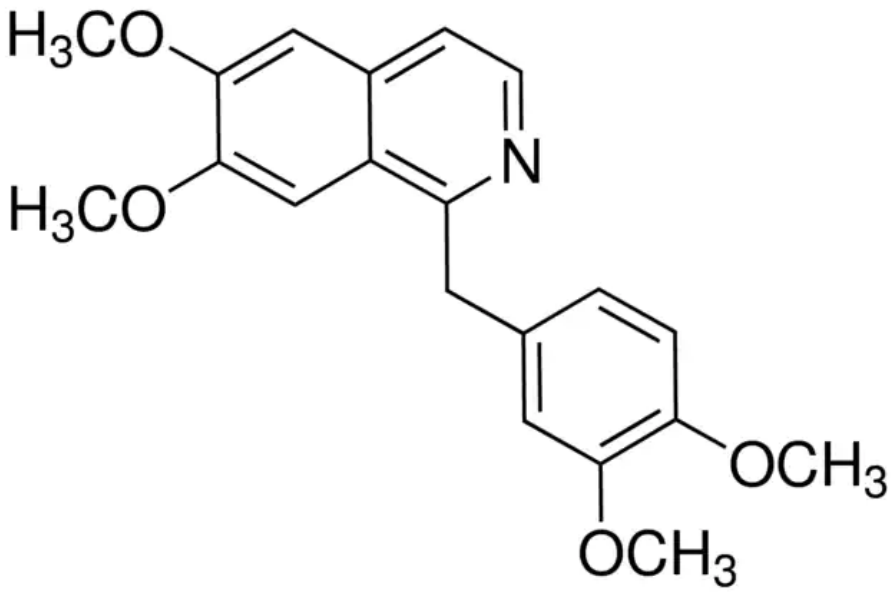
DEVELOPMENTS IN THE TOTAL SYNTHESIS OF "PAPAVERINE" ALKALOID



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DEVELOPMENTS IN THE TOTAL SYNTHESIS OF "PAPAVERINE" ALKALOID

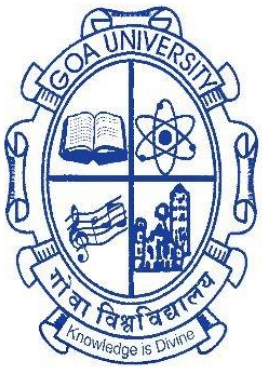
Submitted in the Partial Fulfilment

Of

The Degree of M. Sc. (Organic Chemistry)

By

Mr. GOPAL KRISHNA PARAB



SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

DECLARATION

I declare that the literature review titled “DEVELOPMENTS IN THE TOTAL SYNTHESIS OF “PAPAVERINE” ALKALOID” has been carried out by me in the School of Chemical Sciences, Goa University under the guidance of Dr. Kashinath Dhumaskar and the same has not been submitted elsewhere for the award of a degree or diploma. The Information derived from the literature has been duly acknowledged in the text and a list of references are provided.

Signature

(Gopal K. Parab)

CERTIFICATE

This is to certify that the literature review titled “DEVELOPMENTS IN THE TOTAL SYNTHESIS OF “PAPAVERINE” ALKALOID” is bonafide work carried out by Mr. Gopal Krishna Parab under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Dr. Kashinath Dhumaskar
(Guiding Teacher)

Prof. Dr. Vidhyadatta Verenkar
Dean of School of Chemical Sciences
Goa University

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The literature review titled “DEVELOPMENTS IN THE TOTAL SYNTHESIS OF “PAPAVERINE” ALKALOID” has been successfully completed under the guidance of Dr. Kashinath Dhumaskar during the year 2021-2022 in the partial fulfilment of the requirements for the degree of Master of Science in Chemistry.

I had a good learning experience learning the importance and future prospects of undertaking a literature survey which was possible due to the timely guidance of Dr. Kashinath Dhumaskar and our respected Dean Dr. Vidhyadatta Verenkar. I also thank the entire library faculty for helping me out for searching relevant books with respect to my topic.

Last but not the least I thank my parents, friends and other people who are directly or indirectly in the successful completion of my Literature survey.

INDEX

Abstract

Alkaloids are very important class of compounds as they are very essential in our daily life. Alkaloids are present naturally in plants and have always been a basis for the traditional medicine system and they have provided continuous remedies to the mankind for thousand of years.

Papaverine is an alkaloid which occurs in opium poppy plant and shows various medicinal properties like vasodilator, smooth-muscle relaxant, antispasmodics, etc

Numerous methods have been reported for the total synthesis of this alkaloid. This review summarizes developments in total synthesise of papaverine alkaloid and provides information about the different strategies used by researchers in synthesis of papaverine.

Introduction

Papaverine is a benzylisoquinoline alkaloid with isoquinoline substituted by methoxy groups at positions 6 and 7 and a 3,4-dimethoxybenzyl group at position 1, that was discovered by Georg Merck (1848) as a minor component in the latex of the opium poppy (Papaver somniferum L.). It occurs also in other members of the genus Papaver[1]. Merk assigned the correct empirical formula as $C_{20}H_{21}O_4N$.

Image.(I) flower of opium poppy[2]

IUPAC name of papaverine is 1-[(3,4-dimethoxyphenyl)methyl]-6,7-dimethoxyisoquinoline. The structure of the alkaloid was determined mainly by Goldschmiedt and his co-workers[3].

Natural products that contain an isoquinoline nucleus often exhibit biological activity, such as antimalarial, anti-HIV, antitumor, antimicrobial, and antibacterial. As a result, there is much interest in the synthesis of substituted isoquinolines[4]. Papaverine is a vasodilator that relaxes smooth muscles in your blood vessels to help them dilate (widen). This

lowers blood pressure and allows blood to flow more easily through your veins and arteries. Papaverine is used to treat many conditions that cause spasm of smooth muscle like cerebral vasospasm[5]. It is a direct-acting smooth-muscle relaxant. It acts as a vasodilator, and is the first clinically effective drug for the treatment of erectile dysfunction. Papaverine, when injected in penile tissue, causes direct smooth muscle relaxation and consequent filling of the corpus cavernosum with blood resulting in erection.

It is also commonly used in cryopreservation of blood vessels along with the other glycosaminoglycans and protein suspensions. Functions as a vasodilator during cryopreservation when used in conjunction with verapamil, phentolamine, nifedipine, tolazoline or nitroprusside[6].

In study of potential applicability of alkaloids for treating COVID-19[7], it was found that in docking study using the main protease (Mpro) enzymes active sites (5R7Y, 5R7Z, 5R80, 5R81) showed that papaverine had the highest binding energies with 5R7Y and with 5R7Z along with other alkaloids like erberine, cephaeline, emetine, homoharringtonine, lycorine, narciclasine, quinine, etc. The possible ability of alkaloids to inhibit protein targets and to reduce inflammatory markers show the potential for development of new treatment strategies against COVID-19.

Papaverine is found as a contaminant in some heroin and can be used by forensic laboratories in heroin profiling to identify its source. The metabolites can also be found in the urine of heroin users, allowing street heroin to be distinguished from pharmaceutical diacetylmorphine.

The *in vivo* mechanism of action is not entirely clear, but an inhibition of enzyme phosphodiesterase causing elevation of cyclic AMP and cyclic GMP levels is significant. It may also alter mitochondrial respiration. Papaverine has also been revealed as a selective phosphodiesterase inhibitor for the PDE_{10A} subtype found mainly in the striatum of the brain. When administered chronically to mice, it produced motor and cognitive deficits and increased anxiety, but conversely may produce an antipsychotic effect[8], although not all studies support this view.

