Nucleophilic Reactions of Hexafluoro-1,2-epoxypropane with 1,2-Bifunctional Ethanes

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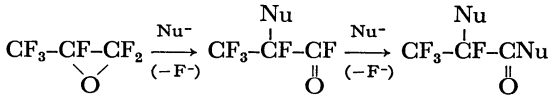
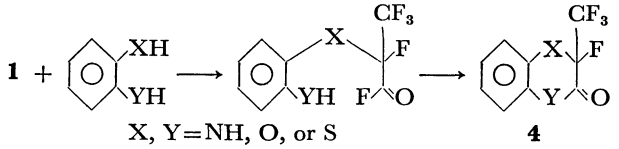
Reactions between hexafluoro-1,2-epoxypropane and 1,2-bifunctional ethanes were studied. Ethylenediamine, 2-aminoethanol and 2-aminoethanethiol gave corresponding *N*- and *O*-pentafluoropropionylated products, while ethylene glycol, 2-mercaptoethanol, and 1,2-ethanedithiol afforded ring closed products, such as 1,4-dioxanone, 1,4-oxathianone, and 1,4-dithianone compounds.

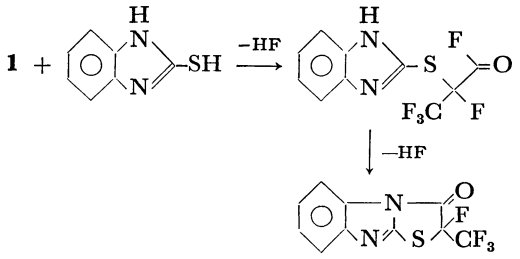
Hexafluoro-1,2-epoxypropane (**1**) is easily attacked by nucleophiles usually at the 2-position, and the resulting carboxylic acid fluorides (**2**) further react with another molecule of the nucleophile to give 2-substituted tetrafluoropropanoic acid derivatives (**3**).[1-3] Utilizing



these reactivities of **1** for nucleophiles, we have prepared several fluorinated 2,3-benzo-fused 1,4-diheteracyclic compounds (**4**) by the reaction between **1** and 1,2-bifunctional benzenes.[4] Another example of the



preparation of fluorinated heterocycles from **1** is the condensation with mercaptobenzimidazoles giving thiazolobenzimidazolones which are interesting from the pharmaceutical point of view.[5] Since the formation of

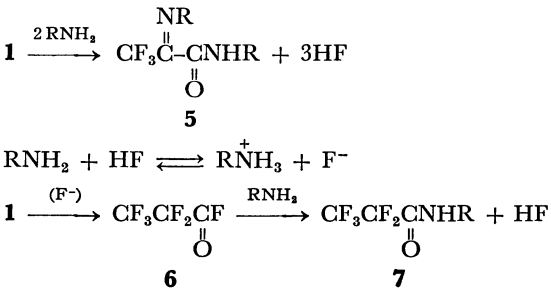


other kind of 1,4-diheteracyclic compounds had been expected, these works have now been extended and reactions between **1** and 1,2-bifunctional ethanes were examined. The reactions were, however, not so simple like those with 1,2-bifunctional benzenes and some interesting behaviors of 1,2-bifunctional ethanes were observed.

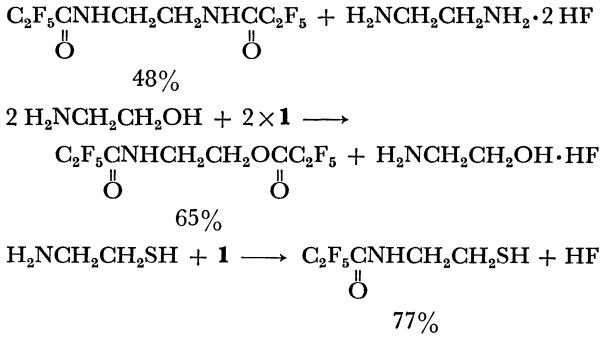
Results and Discussion

Reactions of Hexafluoro-1,2-epoxypropane with Ethylenediamine, 2-Aminoethanol and 2-Aminoethanethiol. Hexafluoro-1,2-epoxypropane is known to isomerize easily into pentafluoropropanoic acid fluoride (**6**) by the aid of a fluoride ion or a strong base.[6,7]

The reaction with an alkylamine is reported to give some amount of *N*-alkylpentafluoropropionamide (**7**)



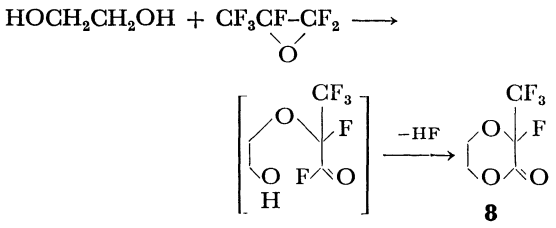
together with the main 2-substituted amide (**5**). When we allowed **1** to react with an equimolar amount of ethylenediamine, 2-aminoethanol or 2-aminoethanethiol in diglyme at room temperature, only *N*- and *O*-pentafluoropropionylated products were obtained and no 2-substituted tetrafluoropropanoic acid derivatives.



