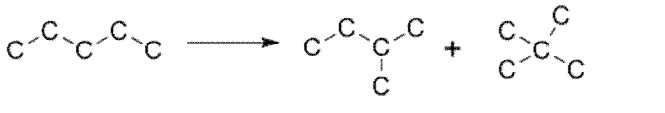
Rearrangement Reactions

A rearrangement reaction is a broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule.

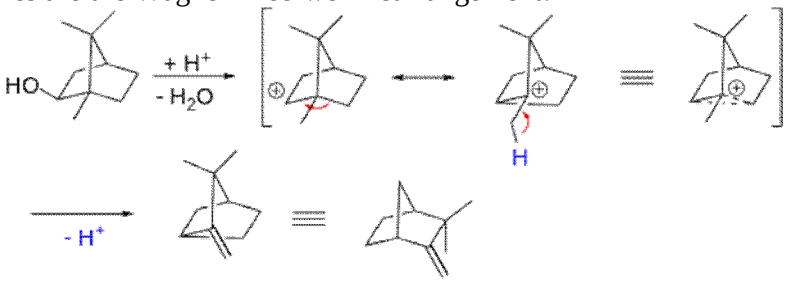
1, 2-Rearrangements

A 1, 2-rearrangement is an organic reaction where a substituent moves from one atom to another atom in a chemical compound. In a 1, 2 shift the movement involves two adjacent atoms but moves over larger distances are possible. In general straight-chain alkanes, are converted to branched isomers by heating in the presence of a catalyst. Examples include isomerisation of n-butane to isobutane and pentane to isopentane. Highly branched alkanes have favorable combustion characteristics for internal combustion engines.

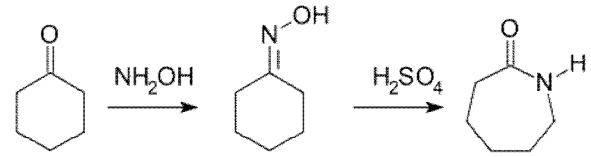


pentane 2-methylbutane 2,2-dimethylpropane

Further examples are the Wagner-Meerwein rearrangement:



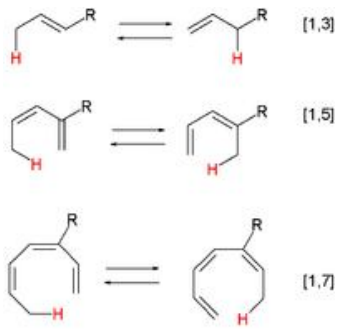
and the Beckmann rearrangement, which is relevant to the production of certain nylons:



cyclohexanone cyclohexanoxime caprolactam

Pericyclic reactions

A pericyclic reaction is a type of reaction with multiple carbon-carbon bonds making and breaking wherein the transition state of the molecule has a cyclic geometry and the reaction progresses in a concerted fashion. Examples are hydride shifts

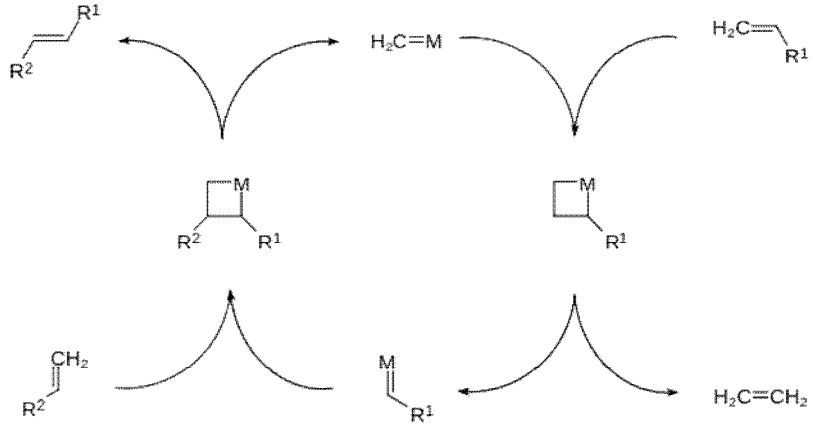


drmurugesanchemistry@gmail.com

and the Claisen rearrangement:

Olefin metathesis

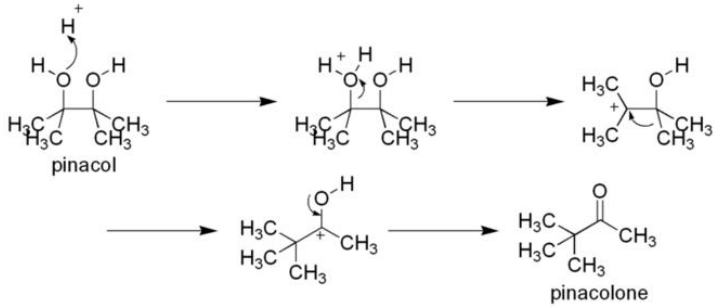
Olefin metathesis is a formal exchange of the alkylidene fragments in two alkenes. It is a catalytic reaction with carbene, or more accurately, transition metal carbene complexintermediates.



In this example (ethenolysis, a pair of vinyl compounds form a new symmetrical alkene with expulsion of ethylene.

Pinacol 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.

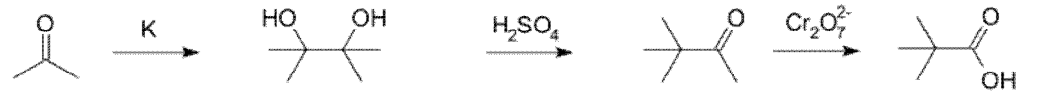


Mechanism

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 > tertiary carbocation (if formed by migration) > secondary carbocation (if formed by migration) > methyl cation . The conclusion which group stabilizes carbocation more effectively is migrated

Stereochemistry of the rearrangement

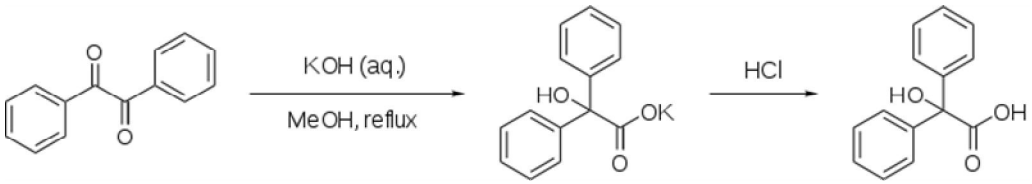
In cyclic systems, the reaction presents more features of interest. In these reactions, the stereochemistry of the diol plays a crucial role in deciding the major product. An alkyl group which is situated trans- to the leaving –OH group alone may migrate. If otherwise, ring expansion occurs, i.e. the ring carbon itself migrates to the carbocation centre. This reveals another interesting feature of the reaction, viz. that it is largely concerted. There appears to be a connection between the migration origin and migration terminus throughout the reaction. Moreover, if the migrating alkyl group has a chiral center as its key atom, the configuration at this center is *retained* even after migration takes place.



acetone pinacol pinacolone trimethylacetic acid

Benzilic acid rearrangement

The benzilic acid rearrangement is formally the rearrangement reaction of 1,2-diketones into α-hydroxy–carboxylic acids using base. This reaction receives its name from the reaction of benzil with potassium hydroxide to form benzilic acid. It can be viewed as an intramolecular disproportionation reaction, as one carbon center is oxidized while the other is reduced.

