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SUBJECT : Organic Chemistry- II

UNIT IV: MOLECULAR REARRANGEMENTS

Rearrangement Reaction

What is Rearrangement Reaction?

The term “rearrangement” is used to describe two different types of organic chemical reactions. A rearrangement may involve the one step migration of an H atom or of a larger molecular fragment within a relatively short lived intermediate.

On the other hand a rearrangement may be a multi step reaction that includes the migration of an H atom or of a larger molecular fragment as one of its steps.

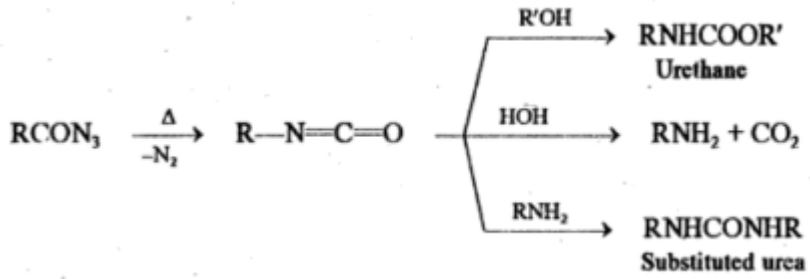
In many rearrangements, the migrating group connects to one of the direct neighbors of the atom to which it was originally attached. Rearrangements of this type are the so-called [1,2] – rearrangements or [1,2] – shifts. These rearrangements can be considered as sigma-tropic processes, the numbers 1 and 2 characterizing the subclass to which they belong.

Curtius Rearrangement or Curtius Reaction

Curtius’ reaction involves the heating of an acyl azide which loses nitrogen and then rearranges to an isocyanate.

$RCON_3 \rightarrow R\text{-}N{=}C{=}O + N_2$

If the reaction is performed in alcoholic or aqueous medium, the isocyanate further reacts to form urethane, amine or substituted urea.



The conversion of acyl azides to isocyanates involves curtius rearrangement whereas curtius reaction involves the conversion of acids to amines, urethane and substituted urea via curthius urea via curtius rearrangement.

Acyl azide required for the reaction is obtained as follows.

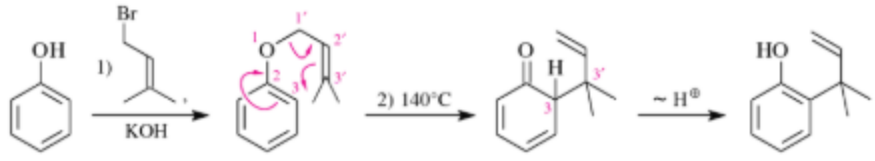
$RCOCl + NaN_3$ (Sodium azide) → $RCON_3$ (Acyl azide) + NaCl

$RCOOC_2H_5$ → $RCONHNH_2$ (Acyl hydrazide) → $RCON_3 + 2H_2O$

Claisen Rearrangement

The classical claisen rearrangement is the first and slow step of the isomerization of allyl aryl ethers to ortho allylated phenols. A cyclohexadienone is formed in the actual rearrangement step which is a [3,3]-sigmatropic rearrangement. Three valence electron pairs are shifted simultaneously.

Cyclohexadienone, a non aromatic compound, cannot be isolated and tautomerizes immediately to the aromatic and consequently more stable phenol.

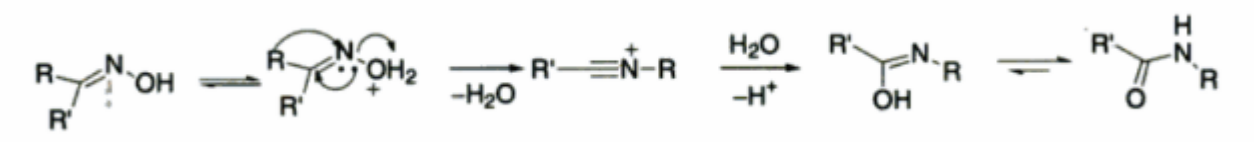


The claisen rearrangement is a thermal rearrangement of allyl aryl ethers and allyl vinyl ethers respectively. It may be regarded as the oxa-version of the closely related cope rearrangement. Claisen has discovered this reaction first on allyl vinyl ethers and then extended to the rearrangement of allyl aryl ethers to yield o-allylphenols.

Beckmann Rearrangement

In the Beckmann rearrangement , an oxime is converted to an amide . An oxime is easily obtained by treatment of aldehyde or ketone with hydroxylamine. The OH group of ketoximes can become a leaving group. The Beckmann rearrangement of cyclic oximes results in lactams.

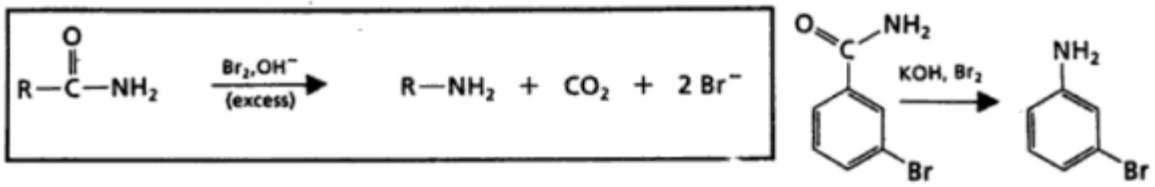
The comparison of the structure of the starting ketone with those of the products reveals that the combination of oxime formation and Beckmann rearrangement accomplishes the insertion of an NH group between the carbonyl carbon and the alpha carbon.



Beckmann rearrangement of the oxime of cyclohexanone is carried out on a very large scale industrially because the product, caprolactam, is the direct precursor of nylon 6, a versatile polymer that has many applications: for example, the manufacture of fibres for carpeting and other textiles. Concentrated sulphuric acid is used as both the acid catalyst and the solvent for the reaction.

Hofmann Rearrangement

The Hofmann rearrangement results from the treatment of a primary amide with bromine and hydroxide ion in water, ultimately forming an amine in which the carbonyl group of the starting amide has been lost.



Thus the Hofmann rearrangement results in a shortening of the carbon chain by one atom and a change in functional group from an amide to an amine. The Hofmann rearrangement occurs through a pathway similar to that for the Beckmann rearrangement.

Pericyclic Rearrangement

Pericyclic reactions are defined as the reactions that occur by a concerted cyclic shift of electrons. This definition states two key points that characterise a pericyclic reaction.

- First point is that reaction is concerted. In concerted reaction, reactant bonds are broken and product bonds are formed at the same time without intermediates.
- Second key point in pericyclic reactions involves a cyclic shift of electrons. The word pericyclic means around the circle. Pericyclic words come from the cyclic shift of electrons. Pericyclic reactions thus are characterised by a cyclic transition state involving the pi bonds.

The energy of activation of pericyclic reactions is supplied by heat or by UV light. Pericyclic reactions are stereospecific and it is not uncommon that the two modes of induction yield products of opposite stereochemistry.

Three features of any pericyclic reaction are intimately interrelated. These are

- ***Activation –*** Pericyclic reactions are activated either by thermal energy or by UV light. However, many reactions that require heat are not initiated by light and vice versa.
- The number of pi bonds involved in the reaction.
- The stereochemistry of the reaction

Photochemical rearrangements

Many photo reactions are known to interconvert isomeric compounds. The term "***rearrangement***" is more general than "isomerization" but for the reactions under photochemical rearrangement will not be concerned with a distinction between these terms.

For convenience we shall classify primary photochemical rearrangements as the following types.

1. Cis trans isomerization
2. Sigmatropic rearrangements
3. Electrocyclic rearrangements
4. Structural rearrangements which result from intramolecular cycloadditions.

In a broad sense all four of these classes are special cases of pericyclic rearrangements and for concerted reactions, they all may be treated under a unifying framework guided by the rules derived from orbital symmetry considerations.

