# Synthesis of Some Disubstituted 3,4,5,6,– Tetrafluorobenzenes [1,2]

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The preparation of 1,2,3,4-tetrafluorobenzene from 2-chloroheptafluorotoluene in a two-step synthesis is described. A new method for the hydrolysis of the trifluoromethyl group was developed using alumina and steam at high temperatures. The products obtained from the hydrolysis of 2-chloroheptafluorotoluene were 2-chloro-3,4,5,6-tetrafluorobenzoyl fluoride and 2,3,4,5-tetrafluorochlorobenzene, the decarboxylated product. The latter compound was converted to 1,2,3,4-tetrafluorobenzene by reduction with hydrogen and palladium at 280° C and atmospheric pressure. Some of the new compounds prepared, in addition to those mentioned previously, include 2-chloro-3,4,5,6-tetrafluorobenzoic acid, 2-chloro-3,4,5,6-tetrafluoroiodobenzene, and 1,2-diiodo-3,4,5,6-tetrafluorobenzene.

1. Introduction

Recently the preparation of a perfluoropolyphenyl by the condensation of 1,4-diiodo-2,3,5,6-tetrafluorobenzene with activated copper [1][3] was reported. Since the synthesis of the precursor, 1,2,4,5-tetrafluorobenzene [2] was a tedious process, consideration was given to the possibility of converting a highly fluorinated toluene derivative into a tetrafluorobenzene, with the anticipation that the symmetrical isomer would be obtained. On the basis of availability, chloroheptafluorotoluene was chosen as the starting material. This compound, obtained as a byproduct from the synthesis of perfluorotoluene [4], was first reported by McBee [3]. No structure was assigned to the chloroheptafluorotoluenes. As it will be shown subsequently, this compound is predominantly the ortho isomer, i.e., 2-chloroheptafluorotoluene (I), with small amounts of the para isomer (II) present. None of the meta isomer (III) was observed.
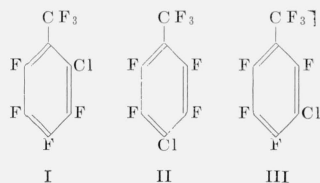
All the compounds obtained from the synthesis beginning with these materials were new and hitherto unknown. Since rearrangements were unlikely to occur during the reactions, characterization of the final tetrafluorobenzene as the 1,2,3,4-isomer established the fact that the chlorine atom was adjacent to the trifluoromethyl group in I and that it occupied the 2-position in the resulting compounds, IV to VIII. The reactions that were investigated (see scheme below), such as hydrolysis, decarboxylations, and reductions, also serve to illustrate some generally applicable methods of synthesis in the aromatic fluorocarbon series.
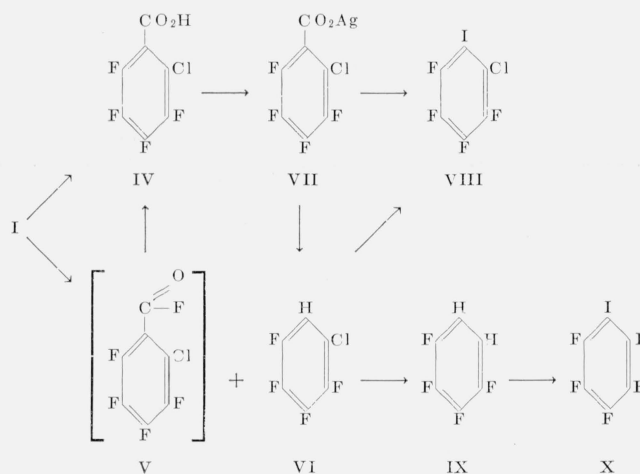
2. Results

2.1. Hydrolysis of the Trifluoromethyl Group

Methods for this type of reaction have been described for benzotrifluoride [5] and perfluorotoluene [6]. The best results were obtained by prolonged refluxing with concentrated sulfuric acid. This technique was adapted to the hydrolysis of 2-chloroheptafluorotoluene (I) and gave a 49-percent yield of 2-chloro-3,4,5,6-tetrafluorobenzoic acid (IV).

