1,2,5-THIADIAZOLE-1-OXIDES.II. THE CHEMISTRY OF THE AMINES

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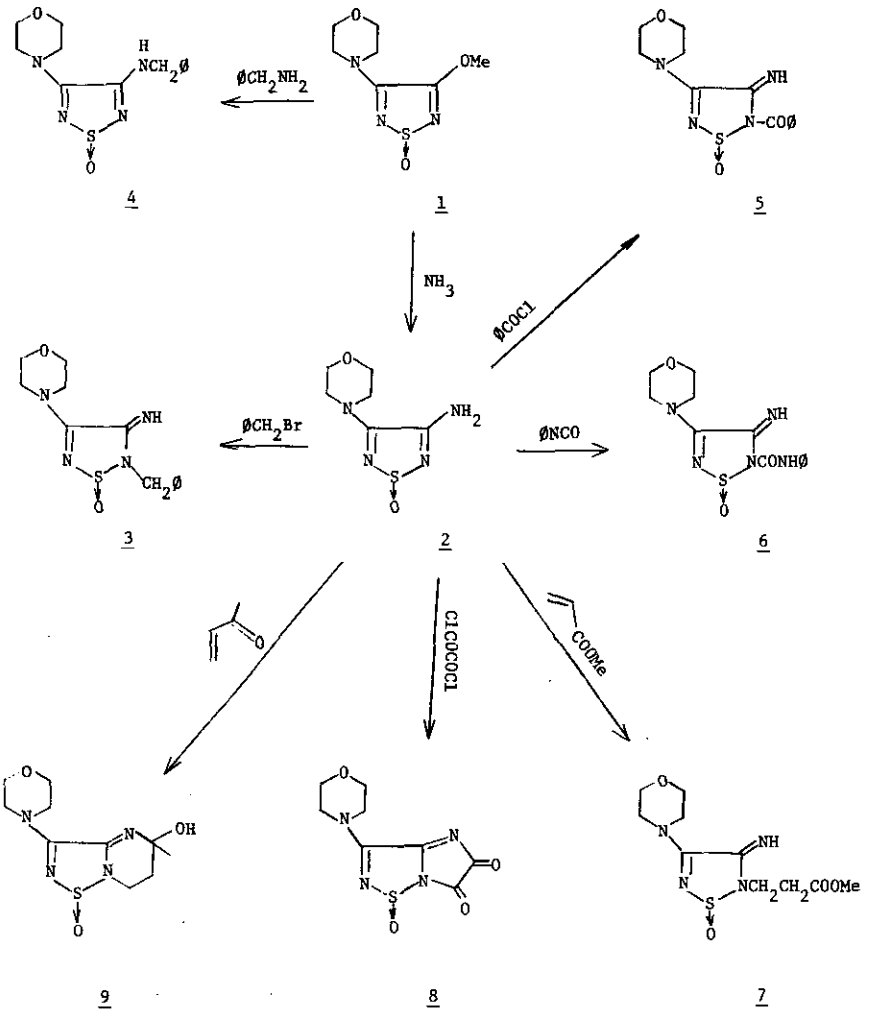
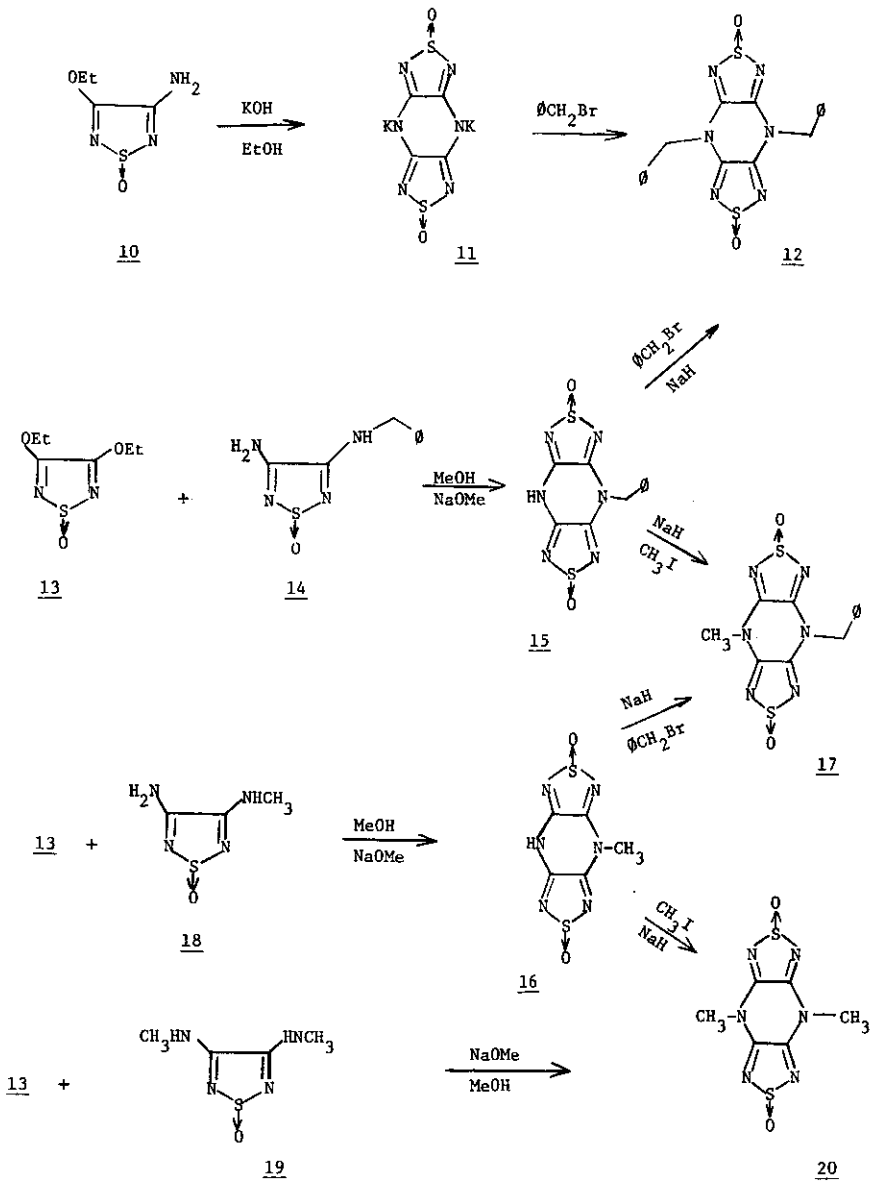
Abstract - Amino-substituted 1,2,5-thiadiazole-1-oxides form salts with NaOMe or NaH. These reacted with alkyl halides, acyl chlorides, isocyanates and methyl acrylate to afford ring nitrogen substituted products. The 3-amino, 4-ethoxy analog participates in a self condensation with KOH to form bis-thiadiazolopyrazine oxide dipotassium salt. Alkylation of this with benzyl bromide afforded a dibenzyl derivative with the benzyl groups attached to the central pyrazine nitrogens. Alkylaminothiadiazole oxides cyclized with the diethoxy derivatives to produce similar tricyclic compounds. These tricyclic bis sulfoxides formed diastereomers, indicating that the sulfur is pyramidal and the two forms are stable, i.e. there is no sulfur inversion at room temperature.

