Synthesis of Multiply *ortho*-Substituted Diaryl Ethers via Lithiation and Oxidation of a Dibenzosiloxane (Phenoxasilin)

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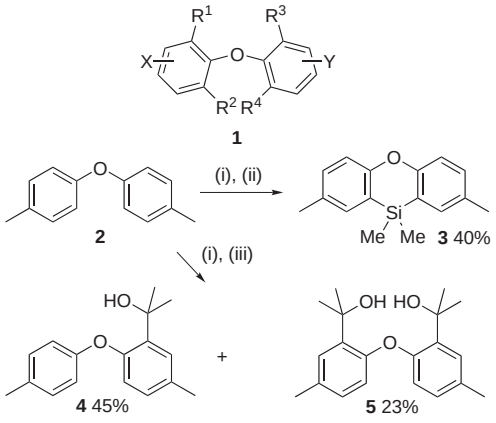
Abstract: Lithiation of dibenzosiloxanes (phenoxasilins or 9-silaxanthenes), followed by oxidation of the C–Si bonds, provides a versatile method for the synthesis of 2,6,2′,6′-tetrasubstituted diaryl (biaryl) ethers.

Key words: diaryl ether, synthesis, lithiation, *ipso* electrophilic aromatic substitution

Diaryl ethers **1** are key structural features of important biologically active compounds such as thyroxine, the bastadins,[1] vancomycin and its analogues[2] and have generally been made by metal-promoted coupling or nucleophilic aromatic substitution.[3] As part of an investigation of the stereochemistry of diaryl ether compounds, we needed a versatile way of introducing up to four substituents *ortho* to the diaryl ether C–O bond. An OAr group is a moderately effective director of lithiation,[4,5] so we attempted directed metallation reactions of **2**. Ether **2** was treated with 2.5 equivalents *n*-BuLi in neat TMEDA (0–20 °C, 24 h) and acetone was added. A mixture of single and double addition products **4** and **5** were formed, along with remaining **2** (Scheme 1). Even after protection as their methyl or trimethylsilyl ether derivatives, these compounds were highly resistant towards further lithiation.



Scheme 1 Lithiation of di-*p*-tolyl ether. *Reagents and conditions*: (i) *n*-BuLi, TMEDA, 20 °C; (ii) Me_2SiCl_2; (iii) acetone.

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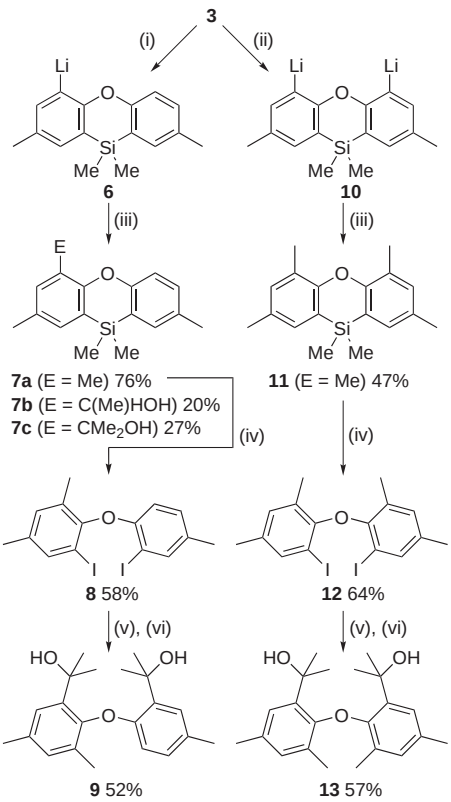
Tricyclic diaryl ethers are cleanly doubly lithiated,[5,6] so we turned to the dibenzosiloxane (phenoxasilin) **3** in the hope that (a) its lithiation would be straightforward and (b) subsequent oxidation (*ipso* electrophilic aromatic substitution) of the C–Si bonds[7] would allow the formation of functionalized acyclic ethers. Taking di-*p*-tolyl ether **2** in diethyl ether, we added *s*-BuLi (3 equiv) in TMEDA. Quench with dichlorodimethylsilane yielded the dibenzosiloxane **3**[8] in 40% yield on a multigram scale.[9]



