Preparation of Perfluoroalkylated Benzoheterocyclic Compounds Using Hexafluoro-1,2-epoxypropane

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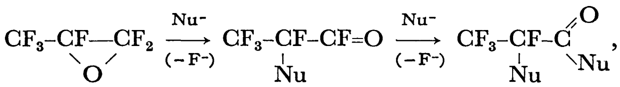
Utilizing the high reactivity of hexafluoro-1,2-epoxypropane (HFPO, hexafluoropropylene oxide), several new benzoheterocyclic compounds containing CF_3 and C_2F_5 were prepared as follows: (1) 2-(pentafluoroethyl)benzoxazoles by treating 2-aminophenols with HFPO/Et_3N, followed by dehydrating cyclization, (2) 3-(trifluoromethyl)-2*H*-1,4-benzoxazin-2-ones, 3-(trifluoromethyl)-2(1*H*)-quinoxalinone and 2-fluoro-2-(trifluoromethyl)-2,3-dihydro-1,4-benzothiazin-3-one by reactions of ortho-bifunctional benzenes with HFPO, and (3) 2-(pentafluoroethyl)-4*H*-3,1-benzoxazin-4-one by treating anthranilic acid with HFPO/Et_3N.

A number of heterocyclic compounds containing a perfluoroalkyl group, especially CF_3, are known pharmaceutically and agrochemically.[1] However, knowledge of the structure of this kind of compound is limited, because the introduction of a perfluoroalkyl group into a heterocyclic ring is usually not easy.[2,3]

On the other hand, it is well known that nucleophiles readily attack the central carbon atom of HFPO, resulting in the formation of α-substituted tetrafluoropropionyl fluoride, which further reacts with an additional molecule of the nucleophile, forming an ester or an amide,[4-6] thus



where NuH=ROH, RSH, or RNH_2.

HFPO is also known to isomerize to pentafluoropropionyl fluoride under the action of a base.[7] The present authors have reported a convenient preparative method for esters and amides of pentafluoropropionic acid by reactions of HFPO and alcohols, thiols or amines in acetonitrile in the presence of triethylamine,[8] thus

$$\text{HFPO} \xrightarrow{\text{Base}} CF_3CF_2CF{=}O$$

$$\text{HFPO} + \text{R-XH} \xrightarrow{Et_3N} CF_3CF_2\text{-}\underset{\underset{O}{\|}}{C}\text{-XR},$$

where X=O, S, NH. They have also reported that non-fluorinated carboxylic acids are readily converted into their fluorides by treating them in a HFPO-triethylamine system,[9] thus

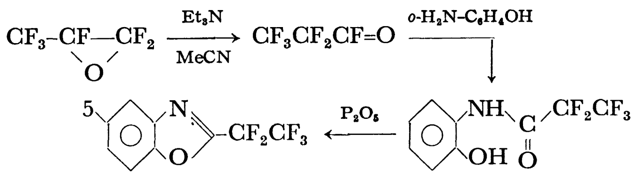
$$\text{HFPO} + \text{R}\underset{\underset{O}{\|}}{C}\text{OH} \xrightarrow{Et_3N} C_2F_5CO_2H + \text{R}\underset{\underset{O}{\|}}{C}\text{F}.$$

The reactivities of HFPO described above were applied to the preparation of benzoheterocyclic compounds and several kinds of new heterocyclic compounds which contain a trifluoromethyl or a pentafluoroethyl group were obtained.

