Aryl, Alkyl *bis*-Silyl Ethers: Rapid Access to Monoprotected Aryl Alkyl and Biaryl Ethers

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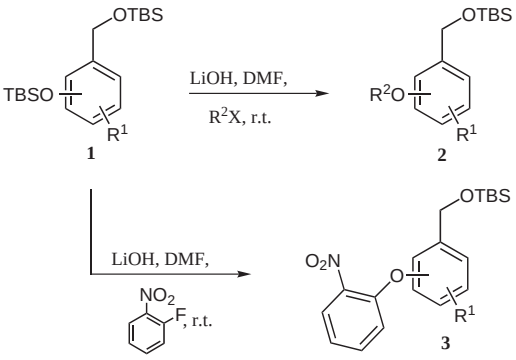
Abstract: A simple one-pot procedure has been developed for the selective etherification of aryl silyl ethers in aryl, alkyl *bis*-silyl ethers to generate alkyl *tert*-butyldimethylsilyl-protected aryl alkyl ethers and biaryl ethers in good to excellent yields.

Key words: protecting groups, phenols, LiOH/DMF, ethers, selective etherification

As the complexity of synthetic targets has grown more demanding, discrimination between similar types of protecting groups and direct transformation of one protecting group into another have become essential for increasing the efficiency of natural product synthesis. Among the many protecting groups available for hydroxyl groups, silyl and alkyl ethers are the most commonly used due to their stability under various reaction conditions.[1]

While many procedures are available for the formation of aryl alkyl ethers from phenols, no general method exists for the direct conversion of aryl, alkyl *bis*-silyl ethers into aryl alkyl ethers, keeping the alcoholic silyl group intact. Cesium fluoride[2a] and tetrabutylammonium fluoride,[2b] which are exploited as bases for the formation of aryl alkyl ethers from aryl silyl ethers, are not suitable for this particular transformation because of their ability to cleave both alcoholic and phenolic *tert*-butyldimethylsilyl (TBS) groups.[3] Such a selective transformation is indeed of potential use, as many natural products and amino acids are endowed with both alcoholic and phenolic hydroxyl groups.[4] In addition, generation of aryl alkyl ethers from phenols is an efficient way to produce a library of aryl alkyl ethers,[5] which are important constituents of many pharmacologically important chemical templates.

We recently developed a novel methodology for the selective deprotection of either aryl or alkyl silyl ethers from aryl, alkyl *bis*-silyl ethers.[6] These efforts stemmed from our need to synthesize certain analogs of a new inhibitor of cell migration which we discovered, for use in structure-activity relationship studies.[7] Our success with the selective deprotection of aryl TBS ethers in the presence of alkyl TBS ethers using LiOH/DMF[6] prompted us to investigate the utility of this reagent system in the formation of aryl alkyl ethers and biaryl ethers (Scheme 1). Using this system, we accomplished the selective etherification



Scheme 1

of aryl silyl ethers in the presence of alcoholic silyl ethers in a one-pot procedure. Several substituted phenols were reacted with alkyl halides to form the corresponding aryl alkyl ethers in good yields (Table 1). In addition, since benzoate is a versatile protecting group for hydroxyl groups,[1] we wanted to examine this methodology in benzoate formation. We found that this protocol allows for the synthesis of aryl benzoates from the *bis*-silyl ethers in good yields. The reaction was general both in terms of phenol and alkyl halide and gave good to excellent yields, irrespective of the substitution pattern on the aromatic ring (Table 1).

With the intention of further expanding the scope of this methodology, we explored the S_NAr reaction of activated aryl halide such as *o*-nitrofluorobenzene with various aryl, alkyl *bis*-silyl ethers for the formation of monoprotected biaryl ethers. Biaryl ethers are present in many biologically interesting natural products, such as combretastatins D-1 (**4**) and D-2 (**5**)[8] (Figure 1), piperizenomycin,[9] deoxybouvardin[10] and many commercial polymers. Due to the structural importance of biaryl ethers, there has been considerable effort toward the development of general methods for their construction. The most prominent procedures for the synthesis of biaryl ethers include the Ullmann reaction,[11a] oxidative phenolic coupling,[11b] metal-activated nucleophilic aromatic substitution,[11c] S_NAr reaction[11d] and boronic acid-driven biaryl ether synthesis.[11e] Although the Ullmann reaction is a particularly important method for the synthesis of biaryl ethers, it has several drawbacks, such as requirement for harsh reaction conditions and long reaction times. Furthermore, it is suitable only for electron-rich phenols. Several bases have been studied for inter- and intramolecular biaryl ether

