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Supplementary Information A

Two-Step Synthesis of Paracetamol (Acetaminophen), a Practical Illustration of Carbonyl Reactivity for Year-One Biosciences Students

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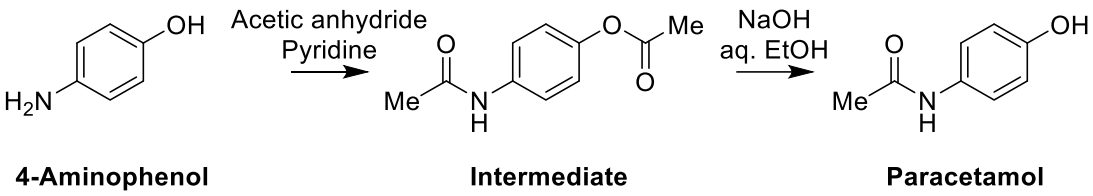
Synthesis of Paracetamol – Week One – Preparation of the Intermediate



4-Aminophenol **Intermediate** **Paracetamol**

In this practical class, the analgesic drug paracetamol will be synthesised in two steps from 4-aminophenol. In Week One, an intermediate will be prepared and identified. In Week Two, this intermediate will be converted into paracetamol.

Objective

The objective of the procedure is to synthesise paracetamol in two steps.

Health and safety information

Personal protection: Laboratory coats, safety spectacles / goggles and protective gloves should be worn at all times. Laboratory coats must be fastened. Long hair must be tied back.

The hazards of the individual chemicals are given at the end of this protocol. All spillages and breakages of glassware must be reported to the class lecturer. Do not attempt to clear them up without reporting. All procedures must be carried out in the fume cupboard.

Chemistry

4-Aminophenol contains two nucleophilic groups, the amine and the hydroxy group. These react with the electrophilic acetic anhydride to give the intermediate, which contains two acetyl groups.

To make paracetamol, the ester has to be hydrolysed with sodium hydroxide, without hydrolysing the amide.

Protocol for Week One

1. Take a glass boiling tube containing 4-aminophenol (200 mg, 1.8 mmol) and ethyl acetate (2.0 mL). The tube also contains a magnetic stirrer bar.
2. Place the boiling tube in the rack on the stirrer plate and stir the mixture slowly.
3. Add pyridine (4 drops) using a glass Pasteur pipette.
4. Add acetic anhydride (1.0 mL) using a glass graduated pipette.
5. Allow the mixture to stir for 30 minutes. After this time, monitor the progress of the reaction by TLC. The reaction is complete when the spot corresponding to the starting material 4-aminophenol has disappeared.

TLC

a. Prepare the TLC mobile phase by mixing ethyl acetate (10 mL) and petroleum ether (5.0 mL) in a 250 mL glass beaker. Cover the beaker with a clock glass.

b. Cut a piece of silica TLC stationary phase plate ("TLC plate") with scissors to a size 10 cm $\times$ 4 cm. Using a pencil, mark the headings (SM, Mix, RM) near the top edge of the plate as shown.

c. A glass vial is provided, containing 4-aminophenol (1.0 mg) in ethyl acetate (0.5 mL) as a standard. Dip the end of a fine glass capillary tube into this solution and spot the TLC plate under "SM" 1.0 cm from the bottom. Repeat this to spot the plate under "Mix" 1.0 cm from the bottom.

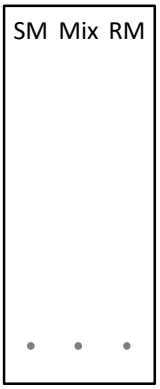
d. Dip the end of a fine glass capillary tube into the reaction mixture and spot the TLC plate under "RM" 1.0 cm from the bottom. Repeat this to spot the plate under "Mix" 1.0 cm from the bottom; this spot should have the same Rf as the 4-aminophenol spot. Wave the TLC plate in the air a few times to evaporate the solvents.

e. Place the prepared TLC plate vertically in the beaker and cover with the clock glass. Watch the mobile phase rise up the plate by capillary action.

f. When the top of the mobile phase ("solvent front") reaches approx. 1 cm from the top of the TLC plate, remove the plate from the beaker and mark the position of the solvent front with a pencil. Allow the mobile phase to evaporate from the plate.

g. Examine the TLC plate under short-wavelength UV light. Draw pencil lines around any dark purple spots.

h. There is a specific chemical test which will identify any spots which contain a phenolic OH. After the plate has been examined under UV light, using forceps, dip the plate into the solution of iron(III) chloride in methanol provided. Take the plate out of the solution and warm it gently with the hot air gun. Spots corresponding to phenols will turn red-brown.



6. When the reaction is complete (shown by the absence of a spot in the reaction mixture lane corresponding to 4-aminophenol), pour the reaction mixture into a separating funnel. MAKE SURE THAT THE TAP IS CLOSED BEFORE THE MIXTURE IS ADDED. Wash the boiling tube with ethyl acetate (30 mL) and transfer the washings to the separating funnel.