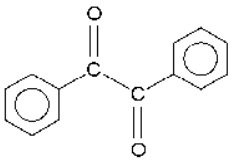


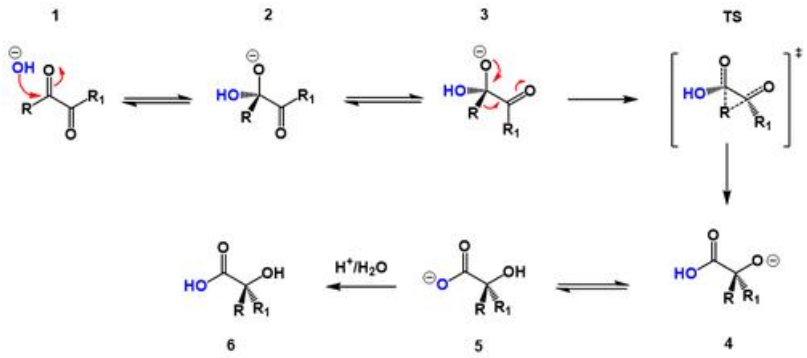
The reaction has been shown to work in aromatic, semi-aromatic, aliphatic, and heterocyclic substrates. The reaction works best when the ketone functional groups have no adjacent enolizable protons, as this allows aldol condensation to compete. The reaction is formally a ring contraction when used on cyclic diketones. It has been found that aryl groups more readily migrate than alkyl groups, and that aryl groups with electron-withdrawing groups migrate the fastest.

Reaction mechanism

The reaction is a representative of 1, 2-rearrangements. These rearrangements usually have migrating carbocations but this reaction is unusual because it involves a migrating carbanion. The long established reaction mechanism was first proposed in its entirety by Christopher Kelk Ingold, and has been updated with in silico data as outlined below. The reaction is second order overall in terms of rate, being first order in diketone and first order in base.

A hydroxide anion attacks one of the ketone groups in **1** in a nucleophilic addition to form the alkoxide **2**. The next step requires a bond rotation to conformer **3** which places the migrating group R in position for attack on the second carbonyl group. In a concerted step, the migrating R group attacks the α-carbonyl group forming another alkoxide with concomitant formation of a keto-group at the other carbon. This migration step is rate-determining. This sequence resembles a nucleophilic acyl substitution. Calculations show that when R is methyl the charge build-up on this group in the transition state can be as high as 0.22 and that the methyl group is positioned between the central carbon carbon bond.





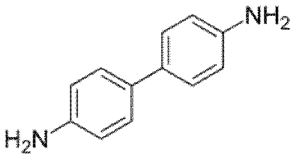
The carboxylic acid in intermediate **4** is less basic than the alkoxide and therefore reversible proton transfer takes place favoring intermediate **5** which is protonated on acidic workup to the final α-hydroxy–carboxylic acid **6**. Calculations show that an accurate description of the reaction sequence is possible with the participation of 4 water molecules taking responsibility for the stabilization of charge buildup. They also provide a shuttle for the efficient transfer of one proton in the formation of intermediate **5**.

The above mechanism is consistent with all available experimental evidence. The equilibrium between species **1** and **2** is supported by ^{18}O Isotopic labeling experiments. In deuterated water, carbonyl oxygen exchange occurs much faster than the rearrangement, indicating that the first equilibrium is not the rate-determining step. Further experiments showed a larger relative rate in a deuterated solvent system compared to a non-deuterated solvent system of otherwise identical composition. This was explained as being due to the greater relative basicity of the deuterated hydroxide anion compared to the normal hydroxide anion, and was used to indicate that hydrogen migration did not occur in the rate determining step of the reaction. This ruled out a concerted mechanism for the reaction, as hydrogen transfer would occur in the rate determining step.

Benzilic Ester Rearrangement

This reaction is identical to the normal Benzilic acid rearrangement, except that an alkoxide or an amide anion is used in place of a hydroxide ion. The alkoxide used should not be easily oxidizable as this favors the Meerwein–Ponndorf–Verley reduction pathway as a side reaction. The reaction is second order overall in terms of rate, being first order in terms of alkoxide and first order in terms of diketone. The product of the reaction is an α-hydroxy–ester or an α-hydroxy-amide.

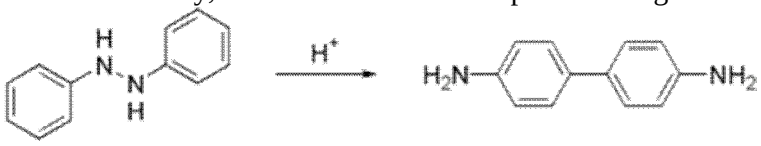
Benzidine



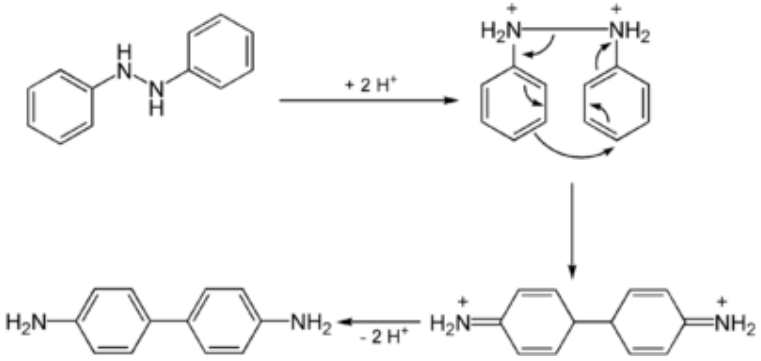
Benzidine also called 1,1'-biphenyl-4,4'-diamine is an organic compound with the formula $(C_6H_4NH_2)_2$. It is an aromatic amine. It is a component of a test for cyanide. Related derivatives are used in the production of dyes. Benzidine has been linked to bladder and pancreatic cancer.

Synthesis and properties

Benzidine is prepared in a two step process from nitrobenzene. First, the nitrobenzene is converted to 1,2-diphenylhydrazine, usually using iron powder as the reducing agent. Treatment of this hydrazine with mineral acids induces a rearrangement reaction to 4,4'-benzidine. Smaller amounts of other isomers are also formed. The benzidine rearrangement, which proceeds intramolecularly, is a classic mechanistic puzzle in organic chemistry.



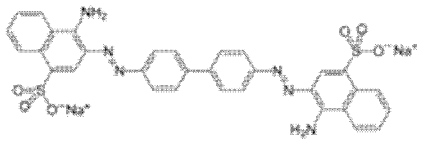
The conversion is described as a [5,5]sigmatropic reaction.



In terms of its physical properties, 4,4'-benzidine is poorly soluble in cold water but can be recrystallized from hot water, where it crystallises as the monohydrate. It is dibasic, the deprotonated species has K_a values of 9.3×10^{-10} and 5.6×10^{-11}. Its solutions react with oxidizing agents to give deeply coloured quinone-related derivatives.

Applications

Conversion of benzidine to the bis(diazonium) salt was once an integral step in the preparation of direct dyes (requiring no mordant). Treatment of this bis(diazonium) salt with 1-aminonaphthalene-4-sulfonic acid gives the once popular congo red dye. In the past, benzidine was used to test for blood. An enzyme in blood causes the oxidation of benzidine to a distinctively blue-coloured derivative. The test for cyanide relies on similar reactivity. Such applications have largely been replaced by methods using phenolphthalein/hydrogen peroxide and luminol.



