

E. Dithianes (*S,S*-Acetals)

Objectives

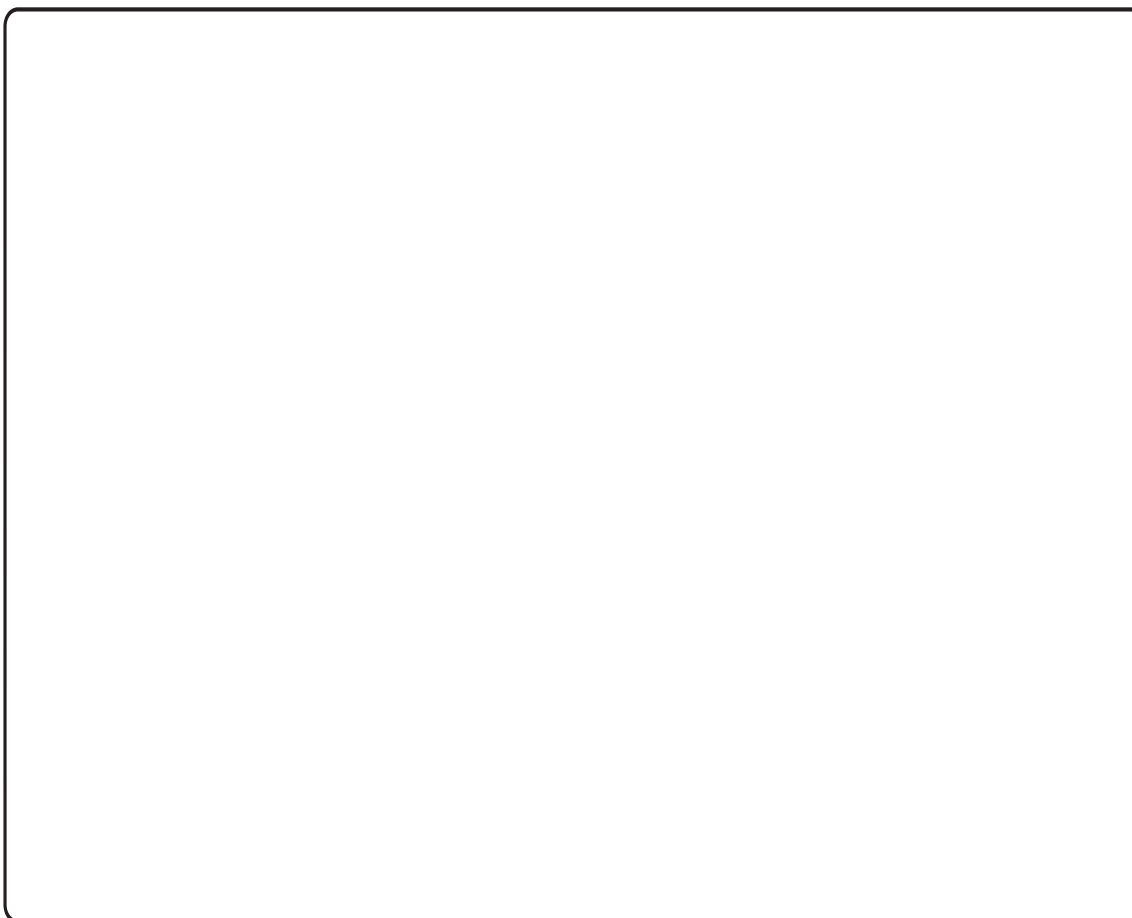
By the end of this section you will be able to:

- 1) prepare *S,S*-acetals (dithianes) from aldehydes and ketones;
- 2) draw an arrow-pushing mechanism for the formation of dithianes from carbonyl compounds;
- 3) hydrolyse *S,S*-acetals back to the corresponding carbonyl compounds;
- 4) draw an arrow-pushing mechanism for this hydrolysis reaction;
- 5) use dithianes as acyl anion equivalents in synthesis;
- 6) rationalise the increased pK_a of the α -C-H in a dithiane compared with that in the corresponding *O,O*-acetal.

Q? *How might we synthesise an unsymmetrically substituted α -hydroxy ketone?*



Retrosynthetic Analysis involving Polar Bond Disconnections



The best polar bond disconnection in this type of molecule is obviously that between the two functional groups (*i.e.* the carbonyl group and the alcohol) as this breaks up the molecule into two of similar complexity. However, whichever disconnection we choose requires a reagent that displays the unnatural polarity of the functional group. Synthons that temporarily reverse the characteristic pattern of reactivity of a functional group are known as *umpolung* species.

