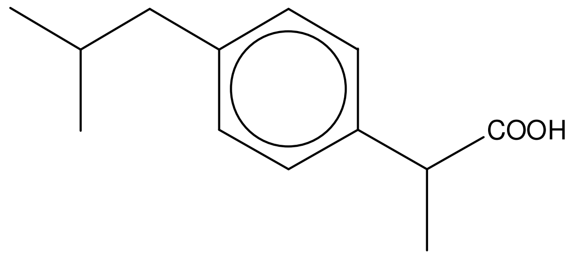
Ibuprofen – a case study in green chemistry

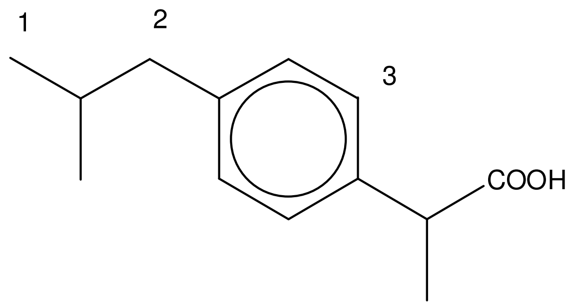
The UK market for over-the-counter pain-killers (for headache, toothache, muscular aches, period pain *etc*) is worth about £300 million per year. In the UK, all such medicines are formulated from just four active ingredients – aspirin, paracetamol, codeine and ibuprofen. These may be sold separately under their own names, as a branded product (Aspro, Panadol, Nurofen *etc*), or as combined preparations containing two or more of these ingredients (Veganin contains aspirin, codeine and paracetamol, for example).

Ibuprofen is the most recent addition to this list. It was patented by the Boots company in the 1960s and became available without prescription in the UK in the mid-1980s.

The skeletal formula of ibuprofen is given below. This type of formula does not show all the carbon and hydrogen atoms. Each line represents a carbon-carbon bond. A carbon atom is assumed to be at the end of each line. Each carbon atom is assumed to form enough C-H bonds to make a total of four bonds.



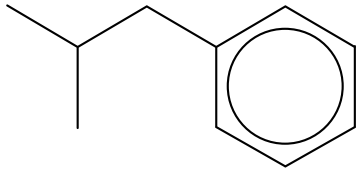
Q 1. Look at the skeletal formula of ibuprofen below. How many hydrogen atoms are bonded to each of the carbon atoms labelled 1, 2 and 3? Explain your answers.



Ibuprofen

The Boots' synthesis

Boots' method of making ibuprofen described in their patent starts from the compound 2-methylpropylbenzene that can be made from compounds separated from crude oil. This compound has a similar carbon skeleton to that of ibuprofen.



2-methypropylbenzene

Q 2. (a) What is the only functional group of 2-methylpropylbenzene?

