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TETRABUTYLAMMONIUM DIHYDROGENTRIFLUORIDE: AN EFFICIENT CATALYST FOR REGIO AND STEREOSELECTIVE CONVERSION OF EPOXIDES TO FLUOROHYDRINS UNDER SOLID-LIQUID PHASE-TRANSFER CATALYSIS CONDITIONS.

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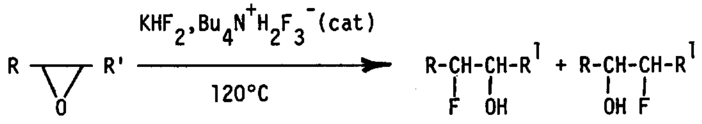
Abstract. Tetrabutylammonium dihydrogentrifluoride is an efficient and easy-to-handle hydrofluorinating agent in the ring-opening reaction of oxiranes to give good or excellent yields of fluorohydrins under solid-liquid PTC conditions.

In recent years much interest has been shown in the ring-opening reaction of epoxides to give fluorohydrins as a method for the introduction of a fluorine atom into organic molecules.[1,2] Potassium hydrogendifluoride,[3] pyridine polyhydrofluoride,[4] triethylamine[5] and diisopropylamine[6] trishydrofluoride, silicon tetrafluoride[1] and a hydrogendifluoride salt-aluminium trifluoride[2] were successfully employed for the epoxide to fluorohydrin conversion, avoiding the use of the dangerous anhydrous hydrogen fluoride.[2]

It was recently shown[7,8] that the $H_2F_3^-$ anion as the lipophilic quaternary ammonium salt, $Q^+H_2F_3^-$,[9] combines good nucleophilicity with a good tendency to provide an electrophilic H^+. Therefore quaternary ammonium dihydrogentrifluorides appeared to us as particularly suitable reagents for promoting the hydrofluorination of epoxides.

We report that this reaction can be successfully realized by using potassium hydrogendifluoride in the presence of catalytic amounts of tetrabutylammonium dihydrogentrifluoride under solid-liquid phase-transfer catalysis (SL-PTC) conditions.

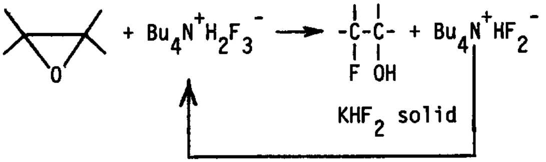
In a typical procedure the epoxide (**1**) (1 mol) and the catalyst (0.1 mol) were heated at 120°C under magnetic stirring over solid KHF_2 (2 mol) in a pyrex flask until complete disappearance of the substrate (**1**). The reaction mixture was diluted with CH_2Cl_2, filtered, and the solvent evaporated. The crude was purified by flash chromatography (silica gel) to give fluorohydrins (**2**) and (**3**) in 47-90% overall yields[10] (Table 1). As shown in the case of substrates (**1a-e**) (Table 1) the reaction occurred with high regioselectivity affording the fluorohydrins (**3**) as the sole, or largely prevalent, regioisomers (**3**).[11]



(1) (2) (3)

The reaction was trans-stereoselective. Thus cyclohexene oxide **(1f)** gave exclusively trans-2-fluorocyclohexanol, cis- and trans-stilbene oxide **(1g)** and **(1h)** afforded threo- and erythro-1-2-diphenyl-2-fluoroethanol **(2g)** and **(2h)**, respectively. In the case of **(1g)** and **(1h)**, the catalytic process was very slow, due to the increased steric hindrance, therefore a stoichiometric amount of $Bu_4N^+H_2F_3^-$ without KHF_2 was used. Under the latter reaction conditions 3β-hydroxy-5α,6α-epoxycholestane **(1i)** yielded 3β,5α-dihydroxy-6β-fluorocholestane **(2i)**. Functional groups such as phenoxy and allyloxy ones were not affected.

