MICROWAVE-ASSISTED SYNTHESIS OF NITROGEN HETEROCYCLES

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Abstract. *Microwave-assisted synthesis of nitrogen heterocycles has gained widespread attention in the past two decades as this strategy allow the synthesis of several bioactive scaffolds in excellent yields and in shorter reaction times compared to conventional heating. Likewise, the synthesis of N-containing heterocycles occupies a special place as several pharmaceutically significant natural products and synthetic drugs possess N-heterocycles as the core moiety. Consequently, the development of novel synthetic strategies to construct N-heterocycles employing greener methods including microwave irradiation remains an essential task. This chapter summarizes the advancement in microwave-assisted synthesis of various 3- to 7-membered N-heterocycles including pyrroles, pyrrolidines, pyrazoles, pyridines, quinolines, azepines, aziridines, azetidines and their fused analogs.*

Contents

1. Introduction

Nitrogen heterocycles are an important class of organic compounds as they are widespread in natural products and pharmaceutically significant synthetic molecules. These compounds are part of biologically relevant nucleic acids, proteins, vitamins, antibiotics *etc*. Apart from their use as drug molecules, they show extensive application in diverse fields including agrochemicals, material science, and synthetic chemistry.[1] A database of all U.S. FDA approved pharmaceuticals compiled by Njardarson *et. al*. suggests that 59% of the unique small-molecule drugs possess at least one nitrogen heterocycle.[2] Thus, these compounds occupy a unique position in drug development as they serve as building blocks for new drugs which are due to the inherent nature of nitrogen atom capable of forming H-bonding with target molecules.[3] Henceforth, development of novel synthetic strategies for the construction of nitrogen-containing heterocycles is highly desirable.

Owing to the stringent environmental policies, synthetic chemists look for alternate strategies based on green chemistry principles. This leads to many non-conventional reaction strategies including microwave,

ultrasound irradiations and mechanical grinding. The microwave radiation has been frequently employed in synthetic chemistry as an alternate source of energy due to its unique interaction with polar molecules, usually with solvents like ethanol, water, acetonitrile, DMSO, DMF *etc*., and due to its dielectric heating leads to rapid generation of heat.[4] The foremost advantage of employing MW for organic synthesis is significant reduction in reaction time, thereby eliminating the unwanted side reaction and increasing the yield of the desired product, thus making it as an efficient alternate strategy for the synthesis of *N*-heterocycles.

Consequently, it proves to be a superior and more efficient technique compared to the conventional heating process which results in remarkable development in the field of heterocyclic synthesis as evidenced by a vast number of reported papers and chapters.[5] The microwave-assisted synthesis obeys most of the principles of green chemistry.[6] Moreover, the green-metrics can be amplified by coupling MW irradiation with green solvents or solvent-free conditions.[7] It has been known that the classical multicomponent reactions and the newer ones were either assisted or accelerated by microwave irradiation for the construction of simple nitrogen, oxygen, and sulfur-containing heterocycles. This chapter summarizes the advancement in microwave-assisted synthesis of nitrogen heterocycles.

2. Synthesis of five-membered nitrogen heterocycles

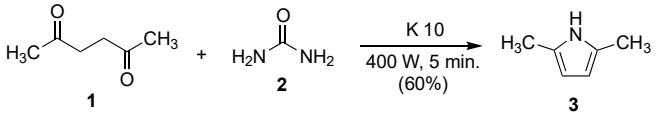
In this section, the synthesis of five-membered nitrogen-containing heterocycles including pyrroles, pyrrolidines, pyrazoles, thiazoles, benzothiazoles and other fused analogs under microwave-assisted conditions are discussed.

2.1. Pyrroles and fused pyrroles

The basic five-membered *N*-heterocycle, pyrrole, is present extensively in numerous natural products and possesses a broad range of bioactivity.[8] Inclusion of pyrrole moiety into a drug molecule imparts beneficial properties like improved bioavailability, better binding affinity towards biological targets and enhanced metabolic stability.[9] Numerous drugs available in the market possess pyrrole skeletal, which shows several biological activities such as anti- inflammatory, antibacterial, antifungal, anti-hyperlipidemic, anticancer and anti-proliferative activity.[10] In addition, the pyrrole skeleton plays a crucial role as a functional material and acts as a vital component in piezoresistive sensors, conducting polymers, catalysis and as a valuable precursor for the synthesis of *p*-type semiconducting materials.[11]

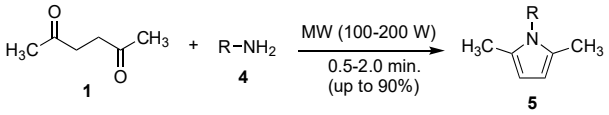
The classical method for the synthesis of pyrroles include the Paal-Knorr synthesis,[12] the Knorr synthesis,[13] the Hantzsch pyrrole synthesis,[14] the Clauson-Kaas synthesis,[15] the Barton-Zard reaction,[16] and the Piloty-Robinson synthesis.[17] The limitations of these methods include the use of acid catalysts, organic solvents and prolonged reaction times.

The condensation between primary amines and 1,4-dicarbonyl compounds in the presence of an acid catalyst is known as Paal-Knorr synthesis and is extensively employed for the synthesis of pyrroles and furans. There were several variations of this method and several acid catalysts were employed for the synthesis of pyrroles.[18] Nevertheless, the major limitations of this process include the lack of regioselectivity, use of harmful organic solvents, prolonged reaction times, use of excess catalysts *etc*.[19] Consequently, several developments and variations of this reaction have been reported including the microwave and ultrasound-assisted approaches.[20] Amongst the first reports, synthesis of 2,5-disubstituted pyrrole **3** was achieved starting from 1,4-diketone **1** and urea **2** using domestic microwave oven in the presence of K10 clay (Scheme 1).[21]



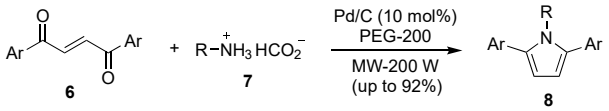
Scheme 1. K10 clay-catalyzed microwave-assisted synthesis of 2,5-dimethylpyrrole.

A variety of primary amines **4** were coupled with 1,4-diketone **1** to access *N*-substituted pyrroles **5** under microwave-assisted conditions. The rate of the reaction was drastically improved compared to conventional heating and the reaction eliminates the use of Lewis acid catalysts (Scheme 2).[22]



Scheme 2. Synthesis of *N*-unsubstituted pyrroles under microwave irradiation.

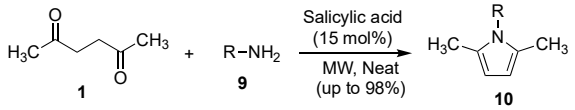
In advancement to this strategy, polyethylene glycol 200 (PEG-200) was employed as a solvent under MW to obtain 2,5-di- and 1,2,5-trisubstituted pyrroles **8**. The reaction involves palladium-assisted transfer hydrogenation of (*E*)-1,4-diaryl-2-butene-1,4-diones **6** followed by Paal-Knorr reaction using alkyl/aryl ammonium formates **7** in one-pot (Scheme 3).[23]



Scheme 3. Microwave-assisted synthesis of 2,5-di- and 1,2,5-trisubstituted pyrroles.

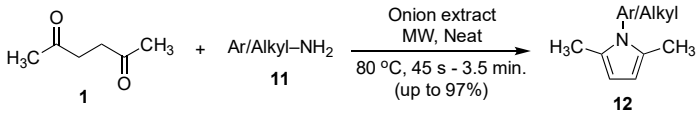
Further, Aghapoor and co-workers reported a calcium(II) chloride-catalyzed Paal–Knorr pyrrole synthesis under microwave irradiation and solvent-free conditions by coupling various aliphatic/aromatic primary amines with hexane-2,5-dione.[24] The yields of the synthesized products were near quantitative and the utility of the reaction in gram-scale was also explored. Mukhopadhyay and co-workers reported the synthesis of DABCO based amphoteric ionic liquid supported TiO_2 nanoparticles and subsequently applied this recyclable pseudo-heterogeneous catalyst for the synthesis of highly substituted pyrroles under microwave-assisted solvent-free conditions in excellent yields.[25]

In 2021, Aghapoor and co-workers demonstrated a solvent-free Paal-Knorr condensation between 2,5-hexadione **1** and primary aromatic and aliphatic amines **9** to access *N*-alkyl/aryl pyrroles **10** under microwave irradiation in the presence of salicylic acid as organocatalyst (Scheme 4).[26] A variety of aromatic and aliphatic carboxylic acids were screened as organocatalysts and salicylic acid was identified as the best one. When salicylic acid was employed along with 420 W microwave irradiation, the highest turnover frequency (TOF) of 1472 h^{-1} was observed.



