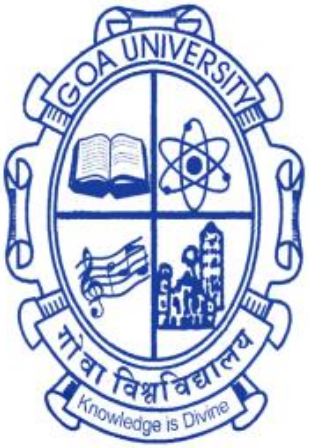
LITERATURE REVIEW ON

SYNTHESIS OF AZEPINES AND

AZOCINES STRUCTURE

M.Sc. Dissertation report by: -

MISS KRITIKA SONU SHIRODKAR



SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

LITERATURE RIVIEW ON SYNTHESIS OF AZEPINE AND AZOCINE STRUCTURES

A DISSERTATION REPORT

SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE OF MSC

(ANALYTICAL CHEMISTRY)

BY

MISS KRITIKA SONU SHIRODKAR

TO THE

SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

CERTIFICATE

This is to certify that the dissertation entitled "LITERATURE REVIEW ON SYNTHESIS OF AZEPINES AND AZOCINES" is bonified work carried out by miss Kritika Sonu Shirodkar of M.Sc. Analytical Chemistry, under the supervision of partial fulfilment of the requirement for the award of degree in Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Dr. Prajesh Volvoikar

Dissertation guide,

School of Chemical Sciences,

Goa University

Dr. V. Verekar

Dean of SCS, Goa university

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ABSTRACT

The synthesis of unsaturated heterocyclic compounds containing nitrogen atoms in the ring is very important due to its various biological applications in pharmaceutical industry. Azepine and Azocine derivatives find numerous applications most of the fields of medicinal chemistry and numerous of which are commercially available as drugs.

Azepine derivatives synthesized via aniline, maleic anhydride condensation; Pd-catalysed condensation; Au-catalysed cycloisomerization; Rh-catalysed [4+3] & [5+2] cycloaddition; Cu & Rh-aza [4+3]-annulation; Rh-catalysed arylation.

Azocine derivative prepared via addition reaction of enaminone & acenaphthoquinone; intramolecular Friedel Crafts Acylation; Cyclization; [1,2]-Meisenheimer Rearrangement; Cyclohydration; intramolecular condensation.

INTRODUCTION

[1]Azepines and [2]Azocines are an unsaturated heterocyclic organic compound of seven and eight members, with nitrogen replacing one carbon atom at one position. Its chemical formula is C_6H_7N and C_7H_7N. Its molar mass is 93.13 g/mol[3] and 105.14 g/mol respectively.

[1]Azepine is a seven-membered nitrogen heterocycle with a biologically active epitope and a useful building block in the construction of various organic molecules. When a group or group of atoms is attached to the Azepine ring, where there are profound novel influences in the biological activity of these molecules.[4] Azepine and its derivatives are imperative types of compounds that have been widely explored for the biological activities in the pharmaceutical industry. Pharmacological activities of Azepines include antibacterial[5], antiviral, antioxidant, anticancer and antitumor.

[6]The synthesis of Azepines and its derivatives is a subject of interest because of their therapeutic uses (i.e., antiepileptic, antidepressant, Alzheimer's disease, anticancer and Gram-positive antibacterial agents). Considering high pharmaceutical value of Azepine derivatives, various routes to produce them have developed. Nevertheless, the required condition normally doesn't allow for the structural variations and functionalization.

