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A Convenient Synthesis of High-Purity 1-Chloro-2,6-difluorobenzene

Robert M. Moore, Jr.*,[1]

Strategic Development, Albemarle Corporation, Gulf States Road, Baton Rouge, Louisiana 70805, U.S.A.

Abstract:

A convenient preparation of high-purity 1-chloro-2,6-difluorobenzene has been developed. The key to the isolation of the desired isomer, without contamination of the difficult-to-separate isomer 1-chloro-2,3-difluorobenzene, is the use of sulfonyl chloride to direct fluorine substitution to the ortho and para positions of the aryl ring. Although activation with sulfonyl chloride requires additional reaction steps, the process results in good overall yield and requires only low-cost commodity chemicals. The high-purity 1-chloro-2,6-difluorobenzene is useful as an intermediate for active ingredients in agricultural and pharmaceutical applications.

Difluorobenzene compounds such as 1-chloro-2,4-difluorobenzene or 2,6-difluorobenzonitrile are used as intermediates for active ingredients in agricultural and pharmaceutical applications.[2] Syntheses of these compounds are relatively straightforward. However, there are few, direct regiospecific methods for preparing 1-chloro-2,6-difluorobenzene (**1**).

We required a synthesis of **1** that used economic raw materials and could be easily scaled up into a commercial reactor. Preparations from the economic starting material 1,2,3-trichlorobenzene are known but suffer from a number of significant drawbacks. In 1972, Shiley[3] attempted the KF exchange of 1,2,3-trichlorobenzene. A number of isomers were produced**,** with no single isomer present in greater than 30% yield. A patent by Soula[4] describes the chlorination of 1,3-difluorobenzene as a successful route to the desired compound, but even though **1** is the major product, a substantial amount (10%) of the difficult-to-separate 1-chloro-2,4-difluorobenzene and 1-chloro-3,5-difluorobenzene are present as well. A patent by Dow Elanco[5] describes a preparation for **1** relatively free of contamination from other isomers. 1,2,3-Trichlorobenzene is partially fluorinated to produce a mixture of components, with the monofluorodichlorobenzene and the chlorodifluorobenzene isomers comprising up to 20 and 60 mol %, respectively, of the final reaction mixture. The chlorodifluorobenzenes are separated from the other components of the mixture by distillation. To separate **1** from 1-chloro-2,3-difluorobenzene (**1b**), compound **1b** is selectively reduced with hydrogen and palladium on carbon. The resulting 1,2-difluorobenzene is easily separated from **1** by distillation. However, the Dow Elanco process for **1** still has a number of drawbacks. On the basis of information from the patent, the best yield of **1**, after reduction of the other isomers, is 44%, and that is only if excess CsF is used as the fluorinating agent. Yields with KF are considerably lower, even when an excess of KF is used. The fluorination requires very high temperatures (>250 °C) and exotic-metal pressure equipment. The reduction also requires a pressure reactor, a hydrogen-transfer agent, and an acid scavenger. However, since the process requires only two reaction steps to the product, **1**, it has been the most convenient process to date.

We have now developed a new, high-purity synthesis of 1-chloro-2,6-difluorobenzene. Although the process requires five reaction steps, it does offer some advantages. It uses cheap raw materials, such as chlorosulfonic acid, potassium fluoride, and trichlorobenzene. It requires no exotic pressure equipment, although the use of chlorosulfonic acid requires some caution. Less fluoride salt is wasted due to less excess needed for the reaction and smaller losses to undesirable side products. Isolation of intermediates is simple and requires no chromatography. Best of all, the desired product can be produced in greater than 99.5% purity since no hard-to-separate 1-chloro-2,3-difluorobenzene is produced. With proper control of reaction variables, less than 10% total of trifluorobenzene and monofluorodichlorobenzene results. The process is also convenient to carry out on a small scale using simple, available laboratory equipment.

Results and Discussion

Kageyama et al., reported on an efficient preparation of 2,6-difluorotoluene via chlorosulfonation of dichlorotoluene, followed by KF exchange, and desulfonation.[6,7] We speculated that, like other electron-withdrawing groups, the sulfonyl chloride was activating the ortho- and para-substituted chlorines to KF exchange. Thus, it might be possible to selectively fluorinate only two of the chlorines in 1,2,3-trichlorobenzene (1,2,3-TCB) and prepare the desired compound **1**.

