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Rearrangement Reactions

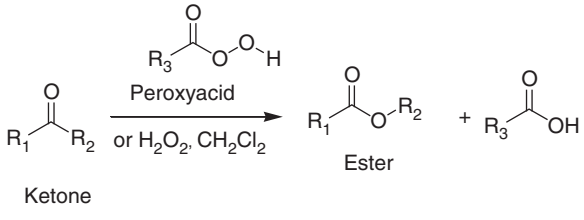
A rearrangement reaction is a board class of organic reactions in which an atom, ion, group of atoms, or chemical unit migrates from one atom to another atom in the same or different species, resulting in a structural isomer of the original molecule. Rearrangement reactions mostly involve breaking and/or making C—C, C—O, or C—N bonds. The migration origin is the atom from which the group moves, and the migration terminus is the atom to which it migrates.

Baeyer–Villiger Oxidation or Rearrangement

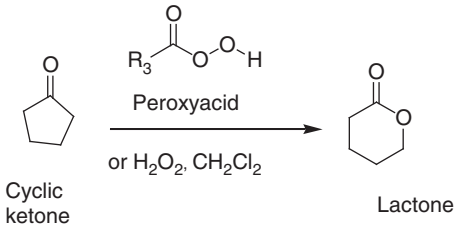
The Baeyer–Villiger oxidation is an organic reaction that converts a ketone to an ester or a cyclic ketone to a lactone in the presence of hydrogen peroxide or peroxy acids [1]. The reaction was discovered in 1899 by Adolf von Baeyer and Victor Villiger. It is an intramolecular anionotropic rearrangement where an alkyl group migrates from the carbonyl carbon atom (migration origin) to an electron-deficient oxygen atom (migration terminus). The most electron-rich alkyl group (most substituted carbon) that is able to stabilize a positive charge migrates most readily. The migration order is as follows:

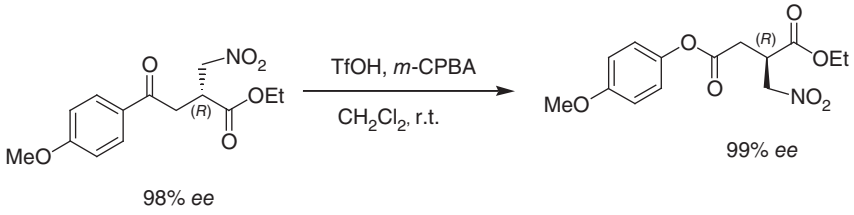
Tertiary alkyl > cyclohexyl > secondary alkyl > phenyl > primary alkyl > CH_3 > H.

Several new catalysts including organics, inorganics, and enzymes have been developed for this reaction [2–76]. Amine or alkene functional groups are limitations, however, because of their easy and undesirable oxidation.

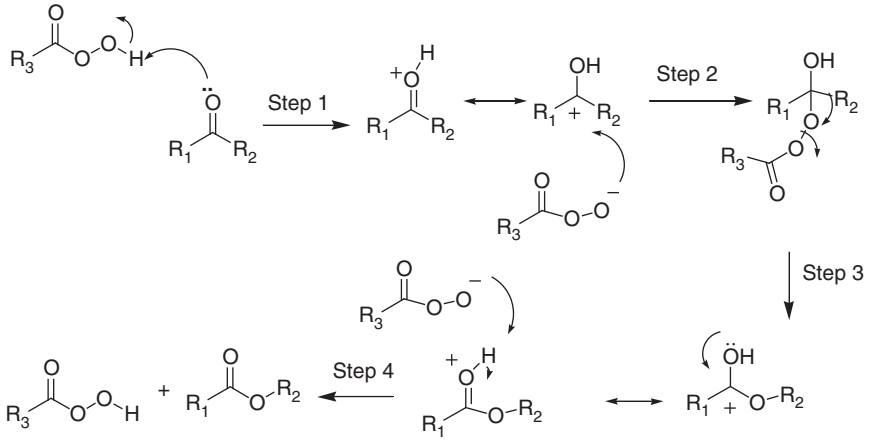


Applied Organic Chemistry: Reaction Mechanisms and Experimental Procedures in Medicinal Chemistry, First Edition. Surya K. De.





Mechanism



Step 1: The oxygen atom of the ketone is protonated to form a carbenium ion.
Step 2: Nucleophilic attacks by aperoxycarboxylate ion at electron-deficient carbonyl carbon atom.
Step 3: One of the alkyls on the ketone migrates to the oxygen of the peroxide group, while a carboxylic acid departs.
Step 4: Deprotonation of the oxocarbenium ion produces the desired ester.

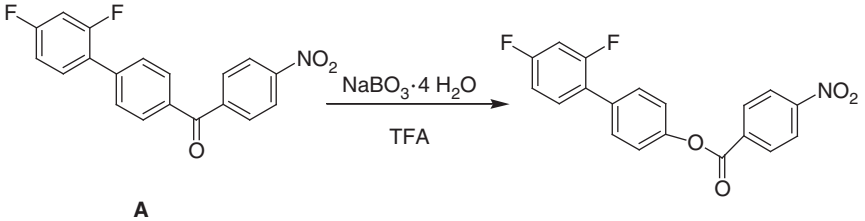
Application

Zoapatanol and testololactone (anticancer agent) were synthesized using Baeyer–Villiger oxidation reaction conditions. Total syntheses of several natural products such as 9-epi-pentalenic acid [40], (+)-hippolachnin A,

(+)-gracilioether A, (−)-gracilioether E, (−)-gracilioether F [71], and salimabromide [76] have been accomplished utilizing this reaction.

Experimental Procedure (from patent US 5142093A)

Preparation of 4-(2,4-Difluorophenyl)-phenyl 4-nitrobenzoate

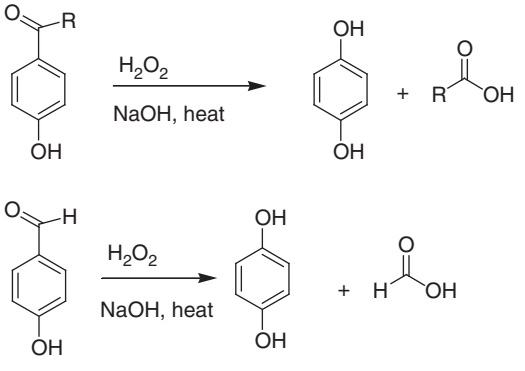


A **B**

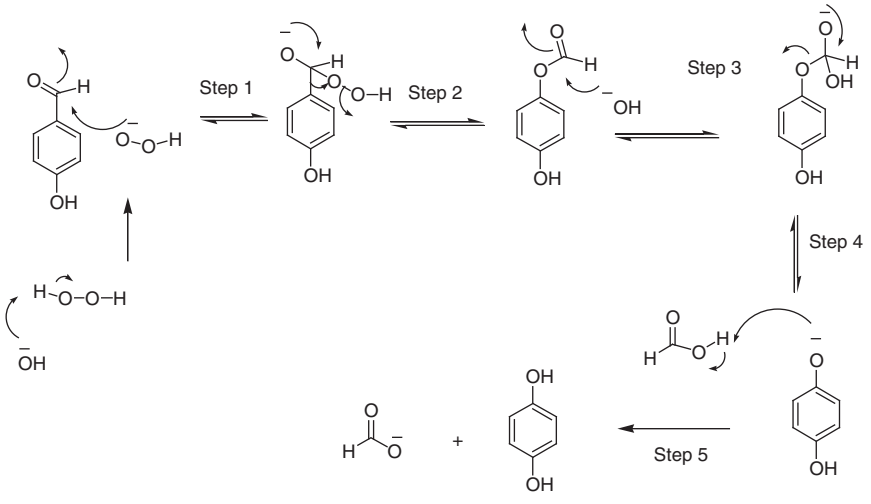
Sodium perborate tetrahydrate (1.5 g, 9.7 mmol) was added to a mixture of 4-(2,4-difluorophenyl)-4-nitro-benzophenone (**A**) (1 g, 2.9 mmol) and trifluoroacetic acid (9 ml) at 20 °C under stirring and under nitrogen for 24 hours and then poured into a mixture of methylene chloride (10 ml) and water (10 ml). The organic phase was washed with an 8% aqueous solution of sodium bicarbonate. After drying with sodium sulfate and evaporation of the solvent under reduced pressure, a crude (1.03 g) containing a mixture of ester and ketone starting material in the ratio 98 : 2 from ^{19}F NMR analysis was obtained. The amount of ester (**B**) (0.946 g, 91.9% yield) in the crude was determined by high-performance liquid chromatography (HPLC) analysis. An analytical sample (0.89 g) of the crude was crystallized from ethyl acetate giving pure product (0.70 g).

Dakin Oxidation (Reaction)

Dakin reaction is a redox reaction used to convert an *ortho*- or *para*-hydroxylated phenyl aldehyde or a ketone to a benzenediol with alkaline hydrogen peroxide. This reaction, which is named after British chemist Henry Drysdale Dakin, is closely related to Baeyer–Villiger oxidation [1–17].



Mechanism



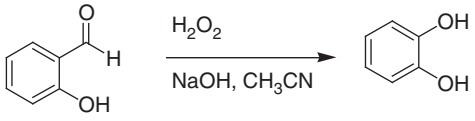
Step 1: Nucleophilic attack by a hydroperoxide anion to the electron-deficient carbonyl carbon atom forms a tetrahedral intermediate.
Step 2: Aryl esmigration, elimination of hydroxide, and formation of an aryl ester.
Step 3: Nucleophilic addition of hydroxide to the ester carbonyl carbon atom forms a second tetrahedral intermediate.
Step 4: The unstable tetrahedral intermediate collapses to eliminate a phenoxide and forms a carboxylic acid.
Step 5: Proton transfers from carboxylic acid to phenoxide.

Application

Catecholamine, a neurotransmitter, and (±)-fumimycin, a natural product [14], were synthesized by Dakin oxidation.

Experimental Procedure (from patent EP0591799B)

Preparation of Catechol (*o*-Dihydroxybenzene)



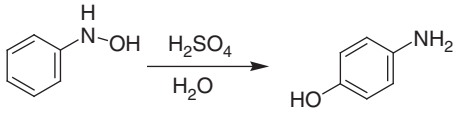
A **B**

6.1 g (0.05 mol) of salicylaldehyde (**A**) and 0.01 g (0.25 mol) of NaOH in 50 ml of acetonitrile were introduced and mixed with 17.2 g of a 11.8% strength (0.06 mol) of hydrogen peroxide aqueous solution and stirred at 50 °C for 48 hours. Any remaining peroxide was removed with a dilute sodium sulfite solution. The

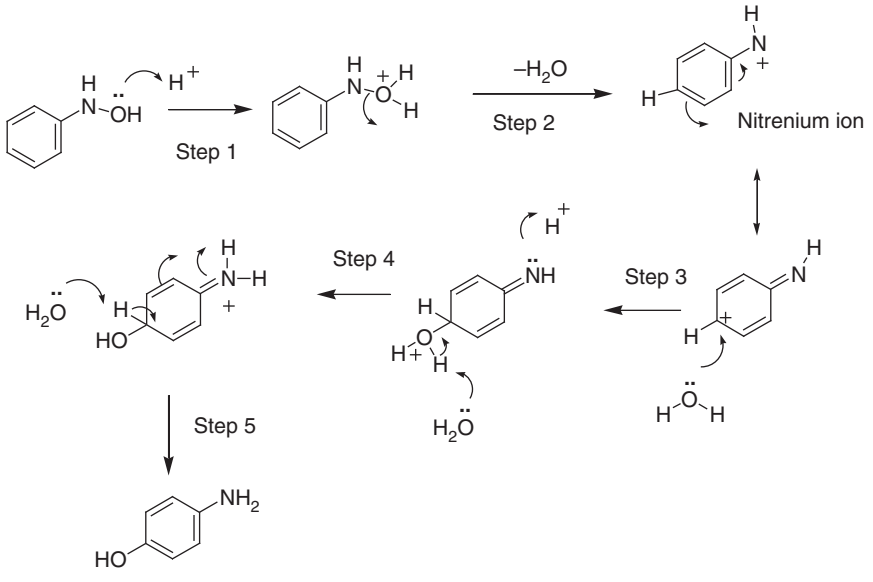
reaction mixture was then mixed with essigester, the organic phase separated, and aqueous phase was washed several times with essigester. Then the combined organic phases were dried and freed of solvent *in vacuo* to obtain 5.4 g, which was ^{1}H NMR spectroscopy identified by a comparative sample as catechol (**B**). (Purity was determined by gas chromatography: 98%; yield 96% of theoretical.)

Bamberger Rearrangement

The Bamberger rearrangement is an organic reaction used to convert *N*-phenylhydroxylamine to 4-aminophenol in the presence of strong aqueous acid [1, 2]. The reaction is named after German chemist Eugen Bamberger. Several new catalysts have been developed for the preparation of 4-aminophenol from directly nitrobenzene [3–19].



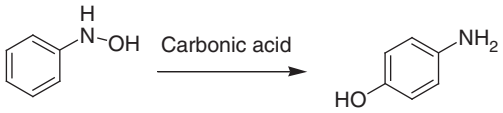
Mechanism



Step 1: Mono-protonation of *N*-phenylhydroxylamine.
Step 2: Elimination of water and formation of carbocation via a nitrenium ion.
Step 3: Nucleophilic attack by water at the carbocation.
Step 4: Protonation and deprotonation.
Step 5: Deprotonation and rearomatization.

Experimental Procedure (from patent CN102001954B)

Preparation of *p*-Aminophenol from *N*-Phenylhydroxylamine

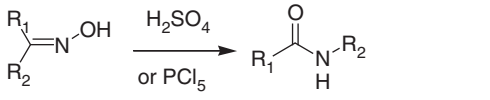


A **B**

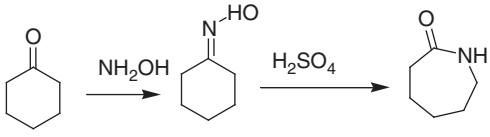
In a 100 ml reactor, 0.5 mmol *N*-phenylhydroxylamine (**A**) was added; in a 50 ml of water, the closed reactor with CO_2 substituted three times and then charged with CO_2; the reaction was heated at 100 °C; in CO_2 pressure 8 MPa conditions, the reaction was stirred for one hour. The reaction mixture was extracted with ethyl acetate and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed over silica gel to afford a pure product (**B**).