Results and Discussion

Preparation of 2-(Pentafluoroethyl)benzoxazoles. According to the method of preparation for pentafluoropropionyl amides,[8] 2-(pentafluoropropionylamino)-phenol (**1**) was obtained in a good yield by the reaction between *o*-aminophenol and HFPO–triethylamine in acetonitrile. The structure of **1** was evident from its IR and ^{19}F NMR data. In the IR spectrum, a broad band due to an OH group, and a characteristic band due to the C=O of an amide group were observed at 3320 and 1695 cm^{-1}, respectively. In the ^{19}F NMR spectrum two signals due to CF_3 and CF_2 groups appeared at 6.0 and 45.3 ppm.*

The dehydrating ring closure of **1** was carried out by heating in diphosphorus pentaoxide at 200—230 °C, affording 2-(pentafluoroethyl)benzoxazole (**2**) in an 84% yield. In the IR spectrum of this compounds, the characteristic absorption bands for **1** due to OH and C=O disappeared, and a new band due to C=N appeared at 1615 cm^{-1}.



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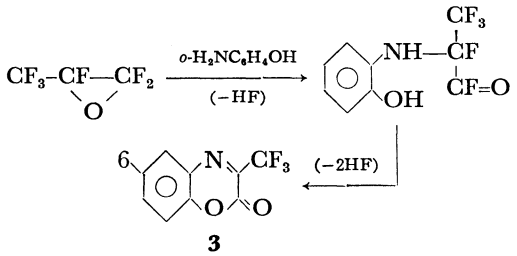
2-Amino-4-methyl- and 2-amino-4-chlorophenols, containing an electron donor or attractive group on the benzene ring, also gave 5-substituted 2-(pentafluoroethyl)benzoxazoles by a similar procedure. Although a number of 2-trifluoromethylbenzoxazoles are known,[10] no 2-pentafluoroethyl derivatives have been reported in the literature, The synthetic route described here appears to be a useful method for preparing this kind of compound.

*Preparation of 3-(Trifluoromethyl)-2*H*-1,4-benzoxazin-2-ones, 3-(Trifluoromethyl)-2(1*H*)-quinoxalinone and 2-Fluoro-2-(trifluoromethyl)-2,3-dihydro-1,4-benzothiazin-3-one.* When 2-aminophenol was allowed to react with HFPO in dioxane, without any base, it readily gave 3-(trifluoromethyl)-2*H*-1,4-benzoxazin-2-one (**3**) in an 85% yield, together with a small amount (7%) of 2-(pentafluoropropionylamino)phenol (**1**).** The reaction must be as follows:

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

** These yields are based on the ^{19}F-NMR signal intensities.



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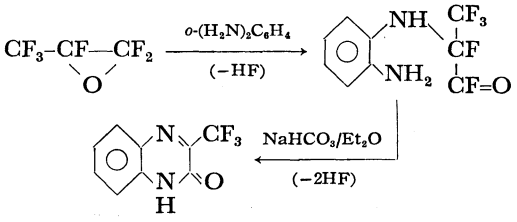
Thus, the amino group of *o*-aminophenol first attacks the central carbon atom of HFPO, as usual, and the resulting fluoroformyl group condensed with the ortho hydroxy group forming an oxazine ring. On the other hand, pentafluoropropionyl fluoride, formed by the isomerization of HFPO, pentafluoropropionated 2-aminophenol giving a small amount of **1**. When acetonitrile was used as the solvent, **3** and **1** were formed in yields of 45 and 22%, respectively. This probably means that the ionic isomerization of HFPO is accelerated by the polar solvent.

The structure of **3** was established from its spectral data. In the ^{19}F NMR spectrum, only one singlet signal was observed at −6.9 ppm, which means that there are no hydrogen or fluorine atoms around the CF_3 group. The IR spectrum indicates a characteristic band at 1765 cm^{-1} due to ester bonding, and the mass spectrum showed the expected parent peak at *m/e* 215.

6-Methyl- and 6-chloro-3-(trifluoromethyl)-2*H*-1,4-benzoxazin-2-ones were also obtained in good yields from 2-amino-4-methyl- and 2-amino-4-chlorophenols, respectively.

