The Reactions of Tetrafluorobenzyne with Carboxylic Acids in Cyclic Ethers

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The reactions between tetrafluorobenzyne generated from tetrafluorobenzenediazonium-2-carboxylate and several carboxylic acids in cyclic ethers, such as THF and dioxane, were carried out. During these reactions, the cyclic ethers were cleaved and participated in the reactions to give acetate, benzoate, and salicylate esters of 4-(2′,3′,4′,5′-tetrafluorophenoxy)butanol and 2-[2′-(2″,3″,4″,5″-tetrafluorophenoxy)ethoxy]ethanol.

A number of cases have been reported of the reactions of unsubstituted or tetrahalogeno-substituted benzynes with ethers.[1,2] As for the ring cleavage of cyclic ethers during the reactions, Wolthuis *et al.* reported that tetrahydrofuran (THF) was cleaved by benzyne, thus affording a betaine intermediate, which was intercepted with water to give 23% 4-phenoxybutanol and 8% 1,4-diphenoxybutane.[3] In our own previous paper, we reported that dioxane was cleaved by tetrafluorobenzyne generated from tetrafluorobenzenediazonium-2-carboxylate and that the resulting betaine intermediate (**6**) was intercepted with bromine to give 28% 1-[2′-(2″-bromoethoxy) ethoxy]-2-bromo-3,4,5,6-tetrafluorobenzene.[4]

We shall now describe further examples of this type of reaction, *i.e.*, those between tetrafluorobenzyne and carboxylic acids in the cyclic ethers, such as THF and dioxane, in which the solvents participate through their cleavage.

Results and Discussion

It is known that benzynes generated from benzenediazonium-2-carboxylate[5] or its tetrahalogeno derivatives[6–8] sometimes yield acridones by reactions with anthranilic or tetrahalogenoanthranilic acid. By analogy with these, we attempted to have tetrafluorobenzyne react with salicylic acid, expecting to obtain 2-(2′,3′,4′,5′-tetrafluorophenoxy)benzoic acid or its dehydrocyclized product, tetrafluoroxanthenone.

The reaction was carried out in THF by diazotizing tetrafluoroanthranilic acid with *n*-butyl nitrite in the presence of salicylic acid, and by subsequent refluxing for several hours. The main products were crystals with a melting point of 84—85 °C; unexpectedly, the compound contained four methylene groups. The structure of this compound was established, by means of the NMR and the mass spectra, as 4-(2′,3′,4′,5′-tetrafluorophenoxy)butyl salicylate (**4c**).

In the NMR spectrum three signals appeared at τ 5.58, 5.95, and 8.03 in a 1 : 1 : 2 ratio of strength; they are due to two $-OCH_2-$ groups and one $-CH_2CH_2-$ group. Other signals due to four protons appeared in the non-fluorinated benzene ring at τ 2.25—3.25, while signals due to a proton appeared in the fluorinated ring at τ 3.23—3.67. The signal of the OH proton appeared at an unusually lower magnetic field, τ −0.73; this may be supposed to have resulted from a strong intramolecular hydrogen bonding. The ^{19}F NMR spectrum showed the presence of four unequivalent aromatic fluorine atoms.

In the mass spectrum, the molecular ion, M^+ 358, is in agreement with the calculated value and the fragmentation is as is shown in Fig. 1. The base peak, *m/e* 149, corresponded to the tetrafluorophenyl fragment; another characteristic fragment peak, *m/e* 120, probably resulted from the elimination of 4-tetrafluorophenoxybutanol from the molecular ion. The **4c** structure was adequately