Frequently Asked Questions on Rearrangement Reaction

What is rearrangement reaction with example?

Usually straight-chain alkanes are converted by heating in the presence of a catalyst to branched isomers. Examples include n-butane isomerization to isobutane, and pentane to isopentane. Highly branched alkanes have favorable properties for internal combustion engines.

What is meant by Beckmann rearrangement?

The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann (1853–1923), is a rearrangement to replace amides by an oxime functional group. The rearrangement of Beckmann is mostly catalyzed by acid, but other reagents were known to facilitate the rearrangement.

What is rearrangement in organic chemistry?

A rearrangement reaction is a large class of organic reactions, in which a molecule's carbon skeleton is rearranged to give the original molecule a structural isomer. A substituent passes in the same molecule frequently from one atom to another.

What do you mean by the concerted path of a reaction?

A coordinated reaction is a chemical reaction in which all breaking of bonds and making of bonds occurs in one single step. There are no intermediate reactive intermediates or other high energy

unstable intermediates involved. The reaction, like all bonds are formed and broken in concert, is said to progress through a coordinated process.

What is regioselective reaction?

Regioselectivity is the advantage of having or breaking a chemical bond in one direction over all other possible directions. Regioselectivity can also be extended to different reactions, such as pi-ligands addition. Selectivity occurs also in carbene insertions, e.g. in the Baeyer-Villiger reaction.

Pinacol rearrangement

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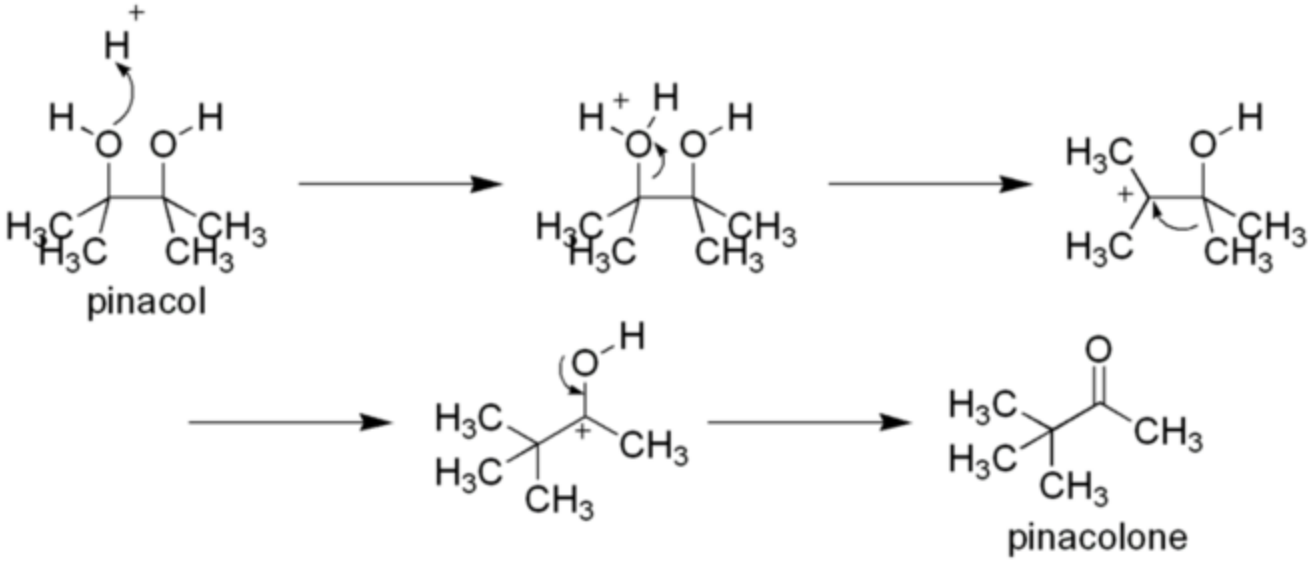
The **pinacol–pinacolone rearrangement** is a method for converting a 1,2-diol to a carbonyl compound in organic chemistry. The 1,2-rearrangement takes place under acidic conditions. The name of the rearrangement reaction comes from the rearrangement of pinacol to pinacolone.



This reaction was first described by Wilhelm Rudolph Fittig in 1860 of the famed Fittig reaction involving coupling of 2 aryl halides in presence of sodium metal in dry ethereal solution.[1]

MechanismEdit

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

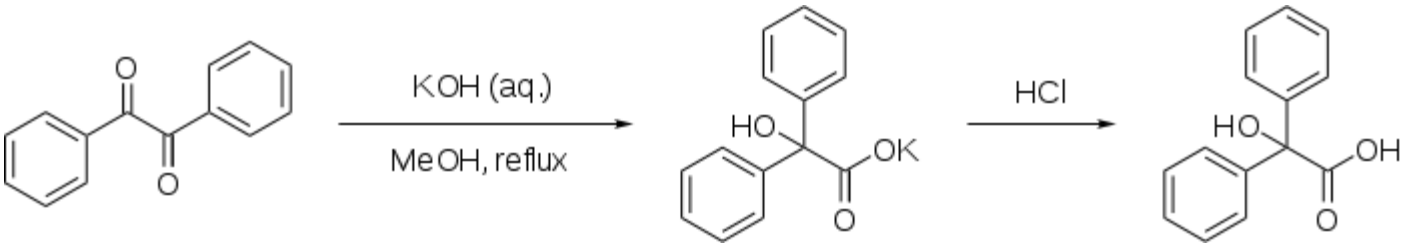
configuration at all centers (as opposed to the preceding carbocation). The migration of alkyl groups in this reaction occurs in accordance with their usual migratory aptitude, i.e.hydride > phenyl carbanion > tertiary carbanion (if formed by migration) > secondary carbanion (if formed by migration) > 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.

Stereochemistry of the rearrangementEdit

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.

Benzilic acid rearrangement

The **benzilic acid rearrangement** is formally the 1,2-rearrangement of 1,2-diketones to form α-hydroxy–carboxylic acids using a base. This reaction receives its name from the reaction of benzil with potassium hydroxide to form benzilic acid. First performed by Justus von Liebig in 1838,[1] it is the first reported example of a rearrangement reaction.[2] It has become a classic reaction in organic synthesis and has been reviewed many times before.[3][4][5] It can be viewed as an intramolecular disproportionation reaction, as one carbon center is oxidized while the other is reduced.

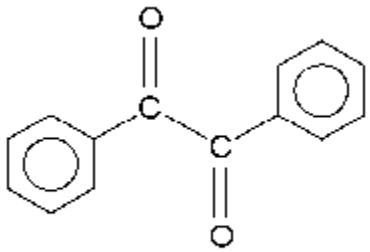


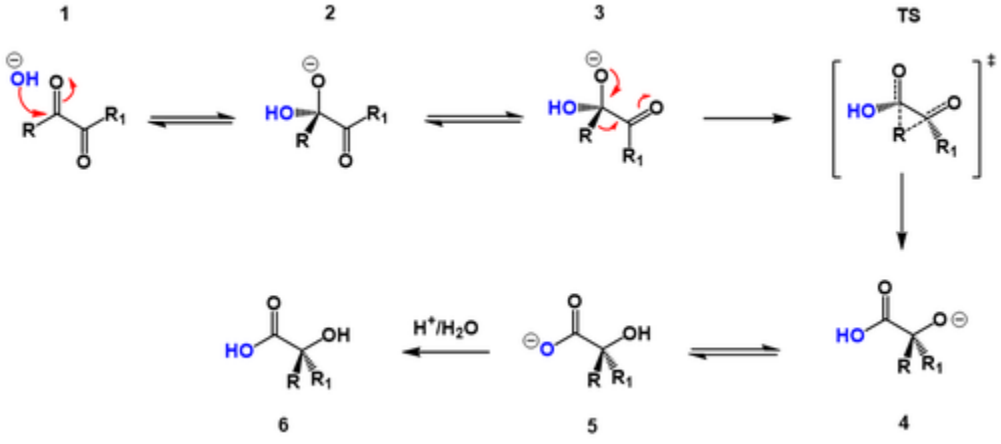
The reaction has been shown to work in aromatic, semi-aromatic, aliphatic, and heterocyclic substrates. The reaction works best when the ketone functional groups have no adjacent enolizable protons, as this allows aldol condensation to compete. The reaction is formally a ring contraction when used on 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[Edit]

The reaction is a representative of 1,2-rearrangements. The long-established reaction mechanism was first proposed in its entirety by Christopher Kelk Ingold, and has been updated with in silico data[6] 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.[3] 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.

