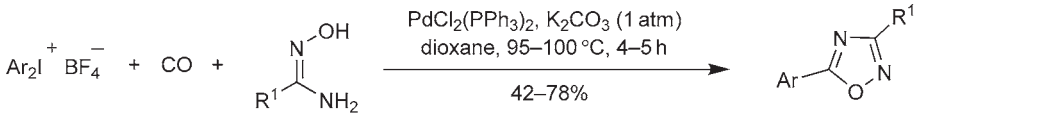
Young and DeVita have shown that 1,2,4-oxadiazoles can be prepared by a new route in a novel one-pot procedure by the palladium-mediated coupling of an aryl iodide with an amidoxime in the presence of carbon monoxide (Equation 40) <1998TL3931>.



(40)

Ar = XC_6H_4; X = CO_2Me, 4-MeO, 4-NO_2, 4-Br, 2-OMe; R^1 = Me, CO_2Et

As part of a later investigation into palladium-catalyzed reactions of diaryliodonium salts **220**, Chen and Zhou found that reaction with amidoximes in the presence of carbon monoxide also gave 1,2,4-oxadiazoles (Equation 41) <2002SC887>.

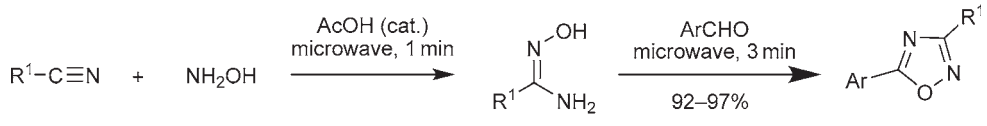


220 **206**

(41)

Ar = XC_6H_4; X = H, 4-Me, 4-Cl, 4-MeO, 3-NO_2
R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, Bn

Microwave irradiation of amidoximes in the presence of an aldehydes under solvent-free conditions has been reported to give fully conjugated 1,2,4-oxadiazoles directly, a process that is notable because the amidoximes can be prepared in the same reaction vessel from a nitrile and hydroxylamine (**Scheme 33**) <2006TL2965>.



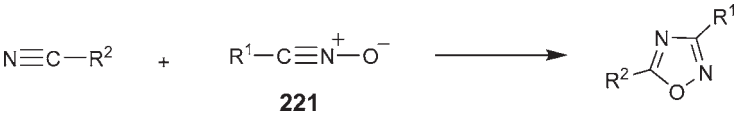
R^1 = Ph, 4-Tol, 3-ClC_6H_4; Ar = Ph, 4-Tol, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 33

5.04.9.1.3 Ring syntheses of 1,2,4-oxadiazoles from a two-atom component and a three-atom component

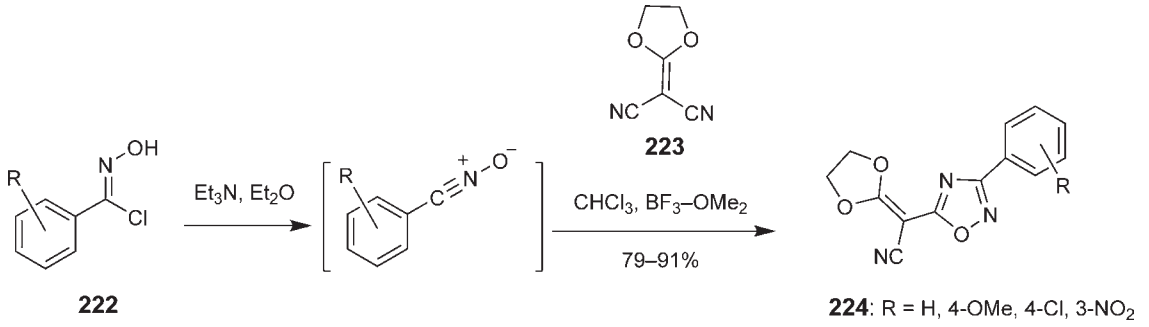
5.04.9.1.3(i) Syntheses via 1,3-dipolar cycloaddition of nitrile oxides to nitriles

The 1,3-dipolar cycloaddition between a nitrile and a nitrile oxide gives direct access to the 1,2,4-oxadiazole nucleus (Equation 42). This is another well-established route to 1,2,4-oxadiazoles and was discussed extensively in CHEC(1984) <1984CHEC(6)365> and CHEC-II(1996) <1996CHEC-II(4)179>. The large upsurge in facile methodologies that rely upon carboxylic acid derivatives (Section 5.04.9.1.2) has not been matched by an upsurge in 1,3-dipolar cycloaddition approaches, and the method appears to have fallen out of favor. The information on 1,3-dipolar cycloadditions of nitrile oxides to nitriles in CHEC-II(1996) <1996CHEC-II(4)179> and elsewhere <2004HOU(13)127> is, correspondingly, still very relevant.

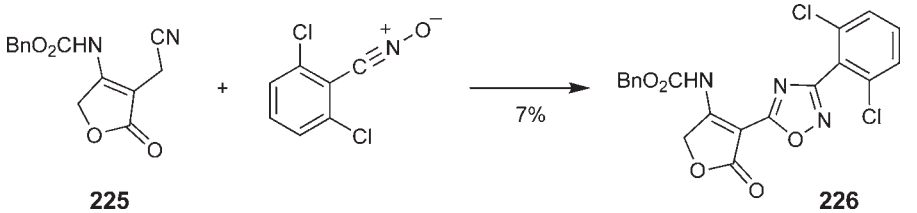


(42)

The nitrile oxides required for these reactions can be generated via the dehydrodehalogenation of an imidoyl halide, and **Scheme 34** shows an example of such an approach that has appeared since CHEC-II(1996) <1996CHEC-II(4)179>, in which imidoyl halides **222** undergo loss of HCl to give the nitrile oxide which undergoes cycloaddition to the dicyanoketene acetal **223**, producing the 1,2,4-oxadiazoles **224** <1996JHC1943, 1995SC2379>. In another example, the dipolarophile **225** reacted with 2,6-dichlorobenzonitrile oxide to give the 1,2,4-oxadiazole **226** in poor yield (Equation 43) <2003ARK37>.

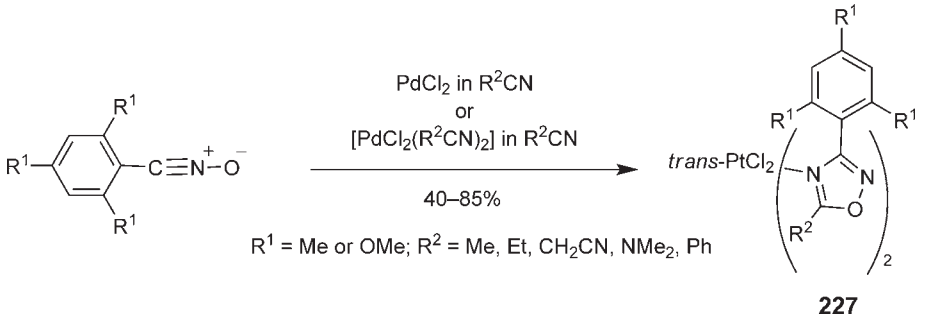


Scheme 34



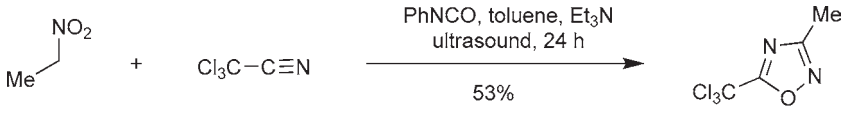
(43)

The cycloaddition of nitrile oxides to nitriles in the presence of a Pd(II) center allowed the isolation of the previously unknown 1,2,4-oxadiazole–Pd(II) species **227** (Equation 44) <2005EJI845>.



(44)

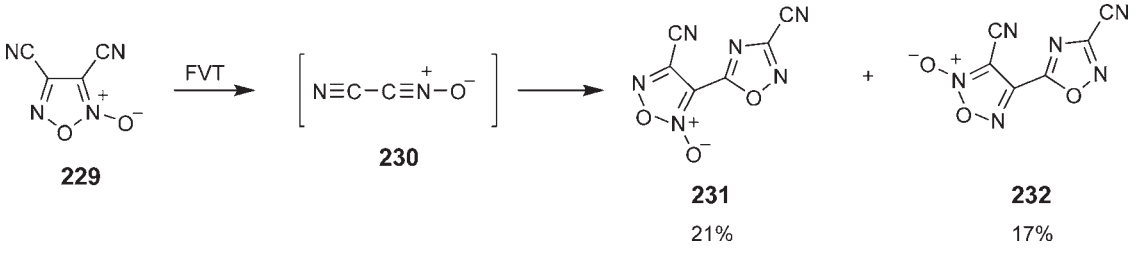
The Mukaiyama–Hoshino reaction between a nitroalkane and phenyl isocyanate generates a nitrile oxide, and this method has been used in the synthesis of 1,2,4-oxadiazoles as discussed in CHEC-II(1996) <1996CHEC-II(4)179>. In a more recent advance, nitroethane undergoes ultrasound-mediated cycloaddition with trichloroacetonitrile to give the extremely useful (see Equation 11) 5-trichloromethyl-1,2,4-oxadiazole **228** (Equation 45) <1995TL4471>.



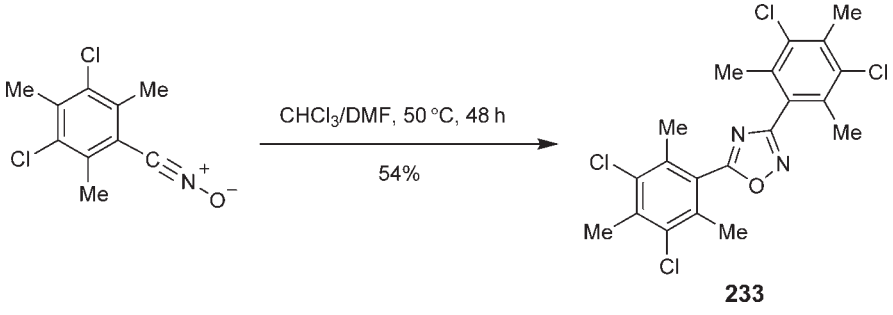
(45)

228

A number of less common methods have emerged for the generation of the nitrile oxide since the appearance of CHEC-II(1996) <1996CHEC-II(4)179>. Thus, the flash vacuum thermolysis of the dicyanofuroxan **229** results in the generation of the nitrile oxide **230** (**Scheme 35**) which goes on to form the 1,2,4-oxadiazoles **231** and **232** <2000JP2473>. The 1,3-dipolar cycloaddition of stable nitrile oxides to nitriles under microwave irradiation in solvent-free conditions has been investigated <1996H(43)1021>, and the process was shown to give higher yields of 1,2,4-oxadiazoles than the classical methods. 3,5-Dichloro-2,4,6-trimethylbenzonitrile oxide is a stable nitrile oxide that has been shown to undergo dimerization and deoxygenation to give the 1,2,4-oxadiazole **233** (Equation 46) <2000H(53)1915>.

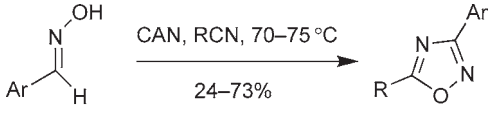


Scheme 35



(46)

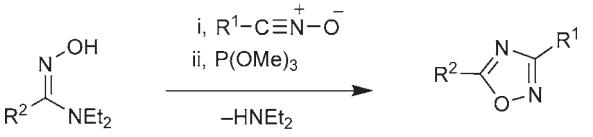
The oxidation of aromatic aldoximes with ceric ammonium nitrate produces nitrile oxides which undergo subsequent cycloaddition to nitriles to produce 1,2,4-oxadiazoles (Equation 47) <1997PJC1093>. The anodic oxidation of aromatic aldoximes in the presence of acetonitrile has been reported to give low yields of either 3-aryl-5-methyl-1,2,4-oxadiazoles (2–25%) or 3,5-bis-aryl-1,2,4-oxadiazoles (6–28%), although the synthetic utility of this route is limited by competitive deoximation to the carbonyl being the major reaction pathway <1997MI3509>.



(47)

R = Et, Me
Ar = XC_6H_4; X = H, 4-Me, 4-MeO, 4-Ph, 2-, 3-, or 4-Cl, 4-Br, 2-, 3- or 4-NO_2

The cycloaddition of nitrile oxides to amidoximes **234** leads to 1,2,4-oxadiazole 4-oxides which can then be deoxygenated with trimethyl phosphite (Equation 48) <1997T1787>.



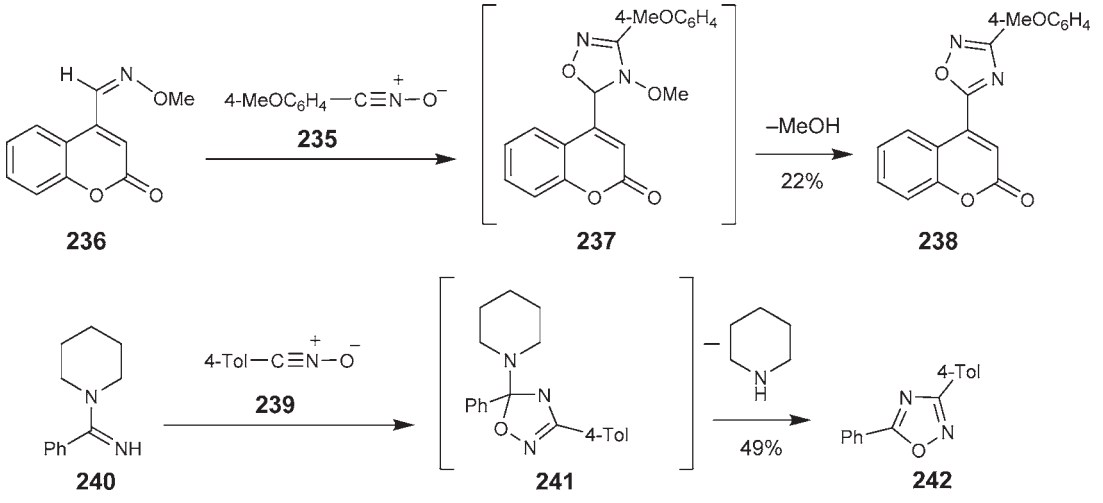
234

(48)

R^1 = Ph, 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, Me;
R^2 = Ph, 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$

5.04.9.1.3(ii) Syntheses via other two-atom plus three-atom component reactions

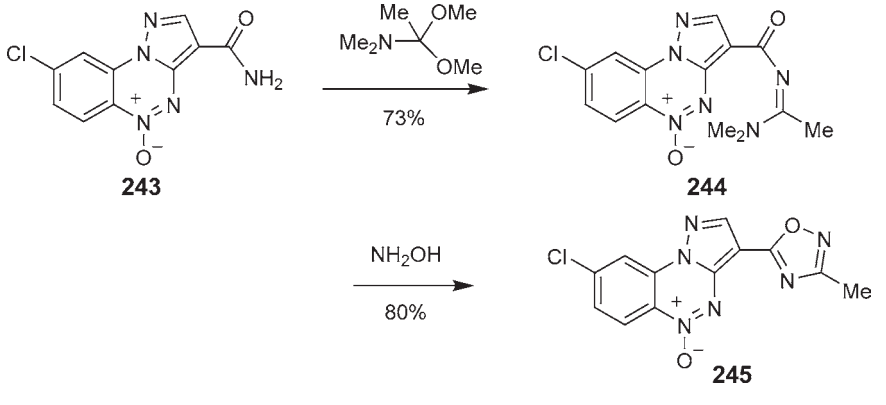
The cycloaddition of nitrile oxide **235** to the 4-iminobenzopyran-2-one **236** gave the fully conjugated 1,2,4-oxadiazole **238** directly, a reaction that most likely proceeds via loss of methanol from the intermediate **237** (**Scheme 36**) <1996JHC967>. Similarly, nitrile oxide **239** reacted with imine **240** to give the 1,2,4-oxadiazole **242** via the nonisolable intermediate **241** <2002PJC1137>.



236 **237** **238** **240** **241** **242**

Scheme 36

The intermediate acylamidine **244** functions as the three-atom component in reaction with hydroxylamine to give the [1,2,4-oxadiazol-5-yl]pyrazole **245**, where the intermediate acylamidine **244** was obtained in good yield from reaction of the corresponding amide **243** with dimethylacetamide–dimethyl acetal (**Scheme 37**) <1999JME2218>.

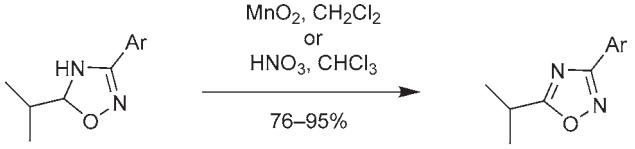


243 **244** **245**

Scheme 37

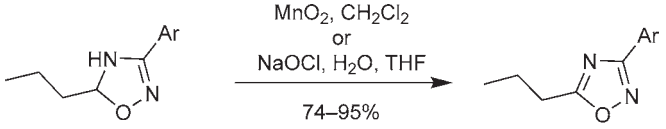
5.04.9.1.4 Ring syntheses of 1,2,4-oxadiazoles from dihydro-1,2,4-oxadiazoles

The synthesis of dihydro-1,2,4-oxadiazoles is detailed in Section 5.04.10. Oxidation of these systems gives the fully conjugated 1,2,4-oxadiazoles and CHEC-II(1996) reviewed advances in this area before 1996 <1996CHEC-II(4)179>. More recently, the oxidation has been performed with MnO_2 <2000HCO41, 2003BMC1821>, nitric acid <2000HCO41>, NaOCl <2003BMC1821>, or *N*-chlorosuccinimide <1996JHC1583>, as shown in Equations (49)–(51).



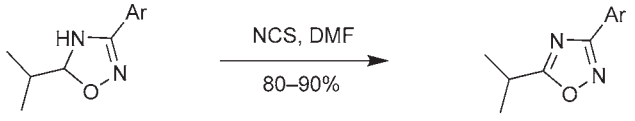
(49)

Ar = Ph, 2-, 3- or 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$



(50)

Ar = Ph, 2-, 3-, or 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4



(51)

Ar = Ph, 4-Tol, 4-ClC_6H_4

The reaction of the bicyclic 4,5-dihydro-1,2,4-oxadiazoles **246** with silver tetrafluoroborate and 2,4,6-collidine gave the fully conjugated 5-fluoroalkyl-1,2,4-oxadiazoles **247**, while heating the bicyclic 4,5-dihydro-1,2,4-oxadiazole **246** ($R^1 = 2\text{-}N_3C_6H_4$) in toluene gave the fully conjugated 1,2,4-oxadiazole **248** (**Scheme 38**). These processes are believed to proceed via the loss of the ethylthio moiety to give an oxadiazolium cation which undergoes ring opening to form the fully- conjugated ring together with a tertiary carbocation, which upon fluorination or deprotonation yields the isolated products **247** and **248** (**Scheme 38**). Interestingly, the phenyl-substituted bicyclic 4,5-dihydro-1,2,4-oxadiazole **249** undergoes a retro-[2+2] cycloaddition to give the fully conjugated 5-ethylthio-1,2,4-oxadiazole **250** via loss of styrene <2000JFC83, 2006TH1>.

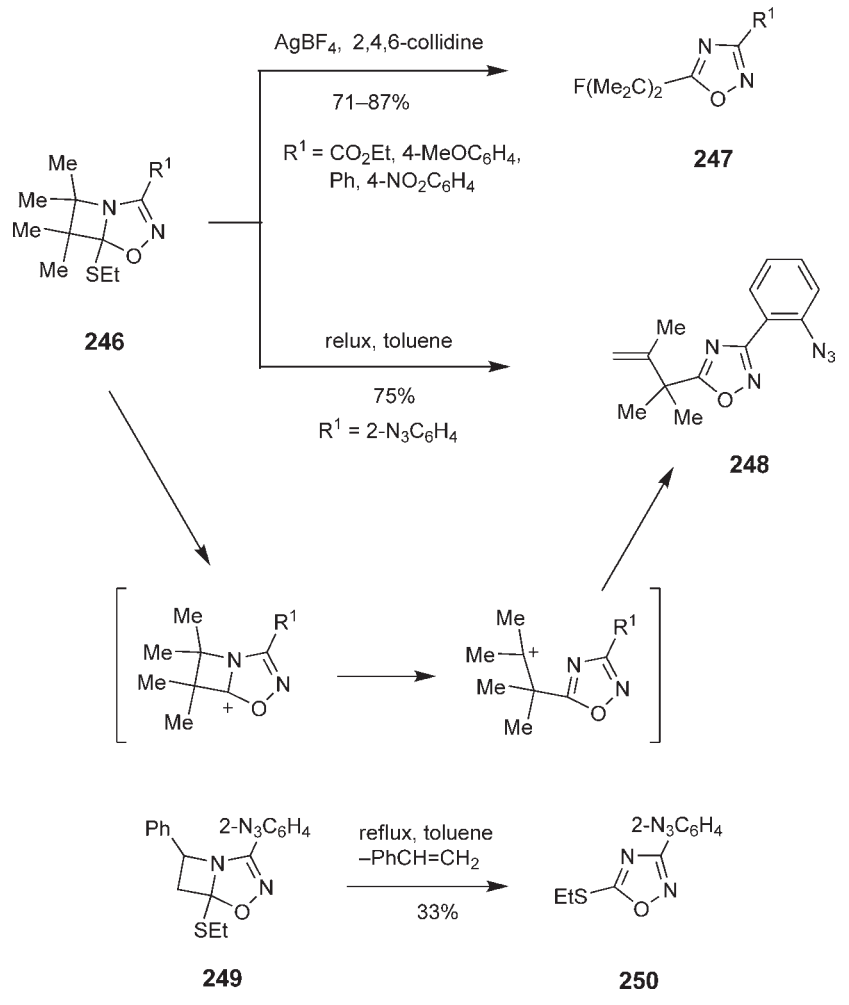
5.04.9.1.5 Ring syntheses of 1,2,4-oxadiazoles from 1,2,4-oxadiazolidines

This route remains an unknown approach to the fully conjugated heterocycle. The synthesis of 1,2,4-oxadiazolidines is detailed in Section 5.04.10.4.

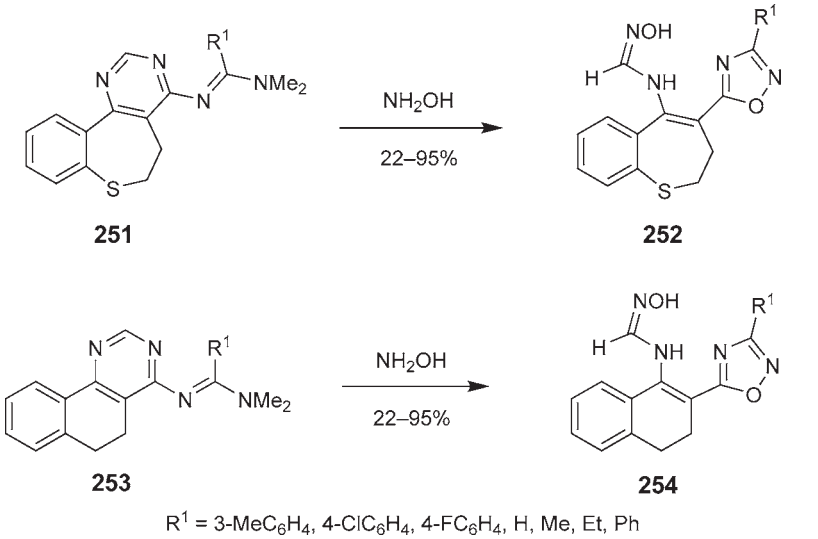
5.04.9.1.6 Ring syntheses of 1,2,4-oxadiazoles from other heterocycles

Reaction of (benzothiepino[5,4-*d*]pyrimidin-4-yl)amidines **251** (**Scheme 39**) with an excess of hydroxylamine gave the 1,2,4-oxadiazol-5-yl-benzothiepines **252** <1999JHC787>, a process that also allows access to 1,2,4-oxadiazol-5-yl-dihydronaphthalenes **254** when the benzoquinazolinylamidines **253** are used as starting materials <1999JCM92>.

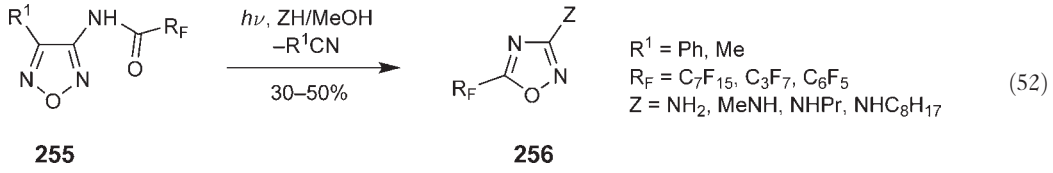
Fluorinated 1,2,5-oxadiazoles **255** (Equation 52) undergo photolytic loss of a nitrile fragment and reaction with a nucleophile to give the fluorinated 1,2,4-oxadiazoles **256** <2000TL7977, 2001T5865, 2004JFC165>.



Scheme 38



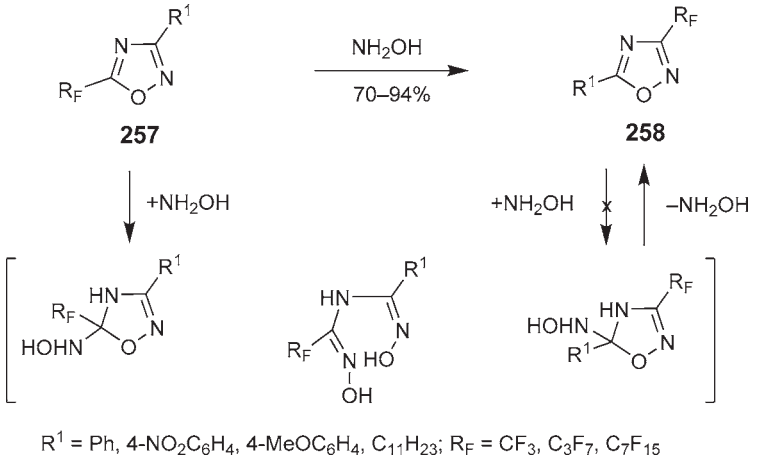
Scheme 39



(52)

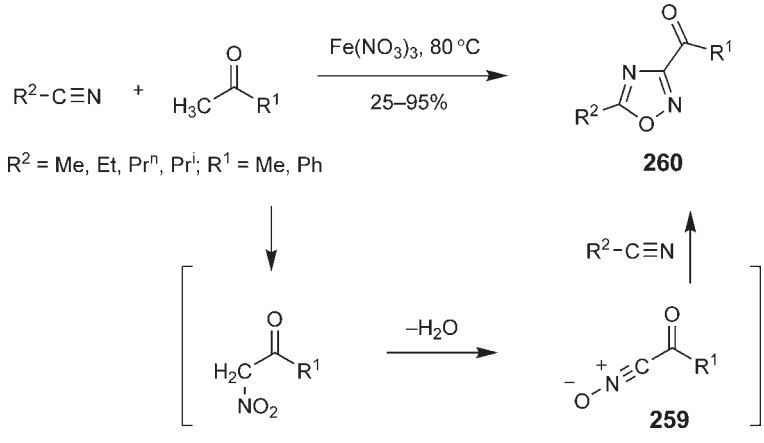
5.04.9.1.7 Miscellaneous ring syntheses of 1,2,4-oxadiazoles

Reaction of the 5-fluoroalkyl-1,2,4-oxadiazoles **257** with hydroxylamine results in the formation of high yields of the corresponding 3-fluoroalkyl-1,2,4-oxadiazoles **258** via attack of the hydroxylamine at the reactive 5-position. The 3-position (see Section 5.04.5.4) is unreactive toward nucleophiles, and the reaction is not reversed, proceeding by the mechanism shown in **Scheme 40**, which is of interest as the first example of an irreversible ring-degenerate rearrangement in a five-membered heterocycle involving attack of an external bidentate nucleophile <2004EJO974>.



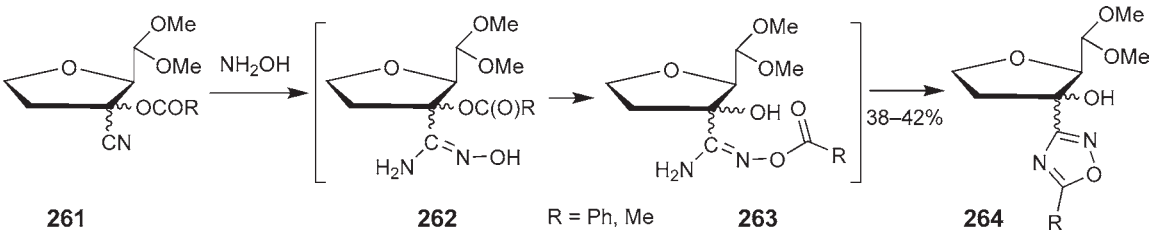
Scheme 40

In a significant addition to the synthesis of 1,2,4-oxadiazoles (**Scheme 41**), Itoh *et al.* discovered that the treatment of nitriles with iron(III) nitrate in the presence of acetone or acetophenone gives the 3-acetyl- or 3-benzoyl-1,2,4-oxadiazoles **260**, proposing that enolization and nitration gives an α-nitroketone, which then undergoes an acid-catalyzed dehydration to give the nitrile oxides **259** <2005S1935>.



Scheme 41

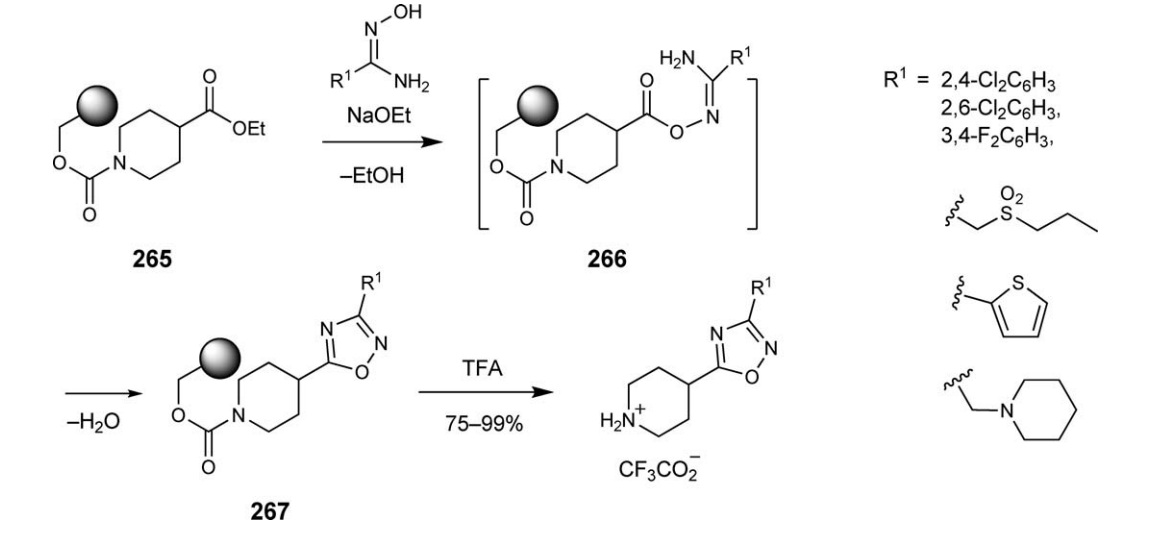
The reaction of the acylated cyanohydrins **261** (**Scheme 42**) with hydroxylamine gave the nonisolable amidoximes **262**. This then underwent intramolecular transacylation to give the intermediate **263**, which produced the 1,2,4-oxadiazoles **264** in both epimeric forms (depending on the starting material) on cyclization <2000TA1527>. Strong evidence for neighboring group participation was found.



Scheme 42

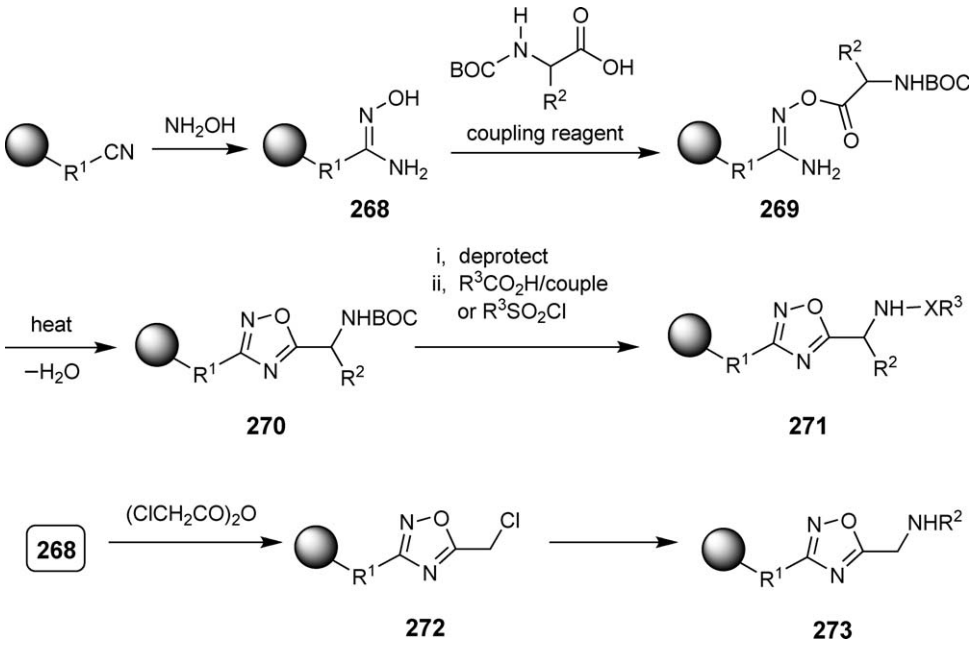
5.04.9.1.8 Solid-phase and polymer-supported syntheses

Given the huge amount of interest in the biological properties of the diverse range of molecules that contain the 1,2,4-oxadiazole moiety <2001JCM209, 2004HOU(13)127>, it is not surprising that several of the approaches discussed above have been adapted to allow solution-phase combinatorial and polymer-supported syntheses of this heterocycle. Liang and Qian have demonstrated that the use of a TentaGel resin, activated by 4-nitrophenyl chloroformate, and then captured by ethyl isonipecotate, gives the resin-bound ethyl ester **265** (**Scheme 43**). Room temperature reaction of this with sodium ethoxide and an amidoxime gives the *O*-acylamidoximes **266**, which then furnished the resin-bound isonipecotyl 1,2,4-oxadiazole **267** and were cleaved from the resin with trifluoroacetic acid <1999BML2101>. The process was found to be suited to parallel synthesis using a semi-automated synthesizer. The same work also demonstrated that the reaction of resin-bound carboxylic acids with an amidoxime and a peptide coupling reagent gave 1,2,4-oxadiazoles, although the reaction did require heating and specialized equipment for rocking the tubes at elevated temperature.



Scheme 43

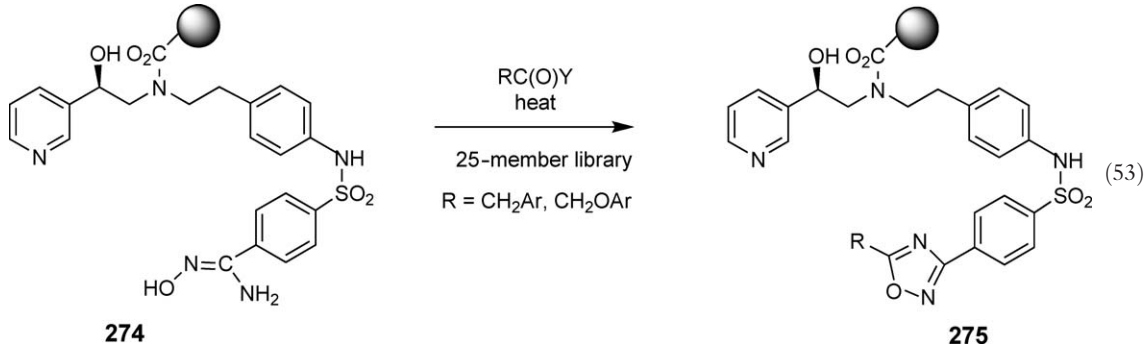
In an alternative approach (**Scheme 44**), the treatment of a series of resin-bound nitriles with hydroxylamine furnished the resin-bound amidoximes **268**. Acylation with a BOC- or Fmoc-protected amino acid under peptide coupling conditions gave the polymer-supported *O*-acylamidoximes **269**, which, upon heating, underwent cyclization to produce the resin-bound 5-amino-1,2,4-oxadiazoles **270** (BOC = *t*-butyloxycarbonyl; Fmoc = 9-fluorenylmethyloxycarbonyl). Extremely hindered amino acids, and glutamine and asparagine derivatives, gave poor yields of oxadiazoles. Alkyl carboxylic acids, succinic and glycolic anhydrides were successful; however, aromatic carboxylic acids gave poor yields <1999TL8547>. The resin-bound 5-amino-1,2,4-oxadiazoles **270** were easily deprotected at



Scheme 44

nitrogen and coupled to give amides and sulfonamides **271**. The same work also demonstrated that amidoxime **268** could be reacted with chloroacetic anhydride to produce the extremely useful 5-chloromethyl-1,2,4-oxadiazole **272**, which could be converted to the amine **273** and thence into sulfonamides and amides.

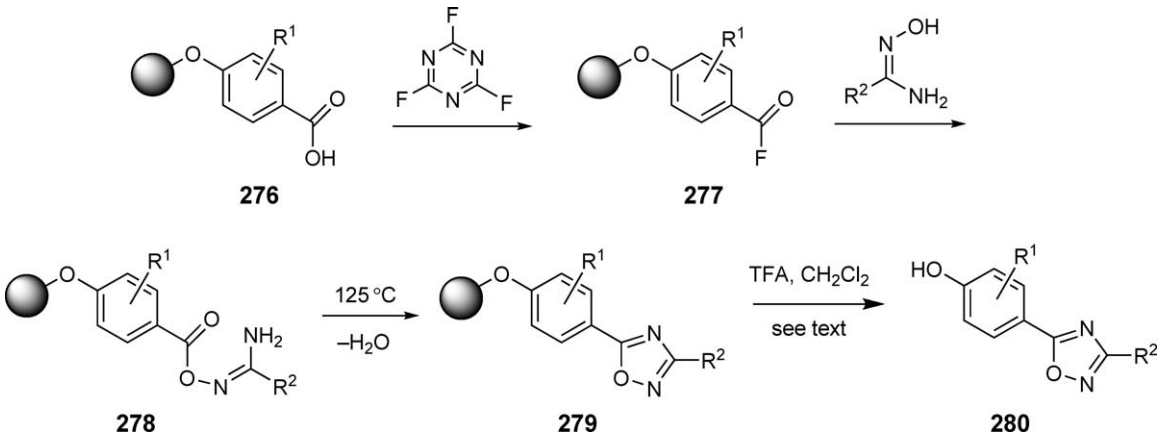
In a similar approach (Equation 53), the use of a resin-bound nitrile allowed access to the corresponding resin-bound amidoximes **274**, which could be converted into 1,2,4-oxadiazoles **275** via acylation with either an appropriate acid halide/anhydride in the presence of a base or a carboxylic acid in the presence of a coupling reagent followed by cyclization, where the latter step was performed by heating in pyridine or diglyme and could be accelerated by the use of a microwave oven. Cleavage from the resin was easily achieved by the use of TFA in dichloromethane <2000BML1431>.



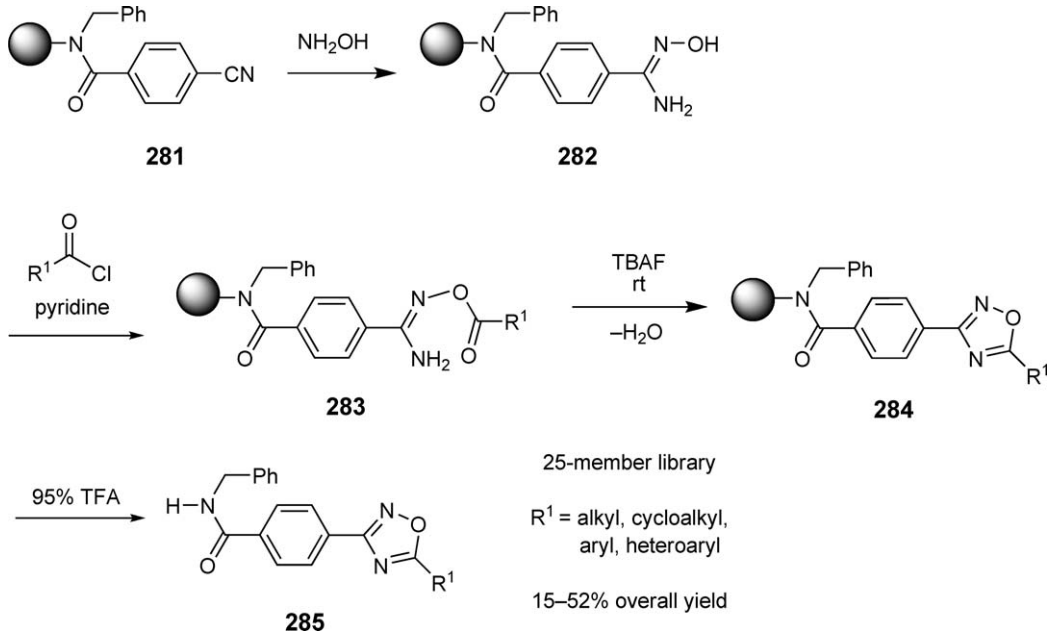
(53)

In another approach (**Scheme 45**), a series of benzoic acids **276** bound to the Wang linker were activated with cyanuric fluoride to give the resin-bound acyl fluoride **277**. The reaction of the acid fluoride with an amidoxime gave the resin-bound *O*-acylamidoxime **278**, which yielded the resin-bound 1,2,4-oxadiazoles **279** upon heating. Cleavage from the resin was facile with a mixture of dichloromethane and trifluoroacetic acid, giving the 1,2,4-oxadiazoles **280**. The procedure tolerated aliphatic, aromatic, polar, and nonpolar amidoximes, gave an average yield of 82%, and was suitable for automation, producing an 80-member library <1999TL9359>.

Rice and Nuss report that the Argopore MB-CHO polymer-supported amidoximes **282** (readily available from the nitrile **281**), shown in **Scheme 46**, can be acylated with acid chlorides in the presence of excess pyridine to give the *O*-acylamidoximes **283**. Cyclization was carried out with TBAF in THF at ambient temperature, to give the polymer-supported 1,2,4-oxadiazoles **284**. Release of the 1,2,4-oxadiazoles **285** from the polymer support was achieved by treatment with 95% trifluoroacetic acid <2001BML753>.



Scheme 45

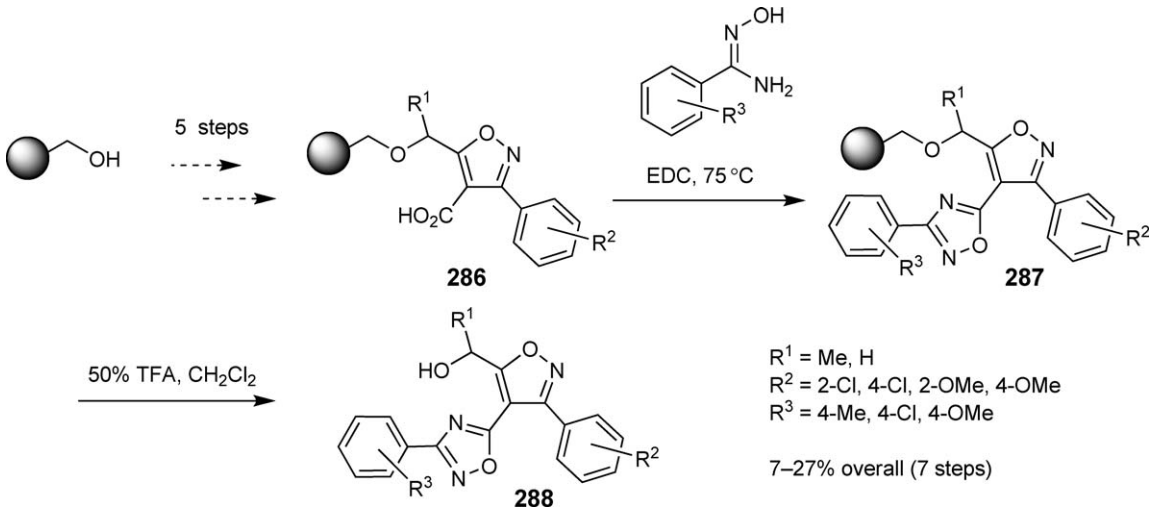


Scheme 46

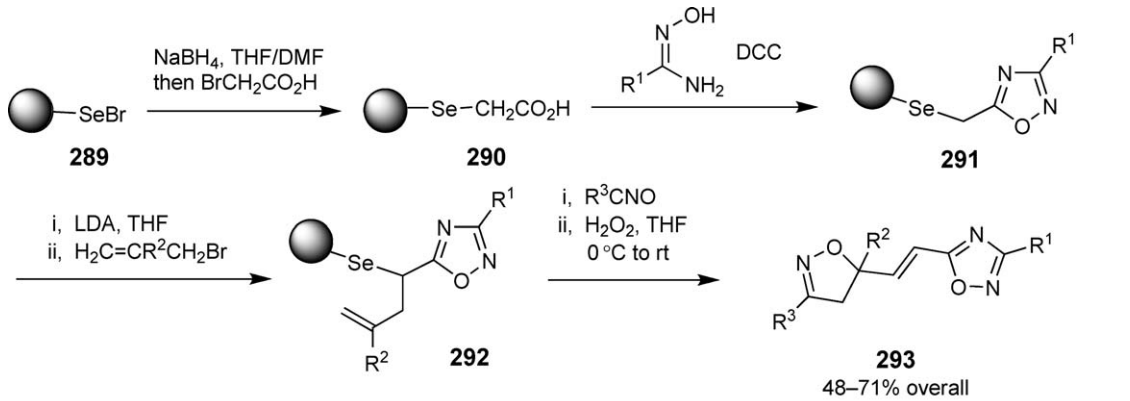
Kurth and Quan (**Scheme 47**) were able to synthesize the Wang resin-derived carboxyisoxazole **286** and react it with an amidoxime in the presence of EDC as a coupling agent to give the resin-supported 1,2,4-oxadiazole **287**. Cleavage from the resin was achieved with TFA, yielding the resin-free heterocycles **288** <2004JOC1470>.

The conversion of the polystyrene-supported selenyl bromide **289** into the corresponding acid **290** allowed dicyclohexylcarbodiimide (DCC)-mediated coupling with an amidoxime to give the 1,2,4-oxadiazolyl-substituted selenium resin **291** (**Scheme 48**). Reaction with lithium diisopropylamide (LDA) and allylation gave the α-substituted selenium resin **292**, which was then used as an alkene substrate for 1,3-dipolar cycloaddition with nitrile oxides. Cleavage of heterocycles **293** from the resin was executed in an elegant manner via selenoxide *syn*-elimination from the resin <2005JCO726>.

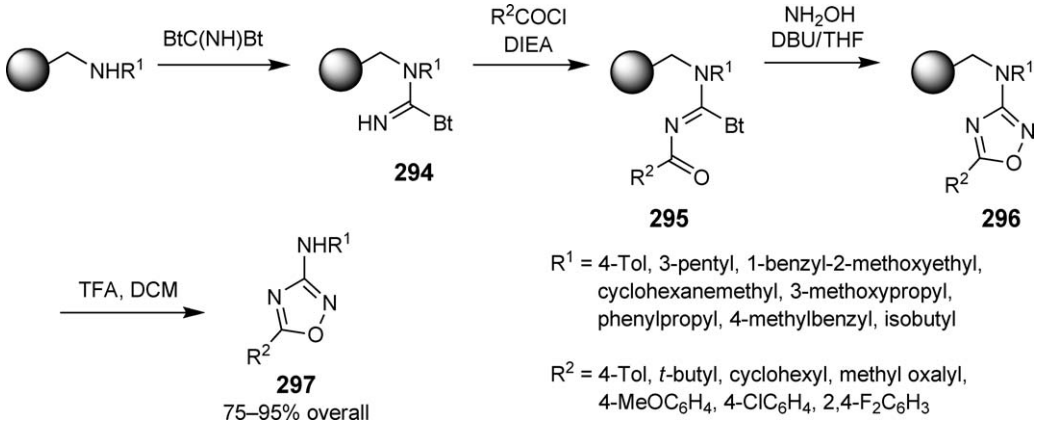
Each of the routes discussed thus far in this section are reliant upon amidoxime-based methods. In a change from this paradigm, Makara *et al.* produced the polymer-supported benzotriazoles **294** and converted them easily into the *N*-acyl-1*H*-benzotriazole 1-carboximidamides **295**. Cyclization with hydroxylamine gave the supported 3-amino-1,2,4-oxadiazoles **296** which were cleaved with TFA to give the free 3-amino-1,2,4-oxadiazoles **297** (**Scheme 49**) <2002TL5043>.



Scheme 47

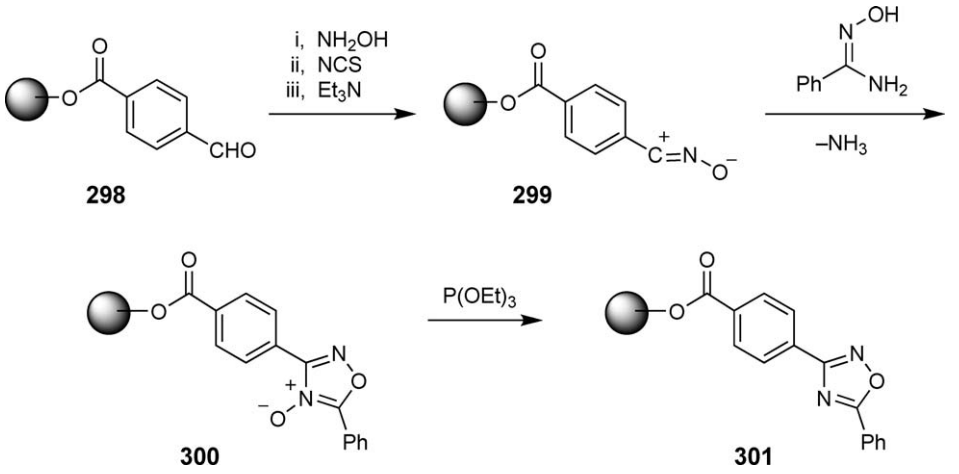


Scheme 48

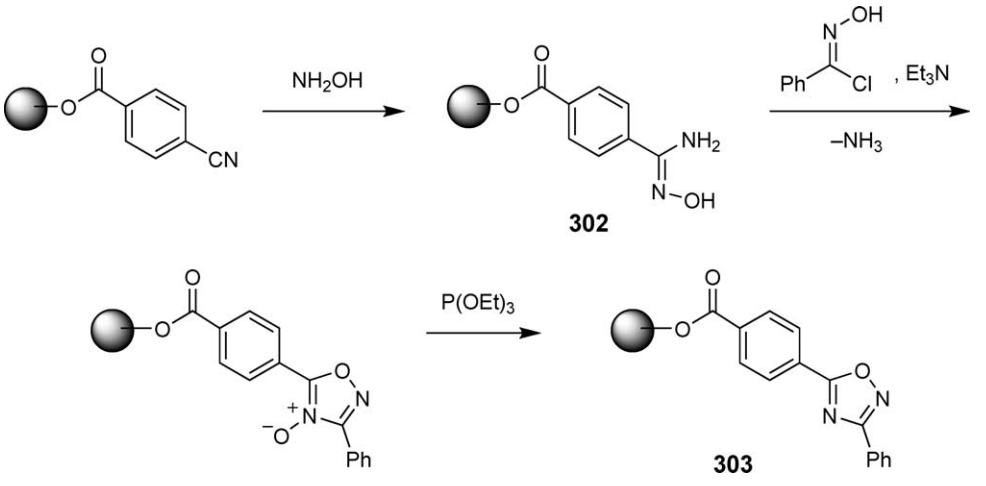


Scheme 49

1,2,4-Oxadiazoles can also be synthesized using polymer-supported 1,3-dipolar cycloaddition reactions with either the dipole or dipolarophile as the immobilized fragment. Thus, the Wang coupled aldehyde **298** was converted into the nitrile oxide **299** using the standard protocol of sequential treatment with hydroxylamine, *N*-chlorosuccinimide, and TEA (**Scheme 50**). 1,3-Dipolar cycloaddition with an amidoxime gave the Wang supported 1,2,4-oxadiazole 4-oxide **300** which was deoxygenated with triethylphosphite to give the Wang supported 5-phenyl-1,2,4-oxadiazole **301** <2005JCO887>. The corresponding Wang supported 3-phenyl-1,2,4-oxadiazole **303** was synthesized (**Scheme 51**) whereby the amidoxime dipolarophile **302** is supported on the Wang resin and the 1,3-dipole is generated in solution <2005JCO887>.



Scheme 50



Scheme 51

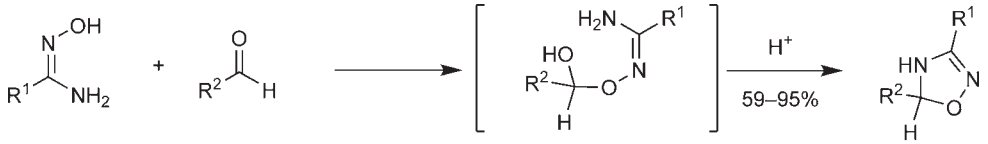
The use of polymer-supported reagents in combinatorial chemistry has received much attention in recent years, and a polymer-supported acylating reagent (supported on a ROMPGEL) has been used for the synthesis of 1,2,4-oxadiazoles in solution, (see Equation 37), <2000CCHT131>.

5.04.10 Ring Syntheses of Nonconjugated 1,2,4-Oxadiazoles

5.04.10.1 Ring Syntheses of 4,5-Dihydro-1,2,4-oxadiazoles

5.04.10.1.1 From the reaction of amidoximes with carbonyl compounds

The reaction of an aldehyde with an amidoxime still constitutes a major route to 4,5-dihydro1,2,4-oxadiazoles **305** (see CHEC(1984) <1984CHEC(6)365> and CHEC-II(1996) <1996CHEC-II(4)179>), and recent examples (**Scheme 52**) serve to illustrate this <1998EJM715, 2000PHA22, 2000HCO41, 2003BMC1821>. The reaction proceeds via the ring closure of intermediate **304**, a process now usually carried out with acidic Amberlite catalysts. The reaction works with acetone rather than an aldehyde <2000PHA22> to give 5-methyl-4,5-dihydro-1,2,4-oxadiazoles and also works with formaldehyde to give 5-unsubstituted systems <1998EJM715>.

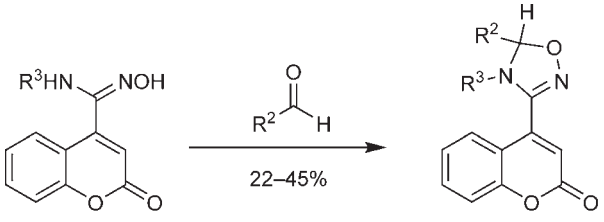


304 **305**

R^1 = Ph, Bn, 2-furyl, 2-thienyl-methyl, 1-naphthyl-methyl, 4-$MeOCH_2C_6H_4$, 2-, 3-, or 4-Tol, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$
R^2 = H, Me, Pr^i, Pr^n

Scheme 52

As Equation (54) shows, N-substituted amidoximes **306** will also react with either formaldehyde or acetaldehyde to give the 4,5-dihydro-1,2,4-oxadiazoles **307**. Acetaldehyde required the presence of acetic acid, whereas the use of formaldehyde allowed the reaction to proceed in the absence of acid <1998EJM715>.



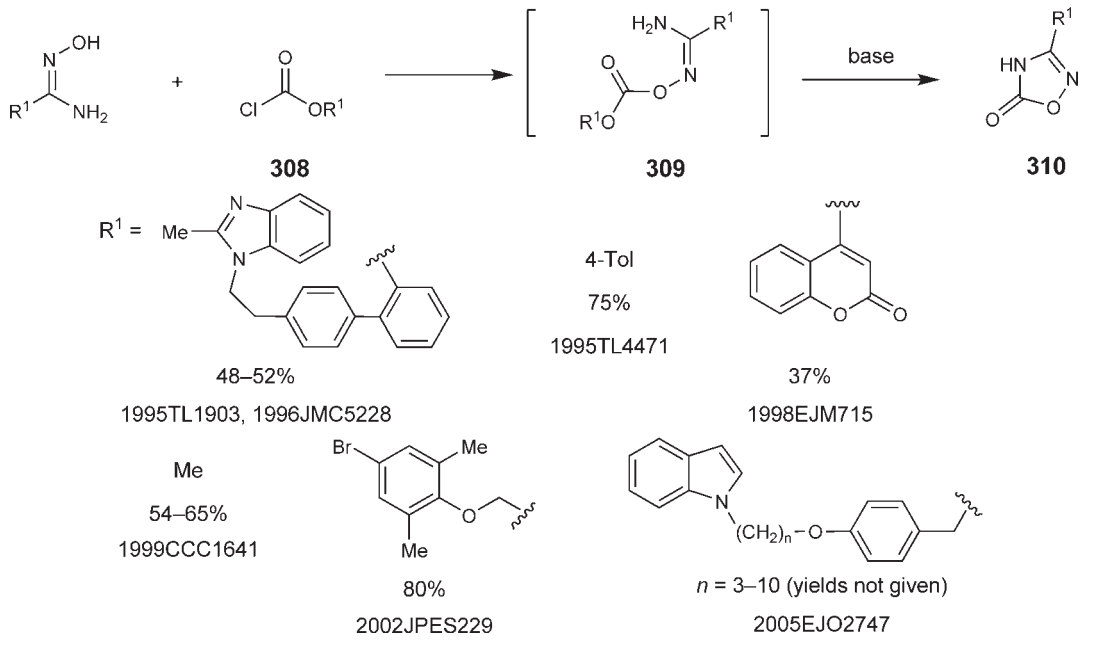
306 **307**

R^3 = Ph, H, Me
R^2 = H, Me

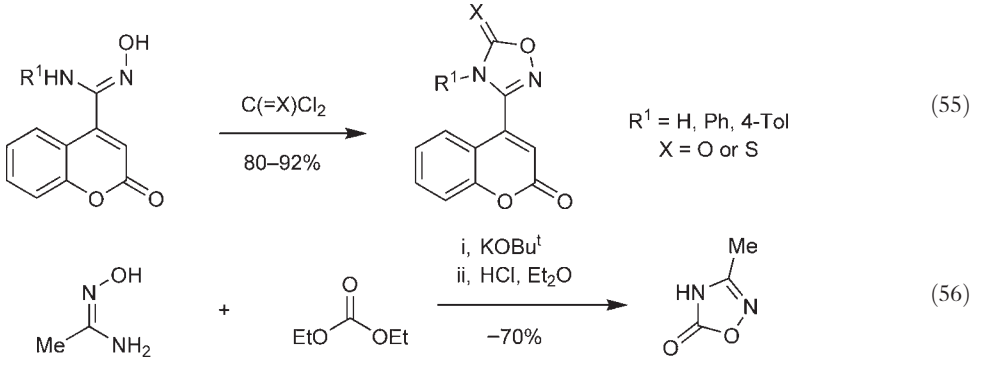
(54)

If the carbonyl component that reacts with the amidoxime is a chloroformate **308**, then 4,5-dihydro-1,2,4-oxadiazol-5-ones **310** result, and this is the main route to these compounds (**Scheme 53**). The reaction proceeds via an intermediate acetamido oxime **309** which usually cyclizes under the reaction conditions <1995TL1903, 1995TL4471, 1996JME5228, 1998AP375, 1998EJM715, 2002JPES229, 2005EJO2747>, but can be isolated prior to cyclization <1999CCC1641>. **Scheme 53** shows a selection of the substrates that have been used in this reaction since the appearance of CHEC-II(1996) <1996CHEC-II(4)179>. The base used can be pyridine <1995TL1903, 1995TL4471, 1996JMC5228>, TEA <1995TL1903, 1998EJM715, 2005EJO2747>, or sodium hydroxide <1998AP375, 1999CCC1641, 2002JPES229>. The reaction is often carried out under reflux in pyridine, xylene, or toluene in order to facilitate the ring-closure step.

The carbonyl-containing component can also be phosgene or thiophosgene (Equation 55) <1998EJM715> or diethyl carbonate (Equation 56) <2002OPD896, 2004T10907>, each of which gives alternative routes to 4,5-dihydro-1,2,4-oxadiazol-5-ones to that in **Scheme 53**. The latter of these two methods (Equation 56) has been optimized on a 600 l, 20 kg scale <2002OPD896>.

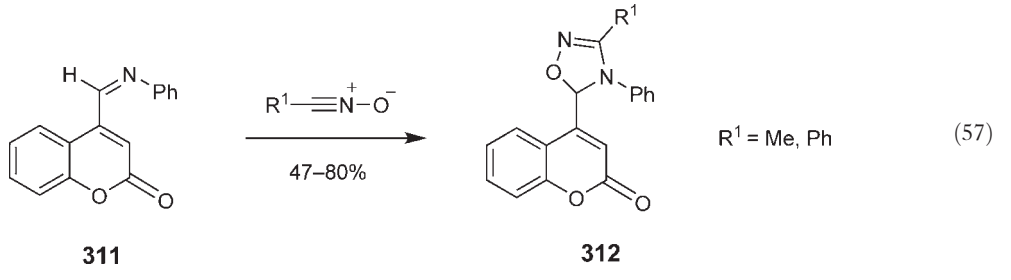


Scheme 53

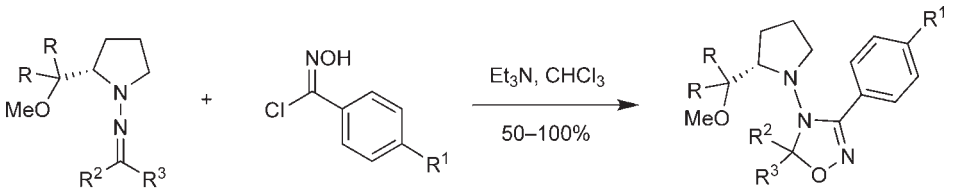


5.04.10.1.2 From the 1,3-dipolar cycloaddition of nitrile oxides to azomethines (imines)

Nitrile oxides reacting with azomethines (imines) has been the method most used to access 4,5-dihydro-1,2,4-oxadiazoles since the subject was last reviewed in CHEC-II(1996) <1996CHEC-II(4)179>, and the examples shown therein provide an excellent picture of the range of substrates that react. More recent examples include the synthesis of 5-benzopyranyl-4,5-dihydro-1,2,4-oxadiazoles **312** from phenylimino compound **311** (Equation 57) by reaction with either acetonitrile oxide ($R^1 = Me$), generated from nitroethane via Mukaiyama–Hoshino reaction, or benzonitrile oxide ($R^1 = Ph$), generated via dehydrochlorination of the corresponding hydroximoyl chloride <1996JHC967>.



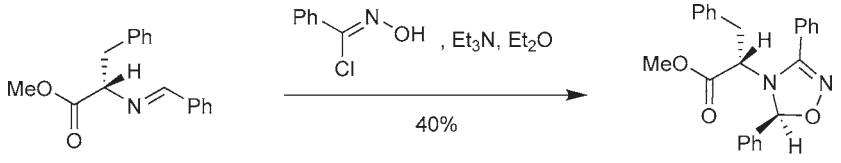
The reaction of hydroximoyl chlorides with the chiral, nonracemic hydrazones **313** (Equation 58) in the presence of TEA gave the 4,5-dihydro-1,2,4-oxadiazoles **314** as single diastereomers from which the chiral auxiliary was easily removed to furnish the corresponding 4-unsubstituted 4,5-dihydro-1,2,4-oxadiazoles with high ee's <1999H(50)995>.



(58)

313 R = Ph or H; R^1 = H, F, OMe; R^2 = alkyl or aryl; R^3 = alkyl **314**

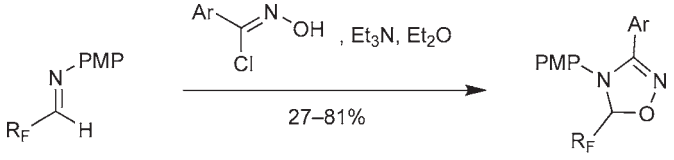
The reaction of the (*S*)-configured Schiff base **315** with benzonitrile oxide gave the 4,5-dihydro-1,2,4-oxadiazole **316** as a single diastereomer (Equation 59) <1999AXC650>.



(59)

315 **316**

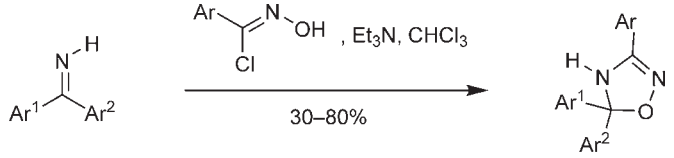
The range of imines that are suitable for reaction has been extended to include the fluoro-substituted aldimines **317** <2002JCM131> and N-unsubstituted imines **319** <1999AXC2158, 2002PJC1137, 2003TL2015>, thus allowing access to 5-fluoroalkyl-4,5-dihydro-1,2,4-oxadiazoles **318** and 4-unsubstituted 4,5-dihydro-1,2,4-oxadiazoles **320** as shown in Equations (60) and (61), respectively.



(60)

317 **318**

R_F = CF_3, 4-$CF_3C_6H_4$, 2,3-$F_2C_6H_3$
Ar = 3,5-Cl_2-2,4,6-Me_3C_6, 2,6-$Cl_2C_6H_3$; 2,4,6-$Me_3C_6H_2$

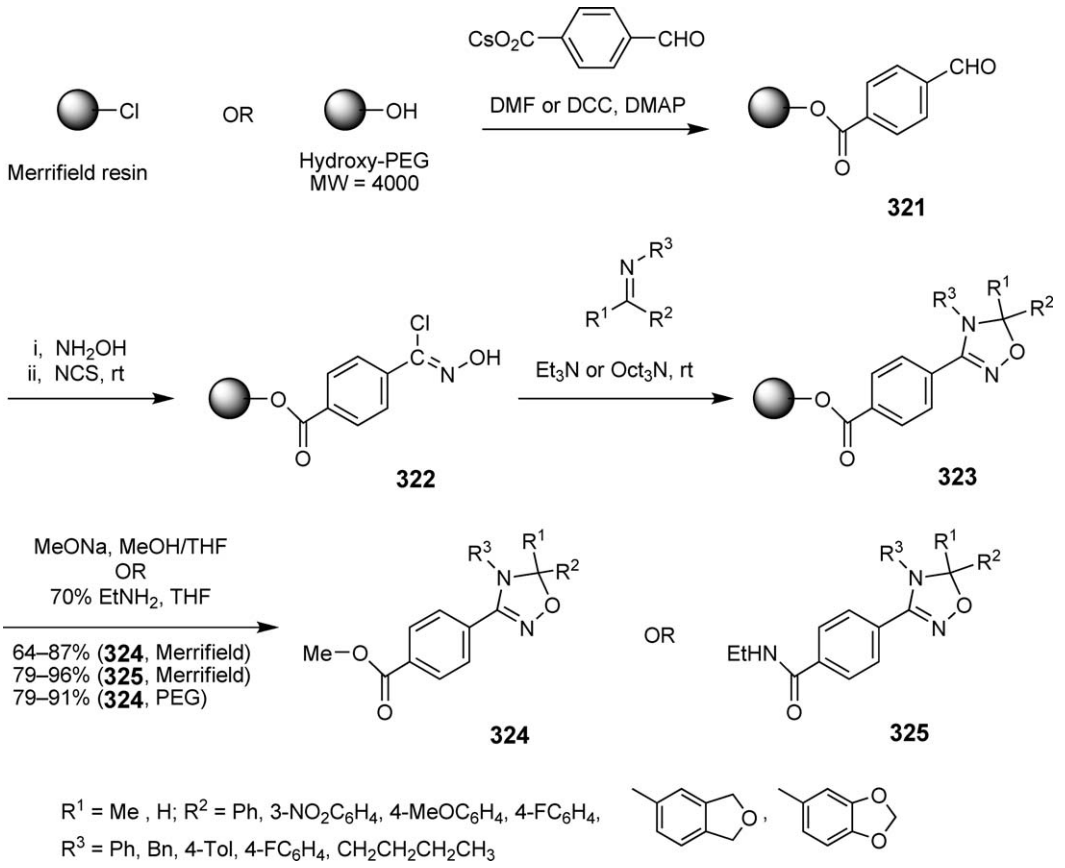


(61)

319 **320**

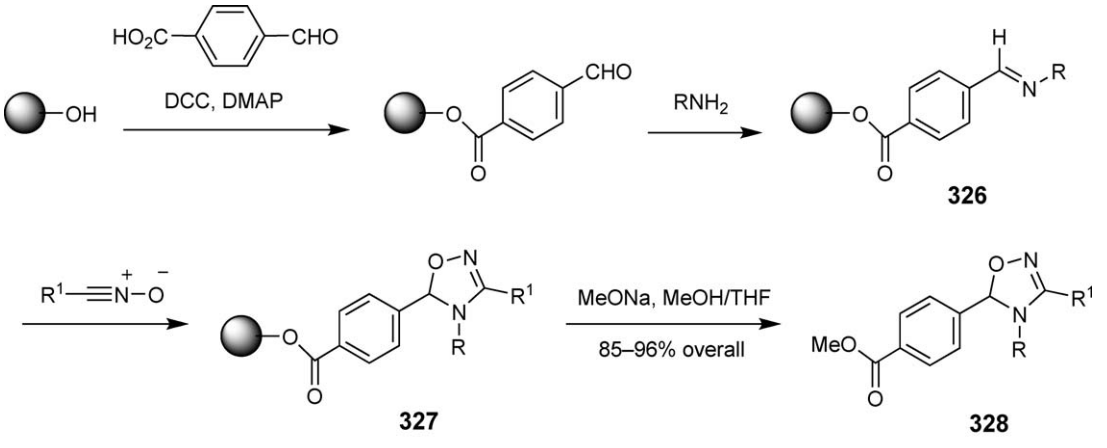
Ar = Ph, 4-Tol, 3-$NO_2C_6H_4$, 3- or 4-ClC_6H_4, 4-BrC_6H_4,
Ar^1 = Ph or 4-Tol; Ar^2 = Ph or 4-Tol

Polymer-supported versions of these processes have been reported. In two related publications from the same research group, the Merrifield solid-phase resin <2003CL842> or a soluble polyethylene glycol (PEG) polymer <2003TL4113> was functionalized with an aryl aldehyde to give the supported aldehydes **321** (**Scheme 54**). Standard treatment with hydroxylamine and *N*-chlorosuccinimide gave the Merrifield or PEG-supported hydroximoyl chlorides **322**, which after treatment with TEA (Merrifield) or trioctylamine (PEG) and reaction with an imine gave the polymer-supported 4,5-dihydro-1,2,4-oxadiazoles **323**. Cleavage from the Merrifield resin or PEG with methoxide gave the 4,5-dihydro-1,2,4-oxadiazoles as methyl esters **324**, while cleavage from the Merrifield resin with ethylamine gave the 4,5-dihydro-1,2,4-oxadiazoles as ethyl amides **325**. Surprisingly, the same workers reported identical work with PEG in a third publication <2003S1569>, with only the very minor addendum that the use of a chiral nonracemic α-branched imine gives very little diastereocontrol during the cycloaddition step.



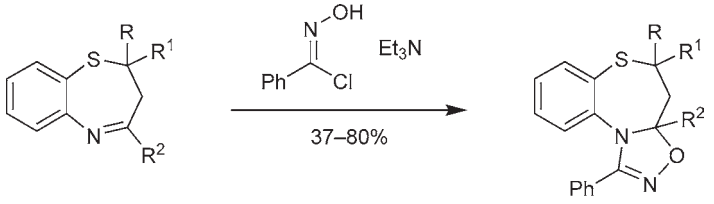
Scheme 54

The use of a PEG-supported imine **326** allows the imine to be the supported component (**Scheme 55**). 1,3-Dipolar cycloaddition then proceeds smoothly to give the supported 4,5-dihydro-1,2,4-oxadiazoles **327**, which were cleaved easily from the polymer with methoxide to give the 4,5-dihydro-1,2,4-oxadiazoles **328** <2003SL1064>.



Scheme 55

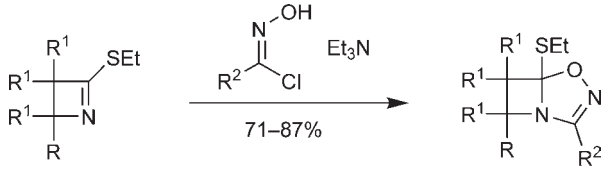
Cyclic imines are excellent substrates for cycloaddition and provide routes to many types of fused 4,5-dihydro-1,2,4-oxadiazoles. The range of fused systems that have been synthesized since CHEC-II(1996) <1996CHEC-II(4)179> include oxadiazolo-1,5-benzothiazepines **329** <1995EJM925>, oxadiazobicyclo[3.2.0]heptenes **330** <2000JFC83, 2006TH1>, oxadiazolo-1,4-diazepines **331** <2001NJC1479>, oxadiazolo-1,5-benzodiazepine **332** (R = SMe) <2002AXE548>, together with the corresponding bis-oxadiazolo-1,5-benzodiazepines derived from a second cycloaddition to oxadiazolo-1,5-benzodiazepine **332** (R = Me) <2004SC3565>, oxadiazolo-pyrrolobenzothiadiazepines **333** <2004TL7553, 2006TH2), oxadiazolotriazolo-1,5-benzodiazepines **334** <2006SC573>, and oxadiazolo-1,3,4-benzotriazepinones **335** <2002SC1815>, as shown in Equations (62)–(68).



(62)

329

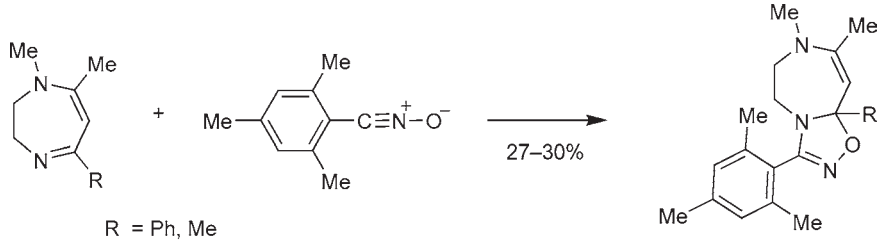
R = H, Me; R^1 = Ph, Me
R^2 = 2-thienyl, Ph, 4-Tol, 4-BrC_6H_4, 4-CNC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$



(63)

330

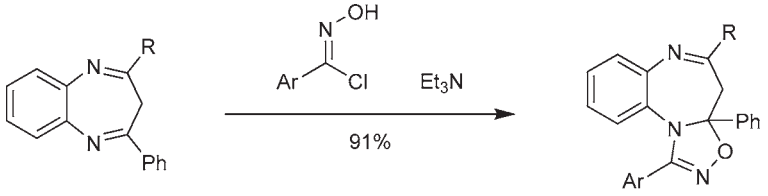
R^1 = R = Me; R^1 = H, R = Ph
R^2 = CO_2Et, Ph, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 2-$N_3C_6H_4$



(64)

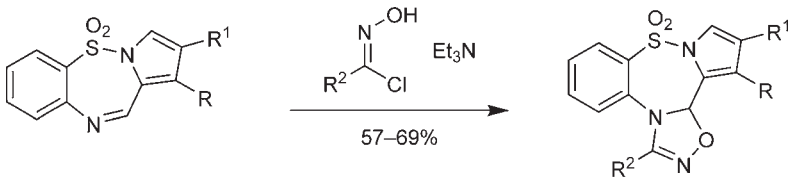
R = Ph, Me

331

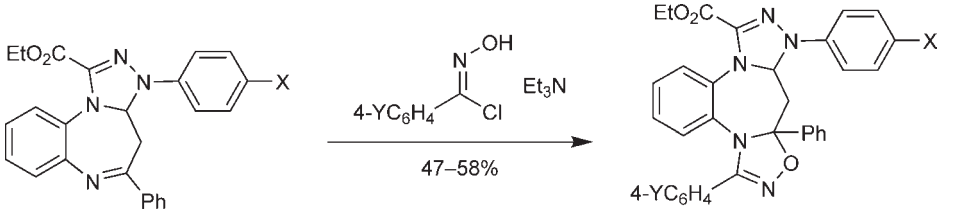


(65)

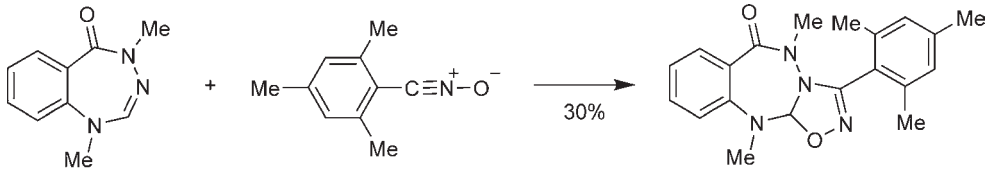
332: R = SMe;
Ar = 3-Cl,4-Me(C_6H_3)



333 (66)

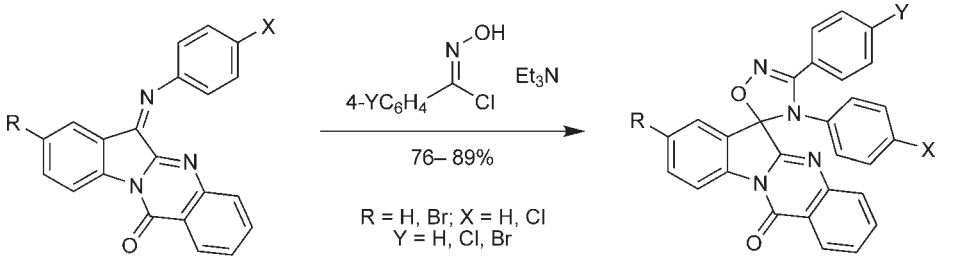


334 (67)



335 (68)

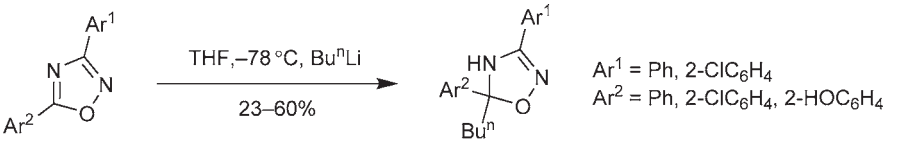
One example of a spiro-4,5-dihydro-1,2,4-oxadiazole has appeared, whereby the spiro[indoloquinazoline]-4,5-dihydro-1,2,4-oxadiazoles **337** were prepared in good yields from the imines **336** (Equation 69) <2005SC765>.



336 **337** (69)

5.04.10.1.3 Other methods for the synthesis of 4,5-dihydro-1,2,4-oxadiazoles

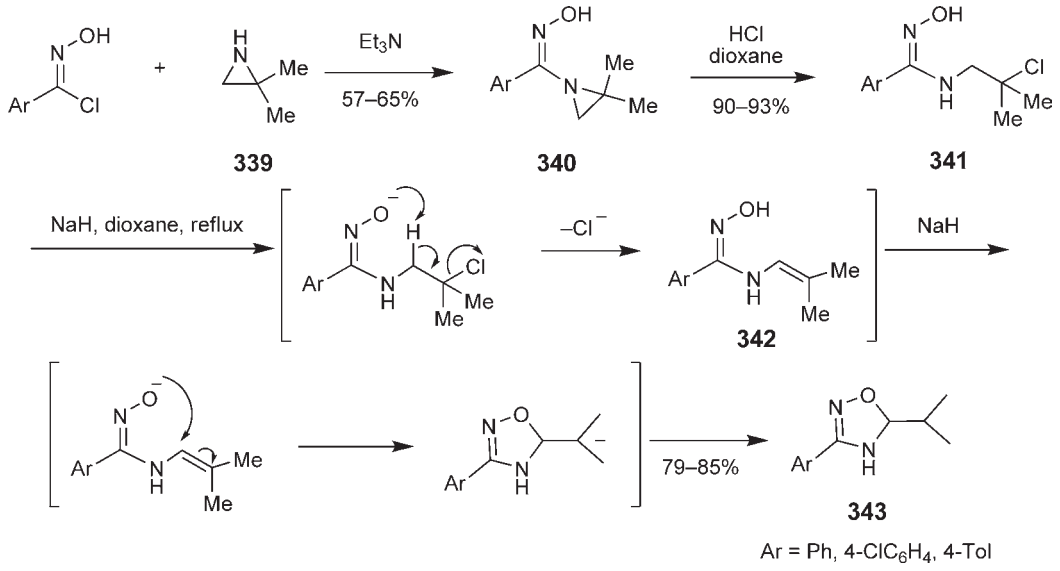
The reaction of fully conjugated 3,5-diaryl-1,2,4-oxadiazoles with butyllithium allows facile access to 5-butyl-3,5-diaryl-4,5-dihydro-1,2,4-oxadiazoles **338** (Equation 70) <2000H(53)191>.



338 (70)

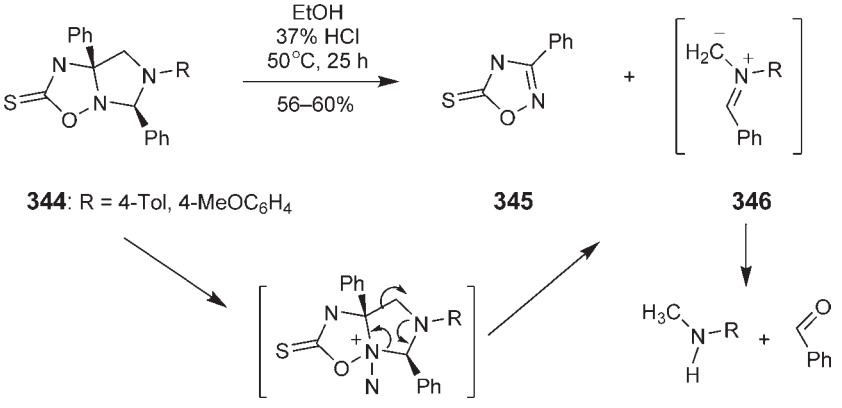
Aziridinylbenzaldoxime **340**, formed from the reaction of a hydroximoyl chloride with aziridine **339** (**Scheme 56**), reacts with HCl to form the chloroalkyl-substituted amidoxime **341**. Reaction with sodium hydride affects ring closure to give the 3-aryl-4,5-dihydro-5-isopropyl-1,2,4-oxadiazoles **343**. This latter reaction is proposed to proceed

via deprotonation of the hydroxyl group in species **341**, followed by an intramolecular E2-type elimination to form the conjugated enamine **342**. Further deprotonation, ring closure, and reprotonation then gives the isolated 4,5-dihydro-1,2,4-oxadiazoles **343** <1996JHC1583>.



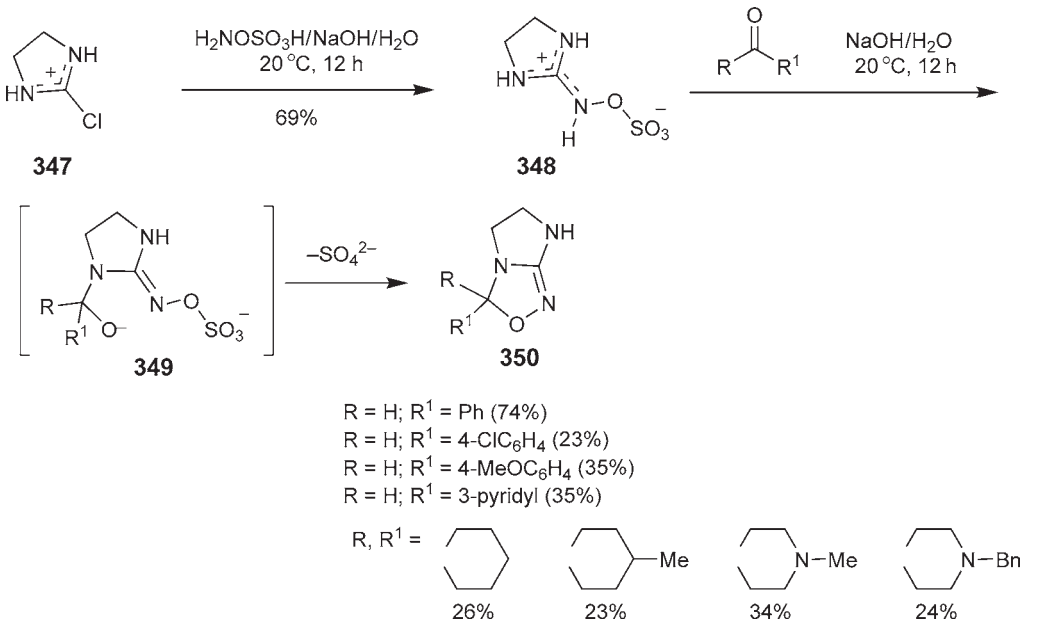
Scheme 56

Ring opening of the bicyclic 1,2,4-oxadiazolidines **344** in ethanolic HCl gives 3-phenyl-4,5-dihydro-1,2,4-oxadiazole 5-thione **345** together with the azomethine ylide **346** (**Scheme 57**), a process that is proposed to occur via protonation of the bridgehead nitrogen followed by retro-1,3-dipolar cycloaddition. The azomethine fragment could not be isolated or trapped, but degraded to the corresponding amine and aldehyde <2003PS881>.



Scheme 57

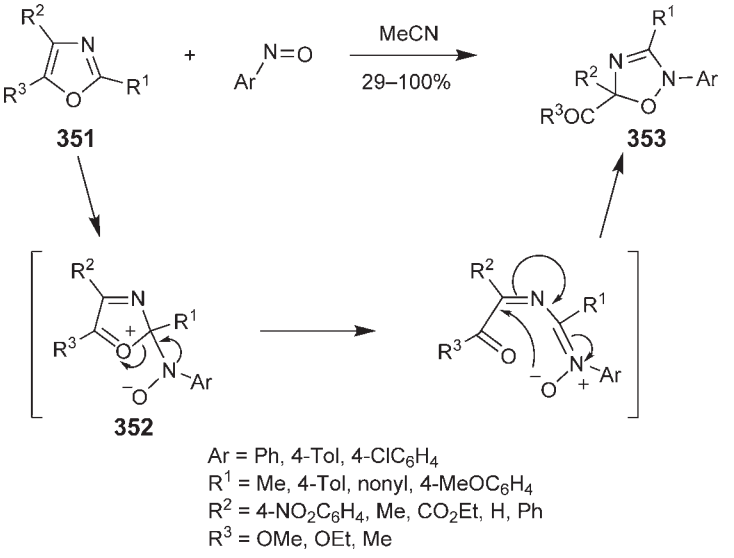
The reaction of 2-chloro-4,5-dihydroimidazole **347** with hydroxylamine-*O*-sulfonic acid gives 2-hydroxylamino-4,5-dihydroimidazolium-*O*-sulfonate **348**, which reacts with aldehydes and cyclic ketones to give the imidazo[1,2-*c*] fused 4,5-dihydro-1,2,4-oxadiazoles **350** (**Scheme 58**). Mechanistically, the reaction may be explained by the reaction of an imidazoline NH with the carbonyl followed by intramolecular electrophilic amination of the anionic oxygen present in the resultant intermediate **349** and elimination of the sulfate group <2003JOC4791>.



Scheme 58

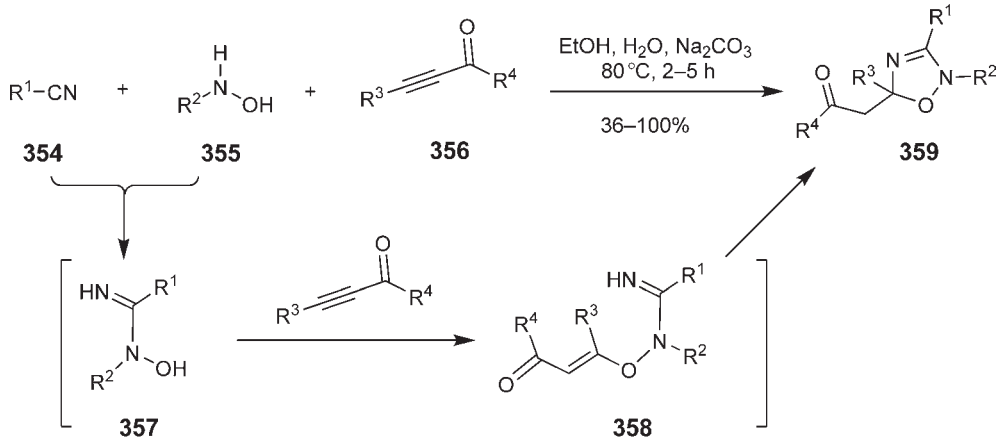
5.04.10.2 Ring Syntheses of 2,5-Dihydro-1,2,4-oxadiazoles

As is apparent from CHEC-II(1996) <1996CHEC-II(4)179>, this class of heterocycle lacks a general synthetic approach, although many interesting, albeit specific, routes were detailed. Since the appearance of CHEC-II(1996), one of the methods discussed therein has attracted further attention and this is detailed in **Scheme 59**. Thus, the reaction of substituted oxazoles **351** with a nitrosobenzene in acetonitrile at room temperature gave 2,5-dihydro-1,2,4-oxadiazoles **353**, a reaction that is believed to proceed via a nucleophilic attack of the nitroso by the 2-position of the oxazole to give the intermediate **352**, which undergoes ring opening followed by cyclization to afford the isolated 2,5-dihydro-1,2,4-oxadiazoles **353** <1998BCJ1231>.



Scheme 59

A new three-component approach to the highly substituted 2,5-dihydro-1,2,4-oxadiazoles **359** has been reported from the reaction of nitriles **354** under mild conditions with *N*-alkylhydroxylamines **355** in the presence of electron-deficient alkynes **356** (**Scheme 60**) <2005OL1391>. This synthesis is proposed to proceed via the initial formation of the alkyl or arylamidoximes **357**, which then undergo a sequential double Michael addition to the electron deficient alkyne. The intermediate alkyl or arylamidoximes **357** can be isolated and then reacted with the alkyne to produce the product. The initial Michael adduct **358** is stable in cases where R^2 is H.

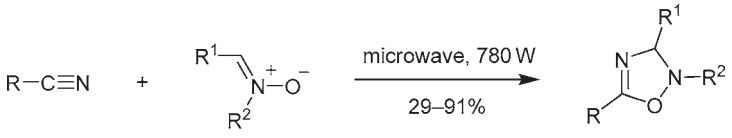


R^1 = Bn, Me, Pr^i, cyclopentyl, Ph, 2-$MeOC_6H_4$, 2,6-$(MeO)_2C_6H_3$, 2,6-$F_2C_6H_3$, 2-furyl, 2-, 3-, or 4-pyridyl
R^2 = Me, Pr^i, cyclohexyl, Bn; R^3 = CO_2Et, H, Me, Et; R^4 = Et, OEt, Me

Scheme 60

5.04.10.3 Ring Syntheses of 2,3-Dihydro-1,2,4-oxadiazoles

The general route to these compounds is 1,3-dipolar cycloaddition of a nitrone to a nitrile compound and this route was discussed in CHEC(1984) <1984CHEC(6)365> and CHEC-II(1996) <1996CHEC-II(4)179>. A recent advance in the area is the use of microwave irradiation under solvent-free conditions, a process that is quicker and higher yielding than the classical heating method, and leading in some cases to the formation of 2,3-dihydro-1,2,4-oxadiazoles **360** (Equation 71) that are unavailable by the classical heating method <1996H(43)1021>.

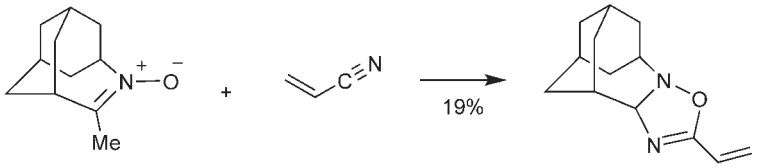


(71)

R = CCl_3, CO_2Et, Ph; R^1 = Ph, 4-$CF_3C_6H_4$; R^2 = Me, Ph

360

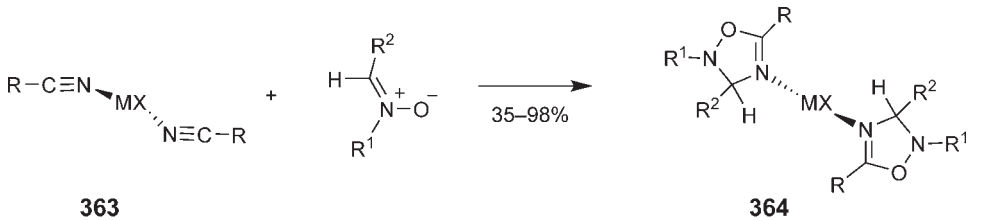
The homoadamantane derived nitrone **361** (Equation 72) reacts with acrylonitrile to give the bicyclic 5-vinyl-2,3-dihydro-1,2,4-oxadiazole **362** in 19% yield, with the major product being that from cycloaddition to the alkene moiety <1997T5413>.



(72)

361 **362**

A range of platinum- or palladium-coordinated nitriles **363** have been shown to undergo cycloaddition with nitrones to give the stable metal-coordinated 2,3-dihydro-1,2,4-oxadiazoles **364**, the first examples of such complexes (Equation 73) <2000JA3106, 2001IC264, 2003JCD2544, 2006JOC582>. It is of note that the dipolarophilicity of the nitrile is enhanced by coordination to the metal center, with cinnamonitrile, for example, undergoing reaction under conditions more mild than those reported previously <2003JCD2544>.

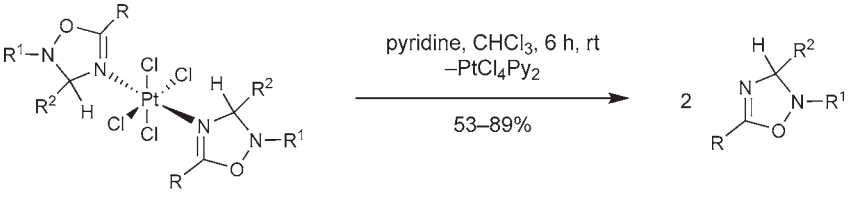


(73)

363 **364**

MX = $PtCl_2$, $PdCl_2$, $PtCl_4$; R = Me, Ph, PhCH=CH; R^1 = Me, Bn
R^2 = Ph, 4-Tol, 2-HOC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$(NMe_2)C_6H_4$

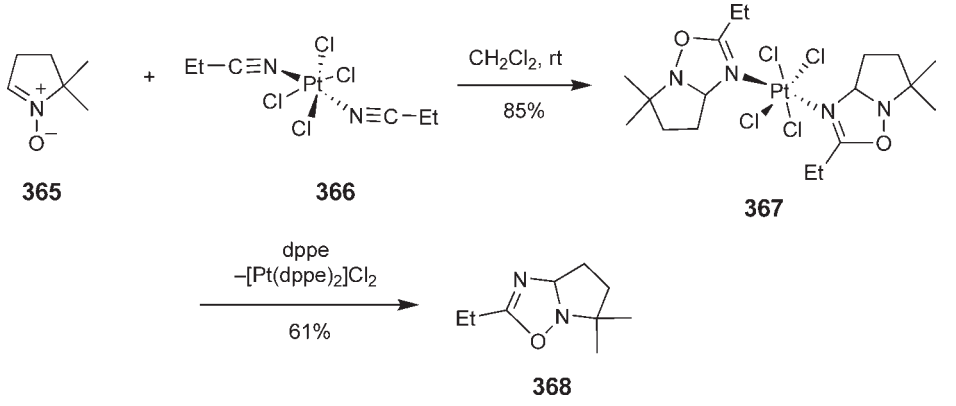
The 2,3-dihydro-1,2,4-oxadiazoles are easily displaced from the complexes **364** with aqueous methylamine (MX = $PdCl_2$) and with pyridine (MX = $PtCl_4$), and less easily with PPh_3 (M = $PtCl_2$); an example of this process is shown in Equation (74) <2001IC264>.



(74)

R = Me, Ph; R^1 = Me, Bn;
R^2 = Ph, 4-Tol, 2-HOC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-$(NMe_2)C_6H_4$

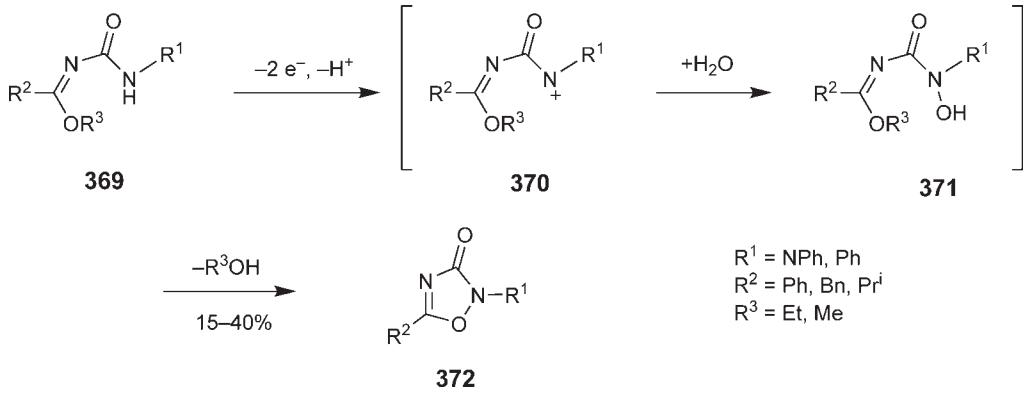
The cyclic nitrone **365** reacts with the metal-coordinated nitrile **366** to give the complex **367** from which the bicyclic 2,3-dihydro-1,2,4-oxadiazole **368** was liberated by the use of 1,2-bis(diphenylphosphanyl)ethane (dppe) (**Scheme 61**) <2003JCD2540>.



365 **366** **367** **368**

Scheme 61

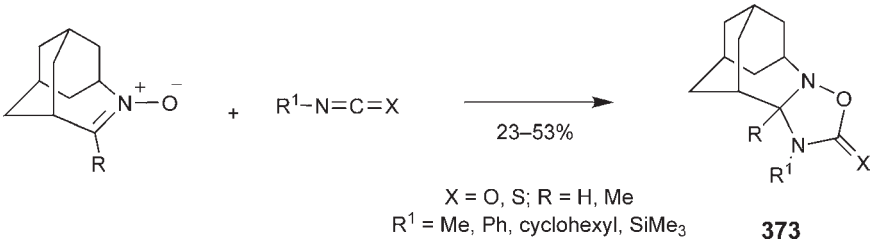
Only one method that does not utilize 1,3-dipolar cycloaddition has appeared since CHEC-II(1996) <1996CHEC-II(4)179> (which gives details of other such methods). Thus, as shown in **Scheme 62**, reaction of the *N*-amidoimidate **369** under conditions of anodic oxidation in acetonitrile plus lithium perchlorate gave the 2,3-dihydro-1,2,4-oxadiazol-3-ones **372**. The process was shown to proceed with charge consumption of two electrons per molecule, leading to the formation of the proposed intermediate cation **370** by a two-electron transfer. Coupling of this intermediate with residual water in the solvent system then forms the hydroxylamines **371** which undergo cyclization to give the final products **372** <2003JEC21>.



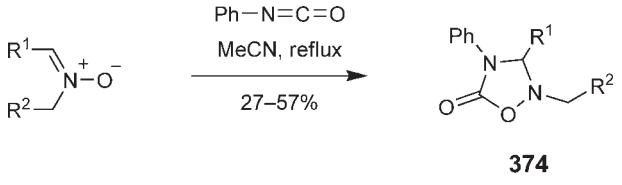
Scheme 62

5.04.10.4 Ring Syntheses of 1,2,4-Oxadiazolidines

The 1,3-dipolar cycloaddition of a nitrone to a C=N species remains (see CHEC-II(1996) for earlier examples) a popular route to 1,2,4-oxadiazolidines. The use of isocyanates and isothiocyanates as the dipolarophile allows access to 1,2,4-oxadiazolidin-5-ones and 5-thiones, as the examples in Equations (75) <1995HCO307> and (76) <2006SC997> show, giving access to 1,2,4-oxadiazolidin-5-ones **373** and **374**, respectively.



(75)



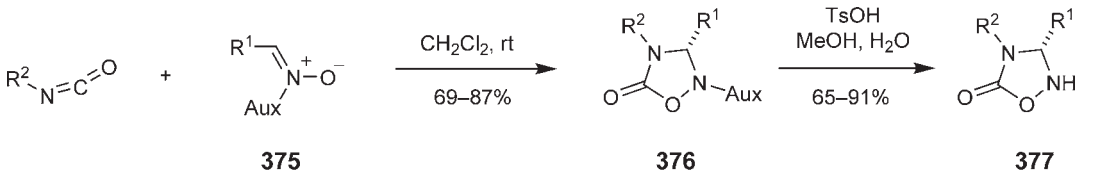
(76)

R^1 = 2,3- or 3,4-$(MeO)_2C_6H_3$, 2- or 3-$NO_2C_6H_4$, Ph; R^2 = H, Ph, 2,3-$(MeO)_2C_6H_3$

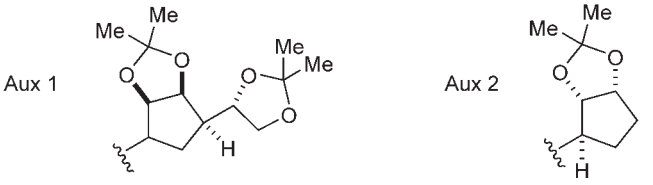
A recent advance in this area has allowed the method to be adapted to give 1,2,4-oxadiazolidinones as stable chiral building blocks. As shown in **Scheme 63**, the mixing of commercially available isocyanates with mannosyl- or erythose-derived nitrones **375** in dichloromethane at room temperature leads to crude 1,2,4-oxadiazolidin-5-ones **376** with 4:1 to 12:1 diastereoselectivities. Trituration of the crude products gave single diastereomers. The configurationally stable enantiopure 1,2,4-oxadiazolidin-5-ones **377** could be accessed in >99% ee by auxiliary removal with toluenesulfonic acid <2005AGE936>.

The reaction of oxaziridines **378** with isothiocyanates has been established as a route to 1,2,4-oxadiazolidin-5-thiones **379** (**Scheme 64**). Two mechanistic possibilities exist via which the products can form, each of which relies upon C–O cleavage, shown as paths a and b in **Scheme 64**. Interestingly, one of these paths involves the generation of nitrone **380**, a species which could be identified as a reaction product <1998H(48)1935>. The nitrone could be generated separately and reacted with isothiocyanates to form identical 1,2,4-oxadiazolidin-5-thiones **379**.

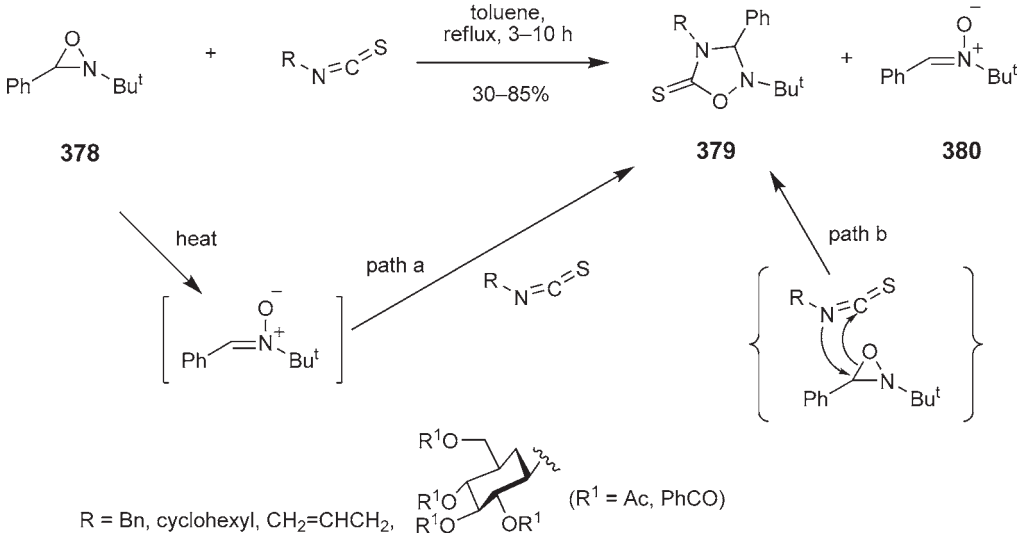
Oxaziridines **381** have been reacted with chlorosulfonyl isocyanate (**Scheme 65**), this time forming 1,2,4-oxadiazolidin-3-ones **382** via C–N bond cleavage. The structure of the product was established by X-ray crystallography as the 3-one rather than the 5-one that might be expected on the basis of the chemistry shown in



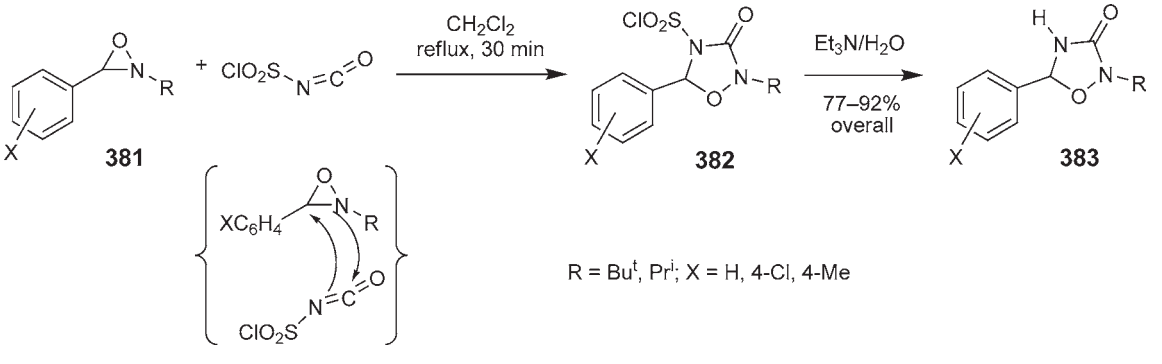
R^1 = 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, 4-$MsOC_6H_4$, 4-FC_6H_4, 3-furyl, 1-naphthyl, Me, cyclohexyl, Me, Bu^t, *(E)*-styryl
R^2 = Ph, Bn, Bz, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-FC_6H_4, 2,6-$Cl_2C_6H_3$, CCl_3



Scheme 63



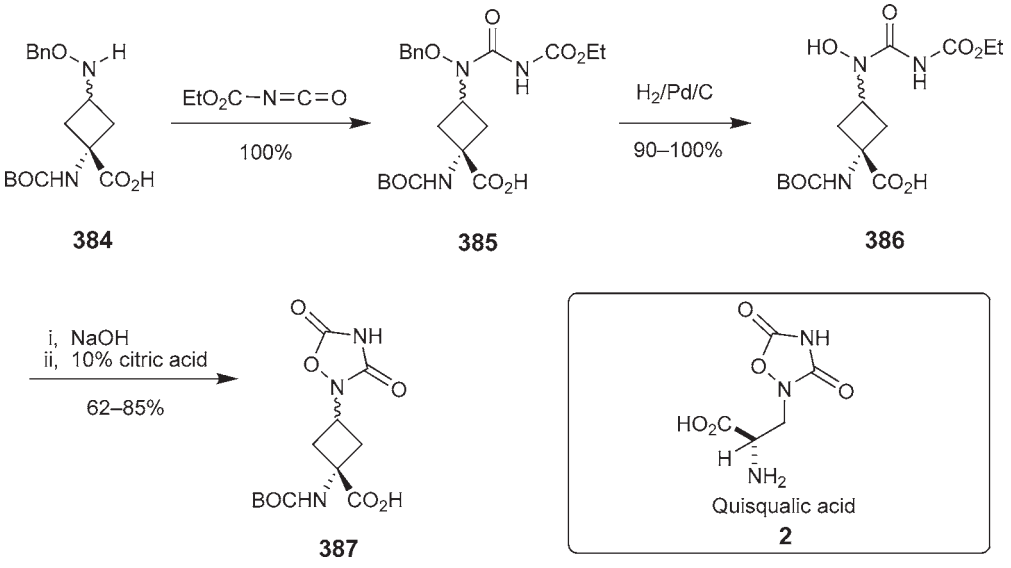
Scheme 64



Scheme 65

Scheme 64. The chlorosulfonyl moiety was easily removed to give the 4-unsubstituted 1,2,4-oxadiazolidin-3-ones **383** <2001TL9131>.

The stepwise synthesis of 1,2,4-oxadiazolidinones, often from *N*-hydroxy compounds, was discussed in CHEC-II(1996), and the routes discussed therein are still used to synthesize these important heterocycles <1997SL263>. A number of useful additions to the literature concerning routes of this type have been made. **Scheme 66** shows one of these and is of great interest as a potential general route to a wide range of analogues of the natural product quisqualic acid **2**, a compound with high neuroexcitatory activity and a potent agonist for metabotropic glutamic acid receptors. The reaction of either isomer of compound **384** with ethoxycarbonyl isocyanate gave the carbamates **385**, which after removal of the benzyl group and cyclization gave the 2-substituted 1,2,4-oxadiazolidin-3,5-diones **387** via the intermediate *N*-hydroxy compounds **386** <1999JME1639>.

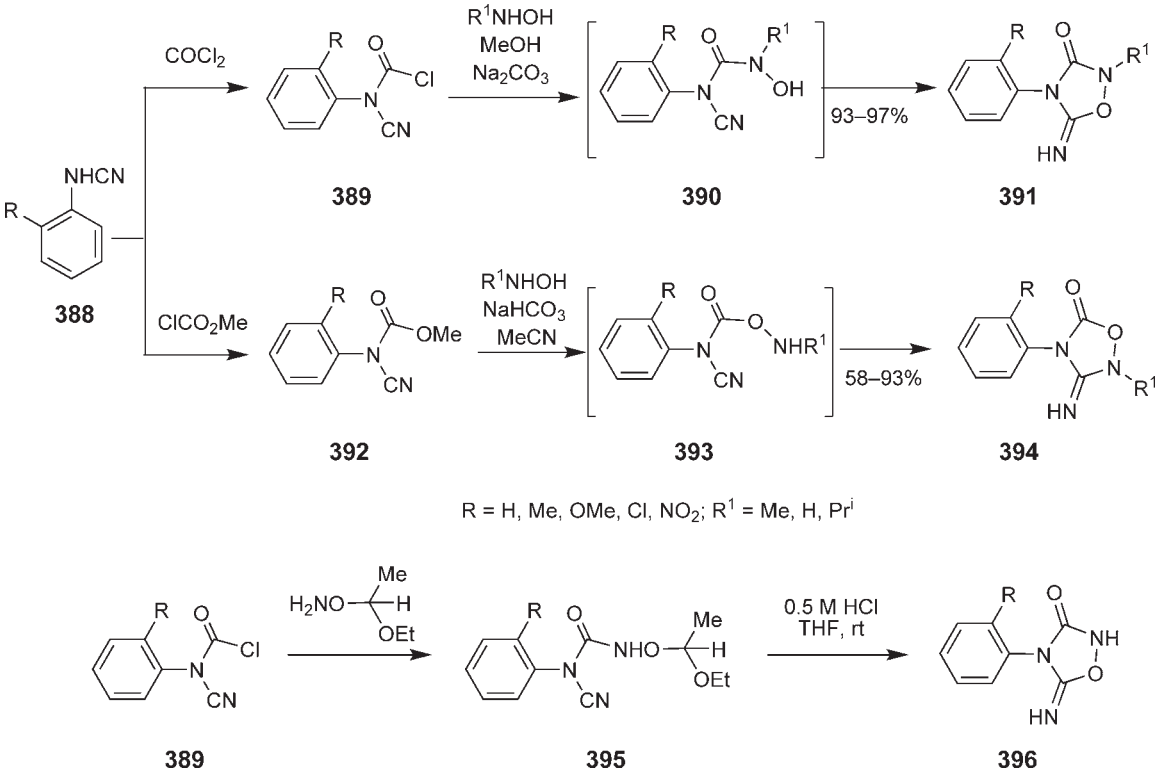


Scheme 66

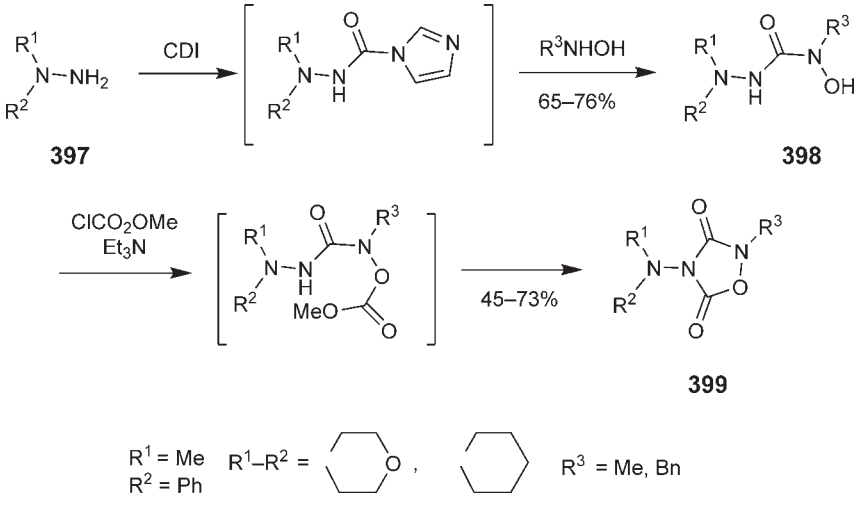
An interesting route to either 5-imino-1,2,4-oxadiazolidin-3-ones **391** or 3-imino-1,2,4-oxadiazolidin-5-ones **394** from cyanamides **388** has been developed (**Scheme 67**). Reaction of the cyanamide with phosgene gave an *N*-aryl-*N*-cyanocarbomoyl chloride **389**, whereas reaction with methyl chloroformate gave the *N*-aryl-*N*-carbomethoxy-cyanamide **392**. Ring closure under carefully optimized conditions then allowed access to either 5-imino-1,2,4-oxadiazolidin-3-ones **391** or 3-imino-1,2,4-oxadiazolidin-5-ones **394** via the intermediates **390** or **393**, respectively <2002SC803>. The same workers also demonstrated that *N*-aryl-*N*-cyanocarbomoyl chlorides **389** could be reacted with an O-protected hydroxylamine to give intermediate **395**, which underwent simultaneous deprotection and cyclization to give the 2-unsubstituted 5-imino-1,2,4-oxadiazolidin-3-ones **396**, also shown in **Scheme 67**.

The activation of the hydrazines **397** (**Scheme 68**) with 1,1′-carbonyldiimidazole (CDI) and reaction with hydroxylamines gave the hydroxy semicarbazides **398**, which could be treated with methyl chloroformate in the presence of TEA to give the first examples of 4-amino-substituted 1,2,4-oxadiazolidin-3,5-diones **399** <2000HCO55>.

The light-induced reaction of *N*-methyl urea **400** in aqueous solution containing the photocatalyst titanium dioxide resulted in the production of 5-imino-1,2,4-oxadiazolidin-3-one **401** in surprisingly high yield, via the suggested mechanism shown in **Scheme 69**, which involves the initial formation of a carbon-centered radical, resulting from an initial C–H cleavage <2006CEJ727>. Elimination of an imine, combination with a second molecule of *N*-methyl urea, reaction with two hydroxyl radicals and accompanying loss of water, followed by loss of a methyl radical, gives the final product.



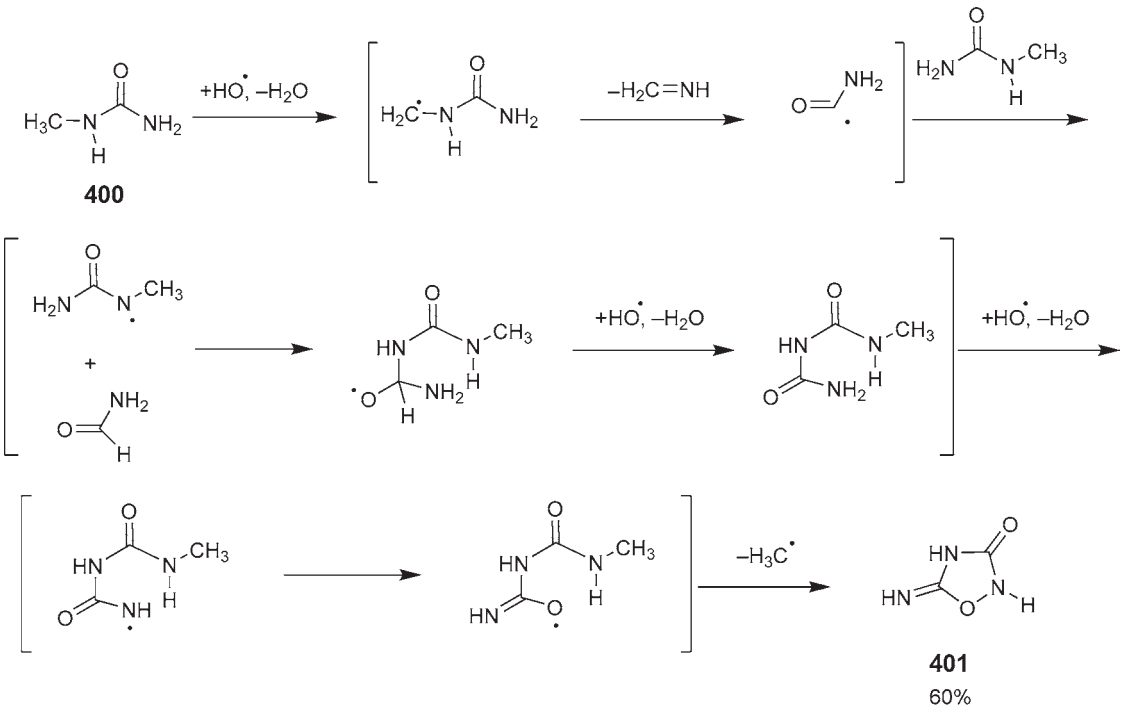
Scheme 67



Scheme 68

5.04.10.5 Ring Syntheses of 1,2,4-Oxadiazolium Salts

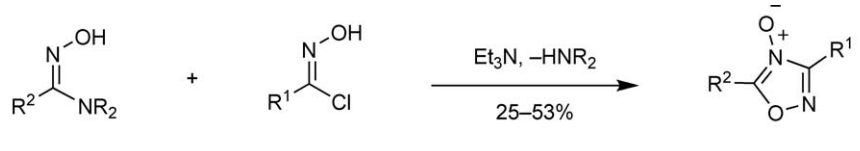
The reaction of nitrile oxides with nitrilium salts, which are more reactive than the corresponding nitriles, as discussed in CHEC-II(1996) <1996CHEC-II(4)179>, is the main route through to oxadiazolium salts. Further advances in this area have not been reported.



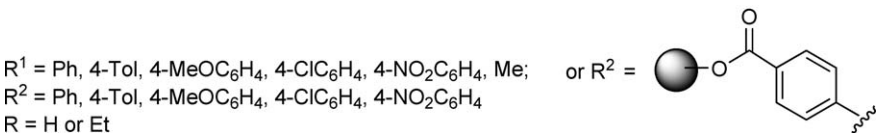
Scheme 69

5.04.10.6 Ring Syntheses of 1,2,4-Oxadiazole-*N*-oxides

The reaction of hydroximoyl chlorides **403** with amidoximes **402** in the presence of TEA leads to 1,2,4-oxadiazole 4-oxides **404** via 1,3-dipolar cycloaddition and elimination of an amine (Equation 77) <1997T1787, 2005JCO887>.



(77)

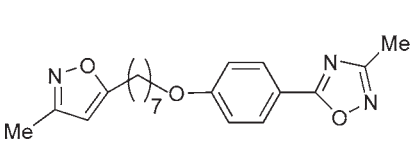


5.04.11 Important 1,2,4-Oxadiazoles and Applications

5.04.11.1 Applications of Fully Conjugated 1,2,4-Oxadiazoles

The application of compounds containing the 1,2,4-oxadiazole moiety as antitussives, anti-inflammatory agents, analgesics, coronary dilators, agonists at muscarinic receptors, 5-hydroxytryptamine (5-HT) receptor antagonists, benzodiazepine receptor agonists, anthelminthics, plant protection agents, and a variety of other uses was reviewed in CHEC-II(1996) <1996CHEC-II(4)179>, and interest has continued unabated <2001JCM209, 2004HOU(13)127>. Much of the recent interest still stems from the use of the fully conjugated 1,2,4-oxadiazole as a hydrolysis-resistant ester or amide bioisostere <2006BML839, 2005ARK36, 2003JOC7316, 2000BML1427, 1994JME2421, 2001BML753, 1999MI1>. Thus, 1,2,4-oxadiazoles have been used as ester bioisosteric replacements in a series of compounds related to the disoxaril precursor

405, and their activities against rhinoviruses determined <1994JME2421>. The replacement of the methyl ester moiety present in cocaine with a 3-phenyl-1,2,4-oxadiazolyl substituent led to compound **406** which has 50 times the affinity for the dopamine transporter than cocaine itself <1996MI109>. Studies regarding the use of 1,2,4-oxadiazoles as peptidomimetic and dipeptidomimetic amino acid-Gly and Phe-Gly mimetics/replacements in biologically active peptides have appeared and their use in pseudopeptide synthesis has been evaluated <2003JOC7316, 1999JME4331, 1995JOC3112>. Several oxadiazoles, for example, compound **407** <1998JME1218, 1998BJP202>, show activity as potent antagonists of the (serotonin) 5-$HT_{1B/D}$ receptors <1998JME1218, 1998BJP202, 2000JME517, 1996JOC3228, 1999JP12725>, which are vasoconstriction-mediating receptors used as putative targets for antimigraine drugs.



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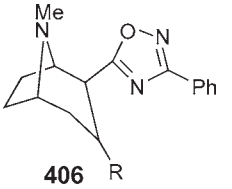
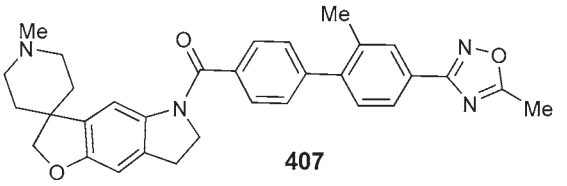
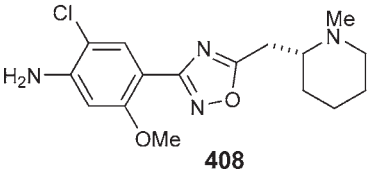


406



407

The 5-(2-piperidylmethyl)-1,2,4-oxadiazole **408** is a selective 5-HT_4 receptor agonist, which may be useful in the search for the treatment of gastrointestinal dysfunctions <1999CPB120>. The affinities of a range of (oxadiazolyl)-methylene azabicycles **409** for the central nicotinic cholinergic receptors have been investigated, but were found to be lower than those of other heterocyclic systems <2000BMC1443>. Several reports concerning the use of 1,2,4-oxadiazoles as muscarinic antagonist/agonists, for example, the muscarinic receptor 'superagonist' **410**, have appeared <1996JOC3228, 1999CPB876, 2000BMC1559>. Antitussive properties have been reported for several 1,2,4-oxadiazoles <1998AF1147, 1998AF395>. A series of α-ketooxadiazole compounds **411** have been shown to be potent and selective inhibitors of human neutrophil elastase <1999MI193>.



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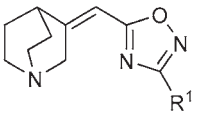

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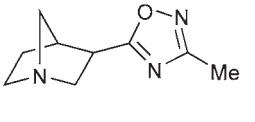
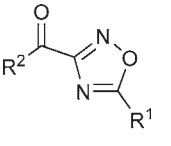
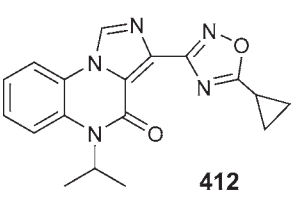


410

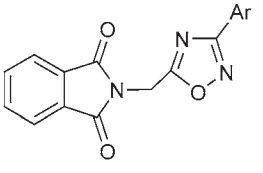


411

A number of 1,2,4-oxadiazoles continue to attract interest as benzodiazepine receptor ligands <1999MI1434, 1995MI213, 2002M1205, 2002M653, 1999JME2218, 1996JME4654>, an example being the imidazoquinoxalinone derivative **412**, also known as panadiplon. (1,2,4-Oxadiazolyl methyl)phthalimides **413** <2003JST1, 1998BML3071, 2000JCX131> and a series of *N*-acylhydrazone-substituted 1,2,4-oxadiazoles <1999FES747> have been shown to have potent analgesic properties. The 5-*n*-pentyl-1,2,4-oxadiazole **414** ($R^1 = n$-pentyl) is a potent and selective β_3 adrenergic receptor agonist <2000BML1427>, while the corresponding benzyl and phenoxymethylene analogues represent useful tools in the synthesis of β_3 adrenergic receptor agonist antiobesity agents <2000BML1431>.



412



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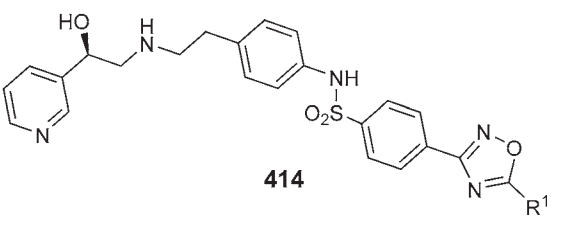
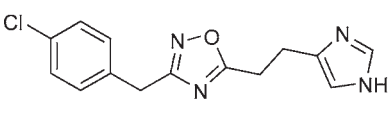
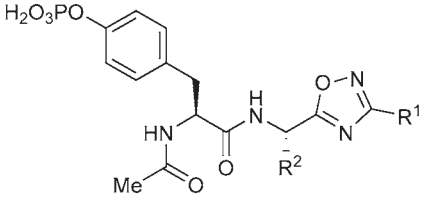


414

3-(Coumarin-4-yl)-1,2,4-oxadiazoles show potent anti-inflammatory activity <1998EJM715>. 1,2,4-Oxadiazolyl compounds, that show antitumor activity, have been reported <1996FES125>. The replacement of the isothiourea grouping of known histamine H_3 antagonists (such as clobenpropit) with the 1,2,4-oxadiazole ring resulted in the formation of compound **415**, and a series of analogues, some of which were potent and selective H_3 antagonists <1996BML833>. The protein tyrosine kinase ZAP-70 is a target for immune suppression, and a series of 1,2,4-oxadiazoles, such as compounds **416**, have been shown to be potent and selective SH2 (Src homology-2) inhibitors of the tyrosine kinase ZAP-70, with activities up to 200–400-fold more potent than the native tetrapeptide <1999BML2359, 1999JME4088, 1999BML3009>. The C-5 tertiary amide **417** and related compounds show excellent analgesic activity <2002JST177, 1999H(51)2961>.



415



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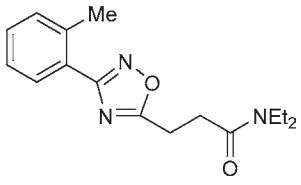
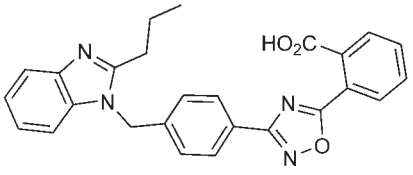


417

Compound **418** is of interest as nonpeptide angiotensin II (AII) receptor antagonist, and structural and pharmacological studies have been reported <2003JST361, 2003S899>. A library of 4-[2-(1,2,4-oxadiazolyl)]piperidines has been designed, synthesized, and then tested as dopamine D_4 ligands <2000CCHT131>. The 5-methyl-1,2,4-oxadiazolyl 7-methylsulfonyloxybenzazepine derivative **419** (SB-414796) shows high dopamine D_3 receptor affinity with excellent selectivity <2003JME4952>. The 3,5-diaryl-1,2,4-oxadiazoles **420** act as interleukin-8 (IL-8) receptor antagonists with low micromolar (but not nanomolar) potency, demonstrating interesting leads in the inhibition of IL-8-induced release of elastase from neutrophils <2004BML4307>. Compound **421** is the 1,2,4-oxadiazol-5-yl analogue of the 1,2,3,4-tetrazol-5-yl nonpeptidic human growth hormone secretagogue L-692,429, showing a slightly higher affinity for growth hormone release <1997BML1293>. The 3-methyl-1,2,4-oxadiazol-5-yl (phenylvinyl)-phenylquinoline **422** is a type-4 cyclic adenosine monophosphate (cAMP) specific phosphodiesterase (PDE4) inhibitor that is typical of those under development as a treatment for pulmonary diseases such as asthma and chronic obstructive pulmonary disease, and has been synthesized on multikilogram scale <2006OPD36, 2000JME3820>.



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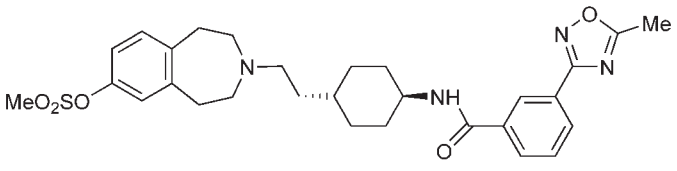
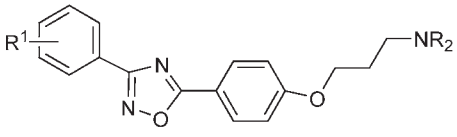
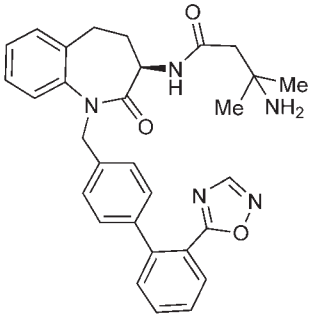


419



420



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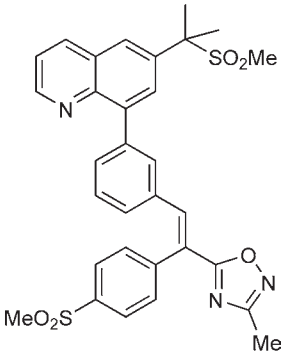
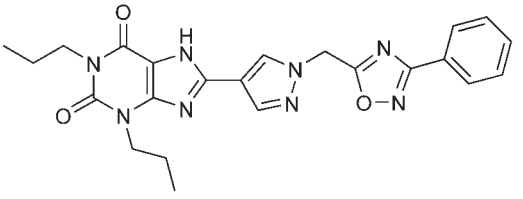


422

The A_{2B} adenosine receptor (A_{2B}-AdoR) is implicated in the response of airway mast cells to allergens, and antagonists at this receptor are of interest in the management of asthma. The 3-phenyl-1,2,4-oxadiazol-5-yl(pyrazolyl) purine **423** represents one of the most active and selective A_{2B}-AdoR antagonists known to date and represents a novel class of such antagonists <2006BML302>. A range of β-substituted 1,2,4-oxadiazole butanoic acid analogues which incorporate a guanidine mimetic, an example of which is compound **424**, have been developed and are potent and selective antagonists of the integrin $\alpha_v\beta_3$, a noncovalently linked, heterodimeric transmembrane receptor found on the surface of tumor cells, antagonists of which have been shown to inhibit angiogenesis <2006BML839>.



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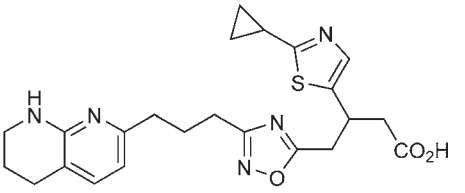
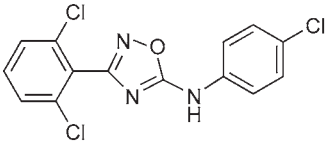


424

5-Anilino-1,2,4-oxadiazoles, of which compound **425** is typical, are strongly implicated as squalene epoxidase inhibitors and show fungicidal activity of significance in plant protection <2001JPES60>. The nonsymmetric disubstituted 1,2,4-oxadiazole **426** and analogues have been investigated and reported as new liquid crystalline oxadiazoles with a nonlinear structure <2000MCL327>. The copper(II) complexation of the 5-(hydroxyphenyl)-1,2,4-oxadiazole **427** results in room temperature fluorescence via metal coordination to the 4-nitrogen and the formation of a dimeric complex <1999ICA1>.



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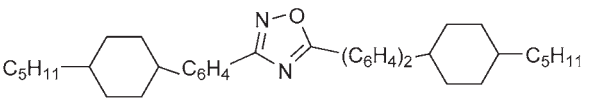

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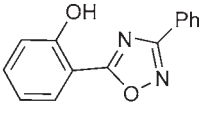
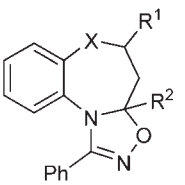


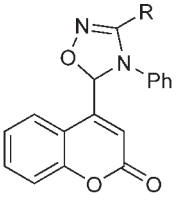
427

5.04.11.2 Applications of Non-Fully Conjugated 1,2,4-Oxadiazoles

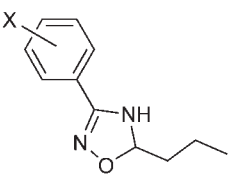
1,2,4-Oxadiazolo[5,4-*d*][1,5]benzothiazepines **428** show good activity as anticonvulsant agents <1995EJM925>. 4,5-Dihydro-1,2,4-oxadiazoles **429** demonstrate anti-inflammatory activity, showing inhibition of *in vitro* proteolysis and the ability to inhibit β-glucuronindase and 12-lipoxoygenase <1996JHC967>. 4,5-Dihydro-1,2,4-oxadiazoles **430** have also been assessed for anti-inflammatory activity, but were less active than the corresponding fully conjugated systems. They did, however, possess reasonable antimicrobial activity against *Staphylococcus aureus*, *Mycobacterium smegtatis*, and *Candida albicans* <2003BMC1821>. 4,5-Dihydro-1,2,4-oxadiazoles have also been reported to possess activity as central nervous system (CNS) depressants <1998CJC84> and anti-HIV activity <1996CH1556>.



428: R^2 = Ph/Me; R^1 = Me, Ph, Ar
X = S or SO_2



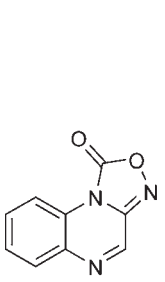
429: R = Me, $MeOC_6H_4$



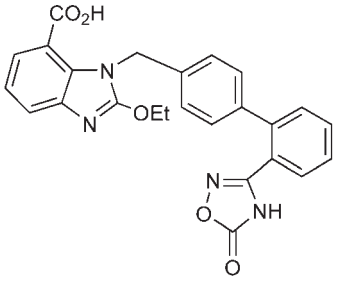
430: X = H, OMe, Cl

Close to 1000 publications have appeared that make use of the soluble guanylyl cyclase inhibitor 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ) **1**, a compound of immense and continuing importance since the appearance of the first reports detailing its use <1995MI184, 1997MI837, 1998BJP299> as a potent and selective inhibitor of nitric oxide-sensitive guanylyl cyclase. A series of benzimidazole-7-carboxylic acids bearing the 5-oxo-1,2,4-oxadiazole ring have been shown to be potent and specific orally active angiotensin II receptor antagonists and compound **431** is a

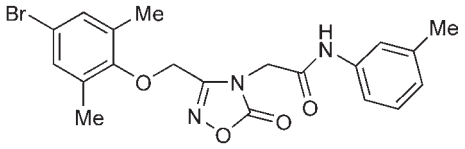
typical example <1995BML1903, 1996JME5228>. The 5-oxo-1,2,4-oxadiazole **432** is a fungicide with strong protective action against rice blast disease which, although it lacked curative and systemic effects, functioned through inhibition of melanization <2002JPES229>.



1

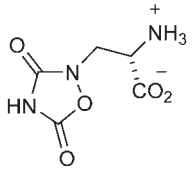


431

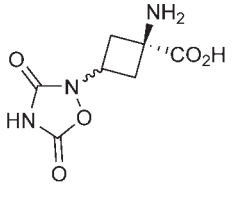


432

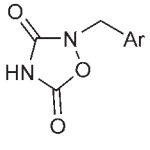
(*S*)-Quisqualic acid **2**, as discussed in CHEC-II(1996) <1996CHEC-II(4)179>, is a neuroexcitatory naturally occurring amino acid isolated from the seeds of the of *Quisqualis indica*, and is the key active in the traditional Chinese anthelmintic Shihchuntze, and has continued to attract interest due to its ability to act as an agonist at several excitatory amino acid receptors within the CNS <1996TL5225>. The conformationally constrained quisqualic acid analogues **433** are selective ligands for the mGluR5a metabotropic glutamic acid receptor, a receptor coupled to phosphoinositide hydrolysis <1999JME1639>. A range of 2-substituted 1,2,4-oxadiazolidin-3,5-diones **434** possess antihyperglycaemic activity with potential for the treatment of non-insulin-dependent diabetes <1997SL263>. The *(Z)*-bis[(1,2,4-oxadiazolidin-3,5-dione)phenoxy]but-2-ene **435** is a hypoglycaemic agent that normalizes hyperglycemia without affecting body weight and is therefore useful for the treatment of non-insulin-dependent diabetes <2000MI411>. The 1,2,4-oxadiazolidin-3,5-dione structure is present in several herbicides (see also CHEC-II(1996) <1996CHEC-II(4)179>), and the herbicide BAS-3820 **436** has attracted further attention <2002SC803>.



2



433



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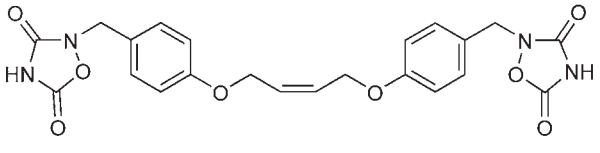

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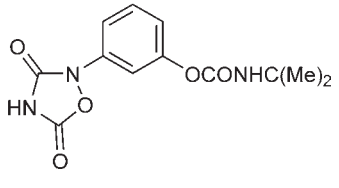

436

5.04.12 Further Developments

Recent work has demonstrated that *N*-oxides of adenosine undergo ring opening followed by exocyclic ring closure in the presence of carboxylic anhydrides and thiophenol to give 1,2,4-oxadiazolyl imidazoles <2006OL4565>. This is a useful addition to ring syntheses of 1,2,4-oxadiazoles from other heterocycles (Section 5.04.9.1.6). 5-Difluoromethylene containing 1,2,4-oxadiazoles have been accessed from 5-difluorodiiodomethyl-3-phenyl-1,2,4-oxadiazole by reaction with a range of alkenes and alkynes in the presence of sodium dithionite <2007S1768>, a very useful addition to Section 5.04.7.3. The group of Buscemi have continued to make additions in the 1,2,4-oxadiazole area and have recently shown that ANRORC (addition of nucleophile, ring-opening and ring-closure) type processes allow the rearrangement of 5-tetrafluorophenyl-1,2,4-oxadiazoles into indazoles upon treatment with hydrazine

<2006T8792>. The use of 3,5-disubstituted 1,2,4-oxadiazoles as peptidomimetic building blocks has attracted further interest (see Section 5.04.11.1) with the preparation of several structures containing a protected amine substituent and a carboxyl or ester substituent <2007TL1465>. The 1,2,4-oxadiazole was constructed using a variation of the four-atom component, one-atom component methods discussed in Section 5.04.9.1.2. This type of synthetic procedure was also used in the design and synthesis of series of keto-1,2,4-oxadiazoles which were shown to be potent inhibitors of human mast cell tryptase and of enormous interest in the treatment of asthma and other allergic diseases <2006BML3434>.

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Biographical Sketch

Karl Hemming obtained his B.Sc. (Hons.) in applied chemistry from the University of Salford in 1989. He did his Ph.D. in the synthesis of four-membered ring nitrogen heterocycles, supervised by Dr. R. K. Smalley, at the University of Salford (1993). He did his postdoctoral work from the universities of East Anglia and York with Professor R. J. K. Taylor on the synthesis of polyene natural products using pyrylium heterocycles. He has lectured at universities of Bath (1995–96) and Hertfordshire (1996–2001), and was appointed senior lecturer in organic chemistry at the University of Huddersfield in 2001. His current research interests include synthesis of oxygen-, nitrogen-, and sulfur-containing heterocyclic compounds of biological and pharmaceutical interest, particularly four-, five-, and seven-membered rings, including serine protease inhibiting β-lactams and β-sultams, antitumor and antibiotic pyrrolobenzodiazepines, and the indolizidines.

5.05
1,2,5-Oxadiazoles

G. N. Nikonov and S. Bobrov
Alchem Laboratories Co., Alachua, FL, USA

5.05.1 Introduction

In this chapter, as in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)393, 1996CHEC-II(4)229>, the chemistry of compounds with the 1,2,5-oxadiazole ring system is considered. The history and nomenclature of these compounds, as well as basic synthetic methods and chemical properties of 1,2,5-oxadiazoles reported before 1996, were reviewed previously <B-1996MI104, 1996CHEC-II(4)229>. This chapter covers the period from 1996 to 2006.

The chemistry of furazans (1,2,5-oxadiazoles) and benzofurazans (benzo[*c*][1,2,5]oxadiazoles) as well as furoxans (1,2,5-oxadiazole-2-oxides) and benzofuroxans (benzo[*c*][1,2,5]oxadiazole-1-oxides) is well known. These systems are widely used in organic chemistry as intermediate compounds for the synthesis of numerous heterocycles. On the one hand, furoxan and furazan derivatives possess an exceptional combination of chemical and physical characteristics: easy ring opening, tautomerism, transformations in reactions with both nucleophiles and electrophiles. On the other hand, furoxan and benzofuroxan derivatives have been extensively studied as bioactive compounds. They possess remarkable biological activities, such as antimicrobial and antiparasitic properties, mutagenic, immunosuppressive and anticancer effects, antiaggregating and vasorelaxant activities among others. In some cases, molecular mechanisms of their action have been proposed. Recent research in the medicinal chemistry of these systems produced hybrid compounds in which furoxan or benzofuroxan moieties together with classical drug moieties are present in single molecules. The furazan and furoxan derivatives with high nitrogen contents have found application as pyrotechnic compounds and propellants, especially for use in gas generators and automobile airbag inflators.

During the period 1996–2006, several reviews of the synthesis and properties of furoxans (1,2,5-oxadiazole-2-oxides) and benzofuroxans (benzo[*c*][1,2,5]oxadiazole-1-oxides) were published. Data on the synthesis and properties of furazan derivatives fused with pyridine, pyran, thiopyran, azepine, and thiepine rings have been surveyed and described systematically <1999RCR137>. The preparation and reactions of monocyclic furazans and furoxans have been reviewed <2001AHC65>. The published data on methods for the synthesis of furazans fused to six-membered heterocycles with two heteroatoms in positions 1 and 4, their reactivity, and practical applications were considered and systematized <2003RCR87>. Methods for the preparation of 1,2,5-oxadiazoles were reviewed, including cyclization, ring transformation, and substituents modification <2004SOS(13)185> (see also synthesis of 1,2,5-oxadiazole-2-oxides (furoxans) by dimerization of nitriles (furoxans) <2004SOS(19)17>). Design, synthesis, and study of the antioxidant and vasodilating properties of new hybrids obtained by linking different antioxidant phenolic moieties to the furoxan substructure present in CHF2363, which can release nitric oxide, have been described <2006ARK301>.

Thermal stability of high-energy compounds, the influence of molecular structure on the stability and decomposition kinetics, and monofunctional compounds and those with mixed functional groups (including 1,2,5-oxadiazoles) have been reported. The sites of primary decomposition were determined and the mutual influence of functional groups on compounds' stability were taken into account <2000RCB234>. Thermodynamic properties, namely dissociation enthalpies of terminal (N–O) bonds, DH° (N–O), in the *N*-oxide derivatives including furoxans were discussed based on published enthalpy of formation, enthalpy of sublimation, and enthalpy of vaporization data <2005MI553>. Fluorescent chiral derivatization reagents possessing benzofurazan structure for the resolution of optical isomers in high-performance liquid chromatography (HPLC) were discussed in a mini review <2005MI57>. The pharmacological properties of furoxans and benzofuroxans have been presented <2005RMC57>.