Thus, by the nucleophilic reactions of **1** with 2-functional ethylamines, none of heterocyclic compounds were obtained. This is in contrast to those with *ortho*-functional anilines which gave 2,3-benzo-fused 1,4-diheteracyclic compounds in good yields.[4] The difference should be ascribed to the stronger basicities of aliphatic amines than those of the aromatic amines. The strong basicity of ethylenediamine or 2-aminoethanol must have promoted the isomerization of **1** to **6** rather than the nucleophilic reaction at the 2-position of **1**.

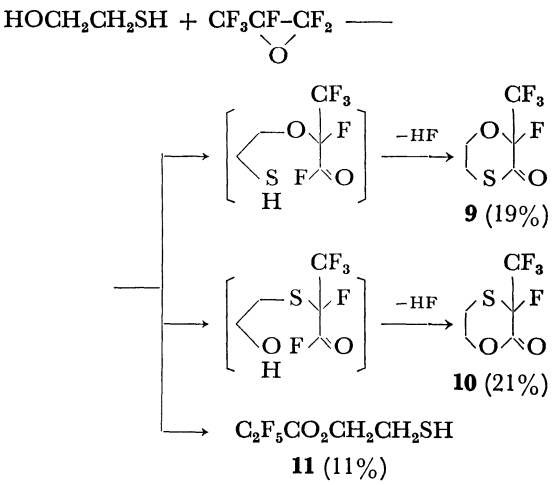
Reactions of Hexafluoro-1,2-epoxypropane with Ethylene Glycol, 2-Mercaptoethanol, and 1,2-Ethanedithiol. As described above, the amino group of 2-functional ethylamines was found to accelerate the formation of acid fluoride **6**. Then we examined the reaction of **1** with non-basic 1,2-bifunctional ethanes, *i.e.*, ethylene glycol, 2-mercaptoethanol and 1,2-ethanedithiol.

Ethylene glycol reacted smoothly with **1** in diglyme and 3-fluoro-3-trifluoromethyl-1,4-dioxan-2-one (**8**) was

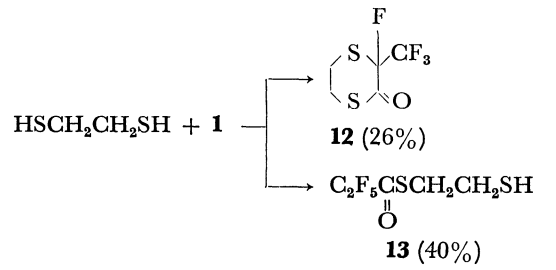


expectedly obtained. In the case of mercaptoethanol, two isomers of 1,4-oxathianone (**9**, **10**) were obtained in almost similar yields.

It is evident that **9** was formed by the nucleophilic attack by the OH group of mercaptoethanol first, while **10** was formed by that of the SH group first. In addition to these two heterocyclic compounds, a considerable amount (11%) of *O*-pentafluoropropionyl compound (**11**) was isolated from the reaction mixture.



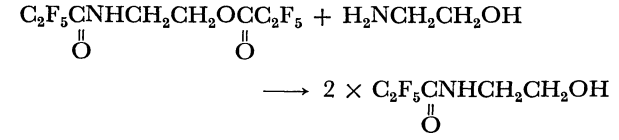
With 1,2-ethanedithiol, 2-fluoro-2-trifluoromethyl-1,4-dithian-3-one (**12**) was expectedly formed, though the yield was rather poor (26%), and a larger amount of *S*-pentafluoropropionyl compound (**13**) was obtained.



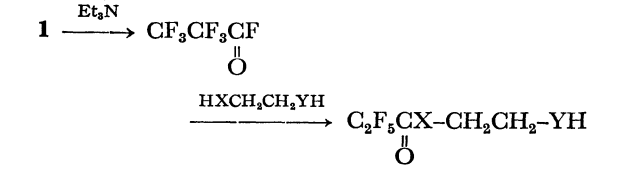
The formation of pentafluoropropionylated products in the case of reactions with the thiol and the dithiol should have resulted from the partial isomerization of **1** to **6** by the aid of the mercapto group, which behaved as a weak base.

