

5.18

Oxatriazoles

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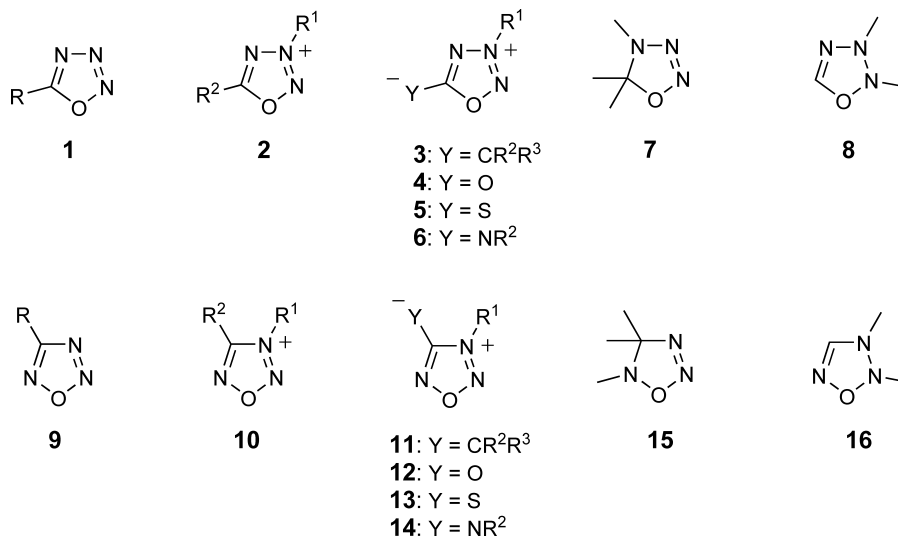
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5.18.1 Introduction

Although the synthesis of mesoionic <B-1997MI1, B-2000MI1, 1976AHC1, 1995PAC1307, 2002ARK224, 2002MOL791> oxatriazoles was described as early as 1896, 1,2,3,4-oxatriazole **1** and 1,2,3,5-oxatriazole **9** ring systems are not known <2000AHC157>. Various substituted derivatives and mesoionic analogues, however, are readily accessible. The purpose of this chapter is to bring the previous coverage of the subject in CHEC(1984) (<1984CHEC(4)579>, Chapter **4.28**) and CHEC-II(1996) (<1996CHEC-II(4)679>, Chapter **4.18**) up to date.

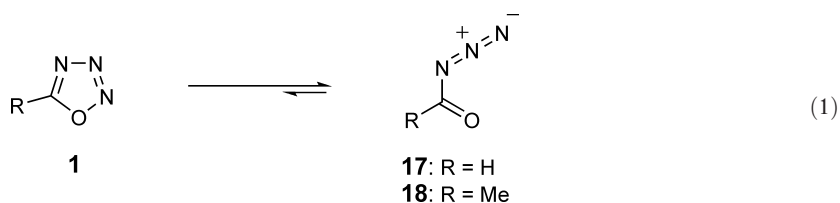
This chapter covers the literature from mid-1995 to mid-2007. Recent advances include the preparation of the first Δ^2 -1,2,3,4-oxatriazolines **7** by intramolecular [3+2] cycloaddition (Section 5.18.9), synthesis of mesoionic derivatives **4** using bromonitroformaldehyde *N*-arylhydrazones as the starting materials (Section 5.18.9), and detailed studies of the biologically active mesoionic oxatriazoles in the context of their nitric oxide donating capabilities (Section

5.18.12). Of the possible structures **1–16** shown, the known structures are represented by 1,2,3,4-oxatriazolium salts **2**, mesoionic derivatives **3–6**, and 1,2,3,5-oxatriazolines **15** and **16**. Derivatives of Δ^2 -1,2,3,4-oxadiazoline **7** have now been synthesized and are the first representatives of this particular ring system.



5.18.2 Theoretical Methods

Although 1,2,3,4-oxatriazole and its 5-methyl-substituted derivative are unknown compounds, the equilibrium between ring-closed **1** (R=H or Me) and ring-open forms **17** and **18** has been examined theoretically (Equation 1) <2000CPL276, 2005CRV3561>.



Like the cyclic forms **1** (R=H or Me), the ring-open isomers **17** and **18** also remain unknown. The calculated charge distributions of the ring-open and ring-closed isomers are compared in **Figure 1**. Molecular orbital calculations predict ΔE values of 20.48 (TZ**), ~ 30 (MP2), and 27 kcal mol⁻¹ (MP4-SDQ) for theoretical cyclization of formyl azide **17** (R=H) to 1,2,3,4-oxatriazole **1** (R=H). Similarly, the calculated ΔE values for conversion of acetyl azide **18** (R=Me) to 5-methyl-1,2,3,4-oxatriazole **1** (R=Me) are 19.08 (HF/6-31G) and 20.08 kcal mol⁻¹ (MP4-SDQ). With the theoretical cyclization of molecules **17** and **18** so highly endothermic, formation of isomer **1** (R=H or Me) is strongly disfavored.

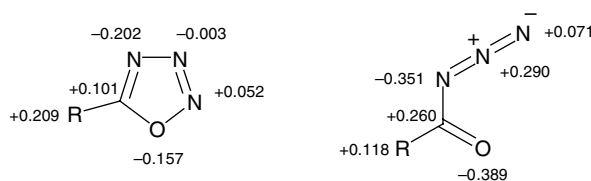


Figure 1 Charge distributions in ring-closed and ring-open isomers of **1** (R=H).

Averaged aromaticity indexes (AIs) for a series of oxazoles including 1,2,3,4-oxatriazole **1** (R=H) and 1,2,3,5-oxatriazole **9** (R=H) have been derived from calculated molecular geometries optimized at the self-consistent field (SCF)/6-31G* level <1998JOC2497>. The averaged AI values are: furan 27.4, isoxazole 32.8, 1,2,3-oxadiazole 25.6, 1,2,4-oxadiazole 25.9, 1,2,5-oxadiazole 35.0, 1,3,4-oxadiazole 10.4, 1,2,3,4-oxatriazole 16.9, 1,2,3,5-oxatriazole 29.7, and oxatetrazole 17.5 <2001T5715>. The results are consistent with other quantitative measures of aromaticity <2001CRV1421> and indicate that the oxazole family is, in general, more localized and exhibits less aromaticity compared with most other members of the azole series <1998JOC2497>.

