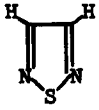
Tetrahedron Letters No.12, pp. 1263-1268, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A GENERAL SYNTHETIC SYSTEM FOR 1,2,5-THIADIAZOLES

Leonard M. Weinstock, Paul Davis,
Barry Handelsman and Roger Tull
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., Rahway, New Jersey, U.S.A.

(Received 3 January 1966)

1,2,5-Thiadiazole (I) (1,2) was shown by gas electron diffraction (3) and microwave spectroscopy (4) to be a planar aromatic ring system with structural parameters very similar to thiophene. The isoelectronic relationship between 1,2,5-thiadiazoles and pyrazines was also demonstrated (1,2).



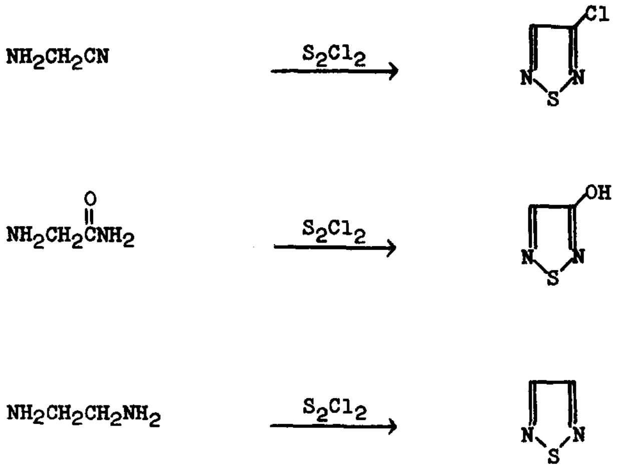
I

In line with the apparent aromatic nature of this ring system considerable driving force should exist for its formation from open-chain compounds and, indeed, 1,2,5-thiadiazoles have been obtained by cyclization of diethyl oxalimidate (5), diaminomaleonitrile (6) and cyanogen (7). The marked tendency toward formation of the 1,2,5-thiadiazole ring is also indicated in its formation by the reaction of sulfur dioxide with potassium cyanide (8).

Our recent finding that α-aminoacetonitrile bisulfate reacts with sulfur monochloride in dimethylformamide at room temperature to form 3-chloro-1,2,5-thiadiazole[*] in 80% yield prompted an investigation aimed at generalization of methods of formation of this heterocyclic ring system. We find that a general model for the structure of aliphatic compounds suitable for the synthesis of 1,2,5-thiadiazoles can be devised in terms of an acyclic N-C-C-N grouping in which the N-C functions are varied over the oxidation levels of amine, imine, nitrile, or oxime. The data now at hand indicate that aliphatic compounds containing these functionalities in any combination react with sulfur monochloride or sulfur dichloride to form an appropriately substituted 1,2,5-thiadiazole. Thus a wide variety of readily available aliphatic compounds such as α-diamines, α-amino acid amides, α-aminonitriles, alkyl cyanoformimidates, α-aminoamidines, and α-dioximes, can serve as starting materials in these reactions. The following are examples of some representative ring closures:

---

[*] B. P. 123-4°; λ_{max}^{MeOH} mμ (log ε) 260 (3.90), 263 (3.94), 267 (3.91), 270 (3.82); n.m.r.s. exhibits single peak in the neat liquid at 1.61 τ.



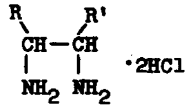
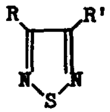
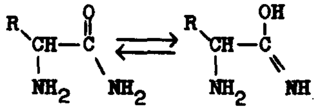
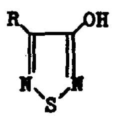
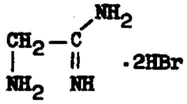
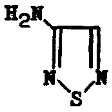
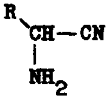
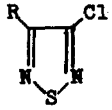
The data in Table I illustrate the versatility of these methods. In typical experiments the aliphatic compound (1.0 mole eq.) is added to a solution of sulfur monochloride (3.0 mole eq.) in two volumes of dimethylformamide in the cold, the mixture is stirred several hours at room temperature[*], water is added, the product internally steam distilled, and extracted from the distillate with petroleum ether. In the case of the nonvolatile hydroxy compounds the quenched reaction mixture is filtered and the filtrate extracted with ether. Yields in these reactions range from 50-90%.

