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The Novel Emerging Approaches for the Synthesis of Tetrahydropyridine Motifs: An Overview

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ABSTRACT: Tetrahydropyridine scaffold is key step in the synthesis of wide variety of natural products, pharmaceuticals and biologically important moieties. This bioactive core has maintained the interest of researchers in gaining the most suggestive and conclusive access in the fields of novel tetrahydropyridine derivatives of medicinally importance from the last few decades. The researchers group are quite engaged with the challenge of developing the simple and facile direct access to the vast libraries of THPDs. However, this review would expectantly shed light on ways to raise the therapeutic worth and recent advancement made in the multicomponent synthesis of THPDs reported in the recent scientific literature.

Keywords: Tetrahydropyridines; Multicomponent reaction; antimicrobial; anti-inflammatory.

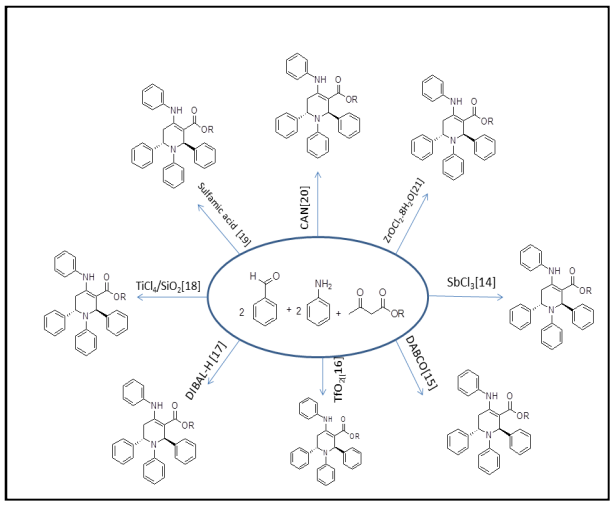
INTRODUCTION: From last two decades and nowadays tetrahydropyridines are centre of attraction and have received significant attention for their diverse biological activities as well as fundamental constructive contribution to the structure of many natural and synthetic molecules [1]. All six active sites present in tetrahydropyridines can be decorated by substituting with wide range of substrates hence make their all-round presence in many natural products such as core nucleus of many naturally occurring bioactive alkaloids [2]. So much importance gained by tetrahydropyridine credited to their broad range of pharmacological activities such as antiviral, antidepressant, antimalarial activities [3], anti-HIV [4], anticancer [5], anti-insecticidal [6], anti-influenza [7], hyperglycaemic [8], anticonvulsant [9]. Tetrahydropyridine derivatives find many applications against several metabolic disorders and human ailments [10]. Apart from this, some of the derivatives have been emerged as inhibitors of farnesyl transferase [11], dihydroorate dehydrogenase [12], M_5 muscarinic acetylcholine receptors [13] and MAO based mechanism in Parkinson's diseases.

Due to such unparallel fascinating medicinal properties tetrahydropyridine become most glamorous molecule in the field of organic synthesis. Hence researchers throughout the world are engaged in development of novel and efficient strategy to synthesize THPDs. Multicomponent coupling reaction (MCRs) represent highly valuable synthetic tic-tacs for the construction of complex molecular structure in minimum efforts. Multicomponent coupling reactions had revolutionized area of organic synthesis. This newer way has advantages over conventional linear synthesis such as high level of atom efficiency, lower costs, shorter reaction time and totally avoid time consuming isolation and purification of reaction intermediates. Hence acknowledge to their fascinating advantages multicomponent coupling reactions have emerged as efficient and powerful tools in modern synthetic organic chemistry. Due to the favourable attributes of this MCRs, are the most attractive, robust, promising and efficient way to construct library of tetrahydropyridines (THPDs) derivatives. THPDs are synthesized by using various amino sources and active methylene groups making their way through Knoevenagel reaction, Mannich reaction, isomerization, cycloaddition reactions and ring-closing metathesis (RCM).

This review is mainly an attempt to present the research work devoted to the development of library of THPDs in the recent scientific literature and continuous improvement made in the way of synthesizing novel compounds of the same.

WAY TO TETRAHYDROPYRIDINES: It is because THPDs has shown extraordinary ubiquitous

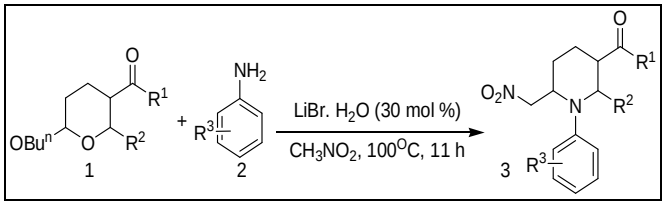
nature to be key scaffold of the novel heterocyclic system used as building block for the next generation of pharmaceuticals as anticancer, anti-HIV and anti-tuberculosis etc. Researchers from all over the world are motivated and started developing different method for the synthesis of these privileged molecules. Several methodologies for realization THPDs are came in light because of extensive efforts of researcher's community. The most straight forward and accepted routes for the synthesis of THPDs is multicomponent cyclocondensation of Anilines, Aromatic Aldehydes, and β-ketoesters in one-pot employing massive range of catalyst such as $SbCl_3$ [14], DABCO [15], TfO_2 [16], DIBAL-H [17], $TiCl_4/SiO_2$ [18], Sulfamic acid [19], CAN [20], $ZrOCl_2.8H_2O$ [21].



Scheme 1: one-pot five component synthesis of THPDs.