Beckmann Rearrangement

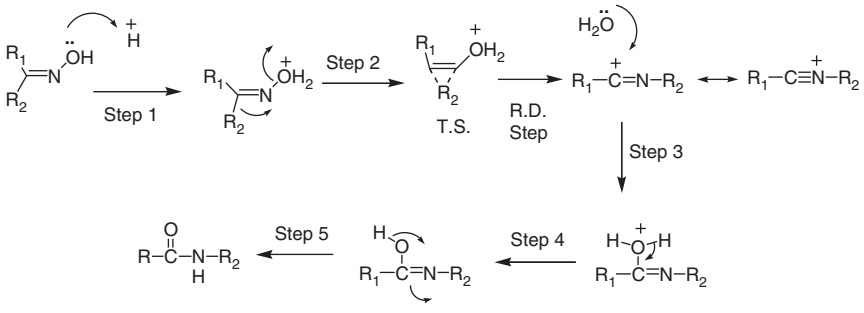
The Beckmann rearrangement, named after the German chemist Ernst Otto Beckmann, is a conversion of an oxime to an *N*-substituted amide in the presence of acid catalyst [1]. The acid catalysts are used including HCl, H_2SO_4, PCl_5, $SOCl_2$, P_2O_5, tosyl chloride, SO_3, BF_3, etc. These catalysts require the excess amounts and produce a large amount of by-products. Most recently, this reaction has been utilized by using a catalytic amount of new types of catalysts such as $RuCl_3$, $BiCl_3$, etc. [2–51].



Anti or *trans* w.r.t. R_2



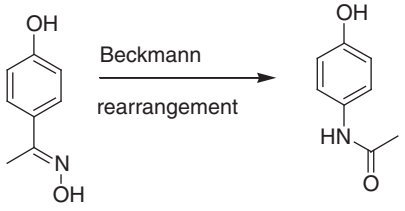
Mechanism



Step 1: Protonation of hydroxyl group and formation of a better leaving group
Step 2: Migration of R_2 group *trans* or anti to the leaving group and loss of water group leading to formation of carbocation. This *trans* (1,2) shift predicts the regiochemistry for this reaction.
Step 3: Water molecule attacks as a nucleophile with a lone pair of electrons to the carbocation.
Step 4: Deprotonation.
Step 5: Tautomerization affords an *N*-substituted amide, the final product.

Application

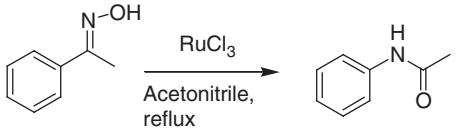
The Beckmann rearrangement reaction is used for the synthesis of paracetamol (acetaminophen), benazepril, ceforanide, olanzapine, elantrine, prazepine, enprazepine, etazepine, and other medicines.



Paracetamol (acetaminophen)

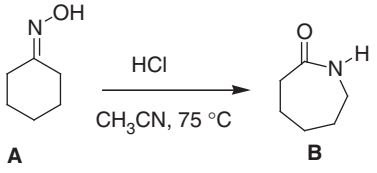
Experimental Procedure (general)

Synthesis of Acetanilide



A mixture of acetophenone oxime (135 mg, 1 mmol) and $RuCl_3$ (100 mg) or any other catalyst in acetonitrile (10 ml) was refluxed until no starting material was left (thin-layer chromatography [TLC] monitored). The solvent was removed by rotary evaporator, and the residue was purified over silica gel chromatography using 30% ethyl acetate in hexane to yield an acetanilide (m.p. 114 °C).

Preparation of Caprolactam (from patent US 3437655A)



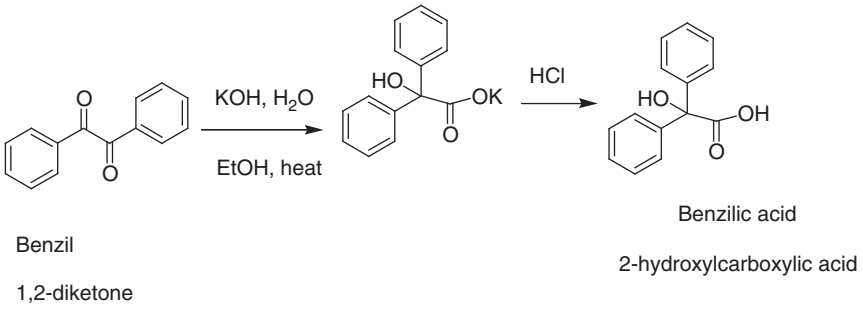
A **B**

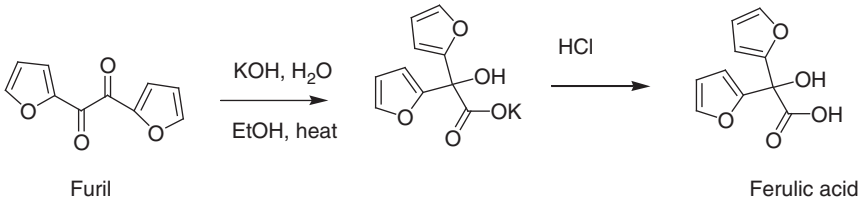
In a 1 l reaction vessel equipped with a stirrer, a reflux cooler, and a gas inlet tube, 113 g of cyclohexanone oxime (**A**) (1 mol) was mixed with 200 ml of acetonitrile,

after which 40 g of gaseous hydrogen chloride (1.1 mol) was introduced at room temperature. Subsequently the temperature was raised and maintained at 75 °C for two hours, after which the rearrangement was completed. After the acetonitrile had been removed by distillation, the reaction product was dissolved in water and the solution neutralized with sodium bicarbonate. The resulting solution, which was saturated with common salt, was extracted with benzene. After removal of the benzene, 81 g of product caprolactam (**B**) was obtained, 71% yield.

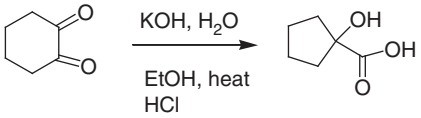
Benzilic Acid Rearrangement

The benzilic acid rearrangement reaction is an organic reaction used to convert 1,2-diketones to 2-hydroxycarboxylic acids using strong base (KOH or NaOH) and then acid work-up [1]. Benzil reacts with base to give benzilic acid that bears the name of the reaction. The reaction works well with aromatic 1,2-diketones. Aliphatic diketones with adjacent enolizable protons undergo aldol-type condensation. The aryl groups with electron-withdrawing groups work the best [2–17].

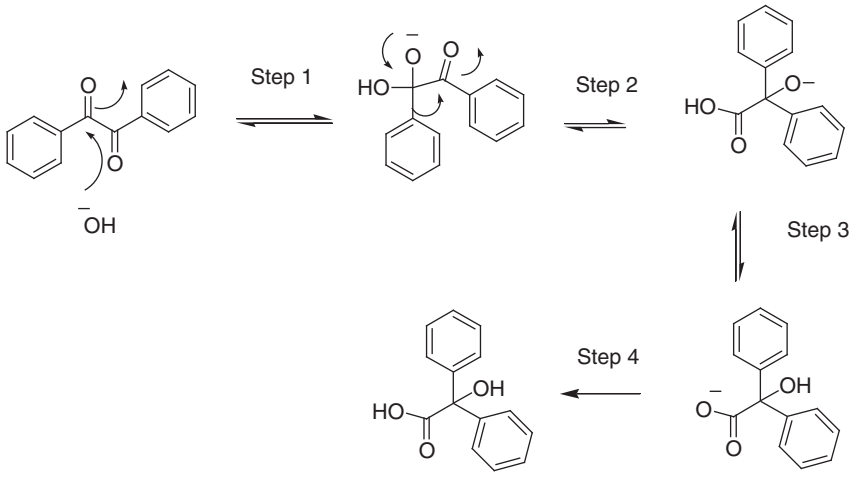




Cyclic diketones lead to form the ring contraction products.



Mechanism



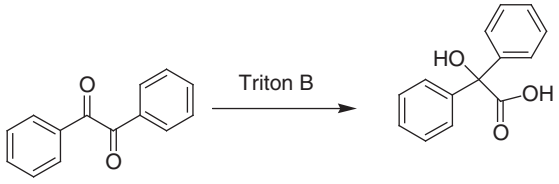
Step 1: Nucleophilic attack by hydroxide at the electron-deficient carbonyl carbon atom.
Step 2: Migration of phenyl group.
Step 3: Proton transfer.
Step 4: Acidic work-up gives the desired product.

Application

The natural product preuisolactone A [16] has been synthesized using this reaction.

Experimental Procedure (from patent US20100249451B)

Synthesis of Benzilic Acid from Benzil

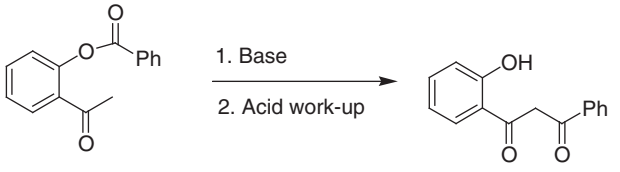


A mixture of benzil (0.1 mol) and Triton B (benzyltrimethylammonium hydroxide) (0.2 mol) was heated at 40 °C for two hours with stirring. The mixture was diluted with water and acidified with 10% hydrochloric acid up to pH 3. The solid was filtered and washed with water to obtain benzilic acid in 92% yield.

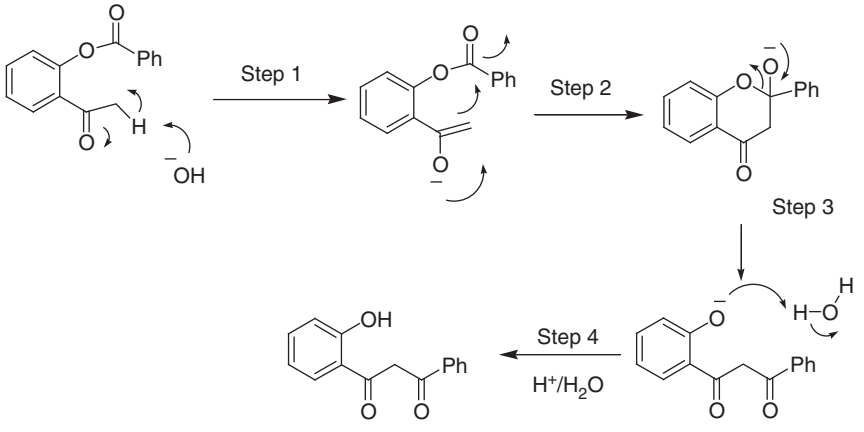
Baker–Venkataraman Rearrangement

The Baker–Venkataraman rearrangement is a base-catalyzed acyl transfer reaction of aromatic *ortho*-acyloxyketones to aromatic β-diketones (1,3-diketones) [1–3]. The reaction is named after chemists Wilson Baker and Krishnaswami

Venkataraman. This reaction has a wide range of applications in organic and medicinal chemistry [4–23].



Mechanism



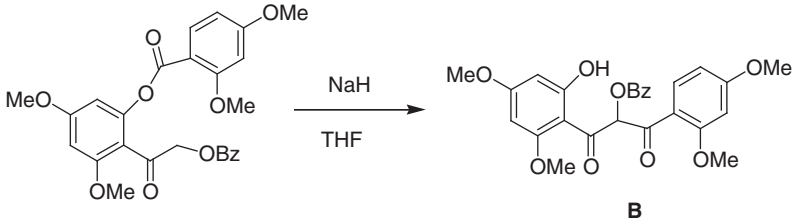
Step 1: The hydroxide abstracts an α-hydrogen atom to form an enolate.
Step 2: The nucleophilic attacks by the enolate to the ester carbonyl to form a cyclic alkoxide.
Step 3: Ring opening and transfer of the acyl group.
Step 4: Protonation from acidic work-up gives the desired product.

Application

Total syntheses of natural products including stigmatellin A [9, 10], zapotin [14], houttuynoid B [19], glycosylflavone aciculatin [21], and dirchromone-1 [23] have been accomplished utilizing this reaction.

Experimental Procedure (from patent CN105985306B)

Synthesis of 2,4-Dimethoxyphenyl-3-(2-hydroxy-4,6-dimethoxyphenyl)-2-propyl-1,3-dicarbonyl-benzoate

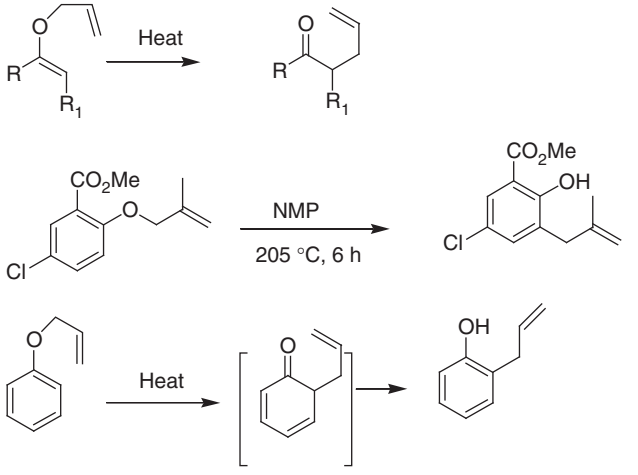


A **B**

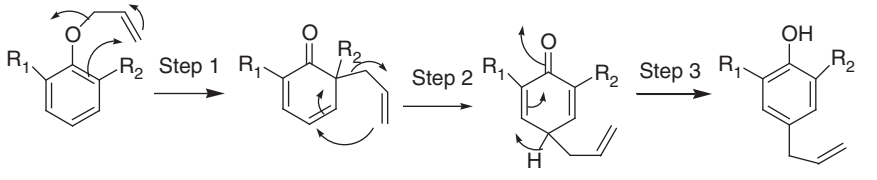
NaH (53 mg, 2.20 mmol) and 400 mg (**A**) were placed into 20 ml of dry tetrahydrofuran (THF), and the reaction mixture was stirred at 75 °C until starting material disappeared. The reaction mixture was cooled to room temperature, immersed in 30 ml ice water, extracted three times with ethyl acetate, and washed with brine three times. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified over silica gel column chromatography (PE/EA 6 : 1) to give 330 mg of the product **B** as a white solid (yield 77%).

Claisen Rearrangement

The Claisen rearrangement is a [3,3]-sigmatropic rearrangement of an allyl vinyl ether to form a γ,δ-unsaturated carbonyl compound under heating or acidic conditions. The reaction is a concerted process where bonds are forming and breaking at the same time [1–31].

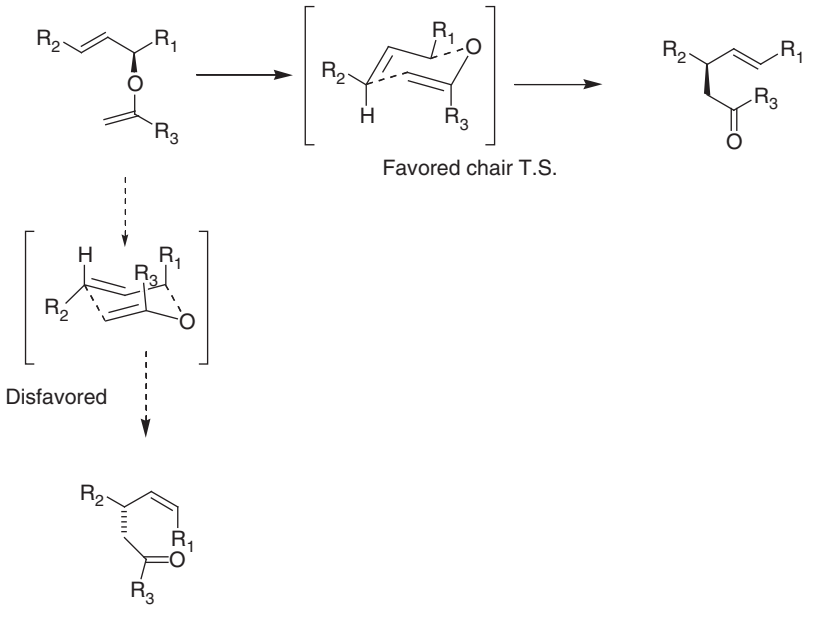


When 2,6-positions are blocked, rearomatization cannot take place; there are no *o*-H atoms. In this case the allyl group will first migrate to the *o*-position, and then second migration will take place to the *p*-position via tandem Claisen and Cope rearrangement.