7. Add aq. sodium hydrogen carbonate (5%, 30 mL) to the separating funnel and shake it carefully, releasing gas pressure as necessary. Run the aqueous layer (lower layer) into a conical flask and then transfer it to the waste bottle.

8. Add aq. hydrochloric acid (2 M, 30 mL) to the ethyl acetate in the separating funnel and shake it carefully, releasing gas pressure as necessary. Run the aqueous layer (lower layer) into a conical flask and then transfer it to the waste bottle.

9. Add aq. copper(II) sulfate (10%, 50 mL) to the ethyl acetate in the separating funnel and shake it carefully. Note any changes in colour of the layers. Run the aqueous layer (lower layer) into a conical flask and then transfer it to the waste bottle.

10. Add saturated brine (30 mL) to the ethyl acetate in the separating funnel and shake it vigorously. Run the aqueous layer (lower layer) into a conical flask and then transfer it to the waste bottle.
11. Tip the ethyl acetate layer into a 100 mL conical flask and add anhydrous magnesium sulfate a spatula-full at a time. Swirl the flask gently between each addition. When some white solid is seen moving freely in the flask, stop adding the $MgSO_4$.
12. Filter off the $MgSO_4$ before the solvent is evaporated. Fold a filter paper into the fluted shape and place into a glass funnel (this will be demonstrated). Place the funnel into the top of a weighed round-bottom flask and pour the solution carefully into the filter paper. When all of the solution has passed through the filter paper, pour a few mL of ethyl acetate onto the collected $MgSO_4$ to wash any residual Intermediate through. Run another TLC on this solution to check that contaminants have been removed.
13. Rotary evaporate the solvent and re-weigh the flask. Identify the flask with a marker pen and place it on a cork ring to keep it for next week.

Hazard statements

4-Aminophenol: H302 + H332 Harmful if swallowed or if inhaled. H341 Suspected of causing genetic defects. H410 Very toxic to aquatic life with long-lasting effects. P273 Avoid release to the environment. P281 Use personal protective equipment as required. P501 Dispose of reagent / container to an approved waste disposal plant.

Acetic anhydride: H226 Flammable liquid and vapour. H302 Harmful if swallowed. H314 Causes severe skin burns and eye damage. H330 Fatal if inhaled. P210 Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P260 Do not breathe vapours / spray. P280 Wear protective gloves / protective clothing / eye protection. P304 + P340 + P310 IF INHALED: Remove person to fresh air and keep comfortable for breathing. Immediately call a POISON CENTRE / doctor. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P370 + P378 In case of fire: Use dry powder to extinguish.

Pyridine: H225 Highly flammable liquid and vapour. H302 + H312 + H332 Harmful if swallowed, in contact with skin or if inhaled. H315 Causes skin irritation. H319 Causes serious eye irritation. P210 Keep away from heat / sparks / open flames / hot surfaces. No smoking. P280 Wear protective gloves/ protective clothing. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

Ethyl acetate: H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness or dizziness. EUH066: Repeated exposure may cause skin dryness or cracking. P210: Keep away from heat / sparks / open flames / hot surfaces. No smoking. P240: Earth container and receiving equipment. P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P403 + P233: Store in a well-ventilated place. Keep container tightly closed.

Hydrochloric acid: H290 May be corrosive to metals. H314 Causes severe skin burns and eye damage. H335 May cause respiratory irritation. P261 Avoid breathing vapours. P280 Wear protective gloves / protective clothing / eye protection / face protection. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310 Immediately call a POISON CENTRE or doctor / physician.

Petroleum ether: H224 Extremely flammable liquid and vapour. H304 May be fatal if swallowed and enters airways. H315 Causes skin irritation. H336 May cause drowsiness or dizziness. H411 Toxic to aquatic life with long lasting effects. P210 Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P301 + P310 IF SWALLOWED: Immediately call a POISON CENTER / doctor. P331 Do NOT induce vomiting. P370 + P378 In case of fire: Use dry powder to extinguish. P403 + P235 Store in a well-ventilated place. Keep cool.

Copper(II) sulfate: H410 Very toxic to aquatic life with long-lasting effects. P273 Avoid release to the environment. P281 Use personal protective equipment as required. P501 Dispose of reagent / container to an approved waste disposal plant.

Synthesis of Paracetamol – Week Two – Preparation of Paracetamol

In this practical class, you will synthesise the analgesic drug paracetamol in two steps from 4-aminophenol. In Week One, you prepared an intermediate and identified it. In Week Two, you will take this intermediate and convert it into paracetamol.

