ELSEVIER

Journal of Fluorine Chemistry 70 (1995) 1–3

JOURNAL OF FLUORINE CHEMISTRY

Preliminary note

Potassium dihydrogen trifluoride: a novel fluorinating reagent for ring-opening of epoxides

Masanori Tamura*, Motonari Shibakami, Takashi Arimura, Shigeru Kurosawa, Akira Sekiya

National Institute of Materials and Chemical Research, 1-1 Higashi, Tsukuba, Ibaraki 305, Japan

Received 21 March 1994; accepted 24 August 1994

Abstract

It has been found that potassium dihydrogen trifluoride is an efficient and easy-to-handle solid reagent for the ring-opening reaction of epoxides giving fluorohydrins regio- and stereo-selectively. The reaction proceeds via *cis*-addition of HF to the epoxide.

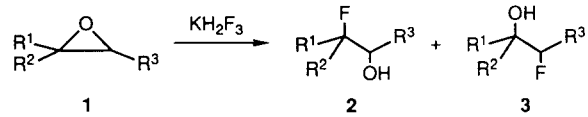
Keywords: Potassium dihydrogen trifluoride; Fluorinating reagent; Ring-opening; Epoxides; Fluorohydrin synthesis

The selective introduction of a fluorine atom into organic molecules has been investigated extensively because of the unique chemical, physical and biological properties of organofluorine compounds [1]. The synthesis of fluorohydrins by the ring-opening of epoxides with hydrogen fluoride has been applied in the chemistry of steroids, amino acids, carbohydrates and prostaglandins as one of the site-selective fluorination reactions [2–4]. A wide variety of reagents such as potassium hydrogen difluoride [3], potassium hydrogen difluoride/aluminium trifluoride [5], potassium hydrogen difluoride/tetrabutylammonium dihydrogen trifluoride [6], various amine-HF reagents [4,7], silicon tetrafluoride [8] and tetrabutylphosphonium fluoride [9] have been employed for fluorohydrin synthesis as alternatives to the very toxic hydrogen fluoride. However, some problems still remain for improvement such as the requirement of high temperature or a co-reagent, the difficulty of handling gaseous or toxic reagent for laboratory use, etc.

Potassium dihydrogen trifluoride (KH_2F_3) is used for the preparation of fluorine gas [10], but has few applications in the synthesis of organofluorine compounds such as electrochemical fluorination [11]. In this paper, we report the use of KH_2F_3 as an effective and easy-to-handle reagent for the regio- and stereo-selective ring-opening reaction of epoxides to give fluorohydrins.

*Corresponding author.

The reaction of styrene oxide (**1a**) with KH_2F_3 was initially attempted [Eq. (1)]. The ring-opening reaction proceeded regioselectively to afford 2-fluoro-2-phenylethanol (**2a**) exclusively. The reaction conditions were examined and the results are listed in Table 1. A good result was obtained when the reaction was carried out at 80 °C in 1,2-dichloroethane using 5 mmol of KH_2F_3 relative to 1 mmol of epoxide (entry 9). The reaction did not proceed when KHF_2 was used instead of KH_2F_3 under the same conditions, indicating that KH_2F_3 is more effective than KHF_2 in this reaction although the latter has been used for the ring-opening of epoxides (entry 10).



1 2 3

	R^1	R^2	R^3	(*trans* : *cis*)
a	Ph	H	H	
b	Ph	CH_3	H	
c	Ph	H	CH_3	(66 : 34)
d	Ph	H	CH_3	(21 : 79)
e	Ph	H	Ph	(100 : 0)
f	Ph	H	Ph	(0 : 100)
g	Ph	H	CO_2Et	(95 : 5)
h	$C_{10}H_{21}$	H	H	
i	H	$-(CH_2)_4-$		

(1)

SSDI 0022-1139(94)03175-4

Table 1
The ring-opening reaction of styrene oxide with KH_2F_3

Entry No.	Amount of KH_2F_3 [a] employed (mmol)	Solvent	Temp. (°C)	Time (h)	Yield [b] of **2a** (%)
1	1	Et_2O	room temp.	24	11
2	1	C_6H_6	room temp.	24	19
3	1	CH_3CN	room temp.	24	34
4	1	CH_2Cl_2	room temp.	24	51
5	1	CH_2ClCH_2Cl	room temp.	24	50
6	1	CH_2ClCH_2Cl	80	2	60
7	2	CH_2ClCH_2Cl	80	1	59
8	3	CH_2ClCH_2Cl	80	1	73
9	5	CH_2ClCH_2Cl	80	1	76 [c]
10	5 [d]	CH_2ClCH_2Cl	80	1	0

[a] Amount of KH_2F_3 relative to 1 mmol of styrene oxide.
[b] Yields determined by ^{19}F NMR analysis of the crude products ($C_6H_5CF_3$ was used as internal standard).
[c] Isolated yield was 68%.
[d] KHF_2 was used instead of KH_2F_3.