Like 2-aminophenol, *o*-phenylenediamine with HFPO gave another heterocyclic compound. In this case, however, more isomerization of HFPO to pentafluoropropionyl fluoride occurred becauseof the higher basicity of phenylenediamine compared to 2-aminonophenol. Thus, the reaction between *o*-phenylenediamine and HFPO in dioxane gave only a 30% yield of 3-(trifluoromethyl)-2(1*H*)-quinoxalinone (**4**). Then using diethyl ether as a solvent, together with sodium hydrogencarbonate to remove the hydrogen fluoride formed, the yield was increased to 84%. Bases stronger than sodium hydrogencarbonate were not used because they accelerate the isomerization of HFPO, and lower the yield of **4**.



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The structure of **4** was also elucidated from spectral data (Table 1).

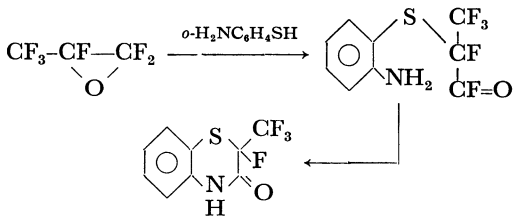
o-Aminobenzenethiol and HFPO in *N,N*-dimethylacetamide provided another heterocyclic compound, 2-fluoro-2-(trifluoromethyl)-2,3-dihydro-1,4-benzothiazin-3-one (**5**). The mercapto group, which is more nucleophilic than the amino group, first attacked the central carbon atom of HFPO, and an intramolecular

Table 1. Physical properties of **1**—**7**

Product	Mp °C or (Bp)	Yield (%)	IR (cm^{-1})	^{19}F NMR (ppm)[a]	MS (*m/e*)	Found (Calcd) % C	H	N
1	117—118	79	3320(OH), 1695(C=O)	6.0(CF_3), 45.3(CF_2)		42.26 (42.38)	2.43 (2.37)	5.40 (5.49)
4-Me-**1**	125	90	3330(OH), 1705(C=O)	5.5(CF_3), 44.7(CF_2)		44.98 (44.62)	2.91 (3.00)	5.30 (5.20)
4-Cl-**1**	151—152	63	3350(OH), 1695(C=O)	5.2(CF_3), 44.5(CF_2)		37.21 (37.33)	1.73 (1.74)	4.87 (4.84)
2	(166—167)	84	1615(C=N)	6.5t (CF_3), 38.1q(CF_2)	237(M^+), 168(M^+-CF_3)	45.17 (45.59)	1.85 (1.70)	5.70 (5.91)
5-Me-**2**	(182—183)	70	1615(C=N)	6.4t (CF_3), 38.4q(CF_2)		47.96 (47.82)	2.51 (2.41)	5.53 (5.58)
5-Cl-**2**	(194—195)	82	1610(C=N)	6.2t (CF_3), 38.4q(CF_2)		40.16 (39.80)	1.26 (1.11)	5.10 (5.16)
3	77—78	66	1765(C=O)	−6.9s(CF_3)	215(M^+), 187(M^+-CO)	49.55 (50.25)	1.94 (1.87)	6.48 (6.51)
6-Me-**3**	119—120.5	76	1760(C=O)	−7.0s(CF_3)		52.31 (52.41)	2.59 (2.64)	6.08 (6.11)
6-Cl-**3**	88—89	83	1750(C=O)	−6.9s(CF_3)		42.96 (43.31)	1.24 (1.21)	5.51 (5.61)
4	233—234.5	84	3330(NH), 1675(C=O)	−7.5s(CF_3)	214(M^+), 186(M^+-CO)	50.09 (50.48)	2.35 (2.35)	13.08 (13.08)
5	182—183	26	3370(NH), 1695(C=O)	−2.3d(CF_3), 70.2q(CF)	251(M^+), 182(M^+-CF_3)	43.03 (43.03)	2.02 (2.01)	5.37 (5.58)
6	48—49	89	1770(C=O)	5.6(CF_3), 42.8(CF_2)	265(M^+)	44.63 (45.30)	1.56 (1.52)	5.24 (5.28)
7	168—169	70	3500—2400(OH) 3250(NH) 1715, 1670(C=O)	5.8(CF_3), 45.8(CF_2)		42.47 (42.42)	2.17 (2.14)	4.75 (4.95)

a) Upfield from external CF_3CO_2H.

amide linkage was subsequently formed.



