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Full Length Article

# Bromofluorination of unsaturated compounds using DMPU/HF as a fluorinating reagent

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ABSTRACT

Bromofluorination reactions were performed by treating of a variety of unsaturated compounds with N-bromosuccinimide (NBS) and DMPU/HF as the fluorinating reagent. The DMPU/HF complex showed to be an efficient fluorinating reagent to convert alkenes into their corresponding bromofluoro compounds. It showed to have high reactivity and the process afforded bromofluorinated products with good Markovnikov regioselectivity. These fluorinated compounds are useful starting materials and serve as building blocks for many fluorinated biologically active molecules.

## 1. Introduction

The synthesis of fluorinated organic molecules has gained demand in recent years and has attracted attention from pharmaceutical, chemical and agrochemical industries [1,2]. The incorporation of fluorine into organic compounds is a strategy used to tune the biological properties of molecules as they change their lipophilicity and metabolic activity [3]. One efficient method for the incorporation of fluorine into molecules is the halofluorination of unsaturated compounds. Accordingly, there has been an extensive effort for the development of methodologies and reagents for the effective synthesis of bromofluoro compounds [4,5]. Existing synthetic strategies to effectively pursue bromofluorination of alkenes relied on utilizing different reagents such as tetrabutylammonium bifluoride [6] and $BrF_3$ [7]. It has been shown that the combination N-bromosuccinimide (NBS) and triethylamine trihydrofluoride ($Et_3N$/3HF) was an efficient way of producing bromofluoro compounds from alkenes [8]. In this case, NBS was acting as electrophilic bromine source and $Et_3N$/3HF is the nucleophilic fluorinating specie. An alternative bromonium ions source was 1,3-dibromo-5,5-dimethylhydantoin [9]. And other HF-based reagents such as pyridine hydrofluoride (Olah's Reagent) [10], potassium fluoride poly (hydrogen fluoride) [11] and tetrabutylphosphonium dihydrogen trifluoride [12] have been used as the nucleophilic source of fluorine.

Recently, our research group has designed an efficient fluorinating reagent DMPU/HF (DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone); when compared with other commonly used fluorinating reagents such as $Et_3N$/3HF and Olah's Reagent, DMPU/HF is superior due to the non-nucleophilic, weakly basic and weakly coordinating properties of DMPU. We also demonstrated the synthetic utility and effectiveness of DMPU/HF in some nucleophilic fluorination reactions: the gold-catalyzed hydrofluorination of alkynes [13], fluoro-Prins cyclization reactions [14] and ring-opening fluorination of aziridines [15]. DMPU/HF exhibited high reactivity and selectivity compared with the other aforementioned HF-based reagents. Herein, we report our studies on the bromofluorination of alkenes using DMPU/HF as fluorinating reagent, and described its efficiency to provide products with good regioselectivity.

The strategy for bromofluorination relies on the acid-catalyzed attack of the pi electrons of an alkene to the positive bromine in NBS to form the electrophilic bromonium ion intermediate. Then, the bromonium ion opens by the attack of nucleophilic fluoride to provide the desired product (Scheme 1).

## 2. Results and discussion

A series of alkenes were used to examine the capability of DMPU/HF in producing the corresponding fluorinated products. The results are summarized in Table 1. The products were isolated in good to excellent yields (66–89%) and good regioselectivity. Specifically, alkenes derived from aryl vinyl substituted with halogens and an ether group (compounds **1b–1d**) furnished the corresponding bromofluoro compound when using 7 equivalents of DMPU/HF in the presence of 1.5

