An Efficient Strategy for the Synthesis of Aryl Ethers

Tongen Wang, Jennifer A. Love*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, V6T 1Z1, Canada
Fax +1(604)8223187; E-mail: jenlove@chem.ubc.ca

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Dedicated to Professor Paul A. Wender on the occasion of his 60th birthday

Abstract: An efficient strategy for the construction of aryl ethers using aryl fluorides and silyl ethers is described. This protocol uses a sub-stoichiometric amount of silicon-based reagent and proceeds under milder conditions than previously reported reactions of this type.

Key words: nucleophilic aromatic, substitutions, aryl ether, aryl fluoride, silicon reagents, synthetic method

The aryl ether moiety is found in a wide range of bioactive molecules[1,2] and materials.[3] Not surprisingly, efforts toward developing efficient and convenient protocols for the synthesis of aryl ethers has received considerable attention.[4] The Ullmann coupling has been used extensively for aryl ether synthesis, yet suffers from the requirement for high reaction temperatures and excess Cu salt.[5] Efforts to circumvent these limitations have been reported,[6,7] with the first example of a catalytic Ullmann coupling appearing in 1997.[7] Despite this considerable advance, high reaction temperatures were still required. In comparison, Cu-mediated cross couplings of aryl boronic acids can be run at room temperature, but require stoichiometric copper.[8] Pd-catalyzed cross-coupling of aryl bromides with phenoxides and alkoxides was introduced in 1999 independently by Hartwig and Buchwald.[9] These methods still required high temperatures, as well as pre-formation of the alkoxide or aryl oxide. Shortly thereafter, room-temperature coupling was achieved, but a limited substrate scope was described.[10]

More recently, S_NAr reactions have been developed as a strategy for diaryl ether formation. For example, activated aryl fluorides have been coupled with aryl alcohols using excess $KF{\cdot}Al_2O_3$ and catalytic 18-crown-6, in refluxing acetonitrile.[11] Addition of phenols to benzynes generated from silylaryl triflates has also been reported.[12]

An alternate strategy involves the coupling of silyl-protected aryl alcohols with aryl fluorides. A variety of reagents have been used to promote deprotection of the silyl group, including CsF,[13] TBAF,[14] phosphazenes[15] or proazaphosphatranes.[16] These protocols all use trialkylsilyl-protected aryl alcohols. As such, these reactions produce one equivalent of silicon by-product relative to the amount of aryl ether formed. A more efficient protocol would be to use readily available tetraaryloxysilanes, which would substantially reduce the amount of silicon by-product. In addition, the ability to generate aryl alkyl ethers using tetraalkoxysilanes would increase the generality of the methodology.

We report herein that tetraphenoxysilane and tetraalkoxysilanes react readily with aryl fluorides in the presence of TBAF and that a sub-stoichiometric amount of silane, relative to the aryl fluoride, can indeed effect the transformation without compromising reaction outcome. Moreover, the reaction scope is broader and the reaction conditions are milder than those reported for related fluoride-promoted reactions.[13,14]

Our study began with 2,4-dinitrofluorobenzene (**1a**), which was reacted with 0.3 equivalent of tetraphenoxysilane in acetone at 50 °C for 24 hours to generate phenyl ether **2a** in 73% isolated yield (Table 1, entry 1). The conditions reported by Wang[14b] as well as Burgess and Zhu[14c] indicated the use of base (Et_3N and K_2CO_3, respectively), whereas we found that this was not necessary for high conversion. We also found that the reaction proceeded efficiently at a considerably lower reaction temperature than reported by Wang (50 °C compared with 100 °C).[14b]

Based on this initial success, we investigated aryl fluorides containing only one additional activating group. Both 4-nitrofluorobenzene (**1b**) and 2-cyanofluorobenzene (**1c**) reacted smoothly to generate the corresponding diaryl ethers in 92% and 80% yields, respectively (entries 2 and 3).

To test the selectivity of the process, we explored the use of 5-chloro-2,4,6-trifluoropyrimidine (**1d**). With tetraphenoxysilane, **1d** reacted efficiently to generate the triphenoxy pyrimidine **2d** in 82% yield (entry 4). Importantly, only substitution of fluorine was observed, consistent with an S_NAr mechanism. The generality of the methodology was demonstrated by the use of tetraalkoxysilanes. For example, pyrimidine **1d** reacted with tetramethoxysilane (entry 5) and tetraethoxysilane (entry 6) in 81% and 75% yield, respectively. Likewise, the use of tetraallyloxysilane allows the generation of aryl allyl ethers (entry 7).

In summary, we have established a convenient protocol for the synthesis of aryl ethers from aryl fluorides and silyl-protected alcohols. Notably, less than one equivalent of silyl reagent is consumed in the reaction. Both tetraphenoxy- and tetraalkoxysilanes can be used. These reactions proceed efficiently at 50 °C and do not require added base.

