F-Propene-Dialkylamine Reaction Products as Fluorinating Agents

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The reaction products of *F*-propene and dialkylamines, mixtures of α,α-difluoroalkylamine and α-fluoro enamine, were found to be useful fluorinating agents for alcohols and carboxylic acids. These reagents were superior to the adduct of chlorotrifluoroethene and diethylamine, the so-called Yarovenko reagent, for their readier preparation and higher stability.

2-Chloro-1,1,2-trifluorotriethylamine (**1**), the adduct of chlorotrifluoroethene and diethylamine, has been known as a useful fluorinating agent for alcohols.[1] This agent, which is sometimes called as "Yarovenko reagent,"[2] can replace a hydroxyl group with a fluorine atom under mild conditions and has been used especially for the syntheses of fluoro steroids.[1]

$$Et_2NH + CF_2{=}CFCl \longrightarrow \underset{\mathbf{1}}{Et_2NCF_2CHFCl}$$

$$ROH + \mathbf{1} \longrightarrow R\text{-}F + Et_2NC(=O)CHFCl + HF$$

However, the addition reaction of chlorotrifluoroethene with diethylamine to give (**1**) is not so easy and it requires rather long time in a sealed vessel in order to get a good yield. Further, the adduct (**1**) is not so stable at room temperature and it can not be stored more than a few days.

For the past several years, we have been studying on the nucleophilic reactions of *F*-propene and its oligomers, and it has been known that *F*-propene reacts with dialkylamines much more easily than with chlorotrifluoroethene. We now wish to report on the utility of the reaction products of the *F*-propene and dialkylamines as fluorinating agents of alcohols and carboxylic acids.

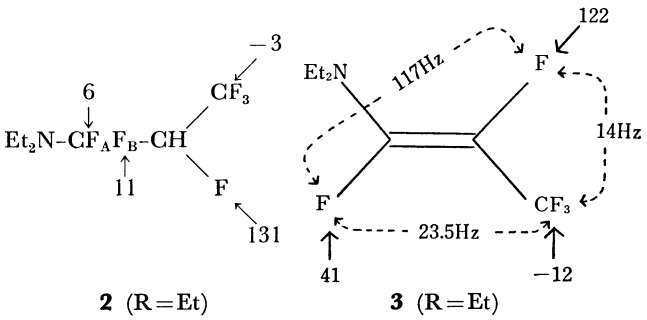
Results and Discussion

Reaction between F-*Propene and Dialkylamines.* Many years ago the nucleophilic reaction of *F*-propene with diethylamine giving addition and substitution products was reported by Knunyants *et al.*, though not in detail.[3] We carried out the reaction of *F*-propene with a number of secondary amines in diethyl ether, and determined the ratios of fluoroalkylamine (**2**) to fluoro enamine (**3**) from the signal intensities of ^{19}F NMR spectra.

$$R_2NH + CF_2{=}CFCF_3 \longrightarrow \underset{\mathbf{2}}{R_2NCF_2CHFCF_3} + \underset{\mathbf{3}}{\begin{matrix} R_2N & & F \\ & \diagdown\!\!=\!\!\diagup & \\ F & & CF_3 \end{matrix}}$$

The assignment of the NMR signals for **2** and **3** (R=Et) was done as shown in Fig. 1. Regarding the geometric isomers of **3**, only *E*-isomer was found in the product. Thus the F-F coupling constant was determined as 117 Hz (R=Et), which agrees to the expected value for *trans* F-F coupling constant, 109—131 Hz, and is quite different form that for *cis* F-F, 19—58 Hz.[4]

The formation of *E*-form rather than *Z*-form can



2 (R=Et) **3** (R=Et)

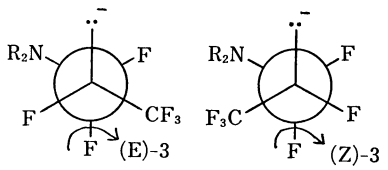
Fig. 1. The ^{19}F NMR spectra for **2** and **3** (R=Et). (Chemical shifts are given in δ ppm up field from external CF_3CO_2H).

