A Mild, Room-Temperature Protection of Ketones and Aldehydes as 1,3-Dioxolanes under Basic Conditions

Alfred Hassner,* Chennakesava Reddy Bandi, Sharad Panchgalle

Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel
Fax +972(3)7384053; E-mail: hassna@biu.ac.il

Received: 20.09.2012; Accepted after revision: 12.10.2012

Abstract: Protection of ketones or aldehydes as 1,3-dioxolane derivatives proceeds within minutes at room temperature in the presence of *N*-hydroxybenzenesulfonamide, its *O*-benzyl derivative, or the tosyl analogue, in the absence of strong protonic acids, and in the presence of base (Et_3N). Acid-sensitive groups such as *O*-THP, *O*-TBS, or *N*-Boc are unaffected.

Key words: ketals, protecting groups, synthetic methods, ketones, aldehydes

Formation of 1,3-dioxolanes is one of the most widely used methods of protection of ketones or aldehydes. These cyclic ketals are stable under most alkaline reaction conditions, as well as to many oxidizing and reducing agents.[1] Furthermore, they can be readily reconverted into ketones by treatment with aqueous acids. A common way to achieve the latter is reaction in acetone–water in the presence of an acid catalyst.

1,3-Dioxolanes are usually prepared from ketones and 1,2-ethanediol in the presence of a strong protonic acid (such as *p*-TsOH)[2a,2b,2e] or Lewis acid (such as BF_3,[2c] $TiCl_4$[2d]) catalyst, often with a Dean–Stark trap and azeotropic removal of water to preclude hydrolysis of the product; sometimes the reaction requires high temperature, long reaction time, or tedious work up. Usually it is desirable to avoid the presence of strong acid conditions during the protection step, not only to prevent ketal hydrolysis but also because of the presence of other acid sensitive groups in the molecule such as THP, Boc, or silyl derivatives. In this context, many mild acid catalysts that have been reported, including oxalic acid in acetonitrile at room temperature,[3] TsOH-pyridine under reflux,[4] acidic ion-exchange resin[5a] or clay,[5b] acidic ionic liquids,[6] metal derivatives such as tin oxide,[7] copper(II) salts,[8] scandium triflate with TMSOTf,[9] and ZrO_2 supported on tungsten polyacids.[10] Furthermore, 1,3-dioxolanes have been prepared by using 1,2-(trimethylsiloxy)ethane with TMSOTf[11] or $Bi(OTf)_3$,[12a] or with iodine.[12b] Clearly, neutral or basic conditions would be desirable for ketone/aldehyde protection.

In the process of examining the reaction of *N*-hydroxybenzenesulfonamide (**1a**; Figure 1) with aldehydes in the presence of base leading to synthesis of hydroxamic acids, we discovered some time ago[13] that **1a** apparently promotes the formation of dimethyl acetals from aldehydes and methanol under mild conditions. Neither benzenesulfonamide nor phenol (which has a similar pK_a to that of **1a**) were effective. However, conversion of benzyl methyl ketone into its dimethylketal proceeded in only 33% yield.

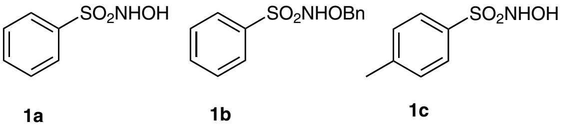
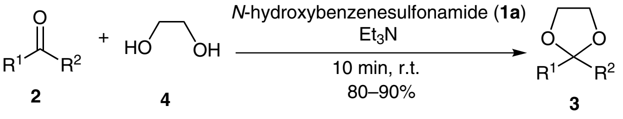


Figure 1 Structures of sulfonamide catalysts **1a**–**c**

In view of the fact that the protection of aldehydes and ketones **2** as dioxolanes **3** is a commonly used reaction that often requires heating in the presence of strong acids, we decided to re-examine the effectiveness of **1a** as a promoter in such reactions. We now report that **1a** promotes conversion of ketones and aldehydes into their 1,3-dioxolanes in the absence of strong protonic acids and in the presence of triethylamine at room temperature, within minutes, in good yield (Scheme 1).



