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COMMUNICATION

A Facile Chemoselective Deprotection of Aryl Silyl Ethers using Sodium Hydride/DMF and *in situ* Protection of Phenol with Various Groups

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An efficient method for the selective removal of aryl silyl protection using NaH in DMF solvent is developed. The method is rapid, operationally simple and can be carried out at room temperature. Excellent chemoselectivity and high yields of phenol products are other advantages of this method. A one-pot desilylation and reprotection as aryl alkyl ethers and esters has also been demonstrated.

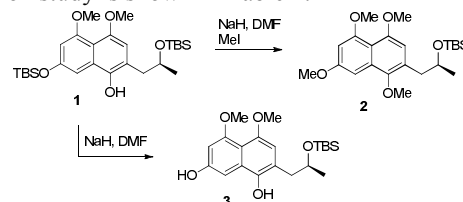
Introduction

The development of new synthetic methodologies and further refinement through modifications is an unending quest in organic synthesis and method development. A developed method is validated for its synthetic potential, general applicability and usefulness. In the target oriented synthesis of complex molecules especially multi-steps total synthesis, the use of protecting groups becomes inevitable.¹ When multiple protecting groups (PGs) are involved, the selective deprotection is most important and often becomes unpredictable even in the most reliable cases due to substrate specificity.¹ It is more difficult when two same groups are involved at different loci. A subtle difference in the surrounding of the PG or electronic factors can be exploited for a chemoselective deprotection. Of the several known protecting groups, the silyl ether protection for hydroxyl group is very common.¹ This is mainly due to simpler reaction conditions available in protection and deprotection and also that the silyl ether group is stable under basic and mild acidic conditions.^{1,2} Tetrabutylammonium fluoride (TBAF) is a very common reagent for the deprotection of silyl ethers. In literature a number of methods are reported for the cleavage of aryl silyl ethers such as fluoride source (TBAF,^{2,3a} KF/18-C-6,^{3b} KF/Al₂O₃^{3c,d} and KF/tetraethylene

glycol^{3e}), acids (HF^{4a,b} and CSA^{4c}), strong bases (alkali hydroxides^{5a-d} and carbonates^{5e-g}), organic bases (TMG^{6a,b} and tetraethyl amine N-oxide^{6c}), LiOAc⁷ and phosphate.⁸ The catalytic use of LiOAc for selective aryl silyl deprotection is noteworthy. They proposed Lewis acid–Lewis base bifunctional catalyst model to rationalize the efficiency and selectivity.⁷ The electronic nature of alkyl and aryl groups revealed that the aryl silyl ethers are more liable to base hydrolysis than alkyl silyl ethers. Although this approach works well for deprotection of silyl ether with above reagents, there are some limitations to use them in multi-steps synthesis such as long reaction time, harsh reaction conditions and low selectivity. Herein we report a simple, efficient and highly chemoselective method for the deprotection of different aryl silyl ethers by using sodium hydride in DMF in a very short reaction time (few minutes) and with excellent yields. In addition, the *in situ* protection of resulting phenolate with other protecting groups like allyl, methyl, isopropyl, MOM, benzyl and acyl is also developed.

Results and discussion

In our recent total synthesis of astropaquinones B and C, the compound **1** on treatment with NaH/MeI delivered compound **2** (Scheme 1).⁹ The aryl silyl ether was cleaved and subsequently both phenolic hydroxyl groups were methylated, while the aliphatic silyl ether was intact. In another reaction, the addition of NaH to compound **1** in DMF gave compound **3** through chemoselective deprotection of aryl silyl ether. We planned to optimize this reaction as literature search revealed that NaH has not been used for selective deprotection of aryl silyl ether. The optimization study is shown in Table 1.



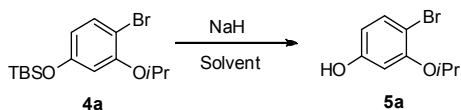
Scheme 1 Chemoselective deprotection of aryl silyl ether.

