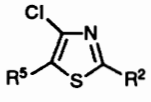
Azoles. Part 9.[1] Synthesis of Derivatives of Thieno[2,3-*d*]thiazole, 4*H*-Pyrrolo-[2,3-*d*]thiazole, 2*H*-Pyrazolo[3,4-*d*]thiazole and Isoxazolo[3,4-*d*]thiazole from Thiazolidine-2,4-dione

Salah Athmani, Mahmoud F. Farhat and Brian Iddon*
The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT, UK

The aldehyde group of 2,4-dichlorothiazole-5-carbaldehyde was protected and the chlorine atom at position 2 was replaced by hydrogen and a methylthio group, *via* Cl ⟶ Li exchange, to give 4-chlorothiazole-5-carbaldehyde and its 2-methylthio derivative, respectively. Ethyl 2-mercaptoacetate reacted with 4-chlorothiazole-5-carbaldehydes to give thieno[2,3-*d*]thiazoles. Saponification of ethyl thieno[2,3-*d*]thiazole-5-carboxylate and attempted decarboxylation of the resulting acid failed to yield enough of the parent thieno[2,3-*d*]thiazole to allow full characterisation owing to its high volatility.

4-Azidothiazole-5-carbaldehydes were prepared by nucleophilic displacement of the chlorine atom in the corresponding 4-chlorothiazole-5-carbaldehyde and converted into alkenes and Schiff's bases by standard procedures. On being heated in toluene these afforded the corresponding 4*H*-pyrrolo-[2,3-*d*]thiazole or 2*H*-pyrazolo[3,4-*d*]thiazole. Isoxazolo[3,4-*d*]thiazole and its 2-methylthio derivative, both unstable, were obtained by heating the corresponding 4-azidothiazole-5-carbaldehyde in bromobenzene.

A good yield (63%) of 2,4-dichlorothiazole-5-carbaldehyde **1** is obtained when commercially available thiazolidine-2,4-dione is subjected to Vilsmeier formylation reaction.[2] In this paper we report how this aldehyde serves as a valuable reactive intermediate for the synthesis of the title compounds.



1 R^2 = Cl, R^5 = CHO

2 R^2 = Cl, R^5 = $O(CH_2)_2OCH$

3 R^2 = Li, R^5 = $O(CH_2)_2OCH$

4 R^2 = H, R^5 = CHO

5 R^2 = SMe, R^5 = CHO

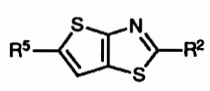
6 R^2 = $(CH_2)_2NMe(CH_2)_2N$, R^5 = CHO

7 R^2 = NMe_2, R^5 = CHO

8 R^2 = $CH_2(CH_2)_4N$, R^5 = CHO

Since all the reactions we planned to carry out with the carbaldehyde **1** involved nucleophilic displacement of the formyl-activated chlorine atom at position 4 and in view of the known[3] high reactivity of 2-chlorothiazoles towards nucleophiles, it seemed sensible to first remove the chlorine atom at position 2 in order to avoid competing reactions. This was achieved through conversion of aldehyde **1** into its ethylene acetal **2** (97% yield) and treatment of the protected aldehyde with butyllithium in tetrahydrofuran (THF) at −78 °C, which gave the 2-lithiated derivative **3**. Treatment of this with either hydrochloric acid or dimethyl disulfide gave 4-chlorothiazole-5-carbaldehyde **4** (78%) and 4-chloro-2-methylthiothiazole-5-carbaldehyde **5** (59%), respectively. The fact that the 2-chlorothiazole **2** undergoes a Cl ⟶ Li exchange reaction is noteworthy since such reactions are rare.

Aromatic aldehydes can be protected *in situ via* the formation

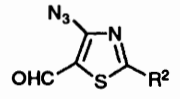


9 R^2 = H, R^5 = CO_2Et

10 R^2 = NMe_2, R^5 = CO_2Et

11 R^2 = H, R^5 = CO_2H

12 R^2 = R^5 = H



13 R^2 = H

14 R^2 = SMe

15 R^2 = $CH_2(CH_2)_4N$

of α-amino alkoxides, *e.g.* with lithium 4-methylpiperazide.[4] However, when the carbaldehyde **1** was treated with this reagent prior to the addition of butyllithium, it gave the product **6** (52% yield) of nucleophilic displacement.

