Chemistry Department

Named Reactions

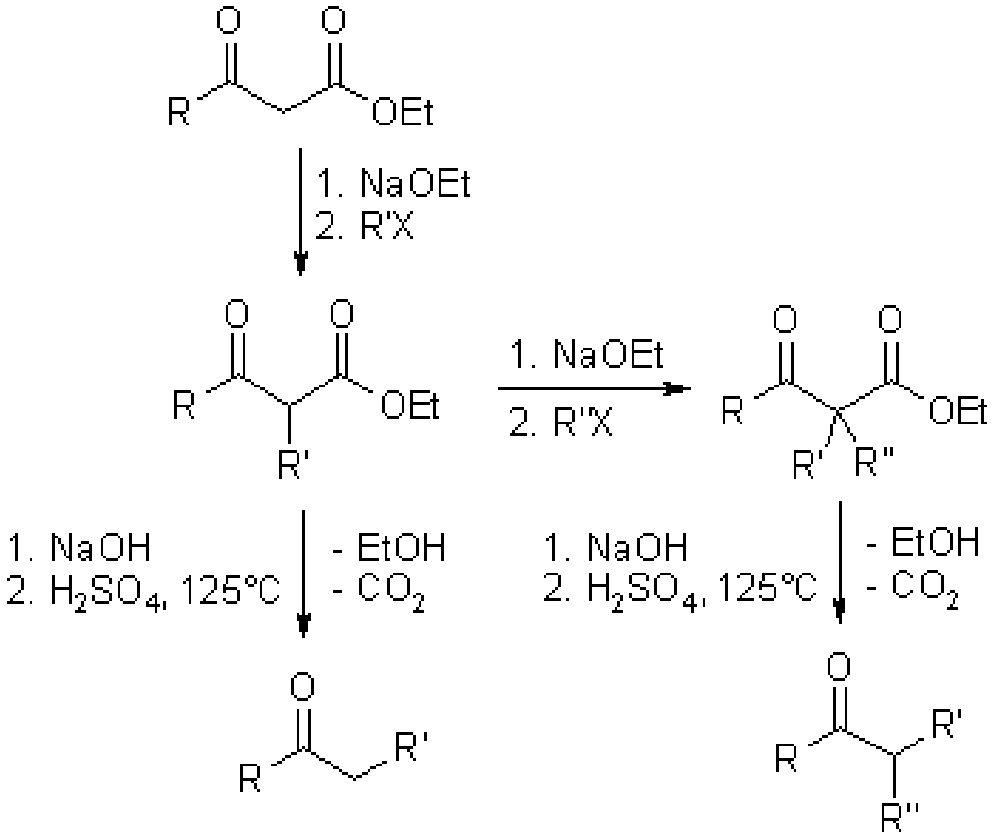
by

Dr Ahmed Mosallam

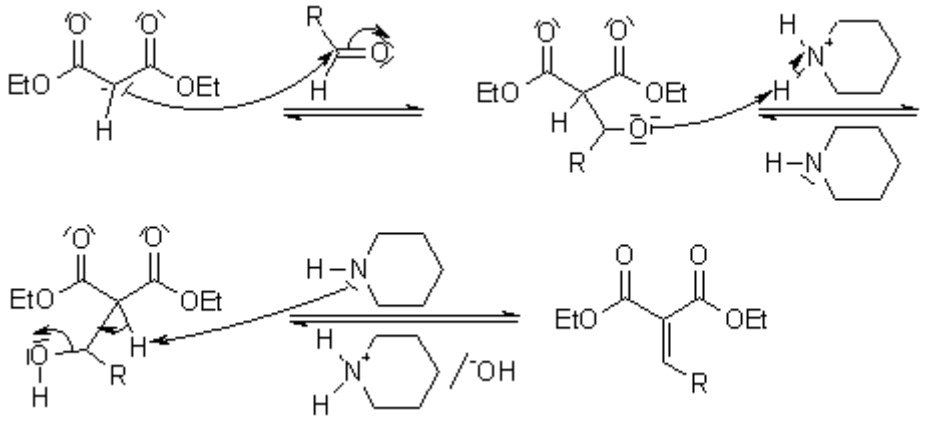
Chemistry Department

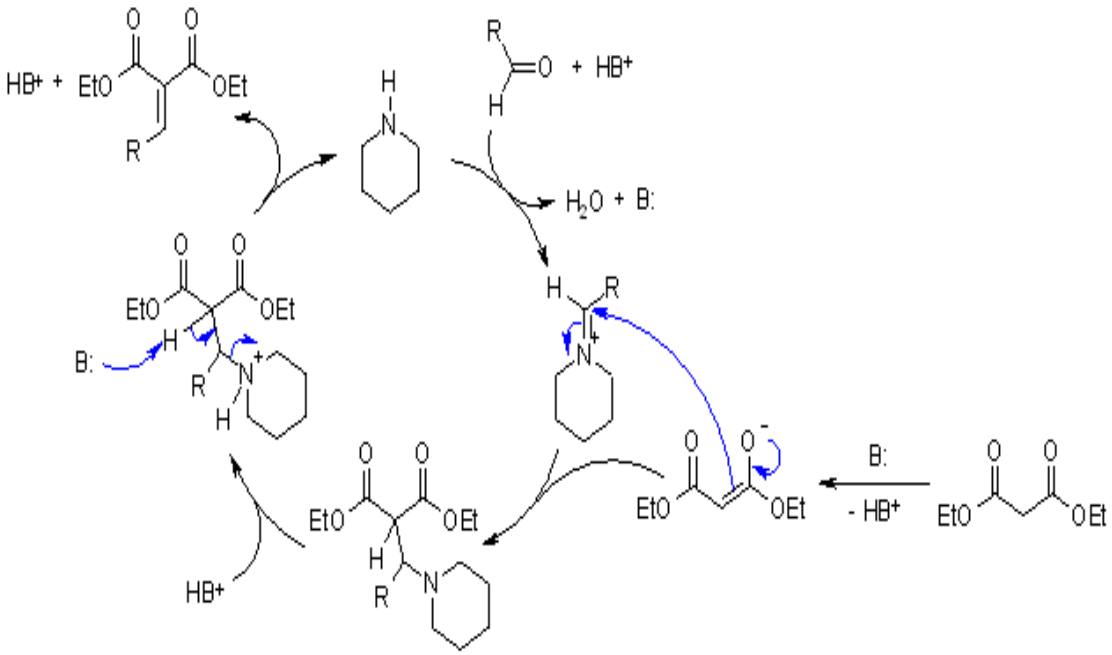
Faculty of Science

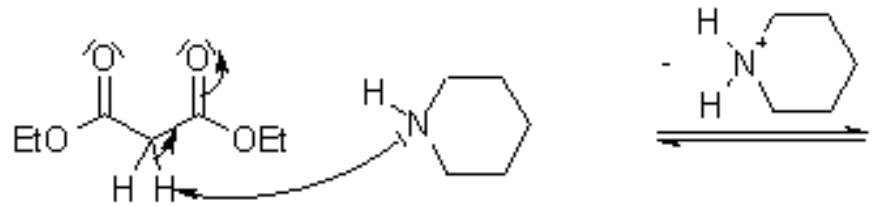
Acetoacetic Ester Synthesis

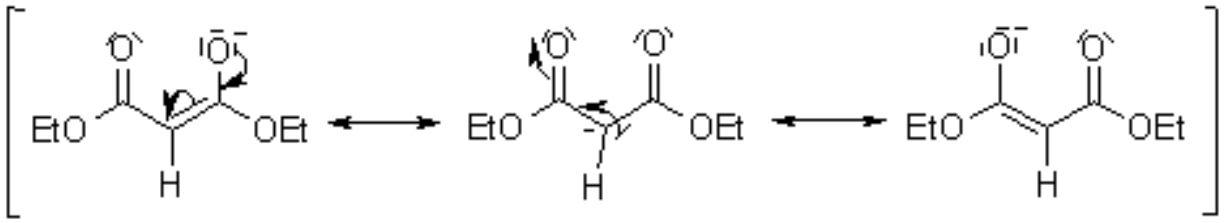


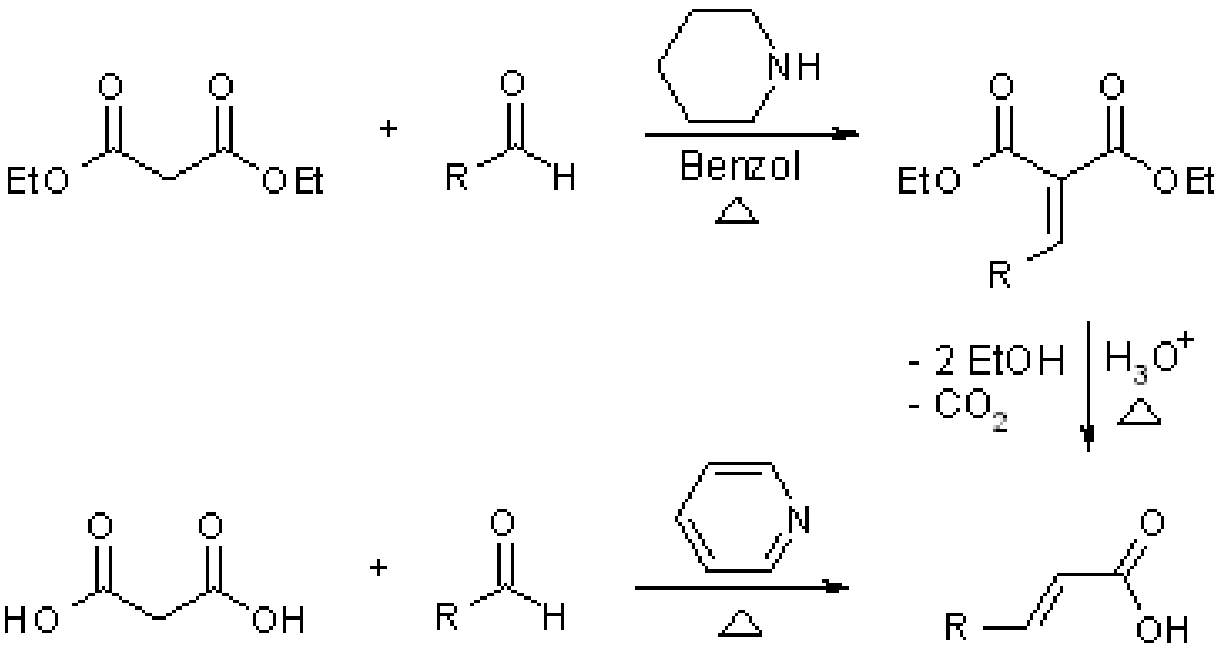
Knoevenagel Condensation
Doebner Modification



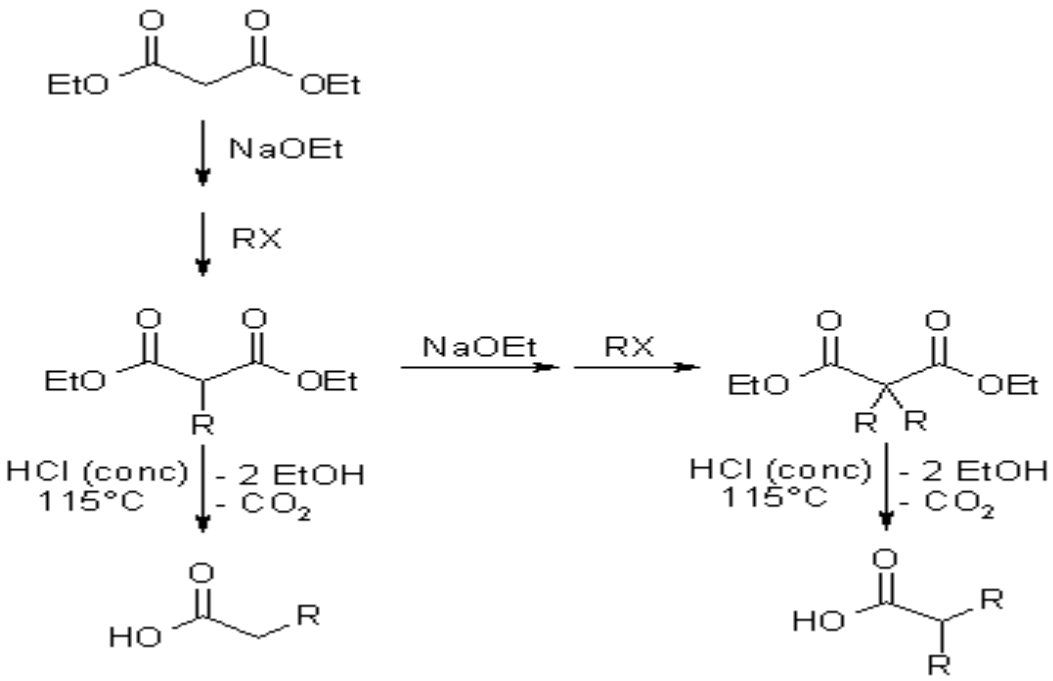




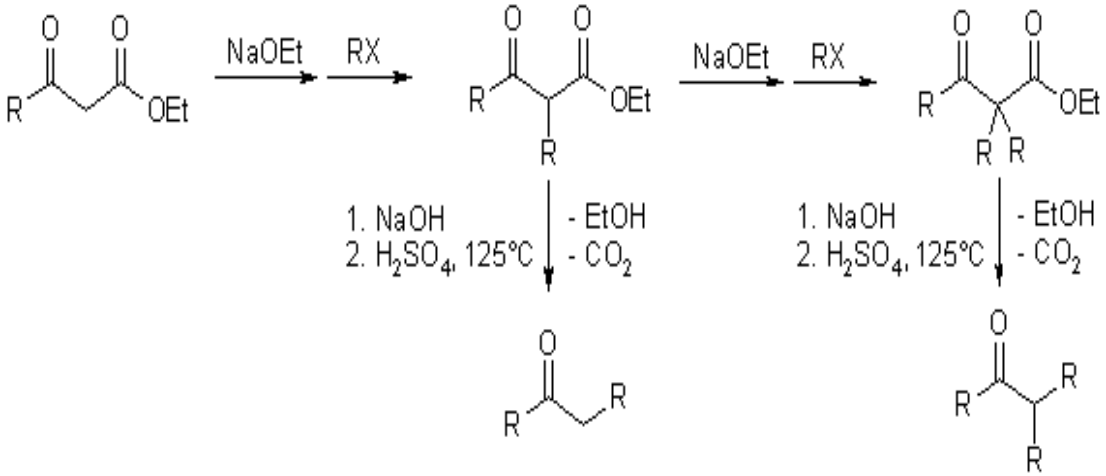



Benzol
- 2 EtOH
- CO2
H3O+

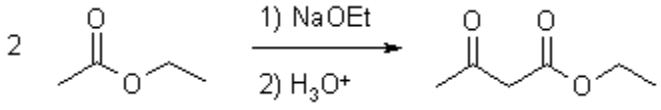
Malonic Ester Synthesis

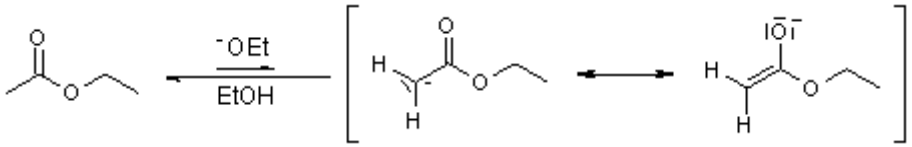


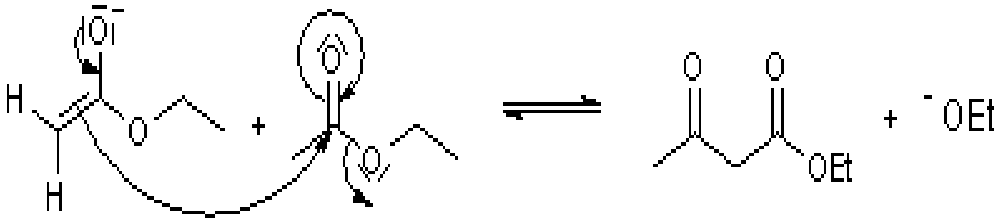
Synthesis of Carbonyl Compounds by Alkylation or Condensation

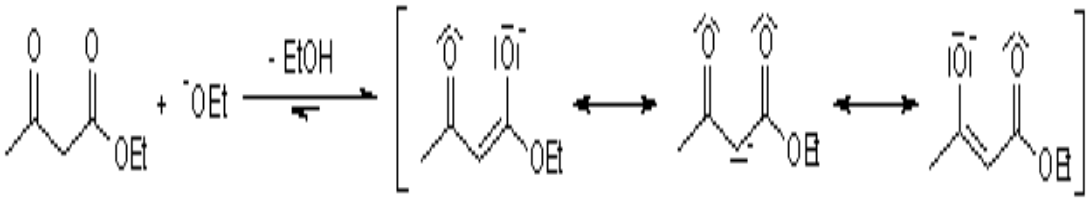


Acetoacetic-Ester Condensation
Claisen Condensation



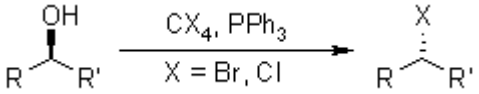


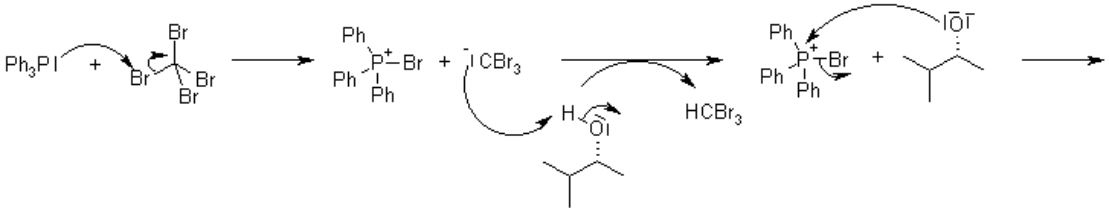


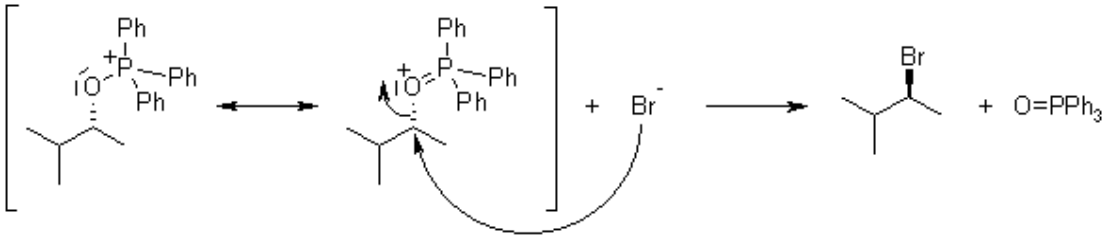


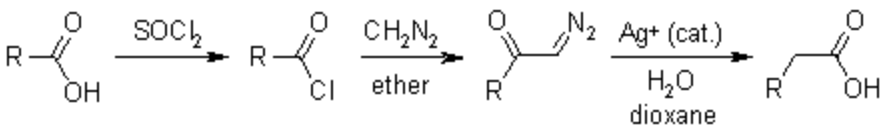
Appel Reaction

The reaction proceeds by activation of the triphenylphosphine by reaction with the tetrahalomethane, followed by attack of the alcohol oxygen at phosphorus to generate an oxyphosphonium intermediate. The oxygen is then transformed into a leaving group, and an S_N^2 displacement by halide takes place, proceeding with inversion of configuration if the carbon is asymmetric.



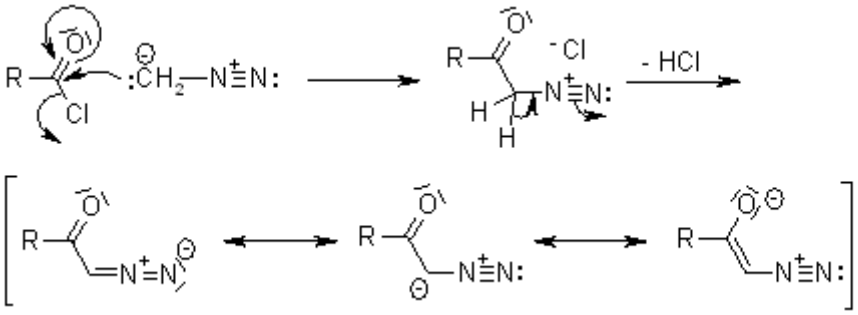




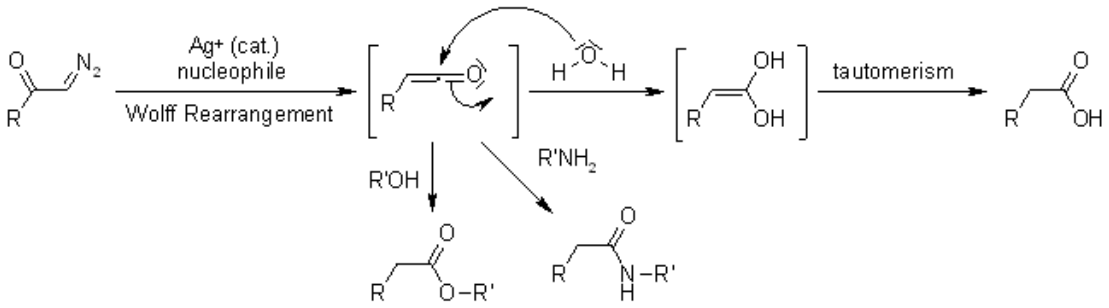


Arndt-Eistert Synthesis

In the first step of this one-carbon homologation, the diazomethane carbon is acylated by an acid chloride or mixed anhydride, to give an α-diazoketone. The excess diazomethane can be destroyed by addition of small amounts of acetic acid or vigorous stirring. Most α-diazoketones are stable and can be isolated and purified by column chromatography

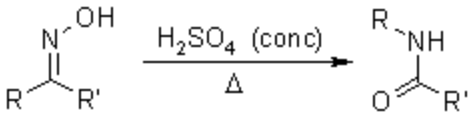


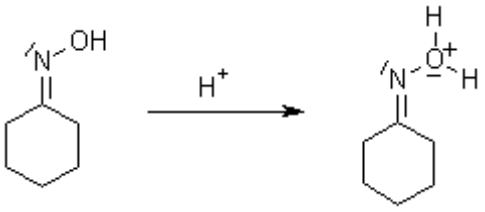
The reaction is conducted in the presence of nucleophiles such as water (to yield carboxylic acids), alcohols (to give esters) or amines (to give amides), to capture the ketene intermediate and avoid the competing formation of diketenes.

