Advances in

HETEROCYCLIC CHEMISTRY

Edited by

A. R. KATRITZKY

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Volume 14

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Preface

Volume 14 of this serial publication comprises six chapters of which four deal with general accounts of ring systems: benzisothiazoles (M. Davis), 1,2-dihydroisoquinolines (S. F. Dyke), benzo[*c*]thiophenes (B. Iddon), and pyrazines (G. W. H. Cheeseman and E. S. G. Werstiuk). One chapter updates a previous review in this series and is concerned with the rapidly expanding chemistry of mononuclear isothiazoles (K. R. H. Wooldridge). The remaining chapter (O. Meth-Cohn and H. Suschitzky) deals with the cyclizations of ortho-substituted *t*-anilines.

A. R. KATRITZKY
A. J. BOULTON

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Recent Advances in the Chemistry of Mononuclear Isothiazoles

K. R. H. WOOLDRIDGE

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Following publication of the first synthesis of a mononuclear isothiazole in 1956, this ring system has attracted considerable interest. The aim of the present review is to present a coherent survey of the

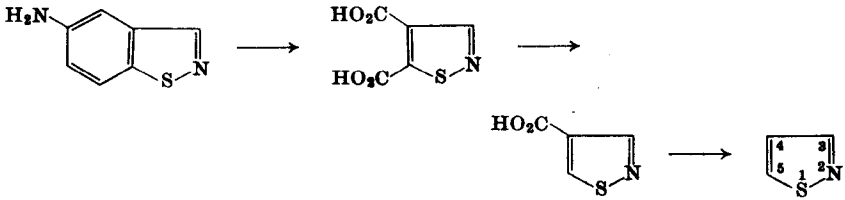
chemistry of isothiazoles in the light of the numerous developments which have taken place since the subject was last reviewed in 1965.[1]

I. Synthesis of Mononuclear Isothiazoles

In this section an attempt has been made to rationalize the numerous routes now available to the isothiazole ring system.

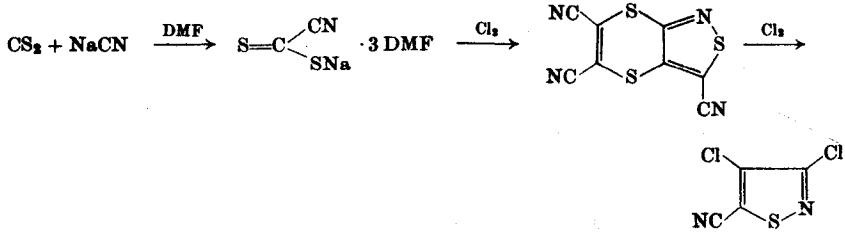
A. Preparation of Isothiazoles from Bicyclic Systems

The parent ring system was first prepared by Adams and Slack[2, 3] by the oxidation of 5-aminobenz[*d*]isothiazole to isothiazole-4,5-dicarboxylic acid, which was degraded stepwise to isothiazole (**1**).



(**1**)

This preparation is of no practical value, but it is of interest that a route (Scheme 1) involving the chlorination of cyanodithioformate probably passes through a bicyclic intermediate.[4, 5]

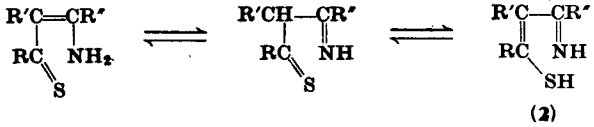


Scheme 1

[1] R. Slack and K. R. H. Wooldridge, *Advan. Heterocycl. Chem.* **4**, 107 (1965).
[2] A. Adams and R. Slack, *Chem. Ind.* (*London*) 1232 (1956).
[3] A. Adams and R. Slack, *J. Chem. Soc.* 3061 (1959).
[4] Pennsalt Chem. Corp., U.S. Patent 3,341,547 (1967) [*Chem. Abstr.* **68**, 114,596 (1968)].
[5] H. E. Simmons, R. D. Vest, D. C. Blomstrom, J. R. Roland, and T. L. Cairns, *J. Amer. Chem. Soc.* **84**, 4746 (1962).

