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# Regioselective Nucleophilic Substitutions of Fluorobenzene Derivatives

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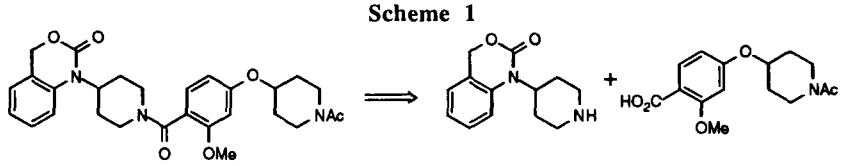
***Abstract:*** *Regioselective nucleophilic substitutions of tri- and di-substituted fluorobenzoates, fluorobenzonitriles, and fluoronitrobenzenes were accomplished by sequential addition of various nucleophiles, such as, potassium N-Boc-4-piperidinyl oxide, potassium methoxide, and piperidine.* Copyright © 1996 Elsevier Science Ltd

Recently, an orally bioavailable, non-peptide oxytocin antagonist L-371,257 (**1**) was identified as an attractive target for treating preterm labor.[1] A highly convergent synthesis of **1** was derived from the intermediates **2** and **3** (Scheme 1).

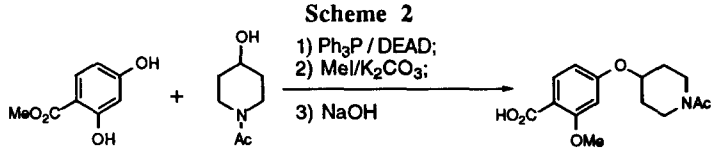
**Scheme 1**




**1** (L-371,257) **2** **3**

The key intermediate **3** was prepared in 50% overall yield via a sequence involving a selective Mitsunobu coupling of methyl 2,4-dihydrobenzoate (**4**) with N-acetyl-4-piperidinol (**5**), methylation of the 2-hydroxyl with methyl iodide, and saponification (Scheme 2).

**Scheme 2**

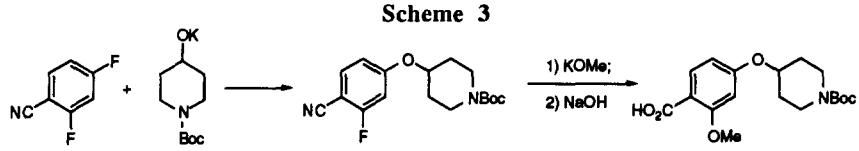



**4** **5** **3**

During our process development on the drug candidate **1**, we desired a more efficient synthesis of aryl ether intermediate **3** that would avoid the Mitsunobu reaction. We envisioned that sequential regioselective addition of alkoxide nucleophiles to an appropriately substituted aromatic fluoro system should allow rapid access to the desired aryl ether linkages. The addition of potassium N-Boc-4-piperidinoxide (**7**)[2] to 2,4-difluorobenzonitrile (**6**) at -55°C, afforded the adduct **8**, which resulted from regioselective displacement at the para position of the difluorinated benzonitrile. Subsequent addition of potassium methoxide to the crude reaction

mixture at -65°C and hydrolysis of the nitrile gave the desired acid **9** in 75% isolated yield for the three step sequence (Scheme 3).

**Scheme 3**

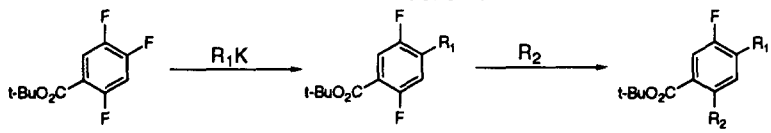



**6** **7** **8** **9**

Nucleophilic displacements of fluoride from polyfluoro aromatic systems have been reported in the literature and have lately found extensive use in organic synthesis and in the preparation of pharmaceutically active compounds.[3] However, while these displacements are useful for single displacements of fluoride from a polyfluoro aromatic, a systematic study of the regiochemistry of multiple displacement reactions of di- and tri-fluorinated aromatic compounds has not been reported.[4]

In the course of our study of the alternative synthesis of **9**, we envisioned that the sequential regioselective addition to fluoroaromatics may have broader synthetic utility than has been reported to date. Herewith, we report a systematic study of stepwise regioselective additions of various nucleophiles to tri- and di- substituted fluorobenzene derivatives.

