1. The Fluorofen Problem

Summary

Outline of the exercise

In this activity students are presented with a specific chemical problem set in an industrial context. The problem is based on improving the efficiency of a key step in the synthesis of Fluorofen, which is a pharmaceutical product whose patent will expire shortly. The initial handout sets the problem in context – each group of students represents a team of R&D chemists who work for a large company called ACE. Their competitors, Zenaxo, are intending to market Fluorofen at a reduced price when its patent runs out. The teams look at the synthesis of Fluorofen and decide where and how changes could be made to reduce their company's production costs. Some questions are outlined to direct them. The tutor's guide to this problem gives a step-by-step guide to running the hour-long workshop, which brings together aspects of practical organic chemistry, spectroscopic interpretation, mechanism and reaction kinetics.

Key aims

- to introduce team working skills;
- to introduce problem solving skills;
- to develop awareness of industrial issues; and
- to increase students' confidence in their ability to tackle realistic problems.

Time requirements

- 1 hour workshop
- No private study

Timetable

A proposed timetable for running this exercise within a one hour workshop is given below. The exercise is based around two main group discussion sessions, followed by plenary sessions in which ideas from all the groups are pooled.

Introduction	5 mins
Group discussions 1	15 mins
Plenary session 1	10 mins
Group discussions 2	15 mins
Plenary session 2	5 mins
Total	50 mins

S1

The Fluorofen Problem

Fluorofen student handout 1

What is Fluorofen?

- Oral drug
- Anti-inflammatory
- Analgesic
- Treatment for period pains

The ACE company makes Fluorofen

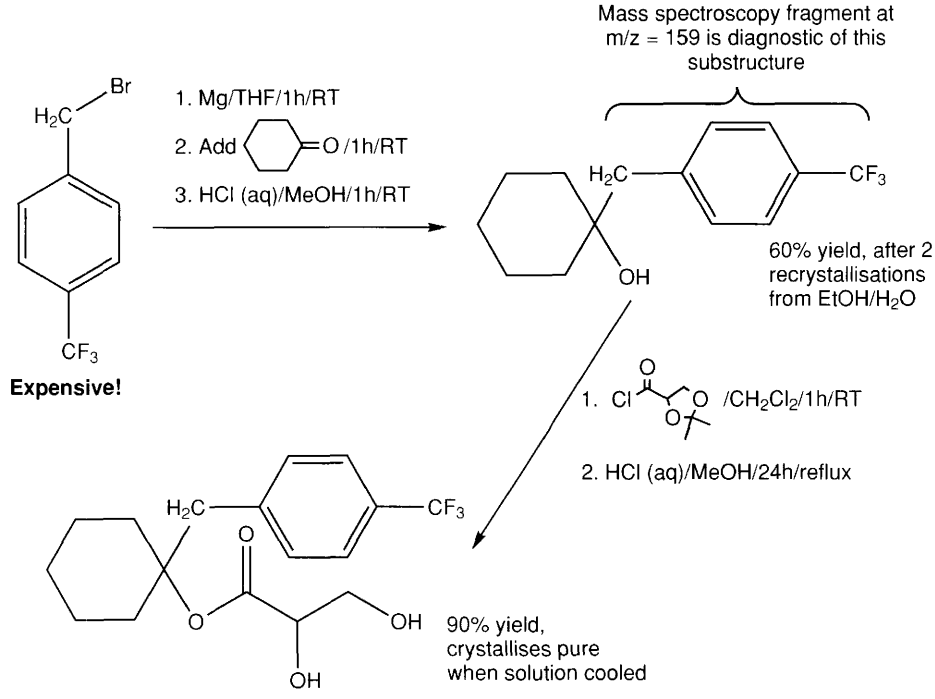
- Your tutor is Head of Medicinal Chemistry at ACE
- You are a crack team from R&D

The Problem

- Patent expires in 6 months
- Zenaxo will compete
- They plan to undercut our post-patent price by 30% (£1.40 vs £2.00 for 100 tablets)