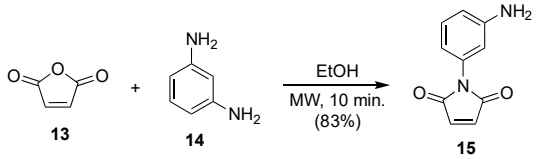
Scheme 4. Salicylic acid-catalyzed synthesis of *N*-substituted pyrroles under microwave irradiation.

Recently, Marvi and co-workers employed onion extract for the synthesis of tri-substituted pyrroles *via* Paal-Knorr reaction under microwave assisted solvent-free conditions (Scheme 5).[27] A variety of primary amines such as aromatic, aliphatic and heterocyclic amines **11** reacted with hexane-2,5-dione **1** to deliver the desired products **12** in good to excellent yields.



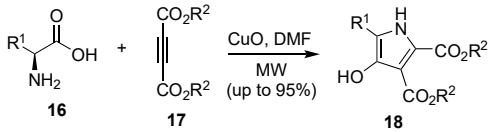
Scheme 5. Onion extract-catalyzed synthesis of tri-substituted pyrrole under microwave irradiation.

The Clauson-Kaas reaction is an important approach for the synthesis of pyrroles starting from primary amines and 2,5-dimethoxytetrahydrofuran.[28] De Souza and co-workers demonstrated the synthesis of *N*-substituted-2,5-dihydro-1*H*-pyrroles and *N*-substituted-1*H*-pyrroles starting from primary amines and *cis*-1,4-dichloro-2-butene under microwave assisted conditions under mild basic conditions.[29] Under oxidative basic conditions (in the presence of KI/I_2), 1*H*-pyrroles were obtained *via* *N*-substituted-2,5-dihydro-1*H*-pyrrole intermediates. Reddy and co-workers reported the synthesis of *N*-arylpyrrole **15** in 83% yield starting from furan-2,5-dione **13** and *m*-phenylenediamine **14** in ethanol under microwave-assisted conditions (Scheme 6).[30] Kumaraswamy and co-workers also reported a related synthesis of *N*-substituted pyrroles involving oxone catalyzed Clauson-Kaas reaction in MeCN under microwave irradiation.[31] The reaction was performed with various aromatic amines and 2,5-dimethoxytetrahydrofuran to give the desired products in good yields within 10-20 minutes.



Scheme 6. Microwave-assisted synthesis of *N*-aryl-1*H*-pyrrole-2,5-dione.

Tetrasubstituted pyrroles **18** having a 3-hydroxyl group were synthesized involving the reaction between naturally occurring as well as synthetic amino acids **16** and dialkyl acetylenedicarboxylates **17** *via* tandem hydroamination and oxidative cyclization strategy (Scheme 7).[32] The reaction was performed using CuO as the catalyst under microwave irradiation to generate the desired compounds in good to excellent yields (83-95%) in shorter reaction time. In the case of conventional heating lower yields (~15%) were obtained for non-polar natural amino acids and the reaction failed to proceed with polar amino acids.



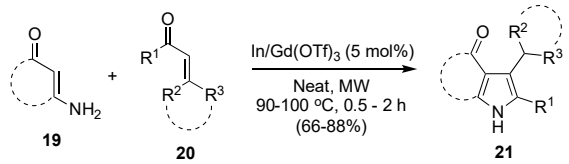
Scheme 7. CuO-catalyzed synthesis of tetrasubstituted pyrroles under microwave irradiation.

Shafi and co-workers have employed microwave irradiation for the cross-metathesis reaction between α,β-unsaturated carbonyl compounds and *N*-allylamines under neat conditions for the synthesis of *N*-substituted pyrrole derivatives.[33] The authors have compared the effect of microwave irradiation with conventional thermal heating which was substantiated by the computational analysis. Rohit and co-workers reported a Mn-catalyzed improved Clauson-Kass synthesis of *N*-substituted pyrroles employing 2,5-dimethoxytetrahydrofuran and various aromatic amines in excellent yields. The reactions were performed without ligands, co-catalysts and acids under microwave assisted conditions and completed in shorter reaction times.[34]

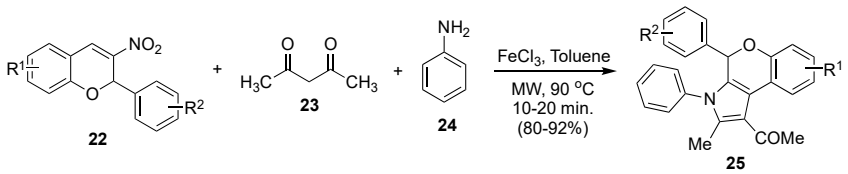
Samanta and co-workers developed a Lewis acid-catalyzed, microwave-assisted solvent-free reaction between various carbo- and heterocyclic enaminones **19** and α-aroyl/heteroaryl/acetylidenemalonates/3-aroylidene-2-oxindoles **20** to generate diversely substituted coumarin, dimedone and naphthoquinone-fused pyrroles **21** (Scheme 8).[35] The authors employed strong Lewis acids like triflates of In(III) and Gd(III) to construct different pyrrole rings in good to excellent yields. Moreover, they synthesized 3-hydroxy-3-pyrrolocoumarinyl-2-oxindoles possessing a tetra-substituted chiral carbon center under metal-free conditions in high yields *via* a direct Csp^3–H hydroxylation of 3-pyrrolocoumarinyl-2-oxindoles.

A variety of 2*H*-chromene-fused pyrrole derivatives **25** were synthesized involving a $FeCl_3$-catalyzed three-component reaction between 3-nitro-2*H*-chromenes **22**, acetylacetone **23** and aniline **24** in toluene under microwave irradiation in excellent yields (Scheme 9).[36] However, under conventional heating, the

desired heterocycles were not observed with several catalysts, solvents, and different conditions. The synthesized compounds were tested for *in vitro* antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

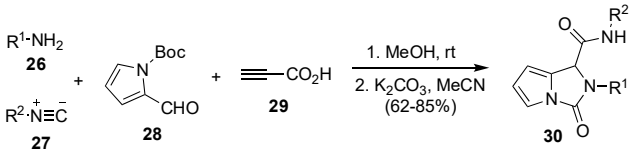


Scheme 8. Lewis acid-catalyzed, microwave-assisted solvent-free synthesis of various fused pyrroles.



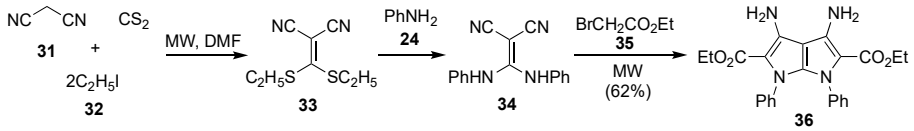
Scheme 9. $FeCl_3$ catalyzed, microwave-assisted construction of 2*H*-chromene-fused pyrroles.

The one-pot four-component cascade reaction of primary amine **26**, isocyanides **27**, *N*-Boc-pyrrole-2-carboxaldehyde **28** and propiolic acid **29** delivers Ugi-adducts which upon base-mediated intramolecular cyclization resulted in the formation of imidazo-pyrrole derivatives **30** (Scheme 10).[37] The reaction was performed under microwave irradiation to generate the desired heterocycles in good yields in a shorter reaction time *via* the Boc-deprotection/cyclization cascade. A variety of haloanilines were tested for the reaction and the synthesized imidazo-pyrrole derivatives were tested for anticancer activity in human pancreatic cancer cell lines PANC and ASPC-1.