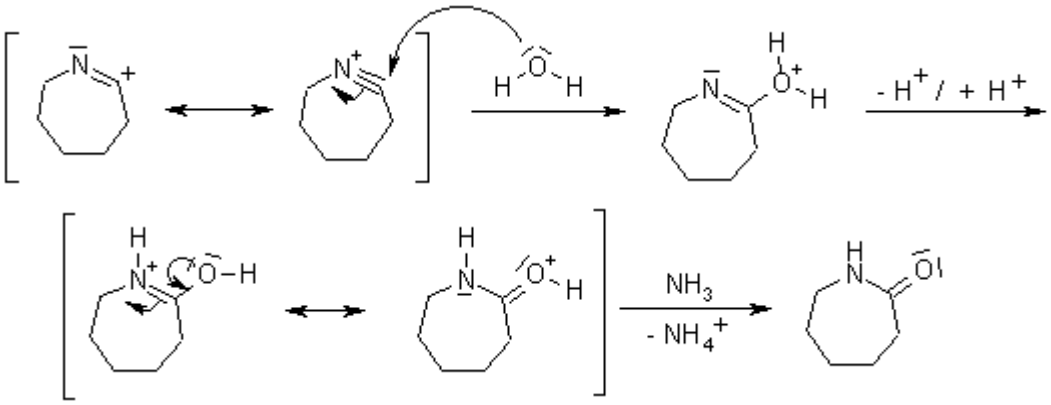


Beckmann Rearrangement

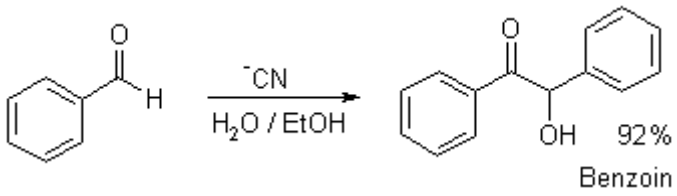
Oximes generally have a high barrier to inversion, and accordingly this reaction is envisioned to proceed by protonation of the oxime hydroxyl, followed by migration of the alkyl substituent "*trans*" to nitrogen. The N-O bond is simultaneously cleaved with the expulsion of water, so that formation of a free nitrene is avoided.







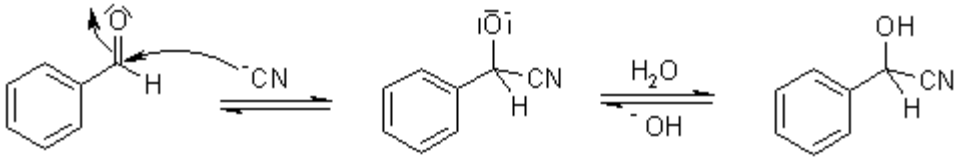
Benzoin Condensation

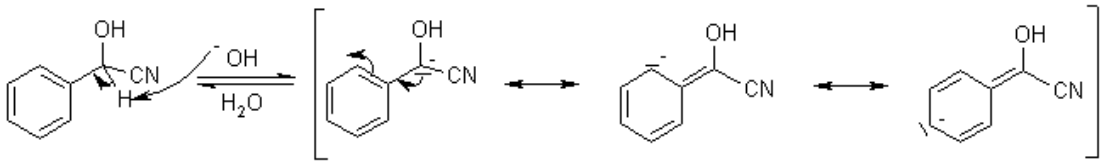


The benzoin condensation is a coupling reaction between two aldehydes that allows the preparation of α-hydroxyketones. The first methods were only suitable for the conversion of aromatic aldehydes.

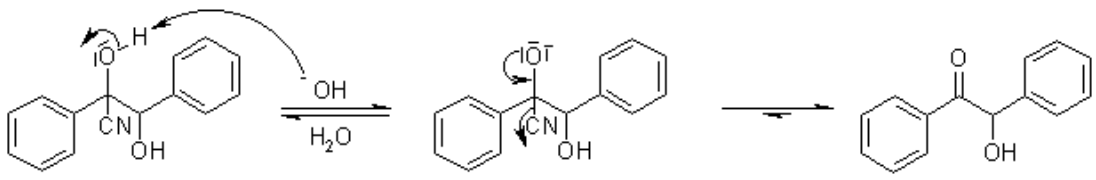
Mechanism of Benzoin Condensation

Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation: A thiazolium salt may also be used as the catalyst in this reaction

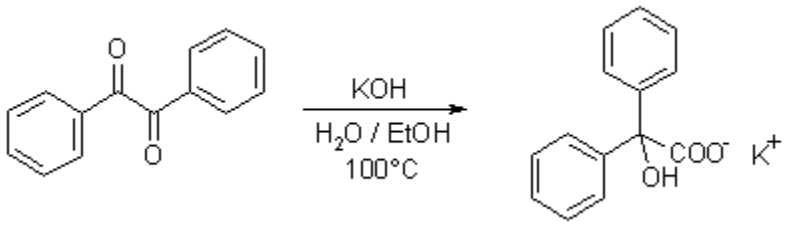




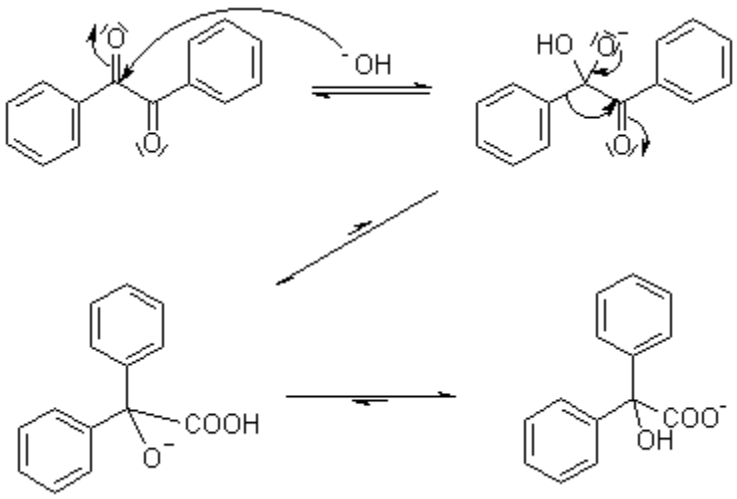
A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction



Benzilic Acid Rearrangement



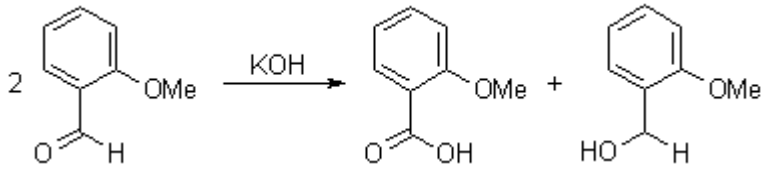
Mechanism of Benzilic Acid Rearrangement

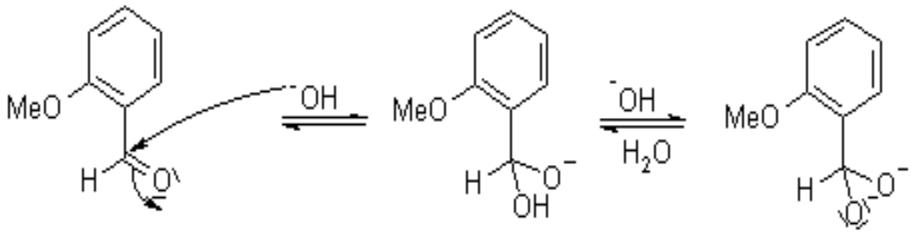


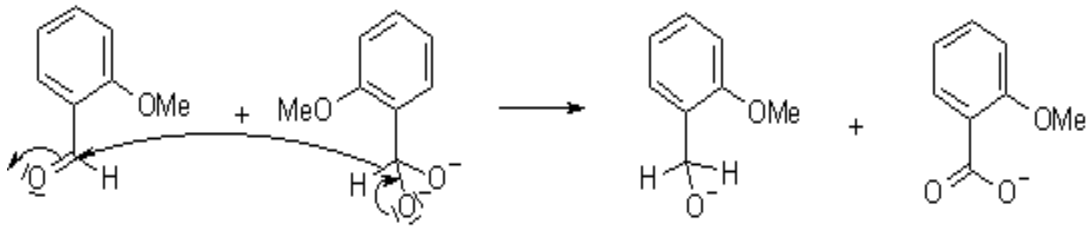
Cannizzaro Reaction

This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base.

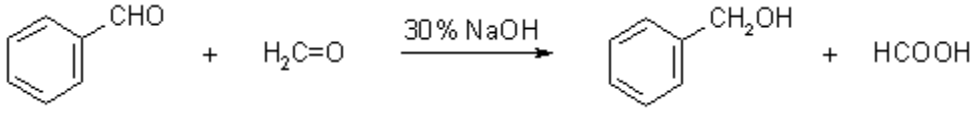
α-Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



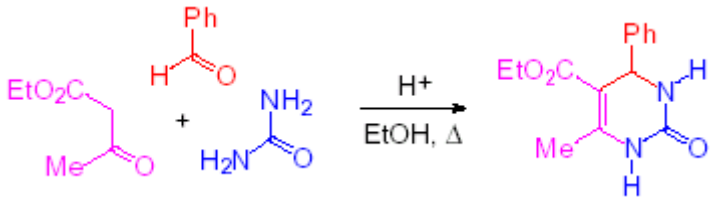




An interesting variant, the Crossed Cannizzaro Reaction, uses formaldehyde as reducing agent



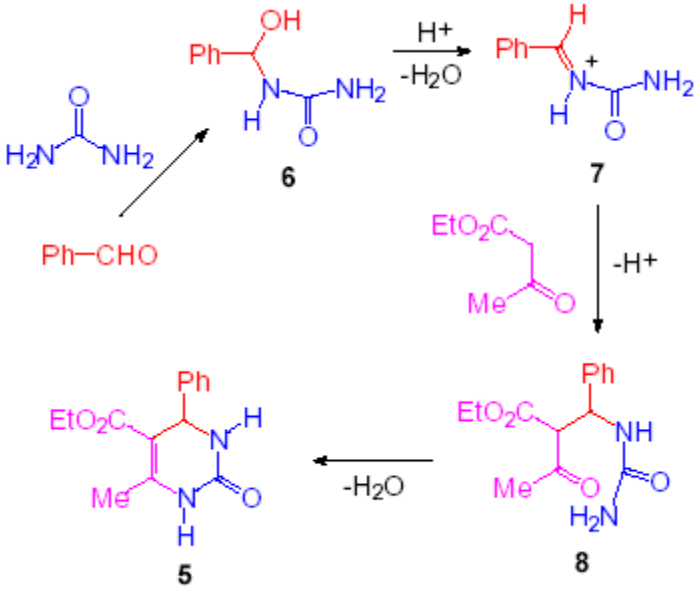
Biginelli Reaction



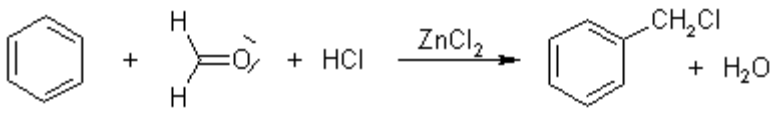
This acid-catalyzed, three-component reaction between an aldehyde, a ß-ketoester and urea constitutes a rapid and facile synthesis of dihydropyrimidones, which are interesting compounds with a potential for pharmaceutical application.

Mechanism of the Biginelli Reaction

The first step in the mechanism is believed to be the condensation between the aldehyde and urea, with some similarities to the Mannich Condensation. The iminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product.



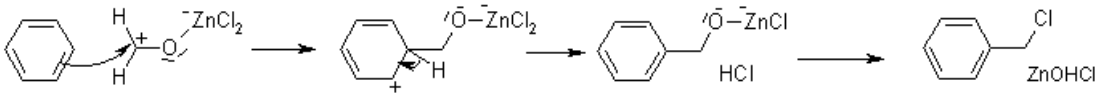
Blanc Reaction



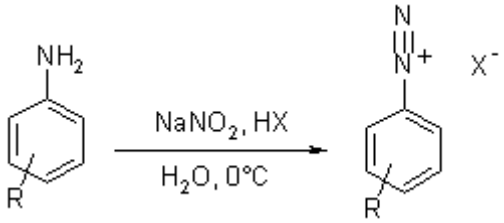
This reaction, which is comparable to a Friedel-Crafts Alkylation, is useful for the preparation of chloromethylated arenes (for example, the Merrifield resin based on polystyrene) from the parent arene with formaldehyde, HCl, and $ZnCl_2$.

Mechanism of the Blanc Reaction

The Lewis acid $ZnCl_2$ effects formation of an oxonium ion which is reactive in electrophilic aromatic substitution. The intermediate zinc alkoxide reacts with the arene to form the chloromethylated product.



Diazotization

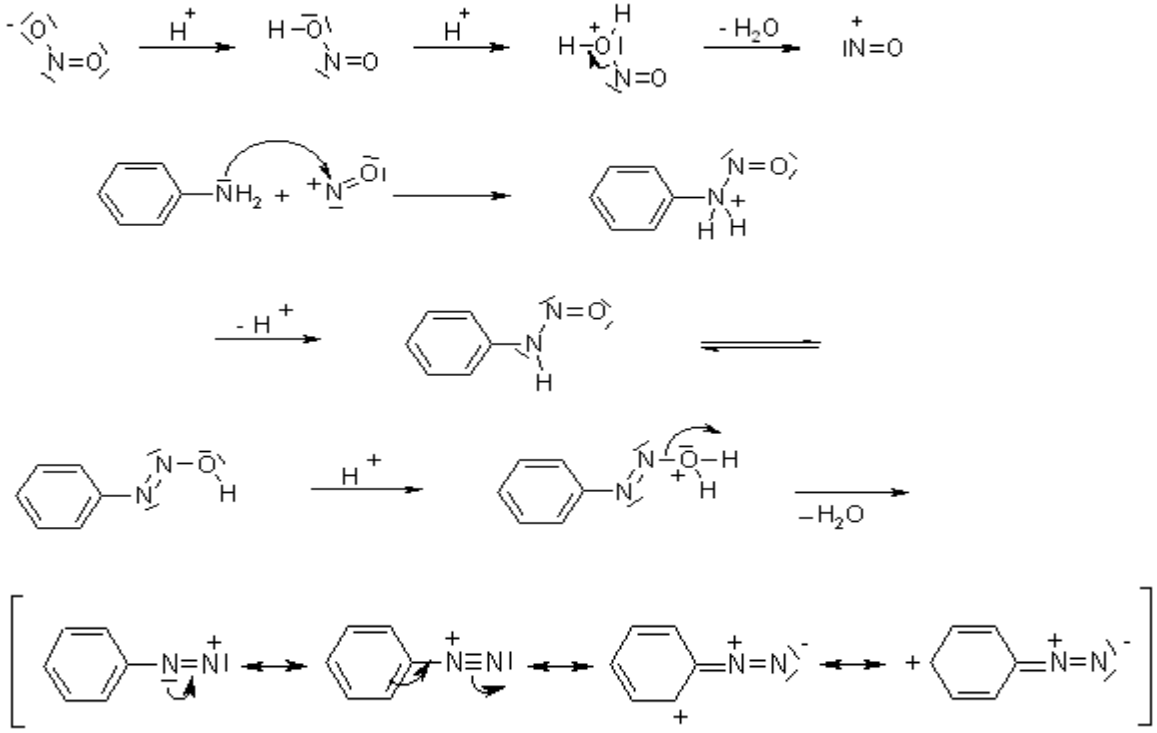


The nitrosation of primary aromatic amines with nitrous acid (generated in situ from sodium nitrite and a strong acid, such as hydrochloric acid, sulfuric acid, or HBF_4) leads to diazonium salts, which can be isolated if the counterion is non-nucleophilic.

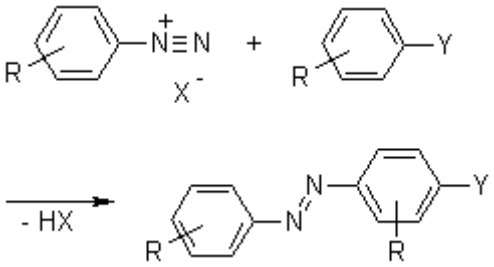
Diazonium salts are important intermediates for the preparation of halides (Sandmeyer Reaction, Schiemann Reaction), and azo compounds. Diazonium salts can react as pseudohalide-type electrophiles, and can therefore be used in specific protocols for the Heck Reaction or Suzuki Coupling.

The intermediates resulting from the diazotization of primary, aliphatic amines are unstable; they are rapidly converted into carbocations after loss of nitrogen, and yield products derived from substitution, elimination or rearrangement processes.

Mechanism of Diazotisation

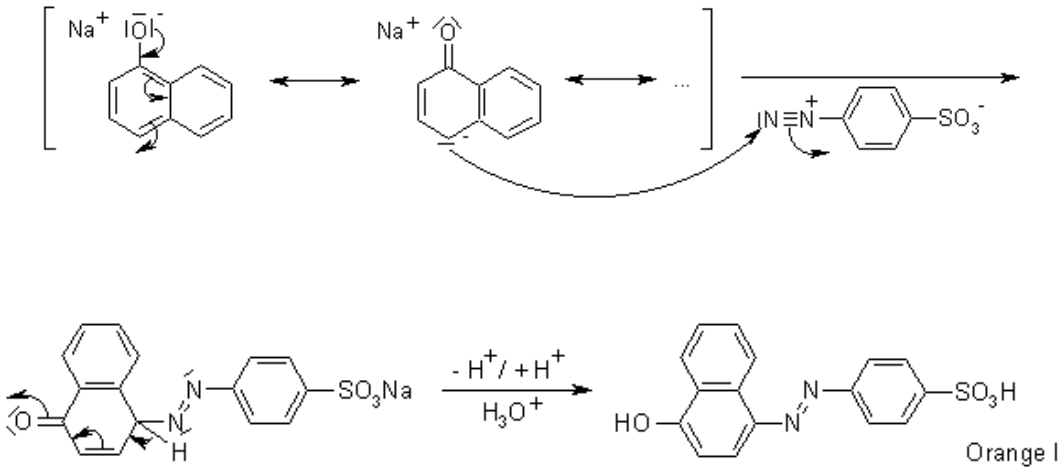


Azo Coupling

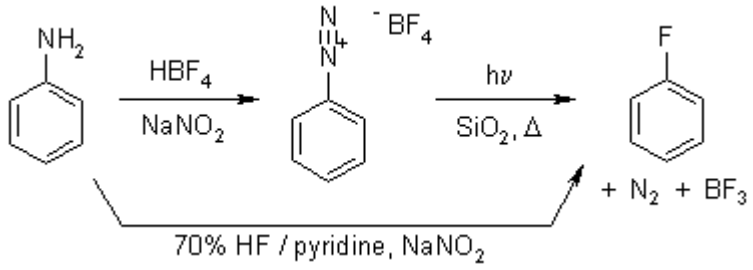


Azo coupling is the most widely used industrial reaction in the production of dyes, lakes and pigments. Aromatic diazonium ions act as electrophiles in coupling reactions with activated aromatics such as anilines or phenols. The substitution normally occurs at the para position, except when this position is already occupied, in which case *ortho* position is favoured. The pH of solution is quite important; it must be mildly acidic or neutral, since no reaction takes place if the pH is too low

Mechanism of Azo Coupling



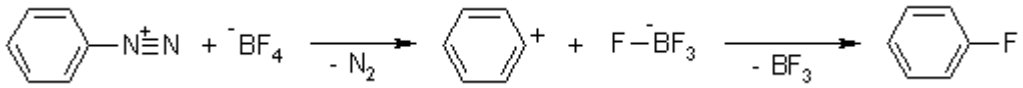
Balz-Schiemann Reaction



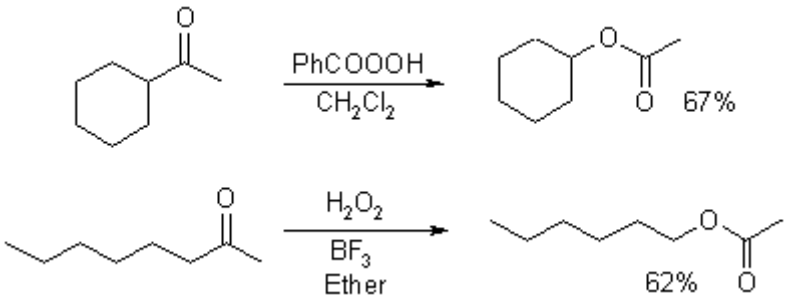
The conversion of aryl amines to aryl fluorides via diazotisation and subsequent thermal decomposition of the derived tetrafluoroborates or hexafluorophosphates. The decomposition may also be induced photochemically.

