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Article

An Efficient and Chemoselective Deprotection of Aryl *tert*-Butyldimethylsilyl (TBDMS) Ethers by NaCN

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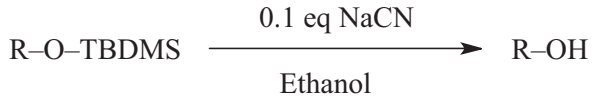
Phenolic *tert*-butyldimethylsilyl (TBDMS) ethers can be deprotected to yield phenols in excellent yield using sodium cyanide (NaCN) as catalyst in ethanol. The deprotectation of various phenolic TBDMS ethers were found to be very convenient, fast, high yielding and chemoselective.

Keywords: deprotectection, *tert*-butyldimethylsilyl, sodium cyanide

Introduction

As the hydroxyl group can devote in various organic transformations under mild reaction conditions, a crucial problem in organic synthesis is to ensure that the hydroxyl function group in a multifunctional molecule is protected from undesired reactions altogether or until such time as it's inherent reactivity is demanded. The chloro(1,1-dimethylethyl)dimethylsilane (TBDMS-Cl) is applied widely for the protection of hydroxyl group in organic synthesis due to their ease of installation, stability towards various reactions, such as reduction and Wittig and Grignard reaction and, finally, remove easily without affecting other organic functional groups.[1,2] Therefore, the efficiency of reaction, the selectivity of deprotection and the stability under the intend reaction conditions, all should be took into consideration in the desilylation reactions. Various methods of desilylation have had a great improvement in silylation chemistry in past years, especially using tetrabutylammonium fluoride (TBAF). However, due to its strong basicity, TBAF can lead to side reactions, which restrict the wide application of this reagent for this purpose.[3,4] Thus, momentous alternative methods, such as Lewis acid/based media protocols, like sulfuric acid (H_2SO_4), pytidinium *p*-toluenesulfonate (PPTS), trifluoroacetic acid (TFA), tosylic acid (TsOH), boron trifluoride etherate (BF_3–OEt_2), boron trichloride (BCl_3), scandium trifluoromethanesulfonate [$Sc(OTf)_3$], ceric triflate [$Ce(OTf)_4$], indium(III) chloride ($InCl_3$), sodium hydroxide/tetrabutylammonium hydrogensulfate ($NaOH/Bu_4NHSO_4$), tetrabutylammonium tribromide (TBATB), potassium carbonate (K_2CO_3), cesium carbonate (Cs_2CO_3),[5-17] halide-source protocols (in particular fluoride); oxidative protocols, like DDQ (2,3-dichloro-5,5-dicyanobenzoquinone),[18] potassium permanganate ($KMnO_4$),[19] barium manganate ($BaMnO_4$);[20] and reductive protocols, like diisobutylaluminium hydride (DIBALH), lithium aluminium hydride ($LiAlH_4$), sodium hydride (NaH),[21,22] have been developed for the deprotection of silyl ethers. However, most of these reagents have synthetic limitations, such as longer reaction time, harsh reaction conditions, use of expensive and corrosive reagents, non-selectivity of deprotection reactions as well as cumbersome work-up procedures. Herein we report a new method for the selective deprotection of phenol TBDMS ethers using NaCN as a catalyst in ethanol solvent in relative short reaction time, as shown in Scheme 1, which utilizes conventional laboratory reagents and equipments, only require a simple work-up and tolerate a wide variety of other functional groups.



Scheme 1. Deprotection of aryl *tert*-butyldimethylsilyl (TBDMS) ethers.

Experimental

The nuclear resonance magnetic (NMR) spectra were recorded on a Bruker Ascend 400 (Billerica, MA, USA) using tetramethylsilane (TMS) as an internal standard. Electrospray ionization mass spectrometry

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(ESI-MS) analyses was recorded in an Agilent 1100 Series MSD Trap SL (Santa Clara, CA, USA). The reactions were monitored by thin-layer chromatography (TLC; HG/T2354-92, GF254), and the products were purified by column chromatography on silica gel (200-300 mesh) made by Qingdao Puke Parting Materials Co., Ltd. (Qingdao, China).

