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## The Protection of Ketones and Aldehydes as 4-Trimethylsilylmethyl-1,3-dioxolanes

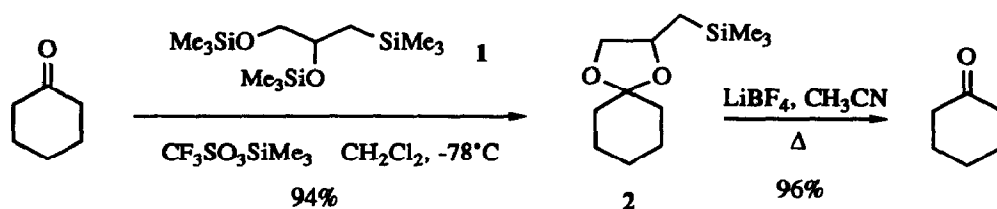
Brett M. Lillie and Mitchell A. Avery\*

Department of Chemistry, University of North Dakota, P. O. Box 9024, Grand Forks, ND 58202-9024

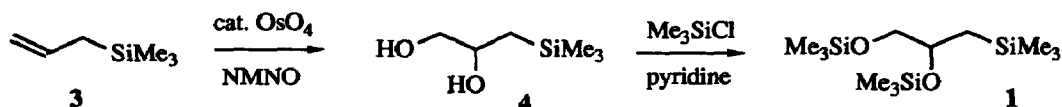
**Abstract:** The 1,3-dioxolanation of carbonyl compounds with 2,3-bis(trimethylsilyloxy)-trimethylsilylpropane (BTTP) in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) has been investigated. BTTP readily converted unhindered ketones and aldehydes to their corresponding 4-trimethylsilylmethyl-1,3-dioxolanes, but failed for more hindered substrates. The 4-trimethylsilylmethyl-1,3-dioxolane can be selectively cleaved to regenerate the carbonyl compound in the presence of a 1,3-dioxolane using either  $\text{LiBF}_4$  or HF in acetonitrile.

A common strategy for the protection of ketones and aldehydes involves their conversion into 1,3-dioxolanes or 1,3-dioxanes.<sup>1</sup> The removal of these protecting groups is normally effected under aqueous acidic conditions, although a plethora of alternative, non-aqueous conditions are available.<sup>2</sup> Frequently, problems can arise associated with lability of the elaborated structure towards deprotection. In order to side-step these difficulties, structurally modified 1,3-dioxanes and 1,3-dioxolanes have been developed which can be removed by a variety of mild processes. For example, the 5,5-dibromo-1,3-dioxane<sup>3</sup> or 4-bromomethyl-1,3-dioxolane<sup>4</sup> protecting group can be removed via mild reductive elimination; the 5-methylene-1,3-dioxane<sup>5</sup> or 4-(3-butenyl)-1,3-dioxolane<sup>6</sup> can be cleaved with Hg(II); the 5-(2-pyridyl)-1,3-dioxane<sup>7</sup> undergoes alkylation to a pyridinium ion and subsequent fragmentation under basic conditions to regenerate the carbonyl compound; and the 4-(2-nitrophenyl)-1,3-dioxolane<sup>8</sup> is labile to photolysis. Each of these methods is virtuous but limited by the introduction of functionality (e.g. olefin, halogen, heterocyclic nitrogen atom, or aryl nitro group).

It seemed that a ketal having a trimethylsilyl group  $\beta$  to oxygen might be readily deprotected under mild, fluoride assisted conditions and that such a ketal would not suffer the disadvantage of introducing unwanted functionality. The conceptual drawback to this approach involved the usual conditions for effecting protection, namely that acid catalyzed removal of water from a mixture of diol and carbonyl compound would likely result in destruction of the  $\beta$ -silyl substituted substrate or product. We found that this problem could be circumvented by modification to Noyori's ketalization<sup>9</sup> approach: when 2,3-bis(trimethylsilyloxy)-trimethylsilylpropane **1** was reacted with certain ketones and aldehydes at low temperature in the presence of TMSOTf,  $\beta$ -silyl substituted ketals such as **2** could be obtained in excellent yields.<sup>10</sup> Further, the resultant 4-(trimethylsilylmethyl)-1,3-dioxolanes (TMSD protecting group, e.g. **2**) could be readily cleaved back to carbonyl compounds in the presence of fluoride sources.