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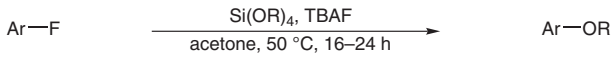
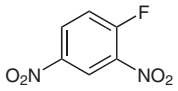
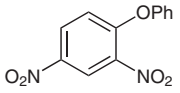
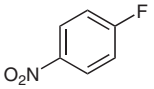
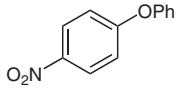
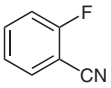
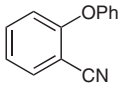
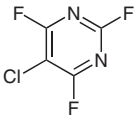
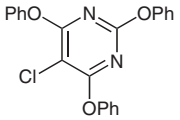
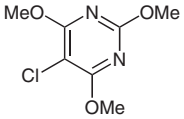
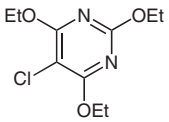
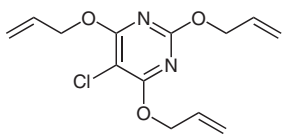
Table 1 Preparation of Aryl Ethers



Entry	Aryl fluoride		Silane	Time (h)	Product		Yield (%)[a]
1		**1a**	$Si(OPh)_4$ (0.3 equiv)	24		**2a**	73[b]
2		**1b**	$Si(OPh)_4$ (0.3 equiv)	24		**2b**	92
3		**1c**	$Si(OPh)_4$ (0.3 equiv)	21		**2c**	80
4		**1d**	$Si(OPh)_4$ (1.2 equiv)	16		**2d**	82
5		**1d**	$Si(OMe)_4$ (1.2 equiv)	24		**2e**	81
6		**1d**	$Si(OEt)_4$ (1.2 equiv)	24		**2f**	75
7		**1d**	$Si(OCH_2CH{=}CH_2)_4$ (1.2 equiv)	24		**2g**	79

[a] Isolated yields.
[b] Yield determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

All reactions were performed using oven-dried glassware sealed with rubber septa under a positive pressure of dry N_2 from a Schlenk line. Similarly sensitive liquids and solutions were transferred via syringe. Reactions were run using Teflon-coated magnetic stir bars. Elevated temperatures were maintained in thermoregulated oil baths. Organic solutions were concentrated using a Büchi rotary evaporator using a water aspirator. TLC plates were visualized by ultraviolet light. Chromatographic purification of products was accomplished by flash chromatography using silica gel (70–230 mesh). All reagents were obtained from commercial sources and used as received. TBAF (1.0 M in THF) solution was purchased from Aldrich. $Si(OPh)_4$ was prepared following the literature procedure.[17] NMR spectra were recorded on Bruker Avance 300 spectrometers. ^1H, ^{13}C and ^{19}F NMR spectra are reported in parts per million and were referenced to residual solvent. All spectra were obtained at 25 °C. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Spectroscopic data for aryl ethers **2a**,[18] **2b**,[19] **2c**,[20] **2e**,[21] and **2f**[21] were identical to reported values.

Aryl Ether Formation; 5-Chloro-2,4,6-triphenoxypyrimidine (2d); Typical Procedure

In an N_2-filled Vacuum Atmospheres glovebox, acetone (1.0 mL) was transferred into a 5 mL test tube equipped with a magnetic stir bar and a screw cap with a septum. 5-Chloro-2,4,6-trifluoropyrimidine (**1e**; 120 μL, 1.0 mmol) and $Si(OPh)_4$ (405 μL, 1.0 mmol) and TBAF (2.2 mL of a 1.0 M solution in THF, 2.2 mmol) were injected by syringe into the test tube. The test tube was put into the preheated oil bath at 50 °C. Analysis by TLC indicated that the reaction was completed in 16 h. The mixture was transferred into a 20 mL vial and the solution was concentrated by rotary evaporation. The residue was purified by column chromatography (SiO_2, 9:1 hexane–EtOAc) to give 332 mg (85%) of **2d** as a white solid.

^1H NMR (acetone-d_6, 300 MHz): δ = 7.41–7.03 (m, ArH).

^{13}C NMR (acetone-d_6, 300 MHz): δ =168.0, 161.7, 158.6, 153.8, 129.6, 129.2, 125.8, 125.1, 121.7, 121.3, 96.0.

HRMS (EI): *m/z* calcd for $C_{22}H_{15}ClN_2O_3$ + Na: 413.0669; found: 413.0655.

2g
Yield: 79%.

^{1}H NMR (acetone-d_6, 300 MHz): δ = 6.07 (m, 3 H), 5.50–5.35 (m, 3 H), 5.30–5.20 (m, 3 H), 4.95–4.93 (m, 4 H), 4.86–4.83 (m, 2 H).

^{13}C NMR (acetone-d_6, 300 MHz): δ = 167.7, 162.6, 134.6, 134.2, 118.9, 97.1, 69.7, 69.4.

MS (ESI): *m*/*z* = 483.0.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{15}N_2O_3Cl$ + H: 283.0849; found: 283.0855.

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