The potential commercial process is shown in Figure 1. A good yield of 2,3,4-trichlorobenzenesulfonyl chloride **(2)** resulted when melted 1,2,3-TCB (mp = 55 °C) was added to an excess of chlorosulfonic acid. Heating to about 75−85 °C was required to complete the reaction. When the mixture was heated to 50 °C for 1 h after the addition of 1,2,3-TCB, the conversion was only 60%. The major isomer produced was **2**, although significant amounts of the 3,4,5-trichlorobenzenesulfonyl chloride **(7)** were also produced (Figure 2). The ratio of the two isomers varied from about 12:1 to 8:1, although the factors which influenced this ratio have not been determined. The minor isomer should be minimized since fluorination of this compound, followed by desulfonation, will result in 1,3-dichloro-2-fluorobenzene (**9**).

(1) Mailing address: Albemarle Corporation P.O. Box 341, Baton Rouge, LA 70821. E-mail: Bob_M_Moore@albemarle.com

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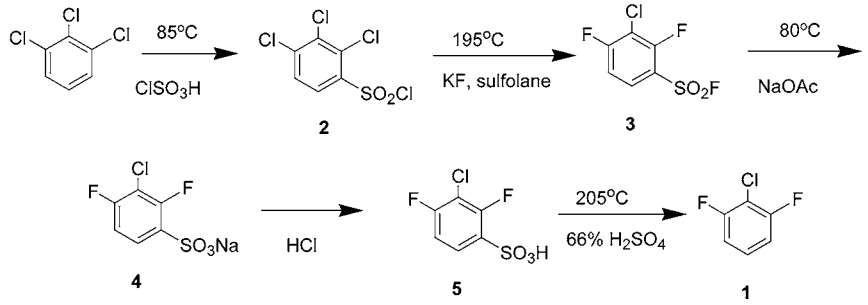

Figure 1. **Commercial preparation of 1-chloro-2,6-difluorobenzene.**

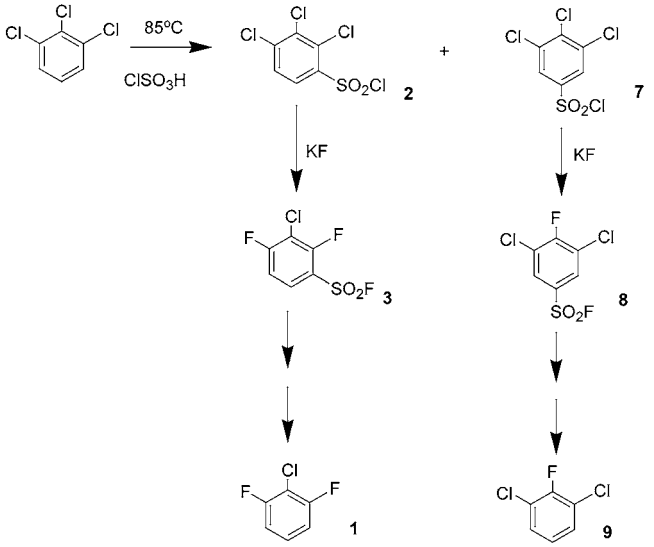

Figure 2. **Production of 1,3-dichloro-2-fluorobenzene from 2,3,4-trichloro-1-benzenesulfonyl chloride.**

Although this compound can be separated from the desired product, it has a negative impact on yield. Once the excess chlorosulfonic acid was quenched in chilled water,[8] a white precipitate formed, which could be isolated and washed on a filter. The wet cake may or may not need drying, depending on how water is removed from the reactor in preparation for KF exchange. For most laboratory preparations, air-dried sulfonyl chloride **2** should be sufficiently dry for the fluorination procedure. Reuse of the diluted sulfuric acid filtrate from this first step for the final desulfonation step can reduce the number of waste streams that would require treatment or disposal.

