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# Synthesis of 4-Fluororesorcinol and 4-Trifluoromethylresorcinol

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## ABSTRACT

*Less expensive, safer, and easily scaled-up methods for the synthesis of 4-fluororesorcinol and 4-trifluoromethylresorcinol have been established, including two methods to give the former compound. One involves the reaction of Selectfluor™ reagent with 1,3-dimethoxybenzene to give 2,4-dimethoxy-1-fluorobenzene followed by hydrolysis to give 4-fluororesorcinol. The overall yield of this two-step reaction is 54%. In the second case, when Selectfluor reagent is reacted directly with resorcinol, under the best reaction conditions, 4-fluororesorcinol is obtained in 66% yield. It is, however, very difficult to separate the starting material from the mono- and difluororesorcinol products. Consequently, the two-step method is the method of choice to prepare 4-fluororesorcinol. The trifluoromethyl group was incorporated into 2,4-dimethoxy-1-iodobenzene to form 1,3-dimethoxy-4-trifluoromethylbenzene followed by mild hydrolysis to give 4-trifluoromethylresorcinol.* © 1998 John Wiley & Sons, Inc. Heteroatom Chem 9:229–239, 1998

## *INTRODUCTION*

The introduction of the fluoro or trifluoromethyl group into organic molecules has recently been the subject of increasing research activity. In particular, the replacement of hydrogen by fluorine or trifluoromethyl groups in aromatic systems confers increased lipophilicity and acidity and modified hydrogen bonding properties that often lead to dramatic changes in their bioactivities. This has resulted in interest in the development of cost-effective and convenient routes to fluorinated or trifluoromethylated aromatic molecules. Recently, several advances in organofluorine chemistry have been translated into products of medicinal importance because of the physiochemical properties the F atom imparts to these products [1]. In this article, we describe our work concerning the synthesis of 4-fluororesorcinol and 4-trifluoromethylresorcinol. 4-Fluororesorcinol and 4-trifluoromethylresorcinol are useful for the preparation of polyfluorinated ion-exchange resins [2a–f]. There is much interest in the biochemistry of other fluorinated catechols and their interactions with chlorocatechol dioxygenase [3a]. Fluorinated catechols have also been used as building blocks for the incorporation of $^{18}F$ into compounds useful as biologically active tracers [3b].

## *RESULTS AND DISCUSSION*

Although electrophilic fluorination of aromatic compounds has been studied over many years [4a], there are only a few reported routes to 4-fluororesorcinol (**1**) using this technique. In 1986, Patrick reported the synthesis of this compound by reacting cesium fluoroxysulfate ($CsSO_4F$) with an activated aromatic system [4b]. Boron trifluoride was employed to catalyze the reaction between $CsSO_4F$ and resorcinol

Dedicated to Prof. William E. McEwen on the occasion of his seventy-fifth birthday.

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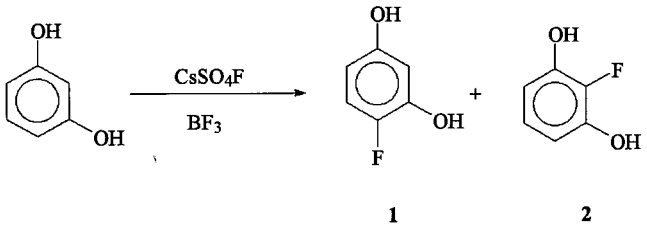
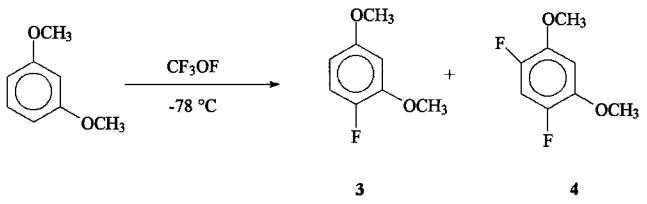
[4c] but gave a mixture of **1** and **2** in a ratio of 3:1 (Scheme 1) with a best conversion yield of only 53%. In addition, the separation of **1** and **2** from the reaction mixture for large-scale preparations is difficult because of their very similar properties.




**1** **2**

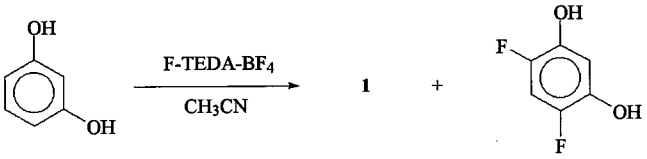
In 1988, Belanger and Darling [5] reported the synthesis of 4-fluororesorcinol (Scheme 2) by direct fluorination of 1,3-dimethoxybenzene with trifluoromethyl hypofluorite ($CF_3OF$) in Freon 11 at −78°C to give 2,4-dimethoxy-1-fluorobenzene (**3**) in a yield of 68%. The ratio of (**3**) to (**4**) by this method is 5.5:1. Subsequently, **3** is demethylated by heating under reflux with 48% HBr in acetic acid to give 4-fluororesorcinol (**1**) in 87% yield. At the same time, these researchers reported the fluorination of 2,6-dimethoxyacetophenone with trifluoromethyl hypofluorite ($CF_3OF$) in Freon 11 at −78°C leading to the formation of 2,6-dimethoxy-3-fluoroacetophenone. Subsequent heating under reflux in 48% HBr in acetic acid gave 4-fluororesorcinol in an overall yield of 74%. More recently, the use of $CF_3OF$ as an electrophilic fluorinating reagent has declined because of the development of safer, easier to use, and more readily available reagents.



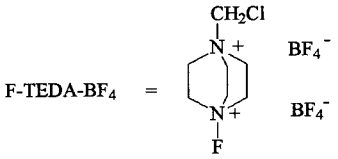

**3** **4**

**3** HAc:HBr (1:1) **1**

In our work, we sought an off-the-shelf synthetic method for the preparation of 4-fluororesorcinol that would be more convenient, that would not involve gas-phase reaction, and that could be easily scaled up. F-TEDA-$BF_4$ (1-chloromethyl-4-fluoro-1,4-diazabicyclo[2,2,2]octane bis(tetrafluoroborate)-Air Products) is a safe, easy-to-use, electrophilic fluorinating reagent, especially for aromatic systems. In order to determine the optimum reaction conditions for fluorination, we selected F-TEDA-$BF_4$ and resorcinol (Scheme 3) or 1,3-dimethoxybenzene as the starting materials. The reaction conditions tried with resorcinol as the starting material and the percentage conversions are reported in Table 1. Based on $^1H$ and $^{19}F$ NMR spectra, the maximum yield obtained is 66%. When working up the reaction mixture, we encountered major separation problems. Many routes to separate the two materials (compounds **1** and **5**) were attempted in order to obtain the pure monofluoro compound. Although column chromatography was found to be the best method for the separation of the products, it is still not easy to obtain **1** pure because of the similar structures and the very close $R_f$ values of the three major components (**1, 5,** and resorcinol). Monofluororesorcinol (**1**) and difluororesorcinol (**5**) are colorless solids.




