Aromatic Fluorine Compounds. IV.[1] The Introduction of More than One Fluorine Atom into the Same Ring by a Novel Method

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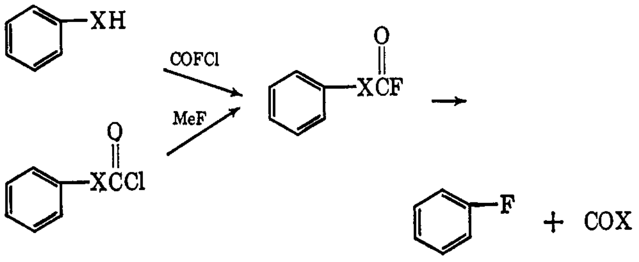
The novel method of gas phase decomposition of aromatic fluoroformates to the corresponding fluorides was extended to the introduction of more than one fluorine atom into the same nucleus. Both *m*- and *p*-difluorobenzene were prepared in one step, while, in the case of *o*-difluorobenzene, the stepwise introduction of each fluorine atom was required. The method was also successfully applied to the one-step preparation of 1,3,5-trifluorobenzene; however, the yield was very low. Attempts to prepare hexafluorobenzene were unsuccessful.

In part II of this series[2] a new method has been reported for introducing a fluorine atom into an aromatic nucleus, which can be described by Scheme I, where X is either an oxygen or a sulfur atom. Its applicability to the preparation of fluorobenzene has been demonstrated. In the preceding article[1] of this series its usefulness has been investigated for substituted aromatics. In this paper we will report the introduction of more than one fluorine atom into the same ring by this method. The preparation of *o*-, *m*-, and *p*-difluorobenzene, 1,3,5-trifluorobenzene, and hexafluorobenzene are described.

SCHEME I



Preparation of *o*-, *m*-, and *p*-Difluorobenzene.—The introduction of a second fluorine atom into an aromatic ring, already containing one fluorine atom in the *ortho* or *para* position, has been described in paper III[1] of this series. Therefore, only the single-step preparation of *m*- and *p*-difluorobenzene and the stepwise preparation of *o*-difluorobenzene will be outlined. In the Schiemann reaction, the only generally applicable method of preparing unsubstituted difluorobenzene, the yield of difluorobenzene in a single-step reaction is lower than the over-all yield in a stepwise introduction of both fluorine atoms. In the case of *p*-difluorobenzene, for example, a 27% yield was reported[3] for the single-step reaction, while the over-all yield in a stepwise preparation was 51%.[4,5]

The preparation of the intermediate *m*- and *p*-phenylene bisfluoroformate from the corresponding diol and COFCl was achieved in nearly quantitative yield. The use of a small amount of tertiary amine as a catalyst and of an inert organic solvent was advantageous. For pyrocatechol, however, the yield of *o*-phenyl bisfluoroformate was only about 50%.[6] The competitive reaction of cyclic pyrocatechol carbonate formation is more favorable, based on steric considerations and on the formation of a stable five-membered ring. After one fluoroformate group has been introduced into the molecule, the hydrogen atom of the second hydroxy group is very close to the fluoroformate group because of chelate formation with the oxygen atom of the first hydroxy group. This favors an intramolecular HF elimination. The physical and spectral properties of *m*- and *p*-phenylene bisfluoroformate are listed in Table I.

m- and *p*-Phenylene bisfluoroformate were successfully decarboxylated in a single-step reaction. Since, as has been found earlier,[2] the high-temperature vapor phase decomposition (on Pt-gauze surfaces as catalyst) gives the best results in the case of phenyl fluoroformate, the decarboxylation of the phenylene bisfluoroformates was investigated under similar reaction conditions. In the latter case, the corresponding difluorobenzene formed in yields up to 15%. The main product was the intermediate decomposition product, *i.e.*, the corresponding fluorophenyl fluoroformate. The results of these reactions are given in Table II. Since the decomposition reaction is run as a continuous flow process, the partial decomposition product, *i.e.*, fluorophenyl fluoroformate, could be easily separated and recycled. In this way considerably higher yields of the corresponding difluorobenzene could be obtained. For example, the decarboxylation of *p*-fluorophenyl fluoroformate to *p*-difluorobenzene can be achieved in yields as high as 40% per pass.