Scheme 2 Diaryl ethers from dibenzosiloxane **3**. *Reagents and conditions*: (i) *s*-BuLi (2 equiv), TMEDA, Et_2O, 0 °C, 2 h; (ii) *s*-BuLi (3.5 equiv), TMEDA, Et_2O, 0 °C, 2 h; (iii) MeI or MeCHO or acetone; (iv) ICl, CH_2Cl_2; (v) *n*-BuLi, THF; (vi) acetone.

Further lithiation[5] was easy. Treating **3** with 2 equivalents *s*-BuLi in TMEDA–Et_2O at 0 °C led to immediate coloration, and quenching this yellow organolithium (presumably **6**) with methyl iodide,[10] acetaldehyde or acetone yielded **7**. Similarly, after lithiation with 3.5 equivalents *s*-BuLi, methylation of the dianion **10** returned the doubly alkylated siloxane **11** (Scheme 2).

Conversion of the alkylated dibenzosiloxanes to acyclic diaryl ethers was achieved with ICl. Double *ipso* electrophilic aromatic substitution of the silyl group[11] yielded the versatile diiodo derivatives **8**[12] and **12**. Further manipulation of the iodo substituents is evidently possible in a variety of ways: we chose to treat **8** and **12** with *n*-BuLi and acetone to yield the tri-*ortho*-substituted and tetra-*ortho*-substituted diaryl ethers **9** and **13**.

Details of our stereochemical investigations of **9**, **13** and other heavily substituted diaryl ethers will be reported shortly.[13]

