Efficient Transformation of Nitrile into Amide under Mild Condition

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Abstract: Transformation of various kinds of nitriles into the corresponding amides or amide salts was performed in good yields by the addition of two equiv of chlorotrimethylsilane and two equiv of water at 0°C to 25°C. © 1998 Elsevier Science Ltd. All rights reserved.

Hydrogen halide generated in situ by TMSX and water is an important reaction especially when HX is needed in requisite amount and under dry reaction conditions. As part of our endeavor to utilize HX thus generated, we have found TMSCI and water can be used for transformation of nitriles into amides under very mild reaction conditions and with satisfactory yields. Interestingly, under the condition of hydration of nitrile, ester of carboxylic acid remains intact. Although there are several reports in the literature to bring about the same transformation, moreover, most of the reported methods have not been proven in general and practical in scope. This paper reports the hydration of a series aliphatic as well as aromatic nitriles into amides at 0°C to 25°C for only 2 to 4 hrs.

As a typical procedure, two equiv of TMSCI is added to one equiv of nitrile at 0 to 5°C, and followed by the dropwise addition of two equiv of water and allowed to warm up to the 25°C in 2 to 4 hrs. In most of the cases, amides separated in the salt form of amide-hydrochloride. The reaction mixture is neutralised with saturated bicarbonate solution at 0-5°C and extracted with dichloromethane. Finally, after drying the organic layer over MgSO4 and stripping off the solvent, mostly pure amides are obtained as shown in Table I.

Solvent is not needed in this transformation. Attempts to use THF, MeNO2, or CH2Cl2 as the solvent results in poor yields. Changing the addition sequence of the three components in the reaction gave almost the same results. Thus, protonation of the nitrile by HCl, generated in situ from TMSCI and half equiv of H2O, and followed by nucleophilic attack by another equiv of H2O to form the amide salt seems to be the possible pathway for this reaction (Scheme I). In order to compensate the escape of HCl generated in situ, one more equiv of HCl is used in this reaction. The yields of amide did not change very much when we used one more equiv of water and HCl.

Scheme I. Plausible Reaction Pathway for the Amide Formation from Nitrile

Another important aspect of this work is the isolation and characterisation by X-ray analysis of the amide-hydrochlorides. After the reaction is over, the reaction mixture is obtained as two phases. While the upper layer is mostly hexamethyldisiloxane. Amide salt remains as the semisolid or solid form in the lower layer. The crystal obtained by the hydration of propionitrile was found to be propionamide-hydrochloride by X-ray analysis (Figure I). The application of these amide-hydrohalides in organic synthesis is still under further investigation.
Table I. Transformation of Nitrile into Amide by TMSCI and Water.

\[
\text{R-CN} + \text{TMSCI} + \frac{3}{2} \text{H}_2\text{O} \rightarrow \text{RCONH}_2 + \text{HCl} + \frac{1}{2} (\text{TMS})_2 \text{O}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile Yields</th>
<th>Entry</th>
<th>Nitrile Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{3}-</td>
<td>75%</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{3}-CH\textsubscript{2}-</td>
<td>79%</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>n-C\textsubscript{5}H\textsubscript{11}-</td>
<td>85%</td>
<td>7\textsuperscript{a}</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>88%</td>
<td>8\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\(\text{a} \) In addition to the equiv amount of reagents used in the typical procedure, one more equiv of TMSCI and 1/2 equiv of H\textsubscript{2}O were used in the reaction to form ammonium salt.

Figure I. ORTEP of Propionamide Hydrochloride. Bond distances (\AA) and angles (deg, errors last digits in parentheses):

- C(1)-O = 1.308(5)
- C(1)-C(2) = 1.486(6)
- C(1)-N = 1.299(6)
- H-CI = 2.006
- N-H\textsubscript{na} and N-H\textsubscript{nb} = 0.95(2)
- O-C(1)-N = 118.0(3)
- C(1)-N-H\textsubscript{na} = 110.3(2)
- C(1)-N-H\textsubscript{nb} = 125.4(2)
- H\textsubscript{na}-N-H\textsubscript{nb} = 124.3(2)
- O-C(1)-C(2) = 118.0(4)
- N-C(1)-C(2) = 123.9(2)

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References and Notes:

(8) A. Galat, J. Am. Chem. Soc. 1948, 70, 3945.
(13) Totally, two equiv of TMSCI, three equiv of water, and one equiv of nitrile were used.