\(\alpha\)-Amidoalkylation of Alkanecarboxylic Anhydrides

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In the course of our research on \(\alpha\)-amidoalkylation reactions\(^1\), we have found that alkanecarboxylic anhydrides, having at least one hydrogen atom in the \(\alpha\) position to the functional group, are new and versatile substrates for this type of reaction.

These anhydrides (4) react\(^2\), at room temperature and in the presence of an acid catalyst, such as sulfuric, \(p\)-toluenesulfonic, methanesulfonic, phosphoric acid, and hydrogen chloride gas\(^3\), with amidoalkylating agents such as the \(N,N'\)-benzylidene-bis-amides 1 or their precursors, aromatic aldehydes plus amides (2+3; Scheme A, and Table, Method A) to give products 5, 6, and 7.

![Scheme A]

Similar results were obtained by reaction of aromatic aldehydes (2) with nitriles (8) and carboxylic acids (9) having hydrogen at the \(\alpha\)-carbon, in the presence of 100\% sulfuric acid at 100° (Scheme B, Table, Method B).

![Scheme B]

Under these conditions, dehydration of the carboxylic acids (9) to anhydrides (4) is possible\(^4\), together with the formation of \(N,N'\)-benzylidene-bis-amides (1) from nitriles (8) and aromatic aldehydes (2). As a result, the course of this reaction is similar to that shown in Scheme A (Method A).

Both methods are likely to involve a similar intermediate (5); however, under the more drastic conditions of Method B compound 5 cannot be isolated and compound 7 is obtained only to a limited extent.

Both methods are suitable for the synthesis of \(N\)-acyl-\(\beta\)-aminoacids 6. Using Method A, treatment of the reaction mixture can be varied, thus giving amides of \(N\)-acyl-\(\beta\)-aminoacids (7) and 6-oxo-5,6-dihydro-4\(H\)-1,3-oxazines (5).

As in the case of the amidoalkylation of olefins\(^5\), the most likely hypothesis on the mechanism involves a regiospecific polar 1,4-cycloaddition of the amidoalkyl ion (11, Scheme C), probably present as an ion pair, to the tautomeric form of the alkanecarboxylic anhydride (12).

![Scheme C]

The tautomeric form 12 is probably responsible for the ketene-like reactivity of anhydrides\(^6\).\(^7\).\(^8\) This hypothesis finds support in the fact that by treating hexafluoroacetone with acetic anhydride at room temperature in the presence of sulfuric acid, 3-hydroxy-3,3-bis-[trifluoromethyl]-propanoic acid was isolated, after alkaline hydrolysis of the reaction mixture, along with hexafluoroacetone diacetate. Other authors\(^9\) reported the formation of \(\beta,\beta\)-bis-[trifluoromethyl]-\(\beta\)-propiolactone, under conditions similar to those employed by us and proposed for this reaction a mechanism involving the tautomeric form of acetic anhydride (12, \(R^3 = R^4 = H\), Scheme C).
Table. N-Acyl-β-amino acids (6) from α-Amidoalkylation of Alkanecarboxylic Anhydrides

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Method¹</th>
<th>Yield¹ of 6 %</th>
<th>m.p.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>A⁴</td>
<td>93</td>
<td>199 (192–193)¹¹</td>
</tr>
<tr>
<td>b</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>B</td>
<td>41</td>
<td>225–229</td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>B</td>
<td>40</td>
<td>182–185</td>
</tr>
<tr>
<td>d</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>B</td>
<td>34</td>
<td>158–162 (160–162)¹²</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>CH₃</td>
<td>CH₃</td>
<td>B</td>
<td>33</td>
<td>172–174 (168–170)¹³</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>A</td>
<td>28</td>
<td>mixture of diastereoisomers</td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>H</td>
<td>-ICH₃</td>
<td>B</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>h</td>
<td>H</td>
<td>H</td>
<td>-ICH₄</td>
<td>B</td>
<td>39</td>
<td>mixture of diastereoisomers</td>
</tr>
</tbody>
</table>

¹ Method A: Alkanecarboxylic anhydride (100 g), N,N'-aryliden-bis-amide (0.1 mol), 100% H₂SO₄ (0.1 mol). T = 15°C, reaction time: 65 hr for compound a and 100 hr for compound f. Method B: Alkanecarboxylic acid (100 g), aromatic aldehyde (0.2 mol), nitric (0.2 mol), 100% H₂SO₄ (0.2 mol), T = 100°C, reaction time: 3 hr.

² Yields were determined on isolated products. Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds listed in the table.

In addition, we have found that triphenylcarbinol reacts with acetic anhydride in the presence of sulfuric acid at 60°C to give 3,3,3-triphenylpropanoic acid together with its anhydride; also in this case the tautomeric form 𝛼 (Scheme C) is likely to be involved.

Work is in progress to extend the scope of the reaction.

The two experimental methods (A and B) used are exemplified by the preparations of 3-benzamido-3-phenylpropanoic acid (6a) and 3-benzamido-3-(4-bromophenyl)propanoic acid (6b), respectively, described in the experimental part. The different possibilities of working up the reaction mixture (Method A) are shown in the preparation of 3-benzamido-3-phenylpropanoic acid (7a) and of 2,4-diphenyl-6-oxo-5,6-dihydro-4H-1,3-oxazine (5a).

The structures of the reaction products were determined by mass, N.M.R., and I.R. spectrometry.

Method A.

3-Benzamido-3-phenylpropanoic Acid (6a):
N,N'-bentziliden-bis-benzamide (33 g, 0.1 mol) is added at ~15°C to a solution of 100% sulfuric acid (9.8 g, 0.1 mol) in acetic anhydride (100 g) previously prepared at 5°C. The suspension is stirred at 15°C for 65 hr; the solution (A), thus obtained, is poured onto crushed ice, made alkaline with 40% aqueous sodium hydroxide, and extracted with diethyl ether. The alkaline aqueous solution is acidified with conc. hydrochloric acid. The product is isolated by filtration, washed with water and then with diethyl ether; yield: 25 g (93%); m.p. 199°C (192–193)¹¹.

C₁₉H₁₆NO₃ calc. C 71.36 H 5.61 N 5.20 (269.29) found 71.14 5.63 5.20

3-Benzamido-3-(4-bromophenyl)-propanoic Acid (6b):
A mixture of 3-benzamido-3-(4-bromophenyl)-propanoic acid (6b) is added to 20°C, poured onto crushed ice, made alkaline with 40% aqueous sodium hydroxide at ~15°C, and extracted with ether. The alkaline aqueous solution is acidified with conc. hydrochloric acid. The product is isolated by filtration, washed with water and then with diethyl ether; yield: 28 g (40%); m.p. 225–229°C.

C₁₉H₁₄BrNO₃ calc. C 55.19 H 4.05 N 4.02 (348.20) found 55.22 4.05 3.95

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1 C. Giordano, G. Ribaldone, G. Borsotti, *Synthesis* 1971, 92
4 Sulfuric acid is the most effective catalyst for this reaction; hydrochloric acid catalyzes the reaction only at higher temperature.
11 C. Giordano, work in progress.