# ACETYLATION

*Substitution of the active hydrogen of phenols, alcohols, thiols or amines (primary and secondary) by an acetyl group* **($CH_3CO$)** (Figure 1) *is known as acetylation*. Acetyl chloride, acetic anhydride or acetic acid can be used as acetylating agent.

## ▪ Acetyl chloride:

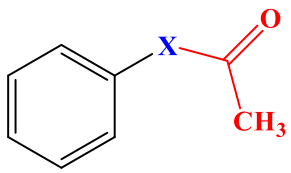
1. It reacts vigorously.
2. Liberating HCl which converts half of the amine to its hydrochloride salt rendering it incapable of participating in the reaction.
3. Has a tendency to get hydrolysed by moisture.
4. The reaction is not reversible.

## ▪ Acetic acid:

1. Its reaction with the compound is reversible and slow (requires long heating).

## ▪ Acetic anhydride: *is preferred for a laboratory synthesis*

1. Acetic anhydride is easy to handle
2. The reaction is not reversible.
3. The procedure gives a product of high purity and in good yield.



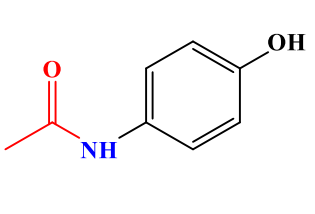

**X= NH, NR, S or O**

***Figure 1: General structure of an acetyl derivative.***

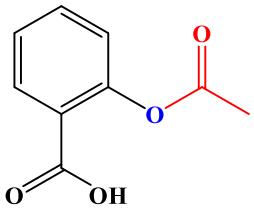
| *Organic compound* | *Acetylation product* | *Organic synthesis purpose* | *Organic Pharmaceutical chemistry purpose* |
|---|---|---|---|
| **R-OH** | **Esters** | **Protection** | **Prodrugs, soft drugs** |
| **Ar-OH** | **Esters** | **Protection** | **Prodrugs, soft drugs** |
| **R-SH** | **Thioesters** | **Protection** | **Prodrugs, soft drugs** |
| **Ar-SH** | **Thioesters** | **Protection** | **Prodrugs, soft drugs** |
| **R-NHR*** | **Amides** | **Protection (not common)** | **Drugs** |