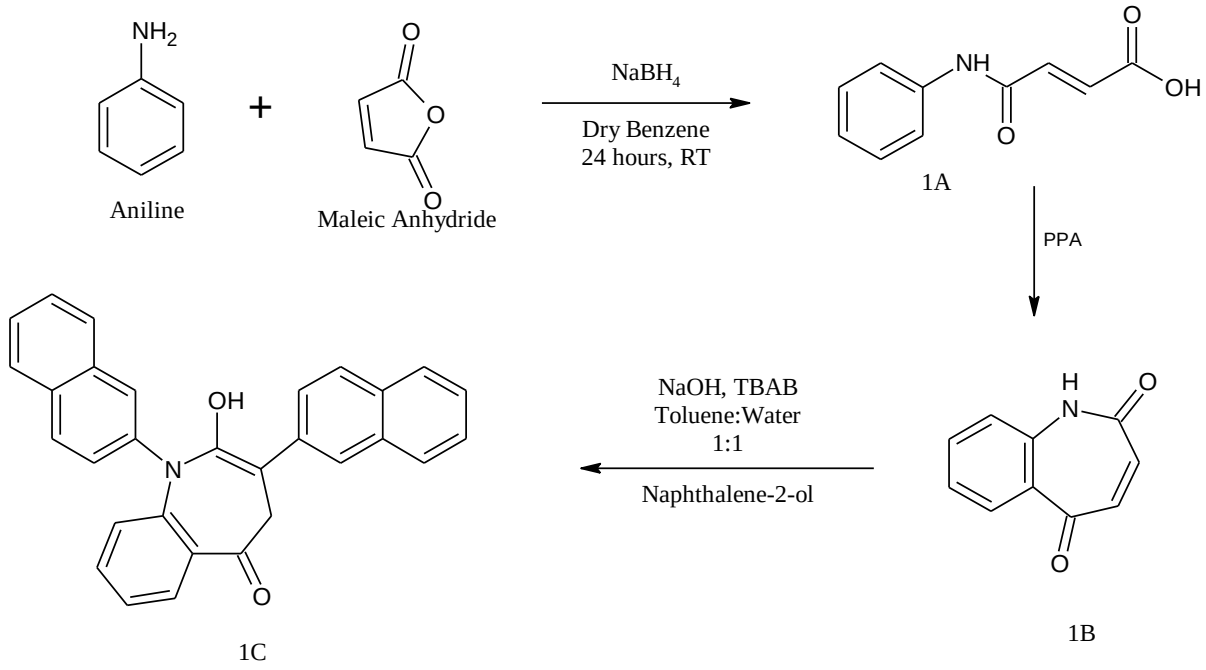
[7]An eight membered Azocine ring play a pivotal role in the structures of various important natural products as well as precursors in the synthesis of biologically active compounds. Azocine derivatives have therapeutic application, such as antitussives, antihypertensives, analgesic, nasal decongestants, and anti-malarial.

Azocine compounds are structurally attractive, as they show interesting conformations. Due to unfavourable and entropy and enthalpy factors, Azocine rings are however difficult to obtain, relatively a few methods are available for its preparation. Several general approaches include, cycloaddition,[8] the fragmentation reaction,[9] Dieckmann cyclization,[10] and tandem hydroboration reactions.[11]

LITERATURE REVIEW

Synthesis of Azepines and its derivatives

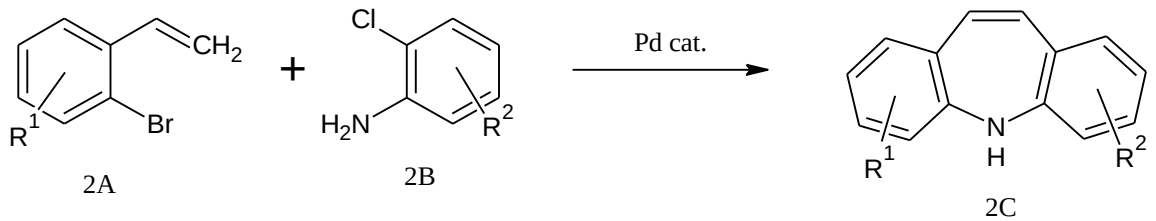
[1]SCHEME 1 (2021)



A recent approach given by Amit Sharma and Ashok Kumar Singh, reaction between aniline and maleic anhydride using catalyst sodium borohydride and dry benzene stirred for an hour approx. at RT, obtained **1a** was refluxed for 3 hours using PPA solution at 80°C. Resulted with **1b**, further 1:1 toluene/water mixture and sodium hydroxide followed by tetra-n-butylammonium bromide was added to **1b** after 15 mins naphthalene-2-ol was added to reaction mixture& heated for 5 hours at 60°C. the outcome of this reaction is **1c**.

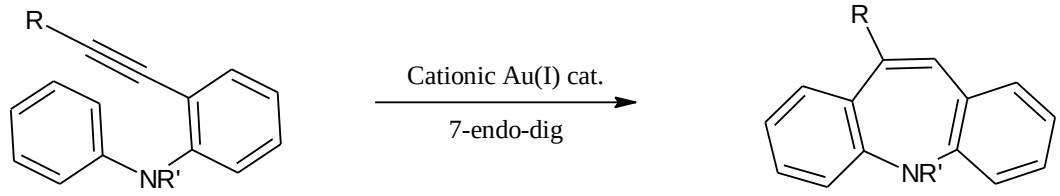
[12]SCHEME 2

a) [13]Pd-catalysed condensation



Buchwald and co-workers reported a Pd-catalysed consecutive Buchwald-Hartwig amination and Heck reaction to provide a dibenzo-azepine derivative.

b) [14]Cycloisomerization

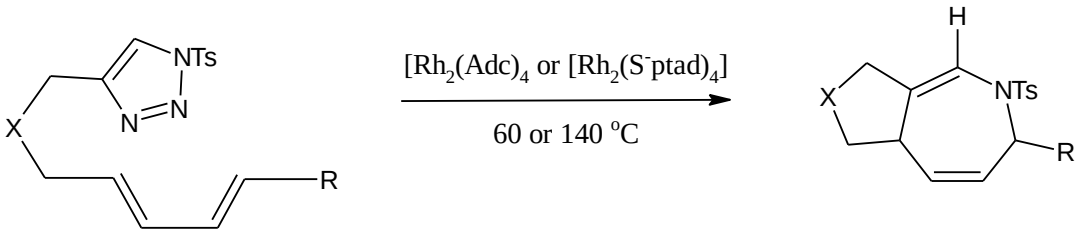


3A 3B

Another recent approach given by Ito and the co-workers based on the development of synthesis of dibenzo-azepine via Au-catalysed 7-endo-dig-selective cycloisomerization of 2-alkynyl-N-arylanilines.