be explained by considering the conformation of the intermediate carbanion (**4**). The *E*-isomer should be formed by the *trans*-elimination of fluoride ion from **4a**, whereas the *Z*-isomer should be from **4b**. However, **4b** must be less stable than **4a** due to the electronic replusion between lone pair electrons of the nitrogen atom and those of the fluorine atom of CF_3. Thus the formation of (*E*)-**3** through **4a** would predominate over the formation of (*Z*)-**3** through **4b**. We have already observed similar phenomenon in the case of nucleophilic aryloxylation of *F*-propene.[5]

$$R_2NH + CF_2{=}CFX \longrightarrow \underset{\mathbf{4}}{R_2N\text{-}CF_2\text{-}\overline{C}FX}$$

$$\xrightarrow{+H^+} R_2N\text{-}CF_2\text{-}CHFX \quad (\mathbf{1}\ X=Cl_3;\ \mathbf{2}\ X=CF_3)$$

$$\xrightarrow{-F^-} R_2N\text{-}CF{=}CFX \quad (\mathbf{3}\ X=CF_3)$$



4a **4b**

As was shown in Table 1, the ratio **2** to **3** in the reaction products increased in the order of the bulkiness of the used amines, *i.e.*, piperazine<diethylamine< dibutylamine. Thus the bulkier the nucleophile is, the more enamine (**3**), which is more released from the steric hindrance than alkylamine (**2**), is formed.

Nucleophilic Reactivities and Reaction Products. Several methods for the preparation of **1**, the "Yarovenko reagent," were reported in the literature. A typical procedure is to have diethylamine and chlorotrifluoroethene react in a sealed vessel at room temperature for 48 h using dichloromethane as solvent[6]

Table 1. C_3F_6/R_2NH reaction products

R_2N	Product		
	Bp/°C (mmHg)	**2** : **3**[a]	Yield/%[b]
Et_2N	56—57(58)	3 : 1	72
n-Bu_2N	55—57(5)	2 : 1	78
Piperidino	49—50(7)	(2 only)	80

a) Determined by ^{19}F NMR. b) Isolated yield.

or without solvent.[7] Another procedure is to bubble chlorotrifluoroethene gas through diethylamine at atmospheric pressure.[2] However, we observed almost no reaction occurred by the latter procedure. In contrast, we found that *F*-propene reacted much more easily with diethylamine, and the perfluoroolefin was exothermally absorbed at room temperature by a solution of diethylamine in diethyl ether. As a result the reaction mixture itself could be used as a fluorinating agent without further purification by distillation.

The reaction product of *F*-propene and diethylamine was, as mentioned above, a mixture of fluoroalkylamine **2** and fluoro enamine **3** (R=Et), whereas that of chlorotrifluoroethene was almost pure fluoroalkylamine **1**. These facts can be explained by the difference between electronic effects of a Cl and a CF_3 group. Chlorine as a substituent group is known to manifest an electron-donative R-effect (or electron-repelling I_π effect by lone pairs) as well as an electron-withdrawing I_σ effect. On the other hand, a trifluoromethyl group behaves solely as an electron-withdrawing group by its strong negative I_σ effect. Therefore, the intermediate carbanion **4** (X=CF_3) formed by the reaction of *F*-propene and dialkylamine should be rather stable than that of chlorotrifluoroethene and dialkylamine,

Table 2. Fluorination of primary-alcohols

$$R\text{-}OH \xrightarrow[Et_2O,\ 20\,h,\ r.t.]{C_3F_6/R'_2NH} R\text{-}F$$

R	Yields[a] of RF with R'_2N			Ref. for R-F
	Et_2N	*n*-Bu_2N	Piperidino	
$EtOCH_2CH_2$	60	76	78	c)
n-C_8H_{17}	87	90	76	d)
o-$C_{16}H_{33}$	78	72	91	e)
$HOC_{10}H_{20}$	82[b]	72[b]	81[b]	f)
$PhCH_2CH_2$	89	82	80	g)

a) Yields were determined by ^{19}F NMR unless otherwise noted. b) The product was $FC_{10}H_{20}F$, of which the yield was determined by GLC. c) E. G. Trochimouski, A. Sorzynski, and J. Wnuk, *Recl. Trav. Chim. Pays-Bas*, **66**, 413 (1947). d) Y. Kobayashi and C. Akashi, *Chem. Pharm. Bull. (Tokyo)*, **16**, 1009 (1968). e) E. D. Bergmann and A. M. Cohen, *Isr. J. Chem.*, **8**, 925 (1970). f) R. G. Woolford, F. L. M. Pattison, J. B. Stothers, and A. I. Vogel, *J. Am. Chem. Soc.*, **78**, 2255 (1956). g) J. Hayamizu, N. Mizuno, and A. Kaji, *Nippon Kagaku Zasshi*, **92**, 87 (1971).

