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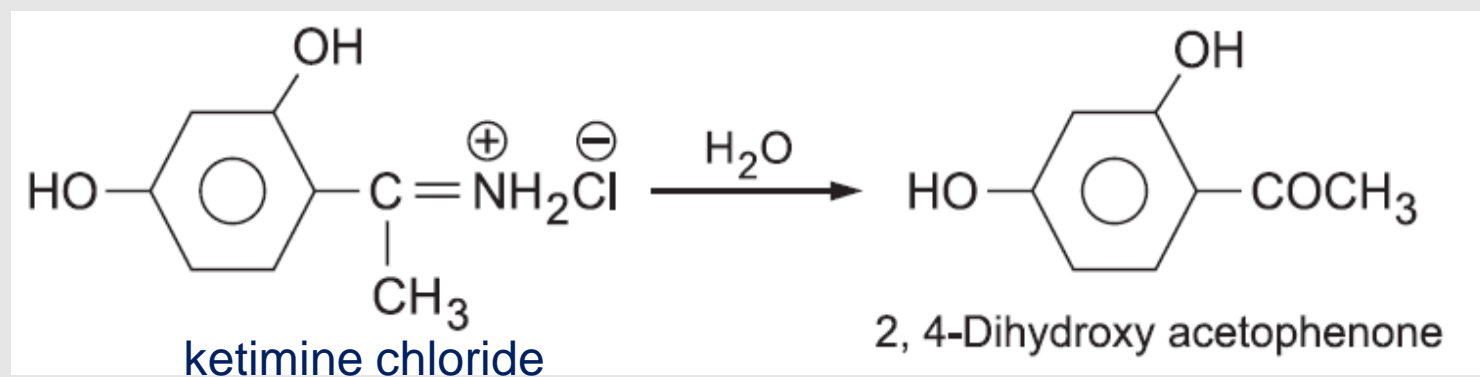
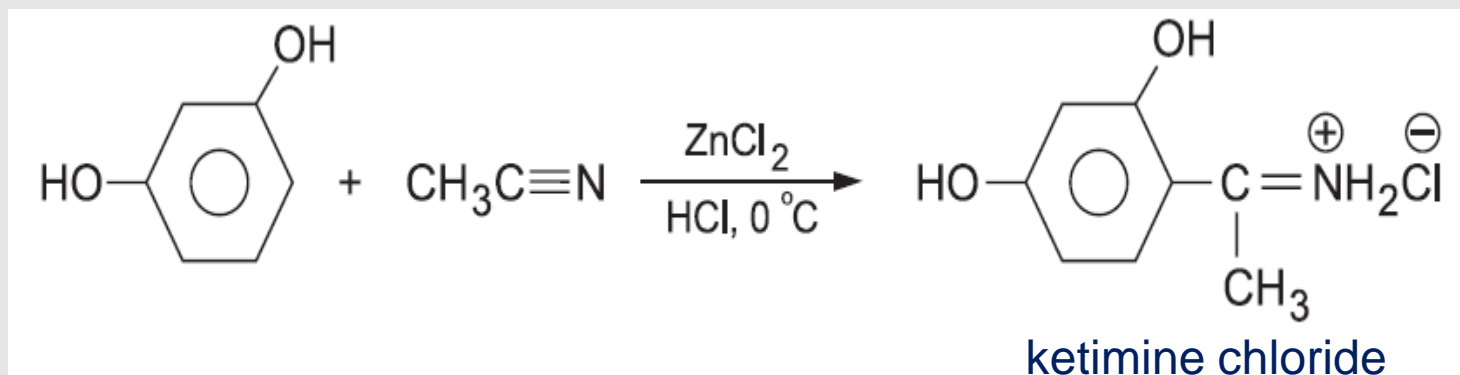
An aerial photograph of a tropical coastline. On the left, a dense forest of green trees and palm trees borders a narrow, sandy beach. To the right, the ocean is a vibrant turquoise color, with white waves crashing against the shore. The overall scene is bright and scenic.