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† Electronic Supplementary Information (ESI) available: [Copies of ¹H and ¹³C NMR spectra for all the compounds]. See DOI: 10.1039/b000000x/

We studied the solvent dependence and equivalents of NaH along with temperature effects in the selective desilylation reaction. The desilylation of model compound **4a** with NaH (2.0 equiv) in DMF occurred within 5 minutes at room temperature giving **5a** in quantitative yield (Table 1, entry 1). The same reaction at 0 °C required 8 min for completion giving **5a** in 95% yield (Table 1, entry 2). Lowering of NaH concentration to 1.5 equiv. and at room temperature the reaction was equally rapid giving **5a** in 99% yield in 9 min (Table 1, entry 3). Further lowering of NaH to 1 equiv., the reaction was comparably slow and produced **5a** in 95% yield after 40 min (entry 4). The desilylation of **4a** in dry THF at room temperature gave **5a** in excellent yield (90%), but the reaction took 6 h to complete (entry 5). The same reaction in other aprotic solvents like benzene (room temperature and 60 °C), toluene and diethyl ether failed to desilylate **4a** (entries 6-9) and resulted in recovery of unreacted **4a** showing a solvent dependence. In case of reaction in 1,4-dioxane solvent at room temperature and at 60 °C, it gave **5a** in 74% and 80% yields respectively (entries 10 and 11). The reaction in DMSO solvent was also rapid (8 min, entry 12) but provided **5a** in lower yield (85%). With the optimized conditions which include the use of NaH (1.5 equiv) in DMF at room temperature we evaluated the scope and limitations of this method (we chose a lower concentration of NaH, i.e. 1.5 v/s 2.0 equivalents as the reaction time was comparable, 9 v/s 5 min, entry 3 v/s entry 1).

Table 1 Optimization of desilylation of silyl ether **4a** using NaH.



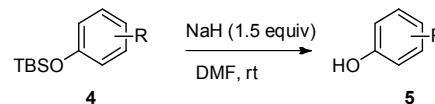
Entry	Solvent	NaH (equiv)	Temp (°C)	Time	Yield (%) ^a
1	DMF	2	rt	5 min	100
2	DMF	2	0 °C	8 min	95
3	DMF	1.5	rt	9 min	99
4	DMF	1	rt	40 min	95
5	THF	2	rt	6 h	90
6	Benzene	2	rt	6 h	-
7	Benzene	2	60 °C	12 h	-
8	Toluene	2	60 °C	12h	-
9	Et ₂ O	2	rt	12h	-
10	1,4-dioxane	2	rt	20 h	74
11	1,4-dioxane	2	60 °C	6h	80
12	DMSO	2	rt	8 min	85

^a Isolated yields

Various aryl silyl ethers were subjected to desilylation using NaH (1.5 equiv) in DMF solvent at room temperature. The results are shown in Table 2. Thus, compounds **4a-c** with 4-bromo-3-alkoxy group (*i*-Pr, Me and Bn) gave the corresponding phenols **5a-c** in excellent yields in just 9 to 12 minutes of reaction time (Table 2, entries 1-3). Similarly compounds with electron rich aryl ring **4d-g** produced the corresponding phenols **5d-g** in good to excellent yields (entries 4-7). Compounds with electron withdrawing groups (CHO, NO₂ or OAc), **4h-l** also reacted effectively producing the phenols **5h-l** in good to quantitative yields (entries 8-12). Other functional groups like MOM (**4m**) or ester (**4n** and **4o**) were also tolerated (entries 13-15). Bis-silylated compound **4p** with

NaH (3 equiv) gave resorcinol **5p** in a 10 minute reaction in quantitative yield (entry 16).

Table 2 Desilylation of aryl silyl ethers with NaH/DMF.