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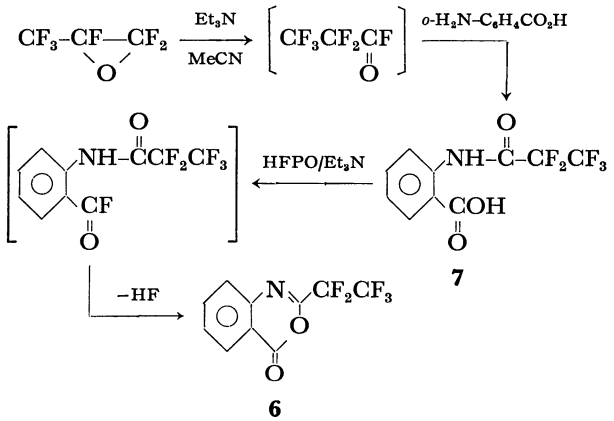
When dioxane or acetonitrile was used instead of *N,N*-dimethylacetamide, the formation of another product, which appeared to contain only a CF_3 group, was observed in the ^{19}F NMR spectrum. This compound was not isolated for identification.

In the ^{19}F NMR spectrum for **5**, two signals, a doublet and a quartet were observed, the mutual coupling constant being $J=10.2$ Hz. This indicates that a fluorine atom and a trifluoromethyl group are geminally attached to one carbon atom.

Preparation of 2-(Pentafluoroethyl)-4H-3,1-benzoxazin-4-one. The reaction of anthranilic acid with two molar amounts of HFPO in acetonitrile, in the presence of triethylamine, afforded 2-(pentafluoroethyl)-4*H*-3,1-benzoxazin-4-one (**6**) in a good yield. The reaction proceeded as follows:



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When an equimolar amount of HFPO was used in this reaction, 2-(pentafluoropropionylamino)benzoic acid (**7**) was obtained.

The structures of these products were obvious from their spectra (Table 1). In particular, in the IR spectrum of **7**, the characteristic bands due to OH and NH groups appeared over 2400—3500 and at 3250 cm^{-1}, respectively, which were not observed in the spectrum of **6**.

Experimental

2-(Pentafluoropropionylamino)phenol (1). 2-Aminophenol (2.18 g, 20 mmol), triethylamine (2.02 g, 20 mmol) and acetonitrile (20 ml) were placed in a glass pressure vessel, which was then cooled to −75 °C in a Dry Ice–acetone bath. Liquefied HFPO (3.32 g, 20 mmol) was introduced into the vessel, and the whole system was brought to room temperature. After stirring for 30 min at that temperature, the reaction mixture was poured into water (200 ml) and the precipitated material was collected by filtration. By treating the precipitate with dilute aqueous hydrochloric acid to remove any basic material, crude 2-(pentafluoropropionylamino)phenol, (mp 113—116 °C, 4.02 g, 79%) was obtained. Recrystallization from benzene gave a pure product, mp 116.5—118 °C. When 2-amino-4-methyl- and 2-amino-4-chlorophenol was used instead of unsubstituted 2-aminophenol, 4-methyl- and 4-chloro-2-(pentafluoropropionylamino)phenols were obtained (Table 1), respectively.

2-(Pentafluoroethyl)benzoxazole (2). A mixture of 2-(pentafluoropropionylamino)phenol (2.55 g, 10 mmol) and diphosphorus pentaoxide (2.84 g, 20 mmol) in a distilling flask was heated gently to 220 °C. An oily product having a boiling point of 166—167 °C was distilled out, and an additional amount of the product was obtained by vacuum distillation of the residue. Almost pure 2-(pentafluoroethyl)benzoxazole (2.00 g, 84%) was thus obtained.

