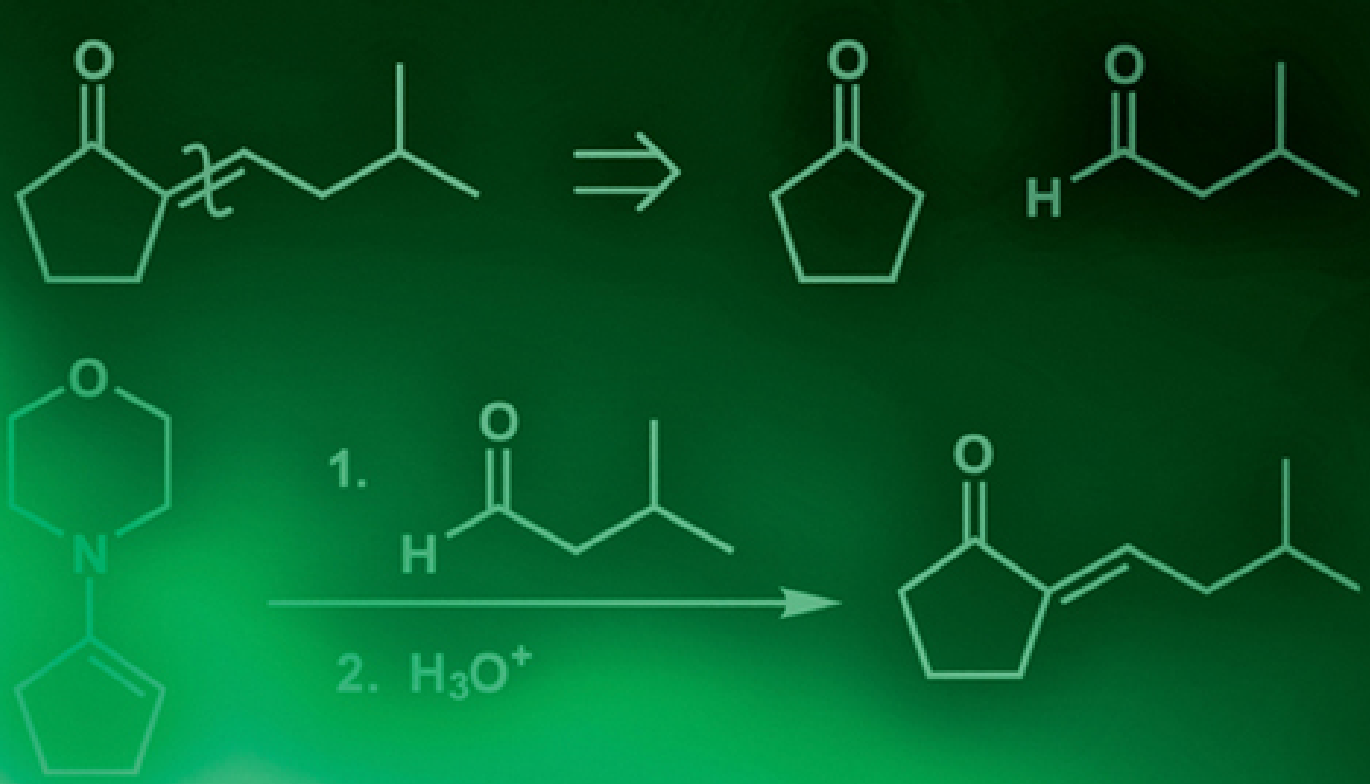

Stuart Warren · Paul Wyatt

Workbook for ORGANIC SYNTHESIS

The Disconnection Approach

Second Edition

WILEY

Contents

Workbook for Organic Synthesis: The Disconnection Approach Second Edition

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WILEY
A John Wiley and Sons, Ltd., Publication

This edition first published 2009

Registered office
John Wiley & Sons Ltd, The Atrium, Southern Gate,
Chichester, West Sussex, PO19 8SQ, United Kingdom

Library of Congress Cataloging-in-Publication Data

Warren, Stuart.
Workbook for organic synthesis: the disconnection approach/Stuart Warren and Paul Wyatt. – 2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 978-0-470-71227-6 – ISBN 978-0-470-71226-9

1. Organic compounds – Synthesis – Textbooks. I. Wyatt, Paul. II. Title.
QD262.W93 2009
547'.2 – dc22
2009030810

A catalogue record for this book is available from the British Library.

