ejpmr, 2020,7(2), 217-224

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SYNTHETIC ADVANCES FOR DIVERSIFIED PYRAZOLES AND PIPERIDINES

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Article Received on 02/12/2019 **Article Revised on 22/12/2019** **Article Accepted on 12/01/2020**

ABSTRACT

Substituted pyrazoles and pyridines are important classes of heterocyclic compounds established as privileged scaffolds. The article describes biological importance and synthetic developments of these heterocycles and provides useful information by giving instant references of previous works and their importance.

KEYWORDS:

INTRODUCTION

Pyridines

The tetrahydropyridine ring is a fundamental structural unit of many natural products[1], preclinical and clinically trail drugs[2] and a number of bioactive molecules.[3] Some of the molecules having piperidine scaffold are useful drugs in the world market.[4] The tetrahydropyridine (piperidine) motif display anti-inflammatory & anticonvulsant[5], antihypertensive[6] and antibacterial[7] properties. Moreover, a few of them found to be inhibitors for enzymes of farnesyl tranferase[8] or dihydroorate dehydrogase(DHODH)[9] and also useful in Parkinson's disease.[10] Some of the established drugs which constituents' piperdine frameworks are shown in **Fig: 1.**

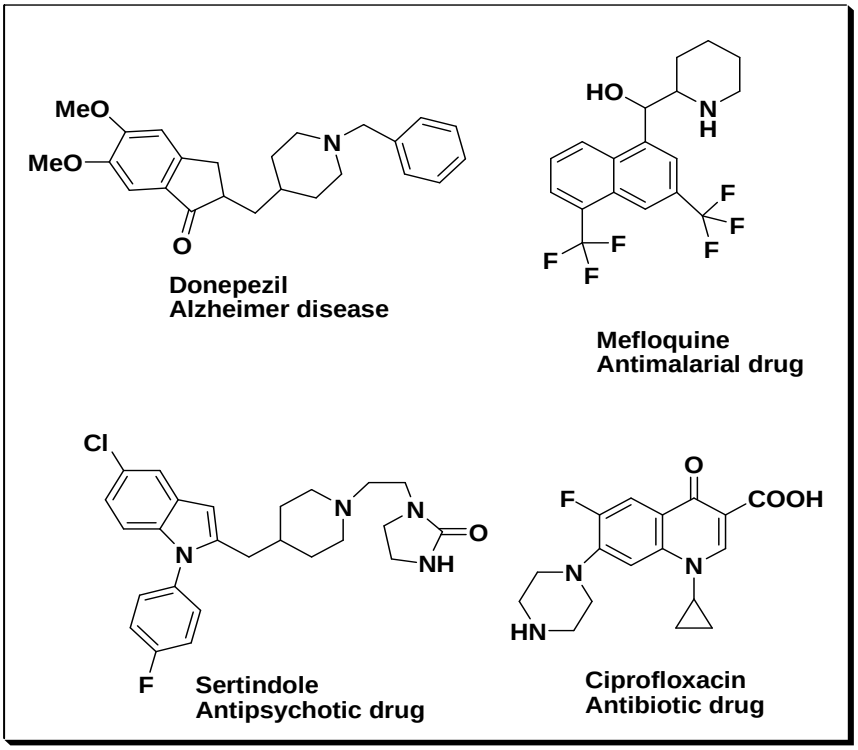
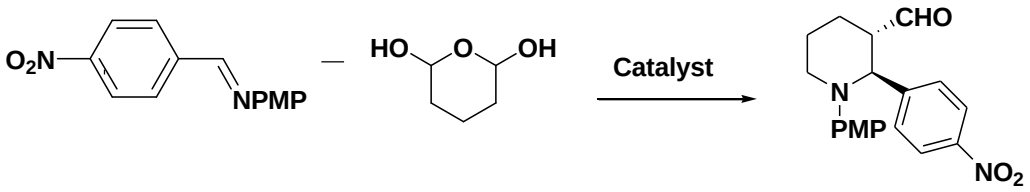


Fig. 1: Established drugs containing tetrahydropyridine motif.