With ethyl 2-mercaptoacetate in ethanol in the presence of sodium ethoxide, the 4-chlorothiazole **4** was converted into the thieno[2,3-*d*]thiazole-5-carboxylate **9** in 52% yield. 2-Dimethylaminothieno[2,3-*d*]thiazole-5-carboxylate **10** (52%) was prepared similarly from 2-dimethylaminothiazole-5-carbaldehyde **7**.[1]

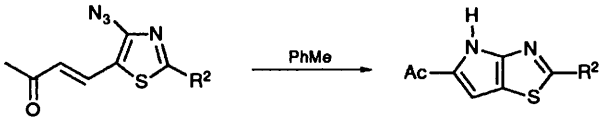
Saponification of ester **9** gave acid **11** which decomposed slowly on storage at ambient temperature. Attempted decarboxylation of a fresh sample of this acid **11** in the presence of copper powder afforded a yellow oil which we found extremely difficult to handle due to its high volatility. Paulmier and Outurquin[5] have reported that they were unable to fully characterise thieno[2,3-*d*]thiazole **12** because of its high volatility. They prepared it by deamination of 2-aminothieno[2,3-*d*]thiazole which, in turn, was prepared starting from 2-nitro-3-thiocyanatothiophene.[5] Isoxazolo[4,3-*b*]thiophene similarly is reported[6] to be highly volatile.

Most thieno[2,3-*d*]thiazoles reported previously have been synthesised from thiophene starting materials.[5,7–18] Only one, as far as we are aware, has been prepared from a thiazole and this was reported since our work was completed.[19]

The 4-chlorothiazole-5-carbaldehydes **4**, **5** and **8**[1] reacted with sodium azide in dimethyl sulfoxide (DMSO) to give azides **13** (80% yield), **14** (75%) and **15** (72%), respectively. Surprisingly, when the carbaldehyde **1** was treated similarly with sodium azide, azidodechlorination occurred as well as

displacement of the chlorine atom at position 4, to give the 4-azidothiazole **13** in 22% yield.

Azides **13** and **14** condensed with acetone in the presence of base to give the *trans*-alkenes **16** (43%) and **17** (52%) which, when heated in toluene, were converted into the corresponding 4*H*-pyrrolo[2,3-*d*]thiazole, **18** (72%) and **19** (87%), respectively (Scheme 1). We can find only one synthesis of this ring system in the literature, starting from a pyrrole derivative.[20]

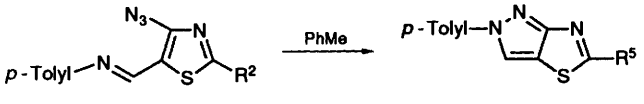


16 R^2 = H
17 R^2 = SMe

18 R^2 = H
19 R^2 = SMe

Scheme 1

The Schiff's bases **20** (85% yield) and **21** (96%) were prepared by heating an intimate mixture of the appropriate 4-azidothiazole-5-carbaldehyde and *p*-toluidine to the m.p. of the amine, when condensation occurred in the melt. Chromatography of the crude products gave a high yield of the Schiff's base which, when heated in toluene, was converted into the corresponding 2*H*-pyrazolo[3,4-*d*]thiazole, **22** (80% yield) or **23** (85%), respectively (Scheme 2). Only with one exception, a reference which describes the synthesis of a highly saturated derivative,[21] the previously reported syntheses of this ring system start with a pyrazole derivative.[22–27]

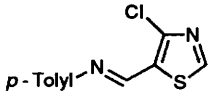


20 R^2 = H
21 R^2 = SMe

22 R^5 = H
23 R^5 = SMe

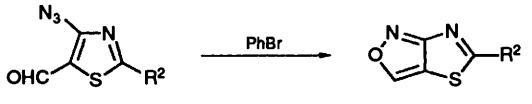
Scheme 2

The Schiff's base **24** was prepared also in 76% yield from the carbaldehyde **4** by a standard procedure but it failed to react with sodium azide in DMSO.



24

When the 5-carbaldehyde **13** was heated in refluxing bromobenzene it gave the hitherto unknown isoxazolo[3,4-*d*]thiazole **25** in 61% yield (Scheme 3). This compound decomposes on being kept in air at ambient temperature but it can be kept under nitrogen in a refrigerator. Similarly, carbaldehyde **14** decomposed with loss of nitrogen in refluxing bromobenzene, presumably to give the isoxazolothiazole **26**, but this product decomposed too rapidly in air and we were not able to characterise it.



13 R^2 = H
14 R^2 = SMe

25 R^2 = H
26 R^2 = SMe

Scheme 3

Most of the azides now reported are unstable to heat. Some decomposition occurred when they were recrystallised from light petroleum (b.p. 40–60 °C) and, consequently, it was not possible to obtain microanalytical data or, in the case of compound **13**, an accurate mass measurement of the parent molecular ion in its mass spectrum. Nevertheless, the IR and ^{1}H NMR spectroscopic data of these azides are consistent with the structures given (see Experimental section for details). Attempted syntheses of the Schiff's bases **20** and **21** in a solvent, *e.g.* methanol, resulted in evolution of nitrogen as the azide starting material decomposed; hence the need for the solid phase technique already described.

