DBU-Promoted Facile, Chemoselective Cleavage of Acetylenic TMS Group

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Abstract: Acetylenic trimethylsilyl (TMS) groups were efficiently removed using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). With either 1.0 or even 0.1 equivalents of DBU, smooth desilylation of various terminal acetylenic TMS groups was accomplished selectively in the presence of alkyl silyl ethers and other base-labile groups. Furthermore, more sterically hindered terminal acetylenic silyl groups such as TBDMS and TIPS remained intact under these conditions.

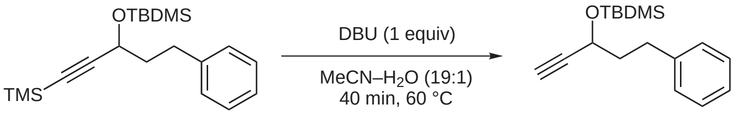
Key words: DBU, silylacetylene, chemoselective, deprotection

Trialkylsilyl functionality has a prominent role in the organic synthesis as a protecting group of alcohols, amines and alkynes.[1] Therefore selective methods for the deprotection of the silyl groups have been investigated extensively for a long time, however, most of them have focused primarily upon alkyl silyl ethers.[2,3] Acetylenic trialkylsilyl groups have been underestimated in spite of the importance of alkynes as building blocks of natural products and polymers,[4] thus there are only a few reports on the selective manipulation of alkynylsilanes.[2b,5] Fluoride ion, a standard deprotecting reagent, hardly provides a reasonable chemoselectivity among different silyl groups.[2b] Selective cleavage of acetylenic silyl groups mainly depends upon hydroxide-based cleavage conditions, and other labile functional groups such as esters seldom survive during the deprotection. Recently, Pale and co-workers reported on the chemoselective removal of acetylenic TMS using silver salts, but this method still suffers from the low selectivity between different silyl groups after long exposure to deprotecting conditions.[6] During our ongoing research program on development of useful synthetic methodologies based upon the unique property of DBU,[3a,7] we encountered remarkably selective removal of acetylenic TMS in the presence of aliphatic TBDMS ethers (Equation 1). Furthermore, even 0.1 equivalents of DBU proved to be sufficient to drive the deprotection to completion, leaving other silyl groups and hydroxide-sensitive groups untouched.

During initial optimization, we noticed that the presence of a protic additive is essential for successful transformation. In solely aprotic medium such as anhydrous acetonitrile, the reaction proceeded negligibly. When a small amount of a protic additive such as water was introduced, the reaction accelerated dramatically, going to completion within 40 minutes (Equation 1).[8]

To evaluate the reactivity of DBU on the cleavage of acetylenic TMS in comparison with other tertiary amine bases, a range of tertiary amine bases were screened (Table 1). Desilylation was carried out using **1** as a representative trimethylsilylated acetylene derivative in aqueous acetonitrile at 60 °C for 40 minutes, and the reaction was monitored through GC analysis. When 1 equivalent of an amine base such as 4-(*N*,*N*-dimethylamino)pyridine (DMAP), diazabicyclo[3,2,0]octane (DABCO), and proton sponge (PS) was applied to desilylation (entries 3–5), trace of or no conversion was detected. Only *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) provided a considerably good conversion (85%, entry 6). However, desilylation using DBU proceeded exceptionally well, exhibiting complete conversion of the starting material (entry 1). Moreover, even a catalytic amount (0.1 equiv) of DBU was effective in cleaving the TMS group, though prolonged reaction time was required (entry 2). Consequently, it became clear that DBU has a surpassing ability to mediate desilylation of silylated acetylene derivatives unlike other tertiary amine bases.