---

[*] In reactions of the diamine dihydrochlorides and the dioximes the reaction is maintained at 60°.

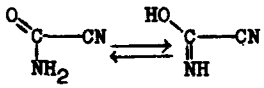
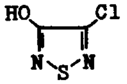
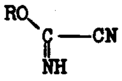
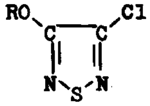
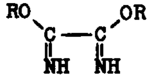
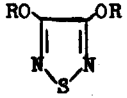
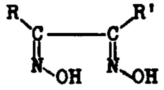
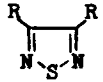
TABLE I

Synthesis of 1,2,5-Thiadiazoles by Reaction of Sulfur Monochloride with Aliphatic Compounds

Starting Material	Name or Type	Substituent	B.P. (M.P.) of Product, °C.	Product
	α-Diamine dihydrochloride	R=R'=H	94	
		R=Me, R'=H	120-2	
		R-R'=(-CH$_2$-)$_4$	64-5/1 mm.	
	α-Amino acid amide	R=H	(128-9)	
		Me, Et,	(151-3), (96-8)	
		nPr, iPr,	(62-4), (84-6)	
		nBu, iBu,	(42-4), (37.5-8.5)	
		Ø-, ØCH$_2$-	(166-8), (137-9)	
	Aminoacetamidine dihydrobromide	---	Not Taken (Product previously reported; see ref. 10).	
	α-Aminonitrile	R=H	123-4	
		R=Ø	109-111/1 mm. (33°)	

Continued

TABLE I (Continued)

Starting Material	Name or Type	Substituent	B.P. (M.P.) of Product, °C.	Product
	1-Cyanoformamide	—	(109-111)	
	Alkyl cyanoformimidate	R=Me Et iPr	63/17 mm. (53-4) 86.5-87.5/17 mm. 68-69/15 mm.	
	Dialkyl oximidate^5	R=Et	(31-2)^5	
NC-CN	Cyanogen*	—	155 101-2/122 mm.	
	α-Dioxime	R=R'=Me	46/20 mm.	

* Cyanogen also reacts with sulfur dichloride to form 3,4-dichloro-1,2,5-thiadiazole (7).

Noteworthy among these methods is the general synthesis of hydroxy - 1,2,5-thiadiazoles from α-amino acid amides and the one step preparation of the unsubstituted 1,2,5-thiadiazole from ethylenediamine dihydrochloride. The latter reaction is related to the recently reported synthesis of aliphatic sulfur diimides (II) (9).

$$RN{=}S{=}NR$$

II

Satisfactory analyses and spectroscopic data were obtained for all new compounds. Details of these reactions and the chemistry of the products will be reported elsewhere.

References

1) M. Carmack, L. M. Weinstock, and D. Shew, *Abstracts*, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., 1959, p. 37P.

2) L. M. Weinstock, *Dissertation Abstracts*, **19**, 3136 (1959).

3) R. A. Bonham and F. A. Momany, *J. Am. Chem. Soc.*, **83**, 4475 (1961); **86**, 162 (1964).

4) Sr. V. Dobyns and L. Pierce, *ibid.*, **85**, 3553 (1963).

5) R. Y. Wen, *Dissertation Abstracts*, **23**, 4121 (1963).

6) D. Shew, *ibid.*, **20**, 1593 (1959).

7) R. D. Vest, U. S. Pat. 3,115,497 (Dec. 24, 1963).

8) J. M. Ross and W. C. Smith, *J. Am. Chem. Soc.*, **86**, 2861 (1964).

9) D. H. Clemens, A. J. Bell and J. L. O'Brian, *Tetrahedron Letters*, No. 20, 1487 (1965).

10) F. H. Marquardt, *Dissertation Abstracts*, **21**, 3272 (1961); K. Menzl, Ger. Pat. 1,175,683, Aug. 13, 1964 [*Chem. Abstr.*, **61**, 12009h (1964)].