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Selective Protection of Secondary Alcohols by Using Formic Acid as a Mild and Efficient Deprotection Reagent for Primary *tert*-Butyldimethylsilyl Ethers

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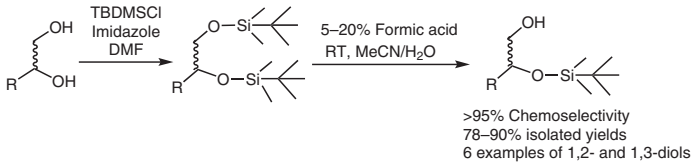

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Abstract A mild, efficient, and environmentally friendly method for the selective protection of secondary hydroxyl groups is described. The method involves the protection of both primary and secondary hydroxyl groups as *tert*-butyldimethylsilyl (TBDMS) ethers and selective deprotection of the primary TBDMS group with formic acid in acetonitrile/water. The rates of desilylation of primary and secondary TBDMS ethers by different concentrations of formic acid are determined. Formic acid of 5–20% concentration is found to selectively deprotect primary TBDMS ethers while keeping more than 95% of their secondary counterparts intact.

Key words selective deprotection, TBDMS ethers, formic acid, secondary alcohol protection, desilylation

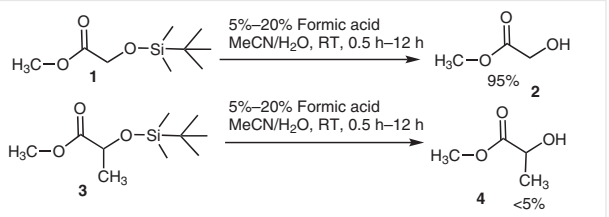
Complex synthetic targets in modern organic chemistry often require different strategies for selective protection and deprotection of various functional groups to facilitate site-specific reactions. *tert*-Butyldimethylsilyl (TBDMS) is one of the most reliable and commonly used groups for hydroxyl protection because of its easy installation and removal.[1] Both primary and secondary hydroxyl groups can be protected as TBDMS ethers without difficulty. Many biomolecules and bioactive therapeutics contain both primary and secondary hydroxyl groups. During the synthesis of complex natural products and biopharmaceuticals, there are many instances in which selective protection of secondary hydroxyls is required without affecting primary hydroxyl groups.[2,3] However, this cannot be achieved directly because primary hydroxyls also react under the conditions that secondary hydroxyl groups are protected. Given that primary and secondary hydroxyls exhibit different chemical reactivity, they may be orthogonally protected so that one can be selectively deprotected over the other. For example, during the synthesis of marine natural product Henoxazole A, Wipf and Lim protected primary and secondary hydroxyl groups as TBDMS and TIPS ethers, respectively. TBDMS ether was then selectively cleaved with LiOH in dioxane/ethanol/water.[3] Kadota and co-workers also protected primary and secondary hydroxyls as respective TBDMS and TIPS ethers while pursuing the total synthesis of gambierol.[4] TBDMS ether was selectively desilylated with 10-camphorsulfonic acid (CSA) in 75% yield.

Alternatively, a better strategy for selective protection of secondary hydroxyls can be achieved by selective deprotection of primary TBDMS ethers after both types of hydroxyls are TBDMS-protected. Numerous investigations have been made to achieve selective deprotection of primary TBDMS ethers. Various acids including HCl,[5] HF,[6] acetic acid,[7,8] CSA,[9] toluenesulfonic acid (TsOH),[10] and trifluoroacetic acid (TFA)[11] have been investigated. Smith and Liu used 1% HCl in ethanol to selectively deprotect primary TBDMS ethers while performing the total synthesis of discodermolide.[5] However, inorganic acids such as HCl and HF are poorly selective and produce a complex mixture of the desired primary alcohol, undesired secondary alcohol, and globally deprotected alcohol.[12,13] Ogilvie and co-workers used aqueous acetic acid to selectively desilylate the 5′-TBDMS group of protected nucleosides.[14] Acetic acid was also used by Battistini and co-workers for selective deprotection of primary TBDMS ethers during the total synthesis of cyclopentadienyl-carboxylic amino acid.[7] However, this method suffers from poor selectivity, low yield (50–60%), requirement for high concentration (80%), and very long reaction time (>24 h). While strong acids such as TsOH and CSA can be used to deprotect TBDMS ethers with much lower concentration and short time, they are less selective against secondary TBDMS ethers, resulting in <60% yield. TFA is another widely used acid for selective desilylation.[11,13,15] Yokokawa and co-workers compared various desilylating reagents including HF, acetic acid, and TFA for