5.05.2 Theoretical Methods

Ab initio calculations, correlations of molecules geometries, spectroscopic data with chemical properties, and quantative structure–activity relationship have been conducted for both furazans and furoxans. Thus, the structures of 1,2,5-oxadiazole (furazan) and benzo[*c*][1,2,5]oxadiazole (benzofurazan) have been calculated by *ab initio* and Becke3-LYP

(B3LYP) density functional theory (DFT) using the 6-31G** basis set. Within a given basis set, DFT methodology seems to be superior to restricted Hartree–Fock (RHF) and MP2 methods <1996HCO397, 1996SAA33>. The latest investigations have shown that DFT methods can provide reliable tools for the prediction of geometries and energies of a wide variety of organic (and inorganic) compounds, especially in those cases where classical Hartree–Fock (HF) methods fail (e.g., for furoxans and benzofuroxans) <2000HCO35, 2000RJO1745, 2003T1059>. The DFT method was used to study the static electronic dipole moments, polarizabilities, polarizability anisotropies, and first- and second-order hyperpolarizabilities of azoles, including 1,2,5-oxadiazole <2003PCA4172>.

Molecular parameters (bond lengths and bond angles, rotational constants, and dipole moments) and vibrational infrared (IR) spectra (harmonic wave numbers and absolute intensities) of 1,2,5-oxadiazole and other cycles have been predicted by DFT with the combined Becke3-LYP gradient exchange-corrected functional (DFT(B3LYP)) and the conventional *ab initio* MP2(full) approach; the standard 6-31G(d,p) basis set was used. Results were compared with the available experimental data. The molecular parameters computed by means of the DFT method are in a good agreement with those predicted by the MP2 approach and with the experimental data. Very good agreement between the calculated IR wave numbers and absorption IR intensities of the molecules and their deuterated species studied by the DFT method and the experimental data was found <1997JST(436)451>.

DFT was used to calculate the heats of formation and infrared active vibrational frequencies of 12 furazan compounds (**Figure 1**). The absolute values of the heats of formation are unreliable but the trends with systematic variations of the bridge and terminal groups are reasonable. The assignments of the vibrational motions to IR frequencies based on a force field analysis are given to clarify the complex coupling in these molecules <2000MI247>.

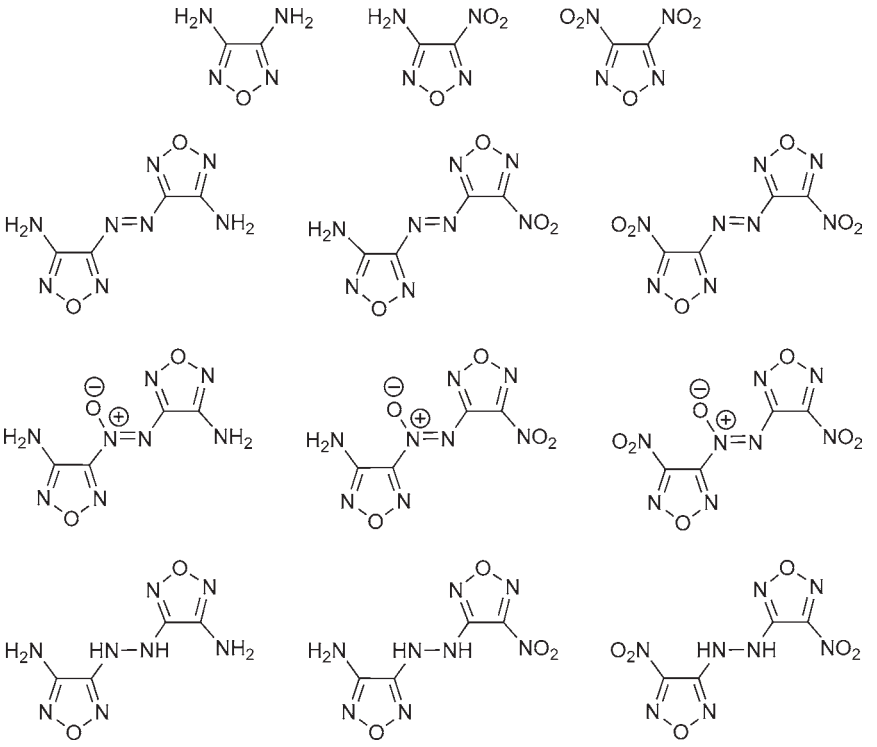


Figure 1 Furazan compounds investigated by DFT computational methods.

Ab initio electron correlated calculations of the equilibrium geometries, dipole moments, and static dipole polarizabilities were reported for oxadiazoles <1996JPC8752>. The various measures of delocalization in the five-membered heteroaromatic compounds were obtained from MO calculations at the HF/6-31G* level and the application of natural bond orbital analysis and natural resonance theory. The hydrogen transfer and aromatic energies of these compounds were also calculated. These were compared to the relative ranking of aromaticity reported by J. P. Bean from a principal component analysis of other measures of aromaticity <1998JOC2497>.

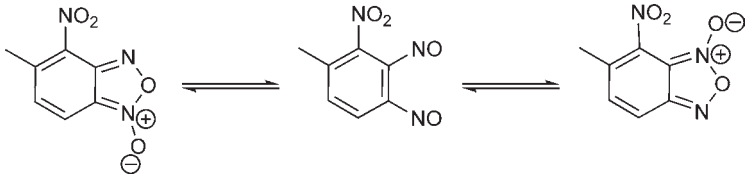
A theoretical study of degenerate Boulton–Katritzky rearrangements concerning the anions of the 3-hydroxyiminomethyl-1,2,5-oxadiazole has been carried out by using semi-empirical modified neglect of diatomic overlap (MNDO) and *ab initio* Hartree–Fock procedures. Different transition structures and reactive pathways were obtained in the two cases. Semi-empirical treatment shows asymmetrical transition states and nonconcerted processes via symmetrical intermediates. By contrast, *ab initio* procedures describe concerted and synchronous processes involving symmetrically located transition states <1998JMT(452)67>.

A detailed *ab initio* and density functional study of the Boulton–Katritzky rearrangement (Equation 1) was presented. Two different reaction paths for the rearrangement of 4-nitrobenzofuroxan were investigated at the RHF, MP2, MP4(SDQ), B3-LYP, and BH&H-LYP levels, with further energy refinements using coupled-cluster theory with singles and doubles (CCSD and CCSD(T)). Electron correlation effects appear to be extremely important for both geometries and relative energies. All methods indicate a one-step mechanism. In agreement with experimental results, the possible tricyclic intermediate could not be found <1998JA13478>.

(1)

A, E = N, N^+-O^-, N^+-N^- R, CR; B, F = O, NR, S; D = N, CR

The molecular rearrangement of 5-methyl-4-nitrobenzofuroxan to 7-methyl-4-nitrobenzofuroxan (**Scheme 1**) was studied by means of *ab initio* and density functional theory. Experimentally obtained IR spectra and X-ray data support the applicability of the theoretical methods and allow for a complete assignment of the vibrational modes. The influence of the methyl substituent on the underlying tautomeric reaction was investigated in detail. Trends for the reactivity of 4-nitrobenzofuroxans with substituents in the 5-position were established on the basis of an energy partitioning, providing insight into the driving forces of the Boulton–Katritzky rearrangement. Rate constants were calculated for this reaction using different implementations of variational transition-state theory <1999JA6700>.



Scheme 1

The equilibrium structure of 1,2,5-oxadiazole has been calculated *ab initio* at the CCSD(T) level using a polarized valence quadruple ζ basis set. The harmonic force field has also been calculated at the MP2/cc-pVTZ, B3LYP/6-311++G(3df,2pd), and B3LYP/cc-pVQZ levels. The different results were compared and it was concluded that the *ab initio* structure is a good approximation of the equilibrium structure. It was also shown that the magnetic correction is not negligible, particularly for the inertial defect. Another interesting conclusion is that the anharmonicity of the C–H stretching might be unusually small <2001JSP224>.

The electron spin resonance (ESR) spectra of free radicals obtained by electrolytic or microsomal reduction of several potential antiprotozoal 1,2,5-oxadiazoles were characterized and analyzed. *Ab initio* MO calculations were performed to obtain the optimized geometries, and the theoretical hyperfine constant was carried out using Zerner's intermediate neglect of differential overlap (ZINDO) semi-empirical methodology. DFT was used to rationalize the reduction potentials of these compounds <2003SAA69>.

C–H and N–H bond dissociation energies (BDEs) of various five- and six-membered ring aromatic compounds (including 1,2,5-oxadiazole) were calculated using composite *ab initio* CBS-Q, G3, and G3B3 methods. It was found that all these composite *ab initio* methods provided very similar BDEs, despite the fact that different geometries and different procedures in the extrapolation to complete incorporation of electron correlation and complete basis set limit were used. A good quantitive structure–activity relationship (QSAR) model for the C–H BDEs of aromatic compounds

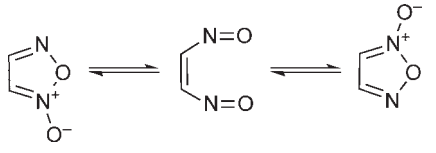
was also established <2003JPO883>. Quantum structure–property relationship (QSPR) calculation of aromaticity in some five-membered heteroaromatic compounds, including 1,2,5-oxadiazole, were provided <2004MI145>. Statistical analyses of quantitative definitions of aromaticity, aromatic stabilization energies (ASEs), resonance energies (REs), magnetic susceptibility exaltation (Λ), nucleus-independent chemical shift (NICS), HOMA, I5, and AJ, evaluated for a series of five-membered π-electron systems, including 1,2,5-oxadiazole, revealed statistically significant correlations among the various aromaticity criteria, provided the whole set of compounds is involved <2002JOC1333>. A significant linear relationship between NICS values and ASEs was demonstrated for a wide range of five-membered heteroaromatic compounds including oxadiazole structures <2002CEJ433>.

An *ab initio* theoretical study was conducted on 1,2,5-oxadiazole and 3-phenyl-1,2,5-oxadiazole to determine the molecular structures of these heterocyclic compounds. The rotational energy barrier between Ph ring and diazole nucleus was also evaluated. No considerable change of bond lengths inside the diazole nucleus was observed in the Ph-substituted heterocyclic compounds as compared to the oxadiazole and thiadiazole alone <2001MI215>.

Ab initio, second-order, Møller–Plesset perturbation theory calculations of quadrupole and octopole moments are reported for 36 different 6π-electron monocycles including 1,2,5-oxadiazole <1999PCA10009>.

Within the framework of the scaled quantum mechanical (SQM) procedure, transferable scaling factors (TSFs) were used to compute the vibrational spectra of dibromofuroxan and diiodofuroxan <2002PCA6810>.

The tautomerism of furoxan (1,2,5-oxadiazole-2-oxide) has been investigated by different computational methods comprising modern density functions as well as single-reference and multi-reference *ab initio* methods. The ring-opening process to 1,2-dinitrosoethylene is the most critical step of the reaction and cannot be treated reliably by low-level computations (**Scheme 2**). The existence of *cis–cis–trans*-1,2-dinitrosoethylene as a stable intermediate is advocated by perturbational methods, but high-level coupled-cluster calculations identify this as an artifact <2001JA7326>.



Scheme 2

Dipole moments of 3-amino-5-R-furazans (R = H, NH_2, OMe, Me, N_3, COOH, COOMe, and NO_2) were determined experimentally and also calculated by HF *ab initio* (STO-3G, 3-21G, 4-31G, 6-31G, 6-31G**/4-31G, 6-31G** levels) and semi-empirical (MNDO, AM1, and PM3) quantum chemical methods. Semi-empirical AM1 and PM3 methods provide generally good agreement with the experimental values of dipole moments. However, a satisfactory description of this aminofurazan property by *ab initio* method is observed only in the case of calculation levels with the electron correlation and the polarization function included. For these compounds amino–imino tautomeric equilibrium is strongly shifted toward the amino form. 3-Aminofurazan-4-carboxylic acid and its methyl ester exist in dioxane or benzene solutions at least as a mixture of two different *s-cis*- and *s-trans*-conformers stabilized by conjugation and H bonding <2003CCA177>.

The relationship between the herbicidal activity of 1,2,5-oxadiazole *N*-oxides and some physicochemical properties potentially related to this bioactivity, such as polarity, molecular volume, proton acceptor ability, lipophilicity, and reduction potential, were studied. The semi-empirical MO method AM1 was used to calculate theoretical descriptors such as dipolar moment, molecular volume, Mulliken's charge, and the octanol/water partition coefficients (log Po/w) <2005MOL1197>.

5.05.3 Experimental Structural Methods

5.05.3.1 Molecular Dimensions

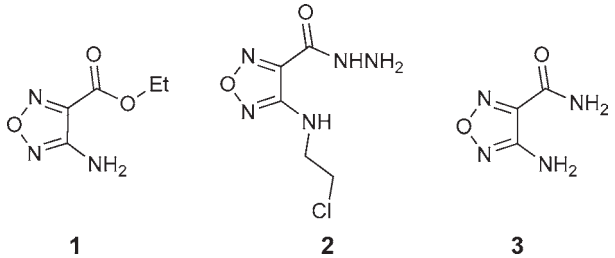
X-Ray crystallography has been commonly used to confirm structures of new 1,2,5-oxadiazoles. X-ray data show that the heterocyclic ring is planar with C_{2v} symmetry. The delocalization of π-bonds depends on the C-substituents.

The crystal structures of five 5,6-disubstituted benzofurazan 1-oxides were compared with five previously reported structures: three polymorphs of 5,6-dichlorobenzofurazan 1-oxide plus 4,5-dichloro- and 4,5-dibromophthalic

anhydride. All but one of these compounds pack in similar two-dimensional layers. The benzofurazan oxides all show disorder about a crystallographic twofold or pseudo-twofold axis. In addition, six complexes of phthalic anhydride and benzofurazan oxides are reported. With the packing in the complexes principally directed by the π-complexing, the disorder, invariably found in the uncomplexed benzofurazan oxides, is diminished and in two cases eliminated <2003HCA1175>.

The molecular structures of five furazan compounds (diaminoazofurazan, diaminoazoxyfurazan, dinitroazoxyfurazan, diaminohydrazofurazan, and dinitrohydrazofurazan) in which two amino- or nitro-substituted furazan rings are bridged by azo, azoxy, or hydrazo groups were determined by single crystal X-ray crystallography <2000MI277>. The structures were compared to those previously reported for dinitroazofurazan, aminonitroazoxyfurazan, and another polymorph of diaminoazoxyfurazan. A conjugated system of the rings should give a planar molecule. These conditions potentially enhance the density. With the exception of one of the NO_2 groups of dinitroazofurazane and dinitroazoxyfurazane, the conjugated difurazan molecules are indeed planar. Even when the single-bonded hydrazo bridge is present, as in diaminohydrazofurazan and dinitrohydrazofurazan, the individual ring systems are planar and stack in the crystal lattice with rings facing rings. The rotation of one of the NO_2 groups out of the plane might be attributed to steric factors within the molecule, but *trans* (D,D) isomer observed in diaminoazoxyfurazane would be less favored if only steric factors dominate. Instead, a complex mixture of both intramolecular and intermolecular interactions appears to be responsible for the variety of isomers observed. The *cis*-conformation about the bridging link was never observed probably because of intramolecular steric crowding. Although rings substituted with NO_2 have slightly more distortion than those with NH_2 groups, the deviations from compound to compound are small <2000MI277>.

The study of the crystal structures of three complexes of 18-crown-6 with 1,2,5-oxadiazoles (guests) having substituents in the 3- or 4-position of the oxadiazole ring (amino and ester group (guest **1**), hydrazide and chloroethylamine group (guest **2**), amino and amide groups (guest **3**) was described <2001MI459>. In the complex with compound **1** the 18-crown-6 and guest molecules are linked by hydrogen bonds of NH···O (crown) and CH···O (crown) types based on the 'head-to-tail' principle, alternating in infinite chains along the *y*-axis in the crystal. In the complex with compound **2**, the guest molecules are assembled into dimers by N–H···O═C hydrogen bonds. The 18-crown-6 molecules and the dimer associate of the guest form chains along in the crystal. The complex of crown ether with compound **3** is disordered over two positions. The NH···O═C and NH···N type hydrogen bonds link the guest molecules into chains. The water molecules serve to bridge the chains with crown ether molecules, forming ribbons whose axis lies along the *z*-direction in the crystal. Compounds **1–3** are coordinated in different ways. The bilateral equivalent coordination mode is met in complex with guest molecule **1**; with guest molecules **3** and **2**, the one- and many-sided coordination was observed respectively. In the complex with guest molecule **3**, there are no direct hosts–guest contacts, although the guest has an easily coordinating amino group. The interaction is mediated by the bridging water molecule and the hydrogen bonds are formed by only two oxygen atoms of the macrocycle. Examples with compounds **1–3** prove that host–guest complexes have diverse topologies depending on changes in the geometry and the nature of the donor groups of the guest <2001MI459>.

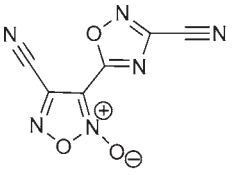


10-Hydroxy-7-phenylindeno[1,2-*b*]-1,2,5-oxadiazolo[3,4-*d*]pyridine can have four polymorphic forms in the solid state, of which two are yellow and two are red. Two of them are interconvertible (yellow/red) upon exposure to different solvents. X-ray crystal structure analysis of one of the red forms shows the phenyl ring and the indenooxadiazolopyridine ring to be coplanar <1999H(50)895>.

Dicyanofuroxan (3,4-dicyano-l,2,5-oxadiazole 2-oxide), the precursor to the NCCNO (see structure **11**) species, has been studied in the solid and gas phases to obtain both structural and electronic information. The solid-state structure determined by X-ray diffraction gives an orthorhombic space group *PnaZ*, with $a = 10.2578(14)$, $b = 10.8818(12)$, and $c = 10.2259(15)$ Å. There are two independent molecules with similar geometries in the asymmetric unit. The gas-phase molecule was characterized by HeI photoelectron, HeI and $HL_{\alpha,\beta,\gamma}$ photoionization, and IR spectroscopy. The

vibrational data are also supported by a Raman study of the solid. The equilibrium geometry of dicyanofuroxan obtained from *ab initio* calculations at the HF and MP2/6-31G* levels provides support to the crystallographic structure of an asymmetric planar five-membered ring with three quite different N–O bonds, including a very short (and strongly polarized) exocyclic *N*-oxide group. Nevertheless, both HF and MP2 calculations are in poor quantitative agreement with the solid-state structure. DFT (B3-LYP) is, however, much more in accord with the crystallographic result, as indeed, it is with the vibrational data <1996J(P2)179>.

The structures of two formal trimers of cyanogen *N*-oxide of the composition $C_6N_6O_3$ were established by X-ray crystal structure analysis. In the crystals, the two rings are almost but not quite coplanar, with dihedral angles of 4.56(0.59)° in the case of structure **4** and 9.43(0.17)° in the case of structure **5** <2000J(P2)473>.



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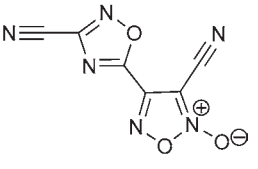


5

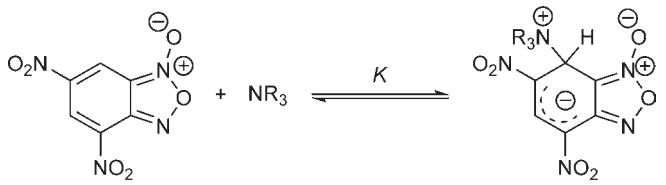
The reactions of 4-nitrobenzodifuroxan (NBDF) with a series of common dienes led to cycloadducts (see Section 5.05.7.2.3), which were investigated by X-ray analysis. It was shown that the C(4)–C(5) double bond of NBDF has a length of 1.339 Å. This is typical of a nitro-olefinic fragment and is in contrast with the structure of 4,6-dinitrobenzofuroxan (DNBF) in which values of 1.37 and 1.40 Å have been measured for the two potentially reactive nitroactivated C(6)–C(7) and C(4)–C(5) double bonds, respectively <1999JOC9254>. In accord with these data, the least aromatic C(6)–C(7) fragment is the one preferentially involved in Diels–Alder interactions, accounting for the regioselectivity observed in the formation of all DNBF monoadducts so far reported. The most interesting feature, however, is that the cycloadditions involving the C(6)–C(7) double bond occur with a significant shortening of the C(4)–C(5) double bond of the carbocyclic moiety of DNBF. This corresponds to the recovery of a strong olefinic character of this fragment, marking it comparable to the C(4)–C(5) bond of NBDF. On this basis, it would be more appropriate to relate the reactivity of NBDF to that of the DNBF monoadducts rather than to the parent molecule <2005T8167>.

Two molecules with comparable geometry in an asymmetric unit were found for 3,4-bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide. The bond length of the dipolar N–O bond is 1.107 (7) Å <2006AXEo4827>. In the molecule of 5-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-4-phenyl-1,2,5-oxadiazole *N*-oxide, the six-membered heterocyclic ring has a flattened boat form. Intermolecular C–H···O hydrogen bonds link the molecules into dimers, which may be effective in the stabilization of the crystal structure <2006AXEo3130>.

5.05.3.2 NMR Spectra

The typical nuclear magnetic resonance (NMR) parameters of compounds with 1,2,5-oxadiazole units were given in CHEC-II(1996) <1996CHEC-II(4)229>. As a rule ^{1}H and ^{13}C NMR spectra data are reported for all synthesized 1,2,5-oxadiazoles to confirm the structure. Sometimes NMR method has been used for a special task, for example, for identification of tautomeric forms, including ring-chain tautomerism, and their ^{17}O, ^{14}N, ^{15}N, ^{19}F NMR spectra have also been reported. Thus, high-precision ^{14}N NMR shielding was reported for oxazoles and oxadiazoles in a variety of solvents. Both solvent polarity and hydrogen-bond effects on the nitrogen nuclear shielding of the solutes are significant and comparable in magnitude; both give rise to shielding increases. The increasing solvent polarity favors delocalization of electrons from oxygen atoms into the heteroarom rings with a concomitant electron charge accumulation on the nitrogen atoms involved <1996MR148>.

Spectroscopic and kinetic investigations of the reactions between 4,6-dinitrobenzofuroxan, 4-nitrobenzofuroxan, and tertiary and secondary amines (i.e., 1,4-diazabicyclo[2.2.2]octane, quinuclidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, and piperidine) indicate the formation of zwitterionic or anionic complexes (Equation 2). The equilibrium between zwitterionic and anionic complexes is discussed (for reaction with piperidine) on the basis of ^{1}H NMR spectral data, which indicate the presence of anionic complexes arising from the zwitterionic complex by a fast proton departure. The stability and the rate of formation of title complexes are discussed and compared to similar reactions of 1,3,5-trinitrobenzene <2001J(P2)1408>.

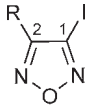


(2)

NR_3 = **a**: DABCO, **b**: QN, **c**: DBU, **d**: PIP

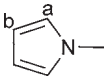
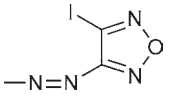
The reaction of 3,4-bis(benzenesulfonyl)furoxan with alcohols and thiols in basic media affords a variety of alkoxy- and alkylthio-substituted (benzenesulfonyl)furoxans. For these derivatives a paramount problem is to determine the position (3- or 4-) of the substitution in the furoxan ring. The structures of these derivatives were assigned on the basis of both chemical and NMR evidence. In particular, ^{13}C NMR substituent constants were obtained by NMR study of suitable furoxan models. By assuming a complete additivity of the substituent effects at the furoxan ring, these values were used for structural determination <1997FES405>.

The investigation of the influence of the substituents on NMR data of the iodofurazans **6a–m** was carried out <2004HAC199>. The ^{13}C NMR spectra were assigned by intensity, peak multiplicity under off-resonance decoupling, and substituent chemical shifts (SCSs) considerations (**Table 1**). Results obtained showed the absence of significant polarization of the furazan ring under substituent influence. Iodofurazans **6a–f** show the diagnostic chemical shift for quaternary carbon of the furazan ring bearing iodo group at δ 95–114.



6a–m

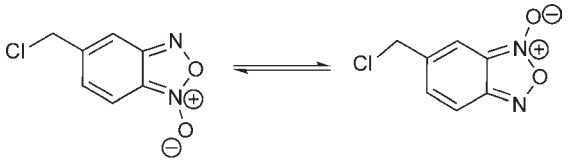
Table 1 Chemical shifts δ NMR ^{13}C and SCS values for iodofurazans in $CDCl_3$

		C(2)		*C(1)*		
	R	δ (*ppm*)	SCS_i	δ (*ppm*)	SCS_o	*R* (δ (*ppm*))
6a	Me	155.3	9.2	105.5	0.7	9.4
6b	Et	159.4	15.6	104.5	−0.5	11.7 (Me), 18.1 (CH_2)
6c	OMe	167.1	31.4	95.7	−14.4	59.6
6d[a]	NH2	159.8	18.2	102.1	−13.4	
6e	Br	141.0	−6.8	108.4	3.2	
6f	I	114.3	−34.1	114.3	8.9	
6g	Ph	156.8	13.1	102.5	−1.1	124.7 (*i*), 128.7, 129.0 (*o*, *m*-), 131.1 (*p*-)
6h[a]	NHAc	155.1	9.5	106.7	−8.1	22.9 (Me), 169.0 (C═O)
6i	N═CCl_2	158.4	15.7	100.3		140.9 (CCl_2)
6j		154.4	11.9	95.6	−8.3	112.5 (b), 120.3 (a)
6k	N_3	158.0	12.0	97.2	−9.1	
6l		162.8	21.0	99.0		99.0, 162.8
6m	NO_2	162.3	19.5	95.1	−4.9	

[a]In DMSO-d_6.

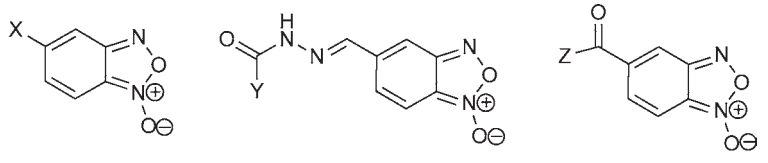
It is well known that benzofuroxan derivatives exist as a mixture of isomers at room temperature (**A** and **B**, Equation 3). At room temperature (303 K), ^1H and ^{13}C NMR spectra of the benzofuroxans show benzo-protons and carbons as broad peaks, indicating fast benzofuroxan isomerization <2005RMC57>. Upon cooling, the broad signals

are resolved below 263 K, making possible the recording of the complete series of spectra (^{1}H, ^{13}C NMR, and heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments) <2005MI294>.



A B (3)

The isomerization of series of furoxans **7–9** was observed through the corresponding NMR spectra (proton and carbon), which showed complex groups of signals in the aromatic zone (7.30–8.50 and 110–155 ppm, respectively) at room temperature. The spectra simplified at higher temperature, where one of these isomers predominates <1999JME1941, 2000JFA2995>.



7

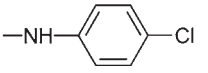
Y = $NH(CH_2)_2OMe$
Y = $NH(CH_2)_2Ph$
Y = morpholine-4-yl
X = CHO

8

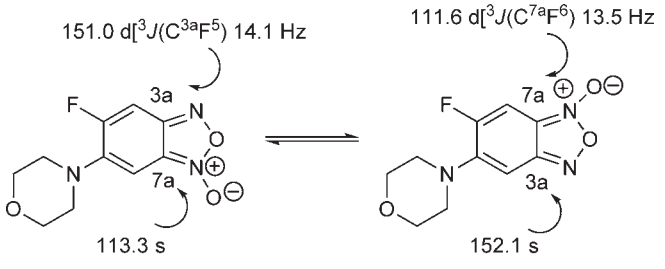
Y = $-NH(CH_2)_2OMe$
$-NH(CH_2)_2Ph$
morpholine-4-yl

9

Z = $-NH(CH_2)_2OMe$
$-NHBu^{n}$
morpholine-4-yl

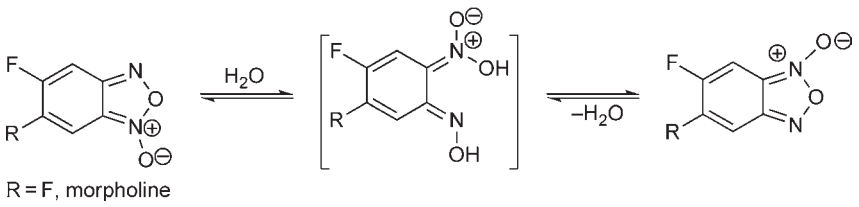


Identification of two isomeric forms of 5(6)-fluoro-6(5)-morpholinobenzofuroxane by ^{1}H, ^{13}C, and ^{19}F NMR spectra was described. Spectra registered in the temperature range −20 to 20 °C showed a ratio of isomers A and B of 7:3 (Equation 4). The difference in resonance frequencies for protons H^{4} (**A**) and H^{7} (**B**) is 89.7 Hz and these signals coalesce at 20 °C. The corresponding difference for protons H^{7} (**A**) and H^{4} (**B**) equals 146.1 Hz and their coalescence occurs at 25 °C. In the spectrum of isomer **A** quaternary atom C^{3a} gave rise to a doublet at δ_C 151.0 ppm with vicinal coupling constant $^{3}J(C^{3a}, F^{5})$ 14.1 Hz, whereas the resonance of C^{7a} appears as a singlet at δ_C 113.3 ppm. In the spectrum of isomer **B** the doublet of C^{7a} was observed at δ_C 111.6 ppm with a coupling constant $^{3}J(C^{7a}, F^{6})$ 13.5 Hz and singlet from C^{3a} appears at δ_C 152.1 ppm. ^{19}F NMR spectrum in the temperature range −20 to 20 °C changed in a similar way and the isomers ratio was found to be the same <2004RJO1167>.



A B (4)

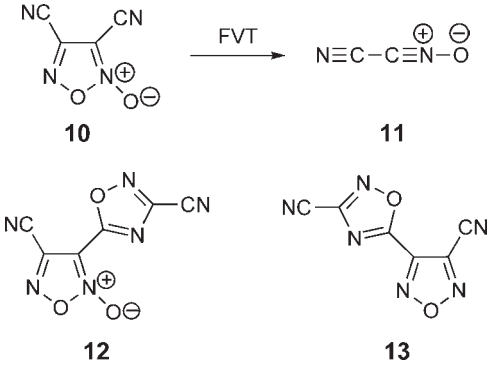
The kinetic parameters of tautomeric equilibrium of 5(6)-fluoro-6(5)-R-benzofuroxans were derived from the measurement of the temperature dependence of the ^{1}H and ^{19}F NMR spectra (**Scheme 3**) <2004RJO1167>.



Scheme 3

5.05.3.3 Mass Spectra

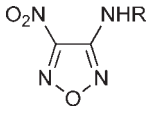
The major fragmentation in mass spectra of 1,2,5-oxadiazoles is attributed to the loss of nitrile and nitrile oxide or expulsion of NO. The conversion of 3,4-dicyano-1,2,5-oxadiazole-2-oxide (3,4-dicyanofuroxan) **10** to cyanogen *N*-oxide **11** (Equation 5) was investigated under the conditions of collisional activation (CA) and neutralization–reionization (NR) mass spectrometry. Flash vacuum thermolysis mass-spectrometry (FVT-MS) and flash vacuum thermolysis infra-red (FVT-IR) investigations of furoxans **10**, **12**, and **13** reveal that small amounts of cyano isocyanate accompany the formation of the main thermolysis product **11** <2000J(P2)473>.



(5)

The ion–molecule reactions of ionized nitrile oxide, R–C≡N$^+$–O·, with several neutral nitriles have been studied using both tandem mass spectrometric techniques and *ab initio* MO calculations. The 1,2,5-oxadiazole, 3,4-dimethyl-1,2,5-oxadiazole, 3,4-dicyano-1,2,5-oxadiazole, dibromoformaldoxime, cyanhydric acid, and cyano-5-methyl-1,2,4-oxadiazole were used as a source of nitrile oxide. Ionized oxygen atom transfer as well as a formal substitution of nitric oxide by the neutral reagent in the radical cation was the main process. Whereas the former reaction yields the corresponding ionized nitrile oxide, the second process gives an even electron species tentatively ascribed, following high-kinetic energy collisional activation experiments, to an aromatic azirinyl cation <2002IJM643>.

The mass spectra of aminofurazans have intense molecular ion peaks. The main path of fragmentation under electron impact is associated with the cleavage of the furazan ring through elimination of the NO molecule to give the [M–NO]$^+$ ions. Aminonitrofurazans undergo specific fragmentation under electron impact. The molecular ions of these compounds readily lose the NO_2 molecule. In these cases, synchronous elimination of both NO and NO_2 is often observed resulting in the formation of the [M –NO–NO_2]$^+$ ions <2004RCB596>.

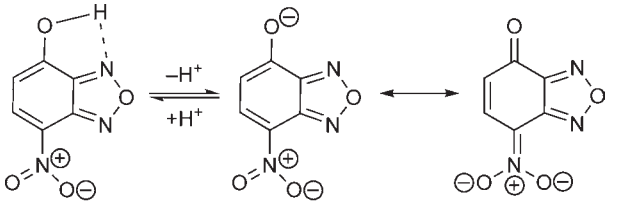


The fragmentation pattern in mass spectrometry of 1,2,5-oxadiazole *N*-oxide derivatives involving deuterium-labeled analogs to identify some critical fragmentations was investigated. A neutral CH_2O loss from 3-hydroxymethyl-*N*-2-oxide-4-phenyl-1,2,5-oxadiazole was confirmed with the corresponding mono-deuterated analog. An OH loss, involving the oxygen of *N*-oxide, via β-H and δ-H rearrangement, was clearly revealed from 3-(4-methylpiperazine-1-ylmethyl)-*N*-2-oxide-4-phenyl-1,2,5-oxadiazole using the adequate tetradeuterated analog. The *N*-oxide isomer and deoxygenated analogs were also used to confirm the participation of the oxide moiety in the fragmentation process <2004JBS232>.

Online coupling of flash-vacuum pyrolysis and mass spectrometry was applied to 3,4-dicyano-1,2,5-oxadiazole-2-oxide (dicyanofuroxan). The 1,2,5-oxadiazole is almost quantitatively pyrolyzed at 500–600 °C. Using collisional activation, the main pyrolysis products were identified as NCCNO and $(CN)_2$ <1997BSB545>.

5.05.3.4 IR and UV Spectra and Miscellaneous Methods

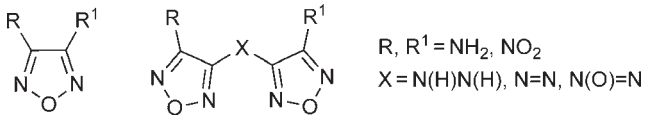
The absorption spectra of 4-hydroxy-7-nitrobenzofurazan **14** and its conjugate anion have been recorded in 23 solvents (**Scheme 4**). The data have been analyzed according to the Taft and Kamlet treatment and compared with that of some parent compounds: 4-methoxy-, 4-propylamino-, and 4-diethylamino-7-nitrobenzofurazan. The phenolate anion **15** has been shown to exhibit the solvatochromic behavior characteristic of this nitro-2,1,3-benzoxadiazole series in aprotic media, although in protic media hydrogen bonding had a drastic effect on the UV–Vis spectrum. Such sensitivity to protogenic solvents was not found for other phenoxide anions such as picrate. This difference of behavior was discussed on the basis of electrostatic potentials obtained by MNDO calculations. Evidence toward the existence of strong negative charges located on the C-5 and C-7 atoms of anion **15** was obtained, indicating that strong hydrogen bonding may take place with solvent molecules. However, this stabilization of the anion by hydrogen bonding does not seem to influence the dissociation equilibrium, with the acidity of compound **14** being perfectly in line with that of other nitrophenols <1996J(P2)73>.



14 **15**

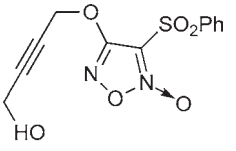
Scheme 4

Nine energetic furazan (1,2,5-oxadiazole) compounds were flash heated by the use of T-jump/FTIR spectroscopy (FTIR – Fourier transform infrared spectroscopy). Thermodynamically relatively stable gaseous products are formed, which reflect several patterns in the stoichiometry of the parent compound. The hydrazo-bridged furazans lose H_2 to form the azo-bridged analog before the ring decomposes. The melting point and sublimation properties qualitatively relate to the crystal structure and hydrogen bonding potential in these compounds <2000MI241>.



The structure and IR spectrum of furazan were studied by vibrational S CF (VSCF) and CI (VCI) calculations based on a high-quality potential derived from electronic structure calculations up to the CCSD(T)/aug-cc-pCVQZ level. Excellent agreement was found between the computed and the experimental results <2005THA327>.

The interaction between 4-(4-hydroxybut-2-ynyloxy)-3-(phenylsulfonyl)-1,2,5-oxadiazole-2-oxide **16** and bovine serum albumin (BSA) was studied by spectroscopic methods including fluorescence and UV–Vis absorption spectroscopy. The results indicate that molecules **16** bind with BSA forming 1:1 complex. Thermodynamic parameters, such as ΔH, ΔG, and ΔS, were calculated. The results indicate that the binding reaction is mainly entropy driven and hydrophobic forces play a major role in this reaction <2006CHJ1050>.

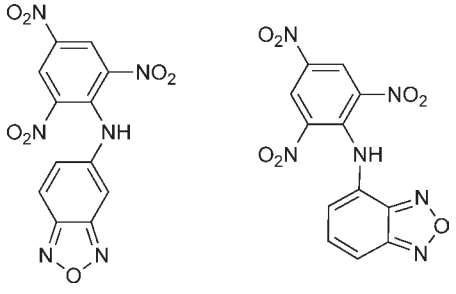


16

Electronic spectra of oxadiazoles were studied <2003IJB429>. MRINDO/S calculations augmented by singly excited CI were performed on oxadiazoles. Net charge distributions, ionization potentials, and electronic spectra of oxadiazoles were reported. The Rydberg transitions were also discussed.

The vibrational spectra of furoxan and dichlorofuroxan have been studied using the local quadratic CI method including single and double excitations (LQCISD) and two density exchange-correlation functionals (B3LYP and B97r). The vibrational spectra of these molecules <2003IJB429> are very sensitive to electron-correlation effects and are therefore well suited as benchmark systems for investigating the impact of local approximations at levels beyond second-order Moller–Plesset perturbation theory (MP2) <2003PCP2001>.

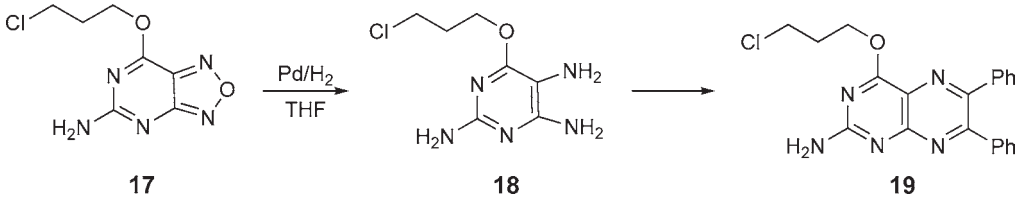
The products of the reactions of picryl chloride with isomeric 4- and 5-aminobenzofurazans in dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were studied by means of nonaqueous potentiometric titration. The effect of the position of the furazan fragment in 4- and 5-picrylaminobenzofurazans on the NH acidity is considered. The electron-acceptor properties of the furazan fragment were evaluated via inclusion of the resulting data into the pK_a–σ correlation for 2,4,6-trinitrodiphenylamines <2005RJC933>.



5.05.4 Reactivity of Fully Conjugated Rings

5.05.4.1 Furazans and Benzofurazans

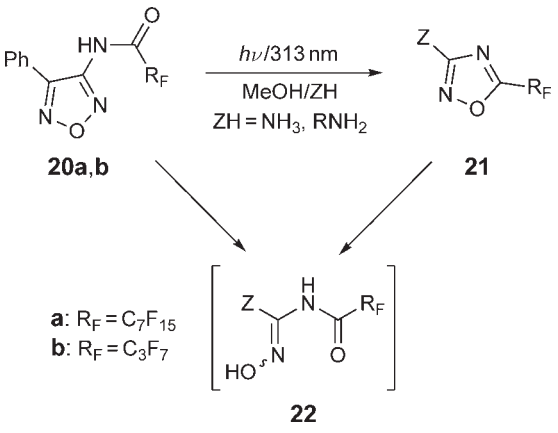
The chemical reactivity of 1,2,3-oxadiazoles and their benzo-analogues was previously considered in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)393, 1996CHEC-II(4)229>. It can be noted that heterocyclic ring is a relatively stable fragment of molecule, but furazans or benzofurazans can undergo cleavage or ring transformation reactions. For example, hydrogenolysis of compound **17** in either methanol or tetrahydrofuran solution, followed by evaporation of the solvent, leads to ring cleavage to give product **18** as an unstable solid. This product on dissolving in dry tetrahydrofuran containing benzil gave 2-amino-4-(3-chloropropoxy)-6,7-diphenylpteridine **19** (**Scheme 5**) <2004OBC3588>.



17 **18** **19**

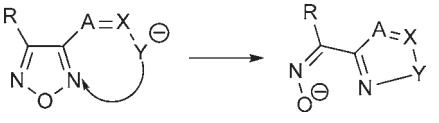
Scheme 5

Photolysis of 3-perfluoroalkanoylamino-furazans **20** in methanol and in the presence of ammonia or primary aliphatic amines allowed the synthesis of 3-amino- or 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles **21** (**Scheme 6**). This photoreaction follows the photofragmentation pattern of the furazan ring into benzonitrile and an acylaminonitriloxide species that the nitrogen nucleophile captures to give the *N*-acylaminoamidoxime intermediate **22** as a precursor to final oxadiazoles **21** (**Scheme 6**) <2000TL7977, 2004JOC4108>.



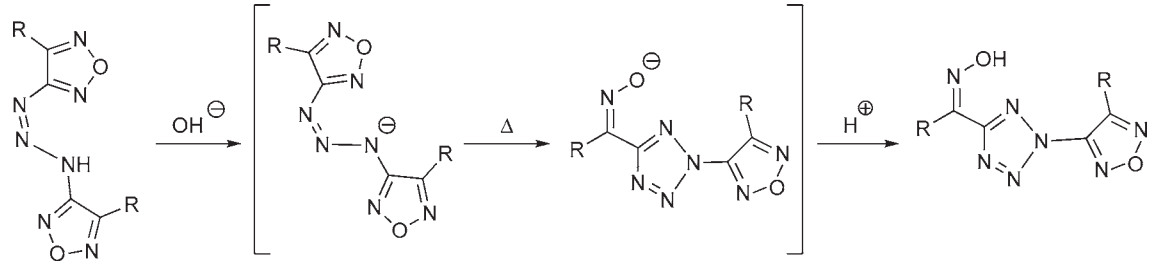
Scheme 6

Mononuclear rearrangements of heterocycles are very common and attract the attention of researchers by their easy occurrence and the possibility of obtaining reactive functionalized derivatives of other classes of heterocyclic compounds. In the series of 1,2,5-oxadiazoles, such rearrangements are being extensively investigated (Equation 6). Oximes, hydrazones, formamidines, and thioureas of the furazan series are known to be capable of undergoing base-catalyzed mononuclear rearrangements at sufficiently high temperatures <2004RCB1121>.



(6)

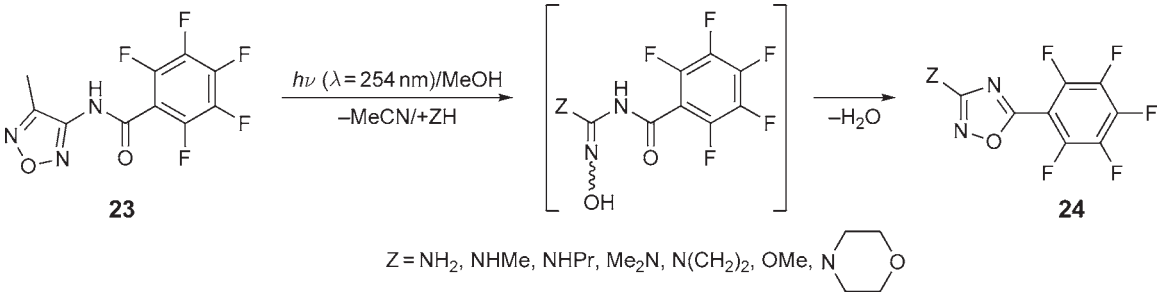
Thus, base-catalyzed rearrangements of one of the heterocycles of difurazanyltriazenes gave the corresponding 2-furazanyltetrazoles (**Scheme 7**) <2004RCB1121>.



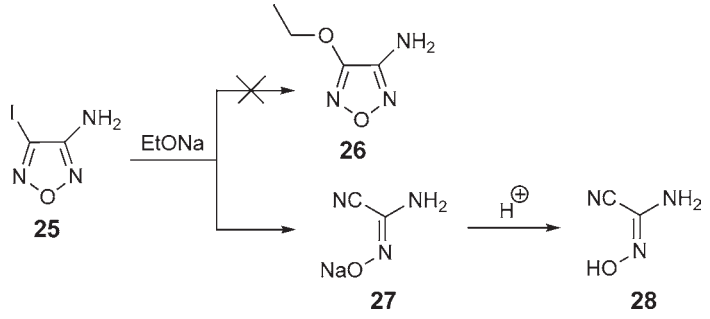
Scheme 7

The 1,2,5-oxadiazole ring can be rearranged into the 1,2,4-oxadiazole ring as illustrated by a photochemical reaction of 3-pentafluorobenzoylamino-4-methyl-1,2,5-oxadiazole **23** upon irradiation at 254 nm in methanol and in the presence of ammonia, primary or secondary aliphatic amines. This protocol produces 3-*Z*-substituted 5-pentafluorophenyl-1,2,4-oxadiazoles **24**. The photoreaction follows the fragmentation pattern of the furazan ring with the extrusion of acetonitrile and the formation of a counterpart fragment which is then captured by the nitrogen nucleophile ZH (**Scheme 8**). Using the same photochemical approach, the synthesis of the 3-methoxy-5-pentafluorophenyl-1,2,4-oxadiazole was also described <2001T5865>.

Iodofurazans react with nucleophilic reagents differently from other halo- and nitrofurazans. For instance, treatment of 3-amino-4-iodofurazan **25** with sodium ethoxide at room temperature did not yield the expected ethoxy derivative **26** but led to the ring-open product, that is, the sodium salt of α-amino-α-hydroxyimino- acetonitrile **27** (**Scheme 9**). Acidification of salt **27** gave cyano oxime **28** <2004RCB1124>.

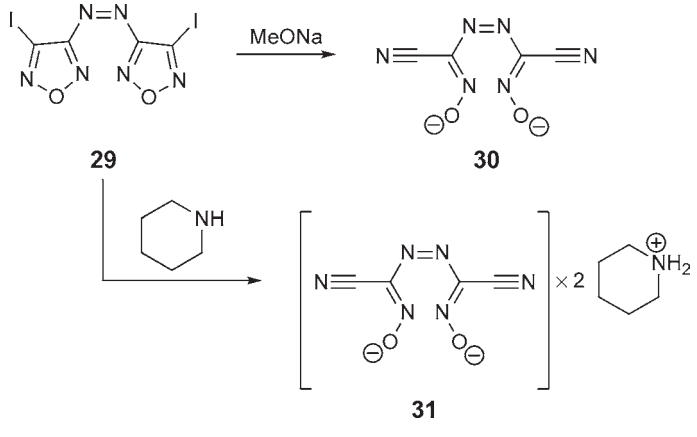


Scheme 8



Scheme 9

Compound **25** does not react with piperidine at room temperature; on heating, iodine is liberated. The more reactive diiodoazofurazan **29** easily reacts with both sodium alkoxides and piperidine. However, in both cases the furazan ring also undergoes opening to give the corresponding salts **30** and **31** (**Scheme 10**) <2004RCB1124>.



Scheme 10

The benzofurazans can be oxidized or form the quaternary salts. For example, phenantro-1,2,5-oxadiazine **32** was readily quarternized to *N*-methylazolium salt on being heated in dimethyl sulfate. Anion exchange with sodium perchlorate gave high yields of the phenanthroazolium perchlorate salts **33** (Equation 7) <1997J(P1)1047>.

(7)

32 **33**

5.05.4.2 Furoxans and Benzofuroxans (1,2,5-Oxadiazole Oxides and Benzo-1,2,5-Oxadiazole Oxides)

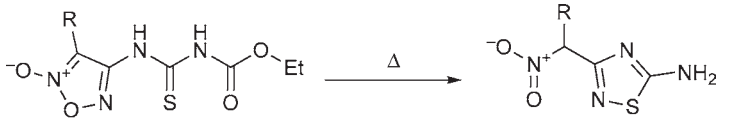
Furoxans and benzofuroxans undergo thermal and photochemical ring cleavage, reactions with nucleophiles, Boulton–Katritzky rearrangement, reduction and deoxygenation, ring transformation, etc. (see also Section 5.05.6.2).

5.05.4.2.1 Thermal ring cleavage

Upon short contact time flash vacuum thermolysis (FVT), compound **10** is cleaved almost quantitatively into the metastable cyanogen *N*-oxide (NC–CNO **11**; Equation (5) <2000J(P2)473>. The isolation and characterization of the trimers **12** and **13** of **11** was reported.

Thermal recyclization of the 3-diazenofuroxanyl unit to form the 4-nitro-1,2,3-triazole fragment has been found in noncondensed 1,2,5-oxadiazole 2-oxide derivatives (3,3′-azofuroxans) with acetamido substituents in the 4,4′-positions <1999MC17>.

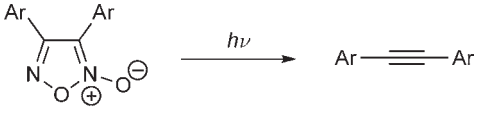
The thermally induced rearrangements in the furoxan series have also been found. In particular, the transformation of 3-R-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides into derivatives of 5-amino-3-(α-nitroalkyl)-1,2,4-thiadiazole and into (5-amino-1,2,4-thiadiazol-3-yl)nitroformaldehyde arylhydrazones has been reported (Equation 8) <2003MC188>.



(8)

R = Me, Ph, Ac
R = -N=NAr, Ar = 4-$MeOC_6H_4$, 2,4,6-$Me_3C_6H_2$

Diarylfuroxans were found to give diarylacetylenes upon irradiation at 254 nm (Equation 9, **Table 2**). Cyclobutaphenanthrenes were also obtained when reaction was carried out in the presence of alkenes (Equation 10). The acetylenic derivative is supposed to arise by loss of $(NO)_2$ from a diazete-*N*,*N*-dioxide. Unimolecular and collision-activated dissociation studies by tandem mass spectrometry also support the loss of $(NO)_2$ from diarylfuroxans molecular ions <1997T17407>.

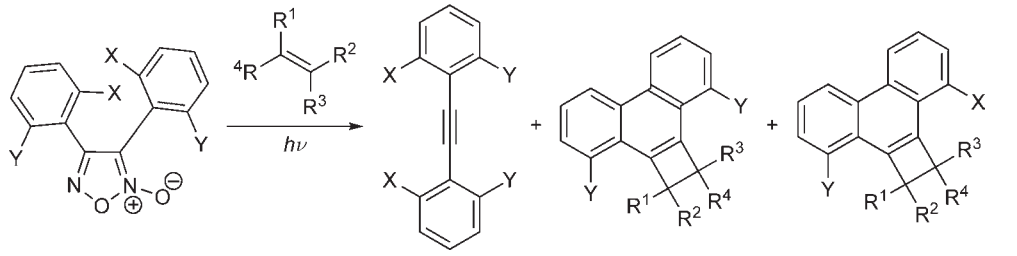


(9)

34a–c **35a–c**

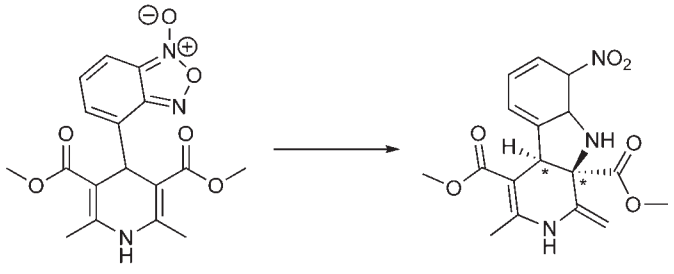
Table 2 Irradiation of furoxans **34a–c**

Furoxan **34**	*Conversion*	**35** (*Yields*)
34a (Ar = Ph)	75%	**35a** (4%)
34b (Ar = ClC_6H_4)	85%	**35b** (12%)
34c (Ar = 2,6-$Cl_2C_6H_3$)	95%	**35c** (18%)



(10)

Thermolysis of the benzofuroxan **36** under reflux conditions in xylene affords heterocycle **37** via cleavage of the 1,2,5-ring (Equation 11) <2001TL4507>.



(11)

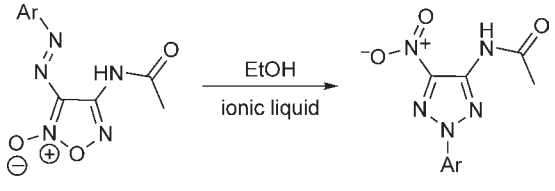
36 **37**

For thermal and photochemical reactions accompanied by ring cleavage, see Section 5.05.4.2.3.

5.05.4.2.2 Reaction with nucleophiles and reducing agents

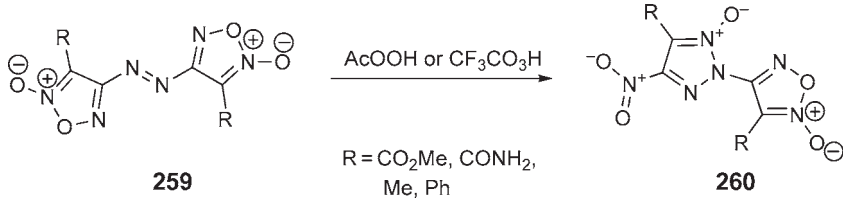
Derivatives of furoxan are promising reagents for the synthesis of various heterocyclic systems due to their easy preparation and a remarkable susceptibility to ring opening and recyclization under the action of nucleophiles. The structure of products depends on the character of the bond in the furoxan ring being broken. The most thoroughly studied are those reactions in which the C–C bond of the furoxan ring remains intact; among them the following reactions should be mentioned: (1) the so-called Beirut reaction, in the course of which the furoxan ring in benzofuroxans transforms under the action of sufficiently strong bases into five- and six-membered heterocycles (imidazoline or pyrazine); (2) the Boulton–Katritzky rearrangement <1999JA6700>; (3) recyclization of the furoxan ring into 1,2,3-triazole-1-oxide <B-1996MI104>, etc.

It was shown that furoxans can be transformed to 1,2,3-triazoles. Thus, 4-acetylamino-3-arylazo-1,2,5-oxadiazole 2-oxides undergo two successive (cascade) mononuclear heterocyclic rearrangements in an aqueous basic medium with the formation of 4-acetylamino-2-aryl-5-nitro-2*H*-1,2,3-triazoles (Equation 12) <2001MC230>, or 3,3′-disubstituted 4,4′-azo-1,2,5-oxadiazole 2-oxides were found to undergo a rearrangement into 2-(furoxan-4-yl)-4-nitro-2*H*-1,2,3-triazole 1-oxides on heating in pertrifluoroacetic or peracetic acids (Equation 13) <2003MC272>.



(12)

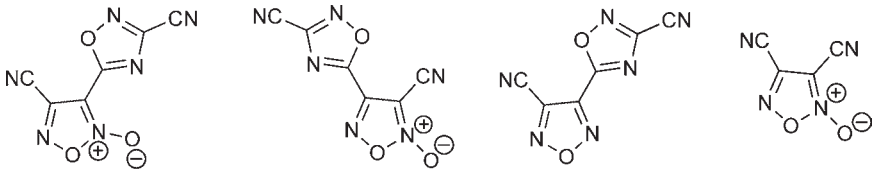
257 **258**



(13)

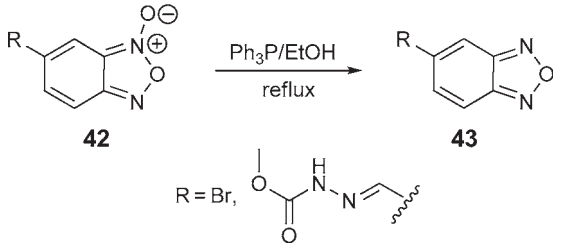
259 **260**

The reduction of furoxans to give furazans is also a well-known process. For example, the triethylphosphite reduction of compounds **38** and **39** affords the 1,2,4-oxadiazolyl-1,2,5-oxadiazole **40**. Deoxygenation of the *N*-oxide moieties in furoxans **38**, **39**, and **41** also takes place under conditions of mass spectrometry <2000J(P2)473>.



38 **39** **40** **41**

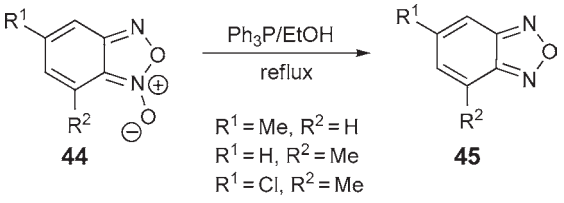
The deoxygenation of the *N*-oxides **42** and **44** with triphenylphosphine or triethylphosphite in boiling EtOH gives corresponding benzofurazans **43** and **45** (Equations 14 and 15) <2000JFA2995, 2002BML233, 2003BMC899, 2003OPD436>.



42 **43**

R = Br,

(14)

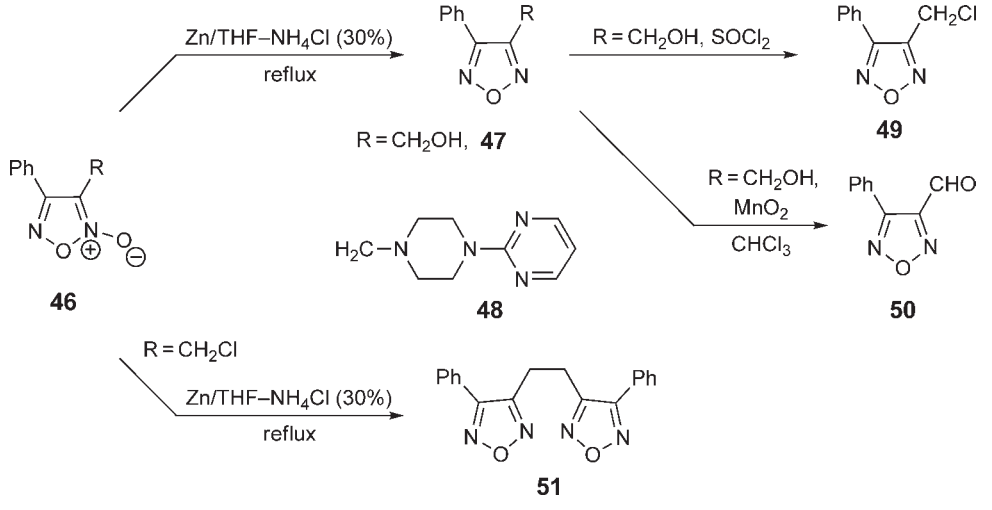


44 **45**

$R^1 = Me, R^2 = H$
$R^1 = H, R^2 = Me$
$R^1 = Cl, R^2 = Me$

(15)

Derivatives **47–51** were prepared from the *N*-oxide **46** using zinc as the deoxygenating agent (**Scheme 11**). The use of Zn in NH_4Cl solution led to the deoxy derivatives **47** and **48** in moderate yields. The reduction was clearly observed by NMR HETCOR experiments (HMQC and HMBC). When the reduction of the derivative **46** ($R = CH_2Cl$) was carried out under the same conditions, compound **51** was generated via a Zn-promoted reductive dimerization process <2001EJM771>.



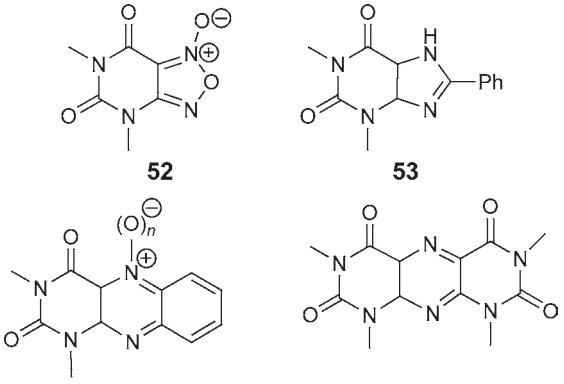
46 **47** **48** **49** **50** **51**

Scheme 11

5.05.4.2.3 Heterocyclic ring transformations

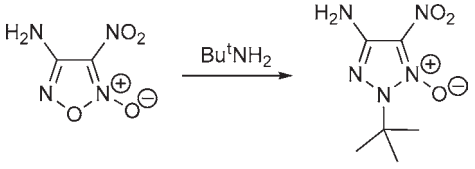
5.05.4.2.3(i) Rearrangements of furoxans

Rearrangement of furoxans leads to the formation of new heterocyclic systems derivatives of triazoles, diazoles, isoxazoles, and pyrimidinones. For example, on the basis of the experimental results using labeled compound **52**-$^{15}N_1$, the formation of 8-phenyltheophylline **53**, the 1,3-dimethylalloxazines (**54**: $n = 0, 1$), and 1,3,7,9-tetramethyl-1*H*,9*H*-pyrimido[5,4-*g*]-pteridine-2,4,6,8-tetraone **55** in the thermal reaction of the *N*-oxide **52** with benzylamine, aniline, or piperidine and the generation of NO or NO-related species in the reaction with *N*-acetylcysteamine were reasonably explained by considering the initial attack of the employed nucleophiles on the 3a-position of compound **52** <2000JOC6670>.



52 **53** **54** **55**

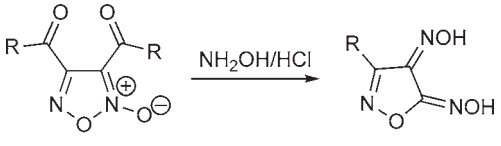
3-Amino-4-nitrofuroxane **56** was transformed to 4-amino-2-*tert*-butyl-5-nitro-1,2,3-triazole 1-oxide **57** by reaction with *tert*-butylamine (Equation 16) <2003CHE608>.



(16)

56 **57**

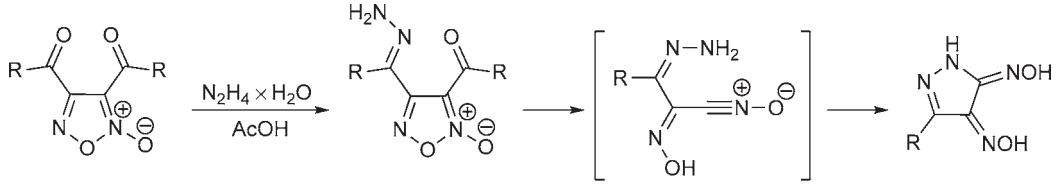
Interaction of 3,4-diacylfuroxans **58** with hydroxylamine hydrochloride results in the formation of substituted 4,5-bis(hydroximino)-4,5-dihydroisoxazoles **59** (Equation 17) <2000HCO35, 2000RJO1745, 2003T1059>.



(17)

58 R = Me or Ar **59**

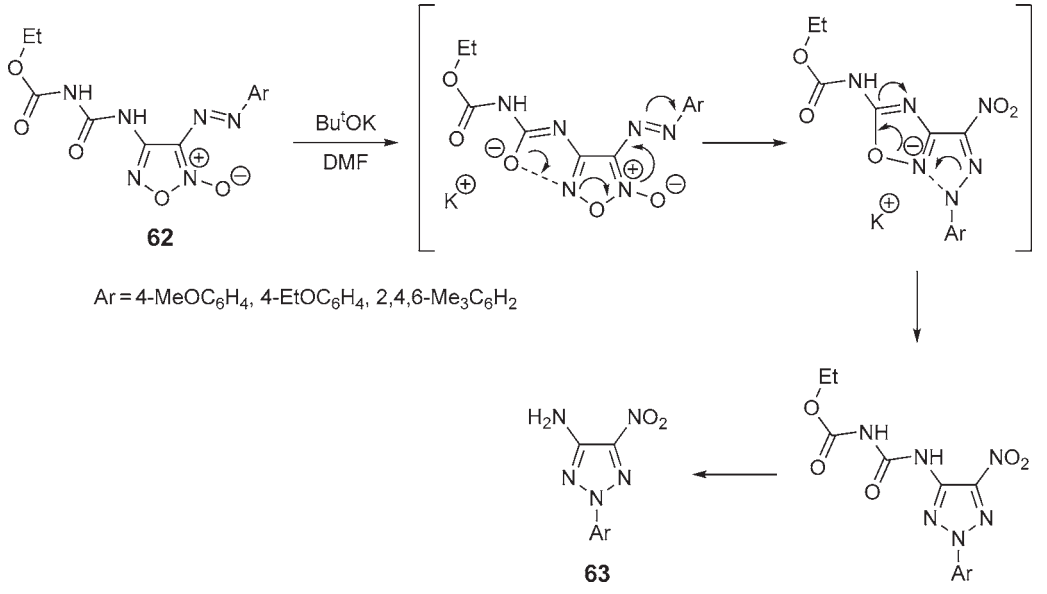
However, the reaction of 3,4-diacylfuroxans **60** with hydrazine hydrate in acetic acid affords 3-[4,5-bis(hydroximino)-4,5-dihydro-1*H*-pyrazol-3-yl]-4-methylfurazans **61** (**Scheme 12**) <2003T1059>.



60 R = 4-methylfurazan-3yl, 3-methylfuroxan-4-yl **61**

Scheme 12

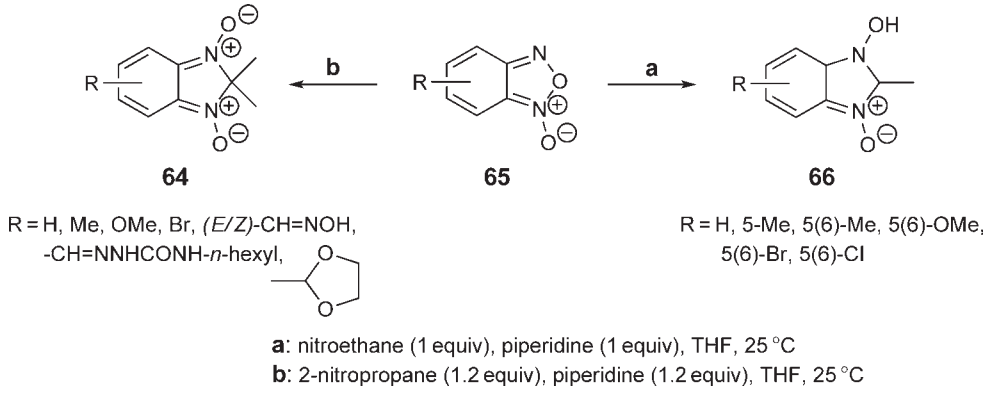
3-Arylazo-4-(3-ethoxycarbonylureido)furoxans **62**, which were synthesized by the reactions of 4-amino-3-arylazofuroxans with ethoxycarbonyl isocyanate, were subjected to cascade rearrangements under the action of potassium *tert*-butoxide in dimethylformamide or by heating in dimethyl sulfoxide to form 4-amino-2-aryl-5-nitro-2*H*-1,2,3-triazoles **63** (**Scheme 13**) <2001MC230, 2003RCB1829>.



Scheme 13

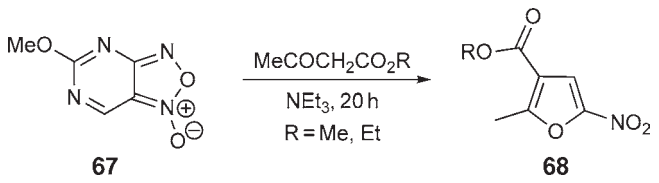
5.05.4.2.3(ii) Rearrangements of benzofuroxans

Benzofuroxans **65** can be transformed into the imidazol-*N*-oxides **66** or 2,2-disubstituted imidazole-*N*,*N*-dioxides **64** (**Scheme 14**) <2004AP259, 2006JME3215>.



Scheme 14

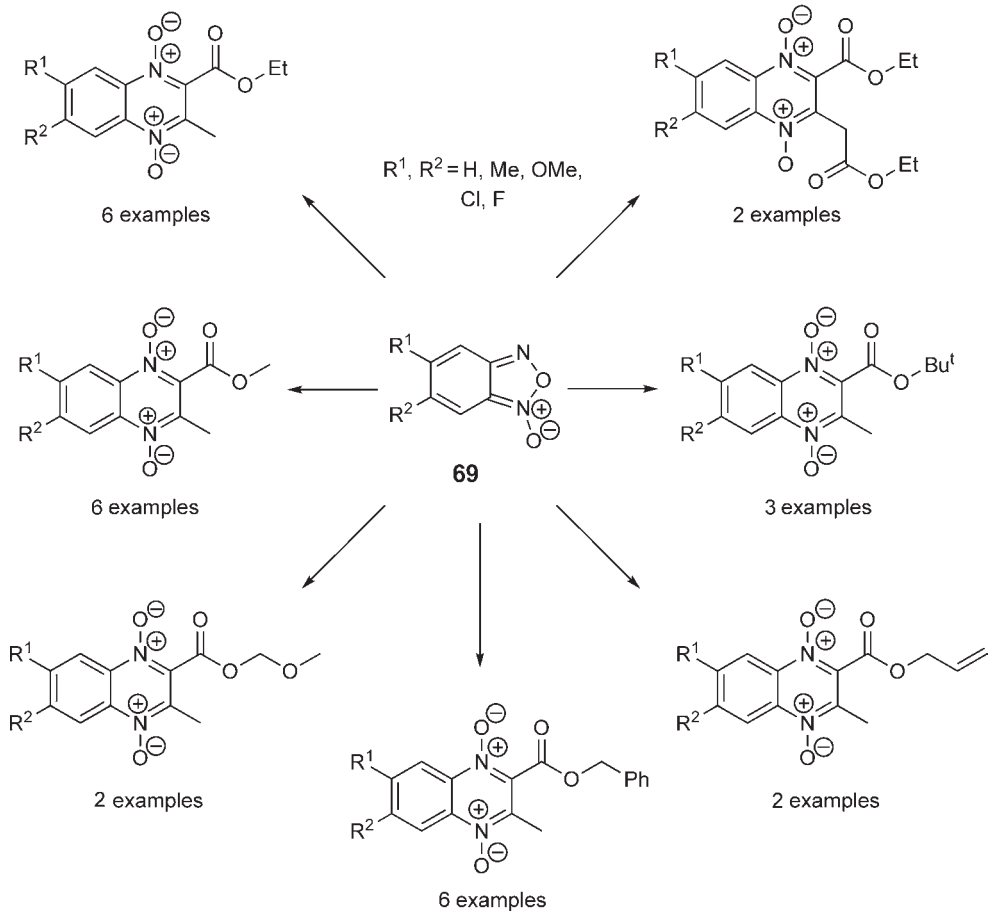
Another ring transformation was encountered in the reactions of 5-methoxyfuroxano[3,4-*d*]pyrimidine **67** with methyl or ethyl acetoacetate in methylene chloride in the presence of triethylamine. This process results in the formation of 2-methyl-5-nitro-3-furancarboxylic esters **68** (Equation 18) <1997CHE879>.



(18)

5.05.4.2.3(iii) Synthesis of quinoxalines and analogs

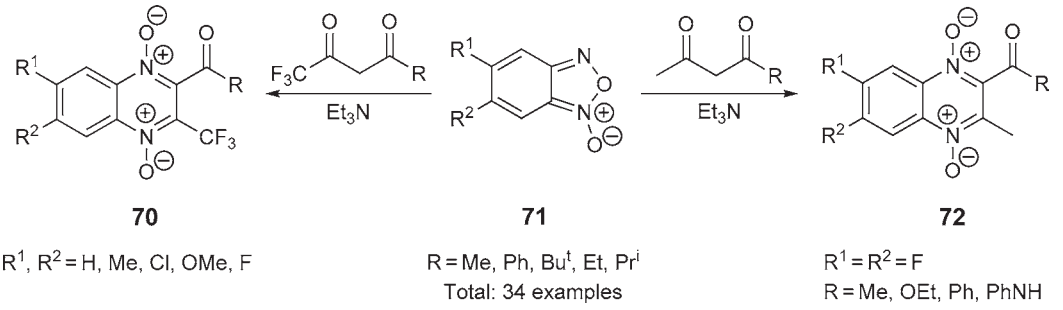
The formation of quinoxaline heterocyclic systems is a well-known transformation of benzofuroxanes, which occurs in the presence of β–dicarbonyl compounds <2001RJO891, 2003BMC2149, 2003EJM791, 2005JME2019>. For example, the synthesis of quinoxaline 1,4-di-*N*-oxides was carried out by reaction of the appropriate benzofuroxane **69** with the corresponding β-ketoester, using triethylamine as the catalyst (**Scheme 15**) <2005JME2019>.



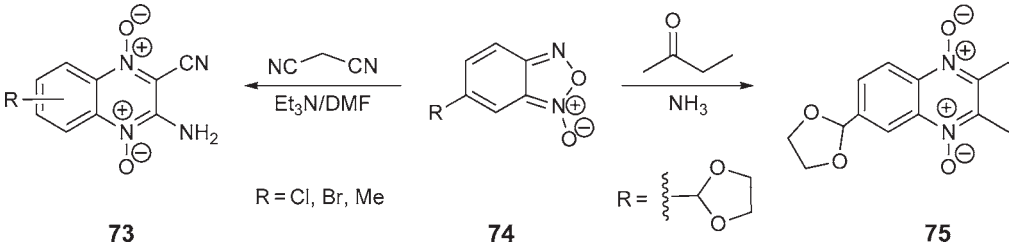
Scheme 15

A series of quinoxaline oxides **70** and **72** was obtained by the classical Beirut reaction of the substituted benzofuroxanes **71** and the 1,3-diketones, β-ketoesters, amides, or 1-(alkyl/phenyl)-4,4,4-trifluoromethyl-β-diacetones (**Scheme 16**) <1999CHE459, 2004BMC3711>.

The quinoxalines **73** and **75** were also prepared with excellent yields by reaction of the corresponding benzofuroxans **74** with malononitrile or butanone (**Scheme 17**) <1999JME1941, 2000JFA2995, 2005EJM473>.

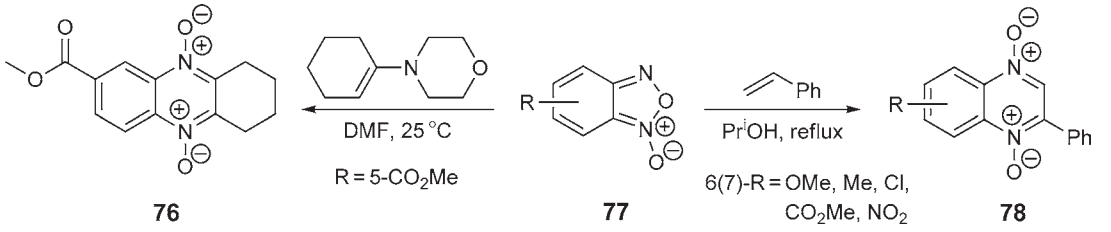


Scheme 16



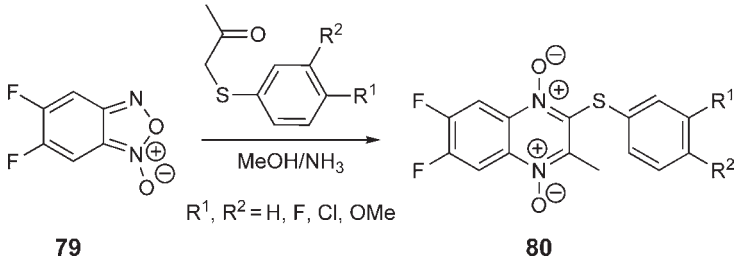
Scheme 17

Quinoxalines **76** and **78** can be synthesized by the reaction of benzofuroxanes **77** with 4-cyclohexenylmorpholine <2001SC2329> or styrene <2001RJO892>, respectively (**Scheme 18**).



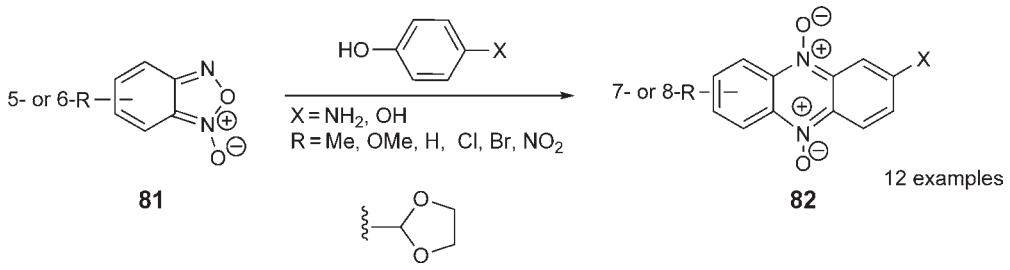
Scheme 18

Nucleophilic attack of 5,6-difluorobenzofuroxane **79** by acetonylphenyl sulfides in methanolic ammonia afforded the compounds **80** in moderate yields (Equation 19) <2004EJM195>.



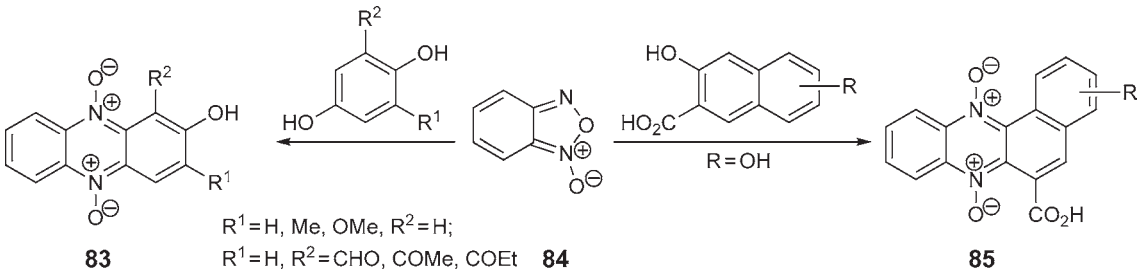
(19)

The reaction of benzofuroxans with phenols produced substituted phenazines; for example, benzofuroxan **81** with phenols gave the corresponding 7- and 8-substituted-2-aminophenazine and 7- and 8-substituted-2-hydroxyphenazine 5,10-dioxides **82** (Equation 20) <2005JME21>.



(20)

Benzofuroxan **84** forms substituted phenazine 5,10-dioxides **83** and **85** with the corresponding dihydroxybenzenes <2000H(53)2151> or 2-hydroxynaphthoic-3-acids in basic condition in good yields (**Scheme 19**) <2002BML415>.



Scheme 19

5.05.5 Reactivity of Substituents Attached to Ring Carbon Atoms

Numerous transformations of functional groups attached to 1,2,3-oxadiazoles have been reported in the last 10 years. The reactivity of substituents attached to ring carbon atoms was thoroughly discussed in CHEC(1984) and CHEC-II(1996).

5.05.5.1 Monocyclic Furazans and Furoxans

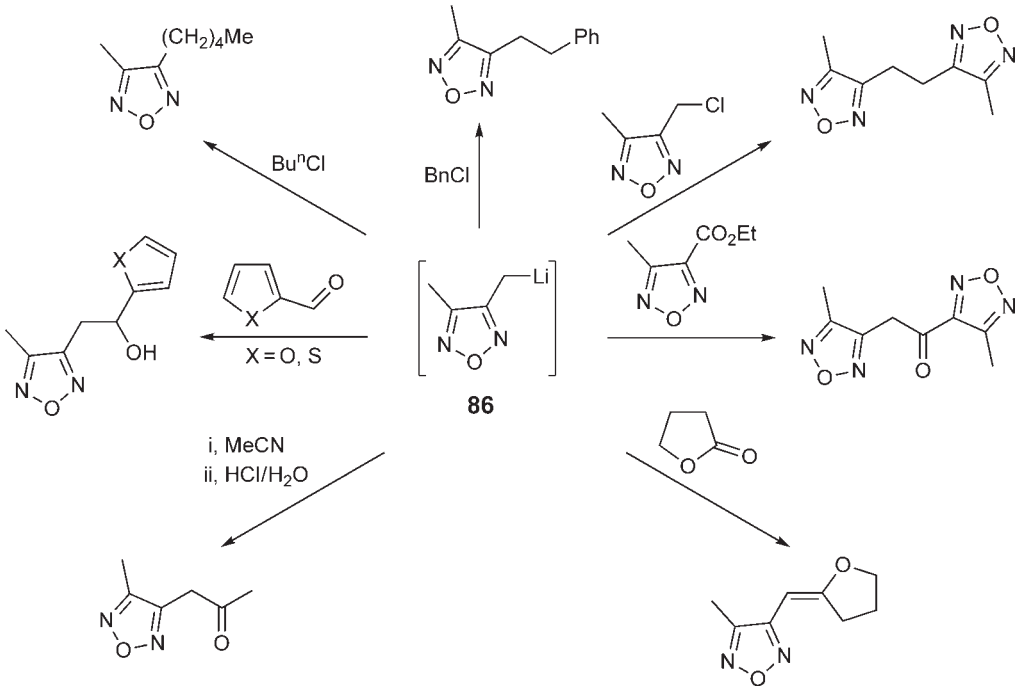
5.05.5.1.1 Alkyl and aryl furazans and furoxans

The lithiation of alkyl furazans has been used for the preparation of substituted furazans. For example, lithiation of 3,4-dimethylfurazan with butyllithium followed by treatment of the resulting intermediate **86** with different electrophilic reagents at −50 °C afforded substituted furazans in 65–85% yields (**Scheme 20**) <2003RCB679>.

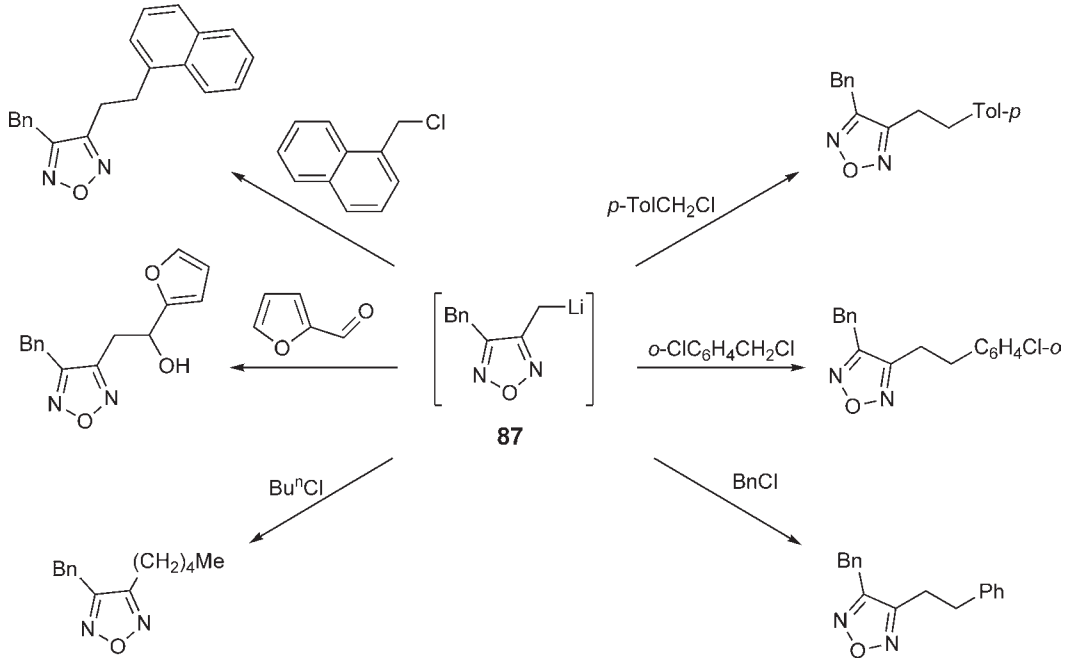
If 3,4-substituted furazans have two different alkyl substituents, the lithiation occurs exclusively at a methyl group. The treatment of intermediate **87** with electrophiles affords a series of products (**Scheme 21**) <2003RCB679>.

The reactions of (lithiomethyl)furazans **88** with chlorosilanes were investigated and a number of silyl derivatives of methylfurazans were prepared (**Scheme 22**). It was shown that the methyl group attached to the furazan ring containing a (trimethylsilyl)methyl fragment can be lithiated to give product **89** and further modified by treatment with C-electrophiles (**Scheme 22**). It was found that silyl derivatives of methylfurazans can react with strong electrophilic reagents with cleavage of the C–Si bond <2003RCB2017>.

An interesting example of intramolecular cyclization has been reported <2004TL3895>. 3-(Buta-1,3-dienyl)-4-methyl-1,2,5-oxadiazoles **90** were synthesized starting from base-induced reaction of 3,4-dimethyl-1,2,5-oxadiazole with α,β-unsaturated carbonyl compounds. The obtained oxadiazoles **90** bearing a butadienyl moiety and a methyl at the adjacent position underwent intramolecular cyclization by the action of lithium diisopropylamide (LDA) to give the corresponding oxadiazoles fused with a seven-membered ring **91** in moderate to high yields (**Scheme 23**).

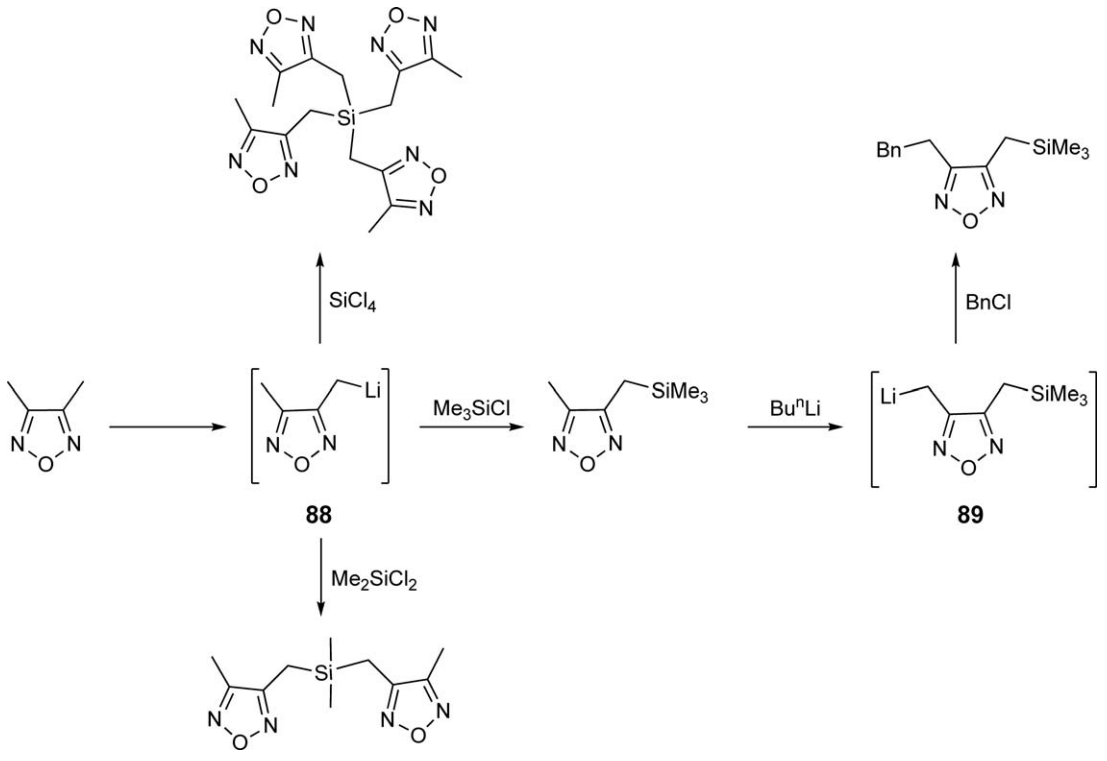


Scheme 20

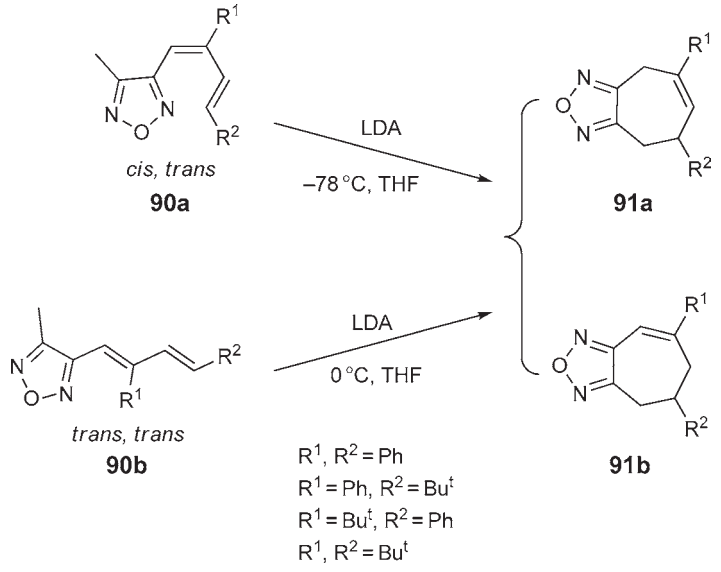


Scheme 21

Halogenalkyl-substituted furazanes were also used for functionalization of the compounds. Thus, 3,4-bis(chloromethyl)-1,2,5-oxadiazole **92** and *2(R)*-[1*(S)*-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-*3(S)*-phenylmorpholine **93** gave *2(R)*-[1*(R)*-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-4-(4-dimethylaminomethyl-1,2,5-oxadiazol-3-yl)methyl-*3(S)*-phenylmorpholine **94** (Equation 21) <1996WO9629328>.



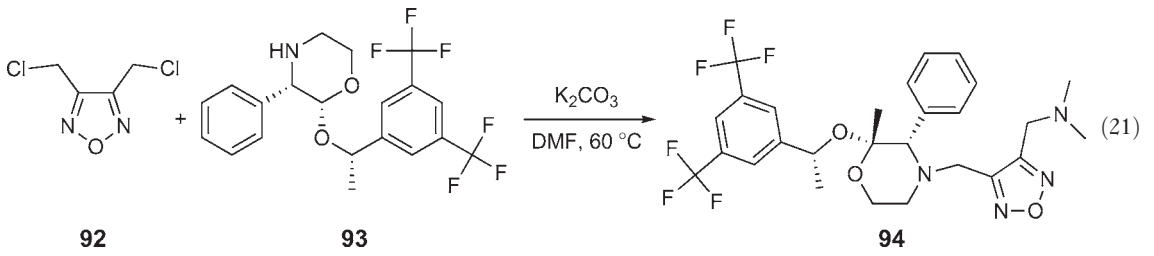
Scheme 22



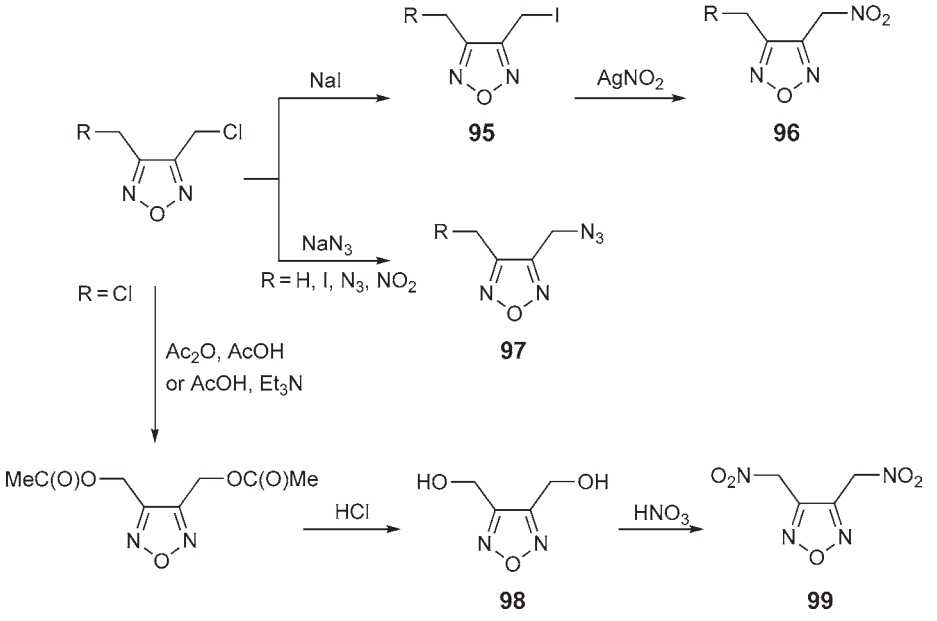
Scheme 23

A series of new 3,4-substituted furazans **95–99** were synthesized by transformation of the functional groups in halogenomethyl and biacyl derivatives of furazan (**Scheme 24**) <2000CHE1091>.

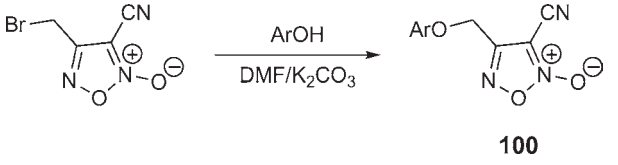
The nucleophilic substitution of the bromine in 4-(bromomethyl)-3-cyanofuroxan by phenols in DMF in the presence of potassium carbonate gives the corresponding phenol ethers **100** (Equation 22) <2003JME3762, 2004JME2688>.



(21)



Scheme 24



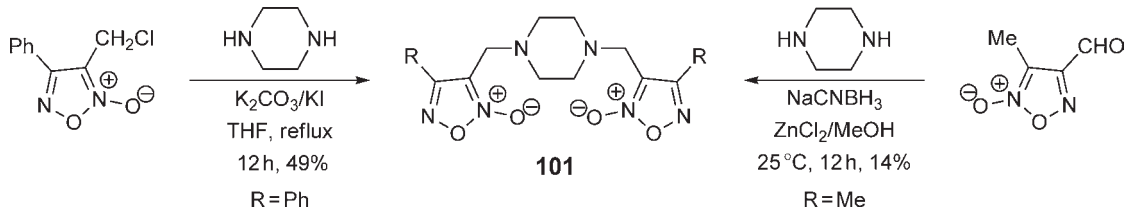
(22)

The bis(1,2,5-oxadiazole *N*-oxide) derivatives **101** with oxadiazole rings linked to piperazine residue were synthesized via modification of chloromethyl or formyl group of furoxans (**Scheme 25**) <2000AP387>.

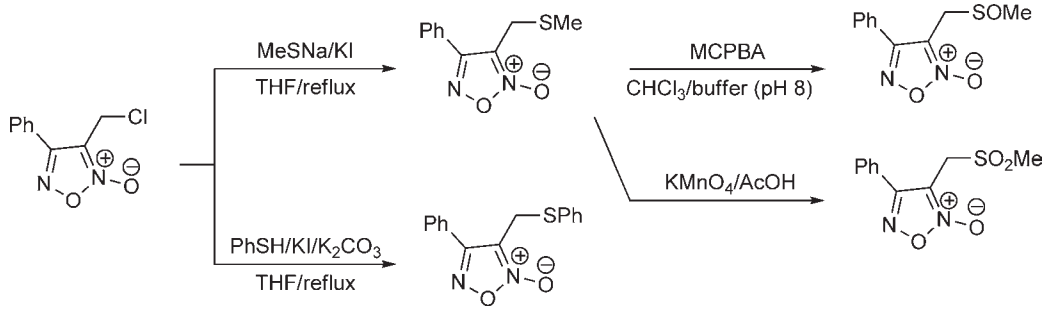
The furoxans with functionally substituted alkyl groups in the 3,4-position have proved to be useful for the synthesis of thiosubstituted furoxanes (**Schemes 26** and **27**), which can be oxidized to sulfonyl derivatives (**Scheme 26**) <2001EJM771>.

3-Mercaptomethyl-4-phenyl-1,2,5-oxadiazol *N*-2-oxide **102** and 3-(4-mercaptophenylmethylidenhydrazinocarbonyloxymethyl)-4-phenyl-1,2,5-oxadiazol *N*-2-oxide **104** were successfully synthesized from 3-chloromethyl- or 3-hydroxymethyl-4-phenyl-1,2,5-oxadiazole *N*-2-oxide **103** (**Scheme 27**) <2006AP59>.

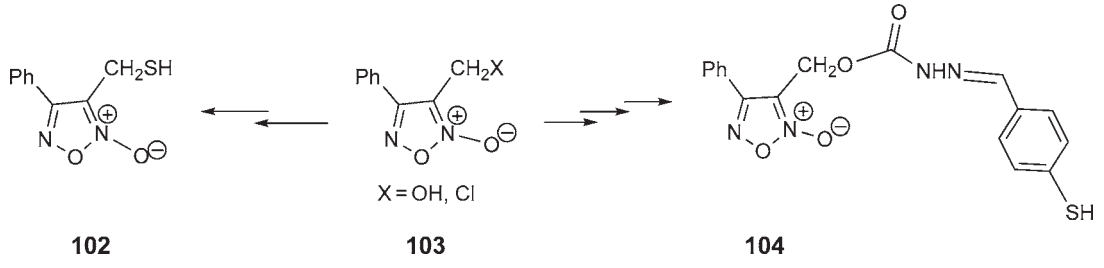
Oxymethyl groups on furaxans can be transformed into an ester fragment with acetic acid (Equation 23).



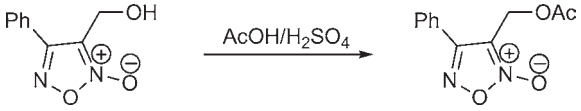
Scheme 25



Scheme 26



Scheme 27

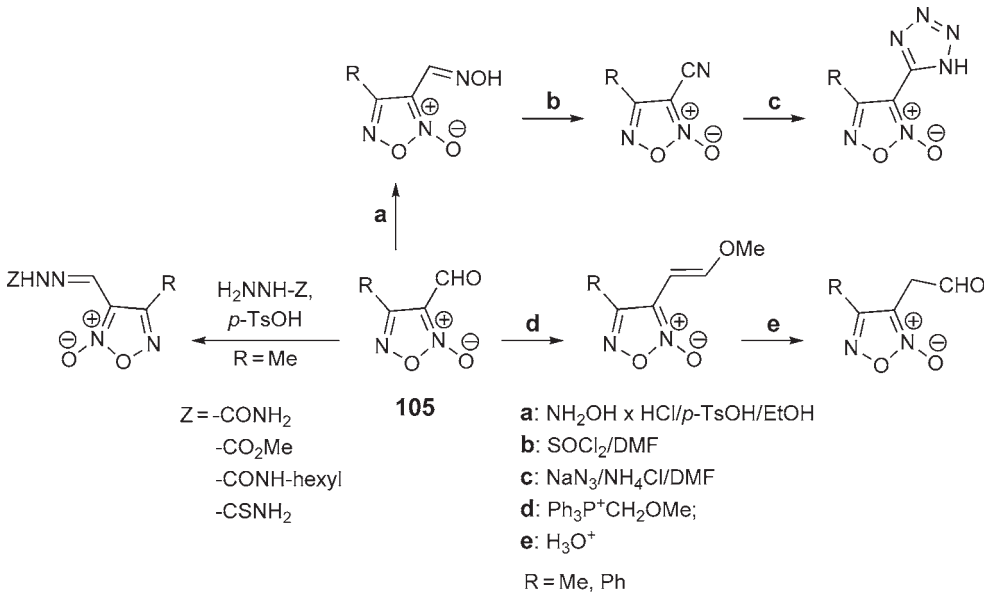


(23)

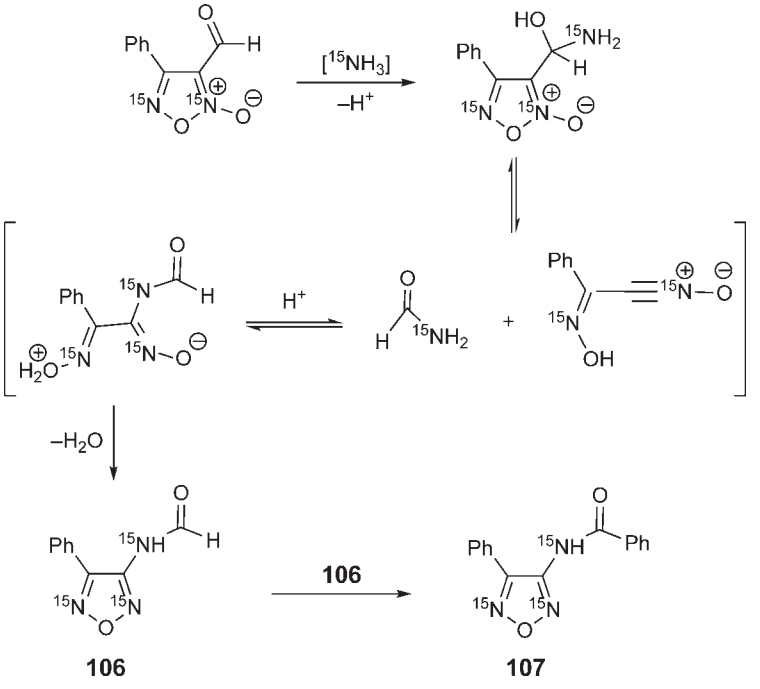
5.05.5.1.2 Acyl- and formyl-substituted furazans and furoxans

The reaction of 3,4-diacyl-1,2,5-oxadiazole 2-oxides (furoxans) with activated nitriles in ionic liquids and in ethanol unexpectedly resulted in 3-acyl-4-acylamino-1,2,5-oxadiazoles (furazans) <2003MC230>. 3-Formyl-4-phenyl-1,2,5-oxadiazole *N*-oxide **105** is a good precursor for the synthesis of functional substituted furoxans (**Scheme 28**) <1999JME1941, 2000MOL520, 2000JFA2995>.

Although the Capdevielle reaction for one-pot conversion of aldehydes to nitriles is a very convenient and widely applicable synthetic procedure, 3-substituted furoxans appear to be susceptible to rearrangement when substitutions with amine nucleophiles are attempted, even under relatively mild conditions (**Scheme 29**) <1999JOC8748>. The formation of the final product **107** in this reaction was explained via phenyl abstraction by carbamoyl radical cation from the second molecule of intermediate product **106** <1999JOC8748>.



Scheme 28



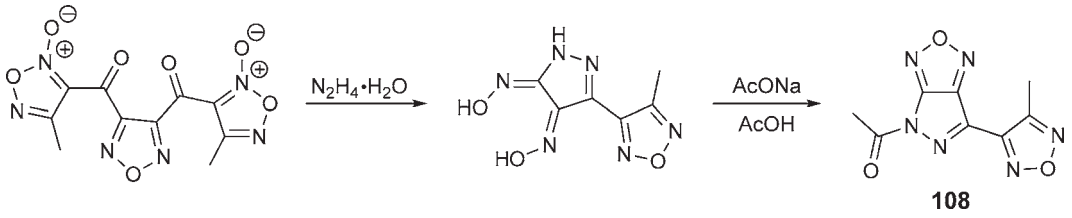
Scheme 29

Reaction of 3,4-bis(4-methyl-3-furazanylcarbonyl)furoxan with hydrazine hydrate in AcOH gave 3-[4,5-bis(hydroxyimino)-1*H*-pyrazol-3-yl]-4-methyl-1,2,5-oxadiazole which on treatment with AcONa in AcOH gave 4-acetyl-6-(4-methyl-1,2,5-oxadiazol-3-yl)pyrazolo[3,4-*c*][1,2,5]oxadiazole **108** (**Scheme 30**) <2000RJO758>.

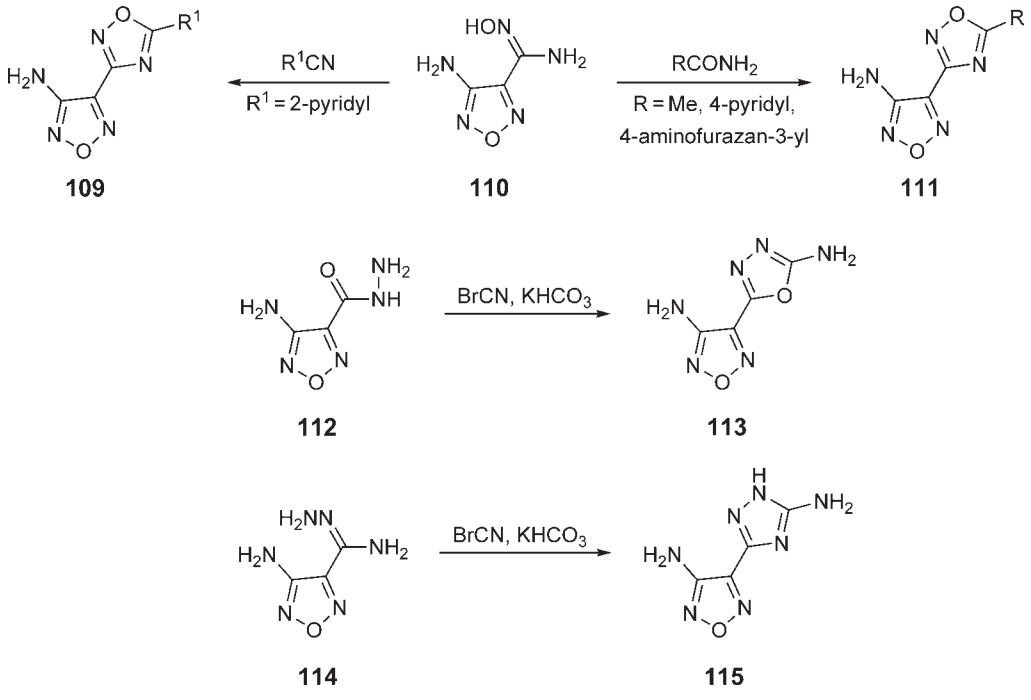
5.05.5.1.3 Furazan- and furoxan-carboxylic acids and their derivatives

Furazan- and furoxan-carboxylic acids are unstable compounds (see CHEC-II(1996); Section 4.05.7.1.3), but their ester and nitrogen derivatives are readily accessible and can be used for subsequent transformations. Thus,

3-aminofurazan-4-carboxamide oxime **110**, 3-aminofurazan-4-carbohydrazide **112**, and 3-minofurazan-4-carboxamidehydrazone **114** were transformed to the 3-aminofurazans **109**, **111**, **113**, and **115** containing 1,2,4-oxadiazole, 1,3,4-oxadiazole, or 1,2,4-triazole substituents in the 4-position (**Scheme 31**) <2002RJO1351>.



Scheme 30



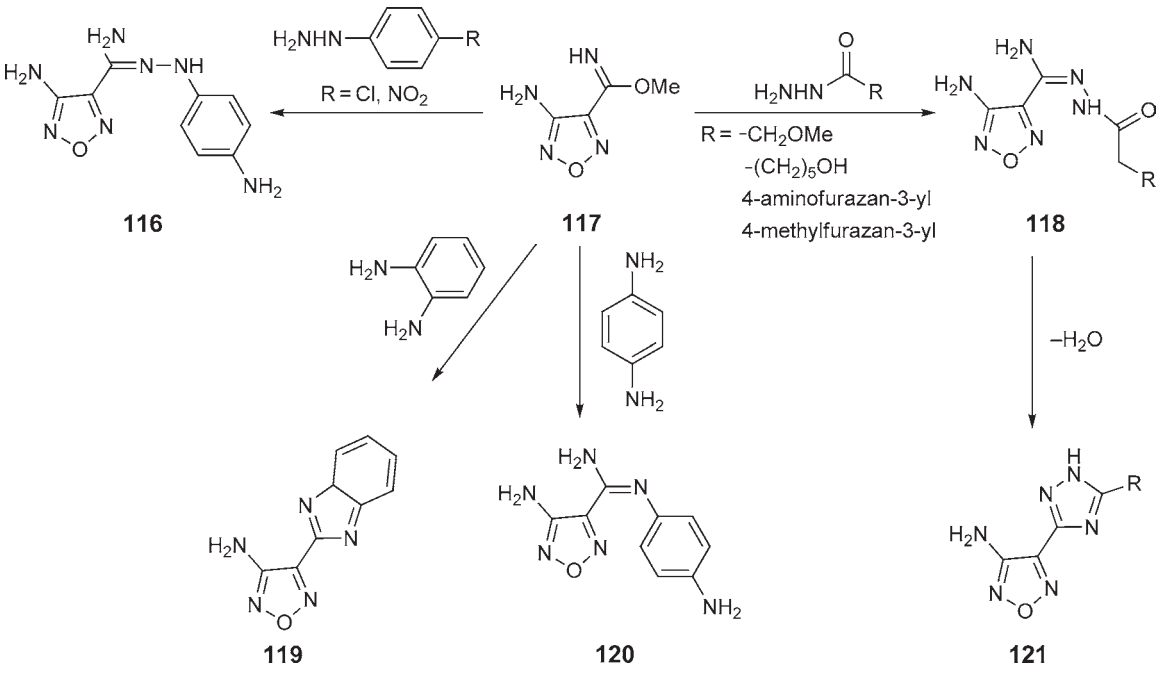
Scheme 31

Methyl 4-aminofurazan-3-carboximidate **117** reacts with aromatic amines and hydrazines to give the corresponding amidines **119**, **120**, and amidrazones **116**, respectively (**Scheme 32**). The reaction of **117** with acylhydrazines gives *N*-2-acyl-4-aminofurazan-3-carbohydrazides **118**, which then undergo thermal intramolecular cyclization with formation of 3-amino-4-(1,2,4-triazol-3-yl)furazan derivatives **121** containing various substituents in position 5 of the triazole ring (**Scheme 32**) <2001RJO717>.

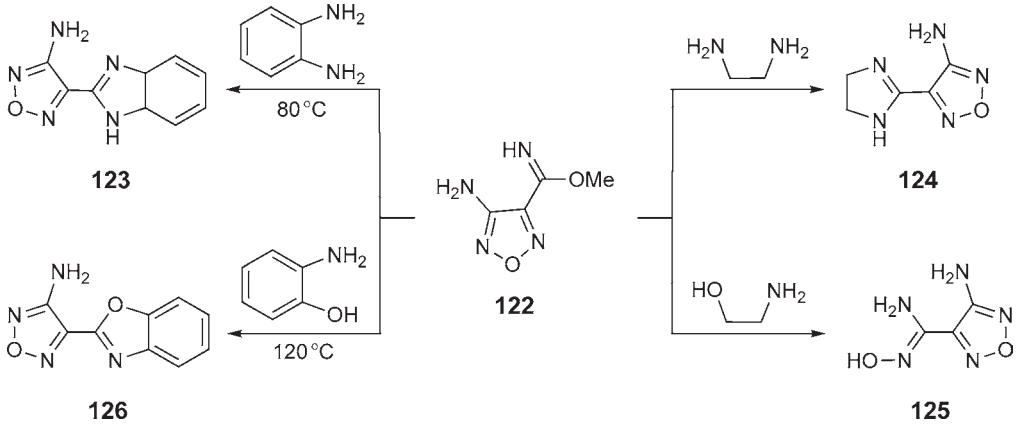
Reactions of 4-aminofurazan-3-carboxylic acid iminoester **122** with *o*-aminophenol, phenylenediamine, ethylenediamine, and aminoethanol give compounds **123–126** (**Scheme 33**) <2002RJO872>.

The nitration of oximes **130** <1997RJO1760> and dioximes **127** <2000CHE1091> with nitric acid gives corresponding geminal furazan dinitro derivatives **129** and **131** (**Scheme 34**).

Diazotization of 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl chloride **132** gives 4-[chloro(hydroxyimino)-methyl]-1,2,5-oxadiazole-3-diazonium salt **133** (**Scheme 35**). Treatment of the latter with NaN_3 afforded 4-azido-1,2,5-oxadiazole-3-carbohydroximoyl chloride **134** and the reaction with $NaNO_2$ yielded 2-cyano-2-hydroxyiminoaceto-hydroximoyl chloride **135**. By oxidation of 4-amino-1,2,5-oxadiazole-3-carbohydroximoyl azide **136**



Scheme 32

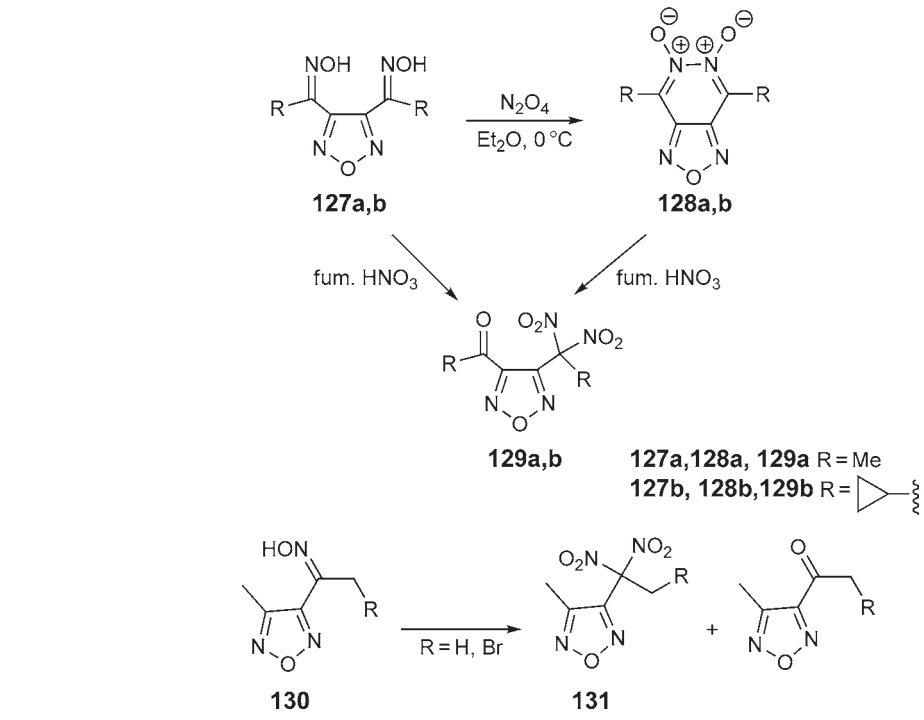


Scheme 33

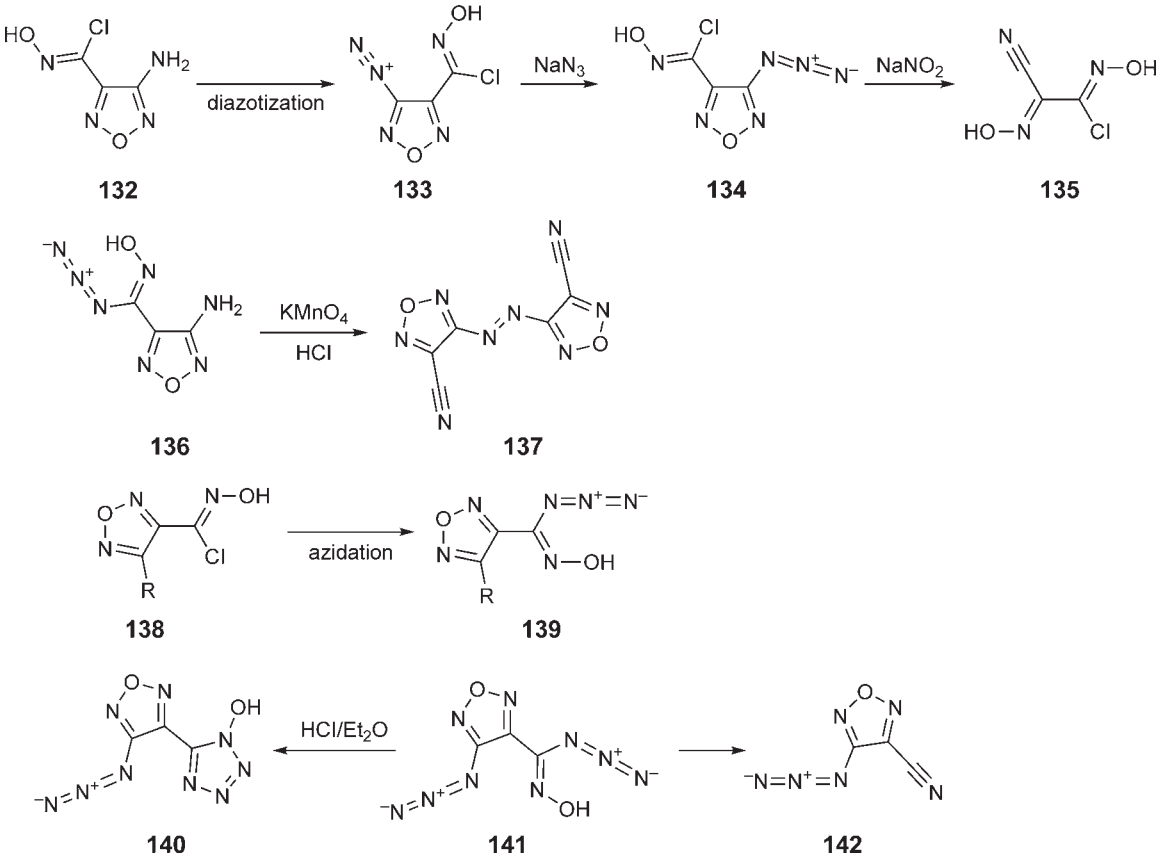
with $KMnO_4$ in hydrochloric acid 4,4′-dicyano-3,3′-azobis(1,2,5-oxadiazole) **137** was obtained (**Scheme 35**). Azidation of 1,2,5-oxadiazole-3-hydroximoyl chlorides **138** resulted in the formation of the corresponding 1,2,5-oxadiazole-3-carbohydroximoyl azides **139**. Decomposition of 4-azido-1,2,5-oxadiazole-3-carbohydroximoyl azide **141** gives 4-azido-1,2,5-oxadiazole-3-carbonitrile **142**; treatment of **141** with gaseous hydrogen chloride in ether afforded 1-hydroxy-5-(4-azido-1,2,5-oxadiazole-3-yl)tetrazole **140** which was converted into the corresponding acetate by reaction with acetic anhydride (**Scheme 35**) <2001RJO1638>.

4-Amino-3-azidocarbonylfuroxan **143** can be transformed to the *N*-alkylamide derivatives **144** of 4-amino-3-furoxancarboxylic acids and their oxidation products **145** (**Scheme 36**) <2003FES677>.

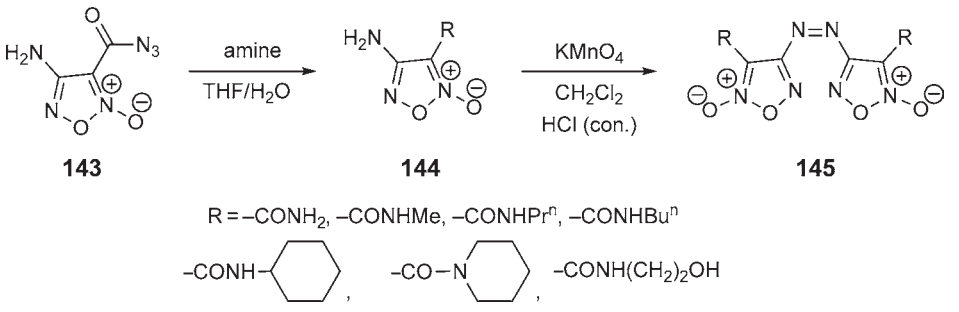
A series of 4-phenyl-1,4-dihydropyridines **146** substituted at the *ortho*- and *meta*-positions of the phenyl ring with NO-donating furoxan moieties and their non-NO-releasing furazan analogs were synthesized by a multistep protocol (**Scheme 37**) <1998JME5393>.



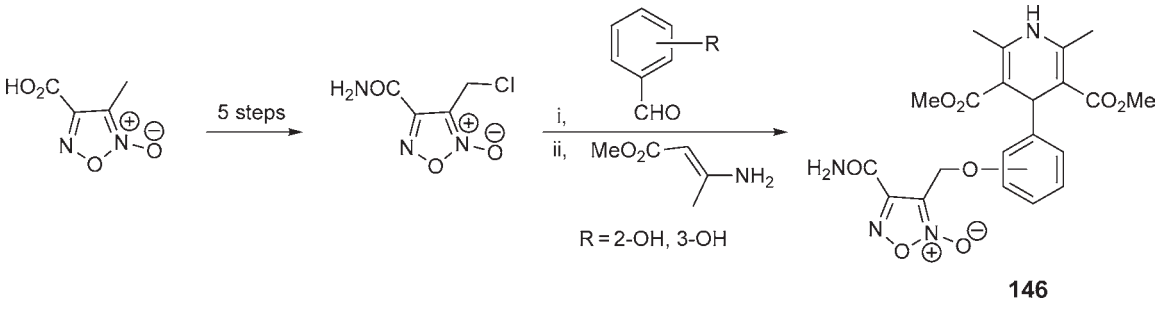
Scheme 34



Scheme 35



Scheme 36



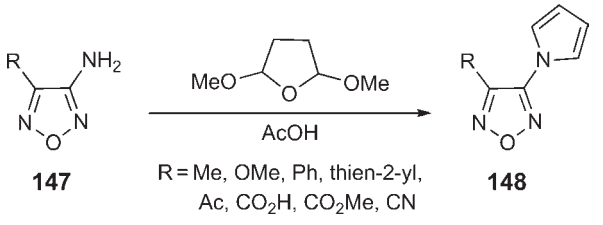
Scheme 37

5.05.5.1.4 Amino- and nitrofurazans and furoxans and their derivatives

The amino- and nitro-substituted furazans and furoxans have been studied in detail because they are useful precursors for the synthesis of new derivatives and, moreover, they can be used as starting materials for the preparation of new heterocyclic systems.

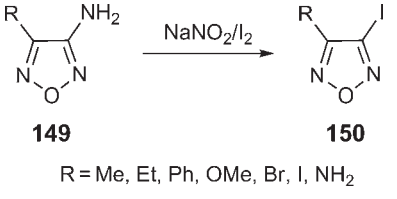
5.05.5.1.4(i) Aminofurazans

Transformation of the amino group of aminofurazans **147** leads to new derivatives of furazans. For example, 3-amino-4-R-substituted furazans containing both donor and acceptor substituents react easily with dimethoxytetrahydrofuran in boiling acetic acid over a short period of time to give the 3-R-substituted 4-(pyrrol-1-yl)furazans **148** in satisfactory yields (Equation 24) <2003RCB1413>.



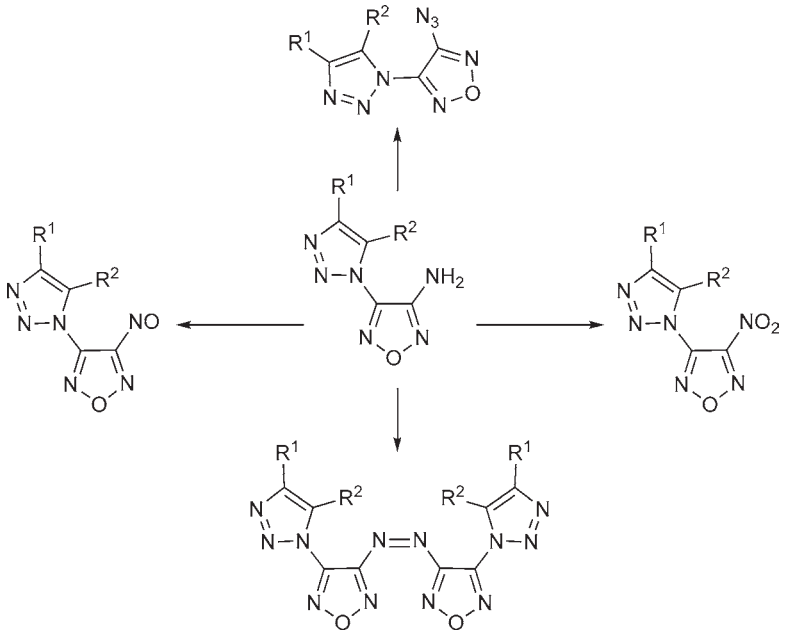
(24)

A synthetic route for the convenient preparation of the 4-substituted-3-iodofurazans **150** has been developed. The approach is accomplished by one-pot diazotization–iodination reaction of the corresponding aminofurazans **149** (Equation 25) <2004HAC199>.



(25)

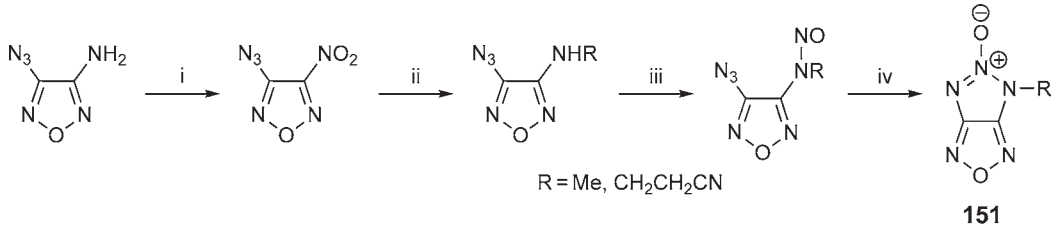
Nitro-, nitroso-, and azo-1,2,5-oxadiazoles with 4-R^1-5-R^2-1,2,3-triazol-1-yl substituents were synthesized by oxidation of amino-(1,2,3-triazol-1-yl)-1,2,5-oxadiazoles (aminotriazolylfurazans). Depending on the nature of the substituents and the reagent, triazolylfurazans can undergo destruction to give amino-R-substituted furazans (R=NO_2, N_3, aminofurazanylazo), the amino group being formed from the triazole ring (**Scheme 38**) <2005RCB1915>.



Scheme 38

The reactivity of amino(triazolyl)furazans in the oxidation and diazotization followed by treatment of the diazonium salt with sodium azide was found to depend appreciably on both the nature of the substituent in the triazole ring and the nature of the reagent. The reductive condensation of 4-nitrofuroxans (4-nitro-1,2,5-oxadiazole 2-oxides) leads to the 4,4′-azoxyfuroxans; these compounds can also be synthesized by oxidation of 4-amino- and 4,4′-azofuroxans and a general method for the synthesis of isomeric azofuroxans was also suggested <1999MC15>. The synthesis of dinitroazofurazan was achieved from readily available diaminofurazan in two steps and 20% overall yield <1998JHC151>. Diazotization of aminofurazans bearing the second substituent that can be eliminated as a cationic species leads to 3,4-dicyanofuroxan [1,2,5-oxadiazole-3,4-dicarbonitrile, 2-oxide] <2001MC30>. The synthesis of 4,4′-dinitro-3,3′-diazenofuroxan from 3-azidocarbonyl-4-aminofuroxan was described in <1998DOK499>.

A synthetic route to the fused 1,2,3-triazole 2-oxide systems **151** via intramolecular cyclization of *N*-nitroso and azido groups on the base 1,2,5-oxodiazoles has been described (**Scheme 39**) <1996TL8577>.



i, N_2O_5, MeCN, –25 to 0 °C, 63%

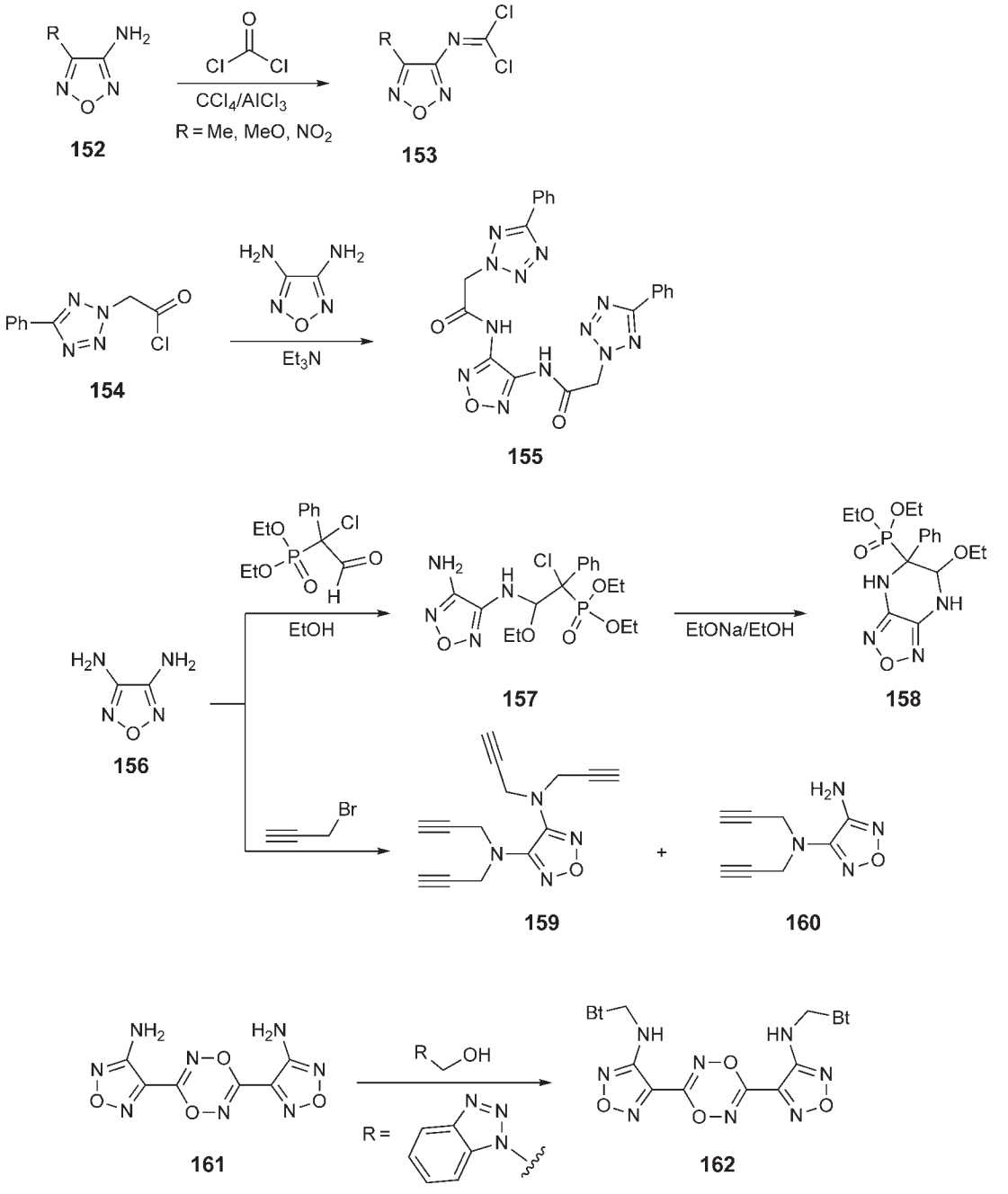
ii, $MeNH_2$, MeCN, 20 °C, 89% (R = Me) or $NCCH_2CH_2NH_2$, MeCN, reflux, 70% (R = CH_2CH_2CN)

iii, $NaNO_2$, HCl, H_2O/dioxane, 0 °C, 90% (R = Me) or $NaNO_2$, AcOH/H_2O, 5 °C, 91% (R = CH_2CH_2CN)

iv, Toluene, reflux, 70% (R = Me) and 92% (R = CH_2CH_2CN)

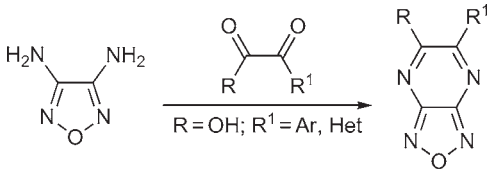
Scheme 39

The reactions of 3-amino-4-R-furazans **152** with CCl_4 in the presence of $AlCl_3$ gave (3-R-furazan-4-yl)dichloroimines **153** in useful yields (**Scheme 40**) <2003MC31>. 3,4-Diaminofurazan **156**, which contains amino groups with reduced nucleophilicity, was acylated with 5-phenyl-tetrazol-2-ylacetyl chloride **154** in the presence of triethylamine to give product **155** <2004CHE854>. Condensation of 3,4-diaminofurazane **156** with $(EtO)_2P(O)C(Cl)PhCHO$ in EtOH gave compound **157**, which reacted with EtONa/EtOH to give phosphorylated cyclic product **158** in 76% yield <2001CHE1052>. Compounds of the acetylene and diacetylene series **159**, **160**, containing a furazan ring, were synthesized by alkylation of 3,4-diaminofurazan **156** and nucleophilic substitution of the nitro group in 3-amino-4-nitrofurazan under conditions of phase-transfer catalysis <2001RJO1629>. Interaction of 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine **161** with oxymethylbenzotriazole gave the corresponding polycyclic compound **162** (**Scheme 40**) <2004RJO884>.



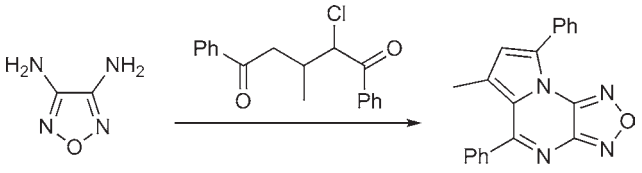
Scheme 40

3,4-Diaminofurazans **156** are useful starting materials for the synthesis of fused heterocyclic compounds. For example, 3,4-diaminofurazans **156** reacted with dicarbonyl compounds (e.g., with α-keto acids) to produce a series of 5-hydroxy[1,2,5]oxadiazolo[3,4-*b*]pyrazines **163** (Equation 26) <2003BML3133>.



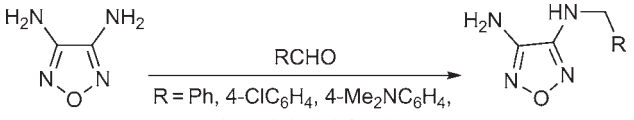
156 **163** (26)

Heating of 3,4-diamino-l,2,5-oxadiazole **156** and the relatively common 2-chloro-l,5-diketone gave 1,2,5-oxadiazolo[3,4-*e*]pyrrolo[1,2-*a*]pyrazine **164** (Equation 27) <1999CHE882>.



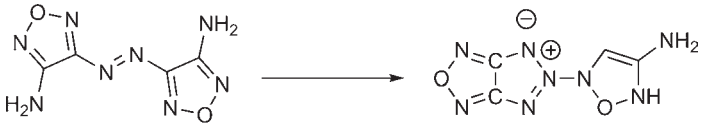
156 **164** (27)

N-Monoarylmethyl aminofurazans **165** were prepared by reductive alkylation of diaminofurazane **156** with the corresponding aryl aldehydes (Equation 28) <1997JHC1057>.



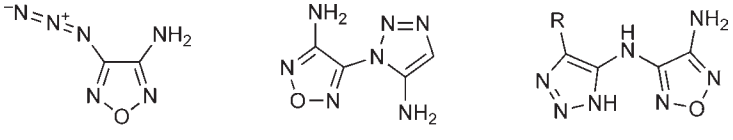
156 **165** (28)

An unusual intramolecular cyclization reaction was demonstrated for 4,4′-diamino-3,3′-azofurazan **166**. The 5-(4-amino[1,2,5]oxadiazolyl)-5*H*-[1,2,3]triazolo[4,5-*c*][1,2,5]oxadiazole **167** was formed by boiling compound **166** with $Pb(OAc)_4$ in PhCl or *o*-$Cl_2C_6H_4$, or by boiling it in $SOCl_2$ (Equation 29) <1996KGS253>.



166 **167** (29)

The 1,3-dipolar cycloaddition of azido-1,2,5-oxadiazoles (azidofurazans) to dicarbonyl compounds has been studied and a new procedure for the synthesis of (1,2,3-triazol-1-yl)-1,2,5-oxadiazoles was proposed <2002MC159>. The cycloaddition of 4-amino-3-azido-1,2,5-oxadiazole **168** to nitriles with activated methylene groups has been studied, and 3-amino-4-(5-amino-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazoles **169** and the products of their Dimroth rearrangement **170** have been synthesized <2004MC76>.

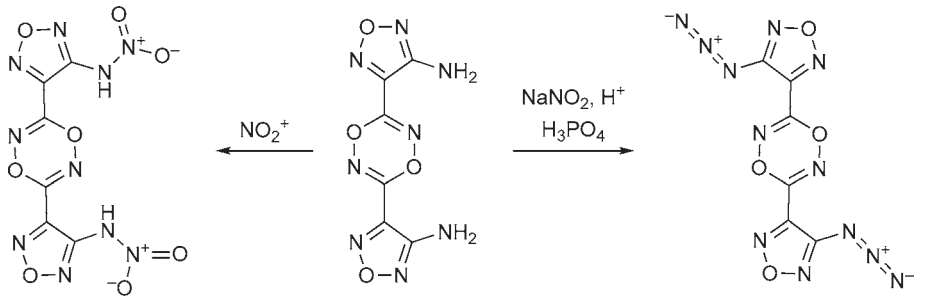


168 **169** **170**

R = CN, H_2NCO, 4-$NO_2C_6H_4$, 4-ClC_6H_4

Diazotization and nitration provide a synthetic approach to furazan azides and nitroamino derivatives. For example, 3,6-bis(4-amino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine **172** gave 3,6-bis(4-azido-1,2,5-oxadiazol-3-yl)-1,4,2,5-

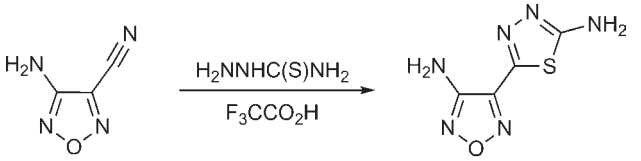
dioxadiazine **173** and 3,6-bis(4-nitroamino-1,2,5-oxadiazol-3-yl)-1,4,2,5-dioxadiazine **171** in diazotization and nitration reactions, respectively (**Scheme 41**) <2004RJO884>.



171 **172** **173**

Scheme 41

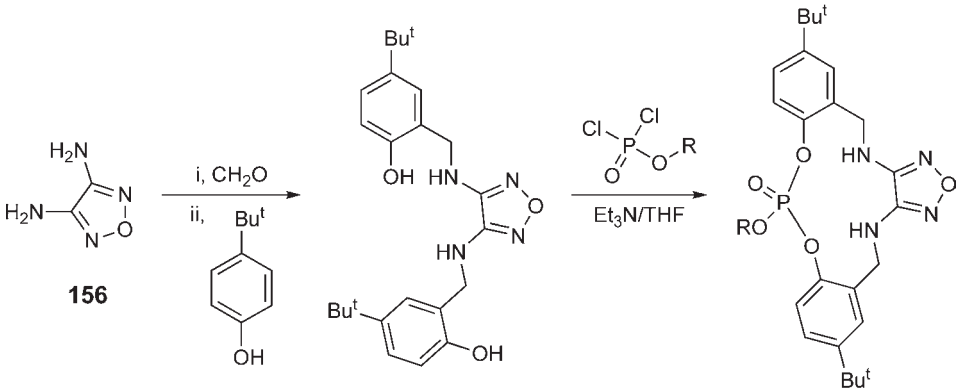
4-(5-Amino-l,3,4-thiadiazol-2-yl)-l,2,5-oxadiazole-3-amine **175** was formed with a yield of more than 75% in a condensation of 3-amino-4-cyano-l,2,5-oxadiazole **174** with thiosemicarbazide in trifluoroacetic acid (Equation 30) <1998CHE1220>.



(30)

174 **175**

A new class of phosphorus macroheterocycles containing the 1,2,3-oxadiazole ring has been synthesized in two steps. The reaction of 3,4-diamino-1,2,5-oxadiazole **156** with aqueous formaldehyde gave a Schiff's base which subsequently underwent addition with 4-*t*-butylphenol in 1,4-dioxane, affording *N*,*N*-bis-(5-*t*-butyl-2-hydroxybenzyl)furazan-3,4-diamine **176**. This was followed by cyclization *in situ* with various substituted aryl phosphorodichloridates in the presence of Et_3N in THF which finally afforded 13-membered macroheterocycles **177** containing P, N, O, and C atoms (**Scheme 42**) <2005JCM587>.



156 **176** **177**

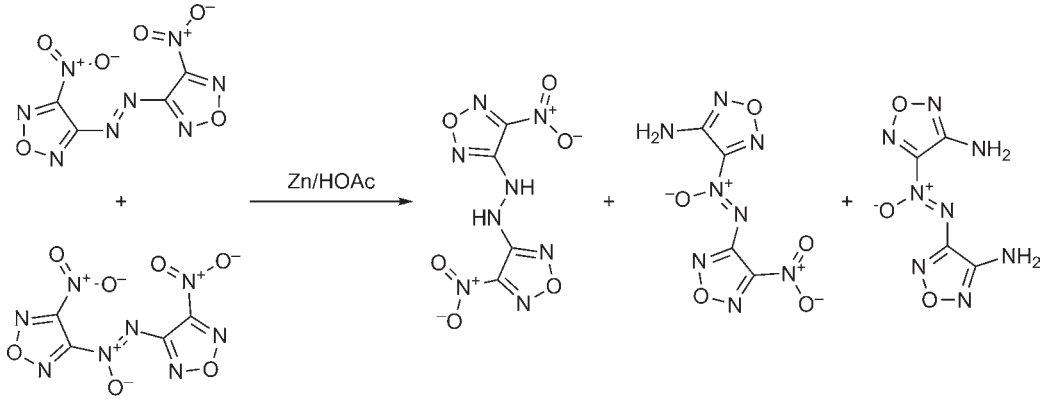
Scheme 42

1,2,5-Oxadiazole-3,4-diamine forms the H-bonded supramolecular monohydrated complex with [1.5]dibenzo-18-crown-6 ([1.5]DB18C6) <2005JPM63>.

5.05.5.1.4(ii) Nitrofurazans

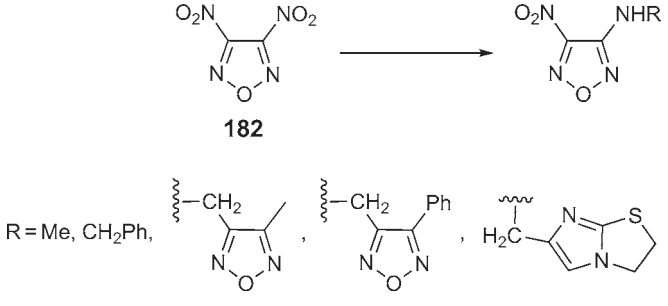
Despite the fact that an activated halogen atom is a common leaving group in nucleophilic (hetero)aromatic substitution reactions, far fewer papers have been devoted to halofurazans than to their more accessible nitro analogs <1996JOC1510, 1996MC141, 1998CEJ1023, 1998MC238, 1998MI142, 1999ZOR1555, 2000HAC48, 2000MC67>. Data from studies of the chemistry of nitrofurazans and also other furazan derivatives suitable for nucleophilic substitution reactions have been generalized in a review <2001AHC65>. As a leaving group in S_N2 reactions, the nitro group has mobility similar to fluorine and is significantly more effective than chlorine. At the same time, specific properties are intrinsic to nitro compounds that occasionally complicate the desired direction of the reaction <1999ACR958>. This first of all involves the ability of nitro compounds to exhibit oxidation properties in a reaction, where reagents such as thiols or aniline are mainly consumed in secondary processes. Second, the nitrite ion formed during substitution of the nitro group can compete with the nucleophile available in the reaction mixture, which also gives rise to secondary products.

Partial reduction of the 3,3′-dinitro-4,4′-azoxyfurazan and 3,3′-dinitro-4,4′-azofurazan mixture **178** with Zn/HOAc (glacial) at room temperature gave the novel energetic material 3,3′-dinitro-4,4′-hydrazofurazan **179**. The reduction also gives such by-products as 3-amino-3′-nitro-4,4′-azoxyfurazan **180** and 3,3′-diamino-4,4′-azoxyfurazan **181** (Equation 31) <2002USP6388087>.



