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1,2,4-Trioxepanes: Redox-Cleavable Protection for Carbonyl Groups

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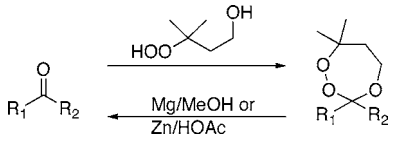
ABSTRACT

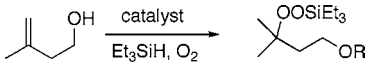


1,2,4-trioxepanes, readily prepared and easily handled derivatives of aldehydes and ketones, are stable to a variety of synthetic conditions and yet easily deblocked with Zn/HOAc or Mg/MeOH to regenerate the parent carbonyl. Trioxepanes may provide an alternative to 1,3-dithianes for acid-stable protection of carbonyl groups.

In the course of efforts directed toward synthesis of peroxide natural products, we recently investigated acetalization of 1,3-hydroperoxyalcohols. Although this known conversion proceeded readily,[1] the resulting 1,2,4-trioxepanes proved to be so acid-stable as to preclude deprotection under conditions compatible with the preservation of the peroxide group. This stability, while frustrating from the perspective of peroxide synthesis, was intriguing in the context of a new strategy for carbonyl protection. We now demonstrate the efficient conversion of aldehydes and ketones to 3,3-dialkyl-1,2,4-trioxepanes, the stability of these cyclic peroxyacetals toward a variety of synthetic conditions, and the regeneration of carbonyl compounds under mild reductive conditions.[2]

Our initial choice of a protection reagent was based upon a known reagent, 3-triethylsilylperoxy-3-methyl-1-butanol **1**, available via cobalt-mediated reductive oxygenation[3] of 3-methyl-3-buten-1-ol (Table 1). The use of a tertiary peroxide was expected to facilitate reagent synthesis and also to enhance the stability of both the reagent and the derived trioxepanes toward base-promoted fragmentation.[4] The desired reagent (**1**) was accompanied by variable amounts of the bissilylated analogue (**2**); the best results were obtained with the bulky diketonate $Co(thd)_2$.[5] Although pure samples of **1** are available via chromatography, the crude reaction

Table 1. Preparation of Reagent



catalyst	solvent	**1** (R = H)	**2** (R = $SiEt_3$)
	CH_2Cl_2	27%	25%
$Co(acac)_2$	EtOH	30−35%	5%
	$EtOH/CH_2Cl_2$	30%	5%
	$ClCH_2CH_2Cl$	50%	5%
$Co(thd)_2$	EtOH	40%	1−2%
	CH_2Cl_2	20%	18%

(1) Oh, C. H.; Kang, J. H. *Tetrahedron Lett.* **1998**, *39*, 2771. Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591. Adam, W.; Duran, N. *J. Chem. Soc., Chem. Commun.* **1972**, 789.

(2) We also briefly investigated the known reaction of carbonyls with 2-hydroperoxy-1-alkanols (Kerr, B.; McCullough, K. J. *J. Chem. Soc., Chem. Commun.* **1985**, 590. Subramanyam, V.; Brizuela, C. L.; Soloway, A. H. *J. Chem. Soc., Chem. Commun.* **1976**, 508. O'Neill, P. M.; Pugh, M.; Davies, J.; Ward, S. A.; Park, B. K. *Tetrahedron Lett.* **2001**, *42*, 4569), but the resulting 1,2,4-trioxanes were formed in lower yield and were less stable compared with the corresponding 1,2,4-trioxepanes.

(3) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573. Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595. Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525.

(4) Kropf, H., Nurnburg, W. In *Methods in Organic Chemistry: Organische Peroxo-Verbindungen*; Kropf, H., Ed.; George Thieme Verlag: Stuttgart, 1988; Vol. E13, p 1968.

