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An Efficient Synthesis of Diaryl Ethers by Coupling Aryl Halides with Substituted Phenoxytrimethylsilane in the Presence of TBAF

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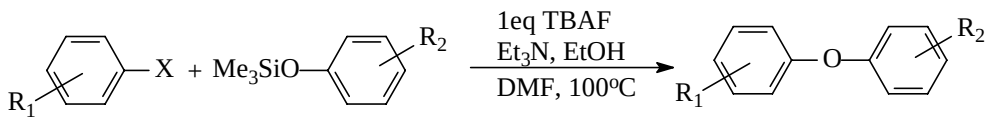
Abstract: A general synthesis of diaryl ethers *via* coupling of aryl halides with substituted phenoxytrimethylsilane in the presence of TBAF is described. The protocol is simple and mild, and gives good to excellent yields.

Keywords: Diaryl ether, TBAF, aryl halide, phenoxytrimethylsilane.

Diaryl ether is a class of important structure in organic chemistry. Its synthesis has absorbed much attention in recent years, especially after the discovery of diaryl ether-containing biological active natural products such as vancomycin aglycon and the combrestatin *etc*[1-3]. Despite limitations under the original conditions, such as elevated reaction temperature, unconvenient purification, lower yields and the use of stoichiometric quantities of copper, the classical Ullmann ether synthesis remains an important process in diaryl ether synthesis. In last decade, some improvements have been performed[4-7]. Recently, a potassium fluoride-alumina mediated S_NAr addition of phenols to electron-deficient aryl halides in the presence of 18-crown-6 was also shown to be an efficient alternative to Ullmann ether synthesis[7-9]. Intramolecular coupling reaction between arylsilyl ether and aryl fluoride in the presence of TBAF in THF, following by treating with K_2CO_3 in DMF, has been reported to afford the cyclic diaryl ether[10]. In this paper, we report a general one-pot synthesis of diaryl ethers *via* coupling of aryl halide with phenoxytrimethylsilane in the presence of TBAF.

Scheme 1



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As shown in **Scheme 1**, the mixture of aryl halides **1** (1 mmol), substitutedphenoxy-trimethylsilanes **2** (1.05 mmol) , TBAF (1 mmol), EtOH (1.2 mol) and Et_3N (2 mmol) in DMF was stirred at 100°C for 12 h to give corresponding diaryl ethers **3**, The results are summarized in **Table 1**.

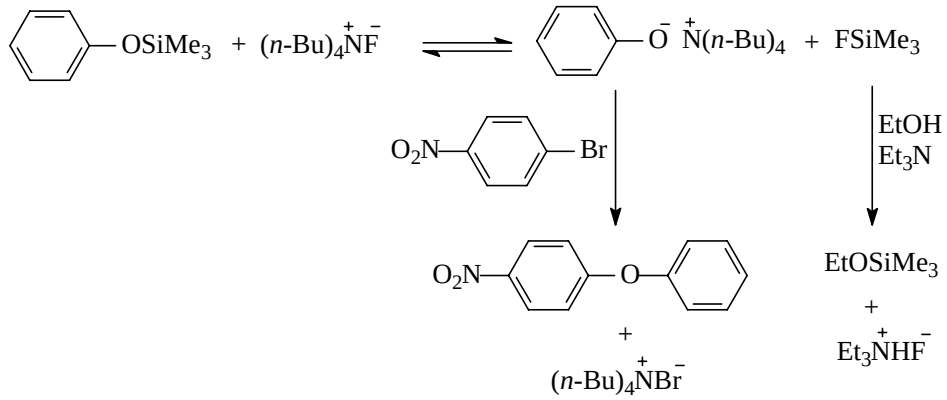
As shown in **Table 1**, all electron-deficient aryl halides could couple with phenoxytrimethylsilanes to give diaryl ethers in high yields (entry 1~16). Unfortunately, electron-rich or electron-neutral aryl halides did not work (entry 17 and 18). These results suggest that the coupling reaction carried out in a S_NAr mechanism[7, 8] (**Scheme 2**). In polar solvent, the trimethylsilyl ethers are readily cleaved by fluoride ion to afford phenoxy anion, which attacks electron-deficient aryl halides to give the coupling product.

Table 1 Diaryl ether synthesis *via* coupling of aryl halides with substituted phenoxytrimethylsilane

Entry	R_1	R_2	X	Isolated Yields (%)
1	4-NO_2	H	F	95
2	4-NO_2	4-CH_3	F	96
3	4-NO_2	3-CH_3	F	92
4	4-NO_2	H	Br	91
5	4-NO_2	4-CH_3	Br	93
6	4-NO_2	3-CH_3	Br	92
7	4-NO_2	H	Cl	92
8	4-NO_2	4-CH_3	Cl	96
9	4-NO_2	3-CH_3	Cl	94
10	2-NO_2	3-CH_3	Cl	90
11	4-CHO	H	Br	78
12	4-CHO	H	Cl	82
13	4-$COCH_3$	3-CH_3	Br	85
14	4-$COCH_3$	3-CH_3	Cl	87
15	4-COPh	4-CH_3	Br	80
16	4-COPh	4-CH_3	Cl	82
17	H	4-CH_3	F	no reaction
18	CH_3	4-CH_3	Br	no reaction

In conclusion, we established an efficient synthetic method of diaryl ethers. Electron-deficient aryl halides reacted with substituted phenoxytrimethylsilanes in the presence of TBAF to give diaryl ethers in good to excellent yields. Zhu's method[10] was only used in the total synthesis of natural product from arylsilyl ether and aryl fluoride in TBAF and K_2CO_3. However, this modified method could be used to prepare diaryl ether from aryl bromide or aryl chloride with substituted phenoxytrimethylsilane. Our protocol avoids the use of air-sensitive and expensive reagents, which is necessary in the methods based on Cu or Pd-catalyzed reactions[11, 12]. For formation of aryl-oxygen bonds, the reactions can be used in the total synthesis of diaryl ether-containing natural product with improved yield than before. Further researches are in progress.

Scheme 2 Possible mechanism for the coupling of aryl halides with phenoxytrimethylsilanes



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