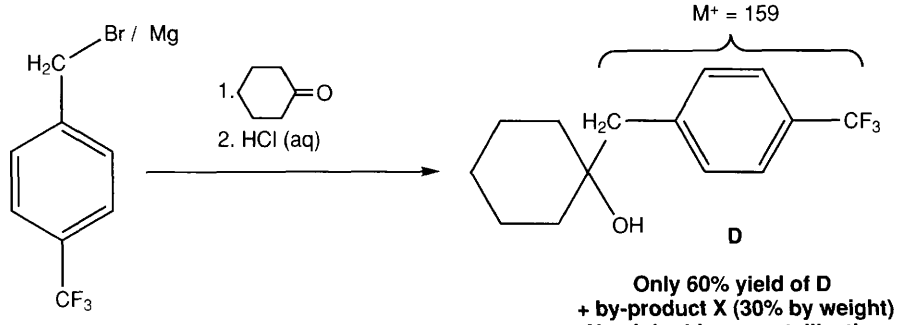
QUESTION 1: How might Zenaxo get their price so low?

Synthesis of Fluorofen



Fluorofen student handout 2

Key synthetic step

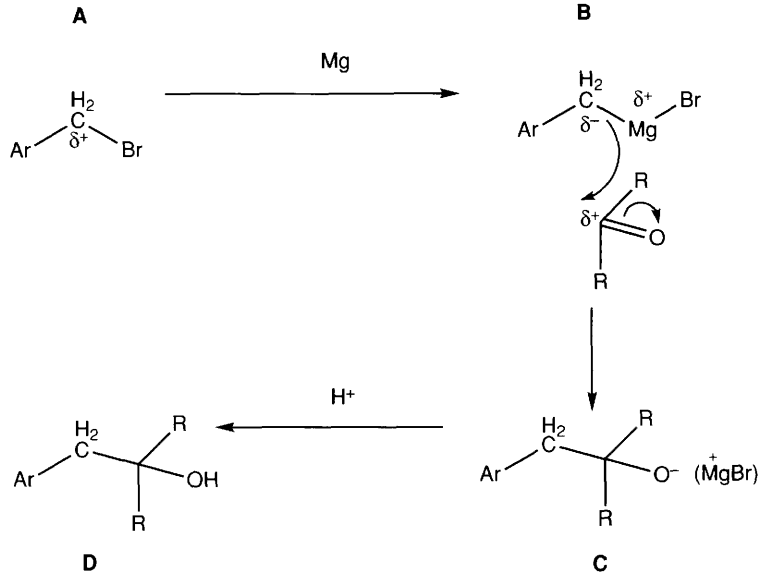


A
Expensive!

D

Only 60% yield of D
+ by-product X (30% by weight)
Need double recrystallisation
to obtain pure D
uncontaminated by X

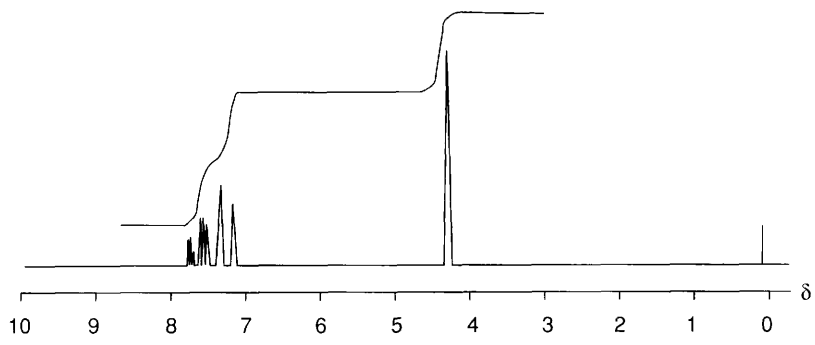
Mechanism for the formation of D



Data on X

MS gives parent ion M^+ at 318

^1H NMR at 60 MHz:



QUESTION 2: What is the structure of X?

QUESTION 3: Add arrows to the diagram of the formation of D to indicate how X is formed

Fluorofen student handout 3

QUESTION 4: What change in concentration of reactants would generate less X?

Higher [A]?

Higher [A] and [Mg]?

Higher [Mg]?

Higher [ketone]?

QUESTION 5: How would you achieve your aim in Q4?

Hint: There are many ways Zenaxo could undercut ACE. Your team would probably want to:

- Optimise reaction conditions
- Economise on solvents, reactants, running costs (time, heat) and waste disposal

You may also want to look at other work on Grignard reactions such as that by John Brown's group in Oxford – they went back to the literature to find clues[1] to improving "difficult Grignard reactions" and carried out a careful study to provide a general procedure[2]. Do you think that this solution would work well for the Fluorofen problem?