Mechanism of the Balz-Schiemann Reaction

The mechanism of the Balz-Schiemann reaction remains obscure. A possible pathway is shown below:



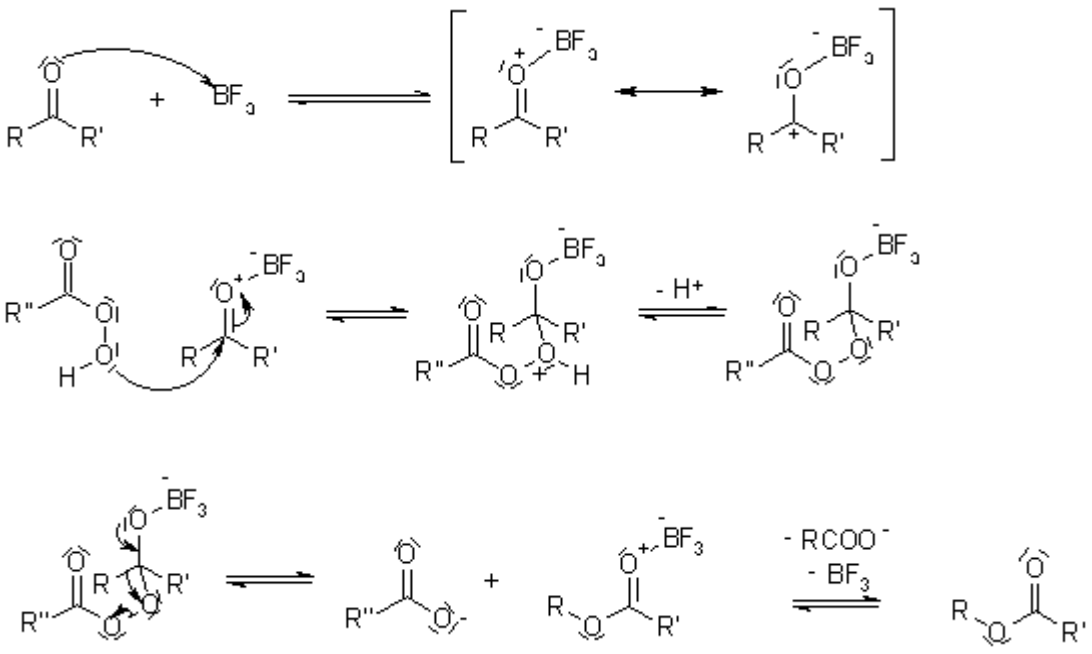
Baeyer-Villiger Oxidation



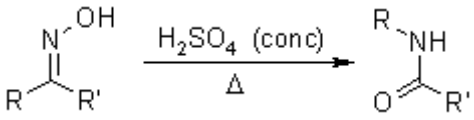
The Baeyer-Villiger Oxidation is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl, which converts ketones to esters and cyclic ketones to lactones. The Baeyer-Villiger can be carried out with peracids, such as MCBPA, or with hydrogen peroxide and a Lewis acid.

The regiospecificity of the reaction depends on the relative migratory ability of the substituents attached to the carbonyl. Substituents which are able to stabilize a positive charge migrate more readily, so that the order of preference is: *tert*. alkyl > cyclohexyl > sec. alkyl > phenyl > prim. alkyl > CH_3. In some cases, stereoelectronic or ring strain factors also affect the regio chemical outcome.

Mechanism of the Baeyer-Villiger Oxidation



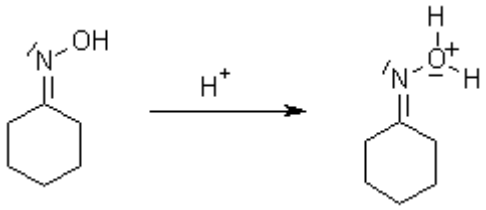
Beckmann Rearrangement



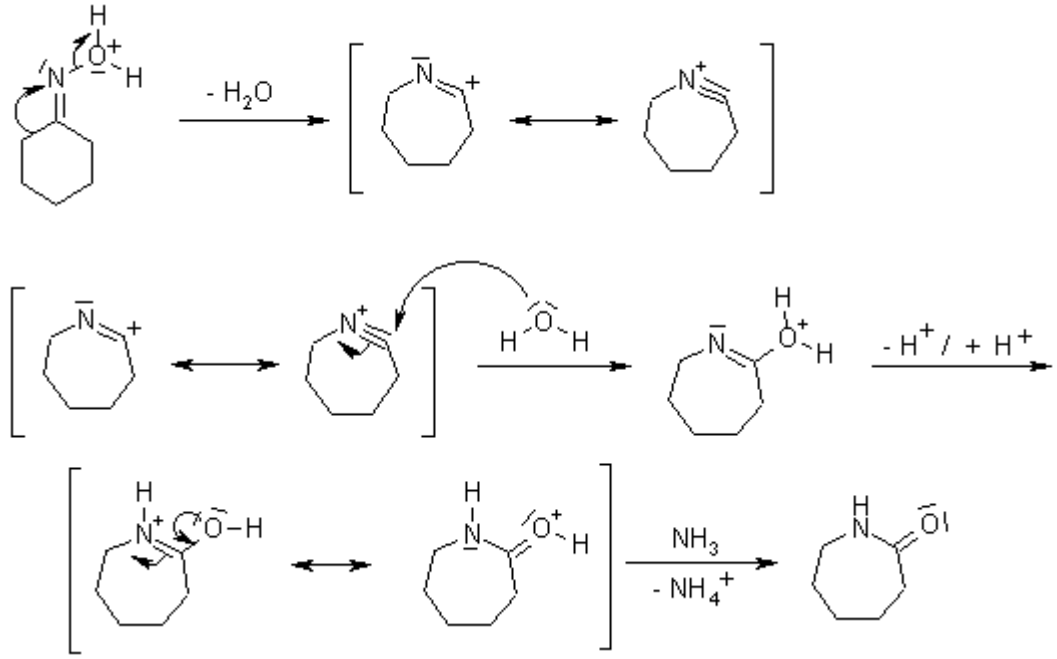
An acid-induced rearrangement of oximes to give amides.

This reaction is related to the Hofmann and Schmidt Reactions and theCurtius Rearrangement, in that an electropositive nitrogen is formed that initiates an alkyl migration.

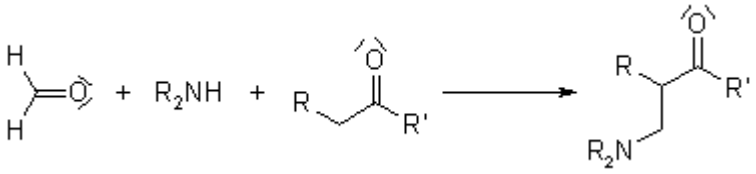
Mechanism of the Beckmann Rearrangement



Oximes generally have a high barrier to inversion, and accordingly this reaction is envisioned to proceed by protonation of the oxime hydroxyl, followed by migration of the alkyl substituent "*trans*" to nitrogen. The N-O bond is simultaneously cleaved with the expulsion of water, so that formation of a free nitrene is avoided.



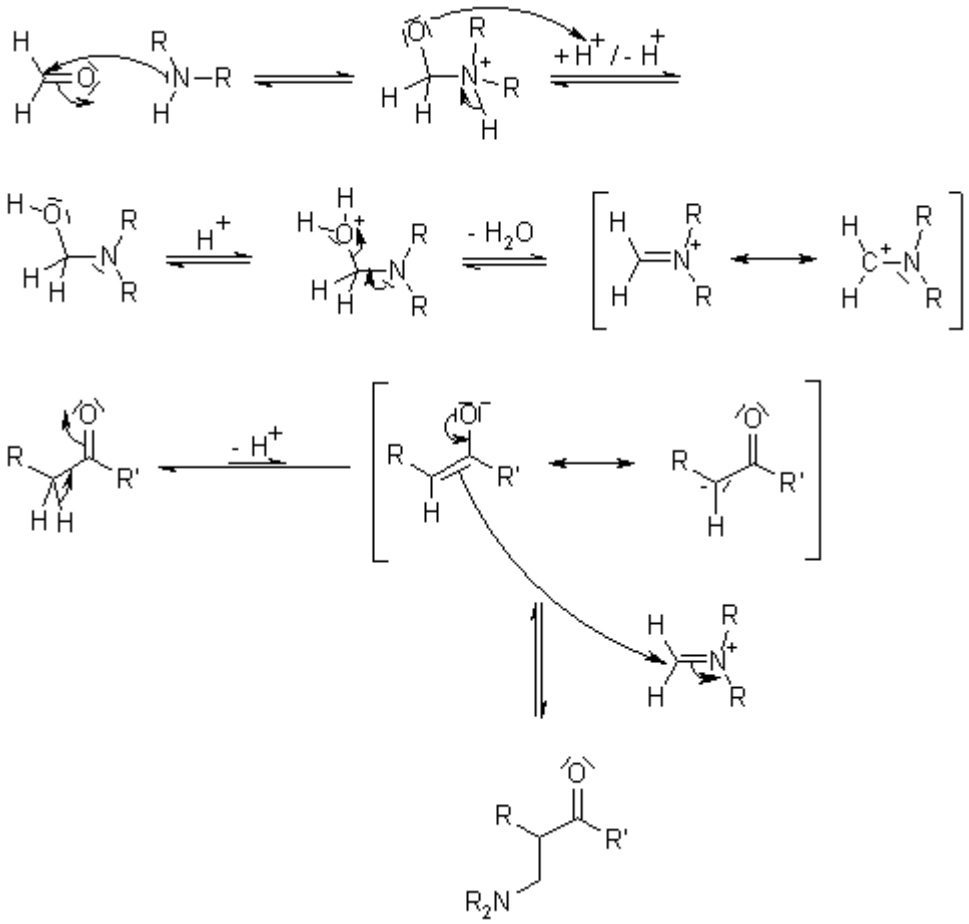
Mannich Reaction



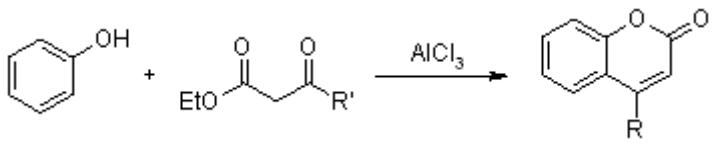
This multi-component condensation of a nonenolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminomethylated products. The iminium derivative of the aldehyde is the acceptor in the reaction.

The involvement of the Mannich Reaction has been proposed in many biosynthetic pathways, especially for alkaloids

Mechanism of the Mannich Reaction



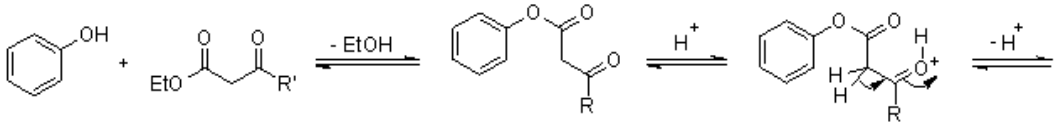
Pechmann Condensation
Coumarin Synthesis



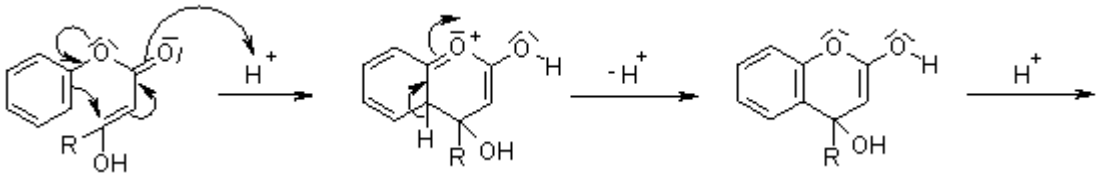
The Pechmann condensation allows the synthesis of coumarin by reaction of phenols with β-keto ester

Mechanism of the Pechmann Condensation

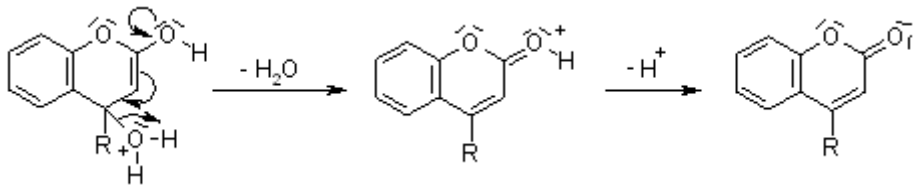
The reaction is conducted with a strong Brønstedt acid such as methanesulfonic acid or a Lewis acid such as $AlCl_3$. The acid catalyses transesterification as well as keto-enol tautomerization.



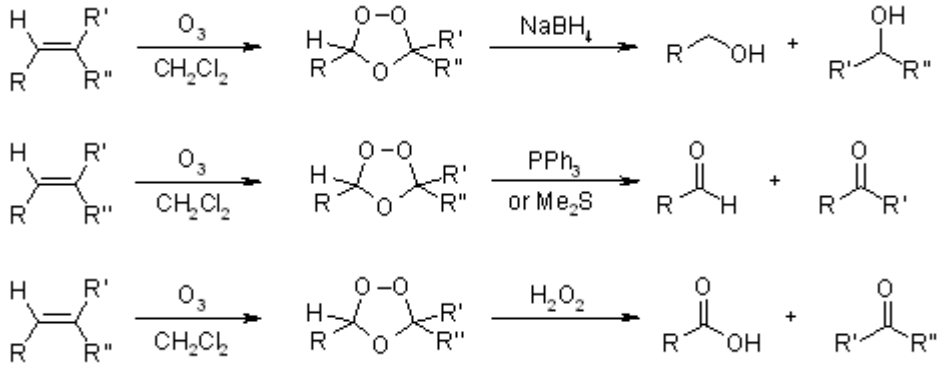
A Michael Addition leads to the formation of the coumarin skeleton. This addition is followed by rearomatisation:



Subsequent acid-induced elimination of water gives the product:



Ozonolysis
Criegee Mechanism

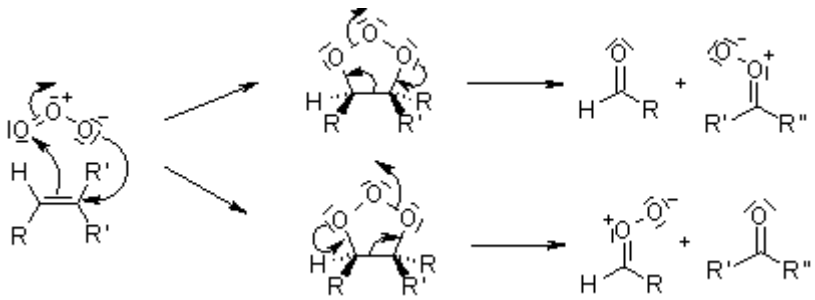


Ozonolysis allows the cleavage of alkene double bonds by reaction with ozone. Depending on the work up, different products may be isolated: reductive work-up gives either alcohols or carbonyl compounds, while oxidative work-up leads to carboxylic acids or ketones.

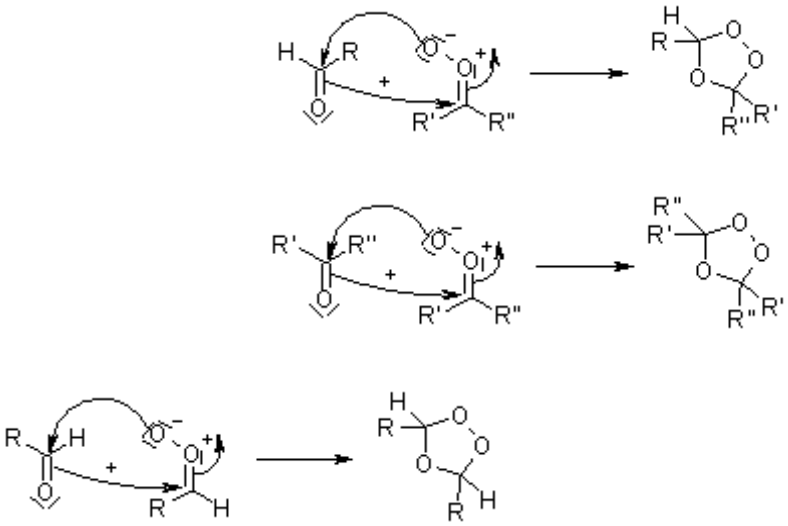
Mechanism of Ozonolysis

The mechanism was suggested by Criegee and has been recently revisited using ^{17}O-NMR Spectroscopy by the Berger Group

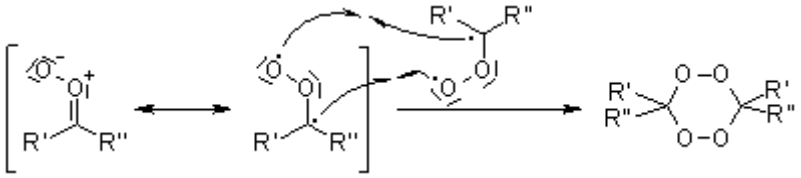
First step is a 1,3-dipolar cycloaddition of ozone to the alkene leading to the primary ozonide (molozonide, 1,2,3-trioxolane, or Criegee intermediate) which decomposes to give a carbonyl oxide and a carbonyl compound:



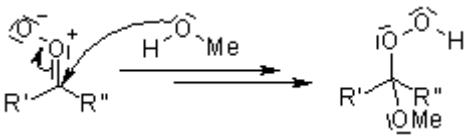
The carbonyl oxides are similar to ozone in being 1,3-dipolar compounds, and undergo 1,3-dipolar cycloaddition to the carbonyl compounds with the reverse regiochemistry, leading to a mixture of three possible secondary ozonides (1,2,4-trioxolanes):



These secondary ozonides are more stable than primary ozonides. Even if the peroxy bridge is shielded by steric demanding groups leading to isolable products, they should not be isolated from an unmodified ozonolysis, because still more explosive side products (tetroxanes) may have been formed:

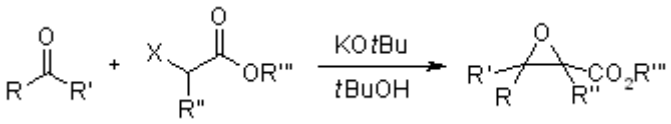


As endoperoxides are investigated as antimalarial compounds, more selective methods have been developed for their preparation (for example the Griesbaum Coozonolysis). Some reactions can be found here: The Criegee mechanism is valid for reactions in hydrocarbons, CH_2Cl_2, or other non-interactive solvents. Alcohols react with the carbonyl oxide to give hydroperoxy hemiacetals:



The synthetic value lies in the way the complex mixtures of intermediates can be worked up to give a defined composition of products and a clean conversion of all peroxide species. The three main possibilities are given above, along with examples for the reagents used.

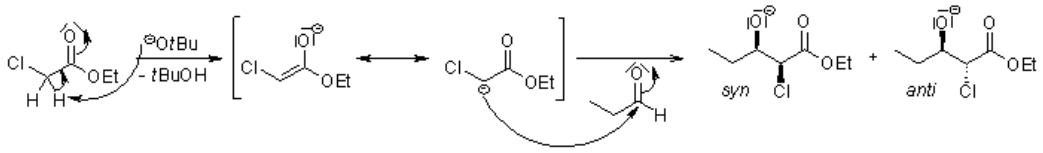
Darzens Reaction
Darzens Condensation



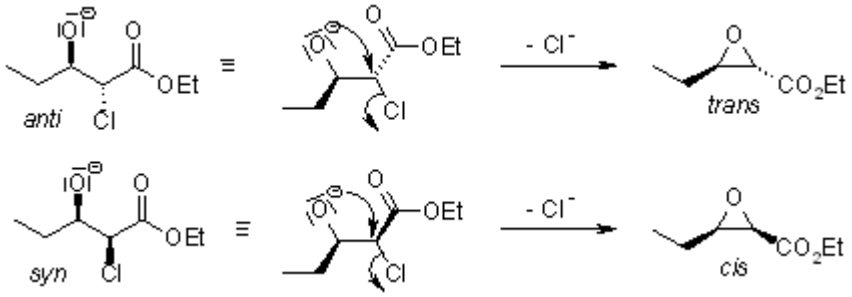
The Darzens Reaction is the condensation of a carbonyl compound with an α-halo ester in the presence of a base to form an α,β-epoxy ester.

