Synthetic Methods and Reactions; 88[1]. Sulfuryl Chloride Fluoride, a Convenient Reagent for the Preparation of Amides from Carboxylic Acids and Primary Amines Under Mild Conditions

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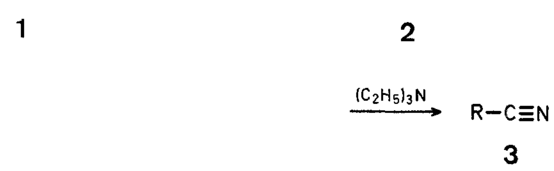
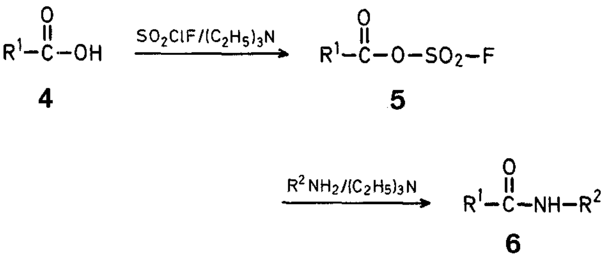
Sulfuryl chloride fluoride was introduced by us as a non-nucleophilic solvent in the spectroscopic investigation of carbocations[2] and other positive ions, but as yet has not found much use in organic synthesis. Recently, we reported its first preparative use in the synthesis of nitriles **3** from aldoximes **1** using sulfuryl chloride fluoride/triethylamine as dehydrating agent[3].



$$\text{R-CH=N-OH}\ (\mathbf{1}) \xrightarrow{SO_2ClF/(C_2H_5)_3N} \text{R-CH=N-O-}SO_2\text{-F}\ (\mathbf{2}) \xrightarrow{(C_2H_5)_3N} \text{R-C}\equiv\text{N}\ (\mathbf{3})$$

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 alkylamines. 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.



$$R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-OH}\ (\mathbf{4}) \xrightarrow{SO_2ClF/(C_2H_5)_3N} R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-O-}SO_2\text{-F}\ (\mathbf{5}) \xrightarrow{R^2NH_2/(C_2H_5)_3N} R^1\text{-}\overset{O}{\overset{\|}{C}}\text{-NH-}R^2\ (\mathbf{6})$$

Table. *Amides **6** from Carboxylic Acids **4** and Amines R^2-NH_2*

R^1	R^2	Yield[a] [%]	m.p. [°C][b] or b.p. [°C]/torr found	m.p. [°C][b] or b.p. [°C]/torr reported
H	C_6H_5	65	*112°/4*	*166°/14*[13]
H_3C	C_6H_5	70	115°	114.3°[13]
C_6H_5	C_6H_5	70	164°	163°[13]
C_6H_5	t-C_4H_9	80	135.1°	135°[14]
C_6H_5	c-C_6H_{11}	90	150°	151°[15]
4-$O_2N-C_6H_4$	C_6H_5	80	210°	211°[13]
$C_6H_5CH_2$	C_6H_5	85	117.6°	118°[13]
$C_6H_5CH_2$	$C_6H_5CH_2$	96	*120°*	*122°*[16]
c-C_7H_{13}	c-C_6H_{11}	81	182.3°	—[c]
2-HOOC$-C_6H_4$	C_6H_5	85	167°	166.5°[17]

[a] Yield of pure, isolated product; purity ≥78%.

[b] All amides were recrystallized from ethanol/heptane mixtures.

[c] $C_{14}H_{25}NO$ (223.4) calc. C 75.28 H 11.28 N 6.27; found 75.07 11.00 6.17

0039-7881/80/0832-0661 $ 03.00

The variety of other methods currently available for the synthesis of amides from carboxylic acids includes the use of ion exchange resins[4], tetrachlorosilane[5], hexachlorocyclotriphosphazatriene[6], diethylphosphoryl cyanide[7], triphenyl phosphine/carbon tetrachloride[8], boron trifluoride etherate[9], and triphenylphosphine ditriflate[10]. A review[11] 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 **6** in high yield. The dichloromethane solution of sulfuryl chloride fluoride is conveniently handled and sulfuryl chloride fluoride is easily prepared[12] if not obtained commercially.

Amides 6 from Carboxylic Acids 4; General Procedure:

To a stirred solution of the carboxylic acid **4** (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 ^{1}H-N.M.R. spectroscopy.

Support of our work by the National Institutes of Health is gratefully acknowledged. One of us (A. G. L.) wishes to thank Consejo Nacional de Ciencia y Technologia (Government of Mexico) for financial support.

Received: March 21, 1980

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