

Protecting Groups in Organic Chemistry for Oxygen-based functionality.

1.1. We are not going to have much other heteroatom functionality in this introductory course other than oxygen.

2. References:

2.1. *Comprehensive Synthetic Organic Chemistry*, 6, 631-701.

2.2. *Protective Groups in Organic Synthesis* 2nd ed. Greene, T.W.; Wuts, P.G.M

2.3. *Synthetic Organic Chemistry* Michael B. Smith, 629-672. A very smart discussion.

2.4. *Advanced Organic Chemistry part B: Reactions and Synthesis* 3rd ed. Carey, F.A.; Sundberg, R.J. pp. 677-92

3. Some things to consider before you use protecting groups

3.1. Know why and when do you need to protect a functional group.

3.1.1. Don't just protect a group because you have to go through x number of steps.

3.1.2. One must use protecting groups when the functionality (you wish to preserve) and the reaction conditions necessary to accomplish a desired transformation are incompatible (non-orthogonal).

3.2. If you can avoid protection of a group in a synthesis, you should

3.2.1. It is much better to plan ahead and avoid protection

3.2.2. Protecting groups add extra steps to your synthesis more steps cost time and money.

4. Oxidation state as a protecting Scheme

4.1. Remember adjustment of oxidation state is often easy

4.2. *Never carry an aldehyde through multiple steps*

4.2.1. These air-oxidize

4.2.2. undergo facile aldol condensation

5. 'Good' protecting groups . . .

5.1. Are small compared to the mass of what you are trying to make.

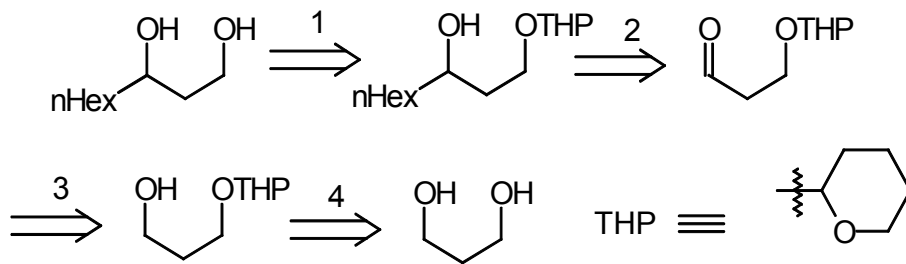
5.2. Can be applied and removed in great yield.

5.3. Allow the functionality to survive the reaction conditions necessary.

5.4. Do not introduce stereocenters. Uncontrolled stereo centers in the protecting group complicate the manipulation and handling of the material because the amount of diastereomers increases.

5.5. Allow selective deprotection under mild conditions.

6. **Example of an oxygen-based functionality protecting scheme:** Kitching *J. Org. Chem.* **1989**, *54*, 3893.



6.1. Starting from the 1,3-diol, what if we want to extend the chain by 6 carbon atoms.

6.2. Remember the arrows above are retroarrows. We are thinking backwards. The numbers below refer to each retrosynthetic step.

6.3. Oxidation of the unprotected alcohol.

6.3.1. Without one of the R-OH groups protected they would have both oxidized to aldehydes.

6.4. OTHP addition to protect one alcohol from oxidation.

6.5. If the functionality on the other end of the molecule were left as the ketone (-)nHexyl would have also attacked this ketone in a 1,2 fashion.

6.6. Deprotection of the ketal might be an issue because the tertiary alcohol is now acid sensitive.

7. The simplest protection of the OH group is the methyl ether

7.1. Protects alcohols and phenols from a variety of chemical conditions

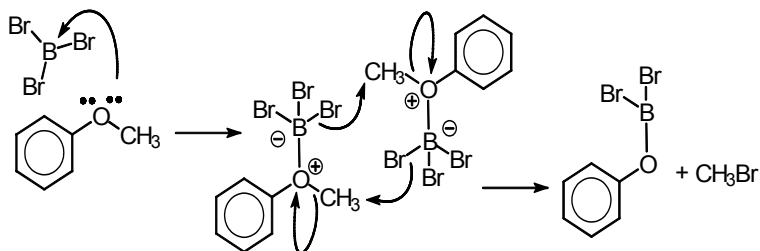
7.2. Difficult to remove, removal is not as difficult with phenols

