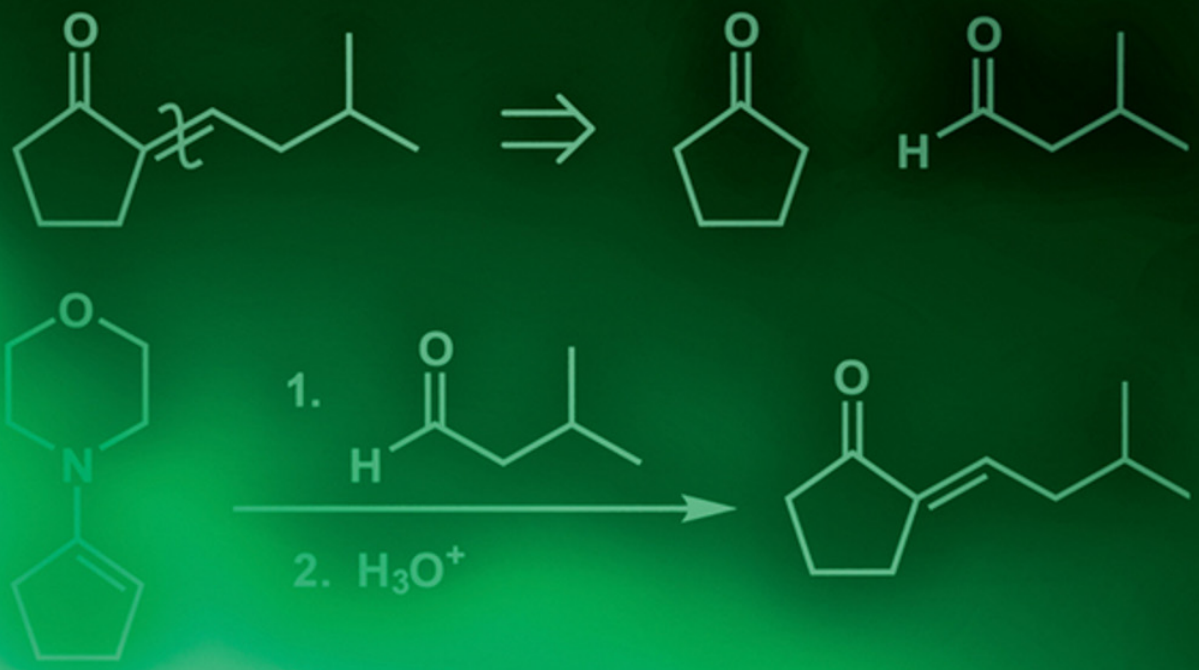

Stuart Warren · Paul Wyatt

Workbook for ORGANIC SYNTHESIS

The Disconnection Approach

Second Edition

WILEY

Workbook for Organic Synthesis: The Disconnection Approach

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)

Contents

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.

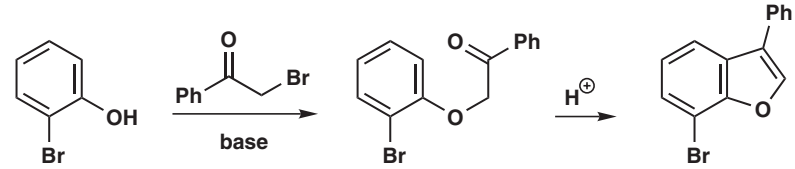
Fieser, *Reagents:* L. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 20 volumes, 1967–2000, later volumes by T.-L. Ho.

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.

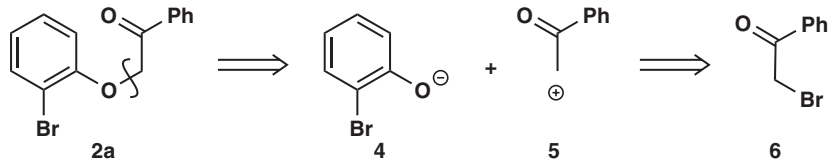
1 The Disconnection Approach

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.