**5**




In a second method, the target compound, 4-fluororesorcinol, was synthesized in two steps (Scheme 4). 2,4-Dimethoxy-1-fluorobenzene was first obtained by the reaction of 1,3-dimethoxybenzene with F-TEDA-$BF_4$. The reaction mixture was then separated by column chromatography to obtain the monofluorocompound. The final product **1** was prepared by the acid hydrolysis of 2,4-dimethoxy-1-

**TABLE 1** Yield of 4-Fluororesorcinol **(1)** and 4,6-Difluororesorcinol **(5)** under Various Reaction Conditions Using F-TEDA-$BF_4$

| | *Yield (%)*[a] | |
|---|---|---|
| *Reaction Conditions* | *4-Fluororesorcinol* (**1**) | *4,6-Difluororesorcinol* (**5**) |
| RT 10 hours | 55 | 22 |
| −5°C, 10 hours | 66 | 13 |
| −40°C, 10 hours | 60 | 6 |

[a]Based on $^1H$ and $^{19}F$ NMR spectra of the mixture.

fluorobenzene and purified by column chromatography on silica gel.

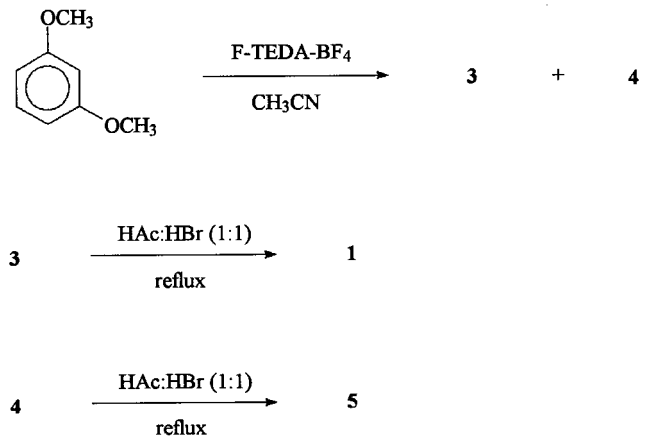
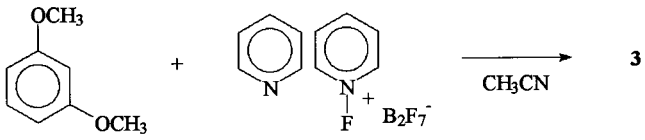



Table 2 shows the yields obtained under different reaction conditions. When the reaction of 1,3-dimethoxybenzene with F-TEDA-$BF_4$ was tested, we found the yield of **4** is directly related to the reaction temperature. If the temperature is less than −15°C, the conversion is very low. The reaction mixture can be separated by chromatatron or by column chromatography. This method can be scaled up easily. After demethylating **3** by refluxing with 48% hydrobromic acid in acetic acid, 4-fluororesorcinol was obtained in 90% yield (overall yield = 54%). Under similar hydrolytic conditions, **4** can be easily converted to 4,6-difluororesorcinol (**5**) in 90% yield (overall yield = 22.5%).

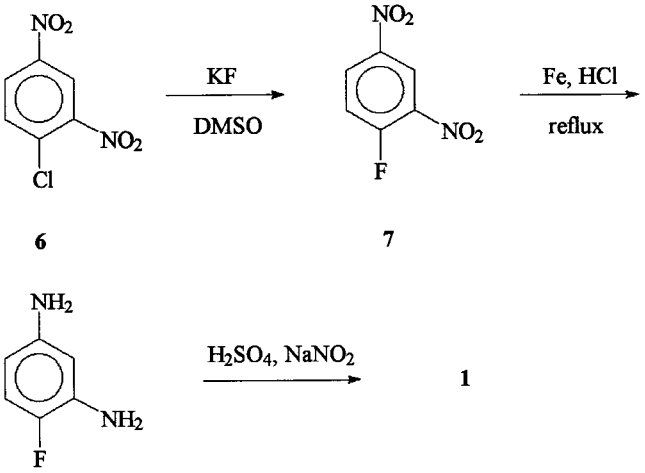
Other fluorinating reagents were tried in order to obtain higher yields and better selectivities. However, after different test reactions, we have not found any other equivalent fluorinating reagent. In general, the reactivity is too low to fluorinate the aromatic compounds of interest here. Scheme 5 shows the reaction of 1,3-dimethoxybenzene with Accufluor™NFPy (*N*-fluoropyridinium pyridine heptafluorodiborate). Table 3 shows the different reaction conditions and the percentage conversion of this reaction.

**TABLE 2** Yield of 2,4-Dimethoxy-1-fluorobenzene **(3)** and 1,5-Difluoro-2,4-dimethoxybenzene **(4)** from the Reaction of F-TEDA-$BF_4$ with 1,3-Dimethoxybenzene

| *Reaction Conditions* | *Yield (%)* | |
|---|---|---|
| | **3** | **4** |
| Reflux, 3 hours | 50 | 32 |
| 0°C, 10 hours | 60 | 25 |




Another approach was tested for the preparation of 4-fluororesorcinol (Scheme 6). 1-Chloro-2,4-dinitrobenzene was converted to 2,4-dinitro-1-fluorobenzene by reaction with KF in DMSO at 95°C for 2.5 hours. The pure product was obtained in a 64% yield by recrystallization from ethanol. The 2,4-dinitro-1-fluorobenzene was reacted with powdered iron and HCl at reflux, which resulted in the reduction of the nitrogroups to amines [6]. The product, 2,4-diamino-1-fluorobenzene, was obtained in a yield of 31.7%. The final product (**1**) was isolated in 35% yield after reaction of (**8**) with 35% $H_2SO_4$ and $NaNO_2$.



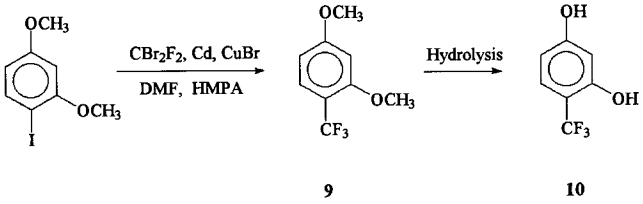

Aromatic compounds that contain trifluoromethyl substituents have very important applications in medicinal and agricultural fields [7a]. A novel route to trifluoromethylation makes use of cadmium and zinc reagents [7b]. On the other hand, Urata and Fu-

**TABLE 3** Percentage Conversion of 1,3-Dimethoxybenzene to Give 2,4-Dimethoxy-1-fluorobenzene **(3)** Using Accufluor NFPy

| *Reaction Conditions* | *Conversion (%)*[a] *2,4-Dimethoxy-1-fluorobenzene* (**3**) |
|---|---|
| RT, 3 days | no reaction |
| 60°C, 2 days | 5 |
| 80°C, 4 hours. The reaction mixture turned black perhaps due to decomposition of the fluororeagent. | |

[a]Based on the $^1H$ and $^{19}F$ NMR spectra of the mixture.

chikami [7c] reported convenient trifluoromethylation of organic halides with $CF_3SiR'_3/F^-/Cu(I)$ under mild reaction conditions. At the same time, Chen et al. [7d] treated halogen compounds, RX, with methylfluorosulfonyldifluoroacetate and copper powder in DMF to prepare the corresponding trifluoromethylation products in good yield. Trifluoromethylation of resorcinol has been accomplished using a previously reported method for trifluoromethylation of aromatics with $CF_3Br$ in $SO_2$ in low yield [7e,7f]. Based on the literature, an alternative method was designed to prepare 4-trifluoromethylresorcinol that utilized readily available, inexpensive, commercial precursors and that could be scaled up easily. By using the Burton reaction, we attempted to incorporate the trifluoromethyl group into the molecule directly via *in situ* generation and coupling of $CF_3Cu$ with aryl halides [7b]. The final product can be obtained by the hydrolysis of the ether bond to form the hydroxyl group. The first test reaction is shown in Scheme 7.




