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A general synthesis of thiazoles. Part 5[1]. Synthesis of 5-acyl-2-dialkylaminothiazoles[2]

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Abstract. Amidinothioureas (7), (11) and (12) obtained by condensation of N, N-disubstituted thioureas with amide acetals have been used as starting materials for the synthesis of thiazoles. Thus, reaction with chloracetone and phenacyl bromides leads to ketones ; the use of chloracetic ester in this reaction yields the thiazole-5-carboxylic ester (10).

Keywords. 5-Acyl-2-dialkylaminothiazoles ; 2-morpholinothiazole-5-carboxylic ester.

1. Introduction

In the original version of the novel synthesis of thiazoles that we have developed (Rajappa and Advani 1970), the adduct (1) of an amidine and an isothiocyanate is condensed with an α-haloketone (scheme 1). Such an approach restricts the 2-substituent to RNH.

Subsequent to our publication, but seemingly unaware of our work, Meslin and Quiniou (1975) described a related synthesis of 2-aryl-5-acyl thiazoles. They utilized as their starting material, the condensation product 3 of an aromatic thioamide with DMF acetal (scheme 2). This route was later extended by the Lederle group (Lin *et al* 1979) to prepare 2-aminothiazoles of type 2, again without reference to our prior work. They condensed N-monosubstituted thioureas with amide acetals to give compounds similar to (1), and then reacted these with α-haloketones.

One of our objectives in this area was to devise a viable route to 5-acyl-2-aminothiazoles (4) in which the exocyclic nitrogen at position 2 carries two substituents (or represents a cyclic amine). One approach to this problem is through the use of acyl thioureas (5) (scheme 3) (Liebscher and Hartmann 1974).

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[1] Part 4. Preceding paper (Rajappa *et al* 1982).

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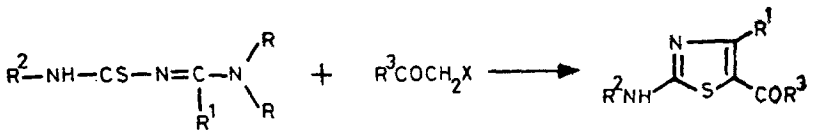
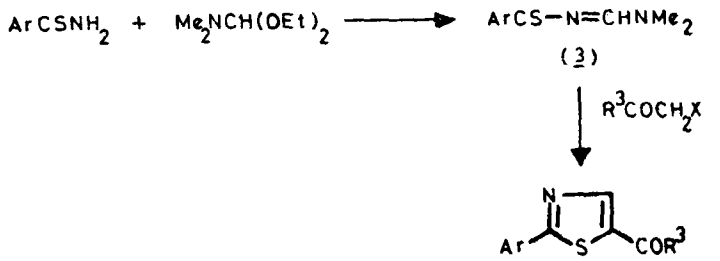
Scheme 1



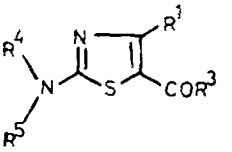
(1) (2)

Scheme 2



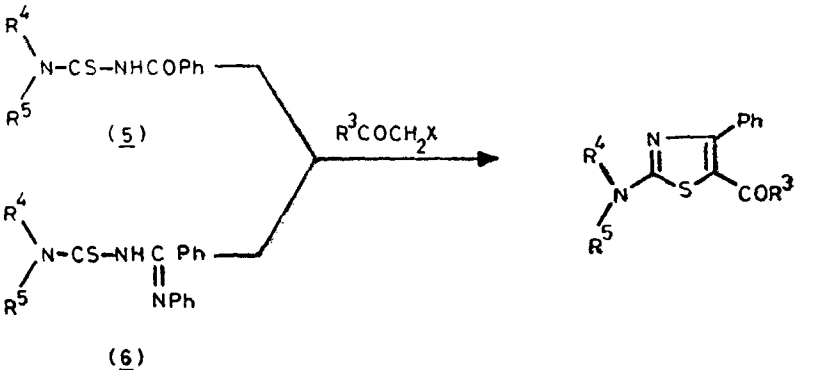
Another precursor which would lead to the desired product is the adduct (6) of a secondary amine and an imidoyl isothiocyanate (Ried and Kaiser 1976) (scheme 3).