Mechanism of the Darzens Reaction

After deprotonation, the α-halo ester adds to the carbonyl compound to give *syn* and *anti* diastereomers:

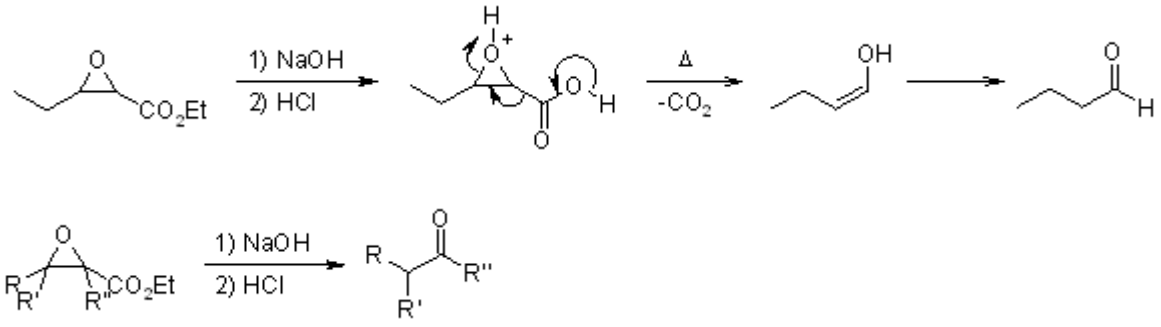


In the subsequent step, an intramolecular S_N2 reaction forms the epoxide:



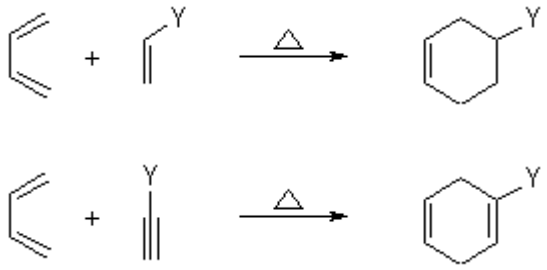
Typically, the *cis:trans* ratio of the epoxide formation lies between 1:1 and 1:2.

In the past, Darzens methodology was primarily used for the synthesis of aldehydes and ketones, as a homologation reaction without any consideration of stereocontrol in the epoxide formation. For this sequence, saponification of the α,β-epoxy ester followed by decarboxylation gives the substituted carbonyl compound:



Darzens methodology for the construction of epoxides can also be used for α-halo carbonyl compounds, or similar compounds that can undergo deprotonation and bear electron-withdrawing groups. In addition, the reaction can be carried out with diazoacetate, where N_2 is the leaving group, or with a sulphur ylide with SR_2 as the leaving group

Diels-Alder Reaction



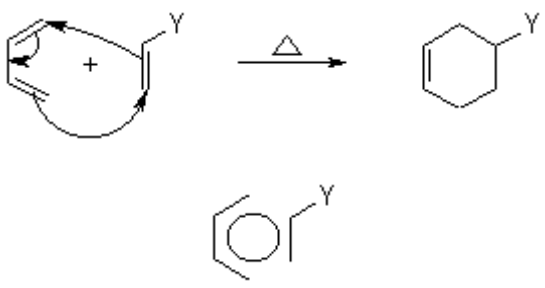
The [4+2]-cycloaddition of a conjugated diene and a dienophile (an alkene or alkyne), an electrocyclic reaction that involves the 4 π-electrons of the diene and 2 π-electrons of the dienophile. The driving force of the reaction is the formation of new σ-bonds, which are energetically more stable than the π-bonds.

In the case of an alkynyl dienophile, the initial adduct can still react as a dienophile if not too sterically hindered. In addition, either the diene or the dienophile can be substituted with cumulated double bonds, such as substituted allenes.

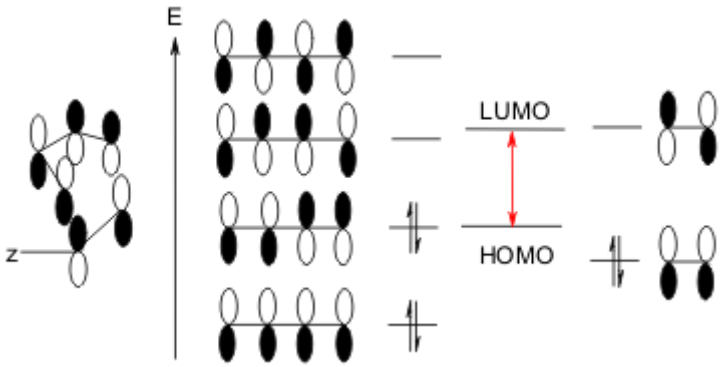
With its broad scope and simplicity of operation, the Diels-Alder is the most powerful synthetic method for unsaturated six-membered rings.

A variant is the hetero-Diels-Alder, in which either the diene or the dienophile contains a heteroatom, most often nitrogen or oxygen. This alternative constitutes a powerful synthesis of six-membered ring heterocycles

Mechanism of the Diels-Alder Reaction

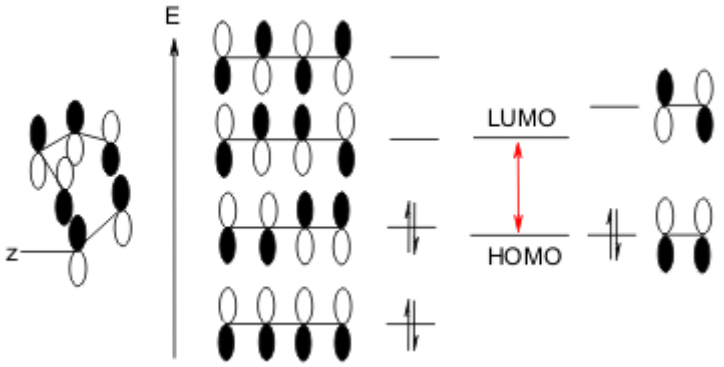


Overlap of the molecular orbitals (MOs) is required:

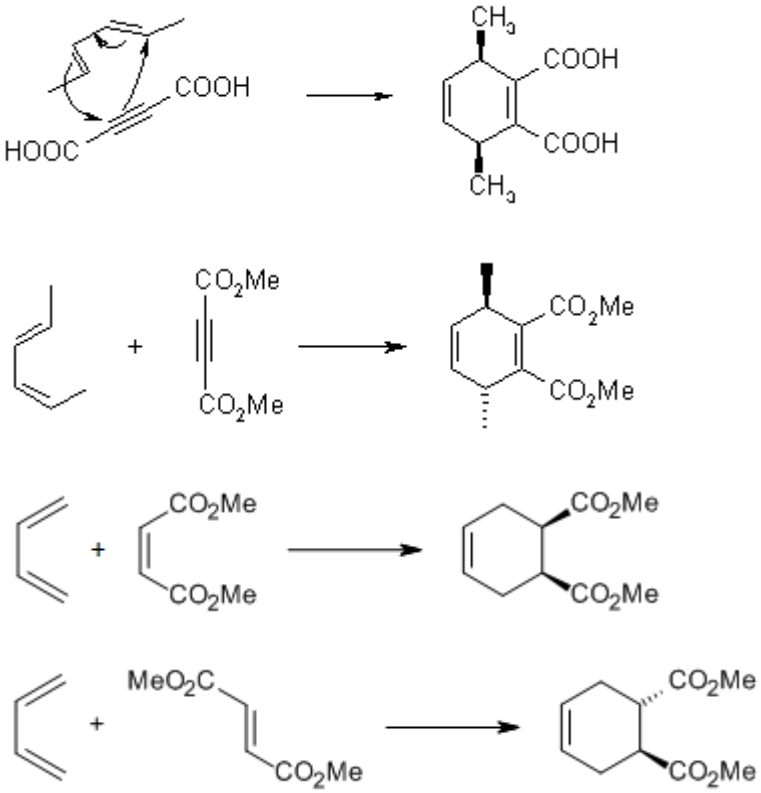


Overlap between the highest occupied MO of the diene (HOMO) and the lowest unoccupied MO of the dienophile (LUMO) is thermally allowed in the Diels Alder Reaction, provided the orbitals are of similar energy. The reaction is facilitated by electron-withdrawing groups on the dienophile, since this will lower the energy of the LUMO. Good dienophiles often bear one or two of the following substituents: CHO, COR, COOR, CN, C=C, Ph, or halogen. The diene component should be as electron-rich as possible.

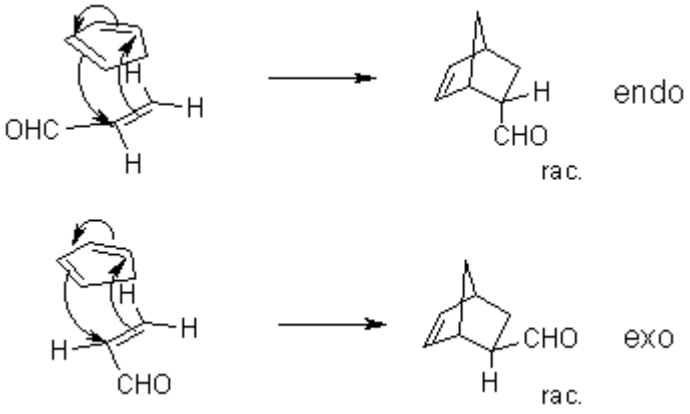
There are “inverse demand” Diels Alder Reactions that involve the overlap of the HOMO of the dienophile with the unoccupied MO of the diene. This alternative scenario for the reaction is favored by electron-donating groups on the dienophile and an electron-poor diene.



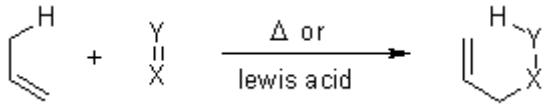
The reaction is diastereoselective.



Cyclic dienes give stereoisomeric products. The endo product is usually favored by kinetic control due to secondary orbital interactions.



Alder-Ene Reaction
Ene Reaction

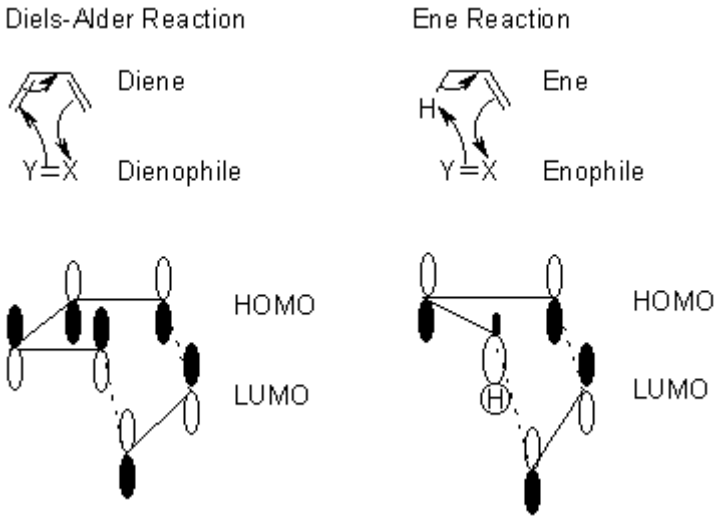


The four-electron system including an alkene π-bond and an allylic C-H σ-bond can participate in a pericyclic reaction in which the double bond shifts and new C-H and C-C σ-bonds are formed. This allylic system reacts similarly to a diene in a Diels-Alder Reaction, while in this case the other partner is called an enophile, analogous to the dienophile in the Diels-Alder. The Alder-Ene Reaction requires higher temperatures because of the higher activation energy and stereoelectronic requirement of breaking the allylic C-H σ-bond.

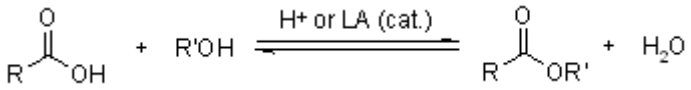
The enophile can also be an aldehyde, ketone or imine, in which case β-hydroxy- or β-aminoolefins are obtained. These compounds may be unstable under the reaction conditions, so that at elevated temperature (>400°C) the reverse reaction takes place - the Retro-Ene Reaction.

While mechanistically different, the Ene reaction can produce a result similar to the Prins Reaction.

Mechanism of the Alder-Ene Reaction



Fischer Esterification
Fischer-Speier Esterification

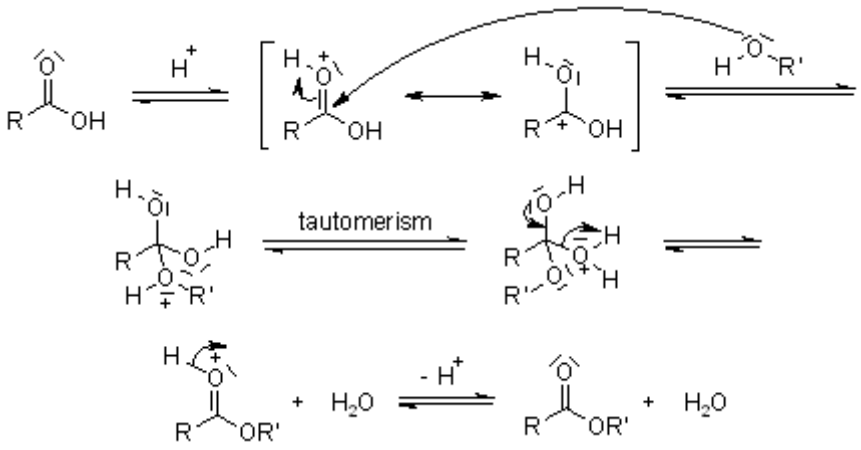


The Lewis or Brønstedt acid-catalyzed esterification of carboxylic acids with alcohols to give esters is a typical reaction in which the products and reactants are in equilibrium.

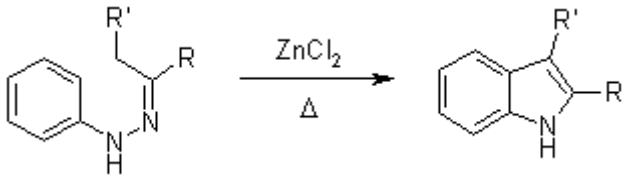
The equilibrium may be influenced by either removing one product from the reaction mixture (for example, removal of the water by azeotropic distillation or absorption by molecular sieves) or by employing an excess of one reactant.

Mechanism of the Fischer Esterification

Addition of a proton (e.g.: *p*-TsOH, H_2SO_4) or a Lewis acid leads to a more reactive electrophile. Nucleophilic attack of the alcohol gives a tetrahedral intermediate in which there are two equivalent hydroxyl groups. One of these hydroxyl groups is eliminated after a proton shift (tautomerism) to give water and the ester.

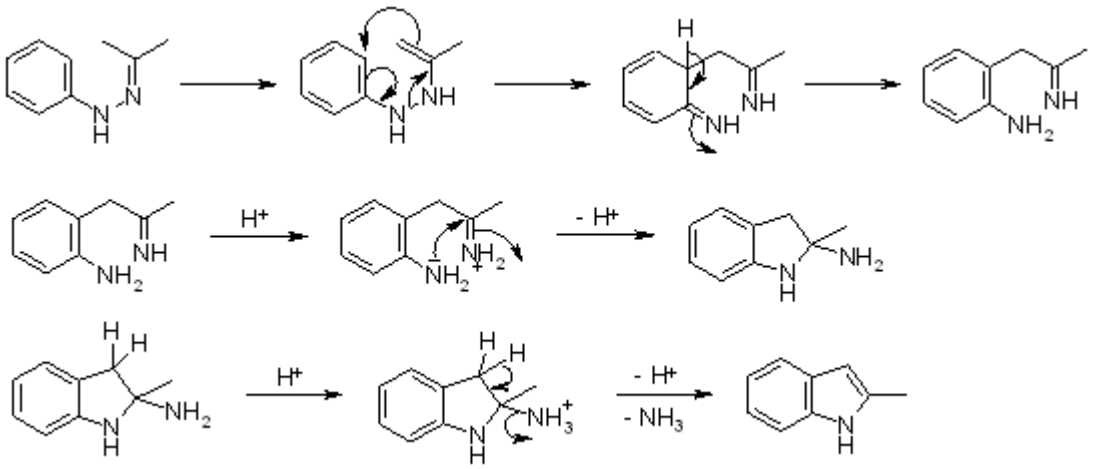


Fischer Indole Synthesis

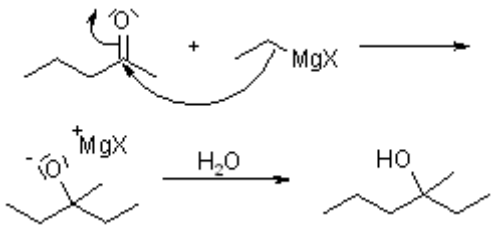


The conversion of aryl hydrazones to indoles; requires elevated temperatures and the addition of Brønsted or Lewis acids. Some interesting enhancements have been published recently; for example a milder conversion when *N*-trifluoroacetyl enehydrazines are used as substrates.

Mechanism of the Fischer Indole Synthesis



Grignard Reaction
Grignard Reagents

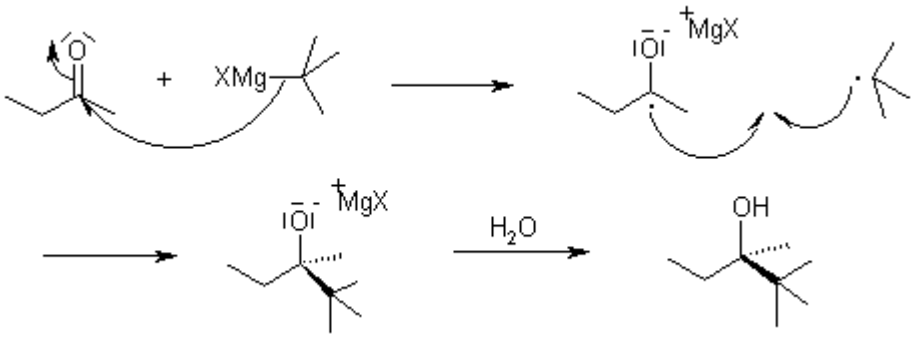


The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate.

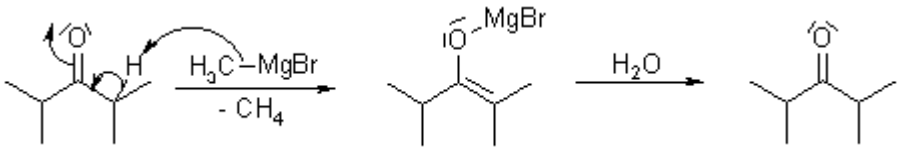
Mechanism of the Grignard Reaction

While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism:

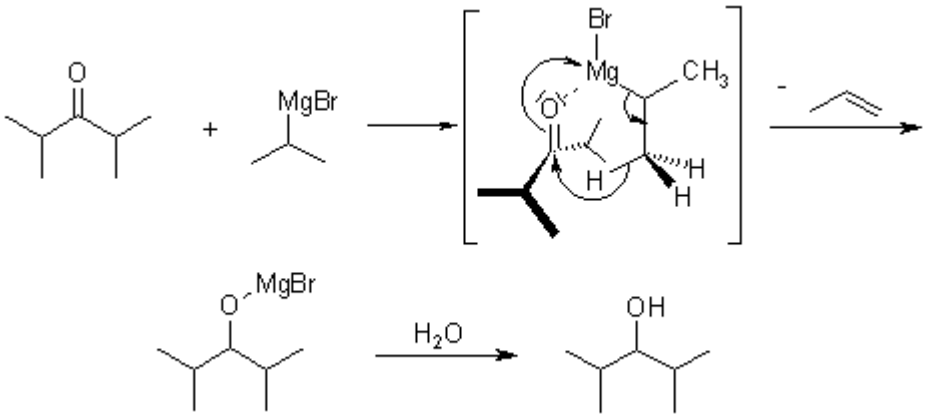


With sterically hindered ketones the following side products are received:

The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered.

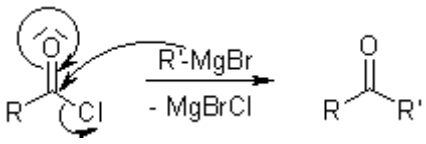


A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state.