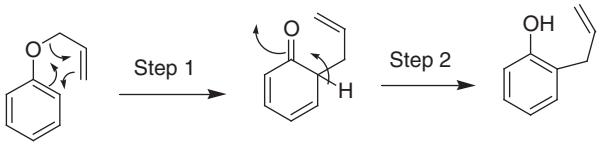
Mechanism

This rearrangement is an exothermic, suprafacial, concerted, and pericylic reaction.



When large groups are in equatorial positions, the 1,3-interaction is minimized. When large groups are in axial positions, the 1,3-diaxial unfavorable interaction is maximized.

The aromatic Claisen rearrangement undergoes [3,3]-sigmatropic rearrangement accompanied by a rearomatization.

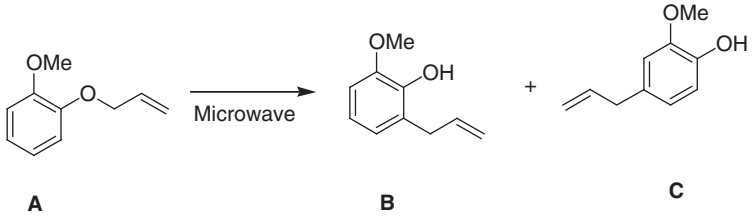


Step 1: [3,3]-Sigmatropic rearrangement.
Step 2: Rearomatization gives the desired product.

Application

Total syntheses of termicalcicolanone A [6], (+)-flavisiamine F [12], schiglautone A [27], hemigossypol, gossypol [28], hybridaphniphylline B [29], (±)-corymine [25], sanggenons C [21], (+)-antroquinonol, (+)-antroquinonol D [20],(−)-teucvidin [13], (+)-jasplakinolide [10], and many more have been achieved using this reaction.

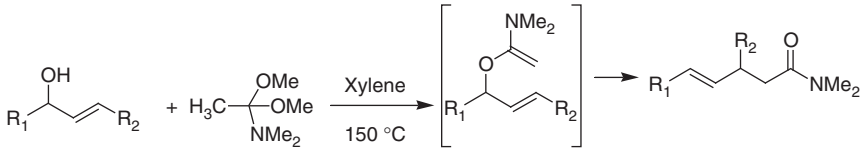
Experimental Procedure (from patent WO2016004632A1)



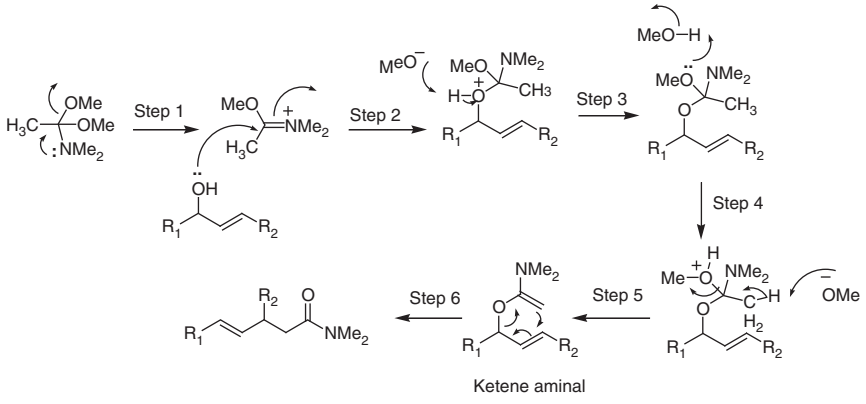
To a 5 ml microwave vial fitted with a magnetic stirrer was charged with calcium bistriflimide (16 mg) and *O*-allylguaiacol (**A**) (438 mg, 2.67 mmol). The vial was then sealed, and the resultant homogeneous mixture was stirred for two minutes at the temperature of 200 °C under an autogenous pressure and a microwave irradiation generated by the Biotage® microwave instrument. After cooling to room temperature, the resulting reaction mixture was analyzed by ^{1}H NMR to determine the conversion ratio (100%) and isomeric composition [76% of *ortho*-eugenol (**B**) and 24% of *para*-eugenol (**C**)].

Eschenmoser–Claisen Rearrangement

When an allylic alcohol is heated in the presence of *N*,*N*-dimethylacetamide dimethyl acetal to produce a γ,δ-unsaturated amide, the reaction is known as the Eschenmoser–Claisen rearrangement [32, 33].



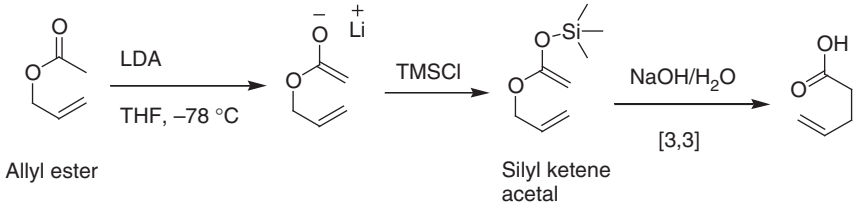
Mechanism



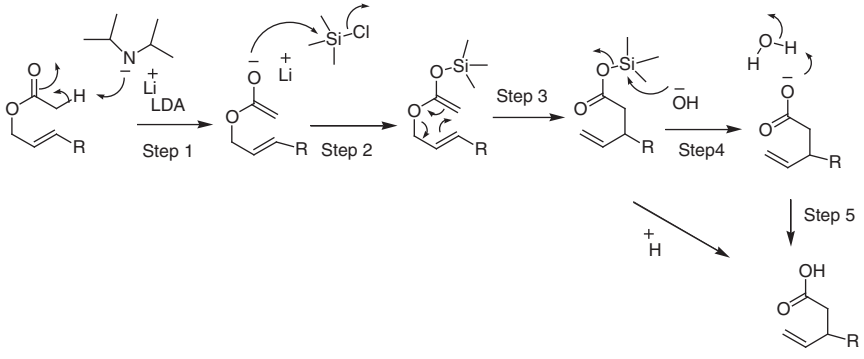
Step 1: The *N*,*N*-dimethylacetamide dimethyl acetal releases one methoxide to form an iminium cation.
Step 2: The alcohol attacks at the iminium.
Step 3: Methoxide abstracts a proton.
Step 4: Protonation.
Step 5: Methoxide abstracts a proton from the methyl, and the intermediate releases a methanol to form a 1,5-diene intermediate (ketene aminal).
Step 6: The ketene aminal intermediate undergoes a [3,3]-sigmatropic rearrangement via a chair-like transition state to produce the desired product.

Ireland–Claisen Rearrangement

The conversion of an allylic ester to a γ,δ-unsaturated carboxylic acid via silyl ketene acetal using lithium diisopropylamide (LDA), TMSCl, and $NaOH/H_2O$ is known as the Ireland–Claisen rearrangement [34–36]. The stereochemical formation of *E*/*Z* silyl ketene acetal is possible using hexamethylphosphoramide (HMPA) [37].



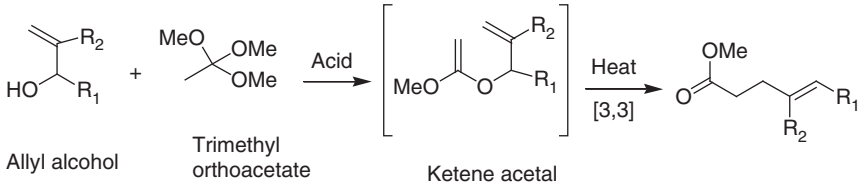
Mechanism



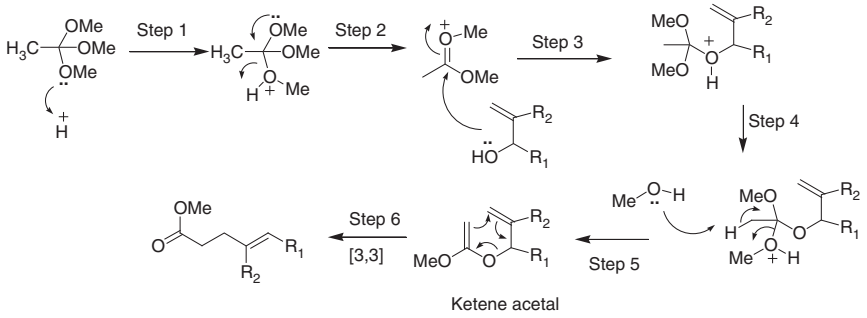
Step 1: LDA abstracts a proton.
Step 2: Nucleophilic substitution reaction.
Step 3: [3,3]-Sigmatropic rearrangement.
Step 4: Desilylation.
Step 5: Proton transfer.

Johnson–Claisen Rearrangement

When an allyl alcohol is heated with an excess of triethyl orthoacetate under mild acidic conditions to yield a γ,δ-unsaturated ester, the reaction is called the Johnson–Claisen rearrangement [38].



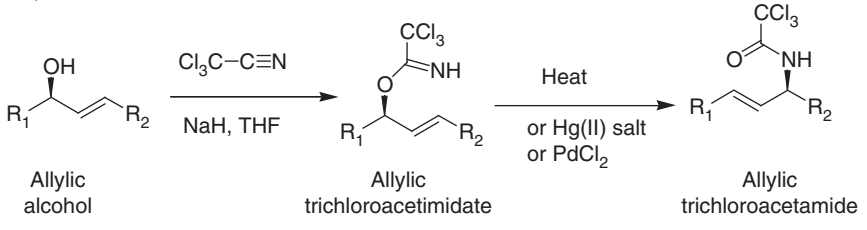
Mechanism



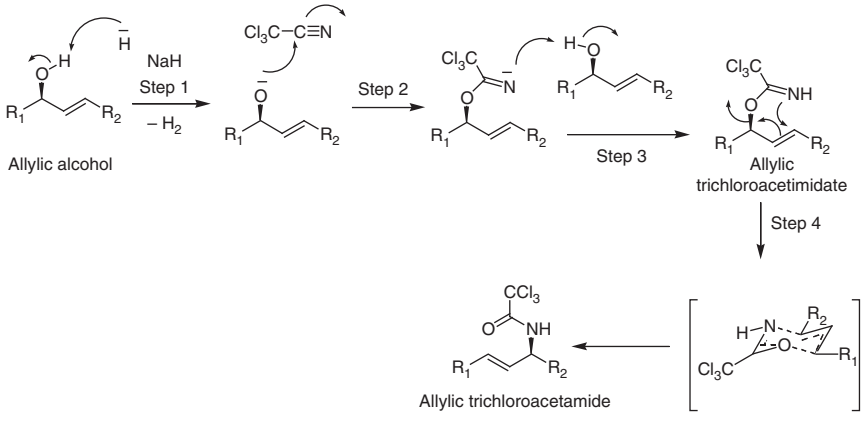
Step 1: Protonation one of methoxy groups.
Step 2: Elimination of methanol forms an oxonium cation.
Step 3: Alcohol attacks at the oxonium intermediate.
Step 4: Proton transfer.
Step 5: Methanol abstracts a proton and releases another methanol to form a ketene acetal intermediate.
Step 6: A [3,3]-sigmatropic rearrangement undergoes to produce γ,δ-unsaturated ester.

Overman Rearrangement

The stereoselective conversion of an allylic alcohol to an allylic trichloroacetamide through an allylic trichloroacetimidate intermediate is known as the Overman rearrangement [39–41]. This rearrangement is similar to the Claisen suprafacial, concerted, nonsynchronous, [3,3]-sigmatropic rearrangement. Larry Overman discovered this reaction in 1974.



Mechanism

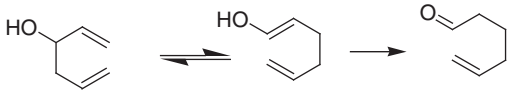


Step 1: Deprotonation with a strong base.
Step 2: The deprotonated alcohol attacks as a nucleophile to trichloroacetonitrile to form an anion intermediate.
Step 3: The anion takes a proton from the starting alcohol to give an allylic trichloroacetimidate intermediate. Since anion takes a proton from the starting alcohol, only a catalytic amount of a strong base is required.
Step 4: This intermediate undergoes a concerted [3,3]-sigmatropic rearrangement via a six-membered chair-like transition state to give an allylic trichloroacetamide.

Cope Rearrangement

The Cope rearrangement is a [3,3]-sigmatropic rearrangement of 1,5-dienes under thermal conditions to produce regioisomeric 1,5-dienes [1]. The reaction mainly proceeds through an intramolecular pathway.

The oxy-Cope rearrangement has a hydroxy group on C-3 (sp^3-hybridized carbon), forming enal or enone after keto–enol tautomerization.



Several improvements on this reaction using different catalysts have been successfully accomplished [2–32].

Mechanism

Chair-like T.S.

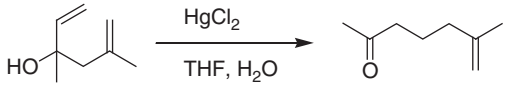
Boat-like T.S.

Both chair-like T.S. and boat-like T.S. can follow the reaction pathway. But chair-like T.S. is energetically more favorable than boat-like T.S.

Application

Total syntheses of amphilectane, serrulatane diterpenoids [26], alkaloids, (+)-sedridine, (+)-allosedridine [20], (−)-acutumine [12, 13], (−)-okilactomycin [15], (±)-trichodermamide B [9], and (±)-actinophyllic acid [10] have been accomplished using this reaction.

Experimental Procedure (from patent US 4421934A)

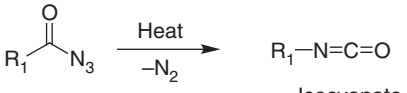


A **B**

A mixture of 3,5-dimethylhexa-1,5-dien-3-ol (**A**) (0.126 g) and mercuric chloride (0.270 g) in a mixture of THF and water (1/1 by volume) (5 ml) was kept at a temperature on the order of 20 °C. After a reaction time of four hours, the reaction mixture was filtered to remove the metallic mercury that was formed. The reaction mixture was extracted with diethyl ether (3 × 25 ml). After drying over anhydrous sodium sulfate and evaporation of the solvent under reduced pressure (20 mm Hg), 6-methylhept-6-en-2-one (**B**) (0.040 g) was obtained.

