Organic chemistry- Naming reactions

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Acetaldehyde

Acetaldehyde			
[[File:Acetaldehyde-tall-2D-skeletal.png	Skeletal structure of acetaldehyde]]	[[File:Acetaldehyde-3D-balls.png	Ball-and-stick model]]
[[File:Acetaldehyde-2D-flat.png	Lewis structure of acetaldehyde]]	[[File:Acetaldehyde-3D-vdW.png	Space-filling model]]
Identifiers			
CAS number	75-07-0 [1] ✓		
PubChem	177 [2]		
ChemSpider	172 [3] ✓		
UNII	GO1N1ZPR3B [4] ✓		
EC number	200-836-8 [5]		
KEGG	C00084 [6] ✓		
ChEMBL	CHEMBL170365 [7] ✓		
RTECS number	AB1925000		
Properties			
Molecular formula	C_2H_4O		
Molar mass	44.05 g mol^{-1}		
Appearance	Colourless liquid Pungent, fruity odor		
Density	0.788 g cm^{-3}		
Melting point	−123.5 °C, **unknown operator: u'\u2212'** K, **unknown operator: u'\u2212'** °F		
Boiling point	20.2 °C, 293 K, 68 °F		
Solubility in water	soluble in all proportions		
Viscosity	~0.215 at 20 °C		
Structure			
Molecular shape	trigonal planar (sp^2) at C_1 tetrahedral (sp^3) at C_2		
Dipole moment	2.7 D		
Hazards			
EU classification	Very flammable (**F+**) Harmful (**Xn**) Carc. Cat. 3		
R-phrases	R12 R36/37 R40		

S-phrases	(S2) S16 S33 S36/37		
NFPA 704			
Flash point	234,15 K (-39 °C)		
Autoignition temperature	458,15 K (185 °C)		
Related compounds			
Related aldehydes	Formaldehyde Propionaldehyde		
Related compounds	Ethylene oxide		
✓ (what is this?) (verify) [8] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)			
Infobox references			

Acetaldehyde (systematically **ethanal**) is an organic chemical compound with the formula CH_3CHO or MeCHO. It is one of the most important aldehydes, occurring widely in nature and being produced on a large scale industrially. Acetaldehyde occurs naturally in coffee, bread, and ripe fruit, and is produced by plants as part of their normal metabolism. It is also produced by oxidation of ethanol and is popularly believed to be a cause of hangovers.[9] Pathways of exposure include air, water, land or groundwater that can expose the human subject directly if they inhale, drink, or smoke.[10]

Production

In 2003, global production was about 10^6 tons/year.[11] The main production method is the oxidation of ethylene via the Wacker process:

$$2\ CH_2{=}CH_2 + O_2 \rightarrow 2\ CH_3CHO$$

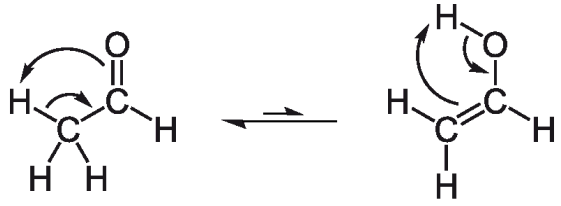
Alternatively, hydration of acetylene, catalyzed by mercury salts gives ethenol, which tautomerizes to acetaldehyde. This industrial route was dominant prior to the Wacker process[12] It is also prepared at smaller levels by both the dehydrogenation and the oxidation of ethanol.

Reactions

Like many other carbonyl compounds, acetaldehyde tautomerizes to give the enol. The enol of acetaldehyde is vinyl alcohol (IUPAC name: ethenol):

$$CH_3CH{=}O \rightleftarrows CH_2{=}CHOH$$

The equilibrium constant is only 6 x 10^{-5} at room temperature, so that the amount of the enol in a sample of acetaldehyde is very small.[13]



Ethanal-ethenol tautomerism

Condensation reactions

Because of its small size and its availability as the anhydrous monomer (unlike formaldehyde), it is a common electrophile in organic synthesis.[14] With respect to its condensation reactions, acetaldehyde is prochiral. It is mainly used as a source of the "$CH_3C^+H(OH)$" synthon

in aldol and related condensation reactions.[15] Grignard reagents and organolithium compounds react with MeCHO to give hydroxyethyl derivatives.[16] In one of the more spectacular condensation reactions, three equivalents of formaldehyde add to MeCHO to give pentaerythritol, $C(CH_2OH)_4$.[17]

In a Strecker reaction, acetaldehyde condenses with cyanide and ammonia to give, after hydrolysis, the amino acid alanine.[18] Acetaldehyde can condense with amines to yield imines, such as the condensation with cyclohexylamine to give N-ethylidenecyclohexylamine. These imines can be used to direct subsequent reactions like an aldol condensation.[19]

It is also an important building block for the synthesis of heterocyclic compounds. A remarkable example is its conversion upon treatment with ammonia to 5-ethyl-2-methylpyridine ("aldehyde-collidine").[20]

Acetal derivatives

Three molecules of acetaldehyde condense to form “paraldehyde,” a cyclic trimer containing C-O single bonds. The condensation of four molecules of acetaldehyde give the cyclic molecule called metaldehyde.

Acetaldehyde forms a stable acetal upon reaction with ethanol under conditions that favor dehydration. The product, $CH_3CH(OCH_2CH_3)_2$, is in fact called "acetal,"[21] although acetal is used more widely to describe other compounds with the formula $RCH(OR')_2$.

Uses

Traditionally, acetaldehyde was mainly used as a precursor to acetic acid. This application has declined because acetic acid is made more efficiently from methanol by the Monsanto and Cativa processes. In terms of condensation reactions, acetaldehyde is an important precursor to pyridine derivatives, pentaerythritol, and crotonaldehyde. Urea and acetaldehyde combine to give a useful resin. Acetic anhydride reacts with acetaldehyde to give ethylidene diacetate, a precursor to vinyl acetate, which is used to produce polyvinyl acetate.

Biochemistry and health effects

In the liver, the enzyme alcohol dehydrogenase oxidizes ethanol into acetaldehyde, which is then further oxidized into harmless acetic acid by acetaldehyde dehydrogenase. These two oxidation reactions are coupled with the reduction of NAD^+ to NADH.[22] In the brain, alcohol dehydrogenase has a minor role in the oxidation of ethanol to acetaldehyde. Instead, the enzyme catalase primarily oxidizes ethanol to acetaldehyde.[22] The last steps of alcoholic fermentation in bacteria, plants and yeast involve the conversion of pyruvate into acetaldehyde by the enzyme pyruvate decarboxylase, followed by the conversion of acetaldehyde into ethanol. The latter reaction is again catalyzed by an alcohol dehydrogenase, now operating in the opposite direction.

Tobacco addiction

Acetaldehyde is a significant constituent of tobacco smoke. It has been demonstrated to have a synergistic effect with nicotine, increasing the onset and tenacity of addiction to cigarette smoking, particularly in adolescents.[23] [24]

Alzheimer's disease

People who have a genetic deficiency for the enzyme responsible for the conversion of acetaldehyde into acetic acid may have a greater risk of Alzheimer's disease. "These results indicate that the ALDH2 deficiency is a risk factor for LOAD [late-onset Alzheimer's disease] …"[25]

Alcohol problems

Acetaldehyde derived from the consumption of ethanol binds to proteins to form adducts that are linked to organ disease.[26]

The drug disulfiram (Antabuse) prevents the oxidation of acetaldehyde to acetic acid, and it has the same unpleasant effect on drinkers. Antabuse is sometimes used as a deterrent for alcoholics who wish to stay sober.

Carcinogen

Acetaldehyde is a probable carcinogen in humans.[27] In the year 1988 the International Agency for Research on Cancer stated, "There is *sufficient* evidence for the carcinogenicity of acetaldehyde (the major metabolite of ethanol) in experimental animals."[28] In October 2009 the International Agency for Research on Cancer updated the classification of acetaldehyde stating that acetaldehyde included in and generated endogenously from alcoholic beverages is a Group I human carcinogen.[29] In addition, acetaldehyde is damaging to DNA[30] and causes abnormal muscle development as it binds to proteins.[31]

A study of 818 heavy drinkers found that those who are exposed to more acetaldehyde than normal through a defect in the gene for acetaldehyde dehydrogenase are at greater risk of developing cancers of the upper gastrointestinal tract and liver.[32]

Safety

Acetaldehyde is toxic when applied externally for prolonged periods, an irritant, and a probable carcinogen.[27] It is an air pollutant resulting from combustion, such as automotive exhaust and tobacco smoke. It is also created by thermal degradation of polymers in the plastics processing industry.[33] Acetaldehyde natually breaks down in the human body[34] but has been shown to excrete in urine of rats.[35]

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External links

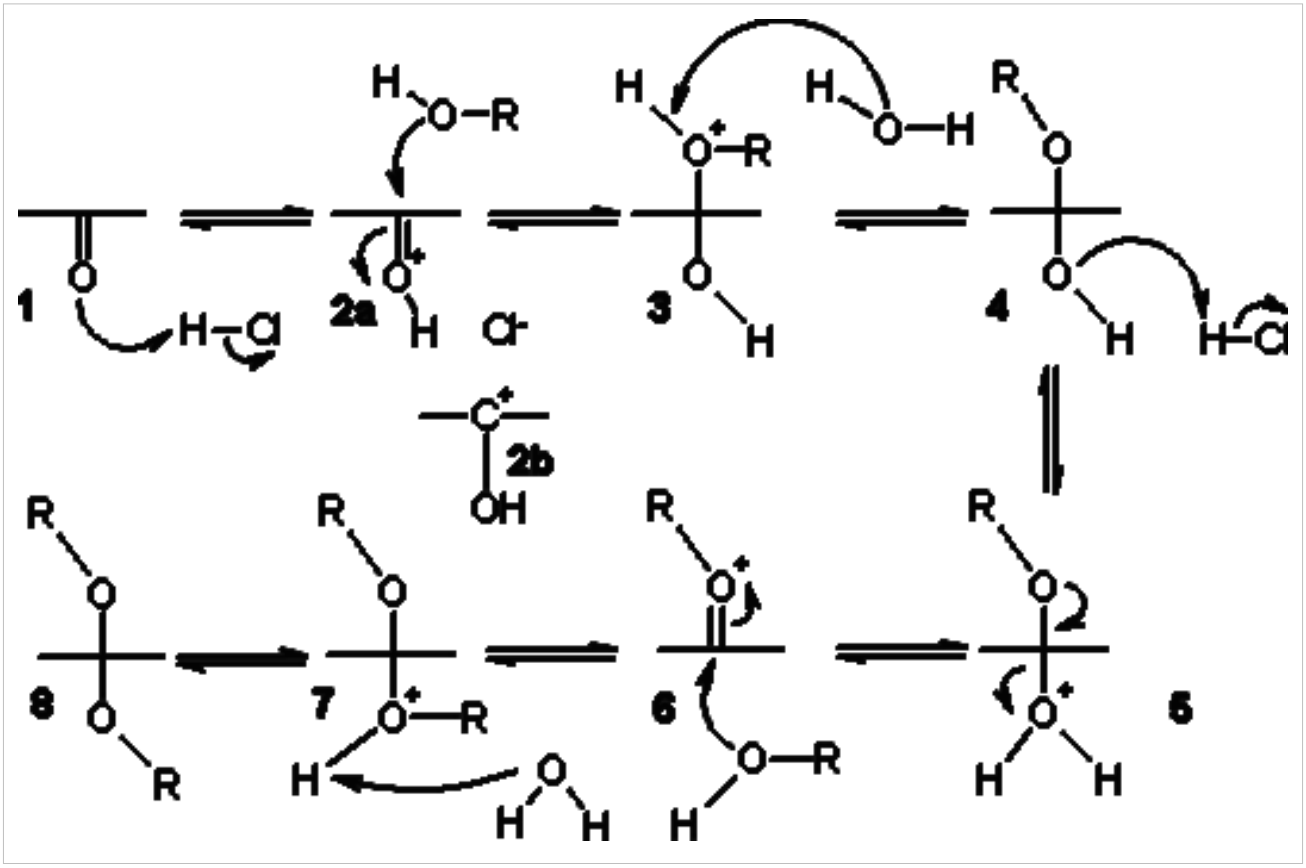
- International Chemical Safety Card 0009 (http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/_icsc00/icsc0009.htm)
- National Pollutant Inventory - Acetaldehde (http://www.npi.gov.au/database/substance-info/profiles/1.html)
- NIOSH Pocket Guide to Chemical Hazards (http://www.cdc.gov/niosh/npg/npgd0001.html)
- Methods for sampling and analysis (http://www.cdc.gov/niosh/nmam/pdfs/2018.pdf)
- IARC Monograph: "Acetaldehyde" (http://monographs.iarc.fr/ENG/Monographs/vol71/index.php)
- Hal Kibbey, Genetic Influences on Alcohol Drinking and Alcoholism (http://www.indiana.edu/~rcapub/v17n3/p18.html), Indiana University Research and Creative Activity, Vol. 17 no. 3.
- United States Food and Drug Administration (FDA) information for acetaldehyde (http://www.grokfood.com/additives/2.htm)

Acetalisation

Acetalisation is an organic reaction that involves the formation of an acetal or ketal. One way of acetal formation is the nucleophilic addition of an alcohol to a ketone or an aldehyde. Acetalisation is often used in organic synthesis to create a protecting group because it is a reversible reaction.

Acetalisation of carbonyl groups by alcohols

Acetalisation is acid catalysed with elimination of water. The reaction can be driven to the acetal when water is removed from the reaction system either by azeotropic distillation or trapping water with molecular sieves or aluminium oxide. The general reaction mechanism for acetalisation of a carbonyl group is shown below.



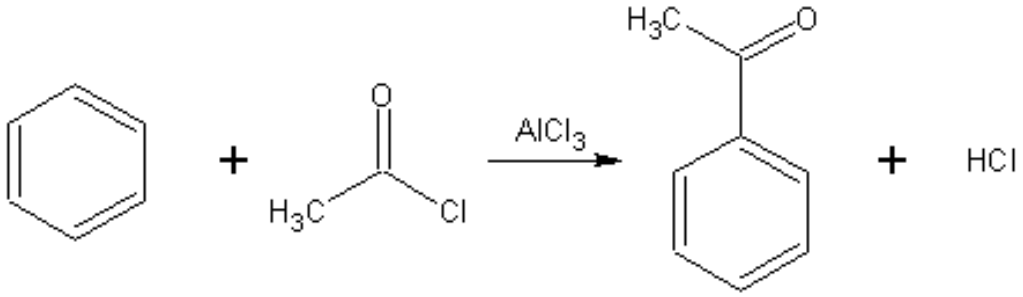
The carbonyl group in **1** abstracts a proton from hydrochloric acid. The protonated carbonyl group 2 is activated for nucleophilic addition of the alcohol. The structures **2a** and **2b** are mesomers. After deprotonation of **3** by water the hemiacetal or hemiketal **4** is formed. The hydroxyl group in **4** is protonated leading to the oxonium ion **6** which accepts a second alcohol group to **7** with a final deprotonation to the acetal **8**. The reverse reaction takes place by adding water in the same acidic medium. Acetals are stable towards basic media. In a **transacetalisation** or **crossacetalisation** a diol reacts with an acetal or two different acetals react with each other. Again this is possible because all the reaction steps are equilibria.

References

Acylation

In chemistry, **acylation** (rarely, but more formally: **alkanoylation**) is the process of adding an acyl group to a compound. The compound providing the acyl group is called the **acylating agent**.

Because they form a strong electrophile when treated with some metal catalysts, acyl halides are commonly used as acylating agents. For example, Friedel-Crafts acylation uses acetyl chloride (ethanoyl chloride), CH_3COCl, as the agent and aluminum chloride ($AlCl_3$) as a catalyst to add an ethanoyl(acetyl) group to benzene:



The mechanism of this reaction is electrophilic substitution.

Acyl halides and anhydrides of carboxylic acids are also commonly used acylating agents to acylate amines to form amides or acylate alcohols to form esters. The amines and alcohols are nucleophiles; the mechanism is nucleophilic addition-elimination. Succinic acid is also commonly used in a specific type of acylation called *succination*. *Oversuccination* occurs when more than one succinate adds to a single compound.

References

- NIH Thesaurus [1]

References

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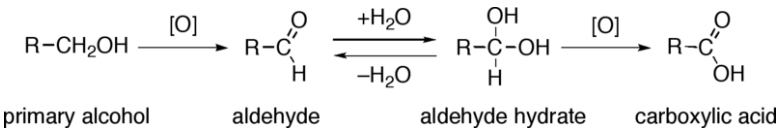
Alcohol oxidation



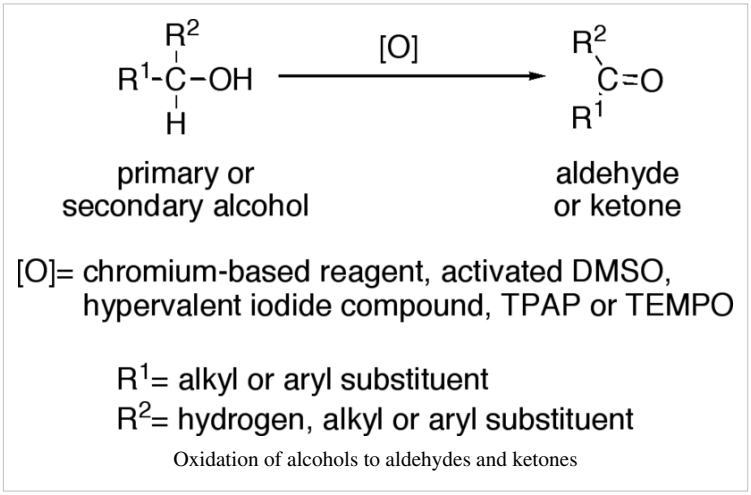
Mechanism of oxidation of primary alcohols to carboxylic acids via aldehydes and aldehyde hydrates

Alcohol oxidation is an important organic reaction. Primary alcohols (R-CH_2-OH) can be oxidized either to aldehydes (R-CHO) or to carboxylic acids (R-CO_2H), while the oxidation of secondary alcohols (R^1R^2CH-OH) normally terminates at the ketone (R^1R^2C=O) stage. Tertiary alcohols ($R^1R^2R^3$C-OH) are resistant to oxidation [1] .

The direct oxidation of primary alcohols to carboxylic acids normally proceeds via the corresponding aldehyde, which is transformed via an **aldehyde hydrate** (R-$CH(OH)_2$) by reaction with water before it can be further oxidized to the carboxylic acid.

Often it is possible to interrupt the oxidation of a primary alcohol at the aldehyde level by performing the reaction in absence of water, so that no aldehyde hydrate can be formed.

Oxidation to aldehydes



Oxidation of alcohols to aldehydes and ketones

Reagents useful for the transformation of primary alcohols to aldehydes are normally also suitable for the oxidation of secondary alcohols to ketones. These include:

- Chromium-based reagents, such as Collins reagent (CrO_3·Py_2), PDC or PCC.
- Activated DMSO, resulting from reaction of DMSO with electrophiles, such as oxalyl chloride (Swern oxidation), a carbodiimide (Pfitzner-Moffatt oxidation) or the complex SO_3·Py (Parikh-Doering oxidation).
- Hypervalent iodine compounds, such as Dess-Martin periodinane or 2-Iodoxybenzoic acid.
- Catalytic TPAP in presence of excess of NMO (Ley oxidation).
- Catalytic TEMPO in presence of excess bleach (NaOCl) (**Anelli's oxidation**).

Allylic and benzylic alcohols can be oxidized in presence of other alcohols using certain selective oxidants such as manganese dioxide (MnO_2).

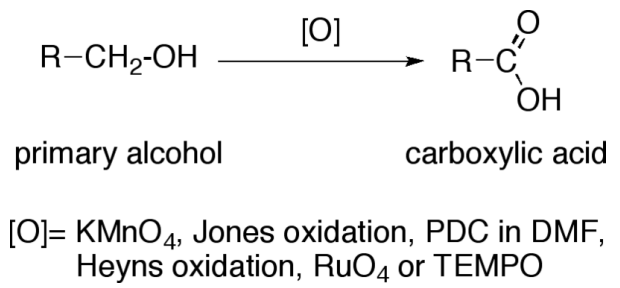
Oxidation to ketones

Reagents useful for the oxidation of secondary alcohols to ketones, but normally inefficient for oxidation of primary alcohols to aldehydes, include chromium trioxide (CrO_3) in a mixture of sulfuric acid and acetone (Jones oxidation) and certain ketones, such as cyclohexanone, in the presence of aluminium isopropoxide (Oppenauer oxidation).

Oxidation to carboxylic acids

The direct oxidation of primary alcohols to carboxylic acids can be carried out using:

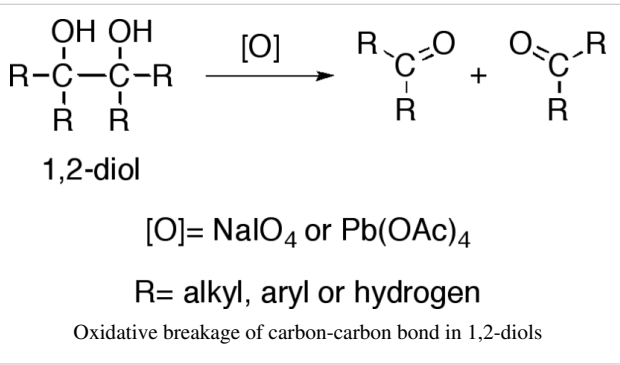
- Potassium permanganate ($KMnO_4$).
- Jones oxidation.
- PDC in DMF.
- Heyns oxidation.
- Ruthenium tetroxide (RuO_4).
- TEMPO.



Oxidation of primary alcohols to carboxylic acids

Diol oxidation

Alcohols possessing two hydroxy groups located on adjacent carbons —that is, 1,2-diols— suffer oxidative breakage at a carbon-carbon bond with some oxidants such as sodium periodate ($NaIO_4$) or lead tetraacetate ($Pb(OAc)_4$), resulting in generation of two carbonyl groups. The reaction is also known as glycol cleavage.



Oxidative breakage of carbon-carbon bond in 1,2-diols

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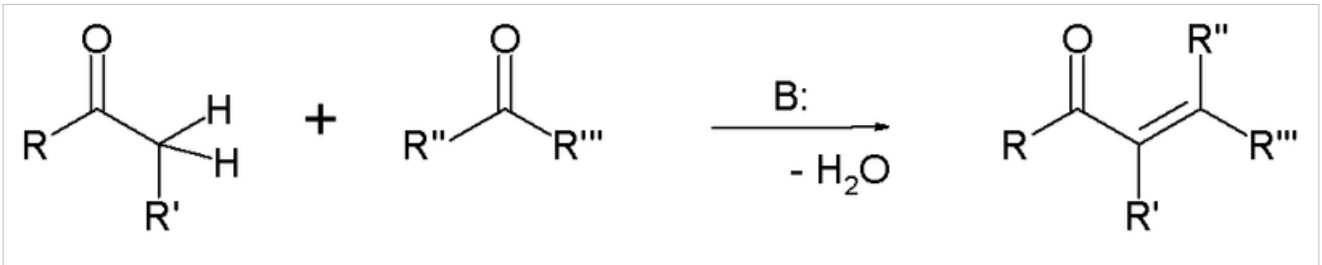
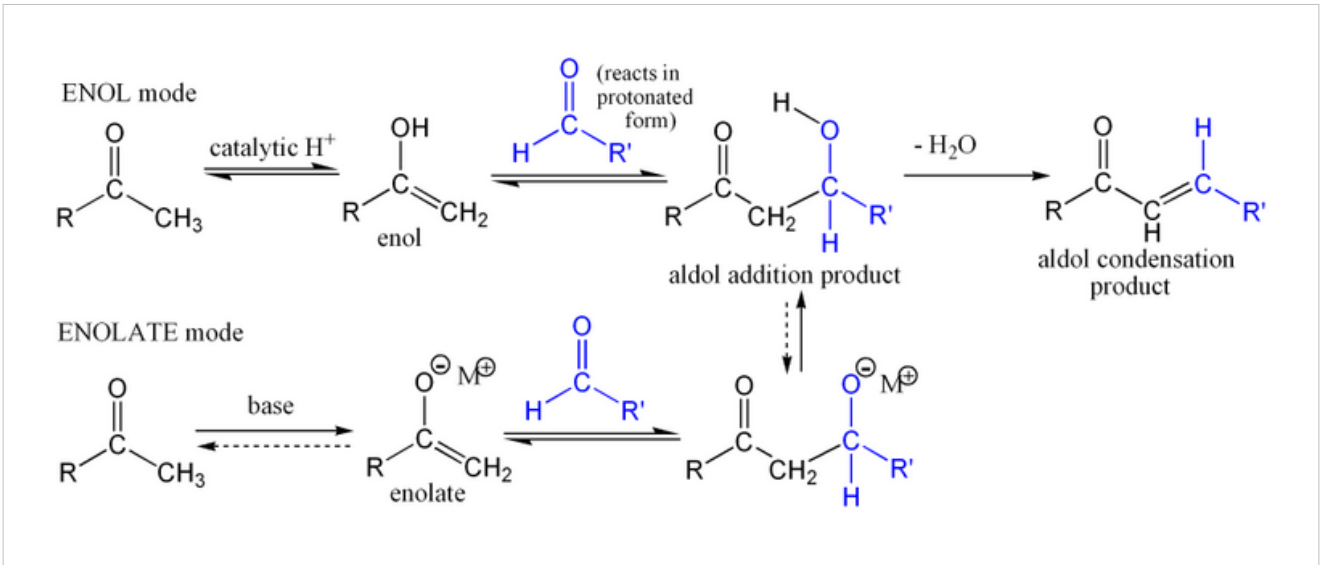
Aldol condensation

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



Aldol condensations are important in organic synthesis, providing a good way to form carbon–carbon bonds. The Robinson annulation reaction sequence features an aldol condensation; the Wieland-Miescher ketone product is an important starting material for many organic syntheses. Aldol condensations are also commonly discussed in university level organic chemistry classes as a good bond-forming reaction that demonstrates important reaction mechanisms.[1] [2] [3] In its usual form, it involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β-hydroxy ketone, or "**aldol**" (**ald**ehyde + alcoh**ol**), a structural unit found in many naturally occurring molecules and pharmaceuticals.[4] [5] [6]

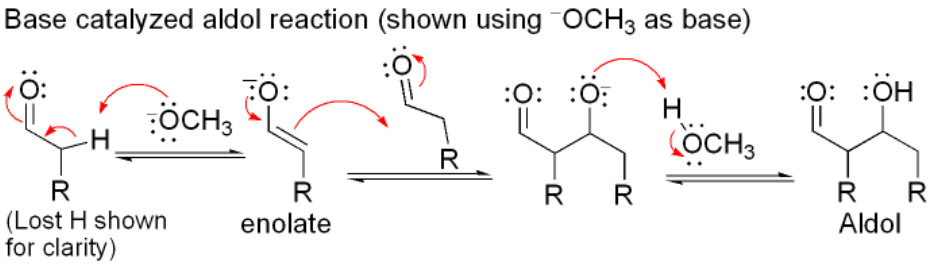


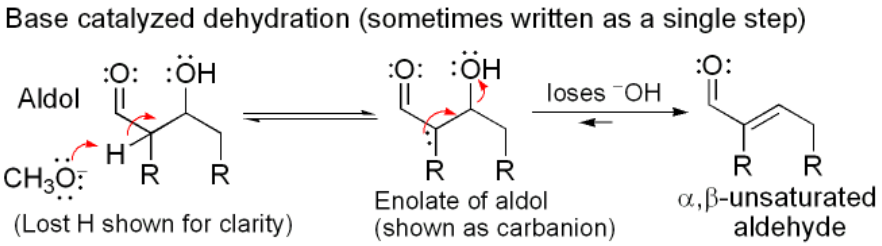
The name **aldol condensation** is also commonly used, especially in biochemistry, to refer to the aldol reaction itself, as catalyzed by aldolases. However, the aldol reaction is not formally a condensation reaction because it does not involve the loss of a small molecule.

The reactions between a ketone and an aldehyde (crossed aldol condensation) or between two aldehydes also go by the name **Claisen-Schmidt condensation**. These reactions are named after two of its pioneering investigators Rainer Ludwig Claisen and J. G. Schmidt, who independently published on this topic in 1880 and 1881.[7] [8] [9] An example is the synthesis of dibenzylideneacetone.

Mechanism

The first part of this reaction is an aldol reaction, the second part a dehydration—an elimination reaction. Dehydration may be accompanied by decarboxylation when an activated carboxyl group is present. The aldol addition product can be dehydrated via two mechanisms; a strong base like potassium *t*-butoxide, potassium hydroxide or sodium hydride in an enolate mechanism,[10] or in an acid-catalyzed enol mechanism.





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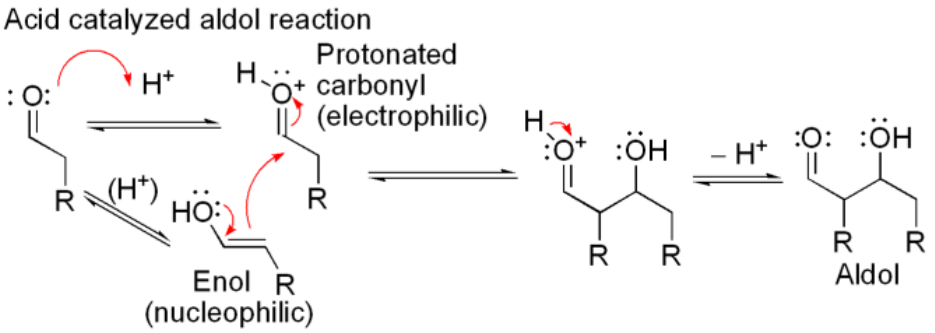
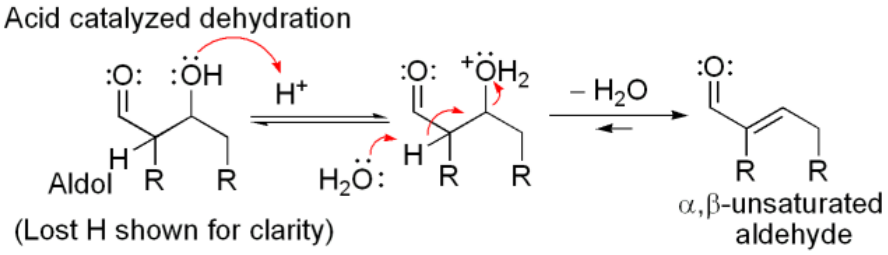




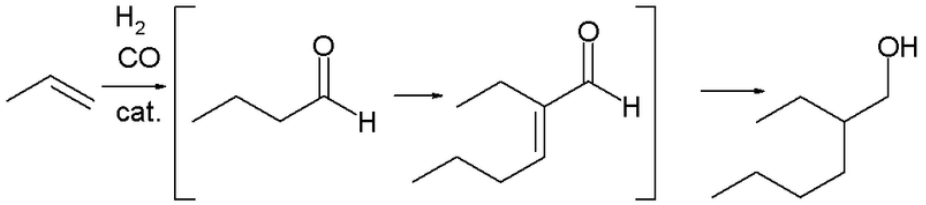
Condensation types

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

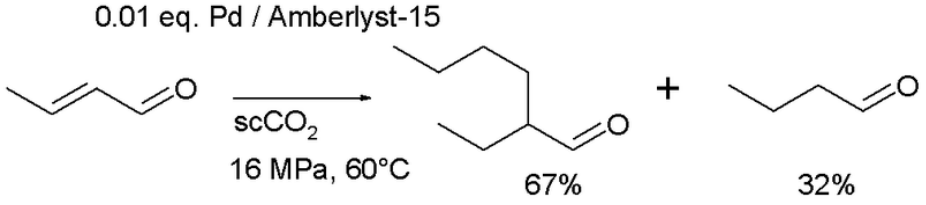
- When the base is an amine and the active hydrogen compound is sufficiently activated the reaction is called a Knoevenagel condensation.
- In a Perkin reaction the aldehyde is aromatic and the enolate generated from an anhydride.
- A Claisen condensation involves two ester compounds.
- A Dieckmann condensation involves two ester groups in the *same molecule* and yields a cyclic molecule
- A Henry reaction involves an aldehyde and an aliphatic nitro compound.
- A Robinson annulation involves a α,β-unsaturated ketone and a carbonyl group, which first engage in a Michael reaction prior to the aldol condensation.
- In the Guerbet reaction, an aldehyde, formed *in situ* from an alcohol, self-condenses to the dimerized alcohol.
- In the Japp-Maitland condensation water is removed not by an elimination reaction but by a nucleophilic displacement

Aldox process

In industry the **Aldox process** developed by Royal Dutch Shell and Exxon, converts propylene and syngas directly to 2-Ethylhexanol via hydroformylation to butyraldehyde, aldol condensation to 2-ethylhexenal and finally hydrogenation.[11]

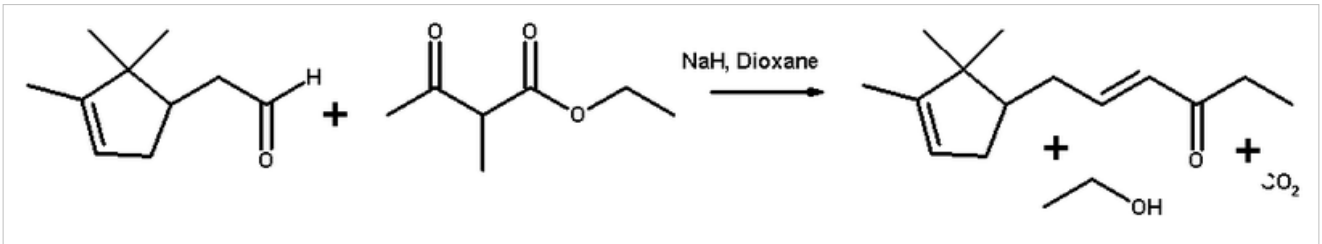


In one study crotonaldehyde is directly converted to 2-ethylhexanal in a palladium / Amberlyst / supercritical carbon dioxide system [12] :



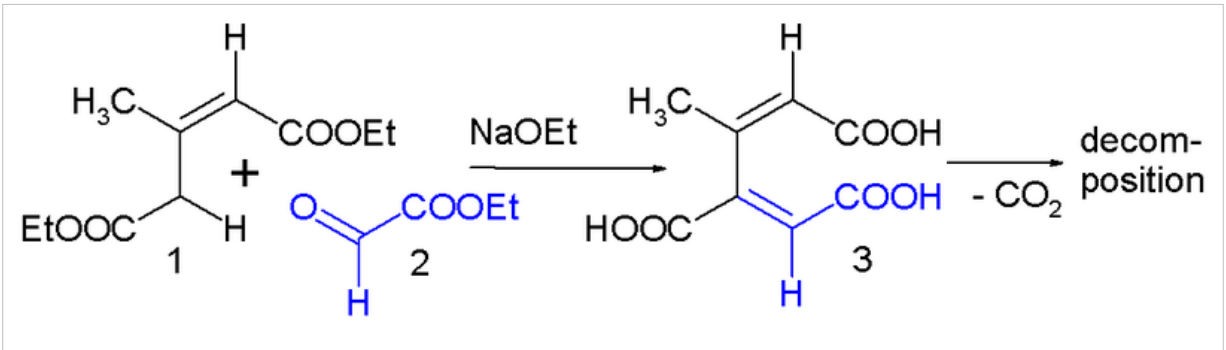
Scope

Ethyl 2-methylacetoacetate and campholenic aldehyde react in an Aldol condensation.[13] The synthetic procedure [14] is typical for this type of reactions. In the process, in addition to water, an equivalent of ethanol and carbon dioxide are lost in decarboxylation.

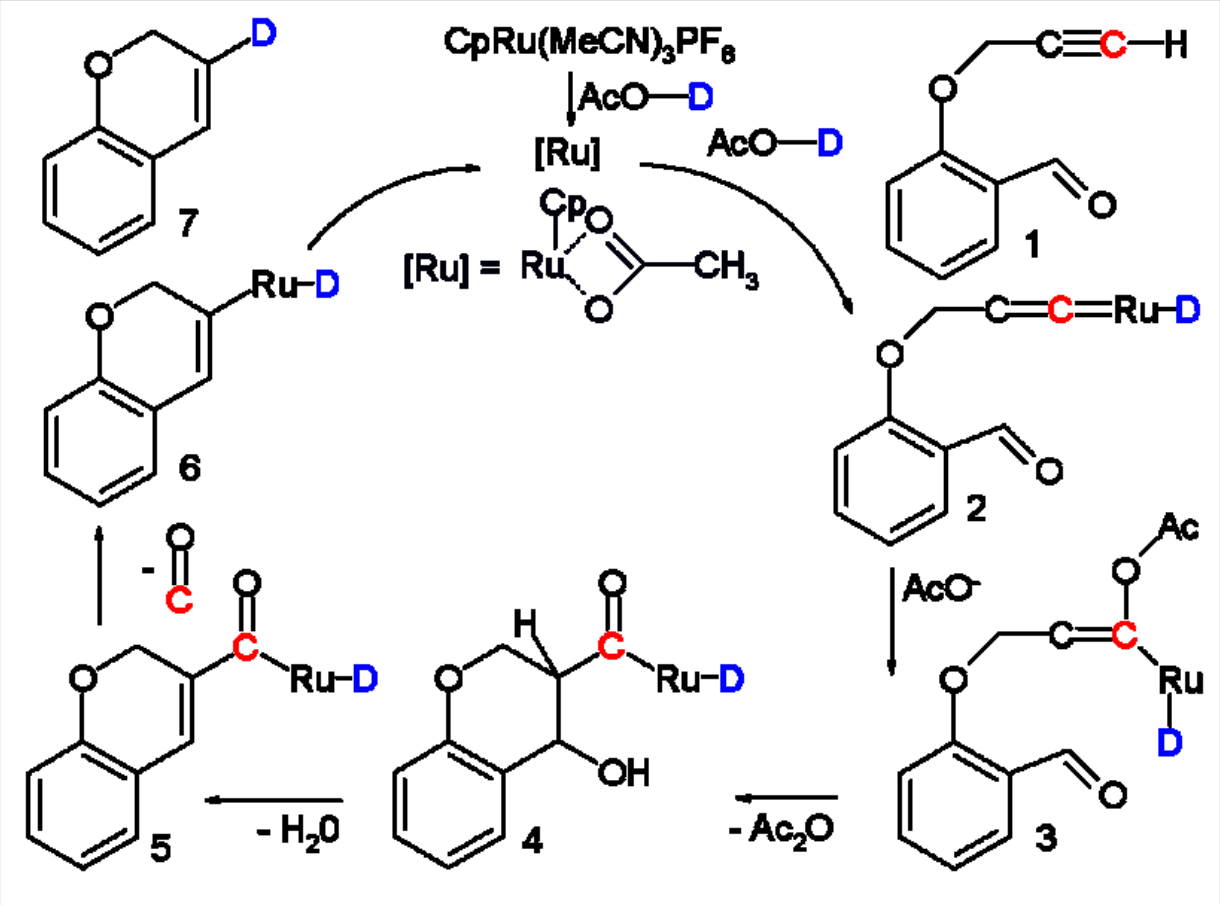


Ethyl glyoxylate **2** and diethyl 2-methylglutaconate **1** react to *isoprenetricarboxylic acid* **3** (isoprene skeleton) with sodium ethoxide. This reaction product is very unstable with initial loss of carbon dioxide and followed by many secondary reactions. This is believed to be due to steric strain resulting from the methyl group and the carboxylic

group in the *cis*-dienoid structure.[15]

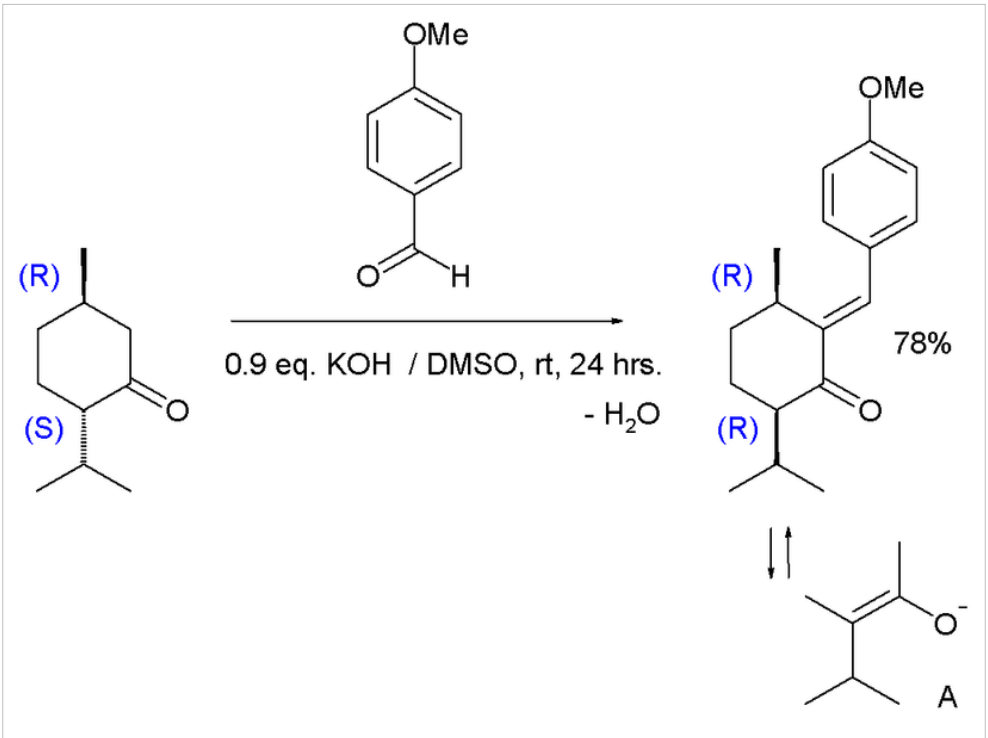


Occasionally an aldol condensation is buried in a multistep reaction or in catalytic cycle such as the one sketched below:[16]



In this reaction an *alkynal* **1** is converted into a cycloalkene **7** with a ruthenium catalyst and the actual condensation takes place with intermediate **3** through **5**. Support for the reaction mechanism is based on isotope labeling.[17]

The reaction between menthone and anisaldehyde is complicated due to steric shielding of the ketone group. The solution is use of a strong base such as potassium hydroxide and a very polar solvent such as DMSO in the reaction below [18] :



Due to epimerization through a common enolate ion (intermediate **A**) the reaction product has (R,R) cis configuration and not (R,S) trans as in the starting material. Because it is only the cis isomer that precipitates from solution this product is formed exclusively.

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[11] For example BG 881979 (http://v3.espacenet.com/textdoc?DB=EPODOC&IDX=BG881979)

[12] *Continuous catalytic "one-pot" multi-step synthesis of 2-ethylhexanal from crotonaldehyde* Tsunetake Seki, Jan-Dierk Grunwaldt and Alfons Baiker Chem. Commun., **2007**, 3562–3564 doi:DOI: 10.1039/b710129e

[13] (E)-6-(2,2,3-Trimethyl-cyclopent-3-enyl)-hex-4-en-3-one Concepcion Bada, Juan M. Castro, Pablo J. Linares-Palomino, Sofia Salido, Joaquan Altarejos Manuel Nogueras, Adolfo Sanchez, Molbank **2004**, M388 Online Publication (http://www.mdpi.net/molbank/molbank2004/m0388.htm)

[14] Ethyl 2-methylacetoacetate (**2**) is added to a stirred solution of sodium hydride in dioxane. Then campholenic aldehyde (**1**) is added and the mixture refluxed for 15 h. Then 2N hydrochloric acid is added and the mixture extracted with diethyl ether. The combined organic layers are washed with 2N hydrochloric acid, saturated sodium bicarbonate and brine. The organic phase is dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure to yield a residue that was purified by vacuum distillation to give **3** (58%).

[15] M. B. Goren, E. A. Sokoloski and H. M. Fales (2005). "2-Methyl-(1*Z*,3*E*)-butadiene-1,3,4-tricarboxylic Acid, "Isoprenetricarboxylic Acid"". *J. Org. Chem.* **70** (18): 7429–7431. doi:10.1021/jo0507892. PMID 16122270.

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[17] The ruthenium catalyst, $[CpRu(CH_3CN)_3]PF_6$, has a cyclopentadienyl ligand, three acetonitrile ligands and a phosphorus hexafluoride counterion; the acidic proton in the solvent (acetic acid) is replaced by deuterium for isotopic labeling. Reaction conditions: 90°C, 24 hrs. 80% chemical yield. The first step is formation of the Transition metal carbene complex **2**. Acetic acid adds to this intermediate in a nucleophilic addition to form enolate **3** followed by aldol condensation to **5** at which stage a molecule of carbon monoxide is lost to **6**. The final step is reductive elimination to form the cycloalkene.

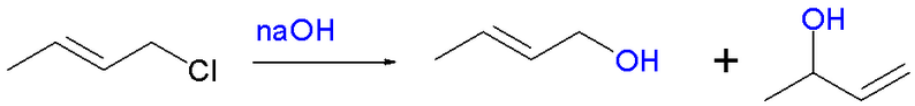
[18] *Simple and Effective Protocol for Claisen-Schmidt Condensation of Hindered Cyclic Ketones with Aromatic Aldehydes* Valeriy Vashchenko, Lidiya Kutulya, Alexander Krivoshey Synthesis **2007**: 2125-2134 doi:10.1055/s-2007-983746

Allylic rearrangement

An **allylic rearrangement** or **allylic shift** is an organic reaction in which the double bond in an allyl chemical compound shifts to the next carbon atom. It is encountered in nucleophilic substitution.

In reaction conditions that favor a S_N1 reaction mechanism the intermediate is a carbocation for which several resonance structures are possible. This explains the product distribution (or **product spread**) after recombination with nucleophile Y. This type of process is called an **S_N1' substitution**.