With the optimized conditions using DBU established, we studied the scope of the chemoselective removal of various acetylenic TMS groups (Table 2). Throughout this examination, it is clear that this protocol is perfectly compatible with bulkier alkyl silyl ethers (entries 1, 3, 8, and 9) and base-sensitive groups such as acetate (entry 4), benzoate (entries 5 and 7), and methyl ester (entry 11). In



1 → **2**, 97%

Equation 1

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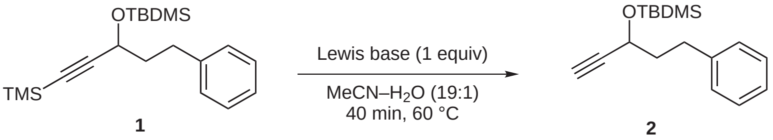
Table 1 Comparative Desilylation of **1** Using Various Tertiary Amine Bases[a]



Entry	Base	Conversion (%)[a]
1	DBU	100
2[b]	DBU	100
3	DMAP	trace
4	DABCO	0
5	PS[c]	0
6	TMG	85

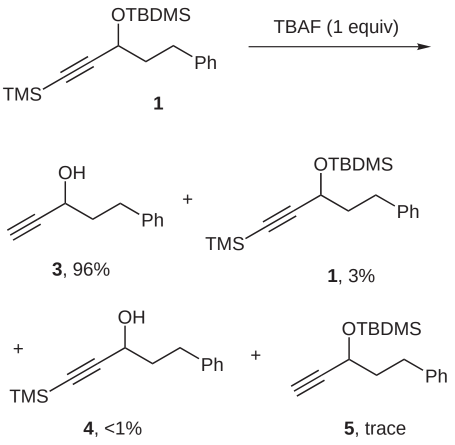
[a] Determined by GC analysis.[9]

[b] Reaction was carried out with 0.1 equiv of DBU at 60 °C for 6.5 h.

[c] Proton sponge [1,8-bis(dimethylamino)naphthalene].

addition, bulkier silyl acetylene derivatives such as those containing TBDMS (entry 12) and TIPS (entry 13) were unaffected under these conditions. However, compounds containing a straight aliphatic chain and bulky silyl ether did not proceed well in 1 hour (entries 7–9). In these cases, more DBU and longer reaction time were needed to complete the TMS removal. Catalytic reactions were attempted to several substrates employing 0.1 equivalents of DBU, and desilylation also underwent successfully when the reactions were run for prolonged periods of time (entries 1, 2, 5, and 11).

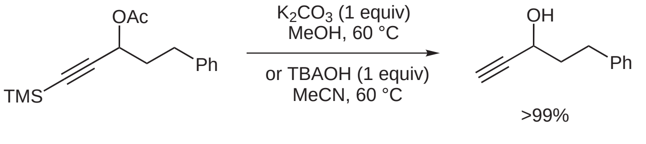
In contrast to the DBU-promoted selective removal of the TMS group from the acetylene unit of compound **1** in the presence of alkyl *tert*-butyldimethylsily ether, nonselective removal of both silyl groups was noted as a major course of the reaction when just 1 equivalent of TBAF was employed in a comparison experiment (Equation 2). A small amount (3%) of the starting material and a minute amount of monodeprotected compound **4** were observed along with compound **3**. However, almost no trace of the monodesilylated compound **5** was obtained from this reaction.