Typical experimental procedure for preparation of *tert*-butyldimethylsilyl ethers

All the *tert*-butyldimethylsilyl ethers were prepared as previously reported in the respective literature.[23] Taking the 1-[[(1, 1-dimethylethyl)dimethylsilyl]oxy]-4-nitrobenzene for example, a 100 mL three-neck flask was equipped with a thermometer, condenser. Chloro(1,1-dimethylethyl) dimethylsilane (2.1 g, 14 mmol) and imidazole (0.476 g, 7 mmol) were added into a mixture of 4-nitrophenol (3 g, 14 mmol) in 20 mL of *N*,*N*-dimethylformamide (DMF). Then, the mixture was continually stirred at 50 °C and the reaction progress was monitored by TLC. After completion, the reaction mixture was concentrated *in vacuo* to obtain crude product, which was purified by silica column chromatography. Other *tert*-butyldimethylsilyl ethers were prepared in similar methods.

Typical experimental procedure for deprotection of *tert*-butyldimethylsilyl ethers

Also taking the 1-[[(1,1-dimethylethyl)dimethylsilyl] oxy]-4-nitrobenzene for example, a 100 mL three-neck flask was equipped with a thermometer, condenser. NaCN (0.04 g, 0.8 mmol) was added into a mixture of 1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-nitrobenzene (2 g, 8 mmol) in anhydrous ethanol (15 mL) and H_2O (1 mL). Then, the mixture was continually stirred at 30 °C and the reaction progress was monitored by TLC. After completion, the reaction mixture was concentrated *in vacuo*, and then the residue was dissolved in water, extracted with dichloromethane three times. The combined organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After, the desiccant was filtered off, the filtrate was evaporated to obtain crude product, which was purified by column chromatography on silica gel (86.4% yield).

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-nitrobenzene (**1**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 2H, *J* 9.2 Hz, Ar-H), 6.90 (d, 2H, *J* 9.2 Hz, Ar-H), 1.00 (t, 9H, *J* 2, CH_3), 0.26 (t, 6H, *J* 1.2 Hz, CH_3).[24]

1-Bromo-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzene (**2**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, 2H, *J* 9.2 Hz, Ar-H), 6.90 (d, 2H, *J* 9.2 Hz, Ar-H), 0.97 (t, 9H, *J* 2.8 Hz, CH_3), 0.18 (t, 6H, *J* 2.8 Hz, CH_3).[25]

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methylbenzene (**3**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, *J* 7.6 Hz, Ar-H), 7.05 (t, 1H, *J* 6.4 Hz, Ar-H), 6.85 (t, 1H, *J* 6.4 Hz, Ar-H), 6.75 (d, 1H, *J* 7.6 Hz, Ar-H), 2.21 (s, 3H, CH_3), 1.02 (t, 9H, *J* 2.8 Hz, CH_3), 0.21 (t, 6H, *J* 2.8 Hz, CH_3), ESI-MS *m/z*: 261.2 $[M + K]^+$.[26]

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-fluorobenzene (**4**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 1H, Ar-H), 7.85-7.83 (m, 1H, Ar-H), 7.53-7.50 (m, 1H, Ar-H), 6.99-6.90 (m, 1H, Ar-H), 1.00 (t, 9H, *J* 2.8 Hz, CH_3), 0.19 (t, 6H, *J* 2.4 Hz, CH_3).

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-methylbenzene (**5**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, *J* 8 Hz, Ar-H), 7.07-7.03 (m, 1H, Ar-H), 6.87-6.83 (m, 1H, Ar-H), 6.76 (d, 1H, *J* 8.0 Hz, Ar-H), 2.21 (s, 3H, CH_3), 1.02 (t, 9H, *J* 2.8 Hz, CH_3), 0.21 (t, 6H, *J* 2.8 Hz, CH_3), ESI-MS *m/z*: 261.2 $[M + K]^+$.

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-4-trifluoromethoxybenzene (**6**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 2H, *J* 8.4 Hz, Ar-H), 6.90 (d, 2H, *J* 9.2 Hz, Ar-H), 0.98 (t, 9H, *J* 2.8 Hz, CH_3), 0.20 (t, 6H, *J* 2.8 Hz, CH_3).

