This book describes Basic name reaction knowledge with respect to organic chemistry. All the necessary information about reagent, catalyst, starting material and product should be taken while performing reaction is described step by step. This book contains all the basic contents, instructions and fundamental step of theory chemistry which decreases random and methodic errors and helps to solve the difficulties faced by the undergraduate students.

Bhavesh N. Socha
Khushbu K. Dodeja
Yogesh O. Bhola

Basic organic name reaction

multi-component, reagent,catalyst

Dr. Yogesh O. Bhola (M.Sc, BSc,NET,GSET,PhD) is working as a lecture (for BSc &MSc Chemistry) at College of Computer, Science & Information Technology (Bhakta Kavi Narsinh Mehta University) Junagadh. He has Published Five Research article.

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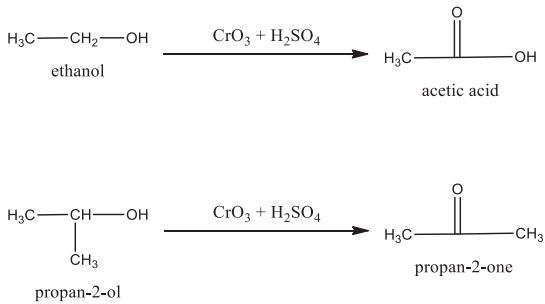
BASIC ORGANIC NAME REACTION

INDEX

(1) Jones Oxidation



The Jones oxidation is an organic reaction for the oxidation of primary and secondary alcohols to carboxylic acids and ketones, respectively. It is named after its discoverer, Sir Ewart Jones.

Jones reagent consists of chromium trioxide and sulfuric acid dissolved in a mixture of acetone and water. As an alternative, potassium dichromate can be used in place of chromium trioxide. The oxidation is very rapid, quite exothermic, and the yields are typically high. The reagent rarely oxidizes unsaturated bonds.

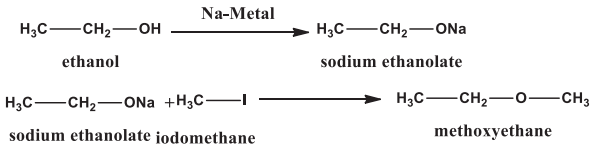
Application

Although useful reagent for some applications, due to the carcinogenic nature of chromium(VI), the Jones oxidation has slowly been replaced by other oxidation methods. It remains useful in organic synthesis. A variety of spectroscopic techniques, including IR can be used to monitor the progress of a Jones oxidation reaction and confirm the presence of the oxidized product. At one time the Jones oxidation was used in primitive breathalyzers. Aminoindans, which are of pharmalogical interest, are prepared by the oxidation of the alcohol to ketone which is converted into an amino group. The alcohol is oxidized to the ketone with the Jones reagent. The reagent was once used to prepare salicylic acid, a precursor to aspirin. Methcathinone is a psychoactive stimulant that is sometimes used as an addictive recreational drug. It can be oxidized from certain alcohols using the Jones reagent.

Related processes

Several other chromium compounds are used for the oxidation of alcohols.[3] These include Collins reagent and pyridinium chlorochromate.The Sarett oxidation is a similar process.

(2) Williamson Synthesis



The Williamson ether synthesis is an organic reaction, forming an ether from an organohalide and a deprotonated alcohol (alkoxide). This reaction was developed by Alexander Williamson in 1850.[2] Typically it involves the reaction of an alkoxide ion with a primary alkyl halide via an S_N2 reaction. This reaction is important in the history of organic chemistry because it helped prove the structure of ethers.

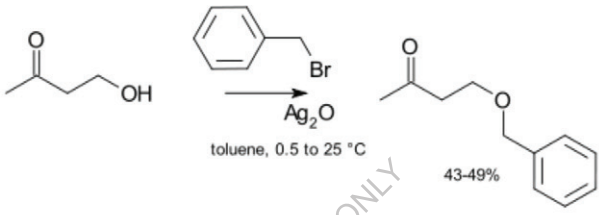
Conditions

Since alkoxide ions are highly reactive, they are usually prepared immediately prior to the reaction, or are generated *in situ*. In laboratory chemistry, *in situ* generation is most often accomplished by the use of a carbonate base or potassium hydroxide, while in industrial syntheses phase transfer catalysis is very common. A wide range of solvents can be used, but protic solvents and apolar solvents tend to slow the reaction rate strongly, as a result of lowering the availability of the free nucleophile. For this reason, acetonitrile and *N*,*N*-dimethylformamide are particularly commonly used.

A typical Williamson reaction is conducted at 50 to 100 °C and is complete in 1 to 8 h. Often the complete disappearance of the starting material is difficult to achieve,

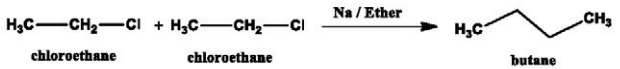
and side reactions are common. Yields of 50–95% are generally achieved in laboratory syntheses, while near-quantitative conversion can be achieved in industrial procedures.

Catalysis is not usually necessary in laboratory syntheses. However, if an unreactive alkylating agent is used (e.g. an alkyl chloride) then the rate of reaction can be greatly improved by the addition of a catalytic quantity of a soluble iodide salt (which undergoes halide exchange with the chloride to yield a much more reactive iodide, a variant of the Finkelstein reaction). In extreme cases, silver compounds such as silver oxide may be added:



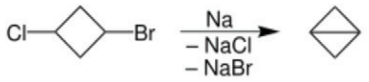
(3) Wurtz Reaction

The Wurtz reaction, named after Charles Adolphe Wurtz, is a coupling reaction in organic chemistry, organometallic chemistry and recently inorganic main group polymers, whereby two alkyl halides are reacted with sodium metal in dry ether solution to form a higher alkane:



Other metals have also been used to effect the Wurtz coupling, among them silver, zinc, iron, activated copper, indium and a mixture of manganese and copper chloride. The related reaction dealing with aryl halides is called the Wurtz-Fittig reaction. This can be explained by the formation of free radical intermediate and its subsequent disproportionation to give alkene. The Wurtz reaction occurs through a

free radical mechanism that makes possible side reactions producing alkene products.

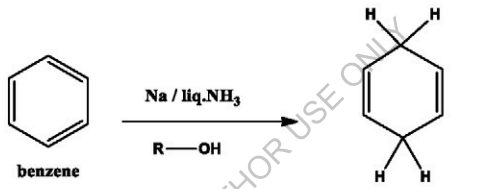


Limitations

The Wurtz reaction is seldom used because of side reactions. It has limited use to the synthesis of symmetric alkanes. If two dissimilar alkyl halides are taken as reactants, then the product is a mixture of alkanes that is often difficult to separate by fractional distillation as the differences between the boiling points of the products is typically very low. Methane cannot be obtained by this method. This type of reaction fails in case of tertiary halides. Also, since the reaction involves free radical species, a side reaction occurs to produce an alkene. This side reaction becomes more significant when the alkyl halides are bulky at the halogen-attached carbon.

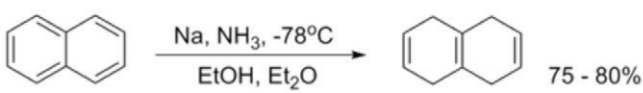
(4) Birch reduction

The Birch reduction is an organic reaction which is particularly useful in synthetic organic chemistry. The reaction was reported in 1944 by the Australian chemist Arthur Birch (1915–1995) working in the Dyson Perrins Laboratory at the University of Oxford, building on earlier work by Wooster and Godfrey published in 1937. It converts aromatic compounds having a benzenoid ring into a product, 1,4-cyclohexadienes, in which two hydrogen atoms have been attached on opposite ends of the molecule. It is the organic reduction of aromatic rings in liquid ammonia with sodium, lithium or potassium and an alcohol, such as ethanol and *tert*-butanol. This reaction is quite unlike catalytic hydrogenation, which usually reduces the aromatic ring all the way to a cyclohexane.



The original reaction reported by Arthur Birch in 1944 used sodium and ethanol. Alfred L. Wilds later discovered that lithium gives better yields.[8] Also the use of *tert*-butyl alcohol has become common. The reaction is widely used in synthetic organic chemistry.

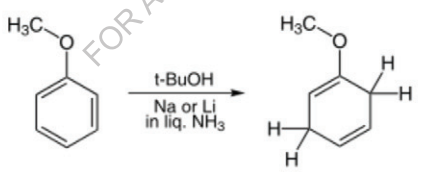
Ex



Regioselectivity

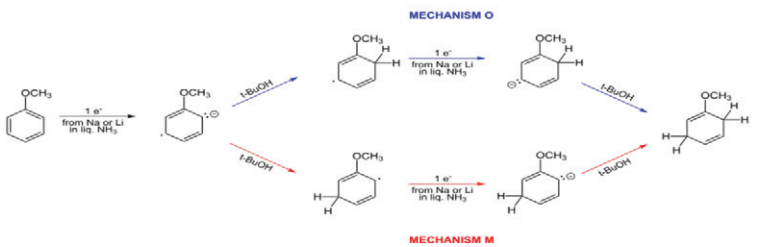
The reduction of anisole is one of the simplest examples and is shown in equation 1. The reduction of benzoic acid is illustrated in equation 2. The location on the ring where the radical anion is initially protonated determines the structure of the product. With an electron donor such as methoxy (MeO), alkyl protonation has been thought by some investigators as being *ortho* (i.e. adjacent or 1,2) to the substituent. Other investigators have thought the protonation is *meta* (1,3) to the substituent. Arthur Birch favoured *meta* protonation. With electron withdrawing substituents, protonation has been thought to occur at the site of the substituent (ipso) or *para* (1,4), but this is also unclear. A. J. Birch's empirical rules say that for the donor substituents the final product has the maximum number of substituents on the final double bonds. For electron withdrawing groups the double bonds of the product avoid the substituents. The placement preference of groups during the reaction and in the final product is termed regioselectivity.

Electron donating group = OH,OR,NH2 etc.

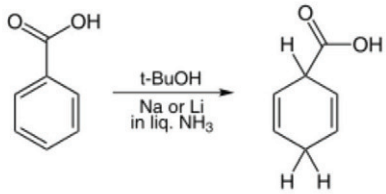


(1)

Mechanism

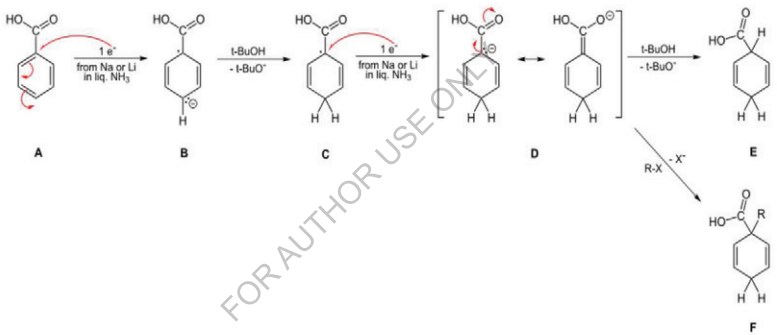


Electron withdrawing group= CHO,COOH,COOR etc.



(2)

Mechanism



Reaction regioselectivity

The Birch reduction has several intricate mechanistic features. These features govern the reaction's regioselectivity and are considered below. Birch's rule for aromatics with electron donors such as methoxyl or alkyl is that the product will have the residual double bonds bearing the maximum number of substituents. For aromatics with electron withdrawing groups such as carboxyl, the substituent groups avoid the double bonds. In both cases, with electron donating and with withdrawing groups, the residual double bonds are unconjugated (see below). The reaction mechanisms accounting for this regioselectivity are a topic of great scientific interest. The essential features are:

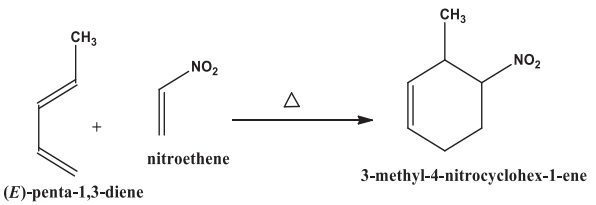
- In liquid ammonia alkali metals dissolve to give a blue solution thought of simplistically as having "free electrons". The electrons are taken up by the aromatic ring, one at a time. Once the first electron has been absorbed, a radical anion has been formed. Next the alcohol molecule donates its hydroxylic hydrogen to form a new C–H bond; at this point a radical has been formed. This is followed by the second electron being picked up to give a carbanion of the cyclohexadienyl type (i.e. with C=C–C–C=C in a six-membered ring with negative charge). Then this cyclohexadienyl anion is protonated by the alcohol present. The protonation takes place in the center of the cyclohexadienyl system. This (regio-)selectivity is characteristic.
- Where the radical anion is initially protonated determines the structure of the product. With an electron donor such as methoxy (MeO) or with an alkyl group, protonation has been thought by some investigators as being *ortho* (i.e. adjacent or 1,2) to the substituent. Other investigators have thought the protonation is *meta* (1,3) to the substituent. Arthur Birch favored *meta* protonation. With electron withdrawing substituents, protonation has been thought to occur at the site of the substituent (ipso), or *para* (1,4). Again, there has been varied opinion. A. J. Birch's empirical rules say that for the donor substituents the final product has the maximum number of substituents on the final double bonds. For electron withdrawing groups the double bonds of the product avoid the substituents. The placement preference of groups in the mechanism and in the final product is termed regioselectivity.
- reaction mechanism provides the details of molecular change as a reaction proceeds. In the case of donating groups, A. J. Birch's preference for *meta* protonation of the radical anion was based on qualitative reasoning, but this has not been experimentally demonstrated.
- In 1961 a simple computation of the electron densities of the radical anion revealed that it was the *ortho* site which was most negative and thus most likely to protonate. Additionally, the second protonation was determined computationally to occur in the center of the cyclohexadienyl anion to give an unconjugated product.
- The uncertainty in the chemical literature is now only of historical significance. Indeed, some further computational results have been reported,

which vary from suggesting a preference for *meta* radical-anion protonation to suggesting a mixture of *ortho* and *meta* protonation.[*citation needed*]

- In 1990 and 1993 an esoteric test was devised which showed that *ortho* protonation of the radical anion was preferred over *meta* (seven to one).[*citation needed*] This was accompanied by more modern computation which concurred. Both experiment and computations were in agreement with the early 1961 computations.
- With electron withdrawing groups there are examples in the literature demonstrating the nature of the carbanion just before final protonation,[*citation needed*] revealing that the initial radical-anion protonation occurs *para* to the withdrawing substituent.
- The remaining item for discussion is the final protonation of the cyclohexadienyl anion. In 1961 it was found that simple Hückel computations were unable to distinguish between the different protonation sites.[*citation needed*] However, when the computations were modified with somewhat more realistic assumptions, the Hückel computations revealed the center carbon to the preferred. The more modern 1990 and 1993 computations were in agreement.