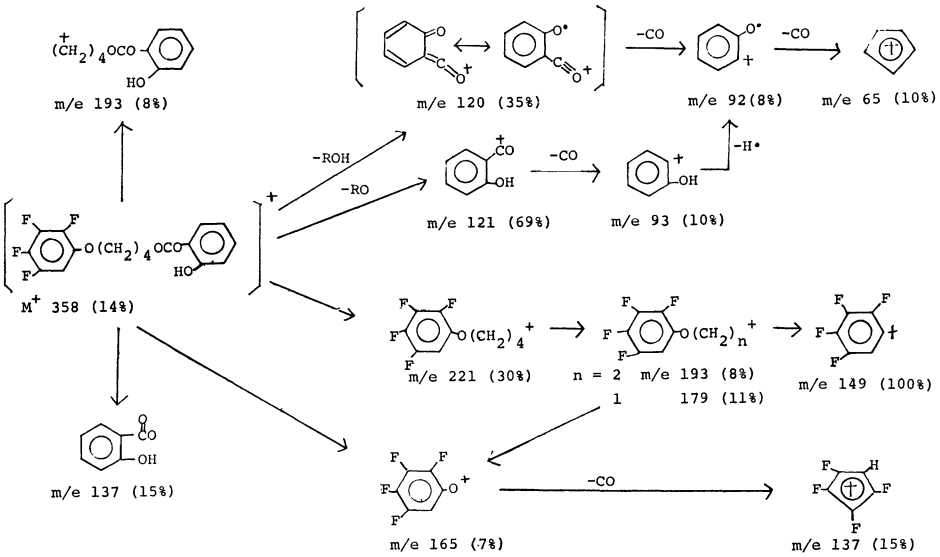


Fig. 1. MS fragmentation for **4c**.

supported by this degradation, which can be explained by the so-called ortho-effect.[9]

In this reaction it is evident that the strong electrophilic tetrafluorobenzyne initially attacked the abundant THF, prior to dilute carboxylic acid, to give **2**, followed by the ring cleavage to a betaine intermediate, **3**, which then electrophilically attacked the oxygen of carboxylic acid to give **4c**. The last two steps, **2** to **3** and **4c**, might have occurred simultaneously.

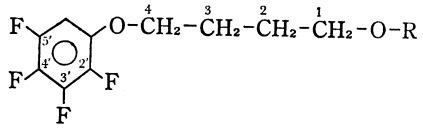
Other carboxylic acids, such as acetic and benzoic acids, were also subjected to the reaction with tetrafluorobenzyne in THF. In these cases, too, we could obtain the analogous compounds, *i.e.*, 4-(tetrafluorophenoxy)butyl acetate (**4a**) and benzoate (**4b**) respectively. The NMR spectra of these products revealed patterns similar to that of **4c** (Table 1).

The **4b** benzoate was alternately prepared by the benzoylation of 4-(2′,3′,4′,5′-tetrafluorophenoxy)butanol which had been obtained by a direct reaction between tetrafluorobenzyne and 1,4-butanediol.

Other hydroxy compounds, such as water and 3-trifluoromethylphenol, when reacted with tetrafluorobenzyne in THF gave similar results. Water yielded 4-(2′,3′,4′,5′-tetrafluorophenoxy)butanol and 2,3,4,5-tetrafluorophenol in yields of 50 and 13% respectively. The latter compound must result from the direct reaction of tetrafluorobenzyne with water, without the participation of THF.

m-Trifluoromethylphenol was chosen as the phenol to be examined, avoiding the diazo-coupling reaction

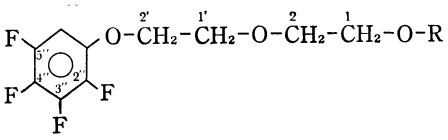
TABLE 1. PHYSICAL DATA OF



Compd. No.	R	Yield %	Bp °C/mmHg (Mp °C)	NMR chemical shift: ^{1}H (τ) 1-CH_2	2,3-$(CH_2)_2$	4-CH_2	6-H	R	^{19}F (δ ppm)[a] 2′-F	3′-F	4′-F	5′-F	F-Anal (%) Found	Calcd
4a	CH_3CO	40	120/4	5.93	8.14	5.93	3.12—3.56	8.00 (CH_3)	83.0	78.5	90.7	62.5	27.0	27.1
4b	C_6H_5CO	29	(41—42)	6.04	8.08	5.70	3.30—3.72	2.14—2.56 (C_6H_5)	81.9	77.8	89.4	62.0	22.1	22.2
4c	2-HO-C_6H_4CO	51	(84—85)	5.95	8.03	5.58	3.23—3.67	2.25—3.25 (C_6H_4) −0.73 (OH)	82.2	77.8	89.4	61.8	21.4	21.2
	H	50	110—111/3	6.02	8.21	6.34	3.23—3.65	5.78 (OH)	83.0	78.6	90.1	62.1	31.4	31.9
4d	3-CF_3-C_6H_4-	29	146—148/3	6.01	8.04	6.01	3.32—3.64	2.62—3.25 (C_6H_4)	82.2	77.8	89.4	61.8	34.9	34.8

a) The ^{19}F NMR chemical shifts are given in δ ppm from ext. CF_3CO_2H, in CCl_4.

