Preparation and Properties of N-Monoalkylated Imidic Esters

ÅKE PILOTTI, ALF REUTERHÅLL and KURT TORSSELL

Institute of Organic Chemistry, University of Stockholm, Stockholm, Sweden

CARL-GUNNAR LINDBLAD

Central Research and Control Laboratory of the Swedish Pharmaceutical Society, Solna, Sweden

Imidic esters were prepared by the action of triethylxonium tetrafluoroborate or dimethylsulphate on secondary amides or by the action of alcohols on nitrilium salts. The compounds hydrolyze easily in water, have basic properties and form crystalline tetrafluoroborates. Salt formation gives rise to two isomeric products. The synthetic utility of the functional group was examined. A mild deacetylation method was worked out. Tetrazoles were formed by the action of hydrazoic acid on nitrilium salts. Acylation of imidic esters leads to 1-alkoxy-1-acylamino-1-alkenes.

Members of the aromatic series are well known and used synthetically for the preparation of diarylamines (Chapman rearrangement). Apart from cyclic imidic esters, few aliphatic derivatives have been described due to their sensitivity to hydrolytic cleavage. Scattered information on preparations and properties is found in the literature. This work presents properties and preparative methods together with an investigation of the synthetic utility of the functional group.

Preparation of imidates. Method A. Addition of alcohols to nitrilium salts, prepared from nitriles and triethylxonium tetrafluoroborate, gave crystalline salts of imidic esters, which upon treatment with base afforded the free imidic esters, eqn. (1).

\[ \text{R} - \text{C} = \bigodot \text{N} - \text{C}_2\text{H}_5 \xrightarrow{\text{R'OH}} \text{R} - \text{C} = \bigodot \text{NHC}_2\text{H}_5 \xrightarrow{\text{OH}^-} \text{R} - \text{C} = \text{NC}_2\text{H}_5 \bigodot \text{OR'} \]

Method B. Secondary amides are O-alkylated in high yields by triethylxonium tetrafluoroborate in methylene chloride, eqn. (2).

* Present address: Institute of Organic Chemistry, University of Aarhus, Aarhus, Denmark.
The neutralization stage is critical and low yields are experienced because of hydrolytic cleavage. \(N\)-Phenylcaproamide, \(N\)-ethyl and \(N\)-phenyl-phenylacetamide, benzamidine, and \(N\)-ethylbenzamidine were \(O\)-alkylated quantitatively, as judged by the IR spectra of the crude products; but on neutralization the starting material was isolated as the main product. In general, higher yields of imidic esters were obtained when the crude product, freed from solvent, was added with cooling to the aqueous base.

**Method C.** \(O\)-Methylation can be accomplished by heating the amide for several hours with dimethyl sulphate, which is less active than the ethyl-oxonium salt. Simple aliphatic amides, acetonilide, \(p\)-methoxyacetanilide (reacts rapidly), benzamide, were alkylated whereas \(p\)-nitroacetanilide and benzamidine were not attacked. Thus a high electron density on the oxygen is favourable for the reaction.

**Properties.** The amidates are colourless basic liquids with an amine-like odour. They give crystalline deliquescent tetrafluoroborates and hydrolyze quickly according to route 3a and/or b in acidic solution, but are fairly stable in alkaline solution.

\[
\text{R} - \text{C} = \text{O} \xrightarrow{(\text{C}_2\text{H}_5)_3\text{O}^+} \text{R} - \text{C} - \text{OC}_2\text{H}_5 + \text{NHR}' + \text{NHR}'
\]

\[
\begin{align*}
\text{O} & \quad \text{R} - \text{C} - \text{OC}_2\text{H}_5 + \text{R}'\text{NH}_4 \\
\text{NR}' & \quad \text{R} - \text{C} - \text{NHR}' + \text{C}_2\text{H}_5\text{OH}
\end{align*}
\]

The polarity of the amidates is lower than that of the amides, which is evident from the difference in boiling points of the isomeric compounds I and II.

\[
\begin{align*}
\text{C}_2\text{H}_5 - \text{C} = \text{O} & \quad \text{C}_2\text{H}_5 - \text{C} - \text{OC}_2\text{H}_5 \\
\text{N}(\text{C}_2\text{H}_5)_2 & \quad \text{N}\text{C}_2\text{H}_5 \\
\text{I} 191^\circ/760 & \quad \text{II} 126^\circ - 127^\circ/760
\end{align*}
\]

According to the IUPAC nomenclature II is to be named ethyl \(N\)-(ethyl) propaniminate.