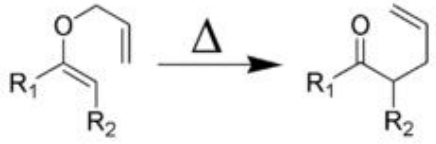
Related 4, 4-benzidines

A variety of derivatives of 4,4'-benzidine are commercially produced on the scale of one to a few thousand kilograms per year, mainly as precursors to dyes and pigments. These derivatives include, in order of scale, the following:

- 3,3'-Dichlorobenzidine
- *o*-tolidine, 2,2'-dimethyl-4,4'-benzidine
- *o*-dianisidine (2,2'-dimethoxy-4,4'-benzidine, CAS# 119-90-4, m.p. 133 °C)
- 3,3',4,4'-Tetraaminodiphenyl, precursor to polybenzimidazole fiber.

Claisen rearrangement

The Claisen rearrangement 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]-sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl.



Discovered in 1912, the Claisen rearrangement is the first recorded example of a [3,3]-sigmatropic rearrangement. Many reviews have been written.

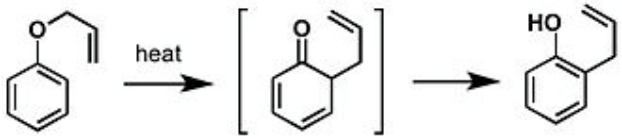
Mechanism

The Claisen rearrangement is an exothermic, concerted (bond cleavage and recombination) pericyclic reaction. Woodward–Hoffmann rules show a suprafacial, stereospecific reaction pathway. The kinetics is 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.

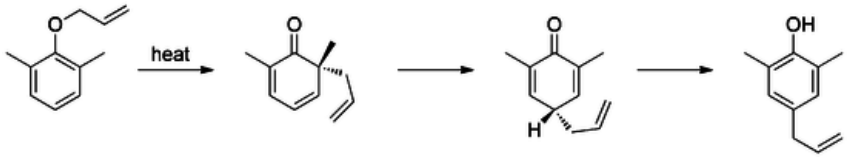
Aromatic Claisen rearrangement

The first reported Claisen rearrangement is the [3,3]-sigmatropic rearrangement of an allyl phenyl ether to intermediate 1, which quickly tautomerizes to an ortho-substituted phenol.



1

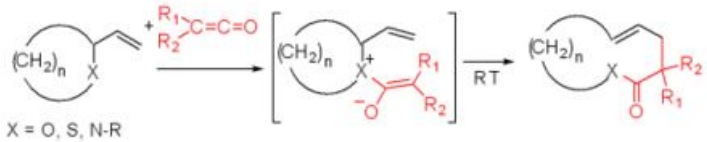
Meta-substitution affects the regioselectivity of this rearrangement. For example, electron withdrawing groups (e.g. bromide) at the meta-position direct the rearrangement to the ortho-position (71% ortho-product), while electron donating groups (e.g. methoxy), direct rearrangement to the para-position (69% para-product). Additionally, presence of ortho-substituents exclusively leads to para-substituted rearrangement products (tandem Claisen and Cope rearrangement).



If an aldehyde or carboxylic acid occupies the ortho or para positions, the allyl side-chain displaces the group, releasing it as carbon monoxide or carbon dioxide, respectively.

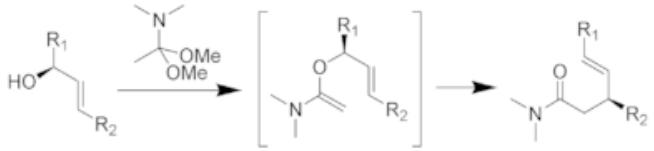
Bellus–Claisen rearrangement

The Bellus–Claisen rearrangement is the reaction of allylic ethers, amines, and thioethers with ketenes to give γ,δ-unsaturated esters, amides, and thioesters. This transformation was serendipitously observed by Bellus in 1979 through their synthesis of a key intermediate of an insecticide, pyrethroid. Halogen substituted ketenes (R_1, R_2) are often used in this reaction for their high electrophilicity. Numerous reductive methods for the removal of the resulting α-haloesters, amides and thioesters have been developed.The B ellus-Claisen offers synthetic chemists a unique opportunity for ring expansion strategies.

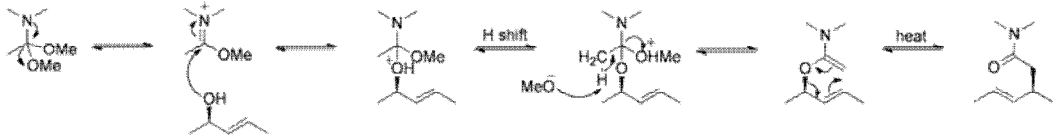


Eschenmoser–Claisen rearrangement

The Eschenmoser–Claisen rearrangement proceeds by heating allylic alcohols in the presence of N,N-dimethylacetamide dimethyl acetal to form γ,δ-unsaturated amide. Eschenmoser-Claisen rearrangement was used as a key step in the total synthesis of morphine.

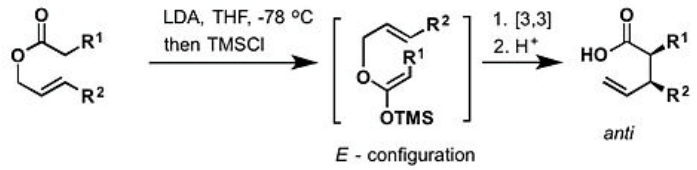


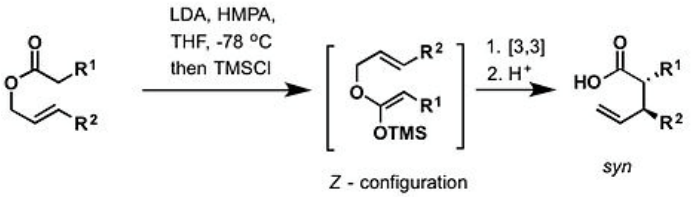
Mechanism:



Ireland–Claisen rearrangement

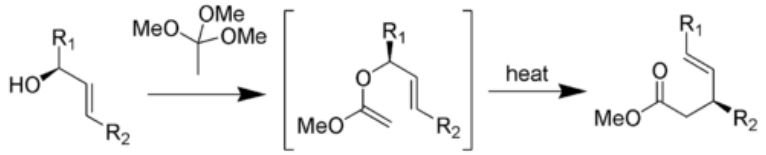
The Ireland–Claisen rearrangement is the reaction of an allylic carboxylate with a strong base (such as lithium diisopropylamide) to give a γ,δ-unsaturated carboxylic acid. The rearrangement proceeds via silylketene acetal, which is formed by trapping the lithium enolate with chlorotrimethylsilane. Like the Bellus-Claisen (above), Ireland-Claisen rearrangement can take place at room temperature and above. The E- and Z-configured silylketene acetals lead to anti and syn rearranged products, respectively. There are numerous examples of enantioselective Ireland-Claisen rearrangements found in literature to include chiral boron reagents and the use of chiral auxiliaries.





Johnson–Claisen rearrangement

The Johnson–Claisen rearrangement is the reaction of an allylic alcohol with an orthoester to yield a γ,δ-unsaturated ester. Weak acids, such as propionic acid, have been used to catalyze this reaction. This rearrangement often requires high temperatures (100 to 200 °C) and can take anywhere from 10 to 120 hours to complete.[34] However, microwave assisted heating in the presence of KSF-clay or propionic acid have demonstrated dramatic increases in reaction rate and yields.



