Selective Bromofluorination of Alkenes with 1,3-Dibromo-5,5-dimethylhydantoin and Silicon Tetrafluoride

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Alkenes have been converted into the corresponding bromofluorides by reaction with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and silicon tetrafluoride in 1,4-dioxane in a highly regio-, stereo-, and chemoselective manner.

One of the most fundamental reactions in organofluorine chemistry concerns the introduction of a fluorine atom into alkenes.[1] However, the known methods for such transformations require hazardous reagents and/or tedious reaction procedures, and the selectivities are not always sufficient for the specific synthesis of fluorinated compounds.[2] We have recently reported the efficiency of SiF_4 in ring opening-fluorination of epoxides[3] and α,β-epoxysilanes.[4] In these reactions the hypervalent fluorosilane species are responsible for the selective fluorination.

In the present paper, we describe a facile method of bromofluorination of alkenes with DBH–SiF_4 (DBH = 1,3-dibromo-5,5-dimethylhydantoin). First, the source of activating species for alkenes was examined (see Table 1); among the halonium ion sources, DBH and *N*-bromosuccinimide (NBS) worked effectively. In particular, good to excellent yields of the bromofluorinated products were obtained with DBH, whereas yields were slightly lowered with NBS. On the other hand, other X^+ species such as *N*-iodosuccinimide (NIS) and *N*-chlorosuccinimide (NCS) did not effect the halofluorination, and the starting alkenes were usually recovered almost unchanged. The effects of the reaction solvent are noteworthy; of various solvents examined (Et_2O, tetrahydrofuran, MeCN, CH_2Cl_2, and 1,4-dioxane), only 1,4-dioxane gave satisfactory results, implying that the reactive BrF species may be formed only in 1,4-dioxane in the present medium.‡ Representative results are shown in Table 2.

This reaction is widely applicable. Aliphatic, aromatic, and alicyclic alkenes studied here all underwent bromofluorination to give the adducts in good to excellent yields. Terminal alkenes were also converted into 2-fluorides exclusively in good yields. The mildness of the reaction conditions allows regio- and stereo-selective bromofluorination of dihydronaphthalene (**3**)§ and indene (**5**),¶ which are very susceptible to polymerization under acidic conditions[2] (see Table 1, entries 2 and 3).

The stereochemical outcome of the aromatic alkenes is noteworthy (see Table 3). Both (*E*)- and (*Z*)-1-phenylpropene gave *anti*-2-bromo-1-fluoro-1-phenylpropane (**11**) exclusively in good yields. Comparison with other common methods employing $(HF)_nPy$–NBS (Py = pyridine) or Et_3N–NBS shows a distinct merit in the stereoselectivity of the present procedure, which may be explained in terms of the involvement of the bridge bromonium ions (**9**) and (**10**) that are stabilized by 1,4-dioxane and isomerize to the more thermodynamically stable intermediate (**9**).

Thus, SiF_4/DBH is a very mild, convenient combination which does not affect acid-sensitive functionalities and the high selectivities found in the cases of aromatic and terminal alkenes may make this procedure applicable to the synthesis of

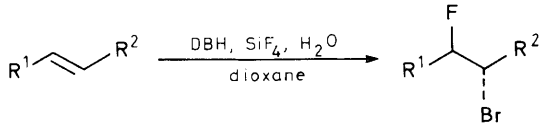
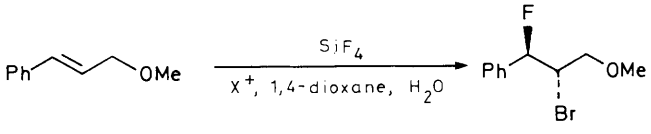


Table 1. Comparison of X^+ sources.[a]



(**1**) (**2**)

Entry	X^+	(**2**) % yield[b]
1	NBS	52
2	DBH	77
3	NIS	0
4	NCS	0

[a] Reaction was carried out according to the typical experiment in the text. [b] Isolated yield.

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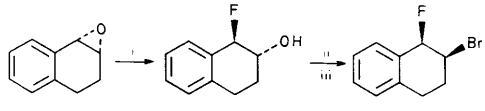
‡ We have examined several systems for the bromofluorination of alkenes (Bu^n_4NF–DBH, HF–DBH, *etc.*), of which SiF_4–DBH in the presence of H_2O worked most effectively. Bu^n_4NF–DBH did not give the bromofluorinated compounds, whereas HF–DBH in 1,4-dioxane gave bromofluorides in low yields (10—40%). In the absence of H_2O, SiF_4–DBH usually gave bromofluorides in less than 50% yield, implying that the hypervalent fluorosilane species[3,4] may be effective in the present bromofluorination.