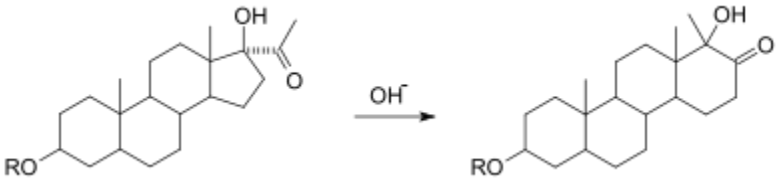
VariationsEdit

Benzilic ester rearrangementEdit

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 (such as potassium ethoxide) 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.

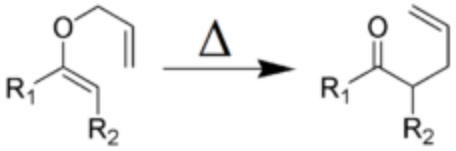
Alpha-ketol rearrangementEdit

The alpha-ketol rearrangement is an interconversion of a hydroxyl alpha to a carbonyl to the complementary carbonyl and hydroxyl groups, with migration of a substituent. It is mechanistically equivalent to the benzyllic acid rearrangement at the point after the nucleophile attacks the 1,2-dicarbonyl. This variation of the reaction has been known to occur in many substrates bearing the acyloin functional group. The picture below shows the ring expansion of a cyclopentane to a cyclohexane ring as an example reaction.[7][8]



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.[1][2][3] Many reviews have been written.[4][5][6][7]

Mechanism

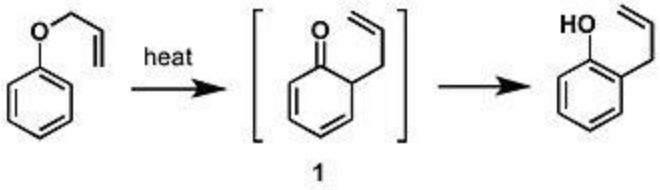
The Claisen rearrangement is an exothermic, concerted (bond cleavage and recombination) pericyclic reaction. Woodward–Hoffmann rules show a suprafacial, stereospecific reaction pathway. The kinetics are of the first order and the whole transformation proceeds through a highly ordered cyclic transition 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.[8][9]

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.[10][11] Trivalent organoaluminium reagents, such as trimethylaluminium, have been shown to accelerate this reaction.[12][13]

Variations

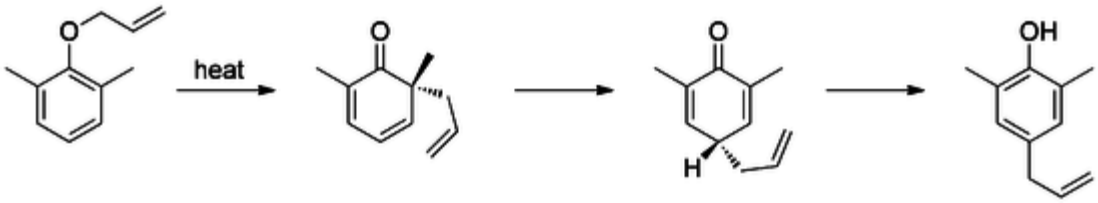
Aromatic Claisen rearrangement

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.



Meta-substitution affects the regioselectivity of this rearrangement.[14][15] For example, electron withdrawing groups (such as bromide) at the *meta*-position direct the rearrangement to the *ortho*-position (71% *ortho* product), while electron donating groups (such as methoxy), direct rearrangement to the *para*-position (69% *para* product). Additionally, presence

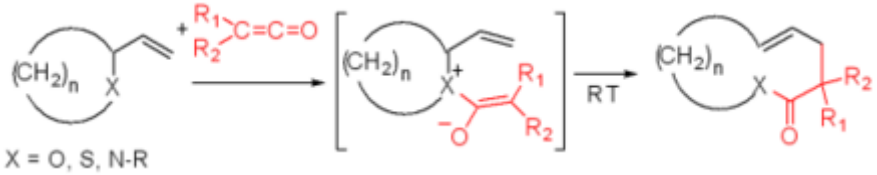
of *ortho* substituents exclusively leads to para-substituted rearrangement products (tandem Claisen and Cope rearrangement).[16]



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.[17][18]

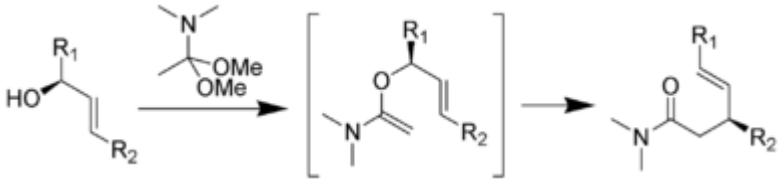
Bellus–Claisen rearrangement

The Bellus–Claisen rearrangement is the reaction of allylic ethers, amines, and thioethers with ketenes to give γ,δ-unsaturated esters, amides, and thioesters.[19][20][21] 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.[22][23] The Bellus-Claisen offers synthetic chemists a unique opportunity for ring expansion strategies.

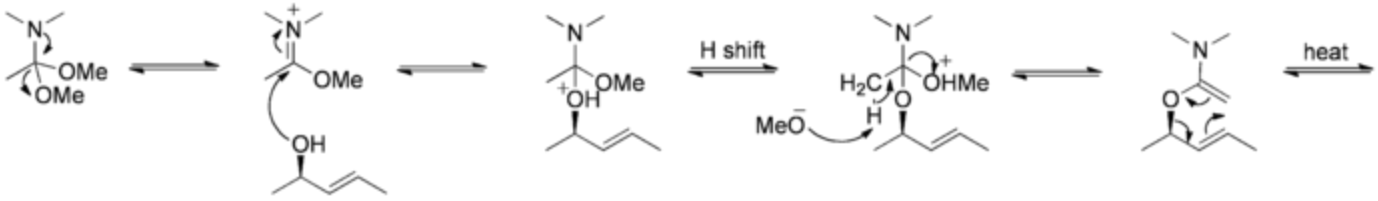


Eschenmoser–Claisen rearrangement

The Eschenmoser–Claisen rearrangement proceeds by heating allylic alcohols in the presence of *N*,*N*-dimethylacetamide dimethyl acetal to form a γ,δ-unsaturated amide. This was developed by Albert Eschenmoser in 1964.[24][25] Eschenmoser-Claisen rearrangement was used as a key step in the total synthesis of morphine.[26]



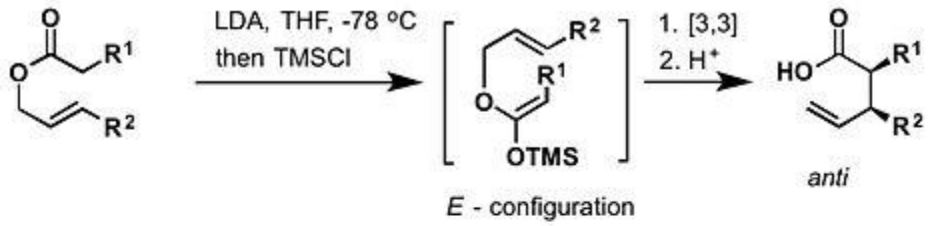
Mechanism:[16]