A considerable amount of work has been carried out on the syntheses of 2-azidothiazoles and their azido–tetrazole tautomerism.[28] However, 5-azidothiazoles appear to be unknown whilst there appears to be only one earlier reference[29] to 4-azidothiazoles in the literature, namely the syntheses of 4-azido-5-(2-furyl)-2-methylthiothiazole and 4-azido-2-methylthio-5-(4-nitrophenyl)thiazole from the corresponding amines *via* diazotisation and treatment of the resulting diazonium salt with sodium azide.

Experimental

The instruments used and the general experimental conditions were the same as those given in Part 8.[1] *J* Values are in Hz.

2,4-*Dichlorothiazole-5-carbaldehyde* **1**.—*N*,*N*-Dimethylformamide (32.1 g, 0.44 mmol) was added dropwise during 15 min to a stirred suspension of thiazolidine-2,4-dione (46.8 g, 0.40 mol) in phosphoryl chloride (368 g, 2.4 mol) at 10–20 °C. After the addition the resulting mixture was kept at ambient temperature for 1 h, after which it was heated to 80–90 °C and stirred at this temperature for a further 1 h. Finally the mixture was heated under reflux and stirred at this temperature (~115 °C) until gas evolution ceased (~4 h). After cooling, the reaction mixture was stirred slowly into ice (2 kg). The product was extracted with dichloromethane (3 × 500 cm^3) and the extracts were combined, washed successively with aqueous sodium hydrogen carbonate and water and then dried ($MgSO_4$); solvent was distilled off under reduced pressure to give the crude product. This was purified by distillation, b.p. 180 °C/20 mmHg (water pump pressure), to give the title carbaldehyde **1** (45.84 g, 63%), m.p. 48–49 °C (from light petroleum) (lit.,[2] 59% and m.p. 48–49 °C).

2,4-*Dichlorothiazole-5-carbaldehyde Ethylene Acetal* **2**.—A mixture of the aldehyde **1** (5.0 g, 27.5 mmol), ethylene glycol (5.0 g, 80.0 mmol), and a catalytic amount of toluene-*p*-sulfonic acid in anhydrous toluene (60 cm^3) was heated under reflux for 4 h with azeotropic removal of water (Dean–Stark apparatus). Then the solution was cooled, washed successively (20% aqueous sodium carbonate and water) and dried ($MgSO_4$). After removal of the solvent under reduced pressure the residual pale yellow oil was distilled, to give the *product* **2** (6.0 g, 97%), b.p. 150–152 °C/3.0 mmHg (Found: C, 31.6; H, 2.3; N, 6.2; M$^+$, 225. $C_6H_5Cl_2NO_2S$ requires C, 31.9; H, 2.2; N, 6.2%; *M*, 225).

4-*Chlorothiazole-5-carbaldehyde* **4**.—Butyllithium in hexane (1.5 mol dm^{-3}; 15.0 cm^3, 22 mmol) was syringed dropwise into a stirred solution of the carbaldehyde ethylene acetal **2** (5.0 g, 22.0 mmol) in anhydrous THF (100 cm^3) cooled at −78 °C under nitrogen and the resulting mixture was stirred at this temperature for a further 1 h. Then the mixture was allowed to warm up to ambient temperature and poured into hydrochloric acid (2 mol dm^{-3}; 30 cm^3). Extraction with diethyl ether (4 × 50 cm^3) gave a product which was added to hydrochloric acid (20%; 10 cm^3) and the resulting mixture was stirred at ambient temperature for 5 h. Then the mixture was neutralised by

addition of aqueous sodium carbonate. Extration of the product with diethyl ether (4 × 100 cm^3) gave a pale yellow oil which solidified. Recrystallisation of the crude product from light petroleum (b.p. 40–60 °C) gave the title *carbaldehyde* **4** (2.5 g, 78%), m.p. 56–57 °C; ν_{max}/cm^{-1} 1676 (CO); $\delta_H(CDCl_3$; 300 MHz) 8.98 (1 H, d, *J* 0.85, 2-H) and 10.8 (1 H, d, *J* 0.85, C*H*O) (Found: C, 32.8; H, 1.45; N, 9.3; M^+, 147. C_4H_2ClNOS requires C, 32.6; H, 1.4; N, 9.5%; *M*, 147).