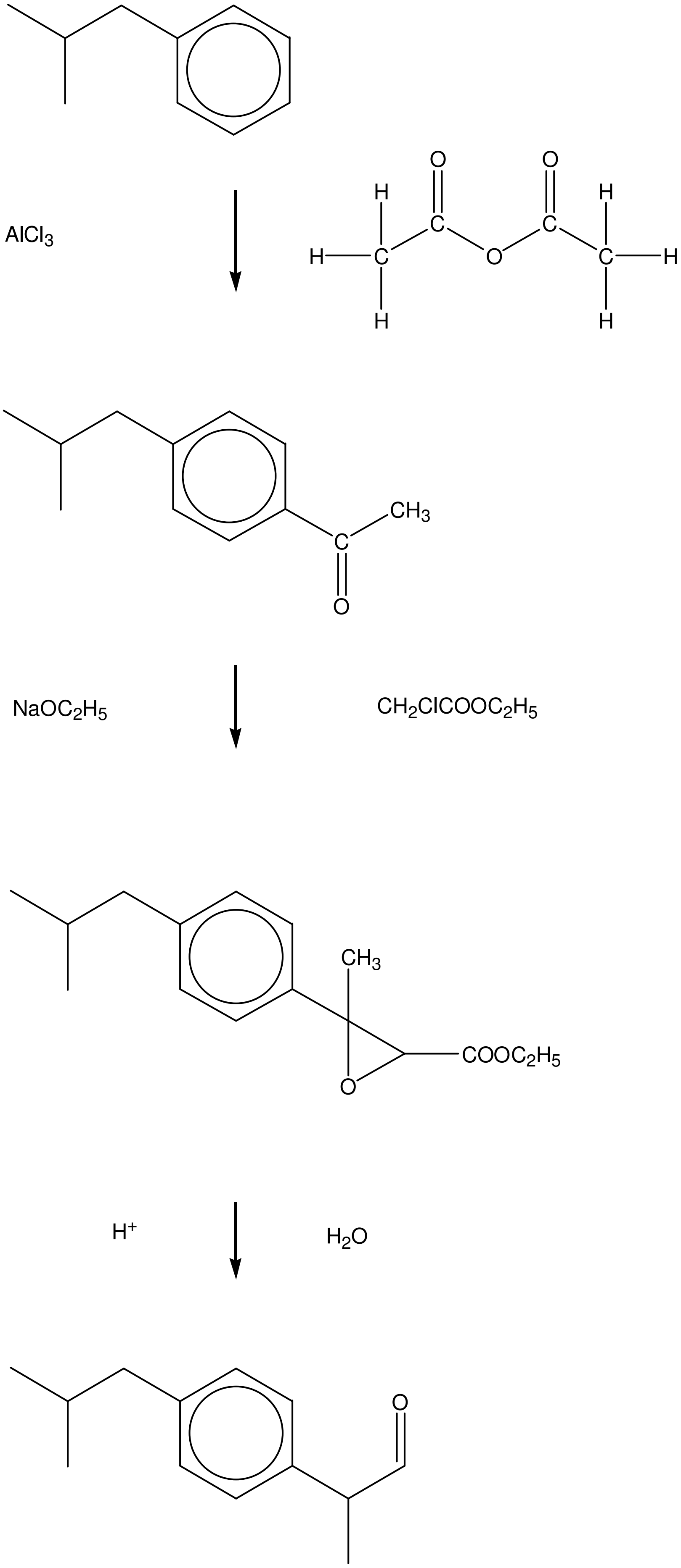
(b) What type of reactions does this functional group usually undergo?

Q 3. (a) What extra functional group does ibuprofen have compared with 2-methylpropylbenzene?

(b) What sorts of reactions can be used to prepare this functional group?

The Boots' synthesis requires six steps. These are shown in Figure 1 (on the following pages).

Q 4. One problem with a synthesis that takes several steps (a multi-step synthesis in the jargon) is that it produces a low overall yield. Imagine each step has a yield of 90%. A 1-step process would have a 90% yield, a 2-step process one of 90 x 90 = 81%. What would be the yield of a 6-step process?