ISBN 978-0-470-7-12276 (h/b) 978-0-470-7-12269 (p/b)

Preface

In the 26 years since Wiley published *Organic Synthesis: The Disconnection Approach* and the accompanying Workbook, this approach to the learning of synthesis has become widespread while the books themselves are now dated in content and appearance. In 2008, Wiley published the second edition of *Organic Synthesis: The Disconnection Approach* by Stuart Warren and Paul Wyatt for which this is the accompanying *Workbook*.

This workbook contains further examples, problems (and answers) to help you understand the material in each chapter of the textbook. The structure of this second edition of the workbook is the same as that of the textbook. The 40 chapters have the same titles as before but all chapters have undergone a thorough revision with some new material. The emphasis is on helpful examples and problems rather than novelty. Many of the problems are drawn from the courses we have given in industry on 'The Disconnection Approach' where they have stimulated discussion leading to deeper understanding. It makes sense for you to have the relevant chapter of the textbook available while you are working on the problems. We have usually devised new problems but some of the problems in the first edition seemed to do such a good job that we have kept them. Usually, the answers are presented in a different and, we hope, more helpful style.

It is not possible to learn how to design organic syntheses just from lectures or from reading a textbook. Only by tackling problems and checking your answers against published material can you develop this skill. We should warn you that there is no single 'right answer' to a synthesis problem. Successful published syntheses give some answers that work, but you may well be able to design others that have a good chance of success. The style of this second edition is to give more discussion of alternative routes.

Stuart Warren and Paul Wyatt
2009

General References

Full details of important books referred to by abbreviated titles in the chapters to avoid repetition.

Clayden *Organic Chemistry*: J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, Oxford, 2000.

Disconnection Textbook: S. Warren and P. Wyatt, *Organic Synthesis: The Disconnection Approach*, Second Edition, Wiley, Chichester, 2008.

Drug Synthesis: D. Lednicer and L. A. Mitscher, *The Organic Chemistry of Drug Synthesis*, Wiley, New York, seven volumes, from 1977.

Fieser, *Reagents:* L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 20 volumes, 1967–2000, later volumes by T.-L. Ho.

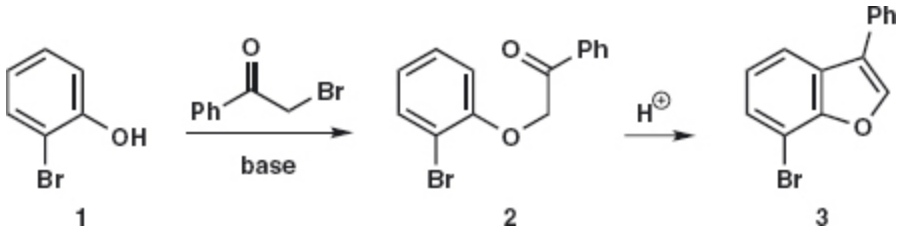
Fleming, *Orbitals*: Ian Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976.

Vogel: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. R. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, Fifth Edition, Longman, Harlow, 1989.

1

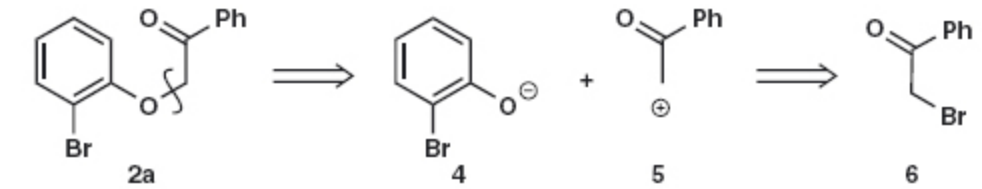
The Disconnection Approach

We start with a few simple problems to set you at ease with disconnections. **Problem 1.1:** Here is a two-step synthesis of the benzofuran **3**. Draw out the retrosynthetic analysis for the synthesis of **2** from **1** showing the disconnections and the synthons.