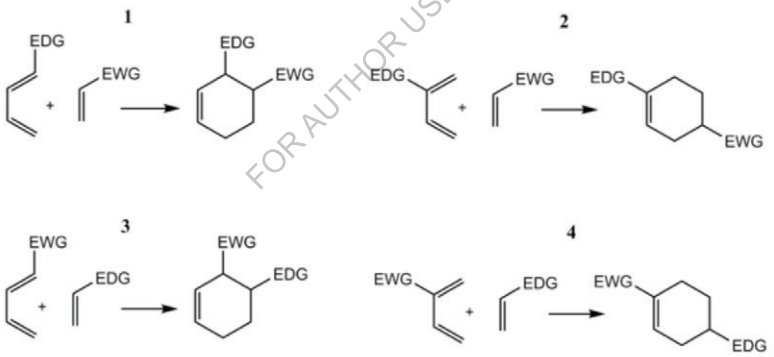
(5) Diels-Alder reaction

In organic chemistry, the Diels–Alder reaction is a chemical reaction between a conjugated diene and a substituted alkene, commonly termed the dienophile (*also spelled dieneophile*), to form a substituted cyclohexene derivative. It is the prototypical example of a pericyclic reaction with a concerted mechanism. More specifically, it is classified as a thermally-allowed [4+2] cycloaddition with Woodward–Hoffmann symbol [$\pi 4_s + \pi 2_s$]. It was first described by Otto Diels and Kurt Alder in 1928. For the discovery of this reaction, they were awarded the Nobel Prize in Chemistry in 1950. Through the simultaneous construction of two new carbon–carbon bonds, the Diels–Alder reaction provides a reliable way to form six-membered rings with good control over the regio- and stereochemical outcomes.[2][3] Consequently, it has served as a powerful and widely applied tool for the introduction of chemical complexity in the synthesis of natural products and new materials.[4][5] The underlying concept has also been applied to π-systems involving heteroatoms, such as carbonyls and imines, which furnish the corresponding heterocycles; this variant is known as the hetero-Diels–Alder reaction. The reaction has also been generalized to other ring sizes, although none of these generalizations have matched the formation of six-membered rings in terms of scope or versatility. Because of the negative values of $\Delta H°$ and $\Delta S°$ for a typical Diels–Alder reaction, the microscopic reverse of a Diels–Alder reactions becomes favourable at high temperatures, although this is of synthetic importance for only a limited range of Diels-Alder adducts, generally with some special structural features; this reverse reaction is known as the retro-Diels–Alder reaction.



Regioselectivity

In general, the regioselectivity found for both normal and inverse electron-demand Diels–Alder reaction follows the ortho-para rule, so named, because the cyclohexene product bears substituents in positions that are analogous to the *ortho* and *para* positions of disubstituted arenes. For example, in a normal-demand scenario, a diene bearing an electron-donating group (EDG) at C1 has its largest HOMO coefficient at C4, while the dienophile with an electron withdrawing group (EWG) at C1 has the largest LUMO coefficient at C2. Pairing these two coefficients gives the "ortho" product as seen in case 1 in the figure below. A diene substituted at C2 as in case 2 below has the largest HOMO coefficient at C1, giving rise to the "para" product. Similar analyses for the corresponding inverse-demand scenarios gives rise to the analogous products as seen in cases 3 and 4. Examining the canonical mesomeric forms above, it is easy to verify that these results are in accord with expectations based on consideration of electron density and polarization.

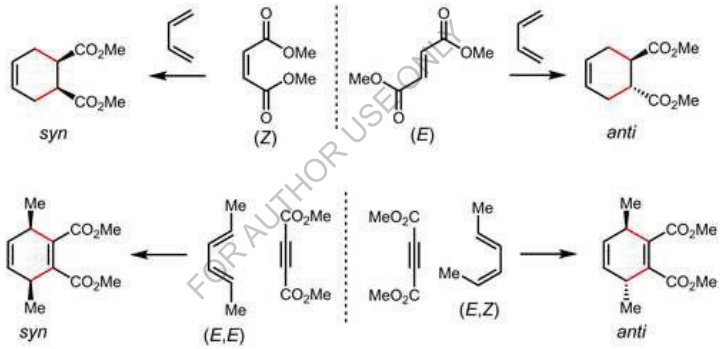


In general, with respect to the energetically most well-matched HOMO-LUMO pair, maximizing the interaction energy by forming bonds between centers with the largest frontier orbital coefficients allows the prediction of the main regioisomer that will result from a given diene-dienophile combination. In a more sophisticated treatment, three types of substituents (**Z** withdrawing: HOMO and LUMO lowering (CF_3, NO_2, CN, $C(O)CH_3$), **X** donating: HOMO and LUMO raising (Me, OMe, NMe_2), **C** conjugating: HOMO raising and LUMO lowering (Ph, vinyl)) are considered, resulting in a total of 18 possible combinations. The maximization of orbital interaction correctly predicts the product in all cases for which experimental data is available. For instance, in uncommon combinations

involving **X** groups on both diene and dienophile, a 1,3-substitution pattern may be favored, an outcome not accounted for by a simplistic resonance structure argument. However, cases where the resonance argument and the matching of largest orbital coefficients disagree are rare.

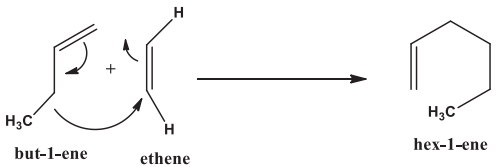
Stereospecificity and stereoselectivity

ls–Alder reactions, as concerted cycloadditions, are stereospecific. Stereochemical information of the diene and the dienophile are retained in the product, as a *syn* addition with respect to each component. For example, substituents in a *cis* (*trans*, resp.) relationship on the double bond of the dienophile give rise to substituents that are *cis* (*trans*, resp.) on those same carbons with respect to the cyclohexene ring. Likewise, *cis*,*cis*- and *trans*,*trans*-disubstitued dienes give *cis* substituents at these carbons of the product whereas *cis*,*trans*-disubstituted dienes give *trans* substituents:

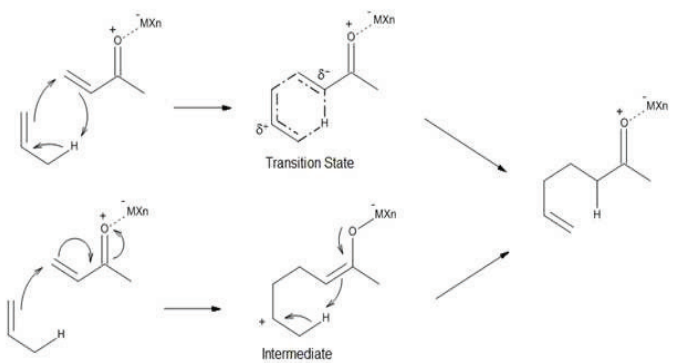


(6) Ene reaction

The ene reaction (also known as the Alder-ene reaction by its discoverer Kurt Alder in 1943) is a chemical reaction between an alkene with an allylic hydrogen (the ene) and a compound containing a multiple bond (the enophile), in order to form a new σ-bond with migration of the ene double bond and 1,5 hydrogen shift. The product is a substituted alkene with the double bond shifted to the allylic position.

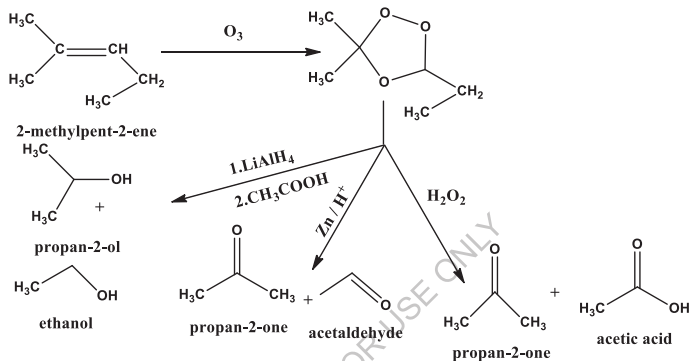


This transformation is a group transfer pericyclic reaction,[2] and therefore, usually requires highly activated substrates and/or high temperatures.[3] Nonetheless, the reaction is compatible with a wide variety of functional groups that can be appended to the ene and enophile moieties. Many useful Lewis acid-catalyzed ene reactions have been also developed, which can afford high yields and selectivities at significantly lower temperatures, making the ene reaction a useful C–C forming tool for the synthesis of complex molecules and natural products.



(7) Ozonolysis

Ozonolysis is an organic reaction where the unsaturated bonds of alkenes, alkynes, or azo compounds are cleaved with ozone. Alkenes and alkynes form organic compounds in which the multiple carbon–carbon bond has been replaced by a carbonyl group while azo compounds form nitrosamines. The outcome of the reaction depends on the type of multiple bond being oxidized and the work-up conditions.

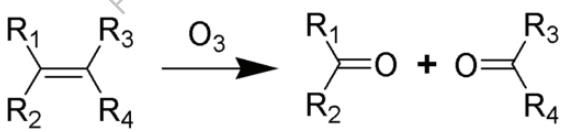


Ozonolysis of alkenes

Alkenes can be oxidized with ozone to form alcohols, aldehydes or ketones, or carboxylic acids. In a typical procedure, ozone is bubbled through a solution of the alkene in methanol at −78 °C until the solution takes on a characteristic blue color, which is due to unreacted ozone. This indicates complete consumption of the alkene. Alternatively, various other chemicals can be used as indicators of this endpoint by detecting the presence of ozone. If ozonolysis is performed by bubbling a stream of ozone-enriched oxygen through the reaction mixture, the gas that bubbles out can be directed through a potassium iodide solution. When the solution has stopped absorbing ozone, the ozone in the bubbles oxidizes the iodide to iodine, which can easily be observed by its violet color.[5] For closer control of the reaction itself, an indicator such as Sudan Red III can be added to the reaction mixture. Ozone reacts with this indicator

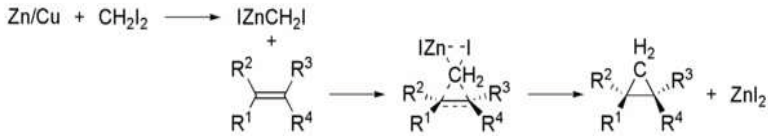
more slowly than with the intended ozonolysis target. The ozonolysis of the indicator, which causes a noticeable color change, only occurs once the desired target has been consumed. If the substrate has two alkenes that react with ozone at different rates, one can choose an indicator whose own oxidation rate is intermediate between them, and therefore stop the reaction when only the most susceptible alkene in the substrate has reacted.[6] Otherwise, the presence of unreacted ozone in solution (seeing its blue color) or in the bubbles (via iodide detection) only indicates when all alkenes have reacted.

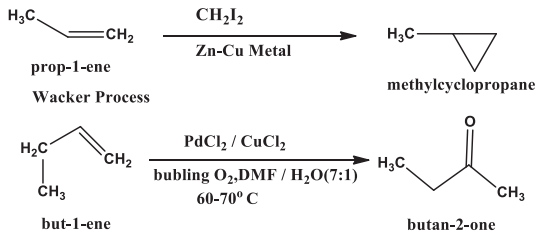
After completing the addition, a reagent is then added to convert the intermediate ozonide to a carbonyl derivative. Reductive work-up conditions are far more commonly used than oxidative conditions. The use of triphenylphosphine, thiourea, zinc dust, or dimethyl sulfide produces aldehydes or ketones while the use of sodium borohydride produces alcohols. The use of hydrogen peroxide produces carboxylic acids. Recently, the use of amine N-oxides has been reported to produce aldehydes directly.[7] Other functional groups, such as benzyl ethers, can also be oxidized by ozone. It has been proposed that small amounts of acid may be generated during the reaction from oxidation of the solvent, so pyridine is sometimes used to buffer the reaction. Dichloromethane is often used as a 1:1 cosolvent to facilitate timely cleavage of the ozonide. Azelaic acid and pelargonic acids are produced from ozonolysis of oleic acid on an industrial scale.



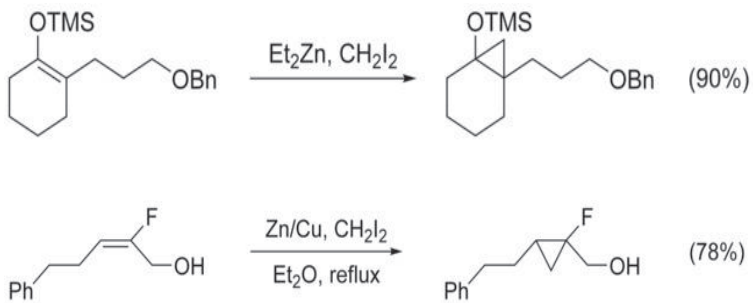
(8) Simmons – smith reaction

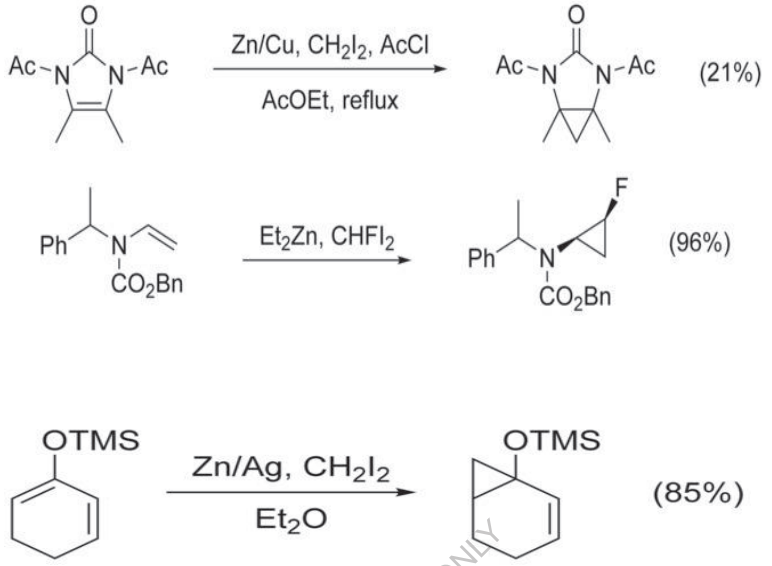
The Simmons–Smith reaction is an organic cheletropic reaction involving an organozinc carbenoid that reacts with an alkene (or alkyne) to form a cyclopropane.[1][2][3] It is named after Howard Ensign Simmons, Jr. and Ronald D. Smith. It uses a methylene free radical intermediate that is delivered to both carbons of the alkene simultaneously, therefore the configuration of the double bond is preserved in the product and the reaction is stereospecific.





Limitations



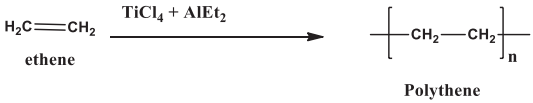


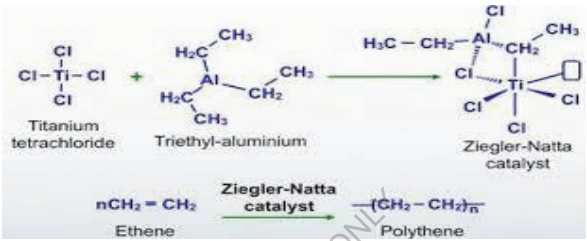
(9) Ziegler- Natta Catalyst

A Ziegler–Natta catalyst, named after Karl Ziegler and Giulio Natta, is a catalyst used in the synthesis of polymers of 1-alkenes (alpha-olefins). Two broad classes of Ziegler–Natta catalysts are employed, distinguished by their solubility:

- Heterogeneous supported catalysts based on titanium compounds are used in polymerization reactions in combination with cocatalysts, organoaluminium compounds such as triethylaluminium, $Al(C_2H_5)_3$. This class of catalyst dominates the industry.
- Homogeneous catalysts usually based on complexes of Ti, Zr or Hf. They are usually used in combination with a different organoaluminium cocatalyst, methyl aluminoxane (or methyl alumoxane, MAO). These catalysts traditionally contains metallocene but also feature multidentate oxygen- and nitrogen-based ligands.