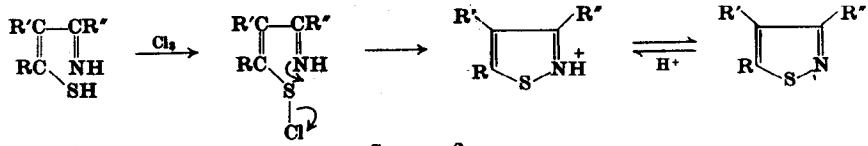
B. Preparation of Isothiazoles Involving Oxidative Formation of a Nitrogen–Sulfur Bond

There are several syntheses which depend on the oxidation of compounds that may be represented by "imino-enethiols" (**2**) as one of their tautomeric forms. Oxidation may be carried out with peracids,



(**2**)

high potential quinones, sulfur, or more commonly, halogens (Scheme 2).



Scheme 2

This route has many ramifications depending on the nature of R and R″ in Scheme 2; thus R may be alkyl, aryl, amino (thioamide), alkylthio, or thiol and R″ may be alkyl, aryl, amino (amidine), hydroxy (amide), or alkoxy (imino ether), although as yet not all of the possible combinations of these groups has been fully examined. In practice, the utility of the route depends on the availability of the requisite intermediates, and the situation is further complicated by the numerous routes which have been devised to these precursors.

Simple 5-aminoisothiazoles are readily prepared by oxidation of β-iminothioamides,[3,6–9] and more complex 5-aminoisothiazoles with electronegative substituents in the 4-position are available following

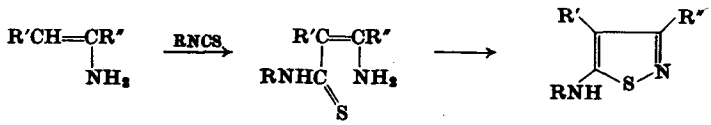
[6] J. Goerdeler and H. W. Pohland, *Chem. Ber.* **94**, 2950 (1961); **98**, 4040 (1965).

[7] Bristol-Banyu Research Inst., U.S. Patent 3,341,518 (1967) [*Chem. Abstr.* **68**, 95810 (1968)].

[8] R. E. Smith, Ph.D. Thesis, University of N. Carolina (1966).

[9] T. Taito, S. Nakagawa, and K. Takahashi, *Chem. Pharm. Bull.* **16**, 148 (1968).

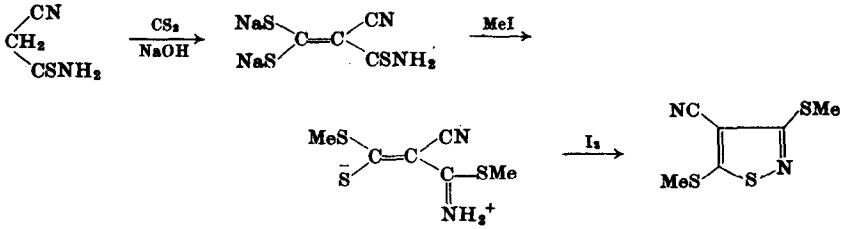
the development of elegant syntheses of the appropriate iminothioamides by Goerdeler and his colleagues[6, 10–15] (Scheme 3).



R = Me, Ph, CO_2Ph, COPh, CONHR″, SO_2Ph
R′ = CN, CO_2Et, $CONH_2$, COMe
R″ = Me, Ph, OH, NH_2, OAlk

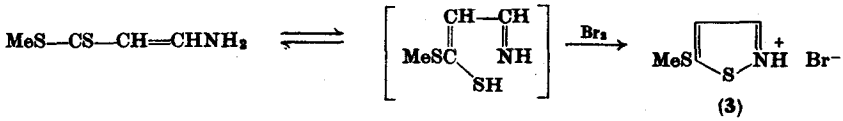
SCHEME 3

The synthesis (Scheme 4) of 4-cyano-3,5-dimethylmercaptoisothiazole by Gewald[16] may be regarded as a variant of this method.



