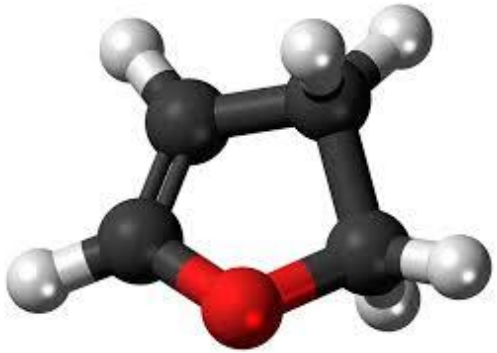
2302687 – Heterocyclic Compounds – Part I

Lecture 2-2

Heteroaromatic Synthesis via Condensation Part 2



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Recommended Textbook:

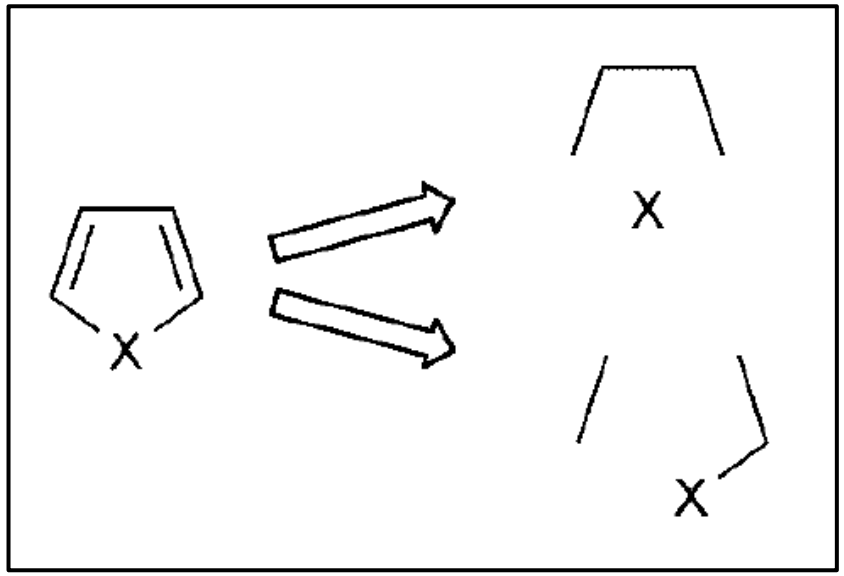
Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

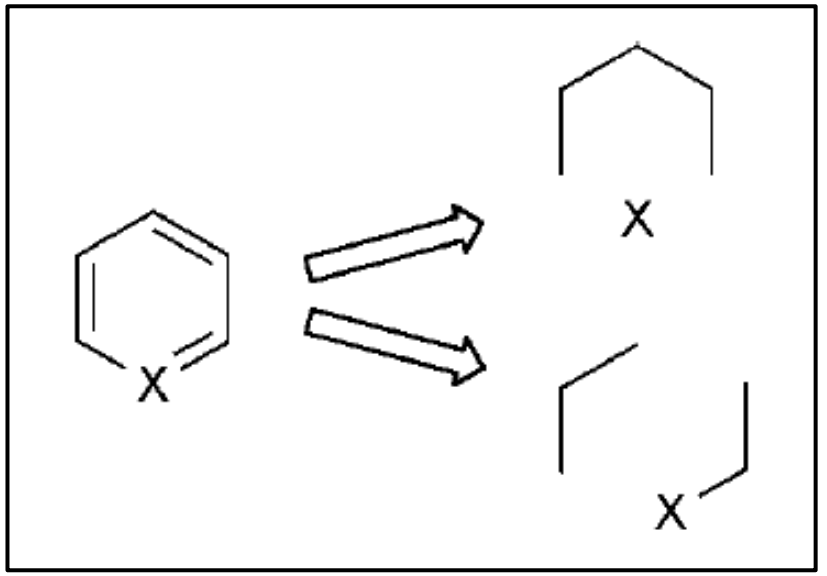
Condensation – Typical Reactant Combinations