Alternatively, it is possible for nucleophile to attack directly at the allylic position, displacing the leaving group in a single step, in a process referred to as **S_N2' substitution**. This is likely in cases when the allyl compound is unhindered, and a strong nucleophile is used. The products will be similar to those seen with S_N1' substitution. Thus reaction of 1-chloro-2-butene with sodium hydroxide gives a mixture of 2-buten-1-ol and 1-buten-3-ol:

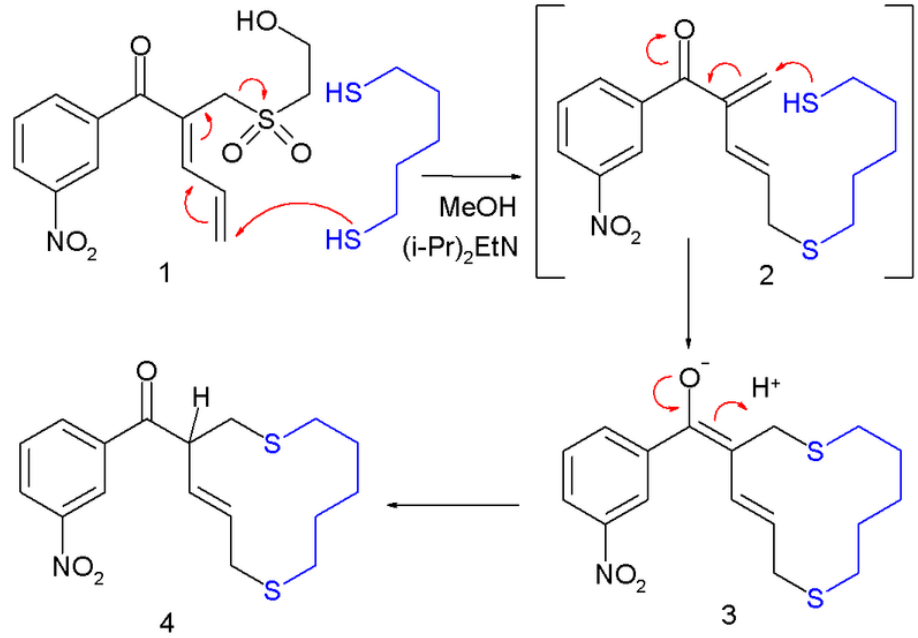


Nevertheless, the product in which the OH group is on the primary atom is minor. In the substitution of 1-chloro-3-methyl-2-butene, the tertiary 2-methyl-3-buten-2-ol is produced in a yield of 85%, while that for the primary 3-methyl-2-buten-1-ol is 15%.

In one reaction mechanism the nucleophile attacks not directly at the electrophilic site but in a conjugate addition over the double bond:

Scope

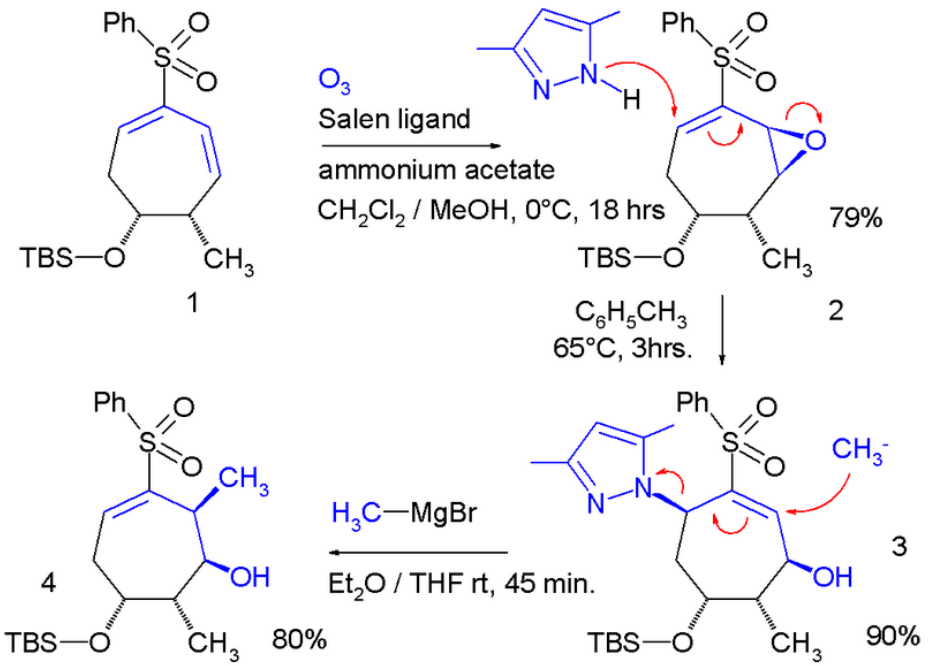
The synthetic utility can be extended to substitutions over butadiene bonds:[1]



Reaction in methanol and catalyst diisopropylethylamine

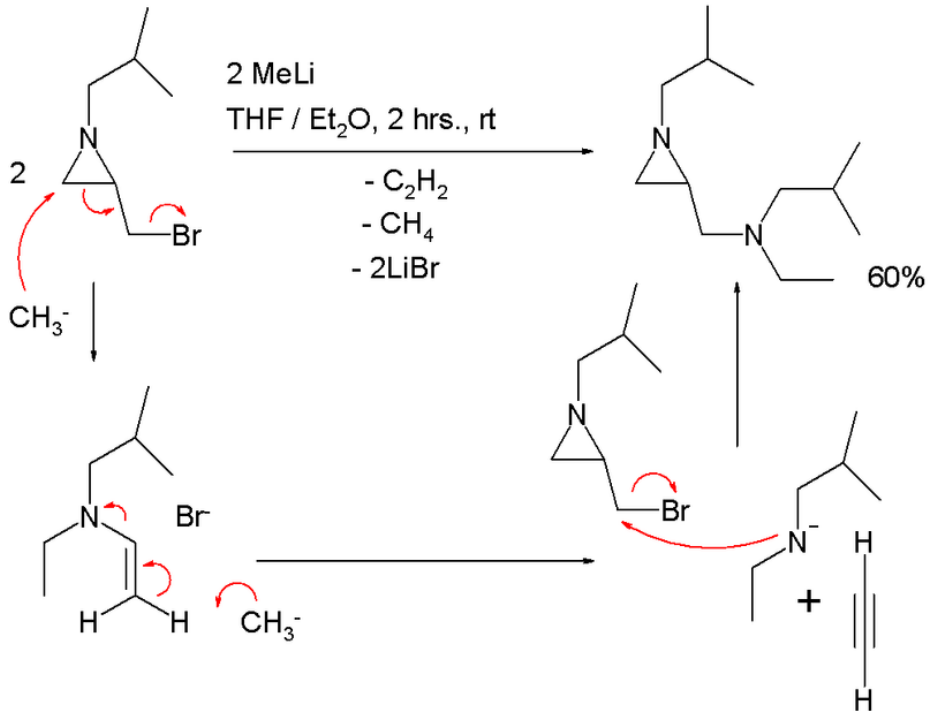
In the first step of this macrocyclization the thiol group in one end of *1,5-pentanedithiol* reacts with the butadiene tail in **1** to the enone **2** in an allylic shift with a sulfone leaving group which reacts further with the other end in a conjugate addition reaction.

In one study[2] the allylic shift was applied twice in a ring system:



In this reaction sequence a Jacobson epoxidation adds an epoxy group to a diene which serves as the leaving group in reaction with the pyrazole nucleophile. The second nucleophile is methylmagnesium bromide expulsing the pyrazole group.

An S_N2' reaction should explain the outcome of the reaction of an aziridine carrying a methylene bromide group with methyllithium [3] :



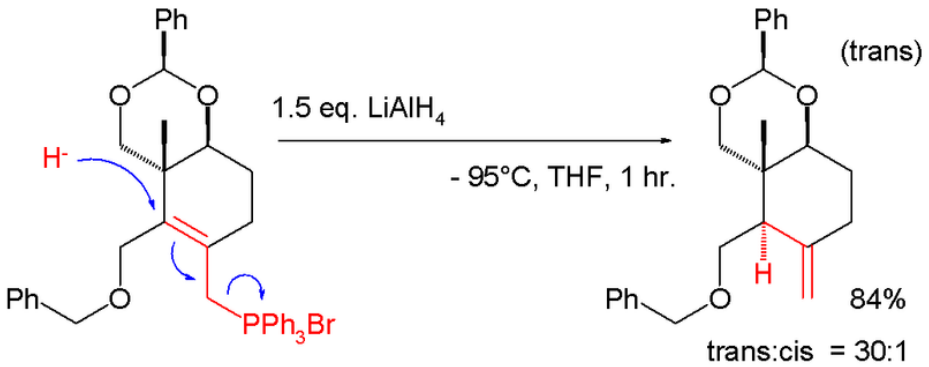
In this reaction one equivalent of acetylene is lost.

Examples of allylic shifts:

- Ferrier rearrangement
- Meyer–Schuster rearrangement

S_N2' reduction

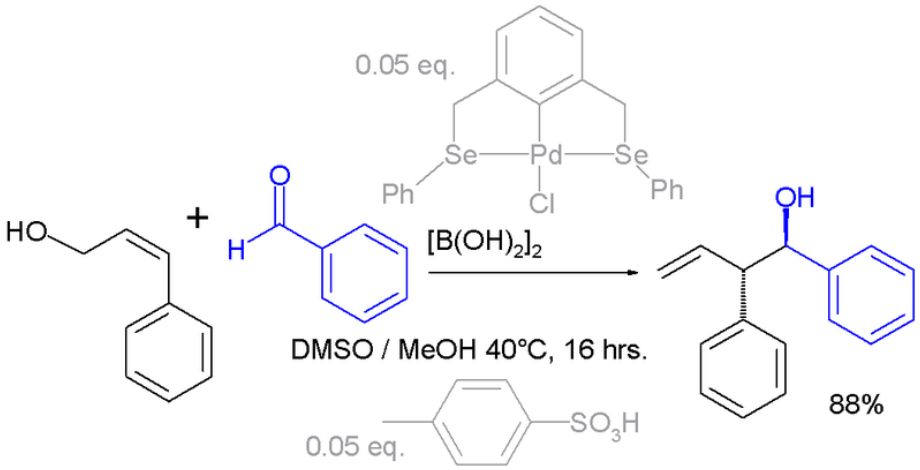
In one adaptation called a **SN2' reduction** a formal organic reduction on an allyl group containing a good leaving group is accompanied by a rearrangement. One example of such reaction is found as part of a Taxol total synthesis (ring C):[4]



The hydride is lithium aluminium hydride and the leaving group a phosphonium salt. The product contains a new exocyclic double bond. Only when the cyclohexane ring is properly substituted will the proton add in a trans position with respect to the adjacent methyl group. A conceptually related reaction is the Whiting reaction forming dienes.

Electrophilic allyl shifts

Allyl shifts can also take place with electrophiles. In the example below the carbonyl group in benzaldehyde is activated by diboronic acid prior to reaction with the allyl alcohol (see: Prins reaction):[5] [6]



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[2] *Double Lawton SN2'Addition to Epoxyvinyl Sulfones: Selective Construction of the Stereotetrads of Aplyronine* A Ahmad El-Awa and Philip Fuchs Org. Lett.; **2006**; 8(14) pp 2905 - 2908; (Letter) doi:10.1021/ol060530l

[3] *Highly unusual conversion of 1-alkyl-2-(bromomethyl)aziridines into 1-alkyl-2-(N-alkyl-N-ethylaminomethyl)aziridines using methyllithium* Matthias D'hooghe and Norbert De Kimpe Chem. Commun., **2007**, 1275 - 1277, doi:10.1039/b616606g

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[5] *Highly Selective and Robust Palladium-Catalyzed Carbon-Carbon Coupling between Allyl Alcohols and Aldehydes via Transient Allylboronic Acids* Nicklas Selander, Sara Sebelius, Cesar Estay, Kálmán J. Szabó European Journal of Organic Chemistry Volume **2006**, Issue 18 , Pages 4085 - 4087 doi:10.1002/ejoc.200600530

[6] The active catalyst system in this reaction is a combination of a palladium pincer compound and *p*-toluenesulfonic acid, the reaction product is obtained as a single regioisomer and stereoisomer

Anthraquinone

9,10-Anthraquinone	
[[Image:Anthraquinone acsv.svg	Skeletal formula]]
[[Image:Anthraquinone-3D-balls.png	Ball-and-stick model]]
Identifiers	
CAS number	84-65-1 [1] ✓
ChemSpider	6522 [2] ✓
KEGG	C16207 [3] ✗
Properties	
Molecular formula	$C_{14}H_8O_2$
Molar mass	208.21 g mol^{-1}
Appearance	yellow solid
Density	1.308g/cm3
Melting point	286 °C
Boiling point	379.8 °C
Solubility in water	Insoluble
Hazards	
R-phrases	R36/37/38
Flash point	185°C
Related compounds	
Related compounds	quinone, anthracene
✗ (what is this?) (verify) [4] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

Anthraquinone, also called **anthracenedione** or **dioxoanthracene** is an aromatic organic compound with formula $C_{14}H_8O_2$, that can be viewed as a diketone derivative of anthracene (with loss of one of the central pi-bonds in the anthracene).

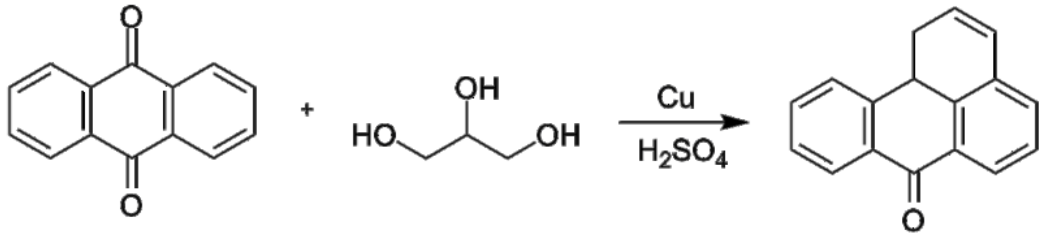
The term usually refers to one specific isomer, **9,10-anthraquinone** or **9,10-dioxoanthracene**, whose ketone groups are on the central ring. This compound is an important member of the quinone family. It is a building block of many dyes and is industrially used in bleaching pulp for papermaking. It is a yellow highly crystalline solid, poorly soluble in water but soluble in hot organic solvents. For instance, it is almost completely insoluble in ethanol near room temperature but 2.25 g will dissolve in 100 g of boiling ethanol.

Several other anthraquinone isomers are possible, such as 1,2-, 1,4-, and 2,6-anthraquinone, but they are of comparatively minor importance. The term is also used in the more general sense of any compound that can be viewed as an anthraquinone with some hydrogen atoms replaced by other atoms or functional groups. These derivatives include many substances that are technically useful or play important roles in living beings.

Synthesis

9,10-Anthraquinone is obtained industrially by the oxidation of anthracene, a reaction that is localized at the central ring. Chromium(VI) is the typical oxidant. It is also prepared by the Friedel-Crafts reaction of benzene and phthalic anhydride in presence of $AlCl_3$. The resulting o-benzoylbenzoic acid then undergoes cyclization, forming anthraquinone. This reaction is useful for producing substituted anthraquinones. The Diels-Alder reaction of naphthoquinone and butadiene followed by oxidative dehydrogenation will also produce 9,10-anthraquinone. Lastly, BASF has developed a process that proceeds via the acid-catalyzed dimerization of styrene to give a 1,3-diphenylbutene, which then can be transformed to the anthaquinone.[5] It also arises via the Rickert-Alder reaction, a retro-Diels-Alder reaction.

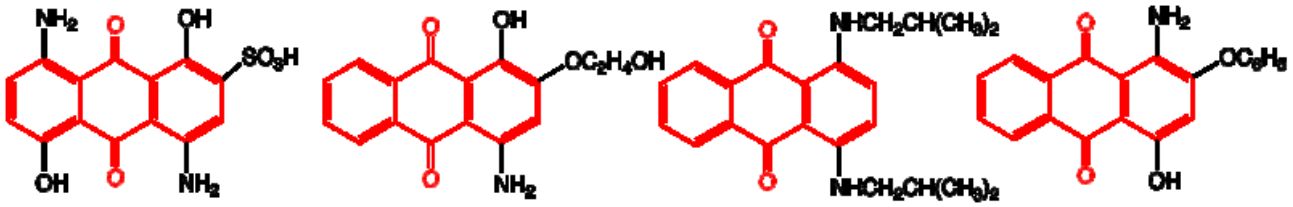
In a classic (1905) organic reaction called the **Bally-Scholl synthesis**, anthraquinone condenses with glycerol forming benzanthrone.[6] In this reaction, the quinone is first reduced with copper metal in sulfuric acid (converting one ketone group into a methylene group) after which the glycerol is added.



Applications and natural occurrence

Dyestuff precursor

Synthetic dyes are often derived from 9,10-anthraquinone, such as alizarin. Important derivatives are 1-nitroanthraquinone, anthraquinone-1-sulfonic acid, and the dinitroanthraquinone.[5] Natural pigments that are derivatives of anthraquinone are found, inter alia, in aloe latex, senna, rhubarb, and Cascara buckthorn), fungi, lichens, and some insects.



Selection of anthraquinone dyes. From the left: C.I.Acid Blue 43 an "acid dye" for wool (also called "Acilan Saphirol SE"), C.I. Vat Violet 1, which is applied by transfer printing using sublimation, a blue colorant commonly used in gasoline, and C.I. Disperse Red 60, a so-called vat dye.

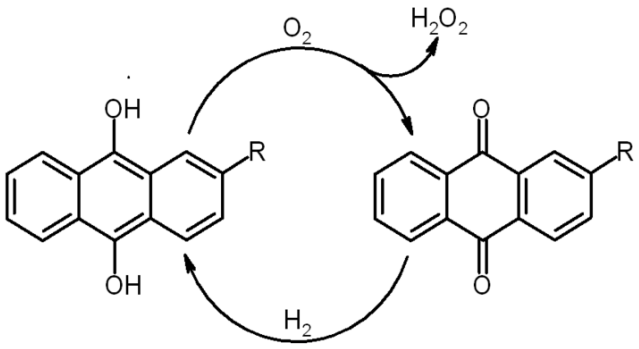
Digester additive in papermaking

9,10-Anthraquinone is used as a digester additive in production of paper pulp by alkaline processes, like the Kraft, the alkaline sulfite or the Soda-AQ processes. The anthraquinone is going through a redox cycle and is giving a catalytic effect. The reaction mechanism is most likely single electron transfer (SET).[7] The antraquinone is oxidizing cellulose and thereby protecting it from alkaline degradation (peeling). The anthraquinone is reduced to 9,10-dihydroxyanthracene which then can react with lignin. The lignin is degraded and becomes more watersoluble and thereby more easy to wash away from the pulp, while the antraquinone is regenerated. This process gives an increase in yield of pulp, typically 1-3 % and a reduction in kappa number.[8]

Sodium 2-anthraquinonesulfonate (AMS) is a watersoluble anthraquinone derivative that was the first anthraquinone derivative discovered to have a catalytic effect in the alkaline pulping processes.[9]

In the production of hydrogen peroxide

A large industrial application of anthraquinones is for the production of hydrogen peroxide. 2-Ethyl-9,10-anthraquinone or a related alkyl derivatives is used, rather anthraquinone itself.[10]

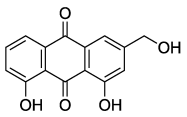


Catalytic hydrogen peroxide production with the anthraquinone process

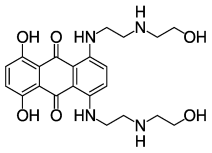
Medicine

Derivatives of 9,10-anthraquinone include many important drugs (collectively called **anthracenediones**). They include

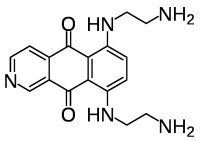
- Laxatives such as dantron, emodin, and aloe emodin, and some of the senna glycosides
- Antimalarials such as rufigallol
- Antineoplastics used in the treatment of cancer, such as mitoxantrone, pixantrone, and the anthracyclines.



Aloe emodin



Mitoxantrone



Pixantrone

Niche uses

9,10-Anthraquinone is used as a bird repellant on seeds and as a gas generator in satellite balloons [11].

Natural anthraquinone derivatives tend to have laxative effects. Prolonged use and abuse leads to melanosis coli.[12] [13]

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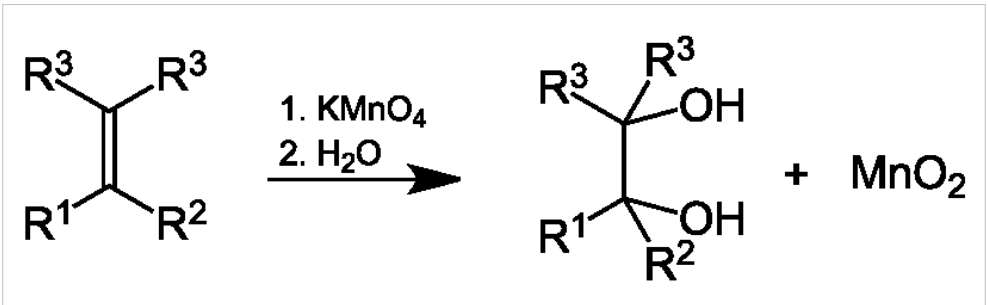
External links

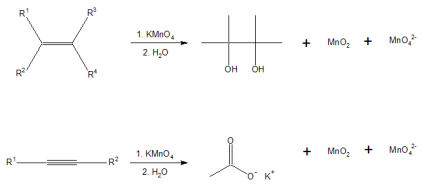
- National Pollutant Inventory - Polycyclic Aromatic Hydrocarbon Fact Sheet (http://www.npi.gov.au/database/substance-info/profiles/74.html)
- Molecules Spontaneously Form Honeycomb Network (http://www.sciencedaily.com/releases/2006/08/060818014819.htm)

Baeyer's reagent

Baeyer's reagent, named after the German organic chemist Adolf von Baeyer, is used in organic chemistry as a qualitative test for the presence of unsaturation, such as double bonds. The bromine test is also able to determine the presence of unsaturation.



Baeyer's reagent is an alkaline solution of potassium permanganate, which is a powerful oxidant. Reaction with double or triple bonds (-C=C- or -C≡C-) in an organic material causes the color to fade from purplish-pink to brown. It is a syn addition reaction. Aldehydes and formic acid (and formic acid esters) also give a positive test.[1]



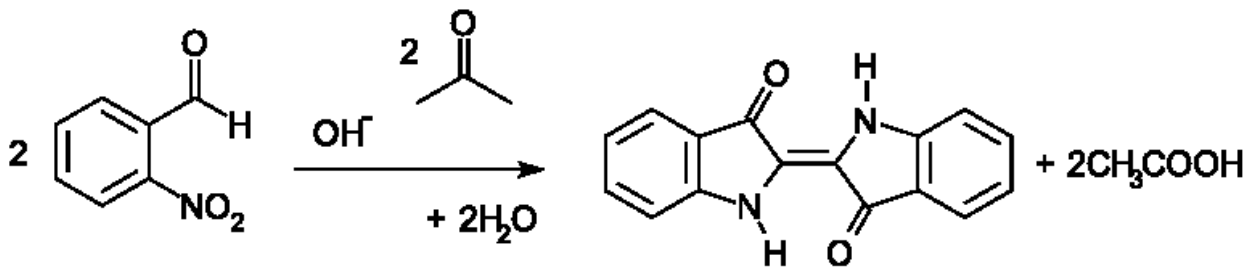
The brown solid manganese(IV) oxide precipitates out of solution when potassium permanganate reacts with a double or triple bond.

References

[1] Explanation from a qualitative analysis lab (http://www.chemistry.ccsu.edu/glagovich/teaching/316/qualanal/tests/baeyertest.html)

Baeyer-Drewson indigo synthesis

The **Baeyer-Drewson indigo synthesis** (1882) is an organic reaction in which indigo is prepared from o-nitrobenzaldehyde and acetone [1] [2]



The reaction is classified as a Aldol condensation. As a practical route to indigo, this method was displaced by routes from aniline.[3]

Note

In the English literature this reaction is usually called Baeyer-Drewson reaction, although the author of the original paper was called Drewsen.

References

[1] Adolf Baeyer, Viggo Drewsen (1882). "Darstellung von Indigblau aus Orthonitrobenzaldehyd". *Berichte der deutschen chemischen Gesellschaft* **15** (2): 2856–2864. doi:10.1002/cber.188201502274.

[2] Helmut Schmidt (1997). "Indigo - 100 Jahre industrielle Synthese". *Chemie in unserer Zeit* **31** (3): 121–128. doi:10.1002/ciuz.19970310304.

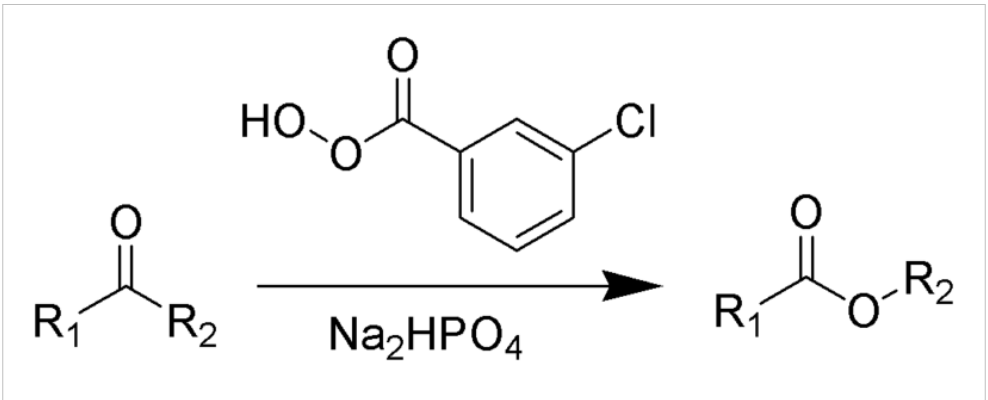
[3] Elmar Steingruber “Indigo and Indigo Colorants” Ullmann's Encyclopedia of Industrial Chemistry 2004, Wiley-VCH, Weinheim. doi: 10.1002/14356007.a14_149.pub2

External links

- Lab Manual (http://firstyear.chem.usyd.edu.au/LabManual/E36.pdf)
- Lab-synthesis of indigo (http://chemlab.truman.edu/Chemistryofartlabs/Synthesis of Indigo.pdf)

Baeyer–Villiger oxidation

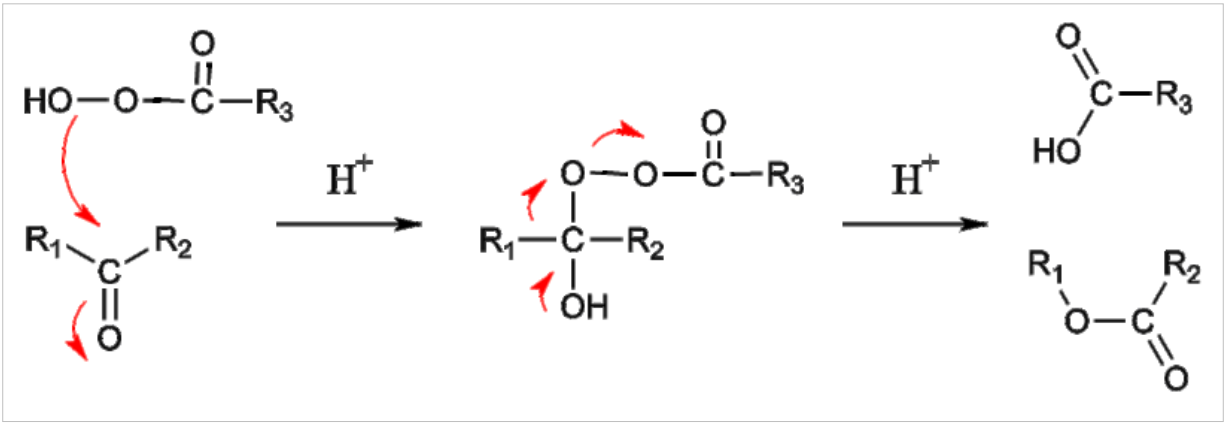
The **Baeyer–Villiger oxidation** is an organic reaction in which a ketone is oxidized to an ester by treatment with peroxy acids or hydrogen peroxide.[1] [2] Key features of the Baeyer–Villiger oxidation are its stereospecificity and predictable regiochemistry.[3] It is named after the German chemist Johann Friedrich Wilhelm Adolf von Baeyer (1835–1917) and the Swiss chemist Victor Villiger (1868–1934).[4]



Reagents typically used to carry out this rearrangement are *meta*-chloroperoxybenzoic acid (mCPBA), peroxyacetic acid, or peroxytrifluoroacetic acid.[5] Reactive or strained ketones (cyclobutanones, norbornanones) react with hydrogen peroxide or hydroperoxides to form lactones. The original reagent in the 1899 publication is Caro's acid discovered just a year earlier.[6] Disodium phosphate or sodium bicarbonate is often added as a buffering agent to prevent transesterification or hydrolysis.

Mechanism

The reaction mechanism of this oxidative cleavage involves first addition of the peroxy acid to the carbonyl forming a tetrahedral intermediate also called the Criegee intermediate for its similarity with rearrangement of that name. The transition state for this step is envisioned as a hydrogen relay involving three peroxy acid molecules with linear O-H-O interactions.[7] Next is a concerted migration of one of the adjacent carbons to oxygen with loss of a carboxylic acid. If the migrating carbon is chiral, the stereochemistry is retained.



Migratory aptitude: H > tertiary alkyl > cyclohexyl > secondary alkyl, aryl > primary alkyl > methyl

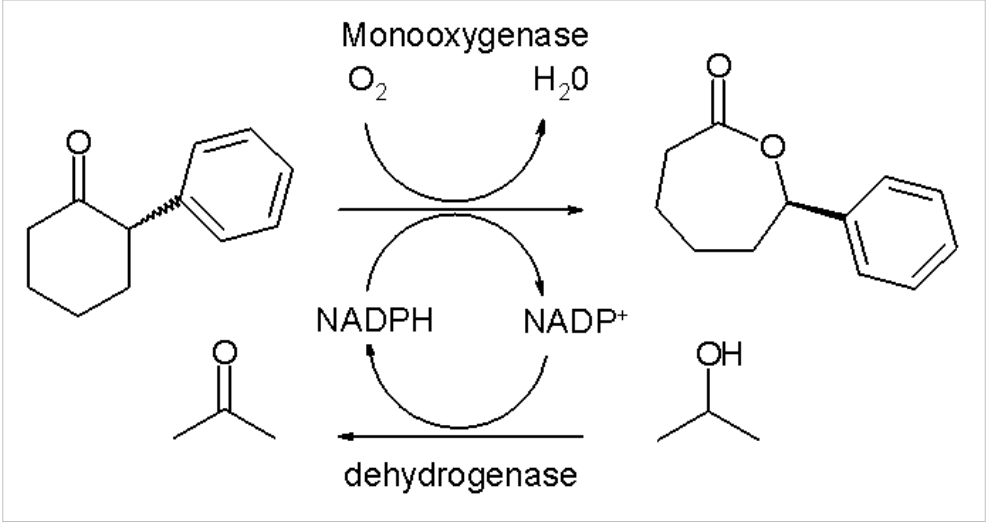
In the transition state for this migration step the R-C-O-O dihedral angle should be 180° in order to maximise the interaction between the filled R-C sigma bond and the antibonding O-O sigma bond. This step is also (at least in silico) assisted by two or three peroxyacid units enabling the hydroxyl proton to shuttle to its new position.[7]

For unsymmetrical ketones, the migrating group is usually the one that can best stabilize positive charge. Thus, cyclic ketones produce lactones and aldehydes usually produce carboxylic acids, although formates can also be formed if the migrating group is tertiary or an electron rich vinyl group or aromatic ring (Dakin reaction). Sometimes the alcohol is formed when the formate is hydrolytically unstable.

Biocatalytic BV oxidation

The Baeyer–Villiger oxidation can also be performed by biocatalysis with a so-called **Baeyer-Villiger monooxygenase** or **BVMO**. Though largely an experimental technique it shows the promise of enantioselectivity and green chemistry for this reaction type. Current stumbling blocks are confinement to water as the reaction medium, substrate specificity, dependence on the stoichiometric use and costs of cofactors such as NADPH and the costs associated with BVMO's themselves because lengthy purification steps are required. In vivo oxidations with metabolically active microbial cells introduce complications on their own.

In one study [8] the enzyme purification issue is addressed and a special thermally stable monooxygenase is isolated from a specific E. coli strain. This enzyme converts racemic 2-phenylcyclohexanone with oxygen to the corresponding (R)-lactone with 50% chemical yield and 94% enantiomeric excess with in a biphasic system of water and hexane. The NADPH cofactor is regenerated in each catalytic cycle by action of a second dehydrogenase enzyme which consumes isopropanol as a sacrificial catalyst. The solubility of the organic reactant and product is low in the aqueous phase thus averting inhibition. On the other hand the catalytic turnover number for this reaction is much larger than can be obtained with classical organic asymmetric catalysts.



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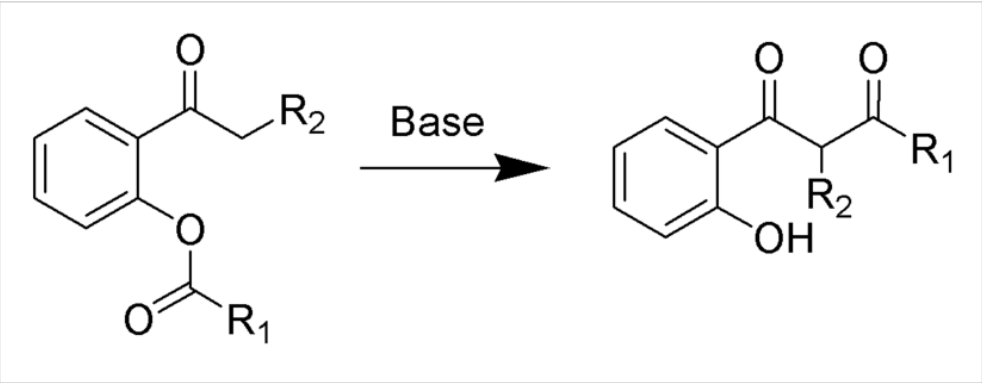
Baker–Venkataraman rearrangement

The **Baker–Venkataraman rearrangement** is the chemical reaction of 2-acetoxyacetophenones with base to form 1,3-diketones.[1] [2]

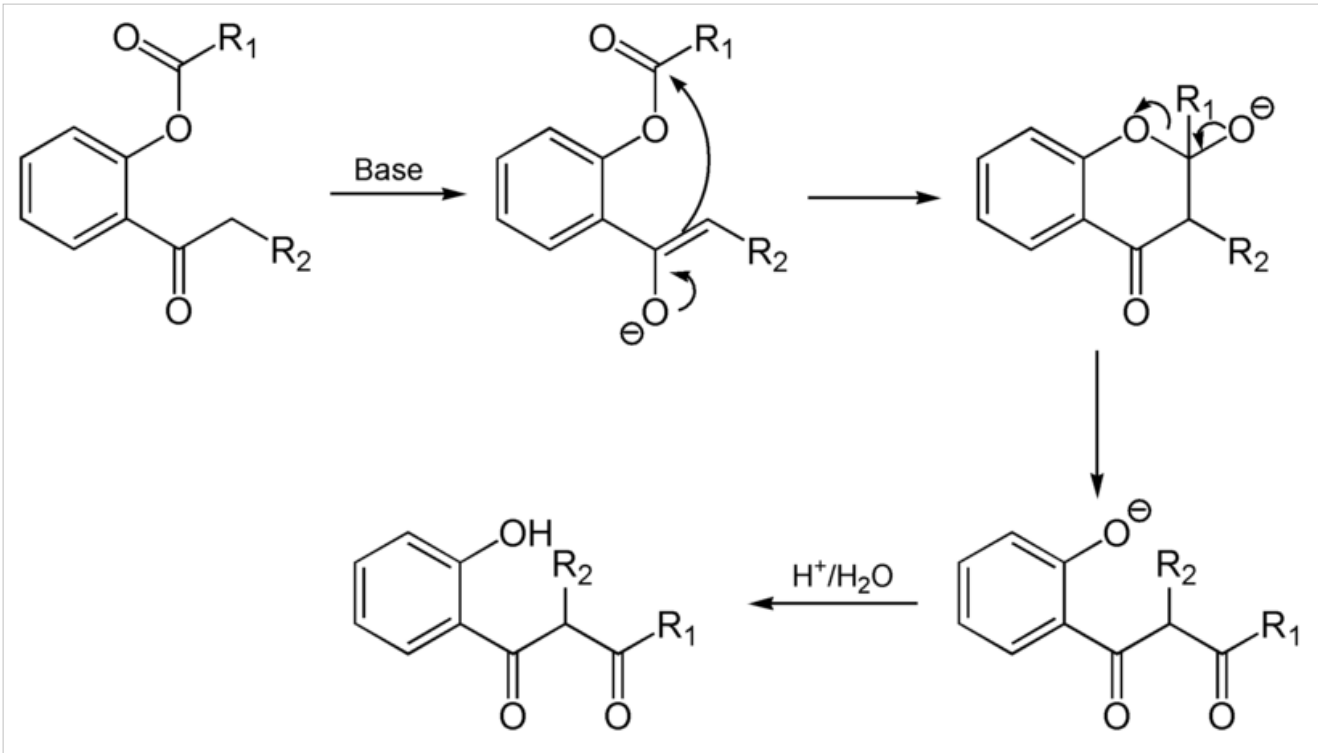


This rearrangement reaction proceeds via enolate formation followed by acyl transfer. It is named after the scientists Wilson Baker and Krishnaswamy Venkataraman.

The Baker–Venkataraman rearrangement is often used to synthesize chromones and flavones.[3] [4] [5] [6] [7] [8] [9] [10]

Mechanism

With a base being a catalyst, it attacks hydrogen atom in Acetophenone and an enolate is formed. Then, the enolate group attacks the carbon in the phenol ester to form a cyclic alkoxide. Finally, it opens up a phenolate which is reprocessed by acid to undergo protonation.



References

[1] Baker, W. (1933). "Molecular rearrangement of some o-acyloxyacetophenones and the mechanism of the production of 3-acylchromones". *J. Chem. Soc.*: 1381–1389. doi:10.1039/JR9330001381.

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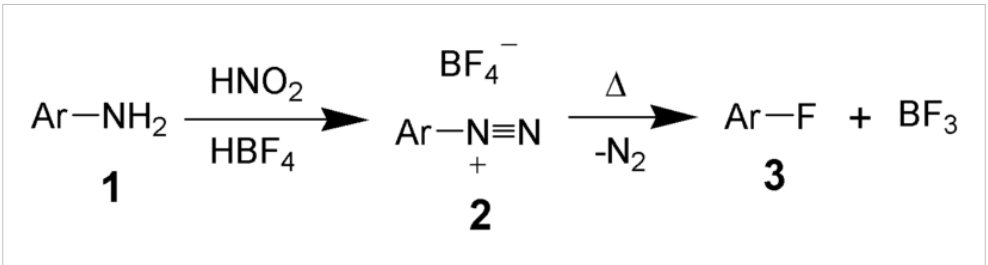
External links

- http://www.organische-chemie.ch/OC/Namen/baker-venkataraman.htm

Balz–Schiemann reaction

The **Schiemann reaction** (also called the **Balz-Schiemann reaction**) is a chemical reaction in which anilines (**1**) are transformed to aryl fluorides (**3**) via diazonium fluoroborates (**2**).[1] [2] Named after the German chemists Günther Schiemann and Günther Balz, this reaction is the preferred route to fluorobenzene and some related derivatives.[3]



The reaction is similar to the Sandmeyer reaction, which converts diazonium salts to other aryl halides.[4]

References

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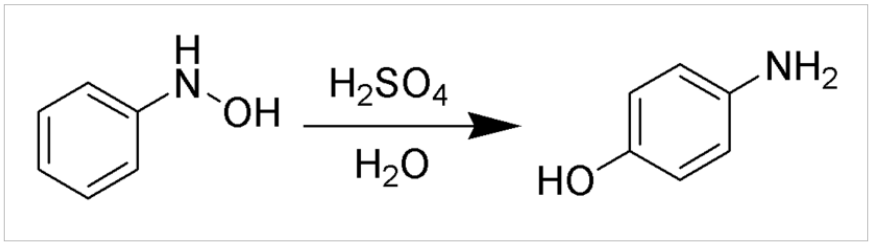
[4] Swain, C. G.; Rogers, R. J. (1975). "Mechanism of formation of aryl fluorides from arenediazonium fluoborates". *J. Am. Chem. Soc.* **97**: 799–800. doi:10.1021/ja00837a019.

Bamberger rearrangement

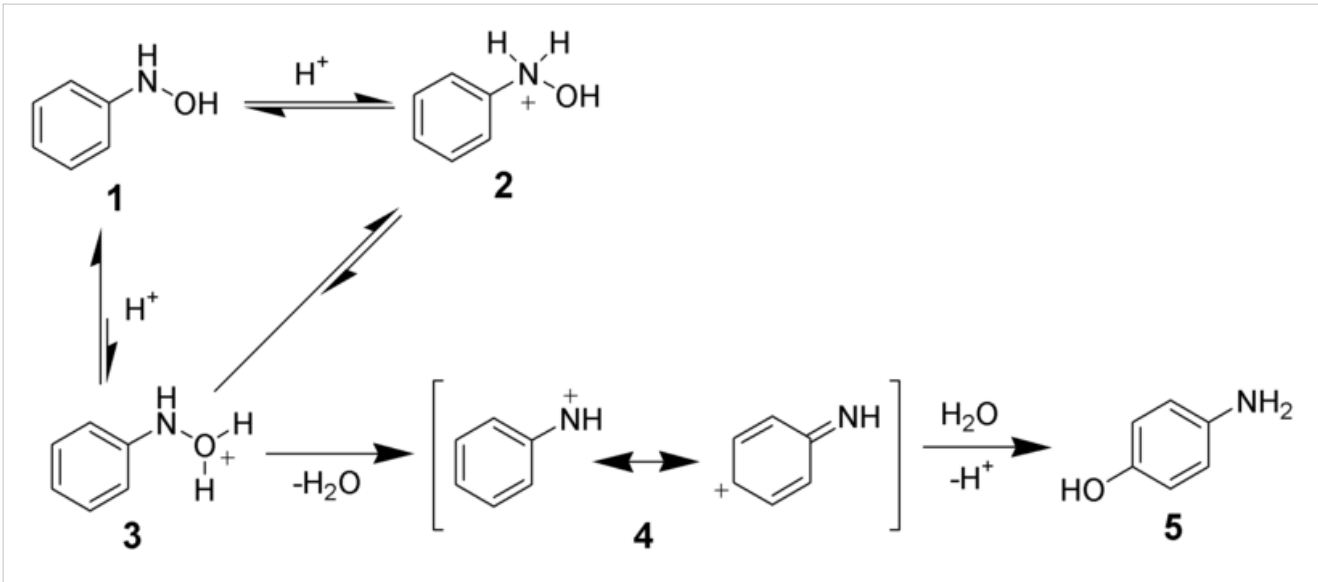
The **Bamberger rearrangement** is the chemical reaction of N-phenylhydroxylamines with strong aqueous acid, which will rearrange to give 4-aminophenols.[1] [2] It is named for the German chemist Eugen Bamberger (1857–1932).



N-Phenylhydroxylamines are typically synthesized from nitrobenzenes by reduction using rhodium[3] or zinc[4] .

Reaction mechanism

The mechanism of the Bamberger rearrangement proceeds from the monoprotonation of N-phenylhydroxylamine **1**. N-protonation **2** is favored, but unproductive. O-protonation **3** can form the nitrenium ion **4**, which can react with nucleophiles (H_2O) to form the desired 4-aminophenol **5**.[5] [6]



References

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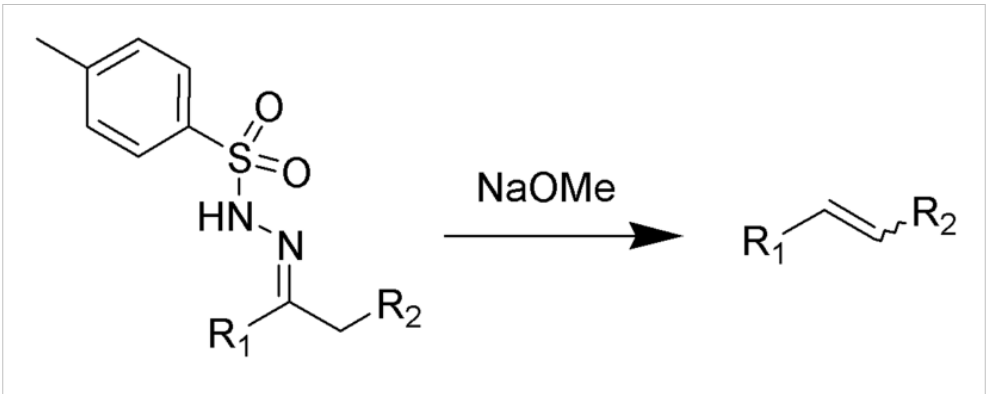
Bamford–Stevens reaction

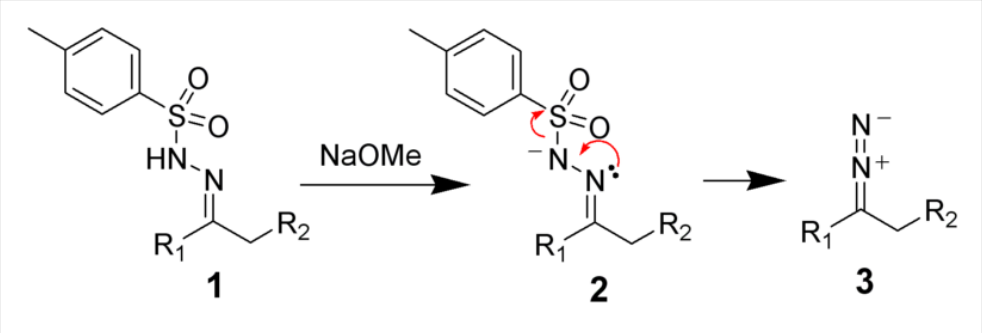
The **Bamford–Stevens reaction** is a chemical reaction whereby treatment of tosylhydrazones with strong base gives alkenes.[1] [2] [3] It is named for the British chemist William Randall Bamford and the Scottish chemist Thomas Stevens Stevens (1900–2000). The usage of aprotic solvents gives predominantly Z-alkenes, while protic solvent gives a mixture of E- and Z-alkenes.



