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A general synthesis of thiazoles. Part 7[1]. Direct generation of chloromethyl 5-thiazolyl ketones[2]

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Abstract. Careful reaction of equimolar amounts of 1, 3-dichloroacetone and the amidinothioureas (4), (5), (6) or (10) has given the (2-amino-5-thiazolyl) chloromethyl ketones (7), (8), (9) and (11) respectively in 20 to 40% yields. The presence of excess amidinothiourea in the reaction mixture leads to the bis thiazolyl ketones (3).

Keywords. (2-amino-5-thiazolyl) chloromethyl ketones; direct synthesis; dichloroacetone; amidinothioureas.

1. Introduction

As part of a project on the synthesis of thiazole analogs of the known anthelmintic, Levamisole (Janssen 1976) we needed chloromethyl 5-thiazolyl ketones of the general structure (1). The disposition of the substituents in (1) was such that it was tempting to apply the general synthetic route developed by us to arrive at this structure directly. One specifically notes the presence of a 2-amino substituent and the carbonyl group attached to position 5 of the thiazole – features which are ideally generated by the novel sequence developed by us (Rajappa and Advani 1970). It is also to be noted that the normal procedure for getting such "phenacyl halides" would be the halogenation of the appropriate methyl ketone—a process which is not likely to yield the required product (1) cleanly when amine substituents are present.

The general synthesis of thiazoles can be represented as shown in scheme 1; here (2) is a functionalised thiourea derivative in which L is a leaving group (NR_2 or OR). The application of this reaction to prepare compounds of the type (1) would entail the use of 1,3-dichloroacetone as the carbonyl component ($R^2 = ClCH_2$-). We recognized that the danger lay in the further condensation

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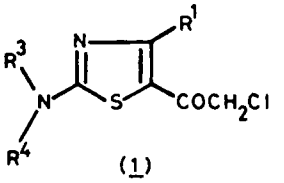
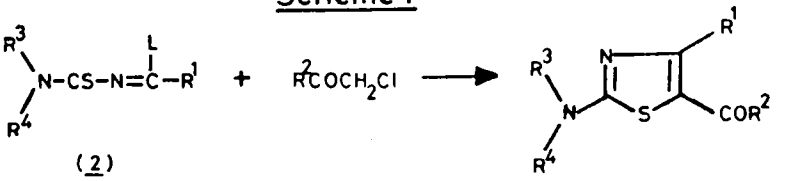


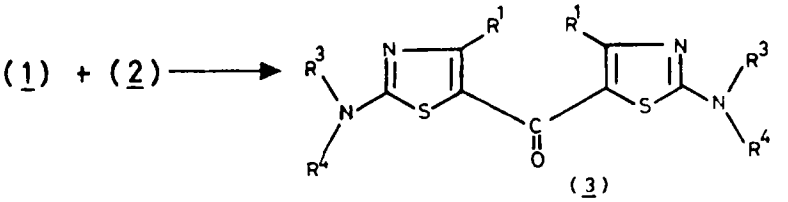
(1)

Scheme 1



(2)

Scheme 2



(3)

of the product (1) with a second molecule of (2) to form the bisthiazolyl ketone (3) (scheme 2).

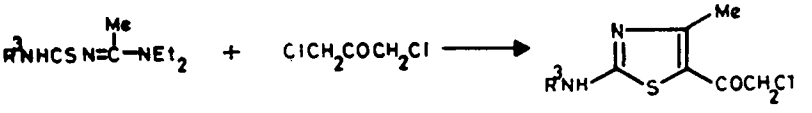
As described in our earlier papers, the nature of the substituents R^1, R^3 and R^4 in compound (1) dictate the choice of the starting material (2) for the thiazole synthesis. We have used thiourea derivatives obtained by three different routes in our present investigations.

2. Results and discussion

2.1. *Amidine-isothiocyanate adducts (scheme 3)*

N,N-Diethyl acetamidine was added to methyl and *n*-butyl isothiocyanates to give the adducts (4) and (5). When equimolar amounts of (4) and 1, 3-dichloro-

Scheme 3



(4) R^3 = Me
(5) R^3 = n-C_4H_9
(6) R^3 = CO_2Et

(7) R^3 = Me
(8) R^3 = n-C_4H_9
(9) R^3 = CO_2Et

acetone were reacted, the chloromethyl ketone (7) was produced in 21% yield. The adduct (5) similarly gave (8) in 35% yield. As expected, the use of two moles of the thiourea component (4) to one of dichloroacetone gave the bisthiazolyl ketone (3) ($R^1 = R^3 = Me$; $R^4 = H$). The adduct (6) of carbethoxy-isothiocyanate and N,N-diethylacetamidine gave both the monomer (9) and dimer (3) ($R^1 = Me$; $R^3 = CO_2Et$; $R^4 = H$) with one mole of dichloroacetone.

