Synthesis of anhydrides from acyl halides and zinc carboxylates under aprotic conditions

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Synthesis of symmetric as well as unsymmetrical carboxylic acid anhydrides from zinc carboxylates and acid chlorides under aprotic conditions in high yields is reported.

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Carboxylic acid anhydrides are very important in organic chemistry since these serve as intermediates for the synthesis of esters, amides and useful in the peptide synthesis. This useful transformation can be accomplished by the reaction of carboxylic acid and a dehydrating agent such as DCC, acetic/trifluoroacetic or phosphoric anhydrides. By treating a carboxylic acid salt with sulfur and bromine, by treating the free acid with a N-trihaloacetylimidazole or with carbon tetrachloride and tris-(dimethylamino)phosphine.

The reaction of acyl halide with metal carboxylate is another common method which affords either symmetrical or unsymmetrical anhydrides. Though several reagents have been developed for the purpose, the most common among them are by the reaction of an acid chloride and metal carboxylates such as thallium carboxylates, mercury carboxylates, silver carboxylates or sodium carboxylates under aqueous conditions.

Zinc carboxylates can be readily prepared by the reaction of zinc oxide or zinc carbonate and carboxylic acids. We now report that, a variety of stable anhydrides can be easily prepared by treating with different acid chlorides under aprotic conditions in toluene as solvent at 40°C to get anhydrides in high yields as shown in Scheme I.

Scheme I

Although various methods have been reported in the literature for the synthesis of anhydrides, we consider the present method to be effective for the synthesis of symmetric as well as unsymmetrical anhydrides in high yields. The yields, physical properties and spectral data of the anhydrides prepared by our method have been presented in Table I.

The RC⁺O cations have been prepared earlier and are shown to be exceptionally stable, the present

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>m.p. °C</th>
<th>IR cm⁻¹</th>
<th>¹H NMR (δ, ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-</td>
<td>Ph-</td>
<td>30</td>
<td>92</td>
<td>42</td>
<td>1790, 1734</td>
<td>7.40-8.20 (10H, m)</td>
</tr>
<tr>
<td>2</td>
<td>Ph CH₂-</td>
<td>Ph</td>
<td>30</td>
<td>95</td>
<td>liq 1</td>
<td>1810, 1730</td>
<td>3.75 (2H, s), 7.75-8.00 (10H, m)</td>
</tr>
<tr>
<td>3</td>
<td>p-Cl PhOCH₂-</td>
<td>Ph-</td>
<td>40</td>
<td>90</td>
<td>53-55</td>
<td>1817, 1756</td>
<td>4.75 (2H, s), 7.08-7.80 (4H, dd)</td>
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<tr>
<td>4</td>
<td>Ph CH=CH-</td>
<td>Ph</td>
<td>20</td>
<td>80</td>
<td>49-52</td>
<td>1792, 1724</td>
<td>6.60-6.90 (1H, m), 730-8.25 (11H, m)</td>
</tr>
<tr>
<td>5</td>
<td>CH₃-</td>
<td>Ph</td>
<td>15</td>
<td>78</td>
<td>liq</td>
<td>1815, 1734</td>
<td>2.25 (3H, s), 7.30-8.00 (5H, m)</td>
</tr>
<tr>
<td>6</td>
<td>p-Cl Ph-</td>
<td>Ph</td>
<td>50</td>
<td>95</td>
<td>72</td>
<td>1786, 1725</td>
<td>7.50 (2H, d), 7.30-8.05 (2H,d), 7.40-8.20 (5H, m)</td>
</tr>
<tr>
<td>7</td>
<td>p-NO₂ Ph-</td>
<td>Ph-</td>
<td>50</td>
<td>93</td>
<td>131</td>
<td>1788, 1729</td>
<td>815 (2H, d), 828 (2H, d) 7.50-7.95 (5H, m)</td>
</tr>
</tbody>
</table>
reaction may be considered to proceed through the following ion-quadruplet mechanism (Scheme II) into anhydrides, as shown in case of reaction between tertiary-alkyl halides and zinc carboxylates under similar reaction conditions.12

\[
\begin{align*}
\text{R'CO}^+ & \quad \text{Cl}^- \\
\text{RCOO}^- & \quad \text{Zn}^+ (\text{-OCOR}) \\
\end{align*}
\]

Scheme II

Experimental Section

All acid chlorides are prepared according to standard procedures and purified before use. Zinc oxide, zinc carbonate and other solvents were purchased from Rankem/BDH and were purified and dried prior to use. Yields refer to the isolated yields of the products after purification by column chromatography using 60-120 mesh silica gel with a suitable eluent. Melting points were obtained by capillary method and are uncorrected. Analytical TLC performed on precoated aluminum plates with Merck silica gel 60 F-254 as the adsorbent. The developed plates were air dried and irradiated with UV light. IR spectra were recorded on a NICOLET 400D FT-IR Spectrophotometer. GC-mass analysis was performed on a Shimadzu GC-MS QP 5050A instrument. The \( ^1 \)H NMR (ppm in \( \delta \) values) spectra were recorded on a Bruker 300 MHz spectrometer with TMS as internal standard.

General Procedure

Preparation of zinc carboxylates I: Zinc oxide (5 mmole) and the carboxylic acid (10 mmole), were magnetically stirred in toluene (25 mL) under reflux for about 2-4 hr in a flask equipped with a Soxhlet extractor filled with anhydrous sodium sulphate to remove the water of dehydration by azeotropic extraction. The course of the reaction was followed by TLC [5% EtOAc: pet. ether (40-60°C)] after the completion of the reaction, employed directly for the synthesis of anhydrides (below).

Preparation of anhydrides 3: To the zinc carboxylate I (from above) in toluene, carboxylic acid chloride (10 mmole) was added while stirring. The mixture was stirred at 40°C till the reaction was complete [TLC – 5% EtOAc: pet. ether (40-60°C)]. The reaction mixture was filtered, washed with ice cold 5% sodium bicarbonate (10 mL) and extracted with ether (2 × 10 mL). The combined extract was dried over anhydrous sodium sulphate and the solvent removed under vacuum to get the anhydride. The yields, physical constants, IR and \( ^1 \)H NMR spectral data of the anhydrides prepared are given in Table I.

Acknowledgement

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References

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