[15]SCHEME 3

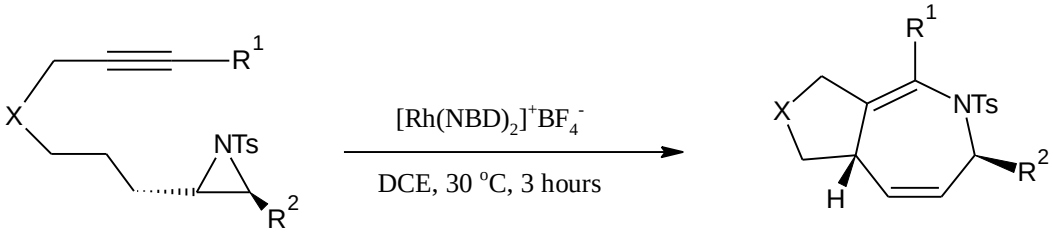
a)



4A 4B

[15]Rhodium catalysed cycloaddition strategy given by [16]Sarpong and [17]Tang in above reaction, both of them independently demonstrated Rh(II)-catalysed formal [4+3] cycloaddition of dienyl triazoles **4A** through a carbene intermediate at temperature 60 or 140°C, an excess provided to fused 2,5 dihydroazepine **4B** formed a racemic form.

b)

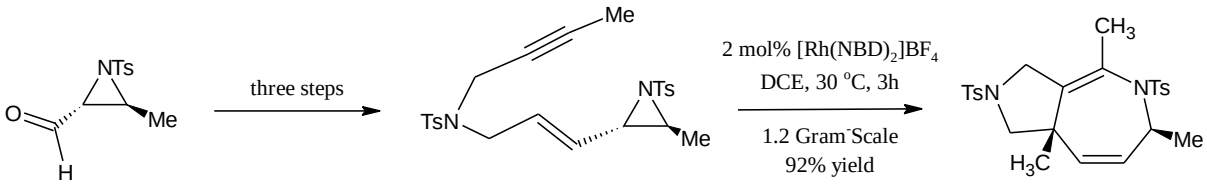


5A 5B

A new reported Rh(I) catalyst used for the synthesis of enantioenriched fused 2,5-dihydroazepines **5B** which forms an intramolecular formal hetero [5+2] cycloaddition of optically pure vinyl-aziridine-alkyne substrate **5A**, using DCE solvent at temperature 30°C and reaction time needed 3 hours. It gave high yield and ee i.e. up to 95%yield and 99%ee, moderately good yield through chirality transfer strategy.

[15]SCHEME 4

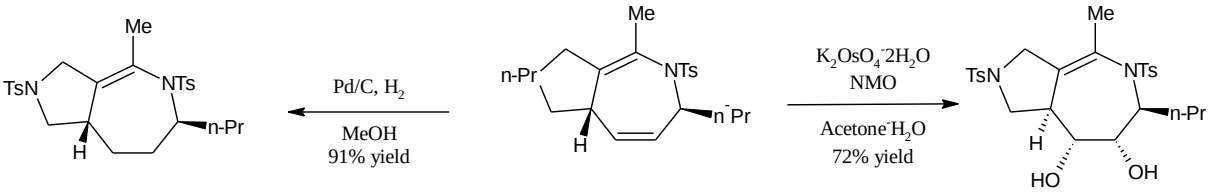
a) Gram scale rection



6A 6B 6C

A stereospecific cycloaddition is easy for scaling up, a gram scale reaction of 1.2g of (S,S) configuration **6B** structure having 95% ee was subjected to minimum loading of the catalyst i.e. 2 mol % Rh and solvent DCE reaction time taken about 30 hours and temperature maintained to 30°. Obtained corresponding (S,R) **-6C** compound with 92% yield 93% ee.