**Spectral data.** The imidates have a strong absorption band around 1666 cm\(^{-1}\) in the IR range, with an intensity of approx. 500. \(N\)- or \(C\)-arylation and salt formation affect the position and intensity only slightly. Tables 1 and 2. The salts show a second band around 1535 cm\(^{-1}\), with less than half the intensity of the former absorption. Our findings have bearings on the interpretation of the origin of the amide bands I and II. The secondary amides

exhibit a strong carbonyl absorption near 1650 cm\(^{-1}\) and a second band in the region of 1550 cm\(^{-1}\). Since the amide I band (N–C=O) and the imidate band (N=C–O) fall in the same position, the assignment of the absorption at 1550 cm\(^{-1}\) to a C=N stretching motion of double bond character is irrelevant. The view that the second band originates from N–H deformation motions is strongly supported.

In the NMR spectra, the OCH\(_3\) group of the imidate function is found at \(\delta=3.63\) (CDCl\(_3\)). II gave the following data (CDCl\(_3\)): \(\delta=4.06\), O–CH\(_2\)--, q; \(\delta=3.28\), N–CH\(_2\)--, q; \(\delta=2.26\), C–CH\(_2\), q; \(\delta=1.23\), OCH\(_2\)CH\(_3\), t; \(\delta=1.13\), NCH\(_2\)CH\(_3\), t; \(\delta=1.11\), CCH\(_2\)CH\(_3\), t. The coupling constant of the ethyl protons is 7.0 cps. In the salts the positions of the protons around the functional group are shifted to lower field. HBF\(_4\) salt of II: \(\delta=4.61\), O–CH\(_2\)--, q; \(\delta=3.45\), N–CH\(_2\)--, quint; \(\delta=2.84\), C–CH\(_2\), q. The N–CH\(_2\) protons couple both with the NH and the CH\(_3\) group and appear as a quintet.

The aliphatic imidates and salts show only end absorption in the UV region, \(\varepsilon_{250}<100\).

_Cis-trans isomerism._ Salt formation is expected to give two products III and IV.

**Table 1. Physical data of imidic esters, R−C=N−R''**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Yield %</th>
<th>B.p. °C/mm Hg</th>
<th>Mol. weight</th>
<th>Method</th>
<th>(\varepsilon_{\text{C=N}}) cm(^{-1}) CHCl(_3)</th>
<th>(\varepsilon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>25</td>
<td>126–127/760</td>
<td>129.2</td>
<td>B</td>
<td>1667</td>
<td>428</td>
</tr>
<tr>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>56</td>
<td>127–130/760</td>
<td>129.2</td>
<td>A</td>
<td>1667</td>
<td>447</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>65</td>
<td>99–99/14(\text{a})</td>
<td>163.2</td>
<td>A</td>
<td>1665</td>
<td>655</td>
</tr>
<tr>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>C(_2)H(_5)</td>
<td>61</td>
<td>97–98/12</td>
<td>177.2</td>
<td>A</td>
<td>1660</td>
<td>624</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>n-C(_6)H(_13)</td>
<td>60</td>
<td>147–148/12</td>
<td>171.3</td>
<td>A</td>
<td>1688</td>
<td>435</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>6</td>
<td>113/760</td>
<td>115.2</td>
<td>A</td>
<td>1674</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>i-C(_6)H(_11)</td>
<td>CH(_3)</td>
<td>37</td>
<td>125/760</td>
<td>129.2</td>
<td>A</td>
<td>1671</td>
<td>409</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>cyclohexyl</td>
<td>CH(_3)</td>
<td>73</td>
<td>92–95/20</td>
<td>169.3</td>
<td>A</td>
<td>1672</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>32</td>
<td>113–115/760</td>
<td>115.2</td>
<td>A</td>
<td>1672</td>
<td>365</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>i-C(_6)H(_11)</td>
<td>CH(_3)</td>
<td>59</td>
<td>42–43/19</td>
<td>143.2</td>
<td>A</td>
<td>1668</td>
<td>473</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>cyclohexyl</td>
<td>CH(_3)</td>
<td>69</td>
<td>100/19</td>
<td>183.2</td>
<td>A</td>
<td>1667</td>
<td>515</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>31</td>
<td>31–33/12</td>
<td>129.2</td>
<td>C</td>
<td>1679</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>36</td>
<td>91–92/17(\text{b})</td>
<td>149.2</td>
<td>C</td>
<td>1666</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>H</td>
<td>37</td>
<td>93–95/12(\text{c})</td>
<td>135.2</td>
<td>C</td>
<td>1628</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>CH(_2)</td>
<td>19</td>
<td>100–102/12</td>
<td>149.2</td>
<td>C</td>
<td>1660</td>
<td>—</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>p-OCH(_3)C(_6)H(_4)</td>
<td>52</td>
<td>115–116/10</td>
<td>179.2</td>
<td>C</td>
<td>1665</td>
<td>—</td>
</tr>
</tbody>
</table>

