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$Et_3N.2HF$, A NEW CONVENIENT REAGENT FOR NUCLEOPHILIC FLUORINE DISPLACEMENT REACTIONS

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Summary : Syntheses of fluoro compounds by nucleophilic substitution of bromides or methanesulfonates using $Et_3N.2HF$ as the reagent are reported. The formation of undesired elimination side products is limited. The synthesis of this new fluorinating reagent is also reported.

Many methods have been developed for introducing fluorine into an organic compound[1] and numerous of them consist of reaction of ionic fluoride by nucleophilic substitution. When the nucleophilicity of the fluoride ion is increased, the basicity is also increased and therefore involves the formation of elimination products.[2]

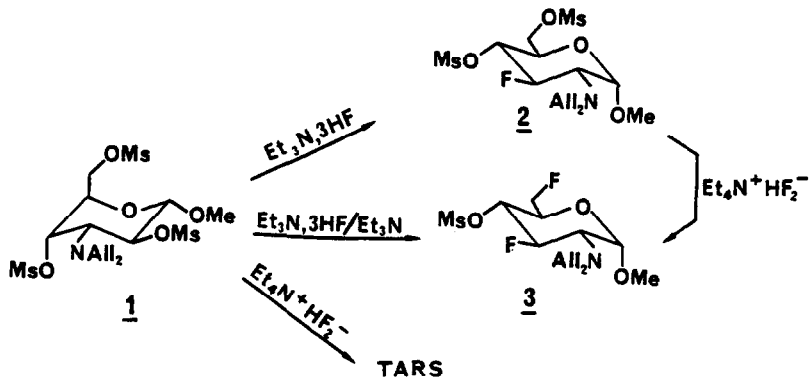
$$R^1R^2CH\text{-}CHXR^3 \xrightarrow{"F^-"} R^1R^2C{=}CHR^3 + R^1R^2CH\text{-}CHFR^3$$

Recently, Cousseau *et al*[3] have reported that polymer supported dihydrogen trifluoride $P^+H_2F_3^-$ (P^+=cationic part of a macroreticular basic anion-exchange resin Amberlyst A 26 or Amberlite IRA 900) provided good yields of fluoro substitution without exhibiting any important basic character.[4] We describe here a new fluorinating reagent, $Et_3N.2HF$ (prepared *in situ* from $Et_3N.3HF$[5] and Et_3N), which is not very basic.

In our laboratory, we are developing a program to synthesize α,β aminofluorosugars by nitrogen atom participation[6] and a moderated neutral nucleophilic fluorinating reagent was needed because many carbohydrates are very sensitive to basic or acidic conditions. For example we wanted to obtain a 3,6-difluoroglucosamine derivative 3 in one step starting from 1 (scheme). When $Et_3N.3HF$ was used, compound 2 was isolated in good yield, but the fluorinating reagent was not nucleophilic enough to give 3 ; other reagents such as $R_4N^+HF_2^-$ were too basic and led to tars due to the axial 4-OMs (elimination of MsOH gave a very unstable enamine). 3 was synthesized by treatment of 2 with $Et_4N^+HF_2^-$ (the 4-OMs is equatorial and the elimination is unfavoured), but we found that on addition of Et_3N to the $Et_3N.3HF$ complex it was possible to obtain 3 in one step starting from 1 in good yield.[7] In the literature various proportions of amines and HF have been previously described[8], but the previous studies did not attribute any difference of selectivity to the stoichiometry of the system, so we tried to understand why Et_3N addition to the $Et_3N.3HF$ complex enhanced its nucleophilicity. We supposed that a new complex was formed and two possibilities were considered :

$$Et_3N.3HF + 2\ Et_3N \longrightarrow 3\ [Et_3N.HF] \quad (A)$$

$$2\ [Et_3N.3HF] + Et_3N \longrightarrow 3\ [Et_3N.2HF] \quad (B)$$



Scheme

When Et_3N was added to the $Et_3N.3HF$ complex without solvent, russian authors[8a] had observed the formation of a liquid of structure $Et_3N.2HF,0.1H_2O$ and Aranda[8b] the formation of a very unstable "diacidic" solid which rapidly turned black and was not further studied. For our part we have noted that the reaction was exothermic and a very hygroscopic white solid was formed. A titration of both $Et_3N.3HF$ and the white solid was carried out according to Fluka's procedure (0.5 N NaOH and phenolphtalein as indicator). We found two "free HF" for $Et_3N.3HF$ (like Fluka : approx. 24 % free HF) and one for the solid complex in accord with equation (B). We also mixed $Et_3N.3HF$ with a three molar ratio of Et_3N and the mixture was submitted to evaporation under vacuum (15 Torr) at room temperature in presence of P_2O_5 until the weight was constant. Stoichiometrically this weight was also in accord with equation (B). When the solid $Et_3N.2HF$ was heated in a drying pistol (15 Torr, 65°C), it lost Et_3N and gave back $Et_3N.3HF$; hence we considered that, depending on the temperature, pressure, solvent, etc..., an equilibrium between the two complexes was possible as follows :

