The Preparation of 5-Substituted and 3,5-Disubstituted Isothiazoles by Nucleophilic Displacement Reactions of the Corresponding Methylsulphonyl Compounds

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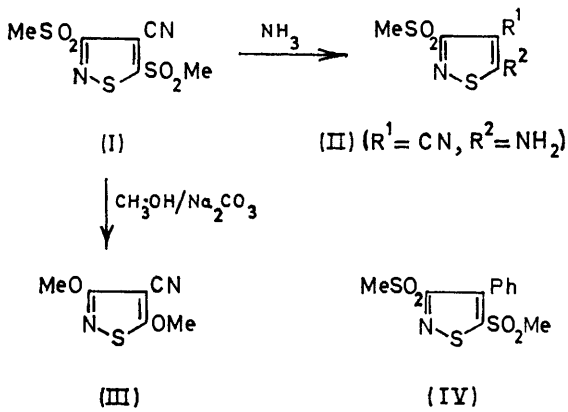
Isothiazoles substituted in the 5-position by hydroxy-, alkoxy-, or amino-groups may be obtained by treatment of the corresponding methylsulphonyl compounds with the appropriate base. In some cases 3,5-disubstituted compounds may be prepared similarly.

In view of current interest in isothiazole chemistry [1] we report a relatively simple method of producing certain isothiazoles substituted at the 5-position by hydroxy-, alkoxy-, or amino-groups. In some cases 3,5-disubstituted isothiazoles may be obtained. Other workers [2,3] have demonstrated the synthetic utility of methylsulphonyl compounds in preparing derivatives of a large number of nitrogen heterocyclic systems. Aminolysis of methylsulphonylpyrimidines, for example, is *ca.* 10^5 times faster than the aminolysis of the corresponding methylthio-compounds; [2] and generally methylsulphonyl derivatives are 40—100 times more reactive than chloro-compounds towards methoxide ion.[3]



Similar displacement reactions on methylsulphonylisothiazoles appear not to have been previously described; this procedure readily affords a variety of novel isothiazoles. For example, 3,5-bis(methylsulphonyl)-isothiazole-4-carbonitrile (I), readily obtained from malononitrile and carbon disulphide,[4] affords 5-amino-3-methylsulphonylisothiazole-4-carbonitrile (II; R^1 = CN, R^2 = NH_2) in high yield on treatment with ammonia solution. We have assigned the 5-amino-structure since previous experience both in this laboratory and elsewhere [5] and electron density calculations [6] indicate that a 5-substituent is much more prone to displacement than a corresponding 3-substituent.

Other amines and hydrazine react analogously with the 4-carbonitrile (I) to give the isothiazoles (II; R^1 = CN, R^2 = NHMe, NMe_2, or $NH{\cdot}NH_2$). A reaction with ethanol in the presence of sodium carbonate afforded a similar monosubstitution product, but with methanol under identical conditions 3,5-dimethoxyisothiazole-4-carbonitrile (III) was produced. It seems likely that the smaller size of the methoxide ion is the determining factor here. Attempts to obtain identifiable products by treatment of compound (I) with sodium hydroxide or sodium cyanide were, however, unsuccessful.

3,5-Bis(methylsulphonyl)-4-phenylisothiazole (IV) was obtained by methylation and then peroxyacid oxidation of 4-phenylisothiazole-3,5-dithiol; [7] it also underwent displacement reactions, for example with methanol in the presence of base, but was less reactive than the corresponding 4-carbonitrile (I), in which the electron withdrawing capacity of the cyano-group assists the nucleophilic displacement reactions.

EXPERIMENTAL

N.m.r. spectra are, generally, reported for *ca.* 5% solutions in deuteriochloroform, with tetramethylsilane as internal standard. In some cases a small proportion of dimethyl sulphoxide was added to aid solubility. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

5-Amino-3-methylsulphonylisothiazole-4-carbonitrile (II).—3,5-Bis(methylsulphonyl)isothiazole-4-carbonitrile [4] (I) (1·0 g) and ammonia solution (*d* 0·880; 10 ml) were mixed and left overnight at room temperature. The excess of ammonia was removed by boiling, and the yellow precipitate was collected. Recrystallisation from ethanol afforded yellow *needles* (0·5 g, 65%), m.p. 315° (decomp.). Other 5-substituted isothiazoles (II) were prepared from the nitrile (I) or from 3,5-bis(methylsulphonyl)-4-phenylisothiazole (IV). Reaction conditions, yields, m.p.s, and analytical data are given in the Table.

3,5-Dimethoxyisothiazole-4-carbonitrile (III).—The nitrile [4] (I) (1·0 g), sodium carbonate (0·4 g), and methanol (10 ml) were heated together under reflux for 4 h. The mixture was poured into water and the precipitate was collected. Recrystallisation from ethanol afforded *needles* (0·4 g, 63%), m.p. 123—124° (Found: C, 42·6; H, 3·7; N, 16·3. $C_6H_6N_2O_2S$ requires C, 42·6; H, 3·7; N, 16·3%), δ 4·0(s) and 4·1(s) p.p.m.

