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Hydroxylation of nitro-(pentafluorosulfanyl)benzenes via vicarious nucleophilic substitution of hydrogen

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ABSTRACT

Para- and *meta*-nitro-(pentafluorosulfanyl)benzenes react with anions of cumyl hydroperoxide in the presence of *t*-BuOK in liquid ammonia to form nitro-(pentafluorosulfanyl)phenols. Their reduction with hydrogen in the presence of Raney-Nickel provides amino-(pentafluorosulfanyl)phenols.

The interest of the life science and material industries in novel fluorine-containing substituents is nowadays prevalent. One of such fluorine-containing groups which has gained considerable attention recently, mainly by the crop science and liquid crystal industries, is the pentafluorosulfanyl (SF_5) group.[1] The SF_5 group imparts an unusual combination of properties to organic compounds such as high lipophilicity, strong electron-withdrawing character, and high thermal and hydrolytic stability. However, the lack of good synthetic routes for the preparation of these compounds and the inaccessibility of basic building blocks are currently the main constraints to the exploration of the chemistry and development of applications of compounds with the SF_5 group.

There has been relatively slow development in aromatic sulfur pentafluoride chemistry, despite the fact that (pentafluorosulfanyl)benzenes were first prepared more than 50 years ago.[2] Currently, there are two main synthetic procedures available for SF_5-benzenes both starting from diaryl disulfides. The first method is based on direct fluorination of *para*- or *meta*-substituted bis(nitrophenyl)disulfides with F_2 providing 1-nitro-4-(pentafluorosulfanyl)benzene (**1a**) and 1-nitro-3-(pentafluorosulfanyl)benzene (**1b**).[3] The second method is based on a two-step conversion of diaryl disulfides into (pentafluorosulfanyl)benzenes.[4] Synthetic transformations of nitro-(pentafluorosulfanyl)benzenes are rather limited. The presence of strongly electron-withdrawing groups has prevented the exploration of electrophilic aromatic substitution. Also, nucleophilic aromatic substitution of nitro-(pentafluorosulfanyl)benzenes has not been reported with the exception of S_NAr reactions of the halogen of halo-nitro-(pentafluorosulfanyl)benzenes.[5] Thus, all known reactions of compounds **1** that give SF_5-benzene derivatives start from reduction of the nitro group to give the corresponding (pentafluorosulfanyl)anilines, and are followed by acylation, electrophilic halogenation, or diazotization.[1d,e,2b,3b] Recently, we realized the potential of nucleophilic aromatic substitution of **1** and reported S_NAr reactions of the nitro group with alkoxides and thiolates to generate SF_5 aryl ethers and sulfides,[6] and vicarious nucleophilic substitution (VNS) of hydrogen with carbon pronucleophiles to give substituted nitro-(pentafluorosulfanyl)benzenes (Scheme 1).[7]

In VNS reactions, an aromatic hydrogen of an electron-deficient aromatic or heteroaromatic system is substituted for the nucleophile, with concomitant departure of the leaving group at the nucleophilic centre. VNS reactions have been studied mainly on nitrobenzene derivatives and represent a good method for the introduction of carbon, oxygen and nitrogen functional groups onto aromatic systems.[8] As an extension of our investigation of nucleophilic aromatic displacement chemistry of compounds **1** we have studied their hydroxylation via VNS, which should provide previously unknown nitro-(pentafluorosulfanyl)phenols (**2**).

Anions of alkyl hydroperoxides (ROO^-) contain a leaving group (RO) at the nucleophilic oxygen anion, and have been shown to undergo hydroxylation of nitroarenes via VNS reactions. Due to the rather low nucleophilicity of alkyl hydroperoxide anions the reaction requires electron-deficient nitroarenes such as 3-chloronitrobenzene or 2,4-dinitrochlorobenzene to obtain good yields of nitrophenols. Potassium hydroxide or *tert*-butoxide was used as the base and the reactions were conducted in DMF, or preferably in liquid ammonia.[9]

