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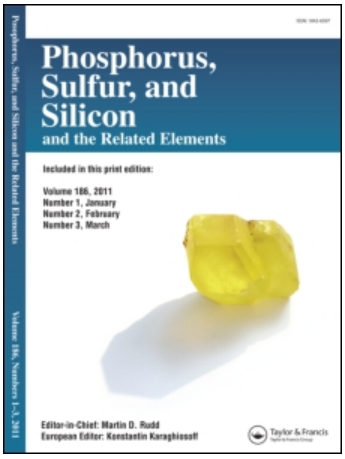

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A DIRECT SYNTHESIS OF HETEROCYCLIC THIOLS

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Heterocyclic thiols (thiones) are conveniently synthesized in good yields by the reaction of heterocyclic halides with sodium thiosulfate. The reaction requires the presence of acid, either added or liberated during the reaction, to hydrolyze the intermediate thiosulfate to thiol.

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An attempted synthesis of purine-6-thiosulfate by refluxing 6-chloropurine with sodium thiosulfate pentahydrate in alcohol gave 6-mercaptopurine in nearly quantitative yield. Although acid hydrolysis of aliphatic and aryl thiosulfates is known to give respectable yields of mercaptans,[1] no example of such a conversion of heterocyclic halides was found in the literature. Also, no direct conversion of organic halides to thiols by reaction with inorganic thiosulfates was encountered. A recent review of the synthesis of heterocyclic thiols[2] did not cite a single instance where thiosulfates were employed, either directly or through hydrolysis.

This finding suggested that other heterocyclic thiols or thiones may be synthesized by this simple and direct procedure. Accordingly, refluxing of 2-chlorobenzothiazole, 2-chlorobenzoxazole, and 2-chloro-4,6-diamino-1,3,5-triazine with sodium thiosulfate in aqueous alcohol gave the corresponding thiol in good yield. In the case of 2-chlorobenzothiazole and 2-chlorbenzoxazole, small amounts of the 2-hydroxy compounds were detected in the products.

Conversion of other heterocyclic halides to the thiol structure was investigated, and comparison of the reaction as run in aqueous alcohol with that at a lower pH, which could allow hydrolysis, was made. In the reaction with 2-chloroquinoxaline, the reaction required $4\frac{1}{2}$ hours to complete at neutral pH and a refluxing temperature of 83°. At a starting pH of 5.0, the reaction required $1\frac{3}{4}$ hours at refluxing temperature, with subsequent formation of elemental sulfur. At a starting pH of 1.7, the reaction required only $1\frac{1}{2}$ hours at room temperature, but with some formation of elemental sulfur. In the three reactions, the yields of thiol were essentially identical: 65%, 63% and 63%.

With relatively unreactive halides, such as 2-bromopyridine and 2-chloro pyrazine, no detectable reaction took place at neutral pH after several hours of refluxing. With acidic pH, the conversion to thiol did take place. To compensate for partial decomposition of thiosulfate to sulfur, however, two equivalents of thiosulfate were used. Yields of 64% and 20%, respectively, were obtained. The heterocyclic thiols or thiones obtained from this reaction are listed in Table I.

The course of the reaction was followed by observing the change in the UV spectrum of the quinoxaline ring and silica gel chromatograms (with a developing solvent of chloroform-methanol (9:1)). Samples were removed every 30 minutes from the reaction of 2-chloroquinoxaline and sodium thiosulfate in 50% aqueous ethanol, and the UV spectra and thin layer chromatograms were observed. No change was found in the quinoxaline spectrum (λ_{max} 95% EtOH 320 nm) until thiol was formed. Thiosulfate absorption was found at λ_{max} 95% EtOH 245 nm. During the first 4.5 hours, no change occurred in either spectral peak, but a new spot on tlc appeared at Rf = 0 which was attributed to the sodium salt of the quinoxaline-2-thiosulfate (the 2-chloro compound had an Rf = 0.8). It is assumed that no alteration of the quinoxaline chromophore takes place on conversion of the 2-chloro to the 2-thiosulfate group.

When the UV spectrum was observed in 0.1 N hydrochloric acid, however, the thiosulfate was rapidly hydrolyzed to the thione, and two new

TABLE I

Heterocyclic thiols from the thiosulfate reaction

Reactant	Product	Starting pH	Yield, %	M.p.	Lit. M.p.	Ref.	Ir, cm^{-1} C=S
6-Chloropurine	6-Mercaptopurine·H_2O	Neutral	88	324–326°	313–314°d	3	1225
2-Chlorobenzothiazole	2-Mercaptobenzothiazole	Neutral	78	178–181°	180–182°	4	1040
2-Chlorobenzoxazole	2-Mercaptobenzoxazole	Neutral	86	196–198°	196°	5	1135
2-Chloro-4,6-diamino-1,3,5-triazine	2,4-Diamino-6-mercapto-1,3,5-triazine	Neutral	84	214–215.5° (picrate)	215° (picrate)	6	1200
2-Bromothiazole	2-Mercaptothiazole	5.0	70	75–77°	79–80°	7	1055
2-Bromopyridine	2-Mercaptopyridine	3.2	63	125–127°	125–128°	8	1145
2-Chloropyrazine	2-Mercaptopyrazine	1.7	20	215–218°	210–215°	9	1168
2-Chloroquinoxaline	2-Mercaptoquinoxaline	6.0	93	203–205°	204–205°	10	1140
3-Chlorobenzo-1,2,4-triazine-1-oxide	Benzo-1,2,4-triazine-3-thiol-1-oxide[a]	5.0	20	155–159°	184°	11	1185
4-Chloro-6-methyl quinoline	6-Methyl-4 (1H)-quinolinethione	5.0	66	200–205°d			1150
4-Chloro-6-methoxy-quinoline	6-Methoxy-4 (1H)-quinolinethione	5.0	69	210–220°d	139°	12	1155
2-Chloropyrimidine	2-Mercaptopyrimidine	1.7	62	230–231°	230°d	13	1160

[a] Anal. Calcd. for $C_7H_5N_3OS$: C, 46.91; H, 2.81; N, 23.45. Found: C, 47.16; H, 3.03; N, 23.68.