TABLE 2. PHYSICAL DATA OF

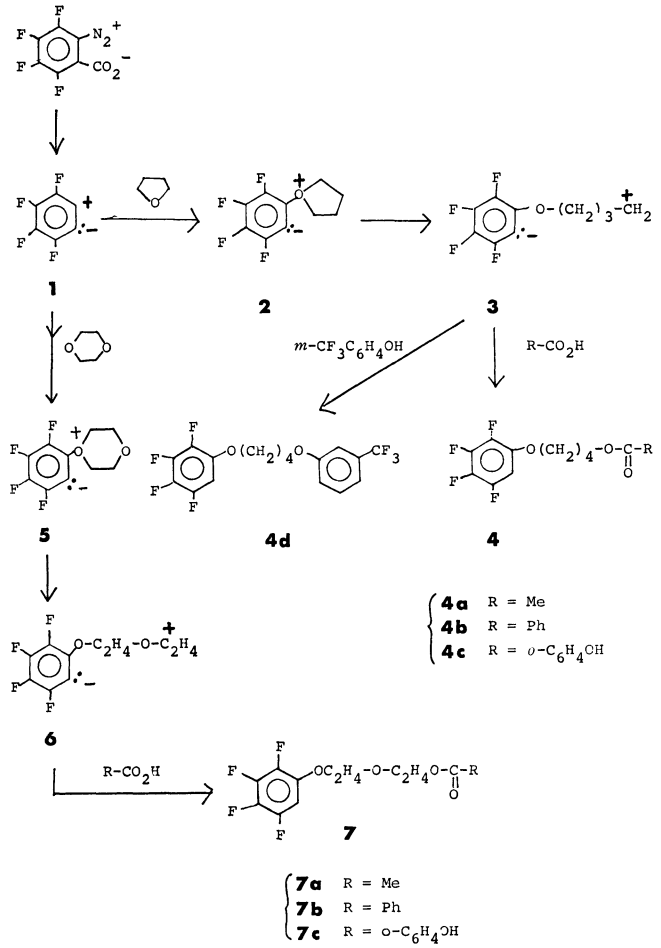


Compd. No.	R	Yield %	Bp °C/mmHg (Mp °C)	NMR chemical shift: ^{1}H (τ) 1-CH_2	2-CH_2 1′-CH_2	2′-CH_2	6″-H	R	^{19}F (δ ppm)[a] 2″-F	3″-F	4″-F	5″-F	F Anal (%) Found	Calcd
7a	CH_3CO	39	129/3	5.90	6.28	5.90	3.08—3.52	8.02 (CH_3)	81.4	77.8	89.1	61.9	25.3	25.7
7b	C_6H_5CO	29	(70.5—71.5)	5.60	6.21	5.92	3.23—3.66	2.0 —2.8 (C_6H_5)	81.8	78.1	89.1	61.9	21.8	21.2
7c	2-HOC_6H_4CO	28	(48—49)	5.52	6.16	5.88	3.20—3.62	2.24—3.14 (C_6H_4) −0.55 (OH)	81.5	77.7	88.8	61.7	19.9	20.3
	H	17	156—157/15	6.36	6.20 6.36	5.81	3.04—3.40	6.37 (OH)	82.0	78.2	89.5	61.9	30.2	29.2

a) Similar to that of Table 1.

with tetrafluorobenzenediazonium-2-carboxylate. The phenol also gave the expected product, 4-(2′,3′,4′,5′-tetrafluorophenoxy)butyl *m*-trifluoromethylphenolate (**4d**), but in a low yield.

Since analogous reactions could be expected when using dioxane instead of THF, we reacted the carboxylic acids, such as acetic, benzoic and salicylic with tetrafluorobenzyne in this solvent. In these cases, the reaction proceeded through the betaine intermediate **6**, and the resulting products were 2-[2′-(2″,3″,4″,5″-tetrafluorophenoxy)ethoxy]ethyl acetate (**7a**), benzoate (**7b**) and salicylate (**7c**).



Compound **7b** was also obtained by the benzoylation of 2-[2′-(2″,3″,4″,5″-tetrafluorophenoxy)ethoxy]ethanol, which had been prepared from tetrafluorobenzyne and diethyleneglycol.

