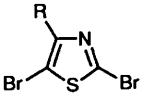
Azoles. Part 8.[1] Metallation and Bromine ⟶ Lithium Exchange Reactions of Polyhalogenothiazoles

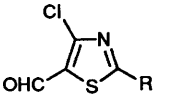
Salah Athmani, Andrew Bruce (in part) and Brian Iddon*
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, UK

2,4-Dichloro- and 2,4-dibromo-thiazole were deprotonated at position-5 with $LiNPr_2^i$ in THF at −78 °C and the resulting lithium compound was quenched with various reagents, to yield various trisubstituted thiazoles. 2,5-Dibromo-4-chlorothiazole reacted with n-butyllithium in THF at −78 °C at position-5 and the resulting lithium derivative gave 2-bromo-4-chloro-5-substituted thiazoles when quenched with the appropriate reagent. Both the 2- and 5-bromine-atoms were reactive in diethyl ether. 2,5-Dibromothiazole failed to deprotonate at position-4 under various reaction conditions, whereas treatment of 2,4,5-tribromothiazole with 1 mole equivalent of n-butyllithium in THF at −90 °C, followed by addition of dimethyl disulfide after 30 min, gave a high yield of the 2,5-bis(methylthio)-compound. The tribromo-compound was also treated with 1 mole equivalent of n-butyllithium or methyllithium under various reaction conditions and the products formed after hydrolysis were analysed by ^1H NMR spectroscopy. The 5-bromine-atom is the most reactive and greater selectivity is obtained with methyllithium.

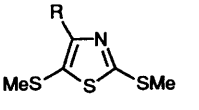
Many common organic compounds are readily poly- or per-brominated and the bromine atoms provide useful 'handles' for the introduction of other substituents *via* bromine ⟶ lithium exchange techniques.[2] Previously we have demonstrated that the bromine atoms in readily available 1-protected 2,4,5-tribromoimidazoles can be replaced stepwise in the order 2 ⟶ 5 ⟶ 4.[3–6] Similar work has been carried out with 1- and 2-protected dibromo-1,2,3-triazoles.[3] We now report an extension of our work to polyhalogenothiazoles.



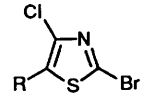
1 R = H
2 R = Cl
3 R = CF_3



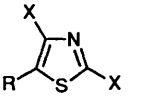
21 R = NMe_2
22 R = piperidino



23 R = Cl
24 R = Br



25 R = H
26 R = CHO
27 R = CO_2H
28 R = $C(OH)Ph_2$
29 R = $SiMe_3$



4 X = Cl, R = H
5 X = Br, R = H
6 X = R = Br
7 X = Cl, R = CHO
8 X = Cl, R = CO_2H
9 X = Cl, R = CO_2Et
10 X = Cl, R = CH(OH)Ph
11 X = Cl, R = $C(OH)Ph_2$
12 X = Cl, R = SMe
13 X = Cl, R = $SiMe_3$
14 X = Cl, R = $SnMe_3$
15 X = Br, R = CHO
16 X = Br, R = CO_2H
17 X = Br, R = $C(OH)Ph_2$
18 X = Br, R = SMe
19 X = Br, R = $SiMe_3$
20 X = Br, R = $SnMe_3$

Discussion

In diethyl ether at −78 °C, 2,4-dibromothiazole **5** reacts with n-butyllithium exclusively by bromine ⟶ lithium exchange at position-2,[7,8] whilst 2,5-dibromo-4-(trifluoromethyl)thiazole **3** is reported[9] to undergo bromine ⟶ lithium exchange with n-butyllithium in hexane at −60 °C at both position-2 and position-5.