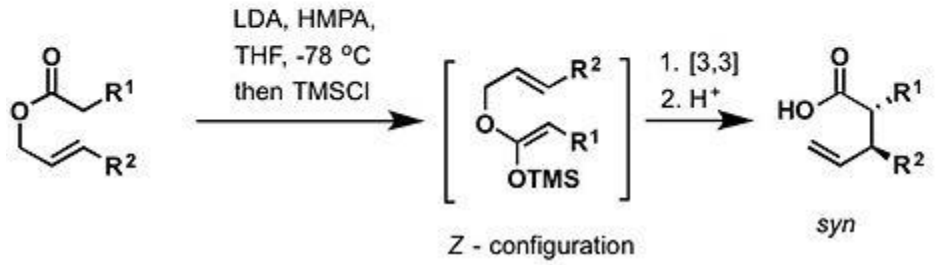


Ireland–Claisen rearrangement

Main article: Ireland–Claisen rearrangement

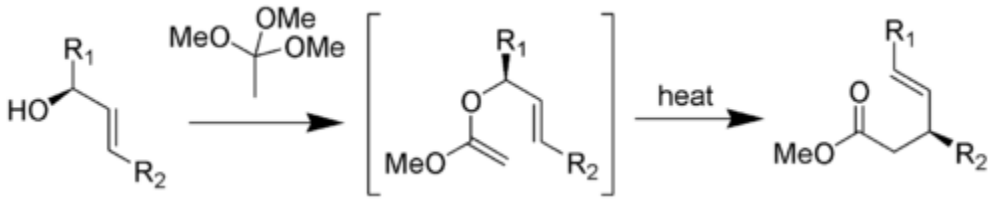
The Ireland–Claisen rearrangement is the reaction of an allylic carboxylate with a strong base (such as lithium diisopropylamide) to give a γ,δ-unsaturated carboxylic acid.[27][28][29] The rearrangement proceeds via silylketene acetal, which is formed by trapping the lithium enolate with chlorotrimethylsilane. 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.[30] There are numerous examples of enantioselective Ireland-Claisen rearrangements found in literature to include chiral boron reagents and the use of chiral auxiliaries.[31][32]





Johnson–Claisen rearrangement

The Johnson–Claisen rearrangement is the reaction of an allylic alcohol with an orthoester to yield a *γ,δ-unsaturated* ester.[33] Weak acids, such as propionic acid, have been used to catalyze this reaction. This rearrangement often requires high temperatures (100–200 °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.[35][36]



Mechanism:[16]

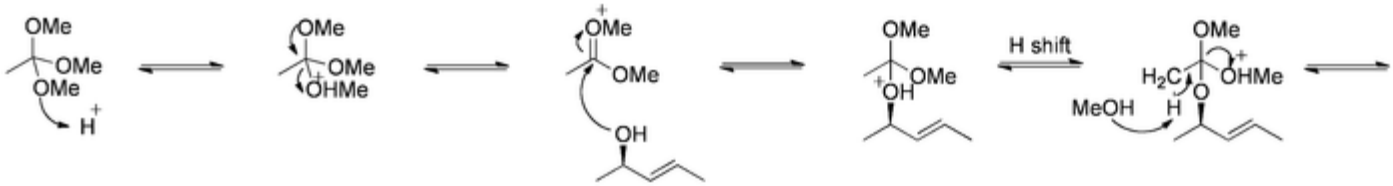


Photo-Claisen rearrangement

The Claisen rearrangement of aryl ethers can also be performed as a photochemical reaction. In addition to the traditional *ortho* product obtained under thermal conditions (the [3,3] rearrangement product), the photochemical variation also gives the *para* product ([3,5] product), alternate isomers of the allyl group (for example, [1,3] and [1,5] products), and simple loss of the ether group, and even can rearrange alkyl ethers in addition to allyl ethers. The photochemical reaction occurs via a stepwise process of radical-cleavage followed by bond-formation rather than as a concerted pericyclic reaction, which therefore allows the opportunity for the greater variety of possible substrates and product isomers.[37] The [1,3] and [1,5] results of the photo-Claisen rearrangement are analogous to the photo-Fries rearrangement of aryl esters and related acyl compounds.

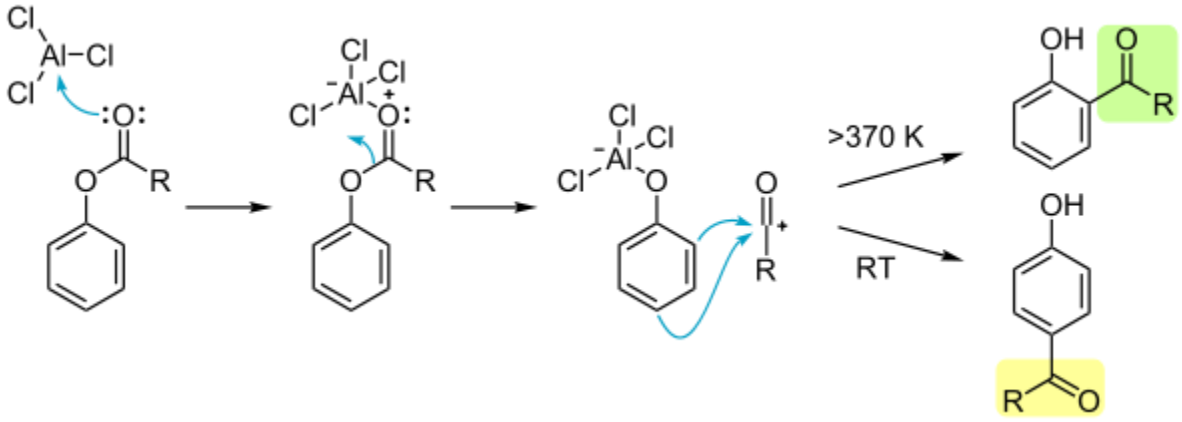
Fries rearrangement

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.[6]

Scope

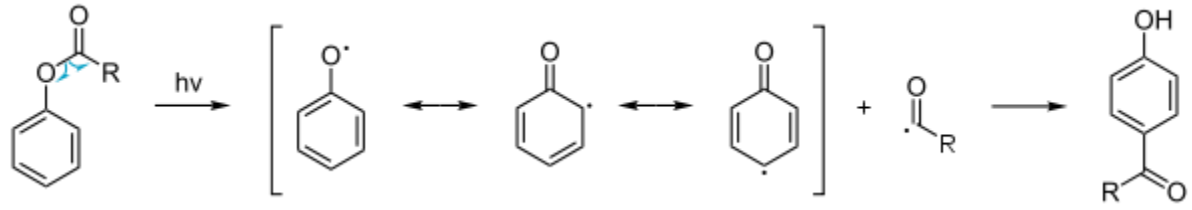
Phenols react to form esters instead of hydroxyarylketones when reacted with acyl halides under Friedel-Crafts acylation conditions. Therefore, this reaction is of industrial importance for the synthesis of hydroxyarylketones, which are important intermediates for several pharmaceuticals. As an alternative to aluminium chloride, other Lewis acids such as boron trifluoride and bismuth triflate or strong protic acids such as hydrogen fluoride and methanesulfonic acid can also be used. In order to avoid the use of these corrosive and environmentally unfriendly catalysts altogether research into alternative heterogeneous catalysts is actively pursued.

Limits

In all instances only esters can be used with stable acyl components that can withstand the harsh conditions of the Fries rearrangement. If the aromatic or the acyl component is heavily substituted then the chemical yield will drop due to steric constraints. Deactivating meta-directing groups on the benzene group will also have an adverse effect as can be expected for a Friedel–Crafts acylation.