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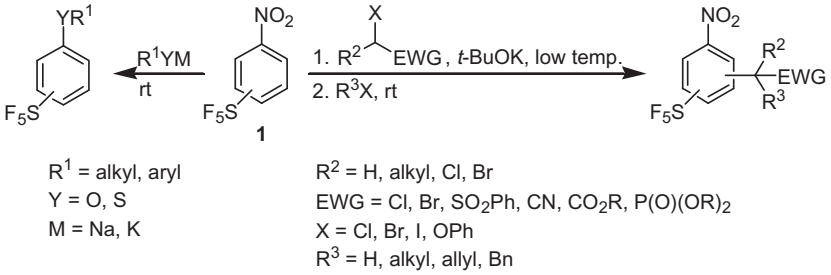
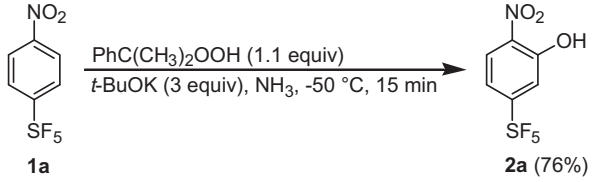


Scheme 1. S_NAr and VNS reactions of **1**.



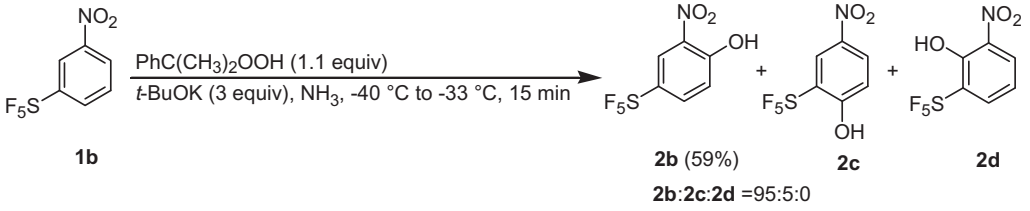
Scheme 2. Hydroxylation of **1a**.

We performed the addition of a mixture of **1a** and cumene hydroperoxide (80% technical, 1.1 equiv) in DMF to a solution of *t*-BuOK (3 equiv) in DMF at −50 °C. Termination of the reaction by addition of aqueous HCl (1 M) after 15 min provided the expected hydroxylation product 2-nitro-5-(pentafluorosulfanyl)phenol (**2a**) in 28% isolated yield. When liquid ammonia was used as the reaction medium under otherwise identical conditions **2a** was isolated in 76% yield (Scheme 2).[10] Increasing the reaction temperature to reflux (−33 °C) and/or increasing the reaction time to 30 min provided **2a** in yields of around 70%.

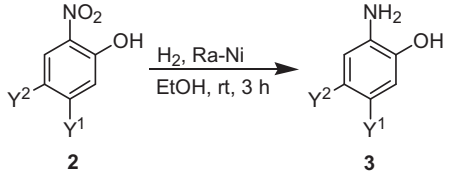
Similar hydroxylation conditions were applied to the *meta*-isomer **1b**. Reaction of **1b**, cumene hydroperoxide and an excess of *t*-BuOK in liquid ammonia at −40 to −33 °C for 15 min gave a mixture of 2-nitro-4-(pentafluorosulfanyl)phenol (**2b**) and its isomer [probably 4-nitro-2-(pentafluorosulfanyl)phenol (**2c**)] in a 95:5 ratio as determined by GC/MS analysis. Our investigations on the VNS reactions of **1b** with carbon pronucleophiles showed that the nucleophile adds preferentially at the *ortho*-position relative to the nitro group (*para*- to the SF_5 group); the minor isomer contained the substituent at the *para*-position relative to the nitro group.[7] Addition of the carbon nucleophile does not take place between the nitro and SF_5 groups probably due to steric reasons. However, in this case, we did not isolate the minor isomer of the hydroxylation reaction and so were unable to prove the structure as **2c** or **2d**. Compound **2b** was isolated from the mixture in 59% yield (Scheme 3).[11] Changing the base to powdered KOH (3 equiv) in either liquid ammonia (−50 °C, 1 h) or DMF (−50 °C, 25 min) did not give any compound **2b** or **2c**; we observed only unreacted **1b** in the reaction mixture. These observations are in contrast to the results reported by Makosza and co-workers on the hydroxylation of *meta*-substituted nitrobenzenes. They identified KOH/NH_3 as the system giving the best yields and observed complete regioselectivity for hydroxylation at the *para*-position relative to the nitro group.[9] The phenol derivatives **2a** and **2b** are new compounds and they have been fully characterized by spectroscopic methods.