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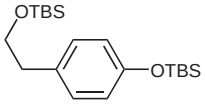
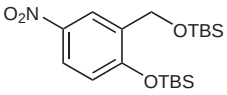
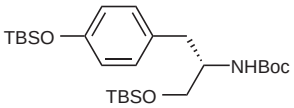
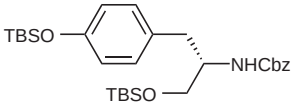
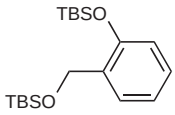
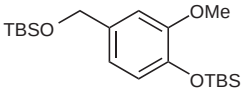
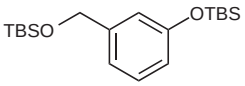
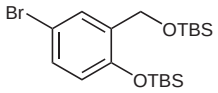
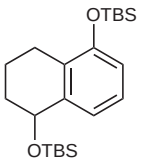
Table 1 Synthesis of Various Aryl Alkyl Ethers from Aryl Alkyl *bis*-Silyl Ethers

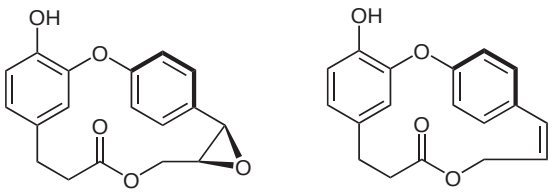
No	*bis*-TBS ether	RX	Time (h)[a]	Product (Yield%)[b]
1a		BnBr	5	**2a** (92)
		Allyl iodide	4.5	**2b** (95)
		Allyl bromide	5	**2b** (94)
		Propargyl bromide	5	**2c** (95)
		PhCOCl	5.5	**2d** (79)
1b		PhCOCl	3	**2e** (70)
		Allyl iodide	2	**2f** (80)
1c		BnBr	6	**2g** (92)
1d		BnBr	4	**2h** (94)
1e		BnBr	9	**2i** (90)
		Allyl iodide	8	**2j** (85)
		MeI	8.5	**2k** (91)
1f		Allyl iodide	15	**2l** (89)
		PhCOCl	15.5	**2m** (76)
		BnBr[c]	16	**2n** (91)
		MeI	16	**2o** (95)
1g		Allyl iodide	5	**2p** (92)
		BnBr	5.5	**2q** (89)
1h		MeI	4	**2r** (89)
		BnBr[c]	4.5	**2s** (91)
		PhCOCl	4.5	**2t** (75)
1i		Allyl iodide	17	**2u** (92)
		BnBr	17	**2v** (92)
		MeI	18	**2w** (89)

[a] Use of less than 3.0 equiv of LiOH also gave products, but the reaction times were increased.
[b] Isolated yields.
[c] These reactions, when performed with CsF as a base, led to a mixture of compounds.

formation from phenols.[12] However, there has been less attention paid to the selective conversion of aryl silyl ethers to biaryl ethers starting from aryl, alkyl *bis*-silyl ethers. Therefore, we sought a general method to generate TBS-protected biaryl ethers from aryl, alkyl *bis*-silyl ethers that is also applicable to electron-deficient phenols.

Several aryl, alkyl *bis*-silyl ethers were reacted with *o*-nitrofluorobenzene in the presence of LiOH/DMF in a one-step protocol to form biaryl ether products of high purity and in good yields (Scheme 2).

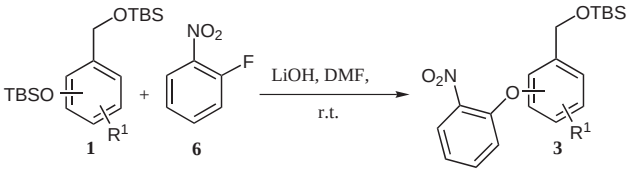
The results summarized in Table 2 clearly show the scope of the method with respect to various substituted aryl, alkyl *bis*-silyl ethers, including tyrosine-derived *bis*-silyl ether. These results demonstrate that the present method is also suitable for electron-deficient phenols, unlike the Ullmann ether synthesis.



Combretastatin D-1 (**4**) Combretastatin D-2 (**5**)

Figure 1

Finally, we wished to show that this methodology could be applied to the synthesis of more complex molecules.