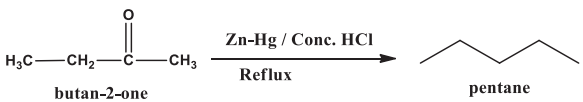
Ziegler–Natta catalysts are used to polymerize terminal alkenes (ethylene and alkenes with the vinyl double bond):





(10) Clemmensen Reduction

Clemmensen reduction is a chemical reaction described as a reduction of Ketones (or aldehydes) to alkanes using zinc amalgam and concentrated hydrochloric acid. This reaction is named after Erik Christian Clemmensen, a Danish chemist.



The original Clemmensen reduction conditions are particularly effective at reducing aryl-alkyl ketones, such as those formed in a Friedel-Crafts acylation. The two-step sequence of Friedel-Crafts acylation followed by Clemmensen reduction constitutes a classical strategy for the primary alkylation of arenes. With aliphatic or

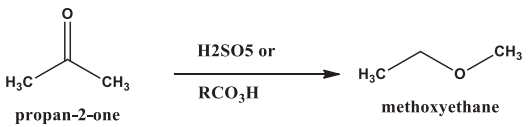
cyclic ketones, modified Clemmensen conditions using activated zinc dust in an anhydrous solution of hydrogen chloride in diethyl ether or acetic anhydride is much more effective.

The substrate must be tolerant of the strongly acidic conditions of the Clemmensen reduction (37% HCl). Several alternatives are available. Acid-sensitive substrates that are stable to strong base can be reduced using the Wolff-Kishner reduction; a further, milder method for substrates stable to hydrogenolysis in the presence of Raney nickel is the two-step Mozingo reduction.

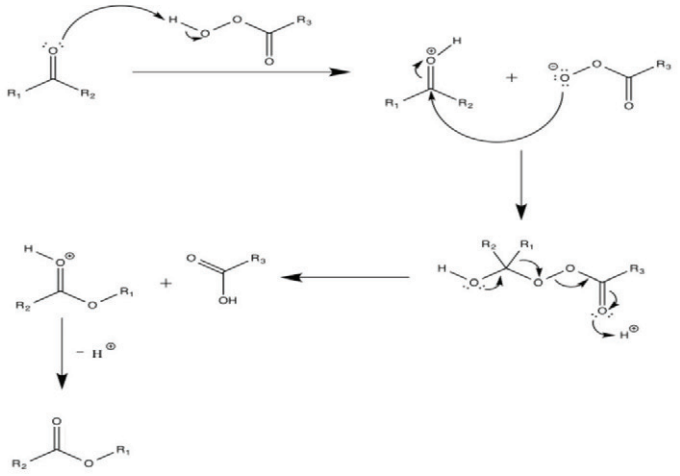
In spite of the antiquity of this reaction, the mechanism of the Clemmensen reduction remains obscure. Due to the heterogeneous nature of the reaction, mechanistic studies are difficult, and only a handful of studies have been disclosed. Mechanistic proposals generally invoke organozinc intermediates, sometimes including zinc carbenoids, either as discrete species or as organic fragments bound to the zinc metal surface. However, the corresponding alcohol is believed not to be an intermediate, since subjection of the alcohol to Clemmensen conditions generally does not afford the alkane product.

(11) Baeyer villager oxidation

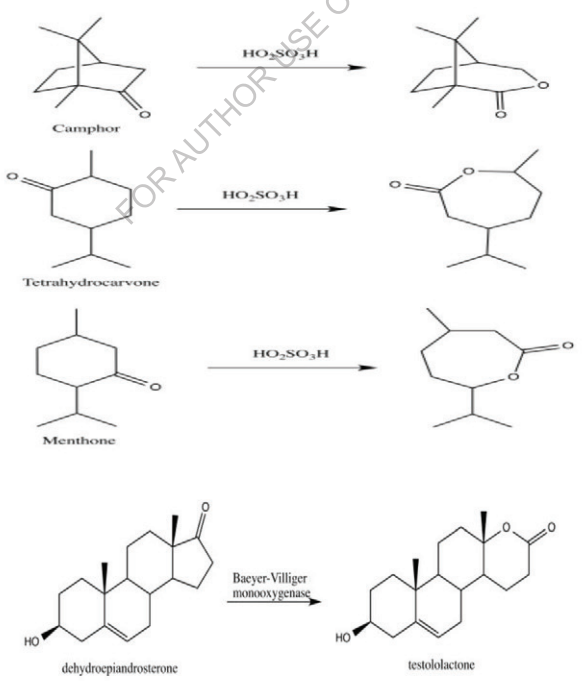
The Baeyer–Villiger oxidation is an organic reaction that forms an ester from a ketone or a lactone from a cyclic ketone, using peroxyacids or peroxides as the oxidant.[1] The reaction is named after Adolf von Baeyer and Victor Villiger who first reported the reaction in 1899.



Migration order is H>pH>30>20>10)

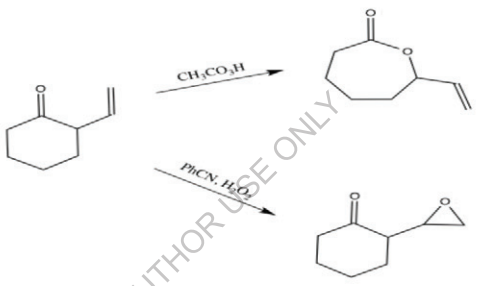


Example



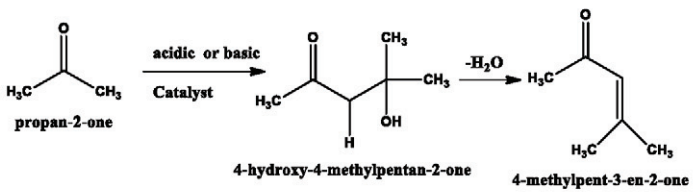
Limitations

The use of peroxyacids and peroxides when performing the Baeyer–Villiger oxidation can cause the undesirable oxidation of other functional groups. Alkenes and amines are a few of the groups that can be oxidized.[21] For instance, alkenes in the substrate, particularly when electron-rich, may be oxidized to epoxides. However, methods have been developed that will allow for the tolerance of these functional groups. In 1962, G. B. Payne reported that the use of hydrogen peroxide in the presence of a selenium catalyst will produce the epoxide from alkenyl ketones, while use of peroxyacetic acid will form the ester.

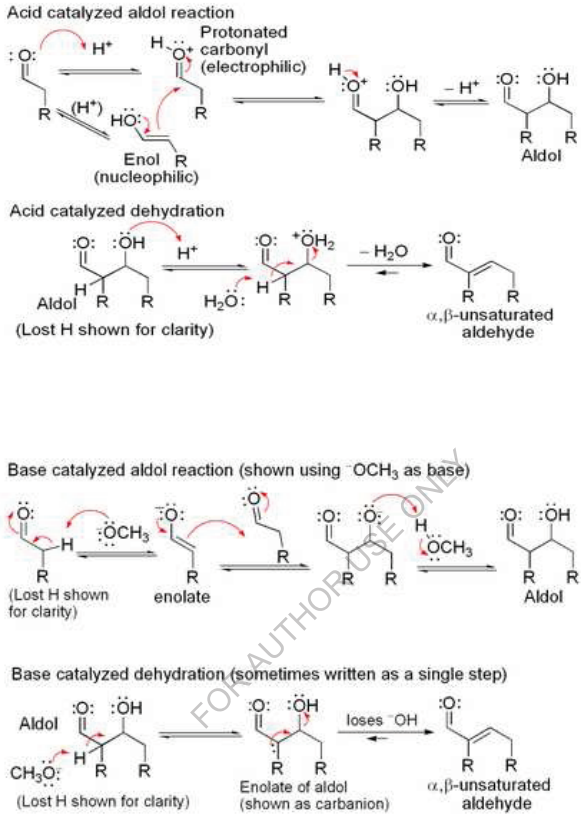


(12) Aldol Condensation

An aldol condensation is a condensation reaction in organic chemistry in which an enol or an enolate ion reacts with a carbonyl compound to form a β-hydroxyaldehyde or β-hydroxyketone (an aldol reaction), followed by dehydration to give a conjugated enone.



Mechanism



Condensation types

It is important to distinguish the aldol condensation from other addition reactions of carbonyl compounds.

- When the base is an amine and the active hydrogen compound is sufficiently activated the reaction is called a Knoevenagel condensation.
- In a Perkin reaction the aldehyde is aromatic and the enolate generated from an anhydride.
- A Claisen condensation involves two ester compounds.

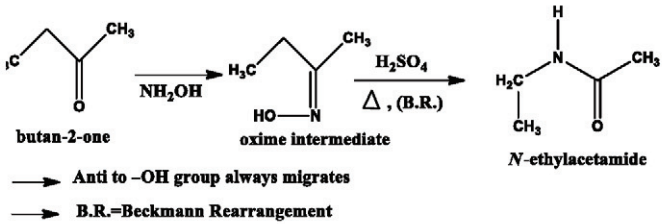
- A Dieckmann condensation involves two ester groups in the *same molecule* and yields a cyclic molecule
- A Henry reaction involves an aldehyde and an aliphatic nitro compound.
- A Robinson annulation involves an α,β-unsaturated ketone and a carbonyl group, which first engage in a Michael reaction prior to the aldol condensation.
- In the Guerbet reaction, an aldehyde, formed *in situ* from an alcohol, self-condenses to the dimerized alcohol.
- In the Japp–Maitland condensation water is removed not by an elimination reaction but by a nucleophilic displacement.

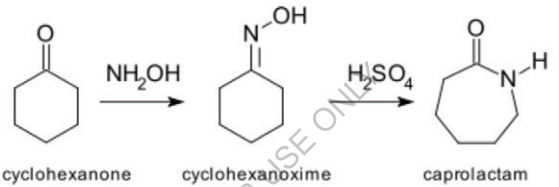
(13) Beckmann Reaction (rearrangement)

The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann (1853–1923), is a rearrangement of an oxime functional group to substituted amides. The rearrangement has also been successful performed on haloimines and nitrones. Cyclic oximes and haloimines yield lactams.

The Beckmann rearrangement is often catalyzed by acid, however other reagents have been known to promote the rearrangement. These include tosyl chloride, thionyl chloride, phosphorus pentachloride, phosphorus pentoxide, triethylamine, sodium hydroxide, trimethylsilyl iodide among others. The Beckmann fragmentation is another reaction that often competes with the rearrangement, though careful selection of promoting reagent and solvent conditions can favor the formation of one over the other, sometimes giving almost exclusively one product. The rearrangement occurs stereospecifically for ketoximes and N-chloro/N-fluoro imines, with the migrating group being anti-periplanar to the leaving group on the nitrogen. Certain conditions have been known to racemize the oxime geometry, leading to the formation of both regioisomers. The rearrangement of aldoximes occurs with stereospecificity in the gas phase and without stereospecificity in the solution phase. A few methodologies allow for the rearrangement of aldoximes to primary amides, but fragmentation commonly competes in these systems. Nitrone rearrangement also occurs without

stereospecificity; the regioisomer formed has the amide nitrogen substituted with the group possessing the greatest migratory aptitude.

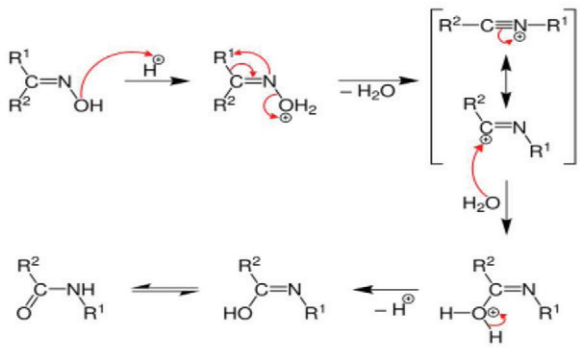




The archetypal Beckmann rearrangement is the conversion of cyclohexanone to caprolactam via the oxime. Caprolactam is the feedstock in the production of Nylon 6.

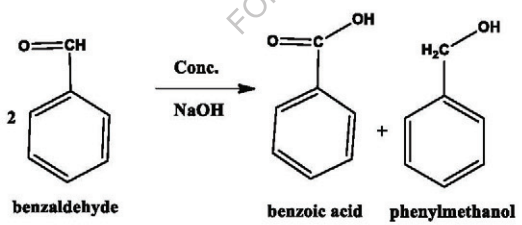
The Beckmann solution consists of acetic acid, hydrochloric acid and acetic anhydride, and was widely used to catalyze the rearrangement. Other acids, such as sulfuric acid, polyphosphoric acid, and hydrogen fluoride have all been used. Sulfuric acid is the most commonly used acid for commercial lactam production due to its formation of an ammonium sulfate by-product when neutralized with ammonia. Ammonium sulfate is a common agricultural fertilizer providing nitrogen and sulfur.

Mechanism



(14) Cannizzaro reaction

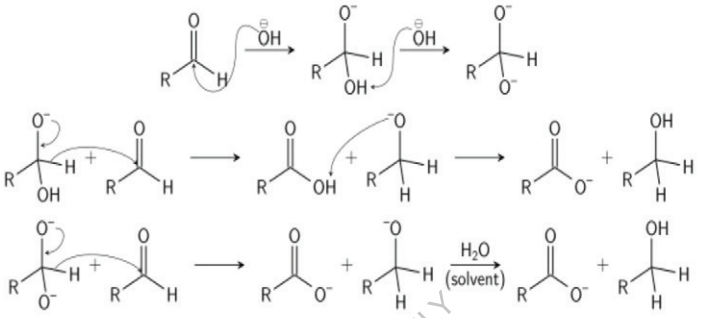
The Cannizzaro reaction, named after its discoverer Stanislao Cannizzaro, is a chemical reaction that involves the base-induced disproportionation of two molecules of a non-enolizable aldehyde to give a primary alcohol and a carboxylic acid.



Mechanism

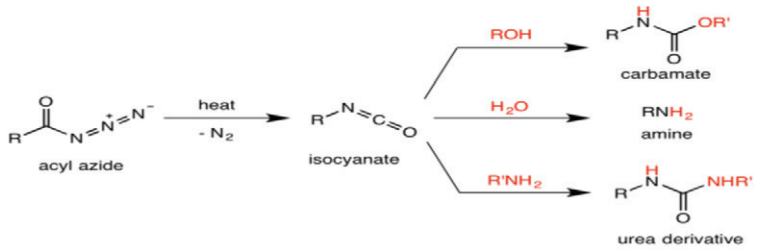
The reaction involves a nucleophilic acyl substitution on an aldehyde, with the leaving group concurrently attacking another aldehyde in the second step. First, hydroxide attacks a carbonyl. The resulting tetrahedral intermediate then collapses, re-forming the

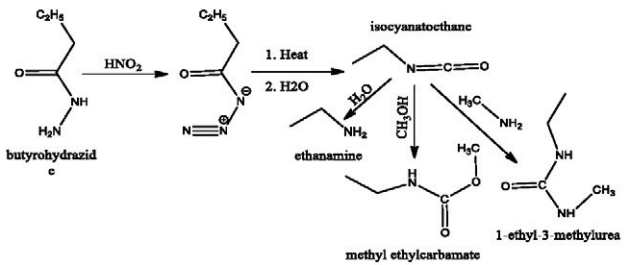
carbonyl and transferring hydride to attack another carbonyl.[4] In the final step of the reaction, the acid and alkoxide ions formed exchange a proton. In the presence of a very high concentration of base, the aldehyde first forms a doubly charged anion from which a hydride ion is transferred to the second molecule of aldehyde to form carboxylate and alkoxide ions. Subsequently, the alkoxide ion acquires a proton from the solvent.