\(\text{a Lit.}^{4} 207–208/760; \quad \text{b Lit.}^{5} 81–82/12; \quad \text{c Lit.}^{5} 95–97/14–15; \quad \text{d Benson, R. E. and Cairns, T. L. J. Am. Chem. Soc. 70 (1948) 2115:} 81–82/26 \text{mm.}\)
The NMR spectra of the free bases at room temperature do not reveal the presence of stable isomers, but in some cases isomeric salt pairs are formed, e.g. \( R = CH_3, C_2H_5; R' = C_2H_5, \) and \( R' = \) phenyl. \( CH_3 \) (s) was located at \( \delta = 2.07 \) and 2.70 and \( OCH_2 \) (q) at \( \delta = 4.43 \) and 4.70. The values for the \( C \)-ethyl derivative were: \( CH_2 \) (q) \( \delta = 2.35 \) and 2.99 and \( OCH_2 \) (q) \( \delta = 4.39 \) and 4.69 (CDCl\(_3\)), respectively.

**Synthetic utility of imidic esters. Reduction.** While this work was in progress, some communications\(^{11,13,14}\) covering part of our work appeared. It was our intention to test if the esters or salts could be reduced selectively by borohydrides. Preliminary experiments showed, however, that aldehydes were

| Table 2. Physical data of imidic ester salts, \( R - C = \text{NHR}'' \), BF\(_4\)\(^{-}\) |
|---|---|---|---|---|---|---|---|---|
| **R** | **R'** | **R''** | **Yield %** | **M.p. °C** | **Mol. weight** | **Method** | **\( p_{C=N} \) \( \text{cm}^{-1} \text{CH}_2\text{Cl}_2 \)** | **\( p_{N-H} \) \( \text{cm}^{-1} \text{CH}_2\text{Cl}_2 \)** |
| \( C_2H_5 \) | \( C_2H_5 \) | \( C_2H_5 \) | 72 | 104–5 | 217.0 | B | 1668 | 537 | 1534 |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 85 | 157–8 | 231.0 | B | 1658 | 524 | 1554 |
| \( C_2H_5 \) | \( C_2H_5 \) | \( C_2H_5 \) | 87 | 77–9 | 263.1 | B | 1630 | 381 | 1549 |
| \( CH_3 \) | \( CH_3 \) | \( n-C_6H_{13} \) | 85\(^a\) | oil | 259.1 | B | 1673 | 475 | 1543 |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 48 | 104–5 | 217.0 | A | — | — | — |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 60 | 88–90 | 203.0 | A | 1674 | 443 | 1532 |
| \( CH_3 \) | \( C_2H_5 \) | \( CH_3 \) | 80 | 116–8 | 221.0 | A | 1665 | 481 | 1526 |
| \( CH_3 \) | cyclohexyl | \( CH_3 \) | 70 | 90.5–1 | 269.1 | A | 1664 | 503 | 1526 |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 85\(^a\) | oil | 187.0 | A | — | — | — |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 87\(^a\) | oil | 203.0 | A | — | — | — |
| \( CH_3 \) | \( C_2H_5 \) | \( CH_3 \) | 92\(^a\) | oil | 217.0 | A | — | — | — |
| \( CH_3 \) | cyclohexyl | \( CH_3 \) | 74\(^a\) | oil | 255.1 | A | — | — | — |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 65\(^a\) | oil\(^c\) | 275.3 | C | 1658 | — | — |
| \( CH_3CH_2 \) | \( CH_3 \) | \( CH_3 \) | 60\(^a\) | oil\(^c\) | 289.3 | C | 1663 | — | — |
| \( CH_3CH_2 \) | \( CH_3 \) | \( CH_3 \) | 20\(^a\) | oil\(^c\) | 337.3 | C | — | — | — |
| \( CH_3 \) | \( CH_3 \) | \( CH_3 \) | 61 | 77–9\(^c\) | 261.3 | C | 1669 | — | — |
| \( CH_3 \) | \( CH_3 \) | \( CH_3OCH_3 \) | 82 | 70–2\(^c\) | 291.3 | C | — | — | — |
| \( CH_3 \) | \( CH_3 \) | \( C_2H_7 \) | 62 | oil\(^c\) | 241.2 | C | 1655 | — | — |
| \( CH_2 \) | \( C_2H_5 \) | \( OC_2H_5 \) | 80 | 48–9.5 | 201.0 | B | 1669 | 863 | — |
| \( CH_2 \) | \( COC_2H_5 \) | \( OC_2H_5 \) | 88 | 61–3 | 229.0 | B | 1663 | 803 | 1506 |