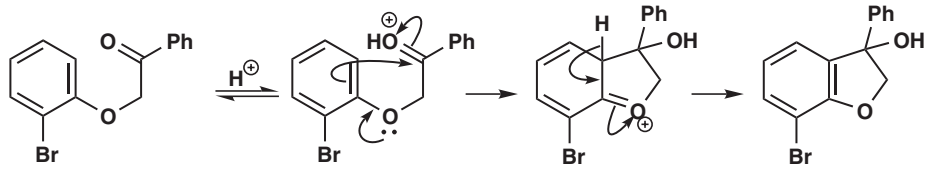
1 2 3

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

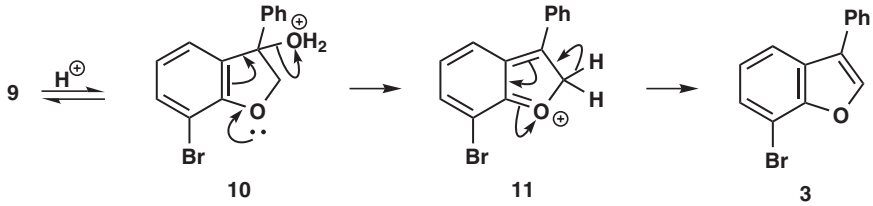
Problem 1.2: Draw the mechanism of the cyclisation of **2** to **3**. This is an unusual reaction and it helps to know what is going on before we analyse the synthesis. **Answer 1.2:** The first step is an acid-catalysed cyclisation of the aromatic ring onto the protonated ketone **7**. Loss of a proton **8** completes the electrophilic aromatic substitution giving the alcohol **9**.



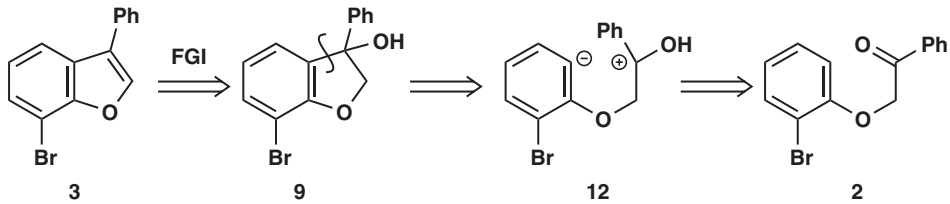
2 7 8 9

Workbook for Organic Synthesis: The Disconnection Approach, Second Edition Stuart Warren and Paul Wyatt

Now protonation of the alcohol leads to loss of water **10** to give a stabilised cation that loses a proton **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.

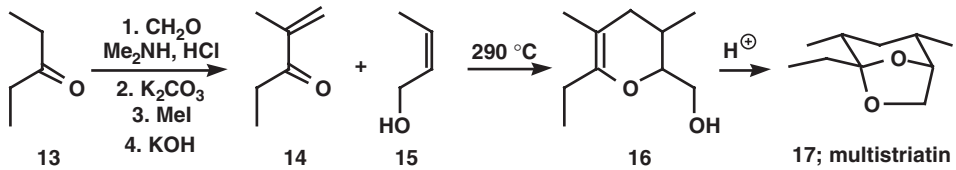


Answer 1.3: We hope you might have drawn the intermediate alcohol **9**. Changing **3** into **9** is not a disconnection but a Functional Group Interconversion (FGI) – changing one functional group into another. Now we can draw the disconnection revealing the synthons **12** represented in real life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

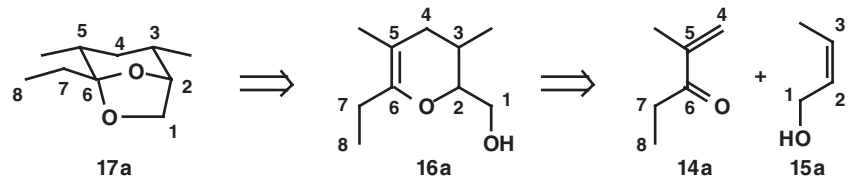


A Synthesis of Multistriatin

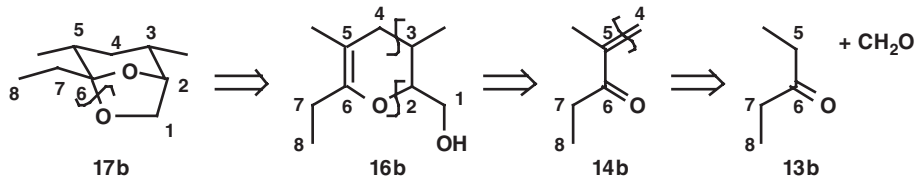
In the textbook we gave one synthesis of multistriatin **17** and here is a shorter but inferior synthesis as the yields are lower and there is little control over stereochemistry.[1] **Problem 1.4:** Which atoms in the final product **17** come from which starting material and which bonds are made in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