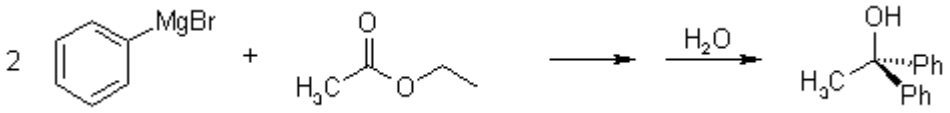


Additional reactions of Grignard Reagents:

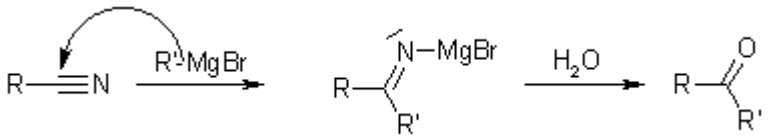
With carboxylic acid chlorides:



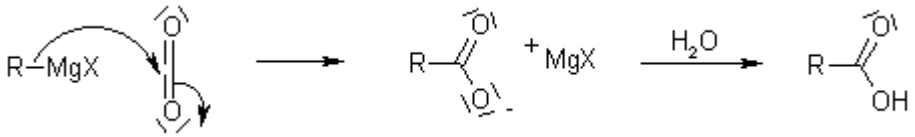
Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent:



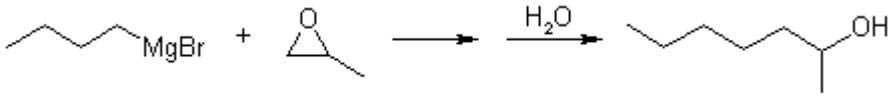
With nitriles:



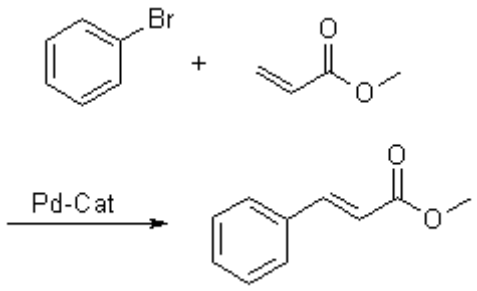
With CO_2 (by adding dry ice to the reaction mixture):



With oxiranes:

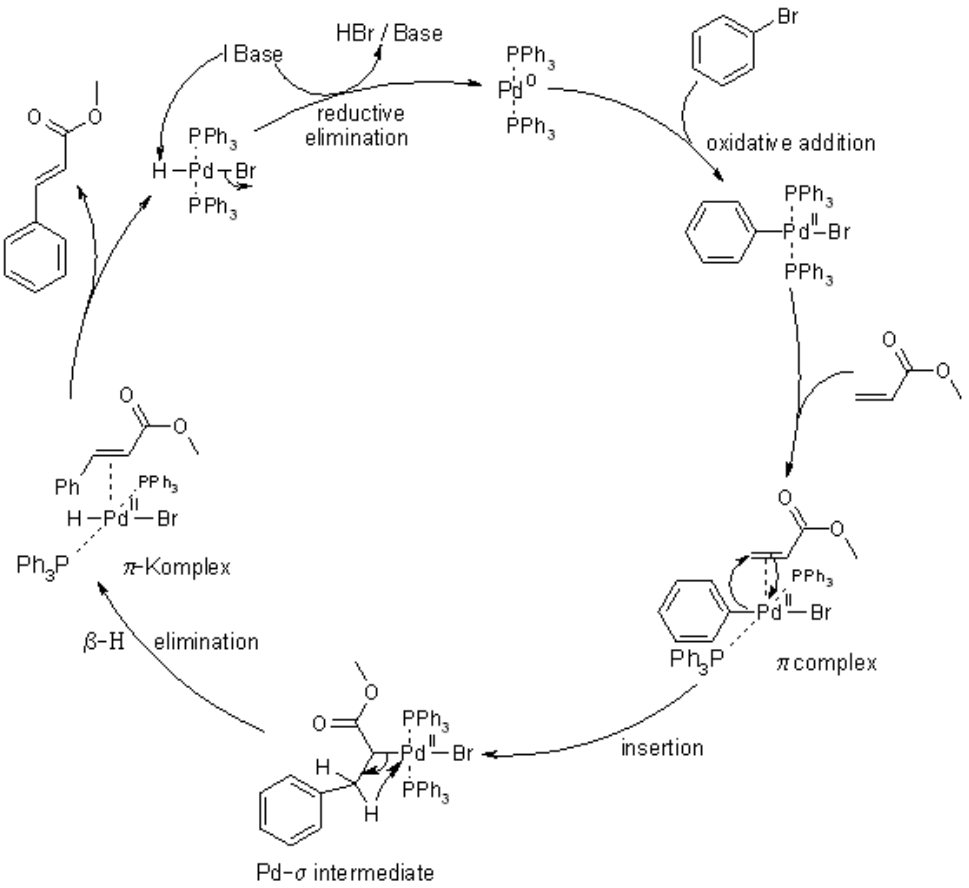


Heck Reaction

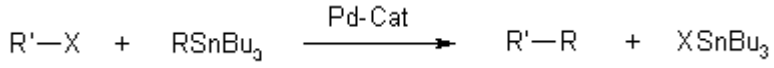


The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and activated alkenes in the presence of a base is referred as the "Heck Reaction". Recent developments in the catalysts and reaction conditions have resulted in a much broader range of donors and acceptors being amenable to the Heck Reaction.

Mechanism of the Heck Reaction

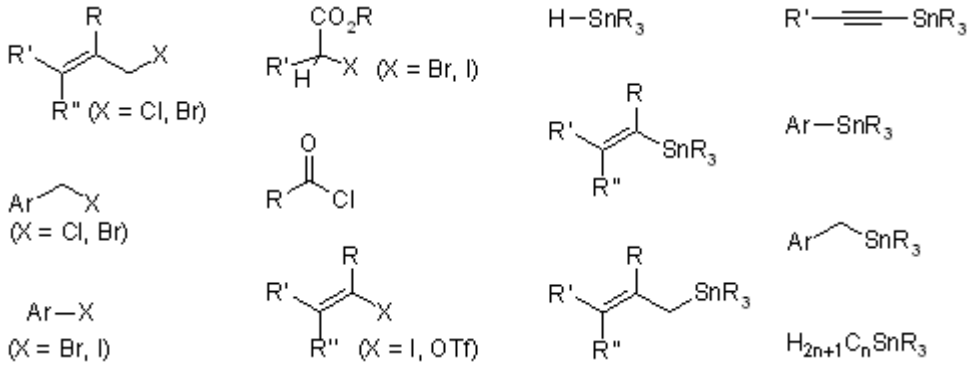


Stille Coupling

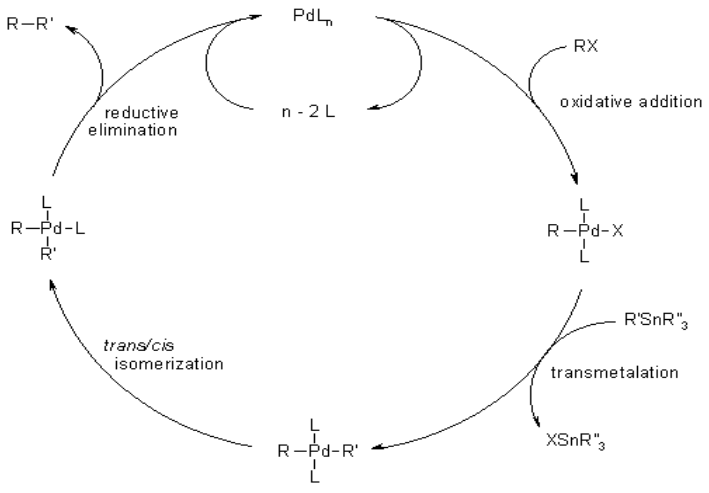


The Stille Coupling is a versatile C-C bond forming reaction between stannanes and halides or pseudohalides, with very few limitations on the R-groups. Well-elaborated methods allow the preparation of different products from all of the combinations of halides and stannanes depicted below. The main drawback is the toxicity of the tin compounds used, and their low polarity, which makes them poorly soluble in water. Stannanes are stable, but boronic acids and their derivatives undergo much the same chemistry in what is known as the Suzuki Coupling. Improvements in the Suzuki Coupling may soon lead to the same versatility without the drawbacks of using tin compounds.

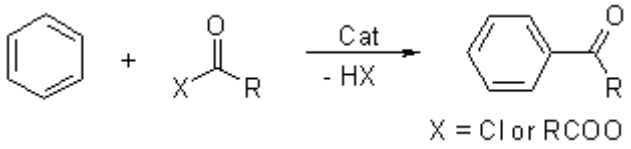
Convenient electrophiles and stannanes:



Mechanism of the Stille Coupling

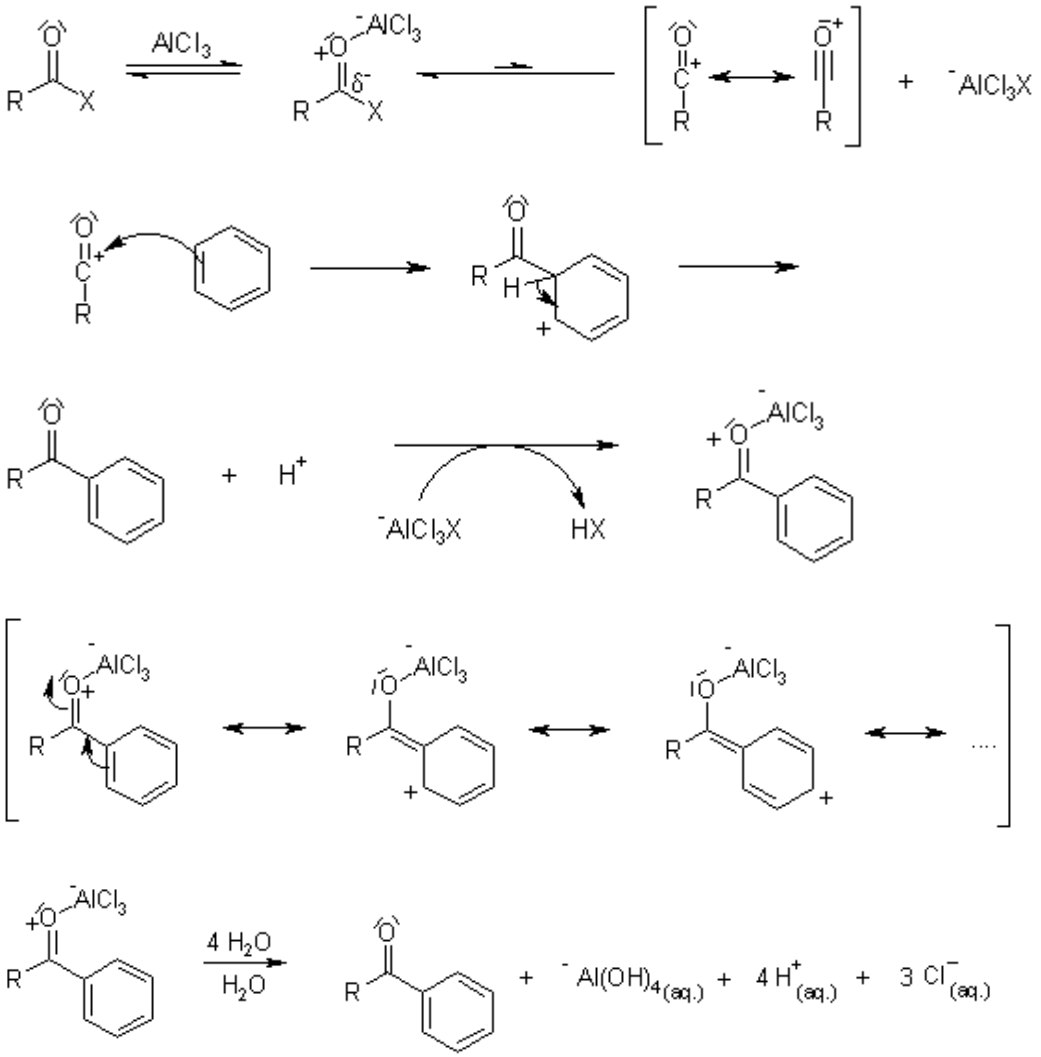


Friedel-Crafts Acylation

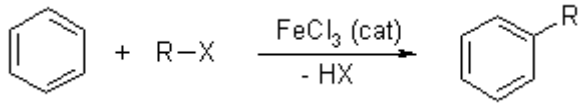


This electrophilic aromatic substitution allows the synthesis of monoacylated products from the reaction between arenes and acyl chlorides or anhydrides. The products are deactivated, and do not undergo a second substitution. Normally, a stoichiometric amount of the Lewis acid catalyst is required, because both the substrate and the product form complexes

Mechanism of Friedel-Crafts Acylation

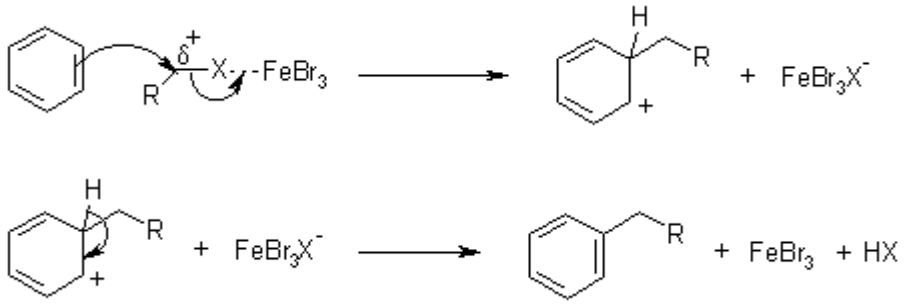


Friedel-Crafts Alkylation

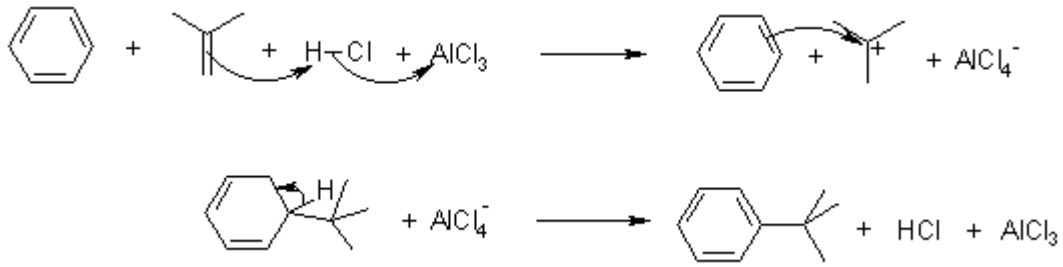


This Lewis acid-catalyzed electrophilic aromatic substitution allows the synthesis of alkylated products via the reaction of arenes with alkyl halides or alkenes. Since alkyl substituents activate the arene substrate, polyalkylation may occur. A valuable, two-step alternative is Friedel-Crafts Acylation followed by a carbonyl reduction.

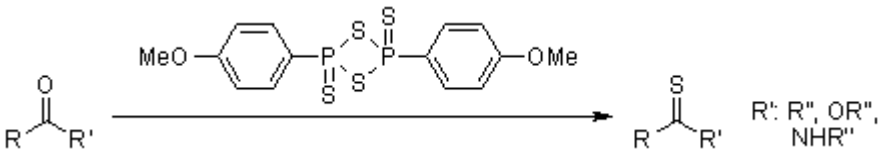
Mechanism of the Friedel-Crafts Alkylation



Using alkenes:



Lawesson's Reagent

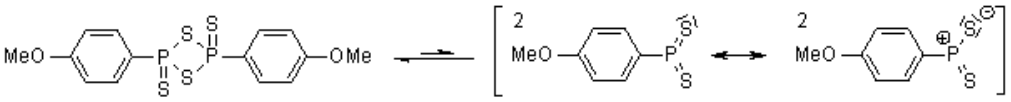


Lawesson's Reagent is a mild and convenient thionating agent for ketones, esters, and amides that allows the preparation of thioketones, thioesters and thioamides in good yields.

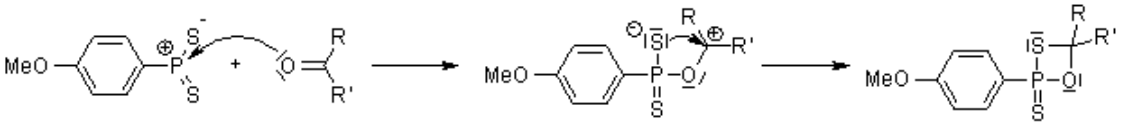
Reactions using the comparable reagent P_4S_{10} normally need higher temperatures and a large excess of the thionating agent.

Mechanism

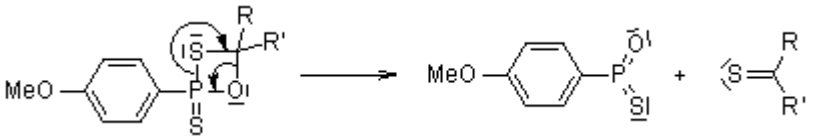
Lawesson's Reagent in solution is in equilibrium with a more reactive dithiophosphine ylide:



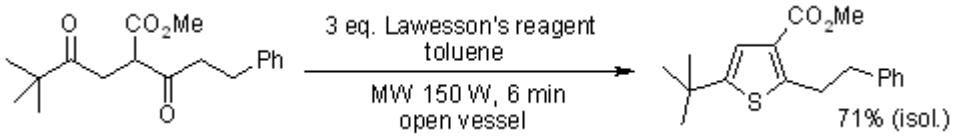
The reaction with a carbonyl gives rise to a thiaoxaphosphetane intermediate:



The driving force is the formation of a stable P=O bond in a cycloreversion step that resembles a portion of the mechanism known for theWittig Reaction:



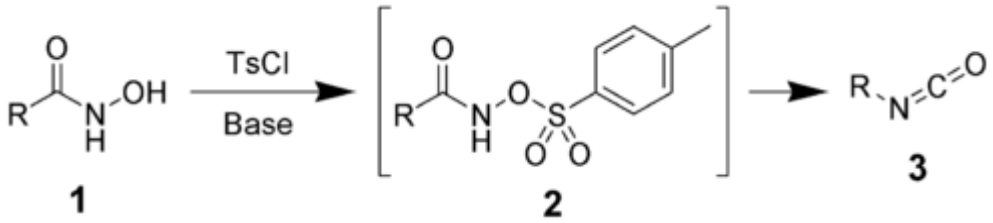
Reactions of ketones, amides, lactams and lactones are normally faster than reactions of esters. Esters are unreactive depending on the reaction conditions, which allows selective transformations:



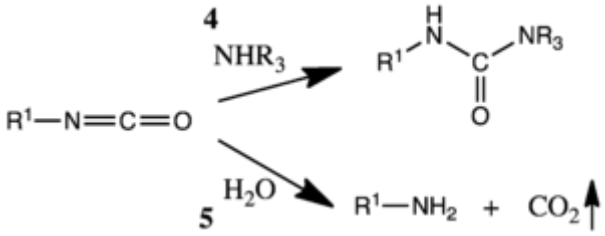
More detailed information can be found in a recent review by Jesberger,

Lossen rearrangement

It is the conversion of a hydroxamic acid (**1**) to anisocyanate (**3**) via the formation of an O-acyl, sulfonyl, or phosphoryl intermediate hydroxamic acid O-derivative (**2**) and then conversion to its conjugate base. Here,4-toluenesulfonyl chloride is used to form a sulfonyl Ortho-derivative of hydroxamic acid



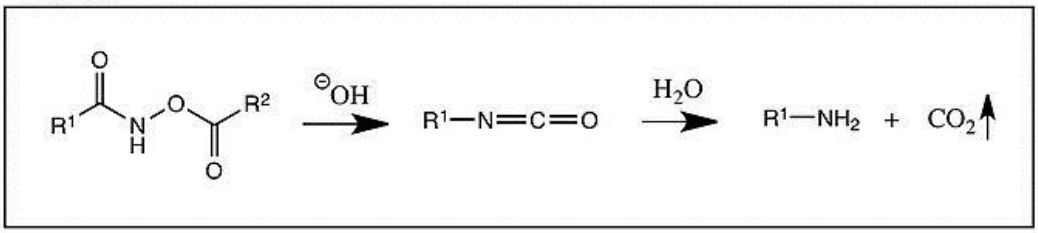
The isocyanate can be used further to generate ureas in the presence of amines (**4**) or generate amines in the presence of H_2O (**5**).



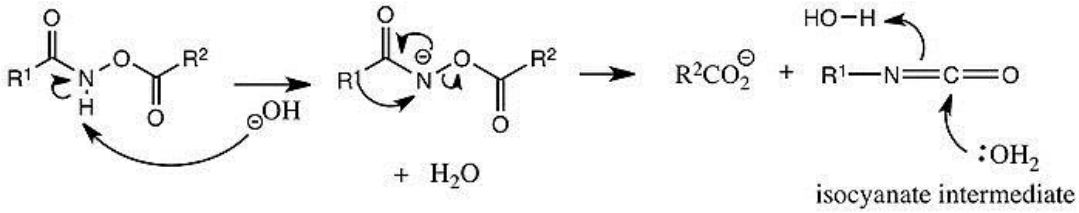
Reaction mechanism for Lossen rearrangement

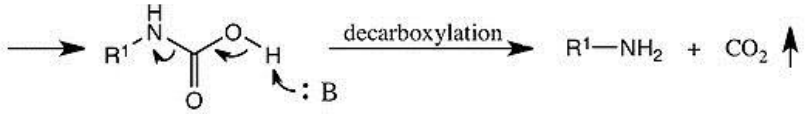
The mechanism below begins with an O-acylated hydroxamic acid derivative that is treated with base to form an isocyanate that generates an amine and CO_2 gas in the presence of H_2O. The hydroxamic acid acid derivative is first converted to its conjugate base by abstraction of a hydrogen by a base. Spontaneous rearrangement kicks off a carboxylate anion to produce the isocyanate intermediate. The isocyanate in the presence H_2O hydrolyzes and then decarboxylation via abstraction of a hydrogen by a base generates an amine and CO_2 gas.

Overall:

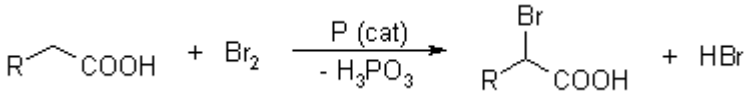


Mechanism:





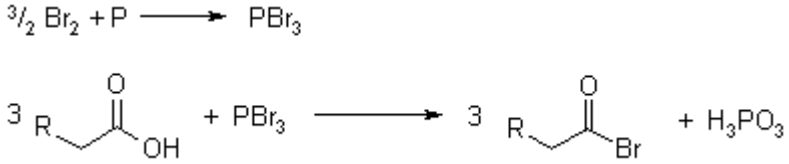
Hell-Volhard-Zelinsky Reaction



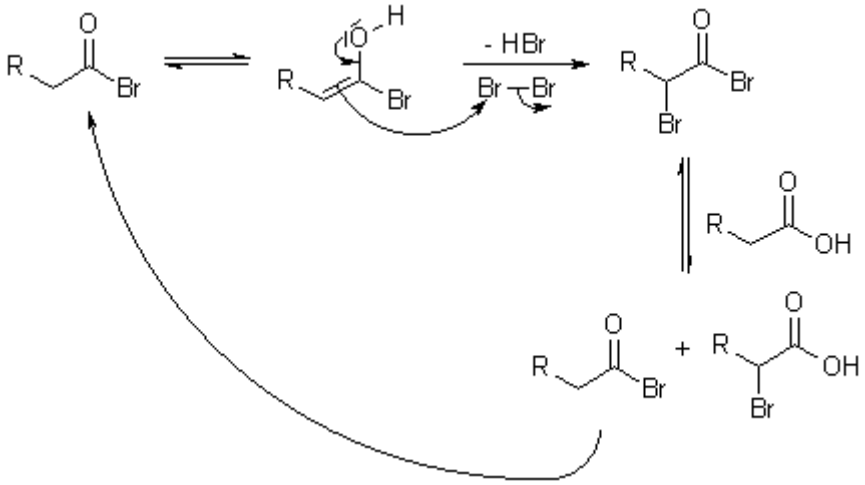
Treatment with bromine and a catalytic amount of phosphorus leads to the selective α-bromination of carboxylic acids

Mechanism of the Hell-Volhard-Zelinsky Reaction

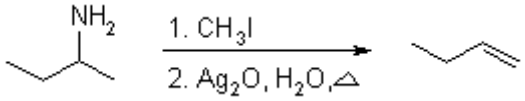
Phosphorus reacts with bromine to give phosphorus tribromide, and in thefirst step this converts the carboxylic acid into an acyl bromide.