In the search for improvement a new method was developed which involved the vapor-phase hydrolysis of I by the use of alumina and steam at high temperatures. The products of the reaction were 2-chloro-3,4,5,6-tetrafluorobenzoyl fluoride (V) and 2,3,4,5-tetrafluorochlorobenzene (VI), the decarboxylated product. The former was recovered by extraction with dilute potassium hydroxide and later acidified to yield (IV), while the latter was obtained by distillation of the residual liquid. The recovered

2-chloroheptafluorotoluene (I) could then be recycled. This reaction was studied at different temperatures, in atmospheres of wet and dry nitrogen, and with different grades of alumina. Maximum conversion was obtained at 330° C. The results are shown in table 1.

The first example shows the results obtained at a lower temperature and in the absence of added moisture. However, there was sufficient water vapor remaining on the alumina to cause hydrolysis but not decarboxylation. Once the water was removed, the reaction stopped, as evidence by the high recovery of (I). With water-pumped nitrogen, i.e., by introducing traces of water, some decarboxylation occurred. The Pyrex glass furnace tube was eventually replaced by a copper tube because occasionally ring fluorine was removed by the reaction of the wet fluorocarbon with glass. This action was eliminated by the use of the copper tube.

Of special interest were the results obtained with the pellet-size alumina. At a slow input rate, a 60 percent conversion to 2,3,4,5-tetrafluorochlorobenzene (VI) was obtained. Then, by increasing the rate, i.e., increasing the nitrogen flow and raising the temperature of the vaporizer, it was possible to increase the relative yield of 2-chloro-3,4,5,6-tetrafluorobenzoyl fluoride (V). This was not surprising, however, since at the slow rate, V was in the furnace longer and hence it had more time to form a complex with the alumina, which in the presence of steam was decarboxylated. At the fast rate, then, the time in the furnace was decreased thereby reducing complex formation. The 8–14 mesh alumina had about the same activity as the pellets. The pellets were more effective than the powder-trail technique, mainly because the vapor had to pass through the reagent, resulting in better contact for reaction to occur.

An attempt was made to elucidate the mechanism by which 2,3,4,5-tetrafluorochlorobenzene (VI) was formed. This could occur either by direct removal of the trifluoromethyl as trifluoromethane or by the hydrolysis of this group, followed by decarboxylation. In one experiment, the effluent gases were collected in a liquid-nitrogen trap and analyzed in the mass spectrometer. The gas sample contained 99.6 percent of carbon dioxide, which confirms the hydrolytic mechanism.

2.2. Replacement Reactions

Several methods of replacing the carboxyl group, in the form of salts that were used so successfully by Hazeldine [7], La Zerte [8], and Henne [9] for the perfluoroaliphatic acids, have been extended to the 2-chloro-3,4,5,6-tetrafluorobenzoic acid (IV).

When an intimate mixture of silver-2-chloro-3,4,5,6-tetrafluorobenzoate (VII) and excess iodine were pyrolyzed, a 16 percent yield of 2-chloro-3,4,5,6-tetrafluoroiodobenzene (VIII) was obtained, along with an unidentified high-boiling residue (probably a coupling product). La Zerte [8] reported that silver-perfluorocaprylate undergoes a coupling reaction in 77 percent yield to $C_{14}F_{30}$. A similar reaction may be occurring with the salt VII.