(15) Curtius rearrangement

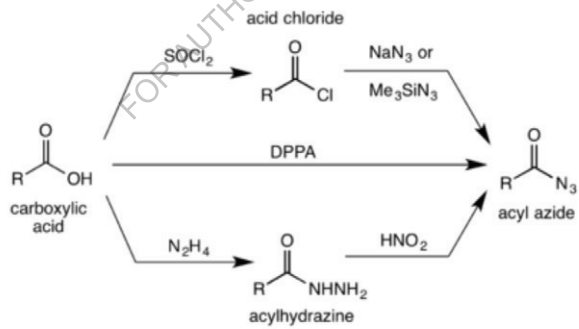
The Curtius rearrangement (or Curtius reaction or Curtius degradation), first defined by Theodor Curtius in 1885, is the thermal decomposition of an acyl azide to an isocyanate with loss of nitrogen gas.[1][2] The isocyanate then undergoes attack by a variety of nucleophiles such as water, alcohols and amines, to yield a primary amine, carbamate or urea derivative respectively.[3] Several reviews have been published.





Preparation of acyl azide

The acyl azide is usually made from the reaction of acid chlorides or anydrides with sodium azide or trimethylsilyl azide. Acyl azides are also obtained from treating acylhydrazines with nitrous acid. Alternatively, the acyl azide can be formed by the direct reaction of a carboxylic acid with diphenylphosphoryl azide (DPPA).

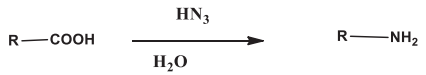


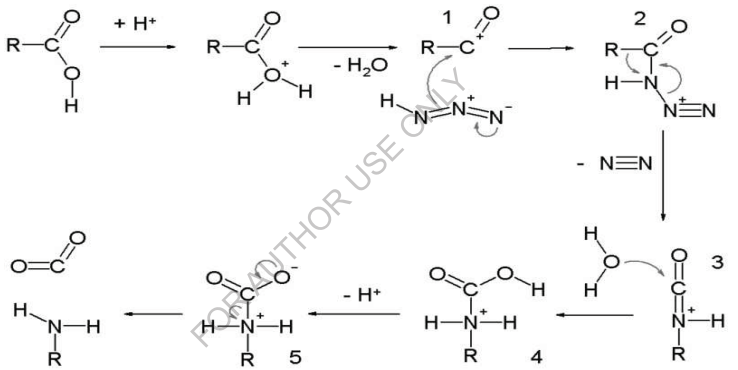
The migration occurs with full retention of configuration at the R-group. The migratory aptitude of the R-group is roughly **tertiary > secondary ~ aryl > primary**. The isocyanate formed can then be hydrolyzed to give a primary amine, or undergo nucleophilic attack with alcohols and amines to form carbamates and urea derivatives respectively.

(16) Schmidt Rearrangement

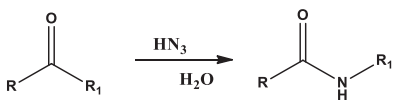
The Schmidt reaction is an organic reaction in which an **azide** reacts with a **carbonyl group** to give an **amine** or **amide**, with expulsion of nitrogen. It is named after ***Sir Karl Friedrich Schmidt***.

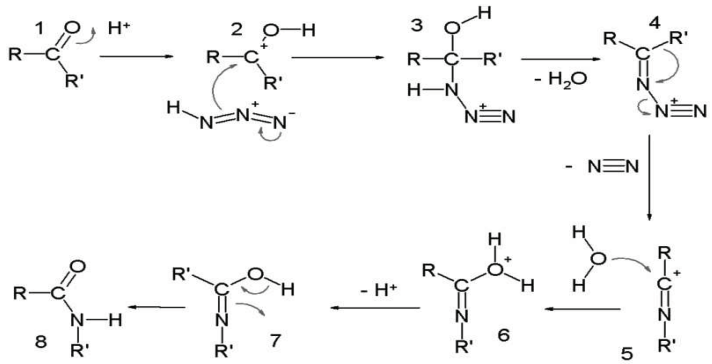
(1)





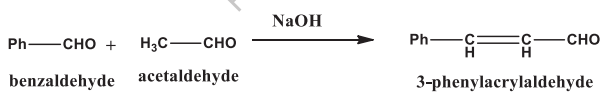
(2)

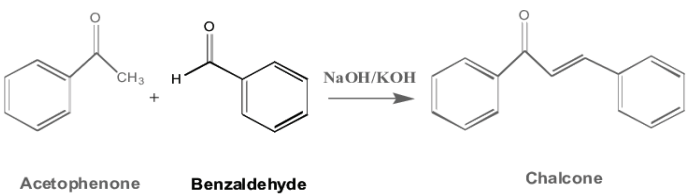




(17) Claisen-Schmidt Condensation

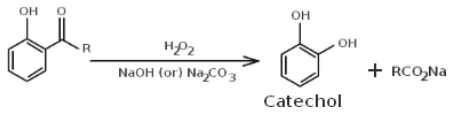
The reaction between an aldehyde or ketone having an alpha-hydrogen with an aromatic carbonyl compound lacking an alpha hydrogen is called the Claisen–Schmidt condensation. In cases where the product formed still has reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.

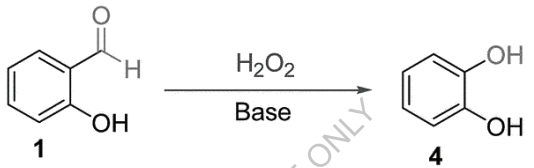




(18) Dakin Reaction

Dakin Reaction is the replacement of the aldehyde group of ortho and para hydroxy and ortho amino-benzaldehyde (or ketone) by a hydroxyl group on reaction with alkaline hydrogen peroxide.

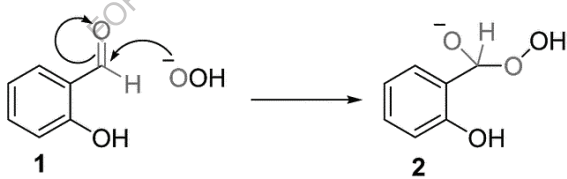




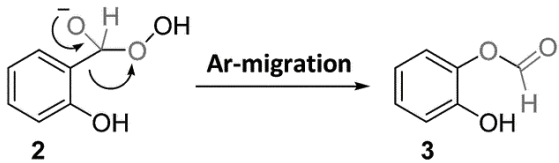
Mechanism:

Step 1: $HOOH + B^- \rightarrow HOO^- + BH$ Base = B^-

Step 2:

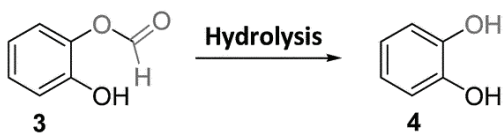


Step 3:



(aryl formate intermediate)

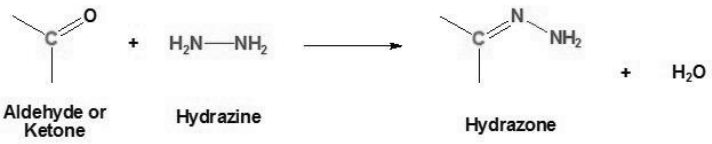
Step 4:



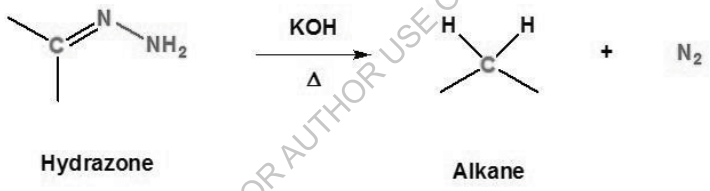
(19) Wolff Kishner Reduction Reaction

The *reduction* of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane.

Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone.

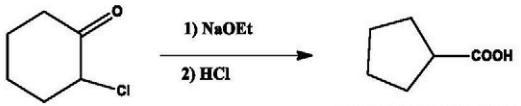


Reaction with a Base and Heat Converts a Hydrazone to an Alkane



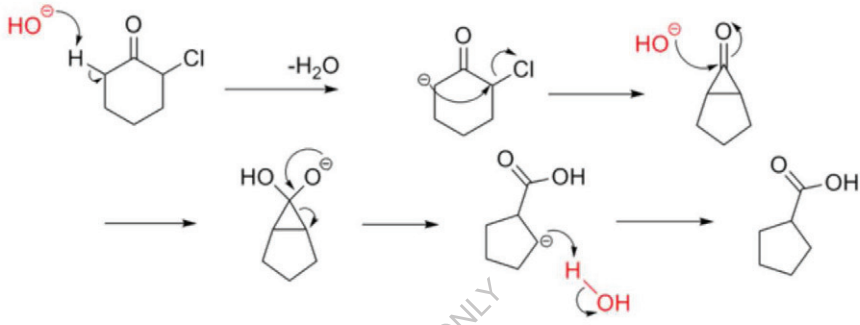
(20) Favorskii rearrangement

The Favorskii rearrangement, named for the Russian chemist Alexei Yevgrafovich Favorskii, is most principally a rearrangement of cyclopropanones and α-halo ketones which leads to carboxylic acid derivatives. In the case of cyclic α-halo ketones, the Favorskii rearrangement constitutes a ring contraction. This rearrangement takes place in the presence of a base, sometimes hydroxide, to yield a carboxylic acid but most of the time either an alkoxide base or an amine to yield an ester or an amide, respectively. α,α'-Dihaloketones eliminate HX under the reaction conditions to give α,β-unsaturated carbonyl compounds.



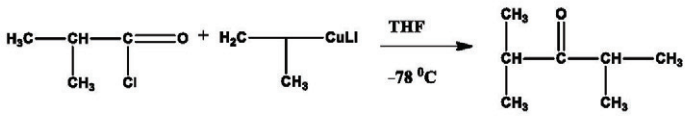
cyclopentanecarboxylic acid

Mechanism



(21) Corey-House Synthesis

The Corey–House synthesis (also called the Corey–Posner–Whitesides–House reaction and other permutations) is an organic reaction that involves the reaction of a lithium diorganylcuprate (R_2CuLi) with an organyl (pseudo)halide (R'X) to form a new alkane, as well as an ill-defined organocopper species and lithium halide as byproducts.

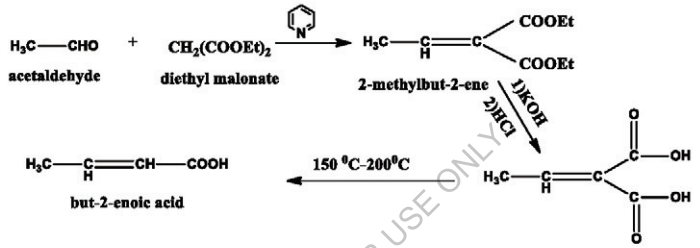


2,4-dimethylpentan-3-one

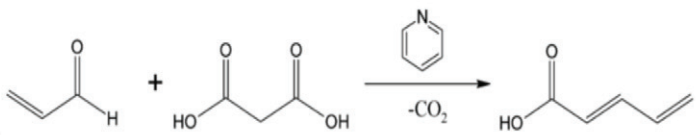
(22) Knoevenagel Condentation reaction

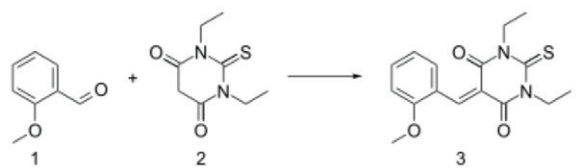
The Knoevenagel condensation (pronounced ['knø:vəna:gl]) reaction is an organic reaction named after Emil Knoevenagel. It is a modification of the aldol condensation.

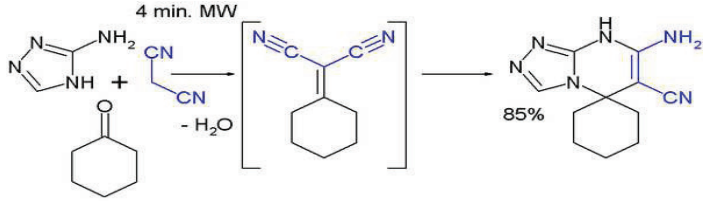
A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated (hence *condensation*). The product is often an α,β-unsaturated ketone (a conjugated enone).

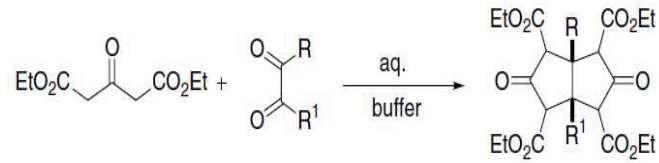


Example



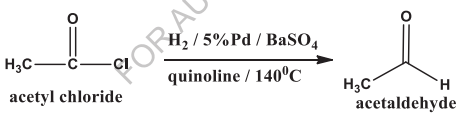






(23) Rosenmund reaction

The **Rosenmund reduction** is a hydrogenation process in which an acyl chloride is selectively reduced to an aldehyde. The reaction was named after Karl Wilhelm Rosenmund, who first reported it in 1918.



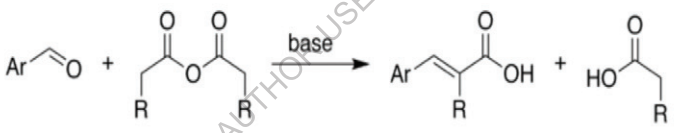
The reaction, a hydrogenolysis, is catalysed by palladium on barium sulfate, which is sometimes called the Rosenmund catalyst. Barium sulfate has a low surface area which reduces the activity of the palladium, preventing over-reduction. However, for certain reactive acyl chlorides the activity must be reduced further, by the addition of a poison. Originally this was thioquinanthrene although thiourea[2] has also been used. Deactivation is required because the system must reduce the acyl chloride but not the subsequent aldehyde. If further reduction does take place it will create a primary alcohol which would then react with the remaining acyl chloride to form an ester.

Rosenmund catalyst can be prepared by reduction of palladium(II) chloride solution in the presence of $BaSO_4$. Typical reducing agent is formaldehyde.

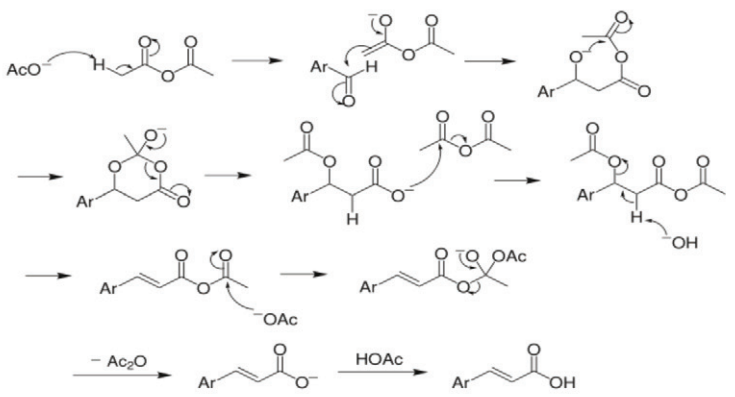
While Rosenmund reduction method can be used to prepare several aldehydes, formaldehyde cannot be prepared, as formyl chloride is unstable at room temperatures.