1 2 3

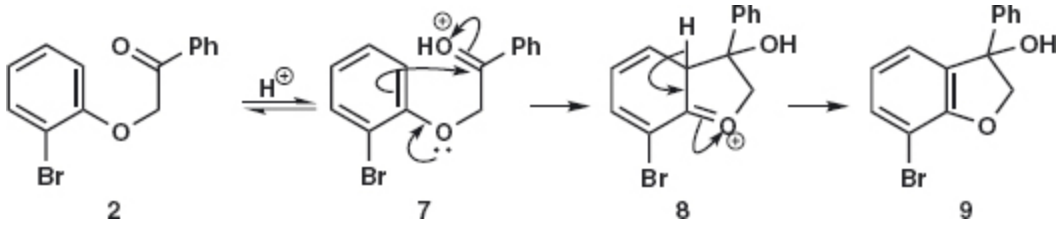
Answer 1.1: As this is a simple S_N2 reaction, the disconnection is of the C–O bond **2a** and the synthons are nucleophilic phenolate anion **4**, which happens to be an intermediate in the reaction, and the cation **5**, which happens not be an intermediate in the reaction but is represented by the α-bromoketone **6**.



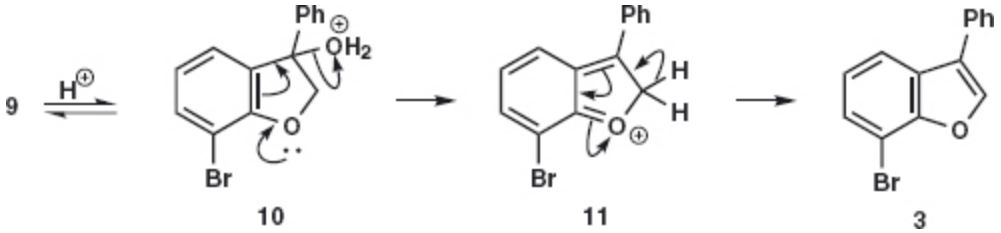
2a 4 5 6

Problem 1.2: Draw the mechanism of the cyclisation of **2** to **3**. This is an unusual reaction and it helps to know what is going on before we analyse the synthesis. **Answer 1.2:** The first step is an acid-catalysed cyclisation of the aromatic ring onto the protonated ketone **7**. Loss of a proton **8**

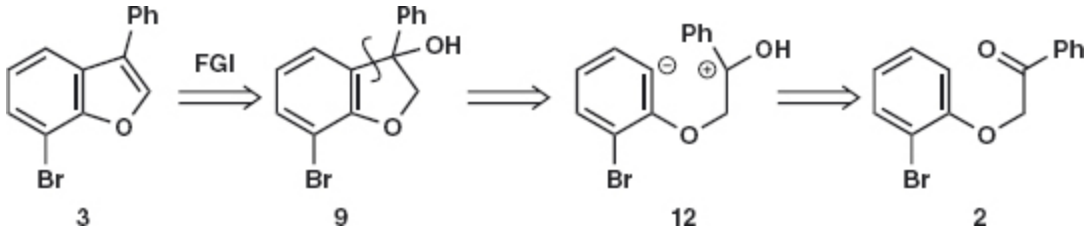
completes the electrophilic aromatic substitution giving the alcohol **9**.



Now protonation of the alcohol leads to loss of water **10** to give a stabilised cation that loses aproton **11** to give the new aromatic system **3. Problem 1.3:** Now you should be in a position to draw the disconnections for this step.



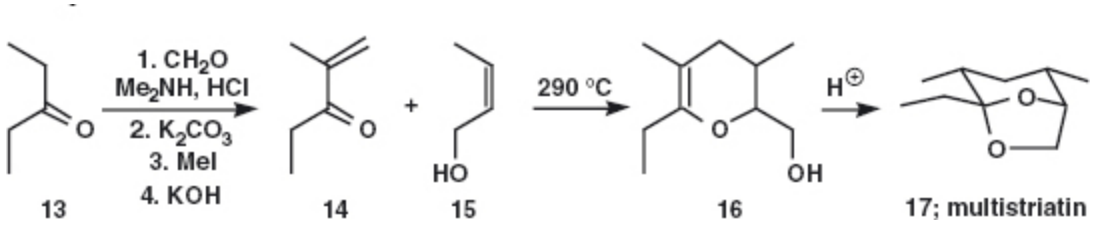
Answer 1.3: We hope you might have drawn the intermediate alcohol **9**. Changing **3** into **9** is not a disconnection but a Functional Group Interconversion (FGI) – changing one functional group into another. Now we can draw the disconnection revealing the synthons **12** represented in real life by **2**.



