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Novel Synthesis of Desymmetrized Resorcinol Derivatives: Aryl Fluoride Displacement on Deactivated Substrates

Aujin Kim,† Jeremiah D. Powers, and Jennifer F. Toczko*

Synthetic Chemistry, Chemical Development, GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, North Carolina 27709

jennifer.f.toczko@gsk.com

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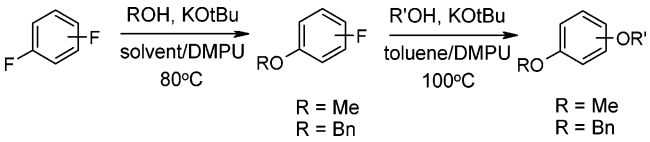

A short, high-yielding synthesis of differentially substituted resorcinol derivatives has been developed that utilizes 1,3-difluorobenzene as the starting material and employs sequential nucleophilic aromatic substitution (S_NAr) reactions to generate desymmetrized products. The scope and limitations of the second S_NAr reaction on the deactivated 1-alkoxy-3-fluorobenzene intermediates have been investigated. This methodology has also been employed in the synthesis of desymmetrized catechol derivatives from 1,2-difluorobenzene.

In the course of our work, it became necessary to synthesize a variety of nonsymmetrical resorcinol derivatives. A survey of the literature showed that this is a nontrivial problem,[1] and traditional methods of differentiating the alcohol moieties on resorcinol have numerous drawbacks. A classical monoalkylation approach requires a large excess of resorcinol to avoid overalkylation.[1b,2] When nearly stoichiometric amounts of resorcinol and electrophile are used, the alkylation reaction is unselective and low yielding, resulting in a mixture of resorcinol, mono-, and bis-alkylated products.[3]

Desymmetrization can be achieved by the selective deprotection of several bis-protected resorcinols;[4] however, syntheses of differentiated 1,3-alkoxybenzenes from these starting materials require numerous protecting group manipulations. Differentiated resorcinols have also been generated by the alkylation of commercially available 3-methoxyphenol;[5] however, highly substituted aryl ethers cannot be synthesized by this method. Metal-catalyzed coupling reactions have been carried out on 3-haloanisoles to generate 3-methoxy-substituted desymmetrized resorcinols. Although many of these coupling reactions are limited to tertiary alcohols,[6] examples of metal-catalyzed couplings of primary and secondary alcohols and 1-alkoxy-3-halobenzenes have been described.[1b,7]

Given this background, we felt that the investigation of a new route of entry into differentially alkylated resorcinols was warranted. Commercially available 1,3-difluorobenzene appeared to be an ideal starting material to access these types of molecules. We reasoned that the first fluoride displacement by an alkoxide should generate a desymmetrized 1-alkoxy-3-fluorobenzene intermediate which is deactivated toward further alkoxide displacement because of the electron-donating ability of the 1-alkoxy substituent. Subjecting this intermediate to more vigorous displacement conditions could then provide the desired resorcinol products.

Although the displacement of aryl fluorides on electron-deficient aromatic rings is well documented, the second fluoride displacement, which will take place on an electron-rich aromatic ring, is less well-known.[8] Current literature methods of fluoride displacement by an alkoxide on deactivated substrates include activation of the alkoxy fluorobenzene by complexation with chromium(III) prior to fluoride displacement, followed by oxidative removal of the metal,[9] and photochemical conditions.[10]

Seeing an opportunity to develop a short, efficient route to differentially substituted resorcinols, we set about exploring their synthesis from 1,3-difluorobenzene (**1**).

Desymmetrization of **1** with a selective S_NAr reaction using benzyl alcohol or methanol generates **2a**,**b** in high yield.

Over the course of our work, we observed that the addition of the polar, aprotic cosolvent 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) consistently resulted in the consumption of the starting material and decreased the reaction time, allowing for better control over the formation of the bis-addition byproducts. Using the potassium alkoxide generated from KO^{t}Bu (2.4−2.5 equiv) and alcohol (3 equiv) in a toluene/DMPU or a DME/DMPU solvent mixture provided the best results (Table 1). DME was chosen as the cosolvent in the 3-fluoroanisole (**2b**) synthesis because of the fact that the lower boiling point allowed for easier isolation of the product.

