A New General Synthesis of 2-(*N*-Mono- and *N*-Di-substituted Amino)thiazoles

Michael D. Brown, David W. Gillon, G. Denis Meakins,* and Gordon H. Whitham
Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY

Although α-mercapto ketones react with cyanamides to give substituted 2-aminothiazoles the yields are satisfactory in only the simplest cases. However, a range of 2-aminothiazoles with substitutents on the ring or the *exo*-nitrogen atom was obtained efficiently by the following one-pot procedure: a solution of an α-mercapto ketone anion was generated by treating an *O*-ethyl *S*-2-oxoethyl dithiocarbonate with piperidine at 20 °C, a cyanamide was added, and the solution was heated for 3—6 h.

In a previous study[1] it was shown that *N*-mono- and *N*,*N*-di-substituted cyanamides are readily prepared from cyanogen bromide; the thioureas derived from the cyanamides were used in Hantzsch synthesis of 2-(*N*-substituted amino)thiazoles. The object of the present work was to examine the feasibility of a new approach to 2-aminothiazoles, from cyanamides and α-mercapto ketones as represented by the disconnection shown in the Scheme. Substituted 2-amino-1,3-oxazoles have been prepared in similar fashion by treating α-hydroxy ketones with cyanamide[2] and *N*-monoalkylcyanamides,[3] but dialkylcyanamides were found to be unreactive. At the outset it was realised that the characteristic differences between α-mercapto ketones (compounds discussed briefly in the next paragraph) and α-hydroxy ketones might cause difficulties in the proposed synthesis. Nevertheless various α-mercapto ketones had been shown to give 2-alkylthiazoles with nitriles (inefficiently in the presence of hydrogen chloride[4] but satisfactorily under catalysis by sodium cyanide[5]), 2-alkylthiazoles and 2-acylthiazoles with appropriate aldehyde oximes,[6] and 2-alkylthiothiazoles with alkyl thiocyanates;[5] three 2-aminothiazoles had been obtained[7] by heating ketones with sulphur and cyanamide in the presence of diethylamine, and the product from cyclohexanone was also prepared from the 2-mercapto ketone and cyanamide.

α-Mercapto ketones are most commonly prepared[8a,9] from α-halogeno ketones and sodium hydrosulphide; a newer method[9] involves hydrolysing 2,5-dihydrothiazoles, themselves obtained by heating ketones with sulphur and ammonia. Dimerisation to cyclic compounds[10] occurs very readily and under acid conditions this is followed by dehydration to bridged ethers,[9,11] as exemplified by the sequence[8] starting from 2-oxopropanethiol (**2a**) in the Scheme. Isolation of the α-mercapto ketones as such is difficult with the simplest members, in which the propensity for dimerisation is greatest. In the case of 2-oxopropanethiol the standard preparation leads directly to dimeric material;[8] two dimers have been obtained and, largely on the basis of an i.r. examination, formulated[12] as (*sic*) different conformers of the *trans*-diol rather than diastereoisomers corresponding to structure (**4**).

Three procedures (A, B, C) for preparing 2-aminothiazoles from cyanamides and α-mercapto ketones or their derivatives were developed successfully using the simplest system [*i.e.* with 2-dimethylamino-4-methylthiazole (**1a**) as the product]. Two of them (A, B) were found to be unsatisfactory with substrates having bigger substituents, but the efficiency of procedure C[13] was not adversely affected. The work is fully described elsewhere[14] and since it consisted mostly of studying experimental variables (*e.g.* reactant ratios, solvent, base, reaction time and temperature) only the salient features are reported here.

Procedure A. It was thought that treatment of the dimer (**4**) with an organic base of low nucleophilicity would generate 2-oxopropanethiol or its anion in a solvent suitable for the ensuing reaction with dimethylcyanamide. In view of the uncertain status of the dimer a sizeable quantity was sublimed and crystallised to give a specimen which was used in all the experiments. Under the best conditions [treatment of the dimer (1 mol equiv.) in ethanol with triethylamine (2.2 mol equiv.) at 20 °C, followed by the addition of *N*,*N*-dimethylcyanamide (2 mol equiv.) and heating for 3 h], the 2-aminothiazole (**1a**) was formed in 81% yield. However, the hindered *N*-t-butylcyanamide (**3g**) gave the corresponding product (**1g**) much less efficiently (42%).