One of the easiest methods for synthesising unsymmetrically substituted α -hydroxy ketones is to react an aldehyde or ketone (a so-called a^1 -synthon) with an *acyl anion equivalent* (a d^1 -synthon).

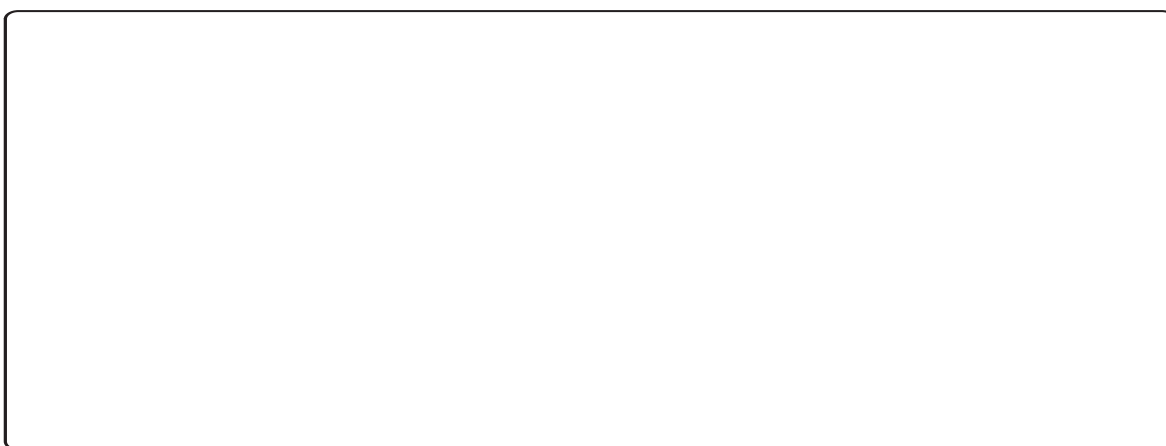
Dithianes are one of the most important acyl anion equivalents; the *S,S*-acetal functionality serves as a temporary mask for the carbonyl functionality and permits formation of the requisite carbanion using a strong base (nBuLi is most often used).

Dithianes as Acyl Anion Equivalents

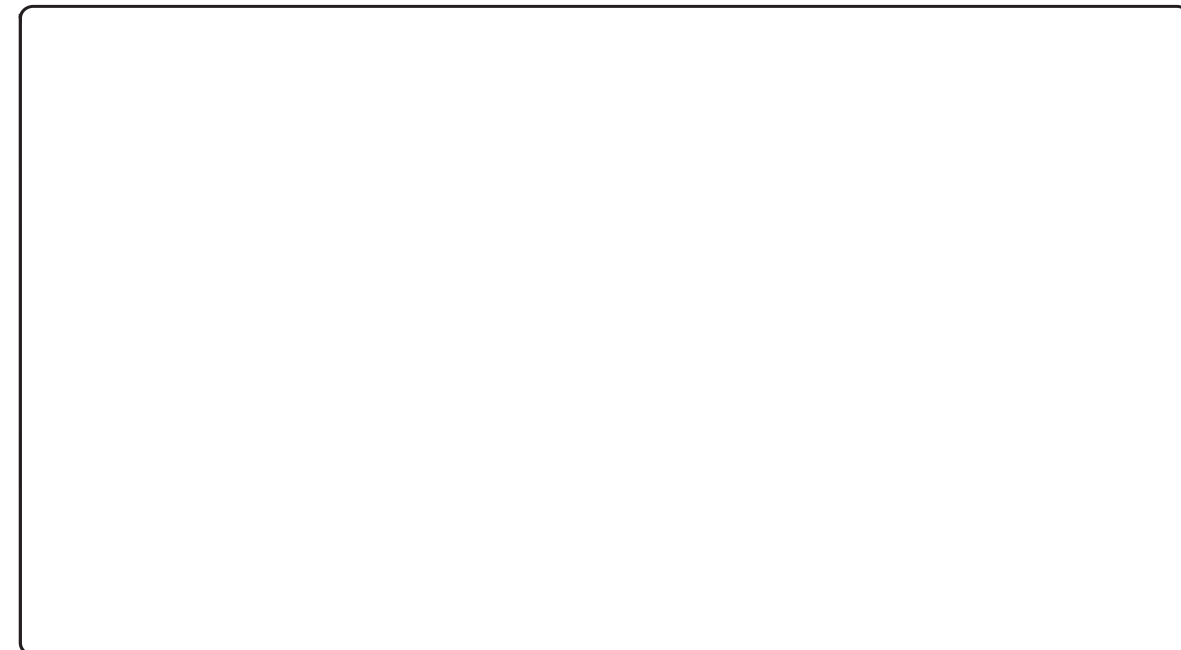
- The pK_a of an aldehyde C–H is far too high (>45) for it to be abstracted by any commonly used base.



