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**AROMATIC FLUORINE CHEMISTRY. PART 1. 3,4-DIFLUOROBENZOIC ACID AND DERIVATIVES VIA 3,4-DIFLUOROBENZOTRIFLUORIDE**

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**SUMMARY**

The preparation of 3,4-difluorobenzotrifluoride from 3,4-dichlorobenzotrifluoride by a KF exchange reaction is described. The conversion of 3,4-difluorobenzotrifluoride to 3,4-difluorobenzoic acid and derivatives is also reported.

**INTRODUCTION**

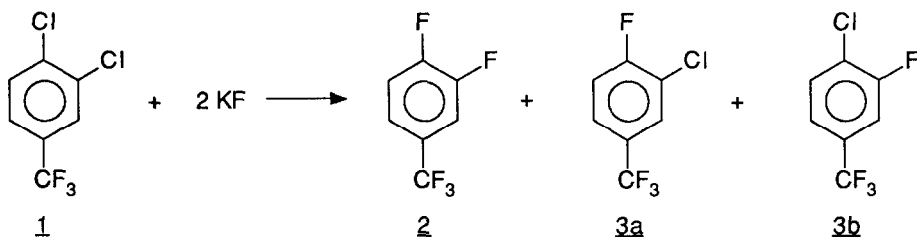
Derivatives of 3,4-difluorobenzoic acid are useful precursors for bioactive compounds [1]. We now describe the preparation of 3,4-difluorobenzotrifluoride and its conversion to 3,4-difluorobenzoic acid and derivatives.

**RESULTS AND DISCUSSION**

**Preparation of 3,4-Difluorobenzotrifluoride**

The synthesis of 3,4-difluorobenzotrifluoride (2) has been reported by Musgrave [2] and coworkers from the pyrolysis of 2-(trifluoromethyl)-4,5,7,7,8,8-hexafluorobicyclo (2.2.2.)octa-2,5-diene. A recent patent application also describes the preparation of 2 by hydrogenolysis of 3,4,5-chlorodifluorobenzotrifluorides with Raney Ni in methanol [3].

Since 3,4-dichlorobenzotrifluoride, **1**, is a readily available potential precursor to **2**, the KF exchange on **1** was investigated. The results are summarized in Table 1.



Initial experiments with cesium fluoride in refluxing dimethyl sulfoxide gave the desired product **2** along with the intermediate fluorochloro isomers, **3a** and **3b**. The latter were characterized by <sup>19</sup>F NMR analysis [4]. However, the lower volatility of the product and intermediates, as well as the expense of CsF, suggested that KF with 1-methyl-2-pyrrolidinone (NMP) under pressure would provide a practical alternative. The results in Table 1 show that respectable yields and mass balances are obtained when the reaction is carried out in NMP at elevated temperatures. At 265°C, an 86% yield of fluorinated products is obtained with a ratio of difluoro:monofluoro of 0.76. Increasing the temperature to 275°C decreases the yield to 71% but increases the above mentioned ratio to 1.30. The results of Table 1 also show that increasing the temperature from 250°C to 285°C results in a gradual decrease in the mass balance of aromatic compounds. When subjected to the reaction conditions of 275°C for 24 hours, *i.e.* KF in NMP, **2** undergoes ~20% decomposition. This result would indicate that continuous removal of **2** would give a near quantitative yield of the desired product.

1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)pyrimidone and 1,3-dimethyl-2-imidazolinone were also found to be comparable solvents for the exchange reaction. Benzonitrile, tetramethylene sulfone, and 1-cyclohexyl-2-pyrrolidinone were also briefly investigated and found to give slower rates of exchange.