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References and Notes

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(8) **3,6,10,10-Tetramethyl-9-silaxanthene (3)**
p-Tolyl ether (5.0 g, 25.2 mmol) was dissolved in dry TMEDA (50 mL) and cooled to 0 °C under a nitrogen atmosphere. *n*-BuLi (2.5 M solution in hexane, 30.3 mL, 75.7 mmol) was added and the mixture stirred for 20 min at 0 °C. The ice bath was removed and the mixture was stirred for 12 h, after which time the solution had turned dark orange. The mixture was cooled to 0 °C and dimethyldichlorosilane (4.60 mL, 37.9 mmol) added dropwise which resulted in an exothermic reaction. The mixture was stirred for a further 2 h at 0 °C and sat. aq NH_4Cl solution (50 mL) added, followed by EtOAc (50 mL). The layers were separated and the aqueous layer washed with EtOAc (3 × 30 mL) and the combined organic fractions were washed with aq HCl (3 M, 30 mL), H_2O (30 mL), brine (30 mL), dried ($MgSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, PE) to give the dibenzosiloxane 3 as a viscous colorless oil (2.47 g, 9.71 mmol, 40%) which crystallized on standing (plates, mp 47–49.5 °C); R_f = 0.50 (PE). IR (film): ν_{max} = 2952 (CH), 2919 (CH), 1458 (aromatic) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.36 (2 H, m, SiCCH), 7.32–7.26 (2 H, m, MeCC*H*), 7.16 (2 H, d, *J* = 8.4 Hz, OCCH), 2.46 (6 H, s, Ph*Me*), 0.54 (6 H, s, $SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 134.1, 132.2, 131.7, 119.0, 118.0, 21.0, –0.0. MS (EI): *m/z* (%) = 254 (50) [M], 239 (100) [M – CH_3]. HRMS: *m/z* calcd for $C_{16}H_{18}OSi$: 254.1121; found: 254.1129.
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(10) **3,6,8,10,10-Pentamethyl-9-silaxanthene (7a)**
The dibenzosiloxane **3** (500 mg, 1.965 mmol) was dissolved in dry Et_2O (10 mL) and dry TMEDA (0.44 mL, 2.95 mmol) and cooled to –78 °C under a nitrogen atmosphere. *s*-BuLi (1.1 M solution in cyclohexane, 2.68 mL, 2.95 mmol) was added and after 10 min the dry ice bath was replaced with an ice bath. The orange solution was stirred for 2 h and MeI (0.18 mL, 2.95 mmol) was added. The mixture was stirred for 14 h with gradual warming to r.t. Then, sat. aq NH_4Cl solution (5 mL) was added and the layers separated. The aqueous layer was washed with Et_2O (3 × 5 mL) and the combined organic fractions were washed with H_2O (2 × 5 mL), brine (5 mL), dried ($MgSO_4$) and solvents removed under reduced pressure. The residue was purified by flash chromatography (silica, PE) to give the dibenzosiloxane **7a** as a colorless oil (400 mg, 1.49 mmol, 76%); R_f = 0.67 (PE). IR (film): ν_{max} = 2951 (CH), 2920 (CH), 1604 (aromatic), 1586 (aromatic) cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.39 (2 H, s, ArH), 7.32–7.14 (4 H, m, 4 × ArH), 2.50 (3 H, s, ArMe_A), 2.45 (3 H, s, ArMe_B), 2.42 (3 H, s, ArMe_C), 0.54 (6 H, s, $SiMe_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.2, 156.2 (O–C), 134.0, 133.6, 132.1, 131.7, 131.5, 126.9, 126.7, 119.2, 118.6, 118.0 (aromatics), 21.0, 20.9, 17.2 (ArMe), –0.06 ($SiMe_2$). MS (EI): *m/z* (%) = 268 (50) [M^+], 253 (100) [M – Me]. HRMS: *m/z* calcd for $C_{17}H_{20}OSi$: 286.1622; found: 286.1622.
(11) Similar ortholithiation–silylation–electrophilic substitution sequences have been employed for ortho halogenation, see: (a) Clayden, J.; Lund, A.; Youssef, L. H. *Org. Lett.* **2001**, *3*, 4133. (b) Zhao, Z.; Snieckus, V. *Org. Lett.* **2005**, *7*, 2523.
(12) **2,2′-Diiodo-4,4′,6-Trimethylbiphenyl Ether (8)**
The dibenzosiloxane **7a** (890 mg, 3.317 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under a nitrogen atmosphere and cooled to 0 °C. Iodine monochloride (1.0 M in CH_2Cl_2, 6.97 mL, 6.97 mmol) was added and the mixture stirred for 30 min after which time the ice bath was removed. And stirred for a further 12 h. Then, sat. aq $Na_2S_2O_3$ solution (25 mL) was added and the layers separated. The aqueous layer was washed with CH_2Cl_2 (3 × 25 mL) and the combined organic fractions were washed with H_2O (2 × 25 mL), brine (25 mL), dried ($MgSO_4$) and solvents removed. The residue was purified by flash chromatography (silica, PE) to give the ether **8** (859 mg, 1.85 mmol, 55%) as a crystalline solid (plates), mp 122.5–124.2 °C (hexane–EtOAc). R_f = 0.55 (PE). IR (film): ν_{max} = 3019 (CH), 2919 (CH), 1602 (aromatic), 1481 (aromatic) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 [1 H, d, *J* = 2.0 Hz, $(ICCH)_A$], 7.58 (1 H, s, $(ICCH)_B$], 7.08 (1 H, s, MeCC*H*CMe), 6.98 (1 H, dd, *J* = 8.5, 2.0 Hz, OCCHC*H*), 6.20 (1 H, d, *J* = 8.5 Hz, OCCH), 2.36 (3 H, s, $ArMe_A$), 2.31 (3 H, s, $ArMe_B$), 2.16 (3 H, s, $ArMe_C$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 151.1, 140.5, 138.3, 138.0, 137.3, 133.4, 132.7, 133.4, 132.7, 132.6, 130.1, 113.1, 92.0 (C–I), 85.4 (C–I), 20.7, 20.4, 17.6. MS (EI): *m/z* (%) = 464 (15) [MH^+], 210 (100) [M – I_2]. HRMS: *m/z* calcd for $C_{15}H_{14}OI_2$: 463.9129; found: 463.9127.
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