4 (X=Cl). These effects should result in the higher reactivity of *F*-propene compared with that of chlorotrifluoroethene. Further, the negative charge of the carbanion **4** (X=Cl) is less delocalized than that of **4** (X=CF_3), and hence the former should be more strongly protophilic. Consequently, chlorotrifluoroethene gave predominantly the alkylamine **1**, while the *F*-propene gave a mixture of the alkylamine **2** and the enamine **3**.

The chlorotrifluoroethene–diethylamine adduct, **1**, is a rather unstable liquid, and it colored gradually

Table 3. Fluorination of secondary and tertiary-alcohols

$$R\text{-}OH \xrightarrow{C_3F_6/Et_2NH} R\text{-}F + \text{alkene} + R_2O$$

R	Reaction conditions			Product yields[a]/%			Ref. for R-F
	Solv.	Temp/°C	Time/h	R-F	Alkene	R_2O	
$C_6H_{13}CH(Me)$	Et_2O	r.t.	20	62 (57)	Octene,[b] 25 (25)	—	e)
$C_6H_{13}CH(Me)$	MeCN	r.t.	20	18	Octene,[b] 52	—	
Cyclohexyl	Et_2O	r.t.	10	—	Cyclohexene, 78	—	
2-Me·cyclohexyl	Et_2O	r.t.	20	—	1- & 3-Methyl-cyclohexene, 31 & 27	—	
PhCH(Me)	Et_2O	r.t.	20	56 (57)	—	29 (25)	f)
PhCH(Et)	Et_2O	r.t.	20	65 (62)	—	27 (20)	f)
$PhCH_2$	Et_2O	r.t.	20	60	—	25	g)
$PhCH(CO_2Et)$	Et_2O	r.t.	20	66	—	—	h)
Bornyl	Et_2O	r.t.	5	58[c]	Camphene, 19	—	i)
Cholesteryl	CH_2Cl_2	0—5	16	83[d]	—	—	j)
t-Bu	CCl_4	r.t.	20	78 (61)	Isobutylene, 9 (8)	—	k)
1-Adamantyl	THF	refl.	5	81	—	—	l)

a) Yields were determined by ^{19}F and ^1H NMR, or by GLC, unless otherwise noted. Figures in parentheses are those obtained with "Yarovenko reagent" under similar conditions. b) *trans*-2-Octene : *cis*-2-octene : 1-octene = 4 : 3 : 1. c) The product is 3-fluoro-2,2-dimethylbicyclo[2.2.1]heptane. d) Isolated yields. e) E. D. Bergmann and I. Shahk, *Bull. Res. Counc. Isr.* **10A**, 91 (1961). f) K. Wiechert, *Z. Chem.*, **8**, 64 (1968). g) Ref. 6). h) K. Fendenberg, *Ann.*, **601**, (1933). i) W. J. Middleton, *J. Org. Chem.*, **40** (5), 575 (1975). j) J. C. Brial and M. Mousseron-Canet, *Bull. Soc. Fr.*, **1968**, 3321. k) K. A. Coper and E. D. Hughes, *J. Chem. Soc.*, **1973**, 1183. l) G. A. Olah, M. Nojima, and I. Kerckes, *Synthesis*, **1973**, 786.

Table 4. The yields of acyl fluorides

$$RCO_2H \xrightarrow[Et_2O,\ 2\,h,\ r.t.]{C_3F_6/Et_2NH} RCOF$$

R	Yield/% I[a]	Yield/% II[b]	^{19}F NMR δ/ppm[c]	Ref. for RCOF
Et	64	61 (40)[d]	−116	e)
n-C_6H_{13}	73		−118	f)
Ph	86	60 (90)[d]	−90	g)
p-MeC_6H_4	71		−91	h)
m-MeC_6H_4	88		−92	h)
p-HOC_6H_4	75		−88	i)

a) Yields determined by ^{19}F NMR. b) Isolated yield. c) Upfield from ext. CF_3CO_2H. d) Yield obtained with the "Yarovenko reagent." e) Ref. 2. f) G. A. Olah, S. Kuhn, and S. Beke, *Chem. Ber.*, **89**, 862 (1956). g) Z. Arnold, *Collect. Czech. Chem. Commun.*, **28**, 2047 (1963). h) H. S. Albert, *Act. Phys. Aust.*, **1**, 352 (1948). i) R. W. Taft, Jr., *J. Chem., Phys.*, **38**, 380 (1963).

in several days even by storage in a refrigerator. It also fumed strongly by contact with atmospheric moisture, and it is recommended to be prepared just before the use.[1] In contrast, the *F*-propene–diethylamine reaction product (**2**+**3**) was so stable that no coloration was observed by storage at room temperature. Even after half a year, it could be used without any deterioration, and it could be handled much easier than **1**.