5.18.3 Experimental Structural Methods

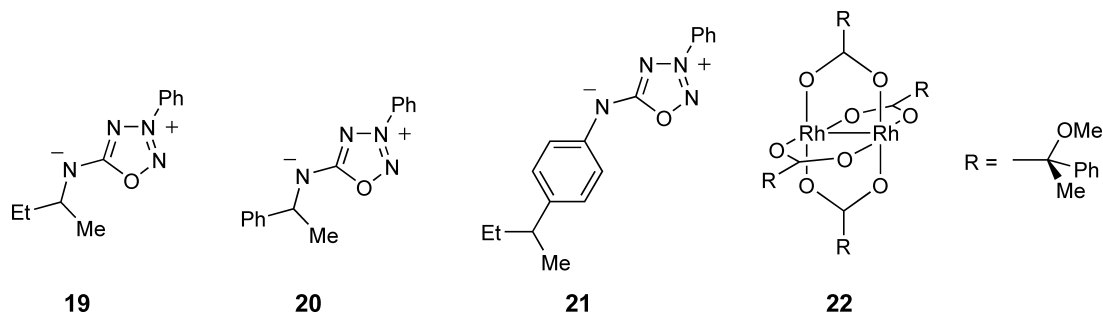
5.18.3.1 NMR Spectroscopy

Various mesoionic 1,2,3,4-oxatriazoles have been studied by multinuclear nuclear magnetic resonance (NMR). ^{14}N NMR spectra give information about the charge distribution where positively charged nitrogen atoms give rise to comparatively narrow line widths <1995CHE1027, 1998MI79, 1999AHC295>.

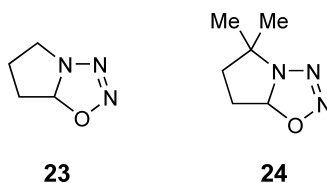
3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** ($\text{R}^1 = \text{Ar}$) have been prepared and studied by ^1H , ^{13}C , ^{14}N , and ^{17}O NMR. The chemical shifts for the exocyclic oxygen attached to C-5 lie in the range -215 to -220 ppm, whereas the ring oxygen shows broader signals within the region -360 to -370 ppm <1997CHE880, 1999CHE363>. In the ^{14}N spectra, the positively charged N-3 group appears as a sharp line near -80 ppm. The chemical shifts for the C-5 signals are listed in **Table 1** (Section 5.18.9). The ^{15}N - ^{15}N coupling constants in the ^{15}N labeled compound **4** ($\text{R}^1 = \text{Ph}$) have been measured: $^1J_{\text{N}(2)-\text{N}(3)} = 15.5$ and $^1J_{\text{N}(3)-\text{N}(4)} = 17.0$ Hz. These values compare well with those of nitrogen–nitrogen double bonds inferring some degree of positive charge delocalization within the ring <1996JST167>.

^{14}N , ^{15}N , and ^{17}O NMR studies of mesoionic 3-phenyl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** confirm that they exist in cyclic, mesoionic form and that protonation occurs at the exocyclic nitrogen atom <1995CHE1103, 2004JST23>. The free bases exist in solution as (*E*)- or (*Z*)-configured rotamers at the C–Y bond that depend on temperature and the nature and size of R^2 . Proton NMR spectra show one set of signals at 318 K and broad signals at 303 K. Pairs of signals are observed at 252 K corresponding to (*E*)- and (*Z*)-rotamers in near-equal proportions <2004JST23>. Slight shifts between the proton and carbon signals from ^1H and ^{13}C NMR analysis were observed for the free bases compared with their salts. The largest shift was observed for the C-5 atom in each case. The chemical shifts and line widths of the ring atoms and the nitrogen attached to C-5 in the free bases and their salts have been tabulated <2004JST23>. *Ab initio* calculations predict an energy difference of less than 1 kcal mol^{-1} between the (*E*)- and (*Z*)-isomers of compound **6** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$) <1997MI71>.

When mixed with equimolar amounts of the dirhodium complex **22**, the enantiomers of mesoionic 1,2,3,4-oxatriazoles **19–21** can be differentiated by proton NMR <2003MRC315>. The negatively charged exocyclic nitrogen atom provides the binding site to the rhodium complex <2003MRC921>.

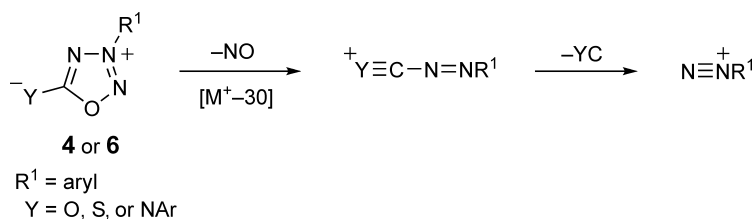


From ^{13}C NMR analysis, the chemical shift of the carbon at the respective ring junctions in Δ^2 -1,2,3,4-oxatriazolines **23** (100.4 ppm) and **24** (105.4 ppm) <2002HAC307> are considerably further upfield compared with the C-5 atoms in the mesoionic analogues **2** ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{OEt}$; 188.7 ppm), **4** ($\text{R}^1 = \text{Ph}$; 166.2 ppm), or **5** ($\text{R}^1 = \text{Ph}$; 193.4 ppm) <1996CHEC-II(4)679>.



5.18.3.2 Mass Spectrometry

No molecular ions appear in the electron ionization (EI) spectra of mesoionic 1,2,3,4-oxatriazoles **4** and **6** or their derivatives. Instead, $[M^+ - 30]$ peaks are observed due to loss of nitric oxide <1979J(P1)747, 1999CHE363>. The typical fragmentation pathway for such compounds and their analogues is summarized in **Scheme 1** <1984CHEC(4)579, 1996CHEC-II(4)679>. In their fast atom bombardment (FAB) spectra, intact molecular ion peaks are observed for the Δ^2 -1,2,3,4-oxatriazolines **23** 114 $[M+H]$ and **24** 142 $[M+H]$ <2002HAC307>.