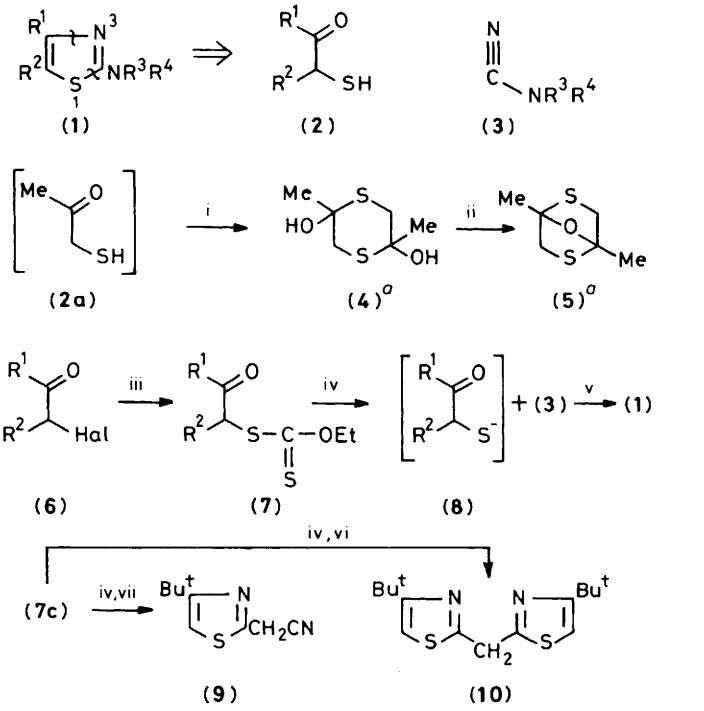
Procedure B. The object was to develop a one-pot preparation and so to avoid isolating the α-mercapto ketones. Accordingly, a solution of sodium hydrosulphide in aqueous ethanol was treated with chloroacetone, and triethylamine and a cyanamide were added, and the mixture was heated. Good yields (*ca.* 71%) were obtained in the preparations of the simple aminothiazoles (**1a, b**) but not in those of the higher members, *e.g.* 2-dimethylamino-4-t-butylthiazole (**1c**), yield 32%.

Procedure C. It seemed possible that the failure of procedures A and B to provide a general synthesis might stem from complications associated with the preparation of α-mercapto ketones by the conventional method. Further, the detailed work[14] had shown that addition to the cyanamides is more effective with the anions of α-mercapto ketones than with the neutral substrates. Attention was turned, therefore, to the possibility of generating the anions from stable starting materials in which the sulphur was already bound to the carbonyl-containing group. Since thiols not containing oxo-groups had been obtained[15] by treating dithiocarbonate esters with ethane-1,2-diamine it was reasoned that *O*-ethyl *S*-2-oxoalkyl dithiocarbonates[16] (**7**) might serve as precursors of the required anions. Six such esters (four of them new) were prepared conveniently (yields 88—97%) from potassium *O*-ethyl dithiocarbonate and solutions of α-halogeno ketones in acetone at 20 °C. Of the range of reagents used for nucleophilic cleavage of the esters, piperidine was found to be the most effective. Thus the addition of piperidine to a solution of the ester (**7a**) in methylene chloride at 20 °C followed after 5 min by careful work-up gave a product (*ca.* 75%) indicated by spectrometric examination to be 2-oxopropanethiol (**2a**) free from the dimer or other contaminants.

The ester (**7a**), in a range of solvents, was then treated with various amounts of piperidine and the solutions were used directly for the subsequent reactions. These experiments led to the final one-pot procedure: a solution of the ester (**7**) (1 mol equiv.) and piperidine (2.2 mol equiv.) in ethanol was kept at 20 °C for 30 min, the cyanamide (**3**) (1 mol equiv.) was added, and the solution was boiled under reflux for 3—6 hours. [In the earlier report[13] the amount of piperidine was specified wrongly as 1.1 mol equiv. Such a reactant ratio results in appreciably

Scheme. Preparation of *N*-substituted 2-aminothiazoles. References are given to known compounds; the rest are new.

