Studies on Organophosphorus Compounds; 1. Reaction of Secondary Carboxamides with Hexamethylphosphorotriamide (HMPA) – A New Method for the Preparation of Amidines

Erik B. Pedersen, N. Ole Vestergaer, and Sven-Olov Lawesson

Department of Organic Chemistry, Chemical Institute, University of Aarhus, 8000 Aarhus C, Denmark

Recently, Monson and Priest found that aliphatic and aromatic carboxamides readily undergo dehydration in hexamethylphosphor triamide (HMPA) at 220°-240°, producing the corresponding nitriles in good yields. They suggested without proof that the initial step of the reaction is the formation of a phosphorodiamidate derivative 1 of the enol form of the amide.

\[ RCONH_2 \xrightarrow{\text{HMPA}} RCONH + \text{HO-} \left( \text{N(CH}_3\text{)}_2 \right) \]

It was then assumed that in an analogous manner the corresponding imidate intermediate 2 could be prepared by treatment of secondary carboxamides with HMPA, but the fate of the intermediate could not be foreseen at that time.

It was now found that gentle refluxing of a series of secondary carboxamides in HMPA produces N,N-dimethylamidines 3 in fair yields.

\[ RCONHR^2 \xrightarrow{\text{HMPA}} \left[ \text{HO-} \left( \text{N(CH}_3\text{)}_2 \right) \right] + \text{HN} \left( \text{CH}_3 \right) \]

Although no attempts were made to optimize this new synthesis, the best yield is obtained when \( R^2 = \text{aryl.} \)

It was also foreseen that heating a secondary carboxamide with HMPA in the presence of a large excess of a secondary amine might give a new amidine 4. This reaction was achieved when starting from acetamidine, although the yields of 4 were low and appreciable amounts of 3d were also formed.

\[ H_3C-CO-NH-C_6H_5 \xrightarrow{\text{HMPA}} 3d + H_3C-C-CN-C_6H_5 \]
Table 1. Preparation of Amidines (3)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Reaction time hr</th>
<th>Yield %</th>
<th>m.p. or b.p.</th>
<th>n D¹/²</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3a</strong></td>
<td></td>
<td>CH₃</td>
<td>2</td>
<td>26</td>
<td>b.p. 72/0.2 mm</td>
<td>1.5206</td>
<td><strong>C₁₃H₂₀N₂</strong> calc. 76.42 H 9.87 N 13.71 found 76.61 9.84 13.15</td>
</tr>
<tr>
<td><strong>3b</strong></td>
<td></td>
<td>CH₃,CH₂</td>
<td>6</td>
<td>40</td>
<td>b.p. 118/0.05 mm</td>
<td>1.5824</td>
<td><strong>C₁₅H₁₈N₂</strong> calc. 80.63 H 7.61 N 11.76 found 80.18 7.60 11.76</td>
</tr>
<tr>
<td><strong>3c</strong></td>
<td></td>
<td></td>
<td>6</td>
<td>49</td>
<td>m.p. 73</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3d</strong></td>
<td>CH₃</td>
<td></td>
<td>2</td>
<td>63</td>
<td>b.p. 85/0.05 mm</td>
<td>1.5747</td>
<td></td>
</tr>
<tr>
<td><strong>3e</strong></td>
<td>H</td>
<td></td>
<td>3</td>
<td>60</td>
<td>b.p. 62/0.05 mm</td>
<td>1.5926</td>
<td></td>
</tr>
<tr>
<td><strong>3f</strong></td>
<td>CH₃</td>
<td></td>
<td>5</td>
<td>64</td>
<td>b.p. 80/0.05 mm</td>
<td>1.5333</td>
<td><strong>C₁₃H₁₄N₂</strong> calc. 77.53 H 10.41 N 12.06 found 77.43 10.41 12.13</td>
</tr>
<tr>
<td><strong>3g</strong></td>
<td></td>
<td></td>
<td>4</td>
<td>56</td>
<td>m.p. 89</td>
<td></td>
<td><strong>C₁₆H₁₆N₂</strong> calc. 75.85 H 7.56 N 16.59 found 75.98 7.52 16.56</td>
</tr>
</tbody>
</table>

¹ From petroleum ether; Ref. ², m.p. 70-72.
² Ref. ³, b.p. 75-77/0.005 mm; n D³ = 1.5775.
³ Ref. ², b.p. 78-80/0.1 mm; n D⁴ = 1.5953.
⁴ From petroleum ether.

General Procedure:
A secondary carboxamide (10 g) in HMPA (50 ml) was heated at reflux temperature until the carbonyl-stretching absorption had disappeared in the I. R. The reaction mixture was allowed to cool to room temperature and was then poured into ice water (400 ml) and extracted four times with ether. The combined ether phases were washed with water, dried with calcium sulfate, the ether was distilled, and the amine purified.

Reaction in the Presence of Morpholine:
Acetanilide (10 g), HMPA (50 ml), and morpholine (15 g) were refluxed for 22 hr and worked up as above.

Yield of 3d: 1.5 g; b.p. 85/0.05 mm.
Yield of 4: 0.5 g; b.p. 110-130/0.1 mm; m.p. 88° (from petroleum ether b.p. 60-80°).

C₁₃H₁₄N₂O calculated C 70.56 H 7.90 N 13.72
found 70.86 7.90 13.92

Received: April 26, 1972