Reimer-Tiemann reaction

Chenjingrong
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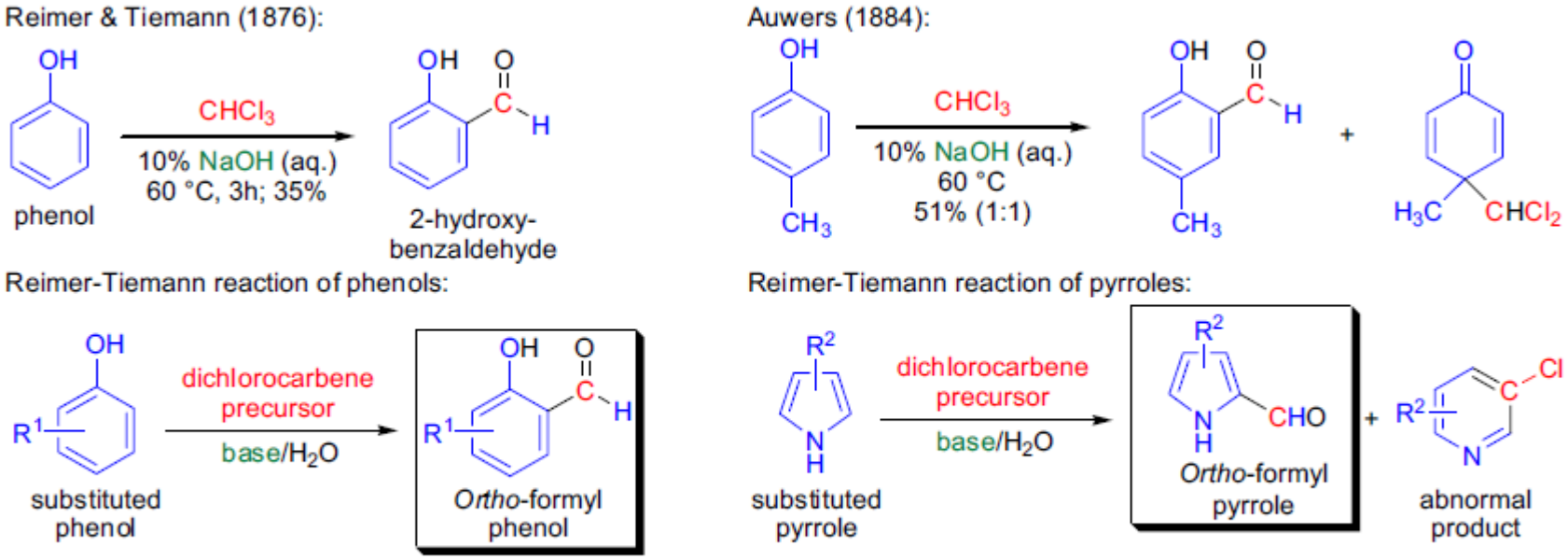
In 1876, K. Reimer and F. Tiemann discovered that the treatment of phenol with chloroform in 10% NaOH solution led to the formation of the corresponding *o*-hydroxy benzaldehyde as the major product. The formylation of phenols and heterocyclic phenols using chloroform in an aqueous alkaline medium is known as the *Reimer-Tiemann reaction*.



R^1 = H, alkyl, OH, *O*-alkyl, CO_2H, NO_2, Cl, Br, I; R^2 = H, alkyl; dichlorocarbene precursor: $CHCl_3$, Cl_3CCO_2H, Cl_3CCHO, Cl_3CNO_2; base: NaOH, KOH, CsOH;

Soon after the disclosure of these seminal findings, several research groups investigated the effect of the same reaction conditions on substituted phenols and electron-rich heterocycles.

