Protective Groups in Organic Synthesis, Third Edition. Theodora W. Greene, Peter G.M. Wuts

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PROTECTION FOR THE CARBONYL GROUP

During a synthetic sequence, a carbonyl group may have to be protected against attack by various reagents such as strong or moderately strong nucleophiles, including organometallic reagents; acidic, basic, catalytic, or hydride reducing agents; and some oxidants. Because of the order of reactivity of the carbonyl group [e.g., aldehydes (aliphatic > aromatic) > acyclic ketones and cyclohexanones > cyclopentanones > α,β-unsaturated ketones or α,α-disubstituted ketones >> aromatic ketones], it may be possible to protect a reactive carbonyl group selectively in the presence of a less reactive one. In keto steroids, the order of reactivity to ketalization is C_3 or Δ^4-$C_3 > C_{17} > C_{12} > C_{20} > C_{17,21\text{-}(OH)_2}C_{20} > C_{11}$.[1] A review discusses the relative rates of hydrolysis of acetals, ketals, and ortho esters.[2]

The most useful protective groups are the acyclic and cyclic acetals or ketals, and the acyclic or cyclic thio acetals or ketals. The protective group is introduced by treating the carbonyl compound in the presence of acid with an alcohol, diol, thiol, or dithiol. Cyclic and acyclic acetals and ketals are stable to aqueous and nonaqueous bases, to nucleophiles including organometallic reagents, and to hydride reduction. A 1,3-dithiane or 1,3-dithiolane, prepared to protect an aldehyde, is converted by strong base to an anion. The oxygen derivatives are stable to neutral and basic catalytic reduction and to reduction by sodium in ammonia. Although the sulfur analogues poison hydrogenation catalysts, they can be reduced by Raney Ni and by sodium/ammonia. The oxygen derivatives are stable to most oxidants; the sulfur derivatives are cleaved by a wide range of oxidants. The oxygen, but not the sulfur, analogues are readily cleaved by acidic hydrolysis. Sulfur analogues are stable to those conditions. The properties of oxygen and sulfur derivatives are combined in the cyclic 1,3-oxathianes and 1,3-oxathiolanes.

The carbonyl group forms a number of other very stable derivatives that are less used as protective groups because of the greater difficulty involved in their removal. Such derivatives include cyanohydrins, hydrazones, imines, oximes, and semicarbazones. Enol ethers are used to protect one carbonyl group in a 1,2- or 1,3-dicarbonyl compound.

Although IUPAC no longer uses the term "ketal," we have retained it to indicate compounds formed from ketones.

Derivatives of carbonyl compounds that have been used as protective groups in synthetic schemes are described in this chapter; some of the more important protective groups are listed in Reactivity Chart 5.[3–5]

1. H. J. E. Loewenthal, *Tetrahedron*, **6**, 269 (1959).
2. E. H. Cordes and H. G. Bull, *Chem. Rev.*, **74**, 581–603 (1974).
3. See also H. J. E. Loewenthal, "Protection of Aldehydes and Ketones," in *Protective Groups in Organic Chemistry*, J. F. W. McOmie, Ed., Plenum, New York and London, 1973, pp. 323–402.
4. J. F. W. Keana, in *Steroid Reactions*, C. Djerassi, Ed., Holden-Day, San Francisco, 1963, pp. 1–66, 83–87.
5. P. J. Kocienski, *Protecting Groups*, Thieme Medical Publishers, New York, 1994, Chapter 5.

ACETALS AND KETALS

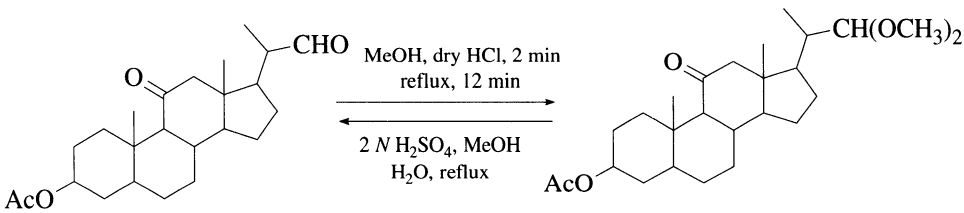
Acyclic Acetals and Ketals

Methods similar to those used to form and cleave dimethyl acetal and ketal derivatives can be used for other dialkyl acetals and ketals.[1]

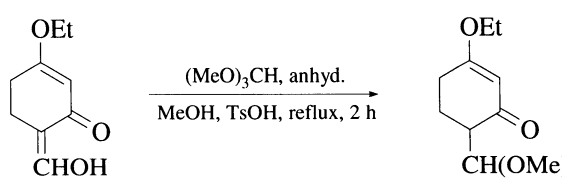
Dimethyl Acetals and Ketals: $R_2C(OCH_3)_2$ (Chart 5)

Formation

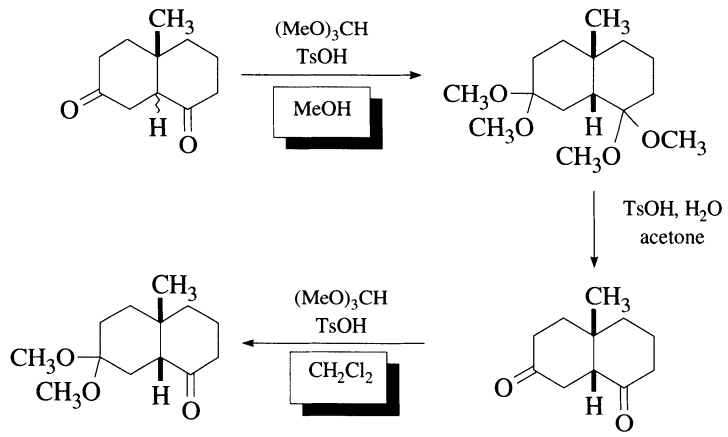
1. MeOH, dry HCl, 2 min.[2]



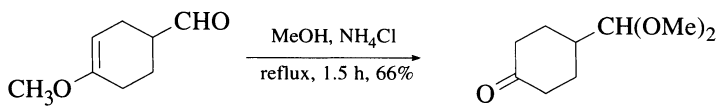
2. DCC–$SnCl_4$; ROH, $(CO_2H)_2$, 90% yield.[3]
3. $CH(OMe)_3$, $MeNO_2$, CF_3COOH, reflux, 4 h, 81–93% yield.[4] This procedure was reported to be particularly effective for the preparation of ketals of diaryl ketones.
4. MeOH, $LaCl_3$, $(MeO)_3CH$, 25°, 10 min, 80–100% yield.[5] Dimethyl acetals can be prepared efficiently under neutral conditions by catalysis with lanthanoid halides, but the results of the reaction with ketones are unpredictable.
5. Me_3SiOCH_3, Me_3SiOTf, CH_2Cl_2, −78°, 86% yield.[6] The use of TMSOFs to catalyze this transformation has also been demonstrated.[7] A norbornyl ketone was not ketalized under these conditions.
6. $(MeO)_3CH$, anhydrous MeOH, TsOH, reflux, 2 h.[8] Diethyl ketals have been prepared under similar conditions (EtOH, TsOH, 0–23°, 15 min to 6 h, 80–95% yield) in the presence of molecular sieves to shift the equilibrium by adsorbing water.[9] Amberlyst-15[10] or graphite bisulfate[11] and $(EtO)_3CH$ have been used to prepare diethyl ketals.



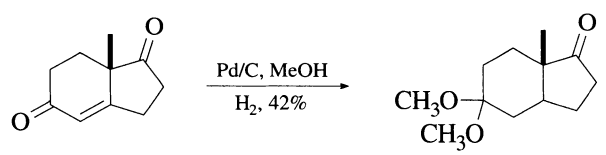
In the following example, a mixture of the *cis*- and *trans*-decalones is converted completely to the *cis*-isomer—in general, the thermodynamically less favored isomer:[12]



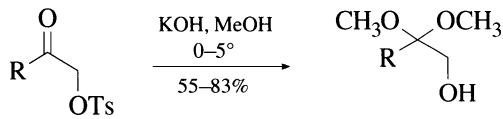
7. MeOH, $(MeO)_4Si$, dry HCl, 25°, 3 days.[13]
8. MeOH, acidic ion-exchange resin, 7–86% yield.[14]
9. $(MeO)_3CH$, Montmorillonite Clay K-10, 5 min to 15 h, > 90% yield.[15] Diethyl ketals have been prepared in satisfactory yield by reaction of the carbonyl compound and ethanol in the presence of Montmorillonite Clay.[16] Kaolinitic clay has also been used.[17]
10. MeOH, NH_4Cl, reflux, 1.5 h, 66% yield.[18]



11. Hydrogenation of enones in MeOH with Pd/C resulted in acetal formation. When ethylene glycol/THF is used as solvent, the related dioxolane is formed in 86% yield.[19]



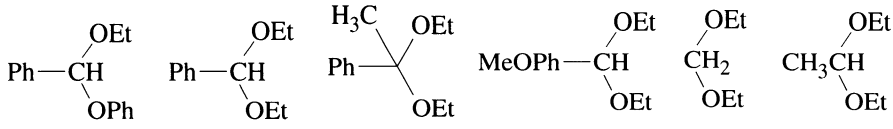
12. MeOH, $PhSO_2NHOH$, 25°, 15 min, 75–85% yield.[20]
13. Me_2SO_4, 2 *N* NaOH, MeOH, H_2O, reflux, 30 min, 85% yield.[21] In this case, the hemiacetal of phthaldehyde is alkylated with methyl sulfate; such use is probably restricted to cases that are stable to the strongly basic conditions.
14. Allyl bromide, $Sb(OEt)_3$, 80°, 2–6 h, 85–98% yield.[22] This method is chemoselective for aldehydes in the presence of ketones.
15. MeOH, Ce^+-exchanged Montmorillonite Clay, 25°, 0.5–12 h, 18–99% yield. Aldehydes can be selectively protected in the presence of ketones.[23]

16. $Sc(OTf)_3$, $HC(OCH_3)_3$ (TMOF), toluene, 0°, 0.5 h, 92% yield.[24]
17. $CeCl_3 \cdot 7\ H_2O$, MeOH, TMOF.[25]
18. 

Ref. 26

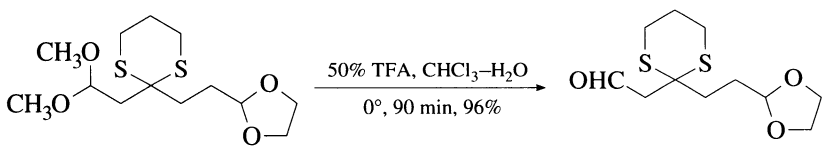
Cleavage

The acid-catalyzed cleavage of acetals and ketals is greatly influenced by the substitution on the acetal or ketal carbon atom. The following values for k_H^+ illustrate the magnitude of the effect:[27]

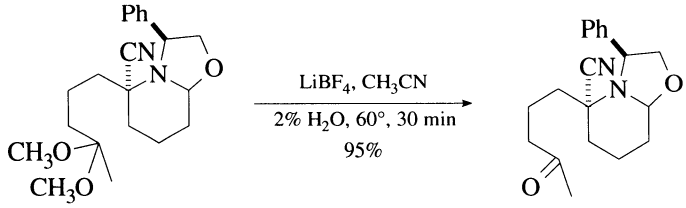


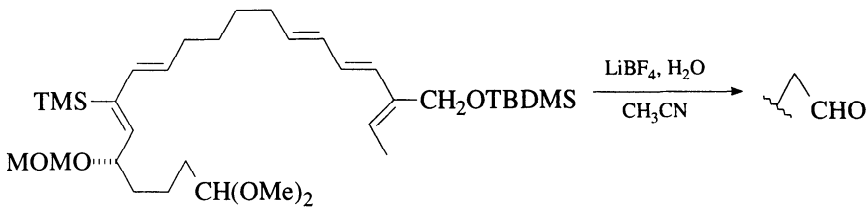
41	160	6×10^3	5×10^3	1.5×10^{-4}	1.6

1. 50% CF_3COOH, $CHCl_3$, H_2O, 0°, 90 min, 96% yield.[28]

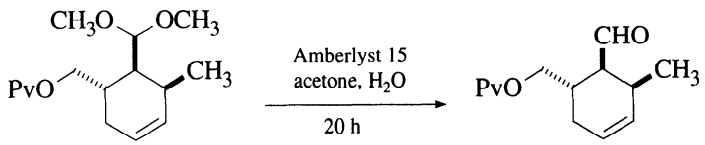


2. TsOH, acetone.[29]
3. SiO_2 and oxalic or sulfuric acid, 0.5–24 h, 90–95% yield.[30]
4. Me_3SiI, CH_2Cl_2, 25°, 15 min, 85–95% yield.[31] Under these cleavage conditions, 1,3-dithiolanes, alkyl and trimethylsilyl enol ethers, and enol acetates are stable. 1,3-Dioxolanes give complex mixtures. Alcohols, epoxides, trityl, *t*-butyl, and benzyl ethers and esters are reactive. Most other ethers and esters, amines, amides, ketones, olefins, acetylenes, and halides are expected to be stable.
5. $TiCl_4$, LiI, Et_2O, rt, 3 h, 75–90% yield.[32]
6. $LiBF_4$, wet CH_3CN, 96% yield. Unsubstituted 1,3-dioxolanes are hydrolyzed only slowly, but substituted dioxolanes are completely stable.[33] This reagent proved excellent for hydrolysis of the dimethyl ketal in the presence of the acid-sensitive oxazolidine[34] and polyene.[35]

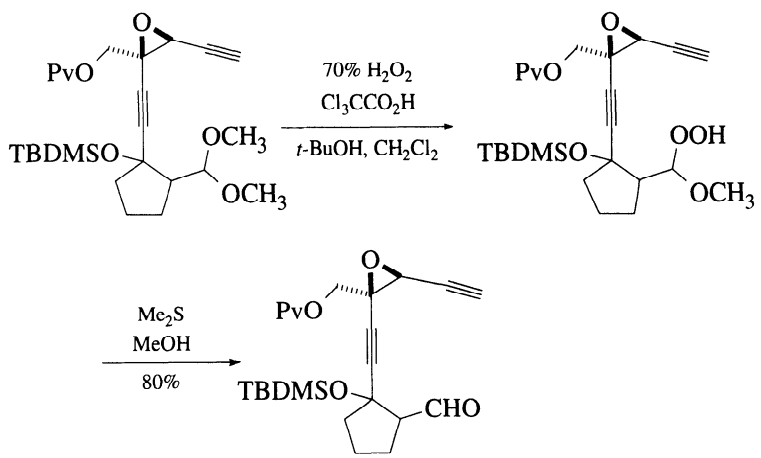




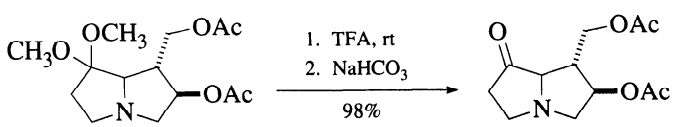
7. HCO_2H, pentane, 1 h, 20°.[36] Under these conditions, a β,γ-double bond does not migrate into conjugation.
8. Amberlyst-15, acetone, H_2O, 20 h.[37] Aldehyde acetals conjugated with electron-withdrawing groups tend to be slow to hydrolyze. The use of HCl/THF or PPTS/acetone in the following case was slow and caused considerable isomerization. A TBDMS group is stable under these conditions.[38]



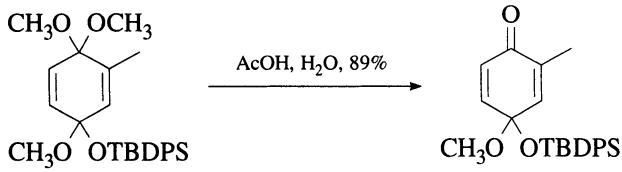
9. 70% H_2O_2, Cl_3CCO_2H, CH_2Cl_2, *t*-BuOH; dimethyl sulfide, 80% yield.[39] Other methods cleaved the epoxide. This method also cleaves the THP and trityl groups.



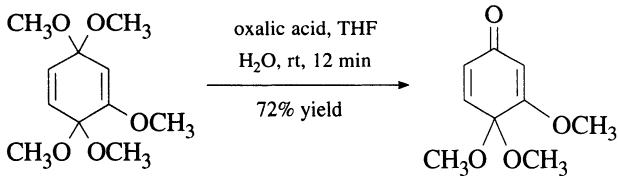
10. CF_3COOH, rt; $NaHCO_3$, 98% yield.[40]



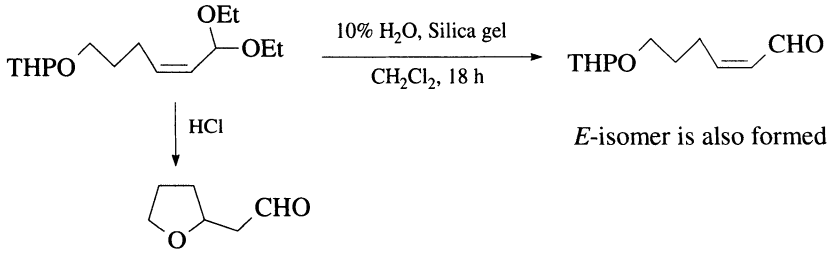
11. AcOH, H_2O, 89% yield.[41] A factor of 400 in the relative rate of hydrolysis is attributed to a conformational effect in which the lone pair on oxygen in the silyl ketals does not overlap with the incipient cation during hydrolysis.



12. Oxalic acid, THF, H_2O, rt, 12 min, 72% yield.[42]

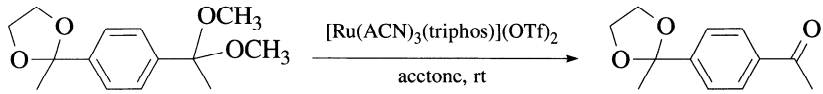


13. $BF_3 \cdot Et_2O$, $Et_4N^+I^-$, $CHCl_3$, 69–82% yield.[43]
14. 10% H_2O, silica gel, CH_2Cl_2, 18 h, rt.[44] In this example, attempts to use HCl resulted in THP cleavage followed by cyclization to form a furan.

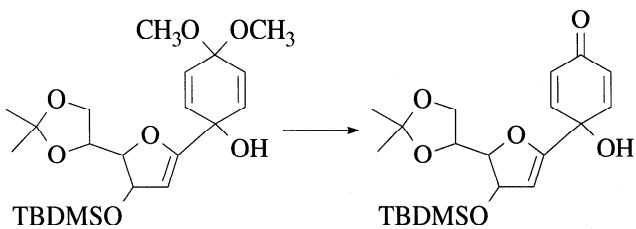


15. DMSO, H_2O, dioxane, reflux, 12 h, 65–99% yield.[45] These conditions cleave a dimethyl ketal in the presence of a *t*-butyldimethylsilyl ether.
16. SiH_2I_2, CH_3CN, −42°, 3–40 min, 90–100% yield. Other ketals are also cleaved under these conditions.[46]
17. The direct conversion of dimethyl ketals to other carbonyl protected derivatives is also possible. Treatment of a dimethyl ketal with $HSCH_2CH_2SH$, $TeCl_4$, $ClCH_2CH_2Cl$ gives the dithiolane in 99% yield.[47]
18. $Mo_2(acac)_2$, CH_3CN, rt, 70–91% yield.[48]
19. Acetyl chloride, $SmCl_3$, pentane, rt, 15 min–24 h, 89–96% yield.[49] The efficiency of dioxolane cleavage is very poor under these conditions.
20. $SnCl_2 \cdot 2H_2O$, C_{60}, CH_2Cl_2, 2 h, 84–99% yield.[50] The presence of the buckyball improves the yield.

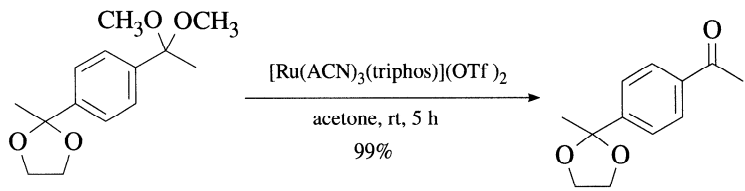
21. $Ru(CH_3CN)_3(triphos)(OTf)_2$, acetone, rt, 99% yield.[51] Nonphenolic THP groups and dioxolane ketals are stable.



22. DDQ, MeCN, H_2O, rt, 75–92% yield.[52,53] It was shown that this reaction does not proceed through acid catalysis by the hydroquinone.
23. HM-Zeolite, H_2O, PhMe, reflux, 9 h, 89% yield.[54]
24. $ISiCl_3$, rt, 20–30 min, 74–95% yield.[55] Esters and phenolic methyl ethers are reported to survive, whereas with the related TMSI they are cleaved.
25. $ZnCl_2$, Me_2S, AcCl, THF, 89% yield.[56] A dimethyl acetal is chemoselectively cleaved in the presence of a dioxolane acetal.