3,5-Bis(methylthio)-4-phenylisothiazole.—Sodium cyano-

[1] For example, see I. D. H. Stocks, J. A. Waite, and K. R. H. Wooldridge, *J. Chem. Soc.* (*C*), 1971, 1314.
[2] D. J. Brown and P. W. Ford, *J. Chem. Soc.* (*C*), 1967, 568.
[3] G. B. Barlin and W. V. Brown, *J. Chem. Soc.*, (*B*) 1967, 648.
[4] W. R. Hatchard, *J. Org. Chem.*, 1964, **29**, 665.
[5] W. R. Hatchard, *J. Org. Chem.*, 1964, **29**, 660.
[6] A. Adams and R. Slack, *J. Chem. Soc.*, 1959, 3061.
[7] M. Davis, G. Snowling,and R. W. Winch, *J. Chem. Soc.* (*C*), 1967, 124.

(phenyl)dithioacetate [7] (10 g), sulphur (1·3 g), and ethanol (40 ml) were heated together under reflux for 4 h, then dimethyl sulphate (7·4 ml) was added to the cooled crimson solution. Extraction with chloroform (3 × 50 ml) yielded, after evaporation, a dark red oil (8 g) which slowly crystallised. Recrystallisation from methanol afforded orange *rhombs* (7·05 g, 75%), m.p. 69—70° (Found: C, 52·3; H, 4·3; N, 5·3. $C_{11}H_{11}NS_3$ requires C, 52·2; H, 4·4; N, 5·5%), δ 2·4(s), 2·5(s), and 7·4(m) p.p.m.

3,5-*Bis*(*methylsulphonyl*)-4-*phenylisothiazole* (IV).—Hydrogen peroxide (30%; 4·8 g) was added cautiously to a stirred solution of 3,5-bis(methylthio)-4-phenylisothiazole (2·53 g) in acetic anhydride (10 ml) and acetic acid (10 ml) with external cooling. The mixture was set aside for 2 days, then added to water (100 ml), and the product was separated. Recrystallisation from methanol afforded *needles* (2·54 g, 80%), m.p. 182—184° (Found: C, 41·8; H, 3·5; N, 4·2. $C_{11}H_{11}NO_4S_3$ requires C, 41·6; H, 3·5; N, 4·4%), δ 3·4(s), 3·5(s), and 7·5 (aromatic). In this preparation oxidations with potassium permanganate dissolved in acetone or perbenzoic acid in chloroform were equally effective.

5-Substituted isothiazoles (II) prepared from bis(methylsulphonyl)isothiazoles (I) and (IV)

Starting compd.	R^1	R^2	Reagent	Temp. (time)	% Yield [a]	M.p. (°C)	Formula	Found (%) C	H	N	Required (%) C	H	N
(I)	CN	NH_2	NH_4OH (*d* 0·88)	Room (overnight)	65	315 † [b]	$C_5H_5N_3O_2S_2$	29·3	2·6	20·4	29·6	2·5	20·7
(I)	CN	NHMe	$MeNH_2$ aq.	Room (overnight)	55	195—196 † [c]	$C_6H_7N_3O_2S_2$	32·9	3·3	19·2	33·2	3·2	19·4
(I)	CN	NMe_2	Me_2NH aq.	Room (overnight)	79	139—140 [d]	$C_7H_9N_3O_2S_2$	36·5	3·8	17·9	36·4	3·9	18·2
(I)	CN	$NH{\cdot}NH_2$	$H_2N{\cdot}NH_2,H_2O$	Room (overnight)	76	211—212 [c]	$C_5H_6N_4O_2S_2$	27·4	2·8	25·4	27·5	2·8	25·7
(I)	CN	EtO	EtOH + Na_2CO_3	Reflux (4 h)	69	103—104 † [b]	$C_7H_8N_2O_3S_2$	36·1	3·3	11·8	36·2	3·5	12·1
(IV)	Ph	MeO	MeOH + Na_2CO_3	Reflux (4 h)	71	120—121 [b]	$C_{11}H_{11}NO_3S_2$ [e]	49·0	4·0	4·7	49·1	4·1	5·2
(IV)	Ph	HO	NaOH aq. (5%) [f]	Reflux (3 h)	25	230 [g]	$C_{10}H_9NO_3S_2$	46·8	3·7	5·0	47·0	3·5	5·5

† Decomp.

[a] Recrystallised material. [b] From EtOH. [c] From MeOH. [d] From benzene. [e] δ 3·2 (3-SO_2Me), 4·0 (5-OMe), and *ca.* 7·5 (aromatic) p.p.m. [f] With subsequent acidification. [g] From water.

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