An Unexpected Outcome of a General Thiazole Synthesis

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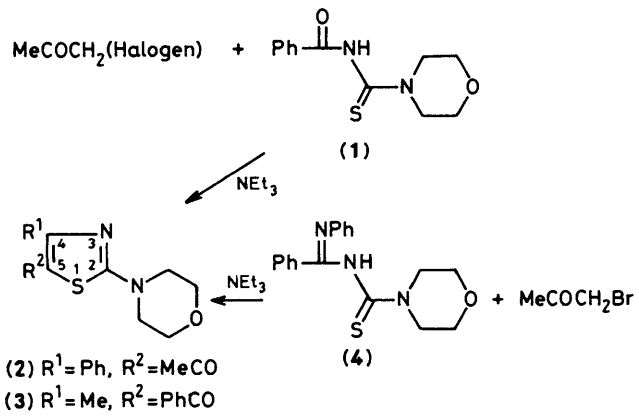
The reaction between *N*-benzoyl-*N'*-methyl-*N'*-phenylthiourea and chloroacetone gives 5-benzoyl-4-methyl-2-(*N*-methyl-*N*-phenylamino)thiazole rather than the 5-acetyl-4-phenylisomer which would be predicted from previous work on this route to thiazoles.

Alternatives to the Hantzsch synthesis of 2-aminothiazoles have been studied actively during the last two decades. One such approach involves condensation between suitable *N,N'*-substituted thioureas and compounds with reactive methylene groups: in effect the ends of a C–N–C–S chain are joined to the methylene C which becomes C-4 of the thiazole ring.[1] The preparation of compound (**2**) from the thiourea (**1**) shown in Scheme 1 is an example from the first general application,[2] and a subsequent variation[3] employs the related *N*-benzimidoyl derivative (**4**) [which may be represented equally well as the Ph–C(NHPh)=N– tautomer]. Later,[4] it was established that an *N*-benzoyl-*N'*-monosubstituted thiourea gives a 2-benzoylimino-3-substituted Δ^4-thiazoline rather than the 2-*N*-monosubstituted aminothiazole, as reported,[2] but the latter is obtained from the corresponding *N*-benzimidoyl-*N'*-monosubstituted thiourea. Notwithstanding this complication no question has been raised hitherto about the nature of the products obtained from the *N',N'*-disubstituted thioureas [*e.g.*, structure (**2**) for the product from the thioureas (**1**) and (**4**)].

In developing work on 2-aminothiazoles with electron-withdrawing groups at position 5 we thought to prepare the 5-acetyl compound (**6**) from *N*-benzoyl-*N'*-methyl-*N'*-phenylthiourea (**7**).[5] Doubts about the product's structure were raised by the mass spectrum which indicated the presence of a benzoyl group, as in structure (**8**). The form and C–H coupling constants of the ^{13}C n.m.r. signals logically ascribed to the C-4 and C(O) atoms also pointed to the isomeric structure, and the matter was put beyond doubt by a crystallographic examination.† For comparison, the compound truly represented by structure (**6**) was prepared unambiguously from 2-(*N*-methyl-*N*-phenylamino)-4-phenylthiazole (**5**) (itself readily obtained from phenacyl bromide and *N*-methyl-*N*-phenylthiourea).[6] The main spectrometric properties of isomers (**6**) and (**8**),‡ both new compounds, confirm the structural assignments, and (*sic*) the 5-acetyl compound (**6**) has its C–Me ^1H n.m.r. signal at δ 1.98. A mechanism for the formation of compound (**8**) from the benzoylthiourea (**7**) will be proposed in the full paper; a key observation is that compound (**8**) is the main product of a Hantzsch condensation between PhCOCHBrCOMe and *N*-methyl-*N*-phenylthiourea.

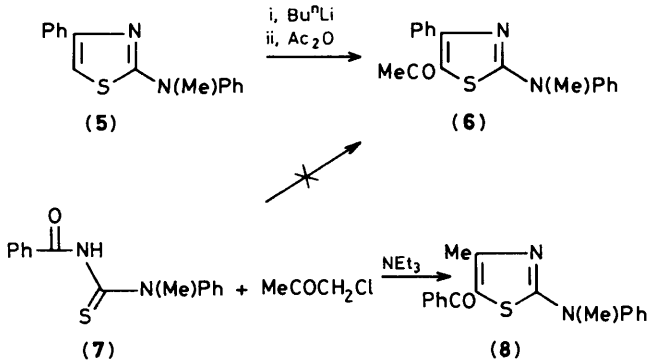
Repetition of the reaction between the benzoylthiourea (**1**) and chloroacetone gave the reported product.[2] Spectrometric examination showed that it, too, has the unexpected features of a benzoyl group *etc.*, denoting structure (**3**) rather than structure (**2**) as published.[2] Now although Ried and Kaiser[3] concluded that the product from the *N*-benzimidoylthiourea (**4**) was the same as that[2] from the *N*-benzoylthiourea, comparison of the experimental details argues strongly against this: the melting points are 150—153 °C[2] and 204 °C.[3] Signifi-



Scheme 1

† We are indebted to Dr. C. K. Prout, Chemical Crystallography Laboratory, Oxford University, for this study.

‡ Spectrometric data: for (**6**), i.r. (CCl_4, cm^{-1}) 1635; u.v. [EtOH, nm (ε)] 252 (13 400), 344 (13 200); *m/z* (abundance) 308 (M^+, 100), 293 (69), 43 (43); n.m.r. ($CDCl_3$, δ), ^1H: 1.98 (CH_3–CO), ^{13}C: 158.5 (t, *J* 3.8 Hz, C-4), 190.5 [q, *J* 6.1 Hz, *C*(O)]. For (**8**), i.r. (CCl_4, cm^{-1}) 1633; u.v. [EtOH, nm (ε)] 242 (10 700), 356 (16 700); *m/z* (abundance) 308 (M^+, 100), 105(43), 77(60); n.m.r. ($CDCl_3$, δ), ^1H: 2.41 (CH_3–C-4), ^{13}C: 160.1 (q, *J* 6.8 Hz, C-4), 188.0 [t, *J* 3.6 Hz, C(O)].



cantly, Ried and Kaiser reported a C–Me ^{1}H n.m.r. signal at δ 1.90 in their product[3] which, therefore, is almost certainly correctly formulated as the 5-acetyl compound (**2**), a conclusion in consonance with the work of Rajappo *et al.*[4] on the *N'*-monosubstituted thioureas. Other related compounds[2,3] will be discussed when the results obtained with a series of *N*-acyl-*N'*,*N'*-disubstituted thioureas and α-halogenoketones[7] are presented.

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