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Research Article

Alternative Synthesis of 1,8-Difluoroanthracene via the Balz-Schiemann Reaction

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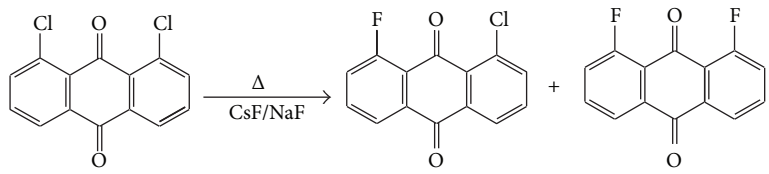
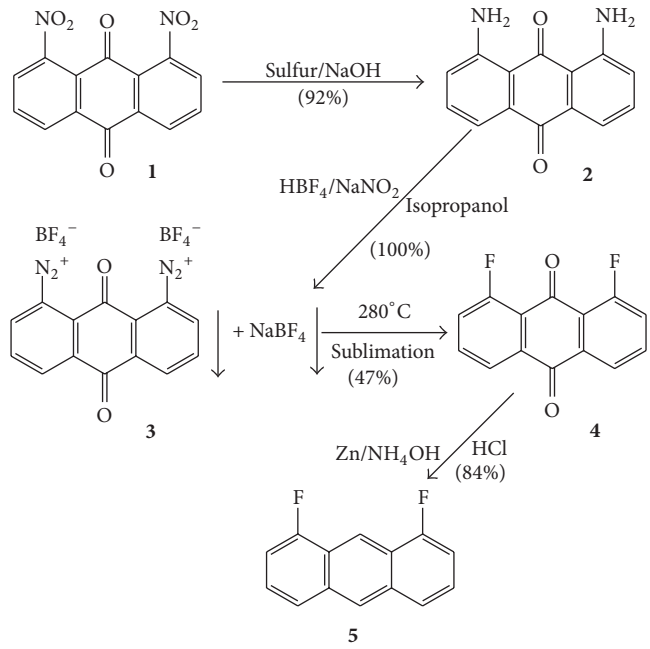
An alternative and improved method for the synthesis of 1,8-difluoroanthracene **5** is described. The precursor 1,8-difluoro-9,10-anthraquinone **4** was synthesized by precipitating the water-soluble 1,8-diazonium-9,10-anthraquinone fluoroborate **3** using isopropanol, before thermally decomposing it via the Balz-Schiemann reaction to yield **4** in the form of pure sublimed crystals. Compound **5** was later synthesized with 84% yield by reducing **4** in a Zn/NH_4OH mixture. Using isopropanol to quantitatively precipitate water-soluble diazonium fluoroborate salts was also used to synthesize other fluoroanthraquinone derivatives with improved yields.

1. Introduction

Organofluorine compounds have found extensive use in industry [1] and medicine [2]. Substituting hydrogen for a fluorine atom can enhance the biological activity of some drugs [3–5]. Of particular interest to organic and medicinal chemists are fluoro-aromatic compounds since they are susceptible to "ipso" nucleophilic aromatic substitution more so than Cl, Br, or I substituents [6]. Fluorine can be substituted with the appropriate nucleophile to form a C-N [7], C-O [8], or C-P [7] bond. In recent years there was extensive interest in fluoro-substituted anthraquinones as precursors for the synthesis of novel antitumor drugs, commercial dyes [9], and more recently photomechanical actuators [10]. Of particular importance is 1,8-difluoro-9,10-anthraquinone **4** [11, 12] and its reduced product 1,8-difluoroanthracene **5** [7, 13–17] which has been used for the synthesis of diphenylphosphino and dimethylamino ligands linked at the 1,8-position of the anthracene backbone. The 1 and 8 carbon positions in **4** or **5** provide a handle onto which a variety of ligands can be attached (via nucleophilic substitution) to form homogenous catalysts [14] or drugs with promising antitumor activity [18]. A quick literature survey reveals that **4** was exclusively synthesized using Cl-F halogen exchange chemistry. Thermal reaction between the commercially available 1,8-dichloro-9,10-anthraquinone and dry KF under pressure and 230°C was the first method described [19] to synthesize **4**. This method was deemed unreliable and could not be reproduced by several authors. More recently Cl-F exchange of 1,8-dichloro-9,10-anthraquinone with anhydrous CsF in anhydrous DMSO [7, 12, 20, 21] became the adopted method. The reagents had to be extensively dried in order to obtain reasonable yields. Tiny amounts of water or failure to obtain bone-dry DMSO and CsF reduced the yield to the single digits. The authors of this paper tried to repeat the described literature procedure [7] using anhydrous CsF and DMSO (vacuum distilled then stored over activated molecular sieves 4 Å) but failed to yield any product. Reaction of 1,8-dichloro-9,10-anthraquinone with flame dried CsF/NaF powder at 300°C yields a mixture of the mono- and difluorosubstituents that sublime out of the reaction mixture along with a significant amount of the starting material, before achieving complete Cl-F halogen exchange (Scheme 1). This method proved to be tedious and corrosive towards laboratory glassware; also separating the sublimed mixture of products and reactant using column chromatography was impractical and reagent consuming.