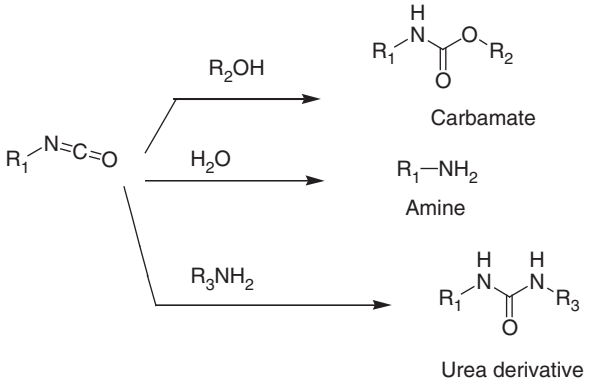
Curtius Rearrangement

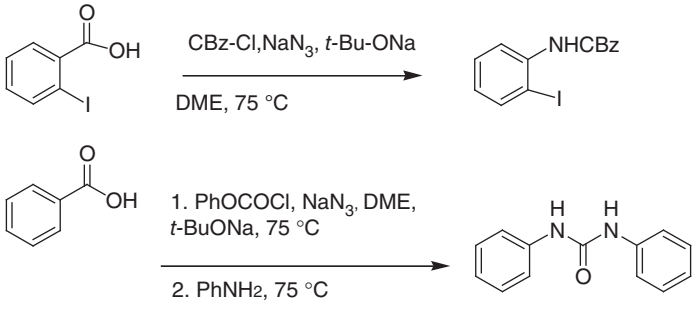
The Curtius rearrangement is the thermal conversion of an acyl azide to an isocyanate [1–3]. The isocyanate is the intermediate of several products such as urea, amine, carbamate-protected amine, amino acid, and other products. Several improvements on this reaction using different reaction conditions and mechanistic studies have been successfully accomplished [4–41].



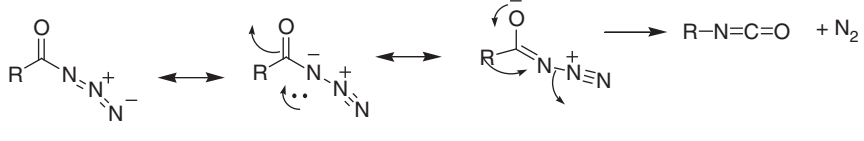
Isocyanate

Acyl azide





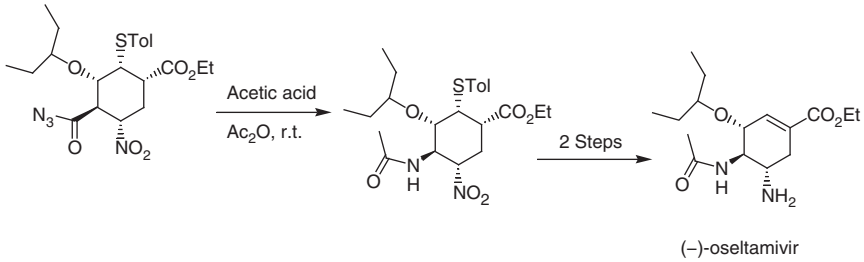
Mechanism



It involves a concerted degradation of an acyl azide into an isocyanate.

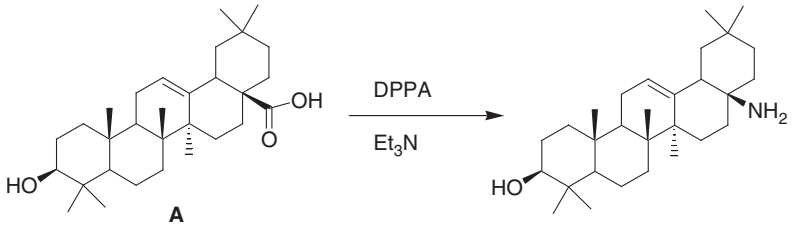
Application

The Curtius rearrangement has been used for the synthesis of several medicines including oseltamivir, tranylcypromine, candesartan, gabapentin, benzydamine, bromadol, igmesine, tecadenoson, terguride, and others.



SB-203207, an altemicidin-type alkaloid that potently inhibits isoleucyl-tRNA synthetase activity [40], and gastroprotective microbial agent AI-77-B [15] were synthesized using this reaction. Total syntheses of several natural products such as (+)-3-demethoxyerythratidinone, (+)-erysotramidine [39], aspeverin, a prenylated indole alkaloid [32], Lycopodium alkaloid (−)-lyconadin C [30], syringolin A [27], (±)-epiquinamide, (±)-epiepiquinamide [21], ningalin D [18], (+)-sinefungin [10], and many more have been accomplished utilizing this reaction.

Experimental Procedure (from patent EP2787002A1)

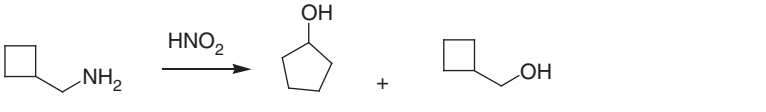


A Oleanolic acid **B**

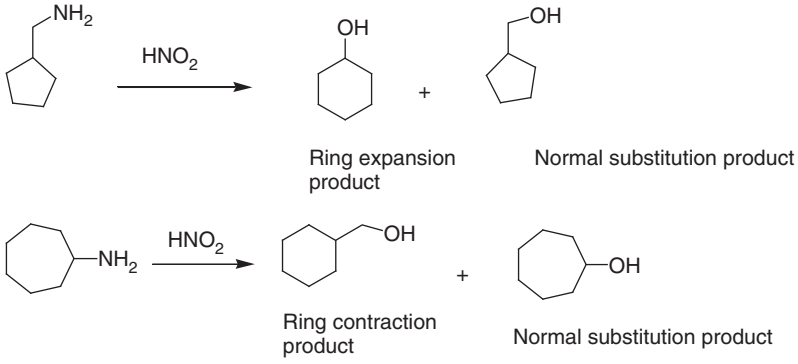
Oleanolic acid (**A**) (2.5 g, 5.5 mmol) was dissolved in chloroform (25 ml), to which diphenylphosphoryl azide (DPPA) (1.8 g, 6.6 mmol) and triethylamine (0.66 g, 6.6 mmol) were added. The reaction mixture was stirred for 12 hours at room temperature, and then 3 M sulfuric acid (15 ml) was added thereto. The reaction mixture was heated at 100 °C, and the stirring continued for six hours. After the reaction was completed, the reaction mixture was cooled to room temperature, adjusted the pH 13 with NaOH (aq. 10%), and then extracted with ethyl acetate (40 ml × 2). The organic layer was combined, dried, and concentrated to give product (**B**) as a yellow oil.

Demjanov Rearrangement

The Demjanov rearrangement is an organic reaction of primary amine with nitrous acid to form rearranged alcohols. The reaction proceeds via diazotization followed by ring expansion or ring contraction. The reaction is named after the Russian chemist Nikolay Yakovlevich Demjanov who discovered it in 1903 [1, 2]. Several improvements and mechanistic studies have been developed on this reaction [3–14].

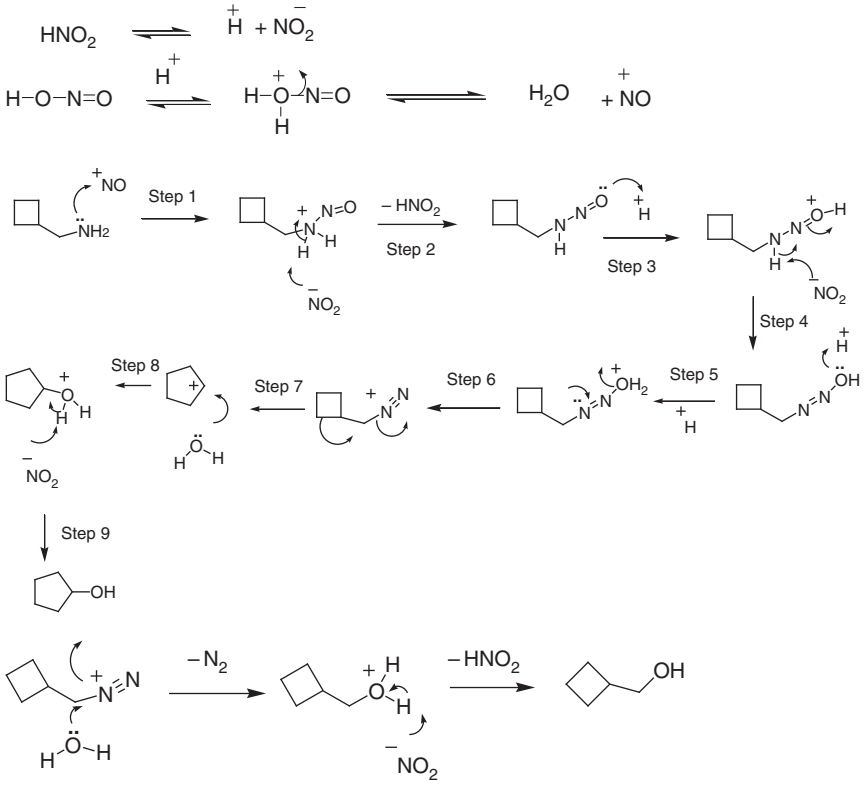


Ring expansion product Normal substitution product



Mechanism

Generation of Nitrosonium Ion



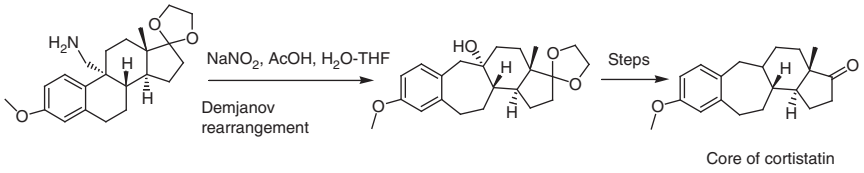
Normal Substitution Product

Step 1: The nitrosonium ion reacts with the primary amine.
Step 2: Abstraction of proton from the amine.
Step 3: Protonation.

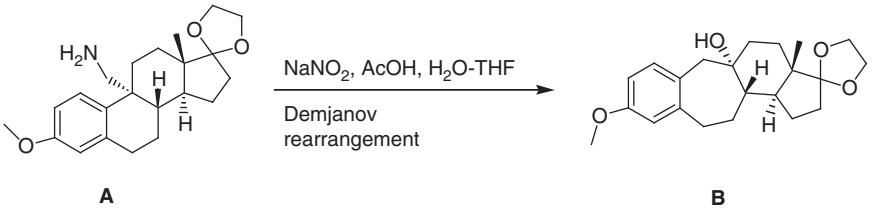
Step 4: Deprotonation.
Step 5: Protonation.
Step 6: Elimination of water and formation of diazonium ion.
Step 7: Rearrangement and formation of carbocation.
Step 8: Nucleophilic attacks by water.
Step 9: Deprotonation and formation of the product.

Application

Carbocyclic core of cortistatin, the potent antiangiogenic natural product, was synthesized starting from (+)-estrone utilizing this reaction [14].



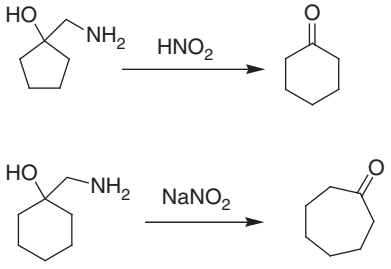
Experimental Procedure (from Reference [14], copyright 2008, American Chemical Society)



A 100 ml round bottom flask, equipped with a PTFE-coated stir bar, was charged with compound **A** (2.23 g, 6.24 mmol, 1 equiv.), THF (22.3 ml), and water (11.25 ml). The resulting mixture was cooled to 0 °C, and first glacial acetic acid (11.25 ml) was added followed by a solution of $NaNO_2$ (2.14 g, 5 equiv.) in water (18 ml). The reaction mixture was then stirred for two hours at 0 °C, and the progress of the reaction was monitored by TLC. When all the starting material was consumed, the reaction mixture was poured into vigorously stirred mixture of aqueous 2 N NaOH (200 ml) and Et_2O (200 ml). The aqueous phase was extracted with Et_2O (2 × 100 ml), and the combined organic layer was washed with saturated aqueous sodium chloride (2 × 100 ml) and evaporated. The crude product (2.21 g) was purified by flash column chromatography (hexane/EtOAc = 4 : 1 → 2 : 1 with 1 v/v% NEt_3). The product **B** (1.35 g, 61%) was obtained as a pale yellow viscous oil, which solidified upon standing in the refrigerator m.p. 120–122 °C. $[\alpha]_D^{20} = +28.80$ (c. 0.01, $CHCl_3$), $R_f = 0.38$ (hexane/EtOAc = 3 : 1).

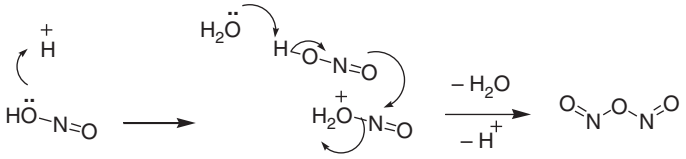
Tiffeneau–Demjanov Rearrangement

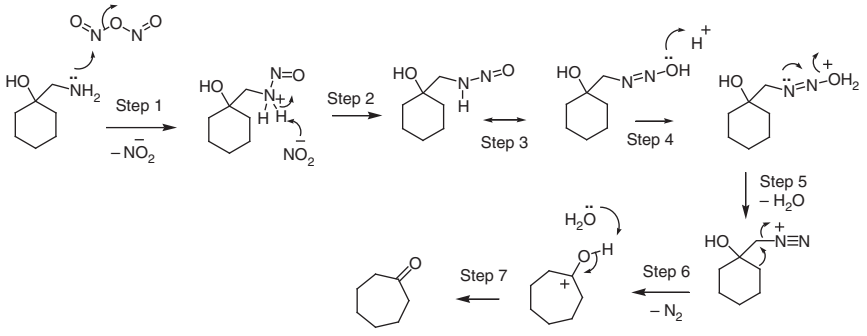
The carbocation rearrangement of β-amino alcohol (1-aminomethyl-cycloalkanol) with nitrous acid to form a ring-enlarged cycloketone is known as the Tiffeneau–Demjanov rearrangement [1, 2]. The ring sizes from cyclopropane to cyclooctane can undergo this reaction with ring expansion, although ideal ring size 5–7 provides good yield [3–10].



Mechanism

Generation of N_2O_3



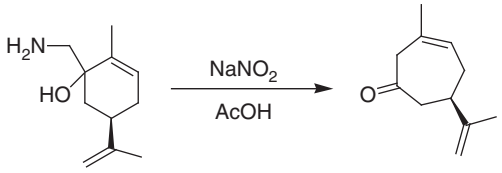


Step 1: Nucleophilic addition of amine to N_2O_3.
Step 2: Deprotonation.
Step 3: Isomerization.
Step 4: Protonation of hydroxyl group.
Step 5: Elimination of water and formation of diazonium ion.
Step 6: A rearrangement reaction with ring expansion.
Step 7: Deprotonation and formation of cycloheptanone.