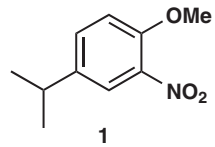
References

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

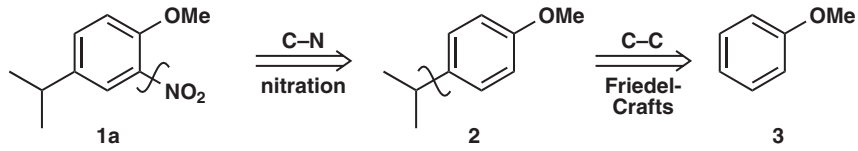
This chapter concerns the synthesis of aromatic compounds by electrophilic and nucleophilic aromatic substitution. All the disconnections will therefore be of bonds joining the aromatic rings to the sidechains. We hope you will be thinking mechanistically, particularly when choosing which compounds can 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.



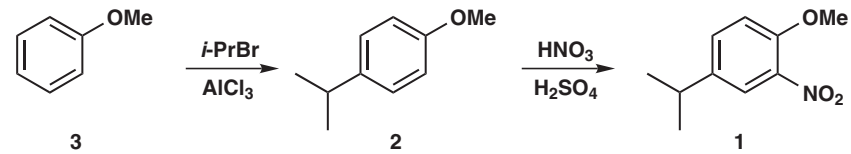
1

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**.



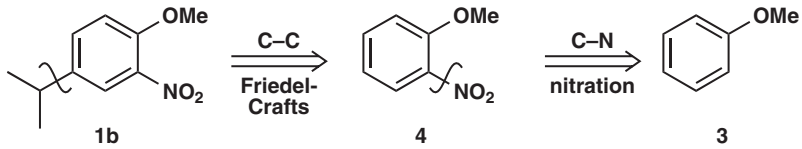
1a **2** **3**

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:

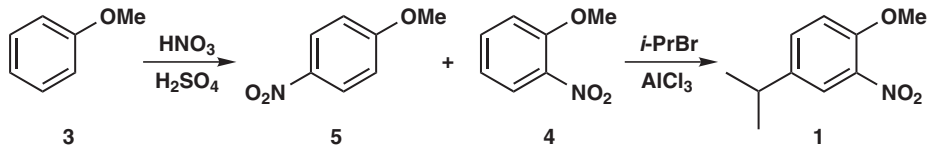


3 **2** **1**

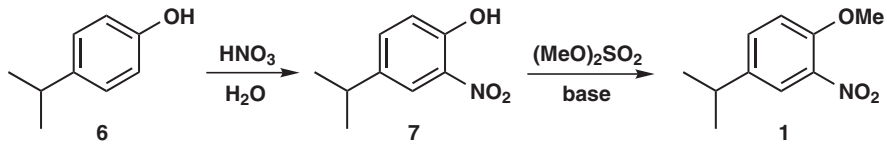
Did you consider the alternative strategy? That is, disconnect the isopropyl group first **1b** to give a new intermediate **4** and disconnect the nitro group second. The starting material, anisole **3**, is the same in both routes.