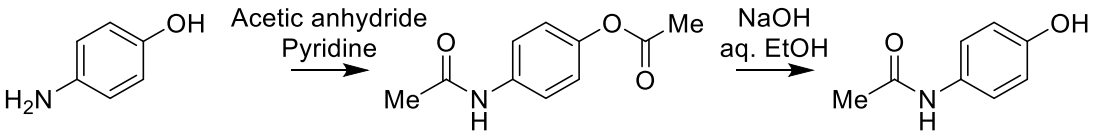
Health and safety information

Personal protection: Laboratory coats, safety spectacles / goggles and protective gloves should be worn at all times. Laboratory coats must be fastened. Long hair must be tied back.

The hazards of the individual chemicals are given at the end of this protocol. All spillages and breakages of glassware must be reported to the class lecturer. Do not attempt to clear them up without reporting. All procedures must be carried out in the fume cupboard.

Chemistry

4-Aminophenol contains two nucleophilic groups, the amine and the hydroxy group. These



4-Aminophenol **Intermediate** **Paracetamol**

react with the electrophilic acetic anhydride to give the intermediate, which contains two acetyl groups. Using curly arrows, draw the chemical mechanisms of the reactions of the two nucleophiles with the acetic anhydride. Which nucleophile would you expect to react first?

To make paracetamol, the ester has to be hydrolysed with sodium hydroxide, without hydrolysing the amide. *Why is the amide less reactive towards the hydroxide nucleophile than the ester?*

Protocol for Week Two

1. Before the next step, take a few crystals of your Intermediate and place them in a small glass vial. Add ethyl acetate (0.5 mL). This is your standard for SM for TLC this reaction step.
2. Add ethanol (4.0 mL) to your Intermediate in the round-bottom flask. Put a magnetic stirrer bar into the flask. Carefully add aqueous NaOH (2.0 M, 2.0 mL) and stir the mixture until TLC indicates the absence of the Intermediate. While the reaction is in progress, carry out IR and UV analysis of the Intermediate. Use the TLC procedure from Week One, except that the SM lane should be spotted with the solution of Intermediate and that the mobile phase is a mixture of ethyl acetate (9.0 mL) and petroleum ether (3.0 mL). Visualise the TLC plates with short-wavelength UV light.
3. *IR analysis of your Intermediate:* A sample (10 mg) of your Intermediate has been placed into a small glass vial. The demonstrator will show you how to run the samples on the infrared spectrometer.

4. *UV analysis of your Intermediate:* A sample (5.0 mg) of your Intermediate has been placed into a glass test tube. Add ethanol (5.0 mL) to make your stock solution of 1.0 mg mL^{-1}. Now add this solution (200 μL) to ethanol (2.8 mL). The demonstrator will show you how to use the UV spectrophotometers.

5. This part MUST be carried out in the fume cupboard. After the reaction is complete, add EtOAc (30 mL) to the flask and then pour the mixture into a separating funnel. Wash this solution with aq. hydrochloric acid (2.0 M, 30 mL), remove the aqueous layer and place it into a waste flask. *Why is the solution washed immediately with acid? What is the function of the hydrochloric acid? Why not wash with water first?*

6. Add saturated brine (30 mL) to the ethyl acetate in the separating funnel and shake it vigorously. Run the aqueous layer (lower layer) into a conical flask and then transfer it to the waste bottle.

7. Tip the ethyl acetate layer into a 100 mL conical flask and add anhydrous magnesium sulfate a spatula-full at a time. Swirl the flask gently between each addition. When you see some white solid moving freely in the flask, stop adding the $MgSO_4$.

8. Fold a filter paper into the fluted shape and place into a glass funnel. Place the funnel into the top of a weighed round-bottom flask and pour your solution carefully into the filter paper. When all of the solution has passed through the filter paper, pour a few mL of ethyl acetate onto the collected $MgSO_4$ to wash any residual paracetamol through.

9. Run another TLC on this solution to check that contaminants have been removed. Compare the TLC with a sample of the drug paracetamol which has been obtained from a local pharmacy. After visualising the spots with short-wavelength UV light and drawing their outlines in pencil, dip the plates in $FeCl_3$ solution as you did in Week One. *How many spots do you see? What is its / their Rf value(s)? Which spot(s) colour with $FeCl_3$? Why?*

10. The ethyl acetate solvent will be evaporated from your paracetamol solution. Weigh the flask with the paracetamol inside and calculate the yield. *What is the yield of paracetamol (in g and %)?*

Task

At the end of the Week Two practical class, you will write a scientific report on the synthesis of paracetamol. The report should include an Introduction, Results and Discussion, Conclusion, Experimental (very concise, in the style of a journal – you will be provided with an example) and References. The questions in Week One and Week Two protocols should be addressed in your report. You are provided with ^{1}H, ^{13}C NMR and mass spectra for 4-aminophenol; ^{1}H and ^{13}C NMR, mass, IR and UV spectra for the intermediate; ^{1}H and ^{13}C NMR, mass and IR spectra for paracetamol. All the spectral data need to be assigned and addressed in your report. TLC data (Rf, mobile phase) should also be included in your report.