Scheme 1

5.18.3.3 IR Spectroscopy

3-Aryl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** ($R^1 = \text{aryl}$) show one, sometimes two strong infrared (IR) absorption bands in the region $1770\text{--}1820\text{ cm}^{-1}$ due to the exocyclic C=O group. Values for a series of such analogues are listed in **Table 1** (Section 5.18.9) <1997CHE880, 1999CHE363>. Electron-withdrawing groups attached to the N-3 phenyl substituent shift the C=O absorption to a higher wave number whereas electron-releasing groups cause shifts to a shorter wave number.

5.18.3.4 UV Spectroscopy

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** ($R^1 = \text{phenyl}$) are colorless. The absorption wavelength in the ultraviolet (UV) is usually influenced by the substituents in the phenyl group. Values for a series of analogues are listed in **Table 1** (Section 5.18.9) <1997CHE880, 1999CHE363>. 3-Substituted anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides **5** are typically yellow <1984CHEC(4)579, 1996CHEC-II(4)679>. 3-Substituted anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** are yellow or deep red, whereas their salts are mostly colorless <2004JST23>.

5.18.3.5 Dipole Moment

Dipole moments for 1,2,3,4-oxatriazole **1** ($R = \text{H}$; 3.250 D) and 5-methyl-1,2,3,4-oxatriazole **1** ($R = \text{Me}$; 4.096 D) were estimated using molecular orbital calculations (TZ**) <2000CPL276>. The calculated dipole moment for compound **6** ($R^1 = \text{H}$, $R^2 = \text{H}$; 5.33 D) agreed well with the observed value 5.42 D <1997MI71>. Quadrupole moments, octopole moments, and polarizability of 1,2,3,4-oxatriazole **1** ($R = \text{H}$) have been determined by *ab initio* methods and simple models <1996JPC8752, 1999PCA10009>.

5.18.3.6 X-Ray Crystallography

No further crystal structures have been reported since the structures of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide **4** ($R^1 = \text{Ph}$) and 3-phenyl-anhydro-5-phenylamino-1,2,3,4-oxatriazolium hydroxide **6** ($R^1 = \text{Ph}$,

$R^2 = \text{Ph}$) were presented in the previous surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. However, X-ray crystal structures of closely related 3- and 5-substituted-5-anhydro-1,2,3,4-thiazolium thiolates have been reported <1999JST181> (see Chapter 5.19).

5.18.4 Thermodynamic Aspects

Mesoionic 1,2,3,4-oxatriazoles are crystalline, polar compounds with melting points in the range 100–150 °C <1996CHEC-II(4)679>. 3-Aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **6** ($R^2 = \text{Ar}$) are comparatively stable. When alkyl groups (CH_2R) replace the aryl substituent R^2 , such derivatives decompose within 24 h at room temperature but may be stored for much longer at dry ice temperature <2004JST23>. The new oxatriazoline compounds **23** and **24** (Sections 5.18.3.1 and 5.18.9) are isolated as colorless oils <2002HAC307>.

From a multinuclear NMR study of mesoionic 1,2,3,4-oxatriazole **6** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$), the barrier to (*E*)- and (*Z*)-interconversion around the C(5)–Y bond was estimated to be ΔG^\ddagger 68 kJ mol⁻¹ at 298 K. The value is comparable to that measured for dimethylformamide 74 kJ mol⁻¹ and simple imines of type $(\text{RX})_2\text{C}=\text{NR}$, where X is oxygen or sulfur <2004JST23>.

The dissociation energy of the C(4)–H bond in unknown 1,2,3,5-oxatriazole **9** ($R = \text{H}$) has been calculated using various methods: 128.7 (CBS-Q), 128.7 (G3), 125.8 (G3B3), and 121.7 kcal mol⁻¹ (B3LYP) <2003JPO883>. The N(3)–C(4)–N(5) dihedral angle (112.1°) was also estimated <2003JPO883>.

5.18.5 Reactivity of Fully Conjugated Rings

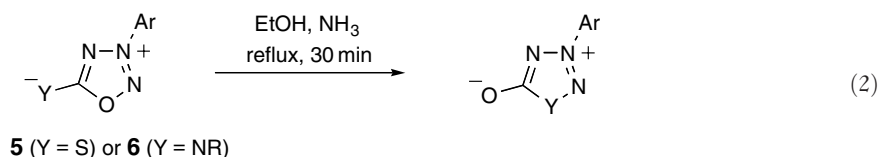
5.18.5.1 Thermal Reactions and 1,3-Dipolar Cycloadditions

3-Substituted anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **6** are relatively stable under neutral conditions in the absence of salt. The stability depends on the nature of the R^2 substituent attached to the exocyclic nitrogen and decreases from very stable to moderately stable along the series $\text{RSO}_2 > \text{RNHCO} > \text{RCO} > \text{R}$ <2002MI167>.

Unlike the mesoionic 1,2,3-oxadiazoles (see Chapter 5.03), mesoionic 1,2,3,4-oxatriazoles **5** and **6** do not undergo 1,3-dipolar cycloaddition reactions. Azides formed by loss of carbon dioxide from anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4**, on prolonged heating with lithium chloride, may be trapped by cycloaddition to an alkyne <1996CHEC-II(4)679>.