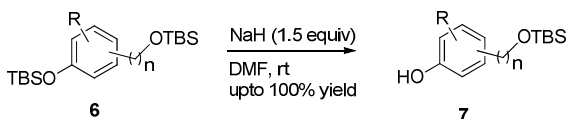
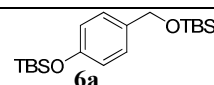
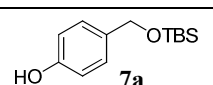
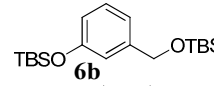
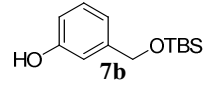
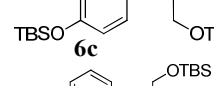
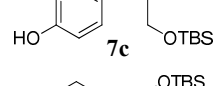
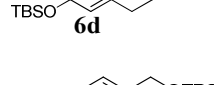
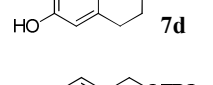
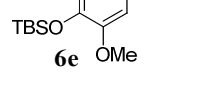
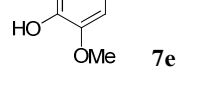
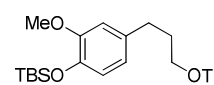
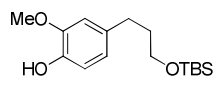
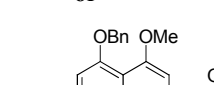
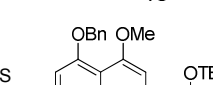
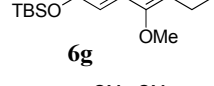
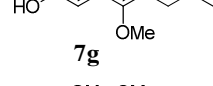
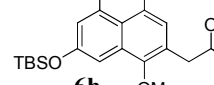
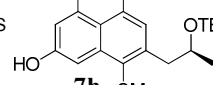


Entry	Substrate	Product	Time (min)	Yield (%) ^a
1	4a , R' = <i>i</i> -Pr	5a	9	100
2	4b , R' = Me	5b	10	93
3	4c , R' = Bn	5c	12	92
4	4d	5d	12	91
5	4e	5e	9	83
6	4f	5f	9	88
7	4g	5g	9	85
8	4h	5h	9	97
9	4i	5i	8	93
10	4j	5j	9	91
11	4k	5k	3	100
12	4l	5l	3	75
13	4m	5m	3	100
14	4n	5n	3	97
15	4o	5o	2	98
16 ^b	4p	5p	10	100

^a Isolated yields. ^b NaH (3.0 equiv) was used.

The desilylation method was further explored for chemoselective deprotection of aryl silyl ethers against the alkyl silyl ethers. There are limited literature methods available for chemoselective deprotection, for example using $\text{K}_2\text{CO}_3/\text{EtOH}$,^{5e} LiOH/DMF ,^{5a} $\text{Cs}_2\text{CO}_3/\text{DMF}/\text{H}_2\text{O}$ ^{5f} or using acid/base conditions.¹⁰ We observed the present method showed excellent chemoselectivity and gave high yields towards mono desilylation of aryl silyl groups producing exclusive phenol products as shown in Table 3. The method was quite rapid and the reactions were completed in a few minutes. Thus various bis-silylated compounds **6a-f** underwent a rapid desilylation of aryl silyl group producing the corresponding phenols **7a-f**

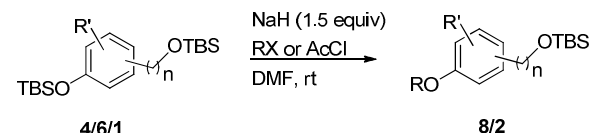
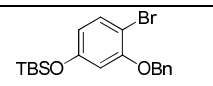
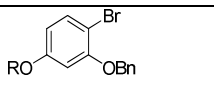

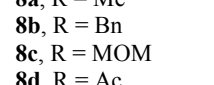
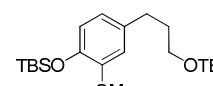
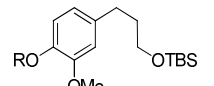