An alternate route to VIII has been accomplished by an indirect approach. The decarboxylation of the silver salt VII in ethylene glycol at 170° C for 1 hr produced an 87-percent yield of the same 2,3,4,5-tetrafluorochlorobenzene (VI) that was obtained from the alumina hydrolysis reaction above. The high yield of the hydrogen compound (VI) rivals those obtained by La Zerte [8] for the aliphatic fluorocarbon hydrides. Iodination of VI in 65 percent oleum gave a 67-percent yield of 2-chloro-3,4,5,6-tetrafluoroiodobenzene (VIII).

a. Reduction

In order to obtain the tetrafluorobenzene (IX) from 2,3,4,5-tetrafluorochlorobenzene (VI), it was necessary to remove the chlorine preferentially without the elimination of any fluorine. This problem was solved neatly by passing the vaporized chloro compound VI together with hydrogen gas through a catalyst composed of 10 percent palladium mounted on activated 1/8 in. charcoal pellets at 280° C. The chlorine was removed predominantly in 70- to 90-percent yields with less than 1 percent of the fluorine eliminated. This reduction reaction should find great use as a tool in synthesis in aromatic fluorocarbon chemistry. Thus the relative ease by which 1,2,3,4-tetrafluorobenzene (IX) can be obtained from 2-chloroheptafluorotoluene (I) in a simple two-step synthesis (I→ VI→ IX) has been demonstrated.

TABLE 1. *Hydrolysis of $C_6F_4ClCF_3$ (I) over alumina*

Weight of compound	Catalyst size	Tube material	N_2 flow	Vaporizer temperature	Furnace temperature	Recovered $C_6F_4ClCF_3$	Conversion		Total time
							C_6F_4ClCOF (I)	C_6F_4ClH (VI)	
g	*Mesh*		*cm³/min*	*° C*	*° C*	*%*	*%*	*%*	*hr*
200	a 80 to 200	Pyrex	d 125	110	324	81.0	63	0	13
100	a 80 to 200	do	e 125	108	335	33.1	33.1	13.8	5.5
966	a 80 to 200	Copper	f 125	110	330	49.4	17.5	34.8	33
549	b 1/8 in. pellets	do	f 200	120	330	48.9	67.1	24.7	12
1000	do	do	f 125	110	330	63.2	22.7	60.1	35
1073	c 8 to 14	do	f 125	110	330	67.1	21.8	59.6	36

a Merck chromatographic grade. Powder trail on the bottom of the tube.
b Harshaw Puralox. Completely filled.
c Fisher Scientific. Completely filled.
d Prepurified nitrogen with no moisture added.
e Water-pumped nitrogen containing traces of water.
f Prepurified nitrogen saturated with water.

3. Discussion

The tetrafluorobenzene (IX) prepared by the above route has a boiling point of 95° C. A mass spectrometer analysis of a fractionated sample showed no observable impurities. Finger [10] stated that the 1,2,3,4-tetrafluorobenzene (IX) prepared by a different method has a boiling point slightly lower than 95° C. The other two isomers, the 1,2,4,5-[2] and the 1,2,3,5-[11] tetrafluorobenzenes, have boiling points of 88° and 83° C, respectively. Furthermore, the nuclear magnetic resonance spectra of IX, obtained by Prof. H. S. Gutowsky at the University of Illinois, have shown conclusively that the two hydrogen atoms are adjacent to one another. Also, this tetrafluorobenzene (IX) was iodinated to a new 1,2-diiodo-3,4,5,6-tetrafluorobenzene (X), mp 50.8° to 51.5° C. Previously the 1,4-diiodo-2,3,5,6-tetrafluorobenzene, mp 109° to 111° C, [1] was prepared in this laboratory. The 1,3-diiodo-2,4,5,6-tetrafluorobenzene is at present unknown. However, the existence of this product was eliminated as a possibility because of the boiling point of the precursor IX. Therefore, on the basis of its boiling point, nuclear magnetic resonance pattern, and iodinated product (X), it is shown that the tetrafluorobenzene (IX) is, indeed, the 1,2,3,4-isomer. Since this compound (IX) was prepared in considerable quantity from a chloroheptafluorotoluene of unknown isomerism, the 2-chloroheptafluorotoluene structure is assigned to (I).

A small fraction (less than 3%) of a tetrafluorobenzene, boiling point 88° to 90° C, contaminated with a trifluorobenzene of unknown structure was obtained as a byproduct. On the basis of its boiling point it was tentatively assigned the known 1,2,4,5-tetrafluorobenzene structure. This compound could have been obtained only from small amounts of the 4-chloroheptafluorotoluene (II) present in the original material.