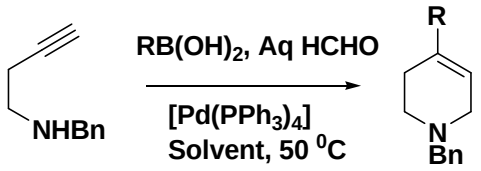
Consequently, the design and development of numerous methods for the synthesis of highly functionalized tetrahydropyridine (piperidines) has evoked considerable interests among synthetic chemists and still deserved attention.

Rong-Gang Han and coworkers[11] have developed synthesis of tetrahydropyridines catalyzed by proline in a cascade Mannich-type intramolecular cyclization reaction from N–PMP aldi-mines and aqueous tetrahydro-2H-pyran-2, 6-diol. 2, 3-disubstituted tetrahydropyridines were produced in diastereo- and enantioselective reaction **(Scheme: 1)**.



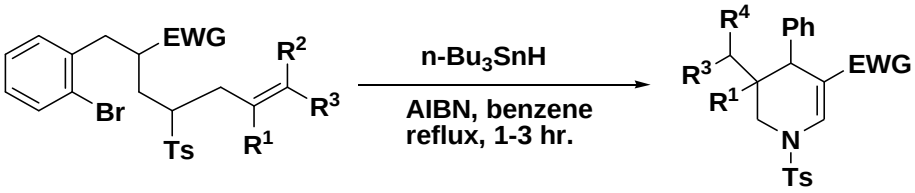
Scheme: 1

Hirokazu Tsukamoto and Yoshinori Kondo[12] developed palladium catalyzed synthesis of 1, 4-disubstituted 1,2,3,6-tetrahydropyridines via allenyl and alkynyl iminium ion cyclization reaction. The mild reaction conditions, wide substrates tolerance, easy availability of the reagents and good regioselectivity make this protocol interesting in term of combinatorial synthesis **(Scheme: 2)**.



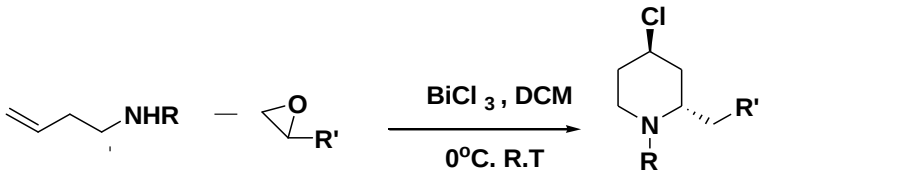
Scheme: 2

Hyun Seung Lee and coworkers[13] developed synthesis of poly-substituted tetrahydropyridine and its derivatives by radical cyclization strategy which involve consecutive 1,5-hydrogen transfer and double bond isomerization starting from Baylis–Hillman adducts **(Scheme: 3)**.



Scheme: 3

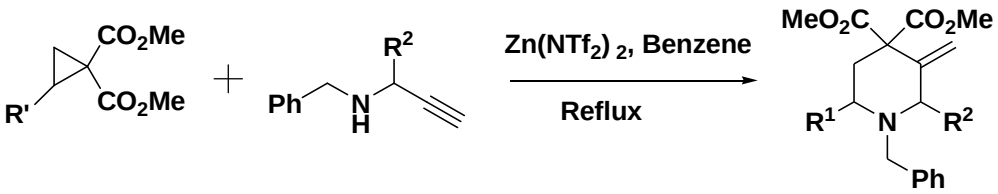
J. S. Yadav and coworkers[14] developed synthesis of *trans*-2, 4-disubstituted piperidine and its analogues by using different N-protected homoallyl amines and epoxides via aza-Prins cyclization catalyzed by $BiCl_3$ **(Scheme: 4)**.



R=Ts, Ms, Boc
R'=Me, Ph, isopropyl etc

Scheme: 4

Terry P. Lebold and coworkers[15] developed synthesis of piperidines from Propargyl amines and cyclopropanes diesters catalyzed by Zn $(NTf_2)_2$. The corresponding piperidines were achieved in excellent yields via a tandem cyclopropane ring-opening/Conia-ene cyclization **(Scheme: 5)**.