SCHEME 4

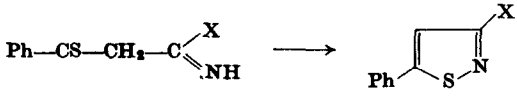
Faust[17] prepared 5-methylmercaptoisothiazole hydrobromide (**3**) from a similar intermediate.



(3)

[10] J. Goerdeler and H. Horn, *Chem. Ber.* **96**, 1551 (1963); see also Ciba, Belgian Patent 740,363 (1969) [*Chem. Abstr.* **73**, 56118 (1970)].
[11] J. Goerdeler and H. W. Pohland, *Chem. Ber.* **96**, 526 (1963).
[12] J. Goerdeler and U. Keuser, *Chem. Ber.* **97**, 3106 (1964).
[13] J. Goerdeler, *Angew. Chem.* **76**, 654 (1964).
[14] J. Goerdeler and U. Krone, *Chem. Ber.* **102**, 2273 (1969).
[15] J. Goerdeler, *Angew. Chem. Int. Ed. Eng.* **2**, 693 (1963).
[16] K. Gewald, *Chem. Ber.* **101**, 383 (1968).
[17] J. Faust, *Z. Chem.* **7**, 306 (1967).

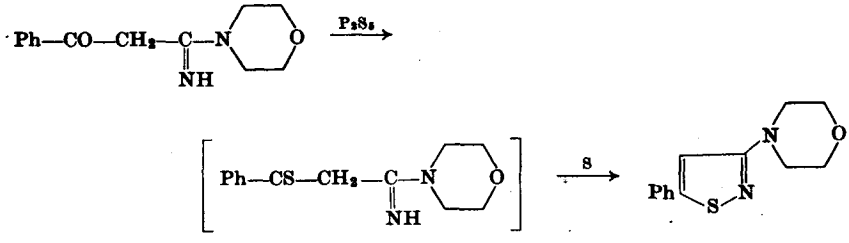
Goerdeler and Mittler[18] employed the appropriate thiones to prepare 3-amino-, 3-hydroxy-, and 3-methoxy-5-phenylisothiazoles [Eq. (1)].



(1)

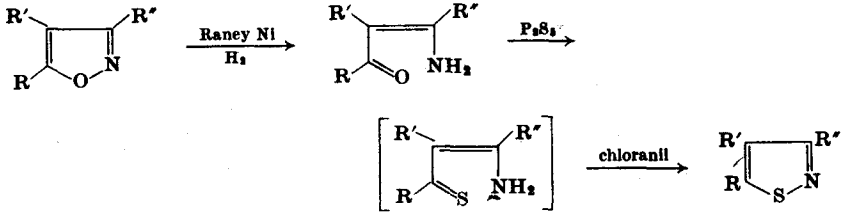
X = NH_2, OH, OMe

A method involving treatment of a β-iminoketone with phosphorus pentasulfide and sulfur[19, 20] may well involve the initial formation of an iminothione which undergoes oxidation with sulfur (Scheme 5).



SCHEME 5

An analogous reaction utilizes the ready availability of certain isoxazoles to give isothiazoles with the same substitution pattern.[21] The intermediate enaminoketones are treated with phosphorus pentasulfide and chloranil or sulfur to give moderate yields of isothiazoles (Scheme 6).

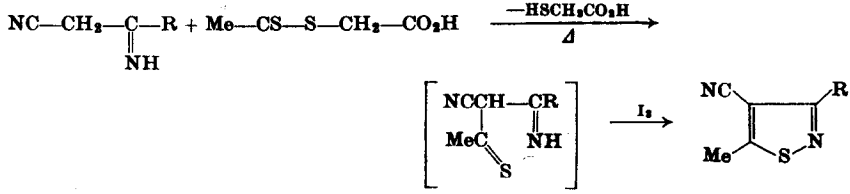


R and R″ = Me or Ph, R′ = H or electronegative substituent

SCHEME 6

[18] J. Goerdeler and W. Mittler, *Chem. Ber.* **96**, 944 (1963).
[19] A. Bruno and G. Purrello, *Gazz. Chim. Ital.* **96**, 1009 (1966).
[20] A. Bruno and G. Purrello, *Gazz. Chim. Ital.* **96**, 986 (1966).
[21] D. N. McGregor, U. Corbin, J. E. Swigor, and L. C. Cheney, *Tetrahedron* **25**, 389 (1969).