\(^a\) Crude yield; \(^b\) missing; \(^c\) dimethyl sulphate salt.

not formed. Borch obtained the same result and showed that reduction with excess sodium borohydride gave amines in good yields.

Hydrolysis. Removal of protecting groups. The hydrolysis proceeds rapidly in a weakly acid medium. The acetyl and propanoyl derivatives are cleaved according to route 3a; thus N-deacetylation can be carried out under mild conditions by O-ethylation, followed by treatment with water. On the other hand debenzylation or cleavage of the peptide bond by the same sequence of reactions was not successful.

Acylation. The imidic function is not prone to react with carbanions. No reaction was noted between acetyl acetone and N-phenyl acetimidate in benzene-pyridine solution. Intramolecular reaction of suitably situated centres has been accomplished. Acylation gave among other products 1-alkoxy-1-acylamino-1-alkenes, eqn. (4), the structure of which was proved by IR and NMR data.

\[
\begin{align*}
\text{OCH} & \xrightarrow{\text{ArCOCl/NET_3}} \text{H_3C} & \text{C}_6\text{H}_7 \\
\text{CH}_3\text{CH}_2\text{C} = \text{NC}_2\text{H}_2 & \xrightarrow{\text{benzene, 25\degree}} \text{C}_6\text{H}_7 \\
\text{N} & \text{COAr} \\
\text{H} & \text{OCH}_2 \\
\text{C} = \text{C} & \xrightarrow{\text{H}_3\text{C}} \text{N} & \text{COAr} \\
\text{H} & \text{OCH}_2 \\
\text{C}_6\text{H}_7
\end{align*}
\]

Pyrolysis. The aliphatic imidates do not undergo Chapman rearrangement nor are olefins formed by elimination. The O-cyclohexyl derivative was stable at temperatures below 250\degree. No N-ethylaniline was formed on heating the tetrafluoroborate of ethyl N-(ethyl)benzimidate at 180\degree for 3 hours.

Tetrazoles. Treatment of nitrilium salts with hydrazoic acid in methylene chloride at room temperature gave tetrazoles in fair yields. Both 1-ethyl-5-phenyltetrazole and the rearrangement product 1-phenyl-5-ethylaminotetrazole were isolated from the N-ethylbenzonitrilium salt.

\[
\begin{align*}
\text{PhC} = \text{NEt, BF_4}^- + \text{HN_3} & \rightarrow \text{PhC} = \text{N} \equiv \text{Et} + \text{EtNH} = \text{C} \equiv \text{N} \equiv \text{Ph} \\
\end{align*}
\]

No tetrazoles could be isolated from the reaction of sodium azide with imidic esters in DMSO at 100\degree.

EXPERIMENTAL

All compounds described gave satisfactory analysis or a correct proton integral of their NMR spectra (Varian A 60-A). The IR spectra were run by a Perkin-Elmer 221 instrument.

Ethyl N-(ethyl)propanimidate and its tetrafluoroborate. Method A. Ethanol (1.0 g) was added to a cooled and stirred solution of the crude nitrilium salt (3.4 g, prepared from propionitril and triethyloxonium tetrafluoroborate) in dry methylene chloride. Half of the solvent was evaporated and the salt was precipitated with ether. It was

*Acta Chem. Scand. 23 (1969) No. 3*
crystallized from methylene chloride-ether, m.p. 104—105°, 72 %. The salt liquefies in contact with humid air, but can be kept for months in a refrigerator.

The free ester was obtained by adding the salt (5 g) in portions to chilled and stirred aqueous sodium hydroxide (25 ml, 4 M). The organic layer was dried over sodium sulphate and distilled, b.p. 127—130°/760 mm Hg, 56 %. A further quantity (impure) was obtained by extraction of the water phase with ether.

The O-methyl, O-isopropyl, O-cyclohexyl derivatives and the compounds derived from the acetoniitrilium salt \( \text{I}^4 \) were prepared analogously.

