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# Selective displacement of aryl fluorides with hydroquinone: synthesis of 4-phenoxyphenols

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**Abstract**—The selective displacement of a variety of aryl fluorides with hydroquinone has been achieved to give substituted 4-phenoxyphenols **3**. In some cases the addition of 18-crown-6 resulted in a significant rate enhancement, and the reactions could be carried out at lower temperature. One of these derivatives, **3a** (X = Cl) was converted to 2-propyl-4-(4-chlorophenoxy)phenol **2a**, a precursor to the PPARγ receptor agonist **1**.


As part of a general program to prepare and evaluate a series of selective peroxisome proliferator-activated receptor-γ (PPARγ) agonists similar to **1a** (Fig. 1), we required quantities of the 2-propyl-4-(4-chlorophenoxy)phenol **2a**, which was elaborated from **3a** (X = Cl) in three steps.[1] The synthesis of **3a** involved displacement of 4-fluorobenzaldehyde with a 4-chlorophenol followed by a Dakin-type oxidation and in situ hydrolysis according to a known process.[2] In order to construct these substrates in a more expeditious fashion, we envisioned the direct $S_NAr$ displacement of 1-chloro-4-fluorobenzene (**4a**) with hydroquinone (**5**). This idea presented two potential challenges, namely the displacement of an unactivated aryl fluoride and the potential for 'trimer' formation due to over arylation of hydroquinone.[3] According to the literature, aryl fluorides with strong electron withdrawing groups (e.g., $NO_2$, CN, and CHO) undergo fluoride displacement with phenol quite easily;[4] there are fewer examples with hydroquinone.[5,6] On the other hand, to the best of our knowledge, the displacement of aryl fluorides containing less electronegative substituents (e.g., Cl, Br, or H) with phenol or hydroquinone does not work well.[7] In this letter, we wish to report our efforts towards the general synthesis of 4-phenoxyphenols using this methodology, and the subsequent conversion of **3a** to **2a**.

Investigation and optimization of the arylfluoride displacement was carried out using 1-chloro-4-fluorobenzene **4a** and hydroquinone (**5**), and these results are summarized in Table 1. When the reaction was run using stoichiometric amounts of hydroquinone and KO-*t*-Bu, no conversion was observed in various solvents at reflux after 24 h (entries 1–3). However, when the reaction was carried out in DMSO significant conversion of starting material to product was observed, but a large amount of the trimer **6a** was also formed (entry 4). Increasing the amount of hydroquinone and base used (4 equiv each, entry 5) resulted in a dramatic decrease in the presence of trimer and the product **3a** could be isolated in 96% yield after 24 h at 170 °C. If this reaction was repeated at 100 °C, full conversion could be achieved after 72 h but the isolated yield of product was lowered to 72%. The use of other high-boiling polar solvents generally resulted in poor isolated yield of **3a** and increased trimer (**6a**) formation. Inorganic bases (entries 11–13) provided product in very low yield due to decomposition of starting material **4a**.

During the course of these investigations, we found that DMSO had the potential to undergo catalytic decomposition at elevated temperatures (>140 °C) under the optimized reaction conditions (Table 1, entry 5).[8] Therefore, in the interest of developing milder reaction conditions, we examined the displacement of **4a** with **5** at 100 °C using 4 equiv of the cation complexing agent, 18-crown-6 (Table 2).[9] Under these conditions, the reaction was driven to near completion after 24 h in good yield (85%) and with minimal trimer formation (Table 2,

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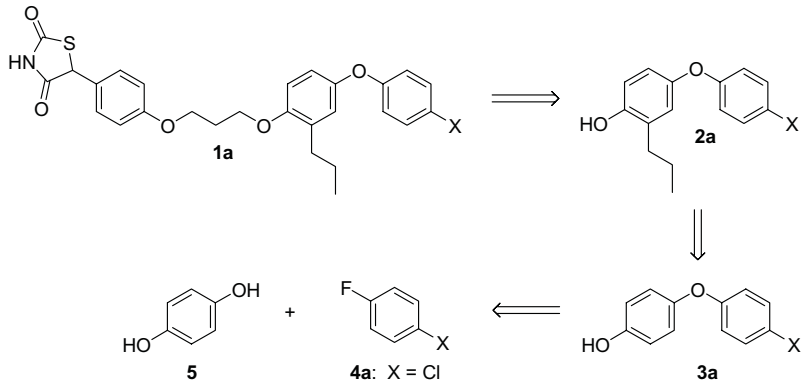
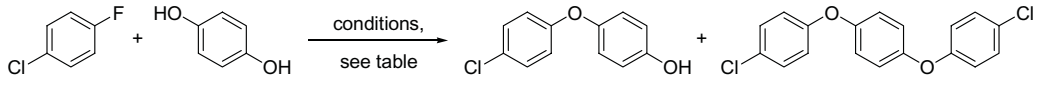



