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A facile nucleophilic displacement of bromine in 2-amino-4-methyl-5-bromothiazole by a thiophenoxide anion

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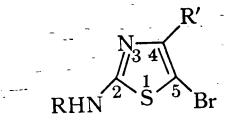
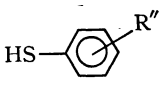
Although we have prepared a number of 2-acetamido-5-phenylthiothiazoles (III*a*) in about a 70% yield by heating a mixture of 2-acetamido-5-bromothiazole (I*a*) and an alkali salt of thiophenol II in propylene glycol for about 2 h at 130° (1, 2), their 4-methyl homologues III*b* could not be obtained in a satisfactory yield (28%) either under similar conditions (3) or by varying the solvent or by heating a mixture of 2-acetamido-4-methyl-5-bromothiazole (I*b*) and excess thiophenol according to a literature method (4). In all experiments, in addition to the 4-methyl homologue, a disulfide of the thiophenol was obtained, and unreacted I*b* was recovered to the extent of 50–60%. These results indicate hindrance by the methyl group in 2-acetamido-4-methyl-5-bromothiazole toward nucleophilic attack at position 5, as expected on the basis of a bimolecular nucleophilic displacement mechanism. However, 2-amino-5-bromothiazole, 2-amino-4-methyl-5-bromothiazole (I*c*), and the corresponding 5-iodo analogues hydrolyzed readily when heated in water, whereas their acetates did not, and I*c* reacted faster with thiophenols (III*c*, R″ = 4′-CH_3 or 4′-Cl; 50%) than did I*b* to give the corresponding compound III*b* (16%, see Experimental) (5, 6). These facts indicate enhanced reactivity of the halogen in the free base compared with that in the acetates, and do not support the view of hindrance by the methyl group in I*c* in a S_N reaction.

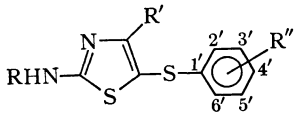
In view of the above results, we studied the reaction of I*c* with a stronger nucleophile, such as thiophenoxide anion, and found that a rapid reaction (30 min) took place when I*c* was heated with the calculated amount of the potassium salt of thiophenol II (R″ = Cl or Cl_2) in ethanol under a nitrogen atmosphere (to minimize oxidation of the thiophenol to its disulfide), the yields of 2-amino-5-phenylthio-4-methylthiazoles III*c* being about 65–70%. Hence, it can be concluded that the use of the more reactive 2-amino-4-methyl-5-bromothiazole (I*c*) instead of its acetate I*b*,



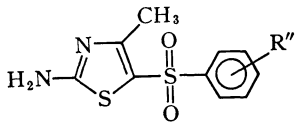
I*a* R = $COCH_3$, R′ = H
I*b* R = $COCH_3$, R′ = CH_3
I*c* R = H, R′ = CH_3



II



III*a* R = $COCH_3$, R′ = H
III*b* R = $COCH_3$, R′ = CH_3
III*c* R = H, R′ = CH_3



IV

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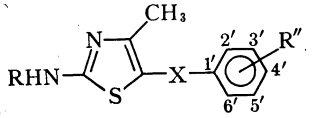
TABLE I

2-Amino-5-phenylthio-4-methylthiazoles III*c*, 2-amino-5-phenylsulfonyl-4-methylthiazoles IV, and their derivatives