Named Reaction: HOUBEN-HOESCH REACTION

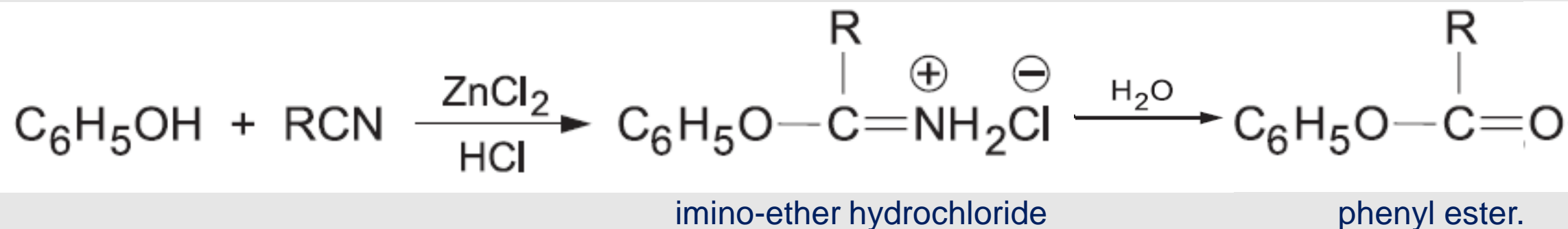
Introduction:

Polyhydroxy phenols, phenolic ethers and some reactive heterocyclic compounds (e.g., pyrrole) undergo **acylation with nitrile and hydrochloric acid in the presence of a Lewis acid**, the most common being zinc chloride and aluminium trichloride. This particular Friedel–Crafts acylation with nitriles is called **Houben–Hoesch reaction**.

The reaction is carried out by passing dry HCl gas through an equimolecular mixture of nitrile and phenol in dry ether containing $ZnCl_2$. The resulting ketimine chloride on hydrolysis gives the aromatic hydroxy ketone. Thus, resorcinol gives 2,4-dihydroxyacetophenone.



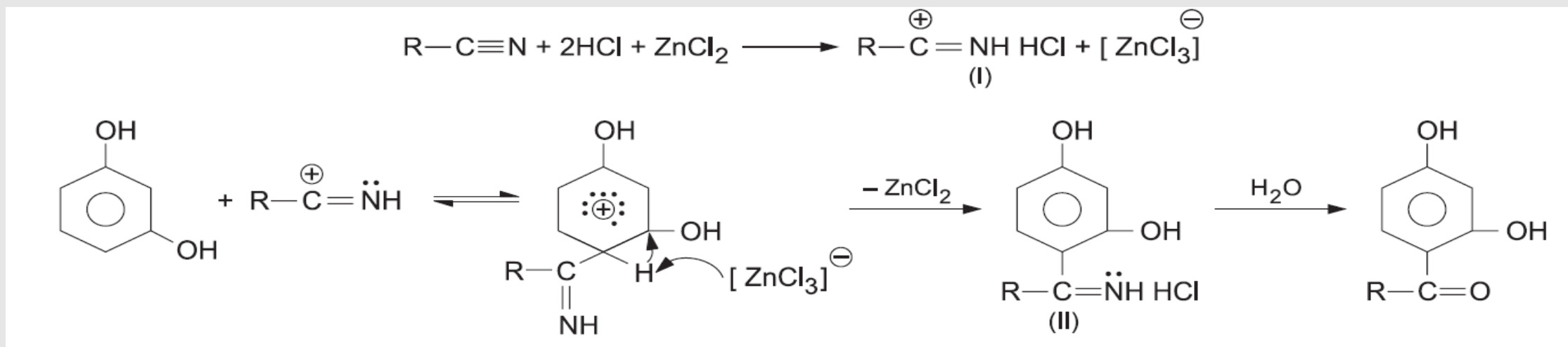
The reaction is very **successful with polyhydroxy phenols especially the m-polyhydroxy phenols**. The reaction, however, is **not successful with phenol** due to the formation of imino-ether hydrochloride as almost the exclusive product resulting from the attack on the hydroxy oxygen, which on hydrolysis gives phenyl ester.



Besides a variety of aliphatic nitriles (e.g., acetonitrile, mono- and trichloro-aceto nitriles), aromatic nitriles have also been found to give good yield. Ether, chloroform, ethyl acetate, etc., may be used as solvent.