Scheme 1: Dry mixed thermal Cl-F exchange between 1,8-dichloro-9,10-anthraquinone **7** and CsF/NaF to yield a sublimed mixture of **4** and **6**.

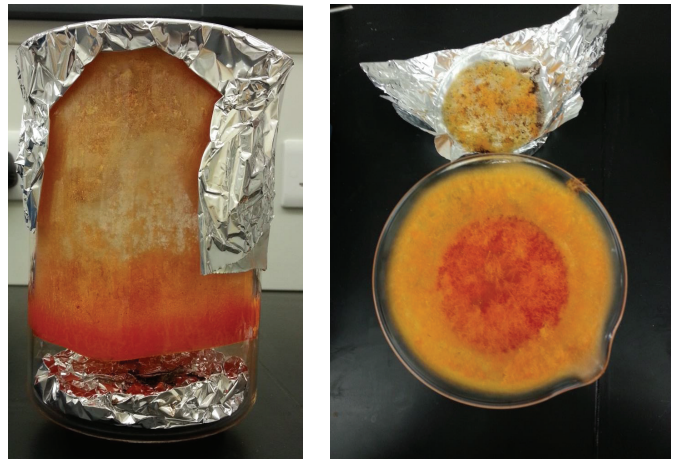


Scheme 2: Synthesis of **4** after the coprecipitation of **3** followed by thermal decomposition (Balz-Schiemann) to give **4**. Compound **5** is made by reducing **4** in Zn/NH_4OH [7] (m.p. = 141–142.5°C, Lit. [7] m.p. = 142°C).

2. Materials and Methods

All reagents were purchased from TCI America and used without further purification. For the GC analysis we used a general-purpose column (30 m long) with a linear velocity flow rate set at 1.2 mL/min.

For the following synthesis refer to Scheme 2. Commercially available 1,8-dinitro-9,10-anthraquinone was converted to the corresponding 1,8-diamino-9,10-anthraquinone by reducing it with sulfur. Thus elemental sulfur (5 g) was dissolved in hot aqueous NaOH (5 g in 80 mL of water) to form the sulfide. 1,8-Dinitro-9,10-anthraquinone **1** (3 g) was added to the sulfide solution, along with 50 mL of ethanol as a cosolvent and stirred for several hours under a blanket of Argon gas till the mixture turns dark red with the formation of a precipitate. 1,8-Diamino-9,10-anthraquinone **2** was suction filtered after diluting the reaction with 500 mL of cold water. The residue was washed with DI water till the filtrate ran clear. Compound **2** was air-dried to obtain 2.1 g (92% yield) of maroon-red crystals. m.p. 268–270°C (Lit. [22] 270-271°C) and 1H-NMR (300 Mhz, DMSO-d6): δ 7.86 (broad singlet, 4H), 7.43 (dd, 2H), 7.35 (d, 2H), and 7.15 (m, 2H). 1,8-Diamino-9,10-anthraquinone (2 g) was stirred with 16 mL of 50% HBF4. Two equivalents of $NaNO_2$ (1.16 g) were gradually added while stirring and maintaining a temperature <5°C. The reaction mixture was stored under a blanket of Argon gas at 0°C for an additional 10–18 hours until all the amine was converted to the diazonium salt. The red-brown colored slurry was slowly added to 100 mL of ice-cold isopropanol and vigorously stirred to precipitate a gray-colored solid composed of a mixture of **3** and $NaBF_4$. The precipitated salts were suction filtered and washed with cold isopropanol to get rid of the excess HBF_4 and water, followed by copious amounts of hexanes. The gray-colored powder was gently dried at 45°C under reduced vacuum to remove any trace amounts of water. The dry powder was mixed with 5 times its weight in dry sand and packed inside an aluminum foil folded into a puck-shape disk and then pressed flat on the bottom of a 500 mL beaker. The beaker was covered with aluminum foil and placed on top of a hot plate set at 280°C for 15 hours to initiate thermal decomposition of **3**. Product **4** sublimes and condenses on the side of the beaker in the form of orange needle shape crystals (Figure 1). Compound **4** (m.p. 227–229°C, Lit. [12] 228-229°C; ^{1}H-NMR (300 Mhz, $CDCl_3$) δ 8.10 (dd, 2H), 7.80 (m, 2H), and 7.55 (m, 2H)) was scraped off and separated from the decomposition byproducts that remained inside the aluminum foil. GC-MS analysis of the orange crystals revealed that they are 100% pure **4** (Figure 2).



(a) (b)

Figure 1: Sublimed **4** after the thermal decomposition of **3**. Residual byproducts remain inside the aluminum puck at the bottom of the beaker separated from the pure **4**.