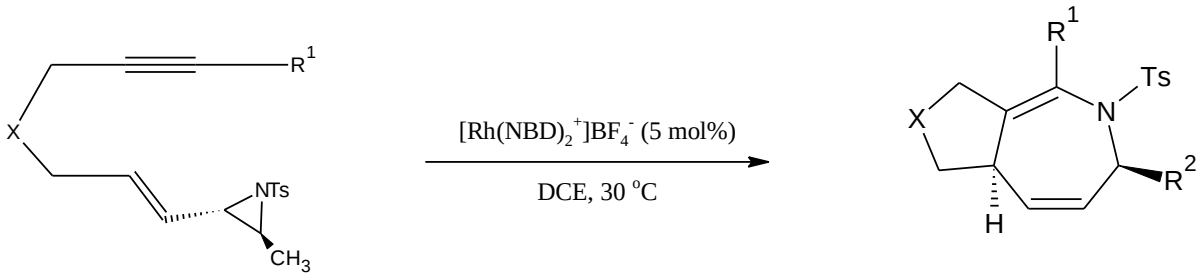
b) Synthetic transformation



7A 7B 7C

Synthetic transformation done to demonstrate potential synthetic utilities of this protocol, diastereoselective hydroxylated product of 98% yield and 93%ee **7C** was obtained after reacting with the catalyst $K_2OsO_4.2H_2O$/NMO and acetone-H_2O with provided (+)-4 & (-)-4 in 72% yield. Alternatively, disubstituted double bond could be selectively hydrogenated to pursue (S,R) 99%ee and (RS) 99% ee **7A** product in 91% yield, by utilizing Pd/C, H_2 and solvent methanol.

[18]**SCHEME 5**

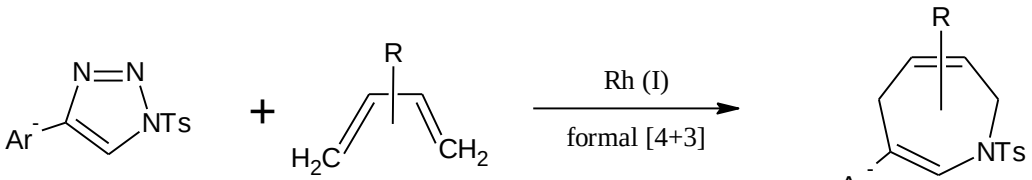


8A 8B

In 2015, Zhange et al, developed rhodium-catalysed an intramolecular hetero [5+2] cycloaddition of optically enriched vinyl aziridine-alkyne substrates **8A** to give the synthesis of chiral fused 2,5-dihydroazepines depends upon Chirality Transfer strategy. To undergo intramolecular hetero [5+2] cycloaddition, vinyl aziridine-alkyne substrate in the presence of 5 mol% of $[Rh(NBD_2)]^+ BF_4^-$ in DCE at 30°C leading to corresponding Azepine derivative **8B**.

[17]**SCHEME 6**

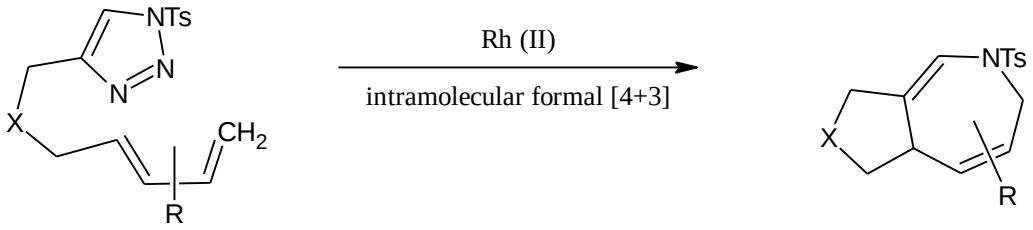
a) Intermolecular formal 4+3 cycloaddition



9A 9B 9C

H. Shang and team reported a formal [4+3] cycloaddition reaction between 1-sulfonyls 1,2,3 triazoles **9A** and 1, 3-dienes **9B** in presence of Rhodium (II) catalyst. The perused product **9C** 2,5-dihydroazepines.[19]

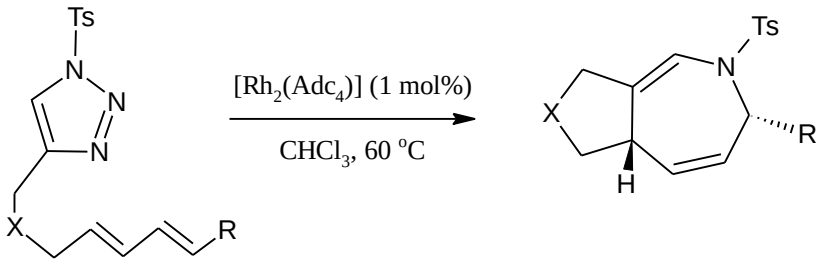
b) Intramolecular formal 4+3 cycloaddition of dienyl triazoles



10A 10B

Another program was directed with an objective of synthesis of more structurally diverse, fused 2,5 dihydroazepines via intramolecular [4+3] cycloaddition of dienyl triazoles.

