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A general synthesis of thiazoles. Part 6[1]. Synthesis of 2-amino-5-heterylthiazoles[2]

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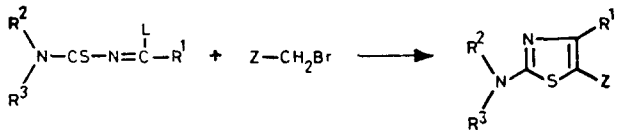
Abstract. 2-Chloromethyl pyridine, 2-chloromethyl quinoline and 2-chloromethyl benzimidazole have been reacted with amidino thioureas to provide the corresponding 2-amino-5-(2-heteroaryl) thiazoles. 4-Chloromethyl thiazole failed to undergo this reaction.

Keywords. 2-Amino-5-heteroarylthiazoles ; amidinothioureas.

1. Introduction

In the previous papers of this series, we have established the generality of the synthetic sequence shown in scheme 1 for preparing a variety of thiazoles. In this sequence, L is a suitable leaving group (NR_2 or OR), and Z is a group that activates the adjacent methylene for cyclization. Normally such activation is provided by a carbonyl ; we have also recorded examples where Z is NO_2 (Rajappa and Sreenivasan 1978). In this paper we have enlarged the scope of the synthesis by proving that Z can also be a suitable heteroaryl radical.

Scheme 1



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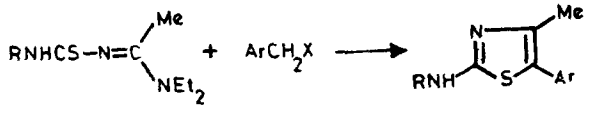
2. Results and discussion

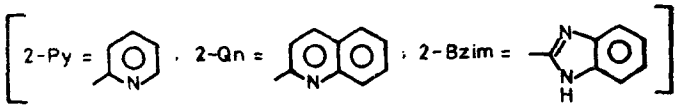
The adduct (1) of methyl isothiocyanate and N,N-diethyl-acetamidine was chosen as the first substrate to be reacted with chloromethyl heterocycles. The feasibility of providing sufficient activation for the methylene group by means of an adjacent suitably substituted aryl group was first proved by condensation of (1) with *p*-nitrobenzyl bromide. This led to the formation of 5-*p*-nitrophenylthiazole (4). A similar reaction has been described by Ried and Kaiser (1976). The stage was now set for investigating halomethyl heterocycles as reactants in this synthesis. We were pleased to find that 2-chloromethylpyridine and 2-chloromethylquinoline gave (5) and (6) respectively in a clean reaction with (1). Likewise, 2-chloromethyl-benzimidazole also participated in the reaction, leading to the 2-benzimidazolyl derivative (7). However, 4-chloromethylthiazole did not possess a methylene group reactive enough to take part in the cyclization.

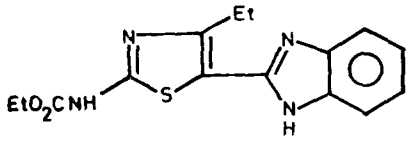
The 2-anilino-5-(2-pyridyl) thiazole (8) was similarly prepared from the phenyl isothiocyanate-N,N-diethyl-acetamidine adduct (2) and 2-chloromethylpyridine. 5-Heteryl thiazole-2-carbamates can be synthesised with equal facility by this procedure. Thus the 5-(2-benzimidazolyl) thiazole-2-carbamates



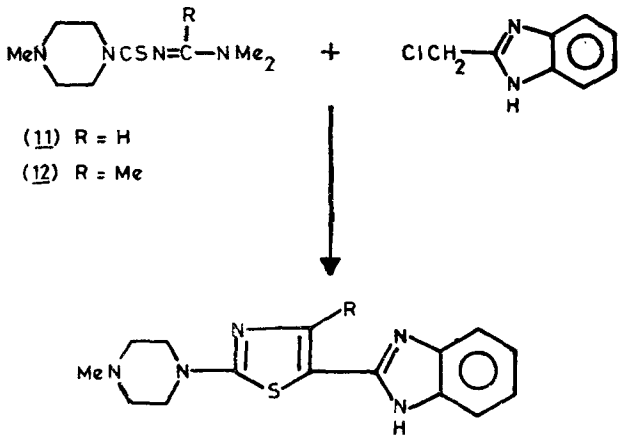
(1) R = Me
(2) R = Ph
(3) R = CO_2Et

(4) R = Me, Ar = 4-$NO_2C_6H_4$
(5) R = Me; Ar = 2-Py
(6) R = Me; Ar = 2-Qn
(7) R = Me, Ar = 2-Bzim
(8) R = Ph, Ar = 2-Py
(9) R = CO_2Et; Ar = 2-Bzim





(10)



(11) R = H
(12) R = Me

(13) R = H
(14) R = Me

(9) and (10) were obtained from the adducts of carbethoxyisothiocyanate with N,N-diethylacetamidine and N,N-diethylpropionamidine respectively.