Fluorohydrin synthesis from several epoxides has been examined using these reaction conditions, and the results are listed in Table 2. The corresponding fluorohydrins were obtained regioselectively in fair to good yield from aromatic epoxides (entries 1–7). With aliphatic epoxides, however, the yield of fluorohydrin was very low because of side-reactions such as polymerization (entries 8 and 9).

It is noteworthy that the stereoselectivity of this reaction is quite different from other fluorohydrin syntheses via the ring-opening of epoxides. Ring-opening with amine-HF reagents has been reported to proceed in a *trans*-stereoselective manner, i.e. *trans*- and *cis*-epoxide predominantly afford *erythro*- and *threo*-fluorohydrin, respectively [4,6,7]. In the case of the reaction with SiF_4, both *trans*- and *cis*-1-methyl-2-phenyloxirane gave *threo*-fluorohydrin [8]. However, this reaction appears to be *cis*-stereoselective in the case of aromatic epoxides, i.e. *trans*- and *cis*-epoxide predominantly afford *threo*- and *erythro*-fluorohydrin, respectively (entries 3–7) [1]. Although the mechanism of this reaction is not as yet clear, one possible explanation for the regio- and stereo-selectivity may be the existence of competitive reactions via an ion pair-like intermediate (**4**) and carbonium ion (**5**) (Scheme 1). The formation of rearrangement products (entries 3–6) suggests that reaction occurs via a carbonium ion **5** stabilized with a phenyl group. However, if the reaction proceeded solely via **5**, the stereoselectivity would be independent of the isomerism of the starting epoxide since the reaction would proceed predominantly from **5T** which exhibits no steric repulsion between the phenyl and the R groups, and the *threo* product would be predominant as a result of attack of a fluoride anion species directed by the *hydroxy* group [8]. For this reason it is assumed that reaction via an ion pair-like intermediate **4** occurs competitively [2], with intermediate **4T** forming from the *trans*-epoxide with subsequent fluorination yielding the *threo*-fluorohydrin **2T**. In the case of the *cis*-epoxide, *erythro*-fluorohydrin **2E** is obtained predominantly via

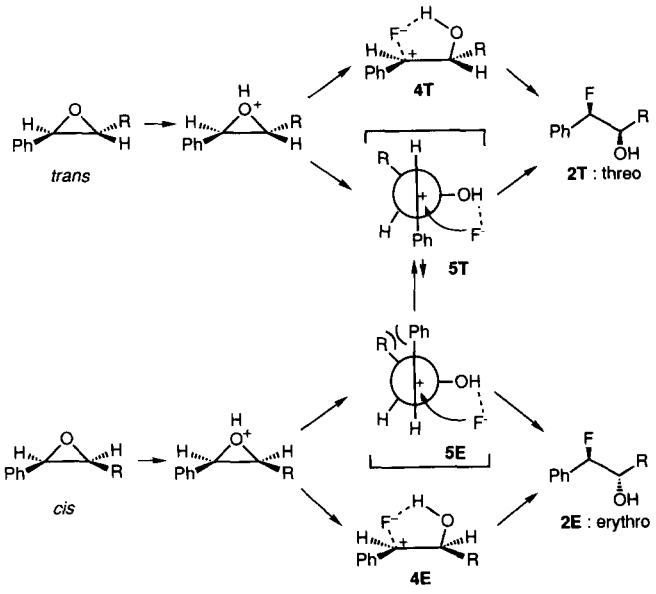
Table 2
Fluorohydrin synthesis using KH_2F_3 [a]

Entry No.	Epoxide	Time (h)	Yield [b] (%)	
			2 (*threo*/*erythro*) [c]	**3**
1	**1a**	1	68	0
2	**1b**	1	42	0
3	**1c**	12	70 [d] (80:20)	0
4	**1d**	12	61 [e] (56:44)	0
5	**1e**	3	59 [f] (100:0)	0
6	**1f**	7	52 [g] (35:65)	0
7	**1g**	70	70 (81:19)	0
8	**1h**	32	8 [h]	1.5 [h]
9	**1i**	2	6 [h] (100:0) [i]	–

[a] Epoxide (1 mmol) and KH_2F_3 (5 mmol) were stirred at 80 °C in 1,2-dichloroethane.
[b] Isolated yield.
[c] Isomer ratio of **2** (determined by ^{19}F NMR). The configuration of these isomers is illustrated in Scheme 1.
[d] 1-Phenyl-2-propanone (12%) was formed.
[e] 1-Phenyl-2-propanone (15%) was formed.
[f] 2,2-Diphenylethanal (30%) was formed.
[g] 2,2-Diphenylethanal (29%) was formed.
[h] Yield determined by ^{19}F NMR of the crude products ($C_6H_5CF_3$ was used as internal standard).
[i] Only *trans*-2-fluorocyclohexanol was formed.

