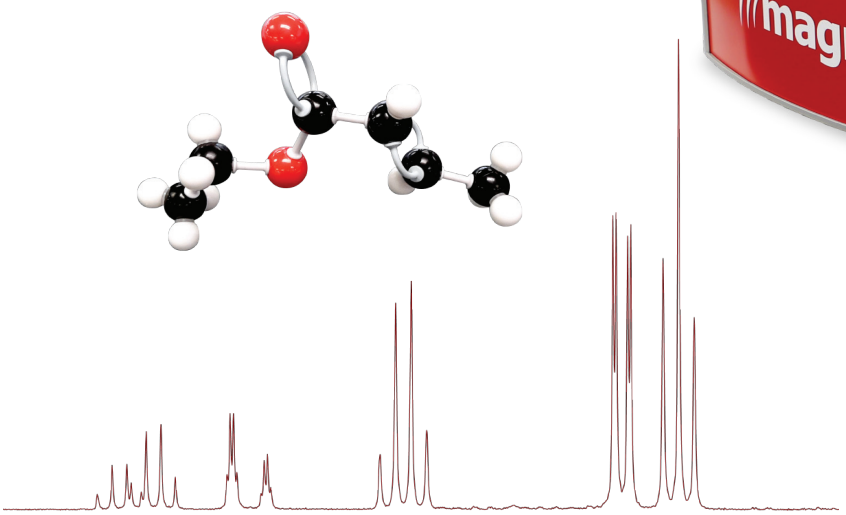
Spinsolve™

Benchtop NMR Spectrometer

Chemistry Education
Experiment Manual



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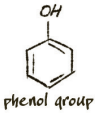
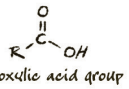
Experiment 7: Synthesis of Aspirin



phenol group

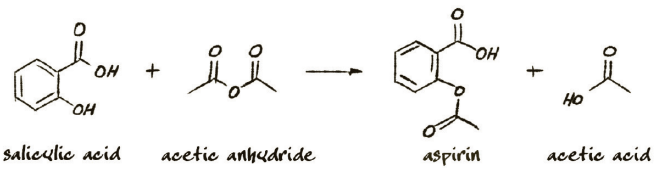


carboxylic acid group

ester

Introduction

Salicylic acid is contained in the extract of willow bark trees and was used for hundreds of years to relieve pain and treat fevers. Unfortunately, salicylic acid has two acidic functional groups – the phenol group and the carboxylic acid group. This gives salicylic acid some unpleasant side effects such as irritation to the mouth, oesophagus and stomach and can cause haemorrhaging of the stomach lining. Fortunately, in 1890, Hoffman of the Bayer Company in Germany found a way to mask the irritating phenol group with an ester to produce aspirin. Aspirin is the common name for acetylsalicylic acid, which is widely used as an effective pain killer and fever reducer. About 35,000 metric tonnes of aspirin, enough for 100 billion tablets, is produced and consumed every year. In this experiment, aspirin will be synthesised using O-acetylation of salicylic acid.



salicylic acid acetic anhydride aspirin acetic acid

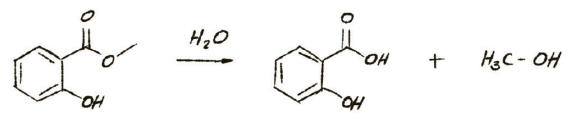
Sodium acetate is used as a basic catalyst to deprotonate the phenol to make it a better nucleophile.

To prepare aspirin, salicylic acid is reacted with acetic anhydride under basic conditions. Acetic anhydride is the activated from of acetic acid and is used because it ensures the reaction goes to completion much more quickly.

Aspirin is a pharmaceutical compound and therefore it must be confirmed that the material is the correct product and highly pure. Typically this is done using a combination of techniques such as thin layer chromatography (TLC), measuring the melting point and spectroscopy (typically IR). In this experiment, ^{1}H NMR spectroscopy is used to identify the product and determine its purity.

Methylsalicylate has a distinctive minty odour and is often incorporated into ointments to treat muscle pain because it can penetrate the skin.