The presence of a sizable amount of (I) among the many products obtained from the synthesis of perfluorotoluene [3, 4], can readily be accounted for by assuming that the fluorination conditions were not drastic enough to overcome the steric effects of the trifluoromethyl group. This resulted in failure to saturate the double bond adjacent to the trifluoromethyl group with fluorine, thereby leaving an unreactive chlorine atom in the molecule which could not be removed by zinc dehalogenation.

4. Experimental Procedure [4]

4.1. Hydrolysis of 2-Chloroheptafluorotoluene I

a. Sulfuric Acid Method

2-Chloroheptafluorotoluene (I), 270 g (1.07 moles), was hydrolyzed to 2-chloro-3,4,5,6-tetrafluorobenzoic acid (IV) (120 g, 49.2% yield, mp 83° to 88° C)

by McBee's method [5] for perfluorotoluene, except that only 48 hr were required. Evolution of HF during this period was fair. One recrystallization from a ligroin-toluene mixture, followed by sublimation at 80° C/10 mm afforded white plates, mp 89° to 91° C.

Analysis: Calculated for $C_7HClF_4O_2$: C, 36.79; H, 0.44; Cl, 15.51; F, 33.25. Found: C, 36.2; H, 0.31; Cl, 15.70; F, 32.8.

The anilide derivative was prepared in the usual fashion, and after several recrystallizations from aqueous alcohol yielded white leaflets, mp 207° to 208.5° C.

Analysis: Calculated for $C_{13}H_6ClF_4NO$: N, 4.61; Cl, 11.67. Found: N, 4.40; Cl, 12.10.

b. Alumina Method

The apparatus consisted of a 500-ml round-bottom flask, which served as the vaporizer, with a side arm attached to a horizontally mounted copper tube furnace (30 in. long, 1⅛ in. diam) by means of a 14/20-mm ball-and-socket joint. The outlet of the furnace was connected to a 500-ml round-bottom receiver containing a stopcock at the bottom for drainage. The vaporizer was fitted with a 24/40-mm through-joint and the lower portion extended almost to the bottom of the flask. The upper end of this joint was Y-shaped. One side was used for filling the vaporizer, while the other side was connected to a gas dispersion trap containing 400 ml of water from which the nitrogen acquired its moisture.

In a typical run, when the furnace had reached the desired temperature (330° C), 1 kg of 2-chloroheptafluorotoluene (I) was placed in the vaporizer maintained at 120° C. It was carried into the furnace by the aid of the wet nitrogen. The rate was controlled by the nitrogen flow and the temperature of the vaporizer bath. The products (899 g) were collected in the receiver maintained at room temperature. They were shaken with three 200-ml portions of 10 percent potassium hydroxide to remove the 2-chloro-3,4,5,6-tetrafluorobenzoyl fluoride (V) as the potassium salt of the acid (IV). Acidification of the combined basic solutions afforded 85 g (22.7% conversion, based on reacted I) of 2-chloro-3,4,5,6-tetrafluorobenzoic acid (IV), mp 88° to 90° C. The base insoluble liquid was washed with 500 ml of water, dried (Na_2SO_4), and distilled. There was obtained 161 g (60%, based on reacted I) of 2,3,4,5-tetrafluorochlorobenzene (V), boiling point 121.5° to 123° C; $n_D^{20} = 1.4391$; $D_{24}^{24} = 1.534$.

Analysis: Calculated for C_6HClF_4: H, 0.54; Cl, 19.21. Found: H, 0.50; Cl, 18.90. The recovered 2-chloroheptafluorobenzene, 632 g, was then recycled.

The crude acid fluoride V (boiling point 161° to 164° C) reacted readily with cold concentrated ammonium hydroxide to form the 2-chloro-3,4,5,6-tetrafluorobenzamide, mp 101° to 103° C after two recrystallizations from 50 percent ethanol.

Analysis: Calculated for $C_7H_2ClF_4NO$: C, 36.9; Cl, 15.6; F, 33.4; N, 6.15. Found: C, 36.9; Cl, 15.7; F, 34.0; N, 6.1.