The single-step preparation of *o*-difluorobenzene from *o*-phenylene bisfluoroformate was not successful, since the latter decomposes readily to pyrocatechol carbonate and carbonyl difluoride. Therefore, a method for the stepwise introduction of two fluorine atoms in the *ortho* position was worked out and is represented in Scheme II.

The preparation, properties, and decarboxylation of *o*-bromophenyl fluoroformate and *o*-fluorophenyl fluoroformate were described earlier.[1] The hydrolysis of 2-bromofluorobenzene was done in analogy to the method described for *p*-bromofluorobenzene.[7] The yield of *o*-fluorophenol was 100% and no *o*-bromophenol was formed, proving that, under the reaction conditions applied, only the bromine atom was hydrolyzed but not the fluorine atom.

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[1] Part III: K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 4104 (1965).

[2] K. O. Christe and A. E. Pavlath, *ibid.*, **30**, 3170 (1965).

[3] G. Schiemann, *et al.*, *Ber.*, **B62**, 3035 (1929).

[4] A. Dornow and H. Theidel, *ibid.*, **88**, 1267 (1955); K. Inukai and Y. Maki, *Nagoya Kogyo Gijutsu Shikensho Hokoku*, **2**, 480 (1953); *Chem. Abstr.*, **50**, 3347 (1954).

[5] This yield also includes the nitration and consecutive reduction step.

[6] K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 1644 (1965).

[7] M. Boudaklan, *et al.*, German Patent 1,135,487 (1962).

TABLE I

PHYSICAL AND SPECTRAL PROPERTIES OF *m*- AND *p*-PHENYLENE BISFLUOROFORMATE AND 1,3,5-PHENENYL TRISFLUOROFORMATE

Compound	Yield,[a] %	Mp,[b] °C	Calcd, % C	Calcd, % H	Calcd, % F	Found, % C	Found, % H	Found, % F	F^{19} nmr[c]
p-$C_6H_4(OCOF)_2$[d,f]	100	67–68	47.55	1.98	18.80	48.05	2.43	18.95	16.5 (s)
m-$C_6H_4(OCOF)_2$[e,f]	94.5	...	47.55	1.98	18.80	47.72	2.29	18.70	16.5 (s)
1,3,5-$C_6H_3(OCOF)_3$[f]	65.5	92	40.91	1.14	21.59	41.23	1.37	21.50	16.5 (s)

[a] The yields were determined by gc ratios of the crude product before distillation or recrystallization. [b] The melting point was taken after recrystallization from hexane in the first case and from diethyl ether in the last case. [c] The chemical shift is quoted as parts per million upfield from $CFCl_3$; s = singlet. The presence of the pure *para* and *meta* compounds was also proven by proton nmr spectra. [d] Molecular weight determination by freezing point depression of benzene gave 208 (calcd 202). [e] Colorless lachrymatory liquid, bp 64° (1 mm), $n^{22}D$ 1.4563, d^{23} 1.412. [f] The infrared spectra show the characteristic fluoroformate absorptions [1840–1850 (C=O), 1220–1260 (COC), and 990–1000 cm^{-1} (C–F)] and the characteristic pattern for the corresponding substituted aromatic rings.