[1] Calculated from the results of entries 3 and 4 (Table 2). Pure *trans*-1-methyl-2-phenyloxirane should predominantly afford *threo*-fluorohydrin (*threo*/*erythro* = 95:5, yield 77%) and pure *cis*-1-methyl-2-phenyloxirane should afford more *erythro*-fluorohydrin than the *threo* isomer (*threo*/*erythro* = 42:58, yield 57%).

[2] A similar intermediate has been suggested in other ring-opening reactions of epoxides [12].



Scheme 1. The F^- ion depicted in the reaction pathways should be considered merely as illustrative of the reacting species which may include $H_2F_3^-$.

the corresponding intermediate **4E**, although the stereoselectivity decreases because another reaction path via **5** gives the *threo*-fluorohydrin predominantly. In the case of aliphatic epoxides, cyclohexene oxide afforded only *trans*-2-fluorocyclohexanol (Table 2, entry 10), suggesting a different mechanism such as S_N2-type attack of fluoride anion although the detail is obscure because of very low yield.

A typical experimental procedure was as follows. To KH_2F_3 (5 mmol) in a Teflon® (PFA) vessel was added a solution of epoxide (1 mmol) in 1,2-dichloroethane (5 ml). The reaction mixture was stirred at 80 °C for the period indicated in Tables 1 and 2, and then quenched with aqueous sat. $NaHCO_3$. After usual work-up, the crude product was purified by silica gel column chromatography or bulb-to-bulb distillation. The products were identified by IR, ^1H NMR and ^{19}F NMR spectroscopy.

In conclusion, we have demonstrated that KH_2F_3 works as an efficient reagent for the ring-opening of epoxides to give fluorohydrins in a regio- and stereoselective manner. The reaction proceeds via predominantly *cis*-addition of HF to the epoxide.

References

[1] G. Resnati, *Tetrahedron, 42* (1993) 9385; J.T. Welch, *Tetrahedron, 43* (1987) 3123; J. Mann, *Chem. Soc. Rev., 16* (1987) 381; J.A. Wilkinson, *Chem. Rev., 92* (1992) 505.

[2] C.M. Sharts and W.A. Sheppard, *Org. React., 21* (1974) 125.

[3] P.A. Grieco, T. Sugahara, Y. Yokoyama and E. Williams, *J. Org. Chem., 44* (1979) 2189; J. Oshida, M. Morisaki and N. Ikekawa, *Tetrahedron Lett., 21* (1980) 1755; W.A. Szarek, G.W. Hay and M.M. Perlmutter, *J. Chem. Soc., Chem. Commun.,* (1982) 1253; E. Ohshima, H. Sai, S. Taketsuto, N. Ikekawa, Y. Kobayashi, Y. Tanaka and H.F. DeLuca, *Chem. Pharm. Bull., 32* (1984) 3525.

[4] A.I. Ayi, M. Remli and R. Guedj, *Tetrahedron Lett., 22* (1981) 1505; A.I. Ayi, M. Remli, R. Condom and R. Guedj, *J. Fluorine Chem., 17* (1981) 565.

[5] J. Ichihara and T. Hanafusa, *J. Chem. Soc., Chem. Commun.,* (1989) 1848.

[6] D. Landini and M. Penso, *Tetrahedron Lett., 31* (1990) 7209.

[7] R. Gardiax and J. Jullien, *Bull. Soc. Chim. Fr.,* (1969) 2721; G. Aranda, J. Jullien and J.A. Martin, *Bull. Soc. Chim. Fr.,* (1965) 1890; M. Muehlbacher and C.D. Poulter, *J. Org. Chem., 53* (1989) 1026; H. Suga, T. Hamatani and M. Schlosser, *Tetrahedron, 46* (1990) 4247; J. Umezawa, O. Takahashi, K. Furuhashi and H. Nohira, *Tetrahedron: Asymm., 4* (1993) 2053.

[8] M. Shimizu and H. Yoshida, *Tetrahedron Lett., 29* (1988) 4101.

[9] H. Seto, Z. Qian, H. Yshioka, Y. Uchibori and M. Umeno, *Chem. Lett.,* (1991) 1185.

[10] A.J. Rudge, *Chem. Ind. (London),* (1949) 247.

[11] A. Tasaka, R. Aki, K. Kawabe, H. Itoh and H. Sakaguchi, *Nippon Kagaku Kaishi,* (1984) 540; [*Chem. Abs., 101* (1984) 80 596r].

[12] G. Berti, F. Bottari, P.L. Ferrarini and B. Macchia, *J. Org. Chem., 30* (1965) 4091; P. Duhamel, B. Leblond and J.-M. Poirier, *J. Chem. Soc., Chem. Commun.,* (1993) 476.