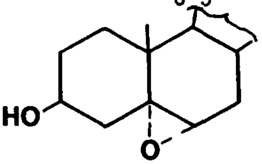
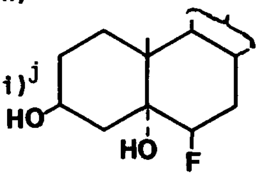
The observed regio- and stereochemistry clearly indicate that the reaction proceeds through an S_N2 type mechanism, where the nucleophilic attack by the fluoride anion[12] at the less substituted carbon atom of the oxirane ring electrophilically assisted by an H^+, is largely prevalent. The $Bu_4N^+H_2F_3^-$ provides the hydrogen fluoride required by the stoichiometry of the reaction (equation 1), and the solid KHF_2 regenerates the quaternary onium dihydrogentrifluoride through a well



(1)

known[8,13] solid-liquid phase-transfer process, realizing the catalytic cycle. In line with this the same results were obtained by using $Bu_4N^+HF_2^-/KHF_2$ instead of $Bu_4N^+H_2F_3^-/KHF_2$ as the hydrofluorinating agent, while no reaction occurred when either stoichiometric amounts of $Bu_4N^+HF_2^-$ alone[14], or KHF_2 without the phase-transfer agent, were employed.

Table 1. Conversion of epoxides **(1)** into fluorohydrins **(2)** and **(3)** catalyzed by $Bu_4N^+H_2F_3^-$ under SL-PTC conditions, at 120°C.[a]

Substrate **(1)** R	R^1	Time h	Isolated yield %	Products[b] % **(2)**	**(3)**
C_6H_5	H **(a)**	8	74	**(a)** 39	**(a)** 61
$C_{10}H_{21}$	H **(b)**	48	84	**(b)** 26	**(b)** 74
$HOCH_2$	H **(c)**	30[c]	47	**(c)** -	**(c)** 100
$C_6H_5OCH_2$	H **(d)**	8	90	**(d)** -	**(d)** 100
$CH_2{=}CH{-}CH_2OCH_2$	H **(e)**	6	70	**(e)** 9	**(e)** 91
$(CH_2)_4$	**(f)**	7	71[d]	**(f)**	
<u>cis</u> C_6H_5	C_6H_5 **(g)**[e]	72	71[f]	**(g)**	
<u>trans</u> C_6H_5	C_6H_5 **(h)**[e,g]	120	72[h]	**(h)**	
	**(i)**[e,i]	78	47	**(i)**[j] 	

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[a] Epoxide **(1)** (1 mol), $Bu_4N^+H_2F_3^-$ (0.1 mol), KHF_2 (2 mol), 120°C. [b] Spectroscopic and analytical data of the products **(2)** and **(3)** were in agreement with the structures proposed. [c] At 80°C. [d] <u>trans</u>-2-Fluorocyclohexanol **(2f)** as sole product. [e] Epoxide **(1)** (1 mol), $Bu_4N^+H_2F_3^-$ (1 mol), 120°C. [f] <u>threo</u>-1,2-Diphenyl-2-fluoroethanol **(2g)** as sole product. [g] The reaction carried out under catalytic conditions furnished 10% of product **(2g)** after 48 h. [h] <u>erythro</u>-1,2-Diphenyl-2-fluoroethanol as sole product. [i] 3<u>β</u>-Hydroxy-5<u>α</u>,6<u>α</u>-epoxycholestane, **(1h)**. [j] 3<u>β</u>,5<u>α</u>-Dihydroxy-6<u>β</u>-fluorocholestane, **(2i)**.

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9) These onium salts are easy to prepare and to handle.[7,8]

10) The catalyst can be recovered in $\geqslant$90% yield at the end of the column chromatography using MeOH as eluant.

11) The fluorohydrins **(3)** derive from the addition of a fluoride ion to the less hindered carbon of the oxirane ring. This behaviour is similar to that previously reported by Poulter et al.[6] for the reaction of epoxides with diisopropilamine trishydrofluoride, and contrary to that found using pyridine polyhydrofluoride.[4]

12) At the present it is difficult to establish the real nature of the nucleophilic attacking species.

13) See inter alia, E.V. Dehmlow, S.S. Dehmlow, "Phase-Transfer Catalysis", 2nd ed., Verlag Chemie, Weinheim, West Germany, 1983; F. Montanari, D. Landini, and F. Rolla, Top. Curr. Chem., 1982, **101**, 147; M. Makosza, M. Fedorynski, Adv. Cat., 1988, **35**, 375.

14) It is well known[7,8] that $Bu_4N^+HF_2^-$ is not a hydrofluorinating agent, because of the very high stability of the HF_2^- anion.

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