The yield for the chlorosulfonation step can be dramatically improved from the typical 80−85% to over 98% by adding thionyl chloride to the reaction after the addition of trichlorobenzene. Thionyl chloride reacts with the water of reaction, which prevents hydrolysis of the sulfonyl chloride, **2**, and formation of 2,3,4-trichlorobenzenesulfonic acid. During a mass balance experiment, it was determined that much of the yield loss was due to the formation of the arylsulfonic acid. Excess chlorosulfonic acid can be distilled and recovered for recycle.

Activation by sulfonyl chloride permits fluorination of **2** with potassium fluoride to form **3** in the absence of catalyst in a polar aprotic solvent at 150−200 °C. Replacement of chlorine with fluorine at the position meta to the sulfonyl chloride is not observed until the other chlorines have first been exchanged. Thus, 2,3,4-trifluorobenzenesulfonyl fluoride (**10**) will form, but 2-chloro-3,4-difluorobenzenesulfonyl fluoride (**11**) will not form. The amount of potassium fluoride added should be optimized to minimize the formation of **10**. A small excess of potassium fluoride (3.2 equiv) is all that is needed to obtain complete conversion of the starting material. One of the three fluorides is lost during hydrolysis of the sulfonyl fluoride, **3**. Sulfolane is an excellent solvent for the reaction. Other solvents, such as nitrobenzene, DMSO, or benzonitrile, resulted in lower product yields than sulfolane. Kageyama[6,7] has recommended the use of a catalyst such as tetraphenylphosphonium bromide for the fluorination of chlorinated toluenes, but we find that no catalyst is required for the chlorinated benzenes if sulfolane is used as the solvent (nitrobenzene requires a phosphorus-based catalyst). Distilling out added toluene with any water present in the reactor was sufficient to dry the reagents for the fluorination step. For a noncatalytic, KF exchange, the process is rapid. Conversion of the starting material is complete in less than 2 h at 195 °C.

To minimize the number of operations, it does not seem necessary to distill the high-boiling sulfonyl fluoride products from the solvent. After filtration to remove potassium chloride, the sulfonyl fluoride **3**, in sulfolane solution, can be hydrolyzed without further purification.

The removal of the sulfonyl fluoride group proved to be one of the more challenging aspects of this project. Sulfonyl fluorides are essentially inert to acidic hydrolysis. Sodium hydroxide hydrolysis occurred rapidly; however, hydroxide also attacked the chlorine of the aryl ring. Instead of detecting **4**, we observed the formation of fluorinated-diaryl ethers. An inexpensive, non-nucleophilic base, sodium acetate, was chosen. Addition of acetic acid reduced the amount of diaryl ether byproduct formation even further. With sulfolane as the solvent, a homogeneous solution of **3,** in water, sodium acetate, acetic acid, and sulfolane resulted at the reaction temperature. The success of the hydrolysis reaction can be attributed to this homogeneous condition. Nitrobenzene formed a two-phase system with aqueous sodium acetate. As a result, slow conversion of the sulfonyl fluoride, **3**, to the desired sodium salt, **4**, was observed with nitrobenzene.

To remove excess sodium acetate and acetic acid from the reaction mixture, concentrated hydrochloric acid was added to the solution containing the sodium salt, **4**. Water, acetic acid, and excess HCl were distilled from the pot. Heating the remaining solution under vacuum to remove sulfolane resulted in the recovery of a solid that consisted

(8) Safety tip: The typical laboratory procedure instructs that the contents of a chlorosulfonation reaction be quenched by pouring onto crushed ice. The much safer procedure of transferring the reaction contents to an addition funnel and slowly adding the solution to chilled ice water in a large flask is recommended.

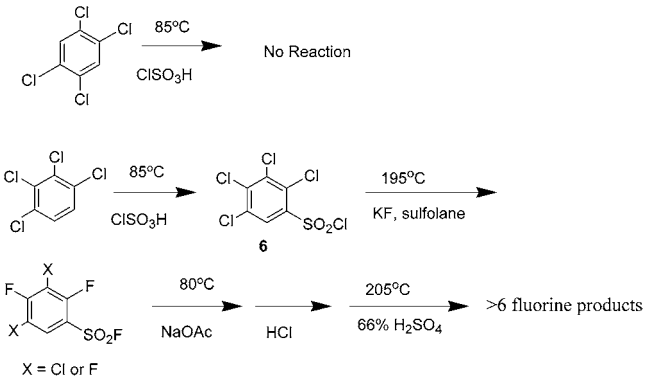

Figure 3. **Attempts to extend the methodology to tetrachlorobenzenes.**

of aryl sulfonic acids, such as **5**, and NaCl. The recovered sulfolane was suitable for recycle. Sulfolane is difficult to isolate after the addition of sulfuric acid. Removing the sulfolane before desulfonation permitted reuse of this expensive solvent. One negative aspect of this procedure was the addition of a solid isolation step.

