A NOVEL SYNTHESIS OF 2-CHLORO-4-FLUORO-5-NITROBENZENESULFONYL CHLORIDE

Submitted by (06/01/05)

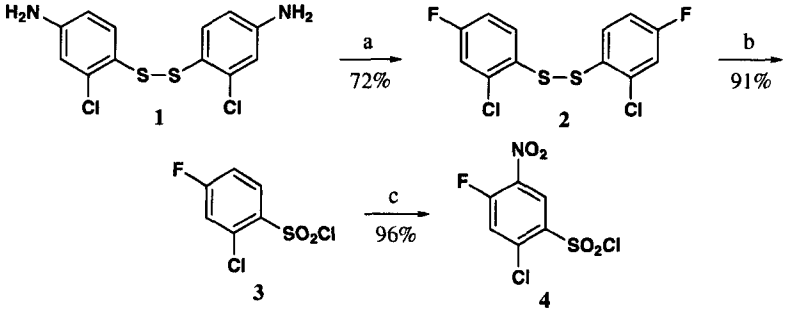
Xiao-Hua Du, Sheng Chen, Mei Zheng and Zhen-Yuan Xu*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology Catalytic Hydrogenation Research Center
Zhejiang University of Technology
Hangzhou, Zhejiang, 310014,. P. R. CHINA
E-mail: duxiaohua@zjut.edu.cn

2-Chloro-4-fluoro-5-nitrobenzenesulfonyl chloride (**4**) is useful in the synthesis of the key intermediate methyl 5-amino-2-chloro-4-fluorophenylthioacetate,[1] which is in turn utilized for the preparation of pesticides such as the herbicidal *fluthiacet-methyl*.[2] Kojima *et al.*[3] prepared **4** in 78% yield by chlorosulfonation of 4-chloro-2-fluoronitrobenzene with chlorosulfonic acid.

Since 4-chloro-2-fluoronitrobenzene is very expensive and difficult to prepare,[4] an alternate route to **4** was sought. Accordingly, we report the synthesis of **4** from *bis*(4-amino-2-chlorophenyl) disulfide (**1**) using the Schiemann reaction, oxychlorination, and nitration as shown in *Scheme*. The starting material **1** had previously been prepared from 3,4-dichloronitrobenzene.[5]

As shown in *Scheme*, *bis*(2-chloro-4-fluorophenyl) disulfide (**2**) was prepared by a typical Schiemann reaction (*step a*), including diazotization with sodium nitrite in acidic conditions (20% sulfuric acid was an optimized medium for this reaction), precipitation with tetrafluoroboric acid and pyrolysis of the precipitated diazonium tetrafluoroborate. The diazonium tetrafluoroborate of **1** was pyrolyzed smoothly in *o*-dichlorobenzene at 130-140°C give **2** in 65-75%. In comparison, **2** was prepared[6] from 2-chloro-4-fluoroaniline in 24% yield, comprising diazotization, sulfurization, hydrolysis and oxidization. In *step b*, 2-chloro-4-fluorobenzenesulfonyl chloride (**3**) was prepared in better than 90% yield by oxychlorination of **2** with chlorine gas in conc. hydrochloric acid at 50-60°C.



a) 20% H_2SO_4, $NaNO_2/HBF_4$; Pyrolysis; b) Conc. HCl, Cl_2; c) 95% HNO_3, Conc. H_2SO_4

Finally, the title compound **4** was readily obtained in 96% yield in better than 98% purity by nitration of **3** with 1.0-1.05 equivalent of 95% fuming nitric acid in conc. sulfuric acid (98%) at 35-40°C for 1 hour. This synthesis provided a higher yield and milder reaction conditions than chlorosulfonation[3] of 4-chloro-2-fluoronitrobenzene which yielded only 78% of **4** and required the use of 5.4 equivalents of chlorosulfonic acid at 120-130°C for 3 hours.