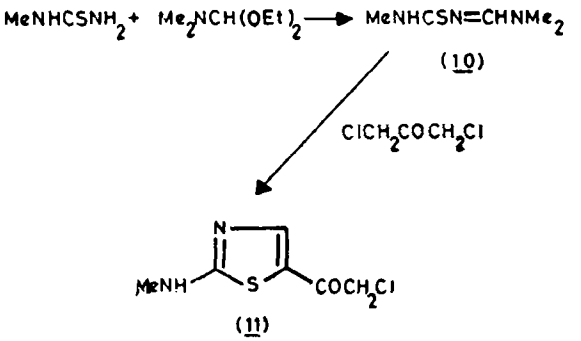
2.2. *Thiourea-DMF acetal condensation product (scheme 4)*

The formamidinothiourea (10) could be obtained from N-methylthiourea and DMF acetal. This reacted with 1,3-dichloroacetone to give the thiazole (11) in 40% yield.

2.3. *Acylthiourea*

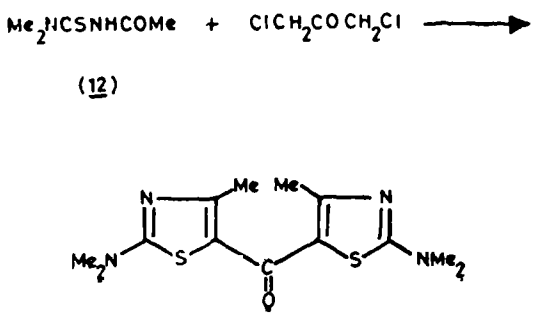
When the acylthiourea (12) was treated with an equimolar quantity of 1,3 dichloroacetone, only the bis thiazolyl ketone (3) ($R^1 = R^3 = R^4 = Me$) was obtained (scheme 5), We therefore abandoned any further attempt to generate chloromethyl 5-thiazolyl ketone of type (1) from acylthioureas.

Scheme 4



(11)

Scheme 5



(12)

3. Experimental

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

3.1. *Reaction of amidine-isothiocyanate adducts with* 1, 3-*dichloroacetone*

The adduct (4) (5·6 g) (Rajappa *et al* 1982) was dissolved in isopropanol (50 ml) and added dropwise with stirring to a solution of 1, 3-dichloroacetone (3·8 g) in isopropanol (50 ml). The mixture was stirred and refluxed for 2 hr, cooled and the solvent evaporated *in vacuo*. The residue was treated with isopropanolic HCl and again evaporated. Addition of isopropanol and ether gave a solid, which was filtered and recrystallized from methanol-isopropanol to yield chloromethyl [(4-methyl-2-methylamino)-5-thiazolyl] ketone hydrochloride (7) (1·5 g), m.p. 225–228° C (d). (Found : C, 35·04 ; H, 4·19 ; N, 11·96. $C_7H_9ClN_2OS \cdot HCl$ requires C, 34·87 ; H, 4·18 ; N, 11·62%). NMR (DMSO–d_6) : 2·2 (s, Me) ; 2·63 (s, Me) ; 4·5 (s, CH_2).

Reaction of 1, 3-dichloroacetone (1·27 g ; 0·01 mole) with the adduct (4) (3·74 g ; 0·02 mole) in refluxing isopropanol for 2 hr gave bis (4–methyl-2-methylamino-5-thiazolyl) ketone (0·5 g), which was recrystallized from aqueous acetic acid ; m.p. 290–295° (d). (Found : C, 46·94 ; H, 5·33 ; N, 20·16. $C_{11}H_{14}N_4OS_2$ requires C, 46·81 ; H, 5·00 ; N, 19·85%). MS : 282 (M^+).

n-Butyl isothiocyanate (3·5 g) was mixed with N,N-diethylacetamidine (3·5 g) ; the mixture was maintained at 100° C for 2 hr and then cooled. The adduct (5) thus obtained was dissolved in isopropanol (50 ml) and added dropwise with stirring to 1, 3-dichloroacetone (3·9 g) in isopropanol (50 ml). The mixture was stirred and refluxed for 3 hr, evaporated and the product converted as before to the hydrochloride. This was recrystallized from methanol-isopropanol to give (2-*n*-butylamino-4-methyl-5-thiazolyl) chloromethyl ketone hydrochloride (8) (3 g), m.p. 185–190° C (d). (Found : C, 43·16 ; H, 6·13 ; N, 10·26. $C_{10}H_{15}ClN_2OS \cdot HCl$ requires C, 42·41 ; H, 5·69 ; N, 9·89%). NMR (TFA) : 1·07 (t, Me) ; 1·7 (m, 4H) ; 2·8 (s, Me) ; 3·57 (q, CH_2), 4·6 (s, CH_2).