- by far the majority of ring syntheses fall into **two categories:**

Type #1: Only **C–heteroatom** bonding is needed, i.e. the rest of the skeleton is present, intact, in one starting component

Type #2: One **C–C bond** and one **C–heteroatom** linkage are required

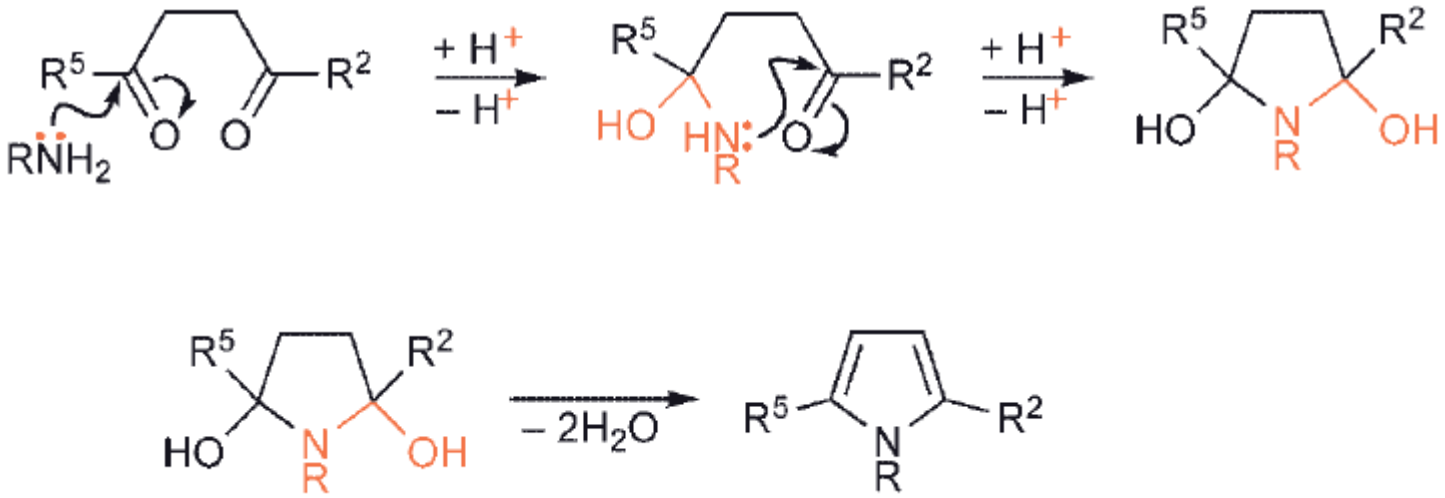




Condensation – Type #1 for 5-Membered Ring

- For the synthesis of **5-membered heterocycles**, precursors with two carbonyl groups related 1,4 are required

- **Synthesis of Pyrrole:** 1,4-diketones react with ammonia or primary amines to give 2,5-disubstituted pyrroles

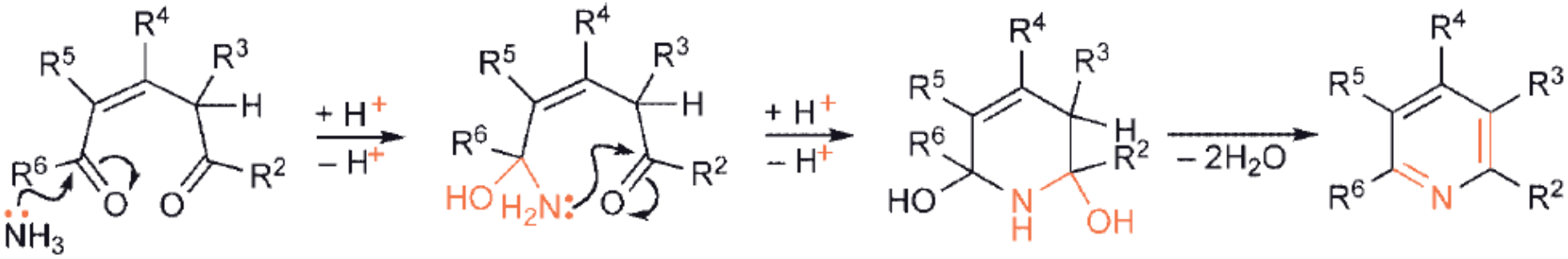


- Two successive carbonyl carbon additions and loss of two molecules of water produce the aromatic ring, though the exact order of these several steps is never certain