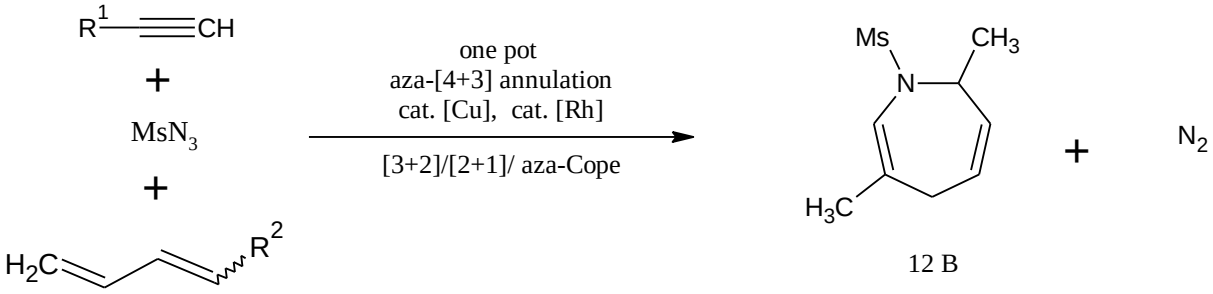
[20]**SCHEME 7**



11A 11B

In 2014, Sarpong reported a simple method for formation of fused Azepine derivatives from dienes and 1-sulfonyl-1,2,3-triazoles via Rh (II) catalysed intramolecular [4+3] cycloaddition reaction. A novel synthetic route was provided for bicyclic heterocycles, NTs, oxygen or nitrogen serves as suitable substrate for transformation.[16]

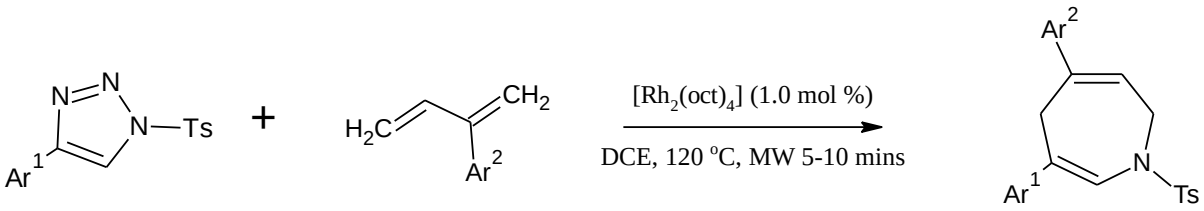
[21]**SCHEME 8**



12 A (i, ii, iii) 12 B

Sanghyuck Kim and co-workers reported an efficient aza- [4+3] annulation to enhance desired Azepine derivative **12B**, in a pot process starting from terminal alkynes **12A(i)**, sulfonyl azides **12A(ii)**, and 1,3-dienes **12A(iii)**.

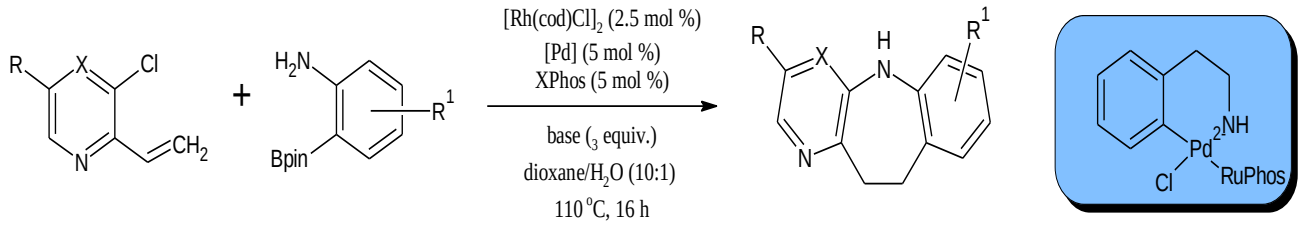
[20]SCHEME 9



13A 13B 13C

Tang and his group developed a straight forward methodology for the synthesis of Azepine derivative **13C** via Rh (II)-catalysed [4+3] cycloaddition reaction with triazoles **13C** and dienes **13B**. Here in, observed a broad substrate scope due to efficient transformation.