R	R″	X	Melting point (°C)	Yield (%)	Formula	Analysis (%) Calculated	Analysis (%) Found	ν_{SO_2} (cm^{-1})	Nuclear magnetic resonance signals (p.p.m.) Methyl	Nuclear magnetic resonance signals (p.p.m.) Phenyl
H	2′-Cl	S	164–165	70	$C_{10}H_9ClN_2S_2$	N 10.91	11.08	—	2.51	7.30–7.67
$COCH_3$	"	S	192–194	80	$C_{12}H_{11}ClN_2OS_2$	N 9.38	9.42	—	—	—
H*	"	S	215–216†	—	$C_{16}H_{12}ClN_5O_7S_2$	N 14.42	14.70	—	—	—
$COCH_3$	"	SO_2	271–273	55	$C_{12}H_{11}ClN_2O_3S_2$	N 8.47	8.11	1 160	—	—
H	"	SO_2	233–234	70	$C_{10}H_9ClN_2O_2S_2$	C 41.59	42.01	1 155	2.57	7.63–8.20
						H 3.12	3.29			
						N 9.70	9.50			
H (HCl)	"	SO_2	218–220†	—	—	—	—	—	—	—
H	2′,3′-Cl_2	S	187–190	68	$C_{10}H_8Cl_2N_2S_2$	N 9.62	9.25	—	2.51	7.21–7.70
$COCH_3$	"	S	196–198	85	$C_{12}H_{10}Cl_2N_2OS_2$	N 8.41	8.76	—	—	—
H*	"	S	262–263†	—	$C_{16}H_{11}Cl_2N_5O_7S_2$	N 13.46	13.30	—	—	—
$COCH_3$	"	SO_2	244–246	60	$C_{12}H_{10}Cl_2N_2O_3S_2$	N 7.67	7.80	1 165	—	—
H	"	SO_2	223–225	78	$C_{10}H_8Cl_2N_2O_2S_2$	C 37.15	37.00	1 165	2.57	7.63–8.20
						H 2.48	2.93			
						N 8.67	8.82			
H (HCl)	"	SO_2	235–239†	—	—	—	—	—	—	—
H	2′,4′-Cl_2	S	140–142	67	$C_{10}H_8Cl_2N_2S_2$	N 9.62	9.48	—	2.52	7.24–7.70
$COCH_3$	"	S	193–195	80	$C_{12}H_{10}Cl_2N_2OS_2$	N 8.41	8.50	—	—	—
H*	"	S	232–233†	—	$C_{16}H_{11}Cl_2N_5O_7S_2$	N 13.46	13.30	—	—	—
$COCH_3$	"	SO_2	242–243	62	$C_{12}H_{10}Cl_2N_2O_3S_2$	N 7.67	7.30	1 160	—	—
H	"	SO_2	200–205	75	$C_{10}H_8Cl_2N_2O_2S_2$	C 37.15	36.94	1 155	2.57	7.63–8.20
						H 2.48	2.85			
						N 8.67	8.58			

TABLE I (*Concluded*)

R	R″	X	Melting point (°C)	Yield (%)	Formula	Analysis (%)		ν_{SO_2} (cm^{-1})	Nuclear magnetic resonance signals (p.p.m.)	
						Calculated	Found		Methyl	Phenyl
H (HCl)	2′,4′-Cl_2	SO_2	233–235	—	—	—	—	—	—	—
H	2′,5′-Cl_2	S	149–150	70	$C_{10}H_8Cl_2N_2S_2$	N 9.62	9.30	—	2.53	7.22–7.70
$COCH_3$	″	S	197–198	82	$C_{12}H_{10}Cl_2N_2OS_2$	N 8.41	8.88	—	—	—
H*	″	S	232–235†	—	$C_{16}H_{11}Cl_2N_5O_7S_2$	N 13.46	13.49	—	—	—
$COCH_3$	″	SO_2	235–236	60	$C_{12}H_{10}Cl_2N_2O_3S_2$	N 7.67	7.78	1 165	—	—
H	″	SO_2	196–197	68	$C_{10}H_8Cl_2N_2O_2S_2$	C 37.15	36.89	1 165	2.58	7.62–8.20
						H 2.48	2.19			
						N 8.67	8.79			
H (HCl)	″	SO_2	234–235†	—	—	—	—	—	—	—
H	3′,4′-Cl_2	S	125–128	70	$C_{10}H_8Cl_2N_2S_2$	N 9.62	9.58	—	2.51	7.30–7.72
$COCH_3$	″	S	175–176	86	$C_{12}H_{10}Cl_2N_2OS_2$	N 8.41	8.94	—	—	—
H*	″	S	234–235†	—	$C_{16}H_{11}Cl_2N_5O_7S_2$	N 13.46	13.73	—	—	—
$COCH_3$	″	SO_2	244–245	64	$C_{12}H_{10}Cl_2N_2O_3S_2$	N 7.67	7.70	1 160	—	—
H	″	SO_2	164–166	70	$C_{10}H_8Cl_2N_2O_2S_2$	C 37.15	37.43	1 160	2.58	7.83–8.20
						H 2.48	2.90			
						N 8.67	8.88			
H (HCl)	″	SO_2	260–263	—	—	—	—	—	—	—
H	3′,5′-Cl_2	S	142–145	67	$C_{10}H_8Cl_2N_2S_2$	N 9.62	9.69	—	2.52	7.25–7.60
$COCH_3$	″	S	177–179	85	$C_{12}H_{10}Cl_2N_2OS_2$	N 8.41	8.63	—	—	—
H*	″	S	213–214†	—	$C_{16}H_{11}Cl_2N_5O_7S_2$	N 13.46	13.60	—	—	—
$COCH_3$	″	SO_2	262–263	58	$C_{12}H_{10}Cl_2N_2O_3S_2$	N 7.67	7.56	1 165 and 1 140	—	—
H	″	SO_2	223–225	74	$C_{10}H_8Cl_2N_2O_2S_2$	C 37.15	37.36	1 165 and 1 140	2.58	7.75–7.93
						H 2.48	2.66			
						N 8.67	8.50			
H (HCl)	″	SO_2	252–255†	—	—	—	—	—	—	—