Application

Spectromycin analog such as a homospectinomycin, an antibiotic useful for the treatment of gonorrhea infections, has been synthesized strategically utilizing this reaction [7].

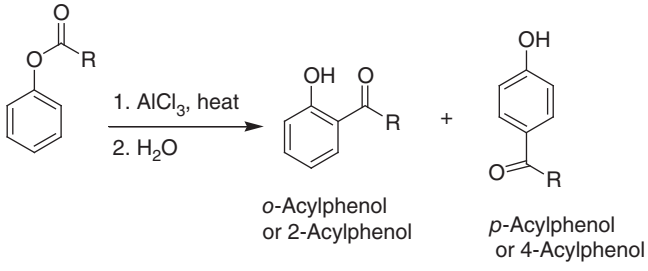
Experimental Procedure (from Reference [10], copyright, The Royal Society of Chemistry)



A solution of the amino alcohols in 10% (v/v) aqueous AcOH at 0 °C was treated with a 1.25 M aqueous solution of $NaNO_2$. The reaction mixture was stirred for four hours at 0 °C. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with 10% (w/v) solution of $NaHCO_3$, brine, and water and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*, and the residue was immediately purified by flash column chromatography to afford the desired product.

Fries Rearrangement

Mostly $AlCl_3$, BF_3, $TiCl_4$, or $SnCl_4$ catalyzed rearrangement of phenolic esters to 2-hydroxy aryl ketone or 4-hydroxy aryl ketone is called the Fries rearrangement [1], named after the German chemist Karl Theophil Fries. The rearrangement can proceed with other acids such as HF, CF_3CO_2H, and $MeSO_3H$ in an inert solvent or without any solvent. The acids are generally required in excess of the stoichiometric amounts, particularly with the Lewis acids (most common is $AlCl_3$) since they form complexes both with the starting materials and the products. Several improvements including photo-Fries and anionic *ortho*-Fries rearrangement have been accomplished [2–36].

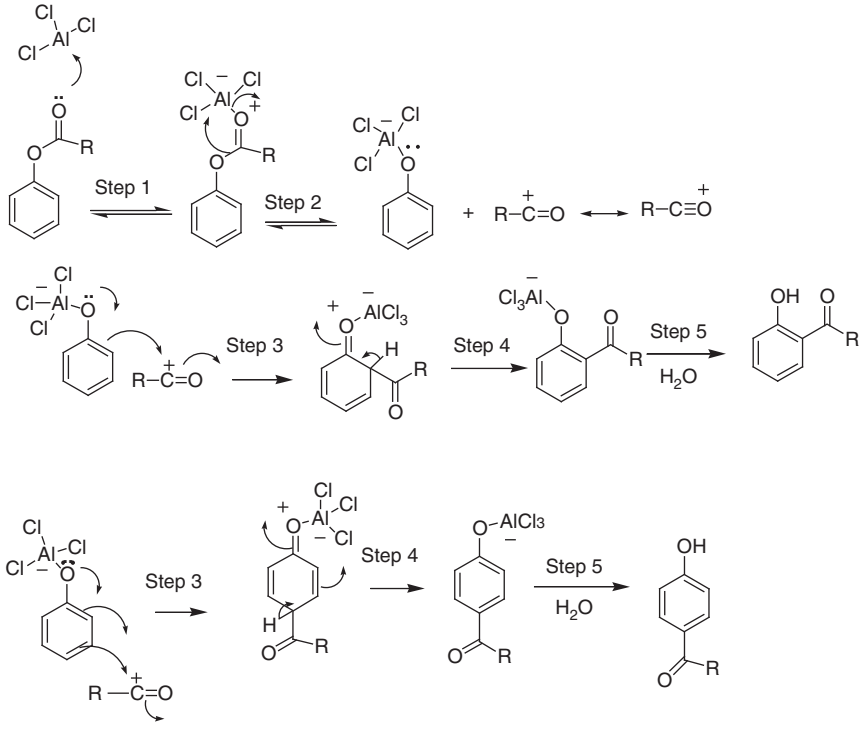


R = Alkyl or aryl group

The Fries rearrangement is *ortho* and *para* selective, and the ratio depends on temperature, solvent, and other reaction conditions. Generally, at low temperature *p*-products and at high temperature *o*-products are predominately formed.

Mechanism

Both intermolecular and intramolecular mechanisms have been reported.



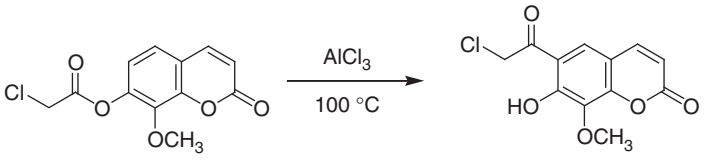
Step 1: $AlCl_3$ forms a complex with phenolic ester. $AlCl_3$ coordinates with carbonyl oxygen atom of carbonyl acyl group as this oxygen atom is more electron rich than phenolic oxygen atom. It is a stable and preferred Lewis base.
Step 2: Reversible formation of an acylium carbocation.
Step 3: Electrophilic attacks by the acylium carbocation at *ortho* and *para* positions of the aromatic ring to give a resonance-stabilized σ-complex.
Step 4: Deprotonation and aromatization.
Step 5: Hydrolysis liberates an acylphenol (or called hydroxyl aryl ketone).

Application

Fries rearrangement is applied for the synthesis of antiviral drug ladanein.

Total syntheses of natural products such as (+)-balanol [9], rhein, diacerhein [20], brazanquinones [22], antibiotic kendomycin [25], (+)-(*R*)-concentricolide [26], and muricadienin [32] have been accomplished strategically applying this reaction.

Experimental Procedure (from patent US9440940B2)

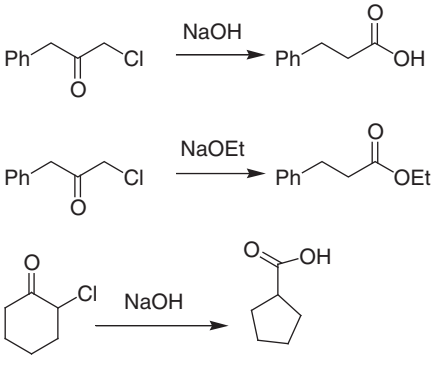


A **B**

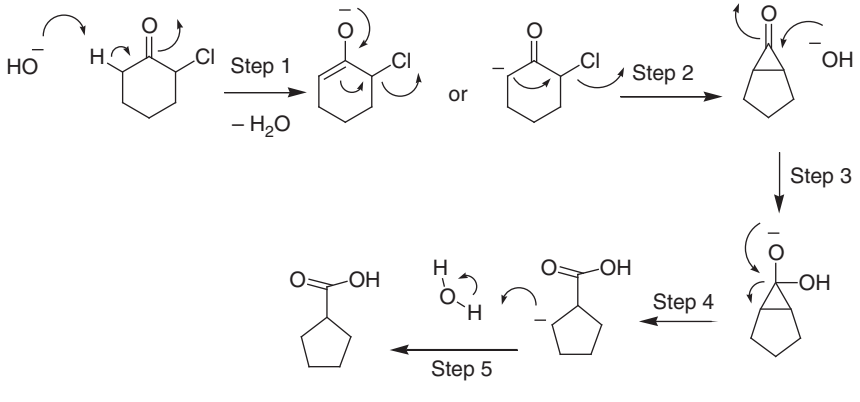
0.01 mol of 7-(2′-chloroacetyloxy)-8-methoxycoumarin (compound **A**) was directly heated in the presence of 0.015 mol aluminum chloride at 100 °C for three hours. After cooling and hydrolysis with diluted hydrochloric acid and ethyl acetate extraction, 6-(2′-chloroacetyl)-7-hydroxy-8-methoxycoumarin (compound **B**) was obtained after evaporation of the organic phase. The yield was 80%.

Favorskii Rearrangement

The Favorskii rearrangement is an organic reaction used to convert an α-haloketone to a rearranged acid or ester using a strong base (hydroxide or alkoxide). In case of cyclic α-haloketone, this reaction gives a ring contracted product [1–21]. The reaction is named after its discoverer the Russian chemist Alexei Yevgrafovich Favorskii [1, 2].



Mechanism

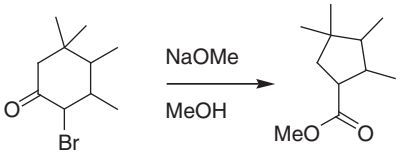


Step 1: Abstraction of α-H on the side of the ketone away from the chlorine atom forms an enolate.
Step 2: S_N2-type reaction and formation of cyclopropanone ring intermediate.
Step 3: Hydroxide as a nucleophile attacks at the ketone.
Step 4: Ring opening gives an anion.
Step 5: Proton transfers from water or solvent gives the final product.

Application

Total syntheses of naturally occurring products (±)-sterpurene [10], (±)-kelsoene [8], tricycloclavulone [11], and (±)-communiol E [17] have been successfully achieved utilizing this reaction.

Experimental Procedure (from patent EP3248959A2)

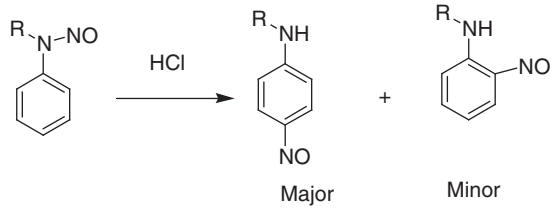


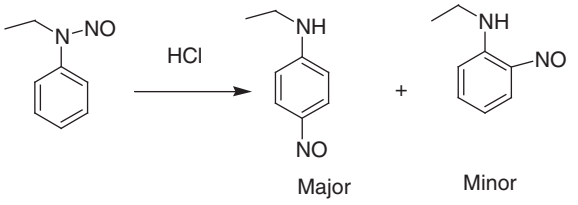
A **B**

To a mixture of 2.60 g of α-bromotetramethylcyclohexanone (compound **A**) (80.4% GC) and 10 g of methanol in a nitrogen atmosphere was added 2.60 g of a 28% solution of sodium methoxide in methanol at room temperature with stirring. After stirring at room temperature for two hours, the reaction mixture was heated with stirring under reflux for two hours and cooled to room temperature. 24 g of diluted hydrochloric acid was added, and an organic layer and an aqueous layer were separated. The separated organic layer was subjected to usual after treatment, i.e. washing, drying, and concentration, to obtain 1.81 g of the envisaged methyl-2,3,4,4-tetramethylcyclopentane carboxylate as a yellowish oil (compound **B**) (33.2% GC, yield: 36%).

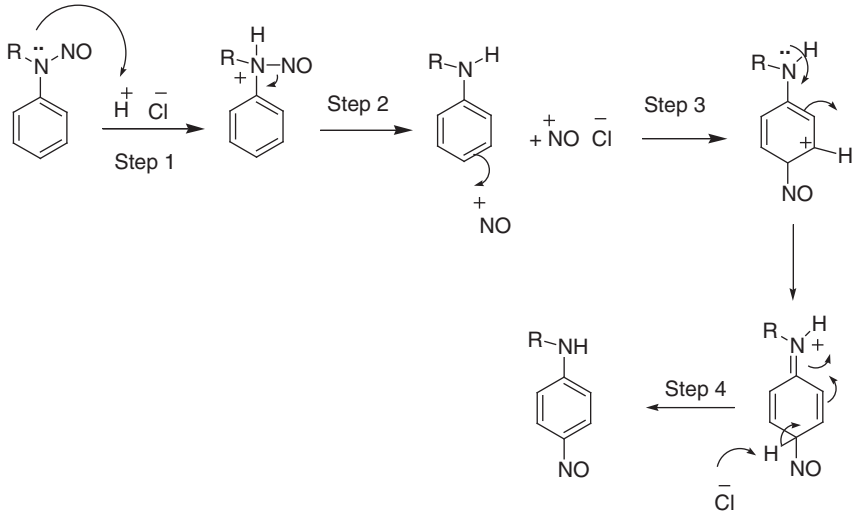
Fischer–Hepp Rearrangement

The Fischer–Hepp rearrangement is an acid-catalyzed conversion of *N*-alkyl-*N*-nitrosoanilines to *N*-alkyl-*para*-nitrosoanilines [1]. This reaction was discovered by the German chemists Otto Philipp Fischer and Eduard Hepp. Several new reaction conditions on this reaction have been developed [2–10].



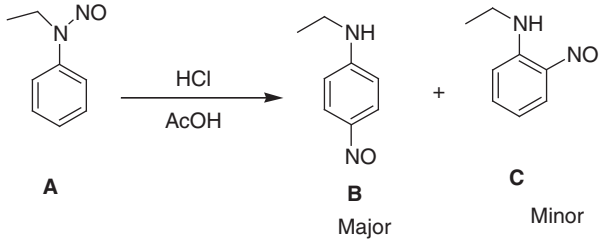


Mechanism



Step 1: Protonation of amino nitrogen atom by HCl.
Step 2: Formation of nitrosonium ion.
Step 3: Aromatic electrophilic substitution at *para* position or intramolecular migration of $^{+}$NO.
Step 4: Abstraction of proton by chloride ion and rearomatization gives the final product.

Experimental Procedure (general)

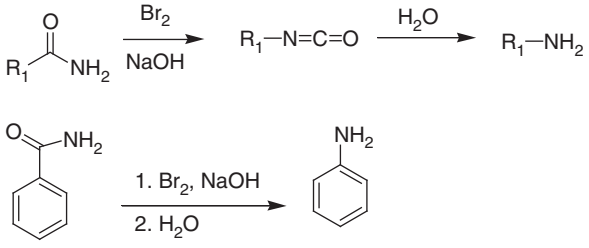


A solution of **A** (1 g) in acetic acid 20 ml and 35% HCl 4 ml was stirred at room temperature for three hours. The AcOH and HCl solution were removed *in vacuo*.

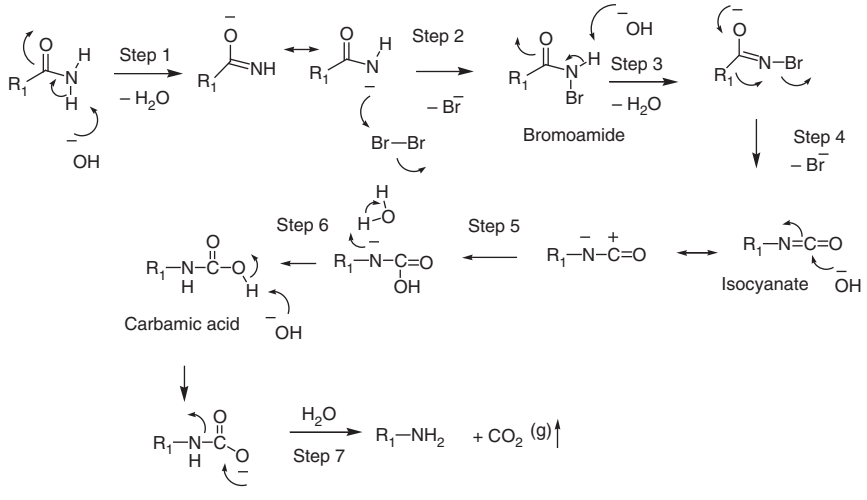
The residue was diluted with ice-cold water and neutralized with ammonia followed by extraction with ethyl acetate. The organic layer was washed with water, saturated $NaHCO_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified over silica gel column chromatography (hexane-ethyl acetate) to afford compound **B** (major) and compound **C** (minor).

