An Easy General Synthesis of 2-(*N,N*-Dialkylamino)thiazol-5-yl Aldehydes and Ketones

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Reaction between 2-chloro-5-thiazolyl-lithium and *N,N*-dialkylformamides or amides gave 2-*N,N*-dialkylaminothiazol-5-yl aldehydes or ketones on quenching with water. Quenching with acid gave 2-chlorothiazole-5-yl aldehydes or ketones, from which chloride was easily displaced by free amines.

2-(*N,N*-Dialkylamino)thiazol-5-yl aldehydes and ketones have attracted considerable attention both for their use as intermediates in the preparation of plant protection and enhancement agents and for investigations of their interesting structural features.[1–4] Broadly, two synthetic approaches have been used. Vilsmeier formylation of a 2-(*N,N*-dialkylamino)thiazole gives the corresponding 5-aldehyde;[1,5] alternatively, selective proton abstraction from C-5 of 2-(*N,N*-dialkylamino)thiazole followed by reaction with *N,N*-dimethylformamide or other *N,N*-dialkylamide and then treatment with acid gives the thiazol-5-yl aldehyde or ketone.[6] The intermediate 2-(*N,N*-dialkylamino)-thiazoles are usually prepared by a Hantzsch condensation between an α-haloketone and a *N',N'*-disubstituted thiourea. The second approach involves reaction between either an *N*-imidoyl[7,8] or *N*-acyl-*N,N*-disubstituted thiourea[7] and an α-haloketone to produce a 2-(*N,N*-dialkylamino)thiazol-5-yl ketone. Unfortunately, mixtures of thiazole ketones are obtained[7] when bromo diketones or *N*-acylthioureas are used. The common intermediates in both approaches are *N,N*-disubstituted thioureas whose synthesis can be quite complex. Both methods are also rather limited in that only specific substituted thiazoles may be produced.

In this paper we report a facile one-pot synthesis of 2-(*N,N*-dialkylamino)thiazol-5-yl aldehydes (**1a–m**) and ketones (**2a–d**) starting from the readily available 2-chlorothiazoles (**3**). This method is based on two important chemical properties of 2-chlorothiazoles and allows considerable variation in the compounds which can be produced. Selective proton abstraction from C-5 has been demonstrated for a variety of 2-substituted thiazoles, such as the 2-chloro[9] or 2-(*N,N*-dialkylamino)[6] compounds. The 5-thiazolide anion reacted easily with a wide variety of electrophiles. In addition 2-halothiazoles readily undergo nucleophilic substitution at C-2 and this reactivity is strongly affected by substituents.[10] Electron-withdrawing groups increase the rate of halogen displacement.

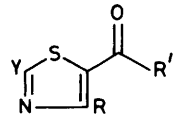
2-Chorothiazol-5-yl-lithium, generated by treatment of 2-chlorothiazole (**3a**) with butyl-lithium at −78 °C in THF, was treated with *N,N*-dimethylformamide. The reaction mixture was quenched with water and after stirring for several hours gave, on work-up (Method A), 2-(*N,N*-dimethylamino)thiazole-5-carbaldehyde (**1a**) in virtually quantitative yield. Reaction of a variety of other *N,N*-dialkylformamides or amides with 2-chlorothiazol-5-yl-lithium by Method A gave the corresponding 2-(*N,N*-dialkylamino)thiazol-5-yl aldehydes (**1b–e**) or ketones (**2a–d**) with similar results (see Table).