26. $Na_2S_2O_4$, THF, H_2O, 90% yield.[57]
27. Montmorillonite K10, CH_2Cl_2, rt or reflux, 92–100% yield. 1,3-Dioxanes and 1,3-dioxolanes are cleaved similarly.[58]
28. Me_2BBr, CH_2Cl_2, −78°, 45 min, 100% yield. These conditions were chosen when conventional acid-catalyzed hydrolysis resulted in aldehyde epimerization during a kainic acid synthesis.[59]
29. $[Ru(ACN)_3(triphos)](OTf)_2$, acetone, rt, 5 h.[51] Dioxolanes are also cleaved when not conjugated, as in the following case:



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Diisopropyl Acetal and Ketals: $(i\text{-PrO})_2CHR$

Formation

$CH(Oi\text{-Pr})_3$, CSA, IPA, removal of MeOH by distillation, 3 h, 68–92% yield.[1,2]

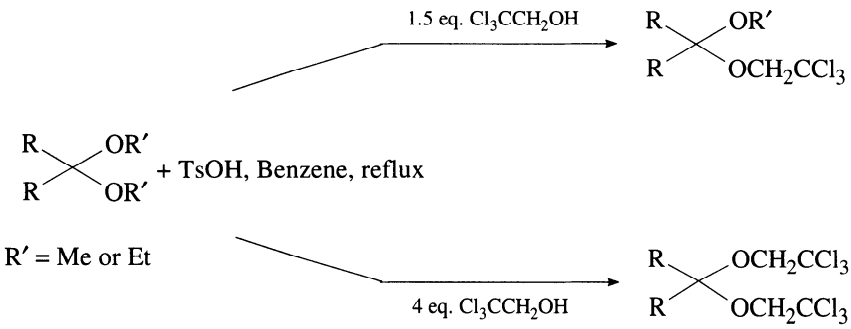
Cleavage

Formic acid, THF, H_2O, 20°, 100% yield. This acetal was chosen to prevent conjugation of a double bond during hydrolysis, which occurred when the corresponding dimethyl acetal was hydrolyzed. [1]

1. J. Sandri and J. Viala, *Synthesis*, 271 (1995).
2. A. Pommier, J.-M. Pons, and P. J. Kocienski, *J. Org. Chem.*, **60**, 7334 (1995).

Bis(2,2,2-trichloroethyl) Acetals and Ketals: $R_2C(OCH_2CCl_3)_2$ (Chart 5)

Formation[1]



It is more efficient to prepare this ketal by an exchange reaction with the dimethyl or diethyl ketal than directly from the carbonyl compound. Hydrolysis can also be effected by acid catalysis.

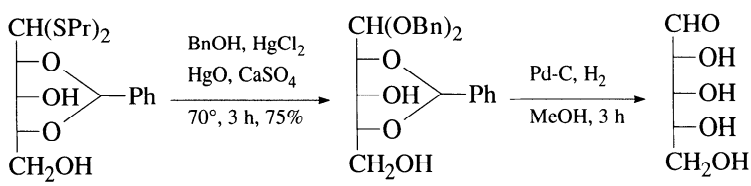
Cleavage

1. Zn/EtOAc or THF, reflux, 3–12 h, 40–100% yield.[1]

1. J. L. Isidor and R. M. Carlson, *J. Org. Chem.*, **38**, 554 (1973).

Dibenzyl Acetals and Ketals: $R_2C(OCH_2Ph)_2$

Formation/Cleavage[1]



1. J. H. Jordaan and W. J. Serfontein, *J. Org. Chem.*, **28**, 1395 (1963).

Bis(2-nitrobenzyl) Acetals and Ketals: $R_2C(OCH_2C_6H_4\text{–}2\text{-}NO_2)_2$

Formation

$2\text{-}NO_2C_6H_4CH_2OSiMe_3$, Me_3SiOTf, $-78°$, 78–95% yield.[1]

Cleavage

Photolysis at 350 nm, 85–95% yield.[1]

1. D. Gravel, S. Murray, and G. Ladouceur, *J. Chem. Soc., Chem. Commun.*, 1828 (1985).

Diacetyl Acetals and Ketals: $R_2C(OAc)_2$

Formation

1. Ac_2O, 1 drop concd. H_2SO_4, 20°, 1 h, 95% yield.[1]
2. Ac_2O, $ZnCl_2$.[2]
3. Ac_2O, $FeCl_3$, rt, < 30 min, 60–93% yield.[3] These conditions selectively protect an aldehyde in the presence of a ketone.[4] This combination also converts *t*-butyldimethylsilyl (TBDMS) ethers to acetates.
4. Ac_2O, PCl_3, 20°, 1–24 h, 30–90% yield.[5] Aromatic aldehydes bearing electron-withdrawing groups tend to give low yields under these conditions.
5. Ac_2O, Nafion H, 50–99% yield.[6]
6. Ac_2O, Expansive Graphite, rt, 0.3–6 h, 65–98% yield.[7]
7. Ac_2O, β-Zeolite, 60°, 1.5–5 h, 51–95% yield.[8]
8. Ac_2O, Environcat EPZG, 60–65°, 1.5–8.5 h, 69–99% yield.[9]
9. Ac_2O, HY-Zeolite, rt, CCl_4 or no solvent, 86–95% yield.[10]
10. Ac_2O, I_2, rt, 30 min, 70–99% yield.[11]

Cleavage

1. NaOH or K_2CO_3, THF, H_2O or MeOH.[3] This protective group is stable to MeOH (18 h); 10% HCl (MeOH, 30 min); 10% Na_2CO_3 (H_2O, Et_2O, 70 min); and $NaHCO_3$ (THF, H_2O, 4 h).
2. Alumina, 35°, 30–40 sec, 88–98% yield.[12]
3. Potassium 3-dimethylaminophenoxide, THF, 0°, 10 min, 92–98% yield. [13]
4. Expansive Graphite, CH_2Cl_2 or benzene, reflux, 10–30 min, 95–99% yield.[14]
5. CAN, Silica gel, CH_2Cl_2, 90–95% yield.[15]
6. Montmorillonite Clay K-10 or KSF, CH_2Cl_2, reflux, 86–98% yield.[16]
7. The use of enzymes for the hydrolysis of acylals is effective, and in the case of racemic derivatives some enantioenrichment of the aldehyde is possible.[17]

1. M. Tomita, T. Kikuchi, K. Bessho, T. Hori, and Y. Inubushi, *Chem. Pharm. Bull.*, **11**, 1484 (1963).
2. I. Scriabine, *Bull. Soc. Chim. Fr.*, 1194 (1961) .
3. K. S. Kochhar, B. S. Bal, R. P. Deshpande, S. N. Rajadhyaksha, and H. W. Pinnick, *J. Org. Chem.*, **48**, 1765 (1983).

4. J. Kula, *Synth. Commun.*, **16**, 833 (1986).
5. J. K. Michie and J. A. Miller, *Synthesis*, 824 (1981).
6. G. A. Olah and A. K. Mehrotra, *Synthesis*, 962 (1982).
7. T.-S. Jin, G.-Y. Du, Z.-H. Zhang, and T.-S. Li, *Synth. Commun.*, **27**, 2261 (1997).
8. P. Kumar, V. R. Hedge, and J. T. P. Kumar, *Tetrahedron Lett.*, **36**, 601 (1995).
9. B. P. Bandgar, N. P. Mahajan, D. P. Mulay, J. L. Thote, and P. P. Wadgaonkar, *J. Chem. Res., Synop.*, 470 (1995).
10. C. Pereira, B. Gigante, M. J. Marcelo-Curto, H. Carreyre, G. Pérot, and M. Guisnet, *Synthesis*, 1077 (1995).
11. N. Deka, D. J. Kalita, R. Borah, and J. C. Sarma, *J. Org. Chem.*, **62**, 1563 (1997).
12. R. S. Varma, A. K. Chatterjee, and M. Varma, *Tetrahedron Lett.*, **34**, 3207 (1993).
13. Y.-Y. Ku, R. Patel, and D. Sawick, *Tetrahedron Lett.*, **34**, 8037 (1993).
14. T.-S. Jin, Y.-R. Ma, Z.-H. Zhang, and T.-S. Li, *Synth. Commun.*, **27**, 3379 (1997).
15. P. Cotelle and J.-P. Catteau, *Tetrahedron Lett.*, **33**, 3855 (1992).
16. T.-S. Li, Z.-H. Zhang, and C.-G. Fu, *Tetrahedron Lett.*, **38**, 3285 (1997).
17. Y. S. Angelis and I. Smonou, *Tetrahedron Lett.*, **38**, 8109 (1997).

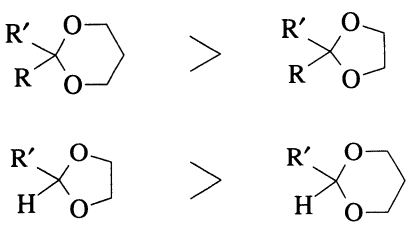
Cyclic Acetals and Ketals

Kinetic studies of acetal/ketal formation from cyclohexanone, and hydrolysis (3×10^{-3} *N* HCl/dioxane-H_2O, 20°), indicate the following orders of reactivity:[1]

Formation

$HOCH_2C(CH_3)_2CH_2OH > HO(CH_2)_2OH > HO(CH_2)_3OH$

Cleavage

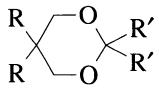


The relative rates of acid-catalyzed hydrolysis of some dioxolanes [dioxolane: aq. HCl (1:1)] are as follows: 2,2-dimethyldioxolane: 2-methyldioxolane: dioxolane, 50,000:5,000:1.[2]

A review[3] discusses the condensation of aldehydes and ketones with glycerol to give 1,3-dioxanes and 1,3-dioxolanes. The chemistry of *O*/*O* and *O*/*S* acetals has been reviewed,[4] and a recent monograph discusses this area of protective groups in a didactic sense.[5]

1. M. S. Newman and R. J. Harper, *J. Am. Chem. Soc.*, **80**, 6350 (1958); S. W. Smith and M. S. Newman, *J. Am. Chem. Soc.*, **90**, 1249, 1253 (1968).
2. P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.*, **15**, 871 (1961).
3. A. J. Showler and P. A. Darley, *Chem. Rev.*, **67**, 427–440 (1967).
4. H. Hagemann and D. Klamann, Eds. *O/O-und O/S-Acetale* [*Methoden der Organischen Chemie*, Houben-Weyl)] 4th ed., G. Thieme, Stuttgart, 1991, Band E 14a/1.
5. P. J. Kocienski, "Carbonyl Protecting Groups," In *Protecting Groups*, Thieme Medical Publishers, New York, 1994, Chapter 5.

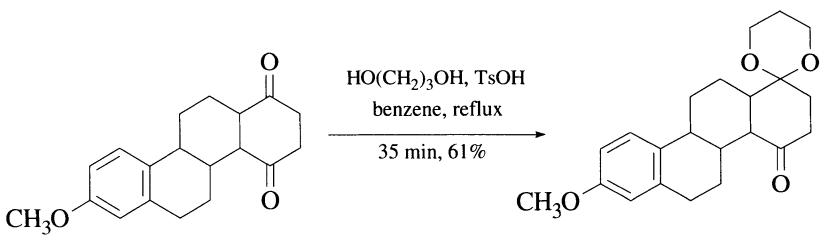
1,3-Dioxanes (Chart 5):



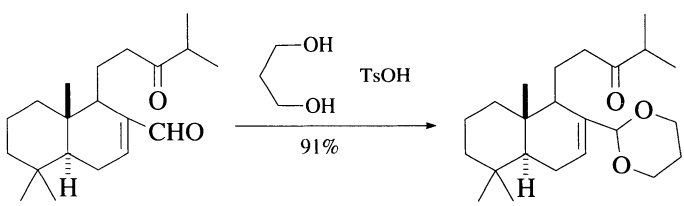
R = H, CH_3

Formation

1. $HO(CH_2)_3OH$, TsOH, benzene, reflux.[1–3]



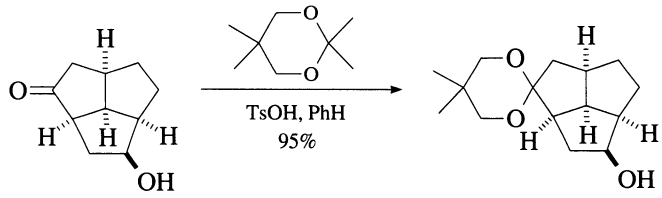
Ref. 1



Ref. 2

In the first example, selective protection was more successful with 1,3-propanediol than with ethylene glycol.[1]

2. 1,3-Propanediol, THF, Amberlyst-15, 5 min, 50–70% yield.[4] This method is also effective for the preparation of 1,3-dioxolanes.
3. TMSCl, $SmCl_3$, THF, 71–99% yield. Ketals are cleaved faster than acetals.[5]
4. $HOCH_2C(CH_3)_2CH_2OH$, $Sc(NTf_2)_3$, toluene, 0°, 3 h, 87–92% yield.[6]

5. 

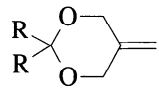
Other methods for ketalization met with failure.[7]

6. $HOCH_2C(CH_3)_2CH_2OH$, *N*-4-methoxybenzyl-2-cyanopyridinium hexafluoroantimonate, toluene, reflux, 1.5–3.7 h, 85–99% yield.[8]
7. $TMSOCH_2C(CH_3)_2CH_2OTMS$, TMSOTf, Pyr, 75% yield.[9]
8. $HOCH_2CH_2CH_2OH$, $Ru(CH_3CN)_3(triphos)(OTf)_2$, 94–99% yield.[10]
9. $HOCH_2C(CH_3)_2CH_2OH$, sulfated Zirconia, benzene, reflux, 88–97% yield.[11]
10. $HOCH_2C(CH_3)_2CH_2OH$, Yittria–Zirconia, rt, $CHCl_3$, 75–96% yield.[12]

Cleavage

The section on the cleavage of 1,3-dioxolanes should be consulted, since a majority of the methods available are applicable to 1,3-dioxanes as well.

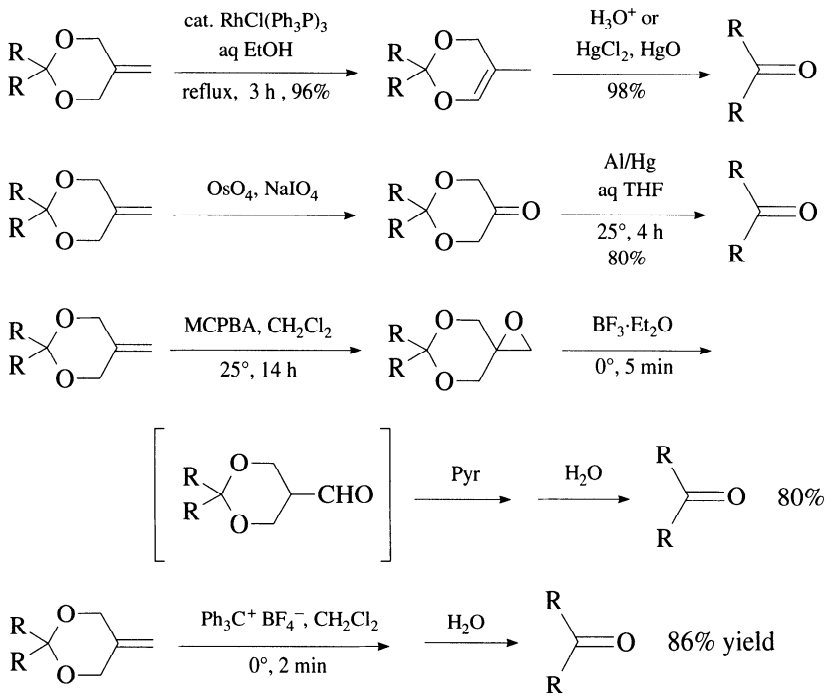
1. J. E. Cole, W. S. Johnson, P. A. Robins, and J. Walker, *J. Chem. Soc.*, 244 (1962).
2. H. Okawara, H. Nakai, and M. Ohno, *Tetrahedron Lett.*, **23**, 1087 (1982).
3. For examples of the use of the related 4,4-dimethyl-1,3-dioxane, see E. Piers, J. Banville, C. K. Lau, and I. Nagakura, *Can. J. Chem.*, **60**, 2965 (1982); M. A. Avery, C. Jennings-White, and W. K. M. Chong, *Tetrahedron Lett.*, **28**, 4629 (1987).
4. A. E. Dann, J. B. Davis, and M. J. Nagler, *J. Chem. Soc., Perkin Trans. 1*, 158 (1979).
5. Y. Ukaji, N. Koumoto, and T. Fujisawa, *Chem. Lett.*, 1623 (1989).
6. K. Ishihara, Y. Karumi, M. Kubota, and H.Yamamoto, *Synlett*, 839 (1996).
7. L. A. Paquette and S. Borrelly, *J. Org. Chem.*, **60**, 6912 (1995).
8. S.-B. Lee, S.-D. Lee, T. Takata, and T. Endo, *Synthesis*, 368 (1991).
9. C. K. F. Chiu, L. N. Mander, A. D. Stuart, and A. C. Willis, *Aust. J. Chem.*, **45**, 227 (1992).
10. S. Ma and L. M. Venanzi, *Synlett*, 751 (1993).
11. A. Sakar, O. S. Yemul, B. P. Bandgar, N. B. Gaikwad, and P. P. Wadgaonkar, *Org. Prep. Proced. Int.*, **28**, 613 (1996).
12. G. C. G. Pals, A. Keshavaraja, K. Saravanan, and P. Kumar, *J. Chem. Res., Synop.*, 426 (1996).

5-Methylene-1,3-dioxane (Chart 5): 

Formation[1]

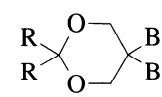
1. $CH_2{=}C(CH_2OH)_2$, TsOH, benzene, reflux, 90% yield.

Cleavage[1]



The rhodium-catalyzed isomerization can also be carried out with the chiral catalyst, $Ru_2Cl_4(diop)_3$ (H_2, 20–80°, 1–6 h, 47–90% yield). In this case, optically enriched enol ethers are obtained.[2]

1. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 3775 (1975).
2. H. Frauenrath and M. Kaulard, *Synlett*, 517 (1994).

5,5-Dibromo-1,3-dioxane (Chart 5): 

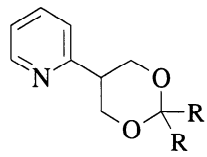
Formation

$Br_2C(CH_2OH)_2$, TsOH, benzene, heat for several hours, 84–94% yield.[1]

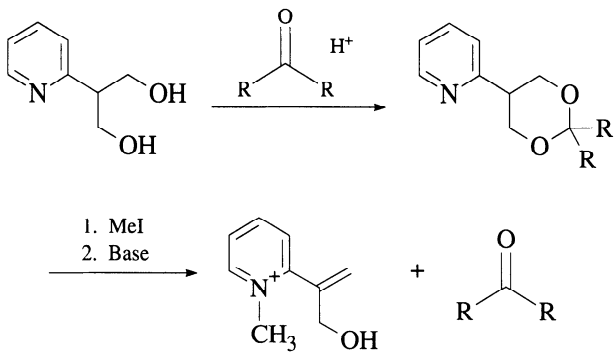
Cleavage

Zn–Ag, THF, AcOH, 25°, 1 h, ~90% yield.[1]

1. E. J. Corey, E. J. Trybulski, and J. W. Suggs, *Tetrahedron Lett.*, 4577 (1976).

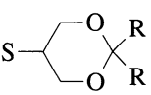
5-(2′-Pyridyl)-1,3-dioxane: 

Formation/Cleavage[1]



This group is stable to 0.1 *M* HCl.

1. A. R. Katritzky, W.-Q. Fan, and Q.-L. Li, *Tetrahedron Lett.*, **28**, 1195 (1987).

5-Trimethylsilyl-1,3-dioxane: 

Formation

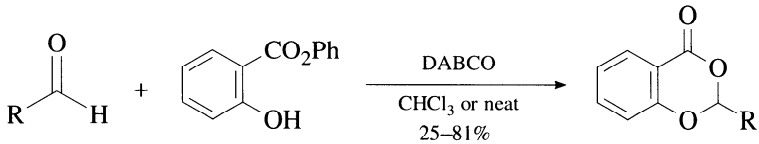
1. 2-Trimethylsilyl-1,3-propanediol, CH_2Cl_2, rt, 3Å ms, CSA, 45–97% yield.[1]

Cleavage[1]

1. $BF_3{\cdot}Et_2O$, THF.
2. $LiBF_4$, THF, 66°, 71–93% yield. 1,3-Dioxolanes of ketones were not affected.