Hazard statements

Sodium hydroxide: H290 May be corrosive to aluminium metal. H314 Causes severe skin burns and eye damage. P280 Wear protective gloves / protective clothing / eye protection. P303 + P361 + P353 IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water. P305 + P351 + P338 IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

Ethyl acetate: H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. H336: May cause drowsiness or dizziness. EUH066: Repeated exposure may cause skin dryness or cracking. P210: Keep away from heat / sparks / open flames / hot surfaces. No smoking. P240: Earth container and receiving equipment. P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P403 + P233: Store in a well-ventilated place. Keep container tightly closed.

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Ethanol: H225: Highly flammable liquid and vapour. H319: Causes serious eye irritation. P210: Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P403 + P233: Store in a well-ventilated place. Keep container tightly closed.

Petroleum ether: H224 Extremely flammable liquid and vapour. H304 May be fatal if swallowed and enters airways. H315 Causes skin irritation. H336 May cause drowsiness or dizziness. H411 Toxic to aquatic life with long lasting effects. P210 Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. P301 + P310 IF SWALLOWED: Immediately call a POISON CENTRE / doctor. P331 Do NOT induce vomiting. P370 + P378 In case of fire: Use dry powder to extinguish. P403 + P235 Store in a well-ventilated place. Keep cool.

Synthesis of Aspirin

Introduction

Most people will use aspirin sometime in their lifetime. The story of aspirin dates back over 3000 years when bark from the willow tree (*Salix*) was used for relief of pain.[1] For centuries, this bark was used as a traditional medicine; it was not until 1828 when Johann Buchner discovered the active component, salicin[1]. A closely related analogue, aspirin (also known as acetylsalicylic acid or 2-acetoxybenzoic acid), was synthesised in 1853 by Charles Frédéric Gerhardt by treating sodium salicylate with acetyl chloride.[1] Aspirin is one of the most widely used medicines in the world. Its role in preventing cardiovascular and cerebrovascular disease and as a non-steroidal anti-inflammatory drug has been revolutionary and it is on the World Health Organisation's List of Essential Medicines.[2] Aspirin is used long-term to prevent heart attacks, ischaemic strokes and blood clots in people who are at high risk of these diseases.[3,4] Aspirin works by inhibiting the cyclooxygenase enzymes, COX-1 and COX-2, in the synthesis of prostaglandins and thromboxane. More recently, aspirin has been shown to be act as a chemopreventative agent by reducing overall incidence and mortality in a number of cancers, including colorectal, gastric, prostate and breast cancer.[5,6] Daily doses between 75 and 300 mg appeared to reduce overall incidence.

There are many routes in the preparation of aspirin. 2-Hydroxybenzoic acid (also known as salicylic acid) can be converted to aspirin by reaction with acetic anhydride in an acid-catalysed reaction.[7] The esterification can also be catalysed by the base pyridine.[8] The overall aim of this study is to synthesise aspirin. The objectives are (1) to treat salicylic acid with acetic anhydride to generate aspirin and (2) to confirm the structure and purity of the product spectroscopically and chromatographically.

Experimental

2-Acetoxybenzoic acid. Acetic anhydride (4.44 mL, 4.80 g, 47 mmol) and pyridine (2.00 mL, 1.96 g, 24.8 mmol) were added to 2-hydroxybenzoic acid (1.00 g, 7.25 mmol) in EtOAc (20 mL) and the mixture was stirred for 4 h at ambient temperature. The mixture was then poured slowly into aq. H_3PO_4 (1.0 M, 30 mL) in a separating funnel. The contents of the round bottomed flask were washed with EtOAc (80 mL) and added to the separating funnel. The aspirin was extracted into the organic layer and was washed with aq. H_3PO_4 (1.0 M, 2 × 20 mL), aq. copper(II) sulfate (10%, 30 mL) and saturated brine (30 mL). The solution was dried (anhydrous $MgSO_4$). The solvent was removed using a rotary evaporator to yield an off-white solid. Recrystallisation (EtOAc) gave 2-acetoxybenzoic acid (aspirin) (1.15 g, 6.4 mmol, 88%) as white crystals: IR ν_{max} 2600 (br, acid OH), 1750 (ester C=O), 1680 (acid C=O), 1605 (Ar) cm^{-1}.^{1}H NMR ($CDCl_3$) δ 2.41 (3 H, s, CH_3), 7.10 (1 H, d, 3-H), 7.46 (1 H, t, 5-H), 7.73 (1 H, t, 4-H), 8.00 (1 H, d, 6-H); ^{13}C NMR δ 20.99 (CH_3), 122.26 (1-C), 124.01 (3-C), 126.17 (5-C), 132.51 (6-C), 134.90 (4-C), 151.28 (2-C), 169.76 (C=O), 170.20 (C=O); MS (ESI) *m/z* 181 $[M + H]^+$, 163 $[M + H – H_2O]^+$, 139 $[M + H – CH_2=C=O]^+$, 121 $[M + H – CH_3CO_2H]^+$, 43 $[COCH_3]^+$; MS (ESI) *m/z* 179 $[M - H]^-$, 137 $[M – H – CH_2=C=O]^-$.