The methodology for preparing 2-dialkylaminothiazoles was discussed in the previous paper of this series. The same starting materials (11) and (12) were also useful in synthesising the 5-(2-benzimidazolyl)-2-(N-methylpiperazino) thiazoles (13) and (14) respectively ; however, the yields were low in this reaction, probably due to the quaternization of the piperazine nitrogen.

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. 5-*Aryl*-4-*methyl*-2-*methylaminothiazoles*

A mixture of methyl isothiocyanate (20 g) and N,N-diethylacetamidine (31 g) was left at 30° overnight, then digested with ether, cooled and filtered to get the adduct (1) (36·1 g), m.p. 69–72° C.

The adduct (1) (3 g) and *p*-nitrobenzyl bromide (3·5 g) were refluxed in isopropanol (25 ml) for 6 hr, cooled and filtered. The solid was taken in cold water, basified with $KHCO_3$ and filtered. Recrystallization of the solid from ethanol gave 4-methyl-2-methylamino-5-(*p*-nitrophenyl) thiazole (4) (3 g), m.p. 203-205° C (Found : C, 53·30 ; H, 4·80 ; N, 16·53. $C_{11}H_{11}N_3O_2S$ requires C, 53·01 ; H, 4·45 ; N, 16·86%). NMR (DMSO-d_6) : 2·33 (s, Me) ; 2·87 (d, Me) ; 7·5 (d, 2 Ar-H) ; 7·83 (q, NH) ; 8·17 (d, 2Ar-H). MS : 249 (M^+).

The adduct (1) (3 g) was refluxed in isopropanol (25 ml) for 6 hr with 2-chloromethylpyridine (liberated from 2·5 g of the hydrochloride). The solvent was then removed *in vacuo*, the residue dissolved in cold water, basified with $KHCO_3$ solution and the solid filtered. Recrystallization from ethanol gave 4-methyl-2-methylamino-5-(2-pyridyl) thiazole (5) (2·3 g), m.p. 188–191° C. (Found : C, 58·48 ; H, 5·68 ; N, 20·75. $C_{10}H_{11}N_3S$ requires C, 58·53 ; H, 5·40 ; N, 20·48%). NMR (DMSO-d_6): 2·43 (s, Me) ; 2·87 (br, s, Me) ; 6·9 to 8·6 (4 Ar-H). MS : 205 (M^+).

A similar reaction of (1) (3 g) with 2-chloromethyl quinoline (liberated from 3·6 g of the hydrochloride) gave, after crystallization from ethanol, 4-methyl-2-methylamino-5-(2-quinolyl) thiazole (6) (2·3 g), m.p. 203–205° (Found : C, 65·58 ; H, 5·25 ; N, 16·43. $C_{14}H_{13}N_3S$ requires C, 65·87 ; H, 5·13 ; N, 16·46%). NMR (DMSO-d_6): 2·43 (s, Me); 2·9 (dr, s, Me); 7·2 to 8·4 (6 Ar-H). MS : 255 (M^+).

The adduct (1) (3 g) and 2-chloromethylbenzimidazole (3 g) were refluxed in isopropanol (50 ml) for 6 hr, cooled and filtered. Conversion of the solid hydrochloride into the free base and crystallization from methanol–ethanol gave 5-(2-benzimidazolyl)-4-methyl-2-methylaminothiazole (7) (0·8 g), m.p. 315-320° C. More of the same substance was obtained from the isopropanol filtrate by evaporation and basification (Found : C, 59·13 ; H, 5·26 ; N, 23·25. $C_{12}H_{12}N_4S$ requires C, 59·01 ; H, 4·95 ; N, 22·94%). NMR (DMSO-d_6) : 2·57 (s, Me) ; 2·83 (d, Me) ; 6·9 to 7·6 (m, 4 Ar-H) ; 7·83 (q, NH). MS : 244 (M^+).

3.2. 2-*Anilino*-4-*methyl*-5-(2-*pyridyl*) *thiazole*

Phenyl isothiocyanate (13·5 g) and N,N-diethylacetamidine (10·2 g) were mixed and stirred at 0° in isopropanol for 2½ hr, and left at 30° overnight. The solid was filtered and recrystallized from methylene chloride–ether to give the adduct (2) (19·3 g), m.p. 132° C (Found : C, 62·31 ; H, 7·66 ; N, 17·07. $C_{13}H_{19}N_3S$ requires C, 62·62 ; H, 7·68 ; N, 16·86%). NMR ($CDCl_3$) : 1·17 (t, 2Me) ; 2·5 (s, Me) ; 3·4 (q, $2CH_2$) ; 6·9 to 7·5 (5 Ar-H) ; 8·9 (NH).

