Rapid Method of Converting Primary Amides to Nitriles and Nitriles to Primary Amides by ZnCl\textsubscript{2} using Microwaves under Different Reaction Conditions

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Rapid Method of Converting Primary Amides to Nitriles and Nitriles to Primary Amides by ZnCl₂ using Microwaves under Different Reaction Conditions

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Abstract: A rapid and facile method for the conversion of primary amides to nitriles using inexpensive and readily available ZnCl₂ in aqueous acetonitrile and their regeneration using ZnCl₂–H₂O–THF in the presence of acetamide under microwave irradiation in good yields is reported. The reactions go to completion within a minute.

Keywords: microwave irradiation, nitriles, primary amides, ZnCl₂

INTRODUCTION

The preparation of amides and nitriles are important synthetic transformations in organic synthesis. Methods for the preparation of nitriles by dehydration of carboxamide using triphenylphosphine/carbontetrachloride,[1] PyBOP,[2] COCl₂/DMSO,[3] PPSC,[4] and CH₃O₂CN/NEt₃[5] have been documented in the literature, and hydration of nitriles to amide is achieved by H₂O₂,[6] MnO₂/SiO₂,[7] and Pt(II) complexes.[8] Maffioli et al.[9] have reported a mild and reversible conversion of primary amides into nitriles by PdCl₂ in aqueous acetonitrile for the forward reaction and PdCl₂–H₂O–THF in the presence of acetamide for the backward reaction.
In continuation of our work on ZnCl₂,[10] we report herein the use of ZnCl₂ as a catalyst for the dehydration of primary amides into nitriles and hydration of nitriles into amides under microwave irradiation using different reaction systems (Scheme 1).

\[
\begin{align*}
\text{R} & = \text{H, CH}_3, \text{OCH}_3, \text{Cl, NO}_2, \text{OH} \\
\text{Scheme 1.}
\end{align*}
\]

RESULTS AND DISCUSSION

Primary amides were dehydrated into nitriles in high yields rapidly under microwave irradiation (Scheme 2) in the presence of ZnCl₂–H₂O–MeCN. This is the first procedure for the synthesis of nitriles by direct reaction of primary amides using ZnCl₂ under aqueous conditions.

\[
\begin{align*}
\text{Scheme 2.}
\end{align*}
\]

To standardize the reaction, different Lewis acids were used to convert benzamide into benzonitrile under different reaction conditions, and results are summarized in Table 1. Table 2 indicates the versatility of the reaction.

It was interesting to find out that hydrolysis of nitrile occurred with ZnCl₂ in 1:1 H₂O–THF in the presence of acetamide under microwave irradiation. These results are summarized in Table 3.

\[
\begin{align*}
\text{Scheme 3.}
\end{align*}
\]
The present procedure provides an efficient, rapid, facile, and reversible method for the conversion of primary amides to nitriles. With addition of acetamide, the reaction was reversed to hydrolyze nitrile into amide.

Table 1. Dehydration of benzamide (1 mmol) with different Lewis acid and reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Solvent</th>
<th>Reaction condition</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW/Reflux</td>
<td>2 min/8 h</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW/Reflux</td>
<td>2 min/8 h</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>AlCl₃&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW/UI</td>
<td>2 min/30 min</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>CuCl&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW/HP</td>
<td>2 min/1 h</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL MeCN</td>
<td>MW/UI</td>
<td>2 min/30 min</td>
<td>ND</td>
</tr>
<tr>
<td>6</td>
<td>ZnCl₂&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW/HP</td>
<td>2 min</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>ZnCl₂&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW</td>
<td>90 s</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>ZnCl₂&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 mL H₂O/MeCN = 1:1</td>
<td>MW</td>
<td>30 s</td>
<td>94</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 mmol.
<sup>b</sup>0.1 mmol.
<sup>c</sup>0.5 mmol.

Notes: MW = Microwave irradiation (320 W); reflux = 80°C; UI = ultrasound irradiation; HP = hot plate (150°C); ND = not detected.

CONCLUSION

The present procedure provides an efficient, rapid, facile, and reversible method for the conversion of primary amides to nitriles. With addition of acetamide, the reaction was reversed to hydrolyze nitrile into amide.