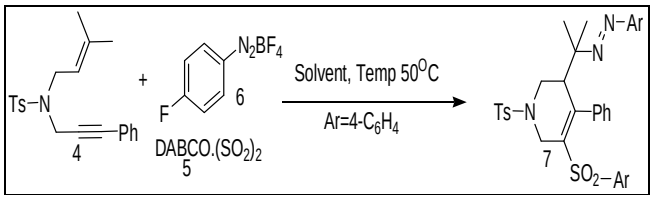
However, some of the fascinating and exciting strategies for the synthesis of THPDs have been developed. In this review some of the recent methodologies here have been selected for the discussion.

The modular assembly reaction in which 3,4-dihydropyran as dual substrate and template for the synthesis of tetrahydropyridine is developed by Shaohuan Sun and Co-workers. New library containing 1,2,3,4-tetrahydropyridine [THPD] **3** is synthesized that involves 2-alkoxy-3,4-dihydropyran **1** which reacts with aniline **2**. Here nitromethane works as both solvent and substrate in presence of $LiBr.H_2O$ proved to be best catalyst [22].



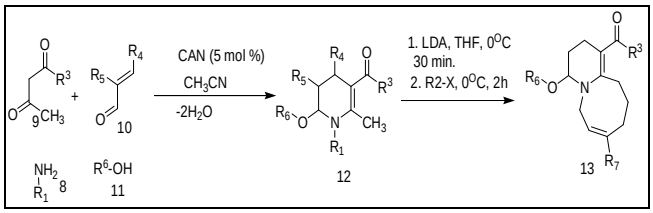
[Scheme 2]

Yuanyuan An And Jie Wu reported radical reaction utilizing 1,6-enynes **4**, sulfur dioxide **5** and aryldiazonium tetrafluoroborates **6** to access Sulphonated THP derivatives **7**. 1,6-enynes can easily participates in the reaction by virtue of C=C and Carbon triple bond in the structure. The radical cyclization process is initiated by the insitu generated sulfonyl radicals generated from interaction between aryldiazonium tetrafluoroborates and $DABCO.(SO_2)_2$. Catalyst and additive free transformation is distinct advantage of this protocol [23].



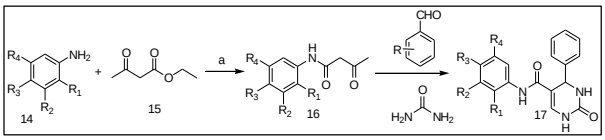
[Scheme 3[

Experimentally convenient, user and environmentally friendly procedure for the synthesis of 6-alkoxy-1,4,5,6-THP **12** was described. The compound synthesized by four component reaction between primary amine **8**, β-Ketoester **9**, α, β-unsaturated aldehydes **10** and alcohol **11**, Cerium (IV) ammonium nitrate (CAN) employed as a catalyst in acetonitrile. The compound No **12** is used as building block for the synthesis of homoquinolizines **13** derivatives in two step reaction pathway comprised of regioselective γ-deprotonation alkylation and Ring Closing Metathesis (RCM) protocols [24].



[Scheme 4]

On the other hand, acetoacetanilides were employed as building blocks for the construction of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridine-5-carboxamides derivatives demonstrated by Vijay Virsodia et.al. Proposed protocol was carried out in two step (a). In first step various substituted acetoacetanilide **16** were prepared by reacting substituted amines **14** and Ethylacetoacetate **15** in toluene with catalytic amount of NaOH or KOH. In next step (b) acetonilides obtained were used as substrate for Biginelli reaction product **17**. The pharmaceutical potential of developed library of THPD were subjected to antitubercular activity, which showed 2% to 63% inhibition M. tuberculae [25].

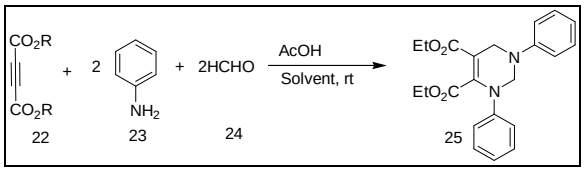


[Scheme 5]

Alkynes are activated by substitution with electron withdrawing groups. Double conjugate adduct produced by conjugate addition of aniline to electron deficient acetylene dicarboxylate . This adduct is proved to be useful as a potential synthon for the construction of highly functionalized THPDs, **21** by the tandem reaction involving dialkyl acetylene dicarboxylate **18**, aryl amines **19** and aryl aldehyde **20**, is described by Sun et.al. Surprisingly same methodology yielded different product in presence of aq. Ethanol and absolute ethanol as shown in the scheme [26]

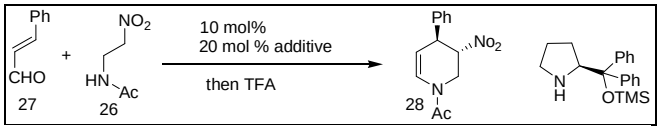
[Scheme 6]

It is not only method, to utilize electron deficient alkynes for the synthesis of THPDs. Zhou and et.al. have developed efficient one pot synthesis of polysubstituted THPDs via proton promoted route. The practical approach includes readily accessible starting materials such as ethylbut-2-ynedioate **22**, aniline **23** and formaldehyde **24** along with AcOH in methanol. Mechanistic study proposed two different routes heat and proton **25** promoted synthesis of THPDs [27].



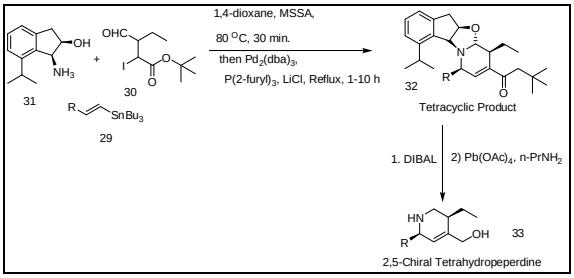
[Scheme 7]

The aza-Michael addition is one of the most important protocol especially for the synthesis of C-N heterocycles. Lele Huo etal. employed TFA for organocatalytic Michael addition of protected 2-amino-1-nitroethane(26) to α,β-unsaturated aldehyde **27** in first step. Which is followed by treatment with TFA gives 4-substituted-3-nitro-1,2,3,4-tetrahydropyridines **28** with excellent distereoselectivity and enantioselectivity. Both electron withdrawing and donating groups co-operate well for the synthesis. It was observed that with 2-substituted aryl α,β-unsaturated aldehyde distereoselectivity could be enhanced compared to alkyl group substitution credit to the influence of steric hindrance [28].



