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Selective Halofluorination of Alkenes with Tetrabutylphosphonium Dihydrogentrifluoride in Combination with *N*-Halosuccinimide or 1,3-Dibromo-5,5-dimethylhydantoin

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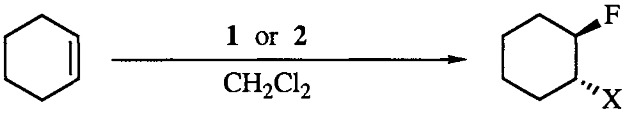
Alkenes and their functionalized derivatives were readily converted to the corresponding halofluorides with tetrabutylphosphonium dihydrogentrifluoride as combined with *N*-halosuccinimides or 1,3-dibromo-5,5-dimethylhydantoin in highly regio-, stereo-, and chemoselective manners. In particular, alkenes having a oxirane or primary hydroxyl group also underwent halofluorination selectively in good yields.

Halofluorination of alkenes is one of the most important reactions to introduce a fluorine atom into organic compounds as associated with synthesis of new fluorinated agrochemicals and medicines. The halofluorination is performed either by treating with halogen fluorides (ClF, BrF, IF)1) or with some halogen sources such as *N*-haloamides or *N*-haloimides combined with appropriate fluoride reagents.2) Recently, silicon tetrafluoride3) or tetrabutylammonium dihydrogentrifluoride4) have been reported to be better applicable to preparation of halofluorides containing acid-sensitive functional group under mild conditions. In addition, halofluorination of the substrates containing a hydroxyl group is of interest, but there exist only a few reports. For example, anhydrous hydrogen fluoride5) and the combination of ammonium hydrogen fluoride and aluminium fluoride6) have been reported for the preparation of halofluoro alcohols, in which the former is described for bromofluorination of unsaturated steroidal alcohol and iodofluorination of *trans*-2-butenol was performed in the latter. We now report a facile method for halofluorination of alkenes with the combination of tetrabutylphosphonium dihydrogentrifluoride (**1**) and *N*-halocarboimides in highly selective manners.

We first conducted halofluorination of cyclohexene with **1** or tetrabutylphosphonium hydrogendifluoride (**2**) and various *N*-halocarboimides and the results are summarized in Table 1. Halofluorination with **1** and *N*-iodosuccinimide (NIS) or *N*-bromosuccinimide (NBS) gave the corresponding halofluoro derivatives in good yields under mild conditions (runs 1 and 2). Bromofluorination with **1** (1.5 equiv. for the alkene) and 1,3-dibromo-5,5-dimethylhydantoin (DBH, 1.5 equiv.) under a milder condition (run 3) gave the similar result with that of the reaction with NBS. On the other hand, **2** required longer reaction time and resulted in the yields lower than those with **1** (see runs 5 and 6). This is contrary to the reactivity for nucleophilic fluorination of aliphatic, aromatic, and *N*-heterocyclic substrates, in which **2** is more active than **1**.7) Chlorofluorination with *N*-chlorosuccinimide (NCS) and **1** or **2** gave the chlorofluoro analog in poor yields, in which *trans*-1,2-dichlorohexane was formed in 13% and 10% yields respectively (runs 4 and 7).

A typical procedure for this halofluorination is given as follows: Cyclohexene (411 mg, 5 mmol), NIS (2.250 g, 10 mmol), tetrabutylphosphonium dihydrogentrifluoride (**1**) (3.185 g, 10 mmol) and CH_2Cl_2 (2 ml) were stirred at room temperature for 4 h under N_2. Then the reaction mixture was quenched with water and extracted with ether. The ethereal layer was washed with 5% $NaHCO_3$, 20% $Na_2S_2O_3$, and water and dried over Na_2SO_4. After evaporation of solvents *in vacuo*, the residue was purified by silica gel chromatography with hexane as eluate to afford *trans*-1-fluoro-2-iodocyclohexane (981 mg, 86% yield) (run 1 in Table 1).