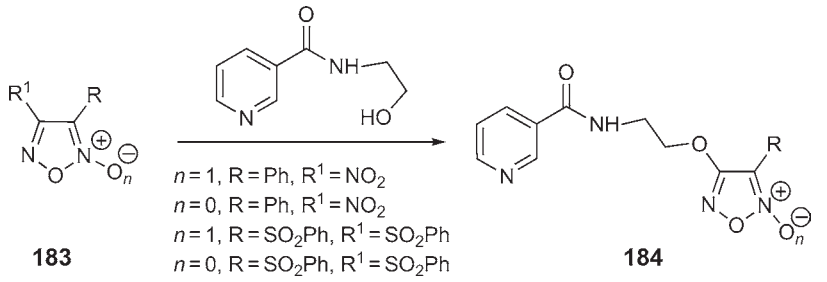
(31)

The effect of the substituent R on the specific features of the nucleophilic substitution reaction observed was considered. The nitro group attached to the furazan ring can act as both the leaving group and the activating group facilitating the displacement of the second substituent. The reactions of 3-nitro-4-R-substituted furazans with ammonia were studied <2002RCB1533>. The nitro group in 3-substituted 4-nitrofuroxans (4-nitro-1,2,5-oxadiazole 2-oxides) can be replaced by hydrogen when treated with $NaBH_4$ in EtOH; this reaction is convenient for the preparation of 3-monosubstituted furoxans <1999MC13>. Replacement of the nitro group of dinitrofurazan **182** with primary and secondary amines has been investigated (Equation 32). Conditions were found which allow the efficient replacement of the nitro group with these nucleophiles <2004RCB596>.



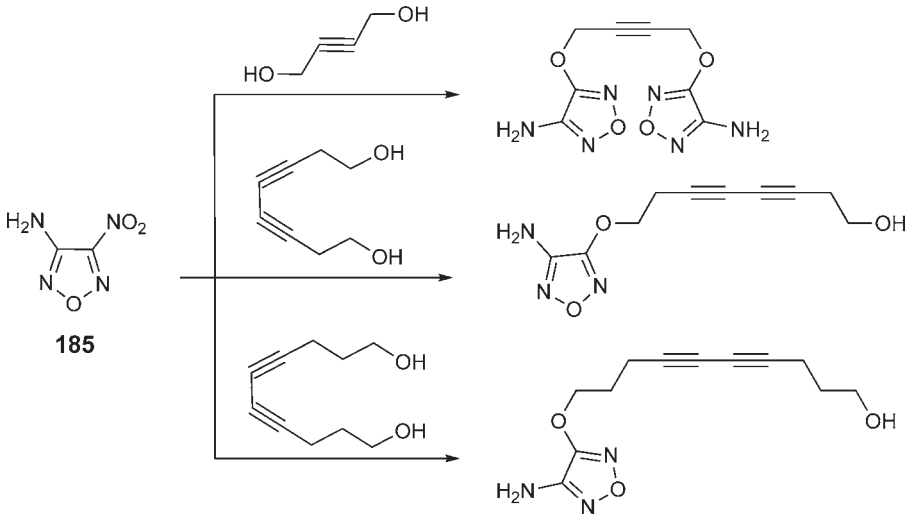
(32)

A series of hydroxy-, alkoxy-, and phenoxyfurazans and difurazanyl ether derivatives **184** were synthesized by reactions of mono- and dinitrofurazans **183** with O-nucleophiles. The effect of the furazan nature and reactant ratio on the structure of products has been discussed <1999RJO1525>. In this way, the nitro group has been replaced by alkoxy derivatives (Equation 33) <2000BMC1727>.



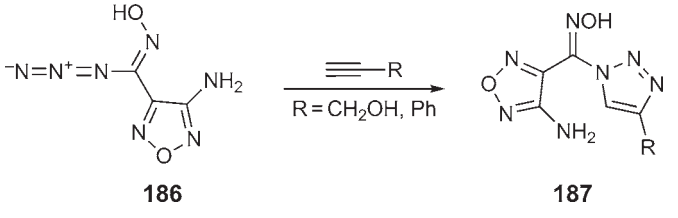
(33)

Nucleophilic substitution of the nitro group in 3-amino-4-nitrofurazan **185** under conditions of phase-transfer catalysis gave a series of acetylene and diacetylene derivatives (**Scheme 43**) <2001RJO1629>.



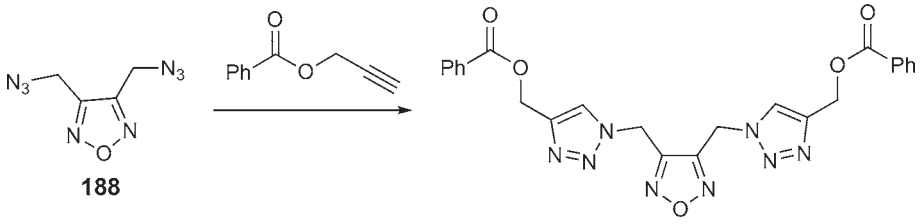
Scheme 43

Azido derivatives of furazans have proved to be particularly useful for the synthesis of heterocyclic systems. Thus, by 1,3-dipolar addition of 1-azido(4-amino-1,2,5-oxadiazol-3-yl)aldoxime **186** to propargyl alcohol and phenylacetylene, bicyclic 4-amino-1,2,5-oxadiazol-3-yl(4-R-1,2,3-triazol-1-yl)ketoximes **187** were obtained (Equation 34) which in reaction with acetic anhydride afforded the corresponding *O*-acyl derivatives <2003RJO574>.



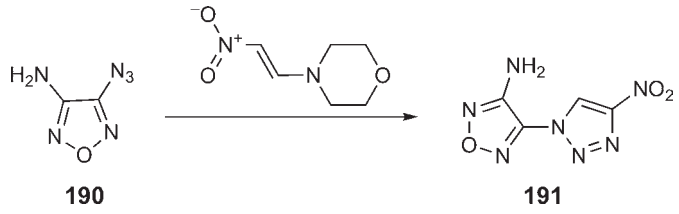
(34)

The reaction of propargyl benzoate with 3,4-bis(azidomethyl)-1,2,5-oxadiazole **188** afforded bistriazole **189** (Equation 35) <2004RJO1156>.

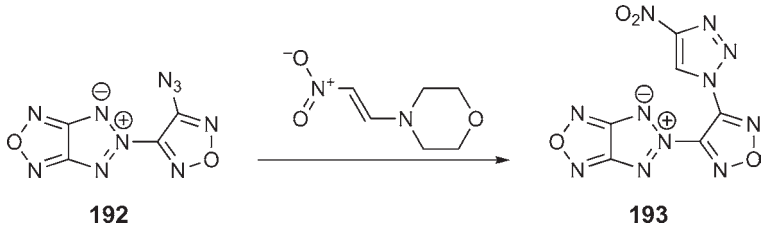


(35)

The reaction of 4-substituted furazans **190** and **192** with morpholinonitroethene gave the corresponding 1,2,3-triazoles **191** and **193** in high yields (Equations 36 and 37). It should also be mentioned that, in order to facilitate the cycloaddition of azide, the reaction was carried out in the presence of orthoformic ester for removal of morpholine from the reaction medium, otherwise decomposition of the starting azide occurs <2000CHE343>.

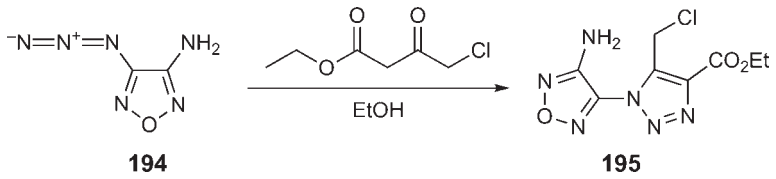


(36)



(37)

The 1,3-dipolar cycloaddition of azidofurazans to acetylenes afforded 1,2,3-triazoles linked with furazan cycle <2000CHE91>. Treatment of 3-azido-2-amino-1,2,5-oxadiazole **194** with ethyl 4-chloroacetoacetate gives access to the functionalized [1,2,3]-triazoles **195**, which are good precursors for GSK-3 inhibitors with favorable water solubility (Equation 38) <2003JME3333>.

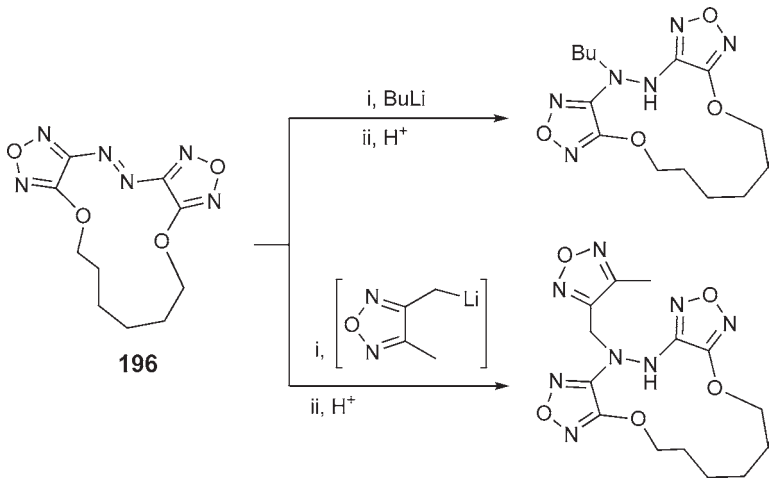


(38)

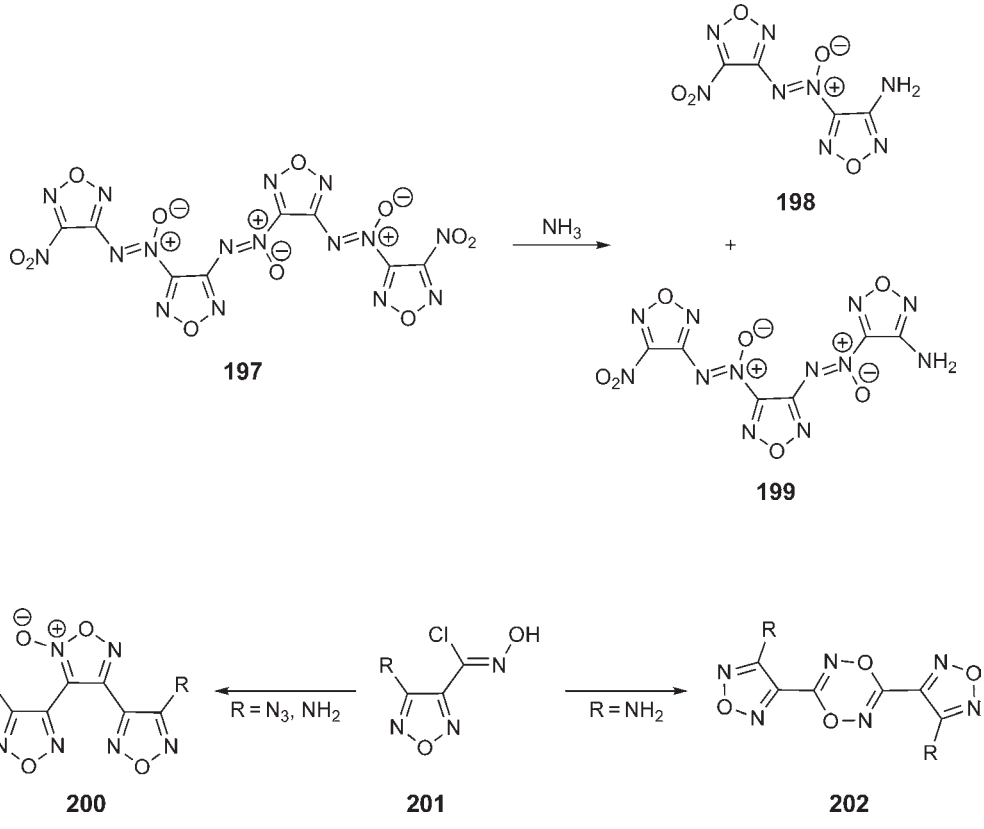
The reactions of azofurazans have been used to obtain the hydrazine and the amino derivatives. For example, reactions of azofurazans, including macrocyclic azofurazan **196**, with Bu^{n}Li and the lithium derivatives of methylfurazans were studied. Several competitive processes were found to occur: (1) the addition of a Li reagent at the N=N bond; (2) the redox reaction giving rise to hydrazofurazans; and (3) the reaction of the side chain of azofurazan (**Scheme 44**) <2004RCB615>.

The azoxyfurazan **197** can be converted into the products **198** and **199** by treatment with ammonia (Equation 39) <2003RCB1447>. Both products **198** and **199** were formed as a result of nucleophilic substitution at the same furazan ring containing two azoxygroups attached through the N atoms of the N(O) fragments.

Dimerization of nitrile oxides derived from 4-amino- and 4-R-substituted 1,2,5-oxadiazole-3-carbohydroximoyl chlorides **201** leads to the formation of tricyclic furoxans **200** or compound **202** (**Scheme 45**) <2001RJO1355>.



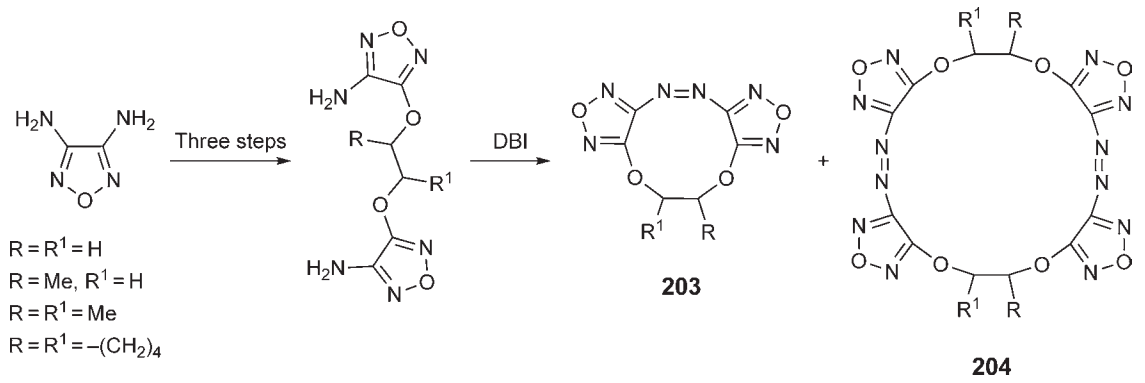
Scheme 44



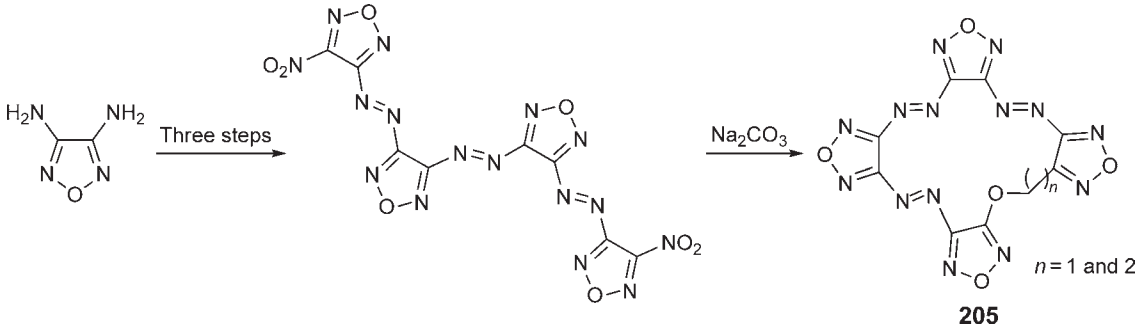
(39)

Scheme 45

A number of novel crown ether analogs **203–205** incorporating the azofurazan subunit have been synthesized by oxidative cyclization of bis(aminofurazanylic)ethers of 1,2-diols by dibromoisocyanurate (**Scheme 46**) and base-promoted coupling of bis[(nitrofurazanyl)azo]compounds (**Scheme 47**). This reaction provides a new and versatile approach to the synthesis of chromophoric macrocycles <1996JOC1510, 2004HAC131>.



Scheme 46

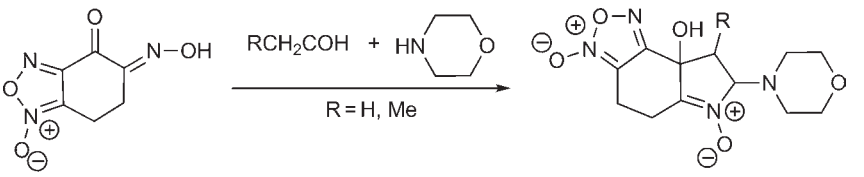


Scheme 47

5.05.5.1.4(iii) Nitrofuroxans

Three different types of rearrangements of noncondensed furoxan derivatives have been identified <2004PAC1691>. The first of them occurs through a dinitrosoethylene intermediate and results in the formation of 1,2,3-triazole 1-oxides [oximes of 5-acetyl-4-phenyl(methyl)-2-phenyl-2*H*-1,2,3-triazole 1-oxides and 2-(furoxan-4-yl)-4-nitro-5-R-2*H*-1,2,3-triazole 1-oxides] by thermal recyclization of 3-methyl-4-acetyl(benzoyl)furoxan phenylhydrazones and 3,3′-R-disubstituted-4,4′-azofuroxans, respectively. The latter reaction was performed in an oxidizing medium. The second kind of rearrangement (classical variant) was employed in the synthesis of new azole containing a 1-nitroalkyl substituent. Three examples of reactions involving this rearrangement have been reported: (1) base-induced interconversion of furoxanyl ketone phenylhydrazones into 5-(1-nitroalkyl)-2*H*-1,2,3-triazole derivatives; (2) conversion of 1-alkyl(aryl)-3-(furoxan-4-yl)amidines into 1-substituted 3-(1-nitroalkyl)-1,2,4-triazoles; and (3) a thermally induced rearrangement of 4-thioureido-3-R-substituted furoxans into derivatives of 5-amino-3-(1-nitroalkyl)-1,2,4-thiadiazole including 5-amino-1,2,4-thiadiazol-3-yl)nitroformaldehyde arylhydrazones (where R = N═N–Ar). Rearrangements of the third kind were those of the cascade type. Three new cascade rearrangements of azofuroxan derivatives (3,3′-azo-4,4′-bis(acetylamino)furoxans, 3-arylazo-4-acetylaminofuroxans, and 3-arylazo-4-(3-ethoxycarbonylureido)furoxans) into 4-amino-5-nitro-2*H*-1,2,3-triazole derivatives have been discovered. These three reactions were assumed to include two consecutive (cascade) rearrangements: a 1,2,4-oxadiazole ring was formed at the first step and then transformed into a 1,2,3-triazole ring with the participation of an azo group. The use of these rearrangements has led to the development of several alternative approaches to the synthesis of 1,2,3-triazole 1-oxides, 1-nitroalkyl derivatives of 1,2,3-triazoles, 1,2,4-triazoles and 1,2,4-thiadiazoles, as well as 4-amino-5-nitro-1,2,3-triazole derivatives.

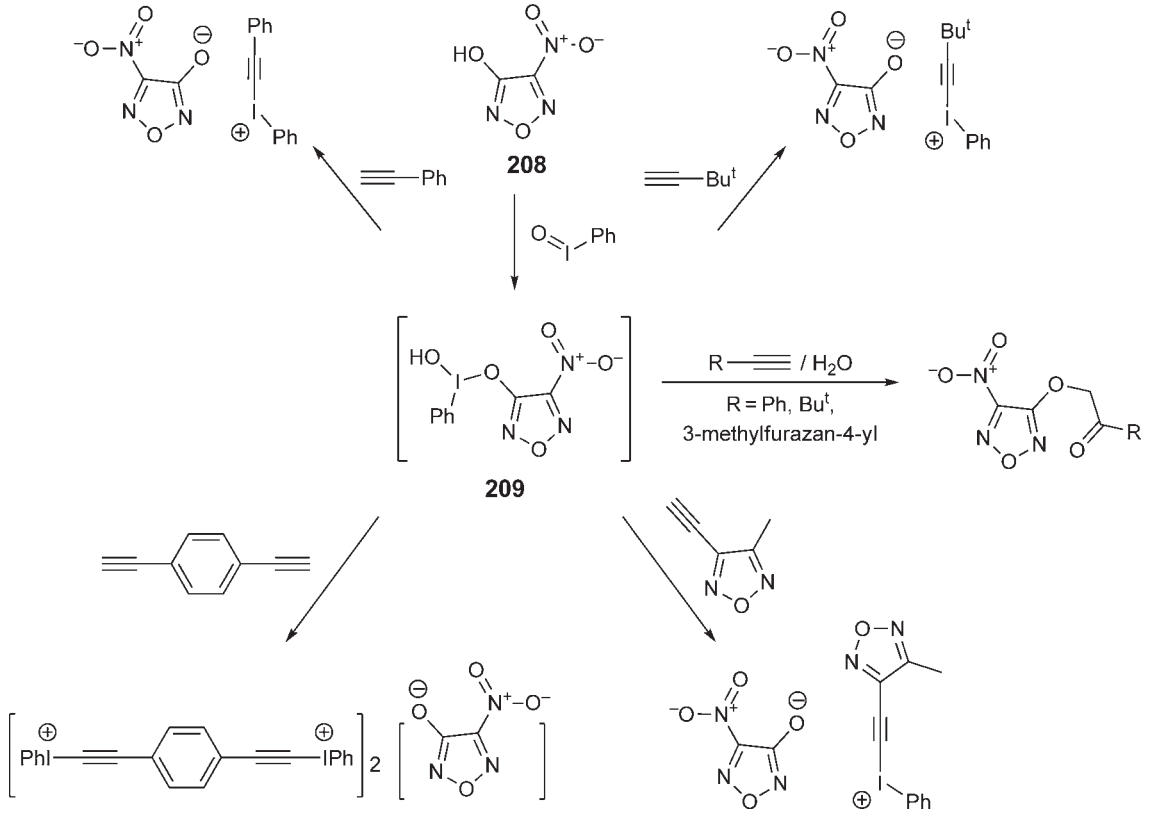
α-Isonitroso ketones **206**, derivatives of tetrahydrobenzofurazan, react with aldehydes and morpholine to form derivatives of 5,7,8,8a-tetrahydro-4*H*-[1,2,5]oxadiazolo[3,4-*e*]indole **207** (Equation 40) <2004CHE1346>.



(40)

5.05.5.1.5 Furazan and furoxan alcohols and thiols and their derivatives

Furoxan and furazans alcohols are relatively uncommon compounds, but they can serve as useful precursors to various new derivatives of 1,2,4-oxadiazole. 3-Hydroxy-4-nitrofurazan **208** reacts with iodosylbenzene to produce a highly reactive intermediate phenyliodonium nitrofurazanylate **209** which can be converted to a series of alkynyl(phenyl)-iodonium nitrofurazanylates and related products (**Scheme 48**) <2001TL5759>.

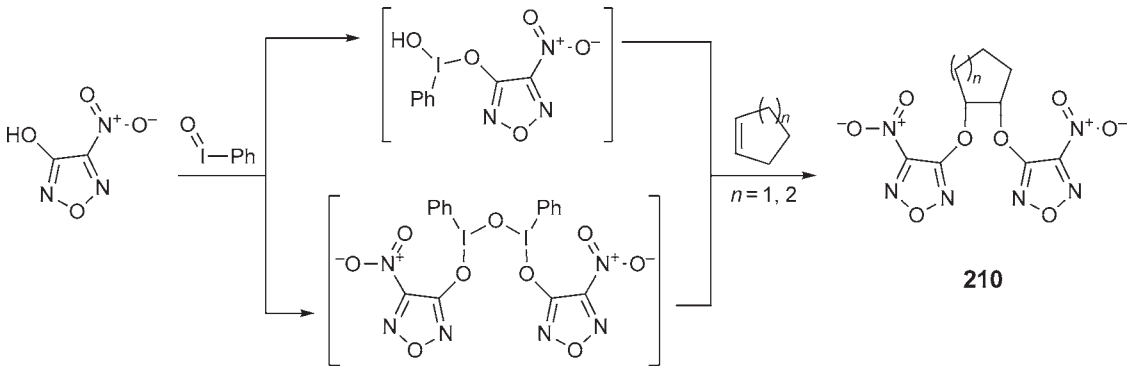


Scheme 48

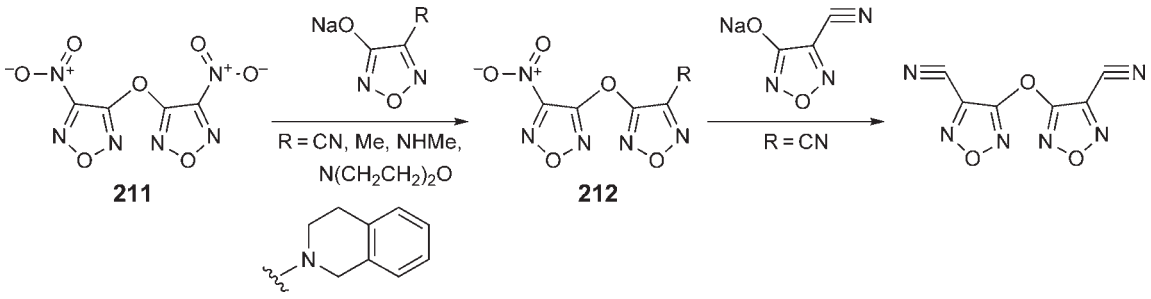
In a similar manner these hypervalent iodine derivatives promote the addition of the non-nucleophilic 4-nitrofurazan-3-olate functions to cycloalkenes to give product **210** (**Scheme 49**) <2001RCB2479>.

The reactions of the 4,4′-dinitrodifurazanyl ether **211** with sodium salts of hydroxyfurazans have been studied. The more nucleophilic R-furazanyl group replaces the nitrofurazanyl fragment; the observed transetherification affords unsymmetrical derivatives of difurazanyl ether **212** (**Scheme 50**) <2002RCB659>.

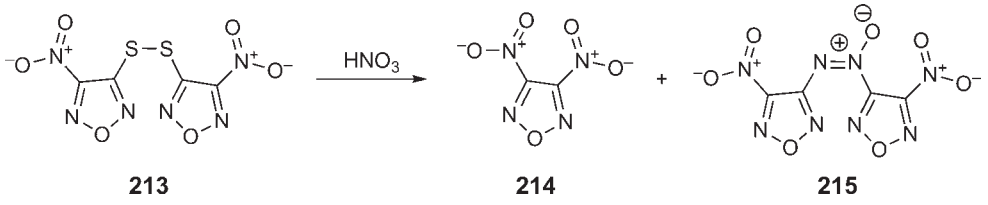
The disulfide bridge of bis(3-nitrofurazan-4-yl)disulfide **213** was shown to undergo transformations of a new type, such as destructive nitration to give 3,4-dinitrofurazan **214** and 4,4′-dinitroazoxyfurazan **215** (Equation 41) <2004RCB722>.



Scheme 49



Scheme 50

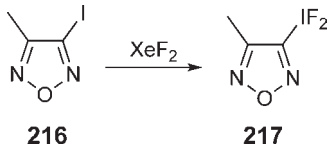


(41)

The preparation and the base-promoted Smiles rearrangement of phenylfuroxans bearing 2-hydroxyethylthio, 2-hydroxyethylsulfonyl, carbamoylmethylthio, and carbamoylmethylsulfonyl functions at the heterocyclic ring have been described. The rearrangement was also investigated in related furazans (1,2,5-oxadiazoles) for comparison <2001J(P1)1751>.

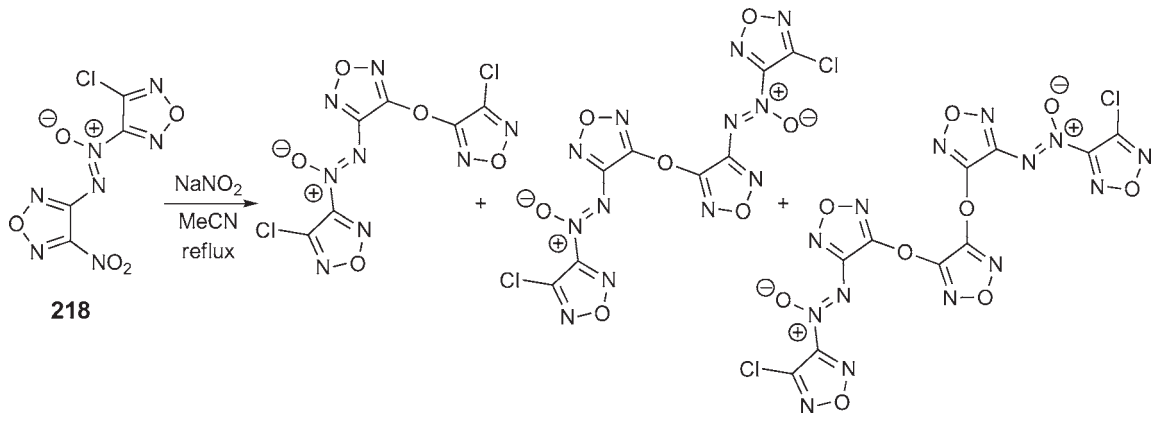
5.05.5.1.6 Halo furazans and -furoxans and miscellaneous derivatives (cyano-, sulfonyl-groups)

Oxidative fluorination of 3-iodo-4-methylfurazan **216** with xenon difluoride in an atmosphere of dry argon at 20 °C in anhydrous MeCN yielded the corresponding difluoroiodanyl azole **217** (Equation 42) <2004RCB1130>.



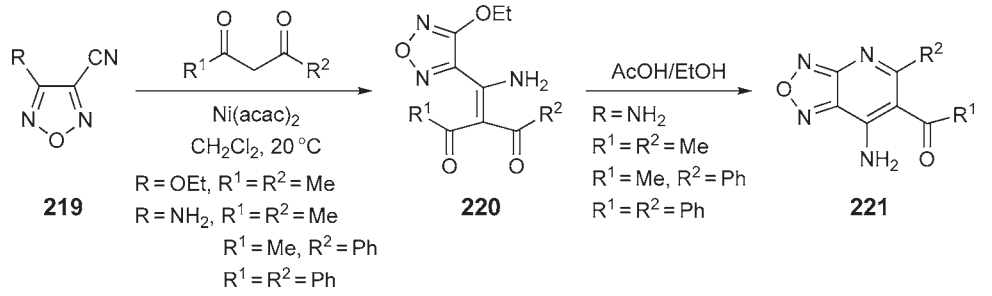
(42)

When 3-(4-chlorofurazanyl-3-*N*(*O*)*N*-azoxy)-4-nitrofurazan **218** reacts with weak bases and nucleophiles, selective attack on the carbon atom bonded to the nitro group occurs, but no products formed by substitution of the chlorine was observed (Equation 43) <2003CHE1357>.



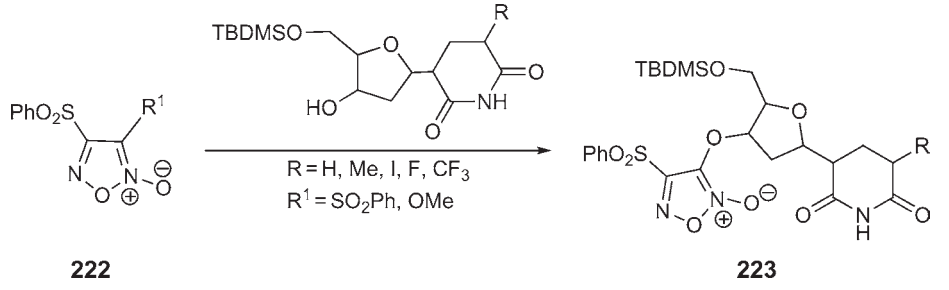
(43)

In the presence of bis(acetylacetonato)nickel, α-dicarbonyl compounds readily add at the nitrile group of 4-R-substituted 1,2,5-oxadiazole-3-carbonitriles **219** to form enaminofurazans **220**. The adducts obtained from 4-amino-3-cyanofurazan underwent intramolecular cyclization upon heating with acetic acid in ethanol to give furazano[3,4-*b*]pyridine **221** derivatives in high yields (**Scheme 51**) <2001RCB1280>.



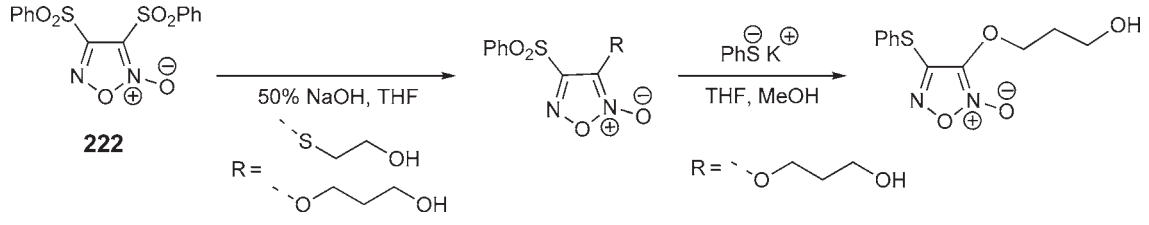
Scheme 51

Reaction of 3,4-bis(phenylsulfonyl)-1,2,5-oxadiazole oxide isomers with ethanol and ethanethiol in basic medium gave the expected alkoxy- and alkylthio-substituted (benzenesulfonyl)furoxans, respectively <1996JHC327, 1997FES405>. Nucleophilic substitution of the sulfonyl group of 3,4-bis-(benzenesulfonyl)furoxan **222** in the presence of aqueous NaOH in tetrahydrofuran (THF) furnished the corresponding 3′-*O*-(3-benzenesulfonylfuroxan-4-yl) derivative **223** in 79–92% yield (Equation 44) <2004JME1840>.

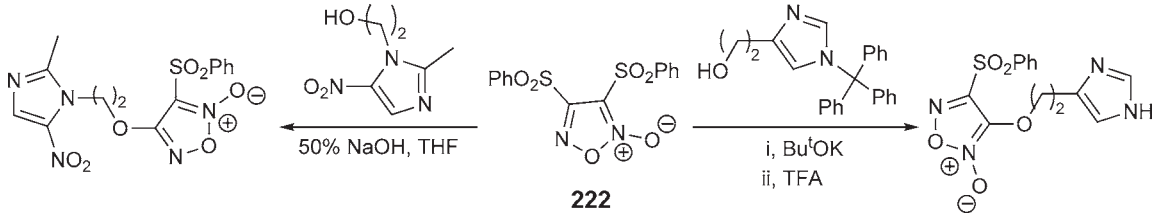


(44)

The sulfonyl group of 3,4-bis(phenylsulfonyl)-1,2,5-oxadiazole oxide **222** can be subjected to the following transformations: (1) reduction in refluxing trimethyl phosphate; (2) etherification with NaOBu in BuOH <1999USP5998404, 2004MI239>; (3) substitution by alkyl or functionalized alkyl group in the reaction with Grignard reagents <2006JME4442>; (4) substitution by mercaptoethanol <2005EJM1335>, 1,3-propandiol and thiophenol (**Scheme 52**) <2001JME3463>; and (5) substitution by imidazolpropanol <2004FES359> and 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl derivatives (**Scheme 53**) <2003MI225>.



Scheme 52



Scheme 53

5.05.5.2 Homocyclic Ring of Benzofurazans and Benzofuroxans

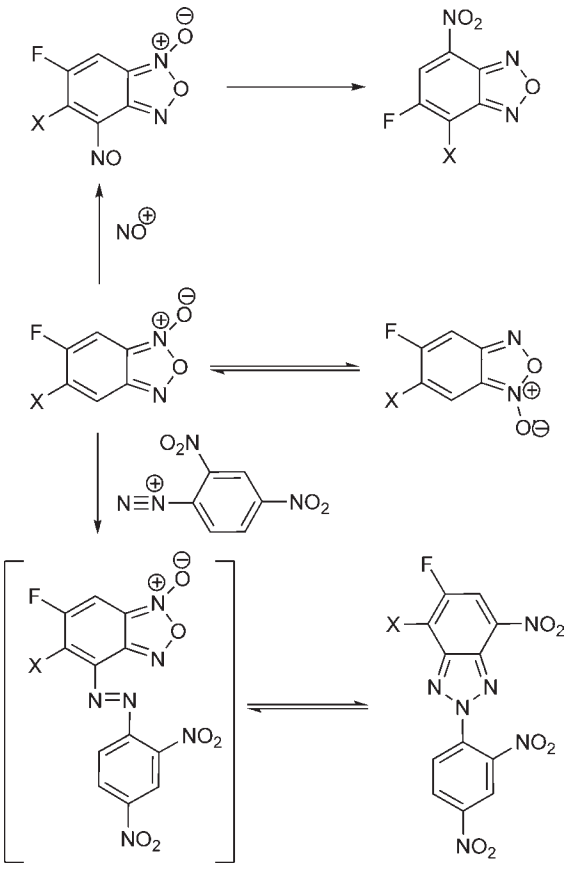
The chemistry of the homocyclic ring of benzofurazans and benzofuroxans has been studied in great detail but it is still attracting significant interest. Benzofurazans and benzofuroxans have attracted particular attention as precursors to new compounds with important biological and pharmacological applications. The chemisty of benzofurazans and benzofuraxans was extensively covered in CHEC(1984) and CHEC-II(1996), and was classified according to reactivity with electrophiles, nucleophiles, transformations involving ring substituents, and miscellaneous reactions.

5.05.5.2.1 Reactions with electrophiles

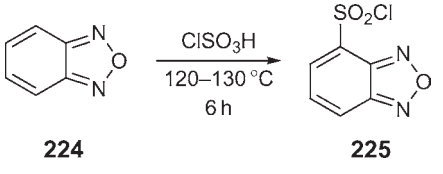
When the nitration of the benzene ring of benzofuroxans occurs in a position adjacent to the heterocycle, the resulting nitro derivative suffers Boulton–Katritzky rearrangement <B-1996MI104>. The features of tautomerism in fluorine-containing benzofuroxans and also their involvement into electrophilic substitution reaction accompanied with Boulton–Katritzky rearrangement have been described <2004RJO1167>. Only one of the existing equilibrium tautomeric forms of 5(6)-fluoro-6(5)-substituted benzofuroxans can be involved into electrophilic substitution. The electrophilic attack occurs on the *ortho*-position with respect to an electron-donor substituent that at the same time is distant from the *N*-oxide group of the heterocycle. Electrophilic substitution followed by Boulton–Katritzky rearrangement gives new possibilities for the synthesis of previously inaccessible fluorinated heterocycles, illustrated by the nitro derivatives of 2,1,3-benzoxadiazoles and 1,2,3-benzotriazoles shown in **Scheme 54** <2004RJO1167>.

Benzofurazan **224** reacts with chlorosulfonic acid to give the chlorosulfonate **225** (Equation 45) <2004S2999>.

The nitration of the polyheterocyclic compound **226** leads to the formation of moisture-sensitive nitration products, which undergo further oxidation to give *o*-quinone-like species (**Scheme 55**) <1996JOC1898>.



Scheme 54



(45)

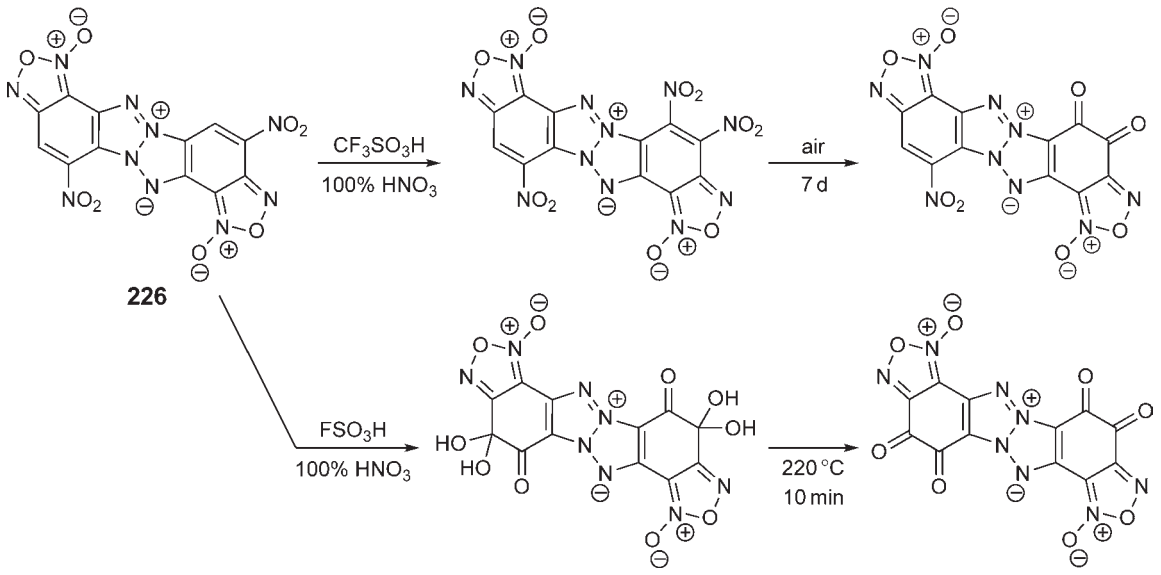
224 **225**

Methoxybenzodifurazan **227** can be nitrated by nitric acid at room temperature to give methoxynitrobenzodifurazan **228**, which reacts with arylamines to yield a series of substituted compounds **229** (**Scheme 56**) <2003PCJ578>.

5.05.5.2.2 Reactions with nucleophiles

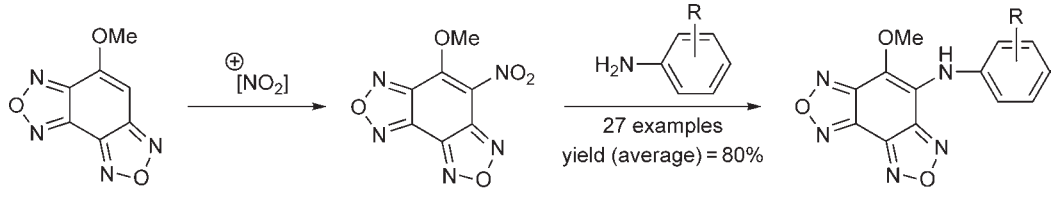
5.05.5.2.2(i) Nucleophilic substitution reaction

Nucleophilic substitution of fluoro, chloro, and nitro groups was described for benzofuroxans. For example, 5(6)-fluoro-6(5)-substituted benzofuroxans were obtained by the reactions of 5,6-difluorobenzofuroxan with a number of nucleophiles, such as alkylamines, cycloalkylimines, sodium azide, and sodium alkoxides <2004JFC(125)421>; chlorine was substituted by functionally substituted amines, such as 1-BOC-4-aminoethyl-piperidine <2003JME2606>, aminoalkylpiperidine <2006BML1938>. 4-Chloro-7-nitrobenzofurazan reacts by nucleophilic substitution with phenoxide anions derived from estriol, ethynylestradiol, phenol, guaiacol, 2,6-dimethoxyphenol, eugenol, isoeugenol, the cytostatic Etoposide and Reichardt's betaine in the presence of crown ethers to afford the corresponding 4-aryloxy-7-nitrobenzofurazan derivatives <2003CEC260>. Chlorobenzodifurazan **230** does not interact with aromatic amines, but the reaction takes place with aliphatic amines (Equation 46) <2003PCJ522>.



226

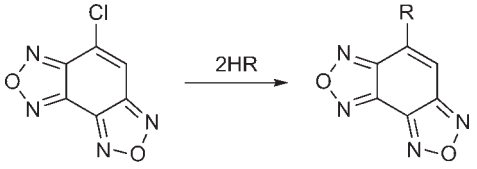
Scheme 55



227 **228** **229**

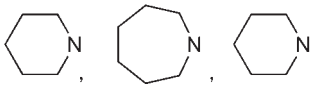
R = 4-OH, 4-OMe, 4-OEt, 3-Me, 4-Me, 4-Et, 2-NH_2, 2-OMe, H, 4-Ph, 4-Cl, 4-F, 4-I, 3-Cl, 4-C_6H_4-4′-NO_2, 3-COOH, 4-COOH, 4-COOMe, 4-COOEt, 4-COMe, 3-CF_3, 4-$CONH_2$, 4-N=NPh, 4-NO_2, 4-$SO_2NHC(NH)NH_2$, 4-SO_2NH_2, 4-$SO_2NHC(O)Me$

Scheme 56

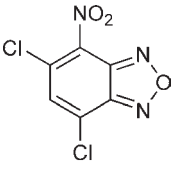


230 (46)

R = NH_2, NHNHMe, $N(Me)_2$, $N(Et)_2$,

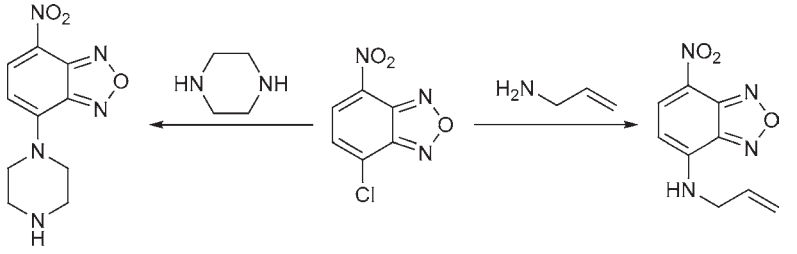


On the other hand, chlorine atoms of furazan **231** can be replaced in its reactions with amines. Depending on the reaction conditions, compounds containing either identical or different fragments of aromatic or aliphatic amines at positions 5 and 7 can be synthesized. It is reasonable that the replacement of the chlorine atom at position 5 by an arylamino or alkylamino group leads to a decrease in mobility of the intact chlorine atom. The introduction of alkylamino or dialkylamino groups possessing strong donor properties has the most pronounced effect on the mobility of the chlorine atom and, what is very important, this effect is different in different cases <2002RCB105>.



231

The activation of nucleophilic substitution was also demonstrated for 4-chloro-7-nitrobenzofurazan **232**. Thus, chlorine is easily replaced by piperazine <2001JME3378> or aminopropylene (**Scheme 57**) <2004TL3625>.

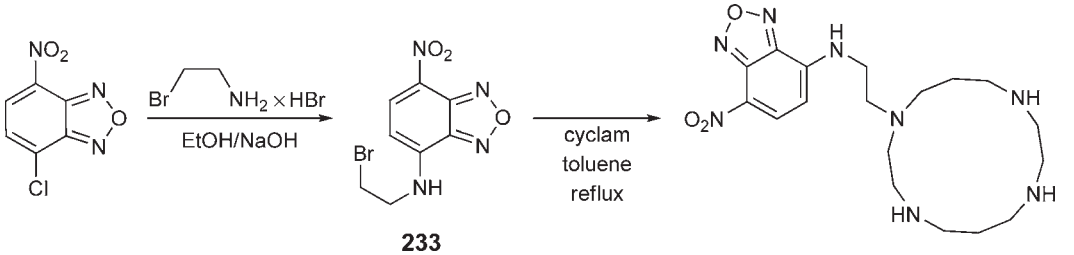


232

Scheme 57

An interesting observation was made when studying the nucleophilic aromatic substitution (S_NAr) reaction between several 4-aryloxy-7-nitrobenzofurazans and several amino acids leading to the formation of fluorescent N-substituted amino acid products. Acidic amino acids reacted very slowly, while basic amino acids reacted fastest with 4-aryloxy-7-nitrobenzofurazans having an unsubstituted phenyl or a 4-formylphenyl group. Among neutral amino acids, proline reacted fastest at room temperature when 4-aryloxy-7-nitrobenzofurazan contained a methoxy-substituted aryl group <2004CEC672>.

A new type of scorpionand in which the pendant arm has been equipped with a chromophore has been synthesized. The chromophore-containing pendant arm was then appended onto the macrocyclic framework by reaction of **233** with cyclam (fivefold excess) in boiling toluene (**Scheme 58**) <2004POL373>.



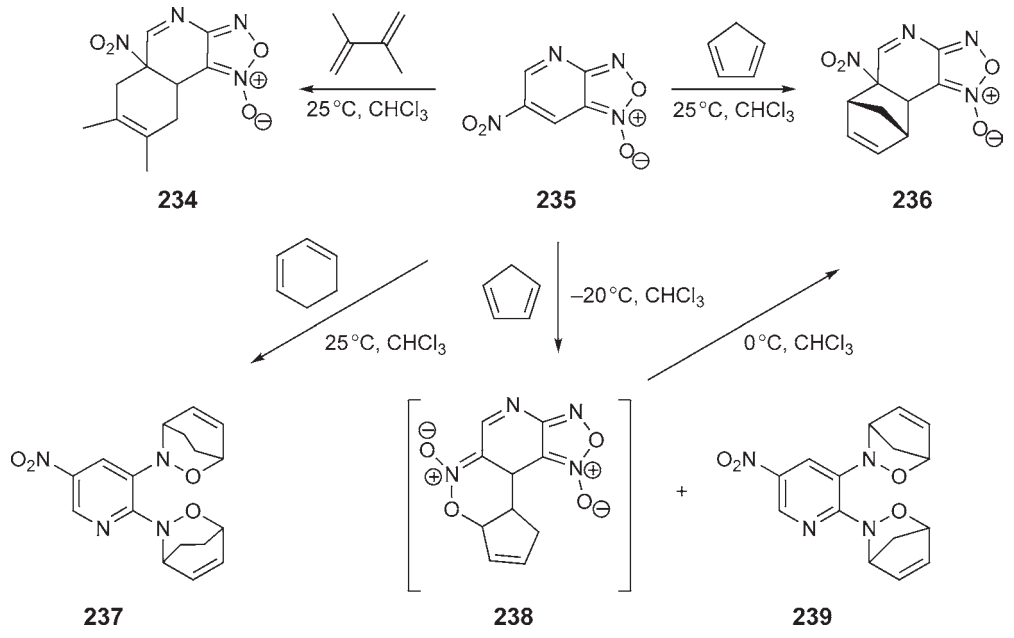
233

Scheme 58

It has been recognized that the exceptional electrophilic character of nitrobenzofuroxans is closely related to the low aromaticity of the carbocyclic ring. Crucial evidence for this relationship has been the discovery that the nitro-activated double bonds of this ring behave similarly to nitroalkene fragments in a variety of Diels–Alder processes, acting as dienophiles or heterodienes depending upon the reaction partner and the experimental conditions <1997JOC7178, 1997JOC8687, 1998CC791, 2000J(P2)51, 2000JOC7391, 2002CC2110, 2002T3249, 2004ARK85, 2006OBC1910>. The benzofurazans and benzofuroxans, as well as their substituted analogs, undergo [3+2] and [4+2] cycloaddition reactions. 4,6-DNBF (4,6-dinitro-2,1,3-benzoxadiazole 1-oxide) exhibit dienophilic and/or

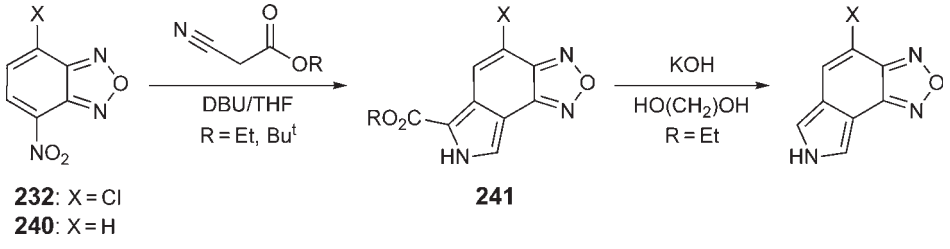
heterodienic behavior upon treatment with isoprene, 2,3-dimethylbutadiene, cyclopentadiene, or cyclohexadiene, affording Diels–Alder mono- or di-adducts which have all been structurally characterized <1999JOC9254, 2000J(P2)51, 2002CC2110, 2002T3249, 2004ARK85, 2006OBC1910>. A major finding is that the order of Diels–Alder reactivity follows clearly the order of electrophilicity, pointing to a direct relationship between superelectrophilic and pericyclic reactivity <2006OBC1910>.

Diels–Alder reactivity of 4-aza-6-nitrobenzofuroxan **235** has been studied via reactions with cyclopentadiene, cyclohexadiene, and 2,3-dimethylbutadiene; this has led to three types of Diels–Alder adducts, namely the normal Diels–Alder adducts **234**, **236**, a Diels–Alder hetero-adduct **238**, and the di-adducts **237**, **239** arising from a minor dinitroso tautomer of compound **235** (**Scheme 59**) <1999CC1009, 2000JOC7391>.



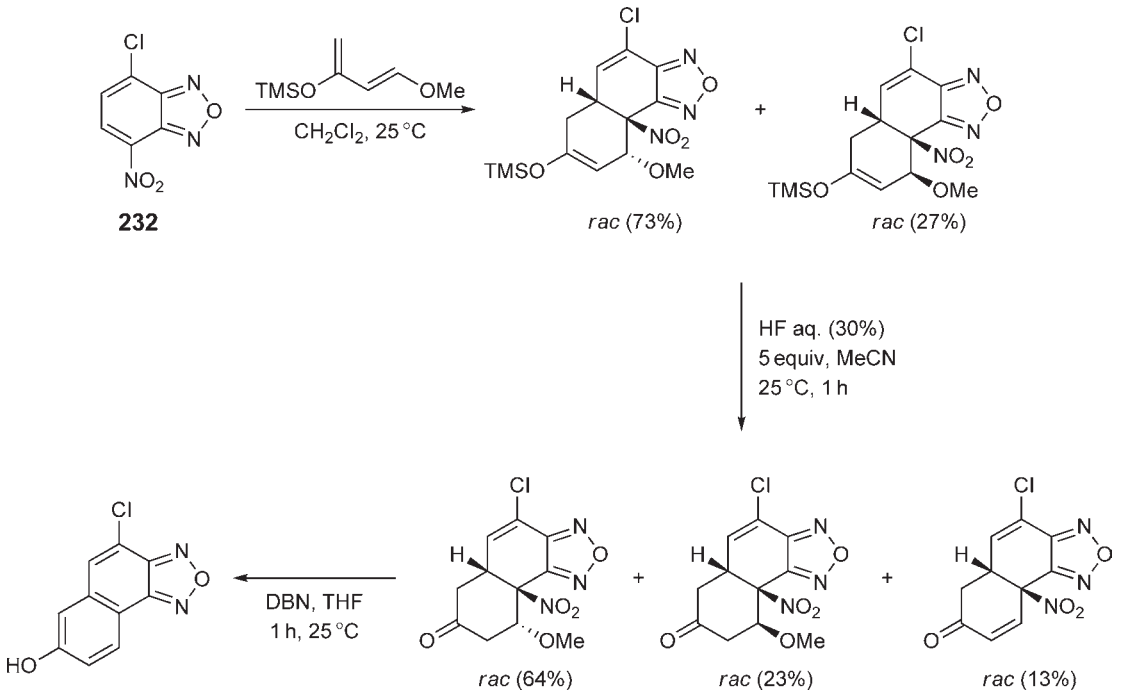
Scheme 59

7-Nitrobenzofurazan **240** and 4-chloro-7-nitrobenzofurazan **232** also condense with isocyanoacetates in the presence of the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give tricyclic pyrrole derivatives **241** in excellent yields (**Scheme 60**) <2005T11615>.



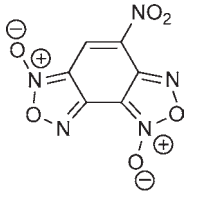
Scheme 60

The reaction of 4-chloro-7-nitrobenzofurazan **232** with the electron-rich Danishefsky diene provides a new and efficient access to a series of functionalized hydroxynaphthofurazans (**Scheme 61**) <2001TL7571>.



Scheme 61

The reactions of 4-nitrobenzodifuroxan **242** with a series of common dienes, such as cyclopentadiene, cyclohexadiene, isoprene, 2,3-dimethylbutadiene, and 1-acetoxybutadiene, with ethoxymethyleneacetylacetone were found to proceed very readily to afford stable cycloadducts, which are the result of highly stereoselective normal electron-demand (NED) Diels–Alder reactions. Due to the additional activation provided by the two adjacent furoxan rings, the nitroalkene double bond of compound **242** is also prone to undergo NED reactions with less reactive dienic structures, such as the enol form of ethoxymethyleneacetylacetone and the *in situ* generated 2-ethoxy-4-(2-furfuryl)buta-1,3-diene <2004TL1037, 2005T8167>.

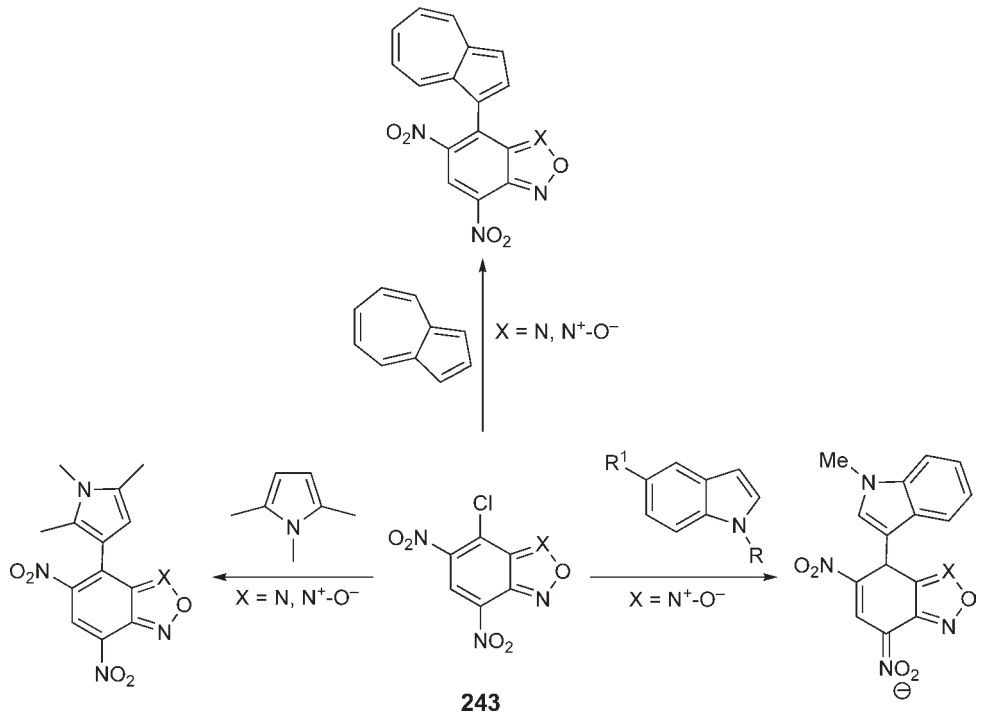


242

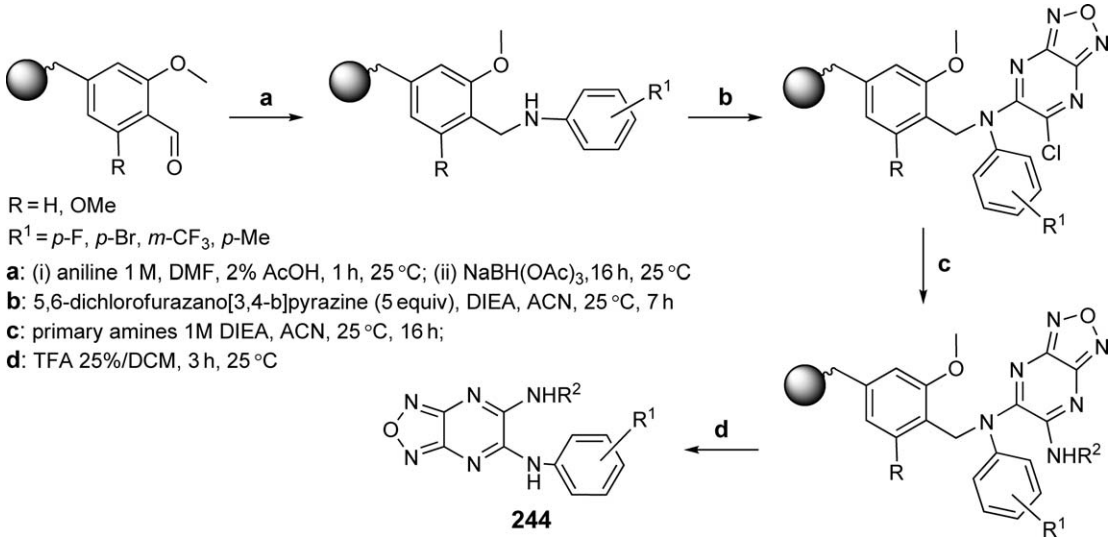
Superelectrophilic halonitro-2,1,3-benzoxadiazole **243** undergoes remarkably facile carbon–carbon couplings with some electron-rich aromatics and heteroaromatics, affording quantitatively products exhibiting an intense visible absorption due to strong intramolecular charge transfer (**Scheme 62**) <2003CC2150>.

A successful solid-phase approach to libraries of asymmetrically disubstituted furazano[3,4-*b*]pyrazines **244** has been developed. By using these solid-phase synthetic protocols, 320 fused heterocyclic derivatives were synthesized (**Scheme 63**) <2002TL4741>.

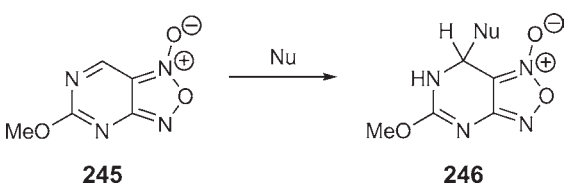
Nucleophilic attack with electron-rich arenes and ethylene derivatives at C-7 of 5-methoxyfuroxano[3,4-*d*]-pyrimidine **245** leads to 7-substituted 6,7-dihydro-5-methoxyfuroxano[3,4-*d*]pyrimidines **246** (Equation 47) <2003JPO431>.



Scheme 62



Scheme 63

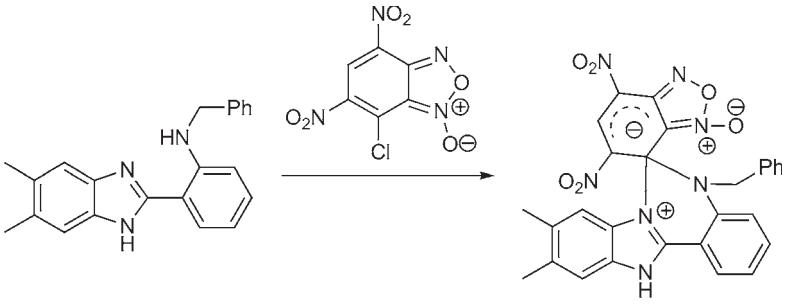


(47)

5.05.5.2.2(ii) Meisenheimer complex formation

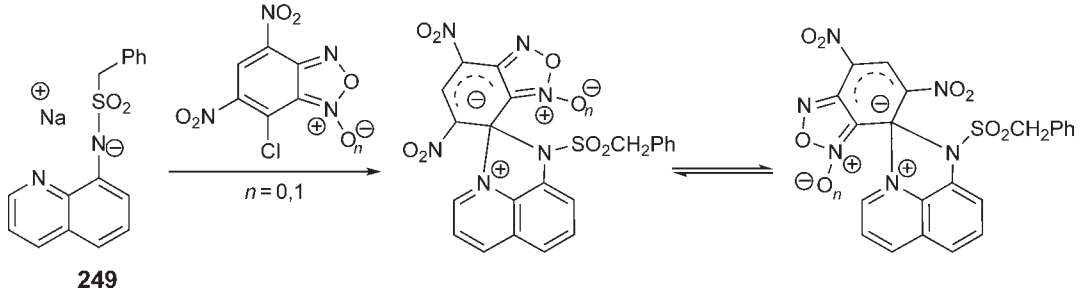
In the last two decades, much evidence has been accumulated showing that nitro-substituted 2,1,3-benzoxadiazoles and related 1-oxides, commonly referred to as nitrobenzofurazans and nitrobenzofuroxans, respectively, are neutral 10π electron-deficient heteroaromatic substrates, which in many processes exhibit extremely high electrophilic character. A good illustration for this behavior is the finding that DNBF, the reference compound in this family, behaves as a stronger electrophile than the 4-nitrobenzenediazonium cation. This has led to many analytical applications with the use of DNBF as a suitable probe to assess the reactivity of extremely weak carbon nucleophiles such as benzenoid aromatic or π-excessive heteroaromatics with large negative pK_a values, for example, 1,3-dimethoxybenzene (pK_a −9), 3-methoxythiophene (pK_a = −6.5) or aniline (pK_a = −6). In all of the above processes, covalent addition of the carbon nucleophile takes place at C-7 of the carbocyclic ring of DNBF to give stable anionic σ-complexes, as it also does in all reported interactions of DNBF with oxygen, sulfur, or nitrogen nucleophiles <1998CHE104, 2001J(P2)1408, 2001TL4499, 2002J(P2)871, 2003OBC1757, 2003OBC2192, 2004RCB2075, 2004RJO1384>.

The reactions of 2-(2-benzylaminophenyl)benzimidazole derivatives **247** with electrophilic 7-chloro-4,6-dinitrobenzofuroxan afforded a new bipolar spiro-σ-complex **248**. The structure of the complex was established by X-ray diffraction analysis (Equation 48) <2002CHE1428, 2004RCB2075>.



247 **248** (48)

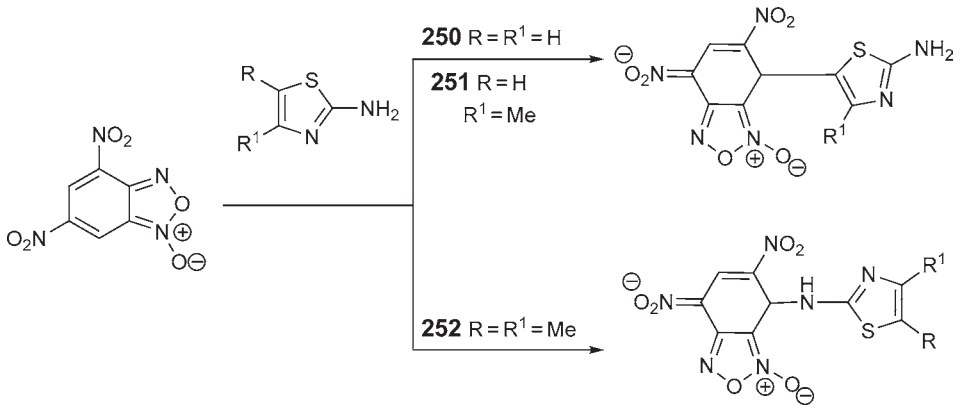
N-(8-Quinolyl)phenylmetanesulfonamide is a synthon suitable for building up dipolar spiro-σ-complexes with π-deficient arenes. σ-Complexes were synthesized by reaction of 7-chloro-4,6-dinitrobenzofuroxan and 7-chloro-4,6-dinitrobenzofurazan with *N*-(8-quinolyl) phenylmethanesulfonamide sodium salt **249** (**Scheme 64**) <2004RJO1384>.



249

Scheme 64

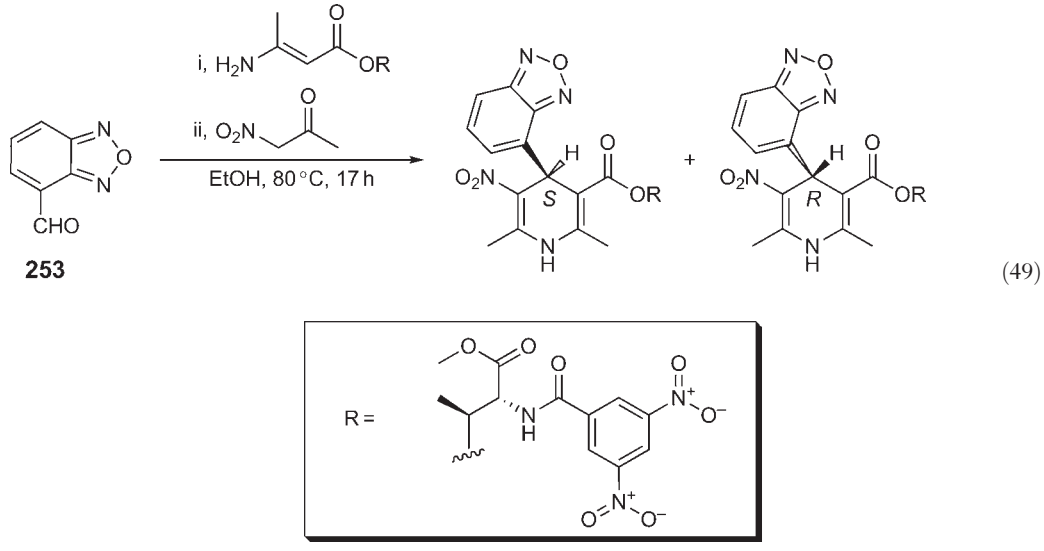
The reactions of 2-aminothiazoles with superelectrophilic DNBF have been studied in acetonitrile and a 70/30 (v/v) H_2O/Me_2SO mixture. While exhibiting somewhat higher nitrogen basicity than that of anilines, compounds **250** and **251** do not react as nitrogen nucleophiles, affording exclusively anionic C-bonded σ-adducts through electrophilic S_EAr substitution of the thiazole ring by DNBF. Only in the case of the 4,5-dimethyl derivative **252** was an N-adduct obtained (**Scheme 65**) <2006JOC5527>.



Scheme 65

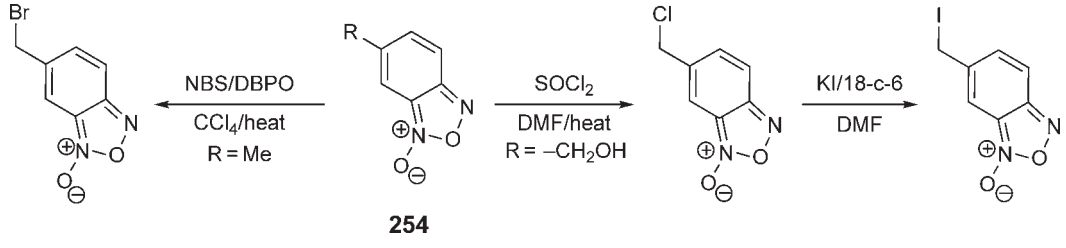
5.05.5.2.3 Miscellaneous reactions and transformations involving homocyclic ring substituents

The modified Hantzsch condensation of nitroacetone, 2,1,3-benzoxadiazol-4-carboxaldehyde **253**, and (1*S*,2*R*)-2-(3,5-dinitrophenylcarbonylamino)-2-methoxycarbonyl-1-methylethyl 3-aminocrotonate afforded a mixture of the two diastereomers that differ in configuration (*S* or *R*) at the C-4 position of the 1,4-DHP ring (DHP – dehydropeptidase) (Equation 49) <2004JME254>.



(49)

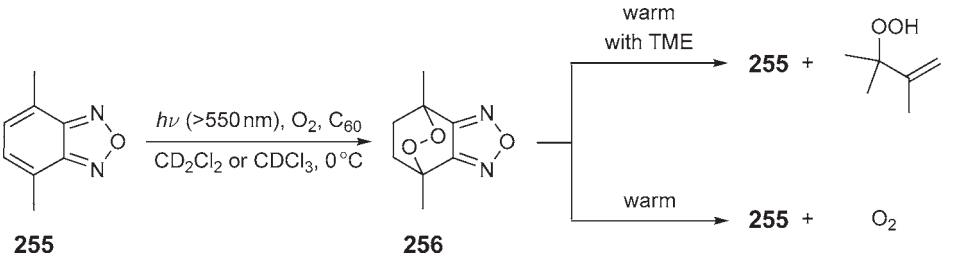
The synthesis of a chloro-, bromo-, and iodomethylbenzo[1,2-*c*]1,2,5-oxadiazole *N*-oxide was performed from methyl- or oxymethylbenzofurazans **254** (**Scheme 66**) <2005MI294>.



Scheme 66

The amido-, thioamido-, sulfonamido-, and semicarbazido-benzofuroxans possessing different lateral chains (heteroaliphatic, heterocyclic, and aromatic) were prepared by traditional methods by transformation of functional group of benzene fragment. The typical chemistry of benzofuroxanes did not take place in these cases <2002AP15>.

4,7-Dimethylbenzofurazan **255** was transformed by $^1O_2$ produced by irradiation of C_{60} into 4,7-dimethylbenzofurazan 4,7-endoperoxide **256** in $CDCl_3$ or CD_2Cl_2 at 0 °C in excellent yields. The endoperoxide **256** decomposed back to compound **255** at room temperature. When tetramethylethylene (TME) was added to the decomposing endoperoxide **256** at 37 °C, the hydroperoxide from reaction of TME with $^1O_2$ was detected (**Scheme 67**) <2001TL987>.



Scheme 67

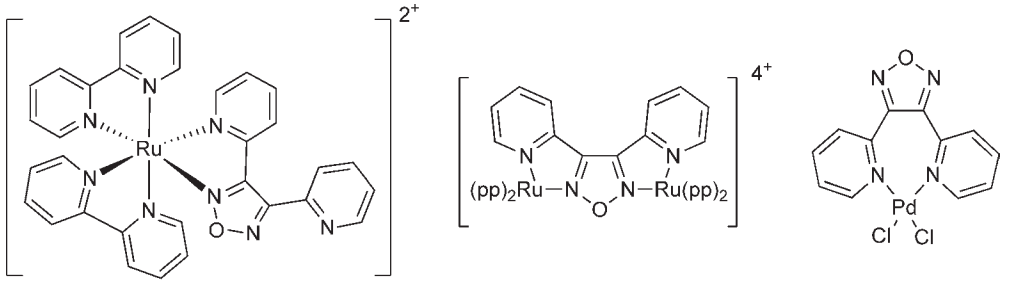
5.05.6 Reactivity of Substituents Attached to Ring Nitrogen

5.05.6.1 Deoxygenation of Furoxans and Benzofuroxans

The reduction of furoxans and benzofuroxans has been reviewed in detail in CHEC(1984) and CHEC-II(1996). The main reducing agents to remove oxygen atoms from nitrogen without cleavage of the heterocyclic ring are phosphines and phosphites. These reactions, namely deoxygenation of furoxans and benzofuroxans, are discussed in Section 5.05.4.2.2.

5.05.6.2 Furazans and Furoxans as ligands

3,4-Di(2-pyridyl)-1,2,5-oxadiazole (dpo) can form complexes with palladium, ruthenium, and copper having seven-membered chelate rings with coordination through the two pyridine nitrogens; several examples are shown below (complexes **257–259**). Studies of the mononuclear ruthenium complexes indicate five-membered chelate rings (involving donor nitrogen atoms from each of a pyridine ring and the oxadiazole or thiadiazole ring) and reveal that these ligands are very electron deficient and possess very low energy π^*-orbitals. Dinuclear ruthenium complexes have been prepared and the diastereoisomers were separated and crystallographically characterized <2002JCD2775>.



257 **258** (pp = bpy or Me_2bpy) **259**

The inclusion complexes of 3-R^1,4-R^2-disubstituted 1,2,5-oxadiazole-2-oxide with polycyclic derivatives of glucopyranose were prepared by heating an aqueous ethanolic solution of β-cyclodedextrin with the corresponding furazan <2002RUP2186782>.

5.05.7 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes

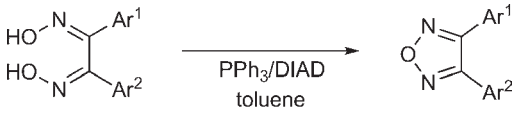
An analysis of the principal methods for construction of compounds with 1,2,5-oxadiazole heterocyclic units was published in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)393, 1996CHEC-II(4)229>. In this chapter only reactions that lead to the formation of 1,2,5-oxadiazole cyclic fragments are considered. The functionalization or replacement of substituents of heterocyclic ring as well as oxidation or deoxidation of nitrogen atoms are described in Section 5.05.4.

5.05.7.1 Furazan

As mentioned in CHEC-II(1996), three main routes have been reported for the formation of furazan rings: (1) the dehydrative cyclisation of 1,2-dioxims; (2) the deoxygenation of furoxans; and (3) the Boulton–Katritzky rearrangement of other five-membered heterocyclic systems <1996CHEC-II(4)229>. In this section the recent publications on the synthesis of furazans published after 1996 are discussed.

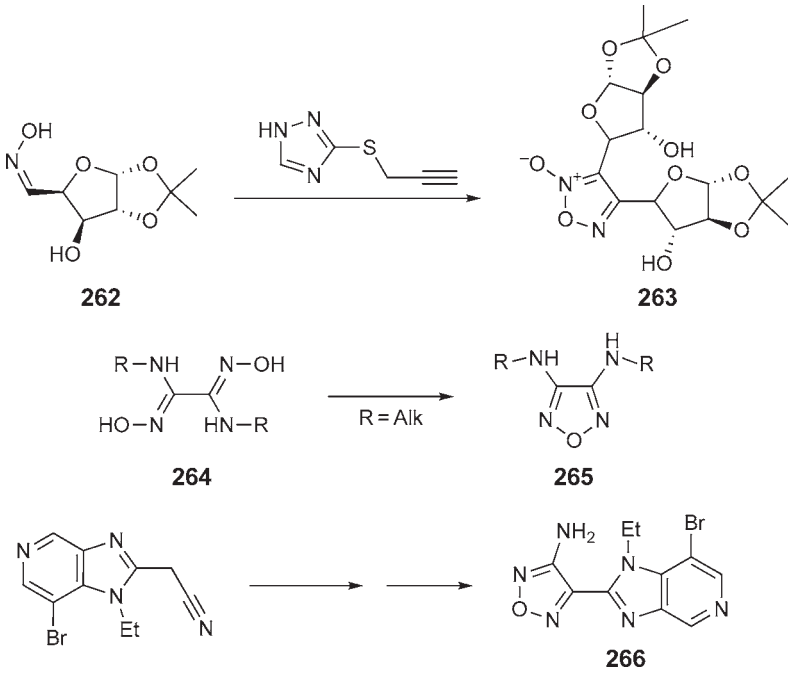
5.05.7.1.1 Dehydration of oximes and 1,2-dioximes

The most common route to furazans consists of the dehydration of readily available 1,2-dioximes <2005JME3260, 2006BML2915>. For example, a new strategy has been developed that exploits the dehydration of vicinal dioximes **260** using the Mitsunobu reaction. Among the advantages of this strategy are the mild conditions used for the construction of the diarylfurazan derivatives **261**, allowing for the presence of highly functionalized substrates and deactivated aromatic rings (Equation 50) <2005JME3260>.



260 **261** (50)

The 1,3-dipolar cycloaddition reaction of 1,2-*O*-isopropylidene-α-D-xylopentodialdo-1,4-furanose oxime **262** with 3-(2-propynylthio)-1*H*-1,2,4-triazole affords 3,4-bis-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)-1,2,5-oxadiazole-2-oxide **263** as a main product (**Scheme 68**) <2000CHC393>. Synthesis of 3,4-bis(alkylamino)-1,2,5-oxadiazoles **265**



262 **263**

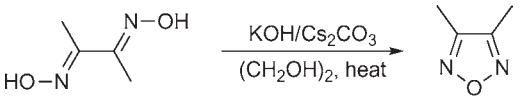
264 **265**

266

Scheme 68

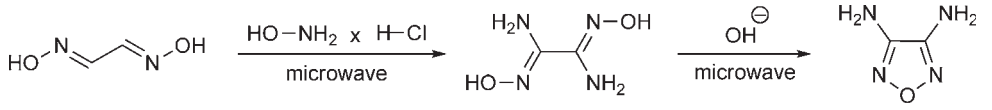
by cyclization of 1,2-bis(methylamino)glyoxime **264** in aqueous KOH at 170–180 °C has been described <2003MI13>. 4-(7-Bromo-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-1,2,5-oxadiazol-3-amine **266** was obtained by a two-step reaction sequence consisting of nitrosylation with sodium nitrite in methanolic HCl followed by heating with a basic aqueous solution of hydroxylamine (**Scheme 68**) <2005BML3402, 2005BML3407>.

Several new methods of synthesis of furazans were developed. Preparation of dimethylfurazan **267** was improved to 95% yield using the dehydration of dimethyldioxime in the presence of catalytic amounts of KOH and Cs_2CO_3 (Equation 51) <2003RCB679>.



267 (51)

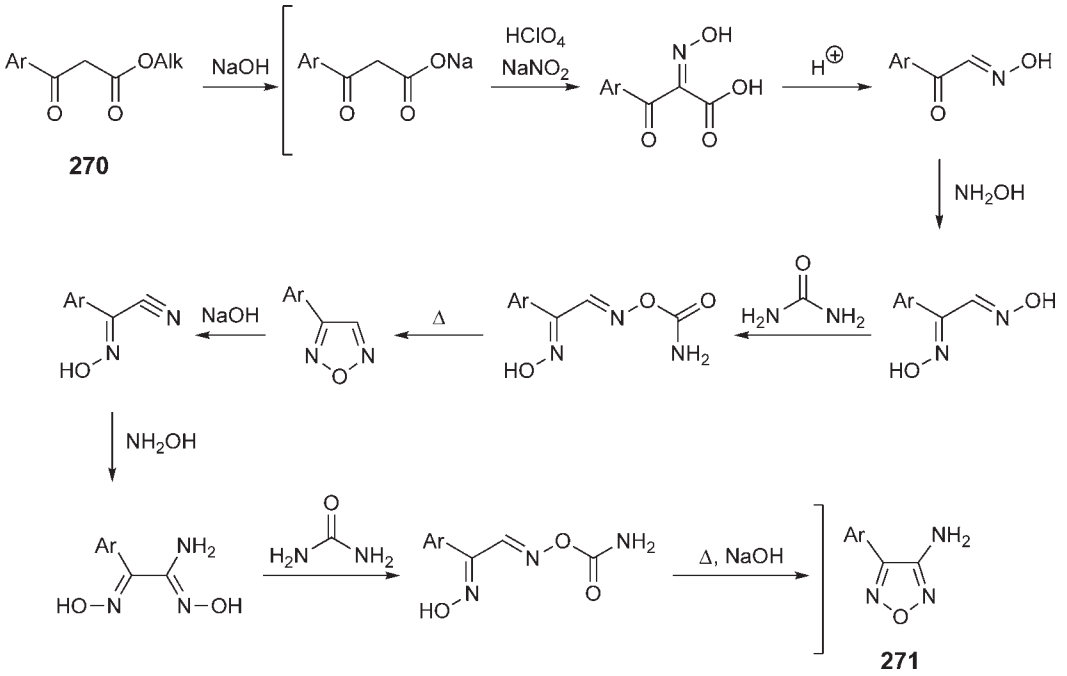
The first microwave-assisted synthesis of 3,4-diaminofurazan **156** was described in <2005JCM245>. The synthesis involves the vicarious nucleophilic substitution of hydrogen in glyoxime **268** using hydroxylamine hydrochloride under microwave irradiation to obtain diaminoglyoxime **269**, which on further irradiation in alkali solution yielded 3,4-diaminofurazan (**Scheme 69**). An improved two-step procedure for the synthesis of 3,4-diaminofurazan from glyoxal has also been reported <1997JHC1057>.



268 **269** **156**

Scheme 69

A one-pot multistep process for the synthesis of 3-amino-4-aryl- and 3-amino-4-hetarylfurazans **271** from *β*-aryl- and 4-*β*-hetaryl-*β*-oxo acid esters **270** was developed (**Scheme 70**) <2005RCB1057>.



270 **271**

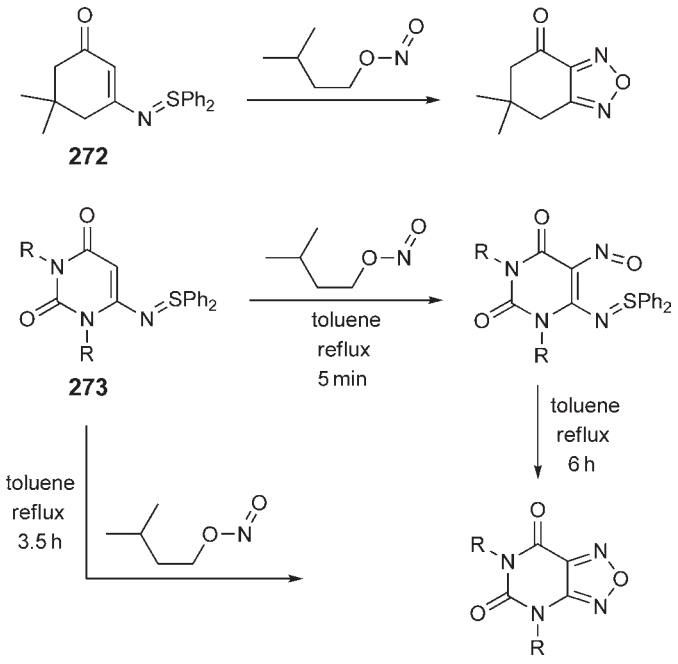
Scheme 70

5.05.7.1.2 Deoxygenation of furoxans

Furazans can be obtained via deoxygenation of furoxans and this widely used method is discussed in Section 5.05.4.2.2 (see also <1997CHE471, 2000J(P2)473, 2001EJM771>).

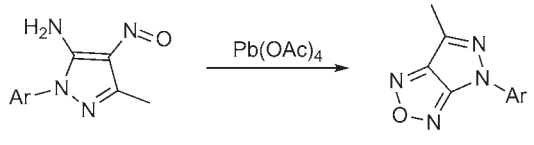
5.05.7.1.3 Miscellaneous

The furazan ring can be constructed by the one-pot reaction of *N*-(5,5-dimethyl-3-oxocyclohexenyl)-*S*,*S*-diphenylsulfilimine **272** with isopentyl nitrite <2006SC2087> and also by a one-pot procedure from sulfinimines **273**, without isolation of the nitroso intermediates, in refluxing toluene (**Scheme 71**) <2002T10073>.



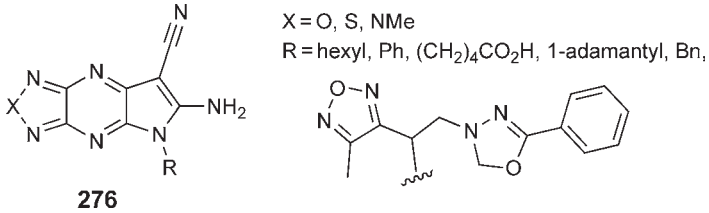
Scheme 71

4-Aryl-substituted 6-methyl-4*H*-pyrazolo[3,4-*c*]-1,2,5-oxadiazoles **275** are easily obtained in 88–97% yields by the oxidation of 2-aryl-5-methyl-4-nitroso-2*H*-pyrazol-3-amines **274** with $Pb(OAc)_4$ (Equation 52) <2000S72>.

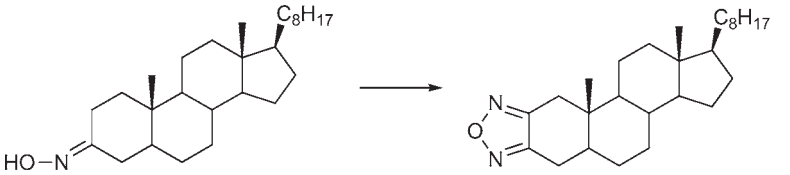


(52)

The fused heterocyclic compounds **276** containing furazan fragment were prepared by reaction of the annelated 2,3-dichloropyrazines with malononitrile, followed by treatment with RH <2001MC152>.

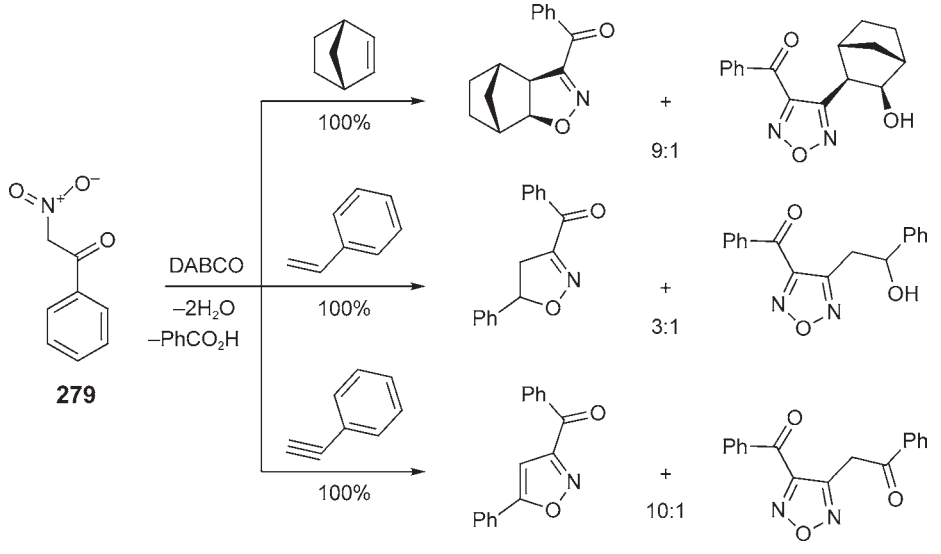


Furazan compound **278** was obtained as a by-product from cholestan-3-one oxime **277** by prolonged heating in an acetic anhydride–pyridine mixture followed by treating with acetyl nitrate prepared from acetic anhydride and nitric acid (Equation 53) <1997T16161>.



(53)

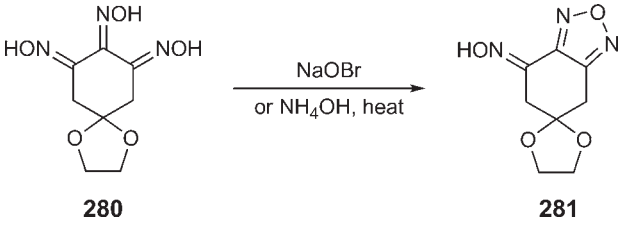
The side products of the reaction between benzoylnitromethane **279** and dipolarophiles (norbornene, styrene, and phenylacetylene) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) were identified as furazan derivatives (**Scheme 72**). The evidence reported indicates that benzoylnitromethane gives the dibenzoylfuroxan as a key intermediate, which is the dimerization product of the nitrile oxide. The furoxan then undergoes addition to the dipolarophile, hydrolysis, and ring rearrangement to the final products (furazans and benzoic acid) <2006EJO3016>.



Scheme 72

5.05.7.2 Benzofurazans

Benzofurazans can be obtained by several methods: (1) by dehydration of *o*-quinone dioxime; (2) from *o*-substituted nitrosoarenes; and (3) deoxygenation of benzofuroxans <1984CHEC(6)393, 1996CHEC-II(4)229>. For example, trihydroxyimino derivative **280** treated with sodium hypobromite, or when boiled in aqueous ammonia, affords the corresponding substituted tetrahydrobenzofurazan **281** (Equation 54) <2000CHE996>.

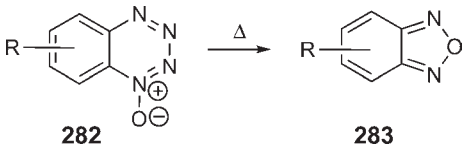


(54)

Deoxygenation of benzofuroxans usually with triphenylphosphine affords corresponding benzofurazans (see Section 5.05.4.2.2 and <2002BML233, 2003BMC899, 2003PCJ522, 2003OPD436> (Equation 55). Use of tributylphosphine in place of triphenylphosphine facilitates the purification of benzofurazans, but the method is less efficient (28–74% yields) <2002BML233, 2003OPD436>.

(55)

Decomposition of 1,2,3,4-benzotetrazine 1-oxides **282** involves opening of the tetrazine ring to afford *ortho*-azidonitroso derivatives, followed by their cyclization with the evolution of the N_2 molecule to give benzofurazans **283** (Equation 56) <2002EJO3435>.

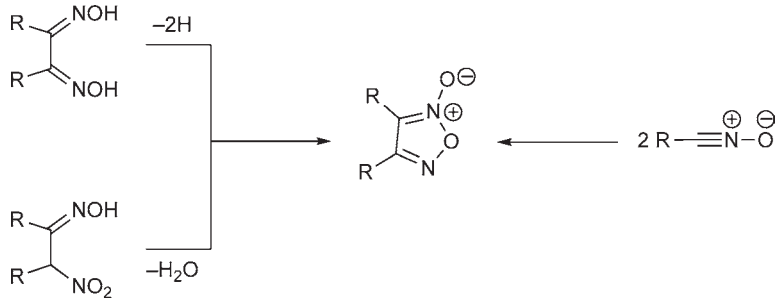


282 **283**

(56)

5.05.7.3 Furoxans (1,2,5-oxadiazole 2-oxide)

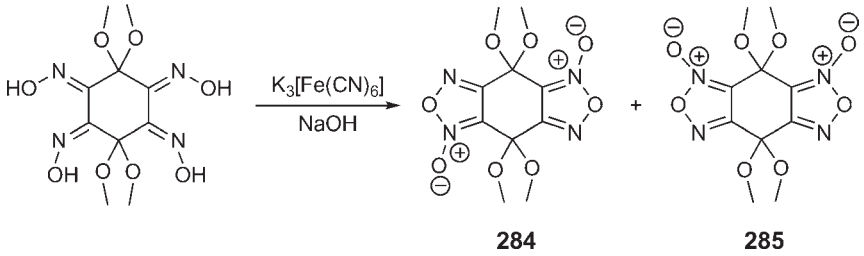
In recent years, the synthesis of new derivatives of 1,2,5-oxadiazole 2-oxide (furoxan) has attracted considerable attention. This interest stems largely from the fact that many furoxan derivatives exhibit biological activities and from the ability of some of these derivatives to serve as donors of nitrogen oxide, see Section 5.05.8 and the following references for example <1996FA617, 1999JME1941, 2000BMC1727, 2000CPB808>. The furoxan ring can be constructed by various methods, the most synthetically useful of which are: (1) the oxidative cyclization of 1,2-dioximes; (2) the dehydration of α-nitroketoximes and symmetrically substituted furoxans; and (3) the dimerization of nitrile oxides (**Scheme 73**). Oxidation of furazans also leads to furoxans (see Section 5.05.4.1) <1997J(P1)1047>.



Scheme 73

5.05.7.3.1 Oxidation

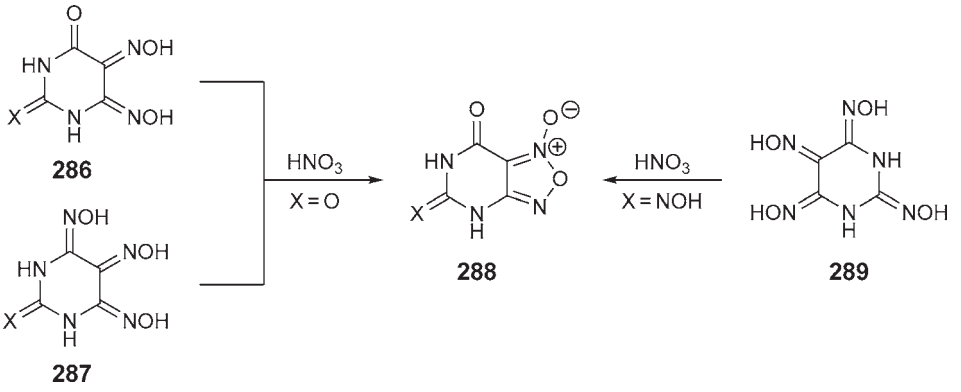
The method based on oxidation of dioximes is illustrated by the oxidation of 1,1,4,4-tetramethoxy-2,3,5,6-tetrahydroximinocyclohexane by an alkaline solution of potassium hexacyanoferrate(III) to give a mixture of isomers **284** and **285** (Equation 57) <1997CHE471>.



284 **285**

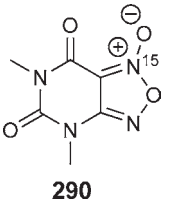
(57)

Pyrimidine oximes **286**, **287**, and **289** are oxidized with nitric acid to furoxanes **288** <2005RJC457, 2004CHE361>; in the case of oximes **287** and **289**, the reaction is accompanied by the hydrolysis of the oxime group in the 4-position of the starting pyrimidine (**Scheme 74**) <2005RJC457>.

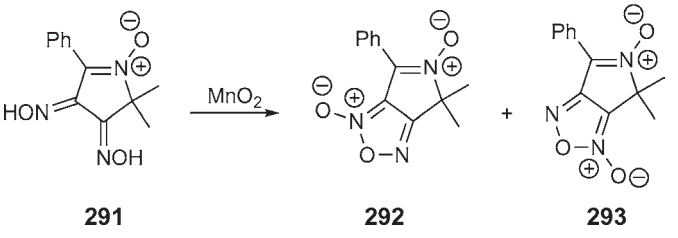


Scheme 74

[^{15}N]-Labeled 4,6-dimethyl-4*H*-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione 1-oxide **290** is conveniently prepared by nitration of commercially available 6-amino-1,3-dimethyl-1*H*-pyrimidine-2,4-dione using ^{15}N-enriched nitric acid followed by an intramolecular oxidative cyclization with iodosylbenzene diacetate under mild conditions <2000JOC6670>.

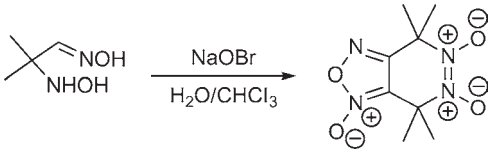


The oxidation of oxime **291** by MnO_2 gave two isomers **292** and **293** in approximately equal amounts with their ratio changing with time toward isomer **293** (Equation 58) <2001RCB874>.



(58)

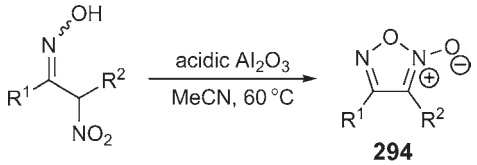
The oxidation of 2-hydroxyamino-2-methylpropanaldoxime by NaOBr leads to 4,4,7,7-tetramethyl-4,7-dihydrofurazano[3,4-*d*]pyrazine 1,5,6-trioxide (Equation 59) <1997CHE343>.



(59)

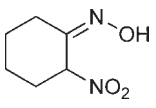
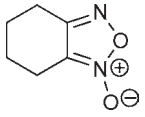
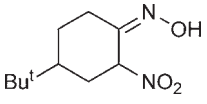
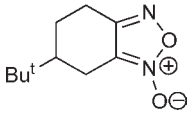
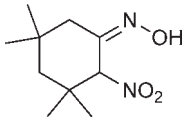
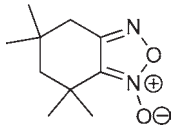
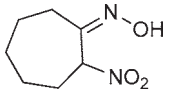
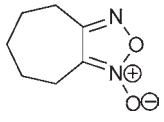
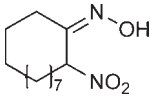
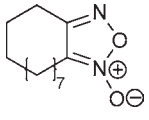
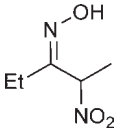
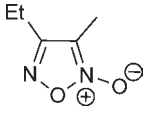
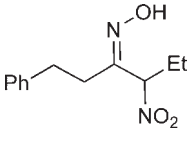
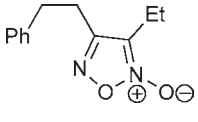
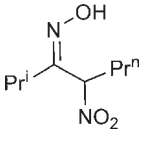
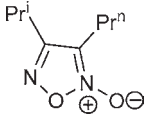
5.05.7.3.2 Dehydration of α-nitroketoximes

A convenient method for the synthesis of 1,2,5-oxadiazole *N*-oxides (furoxans) **294** from α-nitroketoximes using acidic alumina as catalyst has been described (Equation (60), **Table 3**) <2000TL8817>.



294 (60)

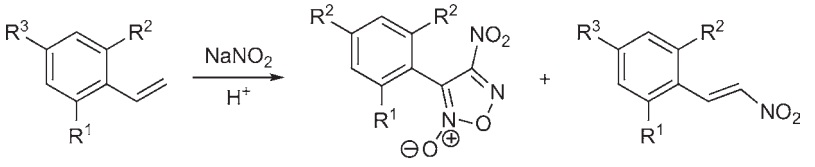
Table 3 Aluminium oxide-promoted synthesis of furoxanes from α-nitro-oximes

Substrate	*Product* (294)	*Time* (*h*)	*Yield* (%)
		1	93
		1	93
		5	75
		3	89
		3	82
		3	91
		4	83
		4	85

The well-known method of furazan formation is based on nitrosation of alkenes. Thus, several NO donor 3,4-disubstituted 1,2,5-oxadiazole 2-oxide derivatives and the related 1,2,5-oxadiazoles, containing methylsulfonylphenyl, phenylsulfonyl, sulfonylamidophenyl, and phenylsulfonylamido groups were synthesized by nitration of

1,2-disubstituted ethenes with sodium nitrite <2005BMC2749, 2005CBI886>. The reaction of $AgNO_2$/TMSCl with alkenes affords nitrosonitrates which are converted into α-nitroximes in good yields. Both nitrosonitrates and nitroximes are converted by reaction with acids into furoxans in high yields <2005LOC602>.

The classical Wieland furoxan synthesis has been reinvestigated and this procedure applied to the preparation of 4-aryl-l,2,5-oxadiazole-3-yl derivatives **295** (Equation 61) <1996BML1993>.



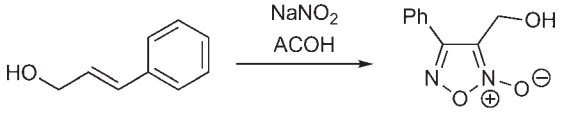
$R^1 = R^2 = R^3 = H$
$R^1 = Cl, R^2 = R^3 = H$
$R^1 = R^2 = Cl, R^3 = H$
$R^1 = R^2 = R^3 = Me$

295

$R^1 = R^2 = Cl, R^3 = H$
$R^1 = R^2 = R^3 = Me$

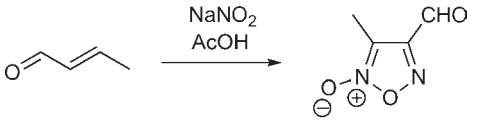
(61)

3-Hydroxymethyl-4-phenylfuroxan **296** and 3-carboxy-4-methylfuroxan **297** were obtained from cinnamyl alcohol and crotonaldenyde, respectively (Equations 62 and 63) <1999JME1941, 2000JFA2995>.



296

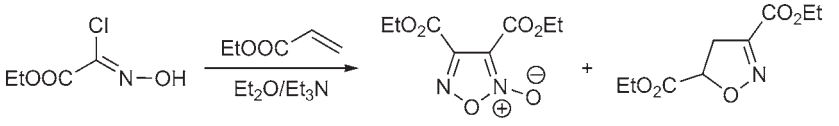
(62)



297

(63)

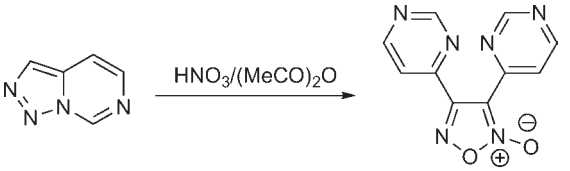
Furoxane **298** was prepared by the reaction of ethyl 2-chloro-2-(hydroxyimino)acetate with carboethoxyethene in the presense of base (Equation 64) <2003TL5327>.



298

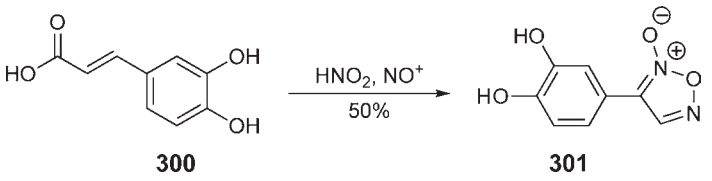
(64)

Reaction of [1,2,3]triazolo[1.5-*c*]pyrimidine with fuming nitric acid gives furoxan derivative **299** in low yield (Equation 65) <2001T10111>. Caffeic acid **300** reacts with acidic nitrite leading to a mixture of three products. The main product has been identified as the furoxan derivative **301** (Equation 66) <2001TL3303>.



299

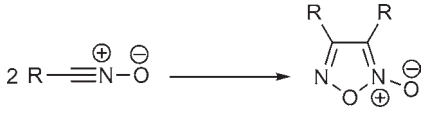
(65)



300 301 (66)

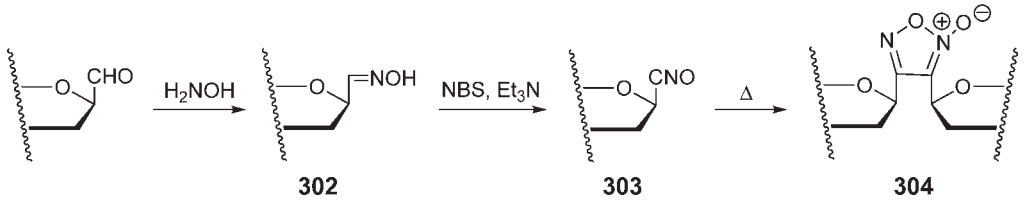
5.05.7.3.3 Dimerization of nitrile oxides

Nitrile oxides are widely used as participants in 1,3-dipolar cycloadditions leading to five-membered heterocycles. Nitrile oxides (especially for lower aliphatic and acyl nitrile oxides) can dimerize easily to form 1,2,5-oxadiazole-2-oxides (Equation 67) <2003JA15420>.



(67)

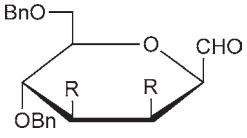
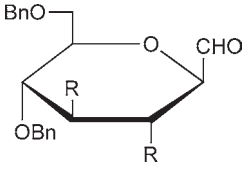
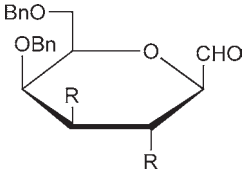
Several examples of the synthesis of furoxans by dimerisation of nitryl oxides are shown below. The treatment of oximes **302** with *N*-bromosuccinimide (NBS) and then with triethylamine leads to the formation of nitrile oxides **303**, as shown by the presence of a strong IR absorption band at around 2300 cm^{-1} typical of the CNO group stretching. Slow dimerization of nitrile oxides **303** took place at room temperature leading to the furoxans **304** in good yields (**Scheme 75** and **Table 4**) <2002S1701>.



302 303 304

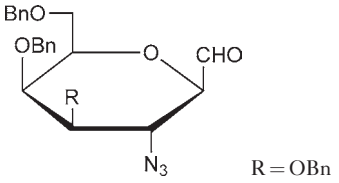
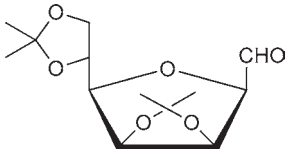
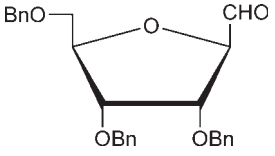
Scheme 75

Table 4 Conversion of anomeric sugar aldehydes to oximes **302** and furoxans **304**

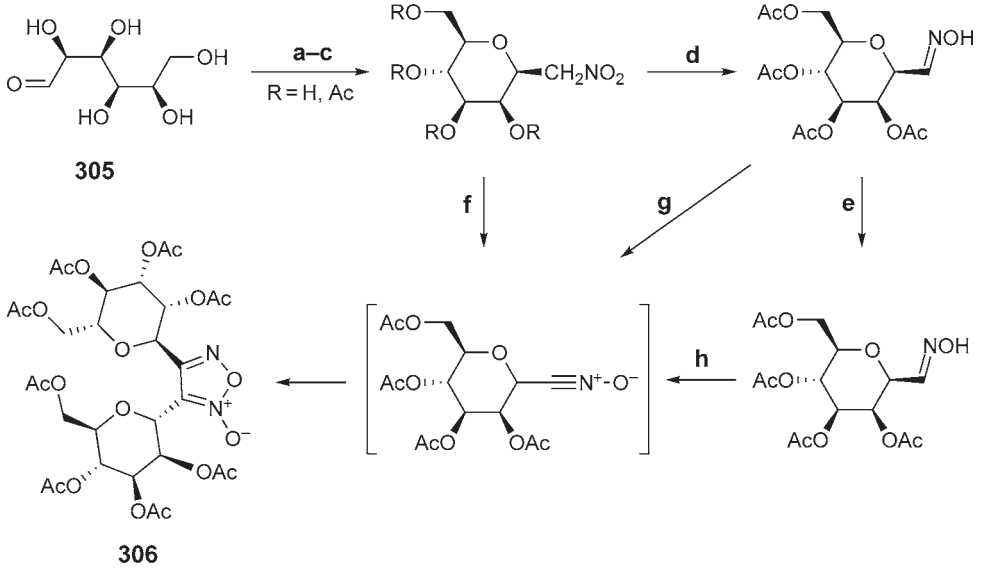
Aldehyde	*Oxime* **302**, *yield* (%)	*Furoxane* **304** *yield* (%)
 R = OBn	78	60
 R = OBn	85	80
 R = OBn	85	80

(*Continued*)

Table 4 (Continued)

Aldehyde	*Oxime* **302**, *yield* (%)	*Furoxane* **304** *yield* (%)
 R = OBn	88	60
	90	75
	85	75

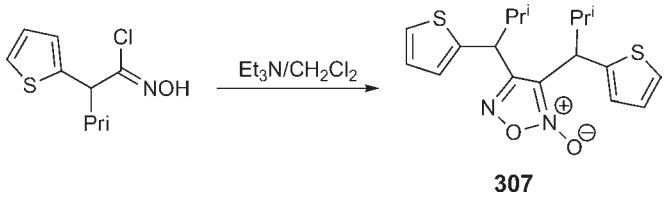
3,4-Di-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-1,2,5-oxadiazole 2-oxide **306** was synthesized from D-mannose **305** by a route involving dimerization of mannopyranosyl nitrile oxide as the key step. Three methods were used for the generation of the nitrile oxide: isocyanate-mediated dehydration of nitromethylmannose derivatives, treatment of aldoxime with aqueous hypochlorite, and base-induced dehydrochlorination of hydroximoyl chloride (**Scheme 76**) <2001TL4065, 2002T8505>.



a: $MeNO_2$/NaOMe, MeOH; **b**: H_2O, reflux; **c**: Ac_2O/CF_3SO_3H; **d**: $SnCl_2$/PhSH/Et_3N, THF; **e**: Cl_2, CH_2Cl_2; **f**: TDI/Et_3N, PhMe, reflux, quench with $H_2NCH_2CH_2NH_2$; **g**: aq. NaOCl, CH_2Cl_2; **h**: Et_3N, Et_2O

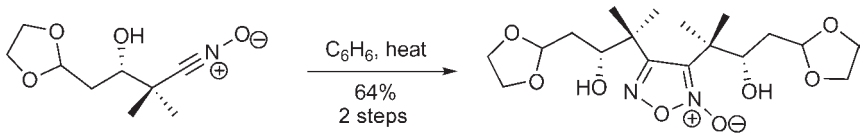
Scheme 76

Nitrile oxides are readily formed upon treatment of hydroximoyl halides with a base such as Et_3N <1998T791, 2000ARK683>. Usually nitrile oxides are unstable and easily dimerize to form furoxans in the absence of a dipolarophile. For example, an almost quantative yield of furoxan **307** is formed in the absence of the trapping reagents (Equation 68) <1998T791>.



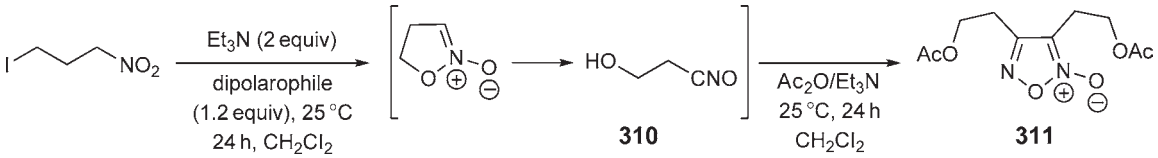
307 (68)

Dimerization under neutral conditions takes place upon refluxing a concentrated solution (1.0 M) of nitrile oxide **308** in benzene for 18 h resulting in clean formation of dimer **309** (Equation 69) <2001JOC6410>.



308 **309** (69)

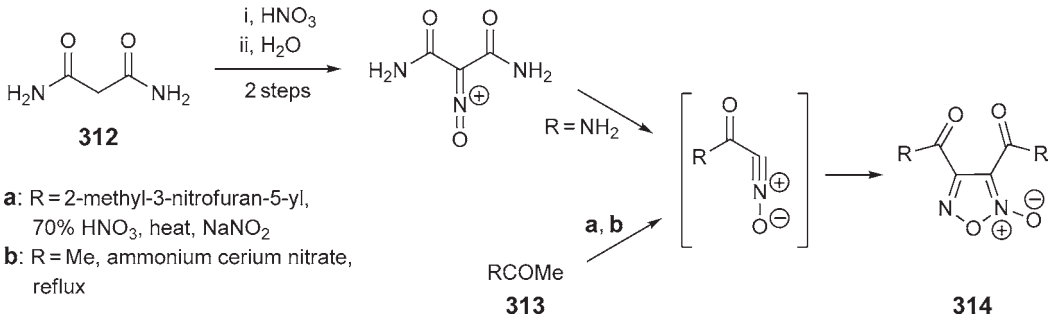
The nitrile oxide **310**, generated from isoxazoline *N*-oxide in the presence of acetic anhydride and triethyl amine, gives acetylated dimer **311** in 30% yield (**Scheme 77**) <1998TL8869>.



310 **311**

Scheme 77

Nitrition of ketones **313** and malonic acid diamide **312** also leads to the formation of furoxans **314** (**Scheme 78**) <1999CHE1415, 2004T1671, 2005MRC563>.

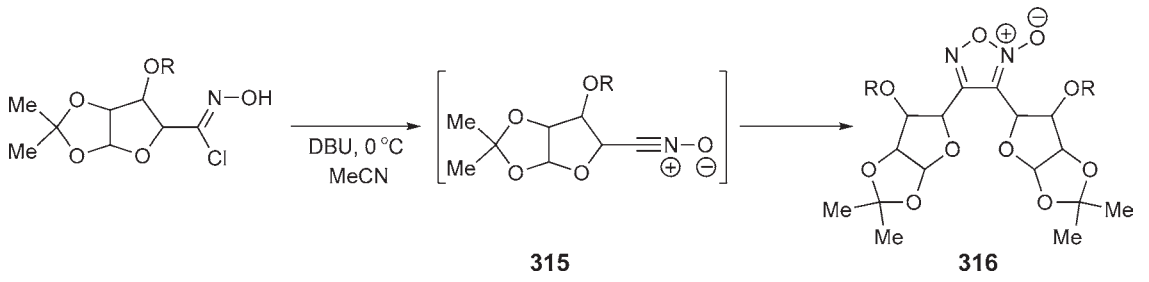


312 **313** **314**

a: R = 2-methyl-3-nitrofuran-5-yl, 70% HNO_3, heat, $NaNO_2$
b: R = Me, ammonium cerium nitrate, reflux

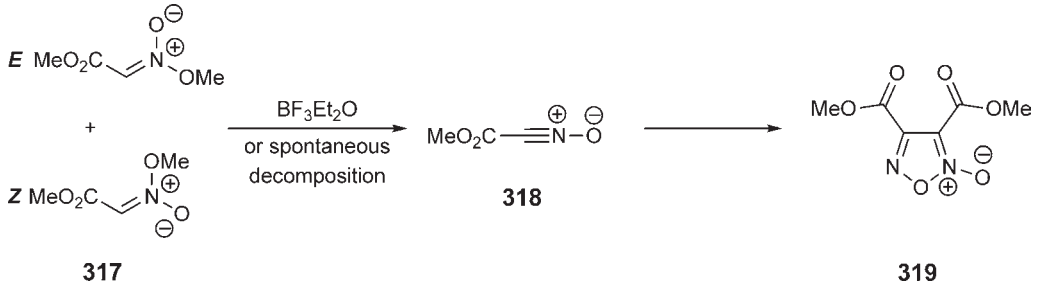
Scheme 78

Glycosyl nitrile oxides **315**, generated *in situ* by reaction of hydroxamoyl chlorides with DBU, participate in 1,3-dipolar cycloaddition with substituted alkenes leading to glycosyl isoxazolines; the 1,2,5-oxadiazole-2-oxides **316** are isolated as by-products in low yields (**Scheme 79**) <2004CHC353>.



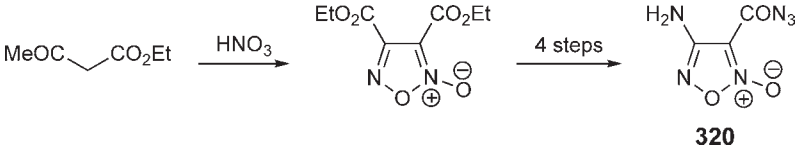
Scheme 79

Dimerization of methoxycarbonylformonitrile oxide **318** generated from precursor **317** by the β-elimination of methanol gives furoxan **319** (**Scheme 80**) <1998TL8865>.



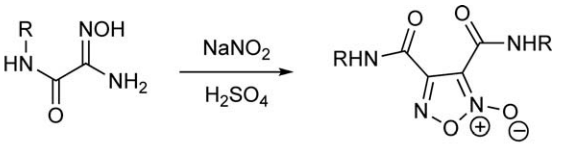
Scheme 80

A convenient method was developed for the synthesis of 4-amino-3-furoxancarboxylic acid azide, which is a universal synthon for the preparation of furoxan derivatives **320** (**Scheme 81**). This method was used for the synthesis of new azo-, azoxy-, azido-, cyano-, nitro-, carbonylamino-, and hydroxylamino-substituted furoxan derivatives that are difficult to prepare using alternative procedures <2003RCB1822>.



Scheme 81

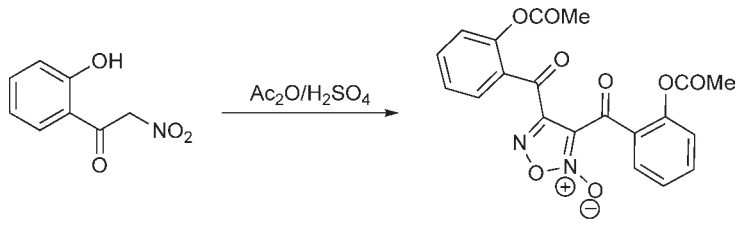
Furoxanes **321** can be prepared from amide oximes in one step by nitrosation of hydroxylamines in the presence of H_2SO_4 (Equation 70) <2002RCB1504>.



(70)

R = Ph, 4-$MeOC_6H_4$, 3,4-$Cl_2C_6H_3$, 4-$NO_2C_6H_4$, 2,3-$Me_2C_6H_3$, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 2,6-$Me_2C_6H_3$

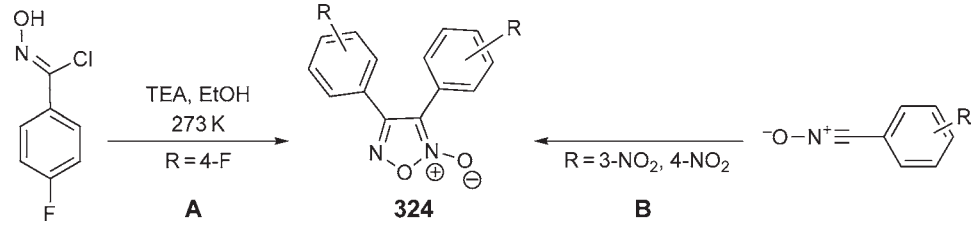
Treatment of compound **322** with acetic anhydride in the presence of a slight excess of sulfuric acid gives the furoxan **323** (Equation 71) <2002IEC3333>.



(71)

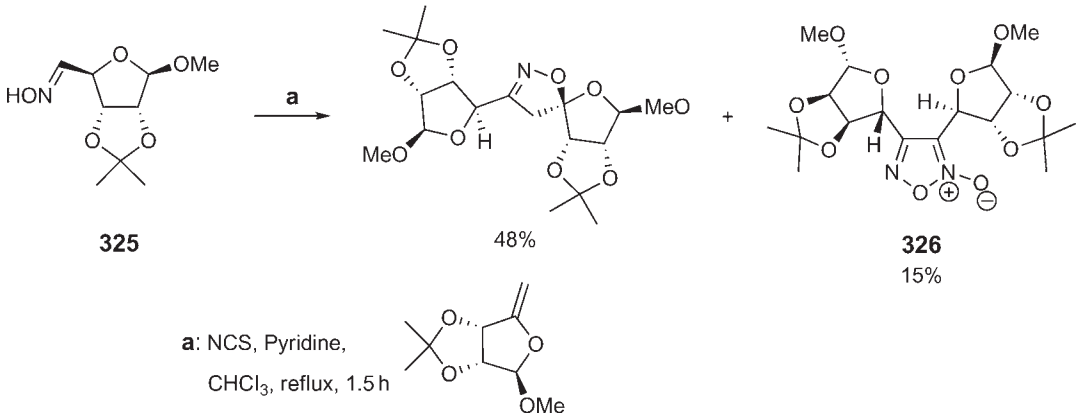
322 **323**

The 3,4-bis(4-fluorophenyl)-1,2,5-oxadiazole 2-oxide **324** was found as a side product in the synthesis of isoxazole derivatives (**Scheme 82**, method **A**) <2006AXEo4827>. Dimerization of 3- and 4-nitrobenzonitrile *N*-oxides gave corresponding 1,2,5-oxadiazole *N*-oxides (**Scheme 82**, method **B**) <1999MI111>.



Scheme 82

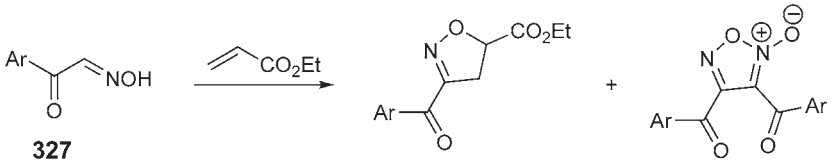
The nitrile oxide generated *in situ* by oxidation of oxime **325** gives the dimer **326** in 15% yield (Equation 72) <2001J(P1)415>.



(72)

325

Oxidation of aldoximes **327** with sodium hypochlorite or NBS is one of the best-known methods for generation of nitrile oxides (Equation 73) <1999BCJ2277>.



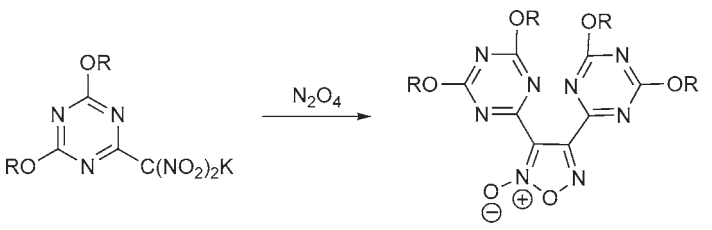
(73)

327

Ar = 3,4-Dimethoxyphenyl

CAN/MeCN	97%	0%
NBS/DMF	10%	72%
$NaClO/CHCl_3–H_2O$	90%	0%

It was established that the reaction of the potassium salts of 2,4-dialkoxy(aryloxy)-6-dinitromethyl-1,3,5-triazines **328** with nitrogen oxides in organic solvents is accompanied by formation of 3,4-bis(2′,4′-dialkoxy(aryloxy)-1,3,5-triazin-6′-yl)-1,2,5-oxadiazole *N*-oxides **329** in 60–85% yield (Equation 74) <2006CHE557>.

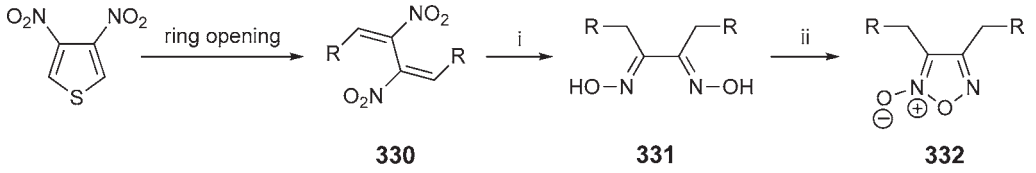


(74)

328 **329**

R = Me, Pr, Pr^{i}, Bu, Cyclo-C_6H_{11}, *p*-C_6H_4Br, *p*-$C_6H_4CO_2Me$

1,4-Dialkyl- and 1,4-diaryl-2,3-bis(hydroxyimino)butanes **331**, from the reduction of the corresponding 1,4-disubstituted 2,3-dinitro-1,3-butadienes **330**, were transformed into 3,4-disubstituted 1,2,5-oxadiazole 2-oxides **332** with satisfactory yields. Dinitrobutadienes **330** were obtained from the reaction of 3,4-dinitrothiophene with diethylamine and subsequent treatment of the ensuing bis(diethylamino)butadiene with Grignard reagents. Thus, the overall transformation represents a novel approach to 1,2,5-oxadiazole via a ring-opening–ring-closure strategy (**Scheme 83**) <1997T1751>.

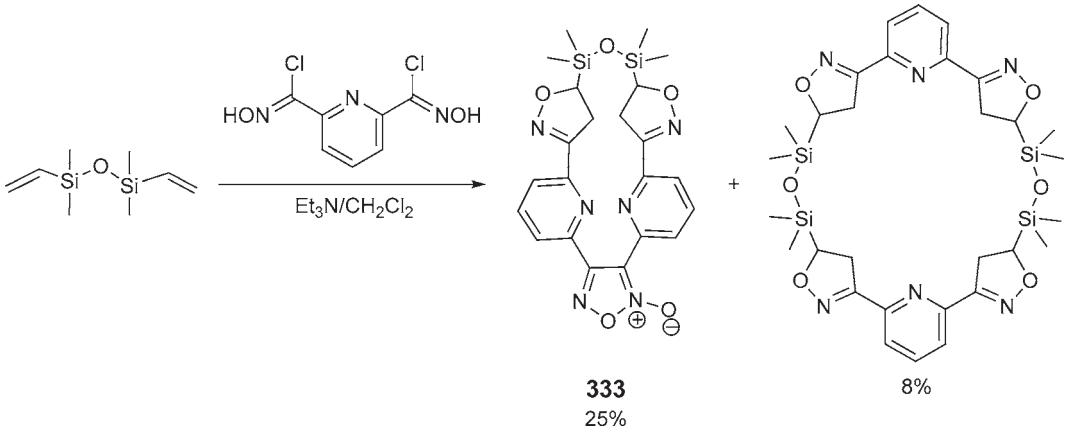


330 **331** **332**

i, DMF-AcOH/Pb powder; ii, EtOH/NaOH/5% aq NaClO;
R = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, cyclo-C_6H_{11}

Scheme 83

Silamacrocycle **333** was synthesized as the major product by the unusual triple cycloaddition shown in Equation 75 <2001S2191, 2000TL4177>.



(75)

333
25%

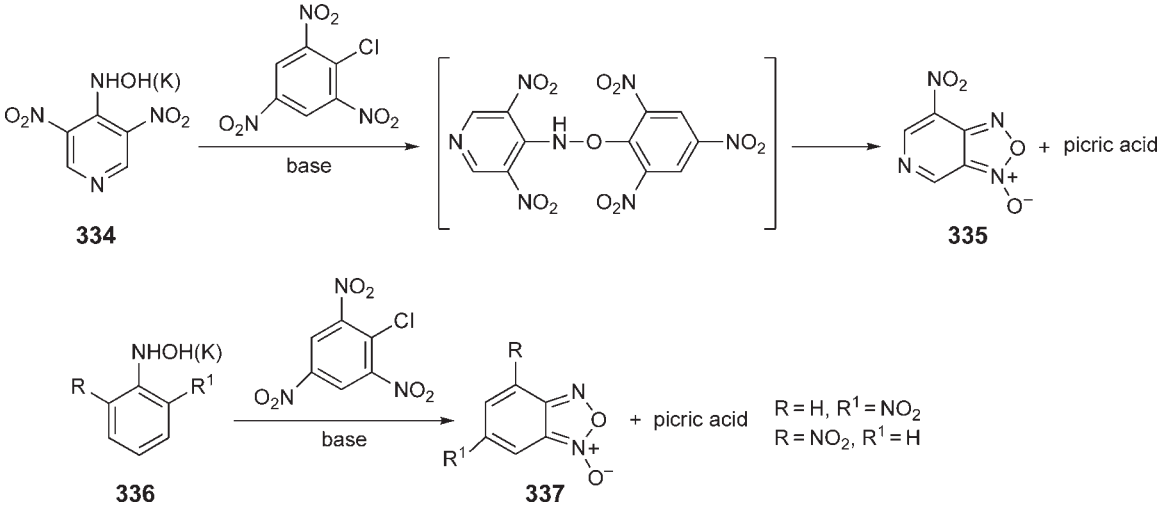
8%

5.05.7.4 Benzofuroxans

The most synthetically useful methods for benzofuroxans are: (1) oxidation of *o*-quinone dioximes; (2) decomposition of *o*-nitroaryl azides; and (3) oxidation of *o*-nitroanilines. Benzofuroxans can also be formed as a result of Boulton–Katritzky rearrangement (see Section 5.05.5.2.1).

5.05.7.4.1 Oxidation of oximes

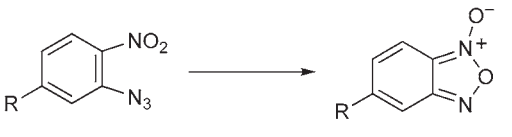
The synthesis of furoxans from oximes has been discussed <2000CHE1003, 2004RJA853>. Preparation of 3-nitro[4,5-*c*]pyridofuroxane **335** by the reaction of 4-hydroxylamino-3,5-dinitropyridine **334** with picryl chloride is shown in **Scheme 84**. Similarly, the reaction of 2,4- or 2,6-dinitrophenylhydroxylamine **336**, or its potassium salt, with picryl chloride yielded, respectively, 4- or 6-nitrobenzofuroxane **337** and picric acid (**Scheme 84**). It was reported that the Nietsky–Dische reaction of 3,5-dinitro-4-hydroxylaminopyridine with picryl chloride in the presence of base leads to 3-nitro-4,5-pyridofuroxan and picric acid. The formation of a furoxan ring is explained by intermediate generation of an unstable hydroxylamine ester, which decomposes to give 3-nitro-4,5-pyridofuroxan and picric acid. Thus, the shown reactions indicate that the furoxan ring-formation mechanisms are identical for both the arene and pyrido derivatives (**Scheme 84**) <2000CHE1003>.



Scheme 84

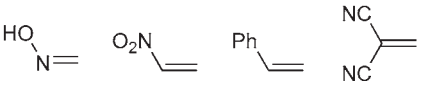
5.05.7.4.2 Decomposition of o-nitroaryl azides

The extrusion of dinitrogen from 2,6-diazido-3,5-dinitropyridine followed by ring closure is a primary method for preparation of benzofuroxans. Thus, a number of benzo[1,2-*c*]1,2,5-oxadiazole *N*-oxides such as **339** (Equation 76) have been prepared by thermolysis of the appropriate nitrophenyl azides **338** in refluxing toluene <1999JME1941, 2000JFA2995>, by the thermal decomposition of 4-bromo-2-methyl-6-nitrophenylazide <2001H(55)2387>, and by cyclocondensation in boiling toluene using Hansch's series design methodology <2005BMC6324>. The thermolysis of 4-fluoro-2-nitroarylazide gave the respective benzofuroxan in 80% yield <2003JFC(121)171>. In the cases of 4,6-difluoro-2-nitrophenylazide and 4,5,6-trifluoro-2-nitrophenylazide, the presence of a fluorine atom in the 6-position on the aromatic ring, *ortho* to the azide, does not inhibit the benzofuroxan formation. However, experimental results suggest that the presence of this fluoro-substituent slows down the equilibrium between the two fluoro-substituted benzofuroxan tautomers <2003JFC(121)171>. 5-Azido-pyrido[2,3-d]pyrimidine-2,4,7-triones afforded the respective cyclization products only at higher temperatures using refluxing bromobenzene <1996MOL201>.

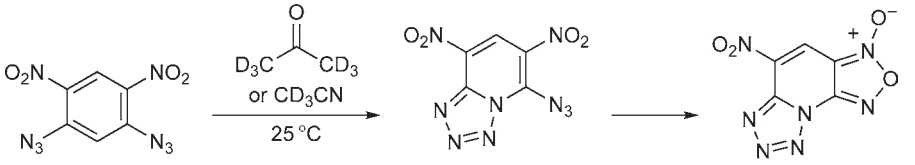


338 **339** (76)

R = H, Me, Ph, Cl, Br, CH_2Cl, CH_2I, NO_2, CHO, COOH, CN, CH_2OH, NMe_2,



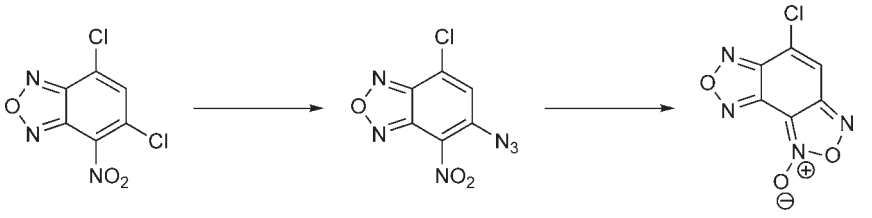
7-Nitrotetrazolo[1,5-*f*]furazano[4,5-*b*]pyridine 1-oxide **340** (NFP) was prepared by the extrusion of nitrogen from 2,6-diazido-3,5-dinitropyridine followed by ring closure (**Scheme 85**) <2005JEM99>.



340

Scheme 85

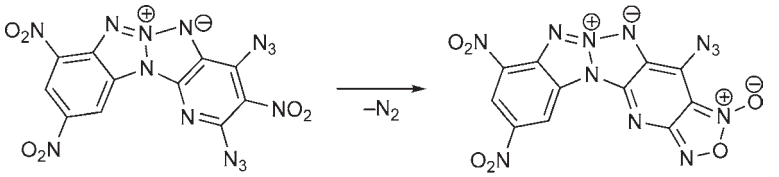
An improved method for the synthesis the 4-chloro-6,7-furoxanobenzofurazan **341** has been reported (**Scheme 86**) <2003PCJ522>.



341

Scheme 86

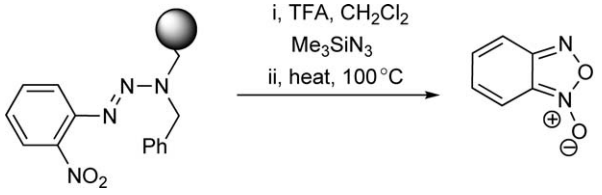
Adjacent 2-azido and 3-nitro groups facilitate the elimination of nitrogen followed by ring closure to form the corresponding furazan *N*-oxide compound **342** (Equation 77) <1996JOC5801, 2005AGE7089>.



342 (77)

The reactions of diazoesters with hydrochloric and sulfuric acids, triphenylphosphine, and dinitrogen tetroxide resulted in aryl chloroacetates, bis(aryloxycarbonylmethyl) sulfates, triphenylphosphoranylidenehydrazones of aryl 2-oxoethanoates, and *N*-oxides of diaryl 1,2,5-oxadiazole-3,4-dicarboxylates <1999RJO1666>.

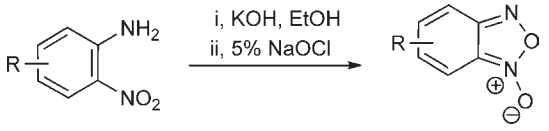
As an example for an application of the method to post-cleavage synthesis of heterocycles, the cyclization of 2-nitroaryl azides based on the *ortho*-nitro resins performed at approximately 100 °C yields benzofuroxane in high purities (Equation 78) <2004SL1163>.



(78)

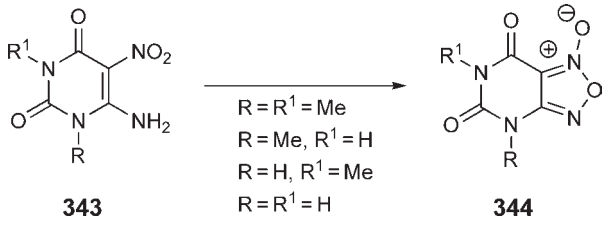
5.05.7.4.3 Oxidation of o-nitroanilines

The oxidative ring-closure method is well known. Halo-substituted benzofurazans are obtained by reaction of aqueous sodium hypochlorite with potassium salts of the corresponding 2-nitroanilines (Equation 79) <2001SC2329, 2002BML233, 2003HCA1175, 2003JFC(121)171, 2003OPD436>.



(79)

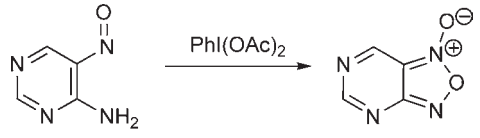
In a similar manner, 4*H*-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine-5,7-dione 1-oxides **344** are conveniently prepared in high yields by the oxidative intramolecular cyclization of 6-amino-5-nitro-1*H*-pyrimidine-2,4-diones **343** employing iodosylbenzene diacetate as an oxidant in the presence of lithium hydride (Equation 80) <1998JOC6947>.



343 **344**

(80)

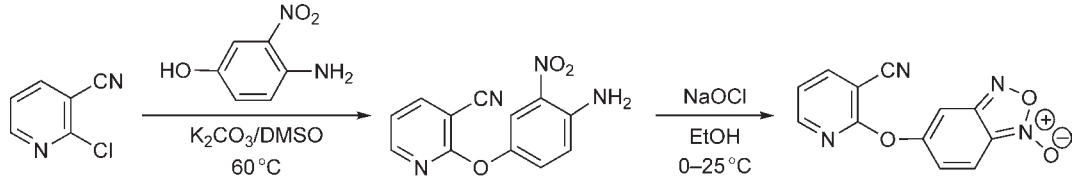
Treatment of the readily available 6-amino-5-nitrosopyrimidines **345** with a slight excess of $PhI(OAc)_2$ or *N*-iodosuccinimide in anhydrous DMF containing 3 equiv of LiH at ambient temperature resulted in a smooth and versatile formation of the corresponding furazano[3,4-*d*]pyrimidines **346** (Equation 81) <1997S1255>.



345 **346**

(81)

A safer, scaleable synthesis of 5-(2-cyano-pyridin-2-yloxy)-benz[1,2,5]oxadiazole **347** has been reported (**Scheme 87**) <2003OPD1043>.



347

Scheme 87

5.05.8 Applications

Derivatives of furozan and furoxan have a wide spectrum of applications. First of all they are used as starting materials in organic synthesis and pharmaceuticals. Particular attention has been focused on furoxans as sources of NO in biological studies, biological markers, fluorescent and energetic materials.

1,2,5-Oxadiazole *N*-oxide derivatives are often tested as potential pharmaceuticals. For example, furazan and furoxan derivatives have been tested as selective hypoxic cell cytotoxins and as DNA-binding agents <2000AP387>, as antitumor agents *in vivo* <2006PHA54> and potential anticancer agents <2001EJM771>, and as muscarinic and nicotinic cholinergic agents <1997EPP776897, 1999USP5998404>, antitrypanosomal compounds <2005BMC6324>. Series of compounds have been tested against the Tulahuen 2 strain of *Trypanosoma cruzi* <1999JME1941, 2005BMC6324>, V79 cells <2000MOL520>. Antimalarial action of furazans and furoxans on the chloroquinesensitive D10 and the chloroquine-resistent W2 strains of *Plasmodium falciparum* has been examined <2005EJM1335>. Structure–activity relationship studies on a series of 1,2,5-oxadiazole *N*-oxide derivatives showing cytotoxic activity have been performed <1998PHA698>. 4-Amino-3-furoxancarboxylic acids and their oxidation products and the azo derivatives were studied for their vasodilating properties. All the products are able to release rat aorta strips precontracted with (–)noradrenaline <2003FES677>. 5-Hydroxy[1,2,5]oxadiazolo[3,4-*b*]pyrazines give rise to the greatest *Haemophilus influenza* antibacterial activity <2003BML3133>. Furoxanes were used for anxiety treatment <1998USP5763457>, for treatment of pain, inflammation, migraine, and emesis <1996WO9629328>. The activity of the compounds (γ)-3-butyloxy-4-(1-azabicyclo[2.2.2]octyl-3-oxy)-1,2,5-oxadiazole is believed to be based on agonist action at the M1 muscarinic cholinergic receptor <1997EPP773021>. Furoxans exhibit potent anti-HIV-1 activity <1996BML1993> and *in vitro* anti-trypanosomal activity <2005MI294>. The substituted 1,2,5-oxadiazole moiety, or its 2-oxide analog, with the [3-(1*H*-imidazol-4-yl)propyl]guanidino pharmacophore is not detrimental to the H3-antagonistic activity, most of the derivatives being more active than the lead compound in the [3-(1*H*-imidazol-4-yl)propyl]guanidine series <2003BMC1197>. A series of nonsteroidal anti-inflammatory drugs (NSAIDs) obtained by linking ibuprofen to selected furoxan moieties and to related furazans were tested for their antiinflammatory, antiaggregatory, and ulcerogenic properties <2001JME3463>. Biological evaluation of a series of 1,2,5-oxadiazole *N*-oxides with potential cytotoxic effects has been described <1998PHA758>. Benzofuroxan derivatives are also able to oxidize HbO_2^{2+} to methemoglobin ($MetHb^{3+}$) (UV detection) and to form *o*-nitroanilines (HPLC detection). From a toxicological point of view this reaction is interesting, since it indicates that the blood is a site for metabolism of these compounds with consequent methemoglobinemia and formation of toxic compounds <2001FES799>.

It was established that oxadiazole oxides are a good inhibitors; for example, 7-chloro-4-nitro-benzo[1,2,5]oxadiazole 1-oxide (FBP-1248) selectively inhibited CDK4 activity *in vitro* by ATP competition. This compound prevented the phosphorylation of retinoblastoma tumor suppressor protein, Rb and inhibited cell growth through cell-cycle arrest <2006MI52>. The iron-NHase inhibitors of high affinity <2001MI227>, and protein kinase inhibitors for the treatment of various diseases <2005WO019190> were described. 5-[2-Methoxy-5-(4-pyridinyl)phenyl]-2,1,3-benzoxadiazole is a selective inhibitor of the phosphodiesterase PDE4D isoenzyme, which is a recognized drug target for the treatment of asthma <2003OPD436>. It was shown that 7-nitro-2,1,3-benzoxadiazole (NBD) thioether derivatives act as suicide inhibitors for human glutathione S-transferases (GSTs) and may represent a new type of potent antitumor agents <2005JBC26397>.

Furoxan derivatives are stable compounds capable of producing NO in physiological solution, under the action of thiol cofactors. Possible mechanisms for NO release from these products in physiological solution and in segments of rabbit femoral artery are briefly considered <2004PAC973>. The substituted furoxan hybrids are assessed as a NO-donor for antioxidant and vasodilating properties *in vitro* <1998JME5393, 2000BMC1727, 2006ARK301> as NO-donor H3-antagonists <2004FES359>. The derivatives of 1,2,5-oxadiazole were used as inhibitor of NO-dependent activation of guanylate cyclase solution isoform <1998RUP2123046, 2000RUP2151799>. The 3,4-disubstituted furoxan derivatives were tested for their COX-inhibiting activities <2005BMC2749, 2005CBI886>. A group of 3′-(4) and 5′-*O*-(3-benzenesulfonylfuroxan-4-yl)-2′-deoxyuridines was designed for evaluation as hybrid nucleoside-NO donor conjugates. Biological evaluation showed that these compounds are effective NO donor agents in the presence of 18 mM L-cysteine and exhibit cytotoxic activity against a battery of cancer cells <2004JME1840>. As NO donors the phenol derivatives of 3-phenylsulfonylfuroxan-4-yloxy moieties were studied. All the compounds proved to inhibit the ferrous salt/ascorbate-induced lipidic peroxidation of membrane lipids of rat hepatocytes <2004BML5971>.The biological characterization of a series of α-tocopherol analogs with NO-releasing capacity is reported <2005BMC5787>. A recent uroselective R1-adrenoceptor antagonist, REC15/2739, has been joined with nitrooxy and furoxan NO-donor moieties to give a series of NO-donor R1-antagonists <2003JME3762>. Calcium channel agonist–antagonist modulation effects and nitric oxide release properties of [3-(benzenesulfonyl)furoxan-4-yloxy]alkyl, 1,4-bihydro-2,6-dimethyl-5-nitro-4-(2-trifluoromethylphenyl,

benzofurazan-4-yl, 2-, 3-, or 4-pyridyl)-3-pyridinecarboxylates] were demonstrated <2002MI1>. New series of NSAIDs in which aspirin is joined by an ester linkage to furoxan moieties, with different ability to release NO, were tested for NO-releasing, anti-inflammatory, antiaggregatory, and ulcerogenic properties <2003JME747>. Artemisinin (10 AM) inhibited the activation of the enzyme by the thiol-dependent nitric oxide (NO) donor, 3,4-dicyano-1,2,5-oxadiazole 2-oxide (10 AM), but did not influence the stimulation of soluble guanylyl cyclase by protoporphyrin 1X <2002EPH69>.