An acyl bromide can readily exist in the enol form, and this tautomer is rapidly brominated at the α-carbon. The monobrominated compound is much less nucleophilic, so the reaction stops at this stage. This acyl intermediate compound can undergo bromide exchange with unreacted carboxylic acid via the anhydride, which allows the catalytic cycle to continue until the conversion is complete.

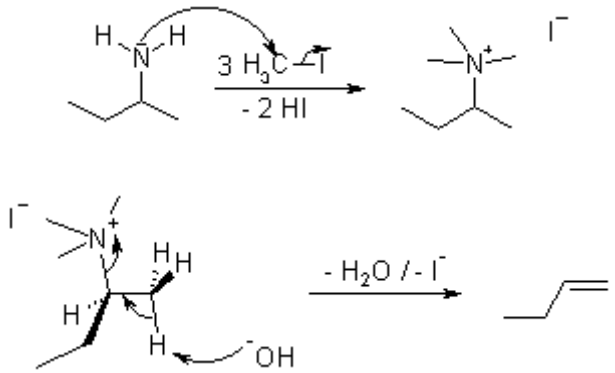


Hofmann Elimination

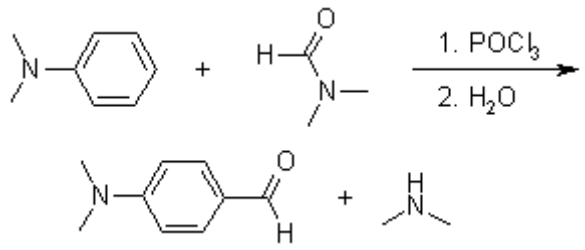


This is an elimination reaction of alkyl trimethyl amines proceeds with *anti*-stereochemistry, and is generally suitable for producing alkenes with one or two substituents. The reaction follows the Hofmann Rule

Mechanism of the Hofmann Elimination



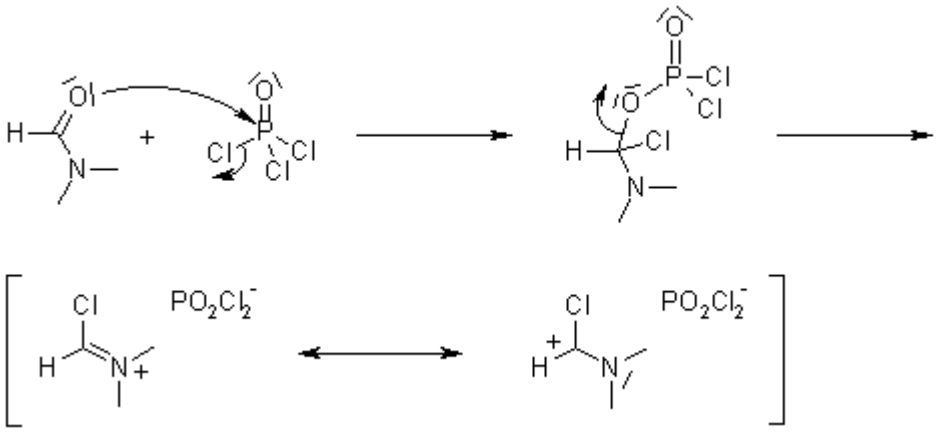
Vilsmeier-Haack Reaction



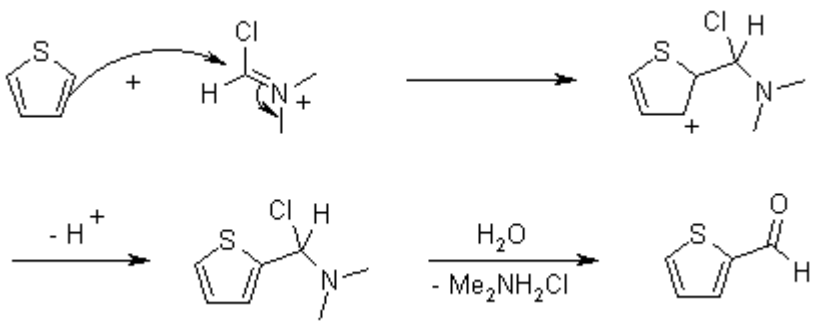
The Vilsmeier Reaction allows the formylation of electron-rich arenes.

Mechanism of the Vilsmeier-Haak Reaction

The formylating agent, also known as the Vilsmeyer-Haack Reagent, is formed *in situ* from DMF and phosphorus oxychlorid:

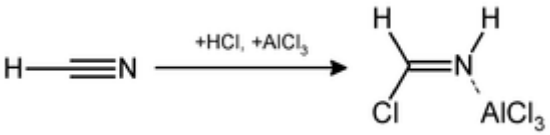


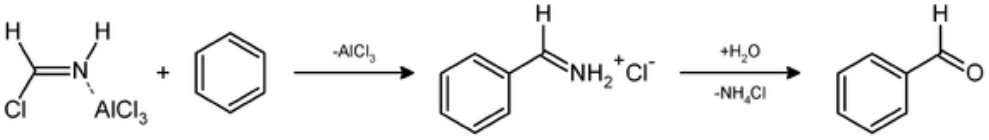
An electrophilic aromatic substitution leads to α-chloro amines, which are rapidly hydrolyzed during work up to give the aldehyde:



Gattermann reaction

The Gattermann reaction is a chemical reaction in which aromatic compounds are formylated by hydrogen cyanide in the presence of a Friedel–Crafts catalyst (e.g. $AlCl_3$). It is named for the German chemist Ludwig Gattermann and is similar to the Friedel-Crafts reaction.

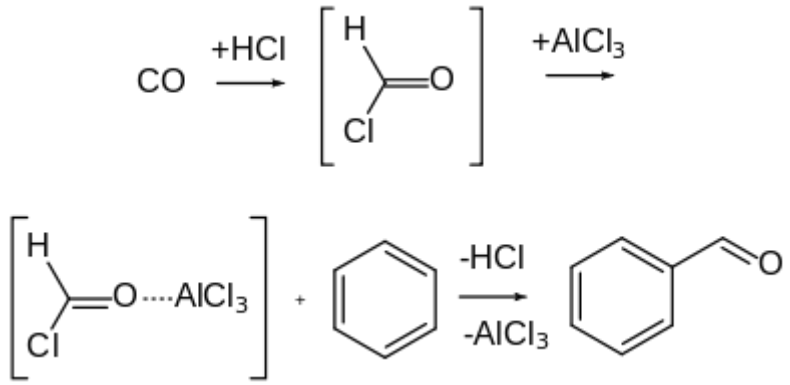




The reaction can be simplified by replacing the $HCN/AlCl_3$ combination with zinc cyanide. Although it is also highly toxic, $Zn(CN)_2$ is a solid, making it safer to work with than gaseous HCN; additionally, because the reaction uses HCl, $Zn(CN)_2$also supplies the reaction with $ZnCl_2$ *in-situ*, where it acts as a Lewis acid catalyst. Examples of $Zn(CN)_2$ being used in this way include the synthesis of 2-Hydroxy-1-nafthaldehyde[2] and Mesitaldehyde.

Gattermann–Koch reaction

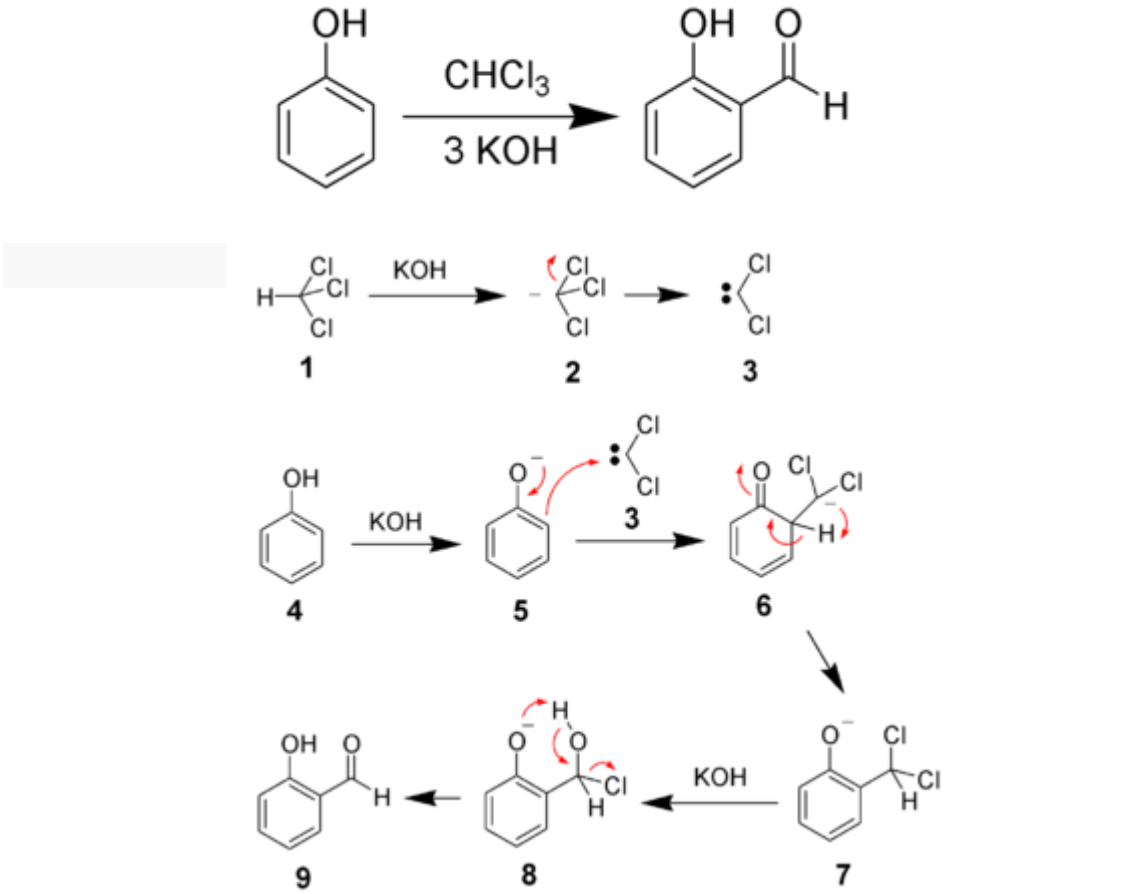
The Gattermann–Koch reaction, named after the German chemists Ludwig Gattermann and Julius Arnold Koch,refers to a Friedel–Crafts acylation reaction in which carbon monoxide, hydrochloric acid, and a Friedel–Crafts catalyst (e.g. $AlCl_3$) are used to produce aromatic aldehydes from various aromatic compounds, including derivatives of benzene and naphthalene:



The applicability of the reaction includes many substituted aromatic derivatives, for example the conversion of toluene to*p*-tolualdehyde. However, unlike the Gattermann reaction with HCN, this reaction is not applicable to phenol and phenolether substrates. Additionally, when Zinc chloride is used as the catalyst, the presence of traces of copper (I) chloride co-catalyst is often necessary.

The Reimer–Tiemann reaction

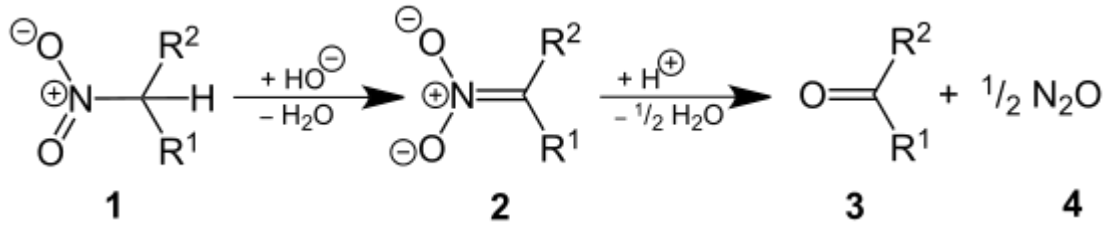
The **Reimer–Tiemann reaction** is a chemical reaction used for theortho-formylation of phenols with the simplest example being the conversion of phenol to salicylaldehyde. The reaction was discovered by Karl Reimer and Ferdinand Tiemann. The Reimer in question was Karl Reimer (1845-1883) not the less known Carl Ludwig Reimer (1856-1921).



Chloroform (**1**) is deprotonated by strong base (normallyhydroxide) to form the chloroform carbanion (**2**) which will quickly alpha-eliminate to give dichlorocarbene (**3**); this is the principal reactive species. The hydroxide will also deprotonate the phenol (**4**) to give a negatively charged phenoxide (**5**). The negative charge is delocalised into the aromatic ring, making it far more nucleophilic and increases its ortho selectivity. Nucelophilic attack of the dichlorocarbene from the ortho position gives an intermediate dichloromethyl substituted phenol (**7**). After basic hydrolysis, the desired product (**9**) is formed.

Nef reaction

The **Nef reaction** is an organic reaction describing the acid hydrolysis of a salt of a primary or secondary nitroalkane (**1**) to an aldehyde or a ketone (**3**) and nitrous oxide (**4**).

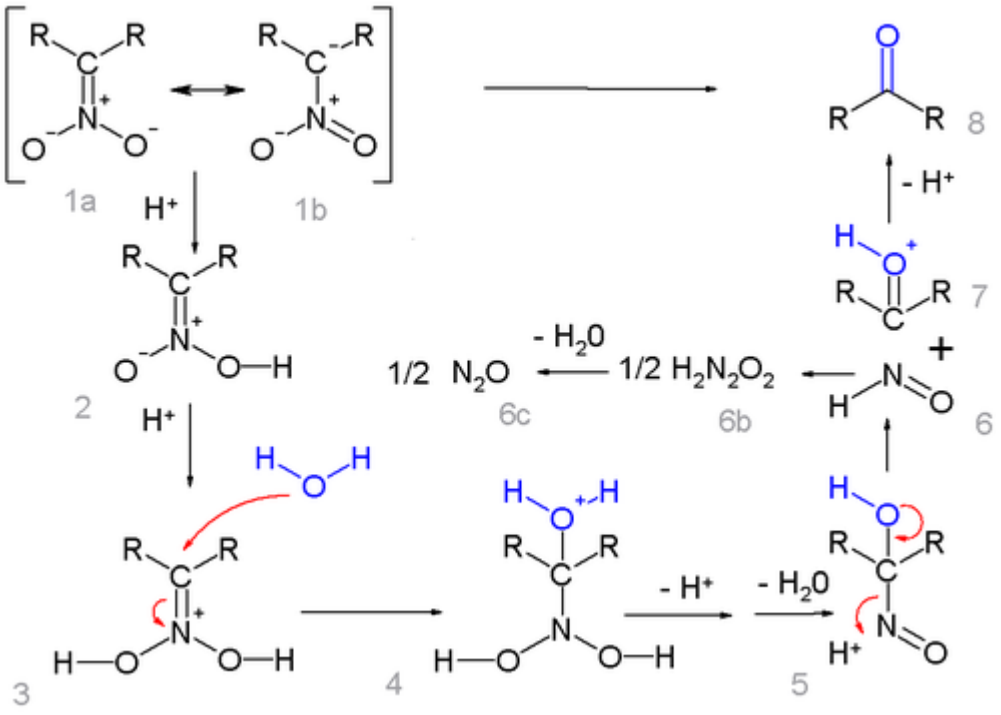


The reaction was reported in 1894 by the chemist John Ulric Nef, who treated the sodium salt of nitroethane with sulfuric acid resulting in an 85–89% yield of nitrous oxide and at least 70% yield of acetaldehyde. However, the reaction was pioneered a year earlier in 1893 by Konovalov, who converted the potassium salt of 1-phenylnitroethane with sulfuric acid to acetophenone.

The *Nef reaction* should not be confused with the Nef synthesis.

Reaction mechanism

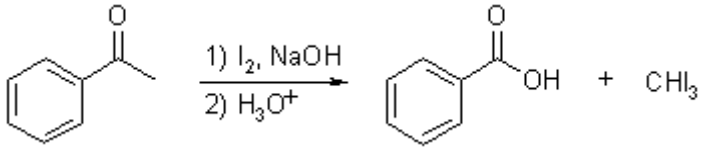
The reaction mechanism starting from the nitronate salt as the resonance structures **1a** and **1b** is depicted below:



The salt is protonated forming the nitronic acid **2** (in some cases these nitronates have been isolated) and once more to theiminium ion **3**. This intermediate is attacked by water in a nucleophilic addition forming **4** which loses a proton and then water to the 1-nitroso-alkanol **5** which is believed to be responsible for the deep-blue color of the reaction mixture in many Nef reactions. This intermediate rearranges to hyponitrous acid **6** (forming nitrous oxide **6c** through **6b**) and the oxonium ion **7**which loses a proton to form the carbonyl compound.

Note that formation of the nitronate salt from the nitro compound requires an alpha hydrogen atom and therefore the reaction fails with tertiary nitro compounds.

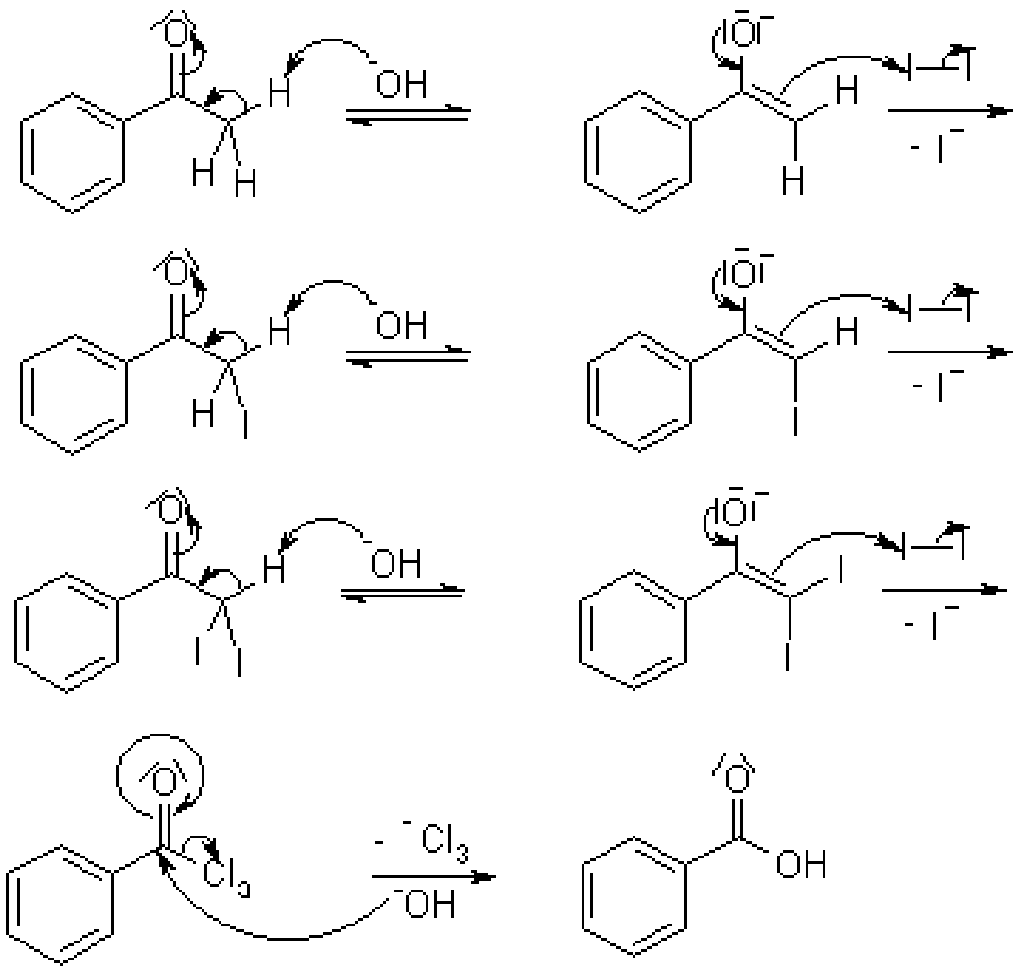
Haloform Reaction



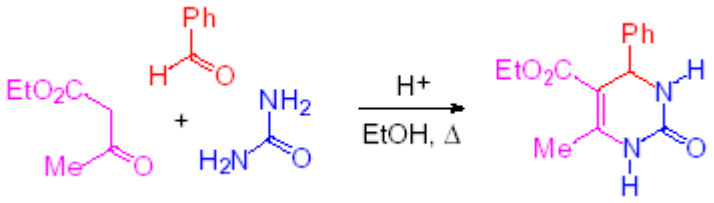
This reaction has been used in qualitative analysis to indicate the presence of a methyl ketone. The product iodoform is yellow and has a characteristic odour. The reaction has some synthetic utility in the oxidative demethylation of methyl ketones if the other substituent on the carbonyl groups bears no enolizable α-protons.