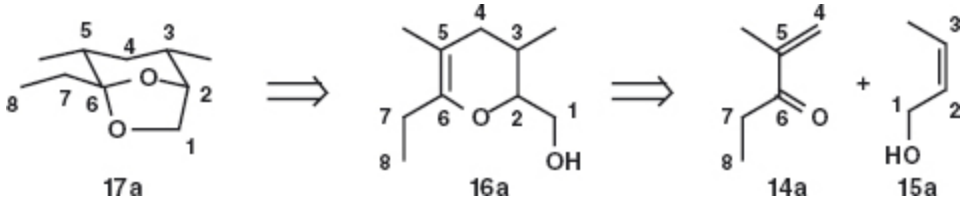
A Synthesis of Multistriatin

In the textbook we gave one synthesis of multistriatin **17** and here is a shorter but inferior synthesis as the yields are lower and there is little control over stereochemistry.[1] **Problem 1.4:** Which atoms in the final product **17** come

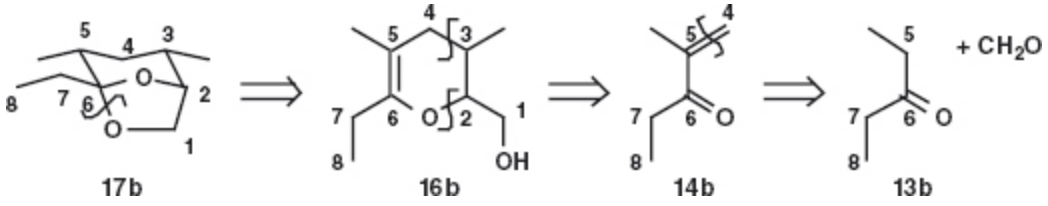
from which starting material and which bonds are made in the synthesis? *Hint*: Arbitrarily number the atoms in multistriatin and try to trace each atom back through the intermediates. Do not be concerned over mechanistic details, especially of the step at 290°C.



Answer 1.4: However you numbered multistriatin, the ethyl group (7 and 8 in **17a**) finds the same atoms in the last intermediate **16a** and the rest falls into place. It then follows which atoms come from **14** and which from **15**. Finally, you might have said that C-4 in our diagrams comes from formaldehyde.



So the disconnections also fall into place. Just one C–O bond was disconnected at first **17b** then one C–O and one C–C **16b** and finally the alkene was disconnected **14b** in what you may recognise as an aldol reaction with formaldehyde. If you practise analysing published syntheses like this, you will increase your understanding of good bonds to disconnect.



References

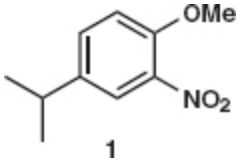
1. W. E. Gore, G. T. Pearce and R. M. Silverstein, *J. Org. Chem.*, 1975, **40**, 1705.

2

Basic Principles: Synthons and Reagents: Synthesis of Aromatic Compounds

This chapter concerns the synthesis of aromatic compounds by electrophilic and nucleophilic aromatic substitution. All the disconnections will therefore be of bonds joining the aromatic rings to the sidechains. We hope you will be thinking mechanistically, particularly when choosing which compounds can undergo nucleophilic aromatic substitution and the orientation of electrophilic aromatic substitution. Any textbook of organic chemistry[1] will give you the help you need.

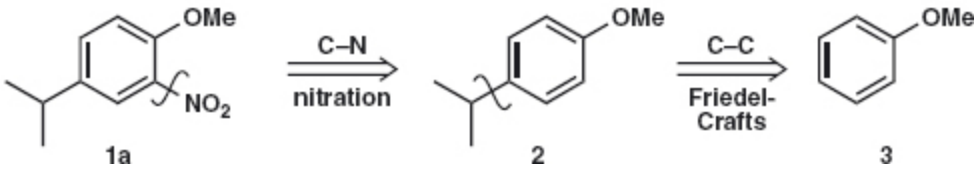
Problem 2.1: Compound **1** was needed[2] for an exploration of the industrial uses of HF. Suggest how it might be made. *Hint*: consider which of the three substituents you would rather *not* add to the ring.