Results and Discussion

In this study, aspirin was synthesised in a one-step reaction by treating 2-hydroxybenzoic acid with acetic anhydride under basic conditions. The reaction was monitored by TLC and the reaction was stopped following the disappearance of the starting material. The aspirin was extracted into the organic layer and washed with H_3PO_4 in order to ionise the pyridine and force it into the aqueous layer. This was followed by washing with copper(II) sulfate to remove any remaining pyridine by forming a water-soluble complex. The organic layer was then washed with brine to remove water from the organic layer and dried with anhydrous $MgSO_4$. Recrystallisation from EtOAc yielded white crystals of aspirin in 88% yield. The aspirin gave a single spot on TLC at higher Rf than the starting 2-hydroxy-benzoic acid (Figure 1), showing that it was less polar and that it was pure. The 2-hydroxybenzoic acid formed a purple-brown spot when dipped in methanolic iron(III) chloride, showing the presence of a phenol, but the aspirin spot did not.

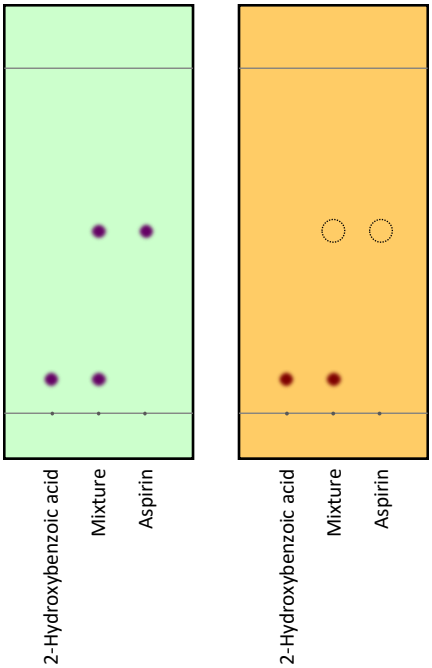


Figure 1. Photographs of TLC plates viewed under UV light (left) and after $FeCl_3$ under visible light.

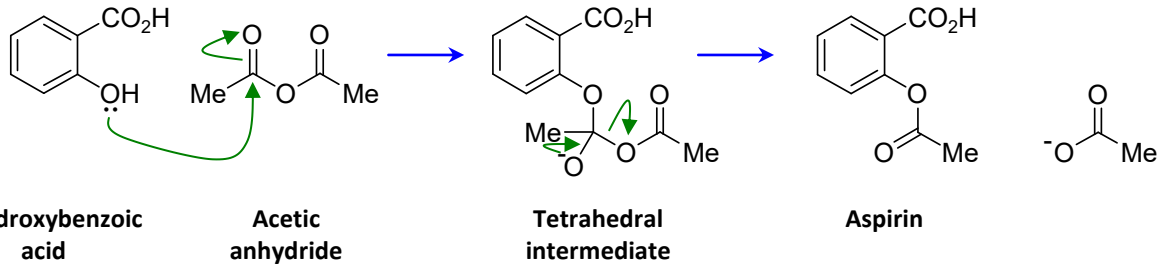
The IR spectrum for 2-hydroxybenzoic acid contained an O–H peak for the phenol at 3240 cm^{-1} and a broad O–H peak for the carboxylic acid at 2724 cm^{-1}. The IR spectrum of aspirin lacked the phenol O–H peak but the broad carboxylic acid O–H peak remained. Only one carbonyl C=O absorption was seen for the 2-hydroxybenzoic acid (1680 cm^{-1}) but two were present in the spectrum for aspirin, one at 1680 cm^{-1} (carboxylic acid) and one at 1750 cm^{-1} (ester). This ester vibrates at particularly high frequency because it has an aromatic ring on the oxygen. Aromatic peaks were seen for both compounds in the region 1600-1470 cm^{-1}. These data are consistent with conversion of the phenol into an acetate ester.

The ^{1}H NMR spectrum of salicylic acid contained peaks at δ 6.85, δ 6.95, δ 7.54 and δ 7.93, corresponding to the aromatic 3-H, 5-H, 4-H and 6-H protons, respectively. For aspirin, an additional peak was seen at δ 2.40, which corresponded to the methyl group of the acetate ester. The chemical shift for 3-H in aspirin was δ 7.10, which is downfield from its position in salicylic acid. This is because the OH in salicyclic acid is a strong mesomeric electron-donating group which moves the 3-proton signal upfield from the usual benzene position (δ 7.27). In aspirin, the acetyl carbonyl stops the oxygen from being a good mesomeric donor and the 3-H signal is closer to the usual chemical shift value of the benzene ring. In salicylic acid, the 5-H resonates at δ 6.95. because the electron-donating group of the OH pushes electron density into positions *ortho* and *para* to it (3-position and 5-position). The 5-H signal is moved downfield in aspirin to δ 7.46, also because the oxygen is no longer electron-donating.

