

Potassium Fluoride–Poly(Hydrogen Fluoride) Salts as Fluorinating Agents for Halofluorination of Alkenes

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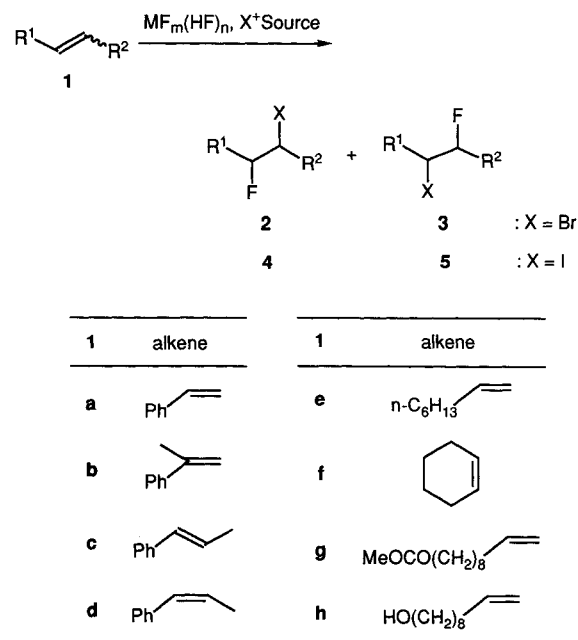
Received 25 October 1994; revised 15 December 1994

It was found that potassium fluoride–poly(hydrogen fluoride) salts are useful fluorine sources for halofluorination of alkenes. The reaction proceeded with these salts and *N*-halosuccinimides or 1,3-dibromo-5,5-dimethylhydantoin in a regio- and stereoselective manner.

Potassium fluoride–poly(hydrogen fluoride) (KF(HF)_n) salts are easy-to-handle solid reagents which are easily prepared from potassium fluoride and anhydrous hydrogen fluoride.¹ We have investigated the utility of these salts for the synthesis of organofluorine compounds, and we have recently reported that potassium dihydrogen trifluoride (KH₂F₃) works as an efficient fluorinating agent for epoxide ring opening.² Among the synthetic methods for the preparation of organofluorine compounds, halofluorination of alkenes is a useful one for the incorporation of one fluorine atom into an organic molecule,³ and various reagents such as organic base–hydrogen fluoride adducts have been investigated as organic fluorinating agents for this reaction.^{4,5} But there have been very few reports concerning the use of metal fluoride salts as a fluorinating agent for halofluorination, and furthermore, these salts can only be used under limited conditions. For example, silver fluoride⁶ or silver fluoride supported on calcium fluoride⁷ were used for halofluorination, however, these reactions must be carried out in the dark because of the photosensitivity of the reagents. The combination of hydrogen difluoride salts (MHF₂, M = NH₄, Na, K) and aluminum fluoride was also reported to be effective in halofluorination, but ultrasonic irradiation is required.⁸ In this paper, we report that potassium fluoride–poly(hydrogen fluoride) salts work as an efficient fluorinating agent in the halofluorination of alkenes, and that the reaction readily proceeds with alkenes, these salts and a halonium ion source giving vicinal halofluorides in a regio- and stereoselective manner.

As an initial attempt, the reaction of styrene (**1a**, 1 mmol) with KH₂F₃ (1.1 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (DBH, 1.1 mmol) was carried out at room temperature in dichloromethane (Scheme 1). The reaction proceeded regioselectively to afford (2-bromo-1-fluoroethyl)benzene (**2a**) exclusively in 62% yield. Various alkali metal or alkaline earth metal fluoride–poly(hydrogen fluoride) salts (MF_m(HF)_n) are known other than KH₂F₃.⁹ The bromofluorination of **1a** was conducted using these various metal fluoride–poly(hydrogen fluoride) salts under the same reaction conditions. As shown in Table 1, although the reaction proceeded with each salt, the best yields were obtained when potassium trihydrogen tetrafluoride (KH₃F₄) and potassium tetrahydrogen pentafluoride (KH₄F₅) were used.

Halofluorination of **1a** with several halonium ion sources was conducted. When *N*-bromosuccinimide was used in



Scheme 1

Table 1. Bromofluorination of Styrene with MF_m(HF)_n^a

MF _m (HF) _n	Time (h)	Yield of 2a (%) ^b
KH ₂ F ₃	6	62
KH ₃ F ₄	5	71
KH ₄ F ₅	4	71 (58) ^c
NaH ₄ F ₅	4	61
CsH ₃ F ₄	3	67
CaH ₂ F ₄	8	38
BaH ₆ F ₈	4	62

^a Styrene (1 mmol), DBH (1.1 mmol) and MF_m(HF)_n (1.1 mmol) were stirred at room temperature in dichloromethane.