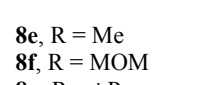

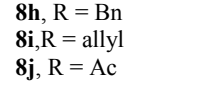
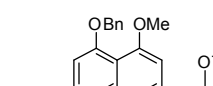
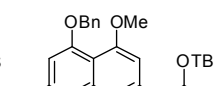
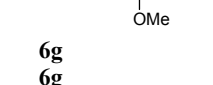
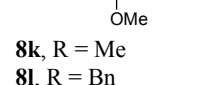
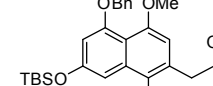
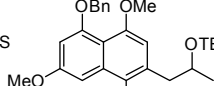
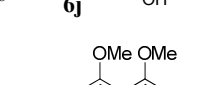
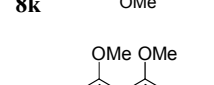
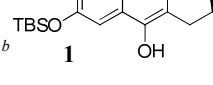
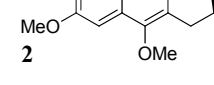
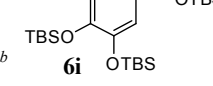
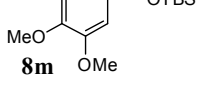
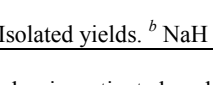
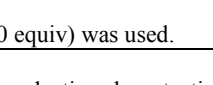
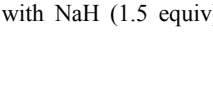
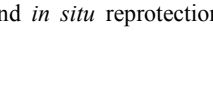


Table 3 Chemoselective desilylation of aryl silyl ethers in presence of alkyl silyl ethers.

				
Entry	Substrate	Product	Time (min)	Yield (%) ^a
1			8	95
2			9	92
3			10	97
4			9	100
5			9	91
6			9	100
7			10	92
8			15	85
9 ^b			60	93

^a Isolated yields. ^b NaH (3.0 equiv) was used.

(Table 3, entries 1-6) in high yields and exclusive chemoselectivity. The naphthalene compounds **6g** and **6h** also reacted well giving **7g** and **7h** respectively in good yields. The compound **6i** with two aryl OTBS group was desilylated in 60 min to give **7i** in 93% yield. The bis-desilylation was slow in the latter case probably that the first formed phenolate retards the second desilylation.

Table 4 One-pot chemoselective deprotection/etherification or acylation with NaH.

				
Entry	Substrate	Product	Time (min)	Yield (%) ^a
1			30	91
2			35	72
3			35	80
4			30	83
5			40	81
6			15	89
7			35	85
8			15	94
9			15	94
10			30	92
11			20	90
12			40	70
13 ^b			30	68
14 ^b			30	70
15 ^b			35	82

^a Isolated yields. ^b NaH (3.0 equiv) was used.

We also investigated a chemoselective deprotection of aryl silyl ethers with NaH (1.5 equiv) and *in situ* reprotection with various

groups giving aryl ethers and esters. Remarkably the one-pot desilylation and etherification or esterification proceeds in a short reaction time with good yields (Table 4). When we subjected the aryl OTBS compound **4c** for one-pot TBS deprotection with NaH in DMF and then etherification with different groups (*viz.* Me, Bn, MOM) and acylation, it delivered the corresponding ethers **8a-c** and ester **8d** in 30 to 35 min in good yields (Table 4, entries 1-4). The chemoselective removal of only aryl silyl ether in **6f** followed by one-pot etherification or esterification of phenol afforded the corresponding ethers **8e-i** and ester **8j** in excellent yields (entries 5-10). Similarly, the naphthalene compound **6g** delivered the ethers **8k** and **8l** in good yields (entries 11 and 12). Compounds **6j** and **1** on one pot methylation produced **8k** and **2** in 68 and 70% yields respectively (entries 13 and 14). The bis-OTBS aryl compound **6i** reacted efficiently in 35 min to give **8m** in 82% yield (entry 15). The reaction time here was shorter than only desilylation (Table 3, entry 9, 60 min). Here the first formed phenolate probably gets immediately methylated. This favours the second desilylation and methylation.

The scope of this method was explored for other silyl groups like TES and TBDPS. In literature there are very few reports for selective deprotection of aryl TES and TBDPS ethers.^{1c} When we subjected the bis-TES ether compound **9a** for chemoselective deprotection of aryl TES it produced the corresponding phenol **10a** in excellent yield of 96% in just 8 minutes of reaction time (Table 5, entry 1). The one-pot deprotection of aryl TES ether and subsequent allyl ether protection also worked well on **9a** giving **10b** in 91% yield (entry 2). Similarly the aryl TBDPS ether in **9b** was also selectively cleaved in 45 min giving **10c** in 88% yield (entry 3). The one-pot desilylation/methylation of **9b** delivered **10d** in 85% yield (entry 4).