In the ^{13}C NMR spectrum of salicyclic acid, the 3- and 5-carbons gave peaks at δ 111.12 and 116.81, respectively. The 1-C, 4-C and 6-C came slightly further downfield at δ 118.70, δ 129.99 and δ 135.51, respectively. The signal for the 2-C was detected even further

downfield at δ 161.78. This was due to the inductive electron-withdrawing effect of the OH group. The carbonyl signal was observed at δ 171.44. In aspirin, a signal was detected at δ20.99 which corresponds to the methyl of the acetyl group. This signal was absent in salicylic acid and provides evidence for the formation of the ester moiety. The 1-, 3-, 5-, 6- and 4-C's of the aromatic ring were detected at δ122.26, 124.01, 126.17, 132.51 and 134.90, respectively. The peak for the 2-C was observed further downfield at δ151.28 due to negative inductive electron-withdrawing properties of the oxygen of the acetyl directly attached the benzene ring. The acid and ester carbonyls were evident at 169.76 and 170.20, respectively. Overall, in both ^{1}H NMR and ^{13}C NMR, it can be seen that the OH is more mesomerically electron-donating than the O-acetyl group.

The mass spectroscopic data were consistent with aspirin and salicylic acid. In positive-ion mode, the ion *m/z* 181 was consistent with the molecular ion $[M + H]^+$ of aspirin. Fragment ion *m/z* 163 corresponded with loss of water from $[M + H]^+$, *m/z* 139 arose from loss of ketene ($H_2C=C=O$), from $[M + H]^+$ (characteristic of acetate esters) and *m/z* 43 corresponded with the acetyl carbocation $CH_3C^+=O$ (arising from the acetate ester). In contrast, the positive-ion spectrum for 2-hydroxybenzoic acid showed a molecular ion at *m/z* 139 $[M + H]^+$ and a fragment ion at *m/z* 121 $[M + H - H_2O]^+$. These data showed that the 2-hydroxybenzoic acid had been acetylated in the reaction. In negative-ion mode, the MS for aspirin had a molecular ion at *m/z* 179 $[M - H]^-$ and a fragment at *m/z* 137 [M – H – ketene]$^-$. The abundant negative molecular ion was easily formed by loss of H^+ from the carboxylic acid.



2-Hydroxybenzoic acid **Acetic anhydride** **Tetrahedral intermediate** **Aspirin**

Scheme 1. Mechanism of the esterification reaction between 2-hydroxybenzoic acid and acetic anhydride.

The mechanism of the reaction is shown in Scheme 1. The nucleophilic phenol oxygen attacks the highly electrophilic carbonyl of the acetic anhydride, forming a tetrahedral intermediate. Acid anhydrides are near the top of the Rank Order of electrophilic reactivity of carbonyl compounds and can react with the relatively weak phenol nucleophile. The electrons return form the oxyanion in the tetrahedral intermediate to re-form the carbonyl and the best leaving group leaves. This is the acetate anion (pK_a of acetic acid = 4.76), compared with the alternative phenoxide anion (pK_a of conjugate acid phenol = *ca*. 10). This second mechanistic step leads to the ester in aspirin. The pyridine is acting as a base in this reaction to sequester the acetic acid by-product and can also contribute as a nucleophilic catalyst.

Conclusions

Overall, the NMR, MS and IR spectral data were consistent with the synthesis of aspirin. Pure aspirin was synthesised in high yield in an esterification reaction between 2-hydroxybenzoic acid and acetic anhydride, a powerful electrophile.