We now find that the condensation products of N, N-disubstituted thioureas with amide acetals form convenient starting materials for the synthesis of thiazoles of type (4).



(4)

Scheme 3



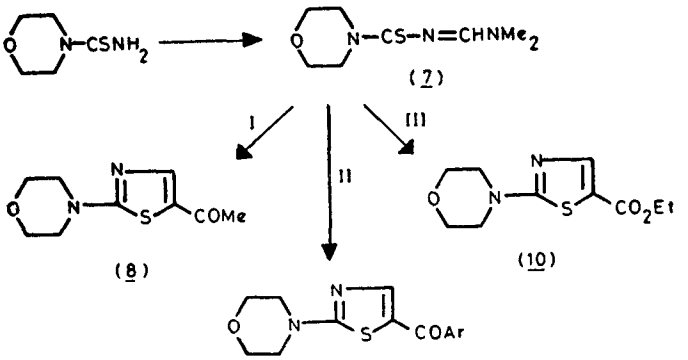
(6)

2. Results and discussion

Thiocarbamoylmorpholine condensed with DMF acetal to give the formamidine derivative (7). This reacted with a variety of α-halo carbonyl compounds as shown in scheme 4. Thus the thiazolyl ketones 8 and 9a were derived by reaction with chloracetone and phenacyl bromide respectively. Interestingly, even the thiazole-5-carboxylic ester (10) could be produced from (7) by reaction with chloracetic ester.

The related 1-thiocarbamoyl-4-methylpiperazine was also reacted with both DMF acetal and DMA acetal to give the amidine derivatives (11) and (12) (scheme 5).

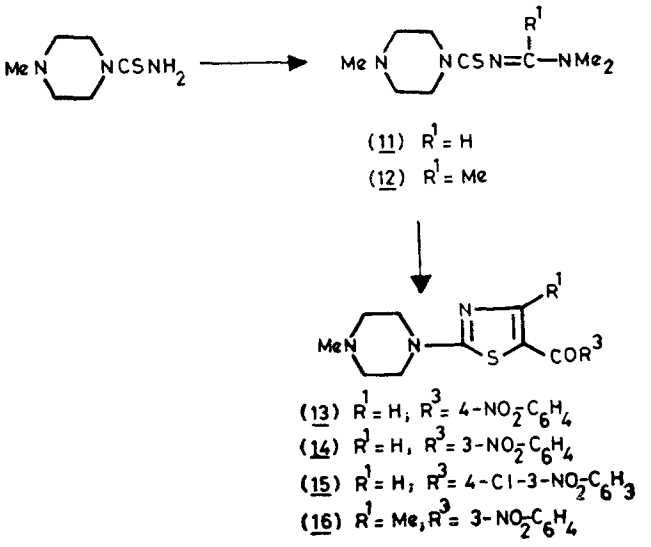
Scheme 4



(9) a: Ar = Ph
b: Ar = 4–Cl–3–NO_2–C_6H_3

I : $ClCH_2COMe$ II : $ArCOCH_2Br$ III : $ClCH_2CO_2Et$

Scheme 5



Thiazoles (13 to 16) were obtained by condensation of these with the appropriate phenacyl bromides.

3. Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded either on a Varian A 60 or a Varian EM 360 L spectrometer. Chemical shifts are expressed in δ values (ppm) downfield from TMS. Mass spectra were determined on a Varian Mat CH 7 instrument at 70 eV utilizing direct insertion.