selective desilylation of primary TBDMS ethers during the total synthesis of micropeptin T-20.[12] HF produced a complex mixture due to the selectivity problem. Acetic acid and TFA deprotected the desired primary TBDMS ether in 28% and 54% yield, respectively. In another report, Gu and Silverman used 90% TFA at room temperature to selectively deprotect primary TBDMS ether in 70% yield.[11] Partially deactivated neutral alumina was used by Guerrero and coworkers to achieve the selective deprotection of TBDMS ethers in the presence of other acid labile protecting groups. However, this method lacks regioselectivity among primary and secondary TBDMS ethers and yields globally deprotected alcohol.[16] Metal Lewis acid hafnium triflate has recently been shown to deprotect silyl ethers including TBDMS ether under mild conditions.[17] In all these examples, while primary TBDMS ethers are preferentially deprotected, secondary TBDMS ethers are also cleaved to various degrees, resulting in undesired byproducts and low yields. Whereas optimal deprotection conditions for achieving high selectivity and yield may exist for specific target molecules, it is by no means a simple task – involving searching for different acids, concentrations, temperature, and reaction time.

Despite being a subject of numerous investigations, a simple, high yielding, and environmentally friendly procedure for selective desilylation of primary TBDMS ethers is not available. Consequently, development of such a procedure will be of great utility for synthetic organic, medicinal, and bioorganic chemists. When examining various procedures for selective deprotection of TBDMS ethers in the literature, it came to our attention that the medium strength formic acid is rarely used, while both stronger (TsOH, CSA, HCl, TFA) and weaker (acetic acid) acids are often utilized. To our knowledge, there are only two reports of TBDMS deprotection with formic acid. Kawahara and co-workers investigated the 2′-O desilylation of nucleotides and found that 20–40% formic acid can be used to effectively deprotect 2′-O TBDMS from protected oligoribonucleotides.[18] In another report, Kende and colleagues used 30% formic acid to deprotect secondary TBDMS ethers during the synthesis of lankacidin C macrolide.[19] While formic acid can be used to globally deprotect TBDMS ethers at high concentrations (>30%), its utility at lower concentrations for selective deprotection of primary TBDMS ethers has not been explored. We hereby report the desilylation rates of primary and secondary TBDMS ethers with 5–20% formic acid in acetonitrile/water, thus establishing formic acid as an excellent reagent for selective desilylation of primary TBDMS ethers.

We used TBDMS-glycolate methyl ester **1** and TBDMS-lactate methyl ester **3** as model compounds to represent primary and secondary TBDMS ethers, as shown in Scheme 1.



Scheme 1 Model compounds for the study of desilylation rates and selectivity with 5, 10, and 20% formic acid, and with acetic acid and TFA

The desilylation reaction was initiated by incubating model compounds **1** and **3** with the desilylation reagent in 1:10 ratio by volume. Three formic acid concentrations were prepared by mixing formic acid/H_2O/MeCN in ratios of 1:3:16 for 5%, 2:3:15 for 10% and 4:3:13 for 20%. Additionally, we included acetic acid and TFA as desilylation reagents for comparison with formic acid. The reaction was quenched at different reaction times with 1 equivalent of NaOH and the mixture was analyzed by HPLC.[20] The amounts of **1** and **3** at different reaction time was determined from peak integration and used to calculate desilylation kinetic curves. The half-lives of TBDMS ethers under different deprotection conditions are presented in Table 1. As can be seen from the table, although 5–20% formic acid can deprotect both primary and secondary TBDMS ethers, there is a strong preference of 40–60 times for the primary over the secondary. While acetic acid also displays such a preference, it takes a long time to deprotect the primary TBDMS ether at similar concentration. TFA, on the other hand, can desilylate both primary and secondary TBDMS ethers much faster. However, the preference for primary over secondary TBDMS ethers decreases dramatically to about 3 times.