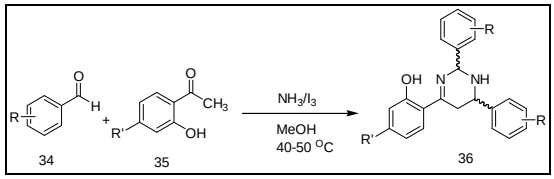
[Scheme 8]

It is very difficult to readily access the chiral 2,4,5-trisubstituted THPDs. One pot very efficient 6π-azaelectrocyclization strategy for the synthesis of 2,4,5-trisubstituted 2,5-chiral 1,2,5,6-tetrahydropyridines established by Kobayashi etal. One pot tandem 6π-electrocyclization assymetric multicomponent reaction was carried out involving various vinyl stannanes **29**, tetra substituted vinyl iodides with tertiary butyl ester group **30** and 7-isopropyl-cis-aminoindanol **31** to afford tetracyclic product **32** with satisfactory yield and stereoselectivity. Which is further reduced to produced 2,5-chiral 1,2,5,6-tetrahydropyridines **33** by DIBAL [29].



[Scheme 9]

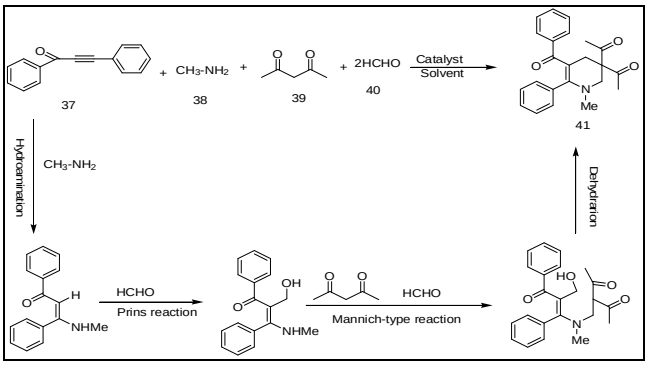
Beside these methods Kavala etal. explored enamine chemistry to describe three component protocol for the construction of scaffold of THPDs. Present protocol includes aromatic aldehydes **34**, ammonoia as nitrogen source and enolizable 2-hydroxy acetophenone **35**. Methanol worked as a solvent and I_2 employed as catalyst. Aldehyde undergoes condensation with ammonia to form imine and 1,2-addition of later to enolizable 2-hydroxy acetophenone moiety is another way to build substituted THPDs **36** [30].



[Scheme 10]

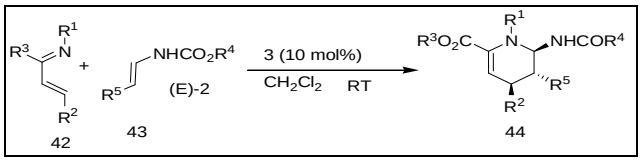
Apart from these, various groups working in this fascinating area also reported interesting results. Jiang etal. Investigated L-Proline or L-Proline/$FeCl_3$ for one-pot multicomponent synthesis of multifunctionalized 1,2,3,4- THPDs (41). Substrates composed of alkynones **37**, amines **38**, active methylene compounds **39** and formaldehyde **40** in DMF solvent. Prins reaction is addition of aldehyde/ketone to alkene

to form allylic alchohol and Mannich type reaction are in focus to develop C-C bond formation. Praposed synthetic strategy undergo completion of reaction through four sequential steps 1) two component hydroamination 2) two component Prins reaction 3) three component Mannich type reaction and 4) intramolecular dehydration cyclization [31].



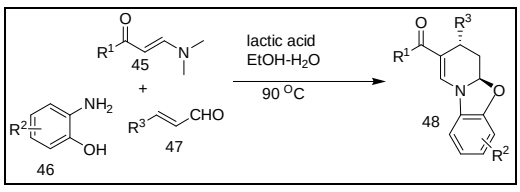
[Scheme 11]

He etal have proposed a protocol for preparation of densely functionalized chiral 4,5,6-trisubstituted 1,4,5,6-tetrahydropyridines **44**. Proposed protocol was accessed through the inverse-electron demand aza-Diels-Alder of azadiens **42** along with β-enacarbamates **43** using a chiral bifunctional phosphoric acid catalyst. This cycloaddition reaction is carried out in presence of DCM as a solvent with good to excellent diastereoselective and enantioselective product yield. Mechanistic study revealed that reaction proceeds by an asynchronous concerted mechanism [32].



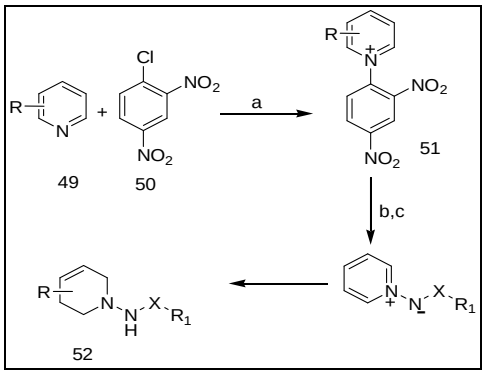
[Scheme 12]

An efficient synthesis of diastereoselective fused THPDs **48** have been established. The assembly of simple starting material enaminone **45**, nitroenamines, ortho-aminophenol **46** and α, β-unsaturated aldehyde **47** resulted in structurally diverse products in the presence of lactic acid in water-ethanol media. Use of green media and application of bio-available catalyst in organic synthesis are some merits of this tactic [33].