$AlCl_3$
O O
H H
C C
H C O C H
H H
CH_3
C
O
$NaOC_2H_5$
$CH_2ClCOOC_2H_5$
CH_3
$COOC_2H_5$
O
H^+
H_2O
O

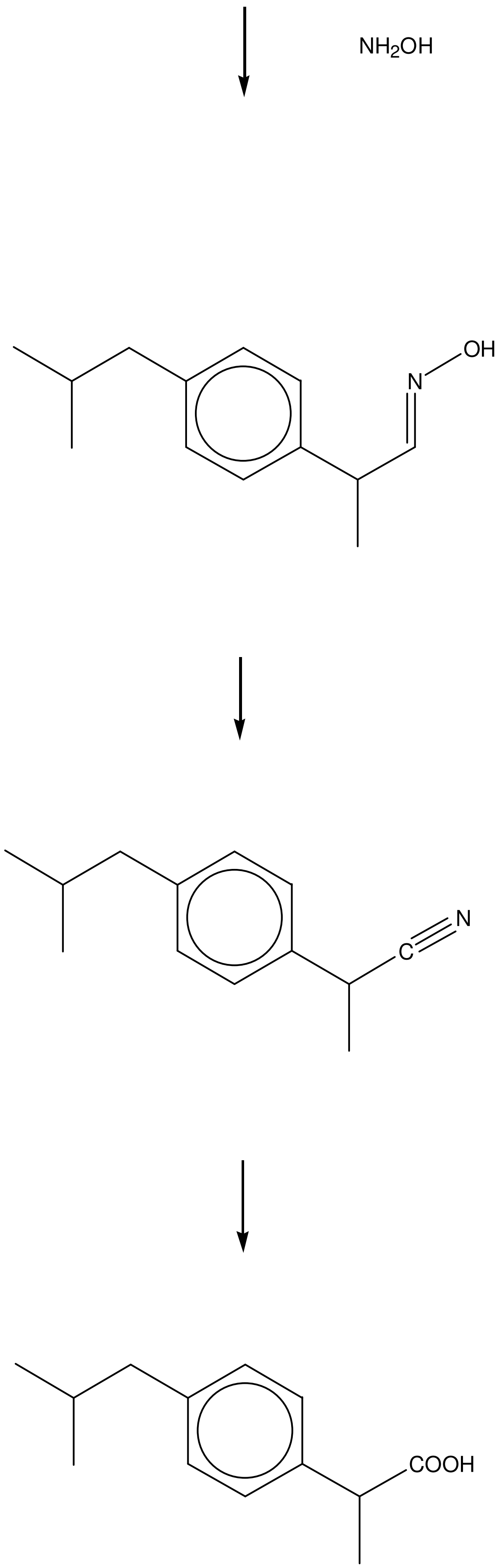


Figure 1 Boots' synthesis of ibuprofen

Atom economy

Of even more importance to the green chemist than **yield** is **atom economy**, the percentage of the raw materials and reagents used in the synthesis that actually end up in the final product, see *What is green chemistry?*. Figure 2 (on the following pages) shows the Boots' synthesis again with the atoms wasted at each step shown in a 'waste box'. A quick glance at Figure 2 shows that many of the atoms of the reactants used do not appear in the final product.

Table 1 shows a calculation of the atom economy of the overall reaction.

Reagent		**Used in ibuprofen**		**Unused in ibuprofen**	
Formula	$\mathbf{M_r}$	**Formula**	$\mathbf{M_r}$	**Formula**	M_r
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_4H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
$C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
C_2H_5ONa	68		0	C_2H_5ONa	68
H_3O	19		0	H_3O	19
NH_3O	33		0	NH_3O	33
H_4O_2	36	HO_2	33	H_3	3
Total		**Ibuprofen**		**Waste products**	
$C_{20}H_{42}NO_{10}ClNa$	514.5	$C_{13}H_{18}O_2$	206	$C_7H_{24}NO_8ClNa$	308.5

Table 1 Atom economy in the Boots' synthesis of ibuprofen

The overall figure is 40%. This means that more than half the materials used in the synthesis are wasted. Since the UK market for ibuprofen is about 3000 tonnes (3000 000 kg) per year this is an awful lot of waste!

Q 5. A typical tablet contains 200 mg of ibuprofen.

(a) How many tablets are produced each year?

(b) The population of the UK is about 60 million.

(i) How many tablets is this per person each year?

(ii) Evaluate how reasonable your answer is.