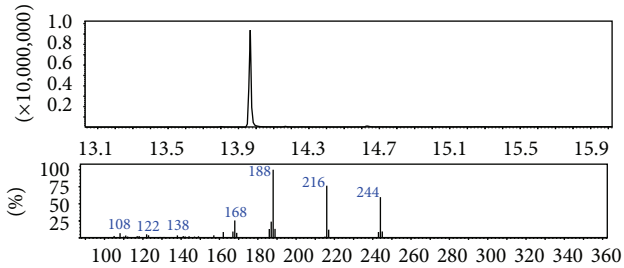


Figure 2: GC-MS chromatogram of sublimed 4 (top) giving single peak with retention time of 13.96 min and an $M^+ = 244$ with a fragmentation pattern (bottom) corresponding to loss of CO from the anthraquinone (216 and 188). GC conditions: general-purpose column (15 m long) with a linear velocity flow rate set at 1.2 mL/min.

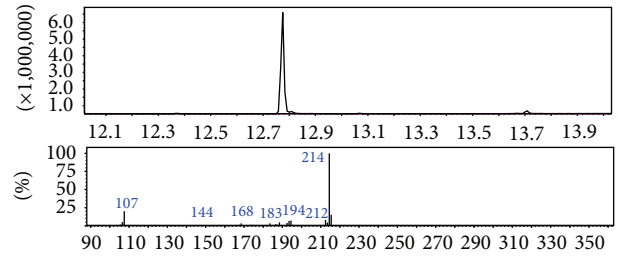


Figure 3: GC-MS chromatogram (top) of 1,8-difluoroanthracene **5** (12.78 min) and the corresponding mass spectrum ($M^+ = 214$) [7].

The yield from the Balz-Schiemann reaction was 47% of pure **4**. It is worth noting that the coprecipitated $NaBF_4$ crystals do not contain any water of hydration, which could reduce the yield. Compound **5** was later synthesized by reducing **4** in aqueous NH_4OH/Zn mixture following the reported literature procedure [7, 17]. GC-MS analysis of crude **5** reveals a very pure product and an $M^+ = 214$ (Figure 3); thus there was no need for further purification using column chromatography.

3. Results and Discussion

Fluoro-substituted aromatic compounds are generally prepared using the Balz-Schiemann reaction [23] in which a diazonium fluoroborate salt, such as **3**, is thermally decomposed to the organofluorine compound with the copious production of BF_3 and dinitrogen gas. The diazonium fluoroborate salt is prepared by precipitating an aqueous solution of a diazonium salt, by adding an inorganic salt containing $[BF_4]^-$ ion ($NaBF_4$ or HBF_4). This method was recently used to synthesize fluorinated derivatives of anthraquinone and anthracene [10]. In general, aromatic diazonium fluoroborates are sparingly soluble in water and thus can be precipitated from aqueous solution with a semiquantitative yield. Thus success of the Balz-Schiemann reaction depends on the ability to precipitate diazonium fluoroborate salt from aqueous solution and washing it free of mineral acids. Unfortunately, partial or complete solubility of some diazonium fluoroborate salts in water will lower the yield. This is one of the reasons why **4** was never synthesized following this rout, since **3** is very soluble in water. Utilization of the Balz-Schiemann reaction to synthesize **4** depends on our ability to reduce the solubility of **3** in water by utilizing other methods to precipitate it out without hydrolyzing the diazonium ion in the process.

In an effort to reduce the water solubility of **3** and force it to precipitate out, **2** was diazotized in 50% HBF_4 saturated with $NaBF_4$; unfortunately this proved unsuccessful and did not motivate **3** to crash out of solution. In an alternative method, we precipitated **3** using a water-soluble organic solvent that does not decompose the diazonium derivative. After several trials we found that isopropanol was the best solvent to quantitatively precipitate out **3** along with $NaBF_4$ without hydrolyzing the diazonium ion. Other water-soluble organic solvents such as methanol or ethanol caused partial dissolution of **3**.

To test the generality of the coprecipitation method, we prepared 1,4-difluoro-9,10-anthraquinone with 39% yield

Table 1: Different fluoroanthraquinones prepared by the isopropanol precipitation method.

Compound	Overall yield after decomposition (%)*	Lit. yield (%) [10]	Purity by GC-MS
1-Fluoro-9,10-anthraquinone	82 (sublimed)	65	98%
2-Fluoro-9,10-anthraquinone	81 (sublimed)	69	98%
2,6-Difluoro-9,10-anthraquinone	49 (sublimed)	38	95%

*The overall yield was calculated based on the amine-anthraquinone starting material yielding the fluoroderivative.

following the same method of coprecipitating the water-soluble diazonium fluoroborate salt with isopropanol. In Table 1 we report the synthesis and yield of various fluoro-substituted anthraquinones prepared by isopropanol precipitation, followed by the Balz-Schiemann reaction.

4. Conclusion

Using isopropanol to precipitate the water-soluble diazonium fluoroborate salt **3** followed by thermal decomposition to yield the fluoroderivative is a greener alternative to using concentrated H_2SO_4, CsF, or dry DMSO for a Cl-F halogen exchange which is highly susceptible to the presence of water and requires a great deal of workup. By following the isopropanol precipitation method we forgo the concern with ultra-anhydrous conditions of the reagents and column chromatography to purify the final product. This method is general enough to be used for the synthesis of other fluoroanthraquinones with the added advantage of a higher yield.

Competing Interests

The author declares that they have no competing interests.

Acknowledgments

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