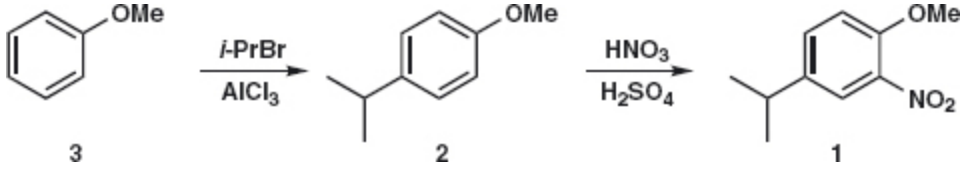
1

Answer 2.1: We can add the nitro group by nitration and the isopropyl group by Friedel-Crafts alkylation (as it is a secondary alkyl group) but we would rather not add the OMe group as there is no good reagent for MeO^+. So we disconnect first the most deactivating group (nitro) **1a** and then the isopropyl group **2**.

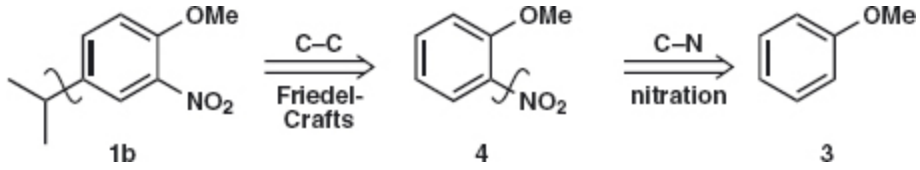
he isopropyl group **2**.



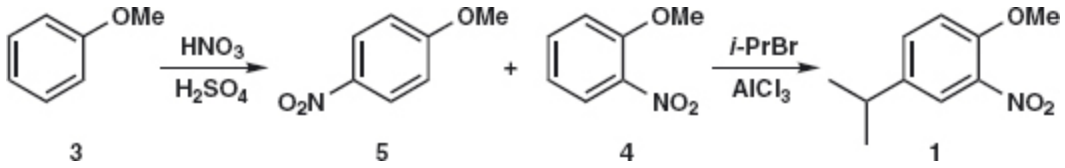
Before writing out the synthesis, we should check that the orientation of the substitution will be what we want. The OMe group is *ortho, para*-directing so alkylation will go mainly *para* because of steric hindrance. Now we have a competition as isopropyl is also *ortho, para*-directing but, since OMe has a lone pair of electrons conjugated with the benzene ring, it will dominate so everything is fine. We therefore suggest:



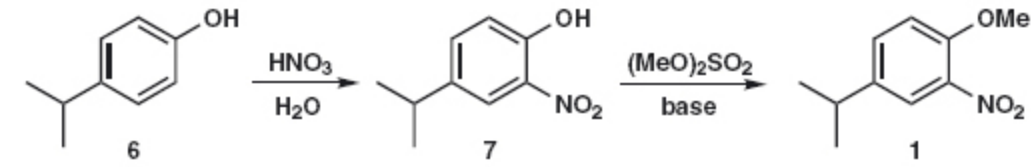
Did you consider the alternative strategy? That is, disconnect the isopropyl group first **1b** to give a new intermediate **4** and disconnect the nitro group second. The starting material, anisole **3**, is the same in both routes.



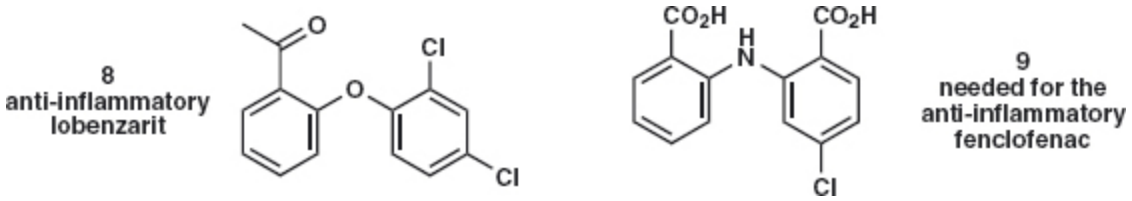
Again we should check the orientation. Nitration of anisole will give a mixture of *ortho* **4** and *para* **5** products so much depends on the ratio and whether they can easily be separated. The Friedel-Crafts reaction will go *ortho* or *para* to the OMe group and *meta* to the nitro group so that is all right. However the deactivating nitro group might make the reaction difficult.



