Aust. J. Chem., 1977, **30**, 1625–7

Hydroxyisothiazoles. I. Preparation of 3- and 5-Isothiazolinones by Nucleophilic Displacement of Isothiazole Sulphones

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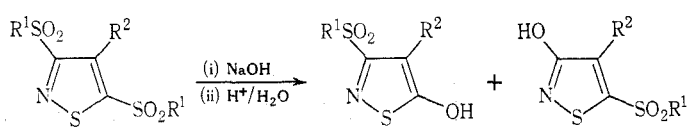
Abstract

Heating of 4-aryl-3,5-bis(alkylsulphonyl)isothiazoles with sodium hydroxide solution under reflux affords in good yield a readily separable mixture of the 3-hydroxy-5-alkylsulphonyl and 5-hydroxy-3-alkylsulphonyl compounds.

In 1972 we showed that many substituted isothiazoles could be prepared by nucleophilic displacement reactions of the corresponding methylsulphonyl compounds.[1] We now report that refluxing of the readily available 3,5-di(alkylsulphonyl)-isothiazoles (1) with aqueous sodium hydroxide solution gives an easily separable mixture of the corresponding 3-alkylsulphonylisothiazol-5-ols (2) and the isomeric 5-alkylsulphonylisothiazol-3-ols* (3).

3-Hydroxyisothiazoles are relatively well known compounds;[2] they have been cited in numerous patents claiming fungicidal or virucidal properties, but the 5-hydroxy compounds have received little attention. In our earlier work[1] we ascribed the 5-hydroxy structure to a compound, (2; R^1 = Me, R^2 = Ph), m.p. 230°, isolated from the reaction of the corresponding disulphone (1; R^1 = Me, R^2 = Ph) with sodium hydroxide. We now know this was incorrect, and that the 230° compound is actually the 3-hydroxy isomer (3; R^1 = Me, R^2 = Ph), on the basis of X-ray crystallographic studies.[3]



(1) (2) (3)

The hydroxy group is acidic in both series (2) and (3) but less so in the 3-substituted compounds (3), and the latter are precipitated by acetic acid from sodium hydroxide solution ($pK_a \approx 5$). Precipitation of the 5-substituted compounds (2) requires mineral

* *Chemical Abstracts* names the 3-hydroxy compounds as isothiazolin-3-ones, although studies indicate that the OH form is the predominant one in most cases.[2]

[1] Davis, M., and Gordon, J. A., *J. Chem. Soc., Perkin Trans. 1*, 1972, 638.
[2] Wooldridge, K. R. H., *Adv. Heterocycl. Chem.*, 1972, **14**, 26.
[3] McVicars, J. L., Mackay, M. F., and Davis, M., *J. Chem. Soc., Perkin Trans. 2*, in press.

Table 1. Some isothiazole derivatives

Substituents			Recrystallization	M.p.	Molecular	Found (%)			Requires (%)		
R^1	R^2	R^3	solvent	(°C)	formula	C	H	N	C	H	N
SMe	*p*-ClPh	SMe	carbon tetrachloride	113–114	$C_{11}H_{10}ClNS_3$	45·7	3·3	4·7	45·9	3·5	4·9
SMe[A]	*p*-MeOPh	SMe[A]	carbon tetrachloride	105	$C_{12}H_{13}NOS_3$	50·6	4·6	4·9	50·8	4·6	4·9
$SCHMe_2$	Ph	$SCHMe_2$	methanol	105–106	$C_{15}H_{19}NS_3$	58·2	6·3	4·4	58·2	6·2	4·5
SCH_2Ph	Ph	SCH_2Ph	ethanol	111–113	$C_{23}H_{19}NS_3$	68·2	4·9	3·1	68·1	4·7	3·4
SO_2Me	*p*-ClPh	SO_2Me	ethanol	185	$C_{11}H_{10}ClNO_4S_3$	37·9	2·9	4·0	37·6	2·9	4·0
SO_2Me	*p*-MeOPh	SO_2Me	dimethylformamide/water	193–194	$C_{12}H_{13}NO_5S_3$	41·7	3·9	4·2	41·5	3·8	4·0
SO_2Et	Ph	SO_2Et	methanol	145–147	$C_{13}H_{15}NO_4S_3$	45·0	4·5	4·2	45·2	4·3	4·1
SO_2Pr	Ph	SO_2Pr	methanol	104	$C_{15}H_{19}NO_4S_3$	48·2	5·1	3·5	48·3	5·1	3·7
SO_2CHMe_2	Ph	SO_2CHMe_2	methanol	165–166	$C_{15}H_{19}NO_4S_3$	48·2	5·1	3·8	48·3	5·1	3·7
SO_2Bu	Ph	SO_2Bu	methanol	80–81	$C_{16}H_{23}NO_4S_3$	50·9	5·7	3·4	50·8	5·7	3·5
SO_2CH_2Ph	Ph	SO_2CH_2Ph	benzene	192–193	$C_{23}H_{19}NO_4S_3$	59·4	4·1	2·8	58·8	4·1	3·0
OH	Ph	SO_2Me[B]	ethanol	230[C]							
SO_2Me[D]	Ph	OH	methanol	163–164	$C_{10}H_9NO_3S_2$	47·6	3·5	5·2	47·0	3·6	5·5
OH	*p*-ClPh	SO_2Me	ethanol	192	$C_{10}H_8ClNO_3S_2$	41·7	2·9	4·7	41·5	2·8	4·8
OH	*p*-MeOPh	SO_2Me	acetic acid/water	198	$C_{11}H_{11}NO_4S_2$	46·6	4·0	4·8	46·3	3·9	4·9
SO_2Me	*p*-MeOPh	OH	methanol	198	$C_{11}H_{11}NO_4S_2$	46·3	4·0	4·8	46·3	3·9	4·9
OH	Ph	SO_2Et	ethanol/water	194–195	$C_{11}H_{11}NO_3S_2$	49·1	4·0	5·0	49·1	4·1	5·2
SO_2Et	Ph	OH	chloroform/hexane	135–136	$C_{11}H_{11}NO_3S_2$	49·0	4·1	4·9	49·1	4·1	5·2
OH	Ph	SO_2Pr	ethanol/water	197–198	$C_{12}H_{13}NO_3S_2$	51·1	4·8	4·9	50·9	4·6	4·9
OH	Ph	SO_2CHMe_2	ethanol/water	244–245	$C_{12}H_{13}NO_3S_2$	50·7	4·8	4·8	50·9	4·6	4·9
OH	Ph	SO_2Bu	ethanol/water	196–197	$C_{13}H_{15}NO_3S_2$	52·5	5·2	4·7	52·5	5·0	4·7

