Chem Factsheet

April 2003 Number 53

Answering Questions on Organic Synthesis

Before working through this Factsheet you should:
- Have a good knowledge of the organic chemistry covered at AS and A2 level;
- Have a good knowledge and understanding of the reagents and conditions required to interconvert organic functional groups;
- Have worked through the organic chemistry Factsheets.

After working through this Factsheet you will:
- Have been shown the two common types of organic synthesis questions.
- Have more experience in answering questions on organic synthesis.

You may find it useful to have Factsheet 52 (reactions of funtional groups) besides you when you work through this Factsheet.

There are two common types of exam questions on organic synthesis. Factsheet 35 has covered the first, more straightforward, style of question. It involves the conversion of functional groups from one type to another.

For example, given the reaction scheme:

$$\underset{A}{CH_3CH_2CH_2Cl} \xrightarrow{\text{step 1}} \underset{B}{CH_3CH_2CH_2OH} \xrightarrow{\text{step 2}} \underset{C}{CH_3CH_2COOH} \xrightarrow{\text{step 3}} \underset{D}{CH_3CH_2COCl}$$

The examiner may test candidates' knowledge of organic reactions by asking for reagents and conditions, or even equations.

Step 1: $CH_3CH_2CH_2Cl + NaOH \rightarrow CH_3CH_2CH_2OH + NaCl$
Conditions: Aqueous, heat under reflux

Step 2: $CH_3CH_2CH_2OH + 2[O] \rightarrow CH_3CH_2COOH + H_2O$
Conditions: $K_2Cr_2O_7$, acidified with conc. H_2SO_4

Step 3: $CH_3CH_2COOH + PCl_5 \rightarrow CH_3CH_2COCl + HCl + POCl_3$
Conditions: Dry.

The second, more difficult, style of organic synthesis question requires candidates to produce their own reaction scheme, or 'flow chart'.
Using the above example, candidates may be supplied with less information.

For example, devise a reaction scheme involving several steps to convert compound A to compound D:

$$\underset{A}{CH_3CH_2CH_2Cl} \rightarrow \underset{D}{CH_3CH_2COCl}$$

The steps required for this are outlined in the previous example, but here candidates are required to produce their own flow chart.

Exam Hint : *- To be successful in answering such questions, candidates:*
- *Require a thorough knowledge of the reactions of all the functional groups.*
- *Should understand that an element of 'trial and error' may be necessary.*
- *Should understand that there may be more than one way to convert the starting molecule to the target molecule, but should look for the simplest route.*

1) The first step in tackling these questions is to identify the functional groups in the starting molecule and the target molecule.

2) The next step is to 'count the carbons' in the starting molecule and the target molecule.

   If the length of the main carbon chain:
   - **Remains the same**, look simply to **interconvert functional groups**.
   - **Increases by one**, look at the introducing a **nitrile group (CN)** within the reaction scheme.
   - **Increases by more than one**, consider including a **Grignard reagent**.
   - **Decreases by one**, consider the use of the **Hoffman degradation** reaction, converting an amide to an amine.

Example 1
Devise a reaction scheme, involving more than one step, to convert:

$CH_3COCl \rightarrow CH_3CH_2NH_2$

- Recognise the functional groups here, and acyl chloride (ethanoyl chloride) must be converted to a primary amine (ethanamine).
- There is no change in the carbon chain length (2 carbons).
- Recalling the reactions of ethanoyl chloride (Factsheet 32) one of the reactions involves introducing nitrogen:

  $CH_3COCl + NH_3 \rightarrow \underset{\text{Ethanamide}}{CH_3CONH_2} + HCl$
  Conditions: Room temp, aqueous.

- The reactions of the amides must now be considered (Factsheet 34). Degradation of the amide (reducing the number of carbons) is not required, so:

  $CH_3CONH_2 \xrightarrow{P_4O_{10}} \underset{\text{Ethanenitrile}}{CH_3CN} + H_2O$
  Conditions: Warm and distil off Ethanenitrile.

- Now consider the reactions of the nitriles (Factsheet 34) and the nitrile can be converted to the target molecule:

  $CH_3CN + 4[H] \xrightarrow{LiAlH_4} \underset{\text{Ethanamine}}{CH_3CH_2NH_2}$
  Conditions: Dry ether solvent, addition of dilute acid.

The reaction scheme is now complete, and all reagents, conditions and equations can be supplied as necessary.