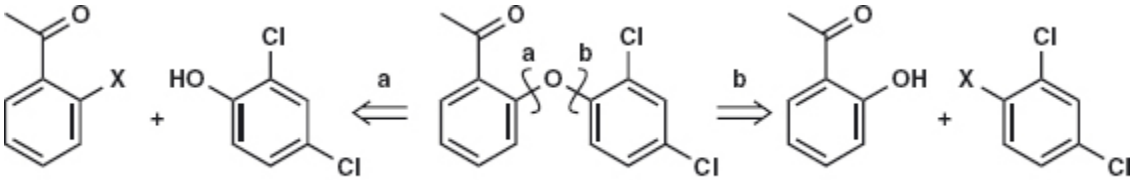
So what did the chemists prefer? One published synthesis[2] used HF as a catalyst to alkylate *ortho*-nitro-anisole **4** with isopropanol. The yield was a respectable 84%. This made sense as they had a supply of **4**. If anisole is nitrated with the usual HNO_3 /H_2 SO_4 , a 31:67 ratio of *ortho:para* products is obtained. If the nitrating agent is an alkyl nitrite in MeCN, the ratio improves to 75:25. The best route nowadays is probably the nitration of available *para*-isopropyl phenol **6**, probably quantitative, and methylation of the product **7** with, say, dimethyl sulfate.



Problem 2.2: These compounds **8** and **9** each have two benzene rings linked by a heteroatom and both are used to make anti-inflammatory drugs. An obvious strategy is to disconnect one C–X bond in each case and combine the two compounds by nucleophilic aromatic substitution. Suggest a synthesis for each compound.



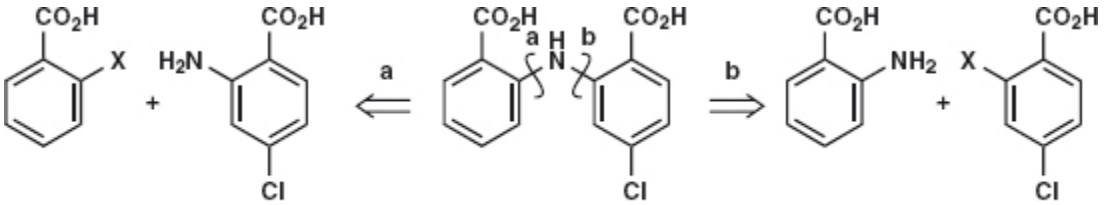
Answer 2.2: The two disconnections **8a** and **8b** illustrate the types of molecules needed for the first problem. In each case X is a leaving group such as a halogen and the phenols **11** and **12** would be used as their anions.



10 11 8a,b 12 13

To be successful, nucleophilic aromatic substitution needs an electron-withdrawing group *ortho* or *para* to the leaving group. A chloride, as in **13** is not adequate but the ketone in **10** is perfectly placed. The reported synthesis[3] uses **10**;X = Cl with **11** and Cu/NaOH as catalyst. We might nowadays prefer available **10**;X = F with the anion of the phenol.

The other compound **9** is easier in one way as both disconnections **9a** and **9b** are feasible. Each ring **14** and **15** has an electron-withdrawing CO_2 H group in the right position (*ortho* to the leaving group X). Compound **17** has another leaving group (Cl) that is *para* to the CO_2 H group so it could react. On the other hand, compound **15** could react with itself and polymerise as it has the nucleophilic amine and the activated chloride in the same molecule.

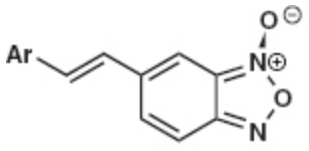


14 15 9a,b 16 17

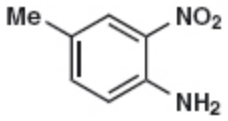
The reported synthesis[4] uses **16** and **17**; X = Cl relying on the CO_2 H group to provide regioselectivity at the more electrophilic *ortho* position. It is possible[5] that the fluoro-compound **17**; X = F would be a better way.

Problem 2.3: Chagas disease causes some 50,000 deaths annually in South America. Drugs based on the structure **18** are urgently needed. You are not expected to understand the chemistry used to make the strange heterocyclic ring but you might appreciate that it could come from an *ortho*-

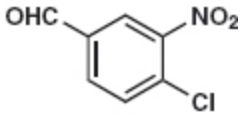
nitro aniline such as **19** or an activated halide such as **20**. Suggest syntheses for these starting materials.