4-Chloro-2-methylthiothiazole-5-carbaldehyde **5**.—Butyllithium in hexane (1.5 mol dm^{-3}; 18.0 cm^3, 26 mmol) was syringed dropwise into solution of the carbaldehyde ethylene acetal **2** (6.0 g, 26.5 mmol) in anhydrous THF (100 cm^3) cooled at −78 °C under nitrogen and the resulting mixture was stirred at this temperature for a further 30 min. Then a solution of dimethyl disulfide (2.5 cm^3, 2.62 g, 27.9 mmol) in anhydrous THF (10 cm^3) was added and stirring was continued for a further 1 h. Work-up as described before gave a pale yellow oil which solidified. Recrystallisation of the crude product from hexane gave the title *carbaldehyde* **5** (3.0 g, 59%), m.p. 56–57 °C; ν_{max}/cm^{-1} 1650 (CO); $\delta_H(CDCl_3$; 300 MHz) 2.71 (3 H, s, SMe) and 9.88 (1 H, s, C*H*O) (Found: C, 30.9; H, 2.0; N, 7.3; M^+, 192.9419. $C_5H_4ClNOS_2$ requires C, 31.1; H, 2.1; N, 7.3%; *M*, 192.9422).

4-Chloro-2-(4-methylpiperazin-1-yl)thiazole-5-carbaldehyde **6**.—Butyllithium in hexane (1.45 mol dm^{-3}; 4.9 cm^3, 7.1 mmol) was syringed into a stirred solution of 4-methylpiperazine (0.78 g, 7.8 mmol) in anhydrous THF (10 cm^3) at −78 °C and the resulting mixture was stirred at this temperature for a further 30 min. Then a solution of carbaldehyde **1** (1.0 g, 5.5 mmol) in anhydrous THF (10 cm^3) was added and the resulting mixture was stirred at this temperature for a further 20 min. Then butyllithium (1.45 mol dm^{-3}; 3.8 cm^3, 5.5 mmol) was added and the resulting mixture was stirred at −78 °C for a further 1 h, after which it was poured into aqueous ammonium chloride (20%, 20 cm^3). Extraction with diethyl ether gave the title *carbaldehyde* **6** (0.7 g, 52%), m.p. 140–141 °C [from light petroleum (b.p. 40–60 °C)]; ν_{max}/cm^{-1} 1676 (CO); $\delta_H(CDCl_3$; 300 MHz) 2.31 (3 H, s, NMe), 2.48 (4 H, m, piperazinyl), 3.60 (4 H, m, piperazinyl) and 9.73 (1 H, s, C*H*O) (Found: C, 43.8; H, 4.7; N, 16.8; $M^+ + 1$, 246. $C_9H_{12}ClN_3OS$ requires C, 44.0; H, 4.9; N, 17.1%; $M + 1$, 246).

Preparation of Thieno[2,3-d]thiazoles.—Ethyl 2-dimethylaminothieno[2,3-d]thiazole-5-carboxylate **10**. Ethyl 2-mercaptoacetate (0.31 g, 0.28 cm^3, 2.60 mmol) was added dropwise during 1 h to a stirred solution of sodium ethoxide [prepared by prior addition of sodium (0.06 g, 2.60 mmol) to the ethanol] in ethanol (10 cm^3) at ambient temperature. Then a solution of the carbaldehyde **7**[1] (0.5 g, 2.60 mmol) in ethanol (10 cm^3) was added and the resulting mixture was heated under reflux for 5 h. The solvent was removed under reduced pressure and water (50 cm^3) was added to the residue. Extraction with chloroform (4 × 40 cm^3) gave the title *carboxylate* **10** (0.35 g, 52%) as pale yellow crystals, m.p. 117–118 °C [from light petroleum (b.p. 40–60 °C)]; ν_{max}/cm^{-1} 1689 (CO); $\delta_H(CDCl_3$; 300 MHz) 1.34 (3 H, t, *J* 8, Me), 3.16 (6 H, s, NMe_2), 4.32 (2 H, q, *J* 8, CH_2) and 7.73 (1 H, s, 6-H) (Found: C, 46.8; H, 4.5; N, 10.9; M^+, 256. $C_{10}H_{12}N_2O_2S_2$ requires C, 46.9; H, 4.7; N, 10.9%; *M*, 256).

Ethyl thieno[2,3-d]thiazole-5-carboxylate **9**. The *carboxylate* **9** (52%) was prepared similarly (reaction mixture stirred overnight at ambient temperature and then heated under reflux for 4 h) and had m.p. 71–72 °C (from hexane); ν_{max}/cm^{-1} 1737 (CO); $\delta_H(CDCl_3$; 300 MHz) 1.39 (3 H, t, *J* 8, Me), 4.38 (2 H, q, *J* 8, CH_2), 7.99 (1 H, s, 6-H) and 8.99 (1 H, s, 2-H) (Found: C, 44.6; H, 3.2; N, 6.4; M^+, 212.9928. $C_8H_7NO_2S_2$ requires C, 45.05; H, 3.3; N, 6.9%; *M*, 212.9918).

