A New General Synthesis of *N*-Mono- and *N*-Di-substituted 2-Aminothiazoles

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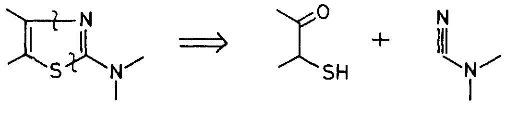
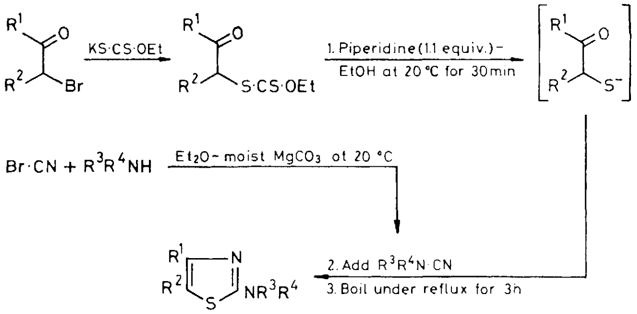
Solutions of α-mercapto-ketone anions, generated from *O*-ethyl *S*-2-oxoethyl dithiocarbonates and piperidine, react with cyanamides to give 2-aminothiazoles with substituents on the heterocycle or the *exo*-nitrogen atom.

In studies of rotational isomerism[1] we wished to synthesise series of 2-aminothiazoles having two substituents (one of them bulky) on the *exo*-nitrogen atom. Although many 2-aminothiazoles have been obtained by the Hantzsch condensation of α-halogeno-ketones with thioureas[2] there was no general route to the required *N*,*N*-disubstituted thioureas at the start of the present work. Attempts to prepare these starting materials by the silicon tetraisothiocyanate method[3] were discouraging and attention was therefore turned to the possibility of an alternative synthesis of 2-aminothiazoles. The new approach (see Scheme 1) was to be based on the reaction of α-mercapto-ketones with substituted cyanamides. A few α-mercapto-ketones have been converted into 2-alkyl- and 2-alkylthio-thiazoles by treatment with nitriles and thiocyanates, respectively,[4] and 2-*N*-monoalkyl-1,3-oxazoles have been obtained in 20—90% yield from α-hydroxy-ketones and *N*-monoalkylcyanamides.[5] However it was realised that difficulties in the proposed synthesis might arise from the characteristic differences between α-hydroxy-ketones and α-mercapto-ketones. (In neutral or acidic media the latter readily dimerise, and the dimers may undergo dehydration.[6])

Development of the monoalkyl cyanamide preparation[5] led to a convenient procedure for the reaction of primary and secondary aliphatic and aromatic amines with cyanogen bromide. Condensation of the resulting cyanamides with α-mercapto-ketones (prepared and isolated by standard methods) gave only modest yields (*ca.* 25%) of 2-aminothiazoles. The key modification was to generate an α-mercapto-ketone anion by treating an *O*-ethyl *S*-2-oxoethyl dithiocarbonate[7] with a secondary amine, and to use the solution directly for reaction with a cyanamide. (Some thiols not containing oxo-groups



Scheme 1



Scheme 2. Yields (%) of 2-aminothiazoles. (Apart from those specified the products are new: all were fully characterised and gave satisfactory analytical results.)

	R^1	Me	Bu^t	Ph	Me		
	R^2	H	H	H	Me	$[CH_2]_3$	$[CH_2]_4$
R^3,R^4	Me,Me	85[a]	72	80[a]	73[a]	63	65
	Bu^t,H	83[b]	75				
	Ph,Me		76				70
	Bu^tCH_2,Me		31	35			

[a] Ref. 2. [b] S. I. Burmistov and V. A. Krasovskii, *Zh. Obshch. Khim.*, 1964, **34**, 685.

have been obtained previously from xanthates and ethane-1,2-diamine.[8]) 2-Aminothiazoles substituted at positions 4 or 5 (and at both) and with bulky substituents on the *exo*-nitrogen can be prepared effectively in this way (see Scheme 2). Severe steric crowding, as for example in the *N*-neopentyl-*N*-methyl system, reduces the yield but the basicity of the products allows them to be isolated without difficulty.

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