Mechanism:

The mechanism of the reaction is complex and not fully understood. The attacking species is supposed to be the imine hydrochloride (I). The resulting imine salt (II) on hydrolysis gives the product.

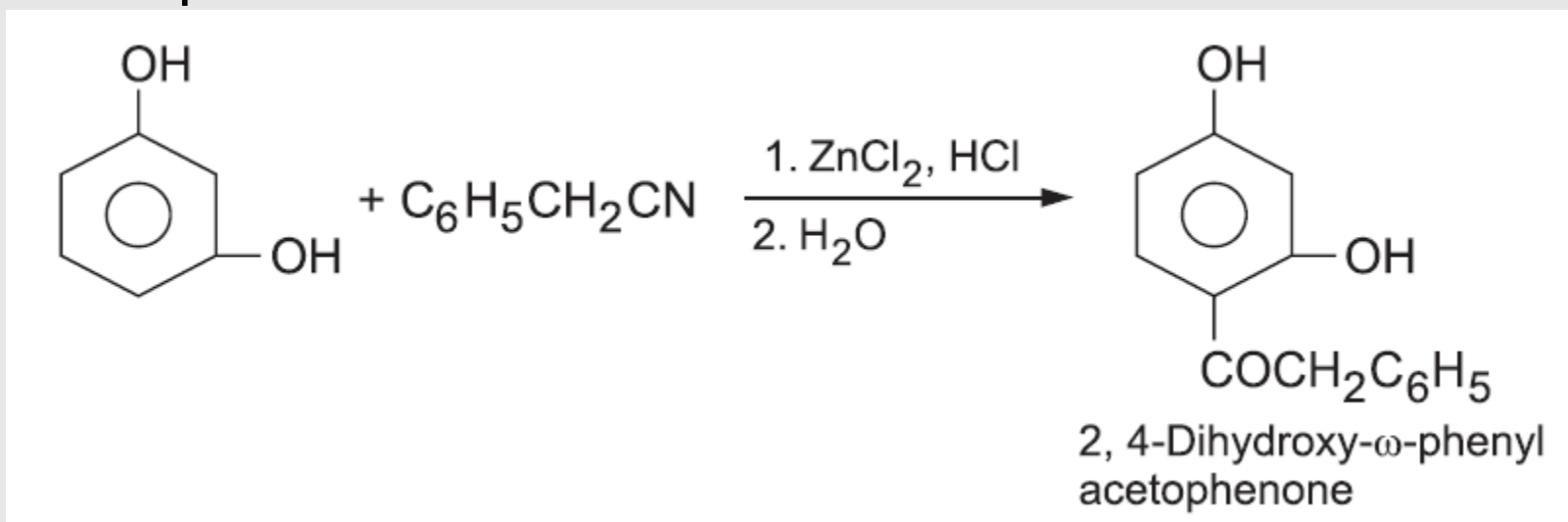


When hydrogen cyanide is employed in place of nitrile, aromatic aldehyde may be obtained. This modification is called Gattermann synthesis of aromatic aldehydes. By this method aldehydes of various aromatic compounds have been prepared.

Applications:

The reaction provides a convenient method for the synthesis of polyhydroxy acetophenones and polyhydroxy benzophenones. Many natural products of medicinal value have been synthesized by this reaction.

1. Synthesis of -substituted acetophenones When benzyl cyanide is used, -phenylaceto phenones are obtained.



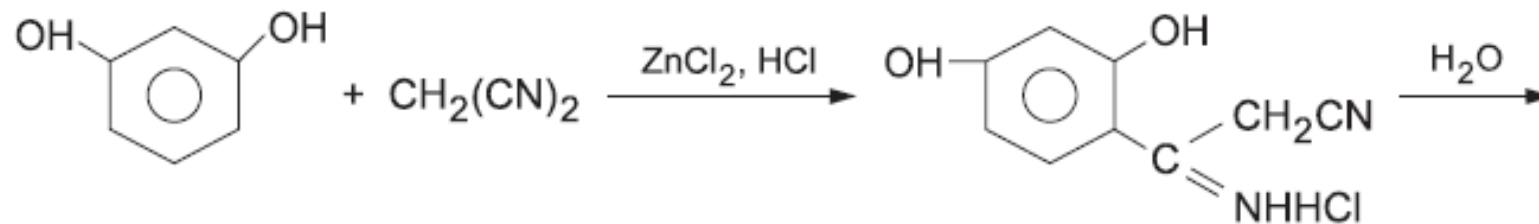
Similarly, on reacting with chloromethyl cyanide ($ClCH_2CN$), 2, 4-dihydroxy-chloroacetophenone is obtained.