7.3. Protection: Williamson Ether synthesis

7.3.1. NaH/THF/ROH/MeX

7.4. Deprotect: BBr₃

7.4.1. Often this reagent is compatible with Lewis acid-sensitive functionality



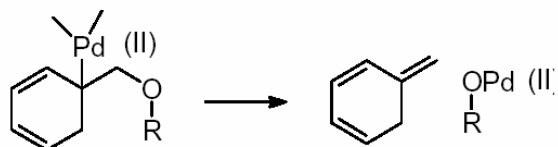
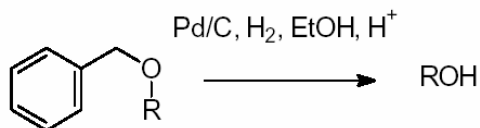
8. Benzyl ether protection of alcohol

8.1. Performs similarly to the methyl ether.

8.2. Protection: Williamson ether synthesis where the electrophile is something like $\text{Ph-CH}_2\text{-Br}$

8.3. Deprotection is much easier

8.3.1. Deprotection is under hydrogenation conditions

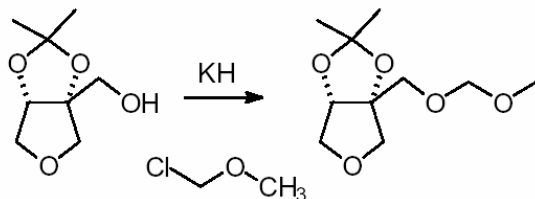


9. Because ethers are difficult to remove other protection options are sought for alcohols.

9.1. MOM: methoxymethyl = $\text{R-CH}_2\text{OCH}_3$. Really an acetal!

9.2. Protection

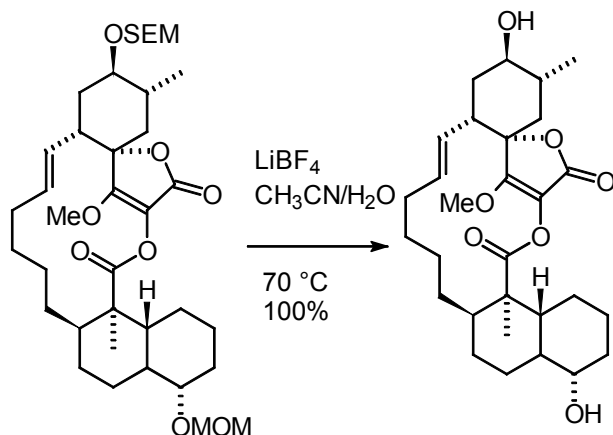
9.2.1. Installed by Williamson ether synthesis



9.3.

9.4. Deprotection

9.5. Sometimes a subtle balance of Lewis Acid and Base



9.6. SEM = 2-(trimethylsilyl)ethoxymethyl $\text{R}-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{SiMe}_3$

9.6.1. above example is from: *Protective Groups in Organic Synthesis* 2nd ed.

Greene, T.W.; Wuts, P.G.M p. 20.

9.6.2. SEM is trimethylsilyloxyethyl

9.6.3. There are F(-) based methods to use these two protecting groups orthogonally.

10. Silyl ethers

10.1. are not as difficult to cleave as the methyl ether and can perform similar function

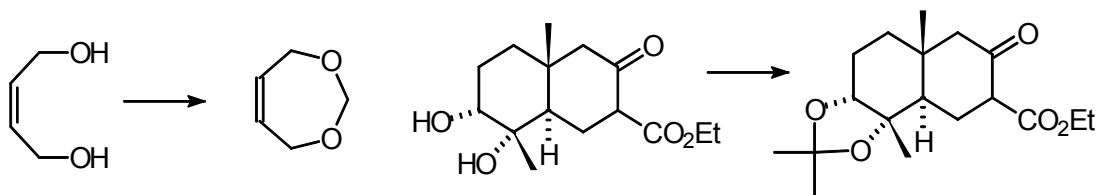
10.2. Ease of cleavage is as follows

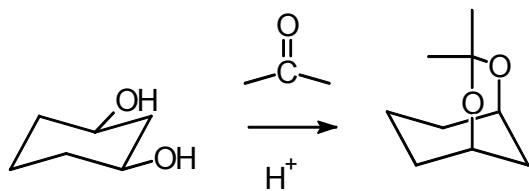
10.2.1. $\text{Me}_3\text{Si}-\text{O} > \text{Et}_3\text{Si}-\text{O} > \text{iPr}_3\text{Si}-\text{O} > \text{tBuMe}_2\text{Si}-\text{O} > \text{EtMe}_2\text{Si}-\text{O} > \text{PhMe}_2\text{Si}-\text{O}$

10.2.2. For example TMSO- can be deprotected in the presence of $\text{tBuMe}_2\text{Si}-\text{O}$

11. **Diols 1,2; 1,3; and 1,4 do not react like regular alcohols.** The reactivity of the OH functionality is moderated by the presence of the other OH group.