Photo-Fries rearrangement

In addition to the ordinary thermal phenyl ester reaction a photochemical variant is possible. The **photo-Fries rearrangement** can likewise give [1,3] and [1,5] products.[7][8] 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.[9]

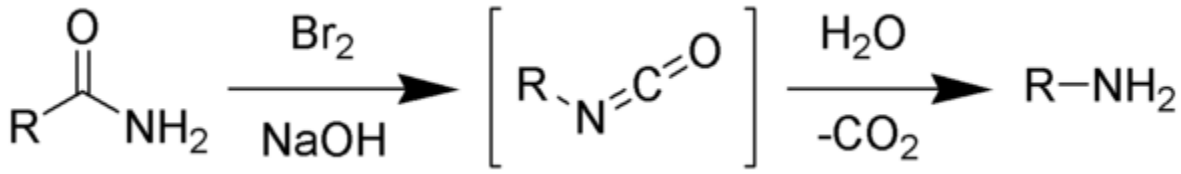


Anionic Fries rearrangement

In the anionic Fries rearrangement ortho-metalation of aryl esters, carbamates and carbonates with a strong base results in a rearrangement to give ortho-carbonyl species.[10]

Hofmann rearrangement

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

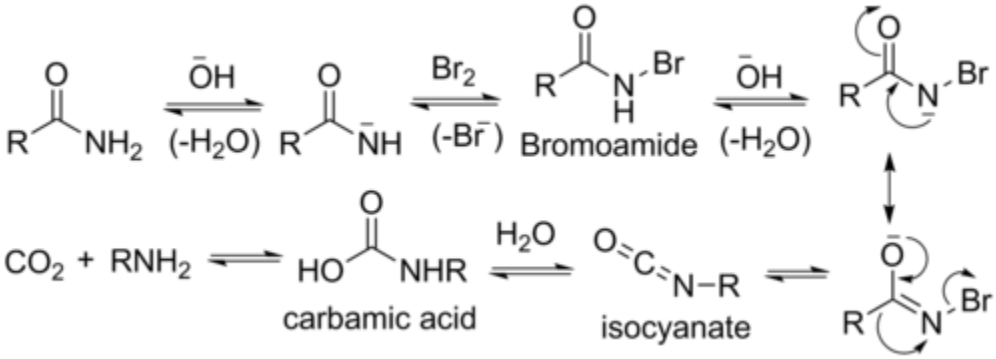


The Hofmann rearrangement.

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 a hydroxamic acid as a byproduct, which has never been observed. The intermediate isocyanate is hydrolyzed to a primary amine, giving off carbon dioxide.[2]



(a) Base abstracts an acidic N-H proton, yielding an anion.

(b) The anion reacts with bromine in an α-substitution reaction to give an *N*-bromoamide.

(c) Base abstraction of the remaining amide proton gives a bromoamide anion.

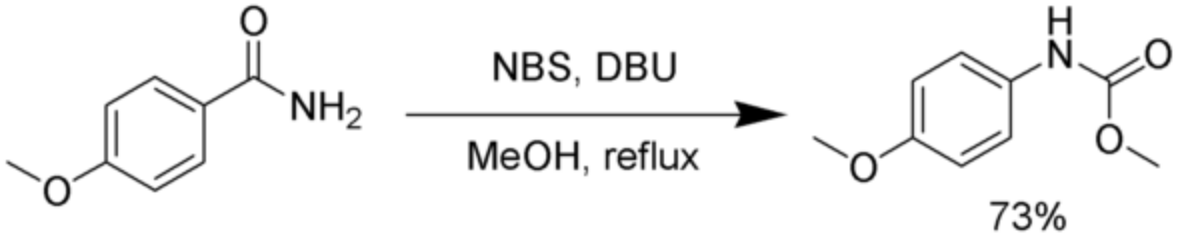
(d) The bromoamide anion rearranges as the R group attached to the carbonyl carbon migrates to nitrogen at the same time the bromide ion leaves, giving an isocyanate.

(e) The isocyanate adds water in a nucleophilic addition step to yield a carbamic acid (aka urethane).

(f) The carbamic acid spontaneously loses CO_2, yielding the amine product.

Variations

Several reagents can be substituted for bromine. Sodium hypochlorite,[4] lead tetraacetate,[5] *N*-bromosuccinimide, (bis(trifluoroacetoxy)iodo)benzene,[6] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) can effect a Hofmann rearrangement. In the following example, the intermediate isocyanate is trapped by methanol, forming a carbamate.[7]



The Hofmann rearrangement using NBS.

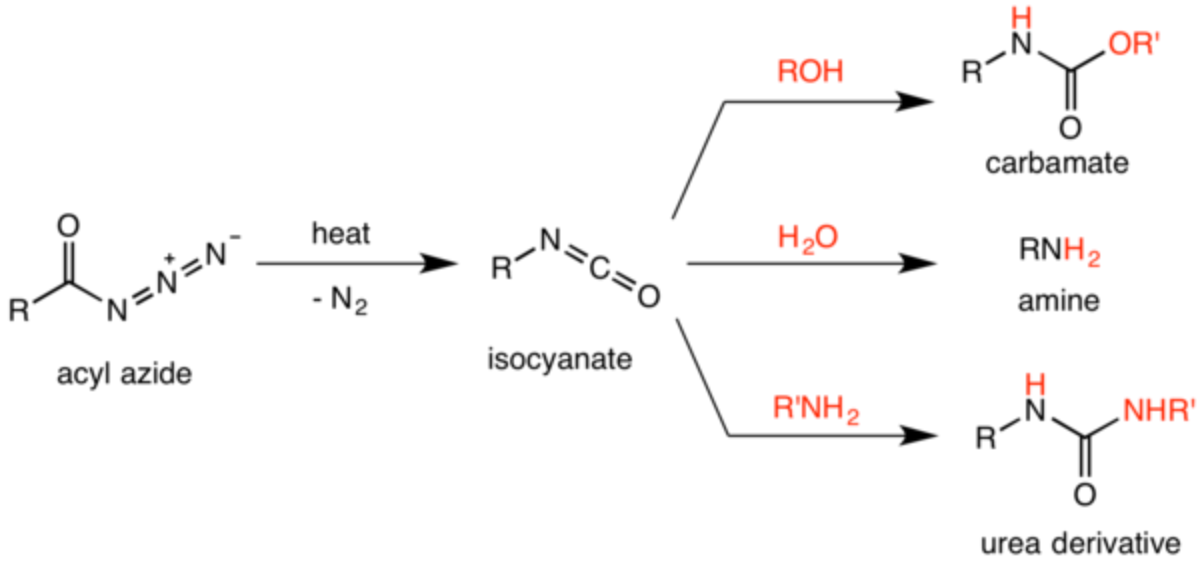
In a similar fashion, the intermediate isocyanate can be trapped by *tert*-butyl alcohol, yielding the *tert*-butoxycarbonyl (Boc)-protected amine.
The Hofmann Rearrangement also can be used to yield carbamates from α,β-unsaturated or α-hydroxy amides[2][8] or nitriles from α,β-acetylenic amides[2][9] in good yields (≈70%).
For amiloride, hypobromous acid was used to effect a Hofmann rearrangement.

Applications

1. Aliphatic and aromatic amides are converted into aliphatic and aromatic amines, respectively
2. In the preparation of anthranilic acid from phthalimide
3. Nicotinic acid is converted into 3-Aminopyridine
4. The symmetrical structure of α-phenyl propanamide does not change after Hofmann reaction.
5. In the synthesis of gabapentin, beginning with the mono-amidation of 1,1-cyclohexane diacetic acid anhydride with ammonia to 1,1-cyclohexane diacetic acid mono-amide, followed by a Hoffmann rearrangement.

