Pergamon

Tetrahedron Letters 43 (2002) 4729–4732

TETRAHEDRON LETTERS

Selective deprotection of either alkyl or aryl silyl ethers from aryl, alkyl bis-silyl ethers

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Received 25 April 2002; revised 14 May 2002; accepted 15 May 2002

Abstract—A pair of complementary methods was developed using $CeCl_3 \cdot 7H_2O/CH_3CN$ and LiOH/DMF to selectively deprotect alkyl and aryl silyl ethers, respectively, from the corresponding bis-silyl ethers in excellent yields.

The derivitization of alcohols as their *tert*-butyldimethylsilyl (TBS) ethers has been recognized as one of the most useful protection methods since its introduction by Corey and Venkateswarlu in 1972 because of its easy installation and general stability to basic and mildly acidic conditions.[1] Although a large number of deprotection methods are available for discriminating between different trialkylsilyl groups,[2,3] relatively few methods have been developed for the selective removal of alkyl TBS ethers in the presence of aryl TBS ethers[4] and vice versa.[5] Considering that both alcoholic and phenolic hydroxyl groups are present in many complex natural products such as vancomycin,[6] teicoplanin,[7] pancreastatin[8] and naturally occurring amino acids,[9] the differential deprotection of alcoholic and phenolic silyl ethers is of considerable interest.

Available methods for the selective cleavage of alkyl silyl ethers in the presence of aryl silyl ethers include the use of $BiBr_3$/wet CH_3CN,[4a] TMSCl/H_2O/CH_3CN,[4b] I_2/MeOH[4c] and 40% aqueous HF/CH_3CN.[4d] While each of the above methods has merit, these deprotection methods involve protic acids, which limits their use in systems containing labile moieties. Similarly, selective deprotection of phenolic TBS ethers has been achieved by various research groups using KF/alumina,[5a] NaOH/*n*-Bu_4NHSO_4,[5b] K_2CO_3/ethanol,[5c] K_2CO_3/kryptofix/CH_3CN,[5d] KF/alumina/ultrasound[5e] and TBAF/THF.[4d] While some of these methods require high temperatures, expensive reagents and non-standard laboratory equipment, others are limited in their use by the nature of the substituents present on the aromatic ring. In this context, we have developed an efficient methodology wherein alkyl silyl ethers are selectively deprotected in the presence of aryl silyl ethers by using $CeCl_3 \cdot 7H_2O$, which is an inexpensive, non-toxic, and mild Lewis acid.[10] Conversely, we have also developed an alternative methodology for the selective deprotection of aryl silyl ethers in the presence of alkyl silyl ethers using LiOH/DMF under mild conditions.

Investigation of reaction conditions for the selective cleavage of alkyl silyl ethers using $CeCl_3 \cdot 7H_2O$ indicated that 2.0 equiv. of cerium chloride in refluxing acetonitrile (0.03 M)[11] was optimal for the desired deprotection, and the results are summarized in Table 1.[†] Efforts to make the reaction sub-stoichiometric in cerium chloride resulted in retardation of progress of the reaction. Substitution patterns and electronic properties of the aromatic ring have an effect on the rate of selective deprotection of alkyl silyl ethers from bis-TBS ethers (Table 1). We observed that the rate of deprotection of alkyl silyl ethers was accelerated if an electron-donating group is present on the aromatic ring (entry 4, Table 1). On the other hand, the presence of an electron-withdrawing group on the aromatic ring decelerated the desired transformation (entries 5 and 6, Table 1). In addition, deprotection of the alkyl TBS group from sterically hindered salicyl alcohol-derived bis-TBS

Keywords: aryl, alkyl bis-silyl ethers; selective deprotection; alkanols; phenols; tyrosine.