Table 1. Halofluorination of Cyclohexene[a)]



(X= I, Br, Cl)

Run	F^-	Halocarboimide	Temp / °C	Time / h	Product X	Yield / % [b)]
1	**1**	NIS	20-25	4	I	86
2	**1**	NBS	20-25	4	Br	75
3	**1**	DBH	0	1	Br	77
4	**1**	NCS	20-25	30	Cl	20
5	**2**	NIS	20-25	24	I	58
6	**2**	NBS	20-25	20	Br	50
7	**2**	NCS	20-25	24	Cl	13

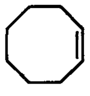
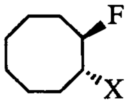
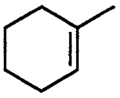
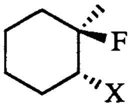
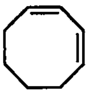
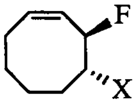
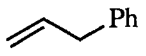
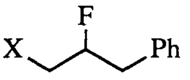
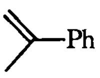
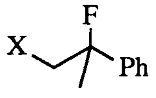
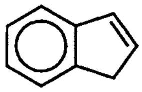
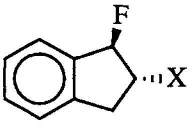
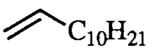
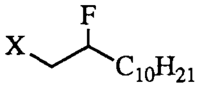
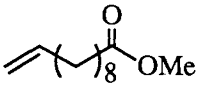
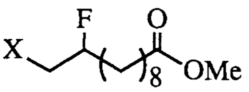
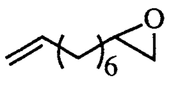
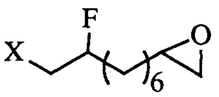
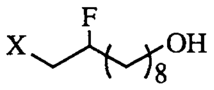
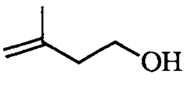
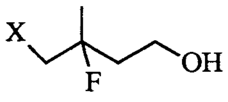
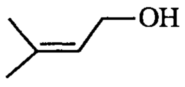
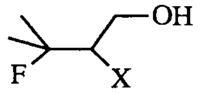
a) Cyclohexene (5 mmol) was allowed to react with NIS, NBS or NCS (10 mmol) and a F^- source (10 mmol) in CH_2Cl_2 (2 ml) except for run 3 (DBH (7.5 mmol) and **1** (7.5 mmol)).

b) Isolated yield.

A variety of alkenes were subjected to the halofluorination with **1** and NIS or DBH, and the results are summarized in Table 2. Aliphatic, aromatic, and alicyclic alkenes were readily converted into the corresponding iodofluoro or bromofluoro derivatives in good to excellent yields. All the reactions appeared to follow the Markovnikov rule for regioselectivity. In the case of cyclic alkenes, the reactions stereospecifically proceeded to give the anti addition products (runs 1-6, 11, and 12). 1,3-Cyclooctadiene was converted into 3-fluoro-4-halo-1-cyclooctene as sole product in 53% and 54% yields respectively (runs 5 and 6). Indene, a rather susceptible substrate to polymerization under acidic conditions was readily converted to the 2-halofluoroindanes in 68% and 74% yields respectively (runs 11 and 12). More importantly, the reaction of 7-octenyloxirane also gave the corresponding halofluoro oxiranes in good yields (runs 17 and 18) whereas oxiranes have been converted to fluorohydrins when treated with **2**[7a)] or silicon tetrafluoride in the presence of $i\text{-}Pr_2NEt$.[8)] As is similar to our runs, Kuroboshi *et al.* reported that iodofluorination of 7-octenyloxirane with $Bu_4NH_2F_3$ and NIS proceeded in 64% yield under mild conditions.[4)]

Furthermore, alkenes having a primary hydroxyl group were converted into the halofluoro derivatives in fair to good yields and in regioselective manners (runs 19-24). In contrast to this, it has been reported that the

Table 2. Halofluorination of Alkenes with **1**[a)]

Run	Substrate	Halogen source	Solvent[b)]	Temp °C	Time h	Product	X=	Yield[c)] %
1		NIS	B	60	5		I	78
2		DBH	A	0	1		Br	61
3		NIS	A	20-25	4		I	91
4		DBH	A	0	1		Br	83
5		NIS	B	60	5		I	53
6		DBH	A	0	1		Br	54
7		NIS	B	60	8		I	76
8		DBH	A	20-25	2		Br	75
9		NIS	A	20-25	5		I	91
10		DBH	A	0	1		Br	80
11		NIS	B	60	5		I	68
12		DBH	A	20-25	2		Br	74
13		NIS	B	50	3		I	80
14		DBH	A	20-25	1		Br	73
15		NIS	A	40	3		I	88
16		DBH	A	20-25	1		Br	72
17		NIS	A	40	2		I	81
18		DBH	A	0	1		Br	70
19		NIS	A	20-25	2		I	44
20		DBH	A	0	1		Br	65
21		NIS	A	20-25	2		I	66
22		DBH	A	0	1		Br	64
23		NIS	A	20-25	2		I	74
24		DBH	A	0	1		Br	73