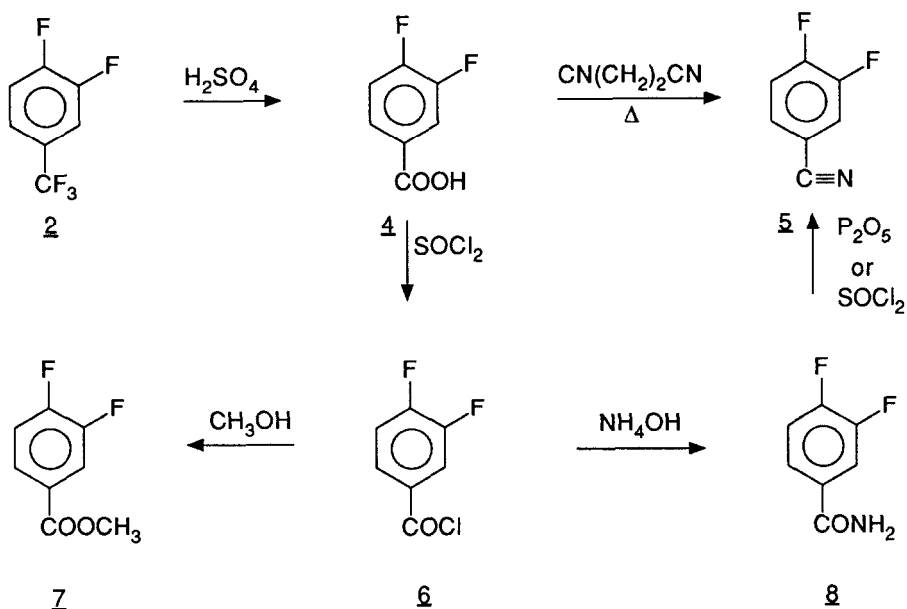
### Conversion of **2** to 3,4-Difluorobenzoic Acid and Derivatives

The conversion of **2** to 3,4-difluorobenzoic acid, **4**, and derivatives are outlined in Scheme 1. Hydrolysis of **2** in concentrated sulfuric acid as described by LeFeve [5] gave 3,4-difluorobenzoic acid in 86% yield. When heated in excess 1,4-dicyanobutane

TABLE 1  
Preparation of 3,4-Difluorobenzotrifluoride (**2**)

Temp. (°C)	Time (Hr)	Solvent* (mL)	Reactants (Mol) KF	1	2	Products (Mol)		Mass Balance
						3a+3b	2:3a+3b	
250	24	NMP (250)	0.80	0.20	0.047	0.156	0.30	101
260	24	NMP (250)	0.80	0.20	0.054	0.120	0.45	87
265	24	NMP (250)	0.80	0.20	0.074	0.098	0.76	86
275	24	NMP (250)	0.40	0.20	0.081	0.062	1.30	71
285	24	NMP (250)	0.80	0.20	0.087	0.061	1.42	74
240	24	DMP (140)	0.40	0.20	0.026	0.109	0.24	71
250	24	DMP (125)	0.40	0.10	0.020	0.056	0.35	76
260	24	DMP (250)	0.80	0.20	0.053	0.083	0.64	68
275	24	DMP (250)	0.80	0.20	0.083	0.031	2.65	57
260	24	DME (125)	0.40	0.10	0.260	0.057	0.46	85

\*NMP = 1-methyl-2-pyrrolidinone; DMP = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidone (N,N-dimethylpropylene urea);  
DME = 1,3-dimethyl-2-imidazolinone (N,N-dimethylethylene urea)



Scheme 1.

as reported by Toland and Ferstandig [6], 3,4-difluorobenzonitrile distilled from the reaction mixture in 94% yield. The acid, 4, was converted to the corresponding acid chloride (6), ester (Z), and benzamide (8) by classical methods.

## EXPERIMENTAL

### KF Exchange Reaction

The exchange reactions were carried out in a 600 ml Hastelloy C Parr reactor equipped with a magnetic drive mechanical stirrer and a sample valve. Potassium fluoride was dried in vacuo (1 mm) for a minimum of 24 hours at  $150^\circ\text{C}$  and loaded 'hot' into the reactor. The solvents were purified by distillation from calcium hydride. The analyses were carried out on a Hewlett-Packard 5700A Gas Chromatograph equipped with 6 foot column packed with 10% OV-17 Gas Chrome Q 100/120 (available from Anspec Company, Inc., 122 Enterprise Drive, P. O. Box 7044, Ann Arbor, MI 48107, U.S.A.). 1,3-Diethylbenzene was employed as the internal standard.