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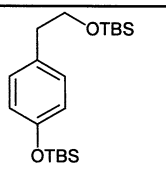
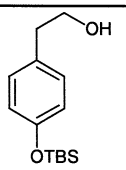
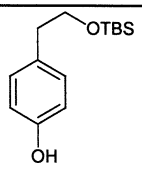
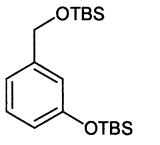
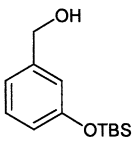
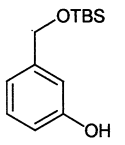
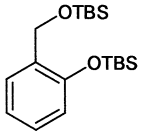
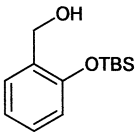
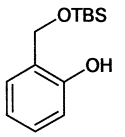
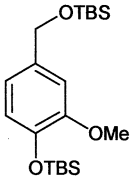
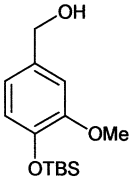
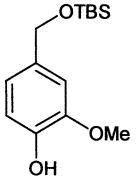
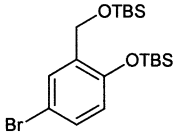
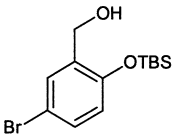
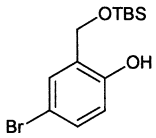
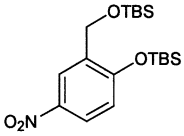
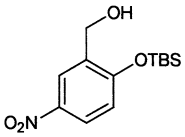
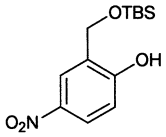
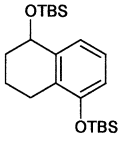
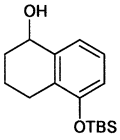
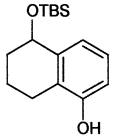
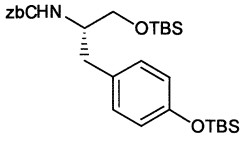
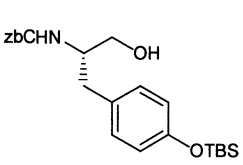
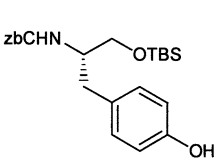
[†] Addition of 1.0 equiv. of sodium iodide increased the solubility of cerium salt in acetonitrile, but led to considerable amount of iodide byproducts in the case of aromatic ring substituted with electron-donating group. See also Table 1.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00942-5

Table 1. Selective deprotections of aryl, alkyl bis-silyl ethers

Entry	bis-TBS ether (**a**)	Alkanol (**b**) (Method I)	Time (h)/ (Yield) [a]	Phenol (**c**) (Method II)	Time (h)/ (Yield) [a]
1			3.5 h (96%)		3 h[b] (97%)
2			4 h (97%)		3.5 h (92%)
3			8 h (92%)		6 h (90%)
4			3 h[c] (92%)		14 h (92%)
5			10 h (93%)		2.5 h (91%)
6			20 h (88%)		1 h (90%)
7			5 h (85%)		16 h (76%)
8			2 h (96%)		2.5 h (87%)

[a] Isolated yields. [b] Catalytic amount (0.5 equiv.) of LiOH also gave quantitative yield of the product, but the reaction time was 48 h. [c] In the presence of 1 equiv. of sodium iodide, the alkanol **4b** was produced in less than 50% yield.

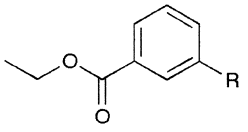
ether (entry 3, Table 1) took longer than what is required for its *meta* and *para* counterparts.

Concurrently, we sought a complementary method to deprotect aryl TBS ethers in the presence of alkyl TBS ethers, since we required this selectivity in the synthesis of bioactive small molecules in our laboratory. To the best of our knowledge, systematic studies of selective deprotection of aryl silyl ethers in the presence of alkyl silyl ethers have been reported only with TBAF/THF,[4d]