Similarly, 2-bromothiazole (more readily available than the parent heterocycle)[7,8,10–13] and its derivatives[7,8,14] react with n-butyllithium in diethyl ether at low temperatures to give the corresponding thiazol-2-yllithium compound. With $LiNPr_2^i$ (LDA), 2-bromothiazole is deprotonated at position-5, to give 2-bromothiazol-5-yllithium.[14,15] By contrast with 5-bromothiazole and its derivatives, which undergo bromine ⟶ lithium exchange reactions with n-butyllithium[8,11,12] or phenyllithium[16] without difficulty, 4-bromothiazole is metallated with n-butyllithium at position-2.[8] However, a number of substituted 4-bromothiazoles undergo bromine ⟶ lithium exchange reactions to yield the corresponding thiazol-4-yllithium compound.[7,12,13] The difference in the reactivities of bromine atoms at C-4 and C-5 in imidazoles[4–6] and thiazoles can be attributed to the effect of a nitrogen lone pair on N-3 (the 'ALP effect'[17]) which destabilises a developing negative charge at C-4.

2-Aminothiazole and thiazolidine-2,4-dione are commercially available. Bromination of the former compound yields 2-amino-5-bromothiazole[18] which can be converted into 2,5-dibromothiazole **1** *via* diazotisation and treatment of the resulting diazonium salt with sodium bromide in the presence of a copper salt (Sandmeyer reaction).[18] Treatment of thiazolidine-2,4-dione with either phosphoryl trichloride or phosphoryl tribromide (an expensive reagent) gives 2,4-dichloro- **4** or 2,4-dibromo-thiazole **5**, respectively.[19] The dibromo compound is unstable, losing bromine slowly on storage at ambient temperature. Bromination of 2,4-dichlorothiazole **4** with bromine in acetic acid gives 2,5-dibromo-4-chlorothiazole **2**,[20] whilst further bromination of the 2,4-dibromo compound **5** similarly gives 2,4,5-tribromothiazole **6**.[20] We chose to study the metallation and bromine ⟶ lithium exchange reactions of these readily available starting materials particularly with the synthesis of 4-halogenothiazole-5-carbaldehydes in mind. These aldehydes are key intermediates for the synthesis of thienothiazoles, through their reaction with ethyl 2-mercaptoacetate (see ref. 1 for the analogous synthesis of thienoimidazoles), and several novel heterocyclic systems.

2,4-Dichloro- **4** and 2,4-dibromo-thiazole **5** were deprotonated at position-5 with LDA in anhydrous tetrahydrofuran (THF) at −78 °C and the resulting thiazol-5-yllithium compounds were quenched with either carbon dioxide, ethyl chloroformate, benzaldehyde, benzophenone, chlorotrimethylsilane, or chlorotrimethylstannane, to give compounds **8–11** and **13** and **14**, or **16**, **17**, **19** and **20**, respectively (see Table 1 for details) (compounds **14** and **20** are very unstable; consequently their purification and analysis proved extremely difficult). In an attempt to prepare 2,4-dichlorothiazole-5-carbaldehyde **7** 2,4-dichlorothiazol-5-yllithium was quenched with *N*,*N*-dimethylformamide (DMF). The product isolated, however, was shown (see Experimental section) to be 4-chloro-2-(dimethylamino)-thiazole-5-carbaldehyde **21**. Quenching of this thiazol-5-yllithium compound with *N*-formylpiperidine gave an analogous product **22**. Since the completion of our work Sawhney and Wilson[21] have reported the synthesis of a series of 2-(dialkylamino)thiazole-5-carbaldehydes by this method. A final quench with water rather than acid is essential if compounds such as **21** and **22** are to be isolated.[21] These reactions proceed *via* initial formation of 2,4-dichlorothiazole-5-carbaldehyde **7**, which undergoes nucleophilic displacement of its activated 2-chlorine atom with the liberated secondary amine. 2,4-Dichlorothiazole-5-carbaldehyde **7** did not react with *N*,*N*-dimethylformamide (neat) at ambient temperature during 5 h, nor did 2,4-dichlorothiazole **4**.[22,23] When 2,4-dibromothiazol-5-yllithium was quenched with DMF, then acid was added to the reaction mixture, it gave 2,4-dibromothiazole-5-carbaldehyde **15**.