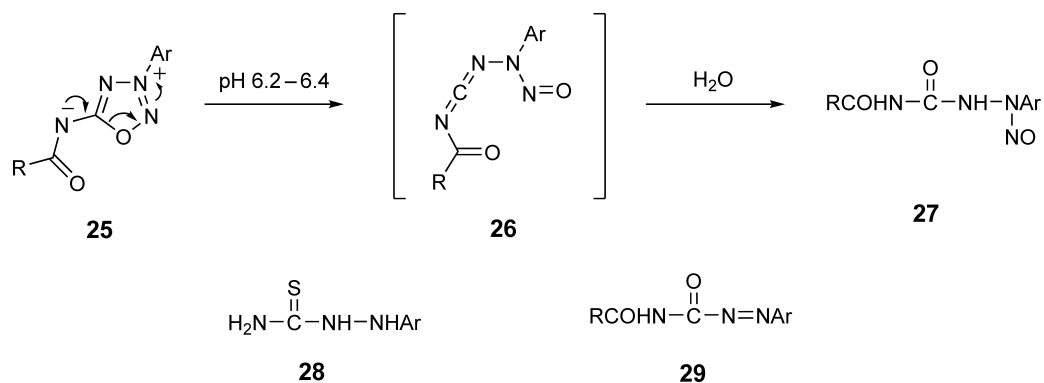
5.18.5.2 Rearrangements

Under basic conditions, mesoionic 1,2,3,4-oxatriazoles **5** and **6** rearrange in alcohol solutions to the respective anhydro-5-hydroxy-thiazolium hydroxides and anhydro-5-hydroxy-tetrazolium hydroxides (Equation 2) <1979J(P1)732, 1996CHEC-II(4)679>. That rearrangement of 1,2,3,4-oxatriazole **5** ($\text{Ar} = \text{Ph}$) to 3-phenyl-5-anhydro-1,2,3,4-thiazolium hydroxide can be induced electrochemically, has been reported for the first time (Section 5.18.5.5) <1997MRC124>.



5.18.5.3 Hydrolysis

The various fates met by mesoionic 1,2,3,4-oxatriazoles when subjected to hydrolysis are detailed in the previous surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. The hydrochloride salts of 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **25** are known to be stable for several years on storage <2002CRV1091>. In solution, however, ring opening and release of nitric oxide (NO) occurs close to the $\text{p}K_a$ values of the salts in the pH range 6.2–6.8. The proposed mechanism of NO release begins as shown in **Scheme 2**.



Scheme 2

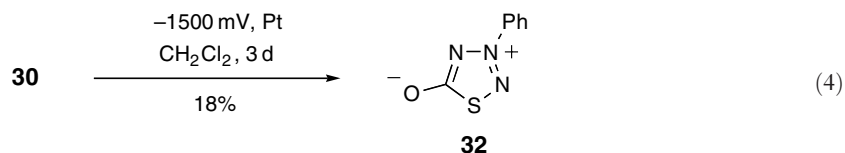
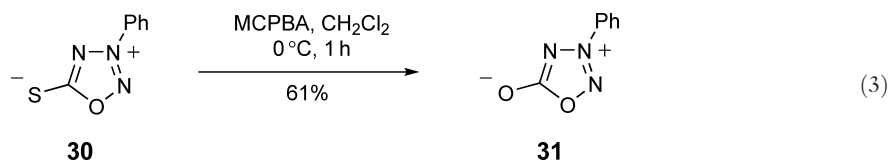
Ring opening produces the intermediate **26** to which water then adds forming the urea **27**. The fate of compound **27** *in vitro* differs from that *in vivo*. The urea **27** loses NO to give the arylthiosemicarbazide **28** *in vitro*, whereas metabolite **29** is the final product of the *in vivo* pathway <2002CRV1091>. The rate of NO release from compounds **25**, *in vitro*, depends strongly on concentration, temperature, pH, and the chemical nature of the R substituent attached to the exocyclic nitrogen <2002MI167>. The presence of thiols may contribute to the increased rate of NO release *in vivo* <1998MI97>.

5.18.5.4 Photolysis

Photolysis of 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxide **4** ($R^1 = \text{Ph}$) gives carbon dioxide and phenyl azide. The phenyl group has been shown to migrate from the central to the terminal nitrogen position during the course of the reaction as described in the last two surveys <1984CHEC(4)579, 1996CHEC-II(4)679>. Since then, no further reports on this topic have appeared.

5.18.5.5 Oxidation and Reduction

The synthesis of mesoionic 1,2,3,4-oxatriazole **31** from compound **30** using *m*-chloroperbenzoic acid (MCPBA) has been reported for the first time (Equation 3) <1997MRC124>. Mesoionic 1,2,3,4-oxatriazole **30** is converted electrochemically to isomer **32**, albeit on a small scale and in modest yield (Equation 4) <1997MRC124>.

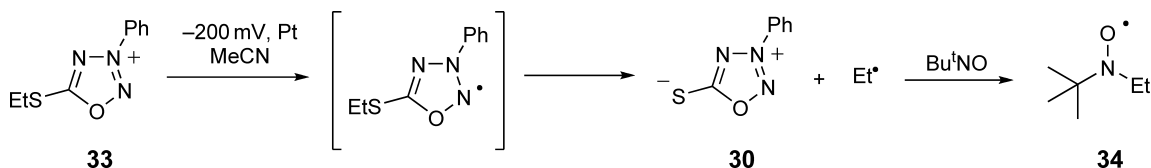


5.18.6 Reactivity of Nonconjugated Rings

New Δ^2 -1,2,3,4-oxatriazolines **23** and **24** (Sections 5.18.3.1 and 5.18.9) have been isolated as stable materials in the form of oils and characterized by spectroscopic methods. No data on their reactivities have been reported. Δ^4 -1,2,3,5-Oxatriazolines **16** are thermally unstable, more so than their Δ^2 -1,2,3,5-oxatriazoline **15** analogues <1996CHEC-II(4)679>.

5.18.7 Reactivity of Substituents Attached to Ring Carbon Atoms

3-Phenyl-anhydro-5-thio-1,2,3,4-oxatriazolium hydroxide **30** was alkylated using triethyloxonium tetrafluoroborate to give product **33**, whereas analogue **31** failed to react under similar conditions <1997MRC124>. De-ethylation of derivative **33** to form compound **30** has been performed electrochemically (Scheme 3) <1997MRC124>.