Papaverine is not closely related to the other opium alkaloids in structure or pharmacological actions; its mechanism of action may involve the non-selective inhibition of phosphodiesterases and direct inhibition of calcium channels.

Papaverine is a hypnotic, but is much weaker in it’s action than morphine. In small doses papaverine causes narcosis, in larger doses respiratory paralysis and tetanus.

Since the alkaloid is one of nature's useful antispasmodics, it soon found its way into the physician's arsenal, and serves in cases when it is

necessary to cause relaxation of smooth muscle. Papaverine, in the form of its hydrochloride, is administered intravenously in treating pulmonary arterial embolism and orally or by injection in treating renal or biliary colic. It is not effective in abolishing neurally excited spasms and has undesirable side-effects, such as causing prolonged fall in arterial blood pressure, when the intestinal tract is relaxed. This is due to lack of selectivity in relaxing smooth muscle. Despite such undesirable side-effects, nature does not produce enough papaverine to meet the demands of medical practice, and many syntheses have been devised for preparation of this alkaloid.

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Literature Review

Pictet and Gams proposed a synthetic method of papaverine in 1909 [9] (fig(I)). Veratrol and homoveratric acid served as the starting materials in this synthesis. The two intermediates in this synthesis are 3,4-dimethoxy-ω-amino-acetophenone and homoveratroyl chloride. 3,4-dimethoxy-acetophenone was obtained through a Friedel-Crafts reaction of veratrole with acetyl chloride[10]. This ketone was converted through the oximino-ketone to the corresponding ω-aminoacetophenone by reduction with stannous chloride.

Veratric aldehyde was obtained by methylation of vanillin. The cyanohydrin was prepared and upon treatment with hydriodic acid, several transformations took place: demethylation of the phenolic ether groups, saponification of the nitrile group and reduction of the secondary hydroxyl group. Remethylation of the product gave homoveratric acid which was converted to its acid chloride by means of phosphorus pentachloride.

Condensation of the hydrochloride of 3,4-dimethoxy-ω-amino-acetophenone with homoveratroyl chloride yielded the β-keto-amide. Reduction with sodium amalgam gave the corresponding β-hydroxy-amide. Dehydration of with phosphorus pentoxide at the reflux temperature of xylene yielded papaverine[11].

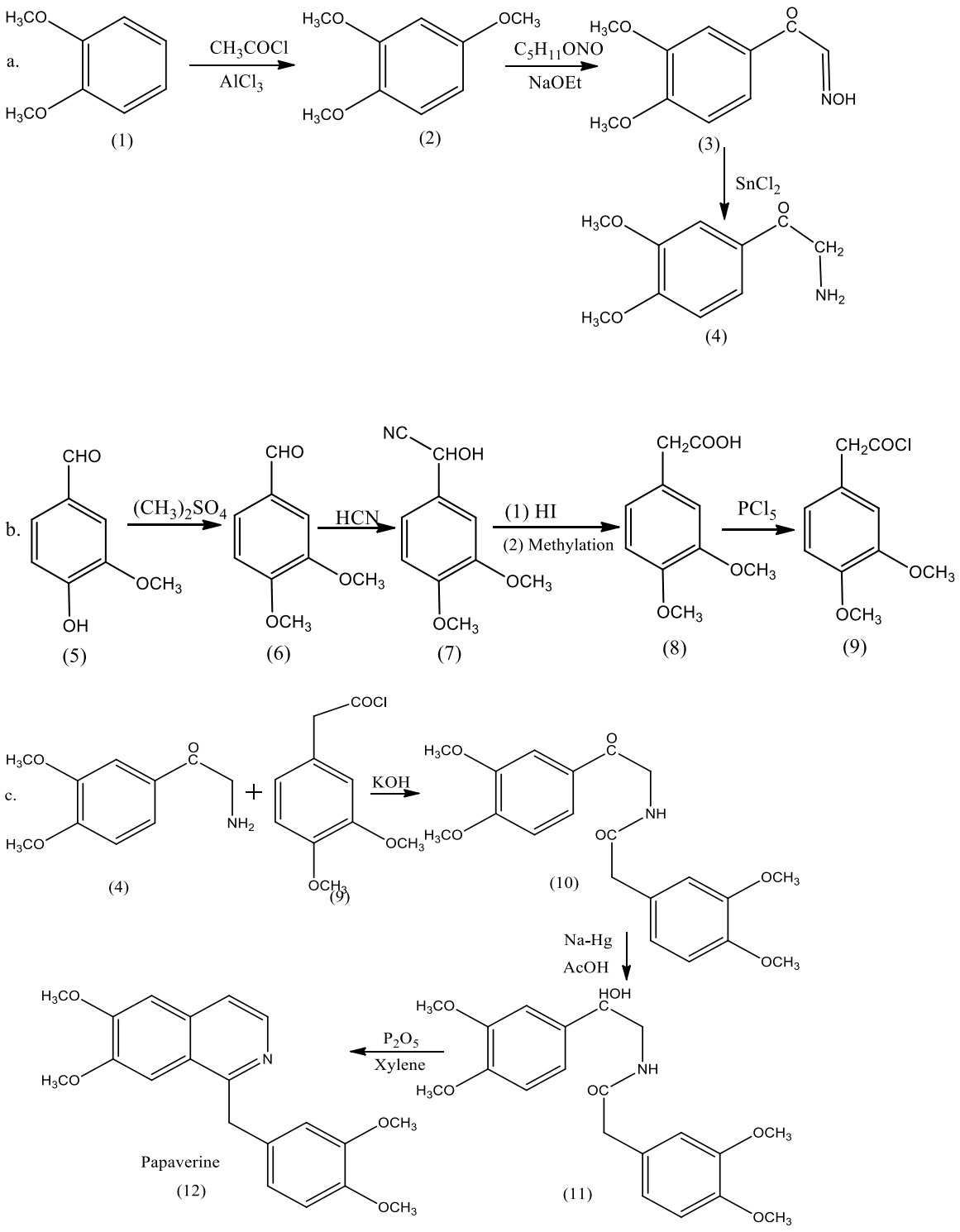


fig. (I) Pictet and Gams synthesis of papaverine

Pictet and Finkelstein[10] modified the synthesis by substituting β-(3,4-dimethoxyphenyl)-ethyl amine (13) for the above ω-amino-acetophenone. Condensation of this amine with homoveratroyl chloride yielded the amide

(14). Cyclization of the amide by the Bischler-Napieralski procedure (phosphorus oxychloride), yielded 3,4-dihydropapaverine (15) (fig. (II)).