The isolated solid was charged to a reactor with 66% sulfuric acid. After heating to 205 °C for 2 h, water was added dropwise to the pot. The water distilled out as an azeotrope with an organic material. The two phases were recovered in a receiving flask and separated by a simple phase cut. The volatile organic product distilled out of the pot was 95% pure **1**. The major impurities at about 2% each were 1,2,3-trifluorobenzene and 1,3-dichloro-2-fluorobenzene (**9**). An additional 1% of the mixture consisted of heavier boiling components such as 1,2,3-TCB with trace amounts of sulfolane and diaryl ethers. To obtain higher-purity material (99%+), fractional distillation of the recovered product was necessary. Distillation with a small-scale Vigreux-indented glass column (4−5 plates) resulted in the isolation of 99.2% pure **1**. The above impurities have at least a 30 °C boiling-point difference from that of **1** so that it should be feasible to obtain a purity of 99.8%+ with the use of a larger, multistage, distillation column. Spectral data from fluorine NMR, proton NMR, and carbon NMR were consistent with the desired product and compared to analogous compounds on file. Because of the presence of solvent, only GC and fluorine NMR were routinely used to monitor the intermediates in the process. The overall isolated yield of 99.2% pure **1** from 1,2,3-TCB was 33%.

Attempts to extend this reaction to the tetrachlorobenzenes were not successful in obtaining high-yield, high-purity products. Chlorosulfonation of 1,2,4,5-tetrachlorobenzene failed at temperatures below 150 °C. When the reaction was carried out at higher temperatures, only decomposition products were observed. Although we did obtain good yields of 2,3,4,5-tetrachlorobenzenesulfonyl chloride (**6**) from 1,2,3,4-tetrachlorobenzene (based on GC area %) with moderate conditions, we did not observe the desired selectivity during the fluorination reaction. Over a range of potassium fluoride to arylsulfonyl chloride ratios, a distribution of mono-, di-, and trifluorobenzenesulfonyl fluorides was isolated (Figure 3). No single compound was detected in greater than 50% yield.

Conclusions

We have successfully prepared high-purity, 1-chloro-2,6-difluorobenzene. The compound can be prepared easily in either routine, laboratory glassware or in large-scale equipment since difficult separations are avoided and operations are kept simple. Purity of greater than 99% is achievable with multistage distillation equipment. Although our attempts to extend this chemistry to tetrachlorinated benzenes were not successful, this chemistry was not extensively explored nor optimized.

Experimental Section

General. All reagents were obtained commercially and used as purchased. The potassium fluoride purchased was spray-dried quality. ^{1}H NMR spectra were determined on a 400 MHz spectrometer.

Preparation of 2,3,4-Trichlorobenzenesulfonyl Chloride (2) with Addition to Chilled Water. A three-neck, 500-mL round-bottom flask was charged with 189.8 g (1.63 mol) of chlorosulfonic acid. 1,2,3-TCB[9] (80.5 g, 0.444 mol) was charged to a jacketed addition funnel, attached to the flask and heated to 80 °C. The melted 1,2,3-TCB was added to the chlorosulfonic acid at 70° for 30 min. The temperature was then raised to 85 °C for 3 h. The reaction mixture was transferred to another addition funnel and added to a three-neck, 1-L flask containing 300 g of water at 2 °C.[8] The resulting precipitate was isolated by filtration, air-dried, and analyzed by ^{1}H NMR spectroscopy. The conversion was 99%+, and the yield of **2** was 81%. The ratio of **2** to **7** was 10 to 1.^{1}H NMR (Major isomer, **2**: doublet, δ 7.55, 1H; doublet, δ 7.95, 1H. Minor isomer, **7**: doublet, δ 7.25, 1H; doublet, δ 7.85, 1H.)