Scheme 3

The ethyl radical formed during the dealkylation process was trapped using 2-methyl-2-nitrosopropane to form *tert*-butylethyl nitroxide **34**, where the coupling constants and *g*-factors of the trapped species measured by electron spin resonance (ESR) analysis matched the literature values for *tert*-butylethyl nitroxide **34** exactly.

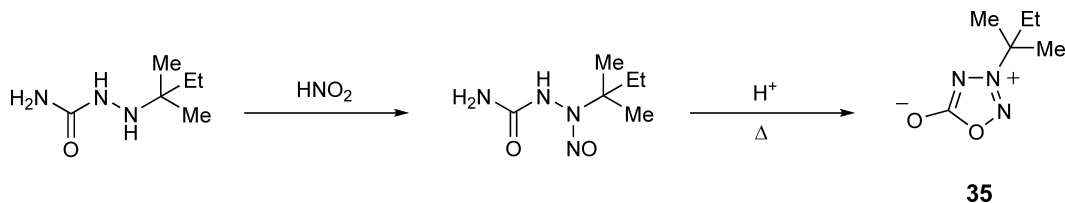
The C–H bond dissociation energy of the methyl group in unknown 4-methyl-1,2,3,5-oxatriazole **9** (R = Me) was estimated at 95.6 (G3B3) or 90.3 kcal mol⁻¹ (B3LYP). The G3B3 method was found to be superior giving the best correlation between calculated values and the experimental ones for known compounds <2005JPO353>. Natural population analysis revealed a charge of 0.076 on the methyl group before homolysis and 0.138 for the CH₂ radical after homolysis together with a spin value of 0.698 <2005JPO353>.

5.18.8 Reactivity of Substituents Attached to Ring Heteroatoms

There are three possible sites, N-2, N-4 or Y, for protonation in mesoionic 1,2,3,4-oxatriazole **4** to **6**. In compound **6**, protonation occurs at the exocyclic nitrogen instead, as evidenced by NMR analysis (Section 5.18.3.1) <2004JST23>. No further reports on the reactivity of substituents attached to ring heteroatoms have appeared since the last survey <1996CHEC-II(4)679>.

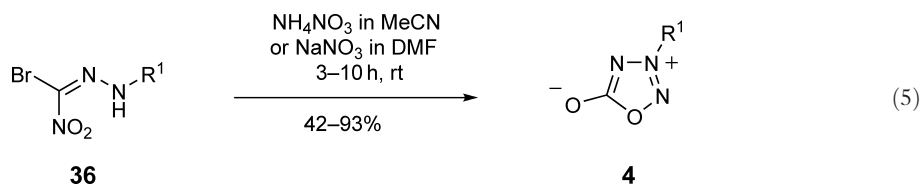
5.18.9 Ring Synthesis from Acyclic Compounds Classified by Number of Ring Atoms Contributed by Each Component

Methods of synthesis of the known 1,2,3,4-oxatriazoles <1979J(P1)732, 1979J(P1)736> and the very rare 1,2,3,5-oxatriazoles have recently been compiled <2003HOU823>. In this section, the examples that have appeared since the last survey of the area <1996CHEC-II(4)679> are presented. 3-Alkyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides such as compound **35** are formed from semicarbazides after nitrosation (Scheme 4) <1999FA316>.



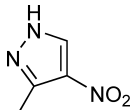
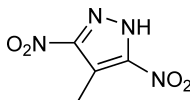
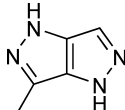
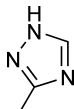
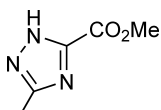
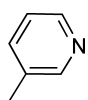
Scheme 4

Similarly, cyclization of bromonitroformaldehyde *N*-hydrazones **36** allows ready access to anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides **4** (R¹ = aryl or hetaryl). For the first time, analogues with heterocyclic substituents attached at N-3 have been prepared by this method (Equation 5) <1997CHE880, 1999CHE363>.

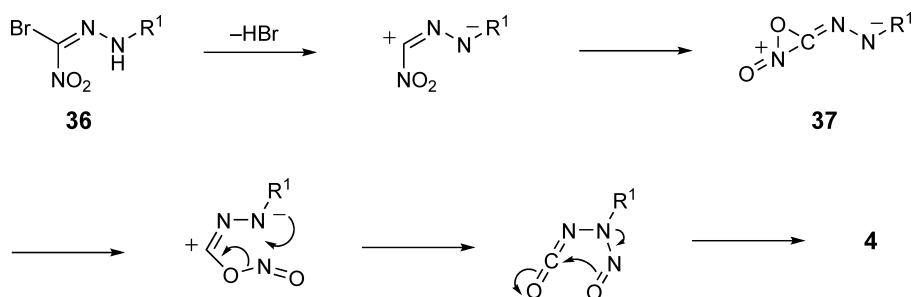


Cyclization occurs fastest when electron-withdrawing groups are attached to the C-3 phenyl substituent and slowest for electron donors. Reaction yields and selected spectroscopic data are listed in **Table 1**.

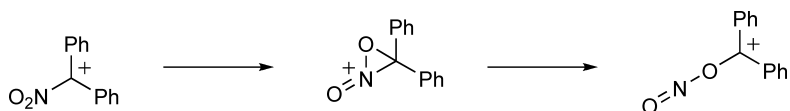
Table 1 Selected values from IR, UV, and ^{13}C NMR analysis of 3-substituted-anhydro-5-hydroxy-1,2,3,4-oxadiazolium hydroxides **4** from nitrosation and cyclization of bromonitroformaldehyde *N*-arylhydrazones **36** (Equation 5) <1997CHE880, 1999CHE363>