Equilibrium among N-, O- *and* S-*Pentafluoropropionyl Groups.* From the results obtained heretofore, we noticed that there are differences among *N*-, *O*-, and *S*-pentafluoropropionyl groups in their thermodynamic stabilities.

For example, when *N*,*O*-bis(pentafluoropropionyl)-2-aminoethanol was treated with an equimolar amount of 2-aminoethanol, proportionation reaction occurred, and the *N*-(pentafluoropropionyl) compound was obtained quantitatively.

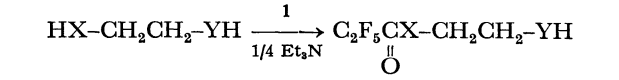


Further, we examined pentafluoropropionylation of 1,2-bifunctional ethanes by having them react with **1** in acetonitrile in the presence of triethylamine, the reaction which was used for the pentafluoropropionylation of



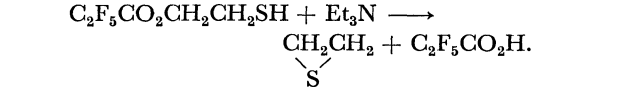
alcohols and amines.[8] The results are shown in Table 1. It is notable that when two different kinds of groups present in a molecule, only one group of them was exclusively pentafluoropropionylated. An amino group was always predominantly pentafluoropropionylated rather than a hydroxyl or a mercapto group, and between the latter two groups, a hydroxyl group was more readily perfluoroacylated. From these results, it was evident that the order of thermodynamic stabilities of pentafluoropropionyl groups is $C_2F_5CONH > C_2F_5CO_2 > C_2F_5COS$. This order is in accordance with the general stabilities of acyl compounds,[9] but the trend seems to be more remarkable in a series of perfluoroacyl compounds.[10]

Table 1. Pentafluoropropionylation of 1,2-bifunctional ethanes



Product		Yield[a]/%
C_2F_5COX	YH	
C_2F_5CONH	C_2F_5CONH	42
C_2F_5CONH	OH	92
C_2F_5CONH	SH	95
$C_2F_5CO_2$	OH	90
$C_2F_5CO_2$	SH	53[b]
C_2F_5COS	SH	72

a) Based on ^{19}F-NMR signal intensities. b) Low yield is due to the formation of thiirane:



The ^{19}*F-NMR Spectra.* Most of the qualitative and quantitative analyses of reaction products in this work were easily done by means of the ^{19}F-NMR spectra.

In a series of $-X-CF-CF_3$ moieties, the NMR signals for C<u>F</u> and C<u>F</u>$_3$ of X=O compounds were characteristically distinguishable from those of X=S compounds. Thus, in comparison with those of X=O compounds, the signals due to <u>F</u> and C<u>F</u>$_3$ of X=S compounds shift considerably up and down field

TABLE 2. THE ^{19}F-NMR FOR Et–X–CF–CO_2Et (CF_3)

X	Chem. Shift (ppm)[a] CF	Chem. Shift (ppm)[a] CF_3	J_{CF-CF_3} (Hz)
O	+53.3	+5.0	2.8
S	+72.0	−3.5	10.8

a) Upfields from ext. CF_3CO_2H in Et_2O.

respectively, and the coupling constants J_{F-CF_3} were much larger. The results are shown in Table 2.

The fluorine atom of the S–CF group is supposed to be more shielded than that of the O–CF group due to the more positive character of the sulfur atom than the oxygen atom. In the case of the –N=C–CF_3 group, the signal due to CF_3 appeared, of course, as a singlet at about −20 ppm.

As to the ^{19}F chemical shifts for $CF_3CF_2C(=O)XR$, characteristic patterns were observed depending on the X atom, as shown in Table 3. In general, the signals due to CF_2 in X=NH, O, and S compounds appeared at 45—46, 43—44, and 42—43 ppm upfield from CF_3CO_2H standard respectively. These values could be used for the identification of the pentafluoropropionyl groups.

TABLE 3. THE ^{19}F-NMR CHEMICAL SHIFTS FOR $CF_3CF_2C(=O)$–XR

δ ppm upfield from ext. CF_3CO_2H in acetonitrile.

X	R	CF_2	CF_3
NH	*n*-Pr	+45.4	+6.2
NH	$PhCH_2$	+45.2	+5.7
NH	Ph	+45.1	+5.8
O	*n*-Pr	+44.3	+6.4
O	$PhCH_2$	+44.3	+6.2
O	Ph	+44.4	+6.2
S	*n*-Pr	+42.3	+5.3
S	$PhCH_2$	+42.5	+5.2
S	Ph	+42.4	+5.0

Experimental

All the ^{19}F-NMR chemical shifts throughout this article are given in δ ppm upfield from external CF_3CO_2H.