9 10

Table 4 shows the different reaction conditions and yields for **9.** Temperature is the key factor in the yield of the product. At room temperature and 60°C, no reaction occurs. The crude product obtained from the reaction mixture after 48 hours at 100°C was purified by column chromatography and eluted with ethyl acetate in hexane (1:4).

After obtaining 2,4-dimethoxy-1-trifluoromethylbenzene, a suitable hydrolysis route to 4-trifluoromethylresorcinol was sought. The hydrolysis reaction was carried out in acidic medium (HAc:HBr = 1:1) under reflux. However, none of the expected product formed, and only resorcinol was obtained, which indicates that 4-trifluoromethylresorcinol is not stable under these reaction conditions. The hydrolysis of 2,4-dimethoxy-1-trifluoromethylbenzene with HI (50%) at 120°C for 3 hours only gave resorcinol, again suggesting that 4-trifluoromethylresorcinol is not stable under these conditions.

From the foregoing two test reactions, it was found that 2,4- dimethoxy-1-trifluoromethylbenzene is a very acid-sensitive compound, thus the hydrolysis of this compound must be carried out under mild conditions. With $BBr_3$, the reaction was initially carried out at −78°C and then for 20 hours at RT. The reaction mixture was purified by column chromatography to give 4-trifluoromethylresorcinol (**10**) in 15% yield. Under mild acidic conditions, **10** exists in equilibrium with its quinoid form (Scheme 8). The $^1H$ NMR spectrum of the mixture shows two doublet resonances (AB pattern) at 3.71 and 3.92 ppm, from the -CH=CH- moiety. In the $^{13}C$ NMR spectrum, the carbonyl carbon chemical shift is at 187.20 ppm. In addition, the infrared spectrum of the quinoid mixture shows a strong bond centered at 1703 $cm^{-1}$.


The molecular structures of **1** (Figure 1), **4** (Fig-

**TABLE 4** Yield of 2,4-Dimethoxy-1-trifluoromethylbenzene **(9)** Obtaining from 2,4-Dimethoxy-1-iodobenzene

| *Reaction Conditions* | *Yield (%)* 2,4-Dimethoxy-1-trifluoromethylbenzene |
|---|---|
| RT 3 days | no reaction |
| 60°C, 3 days | no reaction |
| 100°C, 48 hours | 89 |

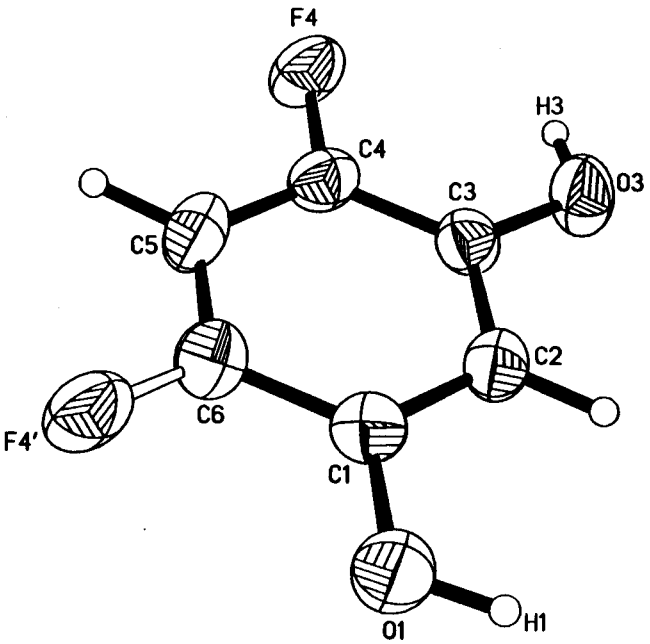



**FIGURE 1** Molecular structure of **1,** with thermal ellipsoides at 50% probability level.

ure 2), and **5** (Figure 3) were determined by X-ray crystallography. Single-crystal X-ray crystallographic parameters for **1, 4,** and **5** are given in Table 5. The asymmetric unit of **1** contains two crystallographically independent molecules situated roughly perpendicular to each other [74.1(1)°]. These two molecules are linked to each other via a hydrogen bond, i.e., O3···H3A = 1.88(4) Å, angle O3···H3A-O3A = 168(3)°, as shown in Figure 4. There is a close intramolecular H···F interaction [H3···F4 = 2.39(5) Å]. The fluorine atoms in both of the molecules show a positional disorder and have occupancies of 87 and 64% for F4 and F4A, respectively. The packing diagram of **1** shows extensive short range H···O and H···F bonding networks in the crystal lattice (Figure 5). These distances as well as some significant O···O and F···F distances are listed in Table 4. It may be pointed out that the F···F interactions are restricted along the *ab* plane and bridge the polymeric chains running along the *bc* plane.

