1,2,5-THIADIAZOLE-1-OXIDES.I.SYNTHESIS AND REACTIONS OF ALKOXY AND ALKYLTHIO ANALOGS

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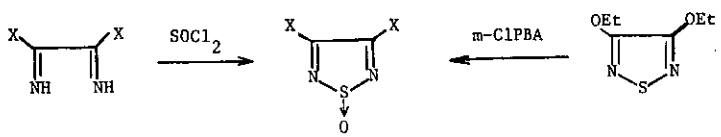
Abstract - Diethoxy and dithiomethyl 1,2,5-thiadiazole oxides were synthesized from the corresponding oxalimidates with thionyl chlorides. The alkoxy and alkythio groups were readily replaced by amines, carbon nucleophiles and hydroxide. The resulting hydroxy compounds were alkylated and acylated on the ring nitrogen. The N-alkyl products could be also obtained by thermal O to N rearrangement of the alkoxy derivatives.

The chemistry of 1,2,5-thiadiazoles has been well explored over the past 20 years[1] and more recently the corresponding 1,1-dioxides were also the subject of a detailed study[2]. Surprisingly, very little is known about the sulfoxides derived from 1,2,5-thiadiazoles[3] and indeed, the literature contains very little on the chemistry of sulfoxides derived from thioaromatic compounds in general[2b,4]. In this series of papers[5] we present the preliminary results of our study on the chemistry of 1,2,5-thiadiazole-1-oxides.

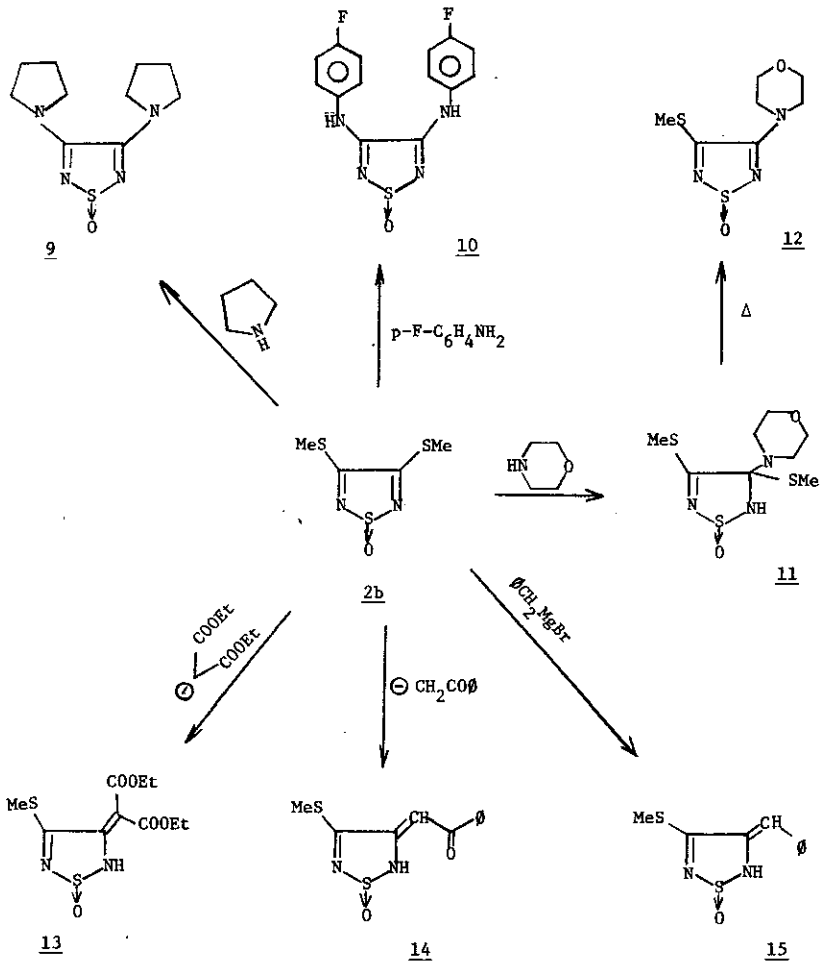
The two basic starting materials of our study, 2a and 2b, were prepared by thionyl chloride cyclization of oxalimidates 1a and 1b[6]. Alternatively, 2a was obtained by m-chloroperbenzoic acid oxidation of thiadiazole 3[1].