Experimental

4-(2′,3′,4′,5′-Tetrafluorophenoxy)butyl Salicylate (4c). A solution of tetrafluoroanthranilic acid (4.18 g, 20 mmol) in THF (40 ml) was added dropwise into a mixture of *n*-butyl nitrite (2.6 g, 25 mmol), salicylic acid (13.8 g, 100 mmol), and THF (10 ml) at 55—56 °C with stirring. After refluxing for 5 hours, the solvent was distilled out under reduced pressure and the residue was dissolved in diethyl ether. The solution was then treated with a dilute aqueous sodium hydroxide solution to remove the excess salicylic acid, washed with dilute hydrochloric acid and water successively, and dried over magnesium sulfate. After the solvent had been removed, the residue was recrystallized from methanol to give crude **4c**. Sublimation gave pure crystals; mp 84—85 °C.

IR (KBr): 3388 (OH, intramolecularly H-bonded), 1661 (C=O), 1136, 1091 cm^{-1} (C–F).

4-(2′,3′,4′,5′-Tetrafluorophenoxy)butyl Acetate (4a), Benzoate (4b) and m-*Trifluoromethylphenolate (4d).* Instead of salicylic acid in the above reaction, acetic acid, benzoic acid and *m*-trifluoromethylphenol were used. When the reactions were carried out and worked-up in the same way, they gave **4a**, **4b**, and **4d** respectively (Table 1).

The benzoate (**4b**) was also obtained by the benzoylation of (2′,3′,4′,5′-tetrafluorophenoxy)butanol. Thus, a mixture of the alcohol (2.00 g), benzoyl chloride (1.18 g), and two drops of concentrated sulfuric acid was heated until the evolution of gas ceased. Upon cooling, the reaction mixture was poured onto ice water; the precipitate was separated by filtration and washed with a dilute aqueous solution of sodium bicarbonate to remove benzoic acid, thus giving crude benzoate (2.42 g). After recrystallization from petroleum ether, a pure material (mp 42—44 °C) was obtained. No depression in mp was observed on admixture with the product described above.

4-(2′,3′,4′,5′-Tetrafluorophenoxy)butanol. A solution of anthranilic acid (2.09 g) in THF (10 ml) was dropped into a mixture of *n*-butyl nitrite (1.3 g), deionized water (10 ml), and THF (10 ml) at 60 °C, and then the mixture was refluxed for 5 hr. The reaction mixture was then worked-up as usual. In addition to the main product (1.20 g, bp 110—111 °C/3 mmHg), a small amount (0.21 g) of an alkaline-soluble material was obtained. This compound was identified as 2,3,4,5-tetrafluorophenol by means of its IR spectrum.

4-(2′,3′,4′,5′-Tetrafluorophenoxy)butanol was also alternatively obtained as follows. Into a mixture of tetrafluoroanthranilic acid (10.45 g) and 1,4-butanol (50 ml), a solution of *n*-butyl nitrite (6.5 g) in dichloroethane (10 ml) was added at 50 °C. After having been refluxed for 3 hr, the reaction mixture was worked-up as usual to give the alcohol (7.50 g, 64%).

2-[2′-(2″,3″,4″,5″-Tetrafluorophenoxy)ethoxy]ethanol. Into a mixture of *n*-butyl nitrile (2.6 g), dioxane (10 ml), and deionized water (15 ml), a solution of tetrafluoroanthranilic acid (4.18 g) in dioxane (20 ml) was added at 50 °C, and then the mixture was worked-up as usual. In addition to the alcohol (0.85 g, 17%; bp 156—157 °C/15 mmHg), 2,3,4,5-tetrafluorophenol (0.37 g, 11%; bp 143—145 °C (lit. bp 145 °C[10])) was obtained as an alkaline-soluble material.

The alcohol was also prepared by the diazotization of tetrafluoroanthranilic acid (4.18 g) in diethyleneglycol (20 ml) with *n*-butyl nitrile (2.6 g). The product (2.90 g) was identified by means of its IR spectrum.

2-[2′-(2″,3″,4″,5″-Tetrafluorophenoxy)ethoxy]ethyl Acetate (7a), Benzoate (7b), and Salicylate (7c). Instead of THF in the procedure for the preparation of **4a**—**4c** described above, dioxane was used. The results are shown in Table 2. The **7b** benzoate was also prepared by the benzoylation of the alcohol with benzoyl chloride.

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