One of the most prevalent and profitable ways of producing pharmaceuticals is to take an abundant, naturally occurring substance and transform it into one with therapeutic value. The salicylic used to synthesise aspirin can be produced by the hydrolysis of methylsalicylate. Methyl salicylate is the major constituent of oil of wintergreen, which makes up over 90% of the essential oil from the wintergreen plant.



methyl salicylate salicylic acid methanol

The strong base, sodium hydroxide, is used to hydrolyse the ester bond, so that it forms the carboxylic acid (salicylic acid) and the alcohol (methanol). ^{1}H NMR spectroscopy is used to determine that the correct product has been made and that it is of suitable purity to continue to the next step of the synthesis.

Overall, the aspirin produced in this experiment will be achieved using multi-step synthesis using a natural starting material.

Experimental Procedure

Reagents Used

Reagent	Molar Mass g mol^{-1}	Moles used mol	Weight g	Density g mL^{-1}	Volume mL
Methyl Salicylate	152.15	0.03	4.68	1.17	4.0
Salicylic Acid	138.12	0.014	2.0		
Acetic anhydride	102.09	0.042	4.0	1.08	4.4
Sodium Acetate	82.03	0.005	0.4		
6 M Sodium Hydroxide					40
8 M Sulphuric acid					50
Chloroform-d					3.0
Distilled water					As needed

Safety Precautions

Methyl salicylate, salicylic acid and aspirin are combustible and harmful if swallowed. Sodium hydroxide is corrosive, alkaline and causes severe burns. Care must be taken when making up the 6 M solution as dissolving sodium hydroxide pellets is exothermic and can become very hot. Sulfuric acid is corrosive, acid and causes severe burns. Care must be taken if the 8 M solution is prepared from conc sulfuric acid that the acid is added to the water (and not the water added to the acid). Acetic anhydride is corrosive, acid, can cause severe burns and is highly flammable.

Procedure for hydrolysis of oil of wintergreen

Add methyl salicylate (4 mL) and 6 M sodium hydroxide (40 mL) to a beaker and stir. Heat with occasional stirring until mixture reaches a gentle boil. Continue gentle boil for 15 minutes. During heating, wash solid from the sides of the beaker with a little distilled water. After heating, cool the reaction mixture in an ice bath until warm to touch. Leaving the beaker in the ice bath, add 8 M sulphuric acid (50 mL) to the reaction mixture with stirring. Leave mixture in the ice bath until chilled and crystals form. Isolate the precipitate using Buchner filtration and rinse the solid with a little cold distilled water. Obtain a yield and ^{1}H NMR spectrum of the crude product. Recrystallise the crude product from distilled water and dry crystals in a desiccator. Obtain a yield and ^{1}H NMR spectrum of the purified product. Also record the ^{1}H NMR spectrum of methyl salicylate.

Procedure for *O*-acetylation of salicylic acid

To a suspension of salicylic acid (2 g) in acetic anhydride (4.5 mL) in a conical flask add anhydrous sodium acetate (0.4 g) with stirring. Heat the reaction mixture for approximately 15 minutes. When the solid has dissolved, remove

from the heat and add distilled water (20 mL). Place the flask in an ice bath until the mixture has chilled and crystals have formed. Collect the precipitate by Buchner filtration and rinse the solid with cold distilled water. Obtain a yield and ^{1}H NMR spectrum of the crude product. Recrystallise the crude product from distilled water and dry crystals in a desiccator. Obtain a yield and ^{1}H NMR spectrum of the purified product. Also record the ^{1}H NMR spectra of acetic anhydride and salicylic acid (if the first step of the synthesis was not carried out).

NMR Instructions

For solid samples, transfer ~ 50 mg of sample to an NMR tube and dissolve in 0.5 mL of chloroform-d.
For liquid samples, add a few drops of the sample to 0.5 mL of chloroform-d.

You will require your own spectrum of the following samples:

1. Crude salicylic acid
2. Purified salicylic acid
3. Crude aspirin
4. Purified aspirin

The following samples may be measured or provided for you you:

1. Methyl salicylate
2. Acetic anhydride

Measure your sample using the Spinsolve by running a 1D proton ‘Standard Scan’. Phase the spectrum and apply resolution enhancement and line broadening. Label the spectrum with your name and the sample. Print the spectrum.