^b Yield determined by ¹⁹F NMR analysis of the crude product (C₆H₅CF₃ was used as an internal standard).

^c Isolated yield.

the bromofluorination of **1a** with KH₄F₅, the reaction proceeded, but the yield of **2a** was lower than in the case with DBH, 60% yield after 23 hours. Iodofluorination of **1a** was also conducted using KH₄F₅ and *N*-iodosuccinimide (NIS).

The reaction was slow at room temperature and the yield of the corresponding iodofluoride **4a** was 36% after 18 hours, however, 83% (isolated yield was 80%) of **4a** was

obtained when the reaction was carried out at 60 °C in chloroform. Chlorofluorination of **1a** with *N*-chlorosuccinimide was very slow even at 60 °C in chloroform resulting in 13% yield of the corresponding chlorofluoride after 24 hours. Bromo- and iodofluorination of various alkenes with KH_4F_5 was examined under these reaction conditions, and the results are summarized in Tables 2 and 3. The corresponding products were obtained in fair to good yields even though the alkenes possess functional groups such as ester and hydroxyl groups. Regioselectivity is exclusive in the case of aromatic substituted alkenes. In the case of aliphatic alkenes, 1-halo-2-fluoro products were predominantly obtained from 1-alkenes. The fluorine atom is introduced into the more substituted carbon, so the regioselectivity can be explained by Markovnikov's rule.⁵ Concerning the stereochemistry, the anti-addition products were obtained in high selectivity with aromatic and aliphatic alkenes.

In conclusion, we have demonstrated that potassium fluoride–poly(hydrogen fluoride) salts are useful metal fluoride reagents as a fluorine source for the halofluorination of alkenes. The reaction is easily carried out by mixing alkenes with these reagents and a halonium ion source to afford the corresponding halofluorides in good yield and in a highly regio- and stereoselective manner.

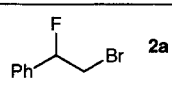
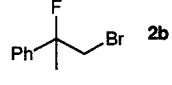
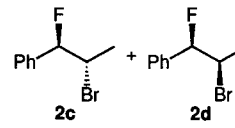
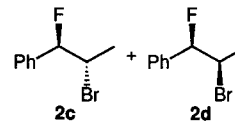
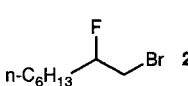
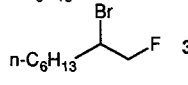
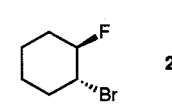
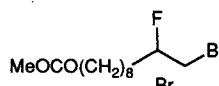
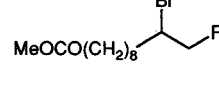
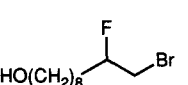
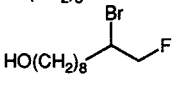
Preparation of $\text{MF}_m(\text{HF})_n$:

Potassium fluoride–poly(hydrogen fluoride) salts were prepared by mixing calculated amounts of potassium hydrogen difluoride and anhydr. hydrogen fluoride in a reaction vessel made of polyethylene or hastelloy B. The mixture was stirred, and heated at 60–70 °C if necessary, to form a homogeneous solution of the salt, which solidified at r.t. Other metal fluoride–poly(hydrogen fluoride) salts were prepared from metal fluoride or metal hydrogen difluoride and anhydr. hydrogen fluoride in a similar manner.

Halofluorination of Alkenes; General Procedure:

To a mixture of KH_4F_5 (1.1 mmol), DBH (1.1 mmol), and CH_2Cl_2

Table 2. Bromofluorination of Alkenes^a

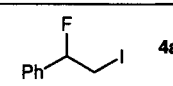
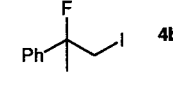
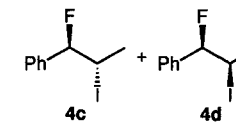
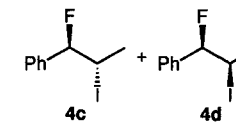
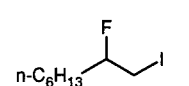
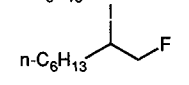
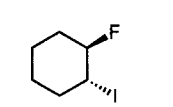
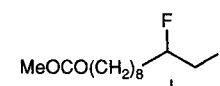
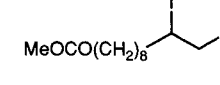
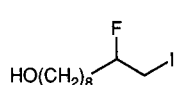
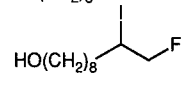
Alkene	Time (h)	Product	Yield (%) ^b
1a	4	 2a	58
1b	9	 2b	51
1c	1	 2c +  2d (97 : 3) ^c	65
1d	1	2c + 2d (23 : 77) ^c	68
1e	1	 2e (87) ^c +  2f (13) ^c	63
1f	1.5	 2f	50
1g	1	 2g (86) ^c +  2h (14) ^c	74
1h	1	 2h (84) ^c +  2i (16) ^c	58