1. B. H. Lipshutz, P. Mollard, C. Lindsley, and V. Chang, *Tetrahedron Lett.*, **38**, 1873 (1997).

Salicylate Acetals

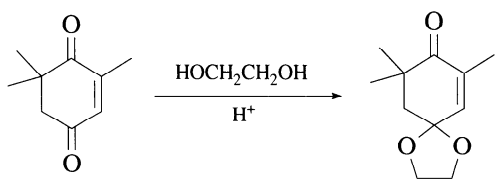


Although aromatic aldehydes failed to react, this is one of the few methods available for the preparation of acetals under basic conditions.[1,2]

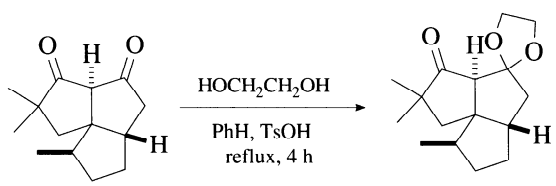
1. P. Perlmutter and E. Puniani, *Tetrahedron Lett.*, **37**, 3755 (1996).
2. A. A. Khan, N. D. Emslie, S. E. Drewes, J. S. Field, and N. Ramesar, *Chem. Ber.*, **126**, 1477 (1993).

1,3-Dioxolanes (Chart 5):

The 1,3-dioxolane group is probably the most widely used carbonyl protective group. For the protection of carbonyls containing other acid-sensitive functionality, one should use acids of low acidity or pyridinium salts. In general, a molecule containing two similar ketones can be selectively protected at the less hindered carbonyl, assuming that neither or both of the carbonyls are conjugated to an alkene.[1]



Ref. 1b



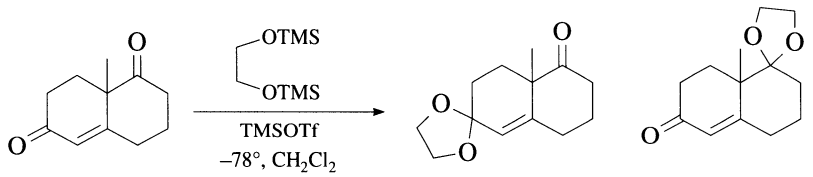
Ref. 1a

If one carbonyl is conjugated with a double bond, the unconjugated carbonyl is selectively protected. This generalization appears to be independent of ring size.[2] Simple aldehydes are generally selectively protected over simple ketones.[3] In the formation of 1,3-dioxolanes of enones, control of the olefin regiochemistry is determined by the acidity of the acid catalyst. Acids of high acidity (pK_a ~1) may cause the double bond to migrate to the β,γ-position, whereas

Table 1[4]

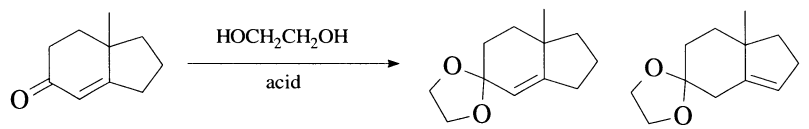
Acid	pK_a	% α,β	% β,γ	% conversion
Fumaric acid	3.03	100	0	90
Phthalic acid	2.89	70	30	90
Oxalic acid[8]	1.23	80	20	93
TsOH acid	<1.0	0	100	100

acids of low acidity (pK_a ~ 3) do not cause double-bond migration (see Table 1).[4] In addition, the use of the bistrimethylsilyl derivative of ethylene glycol and Me_3SiOTf (CH_2Cl_2, −78°, 20 h, pyridine quench, 92%) for the protection of enones proceeds without double-bond migration.[5,6] A similar result was obtained with the Wieland–Miescher ketone using stoichiometric amounts of TsOH.[7]



ratio = 27:1

Ref. 5



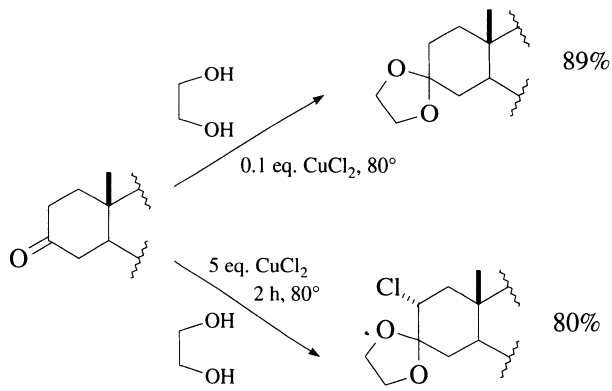
Ref. 4

A polymer-supported 1,2-diol has also been developed for use in carbonyl protection.[9]

Formation

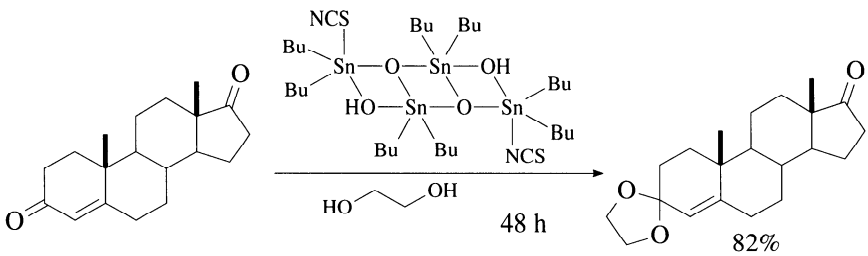
1. $HO(CH_2)_2OH$, TsOH, C_6H_6, reflux, 75–85% yield.[10]
2. $HO(CH_2)_2OH$, TsOH, $(EtO)_3CH$, 25°, 65% yield.[11]
3. $HO(CH_2)_2OH$, $BF_3{\cdot}Et_2O$, HOAc, 35–40°, 15 min, 90% yield.[12]
4. $HO(CH_2)_2OH$, HCl, 25°, 12 h, 55–90% yield.[13]
5. $HO(CH_2)_2OH$, Me_3SiCl, MeOH or CH_2Cl_2.[14]
6. $HO(CH_2)_2OH$, Al_2O_3, $PhCH_3$ or CCl_4, heat, 24 h, 80–100% yield.[3] These conditions are selective for the formation of acetals from aldehydes in the presence of ketones.
7. $Me_3SiOCH_2CH_2OSiMe_3$, Me_3SiOTf, 15 Kbar (1.5 GPa), 40°, 48 h.[15] These conditions were used to prepare the ketal of fenchone, which cannot be done under normal acid-catalyzed conditions.

8. $HO(CH_2)_2OH$, 0.1 eq. $CuCl_2 \cdot H_2O$, 80°, 30 min, 82–100% yield.[16] The use of 5 eq. of $CuCl_2$ results in the formation of the α-chloro ketal.



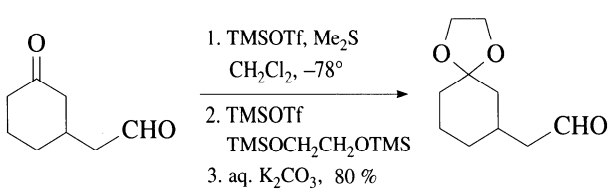
9. $HO(CH_2)_2OH$, oxalic acid, CH_3CN, 25°, 95% yield.[17] Note that ketals prepared with oxalic acid from enones tend to retain the olefin regiochemistry.[8]
10. $HO(CH_2)_2OH$, adipic acid, C_6H_6, reflux, 17–24 h, 10–85% yield.[18]
11. $HO(CH_2)_2OH$, SeO_2, $CHCl_3$, 28°, 4 h, 60% yield.[19]
12. $HO(CH_2)_2OH$, $C_5H_5N^+H\ Cl^-$, C_6H_6, reflux, 6 h, 85% yield.[20]
13. $HO(CH_2)_2OH$, $C_5H_5N^+H\ TsO^-$, C_6H_6, reflux, 1–3 h, 90–95% yield.[21]
14. $HO(CH_2)_nOH$ (n = 2,3)/$MeOCH^+NMe_2\ MeOSO_3^-$, 0–25°, 2 h, 40–95% yield.[22]
15. $HO(CH_2)_nOH$ (n = 2, 3)/column packed with an acid ion-exchange resin, 5 min, 50–90% yield.[23]
16. $HOCH_2CH_2OH$, $(EtO)_3CH$, p-TsOH, 83% yield.[24]
17. 2-Methoxy-1,3-dioxolane/TsOH, C_6H_6, 40–50°, 4 h, 85% yield.[25]
18. 2-Ethoxy-1,3-dioxolane, pyridinium tosylate (PPTS), benzene, heat, 8 h, 89% yield.[26] In this case, protection of an enone proceeds without double-bond migration.
19. 2-Ethyl-2-methyl-1,3-dioxolane/TsOH, reflux, 75% yield.[27,28] These conditions selectively protect a ketone in the presence of an enone.
20. 2,2-Dimethyl-1,3-dioxolane, microwave irradiation, Montmorillonite KSF, 38–95% yield.[29]
21. 2-Dimethylamino-1,3-dioxolane/cat. HOAc, CH_2Cl_2, 83% yield.[30] 2-Dimethylamino-1,3-dioxolane protects a reactive ketone under mild conditions: it reacts selectively with a C_3-keto steroid in the presence of a Δ^4-3-keto steroid. C_{12}- and C_{20}-keto steroids do not react.
22. Diethylene orthocarbonate, $C(-OCH_2CH_2O-)_2$/TsOH or wet $BF_3 \cdot Et_2O$, $CHCl_3$, 20°, 70–95% yield.[31]

23. 1,3-Dioxolanes have been prepared from a carbonyl compound and an epoxide (e.g., ketone/$SnCl_4$, CCl_4, 20°, 4 h, 53% yield[32] or aldehyde/$Et_4N^+Br^-$, 125–220°, 2–4 h, 20–85% yield[33]). Perhalo ketones can be protected by reaction with ethylene chlorohydrin under basic conditions (K_2CO_3, pentane, 25°, 2 h, 85% yield;[34] or NaOH, EtOH–H_2O, 95% yield[35]).
24. When the carbonyl group is very electron-deficient, thus stabilizing the hemiacetal, a dioxolane can be prepared under basic conditions.[34,36]
25. $HOCH_2CH_2OH$, $(i\text{-}PrO)_3CH$, $RhCl_3$(triphos), [triphos = $H_3CC(CH_2PPh_2)_3$], rt, reflux, 80–100% yield.[37]
26. $HO(CH_2)_2OH$, PhH, catalyst, quant.[38]



4.7% of the 17-ketal and 8.3% of the diketal are also obtained.

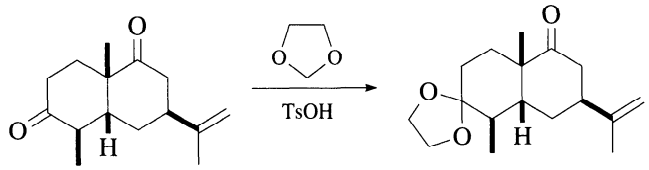
27. $HO(CH_2)_2OH$, $ZrOCl_2 \cdot 8\,H_2O$, aq. NaOH, 65–98% yield.[39]
28. $HO(CH_2)_2OH$, PhH, *N*-benzylpyridinium hexafluoroantimonate, 1.5–9 h, reflux, 72–91% yield.[40] It is also possible to form the 4,4-dimethyldioxane (85–99% yield) under these conditions.
29. $HO(CH_2)_2OH$, $[Ru(MeCN)_3(Ph_3P)](OTf)_2$, PhH, azeotropic distillation, 87–99% yield.[41]
30. Ethylene oxide, $BF_3 \cdot Et_2O$, >120 min, CH_2Cl_2, 25°, 47–95% yield.[42]
31. $HOCH_2CH_2OH$, $BuSnCl_3$, 0°, 10 min, 75–92% yield.[43]
32. From a tosylhydrazone: ethylene glycol, 200°, 89% yield.[44]
33. Selective ketone protection: The –CHO group is converted in Step 1 to a siloxysulfonium salt [$R'CH(OTMS)S^+Me_2\ ^-OTf$] that is reconverted to an aldehyde group in Step 3.[45]



34. $HO(CH_2)_nOH$, n = 2,3, Fe or Al, rt, 52–99% yield.[46]

35. $TMSOCH_2CH_2OTMS$, TfOH or FsOH (fluorosulfonic acid), BTMSA [bis(trimethylsilyl)acetamide] or BTMSU [bis(trimethylsilyl)urea], 76–97% yield.[47]
36. $HO(CH_2)_nOH$, $n = 2,3$, *i*-PrOTMS, TMSOTf, CH_2Cl_2, $-20°$, 3 h, 84–99% yield.[48]
37. $HOCH_2CH_2OH$, $MgSO_4$, PhH, L-tartaric acid, reflux, 20 h, 97% yield. These conditions were optimized for the protection of unsaturated aldehydes to prevent double-bond migration.[49]

38.



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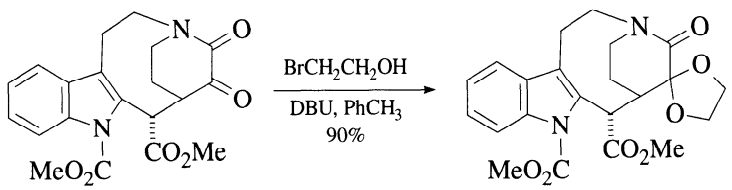
39.



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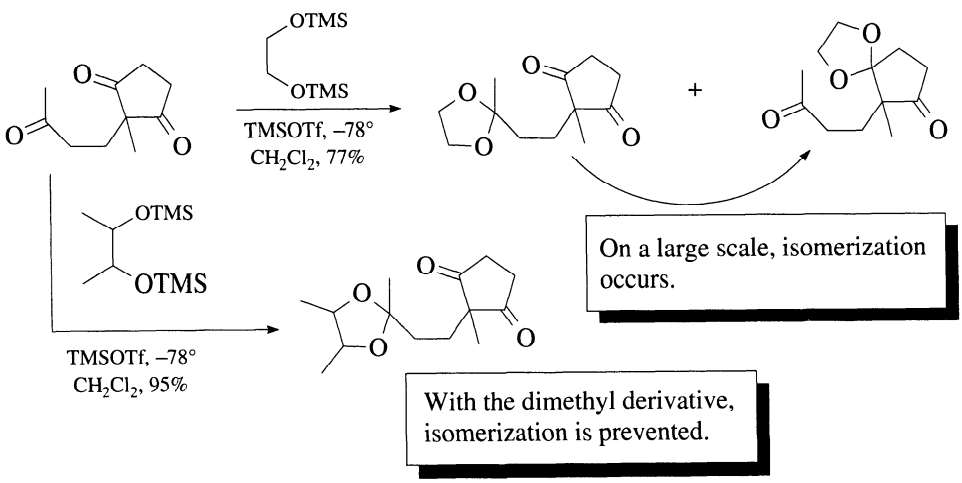
40.

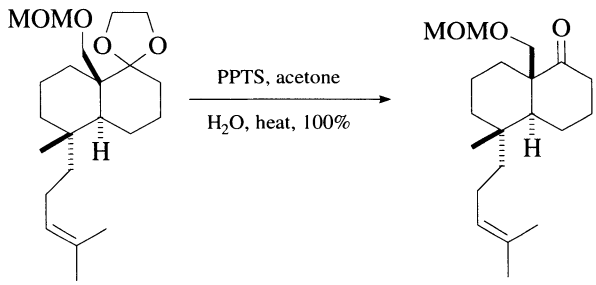


Ref. 52

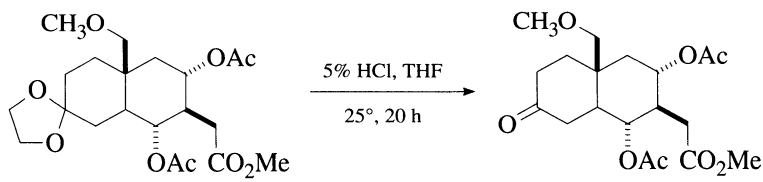
Cleavage

1,3-Dioxolanes can be cleaved by acid-catalyzed exchange dioxolanation, acid-catalyzed hydrolysis, or oxidation. Some representative examples are shown in the following list:

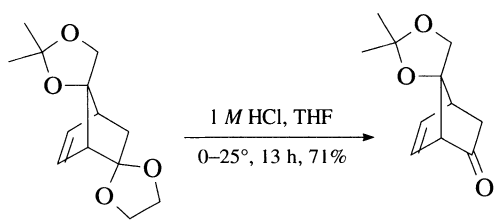
1. Pyridinium tosylate (PPTS), acetone, H_2O, heat, 100% yield.[53]



2. Acetone, TsOH, 20°, 12 h.[54] The reactant is a 3,6,17-tris(ethylenedioxy) steroid; the product has carbonyl groups at C-6 and C-17.
3. Acetone, H_2O, PPTS, reflux, 1–3 h, 90–95% yield.[21]
4. 5% HCl, THF, 25°, 20 h.[55]



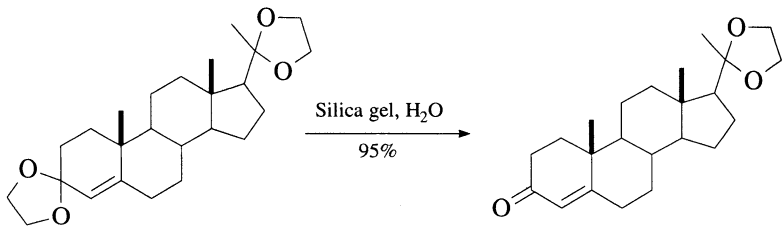
5. 1 *M* HCl, THF, 0° → 25°, 13 h, 71% yield. Note that the acetonide survives these conditions.[56] Some variations have been reported in this system (including the use of 30% AcOH, 90°, high yield).[57]



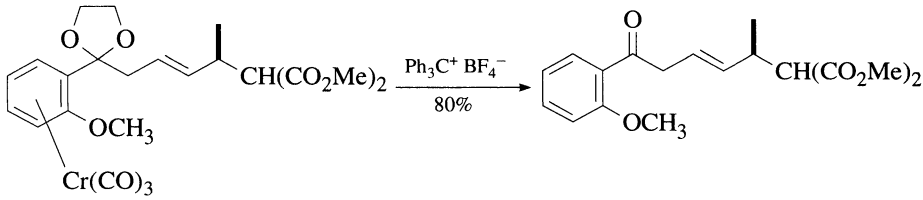
6. 80% AcOH, 65°, 5 min, 85% yield.[58]
7. Wet magnesium sulfate (C_6H_6, 20°, 1 h) effects selective, quantitative cleavage of an α,β-unsaturated 1,3-dioxolane in the presence of a 1,3-dioxolane.[18]
8. Perchloric acid (79% $HClO_4/CH_2Cl_2$, 0°, 1 h → 25°, 3 h, 87% yield)[59] and periodic acid (aq. dioxane, 3 h, quant. yield)[60] cleave 1,3-dioxolanes;

the latter drives the reaction to completion by oxidation of the ethylene glycol that forms. Yields are substantially higher from cleavage with perchloric acid (3 *N* $HClO_4$/THF, 25°, 3 h, 80% yield) than with hydrochloric acid (HCl/HOAc, 65% yield).[61]

9. SiO_2, H_2O, CH_2Cl_2, oxalic acid, 90–95% yield.[62] These conditions selectively cleave α,β-unsaturated ketals.



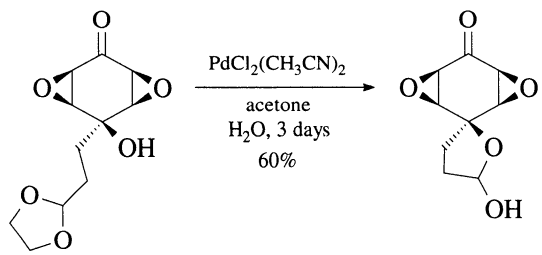
10. $Ph_3C^+BF_4^-$, CH_2Cl_2, 25°, 60–100% yield.[63,64]



Ref. 64

1,3-Dithiolanes are not affected by these conditions, but a 1,3-oxathiolane is cleaved (100% yield).[65]

11. Me_2BBr, CH_2Cl_2, −78°, 90–97% yield.[66] This reagent also cleaves MTM, MEM, and MOM ethers (87–95% yield).
12. $PdCl_2(CH_3CN)_2$, acetone, H_2O, 82–100% yield.[67]



Ref. 68

13. Me_3SiI.[69]
14. *t*-BuOOH, $Pd(OOCCF_3)(OO\text{-}t\text{-}Bu)$, benzene, 50°, 12 h, 60–80% yield.[70] In this case, an acetal is oxidized to the ester of ethylene glycol ($RCO_2CH_2CH_2OH$).
15. $LiBF_4$, wet CH_3CN.[71] Unsubstituted 1,3-dioxolanes are cleaved slowly

under these conditions (40% in 5 h). The 4,5-dimethyl- and 4,4,5,5-tetramethyldioxolane and the 1,3-dioxane are inert under these conditions. Dimethyl ketals are readily cleaved.