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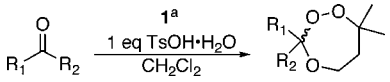
mixtures were used for subsequent carbonyl protections (vida infra) after filtration through a plug of silica gel.

Table 2 illustrates application of the peroxyalkanol for protection of carbonyls. Protection is achieved using only a slight excess of reagent **1** and without any need for drying agents or azeotropic distillation. The resulting trioxepanes are robust compounds completely stable to purification and handling. Trioxepane **5**, for example, could be refluxed in common solvents without decomposition; DSC revealed an exotherm from 184 to 206 °C. Several of the compounds displayed broadened or doubled ^{1}H or ^{13}C signals for atoms on or near the trioxepane ring; in the case of product **5**, coalescence of ^{1}H NMR signals was observed at approximately 50 °C.

Table 2. Synthesis of Trioxepanes

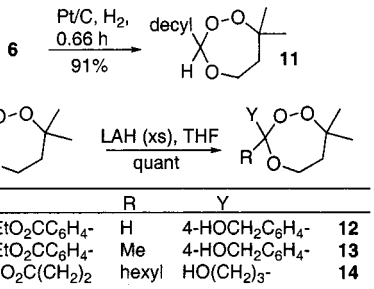


R_1	R_2	product (yield, %)
4-MeO_2CPh−	H	**3** (90)
4-EtO_2CPh−	Me	**4** (91)
Bu	Bu	**5** (>95)
9-decenyl	H	**6** (86)
$MeO_2C(CH_2)_2$−	hexyl	**7** (>90)
4-*tert*-butylcyclohexyl		**8** (89)
$MOMO(CH_2)_4CC$−	$(CH_2)_8CHCH_2$	**9** (82)
PhCHCH	H	**10** (83)

[a] See Table 1.

The trioxepanes proved to be quite stable toward reduction of other functional groups in the same molecule (Scheme 1).

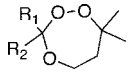
Scheme 1. Stability toward Reductive Transformations



	X	R	Y	
3	4-$EtO_2CC_6H_4$-	H	4-$HOCH_2C_6H_4$-	**12**
4	4-$EtO_2CC_6H_4$-	Me	4-$HOCH_2C_6H_4$-	**13**
7	$MeO_2C(CH_2)_2$	hexyl	$HO(CH_2)_3$-	**14**

Table 3 illustrates the stability of trioxepanes toward typical synthetic reagents. Trioxepane **6** was stable toward all investigated conditions except for alkyllithium. Compared with **6**, ketone-derived trioxepane **5** was somewhat more stable toward alkyllithium but considerably less stable toward a strong acid.

Table 3. Stability of Trioxepanes[a]

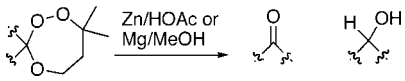


conditions	$t_{1/2}$, **6**	conditions	$t_{1/2}$, **6**
toluene, 110°	>24 h	Me_2NH (5 equiv), CH_2Cl_2	>24 h
Ph_3P (2 equiv)	>24 h	Et_3N, CuCl, hexyne	>24 h
$Pd(PPh_3)_4$	>24 h	NaH, DMSO, 0 °C	>24 h
$NaBH_4$(xs)	>24 h	*n*-BuLi (3 equiv), −78 °C	0.25 h
H_2CrO_4 (xs)	>24 h	10% aq HCl/THF (1:1)	>24 h
DDQ (xs)	>24 h	10% NaOH/MeOH (1:1)	>24 h
Et_3N, THF	>24 h	TsOH, MeOH	>24 h
conditions	**$t_{1/2}$, 5**	**conditions**	**$t_{1/2}$, 5**
KO*t*-Bu (xs) (THF or *t*-BuOH)	>24 h	*n*-BuLi (3 equiv), −78 °C	>0.5 h
		NaH (5 equiv) DMSO, 0 °C	>24 h
		10% aq HCl/THF (1:1)	4−6 h

[a] Unless indicated, stoichometric reagent was used at room temperature. Estimated half-lives based upon recovered trioxepane.