Two possible mechanisms are illustrated in the Scheme; both involve the hemiaminal anion intermediate (**4**), formed by addition of 2-chlorothiazol-5-yl-lithium to *N,N*-dialkylamide. The first mechanism postulates an equilibrium between (**4**) and (**5**) and lithium *N,N*-dialkylamine. Reaction between (**5**) and the amine anion could then lead to (**1**) or (**2**). This route was discounted because acid quenching of the reaction mixture from 2-chlorothiazol-5-yl-lithium and *N,N*-dimethylformamide gave only 2-chloro-5-thiazolecarbaldehyde (**5a**)

The second and probable mechanism again involves (**4**). Treatment of (**4**) with water would presumably give (**5**) and dialkylamine. Displacement of the 2-chloro group from (**5**) by the amine, enhanced by the presence of the electron-withdrawing group at C-5, may lead to the 2-dialkylaminothiazol-5-yl aldehyde (**1**) or ketone (**2**). Evidence for this mechanism came from the reaction of (**5a**) with one equivalent of dimethylamine and lithium hydroxide hydrate in aqueous tetrahydrofuran (Method B), employing the same hydrolysis conditions as in Method A, which led to exclusive formation of 2-(*N,N*-dimethylamino)thiazol-5-yl aldehyde (**1a**) in virtually quantitative yield. Furthermore, addition of an aqueous tetrahydrofuran solution of one equiv. of pyrrolidine to a reaction mixture of 2-chlorothiazol-5-yl-lithium with 4-benzoylmorpholine gave a 3:1 mixture of (**2b**) and (**2a**). A variety of other 2-chlorothiazol-5-yl aldehydes and ketones gave similar results with a range of dialkylamines. Excess amine may be used in place of lithium hydroxide.

The readily available 4-substituted 2-chlorothiazoles (**3b–d**)

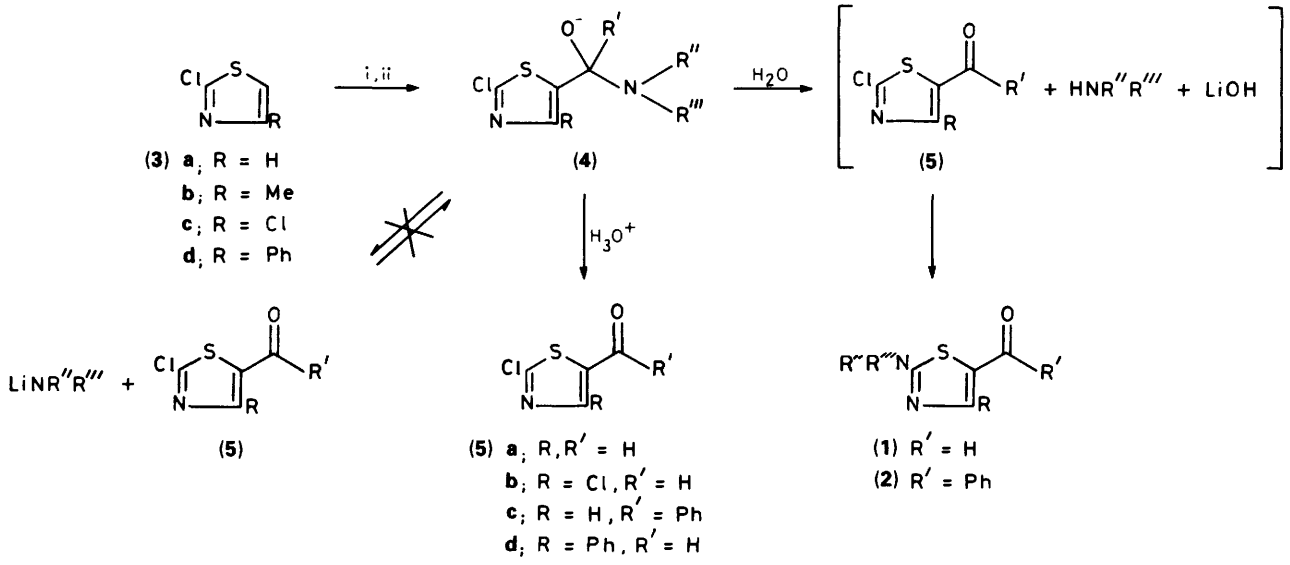
Table



(**1**) and (**2**)