^a Alkene (1 mmol), KH_4F_5 (1.1 mmol), DBH (1.1 mmol) were stirred at room temperature in CH_2Cl_2 .

^b Isolated Yield.

^c Ratio determined by ^{19}F NMR.

Table 3. Iodofluorination of Alkenes^a

Alkene	Time (h)	Product	Yield (%) ^b
1a	19	 4a	80
1b	3	 4b	71
1c	5	 4c +  4d (98 : 2) ^c	77
1d	5	4c + 4d (8 : 92) ^c	78
1e	1	 4e (87) ^c +  4f (13) ^c	64
1f	1	 4f	56
1g	1	 4g (86) ^c +  4h (14) ^c	68
1h	3	 4h (90) ^c +  4i (10) ^c	51

^a Alkene (1 mmol), KH_4F_5 (1.1 mmol), NIS (1.1 mmol) were stirred at 60 °C in CHCl_3 .

^b Isolated Yield.

^c Ratio determined by ^{19}F NMR.

Table 4. NMR and IR Data of Products 2–5

Product	^1H NMR (CDCl_3 , TMS) δ , J (Hz)	^{19}F NMR (CDCl_3 , CFCl_3) δ , J (Hz)	IR (neat) ν (cm^{-1})
2a	3.4–3.7 (m, 2H), 5.6 (ddd, 1H, $J = 46.7, 7.5, 4.2$), 7.2–7.5 (m, 5H)	174.6 (ddd, $J = 46.0, 25.8, 14.7$)	3066, 3035, 2966, 1455, 1210, 1061, 987, 756, 700
2b	1.8 (d, 3H, $J = 22.1$), 3.6 (dd, 1H, $J = 22.4, 11.2$), 3.7 (dd, 1H, $J = 16.8, 11.2$), 7.3–7.4 (m, 5H)	147.8 (ddq, $J_2 = 18.4, J_4 = 22.1$)	3063, 3032, 2992, 1448, 1378, 1293, 1219, 1050, 766, 700
2c	1.7 (dd, 3H, $J = 6.8, 1.2$), 4.3 (ddq, 1H, $J_2 = 16.2, 5.6, J_4 = 6.8$), 5.5 (dd, 1H, $J = 46.4, 5.5$), 7.3–7.4 (m, 5H)	178.4 (dd, $J = 46.0, 16.6$)	3067, 3036, 2981, 2932, 1453, 1020, 968, 756, 770
2d	1.6 (d, 3H, $J = 6.9$), 4.3 (m, 1H), 5.4 (dd, 1H, $J = 45.7, 6.4$), 7.3–7.4 (m, 5H)	171.5 (dd, $J = 46.0, 14.7$)	3067, 3035, 2978, 2930, 1453, 1020, 992, 764, 699
2e	0.9 (t, 3H, $J = 6.8$), 1.3–1.8 (m, 10H), 3.5 (m, 2H), 4.6 (m, 1H)	178.1 (m)	2939, 2860, 1467, 1002 (containing 3e)
3e	0.9 (t, 3H, $J = 6.8$), 1.3–1.8 (m, 10H), 4.1 (m, 1H), 4.6 (m, 2H)	210.1 (dt, $J_2 = 15.0, J_3 = 47.3$)	
2f	1.2–1.9 (m, 6H), 2.1–2.4 (m, 2H), 4.0 (ddt, 1H, $J_2 = 9.9, 4.3, J_3 = 5.4$), 4.5 (ddt, 1H, $J_2 = 48.2, 4.3, J_3 = 5.7$)	168.1 (m)	2947, 2867, 1452, 1371, 1190, 1059, 1048, 1034, 956, 697
2g	1.3–1.8 (m, 14H), 2.3 (t, 2H, $J = 7.6$), 3.5 (m, 2H), 3.7 (s, 3H), 4.6 (m, 1H)	178.1 (m)	2931, 2857, 1736, 1436, 1199, 1173 (containing 3g)
3g	1.3–1.8 (m, 14H), 2.3 (t, 2H, $J = 7.6$), 3.7 (s, 3H), 4.1 (m, 1H), 4.6 (m, 2H)	210.1 (dt, $J_2 = 14.7, J_3 = 47.8$)	
2h	1.2–1.8 (m, 15H), 3.4–3.5 (m, 2H), 3.6 (t, 2H, $J = 6.6$), 4.6 (m, 1H)	178.1 (m)	3356, 2931, 2857, 1465, 1056, 1002 (containing 3h)