16. $TiCl_4$, Et_2O, LiI, rt, 61–91% yield.[72] A THP ether was stable to these conditions, but methyl ethers can be cleaved.
17. AlI_3, CH_3CN, benzene, 10 min, 70–92% yield.[73] Ethyl ketals are cleaved under these conditions, but thioketals are not affected.
18. Dimethyl sulfoxide, 180°, H_2O, 10 h, 89% yield.[74] A diethyl acetal can be cleaved in the presence of a 1,3-dioxolane under these conditions. TBDMS, THP, and MOM groups are stable.
19. NaTeH, EtOH, 25°, 30 min; air, 80–85% yield.[75]
20. H_2SiI_2, $CDCl_3$, −42°, 1–10 min, 100% yield.[76] Aromatic ketals are cleaved faster than the corresponding aliphatic derivatives, and cyclic ketals are cleaved more slowly than the acyclic analogues, such as dimethyl ketals. Substituted ketals such as those derived from butane-2,3-diol, which react only slowly with Me_3SiI, can also be cleaved with H_2SiI_2. If the reaction is run at 22°, ketals and acetals are reduced to iodides in excellent yield.
21. $CuSO_4$–SiO_2, CH_2Cl_2, 20–80 h, 70–90% yield.[77]
22. Dimethyldioxirane, acetone, CH_2Cl_2, 0°, 24 h, > 95% yield.[78] Ethers are also oxidized under these conditions.
23. DDQ, CH_3CN, H_2O, 68–95% yield.[79]
24. NO_2, silica gel, CCl_4, 30°, 40 min, 88–100% yield.[80]
25. PPh_3, CBr_4, THF, 0°, 96% yield.[81]
26. $SmCl_3$, TMSCl, THF, 92% yield. A ketal is cleaved in preference to an acetal.[82]
27. 2,4,6-Triphenylpyrilium tetrafluoroborate, H_2O, CH_2Cl_2, 3 h, *hν*, 67–88% yield.[83]
28. $RuCl_3 \cdot nH_2O$, *t*-BuOH, PhH, 1 h, rt, 46–86% yield. In this case, the acetal is cleaved with simultaneous oxidation to an ethylene glycol ester.[84]
29. NaI, $CeCl_3 \cdot 7H_2O$, CH_3CN, rt, 0.5–21 h, 84–96% yield.[85] Chemoselective cleavage of ketone derivatives is observed in the presence of aldehyde derivatives, and enone ketals are cleaved in the presence of simple ketone ketals.

1. For two examples, see (a) M. T. Crimmins and J. A. DeLoach, *J. Am. Chem. Soc.*, **108**, 800 (1986); (b) M. G. Constantino, P. M. Donate, and N. Petragnani, *J. Org. Chem.*, **51**, 253 (1986).
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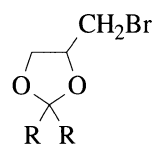
4-Bromomethyl-1,3-dioxolane (Chart 5):



Formation

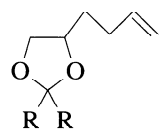
1. $HOCH_2CH(OH)CH_2Br$, TsOH, benzene, reflux, 5 h, 93–98% yield.[1]

Cleavage[1]

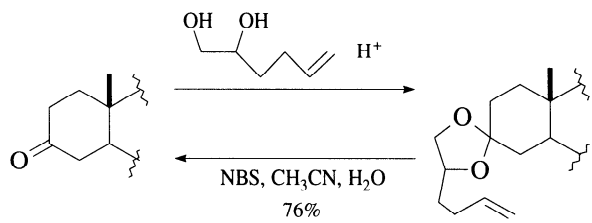
1. Activated Zn, MeOH, reflux, 12 h, 89–96% yield.

This ketal is stable to several reagents that react with carbonyl groups (e.g., *m*-$ClC_6H_4CO_3H$, NH_3, $NaBH_4$, and MeLi). It is cleaved under neutral conditions.

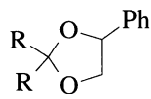
1. E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973).

4-(3-Butenyl)-1,3-dioxolane: 

Formation/Cleavage[1]



1. Z. Wu, D. R. Mootoo, and B. Fraser-Reid, *Tetrahedron Lett.*, **29**, 6549 (1988).

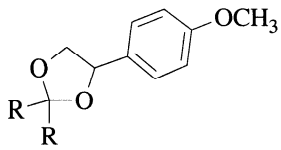
4-Phenyl-1,3-dioxolane: 

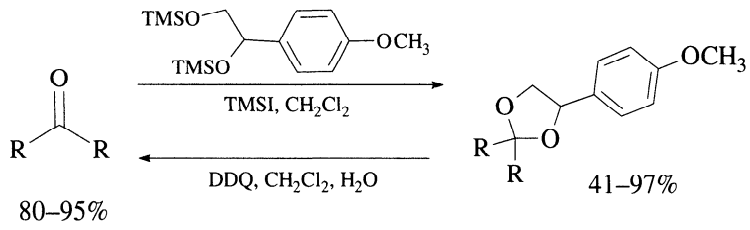
Cleavage

1. Electrolysis: $LiClO_4$, H_2O, Pyr, CH_3CN, *N*-hydroxyphthalimide, 0.85 V SCE, 22–90% yield.[1]
2. Pd/C, H_2.[2]

1. M. Masui, T. Kawaguchi, and S. Ozaki, *J. Chem. Soc., Chem. Commun.*, 1484 (1985).
2. S. Chandrasekhar, B. Muralidhar, and S. Sarkar, *Synth. Commun.*, **27**, 2691 (1997).

4-(4-Methoxyphenyl)-1,3-dioxolane:



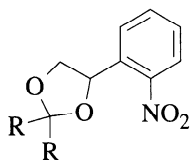


Ref. 1

This protective group can be removed oxidatively in excellent yields.[1]

1. C. E. McDonald, L. E. Nice, and K. E. Kennedy, *Tetrahedron Lett.*, **35**, 57 (1994).

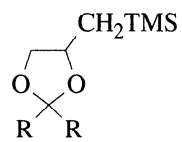
4-(2-Nitrophenyl)-1,3-dioxolane (Chart 5):



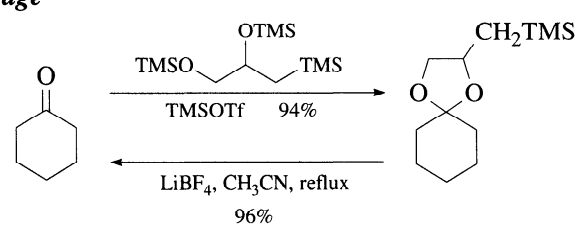
This dioxolane is readily formed from the glycol (TsOH, benzene, reflux, 70–95% yield); it is cleaved by irradiation (350 nm, benzene, 25°, 6 h, 75–90% yield). This group is stable to 5% HCl/THF; 10% AcOH/THF; 2% oxalic acid/THF; 10% aq. H_2SO_4/ THF; and 3% aq. TsOH/THF.[1]

1. J. Hébert and D. Gravel, *Can. J. Chem.*, **52**, 187 (1974); D. Gravel, J. Hébert, and D. Thoraval, *Can. J. Chem.*, **61**, 400 (1983).

4-Trimethylsilylmethyl-1,3-dioxolane:

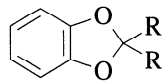


Formation/Cleavage[1]



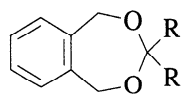
Hindered ketones and enones fail to form the ketal because of competing decomposition of the silyl reagent.

1. B. M. Lillie and M. A. Avery, *Tetrahedron Lett.*, **35**, 969 (1994).

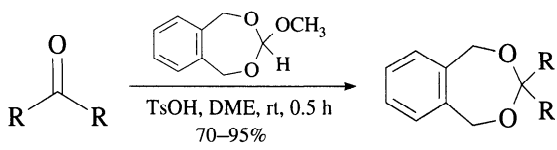
O,O'-Phenylenedioxy Ketal: 

The phenylenedioxy ketal is prepared from catechol (TsOH, 90°, 30 h, 85% yield) and is cleaved with 5 *N* HCl (dioxane, reflux, 6 h). It is more stable to acid than is the ethylene ketal.[1,2]

1. M. Rosenberger, D. Andrews, F. DiMaria, A. J. Duggan, and G. Saucy, *Helv. Chim. Acta*, **55**, 249 (1972).
2. M. Rosenberger, A. J. Duggan, and G. Saucy, *Helv. Chim. Acta*, **55**, 1333 (1972).

1,5-Dihydro-3*H*-2,4-benzodioxepin: 

Formation

1. 

Refs. 1, 2

Camphor cannot be protected with this reagent, indicating that steric factors will prevent its use in very hindered systems.

2. 1,2-Dihydroxymethylbenzene, $CH(OCH_3)_3$, TsOH, 80% yield.[3,4]
3. From a methyl enol ether: 1,2-dihydroxymethylbenzene, Amberlyst H^+, 85% yield.[5]
4. 1,2-Dihydroxymethylbenzene, sulfonated charcoal or TsOH, PhH, reflux, 88–98% yield.[6]
5. 1,2-Ditrimethylsiloxymethylbenzene, TMSOTf, CH_2Cl_2, −78°, 96% yield.[7]
6. 1,2-Dihydroxymethylbenzene, H-Y Zeolite, CH_2Cl_2, reflux, 3–12 h, 46–95% yield.[8]
7. 1,2-Dihydroxymethylbenzene, Environcat EPZG, toluene, reflux, 93–99% yield. Ketones were not reactive under these conditions.[9]

Cleavage

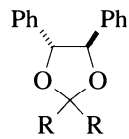
1. H_2, PdO, THF, rt, 0.5 h, 100% yield.[1]

1. N. Machinaga and C. Kibayashi, *Tetrahedron Lett.*, **30**, 4165 (1989).
2. K. Mori, T. Yoshimura, and T. Sugai, *Liebigs Ann. Chem.*, 899 (1988).
3. R. Oi and K. B. Sharpless, *Tetrahedron Lett.*, **33**, 2095 (1992).
4. S. D. Burke and D. N. Deaton, *Tetrahedron Lett.*, **32**, 4651 (1991).
5. L. Schmitt, B. Spiess, and G. Schlewer, *Tetrahedron Lett.*, **33**, 2013 (1992).
6. H. K. Patney, *Tetrahedron Lett.*, **32**, 413 (1992).
7. S. V. D'Andrea, J. P. Freeman, and J. Szmuszkovicz, *Org. Prep. Proced. Int.*, **23**, 432 (1991).
8. T. P. Kumar, K. R. Reddy, and R. S. Reddy, *J. Chem. Res., Synop.*, 394 (1994).
9. B. P. Bandgar, M. M. Kulkarni, and P. P. Wadgaonkar, *Synth. Commun.*, **27**, 627 (1997).

Chiral Acetals and Ketals

Chiral protective groups, although less frequently used in synthesis, provide sought-after protection, diastereochemical control, and enantioselectivity, and can improve the chemical characteristics of a molecule to facilitate a synthesis.[1]

(4*R*,5*R*)-Diphenyl-1,3-dioxolane:



Formation

1. (1*R*,2*R*)-Diphenyl-1,2-ditrimethylsiloxyethane, TMSOTf, 66% yield.[2]
2. (1*R*,2*R*)-Diphenyl-1,2-ethanediol, PPTS, 80°.[3]

Cleavage

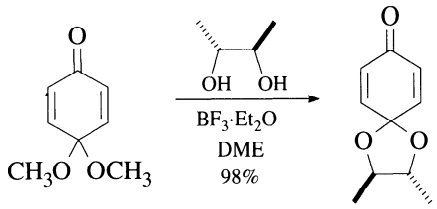
1. 2.7 *N* HCl, MeOH, 25°, 90% yield.[3]
2. $Pd(OH)_2$, H_2, EtOAc, quant.[2]

4,5-Dimethyl-1,3-dioxolane

Formation

1. 2,3-Bistrimethylsiloxybutane, TMSOTf, CH_2Cl_2, 66% yield. The double bond of an enone does not migrate out of conjugation.[4]
2. 2,3-Butanediol, benzene, PPTS, reflux, 66% yield.[5]

3.



Refs. 6, 7

This reaction also works to form the related dioxane, but the yields are lower.[6]

trans-1,2-Cyclohexanediol Ketal

Formation

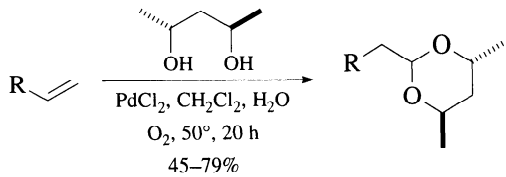
1. *trans*-1,2-Cyclohexanediol, *i*-PrOTMS, TMSOTf, CH_2Cl_2, −20°, 3 h, 85% yield.[8]

trans-4,6-Dimethyl-1,3-dioxane

Formation

1. 2,4-Pentanediol, PPTS, >95% yield.[8,9]

2.

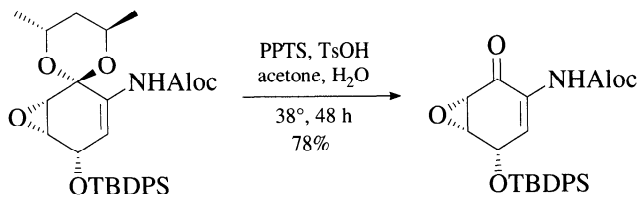


Ref. 10

3. 2,4-Pentanediol, $Sc(OTf)_3$, rt, 13 h–2 days, benzene, THF or CH_2Cl_2, 59–100% yield. This method is also effective for the formation of a 4,5-dimethyldioxolane.[11]

Cleavage

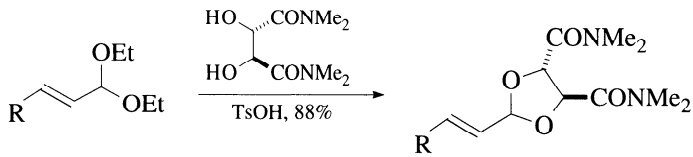
1.



Hydrolysis is facilitated by the increased level of strain imparted by the axial methyl group, thus allowing cleavage under conditions to which the product is stable.[12]

4,5-Bis(dimethylaminocarbonyl)-1,3-dioxolane

Formation[13]



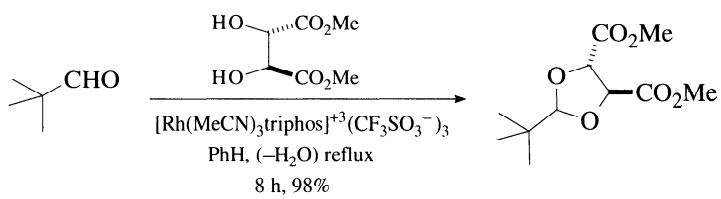
Cleavage[13]

6 *M* HCl, dioxane, >92% yield.
A chiral protective group was developed for use in the synthesis of optically active alcohols.[13]

4,5-Dicarbomethoxy-1,3-dioxolane

Formation

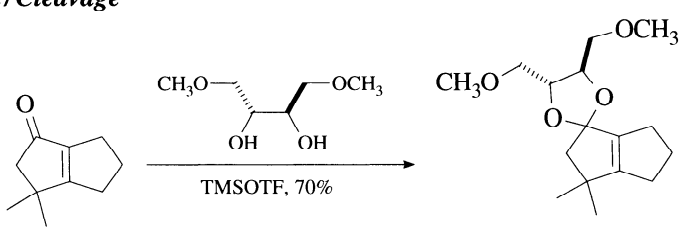
1. Dimethyl tartrate, $Sc(OTf)_3$, MeCN, rt, 3 h, 95% yield.[14]

2. 

Ref. 15

4,5-Dimethoxymethyl-1,3-dioxolane

Formation/Cleavage[16]



This protective group was used to direct the selective cyclopropanation of a variety of enones. Hydrolysis (HCl, MeOH, H_2O, rt, 94% yield) affords optically active cyclopropyl ketones.

1. A review: A. Alexakis and P. Mangeney, *Tetrahedron: Asymmetry*, **1**, 477 (1990).
2. C. N. Eid, Jr., and J. P. Konopelski, *Tetrahedron Lett.*, **32**, 461 (1991).
3. J. Cossy and S. BouzBouz, *Tetrahedron Lett.*, **37**, 5091 (1996).
4. E. A. Mash and S. B. Hemperly, *J. Org. Chem.*, **55**, 2055 (1990).
5. M. Toyota, Y. Nishikawa, and K. Fukumoto, *Tetrahedron*, **52**, 10347 (1996).
6. M. C. Pirrung and D. S. Nunn, *Tetrahedron Lett.*, **33**, 6591 (1992).
7. P. de March, M. Escoda, M. Figueredo, J. Font, A. Alvarez-Larena, and J. F. Piniella, *J. Org. Chem.*, **60**, 3895 (1995).
8. M. Kurihara and N. Miyata, *Chem. Lett.*, 263 (1995).
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10. T. Hosokawa, T. Ohta, S. Kanayama, and S. I. Murahashi, *J. Org. Chem.*, **52**, 1758 (1987).
11. S.-i. Fukuzawa, T. Tsuchimoto, T. Hotaka, and T. Hiyama, *Synlett*, 1077 (1995).
12. P. Wipf, Y. Kim, and H. Jahn, *Synthesis*, 1549 (1995).
13. J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **106**, 5004 (1984).
14. K. Ishihara, Y. Karumi, M. Kubota, and H. Yamamoto, *Synlett*, 839 (1996).
15. J. Ott, G. M. Ramos Tombo, B. Schmid, L. M. Venanzi, G. Wang, and T. R. Ward, *Tetrahedron Lett.*, **30**, 6151 (1989).
16. E. A. Mash, S. K. Math, and C. J. Flann, *Tetrahedron Lett.*, **29**, 2147 (1988).

Dithio Acetals and Ketals

A carbonyl group can be protected as a sulfur derivative—for example, a dithio acetal or ketal, a 1,3-dithiane, or a 1,3-dithiolane—by reaction of the carbonyl compound in the presence of an acid catalyst with a thiol or dithiol. The derivatives are, in general, cleaved by reaction with Hg(II) salts or oxidation; acidic hydrolysis is unsatisfactory. The acyclic derivatives are formed and hydrolyzed much more readily than their cyclic counterparts. Representative examples of formation and cleavage follow.