Tasks

1. Calculate % yield for each step of the synthesis.
2. Assign the peaks in the ^{1}H NMR spectra of all starting materials and products, and identify functional groups that are unique in each sample.
3. Identify the impurities in the crude products. Did recrystallization remove these impurities?

Experiment 7: Synthesis of Aspirin

The aim of the experiment is to introduce NMR spectroscopy into a traditional undergraduate organic chemistry experiment. Students synthesise aspirin, a familiar pain relief compound, and evaluate the purity of their product using ^{1}H NMR spectroscopy. This laboratory introduces students to aspects of practical organic chemistry including synthesis, crystallization, stoichiometry, and percent yield. This laboratory is aimed at the organic chemistry or general chemistry student that has some experience interpreting a ^{1}H NMR spectrum.

Materials List

- 250 mL beaker
- 150 mL conical flask
- Stir bar
- Hotplate
- Vacuum filter flask
- Buchner funnel
- NMR tube
- Dessicator

Chemicals List

This list includes the chemicals required for a class of 15 students.

Chemical	CAS number	Amount required
Methyl Salicylate	119-36-8	60 mL
Salicylic Acid	69-72-7	*
Acetic Anhydride	108-24-7 66	66 mL
Sodium Acetate	127-19-3	24g
6 M Sodium Hydroxide	1310-73-2	600 mL
8 M Sulphuric Acid	7664-93-9	750 mL
Chloroform-d	865-49-6	45 mL**

* Formed in the first reaction and is required in the second. Some may be required if a student doesn't have sufficient quantity or quality to carry on with the second step.

** This may be reduced to 30 mL if students are provided with the spectrum of methyl salicylate and acetic anhydride.

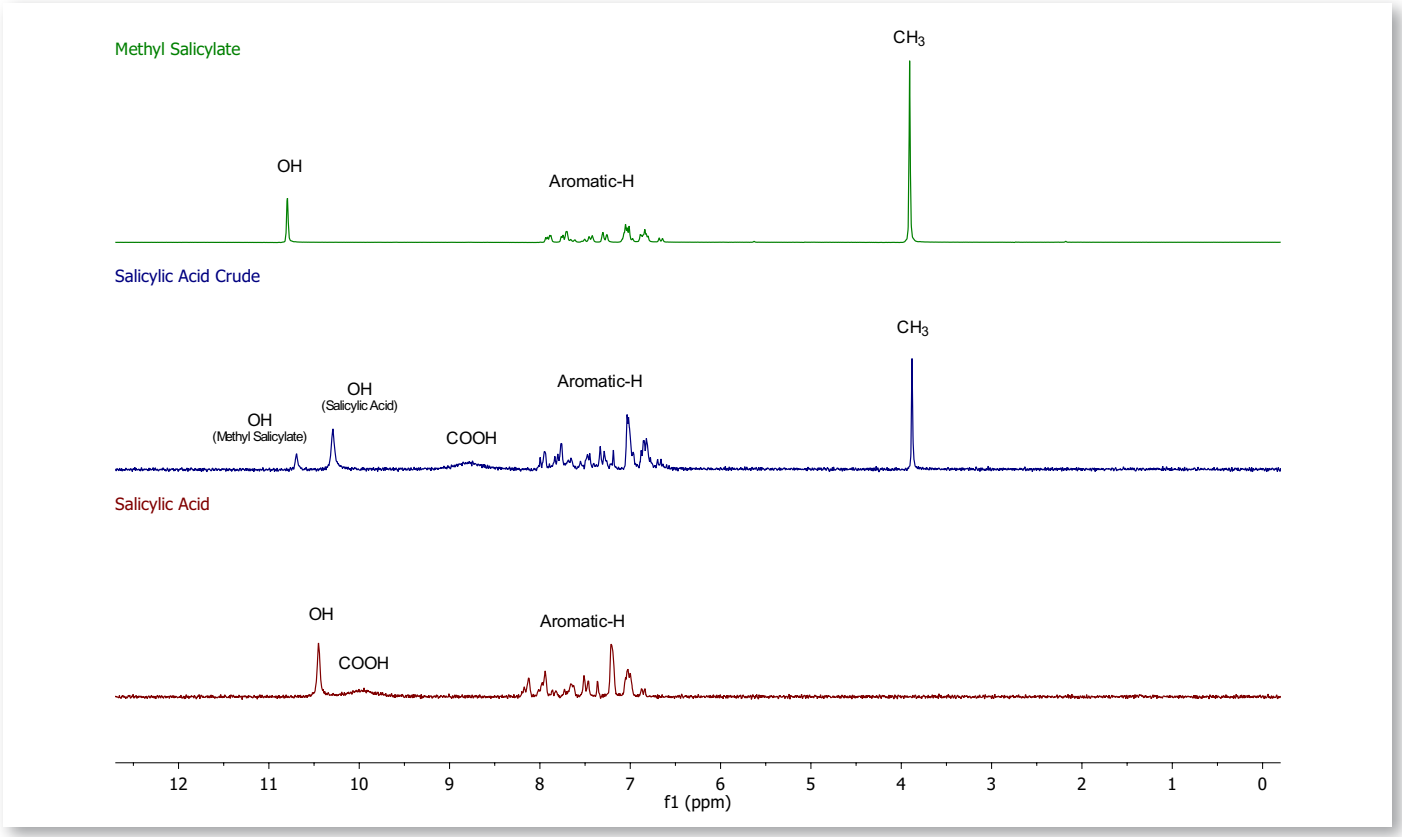
This list includes the products of the reactions and the theoretical yield.