EXPERIMENTAL SECTION

Melting and boiling points were uncorrected. The purity of products was determined using a Shimadzu HPLC with Diamonsil C_{18} column (5 δ, 200 x 4.6 mm). IR spectra were recorded on a Bruker EQUINOX 55 spectrometer. ^{1}H-NMR spectra were obtained on a Bruker AC-400 instrument. Chemical shifts were reported in δ from internal TMS. MS spectra were acquired on an Agilent 6890N/5873N GC/MS. Elemental analyses were performed using a Heraus Carlo Erba 1108 analyser.

bis*(2-Chloro-4-fluorophenyl) Disulfide (2).**- Into a 50 mL three-necked flask with mechanical stirrer, was added 20 mL of 20% sulfuric acid cooled to 0-5°C. Then *bis*(4-amino-2-chlorophenyl) disulfide (2.00 g, 6.2 mmol) was added portionwise with vigorous stirring. After stirring for 30 minutes, an aqueous solution of sodium nitrite (0.81 g, 12.8 mmol, in 10 mL of water) was added dropwise at 0-5°C over a period of 1 hr. After further stirring at the same temperature for 1 hr, tetrafluoroboric acid (40%, 3.3 g, 14.9 mmol) was added to the clear solution. The mixture was stirred at 0-5°C for 2 hrs. The precipitate was collected, washed sequentially with cold water, ethanol, and ether and air dried to give a slightly yellow solid (3.05 g) (CAUTION***: *Dry diazonium salts are explosive*). The dry diazonium salt was mixed with dichlorobenzene (15 mL) with stirring. The mixture was slowly and cautiously (*shield*) heated to 140°C and maintained at this temperature for 1 hr to completely decompose the diazonium salt. After cooling to room temperature, the reaction mixture was poured into 10% sodium carbonate solution. The organic layer was washed twice with water and dried with anhydrous sodium sulfate. The solvent was removed under reduced pressure. The oily residue was purified by TLC (ethyl acetate-petroleum ether 1:1, v/v) and the product was recrystallized from ethanol, to give a pale yellow crystalline solid (1.46 g, 72%, 99.4% purity (HPLC). mp.[8] 82-84°C, *lit.*[6] 60-63°C. IR (KBr): 3077, 1581, 1461, 1254, 1201, 894, 848, 810, 617 cm^{-1}. MS (m/e): 322 (M^+), 161 (1/2 M^+), 126 (161-Cl). ^{1}H-NMR ($CDCl_3$): δ 7.53 (2H, dd, J = 8.8, 6.0), 7.15 (2H, dd, J = 8.2, 2.6), 6.97 (2H, m).

Anal. Calcd for $C_{12}H_6Cl_2F_2S_2$: C, 44.59; H, 1.87; S, 19.84. Found: C, 44.53; H, 1.88; S, 19.62

2-Chloro-4-fluorobenzenesulfonyl Chloride (3).- Compound **2** (3.22 g, 10 mmol) was suspended in 10 mL of conc. hydrochloric acid with vigorous stirring. The mixture was heated to 50-60°C and chlorine was slowly introduced until the concentration of **2** was less than 0.5% (about 3 hrs). The progress of the reaction was monitored with HPLC. After cooling to room temperature, the product was extracted with ether. After separation of the product, the reaction

medium could be reused at least five times with little loss in the yield of **3**. The ethereal extract was washed with 10% aqueous sodium carbonate solution and water and then dried over anhydrous sodium sulfate. The concentrated residue was distilled *in vacuo* to give **5** (4.12 g, 91%) as a slightly yellow liquid, bp. 90-96°C/70Pa, *lit.*[7] 88-90°C *in vacuo*, pressure unreported. IR (film): 3102, 1583, 1465, 1393, 1270, 1215, 1181, 911, 871, 656, 596, 562, 527 cm^{-1}. MS (m/e): 228 (M^+), 193 (M^+-Cl), 129 (193-SO_2). ^{1}H-NMR ($CDCl_3$): δ 8.18 (1H, dd, J = 9.0, 5.4), 7.38 (1H, dd, J = 8.0, 2.4), 7.21 (1H, m).

2-Chloro-4-fluoro-5-nitrobenzenesulfonyl Chloride (4).- Compound **3** (4.56 g, 20 mmol) was dissolved in conc. sulfuric acid (7 mL) cooled below 10°C. Nitric acid (95%, 1.39 g, 21 mmol) was added dropwise at the same temperature over 30 minutes. After stirring for 30 minutes at the same temperature, the mixture was heated at 35-40°C for 1 hr. After cooling, the mixture was decanted into ice-water. The product was extracted twice with chloroform (10 mL x 2), washed with water, 10% aqueous sodium carbonate solution and water, and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*. The solid residue was recrystallized from toluene-*n*-hexane (2:8, v/v) to give a slightly yellow solid (5.24 g, 96%, 98.8% purity (HPLC)), mp. 60-62°C, *lit.*[3] 63-64. IR (KBr): 3105, 1602, 1577, 1381, 1337, 1182, 962, 874, 683, 550, 521 cm^{-1}. MS (m/e): 273 (M^+), 238 (M^+-Cl), 174 (238- SO_2), 128 (174-NO_2), 93 (128-Cl). ^{1}H-NMR ($CDCl_3$): δ 8.91 (1H, d, J = 7.6), 7.68 (1H, d, J = 9.2)

Acknowledgement.- This work was financially supported by the National Basic Research Program of China (2003CB114400) and the Science and Technology Key Project of Zhejiang Province (No. 2004C22004).