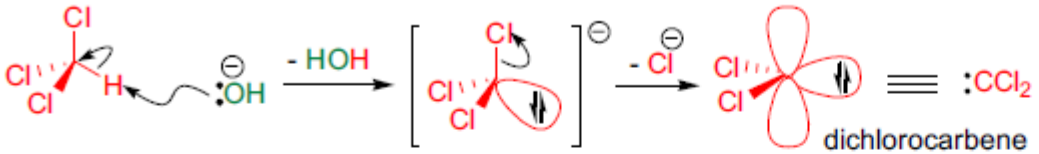
In the 1880s, K. Auwers reported the isolation of chlorine-containing substituted cyclohexadienones that were generated in the formylation of various alkylphenols.These cyclohexadienones were later coined as abnormal Reimer-Tiemann products.

Also in the early 1880s, G.L. Ciamician and M. Dennstedt found that under the original Reimer-Tiemann conditions the
potassium salt of pyrrole underwent ring-expansion to afford 3-chloropyridine, a transformation known today as the
Ciamician-Dennstedt rearrangement (also called as the *abnormal Reimer-Tiemann reaction*).

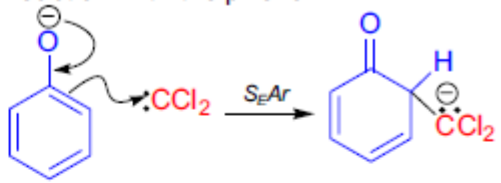
The general features of the *Reimer-Tiemann reaction* are:

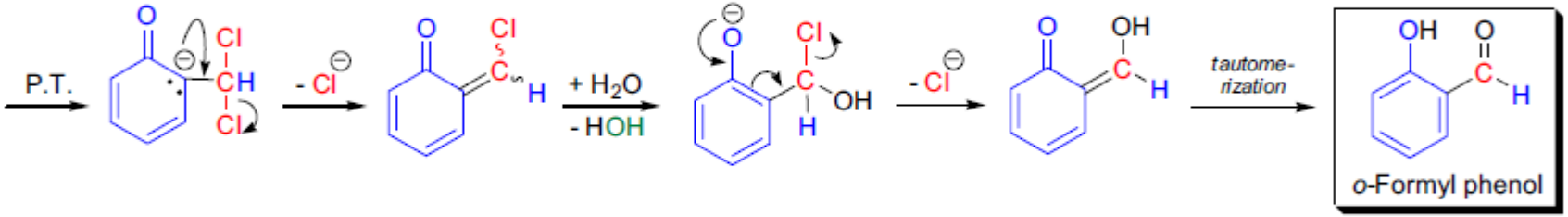
1) it is the only electrophilic aromatic substitution reaction that occurs under basic conditions in a protic solvent;
2) phenols, naphthols,(alkyl-, alkoxy-, and halogenated phenols, salicylic acid derivatives), heterocyclic phenols (such as hydroxyquinolines and hydroxypyrimidines), as well as pyrroles and indoles undergo formylation under the reaction conditions;
3) typically the substrate (phenol) is dissolved in 10-40% alkali hydroxide, excess chloroform is added, and the biphasic solution is vigorously stirred at elevated temperatures;
4) besides $CHCl_3$, other dichlorocarbene precursors such as chloral, trichloronitromethane, etc. can be used;
5) Yields are usually moderate;
6) the regioselectivity is not high, but *ortho*-formyl products tend to predominate;
7) when the*ortho*-position is already substituted, *para*-formyl phenols are obtained;
8) in the case of pyrroles, when the *ortho* substituent is a CO_2H or CO_2R group, decarboxylation is observed and the *o*-formyl product is formed (similar findings were reported for an *o*-alkoxy phenol where the alkoxy group was eliminated to give an *o*-formyl phenol);
9) when the reaction is conducted in the presence of cyclodextrins, the *p*-formyl product is formed predominantly.