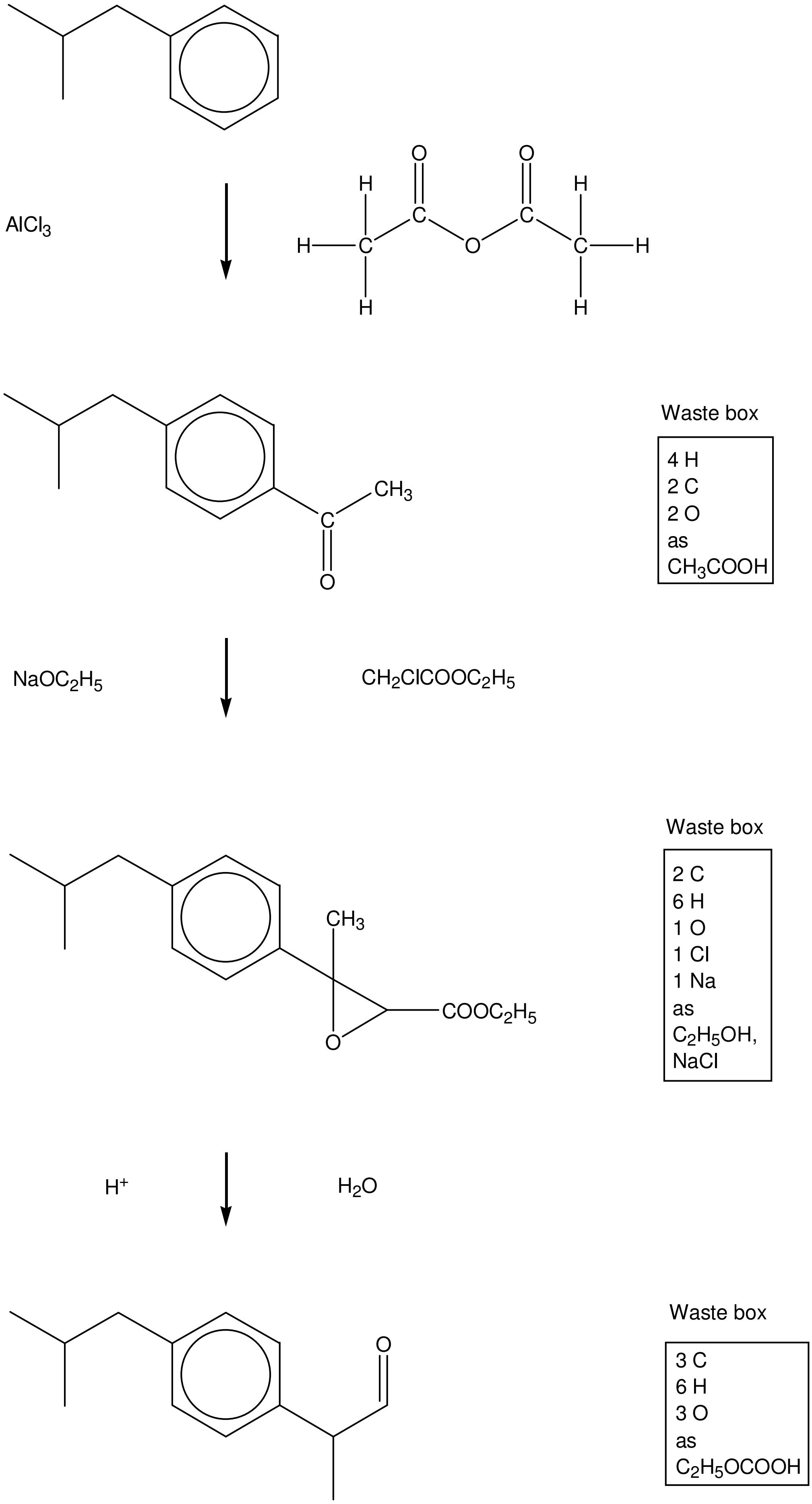
Q 6. What type of reaction is step 1 of the Boots' synthesis?

Q 7. Work out the atom economy of step 1 of the Boots' synthesis.

Q 8. What type of reaction is step 5 of the Boots' synthesis?

Q 9. What reagents are required for step of the Boots' synthesis 6?