18

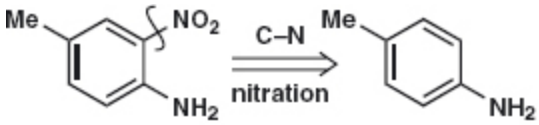


19

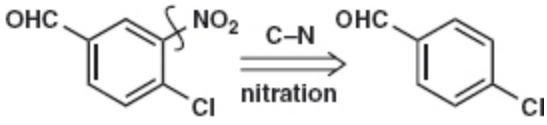


20

Answer 2.3: In both cases, the initial disconnection of the nitro group **19a** and **20a** is very appealing. The starting materials **21** and **22** should be easily made and nitration will go *ortho* to NH_2 rather than Me in **21** and *ortho* to Cl and *meta* to the deactivating aldehyde in **22**.

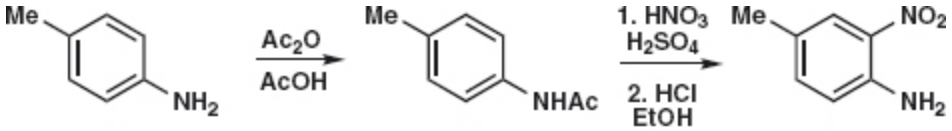


19a 21



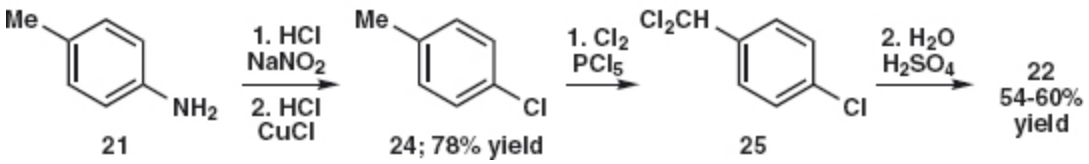
20a 22

The synthesis of **19** is straightforward[6] as the amine **21** is available from the nitration and reduction of toluene. Amide **23** formation reduces the reactivity of the amine so that mono-nitration and hydrolysis give **19**. Nitration of **23** gives **19**.



21 23 19

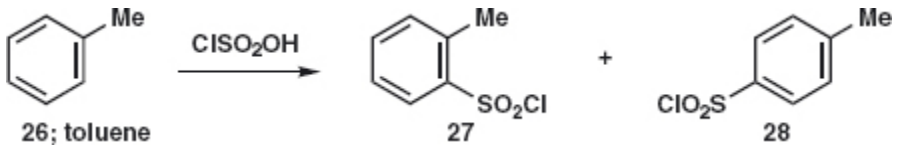
The aldehyde **22** is more difficult as we should need to chlorinate benzaldehyde in the *para* position to get **22**. One solution is to oxidise *para* chloro-toluene **24**, available[7] from **21** via the diazonium salt with, for example, chlorine to give **25** that can be hydrolysed[8] to the aldehyde **22**.



21 24; 78% yield 25

A Problem from the Textbook

When discussing the synthesis of saccharine in chapter 2 of the textbook, we said; 'In practice chloro-sulfonic acid is used as this gives the sulfonyl chloride directly. You may be surprised at this, thinking that Cl might be the best leaving group. But there is no Lewis acid here. Instead the very strong chloro-sulfonic acid protonates itself to provide a molecule of water as leaving group.' The reaction gives a mixture of the *ortho*-**27** and *para*-**28** products. **Problem 2.4:** With those hints, draw a mechanism of the chlorosufonation.



Answer 2.4: 'Strong' means a strong *acid* here so chloro-sulfonic acid **29** protonates itself to give a cation that loses water **30** to give the reactive cation **31**. This is attacked by toluene in the *ortho*-and *para*-positions to give e.g. **32** that loses a proton to give **28**.

References

1. Clayden, *Organic Chemistry*, chapters 22 and 23.

2. W. S. Calcott, J. M. Tinker and V. Weinmayr, *J. Am. Chem. Soc.*, 1939, **61**, 1010.

3. *Drug Synthesis*, vol 4, p. 42.

4. *Drug Synthesis*, vol 3, p. 38.

5. S. M. Kelly and H. Schad, *Helv. Chim. Acta*, 1985, **68**, 1444.

6. W. Porcal, A. Merlino, M. Boiani, A. Gerpe, M. Gonz´alez and H. Cercetto, *Org. Process. Res. Dev.*, 2008, **12**, 156.