$$Et_3N.3HF + Et_3N \rightleftharpoons Et_3N.2HF$$

An NMR study (solvent : CD_3CN) has shown that a small amount of Et_3N is sufficient to shift the signal of ^{19}F and it is only after three equivalents that δ ^{19}F becomes constant (and not for 0.5 equivalent). These two observations support the assumption of an equilibrium. In order to explain these peculiarities, we studied the fluorination of $C_6H_5(CH_2)_3OMs$ as a model with different reagents : $Et_4N^+HF_2^-$ [prepared from $Et_4N^+F^-,2H_2O$ heated at 77° (2 Torr) for 24 h[9]] ; $Et_3N.3HF$ (Fluka) ; $Et_3N.3HF + Et_3N$; $Et_3N.HF$ (Aldrich). Kinetic results showed that $Et_4N^+HF_2^-$ to be better than $Et_3N.3HF/Et_3N$ better than $Et_3N.3HF$ very much better than $Et_3N.HF$ (Table 1). $Et_4N^+HF_2^-$ is regarded as a very good fluorinating reagent, but these results proved $Et_3N.3HF/Et_3N$ is more nucleophilic than $Et_3N.3HF$ [using $Et_3N.HF$ we did not obtain $C_6H_5(CH_2)_3F$ (<5 % by glc) and starting material was recovered].

Table 1

Yield of $\phi(CH_2)_3F$ obtained by treatment of $\phi(CH_2)_3OMs$ by 10 equivalents of the fluorinating reagent (CH_3CN, 80 °C) calculated by glc with ϕtBu as standard (Carbowax 20 M, l = 1.4 m, t° = 80 °C, P = 1.2 bar)

time (h)	$Et_3N.3HF$	$Et_3N.3HF/Et_3N$	$Et_4N^+HF_2^-$	$Et_3N.HF$
0.25			100	
0.5			100	
1.25		5		
2.5		27		
6.5	5.5	52		
11	12			
20	20	81		
38	44			<5
54	74			
79	90	98		
103	100	98		<5
151	100			<5

These first studies led us to test the reactivity of this new complex and to compare its nucleophilic power with that of Cousseau's reagent.[3] Table 2 shows that for the two bromoketones PhCOCBrRMe (R = H, Me), our results were close of Cousseau's and the reaction time was significantly reduced ; for the secondary nonactivated -CHX- groups, it is worth knowing that the reaction times were lower and the selectivity was better for X = OMs than for X = Br.

In conclusion, we think that $Et_3N.2HF$ (easily available from two commercial compounds) is a better fluorinating reagent than $Et_3N.3HF$ and is a useful alternative to $P^+H_2F_3^-$ (harder to prepare) for nucleophilic substitutions.

General procedure : To 0.01 mol of starting material dissolved in CH_3CN (5 mL) was added $Et_3N.3HF$ (2.1 equ.) and Et_3N (1 equ.). The mixture was heated at 80 °C under stirring and monitored by T.L.C. (for the reaction times, see table 2). After cooling to room temperature, the mixture was poured into a saturated aqueous sodium hydrogen carbonate solution (100 mL) and ether (100 mL). The organic layer was washed twice with water (50 mL), dried (Na_2SO_4) and evaporated ; then the crude reaction mixture was analyzed by NMR. The obtained products were purified by column chromatography on silica gel (light petroleum-ether) for identification and were in accordance with data from literature.[3,10]

Table 2

Starting compound	Time (h)	% Reaction products (lit.[3])	
		Fluoro	Ethylenic
PhCOCHBrMe	1.5	91[a] (93)	0
$PhCOCBrMe_2$	20	50[b] (54)	50[b] (33)
2-OMs-Octane	36	90[b] (49)	7[b,c] (18)
3β-OMs-5α-Cholestane[d]	95[e]	50[b] (70)	33[b,f] (30)
2-OMs-4-Phenylbutane	70	79[a,g]	13[a,g,h]
2-Bromooctane	122	48[b] (30)	14[b,c] (10)
2-Bromo-4-phenylbutane	142[e]	40[a,g]	28[a,g,h]

a : isolated yields ; b : yields determined by ^1H NMR ; c : only 2-octene ; d : the solvent is diglyme and the temperature is 120 °C (with CH_3CN at 80 °C, reaction was not complete after 14 days) ; e : 5 % starting material recovered ; f : Δ-2 and Δ-3 cholestene ; g : see ref. 10 ; h : mixture of three ethylenic compounds.

References and notes

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5. $Et_3N.3HF$ is not nucleophilic enough for introducing fluorine. Using $PhCOCBrMe_2$ as starting material, after 4 days only 60 % was converted (*cf* table 2).

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NMR $C_6H_5CH_aH_bCH_cH_dCHFCH_3$: ^1H (300 MHz, $CDCl_3$, J in Hz) δ 7.25 (m, 5H, Ar) 4.65 (dddq, 1H, CHF, J_{HF}=48.8, J_{HCH3}=6.3, J_{HHc}=4.1, J_{HHd}=8) 2.80 (ddd, 1H, Ha, J_{HaHc}=9.8, J_{HaHd}=5.5, J_{HaHb}=13.9) 2.68 (ddd, 1H, Hb, J_{HbHc}=9.4, J_{HbHd}=7) 2.07-1.70 (m, 2H, Hc, Hd) 1.34 (dd, 3H, CH_3, J_{HF}=23.9) ; ^{13}C 90.0 (CHF, J_{CF}=165) 38.6 (CH_cH_d, J_{CF}=20.9) 31.3 (CH_aH_b, J_{CF}=4.8) 21.0 (CH_3, J_{CF}=22.9) ; ^{19}F ($CFCl_3$) 96.5 (dddq, $^2J_{HF}$=48, $^3J_{HF}$=30.3 and 15.6, $^3J_{FCH3}$=24).

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