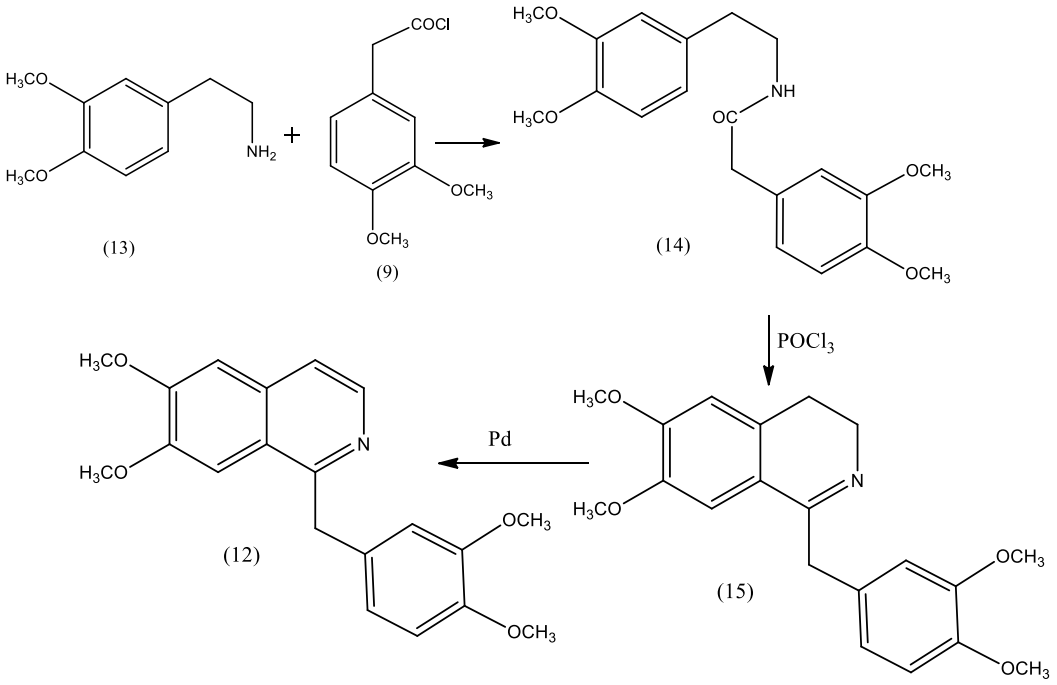


fig. (II) Pictet and Finkelstein synthesis of papaverine

Pictet and Finkelstein were able to carry synthesis as far as 3,4-dihydropapaverine, than Spath and Burger accomplished the dehydrogenation of this substance, by treatment with palladized-asbestos at 200° in the presence of air to give papaverine. The latter workers showed also that 1, 2, 3, 4-tetrahydropapaverine could be dehydrogenated to papaverine by means of the same catalyst.

The synthesis of papaverine by Rosenmund and Mannich [10](fig.(III)), respectively, employed 3,4-dimethoxy-ω-nitro-styrene as an intermediate in the synthesis of papaverine. Mannich prepared papaverine from the methyl ether of the ethanolamine used by Pictet. He prepared other

derivatives in the same way, but stated that the reaction would not proceed if the benzene nucleus of the phenylethylamine was unsubstituted, or in other words if there was no activation of the ortho hydrogen atom. The reaction was further altered by Rosenmund, who cyclized N-benzoyl-β - phenylvinylamine in boiling decalin with activated alumina. He indicated that the reaction performed by Mannich to synthesize papaverine have only 6 % yield when P_2O_5 was the dehydrating agent[12].

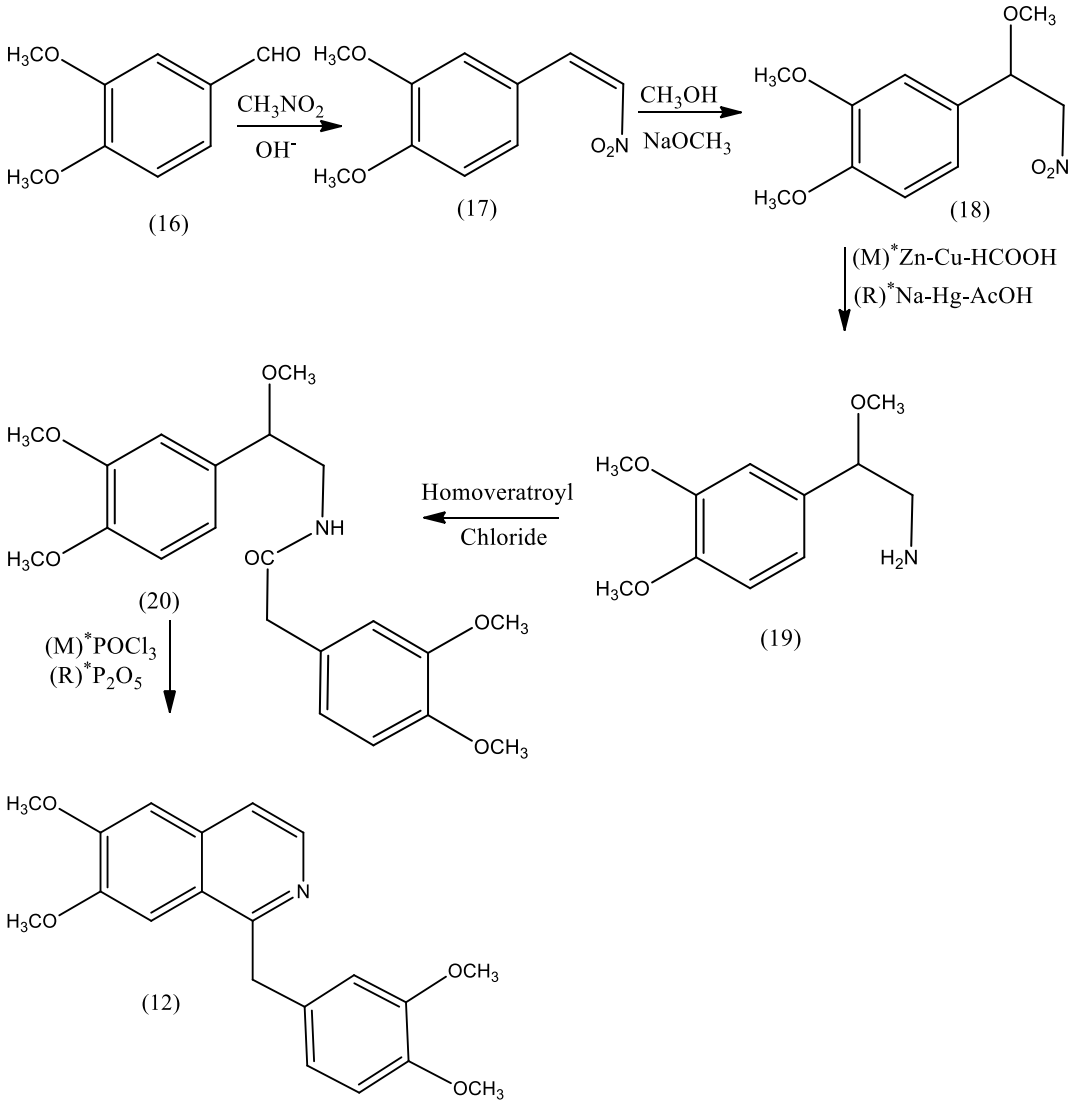


fig. (III) Rosenmund and Mannich synthesis of papaverine

The ω-nitro-styrene (17) is obtained by alkaline condensation of veratric aldehyde with nitromethane. The methyl ether (18) is obtained by the addition of the elements of methanol to the double bond of (17). Reduction either with zinc-copper alloy in the presence of formic acid or with sodium amalgam in the presence of acetic acid, gives the methyl ether of the corresponding amine (19). Treatment of the latter with homoveratroyl chloride yields the methyl ether (20) of the β-hydroxy-amide (11) which is an intermediate in the original Pictet-Gams synthesis.

In analogy to that synthesis (in which two moles of water were removed in the final cyclization step), one mole water and one mole methanol are removed by a cyclization agent, and papaverine is formed.

Spath and Berger synthesized papaverine in low yield[13] by a route which is of interest because it employs intermediates which are likely to be the biogenetic precursors of the alkaloid (fig.(IV)). Ozonization of eugenol methyl ether (21), yielded 3,4-dimethoxyphenyl-acetaldehyde (22). When this biogenetically-feasible intermediate was condensed with β-(3,4-dimethoxyphenyl)-ethyl amine (another substance capable of being available in the plant) the Schiff base (23) is obtained. Upon heating with hydrochloric acid, this gave a low yield of 1, 2, 3, 4-tetrahydropapaverine (24), which, as mentioned previously, can be dehydrogenated to papaverine.