Thieno[2,3-d]thiazole-5-carboxylic acid **11**. A mixture of the carboxylate **9** (0.5 g, 2.35 mmol) and potassium hydroxide (0.5 g, 8.92 mmol) in ethanol (25 cm^3) was heated under reflux for 5 h and then cooled to ambient temperature. The solvent was distilled off under reduced pressure and the residue dissolved in the minimum amount of water. The resulting solution was filtered and then acidified by addition of hydrochloric acid (5%). The precipitate was filtered off, air dried, and crystallised from aqueous ethanol to give the title *carboxylic acid* **11** (0.15 g, 35%), m.p. 155–156 °C; ν_{max}/cm^{-1} 1683 (CO) and 2925–3418br (OH) (Found: M^+, 184.9613. $C_6H_3NO_2S_2$ requires *M*, 184.9605).

Attempted preparation of thieno[2,3-d]thiazole **12**. A mixture of the carboxylic acid **11** (0.30 g, 1.62 mmol) and copper powder (0.10 g, 1.60 mmol) was placed in one leg of an H-shaped tube attached to a vacuum line. The mixture was heated in an oil bath under reduced pressure with the other leg of the H-tube immersed in liquid nitrogen. The acid melted and gas evolution was observed. After the tube had cooled the entire apparatus was washed out with diethyl ether. Careful evaporation of the ether left a pale yellow oil which was very difficult to characterise due to its high volatility at ambient temperature (*cf.* ref. 5).

4-Azidothiazole-5-carbaldehyde **13**.—A solution of sodium azide (0.65 g, 10.0 mmol) in DMSO (15 cm^3) was added dropwise to a stirred solution of the carbaldehyde **4** (0.44 g, 3.0 mmol) in DMSO (5 cm^3) at ambient temperature and the resulting mixture was stirred for a further 15 h and then poured into ice-cold water (100 cm^3). The precipitate was filtered off and the mother liquor was extracted with diethyl ether (3 × 20 cm^3) to yield further crude product. The combined crude product was chromatographed on silica. Light petroleum (b.p. 40–60 °C)–ethyl acetate (9:1) eluted the title carbaldehyde **13** (0.37 g, 80%), m.p. 81.5–82.5 °C [(from light petroleum (b.p. 40–60 °C); some decomposition occurred with loss of nitrogen]; ν_{max}/cm^{-1} 1660 (CO) and 2120 and 2135sh (N_3); $\delta_H(CDCl_3$; 90 MHz) 8.90 (1 H, s, 2-H) and 9.90 (1 H, s, C*H*O) (M^+, too small to measure accurately).

The following compounds were prepared similarly: *4-azido-2-methylthiothiazole-5-carbaldehyde* **14** (75%), m.p. 63 °C [from light petroleum (b.p. 40–60 °C); some decomposition occurred with loss of nitrogen]; ν_{max}/cm^{-1} 1635 (CO), and 2140 and 2180 (N_3); $\delta_H(CDCl_3$; 300 MHz) 2.70 (3 H, s, SMe) and 9.72 (1 H, s, C*H*O) (Found: $M^+ + 1$, 200.9909. $C_5H_4N_4OS_2$ requires $M + 1$, 200.9905); and *4-azido-2-piperidinothiazole-5-carbaldehyde* **15** (72%), m.p. 114–115 °C [from light petroleum (b.p. 40–60 °C); some decomposition occurred with loss of nitrogen]; ν_{max}/cm^{-1} 1625 (CO) and 2120 (N_3); $\delta_H(CDCl_3$; 300 MHz) 1.70br (6 H, m, piperidino), 3.48br (4 H, s, piperidino) and 9.55 (1 H, s, C*H*O) (Found: $M^+ + 1$, 238.0746. $C_9H_{11}N_5OS$ requires $M + 1$, 238.0763).

Reaction of the Carbaldehyde **1** *with Sodium Azide.*—A solution of sodium azide (1.0 g, 15.0 mmol) in DMSO (10 cm^3) was added dropwise during 5 min to a stirred solution of the carbaldehyde **4** (0.55 g, 3.0 mmol) in DMSO (5 cm^3) at 5–10 °C and the resulting mixture was stirred for a further 1 h at this temperature; it was then poured into ice-cold water (100 cm^3) to give a precipitate which was filtered off and air dried (0.35 g, 76%). The crude product was recrystallised from light petroleum (b.p. 40–60 °C) to give the carbaldehyde **13** (0.1 g, 22%), m.p. 79–80 °C, identical (IR and ^1H NMR spectra and mixed m.p.) with the sample prepared as described before.