11.1. These can be protected as their cyclic ketals



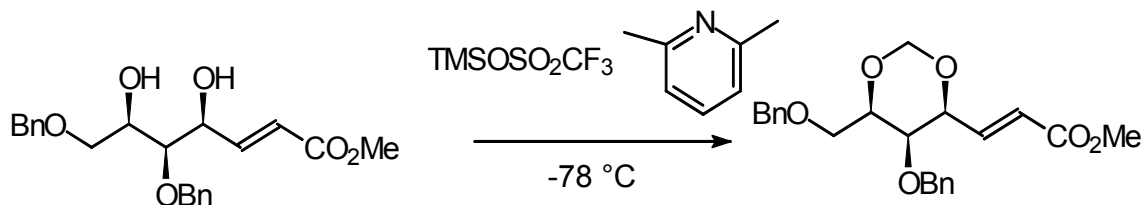


12. Driving force is the removal of water

12.1. Dean Stark conditions



12.2. Often one of the above two reagents are used; one does not have to worry about the removal of water under these conditions . . . why not?

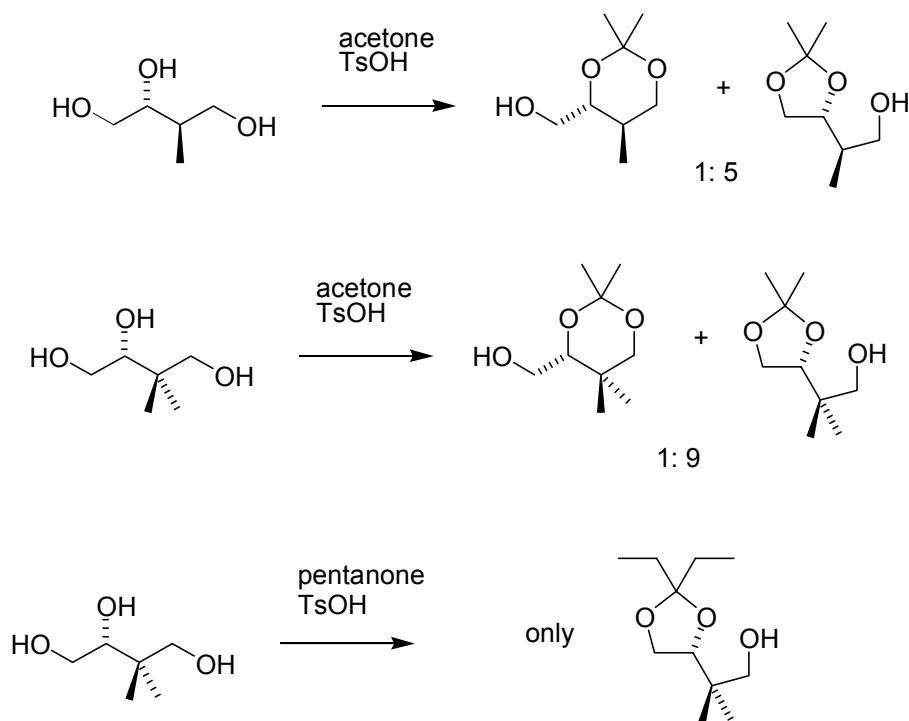


12.3. The above reaction can be run under aprotic conditions; MeO-CH₂-OMe the reagent that produces 1,3-dioxane is also the solvent

12.4. In the above example under protic conditions the methyl ester may have been hydrolyzed.

12.5. The reagent TMSOSO₂CF₃ [(CH₃)₃Si-O-SO₂-CF₃] is a source of (+)SiMe₃.

12.6. This reagent can be used catalytically similarly to the manner in which (+)H is used.



13. The scheme above tells you that the formation of the cyclic acetals depends heavily on ring strain.

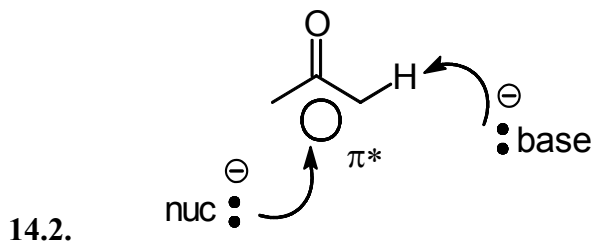
14. PROTECTION OF ALDEHYDES AND KETONES

14.1. Most often you want to protect ketones and aldehydes from strong nucleophiles ketones and aldehydes when treated with strong nucleophiles.