The previous paper in this series described the preparation of various amino-substituted 1,2,5-thiadiazole-1-oxides by displacement of the corresponding alkoxy and alkylthio compounds[1]. In this paper we discuss the chemical reactivity of the amino derivatives.

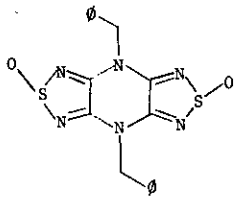
Amino-1,2,5-thiadiazole is weakly basic (pKa 2.9)[2], in contrast to amino derivatives of the 1-oxides which are non-basic and display reactivity closer to that of an amide. For example, they readily form salts with strong base which react with a variety of electrophiles. Thus, amino compound 2, produced by aminolysis of 1, reacts with sodium hydride and benzyl bromide to afford 3. Ring substitution was diagnosed on the basis of a sharp unsplit NH signal in the ^{1}H NMR spectrum and by comparison with the authentic side-chain substituted isomer 4 formed from 1 and benzylamine. Reactions with other electrophiles followed a parallel course. Thus, benzoyl chloride, phenyl isocyanate and methyl acrylate led to 5,6 and 7, respectively. Bifunctional reagents, eg. oxalyl chloride and methyl vinyl ketone produced the annelation products 8 and 9. The experimental conditions[3] for alkylations of 2 requires prior sodium salt preparation with NaOMe in MeOH, evaporation of the methanol and heating the salt with alkylating agent in refluxing acetone. Acylation reactions proceed at room temperature in CH_2Cl_2 in the presence of TEA whereas the reactions with isocyanates take place in refluxing THF.



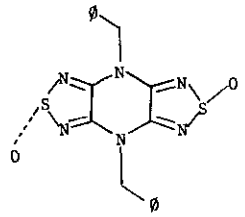
On attempted hydrolysis of aminoethoxy compound 10, self-condensation takes place and dipotassium salt 11 precipitates from the solution in high yield[4]. Alkylation of 11 with an excess of benzyl bromide affords a dibenzyl derivative (12). Since the point of attachment of the benzyl groups could not be determined by spectral means, structure was established via independent synthesis. Alkylamino derivatives do not self-condense in this manner, but authentic central ring-substituted analogs 15 and 16 can be prepared by bimolecular condensations with 13. Reactions of 15 and 16 with appropriate alkylating agents afford dialkyl derivatives 12, 17 and 20. The same compound (20) could also be obtained by the interaction of 19 and 13. These series of reactions firmly established that in each case, alkylation takes place on the central piperazine nitrogen.


OEt
NH2
KOH
EtOH
10
11
ØCH2Br
12
13
14
MeOH
NaOMe
15
ØCH2Br
NaH
NaH
CH3I
17
18
16
CH3I
NaH
19
NaOMe
MeOH
20

Experimentally, the condensations to form 15 or 16 are carried out at room temperature in MeOH. The alkylations require heating the salt (NaH, DMF) with the alkylating agent for several hours. Dibenzyl derivative 12 is a mixture of two isomers which show identical ^{1}H NMR, UV, Mass Spectral characteristics but could be separated on the basis of solubility. A careful study by ^{13}C NMR revealed that each isomer has only one type of ring carbon (sp^2) but the two isomers are distinctly different. We postulate that the isomers are diastereomeric with respect to pyramidal sulfur as indicated on formulas 12a and 12b.



12a



12b

Monobenzyl derivative 15 also shows diastereomerism as indicated by four signals attributed to ring carbons in the ^{13}C NMR spectrum. These results indicate that the sulfur in the 1,2,5-thiadiazole-1-oxide system is pyramidal and the two forms do not interconvert rapidly at room temperature. A future publication in these series will explore the question of sulfur inversion and the aromaticity of this system in a quantitative manner[5]. Other future topics in the area of 1,2,5-thiadiazole-1-oxides will include their use as synthons for the generation of other heterocycles via ring-interconversions.

References

1) Paper I of this series: see previous paper in this Journal.

2) L. M. Weinstock, and P. I. Pollack, "Advances in Heterocyclic Chemistry", Academic Press, Vol. 9, 107 (1968).

3) All intermediates were crystalline and gave satisfactory C,H,N and S elemental analysis. Spectral data, ^{1}H NMR, IR, and Mass Spectra were in accord with the proposed structures.

4) Analogous compounds were reported with 1,2,5-thiadiazole 1,1-dioxides by R. Y. Wen, A. P. Komin, R. W. Street and M. Carmack, J. Org. Chem., 40, 2743 (1975).

5) J. S. Amato, S. Karady, R. A. Reamer, H. B. Schlegel, S. P. Springer, and L. M. Weinstock, manuscript in preparation.

Acknowledgements: The authors wish to thank Dr. A. A. Patchett for good advice and stimulating discussions.

Received, 7th May, 1981