Phase-Transfer-Catalysed N-Alkylation of N-Substituted Carboxamides

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N,N-Disubstituted carboxamides are potentially valuable starting materials for the synthesis of tertiary amines. A number of examples are recorded in the literature in which compounds of this type have been prepared by the alkylation of an alkali salt of the appropriate N-substituted carboxamides. Three main methods of synthesis were used: Hepp’s procedure using an amide and sodium dispersed in an inert solvent such as toluene followed by addition of an alkyl halide; Pictet’s method using an amide, potassium hydroxide and alkyl halide in ethanolic solution; and a method first described by Fones and slightly modified by Park et al. in which sodium hydride in xylene was utilised to form the sodium salt of the alkylated amide. All these methods suffer from producing impure products in relatively low yields, and also from prolonged reaction times under rather drastic conditions. Recently phase-transfer catalysed N-alkylation of acetanilide in a two-phase system consisting of benzene and 50 % aqueous sodium hydroxide was reported by Brehme. As demonstrated in the present study this procedure appears to be limited, however, only to N-arylacetamides in which the enhanced N—H acidity is due to extensive delocalisation of negative charge in an amide ion. Focusing our attention on possible synthetic applications of solid sodium hydroxide/potassium carbonate in PTC-alkylations we have found that this base is particularly suitable for effective N-alkylation of N-substituted carboxamides. The reaction of N-substituted aliphatic or aromatic carboxamides 1 with alkyl halides 2 in the presence of excess powdered
Table 1. Preparation of N,N-Dialkylcarboxamides 3

<table>
<thead>
<tr>
<th>Product No.</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield [%]</th>
<th>b.p./torr</th>
<th>n°</th>
<th>Molecular formula¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C₃H₇</td>
<td>C₆H₅CH₂</td>
<td>C₂H₅</td>
<td>(93)</td>
<td>84-86°/0.15</td>
<td>1.5196</td>
<td>C₄H₉N₂NO (91.3)</td>
</tr>
<tr>
<td>3b</td>
<td>C₂H₅</td>
<td>C₆H₅CH₂</td>
<td>C₂H₅</td>
<td>(98)</td>
<td>98-100°/0.1</td>
<td>1.5082</td>
<td>C₄H₉N₂NO (219.3)</td>
</tr>
<tr>
<td>3c</td>
<td>C₂H₅</td>
<td>C₂H₅H₂</td>
<td>C₂H₅CH₂</td>
<td>(96)</td>
<td>134-136°/0.4</td>
<td>1.5626</td>
<td>C₄H₉N₂NO (253.3)</td>
</tr>
<tr>
<td>3d</td>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>(98)</td>
<td>148-150°/15</td>
<td>1.5217</td>
<td>C₂H₅N₂NO (177.3)</td>
</tr>
<tr>
<td>3e</td>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>n-C₆H₁₄</td>
<td>(95)</td>
<td>154-156°/9</td>
<td>1.5114</td>
<td>C₄H₉N₂NO (205.3)</td>
</tr>
<tr>
<td>3f</td>
<td>C₂H₅</td>
<td>C₂H₅</td>
<td>C₂H₅CH₂</td>
<td>(86)</td>
<td>177-180°/3</td>
<td>1.5752</td>
<td>C₄H₉N₂NO (239.3)</td>
</tr>
</tbody>
</table>

¹ Yields of crude products (practically pure according to I.R. and ¹H-N.M.R.) are given in parentheses.
² Compounds 3a-e have been satisfactorily analysed (C ± 0.2 %, H ± 0.1 %, N ± 0.1 %).
³ Product contaminated (G.L.C., ¹H-N.M.R.) with about 15% of unidentified impurity, probably dibenzyl ether.