Attempted Preparation of 2,3,4-Trichlorobenzenesulfonyl Chloride (2) at 50 °C. A three-neck, 500-mL round-bottom flask was charged with 157.4 g (1.35 mol) of chlorosulfonic acid. 1,2,3- Trichlorobenzene (71.4 g, 0.394 mol) was charged to a jacketed addition funnel attached to the flask and heated to 80 °C. The melted 1,2,3-TCB was added to the chlorosulfonic acid at room temperature for 30 min. A solid formed, and the reaction was heated to 50 °C for 1 h. Eventually, the solid dissolved, and the solution turned blue. The reaction contents were added to water at 15 °C. The precipitate was filtered and analyzed by ^{1}H NMR spectroscopy. Yield of **2** was 60%.

Preparation of 2,3,4-Trichlorobenzenesulfonyl Chloride (2) with Addition of Thionyl Chloride To Eliminate Water of Reaction. A three-neck, 500-mL round-bottom flask was charged with 72.5 g of 1,2,3-TCB (0.40 mol). After melting the trichlorobenzene at 70 °C, 140.7 g of chlorosulfonic acid (1.21 mol) was added dropwise over 30 min. An exotherm increased the temperature to 90 °C. After cooling to 85 °C, 47.6 g of thionyl chloride (0.40 mol) was added over 2 h to react with water of reaction. The reaction was heated at 85 °C for an additional 1.5 h. The reaction mixture was transferred to another addition funnel and added to a three-neck, 1-L flask containing 300 g of ice and 100 g of water. Additional ice (approximately 50 g) was added to keep the temperature below 20 °C.[8] The precipitate was isolated by filtration, air-dried, and analyzed by ^{1}H NMR

(9) In the absence of a jacketed addition funnel, the order of addition can be reversed with chlorosulfonic acid added to 1,2,3-TCB.

spectroscopy. The conversion was 99%+ and the isolated yield of **2** was 110.4 g or 98%. The ratio of **2** to **7** was 11 to 1. Neutralization of the filtrate resulted in the recovery of 1.2 g or 1% of the aryl sulfonic acid.

Attempted Chlorosulfonation of 1,2,4,5-Tetrachlorobenzene. A three-neck, 500-mL round-bottom flask was charged with 43.3 g (0.20 mol) of 1,2,4,5-tetrachlorobenzene and 115.1 g (0.988 mol) of chlorosulfonic acid. The contents were heated to 90 °C for 4 h. The resulting viscous material was quenched over ice. The recovered solid was identified as the starting material. The reaction was repeated at 150 °C to melt the starting material, but after heating for 2 h, a significant amount of solid had formed. The recovered solid consisted of starting material and large amounts of insoluble solids.[10]

Preparation of 2,3,4,5-Tetrachlorobenzenesulfonyl Chloride (6). A three-neck, 500-mL round-bottom flask was charged with 53.7 g of 1,2,3,4-tetrachlorobenzene (0.25 mol). After melting the tetrachlorobenzene at 70 °C, 142.0 g of chlorosulfonic acid (1.2 mol) was added dropwise over 30 min. The reaction was heated for 4 h at 95 °C and quenched in ice water. A white solid was isolated by filtration (83% yield). mp 74−76 °C (lit.[10] 76 °C). ^{1}H NMR (singlet, δ 7.92).

Preparation of 3-Chloro-2,4-difluorobenzenesulfonyl Fluoride (3). A five-neck, 500-mL round-bottom flask was equipped with a mechanical stirrer, a nitrogen inlet, a condenser, and a thermometer. The flask was charged in a nitrogen-flush box with 27.5 g of KF (0.473 mol), 165.2 g of sulfolane, and 47.9 g of toluene. The flask was then connected to a mechanical stirrer, and trace water distilled out of the flask with the toluene. **2** (42.6 g, 0.152 mol) was charged to the flask, and the contents were heated to 195 °C for 3 h. After the reaction was complete, the contents were filtered to remove potassium chloride. The filtrate was weighed (156.3 g), analyzed, and used without further purification in the hydrolysis step. ^{19}F NMR of filtrate in DMSO-d_6 (δ 65.5, δ 98.4, δ 106.7).