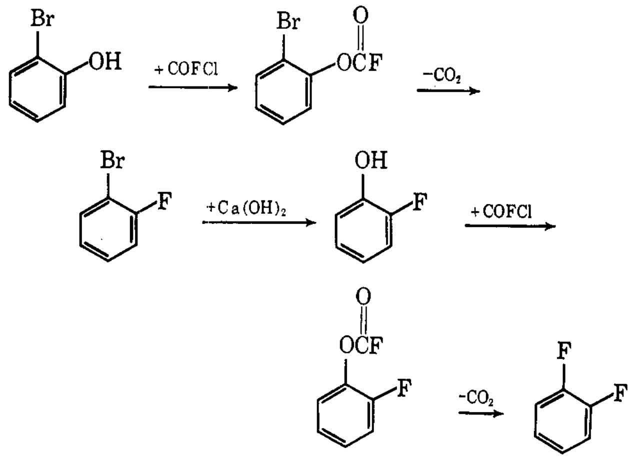
TABLE II

DECARBOXYLATION OF AROMATIC POLYFLUOROFORMATES TO THE CORRESPONDING FLUORIDES[a,b]

Starting material	Reaction temp, °C[c]	Contact time, sec	Conversion of starting material, %[d]	% yield of products[d]				Tar + decompn products
				p-$C_6H_4F_2$	*p*-$C_6H_4F(OCOF)$	*p*-$C_6H_4F(OH)$	C_6H_5F	
p-$C_6H_4(OCOF)_2$	750	3	95	5.5	16.7	9.5	0.4	67.9
	700	5	20.7	9.2	90.0	Trace	0.4	Trace
	700	10	87.6	12.8	61.7	16.2	Trace	9.3
				m-$C_6H_4F_2$	*m*-$C_6H_4F(OCOF)$	*m*-$C_6H_4F(OH)$		
m-$C_6H_4(OCOF)_2$	750	2	100	12.2	24.0	15.0	2.4	46.4
	810	1.5	100	11	1.2	4.5	3.0	80.3
	700	5–6	51	14.5	75.5	7.1	2.4	Trace
				1,3,5-$C_6H_3F_3$	1,3,5-$C_6H_3F_2(OCOF)$			
1,3,5-$C_6H_3(OCOF)_3$	770	1.5	100	Trace				
	700	3	80	Trace	Trace			

[a] All reactions were carried out at atmospheric pressure using a dry nitrogen carrier gas and a quartz tube reactor (diameter = 1 cm, length of heated zone = 33 cm) with Pt-gauze filling. [b] The vapor pressure of the fluoroformate was kept at 100 mm in all cases. [c] The reaction temperature was measured by a thermocouple on the outside wall of the tubular reactor. [d] The conversion of the starting material and the yields were determined by gc ratios of the crude product before separation.

SCHEME II



Preparation of 1,3,5-Trifluorobenzene.—The starting material, 1,3,5-phenenyl trisfluoroformate, was prepared in 65% yield from phloroglucinol and COFCl. Its physical and spectral properties are listed in Table I. Its decarboxylation to 1,3,5-trifluorobenzene was achieved; however, the yield of the latter was very low. The results of these reactions are given in Table II.

Attempted Preparation of Hexafluorobenzene.—The method worked out for the stepwise introduction of two fluorine atoms in *ortho* positions might be applicable to the simultaneous introduction of three fluorine atoms connected to the same ring. In this case the intermediate 1,3,5-tribromophenenyl trisfluoroformate would not contain any hydrogen and might be more stable against complete degradation. Therefore, hexafluorobenzene might be prepared according to Scheme III. All attempts, however, to prepare 1,3,5-tribromophenenyl trisfluoroformate were unsuccessful. Either incomplete bromination of 1,3,5-phenenyl trisfluoroformate or incomplete fluoroformylation of tribromophloroglucinol prevented further investigations.

Experimental Section

Starting Materials.—Carbonyl chloride fluoride was prepared from $COCl_2$ and AsF_3.[8] No purification of the crude COFCl (containing 90 to 95% COFCl) was required, since the presence of $COCl_2$ and COF_2 as impurities did not result in the formation of undesired by-products as long as COFCl was used in excess. All the other chemicals were purchased from supply houses.