Scheme 1

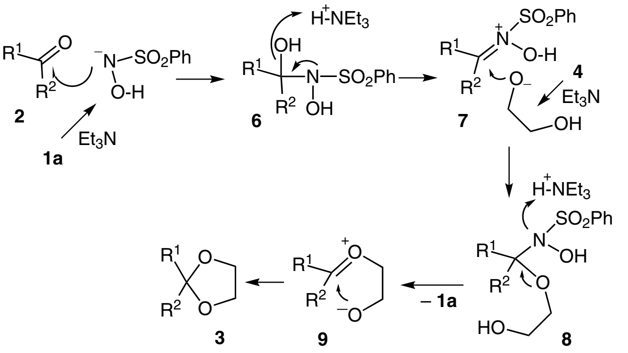
First, we used commercially available **1a** as a promoter and found that even with one equivalent of **1a**, the yields of dioxolane were usually low. When we examined commercial **1a** (Pilloti's acid) in detail, as well as the product obtained on reaction of $PhSO_2Cl$ with NH_2OH, we found it to be composed mainly of a mixture of authentic **1a** and a dimeric salt, as was reported earlier.[14] Although both of these compounds promoted dioxolane formation, the yields were very low (<30%). As long as the medium remains acidic, the presence of water can reverse the formation of dioxolane, which is the reason that azeotropic removal of water is often employed.

As a plausible pathway for the role of **1a** in formation of **3**, we considered the pathway shown in Scheme 2, in which nucleophilic attack of the nitrogen of **1a** at the C=O group leads to formation of a very reactive iminium species **7**, which rapidly captures the alcohol or diol, ulti-

SYNLETT 2012, 23, 2773–2776
Advanced online publication: 13.11.2012
DOI: 10.1055/s-0032-1317529; Art ID: ST-2012-B0225-L

mately leading to the ketal **3** through the conventional mechanism. It is known that N–O and N–N compounds are efficient nucleophiles due to the so-called α-effect.[15] Hence, the first step in the formation of **3** must involve attack of **1a** on the carbonyl group of **2**. To enhance the nucleophilicity of **1a** as well as that of the diol, we added triethylamine, which, by abstracting the acidic H from **1a** in a fast step, should enhance its attack on the carbonyl group of **2**. The presence of triethylamine should also aid in the equilibrium formation of alcoholate anion from **4** and prevent acid-catalyzed hydrolysis of **3** by generated water. The presence of base improved the yield of dioxolane manyfold, with triethylamine being more effective than 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or diisopropylethylamine. One equivalent of triethylamine was optimal.

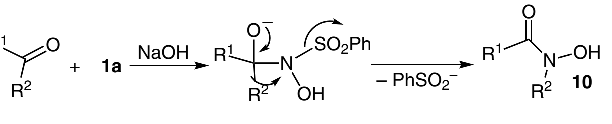
For a promoter such as **1a** to be effective, it has to incorporate two essential features: It must contain a good N-nucleophile that can provide a reactive iminium species **7**, and it must possess a good leaving group enabling formation of an oxonium species **9** necessary for further reaction (preferably intramolecular) with the second ROH. The presence of the $ArSO_2$ group is important because it provides a better leaving group in the subsequent step by stabilizing a negative charge on the nitrogen. Indeed, *p*-$TolSO_2NHOH$ (**1c**; Figure 1), which we prepared according to the literature,[16] proved to be just as effective as **1a** for dioxolane formation (e.g., from cyclohexanone and acetophenone). However, *N*-benzylsulfonamide **5** (Figure 2), a mild acid that is structurally closely related, but lacking the N-OR moiety, was completely inactive in promoting ketalization, indicating that it was not the acidity of the reagent that was essential but the presence of the $PhSO_2N$-O grouping.