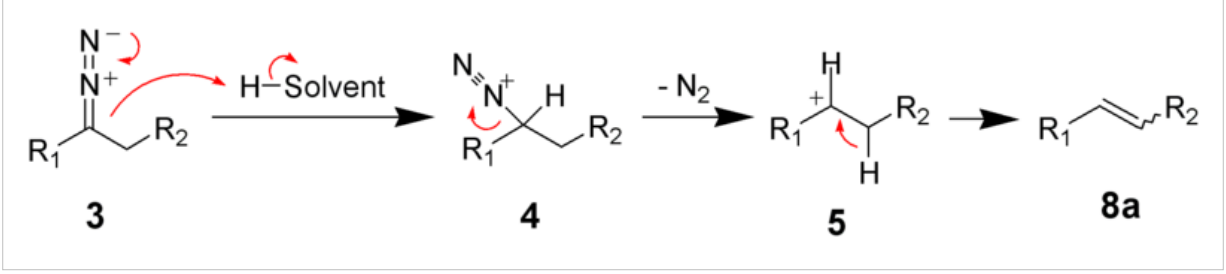
The treatment of tosylhydrazones with alkyl lithium reagents is called the Shapiro reaction.

Reaction mechanism

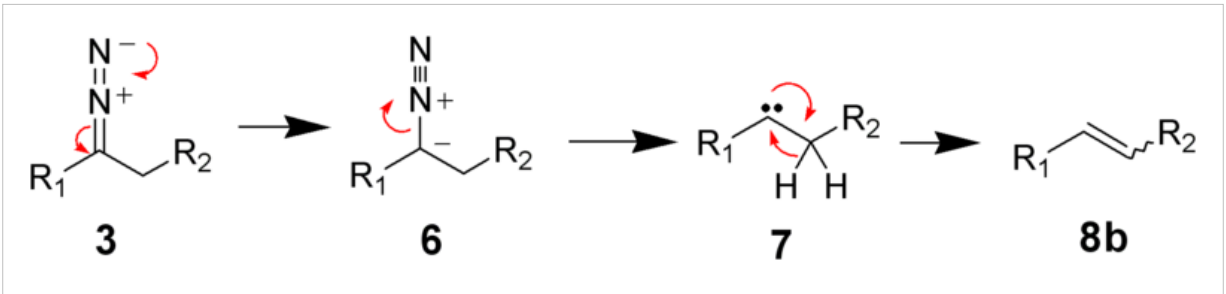
The first step of the Bamford–Stevens reaction is the formation of the diazo compound **3**.[4]



In protic solvents, the diazo compound **3** decomposes to the carbenium ion **5**.



In aprotic solvents, the diazo compound **3** decomposes to the carbene **7**.



References

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Barfoed's test

Barfoed's Test is a chemical test used for detecting the presence of monosaccharides. It is based on the reduction of copper(II) acetate to copper(I) oxide (Cu_2O), which forms a brick-red precipitate.[1] [2]

$$RCOH + 2Cu^{+2} + 2H_2O \rightarrow RCOOH + Cu_2O\downarrow + 4H^+$$

(Disaccharides may also react, but the reaction is much slower.) The aldehyde group of the monosaccharide which normally forms a cyclic hemiacetal is oxidized to the carboxylate. A number of other substances, including sodium chloride,[3] may interfere.

It was invented by Danish chemist Christen Thomsen Barfoed[1] and is primarily used in botany.

The test is similar to the reaction of Fehling's solution to aldehydes.

Composition

Barfoed's reagent consists of a 0.33 molar solution of neutral copper acetate in 1% acetic acid solution. The reagent does not keep well and it is therefore advisable to make it up when it is actually required.[4]

References

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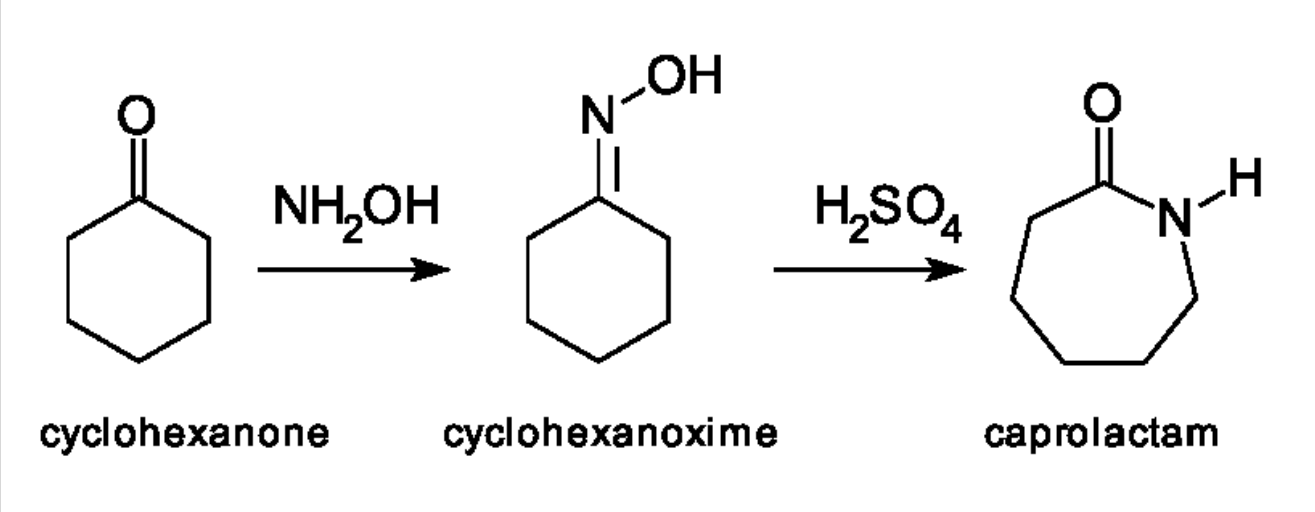
Beckmann rearrangement

The **Beckmann rearrangement**, named after the German chemist Ernst Otto Beckmann (1853–1923), is an acid-catalyzed rearrangement of an oxime to an amide.[1] [2] [3] Cyclic oximes yield lactams.

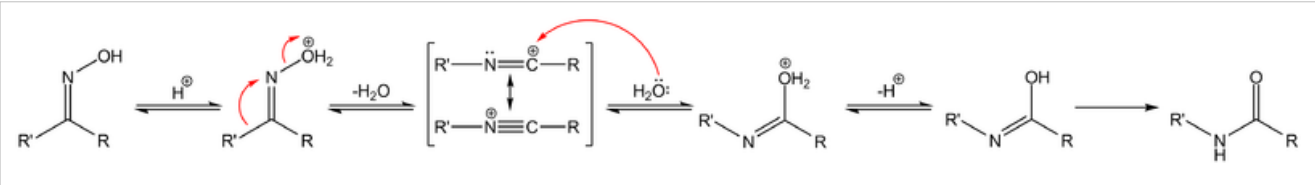


This example reaction[4] starting with cyclohexanone, forming the reaction intermediate cyclohexanonoxime (in the image, the ending 'ono' in the name is missing) and resulting in caprolactam is one of the most important applications of the Beckmann rearrangement, as caprolactam is the feedstock in the production of Nylon 6.

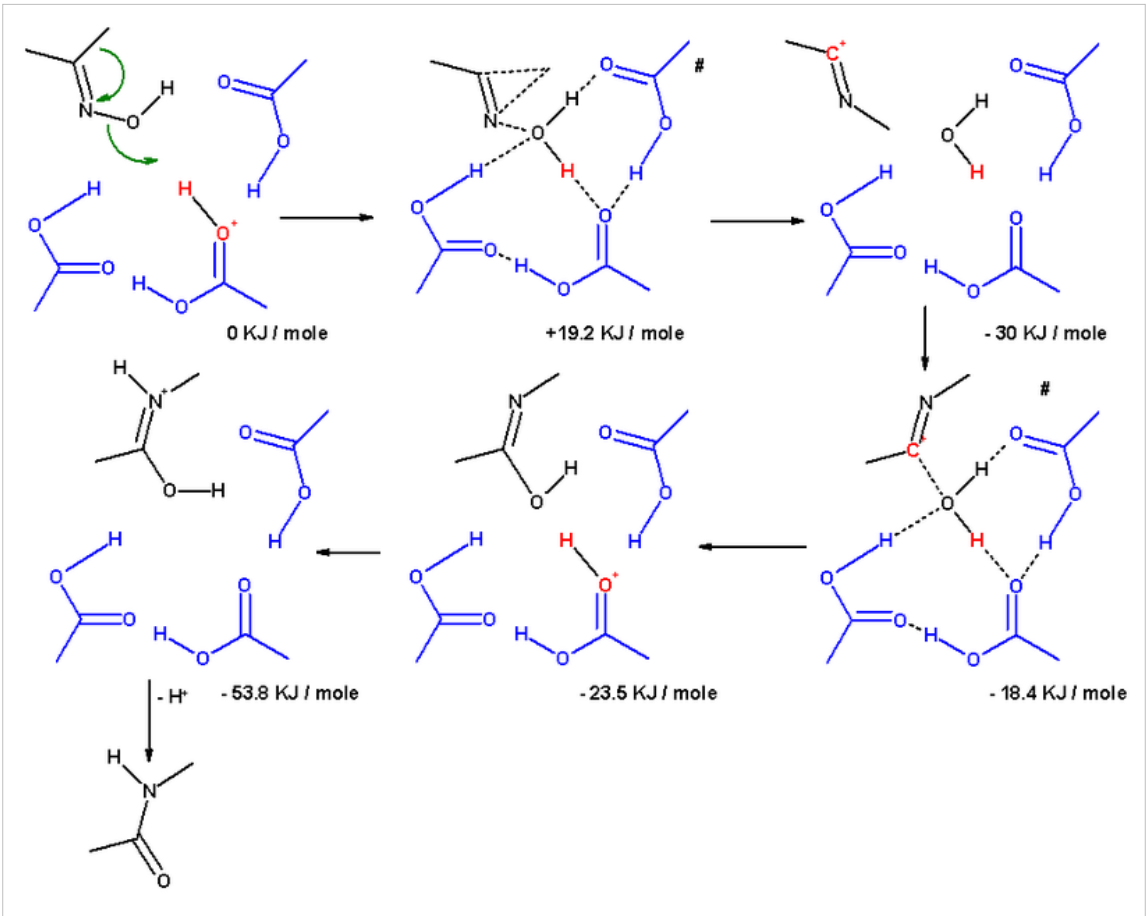
The **Beckmann solution** consists of acetic acid, hydrochloric acid and acetic anhydride, and was widely used to catalyze the rearrangement. Other acids, such as sulfuric acid or polyphosphoric acid, can also be used. sulfuric acid is the most commonly used acid for commercial lactam production due 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

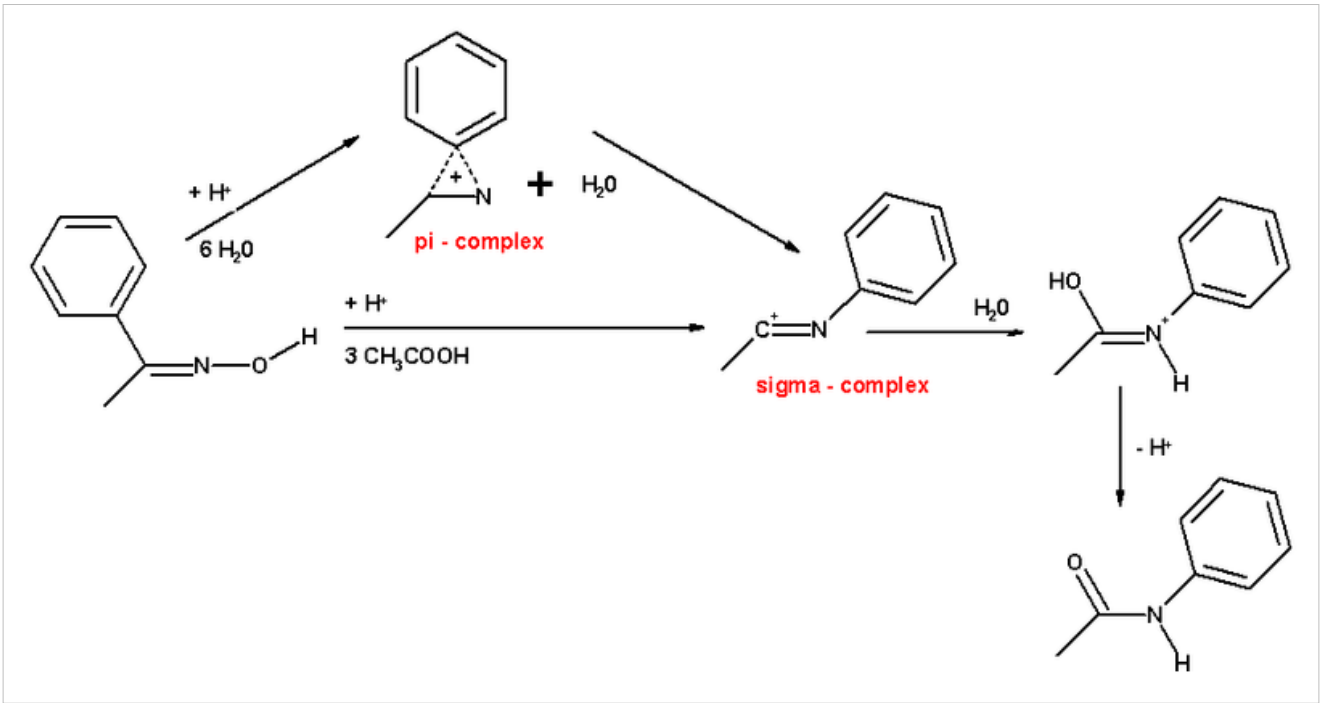
The reaction mechanism of the Beckmann rearrangement is generally believed to consist of an alkyl migration with expulsion of the hydroxyl group to form a nitrilium ion followed by hydrolysis:



In one study, [5] the mechanism is established in silico taking into account the presence of solvent molecules and substituents. The rearrangement of acetone oxime in the Beckmann solution involves 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 and the hydroxyl group is expulsed. The oxygen atom in the hydroxyl group is stabilized by the three acetic acid molecules. In the next step the electrophilic carbon atom in the nitrilium ion is attacked by water and the proton is donated back to acetic acid. In the transition state leading to the N-methyl acetimidic acid, 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 phenyl in the reaction of acetophenone oxime with protonated acetic acid the mechanism favors the formation of an intermediate three-membered π - complex. This π - complex is again not found in the $H_3O^+(H_2O)_6$.

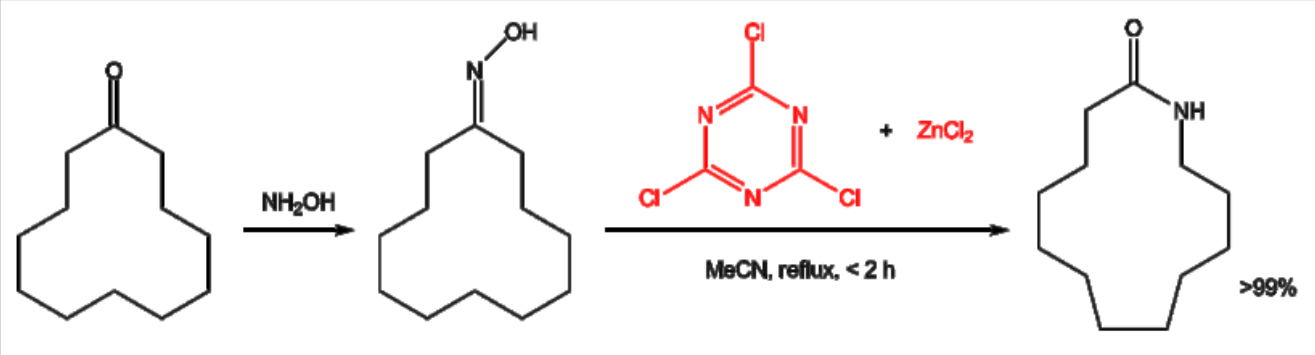


With the cyclohexanone-oxime, the relief of ring strain results in a third reaction mechanism leading directly to the protonated caprolactam in a single concerted step without the intermediate formation of a π - complex or σ -

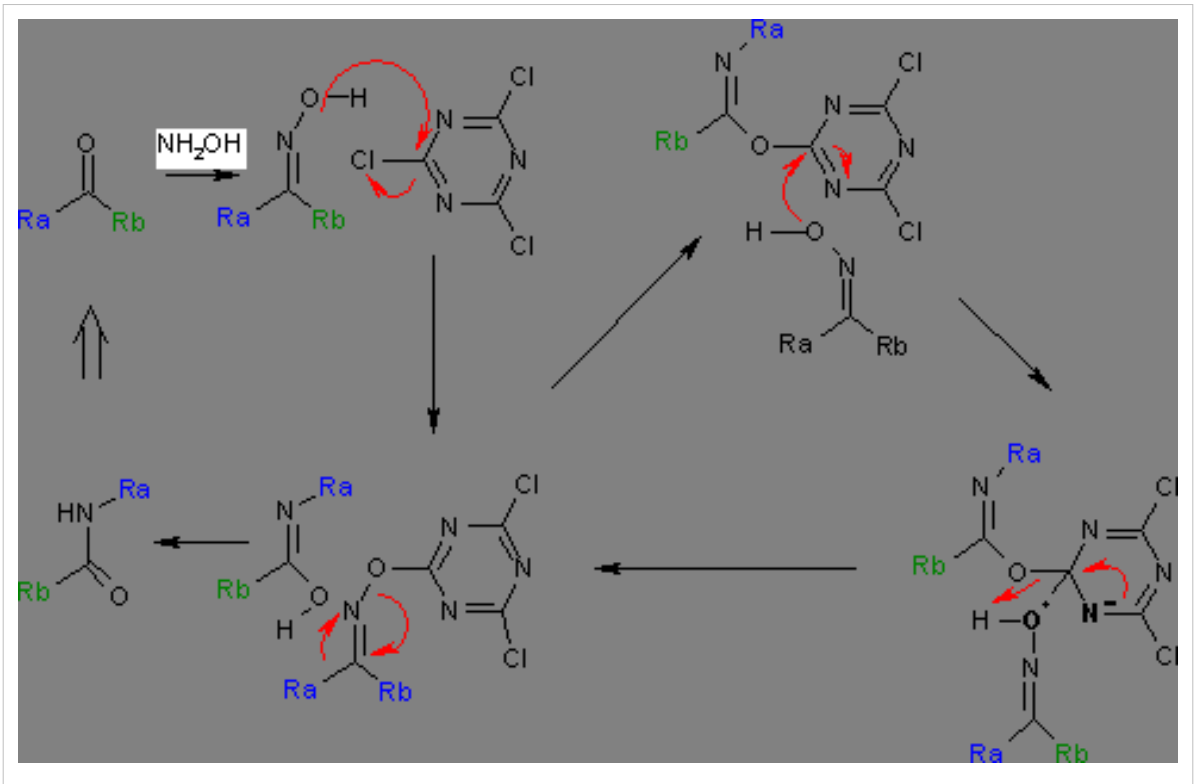
complex.

Cyanuric chloride assisted Beckmann reaction

The Beckmann reaction is known to be catalyzed by cyanuric chloride and zinc chloride co-catalyst. For example, cyclododecanone can be converted to the corresponding lactam, a monomer for the production of nylon 12.[6] [7]

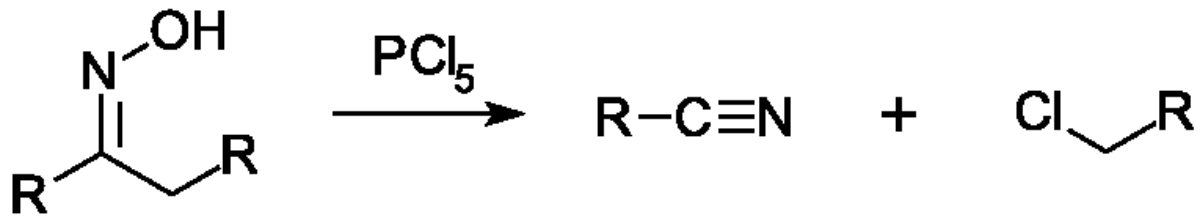


The reaction mechanism for this reaction is based on a catalytic cycle with cyanuric chloride activating the hydroxyl group via a nucleophilic aromatic substitution. The reaction product is dislodged and replaced by new reactant via an intermediate Meisenheimer complex.

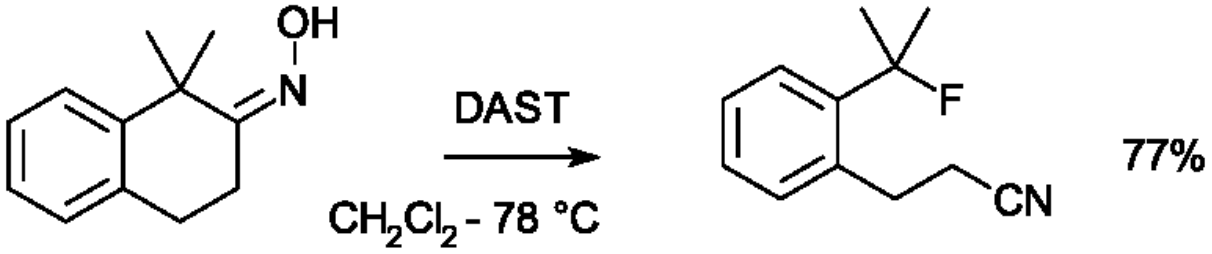


Beckmann fragmentation

When the oxime has a quaternary carbon atom in an anti position to the hydroxyl group a fragmentation occurs forming a nitrile:

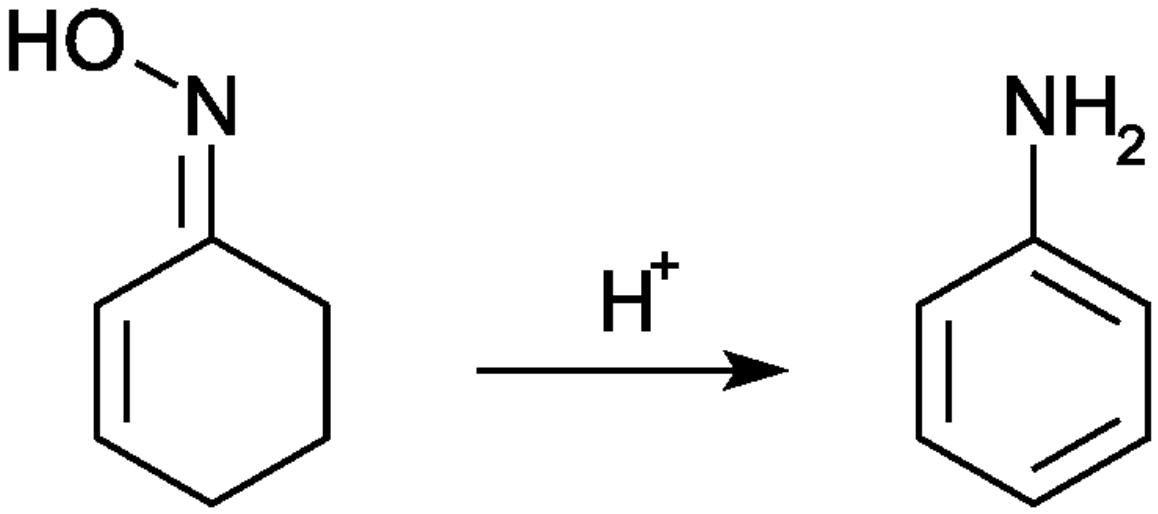


The fluorine donor in this fragmentation reaction is diethylaminosulfur trifluoride (DAST) [8] :



Semmler-Wolff reaction

The oxime of cyclohexenone with acid forms aniline in a dehydration - aromatization reaction called the **Semmler-Wolff reaction** or **Wolff aromatization** [9] [10] [11] [12]



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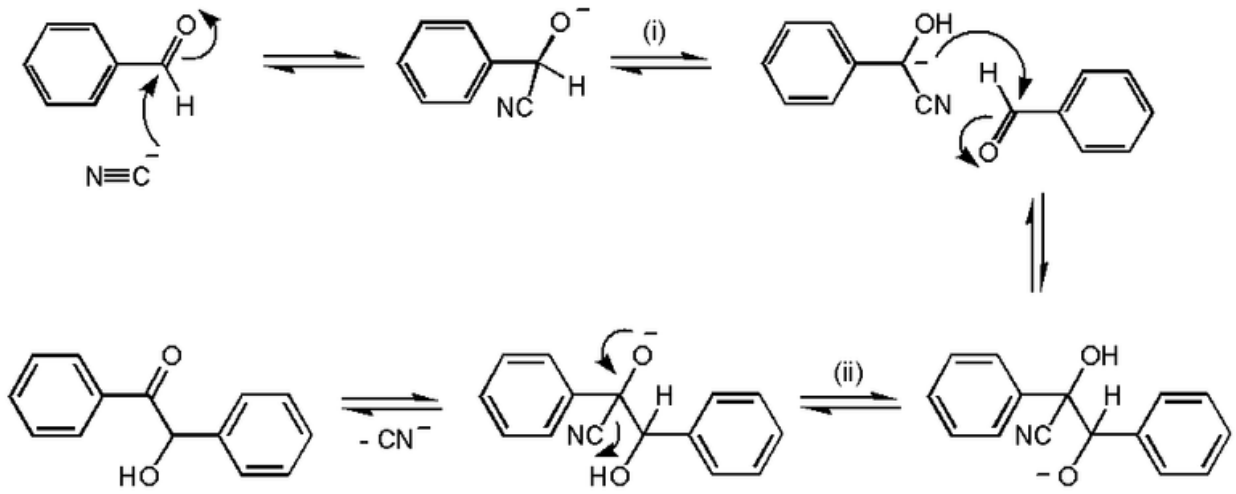
Benzoin condensation

The **benzoin condensation** is a reaction (often called a condensation reaction, for historical reasons) between two aromatic aldehydes, particularly benzaldehyde. The reaction is catalyzed by a nucleophile such as the cyanide anion or an N-heterocyclic carbene. The reaction product is an aromatic acyloin with benzoin as the parent compound.[1] An early version of the reaction was developed in 1832 by Justus von Liebig and Friederich Woehler during their research on bitter almond oil.[2] The catalytic version of the reaction was developed by Nikolay Zinin in the late 1830s,[3] [4] and the reaction mechanism for this organic reaction was proposed in 1903 by A. J. Lapworth.[5]

Reaction mechanism



Scheme 1. Benzoin condensation reaction mechanism. Proton transfers occur at (i) and (ii).

In the first step in this reaction, the cyanide anion (as sodium cyanide) reacts with the aldehyde in a nucleophilic addition. Rearrangement of the intermediate results in polarity reversal of the carbonyl group, which then adds to the second carbonyl group in a second nucleophilic addition. Proton transfer and elimination of the cyanide ion affords benzoin as the product. This is a reversible reaction.

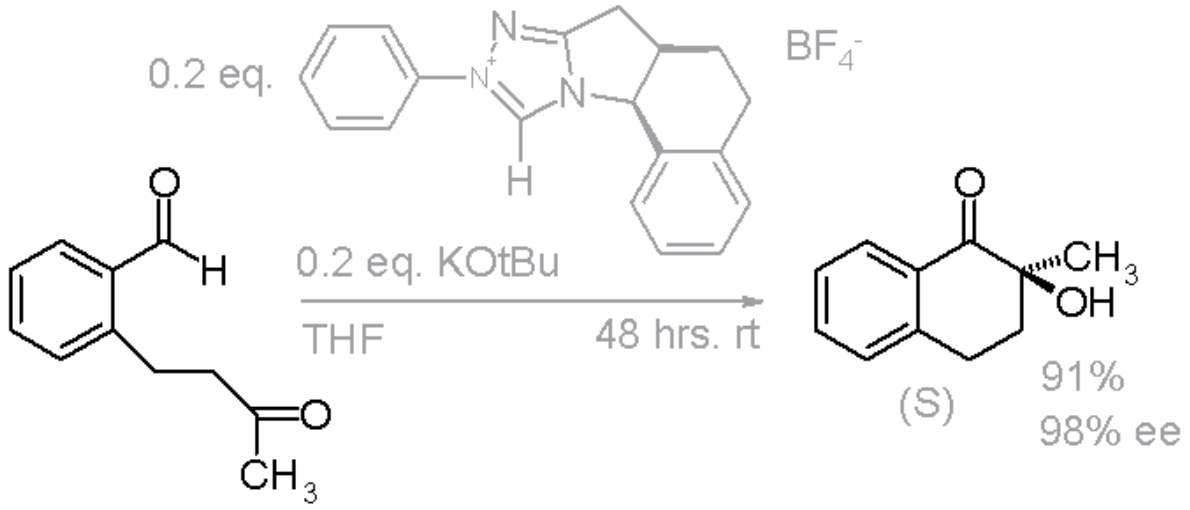
The cyanide ion serves three different purposes in the course of this reaction. It acts as a nucleophile, facilitates proton abstraction, and is also the leaving group in the final step. The benzoin condensation is in effect a dimerization and not a condensation because a small molecule like water is not released in this reaction. For this reason the reaction is also called a **benzoin addition**. In this reaction, the two aldehydes serve different purposes; one aldehyde donates a proton and one aldehyde accepts a proton. 4-Dimethylaminobenzaldehyde is an efficient proton donor while benzaldehyde is both a proton acceptor and donor. In this way it is possible to synthesise mixed benzoins, i.e. products with different groups on each half of the product.

Scope

The reaction can be extended to aliphatic aldehydes with base catalysis in the presence of thiazolium salts; the reaction mechanism is essentially the same. These compounds are important in the synthesis of heterocyclic compounds. The addition is also possible with enones; for instance methyl vinyl ketone is a reagent in the Stetter reaction.

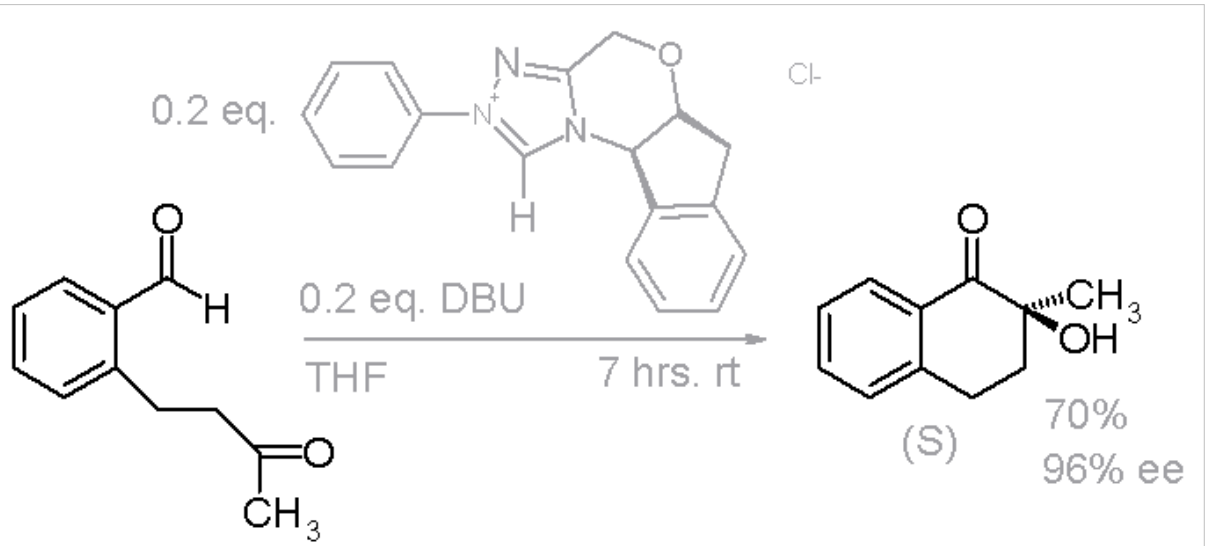
In biochemistry, the coenzyme thiamine is responsible for biosynthesis of acyloin-like compounds. This coenzyme also contains a thiazolium moiety, which on deprotonation becomes a nucleophilic carbene.

In one study, a custom-designed N-heterocyclic carbene (NHC, the framework is related to thiazolium salts) was found to facilitate an enantioselective intramolecular benzoin condensation (*Scheme 2*).[6]



Scheme 2. An intramolecular benzoin condensation

This finding was confirmed in another study with a slightly modified NHC using DBU as the base instead of potassium tert-butoxide (*Scheme 3*).[7]



Scheme 3. A second intramolecular benzoin condensation

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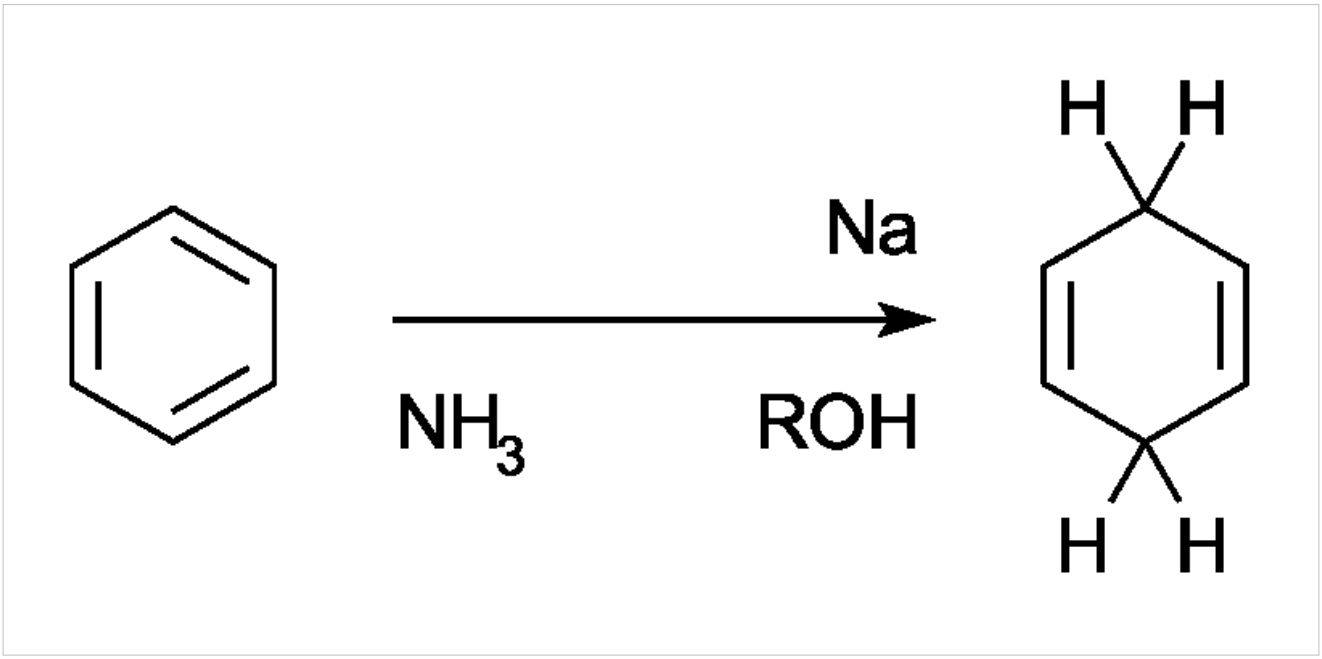
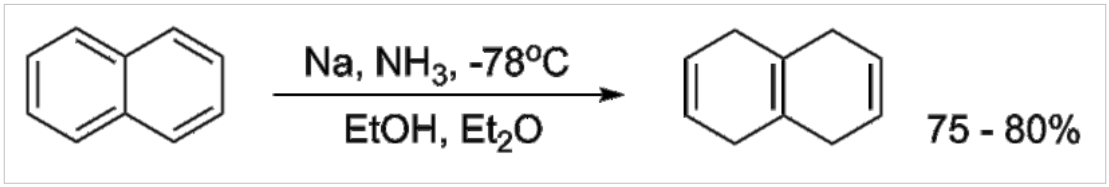
Birch reduction

The **Birch Reduction** is an organic reaction which is particularly useful in synthetic organic chemistry. The reaction was reported in 1944 by the Australian chemist Arthur Birch (1915–1995) working in the Dyson Perrins Laboratory in the University of Oxford,[1] [2] [3] [4] [5] [6] building on earlier work by Wooster and Godfrey in 1937.[7] It converts aromatic compounds having a benzenoid ring into a product, 1,4-cyclohexadienes, in which two hydrogen atoms have been attached on opposite ends of the molecule. It is the organic reduction of aromatic rings in liquid ammonia with sodium, lithium or potassium and an alcohol, such as ethanol and *tert*-butanol. This reaction is quite unlike catalytic hydrogenation, which usually reduces the aromatic ring all the way to a cyclohexane.

The original reaction reported by Arthur Birch in 1944 utilized sodium and ethanol.[8] Subsequently A. L. Wilds noted that better yields result with lithium.[9] Also the use of t-butyl alcohol has become common. The reaction is one of the main organic reactions utilized in all types of syntheses.



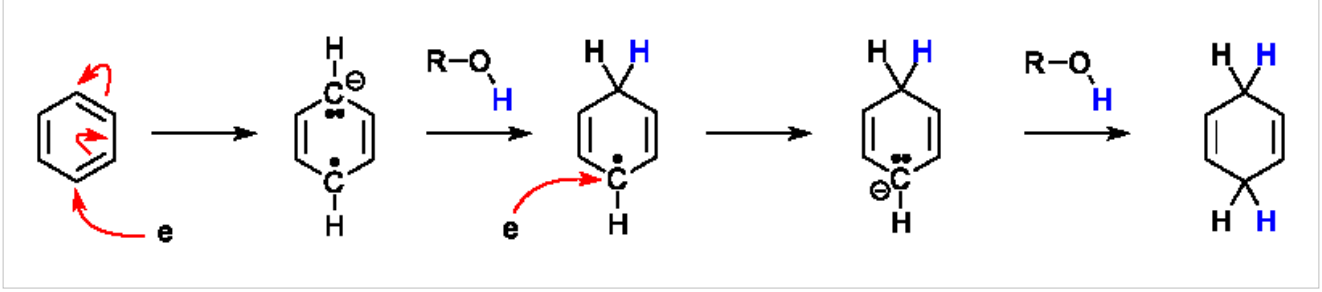
An example is the reduction of naphthalene:[10]



Several reviews have been published.[11] [12] [13] [14]

Basic reaction mechanism

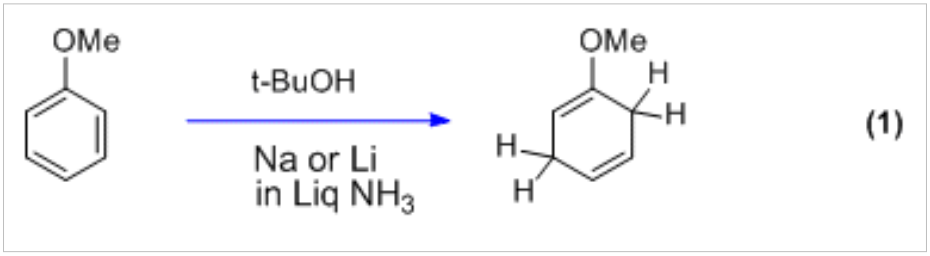
A solution of sodium in liquid ammonia consists of the electride salt $[Na(NH_3)_x]^+ e^-$, associated with the intense blue color of these solutions. The solvated electrons add to the aromatic ring to give a radical anion. The added alcohol supplies a proton to the radical anion and also to the penultimate carbanion; for most substrates ammonia is not acidic enough.[15]

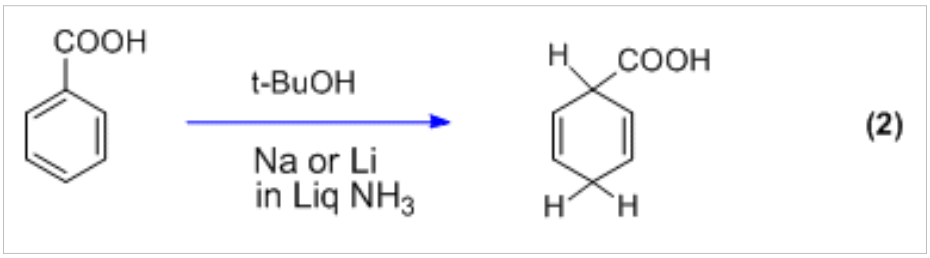


Regioselectivity

The reduction of anisole is one of the simplest examples and is shown in Eqn. 1. Still another example is that of benzoic acid illustrated in Eqn. 2.

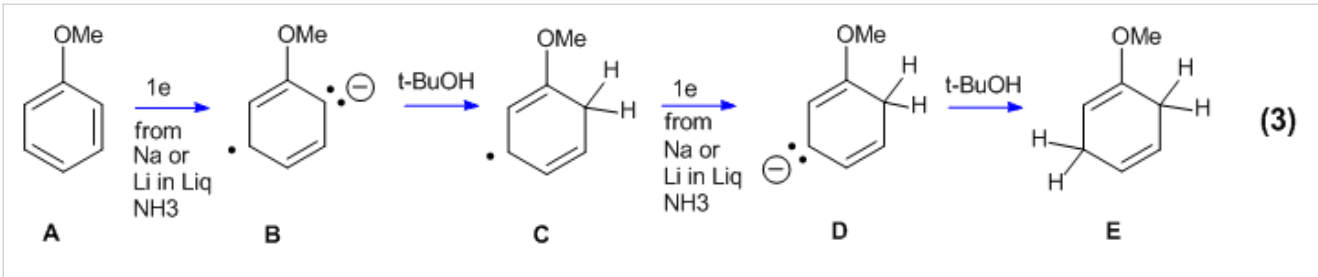
Where the radical-anion is protonated initially determines the structure of the product. With an electron donor as methoxy (MeO) or alkyl protonation has been thought by some investigators as being ortho (i.e. adjacent or 1,2) to the substituent. Other investigators have thought the protonation is meta (1,3) to the substituent. Arthur Birch favored meta protonation. With electron withdrawing substituents protonation has been thought to come at the site (ipso) of the substituent or para (1,4). Again, there has been varied opinion. A. J. Birch's empirical rules say that for the donor substituents the final product has the maximum number of substituents on the final double bonds. For electron withdrawing groups the double bonds of the product have avoided the substituents. The placement preference of groups in the mechanism and in the final product is termed regioselectivity.





Overall details of the reaction mechanism

The solution of metal in ammonia provides electrons which are taken up by the aromatic ring to form the corresponding radical anion B in the first step of the reaction. This is followed by protonation by the alcohol to form a cyclohexadienyl radical C. Next, a second electron is transferred to the radical to form a cyclohexadienyl carbanion D. In the last step a second proton leads the cyclohexadienyl carbanion to the unconjugated cyclohexadienyl product. These steps are outlined below for the case of anisole.



The reaction is known to be third order – first order in aromatic, first order in the alkali metal, and first order in the alcohol.[16] This requires the rate-limiting step to be the conversion of radical anion B to the cyclohexadienyl radical C.

Reaction regioselectivity

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

- In liquid ammonia alkali metals dissolve to give a blue solution thought of simplistically as having "free electrons". The electrons are taken up by the aromatic ring, one at a time. Once the first electron has been absorbed, a radical-anion has been formed. Next the alcohol molecule donates its hydroxylic hydrogen to form a new C-H bond; at this point a radical has been formed. This is followed by the second electron being picked up to give a carbanion of the cyclohexadienyl type (i.e. with C=C-C-C=C in a six-ring and charged minus). Then this cyclohexadienyl anion is protonated by the alcohol present. The protonation takes place in the middle of the cyclohexadienyl system). This (regio-)selectivity is unique and characteristic.
- Where the radical-anion is protonated initially determines the structure of the product. With an electron donor as methoxy (MeO) or alkyl protonation has been thought by some investigators as being ortho (i.e. adjacent or 1,2) to the substituent. Other investigators have thought the protonation is meta (1,3) to the substituent. Arthur Birch favored meta protonation. With electron withdrawing substituents protonation has been thought to come at the site (ipso) of the substituent or para (1,4). Again, there has been varied opinion. A. J. Birch's empirical rules say that for the donor substituents the final product has the maximum number of substituents on the final double bonds. For electron withdrawing groups the double bonds of the product have avoided the substituents. The placement preference of groups in the mechanism and in the final product is termed regioselectivity.
- The reaction mechanism provides the details of molecular change as a reaction proceeds. In the case of donating groups A. J. Birch's preference for meta protonation of the radical anion was based on qualitative reasoning. And it had been noted that no experimental test of this was known.
- In 1961 a simple computation of the electron densities of the radical anion revealed that it was the ortho site which was most negative and thus most likely to protonate. However, A. J. Birch seemed to overlook this result. Additionally, the second proton had been determined by the computations to occur in the center of the

cyclohexadienyl anion to give an unconjugated product.