[1]A Mendel, *J. Organomet. Chem.*, 1966,**6**, 97.
[2]K.V. Baker, J.M. Brown, N. Hughes, A.J. Skarnulis and A. Sexton, *J. Org. Chem.*, 1991, **56**, 698.

T1 The Fluorofen problem

This exercise is particularly effective if run entirely 'in character', with the tutor taking on the role of Head of Medicinal Chemistry throughout the workshop. It may be useful to follow the detailed timetable for each part of the workshop (see Summary), so that the pace can be pushed if necessary – a sense of urgency helps the exercise to be successful and is particularly important if the timetable does not permit the workshop to overrun.

No preparation is required by students. This has two advantages; no assumptions need to be made that students have carried out background reading, and the exercise has immediate interest and impact. The following guidance notes relate to the timetable in the summary at the start of this exercise.

Introduction

Addressing the whole class in a role-play is an effective way of introducing the activity. Possible points to include in an introductory presentation are given below and can be reinforced by using Handout 1. Alternatively, the students can be divided immediately into groups, and simply provided with the information on the handout.

- **Introduction**
  In the role play scenario the tutor acts as head of medicinal chemistry of the company ACE, and the students as a top R&D team.
- **Why has the meeting been called?**
  This urgent and important meeting has been called because the patent of one of the company's leading pharmaceutical products, Fluorofen, will expire in six months and the company is worried about competition from other manufacturers. They have already been informed that Zenaxo is planning to undercut their price by 30%.
- **What does the company plan to do?**
  The customer base cannot be lost, and therefore ACE plans to match Zenaxo's price for a few months at zero profit, while working to cut costs.
- **Information about Fluorofen (Handout 1).**
  Fluorfen has anti-inflammatory and analgesic properties. It is excellent for treating period pains, and has a large and sustainable market worth about £50 million per annum in sales. The structure of Fluorofen and a synthetic sequence for its manufacture are shown on Handout 1.
- **What do the teams have to do?**
  The company feels that a fresh look at the problem is needed and has set up some meetings to brainstorm the problem. The groups therefore have fifteen minutes in which to come up with five or six reasons why Zenaxo may be able to undercut their price.

Group discussions 1

Assigning students to defined groups, rather than letting them choose their own groups, works well. One option is to assign them to 'companies' that are subsidiaries of ACE, and to ask them to invent a company name. Once they have organised themselves into groups, and have received Handout 1,

it is important that they identify a spokesperson, and start to write down ideas – each group must be asked for suggestions when the fifteen minutes are up. If a group is stuck or slow, the suggestions below can be used to guide them.

Plenary session 1

Suggestions for how Zenaxo might be undercutting the companies can be pooled by picking on various groups. Some examples are given in the table below.

Some suggestions for cutting the cost of Fluorofen production

General ideas	Specific ideas
Lower non-chemistry production costs	Cheaper starting materials Less on packaging/marketing
Lower production costs (chemistry)	Better reaction conditions: – Temperature – Pressure – Solvent – Reaction time – Cheaper reagents (*eg* catalyst) More efficient purification Recycling: – Reactants – Solvents – By-products Improved yield(s)
Cheaper route	Completely new route Alternative key step Cheaper analogue of Fluorofen
Someone is cheating!	Zenaxo selling Fluorofen at a loss while they corner the market.

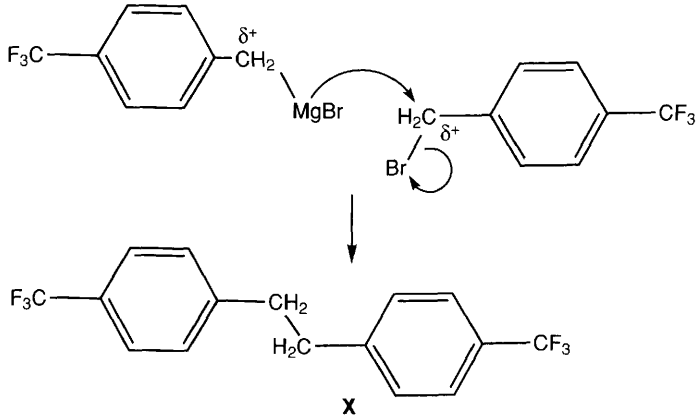
A brief discussion session at the end of this part can be used to eliminate suggestions that are not practicable. At the end of the plenary session, the results of the brainstorming session should be summarised including the following points (either verbally, or on an additional handout):

- The most likely source of cost cuts is through improvement of the efficiency of the Grignard reaction. In particular, the students might have identified the following:
  – High cost of the starting material
  (but note that it probably cannot be bought or made more cheaply)
  – Poor yield
  – High running costs (long reaction time and high purification costs)
- If there is time, students can be asked for suggestions about how the reactions might be made to take place more quickly and cleanly in order to reduce costs.
- It could be suggested to students that, rather than changing conditions by trial and error, they might try to identify impurities in an attempt to design conditions that would reduce the formation of the by-product(s) (see Handout 2).