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[4] Boiling points and melting points are not corrected. Chemical analyses were performed by Messrs. Paulson and Machlan, and mass spectrometer analyses by Miss Edith Quinn.

4.2. Silver-2-Chloro-3,4,5,6-Tetrafluorobenzoate (VII)

Fifty grams (0.22 mole) of the acid IV was dissolved in excess dilute NH_4OH. When the excess ammonia was removed by boiling, a solution of 50 g (0.30 mole) of silver nitrate in 75 ml of water was added with stirring. The mixture was cooled, and the silver salt (VII) was collected by filtration. After washing with 60 ml of cold distilled water, 50 ml of cold methanol, and 100 ml of petroleum ether, the salt (VII) was dried in an oven at 110° C for 72 hr and then for 24 hr more over Drierite. The dried silver salt (VII) weighed 60.5 g; 82-percent yield.

4.3. 2-Chloro-3,4,5,6-Tetrafluoroiodobenzene (VIII)

a. Direct Method

Into a 250-ml round-bottom flask was placed an intimate mixture of 30 g (0.09 mole) of silver-2-chloro-3,4,5,6-tetrafluorobenzoate (VII) and 90 g (0.35 mole) of iodine. The flask was fitted with a reflux condenser which was attached to a solid carbon dioxide trap leading to a mineral-oil bubbler. The reaction was initiated by gently heating the upper edges with a Bunsen burner. The heating was gradually applied around the flask and continued until the reaction ceased. The flask was cooled, and the contents extracted several times with ether. The combined ether solutions were successively washed with 50-ml portions of 10 percent sodium bisulfite, 10 percent sodium carbonate, water, and 10 percent hydrochloric acid, water, and finally dried over anhydrous calcium chloride. After removal of the solvent and distillation of the residue, there was obtained 4.5 g (16.2% yield) of 2-chloro-3,4,5,6-tetrafluoroiodobenzene (VIII), boiling point 71° to 72° C/6 mm; $n_D^{20} = 1.5349$.

Analysis: Calculated for C_6F_4ClI: C, 23.21; F, 24.50; I, 40.83. Found: C, 23.20; F, 24.50; I, 41.95. There was obtained also 2 g of a high-boiling residue (150° to 200° C/1 mm) which has not been identified, but may possibly be a coupling product.

b. Indirect Method

First Step: 2,3,4,5-Tetrafluorochlorobenzene (VI). Thirty grams (0.09 mole) of the silver salt (VII) and 15 g of ethylene glycol were placed into a 250-ml flask, fitted with a reflux condenser leading to a solid carbon dioxide trap. The flask was inserted gradually into a Wood's-metal bath at 160° C. Marked refluxing of the product was evident after about 10 min., and the reaction appeared to be complete after 20 min. However, to insure completion, the temperature was slowly raised to 170° C for 1 hr more. The mixture was cooled to below 100° C and the apparatus rearranged for distillation. The 2,3,4,5-tetrafluorochlorobenzene (VI) distilled at 122° to 123° C, weight 14.3 g (86.5% yield); $D_{24}^{24} = 1.536$: $n_D^{20} = 1.4396$.

Second step: Into a 100-ml three-necked flask, fitted with a stirrer, dropping funnel, and reflux condenser, were placed 13 g (0.05 mole) of iodine and 15 ml of 65 percent fuming sulfuric acid. To the stirred reaction mixture was added 6 g (0.0325 mole) of 2,3,4,5-tetrafluorochlorobenzene (VI) dropwise over a ½-hr period. When the addition was completed, the stirred mixture was heated at 60° C in a water bath for 2 hr. The reaction mixture was cooled, poured onto 50 g of ice, and decolorized by the addition of 100 ml of 10 percent aqueous sodium bisulfite. An ether extraction, followed by drying (Na_2SO_4) and distillation, afforded 6.83 g (66.9% yield) of 2-chloro-3,4,5,6-tetrafluoroiodobenzene (VIII), boiling point 70° to 72° C/5 mm.