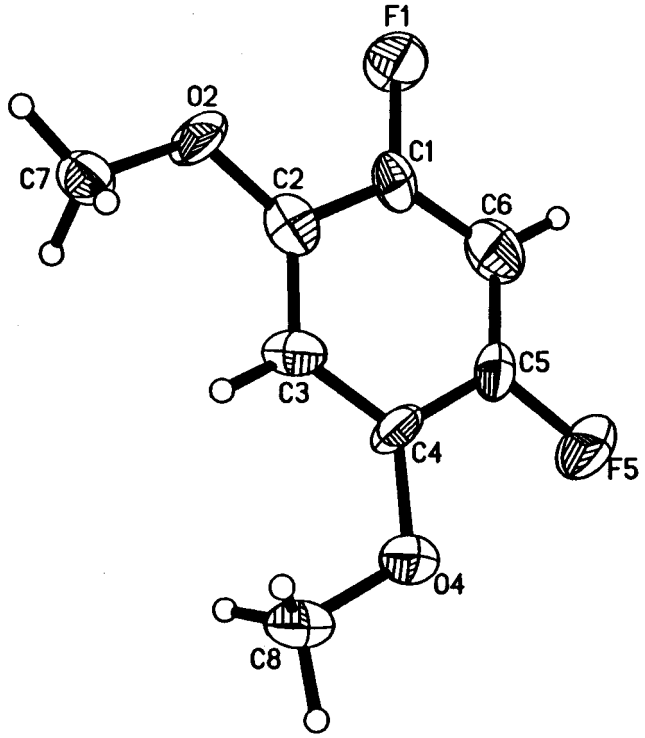



**FIGURE 2** Molecular structure of **4,** with thermal ellipsoides at 50% probability level.

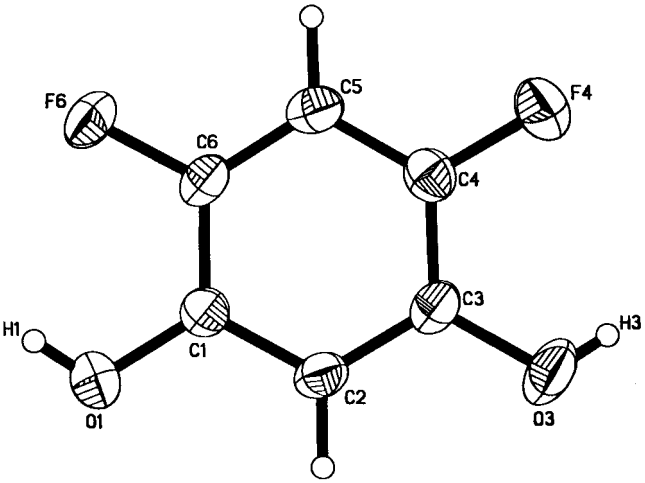



**FIGURE 3** Molecular structure of **5,** with thermal ellipsoides at 50% probability level.

The crystal lattice of **4** (Figure 7) also contains two crystallographically independent molecules within the asymmetric unit that lie parallel to each other [1.1(2)°]. These molecules show a close H···F contact H5···F6A = 2.44(5) Å, angle C5-H5···F6A = 152(3)°. The methoxy groups are oriented away from the fluorine atoms and lie in the plane of the aryl ring as seen from the torsion angles C7-O1-C1-C2 = 5.2(6), C7-O1-C1-C6 = −177.0(3), C8-O3-C3-C2 = 0.4(7), and C8-O3-C3-C4 = −177.7(4)° (Figure 6). The packing diagram of **2** (Figure 7) shows an additional intermolecular H···F interaction, F6···H2A$^a$($a = 1 - x, \frac{1}{2} + y, \frac{1}{2} - z$) at 2.48(5) Å, C6-F6···H2A$^a$ = 169(1)°.

The molecular structure of 4,6-difluororesorcinol **5** (Figure 3) shows that both of the hydroxyl groups are oriented toward the fluorine atoms forming two intramolecular H···F contacts, H1···F6 = 2.39(3) Å and H3···F4 = 2.48(4) Å. The intermolecular interactions found in the crystal packing (Figure 8) are listed in Table 6. The intermolecular H···O bonds from pseudo-octagonal cavities due to the formation of tetramers, as shown in Figure 9.

## *CONCLUSIONS*

1. By using Selectfluor reagent, a safer, less expensive, and easily scaled-up method for the synthesis of 4-fluororesorcinol is available.
2. 4-Trifluoromethylresorcinol is very sensitive to pH.

## *EXPERIMENTAL*

Infrared spectra were recorded on a Perkin-Elmer Model 1710 FT-IR spectrometer. Both $^{19}$F and $^{1}$H NMR spectra were obtained on a Bruker AC 200 Fourier transform NMR spectrometer using $CDCl_3$ as solvent unless otherwise indicated. Chemical shifts are reported with respect to $(CH_3)_4Si$ or $CFCl_3$. Mass spectra were determined with a VG 7070HS mass spectrometer by using electron impact (EI) or chemical ionization (CI) techniques. Products are

**TABLE 5** X-ray Crystallographic Parameters for Compounds **1, 4,** and **5**

| *Crystal Data* | *Compound* **1** | *Compound* **4** | *Compound* **5** |
|---|---|---|---|
| Empirical formula | $C_6H_5FO_2$ | $C_8H_8F_2O_2$ | $C_8H_4F_2O_2$ |
| Formula weight | 128.10 | 174.14 | 146.09 |
| Color, habit | colorless | colorless | colorless |
| Crystal size (mm) | 0.25 × 0.20 × 0.10 | 0.15 × 0.10 × 0.05 | 0.20 × 0.15 × 0.12 |
| Crystal system | Monoclinic | Monoclinic | Monoclinic |
| Space group | C2/C | $P2_1/c$ | $P2_1/n$ |
| Unit cell dimensions | $a$ = 7.425(5) Å | $a$ = 7.8760(10) Å | $a$ = 5.4670(5) Å |
| | $b$ = 22.18(2) Å | $b$ = 17.425(2) Å | $b$ = 10.4659(10) Å |
| | $c$ = 14.074(8) Å | $c$ = 11.4241(14) Å | $c$ = 10.0059(9) Å |
| | $\beta$ = 103.34(5)° | $\beta$ = 96.771(4)° | $\beta$ = 93.288(2)° |
| Volume (Å$^3$) | 2256(3) | 1556.9(3) | 571.57(9) |
| $Z$ | 16 | 8 | 4 |
| $\rho_{calc}$ (Mg/m$^3$) | 1.509 | 1.486 | 1.698 |
| $F$(000) | 1056 | 720 | 296 |
| Absorption coefficient (mm$^{-1}$) | 0.134 | 0.136 | 0.168 |
| Data collection | | | |
| 2$\theta$ range (°) | 3.68 to 56.72 | 4.28 to 45.98 | 5.64 to 56.56 |
| Index ranges | $-9 \le h \le 9$ | $-8 \le h \le 8$ | $-7 \le h \le 7$ |
| | $-29 \le k \le 17$ | $-19 \le k \le 12$ | $-13 \le k \le 13$ |
| | $18 \le l \le 17$ | $-11 \le l \le 12$ | $-13 \le l \le 11$ |
| No. of data collected | 6963 | 5805 | 3498 |
| No.of unique data | 2699 | 2130 | 1355 |
| | ($R_{int}$ = 0.0599) | ($R_{int}$ = 0.0447) | ($R_{int}$ = 0.0296) |
| No. of data | | | |
| with $I > 2\sigma$ ($I$) | 1429 | 1038 | 1063 |
| $T$max/min. | 0.9328/0.8506 | 0.9916/0.9288 | 0.97793/0.79741 |
| Extinction coeff. | 0.0011(2) | 0.0009(5) | 0.0017(7) |
| Solution and refinement on $F^2$ | | | |
| Parameters refined | 204 ($0_{restraints}$) | 217 ($0_{restraints}$) | 108 ($0_{restraints}$) |
| Final $R$ indices (2$\sigma$ data) | $R$ = 0.0595 | $R$ = 0.0687 | $R$ = 0.0396 |
| | $W_R$ = 0.1123 | $W_R$ = 0.1469 | $W_R$ = 0.1037 |
| All data | $r$ = 0.1318 | $R$ = 0.1317 | $R$ = 0.0533 |
| | $W_R$ = 0.1718 | $W_R$ = 0.1763 | $W_R$ = 0.1103 |
| Goodness-of-fit, S ($F^2$) | 1.200 | 1.087 | 1.047 |
| Largest difference peak (eÅ$^{-3}$) | 0.251 | 0.163 | 0.251 |
| Largest difference hole (eÅ$^{-3}$) | −0.297 | −0.199 | −0.162 |

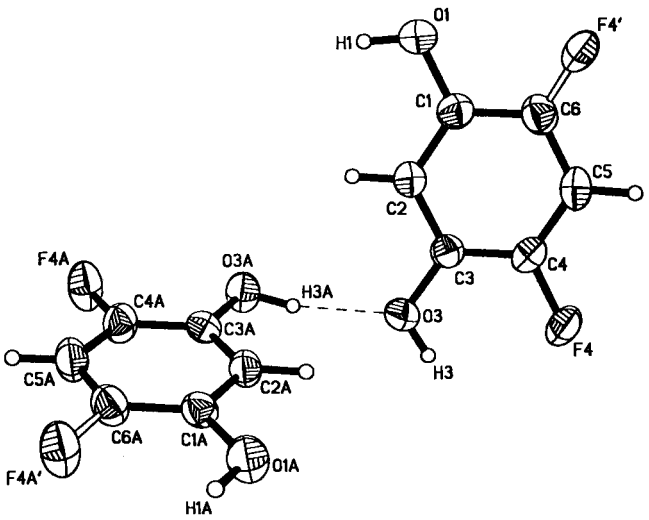



**FIGURE 4** Asymmetric unit of **1** showing intermolecular hydrogen bonding.

separated by column chromatography with 70–230 mesh silica gel and with a chromatatron.