14.1.1. Ketones and aldehydes have π^* orbitals as the lowest unoccupied molecular orbitals.

14.1.2. Nucleophiles interact with this orbital by doing 1,2 addition

14.1.3. Bases interact with this orbital by deprotonation at the alpha position.



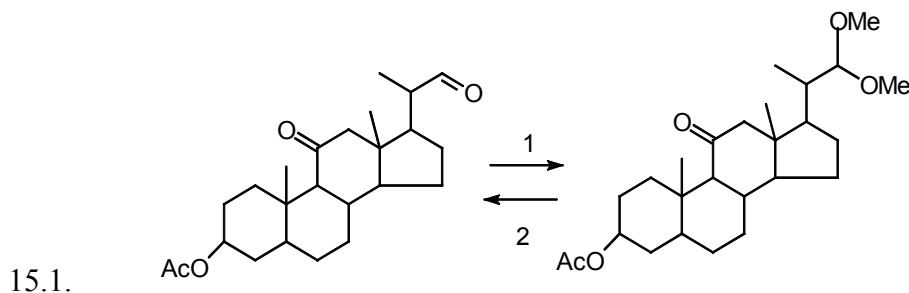
14.2.1. Two things can happen to

14.2.1.1. Addition

14.2.1.2. Deprotonation / polymerization

14.2.2. Both are governed by π^*

15. One can expect to protect the aldehyde selectively in the presence of ketones



15.2. MeOH, dry HCl, 2 min, reflux, 12 min

15.3. **deprotection** 2N H₂SO₄, MeOH, H₂O, reflux

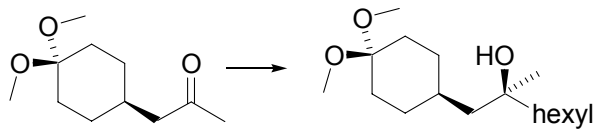
15.4. *J. Chem. Soc.* **1953**, 3864.

15.5. The authors could have pushed the reaction to also make the ketal

15.6. Note the conditions under which the acetal is unmasked

15.7. Substituted alkenes and enol ethers are sensitive to acid don't expect to carry them through a deprotection of this sort.

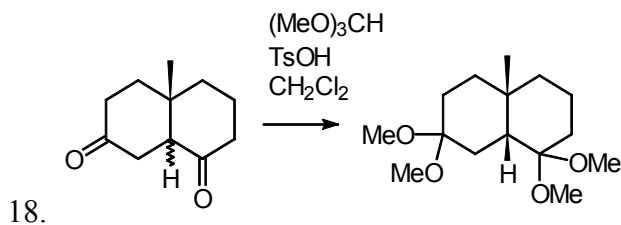
16. Protection of one ketone functionality by stoichiometric control of reagent



16.1. Consider for example, nucleophilic addition of nHexylLi to a ketone followed by aqueous workup.

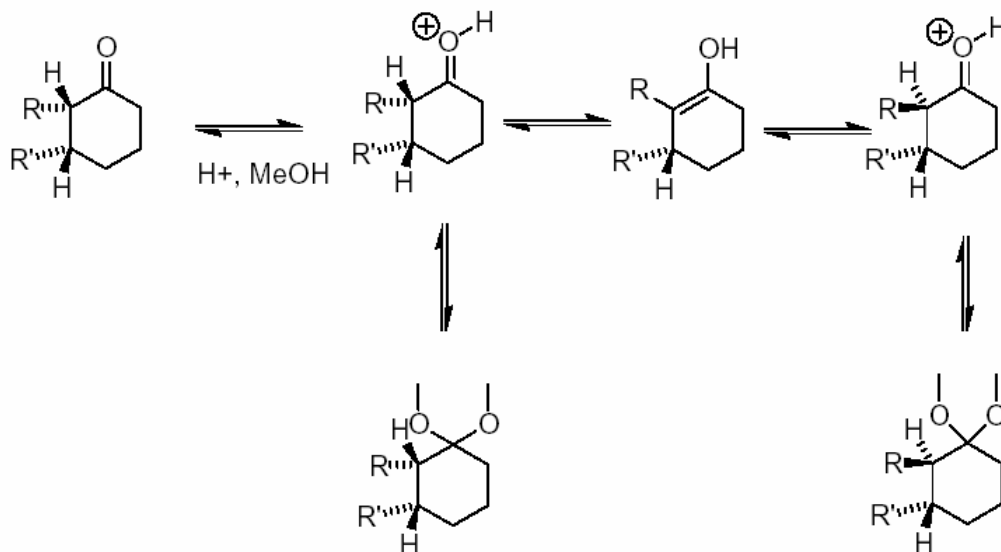
17. Often mild conditions for deprotection are available

