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S_NAr Reactions of Nitro-(pentafluorosulfanyl)benzenes To Generate SF_5 Aryl Ethers and Sulfides

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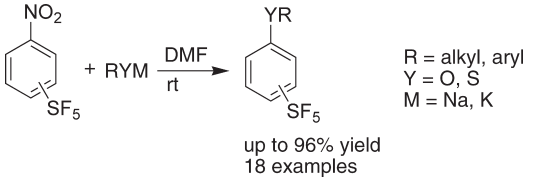
ABSTRACT



Nucleophilic aromatic substitution of the nitro group of *para*- and *meta*-nitro-(pentafluorosulfanyl)benzene with alkoxides and thiolates generates a range of substituted 4- and 3-(pentafluorosulfanyl)benzenes in a single-step reaction.

Organic compounds with pentafluorosulfanyl (SF_5) groups display a unique set of physicochemical properties. This includes extreme kinetic and hydrolytic stability, very strong electron acceptor capability, and high lipophilicity with high SF_5 electronegativity. A very high dipole moment can be achieved by the introduction of the SF_5 group without increasing molecular polarity. These properties make the pentafluorosulfanyl group an increasingly interesting structural motif for the design of bioactive compounds, including agrochemicals and pharmaceuticals as well as functional materials such as polymers or liquid crystals.[1,2]

Selective introduction of the pentafluorosulfanyl group into aliphatic compounds is usually achieved by radical addition of SF_5X (X = Cl, Br) to unsaturated compounds;[3] however access to SF_5Cl and SF_5Br is difficult[4] and the chemistry of aliphatic SF_5 derivatives remains relatively unexplored.[5]

Early syntheses of (pentafluorosulfanyl)benzenes based on the reaction of benzene with S_2F_{10} or oxidative fluorination of diaryldisulfides with AgF_2 suffered from low yields and poor reproducibility.[6] However, in the mid-1990s improved procedures based on direct fluorination of bis(nitrophenyl)disulfides were developed[7] providing access to larger quantities of 1-nitro-4-(pentafluorosulfanyl)-benzene (**1**) and 1-nitro-3-(pentafluorosulfanyl)benzene (**2**).[8] The nitro group is necessary to avoid direct fluorination of the aromatic ring. Another breakthrough came in 2008 when Umemoto developed a two-step procedure for the synthesis of (pentafluorosulfanyl)arenes.[9]

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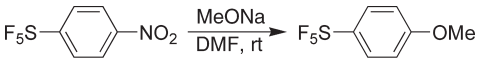
Several straightforward synthetic transformations of aryl-SF_5 compounds are described. (Pentafluorosulfanyl)-benzene is nitrated to give the *meta*-substituted product **2** in 81% yield. The nitroderivatives **1** and **2** undergo reduction to corresponding (pentafluorosulfanyl)anilines in very good yields. These aniline derivatives can be acylated, halogenated, or diazotized. The diazonium salts may be coupled (for example to β-naphthol), hydrolyzed to phenol, converted to halides by the Sandmeyer reaction, or reduced with H_3PO_2 to (pentafluorosulfanyl)benzene. Halo-(pentafluorosulfanyl)benzenes were reported to undergo lithiation, Grignard salt formation, or Pd(0)-catalyzed cross-coupling reactions.[2,6,7,10] Recently, it was shown that the fluorine atom of 1-fluoro-4-nitro-2-(pentafluorosulfanyl)benzene and 1,3-dichloro-2-fluoro-5-(pentafluorosulfanyl)benzene can be replaced by a variety of nucleophiles in moderate yields.[2,11]

The strong electron-withdrawing character of the nitro group makes the aromatic nitro compounds suitable for nucleophilic aromatic substitution.[12] The nitro group also shows high nucleofugacity, and its departure from the aromatic system frequently occurs if there is appropriate activation by other electron-withdrawing groups such as NO_2, CN, CO_2R, and CF_3.[13] Intriguingly, the S_NAr chemistry of the *para*- and *meta*-isomers **1** and **2** has not been studied, and we hypothesized that under appropriate conditions it should be possible to substitute the nitro group by suitable nucleophiles. In this *Letter*, we report successful outcomes which now provide access to a variety of new aromatic SF_5-containing compounds and should be of high utility.

Nucleophilic addition of MeONa provided the initial focus. The addition of MeONa (1.5 equiv) to a solution of **1** in DMF at ambient temperature resulted in a moderately exothermic reaction with formation of a dark violet to black reaction mixture. After 5 min the color changed to light brown and 1-methoxy-4-(pentafluorosulfanyl)benzene (**3a**) formed in 30% conversion as judged by GCMS analysis (Table 1, entry 1). Optimization of the nucleophile equivalence and reaction time revealed that a 3-fold excess of MeONa is necessary for a >90% conversion in 1−2 h. It proved to be beneficial to add MeONa sequentially in two portions rather than all at once (Table 1).

