The Combination of Hydrogen Fluoride Salt and Aluminium Fluoride: an Efficient Solid Reagent for Epoxide Opening to give Fluorohydrins

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The combination of hydrogen fluoride salt and porous aluminium fluoride (MHF_2–AlF_3) (M = alkali metal) is a stable and efficient solid reagent for promoting the ring-opening reaction of simple aliphatic oxiranes to give the fluorohydrins under sonication, as a substitute for anhydrous hydrogen fluoride.

The introduction of fluorine into organic molecules has become increasingly more important in a wide variety of fields owing to the specific physical and biological properties of fluorinated compounds.[1] Among them the ring opening of epoxides with hydrogen fluoride has been employed often in the chemistry of steroids, carbohydrates, and prostaglandins.[2,3] However, the use of anhydrous hydrogen fluoride requires extreme caution because of its toxicity and reactivity. Potassium hydrogen fluoride,[3] pyridine polyhydrofluoride,[4] triethylamine trishydrofluoride,[5] di-isopropylamine trishydrofluoride,[6] and silicon tetrafluoride,[7] *etc.*, have been used successfully as alternatives. However, simple aliphatic epoxides, especially terminal ones, are liable to polymerization or rearrangement under these reaction conditions.[8]

Based on the results obtained in an investigation of the acceleration of the solid–liquid two-phase reaction between inorganic reagents and organic compounds by means of a solid support and/or ultrasound,[9—11] we planned to improve the heterogeneous reaction of epoxides using hydrogen fluoride salts which are easy to handle but less reactive. In this paper, we report that a combination of alkali metal hydrogen fluoride and aluminium fluoride (MHF_2–AlF_3) is a stable and efficient solid reagent for the conversion of simple aliphatic oxiranes into fluorohydrins.

The typical solid–liquid two-phase reaction was carried out as follows. To KHF_2 (5 mmol) and porous AlF_3† (15 mmol) in dimethoxyethane (DME, 4 cm^3), in a Pyrex test tube with a Teflon-coated screw cap, was added cyclohexene oxide (2 mmol). This heterogeneous reaction mixture was subjected to ultrasonic treatment at 55 °C. The ring-opening reaction,

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† Commercially available potassium hydrogen fluoride and porous aluminium fluoride were dried under vacuum at 100 °C prior to use. We thank Mr. Toshio Tatsuno of Morita Kagaku Kogyo Co., Ltd. for his contribution of the porous aluminium fluoride.

Table 1. The heterogeneous reaction of cyclohexene oxide with hydrogen fluoride salts.[a]

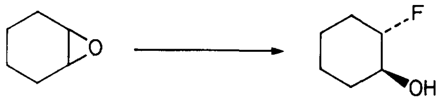
Run	Reagent	Solvent	Ultrasound[b]	Temp./°C	GLC yield (**1**)/% (time/h)	
1	KHF_2	Tetraglyme	–	110		1(20)
2	KHF_2	DME	–	55		0(20)
3	KHF_2	DME	+	55		0(20)
4	KHF_2–AlF_3	DME	–	55	17(2)	50(20)
5	KHF_2–AlF_3	DME	+	55	60(2)	
6	$NaHF_2$	DME	+	55		2(20)
7	$NaHF_2$–AlF_3	DME	+	55	63(0.5)	
8	NH_4HF_2	DME	+	55		0(20)
9	NH_4HF_2–AlF_3	DME	+	55	51(4)	

[a] The reaction of cyclohexene oxide (2 mmol) with the HF_2 salt (5 mmol) and AlF_3 (15 mmol) was carried out in the solvent indicated (4 cm^3). [b] A thermostated ultrasonic cleaner (Branson, 100 W, 45 kHz) was used.

Table 2. The sonochemical synthesis of fluorohydrins using the MHF_2–AlF_3 reagent.[a]

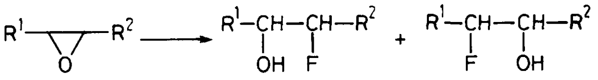
Entry	R^1	R^2	MHF_2	Solvent	Time/h	Isolated yield/% (**2**)	Isolated yield/% (**3**)
1	$(CH_2)_4$		$NaHF_2$	DME	1	43	—
2	$(CH_2)_4$		KHF_2	DME	2	49	—
3	C_6H_{13}	H	$NaHF_2$	DME	4	10	44
4	CH_2=$CH(CH_2)_4$	H	$NaHF_2$	DME	4	7	45
5	$PhOCH_2$	H	KHF_2	DME	2	29	16
6	$(Me)_2CHOCH_2$	H	KHF_2	THF[b]	2	33	5
7	Ph	H	KHF_2	MeCN	1	0	44
8	$ClCH_2$	H	KHF_2	THF[b]	8	31	5

[a] A heterogeneous mixture of an epoxide (4 mmol) with the MHF_2–AlF_3 reagent (1 : 3 molar ratio, 10 mmol of MHF_2) in solvent (8 cm^3) was subjected to ultrasonic treatment at 55 °C. [b] THF = tetrahydrofuran.