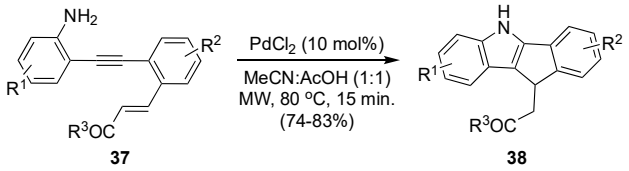
Scheme 10. Microwave-assisted four-component synthesis of imidazo-pyrroles.

A series of pyrrolo[2,3-*b*]pyrrole derivatives were synthesized under microwave irradiation comprising a one-pot reaction between malononitrile **31**, ethyl iodide **32**, carbon disulfide and aniline **24** *via* the intermediacy of compounds 2-(bis(ethylthio)methylene)malononitrile **33** and 2-(bis(phenylamino)methylene)malononitrile **34** (Scheme 11).[38] Intermediate **34** reacted with various electrophiles including ethyl bromoacetate **35**, formamide, formic acid, isatin, phenyl isocyanate, 2,5-dimethoxytetrahydrofuran and methylamine to furnish the corresponding substituted pyrrolo[2,3-*b*]pyrroles **36**. The reaction was performed under basic conditions and the synthesized fused heterocycles were tested for hypolipidemic activity and antimicrobial activity against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.



Scheme 11. Microwave-assisted synthesis of pyrrolo[2,3-*b*]pyrroles.

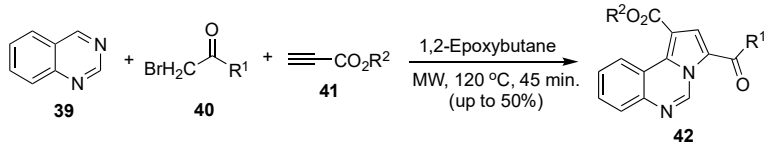
Sridharan and co-workers reported a microwave-assisted, cascade reaction of 2-alkynylanilines bearing an α,β-unsaturated carbonyl moiety **37** for the synthesis of 5,10-dihydroindeno[1,2-*b*]indoles **38** in high yields (Scheme 12).[39] This cascade reaction shows 100% atom economy and constructs two new five-membered rings and two new bonds in a single synthetic operation. The mechanism involves intramolecular aminopalladation followed by carbopalladation and protonolysis steps.



37 **38**

Scheme 12. Microwave-assisted cascade synthesis of 5,10-dihydroindeno[1,2-*b*]indoles.

A library of pyrrolo[1,2-*c*]quinazoline derivatives **42** was synthesized involving a one-pot, three-component reaction between quinazolines **39**, 2-bromoacetyl derivatives **40** and electron-deficient alkynes **41** in 1,2-epoxybutane *via* 1,3-dipolar cycloaddition of quinazolinium-*N*-ylides under microwave irradiation (Scheme 13).[40] In this strategy, 1,2-epoxybutane acts both as a solvent as well as an acid scavenger. The target pyrrolo[1,2-*c*]quinazolines were obtained *via in situ* formation of the quinazolinium salt leading to the respective quinazolinium-*N*-ylide followed by 1,3-dipolar cycloaddition with electron-deficient alkynes.

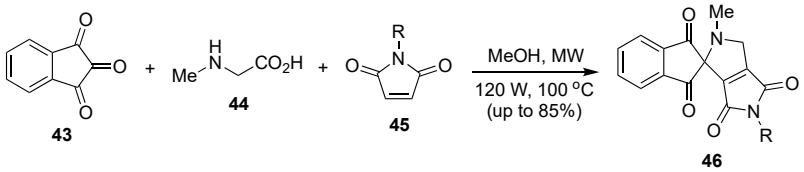


39 **40** **41** **42**

Scheme 13. Microwave-assisted three-component synthesis of pyrrolo[1,2-*c*]quinazolines.

2.2. Pyrrolidine-related compounds

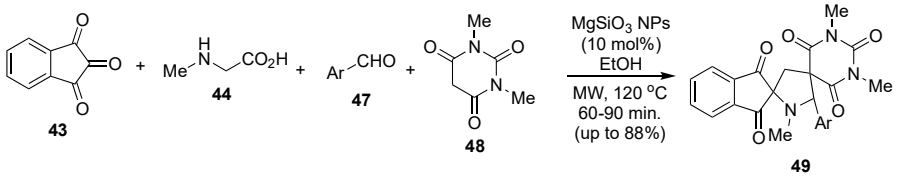
The microwave-assisted one-pot, three-component 1,3-dipolar cycloaddition of azomethine ylides, generated *in situ* from ninhydrin **43** and sarcosine **44**, with various 1-aryl-1*H*-pyrrole-2,5-diones **45** delivered a series of dihydro-2'*H*-spiro[indene 2,1'-pyrrolo[3,4-*c*]pyrrole]-tetraones **46** in good yields (Scheme 14).[41] The synthesized compounds were tested for their antimycobacterial and AChE inhibitory activities.



43 **44** **45** **46**

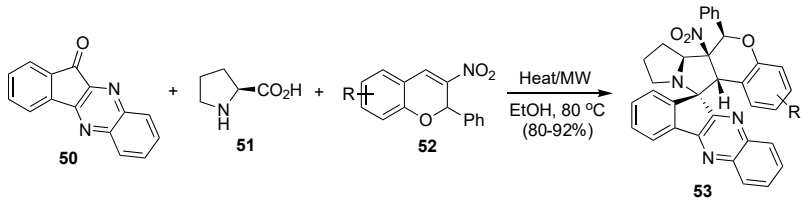
Scheme 14. Microwave-assisted synthesis of dihydro-2'*H*-spiro[indene 2,1'-pyrrolo[3,4-*c*]pyrrole]-tetraones.

A set of dispiropyrrolidine derivatives **49** was constructed *via* one-pot, four-component reaction between ninhydrin **43**, arylaldehydes **47**, sarcosine **44** and *N*,*N*-dimethyl barbituric acid **48** under microwave irradiation (Scheme 15).[42] The reaction was performed in the presence of magnesium silicate nanoparticles as a catalyst in ethanol and excellent yields were obtained under MW irradiation compared to conventional heating. The synthesized compounds were screened for antibacterial and antiproliferative activities (Scheme 15).



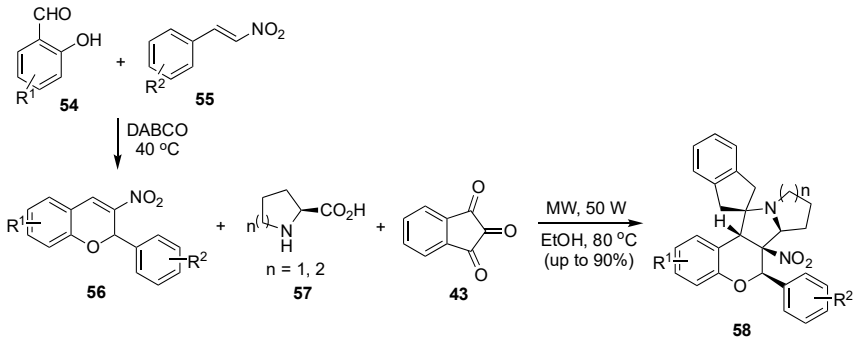
Scheme 15. Microwave-assisted four-component synthesis of dispiropyrrolidine derivatives.

A convenient one-pot, three-component 1,3-dipolar cycloaddition of azomethine ylides, generated *in situ* from indenoquinoxalone **50** and α-amino acid **51**, with 3-nitrochromenes **52** furnished spiroindenoquinoxaline pyrrolidine-fused nitrochromene derivatives **53** in high yields (Scheme 16).[43] The reaction was performed under conventional heating as well as under microwave irradiation. The synthetic advantage of this strategy includes high product yields, mild reaction conditions, and operational simplicity to construct complex structural moieties in a single operation with high regioselectivity.



Scheme 16. Microwave-assisted synthesis of spiroindenoquinoxaline pyrrolidine-fused nitrochromenes.

The same group also developed a three-component reaction between ninhydrin **43**, amino acids **57** and 3-nitrochromenes **56**, which were synthesized from salicylaldehydes **54** and β-nitrostyrenes **55**, under microwave irradiation to access spiroindanone pyrrolidine/piperidine-fused nitrochromene derivatives **58** (Scheme 17).[44] The yields were higher under microwave-assisted conditions when compared to conventional heating.