### Purification of 3,4-Difluorobenzotrifluoride (2)

The crude reaction mixture from the Parr reactor was filtered to remove inorganic salts. The filtrate was distilled with a 12" Vigreux column to separate the benzotrifluorides from the bulk of the solvent. The crude product mixture was distilled in a Nester-Faust spinning band column to give 3,4-difluorobenzotrifluoride (bp 100-102°C) and 4-fluoro-3-chlorobenzotrifluoride, bp 133-135°C). The latter also contained some of the isomeric 4-chloro-3-fluorobenzotrifluoride. MS (70 ev) m/z: 182 ( $M^+$ , calcd for  $C_7H_3F_5$ : 182); m/z: 198 ( $M^+$ , calcd for  $C_7H_3ClF_4$ : 198).

### Preparation of 3,4-Difluorobenzoic Acid (4)

3,4-Difluorobenzotrifluoride (20.0 g, 1.117 mol) and 40 g of concentrated sulfuric acid were placed in a 300 ml Hastelloy C reactor equipped with a magnetic drive. The reactor was sealed and pressure tested, then heated and stirred for 2 hours at 80°C. The reactor was cooled, vented, and the contents added cautiously with stirring to an ice/water mixture (~300 ml) to precipitate the product. Filtration and drying afforded 15.84 g (86%) of 3,4-difluorobenzoic acid.

### Preparation of 3,4-Difluorobenzamide (8)

3,4-Difluorobenzoic acid (10 g, 0.063 mol) and thionyl chloride (10 ml) were refluxed for 2 hours in benzene (40 ml). The excess thionyl chloride and benzene were removed on a Büchi evaporator and the residual acid chloride diluted with 25 ml of tetrahydrofuran and added dropwise to a stirred solution of concentrated ammonium hydroxide at 10-20°C. The excess  $NH_3$  and  $H_2O$  were evaporated on a Büchi evaporator and the product isolated by extraction with ethyl acetate. After drying over  $MgSO_4$  and evaporation of solvent, the residue was recrystallized from ethyl acetate-hexane to give 9.0 g (91%) of product with m.p. 130-132°C. MS (70 ev) m/z: 157 ( $M^+$  calcd for  $C_7H_5F_2NO$ : 157).

### Preparation of 3,4-Difluorobenzonitrile (5)

3,4-Difluorobenzoic acid (10 g, 0.063 mol) and 20 g of 1,4-dicyanobutane were heated at 250°C as described by Toland and Ferstandig [6] to afford a 94% yield of 3,4-difluorobenzonitrile.

### Preparation of 2 with CsF

3,4-Dichlorobenzotrifluoride (107.5 g, 0.5 mol), cesium fluoride (228 g, 1.5 mol), anhydrous potassium carbonate (3 g) and dimethyl sulfoxide (600 ml) were charged to 2 liter flask equipped with thermometer inlet, distillation column and fraction collector. The contents were heated under gentle reflux for 13 hours. During this time, 4 fractions were collected with boiling point ranges of 108-132°C. The fractions were combined and redistilled to give a 44.5 g (49%) of **2**, bp 101-103°C. The 3-chloro-4-fluoro isomer showed ring fluorine resonance at 53.3 ppm downfield from hexafluorobenzene in  $\text{CDCl}_3$ , and the  $\text{CF}_3$  resonance was at 101.7 ppm. The corresponding peaks for the 4-chloro-3-fluoro derivative were at 50.3 and 101.0 ppm. Generally, when pure **1** was treated with either CsF or KF, the monofluoro fraction contained 12-18% of the 3-fluoro isomer [4].

### Preparation of Methyl 3,4-Difluorobenzoate (7)

3,4-Difluorobenzoic (25 g, 0.16 g), thionyl chloride (40 ml) and dimethyl formamide (0.25 ml) were stirred overnight in benzene (100 ml). The solvent and excess thionyl chloride were evaporated on a Büchi evaporator. The residue was diluted with methanol (100 ml) and stirred for 1 hour at room temperature. The excess methanol was evaporated on a Büchi evaporator and the residue distilled to give 20.5 g (74% product, bp 70°C (22 mm))[7].

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