1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-(trifluoromethyl) benzene (**7**)

^{1}H NMR (400 MHz, $CDCl_3$,) δ 7.55 (dd, 1H, *J* 1.2, 8 Hz, Ar-H), 7.40-7.35 (m, 1H, Ar-H), 6.97 (t, 1H, *J* 7.6 Hz, Ar-H), 6.91 (d, 1H, *J* 8 Hz, Ar-H), 1.01 (t, 9H, *J* 2.8 Hz, CH_3), 0.27 (t, 6H, *J* 2.8, CH_3).

1-Bromo-2-chlorophenoxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]benzene (**8**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 1H, *J* 2.4 Hz, Ar-H), 7.13 (q, 1H, *J* 2.8, 8.8 Hz, Ar-H), 6.79 (d, 1H, *J* 8.8 Hz, Ar-H), 1.03 (t, 9H, *J* 2.8 Hz, CH_3), 0.24 (t, 6H, *J* 2.8 Hz, CH_3).

N-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl] acetamide (**9**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 2H, *J* 8.8 Hz,

Ar-H), 6.79 (d, 2H, *J* 8.8 Hz, Ar-H), 7.04 (s, 1H, CH_3), 0.97 (t, 9H, *J* 2.8 Hz, CH_3), 0.18 (t, 6H, *J* 2.8 Hz, CH_3), ESI-MS *m/z* calc. for $C_{14}H_{23}NO_2Si$ $[M + H]^+$: 266.2.[27]

4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]benzenamine (**10**)

^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (dq, 2H, *J* 8.4, 3.2 Hz, Ar-H), 6.57 (dq, 2H, *J* 8.8, 3.2 Hz, Ar-H), 3.37 (s, 2H, NH_2), 0.97 (s, 9H, CH_3), 0.15 (s, 6H, CH_3), ESI-MS *m/z*: 224.2 $[M + H]^+$.[28]

4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-benzoatephenol (**11**)

^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 2H, *J* 7.2 Hz, Ar-H), 7.63 (q, 1H, *J* 7.2 Hz, Ar-H), 7.51 (q, 2H, *J* 7.2 Hz, Ar-H), 7.08 (d, 2H, *J* 8.8 Hz, Ar-H), 6.88 (d, 2H, *J* 8.0 Hz, Ar-H),1.00 (s, 9H, CH_3), 0.21 (s, 6H, CH_3).

4-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-1,2-dimethoxybenzene (**12**)

^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, 1H, *J* 2.4 Hz, Ar-H), 7.13 (dd, 1H, *J* 2.4, 8.8 Hz, Ar-H), 6.79 (d, 1H, *J* 8.8 Hz, Ar-H), 4.68 (s, 2H, CH_2), 1.03 (t, 9H, *J* 2.8 Hz, CH_3), 0.24 (t, 6H, *J* 2.8 Hz, CH_3), ESI-MS *m/z*: 304.9 $[M + Na]^+$.

2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]thiophene (**13**)

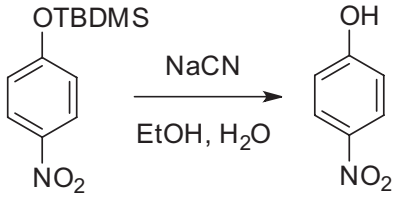
^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, 1H, *J* 1.2, 5.2 Hz, Ar-H), 6.91 (dd, 1H, *J* 3.6, 5.2 Hz, Ar-H), 6.82 (dd, 1H, *J* 0.8, 3.2 Hz, Ar-H), 3.82 (t, 2H, *J* 6.4 Hz, CH_2), 3.02 (t, 2H, *J* 6.8 Hz, CH_2), 0.97 (t, 9H, *J* 2.4 Hz, CH_3), 0.025 (t, 6H, *J* 2.8 Hz, CH_3).