The application of compounds with 1,2,5-oxadiazole rings as fluorogenic reagents is well known. For example, 1,2,5-oxadiazolo[3,4-*c*]pyridines were prepared in the quest for a red fluorescent material useful in organic light emitting devices (OLED). These compounds emit fluorescence of orange to red color in solution and in the solid state <2002H(56)421>. The electroluminescence materials containing 1,2,5-oxadiazoles have been described <2000JPP281663, 2000TL6063, 2000TL8509, 2001CC2500, 2001JOC5241, 2002H(58)165, 2003JPP123974, 2004TL3625>. Short- and long-chain 1-*O*-alkyl-2-acylaminodeoxyglycero- and alkoxy-alkylphosphonic acid *p*-nitrophenyl esters contained nitrobenzoxadiazole as reporter fluorophores covalently bound to the ω-ends of the respective 2-acylamino- and alkoxy- residues <2003CLI103>. 7-Nitro-4-aminobenzofurazan derivatives as fluorophores for a protein kinase sensing system <2005JA7684>, for the peripheral-type benzodiazepine receptor (PBR) binding probes <2005JME3692>, and for the histamine H_2 receptor <2004BMC6495> have been reported. The use of 4-(diphenylphosphino)-7-(methylthio)benzo[*c*][1,2,5]oxadiazoles as fluorescent reagents for the detection of hydroperoxides in biological samples <2005CC1848> has also been reported. The esterification of 11-deacetylwortmannin, 17-hydroxywortmannin, and demethoxyviridin with the fluorescent carboxylic acids NBD-sarcosine and 7-dimethylaminocoumarin-4-acetic acid generated six fluorescent esters <2006BML2518>.

The synthetic (mammalian cell surface) receptors with NBD fluorescent headgroups for human 5-HT4 receptors were synthesized based on a potent 5-HT4 receptor agonist and on piperazine analogue <2004JA16379>. These molecules were derived with three fluorescent moieties, dansyl, naphthalimide, and NBD (7-nitrobenz-2-oxa-1,3-diazol-4-yl), through alkyl chains <2003JME2606>. Potent fluorescence-labeled H1 antagonists are obtained by connecting norme-pyramine and fluoresceine or NBD via spacer groups of appropriate length <2003BML1245>. Nitrobenzoxadiazole having a C_9-carbon chain between the chromanol and the fluorophore was shown to bind specifically and reversibly to recombinant human tocopherol transfer protein (a-TTP) with dissociation constants of approximately 280 and 60 nM, respectively, as compared to 25 nM for the natural ligand 2*R*,40*R*,80*R*-a-tocopherol <2006BMC3721>.

A study of labeled carbohydrates to lectins conjugated to a solid support demonstrated that succinimidyl 6-(*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)hexanoate (NBD-X) dye provides by far the lowest level of nonspecific interaction with immobilized protein. This observation is in stark contrast with the commonly used labeling reagents composed of charged and aromatic groups, for instance, fluoroscein isothiocyanate (FITC) and tetramethylrhodamine (TAMRA) dyes <2005JOC9809>. NBD fluorophore was used in the design of a Grb2 SH2 domain-binding peptide mimetic <2005BML1385>. The 6b-amino group was used for the ligation of the 3-(7-nitrobenzofurazan-4-yl)-aminopropanoyl group as a fluorescent label <1999EJO2563>. 4,7-Diphenyl-1,2,5-oxadiazolo[3,4-*c*]pyridine-6-carboxylic acid (DOPC) led to a new fluorescent, amine-specific reagent, in a good yield. The efficiency of DOPC-ester in protein labeling was evidenced using BSA as a protein target. These characteristics, (including fluorescence energy transfer (FRET)), qualify the DOPC-ester for various applications which involve fluorescent labeling of proteins <2004RRC309>. Series of fluorescently-labeled tri-and pentapeptides with side chains containing a 4-amino-7-nitrobenzofurazan moiety were prepared and shown to selectively bind to anionic vesicle membranes <2006OBC1966>. The NBD-labeled sphingosine and sphingosine 1-phosphate were synthesized from (–)-4-methoxycarbonyloxazolidinone <2003BML661>. High-precision NBD-fluorescence assay for sphingomyelinase activity of isolated enzymes and cell lysates was demonstrated <2002MI815>.

NBD fluorophores can be used as a probe for rapid testing of new sensor designs and for investigating fundamental questions in molecular recognition at the membrane surface <2004T11307>. 4-(Dialkylaminoalkylamino)-7-nitrobenzo-2-oxa-1,3-diazoles were used in the design of a novel hybrid system of fluorescent sensors of the 'fluorophore–$receptor_1$–spacer–$receptor_2$' format <2004T11125>. By attachment of NBD fluorescent groups to these sensors or by immobilizing them to suitable surfaces, one might be able to devise readout systems for monitoring the extent of binding of peptide or other ligands <2004JA15223, 2004T11145>. Several examples of using NBD as LysB29 selectively labeled NBD fluorescent derivatives of human insulin <2004PES470>, NBD fluorescence-labeled sphingosines as substrates of sphingosine kinases <2004BML1555>, site-specific insertion of spin-labeled L-amino acids including fluorescent NBD-alanine in Xenopus ocytes <2004B8470>, fluorescent NBD contained histamine H2 receptor antagonists related to potentidine <2003BML1717>, fluorescently labeled UDP-MurNAc-Pentapeptide <2001JA9916>, NBD as fluorescence group in double-labeled oligonucleotides <2001OL3071>, NBD fluorescent phospholipids–hydrogel conjugate for driving self-assembly of supported lipid membranes <2001MM5759>,

NBD-labeled derivatives of the natural sialyl LewisX glycosphingolipid as targets for investigating microdomain formation in membranes <2001TL377>, and NBD fluorescent nonpeptidic neuropeptide Y receptor ligands <2003AP585> were described. Visible isotope-coded affinity tag (VICAT) reagents containing a carbon-14 visible probe or an NBD fluorophore were also reported. These reagents are most useful for the determination of the absolute quantity of specific target proteins in complex protein mixtures such as serum or cell lysates <2004BCC380>. Fluorescent probes containing 4-nitrobenzo[*c*][1,2,5]oxadiazole fragment reveal that flippase-mediated flip-flop of phosphatidylinositol across the endoplasmic reticulum membrane does not depend on the stereochemistry of the lipid <2005BMC1799, 2005CC453, 2005OBC1275>. A fluorescence study on the nyctinasty of *Cassia mmosoides* L. using fluorescence-labeled probe compounds showed leaf-opening activity <2001T9817>. A number of new tris(aminoethyl)amines (TREN-based) translocases were evaluated for their abilities to bind phosphatidylcholine and translocate a fluorescent phosphatidylcholine probe <2002JOC2168>. An example of a caged fluorescent reporter of intracellular enzymatic activity <2003JA13358> and characteristic lapidated hemagglutinin-derived peptides which additionally carry the fluorescent 7-nitrobenz-2-oxa-1,3-diazole group have been reported <2002CEJ3362>.

The benzo[1,2,5]oxadiazoles were prepared as biomarkers particularly useful for staining brain tissue for detection of Alzheimer's disease <2004WO2004087684>.

Inclusion complex formation with fluorescent NBD-guests corroborated internal hydrophobicity of β-barrel hosts and potential for intratoroidal catalysis <2002CH18>.

Linking the macrocyclic receptor 1,7-diaza-15-crown-5 to the fluorophore 7-nitrobenzofurazane leads to the Hg(II) selective fluorescence probe NBO-crown <1997JFL231S>. The cryptand was functionalized with an electron-withdrawing fluorophore (NBD) which behaves as a fluorescence on/off signaling system by translocating Cd(II) inside and outside the cryptand cavity <2004IC4626>.

The effects of spacer length on the fluorescence quantum yields of the benzofurazan compounds bearing a donor–acceptor system were reported <2002MI11>.

A combinatorial library of fluorescent NBD molecules was used to visualize subcellular transport pathways in living cells, using a kinetic, high content imaging system to monitor spatiotemporal variations of intracellular probe distribution <2004MI414>.

As a perspective energetic compounds 3,4-bis(azidoacetamino)furazan <2003MI25>, 3,3′-diamino-4,4′-azoxyfurazan, 3,3′-diamino-4,4′-azofurazan, bis[1,2,5]oxadiazolo[3,4-*c*:3′,4′-*g*][1,2,5,6]tetrazocine <2000JEM219>, and dicyanofuroxan derivatives <1996JPC16856> were studied. Gas-generating compounds, especially for safety devices in automobiles, fire extinguishers and flotation devices (vinyl furazans) have been described <2005WO097711, 2005WO035466>. 7-Amino-4,6-dinitro benzofuroxan and 5,7-diamino-4,6-dinitro-benzofuroxan are perspective explosives, found to be very safe in handling along with high thermal stability <2005RUP2248354>. Preparation of ultrafine benzotrifurozanes (BTF) (benzotris[1,2,5]oxadiazole, 1,4,7-trioxide) particles for explosives with high-thermal stability and detonation energy was reported <2002MI20>, as well as 3,4-azofurazane derivatives are useful as a thermostable explosive <2005RUP2248354>.

The applications of 1,2,5-oxadiazole *N*-oxide and benzo[*c*][1,2,5]oxadiazole *N*-oxide derivatives as compounds which have herbicidal activity are known. For example, the most active compound, butylcarbamoylbenzo[*c*]1,2,5-oxadiazole *N*-oxide, displayed herbicidal activity at concentrations as low as 24 g ha^{-1} <2000JFA2995>. The preparation of 5,7-disubstituted 4,6-dinitrobenzofuroxane derivatives (2-chlorophenylamino, 2,5-dichlorophenylamino, 2-hydroxyphenylamino, or 4-bromophenylamino), which are useful as agricultural arachnicides and bactericides, was described <2005RUP2255935>.

N,*N*-Dimethyl-*N*′-(7-nitro-2,1,3-benzoxadiazol-4-yl)-1,2-ethanediamine as a dye has been mentioned <2005JA5695>. 4,7-Bis(dialkylamino)benzo[*c*][1,2,5]chalcogenadiazoles represent a class of organic dyes that undergo reversible two-stage one-electron oxidation as well as one-electron reduction. Their redox properties as well as molecular and crystal structures are affected by the alkyl substituents on the amino nitrogen and/or by the chalcogen atom (O, S, Se) in the heterocycle <2001JOC8954>.

NBD derivatives are building blocks in efficient solid-phase method for the synthesis of differently lipidated and additionally modified peptides <2004AGE5839>.

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Biographical Sketch

George N. Nikonov (born 1954, Kazan, Russia) received a degree of master of science in chemistry (chemical technology of rubber and plastics) in 1976 at Kazan Institute of Chemical Technology (now Kazan State Technological University), then entered the A. E. Arbuzov Institute of organic and physical chemistry of the Russian Academy of Sciences (Kazan, Russia) as a postgraduate student. Since then, for more than 15 years he worked under the supervision of the leader of phosphorus chemistry in Russia, world famous academician Boris A. Arbuzov. In 1980 he received PhD degree in the field of organic heteroatom chemistry and in 1987 received a degree of doctor of science (DSc) in the field of organic heteroatom chemistry at Kazan State University. From 1986 to 1989, George Nikonov was a senior researcher at Arbuzov Institute, and later, from 1989 to 1994, became a principal researcher/team leader. He was the head of the laboratory of organophosphorus compounds during the period from 1994 to 1999. In addition in 1996, he was elected into the administration of the Institute as a Scientific Secretary and served in that position until 1999. From 1999–2002 he worked in the Center for Heterocyclic Compounds of the University of Florida, under the supervision of Kenan Professor, Dr. A. R. Katritzky. From 2002–present, George Nikonov has been working in Alchem Laboratories Corp. (Alachua, Florida) He is co-author of about 200 scientific publications including 134 scientific papers, 10 reviews, 24 patents, and 1 book.

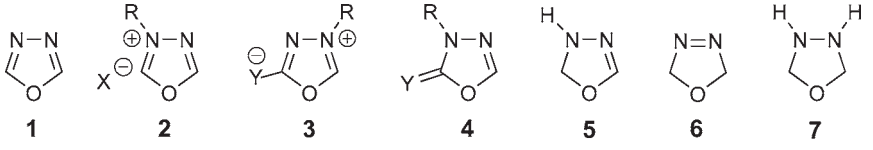
Sergey V. Bobrov (born 1971, Kazan, Russia) received a degree of master of science in chemistry (chemical technology of high-molecular compounds) in 1993 at Kazan Institute of Chemical Technology (now Kazan State Technological University), then entered A. E. Arbuzov Institute of Organic and Physical Chemistry of the Russian Academy of Sciences (Kazan, Russia) as a postgraduate student. In 2000 he received a PhD degree in the field of organic heteroatom chemistry at Kazan State University. From 2001–2006 he worked in the Center for Heterocyclic Compounds of the University of Florida, under supervision of Kenan Professor, Dr. A. R. Katritzky. From 2006–present, Sergey V. Bobrov has been working in Alchem Laboratories Corp. (Alachua, Florida) He is co-author of about 30 scientific publications including, scientific papers, abstracts, reviews, and patent.

5.06
1,3,4-Oxadiazoles

J. Suwiński and W. Szczepankiewicz
Silesian University of Technology, Gliwice, Poland

5.06.1 Introduction

This chapter surveys the literature on 1,3,4-oxadiazole and its derivatives published from 1996 onward. 1,3,4-Oxadiazole **1** belongs to the thermally stable neutral, cyclically conjugated systems. Other fully conjugated systems of similar structure are 1,3,4-oxadiazolium cations **2**, exocyclically conjugated mesoionic 1,3,4-oxadiazoles **3**, and 1,3,4-oxadiazolines **4** (1,3,4-oxadiazolinones, 1,3,4-oxadiazolinethiones, 1,3,4-oxadiazolinimines). Also known are derivatives of the nonconjugated reduced systems derived from 1,3,4-oxadiazole **1**, namely: 2,3-dihydro-l,3,4-oxadiazole (Δ^2-1,3,4-oxadiazoline) **5**, 2,5-dihydro-1,3,4-oxadiazole (Δ^3-l,3,4-oxadiazoline) **6**, and 2,3,4,5-tetrahydro-l,3,4-oxadiazole (1,3,4-oxadiazolidine) **7**. The chemistry of 1,3,4-oxadiazoles has already been reviewed several times: the literature prior to 1965 was collected in a comprehensive review <1966AHC(7)183>. CHEC(1984) <1984CHEC(6)427> covered the literature up until 1982, and CHEC-II(1996) <1996CHEC-II(4)268> dealt with papers published in the period 1983–95. In 1995, Grimmett and Iddon published a review on the synthesis and reactions of lithiated azoles, including 1,3,4-oxadiazoles <1995H(41)1525>. J. Warketin surveyed papers on 2,5-dihydro-1,3,4-oxadiazoles as versatile sources of reactive intermediates <2000J(P1)2161>. For a general review on 1,3,4-oxadiazole syntheses, one may consult *Science of Synthesis* <2004HOU219>.



Developments since the mid-1990s mainly include the synthesis and applications of several new 1,3,4-oxadiazoles substituted with a wide variety of groups. No significant new general routes to 1,3,4-oxadiazoles have been reported. Some reactions of 1,3,4-oxadiazoles have also been mentioned in reviews on particular topics, for example, solvent-free Chapman-like rearrangement of 5-methoxy-2-aryl-1,3,4-oxadiazoles in the solid state <2000CRV1025> or reactions of singlet ground state dimethoxycarbene thermally generated from 2,2-dimethoxy-5,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole <2003CRV1485>. The coordination chemistry of 2,5-di(2-pyridyl)-1,3,4-oxadiazole ligands has been comprehensively reviewed <2003CCR119>.

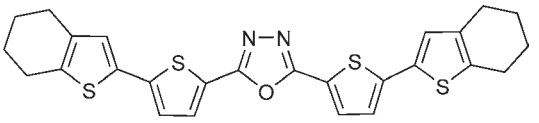
The research on 1,3,4-oxadiazole in 2006–07 has brought main progress in applications of the oxadiazole moieties in optoelectronics. In other fields of the oxadiazole chemistry, for example, concerning reactivity of ring atoms or reactivity of substituents attached to ring atoms, the progress was small or not at all.

5.06.2 Theoretical Methods

Various theoretical methods (self-consistent field molecular orbital (SCF-MO): modified neglect of diatomic overlap (MNDO), complete neglect of differential overlap (CNDO/2), intermediate neglect of differential overlap/screened approximation (INDO/S), and STO-3G *ab initio*) have been used to calculate the electron distribution, structural parameters, dipole moments, ionization potentials, and data relating to ultraviolet (UV), nuclear magnetic resonance (NMR), nuclear quadrupole resonance (NQR), photoelectron (PE), and microwave spectra of 1,3,4-oxadiazole and its derivatives <1984CHEC(6)427, 1996CHEC-II(4)268>.

Typed neglect of differential overlap (TNDO/2) shielding calculations and PM3 geometry optimization calculations were carried out for a series of parent oxazoles and oxadiazoles, including 1,3,4-oxadiazole itself. TNDO/2-calculated nitrogen shieldings, with respect to neat nitromethane, gave a very good linear correlation with experimental results when all of the nitrogen atoms in the molecules studied were taken into account <1996MR148>.

AM1 semi-empirical and B3LYP/6-31G(d)/AM1 density functional theory (DFT) computational studies were performed with the purpose of determining which variously substituted 1,3,4-oxadiazoles would participate in Diels–Alder reactions as dienes and under what conditions. Also, bond orders for 1,3,4-oxadiazole and its 2,5-diacetyl, 2,5-dimethyl, 2,5-di(trifluoromethyl), and 2,5-di(methoxycarbonyl) derivatives were calculated <1998JMT153>. The AM1 method was also used to evaluate the electronic properties of 2,5-bis[5-(4,5,6,7-tetrahydrobenzo[*b*]thien-2-yl)thien-2-yl]-1,3,4-oxadiazole **8**. The experimentally determined redox potentials were compared with the calculated highest occupied molecular orbital/lowest unoccupied molecular orbital (HOMO/LUMO) energies. The performance of the available parameters from AM1 was verified with other semi-empirical calculations (PM3, MNDO) as well as by *ab initio* methods <1998CEJ2211>.



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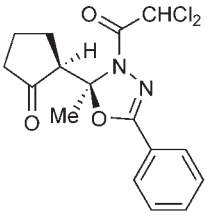
More recent calculations using the AM1 method were applied in order to distinguish between two possible structures **9** and **10**, affording a more stable conformation of each isomer <2003T4591>.



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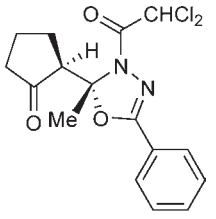

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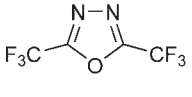
The mechanism of 1,3,4-oxadiazole **11** coupling with alkenes **12**, **13**, and **14** according to Diels–Alder fashion was supported by the results of semi-empirical AM1 calculations, which gave activation energies (in the range 30.0–37.6 kcal mol^{-1}) comparing favorably with those obtained earlier from the more rigorous higher level of theory (HF/3-21G). Additionally, the AM1 calculations correctly predicted the *endo*-specificity in the reaction of 1,3,4-oxadiazole **11** with alkene **14** <1995TL5275>.

Quantum-chemical calculations were carried out and correlated with experimental observations concerning the electronic absorption, emission, and excitation spectra of (5-phenyl-1,3,4-oxadiazol-2-yl)-7-hydroxycoumarin **15** <2000SAA1773>.



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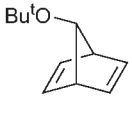

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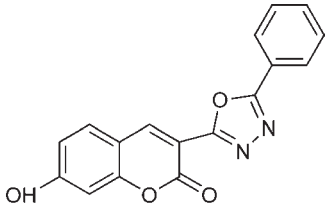

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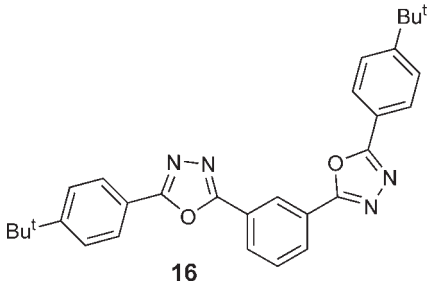
When parameters of the Pariser–Parr–Pople configuration interaction molecular orbital (PPP-CI MO) method were modified so as to reproduce the λ_{obs} values for 1,3-di(5-aryl-1,3,4-oxadiazol-2-yl)benzenes **16** and **17**, the calculated HOMO and LUMO energy levels corresponded with the experimental ionization potential and electron affinity values. The relationships between the electrical properties and molecular structures for the dyes were investigated. The absorption maximum wavelengths for amorphous films were found to be nearly equal to those for solution samples <1997PCA2350>.



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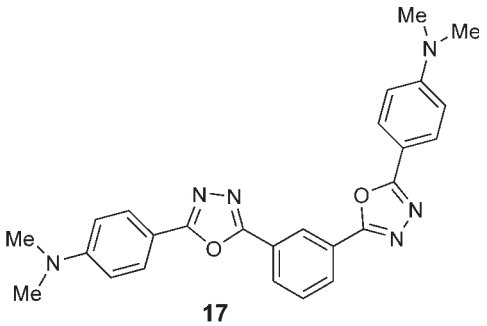

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5.06.3 Experimental Structural Methods

Amino and tosylamino derivatives of oxadiazole possessing intramolecular hydrogen quasi-bond show in various solvents a single, double, triple, or even a four-banded fluorescence, which has not been reported earlier <2006SAA196>. In 5-phenyl-1,3,4-oxadiazole-2(3*H*)-thione, the planar oxadiazole ring is effectively coplanar with the phenyl ring. This facilitates the formation of N–H···S interactions, leading to a thione tautomer in the solid state, and the formation of centrosymmetric dimers <2007AXE782>. The structure of 2,5-diphenyl-1,3,4-oxadiazole (widely used for electron transport in organic light-emitting diodes) on copper was studied using scanning tunneling microscopy and DFT. At incomplete coverage of Cu, the molecules were found horizontally on the surface; once the surface area is insufficient, a film of vertically arranged molecules was formed <2006L857>.

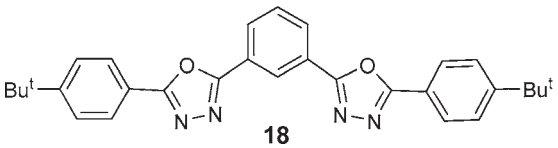
5.06.3.1 Electronic Absorption and Emission Spectroscopy

1,3,4-Oxadiazole itself shows no absorption above 200 nm, which is consistent with the results of MO calculations. Simple 2-alkyl and 2,5-dialkyl derivatives absorb slightly above 200 nm. In contrast, electronic absorption spectra of aryl and diaryl 1,3,4-oxadiazoles are distinct and additionally the compounds show luminescence. Oxadiazolinethione in ethanol is characterized by λ_{max} 260 nm and log ε 4.12 values <1984CHEC(6)427, 1996CHEC-II(4)268>.

1,3,4-Oxadiazoles containing three or more conjugated rings have found various applications as luminescent compounds (see Section 5.06.12.3). Electronic effects have been shown to be transferred efficiently through the oxadiazole ring, and, hence, their absorption and emission spectra have been extensively studied and reported many times. A fluorescence emission from 2,5-diphenyl-1,3,4-oxadiazole resulting from two-photon excitation with two different wavelengths near 380 and 760 nm was reported. For this two-color two-photon excitation, the emission spectra and intensity decays were the same as when observed with single-photon excitation with an equivalent energy at 250 nm <1996JPC19406>. An ultraviolet amplified spontaneous emission laser spike at 365 and 385 nm occurs for unsymmetrical 2-(1-naphthyl)-5-phenyl-1,3,4-oxadiazole in hydrocarbon solutions <1996CPL154>, <1997PCA3260>. The electronic absorption, emission, and excitation spectra of 5-phenyl-1,3,4-oxadiazol-2-yl)-7-hydroxycoumarin are affected by solvent polarity. A shoulder in the absorption spectra at 473 nm indicates the presence of a tautomeric equilibrium. Molecular oxygen acts as a quencher. Quantum-chemical calculations were carried out and correlated with experimental observations <2000SAA1773>.

The fluorescence and laser properties of symmetrically and unsymmetrically substituted 2,5-diaryl-1,3,4-oxadiazoles were experimentally studied. It has been found that symmetrically substituted molecules (e.g., 2,5-di(2-naphthyl)-1,3,4-oxadiazole) give laser oscillation at room temperatures, while unsymmetrical 2-(2-naphthyl)-5-phenyl-1,3,4-oxadiazole does not give laser action under any conditions, even at low temperatures <2000SAA2157>.

The relationships between electrical properties and molecular structures for various nonpolymeric amorphous dyes like 1,3-di(5-aryl-1,3,4-oxadiazol-2-yl)benzenes **18** and **19** were investigated. The absorption maximum wavelengths (λ_{obs}) for amorphous films were found to be nearly equal to those for solution samples <1997PCA2350>.



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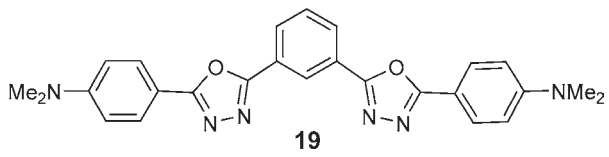

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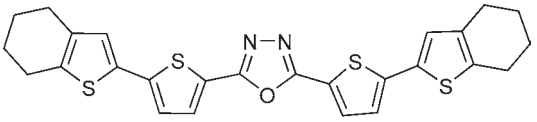
The absorption (λ^{a}_{max} 402 nm, log ε 4.71) and emission (λ^{e}_{max} 453, 477 nm) maxima, fluorescence quantum yields, and the optical energy of 2,5-bis[5-(4,5,6,7-tetrahydrobenzo[b]thien-2-yl)thien-2-yl]-1,3,4-oxadiazole **20** were studied in dichloromethane <1998CEJ2211>.



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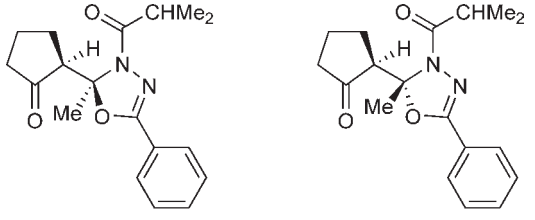
5.06.3.2 NMR Spectroscopy

The chemical shift of the ring protons in the parent compound is 8.73 ppm in $CDCl_3$. In 2-alkyl derivatives it moves upfield and in 2-alkylthio derivatives downfield. The chemical shifts of the ring carbon atoms in several 1,3,4-oxadiazole derivatives have also been reported. Signals of C-2 atoms are shifted upfield by at least ca. 5–6 ppm in comparison with signals of C-5 in, for example, 5-methoxy-l,3,4-oxadiazoles (159.7–160.8 and 166.1–166.6 ppm), oxadiazolinones (143.6–155.4 and 147.5–156.1 ppm), and oxadiazolinethiones (158.4–161.7 and 174–179 ppm). The reverse order of signals was observed in l,3,4-oxadiazolium-2-olates (159.8–160.5 and 152.2–154.4 ppm) <1984CHEC(6)427, 1996CHEC-II(4)268>.

Rather weak effects of 5-substituents (aryl, heteroaryl, and alkyl groups) on C-2 (161.4–164.1 ppm) and much stronger on C-5 (157.5–166.6 ppm) signal shifts in ^{13}C NMR spectra of 1,3,5-tris(5-substituted-1,3,4-oxadiazole-2-yl)-benzenes recorded in DMSO-d_6 were reported (DMSO = dimethyl sulfoxide) <1997MRC549>. During the last decade, several other ^{1}H and ^{13}C NMR spectra of 2-substituted and ^{13}C NMR spectra of 2,5-disubstituted 1,3,4-oxadiazoles have been published to characterize structures of products. Unfortunately, due to the complex structures of several of them, some of the data might be considered uncertain. One of the more important reliable papers deals with ^{13}C and ^{15}N spectra of 10 2-aryl-1,3,4-oxadiazoles substituted in the *para*-position of the benzene ring with groups characterized by Hammett σ values from -0.63 to $+0.81$. The effects on the oxadiazole ring carbon atoms signals shifts were observed (from 162 to 164 ppm for C-2 and from 157.5 to 166.5 ppm for C-5), but no correlation between the ^{13}C chemical shifts and Hammett parameter was found. In contrast, it was shown that the groups on the benzene ring are able to strongly affect the chemical shifts of both the N-3 and N-4 atoms. The range of chemical shifts for N-3 in the studied compounds is 18.07 ppm (from -96.28 to -78.21 ppm), whereas that for N-4 is only 5.18 ppm (from -75.21 to -70.24 ppm). Linear correlations between chemical shifts and Hammett values of substituents in the aryl ring were obtained for both nitrogen atoms <2003MRC689>.

The assigned molecular structures of new 1,3,4-oxadiazole derivatives, for example, compounds **21** and **22**, were based on a rigorous spectroscopic analysis by various NMR methods (^{1}H, ^{13}C, correlation spectroscopy (COSY), nuclear Overhauser enhancement spectroscopy (NOESY), heteronuclear correlation (HETCOR) spectroscopy, and correlation through long-range coupling (COLOC)) as well as on infrared (IR) and mass spectrometry (MS) data, which with the help of semi-empirical calculations allowed distinguishing between two possible isomers <2003T4591>.



21 **22**

The ^{15}N nuclear shielding of 1,3,4-oxadiazole in diethyl ether equal to $+81 \pm 1$ ppm was reported earlier <1996CHEC-II(4)268>. The solvent effect on the high-precision ^{14}N nuclear shielding of 1,3,4-oxadiazole (e.g., +66.65 in CCl_4, +74.84 in DMSO, and +85.37 ppm in water) and of other both oxadiazole and oxazole systems was reported. It was found that the shielding was increased by hydrogen bonding between water molecules and nitrogen atoms in 1,3,4-oxadiazole <1996MR148>.

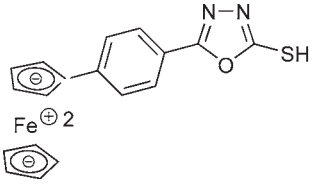
The ^{17}O NMR spectrum of 4,5-diphenyl-l,3,4-oxadiazolium-2-olate was reported earlier <1996CHEC-II(4)268>. Since then, no report on ^{17}O NMR spectra of 1,3,4-oxadiazoles has been published.

5.06.3.3 IR and Raman Spectroscopy

The IR spectra of 1,3,4-oxadiazoles are generally characterized by bands at 1640–1560 ($\nu_{C=N}$), 1030–1020 (ν_{C-O}), and 970 cm^{-1}. Typical for 2-substituted compounds are bands at 3140 (ν_{CH}) 1640–1560 ($\nu_{C=N}$), 1120–1100, and 645–635 cm^{-1}. These bands occur at longer wavelengths in the spectra of 2,5-dialkyl derivatives. Oxadiazolinethiones absorb at 1350–1300 cm^{-1} ($\nu_{C=S}$), oxadiazolinones at 1785–1740 cm^{-1} ($\nu_{C=O}$), oxadiazolinimines at 1710 or 1680 cm^{-1}, and amino-1,3,4-oxadiazoles over 3200 cm^{-1}. Also, Raman spectra of several 1,3,4-oxadiazoles have been reported <1984CHEC(6)427, 1996CHEC-II(4)268>.

2,5-Diphenyl-1,3,4-oxadiazole crystallization revealed two polymorphic forms (centrosymmetric and non-centrosymmetric) of the substance. Raman spectra of both phases recorded between 15 and 1700 cm^{-1} showed well-resolved internal modes and the external lattice vibrations below 200 cm^{-1}, offering a fast tool for discrimination between different polymorphs. The internal modes were dominated by two groups, one around 1000 cm^{-1} and the second one between ca. 1500 and 1600 cm^{-1} <2003JST219>.

In the most recently published papers, the reported absorption bands refer only to vibration characteristics of substituents of the oxadiazole ring or are not ascribed at all. The following can serve as the examples of IR spectra: (1) *N*-[5-(2-(2-chlorophenoxy)phenyl)-1,3,4-oxadiazole-2-yl]-*N*-4-chlorophenylurea (3278, 3209 (ν_{NH}), 1685 ($\nu_{C=O}$) cm^{-1}); (2) *N*-[5-(2-(2-chlorophenoxy)phenyl)-1,3,4-oxadiazole-2-yl]-*N*-phenylurea (3260, 3235 (ν_{NH}), 1680 ($\nu_{C=O}$) cm^{-1}); (3) 2-amino-5-[2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazole (3260, 3235 (NH), 1680 ($\nu_{C=O}$) cm^{-1}); (4) 2-amino-5-[2-(2-chlorophenoxy)phenyl]-1,3,4-oxadiazole (3335, 3124 (ν_{NH2}) cm^{-1}); (5) 2-amino-5-[2-(2-nitrophenoxy)phenyl]-1,3,4-oxadiazole (3403, 3323 (ν_{NH2}), 1653 (ν_{NH2}), 1520, 1348 (ν_{NO2}) cm^{-1}) <2004MI193>. Additional instances are the IR spectra of 2-[(ferrocenyl)-*p*-phenyl]oxadiazol-5-thiol **23** (3079s, 2946s, 2767s, 1612s, 1515s, 1504s, 1423s, 1348s, 1284s, 1178s, 1070s, 966s, 885s, 742s, 696s cm^{-1}) and of 2-[*p*-(ferrocenyl)phenyl]-5-[(ferrocenyl)carbonylmethylthio]-1,3,4-oxadiazole **24** (3220w, 3091s, 2960s, 1656s, 1608s, 1583s, 1513s, 1477s, 1454s, 1378s, 1340s, 1301s, 1218s, 1182s, 1086s, 1031s, 1000s, 887s, 821s, 742s, 701s cm^{-1}) <2003JOM1>.



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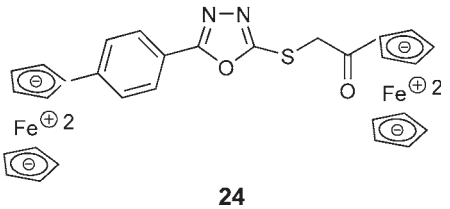
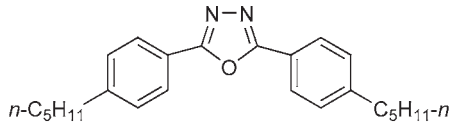


24

A liquid crystal, 2,5-bis(4-pentylphenyl)oxadiazole **25**, was characterized by its IR spectrum in KBr (2931, 2856, 1497, 1113, 1070, 843, 744, 713 cm^{-1}) <2005CM6354>. Spectroscopic data for 1,3,4-oxadiazoles with varying functional groups <1995SAA995, 1996SAA33> and different chain lengths up to the phenyloxadiazole polymer <2004MI21, 2004CC1> can be found.

IR spectra of 1:1 molecular co-crystals of 2,5-bis(3-pyridyl)-1,3,4-oxadiazole **26** or its isomer 2,5-bis(4-pyridyl)-1,3,4-oxadiazole **27** with phthalic, isophthalic, and terephthalic acids <2005MI1199>, with benzene-1,3,5-tricarboxylic acid and benzene-1,2,4,5-tetracarboxylic acid, <2005MI1247> as well as with fumaric, suberic, and benzene-1,4-dioxyacetic acids <2006MI114> were reported. IR absorption bands of coordination polymers of 2,5-bis(4-aminophenyl)-1,3,4-oxadiazole and 2,5-bis(3-aminophenyl)-1,3,4-oxadiazole with inorganic Ag(I) salts were also published <2005MI585>. For 2-methyl-5-(3,3,3-trifluoro-2-methylthio-2-propenyl)-1,3,4-oxadiazole complex with Fe salt in CH_2Cl_2 the following bands were reported: 2072, 2022, 2002, and 1950 cm^{-1} <2002EJI639>. The crystal structure and spectroscopic properties of copper(II) complexes derived from 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole have been studied in details <2002POL2257> in order to rationalize the role the coordination of this kind of oxadiazole derivatives can play with a biologically essential metal ion such as the copper(II). The molecular structure of poly(*p*-phenylene)-1,3,4-oxadiazole, as well as the corresponding dimer and tetramer compounds, were investigated using IR and Raman spectroscopy. The most informative region has been found between 1500 and 1650 cm^{-1} <1997PLM1537>.



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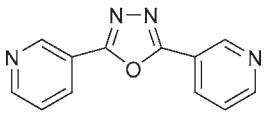

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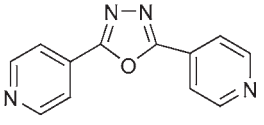


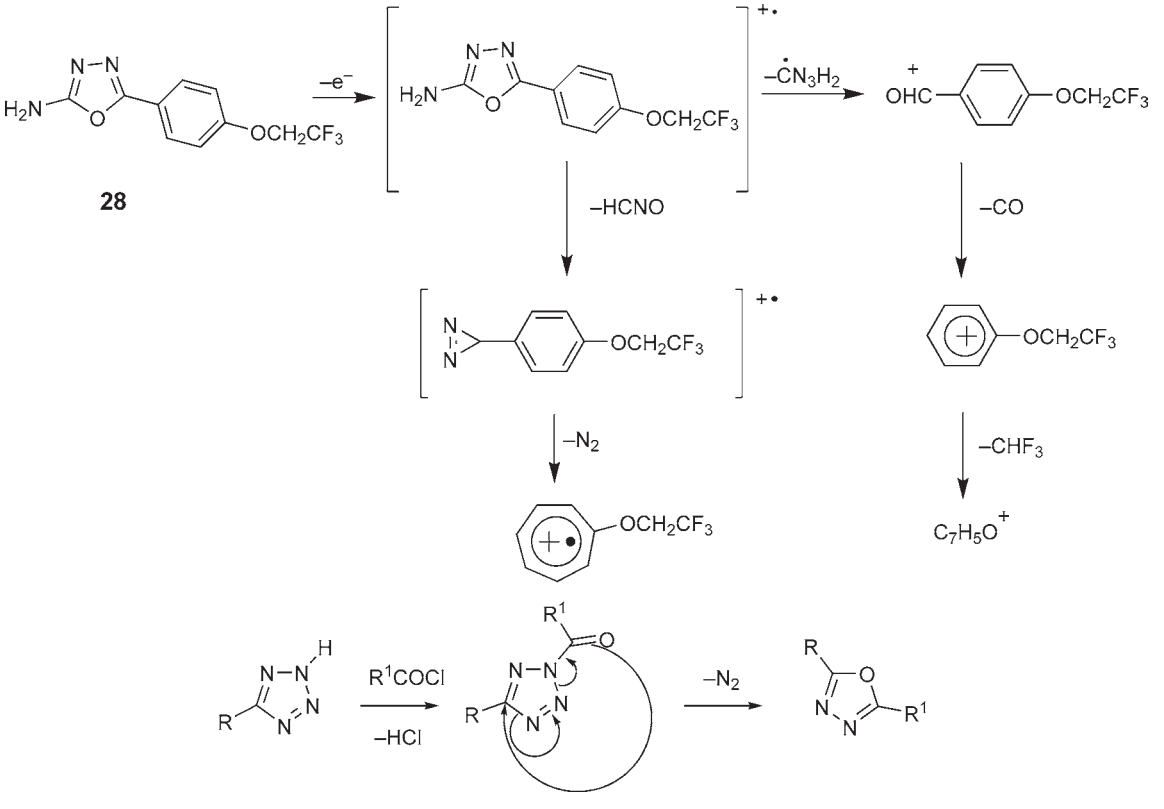
27

5.06.3.4 Mass Spectrometry

Electron ionization (EI) mass spectra of 1,3,4-oxadiazole itself and its 2-mono- and 2,5-disubstituted derivatives, including the proposed main fragmentation pathways have already been discussed in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)427, 1996CHEC-II(4)268>. Molecular ions of the compounds are usually of high intensity and the most important fragmentation pathways of the molecular ions involve loss of respective HCN, RCN molecules, or RCO cations. Loss of HNCO is significant in the spectra of 2-amino derivatives.

More recently, the EI and electrospray ionization (ESI) mass spectra of 2,5-diaryl- and 2-arylamino-5-aryl-1,3,4-oxadiazoles, as well as their complexes with copper cations, were studied. Under ESI conditions, loss of NH_3 and HNCO, from complexes of 2,5-diphenyl-1,3,4-oxadiazole, 2,5-bis(2-pyridyl)-1,3,4-oxadiazole, or 2,5-bis(4-pyridyl)-1,3,4-oxadiazole with copper cation, was observed <2004JMP272>. An unusual elimination of isocyanic acid was found in fragmentation of some protonated 2,5-diaryl derivatives <2002RCM390>.

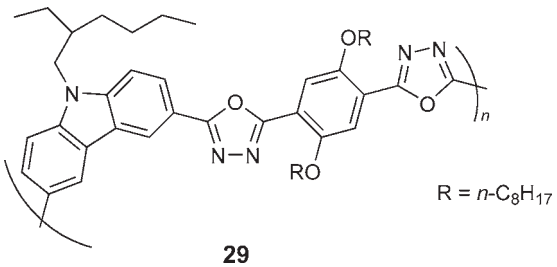
A proposed mass spectral fragmentation pattern of 2-amino-5-(4-trifluoroethoxyphenyl)-1,3,4-oxadiazole **28** is shown in **Scheme 1** <1999JFC39>.



Scheme 1

5-Substituted tetrazoles reacting in the mass spectrometer with acyl ions afforded 2,5-disubstituted 1,3,4-oxadiazoles with nitrogen loss. Tandem mass spectrometry allowed for the collision-induced dissociation of the products. Chemical ionization was the better method to make the transformation. A scheme for the transformation of 5-substituted tetrazoles into 2,5-disubstituted 1,3,4-oxadiazoles was proposed (**Scheme 1**) <2001JMP1069>. The fragmentation patterns of monocyclic 1,3,4-oxadiazolium-2-thiolates have been proposed by Ollis and Ramsden <1974J(P1)645>.

An analytical method based on matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) was applied to provide information on the structure of copolymer **29**, for example, repeat units and end groups <2002ANC6252>.

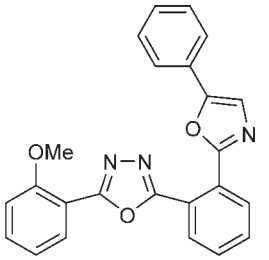


29

5.06.3.5 X-Ray Single Crystal Diffraction

In CHEC(1984) and CHEC-II(1996), only a few papers on crystal studies of 1,3,4-oxadiazole derivatives had been reported. The studies have shown that the oxadiazole and benzene rings in the crystal of 5-phenyl-l,3,4-oxadiazole derivative are nearly coplanar.

Since 1995, several new papers on X-ray studies have appeared reporting bond lengths and angles in 1,3,4-oxadiazole derivatives. Selected data concerning the azole ring in the eight compounds **30–37** are collected in **Table 1**. It is worth mentioning that surprisingly, according to the experimental data, the oxadiazole ring in a single crystal of compound **30** though planar is nonsymmetric (see the differences between bond lengths and angles). The crystal structures of several other oxadiazole derivatives and co-crystals with organic and inorganic compounds were studied by X-ray diffraction <2002MI625, 2005MI1247, 2005MI1199, 2006MI114>.



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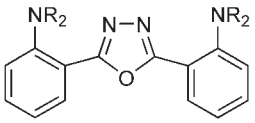

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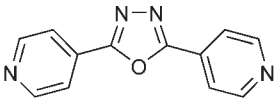
R = *N*-TsLeu-



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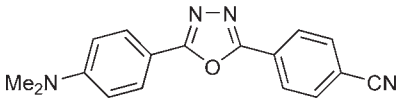

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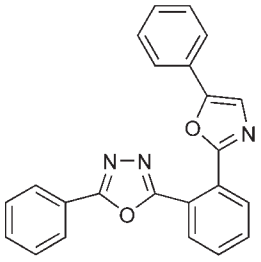

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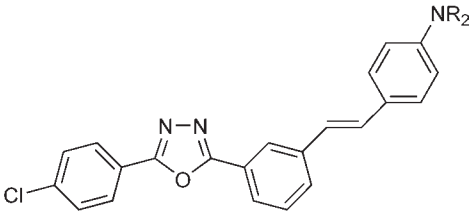

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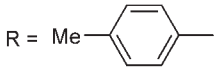

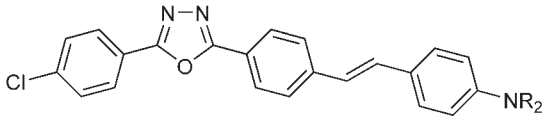

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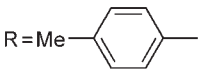

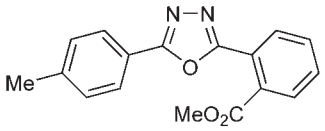

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Table 1 Selected bond lengths and angles in 1,3,4-oxadiazole derivatives

Compound	*Bond*	*Bond length (Å)*	*Angle*	*Bond angle (deg)*	*Reference*
30	O(1)–C(2)	1.367(6)	O(1)–C(2)–N(3)		<2000JST289>
	C(2)–N(3)	1.272(5)	C(2)–N(3)–N(4)		
	N(3)–N(4)	1.407(3)	N(3)–N(4)–C(5)		
	N(4)–C(5)	1.288(4)	N(4)–C(5)–O(1)		
	C(5)–O(1)	1.354(4)	C(2)–O(1)–C(5)		
31	O(1)–C(2)	1.362(6)	O(1)–C(2)–N(3)	112.5(5)	<2000JST109>
	C(2)–N(3)	1.293(6)	C(2)–N(3)–N(4)	106.1(4)	
	N(3)–N(4)	1.394(6)	N(3)–N(4)–C(5)	107.3(4)	
	N(4)–C(5)	1.283(7)	N(4)–C(5)–O(1)	111.5(5)	
	C(5)–O(1)	1.372(6)	C(2)–O(1)–C(5)	102.6(4)	
32	O(1)–C(2)	1.365(2)	O(1)–C(2)–N(3)	112.5(2)	<2001JST175>
	C(2)–N(3)	1.292(3)	C(2)–N(3)–N(4)	106.2(1)	
	N(3)–N(4)	1.409(3)	N(3)–N(4)–C(5)	106.2(1)	
	N(4)–C(5)	1.292(3)	N(4)–C(5)–O(1)	112.5(2)	
	C(5)–O(1)	1.365(2)	C(2)–O(1)–C(5)	102.5(2)	
33	O(1)–C(2)	1.368(2)	O(1)–C(2)–N(3)	111.36(14)	<2001JST175>
	C(2)–N(3)	1.292(2)	C(2)–N(3)–N(4)	106.97(13)	
	N(3)–N(4)	1.407(2)	N(3)–N(4)–C(5)	106.13(14)	
	N(4)–C(5)	1.294(2)	N(4)–C(5)–O(1)	112.36(14)	
	C(5)–O(1)	1.374(2)	C(2)–O(1)–C(5)	102.82(12)	
34	O(1)–C(2)	1.3946(11)	O(1)–C(2)–N(3)	112.69(9)	<2002JST29>
	C(2)–N(3)	1.3967(12)	C(2)–N(3)–N(4)	106.67(8)	
	N(3)–N(4)	1.4241(12)	N(3)–N(4)–C(5)	105.76(8)	
	N(4)–C(5)	1.3046(12)	N(4)–C(5)–O(1)	112.13(9)	
	C(5)–O(1)	1.3775(12)	C(2)–O(1)–C(5)	102.72(7)	
35	O(1)–C(2)	1.368(5)	O(1)–C(2)–N(3)		<2002JST53>
	C(2)–N(3)		C(2)–N(3)–N(4)	107.5(4)	
	N(3)–N(4)	1.396(5)	N(3)–N(4)–C(5)		
	N(4)–C(5)	1.295(5)	N(4)–C(5)–O(1)	112.5(4)	
	C(5)–O(1)		C(2)–O(1)–C(5)	103.1(3)	
36	O(1)–C(2)	1.358(7)	O(1)–C(2)–N(3)	112.1(6)	<2002JST53>
	C(2)–N(3)	1.303(7)	C(2)–N(3)–N(4)	105.5(5)	
	N(3)–N(4)	1.405(7)	N(3)–N(4)–C(5)		
	N(4)–C(5)		N(4)–C(5)–O(1)	111.5(6)	
	C(5)–O(1)		C(2)–O(1)–C(5)	103.4(5)	
37	O(1)–C(2)	1.366(2)	O(1)–C(2)–N(3)	111.69(15)	<2003JST361>
	C(2)–N(3)	1.292(2)	C(2)–N(3)–N(4)	106.65(13)	
	N(3)–N(4)	1.402(2)	N(3)–N(4)–C(5)	106.35(13)	
	N(4)–C(5)	1.292(2)	N(4)–C(5)–O(1)	112.11(14)	
	C(5)–O(1)	1.359(2)	C(2)–O(1)–C(5)	103.20(12)	

5.06.3.6 Other Spectroscopic Methods

The PE spectra of 2,5-di(fluoroalkyl)-1,3,4-oxadiazoles were reported <1996CHEC-II(4)268>.

The fluorescence spectral properties of 2,5-diphenyl-1,3,4-oxadiazole with two-color two-photon excitation were studied <1996JPC19406>. More recently, polymers containing 1,3,4-oxadiazole rings have gained much interest due to the charge-transporting ability of several such products. The properties of poly(aromatic oxadiazole)s were investigated by photoluminescent spectroscopy and cyclic voltammetry <1996SM153>. Similar methods were applied to study a copolymer of an electron-rich carbazole derivative with an electron-deficient oxadiazole <1999SM297>. Bismaleimides and bisitaconimides bearing the 2,5-diphenyl-1,3,4-oxadiazole chromophore as well as their saturated model compounds were synthesized, and their fluorescence spectra were investigated <2003MM3115>. The phosphorescence and photoluminescence behavior of polymers with cross-conjugated oxadiazole segments was also studied <2000SM337>. The electroluminescence spectra of naphthalimide and oxadiazole

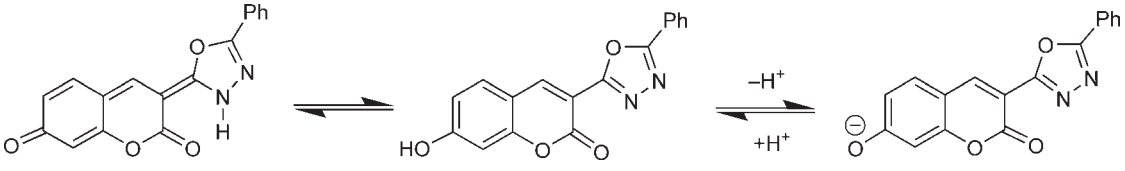
copolymer were reported <2000SM481>. Dipole moment measurements were applied to study the flexoelectric effect in guest–host mixtures of 2,5-di(*n*-pentyl)-1,3,4-oxadiazole with commercial liquid crystals <2005CM6354>. The monomers and chiral conjugated copolymers of 2,5-bis(4-vinylphenyl)-1,3,4-oxadiazole with chiral diiodo-bisbutoxy-binaphthalenes were analyzed by NMR, MS, Fourier transform infrared (FTIR), UV, differential scanning calorimetry–thermal gravimetry (DSC–TG), fluorescent spectroscopy, gel permeation chromatography (GPC), and CD spectra. The copolymers exhibited a strong Cotton effect and strong blue fluorescence <2006MI663>.

Binary molecular co-crystals of 2,5-bis(3-pyridyl)-1,3,4-oxadiazole and 2,5-bis-(4-pyridyl)-1,3,4-oxadiazole with benzene-1,3,5-tricarboxylic and benzene-1,2,4,5-tetracarboxylic acids were studied by X-ray and thermogravimetric analysis of mass loss <2005MI1247>. Dipole moments were used to study the flexoelectric effect in guest–host mixtures of 2,5-(4-pentylbenzene)-1,3,4-oxadiazole with commercial liquid crystal hosts <2005CM6354>. The luminescence properties of many other copolymers were also investigated (see Section 5.06.12.3).

5.06.4 Thermodynamic Aspects

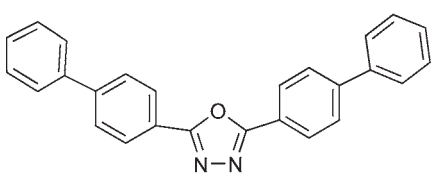
Despite full cyclic conjugation in 1,3,4-oxadiazole, analysis of the values of OC, CN, and NN bond orders for the ring leads to the conclusion that the molecule is not typically aromatic. 2-Amino-l,3,4-oxadiazoles, oxadiazolinones, and oxadiazolinethiones are in tautomeric equilibrium with oxadiazolinimines, 2-hydroxyoxadiazoles, and oxadiazolethiols, respectively. Usually one of the forms distinctly predominates. Nevertheless, the reactions with electrophilic reagents lead to derivatives of both tautomeric forms <1996CHEC-II(4)268> (see Sections 5.06.5.2 and 5.06.7.2). The X-ray crystallographic structure of 5-ethyl-2-trifluoroacetylamino-1,3,4-oxadiazole was shown to be dimeric involving hydrogen bonding. *Ab initio* computational studies (HF/6-311G*) confirmed that amino tautomers are more stable in comparison with imino ones <2002TL1709>.

Also, (5-phenyl-1,3,4-oxadiazol-2-yl)-7-hydroxycoumarin is a tautomeric compound. In dilute solutions it is almost totally present in its protonated nitrogen tautomeric form. The deprotonation is a reversible process (**Scheme 2**). Quantum-mechanical calculations were carried out and correlated with experimental observations <2000SAA1773>.



Scheme 2

Apart from the parent compound **1** and its very simple alkyl derivatives, 1,3,4-oxadiazoles are solids. Solid oxadiazoles containing biphenyl or triphenyl substituents exhibit interesting properties upon heating. The symmetric 2,5-bisbiphenyl-4-yl-1,3,4-oxadiazole **38** melts into an isotropic phase showing small monotropic mesophase. By contrast, the asymmetric (hockey stick-shaped) mesogen 2-terphenyl-4-yl-5-phenyl-1,3,4-oxadiazole **39** exhibits a more stable enantiotropic liquid crystalline phase (a smectic phase as well as a nematic phase) <2001PCB8845>.



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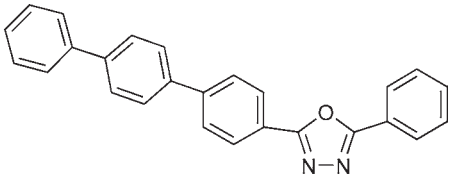

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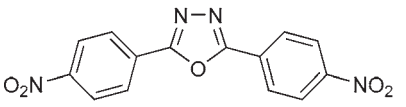
2,5-Diphenyl-1,3,4-oxadiazole is polymorphic (centrosymmetric monoclinic structure with space group P21/c and monoclinic non-centrosymmetric structure with space group P21/c). DSC investigations showed an irreversible transition from the first to the second form at 97 °C <2003JST219>.

Phase transitions in 1,3,4-oxadiazole crystals under high pressure were studied by Orgzall *et al.* <1999MI1949, 2003MI1805>. Later, during Raman spectroscopic investigations of crystalline 2,5-di(4-nitrophenyl)-1,3,4-oxadiazole

40, three phase transitions were detected at 0.88, 1.28, and 2.2 GPa. 2,5-Di-(4-aminophenyl)-1,3,4-oxadiazole **41** formed two crystalline structures; one contained a water molecule. Therefore, the so-called pseudo-polymorphism was observed. X-Ray and calorimetric studies indicated that dehydration occurred at higher temperature. Both structures differed considerably in molecular conformation. The thermal expansion coefficient was measured. High-pressure experiments showed a strong anisotropy of the compression behavior <2005MI994>.



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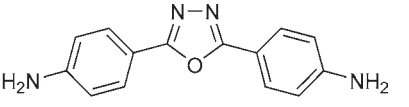

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The barriers for nitrogen inversion in 1,3,4-oxadiazolidine derivatives have been determined by the introduction of chiral substituents on the nitrogen atoms and monitoring diastereomerization by NMR and by following enantiomerization by multidimensional gas chromatography <2000AGE2938>.

Orgzall and co-workers <2006MI1459, 2006MI5269> continued high-pressure structural investigations of 2,5-diaryl-1,3,4-oxadiazoles.

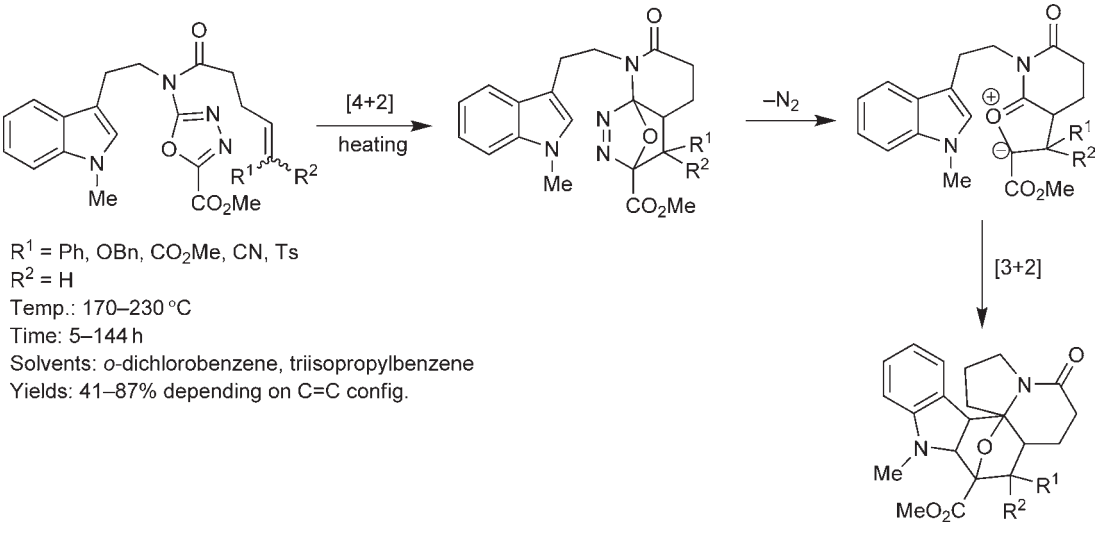
5.06.5 Fully Conjugated Rings; Reactivity of Ring Atoms

A systematic exploration of the intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles was described. The studies permit the use of unsymmetrical dienophiles, dipolarophiles, and oxadiazoles; as well as to control the cycloaddition regioselectivity and diastereoselectivity. The scope and utility of the reaction were defined <2006JA10589>. The tandem intramolecular [4+2]/[3+2] cycloaddition cascade reaction of 1,3,4-oxadiazole was applied to the syntheses of a series of natural products including a total synthesis of (–)- and ent-(+)-vindoline <2006JA10596>.

5.06.5.1 Unimolecular Thermal Reactions

Most of the cyclically conjugated 1,3,4-oxadiazoles are thermally stable, and very high temperatures are required to induce ring cleavage. In 3-alkyl-5-phenyl-2-oxadiazolidinones, the rings open up at 700 °C losing carbon dioxide <1996CHEC-II(4)268>.

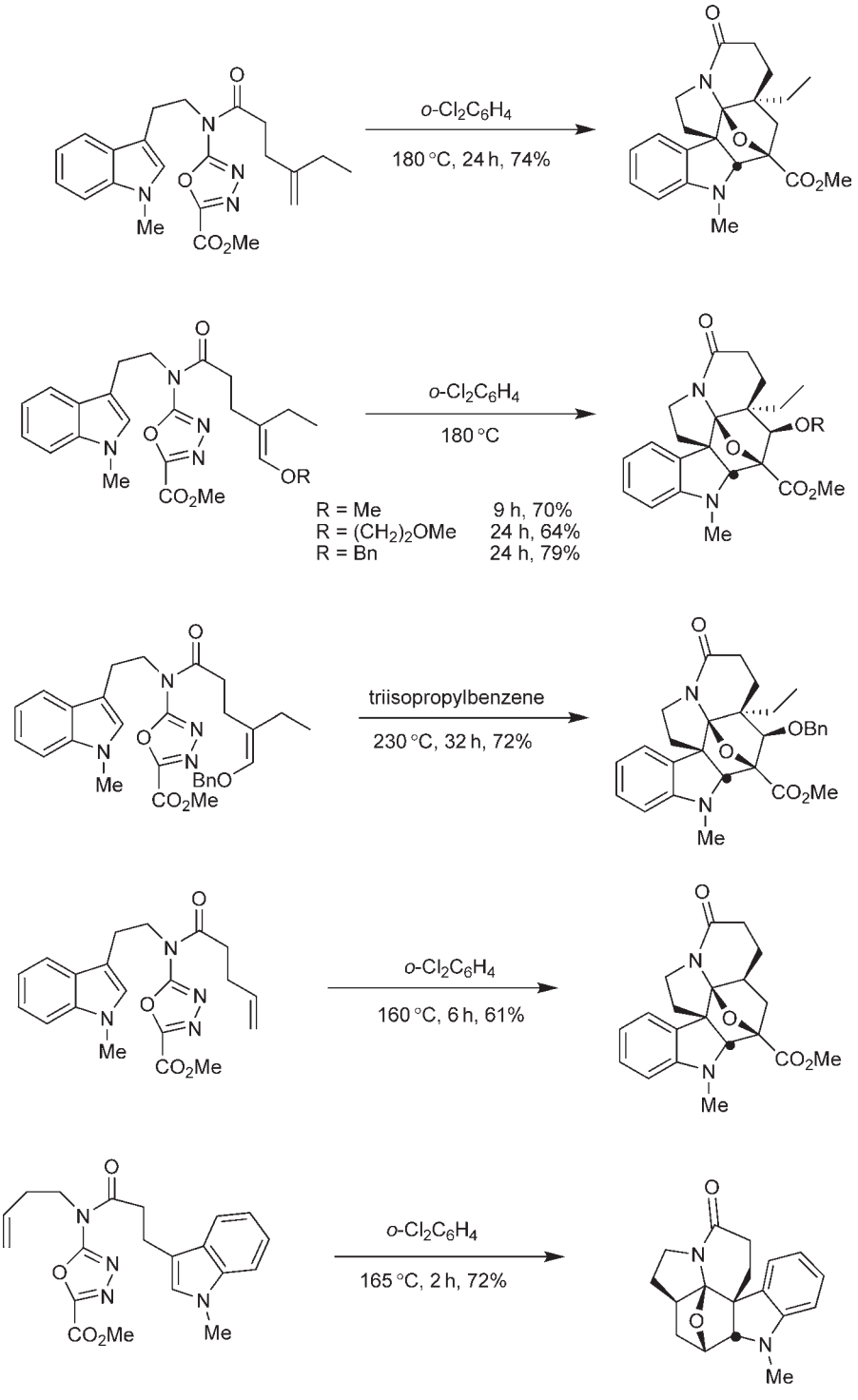
More recently, some examples of intramolecular Diels–Alder and tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition reactions of especially designed 1,3,4-oxadiazole derivatives have been described (**Scheme 3**). The



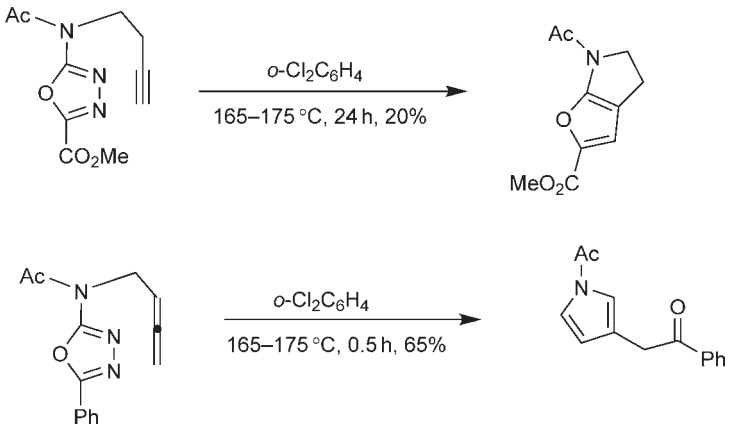
R^1 = Ph, OBn, CO_2Me, CN, Ts
R^2 = H
Temp.: 170–230 °C
Time: 5–144 h
Solvents: *o*-dichlorobenzene, triisopropylbenzene
Yields: 41–87% depending on C=C config.

Scheme 3

reactions occurred at 170–230 °C, often affording high yields of products. The reactions are highly regio- and stereospecific; examples of the reactions between oxadiazole ring and alkene, alkyne, or allene fragments are shown in **Schemes 4** and **5** <2002JA11292>.

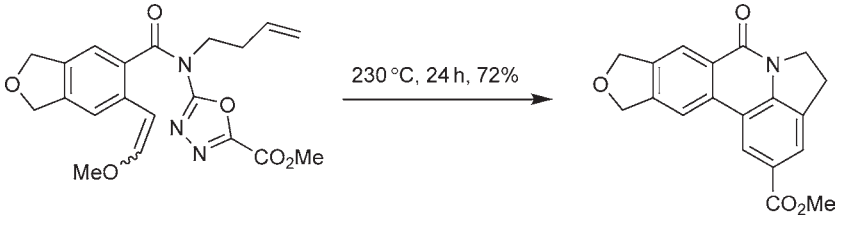


Scheme 4



Scheme 5

Intramolecular thermal [4+2] cycloaddition occurs smoothly, though at a high temperature, upon heating of the appropriately substituted electron-poor oxadiazole containing electron-rich alkene fragment (Equation 1) <2002JOC7361>.

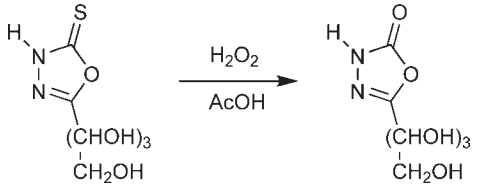


(1)

5.06.5.2 Electrophilic Attack at Nitrogen

1,3,4-Oxadiazoles are weak Hammett bases. The basicity constants of 2,5-diphenyl-1,3,4-oxadiazole (pK_a –2.49) and of 2-(4-methylphenyl)-5-phenyl-1,3,4-oxadiazole (pK_a –1.15) were measured by the method of Yates and MacClelland in an aqueous solution of sulfuric acid in the range from pH 7 to H_o –10. Both compounds exhibited luminescence properties depending on the acid concentration <1996SAA1875>.

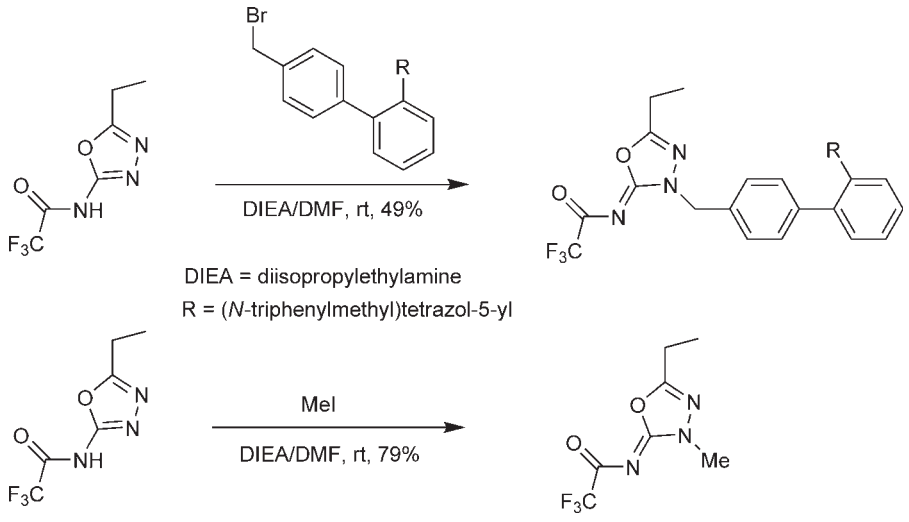
Oxadiazolinethiones are probably too weak bases to be protonated in, for example, acetic acid. Therefore, in their oxidation shown in Equation (2), acetic acid played the role of a solvent and not a protonating agent <1997CAR123>.



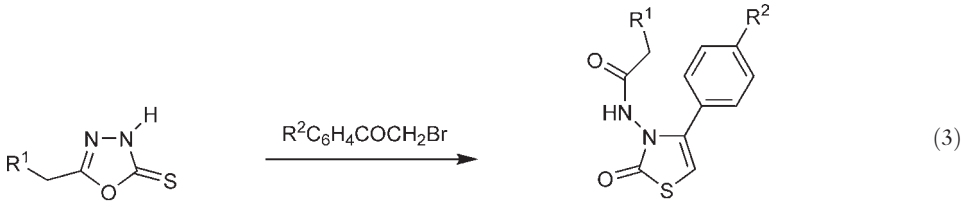
(2)

It appears from examples shown in **Scheme 6** that alkylation of 2-trifluoroacetamido-1,3,4-oxadiazoles regioselectively affords *endo*-N-derivatives <1997H(44)133, 1998JA3104>.

In some cases, this reaction is much more complicated. 5-Substituted-1,3,4-oxadiazoline-2-thiones when alkylated with ω-bromoacetophenones afforded products that might result either from the initial attack of the electrophile on sulfur or on nitrogen (Equation 3) <2001RJC1754>.

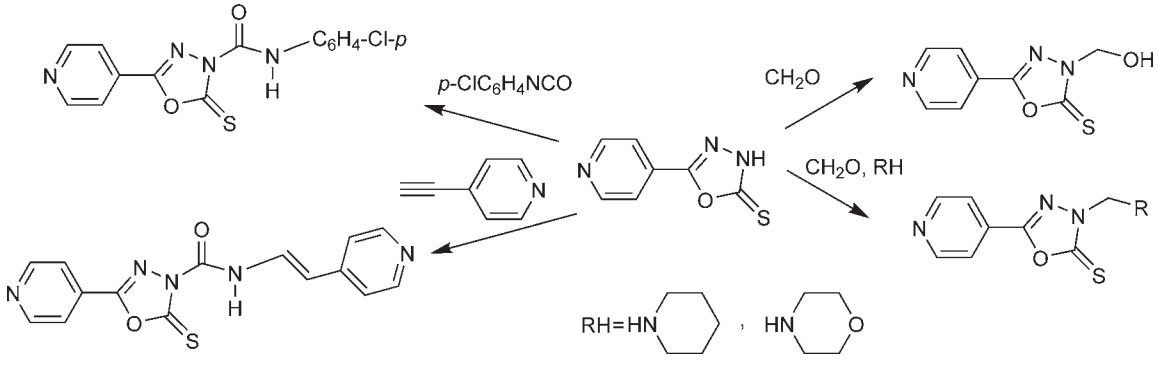


Scheme 6



(3)

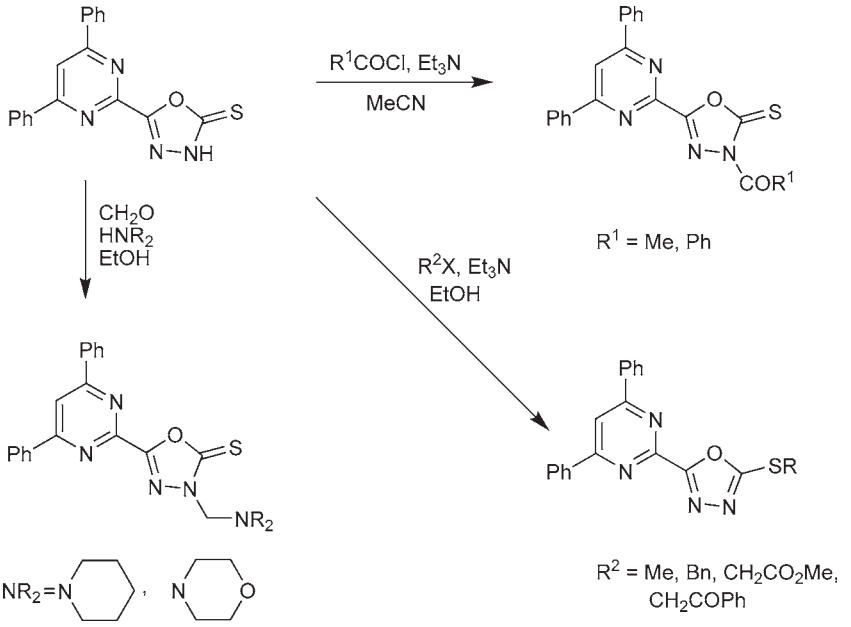
Rutavicius and Kuodis reported several examples of electrophilic alkylations of the ring nitrogen atom in 5-(4-pyridyl)-1,3,4-oxadiazol-2-thiones (**Scheme 7**); sometimes, the reaction on nitrogen was accompanied by alkylation on sulfur atom. The direction of substitution depended both on the structure of the initial reactants and on the reaction conditions <2002CHE852>.



Scheme 7

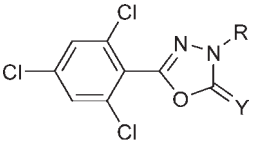
Vainilavicius and co-workers studied the Mannich reaction of oxadiazolethiones in detail and reported several examples pointing to the importance of starting reagent structures and the reaction conditions on the course of the reaction <2002M173, 2003CHE1364>. For example, aminomethylation and acylation of 5-(4,6-diphenyl-2-pyrimidinyl)-

1,3,4-oxadiazole-2-thione yielded *N*(3)-derivatives. In contrast, the thione with haloalkanes gave S-alkylated compounds (**Scheme 8**) <2003CHE1364>. Some similar reactions of compounds **4** are also discussed in Section 5.06.6.1.



Scheme 8

The use of trifluroiodoethane or dibromodifluoromethane for alkylation of 5-aryloxadiazolin-2-ones or 5-aryloxadiazoline-2-thiones led exclusively to N-alkylated products **42a** or **42b**, respectively <1999MI161>.



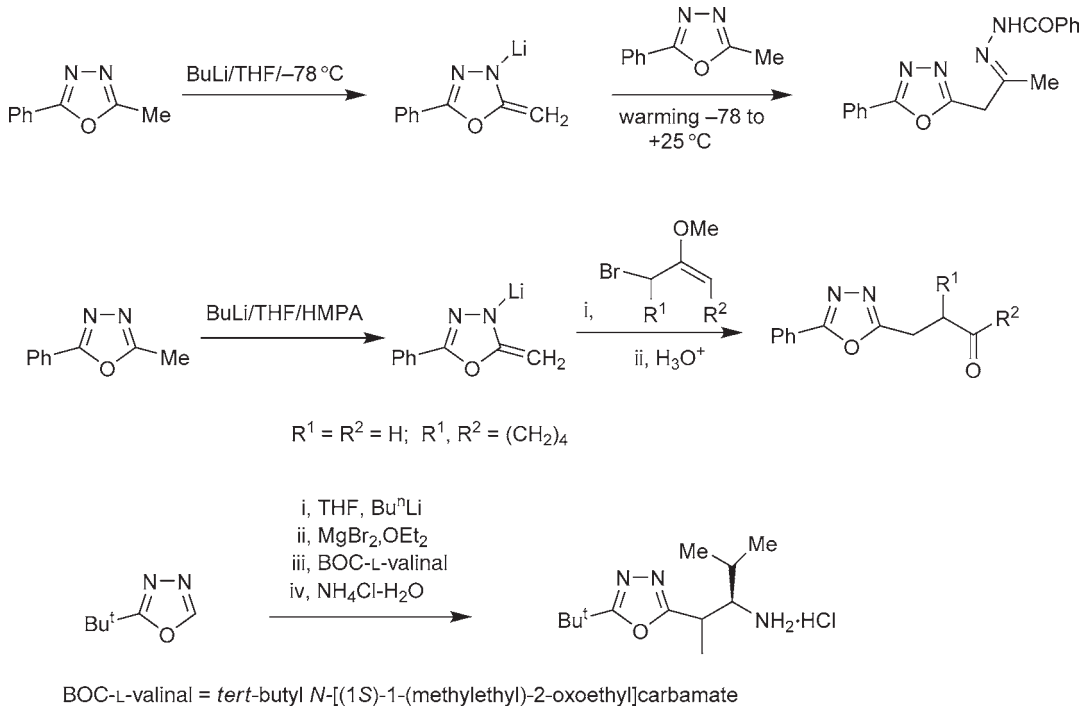
42

a: R = CH_2CF_3; Y = O
b: R = CF_2Br; Y = S

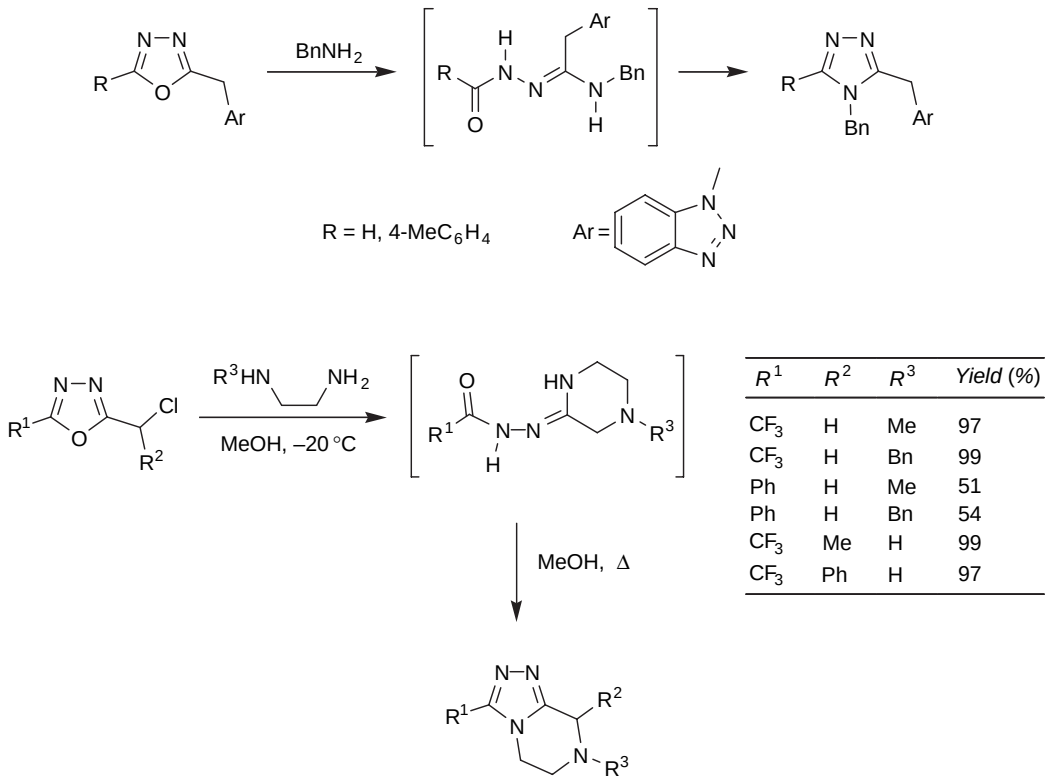
5.06.5.3 Nucleophilic Attack at Carbon

A nucleophilic attack at the ring carbon is a major reaction mode of *C*-alkyl-1,3,4-oxadiazoles. When a strong base is used as the nucleophile, the attack on the ring carbon atom can be preceded by deprotonation of methylene group attached to the ring. Treating 2-methyl-5-phenyl-1,3,4-oxadiazole with butyllithium in the absence of alkylating agents led to the formation of a dimer, in which one of oxadiazole rings then opened to afford the corresponding N-benzoylated hydrazone. The lithium derivative of the starting oxadiazole was easily alkylated with, for example, allyl bromide (**Scheme 9**) <1995H(41)1525>. Also, monosubstituted oxadiazoles not possessing active hydrogen atoms in the substituents were alkylated following deprotonation at the ring carbon atom (**Scheme 9**) <2001JME1268>.

Very often, a nucleophilic attack on the ring carbon atom leads to ring cleavage with the formation of acyclic intermediates that frequently recyclize into triazoles <2001ARK101, 2005OL1039>, particularly in the case of N-nucleophiles, as shown in **Scheme 10** and Equation (4) <2000EJM267>.

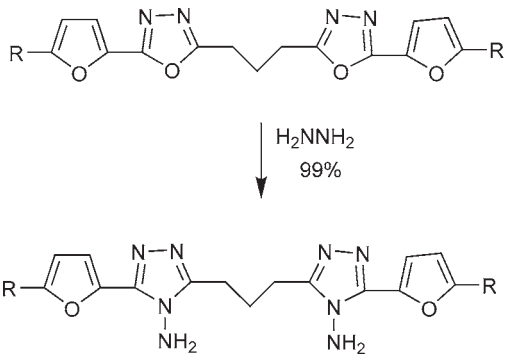


Scheme 9



R^1	R^2	R^3	*Yield* (%)
CF_3	H	Me	97
CF_3	H	Bn	99
Ph	H	Me	51
Ph	H	Bn	54
CF_3	Me	H	99
CF_3	Ph	H	97

Scheme 10

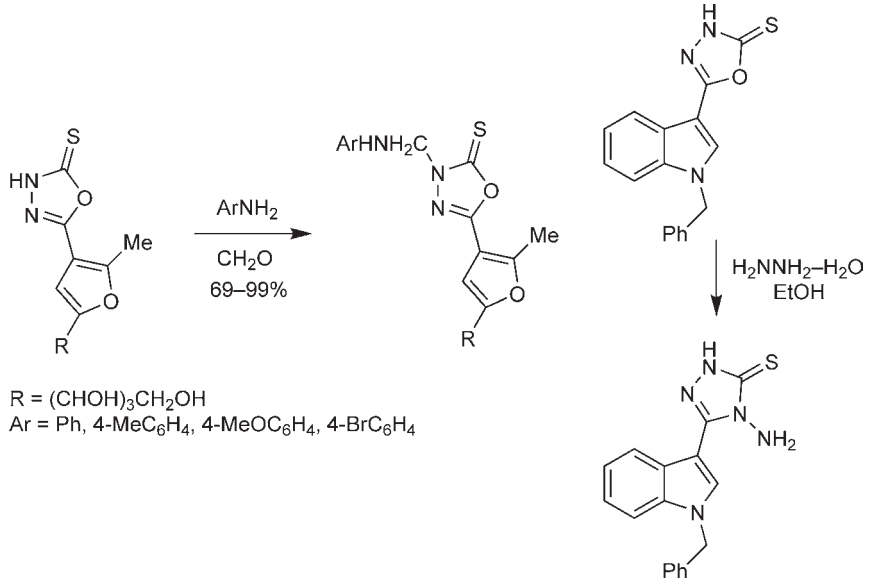


R	*Yield* (%)
NO_2	62
4-$O_2NC_6H_4$	66
4-ClC_6H_4	68
4-BrC_6H_4	64
2,4-$Cl_2C_6H_3$	62

(4)

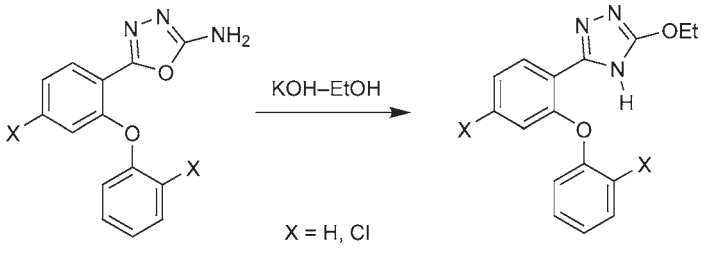
2-Methyl-5-phenyl-1,3,5-oxadiazole when treated with crotylamine in boiling toluene for 7 days afforded 4-(*E*-2-butenyl)-5-methyl-3-phenyl-4*H*-1,2,4-triazole <2001MOL481>.

Similar reactions are also characteristic for 5-substituted-1,3,4-oxadiazol-2-thiones (**Scheme 11**) <1997CAR123, 2004MI147>.



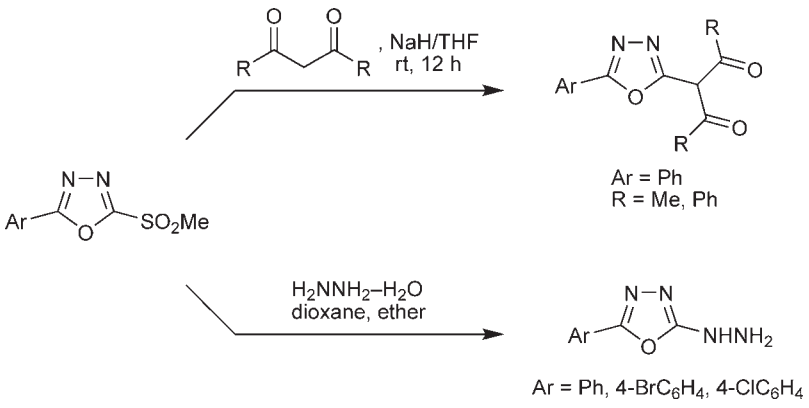
Scheme 11

In the case of 2-amino-1,3,4-oxadiazoles, an external N-nucleophile is not necessary for their conversion into the corresponding triazole derivatives; the reaction occurred in ethanol in the presence of potassium hydroxide (Equation 5) <2003BML769>.



(5)

As we have already mentioned, nucleophilic displacements of ring C-substituents in 1,3,4-oxadiazoles are seldom reported. The reactions occur only for compounds containing very good leaving groups, as shown in **Scheme 12** <2001JA6179, 2004MI1343>.

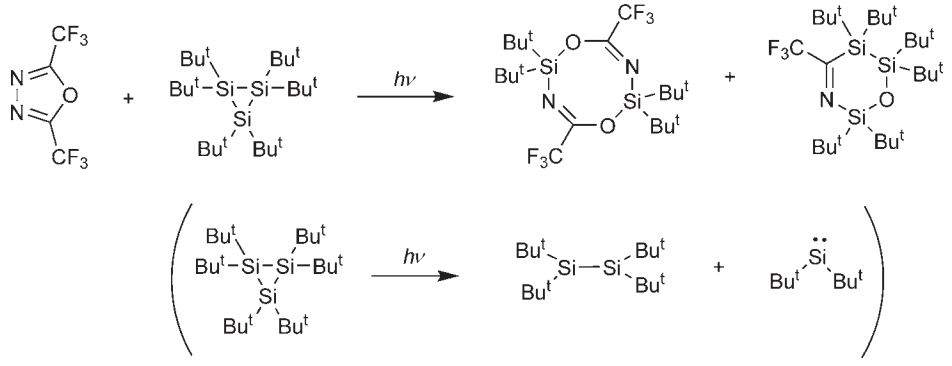


Scheme 12

5.06.5.4 Reactions with Electron-Deficient Species

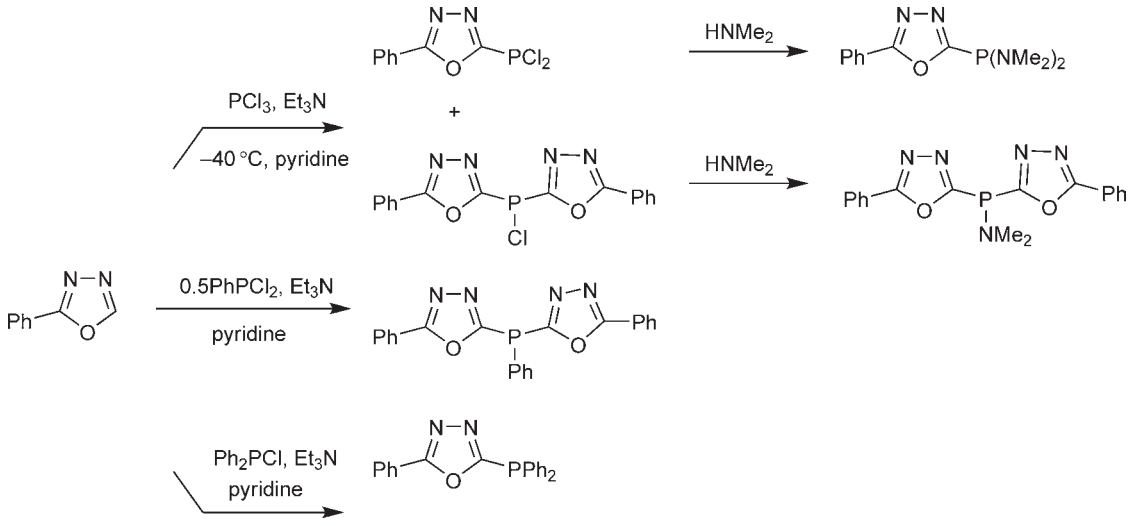
Reactions of 1,3,4-oxadiazoles at the ring atoms with radicals, carbenes, and nitrenes or with other electron-deficient species are rather uncommon. CHEC(1984) and CHEC-II(1996) have reported very few examples of such reactions concerning oxadiazolinones and oxadiazolinethiones. This situation has not changed.

Co-photolysis of 2,5-di(trifluoromethyl)-1,3,4-oxadiazole with cyclotrisilane, which under these conditions decomposes to afford tetra-(*t*-butyl)disilene and di-(*t*-butyl)silylene, provides dihydrodioxadiazadisilocine and trihydrooxazatrisiline derivatives (**Scheme 13**) <1996JOM355>.



Scheme 13

If trivalent phosphorus compounds are to be treated as electron-deficient species, then reactions of oxadiazoles with some Lewis acids should be reported here. 2-Phenyl-1,3,4-oxadiazole reacting with phosphorus trichloride in pyridine solution in the presence of triethylamine at low temperature furnished the respective dichlorophosphine and chlorophosphine, which were trapped by dimethylamine to give the corresponding amides. 2-Phenyl-l,3,4-oxadiazole also interacts over 24 h with the less reactive chlorodiphenylphosphine and dichlorophenylphosphine at room temperature to give phosphines (**Scheme 14**) <1999CHE1117>. These reactions of oxadiazoles resemble the behavior of 1-alkylimidazoles toward trivalent phosphorus derivatives.



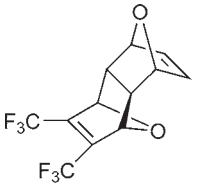
Scheme 14

5.06.5.5 Intermolecular Cyclic Transition State Reactions

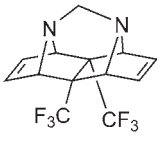
As in CHEC-II(1996), the material gathered in this section concerns all reactions that are formally cycloadditions to the oxadiazole ring (or to the ring and a side chain), including those, which may be stepwise but where no evidence for the mechanism has been provided.

1,3,4-Oxadiazole and most of its simple alkyl or aryl derivatives are not active in thermal reactions toward unsaturated compounds. Photoreactions (UV irradiation) of 2,5-diphenyl-1,3,4-oxadiazole in the presence of thiophene, pyrazole, furan, or indene components lead to the formation of final products probably via [2+2] adducts as intermediates. For the reactions of 2,3-diaryl-1,3,4-oxadiazolium salts with electron-rich alkenes or alkynes, two mechanisms were postulated: thermal [4+2] and polar [3+2] cycloadditions <1984CHEC(6)427>. Also 2-aryl-5-[*N*-(4′-fluorobenzylideno)amino]-1,3,4-oxadiazole participates in thermal [4+2] cycloaddition with aryl isothiocyanates (ArNCS). The Diels–Alder reaction was also observed upon heating 1,3,4-oxadiazoles substituted by strong electron-withdrawing groups with alkynes <1996CHEC-II(4)268>.

From experiments and calculations it appears that the cycloaddition with 1,3,4-oxadiazoles is generally not favorable. The reaction is an inverse Diels–Alder (LUMO diene controlled) reaction with very high activation barriers for nonactivated dienophiles. To be able to perform a cycloaddition, strong electron-withdrawing substituents in 1,3,4-oxadiazoles must be used, such as the trifluoromethyl group. Even when 1,3,4-oxadiazole is properly activated, its reaction is not a simple cycloaddition, but it is a combination of cycloaddition and nitrogen elimination <1998JMT153>. Thermal reactions of oxadiazole **11**, containing strong electron-withdrawing substituents, with alkene partners **12**, **13**, or **14** readily occurred in a Diels–Alder fashion. The results of the experiments concerning mechanism and stereochemistry were supported by AM1 calculations <1995TL5275>. Also, the reaction of two molecules of 7-oxanorbornene **43** with oxadiazole **11**, involving the loss of nitrogen, was investigated and found to yield 100% of a mixture of unsymmetrically and symmetrically coupled products <1995TL6141>. In contrast, diene **44** resisted coupling with oxadiazole **11** <2000OL4003>. Direct coupling of 5,6-dimethylenenorbornene with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole produced molecular tweezers <2001CEJ3406>.

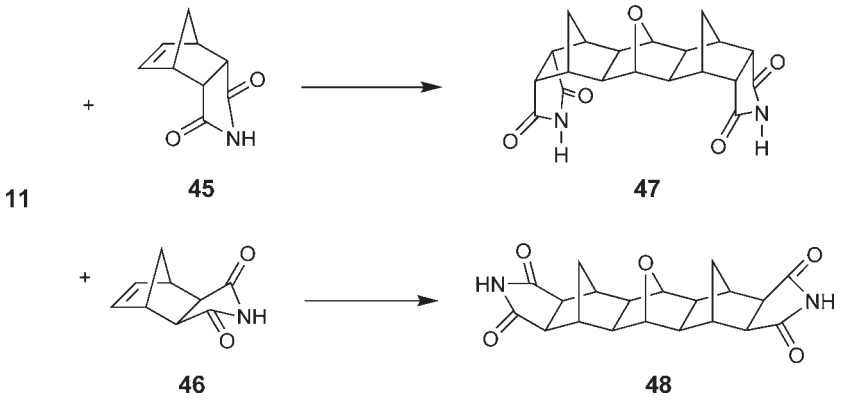


43



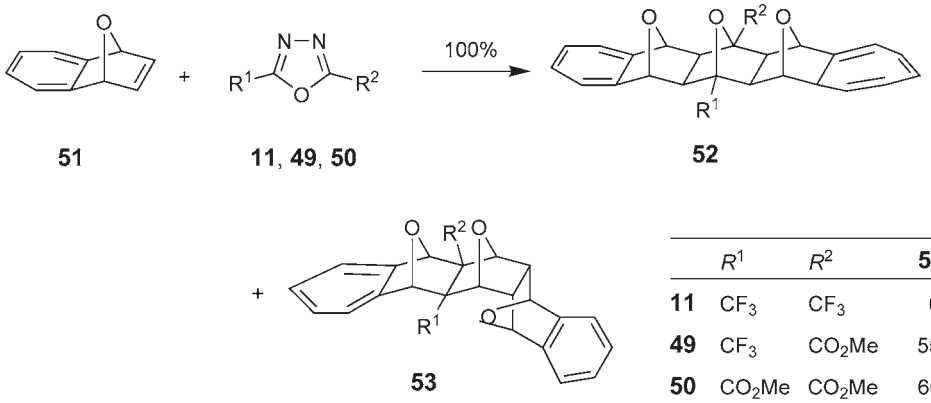
44

Stereoisomeric norbornenosuccinimides **45** and **46** coupled stereoselectively with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **11** to afford respective stereoisomeric alicyclic products **47** and **48**, which were then used as spacers in the syntheses of macrocycles (**Scheme 15**) <2000TL5985>.



Scheme 15

In 2000, Warrener published a review of the cycloaddition reactivity of 1,3,4-oxadiazoles typically bearing such substituents as CF_3, SO_2Et, or CO_2Me <2000EJO3363>. Later, Warrener *et al.* showed that ester-substituted 1,3,4-oxadiazoles **49** and **50** were useful reagents for coupling 7-oxanorbornanes, for example, **51**, and producing predominantly *syn*-facial O-bridged polarofacial system **52** together with its *anti*-facial isomer **53**, which predominated in the reaction with 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole **11** <2001T571> (Equation 6).



(6)

	R^1	R^2	**52**	**53**
11	CF_3	CF_3	0%	100%
49	CF_3	CO_2Me	55%	45%
50	CO_2Me	CO_2Me	60%	40%

Most of the reports that described the cycloaddition reactivity of electron-deficient 1,3,4-oxadiazoles in intermolecular reactions employed symmetrical oxadiazoles bearing strongly electron-withdrawing substituents (CF_3, SO_2Et, CO_2Me). According to Wolkenberg and Boger, who summarized advances in the field, the reactions with alkene dienophiles proceeded through the initial [4+2] cycloadduct that underwent loss of nitrogen to give a carbonyl ylide, which reacted further with the alkene in a 1,3-dipolar cycloaddition. In more recent efforts, they extended the scope of this reaction. In the cases examined, alkenyl dienophiles added to 2-amino-1,3,4-oxadiazole formed regio- and diastereoselectively fused oxabicyclo[2.2.1]heptane products. In these studies, it was observed that alkynyl dienophiles generated high yields of the furan products resulting from a single cycloaddition reaction followed by the loss of nitrogen (**Figure 1**). The reactions were applied to intramolecular cycloadditions <2002JOC7361> (see Section 5.06.5.1).

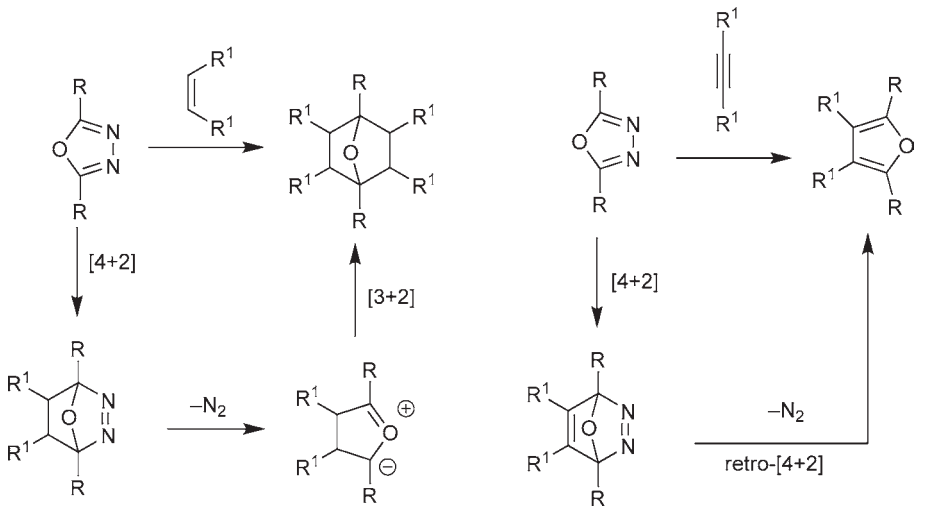


Figure 1

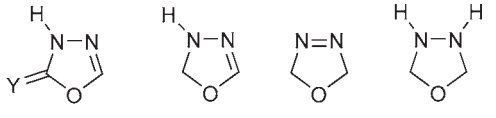
5.06.6 Reactivity of Nonconjugated Rings

Warkentin and co-workers continued studies on gas-phase pyrolysis of oxadiazoline derivatives. DFT calculations and *ab initio* simulations of PE spectra were used in the interpretation of the experimental results <2006CJC546>.

5.06.6.1 2,3-Dihydro-1,3,4-oxadiazoles

There are three nonconjugated reduced systems derived from 1,3,4-oxadiazole **1**, namely: 2,3-dihydro-l,3,4-oxadiazole (Δ^2-1,3,4-oxadiazoline) **5**, 2,5-dihydro-1,3,4-oxadiazole (Δ^3-l,3,4-oxadiazoline) **6**, and 2,3,4,5-tetrahydro-l,3,4-oxadiazole (1,3,4-oxadiazolidine) **7**.

Fully cyclically conjugated 1,3,4-oxadiazol-2-ones **4a** (Y = O) or **54** (R^2 = H, Y = O), which could formally be treated as derivatives of structure **5**, are in dynamic equilibrium with 2-hydroxy-1,3,4-oxadiazoles. A similar situation concerns oxadiazolinethiones **4a** (Y = S) or **54** (R^2 = H, Y = S) tautomeric with the corresponding thiols, and iminooxadiazoles **4a** (Y = NR, R = H) or **54** (R^2 = H, Y = NR) being in equilibrium with aminooxadiazoles. Due to the equilibriums, the reactivity of such systems can be discussed in Section 5.06.5 and here.



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

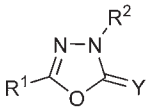
Y = O, S, NR

Oxadiazolinones **54** (R^1 = Ar, R^2 = H, Y = O) reacting with alkyl iodides in the presence of bases afforded 3-alkyl derivatives (R^1 = Ar, R^2 = Alk, Y = O) <1999MI161>. Potassium salts of oxadiazolinethiones **54** (Y = S), when methylated with dimethyl sulfate in hexamethylphosphoric triamide (HMPT) or water, gave mixtures of *N*-3-methyl and *S*-methyl derivatives in proportions 15:85 and 5:95, respectively <1997CHE1109>. In contrast to these results, alkylation of thiones with chloromethylalkyl ethers in acetonitrile or acetone led to the formation of mixtures, in which the products of N-alkylation predominated <1999CHE1104>. S-Alkylation was observed when haloalkanes were used for the reaction without <1999JME1161> and with supersonic irradiation <2004BML6057>, in the reactions with phenacyl bromides <2001CHE496, 2001RJC1754> or chloroacetamides <2002CHE1104>. Hydroxymethylation, Michael addition to 4-vinylpyridine <2002CHE852>, Mannich reactions <2000MOL1429, 2002M173, 2002MI369>, and acylation <2003CHE1364> exclusively occurred on the thioamide nitrogen atom.

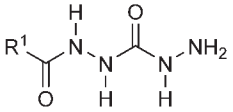
The ring in oxadiazolinones **54** (R^1 = 3-benzyloxyphenyl, CbzNH-L-leucine, R^2 = H, Y = O) in a reaction with hydrazine hydrate cleaved to afford product **55**, which was then used in the syntheses of peptide mimetics <1998JME3923, 1999BMC599>. The reaction of oxadiazolinone **54** (R^1 = Fmoc, R^2 = H, Y = O) with primary

amines was used for a similar purpose <2001JME1938, 2003JME1918>. The reactions of thiones with hydrazine in alcohol solutions led to the oxadiazole ring transformation with formation of 2-substituted derivatives of 4-amino-2,4-dihydro-3*H*-1,2,4-triazole-3-thione <2001M825, 2004MI147, 2004RJO1309>.

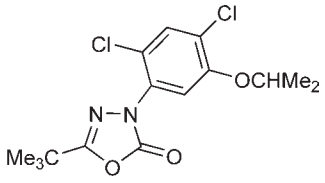
The decomposition of the ring in oxadiazolinone **54** (R^1 = Bn, Y = O, R^2 = CH_2Ar) under the influence of water gave unsymmetrical hydrazine derivatives <2001EJO141>. Ring-opening products were detected after biodegradation of oxadiazone **56** <1995JFA2964, 1999MI943>.



54

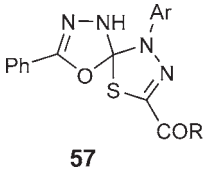


55

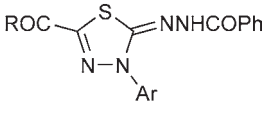


56

Spiro derivatives **57** of 2,3-dihydro-1,3,4-oxadiazoles (R = OMe, OEt, NHPh, Me, Ph, etc., Ar = Ph, 4-$NO_2C_6H_4$) were postulated as intermediates in the transformation of compound **54** (R^1 = Ph, Y = S, R^2 = H) into 2,3-dihydro-1,3,4-thiadiazole derivatives **58**, occurring in the presence of hydrazonoyl chlorides <2003PS1101, 2005SC249>.



57

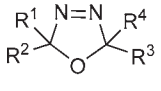


58

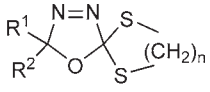
5.06.6.2 2,5-Dihydro-1,3,4-oxadiazoles

In contrast to some 2,3-dihydro-1,3,4-oxadiazole derivatives, for example, compound **4a** discussed in Section 5.06.5 and Section 5.06.6.1, the reactions of 2,5-dihydro derivatives **6** or **59** are only described here.

The acetoxy substituent in compound **59** (R^4 = OAc) was easily replaced by alkoxy <1994JA1161, 2005T5788> and aryloxy groups <1994JA1161, 1999TL1483>. Similar substitutions were observed with dideuterated allyl alcohol <2005T5788>, 2-trimethylsilylethanol <2001JOC7496>, trimethylsilanol <2000OL2733>, perdeuterated methanol <1997JOC4065>, or alkadienols <2004JA9926>. For R^3 = SPr, compound **59** reacted with propanethiol affording the 2,2-di(propylthio) derivative <1999JOC1766>; when R^3 = $HS(CH_2)_nS$, an intramolecular substitution occurred to give dithiospiro derivatives **60** in good yields <2000T10101>.

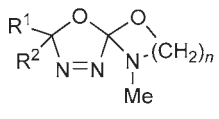


59

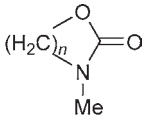


60

Heating compounds **59** (R^1, R^2 = Alk, Ar, R^3 = Ar, OAlk, SAlk, etc., R^4 = OAlk, SAlk, and others) in benzene or toluene led to the formation of ylides that upon decomposing gave carbenes (see Section 4.06.6.2, CHEC-II(1996)). Further fates of the carbenes depend on their structures and co-reagents added. Refluxing compound **61** (n = 3) in benzene at 90 °C gave product **62** in 77% yield; for compound **61** (n = 2), the yield of product **62** dropped to 33% <1996JA4214>.

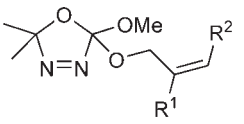


61

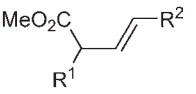


62

Thermolysis of compound **63** (R^1 = Ph, R^2 = H) in benzene at 110 °C afforded a mixture of products **64a** (R^1 = Ph, R^2 = H) and **64b** (R^1 = H, R^2 = Ph) in proportion 2:1 with total yield 60%. Inversion of substituent (R^1 and R^2) positions in the starting material gave the same products as before but in the opposite proportion (1:2) <1998JA11182>.

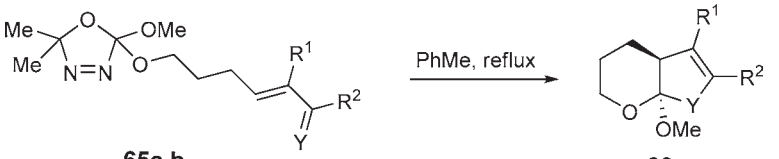


63



64a,b

Bicyclic product **66** was formed in 80% yield (Equation 7) while heating compound **65a** ($R^1 = CO_2Me$, $R^2 = H$, $Y = CH_2$). Compound **65b** ($R^1 = H$, $R^2 = Me$, $Y = O$), containing an α,β-unsaturated carbonyl fragment, reacted in a similar manner <2004JA9926>. Thermolysis of the silyl derivative **59** (R^1, $R^2 = Me$, $Y = O$, $R^3 = SiPh_3$, $R^4 = OMe$) led to a mixture of methoxytriphenylsilane and methoxycarbonyltriphenylsilane in proportion 3:1 <2000OL2733>.



65a,b

$R^1 = CO_2Me$; $R^2 = H$; $Y = CH_2$

$R^1 = H$; $R^2 = Me$; $Y = O$

PhMe, reflux

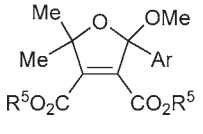
66

(7)

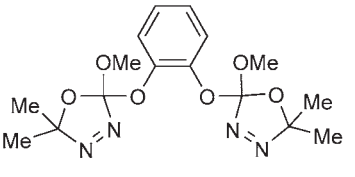
Ylides forming from the thermolysis of compound **59** (R^1, $R^2 = Me$, $R^3 = Ar$, $R^4 = OMe$) reacted also with dimethyl acetylenedicarboxylate (DMAD) or diethyl azodicarboxylate (DEAD) <2003TL5029> in the presence of aldehydes, quinones <2001TL2043>, or ketones <2002OL2821, 2000OL3501> to give 2,5-dihydrofuran derivatives, for example, **67** ($R^5 = Me$, Et).

Silyl derivatives reacted in a similar manner <1995TL7591>. The heating of adamantanethione with compound **59** resulted in addition of dimethoxycarbene to a double bond with the formation of adamanthylthiirane in 92% yield <2001OL2455>; fluorenone reacted analogously <1997JOC4065>. The addition of dimethoxycarbene to cyclobutanethione or cyclopentanethione caused the ring expansion <2002CEJ2184>.

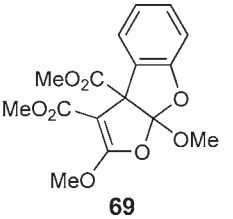
The carbene obtained by heating compound **68** with DMAD at first gave a cyclopropene derivative, which underwent further transformations (*ipso*-substitution and cyclization) to afford tricyclic product **69** in 40% yield <1999TL1483>. The thermolysis carried out in the presence of $ArCH{=}C(CN)_2$ and DMAD used in excess led to the formation of highly functionalized cyclopentene derivatives **70** <2003TL5029, 2005TL201>.



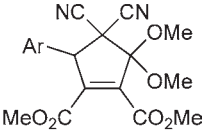
67



68



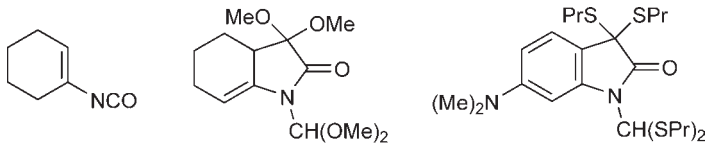
69



70

Cyclopent-2-en-1-one silyl derivatives were obtained in high yields by heating compound **59** (R^1, $R^2 = Me$, R^3, $R^4 = S$-Pr) with silylated α,β-unsaturated ketones <2003OL263>. A reaction of compound **59** (R^1, $R^2 = Me$, R^3, $R^4 = OMe$) with perchlorocyclopentadiene gave cyclopentadienecarboxylic acids as the result of several consecutive S_N2' (or S_N2'', if concerted) reactions <1999JOC4344>. The same starting material and its analogs ($R^4 =$ alkenyl) in the presence of *t*-butanol afforded mixed orthoformates containing not only OMe groups but also alkenyl and *t*-butyl fragments <1998JA11182, 2005OL487, 2005T5788>.

The synthetic scope of thermolysis of dihydrooxadiazole **59** (R^1,$R^2 = Me$, R^3,$R^4 = OMe$) was extended by Rigby *et al.* <1996JA12848>, who showed that dimethoxycarbene underwent [4+1] cycloaddition to α,β-unsaturated isocyanates (e.g., **71**), followed by the addition of a second dimethoxycarbene molecule to the resulting intermediate to produce product **72** in 80% yield <1996JA12848>. Also, aroyl azides, which under the reaction conditions rearranged into arylisocyanates, gave good yields of product **72**. Isocyanates also reacted with sulfur analogs **59** ($Y = S$) to afford tetrahydroindol-2-one, quinolin-2-one, and pyrrol-2-one derivatives <1999JOC1766, 2000T10101>. 3-(*N*,*N*-Dimethylamino)phenyl isocyanate with compound **59** (R^1,$R^2 = Me$; R^3,$R^4 = SPr$) gave indolone **73** in 70% yield <1999TL6891>. Considering the number of readily available isocyanates, the reaction was applied in the total synthesis of several alkaloids, such as tazzetine <1998JA3664> and mesmembrine <2000OL1673>, or in the synthesis of azepineindole fragment of *Stemona* alkaloids <1998JOC5587>.



71 72 73

5.06.7 Reactivity of Substituents on Carbon

Some reactions of tautomeric compounds **4a** have already been discussed in Sections 5.06.5.2 and 5.06.6.1 because assignments of at least of some of these reactions to a particular section may be ambiguous.

5.06.7.1 C-Linked Substituents

Electrophilic substitution of the ring hydrogen atom in 1,3,4-oxadiazoles is uncommon. In contrast, several reactions of electrophiles with C-linked substituents of 1,3,4-oxadiazole have been reported. 2,5-Diaryl-1,3,4-oxadiazoles are brominated and nitrated on aryl substituents. Oxidation of 2,5-ditolyl-1,3,4-oxadiazole afforded the corresponding dialdehydes or dicarboxylic acids. 2-Methyl-5-phenyl-1,3,4-oxadiazole treated with butyllithium and then with isoamyl nitrite yielded the oxime of 5-phenyl-1,3,4-oxadiazol-2-carbaldehyde. 2-Chloromethyl-5-phenyl-1,3,4-oxadiazole under the action of sulfur and methyl iodide followed by amines affords the respective thioamides. 2-Chloromethyl-5-methyl-1,3,4-oxadiazole and triethyl phosphite gave a product, which underwent a Wittig reation with aromatic aldehydes to form alkenes. Alkyl 1,3,4-oxadiazole-2-carboxylates undergo typical reactions with ammonia, amines, and hydrazines to afford amides or hydrazides. It has been shown that 5-amino-1,3,4-oxadiazole-2-carboxylic acids and their esters decarboxylate.

Nucleophilic displacement of a good leaving group at C-2 in 1,3,4-oxadiazoles by some nitrogen or sulfur nucleophiles occurs, though ring opening is much more common. A nucleophilic attack on oxadiazolium salts usually leads to a ring cleavage with possible recyclization to another heterocycle, often providing a useful method for its synthesis <1984CHEC(6)427, 1996CHEC-II(4)268>.

The metalation, particularly lithiation, and halogen-to-metal exchange reactions of 1,3,4-oxadiazoles as well as further reactions of organometallic derivatives were reviewed by Grimmett and Iddon (Equation 8) <1995H(41)1525>.

(8)

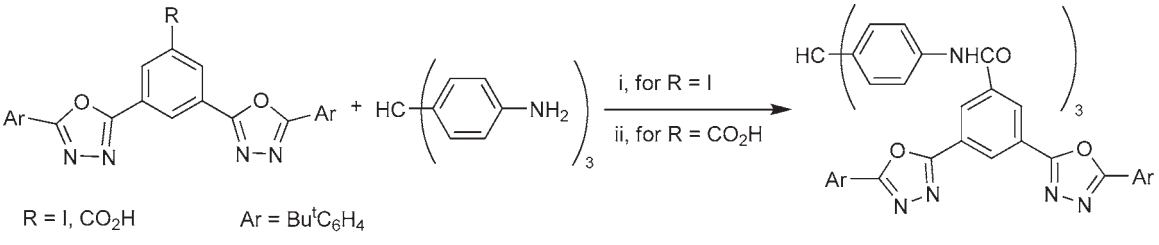
Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$

R = $–CHR^1COCH_2R^2$

$R^1 = R^2 = R^3 = H$ 27–55%

$R^1, R^2 = R^1, R^3 = (CH_2)_3$ 25–56%

Dendrimers, which contain an electron-deficient 1,3,4-oxadiazole ring and aromatic systems linked by amide units to triphenylmethane core, were synthesized (**Scheme 16**) <1997CC1435>.



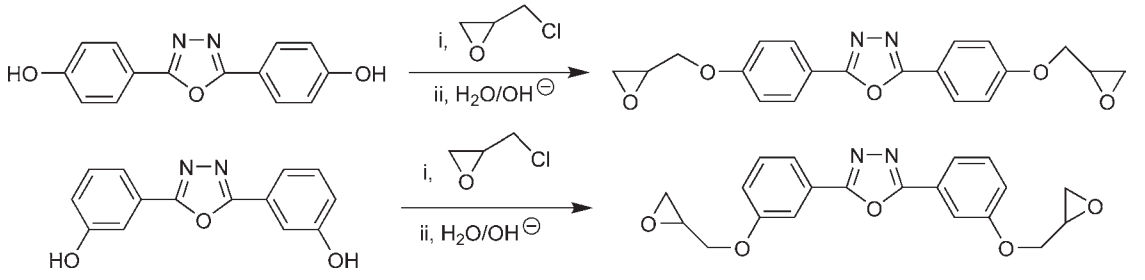
R = I, CO_2H Ar = $Bu^tC_6H_4$

i, $PdCl_2$, $Ph_2P(m\text{-}C_6H_4SO_3Na)$, DBU, NMP, CO
ii, $P(OPh)_3$, pyridine

DBU = diazabicyclo[5.4.0]undec-7-ene

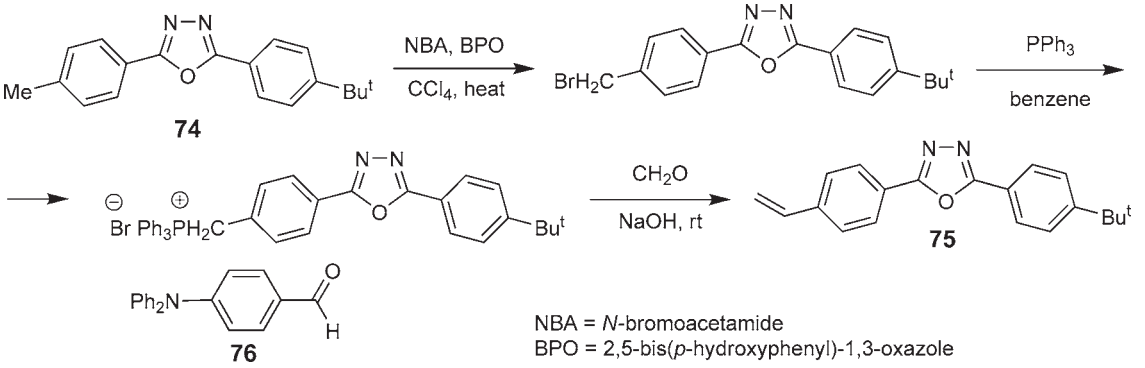
Scheme 16

2,5-Bis(4- and 3-hydroxyphenyl)-l,3,4-oxadiazoles were alkylated in an excess of epichlorohydrin in the presence of NaOH and quaternary ammonium salts, while the temperature was gradually raised from 20 to 90 °C, affording luminescent epoxide monomers (**Scheme 17**) <1999CHE358>.



Scheme 17

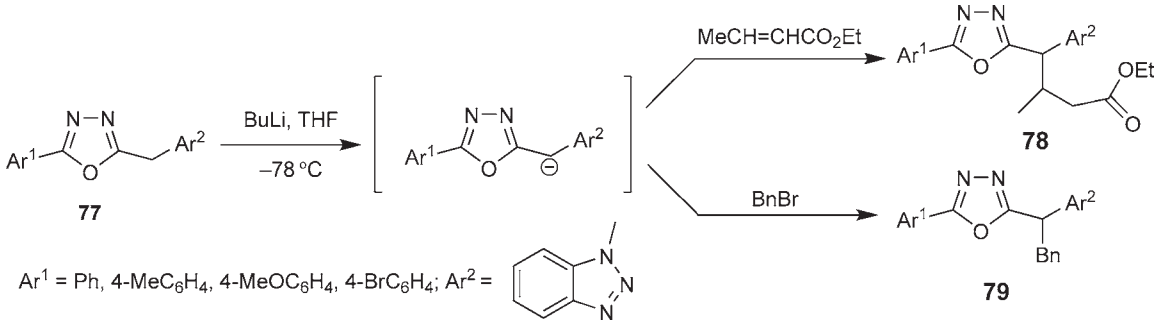
2,5-Diaryl-1,3,4-oxadiazole **74** was brominated and then treated with triphenylphosphine and formaldehyde to afford vinyl derivative **75**. This was condensed with aminoaldehyde **76** using Wittig and Heck reactions to furnish new multibranched chromophores with a oxadiazole system (**Scheme 18**) <1999PCB10741>.



Scheme 18

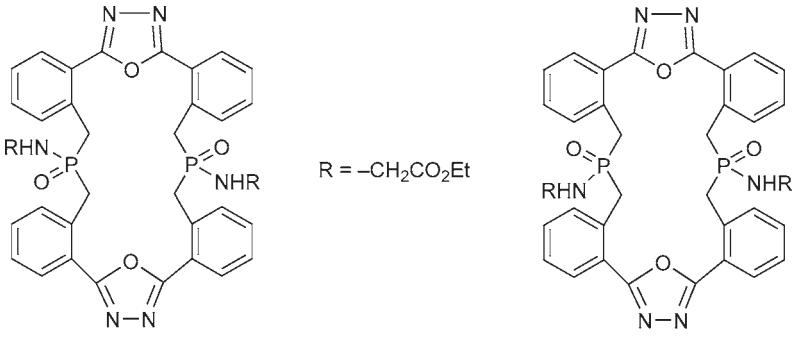
Acylation reactions of 2,5-bis(*o*-amino-phenyl)-1,3,4-oxadiazoles with an excess of chiral *N*-tosyl-*l*-leucyl chloride were performed in dry pyridine <2000JST109>.

The Michael-type reaction of an anion (generated from compound **77**) with ethyl crotonate yielded the corresponding ester **78** in 82% yield (**Scheme 19**). Alkylation of compound **77** with benzyl bromide afforded derivative **79** in 85% yield. The attempted reactions of the anion with oxiranes and trimethylsilyl chloride did not lead to the expected substitution products and the starting oxadiazoles were recovered in 70–80% yields <2001ARK101>.



Scheme 19

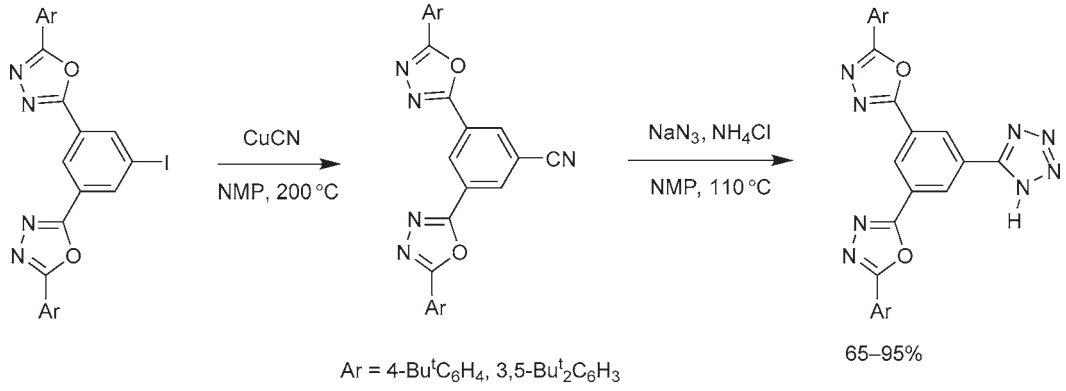
Macrocyclic stereoisomeric phosphoramidates **80** and **81** containing oxadiazole segments were obtained starting from 2,5-(2′-hydroxyphenyl)-1,3,4-oxadiazole, phosphorus oxychloride, and other reagents <2001JST145>. Chiral macrocyclic phosphoramidates were also obtained <2001SC3197>.



80 **81**

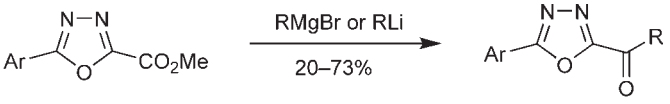
Conjugated Schiff base macrocycles containing a 1,3,4-oxadiazole moiety were prepared by [1+1] cyclic condensation <2002SC3339>.

Interesting oxadiazole-substituted benzonitriles prepared from the respective aryl iodides were transformed into the corresponding (dioxadiazolephenyl)tetrazoles. Despite the high temperature and other drastic conditions, the oxadiazole ring stayed intact during both reactions (**Scheme 20**) <1999JOC6425>.



Scheme 20

Grignard reagents or alkyllithium addition to methyl 2-aryl-1,3,4-oxadiazol-5-yl formates afforded a series of 2-acyl-5-aryl-oxadiazoles (Equation 9) <2005BML1423>.



Ar = Ph, 2-pyridyl; R = $Ph(CH_2)_6$
Ar = Ph, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-furanyl; R = $Ph(CH_2)_5$
Ar = 2-pyridyl, 3-pyridyl; R = 2-pyridyl
Ar = $Ph(CH_2)_5$, $Ph(CH_2)_6$, $Ph(CH_2)_7$, $Ph(CH_2)_8$; R = $Ph(CH_2)_7$

(9)

5.06.7.2 N-Linked Substituents

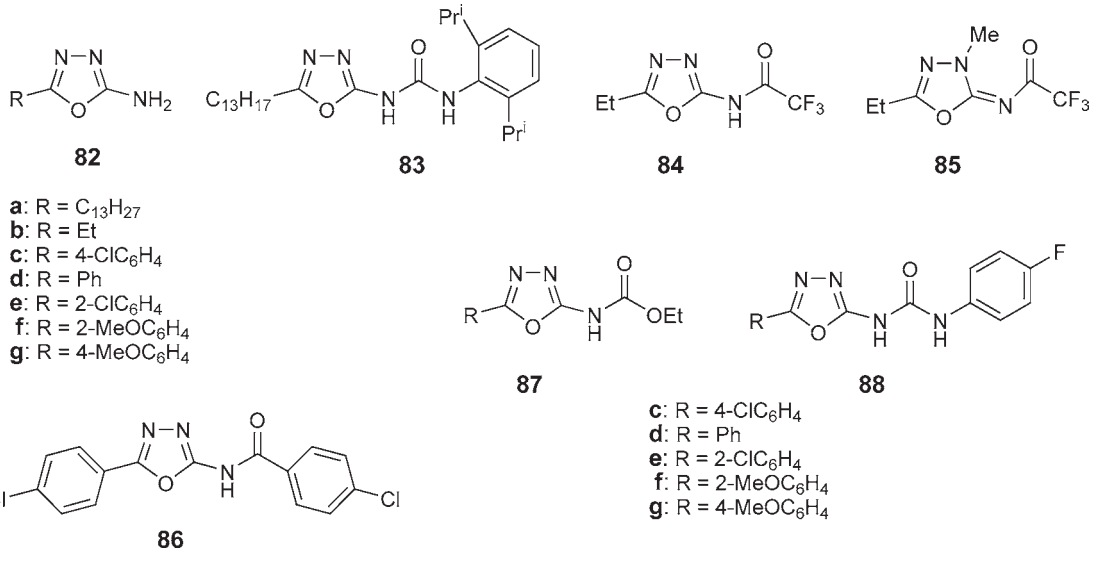
2-Aminooxadiazoles are generally N-alkylated at position 3 and acylated at the 2-amino group (see also Section 5.06.5.2). In some cases, both reactions occur at the same time. Aminooxadiazoles react on the amino nitrogen with aldehydes, thiocyanates, and carbon disulfide–alkyl iodides or with alkyl isothiocyanate–alkyl halide systems. The amino group also reacts with nitrous acid to afford the corresponding diazonium salt. 2-Hydrazidooxadiazoles react

with carbonyl compounds to form hydrazones. 2-Azidooxadiazoles can be used as photochemical acylating agents. Oxadiazolimines can be hydrolyzed to the corresponding oxadiazolinones <1996CHEC-II(4)268>.

Not much progress in the field has been made since the publication of CHEC-II(1996). 5-Alkyl-2-amino-1,3,4-oxadiazole **82a** was coupled in MeCN with 2,6-diisopropylphenyl isocyanate to give the corresponding urea **83** <1996JME4382>. Acylation of 2-amino-5-ethyl-1,3,4-oxadiazole **82b** with trifluoroacetic acid anhydride afforded the corresponding amide **84**, which was then methylated on N-3 to give oxadiazolinimine **85** <1998JA3104>.

The attempted direct trifluoroethoxylation of 2-amino-5-(4-chlorophenyl)-1,3,4-oxadiazole **82c** using 2,2,2-trifluoroethanol and sodium hydride unexpectedly resulted in the formation of *N*-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-chlorobenzamide **86**. A mechanism for the reaction was proposed <1999JFC39>.

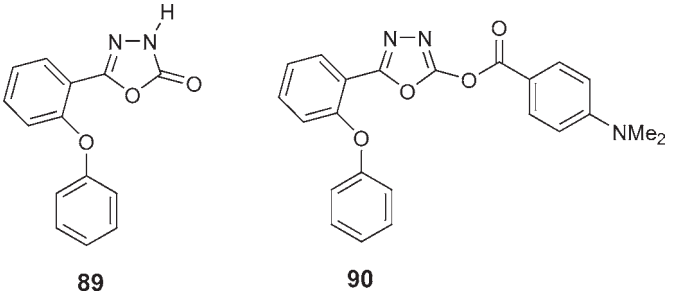
Acylation of 2-amino-5-aryl-1,3,4-oxadiazoles **82c–g** with ethyl chloroformate in the presence of triethylamine gave carbamates **87c–g**, which were sequentially treated with 4-fluoroaniline in boiling ethanol affording ureas **88c–g** <2000JFA5465>. Diazotation of **82d** with *i*-$C_5H_{11}ONO$ in MeCN in the presence of $CuBr_2$ at room temperature gave 2-bromo-5-phenyl-1,3,4-oxadiazole in 90% yield <2004TL7157>.



5.06.7.3 O-Linked Substituents

Most reactions of oxadiazolinones involve a nucleophilic attack at the carbon atom of carbonyl group and often are followed by the ring-opening reactions with possible recyclization. Also, the nucleophilic displacement of oxygen by chlorine atom occurring in oxadiazolinones treated with phosphorus oxychloride and phosphorus pentachloride or with thionyl chloride involves an attack on a carbon atom, though as a result the carbon–oxygen bond breaks. Due to that, and in contrast to <1996CHEC-II(4)268>, these types of reactions are presented in Section 5.06.5.3. Oxadiazolinones can form complexes with metal salts by bonding the metal ion to the oxygen atom of carbonyl group <1996CHEC-II(4)268>.

More recently, the esterification of oxadiazolinone **89** by 4-dimethylaminobenzoic acid in dry CH_2Cl_2 in the presence of dicyclohexylcarbodiimide (DCC) was described to afford compound **90** (70%). The structure of the product was based on NMR, IR, and MS spectra <2000JLR545>. No other similar reaction was found.

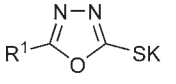


An atempted O-alkylation of 5-aryl-2-oxadiazolinones with alkyl bromides, chlorides, and iodides exclusively led to N-alkylated products (see Section 5.06.5.2).

5.06.7.4 S-Linked Substituents

In *C*-aryl oxadiazolinethione derivatives, thioamide predominates its thiol tautomer in an equilibrium mixture. Nevertheless, oxadiazolinethiones and their salts are alkylated on sulfur, while acylation usually occurs on a ring nitrogen. The N-acylated products are thermodynamically favored whereas *S*-acyl derivatives are formed faster. A rearrangement of the latter into *N*-acyl isomers has been observed at an elevated temperature. Oxadiazolinethiones easily form alkali metal salts, which are better S-nucleophiles than the parent compounds. Oxidation of *C*-alkyl or *C*-aryl oxadiazolinethiones by bromine leads to disulfides, whereas *S*-alkyl derivatives are oxidized to sulfones <1984CHEC(6)427, 1996CHEC-II(4)268>. Displacement of a sulfur atom or fragments containing sulfur in *S*-alkyl, *S*-aryl derivatives of oxadiazolinethiones or in sulfones, described in Section 4.06.7.4 of CHEC-II(1996), now are presented in Section 5.06.5.3 because most of these reactions involve a nucleophilic attack on the ring carbon atom.

Oxadiazolinethione potassium salts **91** reacting with appropriate alkyl halides in refluxing acetone gave sulfides **92**, which were oxidized then with *m*-chloroperbenzoic acid, to afford sulfoxides **93**. In a similar way, derivatives **94** were prepared <1996BML2693>.



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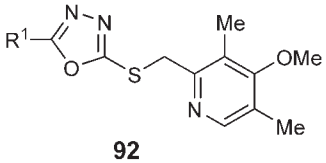
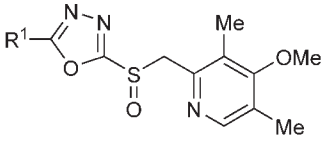
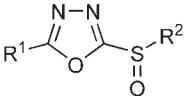


92



93

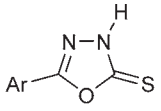


94

R^1 = Me, Et, Pr, Bu, C_5H_{11}, Ph, 3-FC_6H_4, 4-FC_6H_4, 3-$CF_3C_6H_4$, 4-$CF_3C_6H_4$, 2-HOC_6H_4, 2-thienyl

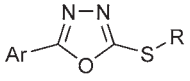
R^1 = Me, 2-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl; R^2 = Bn

Treatment of 5-aryloxadiazolinethiones **95a–c** with dimethyl sulfate resulted in the formation of the corresponding sulfides **96** and isomeric *N*-methyl derivatives <1997CHE1109>. The reaction of the potassium salt of 5-(2′,4′-dichlorophenyl)-l,3,4-oxadiazoline-2-thione with dimethyl sulfate was carried out in water and aprotic (HMPT) solvent. In HMPT, the reaction furnished a mixture of S- and N-methylation products in 85:15 ratio and overall high yield. When water was used, the total yield of the methyl derivatives was 89% with 95:5 ratio. Similar results were obtained for alkylation of compound **95a** with methyl tosylate in dry acetone. It was observed that the direction of the alkylation depended not only on the nature of the solvent but also on the isomeric structure of butyl chlorides used as alkylating agents. Exchange of *s*-butyl chloride by fluoride resulted in the formation of the *S*-alkyl derivative in 10% yield <1997CHE1109>. The use of alkyl iodides or dibromodifluoromethane for alkylation of compound **95d** led exclusively to N-alkylation <1999MI161>.



95

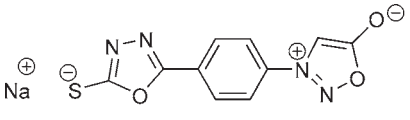
a: Ar = Ph
b: Ar = 2-ClC_6H_4
c: Ar = 2,4-$Cl_2C_6H_3$
d: Ar = 2,4,6-$Cl_3C_6H_2$



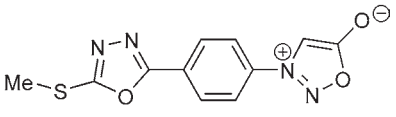
96

a: Ar = Ph; R = Me, Bu^s
b: Ar = 2,4-$Cl_2C_6H_3$; R = Me
c: Ar = 2-ClC_6H_4; R = Me, Bu^n, Bu^s, or Bu^t

When sodium salt **97** was treated with methyl iodide, only the formation of the S-methylation product **98** (yield 91%) was observed <1999MI63>.

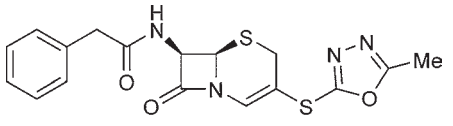


97



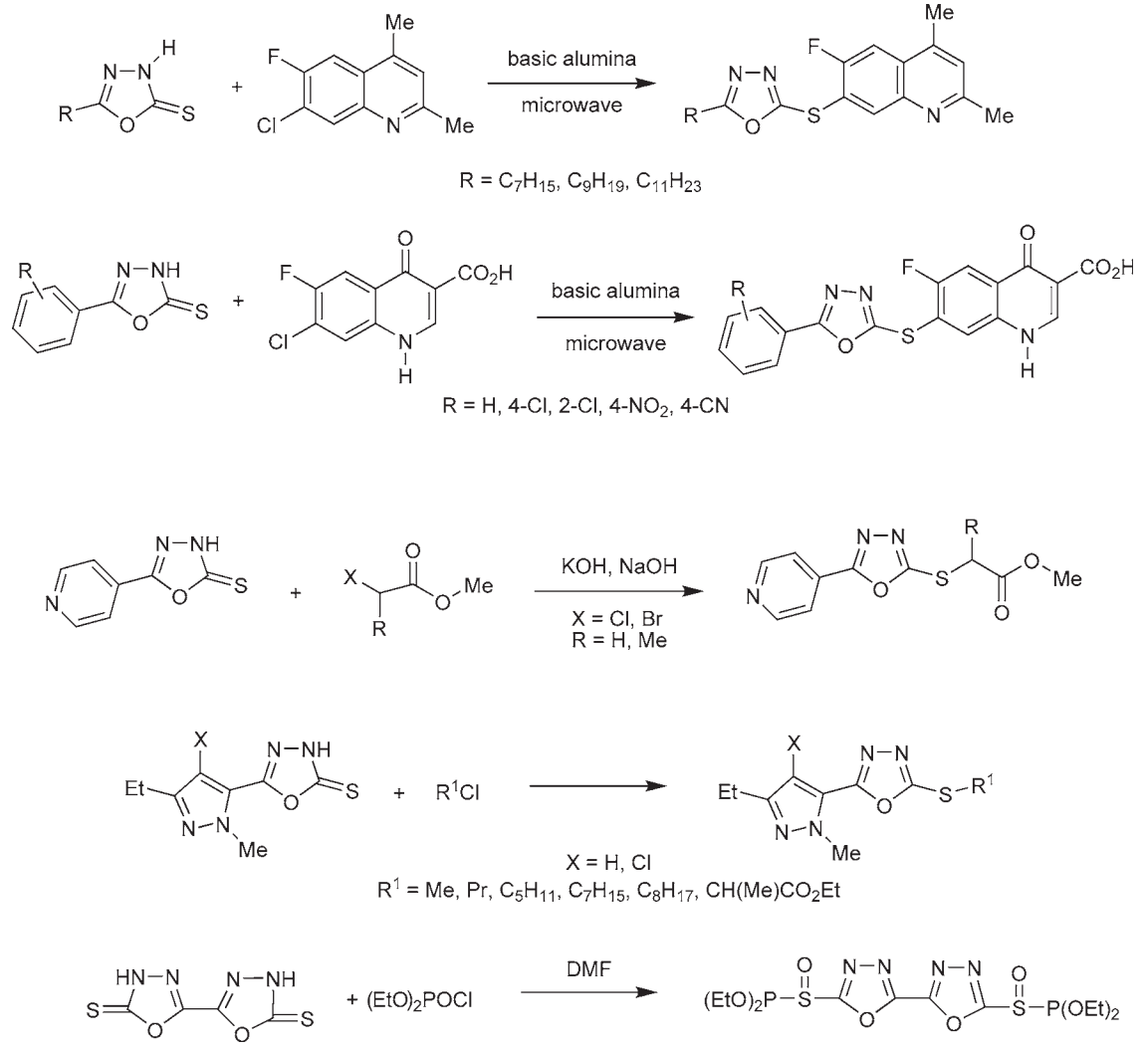
98

The synthesis of cephem derivative **99** involved S-alkylation of 5-methyl oxadiazoline-2-thione with the appropriate tosylate <2000BMC2317>.



99

Microwaves were used to support S-arylation of 5-substituted oxadiazoline-2-thiones <2000BMC69> and <2000M1207>. 5-(4-Pyridyl)oxadiazoline-2-thiones treated with 2-haloesters also afforded *S*-alkyl derivatives <2000CHE851>. A similar reaction occurred in the case of 5-pyrazolyloxadiazoline-2-thiones <2000JFA5312>. Organophosphorus derivatives of 1,3,4-oxadiazole were obtained by the reaction of bis(oxadiazolinethiones) with *O*,*O*-diethylchlorophosphate (**Scheme 21**) <1998JFA1609>.



Scheme 21

Condensation of α-bromo-4-difluoromethylthioacetophenone with 5-benzyl-1,3,4-oxadiazolinethione proceeded readily in the presence of potassium hydroxide to give 5-benzyl-2-[4-(difluoromethylthio)phenacyl]thio-1,3,4-oxadiazole <2003CHE965>. α-Fluoro-α-[2-(5-phenyl-1,3,4-oxadiazolyl)thio]acetonitrile, 1-fluoro-1-[2-(5-phenyl-1,3,4-

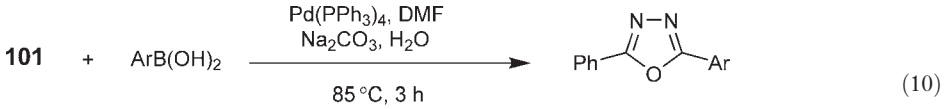
oxadiazolyl)thio]-2-propanone, and other similar compounds have been prepared by highly regioselective electrolytic monofluorination of the respective 2-(5-phenyl-1,3,4-oxadiazolyl) sulfides <2001JOC5633>. Resin-bound α-keto mesylate was cleaved under acidic conditions in the presence of 5-(4-pyridyl)-1,3,4-oxadiazoline-2-thione to give the corresponding thioether <2004TL1381>. 5-Phenyl-1,3,4-oxadiazoline-2-thione was metalated with trialkyl(or aryl)tin(IV) chloride on sulfur atom to yield a series of organotin(IV) complexes, the structures of which were determined by X-ray crystallography <2005POL1773>.

5.06.7.5 Cl-, Br-, or P-Linked Substituents

Chlorooxadiazoles **100** react with N-nucleophiles like primary and secondary amines, hydrazines, or metal azides to afford respective products of chlorine atom nucleophilic displacement. Since such reactions, which in CHEC-II(1996) <1996CHEC-II(4)268> were discussed in the corresponding section, obviously involve an attack of the nucleophiles on the ring carbon linked to the chlorine atom in compound **100**, they are presented here in Section 5.06.5.3. 2-Bromo-5-phenyl oxadiazole **101** was prepared in over 90% yield from 2-amino-5-phenyloxadiazole via the corresponding diazonium compound. Compound **101** underwent palladium-catalyzed Suzuki cross-coupling with aryl boronic acids to afford 5-aryl-2-phenyloxadiazoles (Equation 10) <2004TL7157>. Oxadiazole derivatives containing fluoro or iodo atoms linked to the ring carbon atoms have not been synthesized. Also, no reaction involving an attack of any reagent directly on a chlorine or bromine atom has been reported.

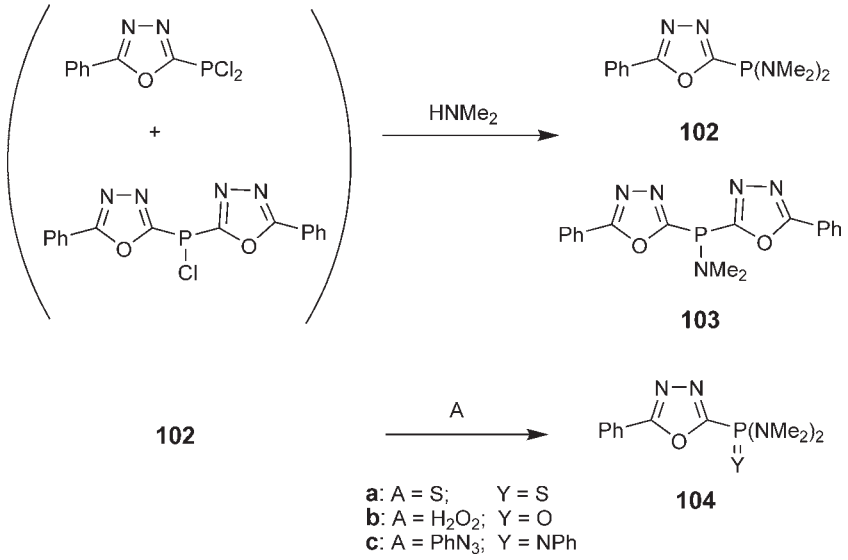
100 **101**

R = alkyl, aryl



(10)

A mixture of oxadiazoledichlorophosphine and dioxadiazolochlorophosphine treated *in situ* in pyridine solution with dimethylamine gave a mixture of the corresponding stable amides **102** and **103**, which were separated and characterized spectroscopically. Amide **102** reacted under standard conditions with sulfur, hydrogen peroxide, or phenylazide, and then was converted to further respective derivatives **104a–c** (**Scheme 22**) <1999CHE1117>.