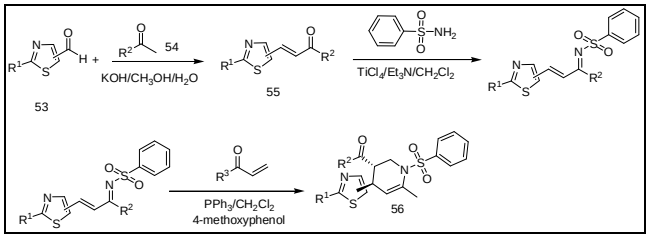
[Scheme 13]

Mohammad A. Ghaffari etal. Developed a novel strategy for the synthesis of N-substituted carbonylamino-1,2,3,6,- THPDs. In this strategy generated pyridinium ylide **51** was reduced by employing sodium borohydride to corresponding THPDs. They cameup with two schemes for the synthesis of N-substituted carbonylamino-1,2,3,6,- THPDs and N-substituted sulfonylamino-1,2,3,6-THPDs respectively **52**. The isolated novel derivatives resulted in significant anti-inflammatory activities [34].



[Scheme 14]

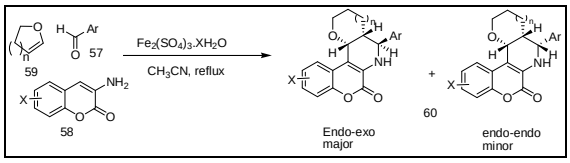
Further an efficient and convenient Aza-Rauhat-Currier reaction was employed to obtained thiazole-containing THPDs **56** by Zhau etal. In proposed protocol thiazole aldehyde **53** reacted with corresponding vinyl ketones **54** and generated α,β-unsaturated carbonyl compound **55** reacted with benzenesulfonamide. Then resulted product undergoes phosphine catalysed [4+2] annulation Aza-Rauhat-Currier reaction. Triphenyl phosphate played the role of catalyst and then methoxy phenol acted ad an additive. The target nucleus shows potential fungicidal and insecticidal activity [35].



[Scheme 15]

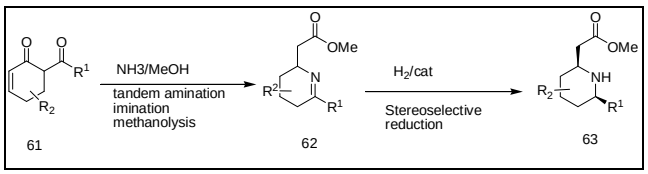
Das etal. have demonstrated 3-amino-coumarin can acts as amino source in the synthesis of THPDs **60**. They carried out the synthesis of fused furo and pyrano-tetrahydropyrido[2,3] coumarin derivatives using one-pot three component reaction between aromatic aldehyde **57**, 3-aminocoumarin **58** and cyclic enol ether **59**. Hydrated ferric sulfate proved to be efficient catalyst for inducing Povaro reaction for the synthesis of target molecules, in presence of acetoni-

trile solvent. The advantages proposed for this protocol includes good yields, high distereoselectivity, use of inexpensive and readily available catalyst [36].



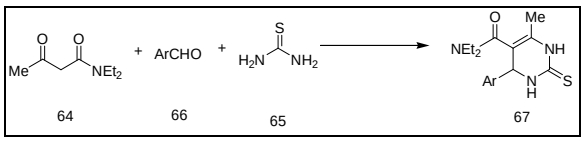
[Scheme 16]

Of course not these are the only methods for synthetic approach for THPDs synthesis. Bioinspired methods have developed for conversion of cyclohexanones **61** into 2,6-disubstituted 2,3,4,5,-tetrahydropyridine **62** which were subsequently subjected to diastereoselective reduction to 2,6-syn-disubstituted piperidine **63** is described by Cuthberston etal. Further purification of the resulted compounds were done by silica gel column chromatography [37].



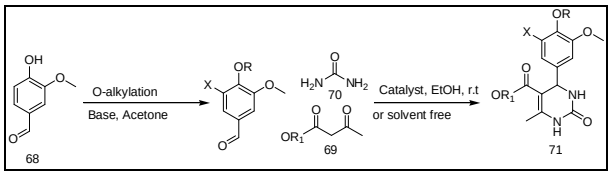
[Scheme 17]

Biginelli reaction is one of the most famous multicomponent reaction which results in synthesis of biologically active pyridine derivatives. Gein etal. Explored potential β-ketoamide in place of β-dicarbonyl compounds approach to the synthesis of THPDs. Three component condensation carried out between N,N-diethyl-3-oxobutanamide **64** with thiourea **65** and aromatic aldehyde **66** and solvent free condition and obtained corresponding 6-aryl-N,N-diethyl-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyridines-5-carboxamides **67**. This was single step, three component condensation approach to access target molecule [38].



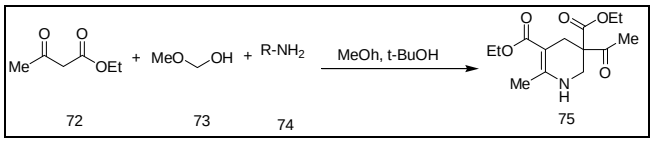
[Scheme 18]

In continuation with this Muskinja etal. developed a small library of novel 2-oxo-tetrahydropyridines **71** via one-pot multicomponent Biginelli reaction. This one-pot multicomponent domino reaction carried out between Vanillic aldehyde **68**, ethyl acetoacetate (EAA) **69** and urea **70** under solvent free condition. This facile and efficient protocol was developed in presence of Copper complex $(PhNH_3)_2CuCl_4$ as homogeneous catalyst. An advantage of proposed synthetic protocol includes mild reaction condition, simple workup procedure and good to excellent yield of products [39].