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peaks appeared at 395 and 280 nm. The peaks at 320 and 245 nm were correspondingly diminished. After 4 hours, the chloro group was completely replaced by thiosulfate, as shown by tlc. The reaction, after 4.5 hours, showed a gradual replacement of the peak for 2-chloro (and 2-thiosulfato) quinoxaline by the quinoxaline-2-thiol peaks. The solution of quinoxaline-2-thiosulfate was then hydrolyzed to thiol in 0.1 N hydrochloric acid at 80° during 10 minutes, and both the original quinoxaline peak at 320 nm and the thiosulfate peak disappeared from the spectrum. It appears that the reaction requires acid hydrolysis to convert the intermediate thiosulfate to thiol.

The nomenclature used agrees with common usage in designating these compounds as thiols. The NMR and Ir spectra both indicate that the major contribution to structure is given by the thione form, however, Ir stretching frequencies for C=S are listed in Table I.

EXPERIMENTAL SECTION

Infrared spectra were taken with a Perkin Elmer model 547A grating spectrometer using potassium bromide pellets. NMR spectra were obtained with a Varian T-60 spectrometer; 10% solutions in DMSO-d6 were used with TMS as internal reference. Thin layer chromatography was done with Baker silica gel plates and exposure to either untraviolet light or I_2.

The following procedures are representative.

6-Mercaptopurine monohydrate. A mixture of 6-chloropurine (1.54g, 0.01 mole) and 2.48g (0.01 mole) of sodium thiosulfate pentahydrate in 50ml of ethanol-water (1:1) was refluxed for 24 hr. Evaporation of the solvent gave a yellow solid which was stirred with water and recrystallized from water; yield 88%, mp 314° (softens), 324–326°. Ir (KBr): 3500 (H_2O), 1225 (C=S), 1020 (ring), 935 (ring) cm^{-1}.

Anal. Calcd. for $C_5H_6N_4OS$: C, 35.32; H, 3.55; N, 32.95; S, 18.86.

Found: C, 34.98; H, 3.24; N, 33.23; S, 18.50.

2-Mercaptoquinoxaline. To a solution of 1.65 g (0.01 mole) of 2-chloroquinoxaline and 3.30g (0.013 mole) of sodium thiosulfate pentahydrate in 50 ml of ethanol-water (1:1) was added 1 ml of 85% phosphoric acid. The solution was refluxed for 1.5 hr, and sulfur was filtered. The ethanol was distilled under reduced pressure, and the remaining aqueous solution was cooled and filtered. The solid was dissolved in 0.1 N sodium hydroxide and the solution was filtered through charcoal, and the filtrate adjusted to a pH of 6 with 1 N hydrochloric acid. After stirring for 1.5hr, the yellow-orange solid was washed with ice water and dried in a vacuum oven; yield 93%; mp 203–205°. Ir (KBr): 1615 (ring), 1580 (ring), 1140 (C=S), 1115 (CH) cm^{-1}.

2-Mercaptopyridine. To 25ml of ethanol-water (1:1) containing 0.25g of 85% phosphoric acid and 0.69g of sodium dihydrogen phosphate were added 0.79g (0.005 mole) of 2-bromopyridine and 2.48g (0.01 mole) of sodium thiosulfate pentahydrate. The mixture was refluxed for 22 hr. and the hot mixture was filtered and the filtrate evaporated. The solid was dissolved in chloroform, filtered, the filtrate was evaporated, and the yellow solid was recrystallized from benzene; yield 63%; mp 125–127°. Ir (KBr): 2520 (SH), 1370 (ring), 1145 (C=S), 990 (ring), 750 (ring) cm^{-1}.

6-Methyl-4(1H)-quinolinethione. A solution containing 25 ml of ethanol-water (1:1), 0.69g of sodium dihydrogen phosphate, 0.45g (0.0025 mole) of 4-chloro-6-methylquinoline, and 0.62g (0.0025 mole) of sodium thiosulfate pentahydrate was refluxed for 2 hr. The ethanol was evaporated, and the pH of the remaining solution was raised to 10 with 10% sodium hydroxide solution. It was filtered and the filtrate was evaporated to 10ml and acidified with 2 N hydrochloric acid; the yellow product was filtered and washed with water; yield 66%, mp 200–205°d. Ir (KBr): 1420 (ring), 1150 (C=S), 820 (CH) cm^{-1}. Nmr (δ ppm): 2.50 (s, 3H, CH_3); 8.45 (s, 1H, 5-H); 12.8 (br, s, 1H, NH).

Anal. Calcd. for $C_{10}H_9NS$: C, 68.53; H, 5.18; N, 7.99; S, 18.30. Found: C, 68.21; H, 5.30; N, 8.35.

6-Methoxy-4(1H)-quinolinethione. The preceding method was used with 0.69g (0.0025 mole) of 4-chloro-6-methoxyquinoline. A 69% yield of yellow powder was obtained: mp 210–220°d (with evolution of H_2S). Ir (KBr): 1425 (ring), 1155 (C=S), 820 (CH) cm^{-1}. Nmr (δ ppm): 3.95 (s, 3H, OCH_3); 8.20 (d, 1H, 5-H); 11.3 (1H, N-H).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.33; S, 16.77. Found: C, 62.39; H, 4.85; N, 7.47.

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