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A general synthesis of thiazoles. Part 4[1]. Synthesis of 5-acyl-2, 4-diaminothiazoles[2]

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Abstract. N,N,N′,N′-tetramethylguanidine has been added to methyl and phenyl isothiocyanates. Reaction of the adducts with α-haloketones has yielded 5-acyl-2-(substituted) amino-4-dimethylaminothiazoles.

Keywords. 5-Acyl-2-amino-4-dimethylaminothiazoles.

1. Introduction

In 1970, we had reported the first example of a novel thiazole synthesis (Rajappa and Advani 1970). In this synthesis, a functionalized thiourea derivative provided two ring carbon atoms and both the hetero atoms of the resultant thiazole ; the remaining carbon atom (C-5) was supplied by the methylene group of an α-haloketone. The synthesis can be schematically expressed as shown in scheme 1. The requisite thiourea derivative was obtained by addition of an amidine to an isothiocyanate. During the subsequent cyclization, the amine HNRR was eliminated (scheme 2). We have also reported on the use of iminoethers as starting materials instead of amidines ; in this case, an alcohol is eliminated at the cyclization stage (Rajappa *et al* 1979).

We have now systematically investigated the possible variations in the substitution pattern of the thiazole. The results are reported in this and in the following papers. The present paper concerns itself with the introduction of a dimethylamino group at position 4 ; the following papers are devoted to the possible changes at positions 2 and 5 of the thiazole.

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[1] Part 3. Rajappa *et al* 1979.

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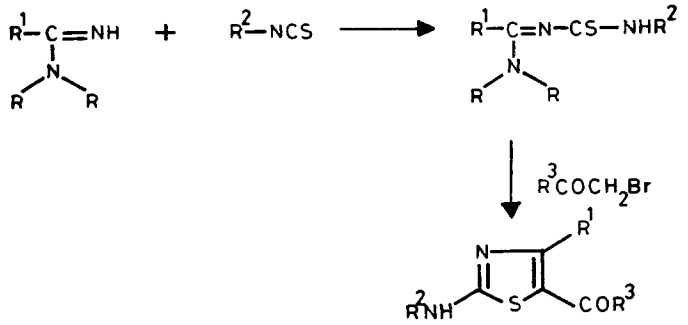
Scheme 1

Scheme 2



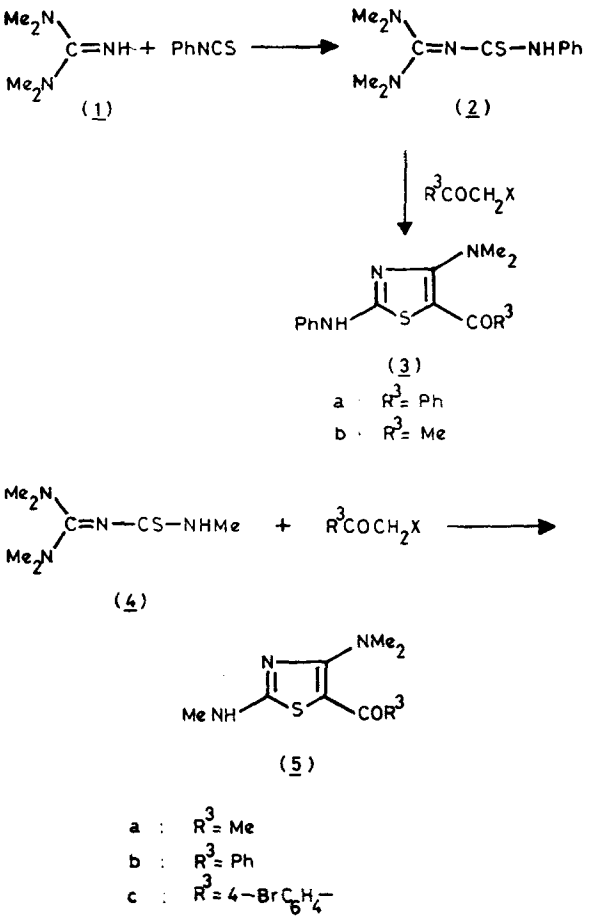
2. Results and discussion

As shown in scheme 2, the synthesis utilizing an amidine-isothiocyanate adduct would invariably lead to thiazoles bearing an alkyl or aryl group at position 4. It is obvious that the use of a guanidine instead of an amidine in the above sequence would lead to thiazole derivatives with an amino group at that position. In order to eliminate the ambiguities associated with an unsymmetrical guanidine, we chose to use tetramethylguanidine 1 as our substrate. Reaction of this with phenyl isothiocyanate gave the adduct 2. Condensation of this with α-haloketones has provided us with 5-acyl-2-anilino-4-dimethylaminothiazoles 3 in good yields. Similarly, reaction of tetramethylguanidine with methyl isothiocyanate gave the adduct 4, which led to the 5-acyl-4-dimethylamino-2-methylaminothiazoles 5 with α-haloketones.

The same concept has recently been utilized to generate 5-benzoyl-2,4-diaminothiazoles by Rajasekharan and Sulekha (1981).

3. Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 360L spectrometer. Chemical shifts are expressed in δ values (ppm) downfield from TMS. Mass spectra were determined on a Varian Mat CH7 instrument at 70 eV utilizing direct insertion.



