SYNTHESIS

Conducting one or more chemical REACTIONS using STARTING MATERIALS to produce the desired substance as a PRODUCT.

What makes a synthesis EFFECTIVE?

IF IT PRODUCES THE DESIRED PRODUCT:

• from reasonable STARTING MATERIALS
• under practical CONDITIONS e.g., accessible temperature & pressure
• at a reasonable RATE (CATALYSTS may be helpful)
• with relatively high YIELD

• in a chemical environment that permits practical SEPARATION OF PRODUCT from excess starting materials and byproducts

• in an ENVIRONMENTALLY RESPONSIBLE way - GREEN CHEMISTRY

all, in a COST-EFFECTIVE manner

For substances that may be consumed by humans or animals, there is an additional concern:

SYNTHESIS must not involve TOXIC BYPRODUCTS that are NOT EASILY REMOVED

Chemical reactions rarely result in a SINGLE PRODUCT.

There are usually BYPRODUCTS and, often, only ONE reactant will be consumed, producing LEFT OVER REACTANTS.

Many reactions don’t go to “COMPLETION”, but REACTANTS and PRODUCTS establish EQUILIBRIUM

Reactants  –  Products
If so, reaction conditions can be chosen to “PUSH” EQUILIBRIUM to favor PRODUCTS

NET RESULT

Must be able to separate product from reaction mixture

Separation may be based on:

Solubility - Extraction / Crystallization
Boiling Point - Distillation
Chromatography
Etc.

How do you decide what starting materials to use?
What are possible starting materials for the synthesis of aspirin, C9H8O4?

Does the structure of the desired product suggest a starting point for the synthesis?

What materials are readily available, and inexpensive?

All that would be needed is a reaction that converts the OH group on the ring to an acetyl group OOCCH3.

A reaction which accomplishes such a conversion is:

The reaction of an alcohol or phenol with an acid anhydride.

A reasonable synthetic pathway, then, is:

ACETIC ANHYDRIDE (AA) + SALICYLIC ACID (SA) \rightarrow ACETYL SALICYLIC ACID (ASA) + ACETIC ACID

Note that ACETIC ACID is also a product of this reaction.

The reaction proceeds slowly.*

What are some properties of the potential reactants and products?

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Mp</th>
<th>Bp</th>
<th>Water @25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>-73°C</td>
<td>139°C</td>
<td>2.2 mg/mL</td>
</tr>
<tr>
<td>SA</td>
<td>157°C</td>
<td>211°C</td>
<td>3.3 mg/mL</td>
</tr>
<tr>
<td>ASA</td>
<td>135°C</td>
<td>DEC</td>
<td>2.2 mg/mL</td>
</tr>
</tbody>
</table>

Under what conditions should the reaction be conducted?

Probably NOT in water solution - AA reacts and SA is not very soluble.

Neither SA nor ASA are very soluble in water.

Could use an organic solvent but, acetic anhydride is itself a liquid at room temperature.

Also, salicylic acid is soluble in acetic anhydride.

Can use AA as the reaction medium (solvent)

But reaction is slow in pure acetic anhydride. Small amount of a strong acid makes reaction proceed more rapidly (i.e., come to equilibrium quickly)

\[ \text{e.g., } \textrm{H}_2\text{SO}_4 \]

Catalysis!

Also, by le Chatelier's principle, excess of reactant forces equilibrium towards product formation. So, it is beneficial to use an excess of acetic anhydride.

IN PRE-LAB, YOU WILL SHOW THAT:

\[ 2.0 \text{ g SALICYLIC ACID} = 2.0 \text{ g} / 138.1 \text{ g/mol SA} = 0.014 \text{ mol} = 14 \text{ mmol SA} \]

\[ 4.0 \text{ mL ACETIC ANHYDRIDE} \times 1.08 \text{ g/ml} = 4.3 \text{ g} / 102.1 \text{ g/mol AA} = 0.042 \text{ mol} = 42 \text{ mmol AA} \]

\[ \therefore \text{ SALICYLIC ACID is LIMITING REAGENT} \]

Incidentally, 5 DROPS of H2SO4:

\[ = 5 \text{ DROPS} \times 0.05 \text{ mL/DROP} \]

\[ = 0.25 \text{ mL} \times 1.84 \text{ g/mL} = 0.46 \text{ g/98 g/mol} \]

\[ = 0.0047 \text{ mol} = 4.7 \text{ mmol} \]

(Consistent with being a Catalyst)
What is in reaction vessel finally?