**Scheme 4**




**10**

**11a** $R_1$ = O-⟨⟩-NBoc (-65°C)

**11b** $R_1$ = OBn (-65°C)

**11c** $R_1$ = N⟨⟩ (25°C)

**12a** $R_1$ = O-⟨⟩-NBoc, $R_2$ = OMe (5°C)

**12b** $R_1$ = O-⟨⟩-NBoc, $R_2$ = OBn (5°C)

**12c** $R_1$ = O-⟨⟩-NBoc, $R_2$ = N⟨⟩ (65°C)

**12d** $R_1$ = $R_2$ = OBn (5°C)

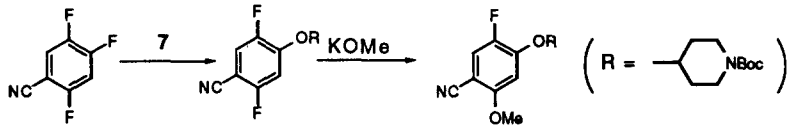
**12e** $R_1$ = OBn, $R_2$ = N⟨⟩ (65°C)

**12f** $R_1$ = N⟨⟩, $R_2$ = OBn (5°C)

Tert-butyl-2,4,5-trifluorobenzoate (**10**) was prepared from its acid using classical methods[5] and was used in our preliminary investigation of regioselective nucleophilic displacements of aromatic fluorides (Scheme 4). In most cases, the initial fluoride displacement gave the best selectivity at -65°C. The second displacement occurred at 5°C. Only in the case of the piperidine displacement was higher temperatures needed for both displacements. Treatment of **10** with the pregenerated potassium alkoxide of N-Boc-4-piperidinol **7**, at -65°C gave exclusive displacement at the 4-position to yield the aryl ether **11a** in 64% yield. When ester **10** was treated in an analogous manner with either potassium benzyl oxide or of piperidine (2.2 eq) the reactions yielded the 4-substituted products **11b** in 95% yield and **11c** in 97% yield, respectively. In all cases, no detectable displacement at the 2-position occurred under these reaction conditions as judged by $^1$H NMR. However, when these reactions were repeated at room temperature, we found that selectively was substantially eroded (i.e. close

to 1/1, para/ortho). Thus displacement of the ortho fluoride is also a facile process. When aryl ether **11a** was treated with potassium methoxide the 2-position reacted to give the methyl ether **12a** in 80% yield. Reaction of **11a** with potassium benzyl oxide or piperidine (2.2 eq) was also carried out to yield **12b** in 78% yield and **12c** in 75% yield, respectively, as the sole products. Likewise treatment of **11b** or **11c** with potassium benzyl oxide or piperidine produced **12d**, **12e**, and **12f**. The yields in each of these cases was 70% or better. In each of these reaction sequences (**10** to **11** to **12**) the selectivity was greater than 20/1.

**Scheme 5**

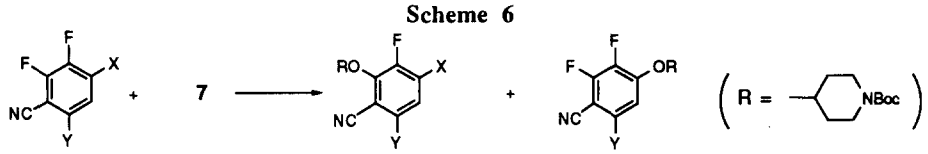



**13** **14** **15**

Trifluorobenzonitriles were also found to undergo highly regioselective substitution reactions. For example, the 4-position of 2,4,5-trifluorobenzonitrile **13** underwent displacement by alkoxide **7** at low temperature to yield the aryl ether **14** in 90% yield (Scheme 5). Again, no displacement of the 2-fluoro substituent was detected. When **14** was subsequently treated with potassium methoxide, reaction at the 2-position occurred giving the methyl ether **15** in 85% yield.

We next explored different substitution patterns on the aromatic ring with interesting results (scheme 6). Thus 2,3,6-trifluorobenzonitrile **16a** was treated with the pregenerated alkoxide of Boc-4-piperidinol **7** resulting in selective displacement at the 2-position yielding **17a** (Scheme 6). This demonstrates a significant ortho directing influence of the 3-fluoro substituent. In the case of 2,3,4 trifluorobenzonitrile (**16b**) a mixture of regioisomers **17b** and **18b** were obtained, suggesting that the ortho effect of the 3-fluoro group is strong enough to overcome the apparent preference of the cyano group to direct para over ortho substitution (as in **6**).

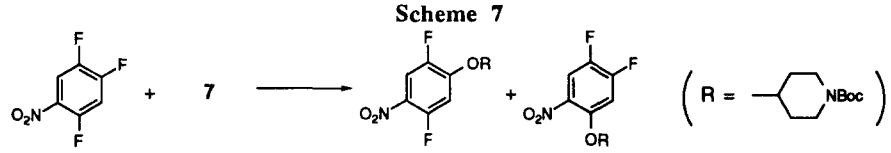
**Scheme 6**




**16a**, X = H; Y = F; **16b**, X = F; Y = H. **17a**, X = H; Y = F; **17b**, X = F; Y = H. **18b**, Y = H

In the case of 2,4,5-trifluoronitrobenzene (**19**), the selectivity was not as great (scheme 7). A 5/1 mixture of 4-substituted **20a**/2-substituted **20b** regioisomers was obtained in 70% yield. This suggests that the nitro group is less para directing than either cyano or alkoxycarbonyl.