## *X-RAY CRYSTAL STRUCTURE ANALYSIS*

The X-ray diffraction data for compounds **1, 4,** and **5** were collected on a Siemens SMART diffractometer equipped with a CCD detector. The final data collection and refinement are listed in Table 3. The frame data are acquired with the SMART[8] software using a Siemens three-circle platform using Mo$K_k$ radiation ($\lambda$ = 0.71073 Å) from a fine-focus tube. The $\chi$-axis on this platform is fixed at 54.74°, and the diffractometer is equipped with a CCD detector maintained near −54°C. Cell constants are determined from 60 ten second frames. A complete hemisphere of data is scanned on omega (0.3°) with a run time of 30 seconds per frame at the detector resolution of 512 × 512 pixels. A total of 1271 frames are collected

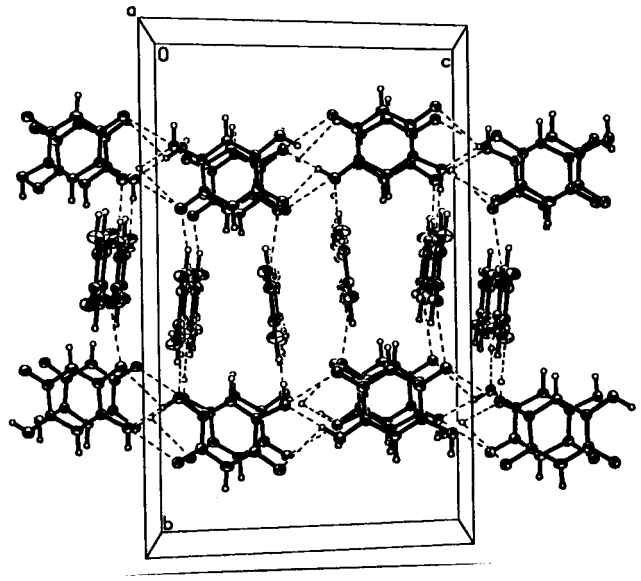



**FIGURE 5** Crystal packing diagram of **1** showing intermolecular H···O, H···F, O···O, and F···F interactions.

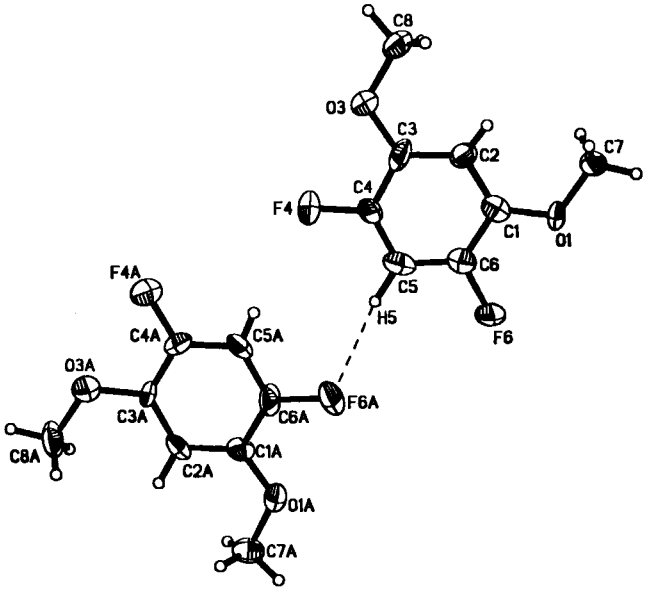



**FIGURE 6** Asymmetric unit of **4** showing intermolecular hydrogen bonding.

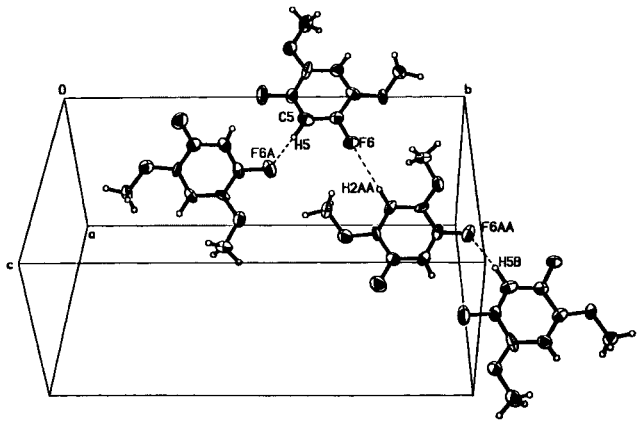



**FIGURE 7** Crystal packing diagram of **4** showing intermolecular H···F interactions.

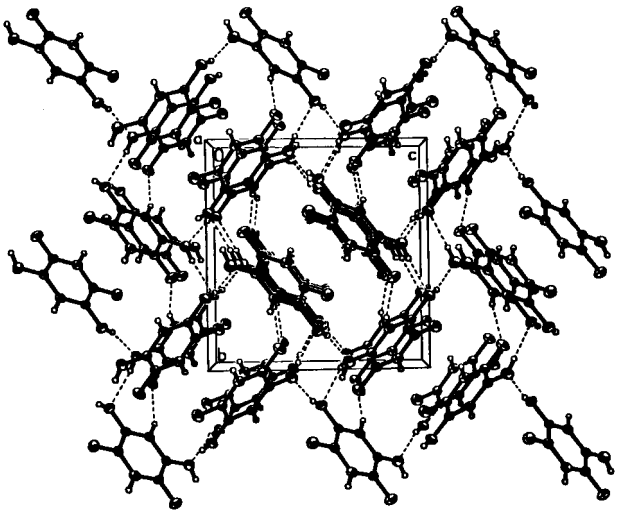


**FIGURE 8** Crystal packing diagram of **5** showing intermolecular hydrogen bonding.

in three sets, and a final set of 50 frames, identical to the first 50 frames, is also collected to determine crystal decay. The frames are then processed on a SGI-Indy/Indigo 2 workstation by using the SAINT software [9] to give the *hkl* file corrected for *Lp*/decay. The structures are solved by the direct method using the SHELX-90 [10] program and refined by least-squares method on $F^2$, SHELXL-93 [11], incorporated in SHELXTL-PC V 5.03 [12]. Absorption correction was performed using the SADABS [13] program. In the case of **1**, the fluorine atom was found to be disordered and was modeled by refining the site occupancy of the disordered site. Final refinement cycles set the occupancies at 87% (aryl ring C1–C6) and 64% (aryl ring C1A–C6A) for the fluorine atoms in the two molecules. All nonhydrogen atoms are refined anisotropically. The hydrogen atoms are located from the difference electron density maps and are included in the refinement process in an isotropic manner. The hydrogen atoms were added by the Riding model on C4, C6, C4A, and C6A in the disordered structures of **1.** All the crystals used for the diffraction studies show no decomposition during data collection.