*Picrate.
†Decomposes.

and of the alkali salt of the thiophenol instead of acidic thiophenol, facilitates the S_N reaction better than any other combination (I*c* and a thiophenol, I*b* and a thiophenol, or I*b* and the alkali salt of a thiophenol).

The amino sulfides III*c* (R″ = Cl or Cl_2) were acetylated to the corresponding compounds III*b* and oxidized by aqueous potassium permanganate solution (cf. ref. 4) to the 2-acetamido-5-phenylsulfonyl-4-methylthiazoles, which, on hydrolysis, gave the 2-amino-5-phenylsulfonyl-4-methylthiazoles IV (R″ = Cl or Cl_2). Complete oxidation of the sulfide group to the sulfone was inferred from an infrared spectrum[2] of the sulfone, which showed strong absorption (with splitting) in the region of 1 165 – 1 135 and 1 350 – 1 300 cm^{-1}, and not in the region of 1 060 – 1 030 cm^{-1} ($\nu_{S=O}$). Moreover, only the sulfur atom of the sulfide group in III*b* was oxidized to SO_2, and the ring sulfur or nitrogen atoms were not affected (as shown by the absence of strong $\nu_{S=O}$ and $\nu_{N\rightarrow O}$ absorption in the region of 1 290 – 1 250 cm^{-1}, and by the elemental analyses). Since the region of 1 350 – 1 300 cm^{-1} (ν_{SO_2}) contains many absorptions in the spectra of sulfides III*b* and III*c*, whereas the region of 1 165 – 1 135 cm^{-1} is almost clear, the absorptions in the latter region were judged to be characteristic of the compound, and are recorded in Table I (only the maximum absorption and not the lateral splitting). This was also proved by the independent synthesis of IV (R″ = 2′,4′-Cl_2) from I*c* and sodium 2,4-dichlorobenzenesulfinate, and by comparing its identity with that of the compound obtained by the oxidation method.

The infrared spectra of III*c* (R″ = Cl or Cl_2) consistently showed a strong band at 3 470 – 3 450 cm^{-1} (asymmetrical NH stretching) and another band of medium intensity around 3 275 cm^{-1} (symmetrical NH stretching), whereas the same bands appeared in the region of 3 420 and 3 290 cm^{-1}, respectively, in the spectra of IV (R″ = Cl or Cl_2). The nuclear magnetic resonance spectra of III*c* and IV in trifluoroacetic acid showed a singlet arising from the 4-Me protons and a multiplet attributable to the phenyl protons in the ratio of 3:4 for III*c* and IV (R″ = 2′-Cl), and 1:1 for the rest of the compounds (Table I). The amino protons appeared as a broad hump between δ 3.00 and 5.50, depending on the concentration of the compound. The paramagnetic shift of the methyl and phenyl protons in a sulfone with respect to its sulfide is attributed to the inductive effect of the electronegative sulfone group in the molecule.

EXPERIMENTAL[3]

o-Chloro-, 2,3-dichloro-, 2,4-dichloro-, 2,5-dichloro-, and 3,4-dichloro-thiophenol and 2-amino-4-methyl-5-bromothiazole were prepared by literature methods (7–12, respectively).