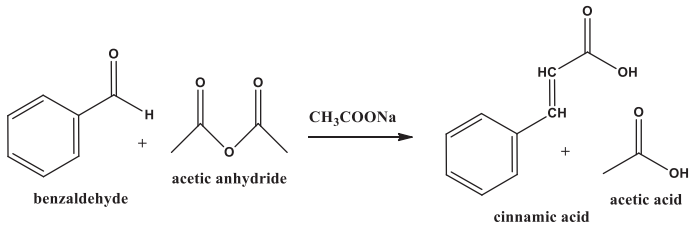
(24) Perkin Condensation reaction

The Perkin reaction is an organic reaction developed by English chemist William Henry Perkin that is used to make cinnamic acids. It gives an α,β-unsaturated aromatic acid by the aldol condensation of an aromatic aldehyde and an acid anhydride, in the presence of an alkali salt of the acid. The alkali salt acts as a base catalyst, and other bases can be used instead.



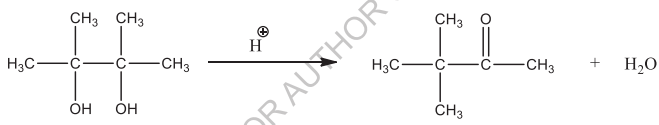
Mechanism



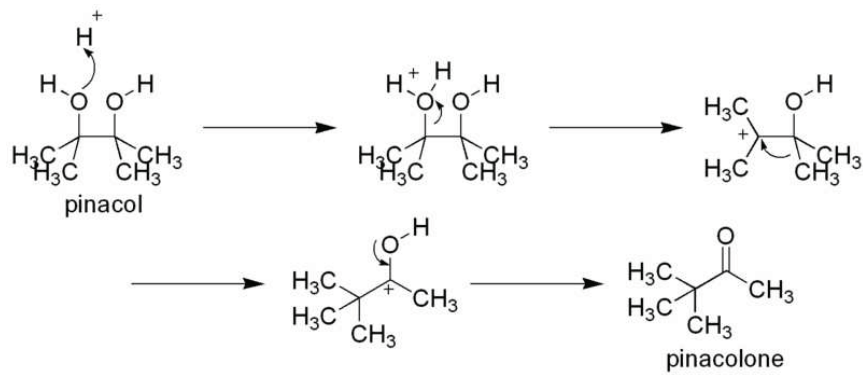


(25) Pinacol-Pinacolone rearrangement

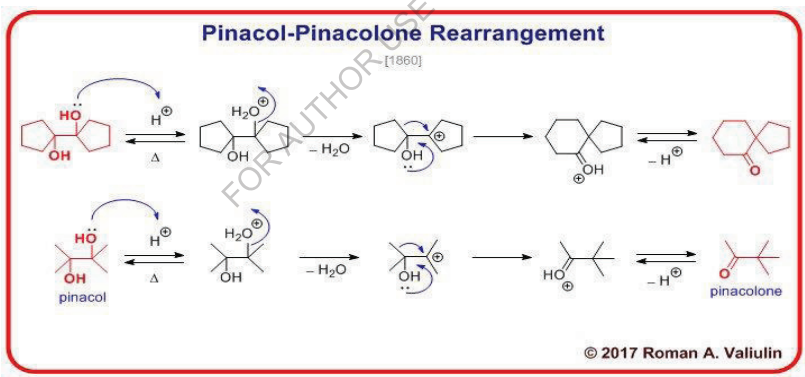
The pinacol–pinacolone rearrangement is a method for converting a 1,2-diol to a carbonyl compound in organic chemistry. The 1,2-rearrangement takes place under acidic conditions. The name of the rearrangement reaction comes from the rearrangement of pinacol to pinacolone.

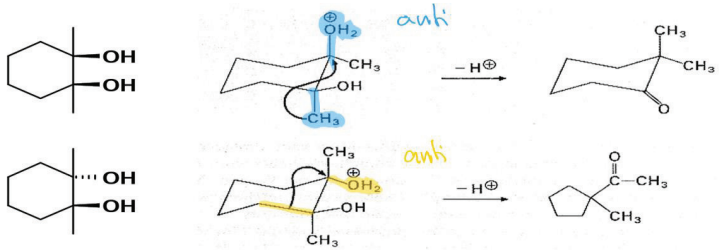


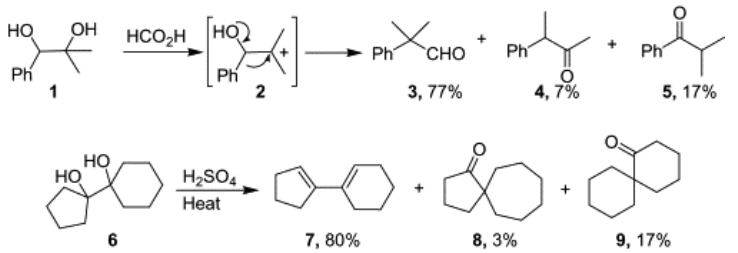
Mechanism



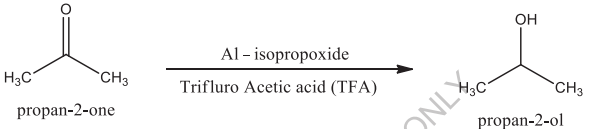
In the course of this organic reaction, protonation of one of the –OH groups occurs and a carbocation is formed. If both the –OH groups are not alike, then the one which yields a more stable carbocation participates in the reaction. Subsequently, an alkyl group from the adjacent carbon migrates to the carbocation center. The driving force for this rearrangement step is believed to be the relative stability of the resultant oxonium ion, which has complete octet configuration at all centers (as opposed to the preceding carbocation). The migration of alkyl groups in this reaction occurs in accordance with their usual migratory aptitude**, i.e.hydride > phenyl carbanion > tertiary carbanion (if formed by migration) > secondary carbanion (if formed by migration) > methyl carbanion** . {Why Carbanion? Because every migratory group leaves by taking electron pair with it.} The conclusion is that the group which stabilizes the carbocation more effectively is migrated.







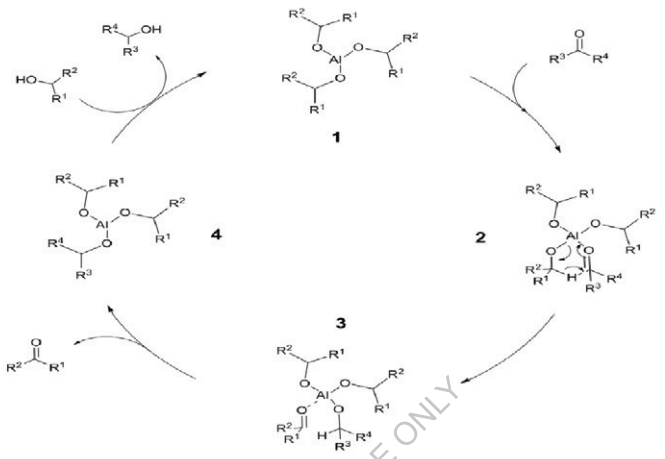
(26) Meerwein-Ponndorf-Verley (MPV) reduction



The Meerwein–Ponndorf–Verley (MPV) reduction in organic chemistry is the reduction of ketones and aldehydes to their corresponding alcohols utilizing aluminium alkoxide catalysis in the presence of a sacrificial alcohol.[1] The advantages of the MPV reduction lie in its high chemoselectivity, and its use of a cheap environmentally friendly metal catalyst.

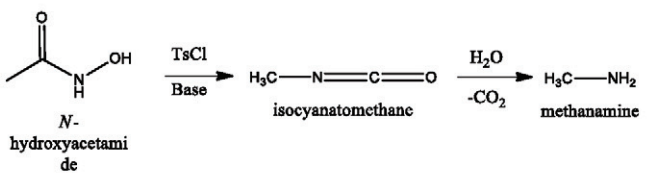
The MPV reduction was discovered by Meerwein and Schmidt, and separately by Verley in 1925. They found that a mixture of aluminium ethoxide and ethanol could reduce aldehydes to their alcohols.[2][3] Ponndorf applied the reaction to ketones and upgraded the catalyst to aluminium isopropoxide in isopropanol.

Mechanism



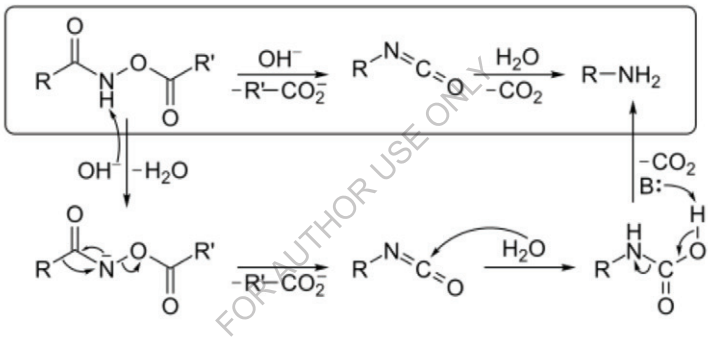
(27) Lossen Rearrangement reaction

The Lossen rearrangement is the conversion of a hydroxamic acid to an isocyanate via the formation of an O-acyl, sulfonyl, or phosphoryl intermediate hydroxamic acid O-derivative and then conversion to its conjugate base. Here, 4-toluenesulfonyl chloride is used to form a sulfonyl O-derivative of hydroxamic acid.



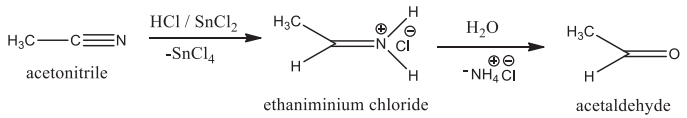
Mechanism

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 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.



(28) Synthesis of aldehyde by Stephen's method

Stephen aldehyde synthesis, a named reaction in chemistry, was invented by Henry Stephen (OBE/MBE). This reaction involves the preparation of aldehydes (R-CHO) from nitriles (R-CN) using tin(II) chloride ($SnCl_2$), hydrochloric acid (HCl) and quenching the resulting iminium salt ($[R\text{-}CH{=}NH_2]^+Cl^-$) with water ($H_2O$).[1][2] During the synthesis, ammonium chloride is also produced.



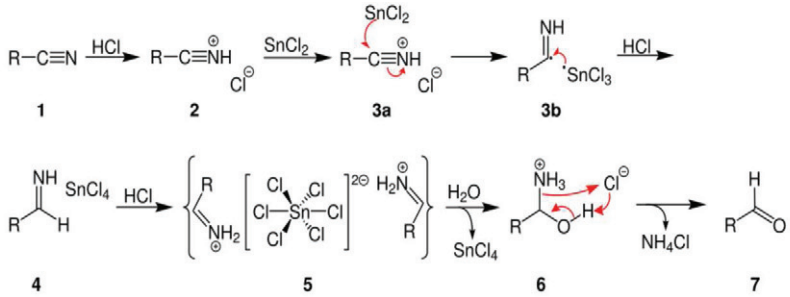
acetonitrile — ethaniminium chloride — acetaldehyde

Mechanism

By addition of hydrogen chloride the used nitrile (1) reacts to its corresponding salt (2). It is believed that this salt is reduced by a single electron transfer by the tin(II) chloride (3a and 3b). The resulting salt (4) precipitates after some time as aldimine tin chloride (5). Hydrolysis of 5 produces a amide (6) from which an aldehyde (7) is formed.

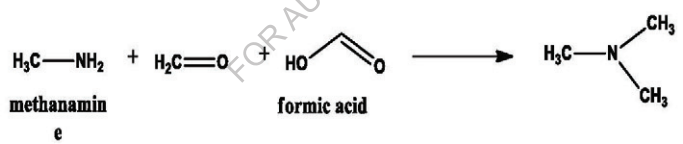
Substitutes that increase the electron density promote the formation of the aldimin-tin chloride adduct. By electron withdrawing substituents, the formation of amide chloride is facilitated. In the past, the reaction was carried out by precipitating the aldimine-tin chloride, washing it with ether and then hydrolyzing it. However, it has been found that this step is unnecessary and the aldimine tin chloride can be hydrolysed directly in the solution.

This reaction is more efficient when aromatic nitriles are used instead of aliphatic ones. However, even for some aromatic nitriles (e. g. 2-formylbenzoic acid ethyl ester) the yield can be low.



(29) Eschweiler–Clarke methylation

The Eschweiler–Clarke reaction (also called the Eschweiler–Clarke methylation) is a chemical reaction whereby a primary (or secondary) amine is methylated using excess formic acid and formaldehyde. Reductive amination reactions such as this one will not produce quaternary ammonium salts, but instead will stop at the tertiary amine stage. It is named for the German chemist Wilhelm Eschweiler (1860–1936) and the British chemist Hans Thacher Clarke (1887-1972).



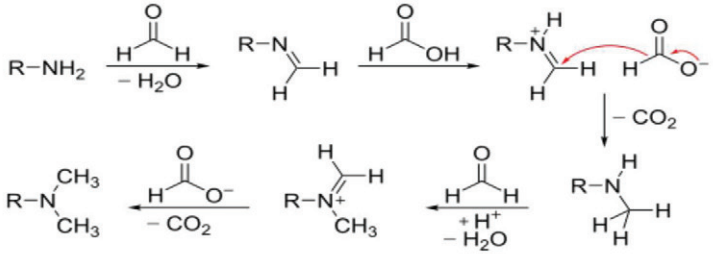
Mechanism

The first methylation of the amine begins with imine formation with formaldehyde. The formic acid acts as a source of hydride and reduces the imine to a secondary amine. The driving force is the formation of the gas carbon dioxide. Formation of the tertiary amine is similar, but slower due to the difficulties in iminium ion formation.

From this mechanism it is clear that a quaternary ammonium salt will never form, because it is impossible for a tertiary amine to form another imine or iminium ion.

Chiral amines typically do not racemize under these conditions.

Altered versions of this reaction replace formic acid with sodium cyanoborohydride.



(30) Cyanide to amide in presence of HCl

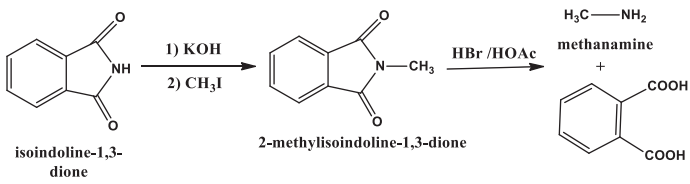
(31) Gabriel-Phthalimide synthesis

Gabriel Phthalimide Synthesis Mechanism has 3 steps. The Synthesis is used to get primary amines from primary alkyl halides and is named after the German scientist Siegmund Gabriel. The reaction has been generalized for applications in the alkylation of sulfonamides and imides & their deprotection in order to obtain amines. Alkylation of ammonia is quite inefficient; therefore, it is substituted with phthalimide anion in the Gabriel synthesis.

Synthesis Details

The biggest advantage of using the Gabriel synthesis is the avoidance of over alkylation. A good nucleophile in the form of an imide ion is also formed with the reaction of potassium hydroxide with the phthalimide. The imide ion executes a nucleophilic substitution reaction on the alkyl halide and creates an intermediate – N-alkyl phthalimide. Hydrolysis or Hydrazinolysis of this phthalimide yields a primary

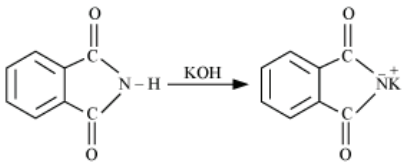
alkyl amine. However, aryl amines cannot be prepared via Gabriel synthesis as aryl halides don't undergo simple nucleophilic substitution.



Mechanism

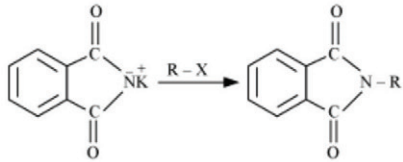
Step 1

When potassium hydroxide is introduced to the phthalimide, an acid-base reaction ensues. The hydroxide ion deprotonates the imide. The resulting proton is more acidic than any simple amine (the two adjacent carbonyl-like groups offer resonance stabilization), generating a strong nucleophile – the imide ion.