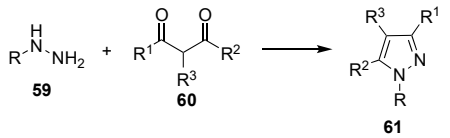
Scheme 17. Synthesis of spiroindanone pyrrolidine/piperidine-fused nitrochromene derivatives.

2.3. Pyrazoles

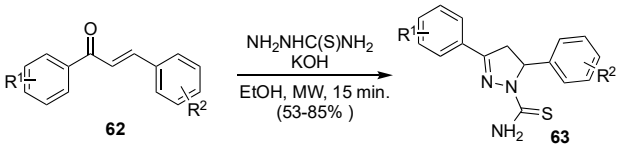
Pyrazoles are an important class of five-membered heterocyclic compounds containing two adjacent nitrogen atoms. Similar to pyrroles, pyrazole **61** was first synthesized by Knorr in 1883 by the condensation reaction of hydrazine derivatives **59** with 1,3-dicarbonyl compounds **60** in acidic medium (Scheme 18).[45]

da Rosa and co-workers demonstrated the synthesis of 1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazoles **63** by the reaction of thiosemicarbazide with diverse chalcones **62** under microwave-assisted and conventional

heating conditions (Scheme 19).[46] The yields were almost comparable in both the cases, but the reaction time was reduced considerably in microwave than in conventional heating.



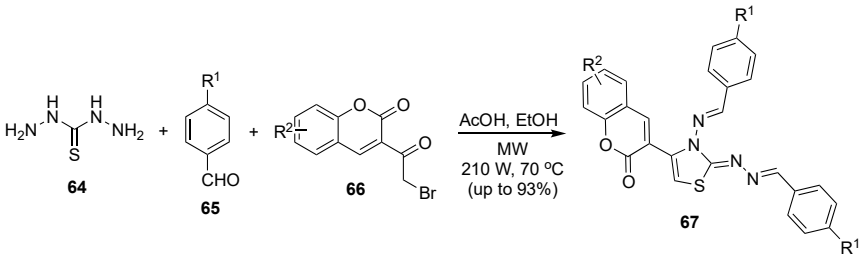
Scheme 18. Synthesis of pyrazoles by Knorr condensation.



Scheme 19. Synthesis of 1-thiocarbamoyl-4,5-dihydro-1*H*-pyrazole under microwave irradiation.

2.4. Thiazoles and benzothiazoles

Mamidala and co-workers synthesized a series of coumarin-tethered thiazoles **67** in high yields (88-93%) involving a three-component reaction between thiocarbohydrazide **64**, aldehydes **65** and coumarins **66** (Scheme 20).[47] Several acids were employed as catalysts and the reaction yield was optimized with acetic acid as catalyst in ethanol under microwave irradiation (70 °C, 210 W).



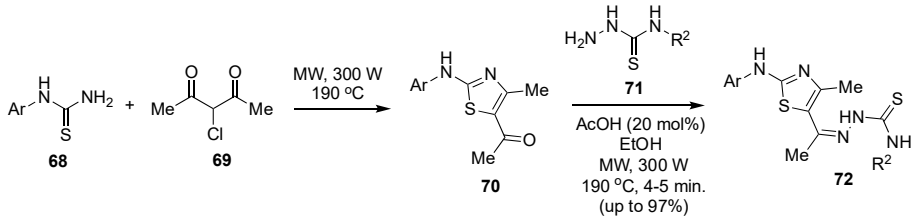
Scheme 20. Three-component synthesis of coumarin-tethered thiazoles under microwave irradiation.

Prajapati and co-workers synthesized a new series of thiazole-fused thiosemicarbazones **72** employing a two-step microwave-assisted strategy. Initially, substituted 1-(4-methyl-2-(phenylamino)thiazol-5-yl)ethanones **70** were generated by the Hantzsch cyclization of substituted phenylthioureas **68** and 3-chloropentane-2,4-dione **69** under microwave irradiation. The synthesized compounds **70** underwent condensation reaction with hydrazinecarbothioamides **71** in the presence of a catalytic amount of glacial acetic acid to generate the corresponding thiazole-fused thiosemicarbazones **72** (scheme 21).[48] The synthesized compounds were tested for biological activities like *in vitro* antimicrobial, antimalarial, and anti-tuberculosis activity *etc*.

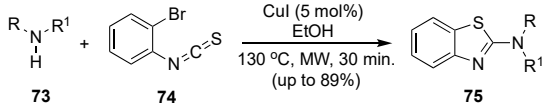
Saranya and co-workers demonstrated the synthesis of 2-aminobenzothiazoles **75** by coupling 2-bromophenyl isothiocyanate **74** with various amines **73** under microwave irradiation in the presence of CuI in ethanol (Scheme 22).[49] Several substituted 2-aminobenzothiazoles were generated in yields ranging from 27-89% by varying amines under the optimized conditions in the presence of CuI under microwave heating at 130 °C for 30 minutes. The advantages of the process include faster reaction without the use of any ligands, bases or other additives thus making the process environmentally benign.

A one-pot, three-component reaction between thiobarbituric acid **76**, arylglyoxals **77**, 2-aminobenzothiazole **78** in ethanol employing AcOH as the catalyst under thermal as well as microwave condition generated a novel class of benzimidazo[2,1-*b*]thiazoles **79** (Scheme 23).[50] The advantage of this

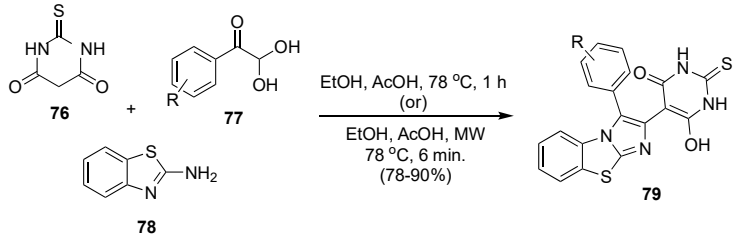
process includes a convenient work-up procedure and simple isolation of products. The reaction proceeded in a shorter reaction time with high yields under microwave-assisted conditions.



Scheme 21. Microwave-assisted synthesis of thiazole-fused thiosemicarbazones.

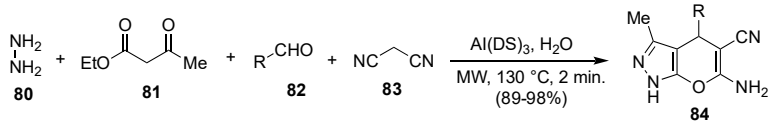


Scheme 22. CuI-catalyzed synthesis of 2-aminobenzothiazoles under microwave irradiation.



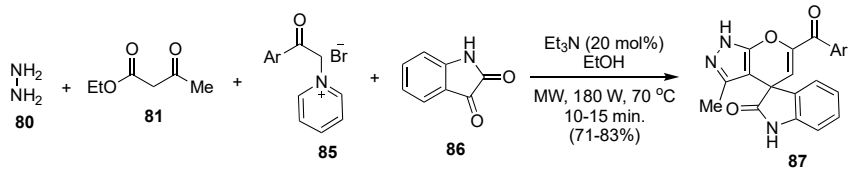
Scheme 23. Microwave-assisted, acid-catalyzed synthesis of benzimidazo[2,1-*b*]thiazoles.

Singh and co-workers reported a one-pot, four-component reaction of hydrazine hydrate **80**, ethyl acetoacetate **81**, aryl aldehydes **82** and malononitrile **83** in an aqueous micellar solution of aluminum tris(dodecyl sulfate)trihydrate under microwave irradiation for the synthesis of pyrano[2,3-*c*]pyrazoles **84** (Scheme 24).[51] The desired heterocyclic compounds were obtained in high yields (up to 98%) under environmentally benign manner.



Scheme 24. Synthesis of pyrano[2,3-*c*]pyrazoles under microwave irradiation.