*** R= H or R groups**

# DRUGS AS ACETYL DERIVATIVES



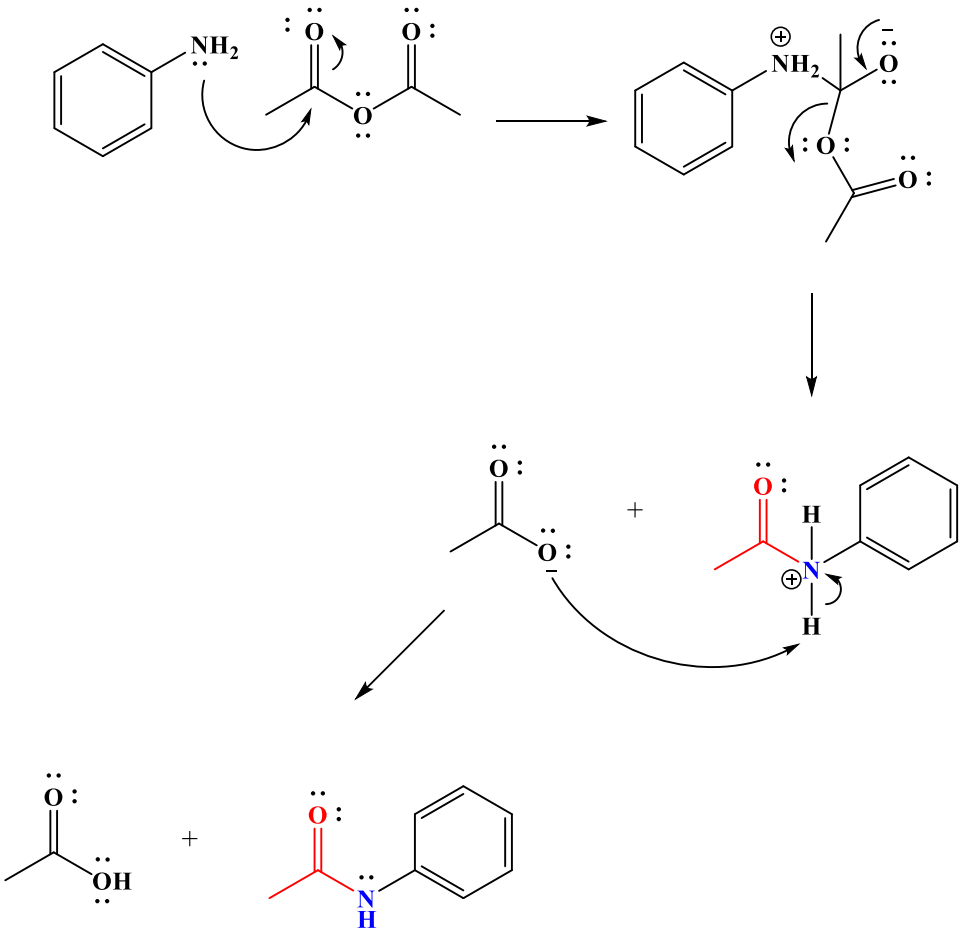

Paracetamol




Aspirin

# CHEMISTRY OF ACETYLATION

Compounds with active hydrogen will react with acetic anhydride to produce acetyl derivatives by nucleophilic substitution reaction as in scheme (1):

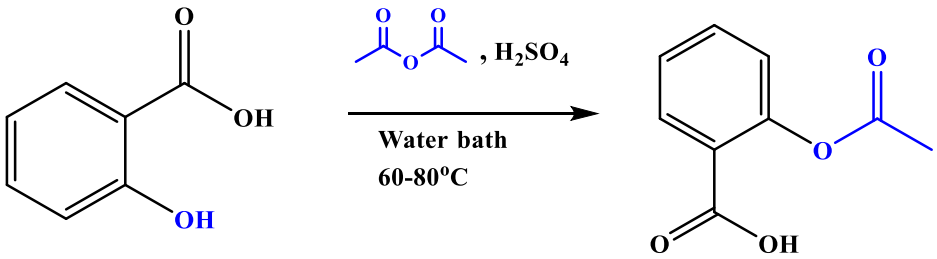



*The same mechanism will be operated if* **O** *or* **S** *was used instead of* **N**

***Scheme (1): Mechanism of acetylation by acetic anhydride.***

## PROCEDURE

**a.** Weigh 1.4g of salicylic acid and transfer to clean, dry round bottomed flask.
**b.** Add 5ml of acetic anhydride and 5 drops of concentrated $H_2SO_4$, use stopper and shake manually for seconds (clear solution may be obtained).
**c.** Float the round bottomed flask in water bath [heated to 60-80°C] for 10-15minutes with stirring.
**d.** Discontinue heating and immediately deliver 2ml of DW, why?
**e.** When the flask is sufficiently cool, remove the stopper, and add 20ml of DW, why?
**f.** Immerse the flask in ice bath with scratching by glass rod until crystallization is completed.
**g.** Isolate the product (ASA), dry, and weigh.




## QUESTIONS

- *The equipments must be dry in this experiment, why?*
- *Heating is by water bath and not direct heating; why?*
- *Sulfuric acid has two possible roles in this experiment, what are they?*
- *Acetylation occurred on phenolic OH not carboxylic OH; why?*
- *What are the purposes of acetylation in organic synthesis and organic pharmaceutical chemistry?*
- *Acetylation and acylation; any different between them??*
- *How to check by chemical tests the progress of the following pathway:*