R^1	<i>C</i> -5 $\text{C}=\text{O}$ str KBr (cm^{-1})	λ_{max} in <i>EtOH</i> (nm)	<i>C</i> -5 δ (ppm)	Yield (%)
4- $\text{O}_2\text{NC}_6\text{H}_4$	1780, 1820	266	165.5	91
4- ClC_6H_4	1780, 1795	272		89
Ph	1775, 1795	267	165.8	64
4- MeOC_6H_4	1775		165.9	48
3- FC_6H_4	1800	265	165.1	76
4- FC_6H_4	1782, 1805	270	167.2	74
2- $\text{F}_3\text{CC}_6\text{H}_4$	1800	270	165.0	53
3- $\text{F}_3\text{CC}_6\text{H}_4$	1770, 1812	260	165.3	68
2- BrC_6H_4	1800	270		54
4- BrC_6H_4	1795	280		87
4- MeC_6H_4	1770, 1785	278	165.8	65
3- MeC_6H_4	1785	275		50
3- MeOC_6H_4	1790	275		88
3- ClC_6H_4		270		42
2- ClC_6H_4		275		55
2- $(\text{HO}_2\text{C})\text{C}_6\text{H}_4$	1770, 1795	268		72
	1790		165.9	93
	1770		165.4	60
	1780	290	165.5	86
	1785, 1815	263	165.7	73
	1790	282	165.0	70
	1780, 1807	265	165.6	72

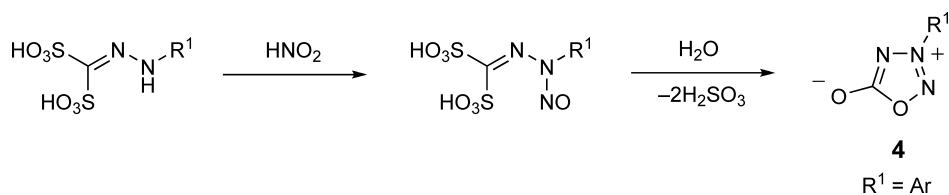
The requisite bromonitroformaldehyde *N*-arylhazones **36** are readily available by the standard methods <1974ZOR2229>. On treatment with ammonium nitrate, 70% nitric acid, or various other catalysts, compounds **36** firstly undergo dehydrobromination, followed by rearrangement via intermediate **37**, then cyclization to give products **4**. The proposed mechanism is shown in **Scheme 5** and is based on literature analogies shown in **Schemes 6** <1982JME1503> and **7** <1978OMS611, 1984JA2378>.



Scheme 5

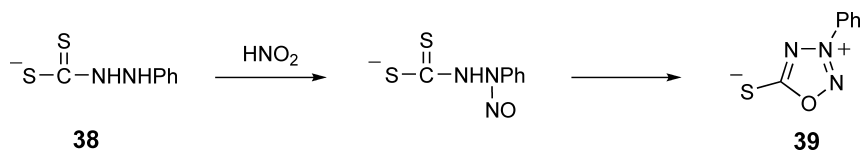


Scheme 6



Scheme 7

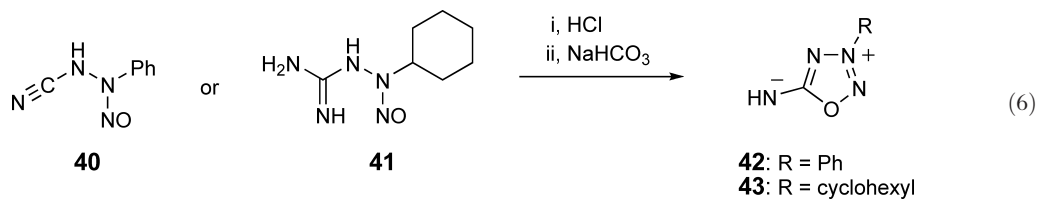
3-Alkyl-anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides **39** are formed from arylhydrazinium dithiocarbamates **38** on nitrosation and cyclization (**Scheme 8**) <1979J(P1)732>.



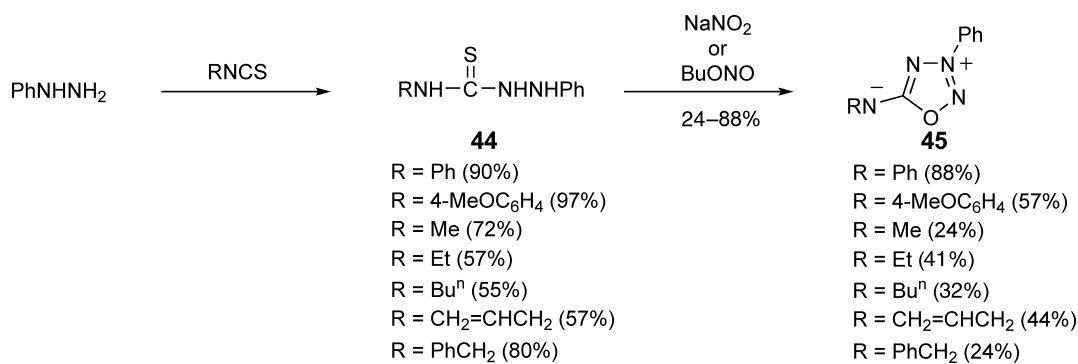
Scheme 8

When Ph¹⁵NH₂ and Na¹⁵NO₂ are used for preparation and nitrosation of the arylhydrazinium dithiocarbamates **38**, each of the nitrogen positions of product **39** may be labeled with ¹⁵N to allow measurement of ¹⁵N-¹⁵N coupling constants (Section 5.18.3.2) <1996JST167>.

The original synthesis of 3-substituted-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides relied on cyanohydrazines or guanidinohydrazines that were converted to the nitrosocyanohydrazines **40** and **41** that then cyclized to give products **42** and **43** as their hydrochloride salts (Equation 6) <2002CRV1091>.