Acyclic Dithio Acetals and Ketals

S,S′-Dimethyl Acetals and Ketals: $RR'C(SCH_3)_2$ (Chart 5)

S,S′-Diethyl Acetals and Ketals: $RR'C(SC_2H_5)_2$

S,S′-Dipropyl Acetals and Ketals: $RR'C(SC_3H_7)_2$

S,S′-Dibutyl Acetals and Ketals: $RR'C(SC_4H_9)_2$

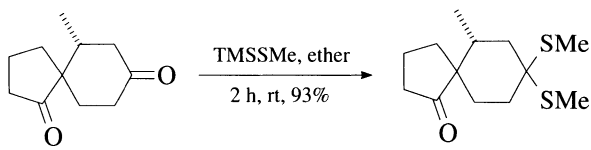
S,S′-Dipentyl Acetals and Ketals: $RR'C(SC_5H_{11})_2$

S,S′-Diphenyl Acetals and Ketals: $RR'C(SC_6H_5)_2$

S,S′-Dibenzyl Acetals and Ketals: $RR'C(SCH_2C_6H_5)_2$

General Methods of Formation

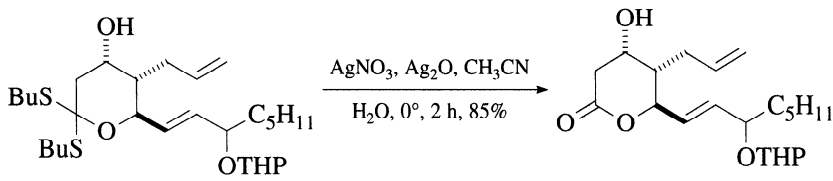
1. RSH, concd. HCl, 20°, 30 min.[1] These conditions were used to protect an aldose as the methyl or ethyl thioketal.
2. $RSSiMe_3$, ZnI_2, Et_2O, 0–25°, 70–95% yield.[2] This method is satisfactory for a variety of aldehydes and ketones and is also suitable for the preparation of 1,3-dithianes. Methacrolein gives the product of Michael addition rather than the thioacetal. The less hindered of two ketones is readily protected using this methodology.[3]



3. RSH, Me_3SiCl, $CHCl_3$, 20°, 1 h, >80% yield.[4]
4. $B(SR)_3$, reflux, 2 h or 25°, 18 h, 75–85% yield.[5]
5. $Al(SPh)_3$, 25°, 1 h, 65% yield.[6] This method also converts esters to thioesters.
6. PhSH, $BF_3{\cdot}Et_2O$, $CHCl_3$, 0°, 10 min, 86% yield.[7] $ZnCl_2$[8] and $MgBr_2$[9] have also been used as catalysts. With $MgBr_2$, acetals can be converted to thioacetals in the presence of ketones.
7. RSH, SO_2, benzene, 54–81% yield.[10]
8. EtSH, $TiCl_4$, $CHCl_3$, 6–12 h, rt, 90–98% yield.[11]
9. ***P***-$PPh_2{\cdot}I_2$, RSH, Et_3N, CH_3CN; K_2CO_3, H_2O, 80–98% yield.[12] This method is also effective for the formation of dioxolanes and dithiolanes.
10. RSSR (R = Me, Ph, Bu), Bu_3P, rt, 15–83% yield.[13] This reagent also reacts with epoxides to form 1,2-dithio ethers.
11. H-Y or H-M Zeolite, hexane or CH_2Cl_2, EtSH, reflux, 0.75–144 h, 50–96% yield.[14]

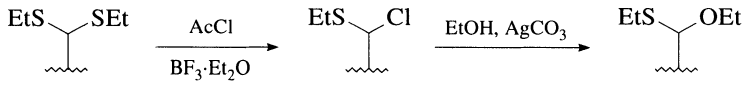
General Methods of Cleavage

1. $AgNO_3/Ag_2O$, CH_3CN–H_2O, 0°, 2 h, 85% yield.[15]



This method has also been used to cleave dithianes and dithiolanes.[16] The *S,S'*-dibutyl group is stable to acids (e.g., HOAc/H_2O–THF, 45°, 3 h; TsOH/CH_2Cl_2, 0°, 0.5 h).[15]

2. $AgClO_4$, H_2O, C_6H_6, 25°, 4 h, 80–100% yield.[17]
3. $HgCl_2$, $CdCO_3$, aq. acetone[18] or $HgCl_2$, $CaCO_3$, CH_3CN, H_2O.[19] In a case where this combination of reagents was not effective, HgO/BF_3·Et_2O was found to work.[20]
4. $Me_2CH(CH_2)_2ONO$, CH_2Cl_2, 25°, 15 min; H_2O, 63–93% yield.[21] Isoamyl nitrite cleaves aromatic dithioacetals in preference to aliphatic dithioacetals and dithioacetals in preference to dithioketals. It also cleaves 1,3-oxathiolanes (1 h, 65–90% yield).
5. $Tl(NO_3)_3$, CH_3OH, H_2O, 25°, 5 min, 73–98% yield.[7] These conditions are also effective for the cleavage of dithiolanes and dithianes.
6. SO_2Cl_2, SiO_2·H_2O, CH_2Cl_2, 25°, 2–3 h, 90–100% yield.[22,23]
7. I_2, $NaHCO_3$, dioxane, H_2O, 25°, 4.5 h, 80–95% yield.[24]
8. I_2, MeOH, reflux, 2 h, 79%; $HClO_4$, H_2O, 25°, 16 h, 87% yield.[25] These conditions also cleave acetonides and benzylidene acetals.[26]
9. H_2O_2, aq. acetone or $NaIO_4$/H_2O, 25°; g HCl/$CHCl_3$, 0°, 50–70% yield.[27]
10. O_2, $h\nu$, hexane, Ph_2CO, 2–5 h, 60–80% yield.[28] 1,3-Oxathiolanes and dithiolanes are also cleaved by these conditions.
11. CuCl, CuO, H_2O, acetone, 2 h, 20°, 61–73% yield.[29]
12. $HgCl_2$, HgO, 80% CH_3CN, H_2O, 30 min, rt, 96% yield.[30]
13. MCPBA, CF_3COOH, CH_2Cl_2, 0°.[31]
14. Ph_3CClO_4, Ph_3COMe, CH_2Cl_2, −45°, 2.5 h; aq. $NaHCO_3$, 84–96% yield.[32] A diethyl thioketal could be cleaved in the presence of a diphenyl thioketal.
15. DDQ, CH_3CN, H_2O, 80°, 43–95% yield.[33] These conditions also resulted in the cleavage of acetyl groups; a dithiolane was stable to the conditions.
16. $GaCl_3$, CH_2Cl_2, H_2O, rt, 20 min.[34] Thioketals are cleaved in preference to thioacetals and dithianes, which do not react.
17. DMSO, 140–160°, 4–5 h, 79–94% yield.[35]
18. Clay supported NH_4NO_3, CH_2Cl_2, rt, 76–90% yield.[36]
19. The dithioacetal can be converted to an *O,S*-acetal.[37] The mixed acetals were then used to prepare furanosides.



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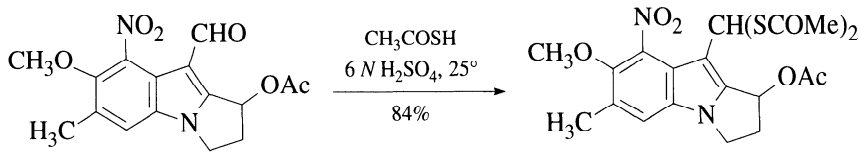
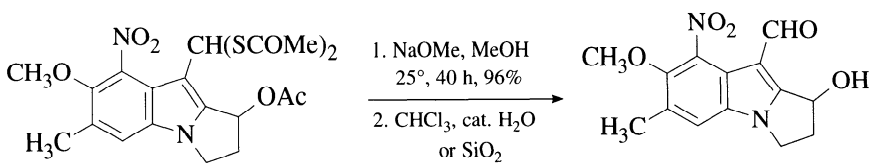
S,S'-Diacetyl Acetals and Ketals: $R_2C(SCOCH_3)_2$

Formation[1]



Cleavage[1]



The formyl group was lost during attempted protection with ethylene glycol, TsOH.

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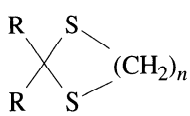
Cyclic Dithio Acetals and Ketals

1,3-Dithiane Derivative ($n = 3$) (Chart 5)

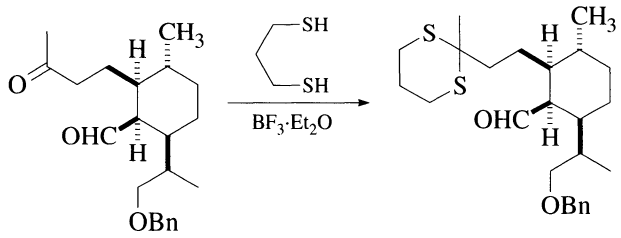
1,3-Dithiolane Derivative ($n = 2$) (Chart 5):

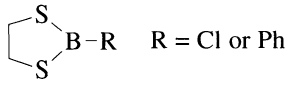


General Methods of Formation

1. $HS(CH_2)_nSH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 25°, 12 h, high yield, $n = 2$,[1] $n = 3$.[2] In α,β-unsaturated ketones, the double bond does not migrate to the β,γ-position, as occurs when an ethylene ketal is prepared.[3] Aldehydes are

selectively protected in the presence of ketones, except when large steric factors disfavor the aldehyde group, as shown in the next example.[4] A TBDMS group is not stable to these conditions.[5] Oxazolidines are converted to the dithiane in 70% yield under these conditions,[6] but the use of methanesulfonic acid as a catalyst is equally effective.[7]



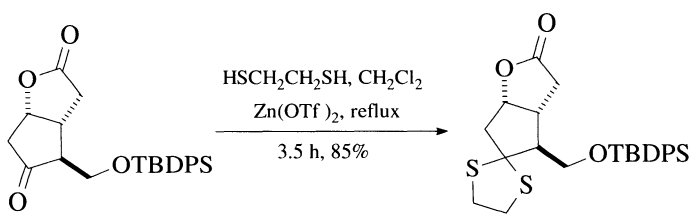
2. 

R = Cl or Ph

$CHCl_3$, 25°, 2 h, 90–100% yield.[8]

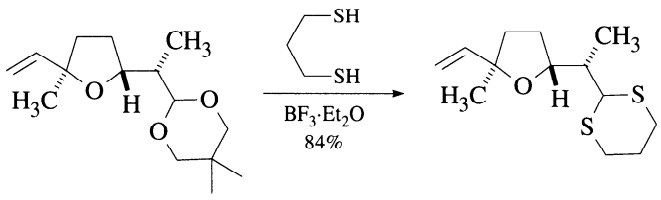
When R = Ph, the reaction is selective for unhindered ketones. Diaryl ketones, generally unreactive compounds, react rapidly when R = Cl.

3. $Me_3SiSCH_2CH_2SSiMe_3$, ZnI_2, Et_2O, 0–25°, 12–24 h, high yields.[9] Less hindered ketones can be selectively protected in the presence of more hindered ketones. α,β-Unsaturated ketones are selectively protected (94:1, 94:4) in the presence of saturated ketones by this reagent.[10]
4. $HS(CH_2)_nSH$, $SOCl_2$–SiO_2, 88–100% yield.[11] Aldehydes are selectively protected in the presence of ketones.
5. $HS(CH_2)_2SH$, $TiCl_4$, $-10° \rightarrow 25°$, 96% yield.[12]
6. $HSCH_2CH_2SH$, $Zn(OTf)_2$ or $Mg(OTf)_2$, $ClCH_2CH_2Cl$, heat, 16 h, 85–99% yield.[13,14] Excellent selectivity can be achieved between a hindered and an unhindered ketone.[15] α,β-Unsaturated ketones such as carvone are not cleanly converted to ketals, because of Michael addition of the thiol.[13]



In this case, other methods failed because of β-elimination.

7. 1,3-Dioxolanes[16,17] and 1,3-dioxanes[18] are readily converted to 1,3-dithiolanes and1,3-dithianes, respectively, in good to excellent yields.



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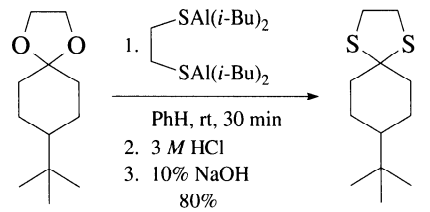
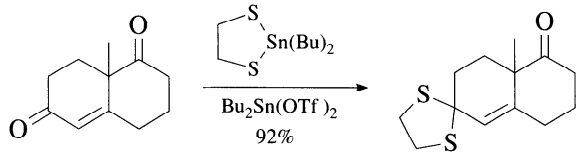


Ref. 17

8. 2,2-Dimethyl-2-sila-1,3-dithiane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°, 82–99% yield.[19] This method was reported to be superior to the conventional synthesis because cleaner products are formed. Aldehydes are selectively protected in the presence of ketones, which do not react competitively with this reagent.
9. 2,2-Dibutyl-2-stanna-1,3-dithiane, $Bu_2Sn(OTf)_2$, $ClCH_2CH_2Cl$, 35°, 1 h, 77–94% yield.[20] TBDMS, TBDPS, THP, and OAc groups are not affected by these conditions.
10. H-Y Zeolite, hexane, or CH_2Cl_2, $HSCH_2CH_2SH$, 0.75–144 h, 50–96% yield.[21]
11. $HS(CH_2)_nSH$, $ClCH_2CH_2Cl$, $TeCl_4$, rt, 80–99% yield.[22] This method is also effective for converting dimethyl acetals to the thioacetal and for selectively protecting an aldehyde in the presence of a ketone.
12. $HSCH_2CH_2SH$, $FeCl_3$–SiO_2, CH_2Cl_2, < 1 min–7 h.[23] Montmorillonite Clay can also be used as a support medium for the ferric ion (75–98% yield). In this case, the reaction is chemoselective for aldehydes.[24]
13. $HSCH_2CH_2SH$, CH_2Cl_2, $(TMSO)_2SO_2$–silica, 75–99% yield.[25]
14. $HSCH_2CH_2SH$, CH_2Cl_2, $CoBr_2$–silica, rt, 3 min–24 h, 87–99% yield.[26]
15. $HSCH_2CH_2SH$, CH_2Cl_2, $LaCl_3$, 1–96 h, 25–93% yield.[27]
16. $HS(CH_2)_nSH$, Montmorillonite KSF Clay, without solvent, 85–90% yield.[28]
17. $HSCH_2CH_2SH$, Amberlyst 15, 83–100% yield.[29]
18. $HSCH_2CH_2SH$, $SnCl_2{\cdot}H_2O$, THF, reflux, 10–240 min, 51–96% yield.[30] Under these conditions, aldehydes react faster than ketones. Dimethyl ketals, which react faster than dimethyl acetals, are also converted to

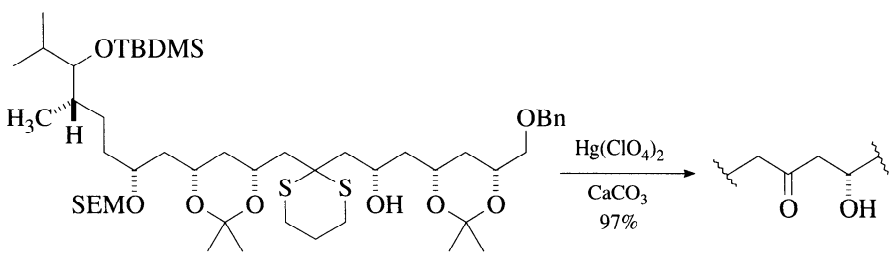
dithianes and dithiolanes under these conditions (75–100% yield).[31]



19. $HSCH_2CH_2SH$, MgI_2, Et_2O, rt, 8 h, 95–96% yield.[32] Aryl ketones are not efficiently protected.
20. $HS(CH_2)_nSH$, McCN, SmI_3, 62–92% yield.[33]
21. $HSCH_2CH_2SH$, Dowex-50W-X8 acidified with HCl, Et_2O, 35–200 min, 60–90% yield.[34]
22. $HSCH_2CH_2SH$, $LiClO_4$, ether, 70–95% yield.[35]
23. $HSCH_2CH_2SH$, THF, $CuSO_4$, 40–96% yield.[36]
24. $HSCH_2CH_2SH$, PhMe, activated Bentonite, 5 h, 99% yield.[37]
25. $HSCH_2CH_2SH$, MeCN, rt, $Bi_2(SO_4)_3$, air, 2.5 h, 93–100% yield.[38]
26. $HSCH_2CH_2SH$, $ZrCl_4$–silica, CH_2Cl_2, rt, 3 h, 98% yield. Unreactive ketones such as benzophenone are efficiently protected.[39]
27. H-Rho–Zeolite, hexane, reflux, 85–94% yield.[40]

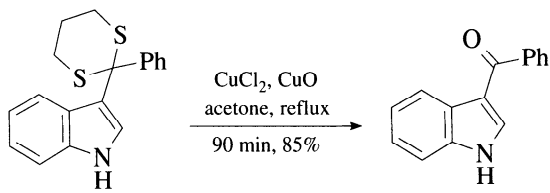
General Methods of Cleavage[41]

1. $Hg(ClO_4)_2$, MeOH, $CHCl_3$, 25°, 5 min, 93% yield.[42,43]

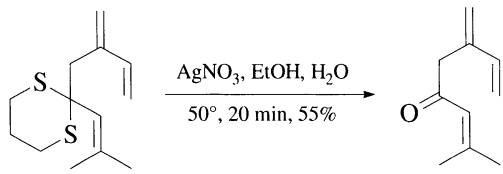


Ref. 43

2. A 1,3-dithiane is stable to the conditions ($HgCl_2$, $CaCO_3$, CH_3CN–H_2O, 25°, 1–2 h) used to cleave a methylthiomethyl (MTM) ether (i.e., a monothio acetal).[44]
3. $CuCl_2$, CuO, acetone, reflux, 90 min, 85% yield.[45]

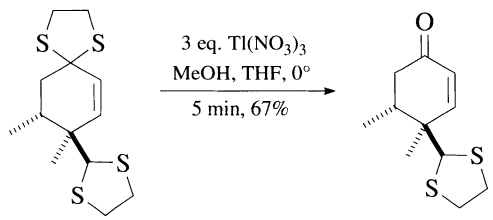


4. $AgNO_3$, EtOH, H_2O, 50°, 20 min, 55% yield.[46]



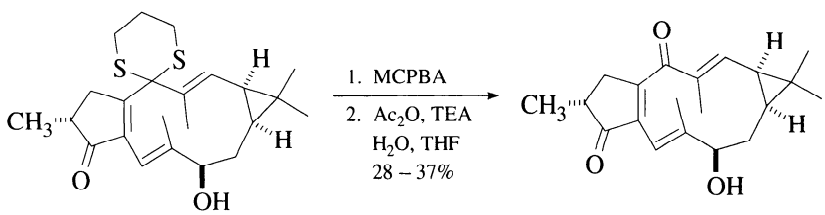
Attempted cleavage using Hg(II) salts gave material that could not be distilled. 1,3-Dithiolanes can also be cleaved with Ag_2O (MeOH, H_2O, reflux, 16 h–4 days, 75–85% yield).[47]

5. For (n = 2): NBS, aq. acetone, 0°, 20 min, 80% yield.[48]
6. For (n = 3): NCS, $AgNO_3$, CH_3CN, H_2O, 25°, 5–10 min, 70–100% yield.[49,50]
7. For (n = 2,3): $Tl(NO_3)_3$, CH_3OH, 25°, 5 min, 73–99% yield. These conditions have been used to effect selective cleavage of α,β-unsaturated thioketals.[51] In this case, $Hg(OAc)_2$ was found not to be reliable.



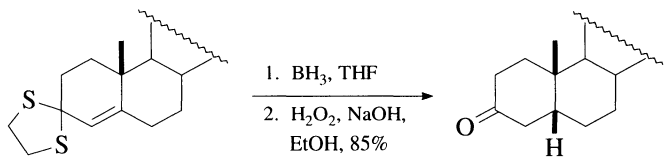
8. For (n = 2,3): $Tl(OCOCF_3)_3$, THF, 25°, 1 min, 83–95% yield.[52] $Tl(TFA)_3$, Et_2O, H_2O, 94% yield.[53] α,β-Unsaturated 1,3-dithiolanes are selectively cleaved in the presence of saturated 1,3-dithiolanes [$Tl(NO_3)_3$, 5 min, 97% yield].[54]
9. For (n = 2,3): SO_2Cl_2, SiO_2, CH_2Cl_2, H_2O, 0–25°, 90–100% yield.[55]
10. For (n = 2): I_2, DMSO, 90°, 1 h, 75–85% yield.[56]
11. For (n = 2,[57] 3[58]): p-$MeC_6H_4SO_2N(Cl)Na$, aq. MeOH, 75–100% yield.
12. 1,3-Oxathiolanes are also cleaved by Chloramine-T.[58]
13. For (n = 2,3): $(PhSeO)_2O$, THF or CH_2Cl_2, 25°, 30 min to 50 h, 63–78% yield.[59]
14. For (n = 3): $Me_2CH(CH_2)_2ONO$, CH_2Cl_2, reflux, 2.5 h, 65% yield.[60] 1,3-Oxathiolanes are also cleaved by isoamyl nitrite.
15. For (n = 2,3): N-Chlorobenzotriazole, CH_2Cl_2, −80°; NaOH, 50% yield.[61] 1,3-Dithianes and 1,3-dithiolanes, used in this example to protect C_3-keto steroids, were not cleaved by $HgCl_2$–$CdCO_3$.
16. For (n = 2,3): $Ce(NH_4)_2(NO_3)_6$, aq. CH_3CN, 3 min, 70–87% yield.[62]
17. For (n = 2):O_2, $h\nu$, 4.5 h, 60–80% yield.[63] 1,3-Oxathiolanes are also cleaved by $O_2/h\nu$.