Table 1 Half-Lives of Primary and Secondary TBDMS Desilylation Reaction under Different Conditions

Desilylation reagent	Concentration (%)	Half-life (min)	
		Primary	Secondary
formic acid	5	150	8600
	10	52	2300
	20	17	630
acetic acid	5	3465	>18,000
	10	990	~18,000
	20	385	~9,000
TFA	5	34	110
	10	12	36
	20	4	12

The significant difference in half-lives of primary and secondary TBDMS ethers under different formic acid concentrations can be exploited to achieve the selective desilylation of one over the other. The deprotection regioselectivity of TBDMS ethers can be determined by the relative amount of primary and secondary alcohols under defined conditions of desilylation reagent concentration and reaction time. As shown in Table 2, 5–20% formic acid can be used to achieve 95% deprotection of primary TBDMS ethers with <5% secondary TBDMS desilylation; i.e., a desilylation regioselectivity of ca. 95:5. In comparison, TFA of 5–20% can reach only about 95:40 regioselectivity.

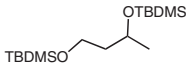
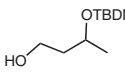
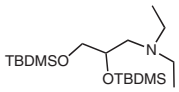
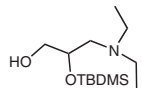
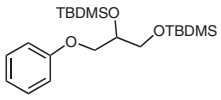
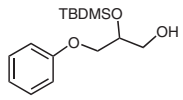
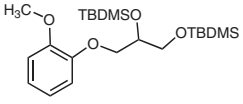
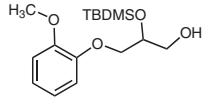
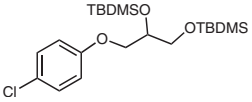
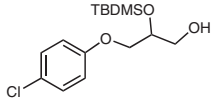
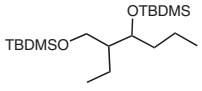
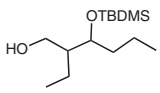
Table 2 Desilylation Selectivity of 5–20% Formic Acid and 5–10% TFA

Desilylation reagent	Concentration (%)	Reaction time (h)	Yield (%)	
			Primary	Secondary
Formic acid	5	10.5	95	<5
	10	4	95	<5
	20	1.2	95	<5
TFA	5	2.5	95	40
	10	0.8	95	36
	20	0.25	95	45

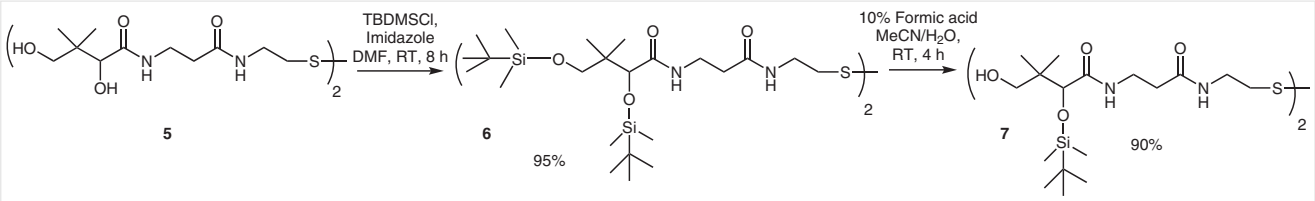
Our data suggest that the desilylation rate and selectivity between primary and secondary TBDMS ethers are dependent on both acid strength and concentration. While TFA exhibits relatively high desilylation rates, it has poor selectivity. On the other hand, slow deprotection of primary TBDMS ethers can be effected by acetic acid. As secondary TBDMS ethers are practically stable in 5–20% acetic acid, it has a high desilylation selectivity between primary and secondary TBDMS ethers. Given that formic acid lies between TFA and acetic acid in terms of acid strength, it came as no surprise that we found formic acid to be an ideal desilylation reagent for optimal desilylation rate and selectivity. Our experiments showed water as an important component in the desilylation reagent for TBDMS ethers. No reaction was observed when a primary TBDMS ether was treated overnight with 5–10% formic acid in anhydrous acetonitrile.