	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a;	Me	H	Me	Me	g;	Me	H	Bu^t	H
b;	Me	Me	Me	Me	h;	Bu^t	H	Bu^t	H
c;	Bu^t	H	Me	Me	i;	Bu^t	H	Ph	Me
d;	Ph	H	Me	Me	j;	$[CH_2]_4$		Ph	Me
e;	$[CH_2]_3$		Me	Me	k;	Bu^t	H	Bu$^tCH_2$	Me
f;	$[CH_2]_4$		Me	Me	l;	Ph	H	Bu$^tCH_2$	Me



Reagents: i, Spontaneous; ii, H^+ or heat; iii, KSCSOEt–Me_2CO, 20 °C; iv, Piperidine (2.2 equiv.)–EtOH, 20 °C; v, Heat; vi, $CH_2(CN)_2$ (0.5 equiv.), 20 °C for 1 day; vii, $CH_2(CN)_2$ (3 equiv.), 20 °C for 1 day.

Yields (%): **(1a)**[b] 85, **(1b)**[b] 73, **(1c)**[c] 72, **(1d)**[d] 80, **(1e)** 68, **(1f)** 65, **(1g)**[e] 83, **(1h)** 75, **(1i)**[d] 76, **(1j)** 70, **(1k)** 31, **(1l)** 35, **(7a)**[f] 94, **(7b)** 96, **(7c)** 96, **(7d)**[g] 97, **(7e)** 88, **(7f)** 92, **(9)** 51, **(10)** 63.

[a] Refs. 8 and 12. [b] Ref. 17. [c] Ref. 19. [d] Ref. 1. [e] Ref. 18. [f] Ref. 16. [g] Ref. 20.

lower yields of 2-aminothiazoles, and this is understandable. Equivalent amounts of the ester (**7**) and piperidine should give the mercapto ketone and 1-ethoxythiocarbonylpiperidine, and a second equivalent of piperidine is needed to catalyse addition to the cyanamide.] The results in the Scheme show that 2-aminothiazoles substituted at positions 4 or 5 (or both) and with bulky substituents on the ring or the *exo*-nitrogen can be prepared conveniently and effectively in this way. Severe steric crowding as in the *N*-neopentyl-*N*-methyl system, reduces the yield but the basicity of the products allows them to be isolated without difficulty.

In a modification of procedure C a cyanide was used in place of the cyanamide. Malononitrile and the ester (**7c**) afforded the thiazoylacetonitrile (**9**) or the di(thiazoyl)methane (**10**) according to the ratio of reactants.

Experimental

General directions were as described in *J. Chem. Soc., Perkin Trans 1*, 1984, 2801. The characterisation of new compounds is shown in the Table; a complete account of their spectrometric features is given elsewhere.[14] Each general procedure is illustrated by an example, and the products so obtained are then listed. *Solutions* of NaSH were prepared by saturating solutions of NaOH at 0 °C with a stream of H_2S; the weights of NaSH specified were calculated from the accounts of NaOH used.

Procedure A.—1-Chloropropan-2-one (92 g) was added during 1.5 h to a stirred solution of NaSH (56 g) in water (250 ml) at 0—5 °C and stirring was continued for 1 h at 10 °C. The insoluble material was collected, washed (cold water, EtOH, then Et_2O), and dried to give material (63 g), m.p. *ca.* 94—101 °C. Sublimation at 115 °C/0.6 mmHg and two crystallisations from C_6H_6 gave the dimer (**4**) (39 g), m.p. 112—114 °C (lit.,[12] 116—117 °C and 136—138 °C for different forms), $\nu_{max.}$(Nujol) 3 650—3 350s, br and 1 720w cm^{-1}; δ [$CDCl_3$–$(CD_3)_2SO$] 5.45 (2 H, brs, OH), 3.46 (4 H, s, CH_2), and 1.58 (6 H, s, Me), and additional weaker signals at 3.38 and 2.29 in the ratio 2:3; *m/z* 90 [$(MeCOCH_2SH)^+$, 29%], 47(18), and 43(100).