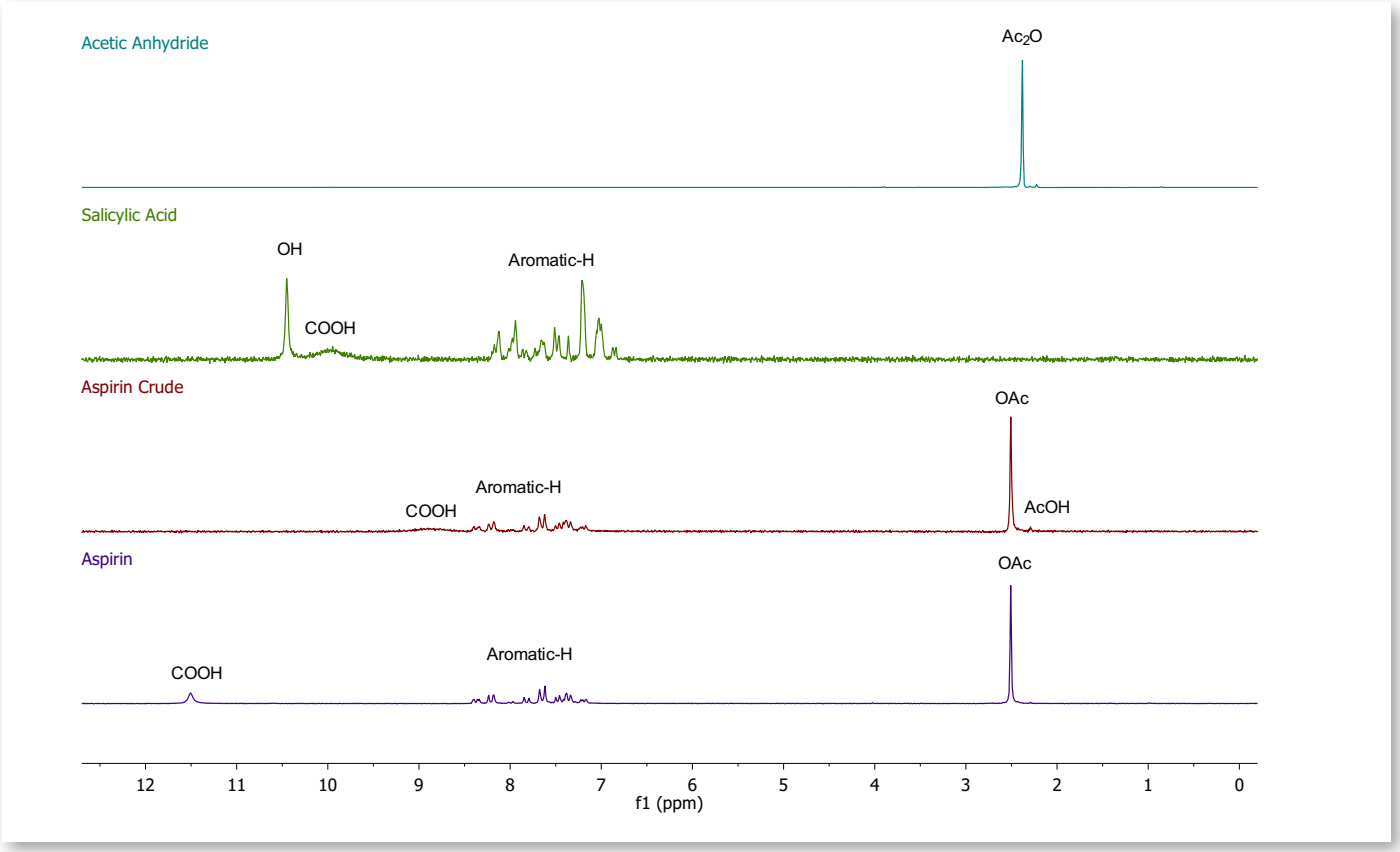
Chemical	CAS number	Theoretical yield
Salicylic Acid	69-72-7	4.14 g
Aspirin	50-78-2	2.52 g
Methanol	67-56-1	
Acetic Acid	64-19-7	