Preparation of *p*-Phenylene Bisfluoroformate.—Hydroquinone (0.1 mole), toluene (50 ml) as solvent, and tributylamine[9] (0.5 ml) as catalyst were placed into a 150-ml stainless steel lecture bottle, equipped with a pressure gauge and a Whitey valve. Carbonyl chloride fluoride (0.63 mole) was condensed at −196° into this lecture bottle. The container was agitated 15 hr at 60° (external heating by two infrared lamps) with its contents at a pressure of 250 psi. The volatile products, mostly HCl and excess of carbonyl halides, were bled off. The product was degassed at room temperature under vacuum. The resulting light yellow solution was filtered, and the toluene was removed by vacuum distillation. The residue (20.2 g; calcd for *p*-phenylene bisfluoroformate, 20.2 g) was twice recrystallized from hexane. Its properties are listed in Table I.

Preparation of *m*-Phenylene Bisfluoroformate.—Resorcinol (0.1 mole), toluene (50 ml) as a solvent, tributylamine (1 ml) as a catalyst, and COFCl (0.72 mole) underwent reaction for 18 hr at 90° in the same way as described for hydroquinone. After removal of the volatile products, filtering, and removal of the

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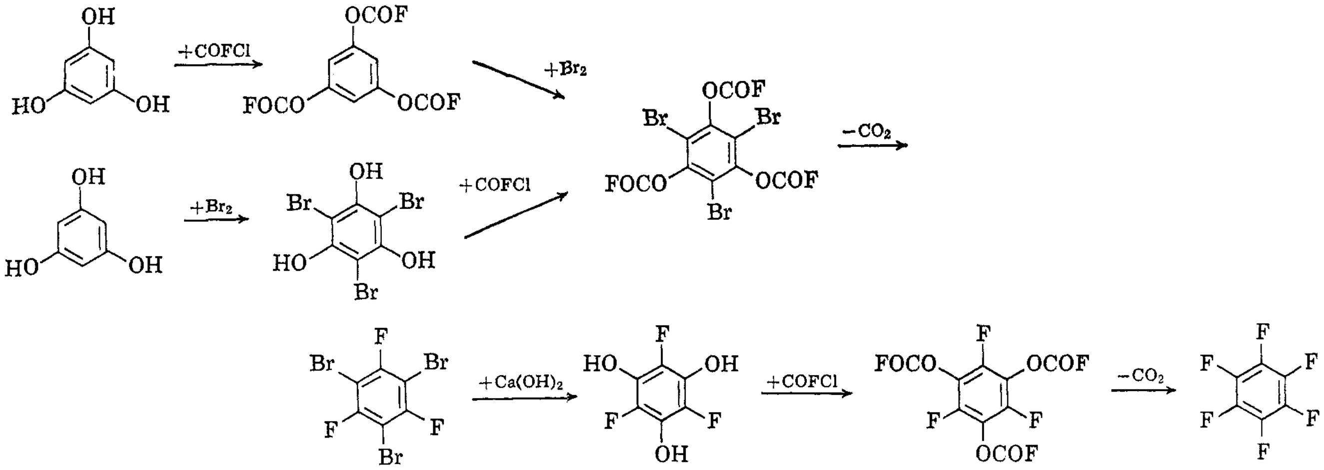
[8] K. O. Christe and A. E. Pavlath, *J. Org. Chem.*, **30**, 1639 (1965).

[9] The isomer composition of the tributylamine (purchased from Matheson Coleman and Bell) was unknown.

SCHEME III



toluene by vacuum distillation, a liquid residue (20.2 g, containing 94.5% of *m*-phenylene bisfluoroformate according to the gc ratios) was obtained and purified further by vacuum distillation. The properties of the compound are listed in Table I.

Preparation of 1,3,5-Phenenyl Trisfluoroformate.—Phloroglucinol (0.3 mole), toluene (150 ml) as a solvent, tributylamine (2 ml) as a catalyst, and COFCl (1.09 moles) underwent similar reaction for 15 hr at 80° in a 500-ml stainless steel lecture bottle. After removal of the volatile material, the solid residue was extracted with diethyl ether until the extract did not show any 1,3,5-phenenyl trisfluoroformate on the gas chromatograph. The product (52 g) was isolated from the diethyl ether solution and recrystallized from the same solvent. Its properties are listed in Table I.