Fluorination of Alcohols. Fluorination of various alcohols using the *F*-propene–diethylamine reaction product (**2**+**3**) mentioned above was carried out. In these reactions, we found that the pure **3**, which was prepared in another route, has no fluorinating ability. Nevertheless, when a mixture of **2** and **3** was used, hydrogen fluoride which was formed by the reaction of **2** and an alcohol added to **3** giving **2**. As a whole, all of **3** was consumed as a fluorinating agent through **2**.

$$ROH + \underset{\mathbf{2}}{Et_2NCF_2CHFCF_3} \longrightarrow RF + \underset{\mathbf{6}}{Et_2NCCHFCF_3} + HF \quad (O)$$

$$Et_2NCF{=}CFCF_3 + HF \longrightarrow \mathbf{2}$$

Several other *F*-propene–dialkylamine reagents were also examined for fluorination, however, there were no differences among their abilities as a fluorinating agent. From the practical point of view, however, it was necessary to choose an appropriate amine component, otherwise the fluorinated product and the formed amide might have similar boiling points, which would make the separation of them difficult.

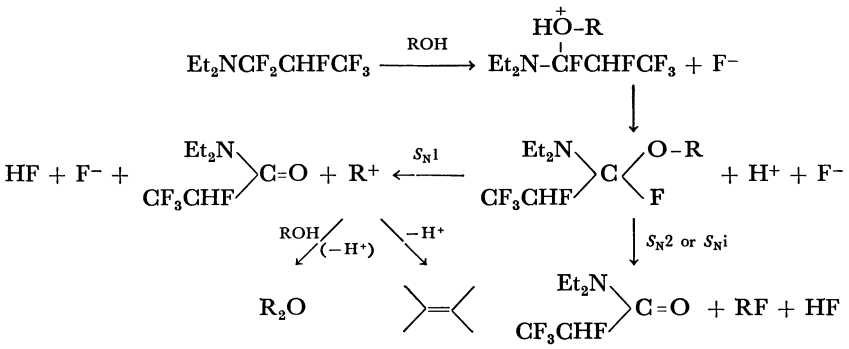
Various primary alcohols were subjected to the fluorination using *F*-propene–dialkylamine reaction products, using diethyl ether as a solvent. After 20 h's reaction at room temperature, the yields of the fluorinated products were determined based on the signal intensities of ^{19}F NMR (Table 2). Most of the primary alcohols were fluorinated in good yields. However, benzyl alcohol, which readily gives a benzyl cation, formed 25% of dibenzyl ether.

Secondary and tertiary alcohols, which also tend to form carbonium ions, gave considerable amounts of alkenes and dialkyl ethers (Table 3). For example, 2-octanol in diethyl ether gave 25% of a mixture of *trans*-2-octene, *cis*-2-octene, and 1-octene (4 : 3 : 1), besides 62% of 2-fluorooctane. When the reaction was carried out in acetonitrile, a highly polar solvent, the formation of alkene reached up to 52%.

Borneol gave a fluorinated product formed through carbonium rearrangement. α-Hydroxycarboxylic acid ester such as ethyl DL-mandelate gave α-fluoro carboxylic acid ester in a good yield. Choresterol also afforded the expected cholesteryl fluoride by fluorination in dichloromethane at low temperature. The fluorination of *t*-butyl alcohol was notable, as it afforded *t*-butyl fluoride in 78% of yield. 1-Adamantanol also gave 1-fluoroadamantane in a high yield.

The reaction mechanism of the fluorination by chlorotrifluoroethene–diethylamine reagent is suggested to involve S_N1, S_N2, or S_Ni, though no diethylamine reagent is suggested to involve S_N1, S_N2, or S_Ni, though no kinetic investigation has been done.