- Of historical interest is the uncertainty in the chemical literature at this point. Indeed, there were some further computational results reported. These varied from suggesting a preference for meta radical-anion protonation to suggesting a mixture of ortho and meta protonation.
- In 1990 and 1993 an esoteric test was devised which showed that ortho protonation of the radical anion was preferred over meta (seven to one). This was accompanied by more modern computation which concurred. Both experiment and computations were in agreement with the early 1961 computations.
- With electron withdrawing groups there are literature examples demonstrating the nature of the carbanion just before final protonation. This revealed that the initial radical-anion protonation occurs para to the withdrawing substituent.
- The remaining item for discussion is the final protonation of the cyclohexadienyl anion. In 1961 it was found that simple Hückel computations were unable to distinguish between the different protonation sites. However, when the computations were modified with somewhat more realistic assumptions, the Hückel computations revealed the center carbon to the preferred. The more modern 1990 and 1993 computations were in agreement.

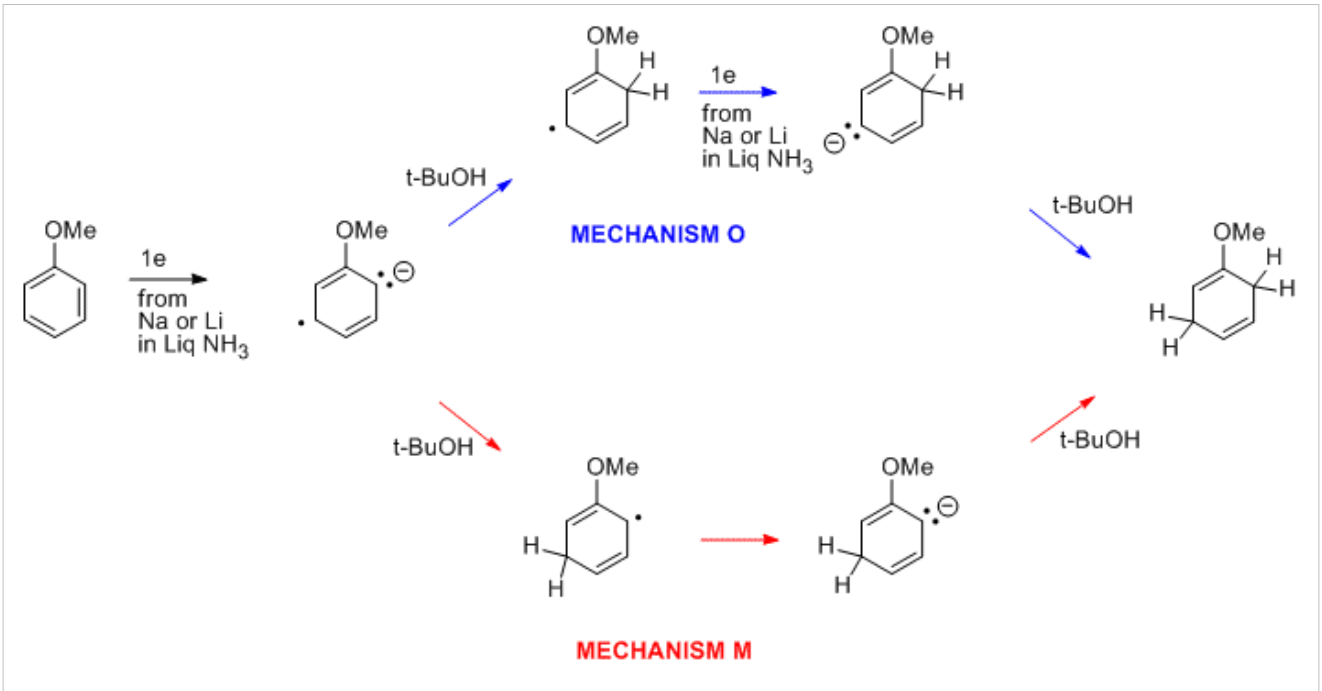
Underlying mechanism of the Birch reduction

The original Birch mechanism suggested that the initial radical anion protonation was meta to the ring methoxy and alkyl groups and the last step, protonation of a cyclohexadienyl anion, was ortho. Birch's original mechanism was based on qualitative reasoning, namely that the radical anion's electron density, resulting from the addition of an electron, would become highest meta to an electron donor (such as methoxy or methyl) due to avoiding the usual ortho-para high density in the neutral species.[8]

Hückel computations

Using simple Hückel computations in 1961 it was shown that the Birch mechanism was incorrect. The correct mechanism O is depicted below.[17] [18]

The two a-priori alternative mechanisms O and M:



Subsequent literature and varying views

However, Birch did not accept this conclusion and continued publications suggesting meta protonation of the radical anion. He suggested the meta attack results from “opposition of the ortho and para initial charge”.[19]

Bothner-By in 1959 had given qualitative arguments favoring meta-protonation[16] as had been suggested previously by Birch.

Burnham in 1969 concluded that protonation is unlikely to occur predominantly at the ortho position and the reaction most probably occurs at the meta position but may occur at both sites at similar rates.[20]

Subsequently, Birch in a review article[21] noted that no experimental method at the time existed which would determine which was correct. But he did note that publication by Burnham[20] favored meta attack.

In 1980 publications Birch collaborated with Leo Radom and considered ortho and meta densities to be close with a slight ortho preference but with mixtures of ortho and meta protonation occurring.[22] [23] RHF/sto-3g and UHF/sto-3g computations were used to conclude that both ortho and meta substitutions would occur with a slight preference for ortho.[22] [23]

Thus there had been a decade of controversy in the literature in which each of these two possible mechanisms was considered to be correct.

Experimental testing and computational verification

Then in 1990 and 1993 a method was finally devised to experimentally assess whether the anisole and toluene radical anion protonated ortho or meta.[24] [25] The esoteric method began with the premise that the isotope selectivity in protonation in a protium–deuterium medium would be greater for the radical anion, of the first protonation step, than for the carbanion of the penultimate step. The reasoning was that carbanions are much more basic than the corresponding radical anions and thus will react more exothermically and less selectively in protonation. Experimentally it was determined that less deuterium at the ortho site than meta resulted (1:7) for a variety of methoxylated aromatics. This is a consequence of the greater selectivity of the radical anion protonation. Computations (e.g. ROHF/6-31g) of the electron densities concurred with the experimental observations. Also, it was ascertained that frontier orbital densities did not, and these had been used in some previous reports.

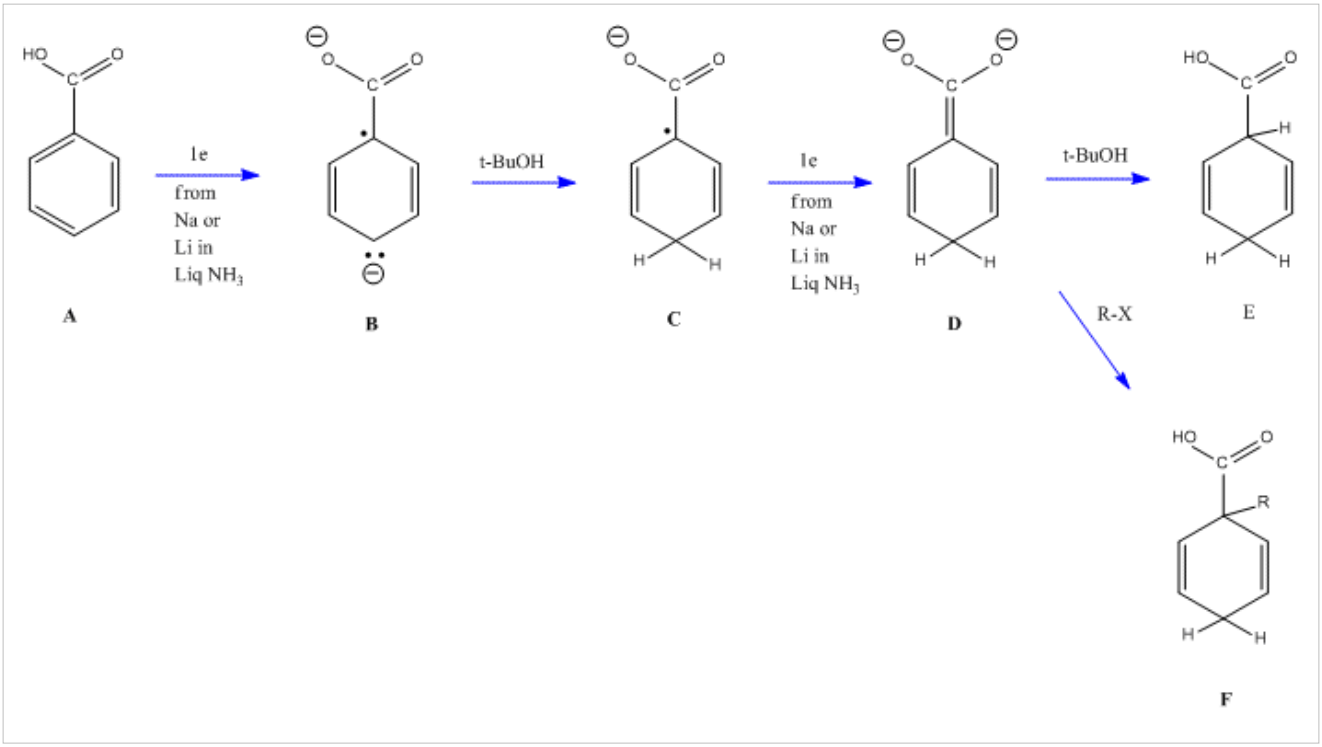
Subsequently, in 1992 and 1996 Birch published twice still suggesting that meta protonation was preferred.[26] [27] This was a reversal of his earlier views as published with Leo Radom.

However, textbooks, publishing on the mechanism of the Birch Reduction, have noted that ortho protonation of the initial radical anion is preferred.[28]

Birch reduction with electron withdrawing substituents

In contrast to the examples with electron donating substituents, the case with withdrawing groups is more readily obvious. Thus, as depicted below, the structure of the penultimate dianion D is characterized by its being subject to trapping by alkyl halides.

Mechanism of reduction of benzoic acids, including possible alkylation

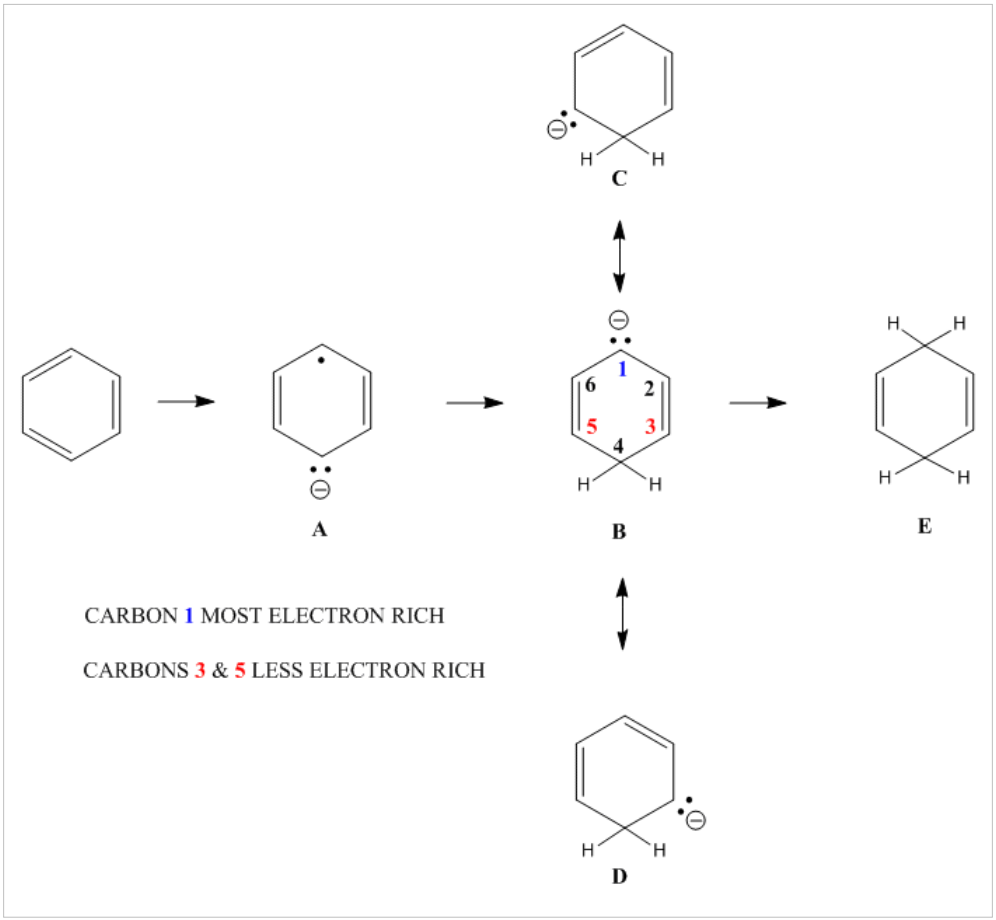


This dianion results independent of whether alcohol is used in the reduction or not. Thus the initial protonation by t-butyl alcohol or ammonia is para rather than ipso as seen in the step from B to C.[29] [30] [31]

Second step of the Birch reduction with regiochemistry giving unconjugated cyclohexadienes

The second step of the Birch reduction affording unconjugated cyclohexadienes also poses mechanistic questions. Thus as shown in the figure below there are three resonance structures B, C and D for the carbanion. Simple Hückel computations lead, as noted in the first entry of the table below, to equal electron densities at the three atoms 1, 3 and 5. However, in contrast to densities the Hückel computation is less naïve about bond orders,[17] [32] [33] and bonds 2-3 and 5-6 will be shortened as shown in the first entry of the table. With bond orders modifying simple exchange integrals in a Mulliken-Wheland-Mann computation it was shown that electron density at the central atom 1 become largest.[32] [33] More modern RHF computations lead to the same result.[24] [25]

Electron introduction to benzene and 3 resonance structures for the carbanion of the second step, and central protonation to give the unconjugated diene:



Five carbons of the cyclohexadienyl anion.[32] [33]

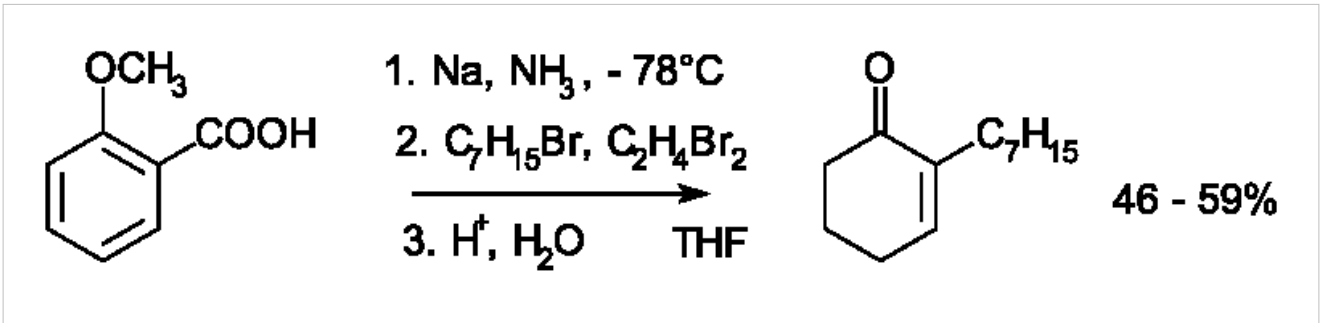
Approximation	Density Atom 3	Density Atom 2	Density Atom 1	Bond Order 2-3	Bond Order 1-2
Hückel (1st Approx)	0.333	0.00	0.333	0.788	0.578
2nd Approx	0.317	0.00	0.365	0.802	0.564
3rd Approx	0.316	0.00	0.368	0.802	0.562

There are known precedents for central anion protonation.[17] [34] Thus conjugated enolates as C=C-C=C-O- have been known for some time as kinetically protonating in the center of the enolate system to afford the β,γ-unsaturated carbonyl compound under conditions where the anion, and not the enol, is the species protonated.

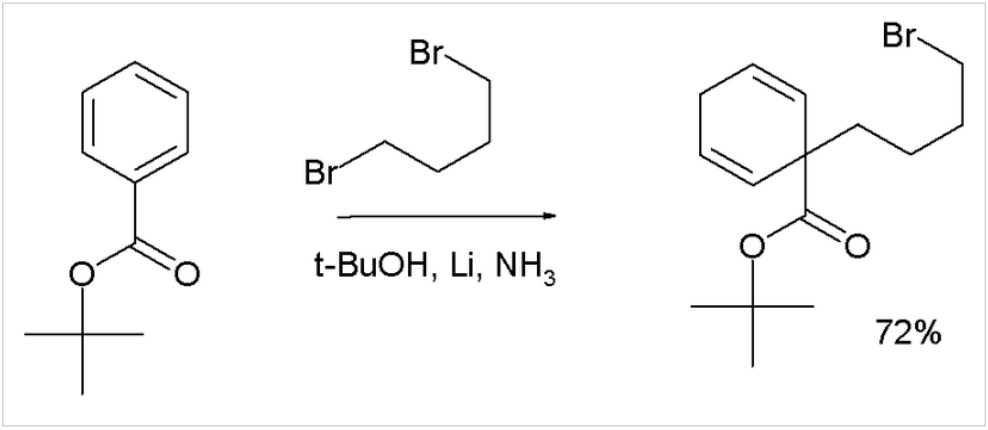
Birch alkylation

In the presence of an alkyl halide the carbanion can also undergo nucleophilic substitution with carbon-carbon bond formation. In substituted aromatic compounds an electron-withdrawing substituent, such as a carboxylic acid,[35] stabilizes a carbanion and the least-substituted olefin is generated. With an electron-donating substituent the opposite effect is obtained.[36] The reaction produces more of the less thermodynamically stable non-conjugated 1,4-addition product than the more stable conjugated 1,3-diene because the largest orbital coefficient of the HOMO of the conjugated pentadienyl anion intermediate is on the central carbon atom. Once formed, the resulting 1,4-cyclohexadiene is unable to equilibrate to the thermodynamically more stable product; therefore, the observed kinetic product is produced. Experimental alkali metal alternatives that are safer to handle, such as the M-SG reducing agent, also exist.

In **Birch alkylation** the anion formed in the Birch reduction is trapped by a suitable electrophile such as a haloalkane, for example:[37]

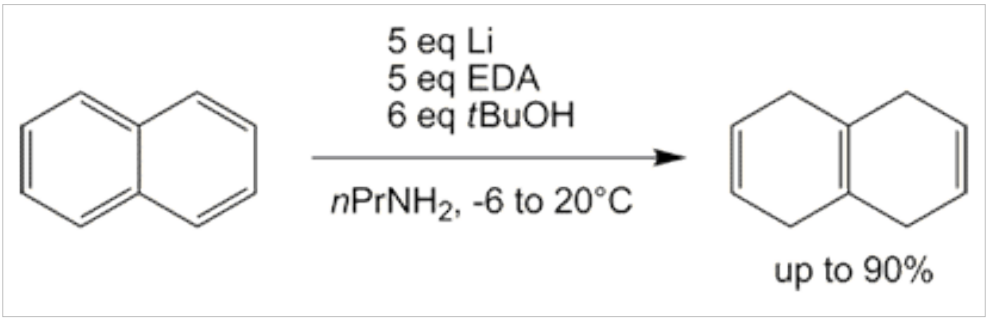


In the reaction depicted below, 1,4-dibromobutane is added to t-butyl benzoate to form an alkylated 1,4-cyclohexadiene product:[38]



Modifications of the Birch reduction

Since liquid ammonia has to be condensed into the flask and has to evaporate overnight after the reaction is complete, the whole procedure can be quite troublesome and time-consuming. However, alternative solvents have been employed, such as THF[39] as well as a mixture of *n*-propylamine and ethylenediamine,[40] both with comparable results. The latter one actually is a modification of the Benkeser Reaction, which in its original forms tends to reduce naphthalene all the way to octahydro- and decahydronaphthalene.



This reduction of naphthalene to isotetralin (1,4,5,8-tetrahydronaphthalene) produces some tetralin (1,2,3,4-tetrahydronaphthalene) as byproduct, as is the case with the regular Birch reduction.

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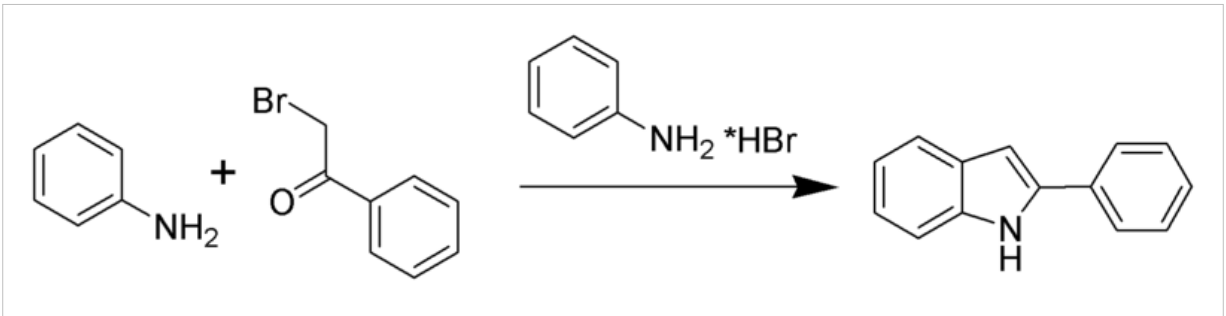
Bischler-Möhlau indole synthesis

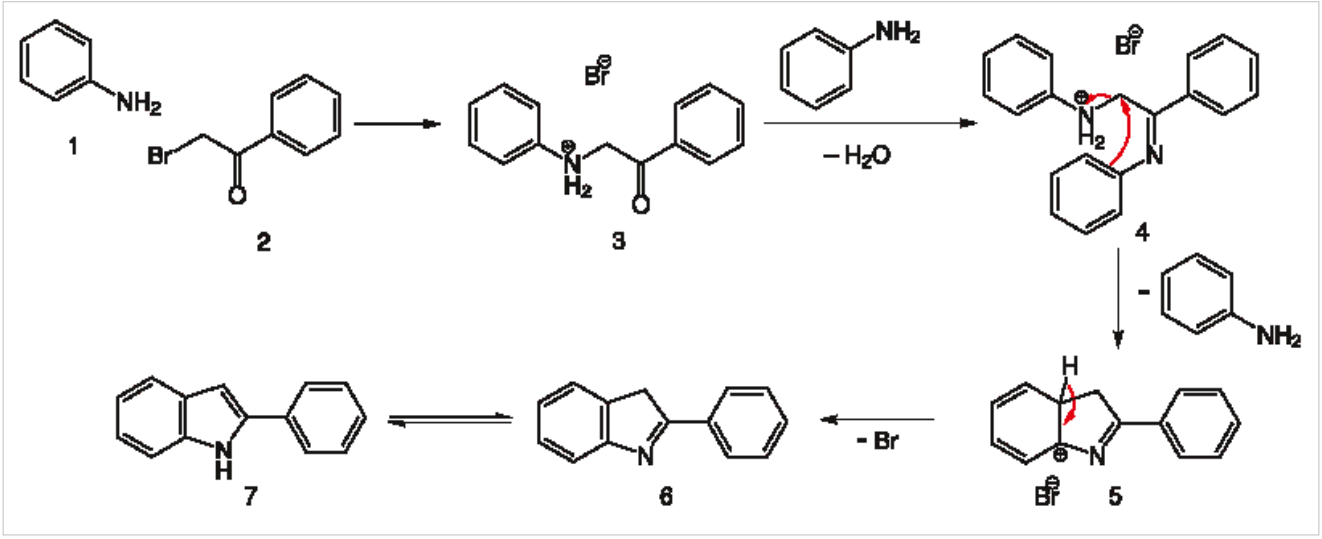
The **Bischler-Möhlau indole synthesis** is a chemical reaction that forms a 2-aryl-indole from an α-bromo-acetophenone and excess aniline.[1] [2] [3] [4] [5]



In spite of its long history, this classical reaction has received relatively little attention in comparison with other methods for indole synthesis, perhaps owing to the harsh reaction conditions that it requires. Recently, milder methods have been developed, including the use of lithium bromide as a catalyst and an improved procedure involving the use of microwave irradiation.[6] [7] [8]

Reaction mechanism

The first two step involve the reaction of the α-bromo-acetophenone with molecules of aniline to form intermediate **4**. The charged aniline forms a decent enough leaving group for an electrophilic cyclization to form intermediate **5**, which quickly aromatizes and tautomerizes to give the desired indole **7**.



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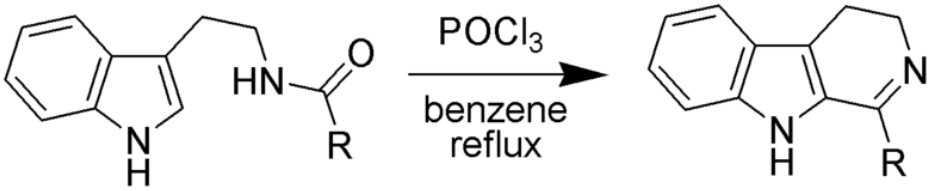
Bischler–Napieralski reaction

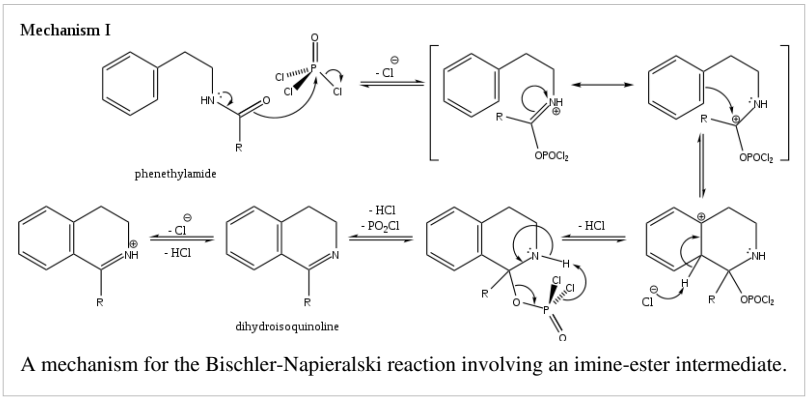
The **Bischler–Napieralski reaction** is an intramolecular electrophilic aromatic substitution reaction that allows for the cyclization of β-arylethylamides or β-arylethylcarbamates. It was first discovered in 1893 by August Bischler and Bernard Napieralski, in affiliation with Basle Chemical Works and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



A general scheme of the Bischler-Napieralski reaction.

Mechanisms

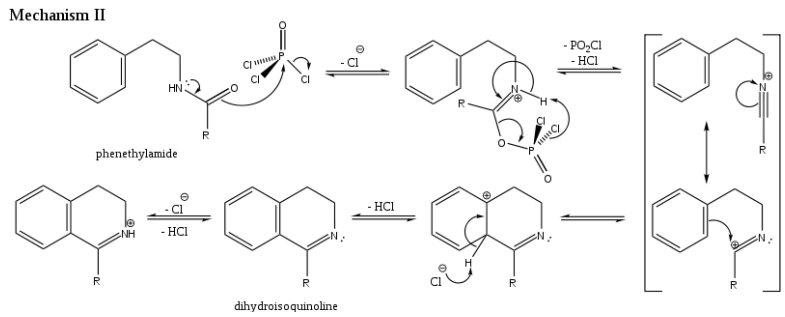
Two types of mechanisms have appeared in literature for the Bischler–Napieralski reaction. Mechanism I involves a dichlorophosphoryl imine-ester intermediate, while Mechanism II involves a nitrilium ion intermediate (both shown in brackets). This mechanistic variance stems from the ambiguity over the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



A mechanism for the Bischler-Napieralski reaction involving an imine-ester intermediate.

In certain literature, Mechanism II is augmented with the formation of an imidoyl chloride intermediate produced by the substitution of chloride for the Lewis acid group just prior to the nitrilium ion.

Because the dehydroisoquinoline nitrogen is basic, neutralization is necessary to obtain the deprotonated product.



A mechanism for the Bischler-Napieralski reaction involving a nitrilium intermediate.

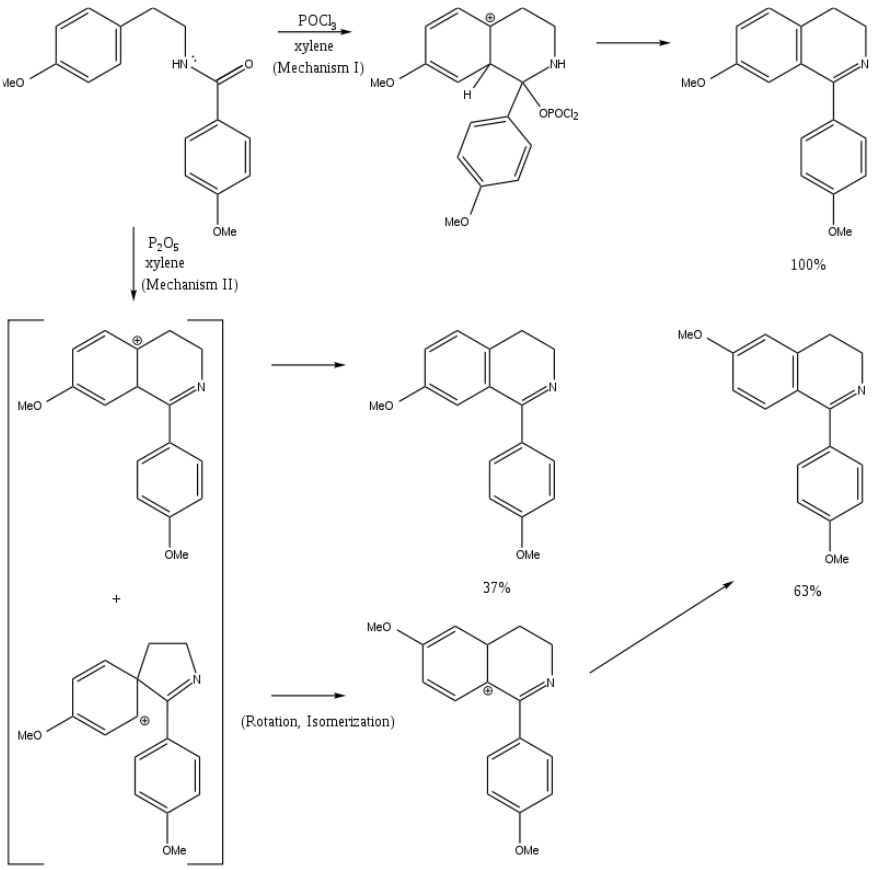
General Reaction Reagents/Conditions

The Bischler–Napieralski reaction is carried out in refluxing acidic conditions and requires a dehydrating agent. Phosphoryl chloride ($POCl_3$) is widely used and cited for this purpose. Additionally, $SnCl_4$ and BF_3 etherate have been used with phenethylamides, while Tf_2O and polyphosphoric acid (PPA, a.k.a. Eaton's reagent) have been used with phenethylcarbamates. For reactants lacking electron-donating groups on the benzene ring, phosphorus pentoxide (P_2O_5) in refluxing $POCl_3$ is most effective. Depending on the dehydrating reagent used, the reaction temperature varies from room temperature to 100°C.

Related Reactions and Variations

Several reactions that are related to the Bischler–Napieralski reaction are known. The Pictet-Spengler reaction proceeds from a β-arylamine via condensation with an aldehyde. The Picter-Gams reaction proceeds from an α-hydroxy-β-phenethylamide and culminates in isoquinoline via condensation instead of dehydrogenation.

There are documented variations on the Bischler–Napieralski reaction whose products differ in virtue of either the structure of the initial reactant, the tailoring of reaction conditions, or both. For example, research done by Doi and colleagues suggests that the presence or absence of electron-donating groups on the aryl portion of β-arylethylamides and the ratio of dehydrating reagents influence the patterns of ring closure via electrophilic aromatic substitution, leading to two possibilities for product (see below). Other research on the variations on the Bischler-Napieralski Reaction have investigated the effects of nitro and acetal aryl groups on product formation (for further information, see references).



An example of mechanistic and product variation in the Bischler-Napieralski reaction. Treatment of N-[2-(4-methoxyphenyl)-ethyl]-4–methoxybenzamide with $POCl_3$ results in the formation of the normal product, 7-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline. Treatment exclusively with P_2O_5 results in a mixture of the normal product and an unexpected product, 6-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline. The formation of the abnormal product is attributed to the cyclization via the ipso carbon on the phenyl ring to yield a spiro intermediate.

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Biuret test

The **biuret test** is a chemical test used for detecting the presence of peptide bonds. In the presence of peptides, a copper(II) ion forms a violet-colored complex in an alkaline solution.[1] Several variants on the test have been developed.

The Biuret reaction can be used to assay the concentration of proteins because peptide bonds occur with the same frequency per amino acid in the peptide. The intensity of the color, and hence the absorption at 540 nm, is directly proportional to the protein concentration, according to the Beer-Lambert law.

In spite of its name, the reagent does not in fact contain biuret ($(H_2N\text{-}CO\text{-})_2NH$). The test is so named because it also gives a positive reaction to the peptide bonds in the biuret molecule.

The characteristic color of a positive biuret test

Procedure

An aqueous sample is treated with an equal volume of 1% strong base (sodium or potassium hydroxide most often) followed by a few drops of aqueous copper(II) sulfate. If the solution turns purple, protein is present. 5–160 mg/mL can be determined.

Biuret reagent

The **biuret reagent** is made of potassium hydroxide (KOH) and hydrated copper (II) sulfate, together with potassium sodium tartrate. The reagent turns from blue to violet in the presence of proteins, blue to pink when combined with short-chain polypeptides.[2]

Not all biuret tests require the biuret reagent. The reagent is commonly used in a biuret protein assay, a colorimetric assay used to determine protein concentration—such as UV-VIS at wavelength 540 nm (to detect the Cu^{2+} ion).

Increasing the sensitivity of the biuret test

Cu^{+} is a strong reducing agent which can react for example with Mo(VI) in Folin-Ciocalteu's reagent to form molybdenum blue. In this way, proteins can be detected in concentrations between 0.005 and 2 mg/mL.[3] Molybdenum blue in turn can bind certain organic dyes (malachite green, Auramin O), resulting in further amplification of the of the signal.[4]

Cu^{+} forms a deep purple complex with bicinchoninic acid (BCA)[5] , which allows proteins in the range of 0.0005 to 2 mg/mL to be determined. This assay is often referred to as "Pierce assay" after the manufacturer of a reagent kit.

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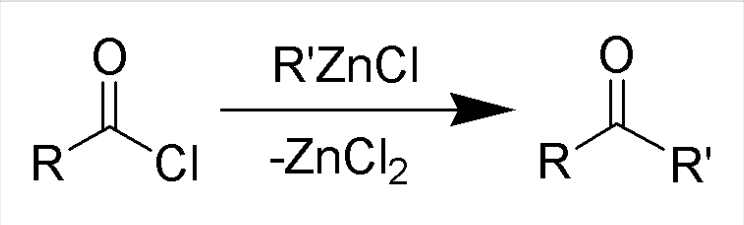
External links

- Chemical Reagents (http://faculty.mansfield.edu/bganong/biochemistry/reagents.htm)

Blaise ketone synthesis

The **Blaise ketone synthesis** is the chemical reaction of acid chlorides with organozinc compounds to give ketones.[Blaise1910 Blaise1911]



The reaction also works with organocuprates.[Posner1976Fujisawa1988]

Reviews have been written.[Cason1947 Shirley1954]

Variations

Blaise-Maire reaction

The **Blaise-Maire reaction** is the Blaise ketone synthesis using β-hydroxy acid chlorides to give β-hydroxyketones, which are converted into α,β-unsaturated ketones using sulfuric acid.[Blaise1907]

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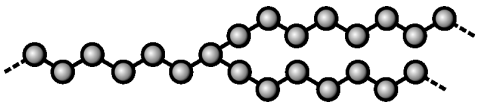
Branching (polymer chemistry)



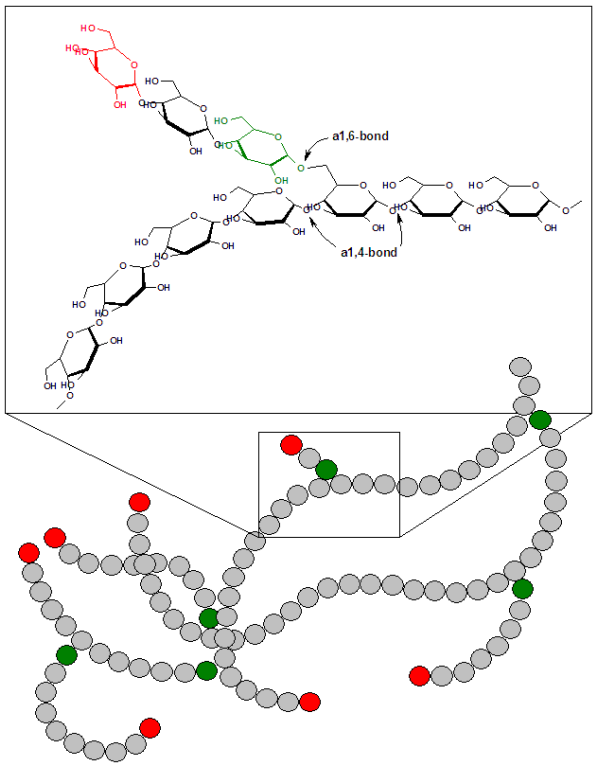
Branch point in a polymer

In polymer chemistry, **branching** occurs by the replacement of a substituent, e.g., a hydrogen atom, on a monomer subunit, by another covalently bonded chain of that polymer; or, in the case of a graft copolymer, by a chain of another type. In crosslinking rubber by vulcanization, short sulfur branches link polyisoprene chains (or a synthetic variant) into a multiply-branched thermosetting elastomer. Rubber can also be so completely vulcanized that it becomes a rigid solid, so hard it can be used as the bit in a smoking pipe. Polycarbonate chains can be crosslinked to form the hardest, most impact-resistant thermosetting plastic, used in safety glasses.[1]

Branching may result from the formation of carbon-carbon or various other types of covalent bonds. Branching by ester and amide bonds is typically by a condensation reaction, producing one molecule of water (or HCl) for each bond formed.

Polymers which are branched but not crosslinked are generally thermoplastic. Branching sometimes occurs spontaneously during synthesis of polymers; e.g., by free-radical polymerization of ethylene to form polyethylene. In fact, preventing branching to produce linear polyethylene requires special methods. Because of the way polyamides are formed, nylon would seem to be limited to unbranched, straight chains. But "star" branched nylon can be produced by the condensation of dicarboxylic acids with polyamines having three or more amino groups. Branching also occurs naturally during enzymatically-catalyzed polymerization of glucose to form polysaccharides such as glycogen (animals), and amylopectin, a form of starch (plants). The unbranched form of starch is called amylose.

The ultimate in branching is a completely crosslinked network such as found in Bakelite, a phenol-formaldehyde thermoset resin.



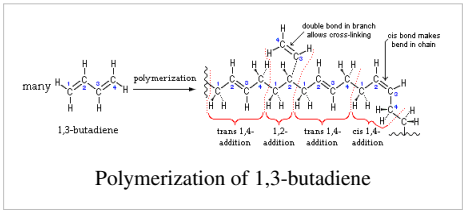
Glycogen, a branched polysaccharide

Special types of branched polymer

- A **graft polymer** molecule is a branched polymer molecule in which one or more the side chains are different, structurally or configurationally, from the main chain.
- A **star polymer** molecule is a branched polymer molecule in which a single branch point gives rise to multiple linear chains or arms. If the arms are identical the star polymer molecule is said to be **regular**. If adjacent arms are composed of different repeating subunits, the star polymer molecule is said to be **variegated**.
- A **comb polymer** molecule consists of a main chain with two or more three-way branch points and linear side chains. If the arms are identical the comb polymer molecule is said to be **regular**.

- A **brush polymer** molecule consists of a main chain with linear, unbranched side chains and where one or more of the branch points has four-way functionality or larger.
- A **polymer network** is a network in which all polymer chains are interconnected to form a single macroscopic entity by many crosslinks[2] . See for example thermosets or interpenetrating polymer networks.

Branching in radical polymerization



Polymerization of 1,3-butadiene

In free radical polymerization, branching occurs when a chain curls back and bonds to an earlier part of the chain. When this curl breaks, it leaves small chains sprouting from the main carbon backbone. Branched carbon chains cannot line up as close to each other as unbranched chains can. This causes less contact between atoms of different chains, and fewer opportunities for induced or permanent dipoles to occur. A low density results from the chains being further apart. Lower melting points and tensile strengths are evident, because the intermolecular bonds are weaker and require less energy to break.

The problem of branching occurs during propagation, when a chain curls back on itself and breaks - leaving irregular chains sprouting from the main carbon backbone. Branching makes the polymers less dense and results in low tensile strength and melting points. Developed by Karl Ziegler and Giulio Natta in the 1950s, Ziegler-Natta catalysts (triethylaluminium in the presence of a metal(IV) chloride) largely solved this problem. Instead of a free radical reaction, the initial ethene monomer inserts between the aluminium atom and one of the ethyl groups in the catalyst. The polymer is then able to grow out from the aluminium atom and results in almost totally unbranched chains. With the new catalysts, the tacticity of the polypropene chain, the alignment of alkyl groups, was also able to be controlled. Different metal chlorides allowed the selective production of each form i.e., syndiotactic, isotactic and atactic polymer chains could be selectively created.

However there were further complications to be solved. If the Ziegler-Natta catalyst was poisoned or damaged then the chain stopped growing. Also, Ziegler-Natta monomers have to be small, and it was still impossible to control the molecular mass of the polymer chains. Again new catalysts, the metallocenes, were developed to tackle these problems. Due to their structure they have less premature chain termination and branching.

Branching index

The branching index measures the effect of long-chain branches on the size of a macromolecule in solution. It is defined[3] as $g = \langle s_b^2 \rangle / \langle s_l^2 \rangle$, where s_b is the mean square radius of gyration of the branched macromolecule in a given solvent, and s_l is the mean square radius of gyration of an otherwise identical linear macromolecule in the same solvent at the same temperature. A value greater than 1 indicates an increased radius of gyration due to branching.

External links

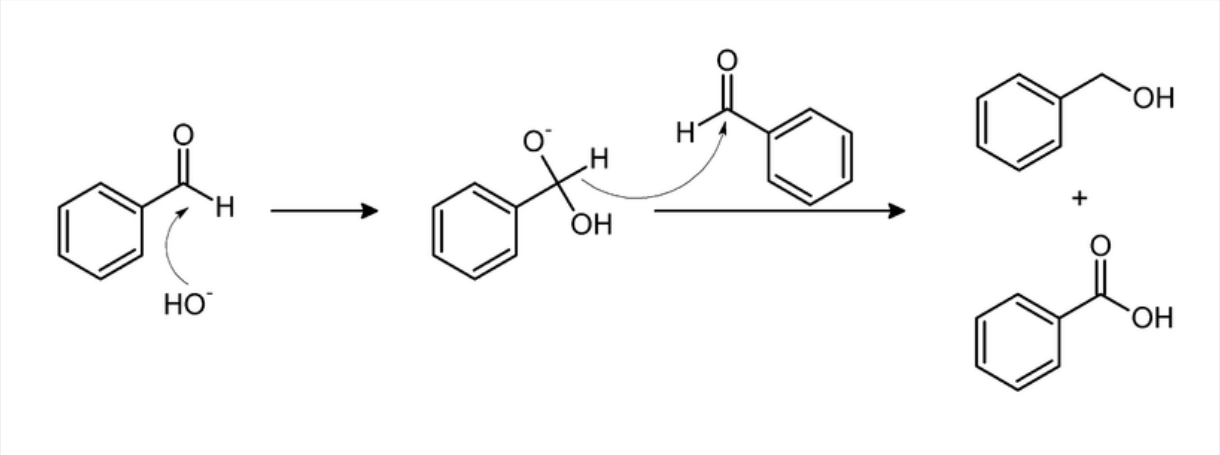
- Polycarbonate [1]

References

[1] http://www.pslc.ws/macrog/pc.htm
[2] network (in polymer chemistry) (http://www.iupac.org/goldbook/N04112.pdf)
[3] http://www.iupac.org/goldbook/B00726.pdf

Cannizzaro reaction

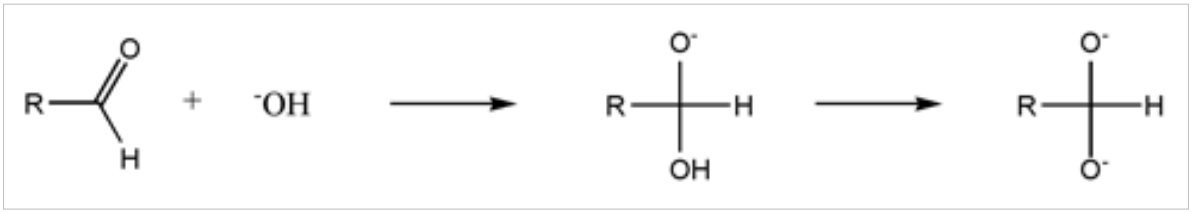
The **Cannizzaro reaction**, named after its discoverer Stanislao Cannizzaro, is a chemical reaction that involves the base-induced disproportionation of an aldehyde lacking a hydrogen atom in the alpha position.[1] [2] Cannizzaro first accomplished this transformation in 1853, when he obtained benzyl alcohol and benzoic acid from the treatment of benzaldehyde with potash (potassium carbonate).