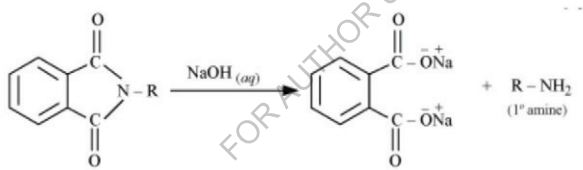
Step 2

The nucleophilic imide ion attacks the electrophilic carbon of the alkyl halide. The nitrogen atom subsequently replaces the halogen (Fluorine, Chlorine, Bromine or Iodine) in the alkyl halide and bonds with the carbon itself. This results in the formation of an N-Alkyl Phthalimide.



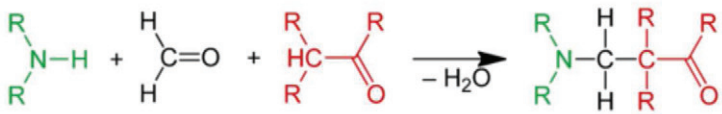
Step 3

The mechanism that takes place here is quite similar to base-catalyzed hydrolysis of esters, with nitrogen attached to the R group instead of oxygen. The hydroxide ion attacks the carbon atom bonded to the nitrogen atom, cleaving the N-Alkyl phthalimide. The cation in the base attaches itself to the oxygen atom as well. It is important to note that the nitrogen atom attached to the R group bonds with the hydrogens ejected from the hydroxide ion when the oxygen atom replaces it in the phthalimide. An example of the third step of the Gabriel phthalimide synthesis mechanism is shown below



(32) Mannich reaction

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound also known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.

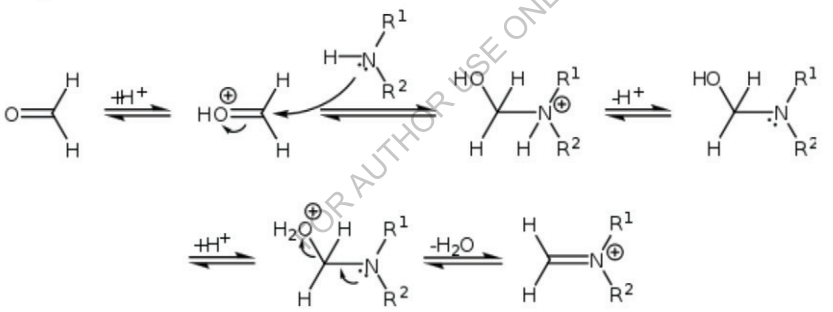


The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become an enol). The Mannich reaction is also considered a condensation reaction.

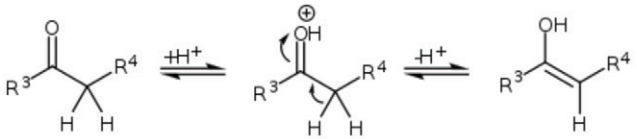
In the Mannich reaction, primary or secondary amines or ammonia, are employed for the activation of formaldehyde. Tertiary amines lack an N–H proton to form the intermediate enamine. α-CH-acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. It is also possible to use activated phenyl groups and electron-rich heterocycles such as furan, pyrrole, and thiophene. Indole is a particularly active substrate; the reaction provides gramine derivatives.

Mechanism

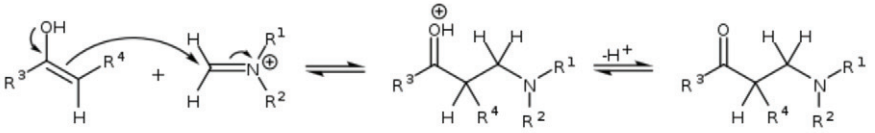
Step 1



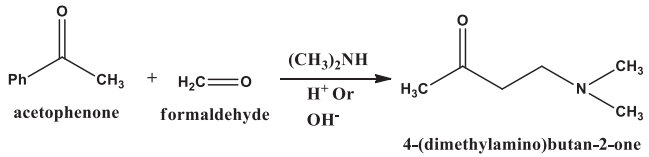
Step 2



Step 3

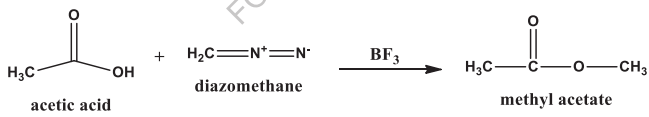


Example



(33) Methylation by Diazomethane

Diazomethane is the chemical compound CH_2N_2, discovered by German chemist Hans von Pechmann in 1894. It is the simplest diazo compound. In the pure form at room temperature, it is an extremely sensitive explosive yellow gas; thus, it is almost universally used as a solution in diethyl ether. The compound is a popular methylating agent in the laboratory, but it is too hazardous to be employed on an industrial scale without special precautions.[4] Use of diazomethane has been significantly reduced by the introduction of the safer and equivalent reagent trimethylsilyldiazomethane**.**



Use

For safety and convenience diazomethane is always prepared as needed as a solution in ether and used as such. It converts carboxylic acids into their methyl esters. The reaction is thought to proceed via proton transfer from carboxylic acid to diazomethane to give methyldiazonium cation, which immediately reacts with the carboxylate ion to give the methyl ester and nitrogen gas. Since proton transfer is required and rate limiting, this reaction exhibits high specificity for carboxylic acids over less acidic oxygenated functional groups like alcohols and phenols.

Safety

Diazomethane is toxic by inhalation or by contact with the skin or eyes (TLV 0.2ppm). Symptoms include chest discomfort, headache, weakness and, in severe cases, collapse. Symptoms may be delayed. Deaths from diazomethane poisoning have been reported. In one instance a laboratory worker consumed a hamburger near a fumehood where he was generating a large quantity of diazomethane, and died four days later from fulminating pneumonia.[15] Like any other alkylating agent it is expected to be carcinogenic, but such concerns are overshadowed by its serious acute toxicity.

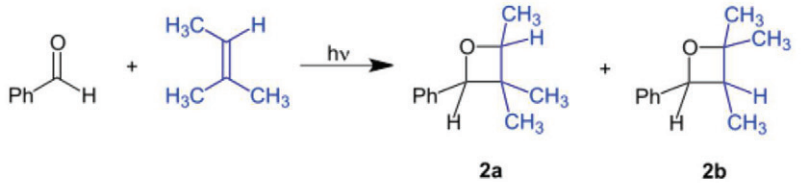
CH_2N_2 may explode in contact with sharp edges, such as ground-glass joints, even scratches in glassware.[16] Glassware should be inspected before use and preparation should take place behind a blast shield. Specialized kits to prepare diazomethane with flame-polished joints are commercially available.

The compound explodes when heated beyond 100 °C, exposed to intense light, alkali metals, or calcium sulfate. Use of a blast shield is highly recommended while using this compound.

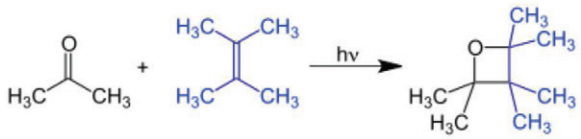
Proof-of-concept work has been done with microfluidics, in which continuous point-of-use synthesis from N-methyl-N-nitrosourea and 0.93M potassium hydroxide in water was followed by point-of-use conversion with benzoic acid, resulting in a 65% yield of the methyl benzoate ester within seconds at temperatures ranging from 0-50 C. The yield was better than under capillary conditions; the microfluidics were credited with "suppression of hot spots, low holdup, isothermal conditions, and intensive mixing."

(34) Paterno-Buchi Reaction

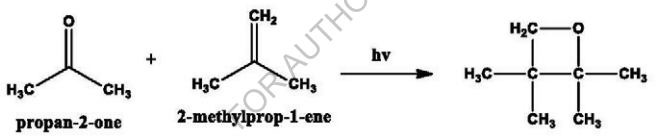
The Paternò–Büchi reaction, named after Emanuele Paternò and George Büchi who established its basic utility and form, is a photochemical reaction that forms four-membered oxetane rings from a carbonyl and an alkene.



2a 2b



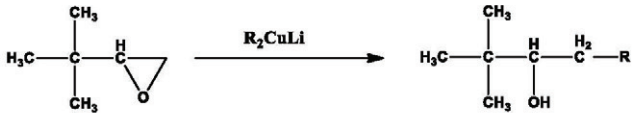
Here an electronically excited carbonyl group is added to a ground state olefin yielding an oxetane. With substrates benzaldehyde and 2-methyl-2-butene the reaction product is a mixture of structural isomers:



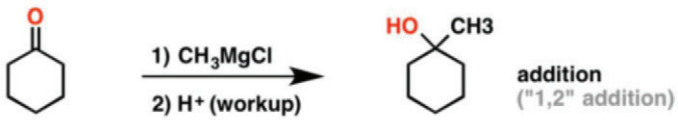
propan-2-one 2-methylprop-1-ene 2,2,3,3-tetramethyloxetane

(35) Gillman reagent

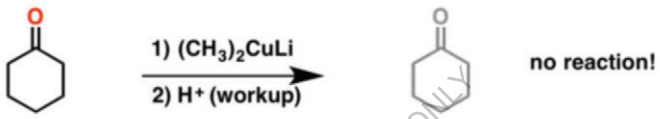
A Gilman reagent is a lithium and copper (diorganocopper) reagent compound, R_2CuLi, where R is an alkyl or aryl. These reagents are useful because, unlike related Grignard reagents and organolithium reagents, they react with organic halides to replace the halide group with an R group (the Corey–House reaction). Such displacement reactions allow for the synthesis of complex products from simple building blocks.



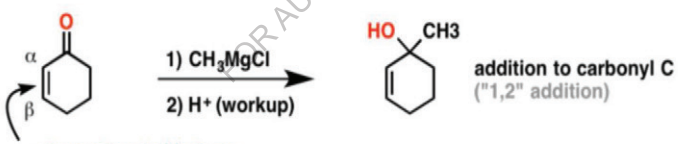
Grignard reagents add to ketones (and other carbonyls)...



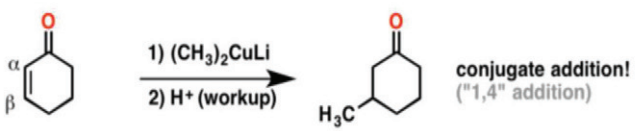
... but Gilman reagents (organocuprates) do not !



Even more interesting: contrast their reactivity with α, β unsaturated ketones



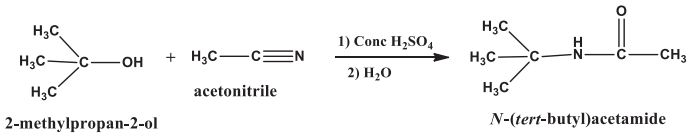
α, β unsaturated ketone
(note the double bond)



the carbon directly adjacent to a carbonyl is referred to as the "alpha" (α) carbon. the next carbon along is the "beta" (β) carbon, then the "gamma" (γ) and so on.

(36) Ritter reaction

The Ritter reaction is a chemical reaction that transforms a nitrile into an *N*-alkyl amide using various electrophilic alkylating reagents. The original reaction formed the alkylating agent using an alkene or alcohol in the presence of a strong acid: The reaction has been the subject of several literature reviews.



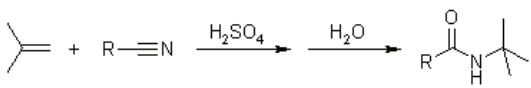
2-methylpropan-2-ol **N-(*tert*-butyl)acetamide**

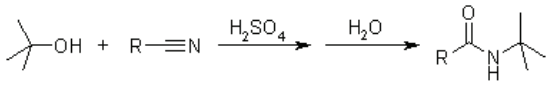
Applications

The Ritter reaction is most useful in the formation of amides in which the nitrogen has a tertiary alkyl group. It is also used in industrial processes as it can be effectively scaled up from laboratory experiments to large-scale applications while maintaining high yield. Real world applications include Merck's industrial-scale synthesis of anti-HIV drug Crixivan (indinavir); the production of the falcipain-2 inhibitor PK-11195; the synthesis of the alkaloid aristotelone; and synthesis of Amantadine, an antiviral and antiparkinsonian drug. Other applications of the Ritter reaction include synthesis of dopamine receptor ligands and licit and illicit production of racemic amphetamine from allylbenzene and methyl cyanide.

A problem with the Ritter reaction is the necessity of an extremely strong acid catalyst in order to produce the carbocation. This poses a safety risk when running the reaction and makes disposal of waste products difficult. However, other methods have been proposed in order promote carbocation formation, including photocatalytic electron transfer[19] or direct photolysis.

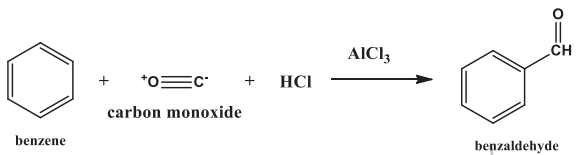
Example





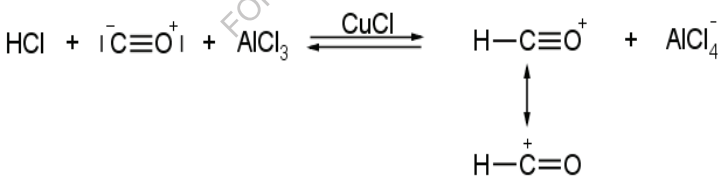
(37) Gatterman-Koch reaction

This reaction doesn't work on unactivated (even the least unactivated). For example, we absolutely couldn't carry this reaction on a nitro-benzene. The utilization of cuprous chloride isn't always necessary.

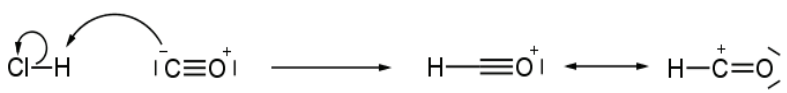


Mechanism

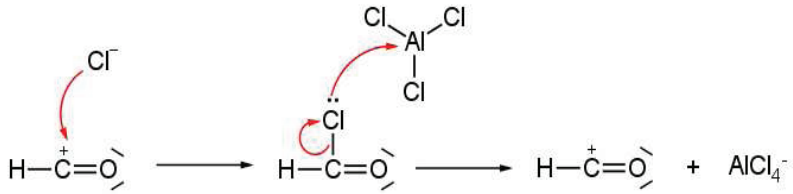
Step 1



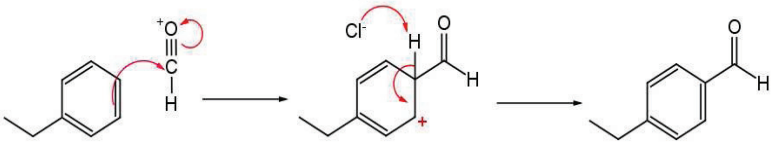
Step 2



Step 3

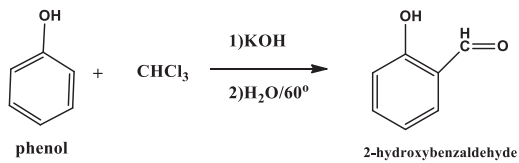


Step 4



(38) Reimer-Tiemann reaction

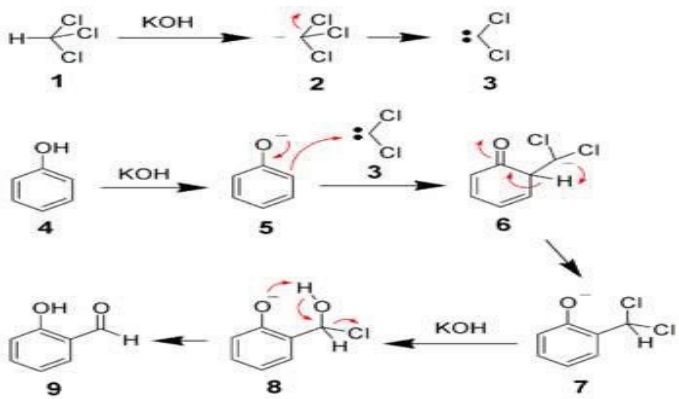
The Reimer–Tiemann reaction is a chemical reaction used for the ortho-formylation of phenols; with the simplest example being the conversion of phenol to salicylaldehyde. The reaction was discovered by Karl Reimer [de] and Ferdinand Tiemann. The Reimer in question was Karl Reimer (1845-1883) not the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



phenol — 2-hydroxybenzaldehyde

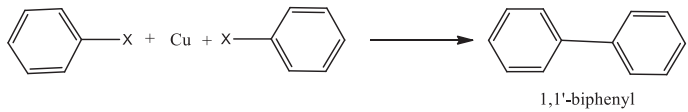
Mechanism

Chloroform (1) is deprotonated by a strong base (normally hydroxide) 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. Nucleophilic attack of the dichlorocarbene gives an intermediate dichloromethyl substituted phenol (7). After basic hydrolysis, the desired product (9) is formed.