Scheme 2 Plausible mechanism

Thus, we settled on the optimal conditions for dioxolane formation: aldehyde or ketone (1 equiv), ethylene glycol (2 equiv), **1a** (commercial, without purification; 0.7 equiv) and triethylamine (1 equiv) in CH_2Cl_2, reaction time 10 min at room temperature.

Although 0.7 equiv of **1a** worked very efficiently and 1.0 equiv of **1a** improved the yield of **3** only marginally, catalytic amounts (0.1–0.4 equiv) led to much reduced yields. Because the promoter **1a** is regenerated in step **8** → **9** Scheme 2, the reason that **1a** is not effective as a catalyst is apparently due to a process in which **1a** is depleted. In fact, it is known[17] that **1a** slowly decomposes, especially in the presence of base, to benzenesulfinic acid anions. Indeed, we found that only about 30% of **1a** can be recovered from the reaction shown in Scheme 1. Furthermore, reaction of aldehydes and ketones with **1a** in the presence of NaOH is known to lead to hydroxamic acids **10** by rearrangement,[13,18] thus depleting **1a**, albeit in a slower reaction (Scheme 3). An advantage of using triethylamine in the reaction depicted in Scheme 2 is that, unlike NaOH, it can still act via $HNEt_3^+$ as a proton donor to **6**, favoring formation of iminium species **7**. $HNEt_3^+$ may also facilitate elimination of **1a** from **8** to produce intermediate **9**.



Scheme 3

Convenient work up by washing and evaporation led to essentially NMR-pure dioxolanes **3** in good yield. The yields of pure dioxolanes after chromatography on alumina were in the order of 80–90% for a variety of ketones and aldehydes (Table 1).

Even hindered ketones such as diisopropyl ketone gave good results. Functional groups such as OTHP, N-Boc, methyl (ethyl) ester, and even O-TBS-phenol, which are sensitive to common acids, remained unaffected (see Table 1). Azeotropic removal of water was not necessary. Dioxolane formation took place within minutes even with aromatic aldehydes and ketones as well as with the electron-poor 4-nitrobenzaldehyde, in contrast to reported reactions requiring hours,[12] especially with electron-poor aldehydes or ketones.

To establish whether hydrogen bonding between the hydroxyl group of **1a** and the ketone played a major role (see Figure 2), we also examined the O-benzyl derivative **1b**. In fact, **1b** was just as effective as a ketalization catalyst as **1a** (essentially the same yields of **3** from cyclohexanone), indicating that the presence of a hydroxyl group was not essential.

In conclusion, we have developed a method that allows protection of aldehydes or ketones as 1,3-dioxolanes in