Mechanism:

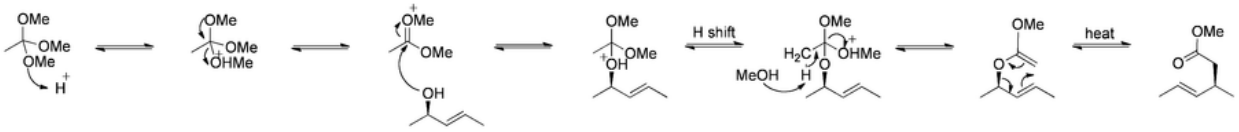


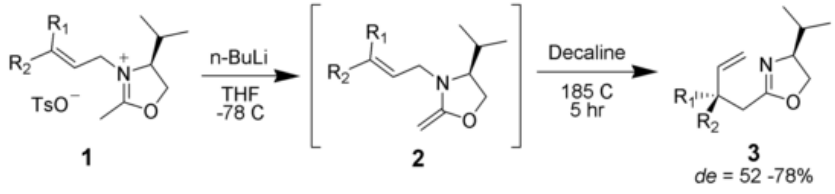
Photo-Claisen rearrangement

The photo-Claisen rearrangement is closely related to the photo-Fries rearrangement, that proceeds through a similar radical mechanism. Aryl ethers undergo the photo-Claisen rearrangement, while the photo-Fries rearrangement utilizes aryl esters.

Hetero-Claisens

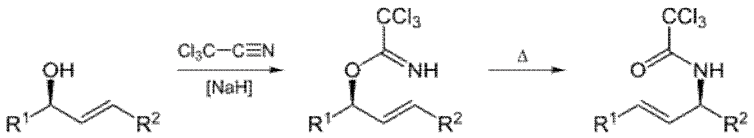
Aza–Claisen

An iminium can serve as one of the pi-bonded moieties in the rearrangement.



Overman rearrangement

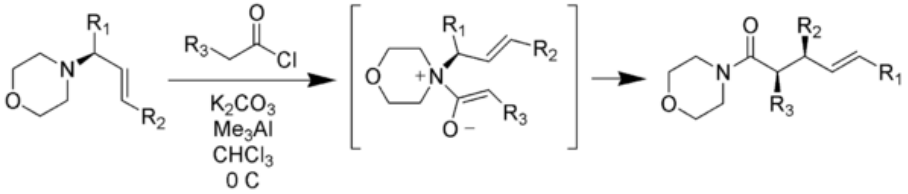
The Overman rearrangement is a Claisen rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.



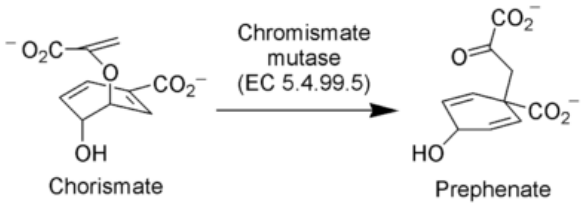
Overman rearrangement is applicable to synthesis of vicinol diamino comp from 1,2 vicinal allylic diol.

Zwitterionic Claisen rearrangement

Unlike typical Claisen rearrangements which require heating, zwitterionic Claisen rearrangements take place at or below room temperature. The acyl ammonium ions are highly selective for Z-enolates under mild conditions.



The enzyme chorismate mutase catalyzes the Claisen rearrangement of chorismate to prephenate.

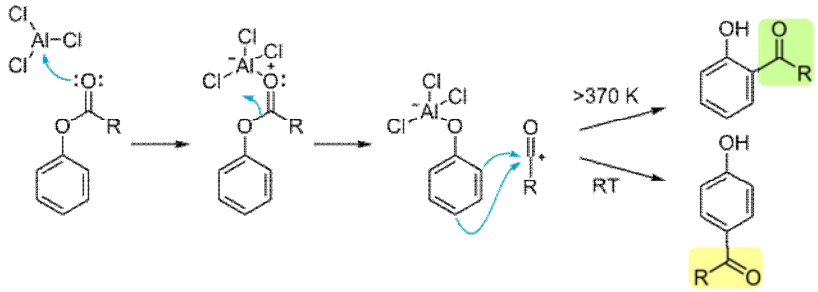


Fries rearrangement

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.

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.

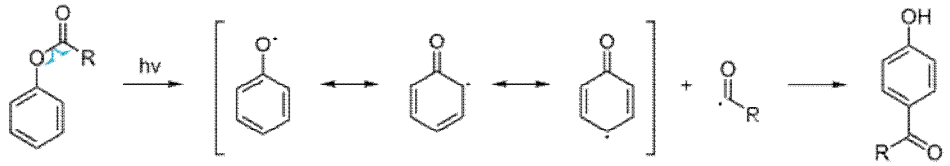


In the first reaction step a Lewis acid for instance aluminium chloride $AlCl_3$ co-ordinates to the carbonyl oxygen atom of the acyl group. This oxygen atom is

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 favors 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.[5] 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.

Photo-Fries rearrangement

In addition to the ordinary thermal phenyl ester reaction a so-called photochemical photo-Fries rearrangement exists that involves a radical reaction mechanism. This reaction is also possible with deactivating substituents on the aromatic group. Because the yields are low this procedure is not used in commercial production. However, photo-Fries rearrangement may occur naturally, for example when a plastic bottle made of polycarbonate (PC) is exposed to the sun, particularly to UV light at a wavelength of about 310 nm, if the plastic has been heated to 40° Celsius or above (as might occur in a car with windows closed on a hot summer day). In this case, photolysis of the ester groups would lead to leaching of phthalate from the plastic.

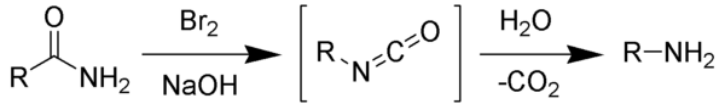


Anionic Fries rearrangement

In addition to Lewis acid and photo-catalysed Fries rearrangements, there also exists an anionic Fries rearrangement. In this reaction, the aryl ester undergoes ortho-metalation with a strong base, which then rearranges in a nucleophilic attack mechanism.

Hofmann rearrangement

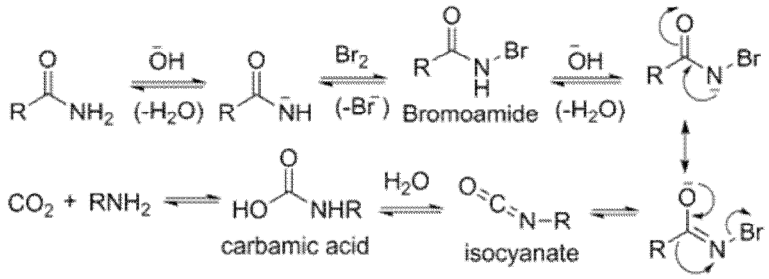
The Hofmann rearrangement is the organic reaction of a primary amide to a primary amine with one fewer carbon atom.



The reaction is named after its discoverer – August Wilhelm von Hofmann. This reaction is also sometimes called the Hofmann degradation, and should not be confused with the Hofmann elimination.