- Aldehydes and ketones are good electrophiles. Sometimes we need to mask this reactivity pattern. We can do this by temporarily protecting the carbonyl group as an *O,O*-acetal.



The pK_a of the C–H in an acetal is still too high for it to be abstracted by a base. However if we prepare the corresponding *S,S*-dithioacetal then we generate a species that possesses an α -C–H that can now be abstracted, albeit with a strong base (e.g. *n*BuLi).



We need to be able to rationalise the increased acidity of the α -C-H in a dithiane compared with that in the corresponding *O,O*-acetal.

There are a number of reasons why two sulfur atoms in the dithiane can more readily stabilise negative charge than can two (more electronegative) oxygen atoms in an acetal.

- 1) Oxygen in period 2 has no low-lying empty orbitals whereas sulfur in period 3 has empty 3d AOs allowing $p\pi \rightarrow d\pi$ electron donation [order of carbanion stabilisation through this mechanism: $\text{CH}_2 < \text{O} < \text{S} < \text{Se}$].



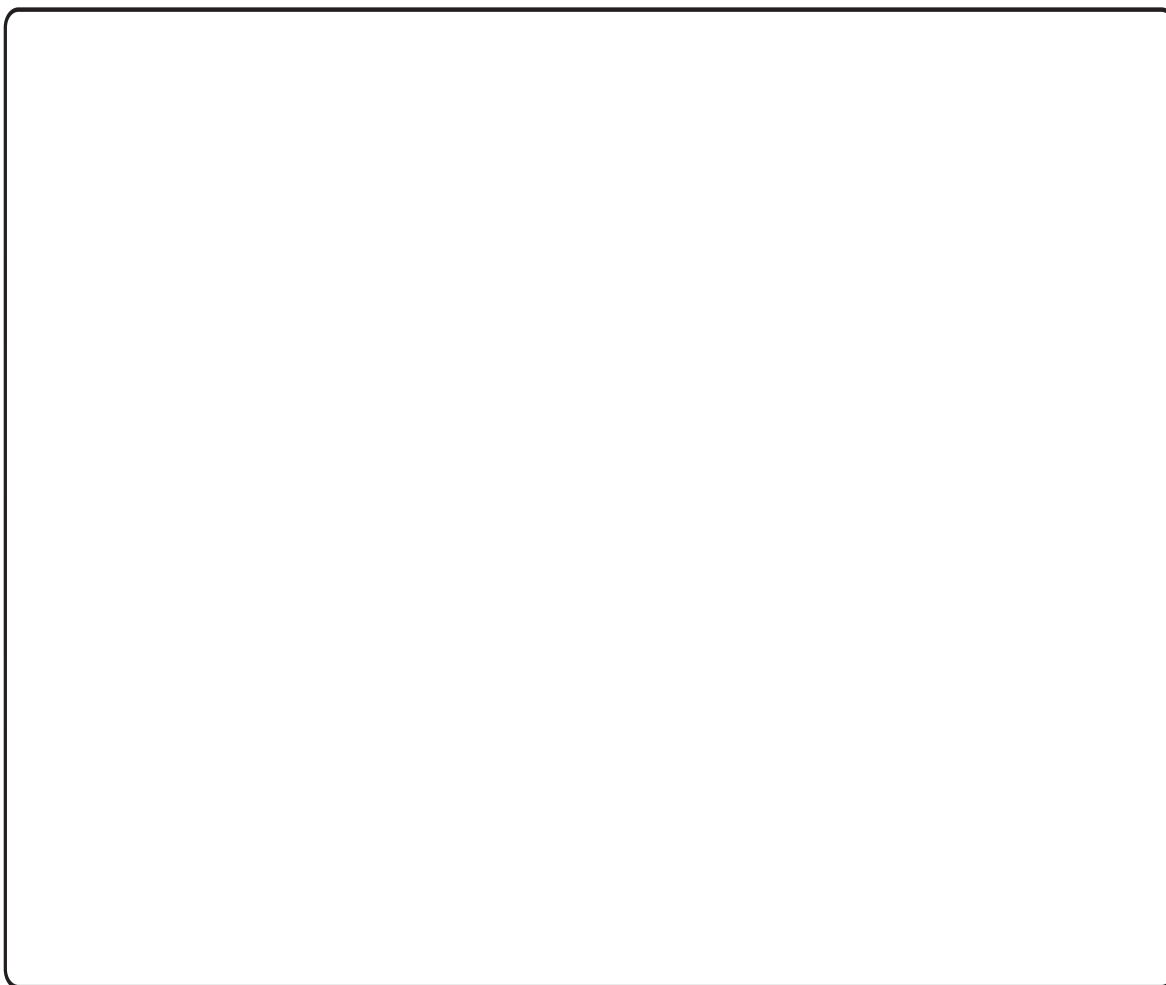
- 2) However, data suggest that the negative charge in lithiated dithiane is very localised on the carbon centre suggesting a more important mechanism for stabilising adjacent negative charge is through induced polarisation effects which are only significant on the larger group 6 atoms (S, and even better, Se).