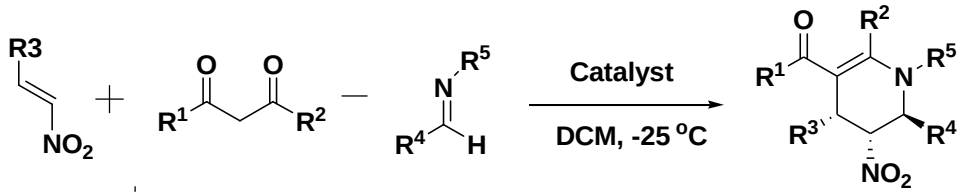


Scheme: 5

Santos Fustero and his team[16] developed synthesis of piperidines alkaloids and other heterocyles by carbamates having α, β-unsaturated aldehydes under organocatalytic conditions via intramolecular aza-Michael reaction.

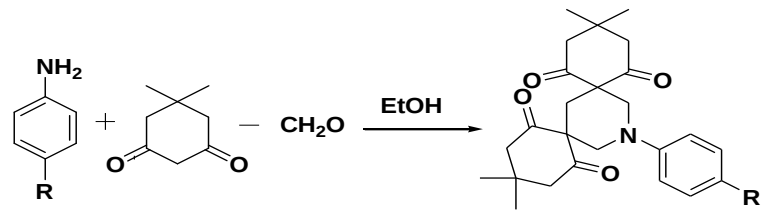
Nowadays multicomponent reactions have gained much attention over their multistep alternatives for reasons of environmental friendliness, energy efficiency and atom economy.[17] Owing to the importance of piperidine chemistry, some multicomponent reactions are also developed.

Marcus Blumel and coworkers[18] synthesized tetrahydropyridines through one-Pot multicomponent reaction of 1,3-dicarbonyl compounds, β-nitroolefins, and aldimines via Michael/Aza-Henry/Cyclization triple domino reaction in excellent enantiomeric excesses, and up to high diastereomeric ratios **(Scheme: 6)**.



Scheme: 6

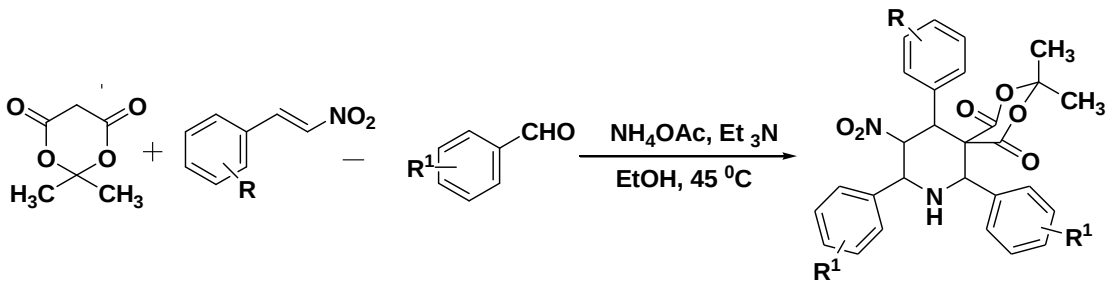
Nikolas G and coworkers[19] developed synthesis of 3, 5-dispirosubstituted piperidines by three component, one-pot reaction of aniline, dimedone and formaldehyde. The protocol offers good to excellent yields of the corresponding piperidines in a catalyst free reaction conditions **(Scheme: 7)**.



