A Simple and Efficient Method for the Preparation of Hindered Alkyl−Aryl Ethers

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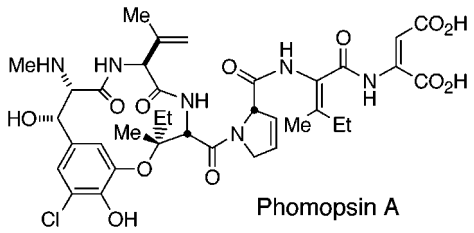
Antimitotic natural products that bind to cellular microtubules can be used as anticancer agents, and we are studying the cellular mechanisms of these compounds.[1] The fungal metabolite phomopsin A is a key structure in these studies, and we are currently pursuing its synthesis.[2] Our retrosynthetic analysis of phomopsin A targeted the chiral tertiary alkyl−aryl ether as a key disconnection within the molecule. Accordingly, we have investigated nucleophilic aromatic substitution (S_NAr) as a mild method to synthesize tertiary alkyl−aryl ethers. In general, alkoxides can serve as bases or nucleophiles, and alkoxides have also been shown to engage in single electron transfer (SET) processes.[3] Increasing steric congestion close to oxygen generally decreases nucleophilicity, leading to an increase in basic or SET mechanistic manifolds. Tertiary alkoxides are rarely used as nucleophiles and are more often utilized as nonnucleophilic bases. Nevertheless, we have recently observed that hindered tertiary alkoxides are effective nucleophiles in S_NAr reactions with activated aryl fluoride electrophiles.

A number of methods exist for the synthesis of alkyl−aryl ethers. Our initial search of the literature suggested that copper-mediated displacements of aryl halides with alkoxides might be promising.[4] Preliminary reactions using potassium *tert*-butoxide were successful; however, attempts with more complex alkoxides proved to be low-yielding. We also investigated S_NAr reactions between alkoxides and aryl halides complexed with either chromium tricarbonyl[5] or cationic cyclopentadienyl ruthenium,[6] as well as the recently reported palladium-catalyzed cross-coupling reactions with alkoxides as nucleophiles.[7] None of these methodologies proved to be suitable for synthesizing the ether linkage found in phomopsin A. Nucleophilic aromatic substitution of nitro-activated aryl halides with phenoxide and primary alkoxide nucleophiles has been shown to be an effective strategy for ether synthesis.[8] However, there are far fewer examples of sterically hindered alkoxides being utilized as nucleophiles in this reaction, with most reports describing forcing conditions and moderate-to-low isolated yields of the desired ethers.[9] Our studies demonstrate that tertiary alkoxides react quickly and efficiently with activated aryl halides to provide the desired tertiary alkyl−aryl ethers under mild conditions and in good yield.

Chart 1



Phomopsin A

Initial experiments explored the reaction between potassium *tert*-butoxide and a variety of aryl halide electrophiles (Table 1). Treatment of 1-fluoro-2-nitrobenzene with potassium *tert*-butoxide at 0 °C using THF, 1,4-dioxane, or toluene as the solvent led to complete conversion within 5 min (entry 1).[10] The isolated yield was highest using THF, and subsequent experiments used THF as the solvent. We next investigated alternative methods for generating potassium alkoxides. Generation of the alkoxide in THF from *tert*-butyl alcohol and a solution of potassium bis(trimethylsilyl)amide (KHMDS) worked well. With the majority of substrates, the alcohol and aryl fluoride are dissolved in THF, and the alkoxide is generated in situ by treatment with KHMDS. With *tert*-butyl alcohol, this protocol provides results identical to those obtained using commercially available KOtBu.

As anticipated from previous reports, aryl fluorides are significantly more reactive in S_NAr reactions than either aryl chlorides or aryl bromides, and good levels of selectivity are observed when reacting aromatic substrates containing several potential halogen leaving groups (entry 2). Para-substituted aryl fluorides serve as good electrophiles (entry 3), and meta-substituted aryl fluorides, as expected, do not produce the desired ether (entry 4). The presence of an electron donating group on the electrophile is tolerated (entry 5), and nitrile-

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(10) All new compounds were fully characterized by spectroscopic and analytical methods.