**Figure 1.** Retro-synthesis of a PPARγ agonist **1**.

**Table 1.** Displacement of **4a** with hydroquinone (**5**)




**4a** **5** **3a** **6a**

| Entry | Base | Base (equiv) | **5** (equiv) | Solvent | Temperature (°C) | Time (h) | **3a**:**6a**[a] | **3a** Yield (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | KO-*t*-Bu | 1 | 1 | Decane | Reflux | 24 | — | 0 |
| 2 | KO-*t*-Bu | 1 | 1 | MeCN | Reflux | 24 | — | 0 |
| 3 | KO-*t*-Bu | 1 | 1 | Toluene | Reflux | 24 | — | 0 |
| 4 | KO-*t*-Bu | 1 | 1 | DMSO | 170 | 24 | 65:35 | — |
| 5 | KO-*t*-Bu | 4 | 4 | DMSO | 170 | 24 | 98:2 | 96 |
| 6 | KO-*t*-Bu | 4 | 4 | DMSO | 100 | 72 | 99:1 | 72 |
| 7 | KO-*t*-Bu | 4 | 4 | NMP | 170 | 72 | 72:28 | 42 |
| 8 | NaO-*t*-Bu | 4 | 4 | NMP | 170 | 24 | 92:8 | 37 |
| 9 | KO-*t*-Bu | 4 | 4 | DMF | Reflux | 24 | 96:4 | 23 |
| 10 | KO-*t*-Bu | 4 | 4 | DMAc | Reflux | 24 | 82:18 | 39 |
| 11 | $K_2CO_3$ | 4 | 4 | DMSO | 170 | 24 | 92:8 | 16 |
| 12 | NaOH | 4 | 4 | DMSO | 170 | 24 | 80:20 | 8 |
| 13 | LiOH | 4 | 4 | DMSO | 170 | 24 | 96:4 | 30 |

[a] Product ratios determined by HPLC analysis.

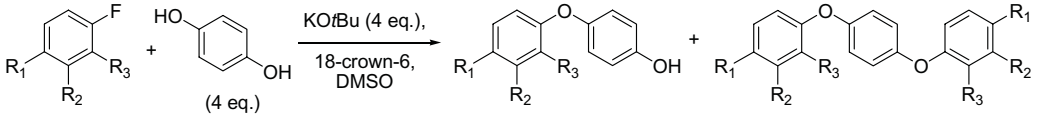
entry 2). Similarly, compounds **4d**,**f**, and **4g** reacted more quickly to give product at 100 °C in the presence of the additive. On the other hand, substrates **4b**,**c**, and **4e** showed no rate enhancement in the reaction with **5** with or without the crown ether at 100 °C. However, substrates **4c** and **4e** could be converted to **6c** and **6e** in better yield, 94% and 99% yield, respectively, when 18-crown-6 was employed.

Another aryl fluoride substrate, 1-fluoro-4-iodobenzene (**7**), exhibited a unique reaction profile as shown in Table 3. When the reaction of this compound with hydroquinone was run at 170 °C the desired product **8** was isolated in low yield (1%) along with the iodide displaced product **9** and the dehalogenated intermediate **10**. Clearly, these by-products arise from benzyne formation via elimination of iodide under the reaction conditions.[10] When the displacement of **7** was run at a lower temperature (100 °C) the desired product **8** was recovered in 72% yield after 72 h. Utilization of the additive 18-crown-6 provided for a similar yield of **8** after 24 h (71%), but elevated amounts of benzyne impurities could be detected.

With a reasonable synthesis of 4-(4-chlorophenoxy)-phenol (**3a**) in hand, we wanted to convert this intermediate to the key starting material **2a** (Scheme 1). Therefore, allylation of **3a** with allyl bromide (1.4 equiv) and $K_2CO_3$ (4 equiv) in refluxing acetone provided the allylated species **11** in nearly quantitative yield after removal of the inorganics by filtration and concentration. This material was taken on crude and subjected to a Lewis acid promoted Claisen rearrangement with $Et_2AlCl$ (1.3 equiv) to give **12** in >95% yield.[11] Workup of this reaction involved quench with 6 N HCl and removal of the resultant aluminum salts by filtration. The crude product containing filtrate could be used in the next reaction without purification after removal of heptane. Hydrogenation of **12** in the toluene solution was accomplished using Wilkinson's catalyst [$RhCl(PPh_3)_3$, 1 mol %] at 45 °C and 45 psi $H_2$ to give the reduced product **2a** in 90% yield after purification.[12]