Amino-(pentafluorosulfanyl)phenols, **3** were synthesized conveniently from nitro-(pentafluorosulfanyl)phenols **2** by catalytic hydrogenation with hydrogen in the presence of Raney-Nickel. Aminophenols **3** are also new compounds and were isolated in good to high yields (Scheme 4).[12]

In summary, in the present work, the hydroxylation of *para*- and *meta*-nitro-(pentafluorosulfanyl)benzenes **1a** and **1b** via vicarious nucleophilic substitutions of hydrogen with cumene hydroperoxide in the presence of excess potassium *tert*-butoxide in liquid ammonia has provided novel nitro-(pentafluorosulfanyl)phenols **2a** and **2b**, respectively, in good to high yields. High regioselectivity was observed for the VNS hydroxylation of **1b**. Reduction of the nitro groups of **2a** and **2b** with hydrogen in the presence of Raney-Nickel gave novel aminophenols **3a** and **3b**, respectively, in good to high yields. These four new phenol derivatives **2** and **3** can be utilized as basic building blocks for the synthesis of SF_5-benzenes.



Scheme 3. Hydroxylation of **1b**.



2	Y^1	Y^2	3	Yield
2a	SF_5	H	**3a**	81%
2b	H	SF_5	**3b**	72%

Scheme 4. Nitro group reduction of nitrophenols **2**.

For example, further derivatization may exploit the nucleophilic character of the hydroxy or amino groups, diazotization of the amino group (and follow-up reactions), or electrophilic aromatic substitution chemistry of compounds **3**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.011.