**Scheme 7**




**19** **20a** **20b**

In conclusion, we have demonstrated that stepwise substitutions of polyfluorobenzene derivatives with various nucleophiles can be controlled with exceptional regioselectivity. This is a powerful method for the

synthesis of diverse multisubstituted benzene derivatives, which are commonly useful in the pharmaceutical area. We have utilized this methodology for the efficient preparation of a key intermediate in the synthesis of the oxytocin antagonist L-371,257 (**1**) and believe that it represents an efficient methodology for production of alternative compounds in this series. In addition, the high regioselectivity observed in sequential additions of a variety of nucleophiles makes this method amenable to combinatorial synthetic techniques.[7]

**Acknowledgments:** We wish to thank Robert Reamer and Lisa DiMichele for assistance with interpretation of NMR spectra.

**References and Notes**

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2. N-Boc-4-piperidinol was prepared from 4-piperidinol (Aldrich) and di-t-butyl-dicarbonate.

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4. A limited report of the selectivity of displacements of o,p-difluorophenyl ketone systems has appeared: Sasajima, K.; Ona, K.; Katsube, J.; Yamamoto, H. *Chem. Pharm. Bull.* **1978**, *26*, 2502-2507.

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6. Typical experimental procedure: Difluoronitrile **14** from Trifluoronitrile **13**. A t-BuOK solution (1.0 M, 5.0 mL) was slowly added to a solution of N-Boc-4-piperidinol (1.0 g, 4.97 mmol) in THF (3.0 mL) at 5 °C and was stirred for 0.5 h. It then was transferred to a cold solution of trifluoronitrile **13** (Aldrich, 0.569 mL, 4.97 mmol) in THF (3.0 mL) at -65°C. The reaction mixture was stirred at -65°C for 3.0 h and then allowed to warm to 25 °C over 1.0 h. The stirring continued at rt overnight. The reaction mixture was quenched with water (25 mL) and diluted with MTBE (100 mL). The organic layer was separated and washed with water (35 mL), brine (35 mL), and dried over $MgSO_4$. Evaporation of the solvent under vacuum provided 1.65 g of a white solid **14** (90% assay yield by HPLC). Spectral data for **14**: $^1H$ NMR (300 MHz) 7.28 (dd, J=10.0, 3.6 Hz, 1H), 6.80 (dd, J= 10.0, 6.6 Hz, 1H, 4.65-4.50 (m, 1H), 3.72-3.64 (m, 2H), 3.43-3.20 (m, 2H), 1.95-1.92 (m, 2H), 1.84-1.79 (m, 2H), 1.43 (s, 9H); $^{13}C$ NMR (300MHz) 160.5 (dd, $J_{C-F}$ = 256.0, 2.6 Hz), 151.9 (d, $J_{C-F}$ = 10.2 Hz) 149.0 (dd, $J_{C-F}$ = 246.4, 2.9 Hz), 119.4 (dd, $J_{C-F}$ = 23.2, 2.5 Hz), 113.2, 104.2 (d, $J_{C-F}$ =24.5 Hz), 92.2 (dd, $J_{C-F}$ = 17.8, 8.5 Hz), 79.9, 79.8, 75.1, 40.3, 30.1, 28.4.

   Monofluoronitrile **15** from Difluoronitrile **14**. MeOH (0.151 mL, 3.73 mmol) was added to a solution of t-BuOK in THF (1.0 M, 3.73 mL) at 5°C, a light suspension was observed, which was stirred for 0.5 h at 5 °C. The light suspension was cannulated into a cold solution of difluoronitrile **14** (0.84 g, 2.485 mmol) in THF (3.0 mL) at -50 °C and then aged for 1.0 h at -50°C. The reaction mixture was warmed to 5 °C over 0.5 h and stirred at 5 °C for 2 h after which the reaction was quenched with water (15 mL). The reaction mixture was diluted with MTBE (100 mL), and organic layer was washed with water (35 mL) and brine (35 mL). After drying over $MgSO_4$ the organic layer was evaporated to dryness to provide a wax solid of difluoronitrile **15** (0.83 g, 95% assay yield by HPLC). Spectral data for **15** : $^1H$ NMR (300 MHz) 7.21 (d, J=10.2 Hz, 1H), 6.53 (d, J= 6.6 Hz, 1H, 4.61-4.57 (m, 1H), 3.86 (s, 3H), 3.70-3.60 (m, 2H), 3.40-3.17 (m, 2H), 1.95-1.86 (m, 2H), 1.81-1.73 (m, 2H), 1.43 (s, 9H); $^{13}C$ NMR (300MHz) 159.0, 154.7, 150.4, 146.9 (d, $J_{C-F}$ = 240 Hz), 120.2 (d, $J_{C-F}$ = 22.8 Hz), 115.7, 101.0, 93.1, 79.7, 74.8, 56.7, 30.4, 28.4, 26.9.

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