$CH_3COCl \rightarrow CH_3CONH_2 \rightarrow CH_3CN \rightarrow CH_3CH_2NH_2$

Example 2

Devise a reaction scheme, involving more than one step, to convert:

$CH_3COCl \rightarrow CH_3NH_2$

- A similar example to the first, converting ethanoyl chloride to a primary amine, but notice the length of the carbon chain has decreased by one. Use of the degradation reaction should be suspected.

  First introduce nitrogen as required:

  $CH_3COCl + NH_3 \rightarrow \underset{\text{Ethanamide}}{CH_3CONH_2} + HCl$

  Conditions: Room temp, aqueous.

- Then use the Hoffman degradation reaction (Factsheet 34) with the amide.

  $CH_3CONH_2 + Br_2 + 2NaOH \rightarrow CH_3NH_2 + CO_2 + 2NaBr + H_2O$

  Conditions: Add Br_2 (l) at room temp, then add conc NaOH and warm.

The target molecule has been attained in two steps. The reaction scheme is:

$CH_3COCl \rightarrow CH_3CONH_2 \rightarrow CH_3NH_2$

Example 3

Devise a reaction scheme, involving more than one step, to convert:

$CH_3CH_2Br \rightarrow CH_3CH_2CHClCH_3$

- Conversion of bromoethane to 2-chlorobutane.
- Note that the carbon chain length has increased by 2, so suspect the use of a Grignard reagent (Factsheet 31).
- Since the starting molecule is a halogenoalkene, formation of the Grignard reagent should be the first step.

  $CH_3CH_2Br + Mg \rightarrow CH_3CH_2MgBr$

  Conditions: Heat under reflux, ether solvent.

- Recalling reactions of Grignard reagents, a **halogenoalkane cannot be formed directly**. Looking at where the Cl atom is to be placed in the target molecule, on the second carbon, it would be logical to move to a secondary alcohol next.
- The Grignard reagent must be reacted with ethanal to achieve the desired 4 carbons in total.

  $CH_3CH_2MgBr + CH_3CHO + H_2O \rightarrow CH_3CH_2CHOHCH_3 + Mg(OH)Br$

  Conditions: Dry ether solvent, hydrolysis with dilute acid.

- Knowledge of the reactions of the alcohols (Factsheet 17) gives a rout to the target molecule:

  $CH_3CH_2CHOHCH_3 + PCl_5 \rightarrow CH_3CH_2CHClCH_3 + HCl + POCl_3$

  Conditions: Dry.

The reaction scheme, therefore:

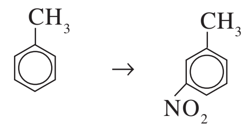
$CH_3CH_2Br \rightarrow CH_3CH_2MgBr \rightarrow CH_3CH_2CHOCH_3 \rightarrow CH_3CH_2CHClCH_3$

As these examples illustrate, a thorough knowledge of the organic reactions covered in the AS and A2 courses are required.

Questions

Devise reaction schemes, including reagents and conditions for each step, for the following conversions.

1. $C_2H_5OH \rightarrow C_2H_5ONH_2$
   Ethanol Ethanamide

2. 

methylbenzene 4-nitrobenzene

(HINT: Factsheet 39)

Answers

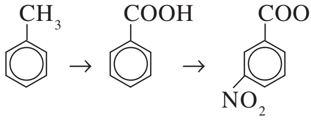
1. Reaction scheme:

$CH_3CH_2OH \rightarrow CH_3COOH \rightarrow CH_3COCl \rightarrow CH_3CONH_2$

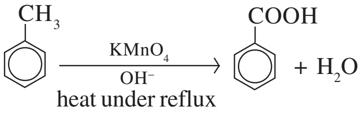
Step 1: $CH_3CH_2OH + 2[O] \xrightarrow{K_2Cr_2O_7} CH_3COOH + H_2O$
Conditions: H^+, heat under reflux.

Step 2: $CH_3COOH + PCl_5 \rightarrow CH_3COCl + HCl + POCl_3$
Conditions: Dry, room temp.

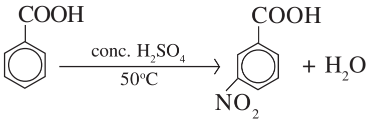
Step 3: $CH_3COCl + NH_3 \rightarrow CH_3CONH_2 + HCl$
Conditions: Aqueous, room temp.

2. 

Step 1:



Step 2:



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Curriculum Press, Unit 305B, The Big Peg, 120 Vyse Street, Birmingham, B18 6NF
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