Hofmann Rearrangement (Hofmann degradation of amide)

The Hofmann rearrangement is a conversion reaction of primary amide to primary amine with one carbon atom less (via the intermediate isocyanate formation) using alkali (NaOH) and halogen (chlorine or bromine) or hypohalite (NaOCl or NaOBr). This reaction is also referred to as the Hofmann degradation of amide [1–26].



Mechanism



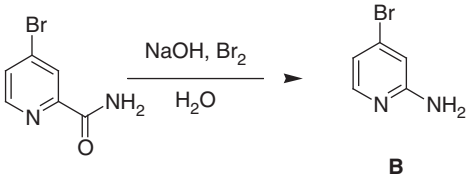
Step 1: Hydroxide abstracts an acidic N–H proton.
Step 2: The anion reacts with bromine to form an *N*-bromoamide.
Step 3: Hydroxide abstracts another acidic H atom from N–H.

Step 4: Elimination of bromide and migration of R_1 group to nitrogen atom occur simultaneously to form an isocyanate.
Step 5: Water or hydroxide reacts with isocyanate.
Step 6: Proton transfer produces a carbamic acid.
Step 6: Abstraction of proton with hydroxide.
Step 7: Carbamic acid loses CO_2 and after protonation gives the amine product.

Application

Total syntheses of (+)-cepharamine [8], capreomycin IB [16], (−)-epibatidine [12], (+)-phakellstatin, and (+)-dibromophakellstatin [14] have been accomplished using this reaction.

Experimental Procedure (from patent CN105153023B)

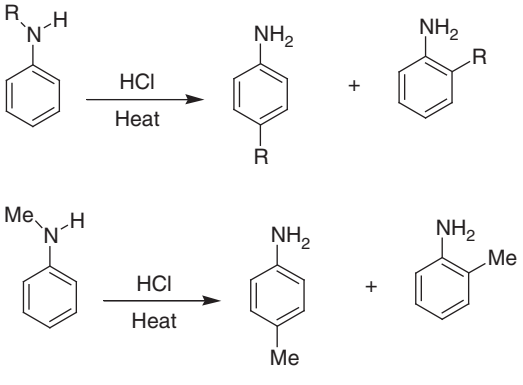


A **B**

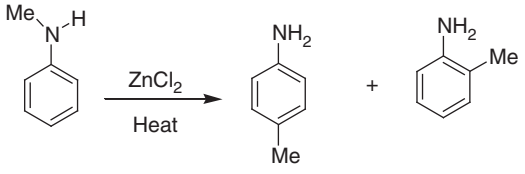
Aqueous sodium hydroxide was cooled to 0 °C by the dropwise addition of elemental bromine, cooling to not lower than 10 °C, and was added portion-wise to 4-bromo-pyridine carboxamide (compound **A**); the addition was complete stirring incubated at least one hour and then heated to 65–90 °C (TLC monitored). The reaction mixture was cooled to room temperature, was centrifuged to obtain a crude product, and was crystallized from toluene to give a pure product, 2-amino-4-bromopyridine (compound **B**).

Hofmann–Martius Rearrangement

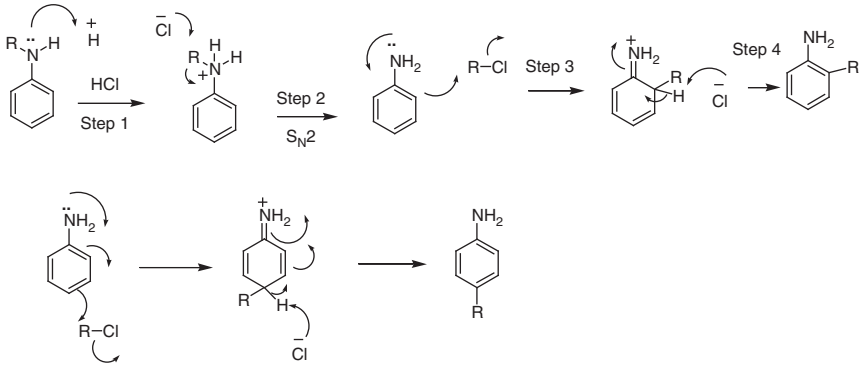
This is a rearrangement reaction of *N*-alkylarylamine to the corresponding *ortho*- and/or *para*-arylalkylated aniline under thermal conditions [1–13].



When the catalyst is a metal halide (Lewis acid) used instead of a protic acid, the reaction is referred to as the Reilly–Hickinbottom rearrangement [3].

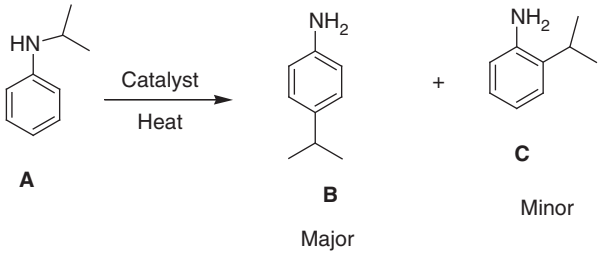


Mechanism



Step 1: Protonation of NH group from HCl.
Step 2: Nucleophilic substitution reaction.
Step 3: Aromatic electrophilic substitution reaction.
Step 4: Deprotonation and rearomatization.

Experimental Procedure (from patent DD295338A5)

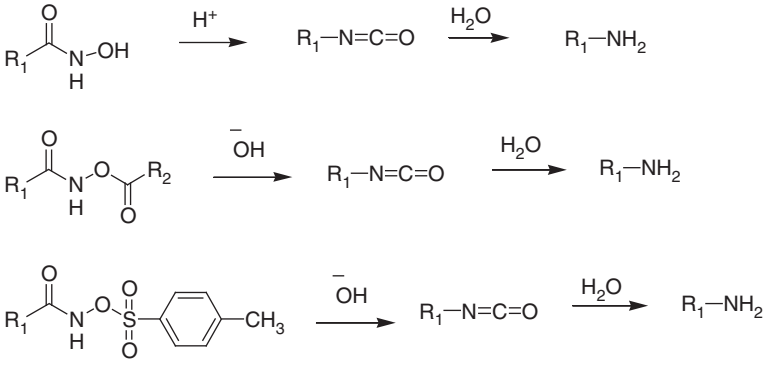


In a reactor filled with Y zeolite in H^+ form, *N*-isopropylaniline (compound **A**) was introduced to produce *p*-isopropylaniline (compound **B**). In the reactor, a pressure of 40 bar and a temperature of 375 °C were maintained. To adjust and maintain said pressure, a gas mixture of 75% by volume of nitrogen and 25% by volume of hydrogen was used. The reactor also contains the aniline obtained during fractionation of the product mixture and also the *o*- and polyisopropylanilines based on the *N*-isopropylaniline in threefold amount.

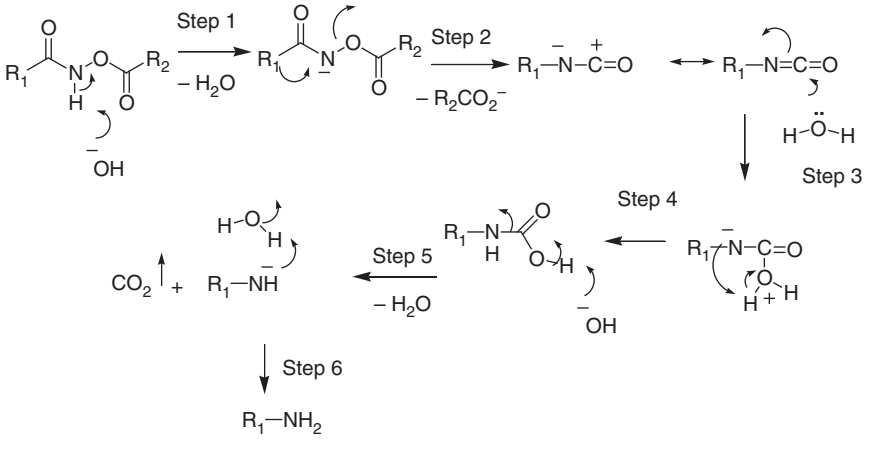
In the continuously operating reactor, a volume velocity of 1 dm^3 mixture per dm^3 of catalyst was set hourly. From the mixture leaving the reactor, the aniline was first distilled off; then the *o*- and *p*-isopropylanilines were separated from the polyisopropylanilines. The *o*- and *p*-isopropylaniline were separated by fractional distillation. The *p*-isopropylaniline was obtained in 99% purity and in relation to the fed *N*-isopropylaniline in a yield of 81%.

Lossen Rearrangement

The Lossen rearrangement is the intramolecular conversion of hydroxamic acids or their *O*-acetyl, *O*-aroyl, and *O*-sulfonyl derivatives into isocyanates under thermal or in the presence of acid or base catalysts [1–3]. Isocyanate can be converted to the corresponding primary amine with water. Several reaction conditions and mechanistic studies have been investigated on this reaction [4–22].



Mechanism

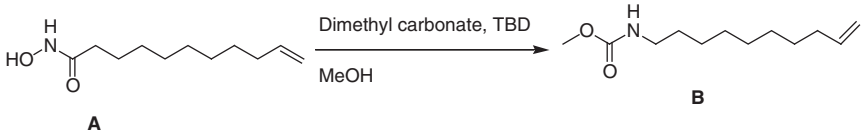


Step 1: Abstraction of the proton from the *N* atom.
Step 2: Migration of R_1 group to the *N*-atom and elimination of carboxylate.
Step 3: Hydrolysis of isocyanate and nucleophilic attack by water.
Step 4: Proton transfer.
Step 5: Decarboxylation and liberation of carbon dioxide.
Step 6: Proton transfer and formation of an amine product.

Application

HIV maturation inhibitor BMS-955176 [17] was synthesized using this reaction. Total synthesis of the sesquiterpene illudinine [15] was successfully completed utilizing this reaction.

Experimental Procedure (from patent EP2615082B1)

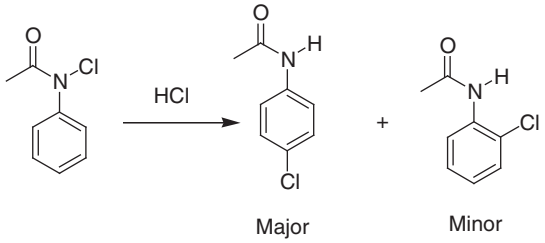


A **B**

The Lossen rearrangement of *N*-hydroxyundec-10-enamide (**A**) (20 g, 100 mmol) with dimethyl carbonate (181 g, 2 mol), methanol (8 ml), and triazabicyclodecene (TBD) (2.79 g, 20 mmol) results in the formation of methyl-dec-9-enylcarbamate. After purification by column chromatography (hexane/ethyl acetate 9 : 1–7 : 3), 12.8 g of pure methyl-*N*-dec-9-enylcarbamate (**B**) was obtained as a colorless oil (yield: 60%).

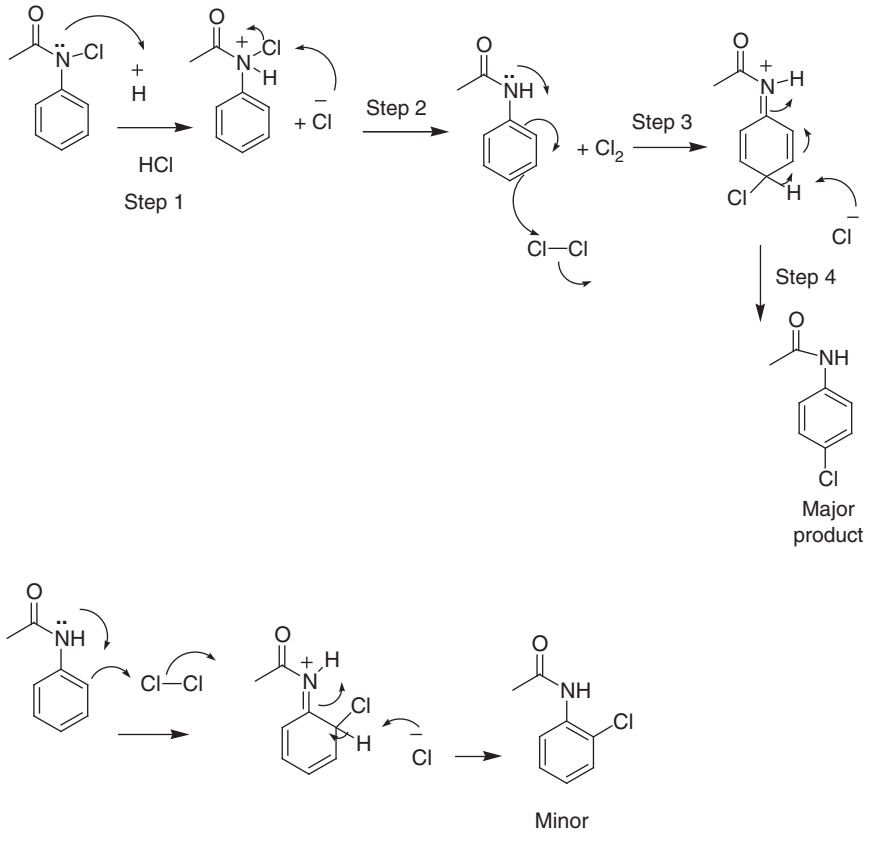
Orton Rearrangement

This is a rearrangement reaction of *N*-chloroanilides to the corresponding *ortho*- and *para*-chloroanilides in the presence of acid such as HCl. This reaction can proceed in the presence of Lewis acid as well as by light. Both solvents and nature of substrates have major role for this rearrangement reaction. This reaction is useful for the preparation of *para*-halo anilides [1–17].



Major Minor

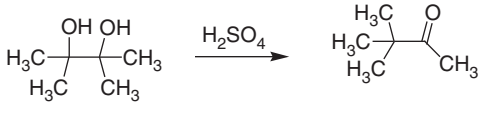
Mechanism



Step 1: Protonation.
Step 2: Nucleophilic substitution reaction.
Step 3: Aromatic electrophilic substitution reaction.
Step 4: Deprotonation ensures rearomatization and formation of the desired product.

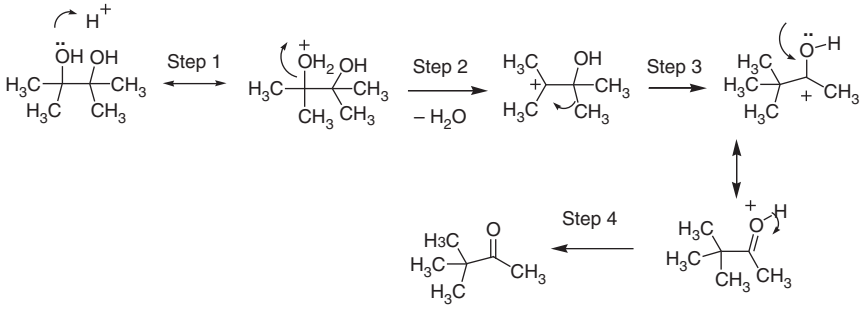
Pinacol–Pinacolone Rearrangement

The pinacol–pinacolone rearrangement is an acid-catalyzed conversion of a 1,2-diol to a carbonyl compound [1–15]. The name of this reaction comes as pinacol rearranges to pinacolone.