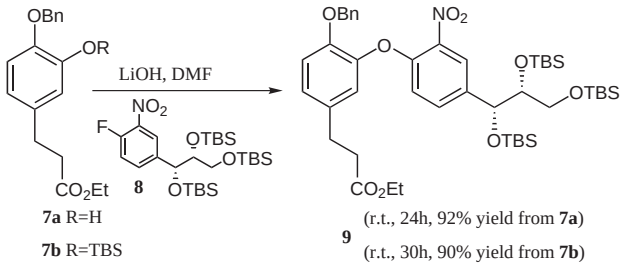
Scheme 2

Table 2 Synthesis of Various Biaryl Ethers from Aryl, Alkyl *bis*-Silyl Ethers

bis-TBS ether	Time (h)[a]	Product (Yield%)[b]
1a	5.5	**3a** (95)
1b	18	**3b** (92)
1c	6	**3c** (93)
1e	10	**3e** (88)
1f	12	**3f** (90)
1g	8	**3g** (93)
1h	10	**3h** (91)

[a] Typical reaction conditions for the desired transformation include the use of 5.0 equiv of LiOH and 1.2 equiv of *o*-nitrofluorobenzene. Decreasing the amount of LiOH used to 3.0 equiv resulted in considerably increased reaction times.
[b] Isolated yields.

We chose to prepare an advanced intermediate for the synthesis of **4** and **5**,[8] compounds that stabilize microtubules.[13] We first prepared the hitherto unknown *tris*-silyl ether **8** starting from commercially available 4-fluoro-3-nitrobenzaldehyde.[14] Treatment of the readily available phenols **7**[8f] with LiOH and the *tris*-silyl ether **8** in DMF gave the anticipated coupled product **9** in excellent yield (Scheme 3).[15]



Scheme 3

In summary, we have developed a mild, efficient and general method for the conversion of aryl, alkyl *bis*-silyl ethers to alkyl TBS-protected aryl alkyl ethers and aryl benzoates. A number of aryl, alkyl *bis*-silyl ethers were smoothly converted to the corresponding biaryl ether frameworks in good yields. The nitro group present in the biaryl ether can be used as a handle to introduce various functionalities on the aromatic ring. The mildness and operational simplicity of the present methodology was demonstrated by synthesizing a potential key intermediate for the synthesis of **4** and **5**. The methodology presented here could also be exploited for the parallel synthesis of compound libraries.

General Experimental Procedure for the Synthesis of Alkyl TBS-Protected Aryl Alkyl Ethers (2)

LiOH (0.90 mmol) was added to a stirred solution of *bis*-TBS ether (0.30 mmol) in anhyd DMF (1 mL) and the reaction mixture was stirred at r.t. After consumption of the starting material, alkyl halide (0.60 mmol) was added and stirring was continued until completion of the reaction as indicated by thin-layer chromatography (TLC). The reaction mixture was then diluted with EtOAc, washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel column using EtOAc/hexanes as eluent.

General Experimental Procedure for the Synthesis of Alkyl TBS-Protected Biaryl Ethers (3)

To a stirred solution of *bis*-TBS ether (0.25 mmol) in anhyd DMF (1 mL), LiOH (1.25 mmol) and *o*-nitrofluorobenzene (0.30 mmol) were added successively at r.t. under argon atmosphere. The reaction mixture was stirred at r.t. until completion, as indicated by TLC. Then the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The resultant biaryl ether was purified by column chromatography over silica gel column using EtOAc/hexanes as eluent.

Spectroscopic Data for Selected New Compounds

Compound 2r: IR (film): 2929, 2370, 2345, 1254, 1093, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 6 H), 0.96 (s, 9 H), 3.79 (s, 3 H), 4.70 (s, 2 H), 6.68 (d, 1 H, *J* = 8.6 Hz), 7.30 (dd, 1 H, *J* = 8.6, 2.3 Hz), 7.56 (d, 1 H, *J* = 2.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 25.9, 55.2, 59.6, 111.0, 112.9, 129.4, 129.9, 132.1, 154.8. HRMS: Calcd for $C_{14}H_{23}O_2SiBrNa$ $[M + Na]^+$: 353.0548. Found: 353.0548.

Compound 2v: IR (film): 2927, 1459, 1251, 1077, 834, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 3 H), 0.17 (s, 3 H), 0.94 (s, 9 H), 1.71–1.80 (m, 2 H), 1.98–2.73 (m, 2 H), 2.73–2.78 (m, 2 H), 4.77–4.80 (m, 1 H), 5.06 (s, 2 H), 6.77 (d, 1 H, *J* = 7.9 Hz), 7.04 (d, 1 H, *J* = 7.7 Hz), 7.15 (t, 1 H, *J* = 7.9 Hz), 7.31–7.45 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 18.9, 22.6, 25.8, 31.5, 69.3, 69.6, 109.3, 120.2, 125.8, 126.9, 127.6, 128.4, 137.5, 141.3, 155.9. HRMS: Calcd for $C_{23}H_{32}O_2SiNa$ $[M + Na]^+$: 391.2069. Found: 391.2069.