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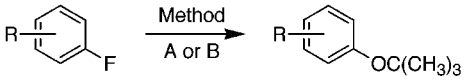
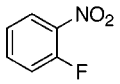
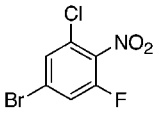
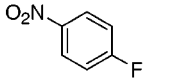
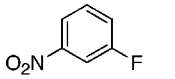
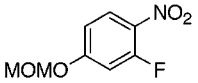
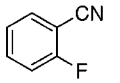
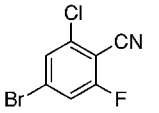
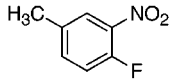
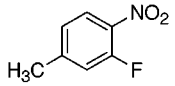
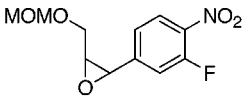
Table 1. Synthesis of *tert*-Butyl Ethers



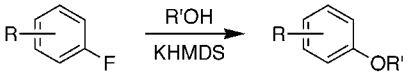
Entry	Substrate	Isolated Yield (%) Method A[a]	Method B[b]
1		99	99
2		87	87
3		94	95
4		0	0
5		94	94
6		99	95
7		92	n/d
8		92	93
9		0	0
10		71	n/d

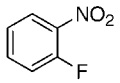
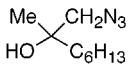
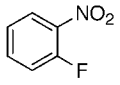
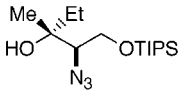
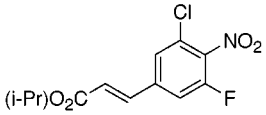
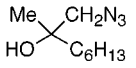
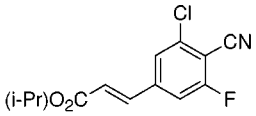
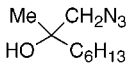
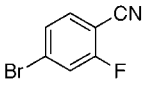
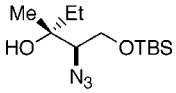
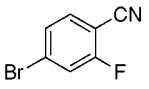
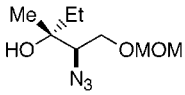
[a] The aryl fluoride was dissolved in THF, cooled to 0 °C, treated with KOtBu (1.2 equiv), and allowed to warm to 23 °C. [b] The aryl fluoride and *tert*-butyl alcohol were dissolved in THF, cooled to 0 °C, treated with KHMDS (1.1 equiv), and allowed to warm to 23 °C. Refer to Supplementary Material for details.

activated aryl fluorides also provide good yields of substitution products, although the rates of reaction as monitored by TLC are somewhat slower than for the corresponding nitro-substituted aryl fluorides (entries 6 and 7). One significant limitation of this etherification reaction is an apparent intolerance for benzylic protons that are conjugated with the activating group, as deprotonation of these acidic protons likely competes with the desired S_NAr reaction. Thus, 4-fluoro-3-nitrotoluene is an acceptable electrophile for this reaction, whereas 3-fluoro-4-nitrotoluene provides none of the desired ether (entries 8 and 9). However, the reaction does tolerate a benzylic epoxide, presumably because resonance stabilization of the benzylic anion is less effective because of ring strain (entry 10).

The S_NAr etherification is also effective using more-complex alkoxide nucleophiles (Table 2). With 1-azido-2-hydroxy-2-methyloctane, the highest yields are obtained when the alkoxide is generated in situ by treating a solution of the aryl fluoride and tertiary alcohol with KHMDS (entry 11). Generation of the alkoxide before addition of the aryl fluoride results in decomposition of the alkoxide. We observed that treatment of the tertiary alcohol in entry 12 with KHMDS led to migration of the silyl protecting group from the primary hydroxyl group to the tertiary hydroxyl group. Subsequent addition of the aryl fluoride resulted in the formation of the corresponding primary alkyl−aryl ether as the main reaction product. In situ generation of the alkoxide alleviates this problem. Nitro-substituted cinnamates are suitable electrophiles. However, with nitrile-substituted cinnamates, transesterification is a competitive side-reaction with substitution (entries 13 and 14). Nitrile-substituted aryl fluorides are less reactive than nitro-substituted aryl fluorides, and competing silyl migration resulted in reduced yields (entry 15). The use of a protecting group that is incapable of migration eliminates this problem (entry 16).