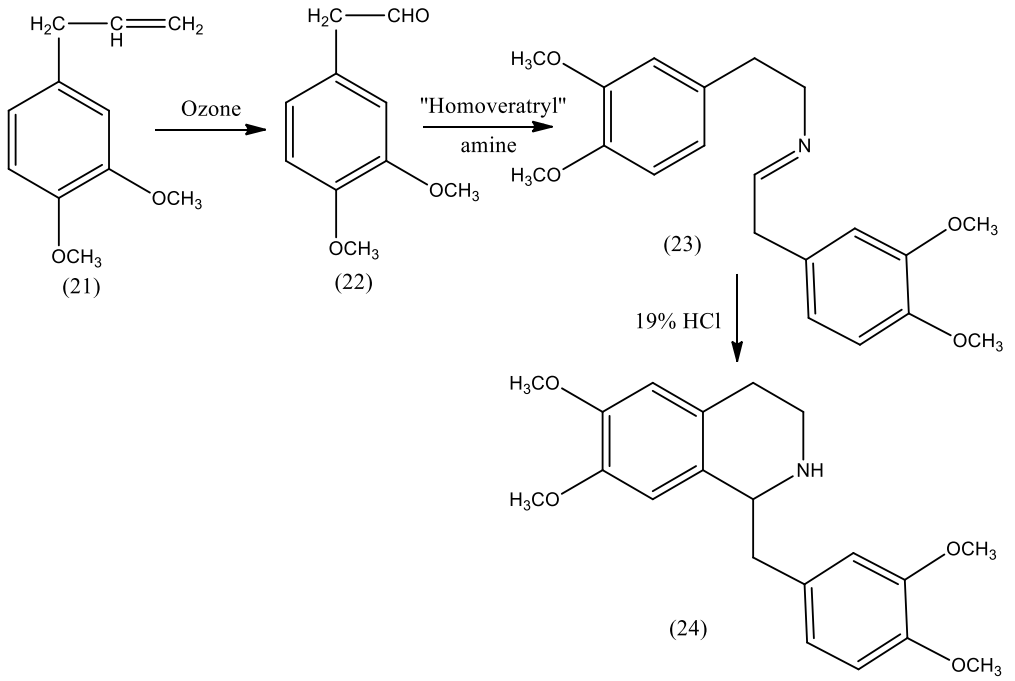


fig. (IV) Spath and Berger synthesis of papaverine

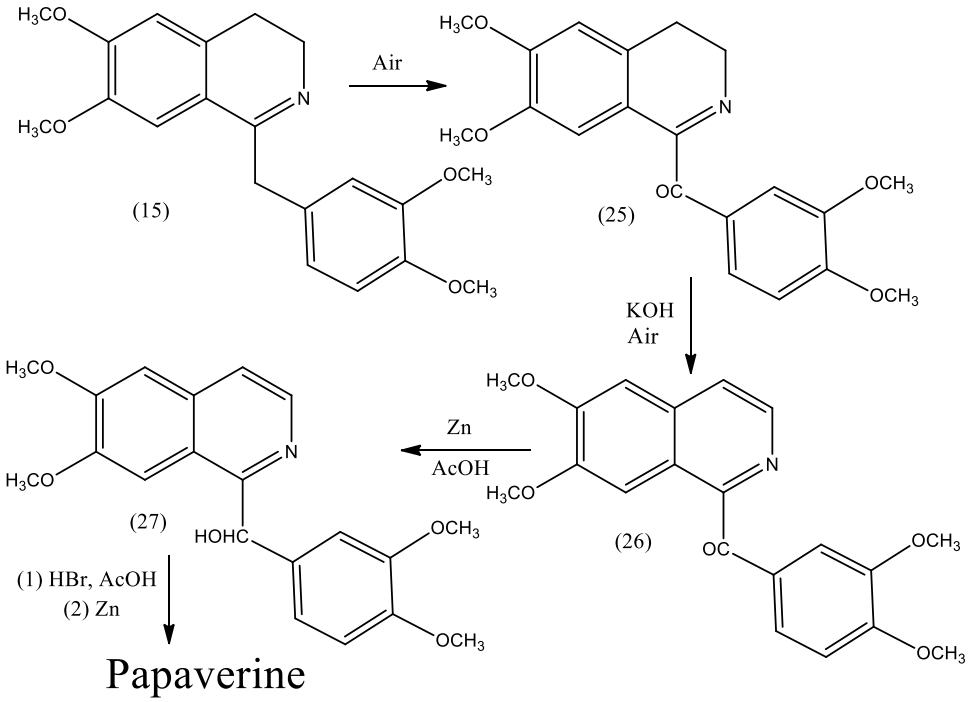


fig. (V) Buck, Perkin and Stevens synthesis of papaverine

Papaveraldine (1-(3,4-dimethoxybenzoyl)-6,7 - dimethoxy-isoquinoline) (26) has been synthesized by Buck, Perkin, and Stevens[14][10] (fig.(V)). Its synthesis is formally a synthesis of papaverine since it has been shown

that papaveraldine can be reduced to papaverine through the intermediate carbinol-papaverinol (27).

In this synthesis, 3,4-dihydropapaveraldine (25) is obtained by air oxidation of 3,4-dihydropapaverine (15) and papaveraldine (26) is obtained by treatment of the dihydro-compound with alcoholic potassium hydroxide in the presence of air.

In 1949, Redel-Boutville gave linear synthesis of papaverine in 8 steps using starting materials as homoveratric acid and glycine[15]. Also in 1974, F.H. Dean synthesised papaverine alkaloid in 8 steps using acetovanillone as starting material.

Synthesis of papaverine given by Christopher D Gilmore, Kevin M. Allan and Brian M Stoltz [16][17][18]; synthesis began with the condensation of homoveratric acid and serine methyl ester-HCl, followed by elimination to provide *N*-acyl enamine (fig.(VI)). In the key annulation, enamide underwent dehydrative addition to the aryne generated from *ortho*-silyl aryl triflate to furnish isoquinoline ester in 70% yield. Lastly, saponification and thermal decarboxylation afforded papaverine in 29% overall yield. This synthesis totals three steps from commercially available materials, which marks the shortest synthesis of papaverine alkaloid reported to date.