17.1. oxalic acid, THF, H₂O room temperature can undo some ketals

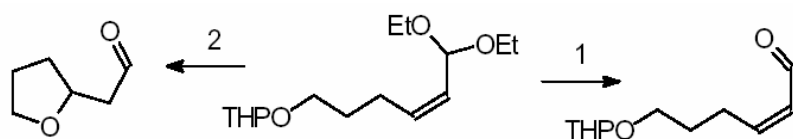


18.1. Ketalization is not the only thing that can happen

18.2. Epimerization can also occur. Why?



18.3.

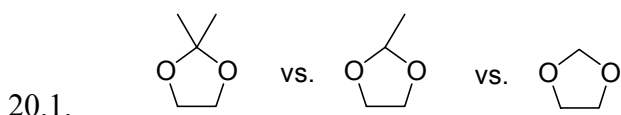


19.

19.1. The ketones can unmasked with (+)H_(cat), H₂O, acetone

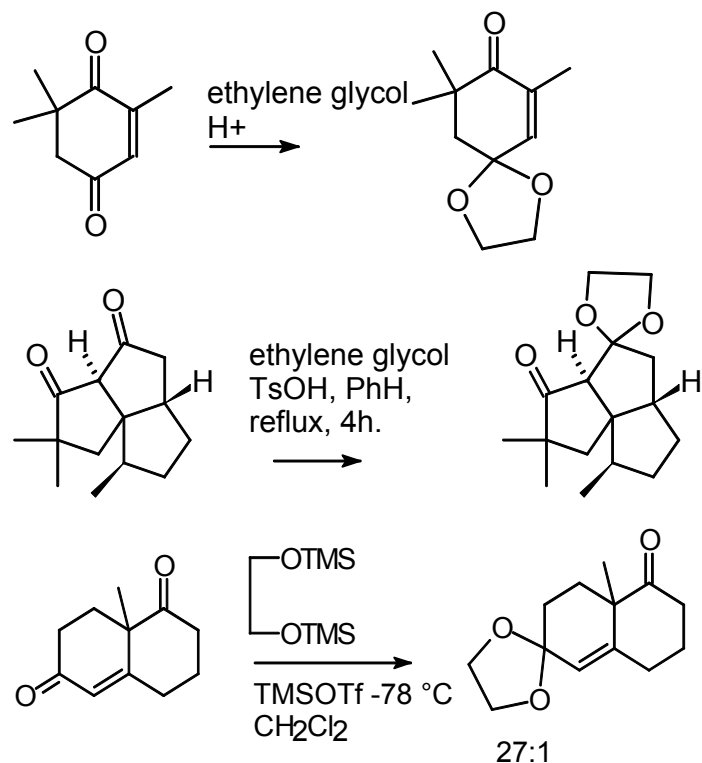
19.2. 10% H₂O, Silical gel, CH₂Cl₂ 18 h.

20. 2,2-dimethyl-1,3-dioxolane: 2-methyl-1,3-dioxolane: 1,3-dioxolane; 50,000: 5000: 1.



20.2. This means that you have a chance of selectively deprotecting ketones

20.3. More steric effects below.



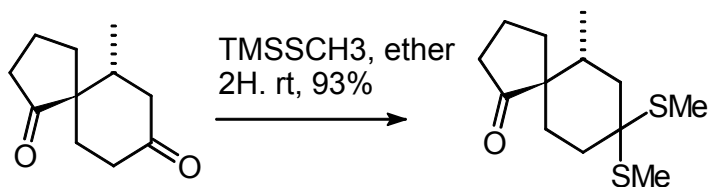
20.3.1. In the last example the steric influence against ketalization wins over the electronic reason against ketalization

20.3.2. With everything else equal α,β -unsaturated ketone are more difficult to ketalize than saturated dialkylketones.

21. Thioketals

21.1. Can be deprotected in the presence of ketals and can survive ketal deprotection

21.2. The two protecting schemes are orthogonal



21.3.