A series of spirooxindole-furo[2,3-*c*]pyrazole derivatives **87** possessing biologically significant pyrazole and spirooxindole moieties was synthesized *via* one-pot, four-component reaction between hydrazine **80**, ethyl acetoacetate **81**, pyridinium ylides **85** and isatin **86** in ethanol under microwave irradiation (Scheme 25).[52] The pyridinium ylides were synthesized employing Et_3N (20 mol%) as catalyst from *N*-phenacyl bromide and pyridine. The reaction proceeds *via* Knoevenagel condensation/Michael addition and final heterocyclization sequence generating five new bonds (2C–C, C–O, C–N, C=N) in a single synthetic operation. The significance of the reaction involves high yields in shorter reaction time, operational simplicity, absence of hazardous or toxic solvents/reagents and simple workup procedure.

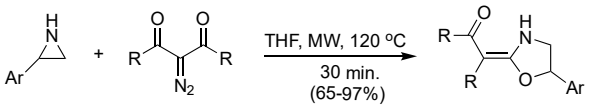


80 81 85 86 87

Scheme 25. Microwave-assisted synthesis of spirooxindole-furo[2,3-*c*]pyrazole derivatives.

2.5. Miscellaneous five-membered nitrogen heterocycles

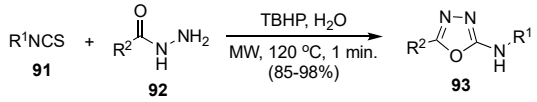
The ring-opening of *N*-unprotected aziridines **88** with *α*-oxoketenes **89** was achieved to obtain 2-alkylidene-1,3-oxazolidines **90** in good to excellent yields under microwave irradiation (Scheme 26).[53] The reaction proceeds *via* regiospecific manner involving a catalyst-free electrophilic ring expansion of aziridines with α-oxoketenes. The ring expansion occurs *via* S_N1 pathway and the stereochemistry was determined by the hydrogen-bonding leading to the *E* configuration of the desired heterocycle.



88 89 90

Scheme 26. Microwave-assisted synthesis of 2-alkylidene-1,3-oxazolidines *via* ring opening of aziridines.

Neelima and co-workers reported a microwave-assisted synthesis of 2-amino-1,3,4-oxadiazoles **93** starting from isothiocyanates **91** and alkyl/aryl hydrazides **92** (Scheme 27).[54] The reaction was performed under catalyst-free conditions using water as the green solvent, and *tert*-butyl hydroperoxide as the terminal oxidant.



91 92 93

Scheme 27. Synthesis of 2-amino-1,3,4-oxadiazoles by oxidative cyclodesulfurization.

3. Synthesis of six-membered nitrogen heterocycles

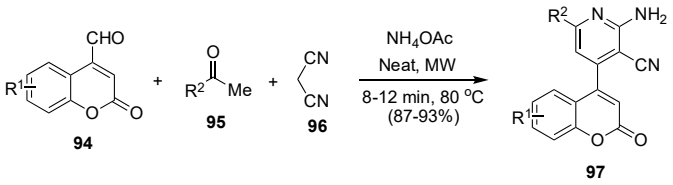
3.1. Pyridines

The pyridine core is widely abundant in nature and is present in vitamins B_3, B_6, certain coenzymes, plant alkaloids and several drug molecules.[55] Owing to their biological significance, syntheses of pyridines become pivotal and the chemists have developed several efficient and green protocols. A detailed review on microwave-assisted synthesis of pyridine was published in 2013 and emphasized the importance and application of microwave to construct the desired heterocycles.[56] Few recent reports on microwave-assisted synthesis of pyridines have been discussed in this section.

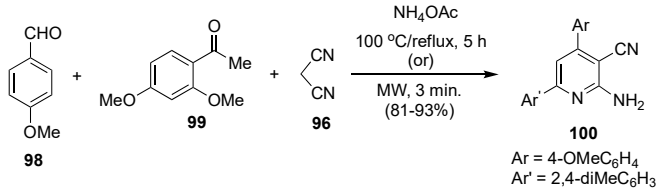
A catalyst-free, microwave-assisted, four-component reaction of coumarin carboxaldehydes **94**, aryl methyl ketones **95**, malononitrile **96**, and ammonium acetate was established for the synthesis of 2-amino-3-cyanopyridines **97** (Scheme 28). Upon optimization, it was established that neat condition and microwave irradiation resulted in excellent yields of the products (up to 93%) in a shorter reaction time (8-12 min.) when compared to conventional reflux conditions.[57] The synthesized compounds were tested for anticancer activity and a few compounds showed excellent IC_{50} values against HT29, HepG2, and KB cell lines which was further confirmed by CT-DNA cleavage, fluorescence quenching studies and molecular docking studies.

Anwer and co-workers reported a related approach for the synthesis of tetrasubstituted pyridine **100** starting from aryl aldehyde **98**, electron rich aryl ketone **99**, malononitrile **96** and ammonium acetate under microwave-assisted conditions and conventional heating conditions (Scheme 29).[58] The synthetic utility of

the developed approach was demonstrated involving various reagents like malononitrile, 2-(4-chlorobenzylidene)malononitrile, ethyl cyanoacetate, cyanoacetic acid *etc*.



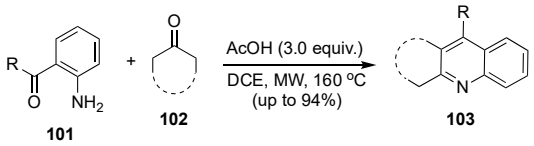
Scheme 28. Microwave-assisted four-component synthesis of 2-amino-3-cyanopyridine derivatives.



Scheme 29. Microwave-assisted four-component synthesis of tetrasubstituted pyridines.

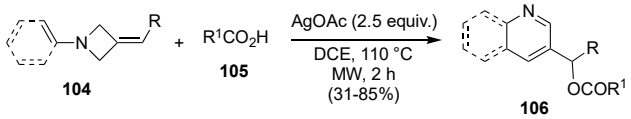
3.2. Quinolines

Potter and co-workers demonstrated the synthesis of quinoline derivatives **103** starting from 2-aminophenylketones **101** and cyclic or acyclic ketones **102** under microwave-assisted conditions in the presence of acetic acid (Scheme 30).[59] The yields were much higher under microwave-assisted conditions when compared to the conventional heating conditions.



Scheme 30. Acetic acid-catalyzed synthesis of quinolines under microwave irradiation.

Li and co-workers demonstrated an oxidative cascade reaction of *N*-aryl-3-alkylideneazetidines **104** with carboxylic acids **105** for the synthesis of a series of functionalized fused pyridines **106** (Scheme 31).[60] The reaction was performed with silver salt which proved to be essential for the chemo- and regioselective ring expansion/oxidative nucleophilic additions/aromatization sequence and the yield of the desired product was found to be superior under microwave-assisted conditions in DCE.

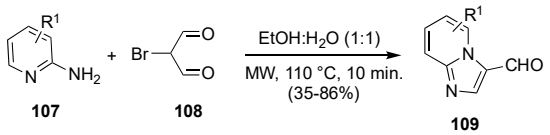


Scheme 31. Ag(I)-catalyzed, microwave-assisted synthesis of functionalized fused pyridines.

3.3. Imidazo[1,2-*a*]pyridines

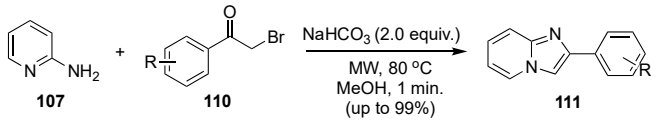
Błazewska and co-workers established a catalyst-free synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes **109** under microwave irradiation in ethanol-water solvent system (Scheme 32).[61] In this strategy, 2-aminopyridines **107** were coupled with bromomalonaldehydes **108** under

microwave to generate the desired heterocycle. The authors proposed a plausible reaction mechanism *via* an enamine intermediate which was also isolated during the reaction.



Scheme 32. Catalyst-free synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes under microwave irradiation.