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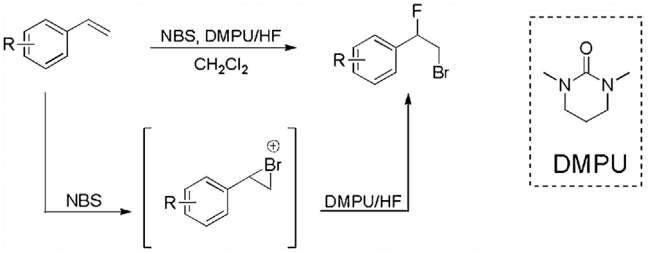
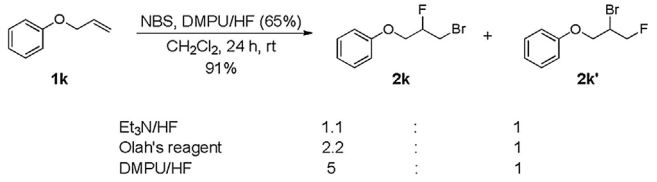


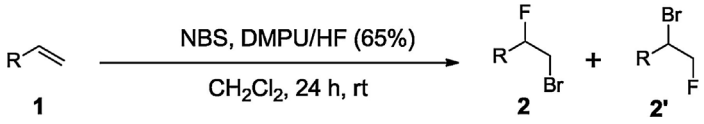

**Scheme 1.** Strategy for the bromofluorination of alkenes using NBS and DMPU/HF.

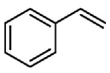
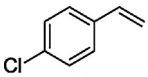
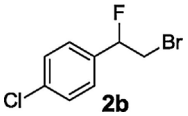
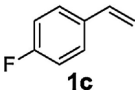
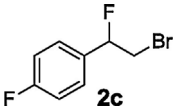
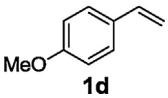
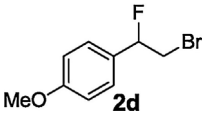
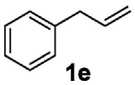
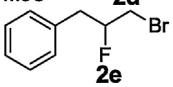
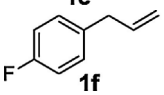
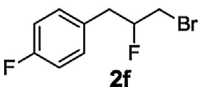
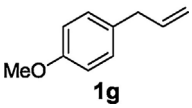
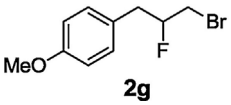
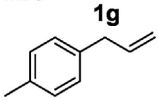
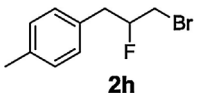
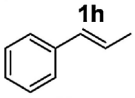
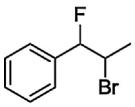
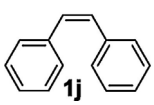
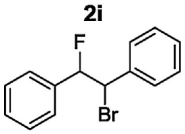



**Scheme 2.** Bromofluorination reaction of allylphenyl ether.

equivalents of NBS in $CH_2Cl_2$. In each case, only the Markovnikov regioselective product was obtained, resulting from fluoride attack at the more substituted carbon atom of the bromonium ion intermediate. This strategy was subsequently applied to allylbenzylic compounds substituted with electron-withdrawing and electron-donating groups (compounds **1f–1h**). These substrates generated a mixture of bromofluorinated regioisomers products under these conditions with the Markovnikov product being the major isomer. Furthermore, this reaction appeared to be stereoselective with substrates bearing an internal double bond. In the case of (*E*)-1-phenylpropene **(1i),** the major product observed was *anti*-2-bromo-1-fluoro-1-phenylpropane **(2i)**. In a similar fashion, the treatment of *cis*-stilbene **(1j)** with NBS followed by DMPU/

**Table 1**
Bromofluorination of alkenes.




| entry | substrate | major product | yield | ratio (2:2′) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 89% | — |
| 2 |  **1b** |  **2b** | 87% | — |
| 3 |  **1c** |  **2c** | 87% | — |
| 4 |  **1d** |  **2d** | 86% | — |
| 5 |  **1e** |  **2e** | 82% | 11:1 |
| 6 |  **1f** |  **2f** | 87% | 11:1 |
| 7 |  **1g** |  **2g** | 86% | 9:1 |
| 8 |  **1h** |  **2h** | 84% | > 20:1 |
| 9 |  **1i** |  **2i** | 79% | — |
| 10 |  **1j** |  **2j** | 66% | — |