Et_3N (3.3 g) was added to a solution of the dimer (**4**) (2.7 g) in EtOH (80 ml) at 20 °C. After 30 min Me_2NCN (2.1 g) was added, and the solution was boiled under reflux for 3 h. The solution was concentrated to *ca.* 30 ml at 80 °C/15 mmHg, cooled, diluted with Et_2O (70 ml), and extracted with 3M-HCl. Basification with 18 M-NH_3 and isolation with Et_2O gave the aminothiazole (**1a**) (3.45 g), m.p. 31—33 °C (lit.,[17] 31—32 °C). Similarly prepared was the aminothiazole (1 g) (42%), m.p. 83—84 °C (lit.,[18] 82.5—83.5 °C).

Table. Characterisation of new compounds.

Compound	M.p. (°C)	B.p. [Bath temp. (°C)/mmHg]	Found (%) Requires (%) C	H	N	Molecular formula
2-Dimethylamino-5,6-dihydrocyclopentathiazole (**1e**)		56—58/0.05	*m/z* 168.0721 (M^+ 168.0721)			$C_8H_{12}N_2S$
2-Dimethylamino-4,5,6,7-tetrahydrobenzothiazole (**1f**)		82—83/0.01	59.2 (59.3)	7.7 (7.7)	15.5 (15.4)	$C_9H_{14}N_2S$
4-t-Butyl-2-t-butylaminothiazole (**1h**)	69—70		62.3 (62.2)	9.3 (9.5)	13.2 (13.2)	$C_{11}H_{20}N_2S$
2-(*N*-Methyl-*N*-phenylamino)-4,5,6,7-tetrahydrobenzothiazole (**1j**)		111—114/0.05	68.6 (68.8)	6.6 (6.6)	11.3 (11.5)	$C_{14}H_{16}N_2S$
2-(*N*-Methyl-*N*-neopentylamino)-4-t-butylthiazole (**1k**)		69—70/0.1	64.7 (64.95)	10.05 (10.1)	11.6 (11.7)	$C_{13}H_{24}N_2S$
2-(*N*-Methyl-*N*-neopentylamino)-4-phenylthiazole (**1l**)	47—49		*m/z* 260.1347 (M^+ 260.1347)			$C_{15}H_{20}N_2S$
O-Ethyl *S*-(3-oxobutan-2-yl) dithiocarbonate (**7b**)		66—68/0.15	43.9 (43.7)	6.4 (6.3)		$C_7H_{12}O_2S$
O-Ethyl *S*-(3,3-dimethyl-2-oxobutyl) dithiocarbonate (**7c**)		81—83/0.01	*m/z* 220.0592 (M^+ 220.0592)			$C_9H_{16}O_2S_2$
O-Ethyl *S*-(2-oxocyclopentyl) dithiocarbonate (**7e**)		($\nu_{max.}$ 1 740 cm^{-1})	49.2 (49.1)	7.2 (7.3)		$C_8H_{12}O_2S_2$
O-Ethyl *S*-(2-oxocyclohexyl) dithiocarbonate (**7f**)		($\nu_{max.}$ 1 710 cm^{-1})	49.3 (49.5)	6.5 (6.5)		$C_9H_{14}O_2S_2$
4-t-Butylthiazol-2-ylacetonitrile (**9**)		71—73/0.05	59.9 (60.0)	6.8 (6.7)	15.2 (15.5)	$C_9H_{12}N_2S$
Bis-(4-t-butylthiazol-2-yl)methane (**10**)	49—51		61.3 (61.2)	7.6 (7.5)	9.35 (9.5)	$C_{15}H_{22}N_2S_2$