<table>
<thead>
<tr>
<th></th>
<th>INIT mmol</th>
<th>FINAL mmol</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRIN</td>
<td>0.0</td>
<td>14.0</td>
</tr>
<tr>
<td>ACETIC ANHYDRIDE</td>
<td>42.0</td>
<td>28.0</td>
</tr>
<tr>
<td>SALICYLIC ACID</td>
<td>14.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ACETIC ACID</td>
<td>0.0</td>
<td>14.0</td>
</tr>
<tr>
<td>SULFURIC ACID</td>
<td>4.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Want to isolate aspirin from the excess acetic anhydride, sulfuric acid and acetic acid in the reaction vessel.

ASPIRIN is only slightly soluble in water (3.3 mg/mL). We can add water to the reaction vessel to cause ASPIRIN to precipitate, which we can then recover by filtration.

Some of the water will react with the excess ACETIC ANHYDRIDE to form additional acetic acid.

Rest of the water will form a solution of all of the final products, insofar as they are soluble.

ACETIC ACID           Soluble
SULFURIC ACID         Soluble

Since ASPIRIN is slightly soluble in water (3.3 mg/mL), using a small amount of water should cause the loss of very little aspirin.

e.g. If 50 mL is used, 50 mL x 0.0033 g/mL = 0.165 g will be lost (out of a maximum of ~2.5 g produced)

**However,** SALICYLIC ACID is even less soluble (2.2 mg/mL) in water than ASPIRIN.

Therefore, any un-reacted SALICYLIC ACID will precipitate with the ASPIRIN.

Calculation of Yield

Suppose you use 2.37 g SALICYLIC ACID

2.37 g SA

\[ \frac{138 \text{ g/mol SA}}{2.37 \text{ g SA}} = 1.72 \times 10^{-2} \text{ mol SA} \]

If completely converted, you should get

Stoichiometry is 1 : 1

\[ 1.72 \times 10^{-2} \text{ mol x 180 g/mol} = 3.10 \text{ g ASA} \]

Suppose the actual weight of your (dry) product is 2.49 g

\[ \% \text{ YIELD} = 100 \times \frac{\text{actual weight}}{\text{Theoretical Yield}} \]

**Summary of Procedure**

*Record Data & Observations in Lab Notebook*

Use 125 mL ERLENMEYER FLASK

- Weigh SALICYLIC ACID on top loading balance
- Transfer ACETIC ANHYDRIDE using DEWICK PIPET* - IN HOOD

*Be sure you know how to use this pipet! If not, ask!!

- Heat in a SECURE water bath - use RING and EXTENSION CLAMP

Cook at 100°C for 20 minutes
Make sure liquid level in flask is below water in bath.

Add H₂O to reaction mixture in Specified amounts
Filter using VACUUM FILTRATION apparatus
Wash with SMALL AMOUNT of water
Save SOLID!

Need PRODUCT for one more exercise

Measure total amount of water used for washing

PRECAUTIONS

ACETIC ANHYDRIDE: CORROSIVE, FLAMMABLE & LACHRYMATOR
CONC. SULFURIC ACID: VERY CORROSIVE
FERRIC CHLORIDE: CORROSIVE
SALICYLIC ACID & ASPIRIN: IRRITANTS DON'T INHALE DUST
ETHANOL: TOXIC AND FLAMMABLE
DISPOSE OF EXCESS REAGENTS IN WASTE CONTAINERS

PERFORM QUALITATIVE TESTS

FERRIC CHLORIDE TEST:
The formation of a similar complex of Fe⁺³ with ASPIRIN is blocked by the CH₃CO group.

2. HEAT TEST - SMELL WITH CARE:

Dry a small amount (1/4 spatula-ful) of sample to determine the melting point of the product.

Perform Qualitative Tests

1. FERRIC CHLORIDE TEST:
Color is based on complex formed by the reaction of Fe⁺³ with Salicylic Acid to form

2. HEAT TEST
-- SMELL WITH CARE:

3. MELTING POINT

Vinegar
One more Test

Infrared Analysis of Product

What do we expect?

![Chemical structures](image)

Please download two supplementary pages to SUSB-028 describing the procedure for determining the IR spectrum of the product.

http://www.ic.sunysb.edu/Class/che134/susb/supl028.pdf

We will actually do the IR three weeks after the synthesis - during SUSB-012 pH Titration of your Synthesized Aspirin

SAVE PRODUCT FOR THE WEEK AFTER NEXT’S EXERCISE !!!!!!!!

Have data sheet initialed by TA and keep it until next week when you will reweigh the aspirin to get your YIELD

NEXT WEEK

Colorimetric Iron in Multivitamins
SUSB - 015 & SUPL - 005 (on Web)
Do Pre-Labs