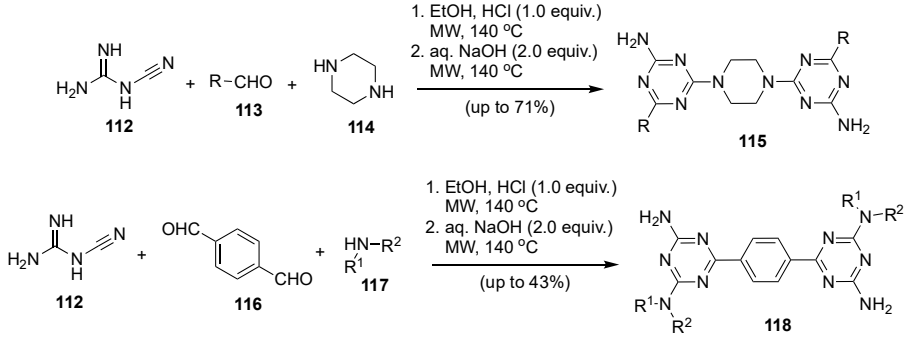
The synthesis of substituted imidazo[1,2-*a*]pyridines **111** was achieved by coupling 2-aminopyridines **107** with *in situ* generated phenacyl bromides **110** obtained by the bromination of acetophenones under microwave-assisted conditions (Scheme 33).[62] The reaction was performed in a one-pot, sequential manner under microwave irradiation and the yields were obtained up to 99%. The photo-luminescence properties of the synthesized compounds were tested and the compounds show intense luminescence emissions in the purple and blue regions of the electromagnetic spectra under UV excitation.



Scheme 33. Synthesis of imidazo[1,2-*a*]pyridines from 2-aminopyridines and phenacyl bromides.

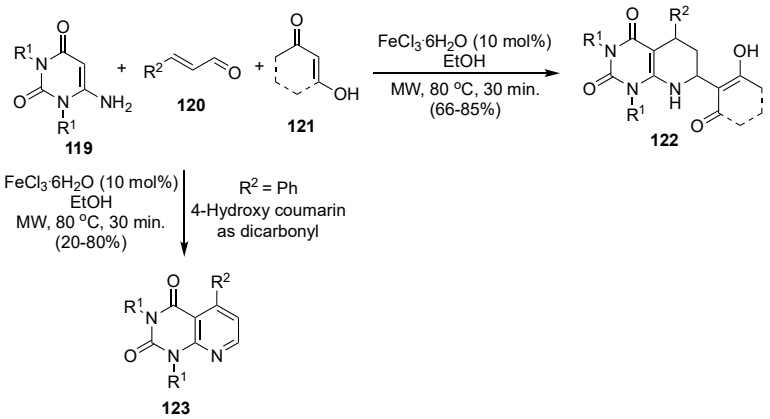
3.4. Miscellaneous six-membered nitrogen heterocycles

Dolzhenko and co-workers reported the synthesis of bis(1,3,5-triazine-2,4-diamines) **115** employing a three-component reaction between cyanoguanidine **112**, aldehydes **113** and piparazine **114** (Scheme 34).[63] This acid-catalyzed reaction yielded dihydrotriazine intermediates under microwave irradiation, which on further treatment with alkali underwent dehydrogenative aromatization to generate the desired *bis*(1,3,5-triazine-2,4-diamines) **115**. Similarly, compound **118** was synthesized from cyanoguanidine **112**, terephthalaldehyde **116** and amines **117** under identical conditions.



Scheme 34. Acid-catalyzed synthesis of bis(1,3,5-triazine-2,4-diamines) under microwave irradiation.

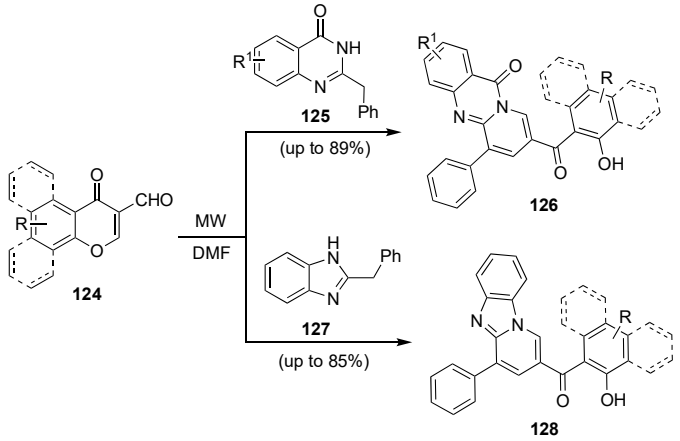
A three-component coupling of 6-aminouracils **119**, α,β-unsaturated aldehydes **120** and cyclic 1,3-dicarbonyl compounds **121** in the presence of $FeCl_3 \cdot 6H_2O$ under microwave irradiation delivered pyrimidine-fused tetrahydropyridines **122** in a regioselective fashion (Scheme 35).[64] When cyclic 1,3-diketones were replaced with 4-hydroxycoumarin, pyrimidine-fused pyridines **123** were obtained in good yields. The advantages of this strategy include shorter reaction times with good yields and regioselective formation of biologically significant heterocycles under facile conditions.



Scheme 35. Fe(III)-catalyzed synthesis of pyrimidine-fused tetrahydropyridines and pyridines.

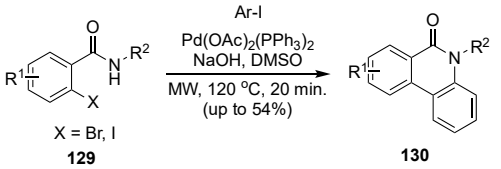
Rao and co-workers established an efficient catalyst-free construction of various *N*-fused heterocycles including imidazo[1,2-*a*]pyridines/pyrimidines/pyrazines under microwave irradiation in H_2O-IPA as the reaction medium.[65] When α-bromoketones are coupled with substituted 2-aminoaminopyridines/pyrazines/pyrimidines, a heteroannulation reaction takes place to generate the corresponding *N*-heterocycles under microwave-assisted conditions in excellent yields. The aforementioned strategy has several benefits compared to the previous reports as it is an environmentally benign approach and three points of structural diversity can be introduced in the desired product.

Lee and co-workers reported microwave-assisted annulations for the synthesis of biologically significant pyrido-fused quinazolinones and pyrido[1,2-*a*] benzimidazole derivatives (Scheme 36).[66] Quinazolinones **125** or benzimidazoles **127** underwent [3+3]-annulations with 3-formylchromones **124** to generate 11*H*-pyrido[2,1-*b*]quinazolin-11-ones **126** and pyrido[1,2-*a*]benzimidazole **128** derivatives respectively. The same methodology was extended for the synthesis of pyrazolo[4,3-*d*], pyrido[1,2-*a*]pyrimidin-10(1*H*)-ones. The unique aspect of this protocol is that three different *N*-fused heterocycles can be generated by suitably modifying the substrates and the desired heterocycles were formed in good yields, and showed high functional group tolerance. The synthesized compounds were employed as an on-off photoluminescent probe for the detection of metal ions like Fe^{3+} and Ag^{+}.



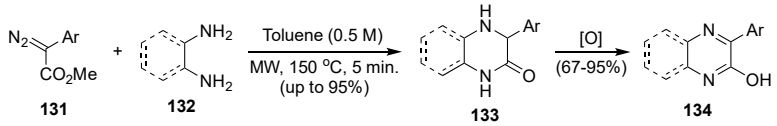
Scheme 36. Microwave-assisted synthesis of pyrido-fused quinazolinones and pyrido[1,2-*a*]benzimidazoles.

Liu and Chen reported a palladium-catalyzed annulation of *o*-halobenzamides **129** with aryl iodides under microwave-assisted conditions to access phenanthridinones **130** (Scheme 37).[67] The reaction proceeds through reductive coupling of aromatic C–X bond and decarbonylative coupling of the amide.



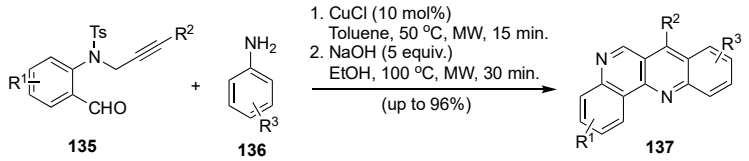
Scheme 37. Microwave-assisted Pd-catalyzed synthesis of phenanthridinones.