R=Me, OMe, OEt, Ph,OPh, Br, NH_2

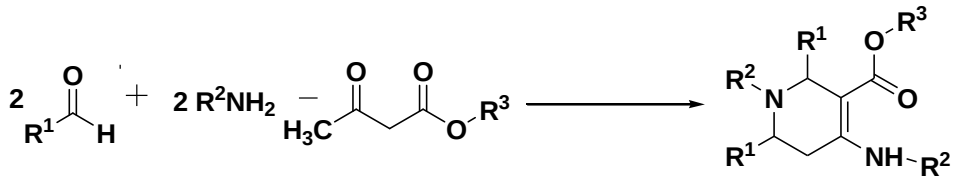
Scheme: 7

Yan Li, Zhiheng Xue and coworkers[20] developed synthesis of highly functionalized piperidines from the multicomponent reaction of ammonium acetate, aromatic aldehydes, substituted β-nitrostyrenes and Meldrum's acid. The reaction involves sequential Michael addition, formation of acyclic imines and intermolecular nitro-Mannich reaction **(Scheme: 8).**



Scheme: 8

Recently, few methods[21-26] have been reported for the multicomponent synthesis of functionalized piperidines by a five component reaction of aldehyde, ethyl acetoacetate and anilines **(Scheme: 9).**



Scheme: 9

Moreover, the five component one pot reaction of aldehyde, ethyl acetoacetate and anilines is further explored by numerous works by utilizing various catalysts and reagents such as $InCl_3$[21], CAN[22], L-proline/TFA[23], tetrabutylammonium tribromide (TBATB)[24], $ZrOCl_2.8H_2O$[25], bromodimethyl sulfonium bromide (BDMS)[26], molecular iodine[27], picric acid[28], bismuth nitrate[29], boric acid[30], PPA–ZrP[31], $B(C_6F_5)$[32] and Nano-$TiCl_4/SiO_2$.[33]

Pyrazoles

Pyrazoles belongs to doubly unsaturated aromatic ring having two nitrogen atom and three carbon atoms. Knorr in 1883[34] synthesized pyrazole for the first time. Antipyrine was the first pyrazolone drug used in the treatment of inflammation, pain and fever in 1884.

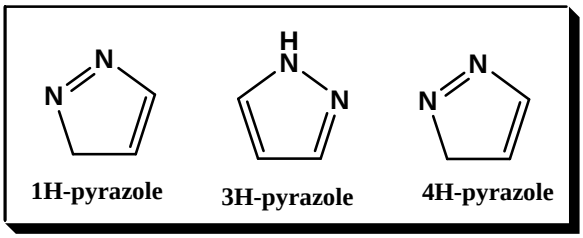


Figure: 2

During past years, pyrazole related compounds gained significant interest as they posses potential medicinal properties such as analgesic, anti-inflammatory, anti-bacterial, anti-cancer, anti-fungal, antidepressant, antidiabetic and antipyretic agents.[35-45]

Some of the pyrazole scaffolds containing drugs are shown in figure **(Figure: 3)** such as Antipyrine, Celecoxib, Novalgine, Fipronil, Tepoxaline and Rimonabant and many more are already established drugs in the market.