18. Electrolysis: 1.5 V, CH_3CN, H_2O, $LiClO_4$ or $Bu_4N^+ClO_4^-$, 50–75% yield.[64,65] 1,3-Dithiolanes were not cleaved efficiently by electrolytic oxidation. This method has been applied to dithiane deprotection to produce α-diketones.[66]
19. For (n = 2,3): $MeOSO_2F$, C_6H_6, 25°, 1 h, 62–88% yield;[67] or liq. SO_2, 70–85% yield.[68]
20. For (n = 2): MeI, aq. MeOH, reflux, 2–20 h, 60–80% yield.[68]
21. For (n = 3): MeI, aq. CH_3CN, 25°.[69]
22. For (n = 2): $Et_3O^+BF_4^-$, followed by 3% aq. $CuSO_4$, 81% yield.[70]
23. For (n = 2): $Me_2S^+Br\ Br^-$, CH_2Cl_2, 25°, 1 h → reflux, 8 h, followed by H_2O, 55–91% yield.[71]
24. OHCCOOH, HOAc, 25°, 15 min–20 h, 60–90% yield.[72]
25. $NO^+HSO_4^-$, CH_2Cl_2, 25°, 45 min; H_2O, 56–82% yield.[73]
26. Electrolysis: 1 V, $(p\text{-}CH_3C_6H_4)_3N$, CH_3CN, H_2O, $NaHCO_3$, 70–95% yield.[74]
27. Diiodohydantoin, −20°, 5:5:1 acetone:THF:H_2O.[10]
28. $(CF_3CO_2)_2IPh$, H_2O, CH_3CN, 85–99% yield.[75] In the presence of ethylene glycol the dithiane can be converted to a dioxolane (91% yield)[75] or in the presence of methanol to the dimethyl acetal.[76] The reaction conditions are not compatible with primary amides. Thioesters are not affected.[75] A phenylthio ester is stable to these conditions, but amides are not. The hypervalent iodine derivative 1-(*t*-butylperoxy)-1,2-benziodoxol-3(1*H*)-one similarly cleaves thioketals.[77]
29. MCPBA; Ac_2O, Et_3N, H_2O, THF, 28–37% yield.[78]



30. Pyr·HBr·Br_2, CH_2Cl_2, pyridine, $Bu_4N^+Br^-$, 0°–rt, 2 h, 80–90% yield.[79] The deprotection proceeds without olefin or aromatic ring bromination.
31. $PhOP(O)Cl_2$, DMF, NaI, 1 h, rt, 71–94% yield.[80]
32. $MeP(Ph)_3^+Br^-$, CH_2Cl_2, H_2O, NaH_2PO_4, Na_2HPO_4, 0–100% yield.[81]
33. For (n = 2): Me_3SiI or Me_3SiBr, DMSO, 65–99% yield.[82]
34. For (n = 3): DMSO, dioxane, 1.8 *M* HCl, 90–96% yield.[83]
35. For (n = 3): $Me_3S^+SbCl_6^-$, −77°; Na_2CO_3, H_2O, 95–97% yield.[83]
36. For (n = 3): MCPBA, TFA, CH_2Cl_2, 0°, 75–96% yield.[84]
37. For (n = 2): $CuCl_2{\cdot}2H_2O$, SiO_2, CH_2Cl_2, H_2O, 50–94% yield.[36]
38. For (n = 2,3): 2,4,6-triphenylpyrylium perchlorate, $h\nu$, O_2, CH_2Cl_2, 13–95% yield.[85,86]

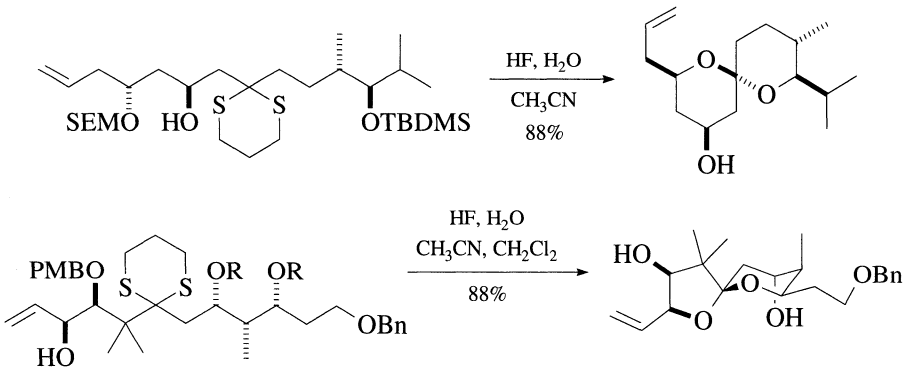
39. TMSOTf, CH_2Cl_2, $NO_2C_6H_4CHO$, rt, 95% yield.[87] Diphenylthio acetals are also cleaved in high yield.
40. DMSO, 140–160°, 4–5 h.[88]
41. For (n = 2,3): visible light, methylene green, CH_3CN, H_2O, 86–97% yield.[89]
42. For (n = 2,3): nitrogen oxides, CH_2Cl_2, 40–96%, yield.[90]
43. For (n = 2): SeO_2, AcOH, rt, 0.5–2 h, 90–98% yield.[91]
44. For (n = 2, 3): H_5IO_5, ether, THF, 77–99% yield.[92] This method also cleaves oxathioacetals, but did not affect the acid-sensitive acetonide or 1,3-dioxolane. Note that ethereal periodic acid has been used to cleave terminal acetonides with subsequent glycol cleavage.[93]
45. $AgNO_3$, I_2, THF, H_2O, 53–100% yield[94]
46. An anomolous cleavage of a dithiolane was observed during an attempted hydroboration.[95]



Ref. 95

47. DDQ, BF_3, CH_2Cl_2, air, H_2O, >90% yield.[96]
48. DDQ, CH_3CN, photolysis or reflux, 1.5–2 h, 90–95% yield.[97]
49. DDQ, CH_3CN, H_2O (9:1), 0.5–6 h, 30–88% yield.[98] Dithiane derivatives of aromatic aldehydes give thioesters in low yields; dithiolanes are not effectively cleaved.
50. HgO, BF_3.[99]
51. $HgCl_2$, HgO, MeOH; $LiBF_4$, H_2O, CH_3CN, 89–91% yield.[99]
52. $h\nu$, sen., O_2, CH_3CN or CH_2Cl_2, 62–96% yield.[100,101]
53. NaTeH; H_2O, air, 80–85% yield.[102]
54. $SbCl_5$, N_2, CH_2Cl_2, 0°, 10 min; aq. $NaHCO_3$, 0°, 10 min, 63–100% yield.[103]
55. $GaCl_3$, MeOH, O_2, CH_2Cl_2, rt, 24 h, 71–99% yield.[104]
56. Amberlyst 15, acetone, CH_2O, H_2O, 80°, 10–25 h, 50–80% yield.[105]
57. *N*-Fluoro-2,4,6-trimethylpyridinium trifluormethanesulfonate, −10°, CH_2Cl_2, THF, H_2O, 68–91% yield.[106]
58. Dowex 50W, acetone, paraformaldehyde, reflux, 50–90% yield.[107]
59. $PhI(O_2CCCl_3)_2$, CH_3CN, H_2O, rt, 5 min, >95% yield.[108]
60. Oxone, wet alumina, $CHCl_3$, reflux, 15–180 min, 70–96% yield.[109]
61. $Pe(phen)_3(PF_6)$, CH_3CN, H_2O, 43–75% yield. Hydroxyl and THP groups are not compatible with these conditions.[110]
62. Deprotection of a thioketal can occur with HF, which usually does not

affect this group, when neighboring group participation occurs, as in the following case.[111]



R = TBDMS PMB = *p*-methoxybenzyl

Note the unusual cleavage of the PMB ether as well.[112]

63. Clayfen, microwave, 87–97%. The reaction is done in the solid state.[113]
64. $Fe(NO_3)_3$, silica gel, hexane, 40–50°, 3–30 min, 86–100% yield.[114] $Fe(NO_3)_3$ and Montmorillonite K10 Clay in hexane are also effective.[115]

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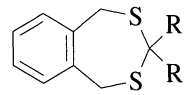
1,5-Dihydro-3*H*-2,4-benzodithiepin Derivative:



Dithiepin derivatives, prepared in high yield ($FeCl_3$–SiO_3, CH_2Cl_2, rt, 84–99%)[1] from 1,2-bis(mercaptomethyl)benzenes, are cleaved by $HgCl_2$ (80% yield). Neither reagents nor products have unpleasant odors.[2]

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Monothio Acetals and Ketals

Acyclic Monothio Acetals and Ketals

Acyclic monothio acetals and ketals can be prepared directly from a carbonyl compound or by transketalization, a reaction that does not involve a free carbonyl group, from a 1,3-dithiane or 1,3-dithiolane. They are cleaved by acidic hydrolysis or Hg(II) salts.

O-Trimethylsilyl-S-alkyl Acetals and Ketals: $R_2C(SR')OSiMe_3$

Formation

1. $RSSiMe_3$, ZnI_2, 25°, 30 min, 80–90% yield.[1]
2. Me_3SiCl, R′SH, Pyr, 25°, 3 h, 75–90% yield.[2]
3. TMSImidazole, RSH, 90 min, 81–94% yield.[3]

Cleavage

1. dil. HCl.[2]
2. In ether or tetrahydrofuran, organolithium reagents cleave the silicon–oxygen bond; in hexamethylphosphoramide, they react at the carbon atom.[2]

1 D. A. Evans, L. K. Truesdale, K. G. Grimm, and S. L. Nesbitt, *J. Am. Chem. Soc.*, **99**, 5009 (1977).
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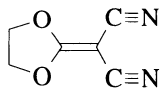
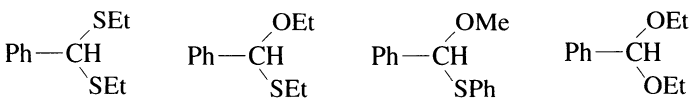
O-Alkyl-*S*-alkyl or -*S*-phenyl Acetals and Ketals: $R_2C(OR')SR''$

Formation

1. From a dimethyl acetal: Et_2AlSPh, 0°, 78% yield.[1]
2. From a dimethyl acetal: $BCl_3{\cdot}Et_2O$, −45°, CH_3SH, 73% yield.[2]
3. From a dialkyl acetal: Bu_3SnSPh, $BF_3{\cdot}Et_2O$, toluene, −78° → 0°, 64–100% yield.[3] These conditions also convert MOM and MEM groups to the corresponding phenylthiomethyl groups in 64–77% yield.
4. From a dialkyl acetal: $MgBr_2$, Et_2O, rt, PhSH, 91% yield.[4] MOM groups are converted to phenylthiomethyl groups in 75% yield, but MEM groups do not react.
5. ROTMS (R = 4-MeBn, 4-MeOBn, 2-butenyl), PhSTMS, $CHCl_3$, TMSOTf, −75°, 37–93%.[5]
6. From a dimethyl ketal: cat.  C≡N,PhSTMS, DMF, 0–60°, 62–90% yield.[6]

Cleavage

1. The mechanisms for hydrolysis of *O,S*-acetals have been reviewed. The following acid-catalyzed cleavage rates show that the *O,S*-acetals have a stability that lies between thioacetals and acetals:[7]



3.5×10^{-4}	1.3	41	160

An extensive review of the chemistry of *O,S*-acetals has been published.[8]

2. Electrolysis: Pt electrode, KOAc, AcOH, 10 V, 18–20°; K_2CO_3, MeOH, 81–91% yield.[9] These cleavage conditions could, in principle, be used to cleave the MTM group.
3. $HgCl_2$, H_2O, $HClO_4$.[10] The section on MTM ethers should be consulted.

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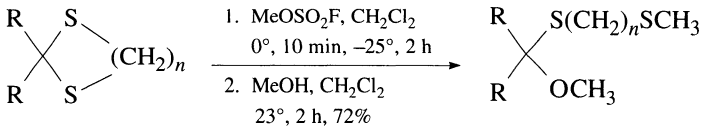
O-Methyl-*S*-2-(methylthio)ethyl Acetals and Ketals: $R_2C(OMe)SCH_2CH_2SMe$

Formation[1]



$n = 2, 3$

Cleavage[1]

1. $HgCl_2$, $CaCO_3$, THF, H_2O, 0°, rapid.

These derivatives are less susceptible to oxidation and hydrogenolysis than are the 1,3-dithiane and 1,3-dithiolane precursors.

1. E. J. Corey and T. Hase, *Tetrahedron Lett.*, 3267 (1975).

Cyclic Monothio Acetals and Ketals

1,3-Oxathiolanes (Chart 5): 

Formation

1. $HSCH_2CH_2OH$, $ZnCl_2$ AcONa, dioxane, 25°, 20 h, 60–90% yield.[1,2]
2. $HSCH_2CH_2OH$, TMSOTf, 10 min, 50–78% yield.[3]

Cleavage

The section on the cleavage of 1,3-dithianes and 1,3-dithiolanes should be consulted, since many of the methods described there are also applicable to the cleavage of oxathiolanes.

1. $HgCl_2$, AcOH, AcOK, 100°, 1 h, 83% yield.[4]
2. $HgCl_2$, NaOH, EtOH, H_2O, 25°, 30 min, 91% yield.[4]
3. Raney Ni, AcOH, AcOK, 100°, 90 min, 92% yield.[4]
4. HCl, AcOH, reflux, 22 h, 60% yield.[5]
5. $AgNO_3$, NCS, 80% CH_3CN, H_2O.[6]
6. Benzyne, $ClCH_2CH_2Cl$, 49–100% yield.[7]
7. 4-Nitrobenzaldehyde, TMSOTf, CH_2Cl_2, rt, 75–97% yield.[8] Dithiolanes are stable to these conditions.

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Diseleno Acetals and Ketals: $R_2C(SeR')_2$

Selenium compounds are generally HIGHLY TOXIC.

Formation

1. RSeH, $ZnCl_2$, N_2, CCl_4, 20°, 3 h, 70–95% yield.[1]
2. From a ketal: $(PhSe)_3B$, CF_3COOH, $CHCl_3$, 20°, 20 min – 24 h.[2]

Cleavage

1. $HgCl_2$, $CaCO_3$, CH_3CN, H_2O, 20°, 2–4 h, 65–80% yield.[1]
2. $CuCl_2$, CuO, acetone, H_2O, 20°, 5 min–2 h, 73–99% yield.[1]
3. H_2O_2, THF, 0°, 15 min → 20°, 3 h, 60–65% yield.[1]
4. $(PhSeO)_2O$, THF, 20° or 60°, 5 min → 6 h, 60–90% yield.[1]
5. Clay-supported ferric nitrate (Clayfen) or clay-supported cupric nitrate (Claycop), pentane, rt, 60–97% yield.[3]

Diseleno acetals and ketals are cleaved more rapidly than their dithio counterparts; a methyl derivative is cleaved more rapidly than a phenyl derivative. Methyl iodide or ozone converts diseleno acetals and ketals to vinyl selenides.[1]

1. A. Burton, L. Hevesi, W. Dumont, A. Cravador, and A. Krief, *Synthesis*, 877 (1979).
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MISCELLANEOUS DERIVATIVES

O-Substituted Cyanohydrins

O-Acetyl Cyanohydrin: $R_2C(CN)OAc$

Formation

1. $Me_2C(CN)OH$, Et_3N, 25°, 2 h, 82% yield; Ac_2O, Pyr, 25°, 40 h, 82% yield.[1]
2. From a cyanohydrin: Ac_2O, $FeCl_3$, 25–92% yield.[2] Other anhydrides are also effective in this conversion.
3. AcCN, K_2CO_3, CH_3CN, 79–96% yield.[3]

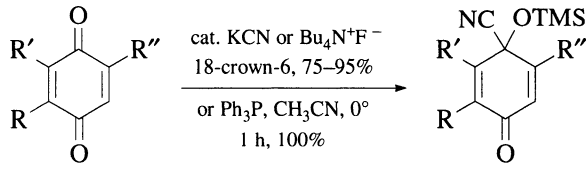
Cleavage

1. $Li(O\text{-}t\text{-}Bu)_3AlH$, THF; KOH, CH_3OH, H_2O, 25°, 5 min, 84% yield.[1]

O-Trimethylsilyl Cyanohydrin: $R_2C(CN)OSiMe_3$ (Chart 5)

Formation

1. Me_3SiCN, cat. KCN or $Bu_4N^+F^-$, 18-crown-6, 75–95% yield.[4]
2. Me_3SiCN, Ph_3P, CH_3CN, 0°, 1 h, 100% yield.[5]



3. $Me_2C(CN)OSiMe_3$, KCN, 130°.[6]
4. Me_3SiCl, KCN, Amberlite XAD-4, CH_3CN, 60°, 8 h, 81–97% yield.[7]
5. Me_3SiCl, KCN, NaI, Pyr, CH_3CN, 50–77% distilled yields, 100% by NMR.[8]
6. R_3SiCl, KCN, ZnI_2, CH_3CN, 86–98% yield.[9] This method was used to prepare the t-$BuPh_2Si$, t-$BuMe_2Si$, and i-Pr_3Si cyanohydrins.
7. TMSCN, THF, $Yb(CN)_3$, 0°→ rt, 84–99% yield.[10]
8. TMSCN, CH_2Cl_2, $Yb(OTf)_3$, 55–95% yield. Aromatic ketones fail to react.[11]
9. TMSCN, CH_2Cl_2, −40°, $Eu(fod)_3$, 45–95% yield.[12]

10. TMSCN, TEA, 91–100% yield.[13]
11. TMSCN, CH_3CN, reflux, 2 h, 89–95% yield.[14] These conditions are selective for aldehydes.
12. TMSCN, $MgAlCO_3$, heptane, 90–99% yield.[15]
13. TMSCN, (−)-DIPT [diisopropyl L-tartrate], Ti(*i*-PrO)$_4$, CH_2Cl_2, 0°, 6 h, rt, 12 h, 95% yield. These conditions afford chiral cyanohydrins.[16]
14. (*R*)-BINOL-Ti(O-*i*-Pr)$_2$, TMSCN, CH_2Cl_2. Enantioselectivity of up to 75% is obtained.[17]
15. Chiral (salene)Ti(IV) complexes, TMSCN. This system is selective for aldehydes; the asymmetric induction is dependent upon aldehyde structure.[18,19]
16. Pybox–$AlCl_3$, [(*S,S*)-2,6-bis(4′-isopropyloxazolin-2′-yl)pyridine], TMSCN. Mandelonitrile was formed in 92% yield (>90% ee).[20]
17. Ti(O-*i*-Pr)$_4$, sulfoximines, TMSCN.[21]
18. Bu_2SnCl_2 or Ph_2SnCl_2, TMSCN, 71–97% yield.[22]

Cleavage

1. AgF, THF, H_2O, 25°, 2.5 h, 77% yield.[5]
2. Dilute acid or base.[23]
3. (*S*)-Hydroxynitrile lyase can be used for the decomposition of cyanohydrins with some level of enantioselectivity.[24]

O-1-Ethoxyethyl Cyanohydrin: $R_2C(CN)OCH(OC_2H_5)CH_3$

The ethoxyethyl cyanohydrin was prepared (NaCN, HCl, THF, 0°, 75% yield, followed by $EtOCH{=}CH_2$, HCl, 50% yield) to convert an aldehyde ultimately to a protected ketone. It was cleaved by hydrolysis (0.01 *N* HCl, MeOH, 25°, followed by NaOH, 0°, 85% yield).[25]

O-Tetrahydropyranyl Cyanohydrin: $R_2C(CN)O$–THP

The tetrahydropyranyl cyanohydrin was prepared from a steroid cyanohydrin (dihydropyran, TsOH, reflux, 1.5 h) and cleaved by hydrolysis (cat. concd. HCl, acetone, reflux, 15 min, followed by aq. pyridine, reflux, 1 h).[26]

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Substituted Hydrazones

_N,N_-Dimethylhydrazone: $RR'C{=}NN(CH_3)_2$ (Chart 5)

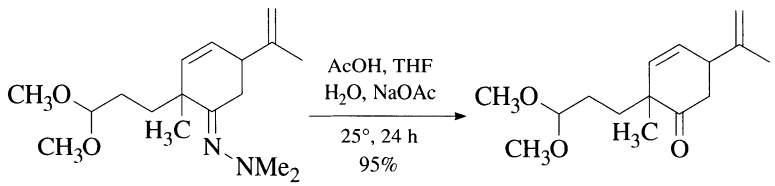
Formation

1. H_2NNMe_2, EtOH-HOAc, reflux, 24 h, 90–94% yield.[1]
2. $Me_2AlNHNMe_2$, $PhCH_3$, reflux, 3–5 h, 77–99% yield.[2]
3. H_2NNMe_2, TMSCl, 25°, 36 h, 92% yield.[3]

Cleavage

1. $NaIO_4$, MeOH, pH 7, 2–3 h, 90% yield.[4]
2. $Cu(OAc)_2$, H_2O, THF, pH 5.4, 25°, 15 min, 97% yield.[5]
3. $CuCl_2$, THF, HPO_4^-, $\rightarrow$ pH 7, 85–100% yield.[5]
4. CH_3I, 95% EtOH, reflux, 80–90% yield.[6]
5. O_3, CH_2Cl_2, $-78°$, 60–100% yield.[7]
6. O_2, *hv*, Rose Bengal, MeOH, $-78° \rightarrow -20°$, followed by Ph_3P or Me_2S, 48–88% yield.[8]

