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Protection of the Carbonyl Group as 1,2,4-Trioxane and Its Regeneration under Basic Conditions[1]

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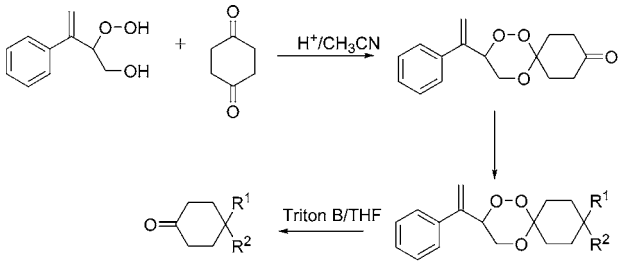
ABSTRACT



R_1, R_2 = H, OH; OH, CH_2CO_2Et; H, NHAr; OH, Me; OH, Ph; OH, CH_2CH_2OH; H, $OCOCH_2CH_2CO_2Me$

An experimental protocol demonstrating the protection of the carbonyl group as 1,2,4-trioxane, the stability of the protecting group under a variety of reaction conditions, and the regeneration of the carbonyl group with Triton B in THF at room temperature is presented. The method provides a useful alternative for the protection of carbonyl compounds having acid-sensitive moieties.

The selective protection of the carbonyl group as *O*,*O*-acetals/ketals and its subsequent regeneration is an important transformation in synthetic organic chemistry. The deprotection is often achieved by aqueous acid hydrolysis, but in recent years several mild reagents/conditions have been reported to accomplish this reaction. These include $CeCl_3 \cdot 7H_2O$,[2] $FeCl_3$,[3] CAN,[4] Bi $(NO_3)_3 \cdot 5H_2O$,[5] $Ce(OTf)_3$,[6] Bi$(OTf)_3$,[7] $SmCl_3$/TMSCl,[8] I_2,[9] and F^-[10] for specially designed silylated ketals. However, considering the importance of this transformation in multistep organic synthesis, new protecting groups removable under complimentary conditions are still needed. As part of our endeavor to develop structurally simple synthetic substitutes for antimalarial drug artemisinin,[11] we have earlier reported a photooxygenation route for the synthesis of 1,2,4-trioxanes. Preparation of β-hydroxy-hydroperoxides by photooxygenation of suitably substituted

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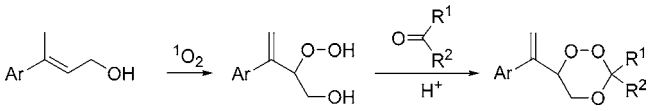
allylic alcohols and their acid-catalyzed condensation with aldehydes/ketones are the key steps of this method.[12,13] In fact, both of these steps can be accomplished in a single pot to furnish 1,2,4-trioxanes in good yields at 0 °C to room temperature (Scheme 1). The reaction of β-hydroxyhydroperoxides with unhindered ketones is fast and gives the corresponding trioxanes in good yields; the reaction with hindered ketones, e.g., comphor, is extremely slow and yields are poor.[14]

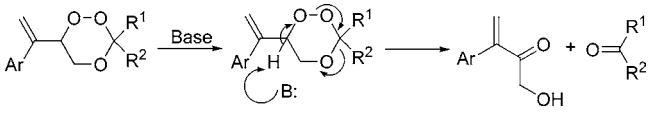
Scheme 1



The method is safe and has been used in our laboratory for the preparation of a large number of β-hydroxyhydroperoxides and 1,2,4-trioxanes on a multigram scale. Several trioxanes prepared by this method have shown promising antimalarial activity against multi-drug-resistant malaria in a mice model.[14] We have further explored the application of this methodology in chemistry and present herein an experimental protocol demonstrating the protection of the carbonyl group as 1,2,4-trioxane, the stability of the protecting group under the conditions of a variety of organic reactions, and the regeneration of the carbonyl group under basic conditions at ambient temperature.

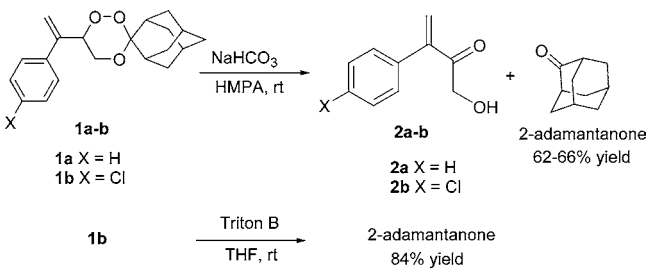
A unique feature of these trioxanes is the presence of a 1-substituted vinyl group at C-6 of the trioxane, which together with a peroxy group makes 6-H quite acidic; it appears at around δ 5.2 ppm in the ^{1}H NMR spectra of these trioxanes and at δ 5.0 ppm for the corresponding 1,3-dioxolanes. Similarly, in ^{13}C NMR spectra C-6 of these trioxanes and the corresponding 1,3-dioxolanes appears at $\sim\delta$ 80.5 and 76.9 ppm, respectively. In fact, during the course of this work it was observed that these trioxanes undergo a very facile cleavage under mild basic conditions to regenerate the carbonyl compounds and α,β-unsaturated keto alcohols (Scheme 2).