**The tetrafluoroborate of ethyl N-(phenyl)acetimidate. Method B.** Acetanilide (15 g), triethylxonium tetrafluoroborate (20.8 g) was stirred in methylene chloride (120 ml) for 6 h at room temperature. Half of the solvent was evaporated and ether (25 ml) was added. The salt was washed with ether and dried, m.p. 157—158°, 85 %. The salt must be stored in a stoppered bottle in a refrigerator.

**Ethyl N-(phenyl)acetimidate.** The crude reaction mixture (above) was evaporated to dryness and added in portions with cooling and stirring to aqueous sodium hydroxide (55 ml, 4 N). Ether (25 ml) was added and the organic phase was separated, dried and freed from solvent. Distillation in vacuo yielded the imidate, b.p. 97—98°/12 mm Hg, 65 %.

**Hydrolysis.** The tetrafluoroborate of ethyl N-(phenyl)acetimidate (2.8 g) was dissolved in water (30 ml). After one hour, aniline was isolated in a yield of 87 %. The solution smelled strongly of ethyl acetate.

When the tetrafluoroborate of ethyl N-(ethyl)benzimidate was hydrolyzed in a similar manner, the amide was recovered as the main product and only small amounts of ester and amine were formed.

**Methyl N-(propyl)propanimidate.** N-Propyl propanamide (11.5 g) and dimethyl sulphate (19 g) were refluxed for 2 h in chloroform (20 ml). The salt was precipitated as an oily mass with ether (125 ml) and washed with an additional quantity of ether (10 ml). The crude yield was 62 %. The salt was added in portions with cooling to sodium hydroxide (25 ml, 5 N) and the organic phase was separated, dried with sodium sulphate and distilled, b.p. 31—33°/12 mm Hg, 31 %.

**Acylation.** To a solution of methyl N-(propyl)propanimidate (3 g) and triethyamine (2.4 g) in ether (75 ml) \( p \)-NO\(_2\)-benzoyl chloride (4.35 g) was added in portions with stirring. After 3 days the triethyamine hydrochloride was filtered off and the ether evaporated. A viscous oil remained (5 g), part of which was chromatographed on silica with chloroform. Two isomeric 1-alkoxy-1-\( p \)-nitrobenzoylamino-1-propenes were obtained as a partly resolved oily main fraction together with N-propyl-\( p \)-nitrobenzamidine, which were analyzed by NMR and IR. One of the isomers gave the following data: IR (CHCl\(_3\)), 1650 cm\(^{-1}\), C=O; 1528 cm\(^{-1}\), NO\(_2\), NMR (CDCl\(_3\)), \( \delta = 7.97 \), AB system, 4H; \( \delta = 4.24 \) (q) \( J = 6.8 \) cps, \( = \text{CH} \); \( \delta = 3.62 \) (t) \( J = 6 \) cps, \( \text{N—CH} \); \( \delta = 3.48 \) (s) \( \text{OCH} \); \( \delta = 2.0—1.3 \) (m) \( \text{NCH}—\text{CH} \); \( \delta = 1.32 \) (d) \( J = 6.8 \) cps, \( = \text{CH} \); \( \delta = 0.98 \) (s) \( = \text{CH} \).

**Tetrazoles.** N-Ethyl-benzonitrilium salt from benzonitril (5.15 g, 50 mmoles) was reacted with hydrazoic acid (50 mmoles) at room temperature in methylene chloride for 6 h. The solvent was evaporated and the oil was poured into water, neutralized with sodium carbonate and extracted once with light petrol ether. Chromatography on silica (chloroform and chloroform/methanol, \( \delta = 10 \) %) gave 1-ethyl-5-phenyltetrazole, m.p. 116—117°, (lit.\(^{10}\) 118—119°), 15 % and 1-phenyl-5-ethylaminotetrazole, m.p. 69—70°, (lit.\(^{10}\) 70—71°), 18 %.

1,5-Diethyltetrazole was obtained in a yield of 27 % by the action of hydrazoic acid on the N-ethyl propionitrilium salt as described above. The crude product was distilled (extraction with petrol ether was omitted), b.p. 138—142°/5 mm Hg, m.p. 31—32 (lit.\(^{20}\) b.p. 83—85°/0.12 mm Hg).

**Acknowledgements.** This work was supported by *Statens Naturvetenskapliga Forskningsråd*. We would like to thank Miss Lena Bäck for running the spectra and Mr. Gert Strandlund for carrying out the tetrazole synthesis.

REFERENCES

4. Lander, G. D. J. Chem. Soc. 79 (1900) 690; 83 (1903) 406.

Received July 10, 1968.