CHEMISTRY 4000

Topic #7: Protecting Groups

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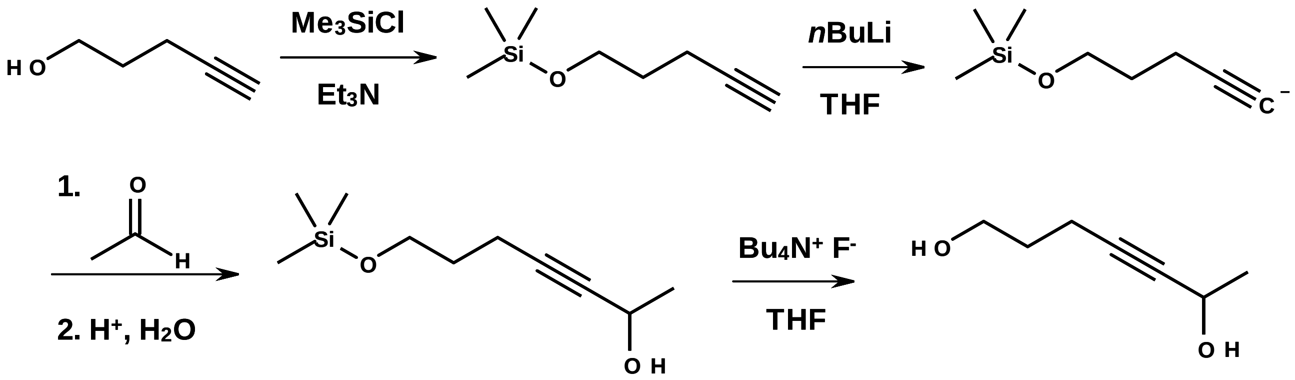
Dr. Susan Findlay

Protecting Groups – A Necessary Evil?

- Synthetic chemists tend to use protecting groups as a crutch. Sometimes they're necessary, but with tools like SciFinder making it easier than ever to peruse the literature for alternative reaction conditions, we need to be careful not to lean on them too heavily.

e.g. A chemist wanting to prepare an alkynyl anion in the presence of an alcohol might be tempted to protect the alcohol first:



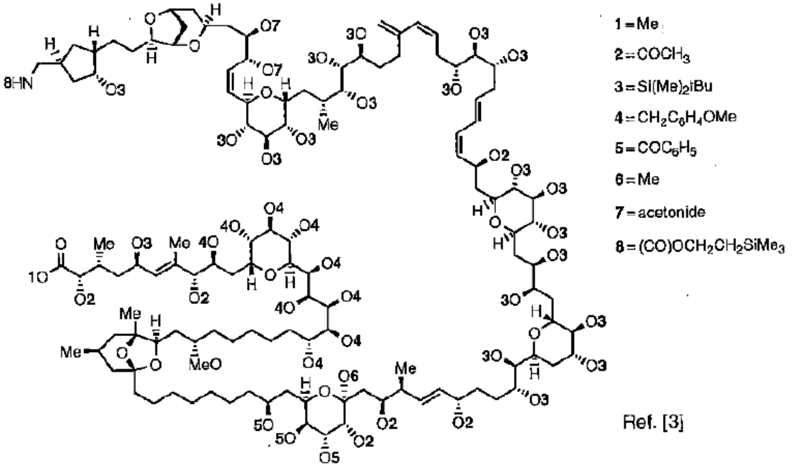
Why might they be tempted to do this?

When would it be necessary to do this?

What is the alternative?

Protecting Groups – A Necessary Evil?

- When protecting groups are necessary, we need to use them intelligently. The worst case scenario is that every protecting group adds two steps to the synthesis – one to attach it and one to remove it. This can quickly increase the number of synthetic steps.
- Consider the palytoxin carboxylic acid in Scheme 7.1 of your text. The synthesis involved 42 protecting groups of 8 different types, adding almost 50 steps to the synthesis! (~42 “add protecting group” steps and 5 “remove a set of protecting groups” steps) If each protecting group had been removed separately, that would have been 84 extra steps!