3,5-Dichlorothiophenol

To a solution of 3,5-dichloroaniline (16.2 g, 0.1 mole) in hydrochloric acid (60 ml, 1:1) that had been diazotized with sodium nitrite (7 g) in water (20 ml) was added, with stirring, a solution of potassium ethyl xanthate (30 g) in water (70 ml) at 70–80°; heating was continued for 1 h. The red oily complex that separated was added to an ethanolic solution of potassium hydroxide (15%, 150 ml) containing glucose (2 g), and the mixture was refluxed for 20 h. The solvent was removed, the residue acidified with 8 *N* sulfuric acid (250 ml), zinc dust (10 g) added, and the mixture heated for 30 min. The thiophenol that separated was dissolved in benzene and distilled, b.p. 125–130° at 12 mm, n_D^{25} 1.5680 (lit. (13) m.p. 50°).

Anal. Calcd. for $C_6H_4Cl_2S$: S, 17.88. Found: S, 18.05.

*2-Amino-5-phenylthio-4-methylthiazoles III*c *(R″ = Cl or Cl_2)*

General Method

To a solution of potassium hydroxide (1.17 g, 0.021 mole) in ethanol (25 ml) was added a chlorothiophenol (0.021 mole) under a nitrogen atmosphere, followed by a solution of I*c* (3.86 *g*, 0.02 mole) in ethanol (25 ml); then the mixture was heated under reflux for 1 h. The solvent was distilled off *in vacuo*, and the residue was triturated with ice-cold water (25 ml) and filtered. The product was washed with

[2]All infrared spectra were determined as Nujol mulls, and were compared with those of Bellamy (14).

[3]All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 337 spectrophotometer. Nuclear magnetic resonance spectra were determined on a Varian A-60 spectrometer, all signals being recorded in parts per million (δ) downfield from tetramethylsilane as an internal reference.

petroleum ether (10 ml, b.p. 40–60°), air-dried, and recrystallized from ethanol. The acetyl derivatives III*b* were prepared by heating III*c* (1 g) with acetic anhydride (10 ml) for 1 h; the product crystallized from acetic acid as colorless needles. The picrates were prepared by the addition of an ethanolic solution of picric acid to that of the amino sulfide (0.1 g), and were recrystallized from ethanol (Table I).

2-Amino-5-phenylsulfonyl-4-methylthiazoles IV (R″ = Cl or Cl_2)

General Method

To a solution of III*b* (1 g) (from above) in glacial acetic acid (20 ml) was added, with stirring, a solution of potassium permanganate (1 g) in the minimal quantity of water at 25–30°; stirring was continued for 1 h. Sulfur dioxide was passed through the reaction mixture until the solution was colorless; then the product was separated by filtration. The filtrate, on dilution with water, gave additional product. These acetates were recrystallized from ethanol, and were hydrolyzed to the amino sulfones IV by heating (0.5 g) in boiling ethanol (25 ml) containing hydrochloric acid (2 ml) for 2 h (when the mixture was cooled, the hydrochloride salt separated). The amino sulfones were recrystallized from ethanol (Table I).

2-Amino-5-(2′,4′-dichlorophenylsulfonyl)-4-methylthiazole

A mixture of sodium 2,4-dichlorobenzenesulfinate (2.33 g, 0.01 mole) and I*c* (1.93 g, 0.01 mole) in ethanol (50 ml) was refluxed for 2 h, and then filtered. The filtrate was concentrated to 20 ml and poured over crushed ice. The product (0.8 g) was crystallized from ethanol, m.p. 200–202°; the mixture melting point with the thiazole obtained by the oxidation method was 200–201°. The infrared spectra of the two samples were superimposable.

2-Amino-5-(4′-chlorophenylthio)-4-methylthiazole (IIIc, R″ = 4′-Cl) and 2-Amino-5-(4′-methylphenylthio)-4-methylthiazole (IIIc, R″ = 4′-CH_3)

A mixture of *p*-chlorothiophenol (5 g) and 2-acetamido-4-methyl-5-bromothiazole (I*b*) (3.86 g) was heated at 100–110° for 2 h under a nitrogen atmosphere; then the cooled product was suspended in water (100 ml) and separated by filtration. Since it was contaminated with 4,4′-dichlorodiphenyl sulfide and unreacted I*b*, it was hydrolyzed with 5 *N* hydrochloric acid and extracted with ether to remove the disulfide. The aqueous phase containing the hydrochloride of the amino sulfide and also some I*c* was made alkaline with 2 *N* ammonium hydroxide solution. The crude product was twice recrystallized from benzene as needles (0.75 g, 14%), m.p. 142–145° (lit. (6) m.p. 145°).

The 4′-methyl analogue was similarly prepared (0.8 g, 17%), m.p. 138–140° (lit. (6) m.p. 141°).

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