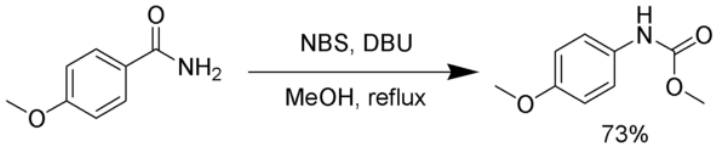
Mechanism

The reaction of bromine with sodium hydroxide forms sodium hypobromite *in situ*, which transforms the primary amide into an intermediate isocyanate. The formation of an intermediate nitrene is not possible because it implies also the formation of an hydroxamic acid as a byproduct, which has never been observed. The intermediate isocyanate is hydrolyzed to a primary amine, giving off carbon dioxide.



- Base abstracts an acidic N-H proton, yielding an anion.
- The anion reacts with bromine in an α-substitution reaction to give an *N*-bromoamide.
- Base abstraction of the remaining amide proton gives a bromoamide anion.
- The bromoamide anion rearranges as the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves, giving an isocyanate.
- The isocyanate adds water in a nucleophilic addition step to yield a carbamic acid (aka urethane).
- The carbamic acid spontaneously loses CO_2, yielding the amine product.

Several reagents can substitute for bromine. Sodium hypochlorite, Lead tetraacetate, *N*-bromosuccinimide, (bis(trifluoroacetoxy)iodo)benzene, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can affect a Hofmann rearrangement. In the following example, the intermediate isocyanate is trapped by methanol, forming a carbamate.



The Hofmann rearrangement using NBS.

In a similar fashion, the intermediate isocyanate can be trapped by *tert*-butyl alcohol, yielding the *tert*-butoxycarbonyl (Boc)-protected amine.

The Hofmann Rearrangement also can be used to yield carbamates from α,β-unsaturated or α-hydroxy amides or nitriles from α,β-Acetylenic amides in good yields (≈70%). For Amiloride, hypobromous acid was used to effect Hofmann rearrangement.

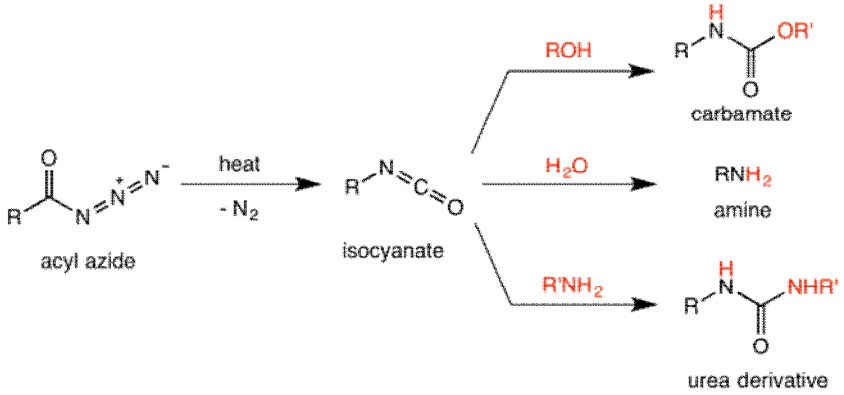
Applications

- Aliphatic & Aromatic amides are converted into aliphatic and aromatic amines, respectively
- In the preparations of anthranilic acid from phthalimide
- Nicotinic acid is converted into 3-Aminopyridine
- The Symmetrical structure of α-phenyl propanamide does not change after Hofmann reaction.
- Gabapentin from mono-amidation 1,1-cyclohexane diacetic acid anhydride with ammonia to 1,1-cyclohexane diacetic acid mono-amide; followed by 'Hoffmann' rearrangement: U.S. Patent 20,080,103,334

Curtius rearrangement

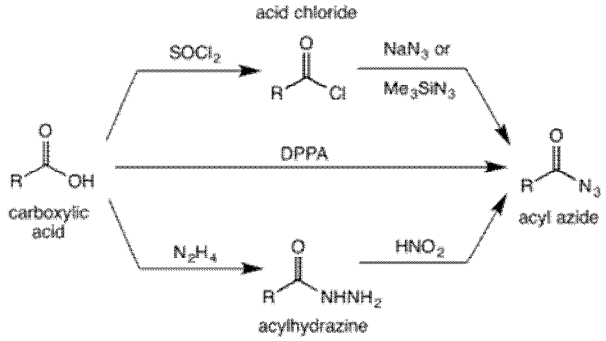
The Curtius rearrangement (or Curtius reaction or Curtius degradation), first defined by Theodor Curtius in 1885, is the thermal decomposition of an acyl azide to an isocyanate with loss of nitrogen gas. The isocyanate then undergoes attack by a variety

of nucleophiles such as water, alcohols and amines, to yield a primary amine, carbamate or urea derivative respectively.[3] Several reviews have been published.



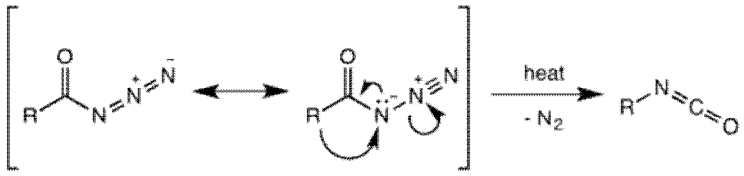
Preparation of acyl azide

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).



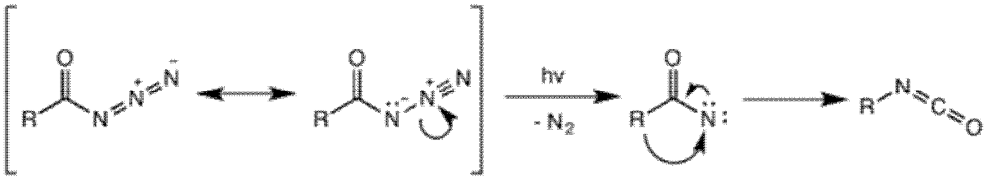
Reaction mechanism

It was believed that the Curtius rearrangement was a two-step process, with the loss of nitrogen gas forming an acyl nitrene, followed by migration of the R-group to give the isocyanate. However, recent research has indicated that the thermal decomposition is a concerted process, with both steps happening together, due to the absence of any nitrene insertion or addition byproducts observed or isolated in the reaction. Thermodynamic calculations also support a concerted mechanism.

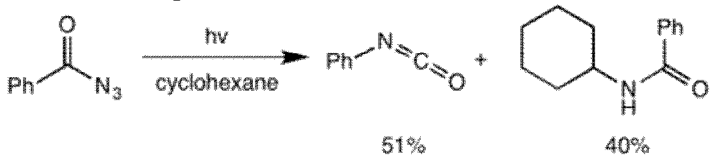


The migration occurs with full retention of configuration at the R-group. The migratory aptitude of the R-group is roughly tertiary > secondary ~ aryl > primary. The isocyanate formed can then be hydrolyzed to give a primary amine, or undergo nucleophilic attack with alcohols and amines to form carbamates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

Photochemical rearrangement

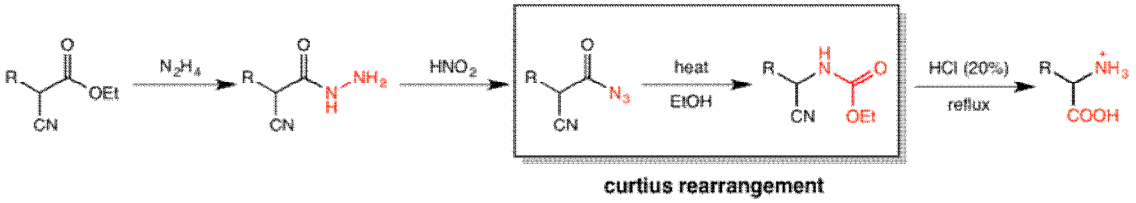


Photochemical decomposition of the acyl azide is also possible. However, photochemical rearrangement is not concerted and instead occurs by a nitrene intermediate, formed by the cleavage of the weak N–N bond and the loss of nitrogen gas. The highly reactive nitrene can undergo a variety of nitrene reactions, such as nitrene insertion and addition, giving unwanted side products. In the example below, the nitrene intermediate inserts into one of the C–H bonds of the cyclohexane solvent to form N-cyclohexylbenzamide as a side product.