Deprotection of the trioxepanes is achieved with either Mg/MeOH or Zn/HOAc.[6] The former is the more powerful reagent; the latter proved to be superior in avoiding over-reduction during deprotection to aldehydes or benzylic ketones (Table 4). Attempted deprotection of styrenyl trioxepane **10** (not shown) resulted in products derived from saturation of the alkene side chain.

Table 4. Regeneration of Carbonyl



trioxepane	conditions	carbonyl	alcohol
3	Zn	85%	
4	Zn	86%	
4	Mg		quant
5	Mg	85%[a]	
6	Zn	85%	
7	Mg	82%	
8	Zn	50%	
8	Mg	40−45%	
9	Mg	80%	

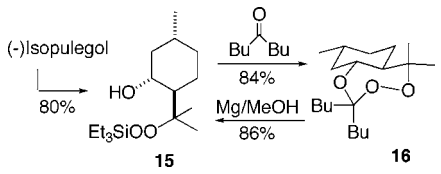
[a] Isolated yield of volatile product. GC yield ≥95%.

Trioxepane **8** was surprisingly stable; reduction with Zn/HOAc required heating to 70 °C and addition of a trace of concentrated HCl. This trioxepane also failed to react with Me_2CuLi, SmI_2, or sodium thiolates, while use of Na/NH_3 or Li/NH_3 resulted in over-reduction. Reaction with ferrous

(5) O'Neill, P. M.; Hindley, S.; Pugh, M. D.; Davies, J.; Bray, P. G.; Park, B. K.; Kapu, D. S.; Ward, S. A.; Stocks, P. A. *Tetrahedron Lett.* **2003**, *44*, 8135. thd = tetramethylheptadionate.

(6) Dai, P.; Dussault, P. H.; Trullinger, T., K. *J. Org. Chem.* **2004**, *69*, 2851.

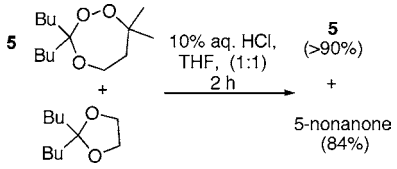
Scheme 2. Protection with a Terpene-Derived 1,3-Peroxyalkanol



salts resulted in rapid decomposition to furnish mixtures in which the desired ketone was a minor component.

Scheme 2 illustrates the use of a 3-peroxyalkanol based upon a chiral, cyclic, backbone. Reductive dioxygenation of isopulegol proceeds efficiently in the presence of either $Co(acac)_2$ or $Co(thd)_2$ to furnish peroxide **15** (Scheme 3).

Scheme 3. Selective Deprotection of 1,3-Dioxolane



This reagent undergoes reaction with 5-nonanone to furnish trioxepane **16**, which displayed no evidence for conformational isomerism. Reduction of **16** occurs readily to regenerate nonanone in high yield. The ease of preparation and handling may render reagent **15** superior to **1** for some applications.

Finally, we compared deprotection of a 1,2,4-trioxepane with a similarly substituted 2,2-dioxolane (Scheme 3). Trioxepane **5** was almost completely recovered under conditions leading to complete deprotection of 2,2-dibutyl-1,3-dioxolane.

In summary, we have demonstrated that 1,2,4-trioxepanes, readily available derivatives of carbonyl compounds, are stable toward a number of common conditions and yet easily deblocked with Zn/HOAc or similar conditions. Protection of carbonyls as 1,2,4-trioxepanes may offer a strategically similar but tactically complementary alternative to the use of 1,3-dithianes.

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Supporting Information Available: Experimental procedures and characterization data for **1** and **3**−**16** and ^1H and ^{13}C spectra for 2,2-dibutyl-1,3-dioxolane. This material is available free of charge via the Internet at http://pubs.acs.org.

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