When 2,4-dichloro- and 2,4-dibromo-thiazol-5-yllithium were quenched with dimethyl disulfide, they gave compound **23** or **24**, respectively, presumably through reaction of the initially formed 2,4-dihalogeno-5-(methylthio)thiazole, **12** or **18**, with the liberated methylthiolate (MeS^-) anion.

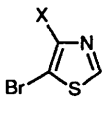
Successive treatment of 2,5-dibromothiazole **1** with LDA in THF (at 0 °C) and dimethyl disulfide resulted in a quantitative return of starting material. A previous attempt to metallate 1-(ethoxymethyl)-5-methylthio-2-(phenylthio)imidazole in position-4 with LDA in THF at −70 °C similarly failed but metallation of this compound was achieved with potassium diisopropylamide–lithium *t*-butoxide (KDA).[24] However, KDA failed to metallate 2,5-dibromothiazole in position-4; again starting material was recovered.

When 2,5-dibromo-4-chlorothiazole **2** was treated with 1 mole equivalent of n-butyllithium in *diethyl ether* at −78 °C the product composition, after quenching of the reaction mixture with water, was dependent on time, presumably as a result of transmetallation reactions occurring after generation of the kinetically controlled initial product(s). Both the 2- and 5-bromine atoms are reactive. After 12 s, the yellow oil obtained was shown by ^{1}H NMR spectroscopic analysis to be a mixture containing 5-bromo-4-chloro- **30**, 2-bromo-4-chloro- **25**, and 4-chloro-thiazole **32** (proportions 7:10:0.9). As time elapsed the amount of 4-chlorothiazole **32** (with two doublets, J 2.0 Hz, at δ 7.07 and 8.67[25]) increased until, after 30 min, it became the exclusive hydrogen-bearing product. 1-Protected tribromoimidazoles (in Et_2O)[3,5] and 2,5-dibromo-4-(trifluoromethyl)thiazole **3** (in hexane)[9] similarly react with 1 mole equivalent of n-butyllithium at both the 2- and 5-positions.

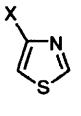
However, when 2,5-dibromo-4-chlorothiazole **2** was treated with 1 mole equivalent of n-butyllithium, but in *THF* (at −90 °C) instead of diethyl ether as the solvent, and the reaction mixture was quenched with water, the only isolable hydrogen-bearing product was 2-bromo-4-chlorothiazole **25** (δ at 7.13 for 5-H). 2-Bromo-4-chlorothiazol-5-yllithium also reacted with carbon dioxide, benzophenone, and chlorotrimethylsilane, to give (after hydrolysis) compounds **27–29**, respectively. Quenching of this lithium derivative with either DMF or *N*-formylpiperidine failed to yield any 2-bromo-4-chlorothiazole-5-carbaldehyde **26**; these reactions gave only intractable black residues. Dimethyl disulfide as the quenching reagent gave compound **23**, identical with the sample prepared as described before.

When 2,4,5-tribromothiazole **6** was treated with 1 mole equivalent of n-butyllithium in diethyl ether, the product composition (by ^{1}H NMR spectroscopy), after treatment of the resulting mixture with 2 mol dm^{-3} hydrochloric acid, was shown to be dependent on time and temperature. After 10 min at −78 °C, a mixture of 2,4-dibromo- **5** and 4-bromo-thiazole **33** (ratio 10:5.5) was obtained. After 30 min at −78 °C, the ratio of these products changed to 3:10 whilst, after 10 min at −90 °C, a mixture of 2,4-dibromo- **5**, 4,5-dibromo- **31**, and 4-bromo-thiazole **33** (proportions 10:4.55:5.45) was obtained. When 2,4,5-tribromothiazole **6** was treated successively at −78 °C with 1 mole equivalent each of n-butyllithium and dimethyl disulfide (after 30 min), 4-bromo-2,5-bis(methylthio)thiazole **24** was obtained in 71% yield, identical with the sample prepared as described before from 2,4-dibromothiazole **5**.