Q 10. Redraw the structural formulae in Figure 1 as displayed formulae (showing every atom and every bond). Colour in green all the atoms of the starting materials that end up in the final product and colour the rest in red.



AlCl3
H
H—C
H
O
C
O
O
C
H
C—H
H
Waste box
4 H
2 C
2 O
as
CH3COOH
CH3
C
O
NaOC2H5
CH2ClCOOC2H5
Waste box
2 C
6 H
1 O
1 Cl
1 Na
as
C2H5OH,
NaCl
CH3
COOC2H5
O
H+
H2O
Waste box
3 C
6 H
3 O
as
C2H5OCOOH
O

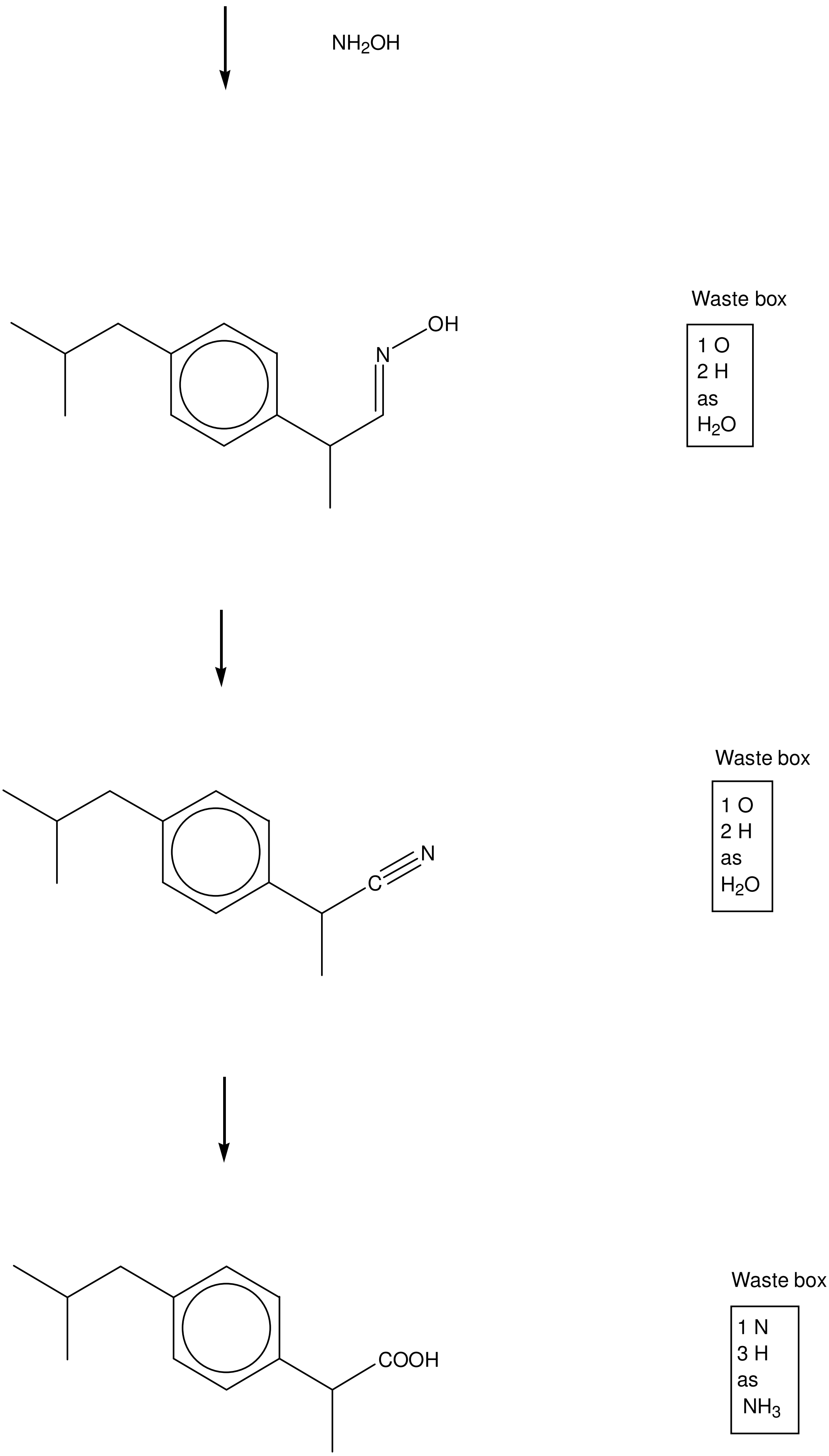


Figure 2 Boots' synthesis of ibuprofen showing the 'waste box'

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The green synthesis of ibuprofen

The ibuprofen patent ran out in the mid-1980s. Prior to that, only Boots had the right to make and sell the drug. The patent system protects the interests of companies that develop drugs, and allows them to sell patented drugs exclusively, normally for 20 years (although by the time the drug gets to the market, there is usually only about ten years left to run). This allows them to recoup the money spent on a drug's development and also make a profit, some of which will go on investment in new drugs.

After the patent ran out, any company could make and sell the drug. A new company, called BHC, was formed to develop a new 'green' synthesis of ibuprofen and to sell the pain-killer. This consortium developed an alternative synthesis of ibuprofen from the same starting material in just three steps. This is shown in Figure 3 (on the following page) which also indicates the atom economy of each step by showing the discarded atoms in the 'waste box'.