The ketalization reagent **1** was readily prepared in two steps from allyltrimethylsilane **3** as follows: To a  $0^\circ\text{C}$  solution of **3** (1 equivalent) in acetone (2 mL/mmol of **3**) was added 4% by weight aqueous osmium tetroxide (1 mol % based on **3**) and *N*-methylmorpholine-*N*-oxide (NMNO, 1.5 equivalents). After 30 min, the mixture was warmed to ambient temperature and stirred an additional hour. The reaction mixture was poured into sat. aq. ammonium chloride and extracted several times with dichloromethane. The organic layer was treated first with solid sodium dithionite, dried over anhydrous sodium sulfate, and concentrated in vacuo to provide a syrupy liquid. Flash chromatography (50% EtOAc/hexane) over silica gel gave the pure diol **4** in 98%



yield. The diol was silylated by treatment under nitrogen of **4** (1 equivalent) in dichloromethane (4 mL/mmol of **4**) at  $0^\circ\text{C}$  with freshly distilled pyridine (3 equivalents) followed by chlorotrimethylsilane (2.2 equivalents). The reaction was monitored by TLC (silica gel, 30%  $\text{CH}_2\text{Cl}_2$ -hexane) and when complete, was poured into sat. aq. ammonium chloride. The combined dichloromethane extracts were washed with aq. sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated to give crude product which was purified by vacuum distillation to provide **1** (89%). The success of subsequent reactions was dependent on the absence of any unreacted alcohol in the product **1**.

**General protection procedure:** In a typical experiment conducted under inert atmosphere, the pure carbonyl compound (1 equivalent) was dissolved in dry dichloromethane (1 mL/mmol ketone) and 2,3-bis(trimethylsilyloxy)-1-trimethylsilylpropane **1** (1.1 equiv.) was added. The mixture was cooled to  $-78^\circ\text{C}$  and treated dropwise with 0.01 equivalents of 0.177 M TMSOTf in dichloromethane. The reaction was monitored by TLC and quenched at  $-78^\circ\text{C}$  by adding dry pyridine (0.25 equiv.). After 10 minutes, the reaction mixture was poured into sat. aq.  $\text{NaHCO}_3$ , and was then extracted several times with dichloromethane. The combined organic layers were washed with sat. aq.  $\text{NH}_4\text{Cl}$ , dried over  $\text{MgSO}_4$  and evaporated. After the solution was concentrated the residue was purified by column chromatography and/or distillation.

**General cleavage procedure:** The ketal (1 equivalent), dissolved in dry acetonitrile (1 mL/mmol ketal) under inert atmosphere, was treated with 1.0 M  $\text{LiBF}_4$  in acetonitrile (1.1 equivalent). After 30 minutes at reflux, the solution was cooled, poured into water, and then extracted several times with dichloromethane. The combined organic layer was washed with sat. aq.  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , and the solvent evaporated to provide the carbonyl compound. Alternatively, the ketal (1 equivalent) was dissolved in acetonitrile (1 mL/mmol ketal) and treated with 0.1 M HF in water (1.1 equivalent). After 15 minutes at room temperature, the solution was cooled, poured into water, and then extracted several times with dichloromethane. The combined

organic layer was washed with sat. aq. NaHCO<sub>3</sub>, dried over MgSO<sub>4</sub>, and the solvent evaporated to provide the carbonyl compound.

As shown in Table 1, a variety of ketones, enones, and an aldehyde were examined in this reaction. As can be seen, unhindered 5 and 6 membered ring ketones are readily protected with BTTP/TMSOTf. As the degree of hindrance increases, the protection method fails. For example, 2,6-di or 2,2,6-trisubstituted ketones give no ketal. For the acyclic ketones 2-octanone and 4-heptanone, only the former ketone underwent protection by this method. The reluctance of the latter ketone to undergo ketalization may be related to a steric effect, or to trace impurities in the starting ketone. Acetophenone was unreactive, but benzaldehyde readily underwent protection.

Table 1. Reaction of Carbonyl Compounds with 2,3-bis(trimethylsilyloxy)trimethylsilylpropane **1** and TMSOTf in Dichloromethane at -78°C.<sup>a</sup>