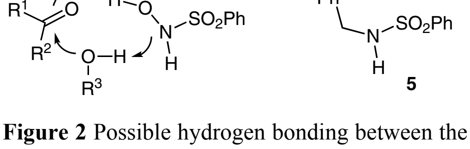
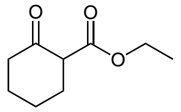
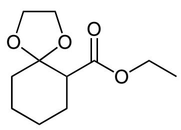
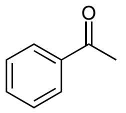
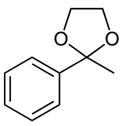
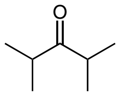
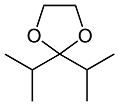
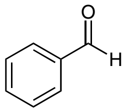
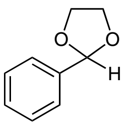
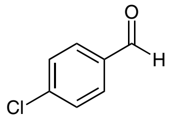
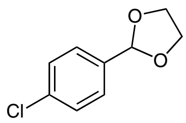
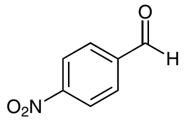
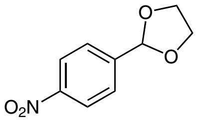
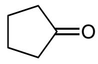
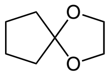
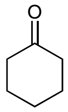
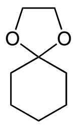
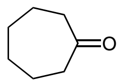
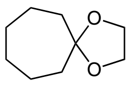
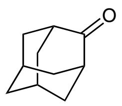
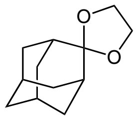
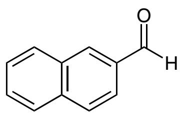
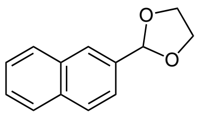
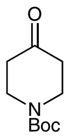
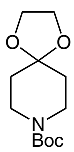
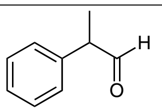
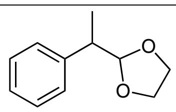
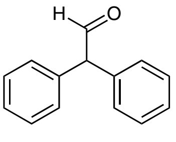
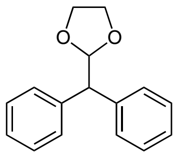
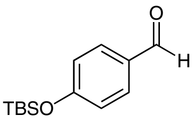
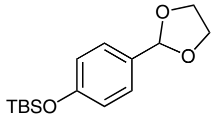
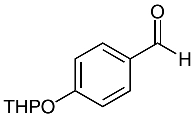
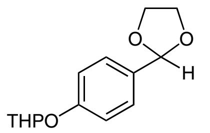
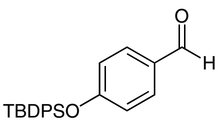
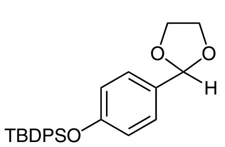
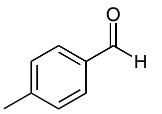
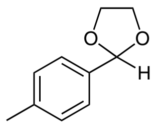


Figure 2 Possible hydrogen bonding between the hydroxyl group of **1a** and the ketone

the presence of triethylamine as base, proceeding within minutes at room temperature and using **1a** (or its *O*-benzyl derivative **1b** or tosyl analogue **1c**) as promoter.[19]

Table 1 Reaction of Ketone or Aldehyde **2** with Ethylene Glycol in the Presence of **1a** and Triethylamine[a]

Entry	Ketone or aldehyde **2**	1,3-Dioxolane **3**	Yield (%)
1			84
2			81
3			90
4			83
5			80
6			83
7			80
8			89
9			81
10			89
11			82[b]
12			80
13			81
14			86
15			87
16			82
17			87
18			82

[a] Reaction conditions: **2** (1 equiv), ethylene glycol (2 equiv), **1a** (0.7 equiv), Et_3N (1 equiv), r.t., 10 min.

[b] Reaction performed on a 3 mmol scale.

Acknowledgment

Support of this research by the Marcus Center for Medicinal and Pharmaceutical Chemistry at Bar-Ilan University is gratefully acknowledged.

References and Notes

(1) (a) Green, T. W.; Wutts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, Chap. 4. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **2005**.

(2) (a) Daignault, R. A.; Eliel, E. L. *Org. Synth.* **1973**, *5*, 303. (b) Smith, A. B. III.; Branco, S. J.; Guaciao, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth.* **1983**, *61*, 65. (c) Torok, D. S.; Fifueroa, J. J.; Scott, W. J. *J. Org. Chem.* **1993**, *58*, 7274. (d) Mahrwald, R. *J. Prakt. Chem.* **1994**, *336*, 361. (e) Danet, M.; Normand-Bayle, M.; Maluteau, J.; D'Angelo, J.; Morgant, G.; Desmaele, D. *Eur. J. Org. Chem.* **2004**, 1911.

(3) Anderson, N. H.; Uh, S.-H. *Synth. Commun.* **1973**, *3*, 125.