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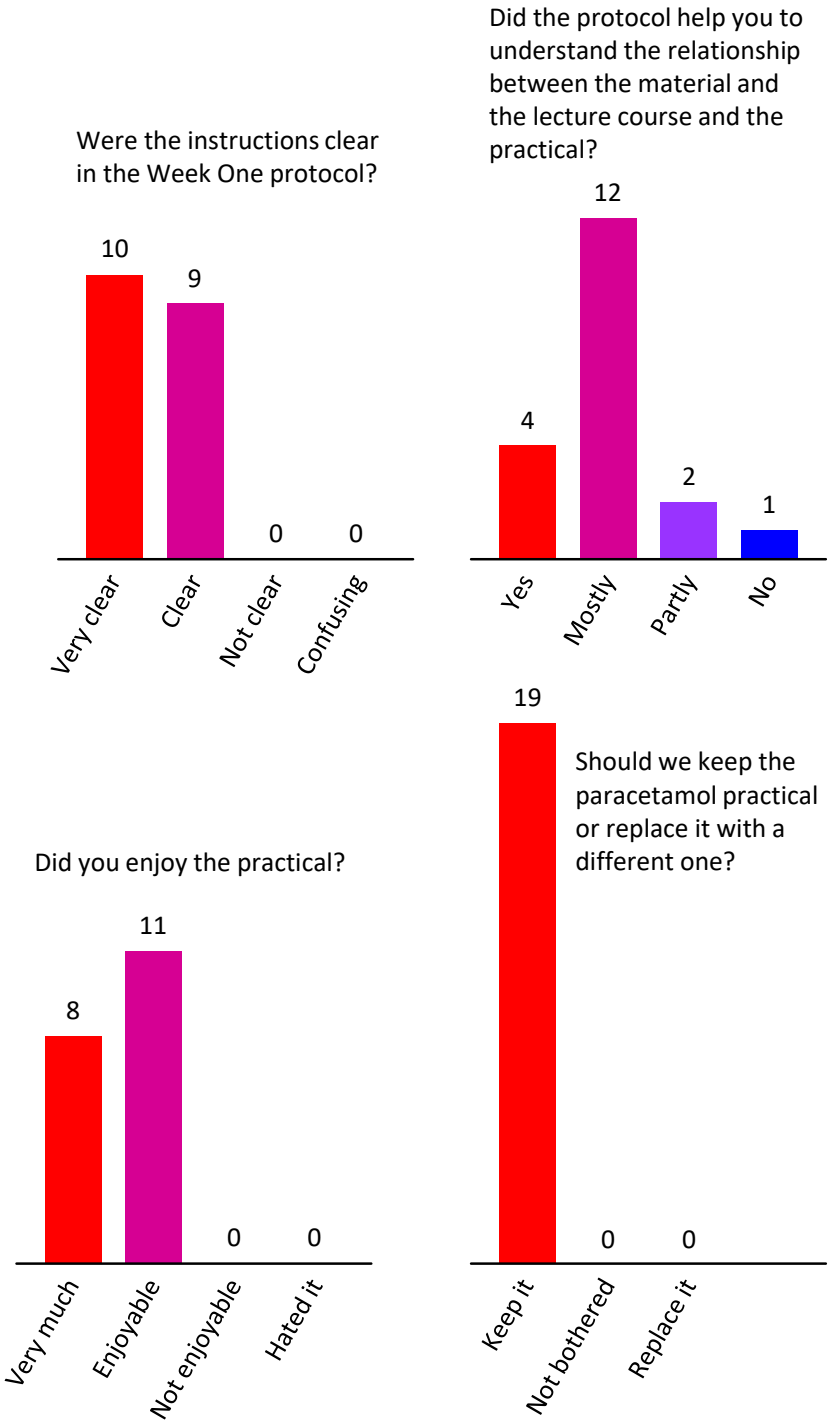
Feedback from students – March 2019