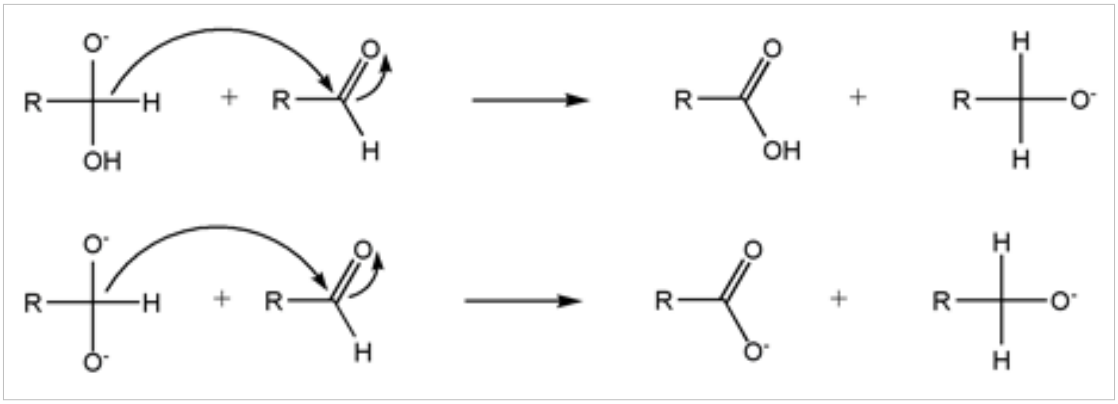
The oxidation product is a carboxylic acid and the reduction product is an alcohol. For aldehydes with a hydrogen atom alpha to the carbonyl, i.e. RC*H*R'CHO, the preferred reaction is an aldol condensation, originating from deprotonation of this hydrogen. Reviews have been published.[3]

Reaction mechanism

The first reaction step is nucleophilic addition of the base (for instance the hydroxide anion) to the carbonyl carbon of the aldehyde. The resulting alkoxide is deprotonated to give a di-anion, known as the **Cannizzaro intermediate**. Formation of this intermediate requires a strongly basic environment. This reaction is self oxidation-reduction reaction. Alcohols are formed in the result of reduction and salts of carboxylic acid in the result of oxidation.



Both intermediates can react further with aldehyde to transfer a hydride, H^-. The hydridic character of the C-*H* is enhanced by the electron-donating character of the alpha oxygen anion. This hydride transfer simultaneously generates an alkoxide anion (RCH_2O^-) and a carboxylic acid, which is rapidly deprotonated to form the carboxylate. Further evidence for the hydridic character of the Cannizzaro intermediate is provided by the formation of H_2 by its reaction with water.



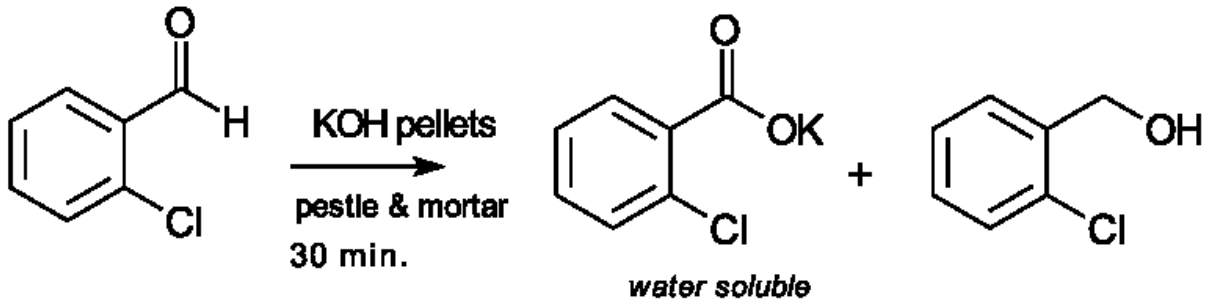
Only aldehydes that cannot form an enolate ion undergo the Cannizzaro reaction. The aldehyde cannot have an enolizable proton. Under the basic conditions that facilitate the reaction, aldehydes that can form an enolate instead undergo aldol condensation. Examples of aldehydes that can undergo a Cannizzaro reaction include formaldehyde and aromatic aldehydes such as benzaldehyde.

Variations

A special condition is the **crossed Cannizzaro reaction**. This variation is more common these days because the original Cannizzaro reaction yields a mixture of alcohol and carboxylic acid. For example any aldehyde with no alpha hydrogens can be reduced when in the presence of formaldehyde. Formaldehyde is oxidized to formic acid and the corresponding alcohol is obtained in a high yield although the atom economy is still low.

Scope

A solvent-free reaction has been reported involving mixing 2-chlorobenzaldehyde with potassium hydroxide in a mortar and pestle [4] :



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[1] Cannizzaro, S. (1853). "Ueber den der Benzoësäure entsprechenden Alkohol". *Liebigs Annalen* **88**: 129–130. doi:10.1002/jlac.18530880114.

[2] List, K.; Limpricht, H. (1854). "Ueber das sogenannte Benzoëoxyd und einige andere gepaarte Verbindungen". *Liebigs Annalen* **90**: 190–210. doi:10.1002/jlac.18540900211.

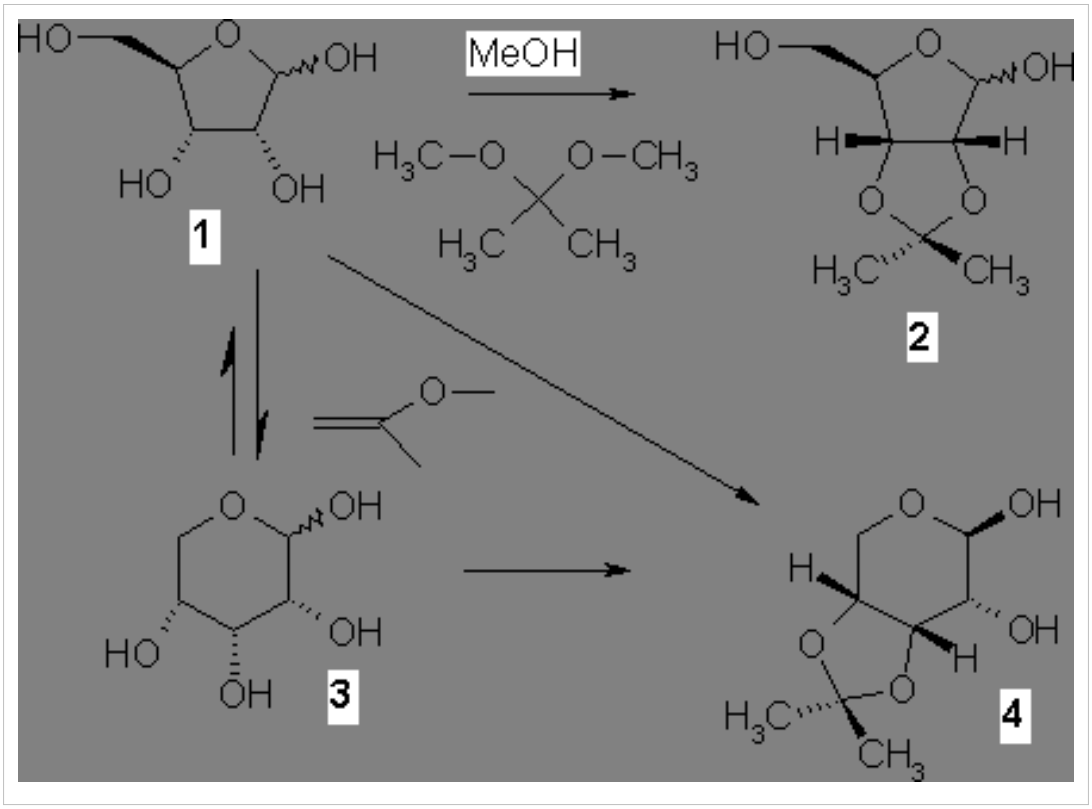
[3] Geissman, T. A. *Org. React.* **1944**, *2*, 94. (Review)

[4] *A Facile Solvent-Free Cannizzaro Reaction* Phonchaiya, Sonthi; ; Panijpan, Bhinyo Rajviroongit, Shuleewan; Wright, Tony; Blanchfield, Joanne T. J. Chem. Educ. **2009**, 86, 85.

SHOULD BE CORRECTED

Carbohydrate acetalisation

In carbohydrate chemistry **carbohydrate acetalisation** is an organic reaction and a very effective means of providing a protecting group. The example below depicts the acetalisation reaction of D-ribose **1**. With acetone or 2,2-dimethoxypropane as the acetalisation reagent the reaction is under thermodynamic reaction control and results in the pentose **2**. The latter reagent in itself is an acetal and therefore the reaction is actually a **cross-acetalisation**.

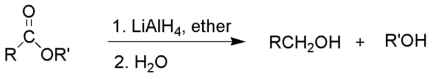


Kinetic reaction control results from 2-methoxypropene as the reagent. D-ribose in itself is a hemiacetal and in equilibrium with the pyranose **3**. In aqueous solution ribose is 75% pyranose and 25% furanose and a different acetal **4** is formed.

Preferences

- *Preparative Carbohydrate Chemistry* Calinaud, P.; Gelas, J. in . Hanessian, S. Ed. Marcel Dekker, Inc.: New York, 1997. ISBN 0-8247-9802-3

Carbonyl reduction



synthesis of an alcohol by ester reduction

Carbonyl reduction in organic chemistry is the organic reduction of any carbonyl group containing compound by a reducing agent. Typical carbonyl compounds are ketones , aldehydes, carboxylic acids and esters. A carbonyl group can be reduced to the alcohol or the oxygen atom can be removed altogether, a process called deoxygenation. Many reducing agents are metal hydrides based on boron and aluminum. A second important method is catalytic hydrogenation. [1] [2] .

Metal hydride mechanism

The reaction mechanism for metal hydride reduction is based on activation of the carbonyl group by the metal followed by nucleophilic addition of hydride. Another general system is catalytic hydrogenation by metal. $LiAlH_4$ is more reactive than $NaAlH_4$ because the smaller lithium cation is a better Lewis acid. A crown ether reduces reactivity. Alkoxide substitution in metal hydrides increases solubility and selectivity. An example is Red-Al.

Aldehyde and ketone reduction

The reaction product of the reduction of an aldehyde is a primary alcohol and that of a ketone a secondary alcohol. Reagents are lithium aluminium hydride [3] [4] [5] , diisobutylaluminium hydride, sodium borohydride, L-selectride, diborane, diazene and aluminum hydride. Sodium borohydride tolerates more functional groups (nitro group, nitrile, ester) than $LiAlH_4$ and can also be used with water or ethanol as a solvent ($LiAlH_4$ reacts with protic solvents). Sodium cyanoborohydride, 9-BBN-pyridine and tributyltin hydride are selective for aldehydes. A method for selective ketone reduction in presence of an aldehyde is $NaBH_4$ / cerium chloride.

In hydrogenation platinum and ruthenium are preferred catalysts. Specific methods are the Meerwein–Ponndorf–Verley reduction (aluminumisopropylate/isopropanol), the Bouveault–Blanc reduction (sodium metal/ethanol) and the Cannizzaro reaction (KOH induced aldehyde disproportionation)

Carboxylic acid reduction

Typical reagents for the reduction of carboxylic acids or carboxylate salts to alcohols are lithium aluminium hydride , diborane, DIBAL and aluminum hydride. Catalytic hydrogenation and $NaBH_4$ are ineffective.

Ester reduction

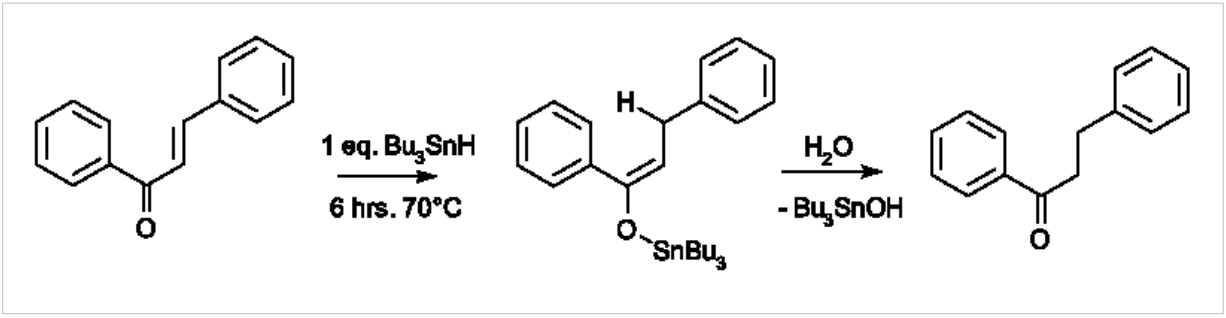
Esters (R(CO)OR') can be reduced to alcohols RCH_2OH and R'OH by lithium aluminium hydride [6] [7] and aluminum hydride. Diisobutylaluminium hydride and lithium tri-t-butoxyaluminum hydride are selective for the formation of the aldehyde. Catalytic hydrogenation over copper chromite is reported.

1,4-reduction

In **1,4-reduction** (also called **conjugate reduction**) the reaction substrate is an unsaturated carbonyl compound, an enone or enal. The 1,2-reduction product (an allyl alcohol) competes with 1,4-reduction to the saturated ketone or aldehyde. In 1,4-reduction the first step is conjugate addition of the hydride to the enolate ion followed by acidic workup forming the ketone.

1,2-reduction is found with DIBAL and 9-BBN and alane. 1,4-reduction can be accomplished with catalytic hydrogenation and by alkylmetal hydrides.

An example is the reduction of chalcone by tributyltin hydride [8] :



Conjugate reduction chalcone

An asymmetric version of this reaction has also been developed [9] .

Asymmetric synthesis

Well known carbonyl reductions in asymmetric synthesis are the Noyori asymmetric hydrogenation (beta-ketoester reduction /Ru/BINAP) and the CBS reduction (BH_3, proline derived chiral catalyst).

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[2] March, Jerry (1985), *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (3rd ed.), New York: Wiley, ISBN 0-471-85472-7

[3] Organic Syntheses, Coll. Vol. 7, p.129 (1990); Vol. 60, p.25 (1981). Link (http://orgsynth.org/orgsyn/pdfs/CV7P0129.pdf)

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[5] Organic Syntheses, Coll. Vol. 6, p.769 (1988); Vol. 56, p.101 (1977). Link (http://orgsynth.org/orgsyn/pdfs/CV6P0769.pdf)

[6] Organic Syntheses, Coll. Vol. 6, p.781 (1988); Vol. 53, p.70 (1973). Link (http://orgsynth.org/orgsyn/pdfs/CV6P0781.pdf)

[7] Organic Syntheses, Coll. Vol. 4, p.834 (1963); Vol. 33, p.82 (1953). link (http://orgsynth.org/orgsyn/pdfs/CV4P0834.pdf)

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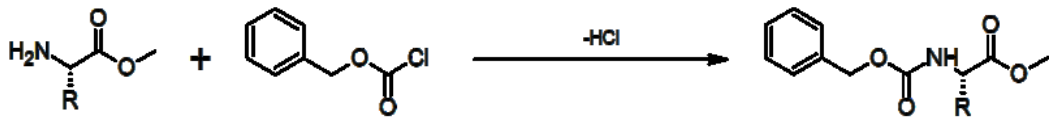
[9] Moritani, Yasunori; Appella, Daniel H.; Jurkauskas, Valdas; Buchwald, Stephen L. (2000). "Synthesis of β-Alkyl Cyclopentanones in High Enantiomeric Excess via Copper-Catalyzed Asymmetric Conjugate Reduction". *Journal of the American Chemical Society* **122**: 6797. doi:10.1021/ja0009525.

Carboxybenzyl

Carboxybenzyl or **Cbz** or **Z** is an amine protecting group in organic synthesis.[1] It is commonly used in peptide synthesis and is formed by reacting an amine with benzyl chloroformate and a weak base:



It is used to protect amines from electrophiles. The protected amine can be deprotected by catalytic hydrogenation or treatment with HBr, yielding a terminal carbamic acid that then readily decarboxylates to yield the free amine.

The method was first used by Max Bergmann in 1932 for the synthesis of peptides.[2]

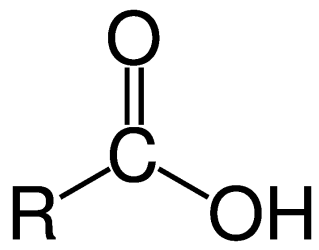
References

[1] Clayden, Jonathan; Greeves, Nick; Warren, Stuart; Wothers, Peter (2000). *Organic Chemistry* (1st ed.). Oxford University Press. pp. 248, 652-654, 1484. ISBN 978-0-19-850346-0.

[2] Max Bergmann, Leonidas Zervas (1932). "Über ein allgemeines Verfahren der Peptid-Synthese". *Berichte der deutschen chemischen Gesellschaft* **65** (7): 1192–1201. doi:10.1002/cber.19320650722.

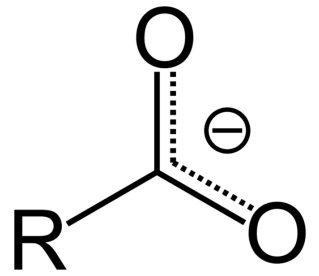
Carboxylic acid

Carboxylic acids (/ˌkɑrbɒkˈsɪlɪk .../) are organic acids characterized by the presence of at least one carboxyl group.[1] The general formula of a carboxylic acid is R-COOH, where R is some monovalent functional group. A **carboxyl group** (or **carboxy**) is a functional group consisting of a carbonyl (RR'C=O) and a hydroxyl (R-O-H), which has the formula -C(=O)OH, usually written as -COOH or -CO_2H.[2]



Structure of a carboxylic acid

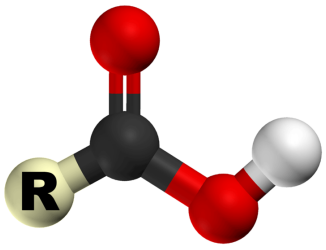
Carboxylic acids are Brønsted-Lowry acids, they are proton donors. They are the most common type of organic acid. Among the simplest examples are formic acid H-COOH, that occurs in ants, and acetic acid CH_3-COOH, that gives vinegar its sour taste. Acids with two or more carboxyl groups are called **dicarboxylic**, **tricarboxylic**, etc. The simplest dicarboxylic example is oxalic acid $(COOH)_2$, which is just two connected carboxyls. Mellitic acid is an example of a hexacarboxylic acid. Other important natural examples are citric acid (in lemons) and tartaric acid (in tamarinds).



Carboxylate ion

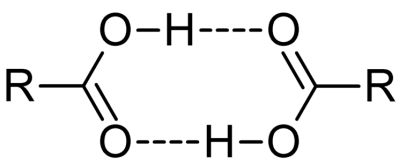
Salts and esters of carboxylic acids are called carboxylates. When a carboxyl group is deprotonated, its conjugate base, a carboxylate anion is formed. Carboxylate ions are resonance stabilized and this increased stability makes carboxylic acids more acidic than alcohols. Carboxylic acids can be seen as reduced or alkylated forms of the Lewis acid carbon dioxide; under some circumstances they can be decarboxylated to yield carbon dioxide.

Physical properties



The 3D structure of the carboxyl group

Solubility



Carboxylic acid dimers

Carboxylic acids are polar. Because they are both hydrogen-bond acceptors (the carbonyl) and hydrogen-bond donors (the hydroxyl), they also participate in hydrogen bonding. Together the hydroxyl and carbonyl group forms the functional group carboxyl. Carboxylic acids usually exist as dimeric pairs in nonpolar media due to their tendency to "self-associate." Smaller carboxylic acids (1 to 5 carbons) are soluble with water, whereas higher carboxylic acids are less soluble due to the increasing hydrophobic nature of the alkyl chain. These longer chain acids tend to be rather soluble in less-polar solvents such as ethers and alcohols.[3]

Boiling points

Carboxylic acids tend to have higher boiling points than water, not only because of their increased surface area, but because of their tendency to form stabilised dimers. Carboxylic acids tend to evaporate or boil as these dimers. For boiling to occur, either the dimer bonds must be broken, or the entire dimer arrangement must be vaporised, both of which increase enthalpy of vaporisation requirements significantly.

Acidity

Carboxylic acids are typically weak acids, meaning that they only partially dissociate into H^+ cations and $RCOO^-$ anions in neutral aqueous solution. For example, at room temperature, only 0.02 % of all acetic acid molecules are dissociated. Electronegative substituents give stronger acids.

Carboxylic Acids	**pKa**
Formic acid (HCO_2H)	3.77
Acetic acid (CH_3COOH)	4.76
Chloroacetic acid (CH_2ClCO_2H)	2.86
Dichloroacetic acid ($CHCl_2CO_2H$)	1.29
Trichloroacetic acid (CCl_3CO_2H)	0.65
Trifluoroacetic acid (CF_3CO_2H)	0.5
Oxalic acid (HO_2CCO_2H)	1.27
Benzoic acid ($C_6H_5CO_2H$)	4.2

Deprotonation of a carboxylic acid gives a carboxylate anion, which is resonance stabilized because the negative charge is shared (delocalized) between the two oxygen atoms increasing its stability. Each of the carbon-oxygen

bonds in a carboxylate anion has partial double-bond character.

Odor

Carboxylic acids often have strong odors, especially the volatile derivatives. Most common are acetic acid (vinegar) and butyric acid (rancid butter). On the other hand, esters of carboxylic acids tend to have pleasant odors and many are used in perfumes.

Nomenclature

The simplest series of carboxylic acids are the alkanoic acids, RCOOH, where R is a hydrogen or an alkyl group. Compounds may also have two or more carboxylic acid groups per molecule. The mono- and dicarboxylic acids have trivial names.[4]

Characterization

Carboxylic acids are most readily identified as such by infrared spectroscopy. They exhibit a sharp band associated with vibration of the C-O vibration bond ($\nu_{C=O}$) between 1680 and 1725 cm^{-1}. A characteristic ν_{O-H} band appears as a broad peak in the 2500 to 3000 cm^{-1} region.[3] By ^{1}H NMR spectrometry, the hydroxyl hydrogen appears in the 10-13 ppm region, although it is often either broadened or not observed owing to exchange with traces of water.

Occurrence and applications

Many carboxylic acids are produced industrially on a large scale. They are also pervasive in nature. Esters of fatty acids are the main components of lipids and polyamides of aminocarboxylic acids are the main components of proteins.

Carboxylic acids are used in the production of polymers, pharmaceuticals, solvents, and food additives. Industrially important carboxylic acids include acetic acid (component of vinegar, precursor to solvents and coatings), acrylic and methacrylic acids (precursors to polymers, adhesives), adipic acid (polymers), citric acid (beverages), ethylenediaminetetraacetic acid (chelating agent), fatty acids (coatings), maleic acid (polymers), propionic acid (food preservative), terephthalic acid (polymers).

Synthesis

Industrial routes

Industrial routes to carboxylic acids generally differ from those used on smaller scale because they require specialized equipment.

- Oxidation of aldehydes with air using cobalt and manganese catalysts. The required aldehydes are readily obtained from alkenes by hydroformylation.
- Oxidation of hydrocarbons using air. For simple alkanes, the method is nonselective but so inexpensive to be useful. Allylic and benzylic compounds undergo more selective oxidations. Alkyl groups on a benzene ring oxidized to the carboxylic acid, regardless of its chain length. Benzoic acid from toluene and terephthalic acid from para-xylene, and phthalic acid from ortho-xylene are illustrative large-scale conversions. Acrylic acid is generated from propene.[5]
- Base-catalyzed dehydrogenation of alcohols.
- Carbonylation is versatile method when coupled to the addition of water. This method is effective for alkenes that generate secondary and tertiary carbocations, e.g. isobutylene to pivalic acid. In the Koch reaction, the addition of water and carbon monoxide to alkenes is catalyzed by strong acids. Acetic acid and formic acid are produced by the carbonylation of methanol, conducted with iodide and alkoxide promoters, respectively and often with high

pressures of carbon monoxide, usually involving additional hydrolytic steps. Hydrocarboxylations involve the simultaneous addition of water and CO. Such reactions are sometimes called "Reppe chemistry":

$$HCCH + CO + H_2O \rightarrow CH_2{=}CHCO_2H$$

- Some long chain carboxylic acids are obtained by the hydrolysis of triglycerides obtained from plant or animal oils. These methods are related to soap making.
- fermentation of ethanol is used in the production of vinegar.

Laboratory methods

Preparative methods for small scale reactions for research or for production of fine chemicals often employ expensive consumable reagents.

- oxidation of primary alcohols or aldehydes with strong oxidants such as potassium dichromate, Jones reagent, potassium permanganate, or sodium chlorite. The method is amenable to laboratory conditions compared to the industrial use of air, which is “greener” since it yields less inorganic side products such as chromium or manganese oxides.
- Oxidative cleavage of olefins by ozonolysis, potassium permanganate, or potassium dichromate.
- Carboxylic acids can also be obtained by the hydrolysis of nitriles, esters, or amides, generally with acid- or base-catalysis.
- Carbonation of a Grignard and organolithium reagents:

$$RLi + CO_2 \; RCO_2Li$$

$$RCO_2Li + HCl \; RCO_2H + LiCl$$

- Halogenation followed by hydrolysis of methyl ketones in the haloform reaction
- The Kolbe-Schmitt reaction provides a route to salicylic acid, precursor to aspirin.

Less-common reactions

Many reactions afford carboxylic acids but are used only in specific cases or are mainly of academic interest:

- Disproportionation of an aldehyde in the Cannizzaro reaction
- Rearrangement of diketones in the benzilic acid rearrangement involving the generation of benzoic acids are the von Richter reaction from nitrobenzenes and the Kolbe-Schmitt reaction from phenols.

Reactions

The most widely practiced reactions convert carboxylic acids into esters, amides, carboxylate salts, acid chlorides, and alcohols. Carboxylic acids react with bases to form carboxylate salts, in which the hydrogen of the hydroxyl (-OH) group is replaced with a metal cation. Thus, acetic acid found in vinegar reacts with sodium bicarbonate (baking soda) to form sodium acetate, carbon dioxide, and water:

$$CH_3COOH + NaHCO_3 \rightarrow CH_3COO^-Na^+ + CO_2 + H_2O$$

Carboxylic acids also react with alcohols to give esters. This process is heavily used in the production of polyesters. Similarly carboxylic acids are converted into amides, but this conversion typically does not occur by direct reaction of the carboxylic acid and the amine. Instead esters are typical precursors to amides. The conversion of amino acids into peptides is a major biochemical process that requires ATP.

The hydroxyl group on carboxylic acids may be replaced with a chlorine atom using thionyl chloride to give acyl chlorides. In nature, carboxylic acids are converted to thioesters.

Carboxylic acid can be reduced to the alcohol by hydrogenation or using stoichiometric hydride reducing agents such as [lithium aluminium hydride].

N,N-dimethylchloromethylenammonium chloride is a highly chemoselective agent for carboxylic acid reduction. It selectively activate the carboxylic acid and is known to tolerate active functionalities such as ketone as well as the moderate ester, olefin, nitrile and halide moeties.[6]

Specialized reactions

- As with all carbonyl compounds, the protons on the α-carbon are labile due to keto-enol tautomerization. Thus the α-carbon is easily halogenated in the Hell-Volhard-Zelinsky halogenation.
- The Schmidt reaction converts carboxylic acids to amines.
- Carboxylic acids are decarboxylated in the Hunsdiecker reaction.
- The Dakin-West reaction converts an amino acid to the corresponding amino ketone.
- In the **Barbier-Wieland degradation**, the alpha-methylene group in an aliphatic carboxylic acid is removed in a sequence of reaction steps, effectively a chain-shortening.[7] [8] The inverse procedure is the Arndt-Eistert synthesis, where an acid is converted into acyl halide and reacts with diazomethane to give the highest homolog.
- Many acids undergo decarboxylation. Enzymes that catalyze these reactions are known as carboxylases (EC 6.4.1) and decarboxylases (EC 4.1.1).
- Carboxylic acids are reduced to aldehydes via the ester and DIBAL, via the acid chloride in the Rosenmund reduction and via the thioester in the Fukuyama reduction.

Nomenclature and examples

The carboxylate anion R-COO^- is usually named with the suffix *-ate*, so acetic acid, for example, becomes acetate ion. In IUPAC nomenclature, carboxylic acids have an *-oic acid* suffix (e.g., octadecanoic acid). In common nomenclature, the suffix is usually *-ic acid* (e.g., stearic acid).

Straight-Chained, Saturated Carboxylic Acids

Carbon atoms	Common name	IUPAC name	Chemical formula	Common location or use
1	Formic acid	Methanoic acid	HCOOH	Insect stings
2	Acetic acid	Ethanoic acid	CH_3COOH	Vinegar
3	Propionic acid	Propanoic acid	CH_3CH_2COOH	Preservative for stored grains
4	Butyric acid	Butanoic acid	$CH_3(CH_2)_2COOH$	Rancid butter
5	Valeric acid	Pentanoic acid	$CH_3(CH_2)_3COOH$	Valerian
6	Caproic acid	Hexanoic acid	$CH_3(CH_2)_4COOH$	Goat fat
7	Enanthic acid	Heptanoic acid	$CH_3(CH_2)_5COOH$	
8	Caprylic acid	Octanoic acid	$CH_3(CH_2)_6COOH$	Coconuts and breast milk
9	Pelargonic acid	Nonanoic acid	$CH_3(CH_2)_7COOH$	Pelargonium
10	Capric acid	Decanoic acid	$CH_3(CH_2)_8COOH$	
12	Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	Coconut oil and hand wash soaps.
14	Myristic acid	Tetradecanoic acid	$CH_3(CH_2)_{12}COOH$	Nutmeg
16	Palmitic acid	Hexadecanoic acid	$CH_3(CH_2)_{14}COOH$	Palm oil
18	Stearic acid	Octadecanoic acid	$CH_3(CH_2)_{16}COOH$	Chocolate, waxes, soaps, and oils
20	Arachidic acid	Icosanoic acid	$CH_3(CH_2)_{18}COOH$	Peanut oil

Other carboxylic acids

Compound class	Members
unsaturated monocarboxylic acids	acrylic acid (2-propenoic acid) – CH_2=CHCOOH, used in polymer synthesis
Fatty acids	medium to long-chain saturated and unsaturated monocarboxylic acids, with even number of carbons examples docosahexaenoic acid and eicosapentaenoic acid (nutritional supplements)
Amino acids	the building blocks of proteins
Keto acids	acids of biochemical significance that contain a ketone group e.g. acetoacetic acid and pyruvic acid
Aromatic carboxylic acids	benzoic acid, the sodium salt of benzoic acid is used as a food preservative , salicylic acid – a beta hydroxy type found in many skin care products
Dicarboxylic acids	containing two carboxyl groups examples adipic acid the monomer used to produce nylon and aldaric acid – a family of sugar acids
Tricarboxylic acids	containing three carboxyl groups example citric acid – found in citrus fruits and isocitric acid
Alpha hydroxy acids	containing a hydroxy group example glyceric acid, glycolic acid and lactic acid (2-hydroxypropanoic acid) – found in sour milk tartaric acid - found in wine

Carboxyl radical

The radical ·COOH (CAS# 2564-86-5) has only a separate fleeting existence.[9] The acid dissociation constant of ·COOH has been measured using electron paramagnetic resonance spectrocopy.[10] The carboxyl group tends to dimerise to form oxalic acid.

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[10] The value is pK_a = -0.2 ± 0.1.Jeevarajan, A. S.; Carmichael, I.; Fessenden, R. W. (1990). "ESR Measurement of the pKa of Carboxyl Radical and Ab Initio Calculation of the C-13 Hyperfine Constant". *Journal of Physical Chemistry* **94** (4): 1372–1376. doi:10.1021/j100367a033.

External links

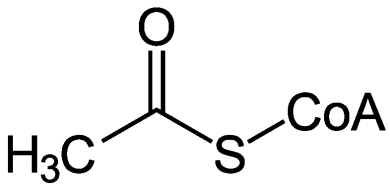
- Carboxylic acids synthesis - Collection of links pertaining to synthesis of Carboxylic acid (http://www.uduko.com/topic_detail/details/40)
- Carboxylic acids pH and titration - freeware for calculations, data analysis, simulation, and distribution diagram generation (http://www2.iq.usp.br/docente/gutz/Curtipot_.html)

Citrate synthase

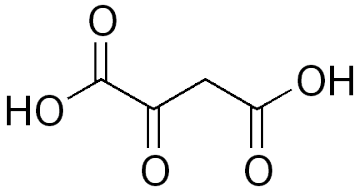
Citrate synthase	
Identifiers	
Symbol	CS
Entrez	1431 [1]
HUGO	2422 [2]
OMIM	118950 [3]
UniProt	O75390 [4]
Other data	
EC number	2.3.3.1 [5]
Locus	Chr. 12 *p11-qter* [6]

The enzyme **citrate synthase** (E.C. 2.3.3.1 [previously 4.1.3.7]) exists in nearly all living cells and stands as a pace-making enzyme in the first step of the Citric Acid Cycle (or Krebs Cycle).[7] Citrate synthase is localized within eukaryotic cells in the mitochondrial matrix, but is encoded by nuclear DNA rather than mitochondrial. It is synthesized using cytoplasmic ribosomes, then transported into the mitochondrial matrix. Citrate synthase is commonly used as a quantitative enzyme marker for the presence of intact mitochondria.

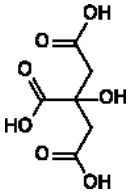
Citrate synthase catalyzes the condensation reaction of the two-carbon acetate residue from acetyl coenzyme A and a molecule of four-carbon oxaloacetate to form the six-carbon citrate.[8] Oxaloacetate will be regenerated after the completion of one round of the Krebs Cycle.



acetyl-CoA



Oxaloacetic acid

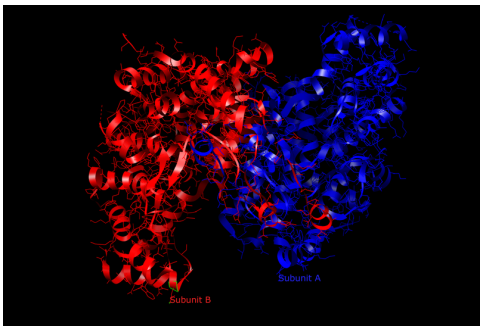


Citric acid

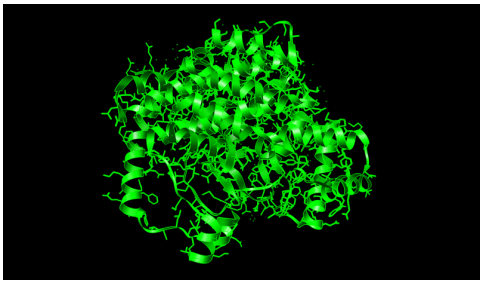
acetyl-CoA + oxaloacetate + H_2O → citrate + CoA-SH

Oxaloacetate is the first substrate to bind to the enzyme. This induces the enzyme to change its conformation, and creates a binding site for the acetyl-CoA. Only when this citroyl-CoA has formed will another conformational change cause thioester hydrolysis and release coenzyme A. This ensures that the energy released from the thioester bond cleavage will drive the condensation.

Structure



The Active Site of Citrate Synthase (open form)

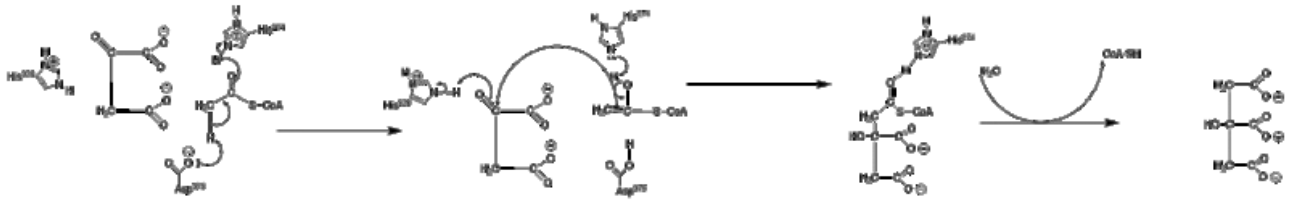


The Active Site of Citrate Synthase (closed form)

Citrate synthase's 437 amino acid residues are organized into two main subunits, each consisting of 20 alpha-helices. These alpha helices compose approximately 75% of citrate synthase's tertiary structure, while the remaining residues mainly compose irregular extensions of the structure, save a single beta-sheet of 13 residues. Between these two subunits, a single cleft exists containing the active site. Two binding sites can be found therein: one reserved for citrate or oxaloacetate and the other for Coenzyme A. The active site contains three key residues: His274, His320, and Asp375 that are highly selective in their interactions with substrates. The image to the right highlights the three key amino acids of citrate synthase's active site in its open state (the substrate is absent).[9] The specific atoms involved in interactions are designated by color, and both a drawing and video of their mechanism can be found in the section labeled "Mechanism" below. The images to the left display the tertiary structure of citrate synthase in its opened and closed form. The enzyme changes from opened to closed with the addition of one of its substrates (such as oxaloacetate).[10]

Mechanism

Citrate Synthase has three key amino acids in its active site which catalyze the conversion of acetyl-CoA (H_3CCO-SCoA) and oxaloacetate (COO-CH_2COCOO-) into citrate (COO-CH_2COHCOOCH_2COO-) and H-SCoA in an aldol condensation reaction. This conversion begins with the negatively charged oxygen in Asp375's R-group deprotonating acetyl CoA's alpha carbon. This pushes the e- to form a double-bond with the carbonyl carbon, which in turn forces the C=O up to pick up a proton for the oxygen from one of the nitrogens in the R-group of His274. This neutralizes the R-group (by forming a lone pair on the nitrogen) and completes the formation of an enol intermediate (CH_2COH-SCoA). At this point, His274's amino lone pair formed in the last step attacks the proton that was added to the oxygen in the last step. The oxygen then reforms the carbonyl bond, which frees half of the C=C to initiate a nucleophilic attack to oxaloacetate's carbonyl carbon (COO-CH_2COCOO-). This frees half of the carbonyl bond to deprotonate one of His320's amino groups, which neutralizes one of the nitrogens in its R-group. This nucleophilic addition results in the formation of citroyl-CoA ($COOCH_2CHCOOCH_2COHSCoA^{2-}$). At this point, a water molecule is brought in and is deprotonated by His320's amino group and Hydrolysis is initiated. One of the oxygen's lone pairs nucleophilically attacks the carbonyl carbon of citroyl-CoA. This forms a tetrahedral intermediate and results in the ejection of −SCoA as the carbonyl reforms. The −SCoA is protonated to form HSCoA. Finally, the hydroxyl added to the carbonyl in the previous step is deprotonated and citrate (-$COOCH_2COHCOO-CH_2COO$-) is formed.[11]



Mechanism for Citrate Synthase (including residues involved)

This link [12] connects to a video demonstrating citrate synthase's mechanism from Lehninger's Principles of Biochemistry page.[13]

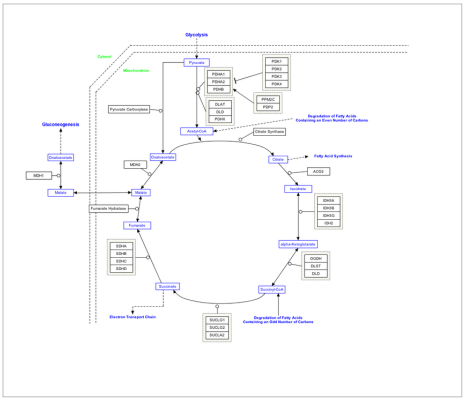
Inhibition

The enzyme is inhibited by high ratios of ATP:ADP, acetyl-CoA:CoA, and NADH:NAD, as high concentrations of ATP, acetyl-CoA, and NADH show that the energy supply is high for the cell. It is also inhibited by succinyl-CoA and citrate, examples of product inhibition. The inhibition of citrate synthase by acetyl-CoA analogues has also been well documented and has been used to prove the existence of a single active site. These experiments have revealed that this single site alternates between two forms, which participate in ligase and hydrolase activity respectively.[14]

Interactive pathway map

Click on genes, proteins and metabolites below to link to respective articles. [15]

[[File:



{{{bSize}}}px

Citric acid cycle edit [16]

External links

- MeSH *Citrate+synthase* [17]

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[13] Lehninger (2005). Principles of Biochemistry: Fourth Edition. W.H. Freeman and Co. Pages 608-609.

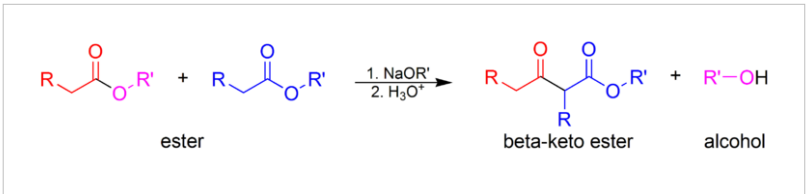
[14] Ernat BAYER, Barbara BAUER, and Hermann EGGERER (1981). "Evidence from Inhibitor Studies for Conformational Changes of Citrate Synthase." Eur J Biochem. 120, 155-160 (http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1432-1033.1981.tb05683.x)

[15] The interactive pathway map can be edited at WikiPathways: "TCACycle_WP78" (http://www.wikipathways.org/index.php/Pathway:WP78). .

[16] http://www.wikipathways.org/index.php/Pathway:WP78

[17] http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?mode=&term=Citrate+synthase

Claisen condensation



The **Claisen condensation** (not to be confused with the Claisen rearrangement) is a carbon-carbon bond forming reaction that occurs between two esters or one ester and another carbonyl compound in the presence of a strong base, resulting in a β-keto ester or a β-diketone[1] . It is named after Rainer Ludwig Claisen, who first published his work on the reaction in 1881 [2] [3] [4] .

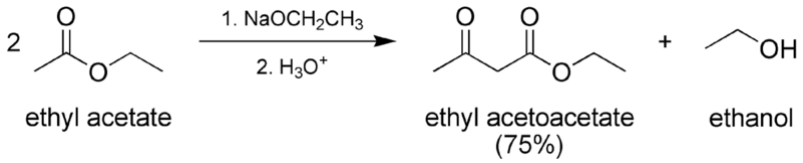
Requirements

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

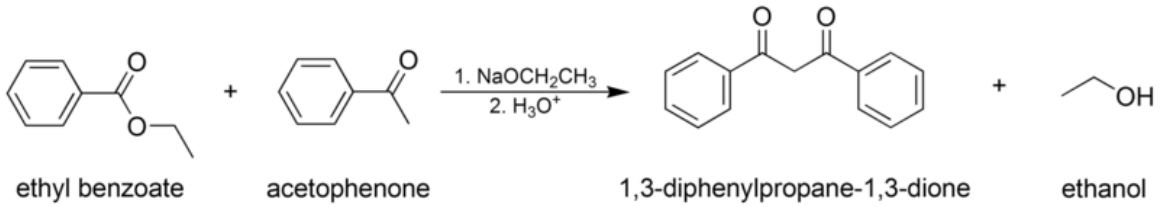
The base used must not interfere with the reaction by undergoing nucleophilic substitution or addition with a carbonyl carbon. For this reason, the conjugate sodium alkoxide base of the alcohol formed (e.g. sodium ethoxide if ethanol is formed) is often used, since the alkoxide is regenerated. In mixed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

The alkoxy portion of the ester must be a good leaving group. Methyl and ethyl esters, which yield the methoxy and ethoxy leaving groups, respectively, are usually used.

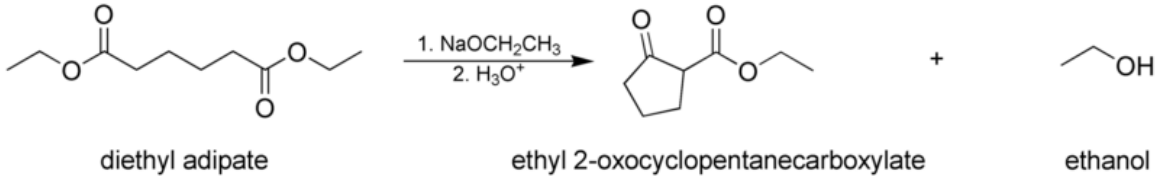
Types



The classic Claisen condensation, where only one enolizable ester is used.

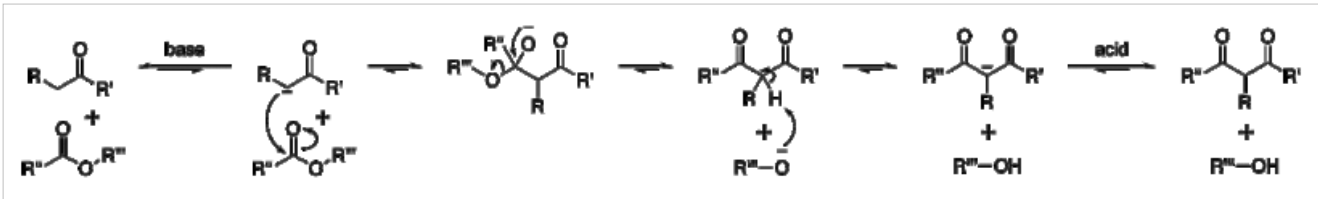


The mixed (or "crossed") Claisen condensation, where an enolizable ester or ketone and a nonenolizable ester are used.



The Dieckmann condensation, where a molecule with two ester groups reacts intramolecularly, forming a cyclic β-keto ester. In this case, the ring formed must not be strained, usually a 5- or 6-membered chain or ring.