Table 2. Microwave-promoted dehydration of primary amides to nitriles with ZnCl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction time (s)</th>
<th>Yield (%)</th>
<th>Melting/boiling point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Benzamide</td>
<td>30</td>
<td>94</td>
<td>188–190; 191–193&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
<tr>
<td>b</td>
<td>p-Toluamide</td>
<td>30</td>
<td>70</td>
<td>103–105; 103–106&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
<tr>
<td>c</td>
<td>p-Chlorobenzamide</td>
<td>20</td>
<td>82</td>
<td>90–92; 91–93&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>d</td>
<td>p-Hydroxybenzamide</td>
<td>20</td>
<td>75</td>
<td>110–112; 111–113&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
<tr>
<td>e</td>
<td>p-Nitrobenzamide</td>
<td>35</td>
<td>72</td>
<td>146–148; 146–149&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>f</td>
<td>p-Methoxybenzamide</td>
<td>30</td>
<td>60</td>
<td>57–59; 57–59&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
<tr>
<td>g</td>
<td>m-Chlorobenzamide</td>
<td>20</td>
<td>80</td>
<td>38–40; 39–42&lt;sup&gt;[2]&lt;/sup&gt;</td>
</tr>
<tr>
<td>h</td>
<td>m-Toluamide</td>
<td>30</td>
<td>65</td>
<td>89–90; 89–90&lt;sup&gt;[1]&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
EXPERIMENTAL

All amides were prepared from carboxylic acid and urea using pyridine, solvents and Lewis acids were purchased from BDH/MERCK, and all solvents were distilled before use. All the reactions were carried out using a conventional (unmodified) household microwave oven (LG, Little Cheff, 230 V, 50 Hz). Reactions were monitored with thin-layer chromatography (TLC) by comparison with the authentic samples. Melting points/boiling points were taken in open capillaries using paraffin bath and corrections are applied wherever necessary. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography. The IR spectra of the products were recorded on Nicolet 400D FT-IR spectrophotometer.

General Procedure

Conversion of Primary Amides to Nitriles

A mixture of ZnCl₂ (0.136 g, 1 mmol) in 1:1 water/acetonitrile (1 ml) was taken into a Pyrex® cylindrical tube; benzamide (0.121 g, 1 mmol) was then added. The mixture was homogenized and irradiated in a commercial microwave oven (320 W) (Scheme 3). At the end of irradiation (30 s), the mixture was cooled to room temperature and extracted with dichloromethane (5 ml). The organic layer was dried over anhydrous sodium sulphate, and the solvent was removed under vacuum. The crude product was chromatographed on a short column of silica gel using 2.5% EtOAc in light petroleum as eluent to get benzonitrile (0.097 g, 94%).

Table 3. Microwave-promoted hydration of nitriles to primary amides with ZnCl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction time (s)</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
<th>Found</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Benzonitrile</td>
<td>40</td>
<td>60</td>
<td>126–127</td>
<td>128–129&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>p-Tolunitrile</td>
<td>45</td>
<td>45</td>
<td>156–158</td>
<td>158–160&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>p-Chlorobenzonitrile</td>
<td>35</td>
<td>55</td>
<td>170–172</td>
<td>172–176&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>p-Hydroxybenzonitrile</td>
<td>30</td>
<td>50</td>
<td>161–163</td>
<td>161–162&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>p-Nitrobenzonitrile</td>
<td>40</td>
<td>62</td>
<td>198–201</td>
<td>199–201&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>p-Methoxybenzonitrile</td>
<td>40</td>
<td>57</td>
<td>163–165</td>
<td>164–167&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>m-Chlorobenzonitrile</td>
<td>35</td>
<td>58</td>
<td>132–134</td>
<td>134–135&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>m-Tolunitrile</td>
<td>40</td>
<td>40</td>
<td>92–93</td>
<td>93–95&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>


<sup>b</sup>Aldrich Handbook of Fine Chemicals.

<sup>c</sup>Isolated yield, and in all the cases, unreacted nitriles were recovered and recycled.
Conversion of Nitriles to Primary Amides

A mixture of ZnCl₂ (0.136 g, 1 mmol) in 1:1 of water/THF (1 ml) taken into a Pyrex® cylindrical tube; benzonitrile (0.103 g, 1 mmol) and acetamide (0.118 g, 2 mmol) were added. The mixture was homogenized and irradiated in a commercial microwave oven (320 W). At the end of irradiation (40 s), the mixture was cooled to room temperature, extracted with dichloromethane (5 ml), and washed with cold water (2 × 5 ml). The organic layer was dried over anhydrous sodium sulphate, and the solvent was removed under vacuum. The crude product was chromatographed on a short column of silica using 5% EtOAc in light petroleum as eluent to get benzamide (0.073 g, 60%).

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