N,N′-Bis(pentafluoropropionyl)ethylenediamine. A mixture of ethylenediamine (1.20 g, 20 mmol) and diglyme (20 ml) was placed in a glass pressure vessel and cooled to≈ −70 °C. Liquefied hexafluoro-1,2-epoxypropane (bp −27 °C, 3.50 g, 21 mmol) was then introduced into the vessel and the whole was brought to room temperature. After stirring of 1 h, the reaction mixture was poured into water and an oily material was extracted with diethyl ether. The extract was dried over magnesium sulfate and the solvent was removed, yielding a solid material. The crude product was recrystallized from aqueous methanol to give pure *N,N′*-(bispentafluoropropionyl)-ethylenediamine (1.69 g, 48%), mp 169 °C. IR: 3315 (NH), 1690 (C=O) cm^{-1}. ^{19}F-NMR (in acetone): δ 5.5 (CF_3), 44.5 (CF_2) ppm. Found: C, 27.43; H, 1.81; N, 7.76%. Calcd for $C_8H_6N_2O_2F_{10}$: C, 27.29; H, 1.72; N, 7.96%.

N,O-Bis(pentafluoropropionyl)-2-aminoethanol. 2-Aminoethanol (1.22 g, 20 mmol) instead of ethylenediamine was used in the above procedure. Reaction was continued for 2 h at room temperature and worked up similarly. Distillation gave 1.70 g (66%) of *N,O*-bis(pentafluoropropionyl)-2-aminoethanol, bp 81—82 °C/3 mmHg. IR (film): 3310 (NH), 1710 (C=O), 1700 (C=O) cm^{-1}. ^{19}F NMR (neat): δ 7.0 (2× CF_3), 45.0, 47.0 (CF_2) ppm. Found: C, 27.64; H, 1.65; N, 4.33%. Calcd for $C_8H_5NO_3F_{10}$: C, 27.21; H, 1.43; N, 3.97%.

N-Pentafluoropropionyl-2-aminoethanol. 2-Aminoethanol (0.30 g, 5 mmol) was added to a mixture of *N,O*-bis(pentafluoropropionyl)-2-aminoethanol (1.29 g, 5 mmol) and diglyme (10 ml) at room temperature. After 30 min of stirring the solvent was removed, and almost pure *N*-pentafluoropropionyl-2-aminoethanol (1.56 g, 98%), bp 99—100 °C/5 mmHg was obtained. IR: 3500—3300 (NH, OH), 1700 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 6.0 (CF_3), 45.5 (CF_2) ppm. Found: C, 29.11; H, 2.87; N, 6.76%. Calcd for $C_5H_6NO_2F_5$: C, 28.99; H, 2.92; N, 6.76%.

N-Pentafluoropropionyl-2-aminoethanethiol. Pentafluoro-1,2-epoxypropane (3.50 g, 21 mmol) and 2-aminoethanethiol (1.54 g, 20 mmol) were allowed to react at room temperature for 2 h in diglyme (20 ml). *N*-Pentafluoropropionyl-2-aminoethanethiol (3.60 g, 77%), bp 108—109 °C/11 mmHg was obtained after usual treatment. IR: 3310 (NH), 2550 (SH), 1700 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 6.0 (CF_3), 45.5 (CF_2), ppm. Found: C, 26.13; H, 2.57; N, 5.82%. Calcd for $C_6H_5NOSF_5$: C, 26.91; H, 2.71; N, 6.28%.

When a mixture of this compound (1.11 g, 5 mmol), 2,4-dinitrochlorobenzene (1.01 g, 5 mmol), potassium hydroxide (0.3 g, 5 mmol) and ethanol (30 ml) was refluxed for 3 h, *S*-(2,4-dinitrophenyl)derivative (1.4 g, 72%) was obtained. Recrystallization from chloroform gave a pure material, mp 138 °C. IR: 3310 (NH), 1700 (C=O) cm^{-1}. ^{19}F-NMR (acetone): δ 6.0 (CF_3), 45.5 (CF_2) ppm. Found: C, 33.68; H, 2.08; N, 10.73%. Calcd for $C_{11}H_8N_3O_5SF_5$: C, 33.94; H, 2.07; N, 10.79%.