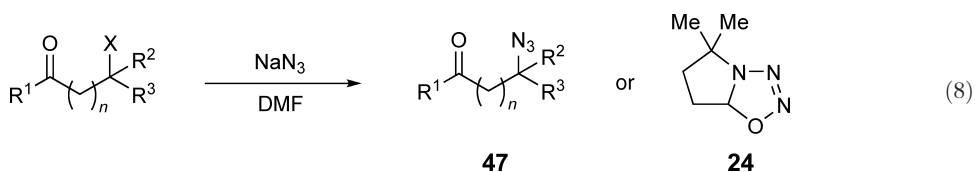
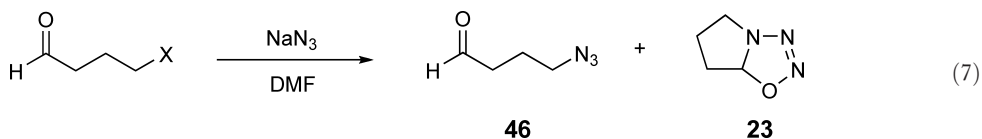
The free bases could then be liberated using sodium bicarbonate or ammonia. The exocyclic amino group at C-5 could then be converted to acyl derivatives by reaction with a variety of acylating agents. Derivatives of 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides **45** with substituents attached to the exocyclic nitrogen atom can be obtained directly from the arylthiosemicarbazides **44** by nitrosation with sodium nitrite followed by cyclization (Scheme 9).



Scheme 9

Use of the more expensive nitrosation reagent butylnitrite is successful when the reaction fails with the cheaper sodium nitrite reagent <2004JST23>. Introduction of a ¹⁵N label at the exocyclic nitrogen in compounds **45** where R = Me is achieved using the ¹⁵N-enriched 1-phenyl-4-methyl-3-thiosemicarbazide formed from ¹⁵N-methylamine via ¹⁵N-methylisothiocyanate <2004JST23>.

Two previously unknown Δ²-1,2,3,4-oxatriazoline derivatives, namely the 5,6,7,7a-tetrahydro-pyrrolo[1,2-*d*][1,2,3,4]oxatriazoles **23** and **24**, have been prepared (Equations 7 and 8) <2002HAC307>. When 4-bromo- or 4-toluenesulfonyloxybutyraldehyde is reacted with sodium azide at 50 °C, high yields of product **23** are obtained (Equation 7; Table 2).



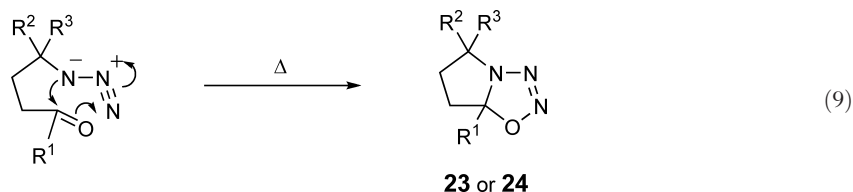
When the reaction is performed at 0 °C, the azide **46** is isolated in high yield with no accompanying oxatriazoline **23**, whereas a mixture of products **23** and **46** is obtained at room temperature. Similarly, the Δ²-1,2,3,4-oxatriazoline derivative **24** is obtained in high yield from 4-bromo-4-methylvaleraldehyde (Equation 8). When other aldehydes or ketones are employed, only the azide products **47** could be isolated (Table 3). Formation of these new oxatriazolines **23** and **24** seems likely to involve a tandem substitution–cycloaddition reaction sequence (Equation 9).

Table 2 Reaction of bromo and sulfonyloxy aldehydes with sodium azide (Equation 7) <2002HAC307>

X	Temp. (°C)	Yield (%)	
		46	23
Br	0	84	0
Br	rt	36	52
Br	50	0	87
TsO	50	0	85

Table 3 Reaction of bromo and sulfonyloxy aldehydes with sodium azide (Equation 8) <2002HAC307>

n	R ¹	R ²	R ³	X	Yield (%)	
					47	24
2	H	Me	Me	Br	0	89
2	Me	H	H	Br	79	0
2	Me	H	Me	TsO	81	0
3	H	H	H	TsO	83	0
4	H	H	H	TsO	86	0
1	H	H	H	Br	72	0
0	H	H	H	Br	63	0
0	Me	H	H	Cl	70	0
0	Ph	H	H	Br	94	0



5.18.10 Ring Syntheses by Transformation of Another Ring

Since the last survey <1996CHEC-II(4)679>, there have been no examples of synthesis of 1,2,3,4-oxatriazoles or 1,2,3,5-oxatriazoles by transformation of another ring.

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

Direct, reliable methods for synthesis of mesoionic 1,2,3,4-oxatriazoles 4–6 are well established. All rely on the transformation of acyclic starting materials. Thus, 3-alkyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium hydroxides 4 (R¹ = alkyl) are readily obtained by nitrosation of semicarbazides followed by cyclization (Section 5.18.9). The 3-aryl-substituted analogues 4 (R¹ = aryl) are prepared either by cyclization of arylazonitromethanes or by nitrosation and cyclization of arylhydrazonomethanesulfonate salts <1984CHEC(4)579, 1996CHEC-II(4)679>.

Similarly, nitrosation and cyclization of arylhydrazinium dithiocarbamates provides a reliable and efficient route to 3-aryl-anhydro-5-thiolo-1,2,3,4-oxatriazolium hydroxides 5, whereas 3-substituted-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxides 6 (R¹ = alkyl or aryl) are directly prepared by nitrosation and cyclization of alkyl- or arylthiosemicarbazides. Alternatively, 3-aryl-substituted analogues 4 (R¹ = aryl) may be prepared by a newer route using bromonitroformaldehyde *N*-arylhydrazones, which has the added benefit of allowing introduction of heterocyclic substituents at the N-3 position in compounds 4 (R¹ = hetaryl) (Section 5.18.9).

1,2,3,4-Oxatriazolines have been prepared by intramolecular [3+2] cycloaddition but the reaction is restricted to particular starting materials and, to date, only two successful examples have been described. 1,2,3,5-Oxatriazolidines are equally rare and routes to these compounds are extremely limited. Δ^4 -1,2,3,5-Oxatriazolines, in particular, suffer badly from instability <1984CHEC(4)579, 1996CHEC-II(4)679>.

5.18.12 Important Compounds and Applications

Mesoionic 1,2,3,4-oxatriazoles display a wide range of biological activities and important new examples have been the focus of several studies since last survey of the subject area <1996CHEC-II(4)679>. These compounds are well represented by structures **48–53** among others <1995AP137, 1996WOP96/11191>.

