An efficient fluoride-mediated O-arylation of sterically hindered halophenols with silylaryl triflates under mild reaction conditions

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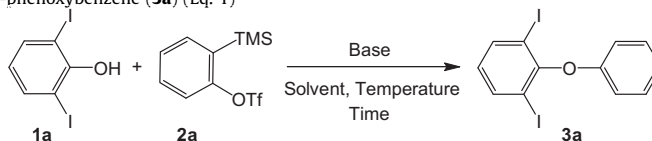
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ABSTRACT

The reaction between 2,6-dihalophenols and 2-(trimethylsilyl)aryl triflates in the presence of CsF using acetonitrile as solvent at room temperature led to the formation of functionalized diaryl ethers in very good yields.

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Diaryl ether subunits are commonly found in a variety of biologically active substances,[1] in natural products,[2] in agrochemicals,[3] and in compounds of interest in materials science.[4] Therefore, a number of methods for diaryl ethers syntheses have been reported in the literature.[5–8] Among them, those which employ transition metals are the most popular and are represented by the following transformations: Ullmann-type reactions which are typified by the coupling of phenols and aryl halides promoted by copper;[6] Buchwald–Hartwig cross-couplings involving phenols and aryl halides in the presence of catalytic amounts of palladium[7]

Table 1
Optimization of the synthesis of 1,3-diiodo-2-phenoxybenzene (**3a**) (Eq. 1)[a]

Entry	**2a** (equiv)	Base (equiv)	Solvent	Time (h)	Temperature (°C)	Isolated yield (%)
1	1.1	CsF (2.2)	MeCN	24	rt	77
2	**1.5**	**CsF (3.0)**	**MeCN**	**24**	**rt**	**90**
3	2	CsF (4.0)	MeCN	24	rt	92
4	1.5	CsF (3.0)	MeCN	24	50	91
5	1.5	CsF (3.0)	MeCN	12	rt	46
6	1.5	*n*-Bu₄NF (1.8)	THF	24	rt	58
7	1.5	KF/[18]crown-6 ether (1.5/1.5)	THF	24	0	79
8	1.5		MeCN	24	rt	0

[a] Reaction conditions: 0.3 mmol of 2,6-diiodophenol (**1a**), the indicated amount of benzyne precursor **2a**, the indicated amount of base, and 5 mL of solvent were stirred at the temperature shown for 24 h.

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and Chan–Evans–Lam-type reactions which may be exemplified by the coupling between phenols and organoboron reagents in the presence of copper.[8]

Although the methodologies for the preparation of diaryl ethers which were mentioned above are of great importance in preparative organic chemistry,[6–8] they have generally employed harsh reaction conditions, or are incompatible with some functionalities present in the phenolic compound, including halide substituents and carbon–carbon triple bonds (for this case undesired reactions can occur mostly in palladium-catalyzed processes), or an organoboron reagent[9] has to be prepared before the coupling reaction is carried out. Besides, in all mentioned transformations toxic or expensive transition metals are used as reagents or catalysts.[6–8]

In order to circumvent the exposed drawbacks related to the O-arylation processes using transition metals,[6–8] Liu and Larock reported in the literature an efficient transition-metal-free reaction for the O-arylation of phenols and carboxylic acids employing arynes generated from silylaryl triflates and a source of fluoride ions.[10]

In the same way, we have used silylaryl triflates to generate arynes under mild reaction conditions, which can undergo synthetically useful cycloaddition[11] and insertion reactions.[12] On a related theme, we wish to present through this work the O-arylation of sterically hindered dihalophenols, in the presence of silylaryl triflates and a source of fluoride ions, in order to produce functionalized diaryl ethers, which may be considered versatile building blocks in synthetic organic chemistry and are in most

Table 2
Synthesis of 1,3-dihalo-2-phenoxybenzenes (**3a–i**) by the reaction of 2,6-dihalophenols (**1a–f**) and aryne precursors (**2a–d**) in the presence of CsF[a]

Entry	Halophenol (**1**)	Aryne precursor (**2**)	Halophenoxybenzene (**3**)	Isolated yield (%)
1	**1a**	**2a**	**3a**	90
2	**1b**	**2a**	**3b**	90
3	**1c**	**2a**	**3c**	Quantitative
4	**1d**	**2a**	**3d**	65
5	**1e**	**2a**	**3e**	Quantitative
6	**1f**	**2a**	**3f**	95
7	**1c**	**2b**	**3g**	85
8	**1c**	**2c**	**3h**	80
9	**1c**	**2d**	**3i**	93

[a] Reaction conditions: 0.3 mmol of 2,6-dihalophenol (**1a–f**), 0.45 mmol of the benzyne precursor **2a–d**, 0.9 mmol of CsF, and 5 mL of acetonitrile were stirred at room temperature for 24 h.

cases novel thyroid hormone derivatives with possible application in medicinal chemistry.[13]

Initially, allowing the reaction of 2,6-diiodophenol (1a) with 1.1 equiv of 2-(trimethylsilyl)phenyl triflate (2a) in the presence of 2.2 equiv of CsF at room temperature for 24 h, we obtained 1,3-diiodo-2-phenoxybenzene (3a) in a 77% yield (Table 1, entry 1). In an attempt to improve the obtained yield (entry 1), subsequent work focused on the optimization of these reaction conditions (Table 1, entries 2–8).