(4) (a) Sterzycki, R. *Synthesis* **1979**, 724. (b) Speare, D. M.; Fleming, S. M.; Beckett, M. N.; Li, J.-J.; Bugg, T. D. H. *Org. Biomol. Chem.* **2004**, *2*, 2942.

(5) (a) Dann, A. E.; Davis, J. B.; Nagler, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 158. (b) Campelle, J. M.; Garcia, A.;

Lafont, F.; Luna, D.; Marinas, J. M. *Synth. Commun.* **1994**, *24*, 1345.
(6) Fang, D.; Gong, K.; Shi, Q.; Liu, Z. *Catal. Commun.* **2007**, *8*, 1463.
(7) Otera, J.; Danoh, N.; Nozaki, H. *Tetrahedron* **1992**, *48*, 1449.
(8) (a) Satoh, J. Y. *Chem. Lett.* **1974**, 1521. (b) Liu, C.-H.; Yu, X.-Y.; Liang, X.-Z.; Wang, W.-J.; Yang, J.-G.; He, M.-Y. *Chin. J. Chem.* **2007**, *25*, 83.
(9) Ishihara, K.; Karumi, Y.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 839.
(10) Justus, J.; Vinu, A.; Devassy, B. M.; Balasubramanian, V. V.; Bohringer, W.; Fletcher, J.; Hallegudi, S. B. *Catal. Commun.* **2008**, *9*, 1671.
(11) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Carlston, R.; Gautun, H.; Westerlund, A. *Adv. Synth. Catal.* **2002**, *344*, 57.
(12) (a) Podgorski, D. M.; Krabbe, S. W.; Le, L. N.; Sierszulski, P. R.; Mohan, R. S. *Synthesis* **2010**, 2771. (b) Banik, B. K.; Chapa, M.; Marquez, J.; Cardona, M. *Tetrahedron Lett.* **2005**, *46*, 2341.
(13) Hassner, A.; Wiederkehr, R.; Kascheres, A. J. *J. Org. Chem.* **1970**, *35*, 1962.
(14) Scholz, J. N.; Engel, P. S.; Glidewell, C.; Whitmore, K. H. *Tetrahedron* **1989**, *45*, 7695.
(15) (a) Gold, V. *Pure Appl. Chem.* **1979**, *51*, 1732. (b) Hoz, S.; Bunsel, E. *Isr. J. Chem.* **1985**, *26*, 313. (c) Bunsel, E.; Um, I.-H. *Tetrahedron* **2004**, *60*, 7801. (d) In oxime formation from ketones, the rate-determining step is attack by NH_2OH to form a tetrahedral intermediate, see: Jencks, W. P. *J. Am. Chem. Soc.* **1959**, *81*, 475.
(16) Fujimoto, M.; Sakai, M. *Chem. Pharm. Bull.* **1965**, *13*, 248.
(17) (a) Smith, P. A. S.; Hein, G. E. *J. Am. Chem. Soc.* **1960**, *82*, 5731. (b) Bonner, F. T.; Ko, Y. *Inorg. Chem.* **1992**, *31*, 2514.
(18) Banerjee, R.; King, S. B. *Org. Lett.* **2009**, *11*, 4580.
(19) **Protection of 2 as 1,3-Dioxolane 3 (Table 1); General Procedure:** A solution of ketone or aldehyde **2** (1 mmol), **1a** (commercial, 121 mg, 0.7 mmol), and ethylene glycol (124 mg, 2 mmol) in CH_2Cl_2 (4 mL) was stirred at r.t. for 10 min. The solution was washed with water and brine, and dried over anhydrous $MgSO_4$ [washing with 2 M NaOH (2 × 10 mL) followed by acidification led to only partial recovery of **1a**]. Concentration under vacuum afforded **3**. Flash chromatography (basic alumina; EtOAc–hexane, 1:9) gave pure **3** in 80–90% yield (Table 1). The analytical data of 1,3-dioxolanes **3** were in good agreement with those of authentic compounds.