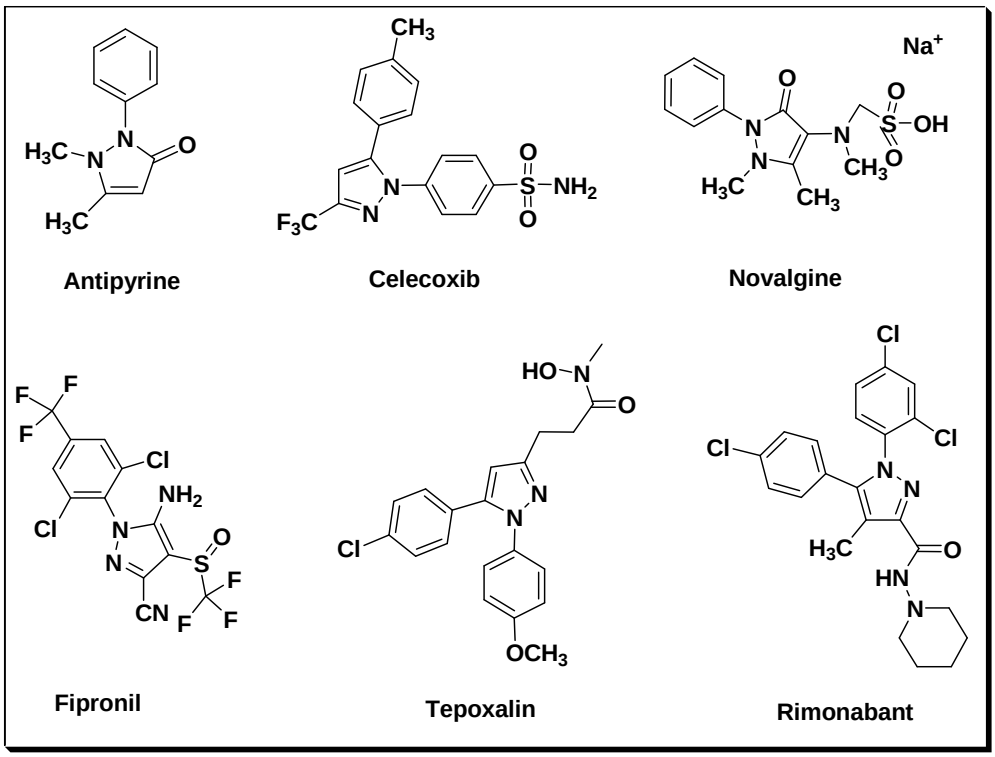
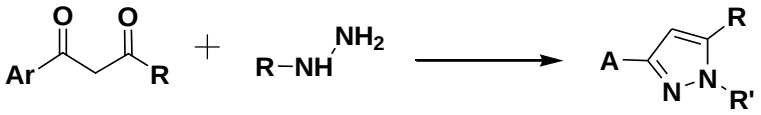


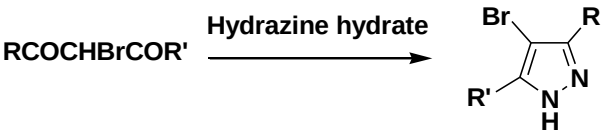
Figure: 3

The significant of pyrazole core in medicinally important molecules has stimulated the need for efficient ways to synthesize these compounds. In 1883 pyrazole was synthesized by Knorr[34] for the first time by condensation reaction of 1, 3 dicarbonyl compounds with hydrazines **(Scheme: 10)**.



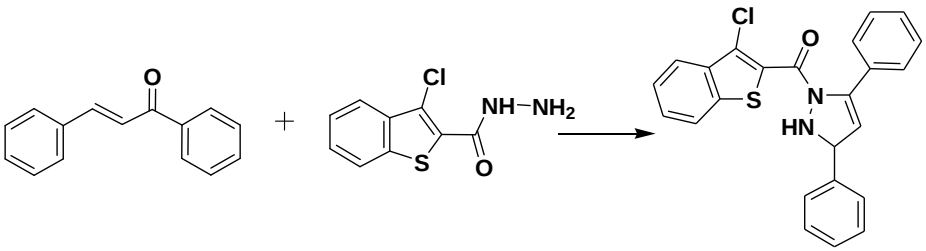
Scheme: 10

Grag and group[46] has extended the reaction to hydrazine hydrate and 2-bromo derivatives of substituted dialkylpropane-1,3-diones, leading to the synthesis of bromopyrazoles (**Scheme: 11**).



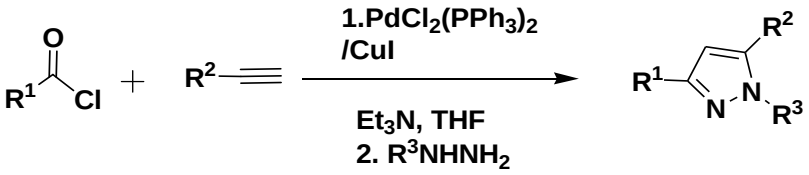
Scheme: 11

Modification of the reaction by replacing 1, 3 diketones with olefinic or acetylenic ketones usually allow good regioselectivity and diversity. Kumara and coworkers[47] have effectively synthesized various biologically active pyrazoles by the reaction of chalcones with 3-chlorobenzo[b]thiophene-2-carboxyhydrazide **(Scheme: 12)**.