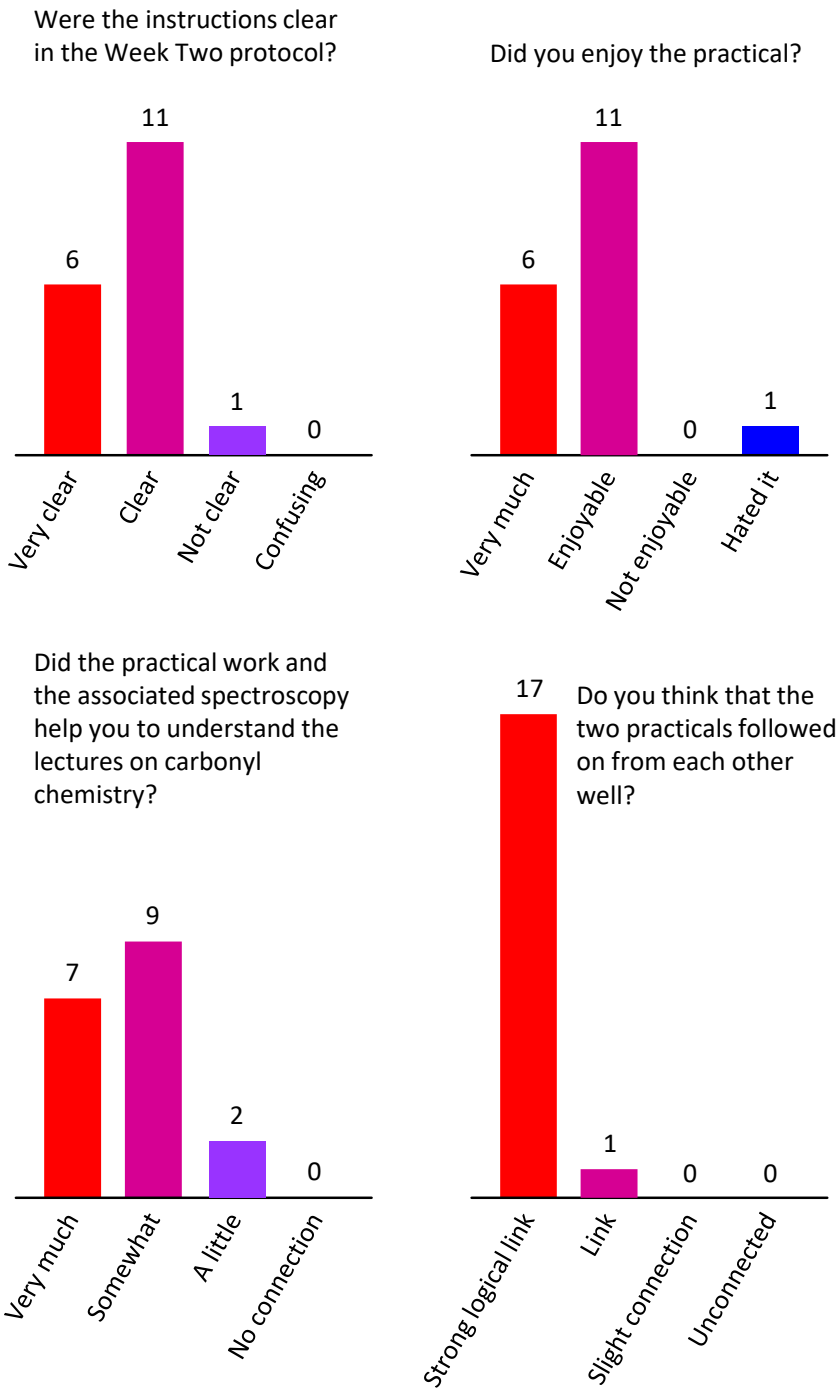


What skills do you think that you have learned from this practical?

Use of separating funnel (×6); use of rotary evaporator (×12); making glass spotting capillaries for TLC (×4); running a TLC (×12); chemical synthesis (×4)

What suggestions can you give to improve the practical?

Responses from 14 students: None; prac was good; nothing; smaller classes; specify amounts to add before washing; smaller classes if possible; amounts of solvents to add; make queues shorter; no suggestions – very good and interesting; more fume hoods & separating funnels



Please give us some constructive comments which would help us to improve the practical class for next year

One response: I have no constructive comments – I think it worked well

Feedback from students – March 2022

Did you enjoy the practical class overall?

Yes (×5)

Yes, I enjoyed it very much.

Yes, it was very informative as to the process of drug creation in industry.

Yes, it was really fun. I think what made it particularly enjoyable was the application of biochemistry to the real world. Everyone knows and has more than likely taken paracetamol in their lifetime, so to be able to understand and apply the biochemistry involved in its synthesis makes it much more personal and relatable. This makes it particularly interesting to learn about.

How useful do you think that the was to support your understanding of the lecture material?

Quite useful.

Really helpful to have an in-person practical as well as the Blackboard resources beforehand.

It was very useful. (×2)

Very useful, since it gave a better image for the context of the work and assessment.

It helped understanding the meaning behind the processes to synthesise the paracetamol.

It was useful.

Again, due to the relatability of paracetamol, I think it was really useful in allowing us to apply/support our knowledge from the lecture material. Providing real world examples really enhance interest and engage the information taught to us in lectures.

How did the lecture course help you in understanding the practical class?

The lecture course taught about reactivity of carbonyl compounds, which was helpful during the practical classes.

The additional Teams meetings with Ifat really helped solidify understanding + gave us a chance to ask questions.

The lecture helped me understand the mechanisms that occurred during the practical.

It helped a lot with my understanding.

The lectures helped me to understand the chemistry in the reactions that we used to make the paracetamol.

It gave the chemical reactions and why they occur for the processes in the synthesis of paracetamol.

The level of detail was excellent.

It provided the knowledge of specific biochemical pathways the molecules take in order to form a specific product. It also specified how certain chemicals interact with each other and how we can utilise this to our benefit of forming different chemicals.

Did the aspirin model report help you in writing the scientific report for the paracetamol practical?

Yes, it was nice to have an example of a Materials & Methods section that was more chemistry focused.

Yes, I didn't realise the structure of a scientific report + wasn't sure on the content before I saw the example report.

Yes (×2)

Yes, it gave me a good basis on how to write a well-planned-out report.

Yes, it gave me an ideal and format for how the paracetamol report was required to be written and the types of data required for the report to be to a good standard.

It was beneficial in terms of providing the format and nature of the content required to produce a comprehensive report of my own. That said, without any prior knowledge of pharmacology, I found it difficult to interpret and describe the spectral data. This led to a very poor mark for the assignment.

Yes, it did. I think it is always important to have that template in order to understand exactly what is expected when it comes to a scientific report. It is one thing being told how to do something but being shown and provided with an example really helps more.

Please give any suggestions for improving the practical class

- (×2)

Longer amount of time (Covid) / smaller classes

Clearer protocol

I can't think of any improvements

Don't have any

A module on pharmacology would perhaps have made identifying compounds and peaks etc through spectral data a little easier.

Potentially reiterate the importance of recording all results at every step – particularly the ones that assist in calculating percentage yield. Other than that, there isn't anything.

Image of experimental apparatus for Week 1