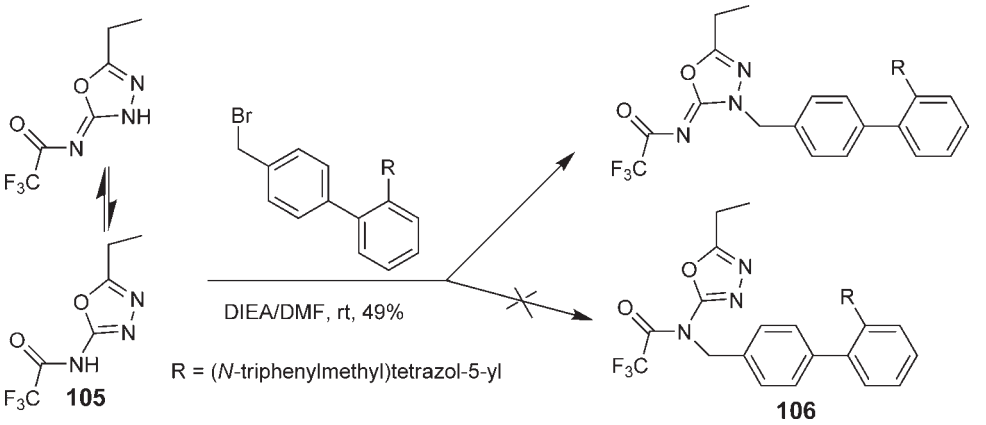


Scheme 22

5.06.8 Reactivity of Substituents on Ring Nitrogen Atoms

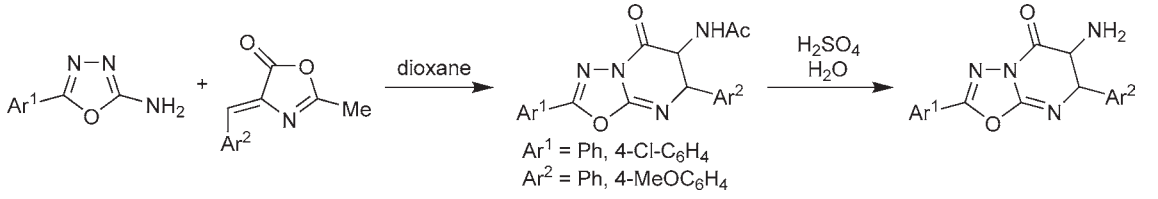
Nucleophilic displacement of chlorine in *N*-chloroalkyloxadiazolinethiones, decarboxylation of *N*-alkoxycarbonyloxadiazolinones, reduction of (nitroaryl)oxadiazolinones to (aminoaryl)oxadiazolinones, and reactions of carbonyldiimides, derived from oxadiazolinethiones, with nucleophiles have been described earlier <1996CHEC-II(4)268>.

The reactions of substituents on ring nitrogen atoms in 1,3,4-oxadiazolium cations **2** and exocyclically conjugated mesoionic 1,3,4-oxadiazoles **3** are uncommon. Similar reactions of compounds **4** and **5** were reported occasionally. Biphenylmethylation of 2-trifluoroacetamido-1,3-4-oxadiazole **105** occurred regioselectively (**Scheme 23**), affording only the 2-acylimino derivative instead of the expected product **106** <1997H(44)133>.

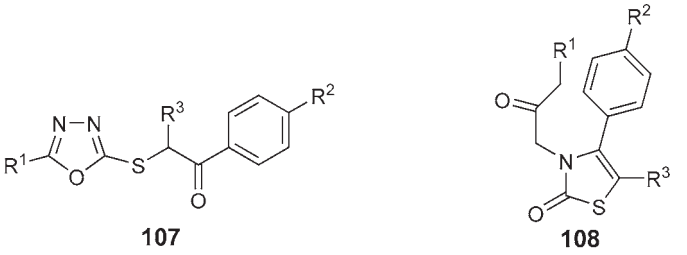


Scheme 23

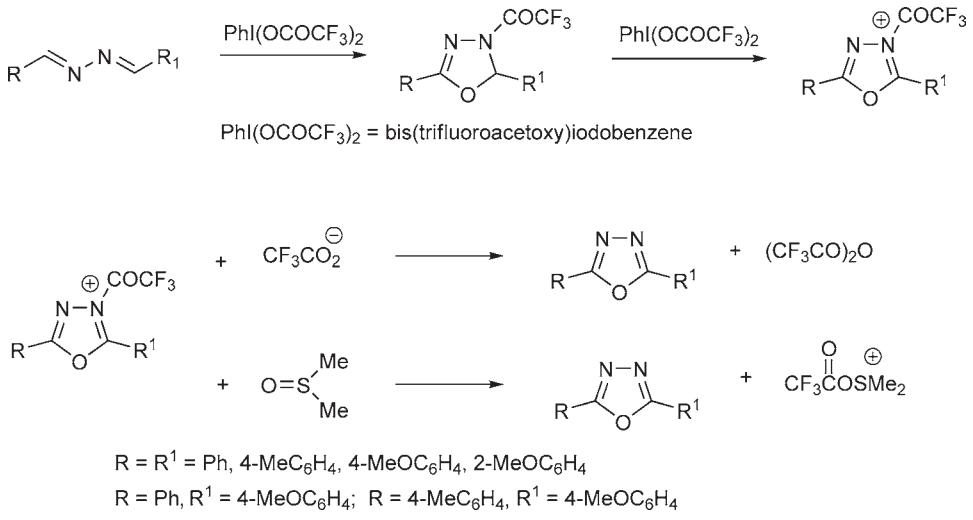
A Michael addition of 2-amino-5-aryl-1,3,4-oxadiazoles to 4-arylidene-5-oxazolones followed by other processes involving reactions of substituents on a ring nitrogen atom yielded 1,3,4-oxadiazolopyrimidinones in a one-pot procedure (**Scheme 24**) <1996JFA1565>. The course of reaction of 5-alkyl-1,3,4-oxadiazolinethiones with ω-bromoacetophenones depended on the acidity of the solution, giving *S*-alkyl derivatives of the starting oxadiazole **107** in the presence of alkalies or N-substituted thiazolone derivatives **108**. The latter reaction probably involved N-alkylation followed by reactions of the *N*-alkyl group on the ring carbon atom <2001RJC1825>. Also, in the first step of the oxidative cyclization of aldazines with bis(trifluoroacetoxy)iodobenzene, the reactions of substituents on the ring nitrogen atom probably took place (**Scheme 25**) <2005TL2701>.



Scheme 24

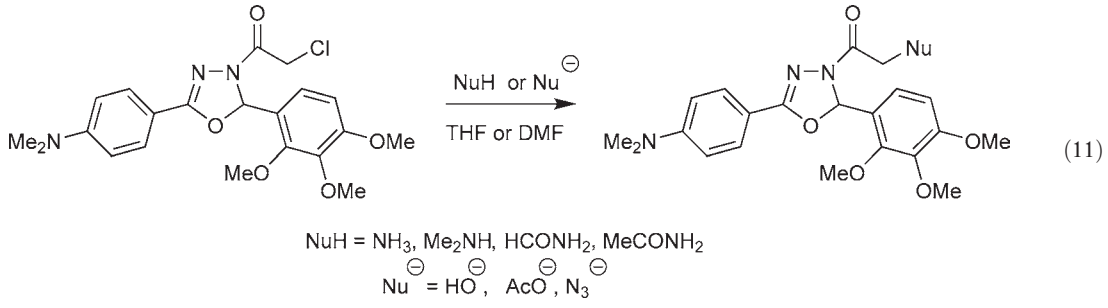


R^1 = Ph, 4-MeOC_6H_4, 4-EtC_6H_4, 2,4-$Cl_2C_6H_3O$, 4-BrC_6H_4O, 4-MeOC_6H_4O
R^2 = H, F, Cl, Br, MeO
R^3 = H, Me



Scheme 25

A typical nucleophilic displacement of chlorine atom in several 3-acyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles by *O*- or *N*-nucleophiles resulted in the formation of new 3-acyl derivatives (Equation 11) <2001JME4416>.



(11)

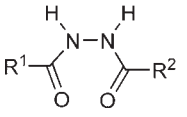
5.06.9 Ring Synthesis from Acyclic Precursors

This section mainly includes variations of previously described syntheses <1984CHEC(6)427, 1996CHEC-II(4)268>. Like the arrangement in CHEC-II(1996), the reactions are divided into two sections: (1) when the ring is obtained by formation of one bond only (Section 5.06.9.1), and (2) when two compounds react leading to 1,3,4-oxadiazoles, even though in the final stage of the reaction only one bond was formed (Section 5.06.9.2). The assignments are somewhat arbitrary.

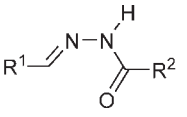
Only a few reports on improvements of standard methods for the synthesis of oxadiazole ring have recently been published. A facile new protocol for the preparation of 2-amino-1,3,4-oxadiazoles was reported. This method involves a tosyl chloride–pyridine-mediated cyclization of thiosemicarbazides, prepared by acylation of hydrazides with the appropriate isothiocyanates. Utilizing this protocol, several 5-alkyl- and 5-aryl-2-amino-1,3,4-oxadiazoles in 78–99% yield were prepared <2006JOC9548>. 2,5-Disubstituted-1,3,4-oxadiazoles were synthesized in high yields by dehydrative cyclization of 2-acyl hydrazides bound to the polymeric support and using trifuoroacetic anhydride as a dehydration agent. The cyclizations were not successful for ureas and thioureas stemming from R^2–NCS or R^2NCO and R^2 bearing aromatic nitro groups, or α-keto groups <2006T10223>. Some compounds of acyclic C-nucleoside type and containing 1,3,4-oxadiazole-2-thione moieties were prepared by standard methods <2006ARK183>. Intermolecular 1,3-dipolar cycloaddition of azomethine imines, prepared from α-substituted aldehydes and *N*-methyl acethydrazide, was applied in a synthesis of N-substituted 2,3-dihydrooxadiazoles <2007ARK152>.

5.06.9.1 Cyclization with Formation of One Bond

For convenience, the syntheses discussed in this section are divided into groups, depending on the structures of the starting materials, despite the fact that all of them contain C–N–N–C–O fragments. Therefore, 1,2-diacylhydrazines **109** are described as O–C–N–N–C–O components, acylhydrazones **110** as C–C–N–N–C–O components, while, for example, dithioates and similar compounds **111** are treated as S–C–N–N–C–O components.



109



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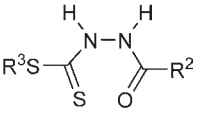

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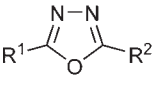
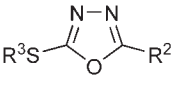


112



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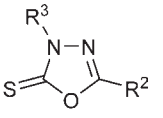
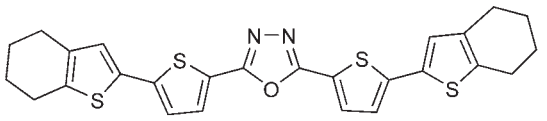


114

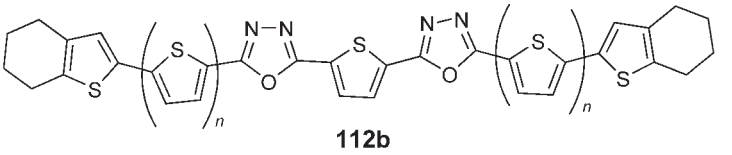
R^1, R^2 = H, alkyl, aryl, NH_2, NHR, NR_2
R^3 = metal, H, alkyl, aryl

5.06.9.1.1 Ring synthesis from O–C–N–N–C–O components

The most popular route to 2,5-disubstituted 1,3,4-oxadiazoles involves cyclodehydration of 1,2-diacylhydrazines **109** with the use of $POCl_3$ to give, for example, compound **112a** <1998CEJ2211>, luminescent oligomers **112b** <2000EJO425>, biologically active diaryloxadiazoles **112c** <2000JFC173>, **112d** <2001JA2296>, **112e** <2001TL2697>, and **112f** <2002CHE165>, unsymmetrical and symmetrical 2,5-diaryloxadiazoles **112g** <2003JFC163>, 2-aryl-5-styryl derivative **112h** <2003MM9295>, 5-aryl-2-chloromethyl-1,3,4-oxadiazoles **112i** <2002JFC63, 2003JFA152>, 5-trimethylsilylethynyl-1,3,4-oxadiazoles **112j** <2003RJO1522>, as well as steroids **112k** <2002STE581>. 1,3,4-Oxadiazoles containing a combination of SF_5-perfluoroalkyl, SF_5-alkyl, polynitroalkyl, and perfluoroalkyl substituents have been synthesized by cyclization (dehydration) of the corresponding diacylhydrazines <1995JFC31>.



112a



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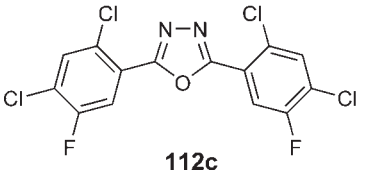

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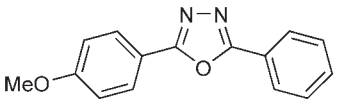
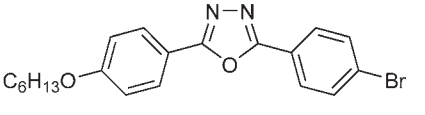


112d



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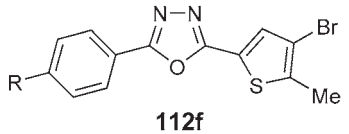
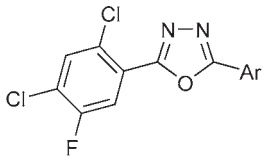


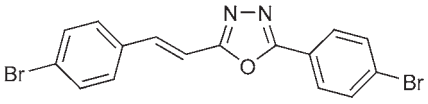
112f

R = H, MeO

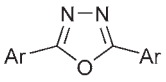


112g

Ar = 2,6-$F_2C_6H_3$, 2,4,5-$F_3C_6H_2$, 2,3,4,5-F_4C_6H, 2-BrC_6H_4, 2-ClC_6H_4, 2-Cl-4,5-$F_2C_6H_2$

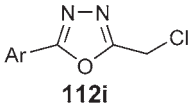


112h



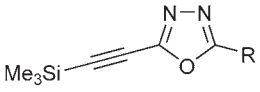
112g

Ar = 2,6-$F_2C_6H_3$, 2,4,5-$F_3C_6H_2$, 2,3,4,5-F_4C_6H, 2-BrC_6H_4, 2-ClC_6H_4, 2-FC_6H_4, 2-Cl-4,5-$F_2C_6H_2$



112i

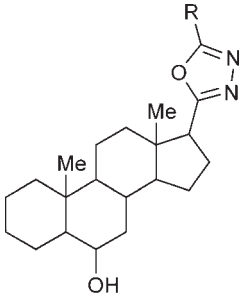
Ar = Ph, 4-EtC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, 2-FC_6H_4, 2,4-$Cl_2C_6H_3$



112j

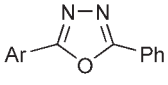
R = PhNH, Ph, 4-$O_2NC_6H_4$

Using phosphorus pentachloride, 2,5-diaryl derivatives **112l** were obtained <2000T4213>. Various symmetric dialkyl and diaryloxadiazoles **112** were synthesized in yields exceeding 90% by trifluoroborane–ethyl ether-promoted cyclodehydration of diacyl- and diaroylhydrazines prepared *in situ* from the corresponding acid chlorides and hydrazine <2001SC1727>. 2-Aminooxadiazole derivative **112m** was obtained by dehydration of 5-bromo-*N*-semicarbazidocarbonylmethyl)anthranilic acid in concentrated sulfuric acid <2002EJM689>. Compound **109** was dehydrated with thionyl chloride to afford products **112n** and **112o** <2002MM2529>. Using phosphorus pentoxide and absolute ethanol, product **112p** was prepared <1996JME3908>. Also PPA served as dehydrating agent in the preparation of compound **112r** <2003MM9295>. Several symmetrically and unsymmetrically substituted diaryloxadiazoles **112s** were conveniently prepared using $ZrCl_4$ in CH_2Cl_2 as a catalyst for dehydratation of the respective precursor **109** <2004SC2387>.



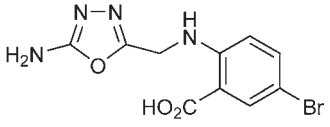
112k

R = Me, Ph

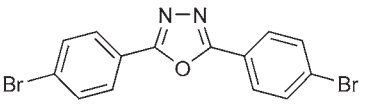


112l

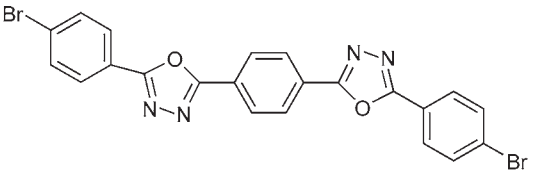
Ar = Ph, 2-MeC_6H_4, 2,4,5-$Me_3C_6H_2$



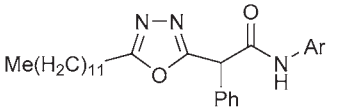
112m



112n

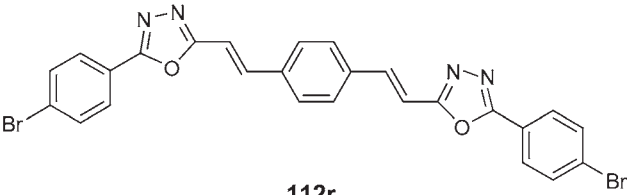


112o

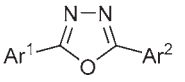


112p

Ar = 2,4,6-$(MeO)_3C_6H_2$, 2,6-$Pr^i_2C_6H_3$



112r

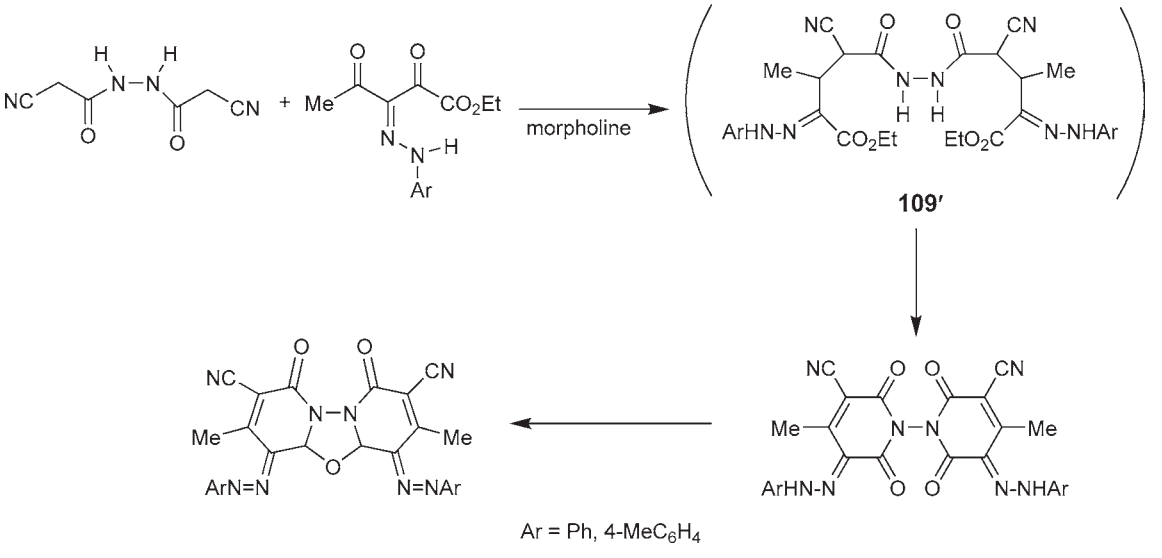


112s

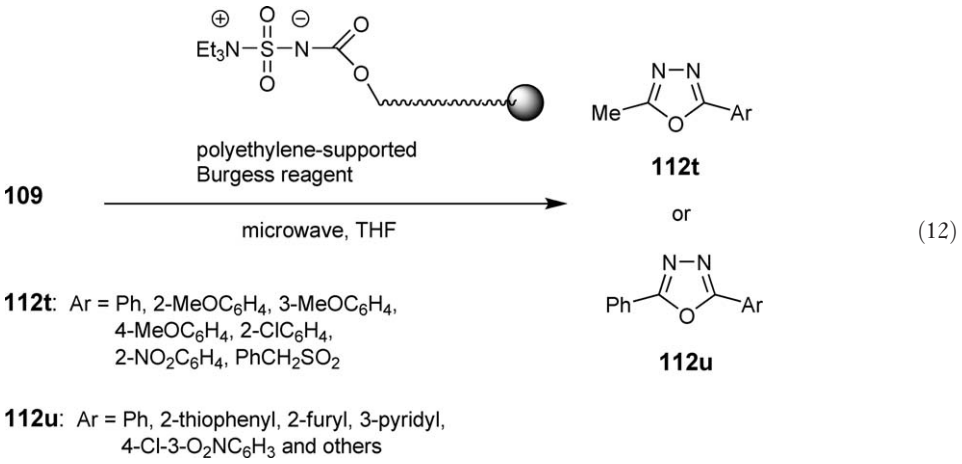
$Ar^1 = Ar^2$ = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4
Ar^1 = Ph; Ar^2 = 4-ClC_6H_4,
Ar^1 = Ph; Ar^2 = 4-$MeOC_6H_4$
Ar^1 = Ph; Ar^2 = 4-$O_2NC_6H_4$
Ar^1 = 4-FC_6H_4; Ar^2 = 4-$MeOC_6H_4$

An interesting example of oxadiazole ring formation from formally O–C–N–N–C–O component **109** is the synthesis of tricyclic system (pyridooxadiazolpyridine) depicted in **Scheme 26** <1998MI655>.

At the end of the twentieth century, a novel and efficient procedure for the synthesis of products **112t** and **112u** from the respective precursor **109** using polymer-supported Burgess reagent under microwave conditions was reported (Equation 12). Yields of products **112t** and **112u** exceeded 75% and the obtained compounds were usually of high purity <1999TL3275>.



Scheme 26



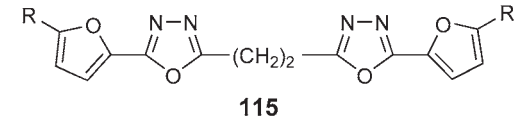
(12)

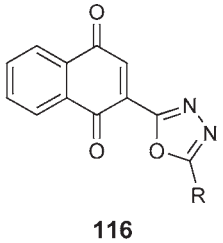
A set of heterocyclic ketones including 1,3,4-oxadiazole-linked compounds were synthesized via a dehydrative cyclization using the Burgess reagent in a single-mode microwave <2003BML3909>.

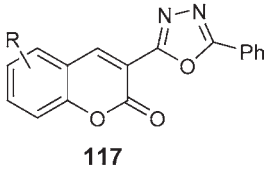
5.06.9.1.2 Ring synthesis from C–C–N–N–C–O components

The second most popular method of oxadiazole preparation starts from acylhydrazones **110**, which undergo cyclization usually under the action of oxidizing agents (Br_2, $PhNO_2$, HgO, iodobenzene diacetate). Also, the use of acetic anhydride can lead to cyclization of compound **110**. The cyclization can be supported by microwave irradiation. In particular cases, heating is sufficient to accomplish the reaction.

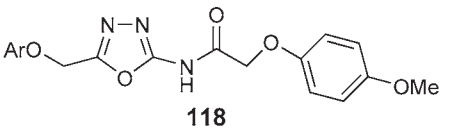
Several antibacterial 1,2-bis(1,3,4-oxadiazol-2-yl)ethanes **115** were synthesized from the respective dihydrazones using bromine in acetic acid with added sodium acetate <2000EJM267>. Also, 3-(5-aryl-1,3,4-oxadiazol-2-yl)chromones **116** were prepared using bromine as an oxidizing agent; this time, the reaction was performed in the presence of sodium hydroxide <2001RJC767, 2003CHE1072>, while in the preparation of compounds **117** the starting acylhydrazones were heated in nitrobenzene <1999CHE167, 2002JFA3757>.





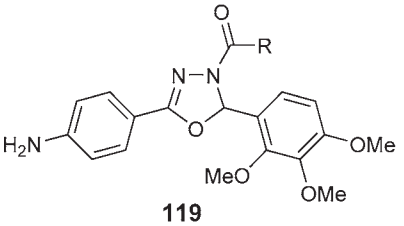


More recently, some oxidative cyclizations of **110** were supported by microwave irradiation, shortening the reaction time. Examples can be synthesis of **118** performed in the presence of $Hg(OAc)_2$ <2002SC1097> or synthesis of several simple 2,5-diaryloxadiazoles **112** (where R^1 = Ph and R^2 = Ph, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$MeO_2CC_6H_4$, and 4-$Me_2NC_6H_4$) carried out in the presence of potassium permanganate <2004TL8753>. A simple and efficient method was developed for the oxidation in the solid state of various heterocyclyl acylhydrazones **110** with iodobenzene diacetate to heterocyclyl-1,3,4-oxadiazoles **112** (where R^1 = 4-pyridyl and R^2 = Ph, 2-Cl C_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-MeC_6H_4, 4-MeC_6H_4, Ph–CH=CH) <2004SC2153>. Symmetrical and unsymmetrical aldazines were efficiently converted to 2,5-disubstituted-1,3,4-oxadiazoles by oxidation with bis(trifluoroacetoxy)iodobenzene <2005TL2701>. Acylhydrazones treated with acetic anhydride afforded 2,5-diaryl-3-acyloxadiazolines **119** <2001JME4416>, **120** <2002MI369>, and **121** <2002PS303>.



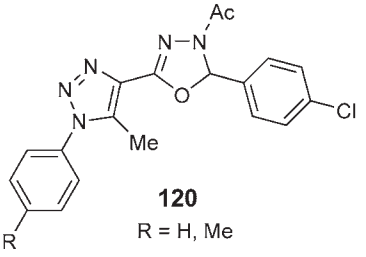
118

Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$



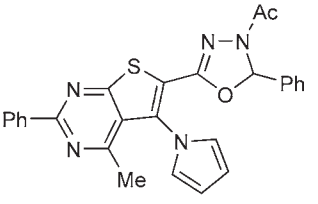
119

R = H, Me, MeO, EtOCO, $ClCH_2$



120

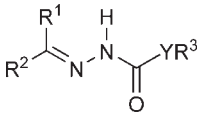
R = H, Me



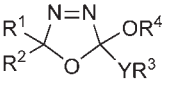
121

4-Phosphorylated derivatives of 2-aryl-5-hydrazinooxazoles upon heating were easily converted to 2,5-disubstituted 1,3,4-oxadiazoles containing the CH(NHCOAr)P(O)$(OMe)_2$ group at one of the side chains (**Scheme 27**) <2001RJC1825>. This unusual reaction could be classified either as a ring synthesis from C–C–N–N–C–O or O–C–N–N–C–O components; however, the proposed mechanism seems to be closer to the classification applied here. Another similar process, accomplishing oxadiazoles upon heating, is the second reaction shown in **Scheme 27**. 2-(*N*-Aroylhydrazono)coumarin-3-carboxamides were readily converted to 3-(1,3,4-oxadiazol-2-yl)coumarins in good yields upon heating in high-boiling solvents (1,2-dichlorobenzene, nitrobenzene, quinoline) or a melt <1999CHE167>.

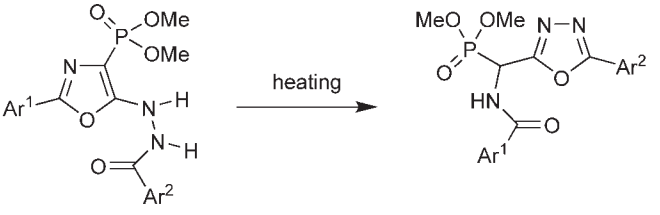
Oxidative cyclization of acylhydrazones **110a**, derived from aldehydes or ketones, with the use of lead tetraacetate (LTA) has been developed into a useful route to several disubstituted and tetrasubstituted oxadiazole derivatives **122**, being a convenient source of relatively stable carbenes, like N(O)C:, S(O)C:, O(O)C:, or S(S)C: <2000J(P1)2161>. Some representative recent examples of the syntheses are collected in **Table 2**.



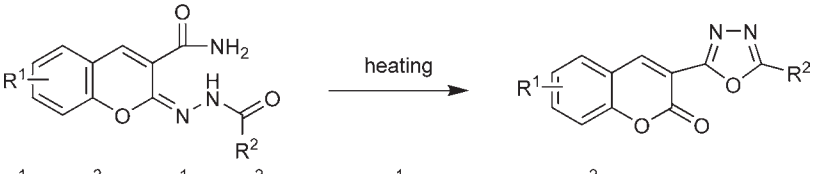
110a



122



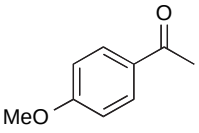
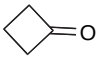
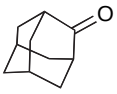
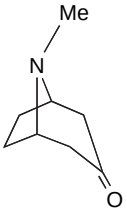
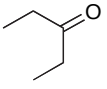
Ar^1 = Ph; Ar^2 = 4-MeC_6H_4
Ar^1 = 4-ClC_6H_4; Ar^2 = 4-MeC_6H_4



R^1 = H, R^2 = Ph; R^1 = H, R^2 = 4-FC_6H_4; R^1 = 6-C_6H_{13}-7-OH, R^2 = Ph
R^1 = 7-Et_2N, R^2 = Ph, 2-ClC_6H_4, 4-MeC_6H_4, or 4-Py
R^1 = 5,6-benzo, R^2 = Ph or 4-$MeOC_6H_4$

Scheme 27

Table 2 Representative examples of the synthesis of oxadiazole derivatives **122** from acylhydrazones **110a**

R^1 and R^{2a}	R^3	R^4	Y	*Yield* (%)	*Reference*
Acetone	Me	Ac	O	60–72	1994JA1161
	Me	Ac	O	37	2005T5788
Acetone	Me	Me	O	70	1998JA8681
	Me	Me	O	42	1998JA8681
	Me	Me	O	56	1998JA8681
	Me	Me	O	66	1999JOC4456
	Me	Me	O	32	1999JOC4456
	Me	Me	O	68	1999JOC4456
Acetone	Pr	Ac	S	91	2000T10101
Acetone	$HS(CH_2)_2$	Ac	S	52	2000T10101

[a]R^1 and R^2 derived from an initial ketone.

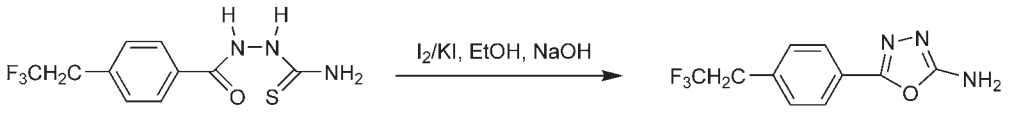
5.06.9.1.3 Ring synthesis from S–C–N–N–C–O components

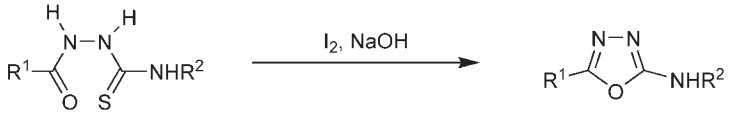
Ring synthesis from S–C–N–N–C–O components through their oxidative cyclization was often applied to obtain mainly aminooxadiazoles, sometimes also oxadiazolinethiones. Several condensing agents were used for that purpose. Newer examples of aminooxadiazole synthesis using iodine in alkaline solution <1999JFC39, 2001CHE1102>, or other reagents <2001RCB272, 2001SC1907, 2002EJM197>, are summarized in **Scheme 28**. Similar examples are also collected in **Scheme 29** <2001SC1907, 2002EJM197, 2002JFA3757>. Two additional examples of aminooxadiazole preparation <2003EJI2639, 2003EJM959> together with a recently published efficient method for the synthesis of a series of 2,5-diaminooxadiazoles on solid support <2005T5565> are shown in **Scheme 30**. The products obtained on the solid support in yields 60–89% were of reasonable purity (75–95%).

Cyclodesulfurization of thiosemicarbazides, containing pyrazole <2002PS67> or benzofuran <2002PS863, 2004PS1577> units, by yellow mercuric oxide or by 1,3-dibromo-5,5-dimethylhydantoin in the presence of potassium iodide <2006TL4889> afforded the respectively substituted oxadiazoles.

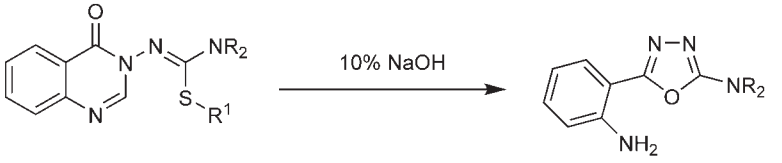
Besides aminooxadiazoles, oxadiazolinethiones can also be prepared from S–C–N–N–C–O components <2002CHE810>, and in this case microwave irradiation facilitates the cyclization (**Scheme 31**) <2002SC111>.

2-Alkyl(or aryl)amino-5-aryl-1,3,4-oxadiazoles were earlier successfully obtained on solid support as shown in **Scheme 32** <2001TL2583>.

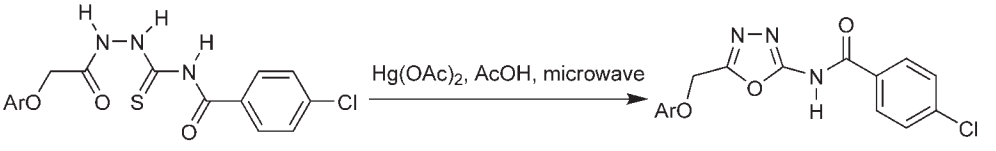




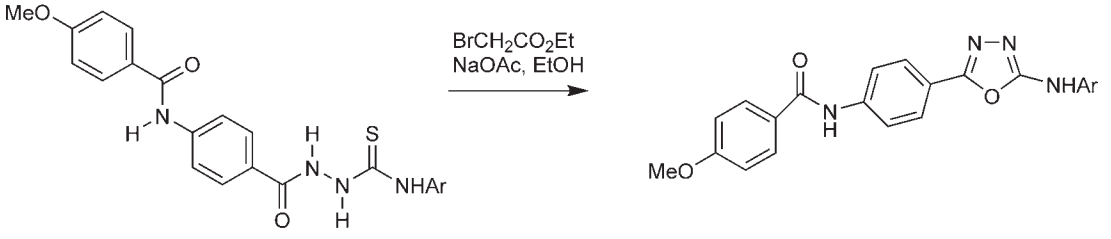
R^1 = 4-$ClC_6H_4SO_2(CH_2)_2$; R^2 = H
R^1 = 4-$BrC_6H_4SO_2CH_2$; R^2 = Ph
R^1 = 4-$MeC_6H_4S(CH_2)_2$; R^2 = Ph



NR_2 = NMe_2, NEt_2, morpholino, piperidino
R^1 = Me, NMe_2, NEt_2, morpholino, piperidino



Ar = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4,
4-$MeOC_6H_4$, 4-ClC_6H_4, 2-$O_2NC_6H_4$,
4-$O_2NC_6H_4$, 2,4-$Cl_2C_6H_3$, 1-naphthyl

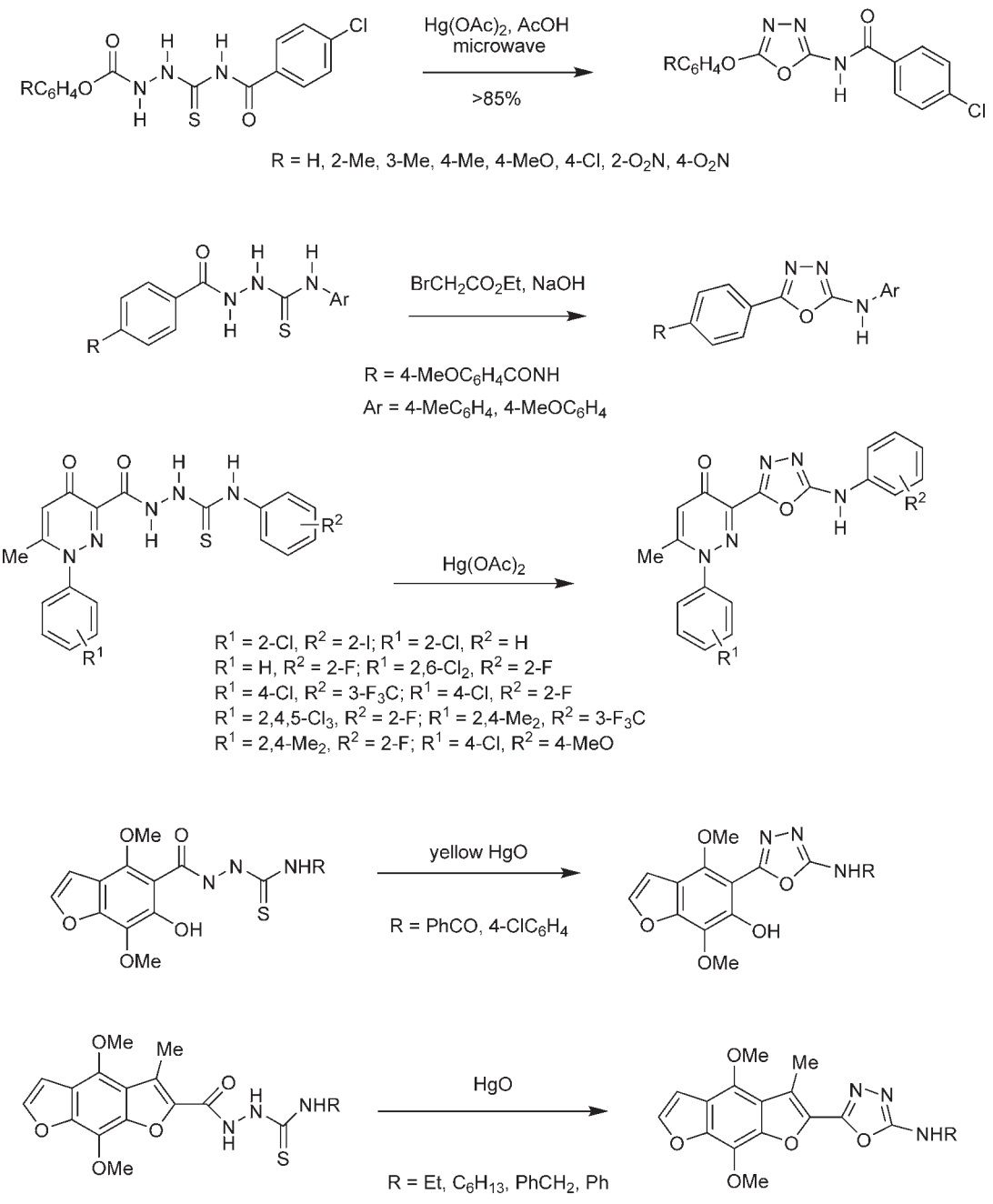


Ar = Ph, 4-$MeOC_6H_4$

Scheme 28

5.06.9.2 Cyclization with Formation of Two Bonds

As in Section 5.06.9.1, the assignments are sometimes arbitrary. Important routes to oxadiazoles, aminooxadiazoles, oxadiazolinones, and oxadiazolinethiones involving the reaction of hydrazides $RCONHNH_2$ with carboxylic acids, acyl chlorides, alkyl esters, or trialkyl orthoesters are described in Section 5.06.9.2.1, reactions with carbon disulfide



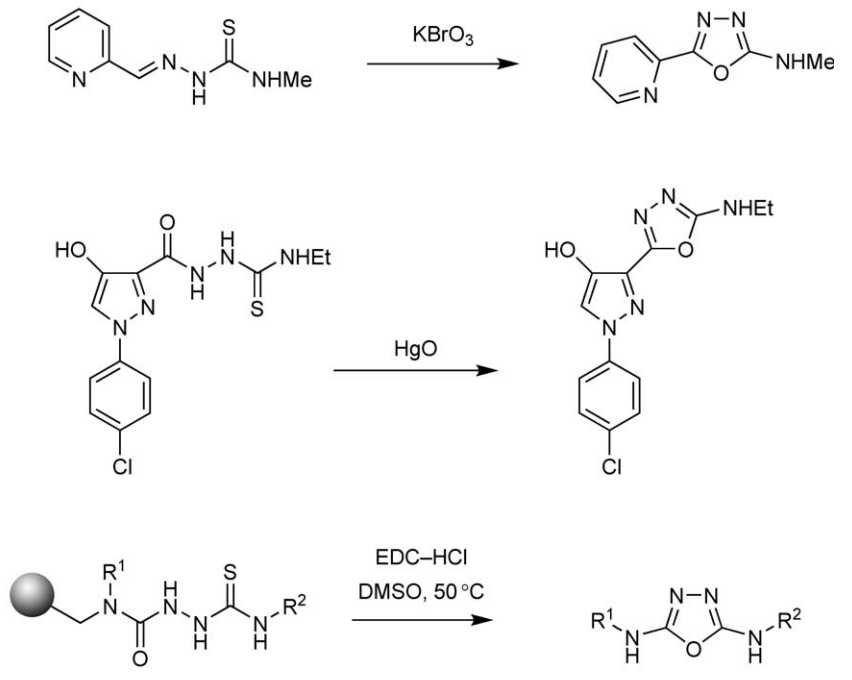
Scheme 29

are collected in Section 5.06.9.2.2, with cyanogen bromide or isocyanates in Section 5.06.9.2.3, and reactions of hydrazides with trichloromethyl compounds in Section 5.06.9.2.4. Some reactions difficult to classify are gathered in Section 5.06.9.2.4.

5.06.9.2.1 Ring synthesis from C–O and N–N–C–O components

The reactions of hydrazides with the respective carboxylic acids afforded oxadiazole derivatives **123** <1996JME2753>, **124** <2000BML1645>, **125** <2003JFC163>, and **126** <2004EJM535>. The reactions

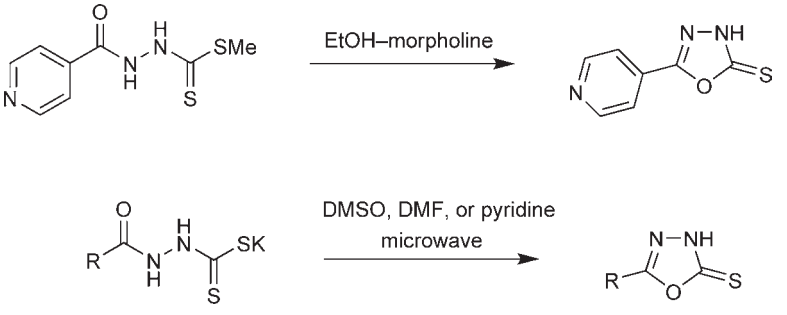
were usually performed in the presence of phosphorus oxychloride. Therefore, they probably involve intermediate formation of acyl chlorides and very much resemble processes where acyl chlorides were reacted with hydrazides.



EDC–HCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

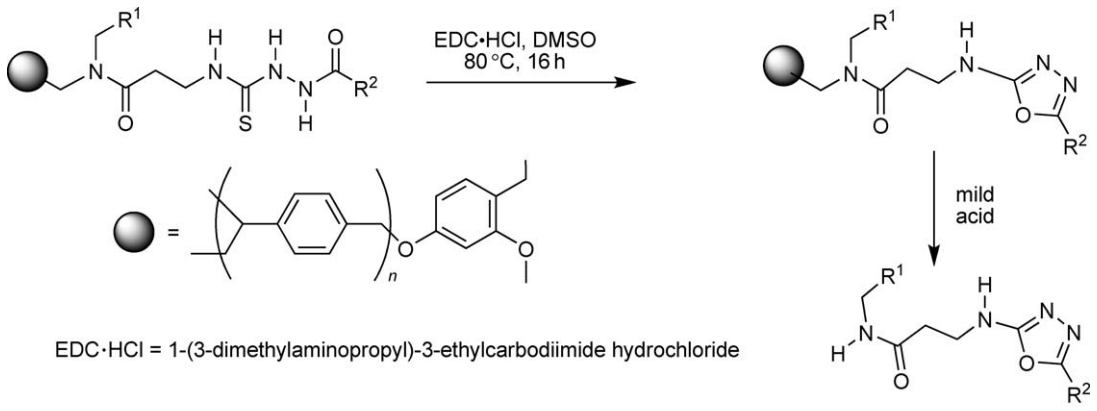
R^1 = 4-$MeOC_6H_4CH_2$, R^2 = Bn; R^1 = 4-$MeOC_6H_4CH_2$, R^2 = $(CH_2)_2CHCH_2$
R^1 = R^2 = Bn; R^1 = Bn, R^2 = $(CH_2)_2CHCH_2$; R^1 = $Ph(CH_2)_2$, R^2 = $(CH_2)_2CHCH_2$
R^1 = Ph, R^2 = Bn; R^1 = Ph, R^2 = $Ph(CH_2)_2$; R^1 = Ph, R^2 = Et
R^1 = Ph, R^2 = $(CH_2)_2CHCH_2$; R^1 = Me, R^2 = $Ph(CH_2)_2$; R^1 = Me, R^2 = $(CH_2)_2CHCH_2$

Scheme 30



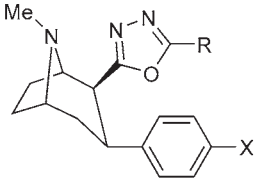
R = Bn, 2-ClC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 4-pyridyl, Ph

Scheme 31



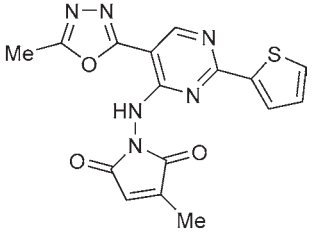
R^1	Ph	2-ClC_6H_4	Bn	CH_2=CH-	2-Thienyl	4-$NO_2C_6H_4$
R^2	4-Pyridyl	2-$MeOC_6H_4$	Ph		Isopropyl	

Scheme 32

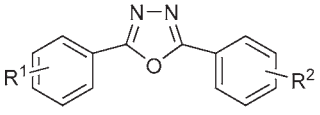


123

R = Ph; X = Cl
R = Ph; X = Me
R = Me; X = Me

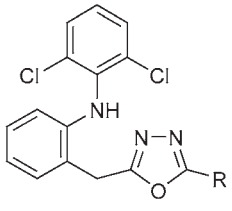


124



125

R^1, R^2 = several combinations of Cl_2, Cl_3, ClF, F, F_2, F_3, Br or MeO

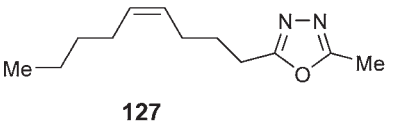


126

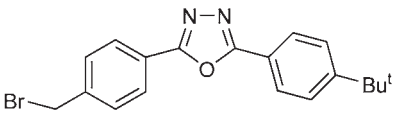
R = 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3OCH_2$, 4-$H_2NC_6H_4$

A one-pot synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from acids and acyl hydrazides has recently been reported. The method involves an activation of an acid with carbonyl diimidazole followed by the addition of benzoyl hydrazide and then the addition of CBr_4 and Ph_3P. Under the conditions, the dehydration proceeds smoothly to provide the desired oxadiazoles in high yields <2006TL4827>.

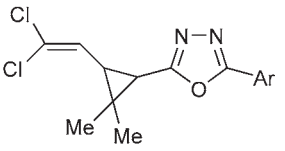
The reactions of hydrazides with acyl chlorides belong to the most popular routes for the preparation of oxadiazoles in recent years. Published examples of oxadiazole derivatives prepared by such reactions are shown in structures **127** <1997JE2755>, **128** <1999PCB10741>, **129** <2001JFA124>, **130** <2000MOL895>, **131** <2001PCB8845>, **132** <2004TL7157>, and **133** <2005BML1423>.



127

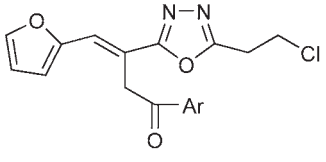


128



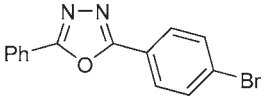
129

Ar = Ph, 4-ClC$_6$H$_4$, 2,4-Cl$_2$C$_6$H$_3$, 2-HSC$_6$H$_4$

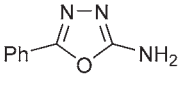


130

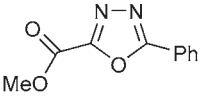
Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$



131

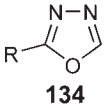


132



133

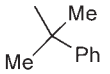
The reaction of hydrazides with trialkyl orthoesters allowed the synthesis of monosubstituted oxadiazoles **134** <2001JME1268>, **135** <2004BML2543>, and 2,5-disubstituted compounds **136** <2002EJP367> and **137** <2004SC2523>. The latter synthesis was performed without a solvent in the presence of microwave irradiation. Also, a variety of 2,5-disubstituted-1,3,4-oxadiazoles were synthesized by condensing monoarylhydrazides with acid chlorides in hexamethylphosphoramide (HMPA) solvent under microwave heating <2003SC2541>.



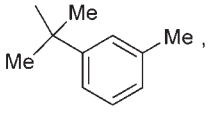
134

R = Me, Pr^i, pentyl, Bu^t, Ph, Bn, 4-MeOC$_6$H$_4$, 3-MeC$_6$H$_4$CH$_2$, 3-pyridyl,

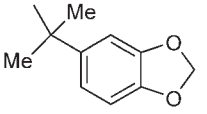
,

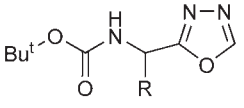


,



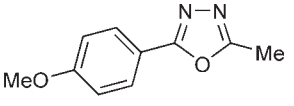
,



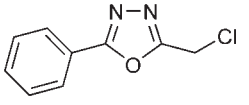


135

R = H, Me



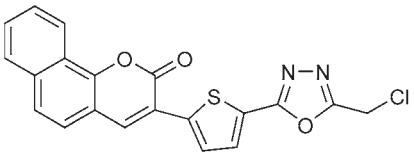
136



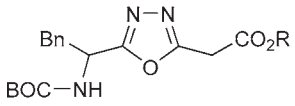
137

Derivatives **138** <2003PS1463>, **139** <1999JME4331>, and **140** <2004PS2059> were obtained in the reactions of hydrazides or semicarbazide with compounds containing the ester function, which remained only in compound **139**, because, in this case, ring formation was accomplished using the acyl group present in the starting ester.

Synthesis of two 5,6-dihydro-2-(1,3,4-oxadiazolyl)pyrazolo[1,5-*c*]quinazolin-5-ones from the corresponding hydrazides has been reported <1996JME2915>. Two-step iodobenzene diacetate-mediated solid-state synthesis of 2-(4-pyridyl)-5-aryl-1,3,4-oxadiazoles **141**, starting from hydrazides and aldehydes, has recently been reported <2004SC2153>. The preparation of a library of 2-aminosulfonamide-1,3,4-oxadiazoles through a three-component coupling of an acylhydrazine, an isocyanate, and sulfonyl chloride, and using polymer-supported reagents with microwave heating, has recently been reported <2005T5323>.

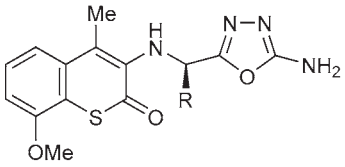


138



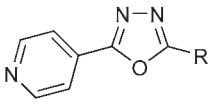
139

R = H, Me



140

R = H, Me, Bn, 4-$HOC_6H_4CH_2$



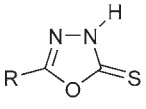
141

R = Ph, 2-ClC_6H_4, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 3-ClC_6H_4, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-HOC_6H_4, 3-MeO-4-HOC_6H_3, Ph–CH=CH

5.06.9.2.2 Ring synthesis from C–S and N–N–C–O components

Very important and popular routes to oxadiazolinethiones involve the reaction of hydrazides ($RCONHNH_2$) with carbon disulfide or with other C–S bond-containing components. A great number of oxadiazole derivatives prepared by this route have been reported in CHEC-II(1996) <1996CHEC-II(4)268>. Several monocyclic mesoionic 1,3,4-oxadiazolium-2-thiolates have been prepared and used in novel synthetic routes to a variety of other heterocycles <1976AHC(19)47, 1982T2965>; mesoionic derivatives containing fused rings have also been reported <1997H(45)2101>.

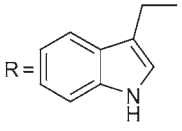
Also, in the last decade, many 5-substituted oxadiazolinethiones **142** have been prepared by the reaction between hydrazides and carbon disulfide, usually in the presence of potassium hydroxide followed by acidification of the post-reaction mixtures. The structures of the following obtained compounds are shown: **142a** <1996BML2693>, **142b** <1996EJM629>, **142c** <1997CAR123>, **142d** <2001RJC1754>, **142e** <2002M255>, **142f** <2002PS2745>, **142g** <2004BML6057>, **142h** <2004EJM535>, **142i** <1999MI63>, **142j** <1999MI161>, **142k** <2000JFA5312>, **142l** <2000MI351>, **142m** <2000MOL1429>, **142n** <2001MI913>, **142o** <2002MI1057>, **142p** <2003MOL744>, **142r** <2004MI1325>, **142s** <2004MI1343>, **142t** <2004MI335> and **142u** <2004PS1983>.



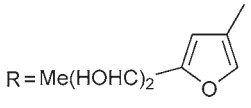
142

R = Me, Et, Pr^i, Bu^n, *n*-pentyl, Ph, 3-FC_6H_4, 4-FC_6H_4, 3-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 2-HOC_6H_4, 2-thienyl, 2-(1′-Me-pyrrolyl)

142a



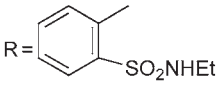
142b



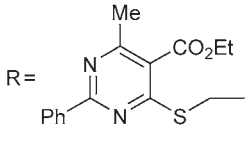
142c

R = Bn, 4-$MeOC_6H_4CH_2$, 4-$EtC_6H_4CH_2$, 2,4-$Cl_2C_6H_3CH_2$, 4-$BrC_6H_4CH_2$, 4-$MeOC_6H_4OCH_2$, 5-Ph-2*H*-1,2,3,4-tetrazolyl

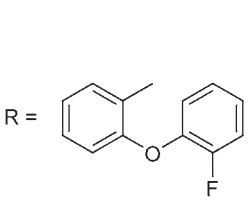
142d



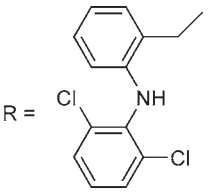
142e



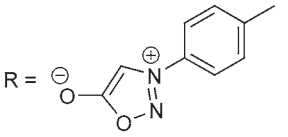
142f



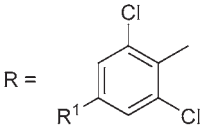
142g



142h

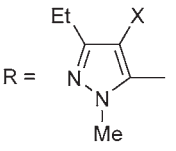


142i



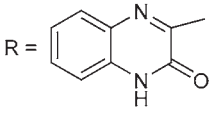
R^1 = H, Cl, F_3C, Bu^t

142j

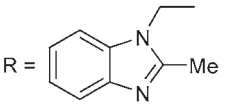


X = H, Cl

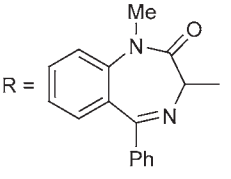
142k



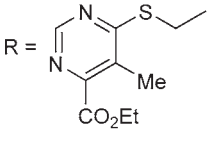
142l



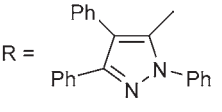
142m



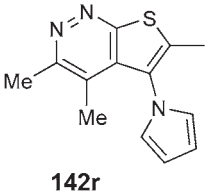
142n



142o



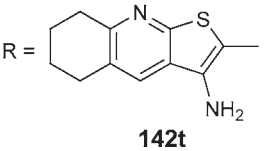
142p



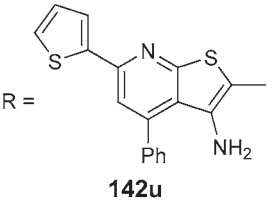
142r

R = Ph, 4-BrC_6H_4, 4-ClC_6H_4

142s

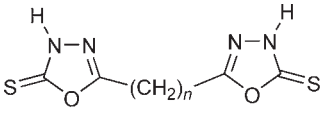


142t



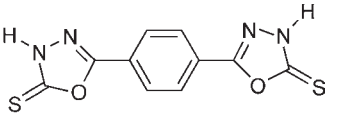
142u

Besides oxadiazolinethiones **142**, compounds **143a** and **143b** containing two oxadiazole rings were also synthesized <1998JFA1609>.



143a

n = 2, 4

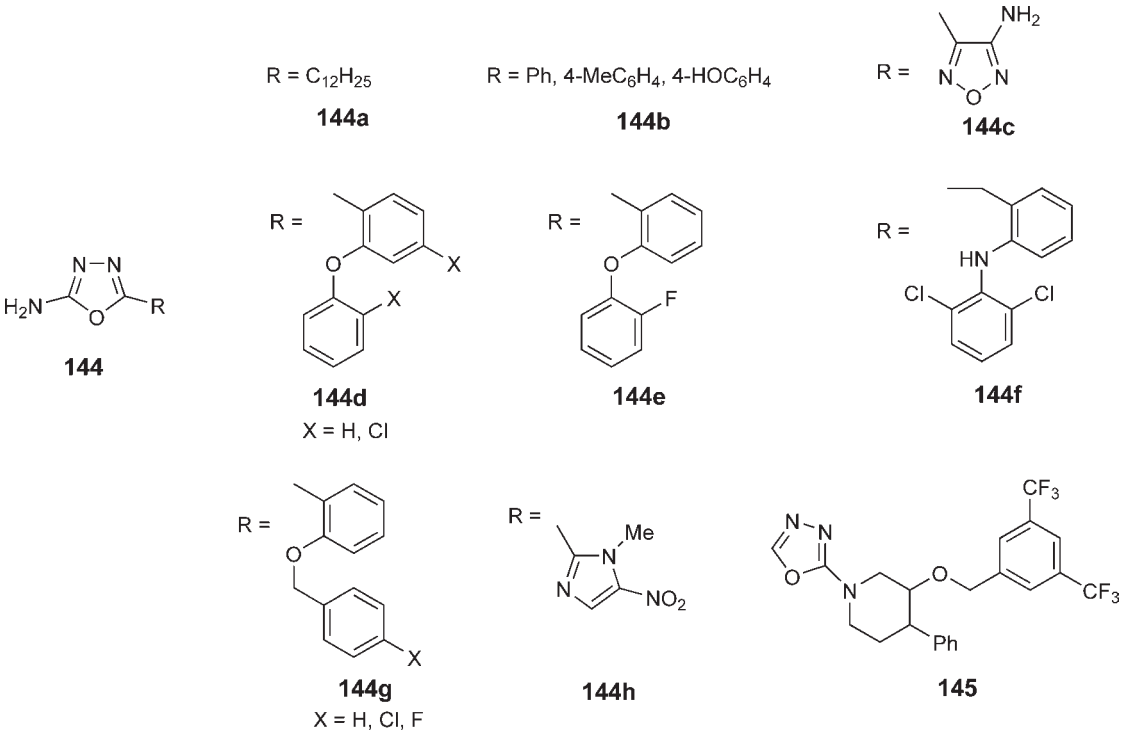


143b

5.06.9.2.3 Ring synthesis from C–N and N–N–C–O components

The well-known reaction of hydrazides with cyanogen bromide, usually performed in the presence of potassium or sodium bicarbonate, affords 2-amino-5-substituted-1,3,4-oxadiazoles. In the past 10 years, this reaction has been applied several times, mainly in order to obtain biologically active derivatives.

The structures of aminooxadiazoles **144a–g** (**144a** <1996JME4382>, **144b** <1998CEJ2467>, **144c** <2002RJO1351>, **144d** <2003BML769>, **144e** <2004BML6057>, **144f** <2004EJM535>, **144g** <2005BML1863>), prepared from hydrazides and BrCN, are shown. A synthesis of oxaminooxadiazole **144h** <2003JME427> started from semicarbazide and 1-methyl-5-nitroimidazol-2-yl-carbonitrile and was performed in trifluoroacetic acid. Compound **145** <1996JME2907> was obtained by refluxing the appropriate hydrazide with KOCN and concentrated HCl followed by treatment with $SOCl_2$ and Et_3N in toluene.



The efficient synthesis of 2-phenyl-1,3,4-oxadiazole and 2-(4-pyridyl)-1,3,4-oxadiazole as pure compounds in 95–98% yields from the respective *N*-aroylhydrazines and using a bentriazole-derived Vilsmeier reagent has been reported <2000JOC2246>.

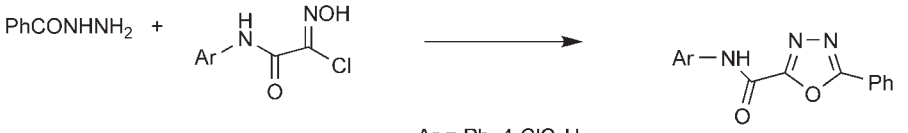
5.06.9.2.4 Ring synthesis from other components

2,5-Bis(5-aryl-1,3,4-oxadiazol-2-yl)furans were synthesized via the reaction of trichloromethylarenes with furan-2,5-dicarboxylic acid dihydrazide in boiling pyridine–methanol mixture <1999CHE871>. *N*-Arylcarbamoylformhydroxymoyl chlorides were synthesized and their reactivity toward phenylhydrazide was examined affording 2-(*N*-aryl)carbamoyl-5-phenyl-1,3,4-oxadiazoles <2002RCB1504>. Synthesis of 3-(1,3,4-oxadiazol-2-yl)coumarins based on the recyclization of 2-(*N*-aroylhydrazono)coumarin-3-carboxamides, readily obtained by the reaction of 2-iminocoumarin-3-carboxamides with arenecarboxylic hydrazides in an acidic medium, was described (**Scheme 33**) <1999CHE167>.

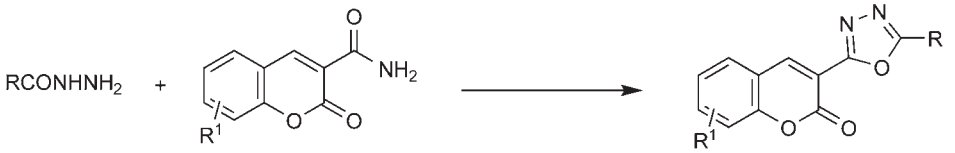
Hydrazones of aromatic and conjugated unsaturated aldehydes were transformed into oxadiazole derivatives under phase-transfer catalysis (PTC) conditions without any formal oxidant <1998TL6885>. 2-Aroylamino-3,3-dichloroacetonitriles treated with hydrazine were converted into 2-aryl-4-cyano-5-hydrazinooxazoles, which upon heating in acetic acid and water easily hydrolyzed into oxadiazole derivatives <2001RJC280>. Thermolysis at 70–80 °C for 24 h of zeolite samples incorporated with $PhClCN_2$ under dry nitrogen conditions led to the formation of benzaldehyde and 2,5-diphenyl-1,3,4-oxadiazole (58%) as the major products <2004OL881>. A number of symmetrical 2,5-diaryl-1,3,4-oxadiazoles were prepared by the reaction of aromatic acids with hydrazine dihydrochloride in a mixture of phosphoric acid and phosphorus pentoxide under microwave irradiation (**Scheme 34**) <2001SC935>.

2,5-Dihydro-2(1,3-dimethyluracil-5-yl)-1,3,4-oxadiazole was obtained in 53% yield by the [3+2] cycloaddition of diazomethane to the formyl group of 1,3-dimethyl-5-formyluracil <1997T7045>. The reaction of 1-acetyl-2-benzylhydrazine with methyl glyoxalate in toluene afforded an oxadiazolidine derivative <1996TL4323>.

Ar = Ph, 4-ClC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$, 2,4,6-Me$_3$C$_6$H$_2$

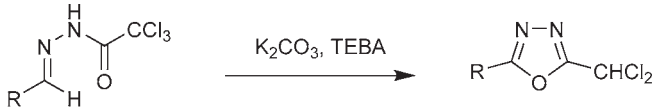


Ar = Ph, 4-ClC$_6$H$_4$

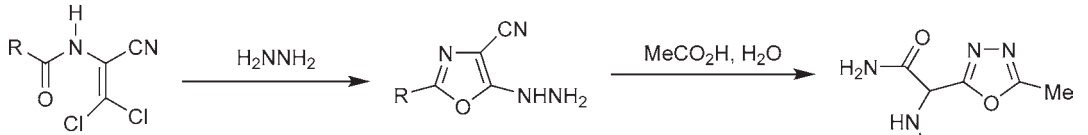


R^1 = H, R = Ph; R^1 = H, R = 4-FC$_6$H$_4$; R^1 = 6-*n*-C$_6$H$_{13}$, 7-OH; R = Ph; R^1 = 7-NEt$_2$, R = Ph
R^1 = 7-NEt$_2$, R = 4-MeC$_6$H$_4$; R^1 = 7-NEt$_2$, R = 2-ClC$_6$H$_4$
R^1 = 7-NEt$_2$, R = 4-Py; R^1 = 5,6-benzo, R = Ph; R^1 = 5,6-benzo, R = 4-MeOC$_6$H$_4$

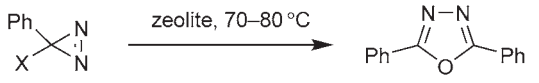
Scheme 33



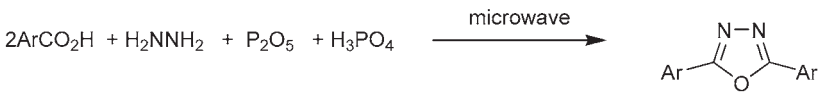
TEBA = triethylbenzylammonium bromide
R = Ph, 4-MeOC$_6$H$_4$, 2-thienyl, PhCH=CH,



R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$



X = Br, Cl



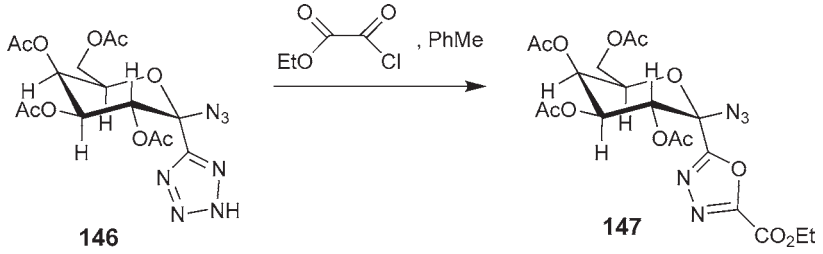
Ar = Ph, 3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-pyridyl, 4-pyridyl, 2-HOC$_6$H$_4$,
4-HOC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-ClC$_6$H$_4$, 4-ClC$_6$H$_4$

Scheme 34

5.06.10 Ring Synthesis by Transformation of Another Ring

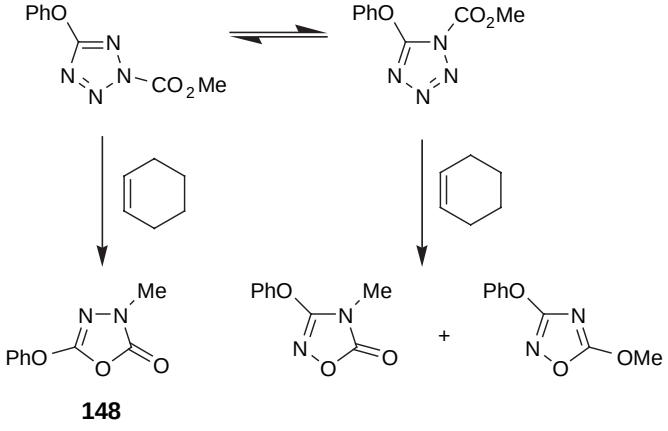
Two variations of the transformation of 3-acyltetrazoles into oxadiazoles are useful from a synthetic point of view. The first transformation involves the reaction of tetrazole with diketene. In the second, the sodium salt of the tetrazole is treated with oxalyl chloride. UV irradiation of some 3-amino-1,2,4-oxadiazoles leads to the formation of the corresponding 2-amino-1,3,4-oxadiazoles <1996CHEC-II(4)268>.

The transformation of 2-acetyl-5-substituted-tetrazoles into the corresponding 1,3,4-oxadiazoles was studied using semi-empirical and *ab initio* methods. Two mechanisms were proposed. The HF/STO-3G and HF/3-21G *ab initio* methods agree with a mechanism where two bonds (C–N and N–N) break almost simultaneously <1994JMT241>. Fatty tetrazoles containing long alkyl N-substituents were converted into the respective fatty 1,3,4-oxadiazoles by heating in acetic anhydride. Three bis(oxadiazoles) were also obtained by the same method <2003EJO885>. The transformation of tetra-(O-acetylated) derivative of galactopyranosyltetrazole **146** by ethyl oxalyl chloride in toluene gave the corresponding oxadiazole **147** (Equation 13); the yield was not reported <1996T9121>. Sugar derivatives of oxadiazoles have also been obtained in high yields by the reaction of tetrazoles and acetic anhydride in pyridine at 110 °C <2003MI433>.



(13)

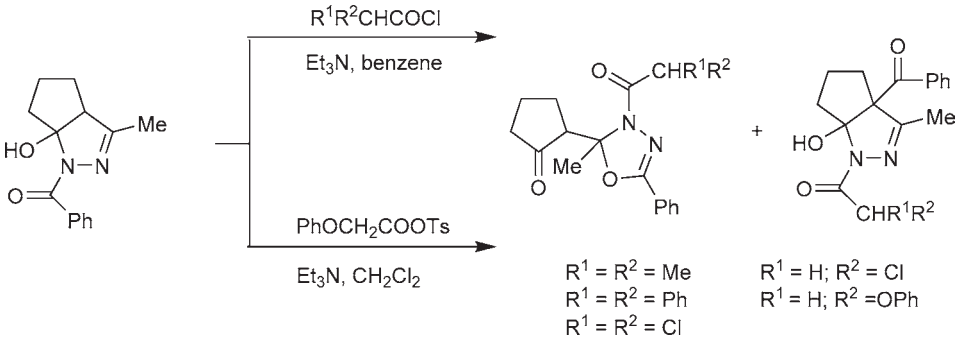
The thermal decomposition of *N*-methoxycarbonyl-*C*-phenoxy-tetrazoles in the presence of cyclohexene produced a mixture of 5-phenoxy-3-methyl-1,3,4-oxadiazol-2-one **148** (39%) and derivatives of 1,2,4-oxadiazol-5-one (69%) (**Scheme 35**) <2000JOC7284>.



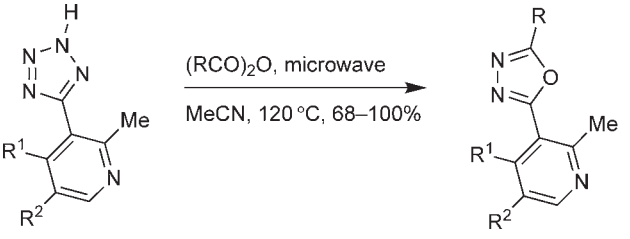
Scheme 35

1-Benzoyl-5-hydroxypyrazoline treated with ketenes, prepared *in situ* either from acyl chloride or mixed phenoxy-acetic and *p*-toluenesulfonic acid anhydride, afforded the corresponding 1,3,4-oxadiazole and eventually pyrazole derivatives (**Scheme 36**). The proposed reaction mechanism was supported by AM1 calculations <2003T4591>. Treatment of olefinic tetrazoles with anhydrides of carboxylic acids provides easy access to vinyloxadiazoles <2002ASC421>.

Several 3-(5-tetrazolyl)pyridines containing bulky groups on pyridine ring were acylated in acetonitrile at elevated temperature and under microwave irradiation to afford various 3-(1,3,4-oxadiazol-2-yl)pyridines in good yields (Equation 14) <2006T1849>.



Scheme 36

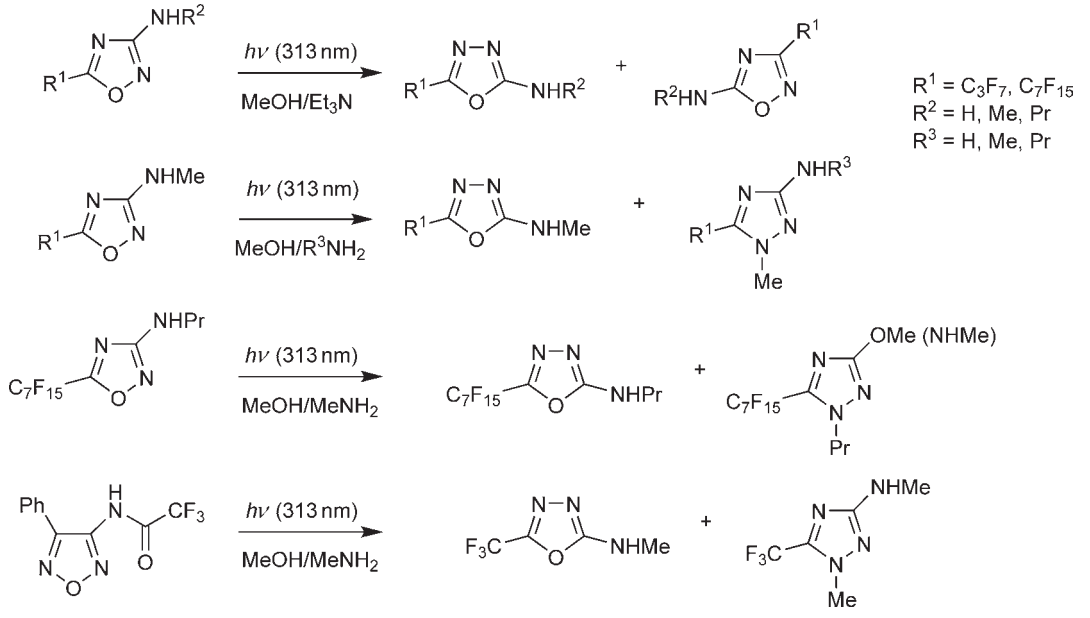


R	R^1	R^2
Me	Ph	H
CF_3	Ph	H
Bu^t	*o*-C_6H_4-$(CH_2)_2$-	
Pr^i	-$(CH_2)_3$-	
4-ClC_6H_4	-$(CH_2)_3$-	

(14)

Electroluminescent phenantroline dyes containing triphenylamine and 1,3,4-oxadiazole fragments were prepared using tetrazole–oxadiazole interconversion performed in the presence of aroyl chlorides <2004TL6361>. Also, *N*-tributylstannyltetrazoles treated with acetic anhydride gave oxadiazole derivatives <2002RCB357>.

The photochemistry of 3-amino- <2002JOC6253> and some 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles <2004JOC4108> was investigated. The latter reaction led to 5-perfluoroalkyl-1,3,4-oxadiazoles followed eventually by their conversion into 5-perfluoroalkyl-1,2,4-triazoles. 1,3,4-Oxadiazoles were also obtained by photochemical interconversion of 3-acylamino-1,2,5-oxadiazole derivatives. Mechanisms of these reactions were proposed <2004JOC4108>. Examples of these interconversions are shown in **Scheme 37**.



Scheme 37

Sauer *et al.* have prepared oligoheterocycles containing 1,3,4-oxadiazole units in sequences <2001EJO697>, 3,4-diazanorcaradienes <2001EJO2629>, homotropilidenes <2001EJO2639>, 1,3,6-cyclooctatrienes <2001EJO3999>, and semibullvalenes <2002EJO791>, all of them with 1,3,4-oxadiazole substituents by the photolysis or thermolysis of the respective tetracyclic azo compounds. 1,2-Bis(1,3,4-oxadiazolyl)ethenes with extended conjugated systems were prepared via Huisgen reaction of stilbenyltetrazoles <2002JPO638>.

5.06.11 Comparison of Various Routes of Ring Synthesis

No significant new general routes to 1,3,4-oxadiazoles have been reported since the mid-1980s. The major routes, as emphasized in CHEC(1984), CHEC-II(1996), and Sections 5.06.9 and 5.06.10, are still: (1) the formation of oxadiazoles by cyclodehydration of diacylhydrazines ($R^1CONHNHCOR^2$); (2) by oxidation of acylhydrazones ($R^1CH{=}NNHCOR^2$); and (3) the formation of oxadiazolinones, oxadiazolinethiones, and aminooxadiazoles by the reactions of hydrazides ($RCONHNH_2$) with phosgene, carbon disulfide, or cyanogen bromide, respectively. In some particular cases, transformations of 3-acyltetrazole into oxadiazole derivatives were performed under microwave irradiation and found to be synthetically useful.

Cyclization of diacylhydrazines with the agents $POCl_3$, $SOCl_2$, PPA, H_2SO_4, PCl_5, $ZrCl_4$, or trifluoroborane–ethyl ether system served as the most convenient method of 2,5-dialkyl and, particularly, 2,5-diaryl derivatives' synthesis. Oxidative cyclization of acylhydrazones ($R^1CH{=}NNHCOR^2$) by LTA, acylsemicarbazides ($RCONHNHCONH_2$) by Br_2, and oxidative cyclization of acylthiosemicarbazides ($RCONHNHCSNH_2$) by HgO afforded particularly high yields of dihydrooxadiazoles and aminooxadiazoles, respectively. Trichloroacetylhydrazones of aromatic and conjugated unsaturated aldehydes were also successfully transformed without any formal oxidant under phase-transfer conditions into dichloromethyloxadiazole derivatives. The reaction of hydrazides ($RCONHNH_2$) with carbon disulfide seems to be the method of choice for the synthesis of oxadiazolinethiones. Cyclization of $R^1CONHNHCS_2R^2$ under microwave irradiation can serve as an alternative method. Also, some other newer reports point out the usefulness of the reactions performed under microwave iradiation, which shortened the times of the reactions and allowed them to be carried out under solvent-free conditions. Important improvements of all the above methods can be achieved by carrying the reactions on solid supports.

1,3-Dipolar cycloaddition of diazomethane to aldehydes can successfully be used for the preparation of tetrahydrooxadiazole derivatives. Photochemical interconversion of 3-acylamino-1,2,5-oxadiazole derivatives leads to 1,3,4-oxadiazoles, though the method suffers from lack of selectivity. Many reports concentrate only on the synthesis and applications of new 1,3,4-oxadiazoles substituted with a wide variety of groups without introducing much of new chemistry.

5.06.12 Applications

Synthesis and the biological evaluation of 2-benzenesulfonylalkyl-5-substituted-sulfanyl-[1,3,4]-oxadiazoles as potential anti-hepatitis B virus agents were reported <2006MI7>. One-pot synthesis of aromatic poly(1,3,4-oxadiazole)s in ionic liquid solvents was described <2006PSA380>. Formation of azobenzene–oxadiazole copolymers with large angular multiplicity by means of photoinduced reorientation has recently been reported <2007L320, 2007L332>. Photomechanics of liquid-crystalline elastomers containing oxadiazole moieties in the side was investigated <2007AGE506>. In 2006–07, a number of new low molecular mass compounds and polymeric materials have been synthesized and analyzed for applications in the field of organic light-emitting devices. More interesting examples of monomers and polymers containing oxadiazole ring either in a chain or as the side substituents are given in this section. Efficient single-layer electroluminescent device based on a bipolar emitting boron-containing material was described <2006CC281>. Blue-light-emitting diodes based on fluorene derivative polymers containing oxadiazole rings have been constructed <2006MI137>. The synthesis, photoluminescent, and electrochromic properties of new thermally stable and organosoluble poly(amine-1,3,4-oxadiazole)s as a new type of hole-transporting and electrochromic materials were reported <2006MI2283, 2006MM6036>. Polymers with an aromatic oxadiazole moiety in the side chain were characterized by low band gap <2006SM135>.

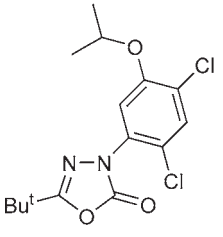
Enhanced photovoltaic cell efficiency was achieved via incorporation of highly electron-deficient oxadiazole moieties on side chains of poly(phenylene vinylene)s and poly(fluorene)s <2006SM949>. The synthesis of terminal

ethynyl and butandiynyl oxadiazole derivatives was developed using palladium cross-coupling reactions. It was found that intramolecular energy transfer through the butadiynylene bridge was less efficient than through the ethynylene bridge <2006JA3789>. Tunable behavior of p–n copolymers based on oligothiophenes and 1,4-bis(oxadiazolyl)benzene was theoretically studied. The study showed that the backbone modification of the p–n copolymer, by changing the number of thiophene units in the p–n diblock copolymer, greatly modifies the optical properties of the polymer <2006PCB23750>. Degradation of oxadiazole-based blue organic light-emitting diodes was monitored and a possible reason for the fast light intensity decrease during the device heating periods was disclosed <2006MI1695>. The third-order nonlinear optical properties of a newly synthesized soluble copolymer containing oxadiazole and thiophene units, a potential material for optical applications, using Z-scan and degenerate four-wave mixing techniques were described <2007MI236>. New electroluminescent molecules containing carbazole and oxadiazole units were synthesized and characterized <2006SM13>. Also, studies on two-dimensional metal coordination polymers containing oxadiazole moiety were in progress. Spectroscopic, thermal, fluorescence, and structural studies of mercury coordination polymer containing 2,5-bis(4-pyridyl)-1,3,4-oxadiazole ligand were reported <2007ICC166>. A neutral nickel coordination polymer with an unsymmetrical 5-(4-pyridyl)-1,3,4-oxadiazole-2-thione was investigated <2007ICC53>. Thermodynamic properties of 2,5-bis(4-methoxyphenyl)-1,3,4-oxadiazole as a corrosion inhibitor for mild steel in normal sulfuric acid medium were reported <2006MI2831>. There is a burgeoning interest in the design of molecular probes, which can selectively respond to traces of ions under various conditions. Photoemittive 2,5-diaryl-1,3,4-oxadiazoles find widespread applications as electronic and photonic materials; however, applications as the signaling component in molecular sensory systems have only recently been described. 2,5-Bis(pentafluorophenyl)-1,3,4-oxadiazole has been prepared and successfully polymerized with hexafluorobisphenol to produce highly fluorinated poly(aryleneether-1,3,4-oxadiazole)s. The monomer and polymers were found to be capable of selectively binding fluoride anion with high affinity <2006MM6054>. Molecular probes incorporating *N*-phenylaza-15-crown-5 and aryl/heteroaryl oxadiazole have recently been designed to function as the new Ca^{2+}-sensitive probes <2007T1680>. Also, oxadiazoles containing efficient plastic scintillators utilizing phosphorescent dopants have recently been prepared <2007MI012117>.

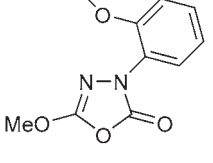
5.06.12.1 Biologically Active 1,3,4-Oxadiazole Derivatives

Bactericidal and fungicidal activity have already been reported for several oxadiazoles, aminooxadiazoles, and oxadiazolinethiones. Anti-inflammatory, sedative, and analgesic properties have been reported for diaryloxadiazoles. Some aminooxadiazoles have shown analgesic and nervous system depressant activity, anti-inflammatory, antiproteolytic, anesthetic, and anticonvulsant properties. Many oxadiazolinones have shown herbicidal or insecticidal activity, and one of them has been found to be an orally active antiallergic agent <1996CHEC-II(4)268>.

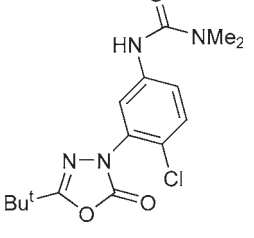
Some 1,3,4-oxadiazolinone herbicides, such as oxadiazon **149a**, methoxydiazone **149b**, and dimefuron **149c**, have already been introduced on the market. A recent field experiment conducted with oxadiazon has shown a great effect of the herbicide on the growth of phosphate-solubilizing microorganisms <2003MI217>.



149a



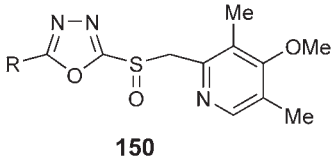
149b



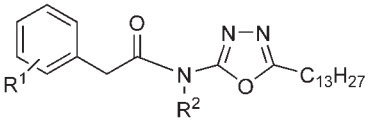
149c

A number of other derivatives were tested in order to evaluate their biological activity. The spectrum of the activity is very broad. Oxadiazole derivatives were active inhibitors of several enzymes: **150** <1996BML2693>, **150a**

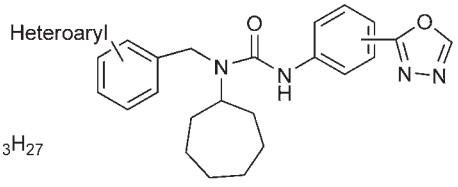
<1996JME3908, 1996JME4382>, **150b** <1998JME2390>, **150c** <1998JME3923>, **150d** <1999BML2199, 2000BMC1713, 1999JME1161>, **150e** <2000BML1645>, **150f** <2000JME1670>, **150g** <2000JME4927, 2001JME1268>, **150h** <2001BMC1307>, **150i** <2002BML1525>, **150j** <2002BML2197>, **150k** <2003HCA2192>, **150l** <2004BBR1053>, **150m** <2002BML2573>, **150n** <2004BML1441>, **150o** <2004BML2543>, **150p** <2004BML6017>, **150r** <2004JME1605>, **150q** <2005JME3991>. Also, HIV-1 protease inhibitors bearing 1,3,4-oxadiazoles were prepared <2004BML4651>.



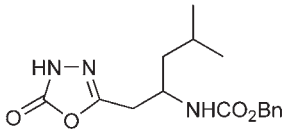
150
R = alkyl, aryl



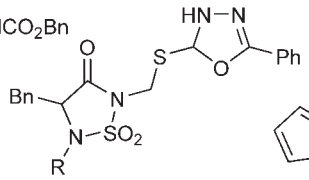
150a



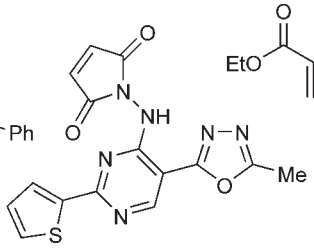
150b



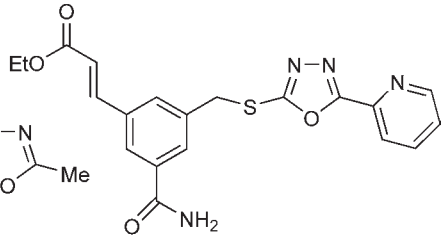
150c



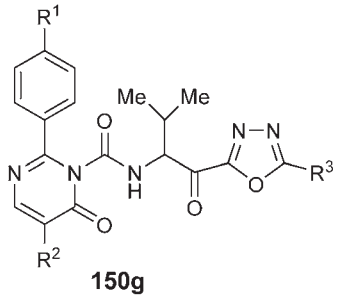
150d



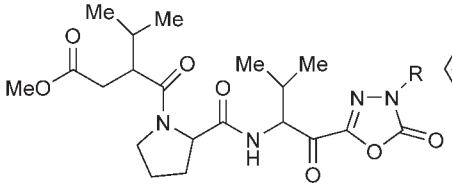
150e



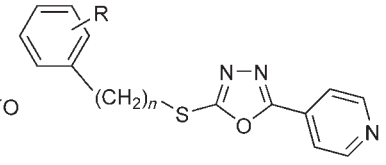
150f



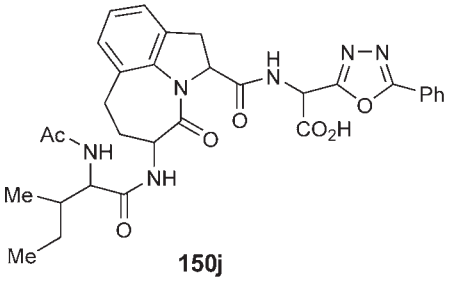
150g



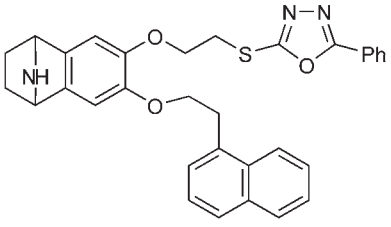
150h



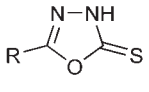
150i



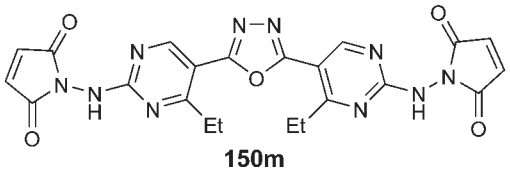
150j



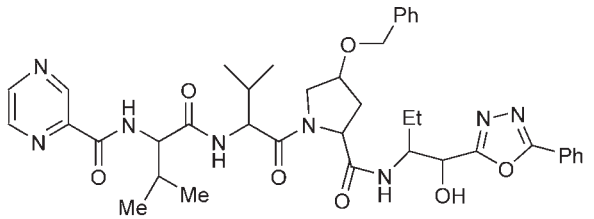
150k



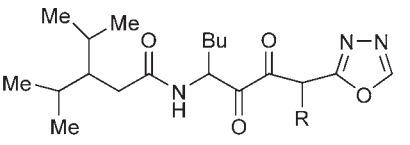
150l
R = Bn, pyridyl, XC_6H_4, others



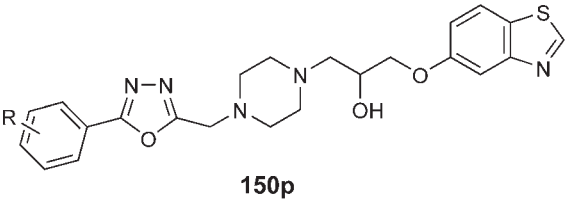
150m



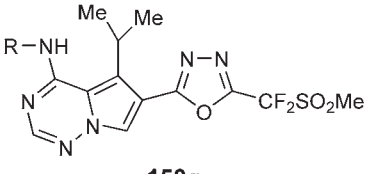
150n



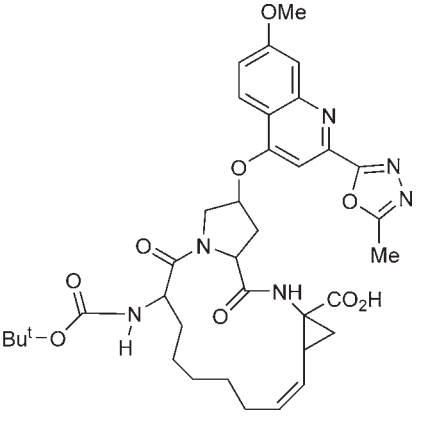
150o



150p

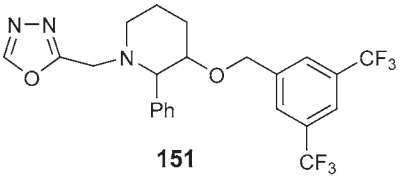


150q

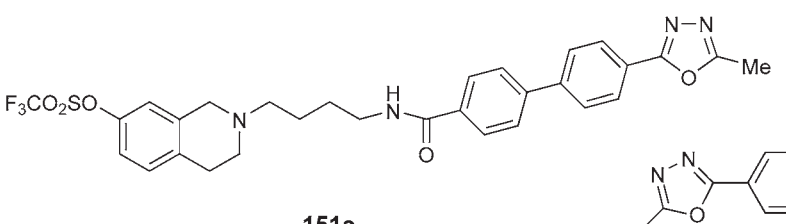


150r

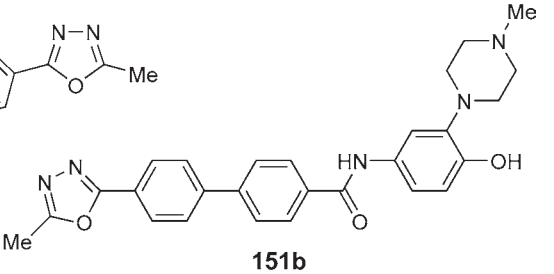
Oxadiazole derivatives were also often evaluated as receptor antagonists: **151** <1996JME2907>, **151a** <1999BML179>, **151b** and **151c** <2000JME517>, **151d** <2001BML1445>, **151e** <2002BML517>, **151f** <2003JST361>.



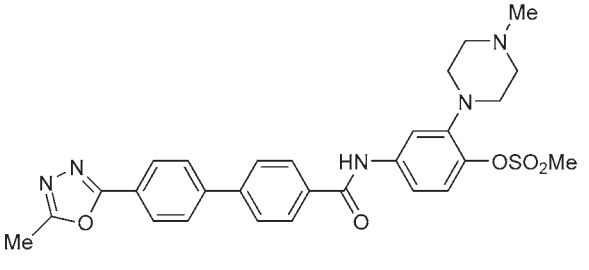
151



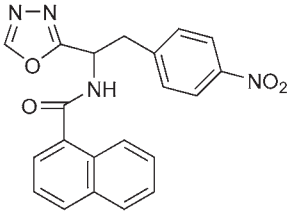
151a



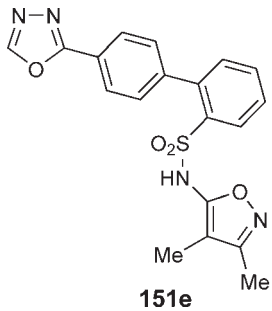
151b



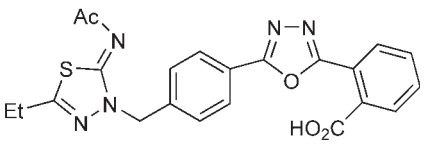
151c



151d

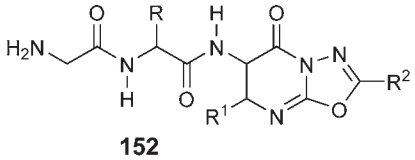


151e



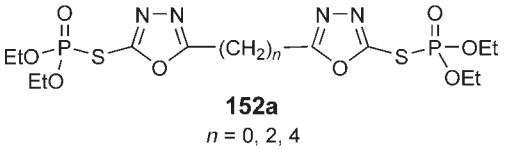
151f

A number of new oxadiazole derivatives exhibited antifungal activity, for example, **152** <1996JFA1565> and **152a** <1998JFA1609>, **152b** <1998JME1855>, **152c** <2000JFA5312>, **152d** <2000JFA5465>, **152e** <2002JFA3757>.



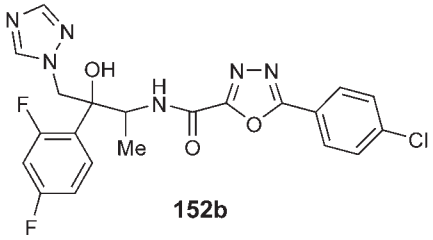
152

R^1, R^2 = alkyl
R = H, Ph

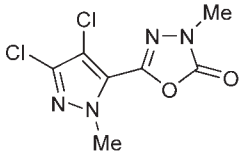


152a

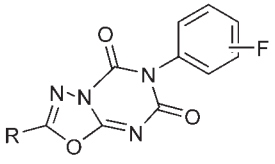
n = 0, 2, 4



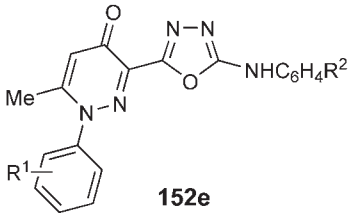
152b



152c



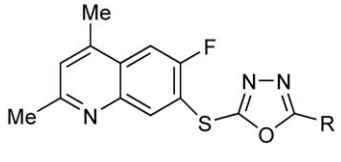
152d



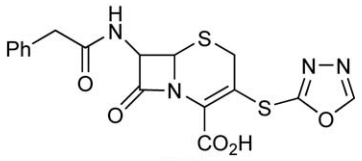
152e

Also, antibacterial activity was shown often by 2,5-disubstituted oxadiazoles <1998IJB180>.The structures of some active compounds are shown: **153** <1998M961>, **153a** <2000BMC69>, **153b** <2000BMC2317>, **153c** <2000EJM267>, **153d** <2001BMC465>, **153e** <2002CHE810>, **153f** <2002MI55>, **153g** <2004MI147>.

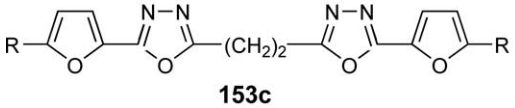
153



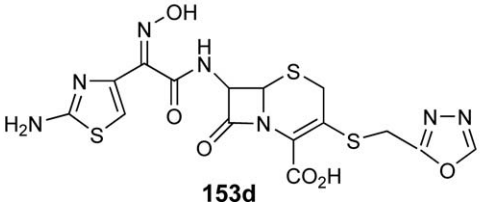
153a



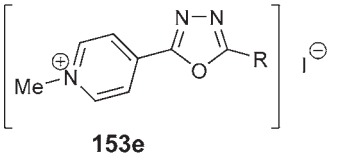
153b



153c

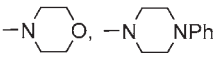


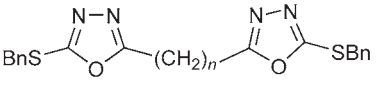
153d



153e

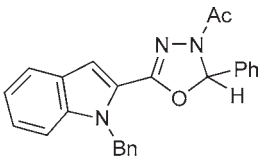
R = $NH(CH_2)_2Me$,





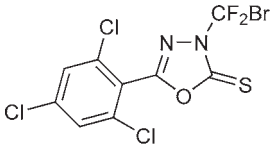
153f

n = 3, 4, 8

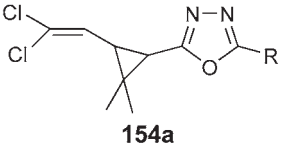


153g

Antimicrobial activity of several 5-aryl-2-[(*N*,*N*-disubstituted-thiocarbamoylthio)acylamino]-1,3,4-oxadiazoles has been reported <1998FA541>. Some oxadiazoles were active as insecticides, for example: **154** <1999MI161>, **154a** <2000JFC173, 2001JFA124>, **154b** <2003JFC163>, **154c** <2003JME427>, **154d** <2003JFA152>.

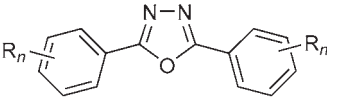


154



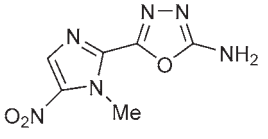
154a

R = 2,4-dichloro-5-fluorophenyl

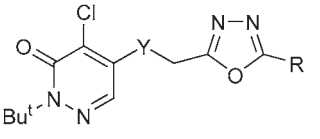


154b

R_n = alkyl



154c

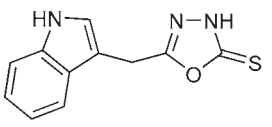


154d

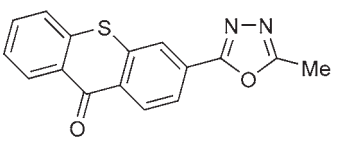
R=phenyl and its several
halo or dihalo derivatives

1*H*-1,2,4-Triazole derivatives containing a 1,3,4-oxadiazole nucleus were synthesized and biological activity of representative compounds was evaluated <1999MI229>. A series of 2-[[α-(4-substitutedbenzoyloxy)-α-phenylacetyl or methylacetyl]amino]-5-(4-methoxyphenyl)-1,3,4-oxadiazoles were obtained, and the antibacterial or antifungal activities of the compounds were tested using disk diffusion method. Some of the compounds were found to be active against *Staphylococcus aureus* ATCC 6538 and against *S. epidermidis* ATCC <2001FA975>.

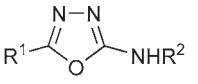
Other potential applications of oxadiazoles involve: antidepressant drugs **155** <1996EJM629>, **155a** <1996JME1857>, anti-inflammatory agents <2004EJM535>, for example, **156** <2005AP373>, anticonvulsants **157** <2004BML6057>, antimiotic agents **158** <2001JME4416>, peptide mimetics **159** <1999JME4331>, and antitumor or antiviral drugs **160** <2003EJM959> and **160a** <2005MI89>.



155



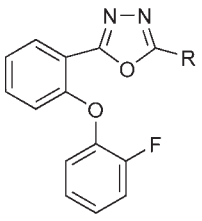
155a



156

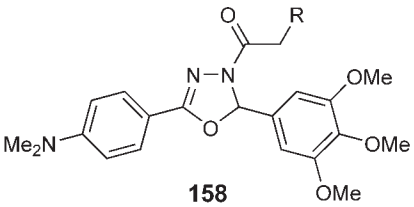
R^1 = 3-pyridyl, 4-pyridyl, 7-quinolinyl

R^2 = Et, cyclohexyl, phenyl, 4-MeC_6H_4



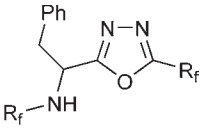
157

R = NH_2, SH, SMe



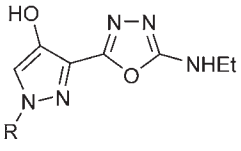
158

R = C_nH_{2n+1}



159

R_f = C_nF_{2n+1}



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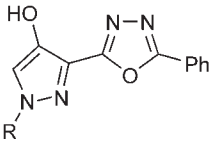


160a

Anti-inflammatory activity of 16 2-aryl-5-alkyl(or aryl)amino-1,3,4-oxadiazoles <1996EJM819, 2002FA101> and antimicrobial properties of six 5-(1- or 2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-thiones, 2-amino-5-(1- or 2-naphthyloxymethyl)-1,3,4-oxadiazoles, and 5-(1- or 2-naphthyloxymethyl)-1,3,4-oxadiazole-2(3*H*)-one derivatives were investigated and reported <2002FA539>. Growth hormone secretagogues containing an oxadiazole unit were synthesized by the transformation of respective tetrazole derivatives <1997BML1293, 1997BML2951>.

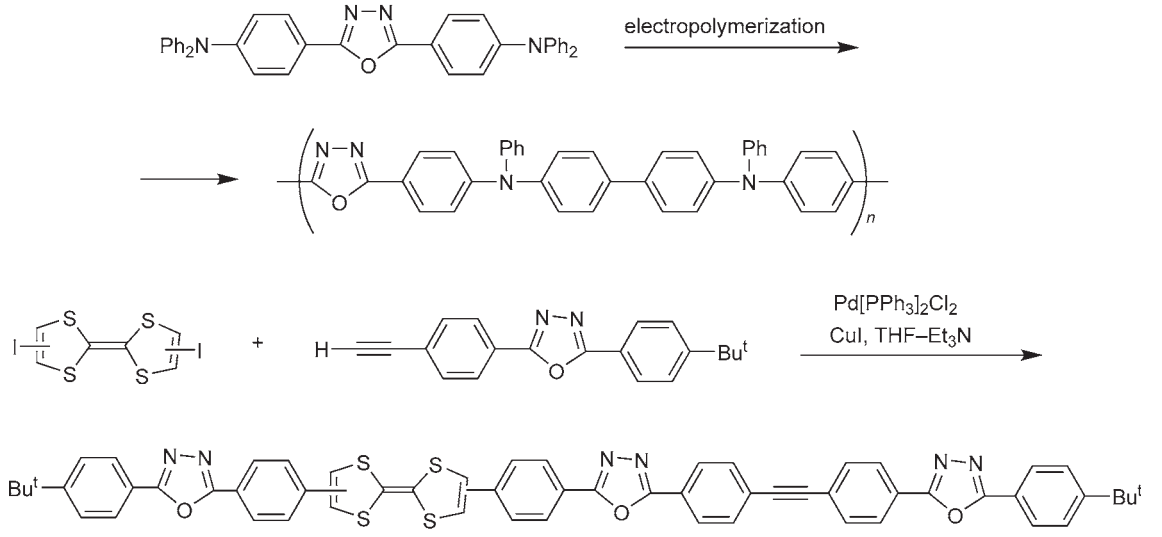
5.06.12.2 Polymers Containing 1,3,4-Oxadiazole Ring

The synthesis and properties of heat-resistant polyazomethines containing 2,5-disubstituted oxadiazole fragments, being insulators convertible into semiconductors by doping with iodine, have been described. The radical copolymerization of alkenes with the fluorescent co-monomer 2-*t*-butyl-5-(4′-vinyl-4-biphenylyl)-l,3,4-oxadiazole has resulted in useful macromolecular scintillators. Anionic polymerization of 2-phenyl-l,3,4-oxadiazolin-5-one has produced a nylon-type product <1996CHEC-II(4)268>.

A comparative study of the thermal properties of related aromatic polyhydrazides and poly(1,3,4-oxadiazole)s was published <1996MI879>. A synthesis of heat-resistant poly(1,3,4-oxadiazole)s of high molecular weight by the direct polycondensation of dicarboxylic acids with hydrazine sulfate, using phosphorus pentoxide–methanesulfonic acid (PPMA), as both a condensing agent and a solvent, was developed. The thermogravimetry of the aromatic poly(1,3,4-oxadiazole)s showed 10% weight loss, both in the air and in nitrogen, at 440–490 °C <1998PSA159>. This method of synthesis was further developed into the one-pot preparation of aromatic poly(1,3,4-oxadiazole)s in ionic liquids using triphenyl phosphite, both as a solvent and condensing agent <2006PSA380>.

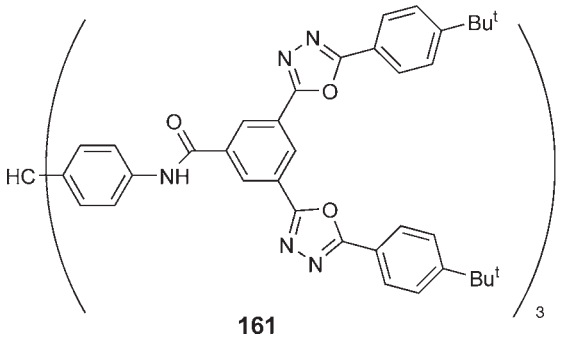
The cyclocondensation of dihydrazides with 4-fluorobenzoic acid and halo displacement polymerizations with bisphenol A led to the formation of poly(arylene ether)s containing 1,3,4-oxadiazole units exhibiting good thermal properties compared to those of other polymers reported in the literature <1999MI405>. Oxadiazole-containing polyethers were also synthesized from 2,5-bis(4-fluorophenyl)-1,3,4-oxadiazole and various aromatic diols <1997MI1799>. Several oxadiazole polymers were prepared and studied due to their electron-transporting ability and luminescent properties, for example: poly(1,3,4-oxadiazole-2,5-diyl-1,2-vinylene) obtained via anionic mechanism <2003MI246>, conjugated poly(*p*-phenylenevinylene) derivatives with 1,3,4-oxadiazoles in the backbone <2003MM9295>, copoly(aryl ether)s with bis(3-(trifluoromethyl)phenyl)-1,3,4-oxadiazole segments <2004PSA5900>, copolymer containing 1,3,4-oxadiazole and carbazole rings <2004JAP2777>, poly(methacrylate) containing 1,3,4-oxadiazole and stilbene units <2004MI1893>, thermally stable poly(amine-1,3,4-oxadiazole)s for luminescent and electrochromic materials <2005PSA3245>, substituted oligo(phenylenevinylene)s (some of them containing 1,3,4-oxadiazole units) <2000JPO587>, conjugated poly(*p*-phenylenevinylene) derivatives containing 1,3,4-oxadiazole and pyridine rings <2004PSA3212> or 2,2′-bipyridine units <2001CEJ4358> in the main chain,

polymeric alkoxy 2-(4-biphenylyl)-5-phenyl-1,3,4-oxadiazole for light-emitting diodes <2001MI47>, macrocyclic and acyclic bis(2,5-diphenyl-1,3,4-oxadiazole)s with electron-transporting and hole-blocking ability in organic electroluminescent devices <2005MI1576>, poly(fluorene)-based copolymers containing various 1,3,4-oxadiazole pendant groups <2005PSA2700>, poly(*p*-phenylenevinylene)-based copolymers containing oxadiazole pendant group for light-emitting diodes <2004JA2474>. Photo- and electroactive polymer materials containing oxadiazole and amine moieties in a side chain were synthesized and studied. One-layer-type electroluminescent devices were fabricated by using the polymers <2003MM3457>. The blue-light-emitting copolymer with triphenylamine and electron-transporting oxadiazole pendant groups at the C-9 position of fluorene was synthesized, and using this copolymer as the emitting material was reported <2003MM6698>. Conjugated donor–acceptor polymers were prepared through electropolymerization of monomers containing oxadiazole segments and diphenylamino terminal groups (**Scheme 38**) <2003OL839>. Statistical poly(methacrylate) copolymer bearing a blue-light-emitting chromophore, a UV-sensitive cross-linkable fragment, and a charge-transporting oxadiazole unit has been synthesized, and its application in light-emitting devices was discussed <1997SM437>. Blue-light-emitting polymers with oxadiazole units prepared earlier were reviewed <2000MI1089>. Block copolymers functionalized with aromatic 1,3,4-oxadiazole and stilbene derivatives have been synthesized by the palladium-catalyzed reaction between polystyrene-*block*-polyisoprene and other functional units. These polymers exhibited emission properties <2002MM850>.

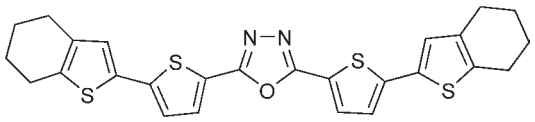


Scheme 38

Electrochromism was demonstrated by electrochemically reversible macromonomers, which were synthesized by Pd-catalyzed cross-coupling of iodo derivatives of tetrathiafulvalene with 2,5-diaryl-1,3,4-oxadiazole derivatives containing terminal ethyne or butadiyne groups (an example is given in **Scheme 38**) <2004CC578>. Organosoluble rigid-rod poly(1,3,4-oxadiazole)s were prepared and studied in the solid state <2002MI427, 2002MI433>. Poly(aramide) dendrimers **161**, possessing electron-deficient 1,3,4-oxadiazole and benzene systems linked by amide units to the triphenylmethane core <1997CC1435> or to benzene <2004CC70>, that are strongly self-associated in solutions through hydrogen bonding, were synthesized. Compound **162** and a similar compound containing other than oxadiazole five-membered conjugated rings were synthesized. Photo- and electroluminescence properties of compound **162** were superior to the other oligomers <1998CEJ2211>. Dendrimers up to the second generation containing three different oxadiazole layers were synthesized using the nucleophilic aromatic substitution reaction as the propagation step <2001JOC4062>.

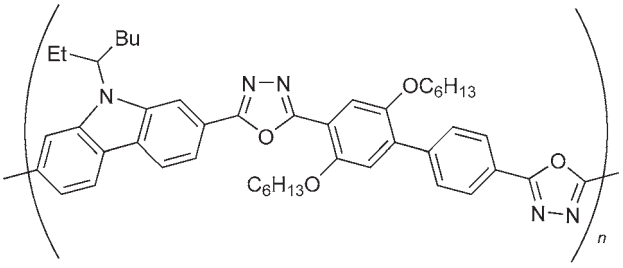


161



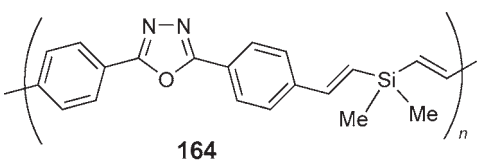
162

Polymer **163** (and similar alternating copolymers of 9,9-dioctylfluorene and oxadiazole <2002MM3474>) with blue-light-emitting activity were synthesized by the Suzuki coupling reaction and studied by GPC, MALDI-TOF MS, UV spectroscopy, and several other techniques <2002ANC6252>.

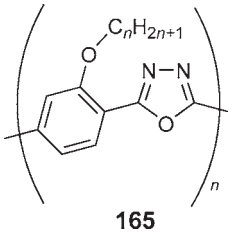


163

Silylene-spaced donor–acceptor divinylarene copolymers **164** were synthesized by hydrosilylation of bisalkynes with bisvinylsilanes; efficient intrachain energy transfer between donor and acceptor chromophores was observed <2002CC1978>. Synthesis of new *ortho*-linked aromatic poly(ether-1,3,4-oxadiazole)s and poly(ether-amide-1,3,4-oxadiazole)s by the polycondensation of the corresponding dihydrazide or amino-hydrazide monomers with the corresponding bis(ether-carboxylic acid)s or their acid chloride derivatives containing *ortho*-phenylene unit via precursor polyhydrazides and poly(amide-hydrazide)s thermally or chemically cyclodehydrated was described too <2004MI21>. The synthesis of a series of conjugated aromatic polyoxadiazoles **165** characterized by having moderate chain flexibility and highly flexible lateral substituents was reported. Films spun on fused silica were characterized by spectroscopic analysis in the whole UV–Vis–NIR range (Vis = visible; NIR = near infrared) showing a high transmission in the NIR region being the typical telecommunication band (1300–1500 nm). A device consisting of the said polymer sandwiched between two electrodes on the top of a glass substrate was constructed <2002CM1539>.

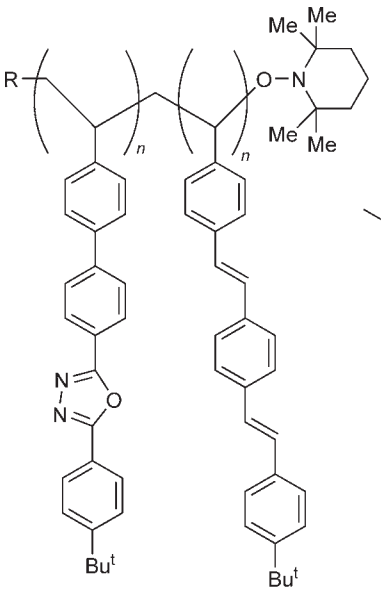


164

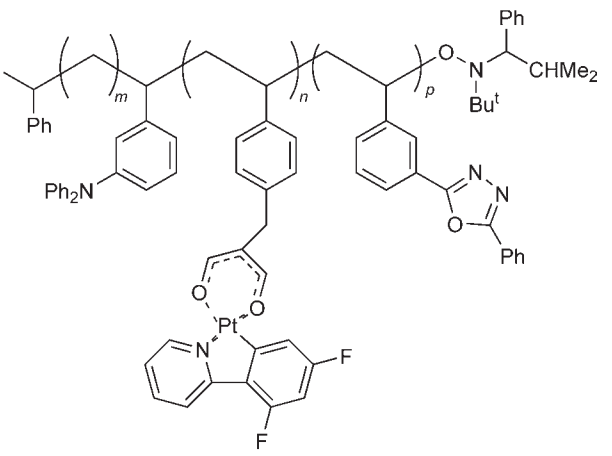


165

An efficient polymerization of a vinyl monomer bearing electron-transporting units, 2-[4-(4′-vinylbiphenylyl)]-5-(4-*tert*-butylphenyl)-1,3,4-oxadiazole, by using a 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-mediated radical polymerization method was reported. This monomer showed a quasi-living free radical character. The corresponding homopolymer was obtained in a high yield. Further reaction of the isolated polymer with another vinyl monomer bearing luminescent groups, 4-*tert*-butyl-4′-(4-vinylstyryl)-*trans*-stilbene, gave a diblock copolymer **166** containing both functional groups <2002MM1543>. Platinum-functionalized random copolymer **167** for the use in solution processible, efficient, near-white organic light-emitting diodes was obtained and fully characterized <2004JA15388>.



166

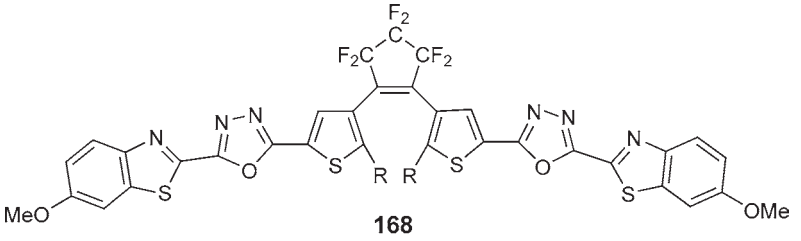


167

5.06.12.3 Luminescent and Photosensitive Materials, Dyes

Conjugated systems containing 2,5-disubstituted-l,3,4-oxadiazoles often fluoresce, which makes them potentially useful as laser dyes, optical brighteners, scintillators, or electrophotographic photoconductors. Several examples of such compounds have been reported in Section 5.06.12.2 and CHEC-II(1996) <1996CHEC-II(4)268>. A comprehensive review of the literature on electron-transport materials used to enhance the performance of organic light-emitting diodes has been published. Several of the materials contained oxadiazole units <2004CM4556>. Particularly, polymers and macromonomers containing 1,3,4-oxadiazole segments were synthesized in order to build blue light-emitting diodes. Some other oxadiazole derivatives are described below.

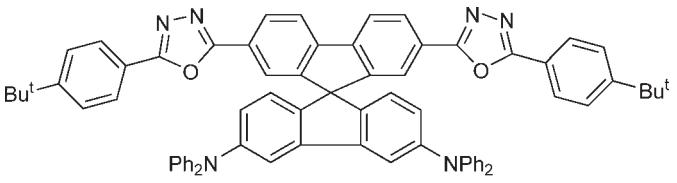
Derivatives of 5-alkyl-2-(1,3,4-oxadiazol-2-yl)thiophenes **168** were synthesized and their photochromic and fluorescent properties studied. A solution of the photochrome was subjected to irradiation over a wide range, including the lines of the mercury spectrum at 313, 365, 405, 436, 546, and 578 nm. It was discovered that the open form of compounds **168** showed strong fluorescence <2002CHE165>.



168

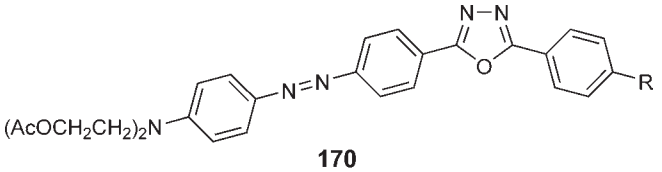
R = Me or Ph

9,9a-Spirobifluorene-bridged bipolar systems containing 1,3,4-oxadiazole-conjugated oligoaryl and triarylamine moieties were synthesized; among them, compound **169** exhibited remarkable solvent-polarity-dependent fluorescence properties due to a highly efficient photoinduced electron-transfer reaction <2002CC2874>.



169

A synthesis and physicochemical characterization, including molecular second-order nonlinear optical properties, of new push–pull-based chromophores **170** properly functionalized for polymerization and containing oxadiazole rings were reported <2002J(P2)1791>.

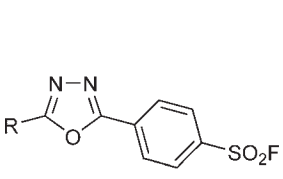


170

R = NO_2

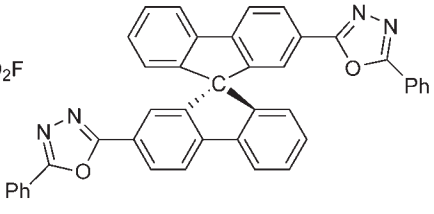
R = –CH=CH-$C_6H_4NO_2$

A synthesis of three isomeric 1,3,4-oxadiazole-pyridine hybrids, namely 2,6-, 3,5-, and 2,4-bis[2-(4-*tert*-butylphenyl)-1,3,4-oxadiazol-5-yl]pyridine, and a 1,3,4-oxadiazole–pyrimidine hybrid, namely 2,5-bis[2-(4-*tert*-butylphenyl)-1,3,4-oxadiazol-5-yl]pyrimidine, was described. Two of these materials proved to be comparable or better than the known efficient electron-injecting materials <2002JMC173>. Crystalline and graft polymer-based chemosensors containing oxadiazole fragments were compared among themselves <2003JA11154>. Synthesis, properties, and electroluminescent device applications of a series of diphenylanthrazoline molecules containing, among other groups, the oxadiazole substituent, were reported <2003JA13548>. Solvatochromic sulfonyl fluoride derivatives of 5-aryl-(heteroaryl)-2-phenyl-1,3,4-oxadiazole **171** were found to be applicable in promising fluorescent probes <1997CHE865>. The electronic structure and optical properties of the propeller-shaped spiro molecules **172** were studied by photoelectron and Raman spectroscopy as well as by spectroscopic ellipsometry. It was concluded that the dimeric spiro molecules maintained most of optical properties typical of the single system <1997JCP2542>. A blue organic light-emitting device having an emissive layer of 2-(2-hydroxyphenyl)-5-phenyl-1,3,4-oxadiazole, that exhibited excited state intramolecular proton transfer, was reported <2002CPL24>. An electroluminescent device made with fluorescent dye containing 1,3,4-oxadiazole **173** was described <1997JMC1395>.

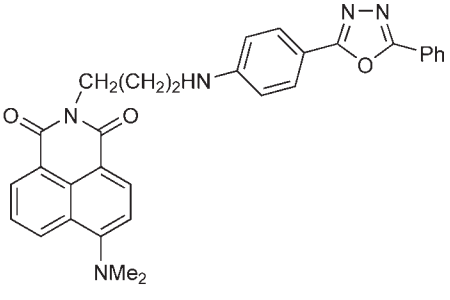


171

R = aryl, heteroaryl



172

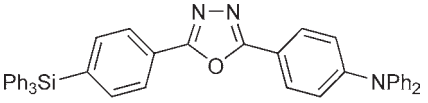


173

Nonpolymeric amorphous dyes for electron transport, some of them containing an oxadiazole ring, were prepared and theoretically studied. It was concluded that reversible electron injections and ejection properties without impurity effects could be obtained for the symmetric and globular amorphous molecules <1997PCA2350>. Amplified spontaneous emission laser spikes were observed for some simple 2,5-diaryl oxadiazoles <1997PCA3260>.

Epoxide derivatives of 2,5-bis-oxyphenyl-l,3,4-oxadiazoles and fluorescein, which are luminescent epoxide monomers, were synthesized and their luminescence properties were studied <1999CHE358>. The excited state intramolecular proton transfer reactions and luminescent properties of the *ortho*-hydroxy derivatives of 2,5-diphenyl-1,3,4-oxadiazole were elucidated to conclude that the proton phototransfer reaction is very efficient in the studied

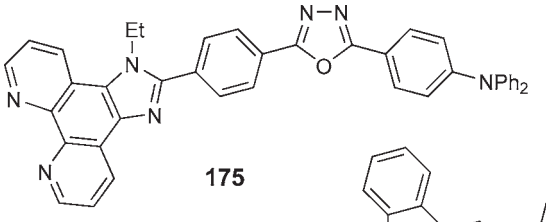
series of compounds <2000JPO253>. The fluorescent properties and dynamics of an excited state structural relaxation were also observed for other *ortho*-substituted oxadiazoles with additional sterical hindrance <2000JST289>. The fluorescence of (5-phenyl-1,3,4-oxadiazol-2-yl)-7-hydroxycoumarin <2000SAA1773, 2001CHE633> and several symmetric and unsymmetrical diaryl oxadiazoles <2000SAA2157> was studied. High-performance blue-light-emitting diodes containing oxadiazole fragment and tetraphenylsilane molecular glass materials **174** were optimized <2002JA6469>.



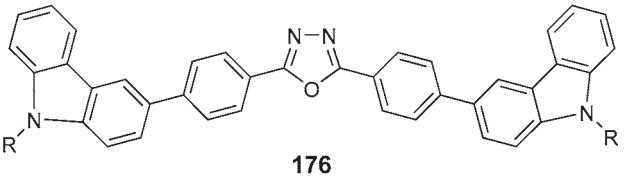
174

Blue-emitting and electron-transporting copolymers based on fluorene and oxadiazole were synthesized and studied <2002MM2529>. Conjugated chromophores based on dithienothiophene, as conjugated linker and having oxadiazole units were synthesized, and their optical and electrochemical properties as electron-transport agents were studied <2002CPL432>. 1,3-Bis-[2-(3,5-trifluoromethylphenyl)-1,3,4-oxadiazole-5-yl)]benzene was proposed as the electron-transport layer in light-emitting diodes or in semiconductor lasers <2002MCL81>.

Luminescent and laser properties of heteroaromatic and aromatic compounds were reviewed and discussed on the basis of all possible mutual arrangements of singlet and triplet states. Symmetrical 2,5-diaryloxadiazoles were classified as extremely effective laser dyes providing high fluorescence rate constants <2002SAA349>. A novel chromophoric but nonfluorescent benzene-1,3,5-tricarboxamide has proven to be a powerful organogelator for some aprotic organic solvents. Supramolecular aggregation of a nonfluorescent gelator yielded highly luminescent organogels in aprotic organic solvents through intermolecular hydrogen bonding <2004CC70>. A strategy to order oxadiazole semiconductors, using cross-linked liquid-crystalline materials, was proposed <2004CM4286>. Phenanthroline derivatives (e.g., **175**) containing a hole-transporting triphenylamine and an electron-transporting 1,3,4-oxadiazole unit were prepared with high yields and their high efficiency as blue- and red-light-emitting materials was shown <2004TL6361>. Also, carbazole derivatives containing oxadiazole unit **176** were used as host materials for triplet emitters in organic light-emitting diodes <2004JA6035, 2004JA7718>.



175

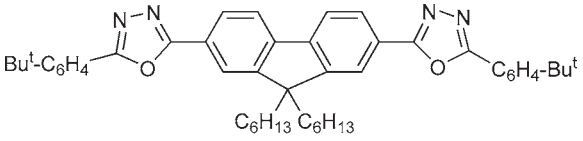


176

R = C_8H_{17}

2,5-Diaryl-1,3,4-oxadiazole–fluorene hybrid **177** as an electron-transporting material for blended-layer organic light-emitting diodes was proposed <2005JMC194>. Trifunctional Pt(II) cyclometalated complex, in which the hole-transporting, electron-transporting, and electroluminescent components were integrated into a single molecule, was prepared. This complex was sublimed and used for the fabrication of neat emissive layer electrophosphorescent devices <2005OM4079>. Employing a blend of poly(*N*-vinylcarbazole) and 5-biphenyl-2-(4-*t*-butylphenyl)-1,3,4-oxadiazole doped with 2,5-diphenyl-1,3,4-oxadiazole platinum(II) complex, green-yellow devices were obtained <2005MI723>. A number of co-crystals, for example, dipyridyloxadiazole with aromatic dicarboxylic acids <2005MI1199>, with trimesic or pyromellitic acids <2005MI1247>, and bisaminophenyloxadiazoles with inorganic salts <2005MI585>, were prepared and characterized by X-ray crystallography and spectroscopic methods. It was

anticipated that this approach would be useful for the construction of a variety of new transition metal complexes and luminescent coordination polymers with novel structures that have the potential of leading to new fluorescent materials.

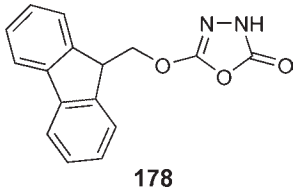


177

5.06.12.4 Other Applications of 1,3,4-Oxadiazoles

2,5-Dipicryl-l,3,4-oxadiazole has been described as an initiating explosive, 2,5-dimethyl-l,3,4-oxadiazole has been used to extract aromatic hydrocarbons from mixtures with alkanes. The use of 4,4′-carbonyl-bis(2-phenyl-5-oxo-l,3,4-oxadiazole) as a blowing agent for foaming thermoplastic compositions (e.g., polycarbonates) has been described <1996CHEC-II(4)268>.

(2-[4-Biphenylyl]-5-[4-*tert*-butylphenyl]-1,3,4-oxadiazole) used in diagnostics as an ultrapure scintillator is on the market under the name "Butyl PBD-ULTRA PURE". Nanotubes formed by 2-phenyl-5-(4-diphenylyl)-1,3,4-oxadiazole and cyclodextrins were obtained and tested <2002CPL515>. Multibranched structures containing oxadiazole units were proposed for constructing photophysical nanoscales in nanophotonics <2002MCL59>. 5-(9*H*-Fluoren-9-ylmethoxy)-1,3,4-oxadiazol-2(3*H*)-one **178** was used as an amine-acylating agent in the syntheses of selective peptidomimetic agonists for the human orphan receptor BRS-3 <2003JME1918>. The same compound was also used in syntheses of nonpeptidic ligands <2004AGE6649>.



178

Corrosion inhibition of mild steel in acid solutions by 2-aryl-5-oxadiazolinethiones (2-hydroxyphenyl, 2-phenyl, and 2-cinnamyl) has been observed <2002MCH425>. The potentiodynamic polarization data have shown that compounds studied predominantly behave as cathodic inhibitors in acid solutions.

A series of model nematic liquid crystals (among them oxadiazole derivatives) with transverse dipole moments were used to study the flexoelectric effect in guest–host mixtures with a commercial liquid crystal host <2005CM6354>.

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Biographical Sketch

Dr. Jerzy Suwiński was born in 1939, graduated in 1961, and obtained his Ph.D. in 1968 in organic chemistry under Prof. C. Troszkiewicz's supervision at the Silesian University of Technology (Gliwice, Poland). In 1973–74, he joined Prof. A. R. Katritzky's research group as a postdoc. Back in Gliwice, he received his D.Sc. degree in 1978 and in 1990 a position of full professor of organic chemistry. He has also lectured as a contract professor in Bologna (Italy; 1986, 1991), Missouri University (USA; 1994), Campinas (Brazil; 1995), Poznań (Poland; 1997) and as visiting professor in other countries. His main research interest is concerned with nitrogen heterocycles and reaction mechanisms. He is the author or co-author of over 130 papers, books, and textbooks for students.

Dr. Wojciech Szczepankiewicz was born in Wolbrom, Poland, in 1959. He received his M.Sc. in polymer chemistry from the Silesian University of Technology in Gliwice, Poland, in 1985 and his Ph.D. in 1994 under the supervision of Prof. Jerzy Suwiński at the same university. In 2002–03, he spent a period at Hasselt University (Belgium) with Prof. Dirk Vanderzande's lighting polymer research group. His research area is focused on the synthesis and reactivity of heterocyclic compounds in the azole and azine series.

5.07
1,2,3-Thiadiazoles

D. J. Wilkins
Key Organics Limited, Camelford, UK

5.07.1 Introduction

This chapter updates the respective chapters on 1,2,3-thiadiazoles published in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)447, 1996CHEC-II(4)289> and covers the literature from 1996 to 2006.

5.07.1.1 Background

Chemists have studied 1,2,3-thiadiazoles since the late nineteenth century, but it was Hurd and Mori's synthesis of 1,2,3-thiadiazoles in 1955, a synthesis that is still used widely today, that catalyzed an expansion of research on this ring system <1955JA5359>. A great deal of 1,2,3-thiadiazole chemistry has focused on the thermal and photochemical reactions of the ring system. Photolysis of 1,2,3-thiadiazoles usually proceeds with extrusion of nitrogen to give thiirenes, which then rearrange to give thioketenes. Modifications to syntheses have been developed and more extensive theoretical studies have been conducted. A number of 1,2,3-thiadiazoles have shown significant biological activity (see Section 5.07.12). X-Ray structures of a number of 1,2,3-thiadiazoles are now available.

5.07.1.2 Reviews

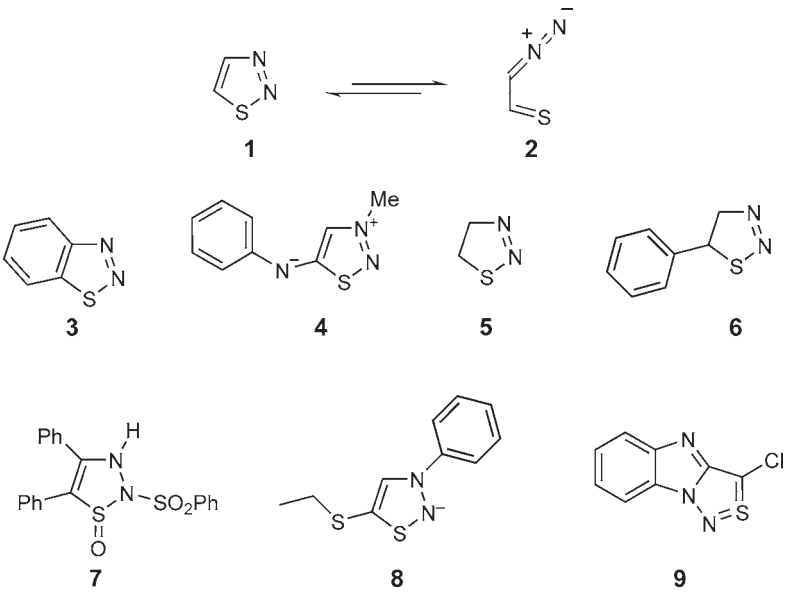
The 1,2,3-thiadiazole literature was extensively reviewed in CHEC(1984) <1984CHEC(6)447> and CHEC-II(1996) <1996CHEC-II(4)289>. It covered the literature up to 1996 and cited many excellent references to 1,2,3-thiadiazoles. A further review on the chemistry of 1,2,3-thiadiazoles, which gives a critical review of methods of synthesis and is accompanied by experimental procedures, appeared in *Science of Synthesis* <2004HOU(13)253>. Another review of 1,2,3-thiadiazoles also appeared in 2004 <B-2004MI1>. An annual review of the chemistry of 1,2,3-thiadiazoles appears in *Progress in Heterocyclic Chemistry* (Chapter 5.5). This review covers the 1,2,3-thiadiazole literature up to 2006.

5.07.1.3 Structures

The 1,2,3-thiadiazole **1** possesses three contiguous heteroatoms in a five-membered ring and exists as a remarkably stable neutral aromatic compound. It is isomeric with the ring-opened α-diazothioketone **2** (Equation 1); although there is evidence that it reacts through this intermediate, all structural methods, including X-ray diffraction, point to **1** as the structure for a 1,2,3-thiadiazole.

1,2,3-Benzothiadiazoles **3** have been extensively studied. Fully aromatic mesoionic compounds such as **4** continue to be synthesized. A number of examples of 4,5-dihydro-1,2,3-thiadiazole derivatives such as compound **5** <1993JOC82> and more recently the phenyl derivative **6** <2003RJO1501> have been reported. The corresponding 2,3-dihydro-1,2,3-thiadiazoles have also been reported and Hurd and Mori reported the *N*-2 phenylsulfonyl derivative **7**. The electron spin

resonance (ESR) spectrum has been published for the 1,2,3-thiadiazolium ion **8** <1998MRC8> (see Section 5.07.3.5). The first example of a *c*-fused 1,2,3-thiadiazole ring system has been reported: the benzimidazo[1,2-*c*][1,2,3]thiadiazole **9** is a novel ring system <2003TL6635>.



(1)

5.07.2 Theoretical Methods

5.07.2.1 *Ab Initio* Studies

Bond angles and lengths obtained from *ab initio* calculations on 1,2,3-thiadiazole **1** are presented in **Table 1** <1991JOM309> and can be compared to values for 4-phenyl-1,2,3-thiadiazole **10** obtained by X-ray diffraction (Section 5.07.3.1). *Ab initio* calculations were also carried out for the ring protonated at N-2 and N-3. These calculations reveal that N-2 is the preferred site of protonation by almost 9 kcal mol^{-1}. This parallels the preferred site of metal coordination to 1,2,3-thiadiazoles found in several studies <1996CHEC-II(4)289>.

Table 1 Calculated molecular dimensions for 1,2,3-thiadiazole **1**

Bond lengths	(*nm*)	*Bond angles*	(*deg*)
S–N(2)	0.167 6	C(5)–S–N(2)	102.8
N(2)–N(3)	0.124 5	S–N(2)–N(3)	101.7
N(3)–C(4)	0.137 5	N(2)–N(3)–C(4)	114.2
C(4)–C(5)	0.134 6	N(3)–C(4)–C(5)	113.6
C(5)–S	0.169 9	C(4)–C(5)–S	107.7

5.07.3 Experimental Structural Methods

5.07.3.1 X-Ray Diffraction

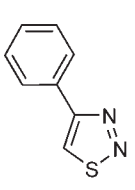
X-Ray diffraction methods remain the definitive structure proof, and the number of X-ray studies on 1,2,3-thiadiazoles published has been steadily increasing. 4-Phenyl-1,2,3-thiadiazole **10** and both the free and manganese cyclopentadienyldicarbonyl complex of 1,2,3-benzothiadiazole have been studied by X-ray diffraction <1991JOM309>. The bond lengths and bond angles are listed in **Table 2** for 4-phenyl-1,2,3-thiadiazole **10**. The N(2)–N(3) and C(4)–C(5) bond lengths suggest nearly double bond character and the bond lengths of S–N(2) and S–C(5) indicate partial double bond character for both sulfur bonds, suggesting that the ring is fully aromatic.

Both the thiadiazole and benzene ring are essentially flat. The distance between C-4 and C-6 (0.1469 nm) is as expected for an sp^2 sp^2 carbon–carbon bond, perhaps indicating that the rings are skewed and that there is little conjugation between the two rings.

Table 2 Molecular dimensions for 4-phenyl-1,2,3-thiadiazole **10**

Bond lengths	(*nm*)	*Bond angles*	(*deg*)
S–N(2)	0.166 6	C(5)–S–N(2)	93.2
N(2)–N(3)	0.128 6	S–N(2)–N(3)	111.2
N(3)–C(4)	0.137 8	N(2)–N(3)–C(4)	114.4
C(4)–C(5)	0.136 3	N(3)–C(4)–C(5)	112.2
C(5)–S	0.167 0	C(4)–C(5)–S	109.0
C(4)–C(6)	0.146 9		

The X-ray structure for the 4-substituted 1,2,3-thiadiazole **11** has been published <2003JHC929>, and the values obtained for bond lengths and angles are in close agreement with those obtained for 4-phenyl-1,2,3-thiadiazole **10**.



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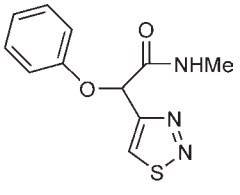

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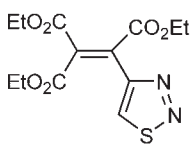
The bond lengths and bond angles found for benzo-l,2,3-thiadiazole by X-ray diffraction are listed in **Table 3**. These values are quite close to those published for a substituted 1,2,3-benzothiadiazole <1984CHEC(6)447>.

Table 3 Molecular dimensions for 1,2,3-benzothiadiazole **3**

Bond lengths	(*nm*)	*Bond angles*	(*deg*)
S–N(2)	0.170 6	C(7a)–S–N(2)	92.6
N(2)–N(3)	0.127 9	S–N(2)–N(3)	112.7
N(3)–C(3a)	0.138 4	N(2)–N(3)–C(3a)	113.4
C(3a)–C(7a)	0.139 7	N(3)–C(3a)–C(7a)	114.2
C(7a)–S	0.170 8	C(3a)–C(7a)–S	107.1

5.07.3.2 Proton NMR Spectroscopy

Proton nuclear magnetic resonance (NMR) chemical shifts of 1,2,3-thiadiazoles give another indication of the aromatic character of these compounds. Compiled in **Table 4** are a number of examples of proton chemical shifts for ring-substituted 1,2,3-thiadiazoles.



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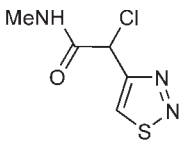

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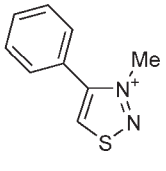

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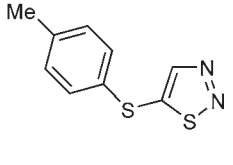

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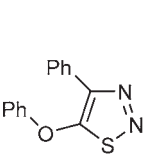

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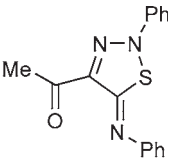

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Table 4 Proton NMR spectral data for ring hydrogens of 1,2,3-thiadiazoles

Compound	*H-4* (δ, *ppm*)	*H-5* (δ, *ppm*)	*Reference*
1	AB centered at 8.8		1996CHEC-II(4)289
10		8.60	1996CHEC-II(4)289
12		8.65	2003JOC1947
13		8.67	2003JHC925
14		10.17	1996CHEC-II(4)289
15	8.29		2001JOC4045

5.07.3.3 Carbon-13 NMR Spectroscopy

Carbon-13 NMR is often a more useful tool than ^{1}H NMR for the elucidation of heterocyclic structures in which there are few or no ring protons. For symmetrically substituted 1,2,3-thiadiazoles, the carbon adjacent to the nitrogen atom is expected to have a lower field chemical shift than the carbon atom adjacent to the sulfur atom, as exemplified in CHEC-II(1996) <1996CHEC-II(4)289>. Several examples that follow this rule are illustrated in **Table 5**. There is now a more extensive body of data available and it is possible to more accurately predict the chemical shift of ring carbons. In the case of monosubstituted 1,2,3-thiadiazoles, the substituted carbon usually has a lower field chemical shift than the unsubstituted carbon.

Table 5 Carbon-13 NMR spectral data for ring carbons of 1,2,3-thiadiazoles

Compound	*C-4* (δ, *ppm*)	*C-5* (δ, *ppm*)	*Reference*
1	147.3	135.8	1996CHEC-II(4)289
10	163.9	130.9	1996CHEC-II(4)289
12	155.6	138.4	2003JOC1947
15	145.0	156.5	2001JOC4045
16	159.7	172.3	2001JOC4045
17	154.9	158.0	2003S2559

5.07.3.4 Nitrogen-15 NMR Spectroscopy

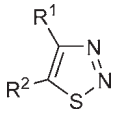
There are very few references to the ^{15}N NMR of 1,2,3-thiadiazoles. The ^{15}N NMR spectra of 15 monosubstituted 1,2,3-thiadiazoles have been published <1993JHC301> and selected data are given in **Table 6**.

When the N-3 atom is quaternized, as is the case of 4,5-diphenyl-3-trimethylsilylmethyl-1,2,3-thiadiazol-3-ium triflate, there is a large upfield shift for the N-3 atom of ~160 ppm, and a smaller shift is also observed for the N-2 atom of ~25 ppm in the ^{15}N NMR spectrum <1999J(P1)1415>.

5.07.3.5 ESR, IR, and UV Spectroscopy

Characteristic infrared (IR) absorptions for 1,2,3-thiadiazoles are: 1560–1475, 1350–1280 cm^{-1} (ring skeletal); 1265–1200, 1190–1175, 1150–950 cm^{-1} (ring breathing and CH in-plane deformations); and 910–890, 705–670 cm^{-1} (CH out-of-plane deformations) <1996CHEC-II(4)289>.

Table 6 Nitrogen-15 NMR spectral data for ring nitrogen of 1,2,3-thiadiazoles



			δ, *ppm*	
R^1	R^2	*Solvent*	*N-2*	*N-3*
H	H	DMSO	409.9	436.0
H	Et	$CDC1_3$	403.7	434.5
H	CHO	$CDCl_3$	427.2	438.4
Ph	H	DMSO	411.2	433.3
Bu^t	H	DMSO	410.4	439.4
CHO	H	DMSO	417.0	438.95

Simple 1,2,3-thiadiazoles show three absorption bands in the ultraviolet (UV): 211–217 (ε_{max} 4380–5300), 249–253 (1460–2100), 290–294 (195–245) nm <1996CHEC-II(4)289>. The ESR spectrum for the radical anion generated by the electrochemical reduction of the 1,2,3-thiadiazolium ion **8** has been reported. A number of 5-substituted derivatives were also examined and the splitting constants in the ESR spectrum were analyzed <1998MRC8>.

5.07.4 Thermodynamic Aspects

5.07.4.1 Melting and Boiling Points

The parent compound, 1,2,3-thiadiazole **1**, is a yellow liquid and its boiling point is 157 °C at atmospheric pressure. When 1,2,3-thiadiazoles are heated above 200 °C they usually decompose (Section 5.07.5). The melting and boiling points for a selection of substituted 1,2,3-thiadiazoles are presented in **Table 7** <1996CHEC-II(4)289>.

Table 7 Melting points for 1,2,3-thiadiazoles

Compound	*m.p.* (°*C*)	*Reference*
4-Phenyl-1,2,3-thiadiazole	75–77	1985JME442
5-Phenyl-1,2,3-thiadiazole	46–48	1985JME442
4,5-Diphenyl-1,2,3-thiadiazole	92–94	1985JME442
5-(4-Methoxyphenyl)-4-phenyl-1,2,3-thiadiazole	81.5–82.5	1985JME442
4-(4-Methoxyphenyl)-5-phenyl-1,2,3-thiadiazole	56.5–58	1985JME442

5.07.4.2 Solubility

No systematic study of the solubility characteristics of 1,2,3-thiadiazoles has been undertaken but most are freely soluble in methylene chloride and chloroform. The parent 1,2,3-thiadiazole **1** is soluble in alcohol, ether, and water. In contrast, a number of 1,2,3-thiadiazoles have been recrystallized from various alcohols and ethers <1985JME442, 1988JHC1873>.

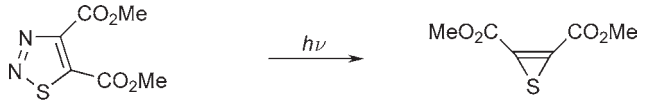
5.07.4.3 Aromaticity

Rings incorporating [4*n*+2] π-electrons are aromatic according to the Hückel definition and on this basis 1,2,3-thiadiazoles can be considered as aromatic. This is supported by ^{13}C and ^{1}H NMR chemical shifts. In 1990, the aromaticities of some five- and six-membered ring heterocycles including 1,2,3-thiadiazole were studied by computational methods and found to correlate well with their chemical natures <1990JPR885>.