Carbethoxy isothiocyanate (32·7g) was added dropwise at 0–5° to N,N-diethylacetamidine (28·5 g) and then stirred at 5° for 2 hr. The adduct thus formed was dissolved in isopropanol (200 ml), added to 1, 3-dichloroacetone (31·8 g) in isopropanol (200 ml) and refluxed for 5 hr. After cooling the solid was filtered, converted to the base with saturated aqueous $KHCO_3$ and filtered to give the dimer, bis (2-carbethoxyamino-4-methyl-5-thiazolyl) ketone, (15 g), m.p. 328° C. (Found : C, 45·59 ; H, 4·91 ; N, 13·85. $C_{15}H_{18}N_4O_5S_2$ requires C, 45·23 ; H, 4·55 ; N, 14·07%). The isopropanol filtrate was evaporated *in vacuo*, basified with saturated aqueous $KHCO_3$ and filtered. Recrystallization of this solid from CH_2Cl_2-ether gave (2-carbethoxyamino-4-methyl-5-thiazolyl) chloromethyl ketone (9) (17 g), m.p. 135–138° C. (Found: C, 41·44 ; H, 4·49; N, 11·03. $C_8H_{11}ClN_2O_3S$ requires C, 41·15; H, 4·22 ; N, 10·67%). NMR

($CDCl_3$) ; 1·4 (t, Me) ; 2·75 (s, Me) ; 4·42 (q, CH_2) ; 4·5 (s, CH_2). MS : 262, 264 (M^+).

3.2. *Reaction of the formamidinothiourea* (10) *with* 1,3-*dichloroacetone*

A mixture of N-methylthiourea (60 g), DMF acetal (80 g) and *p*-toluene sulfonic acid (2 g) in benzene (500 ml) was refluxed in an apparatus attached to a Dean-Stark water-separator for 5 hr. The solution was then concentrated, treated with hexane, cooled and filtered to give (10) (75 g), m.p. 108–112°. (Found C, 41·56 ; H, 7·68 ; N, 29·10. $C_5H_{11}N_3S$ requires C, 41·37 ; H, 7·64 ; N, 28·95%).

A mixture of the formamidinothiourea (10) (4·3 g) and 1, 3-dichloroacetone (3·7 g) was refluxed in isopropanol (100 ml) for 3 hr and the solvent then removed *in vacuo*. The residue was digested with water, filtered and recrystallized from methanol-ethyl acetate to give chloromethyl [(2-methylamino)-5-thiazolyl] ketone (11) (2·3 g), m.p. 162–166° C (d). Found : C, 38·16 ; H, 4·13 ; N, 14·89 $C_6H_7ClN_2OS$ requires C, 37·80; H, 3·70 ; N, 14·70%). NMR ($CDCl_3$ + DMSO-d_6) : 2·97 (s, Me) ; 4·63 (s, CH_2) ; 8·05 (s, Ar-H).

3.3. *Reaction of the acylthiourea* (12) *with* 1,3-*dichloroacetone*

The N-acetylthiourea (12) (4·4 g) (Sandström 1963) was dissolved in isopropanol (50 ml) and added dropwise with stirring to a solution of 1, 3-dichloroacetone (3·8 g) in isopropanol (50 ml). The mixture was refluxed for 3 hr, concentrated and cooled. The solid was filtered and recrystallized from isopropanol to give the hydrochloride of bis (2-dimethylamino-4-methyl-5-thiazolyl) ketone (5 g), m.p. 228–233° C (d). NMR (D_2O) : 2·13 (s, Me) ; 3·0 (s, NMe_2).

The free base was liberated from this by means of $NaHCO_3$ and recrystallized from ethyl acetate-hexane ; m.p. 149–151° C. (Found : C, 50·60 ; H, 6·16 ; N 18·39. $C_{13}H_{18}N_4OS_2$ requires C, 50·31 ; H, 5·85 ; N, 18·06%). MS : 310 (M^+),

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