Curtius rearrangement

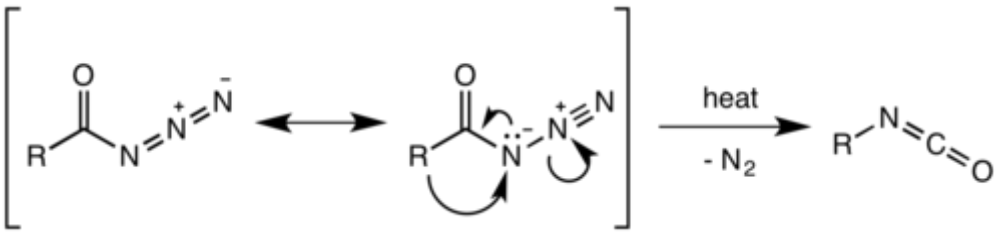
The **Curtis rearrangement** (or **Curtius reaction** or **Curtius degradation**), first defined by Theodor Curtius in 1885, is the thermal decomposition of an acyl azide to an isocyanate with loss of nitrogen gas.[1][2] The isocyanate then undergoes attack by a variety of nucleophiles such as water, alcohols and amines, to yield a primary amine, carbamate or urea derivative respectively.[3] Several reviews have been published.[4][5]



Preparation of acyl azide

Reaction mechanism

It was believed that the Curtius rearrangement was a two-step processes, 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.[10] Thermodynamic calculations also support a concerted mechanism.[11]



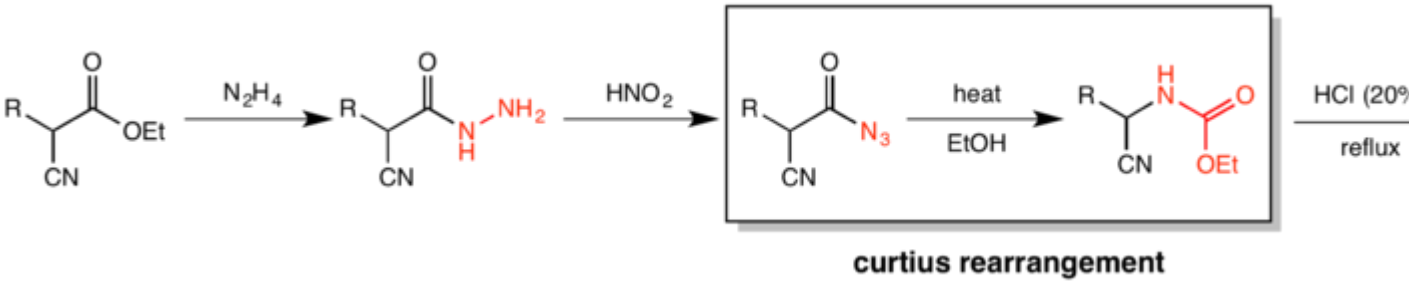
Mechanism of the Curtius rearrangement

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.

Variations

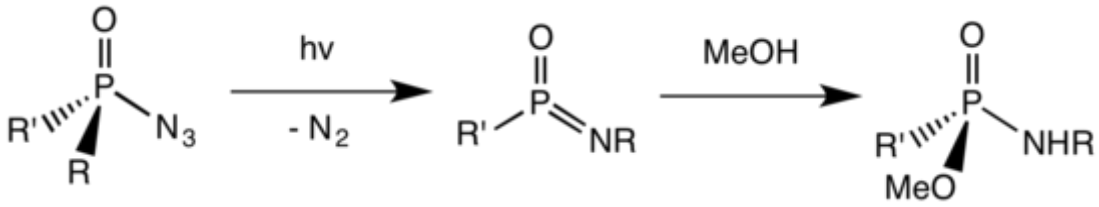
Darapsky degradation

In one variation called the **Darapsky degradation**,[16] 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.[17]



Harger reaction

The photochemical Curtius-like migration and rearrangement of a phosphinic azide forms a metaphosphonimidate[18] in what is also known as the **Harger reaction** (this is named after the late Martin Harger from Leicester).[19] 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.

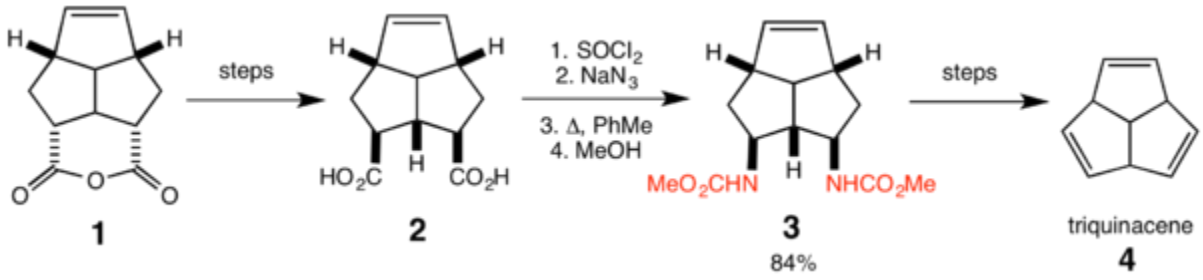
Synthetic applications

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

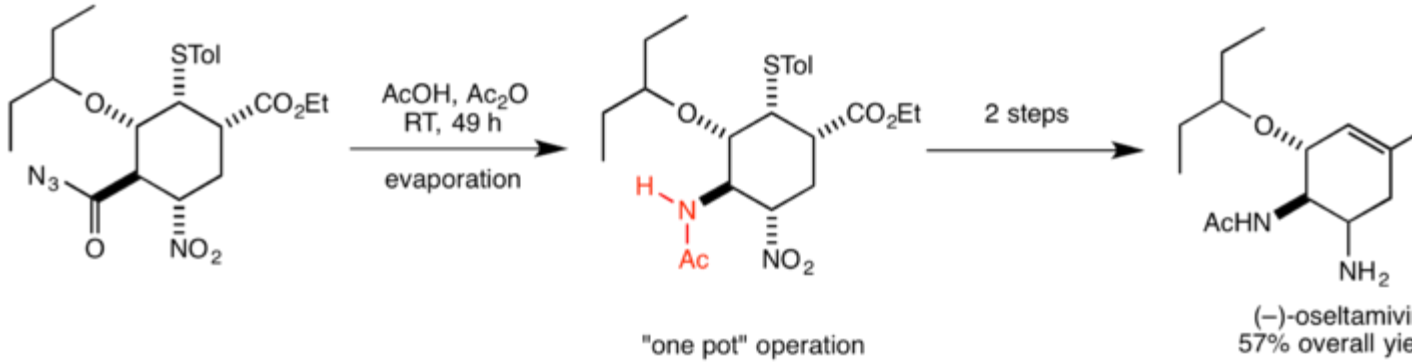
Triquinacene

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**).