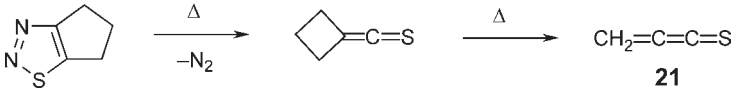
5.07.5 Reactivity of Fully Conjugated Rings

5.07.5.1 Fragmentations

When subjected to photolysis, 1,2,3-thiadiazoles extrude nitrogen and thiirenes can be formed, but their lifetime is fleeting as they rearrange to thioketenes. It was thought that electron-withdrawing substituents would stabilize a thiirene; bis(carbomethoxy)-1,2,3-thiadiazole **18** was irradiated (10 K, 265 nm) in an argon matrix to form almost exclusively bis(carbomethoxy)thiirene **19**, as determined by IR. Upon further irradiation, thiirene **19** underwent fragmentation instead of forming a ketene (Equation 2) <1983ZNB1208>. The pyrolysis of the 1,2,3-thiadiazole derivative **20** formed propadienethione **21** (**Scheme 1**) <1988JA789, 1990CPL1>.



18 **19** (2)

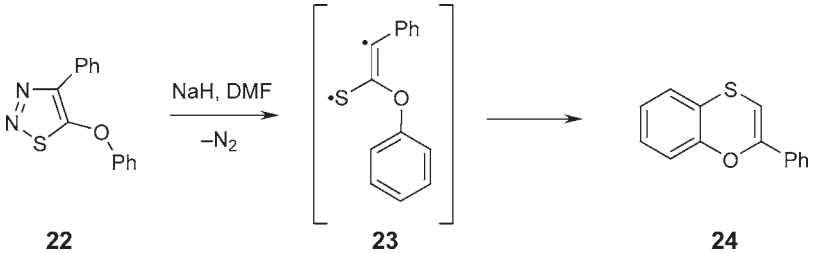


20 **21**

Scheme 1

The base-catalyzed fragmentation of 4-alkyl-1,2,3-thiadiazoles is a useful method for the preparation of alkyne-1-thiolates <1996T3171>. These alkyne-1-thiolates can then react with carbon disulfide to afford 1,3-dithiole-2-thiones. This strategy has been developed to give a synthesis of some novel tetrathiafulvene derivatives <1996T3171>.

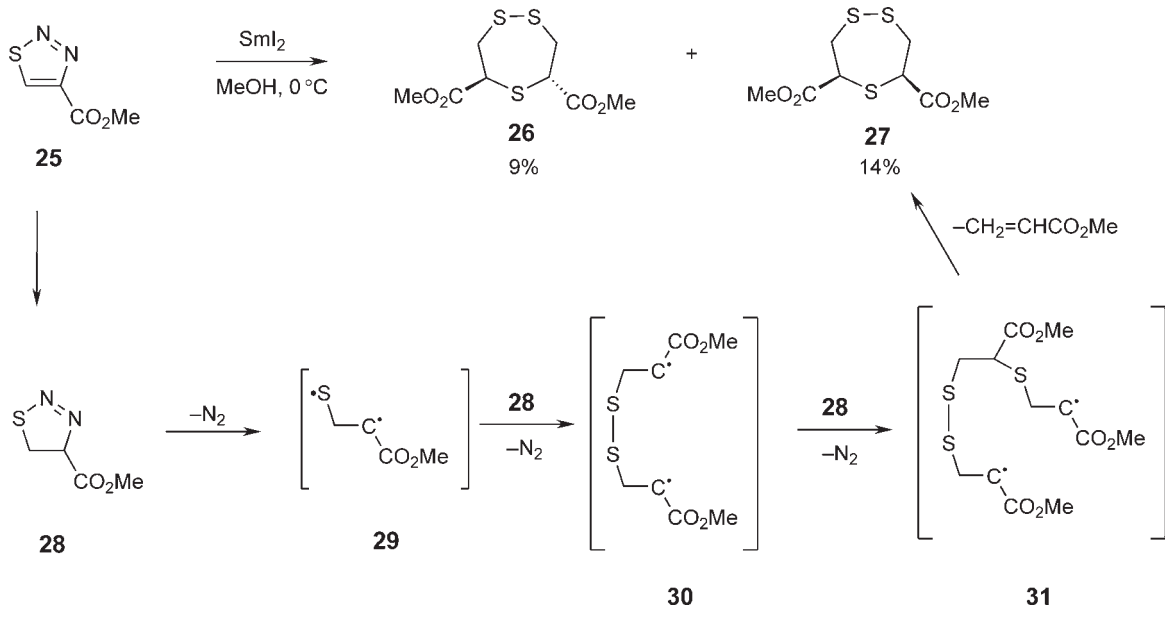
Similarly, 5-chloro-1,2,3-thiadiazoles react with organolithium or Grignard reagents to give alkynyl sulfides by a fragmentation reaction with the loss of nitrogen and chloride anion <1999J(P1)1473>. A similar base-catalyzed fragmentation reaction occurs when solutions of 5-aryloxy-1,2,3-thiadiazoles **22** in dimethylformamide (DMF) are heated to 100 °C in the presence of excess sodium hydride. 1,4-Benzoxathiins **24** are formed in this reaction and the transformation is proposed to proceed via initial ring cleavage of the thiadiazole ring with subsequent nitrogen elimination to give the intermediate **23**. An intramolecular rearrangement then occurs to give the 1,4-benzoxathiin **24** (**Scheme 2**) <2002H(56)483>.



22 **23** **24**

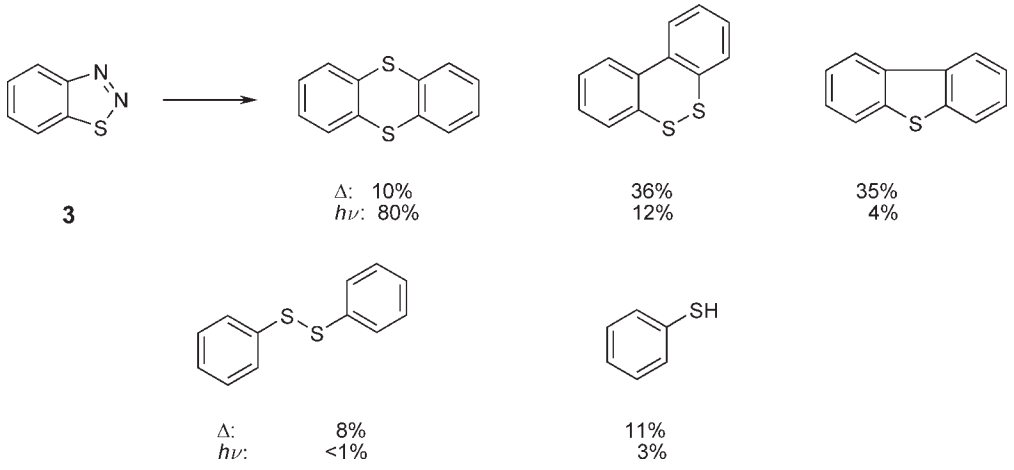
Scheme 2

An unexpected ring enlargement is observed in the attempted reduction of 1,2,3-thiadiazole-4-carboxylate **25** <2004OBC2870>. Treatment of compound **25** with powdered samarium and iodine in methanol at 0 °C leads to a mixture of 1,2,5-trithiepanes **26** and **27**. Presumably, the carbon–carbon bond of thiadiazole **25** is reduced and the resulting thiazoline **28** releases nitrogen to give S,C-biradical **29**, which reacts with thiazoline **28** via S–S bond formation and concomitant loss of nitrogen to produce a symmetrical C,C-biradical **30**. Interception by a second molecule of **28** leads to the third biradical **31**, which undergoes intramolecular cyclization to afford products **26** and **27** after expulsion of methyl acrylate (**Scheme 3**) <2004OBC2870>.



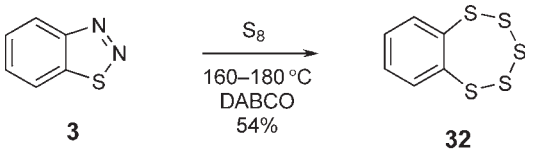
Scheme 3

Unlike simple 1,2,3-thiadiazoles, 1,2,3-benzothiadiazoles do not form thioketenes on thermolysis or photolysis. Instead, they yield many products, depending on the conditions (Equation 3). The mechanisms of these reactions have been extensively studied <1984CB107>.



(3)

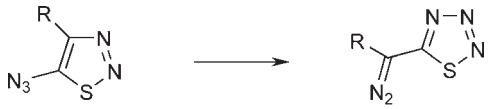
1,2,3-Benzothiadiazole **3**, when heated in the presence of sulfur, first loses nitrogen and then reacts with sulfur to form benzopentathiepin **32** <1984JOC1221>. This method has been extended to the synthesis of several heterocyclic ring compounds fused to pentathiepin starting from the corresponding 1,2,3-thiadiazolo heterocycle (Equation 4) <1985JA3871>.



(4)

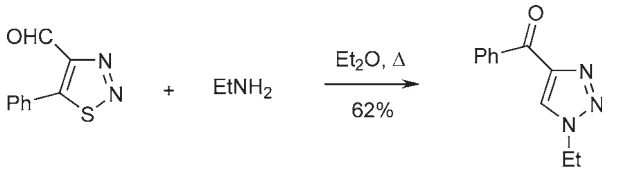
DABCO = 1,4-diazobicyclo[2.2.2]octane

L'abbe has studied the rearrangement reactions of 1,2,3-thiadiazoles to differently substituted 1,2,3-thiadiazoles <1983CC588>. He also studied many 5-azido-1,2,3-thiadiazoles **33** that rearranged to 1,2,3,4-thiatriazoles **34** (Equation 5) <1988BSB163>. He even found that l,2,3-thiadiazole-4-carboxaldehydes **35** upon treatment with amines underwent thermal rearrangement to 1,2,3-triazoles **36** (Equation 6) <1993J(P1)1719>.



33 **34** (5)

R = CO_2Et, PhCO, Ph, 4-$MeOC_6H_4$



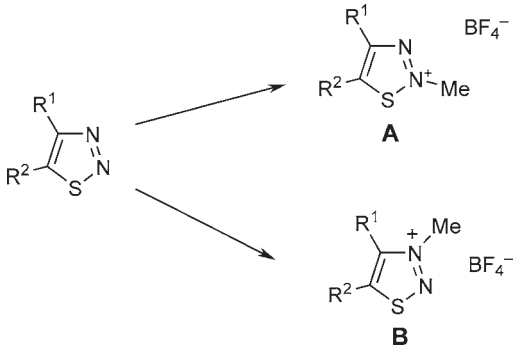
35 **36** (6)

5.07.5.2 Electrophilic Attack at Aromatic Ring

1,2,3-Thiadiazoles are weak bases and form deliquescent hydrochloride salts, which are decomposed by water. No successful attempts to halogenate 1,2,3-thiadiazoles have appeared to date.

5.07.5.2.1 Electrophilic attack at nitrogen

There are several examples of alkyl halides reacting with 1,2,3-thiadiazoles at nitrogen to yield either salts or mesoionic compounds <1996CHEC-II(4)289>. Similarly, with Meerwein's reagent, several substituted thiadiazoles yielded various 2- and 3-methylated 1,2,3-thiadiazoles (**Scheme 4**; **Table 8**) <1993JHC301>. The isomer ratios were determined by integrating the methyl singlets in the ^1H NMR spectra and the compounds were further studied by ^{15}N NMR spectroscopy (Section 5.07.3.4).



A **B**

Scheme 4

4,5-Diaryl-1,2,3-thiadiazoles and 1,2,3-benzothiadiazoles have been alkylated at N-3 with trimethylsilylmethyl trifluoromethanesulfonate and treatment of these salts with cesium fluoride generate new 1,2,3-thiadiazol-3-ium-3-methanide 1,3-dipoles (see Section 5.07.8.1) <1999J(P1)1415>.

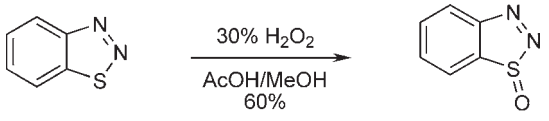
5.07.5.2.2 Electrophilic attack at sulfur

Although electrophilic attack by peracids proceeds first at N-3 in simple 1,2,3-thiadiazoles, the sulfur can be oxidized by an excess of reagent to give an *N*,*S*,*S*-trioxide <1996CHEC-II(4)289>.

Table 8 Product distribution for the methylation of 1,2,3-thiadiazoles with Meerwein's reagent

R^1	R^2	*A* (%)	*B* (%)
H	H	4	96
H	Cl		100
Ph	H	81	19
Bu^t	H	87	13
CO_2Me	H	8	92

However, reaction of 1,2,3-benzothiadiazole **3** with 30% hydrogen peroxide in a mixture of acetic acid and methanol for 45 days afforded product **37** (Equation 7) in 60% yield <1990CJC1950>. Oxidation of 1,2,3-benzothiadiazole **3** with a variety of other oxidizing agents (*m*-chloroperoxybenzoic acid, 30% hydrogen peroxide, hydrogen peroxide in methylene chloride–acetic acid mixtures, etc.) was unsuccessful.



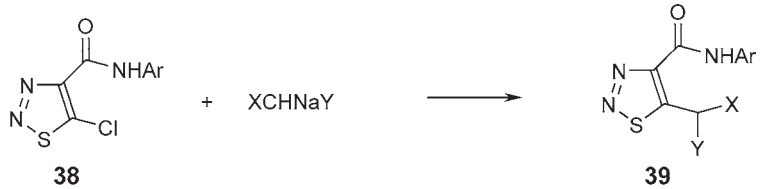
3 **37** (7)

5.07.5.3 Nucleophilic Attack at Aromatic Ring

Nucleophilic attack on 1,2,3-thiadiazole derivatives is restricted to attack at the 5-position. There are no examples where nucleophilic attack has occurred at the 4-position.

The chlorine in 5-chloro-1,2,3-thiadiazole is displaced by methoxide ion <1974JHC343>.

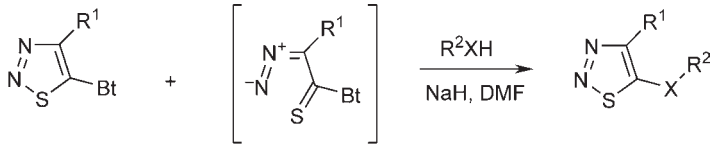
5-Chloro-1,2,3-thiadiazole-4-carboxamides **38** react with the sodium salt of diethyl malonate to give the corresponding malonic acid derivatives **39**. The yield in these reactions falls as the electron-releasing properties of the 4-substituents in the aromatic ring increase (Equation 8) <1997JCM396>.



38 **39** (8)

Ar = Ph, Tol, 4-$MeOC_6H_4$, 4-Cl-C_6H_4, 4-$MeC(O)C_6H_4$
X = CN or CO_2Et

1,2,3-Thiadiazoles that have a 5-benzotriazolyl substituent, such as compound **40**, can be reacted with oxygen and sulfur nucleophiles to afford the corresponding substituted derivatives **41**. Readily accessible α-benzotriazolylalkyl ketones can be converted into useful synthons for the Hurd–Mori reaction to give a variety of 5-benzotriazolyl derivatives. In general, oxygen nucleophiles required more forcing conditions (NaH, DMF, 100 °C) and gave rather variable yields (11–76%) (Equation 9).

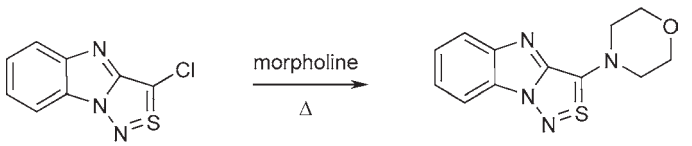


40 **41** (9)

R^1 = H, Ph, thiophen-2-yl, furan-2-yl;
X = O or S; R^2 = *p*-tolyl, 2-naphthyl, Bn,4-ClC_6H_4, 4-$MeOC_6H_4$

The mechanism for the displacement reactions probably involves the known ring-chain isomerization of substituted 1,2,3-thiadiazoles involving cleavage of the 1,2-bond to afford 2-diazothanethione tautomers which then undergo nucleophilic substitution and subsequent ring closure <2001JOC4045>.

The *c*-fused chloro benzimidazo[1,2-*c*][1,2,3]thiadiazole **9** can undergo nucleophilic displacements with secondary amines: heating compound **9** with morpholine affords the adduct **42** (Equation 10) <2003TL6635>.



9 **42** (10)

5.07.6 Reactivity of Nonconjugated Rings

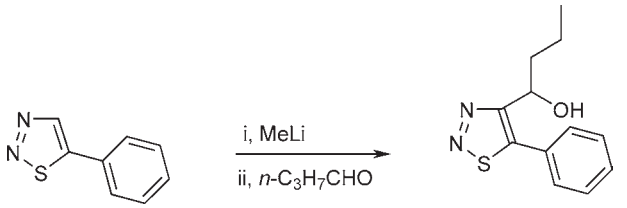
There have been no developments in this area since the publication of CHEC-II(1996) <1996CHEC-II(4)289>.

5.07.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5.07.7.1 Reactions of Hydrogen

Ring protons of 1,2,3-thiadiazoles are known to undergo rapid deuterium exchange under basic conditions. It has been reported that even weak bases such as phenolate can extract the proton at the 5-position of 4-phenyl-1,2,3-thiadiazole <1999J(P1)1473>.

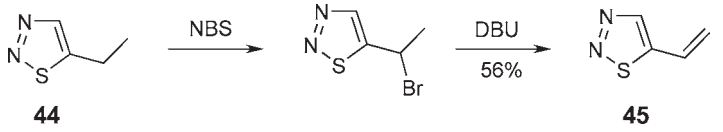
One study found that metalation of 5-phenyl-1,2,3-thiadiazole **43** with methyllithium gives 4-lithio-5-phenyl-1,2,3-thiadiazole, which is stable and reacts with aldehydes and ketones in high yields (Equation 11) <1985S945>.



43 (11)

5.07.7.2 Reactions of C-linked Substituents

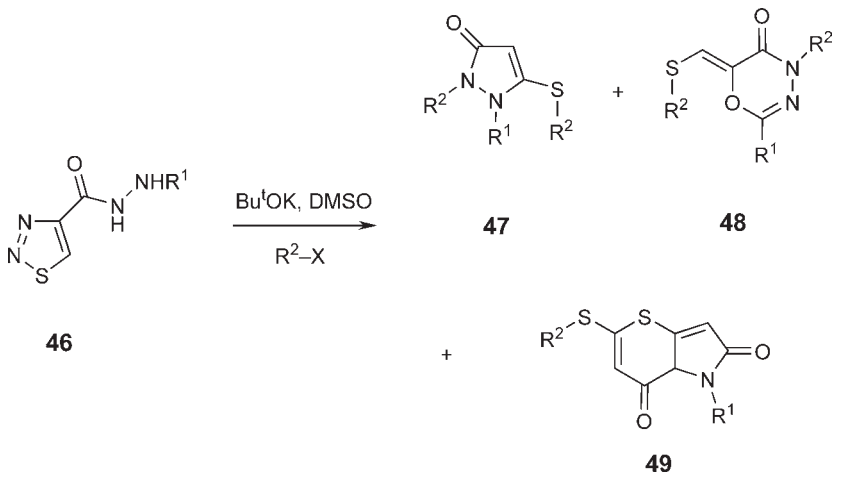
5-Ethyl-1,2,3-thiadiazole **44** is readily brominated at its pseudo benzylic position and subsequent elimination afforded the vinyl thiadiazole **45** (**Scheme 5**) <1986LA1334, 1986LA1344>. To prevent polymerization of the vinyl thiadiazole, hydroquinone was added during the elimination step.



44 **45**

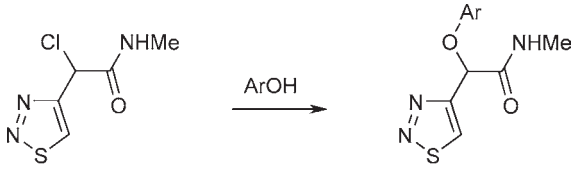
Scheme 5

1,2,3-Thiadiazole-4-carbohydrazides **46** undergo base-catalyzed cleavage with the liberation of nitrogen and recyclization to give 5-thiopyrazolones **47**, 6-thiomethylidene-1,3,4-oxadiazin-5-ones **48**, and 5-thio-7*H*-pyrazolo[5,1-*b*][1,3]thiazone-2,7-diones **49** (Equation 12) <2002TL1015>.



(12)

A novel series of α-substituted phenoxy-*N*-methyl-1,2,3-thiadiazole acetamides **51** is obtained through nucleophilic substitution of the chloro compound **50** with several phenols, and the resultant phenoxy derivatives were evaluated against heptatitis B virus (HBV) (see Section 5.07.12) (Equation 13) <2003JHC925>.



(13)

The naphthalene-like, aromatic structure of 1,2,3-benzothiadiazole imparts stability to the system that survives exposure to 20% potassium hydroxide at 150 °C or 27% sulfuric acid at 200 °C. It is not oxidized by potassium permanganate, potassium ferricyanide, chromic acid, or dilute nitric acid <1996CHEC-II(4)289>. Electrophilic substitution occurs in the benzo ring, predominantly at the 4-position. Chlorine in the 6-position is displaced by a variety of nucleophiles <1975SST670>.

5.07.7.3 Reactions of O-linked Substituents

Mesoionic compounds (Section 5.07.1.3) are fully aromatic and usually have an exocyclic heteroatom bearing a charge attached to the ring. A new one-step method for converting the exocyclic oxygen of 3-phenyl-l,2,3-thiadiazolium-5-olate **52** into the exocyclic sulfur of 3-phenyl-l,2,3-thiadiazolium-5-thiolate **53** makes use of Lawesson's reagent (Equation 14) <1988BCJ2977>.

(14)

5.07.8 Reactivity of Substituents Attached to Ring Heteroatoms

5.07.8.1 Substituents Attached to Nitrogen

The most familiar examples of 1,2,3-thiadiazoles bearing substituents on nitrogen are mesoionic compounds (Section 5.07.1.3) but little has been reported about these compounds since CHEC-II(1996) was published.

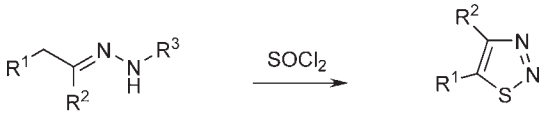
5.07.8.2 Substituents Attached to Sulfur

The Hurd–Mori reaction,where a tosylhydrazone is converted by thionyl chloride to the corresponding thiadiazole, involves the formation of a 1,2,3-thiadiazole-3,3-dioxide. In one example, this type of compound was isolated and subsequently deoxygenated with thiourea <1991PS175>. There have been no further reports of S-linked sulfoxide or sulfone derivatives of 1,2,3-thiadiazoles since the publication of CHEC-II(1996).

5.07.9 Synthesis

5.07.9.1 From Hydrazones and Thionyl Chloride: [4+1] Atom Fragments

The most common, convenient, and versatile synthesis of 1,2,3-thiadiazoles is the one discovered by Hurd and Mori in 1955 <1955JA5359>. This involves the reaction of thionyl chloride with acyl- or phenylsulfonylhydrazones or semicarbazones **54** that contain an α-methylene group; this reaction affords a wide range of 1,2,3-thiadiazoles **55** (Equation 15).



54 **55**

(15)

R^1 = H, alkyl, aryl; R^2 = H, alkyl, aryl, CO_2H, CO_2Et
R^3 = CO_2Et, Ac, SO_2Ph,Ts

Sulfur dichloride (SCl_2) has been shown to be a useful alternative reagent to thionyl chloride in the Hurd–Mori reaction. Treatment of a range of α,β-unsaturated *p*-tosylhydrazones with SCl_2 gave good yields of the 1,2,3-thiadiazole ring system <1981G289>.

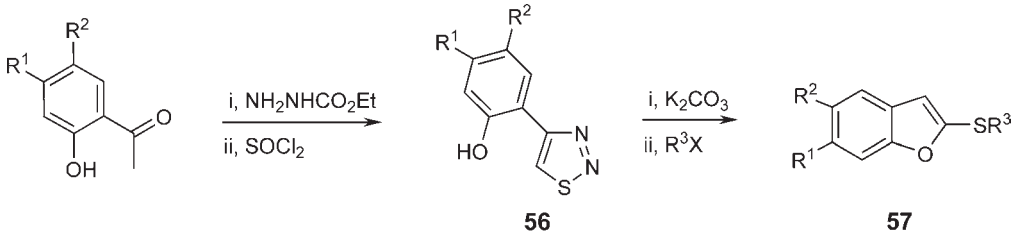
Examples of the synthesis of 1,2,3-thiadiazoles using the Hurd–Mori reaction are prevalent in the most recent literature <2004RJO99, 2003JHC427, 2003JOC1947, 2003JHC925, 2003FA63, 2003JHC149>.

A study of the kinetics and mechanism of the reaction of thionyl chloride with a series of *para*-substituted acetophenone semicarbazones suggests attack of thionyl chloride above the plane of the hydrazone (*E*)-isomer. Subsequent cyclization and loss of carbon dioxide and ammonia produces the 1,2,3-thiadiazole system <1982J(P1)1233>.

A modified reaction mechanism to the one suggested by Hurd and Mori is proposed for the preparation of some thieno[2,3-*d*][1,2,3]thiadiazole derivatives in order to explain the formation of a chlorinated by-product <1998J(P1)853>.

A parallel synthesis of 1,2,3-thiadiazoles employing a catch-and-release strategy has been reported using the Hurd–Mori reaction. A polymer-bound tosyl hydrazide resin reacted with α-methylene ketones to afford a range of sulfonyl hydrazones. Treatment of these sulfonyl hydrazones with thionyl chloride causes 1,2,3-thiadiazole formation and cleavage of the resin in one step <1999JOC1049>.

Reaction of 2-hydroxyacetophenones in the Hurd–Mori reaction led to a range of 4-(*o*-hydroxyaryl)-1,2,3-thiadiazoles **56**. Subsequent treatment of these derivatives with base and an alkyl halide led to the formation of 2-benzofuransulfanyl derivatives **57** (**Scheme 6**) <2000T3933>.

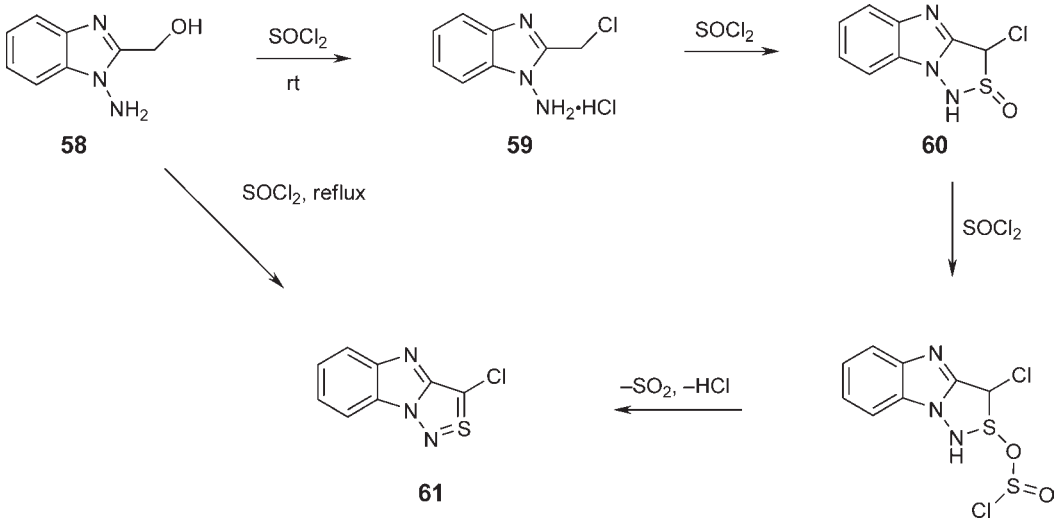


56 **57**

R^1, R^2 = H, alkyl, OH; R^3 = alkyl and benzyl

Scheme 6

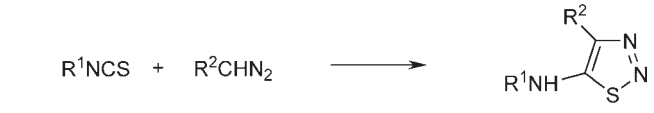
The synthesis of the benzoimidazo[1,2-*c*][1,2,3]thiadiazole **61** can be explained using the same mechanistic model to that used for the Hurd–Mori reaction. The amino benzimidazole **58** when treated with thionyl chloride at reflux affords the benzoimidazo[1,2-*c*][1,2,3]thiadiazole **61**. If, however, the reactant **58** is treated with thionyl chloride at room temperature, the chloromethyl derivative **59** is formed. This derivative was then transformed into product **61** on reflux with thionyl chloride. The proposed mechanism for the formation of product **61** is for the initial formation of the sulfoxide **60**, which then undergoes a Pummerer-like rearrangement, followed by loss of SO_2 and HCl to give the *c*-fused 1,2,3-thiadiazole **61** (**Scheme 7**) <2003TL6635>.



Scheme 7

5.07.9.2 Dipolar Cycloaddition Reactions: [3+2] Atom Fragments

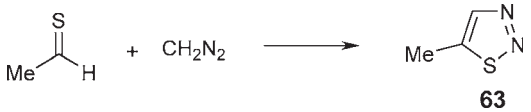
Perhaps the earliest reported method for the synthesis of the 1,2,3-thiadiazole ring system was the one described by Pechmann and Nold in which diazomethane was reacted with phenyl isothiocyanate. Of the four possible isomers that could be obtained from the reaction, 5-anilino-1,2,3-thiadiazole **62** (R^1 = Ph, R^2 = H) was the only product formed (Equation 16) <1896CB2588>. This method continues to be used as a route to 5-amino substituted 1,2,3-thiadiazoles. 4,5-Disubstituted 1,2,3-thiadiazoles have been produced in excellent yield by reaction of 1,1′-thiocarbonyl diimidazole with ethyl diazoacetate <1988SUL155>.



(16)

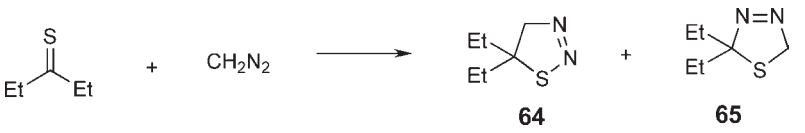
R^1 = aryl, benzyl, CO_2Et; R^2 = H, aryl, $CONH_2$, CO_2Et **62**

1,2,3-Thiadiazoles are often prepared by modifications of Pechmann's synthesis which usually involves a 1,3-dipolar cycloaddition of diazoalkanes to thiocarbonyl compounds <1975SST670>. The use of thiocarbonyl compounds has therefore broadened the scope of this reaction and has made starting materials more readily accessible. For example, reaction of ethyl thioformate with diazomethane gave 5-methyl-1,2,3-thiadiazole **63** (Equation 17). However, many *O*-alkyl thionoesters have given 5-alkoxy-5-methyl-Δ^2-1,2,3-thiadiazolines as the final product rather than the required 1,2,3-thiadiazole <1975SST670>. The regioselectivity of the cycloaddition of diazomethane to thioformaldehyde and thioketones has recently been studied. Polar solvents favor the formation of 1,2,3-thiadiazolines **64** over 1,3,4-thiadiazolines **65** (Equation 18) <1993JOC82>.



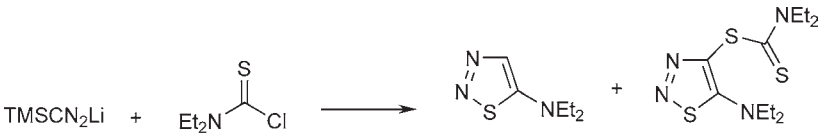
(17)

63



64 65 (18)

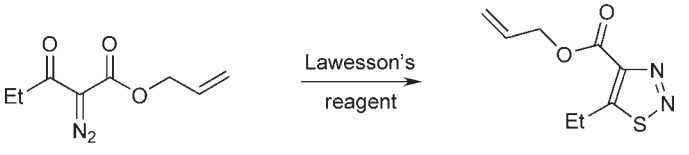
Reaction of lithium trimethylsilyldiazomethane (TMSC(Li)N_2) with thiocarbonyl compounds has proved to be a convenient method for the preparation of 5-substituted 1,2,3-thiadiazoles. This reaction is very similar to the Pechmann–Nold reaction but probably does not proceed through a dipolar cycloaddition pathway. A number of examples of this type of reaction were described in CHEC-II(1996). More recently, it was reported that $TMSCN_2Li$ also reacts with diethylaminothiocarbonyl chloride to afford a mixture of 1,2,3-thiadiazoles **66** and **67** (Equation 19) <1997BSB533>.



66 67 (19)

5.07.9.3 From Diazocarbonyl Compounds

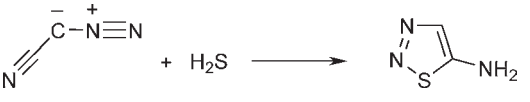
Wolff's synthesis of 1,2,3-thiadiazoles from diazoketones is one of the earliest methods for forming the ring. Typically, diazoketones were prepared by diazotization of α-aminoketones and then subsequent reaction with ammonium hydrosulfide gave disubstituted 1,2,3-thiadiazoles <1952MI(4)3>. Generally, Wolff's synthesis requires the reaction of a diazocarbonyl compound with a thionating agent. The scope of the reaction has recently improved with the develpoment of new methods of diazotransfer reaction which has made diazocarbonyl compounds more accessible. A variety of thionating agents have also been used to effect the final cyclization to give the 1,2,3-thiadiazole ring system. For example, reaction of the diazocompound **68** with Lawesson's reagent has given excellent yields of 4,5-disubstituted 1,2,3-thiadiazoles **69** (Equation 20) <1986JOC4075>. Other thionating agents commonly used in this reaction include P_4S_{10} and arylsulfonyl azides.



68 69 (20)

Contrary to earlier reports that only molecules possessing a rigid *cis*-diazoketone geometry could be converted into 1,2,3-thiadiazoles <1982H(19)241>, Caron prepared a range of 1,2,3-thiadiazoles which suggested that some conformationally flexible diazocarbonyl compounds can undergo the final cyclization <1986JOC4075>. These diazo compounds may be converted into 1,2,3-thiadiazoles through their α-diazothiocarbonyl intermediates, which must adopt the *cis*-geometry in the transition state as suggested by Cava and Levinson <1982H(19)241>.

A variation of Wolff's synthesis involves the reaction of diazonitrile with H_2S as the thionating agent to give 5-amino-1,2,3-thiadiazole in 73% yield (Equation 21) <1997H(44)197>.

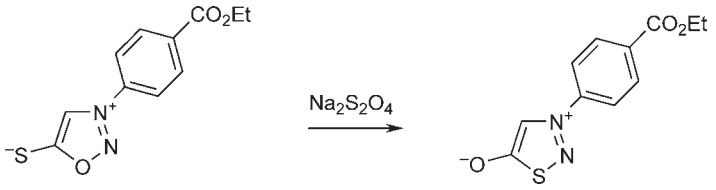


(21)

5.07.9.4 Mesoionic Compounds

Mesoionic derivatives are generally synthesized from the parent 1,2,3-thiadiazoles. A new method based on the rearrangement of oxadiazoles under reductive conditions has been reported. For example, the oxadiazole **70** when

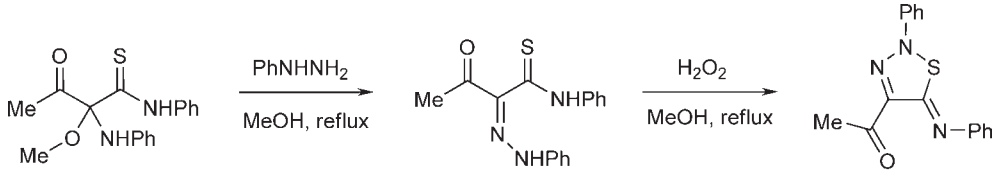
reduced with sodium dithionite afforded the 1,2,3-thiadiazole **71**. Ammonia has been used in the past to effect this rearrangement but with this substrate the amide and not the ester was produced (Equation 22) <1998MRC8>.



70 **71** (22)

5.07.9.5 Synthesis from Thioanilide Derivatives

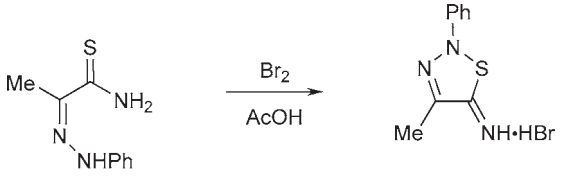
A new method for the synthesis of 1,2,3-thiadiazoles has been reported. The method starts with the thioanilide derivative **72**, which is converted into the hydrazone **73**. Oxidative heterocyclization by treatment with hydrogen peroxide gave exclusively the 1,2,3-thiadiazoline **74** (**Scheme 8**) <2003S2559>.



72 **73** **74**

Scheme 8

This method has been extended to include arylhydrazono thioacetamides, such as **75**, which undergo oxidative cyclization using bromine to afford 2-aryl-1,2,3-thiadiazol-5(2*H*)imines **76** (Equation 23) <2004RJO818>.

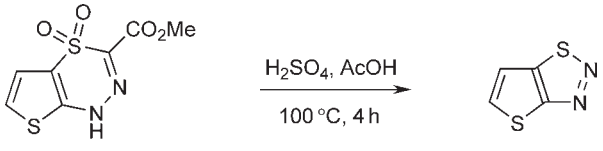


75 **76** (23)

5.07.10 Synthesis by Transformation of Another Ring

A number of interesting examples of the synthesis of 1,2,3-thiadiazoles by ring transformations were described in both CHEC(1984) and CHEC-II(1996).

An unexpected ring contraction reaction has been reported. The attempted hydrolysis of 3-methoxycarbonyl-1*H*-thieno[2,3-*e*][1,3,4]thiadiazine 4,4-dioxide **77** under acidic conditions gave the ring-contracted thieno[2,3-*d*][1,2,3]thiadiazole **78** instead of the expected carboxylic acid (Equation 24). A similar mechanism to the Hurd–Mori reaction has been proposed for this transformation <2000JHC191>.



77 **78** (24)

5.07.11 Synthesis of 1,2,3-Thiadiazoles and a Critical Comparison of the Various Routes Available

5.07.11.1 Comparison of Literature Methods

The Hurd–Mori synthesis of 1,2,3-thiadiazoles is the most widely used method. The availability of aldehydes and ketones which can then be converted into their corresponding hydrazones and the high yields obtained on treatment of these hydrazones with thionyl chloride mean that this method should always be considered as the first choice.

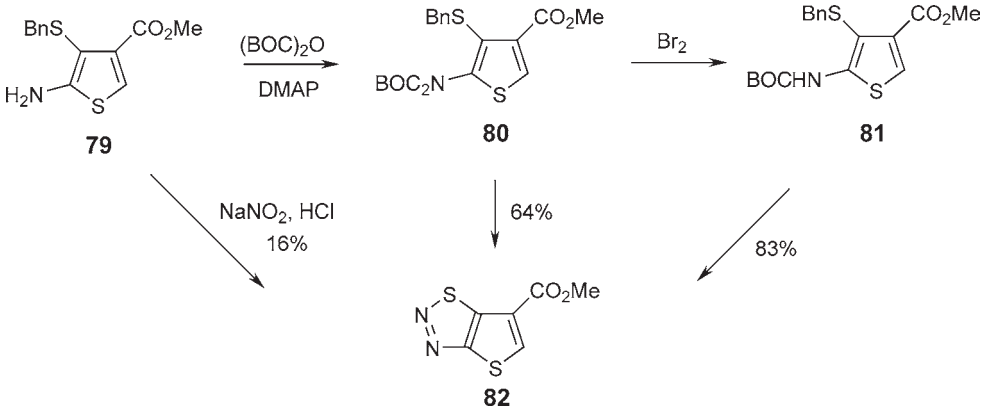
The use of thiocarbonyl compounds and also trimethylsilyldiazomethane in the Pechmann–Nold synthesis has greatly increased the scope of this reaction in recent years. Wolff's synthesis has also benefited from advances in the synthesis of both diazoketones and thionating reagents.

5.07.11.2 Comparison of New Methods

The preparation of 1,2,3-thiadiazoles from thioanilide derivatives (see Section 5.07.9.5) is the only new method to appear since the publication of CHEC-II(1996) <2003S2559>. The versatility of this method is rather restricted compared to established methods due to the complexity of the starting thioanilide derivatives.

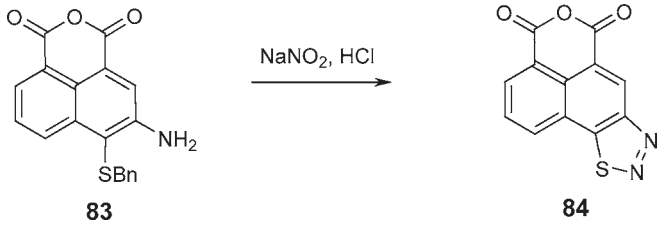
5.07.11.3 1,2,3-Benzothiadiazoles and Heteroaryl Derivatives

The most common method for the preparation of 1,2,3-benzothiadiazoles is the diazotization of 2-aminobenzenethiol. This method was discussed and exemplified in CHEC-II(1996). The method has been extended in recent years to include heterocyclic derivatives. The 2-aminothiophene **79** can be converted into the thienothiadiazole **82** on treatment with sodium nitrite in HCl but in poor yield (16%). The bis(BOC)-protected derivative **80** or the mono(BOC)-protected derivative **81** when reacted under similar conditions afford product **82** in much higher yields (BOC = *t*-butoxycarbonyl; **Scheme 9**). The increase in yield is explained in terms of hard and soft electrophilic character. The intermediate in the BOC-protected examples has a soft character allowing attack by sulfur to proceed more easily <1999JHC761>.



Scheme 9

The thiadiazole naphthalimide **84** was synthesized from the 2-thiobenzyl aniline **83** under similar conditions (Equation 25) <2003BML3513>.



(25)

5.07.12 Important Compounds and Applications

5.07.12.1 Introduction

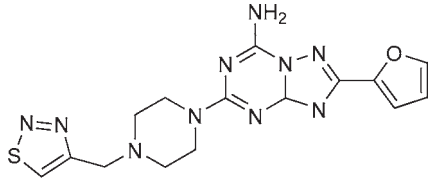
Chemists have found numerous industrial applications for 1,2,3-thiadiazole derivatives. In particular, 1,2,3-thiadiazole derivatives have been used as insecticide synergists, herbicides, and polymer compounds. They have also been shown to have sedative, antibacterial, and antibiotic activity. Examples of these compounds were discussed in CHEC(1984) and CHEC-II(1996).

5.07.12.2 Antibiotics

1,2,3-Thiadiazoles have been incorporated into β-lactams, carbapenems, and quinolone antibiotics <1996CHEC-II(4)289>. There have been no further developments in this area since the publication of CHEC-II(1996).

5.07.12.3 Neurodegenerative Diseases

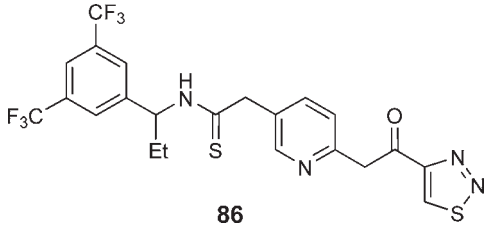
The 1,2,3-thiadiazole derivative **85** was found to be a potent and selective antagonist of the adenosine A_{2a} receptor <2004JME4291>.



85

5.07.12.4 Antiviral Agents

The 1,2,3-thiadiazole ring system has been incorporated into a number of compounds which have antiviral activity. The thioamide **86** is a potent inhibitor of cytomegalovirus (CMV) <2004BML3401>.



86

5.07.12.5 Polymers

The photochemical reactivity of 1,2,3-thiadiazoles has been utilized in the formation of cross-linked polymers <1996CHEC-II(4)289>. No new developments in this area have been reported since the publication of CHEC-II(1996).

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Biographical Sketch

David Wilkins obtained his Ph.D. in 1986 working with Professor A. H. Jackson and Dr. P. V. R. Shannon at University College Cardiff, Wales, working on the synthesis of the *Aspidosperma* indole alkaloids. He then did two years of postdoctoral studies with Professor P. M. Cullis at the University of Leicester, UK, working on the mechanism of thiophosphoryl-transfer reactions. In 1989, he joined the medicinal chemistry department at what was then Boots Pharmaceuticals in Nottingham (UK) and which became part of BASF Pharma in 1995. In 2001, he joined Key Organics Ltd., where he is currently employed as a principal chemist in the Contract Synthesis Department.

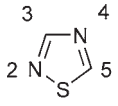
5.08
1,2,4-Thiadiazoles

D. J. Wilkins
Key Organics Limited Camelford, UK

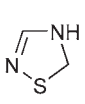
5.08.1 Introduction

This chapter is intended to update CHEC(1984) and CHEC-II(1996), concentrating on new preparations, reactions, and applications <1984CHEC(6)463, 1996CHEC-II(4)307>.

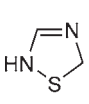
1,2,4-Thiadiazole **1** was first prepared and characterized in 1955 but products containing this ring system were described as early as 1821. The 1,2,4-thiadiazole nucleus is numbered as in structure **1**. The double bonds in the partially reduced rings are designated Δ^2, Δ^3, Δ^4, respectively and these compounds are called thiadiazolines. The fully reduced ring is termed a thiadiazolidine.



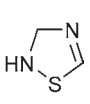
1



Δ^2



Δ^3



Δ^4

5.08.1.1 Reviews

The information published prior to 1980 has been extensively covered in the reviews by Kurzer <1965AHC(5)119, 1982AHC285>. CHEC(1984) and CHEC-II(1996) <1984CHEC(6)463, 1996CHEC-II(4)307> cover the period up to 1996. This chapter covers the period from 1996 to 2006.

A review on the chemistry of 1,2,4-thiadiazoles, which gives a critical discussion of methods of synthesis and is accompanied by experimental procedures, appeared in *Science of Synthesis* <2004HOU277>. An annual review of 1,2,4-thiadiazole chemistry appears in *Progress in Heterocyclic Chemistry* (Chapter 5.5).

5.08.2 Theoretical Methods

The 5-position of the nonprotonated 1,2,4-thiadiazole system was calculated to be the most reactive in nucleophilic substitution reactions using a simple molecular orbital method <1984CHEC(6)463>.

1,2,4-Thiadiazole has been subjected to AM1 calculations <1990JPR885>. The results were used to predict the degree of aromatic character of the heterocycle; some energetic and magnetic parameters were also calculated. Electrostatic potentials at N-2 and N-4 have been calculated for 3,5-dimethyl-1,2,4-thiadiazole; the results for this compound and other 5-substituted-3-methyl-1,2,4-thiadiazoles were used to predict binding to cortical muscarinic receptors <1990JME2052>. Since the publication of CHEC-II(1996), there have been no new reports of theoretical methods relating to 1,2,4-thiadiazoles.

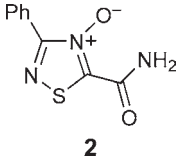
5.08.3 Experimental Structural Studies

5.08.3.1 Molecular Spectra

The number of X-ray structures published since the publication of CHEC-II(1996) has increased, underlining the importance of this technique in structure elucidation. The structure of a number of 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines has been determined by X-ray techniques and they are listed in **Table 1**. The first preparation of an *N*-oxide derivative of a 1,2,4-thiadiazole **2** has been reported. The X-ray structure of compound **2** shows that it has a nearly planar ring; this conformation is stabilized by hydrogen bonding with the carboxamide group <1999J(P1)2243>.

Table 1 X-Ray crystal data for 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines

Compound	*Reference*
3-Phenyl-1,2,4-thiadiazole-5-carboxamide 4-oxide	1999J(P1)2243
2-Ethyl-4-phenyl-5-phenylimino-1,2,4-thiadiazolidin-3-thione	1986BCJ987
5-(1-Imino-*N*-methylethylamino)-3-methyl-1,2,4-thiadiazole	1981AXB180
3-Benzylamino-4-*N*-benzyl-5-imino-4,5-dihydro-1,2,4-thiadiazole	2000JHC63
5-[(1-Aminoethylidene)amino]-3-chloromethyl-1,2,4-thiadiazole	1981AXB185
3-Cyano-1,2,4-thiadiazole-5-carboximidate	1984CB2681
5-Imino-Δ^3-1,2,4-thiadiazoline	1981JHC1309
3,5-Bis(diphenylamino)-1,2,4-thiadiazole	1985AXC1329
4-Ethyl-5-ethylimino-2-phenyl-3-phenylimino-1,2,4-thiadiazolidine	1980AXB2703
3,4-Diphenyl-5-(4-nitrophenyl)-Δ^2-1,2,4-thiadiazoline	1986JCM156



2

The bond lengths and angles determined by double resonance modulation microwave spectroscopy are shown in **Figure 1** <1984CHEC(6)463>.

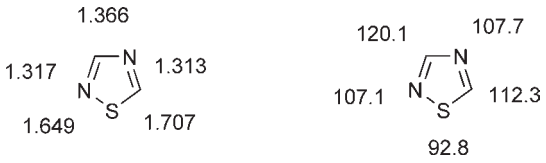


Figure 1 Bond lengths (Å) and angles (°) in 1,2,4-thiadiazole.

5.08.3.2 UV Spectra

1,2,4-Thiadiazole has an absorption maximum at 229 nm (log ε 3.7). The introduction of amino groups into the heteroaromatic nucleus results in a bathochromic shift. Thus, the maximum due to the 1,2,4-thiadiazole ring is moved to 247 nm in 5-amino and to 256 nm in 3,5-diamino-1,2,4-thiadiazole <1996CHEC-II(4)307>. No new publications relating to the ultraviolet (UV) spectra of 1,2,4-thiadiazoles have appeared since the publication of CHEC-II(1996).

5.08.3.3 IR Spectra

The use of infrared (IR) as a technique for structure determination is not very common in recent times. The reviews by Kurzer <1965AHC(5)119, 1982AHC285> contain a table of IR spectral absorptions of 1,2,4-thiadiazoles which covers spectra published before 1982. Additional spectral data was published in CHEC(1984) <1984CHEC(6)463>.

The prominent IR peaks for 1,2,4-thiadiazoles were attributed as follows: to ring skeletal vibrations (1560–1590, 1490–1550 cm^{-1}), to ring breathing and CH-in-plane deformations (1215–1270, 1080–1185, 1020–1050 cm^{-1}), and to CH out-of-plane deformations (~735 and 795–860 cm^{-1}) <1982AHC285>.

5.08.3.4 NMR Spectra

^{1}H nuclear magnetic resonance (NMR) spectral data on 1,2,4-thiadiazoles appear throughout the literature. In general, the chemical shifts of the protons in 1,2,4-thiadiazoles are downfield from benzene, the C-3 proton being farther downfield than the C-5 proton. For example, the C-5 proton in 3-phenyl-1,2,4-thiadiazole resonates at δ 9.9 ppm whereas the C-3 proton in 5-phenyl-1,2,4-thiadiazole resonates at δ 8.66 ppm <1996CHEC-II(4)307>.

The relationship between the structure of 1,2,4-thiadiazolidines and their ^{1}H NMR spectral solvent effects has been studied by measurement of the NMR chemical shift differences ($\Delta\nu$) of 39 derivatives in various solvents (C_6D_6, CCl_4); for methyl or methylene groups attached to an sp^2-hybridized nitrogen, $\Delta\nu$ correlates linearly with Hammett σ constants and for those attached to an sp^3-hybridized nitrogen, with Taft σ° constants <1982AHC285>.

^{13}C NMR spectral data has appeared more widely in the literature. The ^{13}C NMR chemical shifts for a variety of 1,2,4-thiadiazole and 1,2,4-thiadiazolidine derivatives are listed in **Table 2**.

Table 2 ^{13}C NMR spectral data for 1,2,4-thiadiazoles and 1,2,4-thiadiazolidines

Compound	*C-3* (δ, *ppm*)	*C-5* (δ, *ppm*)	*Reference*
2-Methyl-5-phenyl-1,2,4-thiadiazol-3(2*H*)-one	165.8	177.0	1984J(P1)75
5-Cyano-3-phenyl-1,2,4-thiadiazole	174.5	159.3	1999J(P1)2243
3,5-Diphenyl-1,2,4-thiadiazole	188.5	173.3	2000JHC63
3-Azido-5-phenyl-1,2,4-thiadiazole	155.8	168.1	1986CC800
3-Amino-5-phenyl-1,2,4-thiadiazole	171.0	185.7	1986CC800
5-Cyano-3-phenyl-1,2,4-thiadiazole-4-oxide	161.2	136.2	1999J(P1)2243
3-Ethoxycarbonyl-5-methylimino-4-phenyl-1,2,4-thiadiazoline	148.9	162.3	1991JHC333
4-Methyl-5-phenylimino-3-(*p*-toluenesulfonyl)-1,2,4-thiadiazoline	154.9	161.8	1991JHC333
4-Methyl-5-methylimino-3-(*p*-toluenesulfonyl)-1,2,4-thiadiazoline	155.5	161.9	1991JHC333
3,5-Bis(ethoxycarbonylamino)-1,2,4-thiadiazole	158.2	176.8	1989M997
4-Methyl-3-trichloromethyl-1,2,4-thiadiazolin-5-thione	154.4	200.9	1991JOC3268
4-Methyl-3-(*p*-toluenesulfonyl)-1,2,4-thiadiazolin-5-thione	157.5	199.2	1991JOC3268
4-Methyl-3-ethoxycarbonyl-1,2,4-thiadiazolin-5-thione	150.5	199.4	1991JOC3268
3,4-Diphenyl-5-(*p*-nitrophenyl)-Δ^2-1,2,4-thiadiazoline	155.6	74.5	1986JCM156

Solvent and concentration effects in nitrogen NMR studies can be very significant. The ^{15}N NMR chemical shifts for 1,2,4-thiadiazole **1** in ether solution (1:3 v/v) are +106 ppm for N-2, and +70 ppm for N-4. These values are shielded with respect to nitromethane. A similar degree of shielding is observed in the ^{14}N NMR spectra of 1,2,4-oxadiazole and in 1,2,5-thiadiazole <1984OMR215>.

^{15}N NMR has been used to study the mechanism of the photochemical reaction of 5-phenyl-1,2,4-thiadiazole (see Section 5.08.5.2). 5-Phenyl-1,2,4-thiadiazole-4-^{15}N and 3-phenyl-1,2,4-thiadiazole-2-^{15}N were synthesized. The ^{15}N NMR chemical shifts reported for the 4-position derivative was +302.2 ppm (acetone-d_6) and for the 2-position derivative +258.4 ppm ($CDCl_3$) relative to a reference of ammonia <2003JOC4855>.

5.08.3.5 Mass Spectra

The mass spectra of 3,5-disubstituted-1,2,4-thiadiazoles follow two general fragmentation pathways: these were discussed in CHEC(1984) <1984CHEC(6)463>.

A comparison between the positive and negative ion mass spectra of 3-amino-5-methylthio-1,2,4-thiadiazole and a study of the positive ion mass spectrum of 3-amino-5-methylthio-1,2,4-thiadiazole using ^{15}N isotopes appeared in CHEC-II(1996) <1996CHEC-II(4)307>. Since the publication of CHEC-II(1996), no new studies focusing on the mass spectra of 1,2,4-thiadiazoles have appeared.

5.08.4 Thermodynamic Aspects

5.08.4.1 Intermolecular Forces

1,2,4-Thiadiazole **1** is a liquid at room temperature. The effects of substituents on melting and boiling points can be summarized as follows: compounds with simple alkyl substituents in the 3- and 5-positions are oils; compounds with an aryl group in the 3- or 5-position are low-melting solids; and substitution of a second aryl group raises the melting point by approximately 60 °C. Compounds containing an amino, hydroxy, or mercapto group are usually relatively high-melting solids, which is attributed to hydrogen bonding. Halogeno compounds tend to be oils or low-melting solids <1996CHEC-II(4)307>.

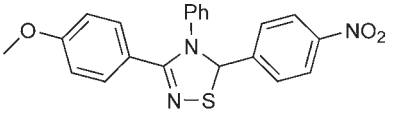
5.08.4.2 Stability and Stabilization

The heat of formation (ΔH_f) for 1,2,4-thiadiazole has been reported <1990JPR885> while other thermodynamic functions (entropy, heat capacity, free energy) have not been reported.

The thermal decomposition of some 3,5-disubstituted-1,2,4-thiadiazoles has been studied and some nonisothermal kinetic parameters have been reported <1986MI239>. Polarographic measurements of a series of methylated 5-amino-1,2,4-thiadiazoles show that thiadiazoles are not reducible in methanolic lithium chloride solution, while thiadiazolines are uniformly reduced at $E_{0.5} = -1.6 \pm 0.02$ V. This technique has been used to assign structures to compounds which may exist theoretically as either thiadiazoles or thiadiazolines <1984CHEC(6)463>. The photoelectron spectrum for 1,2,4-thiadiazole has been published <1996CHEC-II(4)307>.

5.08.4.3 Conformation

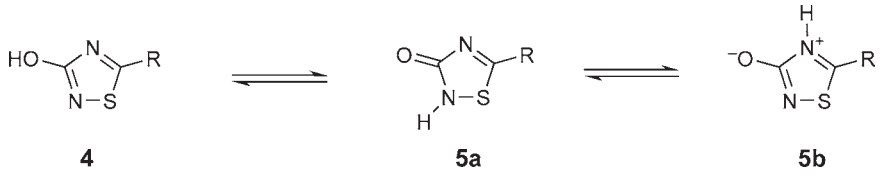
X-Ray crystallographic studies on 1,2,4-thiadiazoles (see **Table 1**) show the 1,2,4-thiadiazole ring to be essentially planar. The X-ray structure of 4-phenyl-5-(*p*-nitrophenyl)-3-(*p*-methoxyphenyl)-Δ^2-1,2,4-thiadiazoline **3** shows that the 1,2,4-thiadiazoline ring has a 30° fold around the S(1)–N(4) vector: atoms S-1, N-2, C-3, and N-4 are nearly coplanar <1986JCM156>.



3

5.08.4.4 Tautomerism

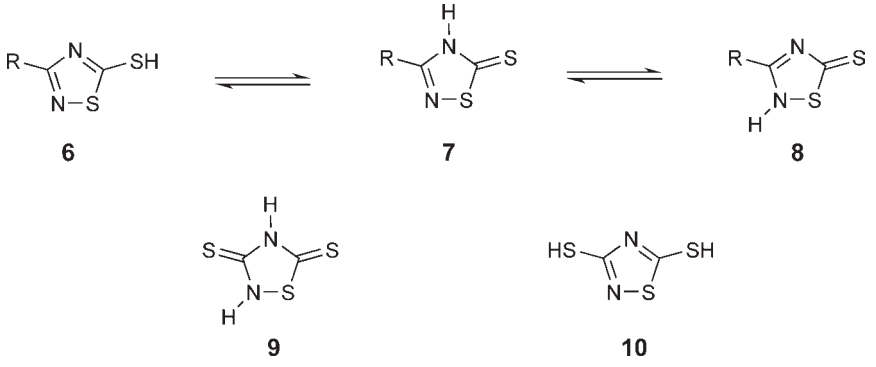
3-Hydroxy-1,2,4-thiadiazoles can exist in 3-tautomeric forms (**Scheme 1**). Chemical evidence suggests that the OH form **4** predominates; however, UV data suggest that the lactam form **5** is the major tautomer in ethanol <1996CHEC-II(4)307>.



4 **5a** **5b**

Scheme 1

3-Amino and 5-amino-1,2,4-thiadiazoles both exist predominantly in the amino forms. The IR spectrum of 5-mercapto-1,2,4-thiadiazole does not show a clear SH absorption as would be expected for structure **6** and therefore the thione tautomers **7** and **8** have been suggested (**Scheme 2**) . Similarly, IR evidence suggests that perthiocyanic acid exists as the dithione **9** as opposed to structure **10** <1984CHEC(6)463>.



6 **7** **8** **9** **10**

Scheme 2

5.08.5 Reactivity of Fully Conjugated Rings

5.08.5.1 General Survey

1,2,4-Thiadiazoles are generally quite stable to heat due to the aromatic nature of the ring. The parent compound reacts with acids and alkalis, and with oxidizing and reducing agents. Studies on the reactivity of 1,2,4-thiadiazole have been performed on 1,2,4-thiadiazoles which have substituents at the 3- and 5-positions, which are more stable toward acid, alkali, oxidizing agents, and reducing agents.

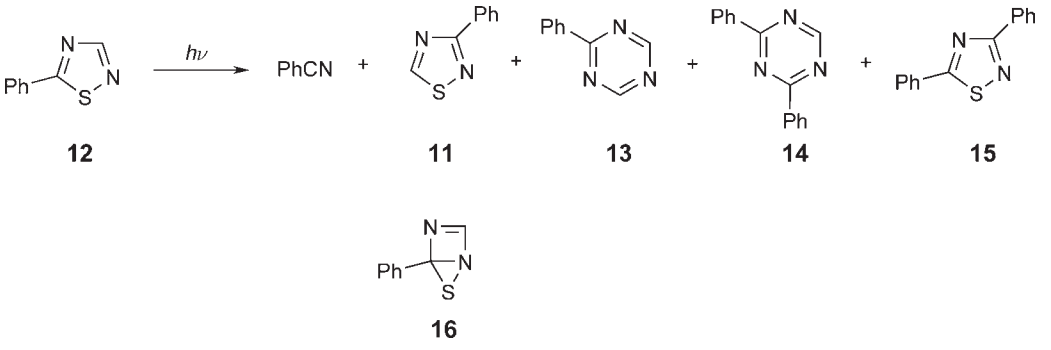
The 5-position in 1,2,4-thiadiazoles is the most reactive in nucleophilic substitution reactions. For example, halogens may be displaced by a variety of nucleophiles <1984CHEC(6)463>; however, halogens in the 3-position are inert toward most nucleophilic reagents.

Electrophilic reactions of 1,2,4-thiadiazoles are very limited. The parent base forms salts with mineral acids, forms a methiodide, and also gives addition compounds with heavy metal salts.

5.08.5.2 Photochemical and Thermal Reactions

As mentioned earlier, 1,2,4-thiadiazoles are generally quite stable to heat due to the aromatic nature of the ring. Irradiation of 3-phenyl-1,2,4-thiadiazole **11**, however, resulted in the formation of benzonitrile in 74% yield <2003JOC4855>.

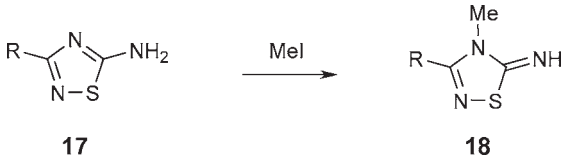
The photochemistry of 5-phenyl-1,2,4-thiadiazole **12** is more complicated. Irradiation of compound **12** also gave benzonitrile (58%) along with 3-phenyl-1,2,3-thiadiazole **11** (18%), phenyl-1,3,5-triazine **13** (4%), diphenyl-1,3,5-triazine **14** (2%), and 3,5-diphenyl-1,2,4-thiadiazole **15** (trace). 3-Methyl-5-phenyl-1,2,4-thiadiazole, when irradiated, affords a similar distribution of compounds. ^{15}N labeling studies suggested the mechanisms of the transformations all proceed via a common intermediate **16** (Equation 1) <2003JOC4855>.



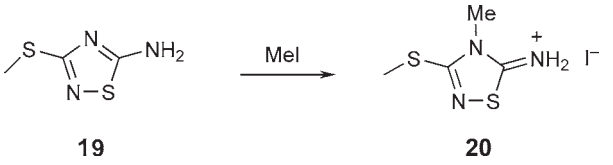
(1)

5.08.5.3 Electrophilic Attack at Nitrogen

1,2,4-Thiadiazoles are weak bases. They form salts with mineral acids and addition compounds with heavy-metal salts. Methylation of 5-amino-1,2,4-thiadiazoles **17** leads to the product of methylation at the 4-position **18** (Equation 2) <1996CHEC-II(4)307>. More recently, the reaction of the 3-methylthio derivative **19** with methyl iodide led to methylation at N-4 to afford product **20** (Equation 3) <2001CHE1005>.

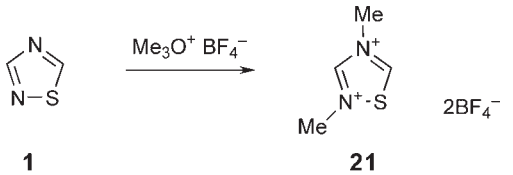


(2)



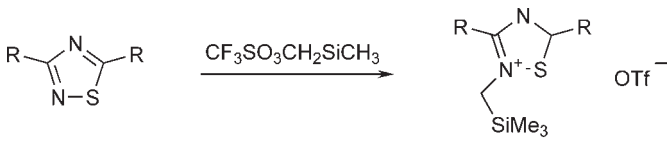
(3)

The diquaternary salt **21** of 1,2,4-thiadiazole **1** is obtained when trimethyloxonium tetrafluoroborate is used as the methylating agent (Equation 4) <1972JOC2259>.



(4)

Alkylation of 3,5-diaryl-1,2,4-thiadiazoles **22** with trimethylsilylmethyl triflate, in contrast to methyl iodide, occurs at N-2 to afford the salt **23** (Equation 5) and the quaternization at N-2 was confirmed by analysis of the ^{15}N NMR spectrum <1999J(P1)1709>.



(5)

22 **23**

The *N*-oxide of 1,2,4-thiadiazole has been reported, but this compound was synthesized by cyclization of suitable substituted precursors as direct oxidation would favor oxidation on the sulfur atom <1999J(P1)2243> (see Section 5.08.5.5).

5.08.5.4 Electrophilic Attack at Carbon

There have been no reports of electrophilic reactions at the ring carbons of 1,2,4-thiadiazole to date.

5.08.5.5 Electrophilic and Nucleophilic Attack at Sulfur

1,2,4-Thiadiazole 1,1-dioxides are known; they are not prepared by direct oxidation of the 1,2,4-thiadiazole ring, as ring cleavage occurs giving sulfate ion. They are only accessible by cyclization of precursors already incorporating the oxidized sulfur functions <1996CHEC-II(4)307>.

Many reactions have been reported where nucleophilic attack at sulfur has been proposed in the mechanism but since the publication of CHEC-II(1996) there have been no further reports of electrophilic attack of 1,2,4-thiadiazoles at the sulfur atom.

5.08.5.6 Nucleophilic Attack at Carbon

Nucleophilic attack at C-5 has been proposed as a reaction mechanism for a number of ring transformations and the instability of the parent compound toward alkalis probably involves initial attack at this carbon. Since the publication of CHEC-II(1996), there have been no definitive reports of nucleophilic attack at ring carbon atoms.

5.08.5.7 Nucleophilic Attack at Hydrogen

When the parent compound **1** is treated with a weak base such as K_2CO_3 in D_2O, the 5-monodeuterated derivative is formed. Since the publication of CHEC-II(1996), there have been no reports of nucleophilic attack at ring hydrogen atoms.

5.08.5.8 Reactions with Radicals and Electron-Deficient Species: Reactions at Surfaces

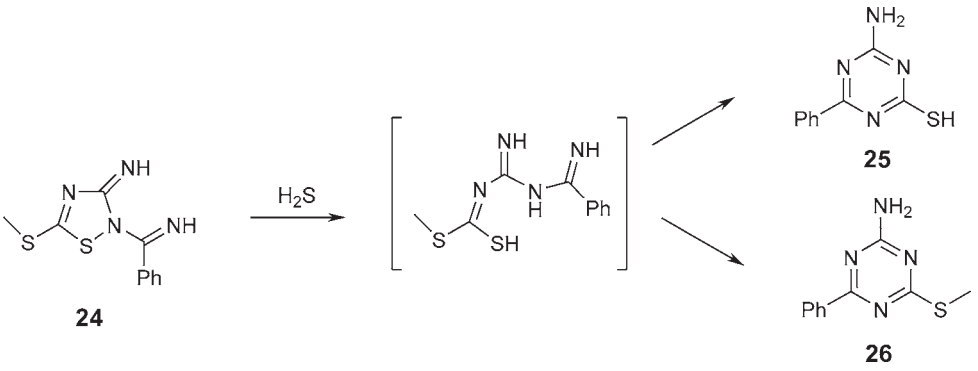
Reactions of 1,2,4-thiadiazoles with radicals and carbenes are virtually unknown. Catalytic hydrogenations and dissolving metal reductions usually cleave the N–S bond in a reversal of the oxidative cyclization procedures used in synthesis of 1,2,4-thiadiazoles (see Section 5.08.9.4).

5.08.6 Reactivity of Nonconjugated Rings

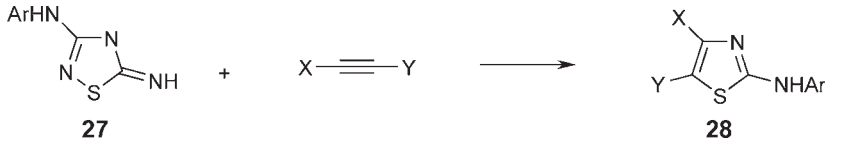
5.08.6.1 Isomers of Aromatic Compounds

Thiadiazolines are less stable compared to 1,2,4-thiadiazoles and this can be attributed to the loss of aromatic character. They are readily cleaved at the N–S bond under fairly mild conditions (H_2S in pyridine); in some cases, the product from ring cleavage can recyclize to give new heterocyclic ring systems. The 3-imino-1,2,3-thiadiazoline **24** when reduced with H_2S affords the two *S*-triazine derivatives **25** and **26** (**Scheme 3**) <1996CHEC-II(4)307>.

5-Imino-1,2,4-thiadiazoles such as **27** react with electron-deficient alkynes to afford arylimino thiazoles such as **28**. There has been some speculation as to the mechanism of this reaction, which may involve a 1,3-dipolar cycloaddition or a stepwise nucleophilic addition (Equation 6) <1996CHEC-II(4)307>.

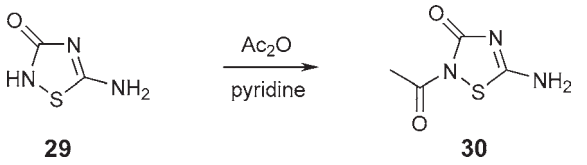


Scheme 3



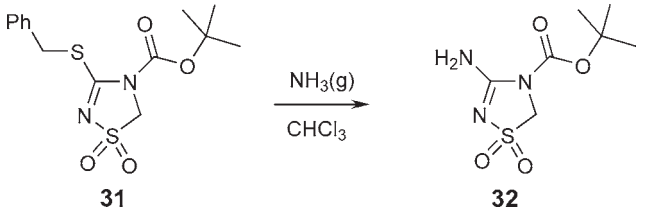
(6)

The 5-amino-1,2,4-thiadiazolidine **29** can be acylated with acetic anhydride in pyridine at N-2 to give the *N*-acyl derivative **30** (Equation 7) <1998JHC1435>.



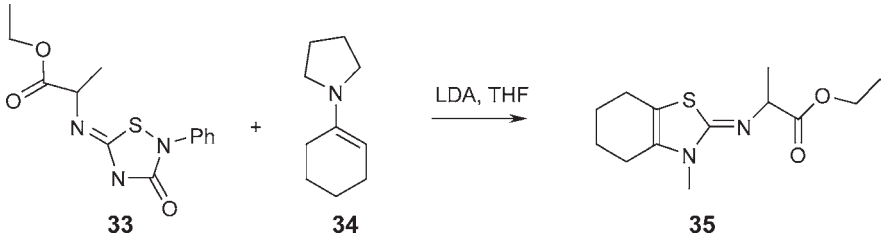
(7)

The thiobenzyl-substituted thiadiazolidine 1,1-dioxide **31** can undergo nucleophilic displacement when treated with ammonia gas to give the 3-amino derivative **32** (Equation 8) <1997AJC1027>.



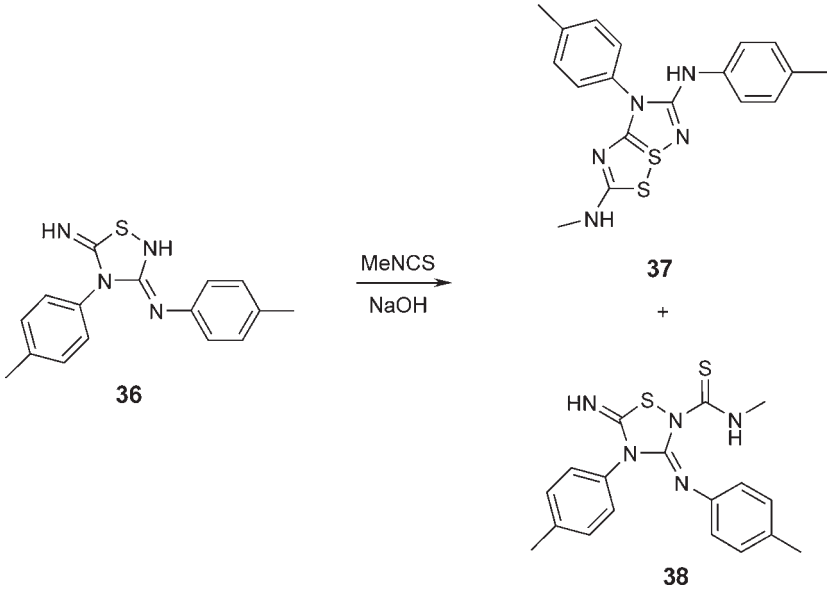
(8)

The thiazolidinone **33** reacts with the enamine **34** in the presence of a strong base to give the benzothiazole **35** (Equation 9) <1998EJO515>.



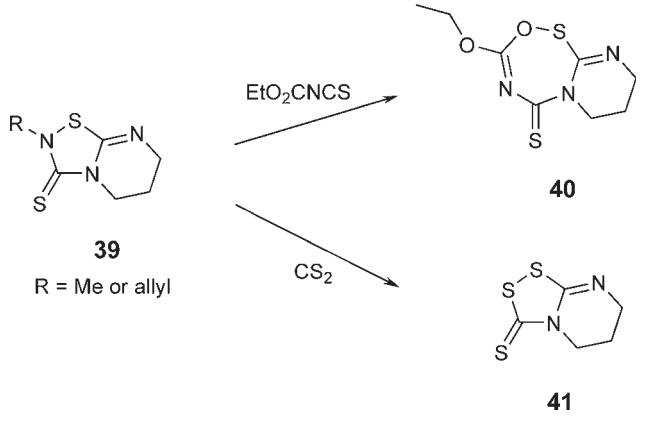
(9)

A similar transformation involving isocyanates instead of enamines has been reported. The imino thiadiazolidine **36** when reacted with methyl isocyanate affords a mixture of two compounds: the bicyclic derivative **37** and the thiourea derivative **38** (Equation 10) <1997IJB399>.



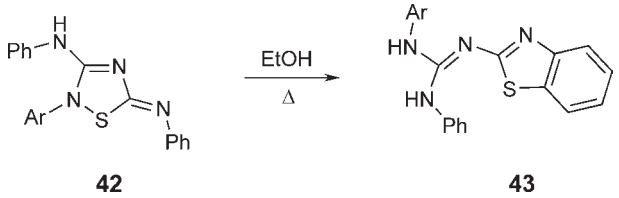
(10)

The thiadiazolopyrimidine derivative **39** reacts with ethoxycarbonyl isothiocyanate and carbon disulfide. In the former case the bicyclic derivative **40** is formed, and with the latter reagent the pyrimido dithiazole **41** is formed (**Scheme 4**) <2004JHC99>.



Scheme 4

Thiadiazolines and thiadiazolium salts can undergo a thermally promoted rearrangement to yield 2-guanidinobenzothiazoles. Thus the thiadiazoline **42** when heated in ethanol at reflux affords the benzothiazole **43** (Equation 11). There is evidence to suggest that this could be an electrophilic aromatic substitution reaction but a free radical mechanism was also proposed <2003SC2053>.



(11)

In CHEC-II(1996), a very similar acid-catalyzed conversion of 3,5-diamino-1,2,4-thiadiazolidines to 2-guanidinobenzothiazoles was reported, and this was described as an electrophilic aromatic substitution reaction <1996CHEC-II(4)307>.

5.08.6.2 Dihydro Compounds

Since the publication of CHEC-II(1996), there have been no reports describing compounds of this type.

5.08.6.3 Tetrahydro Compounds

1,2,4-Thiadiazolidines cannot be prepared by reduction of the corresponding thiadiazoles or thiadiazolines because cleavage of the ring would occur in preference to reduction as a consequence of the harsh conditions required. No preparations of 1,2,4-thiadiazolidines have been reported.

5.08.7 Reactivity of Substituents Attached to Ring Carbon Atoms

5.08.7.1 General Survey of Substituents on Carbon

The parent compound is sensitive to acids and decomposed by cold aqueous alkali. However, substituents in the 3- and 5-positions of 1,2,4-thiadiazoles exert a marked stabilizing influence on the ring toward acids, alkalis, oxidizing agents, and reducing agents.

In the 1,2,4-thiadiazole ring, the electron density at the 5-position is markedly lower than at the 3-position. 5-Halogen-substituted derivatives approach 2-halothiazoles and 4-halopyrimidines in susceptibility to nucleophilic substitution. Conversely, 3-halogen-substituted derivatives are relatively inert <1996CHEC-II(4)307>. Hydroxy and mercapto 1,2,4-thiadiazoles are generally distinctly acidic, whereas amino 1,2,4-thiadiazoles are weak bases. The greater basicity of 5-amino-1,2,4-thiadiazole relative to the 3-amino isomer appears to be anomalous. The diazonium salts of 5-amino-1,2,4-thiadiazoles are considerably more stable and reactive than those of the 3-isomers and are among the most reactive of their kind among heterocycles of all types <1965AHC(5)119>.

5.08.7.2 Benzenoid Rings

See Section 5.08.7.10 for discussion.

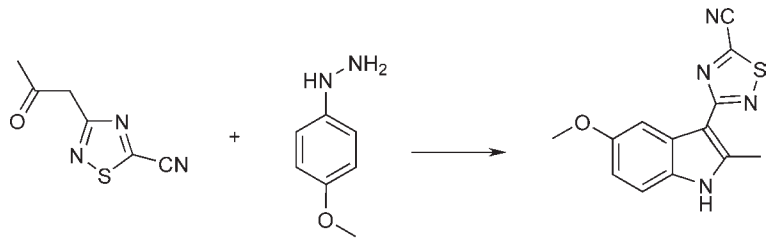
5.08.7.3 Alkyl Groups

Condensations of 5-methyl-substituted 1,2,4-thiadiazoles with aromatic aldehydes lead to 5-styrylthiadiazoles. With carboxylic acid esters, ethoxalyl derivatives are formed, and isoamyl nitrite produces the corresponding oximes <1982AHC285>. These reactions are restricted exclusively to the 5-methyl-substituted 1,2,4-thiadiazoles reflecting the greater reactivity of substituents in the 5-position compared to the 3-position in 1,2,4-thiadiazoles.

3-Chloromethyl-substituted 1,2,4-thiadiazoles can be substituted by nucleophiles (see CHEC-II(1996) for more details) <1996CHEC-II(4)307>.

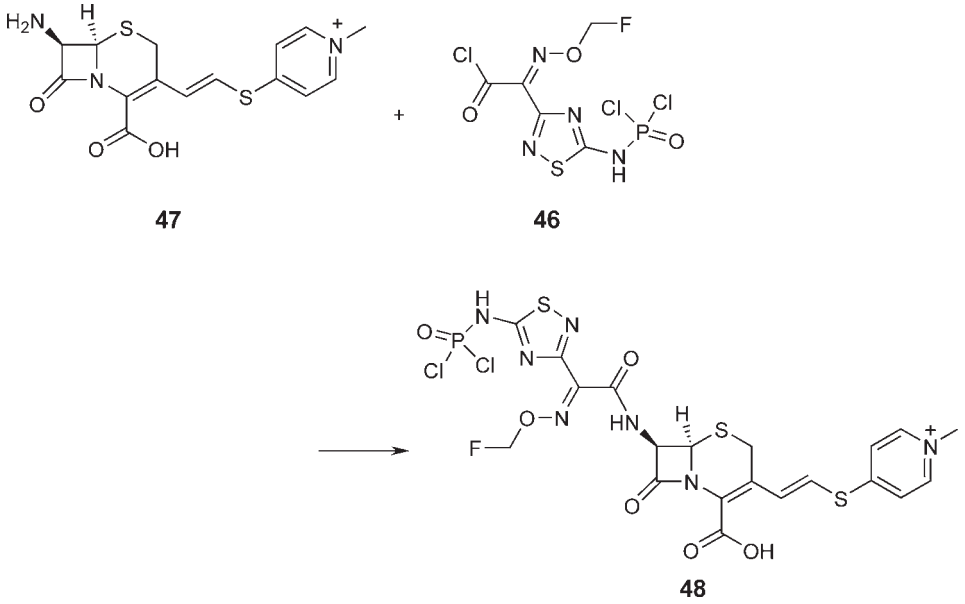
5.08.7.4 Other C-Linked Substituents

The 2-propanone 1,2,4-thiadiazole derivative **44** undergoes the Fisher indole synthesis to give a range of indoles **45** substituted with a 1,2,4-thiadiazole at the 3-position (Equation 12) <2000CPB160>.



44 45 (12)

The antibiotic cephalosporin derivative **48** has been reported; it was prepared by the coupling reaction of the 1,2,4-thiadiazole acid chloride derivative **46** with the amino cephalosporin derivative **47**. Similar cephalosporin derivatives were mentioned in CHEC-II(1996) (Equation 13) <2001JAN364>.



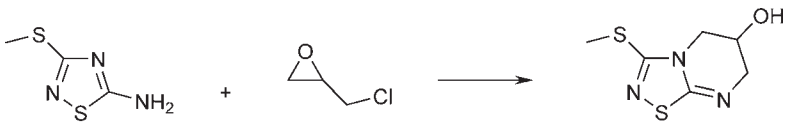
47 46 48 (13)

5.08.7.5 N-Linked Substituents

3-Amino-1,2,4-thiadiazoles are in general weaker bases than their 5-amino isomers and they form salts with mineral acids. In general, these derivatives are stable when treated with acids under mild conditions but are decomposed by hot alkali solutions. They can be acylated under standard conditions: in general, 5-amino isomers give monoacylated products, whereas 3-amino isomers give a mixture of mono- and diacyl derivatives. Treatment of both 3-amino- and 5-amino-1,2,4-thiadiazoles with sulfonyl halides gives only poor yields of the corresponding sulfonamides.

3-Amino- and 5-amino-1,2,4-thiadiazoles can be diazotized and they can be coupled under standard conditions <1996CHEC-II(4)307>.

The 3-thiomethyl-5-amino-1,2,4-thiadiazole **49** reacts with epichlorohydrin to afford the pyrimidino-1,2,4-thiadiazole **50** (Equation 14) <2001CHE1005>.



49 50 (14)

5.08.7.6 O-Linked Substituents

Hydroxy-1,2,4-thiadiazoles are acidic compounds that are generally more acidic than nitrophenol but less acidic than 2,4-dinitrophenol.

In general, 3-hydroxy-1,2,4-thiadiazoles react with hard nucleophiles (acid chlorides, sulfonyl chlorides) at the oxygen atom, whereas soft nucleophiles (isocyanates, acid anhydrides) react at the N-2 position yielding 1,2,4-thiadiazolin-3-ones. Nucleophiles react at the N-4 position of 5-hydroxy-1,2,4-thiadiazoles <1996CHEC-II(4)307>. There have been no new publications on O-linked substituents since the publication of CHEC-II(1996).

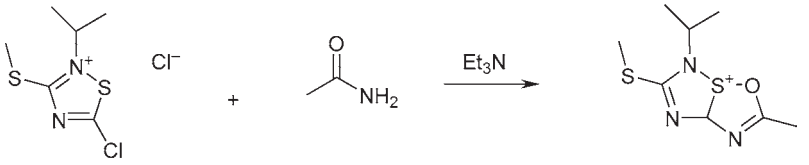
5.08.7.7 S-Linked Substituents

Mercapto-1,2,4-thiadiazoles exist as an equilibrium of tautomers with the equilibrium favoring the thione tautomer. They are acidic with a pK_a of around 5. A variety of methylating agents (e.g., diazomethane, dimethyl sulfate and methyl iodide) give S-methylated products and no N-methylation has been observed. They are readily oxidized to sulfoxides and sulfones with either *m*-chloroperbenzoic acid or hydrogen peroxide in acetic acid <1996CHEC-II(4)307>. There have been no new publications on S-linked substituents since the publication of CHEC-II(1996).

5.08.7.8 Halogen Atoms

The enhanced reactivity of 5-halogeno-1,2,4-thiadiazoles over 3-halogeno-1,2,4-thiadiazoles has been mentioned before (see Section 5.08.7.1). Nucleophilic substitution at this center is a common route to other 1,2,4-thiadiazoles, including 5-hydroxy, alkoxy, mercapto, alkylthio, amino, sulfonamido, hydrazino, hydroxylamino, and azido derivatives. Halogens in the 3-position of 1,2,4-thiadiazoles are inert toward most nucleophilic reagents, but displacement of the 3-halogen atom can be achieved by reaction with sodium alkoxide in the appropriate alcohol <1996CHEC-II(4)307>.

5-Chloro-3-methylthio-1,2,4-thiadiazol-2-ium salts **51** have undergone nucleophilic displacement with a variety of nitrogen and carbon nucleophiles to give bicyclic compounds such as **52**. The substitution reaction and cyclization with acetamide is carried out in the presence of triethylamine (Equation 15) <2003HAC95>.



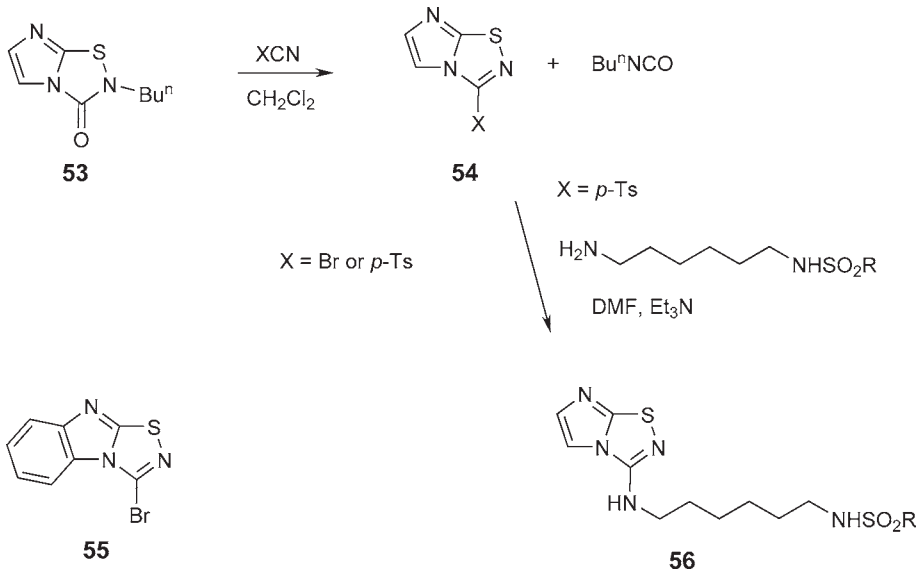
51 **52** (15)

5.08.7.9 Metals and Metalloid-Linked Substituents

Metal derivatives of 1,2,4-thiadiazoles have not been reported, presumably, because of their instability toward bases.

5.08.7.10 Fused Heterocyclic Rings

Reactions of benzimidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-ones with isocyanates, isothiocyanates, carbon disulfide, aryl cyanates, acetylenedicarboxylates, and enamines were covered in CHEC-II(1996). A further paper has subsequently appeared which discusses the reactions of imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-ones. Reaction of the imidazo[1,2-*d*][1,2,4]thiadiazol-3(2*H*)-one **53** with either cyanogen bromide or *p*-toluenesulfonyl cyanide afforded the imidazo[1,2-*d*][1,2,4]thiadiazole **54** via an exchange reaction. The analogous benzimidazo tricyclic 1,2,4-thiadiazole **55** can undergo nucleophilic substitution quite readily with a variety of nucleophiles such as dimethylamine, diethyl malonate, and alcohols: the bicyclic derivative **54**, X = Br, was not as versatile. The 3-*p*-tosyl-substituted derivative **54**, X = *p*-tosyl, did undergo nucleophilic substitution with a variety of diamines to give compounds such as **56** (**Scheme 5**). Compounds like **56** have been investigated as cysteine protease inhibitors (see Section 5.08.12) <2005JOC6230>.



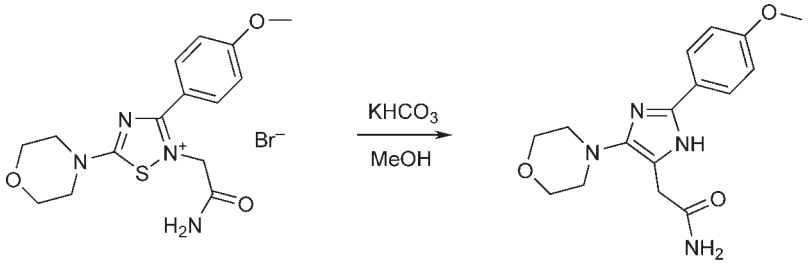
53 54 55 56

Scheme 5

5.08.8 Reactivity of Substituents Attached to Ring Heteroatoms

5.08.8.1 Substituents Attached to Ring Nitrogen Atoms

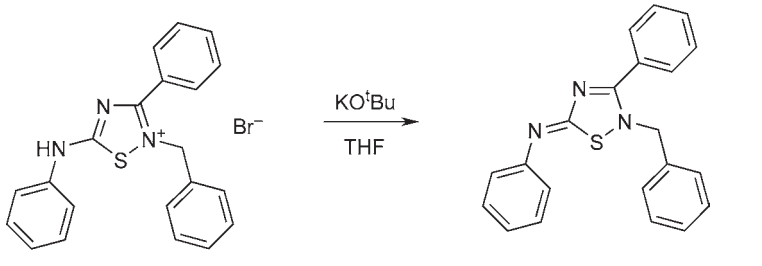
N-4-Phenacyl 1,2,4-thiadiazolium salts, which are usually prepared by reacting phenacyl bromide with 5-amino-1,2,4-thiadiazole, undergo internal cyclization to give fused imidazole derivatives <1996CHEC-II(4)307>. This work has been extended to give a novel method of preparing imidazoles with a substitution pattern that would be difficult to achieve with current methods of synthesis. 2-Substituted-1,2,4-thiadiazolium salts **57** when treated with a mild base undergo a facile desulfurization ring transformation to afford imidazoles **58** (Equation 16) <1997JOC3480>.



(16)

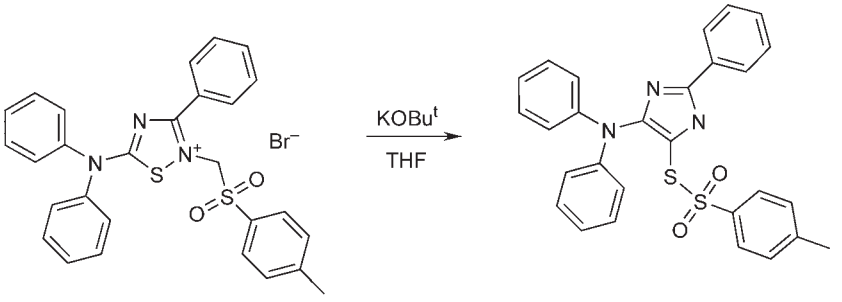
57 **58**

The benzyl 1,2,4-thiadiazolium salt **59** can be isomerized to the 5-imino-1,2,4-thiadiazolidine **60** when treated with a strong base like potassium *t*-butoxide (Equation 17) <1997ZOR1728>. If the 2-substituent is replaced with a tosylmethyl group and the 5-position substituent is a diphenylamino in place of an aniline such as compound **61**, then a rearrangement occurs to give an imidazole **62** (Equation 18) <1997ZOR1728>.



(17)

59 **60**



61 62 (18)

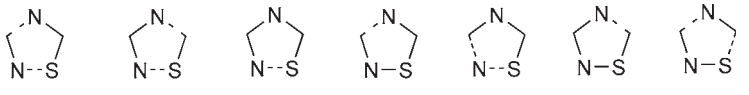
5.08.8.2 Substituents Attached to Ring Sulfur Atoms

There have been no reports describing reactions of this type in the literature to date.

5.08.9 Ring Synthesis from Nonheterocyclic Compounds

5.08.9.1 Introduction

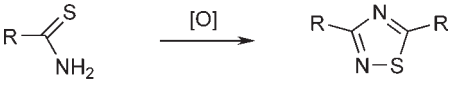
The classification of ring syntheses will follow the format used in CHEC-II(1996). In general, 1,2,4-thiadiazoles are prepared by the appropriate intra- or intermolecular ring-closing reactions. The syntheses of 1,2,4-thiadiazoles are classified according to the nature of the fragments from which the heterocyclic ring is built. The potential ring-closure routes are designated types **A** to **G**. Presumed intermediates in these reactions are not considered sufficient criteria for assignment of reaction type unless they have been isolated and their conversion to 1,2,4-thiadiazoles demonstrated.



A **B** **C** **D** **E** **F** **G**

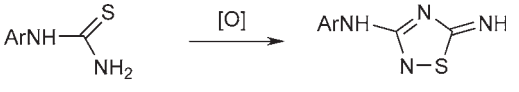
5.08.9.2 Type A Syntheses

The oxidation of thioamides **63** with a wide variety of oxidizing agents is a well-employed method for the synthesis of 3,5-disubstituted-1,2,4-thiadiazoles **64** <1982AHC285>. However, this method is limited mainly to arylthioamides. The most common oxidizing agents tend to be halogens, hydrogen peroxide, dimethyl sulfoxide (DMSO), and nitrous acid. Yields from these reactions are variable and depend on the thioamide, oxidant, and conditions used (Equation 19). By-products such as nitriles and isothiocyanates are usually formed.



63 **64** (19)

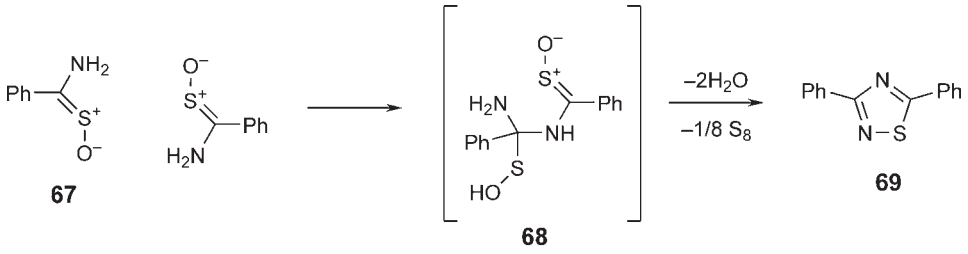
3,5-Diamino-1,2,4-thiadiazoles **66**, also known as Hector's bases, are the oxidation products from *N*-arylthioureas **65**; a large number of examples of this type of reaction are known. Typical oxidants that give good yields are acidic hydrogen peroxide, nitrous acid, and iron(III) chloride (Equation 20) <1996CHEC-II(4)307>.



65 **66** (20)

This reaction has been studied in more detail, and a study of the cyclization of thiobenzamide using DMSO as oxidant led to the following conclusions. There must be an oxygen donor oxidant present and it is essential to use a solvent of high polarity such as dimethyl formanide (DMF). An acid catalyst is essential and the counterion is also important: HCl and HBr are good catalysts but sulfuric acid, methanesulfonic acid, and trifluoroacetic acid do not give 1,2,4-thiadiazole products <2000JHC63>.

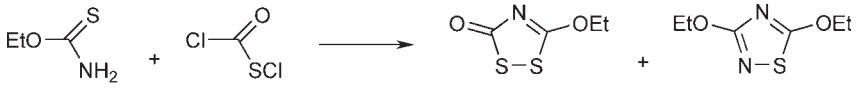
The thiobenzamide *S*-oxide **67** reacts in the presence of HCl without any oxidant present to give 3,5-diphenyl-1,2,4-thiadiazole **69** in almost quantitative yield. This has led to a proposal for the mechanism which is outlined in **Scheme 6**. The oxidation of the sulfur facilitates not only the formation of the N–S bond but also the elimination of sulfur. Acid catalysis may intervene in the step of oxygen transfer and in the elimination of water. Ring closure of the intermediate **68** may take place simultaneously with the first attack. This ring closure is facilitated by delocalization of the positive charge by phenyl or amino groups. This would explain why this reaction is not observed when R in structure **63** is an aliphatic group where no delocalization is possible <2000JHC63>.



Scheme 6

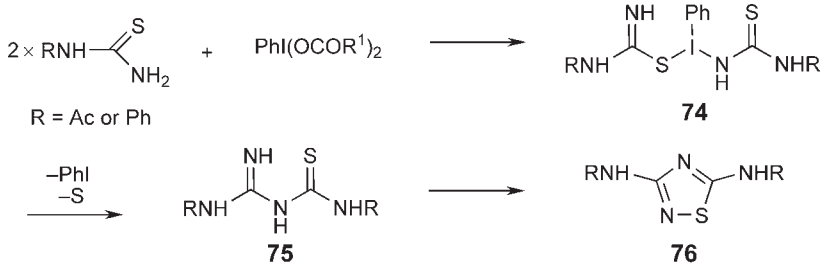
The use of the dehydrating agent 2-chloro-1,3-dimethylimidazolinium chloride (DMC) in combination with DMSO for the preparation of 1,2,4-thiadiazoles via a type A synthesis has been published. Excellent yields >90% are reported along with a mechanism for the transformation <1999JOC6989>.

The reaction of *O*-ethyl carbamate **70** with chlorocarbonylsulfenyl chloride **71** affords a mixture of either 3-ethoxy-1,2,4-dithiazolin-5-one **72** or 3,5-diethoxy-1,2,4-thiadiazole **73**. The distribution of the products is very much dependent on the reaction solvent: diethyl ether gives mainly dithiazolin-5-one **72** whereas chloroform favors the 1,2,4-thiadiazole **73** (Equation 21) <1996JOC6639>.



(21)

The oxidation of acetylthiourea and phenylthiourea to afford the corresponding 1,2,4-thiadiazoles has been reported using [bis(acyloxy)iodo]arenes as the oxidants. The proposed mechanism involves the formation of a polyvalent iodine compound **74**. After the elimination of iodobenzene, the 1,6-diphenyl-dithioformamidine **75** is formed, which is set up to undergo a further oxidation to give the bis 3,5-diamino-1,2,4-thiadiazole **76** (**Scheme 7**) <2003T7521>.

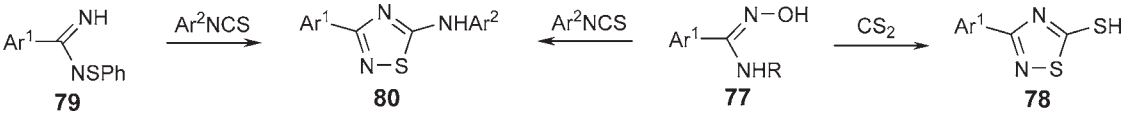


Scheme 7

The preparation of 3,5-bis(β-D-glycopyranosyl)-1,2,4-thiadiazoles has been accomplished via the oxidation of the corresponding acylated *C*-(β-D-glycopyranosyl)thioformamides with potassium and sodium dithionite. The synthesis is completed by a Zemplen deacylation. This is an interesting extension to a type A synthesis which has previously only been suitable for arylthioamides <2001T5429>.

5.08.9.3 Type B Syntheses

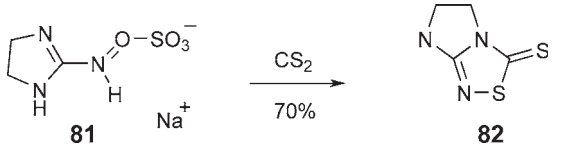
Type B syntheses are characterized by the reaction of an amidoxime **77** with carbon disulfide to afford 5-mercapto-1,2,4-thiadiazoles **78**. The corresponding 5-amino derivatives **80** are obtained from the reaction of *N*-sulfenylamidines **79** with arylisothiocyanates (**Scheme 8**) <1996CHEC-II(4)307>.



Scheme 8

Amidines and cyclic amidines are also converted into 1,2,4-thiadiazoles by reaction with isothiocyanates, iminosulfenyl chlorides, di- and trichloromethyl sulfenyl chlorides, and carbon disulfide in the presence of sulfur. Ureas, thioureas, guanidines, carbodiimides, and cyanimides react with chlorocarbonylsulfenyl chloride to produce 1,2,4-thiadiazol-5-one derivatives in another example of a type B synthesis <1996CHEC-II(4)307>.

In a more recent example of a type B synthesis, the imidazolium-*O*-sulfate salt **81** reacts with CS_2 to afford the imidazo[2,1-*c*][1,2,4]thiadiazole **82** (Equation 22) <2003JOC4791>.

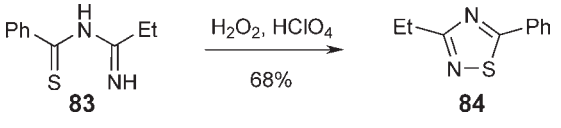


(22)

5.08.9.4 Type C Syntheses

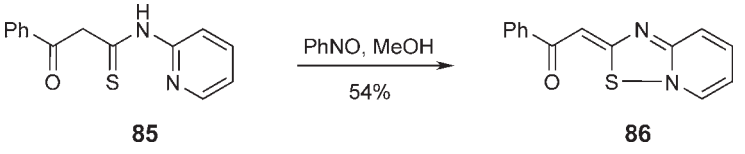
Type C syntheses are typified by the oxidative cyclization of amidinothiono groups, and this has become the basis of a versatile synthesis of 1,2,4-thiadiazoles. This type of reaction is known for its speed and absence of side reactions. The synthesis of unsymmetrical 3,5-disubstituted-1,2,4-thiadiazoles of unambiguous structure in high yields is possible by this method.

The oxidative cyclization of thioacylamidines **83** is one of the best methods for the synthesis of unsymmetrical 3,5-diaryl- or dialkyl-1,2,4-thiadiazoles **84** (Equation 23) <2004HOU277> . Typical oxidants used in the cyclization step include bromine, iodine, or nitric acid, and, more recently, hydrogen peroxide in the presence of perchloric acid has been used. N-Substituted thioacylamidines give rise to 1,2,4-thiadiazolium salts <1997JOC3480>.



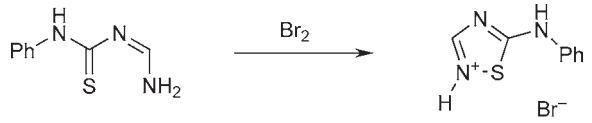
(23)

This type of method has been used to prepare 1,2,4-thiadiazolo[2,3-*a*]pyridine derivatives. The oxidative heterocyclization is exemplified by the formation of compound **86** from thioacetamide **85** using nitrosobenzene (Equation 24) <2004S2975>.



(24)

A variation using thioacylguanidines affords 5-substituted-3-amino-1,2,4-thiadiazoles. If an amidinothiourea is oxidized, 5-amino-1,2,4-thiadiazoles are obtained. A recent example of this type of synthesis has been reported: the amidinothiourea **87** was oxidized to the 1,2,4-thiadiazolium salt **88** on treatment with bromine (Equation 25) <2003SC2053>.

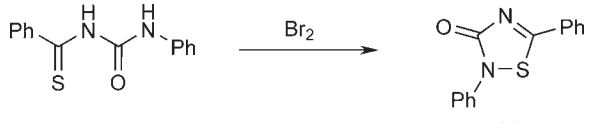


(25)

87 **88**

The oxidative cyclization of amidinothioureas, which is probably the most frequently used variation of this synthesis, provides 3,5-diamino-1,2,4-thiadiazoles with varying degrees of substitution.

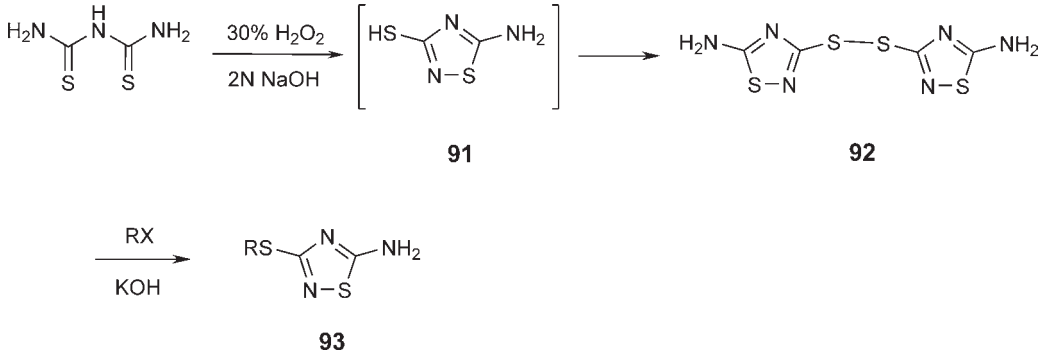
In another variation on a type C synthesis which yields 5-substituted-3-oxo-1,2,4-thiadiazolines, the reaction of arylthioamides with phenylisocyanate affords the arenethiocarboxamide **89**, which can then be transformed into product **90** by direct oxidation with bromine (Equation 26) <1996CHEC-II(4)307>.



(26)

89 **90**

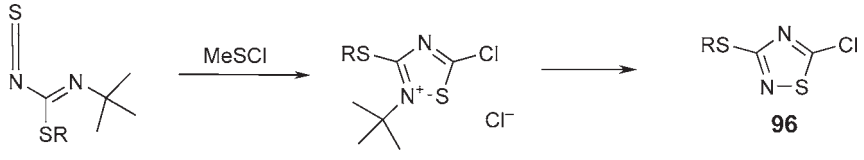
Oxidative cyclization of dithiobiuret under basic conditions provides bis(5-amino-1,2,4-thiadiazolyl)-3,3′-disulfide **92** via oxidative dimerization of the intermediate 5-amino-3-mercapto-1,2,4-thiadiazole **91**. However, alkylation of disulfide **91** under basic conditions gives the thioalkyl-1,2,4-thiadiazole **93** (**Scheme 9**) <2003H(60)1401>.



91 **92** **93**

Scheme 9

The preparation of 5-chloro-1,2,4-thiadiazol-2-ium chlorides **95** by treatment of formimidoyl isothiocyanates **94** with a twofold excess of methanesulfenyl chloride has been reported in an unusual variation of a type C synthesis. These salts show interesting chemical behavior toward several nitrogen and carbon nucleophiles. The nature of the N-substituent determines the stability of the salt **95**. When the substitutent on nitrogen is *t*-butyl, the salt **95** decomposes readily in solution to give the 5-chloro-1,2,4-thiadiazole **96** (**Scheme 10**) <2003HAC95>.

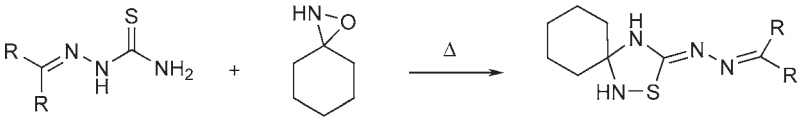


94 **95** **96**

Scheme 10

5.08.9.5 Type D Syntheses

Type D synthesis, where the 3,4-CN bond is being formed, involves the reaction of thiosemicarbazones of aldehydes, ketones, and esters **97** with 3,3-pentamethyleneoxaziridine **98** to afford 5-imino-3,3-pentamethylene-1,2,4-thiadiazolidines **99** (Equation 27). *N*-Acylthioureas also undergo this transformation but, whereas this reaction is fairly general for thiosemicarbazones, only acetyl and benzoyl thioureas give 1,2,4-thiadiazolidines <1996CHEC-II(4)307>. There have been no new reports of type D syntheses since the publication of CHEC-II(1996).



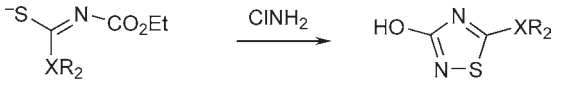
97 **98** **99**

R = alkyl

(27)

5.08.9.6 Type E Syntheses

In this method, the 1,2-N–S bond and the 2,3-N–C bond are formed. This is a useful method for the preparation of 3-hydroxy- or 3-amino-5-substituted-1,2,4-thiadiazoles starting from either an ethoxycarbonyl or a cyano thioiminocarbonate. Thus the condensation reaction of the ethoxycarbonyl thioiminocarbonate **100** with chloramine at low temperatures affords 3-hydroxy-5-substituted-1,2,4-thiadiazoles **100** (Equation 28) <2004HOU277>.



100 **101**

X = O or N

(28)

In another variation of a type E synthesis, thioamides or thioureas condense with *N*,*N*-dimethylacylamide dimethyl acetal to give imino compounds which react with amino-transfer reagents like hydroxylamine-*O*-sulfonic acid and mesitylsulfonyloxyamine (MSH) to give 3,5-substituted-1,2,4-thiadiazoles in excellent yields <1996CHEC-II(4)307>.

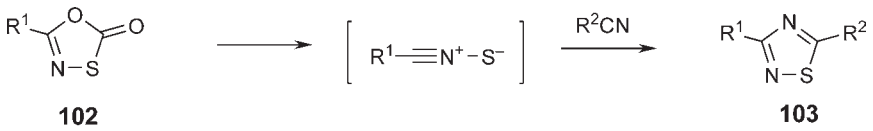
There have been no new reports of type E syntheses since the publication of CHEC-II(1996).

5.08.9.7 Type F Syntheses

Type F syntheses form the 4,5-N–C bond. There are very few references to this type of synthesis: for the few examples that are known see CHEC-II(1996). There have been no new reports of type F syntheses since the publication of CHEC-II(1996).

5.08.9.8 Type G Syntheses

Type G syntheses are typified by the 1,3-dipolar cycloaddition reactions of nitrile sulfides with nitriles. Nitrile sulfides are reactive 1,3-dipoles and they are prepared as intermediates by the thermolysis of 5-substituted-1,3,4-oxathiazol-2-ones **102**. The use of nitriles as dipolarophiles has resulted in a general method for the synthesis of 3,5-disubstituted-1,2,4-thiadiazoles **103** (**Scheme 11**). The thermolysis is performed at 190 °C with an excess of the nitrile. The yields are moderate, but are satisfactory when aromatic nitrile sulfides interact with electrophilic nitriles. A common side reaction results from the decomposition of the nitrile sulfide to give a nitrile and sulfur. This nitrile then reacts with the nitrile sulfide to yield symmetrical 1,2,4-thiadiazoles <2004HOU277>. Excellent yields have been obtained when tosyl cyanide has been used as the acceptor molecule <1993JHC357>.

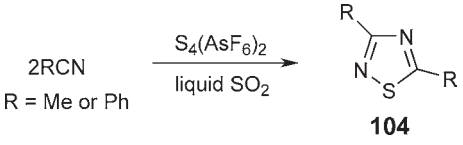


R^1 = aryl, alkyl, CO_2Et; R^2 = aryl, CO_2Et, Ts, CCl_3

Scheme 11

5.08.9.9 Miscellaneous Synthetic Methods

A novel high-yielding synthetic route to 3,5-disubstituted-1,2,4-thiadiazoles **104** has been reported which involves the reaction of nitriles with the arsenic complex $S_4(AsF_6)_2$ in liquid SO_2 (Equation 29) <1999CC1801>.



(29)

5.08.10 Ring Synthesis by Transformation of Other Heterocycles

5.08.10.1 Introduction

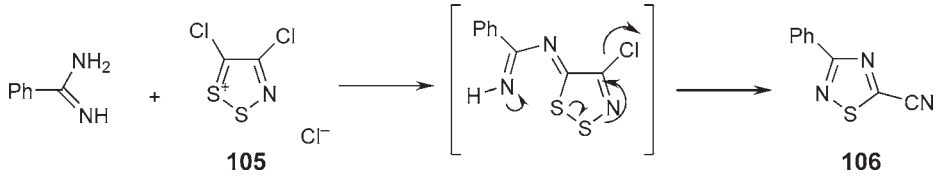
A number of ring systems have been converted into 1,2,4-thiadiazole derivatives. The most common include 5-imino-1,2,4-dithiazolidines, isoxazoles, oxadiazoles, and 5-imino-1,2,3,4-thiatriazolines. In general, a ring-opening reaction is followed by rotation and ring closure, or the heterocyclic ring may act as a masked 1,3-dipole which reacts with a suitable dipolarophile.

5.08.10.2 Dithiazolidine Rearrangements

A good method for the preparation of substituted 3,5-diamino-1,2,4-thiadiazoles is the rearrangement of dithiazolium cations with sodium azide <2004HOU277>. If the amino groups at the 3- and 5-positions are different, then a mixture of isomeric 3,5-diamino-1,2,4-thiadiazoles is obtained.

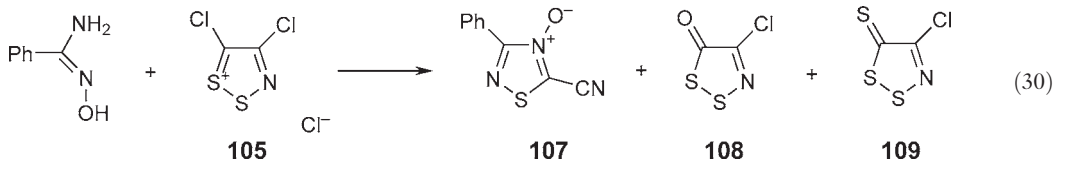
Other methods for the synthesis of 3,5-diamino-1,2,4-thiadiazoles discussed in Section 5.08.9.4 are only suitable for the synthesis of mono- or unsubstituted 3,5-diamino-1,2,4-thiadiazoles.

This methodology has been extended to dithiazolium cations **105** which have been reacted with benzamidine to afford 5-cyano-3-phenyl-1,2,4-thiadiazole **106** in low yield (23%; **Scheme 12**) <1999J(P1)2243>.



Scheme 12

If benzamidine is replaced by benzamidoxime, then the 4-oxide derivative **107** is obtained as a minor product (8%) together with 4-chloro-1,2,3-dithiazol-5-one **108** (32%) and the 5-thione **109** (15%) (Equation 30). The formation of the 4-oxide, as opposed to the isomeric 2-oxide, was confirmed by mass spectral and ^{15}N NMR data. The yield of the 4-oxide product could be improved by using an *O*-acyl benzamidoxime in place of benzamidoxime <1999J(P1)2243>.

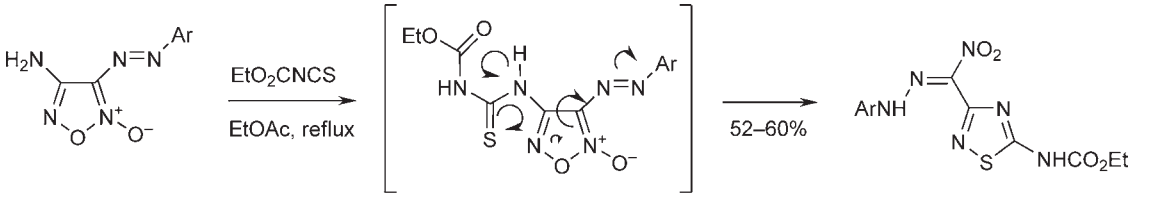


105 107 108 109 (30)

5.08.10.3 Oxazole and Oxadiazole Rearrangements

3-Amino derivatives of 1,2,4-oxadiazoles, isoxazoles, and 1,2,5-oxadiazoles interact with phenyl isocyanate to produce various 3-substituted 5-amino-1,2,4-thiadiazoles, via intermediate thioureides which can be isolated. The tendency to rearrange follows the order 1,2,4-oxadiazoles, isoxazoles, and 1,2,5-oxadiazoles <1996CHEC-II(4)307>.

A novel approach to 1,2,4-thiadiazoles **112** is based on the monocyclic and cascade rearrangement of 1,2,5-oxadiazole-2-oxides **111** <2004PAC1691>. Thus, *N*-oxides **110** upon treatment with ethoxycarbonyl isothiocyanate undergo cascade rearrangement to give 1,2,4-thiadiazoles **112** via intermediate **111** (**Scheme 13**).

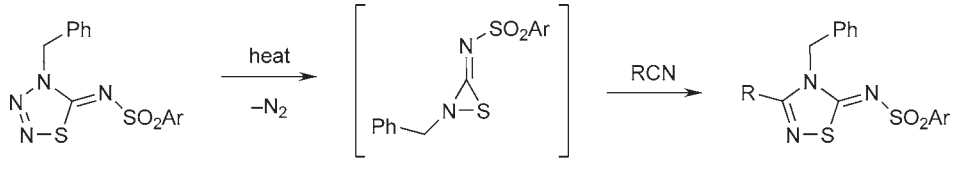


110 111 112

Scheme 13

5.08.10.4 Thiatriazoline Rearrangements

The thermolysis of 4-benzyl-5-sulfonyliminothiatriazolines **113** in the presence of a variety of nitriles yields 5-imino-1,2,4-thiadiazolines **115**. These reactions have been interpreted as proceeding via a thiaziridinimine intermediate **114** (**Scheme 14**) <1996CHEC-II(4)307>.



113 114 115

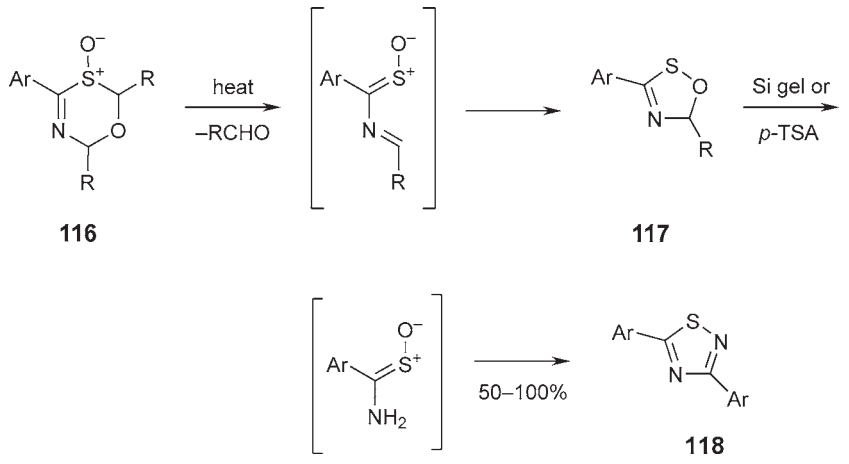
R = Me, Bn, Ph

Scheme 14

1,2,4-Thiadiazoles are also obtained when the thermolysis is carried out in the presence of isocyanates and carbodiimides <1996CHEC-II(4)307>. There have been no new reports of this type of rearrangement since the publication of CHEC-II(1996).

5.08.10.5 Miscellaneous Ring Transformations

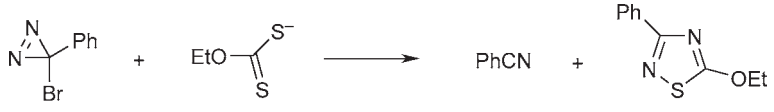
A novel method is reported to convert 1,3,5-oxathiazine-*S*-oxides **116** into 1,2,4-oxathiazoles **117** under thermal conditions. Lewis acid-promoted reaction of compounds **117** furnishes 1,2,4-thiadiazoles **118** and the final step is a type A synthesis (see Section 5.08.9.2) (**Scheme 15**) <2004HAC175>.



116 117 118

Scheme 15

Aryl halodiazarines **119** when reduced with potassium ethyl xanthate are reported to give 3-aryl-5-ethoxy-1,2,4-thiadiazoles **120** (13%) along with the expected product benzonitrile (87%) (Equation 31). A mechanism involving fragmentation of the diazirine **119** is proposed <1999TL29>.



119 **120** (31)

5.08.11 Practical Methods for the Synthesis of Derivatives

5.08.11.1 General Survey

The transformation of 1,2,4-thiadiazoles bearing a reactive substituent such as amino or halogen group in the 5-position is the most useful method for the synthesis of 5-substituted 1,2,4-thiadiazole derivatives. The latter compounds can be reacted with nucleophiles to afford a wide range of derivatives; this is not the case for 3-halogen-substituted compounds.

The oxidation of thioacyl amidines and related compounds is a versatile ring-forming reaction which can furnish a range of 3- and 5-substituted 1,2,4-thiadiazoles (see Section 5.08.9.4). Other ring-forming reactions that can give specific types of derivatives are discussed in the following sections.

5.08.11.2 Parent Compound

The only synthesis of 1,2,4-thiadiazole **1** was reported by Goerdler and co-workers in 1955, and details of this synthesis can be found in CHEC-II(1996) <1996CHEC-II(4)307>. The sensitivity of 1,2,4-thiadiazole **1** to ring-opening reactions means it is not a suitable starting material for the preparation of other derivatives.

5.08.11.3 C-Linked Derivatives

The coupling of thioamides with a variety of oxidizing agents is a widely utilized method for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles (see Section 5.08.9.2). This method is not suitable for alkyl derivatives. 3,5-Dialkyl derivatives can be more effectively prepared from a suitably substituted thioacylamidine (see Equation 22), and this method allows a range of unsymmetrical derivatives to be prepared.

An alternative route to C-linked derivatives involves the 1,3-dipolar cycloaddition reaction of nitrile sulfides with nitriles which yields 3,5-disubstituted-1,2,4-thiadiazoles of unequivocal structure (see Section 5.08.9.8).

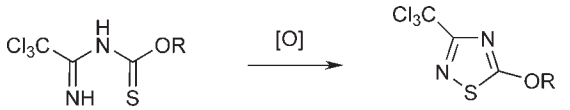
5.08.11.4 N-Linked Derivatives

The oxidation of amidinothioureas by a range of oxidizing agents to give 3,5-diimino derivatives is still one of the most versatile methods for the synthesis of N-linked derivatives (see Section 5.08.9.4). An alternative method which gives symmetrical derivatives is the oxidation of *N*-arylthioureas to produce 'Hector's bases' which readily isomerize to give 3,5-diamino-1,2,4-thiadiazoles (see Section 5.08.9.2).

A variety of 3-amino- and 3,5-diamino-1,2,4-thiadiazoles have been obtained by the treatment of iminocarbonates with chloroamine at low temperatures (see Equation (27), Section 5.08.9.6).

5.08.11.5 O-Linked Derivatives

The oxidation of *N*-alkoxythiocarbonylamidines **121** is a good method for the preparation of 5-alkoxy-1,2,4-thiadiazoles **122**, and this is a variation of a type C synthesis (see Section 5.08.9.4) (Equation 32) <1996CHEC-II(4)307>.

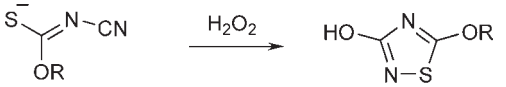


(32)

121 **122**

R = alkyl or aryl

3-Hydroxy and 3-hydroxy-5-alkoxy derivatives **124** are afforded by the oxidation of iminodicarbonates **123** with hydrogen peroxide (Equation 33).



(33)

123 **124**

Products of this type are also obtained from the reaction of iminodicarbonates with chloramine (see Equation (28), Section 5.08.9.6).

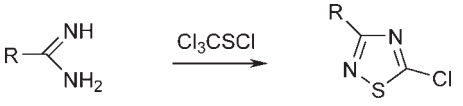
5.08.11.6 S-Linked Derivatives

The most convenient method of preparing thio derivatives of 1,2,4-thiadiazoles is by a type E synthesis. Treating dipotassium cyanodithioiminocarbonate with chlorine gas affords 5-thio-substituted 1,2,4-thiadiazoles. Alternatively, treatment with sulfur followed by chlorine gas affords 3,5-bisthio-substituted 1,2,4-thiadiazoles <1996CHEC-II(4)307>.

Amidines and amidoximes react with carbon disulfide and a mixture of carbon disulfide and sulfur to afford 5-mercapto-1,2,4-thiadiazole derivatives (see Section 5.08.9.3).

5.08.11.7 Halogen-Linked Derivatives

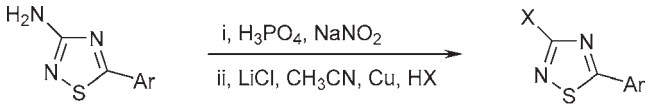
A useful method for the synthesis of 5-chloro-1,2,4-thiadiazoles **125** is the reaction of amidines with trichloromethylsulfenyl chloride (Equation 34).



(34)

125

3-Halo derivatives **127** have been obtained in moderate yields from the corresponding amines **126** via the Sandmeyer–Gatterman reaction (Equation 35) <1996CHEC-II(4)307>.



126 127 (35)

3-Chloro-1,2,4-thiadiazolin-5-ones can be prepared by reacting chlorocarbonylsulfenyl chloride with carbodiimides or cyanamides (see Section 5.08.9.3).

5.08.12 Applications and Important Compounds

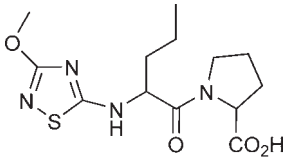
5.08.12.1 Introduction

1,2,4-Thiadiazoles have found applications as pharmaceuticals, fungicides, herbicides, bacteriocides, dyes, lubricant additives, and vulcanization accelerators. Cephalosporins incorporating a 1,2,4-thiadiazole ring into the side chain have good antibiotic and antimicrobial properties.

5-Ethoxy-3-trichloromethyl-1,2,4-thiadiazole has excellent pesticidal and fungicidal properties. It is a commercial product, whose most common trade name is Terrazole.

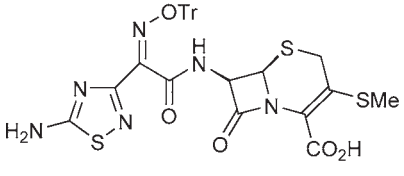
5.08.12.2 Biologically Active Compounds

A novel class of cathepsin B inhibitors has been developed with a 1,2,4-thiadiazole heterocycle as the thiol-trapping pharmacophore. The most potent inhibitor is compound **128** <2003BML5529>.

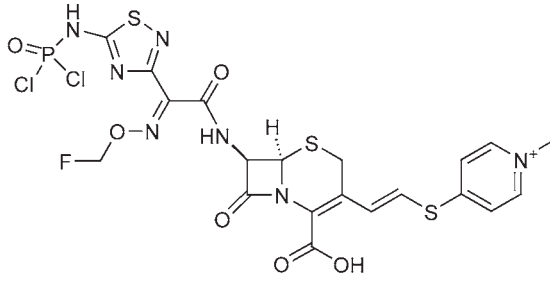


128

The 1,2,4-thiadiazole moiety has been incorporated in β-lactam antibacterials to modulate pharmacokinetic properties and more recently into a cephalosporin. The cephalosporin **129** displays a good balance of serum stability and *in vitro* activity. The cephalosporin derivative **48** (see Section 5.08.7.4) also shows good pharmacokinetic properties <2001JAN364>.

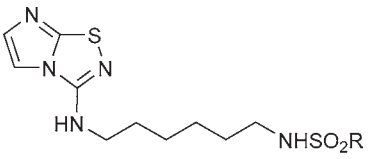


129



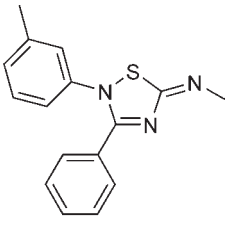
48

2,3-Diaryl-5-anilino-1,2,4-thiadiazoles are found to be potent and selective melanocortin-4-receptor (MC4) agonists for potential use for nerve regeneration and drug addiction <2003BMC185>. Compounds like **56** are being developed as cysteine protease inhibitors (see also Section 5.07.10) <2005JOC6230>.



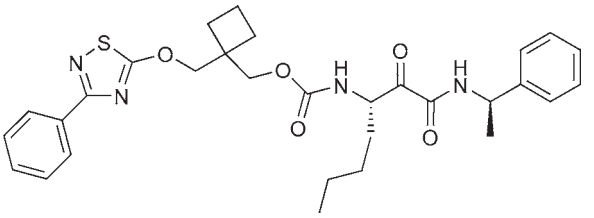
56

2,3-Diaryl-1,2,4-thiadiazoles such as **130** were found to be selective allosteric modulators of human adenosine A_3 receptors <2004JME663>.



130

Inhibitors of cysteine protease cathepsin K, for the treatment of osteoporosis, have been reported. The 1,2,4-thiadiazole derivative **131** showed nanomolar activity <2004JME5057>.



131

5.08.12.3 Other Applications

1,2,4-Thiadiazole derivatives have been found to be useful as additives for lubricating greases and as vulcanization agents <1996CHEC-II(4)307>. No new applications of this type have been reported since the publication of CHEC-II(1996).

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Biographical Sketch

David Wilkins obtained his Ph.D. in 1986 working with Professor A. H. Jackson and Dr. P. V. R. Shannon at University College Cardiff, Wales, working on the synthesis of the *Aspidosperma* indole alkaloids. He then did two years of postdoctoral studies with Professor P. M. Cullis at the University of Leicester, UK, working on the mechanism of thiophosphoryl-transfer reactions. In 1989, he joined the medicinal chemistry department at what was then Boots Pharmaceuticals in Nottingham (UK) and which became part of BASF Pharma in 1995. In 2001, he joined Key Organics Ltd., where he is currently employed as a principal chemist in the Contract Synthesis Department.

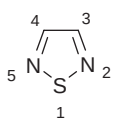
5.09
1,2,5-Thiadiazoles

P. A. Koutentis
University of Cyprus, Nicosia, Cyprus

5.09.1 Introduction

The chemistry of 1,2,5-thiadiazole and its derivatives has been previously covered in both CHEC(1984) <1984CHEC(6)513> and in CHEC-II(1996) <1996CHEC-II(4)355>. A major review which covers the synthetic chemistry of the ring system up to 2002 <2004HOU(13)297> and some broader review articles <1995SR299, 1999JPR99, 2002AHC71> have also appeared. Advances in the chemistry of 1,2,5-thiadiazoles have been annually reviewed in *Progress in Heterocyclic Chemistry* since 1988 <1989PHC(1)164>.

The numbering systems of mononuclear 1,2,5-thiadiazole **1** and 2,1,3-benzothiadiazole **2** are given below. 2,1,3-Benzothiadiazole, also referred to as benzo[1,2,5]thiadiazole, was often called piazthiole in the early literature. 1,2,5-Thiadiazole was also referred to as 2,5-diazathiophene. Both reduced and oxidized derivatives of 1,2,5-thiadiazole are known.



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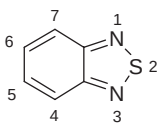


2

This chapter is intended to update the previous work concentrating on new preparations, reactions, and concepts. Reference is made to earlier chapters of CHEC(1984) and CHEC-II(1996), where appropriate.

5.09.2 Theoretical Methods

Density functional theory (DFT) and *ab initio* techniques were used to predict the molecular geometry and the physical and chemical properties of 1,2,5-thiadiazole and its derivatives. In general, DFT methods outperform *ab initio* and the inclusion of d-functions gave a more accurate description of bond lengths, bond angles, and dipole moments. Nevertheless, a very low occupancy, <10% of the expected value for sp^3d hybridization, of d-type functions suggested that they act as polarization functions rather than as d-orbitals of the valence shell <1997JPO33>. Electronic properties are best obtained using single-point calculations with methods that include electron correlation.

5.09.2.1 Molecular Calculations

1,2,5-Thiadiazole was used as a test compound in two studies on the development of optimal force field parameters for molecular modeling <1995MI251, 2003PCA248>. Molecular descriptors related to the physical properties and chemical reactivity of 1,2,5-thiadiazole were determined using the G3-B3 <2005JMT27> and CBS-QB3 <2006JGM455> model chemistries. The data could be useful for QSAR and QSPR studies (QSAR = quantitative structure–activity relationship; QSPR = quantum structure–property relationship). A recent QSAR study using topological substructural molecular descriptors (TOPS-MODE) with deductive estimation of risk from existing knowledge (DEREK) to formulate new alerts for skin sensitization predicted that 3-methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide **21** has a strong skin sensitization profile (see Section 5.09.4.4) <2003CRT1226, 2004JCI688>. Molecular modeling of rhodopsin and several constrained thiadiazole muscarinic receptors was carried out using the pharmacophore distance comparison (DISCO) technique <1999MI565>.

5.09.2.2 Molecular Geometry

Both *ab initio* and DFT computational studies accurately reproduce the molecular geometry of 1,2,5-thiadiazole **1** obtained from double resonance modulation microwave spectroscopy <1995ACS11, 1995JMT385, 1996SAA33, 1997JMT67, 2001JMT153, 2005JSP256>. A statistically modified approach which involved combining the results of both DFT and *ab initio* studies took account of both systematic and random errors and gave improved bond lengths with a very low mean standard deviation after correction (**Table 1**) <2003JMT239>.

Table 1 Calculated vs. experimental bond lengths (pm) for 1,2,5-thiadiazole <2003JMT239>

Computational method	*S–N*	*N–C*	*C–C*	*C–H*	*MSD*
(*Ab initio*) MP2/6-311G(3DF, 3PD)	161.7	134.5	140.0	107.9	0.0114
(DFT) B3LYP/6-311G(3DF, 3PD)	163.3	131.9	141.9	108.05	0.0045
Combined statistical approach	162.8	132.7	141.3	108.0	0.0022
Experimental <1984CHEC(6)513>	163.0	132.7	141.7	108.1	

MSD = mean standard deviation.

Analogous studies have appeared which predict the molecular geometry of 3,4-diphenyl-1,2,5-thiadiazole 1-monoxide **9** (HF/6-31G**) <2002JST195>, 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide **11** (HF/6-31G**), 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide **12** (HF/6-31G**) and 4-ethoxy-5-methyl-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (HF/6-31G**) <2001JST163>, 1,2,5-thiadiazole 1,1-dioxide (HF/6-31G**) <2001JMT41> and (HF/6-31G*) <1996JPO203>, 3,4-dimethyl- **23** (HF/6-31G**), 3-methyl-4-phenyl- **21** (HF/6-31G**), and 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **10** (HF/6-31G**) <1998JPO91>, 1,2,5-thiadiazoline (B3LYP/6-31G**) <2001JMT39>, 1,2,5-thiadiazolidine (B3LYP/6-31G**) <2001JMT201>, phenanthro[9,10-*c*]-1,2,5-thiadiazole 1,1-dioxide **51** (HF/6-31G**), and acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide **53** (HF/6-31G**) <2001JST157>, and even 1,2,5-thiadiazole oligomers (B3LYP/3-21G*) with up to six units <2003JMT67>.

Computational studies on intermolecular bonding interactions have also been performed. A DFT study concerning chalcogen-centered secondary bonding interactions (SBIs) involved in supramolecular association shows the strength of the interaction increases with the weight of the chalcogen. The most dominant contribution was from the donation of a lone pair of the nitrogen into the antibonding orbital of the chalcogen. 1,2,5-Thiadiazole **1** shows relatively weak SBIs owing to long intermolecular S···N contacts that are a little longer than the van der Waals contact <2005JA3184>.

5.09.2.3 Electronic Structures

Ab initio <1998PCA9906> and DFT <2003PCA4172, 2003JMT77> studies were tested for accuracy in computing the dipole moments of isomeric thiadiazoles. An accurate dipole moment was obtained for 1,2,5-thiadiazole **1** calculated at the MP2/6-31G** geometry using MP4/C1 $\mu_{calc} = 1.60$ D <1998PCA9906> while a DFT approach B3LYP/CBSB7 gave $\mu_{calc} = 1.53$ D <2003JMT77>, where $\mu_{expt} = 1.57$ D. Coupled Hartree–Fock (CHF) polarizabilities for 1,2,5-thiadiazole were also determined using finite-field MP2 and MP4(SDQ)/C1 <1998PCA9906> and DFT methods <2003PCA4172>.

Where μ_{expt} was not available, as in the case of the unknown 1,2,5-thiadiazole 1,1-dioxide, estimates were possible by comparing dipole moments calculated at both *ab initio* and DFT levels of theory with those derived from various types of charge distribution analysis such as Mulliken (MPA), NPA, or CHELPG. Both the MP2/6-31G*//HF/6-31G* <1996JPO203, 1997IJQ477> and B3LYP/6-31G*//HF/6-31G* <2001JMT41> methods provided good charge distributions for 1,2,5-thiadiazole 1,1-dioxide and reliable dipole moments μ_{MP2} 5.73 and μ_{DFT} 5.77 D, respectively.

The electronic nature of the NSN fragment was studied, using both *ab initio* and DFT methods, for a series of 1,2,5-thiadiazoles and compared to the established zwitterionic structure of naphtha[1,8-*cd*][1,2,6]thiadiazine **6** (**Figure 1**).

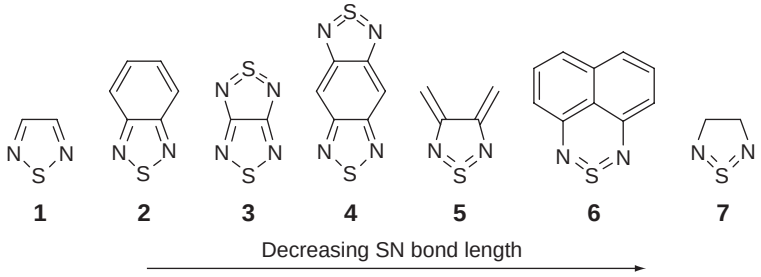


Figure 1 Comparison of S–N bond lengths as calculated by DFT.

The S–N bond length and charge distribution analysis supported the classical 'quinoidal' structure of both 1,2,5-thiadiazole **1** and 2,1,3-benzothiadiazole **2**. Nevertheless compounds **4–7** display significantly shorter S–N bonds accompanied by large charge separations and are therefore more ylidic in structure. Furthermore, DFT-calculated (B3LYP/6-31G*) S_0/T_1 splitting energies indicate that the systems are far from diradicaloid and decrease in the series **1** (97.2) > **3** (73.0) > **2** (50.0) > **7** (22.4) > **4** (20.1) > **6** (7.9) > **5** (4.4 kcal mol^{-1}) <1997JPO33>. The series follows the calculated stabilization energies derived from isodesmic reactions clearly indicating the transition from stable classical to less-stabilized nonclassical structures.

The lowest energy vertical $S_1 \leftarrow S_0$ ($\pi \rightarrow \pi^*$) transitions were calculated using *ab initio* CIS/6-31G* and by PM3 all valence electron PECI calculations based on DFT (B3LYP/6-31G*) optimum geometries are reported in **Table 2** <1997JPO33>. Vertical electronic transitions were also computed for various fused thiadiazoles using time-dependent density functional theory (TDDFT) <2004PCB2516, 2005JPH126>.

Table 2 Calculated *ab initio* vs. experimental lowest energy π–π* (nm) transitions for thiadiazoles **1** and **2** <1997JPO33>

Computational method[a]	**1**	**2**
CIS/6-31G*	202	266
PM3, PEC1 = 10	256	341
Experimental	254	311

[a]Based on DFT B3LYP/6-31G* optimum geometries.

The isotropic hyperfine tensor components (a^{iso}) have been accurately calculated using hybrid DFT for the bicyclic [1,2,5]thiadiazolo[3,4-*d*][1,3,2]-dithiazol-2-yl **32** <1996MRC913, 2000CPL409> and the tricyclic 1,2,5-thiadiazolo[3,4-*b*]-1,2,3-dithiazolo[3,4-*b*]pyrazin-2-yl **35** <2000CPL409> and are in good quantitative agreement with those determined experimentally by electron spin resonance (ESR) spectroscopy (see Section 5.09.3.5). A broader study involving SN radicals, which compared HF and DFT methods, supported the use of DFT using B3LYP basis sets for the determination of hyperfine coupling constants <2001PCA7615>.

5.09.2.4 Chemical Reactivity

The chemical reactivity of 1,2,5-thiadiazole **1** was predicted using DFT to calculate the net atomic charges and the Fukui functions f^+, f^-, and f° (**Table 3**). The unsubstituted thiadiazole was correctly shown to be relatively inert to electrophilic substitution and very reactive toward nucleophilic attack <1995JMT385, 1997JMT67>, the preferred site of attack being sulfur, carbon, or the ring proton depending on the nature of the attacking species. The large f^- value for sulfur implies that the sulfur atom of 1,2,5-thiadiazole **1** is chemically softer and therefore would be the site of attack by soft nucleophiles.

Table 3 The net charges and condensed Fukui functions for 1,2,5-thiadiazole **1** with C_{2v} symmetry <1997JMT67>

Atom	*Net charges*	f^+	f^-	f°
S	0.4067	0.2790	0.3842	0.3316
N	−0.2474	0.1332	0.1490	0.1411
C	−0.2140	0.1519	0.0770	0.1145
H	0.2580	0.0754	0.0818	0.0786

Analogous studies on various thiadiazolines <2001JMT39>, thiadiazolidines <2001JMT201>, thiadiazole 1-monoxides <2000TL3531, 2002JST195>, 1,1-dioxides <1998JPO91, 2000TL3531, 2001JMT41, 2001JST157>, thiadiazoline and thiadiazolidine 1,1-dioxides <2001JST163> have also appeared.

A local frontier orbital (LFO) study involving the variational method to analytically find appropriate combinations of valence atomic orbitals giving the maximum and minimum energies of the occupied and unoccupied LFOs, respectively, was employed to find the acidities of the conjugate cation of 1,2,5-thiadiazole **1** <1997PCA5593>. A later study adopted a projected reactive orbital (PRO) approach, which describes local reactivity better than frontier orbital theory in high-symmetry systems to predict the basicity of 1,2,5-thiadiazole **1** <2005PCA7642>.

5.09.3 Experimental Structural Methods

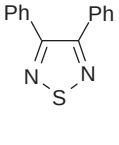
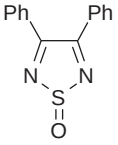
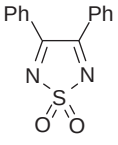
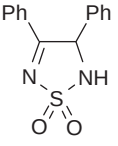
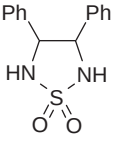
5.09.3.1 X-Ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

The molecular structure of both 1,2,5-thiadiazole **1** and 2,1,3-benzothiadiazole **2** were described in CHEC(1984) <1984CHEC(6)513>. Since the publication of CHEC-II(1996) <1996CHEC-II(4)355>, a large number of single crystal X-ray structures have been published for various monocyclic, fused, and related thiadiazoles.

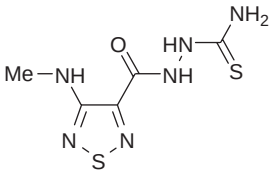
These include: a low-temperature single crystal structure for 2,1,3-benzothiadiazole **2** which showed short S–N bond lengths of 161.4 and 162.0 pm <2001JOC8954>, various substituted and fused 2,1,3-benzothiadiazoles including 4,7-dibromo <2003NCS555>, 4,7-diiodo <2002AXC373, 2004T2953>, 4,7-bis(thien-2-yl) <1995JA6791, 1996CM570>, 4,7-bis(thiaz-2-yl) <2005CC3183>, 4,7-bis(amino) <2001JOC8954>, and various substituted 4,7-bis(ethynyl) derivatives <2002JCM511, 2002JOC7813, 2001AXC751, 2002AXE1202, 2003JCD65>. Many metal complexes involving thiadiazole-bearing ligands were prepared including 3,4-di(2-pyridyl)-1,2,5-thiadiazole complexes with ruthenium <2002JCD2775>, thiadiazolo-fused porphyrazines complexed to metals and in free base form <2001MC45, 2003AGE5863, 2003CEJ4009, 2004CEJ5158, 2005IC8539>, 1,2,5-thiadiazole-3,4-dithiolate bound to copper <2003ICC565>, gold <2003ICC565>, iron <2002AXC240, 2002JMC3570>, and nickel <2001JMC2216, 2003POL2175, 2003POL2311, 2004IC2049>, 2,1,3-benzothiadiazoles bound to copper <1994IC1284, 1998JCD1499, 2001ICA53, 2001CGD191>, cobalt <2001MI371>, osmium, <1998JCD3501>, nickel, and silver <1996IC5120> via the ring nitrogen.

Furthermore, a series of single crystal X-ray diffraction studies were reported for several thiadiazole 1-monoxides and 1,1-dioxides, allowing a direct comparison in bond lengths and angles for an identical 3,4-substitution pattern (Table 4). The related fused phenanthro[9,10-*c*]-1,2,5-thiadiazole 1,1-dioxide **51** and acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide **53** have similar bond lengths to 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **10** <2001JST157>.

