

An Unexpected Outcome of a General Thiazole Synthesis

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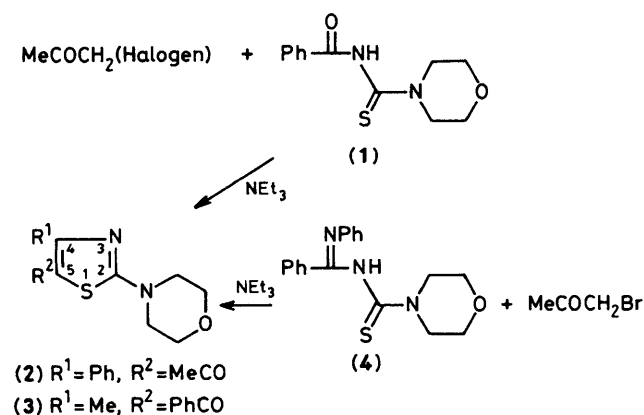
The reaction between *N*-benzoyl-*N'*-methyl-*N'*-phenylthiourea and chloroacetone gives 5-benzoyl-4-methyl-2-(*N*-methyl-*N*-phenylamino)thiazole rather than the 5-acetyl-4-phenylisomer which would be predicted from previous work on this route to thiazoles.

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 variation³ 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 ¹³C 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.

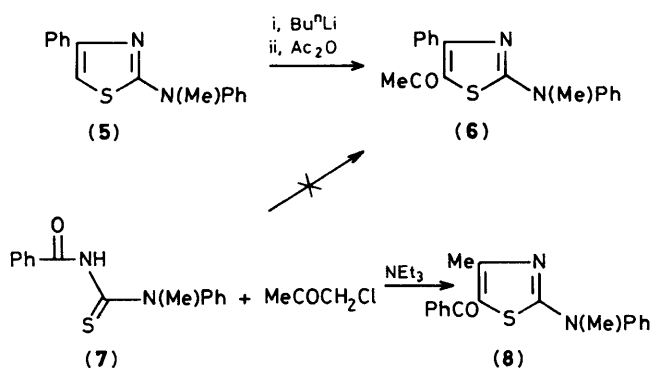
Repetition of the reaction between the benzoylthiourea (1) and chloroacetone gave the reported product.² Spectrometric examination showed that it, too, has the unexpected features of a benzoyl group *etc.*, denoting structure (3) rather than structure (2) as published.² Now although Ried and Kaiser³ concluded that the product from the *N*-benzimidoylthiourea (4) was the same as that² from the *N*-benzoylthiourea, comparison of the experimental details argues strongly against this: the melting points are 150–153 °C² 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. (CCl₄, 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. (CDCl₃, δ), ¹H: 1.98 (CH₃–CO), ¹³C: 158.5 (t, *J* 3.8 Hz, C-4), 190.5 [q, *J* 6.1 Hz, C(O)]. For (8), i.r. (CCl₄, 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. (CDCl₃, δ), ¹H: 2.41 (CH₃–C-4), ¹³C: 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 ^1H n.m.r. signal at δ 1.90 in their product³ which, therefore, is almost certainly correctly formulated as the 5-acetyl compound (2), a conclusion in consonance with the work of Rajappa *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 -halogenoketones⁷ are presented.

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