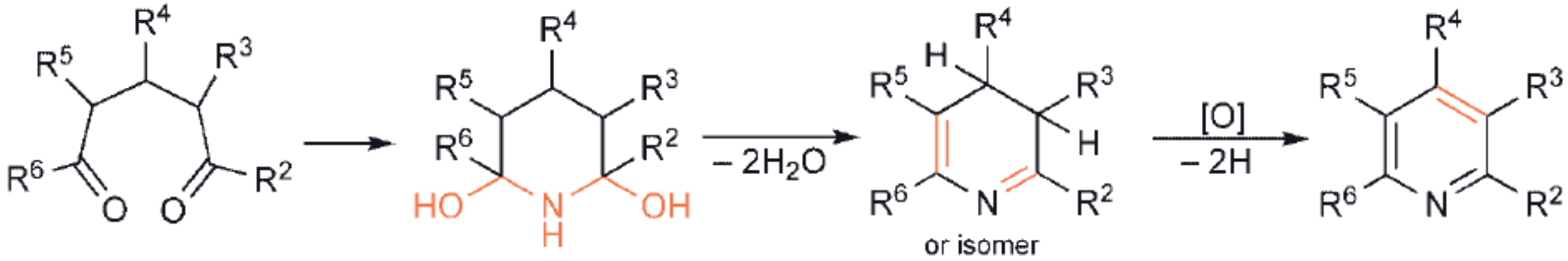
Condensation – Type #1 for 6-Membered Ring

- For **6-membered rings**, the 1,5-dicarbonyl precursor has to contain a C=C double bond in order to lead directly to the aromatic system

- **Synthesis of Pyridine:**

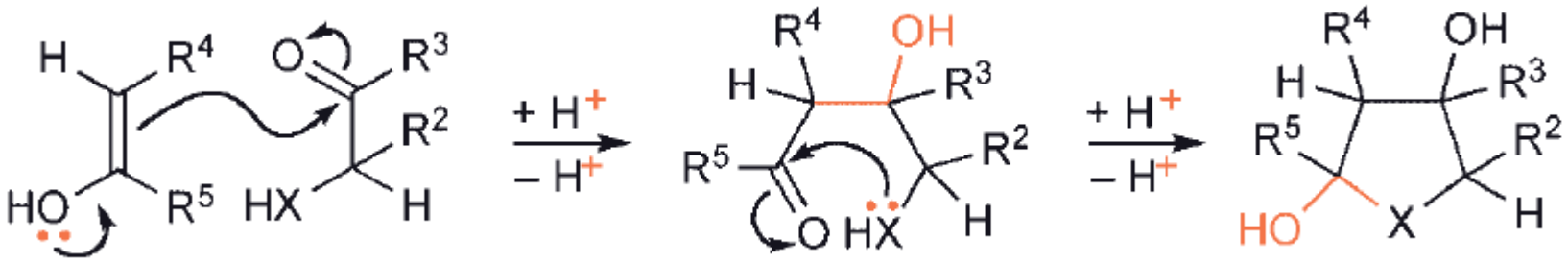


- The use of an otherwise saturated 1,5 - dicarbonyl compound does not lead directly to an aromatic pyridine, though it is easy to **dehydrogenate** the dihydro-heterocycle



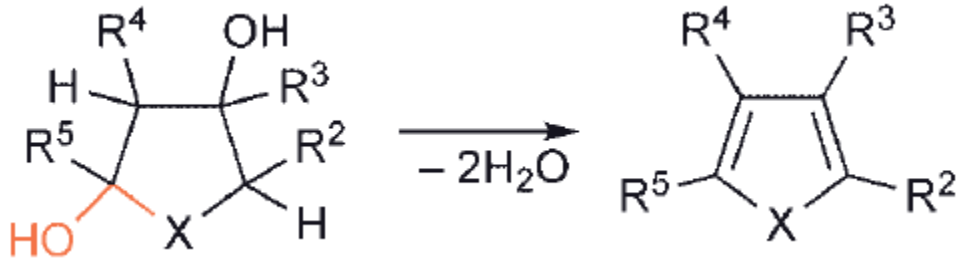
Condensation – Type #2 for 5-Membered Ring