Scheme 2



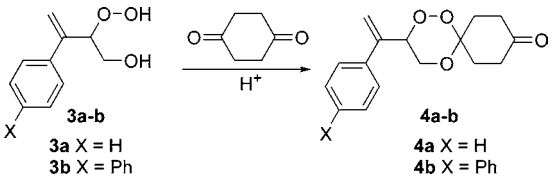
Thus the reaction of trioxane **1a** with $NaHCO_3$ in hexamethylphosphoramide (HMPA) at room temperature for 8 h furnished 2-adamantanone in 62% yield along with keto alcohol **2a** in 38% yield. Similar reaction of trioxane **1b** with $NaHCO_3$ furnished 2-adamantanone in 66% yield and keto-alcohol **2b** in 34% yield. Similar results were observed when trioxane **1b** was treated with *n*-butylamine or diisopropylamine in HMPA. A major solvent effect was observed in the reaction of **1a** with NaOMe. Whereas the reaction was complete in HMPA within 15 min, it took more than 8 h in methanol. After experimenting with several bases and solvents, Triton B in THF was found to be the most efficient system for the regeneration of the ketones. Thus the reaction of trioxane **1b** with Triton B in THF at room temperature was complete within 1 h and furnished 2-adamantanone in 84% yield (Scheme 3).[15]

Scheme 3



From these preliminary experiments it was clear that ketones could be protected as 1,2,4-trioxanes using easily accessible β-hydroxyhydroperoxides and again regenerated under basic conditions at ambient temperature. Having achieved this we examined the stability of 1,2,4-trioxane moiety under conditions of a variety of reactions, an essential requirement of a good protecting group. Toward this end we studied the chemistry of the carbonyl group of trioxanes **4a** and **4b**, easily accessible[16] by monoprotection of 1,4-cyclohexanedione with β-hydroxyhydroperoxides **3a,b** (Scheme 4).

Scheme 4



Trioxanes **4a** and **4b** on Reformatsky reaction with Zn/$BrCH_2CO_2Et$ in benzene furnished the β-hydroxyesters **5a**

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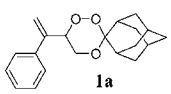
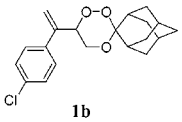
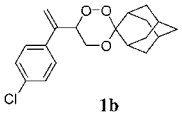
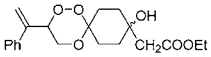
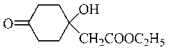
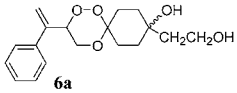
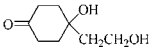
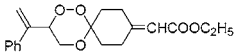
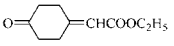
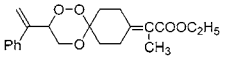
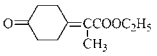
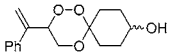
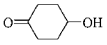
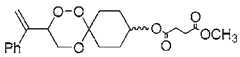
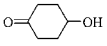
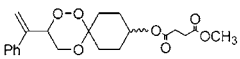
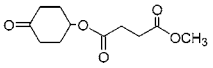
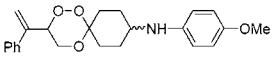
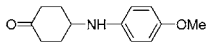
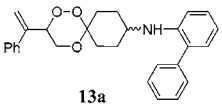
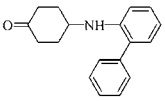
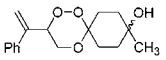
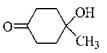
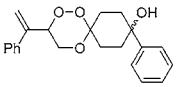
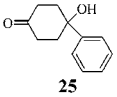
Table 1. Generation of Functionalized Ketones from 1,2,4-Trioxanes

Entry	Functionalized trioxanes	Reaction conditions	Product	Yield (%)
1	 **1a**	$NaHCO_3$, HMPA, rt, 8 h		62
2	 **1b**	$NaHCO_3$, HMPA, rt, 8 h		66
3	 **1b**	Triton B, THF, rt, 1 h		84
4	 **5a**	Triton B, THF, rt, 1 h	 **16**	84
5	 **6a**	Triton B, THF, rt, 1 h	 **17**	85
6	 **7a**	Triton B, THF, rt, 1 h	 **18**	86
7	 **8a**	Triton B, THF, rt, 1 h	 **19**	84
8	 **9**	Triton B, THF, rt, 1 h	 **20**	86
9	 **11**	Triton B, THF, rt, 1 h	 **20**	82
10	 **11**	*n*-butylamine, THF, 70°C, 10 h	 **21**	87
11	 **12a**	Triton B, THF, rt, 1 h	 **22**	85
12	 **13a**	Triton B, THF, rt, 1 h	 **23**	83
13	 **14a**	Triton B, THF, rt, 1 h	 **24**	81
14	 **15a**	Triton B, THF, rt, 1 h	 **25**	85