*Preparation of 2,4-Dimethoxy-1-fluorobenzene*

**TABLE 6** Intermolecular H···O, H···F, O···O, and F···F Distances (Å)

| | *Bond* | *Symmetry of X′* | *Distance (Å) (esd)* |
|---|---|---|---|
| Compound **1** | H3···O1′ | 1 + *x*, *y*, *z* | 1.93(5) |
| | H1···O1A′ | −*x*, *y*, 3/2 − *z* | 1.89(4) |
| | O3···H1A′ | −1/2 + *x*, 1/2 − *y*, −1/2 + *z* | 1.88(5) |
| | F4···H5A′ | 1/2 − *x*, 1/2 + *y*, 3/2 − *z* | 2.56(3) |
| | F4A···H1A′ | −1/2 + *x*, 1/2−*y*, −1/2 + *z* | 2.55(5) |
| | H5A···F(4′)′ | 1/2 + *x*, −1/2 + *y*, *z* | 2.85(3) |
| | H1···F4A′ | −1/2 − *x*, 1/2 − *y*, 1 − *z* | 2.68(4) |
| | O1···O3′ | −1 + *x*, *y*, *z* | 2.684(3) |
| | O1···O1A′ | −*x*, *y*, 3/2 − *z* | 2.780(4) |
| | O3···O3A′ | *x*, *y*, *z* | 2.761(4) |
| | O3A···O1A′ | −1/2 + *x*, 1/2 − *y*, − 1/2 + *z* | 2.753(3) |
| | F4···F(4′)′ | 1 + *x*, *y*, *z* | 2.754(14) |
| | F4′···F4A′ | −1/2 + *x*, 1/2 + *y*, *z* | 2.833(13) |
| Compound **5** | H1···O3′ | −1/2 + *x*, 3/2 − *y*, 1/2 + *z* | 2.02(3) |
| | H3···O1′ | 3/2 − *x*, −1/2 + *y*, 1/2 − *z* | 2.07(3) |
| | H2···F4′ | 3/2 − *x*, 1/2 + *y*, 1/2 − *z* | 2.45(2) |
| | O1···O3′ | 3/2 − *x*, 1/2 + *y*, 1/2 − *z* | 2.770(2) |
| | O1···O3′ | −1/2 + *x*, 1/2 + *y*, 1/2 + *z* | 2.750(2) |

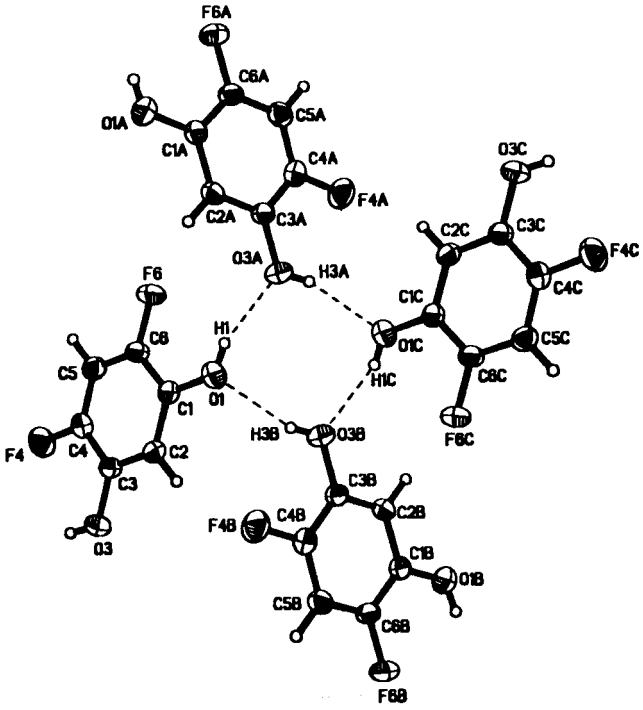



**FIGURE 9** Tetramers of structure of **5** showing intermolecular H···O bonding.

(**3**). In a three-necked flask, a solution of 1,3-dimethoxybenzene (1.38 g, 10.0 mmol) in acetonitrile (5 mL) was cooled to 0°C under nitrogen and Selectfluor fluorinating reagent, 1-chloromethyl-4-fluoro-1,4-diazobicyclo[2,2,2]octane bis(tetrafluoroborate) (3.54 g, 10.0 mmol) in acetonitrile (70 mL) was added to the solution slowly. The reaction mixture was maintained at 0°C for 10 hours and then at room temperature for an additional 10 hours. On completion, the solution was poured into $Et_2O$ (100 mL), washed with water saturated with NaCl (2 × 30 mL), and the volatile materials were evaporated to leave a yellow oil (1.5 g). The mixture was poured onto a silica gel column and eluted with ethyl acetate in hexane (1:40) to give **3** (0.93 g, 60%) and a white solid **4** (0.38 g, 25%). Spectral data for **3:** IR (film) 3010 (w), 1654 (m), 1509 (s), 1210 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.00 (dd, $J_{H6F}$ = 11.2 Hz, $J_{H6H5}$ = 9.0 Hz, 1H, 6), 6.57 (dd, $J_{H5F}$ = 7.2 Hz, $J_{H5H6}$ = 9.0 Hz, $J_{H5H3}$ = 3.0 Hz, 1H, H3), 6.37 (dt, $J_{H3F}$ = 7.2 Hz, $J_{H3H5}$ = 3.0 Hz, 1H, H5), 3.87 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$); $^{19}F$ NMR ($CDCl_3$) $\delta$ −146.07 ppm. 1,5-Difluoro-2,4-dimethoxybenzene (**4**), mp 99°C (Ref. [14] 97–98°C). Spectral data for **4:** IR (KBr) 3016 (m), 1540 (s), 1214 (s), 1054 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.90 (t, $J_{H6F}$ = 12.0 Hz, 1H, H6), 6.63 (t, $J_{H3F}$ = 8.0 Hz, 1H, H3), 3.87 (s, 6H, 2 × $OCH_3$); $^{19}F$ NMR ($CDCl_3$) $\delta$ −141.9 ppm.

*Preparation of 4,6-Difluororesorcinol* (**5**). To a solution of 1,3-difluoro-4,6-dimethoxybenzene (0.453 g, 2.6 mmol) in glacial acetic acid (2 mL) was added 48% hydrobromic acid (2 mL). The mixture was heated under reflux for 10 hours. The resulting mixture was concentrated in vacuo, and the residue was dissolved in a small volume of methylene chloride and chromatographed on silica gel. Elution with (1:4) ethyl acetate in hexane afforded **5** (0.342 g, 90%), mp 130–132°C. Spectral data for **5:** IR (KBr) 3505 (s), 1673 (m), 1524 (s), 1242 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.96 (t, $J_{H5F}$ = 10.8 Hz, 1H, H5), 6.55 (t,

$J_{H2F}$ = 8.5 Hz, 1H, H2); $^{19}$F NMR ($CDCl_3$) $\delta$ −145.61 (s, 2F) ppm; MS (EI) [*m/e* (species) intensity] 147 ($M^+ + 1$) 5.3, 146 ($M^+$) 100, 128 ($M^+ - H_2O$) 2.3.