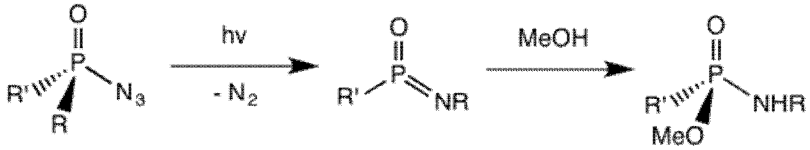
Darapsky degradation

In one variation called the Darapsky degradation, or Darapsky synthesis, a Curtius rearrangement takes place as one of the steps in the conversion of an α-cyanoester to an amino acid. Hydrazine is used to convert the ester to an acylhydrazine, which is reacted with nitrous acid to give the acyl azide. Heating the azide in ethanol yields the ethyl carbamate via the Curtius rearrangement. Acid hydrolysis yields the amine from the carbamate and the carboxylic acid from the nitrile simultaneously, giving the product amino acid.



Harger reaction

The photochemical Curtius-like migration and rearrangement of a phosphinic azide forms a metaphosphonimidate in what is also known as the Harger reaction. This is followed by hydrolysis, in the example below with methanol, to give a phosphonamidate.



Unlike the Curtius rearrangement, there is a choice of R-groups on the phosphinic azide which can migrate. Harger has found that the alkyl groups migrate preferentially to aryl groups, and this preference increases in the order methyl < primary < secondary < tertiary. This is probably due to steric and conformational factors, as the bulkier the R-group, the less favorable the conformation for phenyl migration.

Synthetic applications

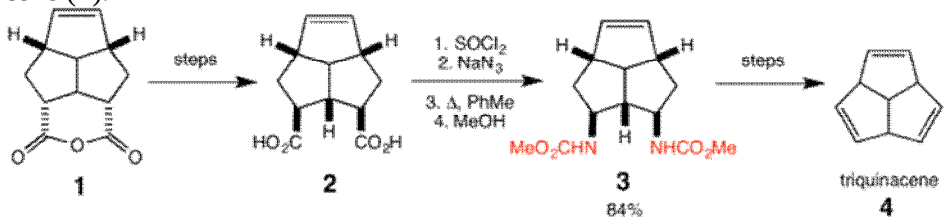
The Curtius rearrangement is tolerant of a large variety of functional groups, and has significant synthetic utility, as many different groups can be incorporated depending on the choice of nucleophile used to attack the isocyanate.

For example, when carried out in the presence of *tert*-butanol, the reaction generates Boc-protected amines, useful intermediates in organic synthesis. Likewise, when the Curtius reaction is performed in the presence of benzyl alcohol, Cbz-protected amines are formed.

The Curtius rearrangement is used in the syntheses of the drugs tranylcypromine, candesartan, bromadol, terguride, benzydamine, gabapentin, igmesine and tecadenoson.

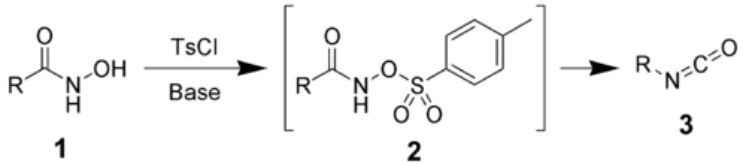
Triquinacene

R. B. Woodward et al. used the Curtius rearrangement as one of the steps in the total synthesis of the polyquinane triquinacene in 1964. Following hydrolysis of the ester in the intermediate (**1**), a Curtius rearrangement was effected to convert the carboxylic acid groups in (**2**) to the methyl carbamate groups (**3**) with 84% yield. Further steps then gave triquinacene (**4**).

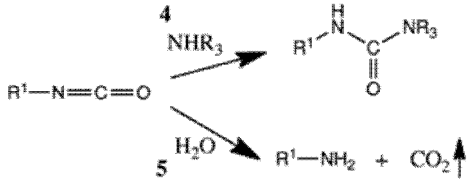


Lossen rearrangement

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



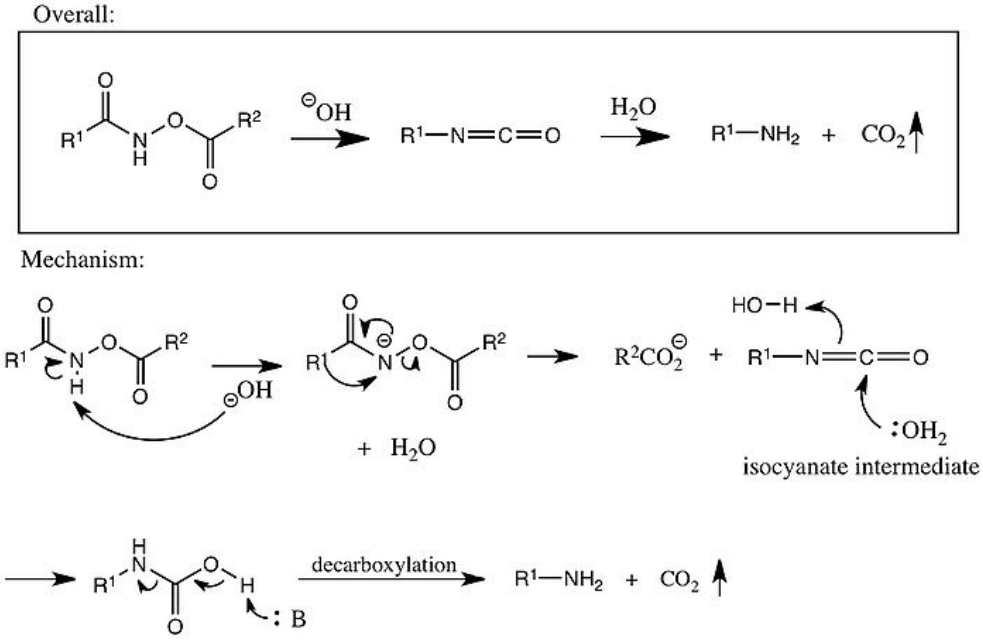
The isocyanate can be used further to generate ureas in the presence of amines (**4**) or generate amines in the presence of H_2O (**5**).



Reaction mechanism

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

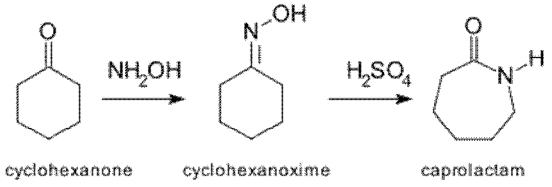
then decarboxylation via abstraction of a hydrogen by a base generates an amine and CO_2 gas.



Beckmann rearrangement

The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann (1853–1923), is a rearrangement of an oximefunctional 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.