Table 2 shows the calculation of the overall atom economy; it is 77% - almost double that of the Boots' synthesis.

Reagent		**Used in ibuprofen**		**Unused in ibuprofen**	
Formula	**M_r**	**Formula**	**M_r**	**Formula**	**M_r**
$C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
$C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
H_2	2	H_2	2		0
CO	28	CO	0		0
Total		**Ibuprofen**		**Waste products**	
$C_{15}H_{22}O_4$	266	$C_{13}H_{18}O_2$	206	$C_2H_4O_2$	60

Table 2 Atom economy in the green synthesis of ibuprofen

Q 11. Imagine the yield of each step in the green synthesis is 90%.

(a) What will be the overall yield of this synthesis?

(b) How does it compare with the yield of the six-step synthesis making the same assumptions?

Q 12. Redraw the structural formulae in Figure 2 as displayed formulae (showing every atom and every bond). Colour in green all the atoms of the starting materials that end up in the final product and colour the rest in red. Compare your drawing with that in Q 10.

Q 13. Work out the atom economy of step 2 of the green synthesis.

Q 14. (a) What type of reaction is step 2 of the green synthesis?

(b) Raney nickel is a spongy form of nickel made by dissolving the aluminium out of an aluminium-nickel alloy to leave holes.

(i) What is the function of this material?

(ii) Why is it made into a spongy form?