3h	1.2–1.8 (m, 15H), 3.7 (t, 2H, $J = 6.1$), 4.1 (m, 1H), 4.6 (m, 2H)	210.1 (dt, $J_2 = 12.9, J_3 = 47.3$)	
4a	3.4–3.5 (m, 2H), 5.5 (ddd, 1H, $J = 46.7, 6.9, 5.4$), 7.2–7.5 (m, 5H)	166.9 (ddd, $J = 46.0, 23.0, 17.4$)	3065, 3033, 2960, 1455, 1177, 1056, 961, 764, 698
4b	1.9 (d, 3H, $J = 21.8$), 3.6 (d, 2H, $J = 20.1$), 7.3–7.4 (m, 5H)	142.6 (tq, $J_3 = 20.2, J_4 = 22.0$)	3061, 3030, 2988, 1447, 1377, 1289, 1200, 1169, 1027, 764, 699
4c	1.9 (dd, 3H, $J = 6.9, 0.7$), 4.4 (ddq, 1H, $J_2 = 17.5, 5.9, J_4 = 6.9$), 5.5 (dd, 1H, $J = 46.5, 5.9$), 7.2–7.4 (m, 5H)	172.2 (dd, $J = 46.0, 18.4$)	3065, 3034, 2974, 2927, 1451, 1006, 964, 759, 699
4d	1.8 (d, 3H, $J = 6.9$), 4.4 (m, 1H), 5.2 (dd, 1H, $J = 45.5, 6.6$), 7.3–7.4 (m, 5H)	165.3 (dd, $J = 44.1, 15.7$)	3065, 3034, 2971, 2924, 1164, 1009, 983, 764, 699
4e	0.9 (t, 3H, $J = 6.8$), 1.3–1.8 (m, 10H), 3.3 (m, 2H), 4.4 (m, 1H)	171.2 (m)	2929, 2859, 1466, 986 (containing 5e)
5e	0.9 (t, 3H, $J = 6.8$), 1.3–1.8 (m, 10H), 4.2 (m, 1H), 4.6 (m, 2H)	198.3 (dt, $J_2 = 12.9, J_3 = 47.8$)	
4f	1.2–2.4 (m, 8H), 4.1 (ddt, 1H, $J_2 = 10.2, 4.3, J_3 = 7.9$), 4.6 (ddt, 1H, $J_2 = 47.5, 4.3, J_3 = 8.6$)	160.0 (m)	2943, 2863, 1450, 1367, 1170, 1032, 951, 662
4g	1.3–1.8 (m, 14H), 2.3 (t, 2H, $J = 7.6$), 3.3 (m, 2H), 3.7 (s, 3H), 4.4 (m, 1H)	171.3 (m)	2928, 2856, 1736, 1436, 1173 (containing 5g)
5g	1.3–1.8 (m, 14H), 2.3 (t, 2H, $J = 7.6$), 3.7 (s, 3H), 4.1 (m, 1H), 4.6 (m, 2H)	198.3 (dt, $J_2 = 14.7, J_3 = 47.8$)	
4h	1.2–1.8 (m, 15H), 3.3 (m, 2H), 3.7 (t, 2H, $J = 6.1$), 4.4 (m, 1H)	171.2 (m)	3332, 3237, 2927, 2852, 1467, 1412, 1071, 1053, 1017 (containing 5h)
5h	1.2–1.8 (m, 15H), 3.7 (t, 2H, $J = 6.1$), 4.1 (m, 1H), 4.6 (m, 2H)	198.2 (dt, $J_2 = 13.5, J_3 = 46.9$)	

(3 mL) in a Teflon (PFA) vessel was added a solution of alkene 1 (1 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at r. t. for 4 h and then quenched with aq solutions of NaHCO_3 and $\text{Na}_2\text{S}_2\text{O}_3$. The aqueous phase was extracted with CH_2Cl_2 (3×5 mL) and the combined organic phase was dried (MgSO_4). After evaporation of the solvent, the crude product 2 was purified by silica gel column chromatography. Halofluorination of other alkenes was carried out with DBH at r. t. in CH_2Cl_2 or with NIS at 60°C in CHCl_3 in a similar manner.

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