Suggested solutions for Chapter 25

PROBLEM 1
Suggest how these compounds might be made by alkylation of an enol or enolate.

Purpose of the problem
An exercise at choosing good routes to simple compounds.

Suggested solution
As you can see the carbonyl groups in these compounds, it is pretty obvious which is the new bond to be made. In both cases, the electrophile will need to be an allylic halide. These are good electrophiles for $S_N$2 reactions so they will work well here. We need to use the electrophile twice in the first case and the enolate is that of diethyl malonate. The second case will require an enol or enolate equivalent to prevent self-condensation: a silyl enol ether (p.595 in the textbook) or an enamine (p.591 in the textbook) is ideal. If you use a silyl enol ether, don’t forget the Lewis acid!

[Diagram of reactions]

The reason why allylic halides make good electrophiles is discussed in the textbook on p. 341.
**PROBLEM 2**

How might these compounds be made using alkylation of an enol or enolate as one step in the synthesis?

Purpose of the problem

An exercise in using enolate chemistry to make carbonyl compounds disguised as acetals.

Suggested solution

The only functional group in either compound is an acetal. Cyclic acetals are made from diols and carbonyl compounds so we need to have a look at the deprotected molecules before taking any further decisions.

If we are going to use enolate chemistry, we have to make the diols by reduction of carbonyl compounds. As both diols have a 1,3-relationship between the OH groups, the carbonyl precursors will be the very enolisable 1,3-dicarbonyl compounds, which can be alkylated and reduced. We have chosen arbitrarily to use ethyl esters here, so we should use ethoxide as the base in the alkylation step.
**PROBLEM 3**

How might these amines be prepared using enolate-style alkylation as part of the synthesis?

![Chemical structures of amines](image)

**Purpose of the problem**

An exercise in using enolates and related compounds in the synthesis of amines.

**Suggested solution**

The first amine could be made by reduction of a nitrile, and that could be made by alkylation of the ‘enolate’ from PhCH₂CN.

![Chemical structures and reactions](image)

The second amine could be made by reductive amination of a ketone so we need to make the ketone by alkylation of an enolate. You could have chosen various specific enol equivalents for this job—we have chosen an enamine.
PROBLEM 4
This attempted enolate alkylation does not give the required product. What has gone wrong? What products would actually be formed? How would you make the required product?

Purpose of the problem
An exercise in trouble-shooting—it is important for you to recognise what might go wrong and how to get round the problem.

Suggested solution
The intention was obviously to make the lithium enolate of the aldehyde and to alkylate it with \( \text{PrCl} \), but \( \text{BuLi} \) will attack the aldehyde carbonyl group rather than remove a proton. Even if it did make some of the enolate, the enolate would react with the aldehyde and self-condense (p. 590 in the textbook).

There is also a problem with \( \text{PrCl} \): it is a secondary halide and chloride is the worst leaving group among the halogens Cl, Br, I—it is prone to elimination rather than substitution reactions. To make the required product, an aza-enolate (p. 593 in the textbook) or a silyl enol ether (p. 595 in the textbook) would be a better bet.
PROBLEM 5

Draw mechanisms for the formation of this enamine, its reaction with the alkyl halide, and the hydrolysis of the product.

Purpose of the problem

Exploration of the details of enamine formation and reaction. These are often misunderstood.

Suggested solution

The first step of the mechanism for enamine formation is not acid-catalysed—amines need no help in attacking carbonyl compounds. But the dehydration step is acid-catalysed as HO⁻ is not a good leaving group. The selectivity for elimination into the unbranched chain is because the enamine is planar and there would be a bad steric clash between the methyl group and the nitrogen substituents (all of which are in the same plane) if elimination occurred the other way.
The reaction of the enamine with the alkyl halide goes as expected – these very good $S_N2$ electrophiles work particularly well with enamines and the first product under the reaction conditions is another enamine.

Finally the enamine is hydrolysed by reprotonation to the same iminium salt and addition of water. These steps are the exact reverse of what happens in enamine formation.