When the transformation was carried out using 1.5 equiv of the silylaryl triflate 2a and 3 equiv of CsF at room temperature for 24 h, we isolated the desired product 3a in a very good yield of 90% (Table 1, entry 2). No significant improvement in the yield for 1,3-diiodo-2-phenoxybenzene (3a) was achieved when 2,6-diiodophenol (1a) was subjected to the reaction with 2 equiv of the silylaryl triflate 2a in the presence of 4 equiv of CsF at room temperature for 24 h (entry 3) or when 2,6-diiodophenol (1a) was allowed to react with 1.5 equiv of the benzyne precursor 2a and 3 equiv of CsF at 50 °C for 24 h (entry 4). Treatment of the diiodinated phenol 1a with 1.5 equiv of the silylaryl triflate 2a and 3 equiv of CsF at room temperature for 12 h gave the desired product 3a in only 46% isolated yield (entry 5). Afterward, in order to explore the effect of the fluoride ions source on the reaction, 1.8 equiv of tetrabutylammonium fluoride (TBAF) was added to the mixture of 2,6-diiodophenol (1a) and 1.5 equiv of 2-(trimethylsilyl)phenyl triflate (2a) in THF at room temperature. After 24 h, 1,3-diiodo-2-phenoxybenzene (3a) was obtained in a low yield of 58% (entry 6). Treatment of the diiodinated phenol 1a with 1.5 equiv of the benzyne precursor 2a, 1.5 equiv of KF and 1.5 equiv of [18]crown-6 ether in THF at 0 °C led to the formation of the diiodinated diaryl ether 3a in 79% yield (entry 7). No further attempts were made to optimize the reactions depicted in entries 6 and 7. As can be seen in Table 1, entry 8, compound 3a was not obtained and the starting materials 1a and 2a were recovered when the reaction was carried out in the absence of CsF. This experiment shows that the success of our reaction depends dramatically on the presence of a source of fluoride ions.

Employing the optimal conditions shown in Table 1, entry 2,[14] we examine the scope of this process using various diiodinated phenols and aryne precursors (Table 2). When the reaction was carried out using a phenol bearing an electron-donating group (1b) and the silylaryl triflate 2a, we obtained the diiodinated diaryl ether 3b in an excellent yield of 90% (entry 2). Treatment of a phenol bearing an electron-withdrawing group (1c) with the benzyne precursor 2a gave the diiodinated diaryl ether 3c in a quantitative yield (entry 3). By performing the transformation between 2,6-diiodo-4-nitrophenol (1d) and the silylaryl triflate 2a, we obtained compound 3d in an isolated yield of 65% (entry 4). In this case, the powerful electron-withdrawing group present in the phenol 1d promoted a more sluggish transformation leading to the desired product 3d in moderate yield. In both reactions where we employed choroiodophenols (1e and 1f), the halogenated diaryl ethers (3e and 3f) were produced in excellent yields ≥95% (entries 5 and 6).

Turning our attention to the effect of substituted silylaryl triflates on the reaction course, we allowed the reaction of 4-acetyl-2,6-diiodophenol (1c) with the electron-rich silylaryl triflate 2b and obtained the diiodinated diaryl ether 3g in a good 85% yield (entry 7). Treatment of the phenol 1c with the electron-poor aryne precursor 2c gave the desired product 3h in an 80% isolated yield (entry 8). To understand better the regioselectivity of the reaction when unsymmetrical arynes are employed, we allowed 4-acetyl-2,6-diiodophenol (1c) to react with the 3-methoxy-substituted aryne precursor 2d and obtained the diiodinated diaryl ether 3i in an excellent yield of 93% (entry 9). This result indicates that electronic and/or steric factors, promoted by the 3-methoxy group present in the aryne produced in the reaction course, oriented the nucleophilic attack of the phenol, leading to the exclusive formation of the regioisomer 3i. Accordingly, the structure proposed for 3i is according to the pattern of regioselectivity followed by a number of reactions between 3-methoxy-1,2-benzyne and nucleophiles.[10,15] So far it remains unclear which factor (electronic or steric) governs the exclusive formation of compound 3i and further experiments ought to be carried out to solve this matter.