Scheme 7.1 Protecting group pattern in the final phase of the synthesis of palytoxin carboxylic acid

Protecting Groups – A Necessary Evil?

- So, even though that was an immensely large number of protecting groups, the number of extra steps was somewhat limited using a few strategies:
    - Use the same protecting group in multiple places (when possible).
    - When using different protecting groups, use groups that can be cleaved using the same reaction conditions (when possible).

- Of course, sometimes you want to deprotect one group (to perform a reaction on it) while leaving another group protected. Then, you will obviously have to choose different protecting groups. You do, however, want to plan your synthesis to minimize the time/steps spent on the "protecting group dance".

- If you can simply do the reactions in a different order and get the same result, that's better than adding protection and deprotection steps. So is choosing a reaction that is will selectively affect one group while leaving the other untouched.

Protecting Groups – A Necessary Evil?

- When planning your synthesis, develop a full retrosynthesis before planning exactly which protecting groups to use.

- To choose a protecting group, you will need to know:
  - What functional group you’re protecting
    - If you’re protecting an alcohol, for example, you’ll want to attach the protecting group at a point in the synthesis where you won’t inadvertently ‘protect’ other alcohols that you didn’t want protected.
  - What reactions the protecting group must survive
    - If you’re protecting an alcohol from oxidation, don’t choose a protecting group that’s cleaved by the same oxidation conditions.
  - What functional groups will be present when you deprotect
    - If your target contains an alkene, using a protecting group that’s cleaved by hydrogenation is not a good choice.

Protecting Groups – A Necessary Evil?

- While you could write a book[1] about all the different protecting groups, most of them can be classified according to the conditions used to remove them (aka “reactions they won’t survive”).
  - Acid-sensitive protecting groups are common. Most of the protecting groups you’ll have seen in CHEM 2600 fall into this category.
  - Base-sensitive protecting groups are much less common.
  - There are a few protecting groups which are both acid- and base-sensitive. These would not tend to be used as long-term protecting groups, but might be chosen for ease of removal in the presence of more robust groups.
  - There are also protecting groups which survive both acidic and basic conditions. These may be good choices for long-term protecting groups as they will persist while acid-sensitive or base-sensitive protecting groups are cleaved.
- Some people reverse these classifications, categorizing protecting groups according to conditions they’ll survive (acid-stable, etc.).

[1] Greene’s Protective Groups in Organic Synthesis by Peter G.M. Wuts and Theodora W. Greene is the standard

Protecting Groups for Alcohols

- Silyl ethers are popular choices for protecting alcohols as they can all be removed using fluoride sources:
  - $Bu_4N^+ F^-$ ("TBAF") in THF (THF will not be dried, so water is present)
  - Aqueous HF (often mixed with a polar organic solvent to aid solubility)
  - Pyridine-HF salt

- Also, certain silyl ethers can be cleaved in the presence of others:
  - Me_3Si-O-R (TMS-O-R) is both acid- and base-sensitive.
    - It can also be cleaved by almost any Brønsted acid in any alcohol.
    - It can also be cleaved by K_2CO_3 in methanol.
  - $tBuMe_2Si$-O-R (TBDMS-O-R or TBS-O-R) is acid-sensitive.
    - It can also be cleaved by HCl in ethanol (and a variety of other acidic conditions).
  - $tBuPh_2Si$-O-R (TBDPS-O-R) is base-sensitive.
    - It can also be cleaved by KOH in methanol.

Protecting Groups for Alcohols

- Silyl ethers are most readily prepared by reacting the alcohol with the appropriate silyl chloride (R_3SiCl) in the presence of an amine:
- Other popular protecting groups involve forming an ester or ketal from the alcohol:

Protecting Groups for Ketones and Aldehydes

- Acetals and ketals are popular choices for protecting ketones and aldehydes:

- As we have seen before, they are acid-sensitive and can be removed by aqueous acid:

Protecting Groups for Ketones and Aldehydes

- Thioacetals and thioketals are neither acid- nor base-sensitive:

- They can be removed using a Lewis acid, often mercury-based:

- While robust under most conditions, thioacetals and thioketals are susceptible to oxidation. Why?