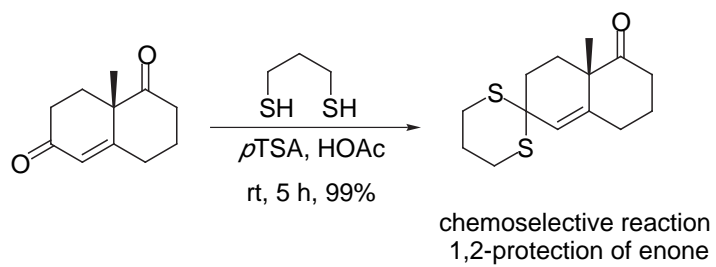
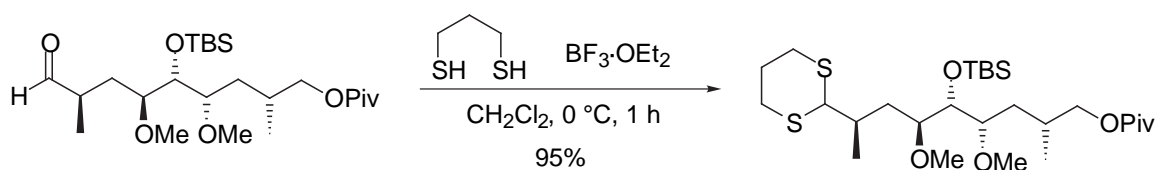
A Comparison between O,O-Acetals and S,S-Acetals

	O,O-acetals	S,S-acetals
hydrolytic stability	fairly acid labile	hydrolytically fairly stable
formation	readily formed from diol and cat. acid (under dehydrating conditions)	more difficult to form - normally use dithiol and a Lewis acid - removal of water less important
pK_a of α -hydrogen	too high to allow metallation	$pK_a = 31$ (dithiane) to 38 (substituted dithianes) - low enough to permit metallation with strong bases <i>e.g.</i> nBuLi
hydrolysis	readily hydrolysed back to C=O compound under aqueous acidic conditions	more difficult to hydrolyse - cannot normally use just aqueous acid
	common protecting group for aldehydes and ketones	rarely used as a simple protecting group - normally exploit its use as an acyl anion equivalent

Formation of *S,S*-Acetals from Carbonyl Compounds



Examples



Reaction of Lithiated Dithianes

Lithiated dithianes react with a variety of electrophiles:

Carbonyl compounds.



- i) Reaction is more rapid with aldehydes than with ketones, which are less electrophilic.
- ii) Under normal conditions, lithiated dithianes react in a 1,2-fashion with enones and enals.

Epoxides



Alkylating Reagents

Double alkylation of commercially available dithiane provides a route to a masked form of an unsymmetrically substituted ketone:



For useful references: 1) D. Seebach, E. J. Corey, *J. Org. Chem.*, 1975, **40**, 231-237; 2) P. C. Page, M. B. van Niel, J. C. Prodger, *Tetrahedron* 1989, **45**, 7643-7677.