(**1**)

Reagents and conditions: KHF_2–AlF_3, ultrasound in DME at 55 °C.

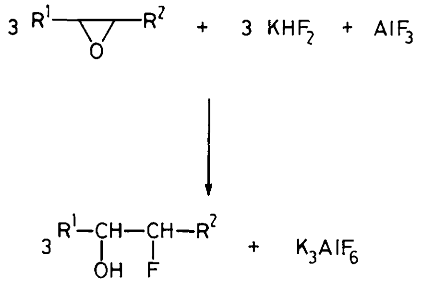


(**2**) (**3**)

Reagents and conditions: MHF_2–AlF_3, ultrasound, 55 °C.

followed by GLC, proceeded smoothly to afford a 60% yield of the corresponding fluorohydrin with complete disappearance of the substrate in 2 h. The solid materials were filtered off and washed with methylene chloride, then the solvent was evaporated. Purification of the crude oil by column chromatography (silica gel, pentane : ether = 5 : 1) gave *trans*-2-fluorocyclohexanol (**1**) in 49% yield.

When KHF_2 was used without AlF_3, at 55 °C with magnetic stirring, this reaction did not take place (Table 1, run 2). In this case, neither higher temperatures nor sonication promoted the formation of the desired product (runs 1 and 3). In contrast, when KHF_2 was used with AlF_3, the heterogeneous reaction gave the fluorohydrin (run 4), and was further accelerated by ultrasonic irradiation (run 5). Thus, the combined use of the KHF_2–AlF_3 reagent and ultrasound was most efficient to open an oxirane ring giving the desired fluorohydrin. Both the $NaHF_2$–AlF_3 and the NH_4HF_2–AlF_3 reagents also showed high reactivity under sonication (runs 7 and 9), while the sole use of $NaHF_2$ or NH_4HF_2 was not effective for the reaction (runs 6 and 8).



(1)

As shown in Table 2, these solid reagents, with ultrasound, were used successfully in the preparation of several other fluorohydrins. Under mild conditions all of the reactions went to completion within several hours to afford the fluorohydrins in reasonable yields.‡ Our solid reagents were not corrosive, and were stable enough to use with ordinary laboratory equipment.

Although the mechanism of the solid–liquid two-phase reaction studied here could not be elucidated in detail, we believe that the solid-phase inorganic reaction between the HF_2 salt and AlF_3 proceeds gradually to generate 'HF' *in situ* with strong complexation of the fluoride anion with the aluminium cation,[10] and that the resulting 'HF' on the surface

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‡ The regioselectivity for the products shown in Table 2 is not much different from that observed with hydrogen fluoride or its equivalent,[6,12] although such selectivity was not clarified.

of AlF_3 solid attacks the epoxide immediately to give the fluorohydrin. Porous aluminium fluoride having a high surface area (*ca.* 45 $m^2 g^{-1}$) acts not only as a reagent but also as a support for activating the HF_2 salt and for enhancing the subsequent epoxide-opening.§ Ultrasound accelerates both the solid-phase inorganic reaction and the following organic reaction, which results in a reduction of the reaction time and an increase in the product yield. Powder *X*-ray diffraction analysis of the inorganic materials recovered after the reaction of cyclohexene oxide with the KHF_2–AlF_3 reagent showed the formation of potassium hexafluoroaluminate (K_3AlF_6), which suggests the above postulate. Thus, the epoxide-opening reaction at the solid–liquid interface is stoicheiometrically represented by equation (1).

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§ Porous aluminium fluoride having a high surface area is synthesized *via* dehydration of $AlF_3{\cdot}3H_2O$ prepared from aluminium hydroxide and an aqueous HF solution, whereas that with a low surface area (<5 $m^2 g^{-1}$) is synthesized usually under nonaqueous conditions. The latter was not effective in the present reaction.

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