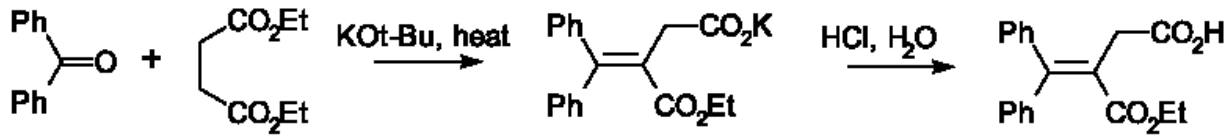
Mechanism



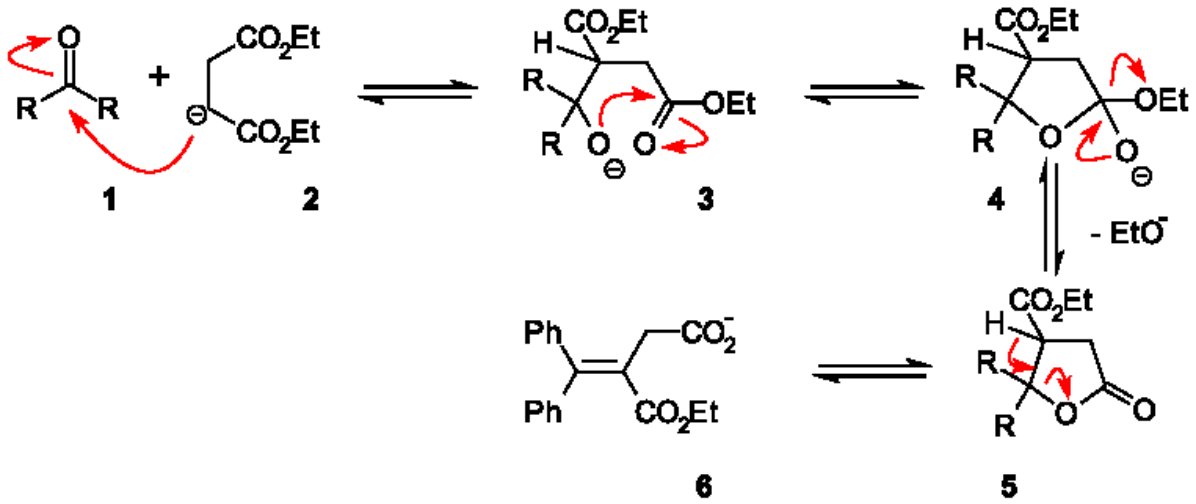
In the first step of the mechanism, an α-proton is removed by a strong base, resulting in the formation an enolate anion, which is made relatively stable by the delocalization of electrons. Next, the carbonyl carbon of the (other) ester is nucleophilically attacked by the enolate anion. The alkoxy group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

Stobbe condensation

The **Stobbe condensation** [5] is a modification specific for the diethyl ester of succinic acid requiring less strong bases [6] . An example is its reaction with benzophenone [7] :



A reaction mechanism which explains the formation of both an ester group and a carboxylic acid group is centered around a lactone intermediate (**5**):



References

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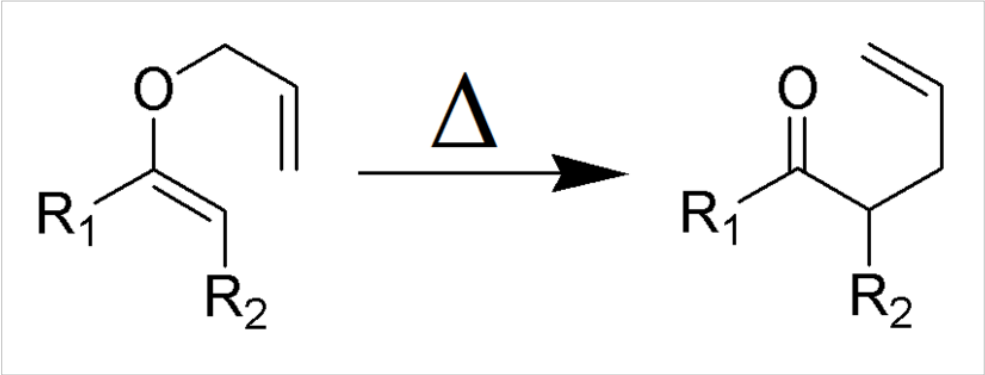
External links

- Organic Chemistry Portal: Claisen Condensation (http://www.organic-chemistry.org/namedreactions/claisen-condensation.shtm)

Claisen rearrangement

The Claisen rearrangement (not to be confused with the Claisen condensation) is a powerful carbon-carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen. The heating of an allyl vinyl ether will initiate a [3,3]-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 (and its variants) are exothermic (about 84 kJ/mol), concerted pericyclic reactions which according to the Woodward-Hoffmann rules show a suprafacial reaction pathway.

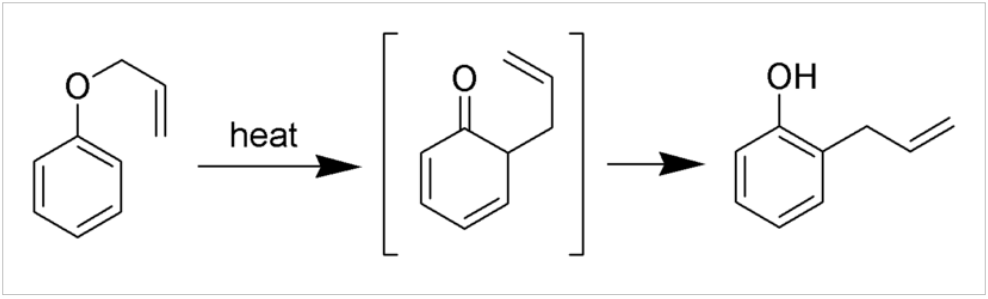
There are substantial solvent effects in the Claisen reactions. More polar solvents tend to accelerate the reaction to a greater extent. Hydrogen-bonding solvents gave the highest rate constants. For example, ethanol/water solvent mixtures give rate constants 10-fold higher than sulfolane.[1][2]

Trivalent organoaluminium reagents, such as trimethylaluminium, have been shown to accelerate this reaction.[8] [9]

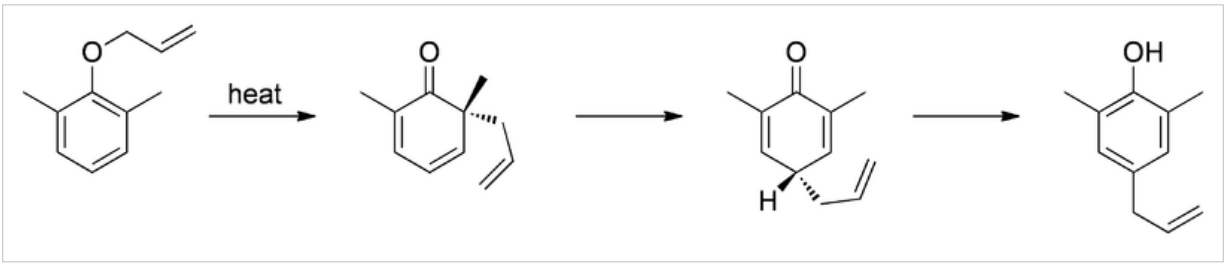
Variations

Aromatic Claisen rearrangement

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

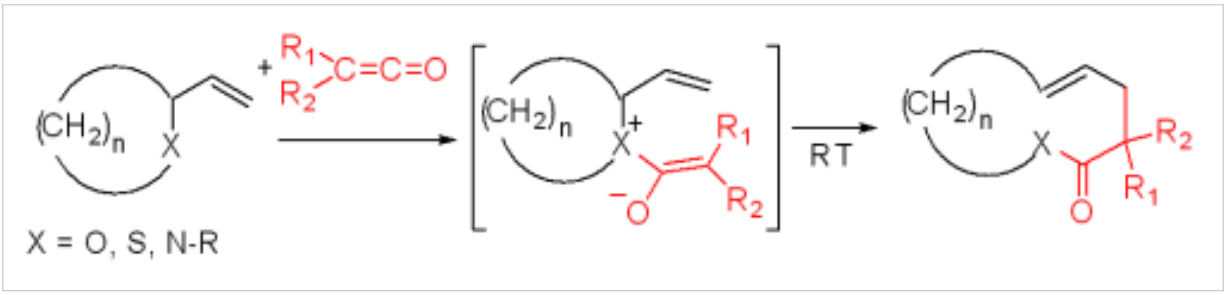


If ortho position is substituted then reaction goes to para position with retention in configration.[10]



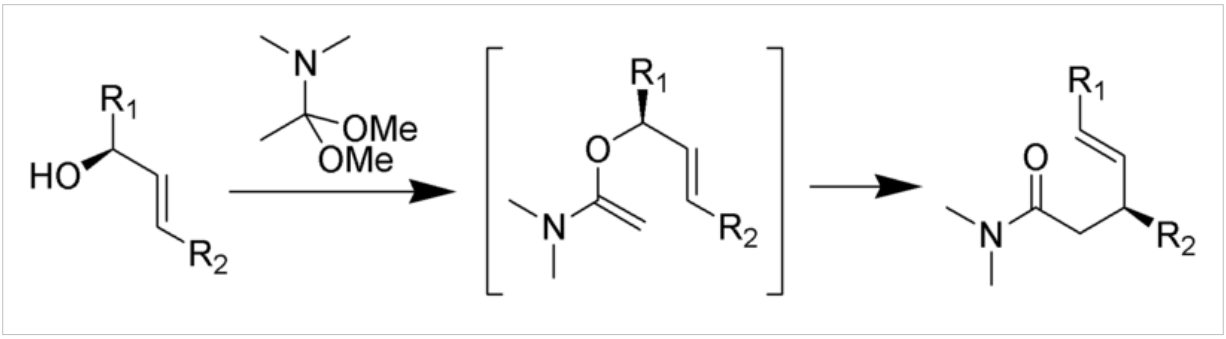
Bellus-Claisen rearrangement

The *Bellus-Claisen rearrangement* is the reaction of allylic ethers, amines, and thioethers with ketenes to give γ,δ-unsaturated esters, amides, and thioesters.[11] [12] [13]

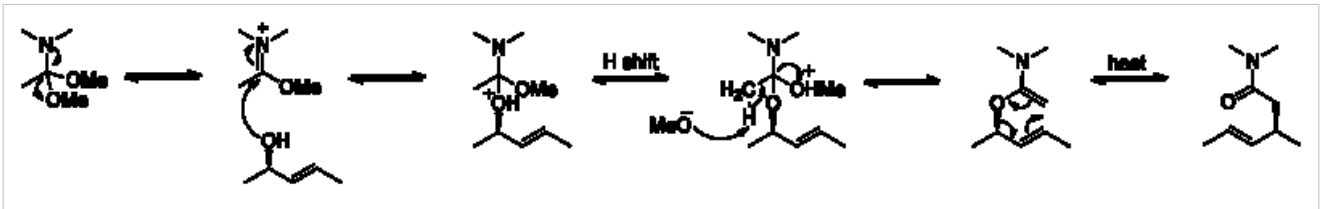


Eschenmoser-Claisen rearrangement

The *Eschenmoser-Claisen rearrangement* proceeds from an allylic alcohol to a γ,δ-unsaturated amide, and was developed by Albert Eschenmoser in 1964.[14] [15]

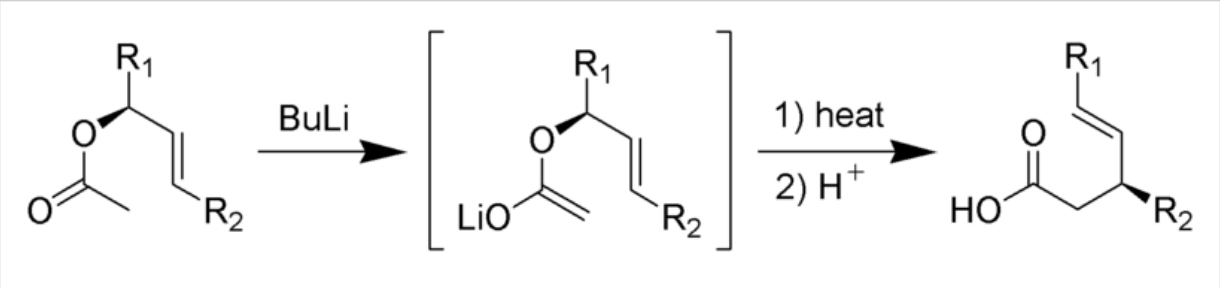


Mechanism:[10]

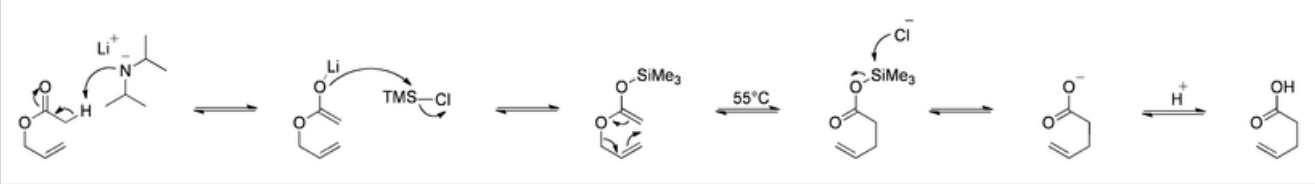


Ireland-Claisen rearrangement

The *Ireland-Claisen rearrangement* is the reaction of an allylic acetate with strong base (such as Lithium diisopropylamide) to give a γ,δ-unsaturated carboxylic acid.[16] [17] [18]

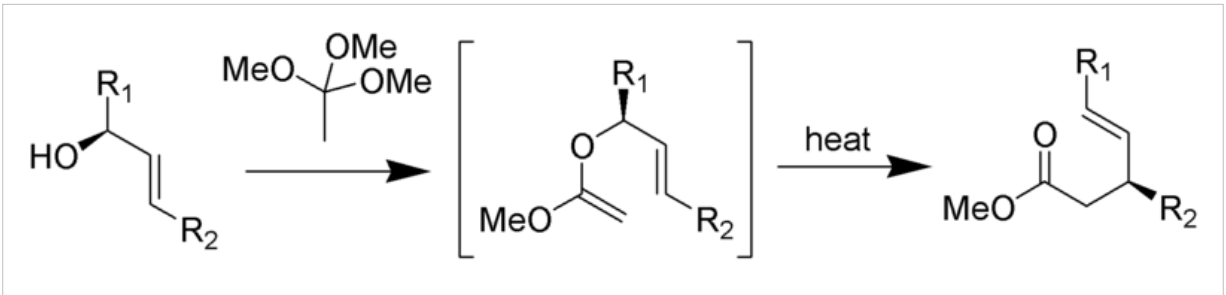


Mechanism:[10]

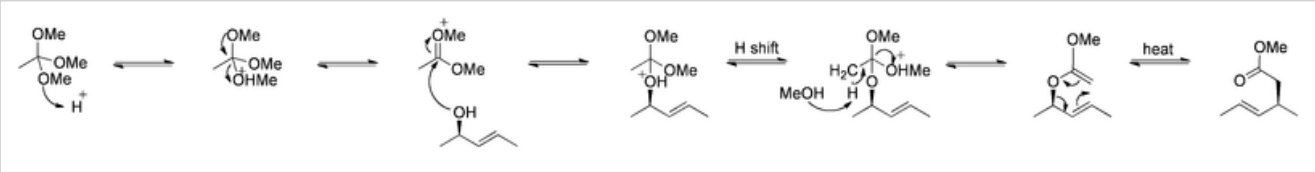


Johnson-Claisen rearrangement

The *Johnson-Claisen rearrangement* is the reaction of an allylic alcohol with trimethyl orthoacetate to give a γ,δ-unsaturated ester.[19]



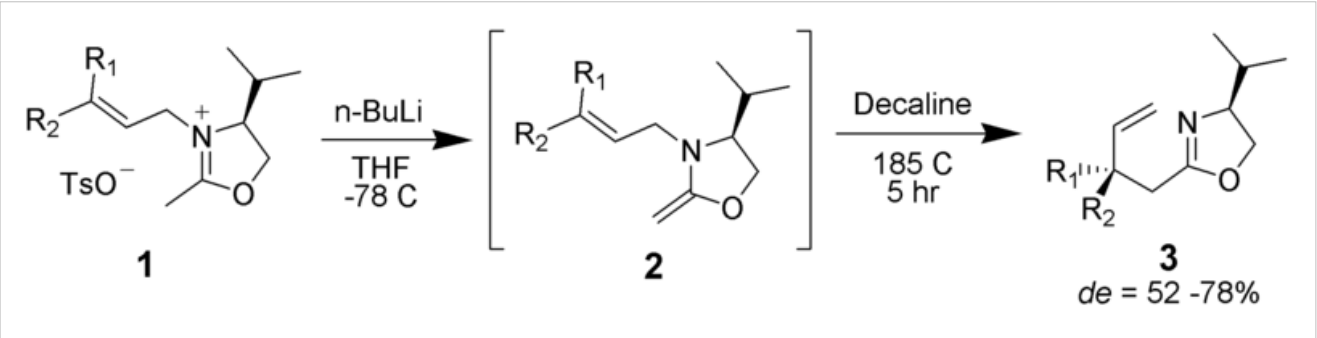
Mechanism:[10]



Hetero-Claisens

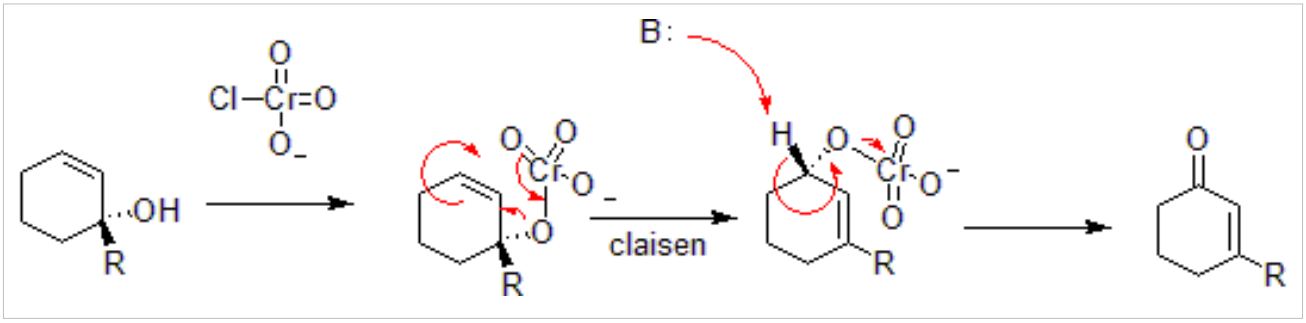
Aza-Claisen

An iminium can serve as one of the pi-bonded moieties in the rearrangement.[20]



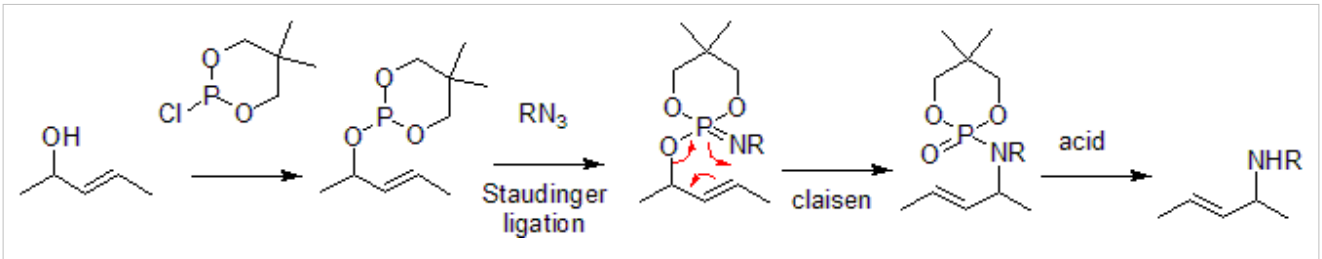
Chromium Oxidation

Chromium can oxidize allylic alcohols to alpha-beta unsaturated ketones on the opposite side of the unsaturated bond from the alcohol. This is via a concerted hetero-claisen reaction, although there are mechanistic differences since the chromium atom has access to d- shell orbitals which allow the reaction under a less constrained set of geometries.[21] [22]



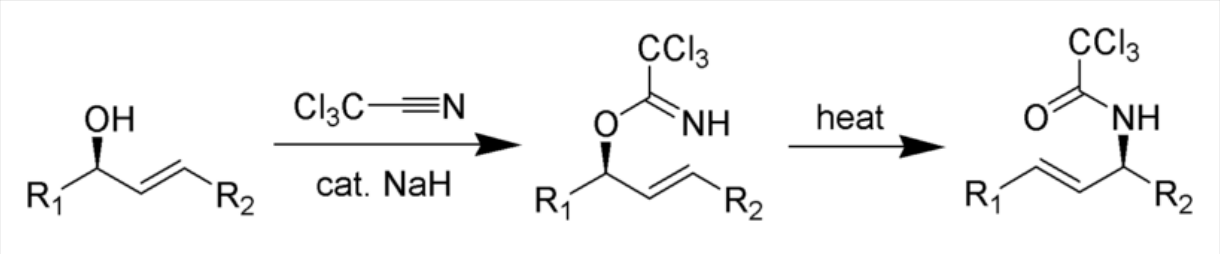
Chen-Mapp Reaction

The **Chen-Mapp reaction** also known as the **[3,3]-Phosphorimidate Rearrangement** or **Staudinger-Claisen Reaction** installs a phosphite in the place of an alcohol and takes advantage of the Staudinger Ligation to convert this to an imine. The subsequent claisen is driven by the fact that a P=O double bond is more energetically favorable than a P=N double bond.[23]



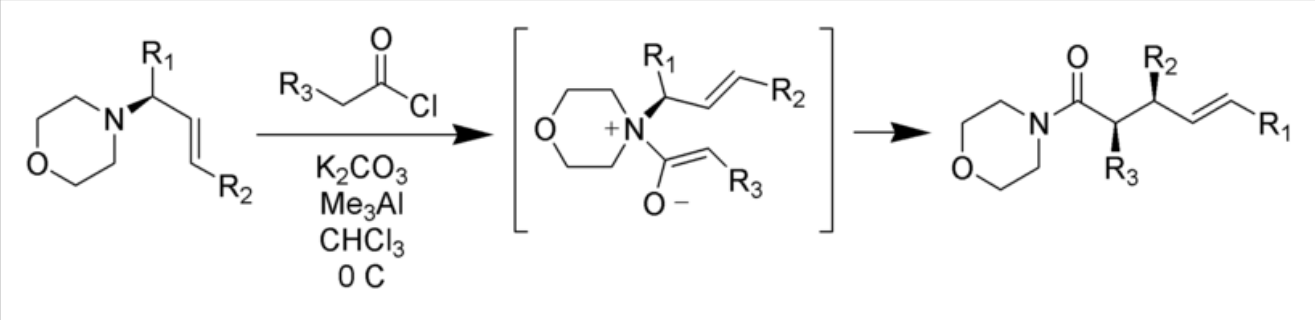
Overman rearrangement

The Overman rearrangement (named after Larry Overman) is a Claisen rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.[24] [25] [26]



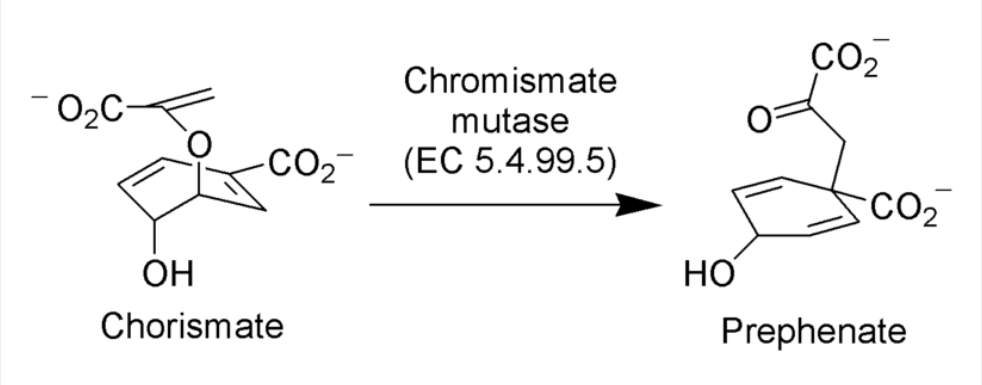
Zwitterionic Claisen rearrangement

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.[27] [28]



Claisen rearrangement in nature

The enzyme Chorismate mutase (EC 5.4.99.5) catalyzes the Claisen rearrangement of chorismate ion to prephenate ion, a key intermediate in the shikimic acid pathway (the biosynthetic pathway towards the synthesis of phenylalanine and tyrosine).[29]



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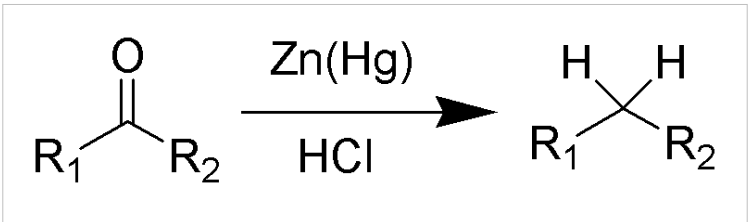
Clemmensen reduction

Clemmensen reduction is a chemical reaction described as a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and hydrochloric acid.[1] [2] [3] This reaction is named after Erik Christian Clemmensen, a Danish chemist.[4]



The Clemmensen reduction is particularly effective at reducing aryl-alkyl ketones.[5] [6] With aliphatic or cyclic ketones, zinc metal reduction is much more effective.[7]

The substrate must be stable in the strongly acidic conditions of the Clemmensen reduction. Acid sensitive substrates should be reacted in the Wolff-Kishner reduction, which utilizes strongly basic conditions. As a result of Clemmensen Reduction, the carbon of the carbonyl group involved is converted from sp^2 hybridisation to sp^3 hybridisation. The oxygen atom is lost in the form of one molecule of water.

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Covalent organic framework

The design and synthesis of crystalline extended organic structures in which the building blocks are linked by strong covalent bonds are core concepts of covalent organic frameworks (COFs). COFs are porous, and crystalline, and made entirely from light elements (H, B, C, N, and O) that are known to form strong covalent bonds in well-established and useful materials such as diamond, graphite, and boron nitride.

The successful realization of COF materials through molecular building blocks would provide covalent frameworks that could be functionalized into lightweight materials optimized for gas storage, photonic, and catalytic applications.[1]

Introduction

What are "Porous Crystalline Solids"?

Porous crystalline solids consists of secondary building units (SBUs) which assemble to form a periodic and porous framework.

An almost infinte numbers of frameworks can be formed through various SBU combinations leading to unique material properties for applications in separations, storage, and heterogeneous catalysis.[2]

Porous crystalline solids can be used to describe materials such as Zeolite, Metal-organic frameworks (MOFs), and Covalent Organic Frameworks (COFs).

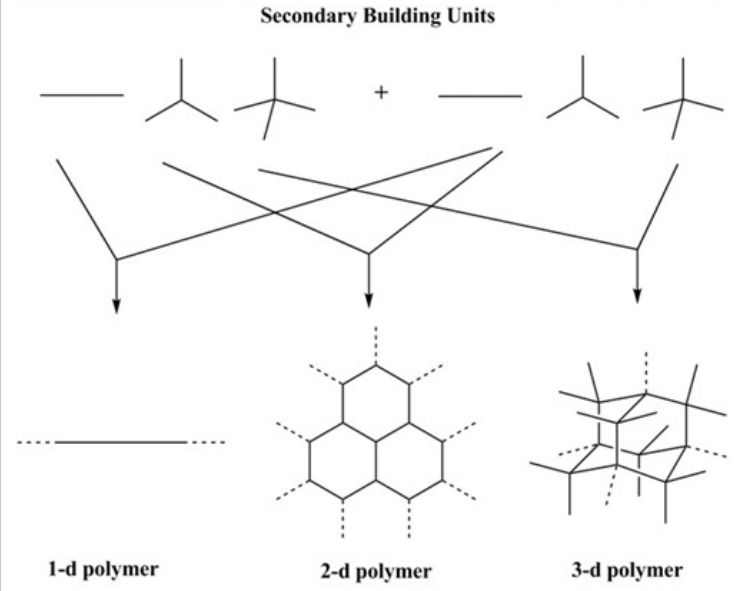
Zeolites are microporous, aluminosilicate minerals commonly used as commercial adsorbents.

MOFs are a class of porous polymeric material, consisting of metal ions linked together by organic bridging ligands and are a new development on the interface between molecular coordination chemistry and materials science.[3]

COFs are another class of porous polymeric materials, consisting of porous, crystalline, covalent bonds that usually have rigid structures, exceptional thermal stabilities (to temperatures up to 600℃), and low densities. They exhibit permanent porosity with specific surface areas surpassing those of well-known zeolites and porous silicates.[1]

Secondary building units

The term 'secondary building unit' has been used for some time to describe conceptual fragments which can be compared as bricks used to build a house of zeolites; in the context of this page it refers to the geometry of the units defined by the points of extension.[4]



Schematic Figure of Reticular Chemistry.

Concept of "Reticular Synthesis"

Although the synthesis of new materials has long been recognized as the most essential element in advancing technology, it generally remains more of an art than a science—in that the discovery of new compounds has mostly been serendipitous,

using methods referred to by critics as ‘shake and bake’, ‘mix and wait’ and ‘heat and beat’. It was caused by that the starting entities do not maintain their structure during the reaction, leading to poor correlation between reactants and products. However, the design of an extended network that will maintain their structural integrity throughout the construction process can be realized by starting with well-defined and rigid molecular building blocks.

In essence, reticular synthesis can be described as the process of assembling judiciously designed rigid secondary building units into **predetermined ordered structures** (networks), which are held together by strong bonding. It is different from retrosynthesis of organic compounds, because the structural integrity and rigidity of the building blocks in reticular synthesis remain unaltered throughout the construction process—an important aspect that could help to fully realize the benefits of design in crystalline solid-state frameworks. Similarly, reticular synthesis should be distinguished from supramolecular assembly, because in the former, building blocks are linked by strong bonds throughout the crystal.[4]

Application

Hydrogen Uptake

Omar M. Yaghi and William A. Goddard III reported COFs as exceptional hydrogen storage materials. They predicted the highest excess H_2 uptakes at 77 K are 10.0 wt % at 80 bar for COF-105, and 10.0 wt % at 100 bar for COF-108, which have higher surface area and free volume, by grand canonical Monte Carlo (GCMC) simulations as a function of temperature and pressure. This is the highest value reported for associative H_2 storage of any material. Thus 3-D COFs are most promising new candidates in the quest for practical H_2 storage materials.[5]

Optical Properties

The ultimate highly ordered π-conjugation TP-COF, consisting of pyrene and triphenylene functionalities alternately linked in a mesoporous hexagonal skeleton, is highly luminescent, harvests a wide wavelength range of photons, and allows energy transfer and migration. Furthermore, TP-COF is electrically conductive and capable of repetitive on–off current switching at room temperature. [2]

Potential Applications

Most studies to date have focused on the development of synthetic methodologies with the aim of maximizing pore size and surface area for gas storage. That means the functions of COFs have not yet been well explored, but COFs can be used as catalyst, or gas separation etc. [1]

History

Frontiers of COF: Omar M. Yaghi

Omar M. Yaghi, a professor at the University of California, Los Angeles and Adrien P Cote published the first paper of COF.[1] They reported the design and successful synthesis of COFs by condensation reactions of phenyl diboronic acid $\{C_6H_4[B(OH)_2]_2\}$ and hexahydroxytriphenylene $[C_{18}H_6(OH)_6]$. Powder X-ray diffraction studies of the highly crystalline products $(C_3H_2BO)_6\&(C_9H_{12})_1$ (COF-1) and $C_9H_4BO_2$ (COF-5) revealed 2-dimensional expanded porous graphitic layers that are either staggered (COF-1, P63/mmc) or eclipsed (COF-5, P6/mmm). Their crystal structures are entirely held by strong bonds between B, C, and O atoms to form rigid porous architectures with pore sizes ranging from 7 to 27 angstroms. COF-1 and COF-5 exhibit high thermal stability (to temperatures up to 500 to 600℃), permanent porosity, and high surface areas (711 and 1590 square meters per gram, respectively). [1]

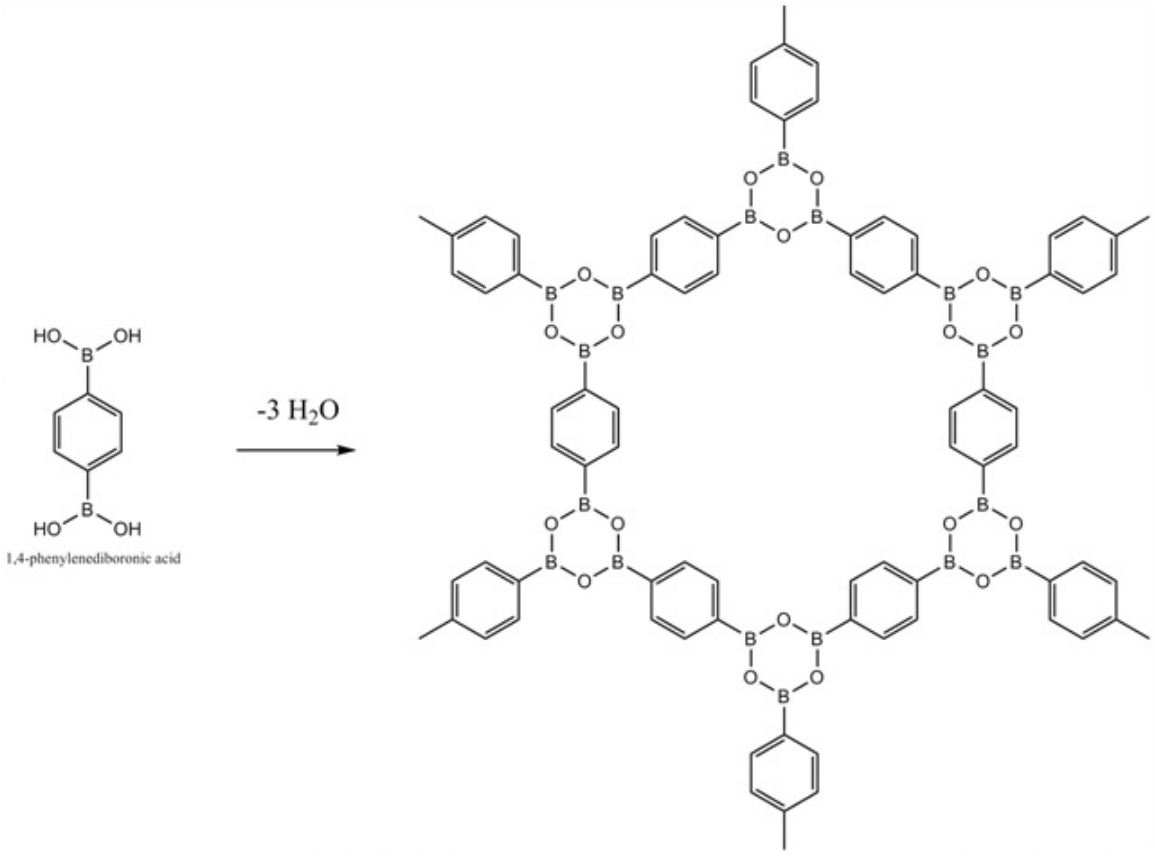
Second generation: 3D COFs

The synthesis of 3D COFs has been hindered by longstanding practical and conceptual challenges. Unlike 0D and 1D system, the insolubility of 2D and 3D structures precludes the use of stepwise synthesis, making their isolation in crystalline form very difficult. The first challenge, however, was overcome by judiciously choosing building blocks and using reversible condensation reactions to crystallize COFs. Examples of 3D COFs are COF-102, 103, 105, 108, 202, and 300. Most of 3D COF show **high surface area**, which surpass those of 2D (3472, 4210, 3214, square meters per gram for COF-102, 103, and 202 respectively). COF-105 and 108 calaulated theoretically to perform **exceptional hydrogen storage** function which is the highest value reported for associative H_2 storage of any material.[1]

Synthetic Chemistry of COFs

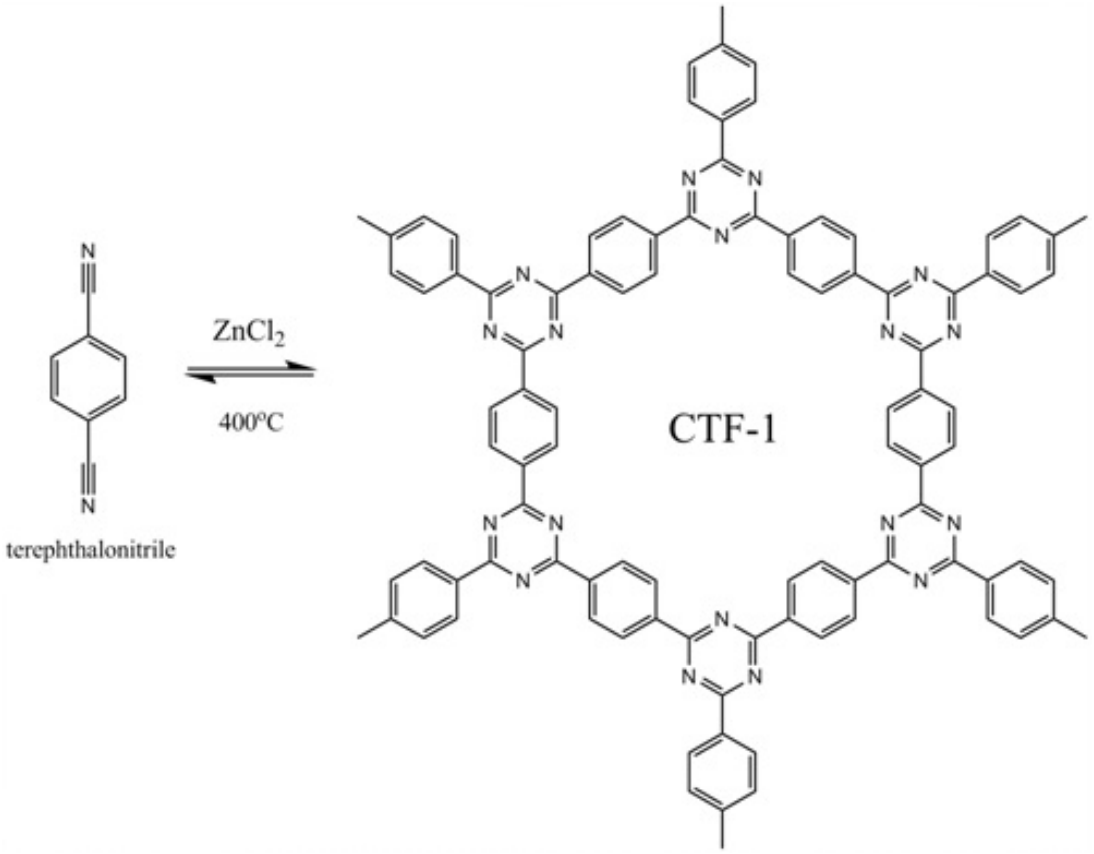
Boron Condensation

The most popular COF synthesis route is a boron condensation reaction which is a molecular dehydration reaction between boronic acids. In case of COF-1, three boronic acid molecules converge to form a planar six-membered B_3O_3 (boroxine) ring with the elimination of three water molecules.[1]



Triazine based trimerization

Another class of high performance polymer frameworks with regular porosity and high surface area is based on triazine materials which can be achieved by dynamic trimerization reaction of simple, cheap, and abundant aromatic nitriles in ionothermal conditions (molten zinc chloride at high temperature (400℃)). CTF-1 is a good example of this chemistry.[6]



Imine condensation

A new class of COFs can be obtained by imine condensation of aniline with benzaldehyde that results in imine bond formation with elimination of water. COF-300 is a good example of this chemistry.[5]

Characterization

Even though COFs are usually harder to characterize properties than MOFs because COFs have no single crystal structure, COFs can be characterized by some following methods. Powder X-ray diffraction (PXDR) is used to determine structure. Morphology is understood by scanning electron microscopy (SEM). Finally, porosity, in most cases surface area, is measured by a N_2 sorption isotherm.

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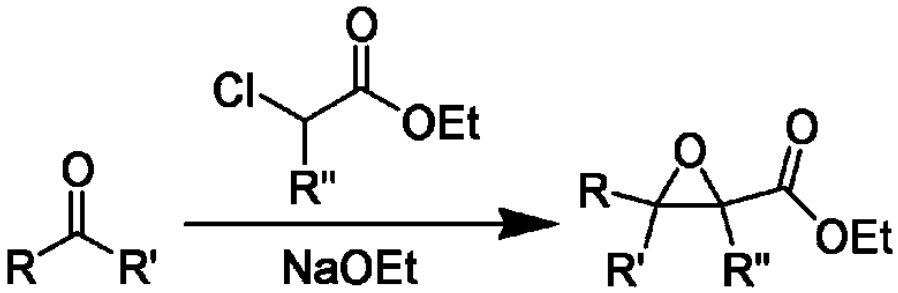
External links

http://yaghi.chem.ucla.edu/

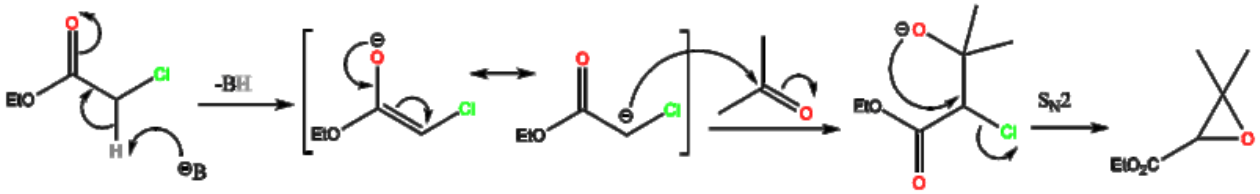
Darzens reaction

The **Darzens reaction** (also known as the **Darzens condensation** or **glycidic ester condensation**) is the chemical reaction of a ketone or aldehyde with an α-haloester to form an α,β-epoxy ester, also called a "glycidic ester".[1] [2] This reaction was discovered by the organic chemist Auguste George Darzens in 1904.[3]



Reaction mechanism

The reaction process begins when a strong base is used to form a carbanion at the halogenated position. Because of the ester, this carbanion is a resonance-stabilized enolate, which makes it relatively easy to form. This nucleophilic structure attacks another carbonyl component, forming a new carbon–carbon bond. These first two steps are similar to a base-catalyzed aldol reaction. The oxygen anion in this aldol-like product then does an intramolecular S_N2 attack on the formerly-nucleophilic halide-bearing position, displacing the halide to form an epoxide.[4] This reaction sequence is thus a condensation reaction, since there is a net loss of HCl when the two reactant molecules join.



The primary role of the ester is to enable the initial deprotonation to occur, and other carbonyl functional groups can be used instead. If the starting material is an α-halo amide, the product is an α,β-epoxy amide.[5] If an α-halo ketone is used, the product is an α,β-epoxy ketone.[4]

Any sufficiently strong base can be used for the initial deprotonation. However, if the starting material is an ester, the alkoxide corresponding to the ester side-chain is commonly in order to prevent complications due to potential acyl exchange side reactions.

Stereochemistry

Depending on the specific structures involved, the epoxide may exist in *cis* and *trans* forms. A specific reaction may give only *cis*, only *trans*, or a mixture of the two. The specific stereochemical outcome of the reaction is affected by several aspects of the intermediate steps in the sequence.

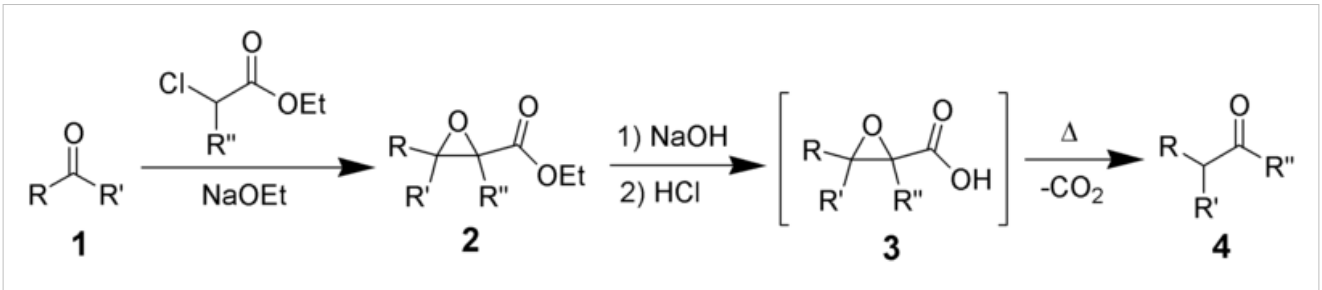
The initial stereochemistry of the reaction sequence is established in the step where the carbanion attacks the carbonyl. Two sp^3 (tetrahedral) carbons are created at this stage, which allows two different diastereomeric possibilities of the halohydrin intermediate. The most likely result is due to chemical kinetics: whichever product is easier and faster to form will be the major product of this reaction. The subsequent S_N2 reaction step proceeds with stereochemical inversion, so the *cis* or *trans* form of the epoxide is controlled by the kinetics of an intermediate step. Alternately, the halohydrin can epimerize due to the basic nature of the reaction conditions prior to the S_N2 reaction. In this case, the initially formed diastereomer can convert to a different one. This is an equilibrium process, so the *cis* or *trans* form of the epoxide is controlled by chemical thermodynamics--the product resulting from the more stable diastereomer, regardless of which one was the kinetic result.[5]

Alternative reactions

Glycidic esters can also be obtained via nucleophilic epoxidation of an α,β-unsaturated ester, but that approach requires synthesis of the alkene substrate first whereas the Darzens condensation allows formation of the carbon–carbon connectivity and epoxide ring in a single reaction.

Subsequent reactions

The product of the Darzens reaction can be reacted further to form various types of compounds. Hydrolysis of the ester can lead to decarboxylation, which triggers a rearrangement of the epoxide into a carbonyl (**4**). Alternately, other epoxide rearrangements can be induced to form other structures.