Y	R	R'	Method[a]	Yield[b](%)
(**1a**) dimethylamino	H	H	A,B	95, 87
(**1b**) diethylamino	H	H	A,B	63, 84
(**1c**) morpholin-4-yl	H	H	A,B	89, 87
(**1d**) piperidin-1-yl	H	H	A,B	78, 70
(**1e**) 2,6-dimethylmorpholin-4-yl	H	H	B	55
(**1f**) dimethylamino	Me	H	A	89
(**1g**) morpholin-4-yl	Me	H	A	86
(**1h**) dimethylamino	Cl	H	A	84
(**1i**) morpholin-4-yl	Cl	H	A	90
(**1j**) dimethylamino	Ph	H	A	94
(**1k**) morpholin-4-yl	Ph	H	A	93
(**1l**) pyrrolidin-1-yl	Ph	H	A	91
(**1m**) piperidin-1-yl	Ph	H	A	87
(**2a**) morpholin-4-yl	H	Ph	A,B	86, 91
(**2b**) pyrrolidin-1-yl	H	Ph	A,B	79, 83
(**2c**) diethylamino	H	Ph	B	91
(**2d**) dimethylamino	H	Ph	A	73

[a] Methods; see Experimental section. [b] Yields were not optimised.



Scheme. *Reagents:* i, BuLi; ii, R′CONR″R‴.

also gave the corresponding 4-substituted 2-(*N,N*-dialkylamino)thiazol-5-yl aldehydes (**1f–m**) in good yields from both Methods (see Table). Confirmation that the C-2 halogen was displaced in the reactions of 2,4-dichlorothiazole came from a heteronuclear Overhauser experiment. Irradiation of the hydrogens on the aminomethyl group of (**1h**) caused an enhancement of the ^{13}C signal for C-2 on the thiazole ring.

Experimental

M.p.s were determined on a Mettler FP62 instrument and are uncorrected. ^1H NMR spectra and ^{13}C NMR spectra (62.3 MHz) were recorded on Nicolet QE300 and Bruker AM250 spectrometers respectively as solutions in $CDCl_3$. Mass spectra were recorded on a Finnigan 4500 mass spectrometer. Solvents and reagents were routinely purified by standard techniques. All chlorothiazoles were prepared using literature procedures.

Preparation of 2-*Chlorothiazole-5-carbaldehyde* (**5a**).—Butyllithium (2.4M; 27 ml) in hexane was added to 2-chlorothiazole (7.2 g, 60 mmol) dissolved in THF (100 ml) at −78 °C under an atmosphere of nitrogen. After 10 min a solution of *N,N*-dimethylformamide (6.0 g) in THF (40 ml) was poured into the reaction mixture which was then allowed to warm to room temperature over 2 h. The reaction mixture was then poured slowly onto 2M HCl (150 ml), made basic by addition of dilute ammonium hydroxide solution, and then extracted into dichloromethane (3 × 200 ml). The combined organic extracts were washed with saturated sodium chloride solution and then dried over magnesium sulphate. Evaporation of the solvent left a yellow solid which was recrystallised from light petroleum (b.p. 60—80 °C)–ethyl acetate to give the title compound (**5a**) (95%), m.p. 85 °C (Found: C, 32.8; H, 1.4; N, 9.5. C_4H_2ClNOS requires C, 32.55; H, 1.4; N, 9.5%); δ_H 9.93 (1 H, s) and 8.17 (1 H,s).

Compounds (**5b–d**) were prepared using the above procedure starting from the corresponding 2-chlorothiazoles:

2,4-Dichlorothiazole-5-carbaldehyde (**5b**) (88%), m.p. 48 °C (lit.,[11] 48–49 °C).

(2-*Chlorothiazol-5-yl*) *Phenyl Ketone* (**5c**) (88%), m.p. 60 °C (Found: C, 53.7; H, 2.8; N, 6.5. $C_{10}H_6ClNOS$ requires C, 53.65; H, 2.7; N, 6.3%); δ_H 8.0 (1 H, s), 7.85 (2 H, d, *J* 6.5 Hz), 7.66 (1 H, t, *J* 6.5 Hz), and 7.54 (2 H, dd, *J* 6.5, 6.5 Hz); *m/z* 224 (M^+ + H, 100%).