21.4. Synthesis/ protection: thioketals are synthesized with oxophilic Lewis Acids.

21.4.1. RSH ($R = Et, Pr, Ph$), Me_3SiCl , $CHCl_3$, $20^\circ C$, 1 h. $> 80\%$ yield

21.4.2. $B(SR)_3$ ($R = Et, Bu, C_5H_{11}$), reflux, 2 h

21.4.3. $PhSH$, $BF_3 \cdot Et_2O$, $CHCl_3$ $0^\circ C$, 10 min, $ZnCl_2$, $MgBr_2$

21.4.4. RSH, TiCl₄, CHCl₃ 0 °C.

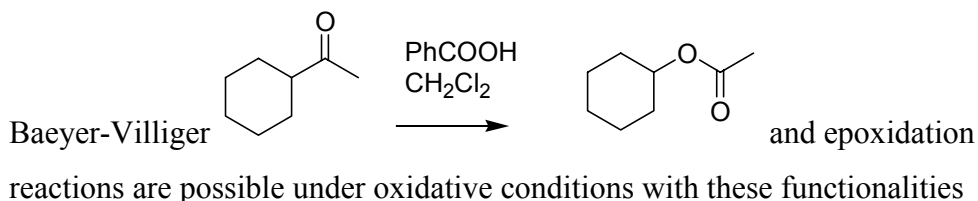
21.4.5. RSSR (R=Me, Ph, Bu), Bu₃P, rt, reagent also reacts with epoxides.

21.5. Deprotection: removed oxidatively or by thiophilic Lewis Acids
(transition metals)

21.5.1. These can be harmful to the environment

21.5.2. R-SR oxidizes easier than -RC=CR- or R₃CH usually oxidative

deprotection is compatible with alkenes, α,β-unsaturated enones and esters,



21.5.3. AgClO₄, H₂O, C₆H₆,

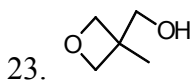
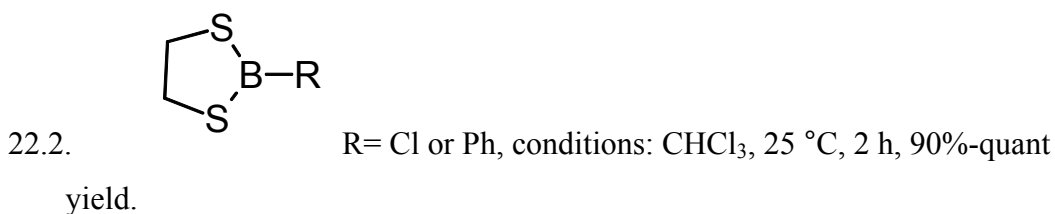
21.5.4. HgCl₂, CdCO₃, aq. acetone

21.5.5. I₂, NaHCO₃, dioxane, H₂O

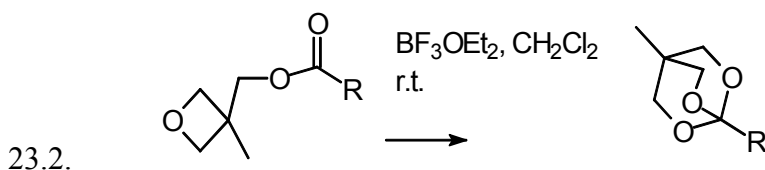
21.5.6. H₂O₂, H₂O, acetone

22. 1,3-dithianes and 1,3-dithiolanes are used as in their oxygen atoms cousins

22.1. The cyclic thioketals are prepared like their acyclic variants are prepared, with oxophilic Lewis acids a good reagent:



23.1. A decent reagent (it's a bit big) for the protection of the carboxylate functionality:



23.3. The product is called an orthoester

23.4. Like the ketals the orthoester function masks the carbonyl π^* from nucleophiles and bases.

24. Applying what we learned.

24.1. We want to make this trione from molecules possessing six or less carbon atoms.

24.1.1. let's just let our minds wander.