trans-*1-(4-Azidothiazol-5-yl)but-1-ene-3-one* **16**.—A solution of the carbaldehyde **13** (0.46 g, 3.0 mmol) in acetone (8 cm^3) was added dropwise to a stirred solution of sodium hydroxide (0.1 g,

2.5 mmol) in water (5 cm^3) at 0–5 °C and the resulting mixture was stirred for a further 1 h at ambient temperature. The precipitate was filtered off, air dried, and chromatographed on silica. Light petroleum (b.p. 40–60 °C)–ethyl acetate (8:2) eluted the *ketone* **16** (0.25 g, 43%), m.p. 106–107 °C [from light petroleum (b.p. 40–60 °C); some decomposition occurred with loss of nitrogen]; ν_{max}/cm^{-1} 1610 (C=C), 1660 (CO), and 2120 and 2140 (N_3); $\delta_H(CDCl_3$; 90 MHz) 2.34 (3 H, s, COMe), 6.40 (1 H, d, *J* 16, CH=), 7.50 (1 H, d, *J* 16, C*H*COMe) and 8.66 (1 H, s, 2-H) (Found: $M^+ + 1$, 195.0337. $C_7H_6N_4OS$ requires $M + 1$, 195.0340).

trans-1-(4-*Azido*-2-*methylthiothiazol*-5-*yl*)*but*-1-*en*-3-*one* **17**.—The *ketone* **17** (52%) was prepared similarly and had m.p. 119–120 °C [from light petroleum (b.p. 40–60 °C)–ethyl acetate; some decomposition occurred with loss of nitrogen]; ν_{max}/cm^{-1} 1590 (C=C), 1675 (CO), and 2120 and 2130sh (N_3); $\delta_H(CDCl_3$; 300 MHz) 2.28 (3 H, s, SMe), 2.68 (3 H, s, COMe), 6.10 (1 H, d, *J* 16, CH=) and 7.41 (1 H, d, *J* 16, C*H*COMe) (Found: $M^+ + 1$, 241.0228. $C_8H_8N_4OS_2$ requires $M + 1$, 241.0218).

5-*Acetyl*-4H-*pyrrolo*[2,3-d]*thiazole* **18**.—A solution of the ketone **16** (0.19 g, 1.0 mmol) in toluene (15 cm^3) was heated under reflux for 2 h and then cooled to ambient temperature. The resulting precipitate was filtered off and the toluene was removed under reduced pressure to give a second crop of the crude product. The combined crude material was chromatographed on silica using light petroleum (b.p. 40–60 °C)–ethyl acetate (8:2) to elute the *product* **18** (0.12 g, 72%), m.p. 229–230 °C [from light petroleum (b.p. 40–60 °C)]; ν_{max}/cm^{-1} 1640 (CO) and 3120 (NH); $\delta_H([^2H_6]$-DMSO; 300 MHz) 3.34 (3 H, s, COMe), 7.34 (1 H, s, 6-H), 9.10 (1 H, s, 2-H) and 12.67 (1 H, s, NH) (Found: C, 50.5; H, 3.4; N, 16.9; $M^+ + NH_4$, 184.0535. $C_7H_6N_2OS$ requires C, 50.6; H, 3.6; N, 16.9%; $M + NH_4$, 184.0545).

5-*Acetyl*-2-*methylthio*-4*H*-*pyrrolo*[2,3-d]*thiazole* **19**.—The *thiazole* **19** (87%) was prepared similarly and had m.p. 223–224 °C [from light petroleum (b.p. 40–60 °C)–ethyl acetate], ν_{max}/cm^{-1} 1640 (CO) and 3150 (NH); $\delta_H(CDCl_3$–$[^2H_6]$-DMSO; 90 MHz) 2.48 (3 H, s, SMe), 2.84 (3 H, s, COMe), 7.68 (1 H, s, 6-H) and 12.65 (1 H, s, NH) (Found: 46.2; H, 4.2; N, 12.9; M^+, 212.0075. $C_8H_8N_2OS_2$ requires C, 45.3; H, 3.8; N, 13.2%; *M*, 212.0078).

N-(4-*Azidothiazol*-5-*ylmethylene*)-p-*toluidine* **20**.—Finely divided carbaldehyde **4** (154 mg, 1.0 mmol) and *p*-toluidine (107 mg, 1.0 mmol), ground together to mix them intimately, were heated gently to 45–50 °C for 5 min. The melt obtained was cooled to ambient temperature and the solidified crude product was chromatographed on alumina (Type-H). Light petroleum (b.p. 40–60 °C) eluted the title *toluidine* **20** (206 mg, 85%), m.p. 75–76 °C [from light petroleum (b.p. 40–60 °C]; ν_{max}/cm^{-1} 1610 (CH=N), and 2120 and 2140sh (N_3); $\delta_H(CDCl_3$; 90 MHz) 2.34 (3 H, s, Me), 7.12 (4 H, s, ArH), 8.45 (1 H, s, CH=N) and 8.80 (1 H, s, 2-H) (Found: $M^+ + 1$, 244.0667. $C_{11}H_{10}N_5S$ requires $M + 1$, 244.0657).