Hansen and co-workers developed a metal-free synthesis of substituted quinoxalinones **133** and quinoxalines **134** under microwave irradiation by coupling *in situ* generated carbene obtained from aryldiazo esters **131** with 1,2-diamines **132** (Scheme 38).[68] The reaction was fast and several substituted quinoxalin-2-ones and their corresponding quinoxalines were obtained in good to excellent yields on further oxidation. The modifications in the substrates led to the generation of several fused heterocycles including symmetrical and unsymmetrical 2,3-diarylquinoxalines, bis-quinoxalines and quinoxaline-substituted diazo esters.



Scheme 38. Metal-free synthesis of quinoxalinones and quinoxalines under microwave irradiation.

Sridharan and co-workers demonstrated a microwave-assisted, one-pot, two-step synthesis of functionalized [1,6]naphthyridines **137** in high yields (up to 96%) (Scheme 39).[69] The reaction between 2-(*N*-propargylamino)benzaldehydes **135** and arylamines **136** in the presence of CuI delivered the target compounds by generating two new heterocyclic rings and three bonds in a single synthetic operation. The mechanism of the reaction involves imine formation, intramolecular [4+2]-hetero-Diels-Alder reaction, and detosylation-aromatization steps.



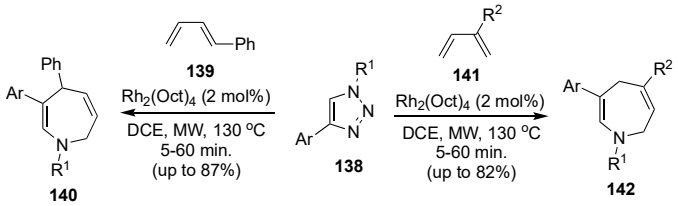
Scheme 39. Microwave-assisted, copper-catalyzed, synthesis of functionalized [1,6]naphthyridines.

4. Synthesis of seven-membered nitrogen heterocycles

Azepine and its analogs are significant in chemistry and medicine as they are widespread in various natural alkaloids like morphine, subincandine F, ngouniensine, ibogamine *etc*. They are present in several synthetic drugs of pharmacological importance such as quetiapine, an atypical antipsychotic agent; pentetrazol, a cough suppressant; omapatrilat, used for the treatment of hypertension; linerixibat, used for the treatment of Type 2 diabetes mellitus to name a few.[70] Due to these aforementioned applications, the construction of azepine skeleton attracted the synthetic chemists attention to explore novel synthetic strategies including microwave irradiation. A few of the recent works have been summarized in this section.

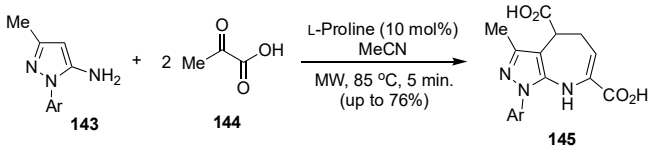
Motornov and Beier demonstrated a Rh-catalyzed chemo- and regioselective *trans*-annulation of *N*-perfluoroalkylated 1,2,3-triazoles **138** with 1,3-dienes **139** or **141** under microwave irradiation for the

synthesis of *N*-perfluoroalkyl-substituted 2,3 or 2,5-dihydroazepines **140** or **142**, respectively (Scheme 40).[71] The reaction proceeded *via* a formal aza-[4+3]-annulations with several substituted 1,3-dienes to deliver dihydroazepines in regioselective manner in good yields. When the reaction was carried out under conventional heating, the desired products were obtained in lower yields after prolonged reaction times (10 h). In similar lines, more complex derivatives of *N*-perfluoroalkylatedazepines possessing a carbonyl group were synthesized when 2-trimethylsilyloxy-1,3-butadiene was employed as the 4π constituent.



Scheme 40. Rh-catalyzed synthesis of 2,3- and 2,5-dihydroazepines.

A new class of pyrazolo[3,4-*b*]azepines **145** was synthesized by the reaction of 5-aminopyrazoles **143** with pyruvic acid **144** employing L-proline as the catalyst under microwave-assisted conditions (Scheme 41).[72] The original aim of the authors was to synthesize a spiro derivative by the reaction of 5-aminopyrazole, isatin and pyruvic acid. The reaction was carried out in the presence of ytterbium triflate in MeCN and when the product was analyzed by various spectroscopic techniques to establish its structure, they observed an unexpected seven-membered pyrazolo[3,4-*b*]azepine as the product. The reaction was found to proceed faster under microwave condition employing L-proline as the catalyst as well as under conventional heating, but the reaction was sluggish in conventional heating conditions. The synthesized compounds were tested for their antioxidant properties following DPPH and ORAC assays and three compounds show inhibition to *Neisseria gonorrhoeae*.



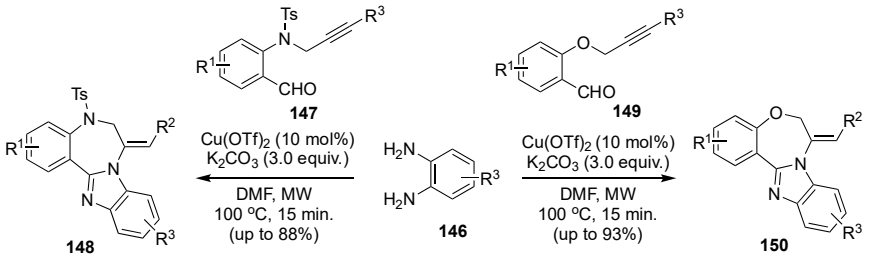
Scheme 41. Microwave-assisted L-proline catalyzed-synthesis of pyrazolo[3,4-*b*]azepines.

Sridharan and co-workers demonstrated a highly efficient copper(II)-catalyzed cascade cyclization of *O*/*N*-propargylated 2-amino or 2-hydroxybenzaldehydes (**147**/**149**) and *o*-phenylenediamines **146** under microwave-irradiation for the synthesis of imidazo[1,2-d][1,4]diazepines **148** and imidazo[1,2-*d*][1,4]oxazepines **150** respectively in high yields (up to 93%) (Scheme 42).[73] The mechanism of the reaction involves imine formation-intramolecular cyclization-air oxidation and 7-*exo*-*dig* cyclization steps. The microwave-assisted protocol was superior in terms of yield and reaction time compared to the conventional heating conditions.

5. Synthesis of three- and four-membered nitrogen heterocycles

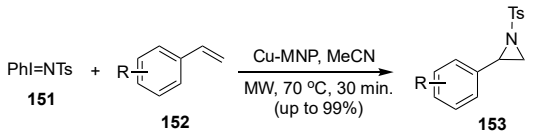
5.1. Aziridines

The smallest nitrogen-containing heterocyclic compound, aziridine, with greater ring strain makes this ring system pretty unique and shows different reactivity.[74] These *N*-heterocycles can be employed as a building block for various chemical transformations,[74a,b] which includes alkaloids synthesis,[74c] nucleophilic ring-opening, and ring expansion reactions.[74d-g] Application of microwaves for the synthesis of aziridine skeletal is discussed in this section.



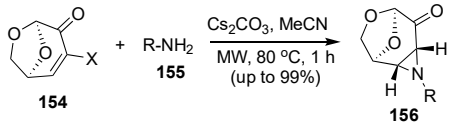
Scheme 42. Microwave-assisted synthesis of imidazo[1,2-*d*][1,4]oxazepines and imidazo[1,2-*d*][1,4]diazepines.

Toumieux and co-workers reported a Cu-catalyzed aziridination of alkenes **152** with compound **151** to access substituted aziridines **153** employing a recyclable magnetic nanoparticles as the catalyst under microwave irradiation (Scheme 43).[75] The reaction employed [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) **151** as the nitrene source and was reacted with various substituted olefins **152** under conventional and microwave heating. The authors observed that under microwave irradiation, the reaction time decreased by four times when compared to conventional heating. Simple magnetic extraction was employed to recover the catalyst and the catalyst was reused efficiently for up to five times without any significant loss of activity.



Scheme 43. Cu-catalyzed aziridination of alkenes under microwave irradiation.