As is the case with 1-protected tribromoimidazoles,[3,5,6] 2,4,5-tribromothiazole **6** was found to be more selective in its reactions with *methyl*lithium, in diethyl ether at −90 °C. After 20 min, quenching of the reaction mixture with 2 mol dm^{-3} hydrochloric acid gave a mixture of 2,4-dibromo- **5** and 4-bromothiazole **33** (ratio 10:1). Unlike 1-protected tribromoimidazoles, which react with ethylmagnesium bromide selectively at the 2-bromine-atom,[3,5] 2,4,5-tribromothiazole **6** failed to react with this reagent in THF, either at ambient (during 5 h) or reflux temperature (overnight); starting material was recovered in each case.



30 X = Cl
31 X = Br



32 X = Cl
33 X = Br

Experimental

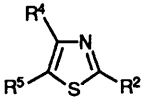
IR spectra were recorded for liquid films or Nujol mulls between sodium chloride plates with a Perkin-Elmer 297 or 1710 FT spectrometer; ^{1}H NMR spectra were recorded with a Perkin-Elmer R32 (90 MHz) or a Bruker AC300 (300.13 MHz) instrument with tetramethylsilane as internal standard; low-resolution mass spectra were obtained using a Finnigan 4500 machine, and high-resolution mass spectra were recorded with a Kratos Concept 1S mass spectrometer, both operating at 70 eV. Reported molecular weights (obtained by low-resolution mass spectrometry) are given for the isotopes ^{79}Br, ^{35}Cl and ^{120}Sn. Isotopic abundance ratios were as expected for the compounds containing these elements.

Camlab Polygram silica G/UV_{254} plates were used for TLC, flash chromatography was carried out on silica gel 60 (Merck 9385), and medium-pressure column chromatography on silica gel (Merck 7736).

Light petroleum had a boiling range of 60–80 °C unless stated otherwise. Ether refers to diethyl ether. Solvents and reagents were dried by standard procedures. In all cases organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure on a rotary evaporator.

Small-scale distillations were carried out with a Kugelrohr microdistillation apparatus and the 'b.p.' temperatures recorded are those of the oven at the time of distillation. M.p.s were recorded with a Buchi m.p. apparatus and are uncorrected.

Table 1 Polysubstituted thiazoles prepared by metallation and bromine ⟶ lithium exchange reactions of polyhalogenothiazoles