3.1. *Synthesis of 2-morpholinothiazoles*

A mixture of N-thiocarbamoylmorpholine (6 g) (Nair 1966) and DMF acetal (12 ml) was heated at 100° for 6 hr. Excess DMF acetal was then removed *in vacuo*, the residue digested with hexane, cooled and filtered to give the formamidine derivative (7) (9 g), m.p. 84–86° C (Found : C, 48·12 ; H, 7·64 ; N, 21·06. $C_8H_{15}N_3OS$ requires C, 47·75 ; H, 7·51 ; N, 20·88%). NMR ($CDCl_3$) : 3·05, 3·17 (2s, NMe_2) ; 3·5 to 4·5 (m, 8H) ; 8·72 (s, CH). MS : 201 (M^+).

The above formamidine derivative (7) (3 g) was refluxed with chloracetone (1·5 g) in isopropanol (50 ml) for 3 hr and then the solvent stripped off. The residue was digested with water and extracted with ethyl acetate. Evaporation of the organic layer and crystallization of the residue from ethyl acetate-hexane gave 5-acetyl-2-morpholinothiazole (8) (2 g), m.p. 145–147° C (Found : C, 51·24 ; H, 5·94 ; N, 13·54. $C_9H_{12}N_2O_2S$ requires C, 50·94 ; H, 5·70 ; N, 13·20%). NMR ($CDCl_3$) : 2·42 (s, Me) ; 3·5 to 4·0 (m, 8H) ; 7·72 (s, Ar-H). MS : 212 (M^+).

The formamidino thiourea (7) (1 g) was refluxed with phenacyl bromide (1 g) in isopropanol (20 ml) for 2 hr and then the solvent removed *in vacuo*. The residue was basified with $NaHCO_3$ solution and extracted with ethyl acetate. The ethyl acetate solution was concentrated to a small volume and treated with hexane to give 5-benzoyl-2-morpholinothiazole (9a) (1 g), m.p. 156–159° C (Found: C, 61·49 ; H, 5·42 ; N, 9·91. $C_{14}H_{14}N_2O_2S$ requires C, 61·31 ; H, 5·15 ; N, 10·21%). NMR ($CDCl_3$) : 3·5 to 4 (m, 8H) ; 7·3 to 7·9 (m, 5 Ar-H) ; 7·67 (s, ArH). MS : 274 (M^+).

The formamidinothiourea (7) (5 g) was refluxed with 4-chloro-3-nitrophenacyl bromide (7 g) in isopropanol (100 ml) for 2½ hr, cooled and the solid filtered. It was recrystallized first from ethyl acetate and then from chloroform-hexane to give 5-(4-chloro-3-nitro) benzoyl-2-morpholinothiazole (9b), (6 g), m.p. 203–205° C (Found : C, 47·46 ; H, 3·69 ; N 11·50. $C_{14}H_{12}ClN_3O_4S$ requires C, 47·53 ; H, 3·42 ; N, 11·88%). NMR (DMSO-d_6) : 3·4 to 3·8 (m, 8H) ; 7·6 to 8·2 (4 Ar-H). MS : 353,355 (M^+).

The formamidino thiourea (7) (3 g) was refluxed with ethyl chloroacetate (1·8 g) in isopropanol (50 ml) for 3 hr. After cooling, water (500 ml) was added, the solid filtered and recrystallized from ethyl acetate-hexane to give ethyl 2-morpholinothiazole-5-carboxylate (10) (1·8 g), m.p. 116–118° C (Found : C, 49·66 ; H, 6·04 ; N, 11·83. $C_{10}H_{14}N_2O_3S$ requires C, 49·58 ; H, 5·83 ; N,

11·57%). NMR ($CDCl_3$) : 1·33 (t, CH_3) ; 3·4 to 3·9 (m, 8H) ; 4·25 (q, CH_2) ; 7·80 (s, Ar-H).