7. *Vogel*, p. 931.

8. W. L. McEwen, *Org. Synth. Coll.*, 1943, **2**, 133.

3

Strategy I: The Order of Events

You should refer to the Guidelines from the textbook when you solve the problems in this chapter.

Guideline 1: Consider the effects of each functional group on the others. Add first (that is disconnect last) the one that will increase reactivity in a helpful way.

Guideline 2: Changing one functional group into another may alter reactivity dramatically.

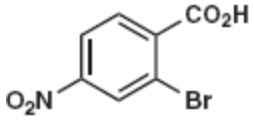
Guideline 3: Some substituents are difficult to add so it is best to start with them already present.

Guideline 4: Some disubstituted compounds are also readily available and they may contain a relationship (especially *ortho*) that is difficult to achieve by electrophilic substitution.

Guideline 5: Some groups can be added to the ring by nucleophilic substitution.

Guideline 6: If a series of reactions must be carried out, start with one that gives a single product unambiguously and not one that would give a mixture.

Remember that these guidelines may conflict or even contradict each other. THINK! **Problem 3.1:** Suggest syntheses of **1** and **2** needed as intermediates: **1** in the synthesis of some brominated acids[1] and **2** to study the mechanism of enzymatic ester hydrolysis.[2]



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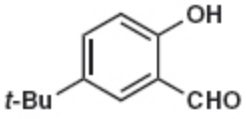
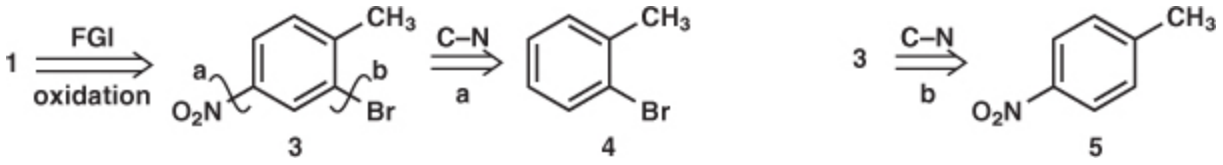
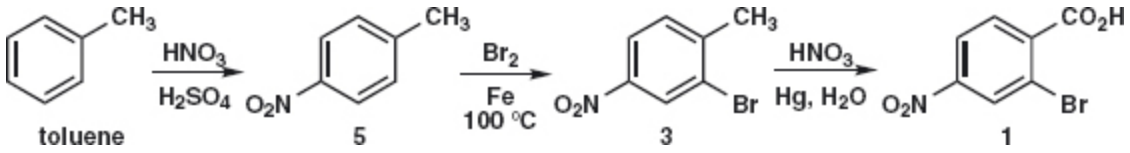


2

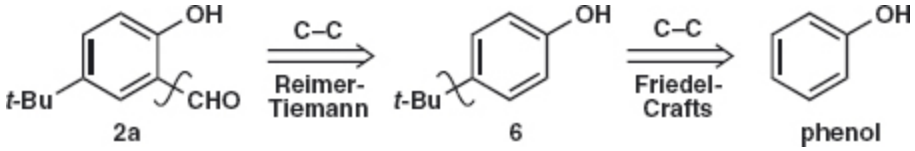
Answer 3.1: With two electron-withdrawing groups in **1**, some FGI is needed to control the orientation and gain some reactivity. There are good ways to introduce Br and NO_2 but no easy way to introduce CO_2H. FGI of CO_2H to Me with oxidation in mind would give an *ortho, para*-directing group where we need it **3**. Now we might disconnect NO_2 **3a** or Br **3b** as there are good reagents for adding both. There might be some doubt as to where **4** would be nitrated as both Me and Br are *ortho, para*-directing, but there is no doubt where **5** will be brominated as Me is *ortho, para*-directing while NO_2 is *meta*-directing.



So the synthesis was nitration of toluene (actually **5** is available), separation of **5** from the *ortho* isomer, bromination of **5**, and oxidation of **3** to give the target molecule.[1]



No doubt the CHO group could also be formed by oxidation of a CH_3 group but it can be inserted next to a phenolic OH by the Reimer-Tiemann reaction.[3] Now we can disconnect the *t*-Bu group with Friedel-Crafts alkylation in mind.



The large *t*-Bu group much prefers the *para* position and the Reimer-Tiemann reaction using chloroform as a source