2-*Chloro*-4-*phenylthiazole-5-carbaldehyde* (**5d**) (83%), m.p. 67 °C (Found: C, 53.7; H, 2.7; N, 6.5. $C_{10}H_6ClNOS$ requires C, 53.65; H, 2.7; N, 6.3%); δ_H 9.93 (1 H, s), 7.7 (2 H, m), and 7.56 (3 H, m).

Preparation of 2-(N,N-*Dialkylamino*)*thiazole-5-carbaldehydes and* [2-(N,N-*Dialkylamino*)*thiazol-5-yl*] *Phenyl Ketones* (**1**) *and* (**2**).—*Method A*. Butyl-lithium (62 mmol) in hexane was added to the 2-chlorothiazole compound (**3**) (60 mmol) dissolved in THF (100 ml) at −78 °C under an atmosphere of nitrogen. After 10 min, a solution of the *N,N*-dialkylformamide or benzamide (65 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature over 2 h. Water (2 ml) was added, the mixture was stirred overnight, and then the THF was evaporated under reduced pressure. The precipitate was filtered off, washed well with water, and then recrystallised from light petroleum–ethyl acetate.

Method B. N,N-Dialkylamine (2.5 equiv. or 1 equiv. and 1.2 equiv. of $LiOH{\cdot}H_2O$) was added to a stirred solution under nitrogen of either 2-chlorothiazole-5-carbaldehyde or [2-chlorothiazol-5-yl phenyl ketone (6 mmol) in aqueous THF (1:40, 20 ml). After 20h, water (20 ml) was added and the THF was evaporated under reduced pressure. The precipitate was filtered off, washed well with water, and then recrystallised from light petroleum–ethyl acetate.

2-Dimethylaminothiazole-5-carbaldehyde (**1a**), method A (95%), method B (87%), m.p. 75 °C (lit.,[1] 74–5 °C) (Found: C, 46.4; H, 5.3; N, 17.9. $C_6H_8N_2OS$ requires C, 46.1; H, 5.2; N, 17.9%); δ_H 9.67 (1 H, s), 7.86 (1 H, s), and 3.22 (6 H, s); *m/z* 173 (M^+ + H, 100%).

2-*Diethylaminothiazole-5-carbaldehyde* (**1b**), method A (63%), method B (84%), b.p. 90 °C/0.8 mmHg (Found: C, 52.7; H, 6.7; N, 14.9. $C_8H_{12}N_2OS$ requires C, 52.15; H, 6.6; N, 15.2%); δ_H 9.55 (1 H, s), 7.83 (1 H, s), 3.56 (4 H, q, *J* 7 Hz), and 1.26 (6 H, t, *J* 7 Hz); *m/z* 185 (M^+ + H, 100%).

2-(Morpholin-4-yl)thiazole-5-carbaldehyde (**1c**), method A (89%), method B (87%), m.p. 162 °C (lit.,[5] 161–165 °C) (Found: C, 48.5; H, 5.3; N, 14.1. $C_8H_{10}N_2O_2S$ requires C, 48.5; H, 5.1; N, 14.1%); δ_H 9.71 (1 H, s), 7.87 (1 H, s), 3.82 (4 H, t, *J* 5 Hz), and 3.63 (4 H, t, *J* 5 Hz); *m/z* 233 (M^+ + H, 100%).

2-(*Piperidin-1-yl*)*thiazole-5-carbaldehyde* (**1d**), method A (78%), method B (70%), m.p. 54 °C (Found: C, 54.95; H, 6.4; N, 14.3. $C_9H_{12}N_2OS$ requires C, 55.1; H, 6.1; N, 14.2%); δ_H 9.66 (1 H, s), 7.82 (1 H, s), 3.6 (4 H, br m), and 1.68 (6 H, br m).