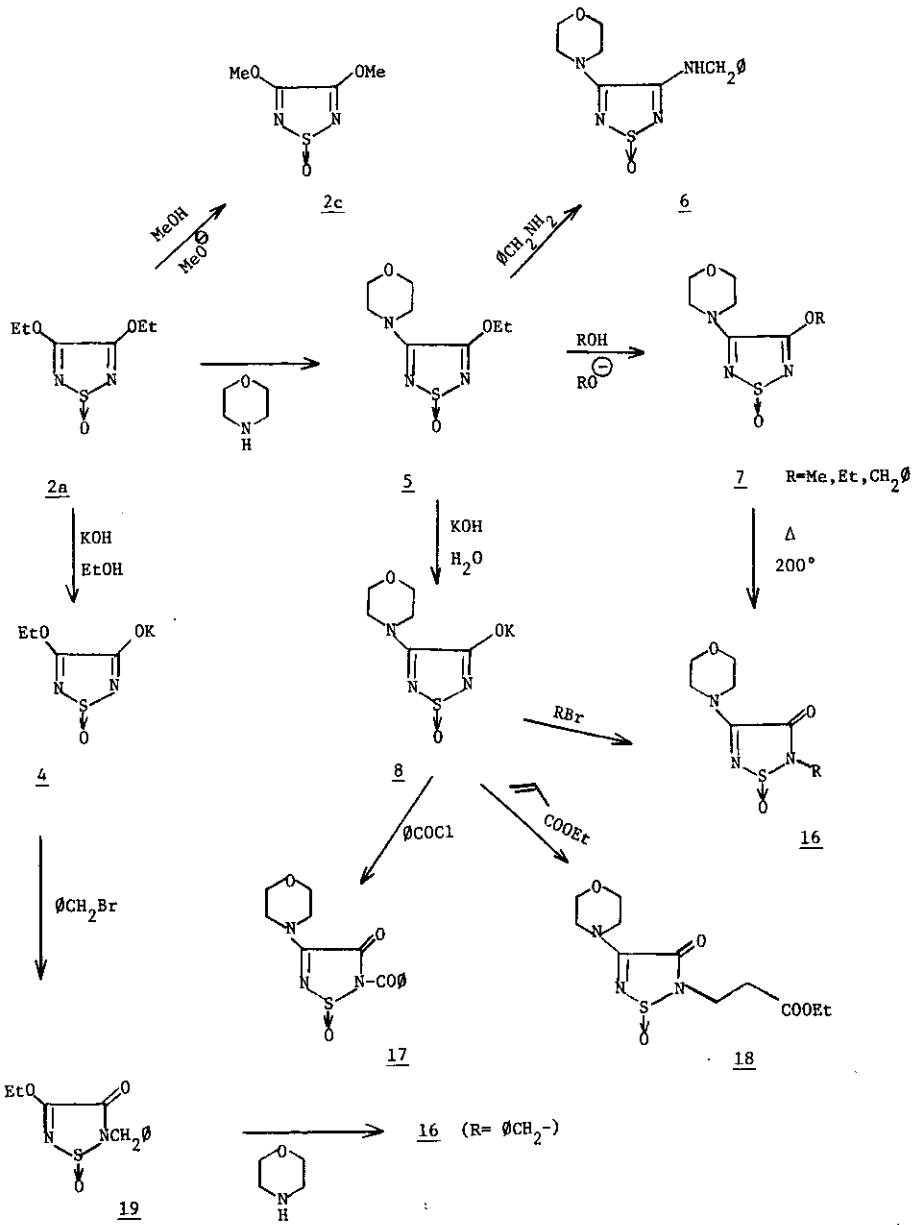


1 2 3

a) X=OEt
b) X=SMe

The 1,2,5-thiadiazole system is aromatic and alkoxy substituents are displaced only under forcing conditions[1]. The sulfur atom in the sulfoxides and 1,1-dioxides, becomes pyramidal[2a,7] and the aromaticity of the system is perturbed. Consequently, the reactivity of the alkoxy derivatives in this series becomes similar to that of imidates and displacements take place easily with a variety of nucleophiles. Thus, the ethoxy groups of 2a and 5 can be readily displaced by amines (2a→5→6), alkoxides (2a→2c and 5→7) and hydroxides (2a→4 and 5→8)[8]. These displacements are general