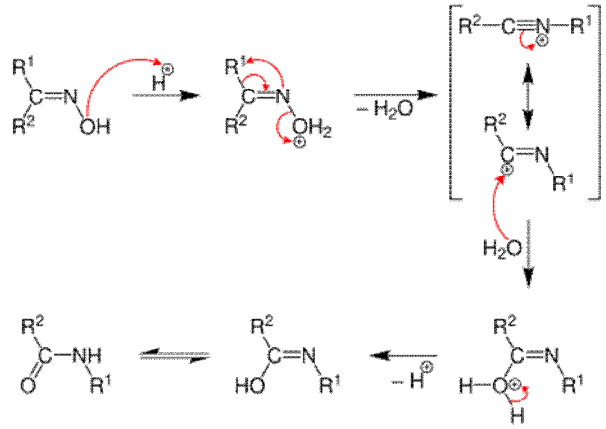


The dominant application of the Beckmann rearrangement is the conversion of cyclohexanone to caprolactam via the oxime. Caprolactam is the feedstock in the production of Nylon 6.

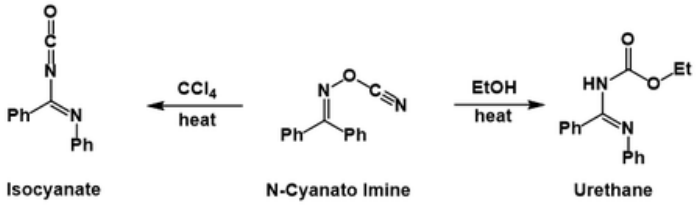
The Beckmann solution consists of acetic acid, hydrochloric acid and acetic anhydride, and was widely used to catalyze the rearrangement. Other acids, such as sulfuric acid, polyphosphoric acid, and hydrogen fluoride have all been used. Sulfuric acid is the most commonly used acid for commercial lactam 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.

Reaction mechanism

The most common reaction mechanism of the Beckmann rearrangement consists generally of an alkyl migration anti-periplanar to the expulsion of a leaving group to form a nitrilium ion. This is followed by solvolysis to an imidate and then tautomerization to the amide:



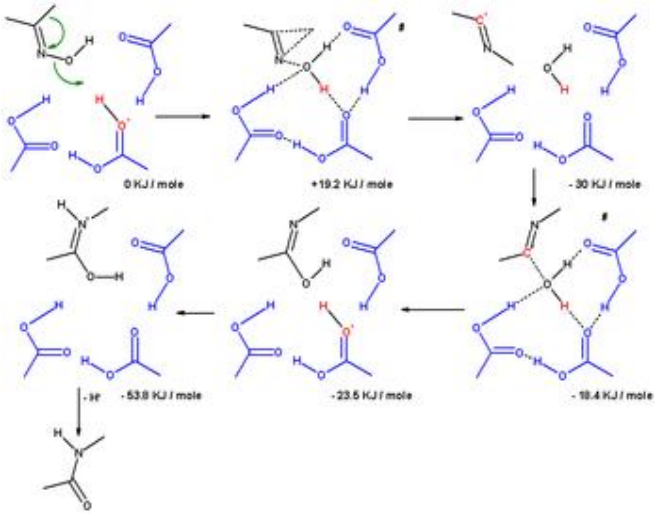
This nitrilium ion has been known to be intercepted by other nucleophiles, including the leaving group from the oxime.



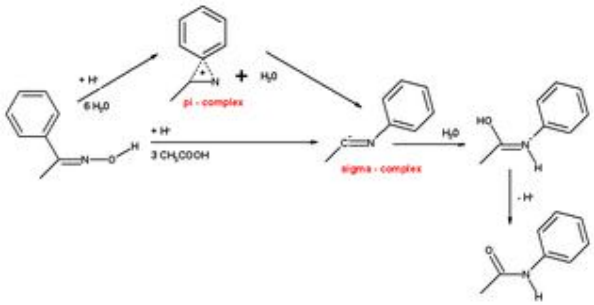
Presumably after the phenyl group migrates and expels the cyanate, it then attacks the nitrillium ion formed. In carbon tetrachloride the isocyanate can be isolated, whereas in ethanol the urethane is formed after solvolysis of the isocyanate.

One computational study has established the mechanism accounting for solvent molecules and substituents. The rearrangement of acetone oxime in the Beckmann solution involved three acetic acid molecules and one proton (present as an oxonium ion). In the transition state leading to the iminium ion (σ-complex), the methyl group migrates to the nitrogen atom in a concerted reaction as the hydroxyl group is expelled. The oxygen atom in the hydroxyl group is stabilized by three acetic acid molecules. In the next step the electrophilic carbon atom in the nitrilium ion is attacked by water and a proton is donated back to acetic acid. In the transition state leading to the imidate, the water oxygen atom is

coordinated to 4 other atoms. In the third step, an isomerization step protonates the nitrogen atom leading to the amide.



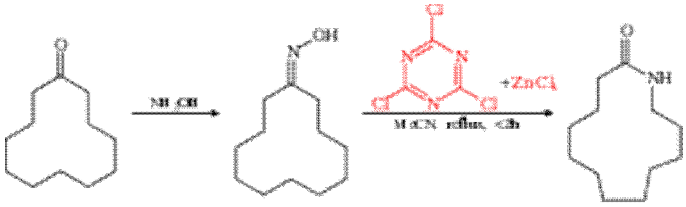
The same computation with a hydroxonium ion and 6 molecules of water has the same result, but when the migrating substituent is a phenyl group, the mechanism favors the formation of an intermediate three-membered π-complex. This π-complex is not found in the $H_3O^+(H_2O)_6$.



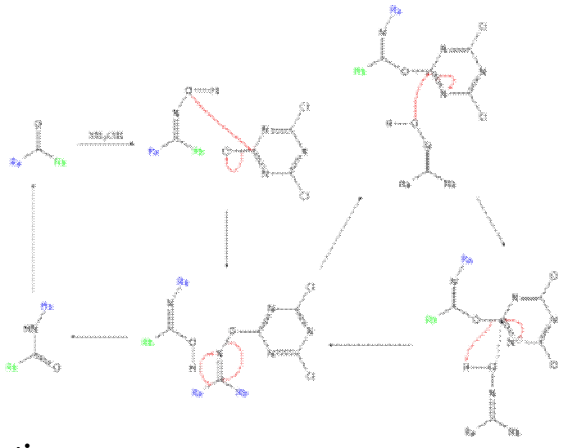
With the cyclohexanone-oxime, the relief of ring strain results in a third reaction mechanism, leading directly to the protonated caprolactam in a single concerted step without the intermediate formation of a π-complex or σ-complex.

Cyanuric chloride assisted Beckmann reaction

Beckmann rearrangement can be rendered catalytic using cyanuric chloride and zinc chloride as a co-catalyst. For example, cyclododecanone can be converted to the corresponding lactam, the monomer used in the production of Nylon 12.

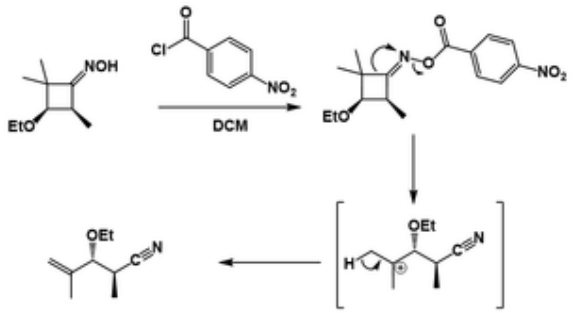


The reaction mechanism for this reaction is based on a catalytic cycle with cyanuric chloride activating the hydroxyl group via a nucleophilic aromatic substitution. The reaction product is dislodged and replaced by new reactant via an intermediate Meisenheimer complex.



