2-Benzamido-4-phenylthiazoles as Unexpected Products of a Novel Rearrangement from the Reaction of 2-Bromo-1,3-bis(4-substituted)phenylpropane-1,3-diones and Thiourea

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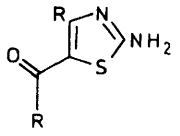
A rearrangement leading to 2-benzamido-4-phenylthiazoles from the Hantzsch reaction under basic conditions is reported.

The most efficient route to 4,5-disubstituted 2-aminothiazoles uses the Hantzsch synthesis involving the reaction of an α-halogeno ketone and thiourea. The preparation of (**1a**) by treating 2-bromo-1,3-diphenylpropane-1,3-dione with thiourea in boiling ethanol has been described.[1] We carried out this reaction in DMF at ambient temperature followed by addition of triethylamine as a base. Column chromatography of the residue from the work-up afforded besides the expected product (**1a**), a major component (**2a**), and a small amount of 5-benzoyl-2-formamido-4-phenylthiazole. The compound (**2a**) was identical (spectra and mixed m.p.) with the product obtained by benzoylating[2] 2-amino-4-phenylthiazole.

On repeating the above reaction and also using other 2-bromo-1,3-bis(4-substituted)phenylpropane-1,3-diones, a variable yield of two respective products (**1**) in 30—80% and (**2**) in 18—60% was obtained in each case. Reverse phase h.p.l.c. was also employed to separate and quantify the products.†

DMF was chosen because of the good solubility of the diketones in this solvent. Besides its solvent effects, it also usually contains a significant amount of dimethylamine. The

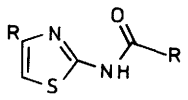
† The structures of all the compounds were characterised using spectroscopic methods. All new compounds gave satisfactory data and elemental analyses (within ±0.4% of theoretical values).



(1) M.p. (°C)

R

a; Ph, 221–222 (lit.,[1] 218–220 °C)
b; C_6H_4F-*p*, 220–221 (from EtOAc)
c; C_6H_4OMe-*p*, 207–208 (from Me_2CO)



(2) M.p. (°C)

R

a; Ph, 124–126 (lit.,[2] 124–125 °C)
b; C_6H_4F-*p*, 219–220 (from EtOH)
c; C_6H_4OMe-*p*, 193–194 (from EtOH)

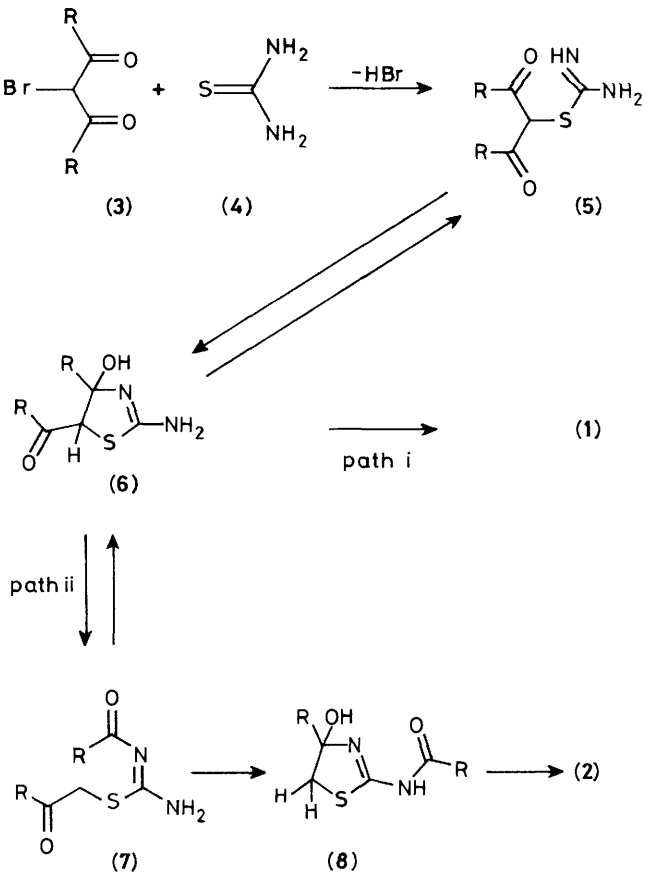
Hantzsch reaction is normally performed in a neutral solvent. The formation of (**2**) under these conditions is intriguing. We carried out a reaction in boiling ethanol, as prescribed by Gudriniece *et al.*[1] This produced, as expected, predominantly (**1a**), but also a small amount of (**2a**) in the ratio of 96:4 respectively. Presumably these authors did not observe this minor component.

A rearrangement involving a migration of an acyl group from the ring carbon to the exocyclic amino function or *vice versa* is not known. In order to discount such a possibility (**1a**) and (**2a**) were separately heated in DMF alone at 110—120 °C for 24 h and also in the presence of added 1 equiv. of HBr or triethylamine. No interconversion was detected.

In order to rationalise the formation of (**2**), we turned to the mechanistic aspect of the reaction. According to the Hantzsch mechanism[3] (see Scheme), the first step is the formation of an isothiourea (**5**) by nucleophilic attack of the sulphur on the carbon bearing the halogen (Br) atom to liberate 1 mol equiv. of hydrogen halide (HBr). The next stage involves attack of the nitrogen at one of the carbonyl functions to form a cyclic aminal (**6**), followed by dehydration to give thiazoles.

We consider (**6**) as a common intermediate. Under normal Hantzsch conditions, it undergoes a facile acid catalysed dehydration (path i) to form expected aminothiazoles (**1**). On the other hand, (**6**) is also set for a retro-aldol reaction (path ii) leading to a new open-chain intermediate (**7**) by cleavage of the C(4)–C(5) bond under basic conditions. It seems that in the absence of acid, a retro-aldol process proceeds in preference to dehydration. The next sequence may involve attack of the unsubstituted nitrogen at the carbonyl function to generate a new cyclic intermediate (**8**), which dehydrates to give the rearranged products (**2**). This explains the formation of (**2**) in variable yields, since arbitrary volumes of DMF containing proportionally varying amounts of dimethylamine were used. That the rearrangement is base catalysed is further confirmed by almost exclusive formation of (**2a**), when the reaction is carried out in the presence of triethylamine either in DMF or in boiling ethanol. On the other hand, predominantly (**1a**) was obtained in the presence of added HBr in either of these solvents [ratio of (**1a**):(**2a**) = 98:2].

It is interesting to note that in a recent study,[4] an analogous cyclic intermediate, such as (**6**), has been proposed to account



Scheme.

for interconversion of an open-chain intermediate, 2-(*N*,*N*-disubstituted amino-*N*-benzoyliminomethyl)thioacetophenone, *cf.* (**7**), to give the corresponding thiodiketone, *cf.* (**5**). The cyclic intermediate in this case is derived from an internal aldol condensation of the former, and undergoes a fission of the N–C(4) bond to generate the latter.

It has been suggested from studies on related systems[5] that open chain intermediate α-thioketones are in equilibrium with the cyclic hydroxythiazolines. Thus, it seems that an interconversion of (**5**) and (**7**) occurs through a common intermediate (**6**). The conversion of (**6**) into (**5**) appears to be influenced in the case, where the exocyclic nitrogen is disubstituted, whereas the reaction takes predominantly path ii when this nitrogen is unsubstituted. Thus, the nature of the required products can be predetermined by a choice of reagents and conditions.

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