Table 2. Synthesis of Hindered Alkyl−Aryl Ethers



Entry	Substrate	Alcohol	Yield (%)[b]
11			86
12			75
13			75
14			30[c]
15			60
16			91

[a] The aryl fluoride and tertiary alcohol were dissolved in THF, cooled to 0 °C, treated with KHMDS (1.1 equiv), and allowed to warm to room temperature. See Supplementary Material for details. [b] Isolated yields of analytically pure products. [c] Lower yield results from competing transesterification.

Several observations lead us to believe that this transformation proceeds via nucleophilic aromatic substitution.[11] Aryl fluorides are the best substrates for this etherification reaction, which is suggestive of S_NAr instead of other possible alternatives such as the radical nucleophilic substitution ($S_{RN}1$) mechanism.[12] In addition,

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we have not observed any side-products that might be indicative of $S_{RN}1$, such as hydro-de-halogenation products or biaryl products. We have not seen evidence of the cine substitution product, suggesting that benzyne intermediates are not being formed. KHMDS has been substituted with NaHMDS in two cases (Table 1, entries 1 and 2), giving identical results. The corresponding lithium alkoxide, however, is unreactive. We have also attempted to use activated aryl chlorides as electrophiles, but the product yields are significantly lower. In conclusion, we have described a useful method for the synthesis of tertiary alkyl−aryl ethers using nucleophilic aromatic substitution reactions between activated aryl fluorides and tertiary alkoxide nucleophiles.

Experimental Section

General Procedures. Complete experimental procedures and product characterization data can be found in the Supporting Information. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were measured in $CDCl_3$ using the solvent resonance as an internal standard (7.26 ppm). Mass spectral data were obtained at the Scripps Research Institute Mass Spectrometry Facility. THF was distilled over sodium metal under an atmosphere of argon. All glassware was evacuated, flame-dried, and flushed with argon before use. Potassium *tert*-butoxide was purchased from Aldrich and transferred to an airtight flask under argon. KHMDS was titrated upon receipt from Aldrich using the method of Duhamel and Plaquevent,[13] transferred to an airtight container and stored under argon at room temperature. The titer was consistent for at least 6 months. All commercially available compounds were used without prior purification. Chromatography was performed using 230−400 mesh silica gel and HPLC-grade solvents.

General Procedure A: Addition of Potassium *tert*-Butoxide to Aryl Fluorides. The aryl fluoride (1.0 equiv) is dissolved in distilled THF (to give a 0.1−0.2 M solution) in a flame-dried flask under Ar and cooled to 0 °C. A 1.0 M solution of potassium *tert*-butoxide (1.2 equiv) is added dropwise, resulting in a pronounced color change to dark orange. This solution is stirred and allowed to warm from 0 °C to room temperature over 2 h and then diluted with CH_2Cl_2 and washed once with saturated aqueous NH_4Cl. The aqueous layer is back-extracted once with CH_2Cl_2. The organic layers are combined, dried over $MgSO_4$, concentrated, and purified using silica gel chromatography.

General Procedure B: In Situ Formation of the Alkoxide Using KHMDS. The aryl fluoride (1.0 equiv) and tertiary alcohol (1.1 equiv) are dissolved in distilled THF (to give a 0.1−0.2 M solution) in a flame-dried flask under Ar and cooled to 0 °C. KHMDS (1.1 equiv, 0.5 M solution) is added dropwise, resulting in a color change from colorless to dark orange. This solution is stirred from 0 °C to room temperature over 2 h and then diluted with CH_2Cl_2 and washed once with saturated aqueous NH_4Cl. The aqueous layer is back-extracted once with CH_2Cl_2. The organic layers are combined, dried over $MgSO_4$, concentrated, and purified using silica gel chromatography.

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Supporting Information Available: Experimental procedures, compound characterization data, and selected spectroscopic data are provided (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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