[20]SCHEME 10

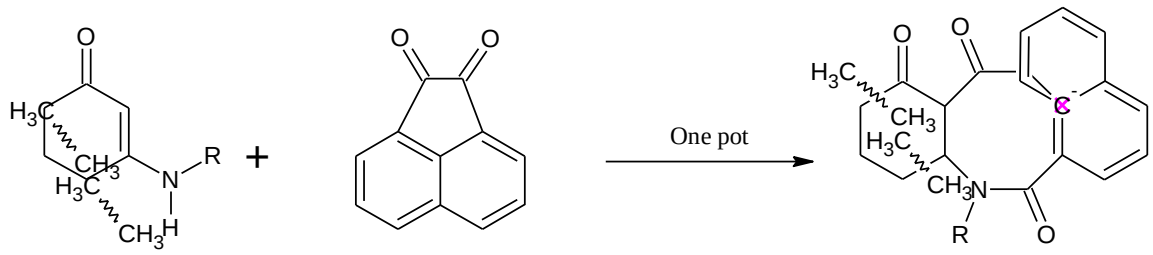


14A 14B 14C

Lauten explored the synthetic utilities of Rh(I)/Pd(0) catalysis for the efficient synthesis of N-H and N-alkyl fused Azepine derivative, helded a great application potential I pharmaceuticals. Using o-amino phenylboronic esters **14B** and halides substrates **14A**, a sequential Rh- catalysed arylation **14C** and Pd-catalysed intramolecular amination with halides involved. This process is highly efficient and performed in one-pot, which might find more synthetic application in expedient access to Azepine containing molecules.[22]

Synthesis of Azocine structures

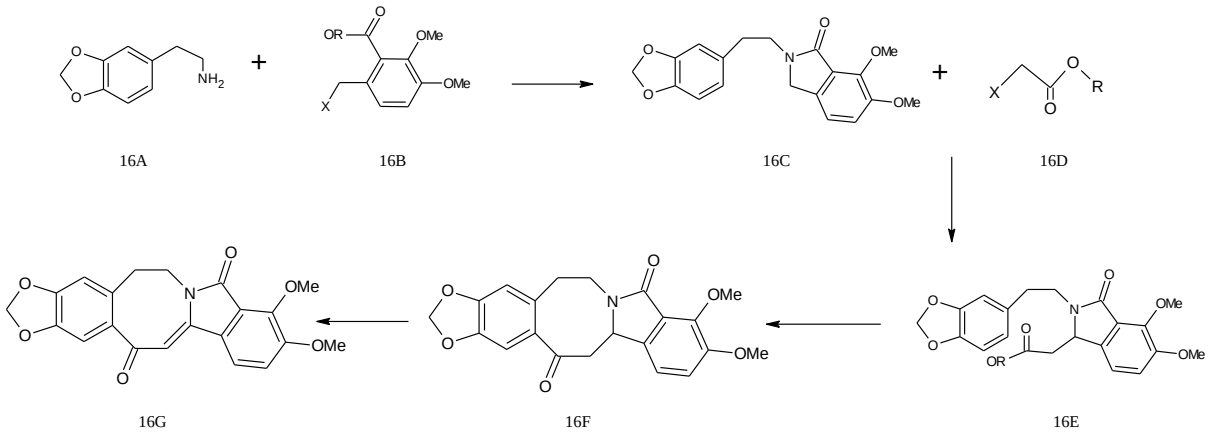
[7]SCHEME 11



15A 15B 15C

S. Hekmat and the co-workers recently developed a new synthesis of preparation Azocine derivative, i.e. One Pot Reaction. Enaminone derivative was synthesized initially via I_2 mediated condensation of amines. This synthesized enaminones **15A** were reacted with acenaphthoquinone **15B** and corresponding Azocine derivative obtained **15C**.