Compound	R^2	R^4	R^5	Quench reagent	Yield (%)	M.p. or B.p.[a] (°C)	ν_{max}/cm^{-1} (Assignment)	^{1}H NMR data (δ-value) (Assignment)	Found (%) C	H	N	Found M$^+$	Formula	Required (%) C	H	N	Required M
8	Cl	Cl	CO_2H	CO_2	40	117–118 (A)[b]	1699 (CO) and 2854–3586br (OH)					196.9114	$C_4HCl_2NO_2S$				196.9105
9	Cl	Cl	CO_2Et	$ClCO_2Et$	66	156–157 (B)	1740 (CO)	1.35 (3 H, t, Me) and 4.36 (2 H, q, CH_2)	32.3	2.3	5.7	225	$C_6H_5Cl_2NO_2S$	32.0	2.2	6.2	225
10	Cl	Cl	CH(OH)Ph	PhCHO	74	150 at 0.2 mmHg	3300–3400br (OH)	3.32 (1 H, s, OH). 6.02 (1 H, s. CH) and 7.34–7.40 (5 H, m. ArH)	46.4	2.9	5.3	259	$C_{10}H_7Cl_2NO_2S$	46.2	2.7	5.4	259
11	Cl	Cl	$C(OH)Ph_2$	Ph_2CO	25	128–129 (C)[c]	3400–3550br (OH)	3.62 (1 H, s, OH) and 7.20–7.50 (10 H, m. ArH)	57.2	3.2	4.0	335	$C_{16}H_{11}Cl_2NOS$	57.2	3.3	4.2	335
13	Cl	Cl	$SiMe_3$	$ClSiMe_3$	71	90 at 0.2 mmHg		0.35 (9 H, s, $SiMe_3$)	31.3	4.05	6.2	225	$C_6H_9Cl_2NSSi$	31.9	4.0	6.2	225
14	Cl	Cl	$SnMe_3$	$ClSnMe_3$	69	55–57 (D)		0.43 (9 H, s, $SnMe_3$)				317	$C_6H_9Cl_2NSSn$				317
15	Br	Br	CHO	DMF	54	80–81 (E)	1661 (CO)	9.79 (1 H, s, CHO)	17.1	0.2	5.0	269	C_4HBr_2NOS	17.7	0.4	5.2	269
16	Br	Br	CO_2H	CO_2	68	178–179 (A)	1699 (CO) and 2854–3586br (OH)		17.2	0.5	4.3	285	$C_4HBr_2NO_2S$	16.7	0.35	4.9	285
17	Br	Br	$C(OH)Ph_2$	Ph_2CO	46	122–123 (D)	3300–3583br (OH)	3.72br (1 H. s, OH) and 7.34 (10 H, m. ArH)	45.3	2.5	3.1	423	$C_{16}H_{11}Br_2NOS$	45.2	2.6	3.3	423
19	Br	Br	$SiMe_3$	$ClSiMe_3$	66	130 at 2.0 mmHg		0.37 (9 H, s, $SiMe_3$)				312.8571	$C_6H_9Br_2NSSi$				312.8593
20	Br	Br	$SnMe_3$	$ClSnMe_3$	48	79–80 (D)		0.37 (9 H, s. $SnMe_3$)				404.7845	$C_6H_9Br_2NSSn$				404.7845
21	NMe_2	Cl	CHO	DMF	76	105–107 (D)[c,d]	1650 (CO)	3.19 (6 H. s. NMe_2) and 9.73 (1 H, s. CHO)	38.2	3.6	14.2	190	$C_6H_7ClN_2OS$	37.9	3.7	14.7	190
22	Piperidino	Cl	CHO	*N*-Formylpiperidine	71	91–92 (D)	1661 (CO)	1.68 (6 H, m, CH_2), 3.57br (4 H, m, CH_2), and 9.73 (1 H, s, CHO)	46.6	4.8	12.3	230	$C_9H_{11}ClN_2OS$	46.8	4.8	12.2	230
23	SMe	Cl	SMe	Me_2S_2	42,[e] 78[f]	Yellow oil[c,g]		2.38 (3 H. s. 5-SMe) and 2.64 (3 H, s, 2-SMe)	28.6	2.9	6.5	211	$C_5H_6ClNS_3$	28.4	2.8	6.6	211
24	SMe	Br	SMe	Me_2S_2	76,[h] 71[i]	Yellow oil[g]		2.39 (3 H, s, 5-SMe) and 2.64 (3 H. s, 2-SMe)	23.9	2.45	5.4	255	$C_5H_6BrNS_3$	23.4	2.4	5.5	255
27	Br	Cl	CO_2H	CO_2	47	160–161 (A)	1680 (CO) and 2700–3310br (OH)					240.8597	$C_4HBrClNO_2S$				240.8600
28	Br	Cl	$C(OH)Ph_2$	Ph_2CO	59	136–138 (E)	3296–3582br (OH)	3.58 (1 H. s. OH) and 7.30–7.42 (10 H, m, ArH)	50.65	3.0	3.5	379	$C_{16}H_{11}BrClNOS$	50.5	2.9	3.7	379
29	Br	Cl	$SiMe_3$	$ClSiMe_3$	61	95 at 0.5 mmHg		0.34 (9 H. s. $SiMe_3$)	27.0	3.5	5.2	269	$C_6H_9BrClNSSi$	26.6	3.35	5.2	269