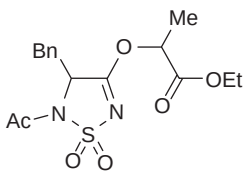
Table 4 Selected bond lengths (pm) of various 3,4-diphenyl-substituted thiadiazoles and related systems

	 **8**	 **9**	 **10**	 **11**	 **12**
S–N	163.5/163.0	169.8/169.0	166.8/166.8	166.1/164.5	164.9/164.0
N–C	132.7/134.2	128.4/128.1	129.1/128.7	128.7/147.6	148.2/147.5
C–C	143.5	150.6	153.6	152.8	156.1
C–C exocyclic	150.0/148.6	145.9	142.0/141.9		
S–O		147.3/147.6	147.0/146.6		
Reference	1976AX(B)1074	2002JST195	1998JPO91		2001JST163

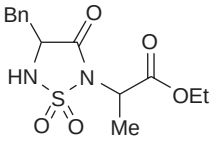
The crystal structure of 1-(4-methylamino-1,2,5-thiadiazole-3-carbonyl)thiosemicarbazide **13** showed a supramolecular architecture involving two N–H···O, three N–H···S hydrogen bonds and N···S electrostatic interactions <2003AXC491>. A structure of the semicarbazide complexed with 18-crown-6 has also appeared <2003JST129>. Thiadiazoline 1,1-dioxide **14** <1998TL7435>, thiadiazolidine 1,1-dioxide **15** <1999EJO2275>, the tetrahydro cyclopent[*c*][1,2,5]thiadiazole-1,3-dicarboxylate **16** <2003TL6709>, and the unusual perfluorothiadiazole **17** <1995CC1437> have also appeared.



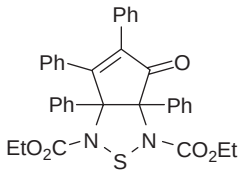
13



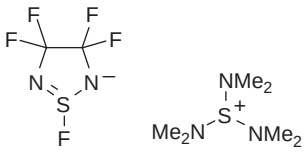
14



15



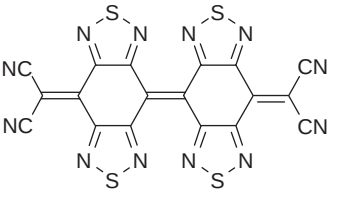
16



17

Structures have been provided for the following 1,2,5-thiadiazolyl radicals: [1,2,5]thiadiazolo[3,4-*d*][1,3,2]dithiazol-2-yl **32** <1999SCI261, 2001JMC1992>, 1,2,5-thiadiazolo[3,4-*b*]-1,3,2-dithiazolo[3,4-*b*]pyrazin-2-yl **34** <1998JA352>, and 1,2,5-thiadiazolo[3,4-*b*]-1,2,3-dithiazolo[3,4-*b*]pyrazinyl **35** <1999JA969> (see Section 5.09.3.5).

The bianthrone analogue **18** crystallizes as yellow plates from 1,2-dichloroethane (m.p. 351–357 °C (decomp.)) and as deep violet needles (m.p. 110–112 °C (decomp.)) from dichloromethane or as deep violet cubes (m.p. 84–86 °C (decomp.)) from benzonitrile solution <1997AGE2495>.

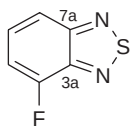


18

The two violet forms are both solvated. X-Ray structure analysis showed that the unsolvated yellow crystal adopts a doubly folded geometry while the violet cubes adopt a twisted conformation. Both structures owe their deformations to repulsive short N···N contacts. The central ethylene bond in the yellow conformer is completely planar (136.2 pm) while in the violet cube conformer the same bond is twisted 48.1° and much longer (138.8 pm).

5.09.3.2 NMR Spectroscopy

A detailed comparative analysis of the ^{1}H, ^{13}C, and ^{15}N nuclear magnetic resonance (NMR) spectra of 1,2,5-thiadiazoles has been previously reported <1984CHEC(6)513, 1996CHEC-II(4)355>. ^{1}H and ^{13}C NMR data have been reported for 2,1,3-benzothiadiazole **2** and several analogues <2005T10975> including 4-fluoro-2,1,3-benzothiadiazole **19** <2001EJI2123>. A comparison of the ^{15}N NMR spectra of 2,1,3-benzothiadiazole **1** ($\delta^{15}N = 329.9$ ppm (t, $J = 0.5$ Hz)) <2001RJC1050> and its 4-fluoro analogue **19** ($\delta^{15}N = 330.1$ ppm (s), 325.1 ppm (d, $J = 2.9$ Hz)) allowed assignment of the low-field signal of the fluoro analogue **19** to N-1 and the high field to N-3 <2001EJI2123>.



19

^{15}N NMR

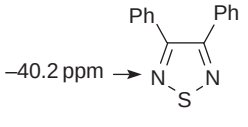
N-1 = 330.1 ppm (s)
N-3 = 325.1 ppm (d, J = 2.9 Hz)

^{19}F NMR = –121.1 ppm (dd)

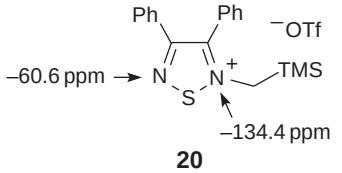
^{13}C NMR

C-3a 145.2 ppm
C-4 152.4 ppm
C-5 112.0 ppm
C-6 128.7 ppm
C-7 116.8 ppm
C-7a 156.0 ppm

^{15}N NMR was used to assist in the characterization of the *N*-trimethylsilylmethyl 3,4-diphenyl-1,2,5-thiadiazolium trifluoromethanesulfonate **20** <1999J(P1)1709>.

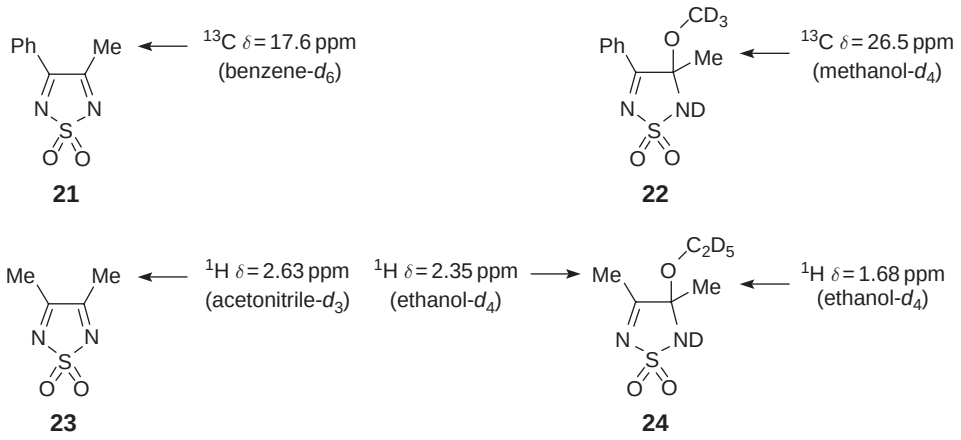


8



20

Both ^{1}H and ^{13}C NMR have been used to monitor the addition of alcohols to methyl-substituted thiadiazole 1,1-dioxides. A ^{13}C NMR study of 3-methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide **21** gave a methyl resonance at $\delta = 17.6$ ppm in benzene-d_6, and at 26.5 ppm in methanol-d_4 solution <1996CJC1564>. The direction and magnitude of the observed shift ($\Delta\delta = 8.9$ ppm) was in agreement with the addition of methanol to the C=N bond on the methyl side of the molecule. Similarly, the ^{1}H NMR spectrum of 3,4-dimethyl-1,2,5-thiadiazole 1,1-dioxide **23** provided evidence of addition of EtOH to one of the C=N bonds <1996CJC1564>. In acetonitrile-d_3, a single methyl signal at $\delta = 2.63$ ppm is observed, while two methyl signals are present in ethanol-d_6 (at $\delta = 2.35$ ppm on the unsubstituted side and 1.68 ppm on the ethoxy-substituted side).

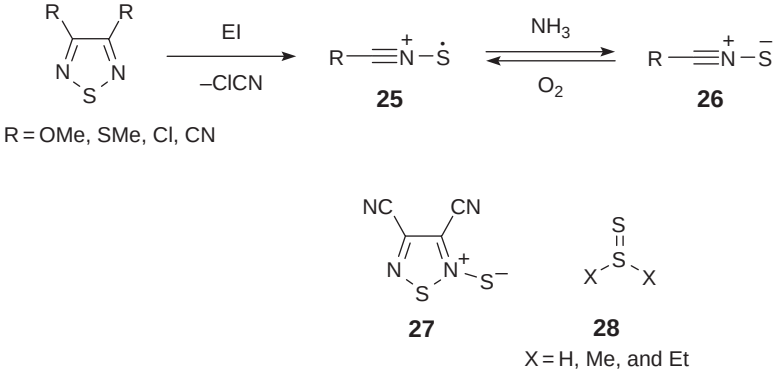


High-precision ^{14}N NMR measurements of the nitrogen shieldings for 1,2,5-thiadiazole **1** in a variety of solvents were reported (+30.57 (cyclohexane) to +44.22 ppm (2,2,2-trifluoroethanol)) <1996J(P2)619>. An increase in solvent polarity favors delocalization of the sulfur lone pairs into the conjugated rings leading to an increase in electronic charge at the nitrogen atoms and hence in the solute nitrogen shielding <1996J(P2)619>. Nitrogen shieldings (26.22 ± 3.00 ppm) for 1,2,5-thiadiazole **1** in the gas phase were also reported <2001J(P2)1117>. The values were similar to those found for the pyridine-type nitrogen atoms in diazole and triazole systems.

An NMR-based method for identifying reactive false positives during high-throughput screening of large compound collections including those that oxidize or alkylate a protein target indicated that compounds with a 1,2,5-thiadiazole substructure were reactive with protein thiol groups <2005JA217>.

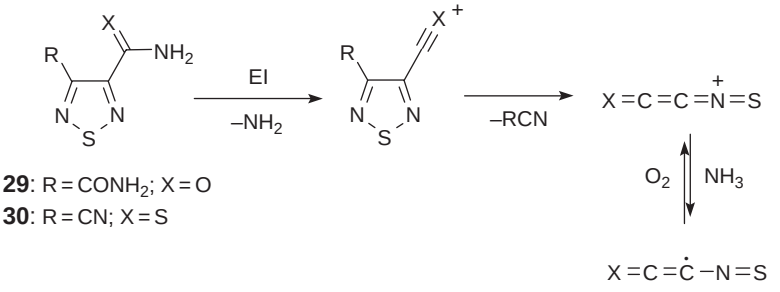
5.09.3.3 Mass Spectrometry

The fragmentation pathways of both 1,2,5-thiadiazole **1** and 2,1,3-benzothiadiazole **2** have appeared in previous reviews <1984CHEC(6)513, 1996CHEC-II(4)355>. Dissociative ionization of substituted 1,2,5-thiadiazoles affords cyanogen *N*-sulfide radical cations (RC≡N–S$^{\cdot+}$; R = CN, Cl, MeO, or MeS) (**Scheme 1**) <1996JPC17452, 1999J(P2)1683>. Under similar conditions, 4-cyano-1,2,5-thiadiazole-3-carboxamide loses carbon monoxide to afford the 3-amino-1,2,5-thiadiazole-4-carbonitrile radical cation which fragments to afford the cyanamide *N*-sulfide radical cation **25** (R = NH$_2$) <1996JPC17452>. While 1,2,5-thiadiazoles are very stable to thermolysis, flash vacuum pyrrolysis (FVP) at 750 °C of 1,2,5-thiadiazole-3,4-dicarbonitrile and mass spectrometric analysis of the products gave the dimer of cyanogen *N*-sulfide **26** (R = CN) (*m*/*z* 168) postulated to be the radical cation of 1,2,5-thiadiazole-3,4-dicarbonitrile *N*-sulfide **27** <1996JPC17452>. A later study on the FVP of substituted 1,2,5-thiadiazoles gave only the corresponding nitriles and sulfur <2001PCA6258>. The cyanogen *N*-sulfide radical cations generated transfer S$^{\cdot+}$ to neutral sulfides X$_2$S to afford thiosulfoxides X$_2$S=S **28** (X = H, Me, and Et) which are stable in the gas phase <2000IJM239>.



Scheme 1

New cumulenic ions, S═N═C═C═O$^+$ and S═N═C═C═S$^+$, have been generated by dissociative ionization and characterized by tandem mass spectrometry techniques starting from 1,2,5-thiadiazole-3,4-dicarboxamide **29** and 3-cyano-1,2,5-thiadiazole-4-thiocarboxamide **30** respectively (**Scheme 2**) <1996JPC10536>.



29: R = $CONH_2$; X = O
30: R = CN; X = S

Scheme 2

5.09.3.4 UV/Fluoresence, IR/Raman, and Photoelectron Spectroscopy

Detailed discussion on the spectroscopy of 1,2,5-thiadiazole has appeared in <1984CHEC(6)513, 1996CHEC-II(4)355>. Ultraviolet/visible (UV/Vis), fluorescence <2002HCA2195>, and infrared (IR) data <2005T10975> were reported for benzothiadiazole **2**. Several UV/Vis and fluorescence studies have been conducted on 4,7-disubstituted 2,1,3-benzothiadiazoles bearing ethynyl <2003JCD65, 2005SM73, 2005T10975>, vinyl <2005MAC664>, aryl <2000CC939, 2004CC2342, 2004JMC1901, 2005T10975>, and heteroaryl <2004JOC2953, 2005CC1468, 2005CC3183, 2005MM244> substituents and on 4,8-diphenylbenzo[1,2-*c*:4,5-*c*′]bis([1,2,5]thiadiazole) **109** (λ_{max}(abs) 558 nm (log ε 3.99), λ_{max}(em) 642 nm) and 4,9-diphenyl[1,2,5]-thiadiazolo[3,4-*g*]quinoxaline (λ_{max}(abs) 471 nm (log ε 3.99), λ_{max}(em) 561 nm) <1997T10169>.

UV/Vis data have also recently been reported for 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide **10** <2000JPO272, 2003JPO220, 2004JPO1091> and for the fused phenanthro[9,10-*c*]-1,2,5-thiadiazole 1,1-dioxide **51** and acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide **53** analogues <2000JPO272>.

IR and Raman spectra were obtained for 3,4-dimethyl-1,2,5-thiadiazole 1,1-dioxide **23** and showed S═O asymmetric and symmetric stretching at 1428 and 1168 cm^{-1}, respectively <1997JMT119>. A high-resolution (*ca.* 0.003 cm^{-1}) gas-phase IR study of 1,2,5-thiadiazole **1** in the range 750–1250 cm^{-1} gave five fundamental bands: ν_{11} (B_1; 1225.2 cm^{-1}, b-type in-plane CH bend), ν_4 (A_1; 1041.4 cm^{-1}, a-type in-plane CH bend), ν_{14} (B_2; 837.9 cm^{-1}, c-type out-of-plane CH bend), ν_5 (A_1; 805.9 cm^{-1}, a-type in-plane ring bend), and ν_{13} (B_1; 779.8 cm^{-1}, b-type in-plane ring bend) <2005JSP256>. Computational vibrational studies of the spectra of 1,2,5-thiadiazole **1** have appeared <1995ACS11, 1996SAA33, 1997JST451>.

Extensive discussion on the ionization potentials of 1,2,5-thiadiazole and its derivatives can be found in CHEC(1984) and CHEC-II(1996) <1984CHEC(6)513, 1996CHEC-II(4)355>. HeI photoelectron spectroscopy, inner-shell electron energy loss spectroscopy involving the S2p, S2s, C1s and N1s edges, and S1s synchrotron radiation photoabsorption spectroscopy were used to probe the occupied and unoccupied valence levels of benzothiadiazole **2** <1991MI165>.

5.09.3.5 ESR Spectroscopy

Discussion on the ESR spectra of 1,2,5-thiadiazoles and 2,1,3-benzothiadiazole radical anions has appeared in both CHEC(1984) <1984CHEC(6)513> and CHEC-II(1996) <1996CHEC-II(4)355>.

Several thiadiazole-fused organic radicals have been characterized by ESR spectroscopy, and significant spin delocalization can be seen from the hyperfine coupling constants (hfcc's) a_N (**Table 5**).

A direct comparison of the signals of the thiadiazolopyrazine-fused 1,3,2-dithiazolyl and 1,2,3-dithiazolyl isomers **34** and **35** <1999JA969> showed that radical **35** had a considerably more complex signal with hyperfine coupling to all five nitrogen nuclei.

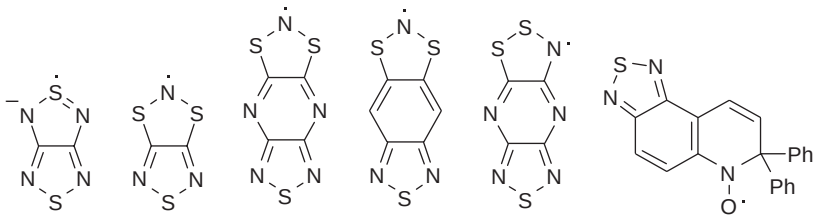
The simulated spectra of 7,7-diphenyl-6,7-dihydro[1,2,5]thiadiazolo[3,4-*f*]-quinoline-6-oxyl **36** gave a small a_N value of 0.81 mT for the N–O site (typical hfcc's for dialkyl *N*-oxyl-localized radical is *ca.* 1.4–1.5 mT) and small but

Table 5 Isotropic hyperfine *g*-value and coupling constants in mT

Radical	*g*	a_N	a_H	*Reference*
31	2.0045	0.314		2005IC7194
32[a]	2.0061	1.115, 0.084		2004JA8256
33[a]	2.0072	1.098, 0.020	0.16	2004JA8256
34[a]	2.0072	0.959, 0.209, 0.028		2004JA8256
35[a]	2.0090	0.514, 0.343, 0.109, 0.051, 0.045		1999JA969
36	No data	0.81, 0.13, 0.06[b]		2005CGD413

[a]X-band spectra at 293 K, in CH_2Cl_2.
[b]Computed a_N values using PEST WinSIM.

appreciable values (0.13 and 0.06 mT) for the thiadiazolo nitrogens supporting delocalization of the unpaired electron in the π-conjugated system <2005CGD413>. On the basis of the ESR data, a half-life of the electrochemically generated radical anion [1,2,5]thiadiazolo[3,4-*c*][1,2,5]-thiadiazolyl **31** was estimated as $\tau_{1/2} = 74.5$ s <2005IC7194>.



31 **32** **33** **34** **35** **36**

Variable-temperature ESR studies have revealed large magnetic bistabilities in thiadiazole-fused 1,3,2-dithiazolyl **32** <2001SM1767, 2001MI451, 2002MI064434>, the thiadiazolopyrazine-fused 1,3,2-dithiazolyl **34**, but not with the benzothiadiazolo-fused 1,3,2-dithiazolyl **33** <2004JA8256>. ESR studies have also been performed on inclusion crystals of the bicyclic [1,2,5]thiadiazolo[3,4-*d*][1,3,2]dithiazol-2-yl **32** in channels of perhydrotriphenylene and tris(*o*-phenylenedioxy)cyclotriphosphazene <2002MI432>.

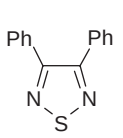
ESR spectra of the radical anions of 3-phenoxy-, 3,4-diphenoxy-, and 3,4-dichloro-1,2,5-thiadiazole and of the radical cations of various 3-aryloxy-4-morpholino-1,2,5-thiadiazoles have been obtained by the electrochemical generation of the ions in 3×10^{-3} M solutions of the thiadiazoles in the system $MeCN/Et_4NClO_4$ (*ca.* 0.1 M) on a platinum helix electrode directly in an ESR resonator at first wave potentials <2003RJC806>.

5.09.4 Thermodynamic Aspects

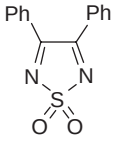
5.09.4.1 Physical Properties

1,2,5-Thiadiazole **1** (m.p. −50.1 °C, b.p. 94 °C/760 Torr or 35 °C/55 Torr) is a colorless and odorless liquid (density $d = 1.268$ g ml^{-1} at 25 °C, refractive index $n = 1.515$ (589 nm at 25 °C), which is weakly basic (pK_a −4.90) and possesses a dipole moment ($\mu = 1.58$ D) <1984CHEC(6)513, 1996CHEC-II(4)355>. The inductive effect of the ring sulfur draws electron density from adjacent nitrogen atoms making 1,2,5-thiadiazole the least basic of the thiadiazoles. The following data are characteristic for various monosubstituted 1,2,5-thiadiazoles (**Table 6**).

A comparison of 3,4-diphenyl-1,2,5-thiadiazole **8** and its 1,1-dioxide **10** is also useful <1999J(P1)1709, 1964JOC1905>.

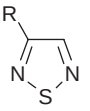


8
m.p. 83–85 °C (hexane)
1999J(P1)1709



10
m.p. 248–250 °C (acetone)
1964JOC1905

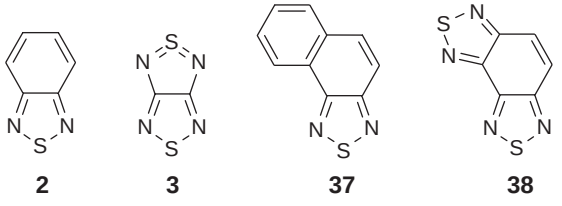
Table 6 Melting and boiling points for selected monosubstituted 1,2,5-thiadiazoles



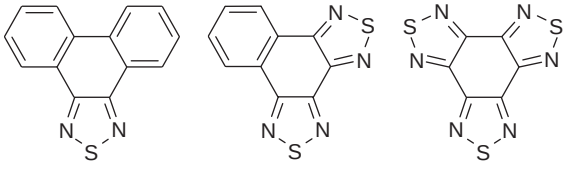
R	*m.p.* (°*C*)	*Reference*	*b.p.* (°*C*/*Torr*)	*Reference*
H	−50	1967AGE364	94/760	1967G1870
Me	−39	1967G1870	121/760	1967G1870
Et	n.d.		40.5/7	1986H(24)1131
Ph	43–44 (pentane)	1967G1614	90/0.9	1967G1614
Cl	n.d.		123–124	2001RJO1330
OH	128.5–130 (benzene)	1964JA2861	n.d.	
OMe	n.d.		124–126	2002EJO1763
CO_2H	164–166 (Et_2O)	1967JOC2823	n.d.	
$CONH_2$	193–194	1962USP3060187	n.d.	
CO_2Me	42	1979JHC1009	n.d.	

n.d. = no data.

2,1,3-Benzothiadiazole **2** (m.p. 45–46 °C (hexane) <2001EJI2123> and b.p. 63–64 °C at 1.5 Torr <2001RJC1050>) can readily be sublimed to give colorless needles and has a pleasant aromatic odor <1984CHEC(6)513, 1996CHEC-II(4)355>. The introduction of an additional fused benzene ring raises the melting point and the systematic replacement of the fused benzenes by other thiadiazoles (structures **3**, **37–41**) raises the melting point further <1972JOC2587, 1975JHC829, 1975JOC2749, 1977JHC963, 2001EJI2123>.



2 **3** **37** **38**

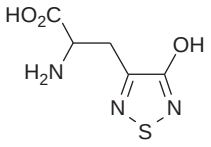


39 **40** **41**

2: m.p. 45–46 °C 2001EJI2123
3: m.p. 115.7–116 °C 1975JOC2749
37: m.p. 80–81 °C 1972JOC2587
38: m.p. 182–184 °C 1977JHC963
39: m.p. 169–170 °C 1972JOC2587
40: m.p. 208–209 °C 1972JOC2587
41: m.p. 344–346 °C 1975JHC829

5.09.4.2 Chromatographic Behavior

(*RS*)-2-Amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid **42** was resolved into the (−)- and (+)-enantiomers using a semipreparative Crownpak CR(+)-column (150 × 10 mm^2) equipped with a Crownpak CR(+) guard column (10 × 4.0 mm^2) (Daicel). The column was eluted at 0 °C (ice bath) with aqueous trifluoroacetic acid (TFA) (pH 2.0) at 1.5 ml min^{-1}. After removal of the acidic mobile phase, the pure enantiomers could be crystallized as zwitterions with high ee (99.9%) <2002BMC2259>. The first eluted (−)-enantiomer has the *(R)*-configuration as proved by an X-ray crystallographic analysis.



42

5.09.4.3 Aromaticity

Discussions on the aromaticity of thiadiazoles have appeared in two recent reviews <2004CRV2777, 2005CRV3773> and CHEC-II(1996) <1996CHEC-II(4)355>. The four main criteria used to quantify the degree of aromaticity are geometric, energetic, magnetic, and reactivity criteria. An attempt to quantitatively relate these four criteria has been made <2002JOC1333>.

Studies on the statistical deviation from an ideal bond order support the relatively high aromaticity of 1,2,5-thiadiazole (**Table 7**). The harmonic oscillator model of aromaticity (HOMA) value for 1,2,5-thiadiazole has not yet been reported.

Table 7 Aromaticity based on geometric criteria (TDA = thiadiazole)

I_A[a]		*ARBOD*[b]		*ARBOD*[b]	
67	1,2,3-TDA	0.225 62	1,3,4-TDA	0.521 06	1,2,5-TDA 1,1-dioxide
80	1,3,4-TDA	0.181 28	1,2,4-TDA	0.450 56	1,2,5-TDA 1-oxide
89	1,2,4-TDA	0.168 89	1,2,3-TDA		
104	1,2,5-TDA	0.166 50	1,2,5-TDA		

More aromatic ↓

[a]Unified Bird aromaticity index <1992T335>.
[b]ARBOD = average ring bond order deviation computed using B3LYP/6-311++G** <2001JMT285>.

Analogous studies on 1-monoxides and 1,1-dioxides support the nonaromaticity of these derivatives. The ^1J(C–C) spin–spin coupling between ^{13}C nuclei has been determined for 1,2,5-thiadiazole (48.1 Hz) and correlated to bond length and tentatively to aromaticity <1994MRC62>. Based on this, a low aromaticity was assigned to 1,2,5-thiadiazole similar to furan and isoxazole while a high aromaticity assignment was made for 1,2,3-thiadiazole, contrary to that reported by Bird.

The energy criteria studies were based on computationally obtained geometries and supported the relatively high aromaticity of 1,2,5-thiadiazole (**Table 8**). However, a study of the vertical resonance energies (VREs) gave a different perspective to the aromaticity of five-membered rings such as furan, pyrrole, thiophene, and their isoelectronic thiadiazole derivatives <2000PCA1736>. This study showed the VREs for five-membered heterocycles to be destabilizing and that these systems were not truly aromatic. Their participation in electrophilic aromatic substitution was attributed to the rigid σ-framework of five-membered heterocycles and the good leaving group ability of the α-hydrogen.

Table 8 Aromaticity based on energy criteria (TDA = thiadiazole)

VRE[a] (*hartree*)		*ASE*[b] (*kcal mol*$^{-1}$)		*ASE*[c] (*kcal mol*$^{-1}$)		$\Delta\Delta HH$[d] (*kcal mol*$^{-1}$)		$\Delta\Delta$ *FMO*[e] (*eV*)	
n.d.	1,2,3-TDA	13.69	1,3,4-TDA	10.52	1,3,4-TDA	19.66	1,3,4-TDA	1.079	1,3,4-TDA
0.0100	1,2,5-TDA	18.28	1,2,4-TDA	14.57	1,2,4-TDA	22.25	1,2,3-TDA	1.089	1,2,5-TDA
0.0030	1,2,4-TDA	20.48	1,2,3-TDA	15.71	1,2,3-TDA	25.72	1,2,5-TDA	1.162	1,2,3-TDA
−0.0001	1,3,4-TDA	22.67	1,2,5-TDA	17.07	1,2,5-TDA	28.58	1,2,4-TDA	1.683	1,2,4-TDA

More aromatic ↓

[a]Computed at the STO-3G level <2000PCA1736>.
[b]Computed at the MP2(fc)/6-311+G** level <2003T1657>.
[c]Computed at the B3LYP/6-311+G** (+ZPE) level <2002JOC1333>.
[d]$\Delta\Delta HH$ = hydrogenation energy changes for heterocycle ring closure at the B3LYP/6-311++G** level <2001JMT285>.
[e]$\Delta\Delta$FMO = frontier orbital energy changes for heterocycle ring closure at the B3LYP/6-311++G** level <2001JMT285>.

As with the above geometric and energetic criteria, the relatively high aromaticity of 1,2,5-thiadiazole was supported by magnetic criteria (**Table 9**).

Table 9 Aromaticity based on magnetic criteria (TDA = thiadiazole) <2002JOC1333>

	Λ[a]		*NICS*[b] (*0*) (*ppm*)		*NICS*[b](*1*) (*ppm*)	
↓ More aromatic	−5.34	1,3,4-TDA	−13.00	1,3,4-TDA	−11.96	1,2,4-TDA
	−6.31	1,2,4-TDA	−13.47	1,2,4-TDA	−12.34	1,3,4-TDA
	−7.60	1,2,5-TDA	−14.38	1,2,3-TDA	−12.96	1,2,5-TDA
	−7.75	1,2,3-TDA	−14.52	1,2,5-TDA	−13.72	1,2,3-TDA

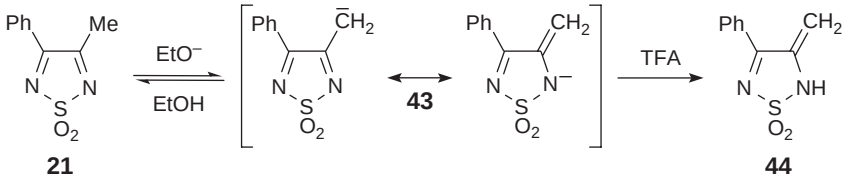
[a]Λ = exaltations of magnetic susceptibility at CSGT/HF/6-311+G**//MP2(fc)/6-311+G**.
[b]NICS = nucleus-independent chemical shifts at GIAO/HF/6-311+G**//MP2(fc)/6-311+G**.

1,2,5-Thiadiazoles undergo substitution reactions reflecting their relatively high aromatic character but in contrast the 1,2,5-thiadiazole 1-oxides and 1,1-dioxides suffer addition chemistry supporting their non- or antiaromatic characters.

While 1,2,5-thiadiazole 1,1-dioxide has not yet been prepared, extrapolation of data on the known 3,4-dimethyl-1,2,5-thiadiazole 1,1-dioxide **23** <1998JPO91> indicated that the nonaromatic or 'antiaromatic' 1,2,5-thiadiazole 1,1-dioxide has a more delocalized structure than its isomeric thiadiazole 1,1-dioxide anologues <1997JMT119, 2001JMT285>.

5.09.4.4 Tautomerism

3-Methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide **21** suffers proton abstraction in basic nonaqueous media to give a resonance stabilized anion **43**, neutralization of which using anhydrous TFA gives the orange tautomer 4-methylene-3-phenyl-1,2,5-thiadiazoline 1,1-dioxide **44** (**Scheme 3**) <2001JPO217>. The tautomeric equilibrium is practically displaced toward **21** in acetonitrile and toward **44** in DMF.



Scheme 3

Interestingly, the tautomeric isomer **44** was predicted to be a strong to moderate sensitizer with a probability of 90%, which was greater than that obtained for thiadiazole **21** (70%) <2003CRT1226, 2004JCI688>.

5.09.5 Reactivity of Fully Conjugated Rings

Excellent accounts of the reactivity of the fully conjugated rings appear in CHEC(1984) <1984CHEC(6)513> and CHEC-II(1996) <1996CHEC-II(4)355> and, with the exception of developments in the selectivity of reagents used for the reduction of benzothiadiazoles to benzenediamines, little has been added to this body of knowledge. Below is a brief general survey of reactivity followed by a short account of improved reduction technology for benzothiadiazoles.

5.09.5.1 General Survey of Reactivity

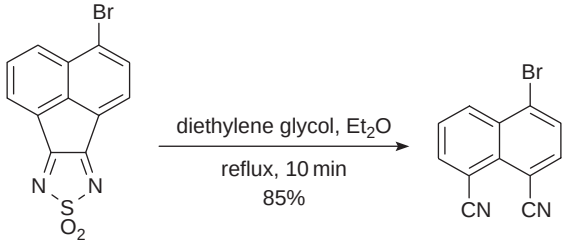
The relatively high aromaticity of the parent 1,2,5-thiadiazole renders it good thermal stability (stable up to 220 °C); despite this, 3,4-diphenyl-1,2,5-thiadiazole **8** suffers slow photochemical degradation to give benzonitrile and sulfur. The low basicity of 1,2,5-thiadiazole indicates a relatively high electron density in the π-orbital and corresponding low electron density of the nitrogen lone pairs. Addition reactions such as *N*-alkylation do not occur readily. *S*-Oxidation is

readily achieved with mild oxidizing agents (dimethyldioxirane, *m*-chloroperbenzoic acid (MCPBA)) to give the nonaromatic thiadiazole-1-oxides and 1,1-dioxides. Oxidative ring cleavage can be achieved under more aggressive conditions. The 1,2,5-thiadiazole ring system can tolerate a wide range of mild reducing agents; however, ring cleavage and desulfurisation leading to 1,2-diamino compounds can be achieved with more powerful reagents (see Section 5.09.5.6). Monocyclic 1,2,5-thiadiazoles reluctantly undergo electrophilic substitution reactions, and only electrophilic deuteration, chloromethylation, and halogenation have been achieved. Mononuclear 1,2,5-thiadiazoles suffer nucleophilic attack on carbon, sulfur, or on a ring proton. Organolithium and Grignard reagents typically attack the ring sulfur, though an additional mode of attack on nitrogen can occur with benzothiadiazoles, presumably driven by the stable benzenoid character of the intermediate. Attack at the ring sulfur results in ring cleavage and 1,2-diimine formation. Halogenated thiadiazoles in most cases react typically to give products of displacement of halide (see Section 5.09.7.6).

Benzothiadiazoles react with electrophiles on the carbon skeleton of the fused carbon ring to give both addition and substitution products. Substitution predominates at C-4 and at C-7 as expected from a consideration of the possible resonance structures. Benzo fusion does little to aid *N*-alkylation, which still requires reactive alkylating agents; in combination with the reductive ring cleavage, this affords a route to *N*-alkyl-1,2-benzenediamines. Electron withdrawal by the heterocyclic ring enhances the leaving group ability of substituents on the benzo-fused ring. In the absence of a good leaving group on carbon, nucleophilic attack occurs on sulfur and results in ring opening.

5.09.5.2 Unimolecular Thermal and Photochemical Reactions

Mass spectrometric analysis (see Section 5.09.3.3) of the flash vacuum pyrolyzed (FVP at 750 °C) products of substituted thiadiazoles affords the corresponding nitriles and sulfur <1996JPC17452, 2001PCA6258>. 4-Bromoacenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide **45**, however, suffered a facile ring opening in diethylene glycol/diethyl ether in only 10 min at reflux to afford 1,8-dicyanonaphthalene **46** (Equation 1) <2002TL2991>; the 4-nitro derivative gave the analogous cleavage product in 68% yield upon heating under vacuum at 220 °C for 30 min <2003TL2087>.



45 **46** (1)

5.09.5.3 Electrophilic Attack at Nitrogen

Addition reactions such as *N*-alkylation do not occur readily, and trimethylsilylmethylation of 3,4-diphenyl-1,2,5-thiadiazole **8** with trimethylsilylmethyl trifluoromethanesulfonate at 80 °C occurred at N-2 <1999J(P1)1709>. The electron-rich 3-hydroxy-1,2,5-thiadiazole can be preferentially methylated on N-2 using trimethyl orthoacetate in toluene to afford the 2-methyl-1,2,5-thiadiazol-3-one in 69% yield <2002EJO1763>, although a mixture of 3-hydroxythiadiazole and neat trimethyl orthoacetate showed a 20:80 ratio of *N*- versus *O*-alkylation products by ^{1}H NMR. Treatment of 3-hydroxy-1,2,5-thiadiazole with *t*-butyl acetate under acid catalysis (Amberlyst 15) gave almost exclusively the *N*-alkylated compound <2002BMC2259>.

5.09.5.4 Electrophilic Attack at Carbon or Sulfur

Electrophilic attack at carbon or sulfur is well documented in CHEC(1984) <1984CHEC(6)513> and in CHEC-II(1996) <1996CHEC-II(4)355>. No recent work has been reported.

5.09.5.5 Nucleophilic Attack at Carbon, Sulfur, or Hydrogen Attached to Carbon

Nucleophilic attack at carbon, sulfur, or hydrogen attached to carbon is well documented in CHEC(1984) <1984CHEC(6)513> and in CHEC-II(1996) <1996CHEC-II(4)355>. No recent work has been reported.

5.09.5.6 Reactions Involving Radicals, Electron-Deficient Species, Reducing Agents, and at Surfaces

The only significant reactions that have appeared regarding this section involve reducing agents. For additional information on reactions with radicals and electron-deficient species, refer to CHEC(1984) <1984CHEC(6)513> and CHEC-II(1996) <1996CHEC-II(4)355>.

Reductive cleavage of the thiadiazole to afford the corresponding 1,2-diamine requires vigorous conditions. Both zinc in acetic acid <2005JOC2754> and tin(II) chloride with aqueous methanolic HCl <1997JCM250> afford benzenediamines from thiadiazoles. The ring system, however, tolerates iron in acetic acid which can be used to reduce nitro substituents (see Section 5.09.7.1). Other typically used reducing agents such as $LiAlH_4$ and Raney-Ni are incompatible with sensitive substituents such as bromo, chloro, or cyano <1996H(42)597, 2001JOC8954>, and the use of $NaBH_4$ was until recently limited to electron-deficient 2,1,3-benzothiadiazoles. By using $NaBH_4$ in the presence of catalytic $CoCl_2{\cdot}6H_2O$ in EtOH, however, bromo substituents could be tolerated but some sensitivity to steric effects was observed <2005TL6843>. Similarly, treatment of benzothiadiazoles with SmI_2 (Kagan's reagent) in tetrahydrofuran (THF) in the presence of methanol at room temperature gave the diamine and the presence of chloro substituents was tolerated; highly reducible groups such as nitro or cyano were, however, reduced by the SmI_2 together with the thiadiazole ring <2005JCM21>. Performing the reaction in the absence of methanol and with triphosgene gave benzimidazolin-2-ones <2005JCM21>. Corey's aluminium amalgam method was used to obtain 1,2-diamino-3,6-dibromobenzene <2005TL6843>. The use of magnesium in methanol tolerated sensitive functional groups such as bromo, chloro, cyano, and carboxylate on the benzothiadiazole <2001TL2277>. Reduction of benzothiadiazole using red-Al has also been reported <1998JA11880>.

A study on the electrochemical reduction and oxidation of various 1,2,5-thiadiazoles showed that the thiadiazole ring is resistant to oxidation and the reversible electron transfer gives rise to fairly stable radical cations <2003RJC806>. The reductive stability of the thiadiazole ring depends on the nature of its substituents and on the medium: when a single nucleofuge substituent was present (e.g., Cl), a two-electron transfer in aprotic media resulted in heterocyclic ring opening with iminonitrile formation, whereas in the presence of two leaving groups, the electron transfer induces cleavage of the complete heteroring into inorganic anions.

5.09.5.7 Cyclic Transition State Reactions

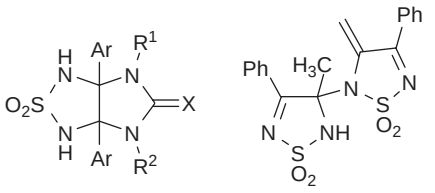
No significant developments have appeared since CHEC-II(1996). Diels–Alder reactions involving the fused benzene ring of benzothiadiazoles have, however, been reported (see Section 5.09.7.1).

5.09.6 Reactivity of Nonconjugated Rings

5.09.6.1 *S*-Monoxides and Dioxides

A detailed review of the chemistry of thiazole and thiadiazole *S*-oxides has recently appeared <2002AHC71>. The electron-withdrawing character of the sulfonyl group makes the heterocyclic carbon atoms of the thiadiazole 1,1-dioxide highly electropositive, which assists nucleophilic additions to the C=N bond and also enhances the acidity of α-protons, thus favoring α-carbanion formation <2001JPO217>. Nonsymmetrical arylamino, alkylamino-disubstituted thiadiazole 1,1-oxides can be obtained from the reactive 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide, while the use of 3,4-dimethoxy- and 3,4-diamino analogues gave mixtures with alkylamines or failed to react with arylamines <1998JHC297>. By comparison, the analogous nonsymmetrical arylamino, alkylamino-disubstituted thiadiazole 1-oxides were readily available from 3,4-diethoxy-1,2,5-thiadiazole 1-oxide <1996BML2187>. Stepwise formation of unsymmetrical alkylamino-disubstituted thiadiazole 1-oxides was also reported starting from 3,4-dimethoxy-1,2,5-thiadiazole 1-oxide <1998FA112, 2001JME1231>.

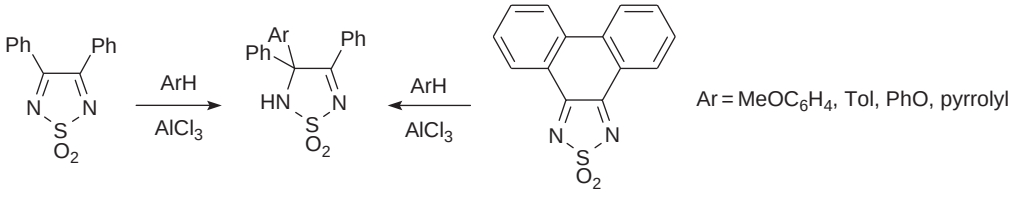
Monofunctional alcohols, thiols, amines, and amides add reversibly in aprotic solvent to only one of the two C=N bonds of 3,4-disubstituted-1,2,5-thiadiazole 1,1-dioxides to give the corresponding thiadiazoline 1,1-dioxides <1996CJC1564, 2000JPO272, 2003JPO220>. The equilibrium constants were measured by either spectroscopic or voltammetric methods. Grignard reagents also add predominantly to only one of the two C=N bonds <1998SL623>. Suprisingly, bis-addition was achievable with urea <2003JPO220> and thioureas <2004JPO1091> to give the bicyclic thiadiazolidines **47** and **48**, respectively. 3-Methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide **21** affords the dimeric species **49** in alcoholic solution on treatment with base <2001JPO217>.



47: X = O
48: Y = S

49

3,4-Diphenyl-1,2,5-thiadiazole 1,1-dioxide **10** in the presence of anhydrous $AlCl_3$ reacts with aromatic nucleophiles possessing electron donor substituent groups to afford 3,4,4-trisubstituted-1,2,5-thiadiazoline 1,1-dioxides **50** in good yields <2000MOL503>, while in the presence of only $AlCl_3$ thiadiazole 1,1-dioxide **10** suffers a slow but practically quantitative intramolecular cyclization reaction (Scholl reaction) to afford phenanthro[9,10-*c*]-1,2,5-thiadiazole 1,1-dioxide **51** <2002S2399>. Interestingly, phenanthro[9,10-*c*]-1,2,5-thiadiazole 1,1-dioxide **51** can be transformed to the thiadiazolidine **50** (Ar = $MeOC_6H_4$) on treatment with anisole in the presence of $AlCl_3$ (**Scheme 4**) <2002S2399>.

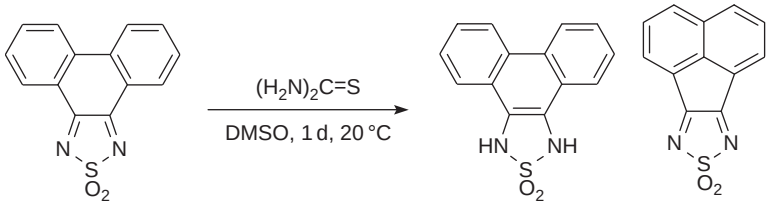


10 **50** **51**

Ar = $MeOC_6H_4$, Tol, PhO, pyrrolyl

Scheme 4

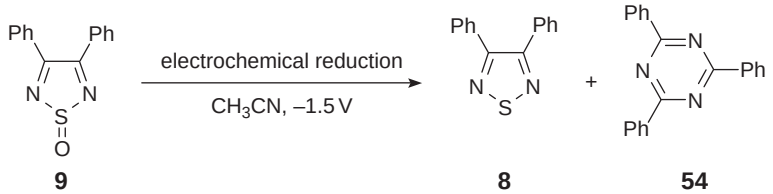
A difference in reactivity was observed between the phenanthro[9,10-*c*]- and acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxides **51** and **53** when treated with thiourea. The acenaphtho derivative **53** gave the expected addition product; however, the phenanthro thiadiazole **51** was reduced to the thiadiazoline 1,1-dioxide **52** (Equation 2) <2004JPO1091>. The difference in reactivity was attributed to the enhanced resonance stability offered by the phenanthrene group.



51 **52** **53**

(2)

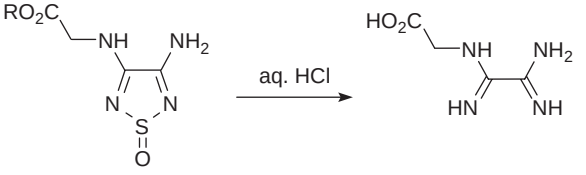
Electrochemical reduction of various 3,4-disubstituted-1,2,5-thiadiazole 1,1-dioxides (3,4-diphenyl- **10**, phenanthro[9,10]- **51**, and acenaphtho[1,2]- **53**) gave the corresponding thiadiazoline 1,1-dioxides <1999CJC511>. Voltammetric and bulk electrolysis electroreduction of 3,4-diphenyl-1,2,5-thiadiazole 1-oxide **9** at *ca.* −1.5 V, in acetonitrile, gave 3,4-diphenyl-1,2,5-thiadiazole **8** (50%) and 2,4,6-triphenyl-1,3,5-triazine **54** (30%) (Equation 3) <2000TL3531>.



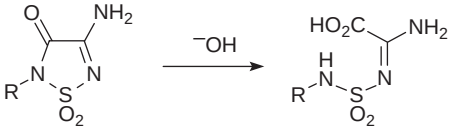
9 **8** **54**

(3)

Hydrolysis of amino-alkylamino-1,2,5-thiadiazole 1-oxides **55** with concentrated aqueous HCl gave the amidines **56** (Equation 4) <2001JME1231>. The hydrolysis reactions of 2-alkyl-4-amino-2,3-dihydro-1,2,5-thiadiazol-3-one 1,1-dioxides **57** in the range 24–73 °C in buffered aqueous solutions gave the corresponding 2-amino-2-[(*N*-alkyl-substituted-sulfamoyl)imino]acetic acid salts **58** (Equation 5) <1998JPO489>.

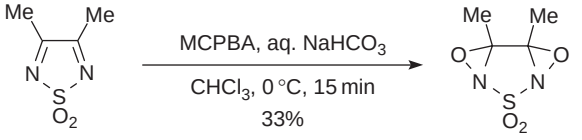


55 **56** (4)



57 **58** (5)

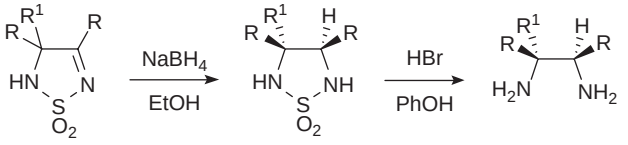
Finally, oxidation of 3,4-dimethyl-1,2,5-thiadiazole 1,1-dioxide **23** with MCPBA gave the oxaziridine-fused derivative **59**, which acts as a bleach enhancer (Equation 6) <1998USP5753599, 1998USP5760222>.



23 **59** (6)

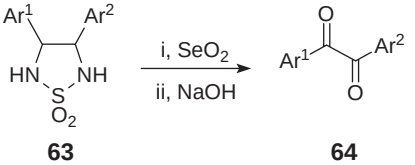
5.09.6.2 Reduced Compounds: Thiadiazolines and Thiadiazolidines

Stereoselective hydride reduction of 1,2,5-thiadiazoline 1,1-dioxides **60** generates unsymmetrical 1,2,5-thiadiazolidine 1,1-dioxides **61** <1998SL623> that can be readily converted to unsymmetrical vicinal diamines **62** with HBr in the presence of phenol (**Scheme 5**) <1996TL2859, 1998SL623>. The unsymmetrical thiadiazolidine 1,1-dioxides **63** can also be converted into 1,2-diketones **64** on treatment with selenium dioxide followed by alkaline hydrolysis (Equation 7) <1997SL671>.



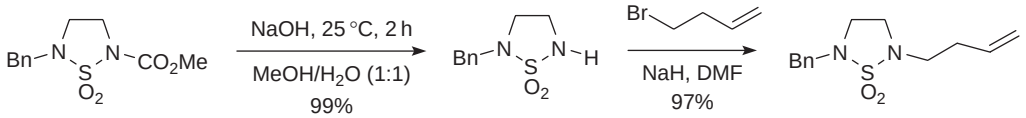
60 **61** **62**

Scheme 5



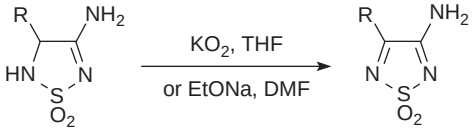
63 **64** (7)

Removal of the carbamate group of thiadiazolidine **65** was achieved with conventional procedures and the resulting deprotected thiadiazolidine **66** can be *N*-alkylated (**Scheme 6**) <2004CEJ5581>.



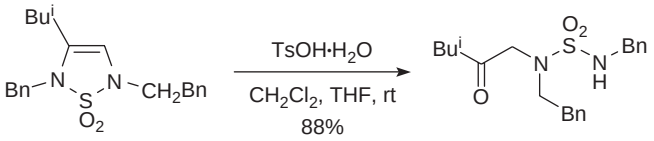
Scheme 6

3-Aminothiadiazoline 1,1-dioxides **67** can be oxidized by KO_2 in THF <1995JKC834, 1996JKC526>, or even by reacting with EtONa in dimethylformamide (DMF) <1998JKC112>, to give the corresponding thiadiazole 1,1-dioxides **68** (Equation 8). Thiadiazoline **67** was also shown to suffer transamination with alkylamines <1995JKC834, 1996JKC526>.



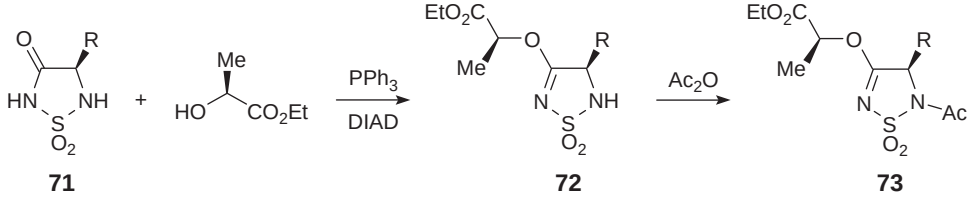
(8)

Treatment of the 2,5-dihydro-1,2,5-thiadiazole 1,1-dioxide **69** with *p*-toluenesulfonic acid monohydrate affords the ring-opened phenylethyl sulfamide **70** (Equation 9) <2004BMC6249>.



(9)

Thiadiazolidinone 1,1-dioxides **71** undergo *O*- rather than the expected *N*-alkylation under Mitsunobu conditions <1998TL7435>. *N*-Acylation can subsequently be performed on the *O*-alkylated product **72** using acetic anhydride to give thiadiazolines **73** (**Scheme 7**).



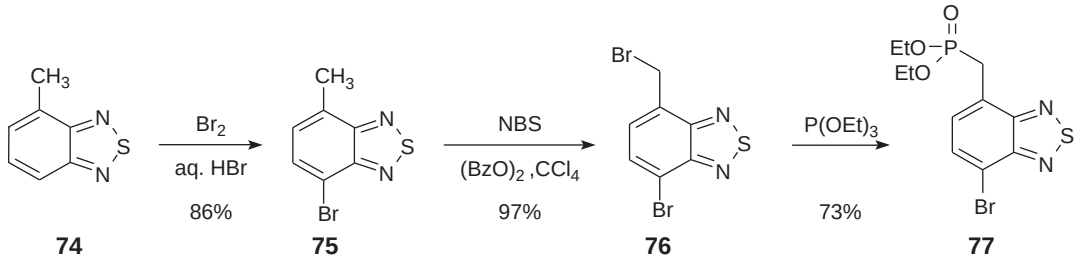
Scheme 7

5.09.7 Reactivity of Substituents Attached to the Ring Carbon Atoms

An extensive coverage of the reactivity of substituents attached to the 1,2,5-thiadiazole ring carbon atoms exists in both CHEC(1984) and CHEC-II(1996). Recent developments are described in this section.

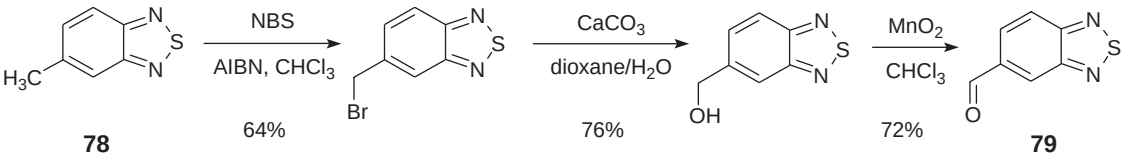
5.09.7.1 Benzenoid Rings

Bromination of 7-methylbenzothiadiazole **74** in aqueous HBr using bromine gave 4-bromo-7-methylbenzothiadiazole **75** <2005JOC6004>. Excess bromine was reported to afford the allylic bromination product **76** <1970JHC629>, but this was best formed starting from bromobenzothiadiazole **75** using NBS in CCl_4 <1997H(45)955, 2005JOC6004>. Treatment of this product with triethylphosphite gave the phosphonic ester **77** (**Scheme 8**) <2005JOC6004>.



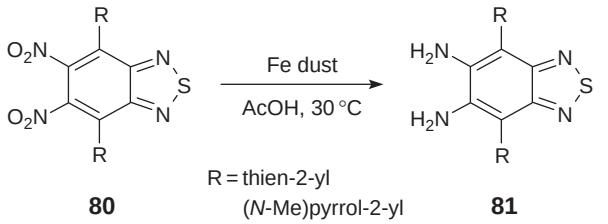
Scheme 8

5-Methylbenzo-2,1,3-thiadiazole **78** was sequentially brominated, hydroxylated, and oxidized to afford the 5-carbaldehyde **79** (**Scheme 9**) <2004JME3163>.



Scheme 9

Nitrobenzothiadiazoles **80** can be readily reduced to the aminobenzothiadiazoles **81** without degradation of the heterocyclic moiety using iron powder in AcOH at 30 °C (Equation 10) <1995JA6791, 1996CL63, 1996CM570, 1997T10169, 2005JA5186>. The use of Zn in AcOH leads to complete reduction of both the nitro group and the thiadiazole ring <2005JOC2754> (see Section 5.09.5.6).

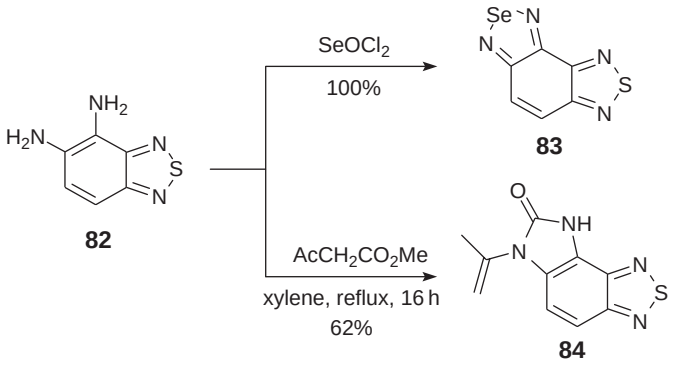


(10)

In this manner, diaminobenzothiadiazoles are readily obtained from dinitro precursors and can then be converted into the benzobis(thiadiazole)s on treatment with *N*-thionylaniline, <1995JA6791, 1997T10169>, or into thiadiazolo[3,4-*g*]quinoxalines on treatment with 1,2-dicarbonyls <1996CL63, 2005JA5186>, imidazo[4,5-*e*]benzothiadiazoles on treatment with aldehydes <2004T2953>, carboxylic acids <1998H(48)113, 2003HCO647>, thiourea <1997H(45)19>, imidazo[4,5-*e*]benzothiadiazol-5(6*H*)-ones with neat urea at 160 °C <1997H(45)19>, and 8*H*-imidazo[4,5-*e*][1,3]thiazole[2,1,3]benzothiadiazoles on treatment with both 2-mercapto acetic acid and 7-hydroxy-4-methylcoumarin-8-aldehydes <2005PS2119>.

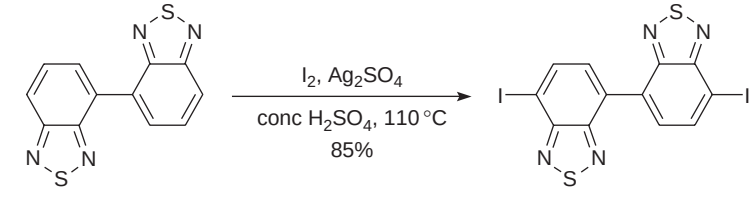
4,5-Diamino-2,1,3-benzothiadiazole **82** affords [1,2,5]selenodiazolo[3,4-*e*]-2,1,3-benzothiadiazole **83** quantitatively on treatment with selenium oxychloride in refluxing chloroform–pyridine <2004JHC955>. This was an improvement of the previous method using selenium dioxide (62% yield) <1984ZNB485>. 6-Isoprenyl-4*H*-imidazo[4,5-*e*]-benzothiadiazolone **84** was obtained when 4,5-diaminobenzothiadiazole was reacted with methyl acetoacetate in xylene at reflux (**Scheme 10**) <1997H(45)19>.

4,7-Dibromobenzothiadiazole **89** and several other halogenated benzothiadiazoles have been shown to undergo a wide range of C–C palladium-catalyzed coupling reactions including Negishi <1996H(42)597>, Stille, <1995JA6791, 1996CM570, 1996CL63, 1997T10169, 1998CEJ1235, 2000CC939, 2002JMC2887, 2004MI83, 2004JOC2953, 2004MM6299, 2005CC3183, 2005JOC6004, 2005MM244>, Suzuki <2000CC939, 2002MM3532, 2004CC2342, 2004JMC1901, 2004JA1942, 2004JA9845, 2005CC1468, 2005MM7636, 2005JA3172>, Heck <2004CC2342, 2005MAC664, 2005PLM11927>, and Sonogashira reactions <2001AM1862, 2001MM7592, 2002HCA2195, 2002JCM511, 2002JOC7813, 2002TL3373, 2003MM4262, 2003JCD65, 2003SM873, 2004CC2342, 2004SL169, 2005JA5186>.

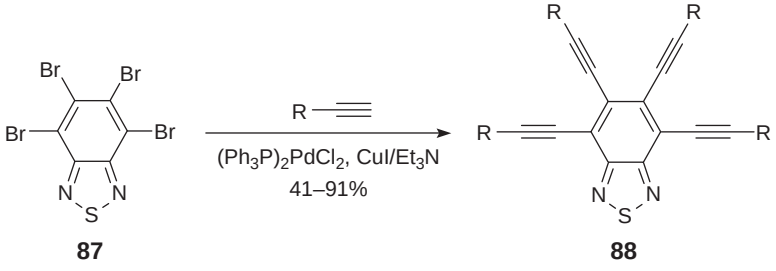


Scheme 10

Reductive coupling of 4-bromobenzothiadiazole with Ni(0) catalysts gave the Ullmann-type product 4,4′-bibenzothiadiazole **85** in 42% yield, iodination of which gave the 7,7′-diiodo derivative **86** (Equation 11) <1999TL1175>. Treatment of the diiodo derivative **86** with sodium dicyanomethide and Pd(0) gave the 7,7′-dimalononitrile analogue **107** (see also Equation 17). The fluorescent tetraethynyl-2,1,3-benzothiadiazoles **88** were prepared via Sonogashira coupling starting from the 4,5,6,7-tetrabromo-2,1,3-benzothiadiazole **87** (Equation 12) <2004SL169>.



(11)

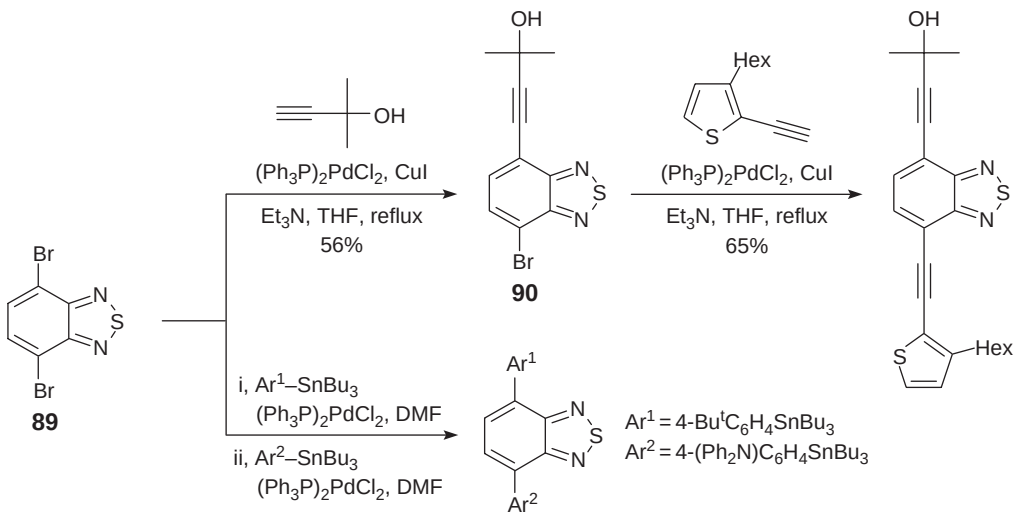


(12)

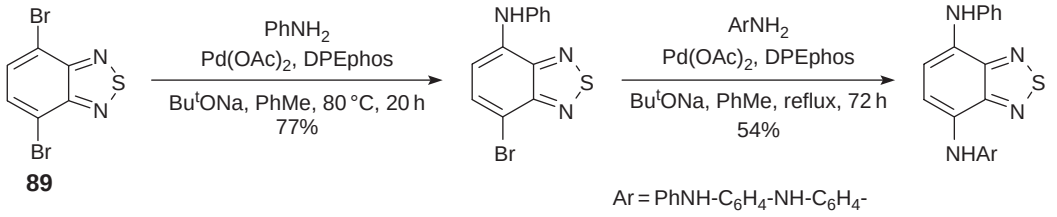
A one-pot stepwise asymmetrical disubstitution of 4,7-dibromobenzothiadiazole **89** can be achieved using the Stille reaction <2004MI83>. Similarly, a two-step asymmetric disubstitution has been reported using the Sonogashira reaction, although in this example the monobromo monoacetylated intermediate **90** was isolated and purified prior to further functionalization (**Scheme 11**) <2002TL3373>. Interestingly, the use of the polar 1-hydroxy-1-methylethyl (HME) protecting group was preferred over the nonpolar trimethylsilyl (TMS) group, since it facilitated the rapid chromatographic separation of the mono- and bis-coupled products.

4,7-Dibromobenzothiadiazole **89** can also undergo asymmetric stepwise Buchwald amination with various anilines (**Scheme 12**) <2002TL9009, 2005JOC2754>, and 4-bromo-7-methylbenzothiadiazole **91** can be aminated using benzophenone imine as an ammonia equivalent via a two-step palladium-catalyzed amination route (**Scheme 13**) <2003JHC713>.

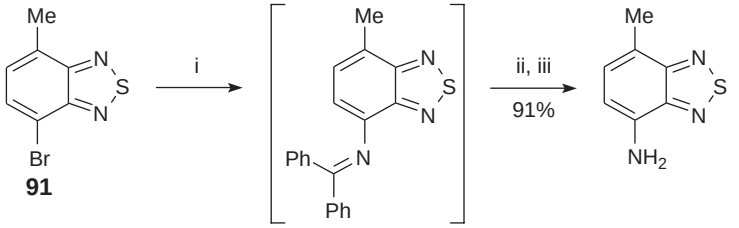
The base-catalyzed condensation of 4-nitrobenzothiadiazole **92** with ethyl isocyanoacetate affords the thiadiazolo[3,4-*e*]isoindoles **93** (**Scheme 14**) <1996J(P1)1403, 1996TL8391, 1997TL2031, 1998JOC8455, 2000J(P1)2671>, which are key intermediates in the preparation of porphyrin chromophores. Amination of 4-nitrobenzothiadiazole **92** using hydroxylamine gave 5-amino-4-nitrobenzothiadiazole **94**, treatment of which with sodium hypochlorite afforded furoxanobenzothiadiazole *N*-oxide **95** (which could be deoxygenated with triethylphosphite) <2004JHC955>. This route gave furoxanobenzothiadiazole **96** in an overall yield of 37% significantly improving an earlier synthesis from the 5-nitrobenzothiadiazole (overall yield *ca.* 11%) <1974JME203>.



Scheme 11



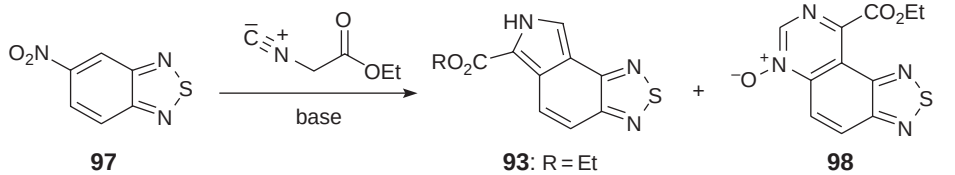
Scheme 12



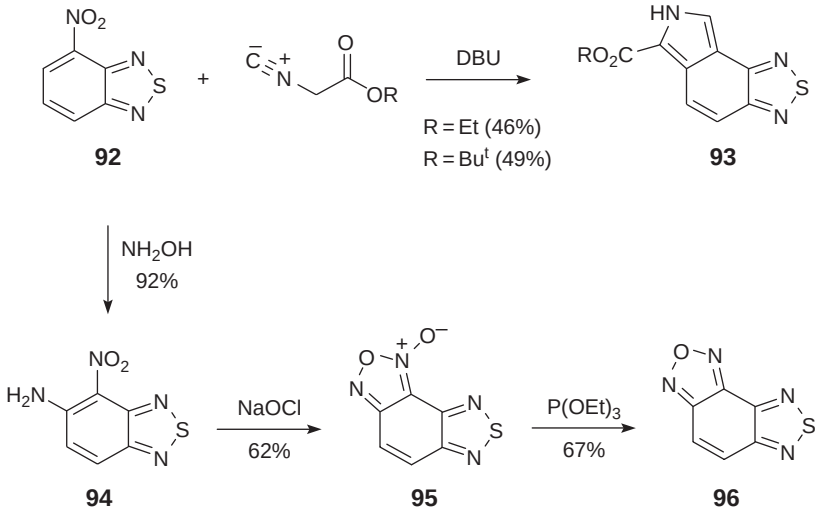
i, $Ph_2C{=}NH$ (1.05 equiv), $Pd(dba)_3$ (0.25 mol%), BINAP (0.75 mol%), MeONa (1.4 equiv), PhMe, 83–87 °C, 24 h; ii, 37% HCl, 70–80 °C, 0.5 h; iii, 5 N NaOH, 55–56 °C

Scheme 13

Similar treatment of 5-nitrobenzothiadiazole **97** with ethyl isocyanoacetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the thiadiazolo[3,4-*e*]isoindole **93** (21%), but when a phosphazene base was employed the major isolated product was the pyrimidine *N*-oxide **98** (46%) (Equation 13) <1996J(P1)1403, 1996TL8391>.

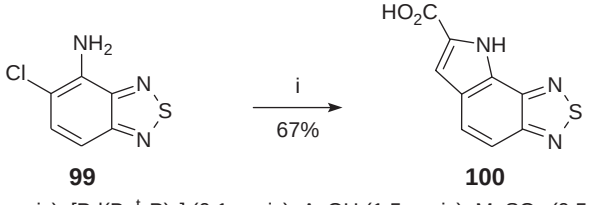


(13)



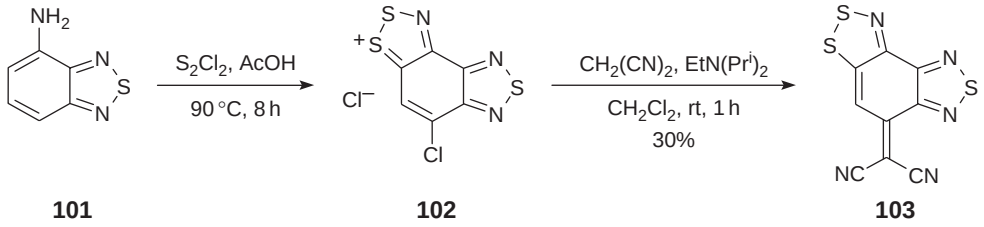
Scheme 14

The thiadiazolo[3,4-*g*]indole **100** was prepared from 4-amino-5-chlorobenzothiadiazole **99** by treatment with pyruvic acid in the presence of $[Pd(Bu^t_3P)_2]$ (Equation 14) <2004AGE4526>. The Herz reaction of 4-aminobenzothiadiazole **101** with disulfur dichloride gave the fused 1,2,3-dithiazolium chloride **102**, which was condensed with malononitrile to give the ylidene **103** (**Scheme 15**) <2002J(P1)315>.



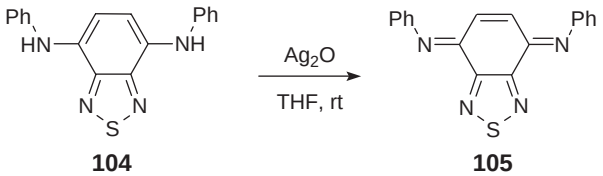
(14)

i, K_3PO_4 (1.3 equiv), $[Pd(Bu^t_3P)_2]$ (0.1 equiv), AcOH (1.5 equiv), $MgSO_4$ (0.5 equiv) in DMA, 14 h 140 °C

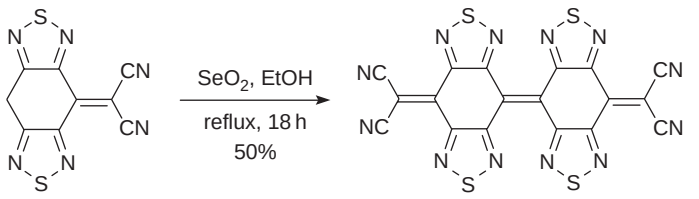


Scheme 15

Bisanilino-substituted benzothiadiazole **104** was oxidized by Ag_2O to afford exclusively the (*E*,*E*)-1,4-quinonediimine **105** (Equation 15) <2002TL9009, 2005JOC2754>. Oxidation of the tricyclic thiadiazole **106** with selenium dioxide in ethanol gave the ethylene **18** (Equation 16) <1997AGE2495> (see Section 5.09.3.1). Bromine oxidation of the dianion of the 7,7′-di(dicyanomethylene)-4,4′-bibenzothiazole **107** gave the quinonedimethane **108** (Equation 17) <1999TL1175>.



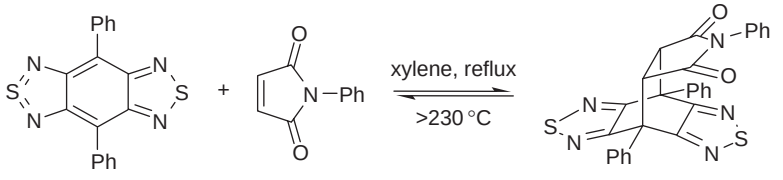
(15)



106 18 (16)

107 108 (17)

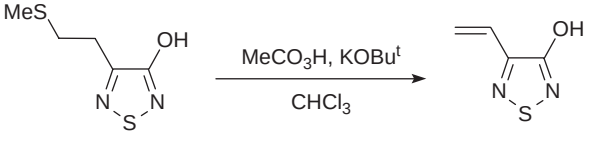
The Diels–Alder reaction of 4,6-dinitrobenzothiadiazole with cyclohexadiene shows only 40% adduct formation (across C-6 and C-7) after 7 days, and this was attributed to the poor electrophilicity as measured by the $pK_a^{H_2O}$ values for water addition ($pK_a^{H_2O} = 7.86$) <2005TL8363>. The deep purple benzobis(thiadiazole) **109** undergoes a Diels–Alder cycloaddition with *N*-phenylmaleimide to afford the colorless 1:1 adduct **110** (Equation 18) <1997T10169>. The adduct reverted to benzobis(thiadiazole) **109** and *N*-phenylmaleimide at its decomposition point (>230 °C).



109 110 (18)

5.09.7.2 Carbon Substituents

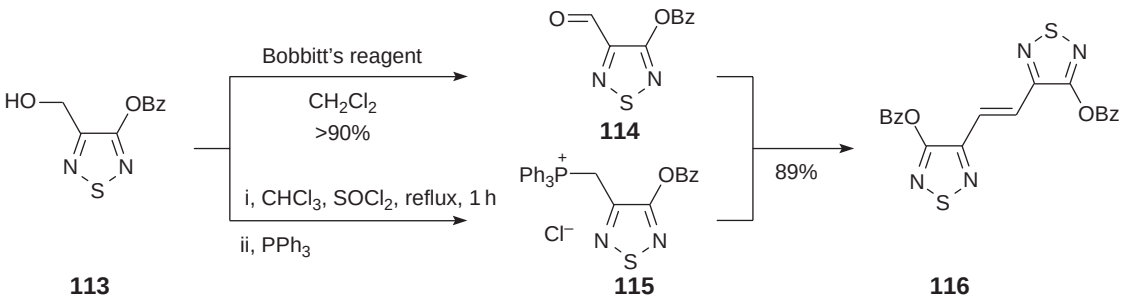
The preparation of the 3-hydroxy-4-vinyl-1,2,5-thiadiazole **112** via oxidative elimination of the thioether **111** according to the published procedure <1966JOC1964> gave unsatisfactory results leading the authors to develop a one-pot procedure for the preparation of the vinylthiadiazole (Equation 19) <2004TL5441>.



111 112 (19)

The olefin metathesis of 3-hydroxy-4-vinyl-1,2,5-thiadiazole **112** and a McMurry coupling reaction (Ti^{3+} under reductive conditions) of the aldehyde **114** were both unsuccessful <2004TL5441>. An alternative approach via a Wittig reaction was successful. With the use of the mild heterogenous oxidant 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perfluoroborate (Bobbitt's reagent), the alcohol **113** was converted into the aldehyde **114**. The phosphonium salt **115** also obtained from the alcohol **113** was treated with the aldehyde **114** to give the symmetrical alkene **116** (**Scheme 16**) <2004TL5441>.

3-Aryl-1,2,5-thiadiazole-4-carboxamides were readily converted into carbonitriles on treatment with either thionyl chloride in benzene at reflux or more surprisingly with P_4S_{10} in pyridine at reflux <2001H(55)75>.

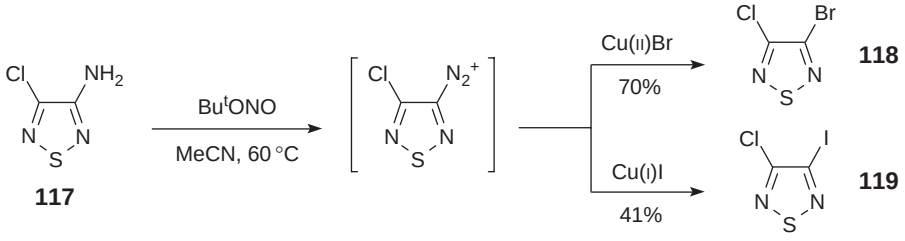


Scheme 16

4-Phenyl-1,2,5-thiadiazole-3-carboxamide can be converted to the methyl 4-phenyl-1,2,4-thiadiazole-3-carboxylate with $BF_3{\cdot}OEt_2$ in MeOH at reflux <2001H(55)75>. Alkyl substituents bearing α-chlorines can be dehalogenated with Pd/C–H_2 in EtOH <1998JME4378>, or with Raney-Ni and H_2 at atmospheric pressure in EtOH <1995USP5418240>.

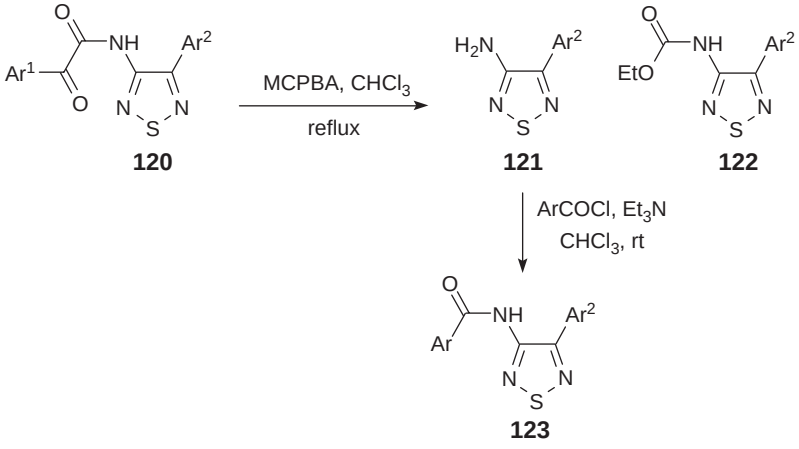
5.09.7.3 Nitrogen Substituents

Unsymmetrical 3,4-dihalo-1,2,5-thiadiazoles **118** and **119** were prepared from 3-amino-4-chloro-1,2,5-thiadiazole **117** via a Sandmeyer-like reaction involving successively *tert*-butyl nitrite and either copper bromide or copper iodide in anhydrous acetonitrile (**Scheme 17**) <2003H(60)29>. The bromo and iodo thiadiazoles **118** and **119** undergo selective Stille and Suzuki C–C coupling chemistry (see Section 5.09.7.6).



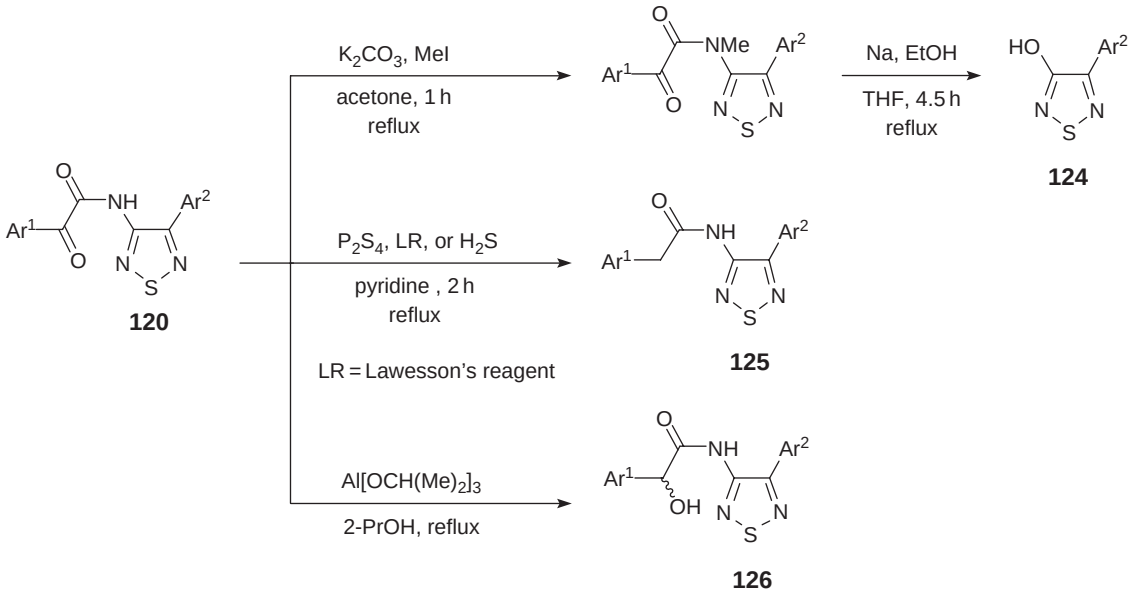
Scheme 17

3-Aroylformamido-4-aryl-1,2,5-thiadiazoles **120** on treatment with MCPBA in chloroform at reflux afford 3-amino-4-aryl-1,2,5-thiadiazoles **121** (**Scheme 18**), but in the presence of ethanol the 3-ethoxycarbamoyl-4-aryl-1,2,5-thiadiazole **122** was also isolated <1999JHC515>. *N*-Aroylation could readily be achieved to give thiadiazoles **123** using the acid chloride in chloroform at room temperature.



Scheme 18

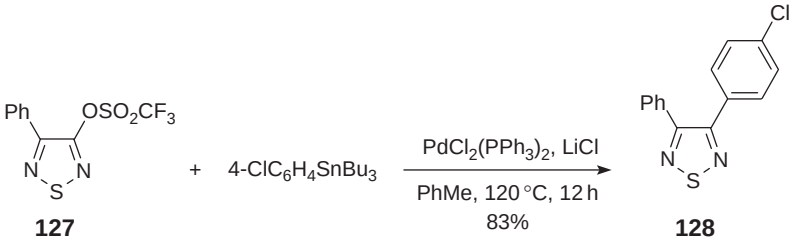
Furthermore, the aroylformamido **120** can be *N*-methylated with MeI in acetone and then subjected to hydrolysis using sodium ethoxide in THF to afford the 3-hydroxythiadiazole **124**. The aroylformamido **120** can also be selectively deoxygenated to 3-aryl-4-arylacetamido-1,2,5-thiadiazole **125** using either phosphorus pentasulfide, Lawesson's reagent, or hydrogen sulfide. Selective reduction to the alcohol **126** can be achieved using aluminium isopropoxide (**Scheme 19**) <1999JHC515>.



Scheme 19

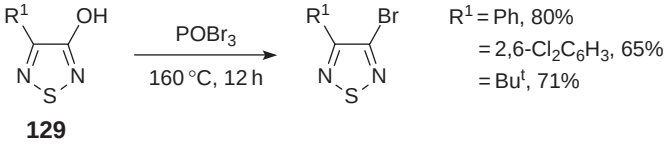
5.09.7.4 Oxygen Substituents

3-(4-Chlorophenyl)-4-phenyl-1,2,5-thiadiazole **128** was prepared from 3-trifluoromethylsulfonyloxy-4-phenyl-1,2,5-thiadiazole **127** by palladium-catalyzed cross-coupling reaction with the tributyl(4-chlorophenyl)stannane (Equation 20) <1996H(43)2435>. The addition of lithium chloride improves the yield. The 3-chloro- and 3-bromo-1,2,5-thiadiazole derivatives were also reactive, but only the bromo compound gave the product in comparable yield (see Section 5.09.7.6).



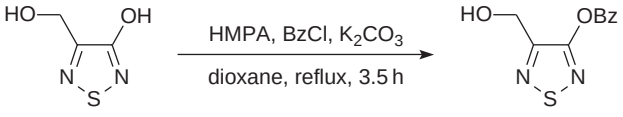
(20)

Bromination of 3-hydroxy-1,2,5-thiadiazoles **129** was achieved using phosphorus oxybromide; however, vigorous conditions are required (Equation 21) <1996H(43)2435>.

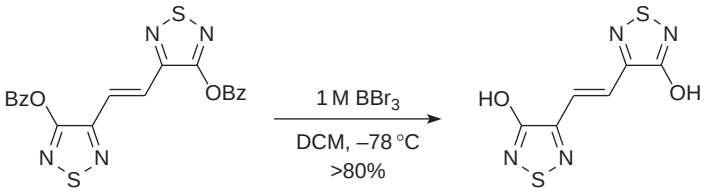


(21)

3-Hydroxythiadiazole and neat trimethyl orthoacetate showed a 20:80 ratio of *N*- versus *O*-alkylation products by ^{1}H NMR <2002EJO1763>. The acidic hydroxyl group of thiadiazole **130** can be selectively protected as the benzyl ether **113** (Equation 22) <2004TL5441>. Nonhydrogenative debenzylation of the bisbenzyl thiadiazole **116** was achieved with boron tribromide to afford the bis-1,2,5-thiadiazole **131** (Equation 23) <2004TL5441>.

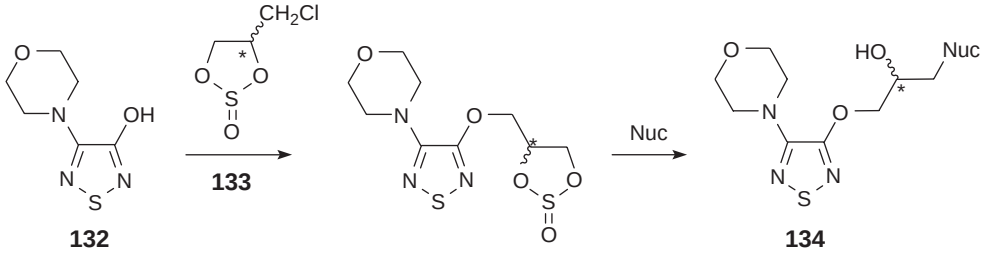


130 **113** (22)



116 **131** (23)

O-Alkylation of 4-hydroxy-3-morpholino-1,2,5-thiadiazole **132** has been achieved with the chiral cyclic chloromethyl sulfite **133** which subsequently suffers ring opening on treatment with simple alcohols <2001RCB436> or alkylamines <2002RJO213> to afford the timolol analogues **134** with very little racemization (**Scheme 20**). This indicated an almost exclusive attack of the oxy anion on the exocyclic carbon atom and is a significant improvement on the previous oxirane method, which suffers from racemization. An alternative biocatalytic asymmetric synthesis of (*S*)- and (*R*)-timolol has also appeared <2004S1625>.

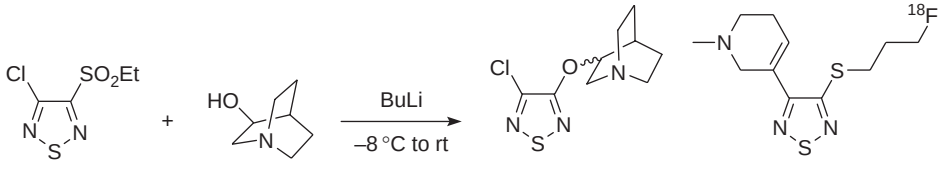


132 **133** **134**

Scheme 20

5.09.7.5 Sulfur Substituents

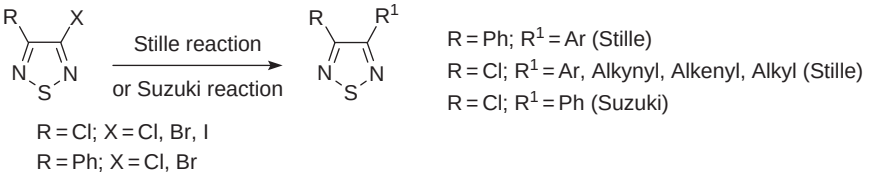
Alkanesulfonyl substituents are good leaving groups and undergo nucleophilic displacement often under mild conditions and in good yields when treated with primary and secondary alkoxides <1998BML2897, 1998JME379, 1999JME1999>, primary alkanethiolates <1998JME379>, and sulfides <1997JME538, 1998BML2897> to afford the corresponding alkyl ethers, thioethers, and thiols. In a direct competition, the sulfonyl group was preferentially displaced from 3-chloro-4-ethanesulfonyl-1,2,5-thiadiazole **135** to give exclusively and in good yield the 3-alkoxy-4-chloro-1,2,5-thiadiazole **136** (Equation 24) <1998JME379>. An automated radiosynthesis of the ^{18}F fluoropropylthio-1,2,5-thiadiazole **137** has recently been developed <2003NMB73>.



135 **136** **137** (24)

5.09.7.6 Halogens

Halogenated thiadiazoles can undergo both Stille <1996H(43)2435, 2003H(60)29> and Suzuki <2003H(60)29> reactions (Equation 25). In the presence of triphenylphosphine ligands, 3,4-dichloro-1,2,5-thiadiazole suffered side reactions resulting from concurrent decomposition of the heterocyclic ring. The problem was overcome with the use of the more reactive and selective 3-bromo-4-chloro- and 3-chloro-4-iodo-1,2,5-thiadiazoles **118** and **119** (see Section 5.09.7.3). The triflate also undergoes the Stille coupling (see Section 5.09.7.4).



(25)

A reinvestigation of the reactions of 3,4-dichloro- and 3-chloro-4-hydroxythiadiazoles with a variety of acetylene nucleophiles (NaC≡CNa, LiC≡C–TMS, LiC≡C–$SnMe_3$) showed consumption of the starting thiadiazoles with no significant higher molecular weight products being formed <2004TL5441>.

Hydrolysis of chloro-substituted thiadiazoles to hydroxythiadiazoles proceeds readily with aqueous sodium or potassium hydroxide in dimethyl sulfoxide (DMSO) at 100 °C <1995JME2038, 1998JME379>. Aryl ethers were successfully prepared using Ullmann-type coupling with copper at elevated temperatures; however, phenols with electron-withdrawing groups (CF_3 or NO_2) failed to react. <2001RJO1330>. Benzyl, allyl, and alkyl ethers can readily be prepared from the corresponding alcohols using a wide range of bases <1999AP191, 2000AP113>. Similarly, tethered 1,2,5-thiadiazole derivatives have been prepared in high yield starting from various ethylene glycols <2001JME4563, 2003JME4273> and from dihydroxyalkanes <2003JME4273>.

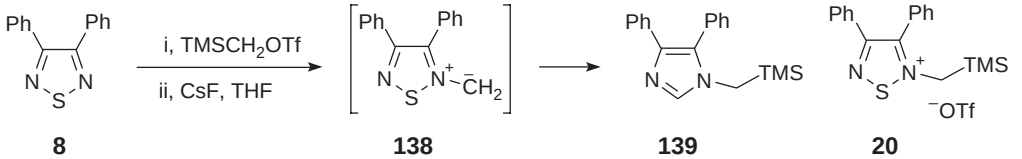
The reaction of chlorothiadiazoles with alkali metal sulfides in DMF or ethanol produces the corresponding thiadiazole thiolate salts <1996JPC17452, 1996EJM221, 1998JME109, 1998JME379, 1998BML2897, 1999JME1999, 2001JME4563>. In almost all cases, the salts are prepared *in situ* and directly *S*-alkylated with alkyl bromides or iodides to give the alkyl thioethers. Treatment of 3,4-dichloro-1,2,5-thiadiazole with Na_2Se prepared *in situ* from $NaBH_4$ and gray Se in EtOH led to only partial selenation and surprisingly some thiolation in a ratio of $Se_{0.4}/S_{0.6}$ <2003POL2175>. The nucleophilic source of sulfur presumably derived from thiadiazole degradation.

There are examples of nucleophilic displacement of halide from halo-1,2,5-thiadiazoles by ammonia, primary alkylamines, secondary alkylamines, arylamines, sulfonamides, and phthalimide <1984CHEC(6)513, 1996CHEC-II(4)355>, but the reactions often require high temperatures and excess of the nucleophile.

5.09.8 Reactivity of Substituents Attached to Ring Heteroatoms

5.09.8.1 *N*-Linked Substituents

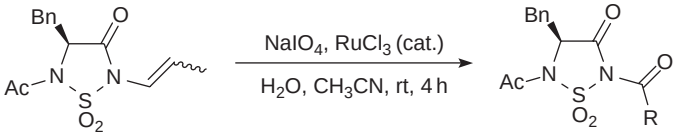
An unexpected one-pot two-step transformation of 3,4-diphenyl-1,2,5-thiadiazole **8** via the intermediate trimethylsilylmethylated 3,4-diphenyl-1,2,5-thiadiazolium triflate **20** gave the 1-trimethylsilylmethyl-4,5-diphenylimidazole **139**. The proposed reaction mechanism invokes desilylation of thiadiazolium **20** with CsF to afford the methide **138** (**Scheme 21**) <1999J(P1)1709>.



8 **138** **139** **20**

Scheme 21

Mild allylic oxidation of the *N*-2-crotyl-substituted thiadiazolidinone 1,1-dioxide **140** by sodium metaperiodate/ruthenium trichloride hydrate ($RuCl_3$) gave the aldehyde **141**. Excess oxidizing agent afforded the carboxylic acid **142** (Equation 26) <1999EJO2275>.

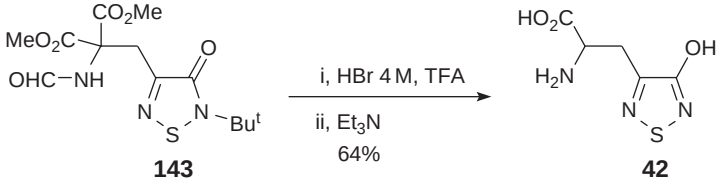


140

141: R = H
142: R = OH

(26)

The *t*-butyl group was removed from the *N*-2-substituted thiadiazol-3-one **143** in the presence of aqueous hydrogen bromide and TFA to afford (*R,S*)-2-amino-3-(3-hydroxy-1,2,5-thiadiazol-4-yl)propionic acid **42** (Equation 27) <2002BMC2259>.



143 **42**

(27)

5.09.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

5.09.9.1 Synthesis of 1,2,5-Thiadiazole Rings

5.09.9.1.1 Formation of one S–N bond

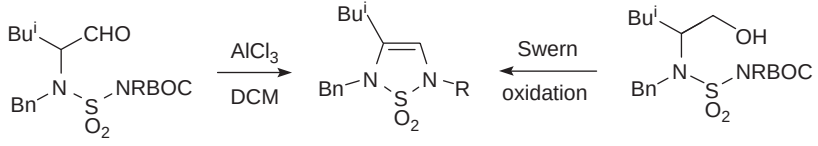
5.09.9.1.1(i) From (1-cyanocyclopentyl)imidosulfurous dichloride

The only example of this kind is the thermal isomerization of 1-cyanocyclopentyl-iminosulfur dichloride into 3-chloro-4-(4-chlorobutyl)-1,2,5-thiadiazole. The reaction has been previously reviewed in CHEC(1984) <1984CHEC(6)513, 1973JOU2522>.

5.09.9.1.2 Formation of one N–C bond

5.09.9.1.2(i) From *N*-(2-haloethyl)sulfamides and related compounds

Intramolecular base-catalyzed cyclization of the acyclic *N*-(2-haloethyl)sulfamides affords thiadiazolidine 1,1-dioxides <2000T381, 2003T6051, 2003TL5483, 2005MOL1387>. A somewhat similar cyclization mode gave the thiadiazolidine 1,1-dioxide **145** in high yield either from the readily available aldehyde **144** on treatment with anhydrous $AlCl_3$ or from the Swern oxidation of the alcohol **146** (**Scheme 22**) <2004BMC6249>.



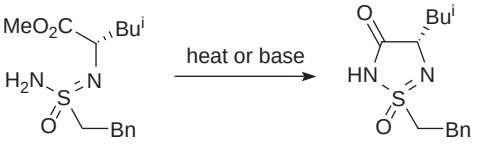
144
R = phenylethyl

145 **146**

Scheme 22

The related intramolecular cyclization of acyclic *N*-(2-hydroxyethyl)sulfamides was successfully achieved using Mitsunobu conditions <2000T381, 2004BMC589>. Cyclizations of acyclic 2-(sulfamoylamino)acetates derived from α-amino esters afford thiadiazolidinone 1,1-dioxides <1996T993, 1999HCA2432, 2000JHC773, 2000T381, 2005BML2503>. Furthermore, a five-step solid-phase synthesis of 2-unsubstituted 1,2,5-thiadiazolidines

1,1-dioxides from N^{α}-FMOC amino acids and aromatic aldehydes was reported <2000TL3161>. Heating of a solution of the acyclic sulfonimidamide **147** at 60 °C or treatment of a methanolic solution of **147** with anhydrous ammonia at room temperature gave the unexpected cyclic sulfonimidamide **148** (Equation 28) <1999BML1527>.

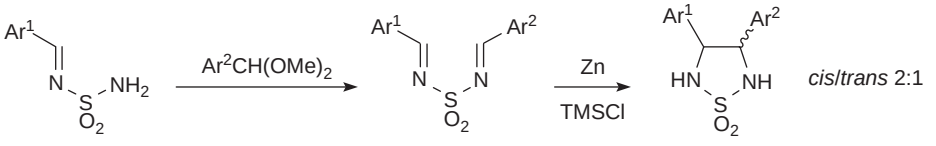


147 **148** (28)

5.09.9.1.3 Formation of one C–C bond

5.09.9.1.3(i) From unsymmetrical dibenzylidene sulfamides

Intramolecular reductive cross-coupling of unsymmetrical dibenzylidene sulfamides **149** generated the corresponding cyclic sulfamides **150** in good yield (**Scheme 23**) <1996TL2859>.



149 **150**

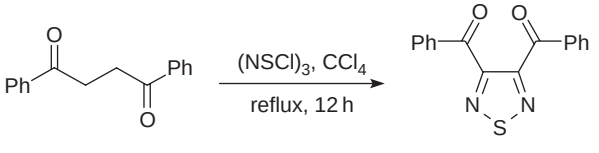
Scheme 23

5.09.9.1.4 Formation of two N–C bonds; [2+3] atom fragments

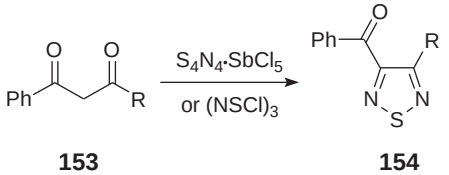
Benzylic methylenes, 1,3-diketones such as diaroylmethanes and aroylacetones, alkenes and alkynes are all known to give 1,2,5-thiadiazoles when treated with a variety of sulfur sources and much of this work has been reviewed in CHEC(1984) and CHEC-II(1996). Recent developments are outlined below.

5.09.9.1.4(i) From activated methylene compounds

The 1,4-diketone 1,2-dibenzoylethane **151** can be transformed in one step into 3,4-dibenzoyl-1,2,5-thiadiazole **152** when treated either with preformed trithiazyl trichloride in tetrachloromethane (Equation 29) <1997J(P1)2831> or with urethane, thionyl chloride, and pyridine in benzene (Katz reagent) <2002ARK90> (see also Section 5.09.9.2.1(iii)(b)). Similarly, treatment of 1,3-diketones **153** with tetrasulfur tetranitride antimony pentachloride complex in toluene at 100 °C <1998J(P1)2175>, or trithiazyl trichloride in boiling tetrachloromethane <1997J(P1)2831>, affords 4-substituted-3-aroyl-1,2,5-thiadiazoles **154** (Equation 30).



151 **152** (29)



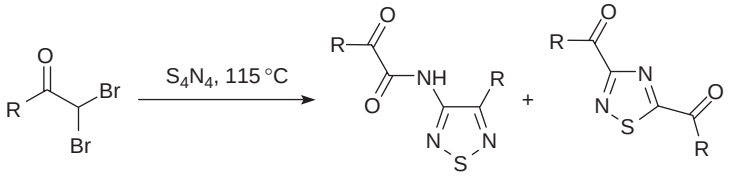
153 **154** (30)

R	*Reagent*	*Yield* [a](%)	*Reference*
Me	S_4N_4·$SbCl_5$	10	1998J(P1)2175
Me	$(NSCl)_3$	25	1997J(P1)2831
Ph	S_4N_4·$SbCl_5$	21	1998J(P1)2175
Ph	$(NSCl)_3$	41	1997J(P1)2831

[a]Based on recovered **153**.

These reactions were proposed to proceed via electrophilic attack on the enol by the SN reagents at N followed by cyclization either via a second enol as in compound **151** or by cyclization onto the more reactive carbonyl <1997J(P1)2831>. Unsymmetrical 1,3-diketones can give a mixture of regioisomers if both carbonyls have similar reactivities; however, aroylacetones react regiospecifically to afford only the 3-aroyl-4-alkyl-1,2,5-thiadiazoles **154** (R = Me).

3-Aroylformamido-4-aryl-1,2,5-thiadiazoles **156** can also be prepared from aryl dibromomethyl ketones **155** on treatment with tetrasulfur tetranitride at 115 °C (Equation 31) <1995J(P1)253>. These reactions are, however, complex, and the 1,2,4-thiadiazole **157** is often produced as a minor product.

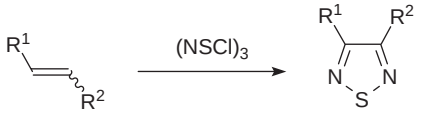


155 **156** **157** (31)

No mechanistic discussion was offered and the proposed conversion of 1,2,5-thiadiazole **156** into 1,2,4-thiadiazole **157** with MCPBA <1995J(P1)253> was incorrect, the error caused by incompletely purified 1,2,5-thiadiazole <1999JHC515>. In contrast, monohalogenated methyl aryl ketones gave 1,2,4-thiadiazoles **157** with tetrasulfur tetranitride in chlorobenzene at 110–115 °C <1992JHC1433>.

5.09.9.1.4(ii) From alkenes

Treatment of ethenes **158** with trithiazyl trichloride afforded 1,2,5-thiadiazoles **159** in moderate to good yields (Equation 32; **Table 10**). The reaction, however, suffers from the possibility of chlorination at allylic or benzylic positions, in particular if excess trimer is used.



158 **159** (32)

Table 10 Reaction of alkenes **158** with trithiazyl trichloride to give 1,2,5-thiadiazoles **159**

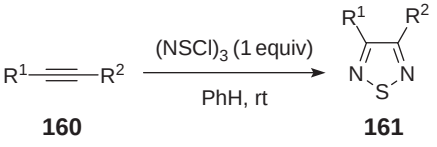
R^1	R^2	*Stereo*	*Equiv.* $(NSCl)_3$	*Conditions*	*Yield* (%)	*Reference*
Ph	CH_2CI	*trans*	1	PhH, reflux, 17 h	56	1997J(P1)2831
Ph	COPh		2	CCI_4, reflux, 12 h	60	1997J(P1)2831
Ph	Ph	*trans*	1.5	PhMe, 16 h	28	1997J(P1)2597
PhCO	COPh	*trans*	1	CCI_4, 10 h	42	1997J(P1)2597
MeO_2C	CO_2Me	*cis*	1	PhH, 16 h	52	1997J(P1)2597
Phthalimido	H		3	THF, 12 h	38[a]	1997J(P1)2597
2-Pyridyl	2-Pyridyl	*trans*	1	PhMe, Py, rt–reflux, 18 h	49	2002JCD2775

[a]With 4 Å molecular sieves.

With trisubstituted ethene (*Z*)-ethyl 4-phenyl-3-benzylbut-2-enoate, debenzylation gave the 4-phenyl-1,2,5-thiadiazole-3-carboxylate <1997J(P1)2831>. The trithiazyl trichloride transformation provided a new route to 3-amino-1,2,5-thiadiazole starting from *N*-vinylphthalimide <1997J(P1)2597>, overcoming a problematic multistep synthesis from aminoacetamidine and disulfur dichloride. Katz reagent (urethane, thionyl chloride, and pyridine in benzene) also afforded 1,2,5-thiadiazole with either *cis*- or *trans*-1,2-dibenzoylethene though in low yield <2002ARK90> (see also Section 5.09.9.2.1(iii)(b)).

5.09.9.1.4(iii) From alkynes

Trithiazyl trichloride <1997J(P1)2597, 1997J(P1)2831> converted ethynes **160** into 1,2,5-thiadiazoles **161** in moderate to good yield although some chlorination was sometimes observed (Equation 33) <1997J(P1)2597>. 1,2-Dibenzoylethyne also gave the corresponding thiadiazole with urethane, thionyl chloride, and pyridine in benzene (Katz reagent) in 27% yield <2002ARK90> (see also Section 5.09.9.2.1(iii)(b)).

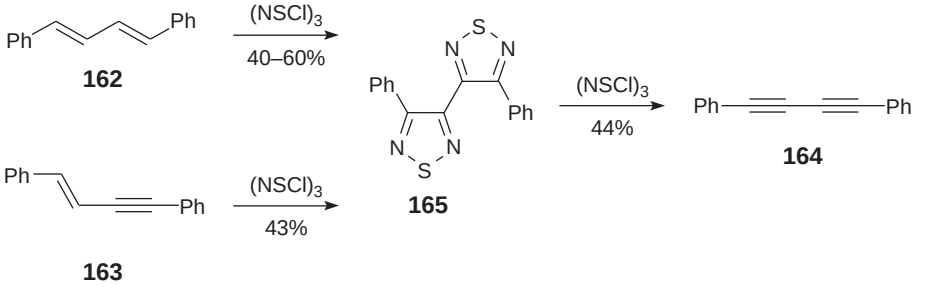


160 **161**

R^1	R^2	*Yield* (%)	*Reference*
Ph	H	62	1997J(P1)2597
Ph	Ph	32	1997J(P1)2597
MeO_2C	MeO_2C	84	1997J(P1)2597

(33)

Similarly, conjugated dienes, enynes, and diynes such as (*E*,*E*)-1,4-diphenylbuta-1,3-diene **162**, (*E*)-1,4-diphenylbut-1-en-3-yne **163**, or 1,4-diphenylbuta-1,3-diyne **164** on treatment with trithiazyl trichloride (2 equiv) afforded the bisthiadiazole **165** in moderate to good yield (40–60%), depending on the reaction conditions (**Scheme 24**) <1997CC1493, 1997J(P1)3189, 1998CC1207>.



162 **165** **164** **163**

Scheme 24

5.09.9.1.5 Formation of two S–N bonds; [4+1] atom fragments

The majority of [4+1] methods has been extensively reviewed in CHEC(1984) and CHEC-II(1996) and includes conversion of aliphatic 1,2-diamines, 1,2-diimines and dioximes, cyanogen, 2-aminoacetamides, 2-aminoacetamidine, ethyl oxamidates, 2-cyano-2-oximino acetamides, and cyanoformamide and its esters. Below, the recent developments over the last decade are highlighted.

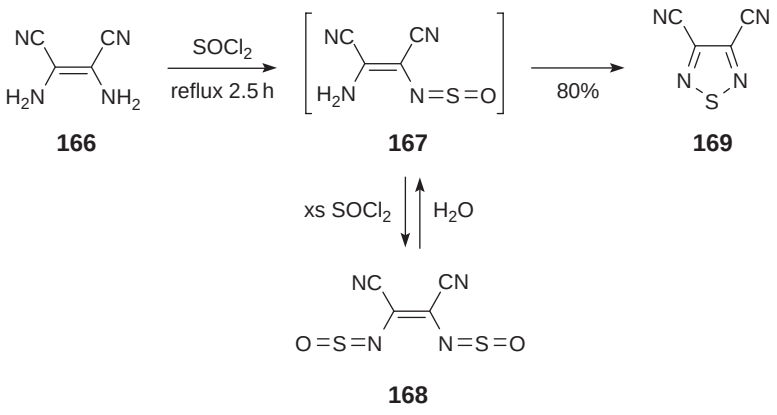
5.09.9.1.5(i) From aliphatic 1,2-diamines

The conversion of aliphatic 1,2-diamines into 1,2,5-thiadiazoles can be achieved using a wide variety of sulfur sources such as tetrasulfur tetranitride, disulfur dichloride, sulfur dichloride, thionyl chloride, and *N*,*N*′-ditosylsulfur diimide. Recently, ethylenediamine has been treated with sulfur dichloride and disulfur dichloride in the presence of catalytic $FeCl_3$ to afford both mono- and bischlorinated thiadiazoles <2001RJO1330>. A reinvestigation of the preparation of 1,2,5-thiadiazole-3,4-dicarbonitrile **169** from (*Z*)-2,3-diamino-2-butenedinitrile (diaminomaleonitrile, DAMN) **166** using neat excess thionyl chloride gave the red crystalline 1,2-bisisothiocyanato derivative **168**, which reacts almost explosively with small amounts of water to produce the thiadiazole **169**. The reaction pathway proposed involves the monoisothiocyanato **167**, and hydrogen chloride generated probably catalyzes the elimination of water to form the thiadiazole (**Scheme 25**) <1995SR299>.

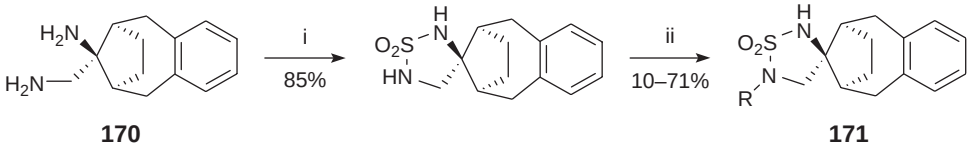
Treatment of enantiomerically pure (*R*,*R*)- and (*S*,*S*)-1,2-bis(pentafluorophenyl)ethane-1,2-diamines with thionyl chloride gave the corresponding thiadiazolidine 1-oxides in high yield <2004BCJ1001>. A series of *N*-alkyl-substituted thiadiazolidine 1,1-dioxides **171** were also prepared from the starting 1,2-diamine **170** by treatment with sulfamide followed by a regioselective monoalkylation (**Scheme 26**) <2005BML4212>.

5.09.9.1.5(ii) From cyanoaminium salts and related compounds

The synthesis of 1,2,5-thiadiazoles from amino acetonitrile salts **172** was reviewed in CHEC-II(1996). Owing to the ready formation of 2-amino acetonitrile salts from aldehydes via a one-pot Strecker synthesis, this synthetic pathway



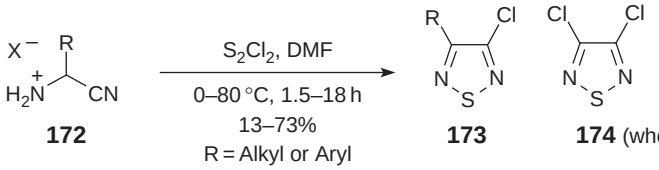
Scheme 25



i, $(H_2N)_2SO_2$, pyridine, reflux, 24 h
ii, NaH, alkyl halide, DMF, rt, 24 h

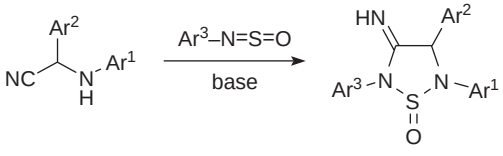
Scheme 26

has remained popular and several chloro-1,2,5-thiadiazoles **173** have recently been prepared (Equation 34) <1995JME2038, 1995USP5418240, 1997BML1293, 1998JME109, 1999JME1999, 1999CPB876, 2000AP113>. Often the amino acetonitriles were not isolated and characterized but added directly to a cooled solution of disulfur dichloride in DMF and the reported yields are based on the aldehyde precursor <1998JME109, 1999CPB876>.



(34)

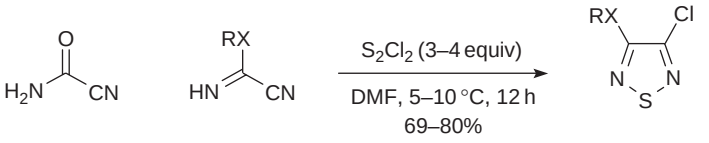
Cycloaddition reactions between *N*-sulfinylanilines and *N*-(α-cyano-α-aryl)methylanilines **175** provide 2,3,5-triaryl-4-imino-2*H*,3*H*,5*H*-[1,2,5]thiadiazolidine 1-oxides **176** in good yields (Equation 35) <1999SC911>.



(35)

5.09.9.1.5(iii) From cyanoformamide and its esters

The preparation of thiadiazoles **180** from 1-cyanoformamide **177** (2-nitrilo-acetimidic acid), or its alkyl esters **178**, using disulfur dichloride under mild conditions was previously reviewed in CHEC(1984) and CHEC-II(1996). The synthesis of thiadiazoles from the thioesters **179**, formed by the addition of alkylthiols to cyanogens, was more recently investigated (Equation 36) <1998JME379>. In several cases, the esters **178** or thioesters **179** prepared from cyanogen were not isolated but added directly to disulfur dichloride <1996WO38431, 1998JME379>.

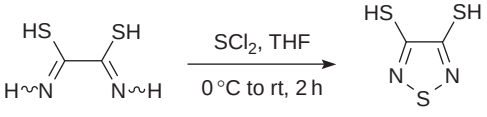


(36)

177 **178**: X = O; R = alkyl
179: X = S; R = alkyl **180**

5.09.9.1.5(iv) From 1,2-diimines and related compounds

N,*N*′-Unsubstituted 1,2-diimines, *N*,*N*′-bistrimethylsilyl- and *N*,*N*′-bischloro-1,2-diimines, 1,2-dioximes, 1,2-bishydrazone, and diimidamides have all been treated with various sources of electrophilic sulfur to afford 1,2,5-thiadiazoles, and these reactions are reviewed in both CHEC(1984) <1984CHEC(6)513> and CHEC-II(1996) <1996CHEC-II(4)355>. Recently, dithiooxamide **181** was treated with sulfur dichloride and gave the thiadiazole **182**; no yields were reported (Equation 37) <2001JMC1992>.

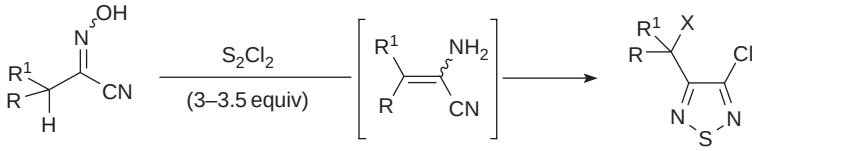


(37)

181 **182**

5.09.9.1.5(v) From 2-oximino acetonitriles

The reaction between 2-oximino acetonitriles **183** and disulfur dichloride was used to prepare several 3-chloro-4-alkyl-1,2,5-thiadiazoles for muscarinic agonist studies <1995USP5418240, 1998H(48)2111, 1996EJM221, 1997JME538, 1997CH739>. The main thiadiazole product **185**, however, suffered chlorination in the α-position. The isolation of 2-amino acrylonitrile **184** from the reaction mixture supported decomposition of the 2-oximino acetonitrile **183**; furthermore, treatment of the pure acrylonitrile under typical reaction conditions gave exclusively α-chloro-3-chloro-1,2,5-thiadiazole **185** (**Scheme 27**; **Table 11**). Mechanisms explaining the formation of both thiadiazoles were proposed <1998H(48)2111>.



183 **184** **185**: X = Cl (major product)
186: X = H (minor product)

Scheme 27

Table 11 Reaction of oximinoacetonitriles with disulfur dichloride to give thiadiazoles **185**

RR^1*CH*[a]	*Conditions*	*Yield* **185**(%)	*Reference*
	DMF, 0 °C to rt, 42 h	n.d.[c]	1996EJM221
	MeCN/MeCONMe$_2$ (3:1), −10 to 30 °C, 15 h	70	1998H(48)2111
	DMF, 0–20 °C, 12 h[b]	65[d]	1997CH739

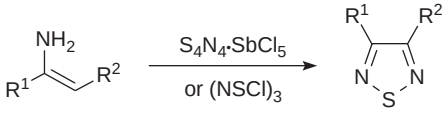
[a]All are epimeric.
[b]12 h = overnight.
[c]n.d. = no data.
[d](2*R*, 3*R*)-tartrate salt, *endo*- and *exo*-diastereomers (9:1).

5.09.9.1.6 Formation of one S–N and one N–C bond; [2+3] atom fragments

The treatment of aliphatic monoamines, benzil monooxime, benzil monohydrazone, and alkyl, monohaloalkyl arylketoximes bearing two or three α-hydrogens with tetrasulfur tetranitride to afford 1,2,5-thiadiazoles was presented in CHEC(1984) and CHEC-II(1996).

5.09.9.1.6(i) From enamines

Enamines **187** with electron-withdrawing groups in the β-position are converted into thiadiazoles **188** in moderate yields (50–60%) on treatment with either tetrasulfur tetranitride antimony pentachloride complex <2000H(53)159> or trithiazyl trichloride <2001J(P1)662> (Equation 38; **Table 12**). Cyclization onto electrophilic β-substituents was not observed, and thus the procedure offers a regiospecific synthesis of 4-substituted-3-aroyl-1,2,5-thiadiazoles.



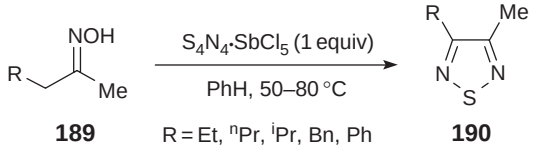
187 **188** (38)

Table 12 Formation of thiadiazoles **188** from enamines

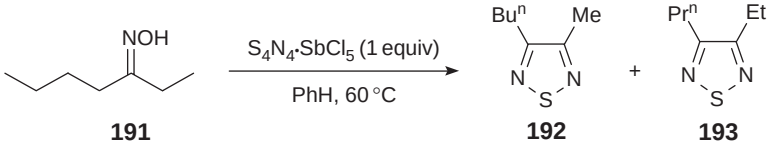
R^1	R^2	*Reagent*	*Solvent*	*Time* (*h*)	*Yield* **188** (%)	*Reference*
Ph	COPh	$S_4N_4{\cdot}SbCl_5$	PhMe, 100 °C	1	50	2000H(53)159
Ph	CO_2Et	$S_4N_4{\cdot}SbCl_5$	PhMe, 100 °C	1	54	2000H(53)159
Me	CN	$(NSCl)_3$	CCl_4, 20 °C	16	28	2001J(P1)662
Me	CO_2Me	$(NSCl)_3$	CCl_4, 20 °C	16	62	2001J(P1)662

5.09.9.1.6(ii) From alkyl aryl ketoximes

Unlike the reaction of alkyl aryl ketoximes with tetrasulfur tetranitride <1996CHEC-II(4)355>, the treatment of alkyl methyl ketoximes **189** with tetrasulfur tetranitride antimony pentachloride complex in either benzene or toluene at 50–80 °C gave low yields (3–37%) of 3-alkyl-4-methyl-1,2,5-thiadiazoles **190** (Equation 39) <1999H(50)147>. Compounds **190** were volatile and the low yields are in part attributed to their loss as the solvent was removed *in vacuo*. Suprisingly, only single regioisomers were obtained. 3-Heptanone oxime **191** did, however, give a mixture of two isomers **192** and **193** (Equation 40).



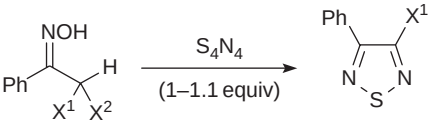
189 **190** (39)



191 **192** **193** (40)

192:**193** 64:100 by GCMS

In a development on the reaction of monohaloalkyl aryl ketoximes with tetrasulfur tetranitride, the introduction of two halogens such as chlorine, bromine, or fluorine at the α-position of alkyl aryl ketoximes significantly improved the yields of thiadiazoles <1998J(P1)109>. The preferential displacement of chlorine over bromine or fluorine allowed the preparation of monobromo- and monofluoro-3-aryl-thiadiazoles **195** from α,α-chlorobromoalkyl- and α,α-chlorofluoro-alkyl aryl ketoximes **194** (Equation 41).



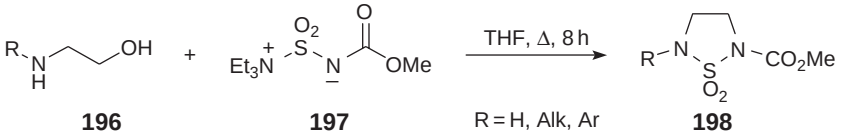
194 195

X^1	X^2	Time (h)	Yield (%)	Reference
Cl	Cl	4	98	1998J(P1)109
Br	Br	3	95	1998J(P1)109
F	Br	5	32	1998J(P1)109
F	Cl	3	65	1998J(P1)109

(41)

5.09.9.1.6(iii) From Burgess-type reagents

Aminoalcohols **196** react with Burgess-type reagents **197** to afford unsymmetrical cyclic sulfamides **198** (Equation 42) <2002AGE3866, 2004CEJ5581>.

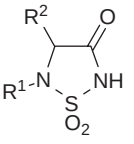


196 197 198

(42)

5.09.9.1.6(iv) From α-amino esters

Treatment of α-amino esters with sulfonamide in the presence of DBU at 160 °C also affords 2-unsubstituted-1,2,5-thiadiazolidin-3-one 1,1-dioxides **199** in moderate yield <2005SL834>.



199

5.09.9.1.7 Formation of three bonds: Two N–S bonds and one C–C bond

5.09.9.1.7(i) Formation by reaction of potassium cyanide with sulfur dioxide

A testament to the aromatic driving forces leading to the 1,2,5-thiadiazole ring system is the three-component synthesis of 4-hydroxy-1,2,5-thiadiazole-3-carbonitrile starting from KCN and SO_2. The reaction has been previously reviewed in CHEC(1984) <1984CHEC(6)513>. While no mechanistic detail on the formation of the thiadiazole was presented, a recent study on the reaction of tetraalkylammonium cyanide and SO_2 under anhydrous conditions gave the 1:1 adduct tetraalkylammonium cyanosulfite R_4N^+ $[NCSO_2]^-$ <1999JA4019>.

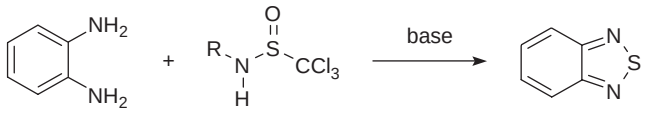
5.09.9.2 Synthesis of Annulated Thiadiazoles

5.09.9.2.1 By annulation to arene

5.09.9.2.1(i) By formation of two S–N bonds

5.09.9.2.1(i)(a) From arene-1,2-diamines

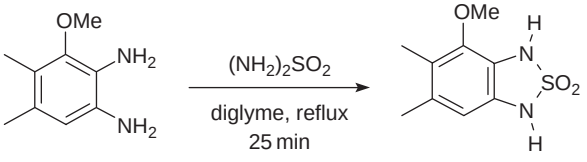
The introduction of sulfur between two *ortho* amino groups is the oldest and still the most commonly used route to benzo- and heteroarene-fused 1,2,5-thiadiazoles. The reaction has been extensively reviewed in both CHEC(1984) and CHEC-II(1996). The *in situ* preparation of *N*-sulfinylaniline via β-elimination of chloroform from trichloromethanesulfinamides **200** was recently supported by trapping with 1,2-benzenediamine to give the benzothiadiazole **2** in 85% yield (Equation 43) <1997TL487>.



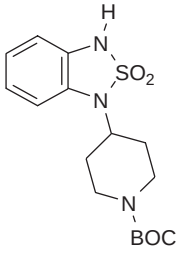
200 2 (43)

Recently, heteroarene-fused thiadiazoles were prepared from the following diamines: 3,4-diamino-4,5-dimethylpyridin-2-one <1995LA787>, 5,6-diaminofurazano[3,4-*b*]pyrazine <1999CHE499>, quinoline-2,3-diamine <2005CGD413>, 4,7-disubstituted-benzothiadiazole-5,6-diamines <1995JA6791, 1997T10169, 2005JA5186>, benzothiadiazole-4,5-diamine <2004JHC955>, and 3,4-dihydro-2*H*-benzo[1,4]oxazine-6,7-diamine <1999CPB971>.

Somewhat less common is the preparation of the analogous *S*-oxides and *S*,*S*-dioxides. Recently, 1,3-dihydro-2,1,3-benzothiadiazole 2,2-dioxides **201** <1999JA10281> and **202** <2004BML5045> were prepared from the corresponding 1,2-diamines using sulfamide (Equation 44).



201 (44)



202

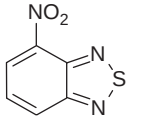
5.09.9.2.1(i)(b) From quinone 1,2-dioximes

Methods for the preparation of fused thiadiazoles starting from quinone 1,2-dioximes have been reviewed in CHEC(1984) and CHEC-II(1996). No recent work has been reported.

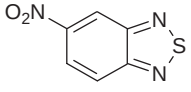
5.09.9.2.1(ii) By formation of one S–N and one N–C bond

5.09.9.2.1(ii)(a) From anilines

This, surprisingly the only reaction of its type, was previously mentioned in CHEC-II(1996) <1996CHEC-II(4)355>, but owing to the ready availability of a wide variety of aniline precursors its repetition here seems appropriate. Nitroanilines react with trithiazyl trichloride in benzene at room temperature to afford 4-nitro- and 5-nitro-substituted benzothiadiazoles **92** and **203** in good yields <1987ZC31>. An investigation of these reactions using ESR spectroscopy revealed the presence of the persistent benzothiadiazol-1-yl radicals in the reaction mixture <1990MRC797>.



92
79% from 2-nitroaniline
75% from 3-nitroaniline



203
89% from 4-nitroaniline

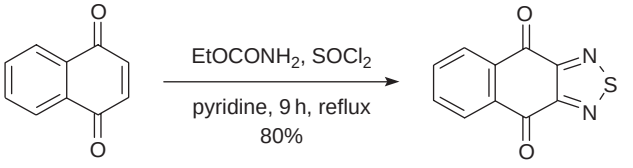
5.09.9.2.1(iii) By formation of two N–C bonds

5.09.9.2.1(iii)(a) From active hydrocarbons, phenols and related compounds, and tetrasulfur tetranitride

The reaction of active hydrocarbons, phenols, and related compounds with tetrasulfur tetranitride affords fused thiadiazoles, and this chemistry is well documented in CHEC(1984) <1984CHEC(6)513> and CHEC-II(1996) <1996CHEC-II(4)355>. No recent work has been reported.

5.09.9.2.1(iii)(b) From quinone or hydroquinones

1,2,5-Thiadiazoles can be fused onto *para*-quinones or hydroquinones using a variety of NSN transfer reagents, such as S_4N_4, $(NSCl)_3$, $S_3N_2Cl_2$, and S_4N_3Cl. A one-pot procedure involving treating the quinones with a mixture of methyl, ethyl, or benzyl carbamate, thionyl chloride, and pyridine in refluxing benzene ('Katz brew') gave the fused thiadiazoles in good yield (cf. Equation 45) <1995JOC1285>. An extensive mechanistic study revealed that the one-pot procedure involved the active species thiazyl chloride (NSCl), which is in equilibrium with the trimer $(NSCl)_3$ <1995JOC1285>.

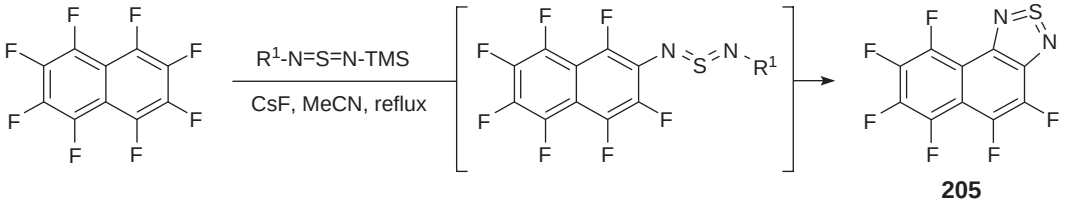


(45)

204

5.09.9.2.1(iii)(c) From perfluoroarenes with sulfur diimides

Treatment of perfluoronaphthalene with *N*-aryl or *N*-alkyl-*N*′-(trimethylsilyl)sulfur diimides <1998CC991> in the presence of CsF gave perfluoro[1,2-*c*][1,2,5]thiadiazole **205** (**Scheme 28**) <2001EJI2123, 2002JFC(115)165>. The CsF deprotects the sulfur diimide to afford a sulfur diimide anion, which can be regarded as a thiazylamide due to the short terminal SN bond <1998CC991>. This reacts with the fluorinated arene to give an intermediate sulfur diimide, which subsequently undergoes intramolecular cyclization to afford the fused thiadiazole (see also Section 5.09.9.2.1(v)(a)).



205

Scheme 28

5.09.9.2.1(iv) By formation of one S–N bond

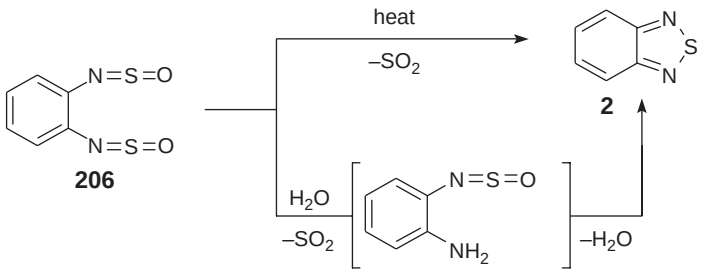
5.09.9.2.1(iv)(a) From 1,2-bis(sulfinylamino)benzene

N,*N*′-Disulfinyl-1,2-diamine **206**, the postulated intermediate in the reaction of benzene-1,2-diamine with thionyl chloride or *N*-sulfinyl toluenesulfonamide to give benzothiadiazole **2** (see Section 5.09.9.2.1(i)(a)), was prepared in near-quantitative yield and fully characterized showing a (*Z*,*Z*)-conformation <2001RJC1050>. On heating or under the action of traces of water, as well as in reactions with $LiN(SiMe_3)_2$ or PCl_5, the sulfinylamine **206** was converted quantitatively into benzothiadiazole **2**. Spectroscopic evidence supported the formation of *N*-sulfinyl-1,2-benzenediamine **207** during the hydrolysis (**Scheme 29**) <2001RJC1050>.

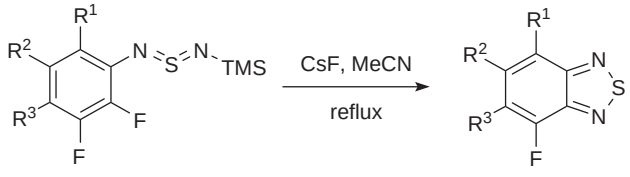
5.09.9.2.1(v) By formation of one N–C bond

5.09.9.2.1(v)(a) From arylsulfur diimides

N-Trimethylsilylarylthiazylamides **208** with an *ortho*-fluoro substituent afford benzothiadiazoles **209** when treated with CsF in refluxing acetonitrile (Equation 46). The reaction has been previously reviewed in CHEC-II(1996) <1990JFC(50)359, 1994HAC561, 2001EJI2123, 2003EJI77>. Arylsulfur diimides are proposed intermediates in the reaction of polyfluorinated arenes and alkyl (trimethylsilyl)sulfur diimides (Section 5.09.9.2.1(iii)(c)) <2002JFC(115)165>.



Scheme 29



R^1	R^2	R^3	*Yield* (%)	*Reference*
H	H	F	58	2003EJI77
F	H	H	55	2001EJI2123
F	F	Me	87	1990JFC(50)359
F	F	Br	66	1990JFC(50)359

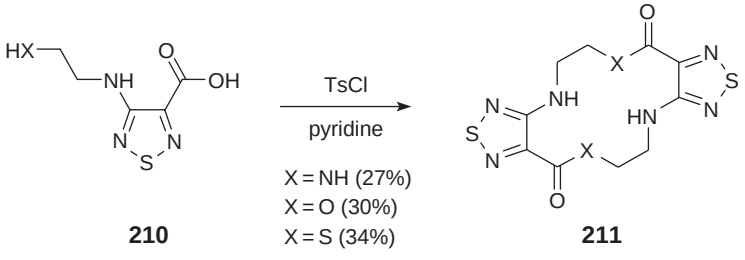
(46)

5.09.9.2.2 By annulation to 1,2,5-thiadiazole

A useful strategy for the formation of fused thiadiazoles is the annulation of suitably functionalized 1,2,5-thiadiazoles. Common routes involve the use of 3,4-difluoro-1,2,5-thiadiazole, 3,4-diamino-1,2,5-thiadiazole, 1,2,5-thiadiazole-3,4-dicarbonyls, 1,2,5-thiadiazole-3,4-dicarbonitrile, amino-1,2,5-thiadiazole-3-carboxamides and carboxamidines. These afford heteroarene-fused 1,2,5-thiadiazoles (which are covered in Volume 9). Below follows a brief description of fused thiadiazoles that fall within the scope of this chapter.

5.09.9.2.2(i) From 1,2,5-thiadiazolamines

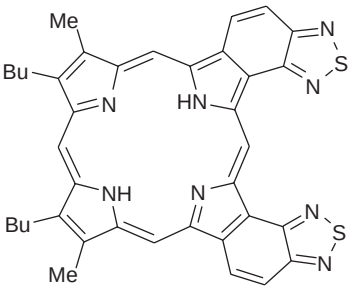
Macrocyclic 14-membered lactams, lactones, and thiolactones **211** have also been prepared from 3-amino-1,2,5-thiadiazole-4-carboxylic acids **210** (Equation 47) <1996CHE975>.



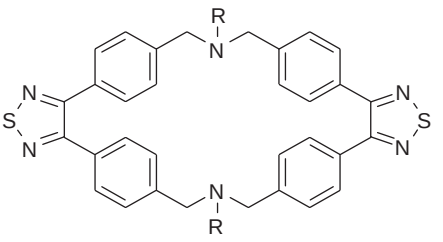
(47)

5.09.9.2.2(ii) Miscellaneous

Several 1,2,5-thiadiazole bearing macrocycles have appeared including the 1,2,5-thiadiazoloporphyrins **212** <1997TL2031, 1998JOC8455> and the acidic (pH < 2) water-soluble diaza-1,2,5-thiadiazolocyclophanes **213** <1997H(46)651>.

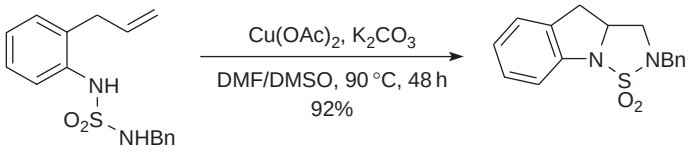


212



213: R = H, *p*-Tos

A $Cu(OAc)_2$-catalyzed intramolecular diamination of alkenes using sulfamide substrates such as compound **214** provides a route to fused thiadiazolidines **215** (Equation 48) <2005JA11250>. In this reaction, the transition metal activates the alkene toward nucleophilic attack by the first nitrogen, then becomes displaced by the second nitrogen nucleophile (a net M^{n+2} to M^n reduction).



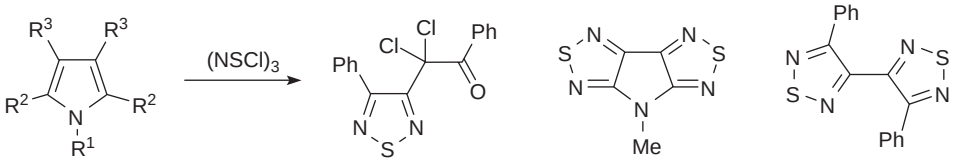
214 **215** (48)

5.09.10 Ring Synthesis by Transformation of Another Ring

CHEC(1984) and CHEC-II(1996) described the preparation of various 1,2,5-thiadiazoles starting from other heterocycles. These include ring transformation of 2-alkyl-1,2,5-thiadiazolium salts, ring contraction of six-membered 1,2,6-thiadiazine and 1,2-thiazine rings, and ring cleavage of a second fused ring. In the latter category, three main degradation methods have been employed: the oxidative degradation of benzothiadiazoles, hydrolysis of heterofused 1,2,5-thiadiazoles such as 7-amino[1,2,5]thiadiazolo[3,4-*d*]-pyrimidines, [1,2,5]thiadiazolo[3,4-*d*]pyrimidinones, and [1,2,5]thiadiazolo[3,4-*c*][1,2,5]-thiadiazole, and Beckmann fragmentation of 4- and 5-monoacetoxime 2,1,3-benzothiadiazole-4,5-diones. A similar degradation was also obtained from the photolytic treatment of [1,2,5]thiadiazolo[3′,4′:3,4]benzo[1,2-*c*][1,2,5]oxadiazole in the presence of triethyl phosphate. Recently, several new transformations have appeared and these are outlined in this section.

5.09.10.1 From *N*-Alkylpyrroles

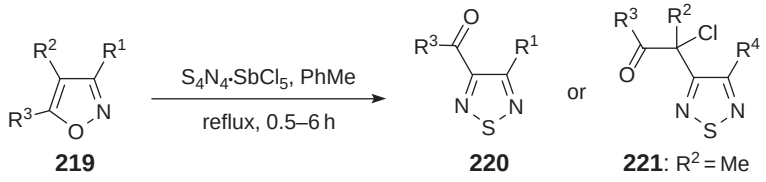
N-Alkylpyrroles undergo cycloaddition reactions with trithiazyl trichloride $(NSCl)_3$ to afford, depending on the substituents R^1, R^2, and R^3, thiadiazoles **216–218**. The reactions are proposed to proceed by addition of the N–S(Cl)–N fragment across the 2,3- and the 4,5-bonds of the *N*-alkylpyrrole, followed by a series of eliminations to give the observed products (Equation 49) <1997CC1493, 1997J(P1)3189>.



216: R^1 = Ph; R^2 = Br **217**: R^1 = Me; R^2 = H **218**: R^2 = Ph; R^3 = H (49)

5.09.10.2 From Isoxazoles

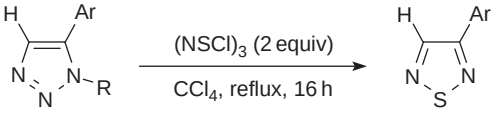
Several substituted isoxazoles **219** react with tetrasulfur tetranitride antimony pentachloride complex ($S_4N_4{\cdot}SbCl_5$) to afford substituted 1,2,5-thiadiazoles **220** <1998J(P1)2175, 2001H(55)75>. The proposed reaction mechanism involves electrophilic attack by sulfur of $S_4N_4{\cdot}SbCl_5$ on the isoxazole ring nitrogen followed by cleavage of the N–O isoxazole bond. This intermediate can then suffer cyclization onto formally the isoxazole ring carbon C-4 to give the thiadiazoles **220**. When the ring carbon at C-4 is blocked by a methyl group, an alternative cyclization onto the alkyl group at C-3 to afford thiadiazoles **221** occured <1998J(P1)2175> (Equation 50). The use of noncomplexed tetrasulfur tetranitride (S_4N_4) in 1,4-dioxane gave lower yields <2001H(55)75>.



219 **220** **221**: $R^2 = Me$ (50)

5.09.10.3 From 1,2,3-Triazoles

Electron-deficient 1,2,3-triazoles **222** can be converted into 1,2,5-thiadiazoles **223** with trithiazyl trichloride (Equation 51). The triazoles were proposed to react by initial ring opening to their diazoimine tautomers <2001J(P1)662>.



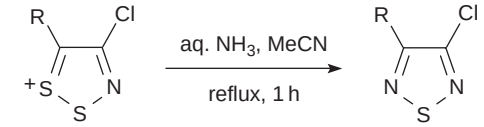
222 **223**

R	*Yield* (%)	*Reference*
Ts	90	2001J(P1)662
H	67	2001J(P1)662

(51)

5.09.10.4 From 1,2,3-Dithiazolium salts

1,2,3-Dithiazolium salts can be readily prepared from acetonitriles and disulfur dichloride <1985CB1632, 1999CC531, 1999JA969, 2005MOL346>. On treatment with aqueous ammonia, 5-aryl-4-chloro-1,2,3-dithiazolium salts **224** gave 3-aryl-4-chloro-1,2,5-thiadiazoles **225** in low to moderate yields (Equation 52). If the 5-substituent can act as a leaving group (Cl or MeS), no 1,2,5-thiadiazoles could be isolated <2005MOL346>.



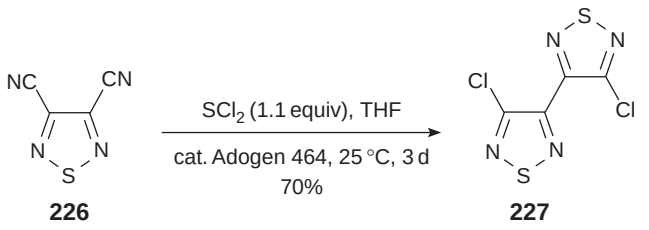
224 **225**

R	*Yield* (%)	*Reference*
Ph	36	2005MOL346
4-$O_2NC_6H_4$	26	2005MOL346
CN	11	2005MOL346

(52)

5.09.10.5 From 1,2,5-Thiadiazole-3,4-dicarbonitrile

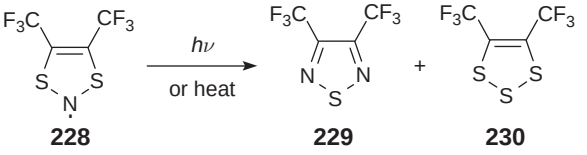
Diiminosuccinonitrile reacts with sulfur dichloride in dichloromethane at room temperature to give 1,2,5-thiadiazole-3,4-dicarbonitrile **226** in 93% yield <1972JOC4136>. The addition of catalytic 'naked' chloride to the reaction mixture gave the bi-1,2,5-thiadiazole **227** <1991CB1517>. No experimental data were given for this transformation, but it was shown that the bi-1,2,5-thiadiazole **227** can be formed directly from dicyanothiadiazole **226** under analogous reaction conditions (Equation 53) <1991CB1517>.



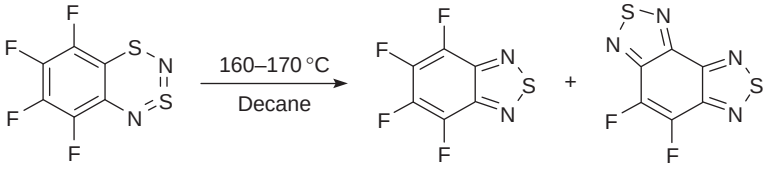
226 227 (53)

5.09.10.6 Miscellaneous

1,3,2-Dithiazolyl radical **228** photochemically and thermally disproportionates to afford the 1,2,5-thiadiazole **229** and the unstable 1,2,3-trithiole **230** (Equation 54) <2000JCD3365>. Thermolysis of perfluoro-1,3$\lambda^4\delta^2$,2,4-benzodithiadiazine **231** affords complex mixtures of heterocycles including perfluoro-2,1,3-benzothiadiazole **232** and 7,8-difluorobenzo[1,2-*c*:3,4-*c*′]bis[1,2,5]thiadiazole **233** (Equation 55) <2005EJI4099>.

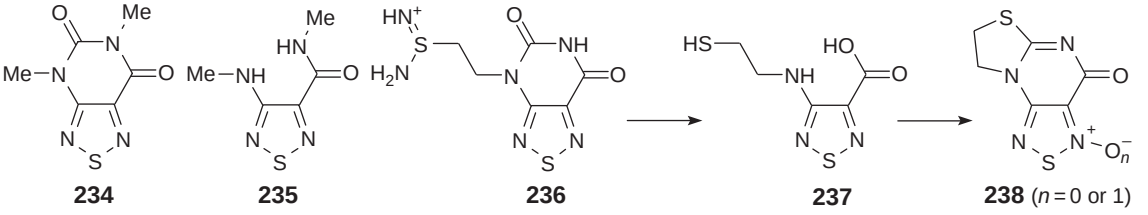


228 229 230 (54)



231 232 233 (55)

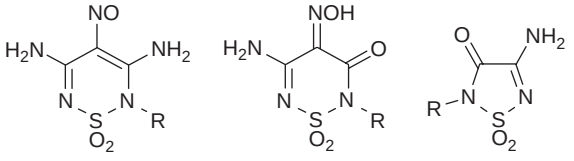
Alkaline hydrolysis of the [1,2,5]thiadiazolo[3,4-*d*]pyrimidinediones **234** and **236** affords the monocyclic 1,2,5-thiadiazoles **235** <1998CHE976> and **237** <1996CHE975>, respectively. Thiadiazole **237** was also obtained from the alkaline hydrolysis of the angular tricyclic thiadiazole **238** providing some evidence for its angular structure (**Scheme 30**) <2000JHC1269>.



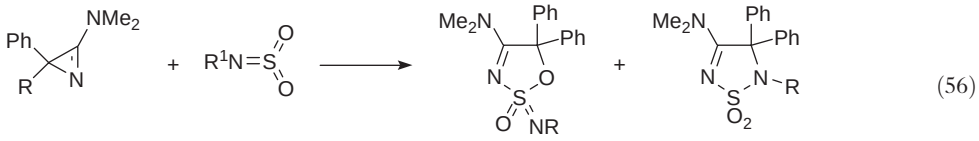
234 235 236 237 238 (*n* = 0 or 1)

Scheme 30

Strong acid hydrolysis of 1,2,6-thiadiazine 1,1-dioxides **239** or **240** results in ring contraction to afford the 1,2,5-thiadiazolinone 1,1-dioxides **241** in low yield <1996J(P2)293>. 3-Dialkylamino-2*H*-azirines **242** suffer ring expansion with *in situ*-prepared *N*-sulfonylamides **243** and carbamates to give both the 1,2,3-oxathiazoline **244** and the thiadiazoline 1,1-dioxide **245** (Equation 56). The oxathiazole **244** isomerizes quantitatively to the thermodynamically favored thiadiazoline **245** <1996J(P1)1629>.