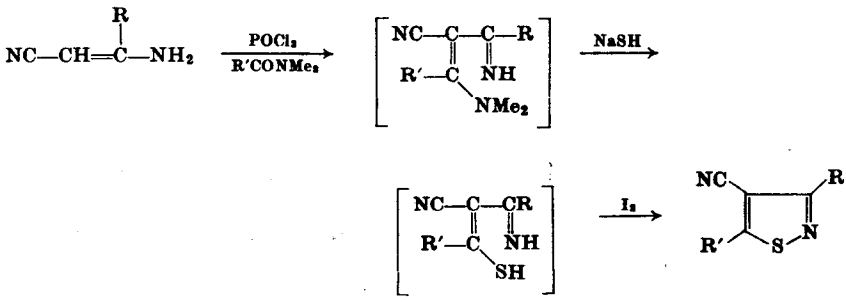
The synthesis (Scheme 7) employed by Crenshaw and co-workers[22, 23] may be rationalized as proceeding via a thione intermediate. In a later variation,[24] a Vilsmeier–Haack reaction was



R = Me or Ph

SCHEME 7

employed to acylate aminoacrylonitriles to give intermediates which, on treatment successively with sodium hydrosulfide and iodine, gave 4-cyanoisothiazoles (Scheme 8).



R and R′ = methyl or phenyl

SCHEME 8

5-Iminoisothiazoles,[15, 25] isothiazolin-5-thiones,[26] and isothiazolin-3-ones[27, 28] have been prepared by oxidation of the appropriate *N*-substituted intermediates. Isothiazolin-3-ones have been chlorin-

[22] R. R. Crenshaw, J. M. Essery, and A. T. Jeffries, *J. Org. Chem.* **32**, 3132 (1967).

[23] Bristol Myers, Netherlands Patents 6,710,248, 671,0,249, 6,710,250 (1968) [*Chem. Abstr.* **71**, 101,850 (1969)].

[24] R. R. Crenshaw and R. A. Partyka, *J. Heterocycl. Chem.* **7**, 871 (1970).

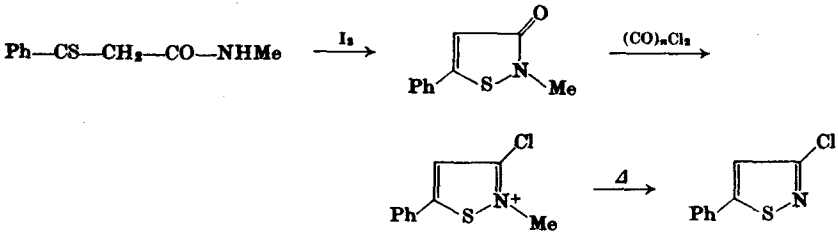
[25] J. Goerdeler and J. Gnad, *Chem. Ber.* **98**, 1531 (1965).

[26] R. Mayer, H. J. Hartmann and J. Jentzsch, *J. Prakt. Chem.* **31**, 312 (1966).

[27] J. Faust, *Z. Chem.* **8**, 170 (1968).

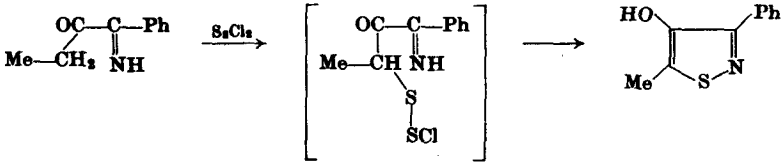
[28] Ciba, French Patent 2,012,336 (1970) [*Chem. Abstr.* **72**, 79026 (1970)].

ated with oxalyl chloride or phosgene to 3-chloroisothiazolium salts which may be thermally degraded to 3-chloroisothiazoles,[27] although the yields are poor (Scheme 9).