Decarboxylation of the Aromatic Fluoroformates.—The same setup was used for all reactions. A stream of dry N_2, controlled by a flowmeter system, was passed through a small flask, containing the fluoroformate starting material. A fluoroformate vapor pressure of 100 mm was maintained by the external heating of the flask with an oil bath. The fluoroformate–nitrogen mixture was passed through an electrically heated quartz tube with Pt gauze as a filling. The products were quenched directly behind the exit of the tube by two cold traps, one at −78° and the other at −196°. The second trap was connected to a mercury blowoff. The reaction tube was automatically heated and its temperature was measured with a thermocouple on its outside wall. The inlet part of the setup between the fluoroformate container and the reaction tube was heated by three infrared lamps to prevent condensation of the starting material. The conversion of the starting material and the yields were determined by weighing of the used up starting material and of the collected products. The composition of the products was analyzed by gc. The compounds themselves were identified by infrared after gc separation. The results of all these reactions are summarized in Table II.

Hydrolysis of *o*-Bromofluorobenzene.—Distilled water (3 moles), *o*-bromofluorobenzene (0.05 mole), $Ca(OH)_2$ (0.05 mole), and CuO (10 mg) were placed into a 150-ml stainless steel cylinder, equipped with a pressure gauge and a valve. The cylinder was agitated for 4 hr at 230° with its contents under a pressure of 400 psi. The product was extracted with diethyl ether. The diethyl ether solution was dried with $MgSO_4$ and filtered, and the ether was removed under vacuum. According to gc analysis the residue consisted of 95.6% *o*-fluorophenol and 4.6% starting material. No *o*-bromophenol was detected.

Bromination of 1,3,5-Phenenyl Trisfluoroformate.—Bromine (25 ml) and 1,3,5-phenenyl trisfluoroformate (6.5 g) were refluxed and stirred for 3 days using a small amount of hydrogen-reduced iron as a catalyst. The bromine was removed by vacuum distillation and a dark brown oily residue remained. Elemental analysis and an infrared spectrum showed only partial bromination of the starting material.

Reaction between 1,3,5-Tribromophloroglucinol and COFCl.—Carbonyl chloride fluoride (0.5 mole), 1,3,5-tribromophloroglucinol (0.03 mole), tributylamine (1.5 ml) as a catalyst, and benzene (40 ml) as a solvent were placed into a 150-ml stainless steel lecture bottle and agitated at 100° for 20 hr. The volatile products were bled off, and the solvent was removed by vacuum distillation. A dark brown oily product was obtained, which according to its fluorine analysis (*Anal.* Calcd for 1,3,5-tribromophenenyl trisfluoroformate: F, 11.38. Found: F, 5.8.) and infrared spectrum was not the desired 1,3,5-tribromophenenyl trisfluoroformate. Attempts to isolate this compound out of the crude product were unsuccessful.

Resolution of a Racemic Substance by Ion-Exchange Chromatography[1a]

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An optically active, strong-base anion-exchange resin was prepared from L-(−)-N,N-dimethyl-α-phenethylamine and chloromethylated, cross-linked polystyrene. It was found possible to resolve partially the optical isomers of mandelic acid by the methods of frontal and displacement ion-exchange chromatography.

A number of reports appear in the literature describing the use of synthetic, optically active polymeric materials as sorbents for the chromatographic resolution of racemic substances. Grubhofer and Schleith[2] prepared a weak-base anion-exchange resin by incorporating quinine into a polymer. On passage of 0.036 *N* racemic mandelic acid in chloroform through this resin, the first fractions of the effluent after the breakthrough of mandelic acid contained 4, 7, 16, 26, 34,

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[1] (a) Taken from the Ph.D. Thesis of J. A. L., 1965. (b) To whom inquiries should be sent: University of Michigan, Flint College, Flint, Mich. 48503.

[2] N. Grubhofer and L. Schleith, *Z. Physiol. Chem.*, **296**, 262 (1954).