Equation 2

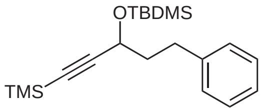
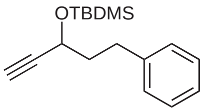
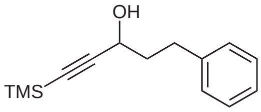
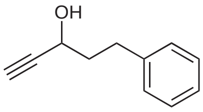
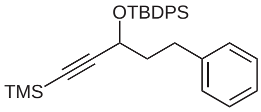
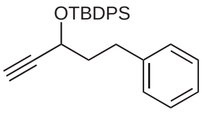
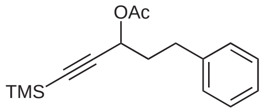
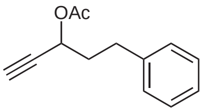
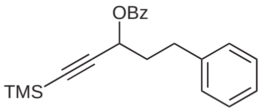
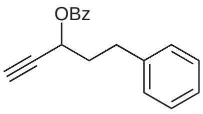
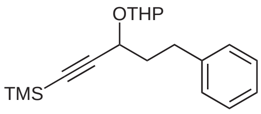
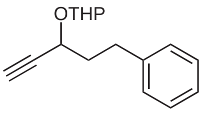
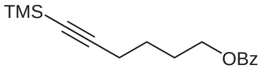
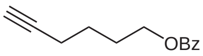
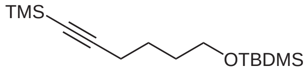
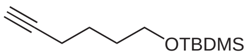
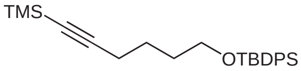
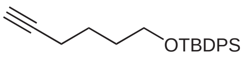
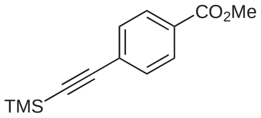
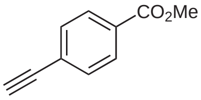
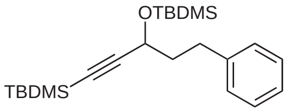
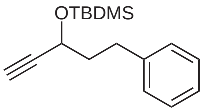
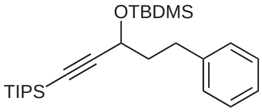
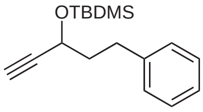
As yet another comparison, a substrate possessing an acetylenic TMS group and an acetate was exposed to desilylation conditions using a frequently employed desilylating reagent, K_2CO_3 in methanol (Equation 3). In this case, both the TMS and the acetyl groups were removed yielding propargylic alcohol derivative exclusively. Furthermore, 1 equivalent of tetra(*n*-butyl)ammonium hydroxide (TBAOH) also afforded the same product. These two cases clearly demonstrate the advantage of the DBU-mediated desilylation compared to the classical methods employing alkoxide or hydroxide reagent, which provided no selectivity.

In conclusion, we disclosed that DBU is a highly efficient promoter for the chemoselective cleavage of acetylenic TMS in the presence of bulkier alkyl silyl ethers. The reaction is compatible with base-sensitive groups such as acetate, methyl ester, and benzyl ester. This novel method is operationally very straightforward and convenient; solvent evaporation and simple filtration of the reaction mixture through a silica gel pad are sufficient to obtain the desired product in pure form. Research on the further utilization of the unique properties of DBU is in progress in our laboratory, and the results will be reported in due course.



Equation 3

Table 2 Deprotection of Acetylenic TMS Using 1 Equivalent of DBU in 5% (v/v) Aqueous Acetonitrile at 60 °C

Entry	TMS alkyne	Alkyne	Time[b]	Yield (%)[a,b]
1			40 min (6.5 h)	99 (99)
2			40 min (6.5 h)	99 (97)
3			1 h	95
4			1 h	97
5			1 h (6.5 h)	97 (95)
6			1 h	96
7[c]			5 h	98
8[c]			6 h	93
9[c]			6 h	94
11			1 h (6.5 h)	93 (94)
12			40 min	0
13			40 min	0

[a] Yield of isolated alkyne.
[b] Values in parentheses are the time and yield of desilylation performed with 0.1 equiv of DBU at 60 °C.
[c] These substrates required 1.5 equiv of DBU for a complete conversion.

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References and Notes

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(8) **A Representative Procedure the Desilylation of Acetylenic TMS**
To a magnetically stirred solution of **1** (195 mg, 0.563 mmol) in MeCN (1.1 mL) and H_2O (56 μL) were added DBU (84 μL, 0.563 mmol) at r.t. The mixture was heated to 60 °C, and the stirring was continued for 40 min. After completion of the reaction, the resulting residue was concentrated under reduced pressure and purified by passing through a short silica gel column (ca. 5 cm) to afford pure alkyne (155 mg, 99% yield).

(9) Determined from GC analysis using HP-5 column (crosslinked 5% PH ME polysiloxane).