9
10
12
p-F-C6H4NH2
Δ
MeS
SMe
2b
HN
O
11
COOEt
COOEt
⊖ CH2COØ
ØCH2MgBr
13
14
15


MeO
OMe
2c
MeOH
MeO⊖
NHCH2Ø
6
ØCH2NH2
EtO
OEt
2a
5
ROH
RO⊖
OR
7
R=Me,Et,CH2Ø
KOH
EtOH
KOH
H2O
Δ
200°
OK
4
8
RBr
16
ØCOCl
COOEt
ØCH2Br
N-COØ
17
COOEt
18
NCH2Ø
19
16 (R= ØCH2-)

and high yielding for primary alcohols and primary and secondary amines but poor with phenols and thiols. Secondary amines and aromatic amines readily react to form mono displacement products (analogs of 5) but usually fail to enter the second displacement. These reactions can be readily achieved, however, by employing the more reactive dimercapto analog 2b (eg. 2b → 9 and 10). It is noteworthy that the normally expected addition intermediate 11 could actually be directly isolated in good yield from reactions run in acetonitrile and only after heating to reflux did the elimination step take place, producing 12.

The reactions of 2a and 2b discussed above are carried out by stirring the reactants at room temperature or at reflux for a few hours in methanol or acetonitrile. The reactions are faster in methanol and the crystalline products usually precipitate directly.

The increased reactivity of the thioalkyl derivative 2b is also advantageous when employing carbon nucleophiles. Thus, while 2a is unreactive, 2b reacts smoothly with stabilized carbanions to afford 13 and 14 in high yield. Reaction with alkyl lithium or Grignard reagents is less satisfactory. For example, compound 15 is isolated in only 10% yield from a complex reaction mixture.

Heating the alkoxy analogs 7 (R=Me, Et, $\emptyset CH_2$-) to 200° results in an O → N alkyl migration producing the 2-alkyl-3-ones 16, which are also accessible via alkylation of 8 with alkyl bromides or (where R=$\emptyset CH_2$-) via the reaction of 19 with morpholine. The potassium salt 8 also reacts on nitrogen with benzoyl chloride and with ethyl acrylate producing 17 and 18[9].

We have thus defined the basic chemical reactivity of the alkoxy, alkylthio and hydroxy analogs of 1,2,5-thiadiazole-1-oxides in reactions involving displacements, thermal O → N alkyl migrations and N-alkylations. In the following paper the chemistry of the amines will be discussed.

References

1. L. M. Weinstock, and P. I. Pollack, "Advances in Heterocyclic Chemistry", Academic Press, Vol. 9, 107(1968).
2. a) R. Y. Wen, A. P. Komin, R. W. Street and M. Carmack, J. Org. Chem., 40, 2743(1975). b) A. Lawson and R. B. Tinkler, Chem. Rev., 70, 593(1970).
3. M. Carmack, I. W. Stapleton, R. Y. Wen, Org. Prep. and Proc., 1, 255(1969).
4. W. L. Mock, J. Am. Chem. Soc., 92, 7610(1970).
5. Paper II is the following publication in this journal.
6. Compound 1a can be prepared via the reaction of sodium cyanide, chlorine and aqueous ethanol according to the procedure of J. D. Behun, U.S. Patent 3,112,334 (Nov. 26, 1963). A ^{14}C radio-labelled sample of 2a from $Na^{14}CN$ was prepared by H. Mertel et al. and will be submitted for publication by these workers to J. Labelled Comp. Radiopharm. Compound 1b was prepared according to the procedure of H. M. Woodburn, J. Org. Chem., 17, 351(1951).
7. J. S. Amato, S. Karady, R. A. Reamer, H. B. Schlegel, S. P. Springer and L. M. Weinstock, manuscript in preparation.
8. 3-Hydroxy-4-morpholine-1,2,5-thiadiazole-1-oxide has been detected as a metabolite of timolol. D. J. Tocco, A. E. Duncan, F. A. deLuna, J. L. Smith, R. W. Walker and J. A. VandenHeuval, Drug. Metab. Dispos., 8, 236(1980).
9. All the products discussed were crystalline and gave satisfactory C,H,N and S elemental analysis. Spectral data, ^1H NMR, IR and Mass Spectra, were in accord with the proposed structures.

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