Results and Discussion

Optimization of reaction conditions

In our former work, we optimized molar ratios of the reagents by using the reaction of 1-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-4-nitrobenzene (**1**) as a model reaction (Table 1). A mixture of **1** (20 mmol), NaCN (2 mmol) in anhydrous ethanol (15 mL) with H_2O (1 mL) was stirred at 30 °C for 2.7 h to give the desired product **1a** in 86.4% yield (Table 1, entry 1). Although double or triple amount of NaCN was used under the same reaction conditions, the yield of **1a** did not increase significantly (Table 1, entries 2 and 3). Besides, the yield of **1a** decreased obviously to 40.1% ~ 65.3% along with one fifth or one tenth amount of NaCN (Table 1, entries 4 and 5). In consideration of reaction efficiency and safety, a model using 0.1 eq of NaCN was chosen for the desilylation reaction.

Table 1. Deprotection of **1** using sodium cyanide (NaCN)



1 **1a**

entry	1:NaCN	time / h	Yield / %
1	0.10	2.7	86.4
2	0.20	2.4	87.8
3	0.30	2.2	88.1
4	0.01	7.5	40.1
5	0.05	4.8	65.3

Based on these results, the molar ratios of NaCN in 0.1 eq for deprotection reaction was established to optimize other reaction conditions. In an effort to obtain improved yields, various solvents were screened (Table 2). Non-polar solvent, such as toluene; and polar aprotic solvents, such as DMF, acetone and tetrahydrofuran (THF), did not present the formation of product (Table 2, entries 2-5) and the reaction in anhydrous ethanol provided poor yields of deprotection of TBDMS (Table 2, entry 6). Mixed solvents with different anhydrous ethanol and water ratios were investigated. The yield could be improved when added little amount of H_2O, but the amount of H_2O did not have significant effect on yield (Table 2, entries 1 and 6-9). Moreover, the reaction took longer time when less water was used and workup was more difficult if more water was used due to the solubility of some phenols in water. Herein, anhydrous ethanol with 1 mL H_2O was chosen as a good solvent for the deprotection reaction.

Table 2. Optimization of reaction solvent

entry	Solvent	time / h	Yield / %
1	EtOH + 1 mL H_2O	1.0	86.4
2	THF	–	–
3	DMF	–	–
4	acetone	–	–
5	toluene	–	–
6	EtOH	8.0	56.7
7	EtOH + 0.5 mL H_2O	4.0	73.5
8	EtOH + 2 mL H_2O	0.8	86.9
9	EtOH + 5 mL H_2O	0.8	87.1

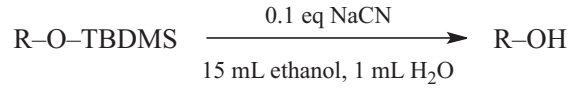
EtOH: ethanol; THF: tetrahydrofuran; DMF: *N*,*N*-dimethylformamide.

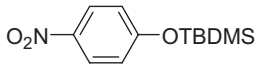
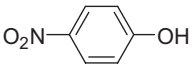
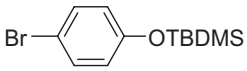
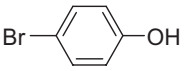
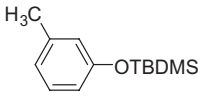
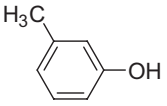
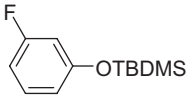
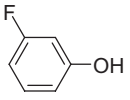
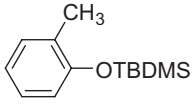
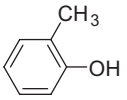
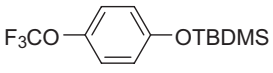
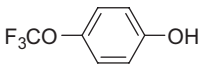
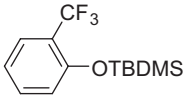
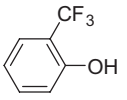
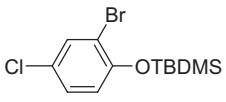
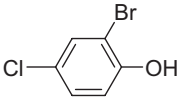
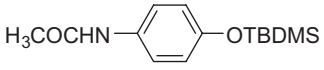
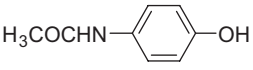
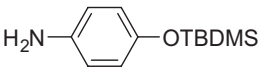
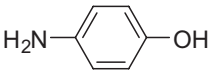
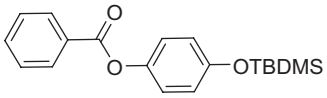
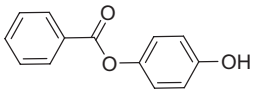
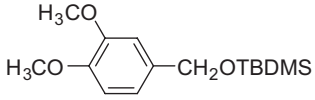
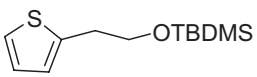
Procedure of deprotection