Hydrolysis of 3-Chloro-2,4-difluorobenzenesulfonyl Fluoride (3), Acidification of the Sodium Salt of 3-Chloro-2,4-difluorobenzenesulfonic Acid (4). A three-neck, 500-mL round-bottom flask was charged with 84.0 g (82 mmol of **3**, theoretical) of the filtrate from the KF exchange containing **3** in sulfolane. To this solution was charged 92.7 g of an aqueous 25% sodium acetate solution with approximately 10 mL of glacial acetic acid added to reduce the pH to 5.5. The temperature of this mixture was raised to 80 °C, resulting in a single homogeneous layer. After 4 h, the sulfonyl fluoride was 97% converted (GC area %) to the sodium salt. At this point, the solution can be extracted with toluene to remove organic impurities; however, we did not observe an improvement in the purity of the final product, and as a result, the extraction was subsequently eliminated. The aqueous solution containing sulfolane, inorganic salts, and **4** was then acidified with concentrated HCL (25 mL). Acetic acid, water, and excess HCL were removed by distillation. The remaining suspension contained sulfolane and the aryl sulfonic acid, **5**. The sulfolane was distilled at 175 °C (30 Torr). A dark solid consisting of the aryl sulfonic acid and inorganic solids remained in the pot. ^{19}F NMR of hydrolysis reaction in DMSO-d_6, **4** (δ 110.7, δ 112.1). ^{19}F NMR of acidification reaction in DMSO-d_6, **5** (δ 111.0, δ 111.3).

Preparation of 1-Chloro-2,6-difluorobenzene(1) 8687-16. To the remaining solid from the above reaction was added 150 mL of 66% H_2SO_4. The solution was heated for 2 h at 205 °C. Water was added dropwise, which resulted in an azeotropic distillation of water and volatile organic material. The two phases were separated, and 5.1 g of 95% pure 1,2,6-CDFB was recovered (42% yield based on the fraction of filtrate used from **2**). The major impurities were 1,2,3-trifluorobenzene, 2,6-dichloro-1-fluorobenzene, 1,2,3-TCB, and a mixture of halogenated diaryl ethers. Distillation with a one-piece vigeroux column (4−5 plates) resulted in the isolation of 99.2% pure **1**. Overall yield of **1** from 1,2,3-TCB was 33%. ^{1}H NMR (multiplet, δ 6.9−7.0, 2H; multiplet, δ 7.1−7.25, 1H). ^{13}C NMR (triplet, δ 110.3, J_{CCF} = 20.6 Hz; multiplet, δ 112.3, J = 24.4 Hz for primary doublet; multiplet, δ 128.0, J_{CCCF} = 9.16 Hz; doublet of doublets, δ 158.3, δ 160.8, J = 251 Hz). ^{19}F NMR (triplet, δ 113.7).

Fluorination of 2,3,4,5-Tetrachlorobenzenesulfonyl Chloride. A five-neck, 500-mL round-bottom flask was equipped with a mechanical stirrer, a nitrogen inlet, a condenser, and a thermometer. The flask was charged in a nitrogen-flush box with 22.5 g of KF (0.39 mol), 147.2 g of sulfolane, and 40.9 g of toluene. The flask was then connected to a mechanical stirrer and trace water distilled out of the flask with the toluene. The sulfonyl chloride, **6** (31.1 g, 0.099 mol), was charged to the flask, and the contents were heated to 195 °C for 2 h. After the reaction was complete, the contents were filtered to remove potassium chloride. Analysis by gas chromatography indicated that a minimum of six fluorinated compounds had formed, including di- and trifluoroaryl species. ^{19}F NMR (major peaks; δ 66.3, δ 65.7, δ 65.2, δ 98, δ 107, δ 108, δ 110, δ 120, δ 130, δ 137, δ 139, δ 152).

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(10) During the review process, it was discovered that previous authors had had difficulty with the chlorosulfonation of this isomer. Bernard, I.; Chivers, G.; Cremlyn, R.; Mootoosamy, K. *Aust. J. Chem.* **1974**, *27*, 171.