a) Alkene (5 mmol) was allowed to react with **1** and NIS or DBH in the solvent (2 ml). Molar ratio of reagents was as follows; **1** : NIS : substrate = 2 : 2 : 1, **1** : DBH : substrate = 1.5 : 1.5 : 1.

b) A : CH_2Cl_2 used as solvent. B : $ClCH_2CH_2Cl$ used as solvent. c) Isolated yield.

reaction of 10-undecen-1-ol with tetrabutylammonium hydrogendifluoride and NBS gave only the dibromo adduct (10,11-dibromoundecan-1-ol) in 86% yield (in CH_2Cl_2, at room temperature, for 21 h).[9] In addition, we carried out the reactions of a few substrates with **1** and NIS in order to examine the regioselectivity of iodofluorination of unsaturated alcohols. It has been reported that the reaction of *trans*-2-butenol with NH_4HF_2-AlF_3 and NIS gave 3-fluoro-2-iodo-1-butanol (**3**) and 2-fluoro-3-iodo-1-butanol (**4**) in a ratio of 77 : 23 (in dimethoxyethane, at 50 °C, for 2 h, in 60% yield).[6] In contrast to this, our case afforded **3** and **4** in a ratio of 92 : 8 in better regioselective manner (in CH_2Cl_2, at 20-25 °C, for 2 h, in 68% yield). The reaction of *trans*-2-hexenol regioselectively gave 3-fluoro-2-iodo-1-hexanol as sole product in 70% yield when treated with **1** and NIS (in CH_2Cl_2, at 20-25 °C, for 2 h). However, coumarin as single example of α,β-unsaturated ketones did not undergo the halofluorination and were recovered as almost unaffected.

In summary, the halofluorination of alkenes with tetrabutylphosphonium dihydrogentrifluoride (**1**) and *N*-haloimides can be a useful procedure to obtain a wide variety of functionalized halofluorides under mild conditions in highly regio-, stereo-, and chemoselective manners.

References

1) S. Rozen and M. Brand, *J. Org. Chem.*, **50**, 3342 (1985).
2) G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, and J. A. Olah, *J. Org. Chem.*, **44**, 3872 (1979); G. Alvernhe, A. Laurent, and G. Haufe, *Synthesis*, **1987**, 562; M. Kuroboshi and T. Hiyama, *Synlett*, **1991**, 185; G. E. Heasley, J. M. Janes, S. R. Stark, and B. L. Robinson, *Tetrahedron Lett.*, **26**, 1811 (1985); T. Ando, D. G. Cork, M. Fujita, T. Kimura, and T. Tatsuno, *Chem. Lett.*, **1988**, 1877.
3) M. Shimizu, Y. Nakahara, H. Yoshioka, *J. Chem. Soc., Chem. Commun.*, **1989**, 1881.
4) M. Kuroboshi and T. Hiyama, *Tetrahedron Lett.*, **32**, 1215 (1991).
5) A. Bowers, L. C. Ibáñeg, E. Denot, and R. Becerra, *J. Am. Chem. Soc.*, **82**, 4001 (1960).
6) J. Ichihara, K. Funabiki, and T. Hanafusa, *Tetrahedron Lett.*, **31**, 3167 (1990).
7) a) H. Seto, Z. Qian, H. Yoshioka, Y. Uchibori, and M. Umeno, *Chem. Lett.*, **1991**, 1185; b) Y. Uchibori, M. Umeno, H. Seto, Z. Qian, and H. Yoshioka, *Synlett*, **1992**, 345; c) Y. Uchibori, M. Umeno, and H. Yoshioka, *Heterocycles*, **34**, 1507 (1992).
8) M. Shimizu and H. Yoshioka, *Tetrahedron Lett.*, **29**, 4101 (1988).
9) F. Camps, E. Chamorro, V. Gasol, and A. Guerrero, *J. Org. Chem.*, **54**, 4294 (1989).

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