At the end of the first plenary session, Handouts 2 and 3 should be distributed and students must work through the questions.

Group discussions 2

Groups should need little tutor input now. The by-product is the dimer of CF_3–C_6H_4–CH_2 , and it is quite easy to come up with a plausible mechanism (see below). (Although a multi-step electron transfer mechanism is very likely the details of the mechanism do not affect the subsequent kinetic argument or solution to the problem, and therefore in depth discussion of it depends on the amount of time available). The tutor need only guide those groups that are getting behind. Group discussions work well if one company is asked to put forward the structure of X (once everyone has determined it), and another is asked to suggest the mechanism for its formation (perhaps adding arrows to Handout 2). At least one group should have an idea for the answer for question 5 (see Handout 3) before the final plenary session.



The structure of X, and a possible mechanism for its formation.

Plenary session 2

This works best as an interactive session. However, a possible summary, which could be presented in the form of a memo from the company, is given below.

MEMO

From: Head of Medicinal Chemistry To: R&D Team
Subject: Flurofen synthesis costs

Cutting the cost of Flurofen
The main problem is the low yield for step 1, due to the formation of a by-product X.

How can we compete?
The structure of **X** and a mechanism for its formation have been identified. If the [Mg] is increased, the formation of the Grignard would be quicker and there would be less time for the dimer by-product to form before all of the starting material is consumed. This would also cut running costs, as the reaction time would drop, and the purification of the product should be easier.

How could the [Mg] be increased?
Suggestions include using a powdered form of magnesium, using a thin film or precipitating/depositing it onto a porous material. However, the 'dry-stir' method (reference 2, Handout 3) will probably solve the Fluorofen problem. This is a cheap and efficient way of introducing magnesium with a high surface area. Using high surface area magnesium and general optimisation of the reaction should allow us to reduce the cost by around 50%.

Adapting/extending the exercise

The scenario of a company needing to improve the efficiency of a synthesis provides a useful backdrop for a number of different chemical problems that could be matched to course content and undergraduate level. *The Fluorofen Problem* requires a range of chemical skills at modest level, but the exercise could be biased towards a particular area of chemistry, if that were deemed more appropriate – *eg* practical problems (including industrial factors relating to scale-up), structure solving from spectra, mechanisms, physical organic chemistry, or literature searching. If several of these aspects were followed in more detail, further workshop time would be required, or the students would need to carry out some private study; the latter option offers an easy way of carrying out an assessment.

Possible extensions:

- Ask the companies for a brief report on possible ways of saving money on the synthesis;
- Provide data on by-products from several of the steps so that the exercise has a larger component of structure determination (which could be assessed);
- Ask for a literature search, in order to:
  – find ways of producing high surface area magnesium
  – find the specific references relating to the exercise (see Handout 3); or
- Link in a subsequent laboratory experiment, in which (on a simpler/cheaper benzyl derivative) students compare yields from old and new synthetic routes.

Assessment

This exercise works particularly well as an ice-breaker for subsequent team work, and there may be no need to generate a specific mark from this workshop. However, it can form part of peer group assessment of team working skills (see Appendix E).

Other methods of assessing the exercise are to ask for written work to be handed in as part of an extension to the exercise (either from individuals, or from the teams). For example through:

- the production of a report summarising the ways in which the synthesis of Fluorofen might be made more cost effective. Reports could be approximately 300 words, and might include a synthetic scheme. As many sources of savings as possible should be identified.
- the production of a report of approximately 300 words summarising how high surface area magnesium might be formed. Reports could briefly explain why this is of relevance to *The Fluorofen Problem,* and identify six literature references, including a 1966 paper by Mendel *et al.*, and a 1991 paper by Baker *et al.* (see Handout 3).