Mechanism

If both the –OH groups are not similar, then the one that gives a more stable carbocation participates in the reaction. Subsequently, an alkyl group from the adjacent carbon migrates to the carbocation center.

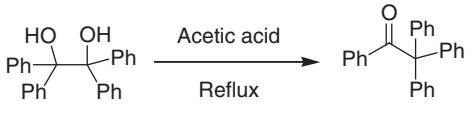


Step 1: Protonation of one hydroxyl group.
Step 2: Elimination of water and formation of a carbocation.
Step 3: Migration of one methyl group.
Step 4: The loss of proton and formation of final product.

Application

Syntheses of several natural products including (±)-furoscrobiculin B [7], protomycinolide IV [6], 13-keto taxoid compounds [11], and sesquiterpene onitin [15] have been accomplished utilizing this reaction.

Experimental Procedure (general)



A **B**

To benzopinacol (1.83 g, 5 mmol) (compound **A**) in acetic acid (20 ml) was added one crystal of iodine. The reaction mixture was stirred at 118 °C until starting material disappeared (TLC monitored) and then cooled to room temperature. The white benzopinacolone (compound **B**) was precipitated, filtered, washed with cold ethanol, and dried.

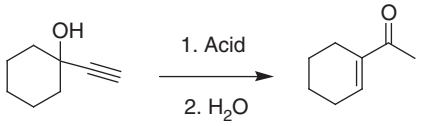
Rupe Rearrangement/Meyer–Schuster Rearrangement

The acid-catalyzed rearrangement of tertiary alcohols containing a terminal α-acetylenic group (e.g. tertiary propargylic alcohols) via an enyne intermediate

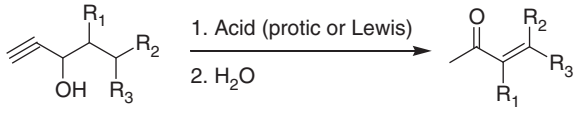
to give the corresponding α,β-unsaturated ketones is called the Rupe rearrangement [1–3]. The acid-catalyzed rearrangement of secondary and tertiary propargylic alcohols to the corresponding α,β-unsaturated aldehydes or ketones is referred to as the Meyer–Schuster rearrangement [4].

Several protic acids, Lewis acids, and acidic cation exchange resins have been applied on this reaction [5–34].

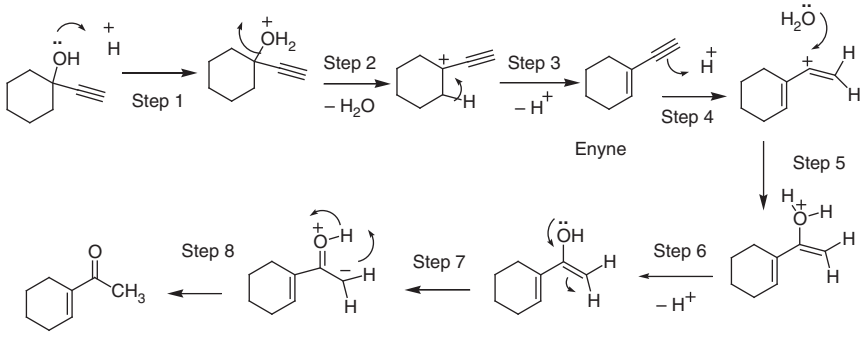
Rupe Rearrangement



Meyer–Schuster Rearrangement



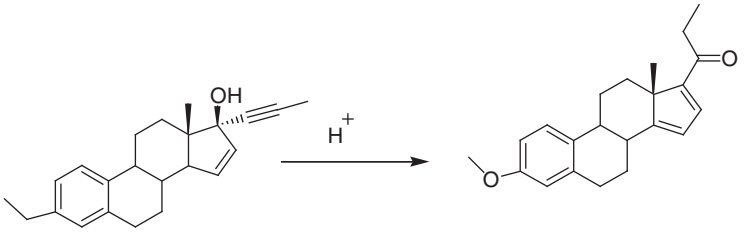
Mechanism



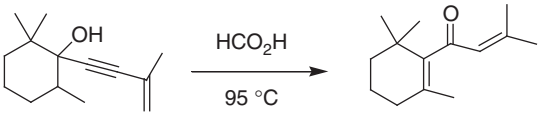
Step 1: Protonation of hydroxyl group makes a better leaving group.
Step 2: Elimination of water and formation of carbocation.
Step 3: 1,2-Shift forms an enyne.
Step 4: Protonation.
Step 5: Nucleophilic attacks by water to the carbonium ion.
Step 6: Deprotonation.
Step 7: Tautomerization.
Step 8: Proton transfer forms the desired product.

Application

A new steroidal drug was synthesized in large scale (pilot plant) using this reaction [22].



Experimental Procedure (from patent US4088681A)

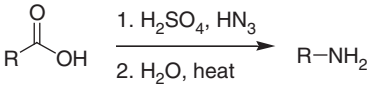


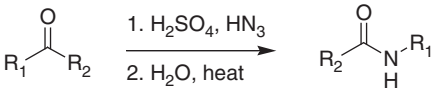
A **B**

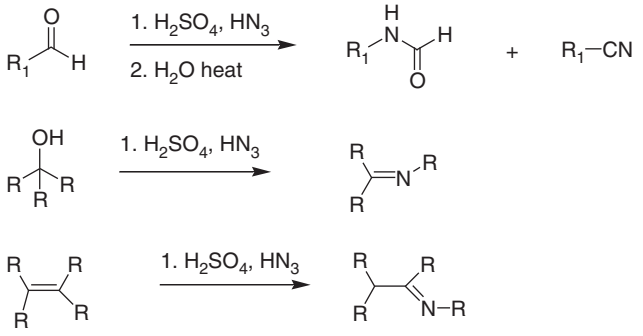
16 g of the acetylene alcohol **A** was added dropwise at 95 °C to 80 ml of 80% strength formic acid. The reaction mixture was kept for one hour at this temperature. The formic acid was then distilled off under reduced pressure, the residue was taken up in ether, and the ether solution was washed with 10% sodium bicarbonate solution, dried ($MgSO_4$), and distilled. 6.4 g (corresponding to 40% of theory) of the corresponding β-damascone **B** (2,2,6-trimethyl-1-(1′-oxo-3′-methyl-but-2′-en-1′-yl)-cyclohexene) of boiling point 73–76 °C/0.3 mm Hg was obtained.

Schmidt Rearrangement or Schmidt Reaction

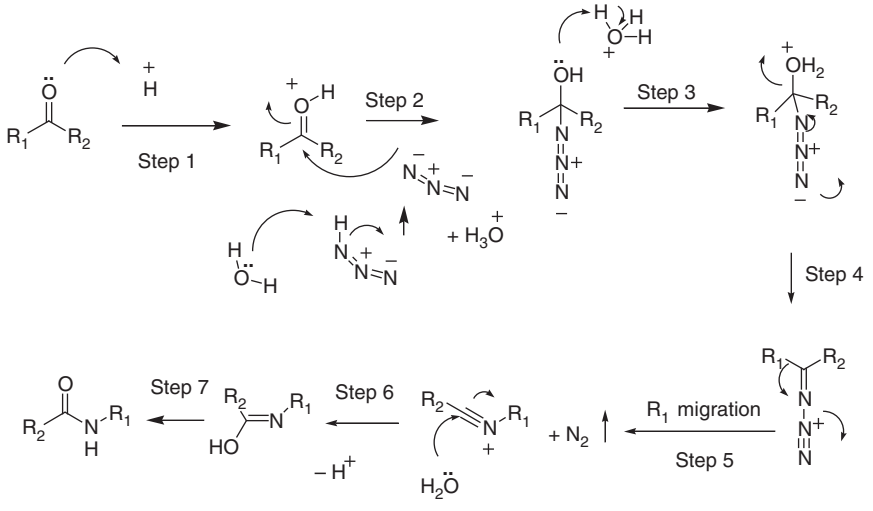
The Schmidt reaction or rearrangement is an acid-catalyzed reaction of hydrogen azide with a carbonyl compound such as an aldehyde, a ketone, or a carboxylic acid to give an amine, amide, or nitrile, respectively, after a rearrangement and the loss of a molecule of nitrogen gas [1–24]. This reaction is extended with tertiary alcohol or olefin to give an imine. The reaction is named after Carl Friedrich Schmidt [1].







Mechanism

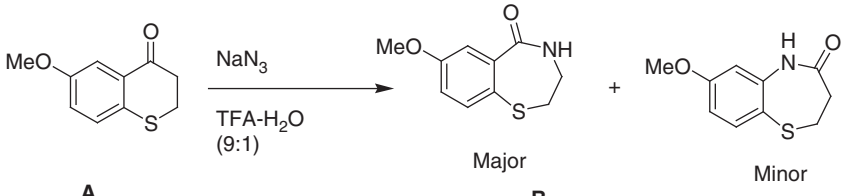


Step 1: Protonation of oxygen atom of the carbonyl compound.
Step 2: Nucleophilic attack by an azide to the electron-deficient carbonyl carbon atom.
Step 3: Protonation.
Step 4: Elimination of water.
Step 5: R_1 group migration and formation of nitrilium ion.
Step 6: Nucleophilic attack by water and deprotonation.
Step 7: Tautomerization gives the desired product.

Application

Total syntheses of several natural products such as (+)-sparteine [5], stemona alkaloid (±)-stemonamine [10], lepadiformines A and C [13], (−)-FR901483 [15], (±)-stemonamine [19], and (+)-erysotramidine [20] have been accomplished strategically using this reaction.

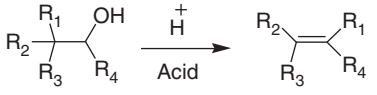
Experimental Procedure (from patent WO2009026444A1)



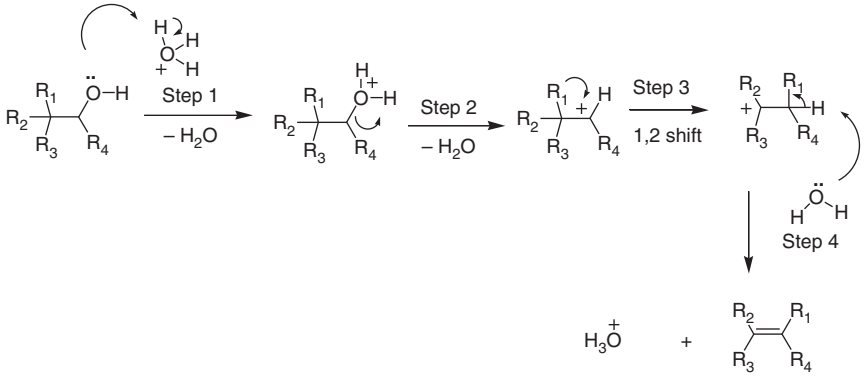
To a solution of **A** (0.20 g, 1.0 mmol) in TFA-H_2O (5 ml, v/v 9 : 1) was added NaN_3 (50 mg, 0.75 mmol). After being stirred at room temperature for 24 hours under nitrogen, same amount of NaN_3 was added to the reaction mixture. After 42 hours, the reaction mixture was then gently poured into a mixture of ice and solid K_2CO_3 and basified to pH ~10. The aqueous solution was extracted with dichloromethane, and the organic layer was washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The title compound was isolated by column chromatography (dichloromethane/ethyl acetate 1 : 1) in 51% yield of **B** (major product) and 25% of **C**.

Wagner–Meerwein Rearrangement

The Wagner–Meerwein rearrangement is an acid-catalyzed alkyl group migration of an alcohol to give an olefin with more substituted. This is a cationic [1, 2]-sigmatropic rearrangement reaction. This reaction has been applied to synthesize complex natural products and drug molecules [3–38].



Mechanism



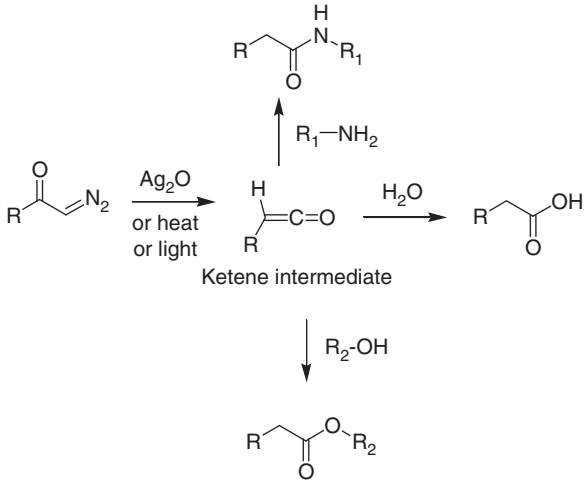
Step 1: Protonation of the alcohol with the acid.
Step 2: Elimination of water forms a carbocation.
Step 3: A 1,2-shift (R_1 group migration) forms a more stable carbocation.
Step 4: Deprotonation with water gives a more substituted olefin and regeneration of acid catalyst.

Application

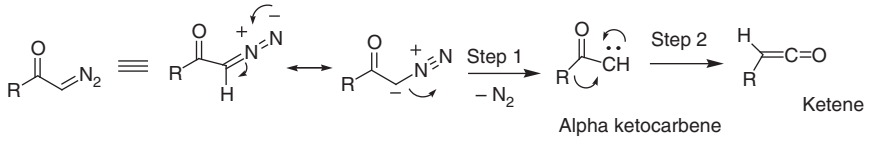
H1N1 influenza virus strains [27] and salimabromide antibiotic polyketide [35] have been synthesized using this reaction. Talatisamine is a member of the C_{19}-diterpenoid alkaloid family, exhibits K^+ channel inhibitory and antiarrhythmic activities [38], and was synthesized utilizing this reaction. Total syntheses of several natural products such as (+)-quadrone [6], guanacastepene A [14], (−)-isoschizogamine [25], and Lycopodium alkaloid (−)-huperzine A [26] have been accomplished utilizing this reaction.