Conversion of biomass into value added products is highly desired in synthetic organic chemistry as it will cover several principles of green chemistry. Ledingham and Greatrex developed an efficient diastereoselective aziridination of 3-halolevoglucosenone **154** with primary aliphatic amines **155** to obtain the biomass pyrolysis product (−)-levoglucosenone **156** (Scheme 44).[76] When aromatic amine, 4-methoxyaniline was taken as the amine variant, aza-Michael initiated dimerization reaction took place. The aziridine products were further transformed into novel class of sulfonamide and amine-substituted 6,8-dioxabicyclo[3.2.1]oct-3-enes were obtained *via* aza-Wharton reaction.



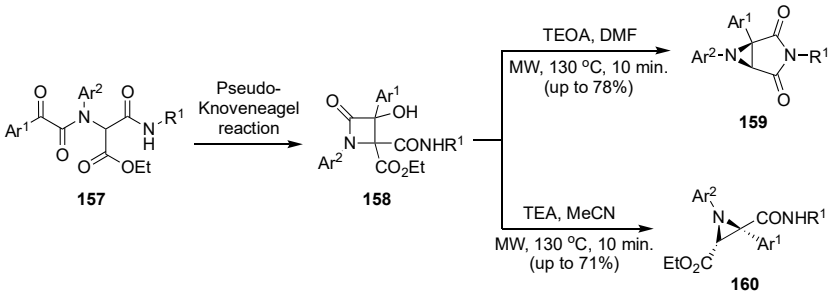
Scheme 44. Diasteroselective aziridination of (−)-levoglucosenone under microwave irradiation.

Xu and co-workers demonstrated a one-pot pseudo-Knoevenagel, ring expansion reaction of Ugi adduct **157** for the synthesis of aziridinyl succinimides **159** (Scheme 45).[77] Further, densely functionalized aziridines **160** were also synthesized through a similar cascade process and the reaction proceeds *via* a common β-lactam intermediate **158**. Anticancer activities were performed and one of the synthesized compounds showed comparable potency to sorafenib in liver cancer cell lines.

5.2. Azetidines

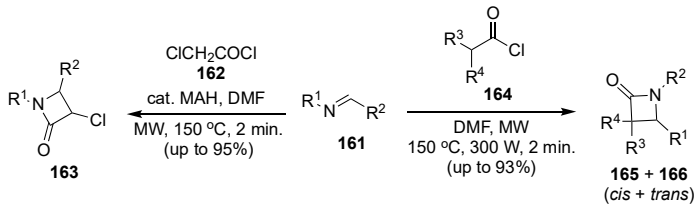
Azetidine is the four-membered *N*-heterocycle and plays an important role in antibiotic activity as β-lactams, which are widespread in nature. For instance, penicillins, cephalosporins, monobactams,

carbapenems and other synthesized pharmaceutically significant molecule possess β-lactam ring.[78] Azetidines act as exceptional building blocks due to their inherent ring strain, thus they can be easily modified into different ring expanded *N*-heterocycles. Several strategies to construct this ring either in the form of azetidines or β-lactams have been developed by sustainable methods including microwave-assisted synthesis.



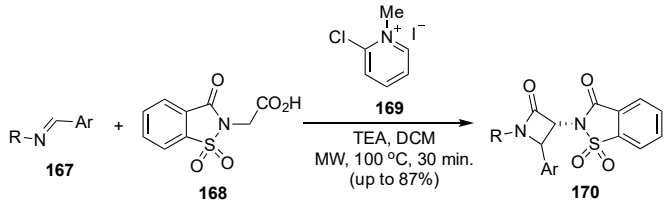
Scheme 45. Microwave assisted, pseudo-Knoevenagel-ring expansion sequence for the synthesis of aziridines.

Vázquez and co-workers reported the synthesis of azetidin-2-ones employing Mg-Al hydroxide (MAH) as the heterogeneous catalysis under microwave-assisted conditions (Scheme 46).[79] The imines **161** reacted with chloroacetyl chloride **162** to deliver the chlorinated azetidin-2-ones **163** in good yields. When substituted acid chlorides **164** reacted with imines **161**, a mixture of *cis* and *trans* azetidin-2-ones **165** and **166** were obtained. The *cis*/*trans* configuration of the products was determined by the aromatic ring of the imines **161**, where electron-donating substituents favored *trans*-azetidinones, while the electron-withdrawing groups in imines delivered *cis*-azetidinones.



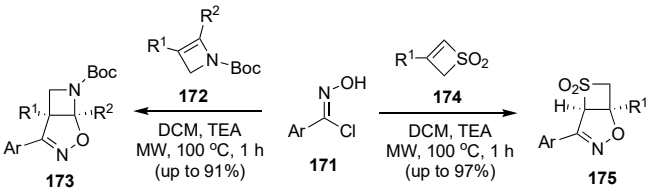
Scheme 46. Microwave-assisted synthesis of azetidin-2-ones.

Ovaa and co-workers developed an efficient microwave-assisted synthesis of 3-saccharinyl-*trans*-β-lactams **170** in a diastereoselective fashion by the reaction between *in situ* generated imine **167** and saccharinylacetic acid **168** in the presence of 2-chloro-*N*-methylpyridinium iodide **169** as catalyst (Scheme 47).[80] Using this methodology, the authors have added a library of around 263 compounds to the European Lead Factory (ELF) consortium.



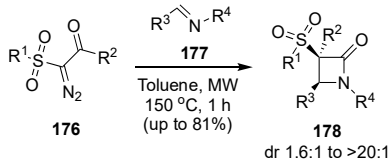
Scheme 47. Microwave-assisted synthesis of 3-saccharinyl-*trans*-β-lactams.

Didier and co-workers established a highly regio- and diastereoselective synthesis of substituted azetidines **173** and thietanes **175** starting from azetines **172**/thietes **174** and *N*-hydroxybenzimidoyl chlorides **171** (Scheme 48).[81] The reaction proceeds *via* a formal [3+2]-cycloaddition under microwave irradiation to deliver the desired products in excellent yields (up to 97%).



Scheme 48. Regio- and diastereoselective synthesis of substituted azetidines and thietanes.

Krasavin and co-workers established a tandem Wolff rearrangement-Staudinger [2+2]-cycloaddition of a wide range of α-diazo-β-ketosulfones **176** with imines **177** to generate polysubstituted β-lactams **178** (Scheme 49).[82] The reaction proceeds in diastereoselective fashion and only *syn*-diastereomers were obtained in good yields and the relative stereochemistry was established by single-crystal X-ray crystallography. This methodology enables flexible exploration of new substitution patterns around the privileged β-lactam core for drug design and lead optimization.



Scheme 49. Microwave-assisted synthesis of polysubstituted β-lactams.

6. Conclusions

In summary, we have discussed various synthetic strategies established in the past few years for the construction of three- to seven-membered nitrogen heterocycles and their fused analogues. It was exciting to observe that microwave played a substantial role to achieve several objectives of green chemistry. The advantages of microwave irradiation cannot be limited to the improvement in the yields of the desired products in shorter reaction times as it has other benefits including lower yields of the side products, improved chemo- and regioselectivity. Apart from the reactions summarized, it was well-established that many classical multicomponent reactions and the contemporary strategies were either assisted or accelerated by microwave irradiation for the construction of simple *N*-, O- and *S*-containing heterocycles. Compared to other environmentally benign methods like ultrasonication, ball-milling, mechanical grinding *etc.*, microwave-assisted reactions are more efficient as they do not involve complex work-up procedures and the separation of the desired heterocycles is easier. Other important facet of the microwave irradiation process was that improvement in the green chemistry metrics, which can be achieved by performing the reaction under neat conditions, thereby lowering the *E*-factor of the process. It was well-established that many microwave-assisted reactions can be performed employing heterogeneous catalysts. The main disadvantage of the process is its scalability that limits its usage for commercial and industrial applications. Recently, this was partially circumvented by coupling of flow-chemistry with microwave irradiation which opens a new horizon for synthetic chemists aiming at scaling up the protocol to a large scale. Still, this is in its infancy and a lot more work needs to be performed to make it an industrially favorable process. Like in any field of science, there is ample scope for improvement in this area to design effective protocols and catalysts employing microwave irradiation. In this aspect, the chapter might help the researchers to navigate various

recent strategies and guide them to develop new protocols under microwave irradiation for the synthesis of various biologically significant *N*-heterocycles.

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