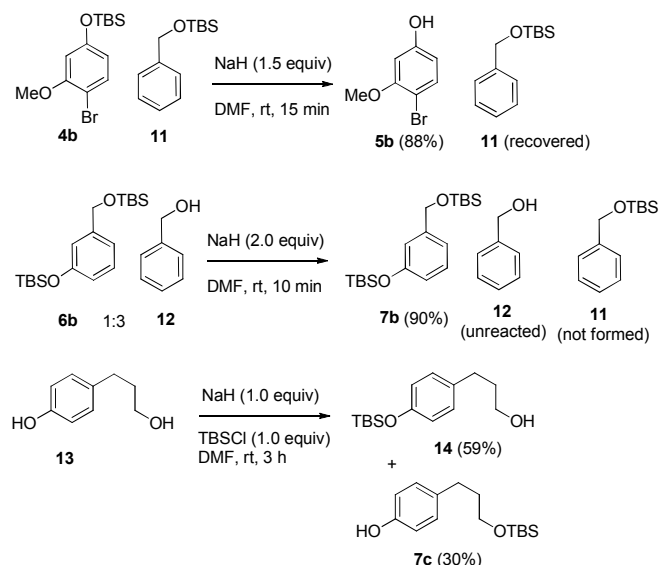
Table 5 Chemoselective deprotection/etherification of TES and TBDPS ethers with NaH.

9 R = TES, TBDPS **10** R' = H, Me, Allyl
R = TES, TBDPS

Entry	Substrate	Product	Time (min)	Yield (%) ^a
1			8	96
2	9a		10	91
3			45	88
4	9b		60	85

^a Isolated yields

An intermolecular selectivity experiment with equimolar mixture of **4b** and **11** treated with NaH (1.5 equiv) in DMF, gave **5b** (88%) and with complete recovery of **11** (Scheme 2). A cross-over experiment to check silyl migration¹¹ with **6b** and **12** mixture (1:3) treated with NaH (2.0 equiv) in DMF produced only **7b** (90%) and compound **12** was recovered unreacted, while formation of **11** was not detected. A selective protection experiment with compound **13** treated with NaH (1.0 equiv) and TBSCl (1.0 equiv) produced **14** (59%) and **7c** (30%) in 2:1 ratio showing moderate selectivity for protection of phenolic OH group. Thus the method was chemoselective for deprotection of only aryl silyl ether. The probable reason could be attributed to the activated aryl silyl ether and the stabilized phenolate formation.



Scheme 2 Intermolecular selectivity experiments and selective protection of phenol.

Conclusion

In conclusion, we have developed an efficient method for the selective removal of aryl silyl protection using NaH in DMF solvent. The method is rapid, operationally simple and can be carried out at room temperature. High yields of phenol products and excellent chemoselectivity are other advantages of this method. A one-pot desilylation and re-protection also worked well.

Experimental

General Procedure: Aryl silyl ether deprotection: To a stirred solution of aryl silyl ether (0.1 mmol, 1.0 equiv) in dry DMF (3 mL) was added sodium hydride (0.15 mmol, 1.5 equiv) at room temperature and stirred for specified time. After completion of reaction (monitored by TLC) it was quenched with water (1 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with water (3 × 5 mL), dried (Na₂SO₄) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc as eluent to give the phenol.

General procedure for one pot chemoselective aryl silyl deprotection/reprotection with other protecting groups: To a stirred solution of aryl silyl ether (0.1 mmol, 1.0 equiv) in dry DMF (3 mL) was added sodium hydride (0.15 mmol, 1.5 equiv) at room temperature and subsequently the alkyl halide or acetyl chloride (0.1 mmol, 1.0 equiv) was added. After completion of reaction (monitored by TLC) it was quenched with water (1 mL) and diluted with EtOAc (10 mL). The organic layer was separated, washed with water (3×5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc as eluent to give differently protected product.

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GRAPHICAL ABSTRACT

A Facile Chemoselective Deprotection of Aryl Silyl Ethers using Sodium Hydride/DMF and *in situ* Protection of Phenol with Various Groups

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Abstract : A facile method for chemoselective aryl silyl ethers deprotection with NaH/DMF is developed and a one-pot desilylation/reprotection as different aryl silyl ethers/esters has also been realized.