Wolff Rearrangement

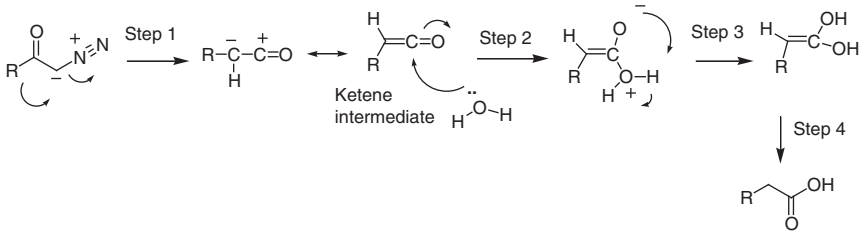
The Wolff rearrangement is a conversion of an α-diazoketone to a ketene with the loss of molecular nitrogen accompanying 1,2-rearrangement using a silver oxide catalyst or thermal or photochemical conditions. Generally, these ketenes are not stable to isolate. These can undergo a nucleophilic attack by water or alcohol or amine to form one carbon homologation of acid or ester or amide (having one carbon more from starting material). The German chemist Ludwig Wolff discovered this reaction in 1902 [1, 2]. Several new catalysts or improved reaction conditions have been developed on this reaction [3–21].



Mechanism



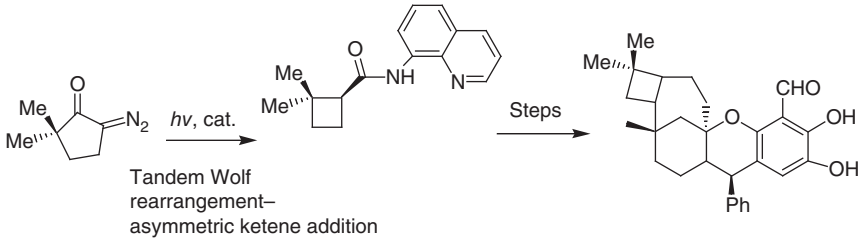
Alternatively



Step 1: Elimination of a molecule of nitrogen gas, R group migration, and formation of ketene intermediate.
Step 2: Water attacks as a nucleophile to the ketene.
Step 3: Proton transfer.
Step 4: Tautomerization gives the desired product.

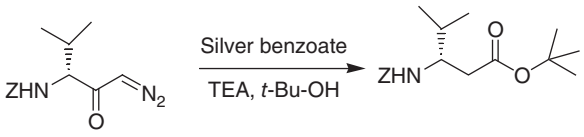
Application

(+)-Psiguadial B is a plant natural product with potent cytotoxicity toward human liver cancer cells that has been synthesized using this reaction [19].



Total syntheses of natural products including (±)-Δ9(12)-capnellene [12] and diterpene salvilenone [10] have been accomplished utilizing this reaction.

Experimental Procedure (from patent US9175041B2)9175041B2

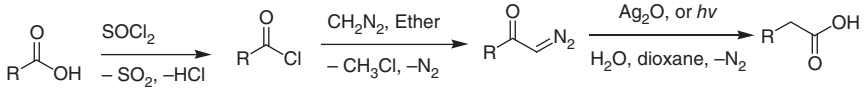


Diazo derivative (0.602 g, 2.19 mmol) was dissolved in *t*-BuOH (9 ml) under N_2 at 70 °C. Silver benzoate (80.2 mg, 0.35 mmol) in TEA (0.94 ml, 685 mg, 6.70 mmol) was added dropwise, and the mixture stirred at 70 °C in the dark for four hours. The mixture was allowed to cool, filtered through a pad of celite, and the solvent was evaporated. The residue was partitioned between EtOAc (100 ml) and saturated $NaHCO_3$ (20 ml). The organic phase was separated; washed with saturated $NaHCO_3$ (20 ml), H_2O (20 ml), and 5 M NaCl (20 ml); and dried, and the

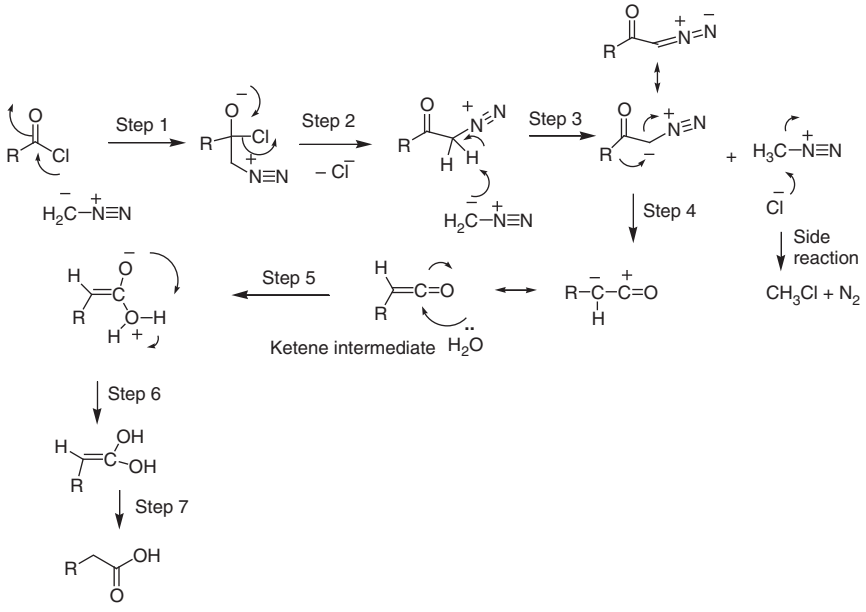
solvent was evaporated. The residue was chromatographed (silica gel, 23 g; 9 : 1 hexane/acetone) to provide 0.443 g (63%) product as a colorless oil.

Arndt–Eistert Homologation or Synthesis

The Arndt–Eistert reaction is a conversion of carboxylic acid to one-carbon homologated carboxylic acid via α-diazoketone formation and subsequently Wolf rearrangement of the intermediate in the presence of water and silver oxide catalyst or thermal or photochemical conditions [1–28]. The reaction is named after the German chemists Fritz Arndt and Bernd Eistert [1].



Mechanism



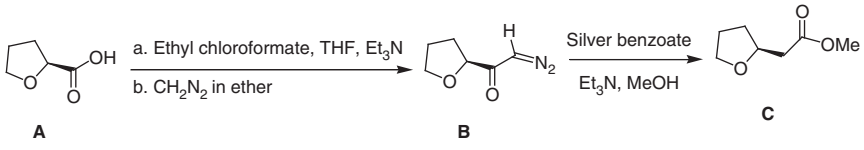
Step 1: Nucleophilic attack by diazomethane into carbonyl carbon atom of acyl chloride forms a tetrahedral intermediate.
Step 2: Elimination of chloride and formation of the diazoketone.
Step 3: Abstraction of proton.
Step 4: Migration of R group and formation of the ketene intermediate.
Step 5: Nucleophilic attack by water to the ketene.
Step 6: Proton transfer.
Step 7: Tautomerization gives the desired product.

Application

The reaction is used for the preparation of β-amino acids from α-amino acids. Peptides containing β-amino acids have a lower rate of metabolic degradation than regular peptides with α-amino acids. Hence these peptides may have the interest for pharmaceutical drug discovery field.

Nonsteroidal anti-inflammatory agent 2-chloroindolecarboxylic acid [6] was synthesized using this reaction. Total syntheses of several natural products such as bellenamine [11], dragmacidin D [17], phenalenone diterpene salvilenone [13], and CP-225917 [14] have been accomplished utilizing this reaction.

Experimental Procedure (from patent US9399645B2)



Step 1

A solution of **A** (40.0 g, 344.8 mmol) in THF (800 ml) was cooled to −25 °C and treated with TEA (62.4 ml, 448.2 mmol). Ethyl chloroformate (42.4 ml, 448.2 mmol) was then added dropwise at the same temperature. The mixture was stirred for 30 minutes and then filtered. The filtrate was cooled to 0 °C and treated with an excess of diazomethane in ether. The mixture was allowed to stir while warming to room temperature overnight. The solution was treated with HOAc and then concentrated to approximately one-half its volume. The mixture was poured into water (1 l) and extracted with EtOAc (500 ml × 2). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated *in vacuo* to give diazoketone **B**, which was used as such in the next step.

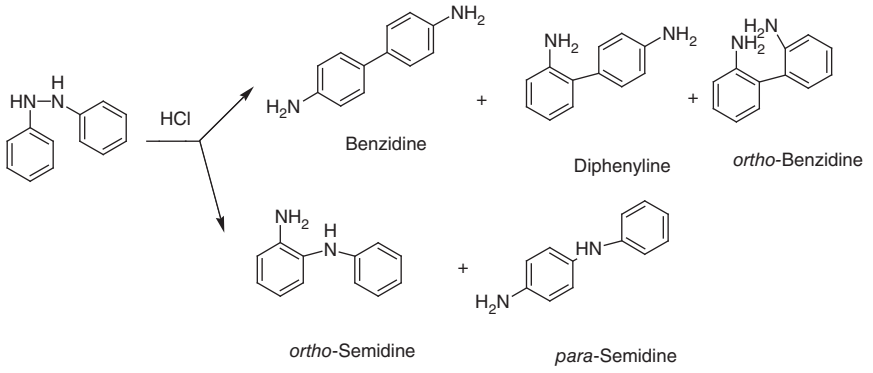
Step 2

A solution of diazoketone **B** (40.0 g, 285.7 mmol) in MeOH (500 ml) was cooled to 0 °C and treated with a solution of silver benzoate (6.5 g, 28.6 mmol) in TEA (67 ml). The mixture was protected from light and stirred while warming to room temperature. The crude reaction mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was distilled in vacuum (60 °C, 20 mmHg) to afford ester **C** ((*S*)-(tetrahydrofuran-2-yl)-acetic acid methyl ester).

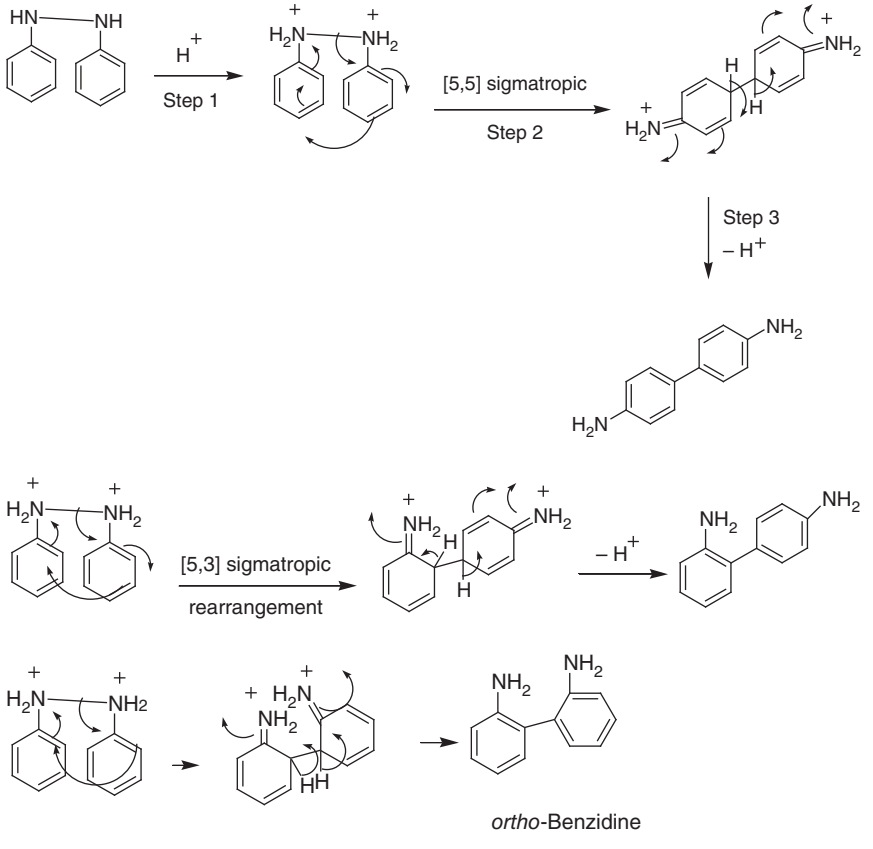
Zinin Rearrangement or Benzidine and Semidine Rearrangements

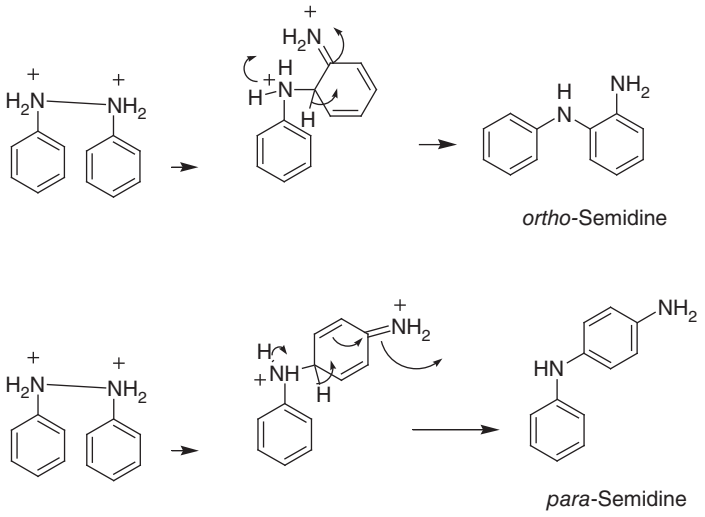
Acid-catalyzed conversion of hydrazobenzene into 4,4′-diaminobiphenyl (*para*-benzidine) and 2,2′-diaminobiphenyl (*ortho*-benzidine) is called benzidine rearrangement. Similarly, acid-promoted conversion of hydrazobenzene to

2-phenylaminoaniline (*ortho*-semidine) and 4-phenylaminoaniline (*para*-semidine) is called semidine rearrangement. Side product 2,4-diaminebiphenyl is also obtained for this rearrangement reaction. Improvements and mechanistic studies of these types of rearrangements have been reported [1–33].



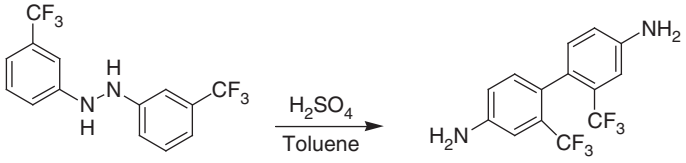
Mechanism





Step 1: Protonation of two amino groups.
Step 2: Sigmatropic rearrangement and formation of several polar transition steps (T.S.).
Step 3: Rearomatization through deprotonation and formation of product.

Experimental Procedure (from patent US20090069602A1)



A **B**

4.19 g of compound **A** was dissolved in 14.0 g of toluene, and the solution was dropped into 15.0 g of 50% sulfuric acid aqueous solution. The rearrangement reaction was conducted for five hours after the dropping. After the reaction was finished, reaction mixture was neutralized and extracted with toluene to obtain 41.4 g of toluene layer. As a result of analysis of the toluene layer, the concentration of 2,2′-bis(trifluoromethyl)-4,4′-diaminobiphenyl was 3.11%, and the yield thereof was 31.8% based on purity of starting material 3,3′-bis(trifluoromethyl)hydrazobenzene. The toluene solution separated above was concentrated for crystallization. A crystallized product was recrystallized to obtain a white crystal. The result of analysis of the crystal showed that it was 2,2′-bis(trifluoromethyl)-4,4′-diaminobiphenyl (compound **B**) having purity of 99.9% and melting point of 183 °C.

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Beckmann Rearrangement

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