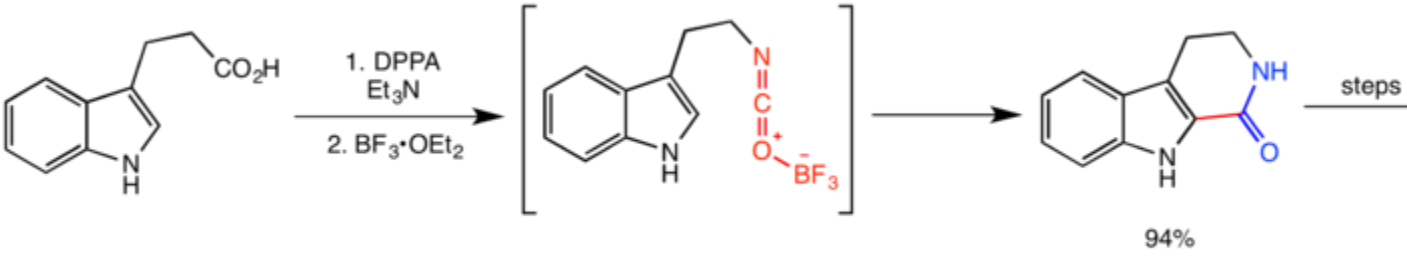
Oseltamivir

In their synthesis of the antiviral drug oseltamivir, also known as Tamiflu, Ishikawa et al. used the Curtius rearrangement in one of the key steps in converting the acyl azide to the amide group in the target molecule. In this case, the isocyanate formed by the rearrangement is attacked by a carboxylic acid to form the amide. Subsequent reactions could all be carried out in the same reaction vessel to give the final product with 57% overall yield. An important benefit of the Curtius reaction highlighted by the authors was that it could be carried out at room temperature, minimizing the hazard from heating. The scheme overall was highly efficient, requiring only three "one-pot" operations to produce this important and valuable drug used for the treatment of avian influenza



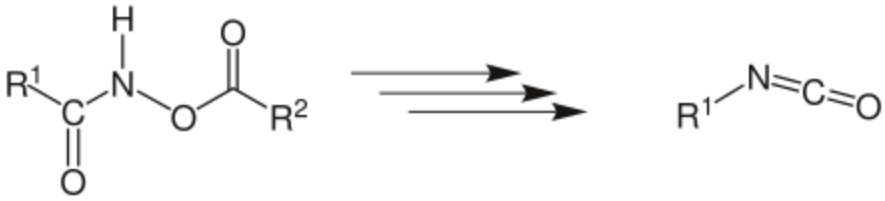
Dievodiamine

Dievodiamine is a natural product from the plant Evodia rutaecarpa, which is widely used in traditional Chinese medicine. Unsworth et al.'s protecting group-free total synthesis of dievodiamine utilizes the Curtius rearrangement in the first step of the synthesis, catalyzed by boron trifluoride. The activated isocyanate then quickly reacts with the indole ring in an electrophilic aromatic substitution reaction to give the amide in 94% yield, and subsequent steps give dievodamine.



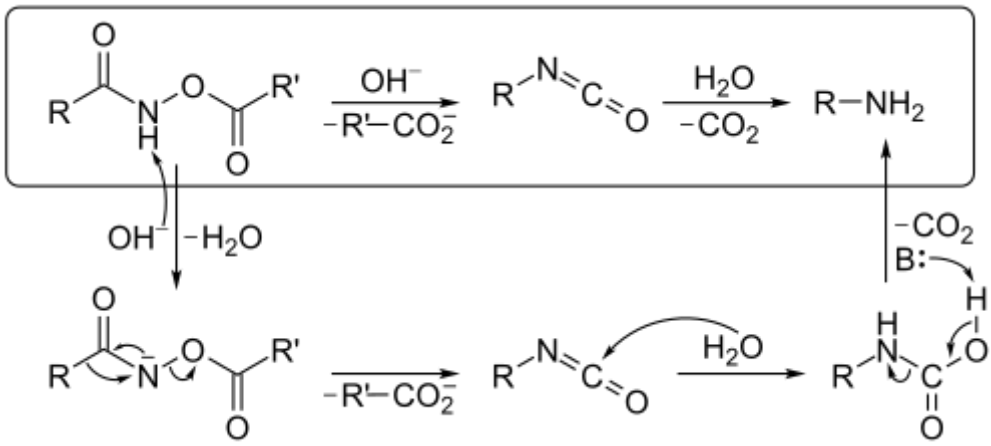
Lossen rearrangement

The **Lossen rearrangement** is the conversion of a hydroxamate ester to an isocyanate. Typically O-acyl, sulfonyl, or phosphoryl O-derivative are employed.[1][2][3][4]The isocyanate can be used further to generate ureas in the presence of amines or generate amines in the presence of H_2O.



Reaction mechanism

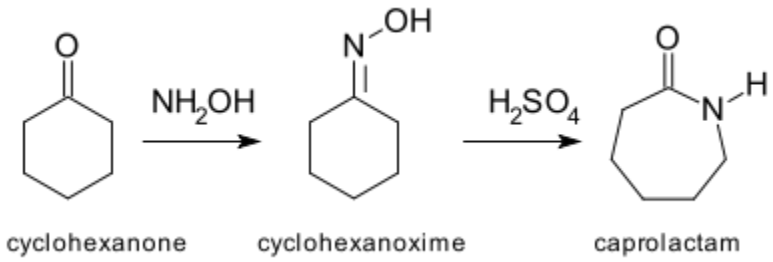
The mechanism below begins with an O-acylated hydroxamic acid derivative that is treated with base to form an isocyanate that generates an amine and CO_2 gas in the presence of H_2O. The hydroxamic acid derivative is first converted to its conjugate base by abstraction of a hydrogen by a base. Spontaneous 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.



Hydroxamic acids are commonly synthesized from their corresponding esters.

Beckmann 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.[1][2] 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.[3] 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.

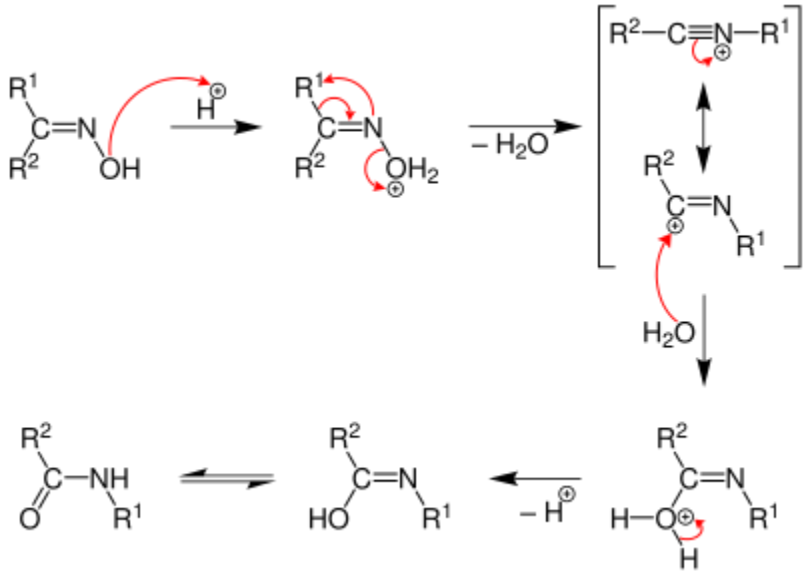


The archetypal Beckmann rearrangement[4] is the conversion of cyclohexanone to caprolactam via the oxime. Caprolactam is the feedstock in the production of Nylon 6, 5.

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

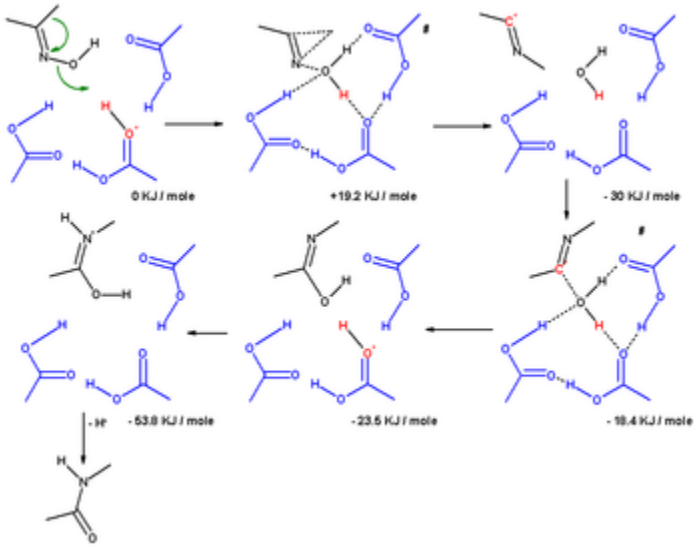
The most common reaction mechanism of the Beckmann rearrangement consists generally of an alkyl migration anti-periplanar to the expulsion of a leaving group to form a nitrilium ion. This is followed by solvolysis to an imidate and then tautomerization to the amide:



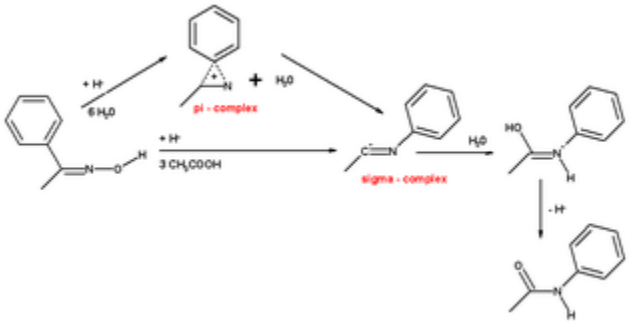
This nitrilium ion has been known to be intercepted by other nucleophiles, including the leaving group from the oxime.[3]

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.[6] 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.