[a] Recrystallisation solvents: A water; B ethanol: C light petroleum–ethyl acetate; D light petroleum; E light petroleum (40–60 °C); Liquids distilled using Kugelrohr distillation apparatus. [b] Synthesized[20] as a minor isomer by treatment of 2,4,5-trichlorothiazole with BuLi followed by carbonation of the reaction mixture (no details, including absence of a m.p.) –the major product was 4,5-dichlorothiazole-2-carboxylic acid. [c] Andrew Bruce. Honours BSc. Degree in Applied Chemistry final year Dissertation. 1989. [d] Lit.,[21] yield 84% and m.p. 108 °C (from light petroleum–ethyl acetate). [e] From 2,4-dichlorothiazole. [f] From 2,5-dibromo-4-chlorothiazole. [g] Purified by column chromatography on silica. Light petroleum (40–60 °C) eluted the product. [h] From 2,4-dibromothiazole. [i] From 2,4,5-tribromothiazole.

Microanalytical (for C, H and N) results were supplied by Butterworth Laboratories Ltd of Teddington.

The following compounds were prepared by literature procedues: 2-amino-5-bromothiazole (61%), m.p. 95–96 °C (from toluene) (lit.,[11] 34% and m.p. 93–94 °C, lit.,[18] 59% and m.p. 80 °C); 2,5-dibromothiazole **1** (50%), m.p. 44–46 °C (from EtOH) (lit.,[18] 65% and m.p. 46–47 °C); 2,4-dichlorothiazole **4** (65%), m.p. 42–43 °C (from aq. EtOH) (lit.,[19] 51% and m.p. 42–43 °C); 2,4-dibromothiazole **5** (38.5%), m.p. 81–82 °C (sublimed at 90 °C and 1.00 mmHg) (lit.,[19] 60% and m.p. 82 °C); 2,5-dibromo-4-chlorothiazole **2** (58%), b.p. 78 °C at 1.1 mmHg (lit.,[20] 73% and b.p. 78 °C at 1.1 mmHg); and 2,4,5-tribromothiazole **6** (87%), m.p. 36 °C (sublimed at 45 °C and 0.2 mmHg) (lit.,[20] 87% and m.p. 36 °C).

Reactions of 2,4-*Dichloro-* **4** *and* 2,4-*Dibromo-thiazole* **5** *with LDA.—General reaction.* n-Butyllithium in hexane (1.1 mol equiv.) was syringed dropwise through a rubber septum cap into a round-bottomed flask containing a stirred solution of diisopropylamine (1.1 mol equiv.) in anhydrous THF (15 cm^3) at −78 °C (internal temperature) under nitrogen and the resulting solution was allowed to warm up to 0 °C, then cooled again to −78 °C. A solution of either 2,4-dichloro- **4** or 2,4-dibromo-thiazole **5** (0.5 g) in anhydrous THF (10 cm^3) was added dropwise at such a rate that the temperature did not exceed −70 °C. The resulting solution was stirred at −78 °C for 30 min. Then the quenching reagent (1.1 mol equiv.) was syringed in dropwise as a solution in THF (10 cm^3) and the mixture was allowed to warm up to ambient temperature. Water (10 cm^3) was added and extraction with ether (3 × 50 cm^3) gave the crude product. Solids were crystallised whilst liquids were either distilled (Kugelrohr apparatus) or purified by chromatography on a silica column. For the synthesis of carboxylic acids an excess of Cardice was added to the reaction mixture prior to quenching with water. Addition of 10% hydrochloric acid caused precipitation of the crude products. After quenching with chlorotrimethylsilane or chlorotrimethylstannane, reaction mixtures were washed with saturated aq. sodium hydrogen carbonate (30 cm^3) before extraction with ether.

Details of the products are given in Table 1.