To demonstrate the broad utility of formic acid as a simple and efficient reagent for selective desilylation of primary TBDMS ethers, we investigated six different diols containing both primary and secondary alcohols, as shown in Table 3. All the hydroxyls were fully protected as TBDMS ethers, which were treated with 10% formic acid in acetonitrile/water for 4 h at room temperature to achieve selective deprotection of primary TBDMS groups. As can be seen from Table 3, the treatment procedure yielded the corresponding primary alcohols in excellent yields for all TBDMS protected diols. After a simple ethyl acetate extraction procedure, the mono TBDMS protected diols were isolated in high purity, as confirmed by ^{1}H NMR spectroscopy (see the Supporting Information).

Table 3 Selective Deprotection of Disilylated Alcohols with 10% Formic Acid for 4 h at Room Temperature

Entry	Reactant	Product	Isolated yield (%)
1			78
2			81
3			86
4			88
5			85
6			90

Finally, we applied this method in one of our ongoing projects involving the chemical synthesis of dephospho-coenzyme A.[21] We needed to selectively protect the two secondary hydroxyls of pantethine while keeping the two primary hydroxyl groups available for phosphorylation. As shown in Scheme 2, after the global TBDMS protection of



Scheme 2 Synthesis of secondary hydroxyl protected pantethine by selective desilylation of primary TBDMS ether with 10% formic acid

the four hydroxyls of pantethine **5**, selective desilylation of tetra-TBDMS pantethine **6** with 10% formic acid yielded the disilylated pantethine **7** in 90% isolated yield.[22]

In summary, selective protection of secondary hydroxyl groups in the presence of primary hydroxyls is of considerable interest in chemical synthesis. However, a simple and efficient procedure is not currently available. Various methods explore either orthogonal protection/deprotection or global protection followed by deprotection under conditions with different acids, concentrations, and reaction time, with varying degrees of success. In contrast, our selective desilylation of primary TBDMS ethers with 5–20% formic acid in MeCN/water offers a simple, efficient, remarkably mild, and environmentally friendly method. With its acid strength between those of TFA and acetic acid, formic acid displays an optimal balance between the desilylation rate and selectivity for primary over secondary TBDMS ethers. As a result, high yields of primary alcohols with secondary alcohol protected by TBDMS can be achieved without difficulty.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611757.

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(20) HPLC conditions: Gemini C18 4.6 × 50 mm column, flow-rate 1 mL/min. The column was run in isocratic mode at 40% MeCN and 10% 40 mM KH_2PO_4 for 1 h. Under these conditions, the retention time for TBDMS-glycolate and TBDMS-lactate were 3.2 min and 3.5 min, respectively. The same amount of each of the reactions at time 0 were injected and used as a control. The area of peaks of 1 and 3 at different time points of reaction were quantified using EZChrom Elite software.
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(22) Di-TBDMS-pantethine: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (t, *J* = 6.2 Hz, 4 H), 6.87 (t, *J* = 5.9 Hz, 4 H), 3.98 (s, 2 H), 3.57 (s, 4 H), 3.44–3.35 (m, 4 H), 2.80 (t, *J* = 6.5 Hz, 4 H), 1.00 (s, 6 H), 0.95 (s, 18 H), 0.91 (s, 12 H), 0.80 (s, 6 H)