Table 2. Spectroscopic Data for N,N-Dialkylcarboxamides 3

<table>
<thead>
<tr>
<th>Product No.</th>
<th>¹H-N.M.R. (CCl₄/TMS)¹</th>
<th>δ ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>(C==O), 1.05 (t, 3H, J₉=7.0 Hz); 1.17 (t, 3H, J₉=7.0 Hz); 2.30, 2.38 (2q, 2H, J₉=7.0 Hz); 2.32, 3.41 (2q, 2H, J₉=7.0 Hz); 4.49, 4.58 (2x, 2H); 7.21 (br, s, 5H)</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>(C==O), 2.50 (m, 2H); 2.95-3.43 (m, 2H); 4.46 (br, s, 2H); 7.15 (br, s, 5H)</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>(C==O), 2.35 (q, 2H, J₉=7.3 Hz); 4.40, 4.50 (2 br, s, 4H); 7.23 (br, s, 10H)</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>(C==O), 1.35 (q, 2H, J₉=7.5 Hz); 3.25 (q, 4H, J₉=7.5 Hz); 7.25 (s, 5H)</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>(C==O), 0.67, 1.77 (m, 10H); 3.30 (m, 4H); 7.22 (s, 5H)</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>(C==O), 1.07 (t, 3H, J₉=7.0 Hz); 4.45, 4.52 (2s, 2H); 3.22 (br, 2H); 7.50 (m, 10H)</td>
<td></td>
</tr>
</tbody>
</table>

¹ The I.R. spectra were recorded on a Spectord 71 IR (C. Zeiss) spectrophotometer. The strong and medium intensity absorption bands are given only.
² The ¹H-N.M.R. spectra were measured at 80 MHz with a Tesla BS 487C spectrometer using TMS as internal standard.

Sodium hydroxide/potassium carbonate and 10 mol.-% of tetra-n-butylammonium hydrogen sulfate as catalyst proceeds smoothly in boiling benzene to afford the corresponding N,N-disubstituted carboxamides 3 in almost quantitative yield.

\[
\text{R}^1\text{C}_3\text{NH}+\text{R}^2\times\text{R}^3\text{X} + \text{NaOH/K}_2\text{CO}_3/\text{C}_6\text{H}_5\text{SO}_4 \rightarrow 10 \text{ mol.-% In-C}_6\text{H}_5\text{OH}^+\text{H}_2\text{SO}_4 \rightarrow 80^\circ \\
\]

N-Benzylpropanamide (1; R¹ = C₃H₇, R² = C₆H₅CH₂): The compound is prepared by the action of benzylamine (112.3 g, 1.05 mol) on propionyl chloride (46.25 g, 0.5 mol) in benzene (850 ml) at 15-20°; yield: 81.5 g (100 %); m.p. 49-51°.

I.R. (KBr): νmax = 3320 (NH), 1650 (C==O), 1555, 1460, 1438, 1238, 745, 700 cm⁻¹.

¹H-N.M.R. (CCl₄): δ = 0.95 (t, 3H, J₉=7.5 Hz); 2.04 (q, 2H, J₉=7.5 Hz); 4.14 (d, 1H, J₉=6.0 Hz); 7.10 (s, 5H); 7.93 ppm (br, s, 1H).
\(N\)-Ethylbenzamide \((1); \ R^1 = \text{C}_6\text{H}_5, \ R^2 = \text{C}_2\text{H}_5)\):
The amide is obtained as described above starting from ethylamine (47.25 g, 1.05 mol) and benzoyl chloride (70.25 g, 0.5 mol) in benzene (650 ml); yield: 68.5 g (91\%); m.p. 69–71° (Lit. 7 m.p. 70–71°).
\(^1\text{H}\) N.M.R. (\text{CDCl}_3): \(\delta = 1.17 (t, 3H, J_{\text{HH}} = 7.25\, \text{Hz})\); 3.45 (dq, 2H, \(J_{\text{HH}} = 7.25\, \text{Hz}, J_{\text{HH}} = 5.5\, \text{Hz})\); 7.02–7.50 and 7.81–8.00 ppm (2m, 5H).

\(N,N\)-Dialkylcarboxamides (3); General Procedure:
The solution of alkyl halide 2 (0.075 mol) in benzene (10 ml) is added dropwise with efficient stirring to the refluxing mixture of \(N\)-substituted carboxamide 1 (0.05 mol), finely powdered sodium hydroxide (7.0 g), potassium carbonate (14.0 g), tetra-n-butylammonium hydrogen sulfate (1.7 g, 0.005 mol), and benzene (50 ml). Stirring is continued for 4 h at reflux temperature. The resultant mixture is cooled to room temperature, diluted with benzene (50 ml), and treated with water (50 ml). The organic phase is separated, washed with water (2 x 40 ml), dried over anhydrous magnesium sulfate, and evaporated to give crude 3 as an oil. Analytically pure samples of 3 are obtained by distillation in vacuo.

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