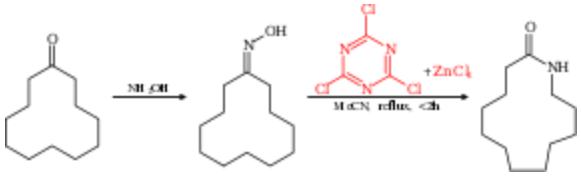
The same computation with a hydroxonium ion and 6 molecules of water has the same result, but when the migrating substituent is a phenyl group, the mechanism favors the formation of an intermediate three-membered π-complex. This π-complex is not found in the $H_3O^+(H_2O)_6$.



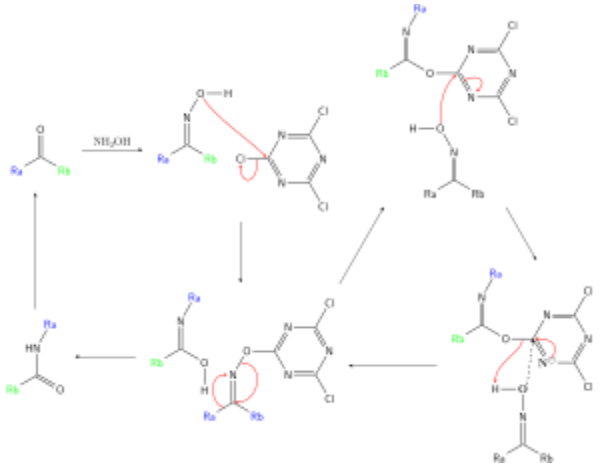
With the cyclohexanone-oxime, the relief of ring strain results in a third reaction mechanism, leading directly to the protonated caprolactam in a single concerted step without the intermediate formation of a π-complex or σ-complex.

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.[7][8]

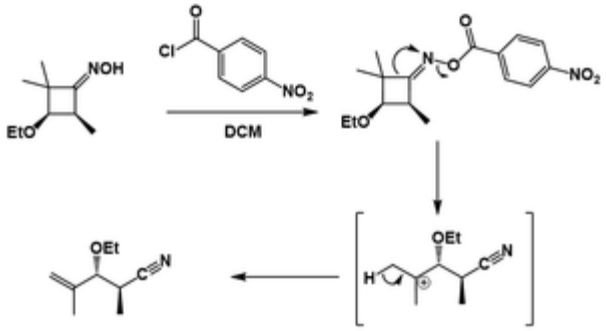


The reaction mechanism for this reaction is based on a catalytic cycle with cyanuric chloride activating the hydroxyl group via a nucleophilic aromatic substitution. The reaction product is dislodged and replaced by new reactant via an intermediate Meisenheimer complex.

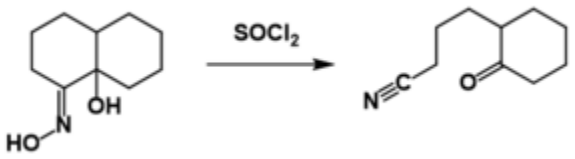


Beckmann fragmentation

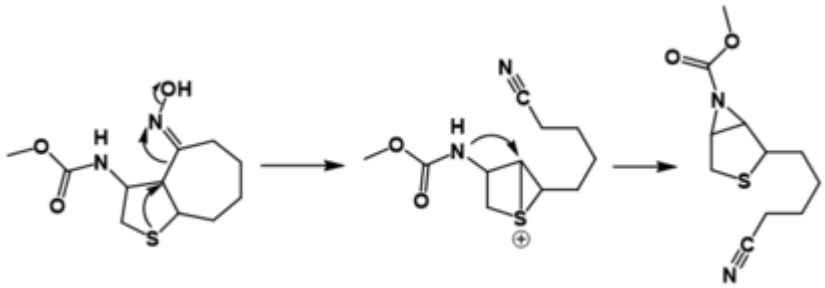
The Beckmann fragmentation is a reaction that frequently competes with the Beckmann rearrangement. When the group α to the oxime is capable of stabilizing carbocation formation, the fragmentation becomes a viable reaction pathway. The reaction generates a nitrile and a carbocation, which is quickly intercepted 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.



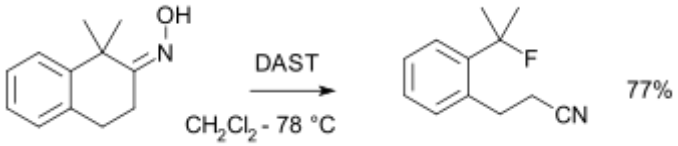
Quaternary carbon centers promote fragmentation by stabilizing carbocation formation through hyperconjugation. As shown in the above picture, the "stable" carbocation is formed, which then loses a hydrogen to give a site of unsaturation. Oxygen and nitrogen atoms also promote fragmentation through the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



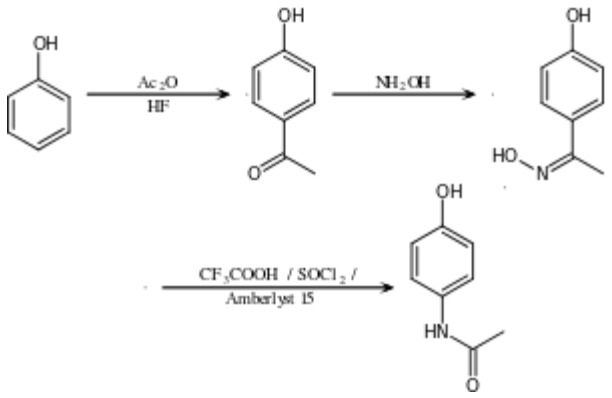
Sulfur is also capable of promoting fragmentation, albeit at a longer range than oxygen or nitrogen.



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):[9]



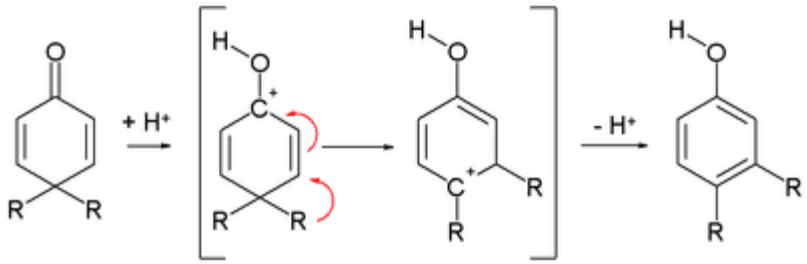
Applications in drug synthesis



This route also involves the Beckmann rearrangement

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:



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 conjugated structure". The class includes some heterocyclic compounds.

Transformation of a diketone to phenol in presence of acid as known as the Dienone Phenol Rearrangement. As the name implies, this reaction results in the transformation of a quinoid structure to a benzenoid ring. … Thus the driving force of this reaction is the creation of aromatic ring in the product.