N-(4-*Azido*-2-*methylthiothiazol*-5-*ylmethylene*)-p-*toluidine* **21**.—*Toluidine* **21** (96%) was prepared similarly; m.p. 107 °C [from light petroleum (b.p. 40–60 °C)]; ν_{max}/cm^{-1} 1610 (CH=N) and 2120 (N_3); $\delta_H(CDCl_3$; 90 MHz) 2.33 (3 H, s, Me), 2.70 (3 H, s, SMe), 7.13 (4 H, s, ArH) and 8.36 (1 H, s, CH=N) (Found: $M^+ + 1$, 290.0529. $C_{12}H_{11}N_5S_2$ requires $M + 1$, 290,0534).

2-(p-*Tolyl*)-2H-*pyrazolo*[3,4-d]*thiazole* **22**.—A solution of the toluidine **20** (243 mg, 1.0 mmol) in toluene (15 cm^3) was heated under reflux for 2 h. The toluene was distilled off under reduced pressure to give a solid which was chromatographed on alumina (Type-H). Light petroleum (b.p. 40–60 °C)–ethyl acetate (6:4) eluted the 2H-*pyrazolo*[3,4-d]*thiazole* **22** (172 mg, 80%), m.p. 168–169 °C [from light petroleum (b.p. 40–60 °C)–ethyl acetate]; $\delta_H(CDCl_3$; 90 MHz) 2.40 (3 H, s, Me), 7.28 (2 H, d, *J* 8, ArH), 7.68 (2 H, d, *J* 8, ArH), 8.05 (1 H, s, 6-H) and 8.88 (1 H, s, 2-H) (Found: $M^+ + 1$, 216.0591. $C_{11}H_9N_3$ requires $M + 1$, 216.0595).

5-*Methylthio*-2-(p-*tolyl*)-2H-*pyrazolo*[3,4-d]*thiazole* **23**.—The *thiazole* **23** (85%) was prepared similarly and had m.p. 148 °C [from light petroleum (b.p. 40–60 °C)–ethyl acetate]; $\delta_H(CDCl_3$; 90 MHz) 2.40 (3 H, s, Me), 2.71 (3 H, s, SMe), 7.27 (2 H, d, *J* 8, ArH), 7.62 (2 H, d, *J* 8, ArH) and 7.88 (1 H, s, 6-H) (Found: C, 55.2; H, 4.2; N, 16.0%; $M^+ + 1$, 262.0477. $C_{12}H_{11}N_3S_2$ requires C, 55.15; H, 4.2; N, 16.1%; $M + 1$, 262.0473).

N-(4-*Chlorothiazol*-5-*ylmethylene*)-p-*toluidine* **24**.—A solution of the carbaldehyde **4** (0.15 g, 1.0 mmol) and *p*-toluidine (0.11 g, 1.0 mmol) in benzene (30 cm^3) was heated under reflux for 30 min with azeotropic removal of water (Dean–Stark apparatus). The solvent was distilled off under reduced pressure and the residue was crystallised from light petroleum (b.p. 40–60 °C) to give the *product* **24** (0.18 g, 76%) as yellow needles, m.p. 75–76 °C (Found: $M^+ + 1$, 237.0245. $C_{11}H_{10}ClN_2S$ requires $M + 1$, 237.0253).

Isoxazolo[3,4-d]*thiazole* **25**.—A solution of the carbaldehyde **4** (0.3 g, 1.95 mmol) in bromobenzene (10 cm^3) was heated under reflux for 20 min, until evolution of nitrogen ceased. The solvent was distilled off under reduced pressure and the remaining solid was digested with cyclohexane (20 cm^3). The remaining solid was filtered off, washed with cyclohexane, and air dried to give the *product* **25** (0.15 g, 61%), m.p. 140–142 °C (Found: $M^+ + NH_4$, 144.0224. $C_4H_2N_2OS$ requires $M + NH_4$, 144.0232). This compound is unstable in air, but can be kept for a limited period when stored in a refrigerator under nitrogen.