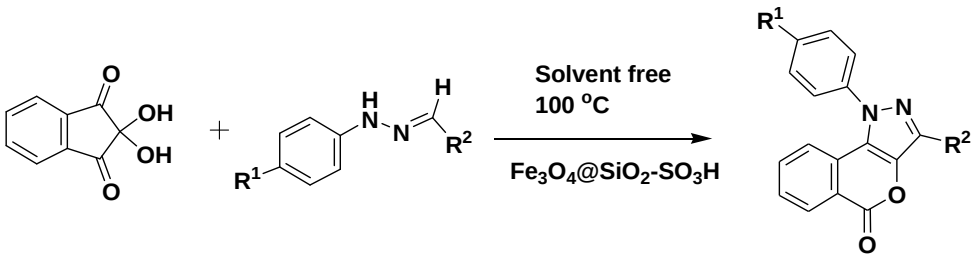
Scheme: 12

Liu and his team[48] have developed a one pot protocol for the synthesis of pyrazoles from terminal alkynes, acid chlorides and hydrazines via a coupling and cyclocondensation sequence **(Scheme: 13)**.



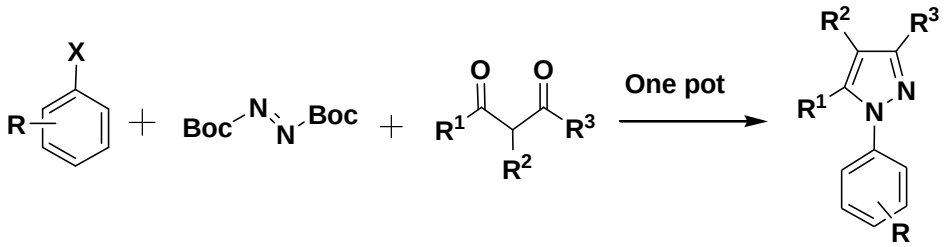
Scheme: 13

Sayan Mukherjee and coworkers[49] developed an efficient protocol for the synthesis of pyrazole-fused isocoumarins from ninhydrin and arylhydrazones under solvent free conditions by using magnetically separable $Fe_3O_4@SiO_2$-SO_3H nanoparticles as solid acid support **(Scheme: 14)**.



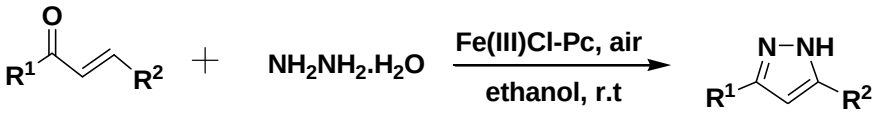
Scheme: 14

Gerstenberger and his team[50] synthesized N-Arylpyrazoles from simple one-pot reaction of different aryl halides, 1, 3-dicarbonyl compounds and di-tert-butylazodicarboxylate **(Scheme: 15)**.



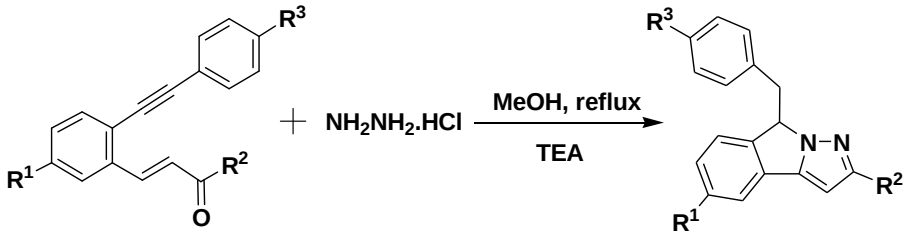
Scheme: 15

Junlong Zhao and coworkers[51] developed synthesis of 3, 5-disubstituted 1*H*-pyrazoles by oxidation-aromatization of nα, β-unsaturated ketones with hydrazine hydrate catalyzed by iron(III) phthalocyanine chloride. This protocol offers several benefits including room-temperature conditions, short reaction time, high yields, simple work-up procedure and reusability of catalyst **(Scheme: 16)**.



