Synthetic Methods and Reactions; 88. Sulfuryl Chloride Fluoride, a Convenient Reagent for the Preparation of Amides from Carboxylic Acids and Primary Amines Under Mild Conditions

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Sulfuryl chloride fluoride was introduced by us as a non-nucleophilic solvent in the spectroscopic investigation of carbocations\(^1\) and other positive ions, but as yet has not found much use in organic synthesis. Recently, we reported its first preparative use in the synthesis of nitriles 3 from aldoximes 1 using sulfuryl chloride fluoride/triethylamine as dehydrating agent.\(^1\)

\[
\begin{align*}
R=CH=N-OH & \overset{SO_2ClF/(C_2H_5)N}{\longrightarrow} R=CH=N-O-SO_2-F \\
1 & \text{2} \\
(C_2H_5)N & \overset{\text{R} = \text{N}=\text{C}=\text{R}}{\longrightarrow} \\
3 & \text{4} \quad \text{5} \quad \text{6}
\end{align*}
\]

We have extended our investigation to the reaction of sulfuryl chloride fluoride with various oxygen, nitrogen, and sulfur nucleophiles and now report that carboxylic acids 4 react readily with sulfuryl chloride fluoride in the presence of triethylamine. The resulting intermediate acylfluorosulfonates 5, the mixed anhydrides of the carboxylic acid and fluorosulfuric acid, without their separation are then reacted with a primary amine at room temperature to yield the corresponding amides 6 in good to excellent yield. The reaction most conveniently is carried out in dichloromethane solution. The reaction is general being equally applicable to aryl, aralkyl, and alkyl carboxylic acids, as well as to primary aryl-, aralkyl-, and alkyamines. However reaction with secondary amines is very sluggish. In order to obtain satisfactory yields, either excess sulfuryl chloride is removed by purging the reaction mixture with dry nitrogen, or, otherwise, excess amine is required.

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Yield(^a)</th>
<th>m.p. [°C] or b.p. [°C]/torr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>[%]</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>C(_2)H(_4)</td>
<td>65</td>
<td>112°/4°</td>
</tr>
<tr>
<td>H(_2)</td>
<td>C(_2)H(_4)</td>
<td>70</td>
<td>115°</td>
</tr>
<tr>
<td>C(_2)</td>
<td>C(_2)H(_4)</td>
<td>70</td>
<td>164°</td>
</tr>
<tr>
<td>C(_3)</td>
<td>t-C(_3)H(_8)</td>
<td>80</td>
<td>135,1°</td>
</tr>
<tr>
<td>C(_3)</td>
<td>c-C(_3)H(_11)</td>
<td>90</td>
<td>150°</td>
</tr>
<tr>
<td>4-O(_2)N</td>
<td>C(_2)H(_4)</td>
<td>80</td>
<td>210°</td>
</tr>
<tr>
<td>C(_2)H(_2)CH(_3)</td>
<td>C(_2)H(_4)</td>
<td>85</td>
<td>117,6°</td>
</tr>
<tr>
<td>C(_2)H(_2)CH(_3)</td>
<td>c-C(_3)H(_11)</td>
<td>96</td>
<td>120°</td>
</tr>
<tr>
<td>C(_2)H(_2)CH(_3)</td>
<td>c-C(_3)H(_11)</td>
<td>81</td>
<td>182,3°</td>
</tr>
<tr>
<td>2-HOOC-C(_2)H(_4)</td>
<td>C(_2)H(_4)</td>
<td>85</td>
<td>167°</td>
</tr>
</tbody>
</table>

\(^a\) Yield of pure, isolated product; purity > 98%.
\(^b\) All amides were recrystallized from ethanol/heptane mixtures.

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The variety of other methods currently available for the synthesis of amides from carboxylic acids includes the use of ion exchange resins, tetrachlorosilane, hexachlorocyclotriphosphazatriene, diethylphosphoryl cyanide, triphenyl phosphine/carbon tetrachloride, boron trifluoride etherate, and triphenylphosphine ditriflate. A review is available on the various other reagents available for the synthesis of amides from carboxylic acids. Many of the available methods however, require either relatively harsh reaction conditions, complex reagents, and/or elaborate workup procedures. In contrast, the present method takes place under mild reaction conditions and requires only a simple workup to afford the desired amides in high yield. The dichloromethane solution of sulfuryl chloride fluoride is conveniently handled and sulfuryl chloride fluoride is easily handled if not obtained commercially.

**Amides from Carboxylic Acids 4: General Procedure:**
To a stirred solution of the carboxylic acid (10 mmol) and triethylamine (11 mmol) in dichloromethane (50 ml), sulfuryl chloride fluoride (20 mmol) is added under a dry nitrogen atmosphere. The reaction mixture is stirred for 1 h at room temperature and then dry nitrogen is bubbled through the reaction mixture for 15 min. The amine (10 mmol) is then added and the reaction mixture stirred further for 2 h. The reaction mixture is quenched with ice/water (100 ml), the organic layer is washed successively with water and 15% aqueous sodium hydrogen carbonate solution and dried with anhydrous sodium sulfate. The solvent is evaporated and the products are further purified by recrystallization or distillation. The products are further characterized by microanalysis, I.R., U.V., and 1H-N.M.R. spectroscopy.

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