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Review articles

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- Ballester, M. (1955). "Mechanisms of The Darzens and Related Condensations Manuel Ballester". *Chem. Rev.* **55**: 283. doi:10.1021/cr50002a002.
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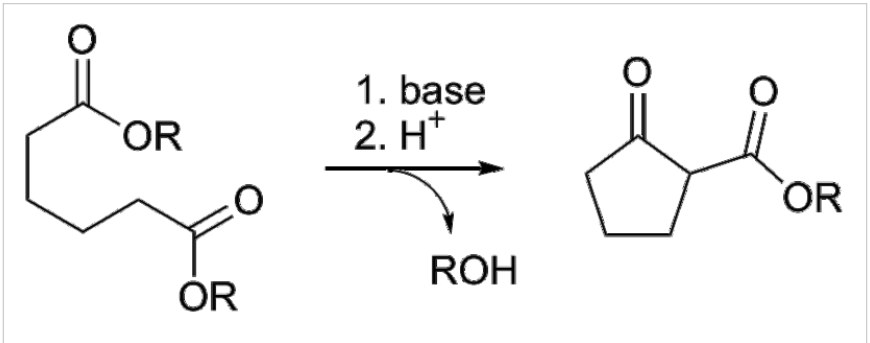
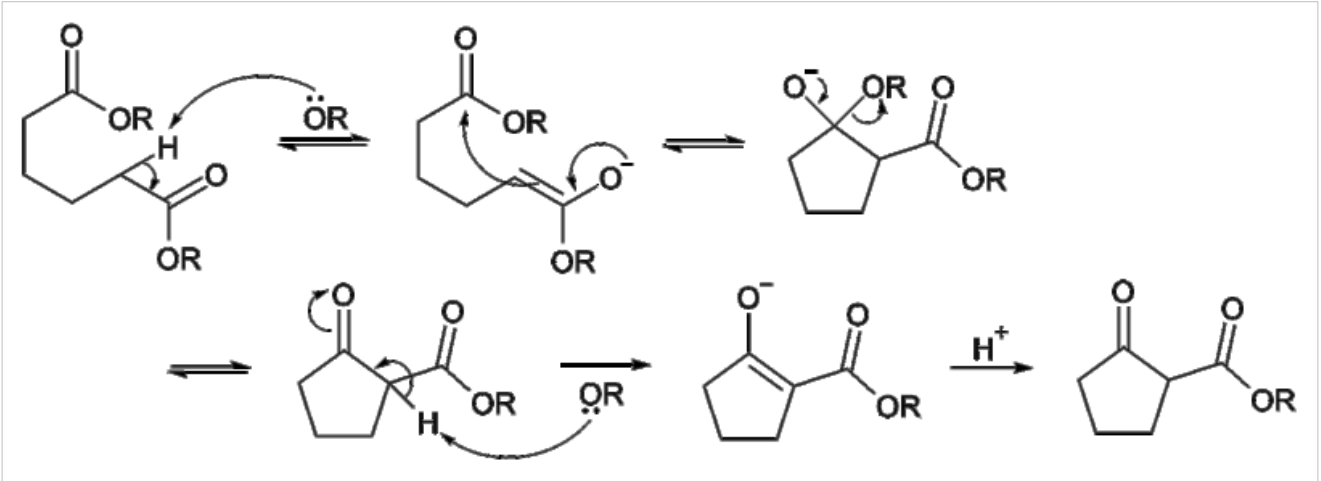
Dieckmann condensation

The **Dieckmann condensation** is the intramolecular chemical reaction of diesters with base to give β-ketoesters.[1] [2] [3] [4] [5] It is named after the German chemist Walter Dieckmann (1869–1925). The equivalent intermolecular reaction is the Claisen condensation.



Reaction Mechanism

The acidic hydrogen between the two carbonyl groups is deprotonated in step four. Protonation with a Brønsted-Lowry acid (H_3O^+ for example) re-forms the β-keto ester. [6] This deprotonation step is the driving force for this reaction.



Owing to the steric stability of five- and six-membered ring structures, these will preferentially be formed. 1,4- and 1,6 diesters will form five-membered cyclic β-keto esters, while 1,5- and 1,7 diesters will form six-membered β-keto esters. [7]

References

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Emil Knoevenagel

Emil Knoevenagel	
Born	June 18, 1865Hannover, Germany
Died	August 11, 1921 (aged 56)Berlin, Germany
Residence	Germany
Nationality	German
Doctoral advisor	Viktor Meyer
Known for	Knoevenagel condensation

Heinrich Emil Albert Knoevenagel (18 June 1865 – 11 August 1921) was the German chemist who established the Knoevenagel condensation reaction. The Knoevenagel condensation reaction of benzaldehydes with nitroalkanes is a classic general method for the preparation of nitroalkenes, which are very valuable synthetic intermediates.

External links

- Reaction description (in German) [1]

References

- "Emil Knoevenagel". *Angewandte Chemie* **35** (5): 29 – 30. 1922. doi:10.1002/ange.19220350503.

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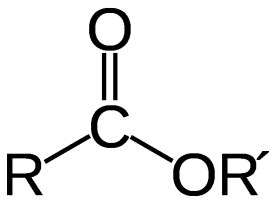
Ester

Esters are chemical compounds derived by reacting an oxoacid with a hydroxyl compound such as an alcohol or phenol.[1] Esters are usually derived from an inorganic acid or organic acid in which at least one -OH (hydroxyl) group is replaced by an -O-alkyl (alkoxy) group, and most commonly from carboxylic acids and alcohols. That is, esters are formed by condensing an acid with an alcohol.



A carboxylic acid ester. R and R' denote any alkyl or aryl group, respectively

Esters are ubiquitous. Most naturally occurring fats and oils are the fatty acid esters of glycerol. Esters with low molecular weight are commonly used as fragrances and found in essential oils and pheromones. Phosphoesters form the backbone of DNA molecules. Nitrate esters, such as nitroglycerin, are known for their explosive properties, while polyesters are important plastics, with monomers linked by ester moieties.

Nomenclature

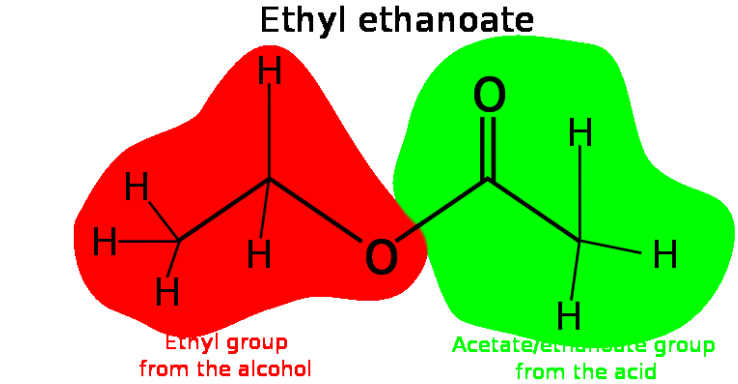
Etymology

The word 'ester' was coined in 1848 by German chemist Leopold Gmelin.[2]

IUPAC nomenclature of Esters

Ester names are derived from the parent alcohol and carboxylic acid. Esters based on the simplest carboxylic acids use the traditional names, such as formate, acetate, propionate, and butyrate. Esters from more complex carboxylic acids use the systematic name for the acid followed by the suffix *-oate*. For example, hexyl octanoate, also called hexyl caprylate, has the formula $CH_3(CH_2)_6CO_2(CH_2)_5CH_3$.

The chemical formulas of esters are typically written in the format of RCO_2R', where R and R' are the organic parts of the carboxylic acid and alcohol, respectively. For example butyl acetate, derived from butanol and acetic acid would be written $CH_3CO_2C_4H_9$. Alternative presentations are common including BuOAc and $CH_3COOC_4H_9$.



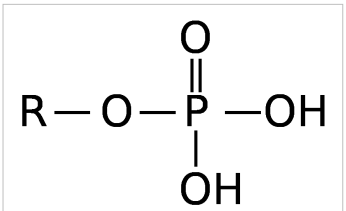
Cyclic esters are called lactones. One example of many is valerolactone.

Orthoesters

An uncommon class of organic esters are the orthoesters, which have the formula $RC(OR')_3$. Triethylorthoformate ($HC(OC_2H_5)_3$) is derived, in terms of its name (but not its synthesis) from orthoformic acid ($HC(OH)_3$) and ethanol.

"Inorganic esters"

Ester is a general term for the product derived from the condensation of an oxo acid and an alcohol. Thus, the nomenclature extends to inorganic acids, especially phosphoric acid, sulfuric acid, and nitric acid. Cyclic esters are called lactones. The preparation of an ester is known, general, as an esterification reaction. For example, triphenyl phosphate is the ester derived from phosphoric acid and phenol. Organic carbonates, such as ethylene carbonate, are derived from carbonic acid and ethylene glycol. The term boronic ester is widely used but these compounds are not formally esters because they lack a B=O bond.



A phosphoric acid ester

Structure and bonding

Esters contain a carbonyl center, which gives rise to 120°C-C-O and O-C-O angles. Unlike amides, esters are structurally flexible functional groups because rotation about the C-O-C bonds has a low barrier. Their flexibility and low polarity is manifested in their physical properties; they tend to be less rigid (lower melting point) and more volatile (lower boiling point) than the corresponding amides.[3] The pKa of the alpha-hydrogens on esters is around 25[4] .

Physical properties and characterization

Esters are more polar than ethers but less polar than alcohols. They participate in hydrogen bonds as hydrogen-bond acceptors, but cannot act as hydrogen-bond donors, unlike their parent alcohols. This ability to participate in hydrogen bonding confers some water-solubility. Because of their lack of hydrogen-bond-donating ability, esters do not self-associate. Consequently esters are more volatile than carboxylic acids of similar molecular weight.[3]

Characterization and analysis

Esters are usually identified by gas chromatography, taking advantage of their volatility. IR spectra for esters feature an intense sharp band in the range 1730–1750 cm^{-1} assigned to $\nu_{C=O}$. This peak changes depending on the functional groups attached to the carbonyl. For example, a benzene ring or double bond in conjugation with the carbonyl will bring the wavenumber down about 30 cm^{-1}.

Applications and occurrence

Esters are widespread in nature and are widely used in industry. In nature, fats are, in general, triesters derived from glycerol and fatty acids.[5] Esters are responsible for the aroma of many fruits, including apples, pears, bananas, pineapples, and strawberries.[6] Several billion kilograms of polyesters are produced industrially annually, important products being polyethylene terephthalate, acrylate esters, and cellulose acetate.[7]

Preparation

Esterification is the general name for a chemical reaction in which two reactants (typically an alcohol and an acid) form an ester as the reaction product. Esters are common in organic chemistry and biological materials, and often have a characteristic pleasant, fruity odor. This leads to their extensive use in the fragrance and flavor industry. Ester bonds are also found in many polymers.

Esterification of carboxylic acids

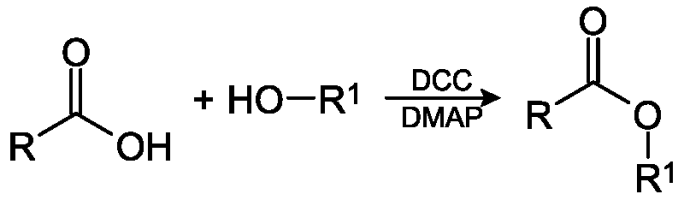
The classic synthesis is the Fischer esterification, which involves treating a carboxylic acid with an alcohol in the presence of a dehydrating agent:

$$RCO_2H + R'OH \rightleftharpoons RCO_2R' + H_2O$$

The equilibrium constant for such reactions is about 5 for typical esters, e.g., ethyl acetate.[8] but the reaction is slow in the absence of a catalyst. Sulfuric acid is a typical catalyst for this reaction. Many other acids are also used such as polymeric sulfonic acids. Since esterification is highly reversible, the yield of the ester can be improved using le Chatelier's principle:

- using the alcohol in large excess (i.e., as a solvent)
- using a dehydrating agent: Sulfuric acid not only catalyzes the reaction but sequesters water (a reaction product). Other drying agents like molecular sieves can also be used.
- removal of water by physical means such as distillation as a low-boiling azeotropes with toluene, in conjunction with a Dean-Stark apparatus.

Reagents are known that drive the dehydration of mixtures of alcohols and carboxylic acids. One example is the Steglich esterification, which is a method of forming esters under mild conditions. The method is popular in peptide synthesis, where the substrates are sensitive to harsh conditions like high heat. DCC (dicyclohexylcarbodiimide) is used to activate the carboxylic acid to further reaction. DMAP (4-dimethylaminopyridine) is used as an acyl-transfer catalyst.[9]



Another method for the dehydration of mixtures of alcohols and carboxylic acids is the Mitsunobu reaction:

$$RCO_2H + R'OH + P(C_6H_5)_3 + R_2N_2 \rightarrow RCO_2R' + OP(C_6H_5)_3 + R_2N_2H_2$$

Carboxylic acids can be esterified using diazomethane:

$$RCO_2H + CH_2N_2 \rightarrow RCO_2CH_3 + N_2$$

Using this diazomethane, mixtures of carboxylic acids can be converted to their methyl esters in near quantitative yields, e.g., for analysis by gas chromatography. The method is useful in specialized organic synthetic operations but is considered too expensive for large scale applications.

Alcoholysis of acyl chlorides and acid anhydrides

Alcohols react with acyl chlorides and acid anhydrides to give esters:

$$RCOCl + R'OH \rightarrow RCO_2R' + HCl$$

$$(RCO)_2O + R'OH \rightarrow RCO_2R' + RCO_2H$$

The reactions are irreversible simplifying work-up. Since acyl chlorides and acid anhydrides also react with water, anhydrous conditions are preferred. The analogous acylations of amines to give amides are less sensitive because amines are stronger nucleophiles and react more rapidly. This method is employed only for laboratory-scale procedures, as it is expensive.

Alkylation of carboxylate salts

Although not widely employed for esterifications, salts of carboxylate anions can be alkylating agent with alkyl halides to give esters. In the case that an alkyl chloride is used, an iodide salt can catalyze the reaction (Finkelstein reaction). The carboxylate salt is often generated *in situ*. In difficult cases, the silver carboxylate may be used, since the silver ion coordinates to the halide aiding its departure and improving the reaction rate. This reaction can suffer from anion availability problems and, therefore, can benefit from the addition of phase transfer catalysts or highly polar aprotic solvents such as DMF.

Transesterification

Transesterification, which involves changing one ester into another one, is widely practiced:

$$RCO_2R' + CH_3OH \rightarrow RCO_2CH_3 + R'OH$$

Like the hydrolysis reaction, transesterification is catalysed by acids and bases. The reaction is widely used for degrading triglycerides, e.g. in the production of fatty acid esters and alcohols. Poly(ethyleneterephthalate) is produced by the transesterification of dimethyl terephthalate and ethylene glycol:[7]

$$(C_6H_4)(CO_2CH_3)_2 + 2\ C_2H_4(OH)_2 \rightarrow 1/n\ \{(C_6H_4)(CO_2)_2(C_2H_4)\}_n + 2\ CH_3OH$$

Carbonylation

Alkenes undergo "hydroesterification" in the presence of metal carbonyl catalysts. Esters of propionic acid are produced commercially by this method:

$$C_2H_4 + ROH + CO \rightarrow C_2H_5CO_2R$$

The carbonylation of methanol yields methyl formate, which the main commercial source of formic acid. The reaction is catalyzed by sodium methoxide:

$$CH_3OH + CO \rightarrow CH_3O_2CH$$

Addition of carboxylic acids to alkenes

In the presence of palladium-based catalysts, ethylene, acetic acid, and oxygen react to give vinyl acetate:

$$C_2H_4 + CH_3CO_2H + 1/2\ O_2 \rightarrow C_2H_3O_2CCH_3 + H_2O$$

Direct routes to this same ester are not possible because vinyl alcohol is unstable.

Other methods

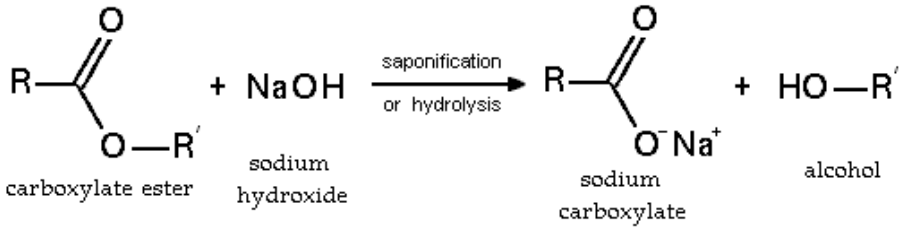
- Favorskii rearrangement of α-haloketones in presence of base
- Baeyer-Villiger oxidation of ketones with peroxides.
- Pinner reaction of nitriles with an alcohol.

Reactions

Esters react primarily at one of two locations, the carbonyl at the carbon adjacent the carbonyl group. The carbonyl is weakly electrophilic and is attacked by strong nucleophilies (amines, alkoxides, hydride sources, organolithium compounds, etc.). The C-H bonds adjacent to the carbonyl are weakly acidic but undergo deprotonation with strong bases. This process is the one that usually initiates condensation reactions.

Addition of nucleophiles at carbonyl

Esterification is a reversible reaction. Esters undergo hydrolysis under acid and basic conditions. Under acid conditions, the reaction is the reverse reaction of the Fischer esterification. Under basic conditions, hydroxide acts as a nucleophile, while an alkoxide is the leaving group. This reaction, saponification, is the basis of soap making.



The alkoxide group may also be displaced by stronger nucleophiles such as ammonia or primary or secondary amines to give amides:

$$RCO_2R' + NH_2R'' \rightarrow RCONHR'' + R'OH$$

This reaction is not usually reversible. Hydrazines and hydroxylamine can be used in place of amines. Esters can be converted to isocyanates through intermediate hydroxamic acids in the Lossen rearrangement.

Sources of carbon nucleophiles, e.g., Grignard reagents and organolithium compounds, add readily to the carbonyl.

Reduction

Compared to ketones and aldehydes, esters are relatively resistant to reduction. The introduction of catalytic hydrogenation in the early part of the 20th century was a breakthrough; esters of fatty acids are hydrogenated to fatty alcohols.

$$RCO_2R' + 2\ H_2 \rightarrow RCH_2OH + R'OH$$

A typical catalyst is copper chromite. Prior to the development of catalytic hydrogenation, esters were reduced on a large scale using the Bouveault-Blanc reduction. This method, which is largely obsolete, uses sodium in the presence of proton sources.

Especially for fine chemical syntheses, lithium aluminium hydride is used to reduce esters to two primary alcohols. The related reagent sodium borohydride is slow in this reaction. DIBAH reduces esters to aldehydes.[10]

Claisen condensation and related reactions

As for ketones and aldehydes, the hydrogen atoms on the carbon adjacent ("α to") the carboxyl group in esters are sufficiently acidic to undergo deprotonation, which in turn leads to a variety of useful reactions. Deprotonation requires relatively strong bases, such as alkoxides. Deprotonation gives a nucleophilic enolate, which can further react, e.g., the Claisen condensation and its intramolecular equivalent, the Dieckmann condensation. This conversion is exploited in the malonic ester synthesis, wherein the diester of malonic acid reacts with an electrophile (e.g., alkyl halide), and is subsequently decarboxylated.

Other reactions

- Phenyl esters react to hydroxyarylketones in the Fries rearrangement.
- Specific esters are functionalized with an α-hydroxyl group in the Chan rearrangement.
- Esters with β-hydrogen atoms can be converted to alkenes in ester pyrolysis.

Protecting groups

As a class, esters serve as protecting groups for carboxylic acids. Protecting a carboxylic acid is useful in peptide synthesis, to prevent self-reactions of the bifunctional amino acids. Methyl and ethyl esters are commonly available for many amino acids; the *t*-butyl ester tends to be more expensive. However, *t*-butyl esters are particularly useful because, under strongly acidic conditions, the *t*-butyl esters undergo elimination to give the carboxylic acid and isobutene, simplifying work-up.

References

[1] IUPAC, *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006-) " esters (http://goldbook.iupac.org/E02219.html)".

[2] Leopold Gmelin, *Handbuch der Chemie*, vol. 4: *Handbuch der organischen Chemie* (vol. 1) (Heidelberg, Baden (Germany): Karl Winter, 1848), page 182 (http://books.google.com/books?id=4ooMAQAAIAAJ&pg=PA182&lpg=PA182#v=onepage&q&f=false).
Original text:

> b. Ester oder sauerstoffsäure Aetherarten.
> Ethers du troisième genre.
> Viele mineralische und organische Sauerstoffsäuren treten mit einer Alkohol-Art unter Ausscheidung von Wasser zu neutralen flüchtigen ätherischen Verbindungen zusammen, welche man als gepaarte Verbindungen von Alkohol und Säuren-Wasser oder, nach der Radicaltheorie, als Salze betrachten kann, in welchen eine Säure mit einem Aether verbunden ist.

Translation:

> b. Ester or oxy-acid ethers.
> Ethers of the third type.
> Many mineral and organic acids containing oxygen combine with an alcohol upon elimination of water to [form] neutral, volatile ether compounds, which one can view as coupled compounds of alcohol and acid-water, or, according to the theory of radicals, as salts in which an acid is bonded with an ether.

[3] March, J. “Advanced Organic Chemistry” 4th Ed. J. Wiley and Sons, 1992: New York. ISBN 0-471-60180-2.

[4] Chemistry of Enols and Enolates - Acidity of alpha-hydrogens (http://pharmaxchange.info/press/2011/02/chemistry-of-enolates-and-enols-acidity-of-alpha-hydrogens/)

[5] Isolation of triglyceride from nutmeg: G. D. Beal "Trimyristen" Organic Syntheses, Coll. Vol. 1, p.538 (1941). Link (http://orgsynth.org/orgsyn/pdfs/CV1P0538.pdf)

[6] McGee, Harold. On Food and Cooking. 2003, Scribner, New York.

[7] Wilhelm Riemenschneider1 and Hermann M. Bolt "Esters, Organic" Ullmann's Encyclopedia of Industrial Chemistry, 2005, Wiley-VCH, Weinheim. doi:10.1002/14356007.a09_565.pub2

[8] Roger J. Williams, Alton Gabriel, Roy C. Andrews “The Relation Between the Hydrolysis Equilibrium Constant of Esters and the Strengths of the Corresponding Acids” J. Am. Chem. Soc., 1928, volume 50, 1267. doi:10.1021/ja01392a005

[9] B. Neises and W. Steglich, "Esterification of Carboxylic Acids with Dicyclohexylcarbodiimide/4-Dimethylaminopyridine: tert-Butyl ethyl fumarate" (http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv7p0093), *Org. Synth.*, ; *Coll. Vol.* **7**: 93

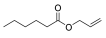
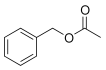
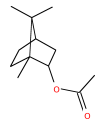
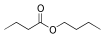
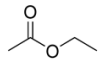
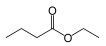
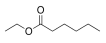
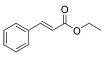
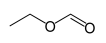
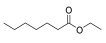
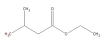
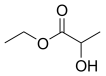
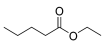
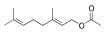
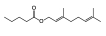
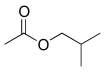
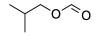
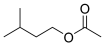
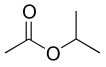
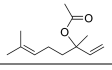
[10] W. Reusch. "Carboxyl Derivative Reactivity" (http://www.cem.msu.edu/~reusch/VirtualText/crbacid2.htm#react2). *Virtual Textbook of Organic Chemistry*. .

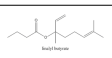
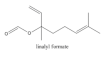
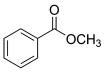
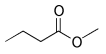
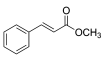
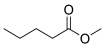
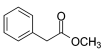
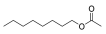
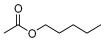
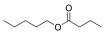
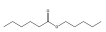
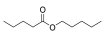
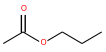
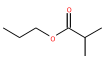
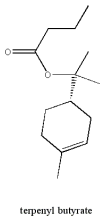
External links

- An introduction to esters (http://www.chemguide.co.uk/organicprops/esters/background.html)
- Molecule of the month: Ethyl acetate and other esters (http://www.chm.bris.ac.uk/motm/ethylacetate/ethylh.htm)
- An example of esters commercial application (http://www.forearthonline.com/allgreenplanet/moreaboutesters.html)

Appendix A: List of ester odorants

Many esters have distinctive fruit-like odors, which has led to their commonplace use in artificial flavorings and fragrances.

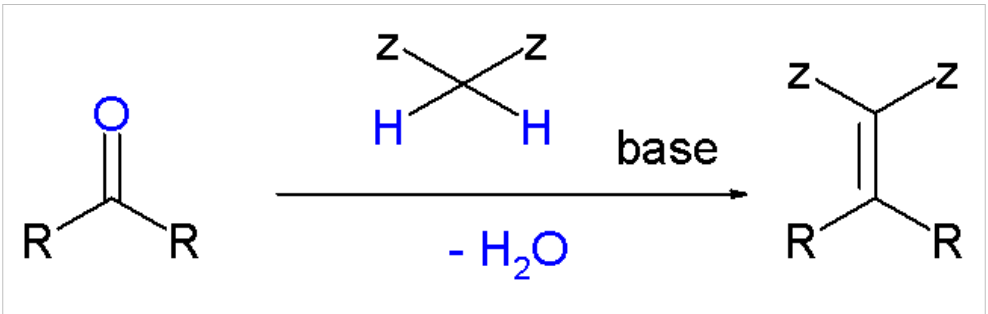
Ester Name	Structure	Odor or occurrence
Allyl hexanoate		pineapple
Benzyl acetate		pear, strawberry, jasmine
Bornyl acetate		pine tree flavor
Butyl butyrate		pineapple
Ethyl acetate		nail polish remover, model paint, model airplane glue
Ethyl butyrate		banana, pineapple, strawberry
Ethyl hexanoate		pineapple, waxy-green banana
Ethyl cinnamate		cinnamon
Ethyl formate		lemon, rum, strawberry
Ethyl heptanoate		apricot, cherry, grape, raspberry
Ethyl isovalerate		apple
Ethyl lactate		butter, cream
Ethyl nonanoate		grape
Ethyl pentanoate		apple
Geranyl acetate		geranium
Geranyl butyrate		cherry
Geranyl pentanoate		apple
Isobutyl acetate		cherry, raspberry, strawberry
Isobutyl formate		raspberry
Isoamyl acetate		pear, banana (flavoring in Pear drops)
Isopropyl acetate		fruity
Linalyl acetate		lavender, sage

Linalyl butyrate		peach
Linalyl formate		apple, peach
Methyl acetate		glue
Methyl anthranilate		grape, jasmine
Methyl benzoate		fruity, ylang ylang, feijoa
Methyl butyrate (methyl butanoate)		pineapple, apple, strawberry
Methyl cinnamate		strawberry
Methyl pentanoate (methyl valerate)		flowery
Methyl phenylacetate		honey
Methyl salicylate (oil of wintergreen)		Modern root beer, wintergreen, Germolene and Ralgex ointments (UK)
Nonyl caprylate		orange
Octyl acetate		fruity-orange
Octyl butyrate		parsnip
Amyl acetate (pentyl acetate)		apple, banana
Pentyl butyrate (amyl butyrate)		apricot, pear, pineapple
Pentyl hexanoate (amyl caproate)		apple, pineapple
Pentyl pentanoate (amyl valerate)		apple
Propyl acetate		pear
Propyl isobutyrate		rum
Terpenyl butyrate		cherry

Knoevenagel condensation

The **Knoevenagel condensation** reaction is an organic reaction named after Emil Knoevenagel. It is a modification of the Aldol condensation[1] [2] .

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



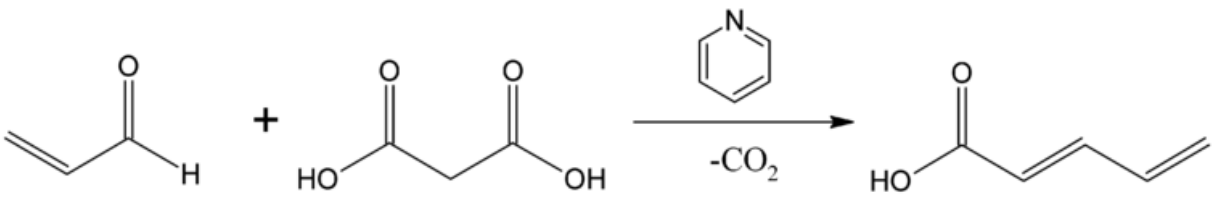
In this reaction the carbonyl group is an aldehyde or a ketone. The catalyst is usually a weakly basic amine. The active hydrogen component has the form [3]

- Z-CH_2-Z or Z-CHR-Z for instance diethyl malonate, Meldrum's acid, ethyl acetoacetate or malonic acid.
- Z-CHR_1R_2 for instance nitromethane.

where Z is an electron withdrawing functional group. Z must be powerful enough to facilitate hydrogen abstraction to the enolate ion even with a mild base. Using a strong base in this reaction would induce self-condensation of the aldehyde or ketone.

The Hantzsch pyridine synthesis, the Gewald reaction and the Feist-Benary furan synthesis all contain a Knoevenagel reaction step. The reaction also led to the discovery of CS gas.

Doebner modification

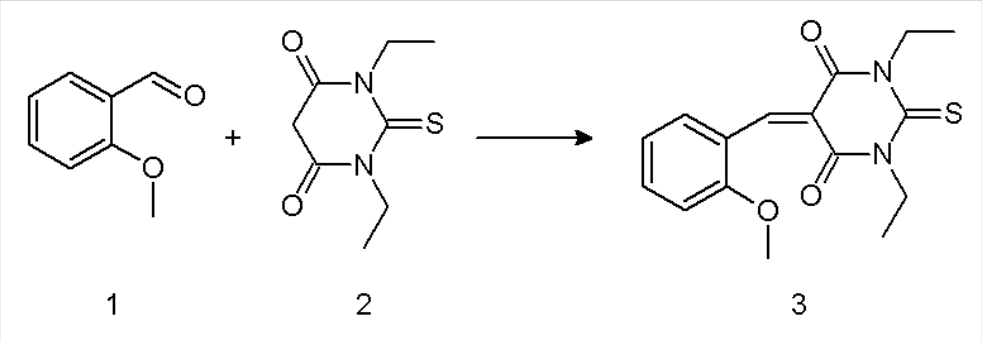


The Doebner modification of the Knoevenagel condensation. Acrolein and malonic acid react in pyridine to give trans-2,4-pentadienoic acid with the loss of carbon dioxide.

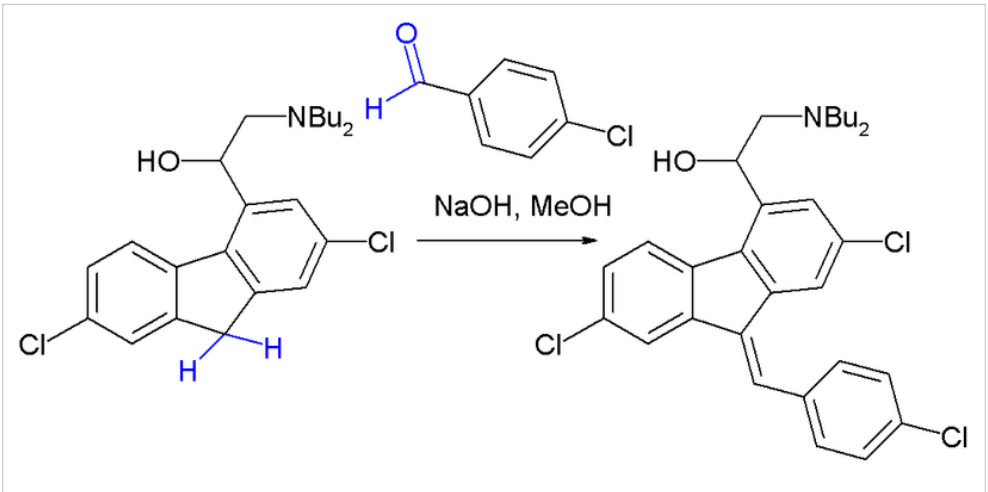
With malonic compounds the reaction product can lose a molecule of carbon dioxide in a subsequent step. In the so-called **Doebner modification** [4] the base required is pyridine. For example the reaction product of acrolein and malonic acid in pyridine is *trans-2,4-Pentadienoic acid* with one carboxylic acid group and not two [5]

Scope

A Knoevenagel condensation is demonstrated in the reaction of 2-methoxybenzaldehyde **1** with the barbituric acid **2** in ethanol using piperidine as a base [6] . The resulting enone **3** is a charge transfer complex molecule.

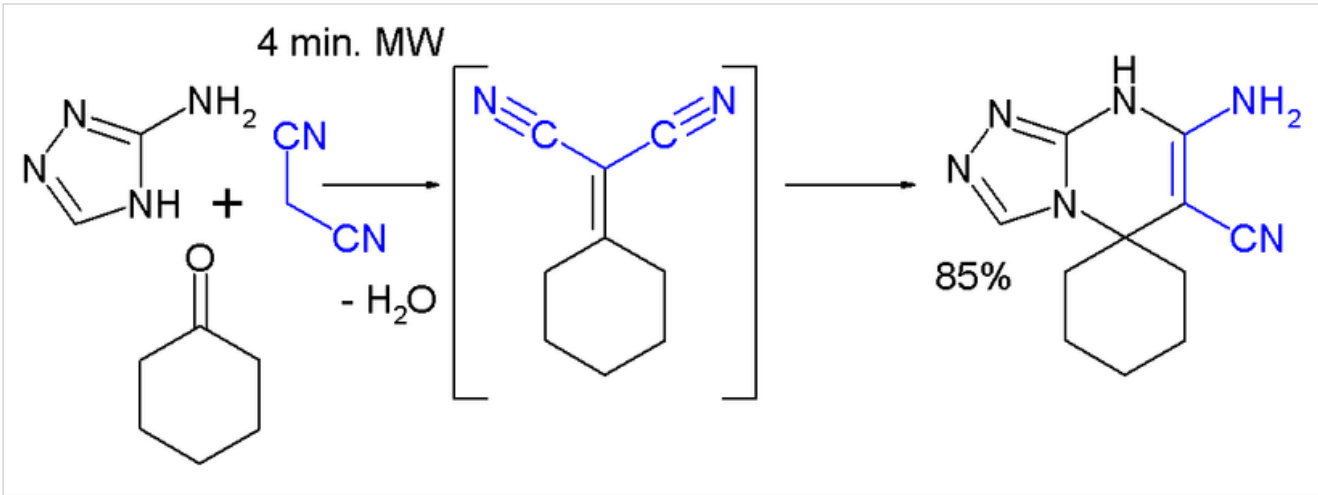


The Knoevenagel condensation is a key step in the commercial production of the antimalarial drug lumefantrine (a component of Coartem) [7] :



The initial reaction product is a 50:50 mixture of E and Z isomers but because both isomers equilibrate rapidly around their common hydroxyl precursor, the more stable Z-isomer can eventually be obtained.

A multicomponent reaction featuring a Knoevenagel condensation is demonstrated in this MORE synthesis with cyclohexanone, malononitrile and 3-amino-1,2,4-triazole [8] :



References

[1] Jones, G. *Org. React.* **1967**, *15*.

[2] Emil Knoevenagel (1898). "Condensation von Malonsäure mit Aromatiachen Aldehyden durch Ammoniak und Amine" (http://gallica.bnf.fr/ark:/12148/bpt6k90751n/f268.chemindefer). *Berichte der deutschen chemischen Gesellschaft* **31**: 2596–2619. doi:10.1002/cber.18980310308. .

[3] March, Jerry (1985), *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (3rd ed.), New York: Wiley, ISBN 0-471-85472-7

[4] O. Doebner (1902). "Ueber die der Sorbinsäure homologen, ungesättigten Säuren mit zwei Doppelbindungen". *Berichte der deutschen chemischen Gesellschaft* **35**: 1136–1136. doi:10.1002/cber.190203501187.

[5] Peter J. Jessup, C. Bruce Petty, Jan Roos, and Larry E. Overman (1988), "1-N-Acylamino-1,3-dienes from 2,4-pentadienoic acids by the curtius rearrangement: benzyl trans-1,3-butadiene-1-carbamate" (http://www.orgsyn.org/orgsyn/orgsyn/prepContent.asp?prep=cv6p0095), *Org. Synth.*, ; *Coll. Vol.* **6**: 95

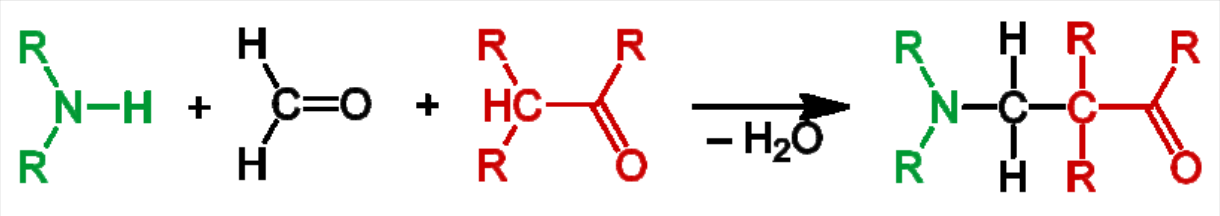
[6] *1,3-Diethyl-5-(2-methoxybenzylidene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione* Abdullah Mohamed Asiria, Khaled Ahmed Alamrya Abraham F. Jalboutb, Suhong Zhang Molbank **2004**, M359 (http://www.mdpi.net/molbank/molbank2004/m0359.htm) publication.

[7] *An Improved Manufacturing Process for the Antimalaria Drug Coartem. Part II* Ulrich Beutler, Peter C. Fuenfschilling, and Andreas Steinkemper Org. Process Res. Dev.; **2007**; 11(3) pp 341 - 345; (Article) doi:10.1021/op060244p

[8] *Mild and ecofriendly tandem synthesis of 1,2,4-triazolo[4,3-a]pyrimidines in aqueous medium* Arkivoc **2007** (06-2251BP) Anshu Dandia, Pritima Sarawgi, Kapil Arya, and Sarita Khaturia Link (http://content.arkat-usa.org/ARKIVOC/JOURNAL_CONTENT/manuscripts/2006/06-2251BP as published mainmanuscript.pdf)

Mannich reaction

The **Mannich reaction** is an organic reaction which consists of an **amino alkylation** of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a Mannich base.[1] Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes. The reaction is named after chemist Carl Mannich.[2] [3]

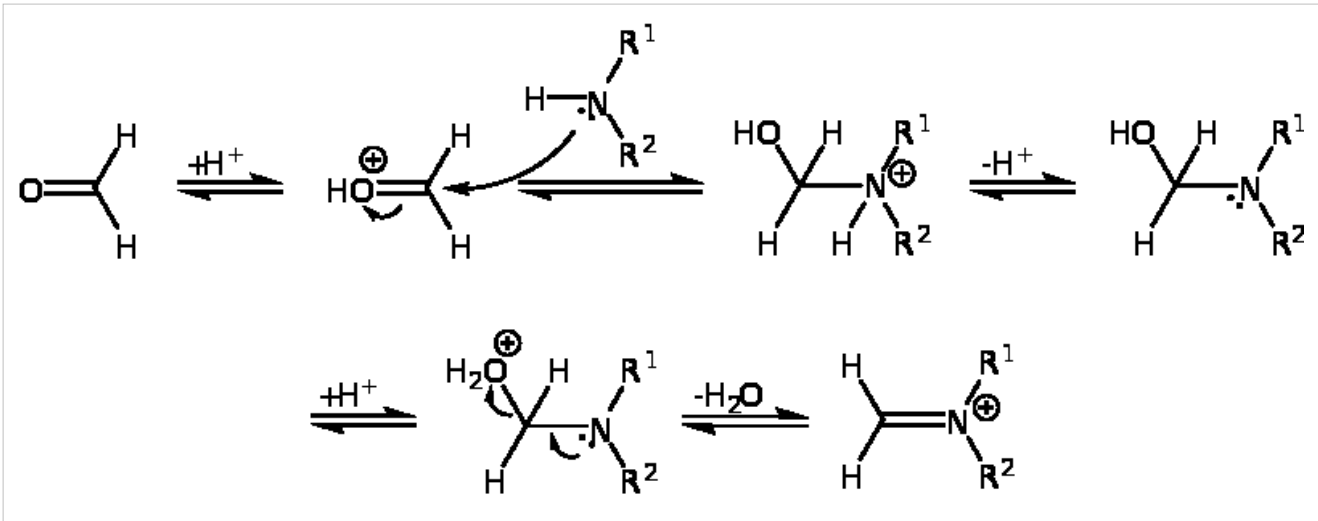


The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in a electrophilic addition with a compound containing an acidic proton(which is, or had become an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

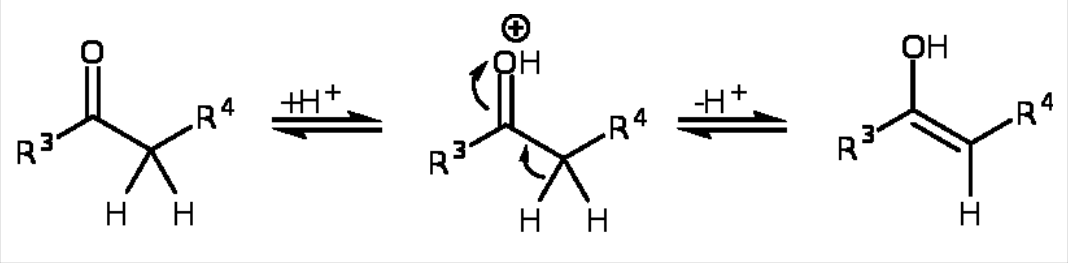
In the Mannich reaction, ammonia or primary or secondary amines are employed for the activation of formaldehyde. Tertiary amines lack an N-H proton to form the intermediate imine. α-CH-acidic compounds (nucleophiles) include carbonyl compounds, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines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

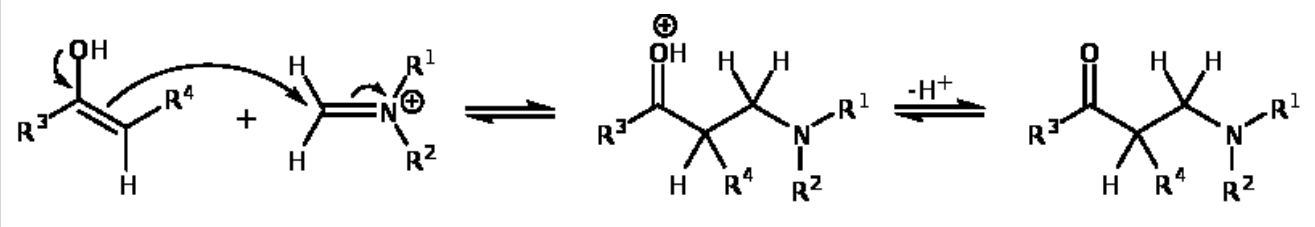
Reaction mechanism

The mechanism of the Mannich reaction starts with the formation of an iminium ion from the amine and the formaldehyde.



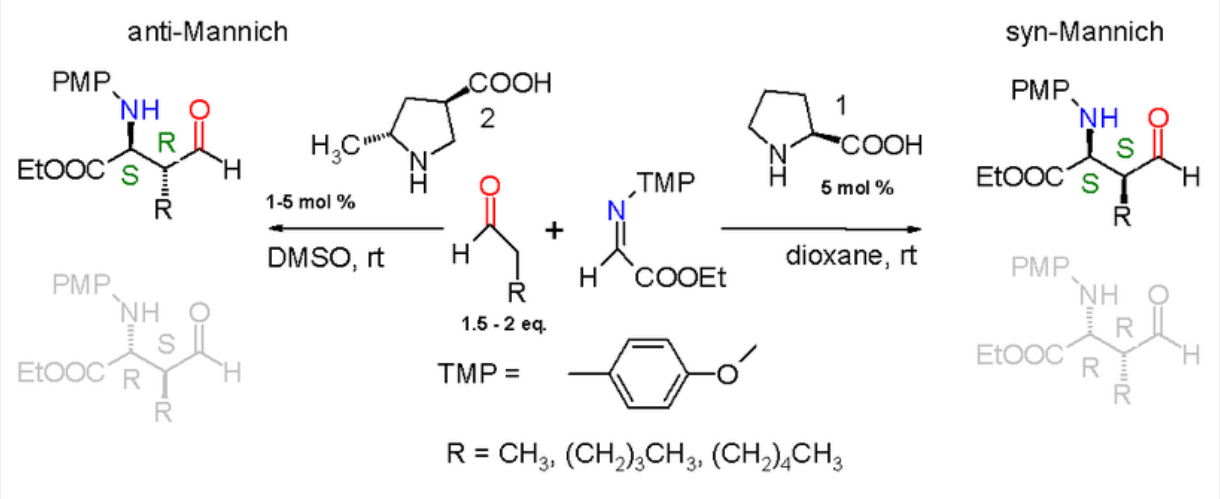
Because the reaction takes place under acidic conditions, the compound with the carbonyl functional group (in this case a ketone) can tautomerize to the enol form, after which it can attack the iminium ion.