- One component must contain an enol/enolate/enamine, or the equivalent thereof, while the second must have electrophilic centres to match



(note: R^4 must be an **acidifying group**: ketone, ester, nitrile, or nitro)

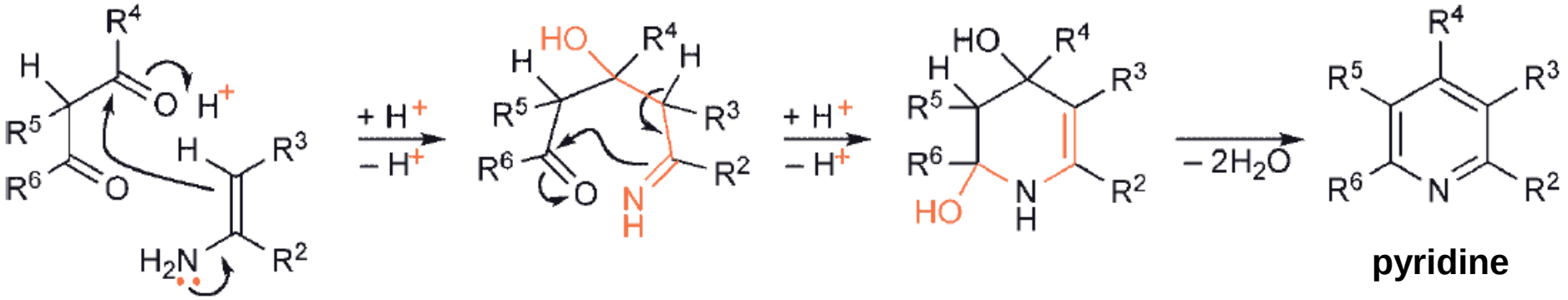
- Loss of two molecules of water produce the aromatic ring



furan/thiophene/pyrrole

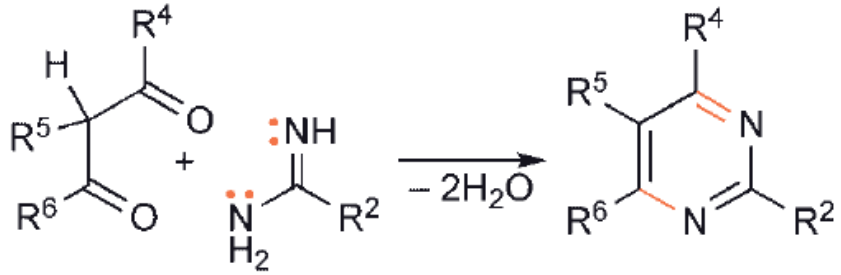
Condensation – Type #2 for 6-Membered Ring

- Typical sequence for the **synthesis of a pyridine** from a 1,3-dicarbonyl compound and an enamine

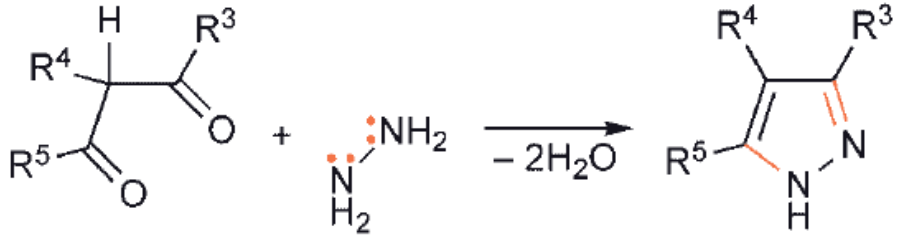


pyridine

- The two nucleophilic centres can both be **heteroatoms**, as in syntheses of pyrimidines and pyrazoles



