Dialkylaminodifluorosulfinium Salts: XtalFluor-E and XtalFluor-M
Compiled by Antonio Franconetti

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Introduction
Fluorination is an important reaction in medicinal chemistry. Fluorinated analogues of biomolecules frequently show increased biological power, lipidic permeability and metabolic stability. Diethylaminosulfur trifluoride (DAST) has been widely used for directly replacing a hydroxyl group by fluorine under very mild conditions. Nevertheless, the corrosive properties of DAST make it unsuitable for high-scale usage.

In this context, commercially available aminodifluorosulfinium salts, such as XtalFluor-E (1) or XtalFluor-M (2), are efficient alternatives. These fluorinating agents are crystalline, more selective and significantly more stable than Deoxo-Fluor or DAST and do not react violently with water.

Abstracts

(A) Failure of Hydrocinnamyl Alcohol with XtalFluor-M:
The reaction of hydrocinnamyl alcohol with 2 or 1 in acetonitrile provided an intractable mixture. For this reaction to proceed, the addition of exogenous sources of fluoride, such as Et3N·3HF or Et3N·2HF, was necessary.

(B) Halogenation of Alcohols with XtalFluor Reagents:
Reaction of primary, secondary and tertiary alcohols with 1 using Et3N·3HF as a promoter gave the fluorinated nucleophilic substitution products. The addition order was a key parameter in this reaction. To obtain good selectivity and stereochemical integrity, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) had to be used together with the fluorination agents. A mixture of fluorinated bridged biphenyl systems has been obtained from 3-hydroxyspirodienones by means of a XtalFluor-E-promoted rearrangement. When compound 2 was used instead of compound 1, substrate decomposition was observed. Chlorination, bromination and iodination reaction of primary alcohols in good yield has been described using a combination of tetraethylammonium halide and XtalFluor-E.
(C) Geminal Difluorination of Carbonyl Groups:
L’Heureux et al. have reported the geminal difluorination of carbonyl groups of aldehydes and ketones. They demonstrated that compound 1 alone was incapable of performing such transformations. To obtain geminal difluorinated products, it was necessary to use a promoter and increase the temperature (e.g., CH$_2$Cl$_2$ or 1,2-dichloroethane at reflux).

(F) Enantioselective Ring Expansion of Prolinols:
Direct ring expansion of N-alkyl prolinals to produce the corresponding 3-azidopiperidines in good and excellent regio-, diastereo- and enantioselectivity was achieved by using XtalFluor-E. Formation of an aziridinium intermediate which reacts with a nucleophile such as tetrabutylammonium azide (Bu$_4$NN$_3$) is proposed.

(G) Activating Agents for Carboxylic Acids:
Compound 1 has proved to be an efficient coupling agent for the synthesis of amides by activation of the carboxylic acid. Moreover, this reaction is carried out with primary and secondary amines in good yield without epimerization or racemization.

References