Following a similar procedure, 5-methyl and 5-chloro derivatives of **2** were obtained from 2-(pentafluoropropionylamino)-4-methyl- and -4-chlorophenols, respectively (Table 1).

3-(Trifluoromethyl)-2H-1,4-benzoxazin-2-one (3). Into a pressure vessel containing 2-aminophenol (1.09 g, 10 mmol) and dioxane (20 ml), liquefied HFPO (1.91 g, 11.5 mmol) was introduced as described above. After 3 h of stirring at room temperature, the reaction mixture was thrown into water, and the precipitated product was collected by filtration. An additional amount of the product was obtained from the filtrate by extraction with diethyl ether. Crystallization of the combined material from hexane gave a crude product (1.42 g, 66%), which was purified by recrystallization, mp 77—78 °C.

From 4-methyl- and 4-chloro-2-aminophenols, 6-substituted derivatives of **3** were obtained by the same procedure (Table 1).

3-(Trifluoromethyl)-2(1H)-quinoxalinone (4). A mixture of *o*-phenylenediamine (1.08 g, 10 mmol) and sodium hydrogen carbonate (2.54 g, 30 mmol) in diethyl ether (30 ml) was allowed to react with HFPO (2.09 g, 12.6 mmol) for 3 h at room temperature. A solid product was separated by filtration, washed with water, and dried to give crude benzodiazinone (1.27 g), mp 230—232 °C. Concentration of the parent solution yielded an additional product (0.53 g), mp 232—233.5 °C. The combined material (1.80 g, 84%) was recrystallized from benzene to give pure **4**, mp 233—234.5 °C.

2-Fluoro-2-(trifluoromethyl)-2,3-dihydro-1,4-benzothiazin-3-one (5). 2-Aminophenol (2.50 g, 20 mmol) in *N,N*-dimethyl acetamide (20 ml) was allowed to react with HFPO (3.82 g, 2.3 mmol) for 3 h at room temperature. The reaction mixture was poured into water and extracted with diethyl ether. The extract was washed with water, dried over magnesium sulfate and concentrated. The residue was recrystallized from benzene, yielding crude crystals of **5** (1.29 g, 26%), mp 177—178 °C. Further crystallization gave pure material, mp 181.5—182.5 °C.

2-(Pentafluoropropionylamino)benzoic Acid (7). Anthranilic acid (2.74 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) in acetonitrile (20 ml) were allowed to react with HFPO (3.03 g, 18.3 mmol) in the usual manner. After 15 min of stirring at room temperature, the reaction mixture was poured into water and the precipitate formed was separated by filtration. By washing the precipitate with dilute aqueous hydrochloric acid, a crude product (2.53 g) was obtained. An additional amount of the product (1.13 g) was obtained by extraction of acidified aqueous layer with diethyl ether. The combined material was recrystallized from benzene, providing **7** (3.62 g, 70%), mp 166—169 °C. Further crystallization gave a pure product, mp 168—169 °C.

*2-(Pentafluoroethyl)-4*H*-3,1-benzoxazin-4-one (6).* (*a*): Anthranilic acid (1.37 g, 10 mmol) and triethylamine (3.03 g, 30 mmol) in acetonitrile (20 ml) were allowed to react with HFPO (3.40 g, 20.5 mmol) for 30 min at room temperature. The reaction mixture was worked up as usual. The residue from an ether extract was treated with pentane, and the insoluble material was removed by filtration. Evaporation of the solvent yielded a crude product (2.37 g, 89%), which was recrystallized to give pure material, mp 48—49 °C. (*b*): 2-(Pentafluoropropionylamino)benzoic acid (2.83 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in acetonitrile (15 ml) were allowed to react with HFPO (1.84 g, 11.1 mmol) as usual. The reaction mixture was worked up to give crude 2-(pentafluoroethyl)-4*H*-3,1-benzoxazin-4-one (2.45 g, 92%), mp 46—48 °C.

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