Procedure B.—A solution of 3-chlorobutan-2-one (5.3 g) in EtOH (20 ml) was added during 1 h to a stirred solution of NaSH (2.9 g) in water (10 ml)–EtOH (40 ml) at 0—5 °C. Stirring was continued for 30 min at 20 °C while a slow stream of N_2 was passed through the mixture (to remove residual H_2S). Et_3N (5.1 g) and, after a further 20 min, Me_2NCN (3.5 g) were added, and the solution was boiled under reflux for 3 h. Work-up as in procedure A and distillation of the material so obtained gave the aminothiazole (**1b**) (5.5 g), b.p. 90—92 °C/15 mmHg (lit.,[17] 90 °C/15 mmHg). Similarly prepared were the aminothiazoles (**1a**) (72%); (**1c**) (32%), b.p. 117—119 °C/16 mmHg (lit.,[19] 101—103 °C/11 mmHg); (**1f**) (28%).

Procedure C.—A solution of 1-chloropropan-2-one (18.5 g) in Me_2CO (100 ml) was added during 30 min to a stirred suspension of KSCSOEt (32 g) in Me_2CO (240 ml) at 20 °C, and stirring was continued for 1 h. Me_2CO was removed at 60 °C/15 mmHg, water (100 ml) was added, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and the solvent evaporated. Distillation of the residue gave the dithiocarbonate (**7a**) (33.5 g), b.p. 72—74 °C/0.1 mmHg (lit.,[16] b.p. 84—86 °C/0.2 mmHg). Similarly prepared were the dithiocarbonates (**7b**) (96%) from MeCOCHClMe; (**7c**) (96%) from Bu^tCOCH_2Br; (**7d**) from $PhCOCH_2Br$, obtained as a solid (97%), m.p. 28—31 °C (lit.,[20] 32 °C), which was not distilled. The dithiocarbonates (**7e, f**) underwent partial decomposition during distillation. Further batches were purified by flash chromatography on SiO_2 [elution with light petroleum–EtOAc (9:1)] to give (**7e**) (88%) from 2-chlorocyclopentanone, and (**7f**) (92%) from 2-chlorocyclohexanone.

Piperidine (105 mg) was added to a solution of *O*-ethyl *S*-2-oxopropyl dithiocarbonate (**7a**) (210 mg) in CH_2Cl_2 (10 ml) at 20 °C. After 5 min 2M-NaOH (40 ml) was added, the mixture was shaken for 15 min, allowed to settle, and the layers were separated. CH_2Cl_2 (10 ml) was added to the aqueous layer, the mixture was cooled to *ca.* 5 °C, neutralised carefully with 2M-HCl, and shaken. The CH_2Cl_2 layer was dried ($MgSO_4$), filtered, and evaporated at 20 °C/*ca.* 400 mmHg to give an oil (80 mg), δ 3.38 (2 H, d, *J* 8 Hz, CH_2S), 2.29 (3 H, s, Me), and 1.95 (1 H, t, *J* 8 Hz, SH), $\nu_{max.}$($CHCl_3$) 1 722 cm^{-1}, formulated as 2-oxopropanethiol (**2a**).

Piperidine (1.93 g) was added to a stirred solution of *O*-ethyl *S*-(3,3-dimethyl-2-oxobutyl) dithiocarbonate (**7c**) (2.23 g) in EtOH (10 ml) at 20 °C and stirring was continued for 30 min. Me_2NCN (0.71 g) was added, and the solution was boiled under reflux for 3 h. The standard work-up (dilution with Et_2O, extraction with 3M-HCl, neutralisation with 18M-NH_3, and isolation with Et_2O) gave the aminothiazole (**1c**) (1.34 g). The aminothiazoles thus prepared [except that the solutions were boiled for 6 h in the preparations of compounds (**1k**) and (**1l**)] and the yields obtained are shown in the Scheme. Four known aminothiazoles are described under procedures A and B; the others are compounds (**1d**), b.p. 84—86 °C/0.01 mmHg, and (**1i**), m.p. 35—36 °C, identified by comparison with authentic specimens.[1]