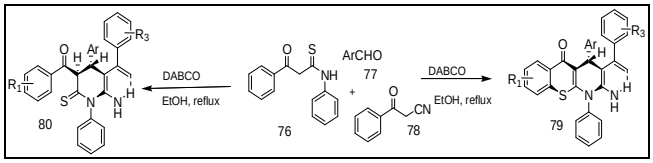
[Scheme 19]

Monocyclic or bicyclic 1,2,3,4-THPDs derivatives have been synthesized by Ishmiyarov etal. An interaction of EAA **72** with methoxy methanal **73** and primary amines or diamines **74** was reported in methanol and in presence of tert-butyl alcohol. Large number of amines were employed as an amino source to generate fused bicyclic polysubstituted 1,2,3,4-THPDs **75** [40].



[Scheme 20]

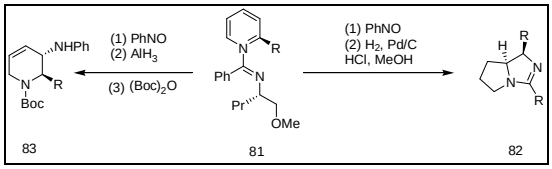
The group of Wen etal. Utilized reactivity of functionalized N-S keteneacetals to generate THPDs. It proved to be important building block to generate target THPDs, attributed to 3 or 4 active centre present in α-oxoketene N,S acetals, such as Nitrogen atom , Sulphur atom, C=O and particularly significant to potential leaving halogen group. The new domino and multicomponent procedure was designed and developed to synthesize 1,2,3,4-THPDs. Derivatives from β-aroylthioacetanilides **76**, aldehydes **77** and aroyl acetonitrile **78** via DABCO catalysed annulation reaction. This proved to be facile and efficient protocol for synthesis of THPDs derivatives **79,80** [41].



[Scheme 21]

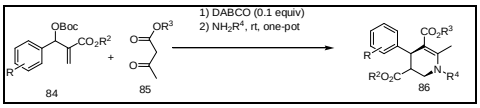
A new and stereoselective [4+2] cycloaddition reaction affording trans-2-substituted 3-amino-1,2,3,6-tetrahydropyrimidines is presented. Treatment of Nitrosoarenes with 2-substituted 1,2-dihydropyridines generates cycloadduct **81** which on chemo selective reduction furnishes 3-amino-1,2,3,6-THPDs **82,83**, in high yield. Here nitroarenes functioned as reactive dienophiles to introduced stereocentre at C-3 and

alane proved to be effective reducing agent for reduction of adduct to the desired transformation [42].



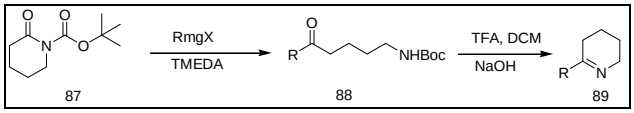
[Scheme 22]

A different protocol proceeding with steadily available Mortia-Baylis-Hilman (MBH) carbonates as the starting material to access the array of synthetically valuable THPDs have been developed. In this method different MBH carbonates **84** reacted with 1,3-ketoesters **85** and primary amines in presence of DABCO (1,4-diazabicyclo [2.2.2] octane leading to the synthesis of substituted 4-aryl-1,2,3,4-tetrahydropyridines **86**. The product obtained in good to excellent yield. Operational simplicity, good functionality tolerance and excellent efficiency are the advantages of proposed protocol [43].



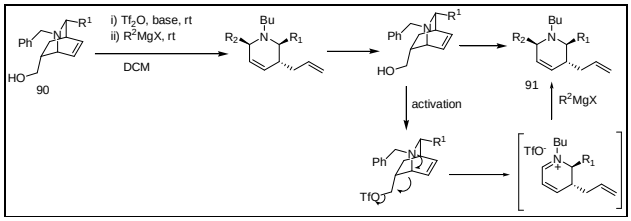
[Scheme 23]

N-Boc-pyrrolidinone, find synthetic importance particularly in construction of N-heterocyclic compound such as THPDs. Dai etal first time exploited N-Boc-pyrrolidinone in the synthesis of 6-Alkyl-2,3,4,5-THPDs, in two step. In this reported strategy commercially available N-Boc-pyrrolidinone **87** reacted with Grignard Reagent R-Mg-Br or R-Mg-Cl and TMEDA in THF or hexane to afford N0Boc-w-aminoketones **88**. In next step aminoketones on treatment with TFA and NaOH in DCM furnished the final product 6-alkyl-2,3,4,5-THPD **89** were synthesized which has shown potential antifungal activity [44].



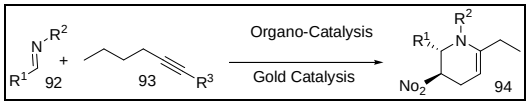
[Scheme 24]

Grob fragmentation is yet another path to proceeds THPDs scaffold. Lemonnier etal. explored stereoselective synthesis of 2,3,6-trisubstituted THPDs from Grob fragmentation of γ-amino hydroxide containing bicyclo[2.2.2] octene scaffold. Here triflic anhydride used as an activating agent for aza-bicyclo[2.2.2] octene **90** which in turn undergo Grob fragmentatiom to generate dihydro pyridinium ion. Which can react with a wide variety of G.R. giving access to 2,3,6-trisubstituted THPDs **91**. Excellent product yield with high regio and stereoselectivities under mild reaction condition were reported [45].