7. CoF_3 ($CHCl_3$, reflux, 67–93% yield);[9] $MoOCl_3$ or MoF_6 (H_2O, THF, 25°, 4 h, 80–90% yield);[10] WF_6 ($CHCl_3$, 0° → 25°, 1 h, 84–95% yield);[11] UF_6 (50–95% yield).[12]
8. N_2O_4, −40° → 0°, CH_3CN, THF, $CHCl_3$, CCl_4, ~10 min, 75–95% yield.[13] This method is also effective for the regeneration of ketones from oximes (45–95% yield).
9. $NaBO_3 \cdot 4H_2O$, *t*-BuOH, pH 7, 60°, 24 h, 70–95% yield.[14]
10. AcOH, THF, H_2O, AcONa, 25°, 24 h, 95% yield.[15]



N,N-Dimethylhydrazones are stable to CrO_3/H_2SO_4(0°, 3 min), to $NaBH_4$ (EtOH, 25°), to $LiAlH_4$ (THF, 25°), and to B_2H_6 followed by H_2O_2/OH^-. They are cleaved by CrO_3/Pyr and by *p*-$NO_2C_6H_4CO_3H/CHCl_3$, 25°.[6]

11. Silica gel, THF, H_2O, rt, 3–10 h, 60–74% yield[16] or silica gel, CH_2Cl_2, 77–100% yield.[17]
12. $BF_3 \cdot Et_2O$, acetone, H_2O, 93–100% yield.[18]
13. MCPBA, DMF, −63°, 100% yield.[19] Hydrazones of aldols are cleaved without elimination under these conditions.[20] An axial α-methyl group on a cyclohexanone does not epimerize under these conditions.[19]
14. $MMPP \cdot 6H_2O$ (magnesium monoperoxyphthalate), pH 7 buffer, MeOH, 0°, 5–120 min, 76–99% yield.[21] These conditions were used to cleave the related SAMP hydrazone in the presence of two trisubstitued alkenes in 46% yield.[22]
15. Peracetic acid.[23]
16. Dimethyldioxirane, acetone, 89% yield.[24]
17. $NOBF_4$, CH_2Cl_2, Pyr, 59–86% yield. Oximes are cleaved similarly in 55–82% yield.[25]
18. $Pd(OAc)_2$, $SnCl_2$, DMF, H_2O, 53–100% yield. This is the only catalytic procedure for the cleavage of dimethylhydrazones.[26]
19. $[(n\text{-}Bu)_4N]_2S_2O_8$, $ClCH_2CH_2Cl$, reflux, 0.6 h, 89–97% yield.[27]

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Phenylhydrazone: $C_6H_5NHN{=}CR_2$

Formation

1. $PhNHNH_2$, AcOH, EtOH.[1]

Cleavage

1. $PhI(OTFA)_2$, CH_3CN, H_2O, 82–90% yield or $PhI(OH)OTs$, $CDCl_3$, rt, 2 h, 74–98% yield.[2] Mild oxidative regeneration of ketones occurs in good yields.
2. $(NH_4)_2S_2O_8$, clay, microwaves or ultrasound, 62–90% yield.[3]

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2,4-Dinitrophenylhydrazone (2,4-DNP group):
$R_2C{=}NNHC_6H_3$-2,4-$(NO_2)_2$ (Chart 5)

Formation

1. 2,4-$(NO_2)_2C_6H_3NHNH_2{\cdot}H_2SO_4$, EtOH, H_2O, 25°, 10 min, 80% yield.[1] In a synthesis of sativene a carbonyl group was protected as a 2,4-DNP, while a double bond was hydrated with $BH_3/H_2O_2/OH^-$. Attempted protection of the carbonyl group as a ketal caused migration of the double bond; protection as an oxime or oxime acetate was unsatisfactory, since both of these would be reduced with BH_3.

Cleavage

2,4-Dinitrophenylhydrazones are cleaved by various oxidizing and reducing agents, and by exchange reactions.

1. O_3, EtOAc, −78°, 70% yield.[1]
2. $TiCl_3$, DME, H_2O, N_2, reflux, 80–95% yield.[2]
3. Acetone, sealed tube, 75°, 20 h, 80–85% yield.[3]

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Tosylhydrazone: $CH_3C_6H_4SO_2NHN{=}CR_2$

Formation

$TsNHNH_2$, AcOH, EtOH.[1]

Cleavage

1. TS-1(titanium silicate molecular sieve), H_2O_2, MeOH, reflux, 4–18 h, 60–64% yield.[2]
2. Dimethyldioxirane, acetone, 95% yield.[3]
3. $Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$, acetone, H_2O, reflux, 70–95% yield.[4]
4. $KHSO_5$, aq. CH_3CN, 63–99% yield.[5]
5. Dimethyldioxirane, acetone, pH 6 , 10–144 h, 67–99% yield.[6]
6. 70% *t*-Butyl hydroperoxide, CCl_4, reflux, 4–18 h, 50–100% yield.[7] Cleavage is effective only for aromatic tosylhydrazones.

7. Na_2O_2, pentane, H_2O, reflux, 6 h, 69–72% yield.[8]

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Semicarbazone: ($NH_2CONHN=CR_2$)

Formation

$NH_2CONHNH_2$, NaOAc, MeOH.[1]

Cleavage

1. $PhI(OAc)_2$, CH_3CN, H_2O, 70–83% yield.[2]
2. $(Bu_4N^+)_2S_2O_8^-$, $ClCH_2CH_2Cl$, reflux, 89–97% yield.[3]
3. Pyruvic acid, acetic acid, $CHCl_3$, 43–61%.[4]
4. $CuCl_2 \cdot 2H_2O$, CH_3CN, reflux, 10–390 min, 7–97% yield.[5]
5. TMSCl, $NaNO_2$ or $NaNO_3$, Aliquat 366, 3–5 h, CH_2Cl_2, 75–95% yield.[6]

Diphenylmethylsemicarbazone: ($Ph_2CHNHCONHN=CR_2$)

This derivative was used to improve the solubility characteristic of an argininal semicarbazone for solution-phase peptide synthesis.

Formation

$Ph_2CHNHCONHNH_2$, NaOAc, EtOH, H_2O, reflux, 1 h, 78% yield.[7]

Cleavage

Since hydrogenolysis resulted in only a 20% yield of the free aldehyde, a two-step procedure was developed in which the diphenylmethyl group was first cleaved with HF/anisole and then the unsubstituted semicarbazone was cleaved with formalin in 40–60% overall yield.

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Oxime Derivatives: $R_2C{=}NOH$

Formation

1. $H_2NOH{\cdot}HCl$, Pyr, 60°. This is the standard method for the preparation of oximes. Ethanol or methanol can be used as cosolvents.
2. $H_2NOH{\cdot}HCl$, DABCO, MeOH, rt, 87% for a camphor derivative.[1] This method was reported to be better than when pyridine was used as the solvent and base.
3. TMSNHOTMS, KH, 100% yield.[2]
4. $H_2NOH{\cdot}HCl$, Amberlyst A21, EtOH, 1–10 h, 70–97% yield.[3]

Cleavage

Oximes are cleaved by oxidation, reduction, or hydrolysis in the presence of another carbonyl compound. Following are some synthetically useful methods:

1. $CH_3CO(CH_2)_2COOH$, 1 *N* HCl, 25°, 3 h, 94% yield.[4] Pyruvic acid (HOAc, reflux, 1–3 h, 77% yield)[5] and acetone (80–100 h, 72% yield)[6] effect cleavage in a similar manner.
2. $(PhSeO)_2O$/THF, 50°, 1–3 h, 80–95% yield.[7] An *O*-methyl oxime is stable to phenylselenic anhydride.
3. $Na_2S_2O_4$, H_2O, 25°, 12 h or 40°, few hours ~95% yield.[8]
4. $NaHSO_3$, EtOH–H_2O, reflux, 2–16 h; dil. HCl, 30 min, 85% yield.[9,10]
5. Ac_2O, 20°; $Cr(OAc)_2$/THF–H_2O, 25–65°, 75–95% yield.[11] Chromous acetate also cleaves unsubstituted oximes, but the reaction is slow and requires high temperatures.
6. $NaNO_2$, 1 *N* HCl, CH_3OH, H_2O, 0°, 3 h, 76% yield.[12] In the last step of a synthesis of erythronolide A, acid-catalyzed hydrolysis of an acetonide failed because the carbonyl-containing precursor was unstable to acidic hydrolysis (3% MeOH, HCl, 0°, 30 min, conditions developed for the synthesis of erythronolide B). Consequently, the carbonyl group was protected as an oxime, the acetonide was cleaved, and the carbonyl group was regenerated.
7. NOCl, Pyr, −20°; H_2O, reflux, 70–90% yield.[13] Olefins were not affected under these conditions. The related nitrosyl tetrafluoroborate has also been used.[14]

8. $TiCl_3$, H_2O, rt, 1 h, 85% yield.[15] This is an excellent reagent that works when cleavage of a methoxy oxime with chromous ion fails.
9. VCl_2, H_2O, THF, 8 h, rt, 75–92% yield.[16]
10. Et_3NH^+ $ClCrO_3^-$, $ClCH_2CH_2Cl$, 2 h, rt, 60–90% yield.[17] This reagent was reported to work better than PCC (pyridinium chlorochromate). Trimethylsilyl chlorochromate is also effective.[18]
11. Bu_3P, PhSSPh, THF, 85% yield.[19]
12. *t*-BuONO, *t*-BuOK; H_2O, NaOH; acidify, 40°.[20]
13. TMSCl, $NaNO_2$, CCl_4, 5% Aliquat 336, rt, 3–5 h, 64–98% yield.[21]
14. NaOCl, MeCN, rt, 23–99% yield.[22]
15. Zinc bismuthate, $PhCH_3$ or CH_3CN, reflux, 0.5–2 h, 56–85% yield.[23]
16. MnO_2, hexane or CH_2Cl_2, rt, 70–92% yield.[24] The oximes of pyruvates and *O*-alkyl oximes are not cleaved under these conditions.
17. $PhICl_2$, Pyr, $CHCl_3$, 3 h, 10°, 65–80% yield.[25]
18. $TiCl_4$, NaI, CH_3CN, rt, 63–97% yield.[26]
19. Baker's yeast, pH 7.2, H_2O, EtOH, 62–95% yield with sonication.[27]
20. TS-1 Zeolite, H_2O_2, acetone, reflux, 65–86% yield.[28]
21. Dimethyldioxirane, acetone, 0° or rt, 80–100% yield.[29]
22. $Ru_3(CO)_{12}$, CO, 20 atm, 4 h, 100°. These conditions reduce the oxime to an imine that is easily hydrolyzed with water.[30] Aldehyde oximes give low yields of nitriles.
23. $Cu(NO_3)_2$, Bentonite, hexane, acetone, 60–97% yield.[31] When silica gel is used as the support, tosylhydrazones and thioketals are also cleaved in excellent yield.[32]
24. $KMnO_4$, CH_3CN, H_2O, rt, 25-96% yield.[33]
25. $Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$, acetone, water, reflux 30 min–24 h, 70–95% yield. Semicarbazones, tosylhydrazones, and hydrazones are also cleaved.[34]
26. $(NH_4)_2S_2O_8$–silica gel, microwave irradiation, 59–83% yield.[35]
27. $BiCl_3$, microwave irradiation, 2 min, THF, 70–96% yield. α,β-Unsaturated systems were not effectively cleaved under these conditons.[36]
28. 70% *t*-Butyl hydroperoxide, CCl_4, reflux, 4–18 h, 30–100% yield.[37]
29. NBS, CCl_4, 25°, 80–96% yield.[38]
30. $Mo(CO)_6$, CH_3CN, H_2O, 59–94% yield.[39]
31. $Mn(OAc)_3$, benzene, reflux, 1–2 h, 86–96% yield.[40]
32. Wet $NaIO_4$–silica, microwave, 68–93% yield.[41]
33. $KHSO_5$, AcOH, 70–88% yield.[42]

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20. E. J. Corey, M. Narisada, T. Hiraoka, and R. A. Ellison, *J. Am. Chem. Soc.*, **92**, 396 (1970).
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24. T. Shinada and K. Yoshihara, *Tetrahedron Lett.*, **36**, 6701 (1995).
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26. R. Balicki and L. Kaczmarek, *Synth. Commun.*, **21**, 1777 (1991).
27. A. Kamal, M. V. Rao, and H. M. Meshram, *J. Chem. Soc., Perkin Trans. 1*, 2056 (1991).
28. R. Joseph, A Sudalai, and T. Ravindranathan, *Tetrahedron Lett.*, **35**, 5493 (1994).
29. G. A. Olah, Q. Liao, C. S. Lee, and G. K. S. Prakash, *Synlett*, 427 (1993).
30. M. Akazome, Y. Tsuji, and Y. Watanabe, *Chem. Lett.*, 635 (1990).
31. R. Sanabria, P. Castañeda, R. Miranda, A. Tubón, F. Delgado, and L. Velasco, *Org. Prep. Proced. Int.*, **27**, 480 (1995).
32. J. G. Lee and J. P. Hwang, *Chem. Lett.*, 507 (1995).
33. A. Wali, P. A. Ganeshpure, and S. Satish, *Bull.Chem. Soc. Jpn.*, **66**, 1847 (1993).

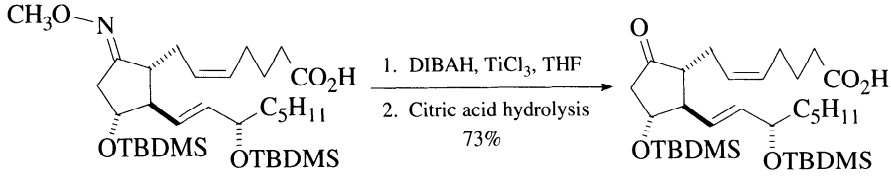
34. M. Curini, O. Rosati, and E. Pisani, *Synlett*, 333 (1996).
35. R. S. Varma and H. M. Meshram, *Tetrahedron Lett.*, **38**, 5427 (1997).
36. A. Boruah, B. Baruah, D. Prajapati, and J. S. Sandhu, *Tetrahedron Lett.*, **38**, 4267 (1997).
37. N. B. Barhate, A. S. Gajare, R. D. Wakharkar, and A. Sudalai, *Tetrahedron Lett.*, **38**, 653 (1997).
38. B. P. Bandgar, L. B. Kunde, and J. L. Thote, *Synth. Commun.*, **27**, 1149 (1997).
39. F. Geneste, N. Racelma, and A. Moradpour, *Synth. Commun.*, **27**, 957 (1997).
40. A. S. Demir, C. Tanyeli, and E. Altinel, *Tetrahedron Lett.*, **38**, 7267 (1997).
41. R. S. Varma, R. Dahiya, and R. K. Saini, *Tetrahedron Lett.*, **38**, 8819 (1997).
42. D. S. Bose and P. Srinivas, *Synth. Commun.*, **27**, 3835 (1997).

O-Methyl Oxime: $R_2C{=}NOCH_3$

Formation[1]

1. $MeONH_2{\cdot}HCl$, Pyr, MeOH, 23°, 30 min, 81% yield.

Cleavage[1]

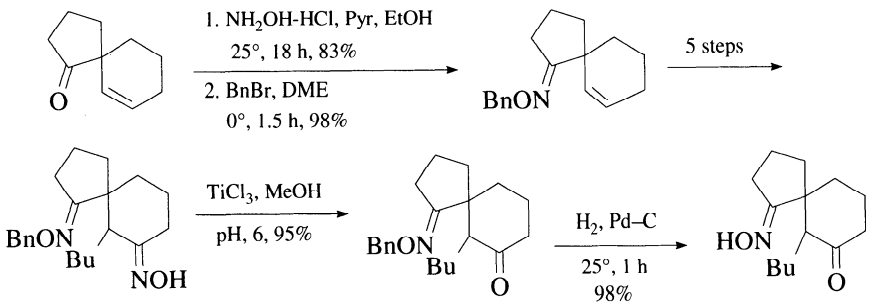


This method was developed because conventional procedures failed to cleave the oxime.

1. E. J. Corey, K. Niimura, Y. Konishi, S. Hashimoto, and Y. Hamada, *Tetrahedron Lett.*, **27**, 2199 (1986).

O-Benzyl Oxime: $R_2C{=}NOCH_2Ph$

The following reactions were used in a synthesis of perhydohistrionicotoxin; the carbonyl groups were protected as an oxime and an *O*-benzyl oxime.[1]



The **2-chlorobenzyl** group has been used in the protection of an oxime during the modification of erythromycin A.[2]

1. E. J. Corey, M. Petrzilka, and Y. Ueda, *Helv. Chim. Acta*, **60**, 2294 (1977).
2. Y. Watanabe, S. Morimoto, T. Adachi, M. Kashimura, and T. Asaka, *J. Antibiot.*, **46**, 647 (1993).

O-Phenylthiomethyl Oxime: $R_2C{=}NOCH_2SC_6H_5$ (Chart 5)

In a prostaglandin synthesis, a carbonyl group was protected as an oxime that had its hydroxyl group protected against Collins oxidation by the phenylthiomethyl group. The phenylthiomethyl group is readily removed to give an oxime that is then cleaved to the carbonyl compound.[1]

Formation[1]

1. $PhSCH_2ONH_2$, Pyr, 25°, 24 h, 100% yield.

Cleavage[1]

1. $HgCl_2$, HgO, AcOH, AcOK, 25–50°, 0.5–48 h, 75% yield; K_2CO_3, MeOH, 25°, 5 min, 100% yield. These conditions remove the $PhSCH_2$– group from the oxime, which is then cleaved with AcOH/$NaNO_2$ (10°, 1 h). This group was also stable to acid, base, and $LiAlH_4$.

1. I. Vlattas, L. Della Vecchia, and J. J. Fitt, *J. Org. Chem.*, **38**, 3749 (1973).

Imines

In general, imines are too reactive to be used to protect carbonyl groups. In a synthesis of juncusol,[1] however, a **bromo**- and an **iodocyclohexylimine** of two identical aromatic aldehydes were coupled by an Ullmann coupling reaction modified by Ziegler.[2] The imines were cleaved by acidic hydrolysis (aq. oxalic acid, THF, 20°, 1 h, 95% yield). Imines of aromatic aldehydes have also been prepared to protect the aldehyde during ring metalation with *s*-BuLi.[3]

1. A. S. Kende and D. P. Curran, *J. Am. Chem. Soc.*, **101**, 1857 (1979).
2. F. E. Ziegler, K. W. Fowler, and S. Kanfer, *J. Am. Chem. Soc.*, **98**, 8282 (1976).
3. B. A. Keay and R. Rodrigo, *J. Am. Chem. Soc.*, **104**, 4725 (1982).

Substituted Methylene Derivatives: RR′C=C(CN)R″ (Chart 5)

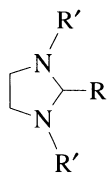
RR′ = substituted pyrrole; R″ = –CN,[1] $-CO_2Et$[2]

The substituted methylene derivative, prepared from a 2-formylpyrrole and a malonic acid derivative, was used in a synthesis of chlorophyll.[1] It is cleaved under drastic conditions (concd. alkali).[1,2]

1. R. B. Woodward and 17 co-workers, *J. Am. Chem. Soc.*, **82**, 3800 (1960).
2. J. B. Paine, R. B. Woodward, and D. Dolphin, *J. Org. Chem.*, **41**, 2826 (1976).

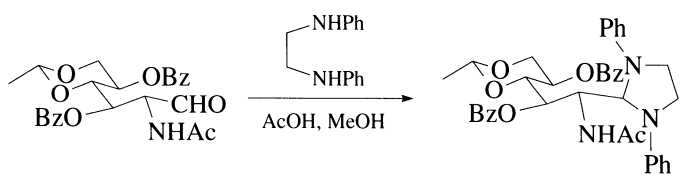
Cyclic Derivatives

***N,N′*-Dimethylimidazolidine and *N,N′*-Diarylimidazolidine:**



R′ = Me, Ar

The imidazolidine was prepared from an aldehyde with *N,N′*-dimethyl-1,2-ethylenediamine (benzene, heat, 78% yield) and cleaved with MeI (Et_2O; H_2O, 92% yield). Derivatization is chemoselective for aldehydes. The imidazolidine is stable to BuLi and LDA[1,2] and to Li/NH_3.[3] The **diphenylimidazolidine** has been prepared analogously and can be cleaved with aqueous HCl.[4,5] Alternatively, it can be prepared by using thionyl chloride (Pyr, CH_2Cl_2, 0–25°, 7 h, 93% yield).[6] A chiral version using *N,N′*-dimethyl-1*S*,2*S*-diphenyl-1,2-ethylenediamine has been used for protection as well as asymmetric induction.[7,8]



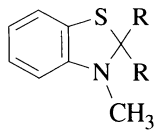
Ref. 4

The related **bis-*N,N′*-(3,5-dichlorophenyl)imidazolidine** has been used to protect an aldehyde. It is prepared from bis-*N,N′*-(3,5-dichlorophenyl)-1,2 diaminoethane (CSA, DMF, rt, 18 h, 72% yield) and is cleaved with aq. AcOH (rt, overnight, 98% yield).[9]

1. A. J. Carpenter and D. J. Chadwick, *Tetrahedron*, **41**, 3803 (1985).
2. M. Gray and P. J. Parsons, *Synlett*, 729 (1991).
3. L. E. Overman, D. J. Ricca, and V. D. Tran, *J. Am. Chem. Soc.*, **119**, 12031 (1997).