We examined a variety of substrates, including electron-withdrawing groups and electron-donating groups containing compounds. As shown in Table 3, most phenol TBDMS ethers could be removed quickly (Table 3, entries 1-9).

Besides, we also found that the rate of cleavage of phenolic TBDMS ethers was accelerated if the molecule includes electron-withdrawing groups (Table 3,

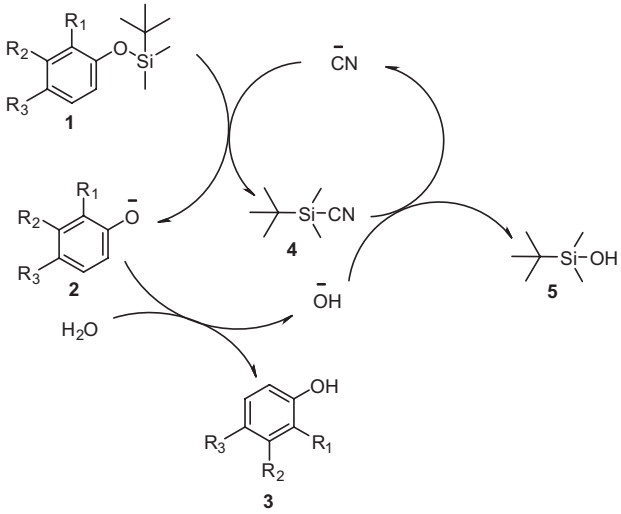
Table 3. Deprotection of substituted phenol tert-butyldimethylsilyl (TBDMS) ethers using 0.1 eq solid sodium cyanide (NaCN)



entry	Silyl ether	time / h	Temperature / °C	Product	Yield / %
1		1	30		86.4
2		1.5	80		85.2
3		17	80		83.7
4		7	80		84.0
5		15	80		84.5
6		12	50		92.3
7		4	50		95.2
8		7	80		82.5
9		4.5	80		83.3
10		38	80		27.3
11		12	50		81.9
12		41	80	–	no reaction
13		47	80	–	no reaction

entries 1 and 7). In addition, the sequence of increasing rate is consistent with the strength of electron-withdrawing groups (Table 3, entries 1, 2, 6 and 8-10). At the same time, it could be observed that the steric effects have influence on the rate of deprotection reaction (Table 3, entries 3 and 5). The rate of deprotection of 1-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-2-methylbenzene was faster than that of 1-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methylbenzene. Moreover, the alkyl silyl ethers of alcohols or benzyl alcohols cannot be deprotected by NaCN (Table 3, entries 12 and 13).

As for reaction mechanism, we supposed these results to be most conveniently explained by a reaction sequence (Scheme 2). Probably, silylation of the ether **1** transforms into its anion **2** via the nucleophilic substitution reaction of base (CN^-), generating silane carbonitrile **4** at the same time. Then, through the nucleophilic substitution reaction with hydroxide, silane carbonitrile **4**, which is inherently unstable to both nucleophiles and aqueous media transforms into silanol **5** giving CN^-, which continue the next circulation reaction. Meanwhile, phenolate anion **2** rapidly intercepts hydrogen ion into phenol. However, the alcohols do not present the formation of product using NaCN as the alkalinity of sodium alcoholate is stronger than NaCN.



Scheme 2. Possible mechanism of deprotection reaction.

Conclusions

In summary, we have developed a mild, efficient, inexpensive and selective procedure for the deprotection of aryl silyl ethers in the presence of alkyl silyl ethers using 0.1 eq of NaCN in ethanol. Moreover, this catalytic system was compared with the other organic catalyst, and results showed that NaCN catalyst having high performance ability in short reaction time in phenolic desilylation reaction.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

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