**Problem 6**

How would you produce specific enols or enolates at the points marked with the arrows (not necessarily starting with the ketones themselves)?

**Purpose of the problem**

First steps in making enol(ate)s with regiochemical control.
Suggested solution

The last two ketones have two different α-positions so there is a good chance of controlling enol formation from the parent ketone. But the first ketone has two primary α-positions and the difference appears only in the two β-positions. The obvious solution is conjugate addition and trapping (described in the textbook on p. 603). The thermodynamic enol is needed from the second ketone and direct silylation is a good bet. The third requires kinetic enolate formation and LDA is a good way to do that.

PROBLEM 7

How would the enol(ate) equivalents we have just made react with (a) bromine and (b) a primary alkyl halide RCH₂Br?

Purpose of the problem

Moving on from the formation of enol(ate)s to their reactions.

Suggested solution

The two silyl enol ethers will react well with bromine and won’t need Lewis acid catalysis as bromine is such a powerful electrophile—so powerful that it might be dangerous to react the lithium enolate directly with bromine and making the silyl enol ether first might be advisable.
In the reaction with the primary alkyl halide, the boot is on the other foot as there will be a good reaction with the lithium enolate but no reaction with the more stable silyl enol ethers. Lewis acid won't help here either as primary cations are unstable. Preliminary conversion into a lithium enolate or a 'naked' enolate (using fluoride ion) would be better.

PROBLEM 8
Draw a mechanism for the formation this imine:

Purpose of the problem
Revision of the often forgotten mechanism for imine formation.

Suggested solution
The main points in the mechanism are addition of the amine to the carbonyl group without catalysis and dehydration of the intermediate with acid catalysis.
**PROBLEM 9**
How would the imine from problem 8 react with the reagents below? Draw mechanisms for each step: the reaction with LDA, the addition of BuBr, and the work-up.

![Mechanism for Problem 9](image)

**Purpose of the problem**
Checking you know how to make and use an aza-enolate.

**Suggested solution**
LDA removes the most acidic proton of the imine so that the Li atom is transferred to the nitrogen atom to give the aza-enolate. Electrophiles, even alkyl halides, then add to the ‘enolate’ position and the work-up is hydrolysis of the imine with aqueous acid.

![Mechanism for Suggested Solution](image)

**PROBLEM 10**
What would happen if you tried this short cut for the reactions in problems 8 and 9?

![Mechanism for Problem 10](image)

**Purpose of the problem**
Reminder of the problems with lithium enolates of aldehydes.
Suggested solution

Some aldehydes can be converted directly into lithium enolates but this is not usually very successful because the rate of reaction of the lithium enolate with the very electrophilic aldehyde is too great and at least some aldol reaction will occur.

PROBLEM 11

Suggest mechanisms for these reactions.

Purpose of the problem

Learning to unravel complicated looking sequences that are quite easy when you get into them.

Suggested solution

Double alkylation of the malonate enolate gives the four-membered ring and hydrolysis and decarboxylation gives the carboxylic acid product.
PROBLEM 12
How does this synthesis of a cyclopropyl ketone work?

Purpose of the problem
Enols and enolates are involved in an unlikely looking sequence that you can work out if you persist.

Suggested solution
Alkylation of the enolate with the epoxide gives and alkoxide that cyclises to give the lactone.

Now S<sub>n</sub>2 opening of the protonated lactone with the soft nucleophile (bromide ion) gives the γ-bromoketone that cyclises through its enolate. The formation of three-membered rings is favoured kinetically.
PROBLEM 13
Give the structures of the intermediates in the following reaction sequence and mechanisms for the reactions.

Purpose of the problem
A reminder that enolate-like intermediates can be formed at nitrogen as well as carbon providing that an oxygen atom can carry the negative charge.

Suggested solution
The first base removes the proton from nitrogen to make an enolate-like intermediate that reacts at nitrogen. Now that the NH is blocked, the second base makes the amide enolate that is alkylated on carbon.