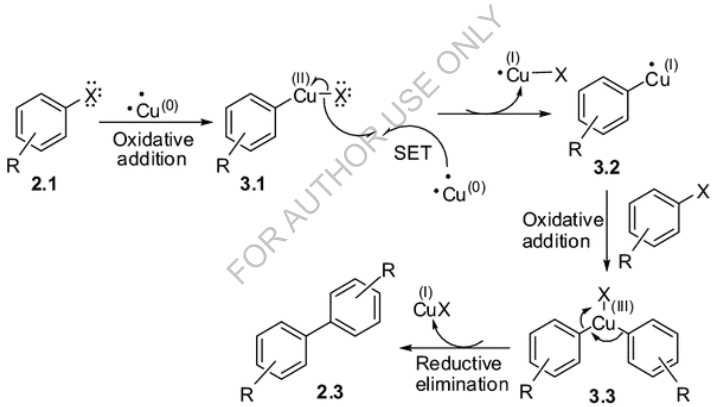
(39) Ullmann synthesis

The Ullmann reaction or Ullmann coupling is a coupling reaction between aryl halides and copper. The reaction is named after Fritz Ullmann.



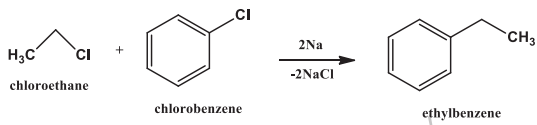
X= Cl,Br,I

Mechanism



(40) Wurtz- Fittig reaction

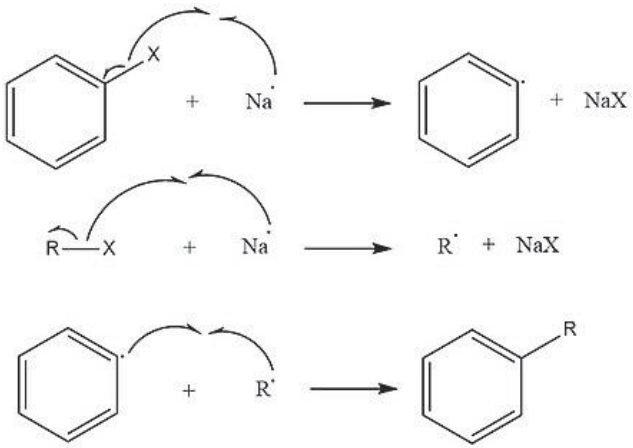
The Wurtz–Fittig reaction is the chemical reaction of aryl halides with alkyl halides and sodium metal in the presence of dry ether to give substituted aromatic compounds. Charles Adolphe Wurtz reported what is now known as the Wurtz reaction in 1855, involving the formation of a new carbon-carbon bond by coupling two alkyl halides. Work by Wilhelm Rudolph Fittig in the 1860s extended the approach to the coupling of an alkyl halide with an aryl halide. This modification of the Wurtz reaction is considered a separate process and is named for both scientists.



The reaction works best for forming asymmetrical products if the halide reactants are somehow separate in their relative chemical reactivities. One way to accomplish this is to form the reactants with halogens of different periods. Typically the alkyl halide is made more reactive than the aryl halide, increasing the probability that the alkyl halide will form the organosodium bond first and thus act more effectively as a nucleophile toward the aryl halide. Typically the reaction is used for the alkylation of aryl halides; however, with the use of ultrasound the reaction can also be made useful for the production of biphenyl compounds.

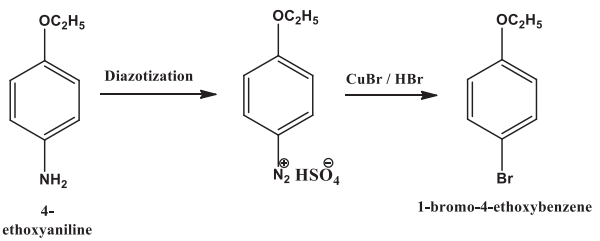
Mechanism

There are two approaches to describing the mechanism of the Wurtz–Fittig reaction. The first involves the sodium-mediated formation of both alkyl and aryl radicals. The alkyl and aryl radicals then combine to form a substituted aromatic compound.



(41) Sandmeyer reaction

The Sandmeyer reaction is a chemical reaction used to synthesize aryl halides from aryl diazonium salts using copper salts as reagents or catalysts. It is an example of a radical-nucleophilic aromatic substitution. The Sandmeyer reaction provides a method through which one can perform unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation, and hydroxylation.



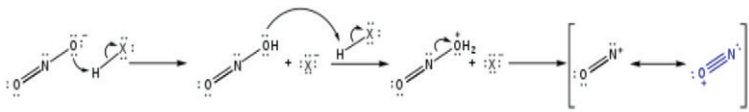
4-ethoxyaniline

1-bromo-4-ethoxybenzene

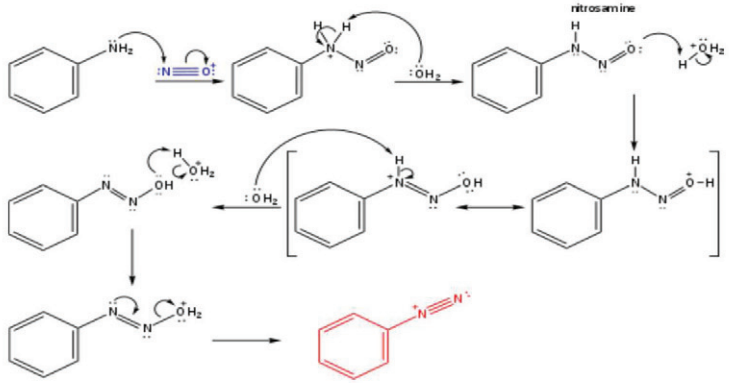
The reaction was discovered in 1884 by Swiss chemist Traugott Sandmeyer, when he attempted to synthesize phenylacetylene from benzenediazonium chloride and cuprous acetylide. Instead, the main product he isolated was phenyl chloride.[4] In modern times, the Sandmeyer reaction refers to any method for substitution of an aromatic amino group via preparation of its diazonium salt followed by its displacement with a nucleophile in the presence of catalytic copper(I) salts. (Due to the low cost of copper salts, a stoichiometric amount is often employed for better reactivity even when catalysis is possible.) The most commonly employed Sandmeyer reactions are the chlorination, bromination, cyanation, and hydroxylation reactions using CuCl, CuBr, CuCN, and Cu_2O, respectively. More recently, trifluoromethylation of diazonium salts has been developed and is referred to as a 'Sandmeyer-type' reaction. Diazonium salts also react with boronates, iodide, thiols, water, hypophosphorous acid and others,[5] and fluorination can be carried out using tetrafluoroborate anions (Balz–Schiemann reaction). However, since these processes do not require a metal catalyst, they are not usually referred to as Sandmeyer reactions. In numerous variants that have been developed, other transition metal salts, including copper(II), iron(III), and cobalt(III) have also been employed. Due to its wide synthetic applicability, the Sandmeyer reaction, along with other transformations of diazonium compounds, is complementary to electrophilic aromatic substitution.

Reaction conditions and mechanism

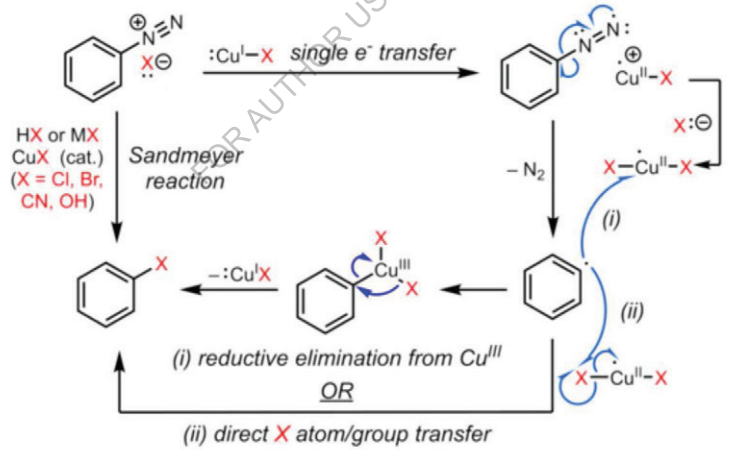
Step 1



Step 2

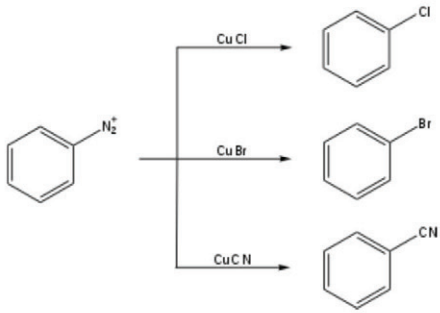


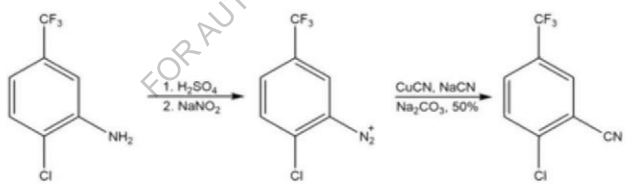
Step 3

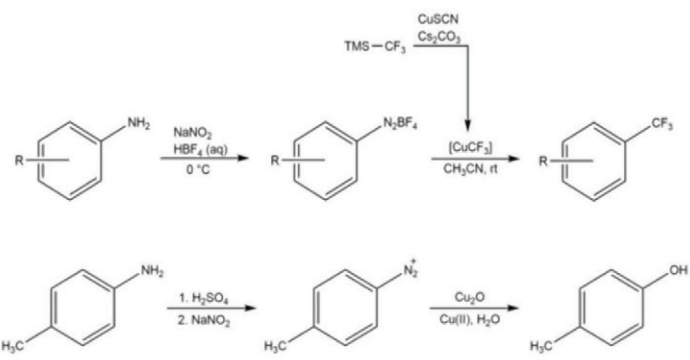


Applications

Variations on the Sandmeyer reaction have been developed to fit multiple synthetic applications. These reactions typically proceed through the formation of an aryl diazonium salt followed by a reaction with a copper(I) salt to yield a substituted arene according to the scheme below.

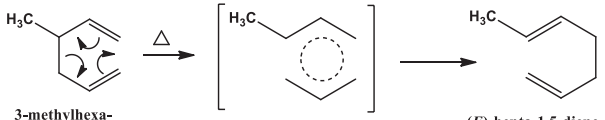






(42) Claisen rearrangement

The Claisen rearrangement (not to be confused with the Claisen condensation) is a powerful carbon–carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen. The heating of an allyl vinyl ether will initiate a [3,3]-sigma tropic rearrangement to give a γ,δ-unsaturated carbonyl.



3-methylhexa-1,5-diene

(*E*)-hepta-1,5-diene

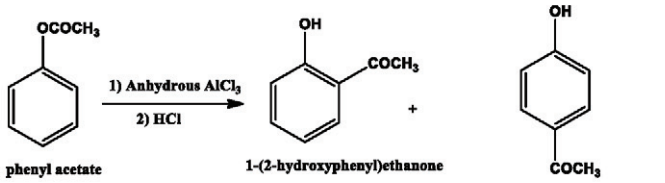
The Claisen rearrangement is an exothermic, concerted (bond cleavage and recombination) pericyclic reaction. Woodward–Hoffmann rules show a suprafacial, stereospecific reaction pathway. The kinetics are of the first order and the whole transformation proceeds through a highly ordered cyclic transition state and is intramolecular. Crossover experiments eliminate the possibility of the rearrangement occurring via an intermolecular reaction mechanism and are consistent with an intramolecular process.

There are substantial solvent effects observed in the Claisen rearrangement, where polar solvents tend to accelerate the reaction to a greater extent. Hydrogen-bonding solvents gave the highest rate constants. For example, ethanol/water solvent mixtures give rate constants 10-fold higher than sulfolane. Trivalent organoaluminium reagents, such as trimethylaluminium, have been shown to accelerate this reaction.

(43) Fries rearrangement

The Fries rearrangement, named for the German chemist Karl Theophil Fries, is a rearrangement reaction of a phenolic ester to a hydroxy aryl ketone by catalysis of Lewis acids.

It involves migration of an acyl group of phenol ester to the aryl ring. The reaction is ortho and para selective and one of the two products can be favoured by changing reaction conditions, such as temperature and solvent.



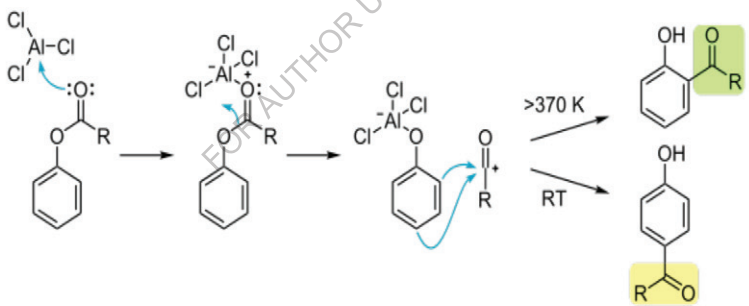
phenyl acetate

1-(2-hydroxyphenyl)ethanone

1-(4-hydroxyphenyl)ethanone

Mechanism

Despite many efforts, a definitive reaction mechanism for the Fries rearrangement has not been determined. Evidence for inter- and intramolecular mechanisms have been obtained by crossover experiments with mixed reactants. The Reaction progress is not dependent on solvent or substrate. A widely accepted mechanism involves a carbocation intermediate.