2-(2,6-*Dimethylmorpholin-4-yl*)*thiazole-5-carbaldehyde* (**1e**), method B (55%), m.p. 81 °C (Found: C, 53.3; H, 6.3; N, 12.3.

$C_{10}H_{14}N_2O_2S$ requires C,53.1; H, 6.2; N, 12.4%); δ_H 9.7 (1 H, s), 7.82 (1 H, s), 3.9 (2 H, br m), 3.71 (2 H, br m), 2.87 (2 H, dd, *J* 10, 12 Hz), and 1.25 (6 H, d, *J* 5 Hz).

2-Dimethylamino-4-methylthiazole-5-carbaldehyde (**1f**), method A (89%), m.p. 117 °C (lit.,[5] 115–117 °C) (Found: C, 49.9; H, 6.0; N, 16.3. $C_7H_{10}N_2OS$ requires C, 49.4; H, 5.9; N, 16.5%); δ_H 9.77 (1 H, s), 3.2 (6 H, s), and 2.5 (3 H, s).

4-Methyl-2-(morpholin-4-yl)thiazole-5-carbaldehyde (**1g**), method A (86%), m.p. 165 °C (lit.,[5] 160–162 °C) (Found: C, 50.8; H, 5.8; N, 13.0. $C_9H_{12}N_2O_2S$ requires C, 50.9; H, 5.7; N, 13.2%); δ_H 9.79 (1 H, s), 3.78 (4 H, t, *J* 5 Hz), 3.61 (4 H, t, *J* 5 Hz), and 2.5 (3 H, s).

4-*Chloro*-2-*dimethylaminothiazole*-5-*carbaldehyde* (**1h**), method A (84%), m.p. 108 °C (Found: C, 37.4; H, 3.6; N, 14.4. $C_6H_7ClN_2OS$ requires C, 37.8; H, 3.7; N, 14.7%); δ_H 9.74 (1 H, s) and 3.2 (6 H, s); δ_C 179.6 (J_{C-H} 180 Hz, CHO), 172.1 (C-2), 147.9 (C-4), 119 (J_{C-H} 33 Hz, C-5), and 40 (CH_3N); *m*/*z* 191 (M^+ + H, 100%). Irradiation of the proton signal at δ 3.2 caused an enhancement of the ^{13}C signal at δ 172.1.

4-*Chloro*-2-(*morpholin*-4-*yl*)*thiazole*-5-*carbaldehyde* (**1i**), method A (90%), m.p. 200 °C (Found: C, 41.4; H, 3.9; N, 12.0. $C_8H_9ClN_2O_2S$ requires C, 41.3; H, 3.9; N, 12.0%; δ_H 9.77 (1 H, s), 3.8 (4 H, t, *J* 5 Hz), and 3.51 (4 H, t, *J* 5 Hz).

2-*Dimethylamino*-4-*phenylthiazole*-5-*carbaldehyde* (**1j**), method A (94%), m.p. 123 °C (Found: C, 62.4; H, 5.4; N, 12.2; $C_{12}H_{12}N_2OS$ requires C, 62.1; H, 5.2; N, 12.05%); δ_H 9.69 (1 H, s), 7.69 (2 H, m), 7.46 (3 H, m), and 3.25 (6 H, s); *m*/*z* 233 (M^+ + H).

2-(*Morpholin*-4-*yl*)-4-*phenylthiazole*-5-*carbaldehyde* (**1k**), method A (93%), m.p. 189 °C (Found: C, 61.5; H, 5.2; N, 10.6. $C_{14}H_{14}N_2O_2S$ requires C, 61.4; H, 5.2; N, 10.8%); δ_H 9.72 (1 H, s), 7.67 (2 H, m), 7.47 (3 H, m), 3.82 (4 H, t, *J* 6 Hz), and 3.69 (4 H, t, *J* 6 Hz); *m*/*z* 275 (M^+ + H, 100%).