3.2. *Synthesis of* 2-(*N-methylpiperazino*) *thiazoles*

A mixture of 1-thiocarbamoyl-4-methylpiperazine (Remers *et al* 1971) (12 g) and DMF acetal (18 g) was stirred and heated at 130° for 6 hr. The excess DMF acetal was then removed *in vacuo* and the residue digested with hexane, cooled and filtered to give the formamidine derivative (11), (11 g). A sample was recrystallized from methanol-ethyl acetate to give pure (11), m.p. 107–111° (Found : C, 46·74 ; H, 8·13 ; N, 23·73. $C_9H_{18}N_4S.H_2O$ requires C, 46·53 ; H, 8·68 ; N, 24·12%). NMR ($CDCl_3$) : 2·27 (s, NMe) ; 2·43 (t, $2CH_2$) ; 3·0 (s, NMe) ; 3·1 (s, NMe) ; 4·07 (t, CH_2) ; 4·30 (t, CH_2) ; 8·77 (s, CH). MS : 214 (M^+).

A similar reaction with DMA acetal gave the acetamidine derivative (12) as a gum which was used as such for the subsequent reaction.

A mixture of the formamidinothiourea (11) (9·6 g) and *p*-nitrophenacyl bromide (11 g) in isopropanol (300 ml) was stirred and refluxed for 4 hr. then cooled and the solid filtered. This solid hydrobromide was basified with 2N NaOH, the liberated base extracted in methylene chloride, the solvent dried and evaporated. Recrystallization of the residue from ethyl acetate-methanol gave 2-(N-methyl piperazino)-5-(*p*-nitrobenzoyl thiazole (13) (11 g), m.p. 187–190° C (Found : C, 53·92 ; H, 5·14 ; N, 16·74. $C_{15}H_{16}N_4O_3S$ requires C, 54·21 ; H, 4·85 ; N, 16·86%). MS : 332 (M^+).

A similar reaction of (11) (8·3 g) with *m*-nitrophenacyl bromide (9·5 g) in isopropanol gave 2-(N-methylpiperazino)-5-(*m*-nitrobenzoyl) thiazole (14) (6·7 g) which was crystallized from ethyl acetate, m.p. 153–157° C (Found : C, 54·08 ; H, 5·16 ; N, 16·97. $C_{15}H_{16}N_4O_3S$ requires C, 54·21; H, 4·85 ; N, 16·86%). MS : 332 (M^+).

Likewise, reaction of (11) (10·7 g) with 4-chloro-3-nitrophenacyl bromide (13·9g) gave 5-(4-chloro-3-nitrobenzoyl)-2-(N-methylpiperazino) thiazole (15) (11 g), m.p. 156–160° C (from ethyl acetate-hexane) (Found : C, 49·21 ; H, 4·39 ; N, 14·97. $C_{15}H_{15}ClN_4O_3S$ requires C, 49·12 ; H, 4·12 ; N, 15·28%). NMR ($CDCl_3$) : 2·27 (s, NMe) ; 2·47 (t, $2CH_2$) ; 3·70 (t, $2CH_2$) ; 7·5 to 8·3 (4Ar-H).

A mixture of the gummy acetamidino thiourea (12) (2·3 g) and *m*-nitrophenacyl bromide (2·4 g) was refluxed in isopropanol (50 ml) for 4 hr, cooled and filtered. The solid was basified with 2N NaOH and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated. Recrystallization of the residue from ethyl acetate-hexane gave 4-methyl-2-(N-methylpiperazino)-5-(*m*-nitrobenzoyl) thiazole (16) (1·2 g), m.p. 144-147° C. (Found : C, 55·48 ; H, 5·55 ; N, 16·39. $C_{16}H_{18}N_4O_3S$ requires C, 55·48 ; H, 5·24 ; N, 16·18%). NMR ($CDCl_3$) : 2·27 (s, Me) ; 2·33 (s, NMe) ; 2·43 (t, $2CH_2$) ; 3·0 (t, $2CH_2$) ; 7·2 to 8·7 (4 Ar-H). MS : 346 (M^+).

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