3.1. *Addition of tetramethylguanidine to isothiocyanates*

A solution of phenyl isothiocyanate (13·5 g) in isopropanol (40 ml) was cooled to 0–5° and treated dropwise with stirring with a solution of tetramethyl-guanidine (12·7 g) in isopropanol (40 ml). Stirring was continued for 2½ hr at this temperature and then for 1 hr at 30°. The solid was filtered and recrystallized from isopropanol to give the adduct (_) (23·5 g), m.p. 186° (Found : C, 57·88 ; H, 7·37 ; N, 22·49. $C_{12}H_{18}N_4S$ requires C, 57·58 ; H, 7·25 ; N, 22·39%). NMR (DMSO-d_6) : 2·9 (s, 4Me) ; 6·8 to 7·6 (m, 5 Ar-H). MS : 250 (M^+).

A solution of methyl isothiocyanate (4 g) in isopropanol (10 ml) was similarly treated with tetramethylguanidine (6 g) in isopropanol (20 ml). The solution was left at 30° for 16 hr and then warmed at 70° for 1½ hr. The solvent was then removed *in vacuo* and the residue recrystallized from chloroform-hexane to give the adduct (4) (7 g), m.p. 159–161° (Found : C, 44·99 ; H, 8·81 ; N, 29·53, $C_7H_{16}N_4S$ requires C, 44·66 ; H, 8·57 ; N, 29·77%). NMR ($CDCl_3$) : 2·93 (s, 5 Me). MS : 188 (M^+).

3·2. *Condensation of the adducts with α-haloketones*

The adduct (2) (5 g) was stirred and refluxed in isopropanol (350 ml) with phenacyl bromide (4·4 g) for 5 hr. The solvent was then removed *in vacuo*, the residue left in cold water for 3 hr and the yellow solid filtered. This was basified with $KHCO_3$ solution and extracted with ethyl acetate. The solution was dried and evaporated. The product was crystallized from ethanol to give 2-anilino-5-benzoyl-4-dimethylaminothiazole (3a) (5·7 g), m.p. 128° (Found : C, 63·66 ; H, 5·85 ; N, 12·45. $C_{18}H_{17}N_3OS \cdot H_2O$ requires C, 63·33 ; H, 5·61 ; N, 12·31%). NMR ($CDCl_3$) : 3·07 (s, 2Me) ; 6·8 to 7·8 (m, 10 ArH). MS : 323 (M^+).

The adduct (2) (3·45 g) was similarly condensed with chloracetone (2 ml) in isopropanol (270 ml). After refluxing for 6 hr, the product was worked up as above to give 5-acetyl-2-anilino-4-dimethylaminothiazole (3b) (2·3 g), m.p. 156–158° (from ethyl acetate–toluene) (Found : C, 59·73 ; H, 6·10 ; N, 16·22. $C_{13}H_{15}N_3OS$ requires C, 59·76 ; H, 5·79 ; N, 16·08%). NMR ($CDCl_3$ + DMSO-d_6) : 2·25 (s, Me) ; 3·13 (s, 2Me) ; 6·8 to 7·7 (m, 5 Ar-H). MS : 261 (M^+).

A mixture of the adduct (4) (2 g) and chloracetone (1 g) in isopropanol (25 ml) was refluxed for 6 hr and the solvent then removed *in vacuo*. The residue was cooled, basified and extracted with ethyl acetate. The organic extract was dried and evaporated. The product was crystallized from ethyl acetate–ether to give 5-acetyl-4-dimethylamino-2-methylaminothiazole (5a) (0·75 g), m.p. 150–151°. (Found : C, 48·58 ; H, 6·76 ; N, 21·03. $C_8H_{13}N_3OS$ requires C, 48·23; H, 6·58; N, 21·10%). NMR ($CDCl_3$): 2·17 (s, Me); 3·05 (s, 2Me); 3·47 (s, Me). MS : 199 (M^+).

The adduct (4) (2 g) was refluxed in isopropanol (25 ml) for 6 hr with phenacyl bromide (2·1 g). The solution was cooled and filtered. The solid was basified with $KHCO_3$ solution and the base recrystallized from ethanol to give 5-benzoyl-4-dimethylamino-2-methylaminothiazole (5b) (1·8 g), m.p. 203°. A further small quantity of the product was obtained from the isopropanol filtrate (Found : C, 60·00 ; H, 6·07 ; N, 15·76. $C_{13}H_{15}N_3OS$ requires C, 59·76 ; H, 5·79 ; N, 16·08%). NMR (DMSO-d_6): 2·8 (d, Me); 3·0 (s, 2Me); 7·4 to 7·8 (m, 5 Ar–H) ; 8·32 (q, NH). MS : 261 (M^+).

A similar reaction of the adduct (4) with *p*-bromo-phenacyl bromide gave the thiazole (5c), m.p. 209° (Found : C, 46·09 ; H, 4·43 ; N, 12·14. $C_{13}H_{14}BrN_3OS$ requires C, 45·90 ; H, 4·15 ; N, 12·35%). NMR (DMSO-d_6) : 2·75 (d, Me) ; 2·93 (s, 2Me); 7·3 to 7·7 (4Ar–H) ; 8·37 (q, NH). MS : 339, 341 (M^+).

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