The structures of compounds 3a–i were assigned on the basis of a variety of spectroscopic techniques, namely, according to their IR, LRMS, ^{1}H, and ^{13}C NMR spectra. All new compounds (3c–i) provided HRMS that agree with the proposed structures.

In summary, a simple and efficient O-arylation reaction between sterically hindered halophenols and silylaryl triflates in the presence of CsF using acetonitrile as solvent at room temperature was developed and functionalized diaryl ethers were produced in excellent yields. Through this transition-metal-free process carbon–oxygen bonds were formed presumably via arynes produced under mild reaction conditions. The synthetic methodology described led to functionalized diaryl ethers, which are versatile building blocks in preparative organic chemistry and are in most cases novel thyroid hormone derivatives with possible application in medicinal chemistry.

Acknowledgments

Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.124.

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14. *General procedure for O-arylation of sterically hindered halophenols*: To a vial (10 mL) were added the appropriate 2,6-dihalophenol **1a–f** (0.3 mmol), the appropriate aryne precursor **2a–d** (0.45 mmol), acetonitrile (5 mL), and CsF (0.9 mmol, 0,1368 g). The vial was sealed using a cap, and the reaction mixture was stirred for 24 h at room temperature. Afterward, brine (5 mL) was added to the mixture, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, using hexane as eluent unless otherwise indicated, affording the desired products **3a-i**.

1,3-Diiodo-2-phenoxybenzene (**3a**): yield 113.9 mg (90%); off-white solid; mp 61–63 °C (lit.[16] mp 68.5–68.9 °C); ^{1}H NMR 300 MHz ($CDCl_3$, ppm): 7.86 (d, $J = 7.8$ Hz, 2H), 7.34–7.27 (m, 2H), 7.05 (tt, $J = 7.4$, 1.2 Hz, 1H), 6.81–6.77 (m, 2H), 6.68 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR 75 MHz ($CDCl_3$, ppm): 156.2, 153.9, 140.2, 129.6, 128.5, 122.4, 115.5, 91.4; IR (KBr, cm^{-1}): 1588 (m), 1484 (S), 1548 (m), 1417 (S), 768 (S), 850 (F), 489 (w); LRMS (*m/z,%*): 139 (8.0), 168 (37.0), 422 (M$^+$, 100.0).

5-Acetyl-1,3-diiodo-2-phenoxybenzene (**3c**): yield 139.0 mg (quantitative); yellowish solid; mp 195–198 °C; ^{1}H NMR 300 MHz ($CDCl_3$, ppm): 8.42 (s, 2H), 7.34–7.29 (m, 2H), 7.11–7.05 (m, 1H), 6.79–6.77 (m, 2H), 2.60 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$, ppm): 194.3, 157.7, 155.7, 140.4, 136.8, 129.8, 122.8, 115.6, 91.4, 26.6; IR (KBr, cm^{-1}): 3056 (w), 3011 (w), 1687 (S), 1589 (m), 1567 (m), 1535 (m), 1488 (m), 1470 (m), 718 (S), 706 (S), 496 (m); LRMS (*m/z,%*): 43 (20.0), 139 (7.3), 464 (M$^+$, 100.0); HRMS Calcd for $[C_{14}H_{10}I_2O_2+Na]^+$: 486.8668. Found: 486.8659.

5-Acetyl-1,3-diiodo-2-(3-methoxyphenoxy)benzene (**3i**): yield 138.0 mg (93%); off-white solid; mp 171–173 °C; ^{1}H NMR 300 MHz ($CDCl_3$, ppm): 8.41 (s, 2H), 7.19 (t, $J = 8.3$ Hz, 1H), 6.63 (dd, $J = 8.3$, 1.7 Hz, 1H), 6.40 (t, $J = 2.4$ Hz, 1H), 6.30 (dd, $J = 8.3$, 1.7 Hz, 1H), 3.79 (s, 3H), 2.59 (s, 3H); ^{13}C NMR 75 MHz ($CDCl_3$, ppm): 194.2, 161.1, 157.6, 156.7, 140.4, 136.8, 130.1, 108.2, 107.7, 102.4, 91.4, 55.4, 26.5; IR (KBr, cm^{-1}): 3001 (w), 1681 (S), 1265 (S), 757 (m), 709 (m), 683 (m), 637 (m), 487 (w); LRMS (*m/z,%*): 43 (27.8), 225 (8.0), 367 (16.2), 494 (M$^+$, 100.0); HRMS Calcd for $[C_{15}H_{12}I_2O_3+H]^+$: 494.8954. Found: 494.8957.

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