[2]SCHEME 12

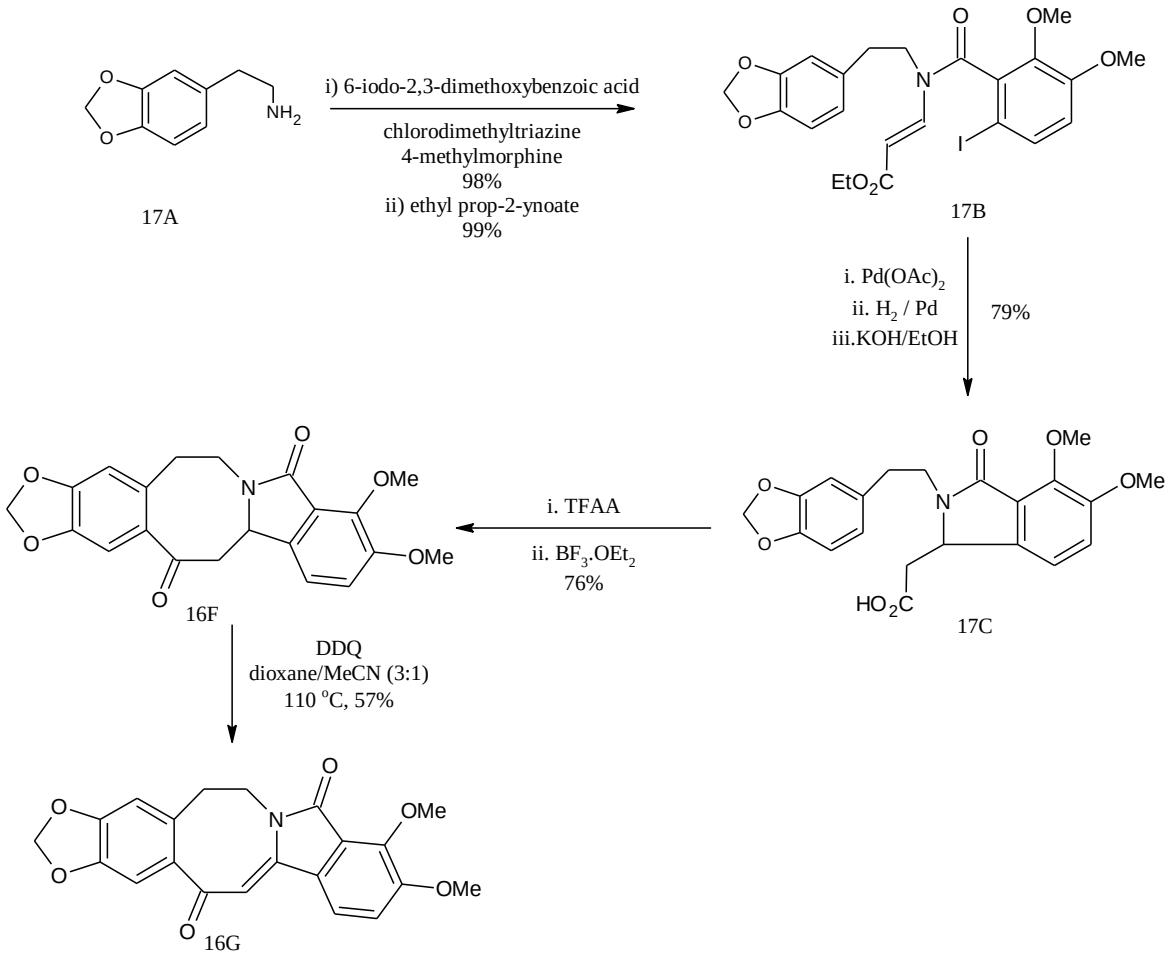


16A 16B 16C 16D 16E 16F 16G

A general route is reported by Prajesh Volvoikar for the construction of an Azocine ring system. The dihydrobenzoazocine derivative **16G** could be obtained from its tetrahydro derivative **16F**. The construction of an eight membered tetrahydro benzoazocine ring B of **16F** could be obtained from the corresponding ester **16E** by intramolecular Friedel Crafts Acylation reaction. The ester **16E** could be

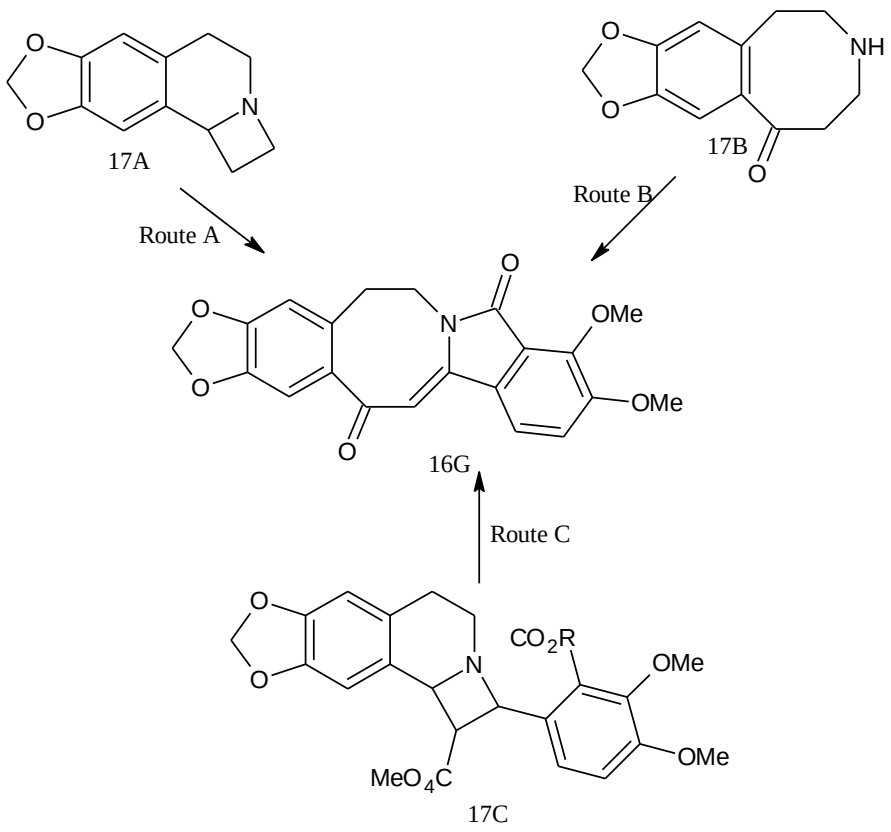
acquired by C-C bond formation via anion chemistry of isoindolinone derivative **16C** which in turned prepared by one pot alkylation-amidation from **16A** and **16B**.