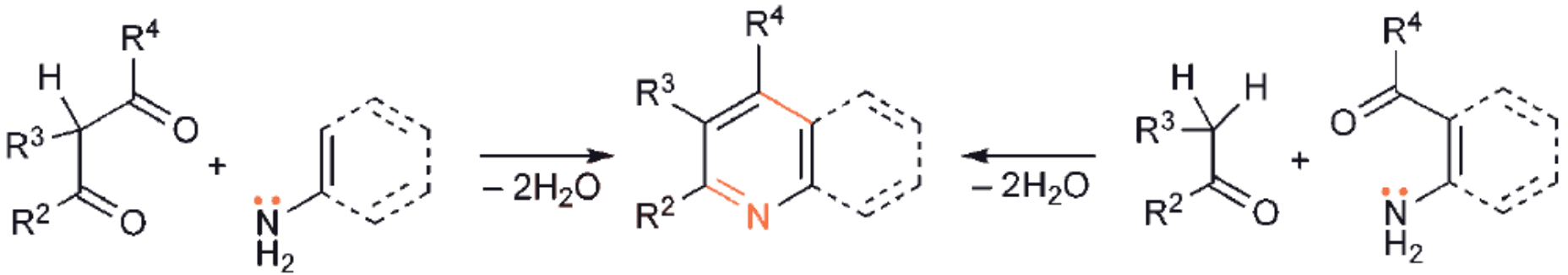
pyrimidine



pyrazole

Condensation – Type #2 for 6-Membered Ring

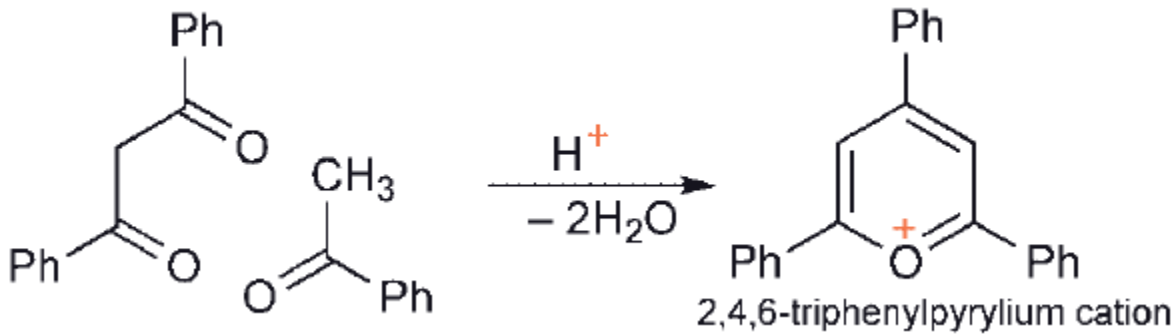
- In **quinoline** syntheses, **anilines** are like the enamines in pyridine syntheses



quinoline

Condensation – Type #2 for 6-Membered Ring

- Suggest the mechanism for the reaction of 1,3-diphenylpropane-1,3-dione with acetophenone giving 2,4,6-triphenylpyrylium