2. Synthesis of heterocyclic ketones A few pyrrol ketones have been synthesized.



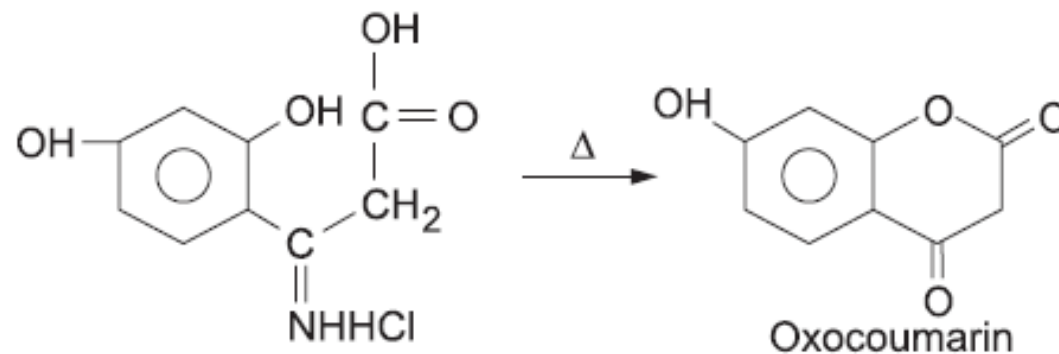
2, 4-Dimethyl-5 acetyl pyrrole

3. Synthesis of coumarins Oxocoumarin has been synthesized from malononitrile and resorcinol.



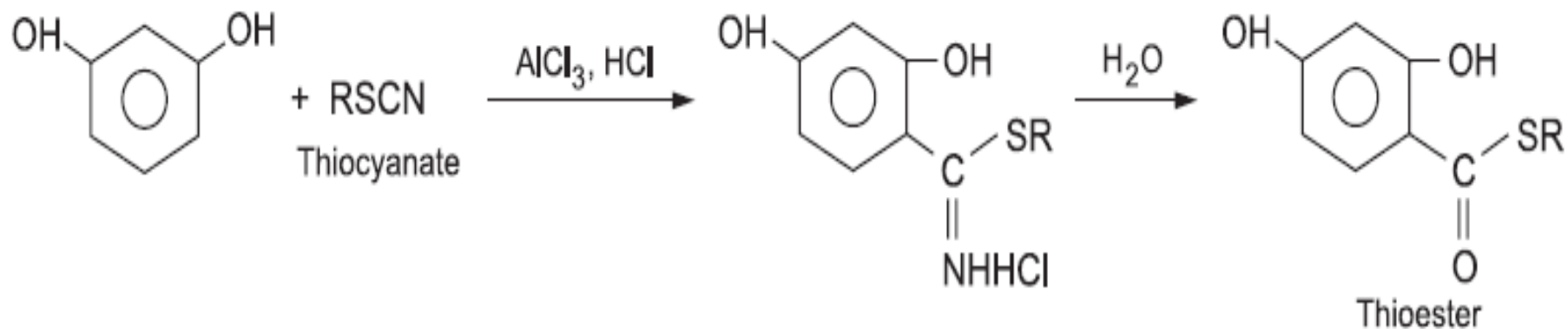
Resorcinol

Malononitrile



Oxocoumarin

4. Synthesis of thioesters Thioester may be prepared by using thiocyanate (RSCN).



Fries rearrangement is not convenient for monoacylation of a polyhydroxy phenol due to the formation of polymeric aluminium phenoxide. Hence, Houben–Hoesch reaction is preferred for acylation of such substrates.