*Preparation of 4-Fluororesorcinol* (**1**) (*a*). To a solution of 2,4-dimethoxy-1-fluorobenzene (0.4 g, 2.6 mmol) in glacial acetic acid (2 mL) was added 48% hydrobromic acid (2 mL). The mixture was refluxed for 5 hours. The resulting mixture was concentrated in vacuo, and the residue was dissolved in a small volume of methylene chloride and chromatographed on silica gel. Elution with ethyl acetate in hexane (1:4) afforded **1** (0.30 g, 90%), mp 97–98°C, (Ref. [4b] 97–98°C). Spectral data for **1:** IR (KBr) 3452 (s), 1653 (m), 1574 (s), 1505 (s) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.00 (dd, $J_{H5F}$ = 11.2 Hz, $J_{H5H6}$ = 9.0 Hz, 1H, H5), 6.55 (dd, $J_{H2F}$ = 7.4 Hz, $J_{H2H6}$ = 3.0 Hz, 1H, H2), 6.32 (dt, $J_{H6F}$ = 5.0 Hz, $J_{H2H6}$ = 3.0 Hz, $J_{H5H6}$ = 9.0 Hz, 1H, H6); $^{19}$F NMR ($CDCl_3$, $\delta$) −150.60 ppm; MS (EI) [*m/e* (species) intensity] 128 ($M^+$) 100.

(*b*). 1-Fluorodiaminobenzene (0.252 g, 2.00 mol) was dissolved in 4 mL of 35% $H_2SO_4$ and then allowed to cool to below 15°C. Ice (2.0 g) was added. A solution of sodium nitrite (0.36 g, 95.22 mmol) in ice water (4.2 mL) was added dropwise under the surface of the ice-cooled solution with stirring at such a rate as to maintain the temperature at 0–5°C. The solution was stirred for an additional 3.5 hours. To the cold (0°C) solution of the diazonium bisulfate was added a solution of cupric nitrate trihydrate (15.2 g, 73.2 mmol) in water (150 mL) at RT with vigorous stirring. Copper (I) oxide (0.434 g, 6.72 mmol) was then added to the solution. The liquid became dark blue and was stirred vigorously and allowed to stand overnight. Then it was filtered to remove a brown solid. The aqueous solution was extracted with ethyl acetate (3 × 50 mL). After removal of the solvent and subsequent sublimation, a yellow solid product (**1**) was obtained (0.09 g, 35%).

*Preparation of 2,4-Dimethoxy-1-trifluoromethylbenzene* (**9**). Into a mixture of Cd powder (5.058 g, 45 mmol) in DMF, $CF_2Br_2$ (2.74 mL, 30 mmol) was added slowly at 0°C. The mixture was stirred at RT for 30 minutes, and HMPA (20 mL) was added. The reaction mixture was cooled to 0°C, and CuBr (2.152 g, 15 mmol) was added. The mixture was then warmed to 25°C and stirred for 10 minutes, and 2,4-dimethoxy-1-iodobenzene (1.32 g, 5 mmol) was added. The solution was heated for 48 hours at 100°C. The reaction mixture was cooled to room temperature, and diethyl ether (150 mL) was added. The solids were removed by filtration. Water (3 × 100 mL) saturated with NaCl was used to wash the organic layer that was dried with $MgSO_4$. The crude product was purified by column chromatography and eluted with ethyl acetate in hexane (1:4) to give a colorless oil (700 mg, 89%). Spectral data for **9:** IR (film) 3007 (m), 1605 (s), 1352 (s), 1323 (s), 1212 (s) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.43 (d, $J_{H6H5}$ = 8.5 Hz, 1H, H6), 6.42–6.52 (m, 2H, H3, and H5), 3.84 (s, 2-$OCH_3$, 3H), 3.80 (s, 4-$OCH_3$, 3H); $^{19}$F NMR ($CDCl_3$) $\delta$ −61.56 ppm; MS (EI) [*m/e* (species) intensity] 206 ($M^+$) 100, 187 ($M^+$-F) 16, 176 ($M^+$-$OCH_3$ + H) 18.4, 69 ($CF_3^+$) 20.5.

*Preparation of 4-Trifluoromethylresorcinol* (**10**). $BBr_3$ (0.3 mL, 3 mmol) was added to 2,4-dimethoxy-1-trifluoromethylbenzene (0.206 mg, 1 mmol) in $CH_2Cl_2$ (40 mL) at −78°C. After 2 hours at this temperature, the mixture was allowed to warm to room temperature, then it was stirred for about 20 hours. It was poured into ice water (50 mL) and stirred vigorously for 1 hour. The water phase was extracted with $CH_2Cl_2$ (30 mL × 3). The organic layer was washed with an aqueous saturated NaCl solution (30 mL × 3), and the organic layer was dried with $MgSO_4$. The crude product was purified by column chromatography and eluted with (1:4) ethyl acetate in hexane. A colorless solid was obtained (26.7 mg, 15%), mp 89–91°C. Spectral data for **10:** IR (KBr) 3430 (s), 1642 (m), 1545 (s), 1512 (s), 1022 (s) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 7.40 (dd, $J_{H5H6}$ = 12.0 Hz, $J_{H5H3}$ = 8.0 Hz, 1H, H5), 6.42 (m, 2H, 2 H, and 6 H); $^{19}$F NMR ($CDCl_3$) $\delta$ −60.99 ppm; MS (CI) [*m/e* (species) intensity] 178 ($M^+$) 7.7, 159 ($M^+$-$H_2O$-H) 16, 151 ($M^+$-CO + H) 18, 111 ($M^+$-$CF_3$ + 2H) 9.5, 84 ($M^+$-$CF_3C_2H$) 100, 69 ($CF_3^+$) 36.2, 55 ($C_2H_2COH^+$) 92.

*Preparation of 2,4-Dinitro-1-fluorobenzene* (**7**). Into a 100 mL three-necked round-bottomed flask equipped with a thermometer, 1-chloro-dinitrobenzene (20.4 g, 0.1 mol), anhydrous KF (11.6 g, 0.2 mol) and DMSO (20.4 g) were placed. The contents were stirred at 100°C for 2.5 hours under nitrogen. The mixture was filtered to remove the potassium salts and then poured into ice water. The solid product was separated by filtration and purified by recrystallization from ethanol. The yield is 64%, mp 28–30°C, (Ref. [6], 27.5–30°C). Spectral data for **7:** IR (KBr) 3109 (s), 1612 (s), 1574 (s), 1335 (s), 1270 (s) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 8.94 (dd, $J_{H3F}$ = 6.4 Hz, $J_{H3H5}$ = 2.7 Hz, 1H, H3), 8.53 (tt, $J_{H5F}$ = 6.4 Hz, $J_{H5H6}$ = 9.2 Hz, and $J_{H5H3}$ = 3.4 Hz, 1H, H5), 7.54 (t, $J_{H6F}$ = 9.3 Hz, 1H, H6); $^{19}$F NMR ($CDCl_3$) $\delta$ −106.5 ppm.