Reactions of 2,5-*Dibromo*-4-*chlorothiazole* **2** *with* n-*Butyllithium.—General reaction.* 1.6 mol dm^{-3} n-Butyllithium in hexane (1.13 cm^3, 1.8 mmol) was syringed dropwise through a rubber septum cap into a round-bottomed flask containing a stirred solution of 2,5-dibromo-4-chlorothiazole **2** (0.5 g, 1.8 mmol) in anhydrous THF (10 cm^3) at −90 °C (internal temperature) under nitrogen and the resulting mixture was stirred at this temperature for a further 30 min. The quenching reagent (1.8 mmol) was added as a solution in THF (10 cm^3) and the mixture was allowed to warm up slowly to ambient temperature. After quenching of the mixture with an excess of 2 mol dm^{-3} hydrochloric acid, it was treated as described in the previous general reaction.

Details of the products are given in Table 1.

Attempted Deprotonation of 2,5-*Dibromothiazole* **1**.—(*a*) *With LDA at* −90 °C. 1.6 mol dm^{-3} n-Butyllithium in hexane (1.40 cm^3, 2.25 mmol) was syringed through a rubber septum cap into a round-bottomed flask containing a stirred solution of diisopropylamine (0.23 g, 0.32 cm^3, 2.25 mmol) in anhydrous THF (10 cm^3) cooled at −90 °C (internal temperature) under nitrogen and the resulting mixture was stirred for 30 min at this temperature. A solution of 2,5-dibromothiazole (0.5 g, 2.06 mmol) in THF (10 cm^3) was added and the mixture was stirred at −90 °C for a further 30 min. Then a solution of dimethyl disulfide (0.21 g, 0.25 cm^3, 2.25 mmol) in THF (10 cm^3) was added and the mixture was allowed to warm up slowly to ambient temperature. Work-up as described before gave only starting material (100% recovery), identified by its m.p. and IR and ^1H NMR spectra.

(*b*) *With LDA at* 0 °C. Deprotonation was carried out as described in (a) but at 0 °C. Work-up, after quenching with dimethyl disulfide, as before gave a quantitative recovery of starting material.

(*c*) *With KDA at* −78 °C. Deprotonation was carried out as described in (a) but with KDA[24] instead of LDA and at −78 °C. Work-up, after quenching with dimethyl disulfide, as described in (a) gave only starting material (100% recovery).

Reactions of 2,4,5-*Tribromothiazole* **6** *with n-Butyllithium or Methyllithium.*—(a) 1.3 mol dm^{-3} n-Butyllithium in hexane (0.71 cm^3, 0.93 mmol) was dissolved in anhydrous THF (15 cm^3) and added dropwise to a stirred solution of 2,4,5-tribromothiazole (0.3 g, 0.93 mmol) in anhydrous THF (10 cm^3) at −78 or −90 °C (internal temperature) under nitrogen and the resulting mixture was stirred for a further 10 or 30 min at this temperature. Then an excess of 2 mol dm^{-3} hydrochloric was added and extraction with ether (3 × 50 cm^3) gave the crude product, which was analysed by ^1H NMR spectroscopic analysis. See Discussion section for results.

(b) The above reaction was repeated but using methyllithium in place of the n-butyllithium (reaction temperature −90 °C; the time before hydrolysis was 20 min). The result is given in the Discussion section.

(c) The experiment described in (a) was repeated but the reaction mixture was quenched (after 30 min at −90 °C) with a solution of dimethyl disulfide (0.1 g, 1.06 mmol) in anhydrous THF (10.0 cm^3), then allowed to warm up slowly to ambient temperature. An excess of water was added and extraction with ether (3 × 50 cm^3) gave the crude product, which was chromatographed on silica. Light petroleum (40–60 °C) eluted 4-bromo-2,5-bis(methylthio)thiazole **24** as a yellow oil (0.17 g, 71%), identical with the sample prepared as described before.

Attempted Reactions of 2,4,5-*Tribromothiazole* **6** *with Ethylmagnesium Bromide.*—(a) A solution of 2,4,5-tribromothiazole (0.3 g, 0.93 mmol) in anhydrous THF (10 cm^3) was added dropwise to a stirred solution of ethylmagnesium bromide [prepared from magnesium (0.023 g, 0.93 mg-atom) and bromoethane (0.1 g, 0.93 mmol)] in anhydrous THF (20 cm^3) at ambient temperature and the resulting mixture was stirred for a further 5 h. Then 2 mol dm^{-3} hydrochloric acid (10 cm^3) was added and extraction of the product with ether (3 × 50 cm^3) gave starting material (80% recovery).