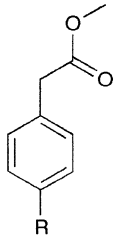
$NaOH/n\text{-}Bu_4NHSO_4$/1,4-dioxane[5b] and K_2CO_3/kryptofix/CH_3CN.[5d] Although TBAF is widely used for deprotection of silyl ethers, its use in this particular transformation requires careful control of reaction conditions. In the case of K_2CO_3/kryptofix/CH_3CN, 0.5 equiv. of kryptofix is needed for each equiv. of substrate, thus limiting its utility in large scale synthesis. Crouch et al. reported achieving selective deprotection of aryl silyl ethers in the presence of alkyl silyl ethers using 10 equiv. of NaOH and a phase transfer catalyst, $n\text{-}Bu_4NHSO_4$. Furthermore, a study of the stability of alkyl and aryl silyl ethers under acidic and basic conditions by Davies et al. revealed that while acidic conditions facilitate cleavage of alkyl silyl ethers, basic conditions favor cleavage of aryl silyl ethers.[12] In view of these facts, we examined the ability of LiOH to act as a base to perform the required selective deprotection in DMF. We reasoned that DMF, being a polar aprotic solvent, would generate an unencumbered hydroxide ion, thus obviating the need to use a large excess of base.

The bis-TBS ether **1a** was deprotected smoothly to phenol **1c** in 3 h using 3.0 equiv. of LiOH in DMF at room temperature. Indeed, we found that complete desilylation can be achieved with catalytic amounts of LiOH (0.5 equiv.), but the reaction time increased considerably. We also observed that deprotection of phenolic TBS ethers is faster when electron-withdrawing groups are present at the *para* position (entries 5 and 6, Table 1). In order to examine the stability of the ester group functionality under the reaction conditions required for phenolic TBS–ether deprotection, compounds **9** and **10** were deprotected separately under the optimized conditions. It was found that **9** afforded **11** in 86% yield, while **10** furnished **12** in 78% yield, indicating that an ester group is well tolerated on both the aromatic ring and the side chain.

In summary, we describe a mild and efficient method for the selective cleavage of alkyl silyl ethers from systems containing both alkyl and aryl silyl ethers using $CeCl_3 \cdot 7H_2O$ in acetonitrile. We report also that silyl-protected phenols can be selectively deprotected in the presence of silyl-protected alcohols using LiOH/DMF under operationally simple conditions and mild temperatures. Furthermore, the above methods successfully enable the selective deprotection of alkyl and aryl silyl ethers from tyrosine derived bis-silyl ether, which shows that this methodology is quite general and can be readily applied to the synthesis of complex molecules.



R=OTBS **9**
R=OH **11**



R=OTBS **10**
R=OH **12**

General experimental procedure:

Method I: $CeCl_3 \cdot 7H_2O$ (0.5 mmol) was added to a solution of bis-TBS ether (0.25 mmol) in acetonitrile (7.5 mL) and the reaction mixture was refluxed until completion of the reaction as indicated by thin-layer chromatography (TLC). Then the reaction mixture was cooled and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography over silica gel using ethyl acetate/hexane as eluent.

Method II: LiOH (0.75 mmol) was added to a stirred solution of bis-TBS ether (0.25 mmol) in DMF (0.3 mL) and the reaction mixture was then stirred at room temperature until completion, as indicated by TLC. The reaction mixture was then diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The phenol so obtained was purified by flash chromatography over a silica gel column using ethyl acetate/hexane as eluent.

Supplementary material

Spectral data for bis-TBS ether **6a**: IR (film): 2989, 2930, 1341, 1110, 843, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.37(d, 1H, $J=2.9$ Hz), 8.03 (dd, 1H, $J=8.8$, 2.9 Hz), 6.79 (d, 1H, $J=8.8$ Hz), 4.74 (s, 2H), 1.01 (s, 9H), 0.96 (s, 9H), 0.28 (s, 6H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.51, 141.99, 133.64, 123.51, 122.95, 117.32, 59.93, 25.82, 25.43, 18.32, 18.12. HRMS: Calcd for $C_{19}H_{36}NO_4Si_2$ $(M+H)^+$: 398.2183. Found: 398.2187.

Spectral data for alkanol **6b**: IR (film): 3282, 2929, 2858, 1512, 1255, 785 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, 1H, $J=2.9$ Hz), 8.07 (dd, 1H, $J=8.9$, 2.9 Hz), 6.83 (d, 1H, $J=8.9$ Hz), 4.73 (s, 2H), 2.09 (br s, 1H), 1.01 (s, 9H), 0.30 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.61, 141.71, 132.70, 124.37, 123.89, 117.74, 60.40, 25.47, 18.14. HRMS: calcd for $C_{13}H_{22}NO_4Si$ $(M+H)^+$: 284.4036. Found: 284.4039.