Mechanism of the Haloform Reaction

The reaction readily proceeds to completion because of the acidifying effect of the halogen substituents.



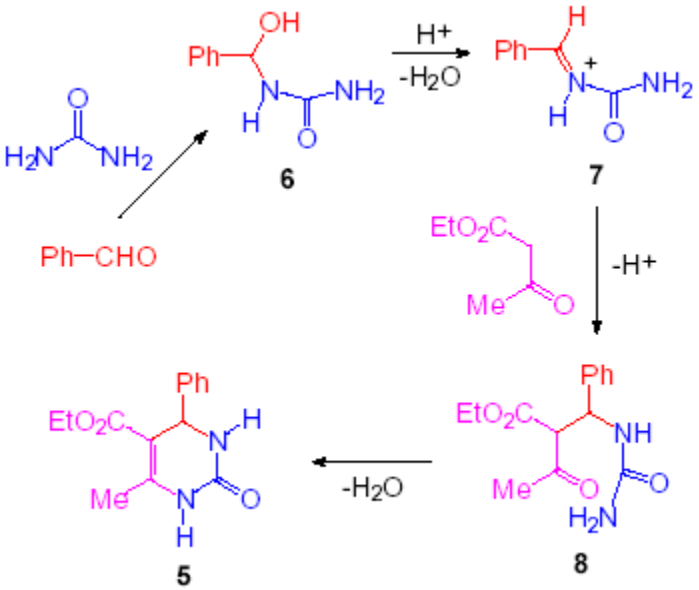
Biginelli Reaction



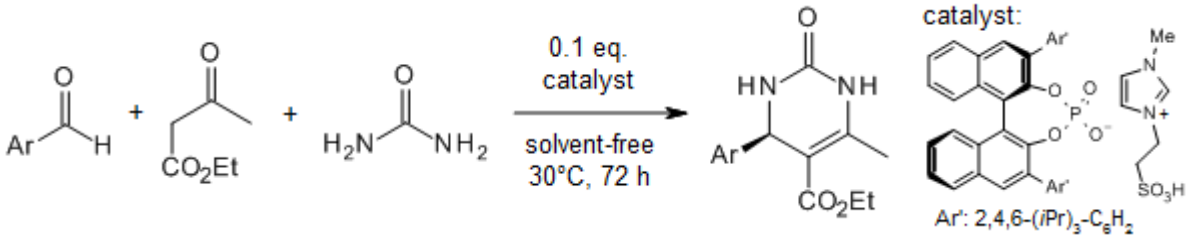
This acid-catalyzed, three-component reaction between an aldehyde, a ß-ketoester and urea constitutes a rapid and facile synthesis of dihydropyrimidones, which are interesting compounds with a potential for pharmaceutical application.

Mechanism of the Biginelli Reaction

The first step in the mechanism is believed to be the condensation between the aldehyde and urea, with some similarities to the Mannich Condensation. The iminium intermediate generated acts as an electrophile for the nucleophilic addition of the ketoester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea NH_2 to give the cyclized product.

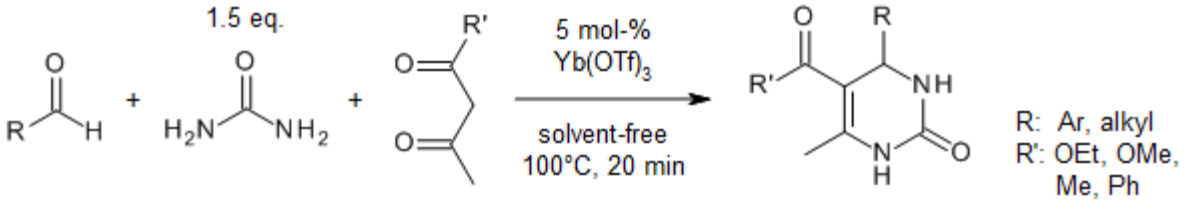


Recent Literature

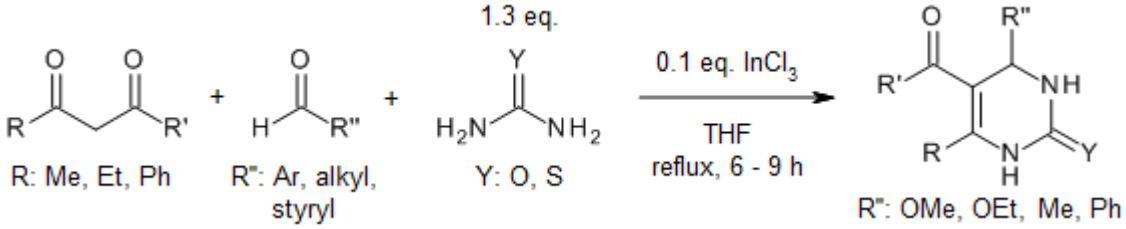


Combined Role of the Asymmetric Counteranion-Directed Catalysis (ACDC) and Ionic Liquid Effect for the Enantioselective Biginelli Multicomponent Reaction

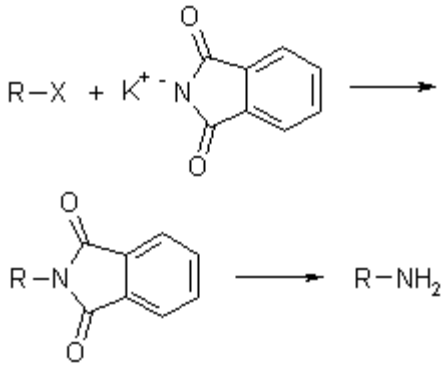
H. G. O. Alvim D. L. J. Pinheiro, V. H. Carvalho-Silva, M. Fioramonte, F. C. Gozzo, W. A. da Silva, G. W. Amarante, B. A. D. Neto, *J. Org. Chem.*, **2018**, *83*, 12143-12153.



By using $Yb(OTf)_3$ as a catalyst and under solvent-free reaction conditions, the yields of the one-pot Biginelli reaction can be increased while the reaction time was shortened. In addition, the catalyst can be easily recovered and reused. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes.
Y. Ma, C. Qian, L. Wang, M. Yang, *J. Org. Chem.*, **2000**, *65*, 3864-3868.



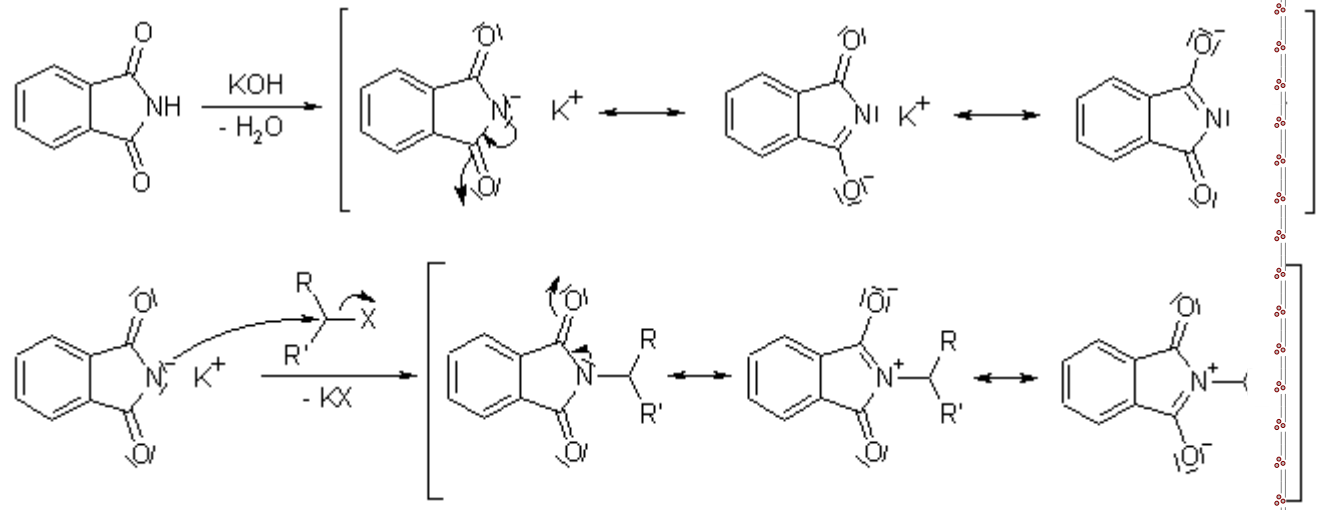
Gabriel Synthesis



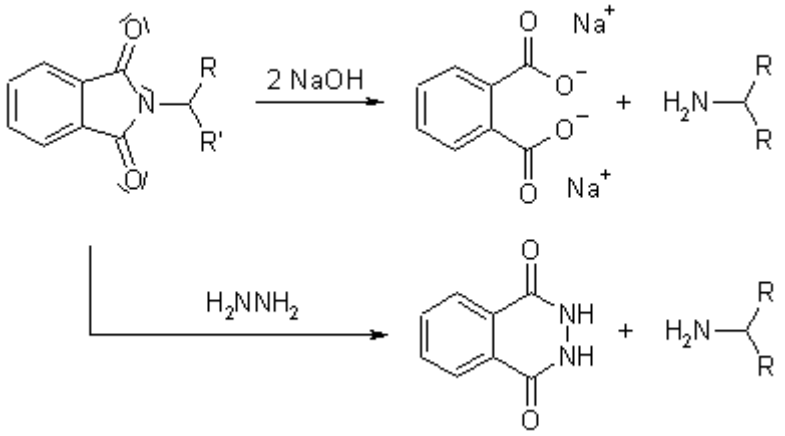
Potassium phthalimide is a $^{-}NH_2$-synthon which allows the preparation of primary amines by reaction with alkyl halides. After alkylation, the phthalimid is not nucleophile and does not react anymore. Product is cleaved by reaction with base or hydrazine, which leads to a stable cyclic product.

Mechanism of the Gabriel Synthesis

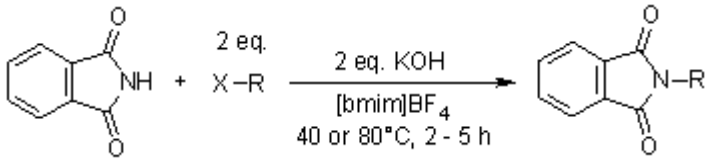
Note: Phthalimide is acidic!



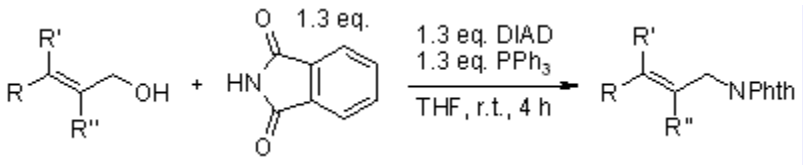
Cleavage:



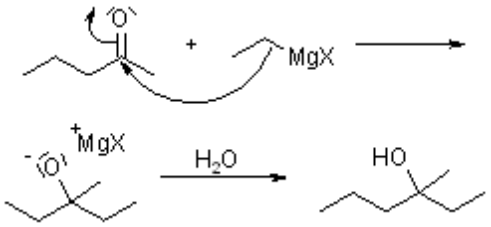
Recent Literature



Organic Reactions in Ionic liquids: N-Alkylation of Phthalimide and Several Nitrogen Heterocycles
Z.-G. Le, Z.-C. Chen, Y. Hu, Q.-G. Zheng, *Synthesis*, **2004**, 208-212.

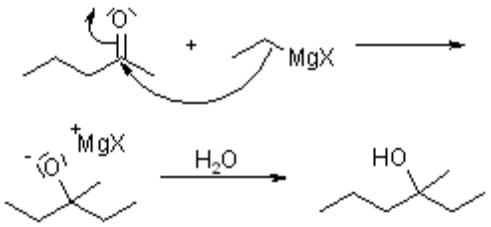


Grignard Reaction
Grignard Reagents



The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketGrignard Reaction
Grignard Reagents

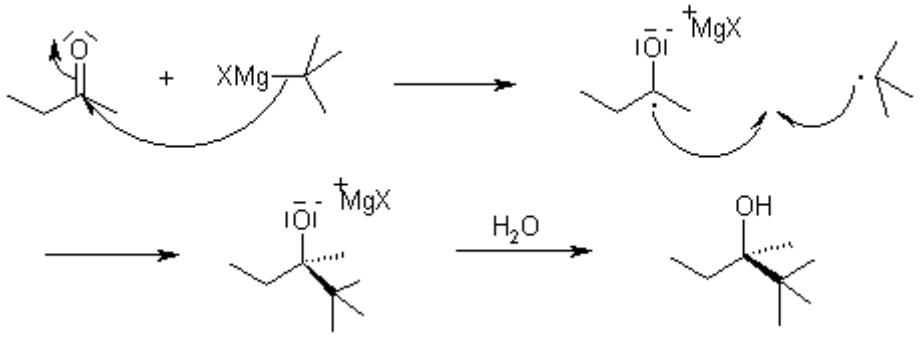


The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol.

Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate. (Some more reactions are depicted below)

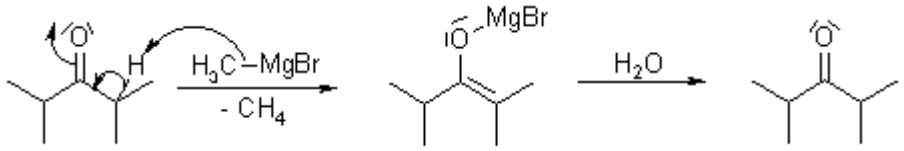
Mechanism of the Grignard Reaction

While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism:

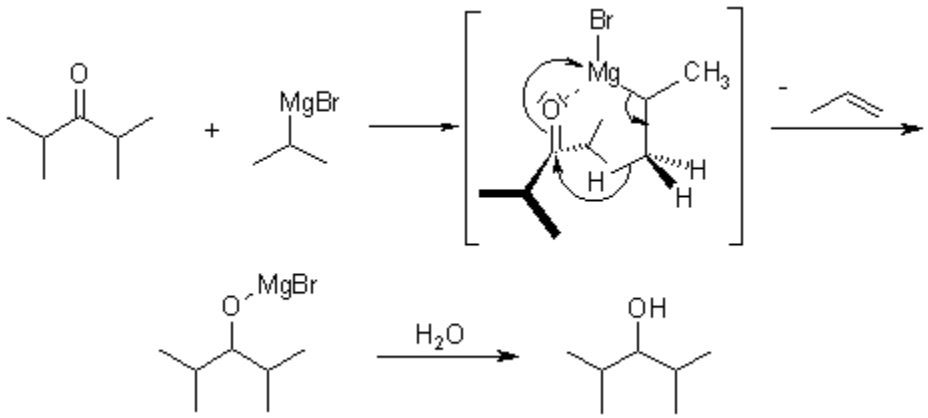


With sterically hindered ketones the following side products are received:

The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered.

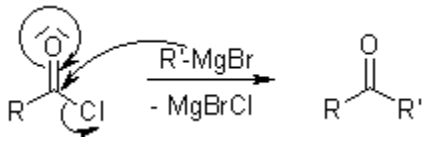


A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state.

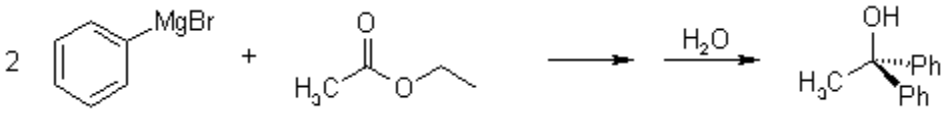


Additional reactions of Grignard Reagents:

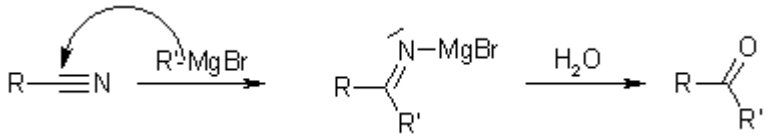
With carboxylic acid chlorides:



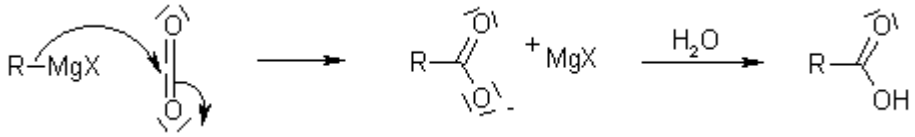
Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent:



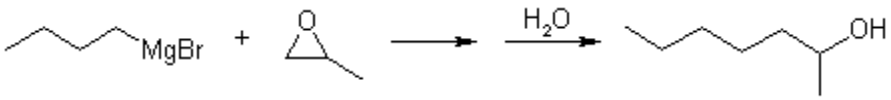
With nitriles:



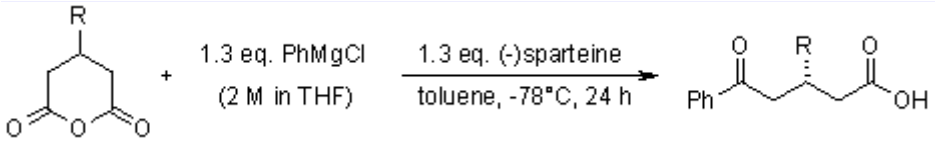
With CO_2 (by adding dry ice to the reaction mixture):



With oxiranes:



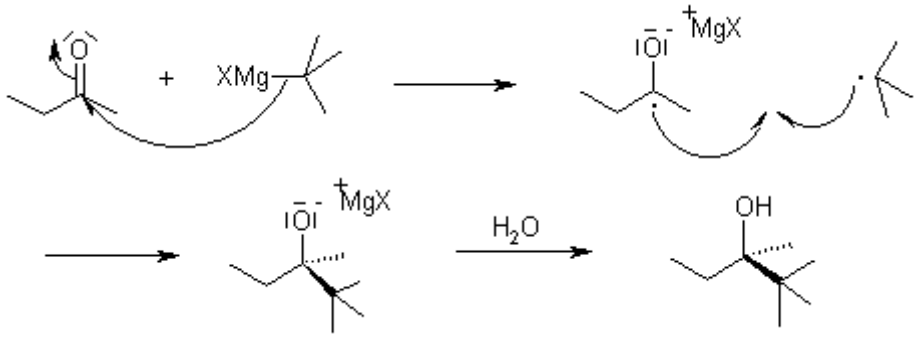
Recent Literature



one via a metalloimine intermediate. (Some more reactions are depicted below)

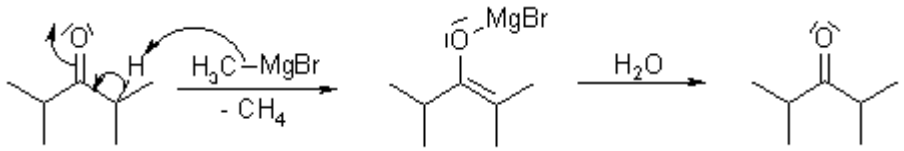
Mechanism of the Grignard Reaction

While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism:

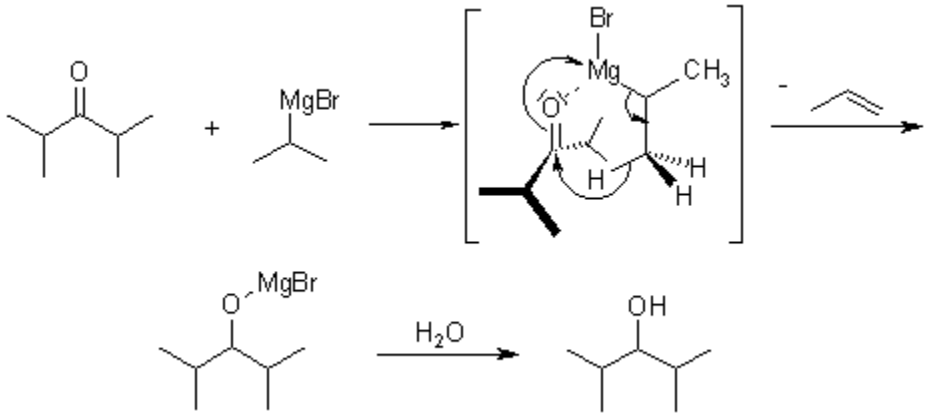


With sterically hindered ketones the following side products are received:

The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered.

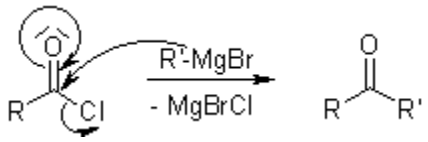


A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state.