Acknowledgements

We thank the Algerian Government and Alfateh University, Tripoli, Libya, for financial support (to S. A. and M. F. F., respectively), Mrs. Ruth Howard and Mrs. Valerie Boot (University of Manchester) for recording the low and high resolution mass spectra, respectively, and Dr. M. A. Stuckey for recording the 300 MHz ^1H NMR spectra.

References

1 Part 8; S, Athmani, A Bruce and B. Iddon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 215.
2 G. Beck, Ger. Offen., DE 3 303 704/1984 (*Chem. Abstr.*, 1984, **101**, 211130j); USP 4 555 577/1985.
3 L. Forlani and P. E. Todesco, in *Thiazole and Its Derivatives, Part 1*, ed. J. V. Metzger, Wiley Interscience, New York, 1979, ch. V, p. 565.
4 D. L. Comins and J. D. Brown, *J. Org. Chem.*, 1984, **49**, 1078 and references therein.
5 C. Paulmier and F. Outurquin, *J. Heterocycl. Chem.*, 1983, **20**, 113.
6 S. Gronowitz, C. Westerlund and H.-B. Hörnfeldt, *Chem. Scr.*, 1976, **10**, 165.
7 V. G. Zhiryakov and I. I. Levikoev, *Dokl. Akad. Nauk SSSR*, 1958, **120**, 1035 (*Chem. Abstr.*, 1958, **52**, 20128h).
8 V. G. Zhiryakov, *Khim. Nauka Prom.*, 1959, **4**, 680 (*Chem. Abstr.*, 1960, **54**, 8792g).
9 P. I. Abramenko and V. G. Zhiryakov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1970, **6**, 1515.
10 K. Gewald, M. Hentschel and R. Heikel, *J. Prakt. Chem.*, 1973, **315**, 539.
11 V. I. Shvedov, I. A. Kharizomenova and A. N. Grinev, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1974, **10**, 1045.

12 N. I. Astrakhantseva, V. G. Zhiryakov and P. I. Abramenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1975, **11**, 1364.
13 N. I. Astrakhantseva, V. G. Zhiryakov and P. I. Abramenko, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1976, **12**, 1123.
14 P. I. Abramenko, T. K. Ponomareva and G. I. Priklonskikh, *Zh. Vses. Khim. Ova*, 1978, **23**, 711.
15 P. I. Abramenko, T. K. Ponomareva and G. I. Priklonskikh, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1979, **15**, 387.
16 Gosei Senryo Gijutsu Kenkyu Kumiai, *Jpn. Kokai Tokkyo Koho*, Jap P 58 38 756 [83 38 756]/1983 (*Chem. Abstr.*, 1983, **99**, 106766p).
17 L. D. Pinkin, V. G. Dzyubenko, P. I. Abramenko and I. S. Shpileva, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 1987, **23**, 345.
18 H. Aoki, K. Kodera, M. Hikasa and T. Okugawa, *Jpn. Kokai Tokkyo Koho*, Jap P 01 146 960 [89 146 960]/1989 (*Chem. Abstr.*, 1989, **111**, 235045t).
19 B. Rezessy, L. Toldy, G. Horváth and P. Sohár, *Tetrahedron*, 1991, **47**, 10045.
20 L. Grehn, *Chem. Scr.*, 1979, **13**, 78.
21 R. M. Abdel-Rahman, Z. El-Gendy and M. B. Mahmoud, *J. Indian Chem. Soc.*, 1990, **67**, 61.
22 Z. I. Moskalenko and M. A. Al'perovich, USSR P 178 381/1966 (*Chem. Abstr.*, 1966, **64**, 19628g).
23 D. L. Smith, *Acta Crystallogr., Sect. B*, 1969, **25**, 625.
24 H. K. Gakhar, V. Parkash and K. Bhushan, *J. Indian Chem. Soc.*, 1974, **51**, 941.
25 H. Eilingsfeld and R. Niess, *Ger. Offen.*, 2 429 195/1976 (*Chem. Abstr.*, 1976, **84**, 135649y).
26 M. H. Elnagdi, S. M. Fahmy, M. R. H. Elmoghayar and E. M. Kandeel, *J. Heterocycl. Chem.*, 1979, **16**, 61.
27 E. A. A. Hafez, M. R. H. Elmoghayar and M. M. M. Ramiz, *Liebigs Ann. Chem.*, 1987, 65.
28 R. Barone, M. Chanon and R. Gallo, in *Thiazole and Its Derivatives, Part 2*, ed. J. V. Metzger, Wiley Interscience, New York, 1979, ch. VI, p. 9 (see p. 113).
29 G. D. Krapivin, A. Jurášek, J. Kováč and V. G. Kul'nevich, *Collect. Czech. Chem. Commun.*, 1984, **49**, 2285.

Paper 2/00083K
Received 7*th January* 1992
Accepted 20*th January* 1992