3-Fluoro-3-trifluoromethyl-1,4-dioxan-2-one (8). A mixture of pentafluoro-1,2-epoxypropane (5.81 g, 35 mmol), ethylene glycol (1.86 g, 30 mmol) and diglyme (20 ml) in a sealed glass tube was allowed to react for 50 h at room temperature. The reaction mixture was poured into water and the resulting organic layer was separated and dried over magnesium sulfate. Vacuum distillation gave pure dioxanone (2.25 g, 40%), bp 100—101 °C/25 mmHg. IR: 1780 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 3.6 (CF_3), 35.4 (CF) ppm. Found: C, 31.74; H, 2.10%. Calcd for $C_5H_4O_3F_4$: C, 31.91; H, 2.13%.

2-Fluoro-2-trifluoromethyl-1,4-oxathian-3-one (9) and 3-Fluoro-3-trifluoromethyl-1,4-oxathian-2-one (10). 2-Mercaptoethanol (2.34 g, 30 mmol) was allowed to react with pentafluoro-1,2-epoxypropane (5.81 g, 35 mmol) in diglyme (20 ml) for 20 h at room temperature. The reaction mixture was poured into water and the separated oil was dried ($MgSO_4$) and distilled carefully to give the following products:

O-Pentafluoropropionyl-2-mercaptoethanol (0.74 g, 11%), pb 68 °C/77 mmHg. IR: 1785 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 4.8 (CF_3), 43.1 (CF_2) ppm. Found: C, 26.48; H, 2.42%. Calcd for $C_5H_5O_2SF_5$: C, 26.79; H, 2.42%.

The mixture of two isomers 1,4-oxathianone (2.45 g, 40%), bp 60—85 °C/2 mmHg. The ratio of these two isomers, **9**: **10**=1: 1, was determined by ^{19}F-NMR and they were practically separated by column chromatography (Silica Gel) using hexane as an eluent.

9: bp 93.5—94.5 °C/16 mmHg. IR: 1680 (C=O) cm^{-1}.

^{19}F-NMR (neat): δ 2.9 ($C\underline{F}_3$), 36.0 ($C\underline{F}$) ppm.

Found: C, 29.16; H, 1.90%. Calcd for $C_5H_4O_2SF_4$: C, 29.41; H, 1.96%. **10**: bp 84—85 °C/2 mmHg. IR: 1770 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ −1.2 ($C\underline{F}_3$), 55.0 (CF) ppm. Found: C, 29.21; H, 1.88%.

2-Fluoro-2-trifluoromethyl-1,4-dithian-3-one (12). The reaction of 1,2-ethanedithiol (2.82 g, 30 mmol) and pentafluoro-1,2-epoxypropane (5.81 g, 35 mmol) in diglyme (20 ml) was carried out for 12 h at room temperature. The reaction mixture was then poured into water and worked up as usual. Fractional distillation gave the following two porducts:

S-Pentafluoropropionyl-1,2-ethanedithiol (2.88 g, 40%): bp 69—70 °C/30 mmHg. IR: 1680 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 4.7 ($C\underline{F}_3$), 42.0 ($C\underline{F}_2$) ppm. Found: C, 24.66, H, 2.00%. Calcd for $C_5H_5OS_2F_5$: C, 25.00; H, 2.08%. **12** (1.72 g, 26%): bp 83—84 °C/6 mmHg. IR: 1680 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ −3.0 ($C\underline{F}_3$), 52.5 ($C\underline{F}$) ppm. Found: C, 27.03; H, 1.80%. Calcd for $C_5H_4OS_2F_4$: C, 27.27; H, 1.82%.

Reaction of 1,2-Bifunctional Ethanes with Hexafluoro-1,2-epoxypropane in the Presence of Triethylamine. General Procedure. A solution of 1,2-bifunctional ethane (10 mmol) and triethylamine (0.25 g, 2.5 mmol) in acetonitrile (10 ml) was cooled to −70 °C, then liquefied pentafluoro-1,2-epoxypropane (1.66 g, 10 mmol) was introduced into the vessel and the whole was brought to room temperature. After 30 min of stirring, benzylidyne trifluoride (1.46 g, 10 mmol) was added as an internal standard and the yield was determined by ^{19}F-NMR spectral analysis (Table 1).

For the isolation of the product, the reaction mixture was poured into water and the separated oily material was subjected to vacuum distillation. *O*-Pentafluoropropionylethylene glycol, for example, was obtained in 63% yield. bp 44 °C/5 mmHg. IR: 3350 (OH), 1710 (C=O) cm^{-1}. ^{19}F-NMR (neat): δ 5.5 ($C\underline{F}_3$), 44.5 (CF_2) ppm. Found: C, 27.08; H, 2.42%. Calcd for $C_5H_5O_3F_5$: C, 26.80; H, 2.25%.

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