Solvent screening measuring conversions under otherwise identical conditions to those reported in Table 1, entry

Table 1. Initial Optimization in the Preparation of **3a** from **1**[a]



1 **3a**

no.	MeONa/equiv (time of addition/min)	time/min	**3a**, conv, %[b]
1	1.5	5	30
2	1.5	30	42
3	1.5 + 1.5 (420)	450	76
4	1 + 1 (13) + 1 (33)	150	65
5	1 + 1 (13) + 1 (33) + 1 (240)	270	87
6	1.5 + 1.5 (30)	35	69
7	1.5 + 1.5 (30)	45	84
8	1.5 + 1.5 (30)	60	90 (83)
9	3	30	>95 (76)

[a] Reaction conditions: **1** (0.5 mmol), MeONa, DMF (1 mL), rt. [b] Conversion of **3a** was determined by GCMS, in brackets isolated yields.

8 identified DMF as the best solvent (toluene or methanol 0%, THF <2%, DMF 90%, DMA 73%, DMSO 75%, DMP 13%, DMPU 13%, HMPA 81%); using DMF as the optimal solvent, concentration optimization in the range 0.1−4.0 M was explored. The reaction tolerates a wide concentration range where high product conversions can be achieved. However, the optimal concentration range was found to be 0.25−2.0 M, where **3a** was prepared in 83% yield (97% based on recovered **1**).

The scope of the S_NAr reaction with various metal alkoxides and thiolates (Table 2) was explored. Commercial reagents were added to the solution of **1** in DMF. Alternatively, they were prepared in situ by the reaction of alcohol or thiol with sodium metal or *t*-BuOK. The presence of *t*-BuOH in the reaction mixture did not have any detrimental effect. Alkoxides derived from primary alcohols gave products in good to excellent yields (Table 2, entries 1−5). A reduced yield in the reaction with 2-phenylethanolate was due to the formation of styrene as a side product (Table 2, entry 6). Sodium trifluoroethanolate gave only a moderate yield of **3g**, presumably because of its relatively low nucleophilicity (Table 2, entry 7). The potassium salt of 1,2-isopropylideneglycerol generated **3h** in good yield (Table 2, entry 8). Straightforward ketal deprotection[14] gave 3-(4-(pentafluorosulfanyl)phenoxy)-propane-1,2-diol (**4**) in 97% yield — a derivative of the commercially successful beta-blocker drugs used as antiarrhythmic, muscle relaxant, antihypertensive, antianginal, and antifungal agents.

Sterically more demanding alkoxides derived from secondary alcohols gave satisfactory results (Table 2, entry 9), while the use of *t*-BuOK was largely unsuccessful despite the formation of a deep violet complex in the reaction mixture (Table 2, entry 10). The reaction of **1** with potassium phenolate also gave 1-nitro-4-phenoxybenzene as a

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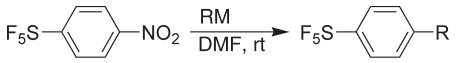
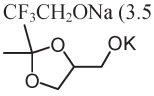
Table 2. Reaction Scope of the Preparation of **3** from **1**



1 **3**

no.	reagent (RM)	time/h	**3**, yield, %[a]
1	MeONa (2 × 1.5 equiv)	1	**3a**, 83
2	EtONa (2 × 1.5 equiv)	1	**3b**, 74
3	*n*-PrONa (2 × 1.5 equiv)	0.5	**3c**, 71
4	*n*-$C_8H_{17}OK$ (4 equiv)	0.3	**3d**, 83
5	$PhCH_2OK$ (2 × 1.5 equiv)	1	**3e**, 96
6	$PhCH_2CH_2OK$ (2 × 1.5 equiv)	0.5	**3f**, 63
7	CF_3CH_2ONa (3.5 equiv)	3	**3g**, 69
8	 (3 equiv)	0.5	**3h**, 58
9	*i*-PrOK (2 × 1.5 equiv)	1.5	**3i**, 53
10	*t*-BuOK (3 equiv)	120	**3j**, 3[b]
11	PhOK (5 equiv)	17	**3k**, 59
12	C_6F_5OK (4 equiv)	24	**3l**, 0
13	MeSNa (3 equiv)	16	**3m**, 64
14	*n*-$C_8H_{17}SK$ (0.5 equiv)	1	**3n**, 43
15	*t*-BuSNa (3 equiv)	1	**3o**, 14[c]
16	PhSNa (3 equiv)	1	**3p**, traces[d]

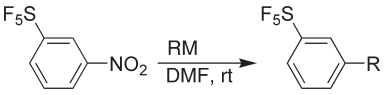
[a] Isolated yield. [b] GCMS conversion. [c] Inseparable mixture of **3o** and *t*-BuSSBu-*t* was obtained. The yield is calculated on **3o**. [d] The main product (4-nitrophenyl)(phenyl)sulfane formed in 45% conversion.