(b) The experiment described in (a) was repeated but the reaction mixture was heated under reflux overnight before hydrolysis. Work-up gave only starting material (80% recovery).

Acknowledgements

We thank the Algerian Government for financial support (to S. A.), Mrs. Ruth Howard for recording the low-resolution mass spectra, Mrs. Valerie Boote (University of Manchester) for recording the high-resolution mass spectral data, and Mr. M. A. Stuckey for recording ^1H NMR spectra at 300 MHz.

References

1 Part 7, B. Iddon, N. Khan and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1987. 1457.
2 B. Iddon and B. J. Wakefield, in *Bromine Compounds: Chemistry and Applications*. ed. D. Price. B. Iddon and B. J. Wakefield. Elsevier, Amsterdam, 1988. ch. 4. p. 181.
3 B. Iddon, in *Studies in Organic Chemistry 35: Chemistry of Heterocyclic Compounds*. ed. J. Kovác and P. Zálupsky, Elsevier. Amsterdam, 1988. p. 24.

4 B. Iddon, *Heterocycles*, 1985, **23**, 417.
5 B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1445.
6 B. Iddon and N. Khan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1453.
7 A. Dondoni, A. R. Mastellari, A. Medici, E. Negrini and P. Pedrini, *Synthesis*, 1986, 757.
8 A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *J. Org. Chem.*, 1988, **53**, 1748.
9 P. T. Kaye, G. D. Meakins, C. Willbe and P. R. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2335.
10 A. Medici, P. Pedrini and A. Dondoni, *J. Chem. Soc., Chem. Commun.*, 1981, 655.
11 H. C. Beyerman, P. H. Berben and J. S. Bontekoe, *Recl. Trav. Chim. Pays-Bas*, 1954, **73**, 325.
12 R. P. Kurkjy and E. V. Brown, *J. Am. Chem. Soc.*, 1952, **74**, 6260.
13 A. Dondoni, G. Fantin, M. Fogagnolo, A Medici and P. Pedrini, *Synthesis*, 1987, 998.
14 A. R. Katritzky, K. S. Laurenzo and D. I. Relyea, *Can. J. Chem.*, 1988, **66**, 1617.
15 S. C. Dillender, T. D. Greenwood, M. S. Hendi and J. F. Wolfe, *J. Org. Chem.*, 1986, **51**, 1184.
16 B. M. Mikhailov and V. P. Bronovitskaya, *Zh. Obshch. Khim.*, 1956, **26**, 66 (*Chem. Abstr.*, 1956, **50**, 13874).
17 K. L. Kirk, *J. Heterocycl. Chem.*, 1985, **22**, 57.
18 P. Roussel and J. Metzger, *Bull. Soc. Chim. Fr.*, 1962, 2075 (see also ref. 7).
19 P. Reynaud, M. Robba and R. C. Moreau, *Bull. Soc. Chim. Fr.*, 1962. 1735.
20 F. E. Herkes and T. A. Blazer, *J. Heterocycl. Chem.*, 1976, **13**, 1297.
21 I. Sawhney and J. R. H. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1990, 329.
22 L. Joseph and A. H. Albert, *J. Heterocycl. Chem.*, 1966, **3**, 107.
23 J. J. D'Amico, S. T. Webster, R. H. Campbell and C. E. Twine, *J. Org. Chem.*, 1965, **30**, 3618.
24 B. Iddon and B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1983, 279; *J. Chem. Soc., Chem. Commun.*, 1981, 1095.
25 E. J. Vincent, R. Phan-Tan-Luu, J. Metzger and J. M. Surzur, *Bull. Soc. Chim. Fr.*, 1966, 3524.

Paper 1/04859G
Received 20*th September* 1991
Accepted 10*th October* 1991