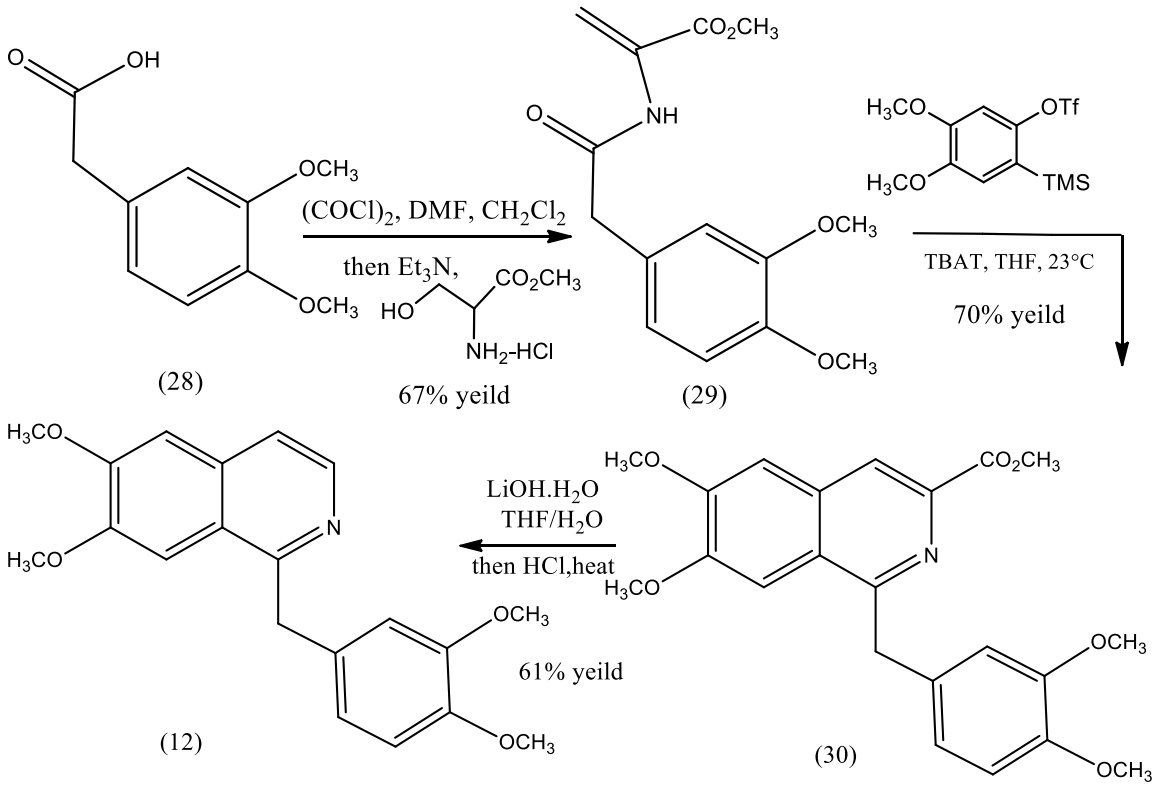


fig. (VI) synthesis of papaverine by Christopher D Gilmore, Kevin M. Allan and Brian M Stoltz

Alexander Galat synthesised papaverine using scheme [19] (fig.(VII)); also Wahl (1950) reported similar method independently. In this approach a 3-carbosy-3,4-dihydropapaverine, is the intermediate which Wahl decarboxylated and dehydrogenated in one step, while Galat isolated the intermediate 3,4-dihydropapaverine and then dehydrogenated this in the usual way. The yield of amide formed is higher when (32) is treated with ammonia than (31) treated with ammonia. Esterification of the free acid followed by phosphorus oxychloride cyclization of the methyl ester yields the 3-carbomethoxy-3,4-dihydropapaverine. Dehydrogenation of this compound is known to give 3-carbomethoxypapaverine. The ester was therefore saponified and the free acid obtained converted to papaverine.

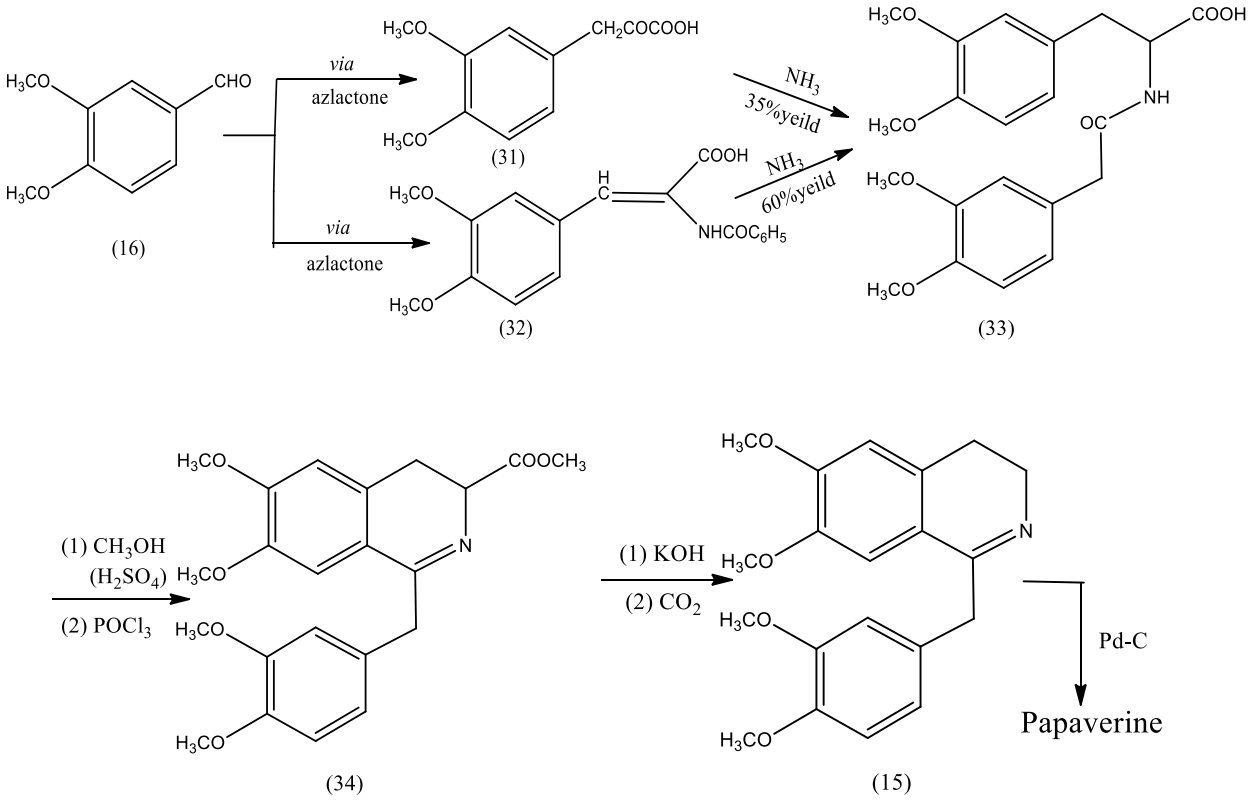


fig. (VII) synthesis of papaverine by Alexander Galat

Meng-Yang Chang , Ming-Hao Wu, Nein-Chia Lee, Ming-Fang Lee synthesised papaverine (fig.(VIII)) by taking 2-allylbenzaldehyde starting material, which was isolated from commercially available compounds in 44–55% overall yields of three-steps according to the reported procedures with the reaction sequence of O-allylation and the Claisen rearrangement followed by the O-methylation[4]. ketone formed was obtained from the Grignard addition of aldehyde followed by oxidation with PCC in a 66% yield of two steps. By the efficient one pot OsO4–$NaIO_4$–NH_4OAc combination, papaverine with analgesic activities was prepared in a 77% yield from ketone.