The above adduct (2) (2 g) was refluxed in isopropanol (25 ml) with 2-chloromethylpyridine (liberated from 1·3 g of the hydrochloride) for 6 hr. The solvent was then removed *in vacuo*, the residue dissolved in cold water, basified with $KHCO_3$ solution and extracted with ethyl acetate. The organic layer was dried and concentrated. Addition of ether to this gave 2-anilino-4-methyl-5, (2-pyridyl) thiazole (8) (0·85 g), m.p. 153°C (Found: C, 67·25 ; H, 5·01 ; N-15·42. $C_{15}H_{13}N_3S$ requires C, 67·40 ; H, 4·90 ; N, 15·72%). NMR ($CDCl_3$) : 2·5 (s, Me) ; 6·8 to 8·6 (9 Ar-H and 1 NH). MS : 267 (M^+).

3.3. 4-*Alkyl*-5-(2-*benzimidazolyl*) *thiazole*-2-*carbamates*

Carbethoxyisothiocyanate (3·6 g) and N, N-diethylacetamidine (3·5 g) were mixed at 0° and let stand at 30° for 2 hr. Ethanol (200 ml) was then added, followed by 2-chloromethylbenzimidazole (5 g) and the solution refluxed for 5 hr. The solid was filtered, the free base liberated from this, and recrystallized from

ethanol to give 5-(2-benzimidazolyl)-4-methylthiazole-2-carbamic acid ethyl ester (9) (4·5 g), m.p. 260–261° C (Found : C, 55·60 ; H, 4·90 ; N, 18·62. $C_{14}H_{14}N_4O_2S$ requires C, 55·62 ; H, 4·67 ; N, 18·54%). NMR (DMSO-d_6) : 1·2 (t, Me) ; 1·5 (s, Me) ; 4·05 (q, CH_2) ; 6·9 to 7·6 (4 Ar-H).

A similar addition of carbethoxy isothiocyanate (10 g) to N,N-diethyl-propionamidine (10 g) followed by reaction with 2-chloromethyl benzimidazole (13 g) in ethanol (400 ml) gave 5-(2-benzimidazolyl)-4-ethylthiazole-2-carbamic acid ethyl ester (10), (11·5 g), m.p. 237° C (Found : C, 57·02 ; H, 5·39 ; N, 18·08. $C_{15}H_{16}N_4O_2S$ requires C, 56·96 ; H, 5·10 ; N, 17·71%). NMR (DMSO-d_6) : 1·33 (t, 2Me) ; 3·2 (q, CH_2) ; 4·33 (q, CH_2) ; 7·1 to 7·8 (4 Ar-H). MS : 316 (M^+).

3.4. 5-(2-*Benzimidazolyl*)-2-(*N-methylpiperazino*) *thiazoles*

The formamidinothiourea (11) (Rajappa *et al* 1982) (10·4 g) was stirred and refluxed in isopropanol (500 ml) with 2-chloromethyl benzimidazole (8·2 g) for 6 hr. The solvent was removed *in vacuo*, the residue dissolved in water, basified and extracted with methylene chloride. After drying, the solvent was evaporated and the residue crystallized from ethanol to give 5-(2-benzimidazolyl)-2-(N-methylpiperazino) thiazole (13) (0·8 g), m.p. 255–258° C. (Found : C, 60·49 ; H, 5·97 : N, 23·05. $C_{15}H_{17}N_5S$ requires C, 60·19 ; H, 5·72 ; N, 23·40%). NMR (DMSO-d_6) : 2·27 (s, Me) ; 2·53 (m, 4H); 3·5 (m, 4H) ; 7·0 to 7·7 (m, 4 Ar-H) ; 7·9 (s, Ar-H). MS : 299 (M^+).

Similar reaction of the acetamidino thiourea (12) (12 g) with 2-chloromethyl benzimidazole (8·5 g) gave 5-(2-benzimidazolyl)-4-methyl-2-(N-methylpiperazino) thiazole (14) (1·2 g), m.p. 257–260° C (Found : C, 61·65 ; H, 6·40 ; N, 22·46. $C_{16}H_{19}N_5S$ requires C, 61·32 ; H, 6·11 ; N, 22·35%). NMR (DMSO-d_6) : 2·23 (s, Me) ; 2·47 (m, 4H) ; 2·57 (s, ME) ; 3·4 (m, 4H) ; 7·0 to 7·7 (m, 4 Ar-H) ; 12·0 (NH). MS : 313 (M^+).

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