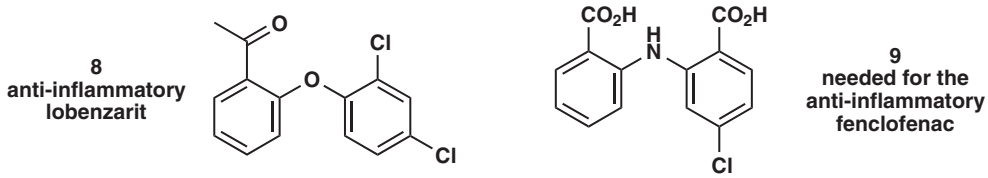
Again we should check the orientation. Nitration of anisole will give a mixture of *ortho* **4** and *para* **5** products so much depends on the ratio and whether they can easily be separated. The Friedel-Crafts reaction will go *ortho* or *para* to the OMe group and *meta* to the nitro group so that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



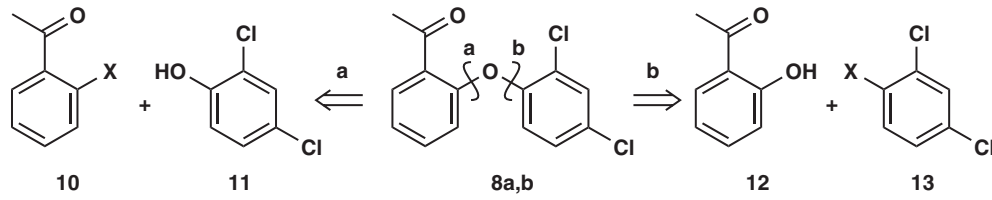
So what did the chemists prefer? One published synthesis[2] used HF as a catalyst to alkylate *ortho*-nitro-anisole **4** with isopropanol. The yield was a respectable 84%. This made sense as they had a supply of **4**. If anisole is nitrated with the usual HNO_3/H_2SO_4, a 31:67 ratio of *ortho:para* 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.

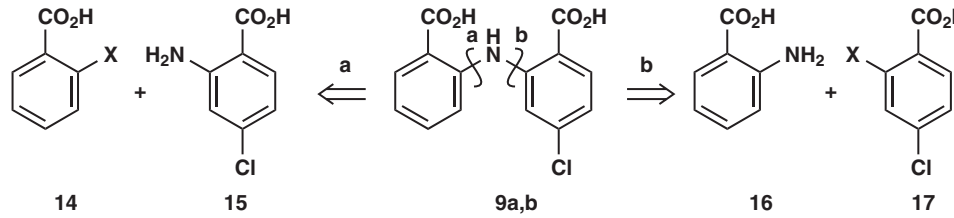


Answer 2.2: The two disconnections **8a** and **8b** illustrate the types of molecules needed for the first problem. In each case X is a leaving group such as a halogen and the phenols **11** and **12** would be used as their anions.



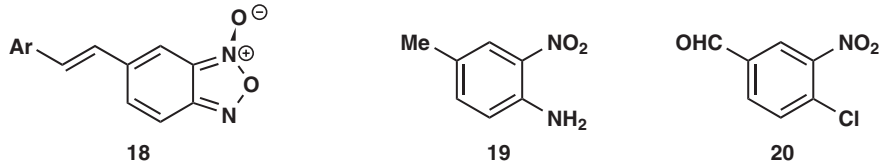
To be successful, nucleophilic aromatic substitution needs an electron-withdrawing group *ortho* or *para* to the leaving group. A chloride, as in **13** is not adequate but the ketone in **10** is perfectly placed. The reported synthesis[3] uses **10**; X = Cl with **11** and Cu/NaOH as catalyst. We 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_2H group in the right position (*ortho* to the leaving group X). Compound **17** has another leaving group (Cl) that is *para* to the CO_2H 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.

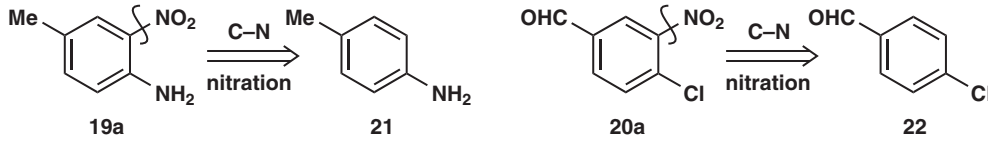


The reported synthesis[4] uses **16** and **17**; X = Cl relying on the CO_2H group to provide regioselectivity at the more electrophilic *ortho* position. It is possible[5] that the fluoro-compound **17**; X = F would be a better way.

