A New Synthesis of 4-Cyanothiazole

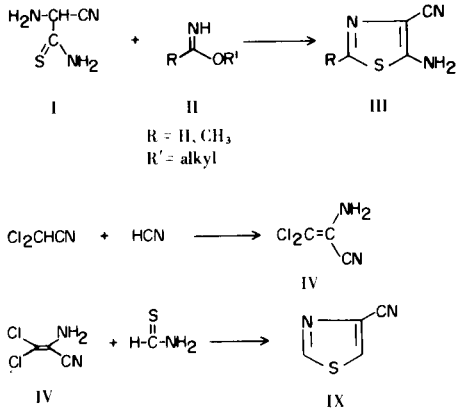
G. D. Hartman, M. Sletzinger and L. M. Weinstock

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065

Received August 7, 1975

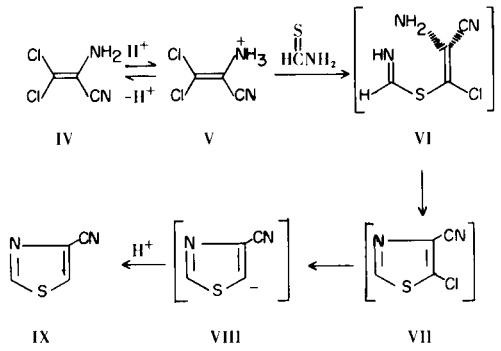
Sir:

Despite the fascinating array of methods for construction of the thiazole nucleus (1), there exists in the literature but a single instance of cyclization directly to a cyano-substituted thiazole. Shaw and Butter (2) demonstrated that treatment of α-amino-α-cyanothioacetamide (I) with alkyl imidate hydrochlorides (II) afforded 5-amino-4-cyanothiazoles (III) in yields of 17% (R = H) and 33% (R = methyl). We now wish to report the facile synthesis of the parent, 4-cyanothiazole (IX) by reaction of β,β-dichloro-



α-aminoacrylonitrile (IV), with thioformamide. Compound IV is readily obtained by treatment of dichloroacetonitrile with hydrogen cyanide (3). Thus, treatment of one equivalent of IV with two equivalents of thioformamide in acetone solution along with 5-10 mole % of *p*-toluenesulfonic acid afforded a 50% yield of 4-cyanothiazole (IX); nmr (deuteriochloroform, 60 M_3): 8.25 (1H, d), 9.05 (1H, d) δ.

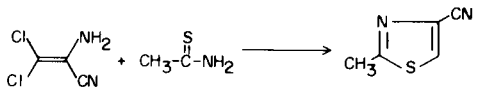
The observation that no reaction occurs between IV and thioformamide in the absence of an acid catalyst lends support to a mechanism involving initial protonation of enamino nitrogen to give V followed by the nucleophilic attack of thioformamide at the β-carbon. This latter reaction yielding VI has obviously been greatly facilitated by the presence of the strongly electron-withdrawing ammonium function in V. Internal cyclization culminating with



extrusion of ammonia would then afford 5-chloro-4-cyanothiazole (VII) as a possible reactive intermediate. At this stage, apparently VII is dechlorinated by the excess thioformamide present in solution to give 4-cyanothiazole (IX). This latter type of reaction is not without precedent since sulfur, as well as phosphorus, is known to be a strong nucleophile toward halogen in a variety of reactions (4). Specifically, thioamides have been shown to be efficient dechlorinating agents toward α,α-dichlorocarbonyl compounds (5), in which case nucleophilic attack on halogen yields a stabilized enolate ion. In the present case, the observation that the use of an equivalent amount of thioformamide afforded only an 11% yield of IX, whereas two equivalents led to a 50% yield, strongly supports the notion that the thioamide has the dual role of attacking V as well as carrying out a subsequent dechlorination.

Support for a mechanism involving the dechlorination of 5-chloro-4-cyanothiazole (VII) by thioamide was obtained by an nmr determination of the relative rates of deuterium exchange at H-5 of thiazole and 4-cyanothiazole (IX). Thus, observation of the rate of disappearance of H-5 in each of these compounds in sodium methoxide/methanol-d_4 at 36° (probe temperature) showed that H-5 of IX was exchanged *ca.* 10^7-10^8 times faster than H-5 of thiazole itself (6) intimating the stability conferred upon VIII by the adjacent cyano group. Thus, a mechanistic scheme involving VIII is an attractive possibility.

In separate experiments the scope of the reaction reported herein was extended to the preparation of 2-methyl-4-cyanothiazole (X) (7), by treatment of IV with thioacetamide. Under conditions similar to those previously reported, X was formed in 42% yield; m.p. 59-61°; nmr (deuteriochloroform, 60 M_3): 2.75 (3H, s), 7.85 (1H, s) δ.



VI X

REFERENCES

(1) J. M. Sprague and A. H. Land in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 157, p. 484.

(2) G. Shaw and D. N. Butter, *J. Chem. Soc.*, 4040 (1959).

(3) K. Matsumura, T. Saraie, and N. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 705 (1972).

(4) B. B. Jarvis and J. C. Saukaitis, *J. Am. Chem. Soc.*, **95**, 7708 (1973), and references cited therein; D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. (C)*, 3262 (1971).

(5) Nencki and Sieber, *J. Prakt. Chem.*, 25, 74 (1882); H. Erlenmeyer and H. P. Furger, *Helv. Chim. Acta.*, **30**, 585 (1947); E. Sorkin, W. Krahenbuhl and H. Erlenmeyer, *ibid.*, **31**, 65 (1948).

(6) J. M. Landesberg, K. N. Houk and J. S. Michelman, *J. Am. Chem. Soc.*, **88**, 4265 (1965).

(7) D. G. Jones and G. Jones, *J. Chem. Soc. (C)*, 707 (1969).