Compound 3h: IR (film): 2928, 2360, 1530, 1252, 838, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H), 0.90 (s, 9 H), 4.73 (s, 2 H), 6.70 (d, 1 H, *J* = 9.0 Hz), 6.94 (d, 1 H, *J* = 8.3 Hz), 7.19–7.26 (m, 1 H), 7.34 (d, 1 H, *J* = 8.3 Hz), 7.50 (t, 1 H, *J* = 7.9 Hz), 7.72 (s, 1 H), 7.96 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 25.8, 59.4, 117.8, 119.6, 119.8, 123.3, 125.8, 130.9, 131.1, 134.2, 135.1, 150.4, 152.3. HRMS: Calcd for $C_{19}H_{24}BrNO_4SiNa$ $[M + Na]^+$: 460.0556. Found: 460.0554.

Compound 3c: IR (film): 2929, 1711, 1504, 1249, 1166, 837 cm^{-1}. $[\alpha]_D^{20}$ –19.4 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H), 0.92 (s, 9 H), 1.42 (s, 9 H), 2.82 (d, 2 H, *J* = 6.8 Hz), 3.49–3.57 (m, 2 H), 3.70–3.85 (m, 1 H), 4.76 (s, 1 H), 6.96–6.99 (m, 3 H), 7.14–7.26 (m, 3 H), 7.46 (t, 1 H, *J* = 7.6 Hz), 7.93 (dd, 1 H, *J* = 1.2, 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 25.8, 28.3, 36.7, 52.9, 63.0, 79.2, 119.3, 119.9, 122.7, 125.6, 130.9, 133.9, 134.9, 155.3. HRMS: Calcd for $C_{26}H_{38}N_2O_6SiNa$ $[M + Na]^+$: 525.2397. Found: 525.2397.

Compound 8: IR (film): 2929, 1541, 1255, 1093, 835 cm^{-1}. $[\alpha]_D^{20}$ –24.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.20 (s, 3 H), –0.10 (s, 3 H), –0.02 (s, 3 H), 0.02 (s, 6 H), 0.09 (s, 3 H), 0.84 (s, 9 H), 0.86 (s, 9 H), 0.88 (s, 9 H), 3.13–3.18 (m, 1 H), 3.62–3.75 (m, 2 H), 4.80 (d, 1 H, *J* = 2.8 Hz), 7.16–7.21 (m, 1 H), 7.59–7.67 (m, 1 H), 8.08 (dd, 1 H, *J* = 2.0, 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 18.0, 18.2, 25.6, 25.8, 63.5, 72.9, 77.2, 117.0, 117.5, 124.3, 133.4, 133.6, 139.3. HRMS: Calcd for $C_{27}H_{52}NO_5Si_3FNa$ $[M + Na]^+$: 596.3035. Found: 596.3052.

Compound 9: IR (film): 2929, 1736, 1532, 1256, 1091, 777 cm^{-1}. $[\alpha]_D^{20}$ –46.0 (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.19 (s, 3 H), –0.12 (s, 3 H), –0.02 (s, 3 H), 0.00 (s, 6 H), 0.06 (s, 3 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 0.90 (s, 9 H), 1.22 (t, 3 H, *J* = 7.2 Hz), 2.57 (t, 2 H, *J* = 7.6 Hz), 2.87 (t, 2 H, *J* = 7.6 Hz), 3.13–3.17 (m, 1 H), 3.63–3.72 (m, 2 H), 4.07–4.13 (q, 2 H, *J* = 7.2 Hz), 4.78 (d, 1 H, *J* = 3.1 Hz), 5.03 (s, 2 H), 6.76 (d, 1 H, *J* = 8.7 Hz), 6.92–6.98 (m, 3 H), 7.28–7.40 (m, 5 H), 7.42 (dd, 1 H, *J* = 2.1, 8.7 Hz), 7.96 (d, 1 H, *J* = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.9, 18.1, 18.2, 25.7, 25.9, 30.1, 35.8, 60.4, 63.6, 70.9, 73.0, 77.5, 115.6, 117.1, 121.8, 123.9, 125.6, 126.8, 127.7, 128.4, 128.5, 132.1, 134.4, 136.5, 136.6, 139.1, 143.9, 148.5, 150.5, 172.6. HRMS: Calcd for $C_{45}H_{71}NO_9Si_3Na$ $[M + Na]^+$: 876.4334. Found: 876.4312.

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(14) Preparation of **8** will be reported elsewhere.

(15) It is noteworthy that the ester groups in both **7a** and **7b** remained intact after exposure to 3.0 equiv of LiOH/DMF at r.t. and the coupled product **9** could be obtained in excellent yields.