239 240 241



242 243 244 245 (56)

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

5.09.11.1 Comparison of Methods Prior to 1995

The major synthetic routes for both monocyclic and fused 1,2,5-thiadiazoles were developed prior to 1995. In choosing a route, there are three important factors: (1) the availability of the primary carbon source; (2) the availability of the sulfur or sulfur–nitrogen source; and (3) the desired substitution of the target thiadiazole. Many of the classical routes require the preparation of reagents that are not readily available such as tetrasulfur tetranitride or trithiazyl trichloride and these limit synthetic routes involving nitrogen-free carbon sources. Owing to the very wide variety of available sources of sulfur, the most efficient synthetic strategy for monocyclic and for fused thiadiazoles involved the [4+1] introduction of sulfur to an N–C–C–N fragment (see Section 5.09.9.1.5).

5.09.11.2 Comparison of Methods After 1995

Two major developments in the chemistry of 1,2,5-thiadiazoles have appeared since 1995. The first involves the high-yielding functionalization of halogenated thiadiazoles using palladium cross-coupling methodology (see Section 5.09.7.6), and the second involves the *in situ* formation of trithiazyl trichloride (Katz reagent) (see Section 5.09.9.2.1(iii)(b)). The latter development allows a more facile route to thiadiazoles starting from carbon sources poor in nitrogen. Studies have recently shown that there are, however, subtle differences between the use of preformed trithiazyl trichloride and the *in situ* formation of trithiazyl trichloride using the Katz reagent <2002ARK90>.

5.09.12 Important Compounds and Applications

The survey of the uses of 1,2,5-thiadiazoles has appeared previously in CHEC(1984) <1984CHEC(6)513>. Recently, a review on the chemistry of thiadiazole *S*-oxides also highlighted their applications <2002AHC71>.

5.09.12.1 Uses in Organic Synthesis

In combination with the use of tetrasulfur tetranitride, trithiazyl trichloride, or any equivalent source of 'N–S–N', the technique of functionalizing a two-carbon source such as active methylene, alkene, or alkyne into thiadiazole (see Section 5.09.9.1.4) followed by reduction (see Section 5.09.5.6) provides a rapid route to 1,2-diamines.

Thiadiazoles have been used as bioisosteric replacements of esters <1992JME2274, 1995MI118> and amides <2003BML4179>; 3,4-diamino-1,2,5-thiadiazole 1-oxides were good replacements of guanidines <1995BMC1145, 1996BML2187> and urea <1998FA112, 2004BMC507>; the 3-hydroxythiadiazole was a good bioisosteric replacement for the carboxylic acid group <2000MI41, 2002BMC2259>; and benzothiadiazole was an excellent bioisosteric replacement for the methylenedioxyphenyl group <1998BML11, 1998BML17, 1998BML1771, 2001JME3391>.

5.09.12.2 Medicinal Applications

The two most commonly known 1,2,5-thiadiazoles for use in medicinal applications are timolol, used for the treatment of glaucoma, and tizanidine, which is sometimes used to treat multiple sclerosis. Advances involving 1,2,5-thiadiazoles over the last decade have been with the development of novel xanomeline derivatives as muscarinic selective agonists and antagonists for the treatment of Alzheimer's disease, schizophrenia, other psychotic illnesses, chronic pain therapy, irritable bowl syndrome (IBS), and other illnesses <1996EJM221, 1997CH739, 1997JME538, 1998BML2897, 1998JME109, 1998JME379, 1998JME4378, 1999JME1999, 2003AP230, 2003MI159, 2005MI3353, 2006MI553>. 1,2,5-Thiadiazoles have also been incorporated into a wide variety of biologically active compounds including cephalosporin- <2000BMC2317, 2000T5657, 2001BMC465> and oxazolidonone- <2003BML4179> based antibacterial agents, antagonists of gonadotropin-releasing hormone (GnRH) receptors <2000BML443, 2003JLR993, 2004BML5599, 2005BML693>, human growth hormone release agents <1997BML1293>, inhibitors of thrombin <1995BMC1145>, human leukocyte elastase, <2002JME4240, 2004BMC589>, neuropeptide Y receptors <2004BMC507>, *Plasmodium falciparum* lactate dehydrogenase (*pf*LDH) for the treatment of malaria <2004JBC31429>, and inhibitors of cloned excitatory amino acid transporter, EAAT2 <2000MI41, 2004BP2115>, as selective agonists at group II metabotropic glutamate receptors <2002BMC2259, 2002JME4240>, and as selective ligands at human 5-HT_{1A} receptors <2001BML1069>. Furthermore, thiadiazoles have been investigated as alleviators of inflammatory and neuropathic pain <2005BML719>, as anti-inflammatory agents <1996JME2>, and have been incorporated into histamine receptor antagonist analogues of ranitidine for the alleviation of gastrointestinal disorders <1998FA112>. 1,2,5-Thiadiazoles have been incorporated into mammalian antifungal agents <1995WO25107>. 3-Hydroxy-1,2,5-thiadiazole-4-carboxylic acid showed a good affinity toward hydroxyapatite (HA), which is the major inorganic component of bone <1996BML1043>.

5.09.12.3 Agrochemical Applications

Substituted 1,2,5-thiadiazole derivatives were found to be potent pesticides <1995WO03306, 2005WO06858>, and thiadiazolethione derivatives agrochemical fungicides <1999JPP292719, 1999JPP292863>.

5.09.12.4 Corrosion Inhibitors and Oxidation Catalysts

Oil-soluble dimercaptothiadiazoles have been patented as corrosion inhibitors for copper in aqueous hydraulic fluids <2002EPP1191087>. 1,2,5-Thiadiazole dioxide-derived oxaziridines (see Section 5.09.6.1) have been patented as novel bleach catalysts for fabric detergents <1998USP5753599, 1998USP5760222>.

5.09.12.5 Electronic Applications

The benzothiadiazole ring is a useful n-type building block for designing electron-transport materials for organic and polymer light-emitting diodes (LEDs) <2002MM6094, 2004CM4556, 2004SM175, 2005CC1468, 2005MM244, 2005MAC1114, 2005PLM11927, 2005SM73>. Arene- and heteroarene-fused thiadiazoles have also found use in the design of low-band-gap materials for the construction of organic field-effect transmitters (OFETs) <1995SM599, 1997CRV173, 1997SM229, 2002PCB3549, 2005CC3183, 2005MAC1114>, as electron donors <1995SM107, 1997CC1851>, as stable organic radicals (see Section 5.09.3.5), and as one or two photon-absorbing materials for the design of nonlinear near-infrared (NIR) dyes <2004CC2342, 2005MAC664>. Benzothiadiazoles acting as the electron-accepting cores have been incorporated into dendrimer-type light-harvesting materials <2005JA373>.

5.09.12.6 Other Applications

Various substituted 1,2,5-thiadiazoles have been patented as antimicrobial agents in particular for marine microorganisms <1997USP5703102, 1997USP5661165, 1997USP5633219, 1996USP5491155, 1996USP5488060>.

5.09.13 Further Developments

A formally antiaromatic 1,4-dihydropyrazinothiadiazole has been prepared and characterized by single crystal X-ray spectroscopy. The antiaromatic character of which has been supported computationally using NICS measurements <2007OL1073>. CHIH-DFT computational studies on acenaphtho[1,2-*c*]-1,2,5-thiadiazole 1,1-dioxide led to simulations of its infrared (IR) and ultraviolate (UV) spectra, the dipole moment and polarizability <2007JMT373>. 4,6-Dinitrobenzothiadiazole was determined to have an electrophilic reactivity of −8.40 which corresponds to a $pK_a^{H_2O}$ of 7.86 for Meisenheimer complexation with water and is close to the demarcation boundary ($E = -8.5$) between super- and normal-electrophiles and between reactive dienophiles and inert partners in Diels–Alder adduct formation <2007OBC1744>.

A general procedure for the reductive deoxygenation of 3,4-diamino 1,2,5-thiadiazole 1-oxides into the corresponding 1,2,5-thiadiazoles using PPh_3/CCl_4 in dichloromethane has been reported <2007TL5279>. 3,3′:4′,3″-Ter-1,2,5-thiadiazole has been prepared in several steps starting from either 1-(5-methyl-3-isoxazolyl)ethanone or diethyl acetylenedicarboxylate using the tetrasulfur tetranitride antimony pentachloride complex ($S_4N_4{\cdot}SbCl_5$) <2007T5014>. 3,4-Disubstituted-1,2,5-thiadiazoles were prepared *via* ring opening of readily available 3,4-dichloro-1,2,5-thiadiazole with metal amides to afford a stable synthon, which was then transformed into the 3,4-disubstituted-1,2,5-thiadiazole derivatives *via* two consecutive reactions with *O*-, *S*-, *N*- or *C*-nucleophiles <2006TL8285>. An efficient enantioselective synthesis of (*S*)-timolol using chiral Co-salen-catalysed kinetic resolution of the less expensive (±)-epichlorohydrin with 3-hydroxy-4-(*N*-morpholino)-1,2,5-thiadiazole was reported in 55% yield and excellent enantioselectivity (98%) <2007T3026>.

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Biographical Sketch

Panayiotis Andreas Koutentis is assistant professor at the Department of Chemistry, University of Cyprus, Nicosia. He was born in Bristol (1969) in the United Kingdom and obtained his bachelor (1992) and doctorate (1997) degrees at Imperial College London working under the supervision of the late Professor Charles W. Rees. This was followed by a short stay with Professor Roger Alder, University of Bristol (1997), and then postdoctoral work with Professor Fred Wudl (1997-8), University of California, Los Angeles (UCLA), and with Professor Robert Haddon (1999) at the University of Kentucky, Lexington. In 1999, Dr. Koutentis was appointed lecturer at the University of Cyprus, where his primary research activities focus on the synthesis and reactivity of novel and unusual S,N-heterocyclic compounds and the design and synthesis of organic magnets based on radical and diradical polyazaheterocyclic systems. Secondary themes under investigation include the design and synthesis of novel conjugated and nonconjugated polymers, the design and synthesis of non-natural marine alkaloids, and the search for Hbf regenerators based on HDAC inhibitors.

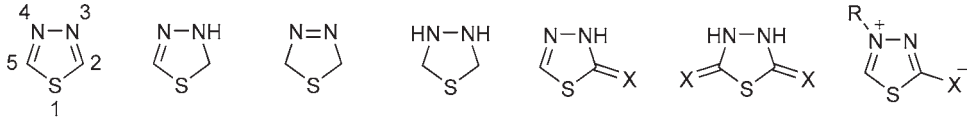
5.10
1,3,4-Thiadiazoles

P. A. Koutentis
University of Cyprus, Nicosia, Cyprus
C. P. Constantinides
The University of Cambridge, Cambridge, UK

5.10.1 Introduction

The chemistry of 1,3,4-thiadiazole and its derivatives has been previously covered in both CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>. A major review which covers the synthetic chemistry of the ring system up to 2002 has also appeared <2004HOU(13)349>. Since 1991 advances in the chemistry of 1,3,4-thiadiazole have been annually reviewed in *Progress in Heterocyclic Chemistry* <1991PHC149>.

The numbering of the 1,3,4-thiadiazole ring is given below. The present chapter is intended to update the previous work on the aromatic 1,3,4-thiadiazole **1**, the nonaromatic Δ^2-thiadiazolines **2**, Δ^3-thiadiazolines **3**, the thiadiazolidines **4**, the tautomeric forms **5** and **6**, and the mesoionic systems **7**. Reference is made to earlier chapters of CHEC(1984) and CHEC-II(1996) where appropriate.



1 **2** **3** **4** **5** **6** **7**

5.10.2 Theoretical Methods

Molecular geometries, and physical and chemical properties of a variety of 1,3,4-thiadiazoles have been predicted using density functional theory (DFT) and *ab initio* methods. In general, DFT techniques outperform *ab initio* and the inclusion of d-functions gives a more accurate description of bond lengths, bond angles, dipole moments and hyperpolarizabilities. Electronic properties are best obtained using single point calculations with methods that include electron correlation.

5.10.2.1 Molecular Calculations

1,3,4-Thiadiazole **1** and its derivatives were used as model compounds for the calculation of molecular parameters related to physical properties for their use in quantitative structure–activity relationship (QSAR) and quantitative structure–property relationship (QSPR) studies <1999EJM41, 2003IJB2583, 2005JMT27>.

5.10.2.2 Molecular Geometry

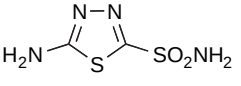
Both DFT and *ab initio* calculations of the molecular geometry of 1,3,4-thiadiazole **1** compare favorably with available experimental data (microwave spectroscopy, electron diffraction, and single crystal X-ray spectroscopy) (**Table 1**) <1995SAA995, 1996SAA33, 1997JMT67, 1997JST451, 2001JST119, 2001JMT153, 2002TL1709, 2003JPO1>.

Table 1 Calculated vs. experimental bond lengths (pm) and angles (degrees) of 1,3,4-thiadiazole **1** <1995SAA995, 1996SAA33>

	Computational method			*Experimental*		
Coordinates	*HF/6-31G***	*MP2/6-31G***	*B3LYP/6-31G***	*A*	*B*	*C*
C–S	172.6	171.7	174.7	172.0	172.2	174
C═S	127.1	131.7	130.0	130.3	130.4	131
N–N	136.4	137.0	137.3	137.1	138.1	138
C–H	107.1	107.7	108.2	107.7	108.1	98
C–S–C	85.7	86.5	85.6	86.4	86.4	87
S–C═N	114.5	114.9	114.7	114.6	114.8	114
C═N–N	112.7	111.9	112.5	112.2	112.0	113
S–C–H	122.7	122.5	122.1	122.5	124.1	123
N═C–H	122.9	122.6	123.3	122.9	121.1	123

A Microwave spectroscopy <1971JST163>.
B Electron diffraction <1970ACS2525>.
C X-ray <1974AXB1642>.

The C–S bond length and C–S–C bond angle were poorly predicted in the DFT B3LYP optimized geometry while the Møller–Plesset (MP2) method gave better agreement with experimental values. Nevertheless, the geometries optimized at the DFT level are overall better than those obtained with the MP2 method. Twenty-seven DFT procedures, differing in their combinations of exchange and correlation functionals and basis sets, were tested for accuracy in computing the geometry of thiadiazole **1** <2001JMT153>. From the density functions (BLYP, B3LYP, SVWN, HF) and the basis sets [6-31G, 6-31G**, 6-31++G**, 6-311G, 6-311G**, 6-311++G**, 6-311G(2d,2p), 6-311++G(2d,2p) and CBSB7] the best combination examined was the B3LYP with the CBSB7 basis set for the prediction of values in agreement with experimental double-resonance modulated (DRM) spectroscopy data. Furthermore, the inclusion of d-functions in DFT calculations was crucial for obtaining an adequate description of the Hartree–Fock (HF) geometry and local and nonlocal DFT optimization were also performed on the 1,3,4-thiadiazoline **2** <2001JMT39>, the 1,3,4-thiadiazolidine **4** <2001JMT201>, the 1,3,4-thiadiazole 1,1-dioxide <2001JMT41>, the 5-amino-1,3,4-thiadiazole-2-sulfonamide **8** <2001JST119>, on acyl- and thioacylaminothiadiazoles <2002TL1709> and on the 5-methyl-1,3,4-thiadiazole-2-thiol **9** (shown as two tautomeric forms) <2003JPO1>.



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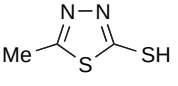

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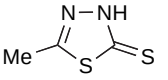


Semi-empirical calculations at the AM1 level performed on 2-amino-5-(4-pyridyl)-1,3,4-thiadiazole determined the most stable conformational arrangement between the heterocyclic unit and the central bridge as well as the rotational barrier around the C(heterocyclic)–N(exocyclic) bond <2001LC1659>.

5.10.2.3 Electronic Structures

The dipole moments and hyperpolarizabilities of a number of donor–acceptor thiadiazoles were calculated using the sum-over-states semi-empirical approach on structures that were optimized at the *ab initio* 3-21G level of theory <1995J(P2)177>. The results showed that thiadiazoles, owing to their small transition moments, have large dipole moments but small hyperpolarizabilities. Dipole moments and static polarizabilities of 1,3,4-thiadiazole **1** were calculated on structures derived from the HF, self-consistent field (SCF), and MP methods <1998PCA9906>. The calculated dipole moment for thiadiazole **1** at the MP2/6-31G** geometry using the MP2/C3 is $\mu_{calc} = 3.62$ D ($\mu_{expt} = 3.28$ D). However, in a detailed study of the influence of the basis set and correlation method on the calculation of dipole moments, a more accurate value $\mu_{calc} = 3.24$ D was calculated at the B3LYP/CBSB7 level of theory <2003JMT77>.

5.10.2.4 Chemical Reactivity

The chemical reactivity of 1,3,4-thiadiazole **1** was predicted using DFT by calculating the net atomic charges and the Fukui functions f^+, f^-, and f^0 (**Table 2**).

Table 2 The net charges and condensed Fukui functions for 1,3,4-thiadiazole **1** with C_{2v} symmetry <1997JMT67>

Atom	*Net charges*	f^+	f^-	f^0
S	0.1818	0.2445	0.2633	0.2539
N	−0.3275	0.2153	0.1233	0.1693
C	−0.0308	0.0930	0.1740	0.1335
H	0.2673	0.0694	0.0711	0.0703

Thiadiazole **1** was shown to be very electron poor and relatively inert toward electrophilic substitution but reactive toward nucleophilic attack <1995JMT385, 1997JMT67>. The preferred sites of attack are the sulfur and carbon atoms or the ring proton depending on the nature of the nucleophile. The sulfur atom of thiadiazole **1**, which has a large f^- value and therefore is chemically softer, is the preferred site of attack by soft nucleophiles. Analogous studies on the 1,3,4-thiadiazoline **2** <2001JMT39>, the 1,3,4-thiadiazolidine **4** <2001JMT201>, and the 1,3,4-thiadiazole 1,1-dioxide <2001JMT41> have also appeared.

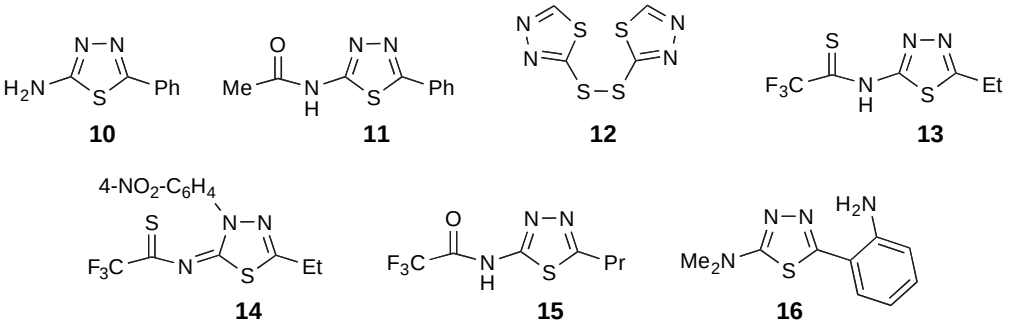
5.10.3 Experimental Structural Methods

5.10.3.1 X-Ray, Neutron and Electron Diffraction, and Microwave Spectroscopy

The molecular structure of 1,3,4-thiadiazole **1** was described in CHEC(1984) <1984CHEC(6)545>. Since the publication of CHEC-II(1996) <1996CHEC-II(4)379>, a large number of single-crystal X-ray structures have been reported for various thiadiazole derivatives. 2-Amino-5-phenyl-1,3,4-thiadiazole **10** forms pseudocentrosymmetric dimers through symmetric intermolecular hydrogen bonds, involving the proton of the amino group and the nitrogen of the ring, which are arranged in infinite layers parallel to the *xy* plane <2001RJO721>. The exocyclic amino group is coplanar to the thiadiazole ring indicating conjugation between the nitrogen lone pair and the heterocycle. The dihedral angle of the latter with the benzene ring is 34.6°.

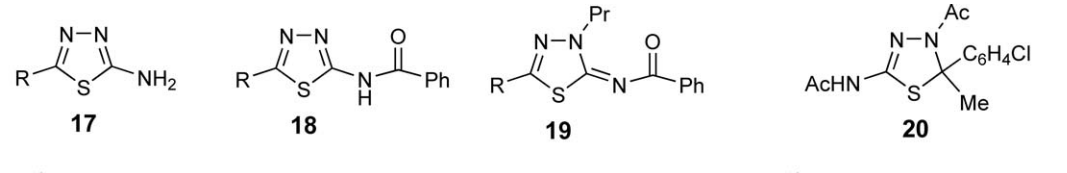
The crystal structure of *N*-(5-phenyl-1,3,4-thiadiazol-2-yl)acetamide **11** showed that the lone pairs on nitrogen and sulfur are conjugated with the double bonds of the thiadiazole ring as evidenced by the C–N (128.3 and 130.2 pm) and the N–N (138.7 pm) bond lengths <2005RJC1962>. The endocyclic N–C bond lengths are intermediate between the standard single and double bond lengths. The whole molecule is planar and forms endless one-dimensional (1D) chains related by the glide reflection plane. A hydrogen bond N–H · · · O (284.8 pm) and a short S · · · N contact (322.5 pm) make possible the formation of a layer on the reflection plane. Molecules related by the inversion center form a layer antiparallel to the latter. The distance between the two layers is 330.7 pm. The 1,2-di-(1,3,4-thiadiazol-2-yl)disulfane **12** crystallizes in the monoclinic system space group C2/*c* <2002AXEo1045>. The N–N distance is 138.2, the C–N 128.6, and the cyclic C–S 171.2 pm. The two planar 1,3,4-thiadiazole rings have a dihedral angle of 70.5° and are related by a twofold rotation axis through the middle of the S–S bond. The X-ray structures of 5-ethyl-2-trifluorothioacetylamino-1,3,4-thiadiazole **13**, 5-ethyl-3-*p*-nitrobenzyl-2-trifluorothioacetylimino-1,3,4-thiadiazole **14**, and 5-*n*-propyl-2-trifluoroacetylamino-1,3,4-thiadiazole **15** are

dimeric and exhibit intermolecular hydrogen bonds and intramolecular nonbonding 1,5-type S · · · S and S · · · O interactions <2002TL1709>. The contacts between the thiocarbonyl sulfur and the thiadiazole ring sulfur are 297.1 in structure **13** and 290.5 pm in compound **14**. The S · · · O contact in structure **15** is 264.8 pm. The 5-(2′-aminophenyl)-2-dimethylamino-1,3,4-thiadiazole **16** crystallizes in the monoclinic system space group $P2_1/c$ <2000MI453>. The dihedral angle between the two rings is 8.9°. The electrostatic 1,4-interaction between the thiadiazole sulfur and the *ortho* carbon of the phenyl ring cause a slight difference in the S–C bond lengths (173.8 and 174.8 pm) while the bond angle at the sulfur atom is 87.1°. The intramolecular interaction between the thiadiazole nitrogen and the nitrogen of the amino group (276.0 pm) can be considered as a N–H · · · N hydrogen bond. Intermolecular hydrogen bonds link molecules into centrosymmetric dimers that are arranged in flat networks parallel to the *xy* plane. These flat networks of dimers, in turn, are interlinked by hydrogen bonds. X-rays of other 1,3,4-thiadiazole derivatives including macrocycles have also been reported <1995CJC1258, 1998AJC499, 1999H(51)2739, 2000JST159, 2001H(55)579, 2002H(57)1919, 2003JPO1, 2003S2851, 2003JST107>.



5.10.3.2 NMR Spectroscopy

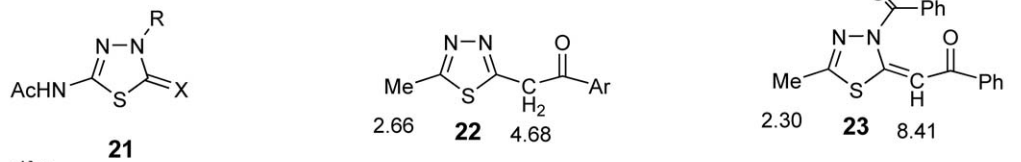
A detailed analysis of the ^1H, ^{13}C, and ^{15}N NMR spectra of 1,3,4-thiadiazoles was reported in CHEC(1984) <1984CHEC(6)545> and summarized in CHEC-II(1996) <1996CHEC-II(4)379>. Representative chemical shifts are given in **Figure 1**.



$\delta^{13}C$ ppm (DMSO-d_6)

R	C2	C5	C2	C5	C=O	C2	C5	C=O
EtS	170.6	151.2	161.6	160.3	165.5	165.7	155.4	174.2
EtO	162.2	164.9	155.6	171.1	165.4	163.2	165.2	174.0

$\delta^{13}C$ ppm ($CDCl_3$): C2 = 78.2
δ^1H ppm ($CDCl_3$): NH = 10.93
CH_3 = 2.24



$\delta^{13}C$ ppm

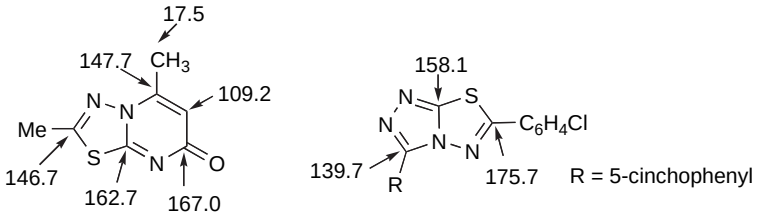
R	X	C2	C5
H	O	153.4	173.4
H	S	161.5	189.1
Et	O	149.8	169.1

δ^1H ppm ($CDCl_3$/TMS)
Ar = o-toluene

δ^1H ppm ($CDCl_3$/TMS)

Figure 1 ^1H and ^{13}C NMR shifts for selected thiadiazoles, **17–19** <2001H(55)579>, **20** <2004H(63)2243>, **21** <1984CHEC(6)545>, **22** and **23** <2004ZNB366>.

1D and 2D NMR techniques including heteronuclear NOE measurements were used to elucidate the structures of several 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones (**Figure 2**) <2005JHC1105>. The NMR spectral assignments of 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole derivatives were analyzed based on gCOSY, gHMQC, and gHMBC experiments (**Figure 2**) <2001MRC411>.

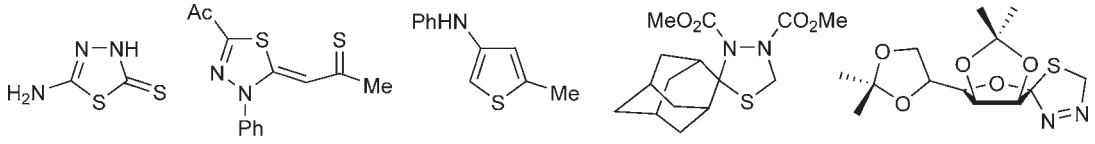


24 **25**

Figure 2 ^{13}C NMR shifts (ppm) for the 1,3,4-thiadiazole[3,2-*a*]pyrimidin-7-one **24** and the 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole **25**.

The bonding and coordination of tin with 5-amino-3*H*-1,3,4-thiadiazole-2-thione **26** was studied using ^{1}H, ^{13}C, and ^{119}Sn NMR spectroscopy <2006SAA148>. The absence of the thiol SH proton resonance in the ^{1}H NMR spectra of the organotin(IV) complex supported the thione as the dominant tautomer. The ^{13}C NMR spectrum of the uncoordinated ligand gave the C-2 (δ 181.2) and C-5 (δ 161.6) signals, but upon coordination the signal of C-5 is shifted to lower field (by 1–7 ppm) and the C-2 signal was shifted to higher field (by 11–18 ppm). ^{13}C NMR was also used for the elucidation of the reaction mechanism in the base-induced conversion of (*Z*)-5-acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazole **27** into 3-(*N*-arylamino)-thiophene **28** (see Section 5.10.6.1) <2003EJO2480>.

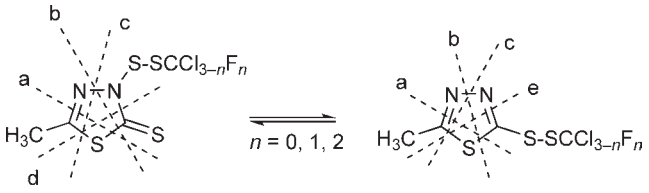
^{1}H and ^{13}C VT NMR studies on the spiro[adamantine-2,2′-(1,3,4)-thiadiazolidine]-3′,4′-dicarboxylate **29** showed that it exists in two chiral conformations (7:3 in $CDCl_3$) which are separated by a barrier of $\Delta G^{\ddagger} = 18.3 \pm 0.6$ kcal mol^{-1} <1999T12783>. The thermolysis of the 2,5-dihydro-1,3,4-thiadiazole **30** (see Section 5.10.5.2) in a $CDCl_3$ solution performed at 20–35 °C was followed by ^{1}H NMR spectroscopy <1997HCA1260>. First-order kinetics and a half-life of 2.3 h at 35 °C (21 h at 20 °C) were observed while the activation energy of the reaction was calculated to be 27.1 kcal mol^{-1}.



26 **27** **28** **29** **30**

5.10.3.3 Mass Spectrometry

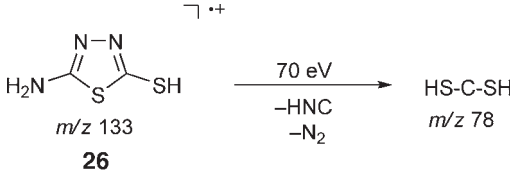
The common fragmentation pathways of 1,3,4-thiadiazoles have appeared in CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>. Several trihalomethylsulfenyl derivatives of 5-methyl-1,3,4-thiadiazole-2-thiol were characterized by mass spectrometry and showed similar fragmentation patterns characterized by the loss of the halogenated substituents (**Figure 3**) <2003JPO1>. In all cases cleavage via fragmentation 'a' generated the base peak of *m*/*z* 59 Da $[CH_3C{=}S]^{+\cdot}$. Fragmentation of the substituent occurs, with high relative abundance, producing Cl_3C^+, Cl_2FC^+, and ClF_2C^+. While fragments $[SSCCl_{3-n}F_n]^+$ were not detected, $[M\text{-}(S\text{-}SCCl_nF_{3-n})]^+$ (*m*/*z* 99) is observed with relative abundance between 6.5 and 17.8. The fragment of *m*/*z* 108, most likely $[CS_3]^+$, is also detected but no significant $[M\text{-}CS_2]^{+\cdot}$ is observed. This supported the presence of the substituent on the nitrogen and allowed for the loss of CS_2 from the molecular ion according to fragmentation 'd'. Fragments and losses common to all derivatives **31** and **32** are $[M\text{-}CCl_nF_{3-n}]^+$, $[M\text{-}SCCl_nF_{3-n}]^+$, $[M\text{-}(S\text{-}SCCl_nF_{3-n}]^+$, $[CS]^+$, and $[CH_3CN]^{+\cdot}$.



31 **32**

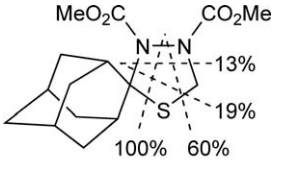
Figure 3 Fragmentation for trihalomethylsulfeny 5-methyl-1,3,4-thiadiazole-2-thiol derivatives <2003JPO1>.

Tandem mass spectrometry (70 eV EI) performed on 5-amino-1,3,4-thiadiazole-2-thiol **26** gave a weak abundance peak at *m/z* 78 Da (2%) corresponding to the $[CH_2S_2]^{+\cdot}$ ion (Equation 1) <1999PCA5123>. The linked-scan spectra of the parent ion (M^+) and the ion at *m/z* 106 showed that loss of HNC followed by N_2 elimination accounted for the formation of the ion at *m/z* 78.



26 (1)

The molecular peak of the spiro[adamantine-2,2′-(1,3,4)-thiadiazolidine]-3′,4′-dicarboxylate **29** appears with 99% intensity and shows four distinct fragmentations <1999T12783>. The molecular formulas of the fragments were confirmed by the intensities of ^{13}C and ($^{34}S+^{13}C_2$) isotope peaks. The two major fragmentations involve cleavage of the weak C–S bonds and afford the base peak at *m/z* 208 (100%) corresponding to $C_{12}H_{18}NO_2^+$ and a peak at *m/z* 239 (60%) $C_{12}H_{17}NO_2S^+$ which corresponds to [M^+-$H_2C{=}N$-CO_2Me]. The splitting of the parent ion (M^+) along the line of the original cycloaddition is of minor importance [*m/z* 180 (13%)].



29

5.10.3.4 UV, CV, Photoelectron, ESR, and Fluorescence Spectroscopy

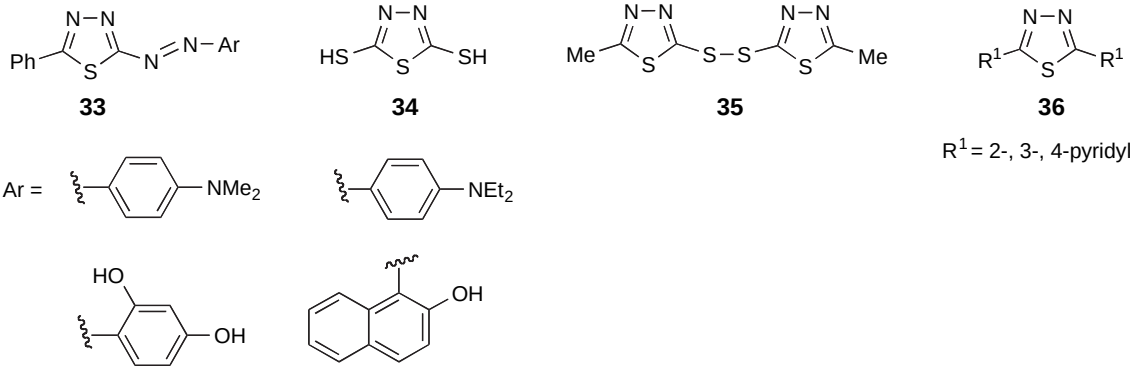
Discussion on some ultraviolet (UV) data for substituted thiadiazoles has been published in CHEC(1984) <1984CHEC(6)545>. The electronic spectra, solvatochromic behavior, and acid–base properties of some 2-arylazo-5-phenyl-1,3,4-thiadiazole derivatives **33** were investigated by studying their visible spectra in pure and mixed organic solvents of different polarities as well as in buffer solutions <2000MI117>. The compounds display two bands in the UV region; the first at 204–238 nm was ascribed to the π–π^* transition within the benzenoid system, while the second at 273–313 nm was attributed to a π–π^* transition within the 1,3,4-thiadiazole part of the molecule. The spectra of the anilino derivatives have a third visible band ascribed to a π–π^* transition arising from a charge transfer (CT) originating from the electron-rich aniline substituent and directed toward the electron-poor heterocyclic thiadiazole moiety. The CT bands of the hydroxyl derivatives are broader and exhibit two maxima due to the azo-hydrazone tautomeric equilibrium. For all compounds, the intramolecular CT band exhibited positive solvatochromism.

The UV–Vis spectra of the noncoordinated 5-amino-3*H*-1,3,4-thiadiazole-2-thione **26** and its organotin(IV) complex exhibit two absorption bands at 256 and 318 nm assigned to the π–π^* and n–π^* transitions of the C=N chromophore, respectively <2006SAA148>. These bands undergo a hyperchromic shift upon complexation supporting the participation of the C=N group in the coordination.

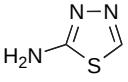
UV–Vis spectroscopy and cyclic voltammetry were used to study the behavior of 2,5-dimerapto-1,3,4-thiadiazole **34** in the presence and absence of pyridine or triethylamine <1997PCB2861>. The neutral form of the dimercapto

thiadiazole **34** absorbs at 320 nm but on addition of triethylamine (1 equiv) the monoanion forms with absorbances at 270 and 352 nm and two isosbestic points at 287 and 331 nm. Addition of a second equivalent gave the dianion, which has a nearly identical spectrum with the monoanion. Addition of 1 or 2 equiv of the weaker base pyridine gave only the monoanion with peaks at 270 and 350 nm. Cyclic voltammetry showed that deprotonation of the 2,5-dimercapto-1,3,4-thiadiazole **34** assisted its electrochemical oxidation, leading either to a disulfide-containing dimer or a disulfide-containing polymer depending on conditions <1997PCB2861>. The polymerization and depolymerization of the dimercaptothiadiazole **34** was studied on platinum by potential sweep voltammetry in acetonitrile <1996JEC53>. The reaction was found to be chemically reversible but kinetically slow at ambient temperature. Oxidation of thiolate occurs via the formation of a thiyl radical that dimerizes to disulfide. Charge transfer is the rate-determining step, whereas chemical dimerization is at equilibrium. For the dithiolate, oxidation proceeds in two steps. The dithiolate of the dimer is first formed and is further oxidized to give oligomers. This reaction is chemically reversible and kinetically hindered. The cleavage and formation of the disulfide bond in poly[dithio-2,5-(1,3,4-thiadiazole)] was examined in hot γ-butyrolactam (90 °C) at −0.1 and 0.1 V versus Ag, respectively <1996JEC229>. Reduction and oxidation peak potentials of the model compound bis(2-methyl-1,3,4-thiadiazoyl)-5,5′-disulfane **35** were observed at −0.65 and 0.2 V, respectively, and correspond to the cleavage and formation reactions of the disulfide bond. A quasi-reversible redox reaction was indicated from a comparison of the shape and response of the cyclic voltammogram between the monomeric and polymeric disulfides.

Electrochemical impedance spectroscopy was used to determine the effect of isomers of 2,5-bis(*n*-pyridyl)-1,3,4-thiadiazole **36** ($n = 2$ or 3) on the corrosion of mild steel in perchloric acid solution <2002MI197>. The inhibition efficiency was structure dependent and the 3-pyridyl gave better inhibition than the 2-pyridyl. X-ray photoelectron spectroscopy helped establish the 3-pyridyl thiadiazoles mode of action toward corrosion. Adsorption of the 3-pyridyl on the mild steel surface in 1 M $HClO_4$ follows the Langmuir adsorption isotherm model and the surface analysis showed corrosion inhibition by the 3-pyridyl derivative is due to the formation of chemisorbed film on the steel surface.



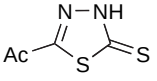
Electron spin resonance (ESR) spectroscopy was used to study the surface complexes of CuX ($X = Cl^-$, Br^-, ClO_4^-) on silica gel chemically modified with 2-amino-1,3,4-thiadiazole **37** <1998MI181>. ESR indicated a tetragonal distorted structure with low degrees of metal loading on the silica gel. ESR and pulsed ESR spectroscopy was used to study the intramolecular magnetic interactions in the $[Cu_2(bptd)(H_2O)Cl_4]$ and $[Ni_2(bptd)_2(H_2O)_4]Cl_3 \cdot 3H_2O$ coordination complexes of 2,5-bis(2-pyridyl)-1,3,4-thiadiazole <2004MI701>. Despite the short contacts between the metals, there is no in-plane magnetic exchange. The charge transfer complexes of the aminothiadiazole **37** with π-acceptors such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), *o*- and *p*-chloranil (CHL), *p*-bromanil and chloranilic acid (CHA) were studied with powdered X-band ESR spectroscopy at room temperature <2005SAA526>. All the CT complexes were ESR active with g_{eff} values of 2.0479, 2.0154, 2.0558, and 2.0117 for the complexes with DDQ, *o*-CHL, *p*-CHL, and CHA, respectively. ESR spectroscopy was also used to characterize the μ-chloro-μ-[2,5-bis(2-pyridyl)-1,3,4-thiadiazole] aqua chlorocopper(II) dichlorocopper(II) <2004IC1865>, the coordination polymers of the 2,5-bis(4-pyridyl)-1,3,4-thiadiazole **36** with Cu(II), Cd(II), and Co(II) <2004IC931> and for the study of the biologically active megazol <1999BP549, 2003JME427>.



37

5.10.3.5 IR and Raman Spectroscopy

The characteristic IR bands of some 1,3,4-thiadiazoles are listed in CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>. Very good agreement between the calculated and the experimental IR wave numbers and absorption intensities of 1,3,4-thiadiazole and its deuterated derivative were obtained using the B3LYP DFT method <1997JST451>. A similar study was also performed on the 5-amino-1,3,4-thiadiazole-2-sulfonamide **8** <2001JST119>. FT-Raman and Fourier transform infrared (FTIR) vibrational assignments were determined for 2,5-dimercapto-1,3,4-thiadiazole **34**, 5-methyl-1,3,4-thiadiazole-2-thiol **9**, and 5-amino-1,3,4-thiadiazole-2-thiol **26** <1995JST51>. The thiol groups of these molecules were shown to participate in a thiol–thione tautomeric equilibrium. The bands at 2485 and 940 cm^{-1} observed in the Raman spectra of the dimercaptothiadiazole **34** represent the ν(S–H) stretching and δ(C–SH) in-plane bending modes, respectively <1995MI617>. A quantitative study of the hydrogen bonding was carried out using the intensity measurements of the bands assigned to hydrogen-bonded and the free δ(C–SH) in-plane deformations at 940 and 919 cm^{-1}, respectively, as a function of temperature, and the average enthalpy for hydrogen-bond formation was obtained ($\Delta H^{\circ} = -3.35 \pm 0.2$ kJ mol^{-1}). The adsorption of dimercapto-thiadiazole **34** on a silver surface was studied by the FT-SERS (SERS – surface-enhanced Raman scattering) technique <2001MI785>. The spectra indicated the dissociative adsorption on the silver surface to the dithiolate ion. The latter has two kinds of adsorption geometries depending on the solution concentration of the thiadiazole. At low concentration the dithiolate ion probably adsorbs through the nitrogen atom, whereas at high concentration the ion probably adsorbs through its π-system. FT-SERS was also used to examine the possibility of solvent trapping within the monolayer interior during the self-assembly of dimercaptothiadiazole **34** molecules from alcoholic solution, or co-adsorbing together with the solute molecules onto the silver surface <2001MI1>. Variations of the relative intensity of the solvent bands to the concentrations showed that the smaller the concentration the larger the relative intensity of the solvent bands. An IR study of the structure of 15 solid complexes formed by Co(II), Cu(II), Cd(II), Hg(II), Pb(II), and Zn(II) with ligands 2,5-dimercapto-1,3,4-thiadiazole **34** and 2-acetyl-1,3,4-thiadiazol-5-thione **38** was performed <1996SPL477>. The authors proposed the coexistence of different tautomers of the dimercapto thiadiazole. Its metal complexes display a unique and similar polymeric structure involving one tautomer.



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5.10.4 Thermodynamic Aspects

5.10.4.1 Physical Properties

The melting, boiling points, and solubilities of many thiadiazoles have been reviewed in CHEC(1984) <1984CHEC(6)545>. Thiadiazoles, thiadiazolines, and thiadiazolidines can have high melting points, especially if they create inter- or intramolecular hydrogen bonds. Thiadiazoles substituted in the 2- and 5-position with small polar groups like amines are soluble in water but generally the water solubility decreases as substituents increase in size, while solubility in organic solvents increases. Solubilities for many 1,3,4-thiadiazoles have been previously recorded <1952HC(4)81>.

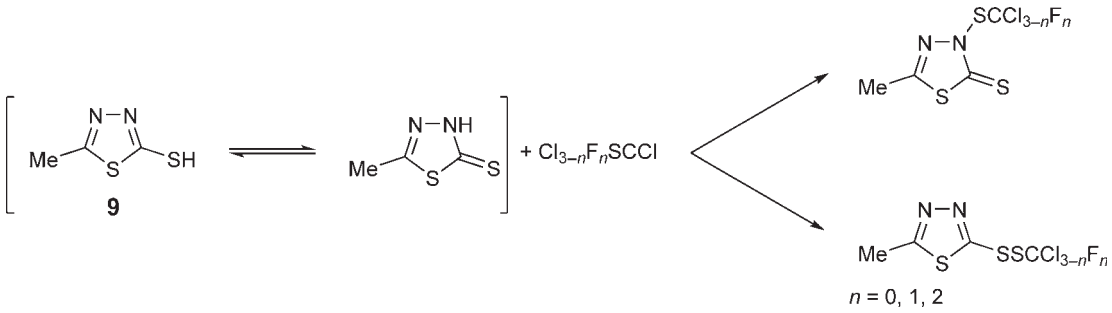
5.10.4.2 Aromaticity

Discussions of the aromaticity of 1,3,4-thiadiazole have appeared in two recent reviews <2004CRV2777, 2005CRV3773> and in both CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>. The average ring bond order deviation computed for 1,3,4-thiadiazole **1** using the B3LYP/6-311++G^{**} method was found to be 0.22562 and, in comparison with the Bird index of 80, supports the relative high aromaticity of 1,3,4-thiadiazole **1** <2001JMT285>. Studies on energy and magnetic criteria based on computationally obtained geometries also supported the relatively high aromaticity of 1,3,4-thiadiazole <2002JOC1333, 2000PCA1736>. Aromaticity-related parameters such as the aromatic stabilization energy (ASE), the nucleus-independent chemical shift (NICS), the harmonic oscillator model of aromaticity (HOMA) have been examined with respect to chemical reactivity of

3-methyl-2-methylthio-1,3,4-thiadiazolium salts <2005ARK415>. An NICS aromaticity study was also performed on the biologically important compound megazol <2005JMT1>. HOMA index calculations were used as a quantitative measure of aromaticity for four bisubstituted 1,3,4-thiadiazole derivatives <2000JST159>. The calculated HOMO indices were substituent dependent and an increase in the substituent electrophilicity led to an increase in aromaticity. The aromaticity of 1,3,4-thiadiazole-1,1-dioxide was estimated based on the *N*, MDQ, $\Delta E_{\pi L}$(NLMO), and $\delta E_{\pi L}$(Boys) criteria as well as comparing with total energies <1997JMT119>. 1,3,4-Thiadiazole 1,1-dioxide was concluded to be less aromatic than the 1,1-dioxides of the 1,2,5-, 1,2,4-, and 1,2,3-thiadiazoles.

5.10.4.3 Tautomerism

Tautomerism was reviewed quite extensively in CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>. The tautomeric ability of the 2-mercapto-5-methyl-1,3,4-thiadiazole **9** was studied by its reaction with the electrophilic $Cl_{3-n}F_nCSCl$ <2003JPO1>. 2-Mercapto-5-methyl-1,3,4-thiadiazole **9** was considered to exist mainly as the thione tautomer; however, electrophilic substitution occurred on the thiol (**Scheme 1**).



Scheme 1

The tautomerism of 2-mercapto-5-methyl-1,3,4-thiadiazole **9** was also examined computationally using DFT calculations and experimentally by high-vacuum thermolysis, and the thione tautomer was the most stable <2002J(P2)1620>. This was further confirmed by vibrational spectroscopy and X-ray crystallography. The theoretically favored thione tautomer was shown to occur not only in cryogenic argon matrices, where the molecule is isolated and no hydrogen bonding was observed in the IR spectra, but also in the solid state, where additional stabilization effect of N–H···S hydrogen bonding can be considered. In fact, it has been shown that compound **9** in contrast to related compounds forms chains via N–H···S hydrogen bonding. The tautomerism of 2,5-dimercapto-1,3,4-thiadiazole **34** was also examined using FTIR and FT-Raman spectroscopy, high-vacuum thermolysis experiments, as well as arylating reactions <1995JST51, 1996SPL477, 1995CJC1258, 2002J(P2)1620>. All the studies concluded that the thiol groups of this molecule participate in a thiol–thione tautomeric equilibrium.

5.10.5 Reactivity of Fully Conjugated Rings

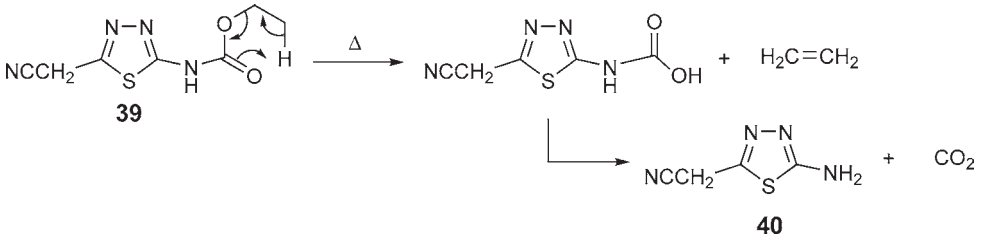
5.10.5.1 Survey of Reactivity

1,3,4-Thiadiazole **1** is less aromatic than thiophene and electrophilic attack at carbon is rare due to the electron-withdrawing effect of the nitrogen atoms. Thiadiazoles suffer electrophilic attack on the ring nitrogens and can be readily N-alkylated or N-acylated and mesoionic thiadiazoles can be prepared in this manner. Electrophilic attack at the sulfur atom has not been observed. Nucleophilic substitution of leaving groups present at either the C-2 or C-5 positions dominates the reactivity of the molecules. While 1,3,4-thiadiazoles are relatively stable, strongly basic conditions can lead to ring fission.

5.10.5.2 Unimolecular Thermal and Photochemical Reactions

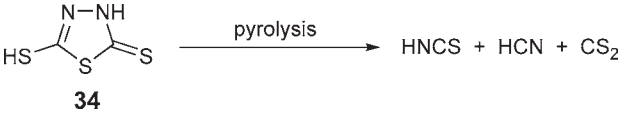
Unimolecular photochemical reactions have been extensively reviewed in CHEC-II(1996) <1996CHEC-II(4)379>. The 1,3,4-thiadiazoles undergo pyrolitic fragmentation similar to that observed during mass spectrometry. The gas-phase

pyrolisis of *N*-(5-cyanomethyl-1,3,4-thiadiazol-3-yl)carbamate **39** proceeds via a six-membered transition state to give ethene, carbon dioxide, and the otherwise not readily obtainable 5-aminothiadiazol-2-ylacetonitrile **40** (**Scheme 2**) <1997HAC293>.

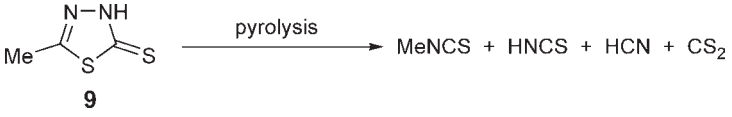


Scheme 2

High-vacuum pyrolysis of 2,5-dimercapto-1,3,4-thiadiazole **34** and 2-mercapto-5-methyl-1,3,4-thiadiazole **9** performed between ambient and 800 °C gave products that were trapped by matrix-isolation techniques and characterized by IR spectroscopy. Pyrolysis of the dimercaptothiadiazole **34** gave HNCS, CS_2, and HCN (Equation 2), whereas the thiadiazolethione **9** showed a more complex fragmentation pattern forming HNCS, CH_3NCS, HCN, and CS_2 (Equation 3) <2002J(P2)1620>.

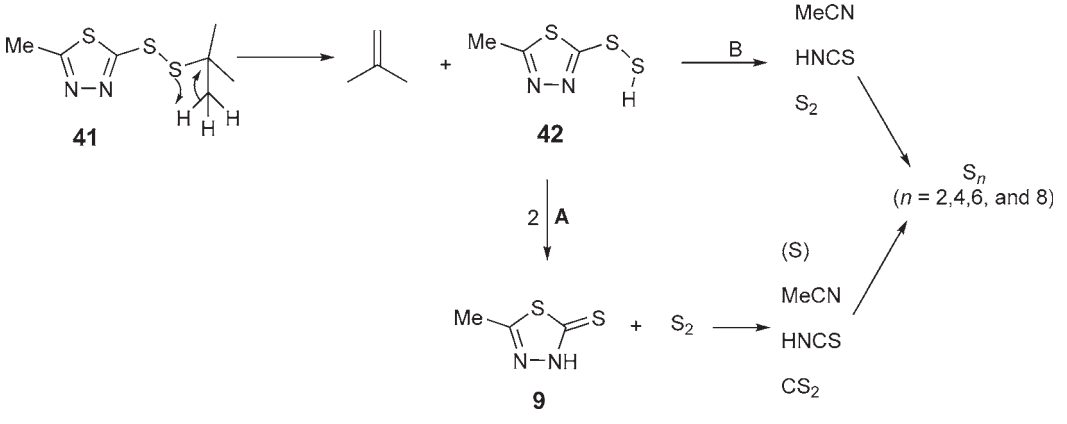


(2)



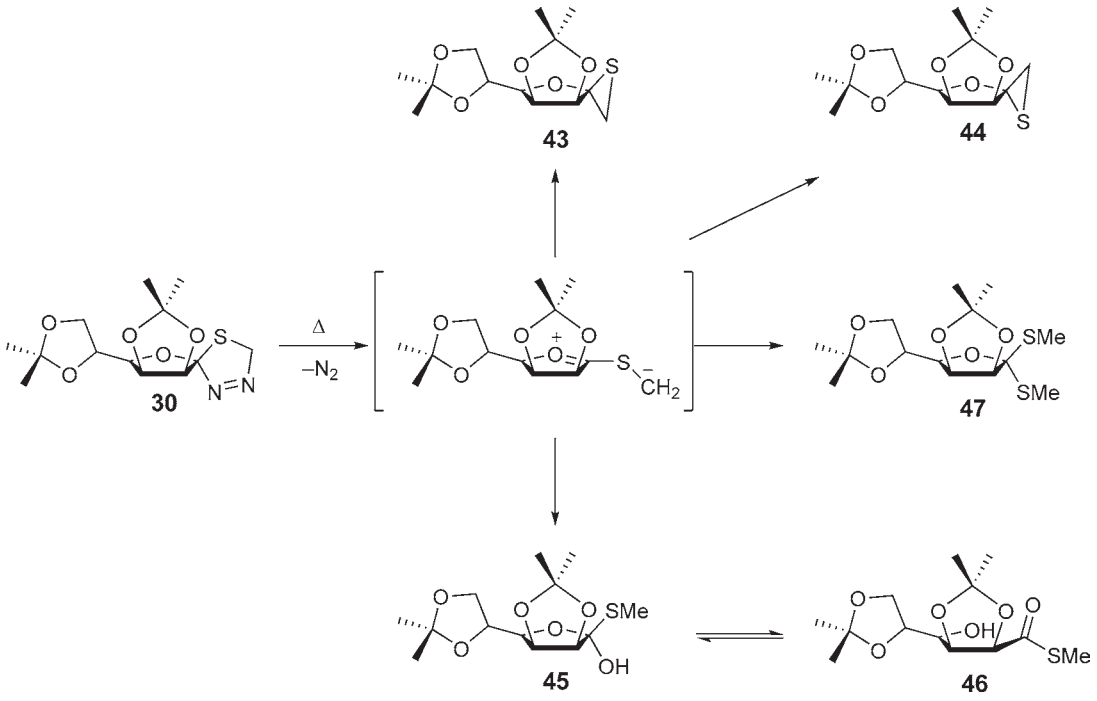
(3)

The analogous high-vacuum pyrolysis of 2-(*tert*-butyldithio)-5-methyl-1,3,4-thiadiazole **41** between ambient and 900 °C gave 2-methylpropene, HNCS, thiadiazole **9**, CS_2, CH_3CN, and sulfur species (**Scheme 3**) <2005PCP731>. The presence of 2-methylpropene might be caused by a β-hydrogen elimination. This reaction would lead to the disulfanyl **42** which fragments further via two main paths (A and B). In reaction path A the bimolecular fragmentation of **42** gives S_2 and the thiadiazole **9**, which above 500 °C decomposes to CH_3CN, HNCS, CS_2, and sulfur. Path B results in direct elimination of S_2 from the disulfanyl **42** to give HNCS and CH_3CN (**Scheme 3**).



Scheme 3

Thermolysis of 2,5-dihydro-1,3,4-thiadiazole **30** in C_6D_5Cl solution at 20–35 °C gave spirothiiranes **43** and **44**, *O*-hydrogen *O*,*O*,*S*-ortholactone **45**, the thio-*S*-ester **46**, and *O*,*S*,*S*-ortholactone **47** (**Scheme 4**) <1997HCA1260>. The ratio of these thermolysis products did not significantly vary between 23 and 35 °C.

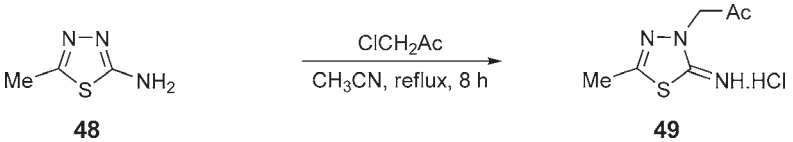


Scheme 4

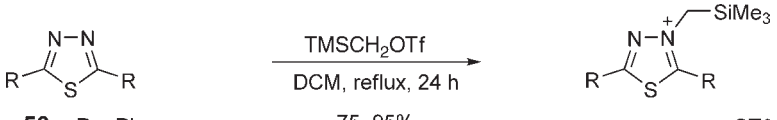
5.10.5.3 Electrophilic Attack at Nitrogen

The ring nitrogens react with electrophiles to afford either 1,3,4-thiadiazolium salts or 1,3,4-thiadiazol-2(3*H*)-ones depending on the tautomerisability of the substituents at the C-2 or C-5 positions. While N-alkylation is the most common electrophilic reaction of 1,3,4-thiadiazoles, reactions with acyl and cyanogen halides as well as Mannich salts have also been reported.

2-Amino-5-methyl-1,3,4-thiadiazole **48** reacts with chloroacetone to give the N-alkylated thiadiazolimine **49** (Equation 4) <2000AF550> and *N*-alkylation of the 2,5-diphenyl- and 2,5-dimethyl-1,3,4-thiadiazole **50a** and **50b** with trimethylsilylmethyl trifluoromethanesulfonate gave the corresponding 1,3,4-thiadiazolium salts **51** (Equation 5) <2002J(P1)2851>. A comprehensive study of the quarternization of the 2,5-disubstituted thiadiazoles has been covered in CHEC(1984) <1984CHEC(6)545>.



48 **49** (4)



50a: R = Ph
50b: R = Me

51 (5)

5.10.5.4 Electrophilic Attack at Carbon

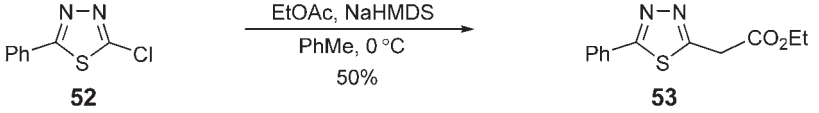
Electrophilic substitution reactions on the carbon atoms of 1,3,4-thiadiazoles are rare due to the low electron density of ring carbons. C-Acylation can be accomplished via rearrangement of intermediate *N*-acylthiadiazolium salts while radical halogenation can give chlorinated or brominated 2-halo-5-substituted thiadiazoles. Examples can be found in CHEC(1984) <1984CHEC(6)545> and in Houben–Weyls' *Science of Synthesis* <2004HOU(13)349>.

5.10.5.5 Electrophilic Attack on Sulfur

No examples of direct oxidation of the 1,3,4-thiadiazole ring sulfur to sulfoxide or sulfone have been reported. Δ^3-1,3,4-Thiadiazoline 1-oxide and 1,1-dioxide, however, can be obtained by indirect methods that are reviewed in CHEC(1984) <1984CHEC(6)545>.

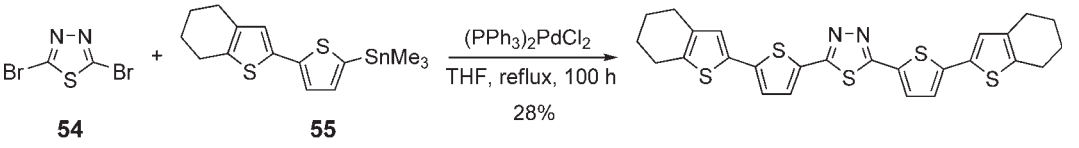
5.10.5.6 Nucleophilic Attack on Carbon

Nucleophilic reactions at the carbon atoms of 1,3,4-thiadiazoles occur readily owing to the electron-deficient nature of this ring. Halo-substituted thiadiazoles are therefore highly activated and react with a wide range of nucleophiles. Carbon-based nucleophiles such as malonates have been used in the synthesis of 2-substituted thiadiazoles. When chlorothiadiazole **52** was treated with ethyl acetate in the presence of NaHMDS, the 2-phenyl-1,3,4-thiadiazol-5-ylacetic ester **53** was obtained (Equation 6) <2006OL1447>.

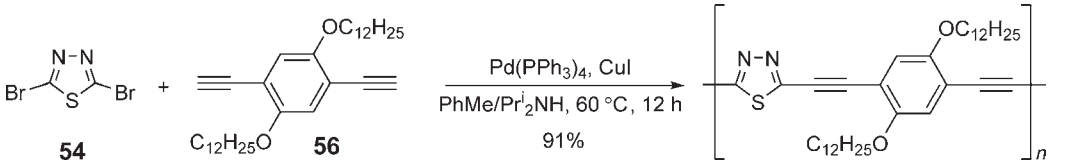


52 **53** (6)

The bromine atoms in 2,5-dibromo-1,3,4-thiadiazole **54** undergo a palladium-catalyzed Stille reaction with the organostannyl derivative **55** (Equation 7) <1998CEJ2211>. The thiadiazole **54** was co-polymerized with diethynyl benzene **56** (Equation 8) and diethynyl pyrrole in a Sonogashira cross-coupling reaction <2005MM4687>.

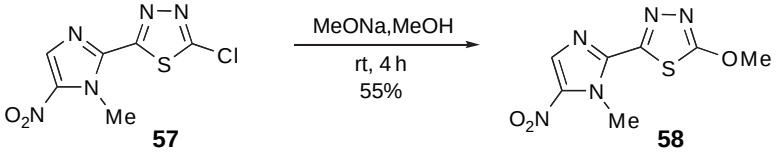


54 **55** (7)

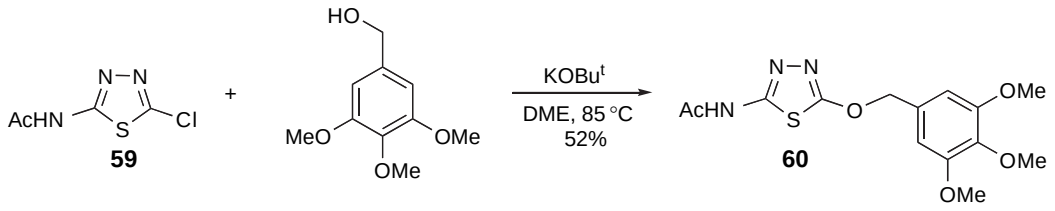


54 **56** (8)

Oxygen, sulfur <2006BML1164, 2000MI31, 1999AF1035, 1998MI95>, and nitrogen <2006BML1735, 2005EJM1346, 2005BML1983, 2005BML4488, 2004BML5967, 2003PHA432, 2003FA1023, 2003EJM851> nucleophiles also react with the halothiadiazoles to give the corresponding halo-displaced products. For example, the thiadiazole **57** reacts with sodium methoxide in methanol to give thiadiazole **58** (Equation 9) <2003JME427> and 2-acetamido-5-chloro-1,3,4-thiadiazole **59** reacted with the 3,4,5-trimethoxybenzyl alcohol in the presence of potassium *t*-butoxide to afford the substituted trimethoxybenzyl ether **60** (Equation 10) <1996TL4065>.

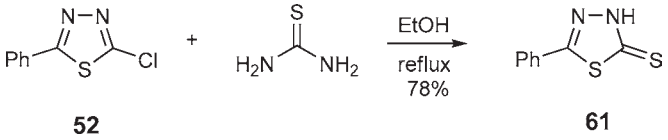


57 **58** (9)

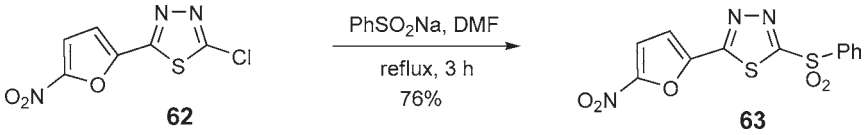


(10)

2-Chloro-5-phenyl-1,3,4-thiadiazole **52** reacts with thiourea in refluxing ethanol to afford the thione **61** (Equation 11) <2000MI31>. The reaction of sodium phenylsulfinate with thiadiazole **62** in refluxing dimethylformamide (DMF) gave the 5-phenylsulfonyl-1,3,4-thiadiazole **63** (Equation 12) <1999AF1035>.

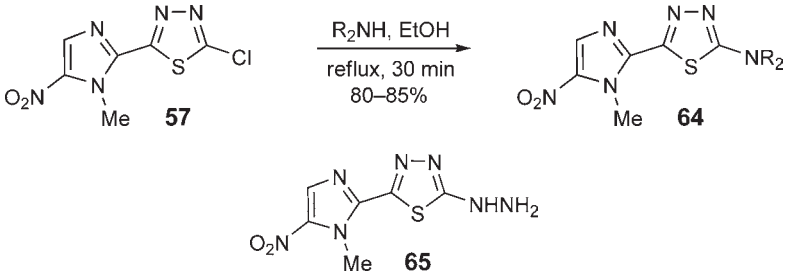


(11)



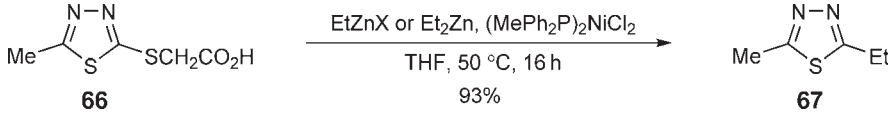
(12)

Thiadiazole **57** reacts with cyclic secondary amines such as piperidine, piperazine, and morpholine to afford the substituted derivatives **64** in 80–85% yield (Equation 13) <2005EJM1346>. Under similar conditions, thiadiazole **57** reacts with hydrazine hydrate to give the thiadiazolhydrazine **65** in 97% yield <2004BML5967>.

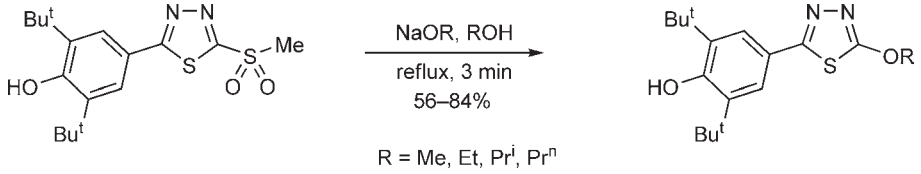


(13)

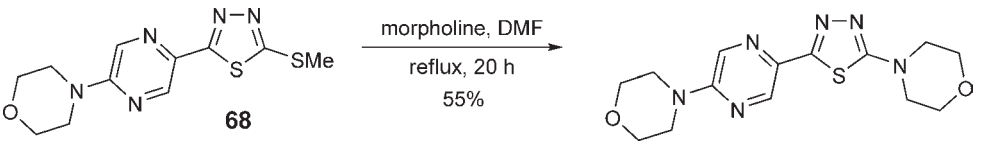
Sulfur substituents at either the C-2 or C-5 positions are also activated and can be substituted by a range of nucleophiles. The thioglycolic thiadiazole acid **66** reacts with diethylzinc in the presence of an Ni catalyst to give the 2-ethyl-substituted thiadiazole **67** (Equation 14) <1999JA9449>. Sulfonyl substituents can be displaced with sodium alkoxides <2004T8627, 1999JME1161> to give ethers, for example, (Equation 15) <1999JME1161>, or by nitrogen nucleophiles to afford the corresponding amino derivatives <2006PS609, 2004CHE1185, 1997CHE1219>. The reaction of the thiadiazole **68** with morpholine in refluxing DMF led to substitution of the methylthio group (Equation 16) <2004CHE1185>.



(14)

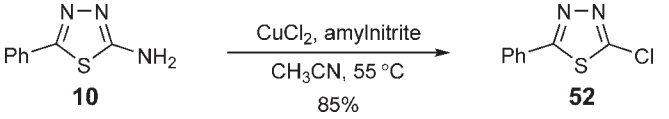


(15)

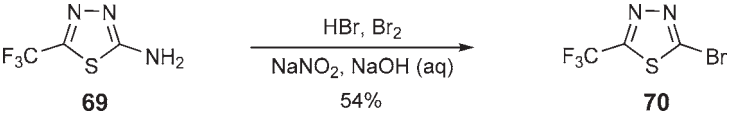


(16)

2-Amino-1,3,4-thiadiazoles undergo Sandmeyer reactions to afford 2-halo-1,3,4-thiadiazoles <2006OL1447, 2006BML1735, 2006BML1164, 2005BML4488, 2005BML1983, 2004BML5967, 2003FA1023, 2003JME427, 2003EJM851, 2000MI31, 1999AF1035, 1998MI95>. Diazotization followed by a Sandmeyer reaction of the 2-amino-5-phenyl-1,3,4-thiadiazole **10** with CuCl generated *in situ* gave 2-chloro-5-phenyl-1,3,4-thiadiazole **52** in 85% yield (Equation 17) <2006OL1447, 2004BML5967> while Sandmeyer bromination of 2-amino-5-(trifluoromethyl)-1,3,4-thiadiazole **69** gave 2-bromo-5-(trifluoromethyl)-1,3,4-thiadiazole **70** in 54% yield (Equation 18) <2006BML1735>.



(17)



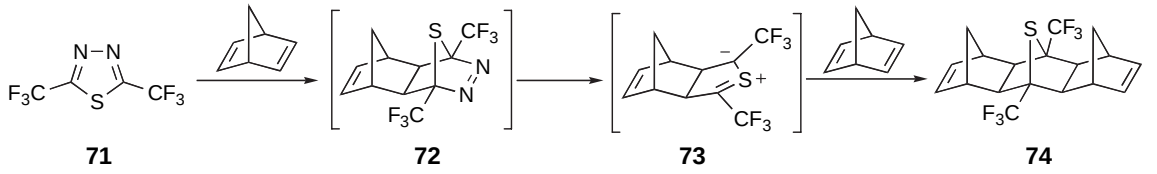
(18)

5.10.5.7 Nucleophilic Attack at Hydrogen Attached to Carbon

Deprotonation of 1,3,4-thiadiazolium salts affords carbenes that can be trapped with aromatic isocyanates to yield spirocyclic compounds. These reactions have been reviewed in CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379>.

5.10.5.8 Reaction with Radicals and Cyclic Transition States

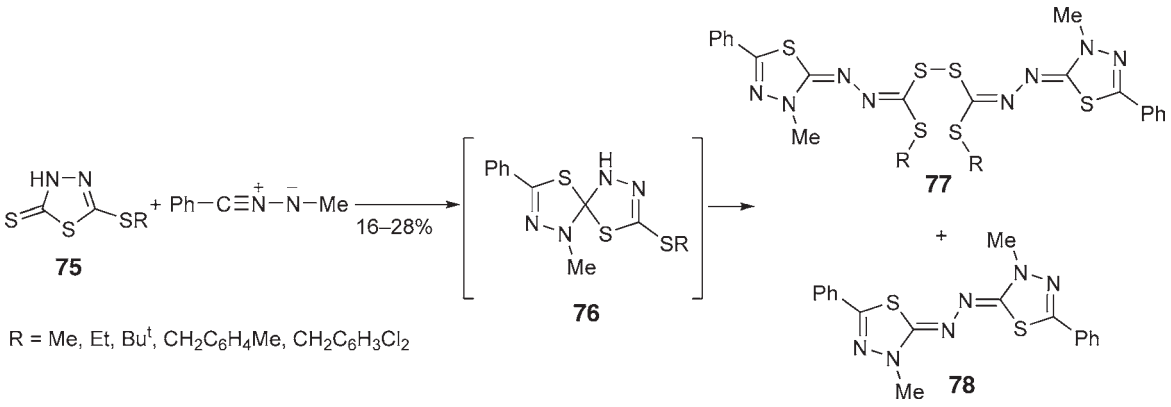
2,5-Bistrifluoromethyl-1,3,4-thiadiazole **71** undergoes a Diels–Alder reaction with norbornadiene under high pressure to give the unstable cycloadduct **72** which rapidly loses dinitrogen forming the 1,3-dipolar intermediate **73**. The [4+2] cycloaddition of the intermediate **73** with a second alkene affords product **74** in 29% yield (**Scheme 5**) <1997SL196>.



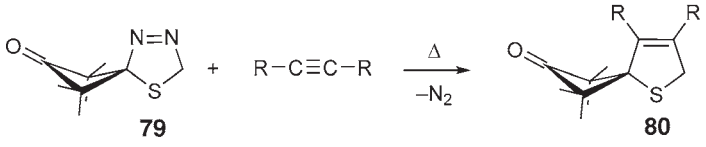
Scheme 5

The 5-thio-substituted 1,3,4-thiadiazole-2(3*H*)-thiones **75** react with *N*-methyl-*C*-phenylnitrilimine in a regiospecific 1,3-dipolar cycloaddition to form not the expected cycloadducts **76** but rather the rearranged products **77** and **78** in 16–28% yields (**Scheme 6**) <1998AJC499>.

The 2,5-dihydro-1,3,4-thiadiazole **79** reacts with a range of acetylenic dipolarophiles to afford the 2,5-dihydrothiophenes **80** in 25–75% yields (Equation 19) <2002HCA451>. The thermal extrusion of dinitrogen from the thiadiazole affords a thiocarbonyl ylide, which reacts with the dipolarophiles to form the thiophenes.



Scheme 6



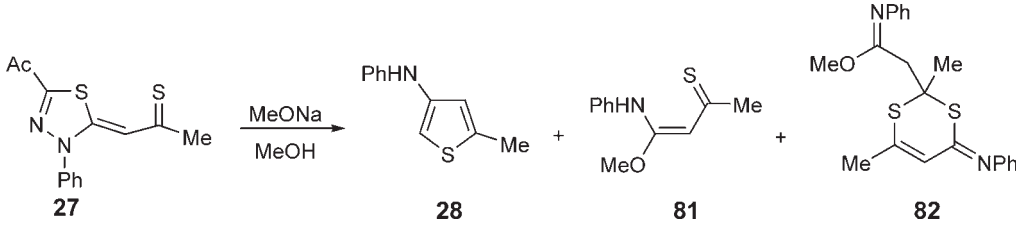
R	*Yield* (%)
MeO_2C	65
CN	41
PhCO	63

(19)

5.10.6 Reactivity of Nonconjugated Rings

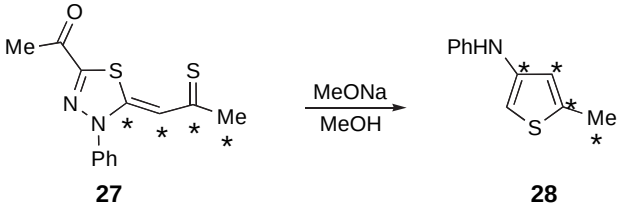
5.10.6.1 Reactivity of Thiadiazolines

The thermal decomposition and cycloaddition reactions of 2,5-dihydro-1,3,4-thiadiazoles are reviewed in Sections 5.10.5.2 and 5.10.5.8. The base-induced conversion of the (*Z*)-5-acetyl-3-aryl-2,3-dihydro-2-[(thioacyl)methylene]-1,3,4-thiadiazole **27** into 3-(*N*-anilino)-5-methylthiophene **28** has been reported <2003EJO2480>. When a solution of the thiadiazole **27** was heated with sodium methoxide in methanol under reflux, 3-(*N*-anilino)-5-methylthiophene **28** was obtained in 25% isolated yield together with two other minor products **81** and **82** (Equation 20).

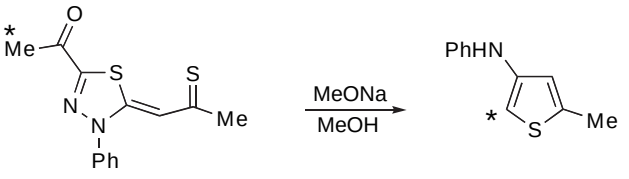


(20)

^{13}C-labeled experiments were undertaken to establish the atom source of the thiophene ring (Equations 21 and 22). The methyl group and the C-3, C-4, and C-5 carbon atoms of the ring come from the (thioacyl)methylene system of **27**, whereas C-2 comes from the methyl group of the 5-acetyl substituent.

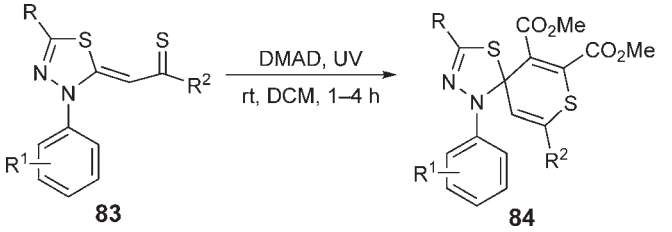


(21)



27 28 (22)

The cycloaddition reactions of [(thioacyl)methylene]thiadiazoles **83** with dimethyl acetylenedicarboxylate (DMAD) under UV irradiation at room temperature gave the spiro[3*H*-1,3,4-thiadiazoline-2,4′-4*H*-thiopyrans] **84** in 50–60% yields (Equation 23) <2003EJO2480>.

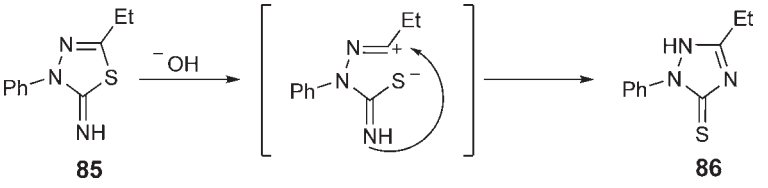


83 84

R	R^1	R^2	*Yield* (%)
COMe	H	Me	53
CO_2Et	3,5-diMe	Me	60
Ph	H	Ph	50

(23)

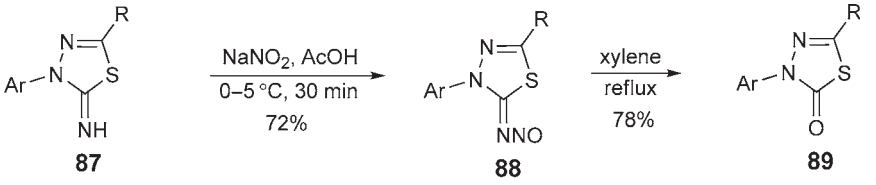
Heating of a solution of 5-ethyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-imine **85** in aq. NaOH to 80 °C for 5 h gave the 5-ethyl-2,3-dihydro-2-phenyl-1*H*-1,2,4-triazole-3-thione **86** via Dimroth rearrangement (**Scheme 7**) <2002HCA1883>. Nucleophilic attack of the hydroxide on the electrophilic C-5 resulted in ring opening and, after rotation around the C(2)–N(3) bond and subsequent recyclization, triazole thione **86** formed.



85 86

Scheme 7

Thiadiazolin-2-imines can also be converted to thiadiazolin-2-ones in two steps <2004PS601, 2003HAC421, 2003PS1101>. The nitrosation of the thiadiazol-2-imines **87** with saturated nitrite in acetic acid at 0–5 °C gave the *N*-nitroso-1,3,4-thiadiazol-2(3*H*)imines **88** in 72% yield. Thermolysis of the latter in refluxing xylene gave the 1,3,4-thiadiazolin-2-one **89** in 78% yield (**Scheme 8**) <2003HAC421>.



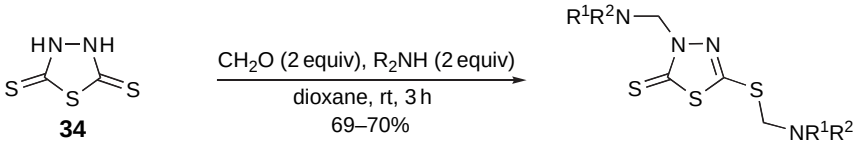
87 88 89

R = 4-$(CH_3)_2CHC_6H_4$
Ar = 4-$O_2NC_6H_4$

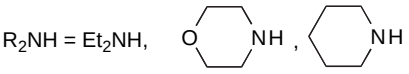
Scheme 8

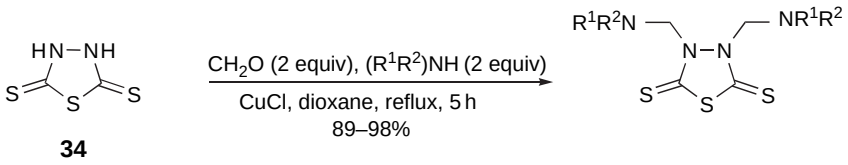
5.10.6.2 Reactivity of Thiadiazolidines

The reaction of 2,5-dimercapto-1,3,4-thiadiazolidine **34** with dialkylamines under Mannich reaction conditions gave N,S-aminomethylated thiadiazoles in 69–70% yields (Equation 24) <1998CHE1431>. With urea, thiourea, semicarbizide, or thiosemicarbazide, thiadiazolidine **34** gave N,N-aminomethylated thiadiazoles in 89–98% yields (Equation 25).



(24)

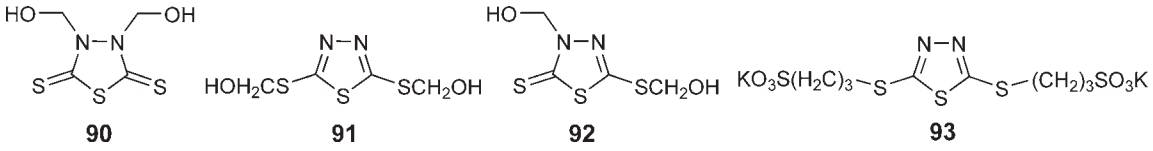




(25)

$(R^1R^2)N$ = $NHCONH_2$, $NHCSNH_2$, $NHNHCONH_2$, $NHNHCSNH_2$

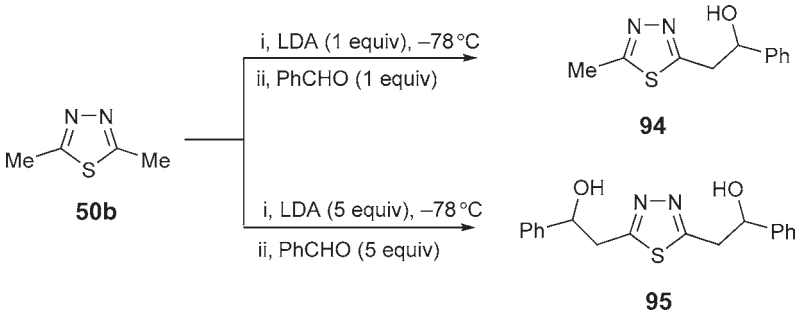
Depending on the pH, condensation of thiadiazolidine **34** with formaldehyde leads to an *N*,*N*-, *N*,*S*-, or *S*,*S*-derivative. At neutral pH the 3,4-bis(hydroxymethyl)-1,3,4-thiadiazol-2,5-dithione **90** was formed in 87% yield while subsequent basification of the reaction mixture to pH 8.0 gave both *N*,*N*- and *S*,*S*-thiadiazoles **90** and **91** in 76% and 24% yield, respectively. In alkaline media, with subsequent acidification to pH 3.0, a mixture of *N*,*N*-, *N*,*S*-, and *S*,*S*-thiadiazole derivatives **90** (60%), **91** (24%), and **92** (16%) was formed. Reaction of thiadiazolidine **34** with 1,3-propanesulfone in an alkaline medium gave the dipotassium *S*,*S*-derivative of thiadiazole **93** (83%).



5.10.7 Reactivity of Substituents Attached to Ring Carbon Atoms

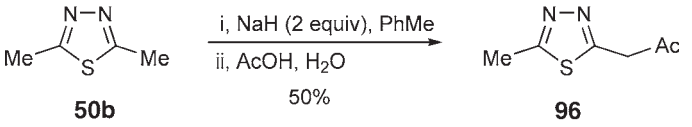
5.10.7.1 Carbon Substituents

The lithiation of 2-methyl-1,3,4-thiadiazoles can be achieved with strong bases but the corresponding organolithium derivatives are unstable toward dimerization. Nevertheless, functionalization of the methyl groups can be achieved via treatment of the methylthiadiazole with a base followed by addition of an electrophile. The lithiation of 2,5-dimethyl-1,3,4-thiadiazole **50b** with lithium diisopropylamide (LDA) followed by quenching with aldehydes or ketones gave either the mono- or bis-hydroxy arylated products **94** and **95** depending on the equivalents of base used (**Scheme 9**) <1999SC145>.



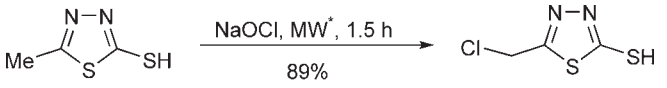
Scheme 9

Thiadiazole **50b** was also acylated when treated with acetic acid in the presence of sodium hydride to give the thiadiazole **96** (Equation 26) <2004ZNB366>.



50b **96** (26)

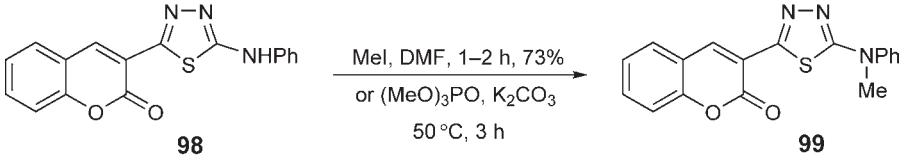
Halogenation of 2-methyl-1,3,4-thiadiazole **9** can be achieved under free radical conditions. Trichloro- and tribromomethyl-1,3,4-thiadiazoles have been obtained by this method <1980LA1216>. Rapid and selective free radical monochlorination of the 2-mercapto-5-methyl-1,3,4-thiadiazole **9** was achieved using sodium hypochlorite under microwave conditions (Equation 27) <1998JCM586>.



9 **97** (27)

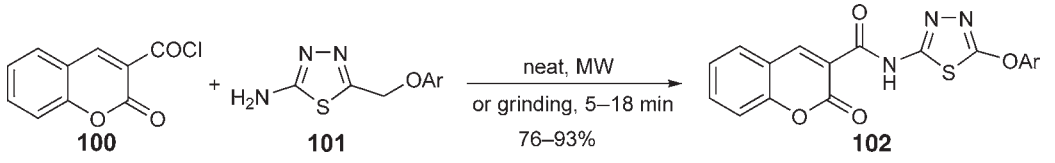
5.10.7.2 Nitrogen Substituents

Selective functionalization of the exocyclic nitrogen atoms can be readily achieved. Exocyclic N-alkylation gives secondary and tertiary amines <2005PS397, 2003TL7575, 2003S899, 2001JME931, 1999JCM76, 2003HAC114>, acylation affords amides <2006PS183, 2006BML307, 2005PHA18, 2005BML635, 2005RJC1962, 2005BML2347, 2004BMC2717, 2004BMC613, 2004JME5593, 2003PHA367, 2003HCO199, 2003RJC1676, 2003SC2891, 2003S899, 2002SC1105, 2002EJM689, 2002JME3905, 2002BMC2893, 2002JHC877, 2002CHE852, 2002H(57)1919, 2001H(55)579, 2001JME931>, reaction with nitriles gives amidines <2000JHC811>, and isocyanates afford ureas <2004JME2796, 2000RCB1202, 1999JME1525>. For example, the secondary amine group in thiadiazole **98** was alkylated by methyl iodide in 73% yield or by trimethyl phosphate (yield not reported) in the presence of anhydrous potassium carbonate to afford the *N*-methyl-1,3,4-thiadiazol-2-yl aniline **99** (Equation 28) <2003HAC114>.



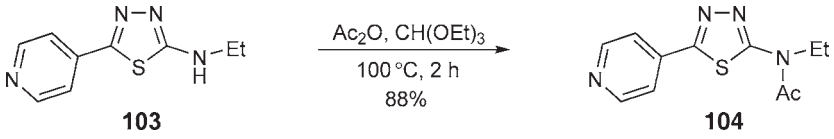
98 **99** (28)

Grinding thiadiazolamines **101** with an equivalent of coumarin-3-carboxylic acid chloride **100** under solvent-free conditions in a mortar gave the corresponding amides **102** in 76–90% yields, or when heated in a microwave oven for 5–18 min in 87–93% yields (Equation 29) <2006PS183>.



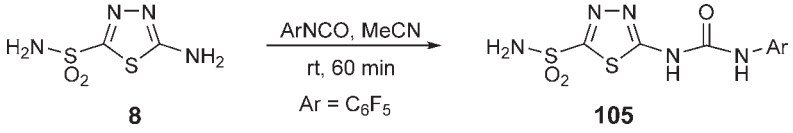
100 **101** **102** (29)

The secondary amine group of the thiadiazole **103** was acylated when heated in the presence of acetic anhydride and ethyl orthoformate to afford the amide **104** in 88% yield (Equation 30) <2002CHE852>.

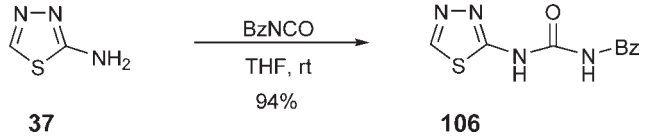


103 104 (30)

The reaction of pentafluorophenyl isocyanate with thiadiazole **8** in acetonitrile at room temperature gave 5-pentafluorophenylureido-1,3,4-thiadiazole-2-sulfonamide **105** (Equation 31) <2004JME2796>. Similarly, 2-amino-1,3,4-thiadiazole **37** reacts with benzyl isocyanate in dry THF to afford the 1,3,4-thiadiazol-2-yl urea **106** in 94% yield (Equation 32) <1999JME1525>.

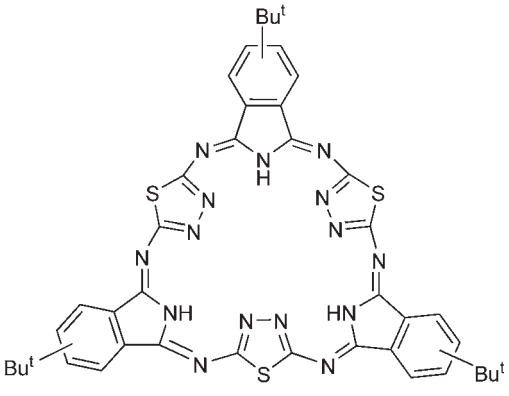


8 105 (31)

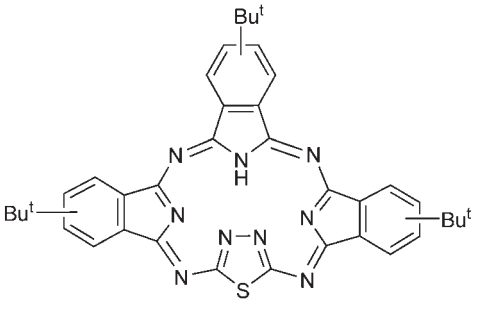


37 106 (32)

Large macrocyclic phthalocyanines can be obtained from the condensation reactions of 2,5-diamino-1,3,4-thiadiazole <2006SC1801, 2006MI837, 2001OL2153>. Diaminothiadiazole reacts with 5-*tert*-butyl-1,3-diiminoisoindoline in 2-ethoxyethanol at 135 °C for 24 h to give macrocycles **107** and **108** in 54% and 15% yields, respectively <2001OL2153>.



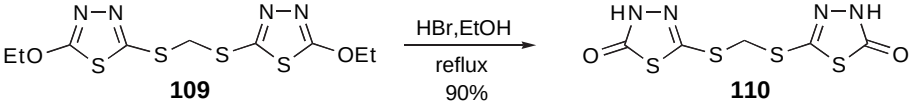
107



108

5.10.7.3 Oxygen Substituents

2-Alkoxy-1,3,4-thiadiazoles can be dealkylated under acidic conditions to give 1,3,4-thiadiazol-2(3*H*)-ones. The selective and clean dealkylation of the ethoxy group in thiadiazole **109** was achieved with HBr in refluxing ethanol to give the thiadiazolone **110** (90%) (Equation 33) <1999H(51)2739>.

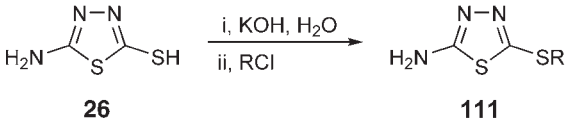


109 110 (33)

Acylation of 1,3,4-thiadiazol-2-(3*H*)-ones is also possible although competitive reaction with the ring nitrogen atoms is often observed. This reaction has been reviewed in the Houben–Weyl *Science of Synthesis* <2004HOU(13)349>.

5.10.7.4 Sulfur Substituents

Sulfur-substituent groups at C-2 and/or C-5 undergo alkylation and dealkylation reactions and can be converted into either sulfoxides or sulfones depending on the oxidation conditions. Alkylations are often carried out in the presence of base with alkyl iodides in ethanol <2002JME3905, 2001JME931, 2000CHE598, 2000MI31, 1997CHE118>. The 5-amino-1,3,4-thiadiazole-2-thiol **26** was suspended in a KOH solution and then treated with alkyl halides to afford the alkylated compounds **111** in 55–91% yields (Equation 34) <2001JME931>.



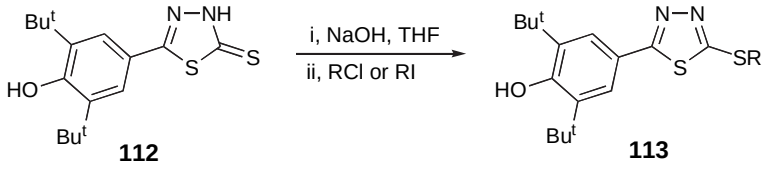
26 **111**

R	*Yield* (%)
Me	55
Pr^n	57
Pr^i	65
Bz	83

(34)

2,5-Dimercapto-1,3,4-thiadiazole **34** was converted into the monoammonium, monopyridinium, monohydrazine, and dihydrazine salts and then alkylated using benzyl chloride, methyl bromoacetate, and 3-phenyl-2-propynyl chloride in ethanol at room temperature <2000CHE598>. The 1,3,4-thiadiazole-2(3*H*)-thiones can be deprotonated by alkali bases and subsequently S-alkylated with alkyl halide to give the corresponding thioethers <2006PS1737, 2003CHE228, 2002H(57)1919, 2000CHE598, 1999H(51)2739, 1999JME1161, 1998MI95>.

The thiadiazole thione **112** was treated with an alkyl halide in sodium hydroxide to afford the thiadiazole derivatives **113** in 35–92% yields (Equation 35, **Table 3**) <1999JME1161>. This reaction results in the aromatization of the reduced thiadiazoline ring (see Section 5.10.9.5.1). The 2-(methylsulfanyl)-1,3,4-thiadiazoles can be S-demethylated to afford 1,3,4-thiadiazole-2-thiones <1994JHC1439>.



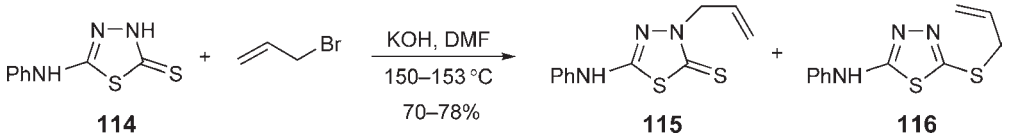
112 **113**

(35)

Table 3 *S*-Alkylation of 1,3,4-thiadiazole-2(3*H*)-thione **112**

R	*Yield* (%)	*Reference*
CH_2CF_3	35	1999JME1161
Pr^n	89	1999JME1161
Pr^i	97	1999JME1161
Bn	92	1999JME1161
$CH_2CH_2NH_2$	71	1999JME1161
$CH_2CH_2NEt_2$	52	1999JME1161

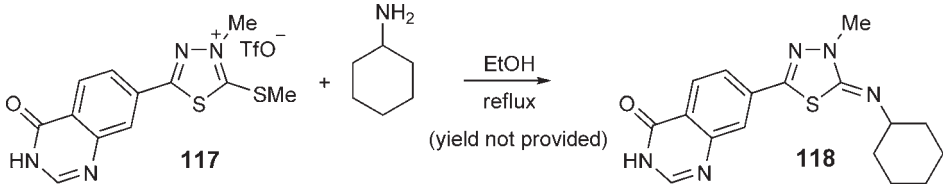
The allylation of thiadiazole-2-thione **114** with allyl bromide gave as the main product the N-allyl derivative **115** with trace amounts of the corresponding S-derivative **116** (Equation 36) <2003CHE228>. Furthermore, it was shown that refluxing the thiadiazole **116** in DMF (3 h) gave thiadiazole-2-thione **115** via a thio-Claisen rearrangement.



114 **115** **116**

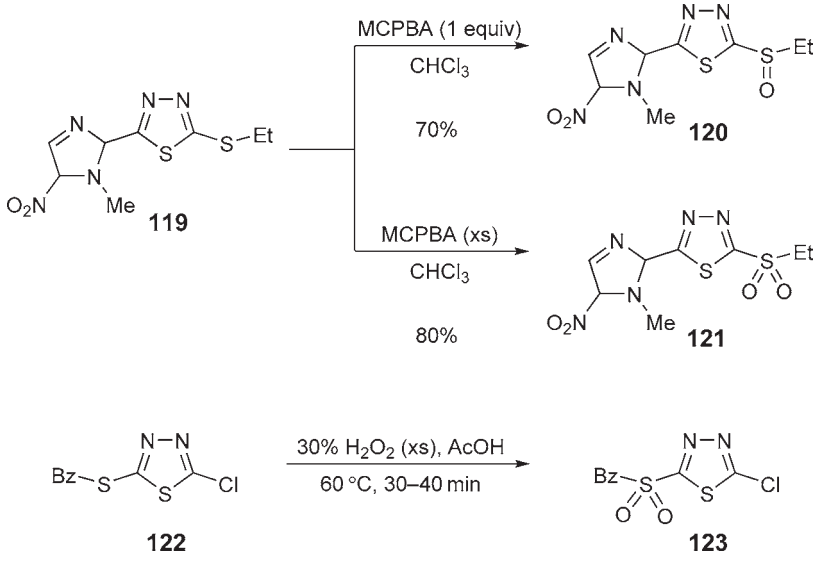
(36)

The sulfide groups in mesoionic 1,3,4-thiadiazolium salts are activated toward nucleophilic substitution. The mercapto substituent of the thiadiazolium salt **117** can be displaced by cyclohexylamine to afford the 2*H*-thiadiazolimine **118** (Equation 37) <2004BML4607>.



(37)

Oxidation of exocyclic sulfides to sulfoxides can be achieved using stoichiometric amounts of *m*-choloperbenzoic acid (MCPBA) <2006BML1164, 1999JME1161, 1998BML2473, 1998MI95>, whereas the use of excess MCPBA or hydrogen peroxide leads to the corresponding sulfones <2006BML1164, 2005BML4488, 2000MI31, 1998MI95, 1997BMC515>. For example, treatment of 2-alkylmercapto-5-aryl-1,3,4-thiadiazole **119** with MCPBA (1 equiv) in chloroform gave the sulfoxide **120** and excess MCPBA gave the sulfone **121** <1998MI95>. Similarly, sulfide **122** reacts with excess 30% hydrogen peroxide in acetic acid to afford the corresponding sulfones **123** (**Scheme 10**) <2005BML4488>.



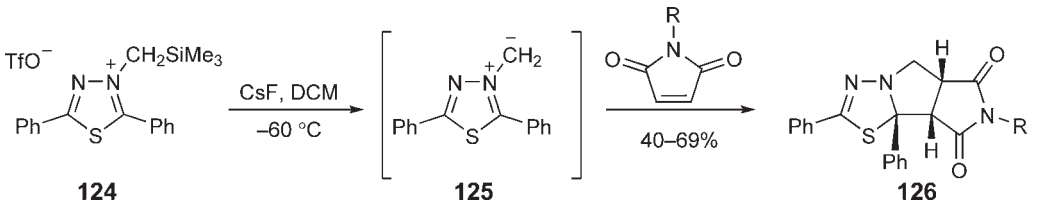
Scheme 10

5.10.7.5 Halogens

Direct nucleophilic displacement of halo substituents proceeds via attack on the ring carbon atom (see Section 5.10.5.6). Nucleophilic attack on the halogen has not been reported.

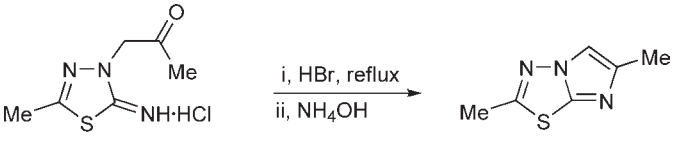
5.10.8 Reactivity of Substituents Attached to Ring Heteroatoms

Few examples on the reactivity of substituents attached to ring atoms are available. The desilylation of the 1,3,4-thiadiazolium salt **124** by CsF gave the unstable 1,3-dipole **125** which was trapped with N-substituted maleimides to afford exclusively the *endo*-pyrrolo[2,1-*b*][1,3,4]thiadiazoles **126** in 40–69% yields (**Scheme 11**) <2002J(P1)2851, 2001CC1950>.



Scheme 11

Substituents on the ring nitrogen can often cyclize to afford fused 1,3,4-thiadiazoles (see also Volume 9). The N-substituent on the 1-(2-amino-5-methyl-3-[1,3,4]thiadiazolyl)acetone **49** was annulated on the ring when treated with HBr (Equation 38) <2000AF550>.



(38)

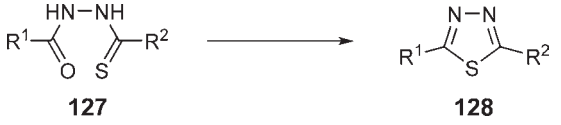
5.10.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

The synthetic procedures in this section are classified by the number of ring atoms contributed by each component and by the number and types of bond generated in the last reaction step.

5.10.9.1 Formation of One Bond

5.10.9.1.1 Fragment S–C–N–N–C: Cyclizations

Monothiodiacylhydrazines **127**, derived from the acylation of thiosemicarbazides or as intermediates in the reactions of (1) thiohydrazides with carboxylic acids and their derivatives (see Section 5.10.9.2.2(i)) or (2) hydrazides with thiocarbonyl compounds (see Section 5.10.9.2.3(i)), cyclize in the presence of an acid catalyst to give 1,3,4-thiadiazoles **128** (Equation 39, **Table 4**).

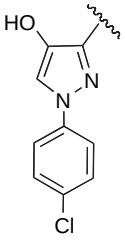
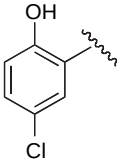
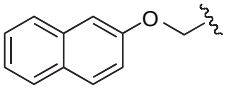


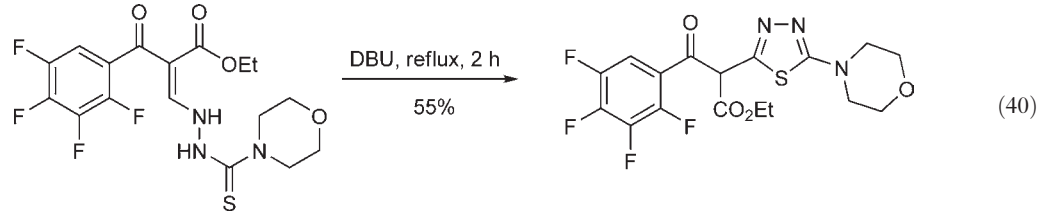
(39)

Phosphoryl chloride <2005PS397, 2004PS1577, 2004PS2509, 2003HAC114, 2002PS863> and acid chlorides <2001PHA617> can also induce cyclization. The use of microwave irradiation for the acid-catalyzed cyclizations can increase product yields and reduce reaction times <2005HCO101, 2003HAC535, 2001SC1829, 2000SC3971>. When a secondary amino group is connected directly to the thiocarbonyl group of the monothiodiacylhydrazine, acid treatment yields 1,3,4-thiadiazoles while base catalysis affords 1,2,4-triazoles and oxidation with $Hg^{II}O$ or I_2/NaOH gives 1,3,4-oxadiazoles <2004EJM535, 2003PHA11>.

Less common synthetic methods for 1,3,4-thiadiazoles include the oxidative thermal base-catalyzed cyclization of thiosemicarbazido arylates (Equation 40) <2005HAC12> and a tetracyanoethylene (TCNE)-assisted cyclization (Equation 41) <2004ZNB910>.

Table 4 Preparation of 1,3,4-thiadiazoles from acid-catalyzed cyclizations of monothiodiacylhydrazines

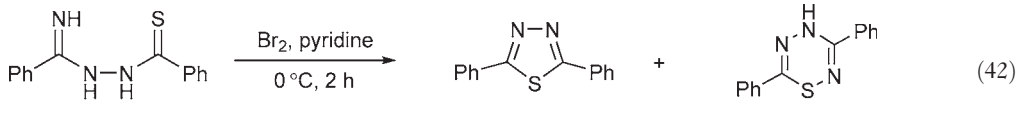
R^1	R^2	*Conditions*	*Yield (%)*	*Reference*
Ph	PhNH	H_2SO_4, H_2O, rt, 30 min	91	2004JME6760
	PhNH	H_2SO_4, EtOH, rt, 4 h	90	2003EJM959
	EtNH	PPA, 120 °C, 2 h	65	2003MI11
Pyrid-4-yl	EtNH	H_3PO_4, 110 °C, 1.5 h	66	2002CHE852
	MeNH	$MeSO_3H$, PhMe, reflux, 45 min	25	2002FA101
4-Bromobenzamide	$PhOCH_2$	AcOH	90	2001IJB422



(40)

(41)

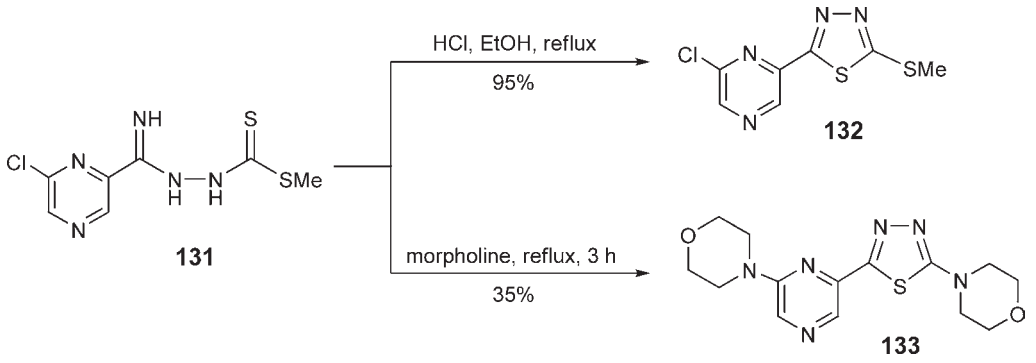
The cyclization of *N*′-imidoylthiohydrazide **129** with bromine in the presence of pyridine gave 2,5-diphenyl-1,3,4-thiadiazole **50a** along with the 3,6-diphenyl-4*H*-1,2,4,5-thiatriazine **130** in a 13:5 ratio (Equation 42). The product ratio was sensitive to the reaction conditions and when compound **129** was treated with oxidants such as NCS, Bu^{t}OCl, I_2/pyridine, or, if deprotonated, with NaH and then treated with I_2 or SO_2Cl_2, thiadiazole **50a** was the major product <2000JOC931>. *N*′-Imidoylthiohydrazide **129** was converted to thiadiazole **50a** in 80% yield upon storage at room temperature for over a year and gave product **50a** exclusively when treated with either pyridine or an acid.



129 **50a** **130**

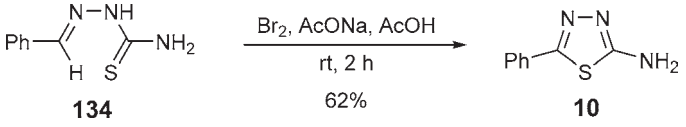
(42)

N′-Imidoylthiohydrazide **131** cyclized to 1,3,4-thiadiazole **132** on treatment with HCl but gave the amino-substituted thiadiazole **133** directly on prolonged heating in neat amine (**Scheme 12**) <2004CHE1185>.



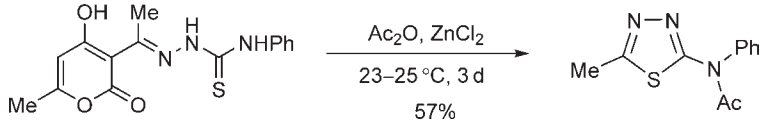
Scheme 12

Oxidative cyclization of thioacylhydrazone **134** also provides 1,3,4-thiadiazole **10** (Equation 43). Common oxidants include bromine <1997PHA350>, ferric chloride <2004BMC613, 2005T10917, 2003PHA367, 2000JHC811, 2003JME427>, ammonium ferric sulfate <2003JME427, 2003EJM851, 2005BML1983>, and potassium permanganate <2004H(63)2243>.

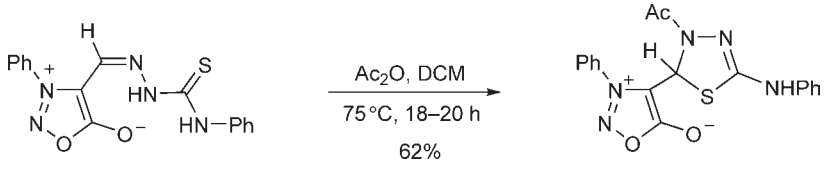


(43)

Cyclization of thioacylhydrazones can also be achieved using acid catalysis <1995LA721>. Acylating reagents such as acetic anhydride in the presence of zinc chloride can also afford 1,3,4-thiadiazoles (Equation 44); however, in some cases acylation can occur on the ring nitrogen (Equation 45) <2005T10917, 1995LA721, 2004H(63)2243>.

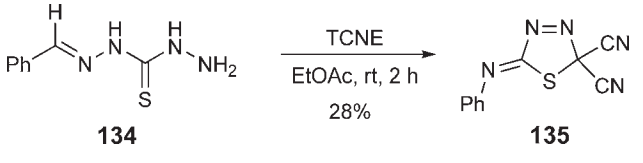


(44)



(45)

The TCNE-promoted cyclization of the thioacylhydrazone **134** gave the phenylimino 5,5-dicyanothiadiazole **135** (Equation 46) <1997M61>.



(46)

5.10.9.2 Formation of Two Bonds

5.10.9.2.1 Fragments C–N–N–C and S: Diazenes and hydrazines with a sulfur source

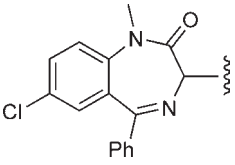
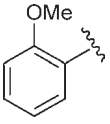
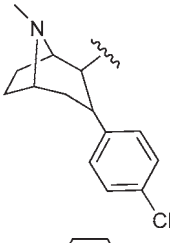
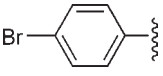
The reaction of 2,3-diazabuta-1,3-dienes with sources of active sulfur to prepare 1,3,4-thiadiazoles has been reviewed in CHEC(1984) <1984CHEC(6)545>, CHEC-II(1996) <1996CHEC-II(4)379> and Chapter 13.12 in the Houben–Weyl *Science of Synthesis* <2004HOU(13)349>.

Since diazenes are intermediates in the one-pot synthesis of 1,3,4-thiadiazoles from the reaction of aldehydes with hydrazine and sulfur (see Section 5.10.9.4.1), synthetic routes that lead to isolable diazenes offer an alternative way of preparing symmetrical and unsymmetrical 1,3,4-thiadiazoles. A variety of sulfur-releasing reagents can be used depending on the nature of the diazene. The most common sulfur sources include phosphorus pentasulfide, sodium thiolate, and hydrogen sulfide. Using this strategy, 2,5- diphenyl-1,3,4-thiadiazole **50a** was prepared from the reaction of diphenyl diazene with *O,O*-diethyl dithiophosphate <1995RJC140>.

1,3,4-Thiadiazoles **137** can also be prepared from the reaction of diformyl- or diacylhydrazines **136** with a sulfur source (Equation 47). The reaction involves thionation of the carbonyl groups followed by cyclization with loss of H_2S (**Table 5**). Phosphorus pentasulfide is commonly used for this cyclization but requires long reaction times and excess reagent, which often leads to low yields and side products such as 1,3,4-oxadiazole <1995JHC1235, 1998JMC1999, 2000EJO425>. The alternative use of Lawesson's reagent gives higher yields and cleaner reactions <1996BML833, 1996JME2753, 2003BMC1319>. This cyclization can also be carried out under microwave and solvent-free conditions to afford 1,3,4-thiadiazoles in high yields and with short reaction times <2001JOC7925>.

136 **137** (47)

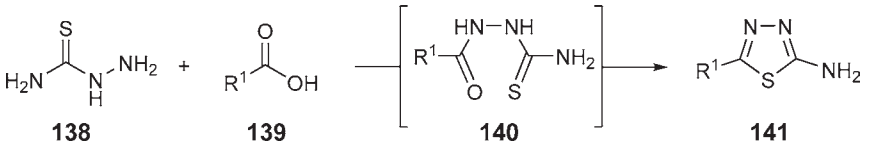
Table 5 Preparation of 1,3,4-thiadiazoles from diformyl- and diacylhydrazines and a sulfur source

R^1	R^2	*Conditions*	*Yield* **137** (%)	*Reference*
	Me	P_2S_5, 150–160 °C, 2 h	40	2001AP263
	Ph	P_2S_5, xylene, 140 °C, 4 h	65	1998JMAC1999
	Ph	Lawesson's reagent, PhMe, reflux, 4 h	58	1996JME2753
	*n*-$C_{13}H_{27}$	Lawesson's reagent, MW (1000 W), 13 min	91	2001JOC7925

5.10.9.2.2 Fragments S–C–N–N and C: Thiohydrazide derivatives with a carbon source

5.10.9.2.2(i) From carboxylic acid derivatives

The reaction of thiohydrazides with carbon source reagents in the presence of dehydrating agents provides a useful route to 1,3,4-thiadiazoles. The reaction proceeds via the monothiodiacylhydrazines **140** (**Scheme 13** and **Table 6**). Carboxylic acids and their derivatives are commonly used carbon sources, while the thiohydrazide derivatives include molecules with heteroatoms adjacent to the thiohydrazide unit, such as thiosemicarbazides. Common dehydrating agents are phosphorus oxychloride <2004BML5967, 2005OBC222>, sulfuric acid <2003ARK297, 2004IJB180>, and polyphosphoric acid <2001CHE1102>.



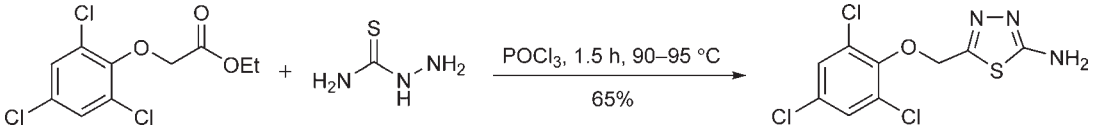
Scheme 13

Table 6 Preparation of 1,3,4-thiadiazoles from thiohydrazide **138** and carboxylic acids

R^1	*Yield* **141** *(%)*	*Conditions*	*Reference*
Ph	94	$POCl_3$, 1 h, 70 °C	2004BML5967
$H_2NSO_2CF_2^-$	33	$POCl_3$, 3 h, 70 °C	2005OBC222
Pr^i	70	H_2SO_4, 7 h, 80–90 °C	2003ARK297
$4\text{-}ClC_6H_4SO_2CH_2CH_2^-$	89	PPA, 3 h, 100–110 °C	2001CHE1102
Benzofur-2-yl	95	$POCl_3$ (1 equiv), 6 min, MW (490 W)	2003SC2891
Me	89	Al_2O_3, MW (2450 MHz)	2000SC3031

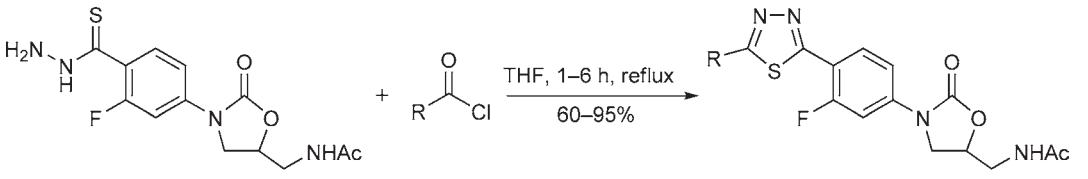
The reaction of benzo-2-furancarboxylic acid with thiosemicarbazide under microwave conditions enables the use of an equivalent amount of phosphorus oxychloride and a short reaction time <2003SC2891>. Moreover, solvent-free conditions are achieved when acidic alumina is used as dehydrating agent under microwave heating in the reaction of alkyl carboxylic acids with thiosemicarbazide <2000SC3031>.

Acid esters and acid chlorides react with thiosemicarbazide to afford monothiodiacylhydrazine intermediates which can be isolated and cyclized by concentrated sulfuric acid to 1,3,4-thiadiazoles (see Section 5.10.9.1.1) <1995JHC1235, 2000IJB464, 2000JIC400, 2002EJM873, 2002IJB2647, 2003AF301, 2004PS2059, 2004JIC342, 2004BMC1257, 2004IJB180>. Treatment of the acid esters with thiosemicarbazide in the presence of phosphorus oxychloride affords the 1,3,4-thiadiazoles in one step (e.g., Equation 48) <2004JIC783>.



(48)

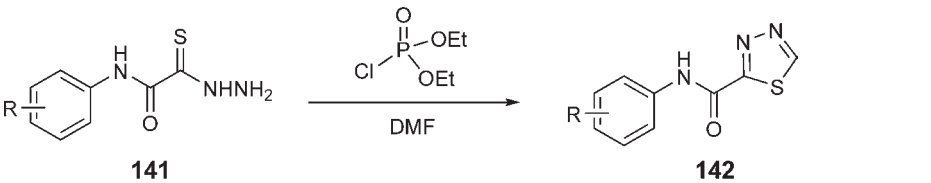
Acid chlorides react with thiohydrazide derivatives in polar solvents to give the corresponding thiadiazoles in a one-pot reaction (e.g., Equation 49) <2003BML4193, 2003RJO1133, 2000JCM544>.



(49)

R = H, OH, Me, Et, CH_2F, $MeOCH_2$, $AcOCH_2$, EtO_2C, $MeCO(CH_2)_2$, $NCCH_2$, $MeSCH_2$

A charge-transfer complex of diethyl chlorophosphate with DMF as the one-carbon source effects the cyclization of thiohydrazides into thiadiazoles **142** (Equation 50) <2004S17>.



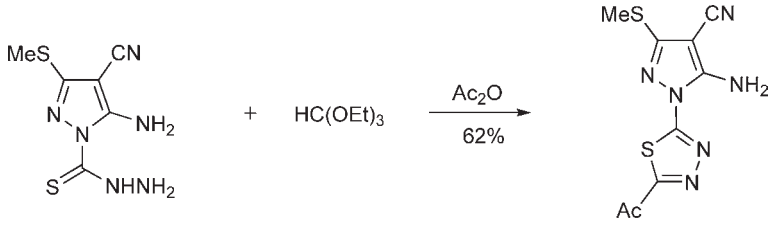
(50)

141 **142**

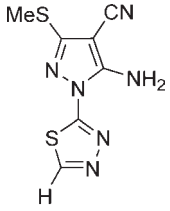
R = H, 4-Cl, 4-Br, 4-F, 4-MeO, 2,3-$(Me)_2$

5.10.9.2.2(ii) From orthoesters, trihalomethyls, imines, isothiocyanates, and nitriles

Alkyl and aryl thiohydrazide derivatives react with orthoesters and trihalomethyls to afford 1,3,4-thiadiazoles. The reactions proceed via a thiosemicarbazone intermediate which cyclizes to eliminate either alcohol or hydrogen chloride. Treatment of the *N*-thiohydrazide pyrazole **143** with triethyl orthoformate in acetic acid at reflux gave the 5-acetamido-1,3,4-thiadiazol-2-ylpyrazole **144** (Equation 51), and in the absence of acetic acid the 5-amino-1,3,4-thiadiazol-2-ylpyrazole **145** in 76% yield <2000JCM544>.



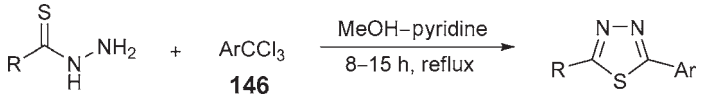
143 **144**



145

(51)

The reaction of the trichloromethylarenes **146** with thiosemicarbazide **138** in a boiling methanol–pyridine mixture afforded the 2-amino-5-aryl-1,3,4-thiadiazoles, while under similar conditions trichloromethylarenes **146** were converted to the diaryl-1,3,4-thiadiazoles with thiobenzhydrazide **147** (Equation 52, **Table 7**) <1996RCB1185>.



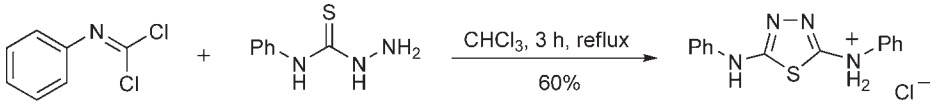
146

(52)

Table 7 Reaction of thiosemicarbazides with trichloromethylarenes

R	*Ar*	*Yields* (%)	*Reference*
Ph **147**	Ph	65	1996RCB1185
Ph	2,4-$Me_2C_6H_3$	50	1996RCB1185
NH_2 **138**	Ph	60	1996RCB1185
NH_2	2,4-$Me_2C_6H_3$	30	1996RCB1185

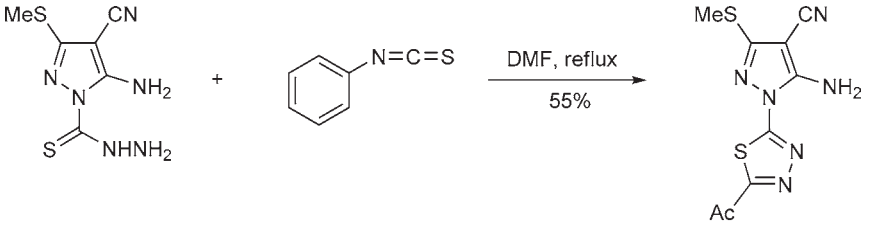
The reaction of imines with thiohydrazides gives 1,3,4-thiadiazole via a thioacylimidohydrazine intermediate. The imidoyl chloride **148** when treated with the *N*-phenyl thiosemicarbazide **149** gave the 1,3,4-thiadiazole hydrochloride **150** (Equation 53) <2002MI1241>.



148 **149** **150**

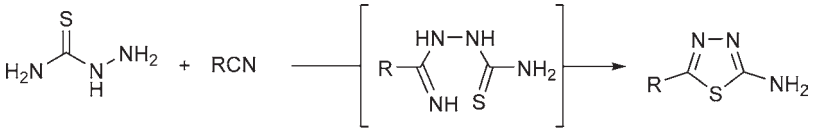
(53)

Thiohydrazides react with isothiocyanates to afford 1,3,4-thiadiazoles. The reaction proceeds via a dithioacylhydrazine intermediate which under the reaction conditions cyclizes with loss of H_2S. When the *N*-thiohydrazide pyrazole **143** is refluxed in DMF in the presence of phenyl isothiocyanate the 5-phenylamino-1,3,4-thiadiazol-2-yl pyrazole **144** is formed (Equation 54) <2000JCM544>.



143 **144** (54)

Alkyl and aryl nitriles **151** react with thiosemicarbazide **138** under acidic conditions to give 1,3,4-thiadiazoles (**Scheme 14** and **Table 8**) <1995BML1995, 1996IJB273, 1997IJB394>. The acidic conditions promote the elimination of ammonia from the intermediate iminothioacylhydrazine **152**.



138 **151** **152**

Scheme 14

Table 8 Preparation of 1,3,4-thiadiazoles from thiohydrazide and nitrile derivatives

R	*Yields (%)*	*Reference*
Ph	98	1995RCB1955
4-$MeOC_6H_4$	92	1995RCB1955
3-$O_2NC_6H_4$	88	1995RCB1955
4-bromo-*N*-methyl-5-nitroimidazol-2-yl	85	2000JHC119

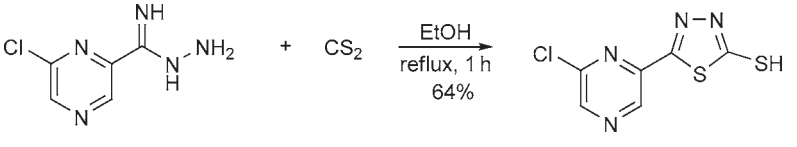
5.10.9.2.3 Fragments N–N–C and S–C: Hydrazides, amidrazones and diazo compounds with thiocarbonyl derivatives

5.10.9.2.3(i) From hydrazides

Hydrazides react with thiocarbonyl compounds to give directly 1,3,4-thiadiazoles via monothiodiacylhydrazine intermediates. The monothiodiacylhydrazines, however, are often isolated and cyclized to thiadiazoles under acidic conditions (see Section 5.10.9.1.1).

5.10.9.2.3(ii) From amidrazones

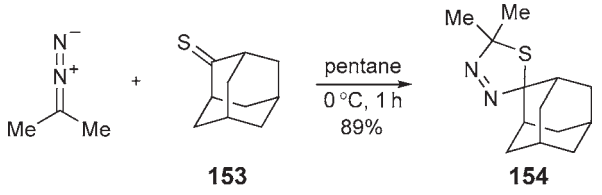
Amidrazones react with carbon disulfide or isothiocyanates to give *N′*-imidoylthiohydrazide intermediates that can be isolated and cyclized to afford 1,3,4-thiadiazoles (see Section 5.10.9.1.1). In some cases, the *N′*-imidoylthiohydrazides are not isolated prior to cyclization and 1,3,4-thiadiazol-2-thiols or 2-thiones are formed directly (e.g., Equation 55) <2004CHE1185>.



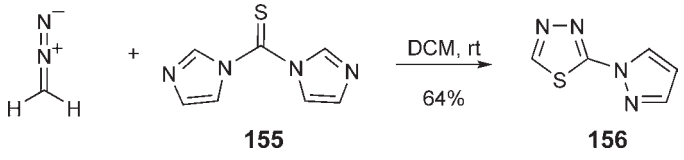
(55)

5.10.9.2.3(iii) From diazo compounds

Diazo compounds react with thiocarbonyl derivatives via a [3+2] dipolar cycloaddition to afford 2,5-dihydro-1,3,4-thiadiazoles <2005EJO1519, 2003S2259, 2001HCA1805, 1998HCA285>. When adamantanethione **153** was treated dropwise with 2-diazopropane in pentane at 0 °C, the spiro 2,5-dihydro-1,3,4-thiadiazole adamantine **154** was formed in 89% yield (Equation 56) <2005EJO1519>. When suitable leaving groups are present, the 2,5-dihydro-1,3,4-thiadiazole can aromatize under the reaction conditions. The reaction of 1,1′-thiocarbonyldiimidazole **155** with diazomethane gave the 1,3,4-thiadiazole **156** in 64% yield (Equation 57) <1998HCA66>.



(56)



(57)

5.10.9.2.4 Fragments C–S–C and N–N: Hydrazines with thiocarbonyl derivatives

Hydrazines react with thiocarbonyl compounds, such as dithioesters, to afford directly symmetrical 1,3,4-thiadiazoles via a dithioacylhydrazine intermediate, which can be isolated and converted to the thiadiazole upon treatment with an electrophilic reagent or under thermal conditions (see Section 5.10.9.1.1). Examples of the direct formation of thiadiazoles from hydrazines and thiocarbonyls can be found in CHEC-II(1996) <1996CHEC-II(4)379>.

5.10.9.3 Formation of Three Bonds

5.10.9.3.1 Fragments N–N–C, S, and C: Methylpyridines and quinolines with aroylhydrazines and sulfur

Methylpyridines and methylquinolines react with aroylhydrazines in the presence of sulfur to afford 5-aryl-1,3,4-thiadiazoles in low yields <1984JHC181>. The method, which requires high temperatures and long reaction times, gives a mixture of the desired product, 1,3,4-oxadiazoles and symmetrical diaryl-1,3,4-thiadiazoles.

5.10.9.4 Formation of Four Bonds

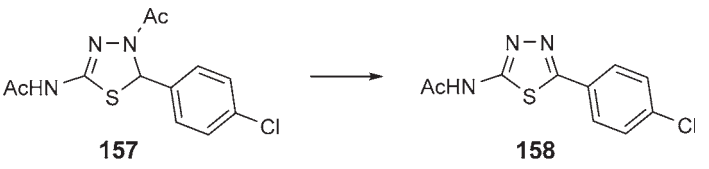
5.10.9.4.1 Fragments N–N, S, and two C fragments: Aldehydes with hydrazine and sulfur

Aldehydes react with hydrazine hydrate and sulfur in a high yielding one-pot synthesis of 2,5-dialkyl- and 2,5-diaryl-1,3,4-thiadiazoles via a diazene intermediate (see Section 5.10.9.2.1) <1980LA1216, 1983JHC1399>. Although this synthetic procedure is rare, examples can be found in CHEC-II(1996) <1996CHEC-II(4)379>.

5.10.9.5 Synthesis of Thiadiazoles by Oxidation of Fully or Partially Reduced Derivatives

5.10.9.5.1 Aromatization

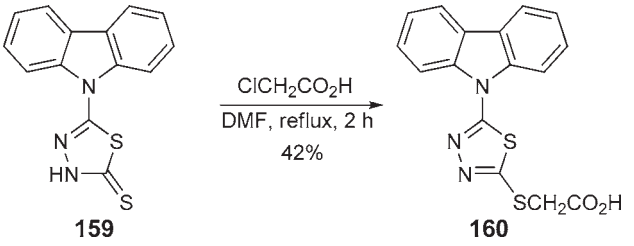
Partially or fully reduced thiadiazoles can be oxidized to yield 1,3,4-thiadiazoles. The 2,5-disubstituted 3-acyl-1,3,4-thiadiazole **157** can be deacylated by numerous methods <2004H(63)2243>. The oxidative deacylation of compound **157** to thiadiazole **158** can be achieved using oxidants such as $KMnO_4$, cerium(IV) ammonium nitrate (CAN), and (diacetoxy)iodobenzene (Equation 58). Better yields and cleaner products are obtained using CAN as oxidant.



(58)

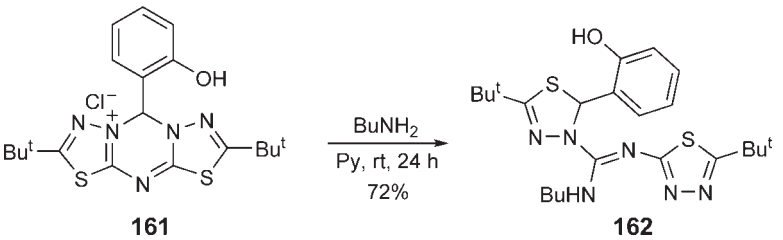
Conditions	*Yield (%)*
$KMnO_4$, $AcOH/H_2O$, 20 °C, 1.5–3 h	70
CAN, $MeCN/H_2O$, 23 °C, 0.3–0.75 h	94.5
$PhI(OAc)_2$, MeOH, 23 °C, 2–36 h	93

5-(9*H*-Carbazol-9-yl)-1,3,4-thiadiazole-2(3*H*)-thione **159** was S-alkylated with monochloroacetic acid to give the 1,3,4-thiadiazole **160** (Equation 59) <2006PS1737>.



(59)

S-Alkylation of 5-anilino-(*p*-toluidino or -morpholino)-1,3,4-thiadiazoline-2-thiones can be achieved with other alkylating reagents such as allyl bromide, benzyl chloride, and phenoxymethyloxirane in the presence of potassium hydroxide in a mixture of alcohol, acetonitrile, and DMF at 78–80 °C or in DMF at 150–153 °C <2003CHE228>. Another synthesis of 1,3,4-thiadiazoles through aromatization is the cleavage of fused-ring compounds. The reaction of the salt **161** with a primary amine in pyridine at room temperature for 24 h results in the ring cleavage of the fused system and the formation of guanidine **162** (Equation 60) <2003EJO1389>.



(60)

5.10.10 Synthesis of Thiadiazoles by Transformation of Other Heterocycles

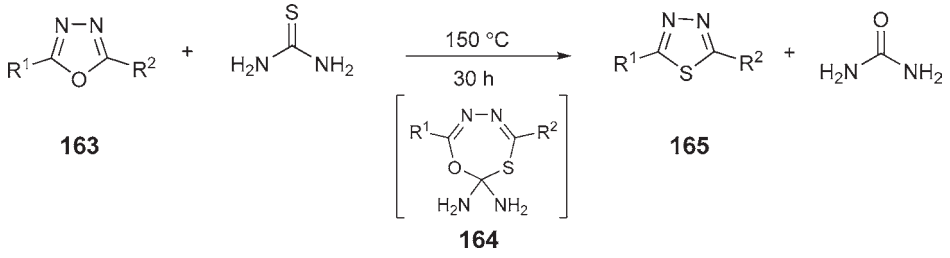
The direct ring transformations of other heterocycles into 1,3,4-thiadiazoles that appeared in the literature prior to 1995 are reviewed in CHEC(1984) <1984CHEC(6)545> and CHEC-II(1996) <1996CHEC-II(4)379> and are briefly summarized here. 1,3,4-Oxadiazoles are converted into 1,3,4-thiadiazoles when treated with phosphorus pentasulfide <1958JA5201> or sodium sulfide <1984UKZ519>. 5-Substituted tetrazoles when treated with thiobenzoyl chloride, phenyl isothiocyanate <1961CB1555>, or benzonitrilium *N*-(4-nitrophenyl)imide <1993JCM306> give 2-substituted 5-phenyl-1,3,4-thiadiazoles. Mesoionic 1,3,4-oxadiazoles are converted into 1,3,4-thiadiazoles when heated in ethanol or ethanethiol <1968CC499>, while 1,4,2-dithiazolium salts upon treatment with amines give 1,3,4-thiadiazoles <1988BCJ4043>. Other transformations include the ring contraction of the six-membered 1,3,4-thiadiazin-6-ones <1981CC1003>. Ring transformations reported after 1995 are reported below.

5.10.10.1 From 1,3,4-Oxadiazoles

2,5-Diaryl-1,3,4-oxadiazoles **163** react with thiourea to give 2,5-diaryl-1,3,4-thiadiazoles **165** (**Table 9**) <1998SC4611>. The proposed mechanism proceeds via ring contraction of an intermediate oxathiadiazepine **164** to give the thiadiazole **165** (**Scheme 15**).

Table 9 Preparation of 2,5-diaryl-1,3,4-thiadiazoles from 2,5-diaryl-1,3,4-oxadiazoles using thiourea

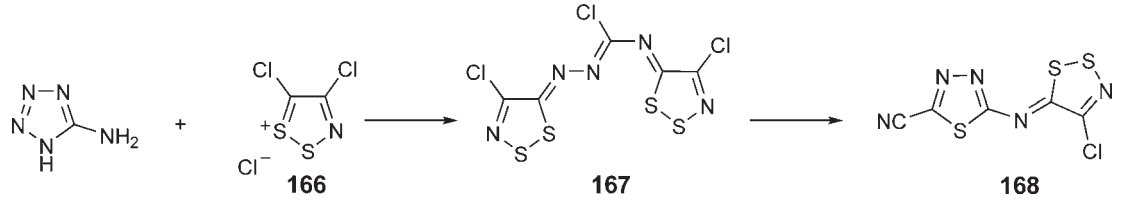
R^1	R^2	*Yields* **165** (%)	*Reference*
Ph	Ph	65	1998SC4611
4-$MeOC_6H_4$	Ph	60	1998SC4611
3,4,5-$(MeO)_3C_6H_2$	Ph	69	1998SC4611
3,4,5-$(MeO)_3C_6H_2$	4-$O_2NC_6H_4$	55	1998SC4611



Scheme 15

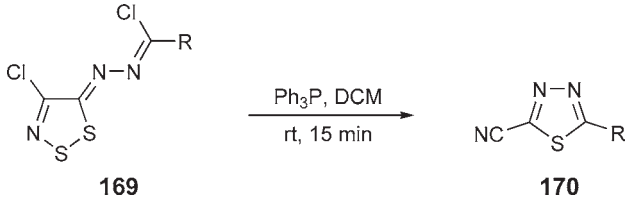
5.10.10.2 From 1,2,3-Dithiazoles

5-Aminotetrazole reacts with 4,5-dichloro-1,2,3-dithiazolium chloride **166** to afford the bis(imino-1,2,3-dithiazole) **167** (20%) which in warm DMSO or DMF converts into the 1,2,3-dithiazolimine **168** (25%) (**Scheme 16**) <2002J(P1)1535>.



Scheme 16

The scope of this reaction (**Scheme 16**) has been extended to other 5-substituted tetrazoles, readily prepared by the reaction of nitriles with aluminium azide <2002J(P1)1543>. Using triphenylphosphine under mild conditions, the resulting dithiazolimines **169** are rapidly converted into cyanothiadiazoles **170** in high yield (Equation 61 and **Table 10**).

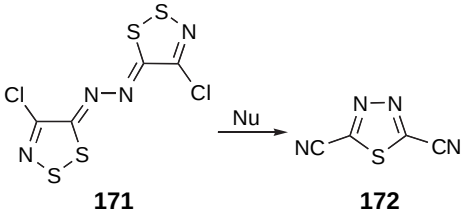


(61)

Table 10 Preparation of 5-cyano-1,3,4-thiadiazoles from dithiazolimines using Ph_3P

R	*Yield* **170** (%)	*Reference*
Ph	82	2002J(P1)1543
4-O_2N-C_6H_4	92	2002J(P1)1543
4-MeO-C_6H_4	99	2002J(P1)1543
2-Thienyl	76	2002J(P1)1543
PhO	75	2002J(P1)1543
MeS	73	2002J(P1)1543
$ClCH_2CH_2$	90	2002J(P1)1543

The thiadiazolecarbonitriles **170** can be further sequentially treated with azide, dithiazolium chloride **166**, and triphenylphosphine to afford unsymmetrical bi- and ter-1,3,4-thiadiazolyl oligomers. Hydrazine reacts with dithiazolium chloride **166** to give the bisdithiazole **171** <2001IC2709> which reacts with $BnEt_3NI$ to give 1,3,4-thiadiazole-2,5-dicarbonitrile **172** (Equation 62) <2006ARK207>. Thiadiazole **171**, prepared previously via a laborious multistep synthesis <1978DEP2253863>, suffers hydration during chromatographic isolation to afford the carboxamide **173**, the formation of which can be avoided when polymer-bound triphenylphosphine is used as nucleophile (Equation 62).



171 **172** **173**

Nu	*Yield* %	%
$BnEt_3NI$	79	19
Ph_3P-Polymer bound	69	0

(62)

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

One of the oldest methods of synthesizing symmetrical and unsymmetrical 1,3,4-thiadiazoles is the treatment of 2,3-diazabuta-1,3-dienes with a variety of sulfur sources (see Section 5.10.9.2.1). The inherent limitation of this one-pot approach has been the availability of diazabutadienes but this has now largely been overcome with the development of several methods of synthesizing the diazabutadienes. The yields in this reaction vary from poor to excellent. A widely used approach to 1,3,4-thiadiazoles requires the treatment of thiohydrazide derivatives with an activated carbon-containing reagent (see Section 5.10.9.2.2). A broad range of thiohydrazides and one-carbon synthons have been used for this transformation, but the commonest substrates are thiosemicarbazides and carboxylic acids. The intermediates formed can be cyclized under the reaction conditions or isolated and cyclized in further reactions. These methods give good-to-excellent yields with one exception: the reaction of thiohydrazide derivatives with isothiocyanates proceeds in variable yields that rarely exceed 80%. The cyclization of the isolated intermediates from the reactions of thiohydrazide derivatives with sources of carbon is the most popular method for the synthesis of 1,3,4-thiadiazoles (see Section 5.10.9.1.1). From these synthetic routes the cyclization of monothiodiacylhydrazine derivatives is the most widely used one. A new development in this acid-catalyzed cyclization of monothiodiacylhydrazines is the use of microwave irradiation, which renders the reactions very rapid while proceeding in higher yields than with conventional heating. Symmetrical dialkyl- and diaryl-1,3,4-thiadiazoles are best synthesized in good-to-excellent yields in one-pot procedures using aldehydes, hydrazine hydrate, and sulfur when heated in an autoclave (see Section 5.10.9.3.1). While the workup can be difficult, due to the presence of sulfur, the method is attractive because of the low cost and simplicity.

5.10.12 Important Compounds and Applications

1,3,4-Thiadiazoles are important compounds in medicine, agriculture, and in many fields of technology. A large number of thiadiazoles have been patented in the medical field for the treatment of a wide variety of diseases and some of them have become commercial products. Thiadiazoles have been patented as useful antagonists of the

platelet glycoprotein IIb/IIIa fibrinogen receptor complex <1997USP5668159>, as inhibitors of 5-lipoxygenase and/or cyclooxygenase providing treatment of conditions advantageously affected by such inhibition including inflammation, arthritis, pain, fever, and the like <1990EPP0371438>, as antiviral mendicants against herpes virus cytomegalovirus (CMV) <1999WO9947507>, as antagonists of alpha v beta 3 and related integrin receptors <2000WO6153628>, as medicants for inflammatory disease such as, hypersensitivity reactions, asthma, rheumatoid arthritis, bacterial meningitis, aspiration lung injury, inflammatory bowel disorder and related complications <1999WO9920618>, and for many other medical applications. A large number of thiadiazoles have also been patented in the agriculture field as herbicides, insecticides, fungicides, and bactericides. 2-Alkylthio-1,3,4-thiadiazoles have been patented as crop protection agents <1991EPP0440959> and acylated 5-amino-thiadiazoles as pesticides and fungicides <1997WO9726251>. Some of the technological uses of the 1,3,4-thiadiazoles involve dyes or metal complexation agents <2004JMP705, 2001AXC1032, 2001OM1895, 2002POL403>, corrosion and oxidation inhibitors <1999MI1867> and optically active liquid crystals and optoelectronic materials <1995MI395, 1998CEJ2211>.

5.10.13 Further Developments

N′-Acylbenzohydrazides can be thionated using a fluorous analog of the Lawesson reagent to afford 1,3,4-thiadiazoles in high yield by a simple filtration (fluorous solid-phase extraction) <2006OL1625>. 2,5-Ditolyl-1,3,4-thiadiazole was synthesized in 93% yield by treating the *N*′-acyltolylhydrazide with the fluorous thionated reagent in THF at 55 °C for 6 h. 2,5-Disubstituted 1,3,4-thiadiazoles have been synthesized in high yield and high purity using an efficient soluble poly(ethyleneglycol) (PEG) polymer support <2006HAC664>. PEG-bound di(aryloxyacetyl)thiosemicarbazides were refluxed in glacial acetic acid to give the PEG-bound 1,3,4-thiadiazoles which upon purification by precipitation, were cleaved from the support using methoxide in methanol to afford the desired compounds in 76–89% overall yield. Other basic reagents such as sodium hydroxide, ammonia and potassium carbonate were also tested for the cleavage reaction but low yields and some separating problems were encountered. 2,5-Disubstituted 1,3,4-thiadiazoles were also synthesized in a rapid and efficient microwave promoted pathway affording clean and high yielding reactions <2006IJB2754>.

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Biographical Sketch

Panayiotis Andreas Koutentis, Ph.D. is assistant professor at the Department of Chemistry, University of Cyprus, Nicosia. He was born in Bristol (1969) in the UK and obtained his bachelor (1992) and doctorate (1997) degrees at Imperial College London working under the supervision of the late Prof. Charles W. Rees. This was followed by a short stay with Prof. Roger Alder, University of Bristol (1997) and then postdoctoral work with Prof. Fred Wudl (1997–98) University of California, Los Angeles (UCLA) and with Prof. Robert Haddon (1999) at the University of Kentucky, Lexington. In 1999, Dr. Koutentis was appointed lecturer at the University of Cyprus where his primary research activities focus on the synthesis and reactivity of novel and unusual *S*,*N*-heterocyclic compounds and the design and synthesis of organic magnets based on radical and diradical poly-azaheterocyclic systems. Secondary themes under investigation include the design and synthesis of novel conjugated and nonconjugated polymers; the design and synthesis of non-natural alkaloids; and the search for Hbf regenerators based on HDAC inhibitors.

Christos Pantelis Constantinides is a Ph.D. student at the Department of Chemistry, The University of Cambridge, UK. He was born in Nicosia (1979) in Cyprus and obtained his Bachelor (2003) at the University of Cyprus, Nicosia. In 2005 Mr. Constantinides began his doctoral studies at the University of Cambridge working under the supervision of Dr. Jeremy Rawson and Dr. Stephen C. Moratti. His doctoral research focuses on the design, synthesis, and characterization of novel thiazyl radicals with magnetic and/or conducting properties.