A solution of piperidine (2.35 g), *O*-ethyl *S*-(3,3-dimethyl-2-oxobutyl) dithiocarbonate (**7c**) (2.75 g), and malononitrile (2.5 g) in EtOH (25 ml) was kept at 20 °C for 1 day. The standard work-up followed by flash chromatography on SiO_2 [elution with light petroleum–EtOAc (20:1)] gave the nitrile (**9**) (1.15 g), δ 6.84 (1 H, s, 5-H), 4.02 (2 H, s, CH_2CN), and 1.28 (9 H, s, Bu^t), $\nu_{max.}$ 2 270 cm^{-1}; *m/z* 181 (100%) and 180 (M^+, 22). A similar experiment using malononitrile (0.41 g) followed by flash chromatography and sublimation of the product at 108—112 °C/0.05 mmHg gave the *di(thiazolyl)methane* (**10**) as yellow crystals (1.15 g), δ 6.75 (2 H, s, two 5-H), 4.63 (2 H, s, CH_2), and 1.35 (18 H, s, two Bu^t); *m/z* 294 (M^+ 37%) and 279 (100).

Acknowledgements

We thank the S.E.R.C. for studentships to M. D. B. and D. W. G.

References

1 T. N. Birkinshaw, D. W. Gillon, S. A. Harkin, G. D. Meakins, and M. D. Tirel, *J. Chem. Soc., Perkin Trans. 1*, 1984, 147.

2 V. Wolf, P. Hauschildt, and W. Loop, *Chem. Ber.*, 1962, **95**, 2419.
3 A. F. Cockerill, A. Deacon, R. G. Harrison, D. J. Osborne, D. M. Prime, W. J. Ross, A. Todd, and J. P. Verge, *Synthesis*, 1976, 591.
4 K. Miyatake and T. Yoshikawa, Jap. P. 7 926/1956 (*Chem. Abstr.*, 1958, **52**, 14698).
5 F. Asinger, K. Fabian, H. Vossen, and K. Hentschel, *Justus Liebigs Ann. Chem.*, 1975, 410.
6 Y. Oka, Jap. P. 71 037/1971 (*Chem. Abstr.*, 1971, **74**, 141757).
7 K. Gewald, H. Böttcher, and R. Mayer, *J. Prakt. Chem.*, 1964, **23**, 298.
8 (*a*) O. Hromatka and E. Engel, *Monatsh. Chem.*, 1947, **78**, 29; (*b*) 1947, **78**, 38.
9 F. Asinger, W. Schäfer, G. Herkelmann, H. Römgens, B. D. Reintges, G. Scharein, and A. Wegerhoff, *Justus Liebigs Ann. Chem.*, 1964, **672**, 156.
10 O. Hromatka and R. Haberl, *Monatsh. Chem.*, 1954, **85**, 830, 1082; A. Kirrman, J. Cantacuzene, and L. Vio, *Rev. Chim.* (*Acad. Rep. Pop. Roum*), 1962, **7**, 1011.
11 References cited by J. M. McIntosh, H. B. Goodbrand, and G. M. Masse, *J. Org. Chem.*, 1974, **39**, 202.
12 R. Haberl, F. Grass, O. Hromatka, K. Brauner, and A. Preisinger, *Monatsh. Chem.*, 1955, **86**, 551.
13 M. D. Brown, D. W. Gillon, G. D. Meakins, and G. H. Whitham, *J. Chem. Soc., Chem. Commun.*, 1982, 444.
14 D. W. Gillon, D. Phil. Thesis, Oxford 1984.
15 K. Mori and Y. Nakamura, *J. Org. Chem.*, 1969, **34**, 4170.
16 A. J. Bridges and G. H. Witham, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1603.
17 Y. Garreau, *Bull. Soc. Chim. Fr.*, 1954, 1048.
18 S. I. Burmistov and V. A. Krasovskii, *Zh. Obshch. Khim.*, 1964, **34**, 685.
19 D. W. Gillon, I. J. Forrest, G. D. Meakins, M. D. Tirel, and J. D. Wallis, *J. Chem. Soc., Perkin Trans. 1*, 1983, 341.
20 B. Groth, *Arkiv Kemi*, 1924, **9**, 63.

Received 15*th October* 1984; *Paper* 4/1753