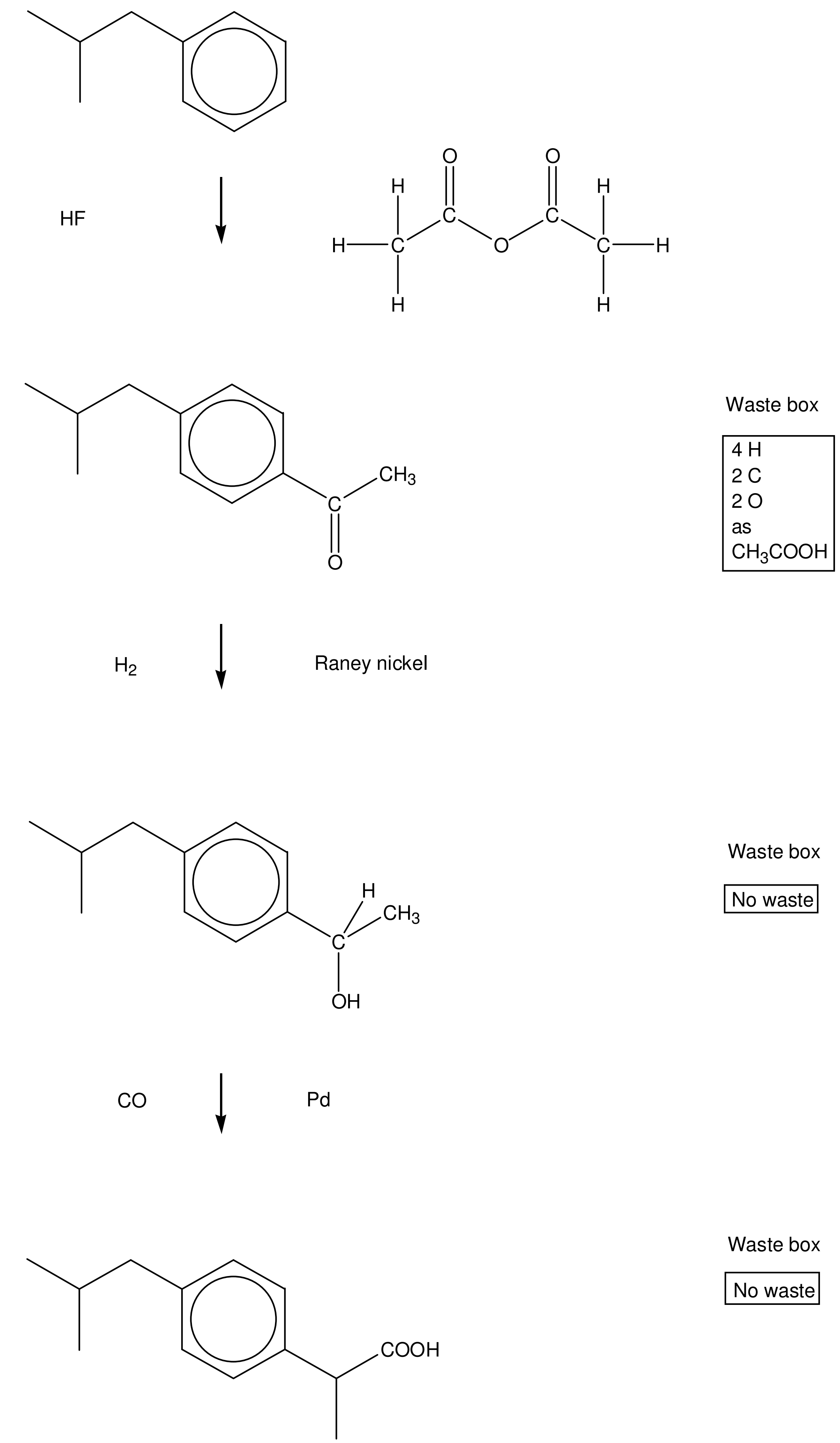

Figure 3 Green synthesis of ibuprofen showing the waste box

The green synthesis has other advantages as well as its fewer steps and greater atom economy.

Look at step 1 of both syntheses; the starting material, reagent and product are the same in each case, only the catalyst differs. However, the ‘catalyst’ in the Boots’ synthesis (aluminium trichloride, $AlCl_3$) is not a true catalyst. In the process it is changed into a hydrated form that has to be disposed of – usually in landfill sites. The disposal of waste is discussed in more detail in *How does waste affect our environment?*. Fresh material is required for the next batch. Therefore it is in effect a reagent rather than a catalyst. The catalyst in the green synthesis (hydrogen fluoride, HF) is a true catalyst – it is recovered and reused so that it generates no waste.

The other two steps of the green synthesis also use catalysts (Raney nickel and palladium) that are recovered and re-used.

These factors make the green synthesis cheaper as well as more environment-friendly.

Q 15.	(a) How might material in a landfill site escape into the environment?
	(b) Find out some of the environmental effects of aluminium compounds.