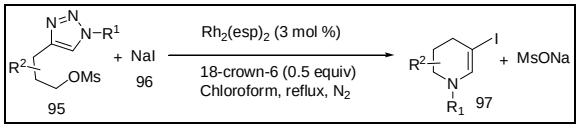
[Scheme 25]

With variety amines substrate available, suitably protected aldimines are fairly useful to synthesize THPDs. Using this amino source, Barber etal have developed a facile and novel one-pot enantioselective synthesis of N-Boc and N-Cbz protected THPDs **94** derivatives using Nitro Mannich/ hydro amination cascade. This novel methodology included synthesis of protected THPDs using readily available nitroalkynes **92** which undergo nitro Mannich reaction with suitably protected aldimines **93**. Resulted β-nitroamines undergoes cyclization under influence of metal catalysis by hydroamination ultimately yielded final product protected THPDs desirably. Here Au salt employed as metal catalyst to activate alkynes towards intramolecular hydroamination reaction [46].



[Scheme 26]

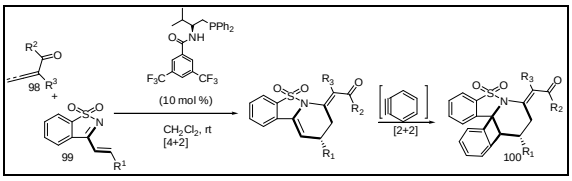
The successful synthesis of various highly substituted 5-Iodo-1,2,3,4-THPDs **97** involving intramolecular nucleophilic attack and intramolecular substitution has been reported. The reaction is carried out between sterically and electronically different arylsulfonyl substituted triazole **95** with potential leaving group and NaI **96** catalysed by Rhodium. It is the first time NaI is used as nucleophile to attack α-imino rhodium carbene as a straight forward access to target molecule. The reaction optimization condition revealed that chloroform is excellent solvent to carried out present protocol [47].



[Scheme 27]

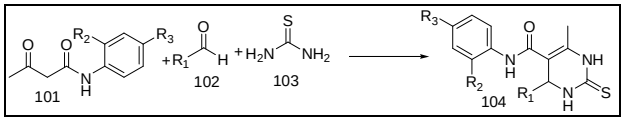
Wang etal. investigated [4+2]/[2+2] reaction sequence to approach chiral THPDs **100** synthesized by [4+2] annulation reaction between α-substituted allene ketone **98** and 1-azadienones **99**. The reaction optimization condition with solvent screening revealed that

CH_2Cl_2 was the solvent of choice. The variation of α-substituents of allene ketones and had little effects on the enantioselectivity of the reaction [48].



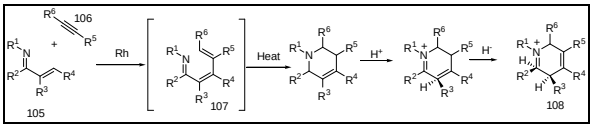
[Scheme 28]

In the search of environment friendly synthesis of polysubstituted THPD Gein etal developed solvent and catalyst free method. In mentioned protocol a series of N, 6-diaryl-2-thioxo-4methyl-1,2,3,6-tetrahydropyridines-5-carboxamide **104** is furnished by three component reaction between acetoacetanilide (2-methylacetoacetanilide, 2,4-dimehylacetoacetanilide, 4-chloroacetanilide **101** with aromatic aldehyde **102** and thiourea **103**. These synthesized compounds were screened for their antimicrobial activity against *St. aureus* and *E.Coli* [49].



[Scheme 29]

The THPDs and their novel analogues have been synthesized utilizing C-H activation/ alkenylation/ electrocyclization cascade, in one pot. The reaction sequence includes C-H activation of α, β-unsaturated imines **105**, followed by coupling with alkynes **106** which generates azatrienes **107**. 1,2 – dihydropyridines (--) is generated by 6-π electrocyclization of azatrienes in situ which is subsequently delivered THPDs **108**. A variety of diverse groups with variety of Nitrogen substituents were added to explore the scope of this methodology [50].



[Scheme 30]

CONCLUSION: The multicomponent synthesis of tetrahydropyridine having massive incentives to replace traditional linear synthesis. The novel drug designing using this molecule as a scaffold is inspired by its biological and pharmaceutical properties. Credits to their pharmaceutical worth chemists are putting their sweat to develop easy access to this privileged motif. In this review we highlighted tremendous scope of MCRs for the construction of THPDs. We are optimistic this review will serve as stepping stone for the researchers for investigating novel routes for the synthesis of THPDs derivatives.

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REFERENCES:

1. Sondhi S. M., Jain S., Dinodia M., Shuklab r., Raghubir R. (2007) One pot synthesis of pyrimidine and bispyrimidine derivatives and their evaluation for anti-inflamattory and analgesic activities. Bioorg. Med. Chem., 15, 3334-3344.
2. Bates R W, Sa-ei K., Synthesis of Sedum and Related alkaloids (2002) Tetrahedron 58, 5957-5978.
3. Kataria Meenal, Pramanik Subhamay, Kumar Manoj, Bhalla Vandana. (2015) One-Pot multicomponent synthesis of tetrahydropyridines promoted by luminescent ZnO nanoparticles supported by the aggregates of 6,6-dicyanopentafulvene. Chem.Commun, 51, 1483-1486
4. Imamura S, Nishikawa Y, Ichikawa T., (2005) Synthesis and biological evaluation of piperidine-4-carboxamide derivatives. Bioorg Med Chem 13, 397-416.
5. Srinivas C, Kumar C N, Raju B C, VJ Rao, Diwan P V, (2009), First stereoselective total synthesis and anticancer activity of new amide alkaloid of roots of pappers., Bioorg Med Chem Letter 19,5915-5918.
6. Bandaraa KAN, Kumara V, Jacobsson U, Molleyres I P, Phytochemistry (2000), 54, 29-32.
7. . Chand P, Kotian P. L, Dehghani A, Lin T. H, Hutchison T.L, Babu Y.s, Bantia S, Elliott A. J, Montgomery J.A., (2001), Triacetoxyborohydride A popular and effective method for converting aldehydes to amines *is* through a reductive amination protocol, J. Med.Chem, 44, 4379-4392.
8. Yeung J. M, Corleto L.A, Knaus E., (1982), Synthesis of N-(carbonylamino)-1,2,3,6-tetrahydropyridines with analgesic, antiinflammatory, and hyperglycemic activity**.** J. Med. Chem 25, 191-195
9. Bin H., Crider A. M., Stables J. P., Eur. J. Med. Chem., 2001, 36, 265-286
10. Misra M, Pandey S. K, Pandey V. P, Pandey J, Tripathi R, Tripathi R. P., (2009), Organocatalyzed highly atom economic one pot synthesis of tetrahydropyridines as antimalrials. Bioorganic & Medicinal Chemistry 17 625-633.

