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# Direct synthesis of trimethyl(2-phenoxyethyl)silanes from aromatic fluorides

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**Abstract**—A direct synthesis of trimethyl(2-phenoxyethyl)silanes from the corresponding aromatic fluorides and 2-(trimethylsilyl)ethanol was developed. A variety of substituents were tolerated and a substitution reaction using 1-bromo-3-chloro-5-fluorobenzene was demonstrated.

Many natural products and drug-like molecules are phenolic compounds.[1,2] Phenols are commonly synthesized through hydroxylation, oxidation of aldehydes, ketones, or organometallic derivatives, Claisen and aldol condensation, cycloaddition, benzannulation rearrangement, and by the direct displacement of halides, sulfonic acids, or nitrogen derivatives.[3] Many of these reactions require high temperatures and harsh conditions.

In our synthetic endeavors, we required a series of phenolic compounds. However, many polysubstituted aromatic compounds of interest to us were not commercially available. Substituted aromatic fluorides are becoming increasingly available and we sought a general process that could be used to make protected phenols directly from these substrates. Recently, Rogers and Green showed that phenols can be obtained directly by reacting 2-(methylsulfonyl)ethanol with electron-deficient aromatic fluorides in the presence of sodium hydride, establishing the viability of performing nucleophilic aromatic substitution ($S_NAr$) reactions on aromatic fluorides as a means of producing phenols efficiently.[4] Phenols are often quite polar and their purification can be challenging. Furthermore, the relative acidity and nucleophilicity of phenols makes them incompatible with many reactions. For these reasons, we sought to synthesize protected phenols that would be tolerant of a variety of reaction conditions and yet be readily converted into the corresponding phenols.[5,6]

Accordingly, we report a direct method for the conversion of aromatic fluorides into trimethyl(2-phenoxyethyl)silanes and show that it is compatible with a variety of substituents.[7–9] This is achieved by treating commercially available 2-(trimethylsilyl)ethanol (TMSE) with KHMDS (potassium bis(trimethylsilyl)amide and aromatic fluorides at room temperature.[10] The resulting TMSE-protected phenols are stable to acidic and strongly basic conditions, allowing further manipulation without undesired side reactions, but are readily deprotected at room temperature with fluoride salts such as tetrabutylammonium fluoride (Eq. 1).[11] Additionally, the TMSE-protected phenols are often easily separated from polar reaction by-products by filtration through a pad of silica gel.

Initially, 4-bromo-2-fluorobenzonitrile was treated with TMSE and KHMDS in THF giving the expected TMSE-protected phenol, which was isolated in 97% yield (Table 1, entry 1).[12] We then surveyed a series of bases including LiHMDS, NaHMDS, LDA, KO-*t*-Bu, and *n*-butyllithium. All gave comparable conversion,

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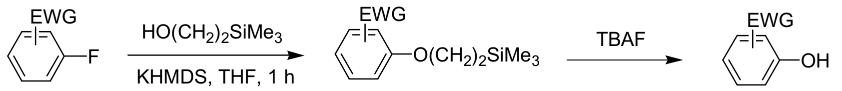


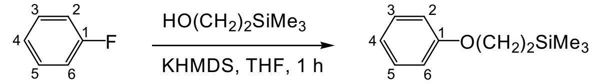
(1)

except LiHMDS, in which case a significant amount of starting aromatic fluoride remained after 5 h.[13] Next we surveyed several solvents and found that 1,4-dioxane, toluene, acetonitrile, and diethyl ether allowed complete conversion to the TMSE-protected phenol within 1 h. When more polar solvents such as DMF and 1-methyl-2-pyrrolidinone were used, more than 40% of the starting aromatic fluoride remained after 1 h.

We then subjected a series of substituted aromatic fluorides to the optimized conditions using KHMDS in THF (Table 1). We found that aromatic fluorides bearing moderate or strong electron-withdrawing groups in the *ortho*- and *para*-position gave modest to high yields, with the highest yields obtained when the aromatic fluorides contained at least two electron-withdrawing groups (entries 1–3). Substituents *ortho* to the fluorine were usually tolerated, with the exception of 1-fluoro-2-nitrobenzene, which provided only 12% yield of the TMSE-protected phenol (entry 8). We failed to obtain any isolable product when aromatic fluorides bearing electron-donating substituents such as –OMe were subjected to the reaction conditions (entry 9).