side product with the expected **3k**. A large excess of the nucleophile (5 equiv) was necessary to drive the reaction to completion, and it proved to be beneficial to add the solution of PhOK slowly using a syringe pump. In this way, **3k** was isolated in 59% yield and the side product in 19% (Table 2, entry 11). Potassium pentafluorophenolate proved to be too weak a nucleophile to effect substitution (Table 2, entry 12). The reaction of **1** with sodium methanethiolate gave good conversion to sulfide **3m** (Table 2, entry 13). With in situ generated potassium *n*-octanethiolate, sulfide **3n** was formed in good conversion; however purification from unreacted thiol and the dioctyldisulfide side product proved to be difficult. Therefore a 2-fold excess of **1** was used in order to avoid the formation of this side products (Table 2, entry 14). Interestingly, in contrast to *t*-BuOK, reaction with *t*-BuSNa gave **3o**, albeit in low yield with *t*-BuSSBu-*t* (Table 2, entry 15).

Next, we investigated analogous nucleophilic substitution reactions using *meta*-substituted nitrobenzene **2** (Table 3). Moderate to good yields of the desired 1-alkoxy-3-(pentafluorosulfanyl)benzenes (**5**) were achieved in the reaction of metal alkoxides derived from primary alkyl alcohols, although a large excess of the alkoxides and longer reaction times relative to the reactions with **1** were needed for good conversions (Table 3, entries 1−3). Reactions with phenolate or alkanethiolates nucleophiles gave only traces of products **5k**−**5n** (Table 3, entries 4−6) confirming that the *meta*-substrate is considerably less activated than the *para*- for S_NAr.

In order to demonstrate the synthetic utility of the method, several subsequent transformations of alkoxy-(pentafluorosulfanyl)benzenes were realized. Deprotections

Table 3. Reaction Scope of the Preparation of **5** from **2**

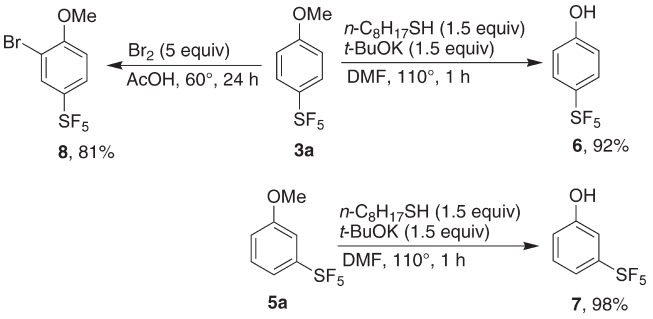


2 **5**

no.	reagent (RM)	time/h	**5**, yield, %[a]
1	MeONa (3 × 1.5 equiv)	5	**5a**, 52
2	*n*-PrONa (6 equiv)	1	**5c**, 41
3	$PhCH_2OK$ (5 × 1 equiv)	2.5	**5e**, 42
4	PhOK (5 equiv)	16	**5k**, traces[b]
5	MeSNa (3 equiv)	21	**5m**, traces[b]
6	*n*-$C_8H_{17}SK$ (0.5 equiv)	1	**5n**, traces[b]

[a] Isolated yield. [b] Detected by GCMS analysis in trace amounts.

Scheme 1. Synthesis of Compounds **6**−**8**



of the methoxyderivatives **3a** and **5a** to 4-(pentafluorosulfanyl)phenol (**6**, in 92% yield) and 3-(pentafluorosulfanyl)phenol (**7**, in 98% yield), respectively, were carried out by modification of the method of Shingare and co-workers.[15] This two-step synthesis of phenols **6** (77% overall yield from **1**) and **7** (51% overall yield from **2**) is superior to published methods (Scheme 1). For example, the best reported synthesis of **6** starts from **1** involving nitro group reduction, diazotation, bromo arene formation, lithiation, a reaction with trimethylborate, hydrolysis, and then oxidation with hydrogen peroxide in an overall 26% yield.[10]

Bromination of **3a** gave 2-bromo-1-methoxy-4-(pentafluorosulfanyl)benzene (**8**) in 81% yield (Scheme 1). Importantly, in the presence of an excess of bromine no overbromination was observed. When the same conditions were applied to **1**, no bromination took place. Halo-(pentafluorosulfanyl)benzenes undergo a variety of Pd(0)-catalyzed C−C cross-coupling reactions, and similar reactivity can be expected for bromobenzene **8**.

In summary, it was demostrated that nucleophilic aromatic substitutions of nitro groups in nitro-(pentafluorosulfanyl)benzenes **1** and **2** with alkali metal alkoxides

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and thiolates is a useful and operationally simple process for the synthesis of SF_5-containing aryl ethers and sulfides. Transformations of methoxy-(pentafluorosulfanyl)benzenes **3a** and **5a** to (pentafluorosulfanyl)phenols **6** and **7**, respectively, took place in excellent yields and represent a new method for their synthesis. Regioselective monobromination of **3a** to 2-bromo-1-methoxy-4-(pentafluorosulfanyl)-benzene **8** was achieved in a very good yield.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.