



## Mild deprotection of 2-(trimethylsilyl)ethyl esters

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**Abstract**—A method for the deprotection of 2-(trimethylsilyl)ethyl (TMSE) esters is described. Treatment of carboxylic esters with NaH in DMF cleanly produces the deprotected acid after extractive work-up. This method can be applied to sterically-hindered substrates as well as esters containing fluoride-labile functionality. A tandem alkylation/ester deprotection procedure is also presented. © 2001 Published by Elsevier Science Ltd.

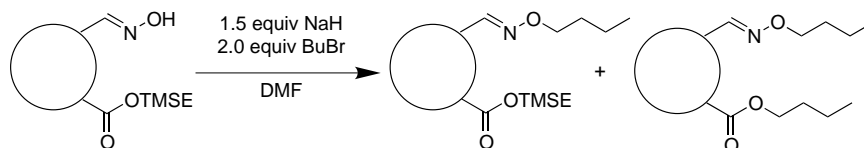
The 2-(trimethylsilyl)ethyl (TMSE) ester functionality enjoys widespread use as a protecting group in organic synthesis, largely due to its chemical stability to the hydrolytic, oxidative, or reductive methods that are commonly used to cleave other ester protecting groups.<sup>1</sup> In fact, the only reported methods to remove TMSE groups from carboxylic acids involve tetrabutylammonium fluoride (TBAF) or other fluoride source, whereby the fluoride anion attacks silicon and expels the carboxylate in addition to 1 equiv. of ethylene. However, deprotection methods relying on fluoride preclude the use of silicon-based protecting groups elsewhere in the molecule, and can also present difficulties when the ester contains base-sensitive functionality. Herein we report a novel method for the deprotection of 2-(trimethylsilyl)ethyl esters that addresses these synthetic limitations.

During the course of our drug discovery efforts, we required the parallel synthesis of carboxylic acid-containing oxime ethers that could display a diverse range of functionality appended to the oxime oxygen. We chose the TMSE ester protecting group to allow for the incorporation of unsaturated substituents, and we envisioned that these side-chains could be introduced via alkylation of the oxime. When our TMSE ester/oxime

scaffold was treated with excess NaH (1.5 equiv.) and electrophile (2.0 equiv.) in DMF, we were surprised to discover that in addition to the desired oxime ether, a side-product was generated where both the oxime and carboxylic acid incorporated the same alkyl side-chain (Scheme 1). We reasoned that this bis-alkylated product must arise from the in-situ deprotection of the TMSE ester and subsequent alkylation by excess electrophile.

Control experiments identified that the combination of NaH in DMF was sufficient to cleanly deprotect TMSE esters in quantitative yields. In a typical procedure,<sup>2</sup> the TMSE ester is simply dissolved in DMF and treated with 1.0 equiv. of NaH (60% dispersion in mineral oil) and stirred at ambient temperature overnight. A screen of other polar aprotic solvents (THF and CH<sub>3</sub>CN) identified DMF as the preferred solvent in terms of reaction rate and product purity.<sup>3</sup> Extractive work-up affords the carboxylic acid in sufficiently pure form, with the only contaminant being mineral oil from the NaH which can be easily removed by trituration with hexanes.

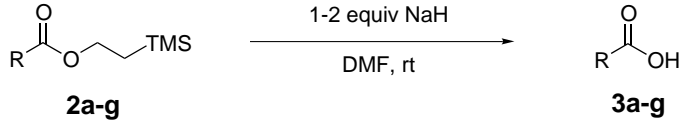
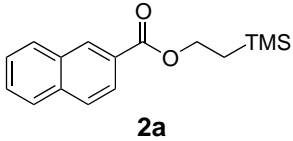
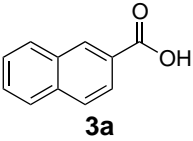
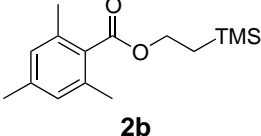
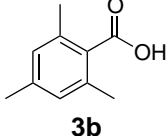
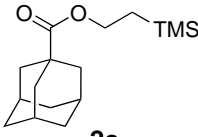
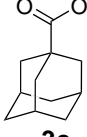
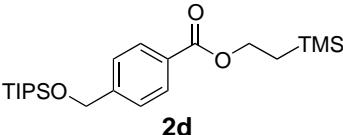
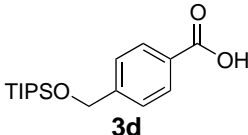
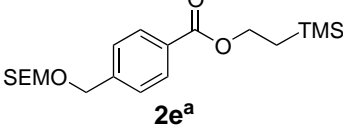
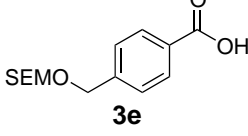
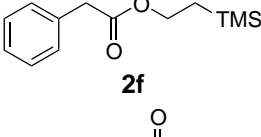
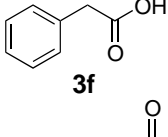
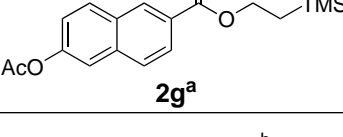
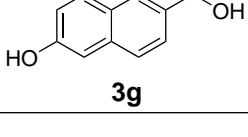
Table 1 summarizes the range of aromatic and aliphatic substrates that were deprotected using this protocol.



Scheme 1.