Dichlorocarbene formation:

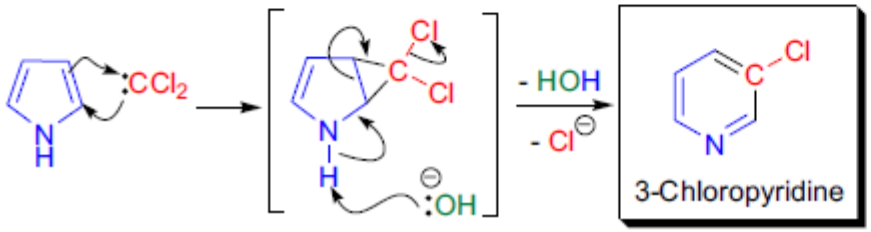


Reaction with the phenol:

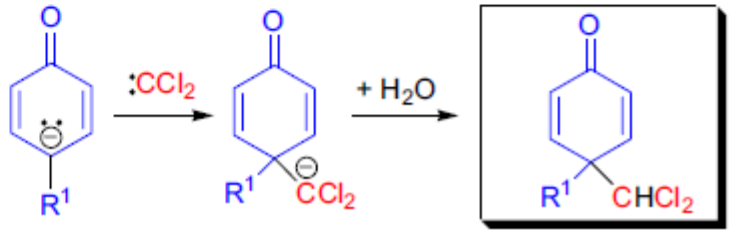




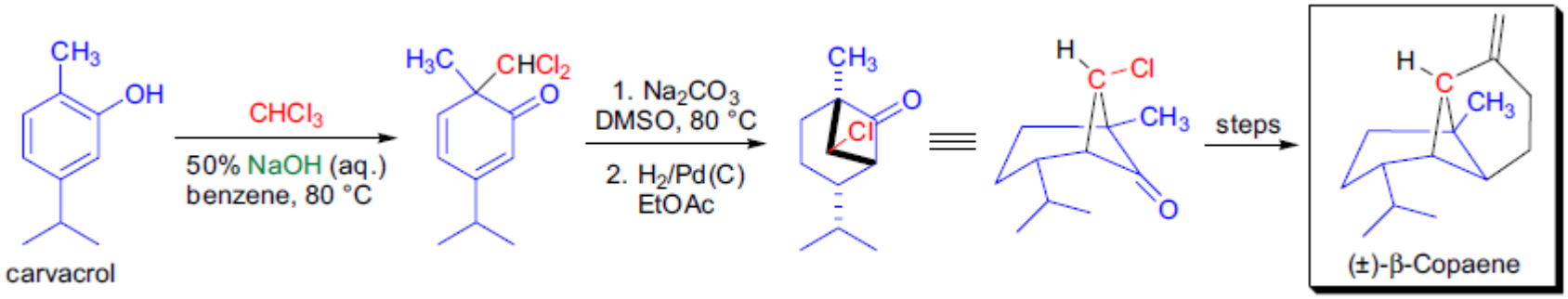
Formation of the abnormal product from pyrrole:



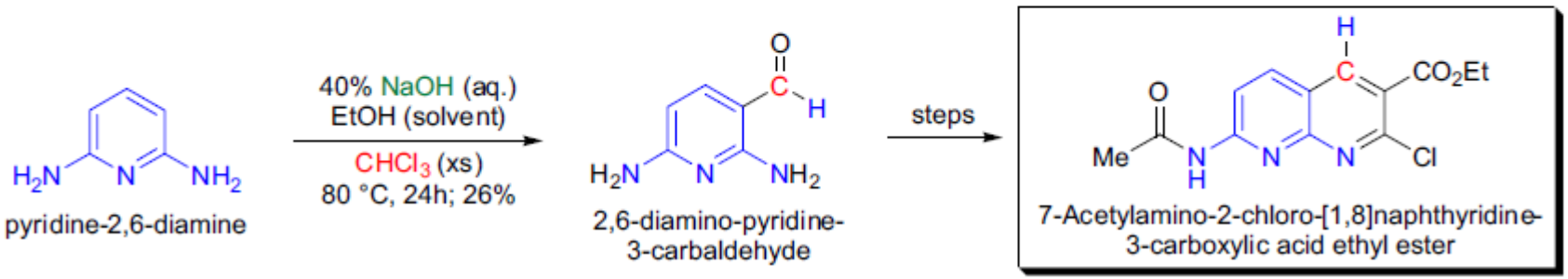
Formation of the abnormal product from alkylphenols:



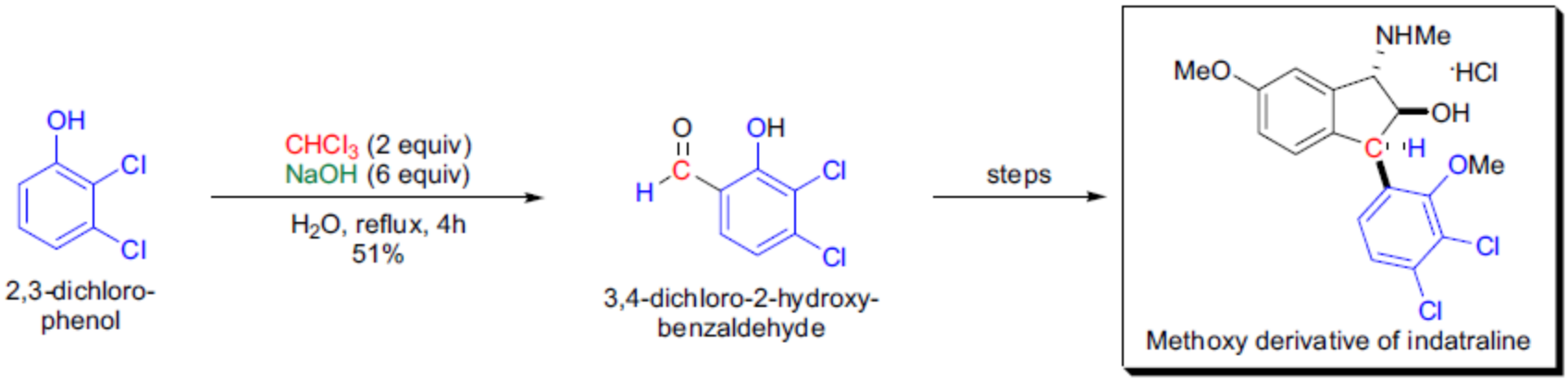
The total synthesis of the tricyclic sesquiterpene (±)-β-copaene was accomplished by E. Wenkert and co-workers. The required bicyclic starting material was prepared in three steps from carvacrol. In the first step, carvacrol was subjected to typical Reimer-Tiemann conditions. The abnormal Reimer-Tiemann product, 6-dichloromethyl-3-isopropyl-6-methyl-cyclohexa-2,4-dienone, was obtained, and upon treatment with sodium carbonate in DMSO, cyclization occurred to afford a bicyclic halo ketone. The double bonds were then hydrogenated in the presence of Pd(C) catalyst.



S.C. Zimmermann et al. developed an efficient synthesis of 2-amino-1,8-naphthyridines that can serve as building blocks for host-guest and self-assembling systems. The synthesis commenced with the *Reimer-Tiemann formylation* of 2,6-diaminopyridine to afford 2,6-diaminopyridine-3-carbaldehyde in modest yield. Next, the *Friedländer reaction* using activated ketones gave rise to the target compounds.



A series of indatraline derivatives containing methoxy groups were synthesized and their monoamine transporter binding site affinities were measured in the laboratory of K.C. Rice.[26] The synthetic effort began with the preparation of the required substituted benzaldehydes. The *Reimer-Tiemann formylation* of 2,3-dichlorophenol was carried out by treating the phenol with excess base and chloroform in water, and heating the mixture at reflux for several hours. Upon acidification of the reaction mixture the product was isolated as a single regioisomer.



The development of a novel hapten for radioimmunoassay of the lignan, enterolactone in plasma (serum) was accomplished by T. Mäkelä et al.[27] The essay utilized enterolactone derivatives that have a carboxylic acid moiety for the production of antiserum and tracer. The preparation of (±)-*trans*-5-carboxytrimethylenoxyenterolactone utilized the *Reimer-Tiemann reaction* for the formylation of 2-benzyloxyphenol.