11. Gwaltney SL, Connor SJ, Nelson LTJ. (2003) Aryl tetrahydropyridine inhibitors of farnesyltransferase: bioavailable analogues with improved cellular potency**.** Bioorg Med. Chem. Letter. 13, 1363-1366.

12. Nallan L, Bauer KD, Bendale P etal (2005), Protein Farnesyltransferase Inhibitors Exhibit Potent Antimalarial Activity. J Med. Chem 48; 3704-3713.

13. Antagonists G. Zheng, Smith A. M., X. Huang, K.L. Subramanian, K. B. Siripurapu, A. Deacius, C. G. Zhan and L.P. Dwoskin, (2013), Structural Modifications to Tetrahydropyridine-3-carboxylate Esters en Route to the Discovery of M_5-Preferring Muscarinic Receptor Orthosteric J. Med. Chem., 56, 1693-1703

14. Seddigheh Mohammadi, Dadkhoda Ghazanfari, Zahed Karimi-Jaberi, Rev. Roum. Chim., 2017, 62(11), 825-829.

15. Li-Rong Wen, Yong-Jie Shi, Guang-Yuan Liu, Ming Li , J. Org. Chem., 2012, 77, 4252-4260.

16. Gerald Lemonnier and Andre B. Charette, J. Org. Chem., 2010, 75, 7465-7467.

17. P. Veeraraghavan Ramachandran, Thomas E. Burghardt, and Layla Bland-Berry, J. Org. Chem., 2005, 70, 7911-7918.

18. Abdolhamid Bamoniri, Bi Bi Fatemeh Mirjalili, Reza Tarazian, J.Chem. Sci 2015, 217, 885-895.

19. Aniket P. Sarkate, Jayprakash N. Sangshetti, Nanasaheb B. Dharbale, Ajinkya P. Sarkate, Devanand B. Shinde, J.Chil.Chem. Soc., 2015, 2832-2836.

20. H.J.Wang, L.P. Mo, Z.H. Zhang, ACS Comb. Sci, 2011, 13, 181-185.

21. S. Mishra, R. Ghosh, Tetrahedron Lett., 2011, 52, 2857-2861.

22. Sun S., Cheng C., Yang J., Taheri A., Jiang D., Zhang B., Gu Y., (2014) Synthesis of Tetrahydropyridine Derivatives through a modular Assembly Reaction 3,4-dihydropyran as Dual Substrate and Template, Org. Lett. 16 (17) 4520.

23. An Y., Wu J., (2017) Synthesis of Tetrahydropyridine Derivatives through a Reaction of 1,6-Enynes, Sulfur Dioxide, and Aryldiazonium Tetrafluoroborates, Org. Lett. 19, 6028-6031.

24. Sridharan V., Maiti S., Menendez J. C., (2009) A Very Efficient Cerium (IV) Ammonium Nitrate Catalyzed, Four Component Synthesis of Tetrahydropyridines and Its Applications in the Concise Generation of Functionalized Homoquinolizine Frameworks, Chem. Eur. J. 15, 4565-4572.

25. Virsodia V., Pissurlenkar R. S., Manvar D., Dholakia C., Adlakha P., Shah A., Coutinho E. C., (2008) Synthesis, Screening for antitubercular activity and 3D-QSAR studies of Substituted N-Phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides, Europ. J. Med. Chem. 43, 2103-2115.

26. Sun J., Wu Q., Xia E-Y., and Yan C-G., (2011) Molecular Diversity of Three-Component Reaction of Aromatic Aldehyde, Arylamines, and Acetylenedicarboxylates, Eur. J. Org. Chem., 2981-2986.

27. Zhu Q., Jiang H., Li J., Zhang M., Wang X., and Qi C., (2009) Practical synthesis and mechanistic study of polysubstituted tetrahydropyrimidines with use of domino multicomponent reactions, Tetrahydron (65), 4604-4613

28. Huo L., Ma A., Zhang y., and Ma D., (2012) Assembly of 4-substituted 3-Nitro-1,2,3,4-tetrahydropyridines via organocatalytic Michael Addition, Adv. Synth. Catal., 354, 991-994

29. Kobayashi T., Tekeuchi K. K., Miwa J., Tsuchikawa H., and Katsumura S., (2009) Efficient synthesis of 2,4,5-trisubstituted 2,5-chiral tetrahydropyridines using a one-pot asymmetric azaelectrocyclization protocol, Chem. Commun., 3363-3365.

30. Kavala V., Lin C., Kuo C-W., Fang H., and Yao C-F., (2012) Iodine catalyzed one-pot synthesis of flavanone and tetrahydropyrimidine derivatives via Mannich type reaction, (68) 1321-1329.

31. Jiang H-F., Li J-H., and Chen Z-Z., (2010) L-Proline-catalyzed five-component domino reaction leading to multifunctionalized 1,2,3,4-tetrahydropyridines, Tetrahedron (66) 9721-9728.