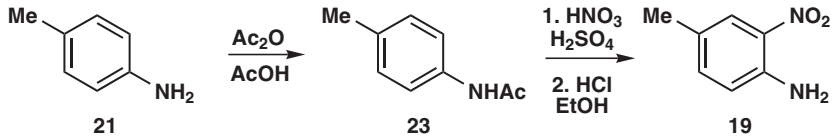
Problem 2.3: Chagas disease causes some 50,000 deaths annually in South America. Drugs based on the structure **18** are urgently needed. You are not expected to understand the chemistry used to make the strange heterocyclic ring but you might appreciate that it could come from an *ortho*-nitro aniline such as **19** or an activated halide such as **20**. Suggest syntheses for these starting materials.



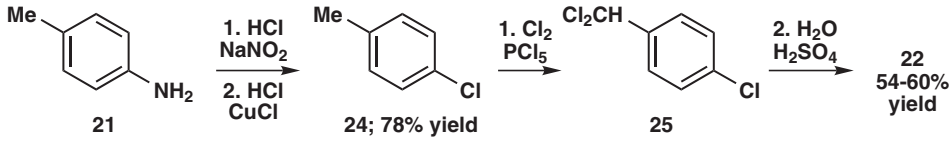
Answer 2.3: In both cases, the initial disconnection of the nitro group **19a** and **20a** is very appealing. The starting materials **21** and **22** should be easily made and nitration will go *ortho* to NH_2 rather than Me in **21** and *ortho* to Cl and *meta* to the deactivating aldehyde in **22**.



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**.

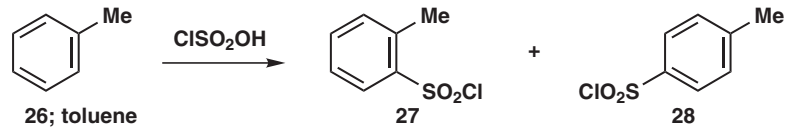


The aldehyde **22** is more difficult as we should need to chlorinate benzaldehyde in the *para* position to get **22**. One solution is to oxidise *para* chloro-toluene **24**, available[7] from **21** via the diazonium salt with, for example, chlorine to give **25** that can be hydrolysed[8] to the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

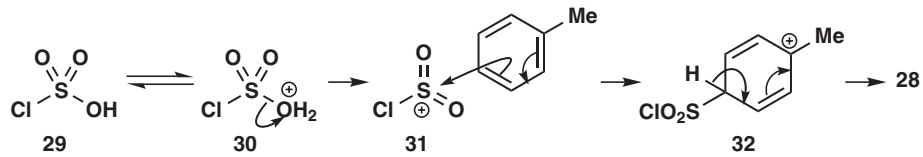


A Problem from the Textbook

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.

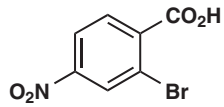
4. *Drug Synthesis*, vol 3, p. 38.
5. S. M. Kelly and H. Schad, *Helv. Chim. Acta*, 1985, **68**, 1444.
6. W. Porcal, A. Merlino, M. Boiani, A. Gerpe, M. González and H. Cercetto, *Org. Process. Res. Dev.*, 2008, **12**, 156.
7. *Vogel*, p. 931.
8. W. L. McEwen, *Org. Synth. Coll.*, 1943, **2**, 133.

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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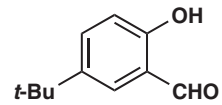
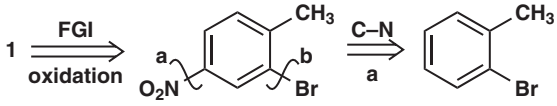
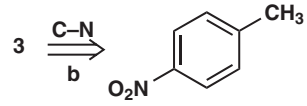


2

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.