The fluorination of alcohols with the *F*-propene–diethylamine reagent should also undergo through the following pathway.



Fluorination of Carboxylic Acids. Carboxylic acids are known to be converted directly to their fluorides by using chlorotrifluoroethene–diethylamine reagent.[2,10] The *F*-propene–diethylamine reagent could also be used for the fluorination of aliphatic or aromatic carboxylic acids into their fluorides (Table 4).

Experimental

Reaction of F-*Propene with Diethylamine.* *a) Reaction under Pressure*: Diethylamine (11 mg, 0.15 mol) and dried

diethyl ether (30 ml) were placed in a glass pressure-vessel, and the whole was cooled to ≈ -70 °C by means of a Dry Ice–acetone bath. Liquefied *F*-propene (25 g, 0.17 mol) was introduced to the vessel and sealed. The cooling bath was removed and the mixture was brought to room temperature with magnetical stirring. After stirring over a night, the reaction mixture was filtered to remove the crystals of diethylamine hydrofluoride, and the solvent was evaporated. Resulting residue was subjected to distillation in a vacuum, and a liquid (23.7 g, 72%) bp 56—57 °C/58 mmHg, was obtained. The ^{19}F NMR spectrum revealed that this oil is a mixture of **2** and **3** in a ratio 3 : 1. When the vessel is stoppered tight, this material could be stocked at room temperature for more than half a year with only a slight discoloration.

b) Reaction at Atmospheric Pressure: A solution of diethylamine (105 g) in dried diethyl ether (200 ml) was placed in a three-necked flask which was equipped with a Dry Ice–acetone-cooled reflux condenser and a gas inlet tube. The whole was cooled to 0—5 °C with an ice-bath and *F*-propene gas (240 g) was bubbled through the mixture. Vigorous stirring was continued throughout this process and the temperature was kept below 10 °C. The whole gas was completely absorbed by 2 h's bubbling. After removing the ice-bath, the reaction mixture was allowed to stand overnight. The mixture thus obtained can be used as a fluorinating agent. However, for further purification, the solvent was evaporated and the residue was distilled in a vacuum giving an oil (273 g, 89%), bp 51—53 °C/40 mmHg. This liquid was a mixture of **2** and **3** in the ratio 1 : 1.

1-Fluorooctane. A solution of the *F*-propene–diethylamine reagent (13 g, 60 mmol) in diethyl ether (50 ml) was dropped into a solution of 1-octanol (6.5 g, 50 mmol) in diethyl ether (30 ml) at 0—5 °C. After stirring for 4 h, the reaction mixture was thrown into water and an oily layer was extracted with diethyl ether. The extract was washed with water, dried over magnesium sulfate, and evaporated to remove the solvent. The residue was distilled to give 1-fluorooctane (5.4 g, 82%), bp 145—146 °C.

Other primary alcohols were fluorinated in similar manners.

2-Fluorooctane. Fluorination of 2-octanol was carried out similarly to that of 1-octanol. The reaction product was subjected to gas chromatographic analysis using benzotrifluoride as a standard material. Following products were found in the reaction mixture: 2-fluorooctane (62%), 2-octene (22%, *trans*/*cis*=3/1), and 1-octene (3%).

Cholesteryl Fluoride. Into a solution of cholesterol (1.17 g) in dichloromethane (7 ml), a solution of *F*-propene–diethylamine reagent (0.81 g) in dichloromethane (3 ml) was dropped at 0—5 °C. Stirring was continued further several hours at that temperature, and the reaction mixture was thrown into water. An oily layer was extracted with dichloromethane, and the extract was washed with water, dried over magnesium sulfate and subjected to column chromatography on silica gel. Petroleum ether was used as the eluent, and the main elution was subjected to evaporation, affording white crystals (0.96 g, 83%) of cholesteryl fluoride, mp 92—93 °C (lit,[11] mp 93—94 °C).

Propionyl Fluoride. Into *F*-propene–diethylamine reagent (11.9 g, 56 mmol), propionic acid (3.9 g, 50 mmol) was dropped at room temperature. The mixture was stirred at 60 °C for 1 h and subjected to distillation. Propionyl fluoride (2.4 g, 62%) came out at bp 43—45 °C (lit,[1] bp 44 °C), followed by *N*,*N*-diethyl-2,3,3,3-tetrafluoropropionamide (10.5 g, 89%), bp 86—89 °C/11 mmHg.

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