Spectral data for phenol **6c**: IR (film): 3302, 2929, 1523, 1339, 1279, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 8.10 (dd, 1H, $J=8.9$, 2.8 Hz), 7.91 (d, 1H, $J=2.8$ Hz), 6.92 (d, 1H, $J=8.9$ Hz), 4.97 (s, 2H), 0.94 (s, 9H), 0.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.39, 140.47, 125.16, 123.99, 122.72, 117.07, 65.28, 25.51, 17.97. HRMS: Calcd for $C_{13}H_{22}NO_4Si$ $(M+H)^+$: 284.4036. Found: 284.4031.

Spectral data for bis-TBS ether **8a**: $[\alpha]_D^{25} = -12.9$ (c 1.27, $CHCl_3$). IR (film): 2929, 2359, 1708, 1508, 1256, 837 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.31 (m, 5H), 7.05 (d, 2H, $J=8.1$ Hz), 6.76 (d, 2H, $J=8.1$ Hz), 5.09 (s, 2H), 4.95 (br d, 1H), 3.91–3.82 (m, 1H), 3.52 (d, 2H, $J=3.5$ Hz), 2.79 (d, 2H, $J=7.0$ Hz), 0.99 (s, 9H), 0.92 (s, 9H), 0.19 (s, 6H), 0.04 (s, 6H). ^{13}C NMR (100

MHz, $CDCl_3$): δ 155.74, 154.04, 136.54, 132.55, 130.62, 130.21, 128.41, 127.95, 119.89, 66.46, 62.67, 53.51, 36.36, 25.79, 25.58, 18.14. HRMS: calcd for $C_{29}H_{48}NO_4Si_2$ $(M+H)^+$: 530.3122. Found: 530.3119.

Spectral data for alkanol **8b**: $[\alpha]_D^{25} = -9.4$ (c 1.0, $CHCl_3$). IR (film): 3321, 2928, 2359, 1696, 1509, 1255, 839 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 7.04 (d, 2H, $J=8.0$ Hz), 6.76 (d, 2H, $J=8.0$ Hz), 5.07 (s, 2H), 4.96 (br d, 1H), 3.91–3.87 (m, 1H), 3.67 (dd, 1H, $J=4.1$, 8.2 Hz), 3.56 (dd, 1H, $J=4.1$, 8.2 Hz), 2.78 (d, 2H, $J=7.1$ Hz), 0.97 (s, 9H), 0.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.42, 154.28, 136.25, 130.08, 129.95, 128.45, 128.07, 127.99, 120.10, 66.74, 64.03, 54.12, 36.43, 25.58, 18.09. HRMS: calcd for $C_{23}H_{33}NO_4Si$ $(M)^+$: 415.2179. Found: 415.2199.

Spectral data for phenol **8c**: $[\alpha]_D^{25} = -15.6$ (c 0.33, $CHCl_3$). IR (film): 3322, 2926, 1693, 1514, 1253, 836 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (m, 5H), 7.06 (d, 2H, $J=8.1$ Hz), 6.73 (d, 2H, $J=8.1$ Hz), 5.08 (s, 2H), 5.01 (br d, 1H), 3.87–3.83 (m, 1H), 3.52 (d, 2H, $J=3.5$ Hz), 2.77 (d, 2H, $J=7.1$ Hz), 0.91 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.71, 154.12, 136.81, 130.41, 130.0, 128.43, 128.0, 115.18, 66.57, 62.74, 53.63, 36.36, 25.80, 18.17. HRMS: calcd for $C_{23}H_{34}NO_4Si$ $(M+H)^+$: 416.2257. Found: 416.2259.

Acknowledgements

This work was supported by the University of Illinois at Chicago (UIC), the UIC Campus Research Board and the National Cancer Institute, NIH (CA095177 to G.F.).

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