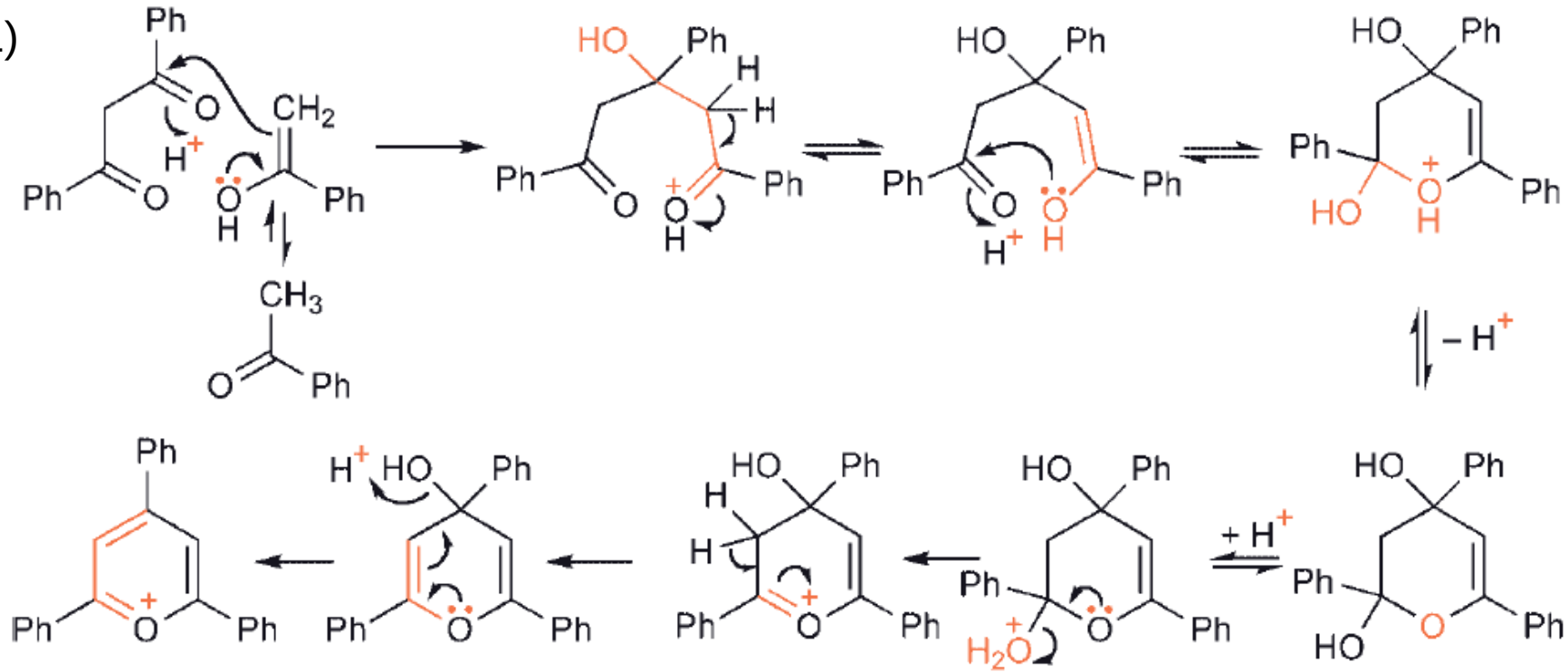


2,4,6-triphenylpyrylium cation

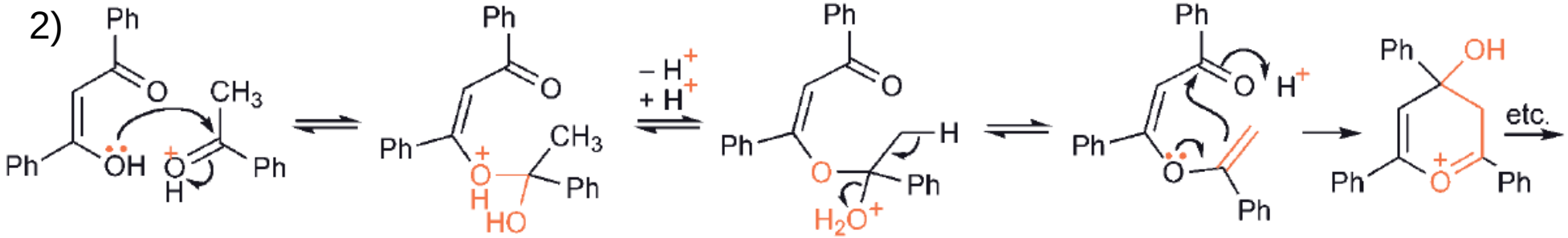
Condensation – Type #2 for 6-Membered Ring

Two of many plausible mechanisms

1)



2)



Synthesis – Condensation at Carbonyl Group

- Most of the steps in such sequences are **reversible**; the overall sequence proceeds to product nearly always because

  1. The product is the thermodynamically **most stable** molecule in the sequence
  2. The product is **removed from the equilibria** by a step which is **irreversible** under the conditions used.

Example: the inter-relationship between **1,4-diketones** and **furans**

- Heating 1,4-diketones, in acid, under conditions which lead to the distillation of the furan

- Furans are hydrolysed to 1,4-diketones by aqueous acid