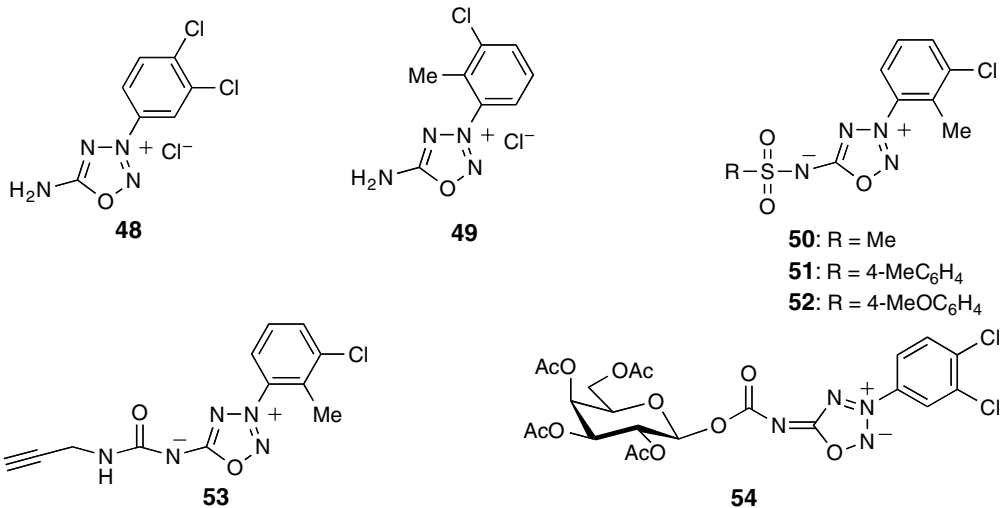
Mesoionic 1,2,3,4-oxatriazoles are structural isosteres of sydnonimines (see Chapter 5.03). Like the sydnonimines, the pharmacological effects of mesoionic 1,2,3,4-oxatriazoles stem largely from their ability to act as NO donors in biological systems <1994MI553, 1996BJP401>. These properties are well documented in recent reviews <B-2004MI1, B-2005MI1, 1998MI113, 1999FA316, 2000MI701, 2000TH1, 2002CRV1091, 2002MI167, 2002RCB1375, 2005MI67>. Application of mesoionic 1,2,3,4-oxatriazoles as blood pressure lowering agents was first reported in 1971 and detailed investigations into their NO-releasing properties began some 15 years ago <1994WOP094/3442>.

Of particular note is the compound 3-(3,4-dichlorophenyl)-anhydro-5-amino-1,2,3,4-oxatriazolium hydroxide **48** (GEA 3162). This particular compound and some of its derivatives have been studied intensively. The compound possesses hypotensive <2000MI701>, vasodilatory <1996BJP1422>, vasoprotective <1997MI(161)55>, antiplatelet <1996BJP401>, antiulcer <1999MI123>, immunosuppressive <1997MI(337)55b>, and pro-apoptotic <2000BP305, 2001BBR1229, 2004BJP179> properties. Additionally, compound **48** inhibits neutrophil function <1997BJP1135> and neutrophil adhesion to endothelial cells <1999MI111>. Compound **48** also inhibits proliferation of human lymphocytes in a cGMP-dependent manner <1998MI215>, suppresses tumor cell growth <1997MI75>, stimulates chloride secretion in the colon <2002MI21>, enhances the permeability of mitochondria <2002MI45>, and inhibits mitogenesis in vascular smooth muscle <1998BJP402>. The NO-releasing ability of compound **48** has been shown to be superior to that of the mesoionic 1,2,3-oxatriazole compound SIN-1 (see Chapter 5.03) <1998MI97>. Like SIN-1, compound **48** is a generator of peroxyxynitrite (ONOO⁻) <2004BJP179>.

Compound **51** (GEA 3175) shows antiplatelet <1996BJP2140, 2004MI1, 2005MI149>, anti-inflammatory <1995MI107>, and antimalarial activity <2002CRV1091>. The compound also causes apoptotic cell death in murine melanoma cells in a dose-dependent manner <2002CRV1091>. Additionally, this compound **51** (GEA 3175) and its analogues **52** (GEA 3268) and **50** (GEA 5145) induce relaxation of the bronchioles <1996MI1309, 1997MI175, 1998BJP895, 2006MI179> and trachea <1998MI110>.

The structures of various substituted 3-aryl-anhydro-5-amino-1,2,3,4-oxatriazoline hydroxides **6** (R¹ = Ar) for the treatment of asthma and thrombosis have been disclosed <1996WOP96/11191> and their diuretic properties have also been alluded to <2006WOP2006/055542>.

Although successful in the sydnonimine series, attempted formation of a galactose conjugate of compound **48** (GEA 3162) for planned evaluation as a galactosidase-mediated nitric oxide donor proved less successful. Decomposition of the 1,2,3,4-oxatriazole ring occurred on attempted removal of the acetyl protecting groups from the sugar ring of the conjugate **54** <2005JOC3518>.



The compound 3-phenyl-anhydro-5-thiolo-1,2,3,4-oxatriazolium oxide **5** ($R^1 = \text{Ph}$) has been incorporated into polymer films where its electronic structure and density contribute equally to the measured changes in photoinduced refractive index. Its analogue, 3-phenyl-anhydro-5-hydroxy-1,2,3,4-oxatriazolium oxide **4** ($R^1 = \text{Ph}$), has been employed as a filter <1999MI6772, 2002MI2290>.

5.18.13 Further Developments

No further developments regarding the chemical synthesis, characterization, reactivity and analysis of 1,2,3,4-oxatriazoles or 1,2,3,5-oxatriazole have been described. Mesoionic 3-(3,4-dichlorophenyl)-anhydro-5-amino 1,2,3,4-oxatriazolium hydroxide **48** (GE3162) and analogue **51** (GEA 3175) continue to find various pharmacological uses in the context of their nitric oxide <2007BJP305> releasing properties <2006MI43, 2006MI162, 2006MI247> (Section 5.18.12).

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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. honours 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.