REFERENCES

1. T. Nagata and T. Kimoto, JP 4,108,771 [*Chem. Abstr.*, **117**, 150695 (1992)].

2. M. Yamaguchi, C. Suzuki, K. Matsunari, T. Miyazawa, and Y. Nakamura, EP 312,064 [*Chem. Abstr.*, **111**, 35142 (1989)].

3. S. Kojima, M. Hatano, and S. Yanaka, JP 1,168,662 [*Chem. Abstr.*, **112**, 157842 (1990)]

4. Examples: a) G. C. Finger, and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956); b) G. Fuller, GB 1,514,082 [*Chem. Abstr.*, **89**, 197149 (1978)]; c) S. Kojima, M. Hatano, and S. Yanaka, JP 1,168,645 [*Chem. Abstr.*, **112**, 76580 (1990)]; d) D. E. M. Wotton, GB 2,058,067 [*Chem. Abstr.*, **92**, 58778 (1980)]; e) T. Nagata, and N. Tanizawa, JP 3,109,360 [*Chem. Abstr.*, **115**, 231845 (1991)]; f) G. C. Finger, and L. D. Starr, *Chem. Ind.*, **7**, 1328 (1962); g) Z. Y. Xu, X. H. Du, X. S. Xu, and Y. B. Ni, *J. Chem. Res.*, **7**, 496 (2004).

5. T. Pfister and H. U. Blank, DE 2,758,786 [*Chem. Abstr.*, **92**, 6226 (1980)].

6. J. Sato, K. Fukuda, and K. Ito, JP 2,221,254 [*Chem. Abstr.*, **114**, 101337 (1991)].

7. K. Sturm, R. Muschaweck and M. Hropot, *J. Med. Chem.*, **26**, 1174 (1983).

8. The melting point of compound **2** does not agree with that of the literature.[6] The spectral data (IR, ^{1}H NMR, MS and EA) of our product support the assigned structure. Furthermore, the data of **4** synthesized from **2** are consistent with those of the literature.[3]

****

EFFICIENT AND COST-EFFECTIVE SYNTHESIS OF DIALKYL CHLOROPHOSPHATES

Submitted by (06/10/05) P. D. Shakya, D. K. Dubey, Deepak Pardasani, Meehir Palit and A. K. Gupta*

Defence R&D Establishment, Jhansi Road, Gwalior-474002, INDIA
Tel. No.: 91-751-2233488 - E-mail: arvindkumargupta2@rediffmail.com

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates.[1] Dialkyl chlorophosphates have been used in the synthesis of phosphorus based insecticides/pesticides and have also been reported as reactive intermediates or synthons for the transformation of various functional groups such as phosphoramidates, phosphates, enolphosphates, phosphorohydrazides, pseudohalogen phosphates, and many other organophosphorus compounds.[1-9] Recently, diethyl chlorophosphate has been used as an efficient reagent in cyclization reactions[7] and regioselective ring opening of epoxides.[8] Because of their wide utility and our interest in their properties, we decided to reinvestigate their synthesis. A variety of methods have been developed for the preparation of dialkyl chlorophosphates from the reaction of the corresponding phosphites (dialkyl-H-phosphonates/trialkyl phosphites) with various reagents such as elemental chlorine,[10] phosgene,[11] SO_2Cl_2,[12] S_2Cl_2,[13] SCl_2,[14] CCl_4,[15] CCl_3NO_2,[16] $PhSO_2NCl_2$,[17] C_2Cl_6,[18] $ClSCCl_3$,[19] $CuCl_2$,[20] perchlorofulvalene,[21] and *N*-chlorosuccinimide.[22]

Among these methods, only a few could be carried out conveniently in the laboratory and most suffer from other drawbacks. Some of the methods involve the use of toxic reagents and hazardous solvents, lack general applicability and are not environmentally friendly.[10-15] The other methods require long reaction times, use of expensive and unstable reagents, and also pose difficulty in the isolation of the pure products. Thus these constitute major obstacles for scale-up methodology. A modified method (so called Atherton-Todd method) makes use of carbon tetra-