§ The structure of the bromofluoride (**4**) was assigned as *trans* by comparison of its NMR spectrum with that of the *cis*-isomer prepared in the following manner.[5]

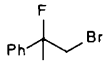
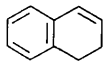
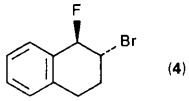
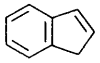
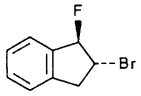
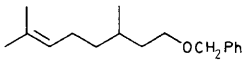
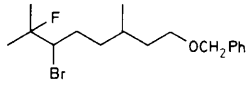
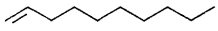
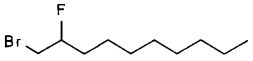
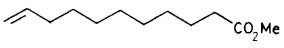
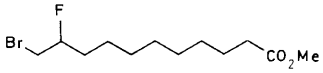


Reagents: i, Et_3·3HF, ii, MsCl/pyridine; iii, KBr/18-C-6.

NMR spectroscopic data for (**4**): ^1H ($CDCl_3$) δ 2.0—2.6 (m, 2 H), 2.6—3.2 (m, 2H), 4.55 (d,d,d,d, 1H, *J* 3.3, 4.8, 6.4, 11.8 Hz), 5.58 (d,d, 1H, *J* 4.8, 50.6 Hz), 7.1—7.4 (m, 4H); ^{19}F ($CDCl_3/CFCl_3$) δ −146.0 p.p.m. For (**7**): ^1H ($CDCl_3$) δ 2.0—2.6 (m, 2H), 2.6—3.2 (m, 2H), 4.45 (d,d,d,d, 1H, *J* 2.9, 4.2, 10.3, 21.3 Hz), 5.53 (d,d, 1H, *J* 2.9, 50.6 Hz), 7.1—7.4 (m, 4H); ^{19}F ($CDCl_3/CFCl_3$) δ −163.3 p.p.m.

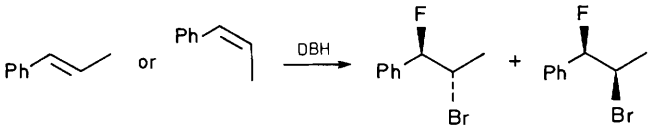
¶ The structure of the bromofluoride (**6**) was assigned on the basis of the NMR spectrum of the *trans*-difluoride.[6] Compound (**6**) gave the following spectra: ^1H n.m.r. ($CDCl_3$) 3.23 (d,d,d, 1H, *J* 2.2, 4.2, 17.1 Hz), 3.76 (d,d, 1H, *J* 6.6, 17.1 Hz), 4.57 (d,d,d,d, 1H, *J* 3.1, 4.2, 6.6, 16.9 Hz), 6.01 (d,d, 1H, *J* 3.1, 56.0 Hz), 7.2—7.5 (m, 4H); ^{19}F NMR ($CDCl_3/CFCl_3$) δ −161.0 p.p.m.

Table 2. Bromofluorination of alkenes.[a]

Entry	Alkene	Product	Yield[b]/%
1			55
2	 (3)	 (4)	59
3	 (5)	 (6)	60
4			68
5			76
6			73

[a] Reaction was carried out as described in the text. [b] Isolated yield.

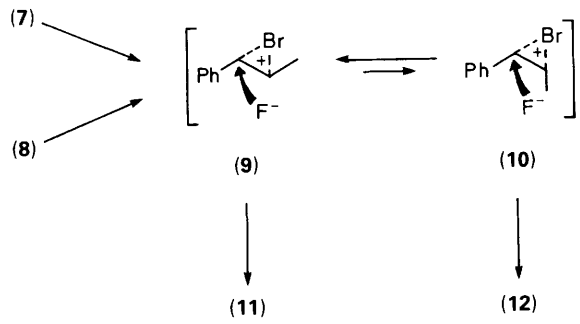
Table 3. Bromofluorination of 1-phenylpropene.



(7) (8) (11) (12)

Alkene geometry	Reagent	Ratio (*anti*:*syn*)	Yield/%
(*E*)	SiF_4–H_2O[a]	1:0	72
(*E*)	$(HF)_n$·Py[b]	1:1	56
(*E*)	Et_3N·3HF[c]	1:0	65
(*Z*)	SiF_4–H_2O[a]	1:0	55
(*Z*)	Et_3N·3HF[c]	1:2	26
(*Z*)	Et_3N·3HF[a]	2:1	40

[a] 1,4-Dioxane as solvent. [b] No solvent. [c] Dichloromethane as solvent.



specifically fluorinated bioactive compounds. The following example represents a typical experimental procedure: to a flask containing a solution of DBH (1.1 mmol) and H_2O (1.0 mmol) in 1,4-dioxane (4 ml) was connected a balloon filled with SiF_4 (*ca.* 100 ml) and the mixture was stirred at room temperature for 15 min. A solution of an alkene (1.0 mmol) in 1,4-dioxane (1 ml) was added, and the mixture was stirred at room temperature for 2—3 h. A saturated aqueous solution of KF (5 ml) was added to the mixture, and after normal work-up the resulting crude mixture was purified by flash silica gel column chromatography to give the bromofluorinated product.

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