[A] $\delta(SCH_3)$ in $CDCl_3$ at 2·42 and 2·53 ppm.
[B] $\delta(CH_3)$ in $(CD_3)_2SO$ at 3·12 ppm.
[C] Lit.[1] m.p. 230°; previously reported as 5-hydroxy compound.
[D] $\delta(CH_3)$ in $(CD_3)_2SO$ at 3·20 ppm.

acid; this indicates a pK_a of much less than 5. The isomeric products are thus easily separated. In each case approximately equal quantities of the two isomers are obtained, and this ratio is almost unaffected by variations in R^1 or R^2. This lack of sensitivity to electronic effects in the aryl group R^2 suggests that the latter is not conjugated with the isothiazole ring. It is interesting that displacement of only *one* sulphonyl group occurs; presumably formation of the anion of (2) or (3) increases electron density at the remaining sulphonyl group and this inhibits further nucleophilic displacement. Both (2) and (3) (R^1 = Me, R^2 = Ph) are completely unaffected by prolonged heating with sodium hydroxide solution; the combined yield of (2)+(3) is essentially quantitative.

New compounds prepared in this work are listed in Table 1.

Experimental

General

Melting points are uncorrected. Microanalyses are by the Australian Microanalytical Service, Melbourne. P.m.r. data are of solutions in deuterochloroform or dimethyl[D_6] sulphoxide, with tetramethylsilane as internal standard.

4-*p*-Chlorophenyl-3,5-bis(methylthio)isothiazole and 4-*p*-methoxyphenyl-3,5-bis(methylthio)isothiazole were prepared from the corresponding phenylacetonitriles in a manner similar to that described earlier.[1]

The bis-ethylthio, -propylthio, -butylthio, etc. compounds were prepared in a similar way except for the use of diethyl sulphate, bromopropane, bromobutane, etc. in the alkylation step. These were frequently intractable red oils and were then not characterized but were oxidized directly to the corresponding disulphonyl derivatives (1).

Oxidation

Oxidation of the thio compounds to sulphonyl compounds was best carried out in acetic acid at *c.* 90° for 1 h with a slight excess of 30% hydrogen peroxide. Cooling of the solution, or dilution with water, afforded the highly crystalline disulphonyl derivatives (1).

Hydrolysis

Hydrolysis of the disulphonyl derivatives (1) was carried out as follows. The disulphonyl compound (1; R^1 = Me, R^2 = Ph) (32 g) was heated under reflux with water (300 ml) and sodium hydroxide (30 g) until all the solid had dissolved (about 2 h). The clear solution was cooled and acidified with acetic acid affording the 3-hydroxy compound (3; R^1 = Me, R^2 = Ph) as colourless plates (13 g, 51%), m.p. 230° after recrystallization from ethanol. Addition of conc. hydrochloric acid (100 ml) to the mother liquor produced an oil which was extracted with chloroform. Drying and evaporating of the extract gave an oily residue which slowly crystallized. Recrystallization from methanol afforded the 5-hydroxy compound (2; R^1 = Me, R^2 = Ph) as colourless prisms (10 g, 39%), m.p. 163–164°. The same procedure was used to hydrolyse the other disulphonyl compounds. Analytical results are given in Table 1.

Manuscript received 21 December 1976