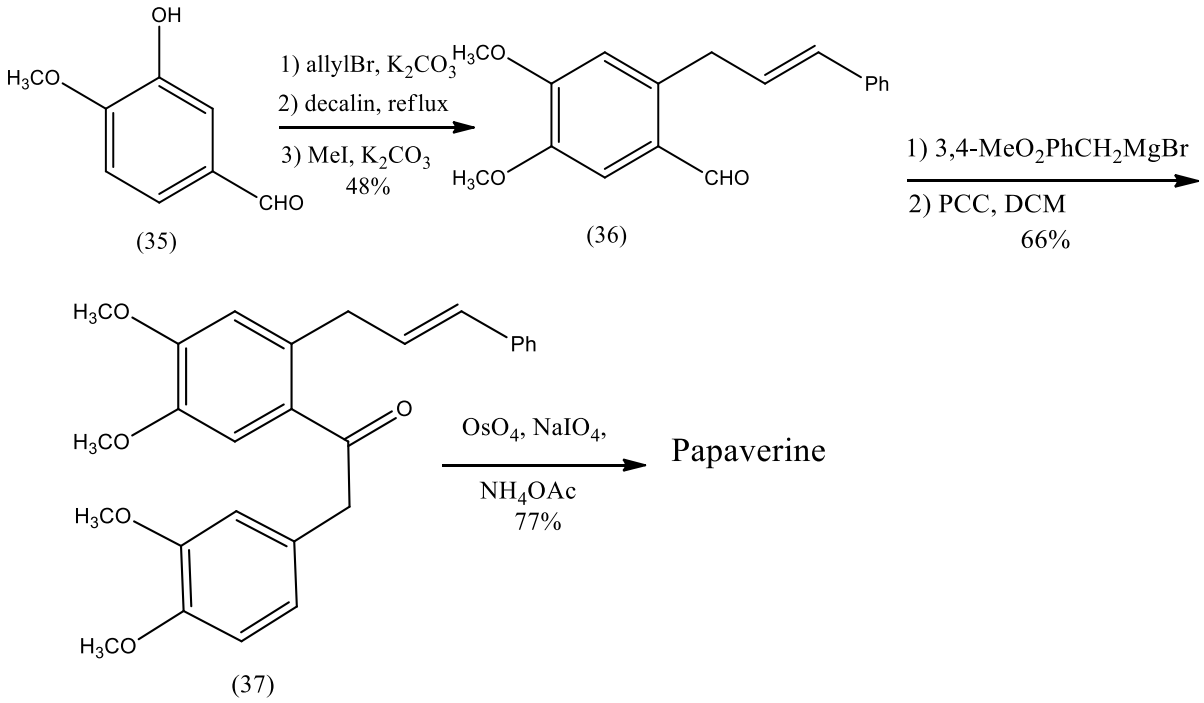


fig. (VIII) synthesis of papaverine by Meng-Yang Chang , Ming-Hao Wu, Nein-Chia Lee, Ming-Fang Lee

In 2015, Haoke Chu, Song Sun, Jin-Tao Yu and Jiang Cheng used methododlogy (fig.(IX))Rh-catalyzed sequential oxidative C–H activation/annulation with geminal-substituted vinyl acetates for total synthesis of papaverine[20]. The commercially available 2-(3,4-dimethoxyphenyl) acetic acid was chosen as the starting material. In the key step, acetophenone acetyl oxime underwent sequential oxidative C–H activation/annulation with vinyl acetate to furnish papaverine in 52% yield. Compared with other total synthetic procedures, this process is easy to handle with cheap and commercially available starting materials.

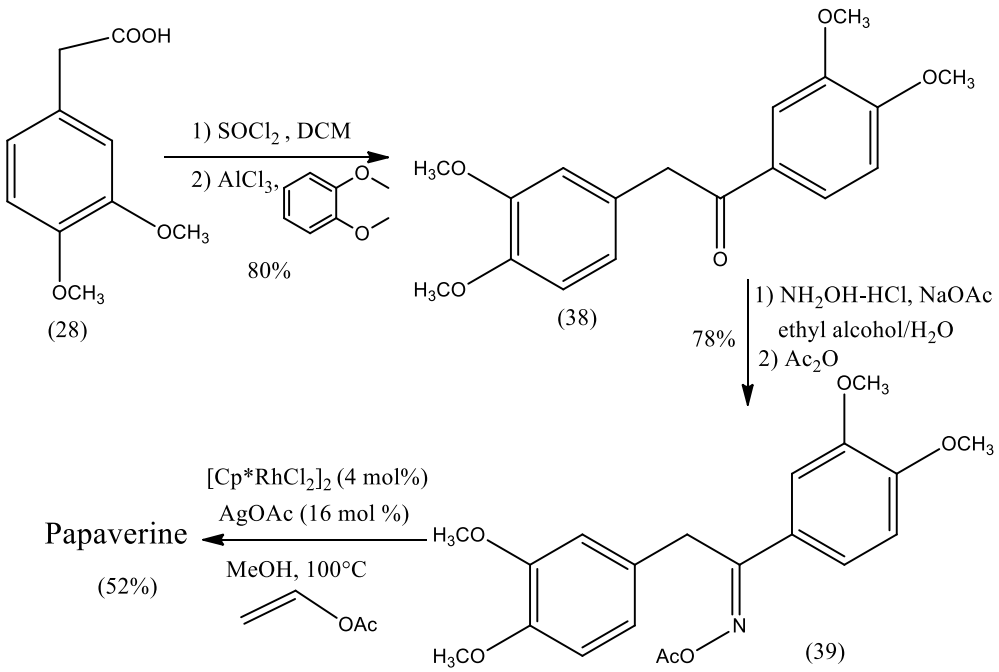


fig. (IX) synthesis of papaverine by Haoke Chu, Song Sun, Jin-Tao Yu and Jiang Cheng

Tomas Opsomer, Max Van Hoof, Andrea D'Angelo, and Wim Dehaen gave three step synthesis of papaverine but in very low yield[21] (fig.(X)).

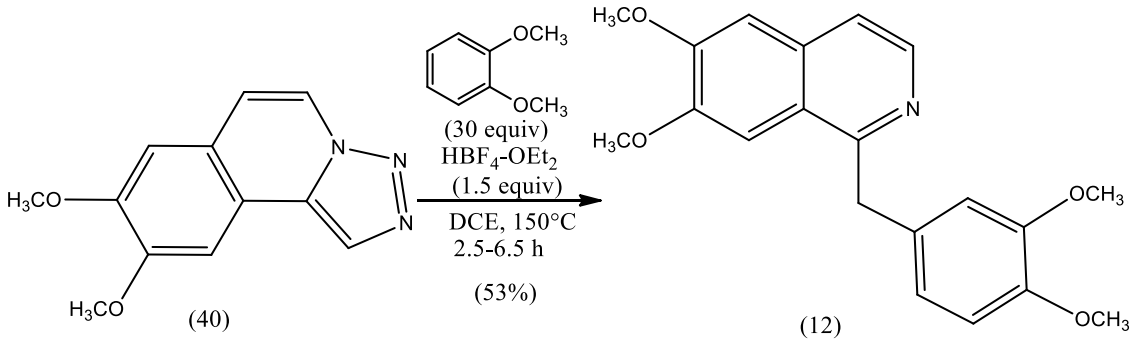


fig. (X) synthesis of papaverine by Tomas Opsomer, Max Van Hoof, Andrea D'Angelo and Wim Dehaen

Using methodology similar to Pictet and Finkelstein synthesis and Rosenmund and Mannich synthesis of papaverine, Sun, Mianmian Li,

Fenglei He, Yungang Zhu, Xingliang Liu, Shiling Shi, Xiaoxin gave synthesis of papaverine in 91% yield[22] (fig.(XI)).