4.4. 1,2,3,4-Tetrafluorobenzene

For the reduction of 2,3,4,5-tetrafluorochlorobenzene (VI) the same apparatus was used as described above for the alumina method of hydrolysis, except that the furnace tube was made of 20 mm Pyrex tubing and only a 5-in. section contained the catalyst. The gas dispersion trap contained concentrated sulfuric acid, instead of water, for drying the hydrogen. Twenty grams of the moist catalyst (10% palladium on ⅛ in. activated charcoal pellets)[5] were placed in the furnace and preheated at 280° C for 2 hr in the hydrogen atmosphere. When the water was removed, 123 g (0.66 mole) of VI was placed in the vaporizer maintained at 110° C. The hydrogen flow rate was adjusted to 100 cm³/min, and 4 hr were required to complete the run. The products (97 g.) were washed with three 100 ml portions of water, dried (Na_2SO_4), and distilled. There was obtained 77.2 g (77% yield) of 1,2,3,4-tetrafluorobenzene (IX); boiling point 94.8–95° C; $n_D^{20.2} = 1.4095$; $D_{23.5}^{23.5} = 1.401$. No impurities were observed from the mass spectrometer analysis.

Analysis: Calculated for $C_6H_2F_4$: C, 48.0; H, 1.3. Found: C, 48.4; H, 1.4.

There was also obtained a small forerun, 3 g., boiling point 88° to 90° C; from the mass spectrometer analysis it was found to be a mixture of 60 percent tetrafluorobenzene (presumably the 1,2,4,5-isomer) and 40 percent trifluorobenzene of unknown structure. These products were not further investigated.

4.5. 1,2-Diiodo-3,4,5,6-Tetrafluorobenzene (X)

The iodination of 1,2,3,4-tetrafluorobenzene (IX) was performed by the same procedure as described for the 1,2,4,5-isomer [1] except that the following quantities were used: 250 g (1.66 moles) of IX 454

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[5] Columbian grade, 4 to 6 mesh, CXAL, activated carbon, Carbide and Carbon Company.

g (1.79 moles) iodine, and 1.3 kg 65 percent fuming sulfuric acid. The 1,2-diiodo-3,4,5,6-tetrafluorobenzene (X) obtained after recrystallization from 60 percent ethanol-water mixture weighed 455 g, 67-percent yield, mp 50.5° to 51.8° C (white plates).

Analysis: Calculated for $C_6F_4I_2$: I, 63.1. Found: I, 62.3.

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5. References

[1] M. Hellmann, A. J. Bilbo, and W. J. Pummer, J. Am. Chem. Soc. **77,** 3650 (1955).
[2] G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort, and R. R. Blough, J. Am. Chem. Soc. **73,** 145 (1951).
[3] E. T. McBee, V. V. Lindgren, and W. B. Ligett, Ind. Eng. Chem. **39,** 379 (1947).
[4] R. E. Florin, W. J. Pummer, and L. A. Wall, J. Research NBS **62,** (1959) RP2938.
[5] G. M. LeFave, J. Am. Chem. Soc. **71,** 4148 (1949).
[6] E. T. McBee and E. Rapkin, J. Am. Chem. Soc. **73,** 1366 (1951).
[7] R. N. Hazeldine, J. Chem. Soc. **1951,** 584.
[8] J. D. La Zerte, L. J. Hals, T. S. Reid, and G. H. Smith, J. Am. Chem. Soc. **75,** 4525 (1953).
[9] I. Auerbach, F. H. Verhoek, and A. L. Henne, J. Am. Chem. Soc. **72,** 299 (1950).
[10] G. C. Finger, R. E. Oesterling, and R. H. White, paper presented before the Division of Organic Chemistry at 130th Meeting of the American Chemical Society, Atlantic City, N.J., September 1956.
[11] G. C. Finger, F. H. Reed, and R. E. Oesterling, J. Am. Chem. Soc. **73,** 152 (1951).