Hydrolysis of S,S-Acetals to Unmask the Carbonyl Group

S,S-Acetals are more difficult to hydrolyse than their oxygen congeners owing to i) the reduced Brønsted basicity of sulfur relative to oxygen, and ii) the higher barrier to formation of the thiocarbenium cationic intermediate.

To facilitate deprotection it is necessary to enhance the *nucleofugacity* (*i.e.* the leaving group ability) of sulfur. This can be achieved in a number of ways:

1) Deprotection by Metal Coordination

Sulfur is a *soft* nucleophile/base (oxygen is a hard nucleophile/base) and therefore forms strong bonds with soft metals such as Hg(II), Ag(I), Tl(I) *etc.* Unmasking the carbonyl group in a dithiane is often carried out using heavy metal salts.

mechanism of deprotection

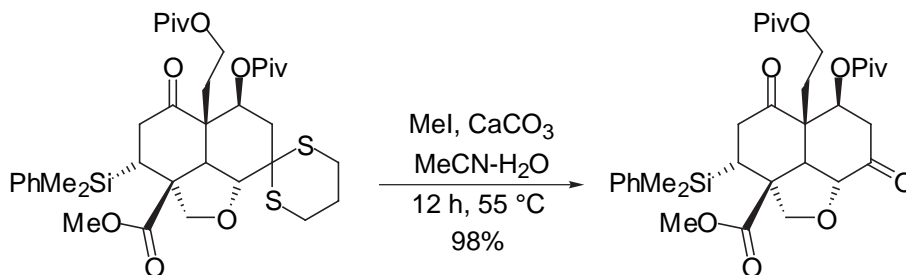


- The reaction is normally buffered using a base such as CaCO_3 which can 'mop up' the liberated acid.
- Ag(I) and Tl(I) salts react similarly.

2) Alkylative Deprotection

The leaving group ability of sulfur can be enhanced by alkylation. A variety of alkylating agents have been used e.g. MeI , Me_3OBF_4 , Et_3OBF_4 . The mechanism is similar to above.

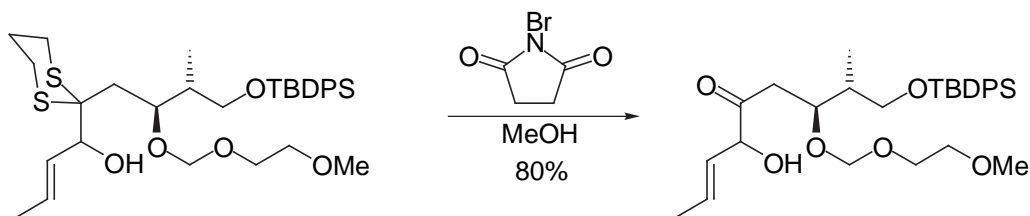
Example



3) Oxidative Deprotection

Oxidation of the sulfur with a range of oxidising agents (e.g. Cl_2 , Br_2 , I_2 , *N*-bromosuccinimide and *m*CPBA) can also be used to facilitate dithiane hydrolysis.

Example



For a review on the mechanism of hydrolysis of thioacetals: D. P. N. Satchell, R. S. Satchell, *Chem. Soc. Rev.*, 1990, **19**, 55-81.

Summary

Dithianes, or dithioacetals, are formed by reacting a bis-thiol with an aldehyde or ketone, generally under Lewis acid catalysis. Since dithioacetals are not electrophilic species, this functional group can be used as a protecting group for an aldehyde or ketone.

However since sulfur is more readily polarisable than oxygen, it can more efficiently stabilise proximal negative charge by setting up induced dipoles and through $p\pi-d\pi$ bonding. As a result, the α -C-H in a dithioacetal is much more acidic ($pK_a(\text{dithiane}) \sim 31$) than the corresponding hydrogen in an *O,O*-acetal ($pK_a > 40$). This allows dithianes to be employed more usefully as *acyl anion equivalents*.

Treatment of a dithiane with a strong base, such as *n*BuLi, provides a nucleophilic acyl anion equivalent that reacts with a range of electrophiles including aldehydes and ketones, epoxides and reactive alkylating agents (R-X). After the reaction, the carbonyl group can be unmasked by hydrolysis.

In contrast to *O,O*-acetals that can be hydrolysed readily under aqueous acidic conditions, dithioacetals require modified conditions to effect this reaction. The sulfur has to be made into a better leaving group; this can be achieved by the use of heavy metals (e.g. Hg(II)), alkylating agents (e.g. Me_3OBF_4) or using oxidising agents (e.g. Cl_2).