Notes

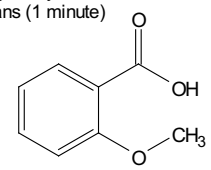
Often, aspirin does not crystallise readily. If cooling does not result in crystallisation, scratch the bottom of the conical flask with a glass rod to induce nucleation.

Example NMR Spectra

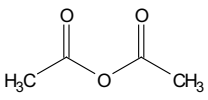




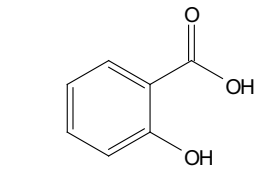
Methylsalicylate in $CDCl_3$
4 scans (1 minute)

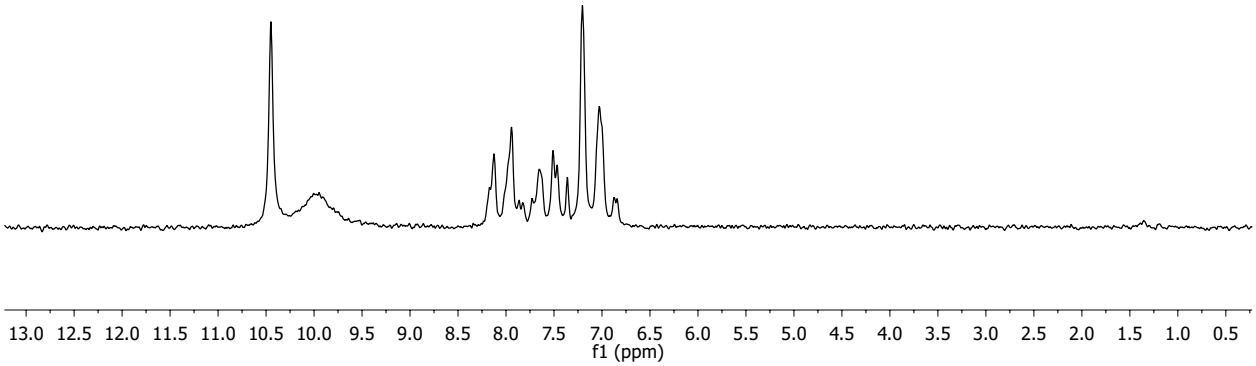


Acetic Anhydride in $CDCl_3$
4 scans (1 minute)



Salicylic Acid in $CDCl_3$
4 scans (1 minute)





Aspirin in $CDCl_3$
4 scans (1 minute)