With **2a**,**b** in hand, we next turned our attention to developing conditions to accomplish the second nucleophilic aromatic

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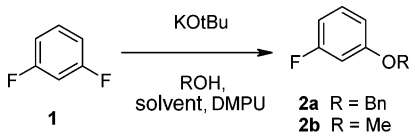
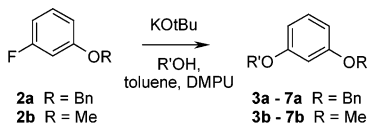
TABLE 1. Selective Fluoride Displacement on 1,3-Difluorobenzene



entry	solvent	time (h)	yield (%)
1	toluene/DMPU	3.5	**2a**, 89
2	DME/DMPU	3	**2b**, 80

TABLE 2. Nucleophilic Aromatic Substitution of 2a,b



entry	fluoride	OR'	time (h)	Yield (%)
1	**2a**	BuO	21	**3a**, 90
2	**2b**		21	**3b**, 71
3	**2a**		21	**4a**, 88
4	**2b**		22	**4b**, 75
5	**2a**		24	**5a**, 65
6	**2b**		46	**5b**, 67
7	**2a**		44	**6a**, 77
8	**2b**		41	**6b**, 81
9	**2a**		46	**7a**, 91
10	**2b**		44	**7b**, 84

displacement with a variety of alkoxides to generate differentially substituted resorcinol products in good yield. The results are summarized in Table 2.

Again, over the course of our investigations, we found that the use of DMPU is key to this displacement as well. In the absence of DMPU, we had difficulty driving the reaction to completion, even with very high alkoxide loadings and extended reaction times. Optimal conditions found are KO^{t}Bu (3.5−4 equiv) and alcohol (5 equiv) in a toluene/DMPU solvent mixture at 100 °C. These operationally simple and straightforward reaction conditions proved to be successful with a variety of primary alcohols (entries 1−6) as well as with the more sterically hindered neopentyl (entries 7 and 8) and secondary (entries 9 and 10) examples.

Although alkoxides can engage in single electron transfer (SET) processes,[11] we believe that the reactions described in this Note proceed through a S_NAr and not a SET mechanism because of the fact that we see no hydrodehalogenation or biaryl coupled products. Additionally, the cyclopropyl group (entries 3 and 4) remains intact, providing evidence that a SET mechanism is not taking place. Moreover, no cine substitution products have been observed that would indicate the formation of a benzyne intermediate.

A limitation of this methodology is an intolerance of alcohols that are electron deficient. For example, alkoxides derived from both phenol and 2,2,2-trifluoroethanol failed to undergo reaction with both starting material **1** and the 1-alkoxy-3-fluorobenzene substrates **2a**,**b**.

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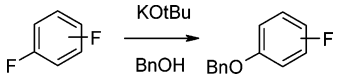
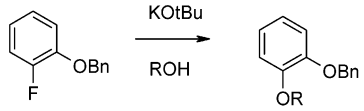
TABLE 3. Selective Fluoride Displacement on 1,2- and 1,4-Difluorobenzene



entry	difluoride	time (h)	yield (%)
1	**8**	3	**10**, 77[a]
2	**9**	5	**11**, 25[b]

[a] Reaction conditions: KO^{t}Bu (2.5 equiv), toluene (5 vol), DMPU (2 vol), BnOH (3 equiv), 80 °C, 3 h. [b] Reaction conditions: KO^{t}Bu (1 equiv), toluene (5 vol), DMPU (2 vol), BnOH (1.2 equiv), 80 °C, 5 h.

TABLE 4. Nucleophilic Aromatic Substitution on 10



entry	OR	time (h)	Yield (%)
1	BuO	18	**12a**, 77[a]
2		29	**12b**, 84[b]
3		44	**12c**, 75[c]

[a] Reaction conditions: KO^{t}Bu (2.5 equiv), ROH (3 equiv), toluene (10 vol), DMPU (2 vol), 100 °C, 18 h. [b] Reaction conditions: KO^{t}Bu (3.8 equiv), ROH (5 equiv), toluene (6 vol), DMPU (2 vol), 100 °C, 29 h. [c] Reaction conditions: KO^{t}Bu (4 equiv), ROH (5 equiv), toluene (5 vol), DMPU (2 vol), 100 °C, 44 h.

After successfully demonstrating this methodology on 1,3 systems, we applied these conditions to 1,2- and 1,4-difluorobenzene (**8** and **9**). The first S_NAr reaction with benzyl alcohol and **8** proceeded in good yield to generate **10** in an analogous manner to the 1,3-difluorobenzene substrate. However, the reaction in the 1,4-difluoro system proceeded poorly and provided **11** in only 25% yield (Table 3).