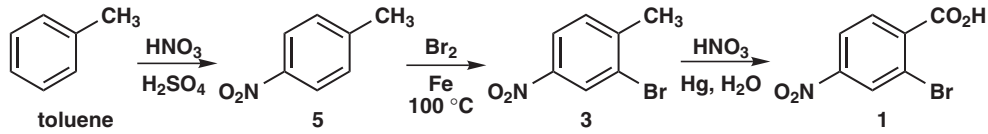


3 **4**

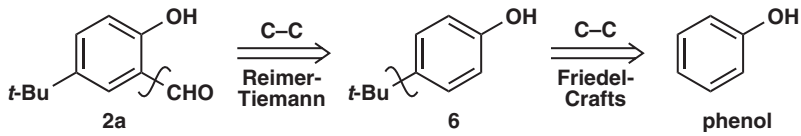


5

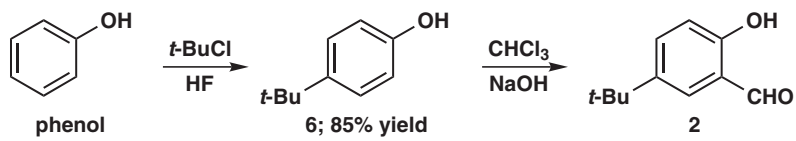
So the synthesis was nitration of toluene (actually **5** is available), separation of **5** from the *ortho* isomer, bromination of **5**, and oxidation of **3** to give the target molecule.[1]



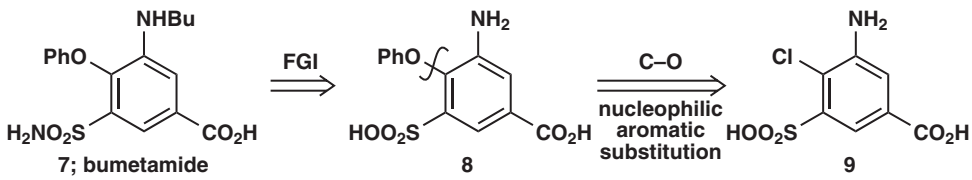
No doubt the CHO group could also be formed by oxidation of a CH_3 group but it can be inserted next to a phenolic OH by the Reimer-Tiemann reaction.[3] Now we can disconnect the *t*-Bu group with Friedel-Crafts alkylation in mind.



The large *t*-Bu group much prefers the *para* position and the Reimer-Tiemann reaction using chloroform as a source of dichlorocarbene (Textbook chapter 30) goes *ortho* to the conjugating OH group.[2,4]

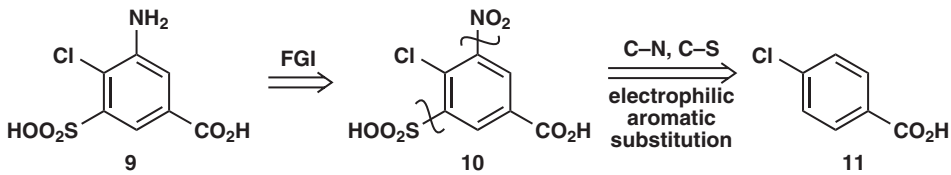


Example and Problem 3.2: Bumetamide **7** is a diuretic from Leo Pharmaceutical Products in Denmark. The synthesis[5] was planned by a number of FGIs to give **8** and then a C–O disconnection to give **9** as a suitable starting material. **Problem 3.2:** Suggest why these FGIs were chosen as a preliminary to disconnection.

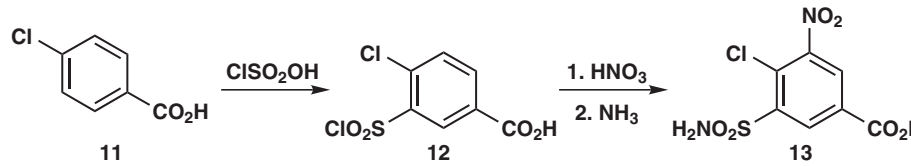


Answer 3.2: The PhO group must be added by nucleophilic aromatic substitution so electron-withdrawing groups are essential. We have two (SO_2X and CO_2H) in the right positions, *ortho* and *para* to Cl in **9**, and could have a third if NH_2 is replaced by NO_2. **Problem 3.3:** Suggest a synthesis of **9**.

