Dialkylaminodifluorosulfinium Salts:
XtalFluor-E and XtalFluor-M

Compiled by Antonio Franconetti

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Introduction
Fluorination is an important reaction in medicinal chemistry.1 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.2,3 Nevertheless, the corrosive properties of DAST make it unsuitable for high-scale usage.

In this context, commercially available aminodifluorosulfinium salts,4 such as XtalFluor-E (1) or XtalFluor-M (2), are efficient alternatives. These fluorinating agents are crystalline, more selective and significantly more stable5 than Deoxo-Fluor or DAST and do not react violently with water.6

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.5

(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 stereochanical integrity, 1,8-diazabicycloundec-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.5 Chlorination, bromination and iodination reaction of primary alcohols in good yield has been described using a combination of tetraethylammonium halide and XtalFluor-E.7

SYNLETT 2013, 24, 0891–0892
Advanced online publication: 19.03.2013
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(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.14 To obtain geminal difluorinated products, it was necessary to use a promoter and increase the temperature (e.g., CH₂Cl₂ or 1,2-dichloroethane at reflux).

(D) Fluorination Processes on Carbohydrate Derivatives:
Fuchs and co-workers have recently reported the preparation of a fluorodisaccharide in excellent yield without side products using XtalFluor-E, thus eliminating the need for purification.9 The effective preparation of glycosyl fluorides from thio-, seleno-, telur- and glycosyl sulfoxides has been performed in 30 minutes by Williams and co-workers with evidence that fluoride is delivered by the tetrafluoroborate counterion 10

(E) 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 (Bu₄NN₃) is proposed.11

(F) Cyclodehydration Agents:
Paquin and co-workers have recently reported the use of I as a practical cyclodehydration agent to obtain 1,3,4-oxadiazoles among other nitrogen-containing heterocycles.13 The addition of acetic acid improved the yield and selectivity of the oxadiazole formation.

(G) Activating Agents for Carboxylic Acids:
Compound I has proved to be an efficient coupling agent for the synthesis of amides by activation of the carboxylic acid.14 Moreover, this reaction is carried out with primary and secondary amines in good yield without epimerization or racemization.

References