4-*Phenyl*-2-(*pyrrolidin*-1-yl)*thiazole*-5-*carbaldehyde* (**1l**), method A (91%), m.p. 114 °C (Found: C, 65.2; H, 5.5; N, 10.9. $C_{14}H_{14}N_2OS$ requires C, 65.1; H, 5.5; N, 10.8%; δ_H 9.65 (1 H, s), 7.68 (2 H, m), 7.46 (3 H, m), 3.59 (4 H, br m), and 2.09 (4 H, br m).

4-*Phenyl*-2-(*piperidin*-1-*yl*)*thiazole*-5-*carbaldehyde* (**1m**), method A (87%), m.p. 112 °C (lit.,[6] 93–94 °C) (Found: C, 66.2; H, 6.0; N, 10.0. $C_{15}H_{16}N_2OS$ requires C, 66.1; H, 5.9; N, 10.2%); δ_H 9.78 (1 H, s), 7.68 (2 H, m), 7.45 (3 H, m), 3.66 (4 H, m), and 1.7 (5 H, br m); *m*/*z* 273 (M^+ + H, 100%).

[2-(*Morpholin*-4-*yl*)*thiazol*-5-*yl*]*Phenyl Ketone* (**2a**), method A (86%), method B (91%), m.p. 153 °C (Found: C, 61.3; H, 5.3; N, 10.4. $C_{14}H_{14}N_2O_2S$ requires C, 61.3; H, 5.1; N, 10.2%); δ_H 7.78 (2 H, d, *J* 6.5 Hz), 7.72 (1 H, s), 7.56 (1 H, t, *J* 6.5 Hz), 7.47 (2 H, dd, *J* 6.5, 6.5 Hz), 3.82 (4 H, t, *J* 5 Hz), and 3.62 (4 H, t, *J* 5 Hz); *m*/*z* 275 (M^+ + H, 100%).

Phenyl [2-(*Pyrrolidin*-1-*yl*)*thiazol*-5-*yl*] *Ketone* (**2b**), method A (79%), method B (83%), m.p. 152.5 °C (Found: C, 65.4; H, 5.5; N, 10.9. $C_{14}H_{14}N_2OS$ requires C, 65.1; H, 5.5; N, 10.8%); δ_H 7.77 (2 H, d, *J* 6.5 Hz), 7.75 (1 H, s), 7.55 (1 H, t *J* 6.5 Hz), 7.46 (2 H, dd, *J* 6.5, 6.5 Hz), 3.57 (4 H, br m), and 2.0 (4 H, br m); *m*/*z* 259 (M^+ + H, 100%).

(2-*Diethylaminothiazol*-5-*yl*) *Phenyl Ketone* (**2c**), method B (92%), m.p. 45 °C (Found: C, 64.6; H, 6.1; N, 11.0. $C_{14}H_{16}N_2OS$ requires C, 64.6; H, 6.2; N, 10.8%); δ_H 7.78 (2 H, d, *J* 6.5 Hz), 7.72 (1 H, s), 7.54 (1 H, t *J* 6.5 Hz), 7.46 (2 H, dd, *J* 6.5, 6.5 Hz), 3.58 (4 H, q, *J* 7.5 Hz), and 1.29 (6 H, t, *J* 7.5 Hz); *m*/*z* 261 (M^+ + H, 100%).

(2-*Dimethylaminothiazol*-5-*yl*) *Phenyl Ketone* (**2d**), method A (73%), m.p. 63 °C (Found: C, 61.8; H, 5.2; N, 11.8. $C_{12}H_{12}N_2OS$ requires C, 62.0; H, 5.2; N, 12.0%); δ_H 7.77 (2 H, d, *J* 7 Hz), 7.72 (1 H, s), 7.55 (1 H, t, *J* 7 Hz), 7.46 (2 H, dd, *J* 7.7 Hz), and 3.23 (6 H, s); *m*/*z* 233 (M^+ + H, 100%).

Acknowledgements

We thank Professor Sir John Cornforth F.R.S. for helpful discussions.

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Paper 9/02338K
Received 5*th June* 1989
Accepted 28*th July* 1989