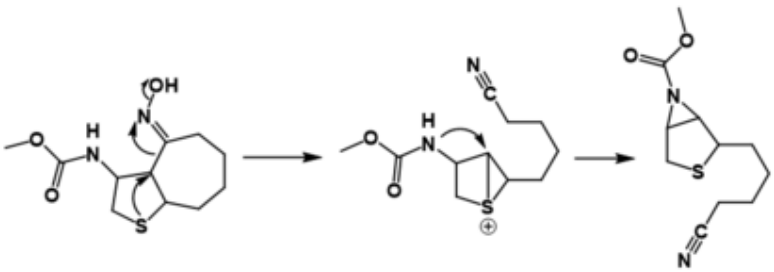
Beckmann fragmentation

The Beckmann fragmentation is a reaction that frequently competes with the Beckmann rearrangement. When the group α to the oxime is capable of stabilizing carbocationformation, the fragmentation becomes a viable reaction pathway. The reaction generates a nitrile and a carbocation, which is quickly intercepted to form a variety of products. The nitrile can also be hydrolyzed under reaction conditions to give carboxylic acids. Different reaction conditions can favor the fragmentation over the rearrangement.



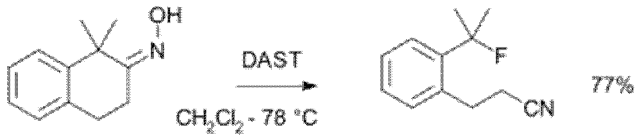
Quaternary carbon centers promote fragmentation by stabilizing carbocation formation through hyperconjugation. As shown in the above picture, the "stable" carbocation is formed, which then loses a hydrogen to give a site of unsaturation. Oxygen and nitrogen atoms also promote fragmentation through the formation of ketones and imines respectively.

Sulfur is also capable of promoting fragmentation, albeit at a longer range than oxygen or nitrogen.



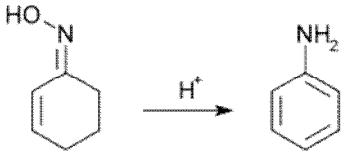
Silicon is capable of directing the fragmentation through the beta-silicon effect.

The carbocation intermediate in this reaction is intercepted by nucleophilic fluoride from diethylaminosulfur trifluoride (DAST):

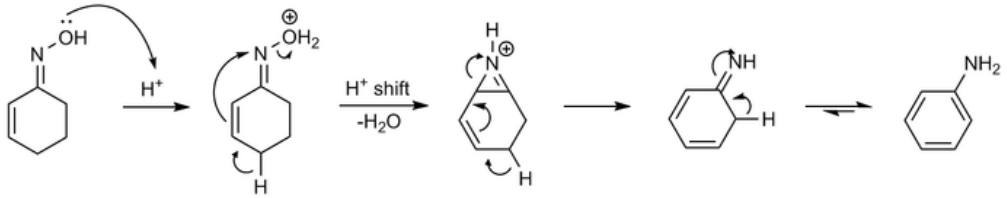


Semmler–Wolff reaction

The oxime of cyclohexenone with acid forms aniline in a dehydration–aromatization reaction called the Semmler–Wolff reaction or Wolff aromatization

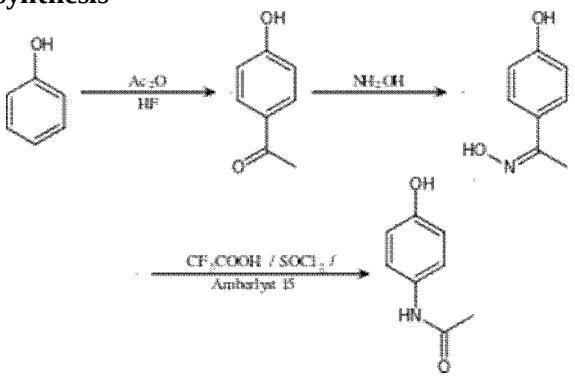


The mechanism can be shown as below:



The reaction is intrinsically a special case of Beckmann rearrangement combined with neighbouring group participation.

Applications in drug synthesis



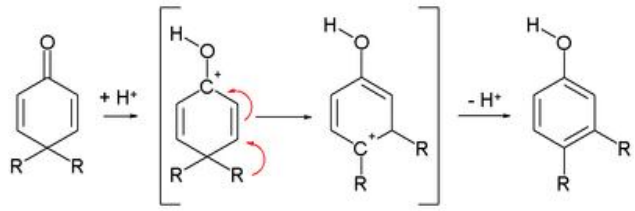
An industrial synthesis of paracetamol developed by Hoechst–Celanese involves the conversion of a methyl ketone to an acetanilide via a Beckmann rearrangement.

The Beckmann rearrangement is also used in the synthesis of DHEA, benazepril, ceforanide, elanzepine, 17-azaprogesterone, elantrine, prazepine, enprazepine, and etazepine.

Dienone-Phenol rearrangement

A dienone is a class of organic compounds that are formally "derived from diene compounds by conversion of a –CH2– groups into –C(=O)– group .", resulting in "a conjugatedstructure". The class includes some heterocyclic compounds.

Rearrangement reaction of 6-membered cyclic dienones generate phenols through the dienone phenol rearrangement:



The Dienone–Phenol Rearrangement

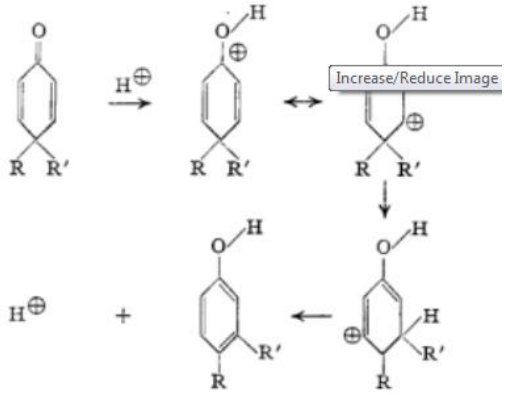
By Richard T. Arnold, Jay S. Buckley, Jr., and John Richter

Rearrangement of semibenzenes into alkylbenzenes has been studied in some detail by v. Auwers and co-workers.[1] These reactions are now regarded as typical examples of pinacol or neopentyl type rearrangements.

In our opinion the dienone–phenol rearrangement observed by Clemo in the conversion of santonin to desmotroposantonin[2] and more recently by Inhoffen[3] and co-workers in the cholestanone and androstenone series is mechanistically the same as the semibenzene–alkylbenzene rearrangement discussed above. These reactions are acid catalyzed and proceed under the same general experimental conditions.

Wilds and Djersassi[4] recently published the first example of this rearrangement in which the structure of both the starting compound and product of the reaction were established by an independent synthesis.

(1) v. Auwers and Ziegler, *Ann.*, **425**, 217 (1921).
(2) Clemo, *J. Chem. Soc.*, 1110 (1930).
(3) Inhoffen, Zuhlsdorf and Huang-Minlon, *Ber.*, **73**, 451 (1940).
(4) Wilds and Djerassi, This Journal, **68**, 1712 (1946).



In this paper is reported a new example which, because of the high yields involved, represents a convenient synthesis of 3,4-dialkyl-1-naphthols. Reaction between γ-methylvalerolactone (I, R = CH_3) and benzene to form 4,4-dimethyl-1-tetralone (II) proceeded smoothly in the presence of