32. He L., Laurent G., Retailleau L. P., Folleas B., Brayer J-L., and Masson G., (2013) Highly Enantioselective Aza-Diels-Alder Reaction of 1-Azadienes with Enecarbamates Catalyzed by Chiral Phosphoric Acids, Angws. Chem. Ins. Ed., (52) 11088-11091.

33. Wan J-P., Zhong S., and Liu Y., (2015) Enaminone-Based Three-Component Reaction For the Diastereo-selective Synthesis of Fused Tetrahydropyridines, Synthesis (47) 3611-3617.

34. Ghaffari M. A., Ardley T. W., Gangapuram M., and Redda K. K., (2011) Synthesis of N-Substituted Carbonylamino-1,2,3,6-tetrahydropyridines as potential Anti-Inflammatory Agents, Synthetic Communications (41) 2615-2623.

35. Zhu Y-J., Guo X-F., Fan Z-J., Chen J., Ma L-Y., Wang H-X., Wei Y., Xu X-M., Lin J-P., and Bakulev V. A., (2016) Approach to thiazole-

containing tetrahydropyridines via Aza-Rauhut-Currier reaction and their potent fungicidal and insecticidal activity, RSC Advances, (6) 112704-112711.

36. Das D. K., Sarkar S., Khan A. T., Saravanan P., and Patra S., (2014) Synthesis of fused tetrahydropyrido{2,3-c}-coumarin derivatives as potential inhibitors for dopamine D3 receptors, catalyzed by hydrated ferric culfate, RSC Advances (4) 3581-3590.

37. Cuthbertson J. D., and Taylor R. J. K., (2013) A telescoped Route to 2,6-Disubstituted 2,3,4,5-Tetrahydropyridines and 2,6-syn-Disubstituted Piperidines: Totsl Synthesis of (-)-Grandisine G, Angew. Chem. Int. ed. (52) 1490-1492.

38. Gein V. L., Buzmakova N. A., Zamaraeva T. M., and Dmitriev M. V., (2016) Synthesis of 6-Aryl-N,N-diethyl-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamides, Russian Journal of Organic Chemisty, 4 (52) 567-570.

39. Muskinja J., Jankovic N., Ratkovic Z., Bogdanovic G., Bugarcic Z., (2016) Vaniline aldehydes for the one-pot synthesis of novel 2-oxo-1,2,3,4-tetrahydropyrimidines, Mol Divers,

40. Ishmiyarov E. R., Rakhimova N. T., Latypova D. R., Spirikhin L. V., Abdullin M. I., and Dokichev V. A., (2015) One-Pot Synthesis of Polysubstituted 1,2,3,4-Tetrahydropyridines, 12 (51) 1770-1773.

41. Won L-R., Shi Y-J., Liu G-Y., and Li M., (2012) Modulating the Reactivity of Functionalized N,S-Ketene Acetal in MCR: Selective Synthesis of Tetrahydropyridines and Thiochromeno[2,3-b]pyridines via DABCO-Catalyzed Tendem Annulation, Journal of Organic Chemistry, 77, 4252-4260.

42. Lemire A., Beaudoin D., Grenon M., and Charette A. B., (2005) [4+2] Cycloaddition of 2-Substituted 1,2-Dihydropyridines with Nitrobenzene: Asymmetric Synthesis of trans-2-Substituted 3-Amino-1,2,3,6-tetrahydropyridines, J. Org. Chem. 70, 2368-2371.

43. Wei J., Li Y., Tao C., Wang H., Cheng B., Zhai H., and Li Y., (2018) Organocatalytic Synthesis of 4-Aryl-1,2,3,4-tetrahydropyridine From Morita-Baylis-Hillman Carbonates through a One-Pot Three-Component Cyclization, J. Org. Chem., 83, 835-842.

44. Dai L., Jacob M. R., Khan S. I., Khan I. A., Clark A. M., and Li X-C., (2011) Synthesis and Antifungal Activity of Natural Product-Based 6-Alkyl-2,3,4,5-tetrahydropyridines, J. Nat. Prod. 74, 2023-2026.

45. Lemonnier G., and Charette A. B., (2010) Stereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyridines Via TF2O-Mediated Grob Fragmentation: Access to Indolizidines (-)-209I and (-)-223J, J. Org. Chem. 75, 7465-7467.

46. Barber D. M., Sanganee H. J., and Dixon D. J., (2012) One-Pot Catalytic Enantioslective Synthesis of Tetrahydropyridines via a Nitro-Mannich/Hydroamination Cascade, (2012) Org. Lett. 14(20) 5290-5293.

47. Man Z., Dai H., Shi Y., Yang D., Li C-Y., (2016) Synthesis of 5-Iodo-1,2,3,4-tetrahydropyridines by Rhodium-Catalyzed Tandem Nuclophilic Attack Involving 1-Sulfonyl-1,2,3-triazoles and Iodides, Org. Lett.

48. Wang Z., Xu H., Su Q., Hu P., Shao P-L., He Y., and Lu Y., (2017) Enantioselective Synthesis of Tetrahydropyridines/Piperidines via stepwise [4+2]/[2+2] Cyclizations, Org. Lett. 19, 3111-3114.

49. Gein V. L., Kholkin I. V., Zamaraeva T. M., Voronina E. V., and Vakhrin M. I., (2012) Synthesis Of Antimicrobial Activity Of N,6-Diaryl-4-Methyl-2-Thioxo-1,2,3,6-Tetrahydropyrimidine-5-Carboxamides, Pharm. Chem. J. 2(46) 49-51.

50. Mesganaw T., and Ellman J. A., (2014) Preparative Synthesis of Highly Substituted Tetrahydropyridines via Rh(I)-Catalyzed C-H Fuctionalization Sequence, Org. Process. Res. Dev. (18) 1105-1109.