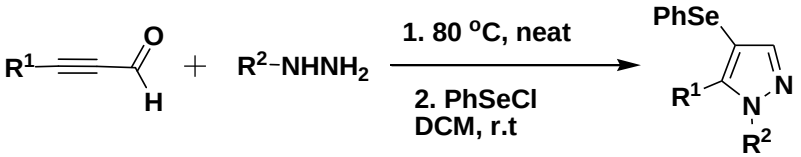
Scheme: 16

Ying Li and Chun-E. Dong[52] described synthesis of various pyrazoles from *o*-alkynylchalcones and hydrazine *via a* simple cyclization under mild reaction condition **(Scheme: 17)**.



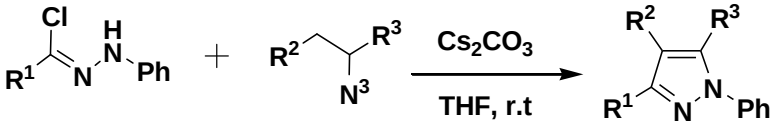
Scheme: 17

Metin Zora and his team[53] have synthesized various 4-(phenylselanyl) pyrazoles from hydrazines, α, β-alkynic aldehydes and phenylselenyl chloride via in situ generated α, β-alkynic hydrazones in good to excellent yields **(Scheme: 18)**.



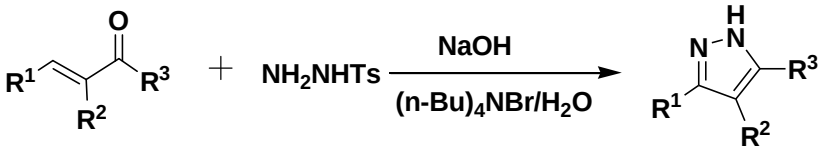
Scheme: 18

Hongbin Zou and coworkers[54] synthesized polysubstituted pyrazoles from hydrazonyl chlorides and vinyl azides under mild conditions in the presence of cesium carbonate as a base **(Scheme: 19)**.



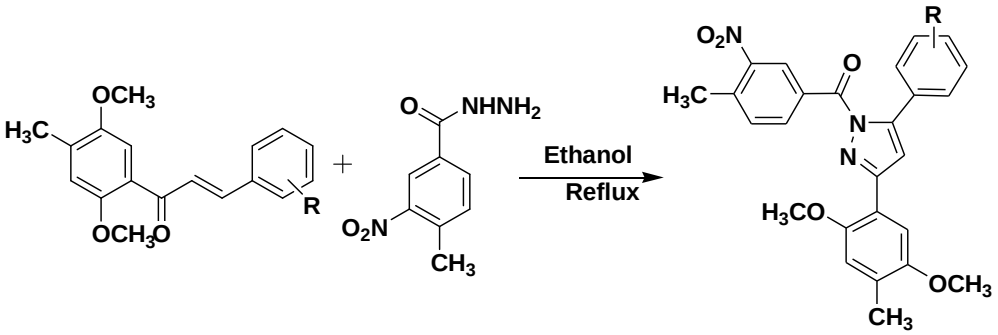
Scheme: 19

Jun Wen and coworkers[55] developed an efficient and eco-friendly protocol or the synthesis of substituted 1*H*-pyrazoles by condensation reaction of α, β-unsaturated carbonyl compounds with tosyl hydrazide in water in good to excellent yields **(Scheme: 20)**.



Scheme: 20

V. M. Barot and coworkers[56] synthesized various substituted pyrazoles in ethanol at reflux conditions and the synthesized derivatives screened for their antimicrobial activity **(Scheme: 21)**.



CONCLUSION

In conclusion, the present review article explores the various synthetic advances to substituted pyridines and pyrazoles. It has covered both conventional and modern strategies developed to obtain a wide variety diversified pyrazoles and substituted pyridines. The article also demonstrated that the synthetic routes to functionalized pyridines and pyrazoles is still widely open to inventiveness and considerate new protocols to efficiently design new pyridine and pyrazole scaffolds which could be more cost effective, environment friendly, more convenient and sustainable.

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