In summary, we have demonstrated the selective $S_NAr$ displacement of a variety of aryl fluorides with hydroquinone (4 equiv) using KO-*t*-Bu (4 equiv) in DMSO

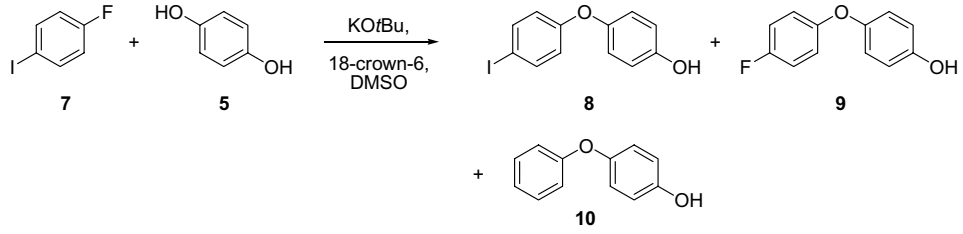
**Table 2.** Scope of the aryl fluoride displacement and effect of 18-crown-6




**4a-g** **5** **3a-g** **6a-g**

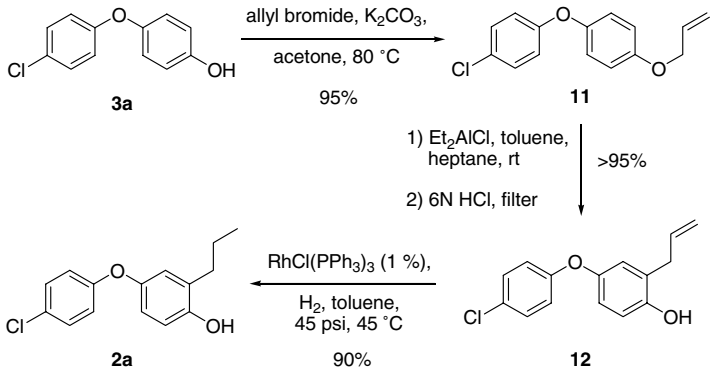
| Entry | **4** | $R_1$ | $R_2$ | $R_3$ | 18-Crown-6 (equiv) | Time (h) | Temperature (°C) | **3**:**6** | **3** Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | a | Cl | H | H | — | 72 | 100 | 99:1 | 72 |
| 2 | a | Cl | H | H | 4 | 24 | 100 | 99:1 | 85 |
| 3 | b | H | Cl | H | — | 24 | 100 | 98:2 | 91 |
| 4 | b | H | Cl | H | 4 | 24 | 100 | 99:1 | 80 |
| 5 | c | H | H | Cl | — | 24 | 100 | 97:3 | 89 |
| 6 | c | H | H | Cl | 4 | 24 | 100 | 97:3 | 94 |
| 7 | d | Br | H | H | — | 24 | 170 | 96:4 | 80 |
| 8 | d | Br | H | H | — | 72 | 100 | 99:1 | 81 |
| 9 | d | Br | H | H | 4 | 24 | 100 | 99:1 | 65 |
| 10 | e | $CF_3$ | H | H | — | 24 | 100 | 98:2 | 85 |
| 11 | e | $CF_3$ | H | H | 4 | 24 | 100 | 99:1 | 99 |
| 12 | f | $OCF_3$ | H | H | — | 24 | 170 | 94:6 | 77 |
| 13 | f | $OCF_3$ | H | H | — | 72 | 100 | 99:1 | 14 |
| 14 | f | $OCF_3$ | H | H | 4 | 24 | 100 | 98:2 | 68 |
| 15 | g | H | H | H | — | 24 | 170 | 92:8 | 16 |
| 16 | g | H | H | H | 4 | 24 | 100 | 99:1 | 53 |

**Table 3.** Displacement of 1-iodo-4-fluorobenzene with hydroquinone




**7** **5** **8** **9** **10**

| Entry | 18-Crown-6 (equiv) | Time (h) | Temperature (°C) | **8**:**9**:**10** | **8** Yield (%) |
|---|---|---|---|---|---|
| 1 | — | 24 | 170 | 65:13:22 | 1 |
| 2 | — | 72 | 100 | 95:4:1 | 72 |
| 3 | 4 | 24 | 100 | 87:12:1 | 71 |




**3a** **11** **2a** **12**

**Scheme 1.** Synthesis of 2-propyl-4-(4-chlorophenoxy)phenol **2a**.

at elevated temperature with a minimum of trimer formation. It was noted that a cation scavenger, 18-crown-6, can significantly accelerate this transformation in some cases, allowing for the reaction to be carried out at lower temperatures. One of these derivatives, **3a**, was efficiently converted to 2-propyl-4-(4-chlorophenoxy)phenol **2a**, an important intermediate in the synthesis of the PPARγ agonist **1**.

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