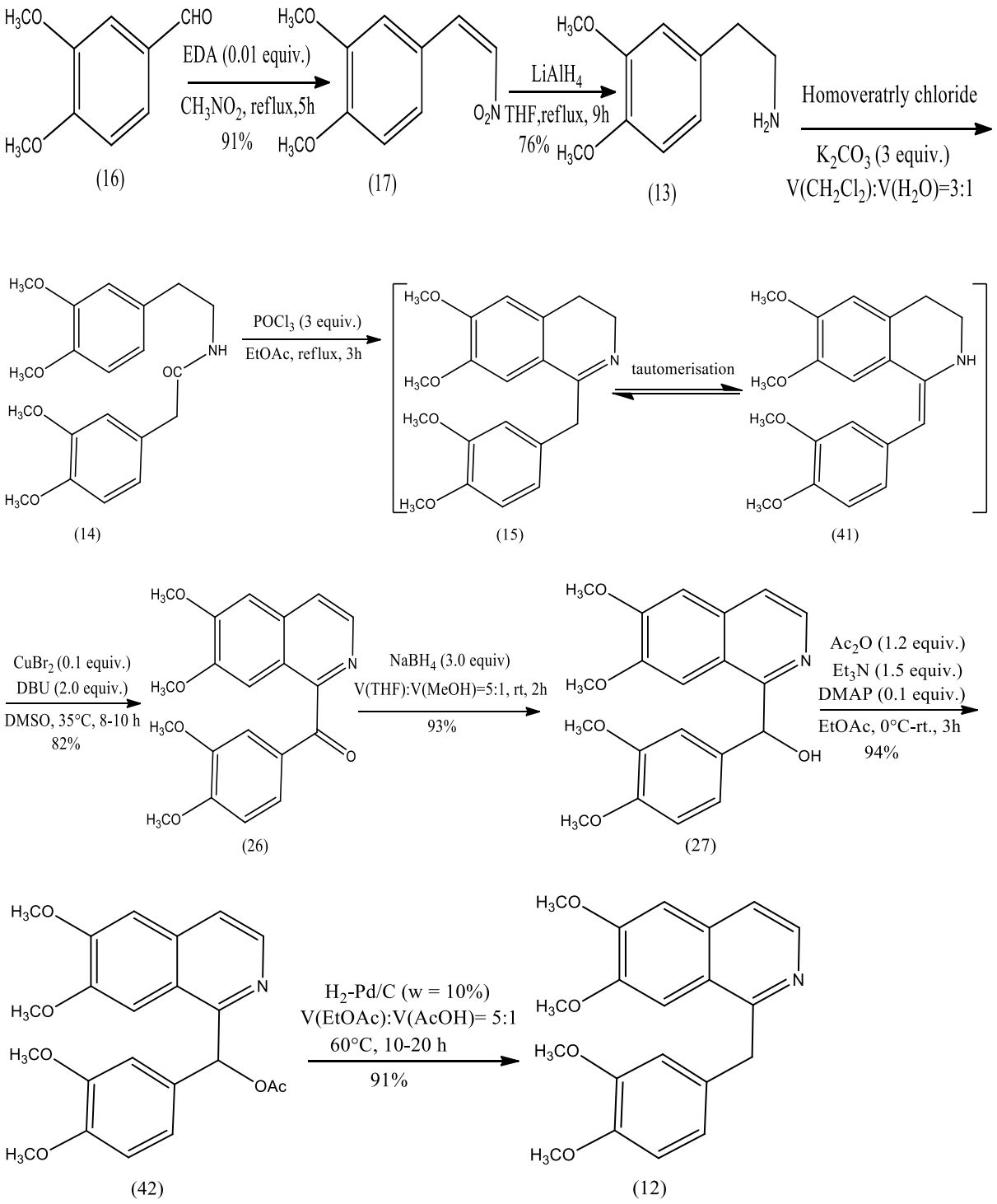


fig. (XI) synthesis of papaverine by Sun, Mianmian Li, Fenglei He, Yungang Zhu, Xingliang Liu, Shiling Shi, Xiaoxin

Kindler-Peschke-Pal Synthesis of Papaverine[23] (fig.(XII)); several modifications were done in Pictet and Gams synthesis increasing the overall yield of papaverine. This method gives a nearly quantitative yield of the Pictet-Finkelstein intermediate ,(fig.(II),(14)). The latter was submitted to cyclization with phosphorus oxychloride and dehydrogenation of the resulting 3,4-dihydropapaverine was accomplished by palladium in boiling dihydrophellandrene which is claimed to be an excellent medium for this reaction.

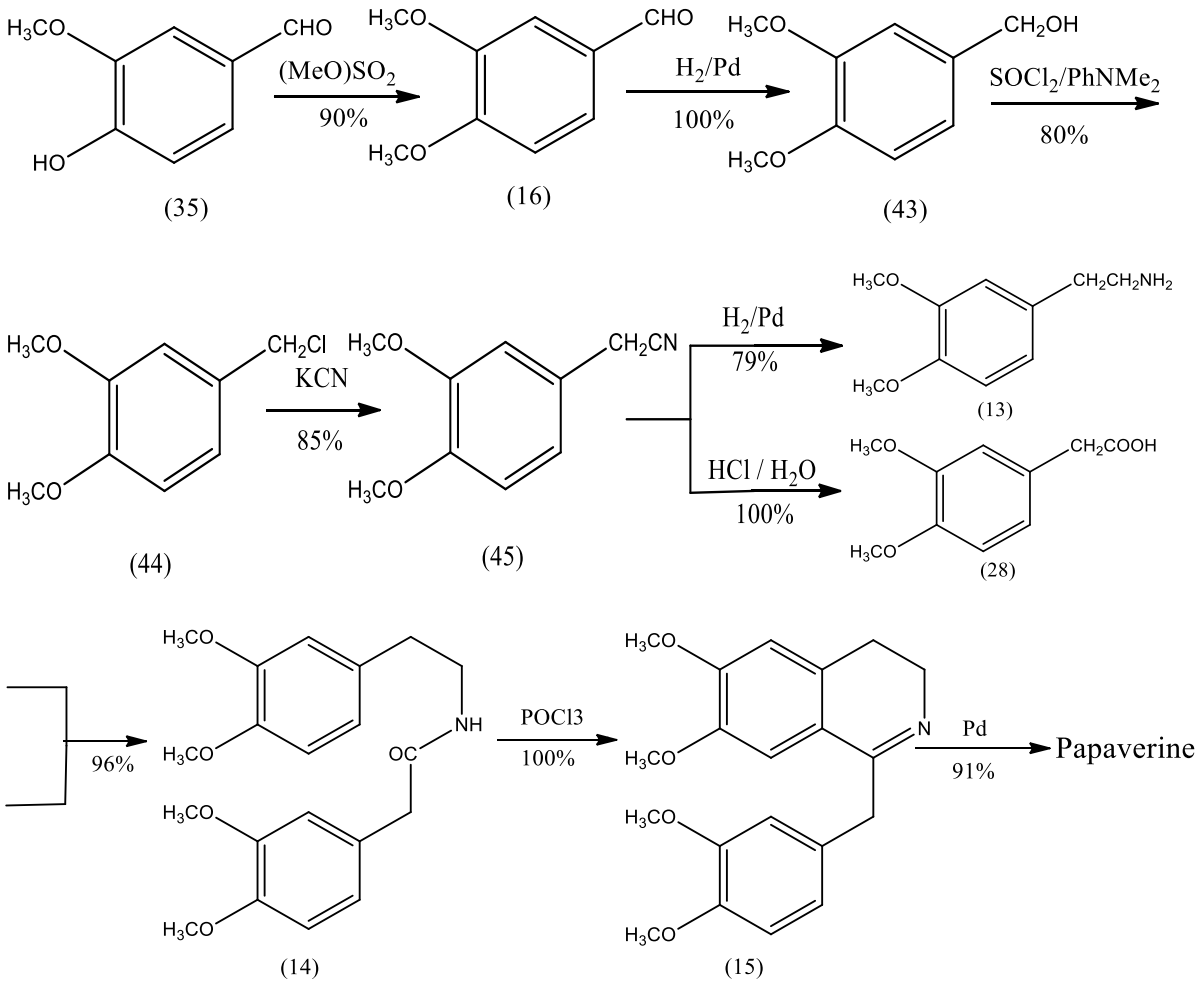


fig. (XII) Kindler-Peschke-Pal Synthesis of Papaverine

In 1903, Fritsch attempted synthesis of papaverine but obtained only higher melting isomer (fig.(XIII)). He condensed amino-acetal with desoxy-veratroin (38) and cyclized the product (46) with concentrated sulphuric acid. Instead of obtaining papaverine, a substance melting 15° higher was formed. Like papaverine, the yellow compound was soluble in acetone and sparingly soluble in ethanol and ether. On the basis of these results, Fritsch claimed that the compound was isomeric with papaverine, but he did not attempt to establish its structure[24].