SCHEME 9

The syntheses by Naito and co-workers of 4-hydroxy, 4-cyano, and related isothiazoles from α-iminoketones or α-iminonitriles and sulfuryl or thionyl chloride[29, 30] may be envisaged as a variant of the general method if it is assumed that the reagents introduce a sulfur atom and also provide chlorine for oxidative cyclization (Scheme 10).



SCHEME 10

C. PREPARATION OF ISOTHIAZOLES FROM OLEFINS

Hübenett and his colleagues observed that a mixture of propylene, sulfur dioxide, and ammonia in the presence of a catalyst at 200° gave isothiazole in 65% yield possibly via an intermediate thionylimide.[31, 32]

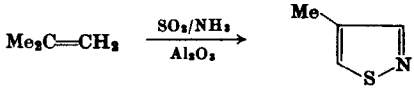
[29] T. Naito, S. Nakagawa, J. OKumuria, K. Takahashi, and K. Kasai, *Bull. Chem. Soc. Jap.* **41**, 959 (1968).

[30] T. Naito, S. Nakagawa, J. OKumuria, K. Takahashi, K. Masuko, and Y. Narita, *Bull. Chem. Soc. Jap.* **41**, 965 (1968).

[31] F. Hübenett, F. H. Flock, and H. Hofmann, *Angew. Chem. Int. Ed. Engl.* **1**, 508 (1962); Hans J. Zimmer Verfahrenstechnik, U.S. Patent 2,257,409 (1966).

[32] F. Hübenett, F. H. Flock, W. Hansel, H. Heinze, and H. Hofmann, *Angew. Chem. Int. Ed. Engl.* **2**, 714 (1963).

Isobutylene gives 4-methylisothiazole[31] [Eq. (2)], which is not available by any other route. 1- or 2-Butene gave a mixture of 3- and

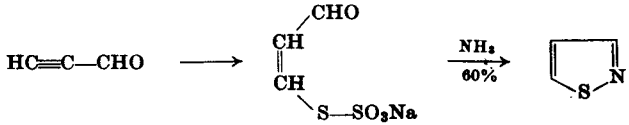


(2)

5-methylisothiazoles, but side reactions occur with higher olefins leading to increasing yields of thiophenes.[18] 4-Cyanoisothiazole and the three monophenylisothazoles have also been prepared by this method.[33]

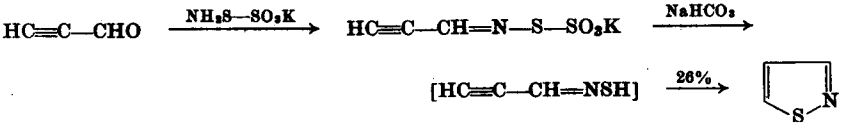
D. Preparation of Isothiazoles from Acetylenes

Probably the most convenient laboratory preparation of isothiazole was devised by Wille and his collaborators[34] (Scheme 11) and depends on the cyclization with liquid ammonia of the cis-addition product from propargyl aldehyde and sodium thiosulfate or thiocyanate.[34, 35]



Scheme 11

A higher yield (90%) may be obtained by ring closure with potassium thiohydroxylamino-*S*-sulfonate (Scheme 12). The same reagent may be condensed with propargyl aldehyde to give an intermediate which forms isothiazole on treatment with alkali, possibly via a transient thiooxime derivative.[36]



Scheme 12

[33] F. Hübenett and H. Hofmann, *Angew. Chem. Int. Ed. Engl.* **2**, 325 (1963).
[34] F. Wille, *Angew. Chem. Int. Ed. Engl.* **1**, 335 (1962).
[35] R. Raap, *Can. J. Chem.* **44**, 1324 (1966).
[36] D. Buttimore and R. Slack, unpublished data.