4. H.-W. Wanzlick and W. Löchel, *Chem. Ber.*, **86**, 1463 (1953).
5. A. Giannis, P. Münster, K. Sandhoff, and W. Steglich, *Tetrahedron*, **44**,7177 (1988).
6. J. J. Vanden Eynde, A. Mayence, and A. Maquestiau, *Bull. Soc. Chim. Belg.*, **101**, 233 (1992).
7. A. Alexakis, N. Lensen, and P. Mangeney, *Tetrahedron Lett.*, **32**, 1171 (1991).
8. I. Marek, A. Alexakis, and J.-F. Normant, *Tetrahedron Lett.*, **32**, 5329 (1991).
9. A. Ono, T. Okamoto, M. Inada, H. Nara, and A. Matsuda, *Chem. Pharm. Bull.*, **42**, 2231 (1994).

2,3-Dihydro-1,3-benzothiazole:

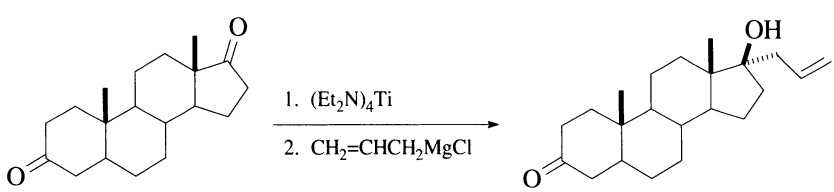


The benzothiazole group is introduced by heating 2-methylaminobenzenethiol with a carbonyl compound in ethanol (70–93% yield).[1] An enone is selectively protected over a ketone, and aldehydes react faster than ketones. Cleavage is effected with $AgNO_3$ (CH_3CN, H_2O, pH 7, 83–93% yield)[2] or by heating in Ac_2O followed by aqueous hydrolysis (HCl, $CHCl_3$, 50°, 1 h, 40% yield) of the resulting enamide.[3] **Nonaromatic thiazolidines** have also been used as protective groups. They can be cleaved by basic hydrolysis (NaOH, 25°, 95% yield).[4]

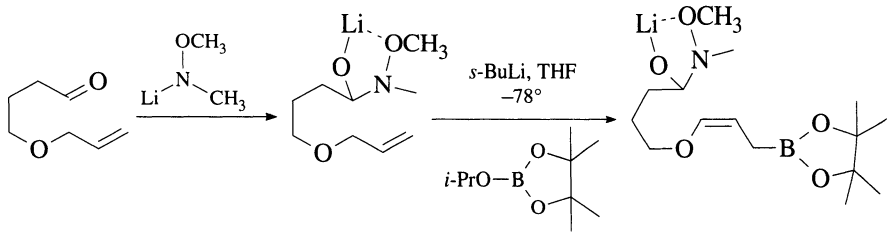
1. H. Chikashita, N. Ishimoto, S. Komazawa, and K. Itoh, *Heterocycles*, **23**, 2509 (1985).
2. H. Chikashita, S. Komazawa, N. Ishimoto, K. Inoue, and K. Itoh, *Bull. Chem. Soc. Jpn.*, **62**, 1215 (1989).
3. G. Trapani, A. Reho, A. Latrofa, and G. Liso, *Synthesis*, 84 (1988).
4. K. Ueno, F. Ishikawa, and T. Naito, *Tetrahedron Lett.*, 1283 (1969).

Diethylamine Adduct: $R_2C[OTi(NEt_2)_3]NEt_2$

Titanium tetrakis(diethylamide) selectively adds to aldehydes in the presence of ketones and to the least hindered ketone in compounds containing more than one ketone. The protection is *in situ*, which thus avoids the usual protection/deprotection sequence. Selective aldol and Grignard additions are readily performed employing this protection methodology.[1]



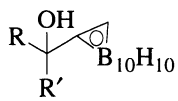
N-Methoxy-N-methylamine Adduct: $[R_2C(OLi)N(OMe)Me]$



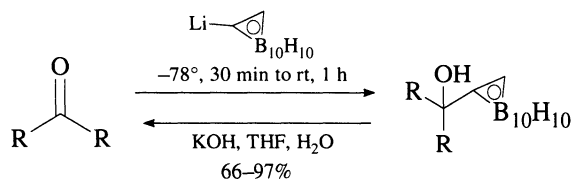
Refs. 2, 3

The use of various amine adducts of carbonyl compounds as a method of carbonyl protection has been reviewed.[4]

1. M. T. Reetz, B. Wenderoth, and R. Peter, *J. Chem. Soc., Chem. Commun.*, 406 (1983).
2. R. W. Hoffmann and I. Münster, *Tetrahedron Lett.*, **36**, 1431 (1995).
3. D. A. Evans, R. P. Polniaszek, K. M. DeVries, D. E. Guinn, and D. J. Mathre, *J. Am. Chem. Soc.*, **113**, 7613 (1991).
4. D. L. Comins, *Synlett*, 615 (1992).

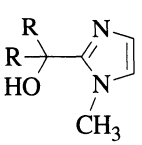
o-Carborane: 

Formation/Cleavage[1]

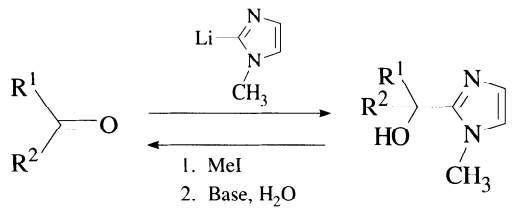


The carboranyl alcohol can also be prepared from the stannyl carborane and an aldehyde using $Pd_2(dba)_3$–$CHCl_3$/dppe. The carborane is stable to Brønsted and Lewis acids and to $LiAlH_4$.

1. H. Nakamura, K. Aoyagi, and Y. Yamamoto, *J. Org. Chem.*, **62**, 780 (1997).

1-Methyl-2-(1′-hydroxyalkyl)imidazoles: 

Formation/Cleavage[1]



This protective group is stable to 1 *N* KOH/MeOH, 70°, 7 h; 20% H_2SO_4, 70°, 7 h; H_2, Pd–C, EtOH, 1 atm, 18 h; $NaBH_4$, $LiAlH_4$, CF_3COOH, Al_2O_3/MeOH.

1. S. Ohta, S. Hayakawa, K. Nishimura, and M. Okamoto, *Tetrahedron Lett.*, **25**, 3251 (1984).

Protection of the Carbonyl Groups by Conversion to an Enolate Anion

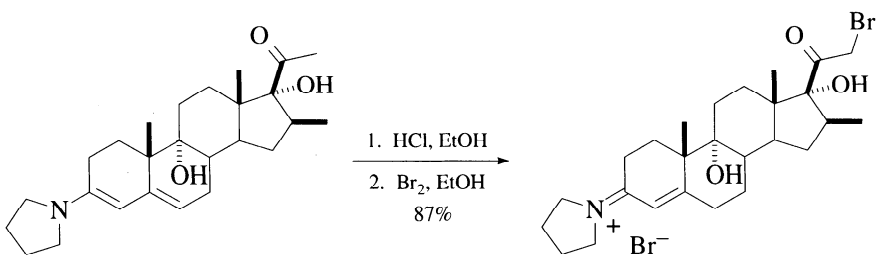
Lithium Diisopropylamide (LDA)

A 17-steroidal ketone was deprotonated by LDA to protect it from reduction during a lithium naphthalenide cleavage of a benzyl ether.[1]

1. H.-J. Liu, J. Yip, and K.-S. Shia, *Tetrahedron Lett.*, **38**, 2253 (1997).

Enamines

The use of enamines as protective groups seems largely to be confined to steroid chemistry, where they serve (in their protonated form) to protect the A–B enone system from bromination[1] and reduction.[2] A large body of literature exists on the preparation and chemistry of enamines,[3] which are easily hydrolyzed with water or aqueous acid.



1. N. I. Carruthers, S. Garshasb, and A. T. McPhail, *J. Org. Chem.*, **57**, 961 (1992).
2. J. A. Hogg, *Steroids*, **57**, 593 (1992).

3. Enamine review: A. G. Cook, Ed., *Enamines: Synthesis, Structure and Reactions*, 2d ed., M. Dekker, New York, 1988.

Methylaluminum Bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) Complex

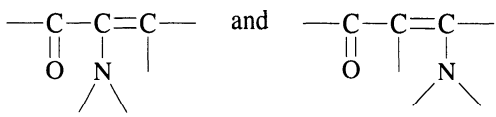
This approach to carbonyl protection uses the relative differences in basicity and the differences in steric effects to protect selectively either the more basic carbonyl group or the less hindered carbonyl group from reactions with nucleophiles such as DIBAH[1] and MeLi.[2]

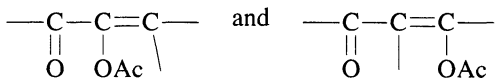
1. K. Maruoka, Y. Araki, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 2650 (1988).
2. K. Maruoka, H. Imoto, and H. Yamamoto, *Synlett*, 441 (1994).

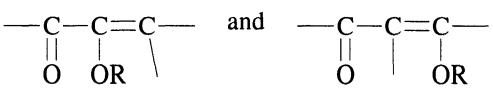
MONOPROTECTION OF DICARBONYL COMPOUNDS

Selective Protection of α- and β-Diketones

α- and β-Diketones can be protected as enol ethers, thioenol ethers, enol acetates, and enamines.

Enamines: 

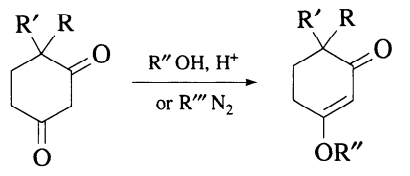
Enol Acetates: 

Enol Ethers: 

Methyl Enol Ether

Ethyl Enol Ether

***i*-Butyl Enol Ether**



R″ = R‴ + H

R″OH: R″ = Me (HCl, 25°, 8 h, 83% yield) [1]

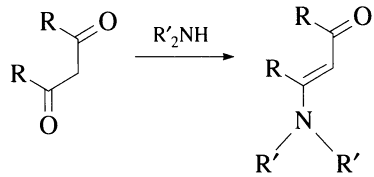
R″ = Et (TsOH, benzene, reflux, 6–8 h, 70–75% yield)[2]

R‴ = $(CH_3)_2CHCH_2$ (i-BuOH, benzene, reflux, TsOH, 16 h, 100% yield).[3] In this case, 2-methyl-1,3-cyclopentanedione was monoprotected.

Methoxyethoxymethyl (MEM) Enol Ether

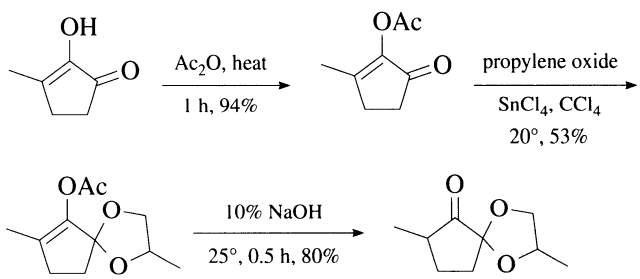
Triethylamine, MEMCl, 92% yield[4]

Enamino Derivatives (Vinylogous Amides)



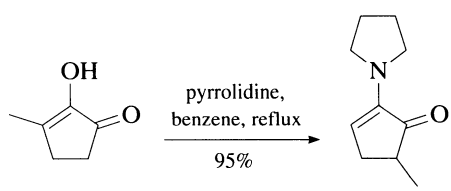
1. R'_2NH = piperidine, TsOH, benzene, reflux, 92% yield.[5]
2. R'_2NH = morpholine, TsOH, $PhCH_3$, reflux, 4–5 h, 72–80% yield.[6]
3. R'_2NH = various, 300 MPa, with or without $Yb(OTf)_3$, 0–99% yield.[7]
4. R'_2NH = various, K10 clay or SiO_2, 1–10 min, microwave, 35–99% yield.[8]
5. R'_2NH = various, $BF_3{\cdot}Et_2O$, benzene, reflux, 4–6 h, 82–96% yield.[9]
6. R'_2NH = various, Montmorillonite or alumina, 20–100°, 1–5 h, 85–99% yield.[10,11]

4-Methyl-1,3-dioxolanyl Enol Acetate



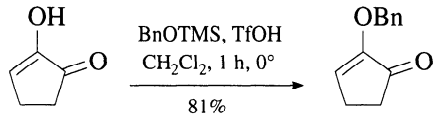
Ref. 12

Pyrrolidinyl Enamine



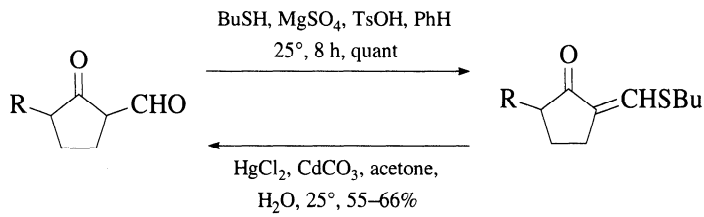
Ref. 13

Benzyl Enol Ether



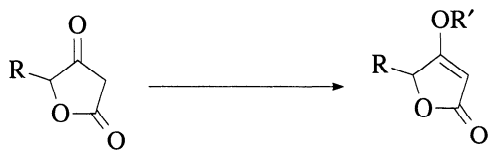
Ref. 14

Butyl Thioenol Ether



Ref. 15

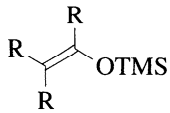
Protection of Tetronic Acids



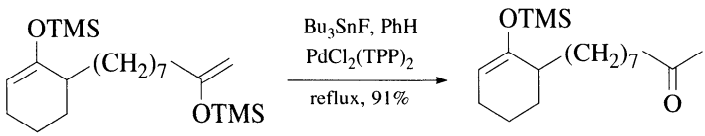
1. R′ = Me (MeI, CsF, DMF, 45–81% yield).[16]
2. R′ = Bn, allyl, Me, $TMSCH_2CH_2$, *t*-Bu, etc. (R′OH, Ph_3P, DEAD, 31–100% yield).[17]

1. H. O. House and G. H . Rasmusson, *J. Org. Chem.*, **28**, 27 (1963).
2. W. F. Gannon and H. O. House, *Org. Synth., Collect. Vol. V*, 539 (1973).
3. M. Rosenberger and P. J. McDougal, *J. Org. Chem.*, **47**, 2134 (1982).
4. A. J. H. Klunder, G. J. A. Ariaans, E. A. R. M. v. d. Loop and B. Zwanenburg, *Tetrahedron*, **42**, 1903 (1986).
5. P. Kloss, *Chem. Ber.*, **97**, 1723 (1964).
6. S. Hünig, E. Lücke and W. Brenninger, *Org. Synth., Collect. Vol. V*, 808 (1973).
7. G. Jenner, *Tetrahedron Lett.*, **37**, 3691 (1996).
8. B. Rechsteiner, F. Texier-Boullet, and J. Hamelin, *Tetrahedron Lett.*, **34**, 5071 (1993).
9. M. Azzaro, S. Geribaldi, and B. Videau, *Synthesis*, 880 (1981).
10. F. Texier-Boullet, B. Klein, and J. Hamelin, *Synthesis*, 409 (1986).
11. M. E. F. Braibante, H. S. Braibante, L. Missio, and A. Andricopulo, *Synthesis*, 898 (1994).

12. J. L. E. Erickson and F. E. Collins, Jr., *J. Org. Chem.*, **30**, 1050 (1965).
13. E. Gordon, F. Martens, and H. Gault, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **261**, 4129 (1965).
14. A. A. Ponaras and Md. Y. Meah, *Tetrahedron Lett.*, **27**, 4953 (1986).
15. P. R. Bernstein, *Tetrahedron Lett.*, 1015 (1979).
16. T. Sato, K. Yoshimatsu, and J. Otera, *Synlett*, 845 (1995).
17. J. S. Bajwa and R. C. Anderson, *Tetrahedron Lett.*, **31**, 6973 (1990).

Trimethylsilyl Enol Ethers: 

Trimethylsilyl enol ethers can be used to protect ketones, but, in general, are not used for this purpose because they are reactive under both acidic and basic conditions. More highly hindered silyl enol ethers are much less susceptible to acid and base. A less hindered silyl enol ether can be hydrolyzed in the presence of a hindered one. [1]



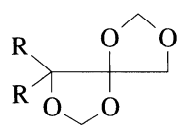
The preparation of silyl enol ethers has been reviewed.[2–4]

1. H. Urabe, Y. Takano, and I. Kuwajima, *J. Am. Chem. Soc.*, **105**, 5703 (1983).
2. E. Colvin, *Silicon in Organic Synthesis*, Butterworths, Boston, 1981, pp. 198–287.
3. W. P. Weber, *Silicon Reagents for Organic Synthesis*, Springer-Verlag, New York, 1983, pp. 255–272.
4. J. Hydrio, P. Van de Weghe, and J. Collin, *Synthesis*, 68 (1997).

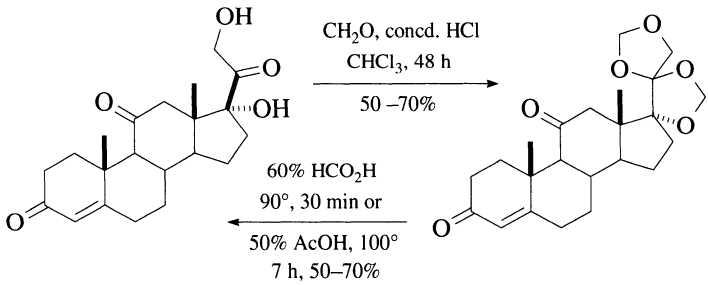
Cyclic Ketals, Monothio and Dithio Ketals

Cyclohexane-1,2-dione reacts with ethylene glycol (TsOH, benzene, 6 h) to form the diprotected compound. Monoprotected 1,3-oxathiolanes and 1,3-dithiolanes are isolated on reaction under similar conditions with 2-mercaptoethanol and ethanedithiol, respectively.[1]

1. R. H. Jaeger and H. Smith, *J. Chem. Soc.*, 160, 646 (1955).

Bismethylenedioxy Derivatives (Chart 5): 

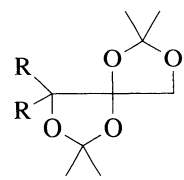
Formation/Cleavage[1,2]



This derivative is stable to TsOH/benzene at reflux and to CrO_3/H^+.[3] It is also stable to NBS/*hv*.[4] In the formation of a related derivative, formaldehyde from formalin (containing methanol) converted a C_{11}-hydroxyl group to the C_{11}-methoxymethyl ether. Paraformaldehyde can be used as a source of methanol-free formaldehyde to avoid formation of the ethers.[5]

1. R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).
2. Y. Nishiguchi, N. Tagawa, F. Watanabe, T. Kiguchi, and I. Ninomiya, *Chem. Pharm. Bull.*, **38**, 2268 (1990).
3. J. F. W. Keana, in *Steroid Reactons*, C. Djerassi, Ed., Holden-Day, San Francisco, 1963, pp. 56–61.
4. D. Duval, R. Condom, and R. Emiliozzi, *C. R. Hebd. Seances Acad. Sci., Ser. C*, **285**, 281 (1977).
5. J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **7**, 528 (1964).

Tetramethylbismethylenedioxy Derivatives



A bismethylenedioxy group in a 4-chloro or 11-keto steroid is stable to cleavage by formic acid or glacial acetic acid (100°, 6 h). The tetramethyl derivative is readily hydrolyzed (50% AcOH, 90°, 3–4 h, 80–90% yield).[1]

1. A. Roy, W. D. Slaunwhite, and S. Roy, *J. Org. Chem.*, **34**, 1455 (1969).