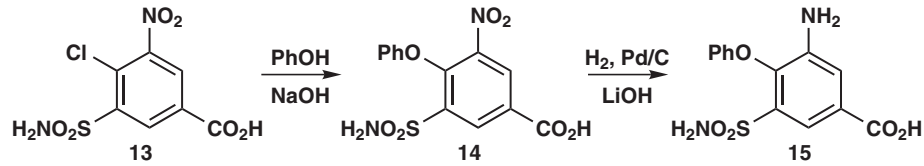
Answer 3.3: Two of the substituents in **9** (SO_2OH and Cl) can be added by electrophilic substitution and we have seen some ways to add the CO_2H group. The most obvious thing to do is to replace NH_2 by NO_2 **10** and disconnect both NO_2 and SO_2OH giving *p*-chlorobenzoic acid **11** as starting material. This compound is available but could be made by chlorination of toluene and oxidation of the methyl group.



Now we need to decide in which order to add the two substituents. The orientation will be decided by the Cl group as it is *ortho, para*-directing. In the published synthesis[5] chlorosulfonation is used followed by nitration and the sulfonamide **13** is formed before the nitro group is reduced to the amine.



With three groups to help nucleophilic substitution, phenoxide was added and catalytic hydrogenation of **14** to the amine **15** was followed by reductive amination (chapter 8) with PrCHO to give bumetamide **7**.



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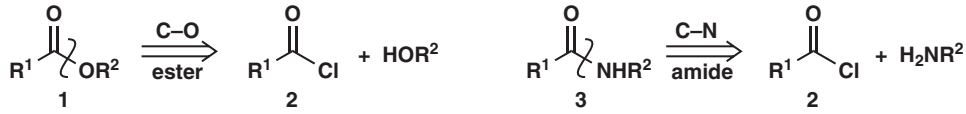
1. K. Friedrich and H. Öster, *Chem. Ber*., 1961, **94**, 834.
2. R. Breslow, M. F. Czarniecki, J. Emert and H. Hamaguchi, *J. Am. Chem. Soc*., 1980, **102**, 762.
3. *Vogel*, pp. 992 and 997.
4. J. H. Simons, S. Archer and H. J. Passino, *J. Am. Chem. Soc*., 1938, **60**, 2956.
5. P. W. Feit, H. Bruun and C. K. Nielsen, *J. Med. Chem*., 1970, **13**, 1071; P. W. Feit, *Ibid*., 1971, **14**, 432.

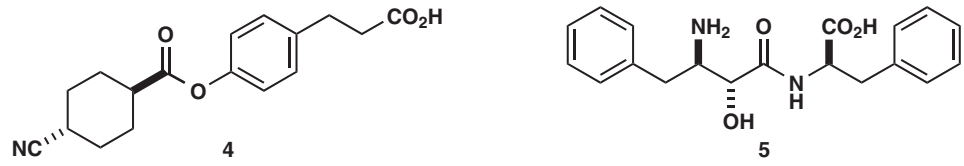
4 One-Group C–X Disconnections

If you have also read chapter 6, you will realise that acid derivatives such as esters **1** or amides **3** are usually made by acylation so that the C–O or C–N bond that is disconnected is the one between the heteroatom and the carbonyl group. In this way we are really using two-group disconnections for these compounds. The synthesis might combine an alcohol or an amine with an acid chloride **2**.



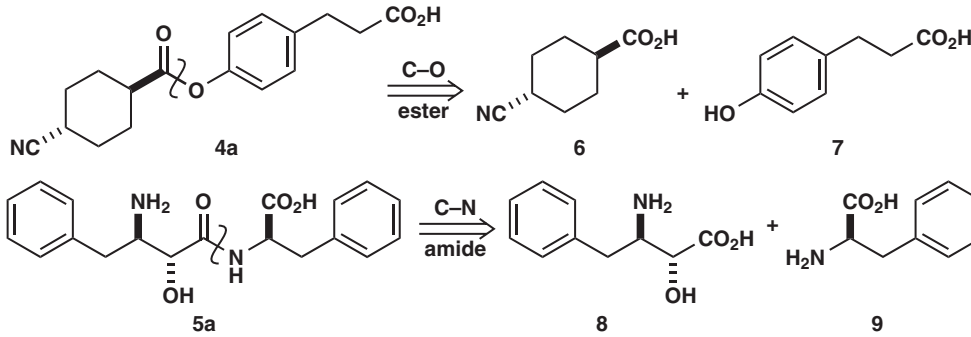
1 2 3 2

Problem 4.1: Suggest which C–X bond would be your first choice for disconnection in these two compounds, explaining your reasons. Draw your proposed starting materials.