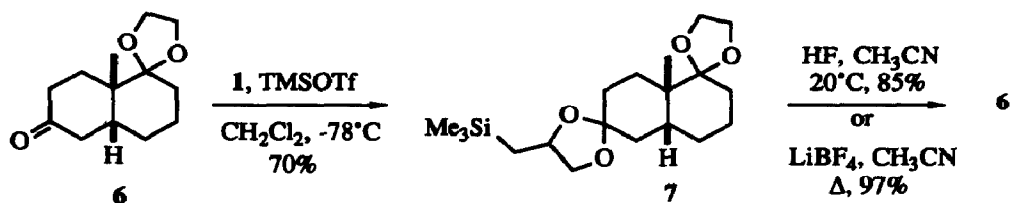
| Substrate   | Reaction Time (hr) | Yield(isolated) | Bp(°C)                 | Diastereomer Ratio |
|---|--------------------|-----------------|------------------------|--------------------|
| benzaldehyde  | 2                  | 100             | 100-102<br>(0.4 mm Hg) | 6:4 <sup>b</sup>   |
| 2-octanone  | 6                  | 85              | 80<br>(1 mm Hg)        | —                  |
| 4-heptanone   | 6                  | 0               |                        |                    |
| cyclohexanone   | 4                  | 94              | 114<br>(9.5 mm Hg)     | —                  |
| 2-methylcyclohexanone                                   | 5                  | 88              | 75-78<br>(0.7 mm Hg)   | 6:2:2 <sup>b</sup> |
| 1,4-cyclohexanedione<br>monoethylene ketal ( <b>5</b> ) | 4.5                | 75              | 130-135<br>(10 mm Hg)  | —                  |
| cyclopentanone  | 4                  | 80              | 66<br>(0.6 mm Hg)      |                    |
| 2,6-dimethylcyclohexanone                               | 88                 | 0               |                        |                    |
| 2,2,6-trimethylcyclohexanone                            | 45                 | 0               |                        |                    |
| 2-isopropyl-5-methyl-<br>cyclohexanone (menthone)       | 6                  | 0               |                        |                    |
| 3-methylcyclohex-2-en-1-one                             | 17                 | 0               |                        |                    |
| acetylcyclohexene                                       | 16                 | 0               |                        |                    |

<sup>a</sup>All products were fully characterized by NMR, IR, M.S., and elemental analysis. <sup>b</sup>Determined by NMR.

We were surprised to find that enones could not be coerced to undergo protection by this method. Noyori<sup>9</sup> and Hwu<sup>11-12</sup> have effected protection of  $\alpha,\beta$ -unsaturated carbonyls using 1,2-bis(trimethylsilyloxy)ethane catalyzed by TMSOTf. Hwu found that saturated ketones undergo Noyori ketalization more rapidly than do  $\alpha,\beta$ -unsaturated aldehydes, and also that sterically unbiased saturated ketones undergo Noyori ketalization more rapidly than do  $\alpha,\beta$ -unsaturated ketones. For the enones studied, BTTP was consumed in the reaction suggesting that the rate of ketalization of enones by BTTP/TMSOTf is significantly slower than the rate of decomposition of **1** by TMSOTf. This suggestion is further supported by the lack of any trace of protected enone in reaction mixtures kinetically quenched at various time intervals.

The selectivity of the protection and deprotection steps were examined. First of all, it was found that

4-(trimethylsilylmethyl)-1,3-dioxolanes (TMSD's) such as **2** were resistant to conventional reagents for silyl cleavage: tetrabutylammonium fluoride (TBAF) in THF; CsF in THF; KF, 18-crown-6, THF. Thus, it would seem likely that silyl ethers could be deprotected in the presence of the TMSD protecting group. Interestingly, unsubstituted 1,3-dioxolanes are not disturbed during the introduction of the TMSD protecting group. For example, either mono-ketal **5**<sup>13</sup> or **6**<sup>14</sup> could be protected to give mixed-bisketals, such as **7**. Furthermore, the TMSD mixed bis-ketal **7** was selectively deprotected by either LiBF<sub>4</sub> or HF in acetonitrile.



The formation of diastereomeric 4-(trimethylsilylmethyl)-1,3-dioxolanes from asymmetrical carbonyls represents a limitation of this method. For example, **7** was obtained as a 1:1:3:3 diastereomeric mixture (NMR). We are currently examining the synthesis of a symmetrical variant of the TMSD group: the 2,2-bis(trimethylsilyl)-1,3-dioxane.

#### References and Notes

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- For ketal **2**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 4.19 (dddd, 1H, J = 5.5, 6.8, 7.7, 7.7 Hz), 4.01 (dd, 1H, J = 5.5, 7.7 Hz), 3.36 (dd, 1H, J = 7.7, 7.7 Hz), 1.07 (AB, 1H, J = 6.8, 14.1 Hz), 0.82 (ΔB, 1H, J = 7.7, 14.1 Hz), 0.06 (s, 9H). Satisfactory IR, EIMS, and elemental analyses were obtained.
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