[23]**SCHEME 13**



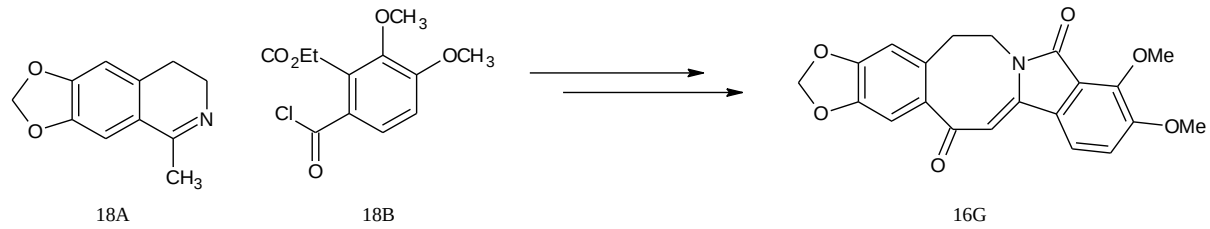
Seong-Ye Seo and Guncheol Kim provided a synthetic representation of an Azocine derivative (Magallanecine). A prerequisite precursor **17B** prepared from **17A** through a coupling reaction with 6-iodo-2.3-dimethoxybenzoic acid using chloromethyl triazine and 4-methylmorphine in 98% yield and using Michael reaction in 99%. Heck reaction, hydrogenation and hydrolysis, applied to obtain **17C**, a Friedel Crafts alkylation of **17C** using TFAA results with a **16F** structure of 76% yield. Treatment of **16F** with DDQ we attain Azocine derivative structure **16G**.

[24]**SCHEME 14**



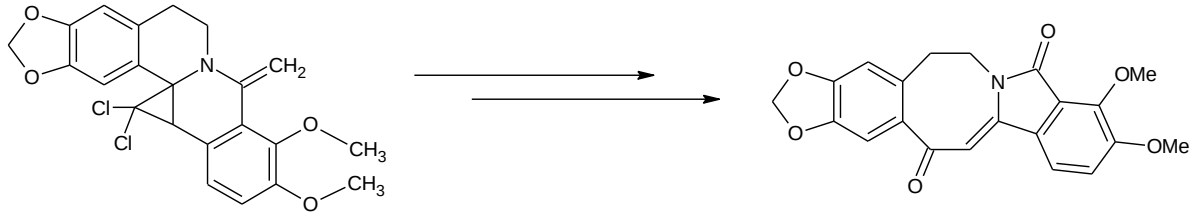
A retrosynthetic format given by Takushi Kurihara and team for Azocine derivative **16G** via 3 routes. Route A by amide cyclisation starting from **17A**, Route B by intermolecular arylation of benzoazocine **17B** and Route C by intramolecular Heck cyclization initially starting from unsubstituted azetidine **17C**.

[25]**SCHEME 15**



A total synthesis method given by J. Danishefsky and co-workers to enhance an Azocine derivative of Magallanecine. A treatment of methyl-β-hydrastine **18A** with acid chloride **18B** provided an imide derivative which was converted to the desired product **16G**.

[26]**SCHEME 16**



19A 16G

Shamma Maurice and Govindarajan Manikumar synthesized a conventional methodology for the development of an Azocine derivative of Magallanecine. The opening of cyclopropane ring of adduct **19A,** followed by an intramolecular condensation and elimination of hydrogen chloride provided the desired keto lactam **16G** i.e. Azocine derivative of Magallanecine**.**

CONCLUSION

This literature review could be summarised as; Azepine derivative synthesized via Rhodium catalysed cycloaddition provides efficient yield compared to Au catalysed isomerisation & Pd catalysed condensation. Also, it is an organic supported catalyst and being recyclable catalyst, it is a cost-efficient method.

Azocine derivative synthesized by intramolecular Friedel Crafts Acylation of an ester is a simple and shorter method to enhance efficient yield.

Most recently, more examples for the expedient's construction of Azepines and Azocines using other transition metal or acid catalysis were also achieved, which provided more synthetically useful insight into these medium N-heterocycles synthesis.

Azepine and Azocine derivative having wider application in pharmaceutical and medical chemistry field are in great demand. Future endeavour in this field is wider, deeper and could be explored more.

Acknowledgement

It is indeed a great sense of joy to complete my M.Sc. dissertation entitled **"Literature Review on Synthesis of Azepine and Azocine derivatives"**. A very great experience to learn new things and pursue ample of knowledge. I would like to express my special thanks of gratitude to my dissertation guide 'Dr. Prajesh Volvoikar' for guiding me in every possible way and providing a great pile of knowledge.

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