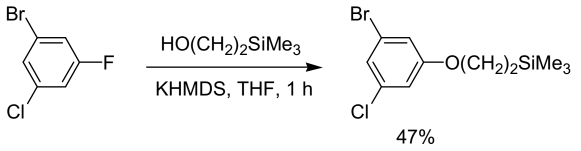
When 3-chloro-5-fluoro-bromobenzene was treated with TMSE and KHMDS in THF, the corresponding TMSE-protected phenol was obtained in 47% yield (Eq. 2). Similar $S_NAr$ reactions performed on 1,3,5-trihalogenated similar substrates are rare.[14] Finally, a disubstitution reaction was demonstrated, furnishing the diprotected phenol in 40% yield when 2.5 equiv of TMSE and KHMDS were used (Eq. 3).

**Table 1.** Base-promoted reactions of 2-(trimethylsilyl)ethanol with aromatic fluorides

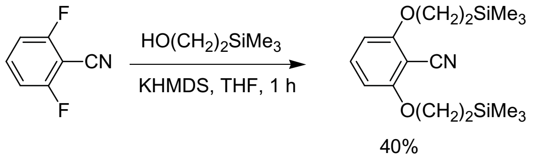


| Entry | Aromatic fluoride | | | | | Yield[a] (%) |
|---|---|---|---|---|---|---|
| | 2 | 3 | 4 | 5 | 6 | |
| 1 | CN | H | H | Br | H | 97 |
| 2 | $SO_2N(Me)_2$ | H | H | Br | H | 89 |
| 3 | Br | H | $CF_3$ | H | H | 59 |
| 4 | H | H | $SO_2Me$ | H | H | 83 |
| 5 | H | H | CN | H | H | 48 |
| 6 | CN | H | H | H | H | 45 |
| 7 | H | H | $NO_2$ | H | H | 45 |
| 8 | $NO_2$ | H | H | H | H | 12 |
| 9 | OMe | H | H | H | H | 0 |

[a] Isolated yield.



(2)



(3)

In conclusion, we have developed a mild and efficient method for the direct synthesis of TMSE-protected phenols using electron-deficient aromatic fluorides and 2-(trimethylsilyl)ethanol. A variety of substituents were tolerated, including bromine and chlorine, furnishing the TMSE-protected phenols in modest to good yields. Additionally, a substitution reaction using 1-bromo-3-chloro-5-fluorobenzene and a disubstitution reaction were demonstrated.

## Acknowledgments

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12. General procedure: to a solution of 6.0 g (0.030 mol) of 4-bromo-2-fluorobenzonitrile and 4.84 mL (0.033 mol) of 2-(trimethylsilyl)ethanol in 200 mL of dry THF at 0 °C, 66 mL of 0.50 M (0.033 mol) KHMDS in toluene was added dropwise. The reaction mixture was then warmed to room temperature and stirred for 1 h, at which time the reaction was quenched with 250 mL of 1.0 M $KHSO_4$, and extracted with 200 mL of diethyl ether. The organic layer was dried with anhydrous $MgSO_4$, filtered, concentrated, and chromatographed (15% EtOAc/hexane) to give 8.36 g (97%) of 4-bromo-2-(2-trimethylsilanyl-ethoxy)-benzonitrile (Table 1, entry 1) as a white solid. $R_f = 0.65$ (15% EtOAc/hexane): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J = 7.0$ Hz, 1H), 7.16 (t, $J = 7.5$ Hz, 2H), 4.18 (d, $J = 7.0$ Hz, 2H), 1.20 (d, $J = 7.0$ Hz, 2H), 0.16 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.4, 135.8, 130.0, 125.2, 117.3, 102.4, 68.8, 18.7, 0.0; ESI MS *m*/*z* 298 ($MH^+$), 196. Anal. Calcd for $C_{12}H_{16}BrNOSi$: C, 48.32; H, 5.41; Br, 26.79; N, 4.70; O, 5.36; Si, 9.42. Found: C, 48.52; H, 5.44; Br, 26.78; N, 4.74; Si, 9.19.
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