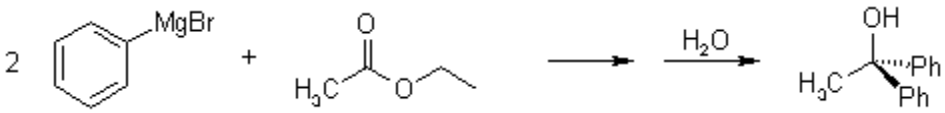


Additional reactions of Grignard Reagents:

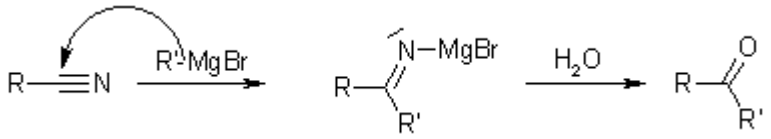
With carboxylic acid chlorides:



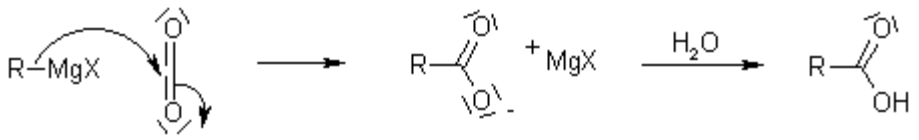
Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent:



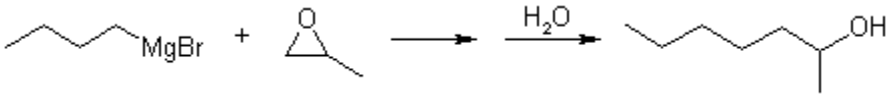
With nitriles:



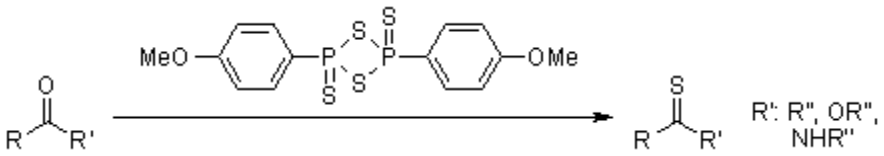
With CO_2 (by adding dry ice to the reaction mixture):



With oxiranes:



Lawesson's Reagent

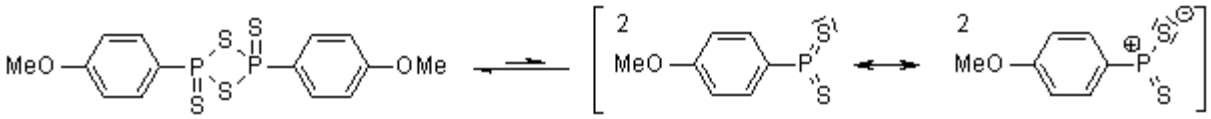


Lawesson's Reagent is a mild and convenient thionating agent for ketones, esters, and amides that allows the preparation of thioketones, thioesters and thioamides in good yields.

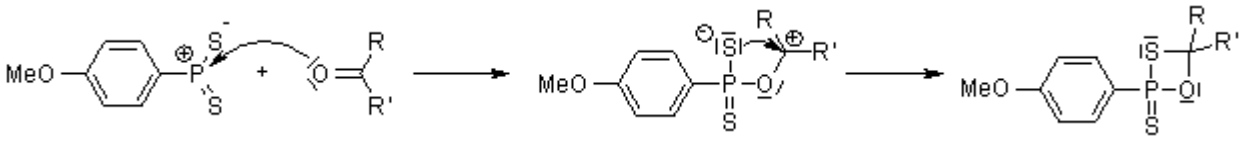
Reactions using the comparable reagent P_4S_{10} normally need higher temperatures and a large excess of the thionating agent.

Mechanism

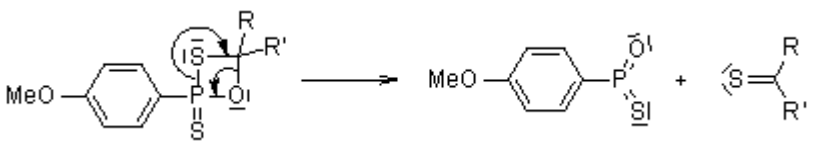
Lawesson's Reagent in solution is in equilibrium with a more reactive dithiophosphine ylide:



The reaction with a carbonyl gives rise to a thiaoxaphosphetane intermediate:



The driving force is the formation of a stable P=O bond in a cycloreversion step that resembles a portion of the mechanism known for the Wittig Reaction:



Gattermann - Koch Reaction Mechanism

Gattermann Koch's reaction mechanism begins with the formation of the reactive species with the help of the acid. The overall aim of the reaction is to attach a formyl group (-CHO group) to an aromatic system. An example of the Gattermann – Koch reaction is given below.

The Gattermann – Koch reaction is not applicable to phenol and phenol ether substrates. If zinc chloride is used as a catalyst in the Gattermann – Koch reaction, traces of copper(I) chloride is often necessary since it acts as a co-catalyst.

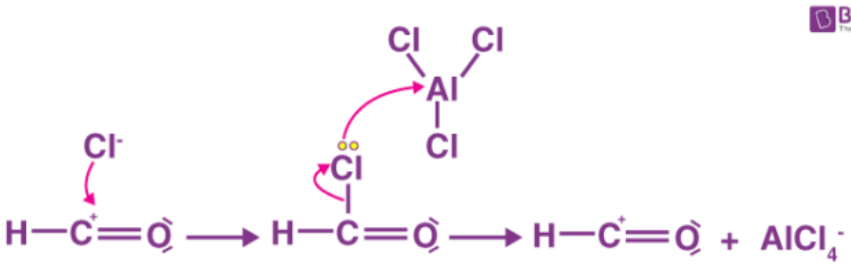
Gattermann – Koch Reaction Mechanism

Step 1

The first step of the Gattermann Koch reaction mechanism is the generation of the reactive species which can later be used to react on the aromatic ring. Since carbon monoxide acts as a lewis base, it can accept a proton from the hydrochloric acid. This results in a positively charged molecule which has different resonance structures. One such resonance structure displays a positive charge on the carbon, explaining the reactivity of the hybrid. This species can act as an electrophile while reacting with the aromatic ring. However, it is more likely to be the target of a nucleophilic attack from the chloride ion in the hydrochloric acid.

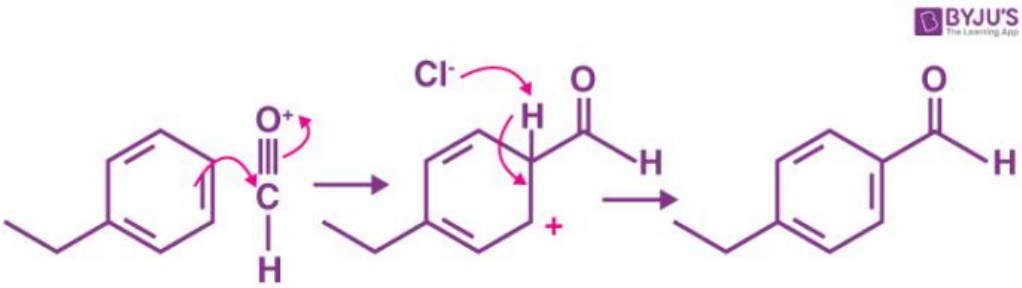
Step 2

When a Lewis acid (aluminium chloride) is added, it easily removes a chloride ion from the species. The species now reverts to the reactive formyl cation.



Step 3

An electrophilic aromatic substitution occurs at the aromatic ring. The aromatic ring acts as a nucleophile and donates an electron pair to the formyl cation. The temporary loss of aromaticity is quickly solved by the expulsion of a proton.



Thus, the formyl group is attached to the aromatic ring via the Gatterman – Koch reaction. In the example shown in the above mechanism, benzaldehyde is formed from the treatment of benzene with carbon monoxide and hydrochloric acid in the presence of aluminium chloride.

Reimer Tiemann Reaction Mechanism

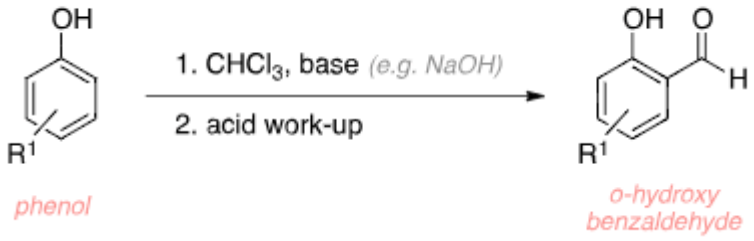
What is Reimer Tiemann Reaction?

Reimer Tiemann reaction is a type of substitution reaction, named after chemists Karl Reimer and Ferdinand Tiemann. The reaction is used for the ortho-formylation of C_6H_5OH (phenols).

Reaction: When phenols i.e. C_6H_5OH is treated with $CHCl_3$ (chloroform) in the presence of NaOH (sodium hydroxide), an aldehyde group (-CHO) is introduced at the ortho position of the benzene ring leading to the formation of o-hydroxybenzaldehyde. The reaction is popularly known as the Reimer Tiemann reaction.

⇒ Jump to: Reimer Tiemann Reaction Mechanism

A common example of the Reimer Tiemann reaction is the conversion of phenol to salicylaldehyde (2-hydroxy benzaldehyde) as shown below.



Reimer Tiemann reaction: Conversion of phenol to salicylaldehyde

Reimer Tiemann Reaction Details

Since hydroxides are not readily soluble in chloroform, a biphasic solvent system is employed to carry out the reaction. This biphasic solvent system can consist of an aqueous hydroxide solution with an organic phase that contains the chloroform.

These two reagents that are separated are brought together for the reaction to occur. Techniques to bring these two reagents together include – rapid mixing, phase-transfer catalysts or the use of an emulsifying agent.

The reaction is quite effective when other hydroxy-aromatic compounds are used, naphthols for example. Heterocyclic organic compounds that are quite rich in electrons, such as pyrroles and indoles also can undergo the Reimer Tiemann reaction.

The reaction needs heat to initiate the process. However, once the reaction is begun, it can prove to be highly exothermic and further increase the reaction rate. This is the reason why the Reimer Tiemann reaction is prone to thermal runaways.

Reimer Tiemann Reaction Mechanism

The mechanism of the Reimer Tiemann reaction begins with the deprotonation of chloroform by a strong base to form a chloroform carbanion. This chloroform carbanion quickly undergoes alpha elimination and gives rise to dichlorocarbene – the principle reactive species for this reaction.

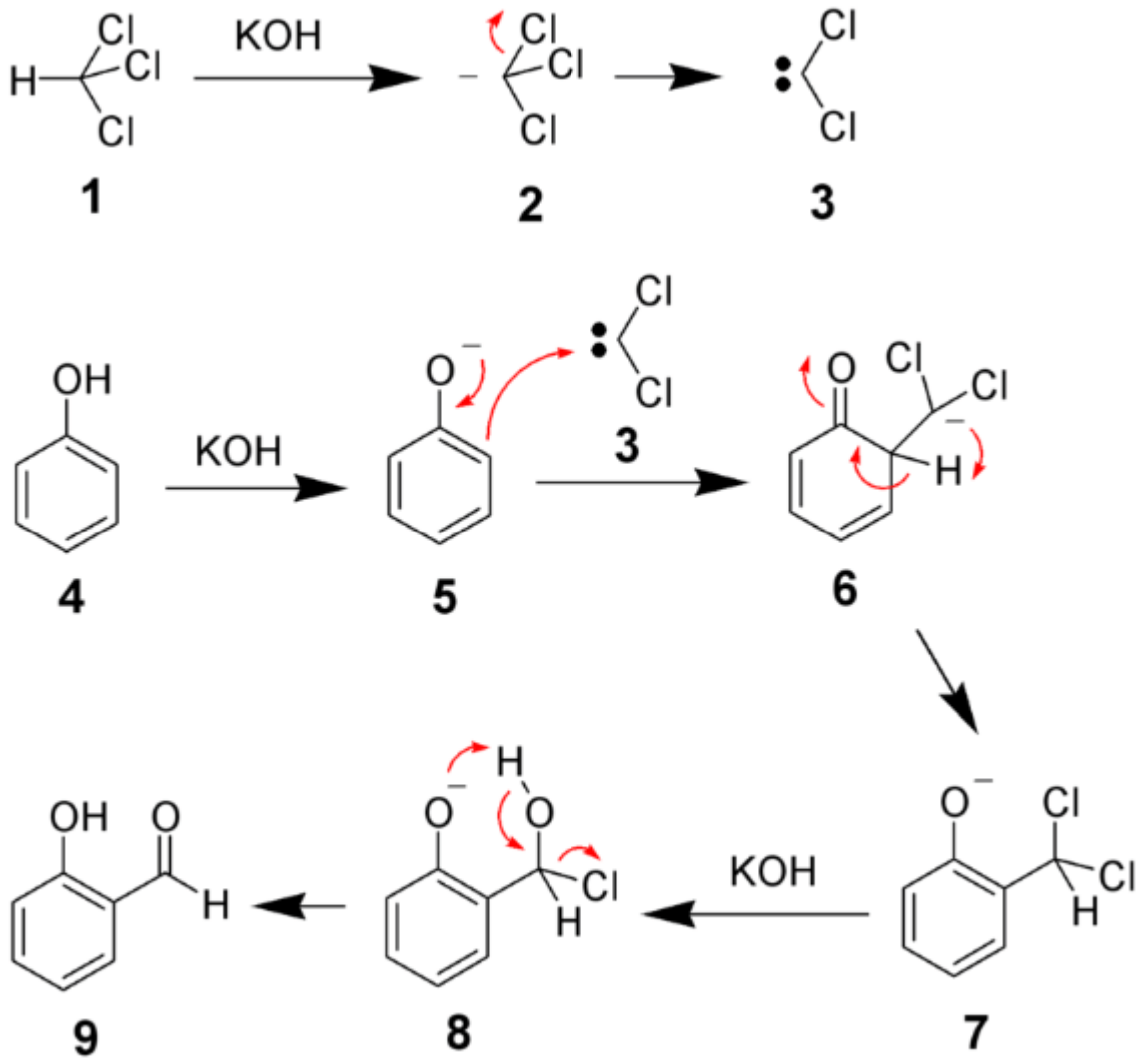
The Reimer Tiemann reaction is an organic chemical reaction where phenol is converted into an ortho hydroxy benzaldehyde using chloroform, a base, and acid workup. This reaction can also be described as the chemical reaction used for the ortho-formylation of phenols.

The mechanism of Reimer Tiemann Reaction can be explained in the below-given steps:

- **The chloroform is deprotonated by the strongly basic aqueous hydroxide solution, giving the chloroform carbanion.**
- **This chloroform carbanion readily undergoes alpha elimination, giving dichlorocarbene as the product. As mentioned earlier, dichlorocarbene is the principle reactive species.**
- **The aqueous hydroxide also deprotonates the phenol reactant, yielding a negatively charged phenoxide.**
- **This negative charge is now delocalized into the benzene ring, causing it to be far more nucleophilic.**
- **This results in a nucleophilic attack on the dichlorocarbene, forming an intermediate dichloromethyl substituted phenol.**
- **This intermediate is subjected to basic hydrolysis to finally achieve the formation of the desired ortho-hydroxybenzaldehyde.**

⇒ Check: Basic Concepts of Organic Chemistry

The illustration of the Reimer Tiemann reaction mechanism is given below:



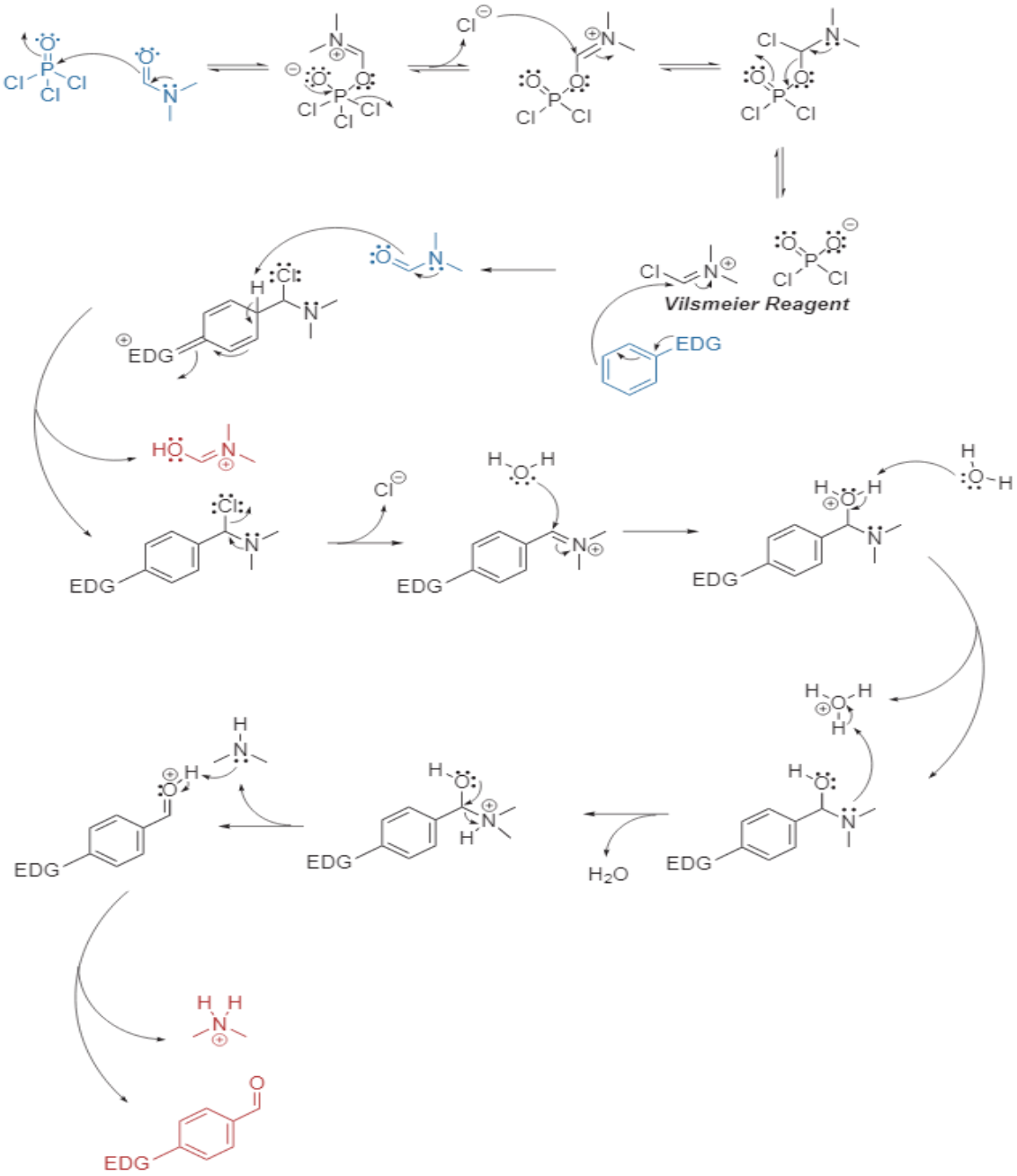
Reactions involved in Reimer Tiemann Reaction Mechanism

Thus, the given phenol is converted into an ortho-hydroxy benzaldehyde using chloroform, a base and acid workup. It can be noted that the carbene is highly electron-deficient due to the electron-withdrawing nature of its two chlorine groups. This is why it is strongly attracted to the phenoxide which is rich in electrons. The interaction favours ortho-formylation of a selective nature.

Vilsmeier-Haack reaction

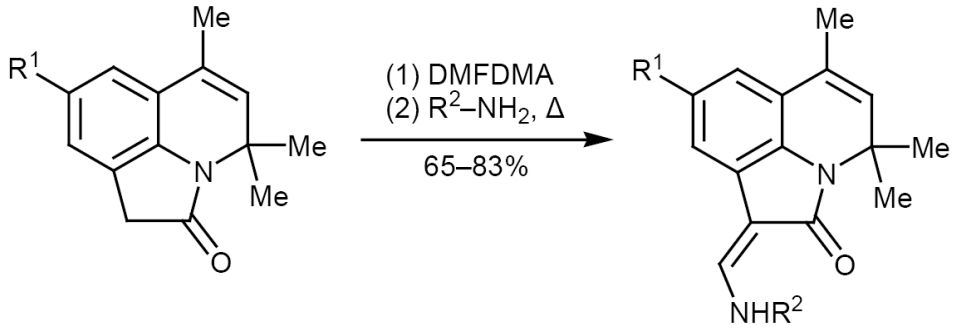
Also known as: *Vilsmeier-Haack formylation*

The Vilsmeier-Haack reaction is an organic reaction used to convert an electron rich aromatic ring to an aryl aldehyde using DMF, an acid chloride, and aqueous work-up. The mechanism begins with the reaction of DMF with the acid chloride to form an iminium salt known as the "Vilsmeier reagent". The electron rich aromatic ring then attacks the iminium ion with loss of aromaticity. A deprotonation step restores aromati-city, which is followed by the release of a chloride ion to form another iminium intermediate. Aqueous work-up then leads to the aryl aldehyde final product.[1]


Vilsmeier Reagent
EDG
H2O

1-{[(Het)arylamino]methylidene}-4*H*-pyrrolo[3,2,1-*ij*]quinolin-2(1*H*)-ones 5a–5f (*general procedure*).

A mixture of 2.4 mmol of pyrroloquinolin-2-one **2b** or **2c** and 2.5 mmol of DMF-DMA in 10 mL of *o*-xylene was refluxed for 1 h. The corresponding amine, 2.4 mmol, and 1–2 drops of acetic acid were added, and the mixture was refluxed until the reaction was complete. The precipitate was filtered off, dried, and recrystallized from petroleum ether with addition of isopropyl alcohol



2b, **2c** **5a–5f**

2, R^1 = Me (**b**), MeO (**c**); **5**, R^1 = Me, R^2 = 1*H*-benzimidazol-2-yl (**a**), pyridin-2-yl (**b**), 2-$MeOC_6H_4$ (**c**), 4-$MeOC_6H_4$ (**d**), 4-$MeC(O)C_6H_4$ (**e**), R^1 = MeO, R^2 = $PhCH_2$ (**f**).