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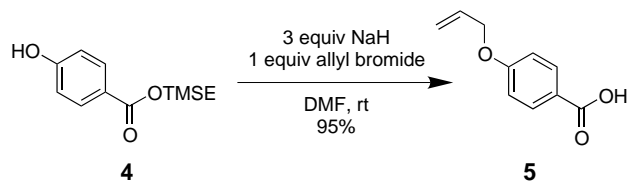
**Table 1.** Deprotection of TMSE esters using NaH/DMF

		
Ester	Product	Yield (%) <sup>b</sup>
 <b>2a</b>	 <b>3a</b>	83
 <b>2b</b>	 <b>3b</b>	92
 <b>2c</b>	 <b>3c</b>	87
 <b>2d</b>	 <b>3d</b>	82
 <b>2e<sup>a</sup></b>	 <b>3e</b>	82
 <b>2f</b>	 <b>3f</b>	88
 <b>2g<sup>a</sup></b>	 <b>3g</b>	86

<sup>a</sup> 2 equiv. of NaH required. <sup>b</sup> Isolated yield.

Deprotection of the hindered esters **2b** and **2c** at ambient temperature exemplify the synthetic utility of this methodology, as elevated temperatures or prolonged reaction times are required for saponification of even the methyl ester of **2b**.<sup>4</sup> Importantly, this protocol also allows the selective deprotection of TMSE esters without affecting fluoride-sensitive groups such as tri-*iso*-propylsilyl (TIPS, ester **2d**) and 2-(trimethylsilyl)-ethoxymethyl (SEM, **2e**) ethers.<sup>5</sup> We also investigated the compatibility of acetate esters with our deprotection methodology (ester **2g**), and we were surprised to discover that with 1 equiv. of NaH, the acetate ester was selectively cleaved; an additional equivalent of base then cleanly produced the hydroxy naphthoic acid **3g**.

For substrates which contain a nucleophilic center, this deprotection method can be combined with an in-situ alkylation event to effect a two-step, one-pot transformation. Namely, when hydroxy ester **4** is treated with excess (3.0 equiv.) NaH and 1.0 equiv. of allyl bromide in DMF overnight, 4-allyloxybenzoic acid (**5**) is isolated in 95% yield (Scheme 2). This tandem alkylation/deprotection

**Scheme 2.**

strategy should be applicable to other bifunctional molecules containing nucleophilic heteroatoms or possibly stabilized carbanions. Moreover, the recent demonstration of the 2-trimethylsilyl ethyl group as a versatile linker for solid phase synthesis suggests an interesting application of our novel deprotection methodology to immobilized ester substrates.<sup>6</sup>

Several mechanistic possibilities may be proposed for the deprotection of TMSE esters by NaH in DMF. We favor a mechanism whereby NaH reacts with adventitious moisture in the solvent, and that NaOH is in fact the active species.<sup>7</sup> In fact, a number of bases (KO-*t*-Bu, KOTMS, KOEt) were identified as competent hydroxide precursors.<sup>8</sup> 'Anhydrous' hydroxide is known to cleave simple (i.e. methyl and ethyl) esters by attack at the carbonyl and subsequent acyl–oxygen bond fission,<sup>9,10</sup> and certainly this mechanism may operate in the hydrolysis of unhindered esters such as **2a**. With sterically-demanding substrates, however, a different reaction pathway involving hydroxide attack at silicon may prevail. Subjecting ethyl mesitoate to the standard reaction conditions affords no hydrolysis product, whereas the corresponding TMSE ester **2b** undergoes clean deprotection at room temperature. Moreover, an aliquot from the deprotection reaction of **2a** revealed the generation of hexamethyldisiloxane (detected by GC/MS), which provides additional evidence for anhydrous hydroxide attacking silicon in a similar fashion to fluoride. The observed stability of a SEM ether to the reaction conditions (ester **2e**) suggests that the collapse of the putative silicate intermediate is facilitated by expulsion of a good carboxylate leaving group for the ester, while no such leaving group is available for the SEM ether.

In summary, we have discovered a novel method for the deprotection of TMSE esters that offers an attractive alternative to existing methodology. In addition to greater functional group tolerance, this mild method generates volatile by-products that are easily removed to afford analytically pure material. The incorporation of this protocol into a tandem alkylation/deprotection strategy contributes to the potential increased utility of the TMSE ester protecting group in organic synthesis.

## Acknowledgements

The authors would like to thank Professor Jim Leighton (Columbia University) for helpful discussions.

## References

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999; pp. 399–400.
2. **General experimental procedure:** To a solution of the TMSE ester (1.0 mmol) in 4 mL DMF (Aldrich) was added NaH (40 mg, 1.0 mmol of a 60% dispersion in mineral oil) in one portion as a solid. The heterogeneous mixture was stirred overnight at room temperature. Upon disappearance of starting material, the reaction was partitioned between 1 N HCl and ether. The organic layer was washed with water and brine, and then dried over MgSO<sub>4</sub> prior to filtration and evaporation. The crude product was purified by trituration with hexanes or flash chromatography.
3. After 24 h at room temperature, the reaction of **2a** in THF proceeded to 31% conversion; in CH<sub>3</sub>CN, 50% conversion. Both reactions were contaminated with unidentified by-products.
4. Bender, M. L.; Dewey, R. S. *J. Am. Chem. Soc.* **1956**, *78*, 317–319.
5. The corresponding TES ether of **2d** was quantitatively deprotected under the reaction conditions to afford 4-hydroxymethyl benzoic acid. Meanwhile, the TBS ether of **2d** gave a mixture of mono- and bis-deprotected material.
6. Wang, B.; Chen, L.; Kim, K. *Tetrahedron Lett.* **2001**, *42*, 1463–1466.
7. When the reaction is performed in the presence of 4 Å molecular sieves, the reaction proceeds to only 18% conversion after 24 h.
8. However, when aqueous 1 N NaOH was used with DMF as solvent, incomplete conversion (53%) of **2a** was observed after 48 h.
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