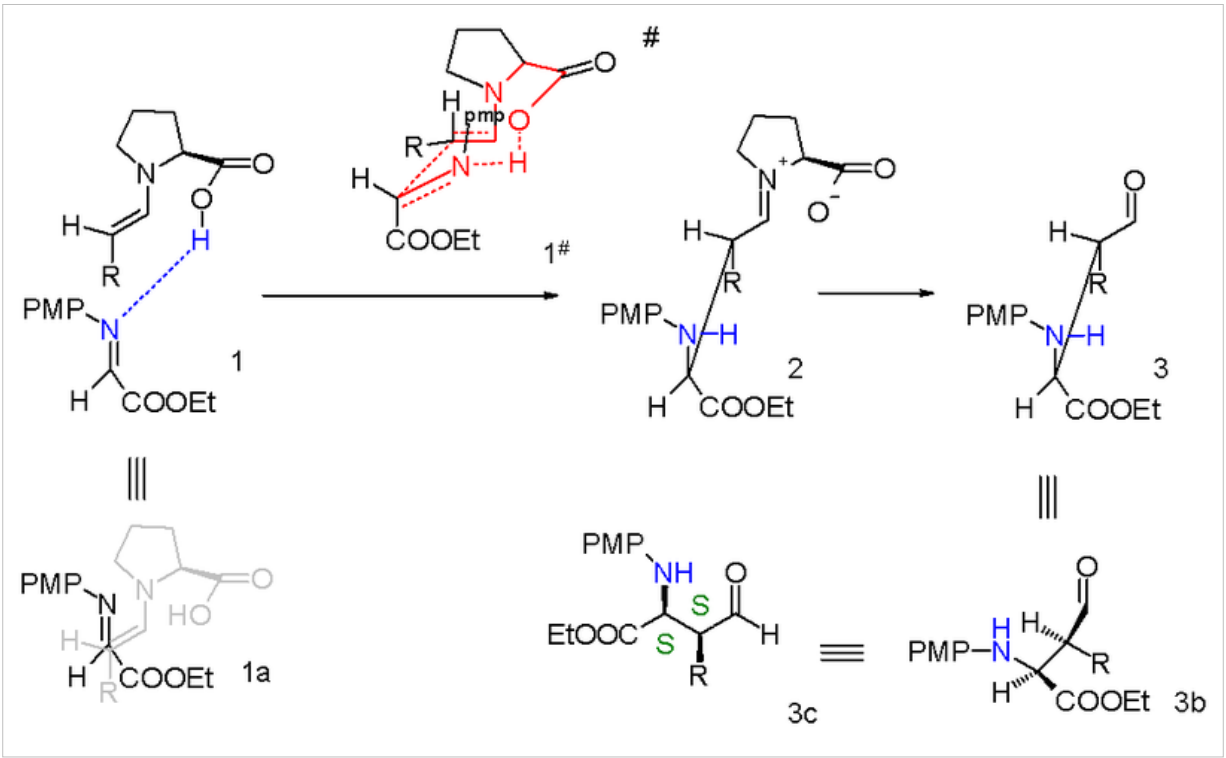


Asymmetric Mannich reactions

Progress has been made towards asymmetric Mannich reactions. When properly functionalized the newly formed ethylene bridge in the Mannich adduct has two prochiral centers giving rise to two diastereomeric pairs of enantiomers. The first asymmetric Mannich reaction with an unmodified aldehyde was carried with (S)-proline as a naturally occurring chiral catalyst.[4]



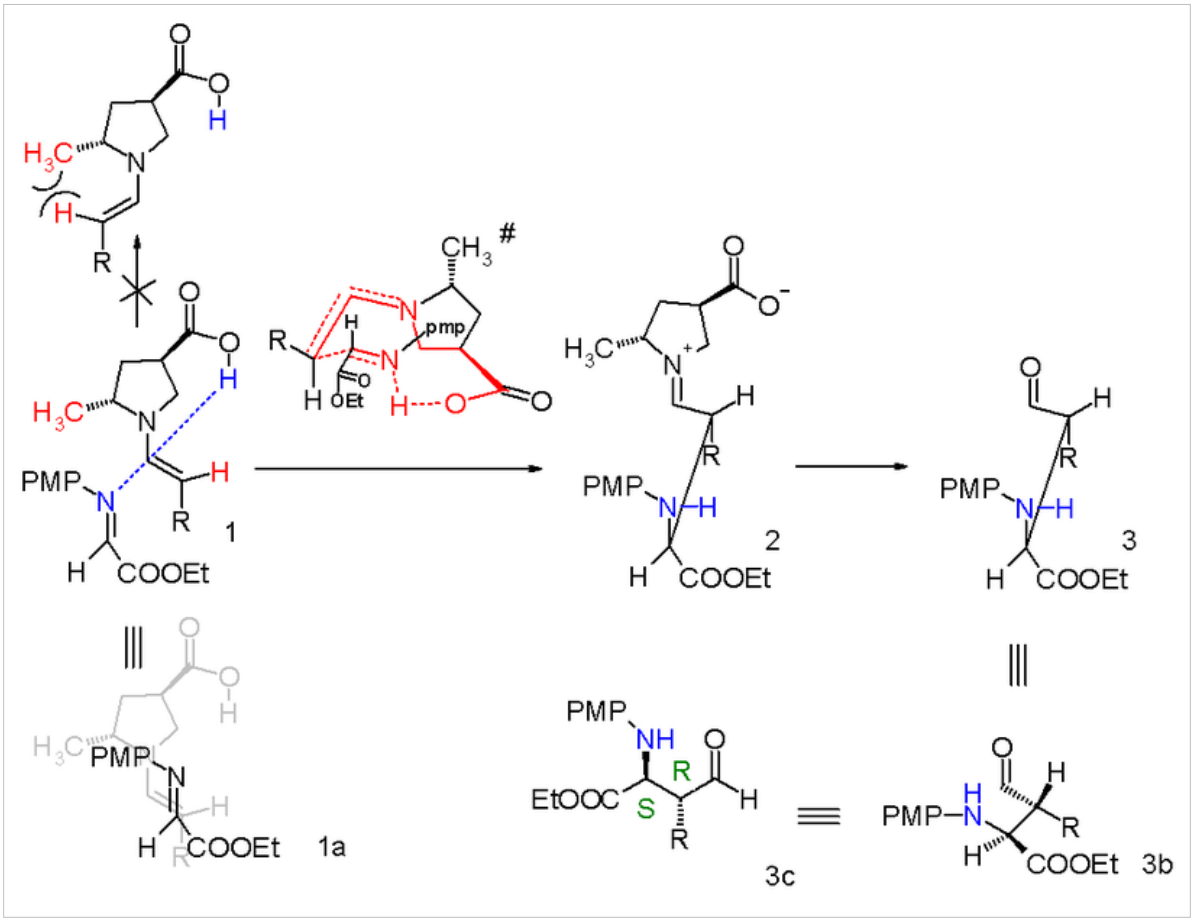
The reaction **taking** place is between a simple aldehyde such as propionaldehyde and an imine derived from ethyl glyoxylate and p-methoxyaniline (PMP = paramethoxphenyl) catalyzed by (S)-proline in dioxane at room temperature. The reaction product is diastereoselective with a preference for the syn-Mannich reaction 3:1 when the alkyl substituent on the aldehyde is a methyl group or 19:1 when the alkyl group the much larger pentyl group. Of the two possible syn adducts (S,S) or (R,R) the reaction is also enantioselective with a preference for the (S,S) adduct with enantiomeric excess larger than 99%. This stereoselectivity is explained in the scheme below.



Proline enters a catalytic cycle by reacting with the aldehyde to form an enamine. The two reactants (imine and enamine) line up for the Mannich reaction with Si facial attack of the imine by the Si-face of the enamine-aldehyde. Relief of steric strain dictates that the alkyl residue R of the enamine and the imine group are antiperiplanar on

approach which locks in the syn mode of addition. The enantioselectivity is further controlled by hydrogen bonding between the proline carboxylic acid group and the imine. The transition state for the addition is a nine-membered ring with chair conformation with partial single bonds and double bonds. The proline group is converted back to the aldehyde and a single S,S isomer is formed.

By modification of the proline catalyst to it is also possible to obtain anti-Mannich adducts.[5]



An additional methyl group attached to proline forces a specific enamine approach and the transition state now is a 10-membered ring with addition in anti-mode. The diastereoselectivity is at least anti:syn 95:5 regardless of alkyl group size and the S,R enantiomer is preferred with at least 97% ee.

Applications

The Mannich-Reaction is employed in the organic synthesis of natural compounds such as peptides, nucleotides, antibiotics, and alkaloids (e.g. tropinone). Other applications are in agro chemicals such as plant growth regulators,[6] paint- and polymer chemistry, catalysts and crosslinking.

The Mannich reaction is also used in the synthesis of medicinal compounds e.g. rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant), tramadol, and tolmetin (anti-inflammatory drug).

References

[1] Original translated from German Wiki

[2] Mannich, C.; Krösche, W. (1912). "Ueber ein Kondensationsprodukt aus Formaldehyd, Ammoniak und Antipyrin". *Archiv der Pharmazie* **250**: 647. doi:10.1002/ardp.19122500151.

[3] Blicke, F. F. *Org. React.* **1942**, *1*.

[4] Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas Cf, 3. (2002). "A highly enantioselective route to either enantiomer of both alpha- and beta-amino acid derivatives". *Journal of the American Chemical Society* **124** (9): 1866–1867. doi:10.1021/ja017833p. PMID 11866595.

[5] Mitsumori, S.; Zhang, H.; Ha-Yeon Cheong, P.; Houk, K.; Tanaka, F.; Barbas Cf, 3. (2006). "Direct asymmetric anti-Mannich-type reactions catalyzed by a designed amino acid". *Journal of the American Chemical Society* **128** (4): 1040–1041. doi:10.1021/ja056984f. PMC 2532695. PMID 16433496.

[6] da Rosa F. A. F., Rebelo R. A., Nascimento II M. G. (2003). "Synthesis of new indolecarboxylic acids related to the plant hormone indoleacetic acid" (http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-50532003000100003). *Journal of the Brazilian Chemical Society* **14**: 11. doi:10.1590/S0103-50532003000100003. .

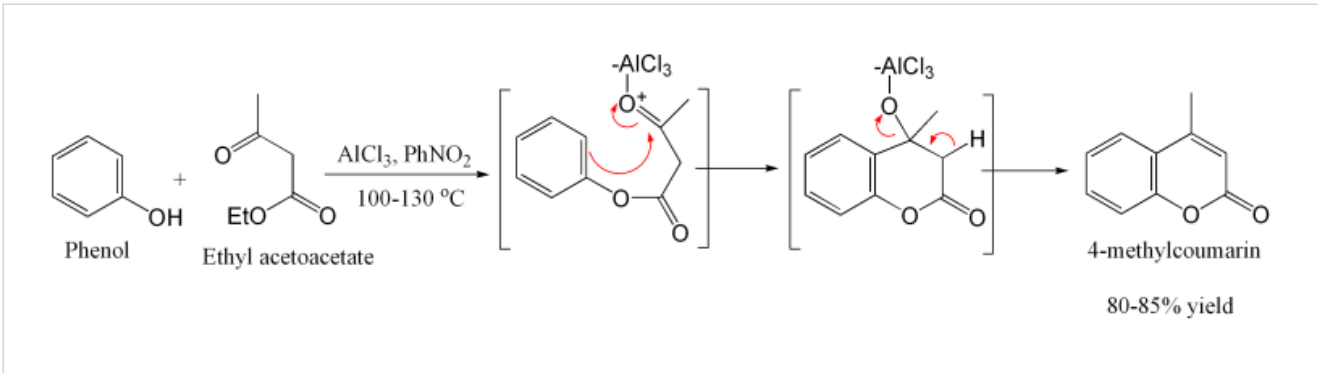
External links

- "Mechanism In Motion: Mannich reaction" (http://www.youtube.com/watch?v=HUVQ3SNz7m0).

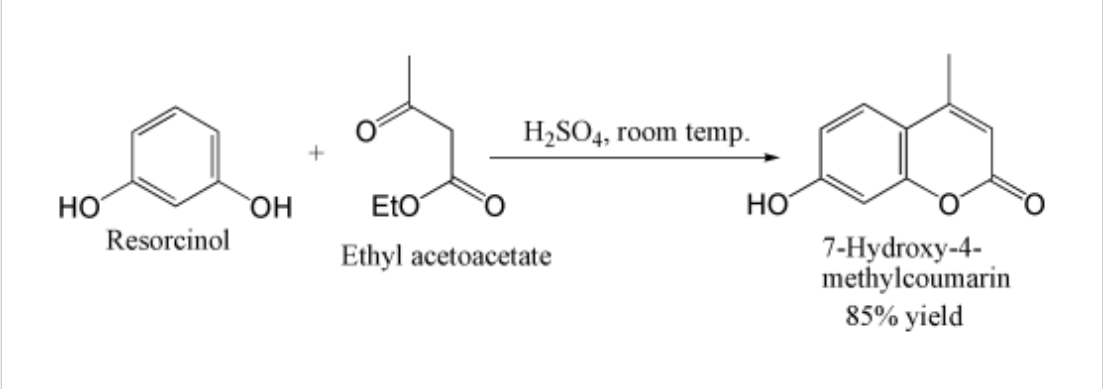
Pechmann condensation

The **Pechmann condensation** is a synthesis of coumarins, starting from a phenol and a carboxylic acid or ester containing a β-carbonyl group [1] . The condensation is performed under acidic conditions. The mechanism involves an esterification/transesterification followed by attack of the activated carbonyl ortho to the oxygen to generate the new ring. The final step is a dehydration, as seen following an aldol condensation. It was discovered by the German chemist Hans von Pechmann [2] .

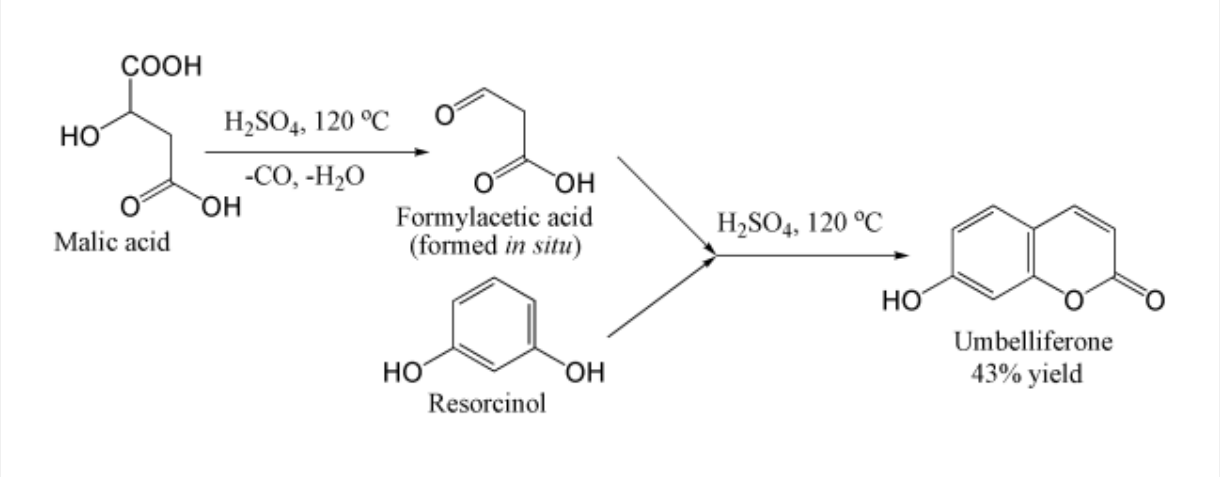
With simple phenols, the conditions are harsh, although yields may still be good [3] .



With highly activated phenols such as resorcinol, the reaction can be performed under much milder conditions. This provides a useful route to umbelliferone derivatives:



For coumarins unsubstituted at the 4-position, the method requires the use of formylacetic acid or ester. These are unstable and not commercially available, but the acid may be produced *in situ* from malic acid and sulfuric acid above 100°C. As soon as it forms, the formylacetic acid performs the Pechmann condensation. In the example shown, umbelliferone itself is produced, albeit in low yield:



Simonis chromone cyclization

In a variation the reaction of phenols and beta-ketoesters and phosphorus pentoxide yields a chromone. This reaction is called **Simonis chromone cyclization** [4] [5] . The ketone in the ketoester is activated by P_2O_5 for reaction with the phenol hydroxyl group first, the ester group in it is then activated for electrophilic attack of the arene.

References

[1] J. A. Joule, K. Mills *Heterocyclic Chemistry*, 4th edition, Blackwell Science, Oxford, UK, 2000.

[2] H. v. Pechmann (1884). "Neue Bildungsweise der Cumarine. Synthese des Daphnetins". *Berichte der deutschen chemischen Gesellschaft* **17** (1): 929–936. doi:10.1002/cber.188401701248.

[3] Eugene H. Woodruff , *Organic Syntheses, Coll. Vol. 3*, p.581. Available online (http://www.orgsyn.org/orgsyn/prep.asp?prep=cv3p0581).

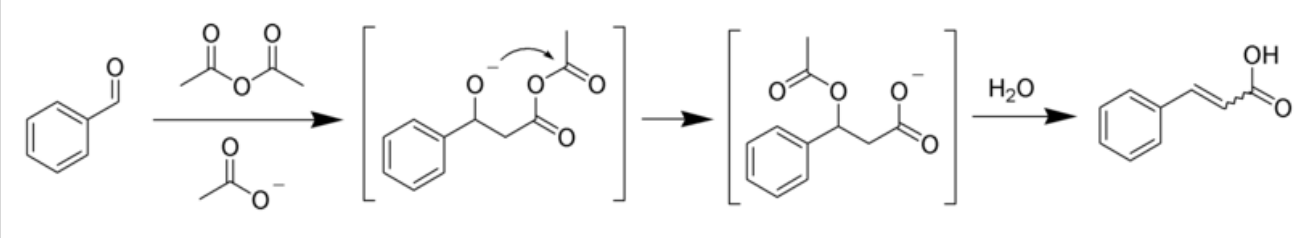
[4] E. Petschek, H. Simonis, Ber. 46, 2014 (1913).

[5] *Name reactions: a collection of detailed reaction mechanisms*, Jie Jack Li

Perkin reaction

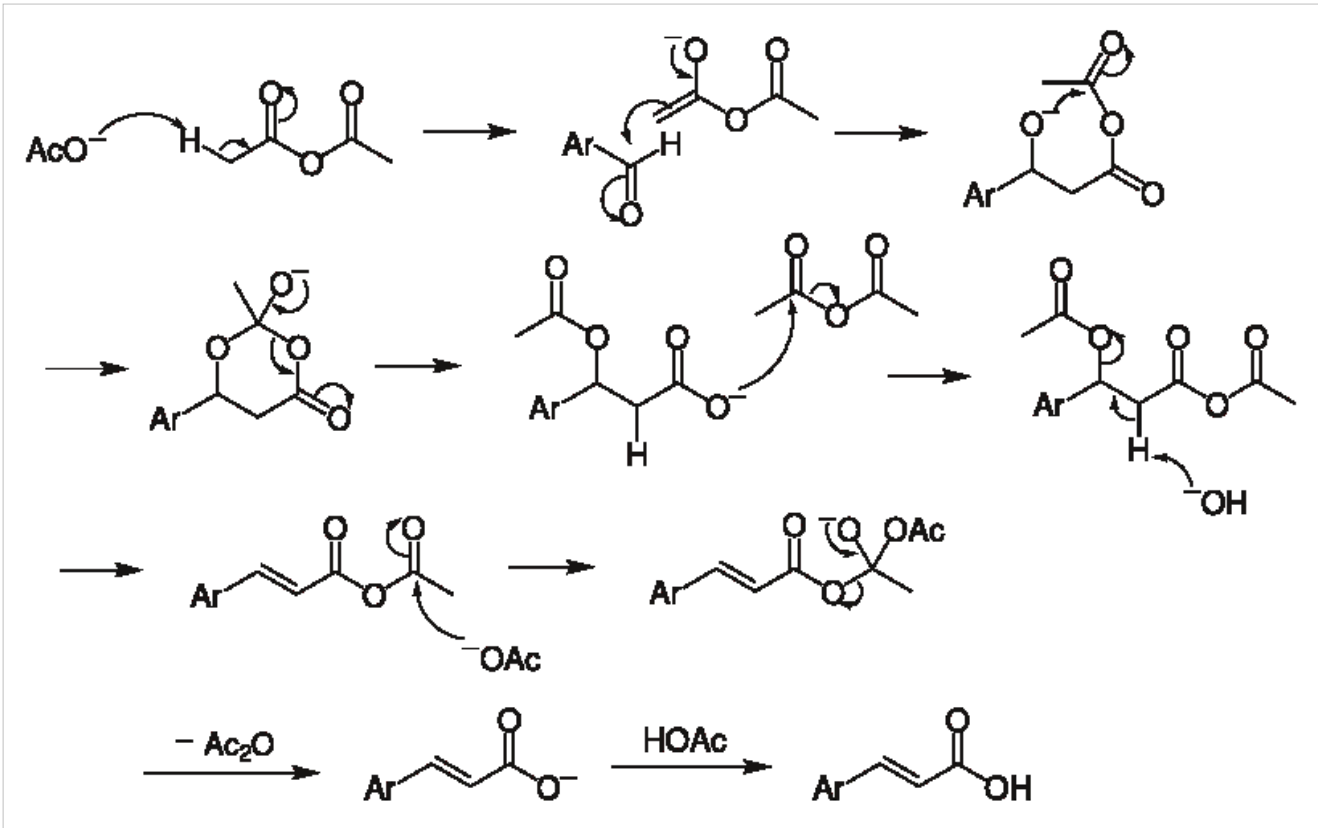
Perkin reaction	
Named after	William Henry Perkin
Reaction type	Condensation reaction
Reaction	
Aromatic aldehyde + **Acid anhydride** + Alkali salt of the acid ↓ **Cinnamic acid derivatives**	
Identifiers	
RSC ontology ID	RXNO:0000003 [1] ✓
✓ (what is this?) (verify) [2]	

The **Perkin reaction** is an organic reaction developed by William Henry Perkin that can be used to make cinnamic acids by the aldol condensation of aromatic aldehydes and acid anhydrides in the presence of an alkali salt of the acid.[3] [4]



Several reviews have been written.[5] [6] [7] . The reaction of phenylacetic acid and benzaldehyde with triethylamine and acetic anhydride to alpha-phenylcinnamic acid is an example of this reaction type.

Reaction mechanism



The above mechanism is not universally accepted, as several versions exist, including decarboxylation without acetic group transfer [8] .

References

[1] http://www.rsc.org/publishing/journals/prospect/ontology.asp?id=RXNO:0000003
[2] http://en.wikipedia.org/w/index.php?&diff=cur&oldid=342064841
[3] Perkin, W. H.; *J. Chem. Soc.* **1868**, *21*, 53, 181.
[4] Perkin, W. H.; *J. Chem. Soc.* **1877**, *31*, 388.
[5] Johnson, J. R.; *Org. React.* **1942**, *1*, 210. (Review)
[6] House, H. O. *Modern Synthetic Reactions* (W. A. Benjamin, Menlo Park, California, 2nd ed, 1972) pp 660-663.
[7] Rosen, T.; *Comp. Org. Syn.* **1991**, *2*, 395-408. (Review)
[8] Bansal, Raj K. *Organic Reaction Mechanisms*, Tata McGraw Hill, 3rd Ed, 1998, pp. 199-201.

Phenanthrene

Phenanthrene	
[[Image:Phenanthrene.png	]]
[[Image:Phenanthrene-3D-balls.png	]]
Identifiers	
CAS number	85-01-8 [1] ✓
PubChem	995 [2]
Properties	
Molecular formula	$C_{14}H_{10}$
Molar mass	178.23 g/mol
Melting point	99 °C
Boiling point	340 °C
Solubility in water	insoluble
Solubility in benzene, carbon disulfide, carbon tetrachloride, diethyl ether, ethanol, hexane	benzene 2.02 M, carbon disulfide 3.05 M,carbon tetrachloride 1.73 M, diethyl ether 1.36 M, ethanol 0.21 M, hexane 0.32 M [3]
Hazards	
NFPA 704	
✓ (what is this?) (verify) [4] Except where noted otherwise, data are given for materials in their standard state (at 25 °C, 100 kPa)	
Infobox references	

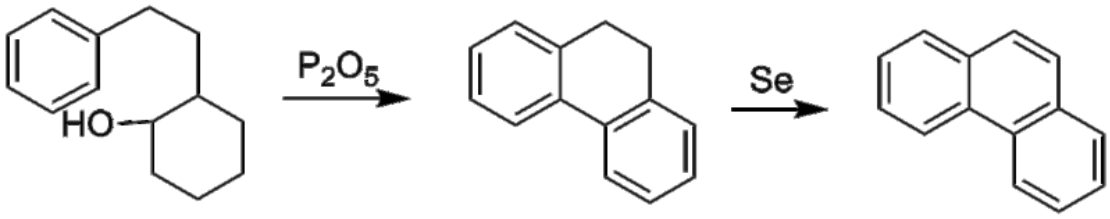
Phenanthrene is a polycyclic aromatic hydrocarbon composed of three fused benzene rings. The name *phenanthrene* is a composite of phenyl and anthracene. The natural opiates (i.e. morphine) and semi-synthetic opioids (i.e. hydromorphone, buprenorphine) have a phenanthrene skeleton. In its pure form, it is found in cigarette smoke and is a known irritant, photosensitising skin to light.[5] Phenanthrene appears as a white powder having blue fluorescence.

The compound with a phenanthrene skeleton and nitrogens at the 4 and 5 position is known as phenanthroline or **4,5-diazaphenanthrene** (IUPAC name).

Chemistry

Phenanthrene is insoluble in water but is soluble in most organic solvents such as toluene, carbon tetrachloride, ether, chloroform, acetic acid and benzene.

A classical phenanthrene synthesis is the ***Bardhan-Sengupta Phenanthrene Synthesis*** (1932). [6]



The first step is simply an electrophilic aromatic substitution reaction, which is allowed when the diphosphorous pentoxide makes the alcohol a better leaving group. However, no alkenes outside of the initial aromatic ring are created. In the second step of this reaction 9,10-dihydrophenanthrene is oxidized with elemental selenium. The aromatization of six-membered rings by selenium is not clearly understood, but it does produce H_2Se.

Phenanthrene can also be obtained photochemically from certain diarylethenes.

Reactions of phenanthrene typically occur at the 9 and 10 positions, including:

- Organic oxidation to phenanthrenequinone with chromic acid [7]
- Organic reduction to[9,10-dihydrophenanthrene with hydrogen gas and raney nickel [8]
- Electrophilic halogenation to 9-bromophenanthrene with bromine [9]
- Aromatic sulfonation to 2 and 3-phenanthrenesulfonic acids with sulfuric acid [10]
- Ozonolysis to diphenylaldehyde [11]

Canonical forms

Phenanthrene is more stable than its linear isomer anthracene. A classic and well established explanation is based on Clar's rule. A novel theory invokes so-called stabilizing hydrogen-hydrogen bonds between the C4 and C5 hydrogen atoms.

Natural occurrence

Ravatite is a natural analogue of (synthetic) phenanthrene. It is found in small amounts among a few coal burning sites. Ravatite represents a small group of organic minerals.

References

[1] http://www.commonchemistry.org/ChemicalDetail.aspx?ref=85-01-8
[2] http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=995
[3] Solubility of phenanthrene in non-aqueous solvents (http://oru.edu/cccda/sl/solubility/allsolvents.php?solute=phenanthrene)
[4] http://en.wikipedia.org/wiki/%3Aphenanthrene?diff=cur&oldid=408237694
[5] (http://deq.mt.gov/HazWaste/PDFs/phenanthrene.pdf)
[6] chempensoftware.com Link (http://www.chempensoftware.com/reactions/RXN039.htm)
[7] Organic Syntheses, Coll. Vol. 4, p.757 (1963); Vol. 34, p.76 (1954) Link (http://www.orgsynth.org/orgsyn/pdfs/CV4P0757.pdf)
[8] Organic Syntheses, Coll. Vol. 4, p.313 (1963); Vol. 34, p.31 (1954) Link (http://www.orgsynth.org/orgsyn/pdfs/CV4P0313.pdf).
[9] Organic Syntheses, Coll. Vol. 3, p.134 (1955); Vol. 28, p.19 (1948) Link (http://www.orgsynth.org/orgsyn/pdfs/CV3P0134.pdf).
[10] Organic Syntheses, Coll. Vol. 2, p.482 (1943); Vol. 16, p.63 (1936) Link (http://www.orgsynth.org/orgsyn/pdfs/CV2P0482.pdf).
[11] Organic Syntheses, Coll. Vol. 5, p.489 (1973); Vol. 41, p.41 (1961) Link (http://www.orgsynth.org/orgsyn/pdfs/CV5P0489.pdf).

External links

- Phenanthrene (http://www.scorecard.org/chemical-profiles/summary.tcl?edf_substance_id=85-01-8) at scorecard.org

Phenol formaldehyde resin

Phenol formaldehyde resins (PF) include synthetic thermosetting resins such as obtained by the reaction of phenols with formaldehyde. Sometimes the precursors include other aldehydes or other phenol. Phenolic resins are mainly used in the production of circuit boards. They are better known however for the production of molded products including pool balls, laboratory countertops, and as coatings and adhesives. In the form of Bakelite, they are the earliest commercial synthetic resin.[1] [2]

Formation and structure

Phenol-formaldehyde resins, as a group, are formed by a step-growth polymerization reaction that can be either acid- or base-catalysed. Since formaldehyde exists predominantly in solution as a dynamic equilibrium of methylene glycol oligomers, the concentration of the *reactive* form of formaldehyde depends on temperature and pH.

Phenol is reactive towards formaldehyde at the ortho and para sites (sites 2, 4 and 6) allowing up to 3 units of formaldehyde to attach to the ring. The initial reaction in all cases involves the formation of a hydroxymethyl phenol:

$$HOC_6H_5 + CH_2O \rightarrow HOC_6H_4CH_2OH$$

The hydroxymethyl group is capable of reacting with either another free ortho or para site, or with another hydroxymethyl group. The first reaction gives a methylene bridge, and the second forms an ether bridge:

$$HOC_{ub>2}O + H_2O.$$

Novolac

Novolacs are phenol-formaldehyde resins made where the molar ratio of formaldehyde to phenol of less than one. The polymerization is brought to completion using acid-catalysis. The phenol units are mainly linked by methylene groups. Novolacs are commonly used as photoresists. See also photolithography. The molecular weights are in the low thousands, corresponding to about 10-20 phenol units.

Hexamethylene tetramine or "hexamine" is a hardener that is added to crosslink novolac. At ≥180 °C, the hexamine forms crosslinks to form methylene and dimethylene amino bridges.

Resols

Base-catalysed phenol-formaldehyde resins are made with a formaldehyde to phenol ratio of greater than one (usually around 1.5). These resins are called resols. Phenol, formaldehyde, water and catalyst are mixed in the desired amount, depending on the resin to be formed, and are then heated. The first part of the reaction, at around 70 °C, forms a thick reddish-brown tacky material, which is rich in hydroxymethyl and benzylic ether groups.

The rate of the base-catalysed reaction initially increases with pH, and reaches a maximum at about pH = 10. The reactive species is the phenoxide anion ($C_6H_5O^-$) formed by deprotonation of phenol. The negative charge is delocalised over the aromatic ring, activating sites 2, 4 and 6, which then react with the formaldehyde.

Being thermosets, hydroxymethyl phenols will crosslink on heating to around 120 °C to form methylene and methyl ether bridges. At this point the resin is a 3-dimensional network, which is typical of polymerised phenolic resins. The high crosslinking gives this type of phenolic resin its hardness, good thermal stability, and chemical imperviousness.

Crosslinking and the phenol/formaldehyde ratio

When the molar ratio of formaldehyde:phenol reaches one, in theory every phenol is linked together via methylene bridges, generating one single molecule, and the system is entirely crosslinked. This is why bakelites (F:P <1) don't harden without the addition of a crosslinking agent, and why resins with the formula F:P >1 will.

Applications

Phenolic resins are found in myriad industrial products. Phenolic laminates are made by impregnating one or more layers of a base material such as paper, fiberglass or cotton with phenolic resin and laminating the resin-saturated base material under heat and pressure. The resin fully polymerizes (cures) during this process. The base material choice depends on the intended application of the finished product. Paper phenolics are used in manufacturing electrical components such as punch-through boards and household laminates. Glass phenolics are particularly well suited for use in the high speed bearing market. Phenolic micro-balloons are used for density control. Snooker balls as well as balls from many table-based ball games are also made from Phenol formaldehyde resin.

Trade names

- Bakelaque is a rigid laminate or tube made from phenolic resin on a substrate cotton fabric, paper or glass.[3]
- Bakelite is made from phenolic resin and wood flour.
- Novotext is cotton fibre-reinforced phenolic, using randomly oriented fibres.
- Oasis is "[a]n open-celled phenolic foam that readily absorbs water and is used as a base for flower arrangements."[4]
- Paxolin Paperstone][5] and Richlite are made from phenolic resin and paper.
- Trymer Green is a rigid cellular phenolic thermal insulation.
- Tufnol is made from phenolic resin and woven cotton or linen fabric.[6]

References

[1] A. Gardziella, L.A. Pilato, A. Knop, Phenolic Resins: Chemistry, Applications, Standardization, Safety and Ecology, 2nd edition, Springer, 2000

[2] Wolfgang Hesse "Phenolic Resins" in Ullmann's Encyclopedia of Industrial Chemistry, 2002, Wiley-VCH, Weinheim. doi:10.1002/14356007.a19_371.

[3] "Attwater Group Industrial Laminates" (http://www.attwater.com/products/laminate.asp). Attwater Group. .

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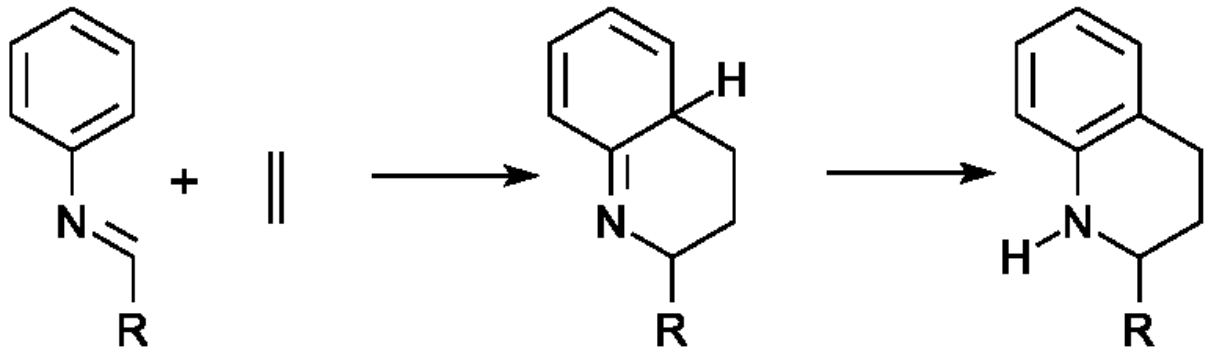
[6] "TUFNOL Fabric laminates" (http://www.tufnol.com/tufnol/default.asp?id=21). Tufnol. .

External links

- Safety data for phenol-formaldehyde resin (http://physchem.ox.ac.uk/MSDS/PH/phenol_formaldehyde_resin.html)

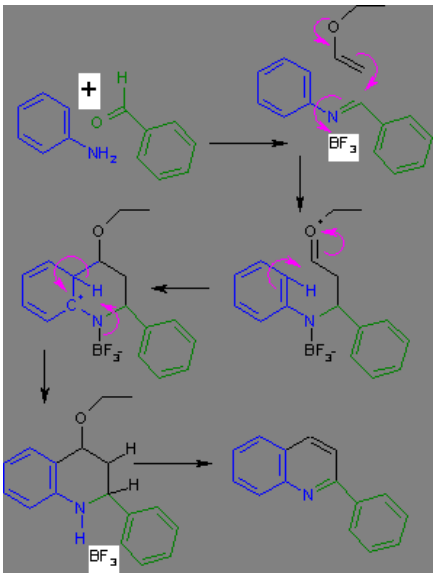
Povarov reaction

The **Povarov reaction** is an organic reaction described as a formal cycloaddition between an aromatic imine and an alkene. The imine in this organic reaction is a condensation reaction product from an aniline type compound and a benzaldehyde type compound [1] [2] [3] . The alkene must be electron rich which means that functional groups attached to the alkene must be able to donate electrons. Such alkenes are enol ethers and enamines. The reaction product in the original Povarov reaction is a quinoline. Because the reactions can be carried out with the three components premixed in one reactor it is an example of a multi-component reaction.



Reaction mechanism

The reaction mechanism for the Povarov reaction to the quinoline is outlined in *scheme 1*. In step one aniline and benzaldehyde react to the Schiff base in a condensation reaction. The Povarov reaction requires a lewis acid such as boron trifluoride to activate the imine for an electrophilic addition of the activated alkene. This reaction step forms an oxonium ion which then reacts with the aromatic ring in a classical electrophilic aromatic substitution. Two additional elimination reactions create the quinoline ring structure.

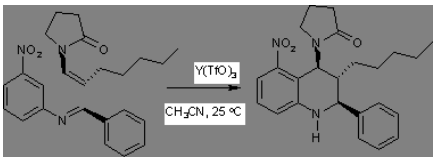


Scheme 1. The Povarov reaction

The reaction is also classified as a subset of aza Diels-Alder reactions [4]

Examples

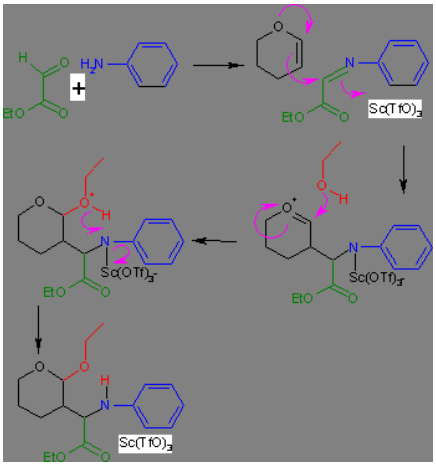
The reaction depicted in *scheme 2* illustrates the Povarov reaction with an imine and an enamine in the presence of yttrium triflate as the lewis acid [5] . This reaction is regioselective because the iminium ion preverentially attacks the nitro ortho position and not the para position. The nitro group is a meta directing substituent but since this position is blocked, the most electron rich ring position is now ortho and not para. The reaction is also diastereoselective because the enamine addition occurs with a preference for trans addition without formation of the cis isomer.



Scheme 2 regio- and diastereoselective Povarov reaction

Variations

One variation of the Povarov reaction is a four component reaction [6] . Whereas in the traditional Povarov reaction the intermediate carbocation gives an intramolecular reaction with the aryl group, this intermediate can also be terminated by an additional nucleophile such as an alcohol. *Scheme 3* depicts this 4 component reaction with the ethyl ester of glyoxylic acid, 3,4-dihydro-2H-pyran, aniline and ethanol with lewis acid scandium(III) triflate and molecular sieves.



Scheme 3 Four component Povarov reaction. In order to clarify the role of the lewis acid, a solid scandium nitrogen bond is drawn. Reaction conditions 2 days in acetonitrile at room temperature

References

[1] Povarov, L. S.; Mikhailov, B. M. Izv. Akad. Nauk SSR, Ser. Khim. **1963**, 953–956.

[2] Povarov, L. S.; Grigos, V. I.; Mikhailov, B. M. Izv. Akad. Nauk SSR, Ser. Khim. **1963**, 2039–2041.

[3] Povarov, L. S. *Russian Chem. Rev.* **1967**, 36, 656.

[4] *Recent synthetic developments in a powerful imino Diels–Alder reaction (Povarov reaction): application to the synthesis of N-polyheterocycles and related alkaloids* Vladimir V. Kouznetsov Tetrahedron 65 (**2009**) 2721–2750 doi:10.1016/j.tet.2008.12.059

[5] *Unprecedented regio and stereocontrol in Povarov reaction of benzylidene-(3-nitrophenyl)amine* Paul J. Stevenson and Isla Graham Arkivoc AM-717D **2003**. (Article (http://www.arkat-usa.org/ark/journal/2003/I07_McKervey/AM-717D/717D.asp))

[6] *Straightforward Access to a Structurally Diverse Set of Oxacyclic Scaffolds through a Four-Component Reaction* Oscar Jiménez, Guillermo de la Rosa, Rodolfo Lavilla Angewandte Chemie International Edition Volume 44, Issue 40 , Pages 6521 - 6525 **2005** Abstract (http://www3.interscience.wiley.com/cgi-bin/abstract/112092897/ABSTRACT)

Self-condensation

Self-condensation is an organic reaction in which a chemical compound containing a carbonyl group acts both as the electrophile and the nucleophile in an aldol condensation. It is also called a **symmetrical aldol condensation** as opposed to a **mixed aldol condensation** in which the electrophile and nucleophile are different species.

For example, two molecules of acetone condense to a single compound mesityl oxide in the presence of an ion exchange resin:[1]

$$2\ CH_3COCH_3 \rightarrow (CH_3)_2C{=}CH(CO)CH_3 + H_2O$$

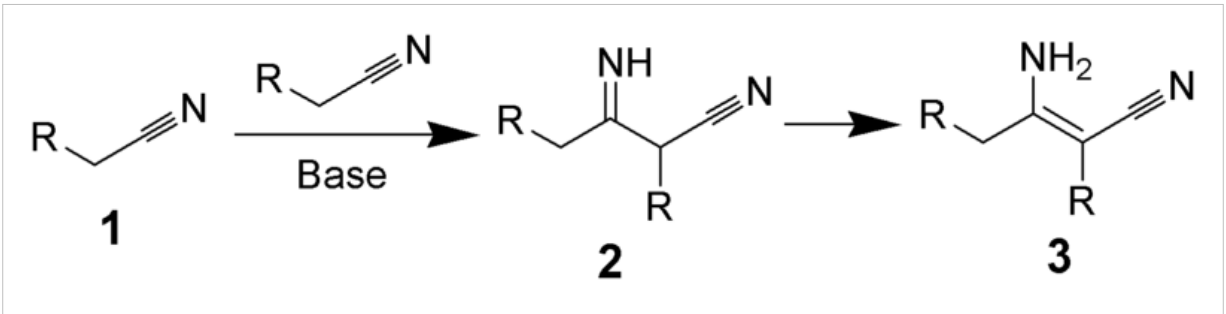
For synthetic uses, this is generally an undesirable, but spontaneous and favored side-reaction of mixed aldol condensation, and special precautions are needed to prevent it.

References

[1] Ketone Condensations Using Sulfonic Acid Ion Exchange Resin N. Lorette; *J. Org. Chem.*; 1957; 22(3); 346-347.

Thorpe reaction

The **Thorpe reaction** is a chemical reaction described as a self-condensation of aliphatic nitriles catalyzed by base to form enamines.[Baron1904Ziegler1933Schaefer1967] The reaction was discovered by Jocelyn Field Thorpe.



Thorpe–Ziegler reaction

The **Thorpe–Ziegler reaction** (named after Jocelyn Field Thorpe and Karl Ziegler), or **Ziegler method**, is the intramolecular modification with a dinitrile as a reactant and a cyclic ketone as the final reaction product after acidic hydrolysis. The reaction is conceptually related to the Dieckmann condensation.

External links

- Thorpe-Ziegler reaction: *4-Phosphorinanone, 1-phenyl-* Organic Syntheses, Coll. Vol. 6, p.932 (1988); Vol. 53, p.98 (1973) Link [1]

References

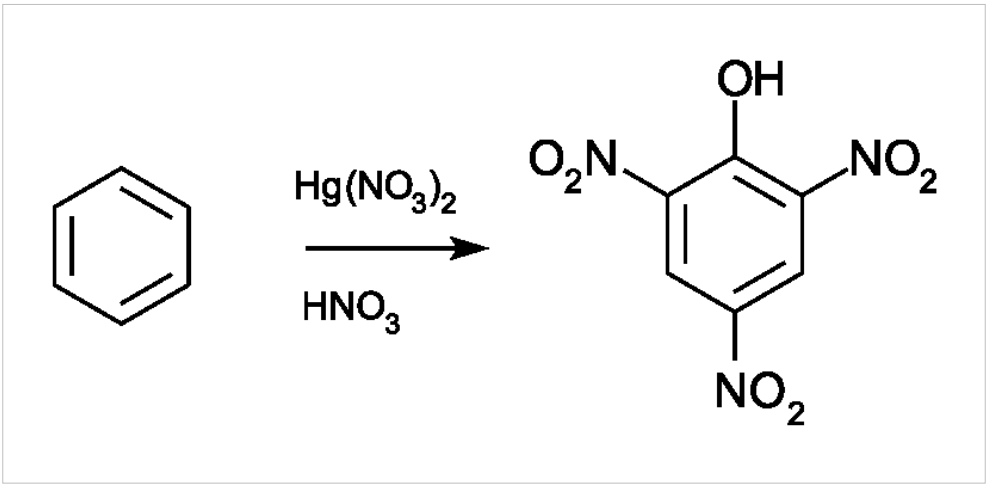
1. Baron, H.; Remfry, F. G. P.; Thorpe, Y. F. *J. Chem. Soc.* **1904**, *85*, 1726.
2. Karl Ziegler *et al. Ann.* **1933**, *504*, 94.
3. Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1. (Review)

References

[1] http://www.orgsynth.org/orgsyn/pdfs/CV6P0932.pdf

Wolffenstein-Böters reaction

The **Wolffenstein-Böters reaction** is an organic reaction converting benzene to picric acid by a mixture of aqueous nitric acid and mercury(II) nitrate.[1] [2] [3]



According to one series of studies the mercury nitrate first takes benzene to the corresponding nitroso compound and through the diazonium salt to the phenol. The presence of nitrite is essential for the reaction; picric acid formation is prevented when urea, a trap for nitrous acid, is added to the mixture. From then on the reaction proceeds as a regular aromatic nitration.[4] [5]

A conceptually related reaction at one time of interest to the pigment industry is the **Bohn-Schmidt reaction** (1889) involving the hydroxylation of *hydroxyantraquinone* with sulfuric acid and lead or selenium to a polyhydroxylated anthraquinone.

External links

- The Bohn-Schmidt reaction @ Institute of Chemistry, Skopje, Macedonia Link [6]

References

[1] Wolffenstein and Boeters, Chem. Abs., I, 489, 1861 (1908); 4, 369 (**1910**);

[2] Richard Wolffenstein, O. Böters (1913). "Über die katalytische Wirkung des Quecksilbers bei Nitrierungen". *Berichte der deutschen chemischen Gesellschaft* **46** (1): 586–589. doi:10.1002/cber.19130460177.

[3] R. Wolffenstein, W. Paar (1913). "Über Nitrierung der Benzoesäure in Gegenwart von Quecksilber". *Berichte der deutschen chemischen Gesellschaft* **46** (1): 589–599. doi:10.1002/cber.19130460178.

[4] *The Mechanism of the Oxynitration of Benzene* F. H. Westheimer, Edward Segel, and Richard Schramm J. Am. Chem. Soc.; **1947**; 69(4) pp 773 - 785; doi:10.1021/ja01196a011

[5] *The Oxynitration of Benzene. I. Studies Relating to the Reaction Mechanisms*Marvin Carmack, Manuel M. Baizer, G. Richard Handrick, L. W. Kissinger, and Edward H. Specht J. Am. Chem. Soc.; **1947**; 69(4) pp 785 - 790; doi:10.1021/ja01196a012

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