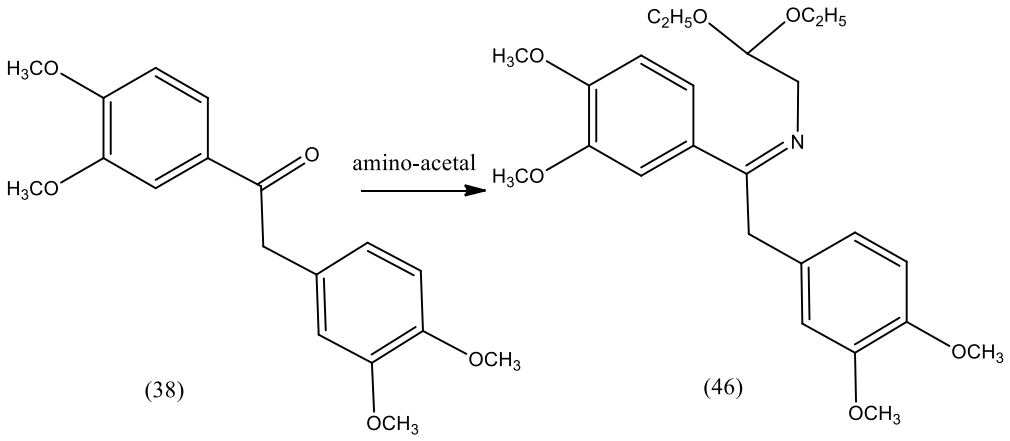
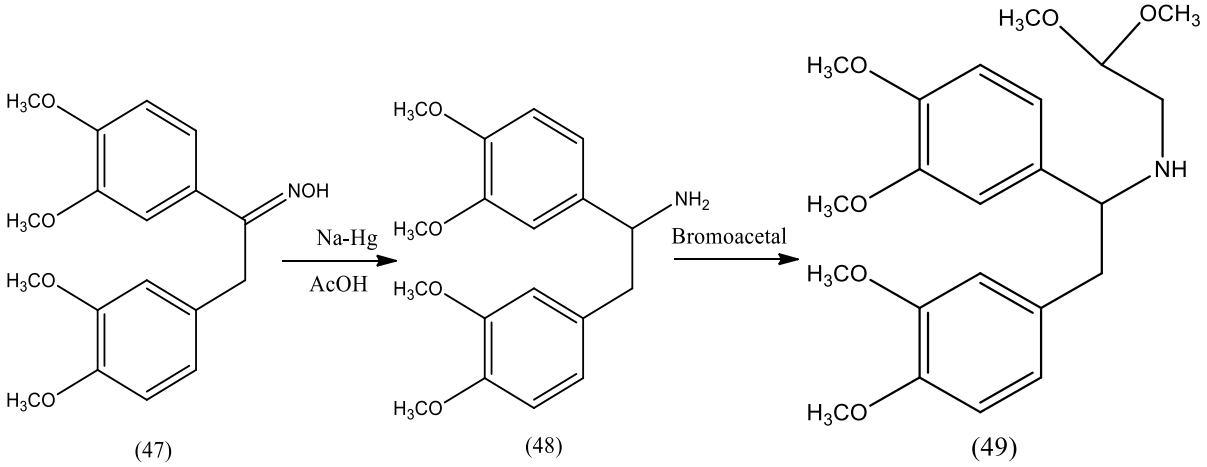


fig. (XIII) Fritsch attempted synthesis of papaverine

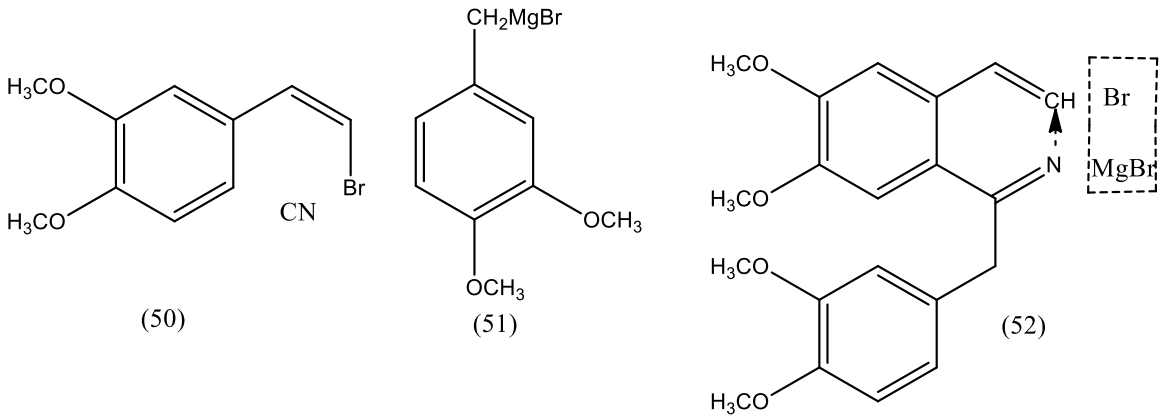
Riigheimer and Schon prepared dimethoxyisoquinoline by condensing veratrylamine with chloro-acetal and cyclizing the product, using sulfuric acid and arsenic pentoxide as cyclizing agents. In a similar manner tetramethoxydiphenylethylamine should condense with chloro-acetal to tetramethoxystilbylamino-acetal and this product be capable of cyclization to papaverine[25]. But upon attempted cyclization, however, decomposition occurred and no papaverine isolated.

Similarly, Allen and Buck (fig.(XIV)), in an attempt to extend Rugheimer and Schon's synthesis of 6,7-dimethoxyisoquinoline, reduced the oxime of desoxyveratroin (47) with sodium amalgam, condensed the resulting amine (48) with bromoacetal and obtained (49). Upon attempted cyclization of the latter substance, however, decomposition occurred and no papaverine isolated.



(47) (48) (49)

fig. (XIV) Allen and Buck attempted synthesis of papaverine



(50) (51) (52)

fig. (XV) compounds in Kefford attempted synthesis of papaverine

Kefford intended to prepare papaverine (fig.(XV)) by condensation of (50) with the Grignard reagent from homoveratryl bromide. The intermediate

expected, (52), would then undergo intramolecular cyclisation. This approach failed because the desired Grignard reagent could not be prepared.

Conclusions

This review has outlined several strategies in the total synthesis of papaverine. Papaverine alkaloid have been synthesized using several methodologies with different starting materials and using various reagents for synthesis. Some of the syntheses are convergent synthesis and most of the synthesis are linear synthesis with different yields of papaverine.

Most of the synthesis like synthesis given by Pictet and Gams, Galat, Dean, Redel-Boutville, Mianmian Li and co-workers, etc were around 8-11steps synthesis. Rosenmund and Mannich synthesis was 5 steps synthesis gave 6% overall yield whereas Gilmore, Allan and Stoltz synthesis gave 29% overall yield of synthesis. Though the steps involved in papaverine synthesis by Kindler-Peschke-Pal and Mianmian Li and co-workers were more, both syntheses gave yield of 91% papaverine. Synthesis given by Tomas Opsomer, Haoke Chu and co-workers and Meng-Yang Chang and co-workers were shorter synthesis with papaverine yields of 53%, 52 % & 77% respectively along with Gilmore, Allan and Stoltz synthesis.

Ever since the first synthesis of papaverine, other synthetic methodologies have been advancing to new level of performance. Applications of papaverine have been equally impressive and expanding in the field of medicinal chemistry. There is need to develop papaverine synthesis with ways having lower number of steps and having higher yield. We can expect the development of new strategies based on more efficient and practical methodologies in the near future, enabling concise syntheses of complex natural products that are otherwise not straightforward.

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