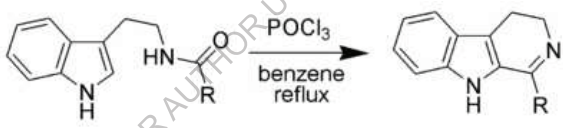


In the first reaction step a Lewis acid for instance aluminium chloride $AlCl_3$ co-ordinates to the carbonyl oxygen atom of the acyl group. This oxygen atom is more electron rich than the phenolic oxygen atom and is the preferred Lewis base. This interaction polarizes the bond between the acyl residue and the phenolic oxygen atom and the aluminium chloride group rearranges to the phenolic oxygen atom. This generates a free acylium carbocation which reacts in a classical electrophilic aromatic substitution with the aromatic ring. The abstracted proton is released as hydrochloric acid where the chlorine is derived from aluminium chloride. The orientation of the

substitution reaction is temperature dependent. A low reaction temperature favours para substitution and with high temperatures the ortho product prevails, this can be rationalised as exhibiting classic Thermodynamic versus kinetic reaction control as the ortho product can form a more stable bidentate complex with the Aluminium. Formation of the ortho product is also favoured in non-polar solvents; as the solvent polarity increases, the ratio of the para product also increases.

(44) Bischler-Napieralski Reaction

The Bischler–Napieralski reaction is an intramolecular electrophilic aromatic substitution reaction that allows for the cyclization of β-arylethylamides or β-arylethylcarbamates. It was first discovered in 1893 by August Bischler and Bernard Napieralski, in affiliation with Basle Chemical Works and the University of Zurich. The reaction is most notably used in the synthesis of dihydroisoquinolines, which can be subsequently oxidized to isoquinolines.

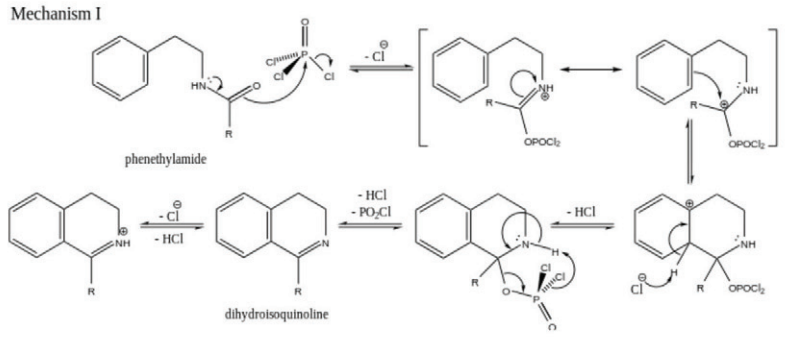


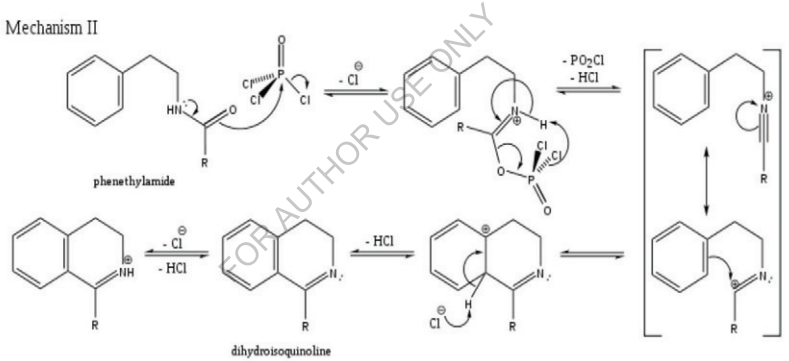
Mechanisms

Two types of mechanisms have appeared in the literature for the Bischler–Napieralski reaction. Mechanism I involve a dichlorophosphoryl imine-ester intermediate, while Mechanism II involves a nitrilium ion intermediate (both shown in brackets). This mechanistic variance stems from the ambiguity over the timing for the elimination of the carbonyl oxygen in the starting amide. In Mechanism I, the elimination occurs with imine formation *after* cyclization; while in Mechanism II, the elimination yields the nitrilium intermediate *prior* to cyclization. Currently, it is believed that different reaction conditions affect the prevalence of one mechanism over the other (see reaction conditions).

In certain literature, Mechanism II is augmented with the formation of an imidoyl chloride intermediate produced by the substitution of chloride for the Lewis

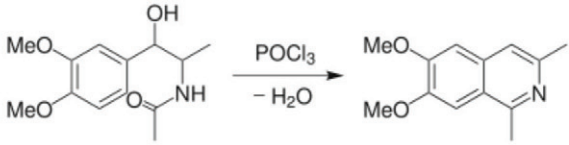
acid group just prior to the nitrilium ion.Because the dihydroisoquinoline nitrogen is basic, neutralization is necessary to obtain the deprotonated product.





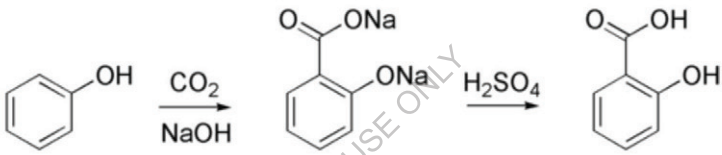
(45) Pictet–Gams reaction

The Pictet–Gams reaction proceeds from an β-hydroxy-β-phenethylamide. It involves an additional dehydration under the same conditions as the cyclization, giving an isoquinoline. As with the Bischler–Napieralski reaction, the Pictet–Gams reaction requires a strongly dehydrating Lewis acid, such as phosphoryl chloride or phosphorus pentoxide.



(46) Kolbe–Schmitt reaction

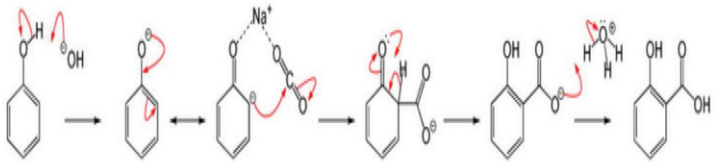
The Kolbe–Schmitt reaction or Kolbe process (named after Hermann Kolbe and Rudolf Schmitt) is a carboxylation chemical reaction that proceeds by heating sodium phenoxide (the sodium salt of phenol) with carbon dioxide under pressure (100 atm, 125 °C), then treating the product with sulfuric acid. The final product is an aromatic hydroxy acid which is also known as salicylic acid (the precursor to aspirin).



By using potassium hydroxide, 4-hydroxybenzoic acid is accessible, an important precursor for the versatile paraben class of biocides used e.g. in personal care products. The methodology is also used in the industrial synthesis of 3-hydroxy-2-naphthoic acid. The regiochemistry of the carboxylation in this case is sensitive to temperature.

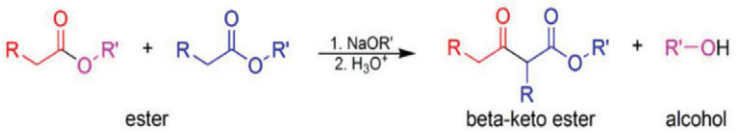
Mechanism

The Kolbe–Schmitt reaction proceeds via the nucleophile addition of a phenoxide, classically sodium phenoxide ($NaOC_6H_5$), to carbon dioxide to give the salicylate. The final step is reaction of the salicylate with acid to form the desired salicylic acid.



(47) Claisen Condensation

The **Claisen condensation** is a carbon–carbon bond forming reaction that occurs between two esters or one ester and another carbonyl compound in the presence of a strong base, resulting in a β-keto ester or a β-diketone. It is named after Rainer Ludwig Claisen, who first published his work on the reaction in 1887.

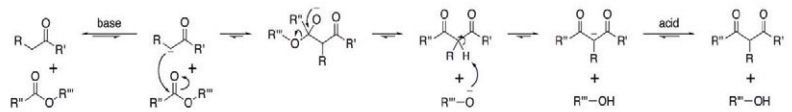


At least one of the reagents must be enolizable (have an α-proton and be able to undergo deprotonation to form the enolate anion). There are a number of different combinations of enolizable and nonenolizable carbonyl compounds that form a few different types of Claisen.

The base used must not interfere with the reaction by undergoing nucleophilic substitution or addition with a carbonyl carbon. For this reason, the conjugate sodium alkoxide base of the alcohol formed (e.g. sodium ethoxide if ethanol is formed) is often used, since the alkoxide is regenerated. In mixed Claisen condensations, a non-nucleophilic base such as lithium diisopropylamide, or LDA, may be used, since only one compound is enolizable. LDA is not commonly used in the classic Claisen or Dieckmann condensations due to enolization of the electrophilic ester.

The alkoxy portion of the ester must be a relatively good leaving group. Methyl and ethyl esters, which yields methoxide and ethoxide, respectively, are commonly used.

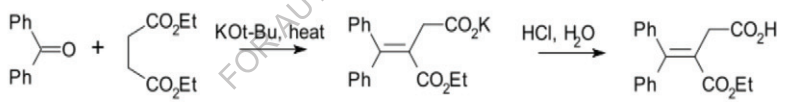
Mechanism



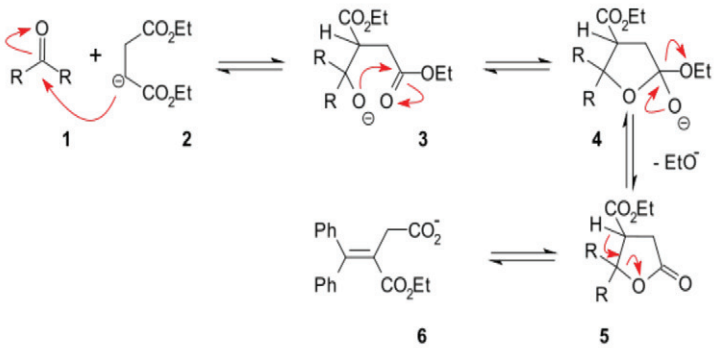
In the first step of the mechanism, an α-proton is removed by a strong base, resulting in the formation of an enolate anion, which is made relatively stable by the delocalization of electrons. Next, the carbonyl carbon of the (other) ester is nucleophilically attacked by the enolate anion. The alkoxy group is then eliminated (resulting in (re)generation of the alkoxide), and the alkoxide removes the newly formed doubly α-proton to form a new, highly resonance-stabilized enolate anion. Aqueous acid (e.g. sulfuric acid or phosphoric acid) is added in the final step to neutralize the enolate and any base still present. The newly formed β-keto ester or β-diketone is then isolated. Note that the reaction requires a stoichiometric amount of base as the removal of the doubly α-proton thermodynamically drives the otherwise endergonic reaction. That is, Claisen condensation does not work with substrates having only one α-hydrogen because of the driving force effect of deprotonation of the β-keto ester in the last step.

(48) Stobbe condensation

The Stobbe condensation is a modification specific for the diethyl ester of succinic acid requiring less strong bases. An example is its reaction with benzophenone:

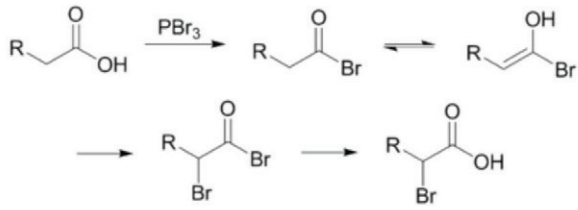


Mechanism



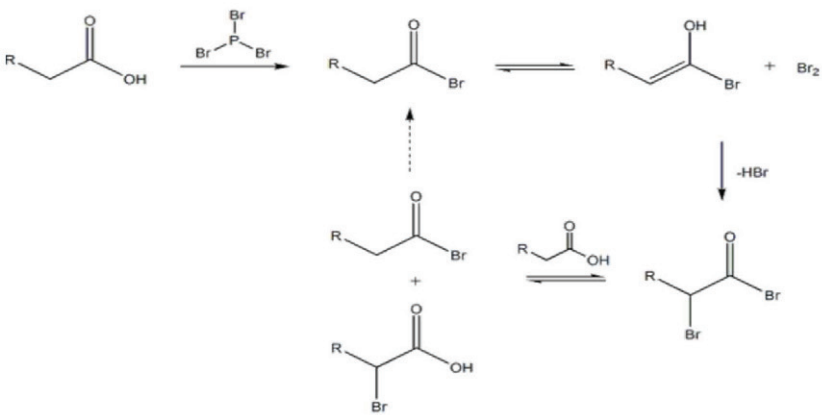
(49) Hell Volhard Zelinsky Reaction (HVZ Reaction)

The Hell–Volhard–Zelinsky halogenation reaction halogenates carboxylic acids at the α carbon. The reaction is named after three chemists, the German chemists Carl Magnus von Hell (1849–1926) and Jacob Volhard (1834–1910) and the Russian chemist Nikolay Zelinsky (1861–1953).



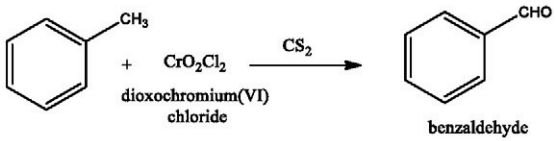
Example

Mechanism



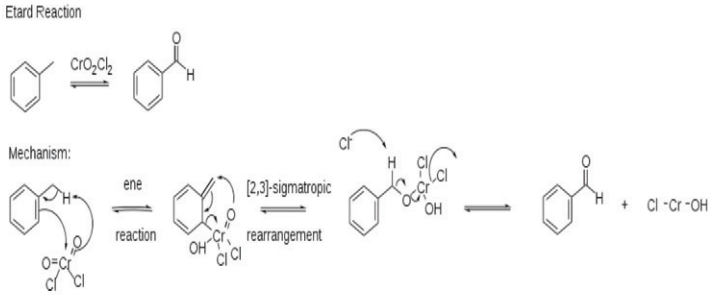
(50) Etard reaction

The Étard reaction is a chemical reaction that involves the direct oxidation of an aromatic or heterocyclic bound methyl group to an aldehyde using chromyl chloride. For example, toluene can be oxidized to benzaldehyde.



Mechanism

The reaction mechanism proceeds via an ene reaction with chromyl chloride, forming the precipitated Étard complex. The Étard complex is then decomposed by a [2,3] sigmatropic rearrangement under reducing conditions to prevent further oxidation to a carboxylic acid. Reducing conditions for the decomposition of the Étard complex are provided by saturated aqueous sodium sulphite. Typical solvents for the reaction include carbon disulfide, chloroform, and carbon tetrachloride, with carbon tetrachloride being the most common. To obtain a highly purified aldehyde product, the Étard complex precipitate is often purified before decomposition in order to prevent reaction with any unreacted reagent. The reaction is normally carried out for a few days to several weeks and the yields are high.



Limitations

The Étard reaction is most commonly used as a relatively easy method of converting toluene into benzaldehyde. Obtaining specific aldehyde products from reagents other than toluene tends to be difficult due to rearrangements. For example, *n*-propylbenzene is oxidized to propiophenone, benzyl methyl ketone, and several chlorinated products, with benzyl methyl ketone being the major product. Another example arises from the Étard reaction of trans-decalin which results in a mixture of trans-9-decalol, spiro [4.5]decan-6-one, trans-1-decalone, cis-1-decalone, 9,10-octal-1-one, and 1-tetralone.

Other oxidation reagents like potassium permanganate or potassium dichromate oxidize to the more stable carboxylic acids.

Uses

Oxidation of toluene to benzaldehyde is quite a useful conversion. Benzaldehyde is routinely used for its almond flavor. The aldehyde is comparatively reactive and readily participates in aldol condensations. Benzaldehyde can serve as a precursor for various compounds, including dyes, perfumes, and pharmaceuticals. For example, the first step in the synthesis of ephedrine is condensation of benzaldehyde with nitroethane[*citation needed*]. Additionally, benzaldehyde is instrumental in the synthesis of phentermine. Unlike other oxidising agents (like $KMnO_4$ or CrO_3 etc.), chromyl chloride does *not* oxidise aldehyde to carboxylic acid.

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