and **5b** in 83% and 88% yields, respectively, as mixtures of diastereomers that were separated by column chromatography. β-Hydroxyester **5a** on reduction with $LiAlH_4$ in dry diethyl ether at 0 °C furnished the diol **6a** in 72% yield. Trioxane **4a** on reaction with triethylphonacetate/NaH and triethylphosphon-2-propionate/NaH in dimethoxyethane furnished the Wittig products **7a** and **8a** in 93% and 83% yields, respectively. Trioxane **4b** under similar reaction conditions furnished **7b** and **8b** in 93% and 84% yields, respectively. These products were isolated as inseparable mixtures of geometrical isomers. Trioxane **4a** reacted smoothly with $NaBH_4$ in methanol to furnish the corresponding hydroxy derivative **9a** in 96% yield as inseparable mixture of diastereomers, which on reaction with succinic anhydride/Et_3N in CH_2Cl_2 furnished the corresponding hemisuccinate **10a** in 91% yield; **10a** on treatment with CH_2N_2 in ether furnished the corresponding methyl ester **11a**. Reductive amination of trioxane **4a** with 4-methoxyaniline and 2-aminobiphenyl in the presence of $NaBH(OAc)_3$ in CH_2Cl_2 furnished the amino-functionalized trioxanes **12a** and **13a** in 61% and 91% yields, respectively, as mixtures of diastereomers. Trioxane moiety was also found stable under the condition of Grignard reaction, though the yields of the products were modest. Thus trioxane **4a** reacted with MeMgBr and PhMgBr at 0 °C to furnish hydroxy derivatives **14a** and **15a** in 54% and 57% yields, respectively (Figure 1). Both of these products were mixtures of diastereomers that were separated by chromatography on silica gel. These experiments demonstrate that a variety of reactions of the carbonyl group can be accomplished without affecting the trioxane moiety.[17] Finally, several of these functionalized trioxanes were reacted with Triton B in THF at ambient temperature to give the corresponding 4-functionalized cyclohexanones in more than 80% yield (Table 1).

The functional groups such as β-hydroxyesters (entry 4) and α,β-unsaturated esters (entries 6 and 7) and amines (entries 11 and 12) were found stable under these conditions. The succinoyl group was hydrolyzed to furnish the 4-hydroxycyclohexanone (entry 9). However, the deprotection in this case could be achieved by heating with *n*-$BuNH_2$ in THF (entry 10).

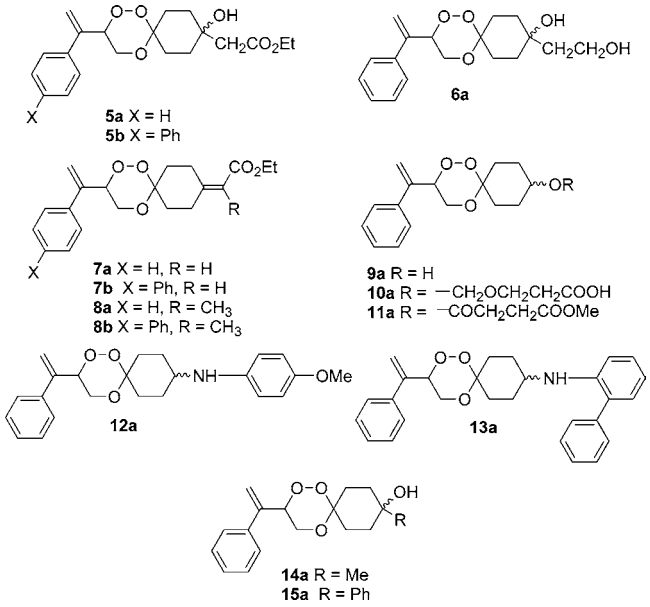


Figure 1. Derivatives of trioxanes **4a** and **4b**.

In conclusion, we have demonstrated that ketones can be protected as 1,2,4-trioxanes using easily accessible β-hydroxyhydroperoxides, that the trioxane moiety survives under conditions of a variety of organic reactions, and that the keto group can be regenerated in high yield under basic conditions at ambient temperature. Historically a ketal group has been commonly used for the protection of the carbonyl group. The trioxane as protective group is very similar to the ketal group as far its formation is concerned and can serve as a useful alternative protecting group for carbonyl compounds as it can be removed under mild basic conditions.[18,19]

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) **Typical Procedure for Regeneration of Ketones with Triton B/THF.** To a solution of the trioxane **1b** (0.10 g, 0.28 mmol) in THF (3 mL) was added Triton B (40% in methanol, 0.1 mL), and the mixture was stirred at room temperature for 1 h. Solvent was evaporated under vacuum, and the crude product was purified by column chromatography over silica gel using AcOEt/hexane (0.2:10) as eluant to furnish 2-adamantanone (0.036 g, 84% yield).

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(17) Some of these functionalized trioxanes have shown a high order of antimalarial activity: (a) Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 459. (b) Singh, C.; Malik, H.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2005,** *15*, 4484

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(19) During the course of our work on antimalarial 1,2,4-trioxanes, we have prepared a large number of β-hydroxyhydroperoxides and 1,2,4-trioxanes on a multigram scale. In our hands these compounds have behaved well, but the usual precautions for handling of peroxides are recommended.