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Unusually Facile Aminolysis of β-Ketoesters

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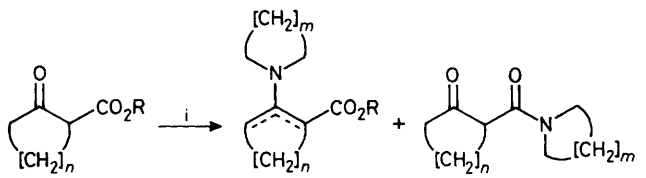
The unusually facile aminolysis of β-ketoesters does not proceed *via* simple amine nucleophilic attack on the ester carbonyl.

The aminolysis of unactivated esters is known to be a difficult reaction, as shown by the number of methods devised to facilitate it.[1] It is especially difficult with substituted amines, where uncatalysed aminolysis by primary amines requires heating over 200 °C for many hours[2] and the corresponding reaction with secondary amines has not been described. In contrast with these slow reactions, we report the very facile aminolysis of β-ketoesters which is possible at temperatures around 100 °C.

In another paper,[3] we described the preparation of β-enaminoesters (**2**) from secondary amines and β-ketoesters (**1**) by gentle reflux in benzene. It was noticed that a stronger reflux (high bath temperature) resulted in the formation of substantial amounts of the corresponding β-ketoamide (**3**) along with the expected enaminoester[4] (Scheme 1). When the solvent was changed to toluene, the reaction of piperidine and methyl 2-oxocyclohexanecarboxylate gave a 2:1 mixture of β-ketoamide and enaminoester, whereas the reaction of azepane with ethyl 2-oxocycloheptanecarboxylate yielded only the β-ketoamide (69%).

Another manifestation of this rapid aminolysis occurs in the v.p.c. monitoring of the enamine formation reactions, where the injection of a β-ketoester–amine mixture into the chromatograph at 190 °C results in the elution of the β-ketoamide as the major peak with little β-ketoester left. The β-ketoamide was proved to be formed on the v.p.c. column by an 'on column pursuit' experiment; the less volatile β-ketoester was injected first on the column, followed by the amine. The result of this injection was again an important β-ketoamide peak, somewhat broadened, and at shorter retention time than that of the authentic material injected in the normal way. The retention time of this peak was found to decrease with increasing delay between the ester and amine injections, therefore showing that the slower moving β-ketoamide is formed further along the v.p.c. column.



(1) (2) (3)

Scheme 1. i, $[\overline{CH_2}]_{m+2}NH$ in refluxing benzene or toluene. $n = 3, 4$, $m = 2$—4. R = Me, Et.

This v.p.c. experiment has been repeated with all the possible combinations of three secondary amines (pyrrolidine, piperidine, and azepane) and ethyl acetoacetate, 2-ethoxycarbonylcyclo-pentanone, -hexanone, and -heptanone. In all these experiments, an exhaustive aminolysis occurred both in premixed coinjection and in 'on column pursuit' experiments.

In order to clarify the mechanistic requirements of this reaction, several esters were tested for the ease of aminolysis by the v.p.c. method. Thus, coinjection of piperidine and ethyl cyclohexanecarboxylate showed no trace of amide, as one might expect from the known unreactivity of simple esters. The less sterically hindered ethyl benzoate also failed to react. These results therefore show the importance of the carbonyl group in the observed effect.

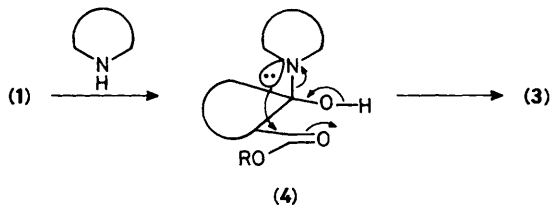
A possible mode of action of the carbonyl group could be to make the ester more electrophilic by a simple inductive effect. This was, however, ruled out by the failure of ethyl *p*-nitrobenzoate to react, which should be a much better electrophile than the β-ketoesters, as judged by the pK_a of the corresponding acids (3.90 for the β-ketoacid[5] and 3.42 for *p*-nitrobenzoic acid[6]).

Another way the carbonyl group could possibly catalyse the reaction would be by an internal proton transfer from the enol form.[7] This mechanism was, however, rejected when ethyl salicylate failed to react.

The remaining possibility to explain the involvement of the carbonyl group in the aminolysis of β-ketoesters is *via* intermediate (**4**). At this point, two possible mechanisms† have been retained.

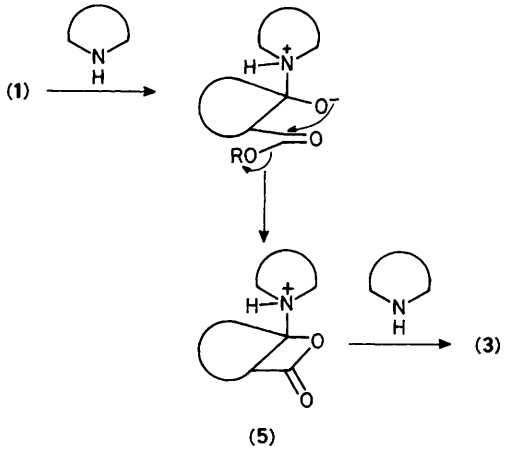
The first mechanism is shown in Scheme 2. It involves an internal amine transfer through a four-membered ring ammonium intermediate or transition state, which is precedented.[8] The degree of concertedness indicated here may not be appropriate.

† A third possible mechanism would involve a retro-Dieckman, anion exchange, Dieckman sequence. This is, however, unlikely since the non-cyclic ethyl acetoacetate would not be expected to recombine to a β-ketoamide under v.p.c. conditions.



(4)

Scheme 2



(5)

Scheme 3

Another possible mechanism is depicted in Scheme 3. It is based on the known case of *o*-formylbenzoate esters,[9] which are also hydrolysed and aminolysed faster than expected. The only difference is that a β-lactone (**5**) would be involved in this case.

Finally, these two mechanisms are also consistent with the observation that ethyl cyanoacetate gave no aminolysis under the v.p.c. conditions. The details of the mechanism of this reaction are currently under investigation.

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