*Preparation of 1-Fluoro-2,4-diaminobenzene* (**8**) *[15].* Into a 250 mL three-necked flask was placed finely powdered iron (6.8 g, 0.12 mol), concentrated

HCl (2.32 mL), and water (23.2 mL). The mixture was heated to 95°C with stirring. After refluxing, a solution of 2,4-dinitro-1-fluorobenzene (3.72 g, 0.02 mol) in ethanol (34.8 mL) was added dropwise. Stirring and refluxing was continued for another 2 hours followed by stirring at RT for 3 hours after addition of $Na_2CO_3$ (1.22 g). The unreacted iron and a sludge of iron oxides was filtered off, and the residue was extracted with ether (3 × 30 mL). The filtrate and extract was distilled to remove the ether and ethanol, the residue was extracted with $CHCl_3$ (3 × 25 mL) and separated from water. The extract was distilled to remove the $CHCl_3$ to give a dark brown oil. After distillation, pure 1-fluoro-2,4-diaminobenzene (**8**) (0.8 g) was obtained in 31.7% yield. Spectral data for **8:** IR (film) 3452 (s), 1633 (s), 1542 (s), 1325 (s), 1245 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.97 (tt, $J_{H5F}$ = 6.4 Hz, $J_{H5H3}$ = 2.9 Hz, and $J_{H5H6}$ = 12.0 Hz, 1H, H5), 6.06 (dd, $J_{H3F}$ = 7.6 Hz, $J_{H3H5}$ = 2.7 Hz, 1H, H3), 6.73 (dd, $J_{H6F}$ = 10.8 Hz, $J_{H6H5}$ = 8.5 Hz, 1H, H6), 3.49 (s, 4H, $NH_2$); $^{19}F$ NMR ($CDCl_3$) $\delta$ −106.5 ppm.

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## *SUPPLEMENTARY MATERIAL*

For compounds **1, 4,** and **5,** see tables listing full data collection and processing parameters, bond lengths and bond angles, atomic coordinates, equivalent isotropic and anisotropic displacement coefficients, and hydrogen atom coordinates and isotropic displacement coefficients (31 pages).

## *REFERENCES*

[1] R. Filler, *Chem. Tech., 4,* 1974, 752.
[2] (a) J. P. Bibler, R. M. Wallace, PCT Int. Appl WO 91,009,891 (11 July 1991), *C. A., 115,* 1991, 234200; (b) L. D. Pennington, M. B. Williams, *Ind. Eng. Chem., 6,* 1959, 759; (c) U.S. 3,933,925 (20 January 1976; N. P. Greco to Koppers Co, Inc.); (d) Hubler, T. L.; J. A. Franz, W. J. Shaw, S. A. Bryan, R. T. Hallen, G. N. Brown, L. A. Bray, J. C. Linehan, "Synthesis, Structural Characterization, and Performance Evaluation of Resorcinol-Formaldehyde (R-F) Ion-Exchange Resin," PNL-10744, Pacific Northwest National Laboratory, Richland, Washington, August 1995; (e) Hubler, T. L.; J. A. Franz, W. J. Shaw, M. O. Hogan, R. T. Hallen, G. N. Brown, J. C. Linehan, "Structure/Function Studies of Resorcinol-Formaldehyde (R-F) and Phenol-Formaldehyde (P-F) Copolymer Ion-Exchange, Resins." PNNL-11347, Pacific Northwest National Laboratory, September 1996. (f) Hubler, T. L.; J. A. Franz, W. J. Shaw, T. R. Hart, G. N. Brown, J. C. Linehan, "Chemical Derivatization to Enhance the Chemical/Oxidative Stability of Resorcinol-Formaldehyde (R-F) Resin." PNNL-11327, Pacific Northwest National Laboratory, September 1996.
[3] (a) J. B. Broderick, T. V. O'Halloran, *Biochemistry, 30* (29), 1991, 7349; (b) P. K. Chakrabortg, M. R. Kilbourn, *Appl. Radiat. Isot., 42* (7), 1991, 673.
[4] (a) H. Vypel, *Chimia, 39,* 1985, 305; A. Haas, M. Lieb, *Chimia, 39,* 1985, 134; S. T. Purrington, B. S. Kangan, T. B. Patrick, *Chem. Rev., 86,* 1986, 997; G. Balz, G. Schiemann, *Ber. Dtsch. Chem. Ges. B, 60,* 1927, 1186; A. Roe, *Org. React., 5,* 1949, 193; R. L. Fern, C. A. Vanderwerf, *J. Am. Chem. Soc., 72,* 1950, 4809; M. Hudlicky: *Chemistry of Organic Fluorine Compounds,* 2nd ed., Ellis Horwood, Chichester, England (1976); C. M. Sharts, W. A. Sheppard, *Org. React., 21,* 1974, 243; T. B. Patrick, G. L. Cantrell, C. Chang, *J. Am. Chem. Soc., 101,* 1979, 7434; O. Lerman, Y. Tor, D. Her, S. Rozen, *J. Org. Chem., 49,* 1984, 806; S. P. Anand, L. A. Quarterman, H. H. Hyman, K. G. Migliorese, R. Filler, *J. Org. Chem., 40,* 1975, 807; C. Niemann, A. A. Benson, J. F. Mead, *J. Am. Chem. Soc., 63,* 1941, 2204. (b) T. B. Patrick, C. K. Lau, H. W. R. Williams, C. Duferesne, J. Scheigetz, *J. Org. Chem., 51,* 1986, 3242; (c) E. H. Appelman, L. J. Basite, R. Hayatsu, *Tetrahedron, 40,* 1984, 189.
[5] P. C. Belanger, D. L. Darling, *Can. J. Chem., 66,* 1988, 1479.
[6] M. Hudlicky, H. M. Bell, *J. Fluorine Chem., 4,* 1974, 19.
[7] (a) R. E. Banks; *Organofluorine Compounds and Their Industrial Applications,* Ellis Harwood Ltd., Chichester (1979); R. Filler, Y. Kobayashi: *Biomedicinal Aspects of Fluorine Chemistry,* Kodansha/Elsevier, New York (1982). (b) D. J. Burton, D. M. Wiemers, *J. Am. Chem. Soc., 107,* 1985, 5014; D. M. Wiemers, D. J. Burton, *J. Am. Chem. Soc., 108,* 1986, 832; G. A. Wheaton, D. J. Burton, *J. Fluorine Chem., 9,* 1977, 25. (c) H. Urata, T. Fuchikami, *Tetrahedron Lett., 32,* 1991, 91. (d) Q. Y. Chen, G. Y. Yang, S. W. Wu, *J. Fluorine Chem., 55,* 1991, 291. (e) C. Wakselman, M. Tordeux, Rhone-Poulenc Specialties Chimiques; Eur. Pat. Appl. EP 206,951, 30 December 1986; *C. A., 106,* P101853t. (f) M. Tordeux, C. Wakselman, B. Langlois, Rhone-Poulenc Chemie; Eur. Pat. Appl. EP 298,803, 11 January 1989; *C. A., 111,* P173730b.
[8] SMART V 4.043 Software for the CCD Detector System, Siemens Analytical Instruments Division, Madison, WI (1995).
[9] SAINT V 4.035 Software for the CCD Detector System, Siemens Analytical Instruments Division, Madison, WI (1995).
[10] G. M. Sheldrick, SHELXS-90, Program for the Solu-

tion of Crystal Structure, University of Göttingen, Germany (1986).
[11] G. M. Sheldrick, SHELXL-93, Program for the Refinement of Crystal Structure, University of Göttingen, Germany (1993).
[12] SHELXTL 5.03 (PC-Version), Program Library for Structure Solution and Molecular Graphics, Siemens Analytical Instruments Division, Madison, WI (1995).
[13] SADABS, Software for the Absorption Correction for Area Detector System, Siemens Analytical Instruments Division, Madison, WI (1996).
[14] O. Lerman, Y. Tor, D. S. Rozen, *J. Org. Chem., 49,* 1984, 806.
[15] S. Sugawara, N. Ishikawa, *C. A., 72,* 1970, 66514p; W. T. Whang, *J. Polym. Sci. Polym. Symp., 74,* 1986, 109.