It is known that in aromatic systems halogens can destabilize negative charges on the carbon to which they are attached. Although this is contrary to the normal electron-withdrawing ability of the halogens, in the case of aromatic systems, the effect arises because the developing negative charge is in a π-system. Moreover, the π-negative charge is greatest at the position para to the point of nucleophilic attack.[12] Therefore, a fluoride atom para to the point of attack is substantially less activating than fluoride atoms in meta and ortho positions. The poor yield in the 1,4-difluoro system is likely due to this *para*-fluoro deactivating effect. Nevertheless, with desymmetrized intermediates **10** and **11** in hand, we turned our attention to the second displacement.

The second displacement on **10** can be carried out in high yield, using the same general reaction conditions as those

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employed in the 1,3 systems, using primary, secondary, and neopentyl alcohols (Table 4) to generate the differentiated catechol products **12a**−**c**.

Not surprisingly, 4-fluorophenyl phenylmethyl ether **11** fails in the second displacement reaction. The difference in reactivities between **10** and **11** is likely due to the same reasoning put forth for the reduced reactivity of difluoride **9**. In this case, the deactivating effect of the *p*-benzyloxy group is even greater than that of the *p*-fluoride and no reaction takes place.

In conclusion, we have described an operationally simple and straightforward method for the synthesis of desymmetrized resorcinol and catechol derivatives using successive S_NAr reactions that employ aryl fluorides and a variety of alkoxide nucleophiles.

Experimental Section

Typical Preparation of 1-Alkoxy-3-fluorobenzenes. Preparation of 3-Fluorophenyl Phenylmethyl Ether (2a). To a solution of KO^{t}Bu (24.6 g, 219 mmol) and toluene (50 mL) was slowly added benzyl alcohol (29 mL, 280 mmol), followed by DMPU (20 mL). The solution was heated at 80 °C for 30 min. 1,3-Difluorobenzene (**1**, 9 mL, 92 mmol) was then added, and the solution was heated for an additional 3.5 h at 80 °C. The reaction mixture was cooled to room temperature, washed with water and 10% brine (2×), dried, and concentrated. The resulting oil was purified by flash chromatography (1% EtOAc in hexanes) to produce 16.7 g (89%) of **2a** as a colorless oil.

^{1}H NMR: δ 5.05 (s, 2H), 6.64−6.78 (m, 3H), 7.23 (q, 1H, J = 8.5, 15.2 Hz), 7.31−7.45 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.2, 102.6 (d, J = 24 Hz), 107.7 (d, J = 21 Hz), 110.6, 127.5, 128.1, 128.6, 130.2, 136.5, 160.1 (d, J = 11 Hz), 163.6 (d, J = 245 Hz). IR: 1025, 1164, 1262, 1277, 1488, 1592, 1610, 2873, 2917, 2931, 3034, 3067, 3090 cm^{-1}. Anal. Calcd for $C_{13}H_{11}OF$: C, 77.21; H, 5.48; O, 7.91; F, 9.1. Found: C, 77.34; H, 5.57; O, 8.06; F, 9.43.

Typical Procedure for the Reaction of an Alkoxide with 1-Alkoxy-3-fluorobenzene: Preparation of 1-(Butyloxy)-3-(methyloxy)benzene (3b). To a solution of KO^{t}Bu (3.5 g, 30.3 mmol) and toluene (5 mL) was slowly added 1-butanol (3.8 mL, 42 mmol), followed by DMPU (2 mL). The solution was heated at 100 °C for 30 min. 3-Fluoroanisole (**2b**, 0.90 mL, 7.9 mmol) was then added, and the solution was heated for an additional 21 h at 100 °C. The reaction mixture was cooled to room temperature and washed with water, 10% brine (2×), and 6 N HCl. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were dried and concentrated. The resulting oil was purified by flash chromatography (2% EtOAc in hexanes) to produce 1.0 g (71%) of **3b** as a colorless oil.

^{1}H NMR: δ 0.96 (t, 3H, J = 7.4 Hz), 1.41−1.54 (m, 2H), 1.70−1.80 (m, 2H), 3.78 (s, 3H), 3.93 (t, 2H, J = 6.5 Hz) 6.45−6.51 (m, 3H), 7.16 (t, 1H, J = 8 Hz). ^{13}C NMR: δ 13.6, 18.7, 30.7, 55.0, 67.0, 100.6, 106.1, 106.5, 129.8, 159.9, 160.5. IR: 1042, 1148, 1199, 1264, 1286, 1453, 1492, 1590, 2835, 2872, 2935, 2985, 3030, 3067, 3090 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.23; H, 9.04.

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Supporting Information Available: Experimental details and characterization data for all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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