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10. *Experimental procedure*: To a stirred solution of *t*-BuOK (337 mg, 3 mmol) in liquid NH_3 (ca. 5 mL) at −40 °C was added dropwise a solution of **1** (249 mg, 1 mmol) and cumene hydroperoxide (80%, 203 μL, 1.1 mmol) in dry THF (1 mL). The resulting brown mixture was stirred at −50 °C (for **1a**) or −40 to −33 °C (for **1b**) for 15 min followed by the addition of solid NH_4Cl and evaporation of NH_3. The resulting mixture was treated with HCl (1 M) to pH 0 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with NaOH (0.5 M, 3 × 15 mL), the alkaline solution was acidified with HCl (6 M) to pH 0 and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$) and evaporated. Column chromatography (SiO_2, hexane/EtOAc) gave products **2**.
Compound **2a** (201 mg, 76%) pale yellow liquid; R_f 0.38 (hexane/EtOAc, 97:3); ν_{max}/cm^{-1} (neat) 3275, 3120, 3077, 1625, 1591, 1540, 1476, 1443, 1318, 1262, 1238, 1181, 1109, 1067, 939, 843, 809, 757; δ_H (400 MHz, $CDCl_3$) 7.40 (dd, 1H, J = 9.3, 2.4 Hz), 7.62 (d, 1H, J = 2.4 Hz), 8.23 (d, 1H, J = 9.3 Hz), 10.56 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 117.6 (quin, J = 4.7 Hz), 118.9 (quin, J = 4.8 Hz), 125.6, 134.6, 154.5, 158.8–159.6 (m); δ_F (376 MHz, $CDCl_3$) 61.3 (d, 4F, J = 150.7 Hz), 79.4–80.7 (m, 1F); m/z (EI) 265 $[M]^+$ (100%), 127 (12), 99 (15), 89 (21), 83 (27), 63 (31), 62 (14), 57 (14), 53 (17); m/z (EI) calcd for $C_6H_4F_5NO_3S$ $[M]^+$, 264.9832; found, 264.9829.
11. Compound **2b** (156 mg, 59%) pale yellow liquid; R_f 0.28 (hexane/EtOAc, 85:15); ν_{max}/cm^{-1} (neat) 3262, 3124, 3104, 1627, 1589, 1545, 1486, 1433, 1334, 1266, 1196, 1109, 1080, 909, 834, 818; δ_H (400 MHz, $CDCl_3$) 7.7 (d, 1H, J = 9.3 Hz), 7.97 (dd, 1H, J = 9.3, 2.7 Hz), 8.57 (d, 1H, J = 2.7 Hz), 10.79 (br s, 1H); δ_C (100 MHz, $CDCl_3$) 120.5, 123.9 (quin, J = 5.0 Hz), 132.3, 134.3 (quin, J = 4.4 Hz), 144.9–145.7 (m), 156.5; δ_F (376 MHz, $CDCl_3$) 63.3 (d, 4F, J = 151.1 Hz), 81.1–82.7 (m, 1F); m/z (EI) 265 $[M]^+$ (100%), 246 (14), 89 (16), 83 (26), 82 (14), 63 (23), 53 (13); m/z (CI) calcd for $C_6H_5F_5NO_3S$ $[MH]^+$, 265.9910; found, 265.9916.
12. *Experimental procedure*: A suspension of Raney-Nickel (100–200 mg) was washed with EtOH (2 × 15 mL). A solution of **2** (150 mg, 0.57 mmol) in EtOH (20 mL) was added, a balloon filled with H_2 was attached, and the system was evacuated and filled with H_2 (3 cycles). The mixture was stirred at ambient temperature for 3 h, followed by filtration, washing with hot THF (5 × 5 mL), and the solvent evaporated to give aniline **3**.
Compound **3a** (108 mg, 81%) white solid; mp 142–143 °C ($CHCl_3$); R_f 0.28 (hexane/EtOAc, 3:1); ν_{max}/cm^{-1} (neat) 3427, 3351, 3074, 2921, 2708, 1611, 1525, 1447, 1291, 1271, 1219, 1099, 848, 804; δ_H (400 MHz, DMSO-d_6) 5.37 (br s, 2H), 6.60–6.63 (m, 1H), 7.04–7.07 (m, 2H), 9.77 (br s, 1H); δ_C (100 MHz, DMSO-d_6) 111.0 (quin, J = 4.4 Hz), 114.4, 117.7 (quin, J = 4.5 Hz), 140.5–141.0 (m), 142.1; δ_F (376 MHz, DMSO-d_6) 67.2 (d, 4F, J = 150.4 Hz), 92.2–93.8 (m, 1F); m/z (EI) 235 $[M]^+$ (100%), 127 (51), 108 (22), 98 (22), 89 (12), 80 (24); m/z (ESI) calcd for $C_6H_7F_5NOS$ $[MH]^+$, 236.01623; found, 236.01630.
Compound **3b** after column chromatography (SiO_2, hexane/EtOAc) (96 mg, 72%) white solid; mp 103–104 °C; R_f 0.25 (hexane/EtOAc, 3:1); ν_{max}/cm^{-1} (neat) 3393, 3319, 3074, 2945, 2808, 2705, 2636, 2578, 1600, 1514, 1451, 1275, 1217, 1079, 937, 902, 830, 813; δ_H (400 MHz, $CDCl_3$) 5.15 (br s, 3H), 6.64 (d, 1H, J = 8.7 Hz), 7.03 (dd, 1H, J = 8.7, 2.6 Hz), 7.14 (d, 1H, J = 2.6 Hz); δ_C (100 MHz, $CDCl_3$) 113.9, 114.3 (quin, J = 4.6 Hz), 117.8 (quin, J = 4.8 Hz), 133.8, 146.5, 146.9 (quin, J = 17.2 Hz); δ_F (376 MHz, $CDCl_3$) 63.8 (d, 4F, J = 149.9 Hz), 85.5–87.1 (m, 1F); m/z (EI) 235 $[M]^+$ (100%), 127 (29), 108 (24), 98 (18), 80 (30); m/z (EI) calcd for $C_6H_6F_5NOS$ $[M]^+$, 235.0090; found, 235.0086.