4 5

Answer 4.1: Though there are many C–X bonds in both molecules, the first disconnection should be of the ester **4a** and of the amide **5a** both because we know of good ways to make these functional groups and because the disconnections are in the middle of the molecules. You might have drawn **6** and **8** as acid chlorides or as acids, as we have done, deciding to work out the reagents later. **Problem 4.2:** What difficulties do you foresee in carrying out the reaction?

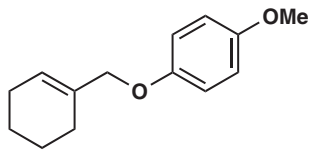


4a 6 7

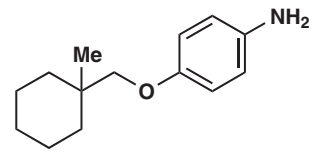
5a 8 9

Answer 4.2: Both **6** and **7** have acid groups, so we shall have to activate the CO_2H group in **6** and perhaps protect the CO_2H group in **7**. The situation for **8** + **9** is worse: not only does each compound have a CO_2H group, but **8** also has two nucleophilic groups (OH and NH_2). Again protection and activation will be needed. This second case is not as bad as it seems as **5** is a dipeptide and standard peptide coupling procedures can be used.[1] Stereochemistry is not a problem as the bond-forming steps do not affect any chiral centre.

We shall concentrate mainly on ethers and sulfides where true one-group C–X disconnections will be needed though mechanistic arguments will still be necessary. **Problem 4.3:** Suggest a synthesis for the ethers **10** and **11**.

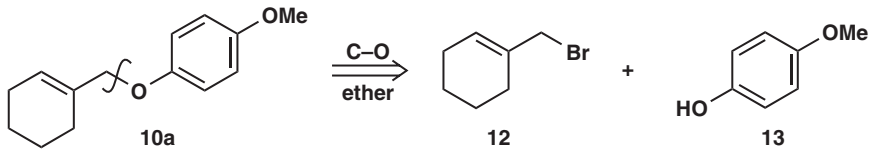


10



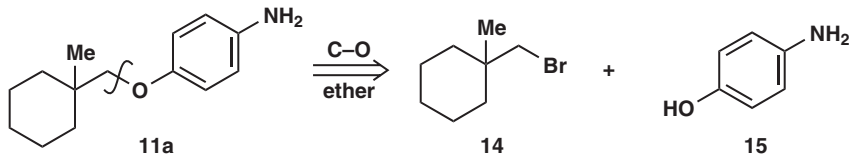
11

Answer 4.3: The first **10** is easy: we much prefer the disconnection on the alkyl side as the aromatic ring is not activated for nucleophilic substitution while the halide **12** is allylic and therefore electrophilic.



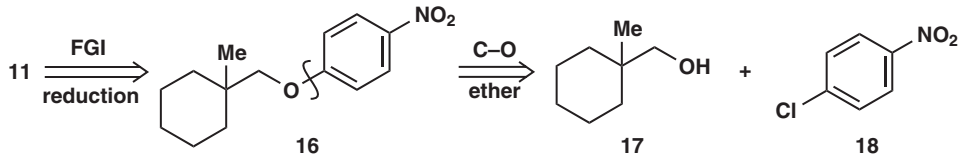
10a **12** **13**

The second **11** requires more thought: The same disconnection **11a** gives a primary halide **14** but it has a quaternary centre joined to it and there will be considerable steric hindrance to an S_N2 reaction. In addition, the amine in **15** is more nucleophilic than the phenolic OH group. Is there an alternative?



11a **14** **15**

The amine **11** could be made by reduction of a nitro group and now the alternative disconnection **16** corresponding to nucleophilic aromatic substitution becomes possible.[2] There is no longer any ambiguity as there is only one nucleophilic group. In addition, the halide **14** would have to be made from the alcohol **17**. Compounds derived from **11** are used in the treatment of diabetes.



16 **17** **18**